Clinical Advances in
HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

July 2018 Volume 16, Issue 7, Supplement 12

A SPECIAL MEETING REVIEW EDITION

Highlights in Chronic Lymphocytic Leukemia From the 2018 American Society of Clinical Oncology Annual Meeting

A Review of Selected Presentations From the 2018 American Society of Clinical Oncology Annual Meeting • June 1-5, 2018 • Chicago, Illinois

Special Reporting on:

- Phase 2 CAPTIVATE Results of Ibrutinib Plus Venetoclax in First-Line Chronic Lymphocytic Leukemia
- Durability of Response to Venetoclax in Patients With CLL Relapsed/Refractory to Ibrutinib and/or Idelalisib
- High, Durable Minimal Residual Disease Negativity With Venetoclax + Rituximab in Relapsed/Refractory CLL: MRD Kinetics From the Phase 3 MURANO Study
- Depth of Response and Progression-Free Survival in CLL Patients on Ibrutinib
- A Phase 2 Study to Assess the Safety and Efficacy of Umbralisib (TGR-1202) in Patients With CLL Who Are Intolerant to Prior BTK or PI3Kδ Inhibitor Therapy
- Change in Tumor Lysis Syndrome Risk After Lead-In Treatment in a Phase 1b/2 Study of Obinutuzumab, Ibrutinib, and Venetoclax for Chronic Lymphocytic Leukemia
- Prognostic Role of Beta-2 Microglobulin in Relapsed/Refractory Chronic Lymphocytic Leukemia Patients Treated With Ibrutinib
- The Efficacy of Duvelisib Monotherapy Following Disease Progression on Ofatumumab Monotherapy in Patients With Relapsed/Refractory CLL or SLL in the DUO Crossover Extension Study

PLUS Meeting Abstract Summaries

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Phase 2 CAPTIVATE Results of Ibrutinib Plus Venetoclax in First-Line Chronic Lymphocytic Leukemia

Ibrutinib is an oral inhibitor of Bruton's tyrosine kinase approved for the first-line treatment of relapsed or refractory chronic lymphocytic leukemia (CLL), including patients with the 17p deletion (del[17p]). In the CLL setting, single-agent ibrutinib has been shown to elicit high response rates and durable responses. However, the majority of patients achieve only partial responses, with evidence of residual disease in the blood or bone marrow.[1-3] Venetoclax is an oral BCL-2 inhibitor that has shown strong activity in CLL.[4] It is approved as therapy for previously treated patients with CLL who have del(17p). The combination of ibrutinib plus venetoclax is of interest for several reasons. Preclinical and ongoing clinical studies have shown synergistic and complementary activities.[5-7] The all-oral combination could provide deeper remissions and might allow ibrutinib treatment holidays.[8,9] In addition, the risk of tumor lysis syndrome could potentially be reduced by incorporating an ibrutinib lead-in treatment for initial debulking.[10]

The randomized phase 2 CAPTIVATE study (PCYC-1142; Ibrutinib Plus Venetoclax in Subjects With Treatment-Naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma) investigated 12 cycles of ibrutinib plus venetoclax in treatment-naive patients with CLL or small lymphocytic leukemia (SLL).[11] Eligible patients had active disease requiring treatment (based on criteria from the International Workshop on Chronic Lymphocytic Leukemia [iwCLL]), were younger than 70 years, and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.[12] All patients received three 28-day cycles of ibrutinib (420 mg, once daily) as lead-in treatment, followed by 12 cycles of ibrutinib plus venetoclax. The latter therapy was escalated to 400 mg once daily. Patients were then randomly assigned to receive ibrutinib plus either venetoclax or placebo. Measures were taken to reduce the risk of tumor lysis syndrome based on the venetoclax prescribing information. Minimal residual disease (MRD) was assessed in peripheral blood after 6 cycles of combination treatment. MRD and bone marrow responses were assessed after 12 cycles of combination treatment. Confirmed, undetectable MRD was defined as 2 consecutive blood analyses separated by 3 treatment cycles. Confirmation of undetectable bone marrow MRD was also required. The study included an MRD cohort and a fixed duration cohort. Results from the fixed duration cohort will be presented at a later date.

The primary objectives for the MRD cohort were to assess drug exposure and safety. A preplanned interim analysis of 164 patients in the MRD cohort included blood MRD for the first 30 patients who received 6 cycles of combination treatment, and bone marrow MRD for the first 14 patients who received 12 cycles of combination treatment. Patients underwent disease assessment at baseline and prior to initiation of venetoclax treatment. MRD assessments were made after treatment cycles 9, 12, and 15. Imaging was performed after cycles 9 and 15, and the full assessment of response, including bone marrow examination, was performed following cycle 15.

In the entire MRD cohort, the median age was 58 years (range, 28-69 years), and 32% of patients had Rai stage III/IV disease. Fifteen percent of patients had del(17p), 18% had

GUIDELINE UPDATE New Recommendations for *IGHV* Testing From the iwCLL

The iwCLL has updated its consensus guidelines addressing the diagnosis, indications for treatment, response assessment, and supportive management for patients with CLL (*Blood*. 2018;131[25]:2745-2760). These guidelines were first published in 2008 (*Blood*. 2008;111[12]:5446-5456). The 2018 update was prompted by research into the disease biology and genetic landscape, as well as new targeted treatment options. The guidelines now recommend that all patients undergo assessment of their *IGHV* mutation status as part of their baseline evaluation before treatment or enrollment in a clinical trial. Unlike del(17p), the mutation status of *IGHV* does not change, and repeated testing is therefore unnecessary. Testing can be performed on the peripheral blood; bone marrow is not needed. Presence of the unmutated gene is considered a poor predictive marker for patients undergoing treatment with chemotherapy-based regimens. On most laboratory reports, a cutoff value of less than 2% is used to define the unmutated status. The guidelines also discuss the use of biomarkers such as serum ß2 microglobulin, del(17p), and *TP53*. New recommendations are provided concerning the assessment of response to targeted therapy, the role of MRD status in clinical evaluation, and ways to diagnose and prevent viral diseases before and during management.

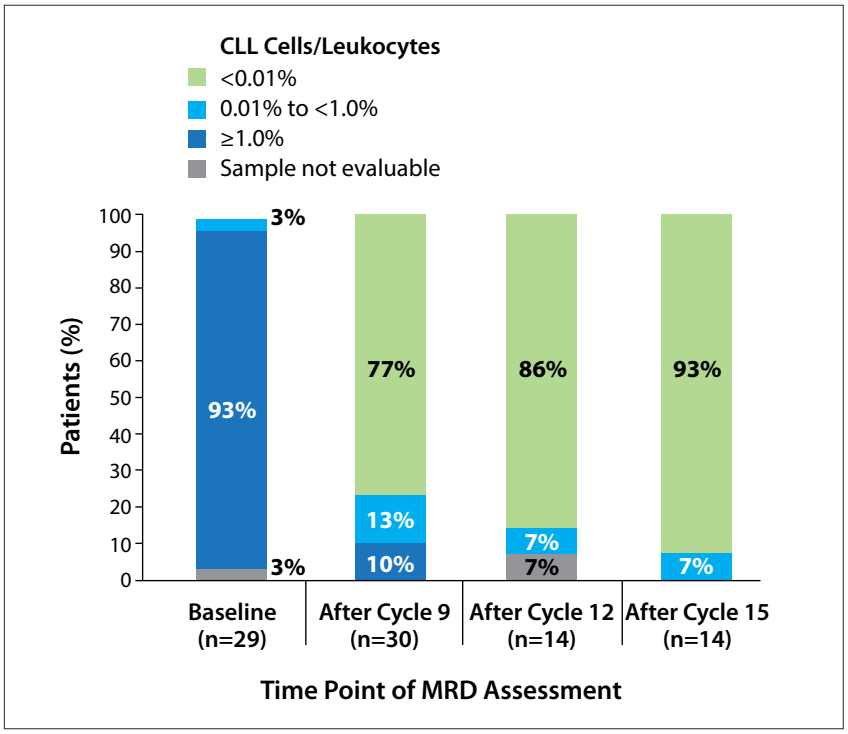

Figure 1. Early undetectable MRD responses sustained over time after first-line treatment with ibrutinib plus venetoclax in the phase 2 CAPTIVATE study. CAPTIVATE, Ibrutinib Plus Venetoclax in Subjects With Treatment-Naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; CLL, chronic lymphocytic leukemia; MRD, minimal residual disease. Adapted from Wierda WG et al. ASCO abstract 7502. *J Clin Oncol.* 2018;36(15 suppl).[11]

del(11q), and 60% had an unmutated immunoglobulin heavy chain variable region gene (*IGHV*). For the 30 patients in the blood MRD cohort, the median age was 57 years (range, 28-69 years), and 40% of patients had Rai stage III/IV disease. Twenty-three percent of patients had del(17p), and 23% of patients had del(11q). *IGHV* was unmutated in 67%. In the entire MRD cohort, the median treatment duration was 8.7 months (range, 0.5-15.2 months) with ibrutinib and 6.0 months (range, 0.8-12.0 months) with venetoclax. Ibrutinib treatment was discontinued in 1 patient (1%) owing to progressive disease and in 7 patients (4%) owing to adverse events (AEs). An AE led to discontinuation of venetoclax in 3 patients (2%). In the blood MRD cohort, the median treatment duration was 10.4 months (range, 10.0-15.2 months) with ibrutinib and 7.6 months (range, 7.0-12.0 months) with venetoclax. None of these patients discontinued treatment with ibrutinib or venetoclax.

Treatment with 3 cycles of ibrutinib lead-in therapy reduced the risk of tumor lysis syndrome. Among the entire MRD population of 164 patients, 24% had a high risk of tumor lysis syndrome at baseline vs 3% after ibrutinib lead-in, and the proportion of low-risk patients increased from 12% to 29%. Lymph node bulk was also reduced.

No unexpected ibrutinib-related toxicities were observed during the lead-in treatment. After a median of 6 months of exposure to combination treatment (range, 0.8-12.0 months), neutropenia was the only grade 4 AE. A treatment-related grade 3/4 AE occurred in 45% of patients, and 16% experienced an AE that required a dose reduction. An AE led 5% of patients to discontinue treatment. A serious AE occurred in 21% of patients, and 11% experienced a treatment-related serious AE. Two patients (1%) developed laboratory tumor lysis syndrome, but no cases of clinical tumor lysis syndrome were observed. No patients died during the study.

In the blood MRD cohort, flow cytometry analysis of the leukocyte population showed that 93% of patients had at least 1.0% CLL cells. The value was between 0.01% and less than 1.0% in 3% of patients. After 3 cycles of ibrutinib lead-in and 6 cycles of combination treatment, 77% of patients had less than 0.01% CLL cells (ie, undetectable peripheral blood MRD), 13% had between 0.01% and less than 1.0%, and 10% had greater than 10%. The proportion of patients with undetectable MRD increased to 86% (12 of 14 patients) after the ninth cycle of combination treatment and to 93% after the final treatment cycle (13 of 14 patients; Figure 1). After the 3 cycles of ibrutinib monotherapy and 12 cycles of combination therapy, 86% of patients (12 of 14) had undetectable bone marrow MRD.

Among the 11 patients who completed 12 cycles of combination treatment, 36% experienced a complete response (CR), 36% had a partial response (PR), 18% had a CR with incomplete blood count recovery (iCR), and 9% had a nodular PR. All 6 of the patients who achieved a CR or iCR and 3 of the patients who achieved a PR or nodular PR also had undetectable MRD. Among all patients in the blood MRD cohort, lymphadenopathy target lesions decreased in bulk by more than 60% to 100% (Figure 2). A reduction in splenomegaly of approximately 35% to 100% was observed among all 24 patients who had spleen enlargement at baseline. The combination of ibrutinib plus venetoclax will be evaluated in a phase 3 study as a fixed-duration regimen in treatment-naive patients with CLL.[13]

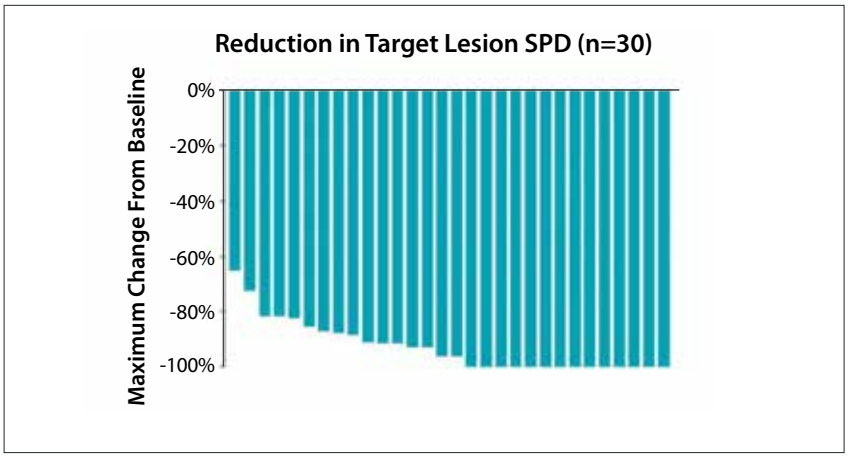

Figure 2. Reduction in lymphadenopathy after first-line treatment with ibrutinib plus venetoclax in the phase 2 CAPTIVATE study. CAPTIVATE, Ibrutinib Plus Venetoclax in Subjects With Treatment-Naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; SPD, sum of the products of lymph node diameters. Adapted from Wierda WG et al. ASCO abstract 7502. *J Clin Oncol*. 2018;36(15 suppl).[11]

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Durability of Response to Venetoclax in Patients With CLL Relapsed/Refractory to Ibrutinib and/or Idelalisib

Ibrutinib and idelalisib are inhibitors of the B-cell receptor pathway, and both agents have yielded high objective response rates (ORRs) in treatment-naive patients with CLL.[1] They are less effective, however, in patients with relapsed or refractory disease, and other treatment options are limited.[2,3] Venetoclax monotherapy has demonstrated activity in heavily pretreated patients with CLL, including those who had received a B-cell receptor pathway inhibitor.[4-6] An open-label, multicenter phase 2 trial evaluated venetoclax monotherapy in patients with CLL who had refractory disease or had progressed after discontinuation of ibrutinib and/or idelalisib.[7] The trial assessed the durability of response to venetoclax monotherapy, and evaluated levels of MRD. Eligible patients had an ECOG performance status of 0 to 2, with adequate bone marrow function and creatinine clearance. The washout period following the most recent prior treatment was 7 days for patients enrolled in the initial cohort and 3 days for the expansion cohort. Venetoclax treatment was initiated at 20 mg daily for 1 week and escalated weekly to reach the target dose of 500 mg daily by week 5. Because tumor lysis syndrome is a concern with this class of drugs, patients received prophylactic treatment starting at least 72 hours before the first dose of study drug. Laboratory monitoring was risk-based. Disease assessments occurred at screening, at weeks 8 and 24, and every 12 weeks thereafter. Responses were evaluated based on 2008 iwCLL criteria.[8] MRD was assessed at a central laboratory using 6-color flow cytometry. Peripheral blood MRD was assessed at week

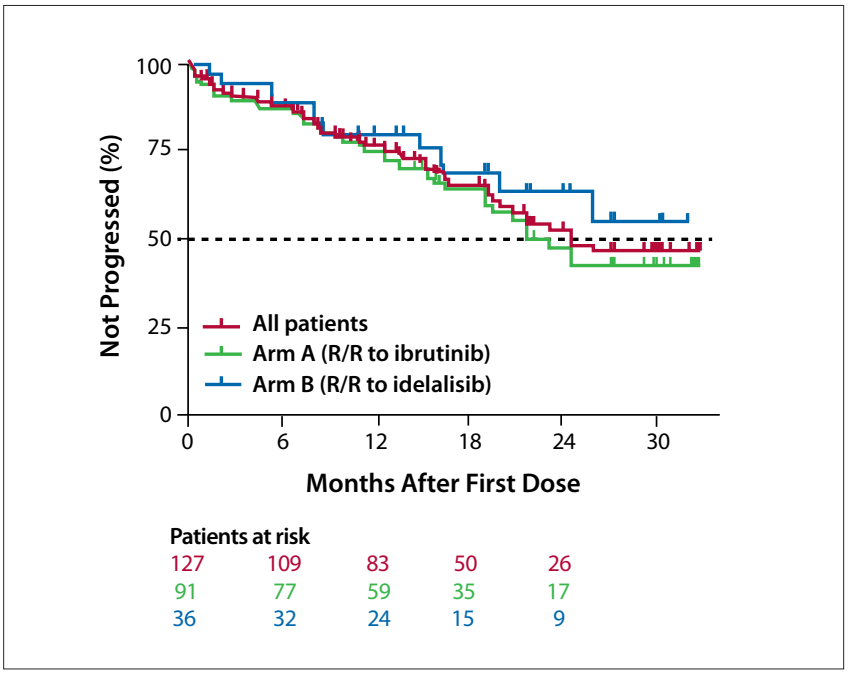

Figure 3. Progression-free survival in a phase 2 trial of venetoclax in patients with chronic lymphocytic leukemia who developed relapsed or refractory disease after treatment with ibrutinib and/or idelalisib. R/R, relapsed/refractory. Adapted from Byrd JC et al. ASCO abstract 7512. *J Clin Oncol*. 2018;36(15 suppl).[7]

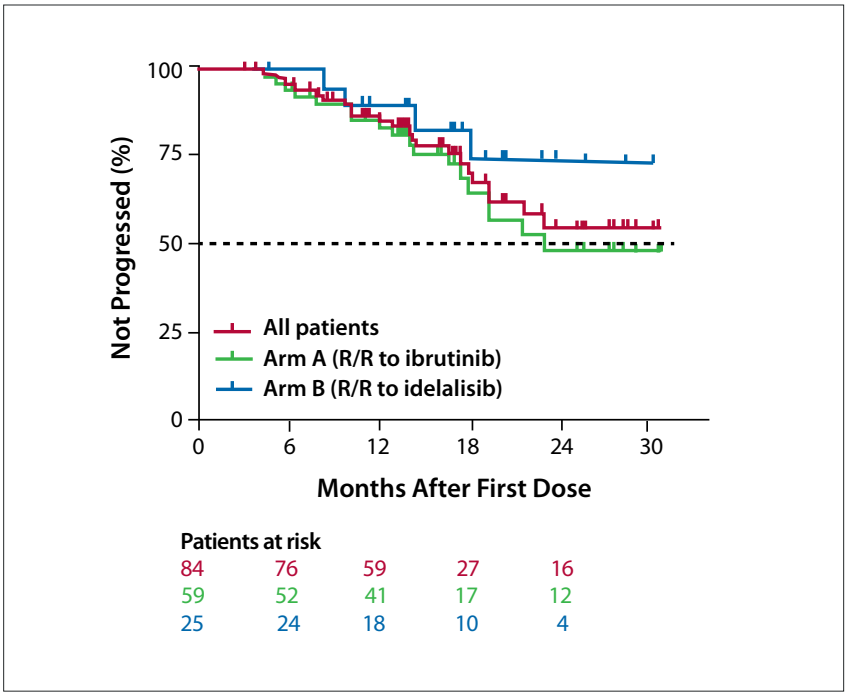

Figure 4. Duration of response in a phase 2 trial of venetoclax in patients with chronic lymphocytic leukemia who developed relapsed or refractory disease after treatment with ibrutinib and/or idelalisib. R/R, relapsed/refractory. Adapted from Byrd JC et al. ASCO abstract 7512. *J Clin Oncol*. 2018;36(15 suppl).[7]

24 for all patients. Bone marrow MRD was assessed 8 weeks after demonstration of a CR, iCR, or PR, and/or after 2 consecutive negative MRD results in the peripheral blood.

The 127 enrolled patients had a median age of 66 years (range, 28-85 years) and had received a median of 4 prior therapies (range, 1-15). Prior therapies inhibiting the B-cell receptor included single-agent ibrutinib in 61%, single-agent idelalisib in 20%, and both treatments combined in 19%. *IGHV* was unmutated in 78% of patients, 40% had del(17p), and 28% had a *TP53* mutation. The median duration of venetoclax treatment was 17.3 months (range, 0.1-35.5 months). Sixty-four patients discontinued study treatment, most commonly owing to disease progression (35%), AEs (8%), Richter transformation (6%), and stem cell transplant (6%).

The ORR was 66% (84/127) per investigator assessment and 70% (89/127) per independent review. Investigator-assessed response rates included CRs in 6%, iCRs in 5%, PRs in 54%, and nodular PRs in 2%. After a median follow-up of 16 months, the median progression-free survival (PFS) based on investigator assessment was 24.7 months. Kaplan-Meier estimates showed a PFS rate of 52% (95% CI, 40%-62%) at 24 months (Figure 3). The median duration of response (Figure 4) and median overall survival were not reached. Kaplan-Meier estimates yielded a 24-month duration of response of 57% (95% CI, 41%-71%), and a 24-month overall survival of 76% (95% CI, 65%-84%). Among 77 patients assessed for MRD, 32 (42%) had undetectable MRD in the peripheral blood (using a cutoff of 10^{-4} CLL cells). Among the latter, bone marrow was MRD-negative in 9 and MRD-positive in 7. (Status was unknown in 16 patients.) Investigator-assessed median PFS was not reached in patients with undetectable MRD in the peripheral blood vs 21.9 months for patients with detectable levels

ABSTRACT SUMMARY Rapid Progression of Disease Following Ibrutinib Discontinuation in Patients With Chronic Lymphocytic Leukemia

A retrospective study investigated characteristics of CLL, management, and outcomes after cessation of ibrutinib therapy (Abstract 7525). The study included all patients with CLL at a single clinic who received ibrutinib and discontinued treatment (N=82). Rapid progression during the 4 weeks after discontinuation was identified through factors presumed to reflect rapid progression, such as fever or fatigue, worsening lymphadenopathy or splenomegaly, and abnormal lymphocyte counts or lactate dehydrogenase levels. After a median follow-up of 10 months, 82 patients had discontinued ibrutinib. *IGHV* was unmutated in 83% of patients (54/65), and 41% (29/70) had *TP53* disruption. Among the 61 patients with adequate records, 15 (25%) had signs of rapid progression in 2 or 3 clinical domains. Among these patients, 14 (93%) had clinical symptoms, 10 (67%) had worsening lymphadenopathy or splenomegaly, and 12 (80%) had increasing laboratory values. Next-line therapy was started the day after ibrutinib discontinuation in 6 patients and after a median of 13 days in 4 patients. New treatment overlapped with ibrutinib in 2 patients. Three patients did not receive subsequent treatment. Univariate analysis did not reveal any factors associated with rapid progression after ibrutinib discontinuation.

(hazard ratio [HR], 0.148; 95% CI, 0.04-0.49; *P*=.0019). The most common grade 3/4 AEs were neutropenia (52%), thrombocytopenia (29%), and anemia (25%). A serious AE was reported in 51% of patients, and included febrile neutropenia in 9% and pneumonia in 6%. Seven patients died during the study from an AE. Two patients developed laboratory tumor lysis syndrome.

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High, Durable Minimal Residual Disease Negativity With Venetoclax + Rituximab in Relapsed/Refractory CLL: MRD Kinetics From the Phase 3 MURANO Study

In patients with CLL, undetectable MRD after treatment with chemotherapy, with or without rituximab, is associated with prolonged PFS and overall survival.[1] The use of CR as an endpoint in trials of CLL is limited by the subjectivity in measuring lymph node size and by the need for multiple computed tomography scans.[2] Undetectable MRD may provide a more objective endpoint. The open-label phase 3 MURANO study (A Study to Evaluate the Benefit of Venetoclax Plus Rituximab Compared With Bendamustine Plus Rituximab in Participants With Relapsed or Refractory Chronic Lymphocytic Leukemia) compared the combination of venetoclax plus rituximab vs bendamustine plus rituximab in patients with relapsed or refractory CLL. The recently published results demonstrated a superior PFS with the venetoclax combination.[3] At the 2018 American Society of Clinical Oncology meeting, Dr Peter Hillmen reported results of the MRD analysis.[4] The study enrolled 389 patients, who were stratified based on del(17p), responsiveness to prior therapy, and geographic region. The population included 17 pediatric patients, who were stratified between the 2 treatment arms. Patients were randomly assigned to receive either venetoclax or bendamustine in combination with rituximab. Rituximab was administered on day 1 of each cycle, starting at 375 mg/m^2 in cycle 1 and followed by 500 mg/m^2 in cycles 2 to 6. Bendamustine was administered at 70 mg/m^2 on days 1 and 2 for all 6 treatment cycles. The venetoclax dose

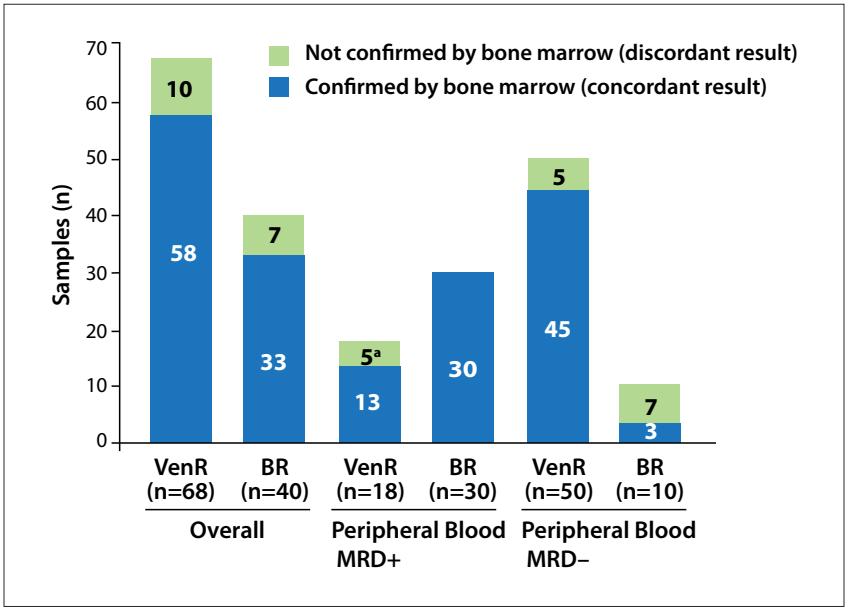

Figure 5. Concordance between levels of MRD in peripheral blood and bone marrow in the phase 3 MURANO trial of venetoclax plus rituximab vs bendamustine plus rituximab in relapsed/refractory chronic lymphocytic leukemia. [a]This value reflects the error rate in samples with MRD levels close to the 10^{-4} cutoff (as recommended by the iwCLL). BR, bendamustine plus rituximab; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRD, minimal residual disease; MURANO, A Study to Evaluate the Benefit of Venetoclax Plus Rituximab Compared With Bendamustine Plus Rituximab in Participants With Relapsed or Refractory Chronic Lymphocytic Leukemia; VenR, venetoclax plus rituximab. Adapted from Hillmen P et al. ASCO abstract 7508. *J Clin Oncol.* 2018;36(15 suppl).[4]

ABSTRACT SUMMARY Role of Ofatumumab Maintenance Treatment in Relapsed Chronic Lymphocytic Leukemia: Final Analysis of the PROLONG Study

The final analysis of the PROLONG study (Ofatumumab Maintenance Treatment vs No Further Treatment in Relapsed CLL Responding to Induction Therapy) showed a continued treatment effect with ofatumumab maintenance compared with observation in 480 patients with CLL (Abstract 7517). The median follow-up was 40.9 months (range, 0.03-79.1 months). The median duration of ofatumumab treatment was 608 days. The median PFS was 34.2 months with active maintenance vs 16.9 months with observation alone (HR, 0.55; 95% CI, 0.45-0.70; *P*<.0001). Overall survival data were not yet mature at the time of the report, and they did not reveal a difference between the 2 arms (HR, 0.99; 95% CI, 0.72-1.37). Death rates were similar with ofatumumab vs observation (32% vs 29%, respectively). AEs were reported in 92% of patients in the ofatumumab arm vs 82% in the observation arm. Serious AEs were slightly more common in the ofatumumab arm (48% vs 46%). The most common AEs of grade 3 or higher were neutropenia (23% in the ofatumumab arm vs 10% in the observation arm), pneumonia (13% vs 12%), and febrile neutropenia (6% vs 4%). In the ofatumumab arm, an AE led 12% of patients to permanently discontinue therapy. There were 7 deaths in the ofatumumab arm and 5 in the observation arm, but none were considered related to study treatment.

was escalated throughout 5 weeks to a dose of 400 mg daily, starting on day 1 of cycle 1. After completion of 6 cycles of venetoclax plus rituximab, venetoclax monotherapy was administered for a maximum of 2 years. Bone marrow MRD was evaluated at baseline and at 3 months after completion of treatment. Peripheral blood MRD was evaluated at baseline, on day 1 of cycle 4, at 3 months after the end of treatment, and every 3 months thereafter. MRD was defined as less than 1 CLL cell in 10,000 leukocytes for peripheral blood and bone marrow and was centrally assessed by allele-specific oligonucleotide polymerase chain reaction and/or multicolor flow cytometry.[5,6] MRD status was reported as positive if either method showed a positive result. Missing MRD data and assay failures were reported as MRD-positive. The primary endpoint was investigator-assessed PFS, and the secondary endpoint was MRD in the peripheral blood at the end of combination treatment.

The analysis was conducted in the intent-to-treat population. After a median follow-up of 23.8 months, the 1-year PFS was 92.7% for the venetoclax combination vs 72.5% for the bendamustine combination. The 2-year PFS was 84.9% vs 36.3%, respectively (HR, 0.17; 95% CI, 0.11-0.25; *P*<.0001). A consistent benefit with the venetoclax combination was observed in all subgroups. The PFS benefit for venetoclax plus rituximab was confirmed by an independent review committee (HR, 0.19; 95% CI, 0.13-0.28; *P*<.0001). A high level of concordance was observed among patients who were evaluated for MRD in both the peripheral blood and the bone marrow.[4]

In the venetoclax combination arm, the paired bone marrow MRD result did not confirm the peripheral blood result in 10 of 68 patients (14.7%; Figure 5). A similar rate of discordance was observed in the bendamustine combination arm (7/40; 17.5%). Among the patients

ABSTRACT SUMMARY Achievement of Complete Remission as an Endpoint for Patients With Chronic Lymphocytic Leukemia Treated With Ibrutinib

A phase 2 study of patients with CLL treated with ibrutinib was conducted to determine whether a deep response is associated with a superior PFS (Abstract 7522). This study retrospectively analyzed the characteristics and outcomes of patients enrolled in a single-institution phase 2 study of ibrutinib (NCT02007044). Patients had received first-line or salvage therapy with or without rituximab between December 2013 and October 2016. The analysis included 27 treatment-naive patients and 179 patients who had received previous treatment. Half of the patients had received ibrutinib plus rituximab. The median duration of treatment with ibrutinib was 22 months (range, 1-40 months). The ORR was 99%, and included CRs in 21% of patients with positive MRD and in 3% of patients with negative MRD. Patient characteristics, treatment history, and disease characteristics were not associated with PFS. However, a prolonged PFS was seen in patients with a CR vs a PR (*P*=.04). The estimated 3-year PFS was 97% for patients with a CR vs 78% for those with a PR.

who were MRD-positive according to peripheral blood analysis, discordant results were seen in 38.5% in the venetoclax arm and no patients in the bendamustine arm. Among patients who achieved MRD negativity, the rates of discordance were 10% in the venetoclax arm (5/50) vs 70% in the bendamustine arm (7/10). Based on these results, peripheral blood analysis was considered a reasonable method for determining MRD.

Peripheral blood analysis at 3 months after the end of treatment yielded an MRD-negative rate of 62% (121/194) in the venetoclax-plus-rituximab arm vs 13% (26/195) in the bendamustine-plus-rituximab arm (*P*<.0001). Among the subset of patients with del(17p) and/or the *TP53* mutation, the rate of MRD negativity was 57% (41/72) with the venetoclax combination vs 5% (4/75) with the bendamustine combination. Among patients without either mutation, rates of MRD negativity were 66% (70/106) and 20% (19/95), respectively. The venetoclax combination was superior regardless of the patient's *IGHV* status. Superior rates of MRD negativity in the peripheral blood were observed across all subgroups, including age, sex, 11q deletion, levels of ß2 microglobulin, bulky disease, and number of prior regimens. Rapid responses were observed among patients treated with the venetoclax combination, and the responses tended to be durable. Among 15 patients in the venetoclax combination arm, the response converted from MRD-negative to MRD-positive. Most of these patients still showed relatively low levels of CLL cells, ranging between 10^{-4} and 10^{-2}, and 11 of them remained progression-free at the time of the study report.

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Depth of Response and Progression-Free Survival in CLL Patients on Ibrutinib

Among patients with CLL, a CR after treatment with chemoimmunotherapy corresponds to a longer PFS.[1,2] A similar relationship, however, has not been demonstrated after treatment with ibrutinib.[1,2] A retrospective study evaluated the association between depth of response and PFS in patients with CLL treated with ibrutinib.[3] The study included patients enrolled in 4 sequential clinical trials of ibrutinib alone or in combination with ofatumumab conducted at Ohio State University. Two independent investigators evaluated

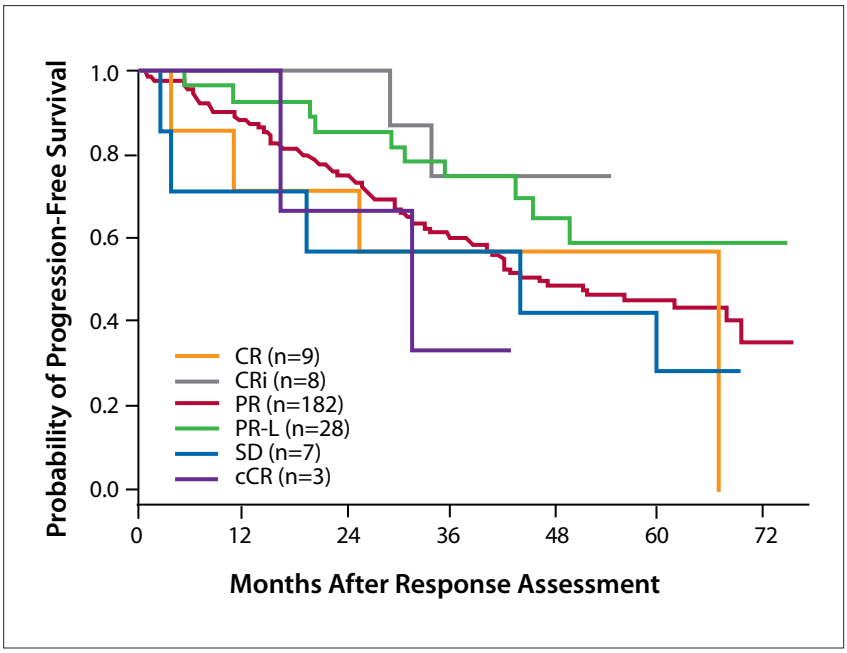

Figure 6. Probability of progression-free survival according to response in a retrospective study of ibrutinib in patients with chronic lymphocytic leukemia. cCR, complete response (no marrow); CR, complete response; CRi, complete response with incomplete marrow recovery; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease. Adapted from Sigmund AM et al. ASCO abstract 7514. *J Clin Oncol*. 2018;36(15 suppl).[3]

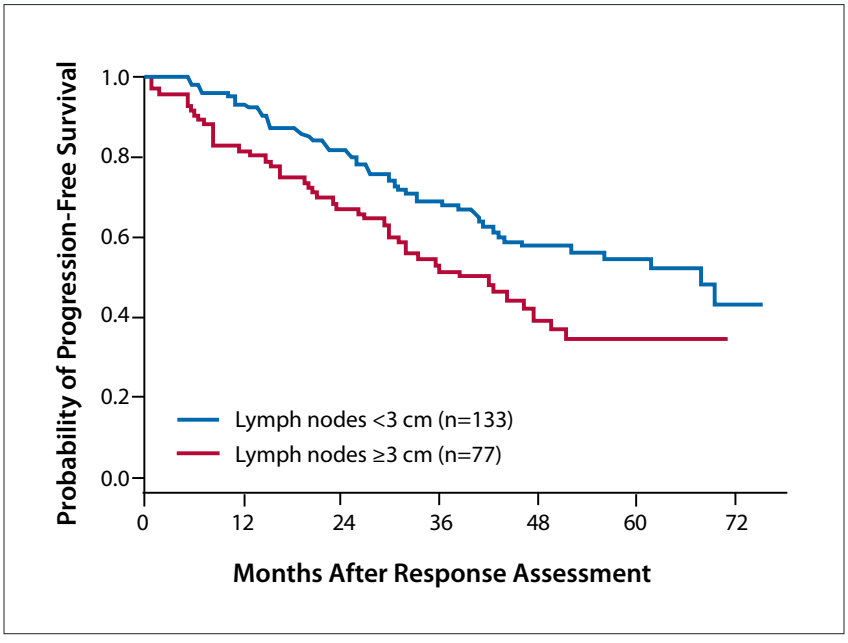

Figure 7. Probability of progression-free survival according to lymph node size in a retrospective study of ibrutinib in patients with chronic lymphocytic leukemia. Adapted from Sigmund AM et al. ASCO abstract 7514. *J Clin Oncol*. 2018;36(15 suppl).[3]

responses using iwCLL 2008 guidelines.[4] For patients without bone marrow analyses, clinical response was used instead. Landmark analysis was performed based on response assessment at 12 ±2 months, and PFS was calculated based on this response. The 237 patients in the analysis had a median age of 65 years (range, 27-89 years), and 70% were male. The Rai stage was low in 4%, intermediate in 31%, and high in 64%. The median number of prior therapies was 3 (range, 0-13). Eighty-two percent of patients had unmutated *IGHV*, 54% had a complex karyotype, 27% had del(11q), and 36% had del(17p).

At the 12-month assessment, 5% of patients had a CR, 3% had an iCR, 77% had a PR, 12% had a PR with lymphocytosis, and 3% had stable disease. A lymph node size of less than 3 cm was seen in 61% of patients with a PR and 79% of those with a PR with lymphocytosis. After a median follow-up of 48 months, the median PFS was 52 months (95% CI, 42-70 months), and no significant difference was observed among the response groups (*P*=.32; Figure 6). However, in a multivariable Cox model, the median PFS was significantly prolonged in patients with lymph nodes smaller than 3 cm (*P*=.01; Figure 7).

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A Phase 2 Study to Assess the Safety and Efficacy of Umbralisib (TGR-1202) in Patients With CLL Who Are Intolerant to Prior BTK or PI3Kδ Inhibitor Therapy

Ibrutinib and other kinase inhibitors are generally well-tolerated in CLL. However, drug intolerance accounts for approximately 50% of discontinuations.[1,2] Interruptions in the administration of ibrutinib lasting 8 days or more are associated with a reduced PFS.[3] Patients who show poor tolerance to one kinase inhibitor can often be successfully treated with a different one. Umbralisib is a novel inhibitor of phosphoinositide 3-kinase delta (PI3Kδ). In an early study, the safety profile of umbralisib differed from that of other drugs in the same class; no cases of grade 3/4 transaminitis, pneumonitis, diarrhea, or colitis were reported.[4] The drug has a half-life compatible with once-daily administration and is highly selective for the δ isoform of PI3K. It also binds to casein kinase-1ε, which may inhibit the function of regulatory T cells.

Umbralisib monotherapy at a dose of 800 mg daily was evaluated in a multicenter, single-arm trial in patients with CLL who were intolerant to prior kinase inhibitor therapy.[5] Eligible patients had received prior treatment with a Bruton's tyrosine kinase inhibitor, such as ibrutinib or acalabrutinib, or a PI3Kδ inhibitor, such as idelalisib or duvelisib. A key eligibility requirement was that the prior kinase inhibitor was discontinued owing to intolerance within 12 months of day 1 of the first cycle. The study enrolled patients who had discontinued prior kinase inhibitor treatment for at least 14 days and showed no disease progression. Resolution of all toxicities to grade 1 or lower was required before initiation of umbralisib.

The study evaluated 47 patients for safety, 46 for PFS, and 22 for response. The patients' median age was 71 years (range, 52-96 years), and 57% were male. Del(17p) was observed in 15% of patients and del(11q) in 17%. *IGHV* was unmutated in 53%, and 43% had bulky disease. Patients had experienced a total of 37 prior grade 2 AEs, 26 grade 3 AEs, and 5 grade 4 AEs. The median number of prior therapies was 2 (range, 1-7). After a median follow-up of 9.5 months, the median PFS had not been reached. The changes in nodal lesion size are shown in Figure 8.

The most common AEs of any grade observed during umbralisib treatment were nausea (43%), diarrhea (40%), and thrombocytopenia (26%). The most common grade 3/4 AEs were neutropenia (15%), thrombocytopenia (9%), and diarrhea (6%). Dose reductions occurred in 3 patients (6%) owing to headache, neutropenia, or colitis. One patient developed colitis after 6 weeks of treatment. This patient recovered after a 2-week break from study treatment. Upon resumption of umbralisib therapy at 600 mg daily, the colitis did not recur, and the patient achieved a CR and continued on the study for more than 16 months. Thirteen percent of patients discontinued study treatment owing to an umbralisib-related AE,

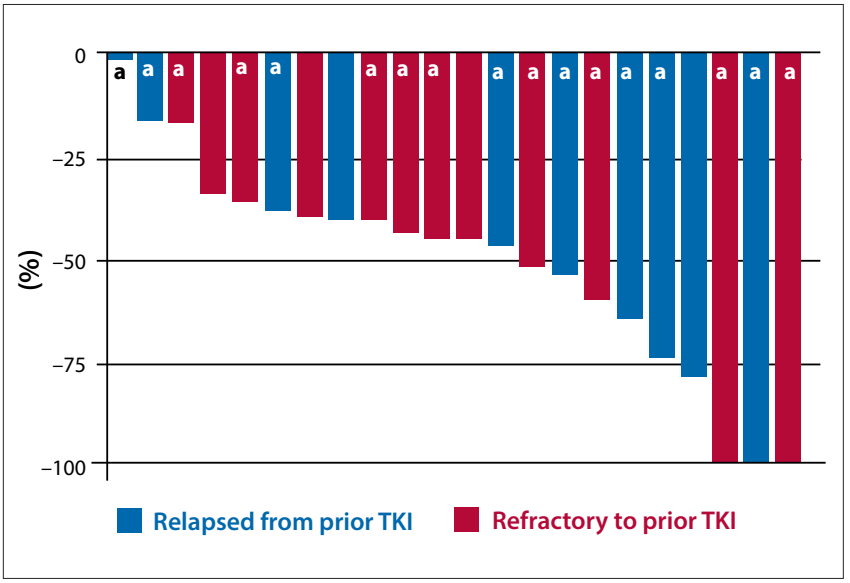

Figure 8. Best percentage in the change of nodal lesions in a phase 2 study of umbralisib in patients with chronic lymphocytic leukemia who were intolerant to prior treatment with a BTK or PI3Kδ inhibitor. Data are shown for patients with progressive disease at study entry. Refractory refers to patients who developed progressive disease from 14 days to 6 months after a TKI. Relapsed refers to patients who progressed 6 months after a TKI. [a]17p/*TP53* mutated/11q and/or *IGHV* unmutated. BTK, Bruton's tyrosine kinase; IGHV, immunoglobulin heavy-chain variable region; PI3Kδ, phosphoinositide 3-kinase δ; TKI, tyrosine kinase inhibitor. Adapted from Mato AR et al. ASCO abstract 7530. *J Clin Oncol.* 2018;36(15 suppl).[5]

including pneumonia, pancreatitis, pneumonitis, dermatitis, and rash. Three patients developed the same AE that had led to intolerance of the prior kinase inhibitor therapy. One of these patients discontinued treatment with umbralisib. In the other 2, the AE was less severe than the first time, and treatment continued.

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Change in Tumor Lysis Syndrome Risk After Lead-In Treatment in a Phase 1b/2 Study of Obinutuzumab, Ibrutinib, and Venetoclax for Chronic Lymphocytic Leukemia

Venetoclax is associated with tumor lysis syndrome, thereby increasing treatment burden and limiting administration to settings that offer appropriate monitoring and management. The risk for tumor lysis syndrome is closely related to CLL tumor burden, which is defined by the absolute lymphocyte count and the largest lymph node diameter observed by cross-sectional imaging. During venetoclax dose ramp-up, monitoring for tumor lysis syndrome is required for all patients, and patients at high risk are hospitalized. Additional strategies to reduce the risk for tumor lysis syndrome and avoid hospitalization are needed.

A retrospective study was conducted to determine whether treatment with lead-in obinutuzumab and ibrutinib prior to venetoclax therapy reduced the risk for tumor lysis syndrome.[1] The analysis included all patients who completed treatment through day 1 of cycle 3. Treatment with each of the 3 drugs was initiated sequentially throughout the first 3 cycles. Obinutuzumab was administered at 100 mg on day 1, 900 mg on day 2, and 1000 mg on days 8 and 15 during cycle 1. Afterward, the drug was administered at 1000 mg on day 1 of each subsequent cycle. Ibrutinib (420 mg daily) was initiated on day 1 of cycle 2. Venetoclax ramp-up was initiated on day 1 of cycle 3. Lymph node diameter was assessed by computed tomography, and the risk of tumor lysis syndrome was calculated as specified in the venetoclax prescribing information.

Sixty-one patients were included in the study. The patients' median age was 61 years (range, 26-79 years), and 67% were male. Fifty-nine percent had relapsed or refractory disease, and 41% were treatment-naive. *IGHV* was unmutated in 78% of patients, ZAP-70 was methylated in 42%, and 35% had the complex CLL karyotype. The

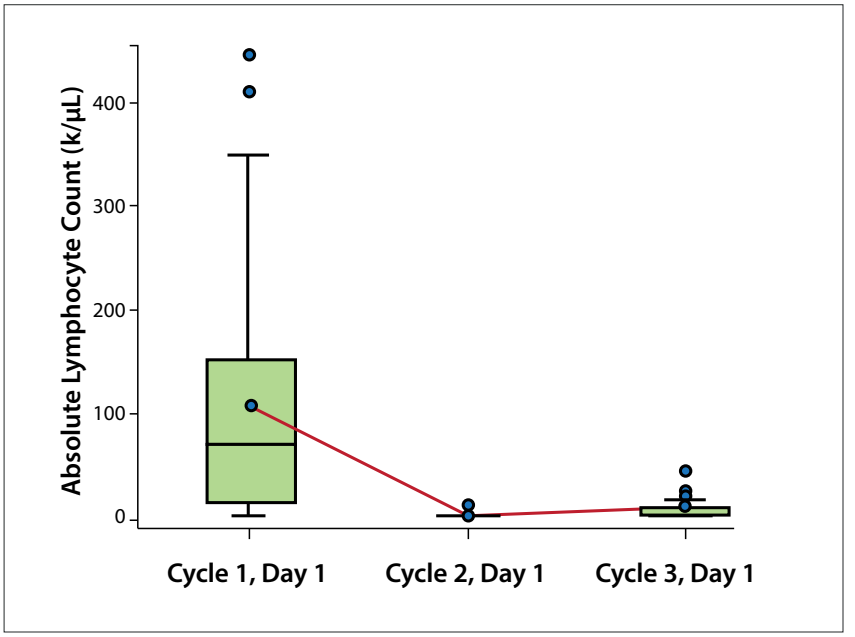

Figure 9. Change in the absolute lymphocyte count in a phase 1b/2 study of obinutuzumab, ibrutinib, and venetoclax in chronic lymphocytic leukemia. Adapted from Rogers KA et al. ASCO abstract 7528. *J Clin Oncol*. 2018;36(15 suppl).[1]

most common chromosomal abnormalities were del(11q) in 36% and del(13q) in 21%.

From the initiation of study treatment through day 1 of cycle 3, the median absolute lymphocyte count decreased significantly, with a median change of –56.5 k/μL (P<.001; Figure 9). From day 1 of cycle 1 through day 1 of cycle 3, the median absolute lymphocyte count increased by a median of 2.1 k/μL (P<.001), reflecting the initiation of treatment with ibrutinib. As measured by the sum of the products of the greatest perpendicular diameters, the lymph node volume decreased after every cycle (P<.001). The median change in lymph node volume from day 1 of cycle 1 to day 1 of cycle 3 was –11.8 cm^2. During this time, 7 patients (11%) remained high risk, 13 (21%) went from high to medium risk, 9 (15%) remained at medium risk, 24 (39%) went from medium to low risk, and 8 (13%) remained low risk. At the start of venetoclax treatment, 52% of patients were at low risk of experiencing tumor lysis syndrome. No incidents of laboratory or clinical tumor lysis syndrome were observed.

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Prognostic Role of Beta-2 Microglobulin in Relapsed/Refractory Chronic Lymphocytic Leukemia Patients Treated With Ibrutinib

Patients with CLL often have elevated levels of ß2 microglobulin, and both disease stage and tumor burden correlate with ß2 microglobulin levels. In patients with CLL who received ibrutinib-containing treatment, normalization of ß2 microglobulin levels was associated with a longer PFS.[1] Multivariable analysis identified a reduced PFS (HR, 16.9; P=.031) among patients with an abnormal level of ß2 microglobulin at 6 months of treatment. A retrospective study investigated the correlation between ß2 microglobulin status and PFS in patients with relapsed or refractory CLL who enrolled in 2 open-label clinical trials that included treatment with ibrutinib monotherapy.[2-4] The time of ß2 microglobulin normalization was defined as the first time the level decreased below the upper limit of normal as defined by the central laboratory used in each trial.

The analysis included 339 patients. Most patients (55%) were 65 years or older, and two-thirds were male. Rai stage III/IV disease was present in 59%, and 58% had bulky disease. Nearly half of patients (47%) had received 3 or more prior lines of therapy. Del(17p) was observed in 61% of patients, del(11q) was observed in 15%, and 77% had unmutated *IGHV*. The creatinine clearance rate was less than 60 mL/min in 25%. The median ß2 microglobulin level was 5.4 mg/L (range, 1.8-20.2 mg/L), and 83% of patients had a ß2 microglobulin level of at least 3.5 mg/L.

In the overall study population, the median ß2 microglobulin level decreased from 5.4 mg/L at baseline to 3.05 mg/L at 3 months (Figure 10). The median ß2 microglobulin level remained low thereafter. ß2 microglobulin levels normalized during ibrutinib treatment in half of the 312 patients who had an abnormally high ß2 microglobulin level at baseline. After a median follow-up of 41.5 months,

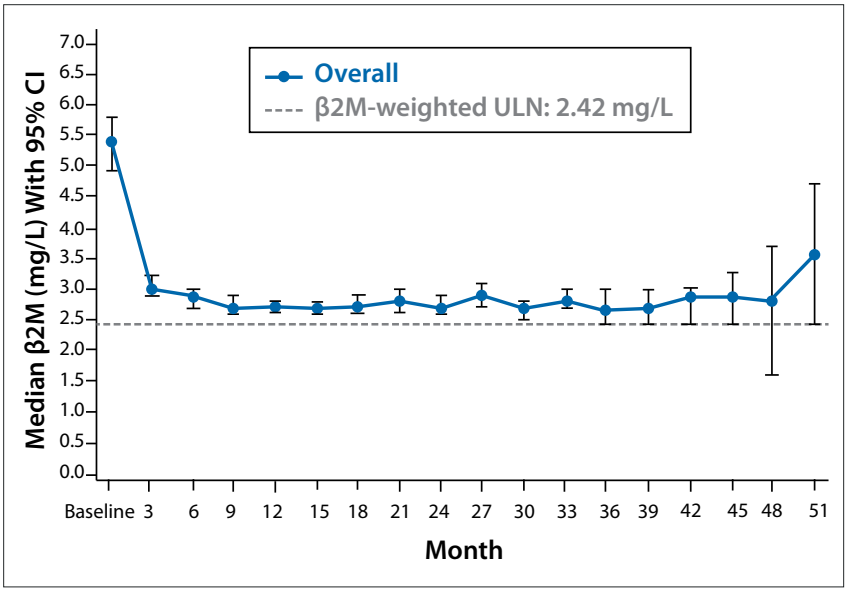

Figure 10. Median β2M over time among patients with relapsed/refractory chronic lymphocytic leukemia treated with ibrutinib. β2M, beta-2 microglobulin; ULN, upper limit of normal. Adapted from Wierda WG et al. ASCO abstract 7521. *J Clin Oncol*. 2018;36(15 suppl).[2]

the median time to ß2 microglobulin normalization was 17 months. The median time to ß2 microglobulin normalization was 14 months in patients with del(17p) vs 26 months in those without this deletion, but this difference was not statistically significant (*P*=.220). Based on multivariate analysis, a baseline ß2 microglobulin level of less than 3.5 mg/mL and a creatinine clearance rate of 60 mL/min or higher were independently associated with normalization of ß2 microglobulin at 6 months. A creatinine clearance rate of at least 60 mL/min was independently associated with ß2 microglobulin normalization at 9 months. PFS was not impacted by normalization of ß2 microglobulin levels by 6 months (HR, 0.699; 95% CI, 0.452-1.080; *P*=.105) At 9 months, however, PFS was significantly improved among patients with normalized levels (HR, 0.579; 95% CI, 0.366-0.915; *P*=.018). These results contrasted with those from a prior report showing that ß2 microglobulin status at 6 months was a prognostic factor for PFS.[1]

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The Efficacy of Duvelisib Monotherapy Following Disease Progression on Ofatumumab Monotherapy in Patients With Relapsed/Refractory CLL or SLL in the DUO Crossover Extension Study

Duvelisib is an oral inhibitor of both PI3Kδ and PI3Kγ.[1] The drug is in development for patients with relapsed or refractory CLL/SLL, as well as other hematologic malignancies. The phase 3 DUO trial (A Phase 3 Study of Duvelisib Versus Ofatumumab in Patients With Relapsed or Refractory CLL/SLL) evaluated duvelisib monotherapy in patients with relapsed or refractory CLL/SLL. The study randomly assigned 319 patients to receive duvelisib (25 mg twice daily) or ofatumumab (300 mg infusion on day 1, then 2000 mg weekly for 7 treatments, then 2000 mg each month for 4 months). The study met its primary endpoint, demonstrating a significant improvement in median PFS with duvelisib (13.3 vs 9.9 months; HR, 0.52; *P*<.0001).[2] The ORR was 74% in the duvelisib arm vs 45% in the ofatumumab arm.

Study IPI-145-12 included 89 patients from DUO who voluntarily crossed over after developing radiologically confirmed disease progression on ofatumumab.[3] Duvelisib (25 mg twice daily) was administered until disease progression, death, or study withdrawal. Patients had a median age of 68 years (range, 39-90 years), and 63% were male. Patients had received a median of 3 prior therapies (range, 2-8), and 61% had received 3 or more prior lines of therapy. Del(17p) was reported in 20% of patients. The median number of years from the initial diagnosis was 7 (range, 0.5-22.0), and half of patients had Rai stage III/IV disease at the beginning of the crossover study. The median lymphocyte count at baseline was 13.96 × 10^9/L. The median exposure to duvelisib during the crossover study was 32 weeks.

The 89 patients who crossed over to duvelisib had an ORR of 73% (95% CI, 64%-82%), and all responses were PRs. In contrast, the ORR for the same patients during ofatumumab treatment in the DUO study was 28%. Among the 20 patients with del(17p), the ORR was 80% (95% CI, 63%-98%). PFS was significantly longer with duvelisib (15 months) compared with the prior ofatumumab treatment (9 months). Among 87 evaluable patients, a reduction in target nodal lesions of greater than 50% was observed in 28% of patients treated with ofatumumab vs 83% of patients treated with duvelisib after crossover. The most common grade 3/4 AEs were neutropenia (22%), diarrhea (17%), colitis (9%), and pneumonia (9%). Three patients experienced severe opportunistic infections. Two patients had *pneumocystis jirovecii* pneumonia, including 1 patient who died and whose death was considered related to treatment with duvelisib. The other severe opportunistic infection was cytomegalovirus pneumonia.

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Highlights in Chronic Lymphocytic Leukemia From the 2018 American Society of Clinical Oncology Annual Meeting: Commentary

Susan M. O'Brien, MD

Studies in chronic lymphocytic leukemia (CLL) at the 2018 American Society of Clinical Oncology meeting evaluated several new management approaches for these patients. The CAPTIVATE trial (PCYC-1142; Ibrutinib Plus Venetoclax in Subjects With Treatment-Naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma) provided important data on ibrutinib and venetoclax in the frontline setting. Other studies of venetoclax evaluated the duration of response in patients previously treated with ibrutinib or idelalisib, and how lead-in therapy can reduce the risk of tumor lysis syndrome. Studies of the novel therapies duvelisib and umbralisib showed promising results.

Ibrutinib and Venetoclax

The CAPTIVATE trial evaluated 2 small molecules, ibrutinib and venetoclax, in the frontline setting.[1] Several presentations at the 2017 American Society of Hematology (ASH) meeting studied similar regimens, with or without antibodies.[2,3] The CAPTIVATE trial did not include an antibody. The results were consistent with those presented at the ASH meeting. The combination of ibrutinib plus venetoclax produced very high response rates. Of even more interest, this combination produced high levels of minimal residual disease (MRD) negativity, which is exciting because it raises the possibility of finite therapy. We can presume that deep remissions will be durable in patients who are MRD-negative. This association has been confirmed in the chemotherapy setting and will likely be seen with small molecules when long-term data are available. It may therefore be possible to stop therapy in some patients.

Venetoclax After Ibrutinib or Idelalisib

Dr John Byrd and colleagues examined the durability of response to venetoclax in patients who developed relapsed/refractory disease after ibrutinib or idelalisib.[4] A 2016 phase 1 trial of venetoclax published in the *New England Journal of Medicine* showed that venetoclax had very good response rates and durable remissions.[5] However, none of the patients in this study had been treated with ibrutinib. This trial was performed predominantly in Australia and Asia, and it began before ibrutinib became available in those regions. Ibrutinib has now been available in the United States for several years, and it is a very effective drug. In current clinical practice, most of the patients who receive venetoclax were intolerant to ibrutinib or relapsed after treatment.

The study by Dr Byrd evaluated venetoclax in patients who had received treatment with ibrutinib or idelalisib. Results were recently published separately for patients previously treated with ibrutinib or idelalisib.[6,7] The response rate was approximately 65% in both groups. These data are impressive because they were seen in patients who had been previously treated with multiple lines of chemotherapy, as well as small-molecule agents. In the ibrutinib group, patients had received a median of 4 prior regimens. As would be expected in a group that required treatment after chemotherapy and ibrutinib, 40% had a 17p deletion. The median progression-free survival (PFS) was 2 years, which is striking. Another interesting finding is that some patients were able to achieve MRD negativity. Among these patients, the median PFS was not reached at the time of the report. As would be expected, these deeper remissions will be even more durable.

Reducing Tumor Lysis Syndrome Associated With Venetoclax

Dr Kerry Rogers presented results of a phase 1b/2 study of obinutuzumab, ibrutinib, and venetoclax, which examined whether lead-in treatment before venetoclax impacted the risk of tumor lysis syndrome.[8] The treatment regimen consisted of obinutuzumab alone for the first month, followed by the addition of ibrutinib in the second month and venetoclax in the third month. In the CAPTIVATE trial, ibrutinib was given for 3 months before venetoclax. Most trials of venetoclax combination regimens include a lead-in therapy to debulk patients and decrease their risk for tumor lysis. Decreasing risk is especially important among patients at high risk. According to the package insert for venetoclax, all high-risk patients must be hospitalized during the initial dosing and then a week later during the ramp-up 50-mg dose.

The study by Dr Rogers assessed the risk for tumor lysis syndrome (based on the lymph node size and absolute lymphocyte count) with venetoclax if the patients were starting

treatment with that agent, and then reassessed it after the 2-month lead-in with obinutuzumab and ibrutinib, when venetoclax was actually started. As in other trials, lead-in treatment markedly reduced the risk of tumor lysis syndrome.[9] A helpful table in the package insert for venetoclax explains how to calculate whether a patient is at high, intermediate, or low risk. Importantly, the study found that lead-in treatment reduced the risk for tumor lysis syndrome among the initially high-risk population, which not only reduces risk but abrogates the need for hospitalization.

Umbralisib

A study by Dr Anthony Mato evaluated the safety and efficacy of umbralisib (TGR-1202) in patients who were intolerant to treatment with a small-molecule therapy, either ibrutinib or idelalisib.[10] Umbralisib is a phosphoinositide 3-kinase (PI3K) δ inhibitor, like idelalisib, but it appears to have a much better safety profile.[11] The incidences of pneumonitis, transaminitis, and colitis are markedly decreased with umbralisib as compared with idelalisib. The trial by Dr Mato showed that umbralisib was very tolerable in this setting. Once umbralisib is approved by the US Food and Drug Administration (FDA), it will provide a good option for patients who are intolerant to ibrutinib or idelalisib. This population is not an insignificant minority of patients.

Duvelisib

A trial from Dr Bryone Kuss evaluated duvelisib in patients with progressive disease after ofatumumab.[12] This study stemmed from a randomized trial of duvelisib vs ofatumumab in relapsed CLL, known as DUO (A Phase 3 Study of Duvelisib Versus Ofatumumab in Patients With Relapsed or Refractory CLL/SLL).[13] Duvelisib is different from idelalisib in that it inhibits both the δ and γ isoforms of PI3K. Idelalisib and umbralisib are both PI3Kδ inhibitors. The γ isoform may be important in T-cell lymphomas; a development program is moving forward with a clinical trial in T-cell lymphoma.[14]

The toxicity profile appears to be reduced with duvelisib vs idelalisib. The randomized trial was a registration trial, and it followed the design of the RESONATE trial (Ibrutinib Versus Ofatumumab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia; PCYC-1112), which led to the approval of ibrutinib.[15] RESONATE compared ibrutinib vs ofatumumab in relapsed CLL, and the DUO study compared duvelisib vs ofatumumab. Presentation of the DUO data at the 2017 ASH meeting showed that the primary endpoint was met; progression-free survival was significantly better with duvelisib than ofatumumab.[13] Based on this randomized trial, it is expected that duvelisib will be approved by the FDA in 2018.

The analysis presented by Dr Kuss evaluated the crossover population: patients who progressed on ofatumumab and were then treated with duvelisib.[12] These patients did very well, with a median progression-free survival of approximately 17 months. Their response was similar to that of the patients treated with duvelisib initially. The approval of duvelisib will provide another option in the armamentarium of treatments for CLL.

Disclosure

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

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#1 PRESCRIBED THERAPY IN FRONTLINE† AND PREVIOUSLY TREATED CLL‡[1]

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

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

†Based on market share data from IMS from November 2016 to April 2017.
‡Based on market share data from IMS from May 2014 to April 2017.

CLL
SLL

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

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

The mechanism for the bleeding events is not well understood.

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

Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding.

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. 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.

Cardiac Arrhythmias: Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA® therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0 to 1% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 0 to 6% of patients. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias.

Periodically monitor patients clinically for cardiac arrhythmias. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias 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.

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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

Statistically significant reduction in risk of death **56%**
HR=0.44
(95% CI: 0.21, 0.92)

41% of patients crossed over to IMBRUVICA® upon disease progression

Estimated survival rates at 24 months

IMBRUVICA® **95%**
(95% CI: 89, 97)

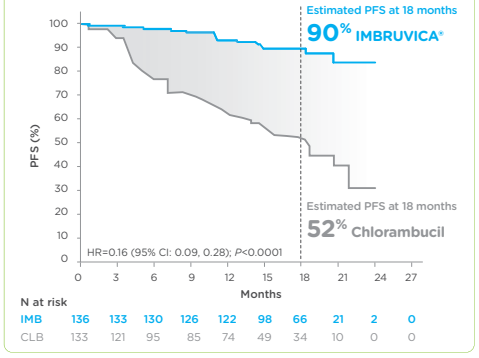
chlorambucil **84%**
(95% CI: 77, 90)

- 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%)

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

ADVERSE REACTIONS

The most 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%), bruising (30%), rash (30%), fatigue (29%), nausea (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% of patients discontinued IMBRUVICA® due to adverse reactions. Adverse reactions leading to discontinuation included hemorrhage (1.3%), pneumonia (1.1%), atrial fibrillation (0.8%), neutropenia (0.7%)*, rash (0.7%), diarrhea (0.6%), bruising (0.2%), interstitial lung disease (0.2%), and thrombocytopenia (0.2%)*. Seven percent of patients had a dose reduction due to adverse reactions.

*Treatment-emergent decreases (all grades) were based on laboratory measurements and adverse reactions.

DRUG INTERACTIONS

CYP3A Inhibitors: Dose adjustments may be recommended.

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment (based on Child-Pugh criteria): Avoid use of IMBRUVICA® in patients with severe baseline hepatic impairment. In patients with mild or moderate 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.

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Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)
IMBRUVICA® (ibrutinib) capsules, for oral use
IMBRUVICA® (ibrutinib) tablets, 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).

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.

Waldenström's Macroglobulinemia: IMBRUVICA is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM).

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.

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.

Cardiac Arrhythmias: Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0 to 1% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 0 to 6% of patients. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias.

Periodically monitor patients clinically for cardiac arrhythmias. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias 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 embryo-fetal 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]*
- Cardiac Arrhythmias *[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
Metabolism and nutrition disorders	Decreased appetite	21	2
	Dehydration	12	4

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 (%)
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

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
Body System Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	48	4	18	2
Nausea	26	2	18	0
Stomatitis*	17	1	6	1
Constipation	15	0	9	0
Vomiting	14	0	6	1
General disorders and administration site conditions				
Pyrexia	24	2	15	1
Infections and infestations				
Upper respiratory tract infection	16	1	11	2
Pneumonia*	15	10	13	9
Sinusitis*	11	1	6	0
Urinary tract infection	10	4	5	1
Skin and subcutaneous tissue disorders				
Rash*	24	3	13	0
Petechiae	14	0	1	0
Bruising*	12	0	1	0

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

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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 HELIOS (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

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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: *Cardiac Arrhythmias:* In randomized controlled trials (n=1227; median treatment duration of 13.1 months for patients treated with IMBRUVICA and 9.0 months for patients in the control arm), the incidence of ventricular tachyarrhythmias (ventricular extrasystoles, ventricular arrhythmias, ventricular fibrillation, ventricular flutter, and ventricular tachycardia) of any grade was 1.0% versus 0.2% and of Grade 3 or greater was 0.2% versus 0% in patients treated with IMBRUVICA compared to patients in the control arm. In addition, the incidence of atrial fibrillation and atrial flutter of any grade was 7% versus 1.5% and for Grade 3 or greater was 2.8% versus 0.3% in patients treated with IMBRUVICA compared to patients in the control arm.

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.

Dose modifications of IMBRUVICA are recommended when used concomitantly with posaconazole, voriconazole and moderate CYP3A inhibitors *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA if these inhibitors will be used short-term (such as anti-infectives for seven days or less) *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

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

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]*.

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

Dose modifications of IMBRUVICA are recommended in patients with mild or moderate hepatic impairment (Child-Pugh class A and B). Monitor patients for adverse reactions of IMBRUVICA closely *[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].*
- *Cardiac Arrhythmias:* 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].*

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- *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 oral dosage (capsules or tablets) should be swallowed whole with a glass of water without opening, breaking or chewing the capsules or cutting, crushing or chewing the tablets 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 doses 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].*

Active ingredient made in China.

Distributed and Marketed by:
Pharmacyclics LLC
Sunnyvale, CA USA 94085
and
Marketed by:
Janssen Biotech, Inc.
Horsham, PA USA 19044

Patent *http://www.imbruvica.com*

PRC-03819


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