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Frontline Management of Chronic Lymphocytic Leukemia

- How I Treat Chronic Lymphocytic Leukemia: An Expert Perspective on Frontline Management
- Highlights from:

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How I Treat Chronic Lymphocytic Leukemia: An Expert Perspective on Frontline Management

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H&O When is frontline treatment initiated in patients with CLL?

RF The current standard of care for patients with chronic lymphocytic leukemia (CLL) is a strategy of "watch and wait." The data for this paradigm were generated in the 1970s and 1980s, when far less information on prognosis was available. With a watch-and-wait strategy, treatment is not initiated until patients meet criteria established by the International Workshop on Chronic Lymphocytic Leukemia (iwCLL). The most common indications for treatment are rapid lymphocyte doubling time, bone marrow failure as manifested by worsening anemia and thrombocytopenia, symptomatic lymphadenopathy or splenomegaly, and B symptoms. The idea behind watch and wait is to defer therapy until signs suggest that the CLL is active. Many physicians and patients attempt to delay therapy for as long as possible, with the idea that every day therapy is delayed translates into an additional day of survival. There are no data suggesting an advantage to delaying therapy once disease is active. The idea behind watch and wait is to initiate therapy once the CLL shows signs of becoming active, and that would be once the iwCLL criteria are met.

This strategy may change in the future, with the identification of prognostic markers that might suggest a poor outcome. For example, patients with risk factors for developing Richter's transformation (eg, the *NOTCH1* mutation, stereotyped V genes) or who have a 17p deletion (which can lead to mutations that make ibrutinib less effective), might benefit from early therapy before these secondary changes occur.

H&O What are the treatment goals?

RF The most important goals are progression-free survival (PFS) and overall survival. With many novel agents, PFS translates into an improvement in overall survival primarily because it is possible to induce very deep responses without cumulative toxicities.

An equally important goal of therapy is to avoid long-term toxicities. CLL-related symptoms resolve rapidly with novel therapies. Therefore, there is no benefit from getting patients into a deep remission quickly. What is most important is to ensure that treatment does not cause damage or toxicities that will impact the patient's long-term survivability. Chemotherapy can impact function of the bone marrow and the immune system, leading to cytopenias, myelodysplastic syndrome or acute leukemia, or recurrent, life-threatening infections.

H&O Does marrow damage or marrow sparing impact your choice of frontline treatment?

RF Very much so. With the array of novel agents for CLL available, we should start to see a significant prolongation of survival. We therefore must keep a very close eye on the toxicities that might emerge much later on, such as bone marrow failure and secondary malignancies. Chemotherapy dramatically increases the risk of these toxicities.

H&O Does your frontline treatment algorithm still include chemoimmunotherapy?

RF I do not use chemoimmunotherapy under any circumstances in any patients. For me, the long-term risks of bone marrow failure and secondary cancers outweigh any benefits with this treatment.

My first choice of frontline therapy for most patients with CLL is ibrutinib as a single agent. For patients with the 11q or 17p deletions, there is currently a clinical trial of ibrutinib plus venetoclax, which should be very promising. My hope is that for patients who are at risk of not doing well long-term with ibrutinib, it will be possible to use this combination.

Patients whose condition is not suitable for treatment

with ibrutinib, such as those with bleeding diathesis or at risk of atrial fibrillation, I treat with either obinutuzumab or venetoclax as frontline therapy.

The long-term efficacy of ibrutinib and the risk of bleeding and atrial fibrillation are the most important components of the decision-making algorithm when choosing frontline therapy. Immunoglobulin gene mutational status does not enter into the algorithm at all because it does not impact long-term outcomes with ibrutinib.

H&O What are the trial data supporting the use of ibrutinib in the frontline setting?

RF The pivotal study that led to the approval of ibrutinib in frontline CLL for all patients was the phase 3 RESONATE-2 trial (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). This study compared ibrutinib vs chlorambucil in patients who were older than 65 years. The results, published in 2015, showed an estimated 24-month PFS of 98% with ibrutinib vs 85% with chlorambucil, and a risk reduction of 84% with ibrutinib compared with chlorambucil. Subsequent analyses of the RESONATE-2 data continue to show improvements in PFS, overall survival, and overall response.

The earlier phase 1b/2 PCYC-1102 study evaluated ibrutinib in patients with CLL. The study enrolled patients with relapsed/refractory disease and patients with treatment-naive disease who were ages 65 years or older. There are now 5 years of follow-up data for the cohort of treatment-naive patients, and these data are important in that they demonstrate the long-term safety, tolerability, and durability of ibrutinib treatment. Data from the relapsed/refractory population of patients who had deletion 17p and were treated in the RESONATE study provided the impetus for the US Food and Drug Administration to approve ibrutinib in all patients with the 17p deletion, regardless of their line of therapy. Although the data generated did not include treatment-naive patients with the 17p deletion, this population was included in the initial approval.

H&O What are the long-term data with ibrutinib?

RF Among 31 treatment-naive patients who received ibrutinib in the PCYC-1102 trial, only 2 have developed progressive disease. The median PFS for the treatment-naive patients was not reached, with an estimated PFS at 60 months of 92%. Both of the patients who progressed had the 17p deletion. Thus, ibrutinib has been extremely effective and well-tolerated in treatment-naive patients, except for those with the 17p deletion.

In the relapsed/refractory population, which consisted of 101 patients, the median PFS was 52 months overall. The 2 most important predictors of long-term outcome are factors identified during interphase fluorescence in situ hybridization (FISH) and the complex karyotype. The median PFS was 26 months for patients with deletion 17p, 55 months for patients with deletion 11q, and not reached for patients without deletion 17p, deletion 11q, or trisomy 12. Patients with deletion 13q do particularly well, with PFS rates of approximately 90% to 95% at 5 years. Therefore, patients with deletion 17p, deletion 11q, or trisomy 12 might benefit from additional therapies in order to improve their response durability.

H&O What therapies have you used successfully after frontline ibrutinib?

RF A beneficial aspect to ibrutinib is that it does not induce genomic instability. When patients progress on ibrutinib, they tend to still be sensitive to other treatment options. My choice after ibrutinib is venetoclax. Other therapies used successfully include idelalisib, obinutuzumab, and chimeric antigen receptor (CAR) T-cell therapy.

H&O Do data support the use of ibrutinib in combination with other agents?

RF There must be a good reason to use ibrutinib in combination with another agent. Many of the abstracts presented at the recent meetings looked at novel combinations with chemoimmunotherapy plus ibrutinib. A patient with deletion 13q, trisomy 12, or a normal cytogenetic profile has nothing to gain from the addition of chemoimmunotherapy to ibrutinib. On the other hand, patients with the 11q or 17p deletions have the potential to gain from combination therapy, given the need to improve the PFS. For these patients, my first choice would be venetoclax plus ibrutinib. Ibrutinib and venetoclax are synergistic in vitro, making the venetoclax more effective, and a lead-in of single-agent ibrutinib will allow for tumor debulking, which would lessen the risk of tumor lysis from venetoclax. Additionally, the rapid response during induction with venetoclax may help prevent any additional tumor clonal evolution during that time, and ibrutinib can induce a deep response, hopefully avoiding Richter's transformation and the development of resistance.

H&O How do you manage the adverse events seen with ibrutinib?

RF The incidence of toxicities with ibrutinib appears to diminish over time. The most common toxicities include bleeding, diarrhea, hypertension, atrial fibrillation, and arthralgias. The bleeding, diarrhea, and arthralgias tend to occur early in the course of treatment. In contrast, atrial fibrillation is seen most often during the first 12 months of therapy, and rarely beyond 2 years. The incidence of hypertension increases over time, reaching approximately 15% at 5 years. Importantly, the incidence of infections diminishes over time, with fewer infections between years 2 and 3, compared with years 1 to 2 and 2 to 3.

The increased bleeding is grade 1 and 2 only, and patients do not require any additional management. For some patients who are small in size and who develop excessive bruising, a dose reduction to 280 mg daily might help. I try to avoid using ibrutinib in combination with anticoagulation, instead opting mostly for venetoclax or obinutuzumab.

The chance of diarrhea can be minimized if patients take ibrutinib at bedtime. If patients have an empty stomach for the 6 to 8 hours after they dose (eg, while asleep), they should be able to eat with minimal signs of diarrhea. I have found that this strategy reduces the incidence of diarrhea to as low as 5%. The diarrhea, when it occurs, ameliorates over time.

The hypertension that occurs with ibrutinib is primarily grade 1 or 2 and is easily managed with antihypertensive therapy.

Atrial fibrillation is more problematic. I always discontinue ibrutinib in these patients, and, in many cases, the patient reverts to normal sinus rhythm. That makes it easier to anticoagulate a patient, if necessary based on his or her cardiac status. When patients are back in normal sinus rhythm and no longer require anticoagulation, ibrutinib can be reinitiated. The addition of a β-blocker may provide some measure of protection against recurrence of atrial fibrillation.

When patients develop arthralgias, I usually administer a low dose of prednisone for approximately 2 to 4 weeks. Most patients improve by then, and I taper the prednisone.

Disclosure

Dr Furman is a consultant for Pharmacyclics, AbbVie, Verastem, Gilead, Genentech, TG Therapeutics, and Sunesis.

Suggested Readings

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

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

Byrd JC, Furman RR, Coutre SE, et al. Three-year follow-up of treatment-naïve and previously treated patients with CLL and SLL receiving single-agent ibrutinib. *Blood.* 2015;125(16):2497-2506.

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

Ghia P, Hillmen P, Moreno C, et al. Outcomes of standard of care regimens in treatment-naïve chronic lymphocytic leukemia (CLL) patients with unmutated immunoglobulin heavy chain variable (IGHV) genes. Abstract presented at: the XVII International Workshop on Chronic Lymphocytic Leukemia; May 12-15, 2017; New York, NY. Abstract 188.

O'Brien SM, Furman RR, Coutre SE, et al. Five-year experience with single-agent ibrutinib in patients with previously untreated and relapsed/refractory chronic lymphocytic leukemia/small lymphocytic leukemia [ASH abstract 233]. *Blood.* 2016;128(suppl 22).

Rossi D, Terzi-di-Bergamo L, De Paoli L, et al. Molecular prediction of durable remission after first-line fludarabine-cyclophosphamide-rituximab in chronic lymphocytic leukemia. *Blood.* 2015;126(16):1921-1924.

Wierda WG, Siddiqi T, Stevens DA, et al. Phase 2 study of the combination of ibrutinib plus venetoclax in patients with treatment-naïve CLL/SLL. Abstract presented at: the XVII International Workshop on Chronic Lymphocytic Leukemia; May 12-15, 2017; New York, NY. Abstract 188.

Highlights in Chronic Lymphocytic Leukemia From the 2017 iwCLL and ASCO Meetings

Commentary by Richard R. Furman, MD

ASCO ABSTRACT Long-Term Efficacy and Safety With Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Up to Four Years Follow-Up of the RESONATE Study

The phase 3 RESONATE trial (A Phase 3 Study of Ibrutinib [PCI-32765] Versus Ofatumumab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia) compared ibrutinib vs ofatumumab in 391 patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).[1] The primary analysis, published in 2014, showed that ibrutinib significantly improved survival, reducing the risk of disease progression by 78% and the risk of death by 57%.[1]

This analysis by Byrd and colleagues provided long-term efficacy and safety from the RESONATE trial, with follow-up extending to 4 years (median, 3.6 years).[2] Progression-free survival (PFS) was not reached for ibrutinib vs 8.11 months for ofatumumab (hazard ratio, 0.133; *P*<.0001). The 3-year PFS was 59% vs 3%, respectively. The overall response rate for ibrutinib was 91% (Figure 1). The rate of complete response (CR) with or without blood count recovery (CRi) was 9%, and increased over time. Most patients in the ofatumumab arm (68%) crossed over to treatment with ibrutinib. Overall survival was longer for ibrutinib vs ofatumumab, but the median overall survival was not reached for either arm (Figure 2). At 3 years, the rate of overall survival was 74% among patients treated with ibrutinib. Among patients with baseline cytopenias, improvements were seen in hemoglobin (85%), platelets (95%), and absolute neutrophil counts (95%) during extended ibrutinib therapy.

Ibrutinib had the strongest PFS benefit among patients with the 11q deletion. However, PFS did not significantly differ in patients with or without the 11q or 17p deletion. Median PFS was longer among patients without the *TP53* mutation than in those with the mutation, but the difference was not statistically significant (not reached vs 40.7 months).

The toxicity profile of ibrutinib was consistent with previous reports. Major hemorrhage and grade 3 or higher atrial fibrillation each occurred in 6% of patients. Grade 3 or higher hypertension occurred in 8% of patients. The incidence of most grade 3 or higher adverse events, including neutropenia, pneumonia, and atrial fibrillation, decreased over time. Treatment discontinuation was attributed to progressive disease in 27% of patients and to adverse events in 12%.

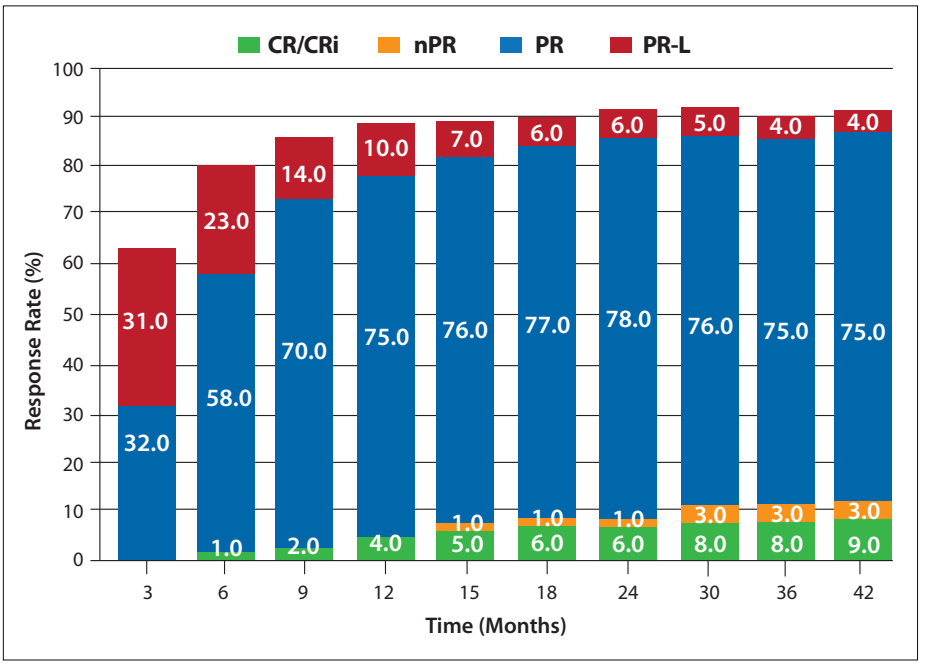

Figure 1. Overall response in a long-term analysis of the RESONATE trial. CR, complete response; CRi, incomplete response; nPR, nodular partial response; PR, partial response; PR-L, partial response with lymphocytosis. RESONATE, A Phase 3 Study of Ibrutinib [PCI-32765] Versus Ofatumumab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia. Adapted from Byrd JC et al. ASCO abstract 7510. *J Clin Oncol.* 2017;35(15 suppl).[2]

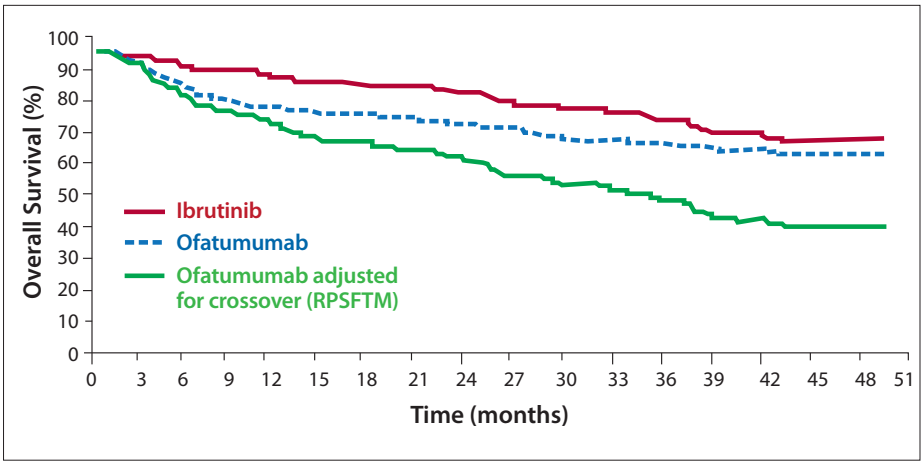

Figure 2. Overall survival in a long-term analysis of the RESONATE trial. In the intention-to-treat analysis, patients in the ofatumumab arm were not censored at the time of crossover. RESONATE, A Phase 3 Study of Ibrutinib [PCI-32765] Versus Ofatumumab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia. RPSFTM, rank preserving structural failure time model. Adapted from Byrd JC et al. ASCO abstract 7510. *J Clin Oncol*. 2017;35(15 suppl).[2]

References

1. Byrd JC, Brown JR, O'Brien S, et al; RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med*. 2014;371(3):213-223.
2. Byrd JC, Hillmen P, O'Brien SM, et al. Long-term efficacy and safety with ibrutinib (ibr) in previously treated chronic lymphocytic leukemia: up to four years follow-up of the RESONATE study [ASCO abstract 7510]. *J Clin Oncol*. 2017;35(15 suppl).

Commentary: Data from the RESONATE study led the US Food and Drug Administration to approve ibrutinib in all patients with the 17p deletion, regardless of their line of therapy. The trial did not include treatment-naive patients, but this population was still included in the initial approval.

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

Dr Nitin Jain and colleagues presented results of an ongoing phase 2 trial evaluating ibrutinib, fludarabine, cyclophosphamide, and obinutuzumab (iFCG) among treatment-naive patients with CLL and the *IGHV* mutation.[1] The study shortened the duration of treatment with fludarabine and cyclophosphamide by switching to ibrutinib and obinutuzumab. All patients began treatment with 3 courses of iFCG followed by ibrutinib and obinutuzumab for 3 cycles. Patients who achieved a CR/CRi and were negative for minimal residual disease (MRD) were then treated with ibrutinib for 6 cycles. Patients with a partial response or who were positive for MRD received ibrutinib and obinutuzumab for 6 cycles. After 12 cycles of treatment, patients who were MRD-positive continued to receive ibrutinib until they developed progressive disease. Patients who were MRD-negative stopped ibrutinib. The primary endpoint was CR/CRi plus bone marrow MRD negativity after 3 cycles of iFCG.

The patients' median age was 60 years (range, 25-71 years). Most patients (83%) were male. The deletion 13q mutation was found in 69%, and 21% had trisomy 12. Among 29 patients who initiated treatment, 24 completed 3 cycles of iFCG and underwent assessment for their response. The median follow-up was 8.3 months.

After 3 cycles of iFCG, the rate of bone marrow MRD negativity was 83%. The overall response rate was 100%, with a CR/CRi rate of 42% and a partial response rate of 58% (Table 1). All of the patients who achieved a CR/CRi were negative for MRD. Among patients who had a partial response, MRD negativity was reported in 71%. All of the 9 patients who received 1 year of treatment were MRD-negative and therefore discontinued ibrutinib.

The most common adverse events were neutropenia (grade 3 in 31% and grade 4 in 41%) and thrombocytopenia (grade 3 in 41% and grade 4 in 3%). Neutropenic fever, the most common infection, occurred in 4 patients.

The authors concluded that iFCG achieved high rates of MRD-negative remission after 3 courses. Enrollment of patients continues.

Reference

1. Jain N, Thompson PA, Burger JA, et al. Ibrutinib, fludarabine, cyclophosphamide, and obinutuzumab (GA101) (iFCG) for previously untreated patients with chronic lymphocytic leukemia (CLL) with mutated *IGHV* and non-del (17p) [ASCO abstract 7522]. *J Clin Oncol*. 2017;35(15 suppl).

Commentary: This study represents a nice attempt to limit the amount of chemotherapy that patients are exposed to. However, it does not address the important issue of whether 3 cycles of fludarabine and cyclophosphamide are still necessary, or if ibrutinib plus obinutuzumab alone would have been sufficient. 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) compared bendamustine and rituximab with or without

Table 1. Clinical Response After 3 Cycles of iFCG

	3 Months		Best Response	
	N=24 (%)	BM MRD (%)	N=24 (%)	BM MRD (%)
Overall response rate	24 (100)	20 (83)	24 (100)	All negative
Complete response/incomplete response	10 (42)	All negative	18 (75)	All negative
Partial response	14 (58)	10 (71)	6 (25)	All negative

BM, bone marrow; iFCG, ibrutinib, fludarabine, cyclophosphamide, and obinutuzumab; MRD, minimal residual disease.

Data from Jain N et al. ASCO abstract 7522. *J Clin Oncol.* 2017;35(15 suppl).[1]

ibrutinib. It found that the patients receiving bendamustine, rituximab, and ibrutinib did much better than the placebo group, but that the Kaplan-Meier PFS curve was superimposable to that of ibrutinib as a single agent. Results from the HELIOS trial raised the question of whether bendamustine and rituximab were necessary. The same question may apply to fludarabine and cyclophosphamide.

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

At the 2017 iwCLL meeting, Dr Thomas Kipps presented data from a pooled analysis of patients with CLL treated with ibrutinib in three phase 3 clinical trials.[1] In each of these trials, the ibrutinib arm was superior to a comparator arm. The RESONATE trial included 391 patients who had received at least 1 prior therapy and were ineligible for or refractory to purine analogue therapy.[2] Patients were randomly assigned to receive ibrutinib or ofatumumab. In the ofatumumab arm, 131 patients crossed over to ibrutinib after they developed progressive disease. The RESONATE-2 trial (Randomized, Multicenter, Open-Label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib Versus Chlorambucil in Patients 65 Years or Older With Treatment-Naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma [PCYC-1115/1116]) randomly assigned 269 treatment-naive patients to ibrutinib or chlorambucil.[3] In the extension study, 64 patients in the chlorambucil arm crossed over to ibrutinib. Patients with deletion 17p were excluded from RESONATE-2. The HELIOS study included 578 patients who had received at least 1 prior therapy.[4] Patients with deletion 17p were excluded. After treatment with bendamustine plus rituximab, patients were randomly assigned to receive ibrutinib or placebo for a maximum of 6 cycles. After they developed progressive disease, 142 patients in the placebo arm crossed over to the ibrutinib arm.

The pooled analysis by Dr Kipps and colleagues evaluated whether outcome was impacted by the presence of the *IGHV* mutation, deletion 11q, trisomy 12, or complex karyotype. (Deletion 17p was not included since patients with this mutation were excluded from 2 of the 3 trials.) Among patients treated with ibrutinib (n=620), the overall response rates and the CR rates were similar regardless of the presence of the *IGHV* mutation, deletion 11q, or complex karyotype (Figure 3). Patients with trisomy 12 had a higher CR rate. The presence of mutated *IGHV*, trisomy 12, complex karyotype, and deletion 11q did not impact overall survival, at a median follow-up of 42 months.

The mutation status of *IGHV* did not impact PFS (median follow-up, 36.4 months) in the ibrutinib arms (Figure 4). In the comparator arms, a superior PFS was seen in patients with mutated *IGHV*. The presence of trisomy 12 did not impact PFS in either patient group. In the ibrutinib arm, the complex karyotype and deletion 11q did not impact PFS. In the comparator arms, however, an inferior PFS was seen in patients with these mutations.

The median exposure to ibrutinib ranged from 33 months to 35 months (range, <1-50 months). The toxicity profile of ibrutinib was not impacted by genomic risk factors. Serious adverse events occurred in 60% to 68% of patients. Adverse events led to treatment discontinuation in 14% to 22% of patients and to death in 5% to 16%. The authors concluded that the genomic risk factors used to predict response with older therapies have limited utility with ibrutinib.

References

1. Kipps TJ, Fraser G, Coutre SE, et al. Outcomes of ibrutinib-treated patients with chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL) with high-risk prognostic factors in an integrated analysis of 3 randomized phase 3 studies. Abstract presented at: the XVII International Workshop on Chronic Lymphocytic Leukemia; May 12-15, 2017; New York, NY. Abstract 19.
2. Byrd JC, Brown JR, O'Brien S, et al; RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med.* 2014;371(3):213-223.
3. Burger JA, Tedeschi A, Barr PM, et al; RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med.* 2015;373(25):2425-2437.
4. Chanan-Khan A, Cramer P, Demirkan F, et al; HELIOS investigators. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. *Lancet Oncol.* 2016;17(2):200-211.

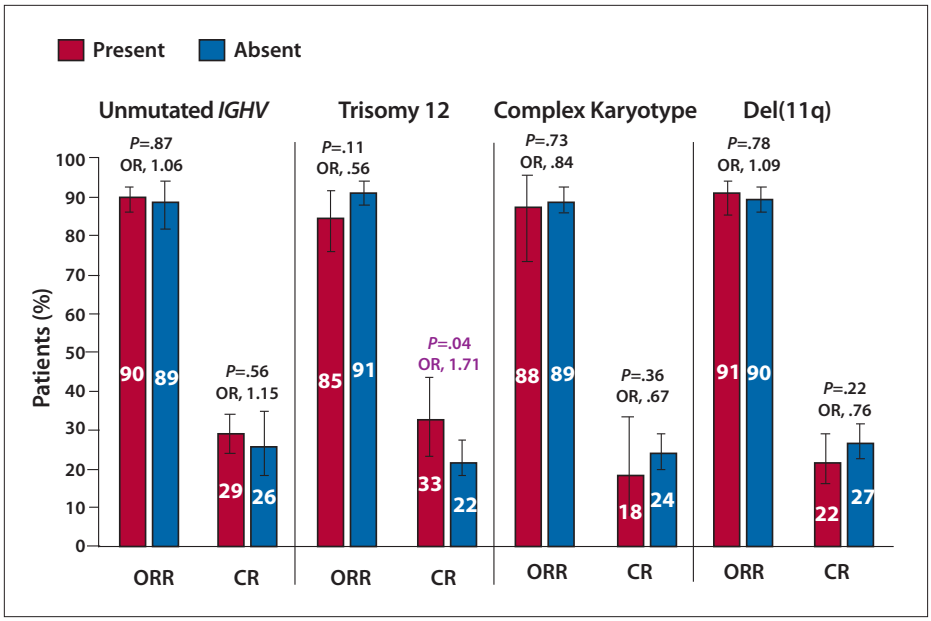

Figure 3. Genomic risk factors were not associated with inferior response rates in patients treated with ibrutinib in three phase 3 trials. CR, complete response; OR, odds ratio; ORR, overall response rate. Adapted from Kipps TJ et al. Abstract 19. The XVII International Workshop on Chronic Lymphocytic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

Commentary: This study showed that the mutational status of the 11q deletion, trisomy 12, or complex karyotyping was not associated with poor outcomes. The follow-up was short.

ASCO ABSTRACT Tolerability and Activity of Chemo-Free Triplet Combination of TGR-1202, Ublituximab, and Ibrutinib in Patients With Advanced CLL and NHL

This phase 1 trial evaluated ibrutinib in combination with 2 novel agents in patients with relapsed/refractory non-Hodgkin lymphoma or patients with CLL/SLL (treatment-naive or relapsed/refractory).[1] The glycoengineered monoclonal antibody ublituximab targets an epitope on the CD20 antigen. TGR-1202 is a next-generation PI3Kδ inhibitor.

The trial enrolled 20 patients with CLL/SLL and 18 with non-Hodgkin lymphoma. Eight CLL patients had a 17p and/or 11q deletion. The patients' median age was 65 years (range, 32-85 years). Two patients had received previous treatment with ibrutinib.

The median follow-up was 11.1 months. The maximum tolerated dose was not reached. Among the 19 evaluable patients with CLL/SLL, the overall response rate was 100%. Six patients had a complete response, and 13 had a partial response. More than half of the evaluable CLL patients (53%) had high-risk cytogenetic features.

An overall response rate of 100% was also seen in patients with mantle cell lymphoma and marginal zone lymphoma. The rate was 80% among patients with follicular lymphoma and 17% among those with diffuse large B-cell lymphoma.

Among all patients, the most common adverse events were diarrhea (47%), fatigue (47%), dizziness (37%), insomnia (34%), nausea (34%), neutropenia (32%), cough (32%), infusion-related reaction (32%), pyrexia (29%), rash (29%), thrombocytopenia (29%), anemia (26%), and sinusitis (24%). The most common grade 3/4 event was neutropenia, occurring in 18% of patients. The authors concluded that the combination of ublituximab, TGR-1202, and ibrutinib was well-tolerated and showed activity across patients with heavily pretreated and high-risk B-cell malignancies.

Reference

1. Nastoupil LJ, Lunning MA, Vose J, et al. Tolerability and activity of chemo-free triplet combination of TGR-1202, ublituximab, and ibrutinib in patients with advanced CLL and NHL [ASCO abstract 7511]. *J Clin Oncol*. 2017;35(15 suppl).

Commentary: This study was important in that it combined inhibitors of Bruton tyrosine kinase and phosphoinositide 3-kinase, an approach under study in several trials of B-cell malignancies. The study found that the signal transduction inhibitors worked well in patients with low-grade lymphomas, such as CLL, follicular lymphoma, marginal zone lymphoma, and mantle cell lymphoma, but not in patients with diffuse large B-cell lymphoma. These results suggest that the large-cell lymphomas need a very different approach from the low-grade lymphomas.

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

Dr Paolo Ghia and colleagues analyzed outcomes in patients with CLL treated with fludarabine, cyclophosphamide, and rituximab (FCR), bendamustine plus

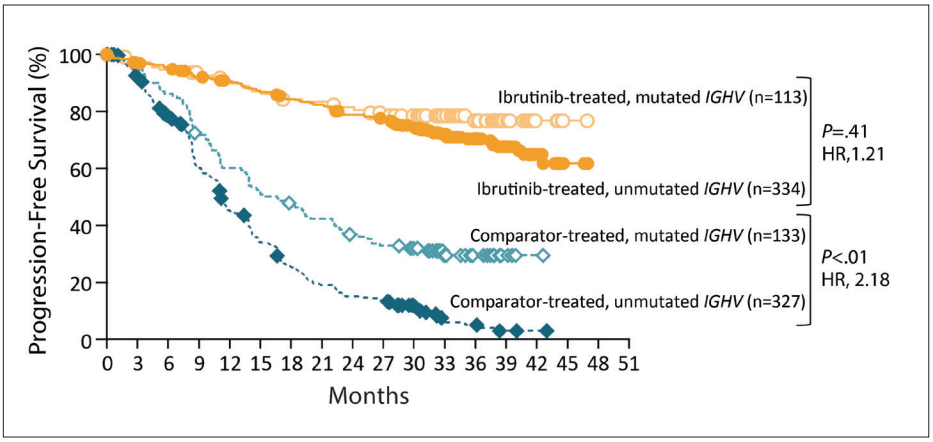

Figure 4. The presence of the *IGHV* mutation did not impact progression-free survival in patients treated with ibrutinib in three phase 3 trials. HR, hazard ratio. Adapted from Kipps TJ et al. Abstract 19. The XVII International Workshop on Chronic Lymphocytic Leukemia.[1]

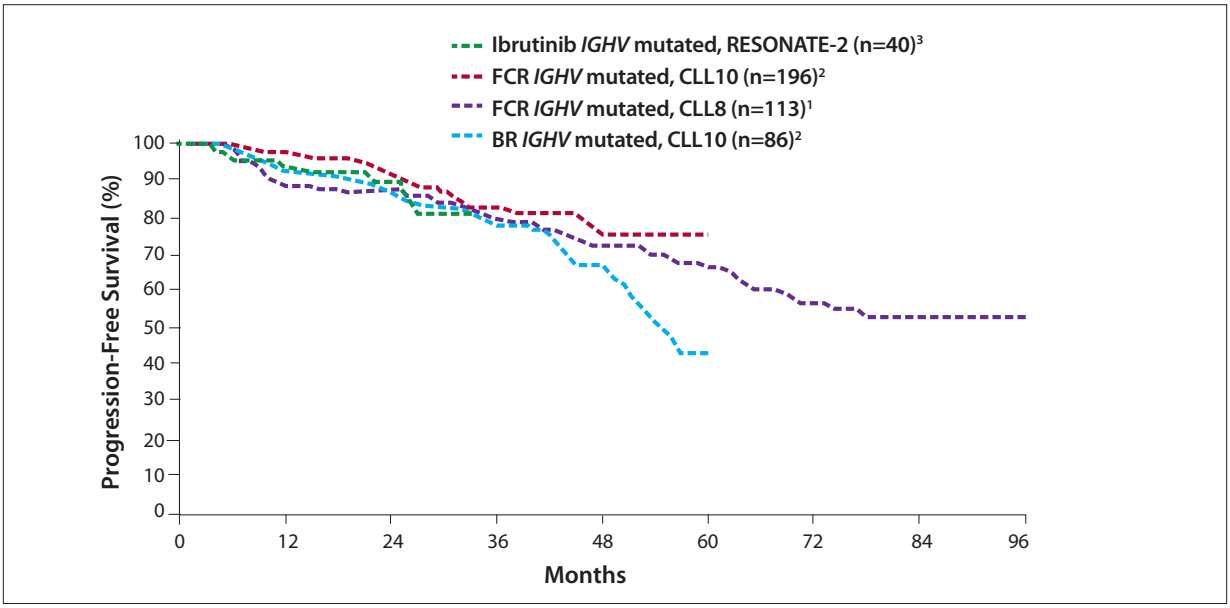

Figure 5. Rates of progression-free survival among CLL patients with the *IGHV* mutation in 3 clinical trials. BR, bendamustine/rituximab; CLL, chronic lymphocytic leukemia; FCR, fludarabine/cyclophosphamide/rituximab; RESONATE-2, Randomized, Multicenter, Open-Label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib Versus Chlorambucil in Patients 65 Years or Older With Treatment-Naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma (PCYC-1115/1116). Adapted from Ghia P et al. Abstract 188. The XVII International Workshop on Chronic Lymphocytic Leukemia.[4]

rituximab, or ibrutinib in the CLL8, CLL10, and RESONATE-2 studies.[1-4] Kaplan-Meier curves that were digitized from the original publications were used to estimate PFS rates. Across the 3 studies, the proportion of patients with unmutated *IGHV* ranged from 43% to 68%.

In the RESONATE-2 trial, *IGHV* status did not impact PFS among patients treated with ibrutinib. Among patients treated with traditional chemoimmunotherapy, inferior outcomes were seen in those with unmutated *IGHV* vs mutated *IGHV*. In CLL10, bendamustine plus rituximab was associated with a higher PFS in patients who had mutated *IGHV* rather than unmutated *IGHV*. Patients with mutated *IGHV* also had a better PFS when treated with FCR in the CLL8 and CLL10 trials. Among patients with mutated *IGHV* from all 3 trials, Kaplan-Meier curves for all treatments overlapped through 36 months. (Data were unavailable for ibrutinib thereafter.) After 36 months, PFS was longer for FCR than bendamustine plus rituximab in patients with mutated *IGHV*. Among patients with mutated *IGHV*, the estimated rates of PFS at 30 months were 81% for those who received ibrutinib, 84% for those treated with FCR in CLL8, 87% for those treated with FCR in CLL10, and 83% for those treated with bendamustine plus rituximab in CLL10 (Figure 5).

A comparison of Kaplan-Meier curves from patients

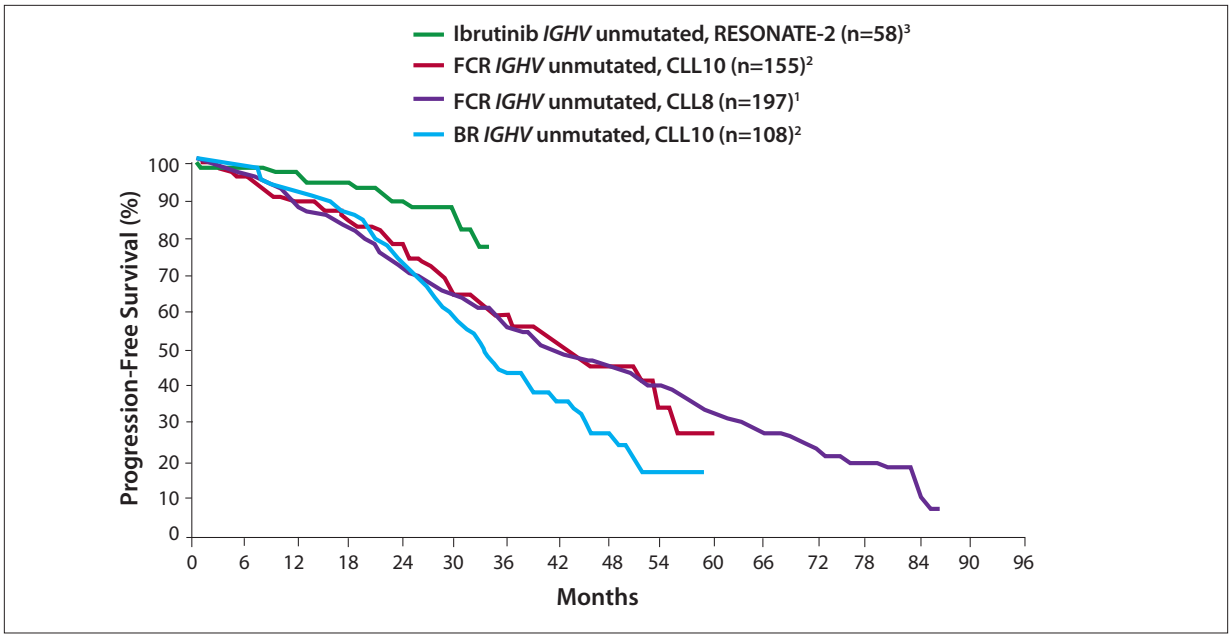

Figure 6. Rates of progression-free survival among CLL patients without the *IGHV* mutation in 3 clinical trials. BR, bendamustine/rituximab; CLL, chronic lymphocytic leukemia; FCR, fludarabine/cyclophosphamide/rituximab; RESONATE-2, Randomized, Multicenter, Open-Label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib Versus Chlorambucil in Patients 65 Years or Older With Treatment-Naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma (PCYC-1115/1116). Adapted from Ghia P et al. Abstract 188. The XVII International Workshop on Chronic Lymphocytic Leukemia.[4]

with unmutated *IGHV* showed similar rates of PFS for patients from CLL8 or CLL10 who received treatment with FCR, a superior PFS for ibrutinib-treated patients with unmutated *IGHV*, and the lowest PFS rate for patients treated with bendamustine plus rituximab (Figure 6). Among patients with unmutated *IGHV*, the estimated 30-month PFS rates were 87% for those treated with ibrutinib, 64% for those who received FCR in CLL8, 65% for those who received FCR in CLL10, and 59% for those treated with bendamustine plus rituximab in CLL10. The *IGHV* mutation did not impact overall survival until approximately 15 months. At this time, overall survival decreased among patients with unmutated *IGHV* and remained lower through 96 months.

This analysis suggested that patients with mutated or unmutated *IGHV* experienced a durable PFS with ibrutinib. After treatment with chemoimmunotherapy, however, patients with unmutated *IGHV* had worse outcomes than those with mutated *IGHV*.

References

1. Stilgenbauer S, Schnaiter A, Paschka P, et al. Gene mutations and treatment outcome in chronic lymphocytic leukemia: results from the CLL8 trial. *Blood*. 2014;123(21):3247-3254.

2. Eichhorst B, Fink AM, Bahlo J, et al; international group of investigators; German CLL Study Group (GCLLSG). First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. *Lancet Oncol*. 2016;17(7):928-942.

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

4. Ghia P, Hillmen P, Moreno C, et al. Outcomes of standard of care regimens in treatment-naïve chronic lymphocytic leukemia (CLL) patients with unmutated immunoglobulin heavy chain variable (*IGHV*) genes. Abstract presented at: the XVII International Workshop on Chronic Lymphocytic Leukemia; May 12-15, 2017; New York, NY. Abstract 188.

Commentary: This study showed that unmutated patients do better with ibrutinib than bendamustine/rituximab and fludarabine/cyclophosphamide/rituximab. These data confirm what is already known, as this study was a subgroup analysis of other studies. It appears that immunoglobulin G mutational status is no longer a prognostic marker with the use of ibrutinib.

ASCO ABSTRACT CD19 CAR-T Cells Combined With Ibrutinib to Induce Complete Remission in CLL

This pilot trial evaluated anti-CD19 chimeric antigen receptor (CAR) T cells in adults with CLL/SLL who had not achieved a CR after treatment with ibrutinib for at least 6 months.[1] All patients in the study had also developed disease progression after 1 or more regimens before they began treatment with ibrutinib, unless they had deletion 17(p13.1) or the *TP53* mutation. The CAR therapy consisted of CD3z, 4-1BB, and humanized anti-CD19 scFv (CTL119). Manufacturing of the CAR T-cell

product was successful in all 10 patients who received the infusion. Treatment with ibrutinib continued throughout the study.

Most patients had the 17p deletion, and 2 patients had increasing BTK C481S clones. The median burden of CLL in the marrow was 10% (range, 10%-50%).

At 3 months, bone marrow was MRD-negative in 8 of 9 evaluable patients (89%). All patients remained in a CR at their last follow-up assessment.

Cytokine release syndrome occurred in 9 patients. It was grade 1 in 2 patients, grade 2 in 6 patients, and grade 3 in 1 patient. No patient required treatment with the interleukin 6 receptor antagonist tocilizumab. Grade 4 tumor lysis syndrome was reported in 1 patient.

Reference

1. Gill S, Frey NV, Hexner EO, et al. CD19 CAR-T cells combined with ibrutinib to induce complete remission in CLL [ASCO abstract 7509]. *J Clin Oncol*. 2017;35(15 suppl).

Commentary: In this study, patients who did not achieve a CR after 6 months of ibrutinib—which is all patients—were treated with CAR T-cell therapy. An interesting finding was that CAR T-cell therapy may be better tolerated in patients with a lower burden of disease. CAR T cells are associated with significant toxicities, however. Given that the patients enrolled in this study might have had a PFS exceeding 5 years with ibrutinib, I do not believe it was justifiable to expose them to the additional risks of CAR T-cell therapy.

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

Dr Massimo Gentile and colleagues evaluated whether the CLL International Prognostic Index can predict overall survival among CLL patients treated with FCR or bendamustine plus rituximab as first-line therapy.[1] The CLL International Prognostic Index consists of *IGHV* status, *TP53* status, clinical stage, age, and β_2-microglobulin level. The 529 patients in this analysis had these data available at the time of progression.

The median follow-up was 3.4 years (range, 3 months-15.7 years). The 3-year overall survival probability was 98.5% for patients at low risk, 93.7% for those at intermediate risk, 87.8% for those at high risk, and 65.6% for those at very high risk. The Harrell C-statistic for predicting survival was 0.70 (P<.0001). The 3-year PFS probability was 86.5% for patients at low risk, 70.6% for those at intermediate risk, 58.3% for those at high risk, and 29.8% for those at very high risk. The Harrell C-statistic for PFS was 0.63 (P<.0001). FCR had a significantly better outcome than bendamustine plus rituximab among patients in the high-risk and very high-risk groups.

Reference

1. Gentile M, Mauro FM, Reda G, et al. Evaluation of the International Prognostic Index for Chronic Lymphocytic Leukemia (CLL-IPI) in previously untreated CLL patients receiving chemo-immunotherapy as first-line approach: analysis of 529 cases. Abstract presented at: the XVII International Workshop on Chronic Lymphocytic Leukemia; May 12-15, 2017; New York, NY. Abstract 143.

Commentary: This study evaluated a prognostic model using *TP53*, *IGHV*, β_2-microglobulin, clinical stage, and age. The model was validated among patients treated with chemoimmunotherapy. In the era of novel agents, in which I hope to see the use of chemoimmunotherapy eliminated, this prognostic model has little utility.

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

Dr William Wierda presented the design of an ongoing phase 2 trial evaluating the combination of ibrutinib and venetoclax as first-line therapy in patients with CLL or SLL.[1] PCYC-1142 is a multicenter, double-blind, placebo-controlled, randomized trial. The primary objectives are to identify the MRD-negative response rate and to determine whether discontinuation of ibrutinib in patients who achieve MRD negativity impacts disease-free survival. Patients will first receive at least 12 cycles of ibrutinib plus venetoclax. Those without MRD at the end of treatment will be randomly assigned to maintenance therapy with either ibrutinib or placebo. Patients who are MRD-positive will be randomly assigned to open-label treatment with ibrutinib plus venetoclax or ibrutinib alone. The primary endpoint for the initial treatment phase of ibrutinib plus venetoclax is the MRD-negative response rate. For the randomized phase of the study, the primary endpoint is the rate of MRD-negative disease-free survival at 1 year. The trial aims to enroll approximately 150 patients.

Reference

1. Wierda W, Siddiqi T, Stevens D, et al. Phase 2 study of the combination of ibrutinib plus venetoclax in patients with treatment-naïve CLL/SLL. Abstract presented at: the XVII International Workshop on Chronic Lymphocytic Leukemia; May 12-15, 2017; New York, NY. Abstract 95.

Commentary: This trial in progress is evaluating ibrutinib plus venetoclax. This combination appears to be the best approach for patients with high-risk FISH abnormalities, the *NOTCH1* mutation, or the *VH 4-39* gene.

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

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

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

CLL
SLL

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

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

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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RESONATE™-2 FRONTLINE DATA

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

EXTENDED OVERALL SURVIVAL

IMBRUVICA® significantly extended OS vs chlorambucil[2]

Statistically significant reduction in risk of death[2]

56%

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

41% of patients crossed over to IMBRUVICA®

Estimated survival rates at 24 months

95% IMBRUVICA®
(95% CI: 89, 97)

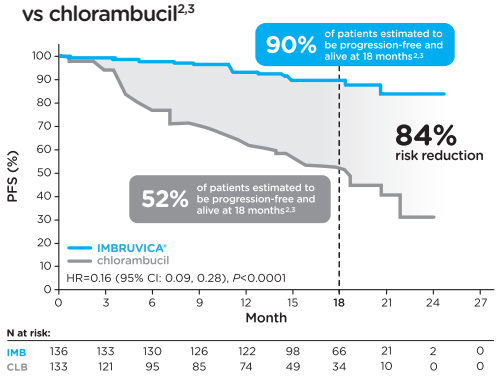
84% chlorambucil
(95% CI: 77, 90)

SECONDARY ENDPOINT: OS

- Median follow-up was 28 months[2]

PROLONGED PROGRESSION-FREE SURVIVAL

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



PRIMARY ENDPOINT: PFS

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

DRUG INTERACTIONS

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

CYP3A Inducers - Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

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

Please see the Brief Summary on the following pages.

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

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

To learn more, visit
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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].*

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Notes


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