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Clinical Implications of the 2018 iwCLL Guidelines Update

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Plus

Highlights in Chronic Lymphocytic Leukemia From the 23rd Congress of the European Hematology Association

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H&O When were guidelines from the iwCLL first published?

SO The original guidelines for chronic lymphocytic leukemia (CLL) were published in the 1980s by a working group from the National Cancer Institute.[1] The first guidelines from the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) were published in 2008.[2] The iwCLL consists of a group of experts from various countries. The guidelines that were published in 2008 were intended to standardize the assessment of patients. The guidelines were adopted by the US Food and Drug Administration (FDA) and the European Medicines Agency for the evaluation of new drugs. Since 2008, there have been many changes in the field of CLL, particularly in treatment. There are now several classes of therapies. Chemoimmunotherapy includes the combination of fludarabine, cyclophosphamide, and rituximab (FCR), bendamustine plus rituximab, and chlorambucil plus an antibody, either obinutuzumab or ofatumumab.[3,4] The newer small-molecule therapies include the Bruton tyrosine kinase inhibitor ibrutinib, the phosphoinositide 3-kinase δ inhibitor idelalisib, and the BCL-2 inhibitor venetoclax.[5-7] Ibrutinib is the only small molecule with FDA approval in the frontline setting for CLL.[8] The patterns of response to these drugs differ from those seen with chemotherapy.

H&O What are the key changes in the most recent update to the iwCLL guidelines?

SO The 2018 guidelines now highlight the relevance of genomic alterations, particularly the deletions in *TP53* and 17p, and the immunoglobulin heavy chain variable (*IGHV*) mutation.[9] Many physicians are aware of the relevance of the 17p deletion and appreciate the importance of administering the test for this mutation. Patients with the 17p deletion respond poorly to chemotherapy, even as upfront therapy.[10] These patients are therefore treated with small-molecule agents. What some physicians may not know is that patients without the 17p deletion may still have a *TP53* mutation, which carries the same relevance in terms of outcome.[11] Fluorescence in situ hybridization (FISH) provides information on some of the prognostically important cytogenetic abnormalities in CLL, including the 17p deletion. However, we also encourage physicians to test for the *TP53* mutation, which excludes the use of chemotherapy even in patients who do not have a 17p deletion.

The iwCLL guidelines now recommend that all patients with CLL undergo testing of their *IGHV* mutation status.[9] We have known for many years that the *IGHV* mutation status has prognostic significance.[12] Among patients under active surveillance with watch and wait, those without a mutated *IGHV* gene tended to need treatment more rapidly than those with the mutation. After treatment with chemoimmunotherapy, response rates were the same regardless of the *IGHV* status, but patients with unmutated *IGHV* had a much shorter time to progression with chemoimmunotherapy. In several studies of FCR, patients with a mutated *IGHV* gene exhibited a plateau on the progression-free survival (PFS) curve; these patients can have very long remissions and may even be cured.[13,14] The longest follow-up data were published by the MD Anderson Cancer Center, which developed the FCR regimen.[14] This study showed that in patients with a mutated *IGHV* gene, the plateau on the PFS curve was 60% at 10 to 16 years.

Many of these patients tested negative for minimal residual disease, again suggesting that there could be a cure fraction. Patients without the mutated *IGHV* gene had a PFS of approximately 3 years, which is a reasonably good response to chemotherapy, although nowhere near the long-term benefits seen in patients with the mutated gene.

Until recently, the significance of *IGHV* status was limited to prognosis. That changed with the advent of small-molecule therapies, which are equally effective regardless of the patient's *IGHV* mutation status.[5,6] For patients with an unmutated *IGHV* gene, most physicians suggest treatment with investigational approaches or a small-molecule therapy, such as ibrutinib, rather than chemotherapy. Therefore, it is now important to ascertain a patient's *IGHV* mutation status before selection of treatment.

H&O How is *IGHV* tested?

SO The test sequences the *IGHV* gene in CLL cells. It can be performed on peripheral blood, like any test in CLL. Bone marrow is not needed. Most of the major laboratories now test for *IGHV*. A mutated *IGHV* gene is defined as one that differs by more than 2% from the known germline sequences.[15] This difference indicates that the cell has gone through the germinal center, encountered an antigen, and mutated in response to the antigen to develop specificity for it.

IGHV is mutated in approximately half of patients with CLL.[16] In clinical trials, however, the population usually has a higher percentage of unmutated patients, who tend to progress and need treatment more quickly. These patients also have a shorter PFS after treatment with chemotherapy, and are therefore more likely to enroll in a clinical trial.

H&O Does the *IGHV* status change over time?

SO The mutation status of *IGHV* does not change, so the test does not need to be repeated. In contrast, FISH testing of chromosome abnormalities can change owing to clonal evolution.

H&O What do the new guidelines recommend about progressive disease?

SO The new guidelines suggest that patients who develop asymptomatic progressive disease may not need treatment at relapse, but can be monitored instead.[9] It is possible to detect progressive disease that meets the established criteria, but is in fact minimal. For example, say a patient is in complete remission after treatment. Then, the lymphocyte count rises to 10,000 µL, or small lymph nodes develop. This patient may still be asymptomatic, just like at diagnosis. The recommendation is to reinstitute watch and wait and initiate treatment only when required, as is done in the upfront setting. This recommendation applies to all patients with CLL, but particularly those in a clinical trial. Because PFS is often an endpoint of clinical trials, enrolled patients tend to undergo more close assessment for progressive disease.

H&O Have the indications for treatment changed?

SO They have not changed. Essentially, treatment is required when the disease starts to cause a problem. For example, constitutional symptoms may be a reason to treat. In general, lymphocytosis by itself is not an indication for treatment. Patients with CLL can be completely asymptomatic, even with very high lymphocyte counts. Treatment of CLL is not necessarily required for autoimmune complications. If patients respond poorly to other interventions for these conditions, such as corticosteroids or rituximab, treatment might then be indicated.

H&O What did the CLL10 and CLL11 trials show?

SO These trials evaluated chemoimmunotherapy. The CLL10 trial (First-Line Chemoimmunotherapy With Bendamustine and Rituximab Versus Fludarabine, Cyclophosphamide, and Rituximab in Patients With Advanced Chronic Lymphocytic Leukaemia) compared bendamustine plus rituximab vs FCR.[3] The FCR regimen produced a significantly longer PFS—more than a year longer—but at the expense of more myelosuppression and infections. The randomized CLL11 trial (A Study of Obinutuzumab [RO5072759 (GA101)] With Chlorambucil in Patients With Previously Untreated Chronic Lymphocytic Leukemia [Stage 1a]) had 3 arms: chlorambucil, chlorambucil plus rituximab, and chlorambucil plus obinutuzumab.[4] In this trial, both antibody arms produced better outcomes compared with single-agent chlorambucil. PFS was better with obinutuzumab vs rituximab. An update of the CLL11 trial, presented at the 23rd Congress of the European Hematology Association, also showed a benefit in overall survival with obinutuzumab vs rituximab.[17]

Both of these trials consistently showed that patients with a mutated *IGHV* gene had significantly better PFS than patients who were unmutated, as would be expected with chemoimmunotherapy.[3,4]

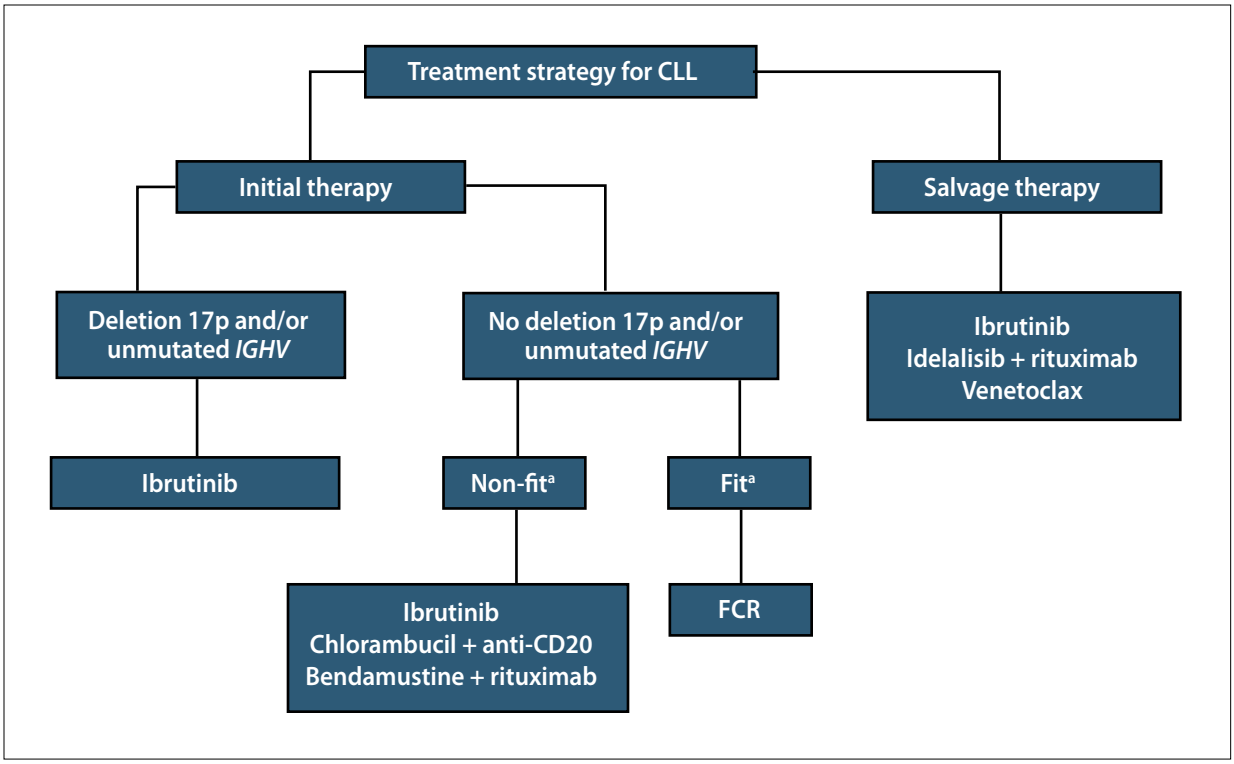

Figure. An algorithm for the management of CLL. [a]In the United States, "fit" is defined as patients younger than 65 years and with a good performance status. CLL, chronic lymphocytic leukemia; FCR, fludarabine, cyclophosphamide, and rituximab; *IGHV*, immunoglobulin heavy chain variable. Reprinted from *Mayo Clinic Proceedings*. Volume 93, Issue 5. Strati P et al. Chronic lymphocytic leukemia: diagnosis and treatment. Pages 651-664. Copyright 2018, with permission from Elsevier.[21]

H&O What did the RESONATE-2 trial show?

SO RESONATE-2 (Randomized, Multicenter, Open-Label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib Versus Chlorambucil in Patients 65 Years or Older With Treatment-Naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma [PCYC-1115/1116]) was a randomized trial in the frontline setting that compared ibrutinib vs chlorambucil in patients who were older than 70 years or who were ages 65 years to 70 years and had a contraindication to chemotherapy.[5] After a median follow-up of 18.4 months, the median PFS was not reached with ibrutinib vs 18.9 months with chlorambucil. At 24 months, the estimated survival rate was 98% with ibrutinib vs 85% with chlorambucil, and the relative risk of death was 84% lower with ibrutinib vs chlorambucil (hazard ratio, 0.16; *P*=.001). The overall response rate was 86% with ibrutinib vs 35% with chlorambucil (*P*<.001). The results of RESONATE-2 led to the approval of ibrutinib in the frontline setting in CLL. Interestingly, although the eligibility for the trial was restricted to older patients, the frontline indication is not age-restricted. The response rate, PFS, and overall survival were better with ibrutinib than chlorambucil.

The control arm in RESONATE-2 may lead some physicians to question the relevance of the results for younger, fit patients, who they would not treat with chlorambucil. For these patients, some physicians might want to see data from a randomized trial comparing ibrutinib vs FCR or bendamustine plus rituximab. Data are forthcoming from 2 large US Intergroup trials. One is a 2-arm randomized trial of FCR vs ibrutinib and rituximab,[18] and the other is a 3-arm trial of ibrutinib alone vs rituximab plus ibrutinib vs rituximab plus bendamustine.[19] These trials are fully accrued and will provide important information.

H&O How does your new treatment algorithm differ from the traditional approach?

SO Before the new algorithm, treatment was usually based on the patient's age and comorbidities. This approach was developed when all treatment options were chemotherapy-based. Patients were divided into 3 groups: younger, fit patients who might otherwise have a normal

lifespan; patients who were older but relatively fit; and patients who were unfit and/or elderly. The German CLL Study Group coined phrases to describe the treatment approach in these patients: "go-go" for the younger, fit patients; "slow-go" for the less fit, somewhat older patients; and "no-go" for the older, unfit patients, who should receive palliative therapy.[20] It made sense to view patients along a spectrum of tolerance to chemotherapy, and to avoid this treatment in older patients and/or those with comorbidities.

The advent of small-molecule therapy, particularly ibrutinib in the upfront setting, changed the approach to treatment in CLL. In the new algorithm, we suggest that the first step in selecting treatment is to determine whether the patient has a 17p deletion or a *TP53* mutation (Figure).[21] As I mentioned earlier, these patients are not candidates for chemotherapy. They should receive ibrutinib. In the future, if other small molecules are approved in the frontline setting, then there will be other options.

The second step in the algorithm recommends testing for the *IGHV* mutation. There appears to be long-term survival, if not a cure, among the subset of patients with a mutated *IGHV* who are treated with chemotherapy. The survival plateau is less strong among patients without the mutation. The algorithm therefore asks if a patient with the *IGHV* mutation is amenable to chemotherapy; if so, then treatment with chemotherapy can be initiated. Patients without the mutation should be treated with ibrutinib. This is a major change from the historical treatment approach. Previously, we knew that the *IGHV* mutation status was prognostically important, but it did not impact treatment selection because the only options were chemotherapy-based. We knew that patients without the mutation would do less well on chemotherapy, but it did not matter because there were no other options. However, now ibrutinib is available. Patients with unmutated *IGHV* should skip chemotherapy and go straight to ibrutinib.

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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Highlights in Chronic Lymphocytic Leukemia From the 23rd Congress of the European Hematology Association

June 14-17, 2018 • Stockholm, Sweden

Ibrutinib Lead-In Followed by Venetoclax in Patients With Chronic Lymphocytic Leukemia: Phase 2 CAPTIVATE Early Safety and Efficacy Results

The phase 2 CAPTIVATE trial (PCYC-1142; Ibrutinib Plus Venetoclax in Subjects With Treatment-Naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma) is evaluating the combination of ibrutinib plus venetoclax as first-line therapy in patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma. The treatment regimen begins with ibrutinib alone (420 mg) for 3 months, for debulking, followed by ibrutinib (420 mg) plus venetoclax (ramp up to 400 mg). After a year of combination treatment, patients will undergo assessment of minimal residual disease (MRD). Those who are MRD-negative will be randomly assigned to continue ibrutinib alone or to stop treatment entirely. Patients who are MRD-positive will be randomly assigned to treatment with ibrutinib alone or in combination with venetoclax. The overall objective of the study is to determine whether MRD negativity will permit treatment holidays.

Dr Paolo Ghia presented preliminary results of the CAPTIVATE trial at the 23rd Congress of the European Hematology Association (EHA).[1] Among the 14 patients who completed 1 year of combination therapy, the objective response rate (ORR) was 100%. The rate of bone marrow MRD negativity was 86%. After 6 cycles of ibrutinib plus venetoclax, 77% of patients were MRD-negative according to testing in peripheral blood. After 12 cycles of ibrutinib plus venetoclax, a confirmed undetectable MRD was reported in 79% of patients.

Analysis of tumor lysis syndrome was available for nearly 80 patients. Three cycles of ibrutinib lead-in treatment reduced the risk of tumor lysis syndrome and bulky disease. Among the 40 patients at high risk for tumor lysis syndrome, 36 (90%) shifted to low or medium risk. Among 37 patients at medium risk of tumor lysis syndrome and with a creatinine clearance of less than 80 mL/min, 7 patients shifted to low risk. No patients developed clinical tumor lysis syndrome. Laboratory tumor lysis syndrome was reported as an adverse event in 2 patients (neither met the Howard criteria). One additional case of laboratory tumor lysis syndrome was not reported as an adverse event (but met Howard Criteria). The combination was well-tolerated, with adverse events reflecting those seen with each agent alone.

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Overall Survival Benefit of Obinutuzumab Over Rituximab When Combined With Chlorambucil in Patients With Chronic Lymphocytic Leukemia and Comorbidities: Final Survival Analysis of the CLL11 Study

The randomized phase 3 CLL11 trial (A Study of Obinutuzumab [RO5072759 (GA101)] With Chlorambucil in Patients With Previously Untreated Chronic Lymphocytic Leukemia [Stage 1a]) evaluated chlorambucil alone or with rituximab or obinutuzumab among treatment-naive patients with CLL and comorbidities. A previous analysis showed that both antibody arms were superior to single-agent chlorambucil.[1] The final analysis of the CLL11 trial, presented at the EHA meeting, showed improvements in overall survival and progression-free survival (PFS) with obinutuzumab vs rituximab.[2]

After a median observation of 59.4 months, the median PFS was 28.9 months with obinutuzumab plus chlorambucil (n=333) vs 15.7 months with rituximab plus chlorambucil (n=330; $P<.0001$). Obinutuzumab plus chlorambucil reduced the risk of progressive disease or death by 79% as compared with chlorambucil alone and by 51% compared with rituximab plus chlorambucil. The median overall survival was not reached vs 73.1 months, respectively ($P=.0245$). This difference translated into a reduction in the risk of death of 32% compared with chlorambucil alone and of 24% compared with rituximab plus chlorambucil. The time to new treatment was 56.4 months in patients treated with obinutuzumab

plus chlorambucil vs 34.9 months with rituximab plus chlorambucil. The analysis identified no new safety signals, and no new late-onset toxicity was reported.

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A Phase Ib/II Study of Duvelisib in Combination With FCR (DFCR) for Frontline Therapy of Younger CLL Patients

A phase 1b/2 study evaluated the addition of duvelisib to fludarabine, cyclophosphamide, and rituximab (FCR) as frontline therapy for younger patients with CLL. Dr Matthew Davids presented the results at the EHA meeting.[1] Duvelisib is a dual phosphoinositide 3-kinase inhibitor that targets both the δ and γ isoforms. The trial enrolled 32 patients, whose median age was 55 years (range, 45-65 years). Duvelisib was administered at 25 mg once or twice daily for 1 week, with FCR added on day 8. Patients received up to 6 cycles of this regimen, followed by duvelisib maintenance for up to 2 years.

The phase 1 portion of the study identified the dose of duvelisib as 25 mg twice daily. Among the 29 patients who were evaluable for response after FCR, the ORR was 97%, which consisted of a complete response (CR)/incomplete CR (CRi) in 28% and a partial response in 69%. Approximately 76% of patients achieved MRD-negative bone marrow. The best rate of MRD negativity in the bone marrow in patients with at least 1 evaluation was 81%. The primary efficacy endpoint, the rate of CR/CRi with bone marrow MRD negativity, was 28%. Two patients with the 17p deletion achieved an MRD-positive partial response, and one achieved an MRD-positive complete response after 12 months of duvelisib maintenance. The 2-year rates of PFS and OS were both 97%. At a median follow-up of 21 months, there were 2 cases of progressive disease. One patient developed asymptomatic progression 6 months after the end of maintenance, and the other, who had a baseline 17p deletion and complex karyotype, developed Richter syndrome and died 29 months after enrolling in the study.

A median of 5.5 cycles of FCR were given, and 10 patients (31%) discontinued chemotherapy early based on toxicity. Nine patients (28%) required a reduction in the dose of duvelisib. Serious adverse events included transaminitis (grade 3 in 5 patients and grade 4 in 4 patients), febrile neutropenia (grade 3 in 7 patients), colitis (grade 2 in 1 patient and grade 3 in 1 patient), and pneumonia (occurring in 6 patients, including 3 cases of *Pneumocystis jirovecii* pneumonia despite planned prophylaxis).

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

The phase 3 MURANO trial (A Study to Evaluate the Benefit of Venetoclax Plus Rituximab Compared With Bendamustine Plus Rituximab in Participants With Relapsed or Refractory Chronic Lymphocytic Leukemia [CLL]) randomly assigned 389 patients with relapsed/refractory CLL to treatment with venetoclax plus rituximab for 6 months followed by single-agent venetoclax for up to 1.5 years or to bendamustine plus rituximab for 6 months.[1] After a median follow-up of 23.8 months, the rate of investigator-assessed PFS was significantly higher with venetoclax plus rituximab (32 events of progression or death in 194 patients) vs bendamustine plus rituximab (114 events in 195 patients). The 2-year rates of PFS were 84.9% and 36.3%, respectively ($P<.001$).

An analysis of the MURANO trial presented at the EHA meeting focused on MRD.[2] A high concordance of MRD in peripheral blood and bone marrow was seen with venetoclax plus rituximab in patients with paired samples (84%). A higher agreement in MRD negativity between bone marrow and peripheral blood was seen among patients treated with venetoclax plus rituximab (90%) vs bendamustine plus rituximab (30%). Rates of best MRD negativity (at any time during the study) were 84% with venetoclax plus rituximab vs 23% with bendamustine plus rituximab. Among 121 patients who achieved undetectable MRD at the end of treatment with venetoclax plus rituximab (n=194), 83% remained MRD negative and were progression-free at 13.8 months of follow-up. The rates of undetectable MRD were not impacted by the presence of 17p deletion, the immunoglobulin heavy chain variable (*IGHV*) mutation, or *TP53* mutations.

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

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]

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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)

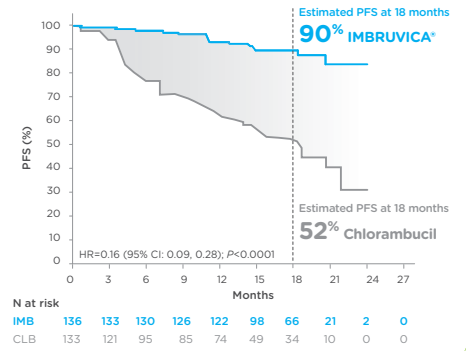
chlorambucil **84%**
(95% CI: 77, 90)

- 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.

References: 1. Data on file. Pharmacyclics LLC. **2.** IMBRUVICA® (ibrutinib) Prescribing Information. Pharmacyclics LLC 2018. **3.** Burger JA, Tedeschi A, Barr PM, et al; for the RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med.* 2015;373(25):2425-2437.

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(ibrutinib)
560, 420, 280, 140 mg tablets | 70 mg capsules

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

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

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

Body System Adverse Reaction	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	28	2	18	1
Arthralgia	17	1	7	0
Nervous system disorders				
Headache	14	1	6	0
Dizziness	11	0	5	0
Injury, poisoning and procedural complications				
Contusion	11	0	3	0
Eye disorders				
Vision blurred	10	0	3	0

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

Table 6: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE

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

RESONATE-2: Adverse reactions described below in Table 7 reflect exposure to IMBRUVICA with a median duration of 17.4 months. The median exposure to chlorambucil was 7.1 months in RESONATE-2.

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

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	42	4	17	0
Stomatitis*	14	1	4	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	36	4	20	0
Arthralgia	16	1	7	1
Muscle spasms	11	0	5	0
Eye disorders				
Dry eye	17	0	5	0
Lacrimation increased	13	0	6	0
Vision blurred	13	0	8	0
Visual acuity reduced	11	0	2	0

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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].*

IMBRUVICA® (ibrutinib) capsules

- *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].*

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