

A SPECIAL MEETING REVIEW EDITION

Highlights in Mantle Cell Lymphoma From the 2020 American Society of Clinical Oncology Annual Meeting

A Review of Selected Presentations From the 2020 ASCO Meeting

Special Reporting on:

- Safety of Acalabrutinib Monotherapy in Hematologic Malignancies: Pooled Analysis From Clinical Trials
- Product Characteristics and Pharmacological Profile of KTE-X19 in Patients With Relapsed/Refractory Mantle Cell Lymphoma in the Phase II Registrational ZUMA-2 Trial
- Clinical Activity of Cirmtuzumab, an Anti-ROR1 Antibody, in Combination With Ibrutinib: Interim Results of a Phase Ib/II Study in Mantle Cell Lymphoma or Chronic Lymphocytic Leukemia
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- Multi-Omics Analysis of Mantle Cell Lymphoma Reveals an Immune-Cold Tumor Microenvironment Associated With Ibrutinib Resistance

PLUS Meeting Abstract Summaries

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Safety of Acalabrutinib Monotherapy in Hematologic Malignancies: Pooled Analysis From Clinical Trials

Bruton tyrosine kinase (BTK) is critical to all aspects of B-cell development, including proliferation, maturation, differentiation, apoptosis, and cell migration. BTK also plays a role in the progression of B-cell lymphoproliferative disorders, such as mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). Ibrutinib, the first-generation BTK inhibitor, is clinically active in MCL.¹ However, a proportion of patients with MCL discontinue ibrutinib after developing adverse events.² The next-generation BTK inhibitor acalabrutinib is indicated for the treatment of relapsed/refractory MCL and CLL/SLL.³ In vitro studies have shown that acalabrutinib has greater selectivity for BTK compared with ibrutinib.^{4,5} It has been hypothesized that this greater selectivity may result in an improved safety profile.⁵⁻⁸

Furman and colleagues conducted a pooled analysis to generate an overall summary of the safety profile of acalabrutinib monotherapy.⁹ The analysis included 1040 patients enrolled in nine phase 1, 2, or 3 clinical trials. The patients had received acalabrutinib for B-cell malignancies, including MCL, CLL/SLL, Richter transformation, activated B-cell like subtype of diffuse large B-cell lymphoma, follicular lymphoma, prolymphocytic leukemia, and Waldenström macroglobulinemia. Most patients were male (68%) and White (89%). Their median age was 67.0 years (range, 32.0-90.0). The median body weight was 79 kg (range, 39-155). Most patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (42%) or 1 (51%). A total of 35% of patients were treatment-naïve, and the remaining 65% had relapsed or refrac-

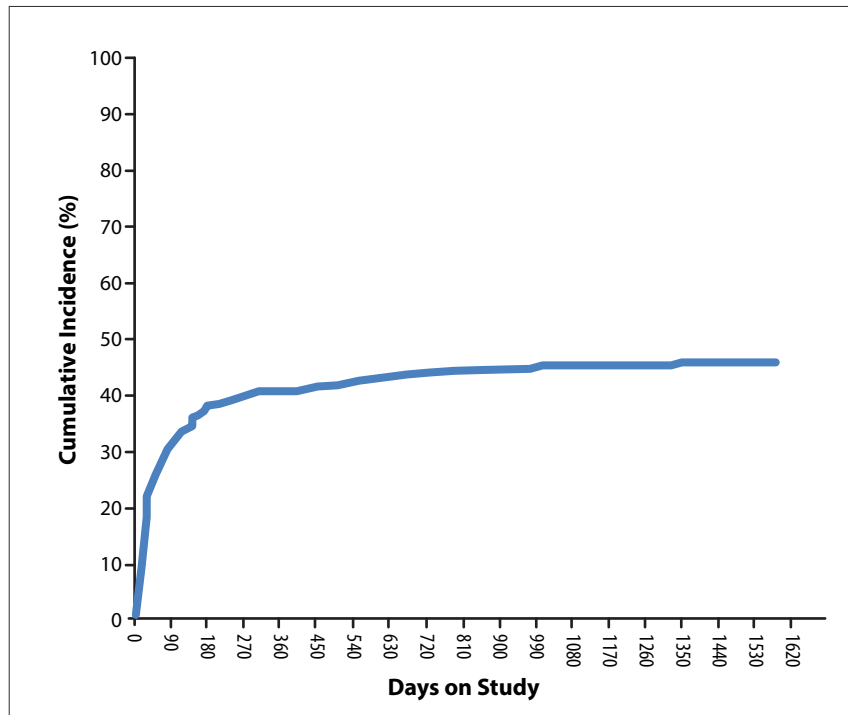


Figure 1. Cumulative incidence of any-grade hemorrhage in a pooled safety analysis of acalabrutinib. Adapted from Furman RR et al. ASCO abstract 8064. *J Clin Oncol*. 2020;38(15 suppl).⁹

tory disease. The median number of prior systemic regimens was 1 (range, 0-13).

After a median follow-up of 26.4 months (range, 0.0-58.5), the median duration of exposure to acalabrutinib was 24.6 months (range, 0.0-58.5). Treatment with acalabrutinib at the recommended monotherapy dose of 100 mg twice daily was administered to 83% of patients. The median relative dose intensity was 98.7%.

Nearly all patients (96%) experienced an adverse event of any grade; the majority of these events were grade 1 or 2 in severity. The 2 most frequent adverse events were headache, occurring in 37.8%, and diarrhea, occurring in 36.7%. Most of these cases were grade 1 or 2, and most occurred

within the first 6 months of treatment. Most headache events occurred early, resolved, and did not recur. One patient (0.1%) discontinued treatment owing to headache. The median duration of headache events was 20 days (range, 1-994).

Other adverse events of note that occurred during or within 30 days after the end of acalabrutinib therapy included neutropenia in 16% of patients (14% with grade ≥ 3), anemia in 14% (8% with grade ≥ 3), and thrombocytopenia in 9% (5% with grade ≥ 3).

Grade 3 or higher adverse events were reported in 54% of patients. The most frequent were neutropenia (11.2%), anemia (7.8%), and pneumonia (5.1%). Serious adverse events of

any grade occurred in 39% of patients. The most frequent serious adverse event was pneumonia, reported in 5%. Pneumonia was also the most frequent fatal adverse event, with a mortality rate of 1% (8 patients).

Several events of clinical interest for acalabrutinib were also investigated.⁹ Infections occurred in 66.7% of patients; grade 3 or higher infections occurred in 17.6%. Upper respiratory tract infections (22%) and sinusitis (11%) accounted for the majority of all-grade infections. The median time to infection onset was 97 days (range, 1-1343). Most patients with infections experienced their first onset within the first 6 months of treatment.

Hemorrhage occurred in 46.3% of patients; cases were grade 3 or higher in 2.7% (Figure 1). Grade 1 or 2 hemorrhage events included contusion in 22%, petechiae in 11%, epistaxis in 7%, ecchymosis in 6%, and an increased tendency to bruise in 5%. There were 3 cases of grade 3 or higher epistaxis, and 4% of patients

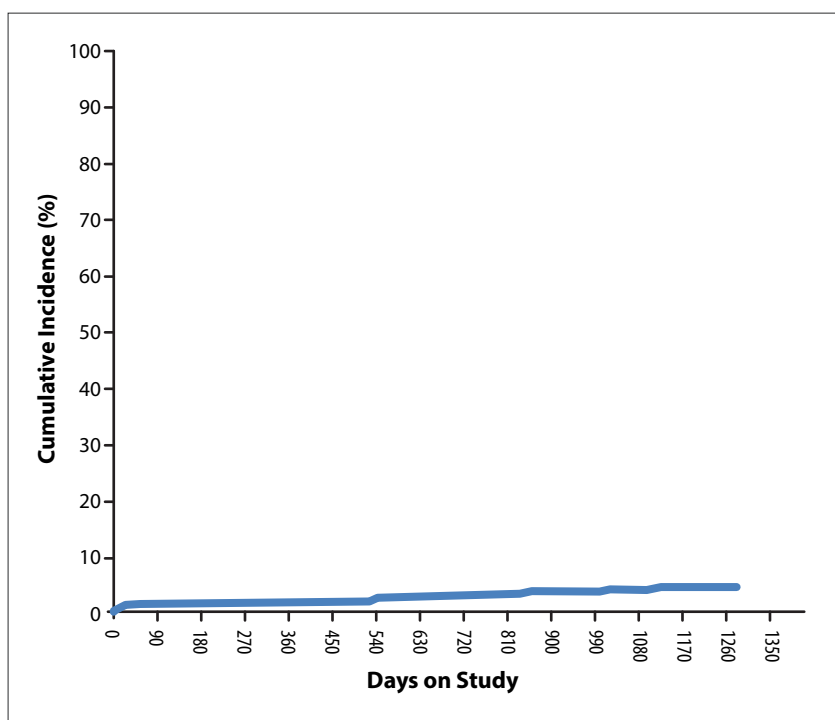


Figure 2. Cumulative incidence of any-grade atrial fibrillation in a pooled safety analysis of acalabrutinib. Adapted from Furman RR et al. ASCO abstract 8064. *J Clin Oncol.* 2020;38(15 suppl).⁹

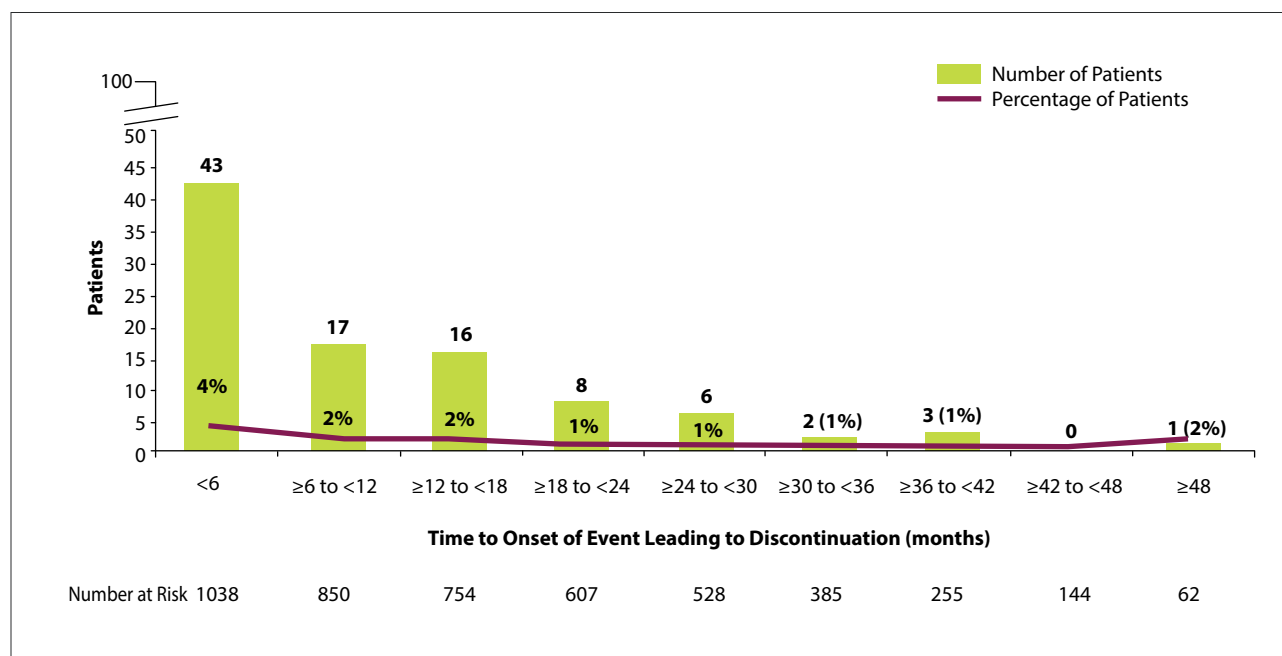


Figure 3. Time to onset of an adverse event that led to discontinuation of acalabrutinib in a pooled safety analysis. A patient could be counted once in each time interval if he or she reported multiple events. The percentage during each time period was calculated using the number of patients who were still on treatment (at risk) during that time period as the denominator. Adapted from Furman RR et al. ASCO abstract 8064. *J Clin Oncol.* 2020;38(15 suppl).⁹

developed a major hemorrhage event. A hemorrhage event of any grade occurred within the first 6 months of therapy in 38% of patients.

Cardiac events occurred in 15.6% of patients; these events were grade 3 or higher in 4.5%. A total of 4.4% of patients developed any-grade atrial fibrillation, which was a combined term that encompassed atrial fibrillation (4%), as well as atrial flutter (0.4%). Atrial fibrillation occurred at an incidence rate of 2.3 per 100 patient-exposure years (Figure 2). There were no grade 4 or 5 cases of atrial fibrillation. Grade 3 cases occurred in 1.3%. One patient (0.1%) developed ventricular tachyarrhythmia.

Second primary malignancies occurred in 12.2% of patients; severity was grade 3 or higher in 4.1%. The most frequently reported second primary malignancy was nonmelanoma skin cancer, occurring in 7% of

patients. Excluding this cancer type, the median time to onset of second primary malignancy was 339 days (range, 7-1499).

At the time of the analysis, 65% of patients were continuing acalabrutinib treatment. Among patients who discontinued treatment, 17% did so owing to progressive disease and 9% owing to an adverse event. In most cases, acalabrutinib discontinuation owing to an adverse event occurred within 6 months of the first treatment dose (Figure 3). Additionally, adverse events led to dose modifications in 4% of patients and dose delays in 38% of patients.

The authors of this pooled analysis concluded that no unexpected safety signals arose throughout these clinical trials, and that the observed toxicity profile supported the long-term safety of acalabrutinib in patients with B-cell malignancies.⁹

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Product Characteristics and Pharmacological Profile of KTE-X19 in Patients With Relapsed/Refractory Mantle Cell Lymphoma in the Phase II Registrational ZUMA-2 Trial

The second-generation chimeric antigen receptor (CAR) T-cell therapy KTE-X19 is directed against CD19. ZUMA-2 was a pivotal phase 2 study that investigated KTE-X19 in patients with MCL.¹ Enrolled patients had received from 1 to 5 prior therapies, including a BTK inhibitor, and had relapsed during treatment or developed relapsed/refractory disease. After enrollment, patients underwent leukapheresis and an optional bridging therapy consisting of dexamethasone, ibrutinib, or acalabrutinib. The bridging therapy was completed 5 days or fewer before initiation of conditioning chemotherapy (fludarabine plus cyclophosphamide). Subsequently, all patients received their CAR T-cell dose (2×10^6 cells/kg).

The primary efficacy analysis of the ZUMA-2 study occurred in 60 patients, after a median follow-up of 12.3 months. The objective response rate (ORR) was 93%, which included complete responses in 67%.¹ At the time of the analysis, 57% of all patients had an ongoing response. Among patients with a complete response, 78% had an ongoing response. Adverse events included grade 3 or higher cytokine release syndrome in 15% of patients, and grade 3 or higher neurologic events in 31% of patients. Most of these cases were reversible.

Wang and colleagues completed an analysis of the ZUMA-2 trial that focused on the pharmacologic profile of KTE-X19 in patients at low-risk vs high-risk.² The study included 65

patients who had received treatment in the trial. The investigators defined high-risk as an elevated Ki-67 proliferation index ($\geq 50\%$) and a *TP53* gene mutation, both of which are associated with a poor prognosis.³

Overall, the CAR T-cell product characteristics were generally comparable across the 2 prognostic groups.² For example, the median ratio of CD4-to-CD8 cells was 0.7 (range, 0.04-3.7) in the overall population, 0.8 (range, 0.4-1.7) in patients with a Ki-67 proliferation index of less than 50%, and 0.7 in patients with a Ki-67 proliferation index of 50% or higher. There was a trend toward a more CD4-based phenotype in patients with a *TP53* mutation vs without. The median ratio was 1.2 (range, 0.7-3.7) vs 0.7 (range,

0.04-1.9), respectively.

There was also a trend toward more differentiated T-cell phenotypes among patients with a high Ki-67 index ($\geq 50\%$).² These patients had a median of 20.1% (range, 0.3-68.8) naive T cells, 12.0% (range, 2.3-51.6) central memory T cells, 29.1% (range, 5.8-70.3) effector memory T cells, and 32.4% (range, 2.8-65.2) effector T cells. In comparison, patients with a low Ki-67 index had a median of 30.4% (range, 11.0-57.0) naive T cells, 10.1% (range, 8.4-45.0) central memory T cells, 19.4% (range, 6.3-56.1) effector memory T cells, and 23.7% (range, 11.5-49.3) effector T cells.

Overall, comparable CAR T-cell expansion was observed regardless of the Ki-67 proliferation index or *TP53* mutation status.² Among the 48 patients with Ki-67 assessments, ORR was 94% in those with a high index vs 100% in those with a low index. *TP53* mutation status was available for 36 patients; a response was achieved by all of them, regardless of whether they had the mutation (n=6) or not (n=30).

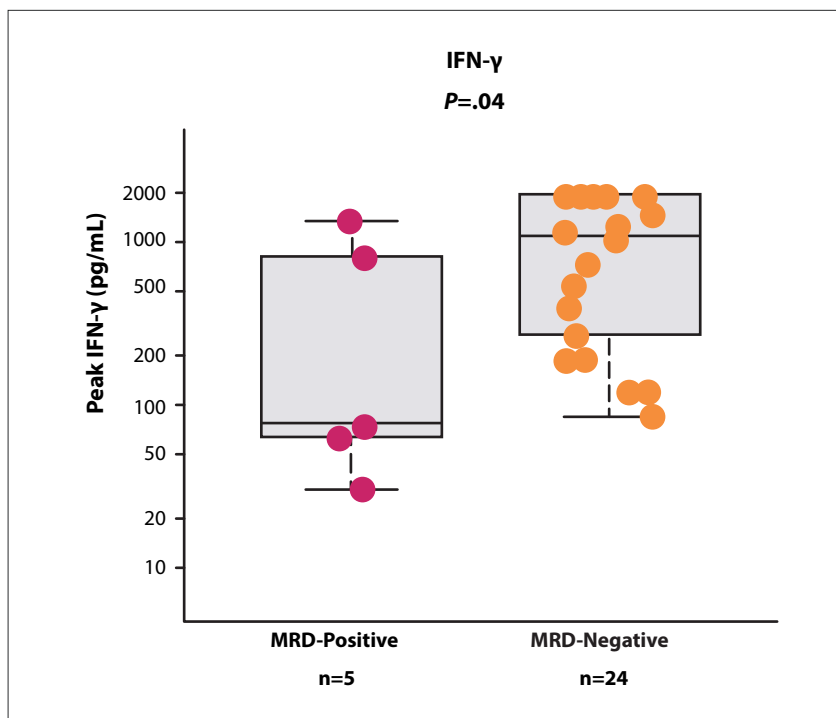


Figure 4. Levels of IFN- γ increased among patients who achieved MRD-negative status after treatment with KTE-X19 in the ZUMA-2 trial. CAR T-cell expansion was ≥ 80 -fold higher in patients who were MRD-negative vs MRD-positive at 1 month. MRD, minimal residual disease. Adapted from Wang M et al. ASCO abstract 3023. *J Clin Oncol.* 2020;38(15 suppl).²

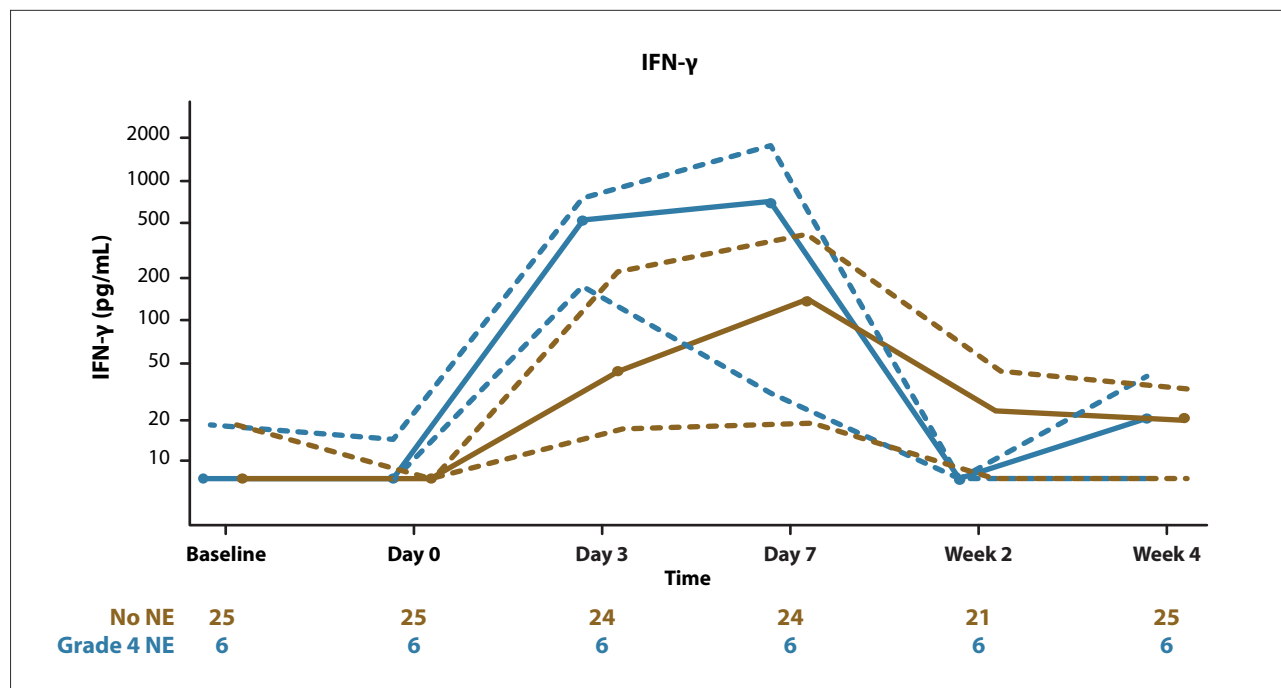


Figure 5. Levels of IFN- γ among patients with or without grade 4 neurologic events in the ZUMA-2 trial of KTE-X19. IFN- γ , interferon gamma. Adapted from Wang M et al. ASCO abstract 3023. *J Clin Oncol.* 2020;38(15 suppl).²

The pharmacodynamic profile of KTE-X19 remained relatively consistent between the high-risk and low-risk prognostic groups (as defined by the Ki-67 index). There was a consistent trend for increased production of serum cytokine levels and their receptors among patients with a mutated *TP53* gene; several differences reached statistical significance. Notably, among the 6 patients with a *TP53* mutation, 3 developed grade 3 or higher neurotoxicity and 2 had grade 3 or higher cytokine release syndrome.

In addition, increased peak levels of cytokine expression in the serum were observed in patients with negative minimal residual disease (MRD) status (n=29). Among these patients, interferon gamma (IFN- γ ; Figure 4) and interleukin (IL) 6 showed statistically significant increases in expression compared with patients who were MRD-positive at 1 month (n=29). IL-2 showed a trend toward increased expression.

Among 6 patients who developed grade 4 neurologic events, 3 patients had concurrent grade 4 cytokine release syndrome. Compared with patients without these events, these 3 patients had higher peak serum levels of IFN- γ (Figure 5), tumor necrosis factor alpha (TNF- α), monocyte chemoattractant protein 1 (MCP-1), IL-2, and IL-6.

ABSTRACT SUMMARY Real-World Healthcare Resource Utilization and Costs Among Relapsed/Refractory Mantle Cell Lymphoma Patients Receiving Ibrutinib or Chemoimmunotherapy

Ghosh and colleagues evaluated healthcare utilization in patients with relapsed/refractory MCL (Abstract e19408). Data were gathered from a US managed care database. The patients had received at least 1 prior therapy and were treated with either ibrutinib (with or without rituximab) or chemoimmunotherapy between May 2013 and June 2019. During the first Oncology Care Model episode (in the first 6 months), patients treated with ibrutinib (with or without rituximab; n=149) experienced significantly fewer monthly days with outpatient services compared with the chemoimmunotherapy cohort (n=151), with a rate ratio of 0.63 ($P<.001$). This significant difference was also observed between the 2 cohorts during the index line of therapy, with a rate ratio of 0.73 ($P=.004$). Although patients in the ibrutinib cohort incurred significantly higher monthly pharmacy costs, these were offset by lower monthly medical costs. During the first Oncology Care Model episode, this translated to a monthly total cost reduction of \$9435 compared with the chemoimmunotherapy cohort ($P<.001$), and \$4628 ($P=.010$) during the index line of therapy.

The one patient who developed grade 4 cerebral edema also experienced an increase of cytokine expression levels that was several-fold higher than the median increase observed in the clinical trial.^{1,2}

The investigators concluded that the pharmacokinetic and pharmacodynamic profiles of KTE-X19 were comparable overall in this group of patients, regardless of the Ki-67 proliferation index or *TP53* mutational status.² The pharmacodynamic profile of

KTE-X19 was associated with efficacy outcomes, particularly MRD-negative status, as well as safety endpoints, such as cytokine expression levels.

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Clinical Activity of Cirmtuzumab, an Anti-ROR1 Antibody, in Combination With Ibrutinib: Interim Results of a Phase Ib/II Study in Mantle Cell Lymphoma or Chronic Lymphocytic Leukemia

The monoclonal antibody cirmtuzumab is directed against ROR1, an onco-embryonic tyrosine kinase receptor whose expression is increased in hematologic malignancies and solid tumors. In tumor cells, ROR1 signaling is associated with enhanced tumor growth and survival, a stem cell-like phenotype (cancer cell stemness), and epithelial-

mesenchymal transition. In preclinical studies, cirmtuzumab showed activity as a single agent and in combination with other treatments, including BTK inhibitors.^{1,2}

A phase 1b/2 clinical trial by Lee and colleagues evaluated the combination of cirmtuzumab with ibrutinib.³ The trial enrolled adult patients with MCL (limited to relapsed/refractory

disease) or CLL (relapsed/refractory or treatment-naïve disease). The patients had radiographically measurable disease, and they had no or limited prior exposure to a BTK inhibitor. Other eligibility criteria included an ECOG performance status of 0, 1, or 2 and a requirement for therapy.

The study consisted of 3 parts. Part 1 was the phase 1 dose escalation

of cirtumzumab. Sequential patients were enrolled and received increasing dose levels of cirtumzumab together with standard doses of ibrutinib (specific to the indication) that were initiated on day 28 of cirtumzumab

treatment. Enrollment into part 1 has been completed, and included 12 patients with MCL and 18 patients with CLL/SLL. Part 2 was designed as an expansion cohort, in which patients were treated with the recommended

cirtumzumab dose of 600 mg together with standard doses of ibrutinib (560 mg for patients with MCL and 420 mg for patients with CLL/SLL). Enrollment into part 2 has been completed for patients with CLL/SLL (n=16),

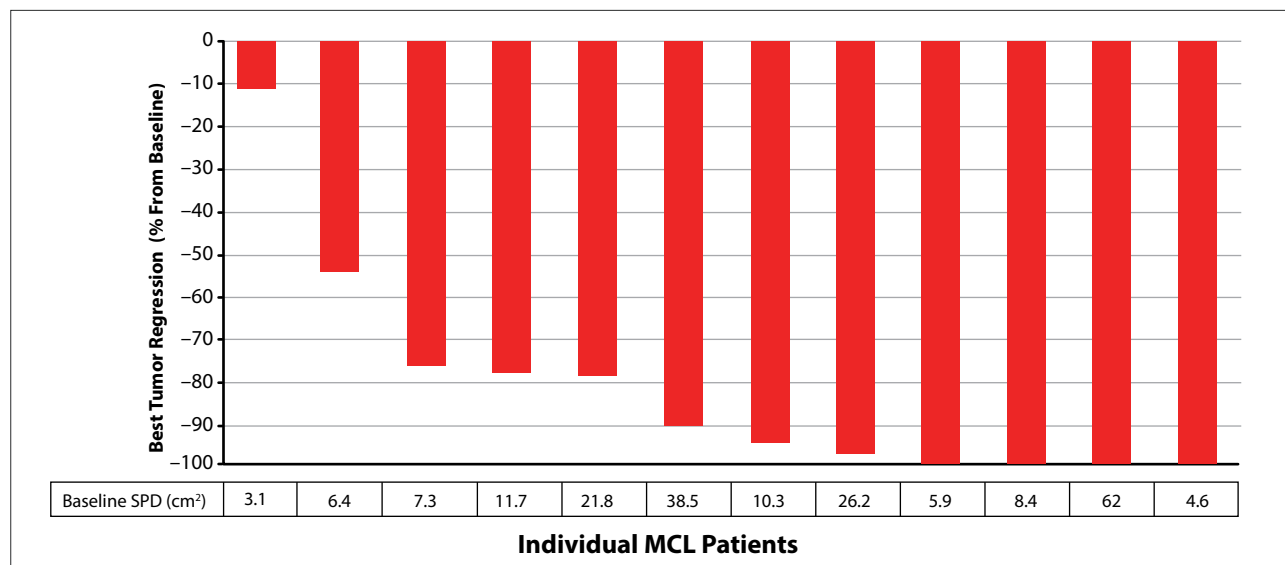


Figure 6. The maximum change in tumor regression from the SPD among patients with mantle cell lymphoma treated with cirtumzumab plus ibrutinib in a phase 1b/2 clinical trial. SPD, sum of the perpendicular diameters. Adapted from Lee HJ et al. ASCO abstract 8036. *J Clin Oncol.* 2020;38(15 suppl).³

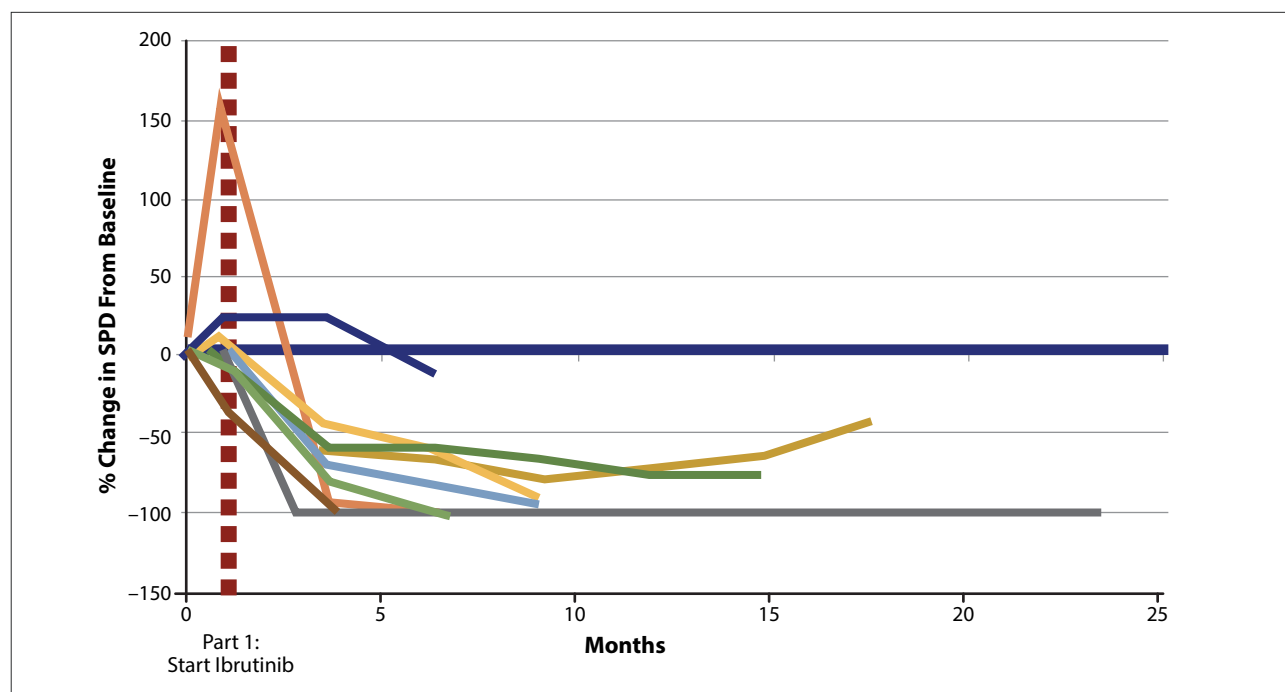


Figure 7. Tumor regression over time among patients with mantle cell lymphoma treated with cirtumzumab plus ibrutinib in a phase 1b/2 clinical trial. SPD, sum of the perpendicular diameters. Adapted from Lee HJ et al. ASCO abstract 8036. *J Clin Oncol.* 2020;38(15 suppl).³

and continues for patients with MCL. Part 3 is the phase 2 portion of the study, in which patients with CLL/SLL are randomly assigned to treatment with cirmtuzumab plus ibrutinib vs ibrutinib alone. This part of the study is actively enrolling patients.

Among the 12 patients with MCL enrolled in part 1, the median age was 63.5 years (range, 49.0-70.0).³ The median time from diagnosis was 2.5 years (range, <1 to 9). Patients had received a median of 2.5 prior therapies (range, 1-5).

There were no dose-limiting toxicities or grade 3 adverse events deemed related to cirmtuzumab alone. Among the 15 patients with MCL who had safety data (including 3 patients from part 2), the most common treatment-emergent adverse events were diarrhea

(46.7%), fatigue (46.7%), confusion (26.7%), and rash (20.0%). The 3 patients in part 1 who discontinued treatment did so owing to progressive disease.

Among the 12 patients with MCL in part 1, the best ORR was 83.3%, which included complete remissions in 58.3% and partial remissions in 25%. An additional 16.7% of patients (n=2) achieved stable disease, equating to a clinical benefit rate of 100%. The maximum change in tumor regression from the baseline sum of the perpendicular diameters (SPD) is shown in Figure 6. Most patients exhibited a rapid and sustained regression in their tumor burden over time (Figure 7). One patient showed transient tumor growth at day 28, but then developed rapid regression that led to

a complete remission. After a median of 8.3 months of follow-up for the MCL patients in part 1, the median progression-free survival (PFS) was 17.5 months. However, the authors noted that at the time of this analysis, only 2 patients had been on-study for longer than 15 months.³

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Mantle Cell Lymphoma: Initial Report From the North American Mantle Cell Lymphoma Consortium

The North American Mantle Cell Lymphoma Consortium presented findings regarding the use of a modified MCL International Prognostic Index (MIPI) scoring system to predict patient prognosis.¹ Since the North American Mantle Cell Lymphoma Project was initiated in 2013, a total of 589 patients with MCL have been recruited from across 23 institutions in North America. For each of these patients, the initial diagnosis of MCL was confirmed by a panel of expert hematopathologists at the University of Nebraska Medical Center.

Among these patients, the median age was 63 years (range, 24-104).¹ The male-to-female ratio was 3.6 to 1. Most patients (89.1%) presented with advanced Ann Arbor stage III or IV disease at diagnosis. Additionally, 28% presented with B symptoms, and 72% showed extranodal involvement. The median follow-up was 5.2 years (range, <1 year to 18.4 years). The 5-year rate

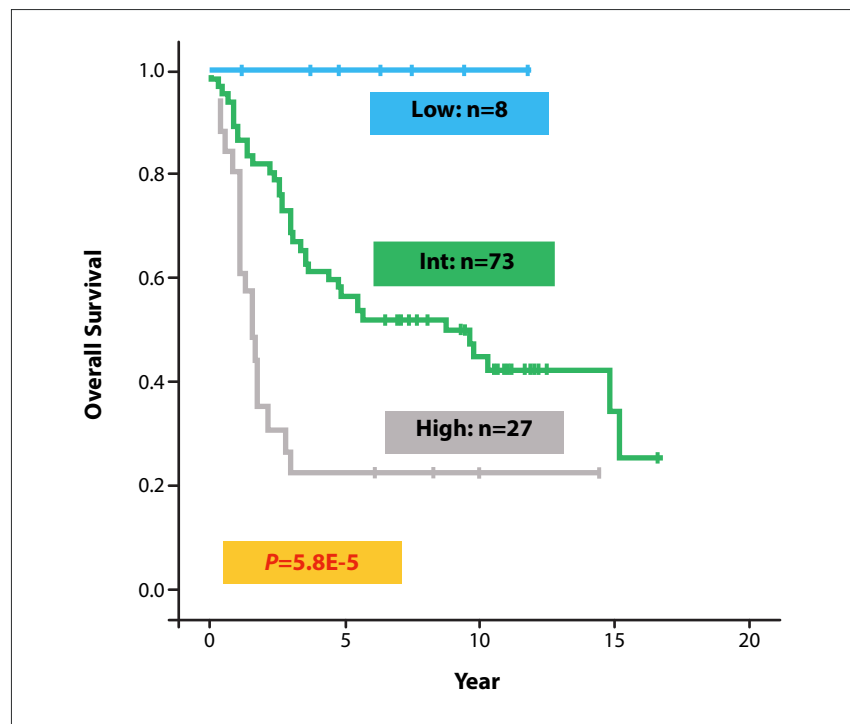


Figure 8. A new scoring system, MIPI-Pathology (MIPI-P), successfully stratified patients with mantle cell lymphoma into 3 risk groups. Adapted from Fu K et al. ASCO abstract 8035. *J Clin Oncol*. 2020;38(15 suppl).¹

of PFS was 24.1%, and the 5-year overall survival rate was 60.2%.

Initially, the investigators conducted a multiple univariate analysis for the entire patient cohort, with the goal of identifying risk factors that significantly correlated with overall survival. The analysis identified several characteristics that significantly correlated with overall survival, although some factors showed distinct predictive values in younger patients (≤ 60 years) vs older patients (> 60 years). For example, 3 factors were significant for overall survival in younger patients but not older patients: disease limited to 1 site vs more than 1 site, classical/small vs blastoid/pleomorphic cytomorphology, and a Ki-67 level of 30% or higher. In contrast, a nodular, diffuse growth pattern was statistically significant for overall survival among older, but not younger, patients. The researchers suggested that these differences may have arisen because some of the factors were evaluated within small sample sizes, and future studies are therefore needed for confirmation.

Traditionally, the MIPI² and the combined MIPI (MIPI-C, a combination of MIPI and the Ki-67 index)³ systems have been effective tools to stratify risk groups in younger patients, but are less accurate for older patients. Thus, a new, simplified scoring system was developed to incorporate more pathologic parameters to predict overall survival. This scoring system is referred to as MIPI-Pathology (MIPI-P). The MIPI-P score includes high Ann Arbor stage (stage III or IV), elevated lactate

ABSTRACT SUMMARY Older Patients With Mantle Cell Lymphoma: Practice Patterns and Predictors of Survival in the Rituximab Era

Karmali and colleagues evaluated the clinical outcomes of older patients with MCL who underwent treatment during the rituximab era, defined as between 2000 and 2015 (Abstract e20064). Data were collected from 12 centers. Among 1168 patients, 465 were ages 65 years or older. Patients were divided into 3 cohorts: younger than 65 years, ages 65 to 69 years, and ages 70 years and older. The 2-year PFS rates were 79%, 69%, and 66%, respectively ($P < .001$), and the 2-year overall survival rates were 92%, 87%, and 84%, respectively ($P < .001$). As a secondary objective of the analysis, the investigators evaluated whether any factors predicted survival among older patients. On multivariate analysis, maintenance rituximab was significantly associated with improved PFS and overall survival ($P < .001$ for both) among older patients. The 2-year PFS rates were 81% with maintenance vs 58% without ($P < .001$). The 2-year overall survival rates were 96% vs 80%, respectively ($P < .001$).

dehydrogenase (above the normal upper limit), cytology (blastoid/pleomorphic), and Ki-67 proliferation index ($\geq 30\%$). One point is assigned to each of these parameters. The MIPI-P was then used to stratify patients from this study into 3 risk groups: low (0), intermediate (1 to 2), and high (3 to 4).

Using the MIPI-P system, patients were successfully stratified into 3 risk groups (Figure 8). The scoring system was particularly accurate among patients ages 60 years or younger ($P = .00093$). MIPI-P was able to stratify older patients into the same risk groups, but the P value was only marginally significant ($P = .07$). This was attributed, at least in part, to the lower number of patients in the low-risk group.

The investigators summarized that in this preliminary report, univariate analysis identified multiple risk factors

that correlate with overall survival in patients with MCL. Some of these factors may have distinct predictive value in younger vs older patient cohorts. Further, this work identified a novel, simplified scoring system, referred to as MIPI-P, that incorporates more pathology parameters and may provide a useful prognostic tool.

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Results of a Completed Phase I Study of LAM-002 (Apilimod Dimesylate), a First-in-Class Phosphatidylinositol-3-Phosphate 5 Kinase (PIKfyve) Inhibitor, Administered as Monotherapy or With Rituximab or Atezolizumab to Patients With Previously Treated Follicular Lymphoma or Other B-Cell Cancers

The novel agent LAM-002 is a selective inhibitor of the phosphatidylinositol-3-phosphate 5 kinase (PIKfyve) protein, a lipid kinase that controls membrane trafficking via the endosome.^{1,2} LAM-002 (also known as apilimod dimesylate), is an orally available small-molecule inhibitor that is highly selective for PIKfyve. Importantly, LAM-002 does not inhibit the different isoforms of phosphoinositide 3-kinase (PI3K), thereby providing a unique mechanism of action distinct from idelalisib, copanlisib, duvelisib, and umbralisib. LAM-002 induces tumor cell death via disruption of lysosomal homeostasis.³ In preclinical animal models, LAM-002 showed antitumor activity both as a single agent and in combination with either anti-CD20 or anti-PD-L1 antibodies.⁴

Diefenbach and colleagues presented results from a phase I clinical trial that evaluated LAM-002 administered as monotherapy or in combination with either the anti-CD20 antibody rituximab or the anti-PD-L1 antibody atezolizumab.⁴ Stage 1 of this study was a dose-ranging portion that aimed to define the maximum tolerated dose and characterize the safety of this agent as monotherapy and in combination. Stage 2 was a dose-expansion portion that continued to evaluate the safety and efficacy of LAM-002 at the selected recommended dosing regimen of 125 mg once daily, either as monotherapy or in combination with rituximab or atezolizumab.

Both stages of the study were conducted in patients with relapsed/refractory non-Hodgkin lymphoma (NHL) who had an ECOG performance status

of 0, 1, or 2 and measurable disease. A total of 40.3% of patients had diffuse large B-cell lymphoma and 30.7% had follicular lymphoma, accounting for the majority of NHL subtypes. Five patients (8.1%) had MCL. The trial evaluated 62 patients through stages 1 and 2. Their median age was 69 years (range, 46-89), and 51.2% were male. The majority of patients had an ECOG performance status of 0 (29.0%) or 1 (62.9%).

The chief toxicities reported during the study were gastrointestinal events and fatigue (Table 1). The gastrointestinal events were dose-dependent, and most often occurred in patients who received doses of LAM-002 that exceeded the recommended regimen during the stage 1 portion. Single-agent LAM-002, at the recommended dosing regimen of 125 mg once daily (n=20), led to fatigue in 45.0% of patients, nausea in 40.0%, decreased appetite in 35.0%, diarrhea

in 25.0%, and vomiting in 20.0%. The combination of LAM-002 plus rituximab or atezolizumab (n=39) led to fatigue in 38.5% of patients, nausea in 35.9%, diarrhea in 25.6%, vomiting in 25.6%, and decreased appetite in 23.1%. The investigators noted that LAM-002 was not associated with myelosuppression, a common toxicity with other treatments for hematologic malignancies, such as lenalidomide or PI3K inhibitors.⁴

At the time of the analysis, efficacy data in patients with MCL were not reported.⁴ Antitumor activity was observed among patients with previously treated follicular lymphoma. The ORR was 53% (9 out of 17 patients), and the median duration of response (in 8 patients) was 6.6 months. The ORR in patients who were treated with LAM-002 as monotherapy (n=7) was 29%. LAM-002 in combination with rituximab (n=8) or atezolizumab (n=2) was associated with ORRs of

Table 1. Adverse Events in ≥20% of Patients Treated With LAM-002 Alone or in Combination

	LAM-002 Monotherapy (n=20)	LAM-002/Rituximab (n=12)	LAM-002/Atezolizumab (n=7)	All Regimens (N=39)
n (%)				
MedDRA Preferred Term				
Fatigue	9 (45.0)	5 (41.7)	1 (14.3)	15 (38.5)
Nausea	8 (40.0)	2 (16.7)	4 (57.1)	14 (35.9)
Diarrhea	5 (25.0)	4 (33.3)	1 (14.3)	10 (25.6)
Vomiting	4 (20.0)	2 (16.7)	4 (57.1)	10 (25.6)
Decreased appetite	7 (35.0)	1 (8.3)	1 (14.3)	9 (23.1)
Anemia	5 (25.0)	0	2 (28.6)	7 (17.9)

MedDRA, Medical Dictionary for Regulatory Activities.

Data from Diefenbach CS et al. ASCO abstract 8017. *J Clin Oncol.* 2020;38(15 suppl).⁴

63% and 100%, respectively. The median PFS (n=17) was 7.0 months. In addition, 1 patient with relapsed/refractory mantle zone lymphoma achieved a partial remission, with a duration of response of 9.2 months. All responses occurred rapidly, by the time of the first (8 weeks) or second (16 weeks) postbaseline scan.

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Multi-Omics Analysis of Mantle Cell Lymphoma Reveals an Immune-Cold Tumor Microenvironment Associated With Ibrutinib Resistance

Although MCL is an incurable B-cell lymphoma, clinical outcomes have greatly improved throughout the last decade with the introduction of new therapies, including BTK inhibitors such as ibrutinib. Although the majority of MCL patients initially respond to ibrutinib, disease progression is common; the rate of 1-year overall survival is only 22%.

The mechanisms that underlie ibrutinib resistance in MCL cells have become an increasing focus of study in the past few years. Several potential mechanisms of resistance have been elucidated, including B-cell receptor signaling, increased signaling through the PI3K pathway, and activation of OXPHOS. Thus far, most resistance mechanisms that have been identified are considered intrinsic to the tumor. Nomie and colleagues presented findings from an investigation of how extrinsic mechanisms within the tumor microenvironment may contribute to ibrutinib resistance.¹

The researchers performed whole-exome sequencing (n=41) and RNA sequencing (n=93) on MCL clinical specimens such as peripheral blood, apheresis samples, and clinical biopsies with an intact tumor microenvironment (harboring components such as macrophages, T cells, NK cells, and monocytes). Additionally, the investigators analyzed 2 previously published cohorts.^{2,3}

The investigators first established 26 knowledge-based gene expression signatures that were related to different activities in the tumor and its microenvironment. The signatures included

angiogenesis and fibroblast activities, protumor immune infiltration, anti-tumor immunity, and malignant cell properties, such as proliferation. Using these 26 gene expression signatures,

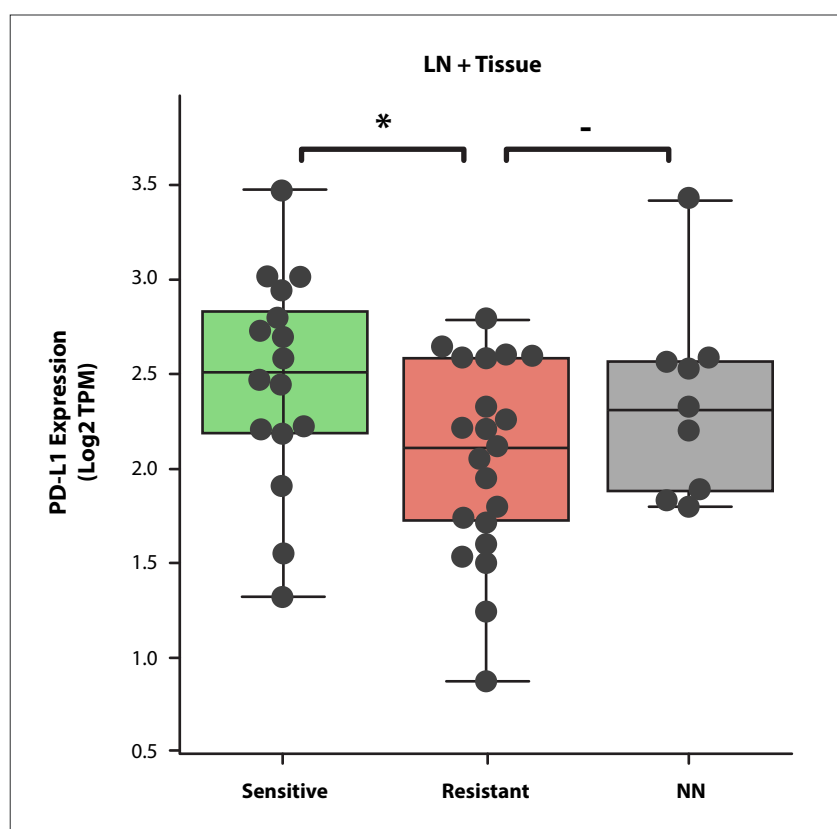


Figure 9. Expression of PD-L1 was decreased in ibrutinib-resistant samples as well as in the immunosuppressive mesenchymal and depleted tumor microenvironment subtypes. The asterisk denotes a statistically significant difference. LN, lymph node; PD-L1, programmed death ligand 1; TPM, transcripts per million. Adapted from Nomie K et al. ASCO abstract 8055. *J Clin Oncol*. 2020;38(15 suppl).¹

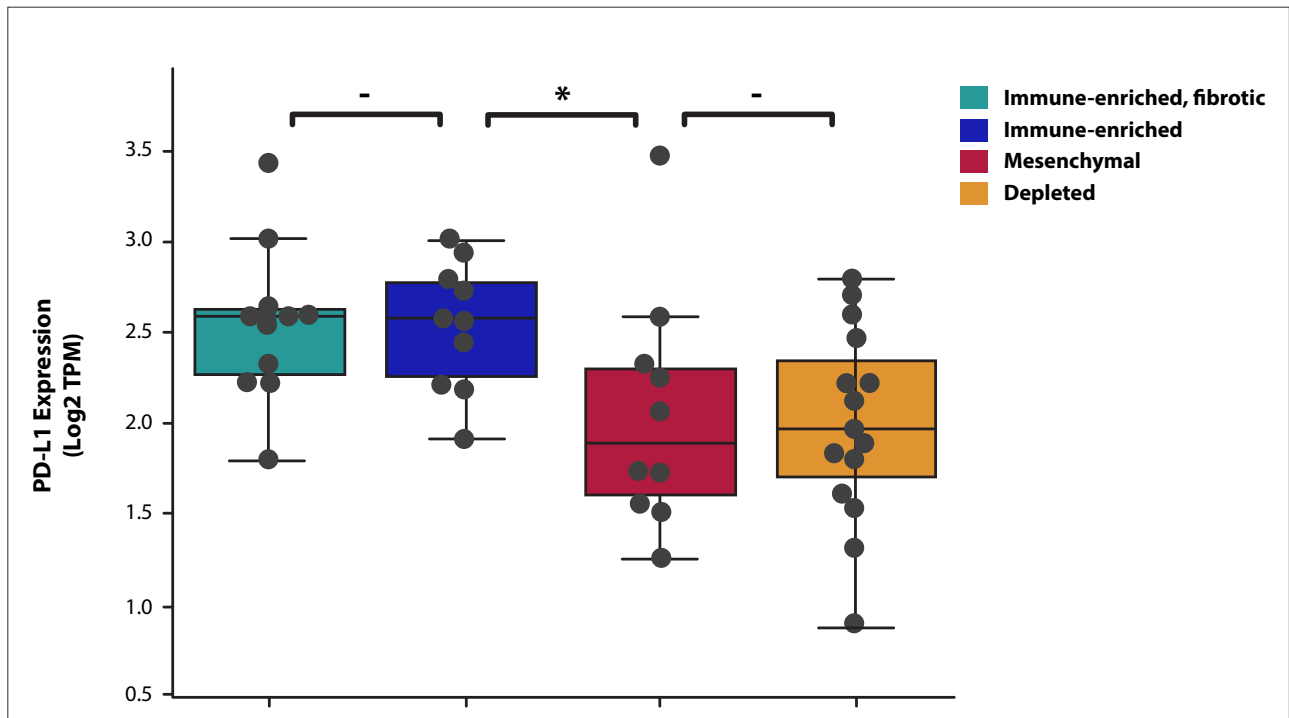


Figure 10. PD-L1 expression levels associated with therapeutic resistance according to the microenvironment cluster. The asterisk denotes a statistically significant difference. PD-L1, programmed death ligand 1; TPM, transcripts per million. Adapted from Nomie K et al. ASCO abstract 8055. *J Clin Oncol.* 2020;38(15 suppl).¹

unsupervised clustering of the previously published datasets revealed 4 distinct subtypes of the MCL tumor microenvironment: immune-enriched fibrotic, immune-enriched nonfibrotic, mesenchymal, and depleted. The immune-enriched fibrotic subtype was defined as showing immune infiltration combined with increased stromal signatures. The immune-enriched nonfibrotic subtype was defined by high expression of immune and checkpoint molecules, combined with low expression of stromal signatures. The mesenchymal subtype was nonimmune, with an increased stromal signature as well as expression of tumor-promoting cytokines. The depleted subtype lacked immune infiltration and stromal expression, and showed the highest content of malignant B cells of the subtypes.

The subtype known as immune-enriched nonfibrotic was composed only of ibrutinib-sensitive samples. In contrast, the majority of the ibrutinib-

resistant samples were divided into the immune-enriched fibrotic subtype and the depleted subtype.

The investigators then evaluated the genetic mutations associated with ibrutinib resistance and the different

ABSTRACT SUMMARY Correlation of PI3K Upregulation With NOTCH2 Mutations in Ibrutinib-Resistant Mantle Cell Lymphoma

The PI3K pathway has been associated with ibrutinib resistance in MCL. Nomie and colleagues analyzed activity of this pathway among both ibrutinib-sensitive and ibrutinib-resistant MCL clinical specimens (including peripheral blood, apheresis, or biopsy samples; Abstract e20065). Whole exome sequencing and RNA-seq were used to characterize these specimens at the genomic and transcriptomic level, respectively. Among 11 cell signaling pathways studied, the PI3K pathway was the most differentially expressed between ibrutinib-sensitive and -resistant MCL specimens. Increased expression of the PI3K pathway was strongly correlated with hyperproliferation ($P=.0000006$) among ibrutinib-resistant MCL tumors. Mutations in the *NOTCH2* gene leading to hyperactivity of the NOTCH2 protein were significantly associated with both hyperproliferation and increased PI3K expression. Mutations of the *TP53* gene were found in 58% of ibrutinib-resistant tumors, which was about 3-fold more frequent than in ibrutinib-sensitive tumors. PI3K signaling is a known p53 activator, and the investigators speculated that this effect may lead to a compensatory tumor suppressive mechanism, by which PI3K activation may induce mutational pressure on *TP53* to promote MCL survival.

tumor microenvironment subtypes. Frequent inactivating mutations in the epigenetic modifier *KMT2D* were identified within the immune-suppressed mesenchymal microenvironment. Additionally, *NOTCH1* gain-of-function mutations were identified exclusively in ibrutinib-resistant samples. Expression of the programmed death ligand 1 (PD-L1) was decreased in ibrutinib-resistant samples, as well as in the immunosuppressive mesenchymal and depleted tumor microenvironment subtypes (Figure 9). The authors suggested that this finding could mean that targeting the PD-1/PD-L1 checkpoint may not help overcome ibrutinib resistance.¹ PD-L1 expression levels associated

with therapeutic resistance according to the microenvironment cluster are shown in Figure 10.

The investigators concluded that classifying the tumor microenvironment using a transcriptomic-based platform provided insight into therapeutic resistance in mantle cell lymphoma.¹ The analysis revealed extrinsic mechanisms regulating the growth and progression of the disease, as well as response to ibrutinib. The identification of an immune-enriched microenvironment, consisting solely of ibrutinib-sensitive samples, suggests that this subset of MCL may be sensitive to immune checkpoint blockade. According to these portraits of the tumor microenvironment, sensitivity

and resistance to ibrutinib are separate. The study suggests that the tumor microenvironment has a prominent role in regulating the activity of ibrutinib and response to treatment.

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Highlights in Mantle Cell Lymphoma From the 2020 American Society of Clinical Oncology Annual Meeting: Commentary

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The American Society of Clinical Oncology (ASCO) annual meeting was presented in a virtual format in 2020. Several important presentations provided data for patients with mantle cell lymphoma.

Dr Richard Furman and colleagues evaluated pooled data from studies of acalabrutinib in hematologic malignancies to generate a more robust safety dataset.¹ The studies evaluated acalabrutinib as a single agent. Acalabrutinib is a newer-generation Bruton tyrosine kinase (BTK) inhibitor that is somewhat more selective than the first-generation BTK inhibitor, ibrutinib.² In theory, the increased kinase selectivity of acalabrutinib might lead to fewer adverse events. Whether acalabrutinib is better tolerated than ibrutinib is an area of interest.

The study by Dr Furman pooled safety data from 9 different trials of acalabrutinib in patients with mantle cell lymphoma, chronic lymphocytic leukemia, Waldenström macroglobulinemia, follicular lymphoma, diffuse large B-cell lymphoma, and a few other less common subtypes.¹ Together, the studies included more than 1000 patients. Approximately one-third were treatment-naïve, and two-thirds had relapsed/refractory disease. The median follow-up was 26 months.

Approximately 96% of patients reported an adverse event. The most commonly reported adverse events were the typical ones associated with

acalabrutinib, and included headache, diarrhea, upper respiratory tract infection, bruising, nausea, and fatigue. Importantly, serious adverse events were relatively infrequent, occurring in 39% of patients. Of note, headache—a frequent adverse event with acalabrutinib³—tends to improve with time and is fairly easy to manage with caffeine and/or acetaminophen. Throughout the entire dataset, headache led only 1 patient to discontinue acalabrutinib, which shows that this side effect is manageable.

The most frequently reported serious adverse event was pneumonia. There is a background risk for infection and pneumonia in patients with mantle cell lymphoma, so it can be difficult to discern whether cases are attributable to the drug vs the underlying disease.

The most important information conveyed by this analysis concerns the treatment discontinuation rate, which indicates the percentage of patients who were unable to continue treatment, even with dose reductions, because of side effects. In this pooled dataset, the discontinuation rate was 9%. This rate is somewhat less than that seen with ibrutinib,⁴ and suggests that acalabrutinib is fairly well-tolerated.

Other adverse events of special interest include atrial fibrillation and hypertension, both of which can be problematic developments in patients

receiving BTK inhibitors. In the pooled data analysis, the rate of atrial fibrillation was 4.4%, which is lower than the rate seen with pooled ibrutinib, which ranges from approximately 6% to 16%.⁵ The rate of hypertension was 7.6%, which is lower than that for ibrutinib.⁶

Bleeding is common to all of the BTK inhibitors.⁷ In the pooled analysis of acalabrutinib data, only 3% of patients developed grade 3 hemorrhage or worse. Therefore, there was not a high rate of serious bleeding in this study.

This pooled analysis of more than 1000 patients provides a valuable dataset. The data provide important insights into the risks of adverse events associated with acalabrutinib. Overall, it appears that acalabrutinib has a fairly favorable safety profile.

Dr Michael Wang and colleagues presented an analysis of the product characterization and pharmacologic profile of KTE-X19, a next-generation chimeric antigen receptor (CAR) T-cell therapy.⁸ The phase 2 ZUMA-2 study evaluated KTE-X19 in patients with relapsed/refractory mantle cell lymphoma.⁹ The data were encouraging, although follow-up was short. Among approximately 60 patients, the overall response rate was 93%, with a complete remission rate of 67%. After a median follow-up of 1 year, approximately 60% of patients maintained an ongoing remission. It is hoped that

these patients will remain in remission for a prolonged period; the results of longer follow-up will be key to understanding the benefits of KTE-X19 in this setting. There is a reasonable chance that the US Food and Drug Administration (FDA) will approve KTE-X19 based on this dataset. Physicians who treat relapsed/refractory mantle cell lymphoma would be interested in having this agent in the armamentarium.

The abstract presented at the ASCO meeting evaluated biomarkers that might predict for response and toxicity.⁸ The investigators measured several serum cytokines. They identified a correlation between increased peak levels of select cytokines, such as interferon gamma, interleukin (IL) 6, and IL-2, and a higher likelihood of negative minimal residual disease (MRD) status. This finding raises the possibility that the T-cell expansion that occurs in these patients after T-cell infusion might be important in generating an optimal response. However, patients who had higher levels of these cytokines were more likely to develop complications of CAR T-cell therapy, including cytokine release syndrome and serious neurologic events. The challenge moving forward will be to develop strategies to fine-tune CAR T-cell proliferation after infusion in order to strike the appropriate balance between efficacy and toxicity.

Dr Hun Ju Lee and colleagues presented a study evaluating the clinical activity of cirmtuzumab, a novel monoclonal antibody.¹⁰ Cirmtuzumab is an antibody that targets a receptor tyrosine kinase known as ROR1. The physiologic function of ROR1 appears to be important in embryonic development.¹¹ It appears to signal through the Wnt pathway, and supports the growth and survival of cells. ROR1 is highly expressed by fetuses, but then expression seems to diminish over time. In some cancers, expression of ROR1 is elevated, making it a therapeutic target for drug therapy.

The investigators identified high ROR1 expression in several hematologic malignancies, particularly chronic lymphocytic leukemia and mantle cell lymphoma.¹⁰ Studies of single-agent cirmtuzumab showed modest single-agent activity in these diseases, providing proof of concept of both preclinical and clinical activity.¹²⁻¹⁴ The investigators were interested in studying this novel monoclonal antibody in combination with ibrutinib in mantle cell lymphoma and chronic lymphocytic leukemia.

The poster presented at the 2020 ASCO meeting provided data for an ongoing phase 1 clinical trial in patients with relapsed chronic lymphocytic leukemia (n=34) or relapsed mantle cell lymphoma (n=12).¹⁰ Of note, there were no reports of grade 3 toxicity. There did not appear to be any significant increased additive toxicity for combining cirmtuzumab with ibrutinib. In the mantle cell lymphoma cohort, the overall response rate was 83%, with a complete response rate of 58%. These responses, particularly the rate of complete response, are somewhat higher than would be expected with ibrutinib alone in mantle cell lymphoma.¹⁵ There may be some additive or synergistic effects with combination treatment. However, a larger dataset would be needed before any definitive statements about clinical activity could be made. Among the CLL cohort, the overall response rate was 88%, consisting almost entirely of partial remissions. This outcome is similar to that expected with ibrutinib alone,¹⁶ so it is unclear whether the addition of cirmtuzumab improved outcome in the CLL population.

These preliminary results are interesting. It is not yet known whether cirmtuzumab will represent a significant advance in the field, but continued study is warranted. The investigators plan to undertake additional dose expansions in both study populations. The study will then pivot into a randomized phase 2 trial, in which

patients will be randomly assigned to treatment with single-agent cirmtuzumab vs cirmtuzumab plus ibrutinib. In CLL/SLL, the investigators have initiated a phase 2 study, which will be the true test of whether the antibody provides additional benefit to ibrutinib in these patient populations.

An initial report provided data on mantle cell lymphoma from the North American Mantle Cell Lymphoma Consortium.¹⁷ The consortium consists of 23 centers, and is led by investigators at the University of Nebraska. This pooled dataset includes 589 patients with mantle cell lymphoma who have been treated and observed over the past 15 to 20 years. The median age of the cohort was 63 years. The population was typical of patients with mantle cell lymphoma. Most patients were male, and the vast majority had stage 3 or 4 disease.

The median follow-up was 5.2 years. An interesting finding is that the median 5-year progression-free survival was only 24%, and the 5-year overall survival was approximately 60%. These outcomes are somewhat inferior to what is usually seen in mantle cell lymphoma.¹⁸ However, most of the survival data in mantle cell lymphoma is derived from clinical trials, and there is always an inherent selection bias in patients who enroll in studies. This population database may provide a more accurate representation of survival among patients with mantle cell lymphoma in the community.

The analysis presented at the 2020 ASCO meeting focused on prognostic factors in mantle cell lymphoma.¹⁷ There are several prognostic tools already in use, such as the Mantle Cell Lymphoma International Prognostic Index (MIPI) and the combined MIPI (MIPI-C).^{19,20} The MIPI-C takes the 4 clinical factors of the MIPI (age, performance status, lactate dehydrogenase [LDH], and leukocyte count) and then incorporates the proliferation index measured by Ki-67 staining. The consortium investigators mined the

data to develop an alternative prognostic system known as MIPI-P, with the “P” standing for pathology. This scoring system assigns 1 point each based on the following factors: disease stage, LDH level, cytology under the microscope, and the Ki-67 score. The investigators identified 3 risk groups with different outcomes. They noted that the prognostic index worked well in both older and younger patients.

This study provided an interesting initial interrogation of this dataset, which will likely provide valuable information. I anticipate seeing more studies of these data in the future. It is not clear whether the new prognostic tool substantially improves upon the existing tools. There are many prognostic indices among the different lymphomas, and they all have value. Further study will be needed to confirm the value of this new scoring system.

Dr Catherine Diefenbach and colleagues reported results from a phase 1 study of the novel agent LAM-002, which is a first-in-class, small-molecule PIKfyve inhibitor.²¹ Several phosphoinositide 3 (PI3) kinase inhibitors are approved in follicular lymphoma and CLL. LAM-002 has a different mechanism of action from the PI 3-kinase inhibitors already in use. PIKfyve is a lipid kinase that regulates endosomal membrane trafficking. LAM-002 disrupts the normal lysosomal homeostasis, which can result in cell death.

Dr Diefenbach reported ongoing experience with a completed phase 1 clinical trial of 62 patients with previously treated B-cell malignancies, including 5 patients with mantle cell lymphoma.²¹ Lower doses of LAM-002 were well-tolerated, but excessive toxicity—in the form of nausea, vomiting, and diarrhea—was seen with doses of 150 mg twice a day. The dose was decreased to 125 mg twice daily for expansion cohorts that evaluated LAM-002 as a single agent, in combination with rituximab, and in

combination with the PD-L1 inhibitor atezolizumab.

The abstract presented at the 2020 ASCO meeting focused on patients with follicular lymphoma.²¹ LAM-002 was fairly well-tolerated at 125 mg administered twice daily. Objective responses were seen in 2 of 7 patients receiving LAM-002 monotherapy, in 5 of 8 patients treated with LAM-002 plus rituximab, and in 2 of 2 patients treated with LAM-002 plus atezolizumab. (In addition, a patient with marginal zone lymphoma had a partial response.) With these small numbers, it is difficult to assess the activity of this agent. The single-agent activity is modest; data for the combination regimens are somewhat better. Of note, there were no reports of significant myelosuppression or any of the typical toxicities associated with PI 3-kinase inhibitors. LAM-002 may be relatively easy to use in combination regimens, and it appears that the investigators will continue this line of study to better characterize the activity of this agent in patients with relapsed follicular lymphoma. The phase 1 study is completed, and provides proof of concept of activity and tolerability. I look forward to seeing results of phase 2 studies.

An electronic abstract from Dr Reem Karmali and coworkers provided retrospective outcome data for older patients with mantle cell lymphoma from a pooled analysis from several academic medical centers.²² The analysis evaluated treatment patterns, practice patterns, and outcomes. The analysis was limited to patients with mantle cell lymphoma receiving frontline therapy who were older than 65 years and had received treatment between 2000 and 2015. The study identified 465 patients, with a median age of 70 years. These patients are therefore a representative older population.

The most commonly used frontline treatment regimen, bendamustine/rituximab, was used in 36% of patients.²² Other treatments included

a cytarabine combination in 16% and lenalidomide-based therapy in 2%. Nineteen percent of the patients were treated in a clinical trial. Of note, after patients completed induction therapy, 24% were referred to autologous stem cell transplant, and 44% were referred to maintenance rituximab. The use of autologous stem cell transplant was not associated with better progression-free survival or overall survival, which is interesting and perhaps unexpected. In contrast, maintenance rituximab improved progression-free survival and overall survival. These valuable data might provide more evidence that intensive strategies in the older patient population may not be the optimal approach. There is some evidence that maintenance rituximab is a beneficial intervention in older patients with mantle cell lymphoma.

In another electronic abstract, Dr Nilanjan Ghosh and colleagues presented results from a health care resource utilization analysis of patients with relapsed/refractory mantle cell lymphoma.²³ They evaluated a database to compare health care costs and utilization with ibrutinib vs chemoimmunotherapy.

The researchers identified 146 patients treated with ibrutinib and 158 treated with chemoimmunotherapy. They looked at healthcare expenditures over a 6-month period and a 12-month period. After factoring in all of the health care costs—such as those for the doctor visits, scans, laboratory tests, monitoring, and hospitalization—chemoimmunotherapy was associated with higher costs for both the 6-month and 12-month intervals. Ibrutinib is generally fairly easy to administer as an outpatient, is not associated with many complications, and rarely results in hospitalizations.

It will be important to evaluate healthcare costs over longer periods than just 6 and 12 months. For example, if a patient receives chemoimmunotherapy, usually the treatment is completed near the 6-month mark.

One would expect that once treatment ends, the healthcare utilization and costs would start to diminish substantially. Among patients treated with ibrutinib or any other continuous oral therapy, expenses will accumulate over time. Therefore, the putative savings for ibrutinib that are realized in the first 6 months may actually diminish substantially in year 2 and year 3, as compared with other approaches. I hope these investigators perform a subsequent analysis to calculate healthcare resource utilization in years 2 and 3.

Disclosure

Dr Kahl has received consulting fees from AbbVie, AstraZeneca, ADC Therapeutics, BeiGene, Celgene, Gilead, Genentech, and Janssen.

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**CALQUENCE® (acalabrutinib) capsules, for oral use
Initial U.S. Approval: 2017**

Brief Summary of Prescribing Information.

For full Prescribing Information consult official package insert.

INDICATIONS AND USAGE

Mantle Cell Lymphoma

CALQUENCE is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

This indication is approved under accelerated approval based on overall response rate [see Clinical Studies (14.1) in the full Prescribing Information]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

DOSAGE AND ADMINISTRATION

Recommended Dosage

CALQUENCE as Monotherapy

For patients with MCL, the recommended dose of CALQUENCE is 100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity.

Advise patients to swallow capsule whole with water. Advise patients not to open, break or chew the capsules. CALQUENCE may be taken with or without food. If a dose of CALQUENCE is missed by more than 3 hours, it should be skipped and the next dose should be taken at its regularly scheduled time. Extra capsules of CALQUENCE should not be taken to make up for a missed dose.

Recommended Dosage for Drug Interactions

Dose Modifications for Use with CYP3A Inhibitors or Inducers

These are described in Table 1 [see Drug Interactions (7) in the full Prescribing Information].

Table 1: Recommended Dose Modifications for Use with CYP3A Inhibitors or Inducers

CYP3A	Co-administered Drug	Recommended CALQUENCE use
Inhibition	Strong CYP3A inhibitor	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for up to seven days), interrupt CALQUENCE.
	Moderate CYP3A inhibitor	100 mg once daily.
Induction	Strong CYP3A inducer	Avoid concomitant use. If these inducers cannot be avoided, increase CALQUENCE dose to 200 mg approximately every 12 hours.

Concomitant Use with Gastric Acid Reducing Agents

Proton Pump Inhibitors: Avoid concomitant use [see Drug Interactions (7) in the full Prescribing Information].

H2-Receptor Antagonists: Take CALQUENCE 2 hours before taking a H2-receptor antagonist [see Drug Interactions (7) in the full Prescribing Information].

Antacids: Separate dosing by at least 2 hours [see Drug Interactions (7) in the full Prescribing Information].

Dose Modifications for Adverse Reactions

Recommended dose modifications of CALQUENCE for Grade 3 or greater adverse reactions are provided in Table 2.

Table 2: Recommended Dose Modifications for Adverse Reactions

Event	Adverse Reaction Occurrence	Dose Modification (Starting dose = 100 mg approximately every 12 hours)
Grade 3 or greater non-hematologic toxicities, Grade 3 thrombocytopenia with bleeding, Grade 4 thrombocytopenia or Grade 4 neutropenia lasting longer than 7 days	First and Second	Interrupt CALQUENCE. Once toxicity has resolved to Grade 1 or baseline level, CALQUENCE may be resumed at 100 mg approximately every 12 hours.
	Third	Interrupt CALQUENCE. Once toxicity has resolved to Grade 1 or baseline level, CALQUENCE may be resumed at a reduced frequency of 100 mg once daily.
	Fourth	Discontinue CALQUENCE.

Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

Refer to the obinutuzumab prescribing information for management of obinutuzumab toxicities.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Serious and Opportunistic Infections

Fatal and serious infections, including opportunistic infections, have occurred in patients with hematologic malignancies treated with CALQUENCE.

Serious or Grade 3 or higher infections (bacterial, viral, or fungal) occurred in 19% of 1029 patients exposed to CALQUENCE in clinical trials, most often due to respiratory tract infections (11% of all patients, including pneumonia in 6%). These infections predominantly occurred in the absence of Grade 3 or 4 neutropenia, with neutropenic infection reported in 1.9% of all patients. Opportunistic infections in recipients of CALQUENCE have included, but are not limited to, hepatitis B virus reactivation, fungal pneumonia, *Pneumocystis jiroveci* pneumonia, Epstein-Barr virus reactivation, cytomegalovirus, and progressive multifocal leukoencephalopathy (PML). Consider prophylaxis in patients who are at increased risk for opportunistic infections. Monitor patients for signs and symptoms of infection and treat promptly.

Hemorrhage

Fatal and serious hemorrhagic events have occurred in patients with hematologic malignancies treated with CALQUENCE. Major hemorrhage (serious or Grade 3 or higher bleeding or any central nervous system bleeding) occurred in 3.0% of patients, with fatal hemorrhage occurring in 0.1% of 1029 patients exposed to CALQUENCE in clinical trials. Bleeding events of any grade, excluding bruising and petechiae, occurred in 22% of patients.

Use of antithrombotic agents concomitantly with CALQUENCE may further increase the risk of hemorrhage. In clinical trials, major hemorrhage occurred in 2.7% of patients taking CALQUENCE without antithrombotic agents and 3.6% of patients taking CALQUENCE with antithrombotic agents. Consider the risks and benefits of antithrombotic agents when co-administered with CALQUENCE. Monitor patients for signs of bleeding.

Consider the benefit-risk of withholding CALQUENCE for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (23%), anemia (8%), thrombocytopenia (7%), and lymphopenia (7%), developed in patients with hematologic malignancies treated with CALQUENCE. Grade 4 neutropenia developed in 12% of patients. Monitor complete blood counts regularly during treatment. Interrupt treatment, reduce the dose, or discontinue treatment as warranted [see Dose Modifications for Adverse Reactions (2.4) in the full Prescribing Information].

Second Primary Malignancies

Second primary malignancies, including skin cancers and other solid tumors, occurred in 12% of 1029 patients exposed to CALQUENCE in clinical trials. The most frequent second primary malignancy was skin cancer, reported in 6% of patients. Monitor patients for skin cancers and advise protection from sun exposure.

Atrial Fibrillation and Flutter

Grade 3 atrial fibrillation or flutter occurred in 1.1% of 1029 patients treated with CALQUENCE, with all grades of atrial fibrillation or flutter reported in 4.1% of all patients. The risk may be increased in patients with cardiac risk factors, hypertension, previous arrhythmias, and acute infection. Monitor for symptoms of arrhythmia (e.g., palpitations, dizziness, syncope, dyspnea) and manage as appropriate.

ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Serious and Opportunistic Infections [see Warnings and Precautions (5.1) in the full Prescribing Information]
- Hemorrhage [see Warnings and Precautions (5.2) in the full Prescribing Information]
- Cytopenias [see Warnings and Precautions (5.3) in the full Prescribing Information]
- Second Primary Malignancies [see Warnings and Precautions (5.4) in the full Prescribing Information]
- Atrial Fibrillation and Flutter [see Warnings and Precautions (5.5) in the full Prescribing Information]

Clinical Trials Experience

As clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot

be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the Warnings and Precautions reflect exposure to CALQUENCE 100 mg approximately every 12 hours in 1029 patients with hematologic malignancies. Treatment includes CALQUENCE monotherapy in 820 patients in 6 trials, and CALQUENCE with obinutuzumab in 209 patients in 2 trials. Among these recipients of CALQUENCE, 88% were exposed for at least 6 months and 79% were exposed for at least one year. In this pooled safety population, adverse reactions in ≥ 30% of 1029 patients were anemia, neutropenia, upper respiratory tract infection, thrombocytopenia, headache, diarrhea, and musculoskeletal pain.

Mantle Cell Lymphoma

The safety data described in this section reflect exposure to CALQUENCE (100 mg approximately every 12 hours) in 124 patients with previously treated MCL in Trial LY-004 [see Clinical Studies (14.1) in the full Prescribing Information]. The median duration of treatment with CALQUENCE was 16.6 (range: 0.1 to 26.6) months. A total of 91 (73.4%) patients were treated with CALQUENCE for ≥ 6 months and 74 (59.7%) patients were treated for ≥ 1 year.

The most common adverse reactions (≥ 20%) of any grade were anemia, thrombocytopenia, headache, neutropenia, diarrhea, fatigue, myalgia, and bruising. Grade 1 severity for the non-hematologic, most common events were as follows: headache (25%), diarrhea (16%), fatigue (20%), myalgia (15%), and bruising (19%). The most common Grade ≥ 3 non-hematological adverse reaction (reported in at least 2% of patients) was diarrhea.

Dose reductions and discontinuation due to any adverse reaction were reported in 1.6% and 6.5% of patients, respectively.

Tables 3 and 4 present the frequency category of adverse reactions observed in patients with MCL treated with CALQUENCE.

Table 3: Non-Hematologic Adverse Reactions in ≥ 5% (All Grades) of Patients with MCL in Trial LY-004

Body System Adverse Reactions*	CALQUENCE Monotherapy N=124	
	All Grades (%)	Grade ≥ 3 (%)
Nervous system disorders		
Headache	39	1.6
Gastrointestinal disorders		
Diarrhea	31	3.2
Nausea	19	0.8
Abdominal pain	15	1.6
Constipation	15	-
Vomiting	13	1.6
General disorders		
Fatigue	28	0.8
Musculoskeletal and connective tissue disorders		
Myalgia	21	0.8
Skin and subcutaneous tissue disorders		
Bruising ^a	21	-
Rash ^b	18	0.8
Vascular disorders		
Hemorrhage ^c	8	0.8
Respiratory, thoracic and mediastinal disorders		
Epistaxis	6	-

* Per NCI CTCAE version 4.03.

^a Bruising: Includes all terms containing 'bruise,' 'contusion,' 'petechiae,' or 'ecchymosis'

^b Rash: Includes all terms containing 'rash'

^c Hemorrhage: Includes all terms containing 'hemorrhage' or 'hematoma'

Table 4: Hematologic Adverse Reactions Reported in ≥ 20% of Patients with MCL in Trial LY-004

Hematologic Adverse Reactions*	CALQUENCE Monotherapy N=124	
	All Grades (%)	Grade ≥ 3 (%)
Hemoglobin decreased	46	10
Platelets decreased	44	12
Neutrophils decreased	36	15

* Per NCI CTCAE version 4.03; based on laboratory measurements and adverse reactions.

Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 4.8% of patients.

DRUG INTERACTIONS

Strong CYP3A Inhibitors		
<i>Clinical Impact</i>	<ul style="list-style-type: none"> Co-administration of CALQUENCE with a strong CYP3A inhibitor (itraconazole) increased acalabrutinib plasma concentrations [see <i>Clinical Pharmacology (12.3) in the full Prescribing Information</i>]. Increased acalabrutinib concentrations may result in increased toxicity. 	
<i>Prevention or Management</i>	<ul style="list-style-type: none"> Avoid co-administration of strong CYP3A inhibitors with CALQUENCE. Alternatively, if the inhibitor will be used short-term, interrupt CALQUENCE [see <i>Recommended Dosage for Drug Interactions (2.3) in the full Prescribing Information</i>]. 	
Moderate CYP3A Inhibitors		
<i>Clinical Impact</i>	<ul style="list-style-type: none"> Co-administration of CALQUENCE with a moderate CYP3A inhibitor may increase acalabrutinib plasma concentrations [see <i>Clinical Pharmacology (12.3) in the full Prescribing Information</i>]. Increased acalabrutinib concentrations may result in increased toxicity. 	
<i>Prevention or Management</i>	<ul style="list-style-type: none"> When CALQUENCE is co-administered with moderate CYP3A inhibitors, reduce acalabrutinib dose to 100 mg once daily. 	
Strong CYP3A Inducers		
<i>Clinical Impact</i>	<ul style="list-style-type: none"> Co-administration of CALQUENCE with a strong CYP3A inducer (rifampin) decreased acalabrutinib plasma concentrations [see <i>Clinical Pharmacology (12.3) in the full Prescribing Information</i>]. Decreased acalabrutinib concentrations may reduce CALQUENCE activity. 	
<i>Prevention or Management</i>	<ul style="list-style-type: none"> Avoid co-administration of strong CYP3A inducers with CALQUENCE. If a strong CYP3A inducer cannot be avoided, increase the acalabrutinib dose to 200 mg approximately every 12 hours. 	
Gastric Acid Reducing Agents		
<i>Clinical Impact</i>	<ul style="list-style-type: none"> Co-administration of CALQUENCE with a proton pump inhibitor, H2-receptor antagonist, or antacid may decrease acalabrutinib plasma concentrations [see <i>Clinical Pharmacology (12.3) in the full Prescribing Information</i>]. Decreased acalabrutinib concentrations may reduce CALQUENCE activity. If treatment with a gastric acid reducing agent is required, consider using a H2-receptor antagonist (e.g., ranitidine or famotidine) or an antacid (e.g., calcium carbonate). 	
<i>Prevention or Management</i>	Antacids	Separate dosing by at least 2 hours [see <i>Recommended Dosage for Drug Interactions (2.3) in the full Prescribing Information</i>].
	H2-receptor antagonists	Take CALQUENCE 2 hours before taking the H2-receptor antagonist [see <i>Recommended Dosage for Drug Interactions (2.3) in the full Prescribing Information</i>].
	Proton pump inhibitors	Avoid co-administration. Due to the long-lasting effect of proton pump inhibitors, separation of doses may not eliminate the interaction with CALQUENCE.

reduced fetal growth in rabbits at maternal exposures (AUC) 2 times exposures in patients at the recommended dose of 100 mg approximately every 12 hours (see *Data*). Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. 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.

Data

Animal Data

In a combined fertility and embryo-fetal development study in female rats, acalabrutinib was administered orally at doses up to 200 mg/kg/day starting 14 days prior to mating through gestational day [GD] 17. No effects on embryo-fetal development and survival were observed. The AUC at 200 mg/kg/day in pregnant rats was approximately 9-times the AUC in patients at the recommended dose of 100 mg approximately every 12 hours. The presence of acalabrutinib and its active metabolite were confirmed in fetal rat plasma.

In an embryo-fetal development study in rabbits, pregnant animals were administered acalabrutinib orally at doses up to 200 mg/kg/day during the period of organogenesis (from GD 6-18). Administration of acalabrutinib at doses ≥ 100 mg/kg/day produced maternal toxicity and 100 mg/kg/day resulted in decreased fetal body weights and delayed skeletal ossification. The AUC at 100 mg/kg/day in pregnant rabbits was approximately 2-times the AUC in patients at 100 mg approximately every 12 hours.

In a pre- and postnatal development study in rats, acalabrutinib was administered orally to pregnant animals during organogenesis, parturition and lactation, at doses of 50, 100, and 150 mg/kg/day. Dystocia (prolonged or difficult labor) and mortality of offspring were observed at doses ≥ 100 mg/kg/day. The AUC at 100 mg/kg/day in pregnant rats was approximately 2-times the AUC in patients at 100 mg approximately every 12 hours. Underdeveloped renal papilla was also observed in F1 generation offspring at 150 mg/kg/day with an AUC approximately 5-times the AUC in patients at 100 mg approximately every 12 hours.

Lactation

Risk Summary

No data are available regarding the presence of acalabrutinib or its active metabolite in human milk, its effects on the breastfed child, or on milk production. Acalabrutinib and its active metabolite were present in the milk of lactating rats. Due to the potential for adverse reactions in a breastfed child from CALQUENCE, advise lactating women not to breastfeed while taking CALQUENCE and for at least 2 weeks after the final dose.

Females and Males of Reproductive Potential

Pregnancy

Pregnancy testing is recommended for females of reproductive potential prior to initiating CALQUENCE therapy.

Contraception

Females

CALQUENCE may cause embryo-fetal harm and dystocia when administered to pregnant women [see *Use in Specific Populations (8.1) in the full Prescribing Information*]. Advise female patients of reproductive potential to use effective contraception during treatment with CALQUENCE and for at least 1 week following the last dose of CALQUENCE. 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.

Pediatric Use

The safety and efficacy of CALQUENCE in pediatric patients have not been established.

Geriatric Use

Of the 929 patients with CLL or MCL in clinical trials of CALQUENCE, 68% were 65 years of age or older, and 24% were 75 years of age or older. Among patients 65 years of age or older, 59% had Grade 3 or higher adverse reactions and 39% had serious adverse reactions. Among patients younger than age 65, 45% had Grade 3 or higher adverse reactions and 25% had serious adverse reactions. No clinically relevant differences in efficacy were observed between patients ≥ 65 years and younger.

Hepatic Impairment

Avoid administration of CALQUENCE in patients with severe hepatic impairment. The safety of CALQUENCE has not been evaluated in patients with moderate or severe hepatic impairment [see *Recommended Dosage for Hepatic Impairment (2.2) and Clinical Pharmacology (12.3) in the full Prescribing Information*].

PATIENT COUNSELING INFORMATION

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

Serious and Opportunistic Infections

Inform patients of the possibility of serious infection and to report signs or symptoms suggestive of infection [see *Warnings and Precautions (5.1) in the full Prescribing Information*].

Hemorrhage

Inform patients to report signs or symptoms of bleeding. Inform patients that CALQUENCE may need to be interrupted for major surgeries [see *Warnings and Precautions (5.2) in the full Prescribing Information*].

Cytopenias

Inform patients that they will need periodic blood tests to check blood counts during treatment with CALQUENCE [see *Warnings and Precautions (5.3) in the full Prescribing Information*].

Second Primary Malignancies

Inform patients that other malignancies have been reported in patients who have been treated with CALQUENCE, including skin cancer and other solid tumors. Advise patients to use sun protection [see *Warnings and Precautions (5.4) in the full Prescribing Information*].

Atrial Fibrillation and Flutter

Counsel patients to report any signs of palpitations, dizziness, fainting, chest discomfort, and shortness of breath [see *Warnings and Precautions (5.5) in the full Prescribing Information*].

Pregnancy Complication

CALQUENCE may cause fetal harm and dystocia. Advise women to avoid becoming pregnant during treatment and for at least 1 week after the last dose of CALQUENCE [see *Use in Specific Populations (8.3) in the full Prescribing Information*].

Lactation

Advise females not to breastfeed during treatment with CALQUENCE and for at least 2 weeks after the final dose [see *Use in Specific Populations (8.2) in the full Prescribing Information*].

Dosing Instructions

Instruct patients to take CALQUENCE orally twice daily, about 12 hours apart. CALQUENCE may be taken with or without food. Advise patients that CALQUENCE capsules should be swallowed whole with a glass of water, without being opened, broken, or chewed [see *Dosage and Administration (2.1) in the full Prescribing Information*].

Missed Dose

Advise patients that if they miss a dose of CALQUENCE, they may still take it up to 3 hours after the time they would normally take it. If more than 3 hours have elapsed, they should be instructed to skip that dose and take their next dose of CALQUENCE at the usual time. Warn patients they should not take extra capsules to make up for the dose that they missed [see *Dosage and Administration (2.1) in the full Prescribing Information*].

Drug Interactions

Advise patients to inform their healthcare providers of all concomitant medications, including over-the-counter medications, vitamins and herbal products [see *Drug Interactions (7) in the full Prescribing Information*].

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Wilmington, DE 19850

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USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings in animals, CALQUENCE may cause fetal harm and dystocia when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of acalabrutinib to animals during organogenesis resulted in dystocia in rats and

3 OUT OF 4 DOCTORS CONTINUE TO CHOOSE CALQUENCE FOR THEIR SUBSEQUENT BTKI-ELIGIBLE R/R MCL PATIENT, AFTER PRESCRIBING CALQUENCE TO 2 OR MORE R/R MCL PATIENTS^{1*}

A BTKi for adult patients with mantle cell lymphoma (MCL) after at least one prior therapy²

CALQUENCE: GO STRONG

CALQUENCE HAS SHOWN STRONG EFFICACY AND DURABLE RESPONSES IN PATIENTS WITH R/R MCL

In the initial data analysis, 80% of patients achieved a response^{2,3,†‡§}

- ◆ **80%** ORR (n=99) [95% CI: 72, 87]
- **40%** CR (n=49) [95% CI: 31, 49]
- **40%** PR (n=50) [95% CI: 32, 50]

Consistent response rates at 24-month update analysis^{4||}

- ◆ **81%** ORR (n=100) [95% CI: 73, 87]
- **43%** CR (n=53) [95% CI: 34, 52]
- **38%** PR (n=47) [95% CI: 29, 47]
- ◆ Median **DoR** of 26 months[¶] [95% CI: 17.5, NR]
- ◆ Median **PFS** of 20 months [95% CI: 16.5, 27.7]
- At the time of PFS analysis, 66 events (53.2%) had occurred[§]
- ◆ Median **OS** not reached at median follow-up of 26 months (range: 0.3 to 35.1 months)[¶]
- At the time of OS analysis, 41 events (33.1%) had occurred[§]

LY-004 trial: an international, Phase 2, open-label, multicenter trial of 124 patients (≥18 years) with MCL who had received ≥1 prior therapy. Patients received CALQUENCE 100 mg twice daily until disease progression or unacceptable toxicity. The primary endpoint was ORR; secondary endpoints included DoR, PFS, and OS.³

The initial data analysis was based on efficacy and safety endpoints that occurred from March 12, 2015, through approximately 14 months after the last subject was enrolled.³

The 24-month update analysis was based on the cumulative efficacy and safety endpoints that occurred from March 12, 2015, until February 12, 2018.^{3,4}

Safety profile from the initial data analysis^{2,4}

- ◆ The most common adverse drug reactions (≥20%) were anemia, thrombocytopenia, headache, neutropenia, diarrhea, fatigue, myalgia, and bruising

Safety profile from 24-month update analysis was consistent with initial data analysis^{4, **}

- ◆ The most common treatment-emergent adverse events (≥20%) were headache (38%), diarrhea (36%), fatigue (28%), cough (22%), and myalgia (21%)
- ◆ 2% dose reduction rate and 8% discontinuation rate due to adverse events

*New prescription data as of September 2019.¹

†Independent Review Committee-assessed per 2014 Lugano Classification.²

‡Median follow-up of 15.2 months.²

§Investigator-assessed response rates were ORR: 81%; CR: 40%; PR: 41%.²

||Investigator-assessed per 2014 Lugano Classification.⁴

¶Duration of response (DoR) was measured in the 100 subjects who achieved a CR or PR.⁴

**Median duration of therapy was 16.6 months (range: 0.1 to 26.6 months).²

***Median duration of therapy was 17.3 months (range: 0.1 to 35.1 months).⁴

BTKi=Bruton tyrosine kinase inhibitor; CI=confidence interval; CR=complete response; NR=not reached; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; R/R=relapsed/refractory.

LEARN MORE AT CALQUENCEHCP.COM

INDICATION AND USAGE

CALQUENCE is a Bruton tyrosine kinase (BTK) inhibitor indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

IMPORTANT SAFETY INFORMATION ABOUT CALQUENCE® (acalabrutinib) capsules

Serious and Opportunistic Infections

Fatal and serious infections, including opportunistic infections, have occurred in patients with hematologic malignancies treated with CALQUENCE.

Serious or Grade 3 or higher infections (bacterial, viral, or fungal) occurred in 19% of 1029 patients exposed to CALQUENCE in clinical trials, most often due to respiratory tract infections (11% of all patients, including pneumonia in 6%). These infections predominantly occurred in the absence of Grade 3 or 4 neutropenia, with neutropenic infection reported in 1.9% of all patients. Opportunistic infections in recipients of CALQUENCE have included, but are not limited to, hepatitis B virus reactivation, fungal pneumonia, *Pneumocystis jirovecii* pneumonia, Epstein-Barr virus reactivation, cytomegalovirus, and progressive multifocal leukoencephalopathy (PML). Consider prophylaxis in patients who are at increased risk for opportunistic infections. Monitor patients for signs and symptoms of infection and treat promptly.

Hemorrhage

Fatal and serious hemorrhagic events have occurred in patients with hematologic malignancies treated with CALQUENCE. Major hemorrhage (serious or Grade 3 or higher bleeding or any central nervous system bleeding) occurred in 3.0% of patients, with fatal hemorrhage occurring in 0.1% of 1029 patients exposed to CALQUENCE in clinical trials. Bleeding events of any grade, excluding bruising and petechiae, occurred in 22% of patients.

Use of antithrombotic agents concomitantly with CALQUENCE may further increase the risk of hemorrhage. In clinical trials, major hemorrhage occurred in 2.7% of patients taking CALQUENCE without antithrombotic agents and 3.6% of patients taking CALQUENCE with antithrombotic agents. Consider the risks and benefits of antithrombotic agents when co-administered with CALQUENCE. Monitor patients for signs of bleeding.

Consider the benefit-risk of withholding CALQUENCE for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (23%), anemia (8%), thrombocytopenia (7%), and lymphopenia (7%), developed in patients with hematologic malignancies treated with CALQUENCE. Grade 4 neutropenia developed in 12% of patients. Monitor complete blood counts regularly during treatment. Interrupt treatment, reduce the dose, or discontinue treatment as warranted.

Second Primary Malignancies

Second primary malignancies, including skin cancers and other solid tumors, occurred in 12% of 1029 patients exposed to CALQUENCE in clinical trials. The most frequent second primary malignancy was skin cancer, reported in 6% of patients. Monitor patients for skin cancers and advise protection from sun exposure.

References: 1. Data on File, REF-32935. AstraZeneca Pharmaceuticals LP. 2. CALQUENCE [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019. 3. Wang M, Rule S, Zinzani PL, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY004): a single-arm, multicenter, phase 2 trial. *Lancet*. 2018;391(10121):659-667. 4. Wang M, Rule S, Zinzani PL, et al. Durable response with single-agent acalabrutinib in patients with relapsed or refractory mantle cell lymphoma. *Leukemia*. 2019;33(11):2762-2766. doi:10.1038/s41375-019-0575-9. 5. Data on File, REF-43179. AstraZeneca Pharmaceuticals LP.

Atrial Fibrillation and Flutter

Grade 3 atrial fibrillation or flutter occurred in 1.1% of 1029 patients treated with CALQUENCE, with all grades of atrial fibrillation or flutter reported in 4.1% of all patients. The risk may be increased in patients with cardiac risk factors, hypertension, previous arrhythmias, and acute infection. Monitor for symptoms of arrhythmia (e.g., palpitations, dizziness, syncope, dyspnea) and manage as appropriate.

ADVERSE REACTIONS

The most common adverse reactions (≥20%) of any grade in patients with MCL were anemia,* thrombocytopenia,* headache (39%), neutropenia,* diarrhea (31%), fatigue (28%), myalgia (21%), and bruising (21%). The most common Grade ≥ 3 non-hematological adverse reaction (reported in at least 2% of patients) was diarrhea (3.2%).

*Treatment-emergent decreases (all grades) of hemoglobin (46%), platelets (44%), and neutrophils (36%) were based on laboratory measurements and adverse reactions.

Dosage reductions or discontinuations due to any adverse reaction were reported in 1.6% and 6.5% of patients, respectively.

Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 4.8% of patients.

DRUG INTERACTIONS

Strong CYP3A Inhibitors: Avoid co-administration with a strong CYP3A inhibitor. If a strong CYP3A inhibitor will be used short-term, interrupt CALQUENCE.

Moderate CYP3A Inhibitors: When CALQUENCE is co-administered with a moderate CYP3A inhibitor, reduce CALQUENCE dose to 100 mg once daily.

Strong CYP3A Inducers: Avoid co-administration with a strong CYP3A inducer. If a strong CYP3A inducer cannot be avoided, increase the CALQUENCE dose to 200 mg approximately every 12 hours.

Gastric Acid Reducing Agents: If treatment with a gastric acid reducing agent is required, consider using an H2-receptor antagonist or an antacid. Take CALQUENCE 2 hours before taking an H2-receptor antagonist. Separate dosing with an antacid by at least 2 hours.

Avoid co-administration with proton pump inhibitors. Due to the long-lasting effect of proton pump inhibitors, separation of doses may not eliminate the interaction with CALQUENCE.

SPECIFIC POPULATIONS

Based on findings in animals, CALQUENCE may cause fetal harm and dystocia when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. Advise pregnant women of the potential risk to a fetus.

Pregnancy testing is recommended for females of reproductive potential prior to initiating CALQUENCE therapy. Advise female patients of reproductive potential to use effective contraception during treatment with CALQUENCE and for at least 1 week following the last dose of CALQUENCE.

It is not known if CALQUENCE is present in human milk. Advise lactating women not to breastfeed while taking CALQUENCE and for at least 2 weeks after the final dose.

Avoid administration of CALQUENCE in patients with severe hepatic impairment. Dose modifications are not required for patients with mild or moderate hepatic impairment.

Please see Brief Summary of Prescribing Information on adjacent pages.

You are encouraged to report negative side effects of AstraZeneca prescription drugs by calling 1-800-236-9933. If you prefer to report these to the FDA, either visit www.FDA.gov/medwatch or call 1-800-FDA-1088.



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