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Highlights in Chronic Lymphocytic Leukemia From the 2017 American Society of Hematology Annual Meeting and Exposition

A Review of Selected Presentations From the 2017 American Society of Hematology Annual Meeting and Exposition • December 9-12, 2017 • Atlanta, Georgia

Special Reporting on:

- Single-Agent Ibrutinib Vs Chemoimmunotherapy Regimens for Treatment-Naive Patients With Chronic Lymphocytic Leukemia: A Cross-Trial Comparison
- Results From the Phase 3 DUO Trial: A Randomized Comparison of Duvelisib Vs Ofatumumab in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma
- Ibrutinib, Fludarabine, Cyclophosphamide, and Obinutuzumab (GA101) for First-Line Treatment of Patients With CLL With Mutated *IGHV* and Without *TP53* Aberration
- Improving Depth of Response With Continued Ibrutinib Therapy in CLL Patients
- Prolonged Improvement in Patient-Reported Outcomes and Well-Being in Older Patients With Treatment-Naive Chronic Lymphocytic Leukemia Treated With Ibrutinib: 3-Year Follow-Up of the RESONATE-2 Study
- Initial Results of the Phase 2 Treatment-Naive Cohort in a Phase 1b/2 Study of Obinutuzumab, Ibrutinib, and Venetoclax in Chronic Lymphocytic Leukemia
- Venetoclax Plus Rituximab Is Superior to Bendamustine Plus Rituximab in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia—Results From Pre-Planned Interim Analysis of the Randomized Phase 3 MURANO Study
- Acalabrutinib Monotherapy in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia: Updated Results From the Phase 1/2 ACE-CL-001 Study

PLUS Meeting Abstract Summaries

With Expert Commentary by:

Susan M. O'Brien, MD
Associate Director for Clinical Sciences, Chao Family Comprehensive Cancer Center
Medical Director, Sue and Ralph Stern Center for Clinical Trials & Research
Professor of Medicine, Division of Hematology/Oncology, Department of Medicine
University of California, Irvine
Orange, California

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Single-Agent Ibrutinib Vs Chemoimmunotherapy Regimens for Treatment-Naive Patients With Chronic Lymphocytic Leukemia: A Cross-Trial Comparison

Chemoimmunotherapy with one or more chemotherapeutic agents and an anti-CD20 monoclonal antibody is the standard of care for the initial treatment of chronic lymphocytic leukemia (CLL). However, there are limitations to chemoimmunotherapy. The responses can be temporary and toxicities can be challenging, particularly in older patients.

The Bruton tyrosine kinase (BTK) inhibitor ibrutinib is approved by the US Food and Drug Administration (FDA) for use in patients with CLL and allows for once-daily oral dosing without chemotherapy. In the randomized, phase 3 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]), single-agent ibrutinib was significantly more effective than chlorambucil in older patients (≥65 years) with CLL without a 17p deletion, demonstrating longer median progression-free survival (PFS; hazard ratio [HR], 0.16; *P*<.001) and longer overall survival (OS; HR, 0.16; *P*<.001).[1] Ibrutinib also had a better hematologic safety profile.[1]

To further assess the potential role of single-agent ibrutinib in the first-line treatment of CLL, Dr Tadeusz Robak and colleagues[2] conducted a cross-trial comparison of updated efficacy and safety outcomes with ibrutinib in RESONATE-2 against outcomes reported in phase 3 trials of various chemoimmunotherapy regimens, including fludarabine, cyclophosphamide, and rituximab (FCR) from CLL8,[3] bendamustine plus rituximab and FCR from CLL10,[4] chlorambucil with obinutuzumab or rituximab from CLL11,[5] and ofatumumab plus chlorambucil from COMPLEMENT-1 (Chlorambucil Plus Ofatumumab Versus Chlorambucil Alone in Previously Untreated Patients With Chronic Lymphocytic Leukaemia).[6] The patient populations differed somewhat across the studies. On average, patients receiving ibrutinib were older, less likely to have unmutated *IGHV*, and more likely to have comorbidities than patients receiving chemoimmunotherapy.

In the overall analysis, primary treatment with ibrutinib was associated with a longer PFS than any chemoimmunotherapy regimen (Figure 1). Investigators noted that the PFS outcomes were better in older, less-fit patients receiving ibrutinib than in younger, fitter patients receiving FCR in the CLL8 trial (Figure 2). PFS outcomes were also better with ibrutinib compared with FCR historical outcomes and with bendamustine/rituximab in CLL10.[4] In patients treated with bendamustine/rituximab or FCR, unmutated *IGHV* remains a poor prognostic factor. In contrast, *IGHV* mutation status did not impact PFS outcomes with ibrutinib. These findings suggest that in older patients, ibrutinib may overcome the poor prognostic effect of unmutated *IGHV.*

Ibrutinib also demonstrated a significant improvement in PFS over historical results with chlorambucil plus rituximab or obinutuzumab in various trials. The benefit of single-agent ibrutinib over chemoimmunotherapy was particularly strong among high-risk subgroups, including patients with advanced disease, unmutated *IGHV*, or the 11q deletion. OS outcomes in ibrutinib-treated patients were comparable with those observed with chemoimmunotherapy; in particular,

ABSTRACT SUMMARY Absolute Percent Deviation of *IGHV* Mutation as a Continuum Is Prognostically Relevant in Patients With CLL

Currently, the cutoff used for dichotomizing patients based on *IGHV* status is a 2% deviation or a 98% sequence identity to germline. Alternative cutoffs ranging from 1% to 5% have been explored. Dr Nitin Jain and colleagues investigated the prognostic significance of *IGHV* percent deviation as a continuous variable (Abstract 3006). Outcomes were assessed based on *IGHV* percent among 203 patients who received FCR during a clinical trial, 332 patients who received FCR off-protocol, and 166 patients treated with ibrutinib. The median follow-up durations for the cohorts were 10.7 years, 5.6 years, and 2 years, respectively. Sustained increases in the percentage deviation of the *IGHV* mutation were associated with significantly better outcomes. In a multivariate analysis, *IGHV* percent as a continuous variable was significantly associated with both PFS (HR, 0.81; 95% CI, 0.73-0.91; *P*<.001) and OS (HR, 0.87; 95% CI, 0.82-0.93; *P*<.001) among FCR-treated patients. However, *IGHV* percent was not significantly associated with PFS or OS among patients who had received ibrutinib. The researchers concluded that the prognostic significance of *IGHV* percent as a continuous variable warrants further research.

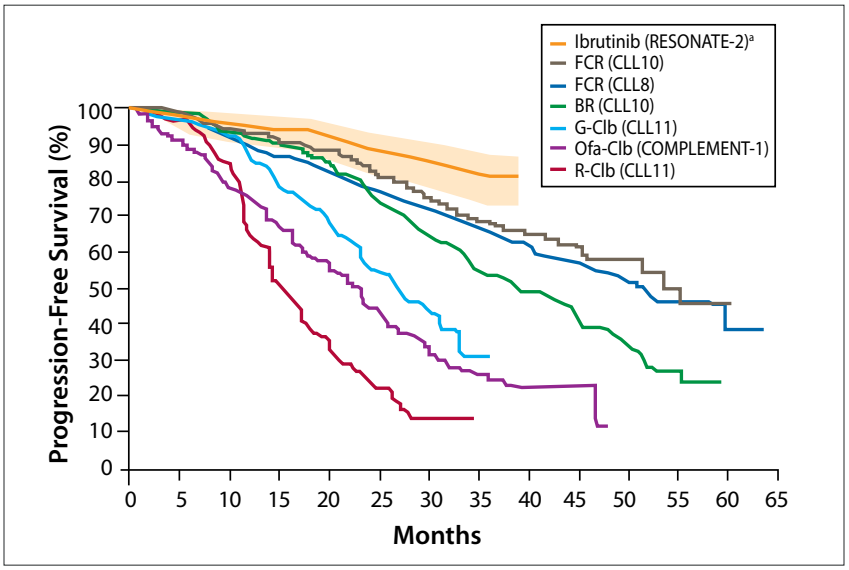

Figure 1. Progression-free survival in a cross-trial comparison of ibrutinib vs chemoimmunotherapy. [a]The shaded area represents the 95% CI with ibrutinib. BR, bendamustine plus rituximab; FCR, fludarabine, cyclophosphamide, and rituximab; G-Clb, obinutuzumab plus chlorambucil; Ofa-Clb, ofatumumab plus chlorambucil; R-Clb, rituximab plus chlorambucil. Adapted from Robak T et al. ASH abstract 1750. *Blood*. 2017;130(suppl 1).[2]

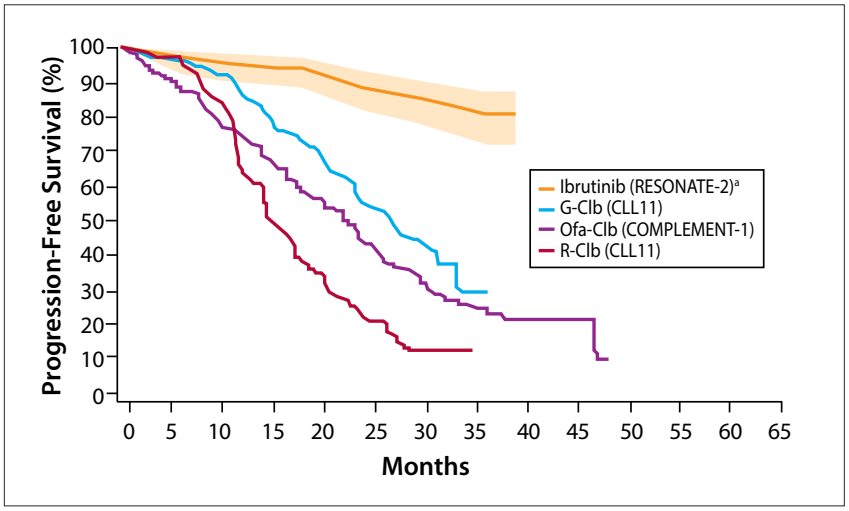

Figure 2. Progression-free survival among older patients or those with comorbidities in a cross-trial comparison of ibrutinib vs chemoimmunotherapy. [a]The shaded area represents the 95% CI with ibrutinib. FCR, fludarabine, cyclophosphamide, and rituximab; G-Clb, obinutuzumab plus chlorambucil; Ofa-Clb, ofatumumab plus chlorambucil; R-Clb, rituximab plus chlorambucil. Adapted from Robak T et al. ASH abstract 1750. *Blood*. 2017;130(suppl 1).[2]

ibrutinib appeared to provide an OS benefit over regimens that contained chlorambucil in the comparator arm.

The patients receiving ibrutinib remained on treatment longer than patients receiving chemoimmunotherapy, with median treatment durations of 34 months vs 5 to 6 months, respectively. Despite the longer treatment period and the older patient population, ibrutinib was associated with lower rates of grade 3 or higher cytopenias compared with FCR or bendamustine/rituximab. Rates of grade 3 or higher infections were similar.

The investigators concluded that single-agent ibrutinib may provide a chemotherapy-free initial regimen that has comparable efficacy with that observed with standard combination chemoimmunotherapy. These data were drawn from cross-trial comparisons. Ongoing prospective, randomized trials are comparing ibrutinib (alone or in combination with an anti-CD20 agent) vs FCR,[7] bendamustine/rituximab,[8] and chlorambucil/obinutuzumab.[9]

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Results From the Phase 3 DUO Trial: A Randomized Comparison of Duvelisib Vs Ofatumumab in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

There is an unmet need for effective therapies for patients with relapsed/refractory CLL. Duvelisib is an orally administered inhibitor of phosphoinositide 3-kinase (PI3K)-delta and PI3K-gamma. It is thought that the ability to target both the delta and gamma isoforms of PI3K will allow duvelisib to exert activity against tumor cells and the microenvironment. Duvelisib initially showed antitumor activity in a phase 1 study in patients with advanced CLL/small lymphocytic lymphoma (SLL), demonstrating an overall response rate (ORR) of 56%.[1] Based on this initial finding, the randomized, phase 3 DUO trial (A Phase 3 Study of Duvelisib Versus Ofatumumab in Patients With Relapsed or Refractory CLL/SLL) compared duvelisib vs ofatumumab in patients with relapsed/refractory CLL who developed progressive disease or relapsed after at least 1 prior therapy.[2] (Patients previously treated with a BTK or PI3K inhibitor were excluded.) Patients had measurable lymph node disease as assessed by computed tomography (CT) and adequate hemoglobin levels and platelet counts. Patients with Richter transformation and prolymphocytic leukemia were excluded.

A total of 319 patients were assigned to duvelisib 25 mg twice daily continuously (n=160) or intravenous ofatumumab administered at 300 mg on day 1, then 2000 mg weekly for 7 weeks followed by monthly for 4 months (n=159). All patients received prophylaxis for *Pneumocystis* pneumonia during treatment, and prophylaxis for cytomegalovirus infection/reactivation was recommended. In an optional crossover study, patients switched to ofatumumab (n=8) or duvelisib (n=89).

During 2014 and 2015, the DUO trial enrolled patients from Europe (74%), the United States (16%), Australia (7%), and New Zealand (4%). The median age of patients was 69 years (range, 39-90 years), and 60% were male. The baseline factors were fairly well-balanced between the arms. Approximately half of patients had bulky disease, and a third of patients

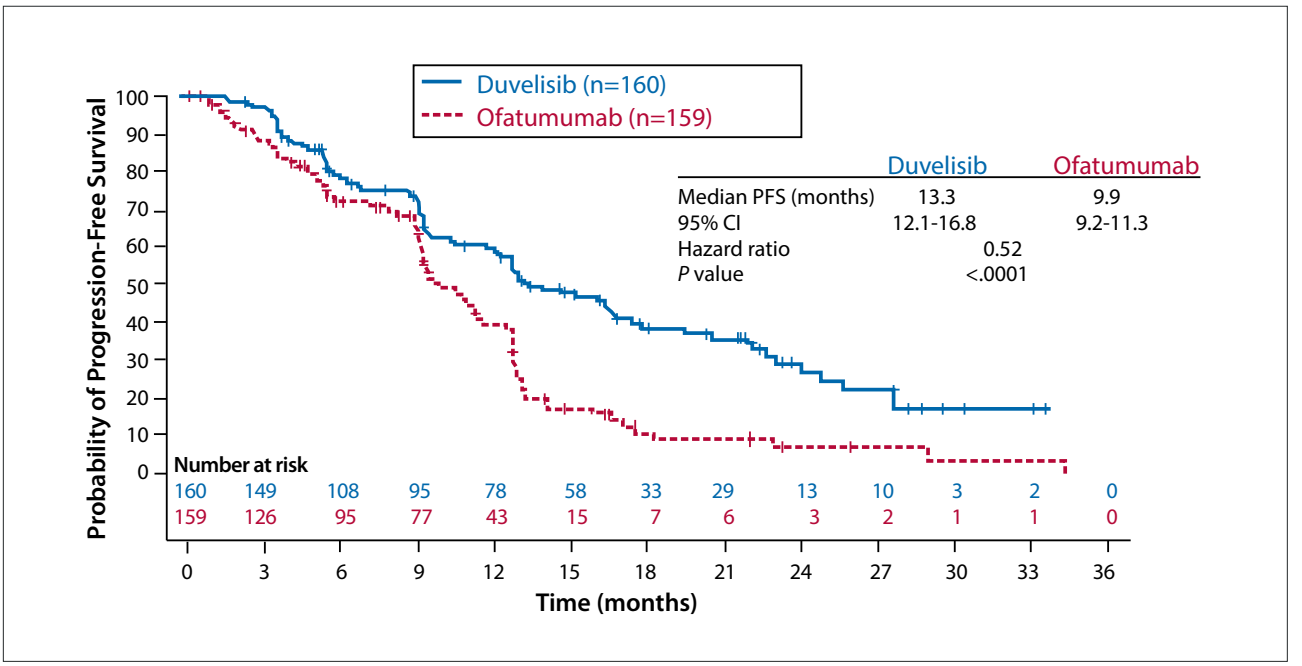

Figure 3. Progression-free survival among patients treated with duvelisib or ofatumumab according to an independent review committee. Adapted from Flinn IW et al. ASH abstract 493. *Blood*. 2017;130(suppl 1).[2]

had a 17p deletion or *TP53* mutation. ZAP70 positivity (defined as ≥20%) was present in approximately 53% of patients. Grade 4 cytopenias were present at baseline in 11% of patients. Patients had received a median of 2 prior therapies (range, 1-10). Approximately two-thirds of patients had been previously treated with a purine analogue, more than 90% had received an alkylating agent, and approximately 80% had received a monoclonal antibody, most often rituximab.

The median duration of treatment was substantially longer with duvelisib than ofatumumab, at 50 weeks vs 23 weeks, respectively. The most common reasons that patients discontinued treatment with duvelisib were adverse events (AEs; 35%) and disease progression (22%). In the ofatumumab arm, 20% of patients discontinued owing to disease progression. At the time of the analysis, 22% of patients in the duvelisib arm remained on treatment. Among the 110 patients in the ofatumumab arm who developed disease progression (69%), 89 crossed over to receive duvelisib.

The trial met its primary endpoint, demonstrating a significant improvement in PFS with duvelisib vs ofatumumab per the independent review committee (Figure 3). Median PFS was 13.3 months with duvelisib vs 9.9 months with ofatumumab (HR, 0.52; *P*<.0001). The PFS benefit with duvelisib was more pronounced among the 77 patients with a 17p deletion, at a median of 12.7 months vs 9.0 months with ofatumumab (HR, 0.41; *P*=.0011). The PFS advantage was maintained across other key subgroups, including patients with refractory or early relapse, those with grade 4 cytopenias, older patients, younger patients, and those with both longer and shorter relapses.

The ORR was also significantly higher with duvelisib vs ofatumumab, in both the overall population (73.8% vs 45.3%; *P*<.0001) and in the subset of patients who had the 17p deletion (70% vs 43%; *P*=.0182). Lymph node responses (defined as ≥50% decrease in the sum of the product of the greatest diameters of the target lymph nodes from baseline) were observed in 85.0% of the duvelisib arm and 15.7% of the ofatumumab arm. The median OS was not reached in either arm, and OS curves were similar between the arms. The investigators noted that many patients went on to receive subsequent anticancer therapies. Among patients in the ofatumumab arm who crossed over, duvelisib was associated with an investigator-assessed ORR of 73% and a median PFS of 15 months.

AE rates were higher with duvelisib vs ofatumumab, even with the longer observation period for duvelisib. Grade 3/4 hematologic AEs included neutropenia (reported in 30% of the duvelisib arm vs 17% of the ofatumumab arm), anemia (13% vs 5%), and thrombocytopenia (8% vs 2%). The most common grade 3/4 nonhematologic toxicities associated with duvelisib were diarrhea (15%), pneumonia (14%), and colitis (12%). Other grade 3/4 AEs occurred in less than 5% of patients. Most cases of diarrhea and colitis were manageable, and they did not require treatment discontinuation. Severe opportunistic infections occurred in 6% of patients. No severe herpes zoster infections were reported. Among the 4 deaths attributed to treatment, the causes were infectious complications in 3 patients and general health deterioration in 1 patient.

ABSTRACT SUMMARY Phase II, Multicenter Trial, Exploring "Chemo-Sparing" Strategy Associating Obinutuzumab + Ibrutinib Followed By a MRD Driven Strategy, in Previously Untreated Symptomatic Medically Fit Chronic Lymphocytic Leukemia Patients (CLL): Preliminary Results of the Induction Phase of the ICLL-07 Filo Study

The phase 2 ICLL-07 trial evaluated an MRD-driven, first-line CLL strategy in which medically fit patients received induction therapy with obinutuzumab for 6 cycles plus ibrutinib for 9 months (Abstract 497). Patients then underwent CT scanning, bone marrow biopsy, and MRD testing. Patients with a CR and MRD-negative bone marrow received ibrutinib for 6 additional months, whereas patients with worse responses received 4 courses of fludarabine plus cyclophosphamide and obinutuzumab plus continued ibrutinib. Among the 135 enrolled patients, the median age was 62 years (range, 35-80 years), 57% had unmutated *IGHV*, 20% had an 11q deletion, 51% had a 13q deletion, 22% had trisomy 12, and 13% had a complex karyotype. Among the first 97 patients evaluable at 9 months, the regimen was associated with an ORR of 100% and a CR rate of 38% (independent of *IGHV* status). MRD-negative bone marrow was reported in 13% of patients. Grade 3/4 hematologic toxicities included thrombocytopenia (31%), neutropenia (24%), and anemia (6%). Serious treatment-related AEs were reported in 24 patients, including 5 patients with cardiac AEs, 3 patients with bleeding events, and 3 patients with tumor lysis syndrome.

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Ibrutinib, Fludarabine, Cyclophosphamide, and Obinutuzumab (GA101) for First-Line Treatment of Patients With CLL With Mutated *IGHV* and Without *TP53* Aberration

FCR is a standard frontline chemoimmunotherapy regimen for younger, fit patients with CLL. FCR has demonstrated efficacy as initial therapy in selected patients, with up to 72% of patients attaining a complete remission (CR) and up to 59% attaining negativity for minimal residual disease (MRD).[1,2] Outcomes with FCR are particularly favorable in patients with *IGHV*-mutated CLL. In an analysis of patients receiving initial therapy for CLL, presence of the *IGHV* mutation was the best pretreatment predictor of which patients would achieve MRD negativity and improved PFS.[3]

It has been hypothesized that MRD negativity may predict improvement in OS, and MRD status is a component of many recent CLL trials. Several trials have improved MRD rates and clinical outcomes by altering standard chemoimmunotherapy regimens. In the CLL11 trial, the use of obinutuzumab rather than rituximab in combination with chlorambucil was associated with a significant increase in MRD negativity rates and a significant improvement in OS (HR, 0.41; *P*=.002).[4] In the HELIOS trial (A Study of Ibrutinib in Combination With Bendamustine and Rituximab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma; CLL3001), the addition of ibrutinib to chemotherapy in patients with relapsed/refractory CLL was associated with a higher rate of MRD negativity and a significant improvement in PFS.[5]

At the 2017 ASH meeting, Dr Nitin Jain reported outcomes from an ongoing, investigator-initiated phase 2 trial that is attempting to improve upon the FCR regimen by using obinutuzumab rather than rituximab and adding ibrutinib.[6] The ibrutinib, fludarabine, cyclophosphamide, and obinutuzumab (iFCG) regimen is being evaluated in patients ages 18 years or older with previously untreated, *IGHV*-mutated, CLL/SLL without a 17p deletion or *TP53* aberrations. Enrolled patients have adequate organ function, with an absolute neutrophil count exceeding 500/mm^3, a platelet count higher than 50,000/mm^3, levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) less than or equal to 2.5 × the upper limit of normal, a total bilirubin less than or equal to 1.5 × the upper limit of normal, and a glomerular filtration rate of 30 mL/min or higher.

In addition to evaluating the addition of ibrutinib to chemotherapy, the trial is assessing the feasibility of a shortened chemotherapy regimen of 3 cycles, with the aim of reducing the risk of secondary acute myeloid leukemia and myelodysplastic syndrome, which occur in 5% of FCR-treated patients.[7] The trial enrolled its first patient in April 2016, and enrollment continued as of December 2017. An estimated 45 patients are now enrolled. The presentation at the 2017 ASH meeting provided outcomes for the first 36 patients who began treatment.

The iFCG regimen consisted of obinutuzumab administered in cycle 1 as 100 mg on day 1, 900 mg on day 2, and 1000 mg on days 8 and 15, followed by 1000 mg on day 1 in courses 2 to 3; fludarabine administered at 25 mg/m^2 on days 2 to 4 in cycle 1, then on days 1 to 3 in cycles 2 to 3; cyclophosphamide administered at 250 mg/m^2 on days 2 to 4 in cycle 1 and on days 1 to 3 in cycles 2 to 3; and ibrutinib at 420 mg once daily continuously. All patients received

ABSTRACT SUMMARY Long-Term Treatment With Ibrutinib in Chronic Lymphocytic Leukemia Patients Normalizes CD3+ and CD8+ T Cells and Immune Checkpoint Expression but Gradually Leads to CD4+ T-Cell Depletion

Dr Marzia Palma presented the results of a study investigating the effects of ibrutinib treatment on the immune system (Abstract 4322). Changes in blood cell counts, including CLL cells, natural killer cells, T-cell subsets, and immune checkpoint expression, were assessed in 11 patients with relapsed/refractory CLL receiving long-term ibrutinib and 9 control subjects matched for age and sex. Ibrutinib treatment was associated with a gradual normalization of CD3-positive and CD8-positive T-cell counts. CD4-positive T-cell counts declined gradually to levels significantly below normal by 24 months. An analysis of helper T-cell subsets showed a normalization of Th1 cells by 12 months and a reduction to below-normal levels of Th2 cells at 12 months. CD4-positive and CD8-positive memory cell subsets also gradually normalized over time. Expression of the immune checkpoint molecules PD-1 and CTLA-4 was significantly elevated at baseline in both CD4-positive and CD8-positive cells. PD-1 expression normalized in CD8-positive cells by 12 months and in CD4-positive cells by 24 months. CTLA-4 expression normalized in CD4-positive cells by week 22. Expression of the proliferation marker Ki-67 normalized in the CD4-positive subset by 10 months and in the CD8-positive subset by 12 months.

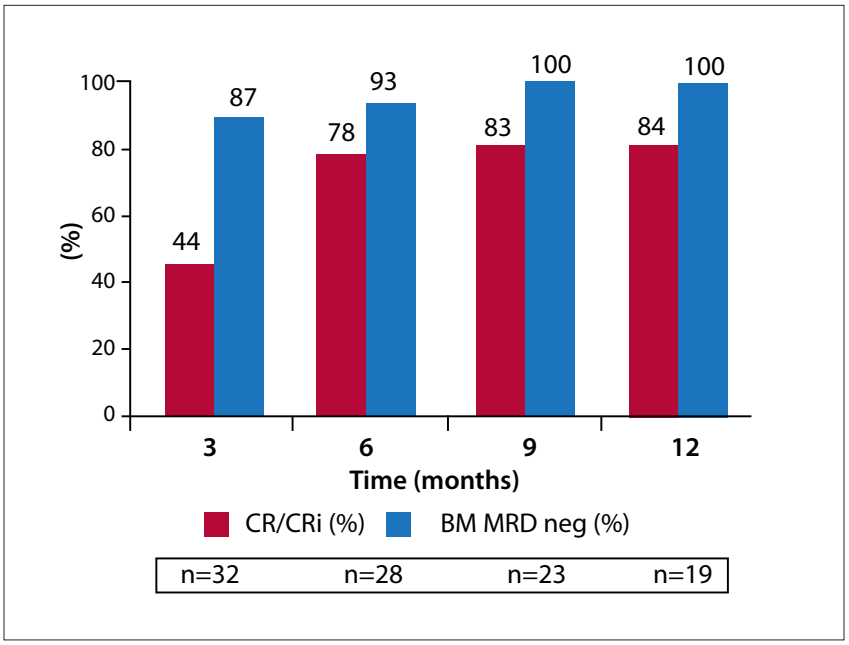

Figure 4. Responses in a study evaluating ibrutinib plus 3 cycles of fludarabine, cyclophosphamide, and obinutuzumab. BM, bone marrow; CR, complete remission; CRi, complete remission with incomplete marrow recovery; MRD, minimal residual disease. Adapted from Jain N et al. ASH abstract 495. *Blood*. 2017;130(suppl 1).[6]

antiviral prophylaxis with acyclovir or valacyclovir. Prophylaxis for *Pneumocystis jiroveci* pneumonia was optional. Initially, administration of prophylactic granulocyte colony–stimulating factor was optional, but the trial was later amended to require it.

After 3 cycles of iFCG, patients were assessed for responses and MRD. Patients with a CR or a complete remission with insufficient count recovery (CRi) and MRD negativity received ibrutinib plus obinutuzumab for 3 cycles, then ibrutinib for 6 cycles. Those with a partial response or MRD positivity after 3 cycles of iFCG received 9 cycles of ibrutinib plus obinutuzumab. After 12 cycles, patients with MRD negativity stopped ibrutinib, and those with MRD positivity continued ibrutinib until they developed progressive disease.

Among the 36 enrolled patients, the median age was 60 years (range, 25-71 years), and 78% were male. Nearly half of patients (47%) had Rai stage III/IV disease. Abnormalities identified through fluorescence in situ hybridization (FISH) included a 13q deletion in 72% of patients and trisomy 12 in 17%. Cytogenetic assessments, obtained for 31 patients, included diploid (68%), 13 deletion (19%), and trisomy 12 (13%). The most common mutations (assessed in 35 patients) were *MYD88* (11%) and *SF3B1* (6%). After a median follow-up of 13.6 months, 32 of the 36 enrolled patients had completed 3 cycles of iFCG. Among the remaining 4 patients, 3 were receiving iFCG at the time of the analysis. One patient discontinued treatment after day 1 of cycle 1, based on a grade 3 infusion-related reaction and grade 4 thrombocytopenia.

The iFCG regimen was associated with high remission rates, with 87% of patients attaining MRD negativity in their bone marrow after 3 cycles (Figure 4). The ORR after 3 cycles of iFCG was 100%, with a CR/CRi rate of 44%. Longitudinal analyses showed that responses improved with time and were observed beyond cycle 6. In an analysis of MRD outcomes by pretreatment characteristics, 3 factors were associated with lower rates of MRD negativity in the bone marrow: higher levels of beta-2 microglobulin, CD38, and ZAP-70 (assessed in 30 patients). MRD negativity rates were similar according to age, sex, Rai stage, FISH features, absolute lymphocyte count, and platelet count.

A total of 19 patients received a year of treatment. All of these patients were MRD-negative and discontinued ibrutinib, as per the protocol. All patients remained MRD-negative after a median follow-up of 5.5 months (range, 0.3-8.5 months) after discontinuation of ibrutinib. At the time of the analysis, all 36 enrolled patients were alive and without disease progression or MRD relapse. The most common grade 3/4 hematologic toxicities were neutropenia and thrombocytopenia, reported in 68% and 27% of patients, respectively, in cycles 1 to 3, and in 42% and 10% of patients, respectively, in cycles 4 to 12. Prophylaxis with granulocyte colony–stimulating factor was mandated for the last 4 patients, and none developed neutropenia.

Grade 3/4 nonhematologic toxicities included elevations of ALT/AST in 4 patients (11%), infusion-related reactions in 2 patients (6%), and arthralgia in 1 patient (3%). An additional 12 patients (33%) had infusion-related reactions of grade 2. Neutropenic fever occurred in 5 patients (14%). Half of patients required dose reductions of fludarabine or cyclophosphamide, and 39% required dose reductions of ibrutinib.

Dr Jain concluded that iFCG induced a high rate of MRD-negative remissions, with 87% of patients attaining MRD negativity in the bone marrow after 3 cycles. All 19 patients who reached the 1-year mark were MRD-negative in the bone marrow and discontinued ibrutinib. The researchers identified molecular factors at baseline that could predict a lower likelihood of attaining MRD negativity.

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Improving Depth of Response With Continued Ibrutinib Therapy in CLL Patients

The safety and efficacy of single-agent ibrutinib in patients with CLL who have *TP53* aberrations was evaluated in a single-arm, phase 2 trial. Previously published efficacy and safety results from the first 47 evaluable patients showed encouraging activity in this high-risk population.[1] At the 2017 ASH meeting, Dr Inhye Ahn reported updated findings, with additional patients and longer follow-up.[2] Among 86 patients enrolled, the median age was 63 years, 58% were male, 62% were treatment-naive, 67% had Rai stage III to IV disease, and 63% had *TP53* aberrations, including a 17p deletion (58%) and *TP53* mutations (4.7%). Most patients (66%) had unmutated *IGHV*.

Throughout a median follow-up of 48 months, the level of MRD declined with continued ibrutinib treatment. Most patients did not attain MRD negativity (defined as <1 monoclonal B-cell per 10,000 leukocytes [10^{-4}]), but MRD levels declined over time. At 2 years, 58 patients tested MRD-high ($\geq 10^{-2}$), and 9 patients tested MRD-low ($<10^{-2}$). CR rates in these groups were 10% vs 22%, respectively. At 3 years, 47 patients tested MRD-high and 16 patients tested MRD-low, with CR rates of 21% vs 38% (Figure 5).

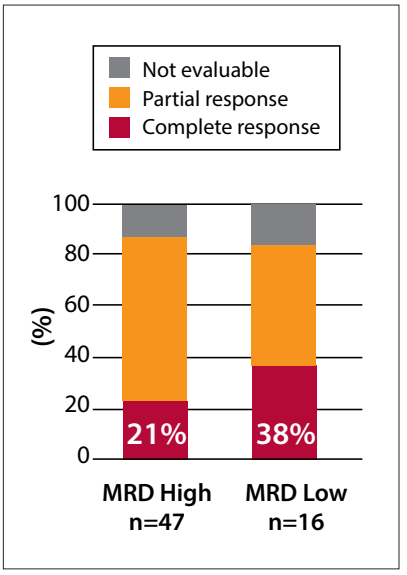

Figure 5. Responses according to levels of MRD after treatment with single-agent ibrutinib. MRD, minimal residual disease. Adapted from Ahn IE et al. ASH abstract 4302. *Blood.* 2017;130(suppl 1).[2]

IGHV mutation status was significantly associated with MRD status. The level of MRD present in the peripheral blood was significantly lower among patients with unmutated *IGHV* than in those with mutated *IGHV* ($P<.05$), starting from the first year of treatment with ibrutinib. (The same trend was not observed in the bone marrow, where MRD outcomes were similar regardless of *IGHV* status.) Researchers noted that the higher levels of MRD in the peripheral blood of patients with mutated *IGHV* are consistent with previously observed differences in redistribution lymphocytosis between these subgroups. They suggested that the correlation between MRD levels and *IGHV* status should be considered by investigators of studies using MRD to determine the duration of treatment with ibrutinib.

After the first year of ibrutinib treatment, the amount of residual CLL burden declined by 36% in the peripheral blood and by 28% in the bone marrow with each additional year. Levels of MRD in the peripheral blood correlated strongly with those measured in the bone marrow. The investigators suggested that this finding raises the possibility of using noninvasive blood testing, rather than bone marrow assessment, to measure MRD in patients receiving ibrutinib.

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Prolonged Improvement in Patient-Reported Outcomes and Well-Being in Older Patients With Treatment-Naive Chronic Lymphocytic Leukemia Treated With Ibrutinib: 3-Year Follow-Up of the RESONATE-2 Study

In the RESONATE-2 trial, single-agent ibrutinib was significantly more effective than chlorambucil in older patients (≥65 years) with treatment-naive CLL, providing an 84% reduction in the risk of progression or death (HR, 0.16; *P*<.001).[1] Other reports have shown that ibrutinib is associated with improvements in quality of life and patient well-being, including in the RESONATE study (Ibrutinib Versus Ofatumumab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia; PCYC-1112) in relapsed/refractory CLL, in which ibrutinib was associated with more clinically meaningful improvements in fatigue and global health compared with chlorambucil at week 24.[2] Patient-reported outcomes from RESONATE-2 have been previously reported, showing greater improvements with ibrutinib vs chlorambucil in the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) score (*P*=.0004) and the European Organization for Research and Treatment core quality-of-life questionnaire (QLQ-C30) global health score (*P*=.0002) after a median follow-up of 18.4 months.[3] At the 2017 ASH meeting, Dr Alessandra Tedeschi presented updated results on quality of life and patient well-being in RESONATE-2.[4] The investigators noted that treatment with ibrutinib continues until patients develop progressive disease or unacceptable toxicity, and therefore any impact on quality of life is especially important.

Among the 136 patients assigned to ibrutinib and the 133 patients assigned to chlorambucil, the most common reasons for starting treatment for CLL were the development of constitutional symptoms (45%), progressive bone marrow failure (38%), lymphadenopathy (37%), and splenomegaly (30%). Patients in the ibrutinib arm received treatment for a median of 34.1 months, and 73% of patients were still receiving ibrutinib at the time of analysis, after a median follow-up of 35.7 months. In the chlorambucil arm, the median treatment duration was much shorter, at 7.1 months, and 48% of patients crossed over to ibrutinib after developing progressive disease. The median follow-up in the chlorambucil arm was 34.4 months.

At baseline, CLL disease-related symptoms included fatigue, night sweats, and weight loss. All of these symptoms improved to a greater extent among patients treated with ibrutinib vs chlorambucil (Figure 6). FACIT-F scores improved consistently over time among ibrutinib-treated patients, whereas they declined over time with chlorambucil. Similar trends were seen for the EQ-5D-5L Visual Analog Scale (VAS) scores. A repeated measure analysis showed that the differences between the treatment arms were significant for both of these scores (*P*=.0021 for FACIT-Fatigue and *P*=.0004 for EQ-5D-5L VAS). Among patients who crossed over from chlorambucil to ibrutinib upon disease progression, there was a trend toward improvements in both the FACIT-F scores and the EQ-5D-5L VAS scores, which persisted over time.

The investigators also reported updated PFS findings. After a median follow-up lasting approximately 35 months, the median PFS had not been reached in the ibrutinib arm and was 15.0 months in the chlorambucil arm (HR, 0.130; 95% CI, 0.081-0.208; Figure 7). PFS rates at 30 months were 85% with ibrutinib vs 28% with

ABSTRACT SUMMARY Randomized Trial of Ibrutinib Versus Ibrutinib Plus Rituximab in Patients With Chronic Lymphocytic Leukemia

Dr Jan Burger presented results of a single-center trial of ibrutinib plus rituximab vs ibrutinib alone in 206 patients with CLL, including 179 patients with relapsed/refractory CLL and 27 treatment-naive patients with a 17p deletion or *TP53* mutation (Abstract 427). Patients were randomly assigned to single-agent ibrutinib or to ibrutinib plus rituximab (administered weekly for 4 weeks and then monthly for cycles 2 to 6). After a 2-year follow-up, the addition of rituximab to ibrutinib was not associated with improvements in PFS or OS. Response rates were not significantly different between arms, regardless of the treatment setting. The combination of ibrutinib and rituximab was associated with a more rapid response than ibrutinib alone (median time to CR/CRi, 11.5 vs 21.1 months; *P*=.032) and a more rapid normalization of absolute lymphocyte count (median, 3.0 vs 8.9 months; *P*<.001). The most common adverse event, respiratory infection, occurred in 44% of the ibrutinib arm and 27% of the combination arm. Neutropenia was seen in 18% vs 19%, respectively. Investigators concluded that single-agent ibrutinib remains the standard of care, although clinicians may consider adding an anti-CD20 antibody when a more rapid response is important.

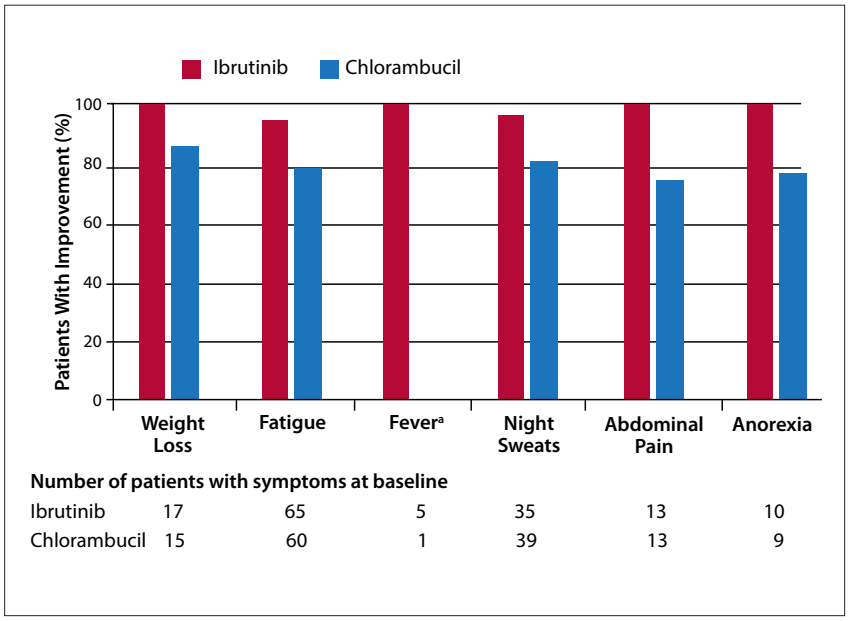

Figure 6. Improvement in disease-related symptoms among patients receiving ibrutinib or chlorambucil. Improvement was defined by a change of ≥1 grade from baseline for ≥2 consecutive assessments at any time, as assessed by the investigator. [a]One patient in the chlorambucil group had baseline fever, which did not improve. Adapted from Tedeschi A et al. ASH abstract 1746. *Blood*. 2017;130(suppl 1).[4]

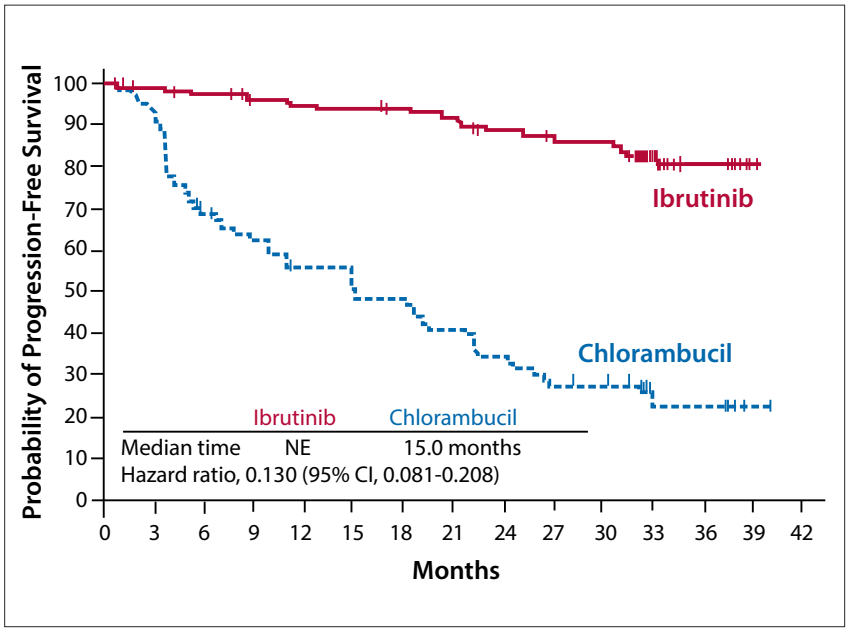

Figure 7. Progression-free survival among patients receiving ibrutinib or chlorambucil. NE, not evaluable. Adapted from Tedeschi A et al. ASH abstract 1746. *Blood*. 2017;130 (suppl 1).[4]

chlorambucil, and improved disease burden was seen in 86% vs 52%. Rates of hematologic improvement were also significantly higher with ibrutinib vs chlorambucil for both hemoglobin (90% vs 45%; *P*<.0001) and platelet count (83% vs 46%; *P*=.0032). These differences were associated with a significant reduction in the need for treatment-emergent hematologic support in the ibrutinib arm.

The most common AEs associated with ibrutinib were diarrhea (47%), fatigue (33%), and cough (30%). Throughout a 3-year period, 7% of ibrutinib-treated patients developed grade 3 or higher bleeding. AEs led to treatment discontinuation in 16% of patients in the ibrutinib arm throughout this time. The Quality-Adjusted Time Without Symptoms or Toxicity (Q-TWiST) analysis, which takes into consideration both the benefits of treatment and the toxicities, indicated a significant improvement in the average time spent without symptoms of progressive disease or grade 3/4 AEs with ibrutinib vs chlorambucil (501 vs 351 days; *P*<.001). Ibrutinib was also associated with a significant extension in the average Q-TWiST duration (386 vs 329 days; *P*=.001).

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Initial Results of the Phase 2 Treatment-Naive Cohort in a Phase 1b/2 Study of Obinutuzumab, Ibrutinib, and Venetoclax in Chronic Lymphocytic Leukemia

An ongoing phase 1b/2 study is evaluating a novel triplet regimen of obinutuzumab, ibrutinib, and venetoclax in patients with CLL. The phase 1b component enrolled 12 patients with relapsed/refractory CLL to receive a regimen that included dose-escalated venetoclax. The phase 2 trial has enrolled 25 patients with relapsed/refractory CLL and 25 treatment-naive patients. At the 2017 ASH meeting, Dr Kerry Rogers presented initial results from the phase 2 study in treatment-naive patients.[1] All enrolled patients had adequate organ function and bone marrow function. Exclusion criteria included uncontrolled autoimmune hemolytic anemia or thrombocytopenia, active Richter syndrome, central nervous system involvement, and use of warfarin or potent CYP3A4 inhibitors or inducers within 7 days before starting the study treatment.

The doses and schedules used in the phase 2 study were established during the 1b phase.[2] Treatment was administered in 14 cycles consisting of 28-day periods. Obinutuzumab was initiated in cycle 1 (100 mg on day 1, 900 mg on day 2, and 1000 mg on days 8 and 15). In cycle 2, obinutuzumab was administered at 1000 mg on day 1, and ibrutinib was added (420 mg/day each day). Starting in cycle 3, venetoclax was introduced, and dose-escalated according to the FDA label. The primary endpoint in the phase 2 study was MRD-negative CR.

Among the 25 treatment-naive patients, the median age was 59 years (range, 24-77 years), 60% were male, 71% had unmutated *IGHV*, and 24% had a complex karyotype. FISH testing revealed an 11q deletion in 20% of patients, a 13q deletion in 20%, a 17p deletion in 12%, and trisomy 12 in 12%. The risk of tumor lysis syndrome was medium in 72% of patients and high in 28% of patients.

At the data cutoff, no patients had developed progressive disease. Among the 3 patients who discontinued study treatment, the reasons were investigator choice in cycle 7, patient preference in cycle 10, and neutropenia and colitis in cycle 10 (this patient died). The most common AEs were hematologic. Grade 3/4 hematologic events included neutropenia (48%), thrombocytopenia (36%), leukopenia (36%), lymphopenia (32%), and lymphocytosis (4%). No cases of grade 3/4 anemia or neutropenia were reported. The most common nonhematologic grade 1/2 treatment-related AEs were infusion-related reactions (76%), nausea (60%), bruising (56%), oral mucositis (52%), dyspepsia (48%), hypertension (44%), diarrhea (44%), fatigue (40%), and maculopapular rash (40%). The only grade 3/4 nonhematologic AE reported in more than 1 patient was hypertension, which occurred in 9 patients (36%). No events related to clinical or laboratory tumor lysis syndrome were noted.

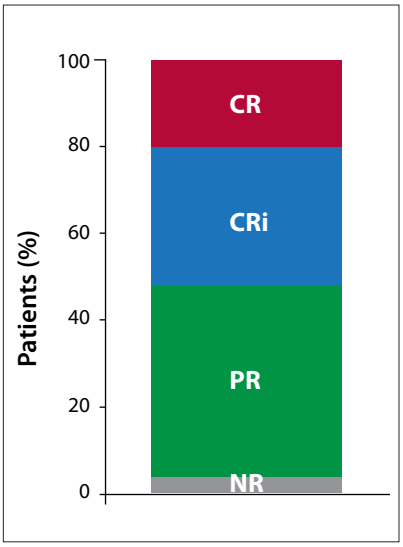

Figure 8. Responses after cycle 8 among patients treated with a novel triplet regimen of obinutuzumab, ibrutinib, and venetoclax. CR, complete remission; iCR, complete remission with incomplete marrow recovery; NR, not reported; PR, partial remission. Adapted from Rogers KA et al. ASH abstract 431. *Blood.* 2017;130(suppl 1).[1]

The responses were evaluated after cycle 8 (during treatment) in 24 patients. The remaining patient discontinued before cycle 8 and was considered to have treatment failure in the intent-to-treat analysis. The regimen was associated with an ORR of 96%, including 5 patients with a CR (20%), 8 patients with a CRi (32%), and 11 patients with a partial response (44%; Figure 8). The cases of CRi were attributed to cytopenias (4 patients; 50%) and cytopenias and hypocellular marrow (4 patients; 50%). Among the 11 patients with a partial response, 6 (55%) would have been considered a CR based on blood counts and bone marrow requirements, but they had lymph nodes larger than 1.5 cm. Moreover, only 1 of the evaluable patients had morphologic evidence of CLL in the bone marrow.

Among the 24 patients evaluable for MRD in both the blood and bone marrow, 14 (58%) attained MRD negativity in both compartments, including 8 of 13 patients (61%) with a CR/CRi and 6 of 11 patients (55%) with a partial response. Only 1 patient with detectable CLL had malignant cells comprising at least 1% in either compartment.

The investigators concluded that the combination of obinutuzumab, ibrutinib, and venetoclax appeared to be a safe combination for use as

a first-line regimen for CLL, with hematologic AEs accounting for most toxicities, and high-grade AEs occurring rarely. The regimen appeared to be active, with a high ORR and a high rate of MRD negativity. Results for the primary endpoint of MRD-negative CR rates are expected in mid-2018.

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Venetoclax Plus Rituximab Is Superior to Bendamustine Plus Rituximab in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia—Results From Pre-Planned Interim Analysis of the Randomized Phase 3 MURANO Study

Venetoclax has been studied in many recent trials of novel therapeutic approaches for CLL. Initially, venetoclax was evaluated as monotherapy. In a phase 1 dose-escalation study that primarily enrolled patients with relapsed/refractory CLL and poor prognostic factors (including 17p deletion), venetoclax was associated with an ORR of 79%.[1] In a subsequent phase 1b study, the combination of venetoclax and rituximab among patients with relapsed/refractory CLL demonstrated an ORR of 86%, including a CR rate of 51% and an MRD negativity rate of 57% overall.[2] In the phase 1b study, 2 patients starting venetoclax at 50 mg developed clinical tumor lysis syndrome (which was fatal for one). No further cases of tumor lysis syndrome occurred after implementation of prophylactic strategies, which included a lower starting dose of 20 mg. Otherwise, the regimen had an acceptable safety profile.

These findings prompted the randomized, phase 3 MURANO trial (A Study of Venetoclax in Combination With Rituximab Compared With Bendamustine in Combination With Rituximab in Participants With Relapsed or Refractory Chronic Lymphocytic Leukemia), which compared venetoclax/rituximab against a standard regimen, bendamustine and rituximab, in patients with relapsed/refractory CLL. Initial findings were presented at the 2017 ASH late-breaking abstract session.[3] The MURANO trial enrolled adults with CLL who had received 1 to 3 prior lines of therapy, including at least 1 chemotherapy-containing regimen. Patients could have received bendamustine if the duration of response was at least 24 months. Patients were randomly assigned to venetoclax/rituximab (n=194) or bendamustine/rituximab (n=195). Venetoclax was introduced over a 6-week ramp-up period, and could reach a dose of

ABSTRACT SUMMARY Combined Venetoclax and Ibrutinib for Patients With Previously Untreated High-Risk CLL and Relapsed/Refractory CLL: A Phase II Trial

A phase 2 trial evaluated venetoclax plus ibrutinib for patients with relapsed/refractory CLL or with previously untreated CLL and high-risk prognostic factors (Abstract 429). Ibrutinib was administered daily until progression, and venetoclax was introduced starting at cycle 4 (with a dose ramp-up) and continued for 2 years. Results of the first evaluable 77 patients (37 with relapsed/refractory CLL and 40 with high-risk untreated CLL) were presented, with a median follow-up of 11.8 months. Seven patients discontinued treatment during ibrutinib monotherapy. The remaining 70 patients (34 with relapsed/refractory CLL and 36 in the frontline cohort) started venetoclax. The combination of venetoclax and ibrutinib was associated with a high ORR in the frontline cohort, with CR/CRi rates of 75% at 6 months (n=20), 80% at 9 months (n=10), and 100% at 12 months (n=3). Rates of bone marrow MRD negativity were 45%, 80%, and 100%, respectively. The regimen was also associated with high response rates in the relapsed/refractory cohort, with CR/CRi rates of 69%, 77%, and 80% at 6 months (n=16), 9 months (n=13), and 12 months (n=5), and bone marrow MRD negativity rates of 13%, 15%, and 40%, respectively. The regimen was well-tolerated. Grade 3/4 neutropenia occurred in 44% of patients, and 8% of patients developed neutropenic fever.

400 mg administered orally once daily for 2 years or until progressive disease or unacceptable toxicity. Rituximab was administered at 375 mg/m^2 on day 1 of cycle 1, then 500 mg/m^2 on day 1 of cycles 2 to 6. Patients in the bendamustine/rituximab arm received bendamustine at 70 mg/m^2 on days 1 and 2 of cycles 1 to 6, plus rituximab.

A total of 389 patients enrolled into the trial between March 2014 and September 2015. Patient demographics and disease characteristics were well-balanced between the arms. The median age was approximately 65 years, 73% of patients were male, 27% of patients had a 17p deletion, and 68% of patients had an unmutated *IGHV*. Approximately 60% of patients had received 1 prior therapy.

After a median follow-up of 23.8 months, the primary endpoint—investigator-assessed PFS—was significantly improved with venetoclax/rituximab vs bendamustine/rituximab. The median PFS was not reached with venetoclax/rituximab vs 17 months with bendamustine/rituximab (HR, 0.17; 95% CI, 0.13-0.28; *P*<.0001). Superiority of venetoclax/rituximab vs bendamustine/rituximab was confirmed in an independent review (HR, 0.19; *P*<.0001). Subgroup analyses showed a similar benefit with venetoclax/rituximab regardless of the number of prior therapies, *TP53* mutational status, baseline *IGHV* mutational status, and 17p deletion status. A lesser benefit and a wider confidence interval was seen in a single subgroup: the 59 patients with refractory CLL (HR, 0.32; 95% CI, 0.15-0.70).

Venetoclax/rituximab was associated with a significant improvement in response rates over bendamustine/rituximab, with investigator-assessed ORRs of 93.3% vs 67.7%, respectively (*P*<.0001; Figure 9). CR/CRi rates were 26.8% and 8.2% (*P*<.0001). The independently assessed CR/CRi rates were substantially lower than the investigator-assessed rates, at 8.2% and 1.6%, respectively. This discrepancy was attributed to residual CT scan nodes ranging from 16 mm to 30 mm in diameter, of which 88% were MRD-negative in the peripheral blood (defined as <10^{-4}). MRD negativity in the peripheral blood was observed starting at 4 months in 45% of patients receiving venetoclax/rituximab vs 6% of those receiving bendamustine/rituximab. Rates of MRD negativity in the venetoclax/rituximab arm increased to 62% at 9 months, and then were maintained over time, reaching 60% at 18 months. In the bendamustine/rituximab arm, MRD negativity peaked at 13% at 9 months and declined to 5% at 18 months.

Venetoclax/rituximab also provided a significant OS benefit over bendamustine/rituximab. OS rates were 95.9% vs 91.1%, respectively, at 1 year and 91.9% vs 86.6% at 2 years (HR, 0.48; 95% CI, 0.25-0.90; *P*=.0186).

Dr Seymour noted that the toxicities observed with venetoclax/rituximab were consistent with those expected in patients with relapsed/refractory CLL. The most common grade 3/4 AE associated with venetoclax/rituximab was neutropenia, reported in 58% of patients compared with 39% of patients receiving bendamustine/rituximab. The higher incidence of neutropenia among patients treated with venetoclax/rituximab should be considered in conjunction with the longer reporting period for this arm. Other grade 3/4 AEs reported in at least 5% of patients receiving venetoclax/rituximab were anemia (11% vs 14% with bendamustine/rituximab), thrombocytopenia (6% vs 10%), and pneumonia (5% vs 8%). AEs led to discontinuation in 12% of patients in the venetoclax/rituximab arm compared with 6% in the bendamustine/rituximab arm.

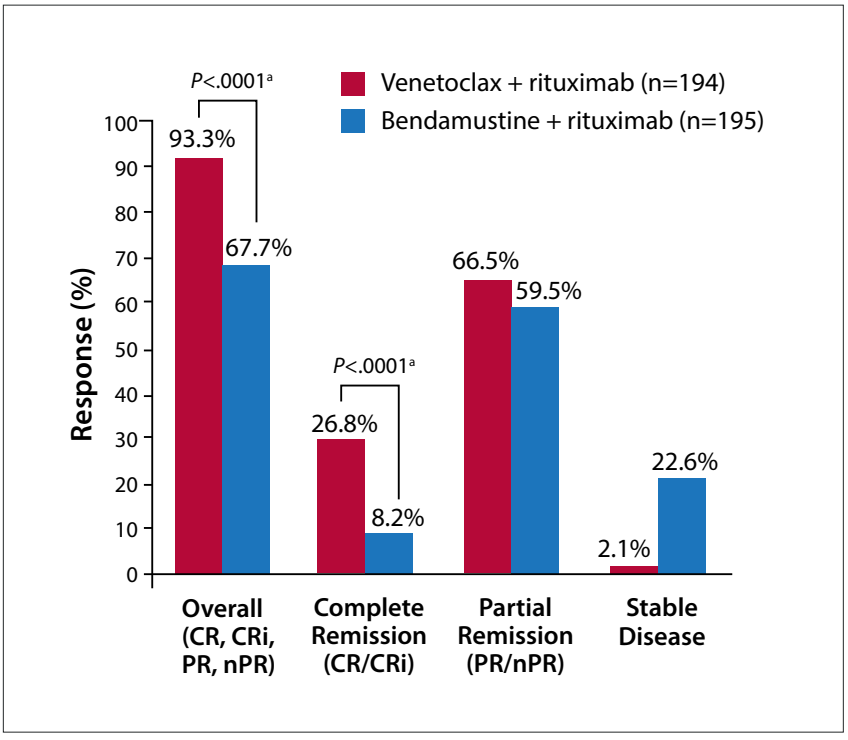

Figure 9. Response rates among patients treated with venetoclax and rituximab or bendamustine and rituximab. [a]Descriptive *P* value. CR, complete remission; iCR, complete remission with incomplete marrow recovery; nPR, nodular partial remission; PR, partial remission. Adapted from Seymour JF et al. ASH abstract LBA-2. *Blood*. 2017;130(suppl 1).[3]

The efficacy benefit observed with venetoclax/rituximab led the investigators to conclude that this treatment should be a standard option for patients with relapsed/refractory CLL.

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ABSTRACT SUMMARY Initial Results of Ibrutinib Plus Venetoclax in Relapsed, Refractory CLL (Bloodwise TAP CLARITY Study): High Rates of Overall Response, Complete Remission and MRD Eradication After 6 Months of Combination Therapy

The CLARITY study (Assessment of Venetoclax in Combination With Ibrutinib in Patients With Chronic Lymphocytic Leukaemia) evaluated ibrutinib plus venetoclax in 54 patients with relapsed/refractory CLL (Abstract 428). Patients received 8 weeks of ibrutinib monotherapy followed by venetoclax plus ibrutinib for up to 2 years. Patients with MRD negativity in the blood and bone marrow at 6 or 12 months discontinued treatment. Patients not attaining MRD negativity continued venetoclax for up to 2 years and ibrutinib monotherapy as clinically indicated. AEs were primarily mild. A single case of laboratory tumor lysis syndrome was observed. The most common AEs were gastrointestinal disorders, musculoskeletal and connective tissue–related events, and neutropenia. After 6 months of ibrutinib plus venetoclax, the ORR was 100%, and 47% of patients (18 of 38) attained a CR/CRi. After 6 months, 32% of patients attained MRD negativity in the bone marrow. Based on outcomes from the CLARITY study, the phase 3 FLAIR trial (Front-Line Assessment of Ibrutinib Plus Rituximab) from the UK National Cancer Research Institute now includes ibrutinib plus venetoclax as a frontline CLL regimen.

Acalabrutinib Monotherapy in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia: Updated Results From the Phase 1/2 ACE-CL-001 Study

Acalabrutinib, an investigational BTK inhibitor, has demonstrated substantial potency and greater selectivity than ibrutinib.[1] Acalabrutinib does not inhibit off-target kinases, including the epidermal growth factor receptor and the interleukin 2–inducible T-cell kinase. The selectivity and pharmacokinetics of acalabrutinib permit twice-daily dosing. Studies in healthy individuals suggest near-complete occupancy of BTK over a 24-hour period.[1]

The safety and activity of acalabrutinib are being evaluated in the phase 1/2 ACE-CL-001 study (ACP-196 [Acalabrutinib], a Novel Bruton Tyrosine Kinase [Btk] Inhibitor, for Treatment of Chronic Lymphocytic Leukemia) in a cohort of patients with relapsed or refractory CLL.[2] Between February 2014 and November 2015, the study enrolled 134 patients who had received at least 1 prior treatment. Patients had an ECOG performance status of 0 to 1 and an absolute neutrophil count of at least 0.75×10^9/L or a platelet count of at least 50×10^9/L (unless bone marrow involvement was present). Exclusion factors included treatment with vitamin K antagonists or proton pump inhibitors and relapsed/refractory disease after treatment with a prior BTK inhibitor.

A dose-escalation phase evaluated acalabrutinib at 100 mg to 400 mg once daily or 100 mg to 200 mg twice daily. An expansion phase then evaluated acalabrutinib at 100 mg twice daily or 200 mg once daily, continuing treatment until patients developed disease progression or unacceptable toxicity. Subsequently, all patients were switched to the 100-mg twice daily dosing.

Outcomes with the first 61 enrolled patients have previously been published.[3] No dose-limiting toxicities were reported in the dose-escalation phase. After a median follow-up of 14.3 months, acalabrutinib was associated with an ORR of 95% in the overall population and 100% in the subset of patients with a 17p deletion. At the 2017 ASH meeting, Dr John Byrd reported updated findings from ACE-CL-001 that included all 134 enrolled patients. The median age was 66 years, 74% were male, and 39% had bulky disease (≥5 cm). Patients

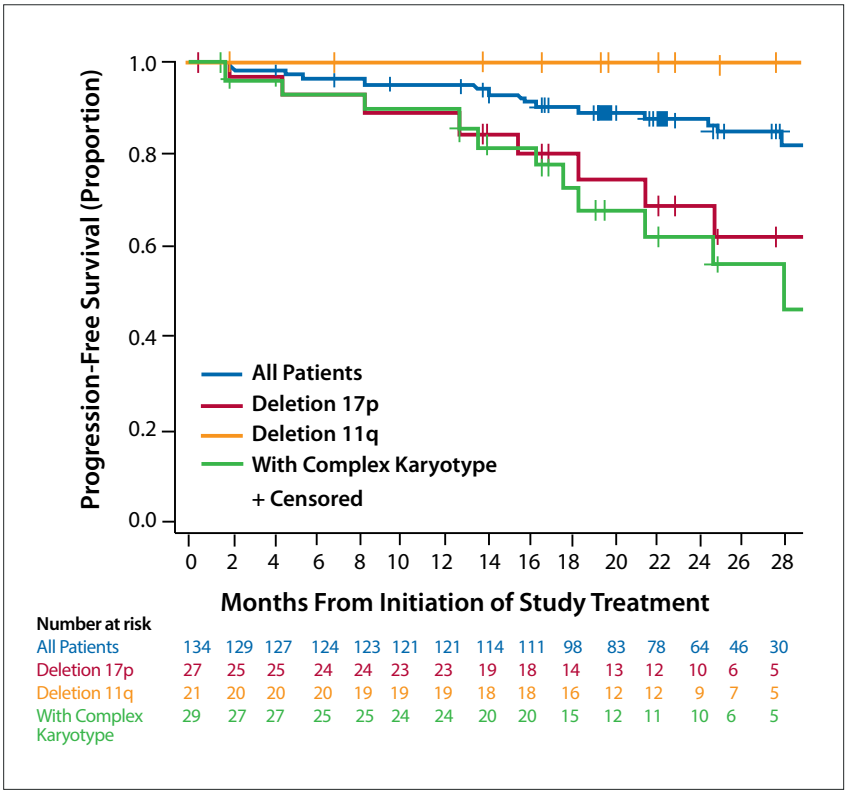

Figure 10. Progres -free survival among patients treated with acalabrutinib. Adapted from Byrd JC et al. ASH abstract 498. *Blood.* 2017;130(suppl 1).[2]

had received a median of 2 prior therapies, 23% had a 17p deletion, 18% had an 11q deletion, 73% had unmutated *IGHV*, and 41% had a complex karyotype.

After a median follow-up of 24.5 months, 78% of patients were still receiving treatment. The most common reasons for treatment discontinuation were AEs (9%; most commonly pneumonia [in 3 patients]) and progressive disease (7%). Acalabrutinib was associated with an ORR of 87%. ORR increased to 93% when including patients with a partial response with lymphocytosis. Among the high-risk subgroups, ORR was 89% in patients with a 17p deletion (n=27), 90% in those with an 11q deletion (n=27), 90% in those with unmutated *IGHV* (n=81), and 79% in those with a complex karyotype (n=29). Acalabrutinib was associated with resolution of cytopenias in most affected patients, including 86% of those with anemia, 97% of those with neutropenia, and 73% of those with thrombocytopenia. Lymphadenopathy improved in 99% of affected patients.

Among the responding patients, the median time to response was 5.3 months. The median PFS was not reached for the overall population or for high-risk subsets, aside from patients with a complex karyotype, in whom the median PFS was 27.9 months (Figure 10). At 18 months, PFS rates were 90% overall, 80% in patients with a 17p deletion, 100% in those with an 11q deletion, and 95% in those with no complex karyotype.

The most common AEs of any grade included diarrhea (48%), headache (47%), upper respiratory tract infection (31%), fatigue (28%), nausea (26%), arthralgia (25%), cough (24%), pyrexia (23%), contusion (23%), weight increase (21%), petechiae (21%), and constipation (20%). The most common grade 3 or higher AEs were neutropenia (12%) and pneumonia (11%). Hypertension occurred in 13% of patients (4% grade ≥3). Atrial fibrillation/flutter occurred in 3% of patients at any grade (1% grade ≥3). Seven patients developed fatal AEs, including 4 patients with pneumonia and 1 patient each with *Candida* sepsis, congestive cardiac failure, and plasmablastic lymphoma. Four patients (3%) developed Richter transformation. A pharmacodynamics analysis, performed in approximately half of patients on day 8 and in 20% of patients at the end of day 28 of cycle 6, showed a median BTK occupancy of 99% at 4 hours after administration of acalabrutinib and 97% to 98% before the next dose.

Three ongoing phase 3 trials are evaluating acalabrutinib for the treatment of CLL. The Elevate CLL TN trial (ACE-CL-007)[4] is comparing acalabrutinib plus obinutuzumab, single-agent acalabrutinib, and obinutuzumab plus chlorambucil in patients with treatment-naive CLL. The Elevate CLL relapsed/refractory trial (ACE-CL-006)[5] is comparing acalabrutinib vs ibrutinib in patients with high-risk relapsed/refractory CLL, and the ACE-CL-309 trial[6] is comparing acalabrutinib vs investigator's choice of idelalisib plus rituximab or bendamustine plus rituximab in patients with relapsed/refractory CLL.

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Highlights in Chronic Lymphocytic Leukemia From the 2017 American Society of Hematology Annual Meeting: Commentary

Susan M. O'Brien, MD

Associate Director for Clinical Sciences, Chao Family Comprehensive Cancer Center
Medical Director, Sue and Ralph Stern Center for Clinical Trials & Research
Professor of Medicine, Division of Hematology/Oncology, Department of Medicine
University of California, Irvine
Orange, California

Many presentations at the 2017 American Society of Hematology (ASH) annual meeting provided important new data in the management of patients with chronic lymphocytic leukemia (CLL). Several studies focused on the use of ibrutinib, alone and in combination. Data were also presented for newer treatments, such as duvelisib, venetoclax, and acalabrutinib.

Ibrutinib vs Chemoimmunotherapy

Dr Tadeusz Robak provided data from a cross-trial comparison of single-agent ibrutinib vs chemoimmunotherapy.[1] Importantly, this analysis showed that ibrutinib was associated with longer progression-free survival (PFS) and a more favorable safety profile than chemoimmunotherapy. Many physicians still use chemotherapy for the frontline treatment of older patients who are somewhat unfit, but could possibly tolerate treatments such as bendamustine/rituximab. The use of chemotherapy in this setting is not unreasonable, and it is based on the rationale that although ibrutinib was superior to chlorambucil in the RESONATE-2 trial (which led to the frontline approval of ibrutinib),[2] there are currently no data to show that ibrutinib is better than bendamustine/rituximab in the frontline setting. Two large US Intergroup trials are comparing ibrutinib vs more effective chemotherapy in the frontline setting. One randomized trial is comparing fludarabine, cyclophosphamide, and rituximab (FCR) vs ibrutinib/rituximab.[3] A 3-arm trial is evaluating bendamustine/rituximab vs ibrutinib monotherapy vs ibrutinib/rituximab.[4] These trials accrued approximately a year ago, but data are not yet available.

In the interim, the study by Dr Robak overlaid data from several trials: CLL8, which evaluated FCR (vs FC)[5]; CLL10, which evaluated bendamustine plus rituximab (vs FCR)[6]; CLL11, which evaluated obinutuzumab plus chlorambucil and rituximab plus chlorambucil (vs single agent chlorambucil)[7]; and COMPLEMENT-1, which evaluated ofatumumab plus chlorambucil (vs chlorambucil).[8] The analysis showed that ibrutinib appeared to have the best PFS.[1] These data are the reason I use ibrutinib for most patients in the frontline setting. An exception is patients with a mutated *IGHV* gene. Recent studies evaluating the long-term outcome of FCR by *IGHV* mutation status consistently showed a plateau on the PFS curve for patients with a mutated *IGHV*,[9-11] and I believe there is a cure fraction. For patients without the *IGHV* mutation, indirect evidence suggests that ibrutinib is better than chemotherapy (although data from randomized trials are lacking). In the studies included in this analysis, patients in the FCR and bendamustine/rituximab arms were younger than patients in the ibrutinib arm, who were older than 65 years. Ibrutinib still appeared favorable, even though older patients are more likely to experience toxicity and interrupt therapy, and thus have a shorter PFS (with chemotherapy). We await confirmation of these data from the randomized trials.

Duvelisib

The randomized phase 3 DUO trial evaluated duvelisib, a phosphoinositide 3 (PI3)-kinase-delta/gamma inhibitor.[12] Idelalisib is a PI3K-delta inhibitor; duvelisib also targets gamma, which may be particularly important in T-cell lymphoma. The DUO trial was designed to provide data for the potential registration of duvelisib and approval by the US Food and Drug Administration (FDA). The design was based on the original RESONATE trial, which compared ibrutinib vs ofatumumab in patients with relapsed disease.[13] Ofatumumab was given at the standard schedule. The overall response rate was significantly higher with duvelisib, at 74%, vs 45% in the ofatumumab arm. The median PFS was also significantly longer, at 17.6 months

based on investigator assessment and 13.3 months according to the independent response committee, compared with approximately 9.9 months for ofatumumab. The data from this study may lead to FDA approval, making a second PI3- kinase agent available for the treatment of CLL.

Ibrutinib in Combination Regimens

A study from MD Anderson presented by Dr Nitin Jain was based on the excellent long-term outcomes seen with FCR among patients with CLL who have the mutated *IGHV* gene.[14] I was a coauthor of this study, which aimed to determine whether it would be possible to limit the cycles of chemotherapy and improve outcomes with the addition of ibrutinib. The standard 6-cycle FCR regimen is associated with short-term toxicity, cumulative myelosuppression, and rare cases of myelodysplastic syndromes and acute myeloid leukemia that occur in the long-term. This study added ibrutinib, changed the antibody from rituximab to obinutuzumab (based on emerging data suggesting that this antibody may be more powerful[7]) and stopped the chemotherapy after 3 cycles. At this point, patients with a complete remission (CR) or complete remission with insufficient count recovery (CRi) who were negative for minimal residual disease (MRD) continued treatment with ibrutinib plus obinutuzumab for 3 cycles, and then received ibrutinib alone for 6 cycles. Patients with a partial response or who were MRD-positive were treated with ibrutinib plus obinutuzumab for 9 cycles. At 12 months, patients who were MRD-positive continued treatment with ibrutinib until progressive disease. Patients who were MRD-negative discontinued all treatment. Although ibrutinib is usually administered until the patient develops progressive disease, in this study, it was not. The primary endpoint was to compare the MRD negativity rate at 3 months with the rate based on historical data for FCR, which is 26%.[15] The study reported an MRD negativity rate of 87%, which is dramatically higher than the historical control rate. All of the patients who reached the 12-month endpoint were MRD-negative and therefore discontinued treatment.

This study explored an attempt to keep using chemotherapy in the mutated setting. Although ibrutinib may be very effective in these patients, there are no long-term data to know if the same type of plateau on the PFS curve will be seen. There is a possibility that ibrutinib is a curative frontline treatment for patients with mutated *IGHV*, but the follow-up data are currently too limited to know. This study maintained the use of chemotherapy in a subgroup it may cure, but attempted to (A) shorten the duration of chemotherapy to decrease the toxicity, (B) achieve higher MRD negativity rates by adding ibrutinib and changing the monoclonal antibody to obinutuzumab, and (C) increase the 60% plateau seen with standard FCR in that population.

A study from Ohio State evaluated the combination of ibrutinib, venetoclax, and obinutuzumab.[16] There is excitement about combining ibrutinib and venetoclax, with or without an antibody, and several presentations at the 2017 ASH meeting explored these regimens. Previously, the only data available for this approach were from an early analysis of this study presented at the 2016 ASH meeting by Dr Jeffrey Jones.[17] The early analysis showed data for 10 relapsed patients. After treatment with ibrutinib, venetoclax, and obinutuzumab, 7 patients were MRD-negative in the blood and 4 patients were MRD-negative in the bone marrow, which was promising. The presentation at the 2017 ASH meeting, by Dr Kerry Rogers, provided data for the frontline cohort of patients in the trial.[16] This small cohort consisted of 25 treatment-naive patients. The overall response rate was 96%. Interestingly, at the midpoint, the rate of MRD negativity in the blood and marrow was 58%. It was surprising to see that the MRD negativity rate was not higher, given that these patients were treatment-naive. That may be attributable to the small number of patients or the early time of the assessment. More follow-up will be needed to see if the MRD negativity rate increases.

Another important finding from this study, as first presented at the 2016 ASH meeting,[17] was that ibrutinib, venetoclax, and obinutuzumab could be given together at full doses. This study had a phase 1 component in which ibrutinib and obinutuzumab were given at the standard doses, but venetoclax was targeted to a final dose of 100 mg/day, 200 mg/day, or 400 mg/day.[17] The phase 1 analysis showed that it was possible to use venetoclax at the full dose. The toxicities reported are what would be expected from each of the drugs used alone. The most common side effect with ibrutinib is diarrhea, and in this study, diarrhea occurred in approximately half of patients, but it was usually mild. Rates of neutropenia were somewhat higher than those reported for the single agents, which is not surprising since neutropenia is seen with both venetoclax and obinutuzumab. In the frontline setting, there were no cases of neutropenic fever, most likely because the neutropenia was often transient.

A study from MD Anderson evaluated venetoclax and ibrutinib in patients with CLL who were previously untreated or who had relapsed/refractory disease.[18] There is much excitement about the use of these 2 small molecules, and this trial evaluated them without an antibody. Standard doses were used: 420 mg/day for ibrutinib and a target dose of 400 mg/day for venetoclax. There were 37 patients in the relapsed/refractory cohort and 40 patients in the frontline cohort. The trial design included a run-in period with ibrutinib. Nearly all of the combination trials evaluating ibrutinib and venetoclax with or without an antibody initiate treatment with single-agent ibrutinib or an antibody

for 1 to 3 months before venetoclax is started. A lead-in period can debulk the patient to some extent, and reduce the risk for tumor lysis associated with venetoclax.

The study evaluated patients at different time points. Among patients in the frontline cohort, 20 were evaluable for response after 6 months of treatment; only 3 were evaluable after 12 months. The overall response rate was 100% at 6 months and 12 months. The CR rate increased with time, from 75% at 6 months to 100% at 12 months (again, only 3 patients were evaluable at 12 months). Bone marrow MRD negativity was reported in 45% of patients at 6 months and in 100% of patients at 12 months. In the relapsed/refractory setting, 16 patients were evaluable for response at 6 months, and 5 were available at 12 months. The overall response was 100% at both 6 and 12 months. The bone marrow MRD negativity was 13% at 6 months, and increased to 40% at 12 months.

These data were impressive, and they raise the question of whether an antibody is needed when 2 small molecules are used. Treatment outcome with venetoclax appears significantly improved when an antibody is added, but the same improvement is not seen when an antibody is added to ibrutinib. Some combination trials are evaluating all 3 drugs, whereas others are omitting the antibody.[19,20] It is too early to tell whether an antibody will improve outcome when added to 2 small molecules. More mature data are needed, and comparisons across trials will need to be done carefully.

Venetoclax Plus Rituximab

Data from a late-breaking abstract presented by Dr John Seymour may potentially lead to a new indication for venetoclax, a BCL2 selective inhibitor.[21] This trial compared venetoclax/rituximab vs bendamustine/rituximab in relapsed CLL. When this trial was designed several years ago, bendamustine/rituximab was a common regimen in the relapsed setting. Currently, ibrutinib is the more common treatment. Nevertheless, bendamustine/rituximab is a reasonable control arm. In this large study of nearly 400 patients, the median PFS was not reached for venetoclax/rituximab vs 17 months for bendamustine/rituximab. The hazard ratio was 0.17, one of the lowest I have seen in a randomized trial. The indication for venetoclax is more narrow in the United States than in Europe and Canada. Single-agent venetoclax is approved by the FDA for patients with the 17p deletion who have relapsed disease. The study by Dr Seymour was not restricted to patients with the 17p deletion. The results will likely expand the indication of venetoclax to include use in combination with rituximab among all patients in the relapsed setting.

Emerging data suggest that the use of an antibody and venetoclax may be synergistic,[22] which is in significant contrast to the use of an antibody with B-cell receptor inhibitors. The data for the combinations of ibrutinib plus rituximab or idelalisib plus rituximab were similar to the data for the single agents alone. An important difference is that the addition of an antibody to a B-cell receptor inhibitor provides a much more rapid response because it abrogates the lymphocytosis typically seen with B-cell receptor inhibitors. A randomized trial presented at the 2017 ASH meeting by Dr Jan Burger was the first to compare ibrutinib alone with ibrutinib plus rituximab.[23] This trial enrolled patients with relapsed disease as well as treatment-naive patients with the 17p deletion, a high-risk cohort not suited for chemotherapy. The study randomly assigned patients to standard-dose ibrutinib vs ibrutinib and rituximab. The PFS curves were the same with both regimens. The follow-up was an average of 2 years, and most patients had not developed relapsed disease. It is possible that the rates of PFS will differ over time. These data suggested that the addition of an antibody to a B-cell receptor inhibitor provides a more rapid response, but not much else. These results are in marked contrast to what is seen with venetoclax and an antibody. There are some data with venetoclax and obinutuzumab showing very high rates of MRD negativity in the frontline setting.[24] More data combining rituximab with ibrutinib will be provided by a US Intergroup trial that is evaluating 3 arms: bendamustine/rituximab vs ibrutinib/rituximab vs ibrutinib alone.[4] This randomized trial enrolled patients for frontline treatment, as opposed to the current study in the relapsed setting.

Acalabrutinib

Dr John Byrd presented updated results with acalabrutinib in CLL.[25] Acalabrutinib is a new Bruton tyrosine kinase (BTK) inhibitor that was recently approved by the FDA for the treatment of mantle cell lymphoma. It is not yet approved for CLL. There are 2 randomized registration trials: one in the relapsed, high-risk setting and one in the frontline setting, but data are not yet available.[26,27] The original data for the phase 1 trial in relapsed CLL were published in 2016.[28] The study enrolled 134 patients, a large number. The median number of prior regimens was 2. The median follow-up was approximately 25 months. The overall response rate, including partial responses with lymphocytosis, was 93%, consisting mostly of partial remissions. The median PFS was not reached, and the 18-month PFS rate was 90%.

The first question is how acalabrutinib compares with ibrutinib. Data for the head-to-head trial are not yet available.[29] Comparing across trials, the data for acalabrutinib appear at least as good. A potential advantage to acalabrutinib is that it may not be associated with the side effects seen with ibrutinib, which are thought to be related to inhibition of kinases other than BTK. Atrial fibrillation and platelet dysfunction might be related to inhibition of the Tec kinase, and

diarrhea might be related to inhibition of the epidermal growth factor receptor. Preclinical assessment of the half maximal inhibitory concentration (IC_{50}) for acalabrutinib against these other kinases shows much higher rates—from tenfold to a thousandfold—than that seen with ibrutinib. The original data showed that diarrhea was not very common with acalabrutinib. Headache is the most common side effect, but it tends to be short-lived, and patients develop tachyphylaxis. With ibrutinib, the most concerning adverse events are atrial fibrillation, major bleeding, and hypertension, which can require patients to discontinue treatment when uncontrollable. In the study by Dr Byrd, hypertension occurred in 13% of patients, which is lower than that seen with ibrutinib.[25] Atrial fibrillation occurred in 3%, vs 10% to 12% for ibrutinib. There was no major bleeding. When comparing adverse events, an important caveat is that the median follow-up with acalabrutinib is 25 months, compared with 5 years for ibrutinib. The data for acalabrutinib are exciting because the efficacy appears at least as good as ibrutinib, and there is a suggestion that the toxicity profile may be better. Results from the randomized trials will help to clarify these data.[26,27,29]

Disclosure

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Monitor and 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 with B-cell malignancies treated with single agent IMBRUVICA®.

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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.

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. Advise women to avoid becoming pregnant while taking IMBRUVICA® and for 1 month after

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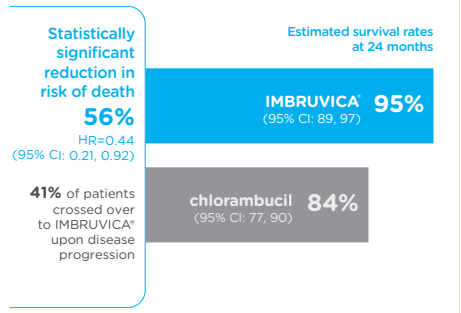
RESONATE™-2 FRONTLINE DATA

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 excluded[3]

EXTENDED OVERALL SURVIVAL[2]

SECONDARY ENDPOINT: OS
IMBRUVICA® vs CHLORAMBUCIL

Reduced risk of death by more than half

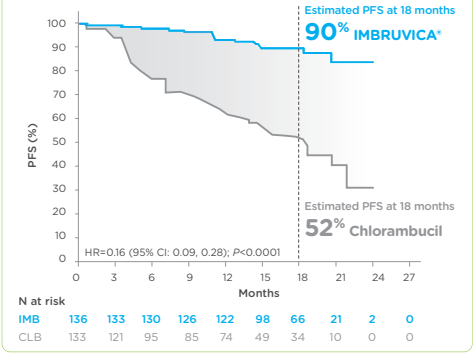


- Median follow-up was 28 months[2]
- Fewer deaths with IMBRUVICA® were observed; 11 (8.1%) in the IMBRUVICA® arm vs 21 (15.8%) in the chlorambucil arm[2]

PROLONGED PROGRESSION-FREE SURVIVAL[2,3]

PRIMARY ENDPOINT: PFS
IMBRUVICA® vs CHLORAMBUCIL

84% statistically significant reduction in risk of progression or death[2,3]



- Median follow-up was 18 months[3]
- With IMBRUVICA®, median PFS was not reached vs 18.9 months (95% CI: 14.1, 22.0) with chlorambucil[2]
- PFS and ORR (CR and PR) were assessed by an IRC according to the revised 2008 iwCLL criteria[3]

RESONATE™-2 Adverse Reactions ≥15%

- Diarrhea (42%)
- Musculoskeletal pain (36%)
- Cough (22%)
- Rash (21%)
- Bruising (19%)
- Peripheral edema (19%)
- Pyrexia (17%)
- Dry eye (17%)
- Arthralgia (16%)
- Skin infection (15%)

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

B-cell malignancies: The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (62%), neutropenia (61%), diarrhea (43%), anemia (41%), musculoskeletal pain (30%), rash (30%), bruising (30%), nausea (29%), fatigue (29%), hemorrhage (22%), and pyrexia (21%).

The most common Grade 3 or 4 adverse reactions (≥5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (39%), thrombocytopenia (16%), and pneumonia (10%).

Approximately 6% (CLL/SLL), 14% (MCL), 11% (WM) and 10% (MZL) of patients had a dose reduction due to adverse reactions. Approximately 4%-10% (CLL/SLL), 9% (MCL), and 9 % (WM [6%] and MZL [13%]) of patients discontinued due to adverse reactions.

cGVHD: The most common adverse reactions (≥20%) in patients with cGVHD were fatigue (57%), bruising (40%), diarrhea (36%), thrombocytopenia (33%), muscle spasms (29%), stomatitis (29%), nausea (26%), hemorrhage (26%), anemia (24%), and pneumonia (21%).

The most common Grade 3 or 4 adverse reactions (≥5%) reported in patients with cGVHD were fatigue (12%), diarrhea (10%), neutropenia (10%), pneumonia (10%), sepsis (10%), hypokalemia (7%), headache (5%), musculoskeletal pain (5%), and pyrexia (5%).

Twenty-four percent of patients receiving IMBRUVICA® in the cGVHD trial discontinued treatment due to adverse reactions. Adverse reactions leading to dose reduction occurred in 26% of patients.

DRUG INTERACTIONS

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

CYP3A Inhibitors: Dose adjustment may be recommended.

SPECIFIC POPULATIONS

Hepatic Impairment (based on Child-Pugh criteria)**:** Avoid use of IMBRUVICA® 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 adult 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 adult 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 adult 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 adult 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 adult 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.

Chronic Graft versus Host Disease: IMBRUVICA is indicated for the treatment of adult patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy *[see Clinical Studies (14.5) in Full Prescribing Information].*

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 (including bacterial, viral, or fungal) 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. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor and 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 with B-cell malignancies 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 (Study 1104) 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

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Metabolism and nutrition disorders	Decreased appetite	21	2
	Dehydration	12	4
Nervous system disorders	Dizziness	14	0
	Headache	13	0

Table 2: Treatment-Emergent* Hematologic Laboratory Abnormalities 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 (Study 1102) and three randomized controlled clinical trials (RESONATE, RESONATE-2, and HELIOS) in patients with CLL/SLL (n=1278 total and n=668 patients exposed to IMBRUVICA). Study 1102 included 51 patients with previously treated CLL/SLL, RESONATE included 391 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab, RESONATE-2 included 269 randomized patients 65 years or older with treatment naïve-CLL or SLL who received single agent IMBRUVICA or chlorambucil, and HELIOS 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 1102, RESONATE, RESONATE-2, and HELIOS 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 1102, RESONATE, RESONATE-2, and HELIOS 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 1102: 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 1102

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

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1102 (continued)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
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
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* Hematologic Laboratory Abnormalities in Patients with CLL/SLL (N=51) in Study 1102

	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.

RESONATE: 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 RESONATE 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 RESONATE

Body System Adverse Reaction	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	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

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 RESONATE (continued)

Body System Adverse Reaction	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
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 Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE

	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

RESONATE-2: 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 RESONATE-2.

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 RESONATE-2

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

IMBRUVICA® (ibrutinib) capsules

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 RESONATE-2 (continued)

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
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

HELIOS: 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 HELIOS 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 HELIOS

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

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 (continued)

Body System Adverse Reaction	Ibrutinib + BR (N=287)		Placebo + BR (N=287)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
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 1118) and 63 patients with previously treated MZL (Study 1121).

The most commonly occurring adverse reactions in Studies 1118 and 1121 (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, fatigue, bruising, hemorrhage, anemia, rash, musculoskeletal pain, and nausea.

Nine percent of patients receiving IMBRUVICA across Studies 1118 and 1121 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 1118: 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 1118.

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 1118 (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

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 1118 (N=63) (continued)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
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 Hematologic Laboratory Abnormalities in Patients with WM in Study 1118 (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

Study 1121: 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 1121.

Table 11: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with MZL in Study 1121 (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
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 Hematologic Laboratory Abnormalities in Patients with MZL in Study 1121 (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

Chronic Graft versus Host Disease: The data described below reflect exposure to IMBRUVICA in an open-label clinical trial (Study 1129) that included 42 patients with cGVHD after failure of first line corticosteroid therapy and required additional therapy.

The most commonly occurring adverse reactions in the cGVHD trial (≥ 20%) were fatigue, bruising, diarrhea, thrombocytopenia, stomatitis, muscle spasms, nausea, hemorrhage, anemia, and pneumonia. Atrial fibrillation occurred in one patient (2%) which was Grade 3.

Twenty-four percent of patients receiving IMBRUVICA in the cGVHD trial discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were fatigue and pneumonia. Adverse reactions leading to dose reduction occurred in 26% of patients.

Adverse reactions and laboratory abnormalities described below in Tables 13 and 14 reflect exposure to IMBRUVICA with a median duration of 4.4 months in the cGVHD trial.

Table 13: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with cGVHD (N=42)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
General disorders and administration site conditions	Fatigue	57	12
	Pyrexia	17	5
	Edema peripheral	12	0
Skin and subcutaneous tissue disorders	Bruising*	40	0
	Rash*	12	0
Gastrointestinal disorders	Diarrhea	36	10
	Stomatitis*	29	2
	Nausea	26	0
	Constipation	12	0
Musculoskeletal and connective tissue disorders	Muscle spasms	29	2
	Musculoskeletal pain*	14	5
Vascular disorders	Hemorrhage*	26	0
Infections and infestations	Pneumonia*	21	10
	Upper respiratory tract infection	19	0
	Sepsis*	10	10
Nervous system disorders	Headache	17	5
Injury, poisoning and procedural complications	Fall	17	0
Respiratory, thoracic and mediastinal disorders	Cough	14	0
	Dyspnea	12	2
Metabolism and nutrition disorders	Hypokalemia	12	7

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

Table 14: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with cGVHD (N=42)

	Percent of Patients (N=42)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	33	0
Neutrophils Decreased	10	10
Hemoglobin Decreased	24	2

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
- Infections: hepatitis B reactivation

DRUG INTERACTIONS

Effect of CYP3A Inhibitors on Ibrutinib: The coadministration of IMBRUVICA with a strong or moderate CYP3A inhibitor may increase ibrutinib plasma concentrations *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. Increased ibrutinib concentrations may increase the risk of drug-related toxicity.

Examples[a] of strong CYP3A inhibitors include: boceprevir, clarithromycin, cobicistat conivaptan, danoprevir and ritonavir, diltiazem, elvitegravir and ritonavir, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), ritonavir, saquinavir and ritonavir, tipranavir and ritonavir, and troleandomycin.

Examples[a] of moderate CYP3A inhibitors include: aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, and verapamil.

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain strong or moderate inhibitors of CYP3A.

Patients with B-cell Malignancies: *Posaconazole:* Reduce IMBRUVICA dose to 140 mg once daily during coadministration with posaconazole at doses of no more than 200 mg BID *[see Dosage and Administration (2.4) in Full Prescribing Information]*. Avoid the coadministration of IMBRUVICA with posaconazole at doses of greater than 200 mg BID.

Voriconazole: Reduce IMBRUVICA dose to 140 mg once daily during coadministration with any dose of voriconazole *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Other Strong Inhibitors: Avoid concomitant administration of IMBRUVICA with other strong CYP3A inhibitors. Alternatively, interrupt IMBRUVICA therapy during the duration of strong CYP3A inhibitors if the inhibitor will be used short-term (such as anti-infectives for seven days or less) *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Moderate Inhibitors: Reduce IMBRUVICA dose to 140 mg once daily during coadministration with any moderate CYP3A inhibitor *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Monitor patients taking concomitant strong or moderate CYP3A inhibitors more frequently for adverse reactions of IMBRUVICA.

Patients with Chronic Graft versus Host Disease: *Moderate CYP3A Inhibitor:* Modify the dose based on adverse reactions *[see Dosage and Administration (2.3) in Full Prescribing Information]* for patients coadministered IMBRUVICA with any moderate CYP3A inhibitor.

Strong CYP3A Inhibitors: Reduce IMBRUVICA dose to 280 mg once daily for patients coadministered IMBRUVICA with

- posaconazole immediate-release tablet 200 mg BID or
- posaconazole delayed-release tablet 300 mg QD or
- voriconazole any dose

Modify the dose based on adverse reactions *[see Dosage and Administration (2.3) in Full Prescribing Information]*

Avoid concomitant administration of IMBRUVICA with posaconazole at higher doses and other strong CYP3A inhibitors. If these CYP3A inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt IMBRUVICA therapy during the duration of the inhibitor *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Effect of CYP3A Inducers on Ibrutinib: The coadministration of IMBRUVICA with strong CYP3A inducers may decrease ibrutinib concentrations. Avoid coadministration with strong CYP3A inducers *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. Examples[a] of strong CYP3A inducers include: carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, and St. John's wort[b].

[a] These examples are a guide and not considered a comprehensive list of all possible drugs that may fit this category. The healthcare provider should consult appropriate references for comprehensive information.

[b] The induction potency of St. John's wort may vary widely based on preparation.

USE IN SPECIFIC POPULATIONS

Pregnancy: *Risk Summary:* IMBRUVICA, a kinase inhibitor, can cause fetal harm based on findings from animal studies. There are no available data on IMBRUVICA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. 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 structural abnormalities *(see Animal 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.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. 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 or MZL 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: Avoid use of IMBRUVICA in patients with moderate or severe hepatic impairment (Child-Pugh class B and C). The safety of IMBRUVICA has not been evaluated in patients with mild to severe hepatic impairment by Child-Pugh criteria.

IMBRUVICA® (ibrutinib) capsules

Monitor patients for adverse reactions of IMBRUVICA and follow dose modification guidance as needed. *[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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