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

February 2017

Perspectives in Chronic Lymphocytic Leukemia: A Post-ASH Update

- Considerations in the Frontline Treatment of Chronic Lymphocytic Leukemia
- Highlights in Chronic Lymphocytic Leukemia From the 2016 American Society of Hematology Annual Meeting and Exposition • December 3-6, 2016 • San Diego, California

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Considerations in the Frontline Treatment of Chronic Lymphocytic Leukemia: A Post-ASH Update

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H&O When is frontline therapy initiated in chronic lymphocytic leukemia (CLL)?

SO The standard approach to CLL is still watch-and-wait. If patients are asymptomatic and have minimal disease, we do not intervene. This approach is based on the fact that approximately a third of patients with CLL will never need treatment. The idea behind watch-and-wait is to spare those patients who would never require therapy. We begin frontline treatment when patients develop problematic symptoms related to the disease, such as bulky lymph nodes, anemia, or low platelets.

My first choice for the management of patients with CLL is always to enroll them in a clinical trial. We cannot advance the science without enrolling patients in clinical trials.

H&O What are the approved frontline therapies?

SO The chemoimmunotherapy regimen fludarabine/cyclophosphamide/rituximab (Rituxan, Genentech/Biogen; FCR) is approved for these patients. The anti-CD20 monoclonal antibodies ofatumumab (Arzerra, Novartis) and obinutuzumab (Gazyva, Genentech) are each approved in combination with chlorambucil. Bendamustine (Treanda, Teva) was approved as a single agent for frontline treatment of CLL, based on a randomized trial that compared it with chlorambucil. However, bendamustine is most commonly used in combination with rituximab, which is known to improve the outcome of chemotherapy. The most recent approval in the frontline setting was for ibrutinib (Imbruvica, Pharmacyclics/Janssen).

H&O What data led to the approval of ibrutinib in the frontline setting?

SO Ibrutinib is the only targeted therapy available for frontline treatment. Approval of ibrutinib was based on a randomized trial comparing it with chlorambucil in older patients with CLL. Patients were older than 70 years or between the ages of 65 to 70 years and with a comorbidity that precluded them from receiving more substantive chemotherapy. The trial showed that ibrutinib was significantly better than chlorambucil. In fact, the progression-free survival achieved with ibrutinib was far superior to that seen in trials evaluating chlorambucil plus a monoclonal antibody.

Ibrutinib first received a frontline indication in patients with CLL who have the 17p deletion. This indication was followed by approval for all patients, regardless of 17p status. Interestingly, although the randomized trial was restricted to older patients, the approved indication is not. Theoretically, ibrutinib can be used as frontline treatment in any patient with CLL.

H&O How do the data for ibrutinib compare with those for chemoimmunotherapy?

SO The data for ibrutinib are clearly much more favorable than those for chlorambucil. Studies are now comparing ibrutinib vs FCR or bendamustine/rituximab in a younger, fit population. Two large, randomized trials from the Intergroup reached accrual in the past year. A 2-arm trial is comparing FCR vs ibrutinib and rituximab. A 3-arm trial is evaluating bendamustine and rituximab vs single-agent ibrutinib vs ibrutinib in combination with rituximab.

H&O How does the older treatment algorithm in CLL differ from your new treatment algorithm?

SO The older treatment algorithm from the German CLL study group had 3 categories. The "go-go" patients were fit, not elderly, and could tolerate a regimen like FCR. The "slow-go" patients were somewhat older or less fit, but still well enough to receive a treatment such as bendamustine/rituximab. A chlorambucil-based regimen might be used in patients who were less well. The "no-go" patients were elderly and had a poor performance status. These patients would receive palliative care, which most often consists of a single-agent antibody in the United States.

My new treatment algorithm also divides patients into 3 groups, but based on different criteria. The first group is older or less-fit patients, who I prefer to treat with ibrutinib irrespective of their mutation status. In younger, fit patients with the immunoglobulin variable region heavy chain (*IgVH*) mutation, I lean toward FCR. The final decision, however, would be made after discussion with the patient. In younger patients without the *IgVH* mutation, absent a clinical trial, I begin treatment with ibrutinib.

Historically, it made sense to base the selection of treatment on age and comorbidities because all of the treatments involved chemotherapy. Now that we have ibrutinib, which is so well-tolerated, that older algorithm has less relevance. For me, older patients are still grouped together. For younger patients, the biggest deciding factor is *IgVH* mutation status.

H&O Does ibrutinib improve outcome when added to chemotherapy?

SO The HELIOS trial (Ibrutinib Combined With Bendamustine and Rituximab Compared With Placebo, Bendamustine, and Rituximab for Previously Treated Chronic Lymphocytic Leukaemia or Small Lymphocytic Lymphoma) randomly assigned patients with relapsed CLL to receive bendamustine/rituximab chemotherapy alone vs bendamustine/rituximab plus ibrutinib. The addition of ibrutinib clearly improved outcomes. But what was not answered by this trial is whether bendamustine/rituximab plus ibrutinib is better than ibrutinib alone. The early data appeared comparable. The updated data, however, showed a significant rise in the complete response rate among patients who received bendamustine/rituximab and ibrutinib, much higher than what is seen with ibrutinib alone. The more recent data are starting to suggest that the combination may be better than ibrutinib alone. A benefit to ibrutinib, like many targeted therapies, is that it avoids the adverse events associated with chemotherapy, such as myelosuppression. Combining ibrutinib with chemotherapy may increase efficacy, at least in the minority of patients who are achieving a complete response, but at the expense of potentially increasing toxicity for all patients who receive it. The choice to add chemotherapy to ibrutinib in the relapsed setting is not an easy one.

H&O What adverse events are associated with ibrutinib?

SO In general, ibrutinib is very well-tolerated. The most common side effect is diarrhea, which is usually mild and self-limiting. There are some significant side effects. Atrial fibrillation occurs in 7% to 10% of patients. There is also an increased risk of bleeding caused by interference with the glycoprotein-mediated platelet-aggregation pathway. Most of the bleeding is minor, usually in the form of ecchymosis, but it can also be severe. The risk of bleeding is a particular concern in patients who are receiving an anticoagulant.

Arthralgia is another potential adverse event. It is generally not severe, but it can become problematic in the long-term. Ibrutinib is administered indefinitely, and continual pain, even low-grade, can be difficult for patients to bear. On the rare occasions when I have discontinued treatment with ibrutinib, the most common reason was arthralgia rather than diarrhea or any of the serious side effects.

H&O Do patients with lymphocytosis or baseline cytopenias require a reduced dose of ibrutinib?

SO Patients with lymphocytosis do not require a reduced dose of ibrutinib. Most patients with CLL can have lymphocyte counts in the hundreds of thousands and still be completely asymptomatic. Therefore, lymphocytosis is generally not a concern.

For patients with baseline cytopenias, I generally start with the full dose. Although there is some sporadic myelosuppression associated with ibrutinib, for the most part, ibrutinib is very good at reversing cytopenias. In contrast, we often reduce the starting dose of chemotherapy in patients with baseline cytopenias.

H&O What factors impact your choice of frontline treatment?

SO In older or less-fit patients, I use ibrutinib regardless of the 17p deletion status because it is clearly better than chlorambucil and much less toxic. The real question concerns younger, fit patients. Most physicians would

not treat a younger, more-fit patient with chlorambucil; they would select a better, somewhat more aggressive regimen. For example, FCR or bendamustine and rituximab are more myelosuppressive, but they also produce significantly longer progression-free survival than a chlorambucil-based regimen. I divide younger, fit patients into 2 groups based on their *IgVH* mutation status. Those with the *IgVH* mutation are candidates for FCR. This approach is supported by 3 articles published in the last year in Germany, Italy, and the United States. The American study, by Thompson and colleagues at MD Anderson, clearly showed very consistent results in terms of a significant plateau in the progression-free survival curve associated with FCR in patients with a mutated *IgVH* gene. The study from MD Anderson has the longest follow-up, because this regimen was developed there. At 12 to 16 years of follow-up, remission persisted in approximately 60% of patients with a mutated *IgVH* gene. The big question is whether to consider some of these patients cured. I would say yes. After this long-term follow-up, some of the patients remained negative for minimal residual disease. Even if they do ultimately relapse, it can still be considered a great outcome if patients remain in remission for 15 years after receiving 6 months of chemotherapy.

For my younger patients with the *IgVH* mutation, I discuss in detail the pros and cons of using chemotherapy. Chemotherapy is associated with more toxicity in the short-term, but it is administered for a limited duration. It can potentially lead to a very long remission, but it carries a small, but real, risk of late acute myeloid leukemia. Ibrutinib is easier to take than chemotherapy, but it is continuous therapy. Long-term data are starting to be reported. At the 2016 American Society of Hematology (ASH) meeting, I presented an analysis of 5-year data from a phase 2 trial of ibrutinib in patients with untreated or relapsed/refractory CLL or small lymphocytic leukemia. At 5 years, progression-free survival was 92% in the treatment-naive patients and 43% in the relapsed/refractory patients. Median progression-free survival was not reached in the treatment-naive cohort and 52 months in the relapsed/refractory cohort. Median overall survival was not reached for both cohorts. At 5 years, overall survival was 92% for the treatment-naive patients and 57% for the relapsed/refractory patients. Over time, the rates of complete response increased to 29% in the treatment-naive patients and to 10% in the relapsed/refractory patients.

We know that in relapsed patients who have received ibrutinib, absent a 17p deletion (which is uncommon in frontline patients), the median progression-free survival is 53 months. I would certainly think it would be longer in the frontline setting, but whether that will be 5 years or 10 years, or whether there will even be a plateau, are unknowns.

H&O Which agents would you consider for patients who are intolerant to ibrutinib?

SO Chemoimmunotherapy is always a possibility, and as far as small molecules, one approved combination is idelalisib (Zydelig, Gilead) and rituximab. The other option is venetoclax (Venclexta, AbbVie/Genentech), although the current indication is only for patients with the 17p deletion. There are, thus far, limited clinical trial data for patients who require treatment after ibrutinib. Mato and colleagues recently published an analysis of pooled data from several institutions evaluating patients who had failed or were intolerant to one kinase inhibitor, whether idelalisib or ibrutinib, and then went on to receive the other one. The response rate to the second inhibitor was approximately 50%. Among patients who were truly resistant to the first kinase inhibitor (as opposed to intolerant), the median progression-free survival was only 7 months. To me, shifting from one kinase inhibitor to another is not an attractive option. It might buy some time and serve as a bridge to transplant in a younger, fit patient. However, it is not a long-term solution.

Jones and colleagues are evaluating venetoclax in patients who have failed ibrutinib or idelalisib. Preliminary results show that the response rates are a bit higher than those achieved by crossing over to another tyrosine kinase inhibitor. Dr Jones presented updated data at the 2016 ASH meeting. Objective response was 70% among patients refractory to ibrutinib and 62% in patients refractory to idelalisib. After 11.8 months of follow-up, median duration of response, progression-free survival, and overall survival have not been reached. The estimated 12-month progression-free survival was 80%. As mentioned, however, venetoclax is approved only for patients with the 17p deletion.

Disclosure

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

Suggested Readings

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Highlights in Chronic Lymphocytic Leukemia From the 2016 American Society of Hematology Annual Meeting and Exposition

December 3-6, 2016 • San Diego, California

Commentary by Susan M. O'Brien, MD

Five-Year Experience With Single-Agent Ibrutinib in Patients With Previously Untreated and Relapsed/Refractory CLL/SLL

As a key cytoplasmic component of the B-cell receptor pathway, Bruton tyrosine kinase (BTK) plays a critical role in controlling proliferation, survival, and differentiation of B-lineage lymphoid cells.[1] Ibrutinib is an orally available small molecule that selectively binds to the cysteine 481 residue in the ATP binding domain of BTK, halting kinase activity and inhibiting signaling downstream from the B-cell receptor. Ibrutinib is approved by the US Food and Drug Administration (FDA) as a once-daily treatment for patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who are treatment-naive or who have relapsed/refractory disease.[2] Results from the phase 1b/2 study PCYC-1102 and the extension study PCYC-1103 demonstrated the efficacy and safety of ibrutinib monotherapy in patients with CLL/SLL, with a manageable safety profile that allows patients to continue on treatment for an extended duration.[3-6] Three-year follow-up data yielded an objective response rate (ORR) of 90% and a complete response (CR) rate of 7% in the overall study population while demonstrating durable remissions and improved quality of response over time.

Dr Susan O'Brien presented 5-year follow-up results from the PCYC-1102 and PCYC-1103 trials.[7] PCYC-1102 enrolled 31 treatment-naive CLL/SLL patients ages 65 years or older and 101 patients with relapsed or refractory CLL/SLL. The latter group included 24 patients with high-risk disease, defined as disease progression within 24 months of initiating chemoimmunotherapy. The immunoglobulin variable region heavy chain (*IgVH*) region was unmutated in 48% of the treatment-naive patients vs 78% of the relapsed/refractory patients. In the relapsed/refractory cohort, patients had received a median of 4 lines of prior therapy (range, 1-12).

The ORR in the entire study population of 132 patients was 89%, including a CR rate of 14%, a partial response (PR) rate of 71%, and a 3% rate of PRs with lymphocytosis. ORR was 87% in the treatment-naive patients vs 89% in the relapsed/refractory patients, including CRs of 29% vs 10%. Among the patients with relapsed/refractory disease, the ORR was 97% in patients with del(11q), 90% in patients with unmutated *IgVH*, 90% in those with complex karyotype, and 79% in those with del(17p), including CR rates of 9%, 9%, 7%, and 6%, respectively.

At 5 years, the PFS rates were 92% in the treatment-naive cohort vs 43% in the relapsed/refractory cohort (Figure 1). Five-year overall survival (OS) rates were 92% vs 57%, respectively. Among the patients with relapsed or refractory disease, patients with mutated *IgVH* vs unmutated *IgVH* demonstrated 5-year PFS rates of 53% vs 38% and 5-year OS rates of 66% vs 55%, respectively. However, the Kaplan-Meier curves for both outcomes showed considerable overlap. In the 34 patients with del(17p) at baseline, median PFS was 26 months, and median OS was 57 months. Five-year PFS was 19%, and 5-year OS was 32%. In the 28 patients with del(11q) at baseline, median PFS was 55 months, and median OS was not reached. Five-year PFS was 33%, and 5-year OS was 61%.

Among patients with a complex karyotype, 90% had relapsed or refractory disease. These patients had received a median of 4 prior therapies. PFS and OS were reduced in this group of patients. For patients without the complex karyotype, 5-year PFS was 69% and OS was 84%, vs 36% and 46% in patients with a complex karyotype. Five-year survival decreased with the number of prior therapies. Five-year PFS was 92% in treatment-naive patients vs 38% in those treated with 4 or more prior therapies. Five-year OS was 92% vs 47%, respectively. Multivariate analysis revealed del(17p) as the only significant predictor of PFS and OS.

Ibrutinib therapy was generally well-tolerated. The rate of adverse events (AEs) of grade 3 or higher decreased over time. In the entire study population, onset of treatment-emergent AEs of grade 3 or greater was highest in the first year of treatment and decreased during subsequent years. The most common AEs of grade 3 or higher were hypertension (26%) and pneumonia (22%). The most common nonhematologic AEs were pneumonia and hypertension in previously treated patients vs hypertension and diarrhea in treatment-naive patients.

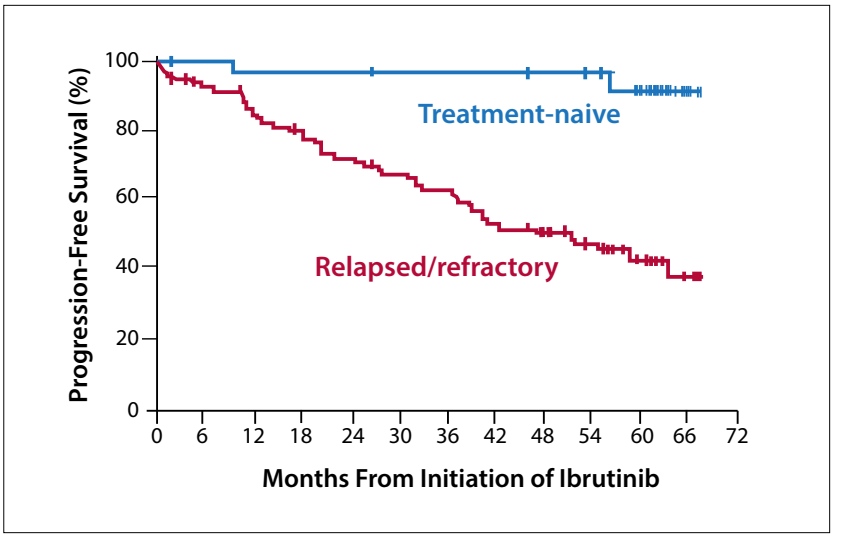

Figure 1. Five-year progression-free survival with single-agent ibrutinib. Adapted from O'Brien SM et al. ASH abstract 233. *Blood*. 2016;128 (suppl 22).[7]

For the treatment-naive patients vs those with relapsed/refractory disease, the median time on study was 62 months vs 49 months (range, 1-67 months). In the 2 cohorts, 65% vs 30% of patients remained on therapy, respectively. Discontinuation of study treatment occurred in 20% of patients owing to an AE and in 26% of patients owing to disease progression. The predominant reasons for discontinuing therapy differed in the 2 patient groups, with progressive disease accounting for 3% in the treatment-naive cohort vs 33% in the relapsed/refractory cohort. AEs accounted for 19% vs 21% of discontinuations, respectively.

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Commentary: These data are important because they represent the longest follow-up available for ibrutinib. The analysis was based on data from the original phase 1b/2 study, which included 2 cohorts: 31 previously untreated patients ages 65 years or older, and 101 patients with relapsed/refractory disease, who had received a median of 4 prior therapies. The relapsed/refractory patients were therefore heavily pretreated. The follow-up analysis shows a best response of 89% for both groups together. In the treatment-naive patients, the CR rate was 29%, which reflects a slight improvement from the 26% that was reported for this group in 2015.

This 5-year analysis provided several new findings concerning PFS. In previous studies of ibrutinib, the median PFS had not been reached for all patients. The only subgroup with a median PFS had been relapsed/refractory patients with del(17p), in whom it was 26 months. A new finding from the 5-year data is a median PFS of 52 months in the overall relapsed/refractory setting. The median PFS for patients with the del(11q) is 55 months. Among patients who do not have either of these high-risk abnormalities—del(17p) or del(11q)—the median PFS has still not been reached, which is quite striking at 5 years, especially given that the median number of prior regimens in these patients was 4. Median overall survival was reached in only one group of patients, relapsed/refractory patients with del(17p), in whom it was 57 months.

Among treatment-naive patients, the survival curve had been very similar for years. There had been 1 early drop in the curve, which reflected a patient who progressed and died within the first year of the study. The 5-year analysis shows another late drop in the curve just before 5 years, which represents a patient in remission who died of a secondary malignancy. Among the original 31 treatment-naive patients, only one-third have come off study. Only 1 patient has progressed. The 5-year PFS in the treatment-naive cohort is 96%. These data are very striking.

A multivariate analysis of the relapsed/refractory patients showed that the relevant predictor was the del(17p), which shortened both PFS and overall survival.

Updated Efficacy and Safety From the Phase 3 RESONATE-2 Study: Ibrutinib as a First-Line Treatment Option in Patients 65 Years and Older With CLL/SLL

Dr Paul Barr presented updated efficacy and safety data from the phase 3 RESONATE-2 trial, which evaluated first-line ibrutinib vs chlorambucil in elderly patients with CLL/SLL.[1,2] The study enrolled 269 patients ages 65 years or older with treatment-naive CLL/SLL who were not candidates for fludarabine-based therapy. Patients with del(17p) were ineligible. After stratification for performance status and disease stage, patients were randomly assigned to receive ibrutinib at 420 mg once daily until disease progression or unacceptable toxicity, or chlorambucil at 0.5 mg/kg up to a maximum of 0.8 mg/kg on days 1 and 15 in 28-day cycles for a maximum of 12 cycles until disease progression, unacceptable toxicity, or lack of efficacy. Patients with progressive disease were enrolled in a separate extension study (PCYC-1116-CA) with treatment based on investigator choice. The updated analysis of data from 269 patients therefore included 55 patients from the chlorambucil arm who experienced disease progression and underwent subsequent treatment with ibrutinib.

After 29 months of follow-up, the PFS was significantly improved in patients treated with ibrutinib (89 months vs 34 months; hazard ratio [HR], 0.121; 95% CI, 0.074-0.198; *P*<.0001). In the subgroup of patients with del(11q), ibrutinib treatment was associated with a 99% reduction in the risk of progression or death compared with chlorambucil (HR, 0.014; 95% CI, 0.002-0.108; *P*<.001; Figure 2). In patients without del(11q), ibrutinib conferred an 82% reduction in the risk of progression or death vs chlorambucil (HR, 0.180; 95% CI, 0.106-0.303; *P*<.0001). Ibrutinib treatment was associated with a 92% risk reduction in patients with unmutated *IgVH* (*P*<.0001) and an 83% risk reduction in patients with mutated *IgVH* (*P*<.001).

For the entire study population, the 24-month OS rate was 95% with ibrutinib vs 84% with chlorambucil. These results confirmed the original findings that yielded an estimated 24-month PFS of 98% with ibrutinib vs 85% with chlorambucil, and a risk reduction of 84% with ibrutinib compared with chlorambucil (*P*=.001).[1] The 136 patients in the ibrutinib arm had an ORR of 92%, including 18% CRs or CRs with incomplete blood count recovery; 1% nodular PRs, indicating persistent nodules in the bone marrow; 71% PRs; and 1% PRs with lymphocytosis. CR rates improved with continued ibrutinib treatment, increasing from 7% at 12 months of follow-up, to 15% at 24 months, to 18% at 29 months. The ORR was 100% in patients with del(11q) vs 90% in those without, and 95% in patients with unmutated *IgVH* vs 88% in those without. With ibrutinib treatment, sustained improvement in the hemoglobin level was achieved in 90% of anemic patients vs 45% with chlorambucil (*P*<.0001). In patients with thrombocytopenia, a sustained improvement in platelet levels was achieved in 80% of those treated with ibrutinib vs 46% of those treated with chlorambucil (*P*=.0055).

The median duration of ibrutinib treatment was 29 months (range, 1-36 months), and 79% of patients were continuing treatment at the time the study was reported. Among the 21% of patients who discontinued treatment, the reasons included AEs (12%), death (4%), and disease progression (3%). In patients treated with ibrutinib, the most common AEs of any grade included diarrhea (45%) and fatigue (33%). Most treatment-emergent AEs of grade 3 or greater occurred during the first year of treatment. However, atrial fibrillation of grade 3 or greater was reported in 1% of patients during the first year of treatment with ibrutinib and in 4% of patients during the third year of treatment. Rates of dose reduction and discontinuation owing to an AE also decreased over time.

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Commentary: Dr Paul Barr presented updated efficacy and safety data from the phase 3 RESONATE trial. This randomized trial led to the approval of ibrutinib as frontline therapy in the United States. Patients were randomly assigned to receive the standard dose of ibrutinib, 420 mg daily, or chlorambucil. Patients were older than 70 years, or ages 65 to 70 years with comorbidities; their median age was 72 years. Chlorambucil was a reasonable comparator arm in this older population. The results, as reported in 2015 in the *New England Journal of Medicine* by Burger and colleagues, showed that PFS was dramatically longer with ibrutinib than with chlorambucil. The updated data presented by Dr Barr continued to show a dramatic difference. Median PFS was not yet reached with ibrutinib vs 15 months with chlorambucil. The 24-month PFS was 89% with ibrutinib. Even though crossover was allowed on this trial, there was still a survival advantage in the ibrutinib arm.

A subset analysis evaluated the impact of del(11q) and mutated vs unmutated *IgVH*. The relevance of this analysis is not focused on response. It is known that with chemotherapy-based regimens, response rates are similar regardless of whether patients have del(11q) or unmutated *IgVH*. Progression-free survival, however, is significantly shorter in patients with del(11q) or unmutated *IgVH*. This difference was seen in

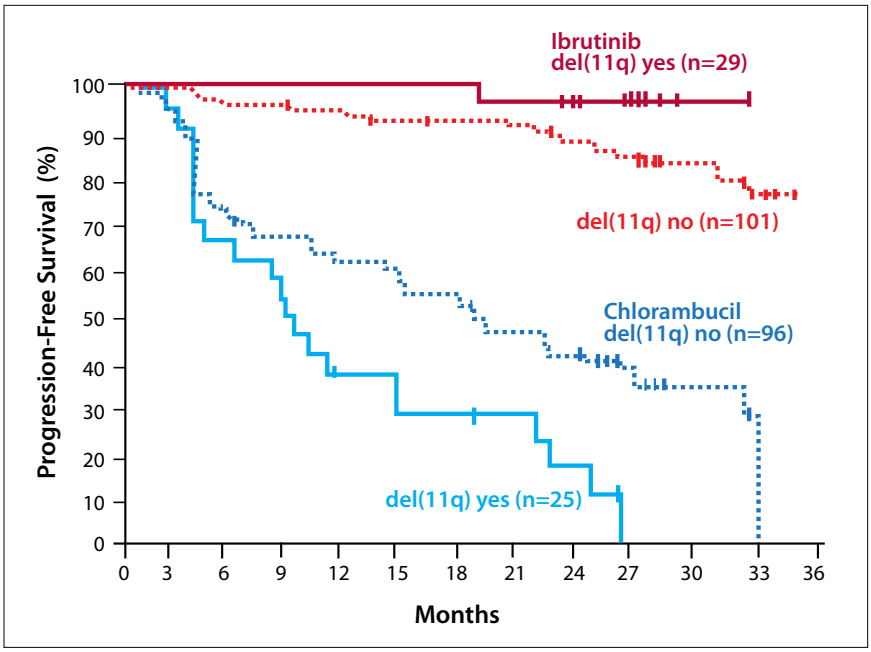

Figure 2. The estimated 24-month progression-free survival according to deletion 11q status in the RESONATE-2 trial. RESONATE-2, PCYC-1115; A Multicenter, Open-Label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib Versus Chlorambucil in Patients 65 Years or Older With Treatment-Naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma. Adapted from Barr PM et al. ASH abstract 234. *Blood.* 2016;128(suppl 22).[2]

the chlorambucil arm in this study. Among patients treated with chlorambucil, those with the del(11q) had a shorter PFS than those without del(11q). Similarly, patients with unmutated *IgVH* had a shorter PFS than those without the mutation when treated with chlorambucil. These differences were not seen in the ibrutinib cohort. The entire ibrutinib cohort had a high response rate of 92%. In addition, the CR rate increased from 7% at 1 year to 18% at 2 years. Based on the phase 2 data, the CR rate could potentially improve with time.

The AEs reported for ibrutinib were as expected. Even though the population was older, 16 patients (approximately 12%) discontinued treatment owing to AEs. It is good to know that the longer follow-up is showing robust data with ibrutinib in the frontline setting.

When interpreting these results, some physicians might mention that the current standard of care is to use chlorambucil plus an antibody, rather than chlorambucil alone. However, the median PFS was only 26 months in the randomized trial that led the FDA to approve obinutuzumab with chlorambucil as a frontline regimen, which is far shorter than that achieved with ibrutinib. Therefore, the results of RESONATE-2 are not negated by the use of chlorambucil without an antibody.

Twice Daily Dosing With BGB-3111 Achieves Complete and Continuous BTK Occupancy in Lymph Nodes, and Is Associated With Durable Responses in Patients With CLL/SLL

BGB-3111 is an irreversible, highly selective, second-generation inhibitor of BTK, with high oral bioavailability and exposure levels.[1] Dr Constantine Tam presented results from the first-in-human clinical trial of BGB-3111.[2] The phase 1 trial included a dose-escalation component followed by expansion. Patients with relapsed or refractory B-cell malignancies were enrolled into cohorts for treatment with BGB-3111 dosed once daily at 40 mg, 80 mg, 160 mg, or 320 mg or dosed twice daily at 160 mg, using a modified 3+3 dose escalation design and disease-specific expansion cohorts. Patients with relapsed or refractory B-cell malignancies were assigned to BGB-3111 at 160 mg twice daily or 320 mg once daily for pharmacodynamic assessments. In order to assess BTK occupancy in the lymph nodes at the time of trough drug exposure, paired lymph node biopsies were taken from these patients at baseline and prior to dosing on day 3. BGB-3111 exposure increased in a dose-dependent manner from 40 mg to 320 mg daily. The maximum concentration and area under the curve of BGB-3111 in patients treated with 80 mg daily were similar to those observed in patients treated with ibrutinib dosed at 560 mg daily.[3] Free drug exposure from BGB-3111 (40 mg daily) was similar to that observed from ibrutinib (560 mg daily). In cohorts receiving the 2 highest doses of BGB-3111, drug exposure levels were approximately 8-fold higher compared with ibrutinib (560 mg daily). Complete BTK occupancy was observed in peripheral blood mononuclear cells in the lowest dose cohort. Twenty patients with relapsed or refractory B-cell malignancies were enrolled in the pharmacodynamic assessment cohorts. The median trough BTK occupancy in the lymph nodes was 100% in patients receiving BGB-3111 at 160 mg twice daily vs 94% in those receiving 320 mg once daily (P=.002), and the proportion of patients with greater than 90% trough occupancy at all time points was 94% vs 58%.

Among the 63 enrolled patients with CLL/SLL, 17 had less than 12 weeks of follow-up and were therefore

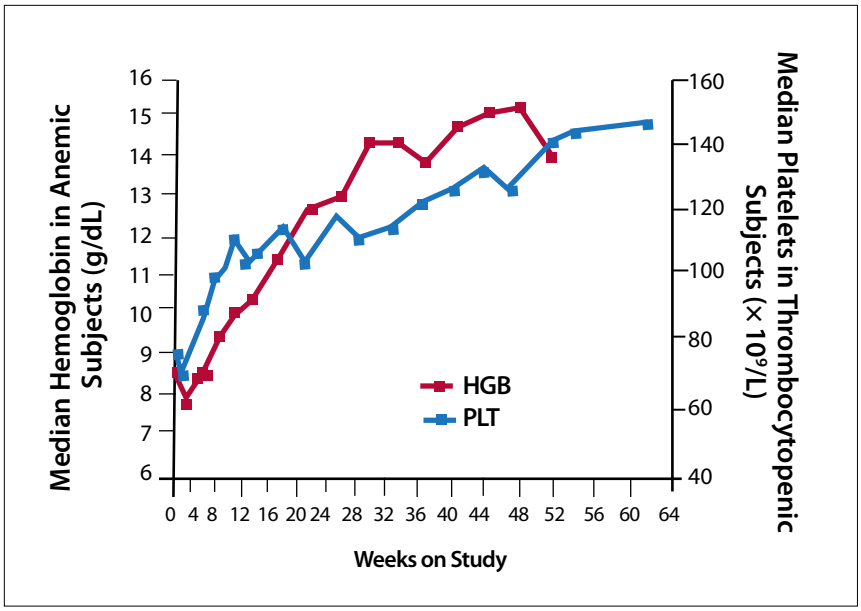

Figure 3. Median hemoglobin levels in patients with anemia treated with the BTK inhibitor BGB-3111. Levels increased over time, from approximately 9 g/dL at baseline to approximately 15 g/dL by week 60. BTK, Bruton tyrosine kinase; PLT, platelet; HGB, hemoglobin. Adapted from Tam CS et al. ASH abstract 642. *Blood.* 2016;128(suppl 22).[2]

not included in the analysis. One patient discontinued treatment owing to an AE. Sixty-two patients remained on the study with no evidence of progressive disease.

The ORR was 96%, including 67% PRs and 28% PRs with lymphocytosis. In the 17 patients with del(17p) and/or del(11q), the ORR was 100%. The overall study group showed a dramatic reduction in lymph node burden by the first scan, which was administered 3 months after treatment was initiated. The median absolute lymph node count peaked at approximately 8 weeks after initiating treatment and returned to baseline after approximately 3 to 4 months. In anemic patients, median hemoglobin levels increased over time (Figure 3). Similarly, in patients with a platelet count of less than 100,000/µL at baseline, the median platelet count improved over time.

The most common AE of any grade was bleeding (48%), followed by upper respiratory tract infection (33%) and fatigue (28%). Sixteen patients (35%) had at least 1 AE of grade 3 or greater, 10 patients (22%) had at least 1 serious AE, and 1 patient (2%) discontinued treatment owing to an AE. In the current analysis of 46 patients, 9 patients (20%) experienced diarrhea; all episodes were grade 1 or 2 in severity.

References

1. Wu J, Liu C, Tsui ST, Liu D. Second-generation inhibitors of Bruton tyrosine kinase. *J Hematol Oncol.* 2016;9(1):80.

2. Tam CS, Opat S, Cull G, et al. Twice daily dosing with the highly specific BTK inhibitor, BGB-3111, achieves complete and continuous BTK occupancy in lymph nodes, and is associated with durable responses in patients (pts) with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma [ASH abstract 642]. *Blood.* 2016;128(suppl 22).

3. Advani RH, Buggy JJ, Sharman JP, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. *J Clin Oncol.* 2013;31(1):88-94.

Commentary: BGB-3111, a new oral agent, is very potent against BTK and has higher IC_{50} for some of the other kinases that ibrutinib targets. For example, it has a higher IC_{50} for the epidermal growth factor receptor, which could theoretically translate into less likelihood of rash or diarrhea compared with that seen with other BTK inhibitors. It has a much higher IC_{50} for IL2-inducible T-cell kinase than ibrutinib, so potentially it will not interfere with the activities of antibodies. The IC_{50} on TEC, however, appears similar between BGB-3111 and ibrutinib, which is important because TEC may be responsible for the atrial fibrillation and bleeding that can be seen with ibrutinib. It would be ideal to have a BTK inhibitor that does not target TEC, such as the novel agent acalabrutinib.

Dr Constantine Tam presented interim results of an ongoing phase 1 study of BGB-3111. The study evaluated a variety of different doses ranging from 40 mg daily to 160 twice daily. The study showed that higher plasma levels are achieved with higher doses of BGB-3111, and all doses were associated with activity. An interesting aspect of this study is that it looked within the lymph nodes to determine BTK occupancy. The optimal dose of ibrutinib, 420 mg daily, was selected because it resulted in almost complete occupancy of BTK in the peripheral blood mononuclear cells. The lymph nodes, however, were not evaluated when determining this dose. This information might be relevant because there are some data suggesting that patients with bulky adenopathy do not have as sustained a PFS with ibrutinib. In the study of BGB-3111, the lymph nodes had a sustained occupancy above 90% at doses of 160 twice daily or 320 daily.

The most common side effects with BGB-3111 were petechiae, purpura, and contusion, suggesting that the low IC_{50} for TEC may lead to minor bleeding, similar to that seen with ibrutinib. Diarrhea, however, was much less frequent

than with ibrutinib, occurring in only 20% of patients. There was 1 episode of serious hemorrhage, and 1 episode of atrial fibrillation. The response rate was 96%, which is quite good, especially considering that the patients in the study had relapsed/refractory disease. These patients also showed improvements in cytopenias. Among the relapsed/refractory patients, the median number of prior regimens was 2, so they were less heavily pretreated than patients in the ibrutinib trials previously discussed. No patient has yet developed progressive disease, and there have been no reports of Richter's transformation. These data are encouraging.

Idelalisib in Combination With Bendamustine and Rituximab in Patients With Relapsed/Refractory CLL

Dr Andrew Zelenetz presented updated results from the randomized, placebo-controlled, double-blind, phase 3 GS-US-312-0115 trial, which examined the addition of idelalisib to bendamustine plus rituximab in patients with relapsed/refractory CLL.[1,2] After a median of 21 months of follow-up, more patients remained on study in the idelalisib arm (34%) than the placebo arm (11%), and 31% vs 0 patients continued on study treatment, respectively. After the initial prespecified interim analysis, patients in the placebo arm were informed and discontinued treatment. The updated analysis demonstrated a significant improvement in survival with idelalisib, with a median OS of not reached vs 40.6 months for placebo (HR, 0.67; 95% CI, 0.47-0.96; *P*=.04). PFS based on independent review was also significantly improved with idelalisib (23.0 months vs 11.1 months; HR, 0.31; 95% CI, 0.24-0.41; *P*<.0001). In the subgroup of patients without del(17p) or *TP53* mutation, the median PFS was 27.8 months in the idelalisib arm vs 11.2 months in the placebo arm (HR, 0.25; 95% CI, 0.17-0.35; *P*<.001).

An AE of grade 3 or greater occurred in 95% of the idelalisib arm vs 78% of the placebo arm, and 71% vs 45% of patients experienced a serious AE. AEs leading to dose reduction occurred in 16% vs 6% of patients, AEs leading to discontinuation occurred in 33% vs 15%, and deaths occurred in 12% vs 9% of patients in the idelalisib vs placebo arms, respectively. Grade 3/4 AEs of interest that occurred more often in the idelalisib arm included neutropenia (60% vs 47%) and febrile neutropenia (24% vs 6%). The most common serious AEs in the idelalisib vs placebo arms were febrile neutropenia (21% vs 5%), pneumonia (17% vs 8%), and pyrexia (12% vs 5%).

Infection with *Pneumocystis jirovecii* pneumonia (PJP) was observed in 4 patients (2%) in the idelalisib arm vs 0 patients in the placebo arm, and cytomegalovirus (CMV) infection was observed in 13 patients (6%) vs 3 (1%), respectively. The only death from these infections occurred in a patient with CMV infection in the placebo arm. The risk of CMV infection decreased over time in both arms. Grade 3/4 alanine or aspartate transaminase elevations were more common in patients treated with idelalisib (21% vs 3% and 16% vs 3%, respectively).

References

1. Zelenetz AD, Brown JR, Delgado J, et al. Updated analysis of overall survival in randomized phase III study of idelalisib in combination with bendamustine and rituximab in patients with relapsed/refractory CLL [ASH abstract 231]. *Blood*. 2016;128(suppl 22).
2. Zelenetz AD, Robak T, Coiffier B, et al. Idelalisib plus bendamustine and rituximab (BR) is superior to BR alone in patients with relapsed/refractory chronic lymphocytic leukemia: results of a phase 3 randomized double-blind placebo-controlled study [ASH abstract LBA-5]. *Blood*. 2015;126(suppl 23).

Commentary: Dr Andrew Zelenetz presented an updated analysis of overall survival in a randomized, placebo-controlled, phase 3 trial of idelalisib added to bendamustine and rituximab in patients with relapsed/refractory CLL. Previous data for this study were presented at the 2015 ASH meeting (abstract LBA-5). The new analysis is based on a longer median follow-up of 21 months. This study shows a survival benefit when idelalisib is added to bendamustine and rituximab. Median overall survival was 40.6 months in the placebo arm—patients who received bendamustine/rituximab without idelalisib—and was not reached in the idelalisib plus bendamustine/rituximab arm. The difference was statistically significant. This survival advantage is a new finding. The PFS continues to be very different, at a median of 11 months with placebo vs 23 months with idelalisib. This improvement was seen in basically all subgroups. An analysis that removed the patients with 17p or *TP53* mutation showed that the median PFS did not change in the placebo arm, but increased to up to 28 months in the idelalisib arm.

More febrile neutropenia was seen with idelalisib than placebo. In the idelalisib group, 24% of patients experienced grade 3 or higher febrile neutropenia vs only 6% in the placebo group. There was more transaminitis in the idelalisib arm, as is seen in single-agent use. There was also more pneumonia among patients who received idelalisib, at 17% vs 8%. Four cases of PJP occurred in the idelalisib plus bendamustine/rituximab arm, vs none in the placebo plus bendamustine/rituximab arm. There were 13 cases of CMV in the idelalisib arm and only 3 in the placebo arm. In March 2016, the FDA closed the frontline trials of idelalisib based on a higher incidence of infection. Most of that patient population received bendamustine/rituximab plus idelalisib as initial therapy. Thus, it was the same regimen in the frontline setting that led to the closing of the frontline studies. Similarly, in the current analysis, there were more cases of PJP and CMV, but the majority of the infections were not atypical. In addition, despite these infections, there was still a significant survival advantage in favor of the idelalisib plus bendamustine/rituximab arm.

#1 PRESCRIBED ORAL CLL THERAPY.*
MORE THAN 20,000 PATIENTS TREATED SINCE APPROVAL[1†]

MAKE IMBRUVICA® YOUR FIRST STEP

Approved in frontline CLL with or without 17p deletion[2]

CLL
SLL

IMBRUVICA® is a once-daily oral therapy indicated for:

- 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 postsurgery depending upon the type of surgery and the risk of bleeding.

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

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

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

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

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

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

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

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RESONATE™-2 FRONTLINE DATA

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

EXTENDED OVERALL SURVIVAL

IMBRUVICA® significantly extended OS vs chlorambucil[2]

Statistically significant reduction in risk of death[2]

56%

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

41% of patients crossed over to IMBRUVICA®

Estimated survival rates at 24 months

95% IMBRUVICA®
(95% CI: 89, 97)

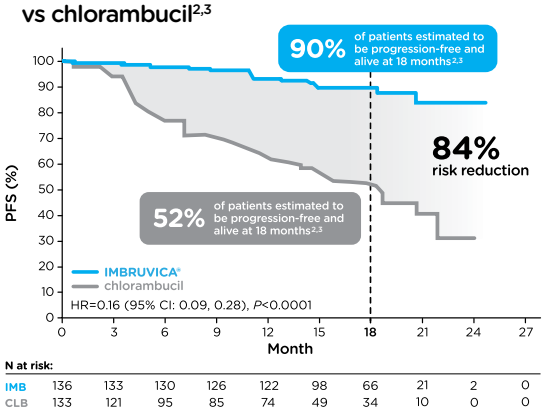
84% chlorambucil
(95% CI: 77, 90)

SECONDARY ENDPOINT: OS

- Median follow-up was 28 months[2]

PROLONGED PROGRESSION-FREE SURVIVAL

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



PRIMARY ENDPOINT: PFS

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

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

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

drug, the patient should be apprised of the potential hazard to a fetus. Advise men to avoid fathering a child during the same time period.

ADVERSE REACTIONS

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

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

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

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

DRUG INTERACTIONS

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

CYP3A Inducers - Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

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

Please see the Brief Summary on the following pages.

*Based on market share 2016 July YTD data from IMS.
†Based on IMS data February 2014 to date.

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 leukemia.

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

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imbruvica®
(ibrutinib) 140mg capsules

Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)

IMBRUVICA® (ibrutinib) capsules, for oral use

See package insert for Full Prescribing Information

INDICATIONS AND USAGE

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

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

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

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

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

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

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

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

The mechanism for the bleeding events is not well understood.

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

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

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

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

Monitor complete blood counts monthly.

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

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

* Based on laboratory measurements and adverse reactions

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

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

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

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

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

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

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

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

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

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

* One patient death due to histiocytic sarcoma.

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

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

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

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

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

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

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

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

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

* Based on laboratory measurements per IWCLL criteria.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

* Based on laboratory measurements.

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

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

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

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

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

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

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

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

* Based on laboratory measurements.

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

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

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

Hepatobiliary disorders: hepatic failure

Respiratory disorders: interstitial lung disease

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

Immune system disorders: anaphylactic shock, angioedema, urticaria

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

DRUG INTERACTIONS

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

Contraception:

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

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

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

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

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

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

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

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

PATIENT COUNSELING INFORMATION

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

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

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-02461

Notes


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