

**A SPECIAL MEETING REVIEW EDITION**

## Highlights in Mantle Cell Lymphoma From the 62nd American Society of Hematology Annual Meeting and Exposition

A Review of Selected Presentations From the All-Virtual 62nd ASH Meeting and Exposition • December 5-8, 2020

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**Special Reporting on:**

- Acalabrutinib Monotherapy in Patients With Relapsed/Refractory Mantle Cell Lymphoma: Long-Term Efficacy and Safety Results From a Phase 2 Study
- Combination of Ibrutinib With Rituximab in Previously Untreated Older Patients With Mantle Cell Lymphoma—A Phase II Clinical Trial
- Adverse Events in Clinical Trials of Ibrutinib and Acalabrutinib for B-Cell Lymphoproliferative Disorders: A Systematic Review and Network Meta-Analysis
- Safety and Preliminary Efficacy in Patients With Relapsed/Refractory Mantle Cell Lymphoma Receiving Lisocabtagene Maraleucel in TRANSCEND NHL 001
- A Pilot Study of Acalabrutinib With Bendamustine/Rituximab Followed by Cytarabine/Rituximab for Untreated Mantle Cell Lymphoma
- LOXO-305, A Next-Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated Mantle Cell Lymphoma, Waldenström's Macroglobulinemia, and Other Non-Hodgkin Lymphomas: Results From the Phase 1/2 BRUIN Study
- One-Year Follow-Up of ZUMA-2, the Multicenter, Registrational Study of KTE-X19 in Patients With Relapsed/Refractory Mantle Cell Lymphoma
- Predictive Power of Early, Sequential MRD Monitoring in Peripheral Blood and Bone Marrow in Patients With Mantle Cell Lymphoma Following Autologous Stem Cell Transplantation With or Without Rituximab Maintenance; Final Results From the LyMa-MRD Project, Conducted on Behalf of the LYSA Group

**PLUS Meeting Abstract Summaries**

**With Expert Commentary by:**

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A BTKi for adult patients with previously treated mantle cell lymphoma (MCL)<sup>1</sup>

# CALQUENCE CONFIDENCE

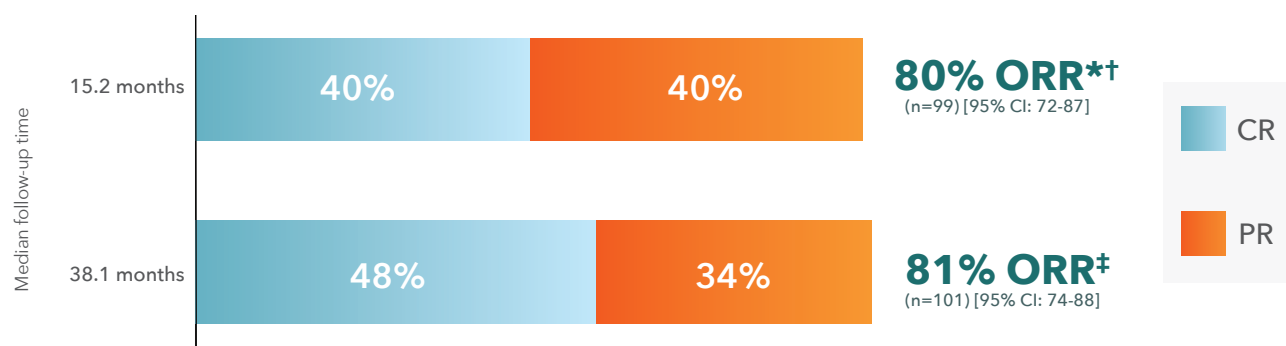
NOW WITH MEDIAN 38-MONTH LONG-TERM DATA<sup>2</sup>



Median follow-up of 38.1 months (range: 0.3 to 59.5 months).<sup>2</sup>

**CALQUENCE HAS CONTINUED TO SHOW STRONG EFFICACY AND DEEP RESPONSES FOR OVER 3 YEARS IN PATIENTS WITH R/R MCL<sup>2</sup>**

## RESPONSE RATES OVER TIME (N=124)<sup>1-3</sup>



**Median DoR:  
29 months<sup>‡2</sup>**  
(95% CI: 17.5-39.1)

**Median PFS:  
22 months<sup>‡2</sup>**  
(95% CI: 16.6-33.3)

Median OS was not reached after a median follow-up of 38.1 months. Estimated 36-month OS rate was 60.5% (95% CI: 51.1-68.7).<sup>2</sup>

Baseline patient characteristics included median prior number of therapies (2; range: 1-5) and blastoid/pleomorphic cytomorphic variants (21%).<sup>2,4</sup>

After a median follow-up of 38.1 months, 24 patients (19%) remained on treatment and an additional 31 patients (25%) remained in follow-up for survival.<sup>2</sup>

### 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.

\*Independent Review Committee-assessed per 2014 Lugano Classification. Median follow-up of 15.2 months.<sup>1</sup>

<sup>†</sup>Investigator-assessed response rates were ORR: 81%; CR: 40%; PR: 41%.<sup>1</sup>

<sup>‡</sup>Investigator-assessed per 2014 Lugano Classification.<sup>2,5</sup>

BR=bendamustine + rituximab; BTKi=Bruton tyrosine kinase inhibitor; CI=confidence interval; CR=complete response; DoR=duration of response; NE=not estimable; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; R/R=relapsed/refractory.

### 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.

## THE 38-MONTH SAFETY PROFILE WAS CONSISTENT WITH INITIAL ANALYSIS<sup>2</sup>

### Initial data analysis\*

- ◆ The most common adverse drug reactions (≥20%) were anemia, thrombocytopenia, headache, neutropenia, diarrhea, fatigue, myalgia, and bruising<sup>1</sup>
- ◆ 1.6% dose reduction rate and 6.5% discontinuation rate due to adverse reactions<sup>1</sup>
- ◆ Events of clinical interest (any grade; Grade 3/4) included infections (53%; 13%), hemorrhage (31%; 1%), cardiac events (8%; 2%), and hypertension (2%; 1%)<sup>3</sup>

\*Median duration of therapy was 16.6 months (range: 0.1 to 26.6 months).<sup>1</sup>

**LY-004 trial:** An international, Phase 2, open-label, single-arm, multicenter trial of 124 patients (≥18 years) with MCL who had received ≥1 prior therapy. Patients received CALQUENCE 100 mg approximately every 12 hours until disease progression or unacceptable toxicity. The primary endpoint was investigator-assessed ORR per 2014 Lugano Classification; secondary endpoints included DoR, PFS, and OS.<sup>3</sup>

### 38-month analysis

- ◆ The most common non-hematological adverse events (≥20%) were headache, diarrhea, fatigue, cough, myalgia, and nausea<sup>5</sup>
- ◆ 2% dose reduction rate and 11% discontinuation rate due to adverse events<sup>2,5</sup>
- ◆ Events of clinical interest (any grade; Grade 3/4) included infections (68%; 17%), bleeding events (37%; 4%), cardiac events (13%; 5%), and hypertension (4%; 2%)<sup>2</sup>

**The initial data analysis** was based on efficacy and safety endpoints from March 12, 2015, to January 5, 2016. The median follow-up time was 15.2 months.<sup>3</sup>

**The 38-month analysis** represents an additional year of follow-up succeeding the 26-month update from March 12, 2015, to February 12, 2018.<sup>2,4</sup>

## SEE MORE DATA AT CALQUENCEHCP.COM

### 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 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.

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**Gastric Acid Reducing Agents:** If treatment with a gastric acid reducing agent is required, consider using an H<sub>2</sub>-receptor antagonist or an antacid. Take CALQUENCE 2 hours before taking an H<sub>2</sub>-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 prescription drugs to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or call 1-800-FDA-1088.

**References:** 1. CALQUENCE [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019. 2. Wang M, Rule S, Zinzani PL, et al. Acabrutinib monotherapy in patients with relapsed/refractory mantle cell lymphoma: long-term efficacy and safety results from a phase 2 study. Poster presented at: American Society of Hematology Annual Meeting and Exposition; December 5–8, 2020 (Virtual Meeting). 3. Wang M, Rule S, Zinzani PL, et al. Acabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY004): a single-arm, multicentre, 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. 5. Wang M, Rule S, Zinzani PL, et al. 2040 acalabrutinib monotherapy in patients with relapsed/refractory mantle cell lymphoma: long-term efficacy and safety results from a phase 2 study. Presented at: American Society of Hematology Annual Meeting and Exposition; December 5–8, 2020 (Virtual Meeting) Abs. 2040.

**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 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 [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 (%)
<b>Nervous system disorders</b>		
Headache	39	1.6
<b>Gastrointestinal disorders</b>		
Diarrhea	31	3.2
Nausea	19	0.8
Abdominal pain	15	1.6
Constipation	15	-
Vomiting	13	1.6
<b>General disorders</b>		
Fatigue	28	0.8
<b>Musculoskeletal and connective tissue disorders</b>		
Myalgia	21	0.8
<b>Skin and subcutaneous tissue disorders</b>		
Bruising <sup>a</sup>	21	-
Rash <sup>b</sup>	18	0.8
<b>Vascular disorders</b>		
Hemorrhage <sup>c</sup>	8	0.8
<b>Respiratory, thoracic and mediastinal disorders</b>		
Epistaxis	6	-

\* Per NCI CTCAE version 4.03.

<sup>a</sup> Bruising: Includes all terms containing 'bruise,' 'contusion,' 'petechiae,' or 'ecchymosis'

<sup>b</sup> Rash: Includes all terms containing 'rash'

<sup>c</sup> 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"> <li>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>].</li> <li>Increased acalabrutinib concentrations may result in increased toxicity.</li> </ul>	
<i>Prevention or Management</i>	<ul style="list-style-type: none"> <li>Avoid co-administration of strong CYP3A inhibitors with CALQUENCE.</li> <li>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>].</li> </ul>	
Moderate CYP3A Inhibitors		
<i>Clinical Impact</i>	<ul style="list-style-type: none"> <li>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>].</li> <li>Increased acalabrutinib concentrations may result in increased toxicity.</li> </ul>	
<i>Prevention or Management</i>	<ul style="list-style-type: none"> <li>When CALQUENCE is co-administered with moderate CYP3A inhibitors, reduce acalabrutinib dose to 100 mg once daily.</li> </ul>	
Strong CYP3A Inducers		
<i>Clinical Impact</i>	<ul style="list-style-type: none"> <li>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>].</li> <li>Decreased acalabrutinib concentrations may reduce CALQUENCE activity.</li> </ul>	
<i>Prevention or Management</i>	<ul style="list-style-type: none"> <li>Avoid co-administration of strong CYP3A inducers with CALQUENCE.</li> <li>If a strong CYP3A inducer cannot be avoided, increase the acalabrutinib dose to 200 mg approximately every 12 hours.</li> </ul>	
Gastric Acid Reducing Agents		
<i>Clinical Impact</i>	<ul style="list-style-type: none"> <li>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>].</li> <li>Decreased acalabrutinib concentrations may reduce CALQUENCE activity.</li> <li>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).</li> </ul>	
<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*].

Cytenias

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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**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

## Acalabrutinib Monotherapy in Patients With Relapsed/Refractory Mantle Cell Lymphoma: Long-Term Efficacy and Safety Results From a Phase 2 Study

Mantle cell lymphoma (MCL) is a rare, aggressive form of B-cell non-Hodgkin lymphoma (NHL).<sup>1-4</sup> Although standard treatments yield high response rates, the median overall survival for patients with MCL is a few years, and the disease relapses in nearly all cases. Acalabrutinib is a next-generation Bruton tyrosine kinase (BTK) inhibitor that is approved by the US Food and Drug Administration (FDA) for patients with previously treated MCL. The open-label, multicenter phase 2 ACE-LY-004 trial evaluated acalabrutinib (100 mg twice daily) in patients with relapsed or refractory MCL.<sup>5,6</sup> Eligible patients had the t(11;14)(q13;q32) translocation and/or cyclin D1 overexpression. They had received up to 5 prior therapies. The trial enrolled patients with measurable nodal disease and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 through 2. The primary endpoint

was the investigator-assessed objective response rate (ORR) according to the Lugano criteria.<sup>7</sup>

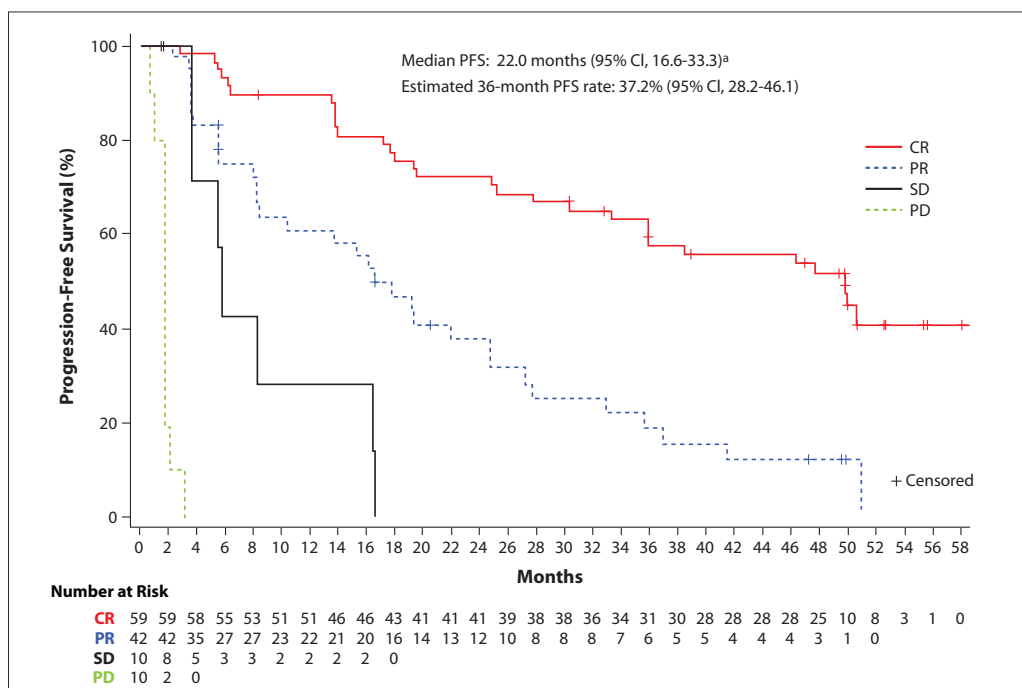
The study enrolled 124 patients with MCL, including 26 patients (21%) with blastoid/pleomorphic disease.<sup>6</sup> The patients' median age was 68 years (range, 42-90), and they had received a median of 2 prior therapies (range, 1-5). Of the 124 patients, 93 (75%) had Ann Arbor stage IV disease, and 46 (37%) had a bulky tumor measuring at least 5 cm. Assessment with the simplified MCL International Prognostic Index (MIPI) score indicated intermediate risk in 54 patients (44%) and high risk in 21 patients (17%). Refractory disease was noted in 30 patients (24%).

An initial analysis, reported after a median follow-up of 26 months, identified an ORR of 81% and a complete response (CR) rate of 43%.<sup>6</sup> The median duration of response was 26 months, and the estimated 24-month

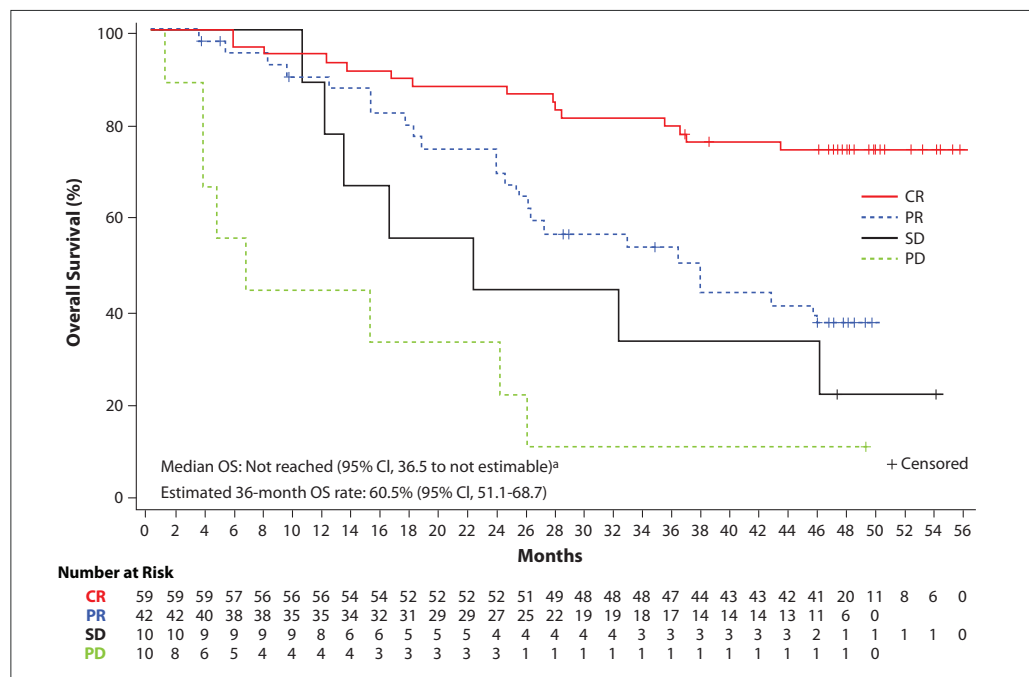
duration of response rate was 52.4%. After a median follow-up of 38.1 months, 24 patients (19%) remained on acalabrutinib.<sup>6</sup> Thirty-one patients remained in follow-up and were evaluable for survival assessment.<sup>6</sup> Among the 100 patients (81%) who had discontinued acalabrutinib, the most common reasons for discontinuation included disease progression (60%) and adverse events (AEs; 11%).

The ORR was 81%, with a CR rate of 48%.<sup>6</sup> The median duration of response was 28.6 months (95% CI, 17.5-39.1 months). At 36 months, the duration of response was estimated to be 41.9% (95% CI, 31.7%-51.8%). The median duration of response was 36.7 months in patients with a low Ki-67 index (<50%) and 15.3 months in patients with a high Ki-67 index (≥50%). The median progression-free survival (PFS) was 22.0 months (95% CI, 16.6-33.3 months), and the estimated 36-month PFS rate was 37.2%

**Figure 1.** Progression-free survival at 36 months in the phase 2 ACE-LY-004 trial, which evaluated acalabrutinib monotherapy in patients with relapsed/refractory mantle cell lymphoma. <sup>a</sup>The median PFS at 26-month follow-up was 20 months (95% CI, 16.5-27.7).<sup>5</sup> CR, complete response; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease. Adapted from Wang M et al. ASH abstract 2040. *Blood*. 2020;136(suppl 1).<sup>6</sup>



**Figure 2.** Overall survival at 36 months in the phase 2 ACE-LY-004 trial, which evaluated acalabrutinib monotherapy in patients with relapsed/refractory mantle cell lymphoma. <sup>a</sup>The median overall survival at 26-month follow-up was not reached (95% CI, 32.2 to not estimable).<sup>5</sup> CR, complete response; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease. Adapted from Wang M et al. ASH abstract 2040. *Blood*. 2020;136(suppl 1).<sup>6</sup>



(95% CI, 28.2%–46.1%; Figure 1). The median overall survival was not reached (95% CI, 36.5 months to not estimable; Figure 2). The median PFS was 35.8 months in patients with a low Ki-67 index and 6.4 months in patients with a high Ki-67 index. The median PFS was 24.8 months in patients who had received 3 or more prior regimens, 13.8 months in patients who had received prior treatment with a proteasome inhibitor, 27.7 months

in patients who had received a prior stem cell transplant (SCT), and 24.9 months in patients previously treated with lenalidomide. Samples evaluable for minimal residual disease (MRD) were available for 30 patients. Six of these patients had a CR and undetectable MRD; undetectable MRD status was maintained at the most recent assessment.

AEs led to dose delays in 50 patients (40%) and to dose modifica-

tions in 2 patients (2%). A total of 57 patients (46%) died, most commonly from disease progression (31%) or AEs (5%). Grade 3/4 AEs of clinical interest included infection (17%), cardiac events (5%), bleeding events (4%), and hypertension (2%). No new safety concerns emerged during additional follow-up.

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### ABSTRACT SUMMARY Venetoclax, Lenalidomide, and Rituximab for Patients With Relapsed or Refractory Mantle Cell Lymphoma—Data From the Nordic Lymphoma Group NLG-MCL7

The phase 1 VALERIA trial evaluated the combination of venetoclax, lenalidomide, and rituximab in patients with relapsed or refractory MCL (Abstract 122). MRD evaluation occurred every 3 months, and patients who were MRD-negative after 2 consecutive evaluations stopped treatment. The trial enrolled 22 patients, whose median age was 71 years (range, 54-81). The patients had received a median of 2 prior lines of therapy (range, 1-7). The most common hematologic grade 3/4 AE was neutropenia (50%), followed by thrombocytopenia (16%). The most common nonhematologic grade 3/4 AE was sepsis (18%). Toxicity led 1 patient to discontinue treatment. No deaths resulted from the study treatment. The ORR was 59%, with a CR rate of 45%. After a median follow-up of 14 months, the median PFS was not reached. After evidence of a molecular CR was found, 7 patients stopped treatment, and the CR was maintained at a median of 5 months after treatment cessation.

## Combination of Ibrutinib With Rituximab in Previously Untreated Older Patients With Mantle Cell Lymphoma—A Phase II Clinical Trial

Previous trials have shown that the combination of rituximab plus ibrutinib is effective in patients who have relapsed/refractory MCL. In a 4-year analysis of a phase 2 trial, treatment with rituximab plus ibrutinib led to a CR rate of 58%.<sup>1</sup> The median PFS was 43 months.

An investigator-initiated phase 2 trial evaluated ibrutinib plus rituximab in treatment-naïve patients ages 65 years and older.<sup>2</sup> The trial enrolled patients with nonblastoid/pleomorphic MCL and a Ki-67 index of less than 50%. Their largest tumor was less than 10 cm. A CR was confirmed via positron emission tomography (PET)/computed tomography, bone marrow biopsy/aspiration, and/or endoscopies with random biopsies.

The trial enrolled 50 patients, with a median age of 71 years (range, 65-84 years).<sup>2</sup> Most patients (94%) had bone marrow involvement. Disease risk was considered high in 50%, intermediate in 38%, and low in 6%. A history of atrial fibrillation was reported in 23%; this condition was controlled before enrollment. The level of Ki-67

was less than 30% in 75% of patients and between 30% to 50% in 25% of patients.

There were 3 patients who discontinued treatment during the first 3 cycles after developing AEs, and they were excluded from the efficacy analysis. Among patients in the intention-to-treat population, the ORR was 90%, with a CR rate of 62%. MRD negativity was reported in 87%. After a median follow-up of 43 months (range, 6-52 months), the median PFS (Figure 3) and median overall survival were not reached.

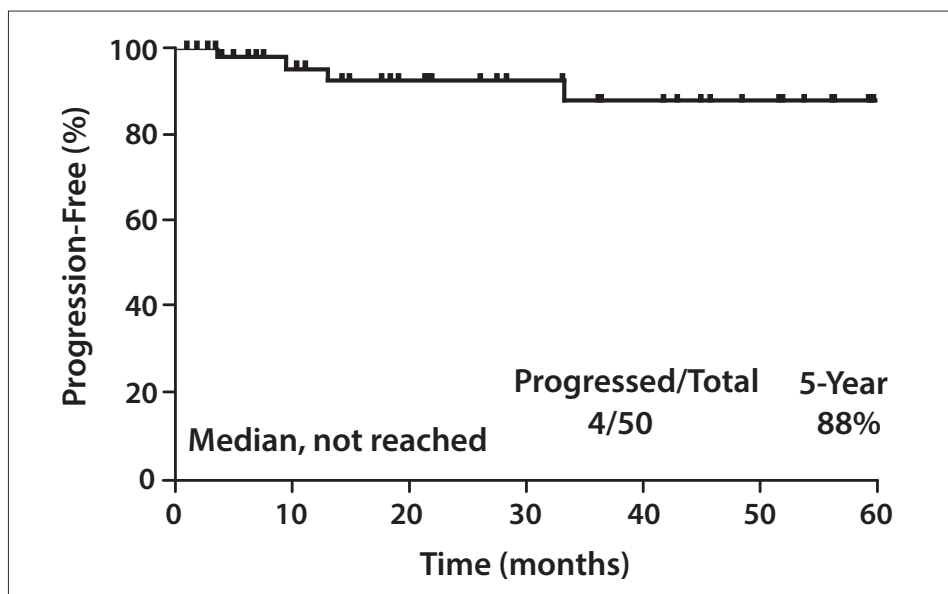
Four patients developed progressive disease (after 4, 10, 13, and 33 months of treatment). Among the 5 patients who died, the cause was disease progression in 3 cases and unknown in 2 cases. All deaths occurred while patients were off the study. Twenty-seven patients left the study, for reasons such as atrial fibrillation (n=10), other cardiac issues (n=3), and disease progression (n=4).

Overall, 34% of patients developed atrial fibrillation.<sup>2</sup> Among these patients, 18% had no history of atrial

fibrillation. The median time to onset of atrial fibrillation was 9.4 months (range, 1.3-48) from the initiation of treatment. The most common hematologic grade 3/4 AEs were neutropenia (8%), thrombocytopenia (4%), and anemia (4%). The most common non-hematologic grade 3/4 AEs were atrial fibrillation (22%), fatigue (18%), diarrhea (14%), and myalgia (14%). The study investigators noted that the increased incidence of arrhythmia likely reflected the high number of cardiovascular risk factors in these patients. They suggested that baseline evaluation of cardiac health and cardiovascular risk factor modification should be components of management with rituximab plus ibrutinib.

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**Figure 3.** The median progression-free survival was not reached in a phase 2 trial of ibrutinib plus rituximab in previously untreated older patients ( $\geq 65$  years) with mantle cell lymphoma. Adapted from Jain P et al. ASH abstract 2042. *Blood.* 2020;136(suppl 1).<sup>2</sup>



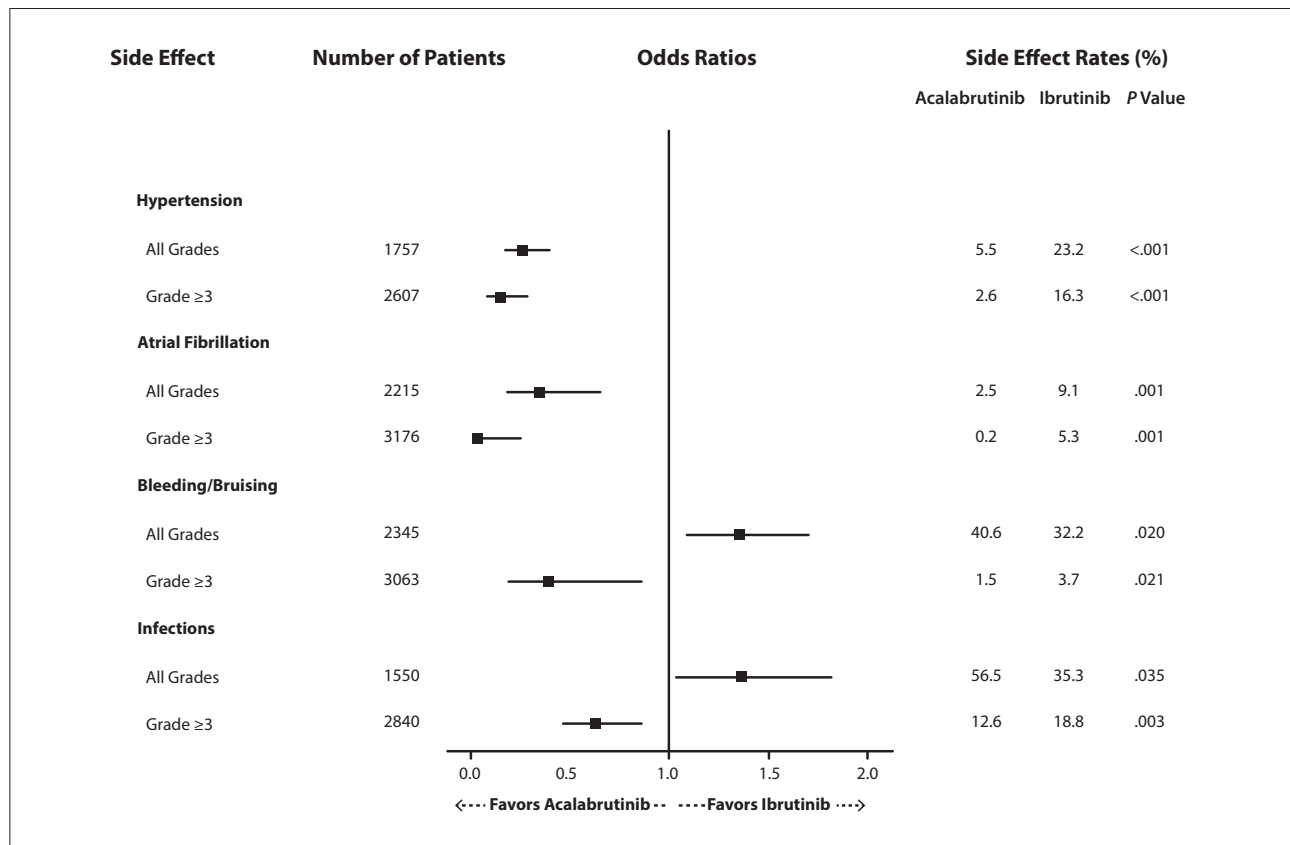
## Adverse Events in Clinical Trials of Ibrutinib and Acalabrutinib for B-Cell Lymphoproliferative Disorders: A Systematic Review and Network Meta-Analysis

Ibrutinib, a first-generation BTK inhibitor, is associated with an elevated risk for cardiovascular AEs, including atrial fibrillation, hypertension, and bleeding.<sup>1</sup> Acalabrutinib binds more selectively than ibrutinib to BTK, which may result in fewer cardiovascular events and other AEs. A systematic review and network meta-analysis evaluated the AEs described in prospective trials of ibrutinib and acalabrutinib among patients with B-cell lymphoproliferative disorders.<sup>2</sup> The study included single-arm and randomized prospective trials of ibrutinib alone, ibrutinib plus anti-CD20

therapy, and acalabrutinib alone. Trials that investigated a BTK inhibitor plus chemotherapy were excluded. Augmented Bayesian network meta-analysis and meta-regression techniques were used to compare the safety profiles of the treatments.

The study analyzed data from 27 prospective clinical trials, which included a total of 29 study arms and 3207 patients.<sup>2</sup> The most common AEs of any grade in patients treated with ibrutinib were diarrhea (46%; 95% CI, 36%-55%), myalgias/arthralgias (37%; 95% CI, 38%-46%), and fatigue (33%; 95% CI, 24%-42%).

Among patients treated with acalabrutinib, the most common AEs of any grade were headache (37%; 95% CI, 26%-48%), diarrhea (30%; 95% CI, 20%-41%), and peripheral edema (21%; 95% CI, 15%-28%). Cases of any-grade bleeding and bruising were reported in 41% (95% CI, 30%-52%) of patients treated with acalabrutinib vs 32% of those treated with ibrutinib (95% CI, 23%-41%). Any-grade hypertension occurred in 23% (95% CI, 15%-32%) of patients treated with ibrutinib vs 6% (95% CI, 1%-11%) of those treated with acalabrutinib. Any-grade atrial fibrillation was reported in



**Figure 4.** Adverse events in a systematic review and network meta-analysis of trials evaluating ibrutinib and acalabrutinib in patients with B-cell lymphoproliferative disorders. Adapted from Hilal T et al. ASH abstract 1317. *Blood*. 2020;136(suppl 1).<sup>2</sup>

9.1% vs 2.5%, respectively.

The difference favoring acalabrutinib was significant for any-grade hypertension (odds ratio [OR], 0.26; 95% CI, 0.17-0.40;  $P < .0001$ ), grade 3 hypertension (OR, 0.15; 95% CI, 0.08-0.27;  $P < .0001$ ), any-grade atrial fibrillation (OR, 0.35; 95% CI, 0.18-0.66;  $P = .0012$ ), and grade 3 atrial fibrillation (OR, 0.04; 95% CI, 0.01-

0.25;  $P = .0009$ ; Figure 4).<sup>2</sup> Acalabrutinib was also associated with a reduced rate of grade 3 or higher bleeding or bruising ( $P = .021$ ) and a reduced rate of grade 3 or higher infections ( $P = .003$ ). The results suggest that the safety profile of acalabrutinib may be superior to that of ibrutinib, particularly in terms of cardiovascular AEs.

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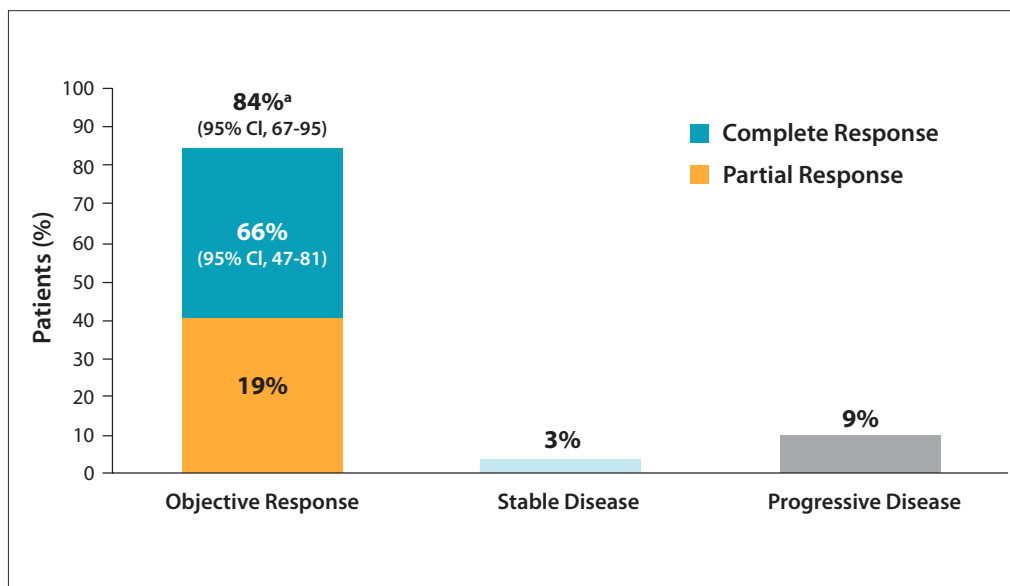
## Safety and Preliminary Efficacy in Patients With Relapsed/Refractory Mantle Cell Lymphoma Receiving Lisocabtagene Maraleucel in TRANSCEND NHL 001

Patients with MCL who develop progressive disease after treatment with a BTK inhibitor have a poor prognosis, with response rates ranging from 25% to 42%, and a median overall survival of 10 months or less after salvage therapy.<sup>1-4</sup> Lisocabtagene maraleucel is an investigational chimeric antigen receptor (CAR) T-cell product that targets CD19. The CAR T-cell product is administered with a defined ratio of engineered CD8-positive and CD4-positive T cells. The open-label, multicenter, phase 1

TRANSCEND-NHL-001 trial evaluated lisocabtagene maraleucel among patients with B-cell malignancies. After 3 days of lymphodepletion with fludarabine (30 mg/m<sup>2</sup>) and cyclophosphamide (300 mg/m<sup>2</sup>), patients received lisocabtagene maraleucel at 1 of 2 doses: 50 × 10<sup>6</sup> CAR-positive T cells or 100 × 10<sup>6</sup> CAR-positive T cells. Lisocabtagene maraleucel yielded an ORR of 73%, with a CR rate of 53% in patients who had relapsed or refractory large B-cell lymphoma.<sup>5</sup> Grade 3 cytokine-release syndrome

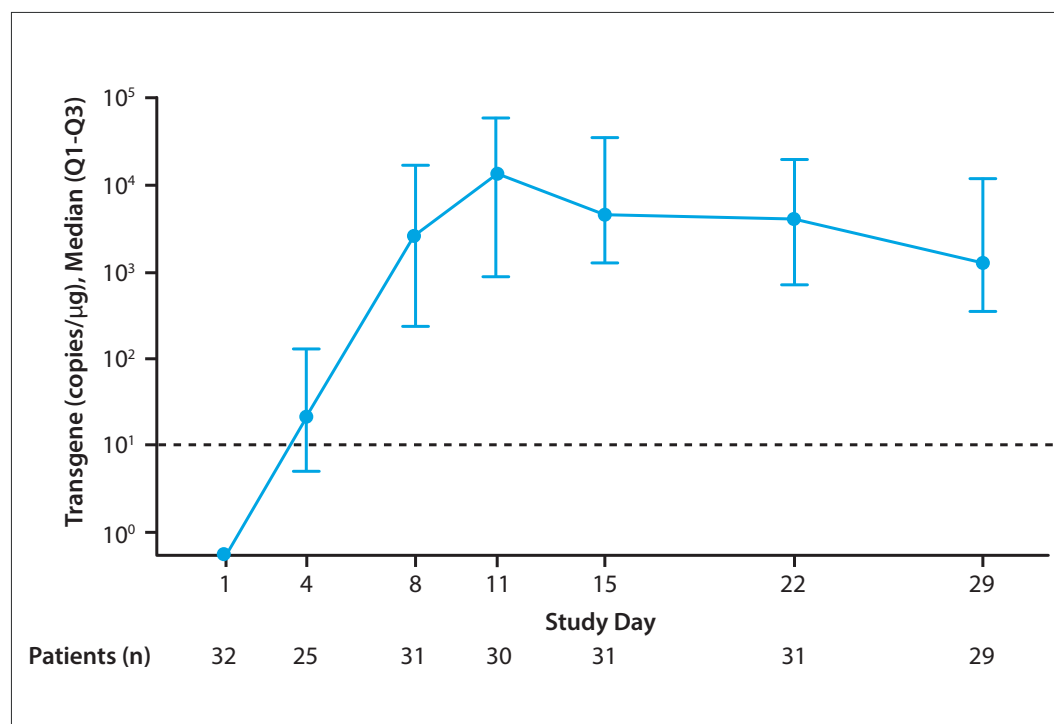
was observed in 2% of patients, and neurologic events occurred in 10%.

The patients with MCL in the TRANSCEND-NHL-001 trial had received 2 or more prior lines of therapy, including a BTK inhibitor, an alkylating agent, and an anti-CD20 agent.<sup>6</sup> The enrollment criteria included patients who had undergone hematopoietic SCT and who had secondary central nervous system lymphoma. The patients had an ECOG performance status of 0 to 2, with adequate heart and kidney function.



**Figure 5.** Best overall response according to investigator assessment among patients with relapsed/refractory mantle cell lymphoma receiving lisocabtagene maraleucel in the phase 1 TRANSCEND-NHL-001 trial. <sup>a</sup>Based on 32 patients treated; 1 patient was not evaluable and is not represented in the figure. Adapted from Palomba ML et al. ASH abstract 118. *Blood.* 2020;136(suppl 1).<sup>6</sup>

**Figure 6.** Cellular kinetics among patients with relapsed/refractory mantle cell lymphoma receiving lisocabtagene maraleucel in the phase 1 TRANSCEND-NHL-001 trial. Adapted from Palomba ML et al. ASH abstract 118. *Blood*. 2020;136(suppl 1).<sup>6</sup>



Among patients with mantle cell lymphoma, 44 underwent leukapheresis. Lisocabtagene maraleucel or a nonconforming product was administered to 33 patients. Results were presented for 32 patients treated with lisocabtagene maraleucel: 6 at the lower dose level and 26 at the higher dose level. The patients had a median age of 67 years (range, 36-80), and 27 (84%) were male. A total of 13 patients (41%) had MCL with blastoid morphology, 23 (72%) had a Ki-67 value of at least 30%, and 7 (22%) had a *TP53* mutation. The patients had received a median of 3 prior therapies (range, 1-7), 81% had disease refractory to their last therapy, and 53% received bridging therapy.

The median follow-up was 5.9 months (range, 0.4-24.8).<sup>6</sup> According to investigator assessment, the ORR was 84%, with a CR rate of 66% (Figure 5). The median time to first CR or partial response (PR) was 0.95 months (range, 0.9-2.0). The ORR was 100% in the patients with a *TP53* mutation, 83% in those with a Ki-67 value of 30% or higher, and 77% in those

with blastoid morphology. The median duration of response was not reached. Maximum lisocabtagene maraleucel expansion was observed 10 days after infusion (Figure 6). Long-term persistence of lisocabtagene maraleucel was observed in 67% of patients (4/6) at 1 year and in 33% of patients (1/3) at 2 years. Enrollment of patients with MCL into the cohort receiving the higher dose level is continuing.

The most common treatment-emergent AEs were cytokine-release syndrome (50%), anemia (47%), and neutropenia (47%). The most common treatment-emergent AEs of grade 3 or higher were neutropenia (44%), anemia (38%), and thrombocytopenia (31%). Two patients developed grade 5 AEs considered related to lisocabtagene maraleucel. Dose-limiting toxicities observed in 2 patients included 1 case of tumor lysis syndrome and 1 case of neutropenia/thrombocytopenia. Grade 3 or higher cytokine-release syndrome occurred in 1 patient (3%), and neurologic AEs of grade 3 or higher occurred in 11 patients (34%). In 3 patients (9%), cytokine-

release syndrome or neurologic events required admission to an intensive care unit. Grade 3 or higher events include prolonged cytopenias in 11 patients (34%), infections in 5 patients (16%), hypogammaglobulinemia in 3 patients (9%), and tumor lysis syndrome in 1 patient (3%).

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## A Pilot Study of Acalabrutinib With Bendamustine/Rituximab Followed by Cytarabine/Rituximab for Untreated Mantle Cell Lymphoma

No consensus exists regarding the optimal induction regimen for treating MCL in young, fit patients.<sup>1</sup> The use of treatment regimens consisting of high-dose cytarabine followed by autologous SCT has improved response rates and PFS, but not overall survival.<sup>2,3</sup> Treatment with bendamustine plus rituximab followed by cytarabine plus rituximab has yielded high rates of CR and MRD negativity.<sup>4</sup> A single-arm, single-institution pilot study evaluated the addition of acalabrutinib to this regimen.<sup>5</sup> The primary endpoint was successful stem cell mobilization, defined as a CD34-positive cell yield that exceeded  $2 \times 10^6/\text{kg}$  following a maximum of 5 sessions of leukapheresis. Key endpoints included the rates of overall response, CR, and MRD. Eligible patients were ages 18 to 70 years, had treatment-naïve MCL, and were candidates for autologous SCT. Patients received 6 cycles of 28 days each. Treatment throughout the first 3

cycles consisted of bendamustine (90 mg/m<sup>2</sup> on days 1 and 2), rituximab (375 mg/m<sup>2</sup> on day 1), and acalabrutinib (100 mg twice daily on days 1-28). Treatment during cycles 4 through 6 consisted of cytarabine (2 g/m<sup>2</sup> every 12 hours on days 1 and 2), rituximab (375 mg/m<sup>2</sup> on day 1), and acalabrutinib (100 mg twice daily on days 1-7 and days 22-28). After 6 cycles, patients underwent MRD testing and PET. Responses were evaluated according to the Lugano classification.<sup>6</sup>

The report provided data for 12 evaluable patients.<sup>5</sup> Their median age was 57 years (range, 52-66), and 92% were male. Eleven patients had stage IV disease, and 1 patient (8%) had stage III disease. All of the patients had an ECOG performance status of 0 or 1. MIPI scores were low in 33%, intermediate in 42%, and high in 25%.

After a median follow-up of 11 months, the ORR was 83%, including a CR rate of 75%.<sup>5</sup> None of the patients with a response developed

relapsed disease. The median number of CD34-positive stem cells collected from each patient was  $3.84 \times 10^6$  (range,  $2.77 \times 10^6$  to  $5.9 \times 10^6$ ). MRD assessment was pending.

Serious grade 4 hematologic AEs included lymphopenia and thrombocytopenia, each observed in all patients, and leukopenia and neutropenia, each observed in 83% of patients. Grade 3 anemia occurred in 66% of patients. All serious nonhematologic AEs were grade 3. These events included febrile neutropenia in 3 patients (25%), and diarrhea, elevated levels of alanine aminotransferase, and infusion reaction, each observed in 1 patient (8%). Therapy was discontinued in 2 patients who developed prolonged thrombocytopenia. No significant bleeding events or cases of treatment-related mortality were reported.

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### ABSTRACT SUMMARY Frontline Sequential Immunochemotherapy Plus Lenalidomide for Mantle Cell Lymphoma Incorporating MRD Evaluation: Phase 2, Investigator-Initiated, Single-Center Study

An investigator-initiated, single-center phase 2 study evaluated sequential immunochemotherapy with lenalidomide in treatment-naïve patients who had stage 2 to 4 high-risk MCL (Abstract 119). Patients received 4 cycles of lenalidomide, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, followed by 2 cycles of rituximab plus high-dose cytarabine, followed by 6 months of maintenance therapy with rituximab plus lenalidomide. MRD was assessed at baseline and after each treatment phase. The primary endpoint was a 3-year PFS rate of 75% or higher. The study achieved a 3-year PFS rate of 63% (95% CI, 49%-79%), thus failing to meet the primary endpoint. The 3-year PFS rate was 77% among patients with wild-type *TP53* and 12% among those with mutated *TP53* ( $P < .0001$ ). *TP53* mutation status was the only factor that significantly correlated with PFS. Many patients converted to MRD-negative status after high-dose cytarabine treatment. MRD negativity of  $10^{-6}$  at 6 months after the end of treatment predicted remission duration. The median PFS was 34.5 months for MRD-negative patients vs 12.1 months for MRD-positive patients ( $P < .001$ ).



## LOXO-305, A Next-Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated Mantle Cell Lymphoma, Waldenström's Macroglobulinemia, and Other Non-Hodgkin Lymphomas: Results From the Phase 1/2 BRUIN Study

The mechanisms of resistance to covalent BTK inhibition in patients with MCL have not been fully described, and survival outcomes after treatment with a covalent BTK inhibitor are poor.<sup>1-3</sup> LOXO-305 is a potent, selective, noncovalent inhibitor of BTK that has shown nanomolar binding against wild-type and C481-mutated *BTK* in cell and enzyme assays.<sup>4,5</sup> In xenograft models, sustained BTK inhibition has been observed with LOXO-305 throughout the dosing interval. The multicenter phase 1/2 BRUIN study evaluated LOXO-305 in patients with advanced B-cell malignancies who had previously received at least 2 systemic

treatments.<sup>6</sup> LOXO-305 was administered orally in 28-day cycles. The doses ranged from 25 to 300 mg daily, and dose escalation followed a standard 3 + 3 protocol. The primary endpoints were the maximum tolerated dose and the recommended phase 2 dose. Inpatient dose escalation to a previously cleared dose level was allowed. Responses were assessed according to either the Lugano classification or criteria from the International Workshop on Waldenström's Macroglobulinemia.

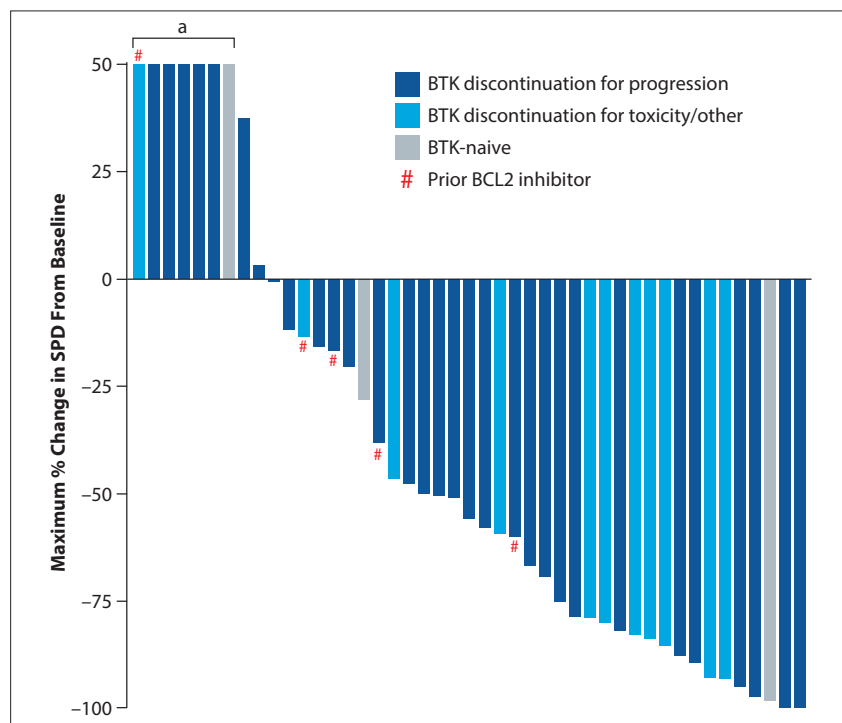
The trial enrolled 203 patients in a phase 1 dose-escalation and expansion cohort (25-300 mg/day) and 120 patients in a phase 2 cohort (200 mg/day).<sup>6</sup> The safety population included

61 patients with MCL, 26 with Waldenström macroglobulinemia, and 66 with other types of NHL. Among these groups, the median ages were 69 years, 68 years, and 68 years, respectively (overall range, 27-87). Patients in the 3 disease cohorts had previously received a median of 3 or 4 therapies (range, 1-11), and 12 had previously received CAR T-cell therapy. Prior exposure to a BTK inhibitor was reported in 93% of the patients with MCL, 69% of those with Waldenström macroglobulinemia, and 37% of those with other B-cell malignancies. Most patients discontinued their prior BTK inhibitor because of disease progression.

Pharmacokinetic analysis showed dose-dependent linear increases in the plasma concentration of LOXO-305 across the entire dose range. Plasma exposures exceeded the BTK 90% maximal inhibitory concentration at daily doses of 100 mg or higher.

Across the entire population of 323 patients, the most common AEs of any grade were fatigue (20%), diarrhea (17%), and confusion (13%). No grade 4 AEs were observed. Grade 3 AEs included fatigue (1%), hypertension (1%), and hemorrhage (<1%). AEs of special interest included bruising (16%) and rash (11%). No dose-limiting toxicities were reported, and the maximum tolerated dose was not reached. LOXO-305 was discontinued in 5 patients (1.5%) owing to treatment-related AEs. The recommended phase 2 dose of LOXO-305 was 200 mg daily.

Among the 56 patients with MCL, the ORR was 52% (95% CI, 38%-65%), with a CR rate of 25%.<sup>6</sup> Among the 52 patients with MCL previously treated with a BTK inhibitor, the ORR was also 52%, with a CR rate



**Figure 7.** The maximum percent change in SPD from baseline among patients with previously treated mantle cell lymphoma who received LOXO-305 in the phase 1/2 BRUIN trial. <sup>a</sup>Indicates patients with a >50% increase in SPD. BTK, Bruton tyrosine kinase inhibitor; SPD, sum of the products of the diameters. Adapted from Wang ML et al. ASH abstract 117. *Blood*. 2020;136(suppl 1).<sup>6</sup>

of 25%. The ORR was 64% (9/14) in patients who had undergone prior SCT and 100% (2/2) in patients who had received prior CAR T-cell therapy. The maximum percent change in the sum of the products of the diameters from baseline is shown in Figure 7. After a median follow-up of 6 months (range, 0.7-18.3+), responses were ongoing in 83% of patients (24/29).

Among 19 patients with Waldenström macroglobulinemia, the ORR was 68% (95% CI, 33%-87%), based on a PR rate of 47% (n=9) and a minimal response rate of 21% (n=4). Among the 13 patients who had received prior treatment with a BTK

inhibitor, the ORR was 69% (39% PR rate, 31% minimal response rate). For the patients with other NHL subtypes, the ORRs were as follows: 75% for Richter transformation, 50% for follicular lymphoma, 22% for marginal zone lymphoma, and 24% for diffuse large B-cell lymphoma (DLBCL). Responses were ongoing in 10 of 13 patients (77%) with Waldenström macroglobulinemia and 5 of 6 patients (83%) with Richter transformation.

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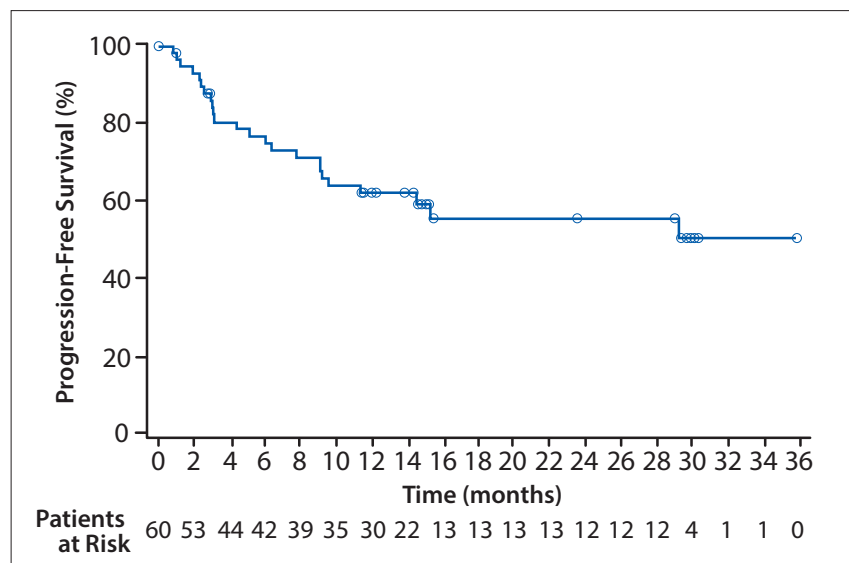
## One-Year Follow-Up of ZUMA-2, the Multicenter, Registrational Study of KTE-X19 in Patients With Relapsed/Refractory Mantle Cell Lymphoma

**K**TE-X19, now also known as brexucabtagene autoleucl, is an autologous CAR T-cell therapy that is directed at the CD19 antigen. This agent is FDA-approved for the treatment of patients with relapsed or refractory MCL. The single-arm, open-label, phase 2 ZUMA-2 study evaluated KTE-X19 in patients with relapsed or refractory MCL who had received 1 to 5 prior therapies, including a BTK inhibitor.<sup>1,2</sup> After leukapheresis, patients could receive optional, protocol-specified bridging therapy. Conditioning chemotherapy consisted of fludarabine (30 mg/m<sup>2</sup>) and cyclophosphamide (500 mg/m<sup>2</sup>) administered on days -5, -4, and -3 before the CAR T-cell infusion. On day 0, patients received a single infusion of  $2 \times 10^6$  KTE-X19 cells/kg. The primary endpoint was the ORR according to the Lugano classification, as assessed by independent review.<sup>3</sup> After a median follow-up of 12.3 months, the primary efficacy analysis showed an ORR of 93%, with a CR rate of 67%.<sup>1</sup>

An updated analysis from the ZUMA-2 study continued to show durable responses among patients with

MCL who received KTE-X19.<sup>2</sup> This analysis provided efficacy data for 60 patients. After a median follow-up of 17.5 months (range, 12.3-37.6), the ORR was 92% (95% CI, 82%-97%), with a CR rate of 67%. At the data cutoff, responses were ongoing in 29 of the 60 patients (48%). Among the

40 patients who had achieved a CR, responses were ongoing in 28 (70%). The median values were not reached for the duration of response (95% CI, 14 months to not evaluable), PFS (95% CI, 10 months to not evaluable; Figure 8), and overall survival (95% CI, range not evaluable). The



**Figure 8.** The median progression-free survival was not reached after a median follow-up of 17.5 months among patients with relapsed/refractory mantle cell lymphoma who received KTE-X19 (brexucabtagene autoleucl) in the phase 2 ZUMA-2 trial. Adapted from Wang ML et al. ASH abstract 1120. *Blood*. 2020;136(suppl 1).<sup>2</sup>

ongoing response rate was consistent across adverse prognostic groups based on age, sex, MCL morphologic characteristics, Ki-67 proliferation index, disease stage, simplified MIPI score, and *TP53* mutation.

No new safety signals were observed with additional follow-up.<sup>2</sup> There were no new cases of cytokine-release syndrome and no new grade 5 events since the prior report. In the safety population of 68 patients, the most common AEs of any grade that were present at 6 months or later after infusion included neutropenia (21%), thrombocytopenia (21%), and anemia

(19%). The most common AEs of grade 3 or higher were neutropenia (16%), thrombocytopenia (13%), and decrease in white blood cell count (9%).

Peak levels of engineered T cells were higher in patients with an ongoing response at 12 months and in those who initially had a response and then relapsed by 12 months as compared with patients who never achieved a response. Among the 57 evaluable patients, 48 (84%) had detectable B cells at baseline. Among patients with an ongoing response at 12 months, B-cell recovery increased through 24 months, whereas levels of genetically

engineered T cells decreased. No association was observed between CAR T-cell levels measured at 2 weeks after the infusion and B-cell aplasia.

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## Predictive Power of Early, Sequential MRD Monitoring in Peripheral Blood and Bone Marrow in Patients With Mantle Cell Lymphoma Following Autologous Stem Cell Transplantation With or Without Rituximab Maintenance; Final Results From the LyMa-MRD Project, Conducted on Behalf of the LYSA Group

The phase 3 LyMa trial evaluated rituximab maintenance therapy after autologous SCT in patients with MCL.<sup>1,2</sup> The trial enrolled 299 patients ages 66 years or younger at diagnosis. All patients first received 4 courses of induction therapy (rituximab, dexamethasone, cytarabine, and a platinum derivative) followed by autologous SCT. Patients were then randomly assigned to 3 years of observation or rituximab (375 mg/m<sup>2</sup> every 2 months). The 4-year event-free survival rate was 79% with rituximab maintenance vs 61% with observation ( $P < .001$ ), and the 4-year PFS rate was 83% vs 64%, respectively ( $P < .001$ ). Rates of overall survival were also better with rituximab maintenance (89% vs 80%;  $P = .04$ ).

The LyMa-MRD project investigated the prognostic significance of MRD status both before and after autologous SCT and assessed the value of combining MRD status with findings from PET to predict outcome.<sup>2</sup> Polymerase chain reaction assays targeted to clonal immunoglobulin gene

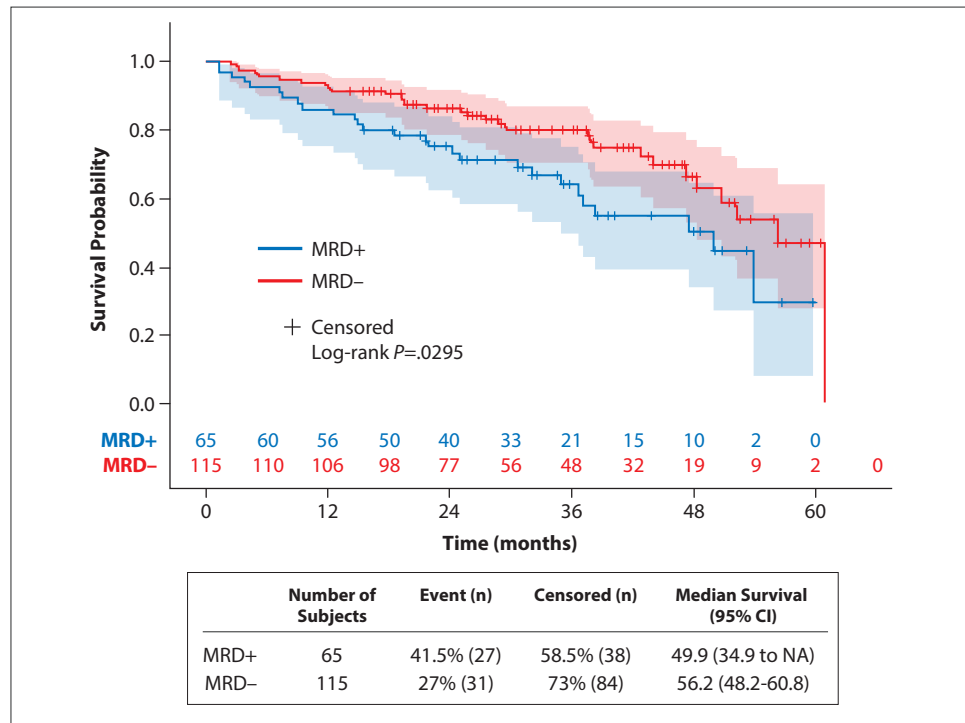
rearrangements were used to assess MRD in the blood and bone marrow at 3 French reference laboratories. MRD assays had a sensitivity of 10<sup>-4</sup>.

A total of 220 patients were evaluable for MRD and included in this analysis.<sup>2</sup> MRD negativity in the peripheral blood was 77% before autologous SCT vs 94% after the procedure. MRD negativity in the bone marrow was 64% before autologous SCT vs 81% after. Patients with undetectable bone marrow MRD before SCT had a longer median PFS (56.2 months vs 49.9 months in those with detectable MRD;  $P = .0295$ ; Figure 9). The median overall survival was not reached vs 60.8 months, respectively ( $P = .0407$ ). Undetectable MRD in the peripheral blood before SCT was also associated with a longer median PFS (60.8 vs 34.9 months;  $P < .0001$ ) and longer median overall survival (60.8 vs 39.6 months;  $P < .0001$ ). MRD status after autologous SCT did not correlate with median overall survival. MRD negativity in the bone marrow after autologous SCT was associated with a

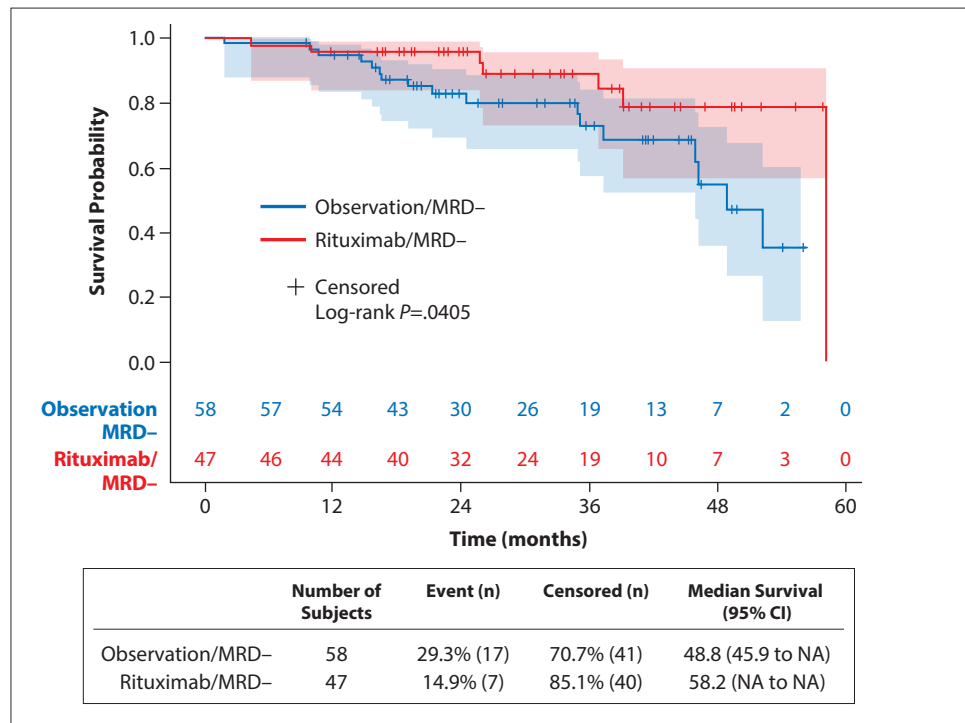
longer median PFS ( $P = .0261$ ), but not with longer overall survival.

Among patients with undetectable MRD in the bone marrow before autologous SCT, the median PFS was 58.2 months with rituximab maintenance vs 48.8 months with observation ( $P = .0405$ ; Figure 10).<sup>2</sup> The median overall survival was longer with rituximab maintenance (58.2 vs 52.2 months;  $P = .0395$ ). Among patients with undetectable MRD in the blood before transplant, the median PFS was longer with rituximab maintenance therapy than with observation (58.2 vs 52.2 months;  $P = .0260$ ), but the median overall survival was similar (58.2 months vs not reached;  $P = .1326$ ). According to the results of peripheral blood analysis after autologous SCT, MRD negativity was associated with a longer median PFS (58.2 vs 48.8 months;  $P = .0072$ ), but the median overall survival was similar (58.2 vs 52.2 months). The median overall survival in patients with a negative PET result and concomitant undetectable MRD in the blood

**Figure 9.** In the phase 3 LyMa trial, progression-free survival from the end of induction therapy was longer among patients with undetectable MRD in the bone marrow before stem cell transplant. MRD, minimal residual disease; NA, not available. Adapted from Callanan M et al. ASH abstract 120. *Blood*. 2020;136(suppl 1).<sup>2</sup>



**Figure 10.** Progression-free survival after treatment with observation vs rituximab maintenance therapy among patients with undetectable MRD in the bone marrow before autologous stem cell transplant in the phase 3 LyMa trial. MRD, minimal residual disease; NA, not available. Adapted from Callanan M et al. ASH abstract 120. *Blood*. 2020;136(suppl 1).<sup>2</sup>



before transplant was superior to that in patients with a positive PET result and detectable MRD in the blood ( $P=.0002$ ). According to the results of analyses performed after autologous SCT, a negative PET result and undetectable MRD were associated with a

superior median PFS (blood,  $P<.0001$ ; bone marrow,  $P=.0082$ ) and a superior median overall survival (blood,  $P<.0001$ ; bone marrow,  $P=.0474$ ).

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## Highlights in Mantle Cell Lymphoma From the 62nd American Society of Hematology Annual Meeting and Exposition: Commentary

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Several studies presented at the 62nd American Society of Hematology (ASH) meeting provided important information for the management of mantle cell lymphoma. Data were presented for treatments such as Bruton tyrosine kinase (BTK) inhibitors, chimeric antigen receptor (CAR) T-cell therapy, LOXO-305, and venetoclax, lenalidomide, and rituximab.

### BTK Inhibitors

BTK inhibitors have become an extremely important therapy for patients with relapsed mantle cell lymphoma. For most patients who develop relapsed disease after chemoimmunotherapy, with or without a stem cell transplant, second-line therapy is now firmly established as a BTK inhibitor. The first BTK inhibitor to gain approval from the US Food and Drug Administration (FDA) was ibrutinib.<sup>1</sup> More recently, the BTK inhibitors acalabrutinib and zanubrutinib were approved.<sup>2,3</sup> At the ASH meeting, Dr Michael Wang presented long-term efficacy and safety results from a phase 2 study of acalabrutinib monotherapy in 124 patients with relapsed/refractory mantle cell lymphoma.<sup>4</sup> The long-term efficacy analysis showed that the remissions were durable. The median duration of response was 28.6 months. Some remissions have lasted more than 2 years. The median progression-free survival was 22 months. For some patients, particularly those with a complete remission, the progression-

free survival was considerably longer. The results from this analysis reaffirm previous data suggesting that acalabrutinib may be better tolerated than ibrutinib.<sup>5</sup> Acalabrutinib was associated with little of the atrial fibrillation that has been seen with ibrutinib.<sup>6</sup> No new safety signals were identified. Acalabrutinib is a well-tolerated oral monotherapy for patients with relapsed mantle cell lymphoma. The question of which BTK inhibitor to use in a particular patient often comes down to adverse events. Based on the adverse event profile, acalabrutinib might be the preferential choice in patients with mantle cell lymphoma who have relapsed after a prior therapy.

Acalabrutinib appears to work exceedingly well in patients with mantle cell lymphoma that is not highly proliferative. For example, outcomes were better in patients with a Ki-67 index of less than 50%, which applies to the majority of those with mantle cell lymphoma.<sup>4</sup> The median progression-free survival was 35.8 months in patients with a Ki-67 index of less than 50% vs 6.4 months in patients with a Ki-67 index of 50% or higher. Otherwise, acalabrutinib appeared to work well across the different prognostic groups.

The fact that BTK inhibitors work so well in patients with mantle cell lymphoma raises the question of whether these agents should be moved earlier in the course of treatment. Many different trials have evaluated the use of BTK inhibitors as frontline

therapy, administered either with or before chemotherapy.<sup>7,8</sup> Dr Preetesh Jain presented a study of older patients with mantle cell lymphoma treated with ibrutinib and rituximab, providing an important step toward the use of BTK inhibitors earlier in the treatment course.<sup>9</sup> The trial enrolled previously untreated patients ages 65 years and older. The combination of ibrutinib and rituximab led to an overall response rate of 90%, including a complete response rate of 62%. The rate of undetectable minimal residual disease was 87%. Compared with chemoimmunotherapy, these results are very strong, or even better, especially in this older patient population.<sup>10</sup>

A substantial number of patients developed cardiac adverse events. Atrial fibrillation was reported in 22% of patients.<sup>9</sup> In fairness to the study, enrollment encompassed patients with a history of atrial fibrillation. However, this rate of atrial fibrillation is still high, even after accounting for these patients.

Based on the results of this study, it may be possible to maintain this high response rate—but reduce the adverse events—by using a second-generation BTK inhibitor that is associated with less atrial fibrillation. The use of acalabrutinib or zanubrutinib might lead to less toxicity. This study is important because the results showed that moving a nonchemoimmunotherapy approach to frontline treatment achieved excellent results among patients with mantle cell lymphoma. Upcoming studies

will likely evaluate a similar approach using other BTK inhibitors that might improve the adverse event profile. The results of this study might prove to be practice-changing for the group of patients who are not candidates for frontline treatment with very aggressive chemoimmunotherapy or stem cell transplant. Early treatment with a BTK inhibitor might be an important option for these patients.

### CAR T-Cell Therapy

Dr Michael Wang presented long-term follow-up for patients with relapsed/refractory mantle cell lymphoma in the phase 2 ZUMA-2 trial, which evaluated KTE-X19 (brexucabtagene autoleucel).<sup>11</sup> In 2020, brexucabtagene autoleucel received accelerated approval from the FDA for the treatment of patients with relapsed or refractory mantle cell lymphoma. This approval was based on earlier results from ZUMA-2.<sup>12</sup> The initial study showed high rates of overall and complete response. The long-term follow-up analysis, performed at a median follow-up of 17.5 months, showed very long remissions. Among 60 evaluable patients, 29 (48%) remained in an ongoing response. A complete response was maintained in 28 of 40 patients (70%). At 15 months, the rate of progression-free survival was 59%.

The ZUMA-2 study enrolled patients with a poor prognosis who were difficult to treat.<sup>11,12</sup> It was challenging to enroll these patients into the trial because of their advanced stage and significant symptoms. It is exciting to see early signs of a plateau in the progression-free survival curves. It will be necessary to follow patients for much longer to confirm the improvement. The follow-up analysis of ZUMA-2 did not identify any new safety signals.<sup>11</sup> However, the initial report showed a high incidence of adverse events.<sup>12</sup>

A concern with CAR T-cell therapy is the toxicity profile, particularly cytokine-release syndrome and neurologic events. Brexucabtagene autoleucel

is unique in that it has a CD28 signaling domain.<sup>12</sup> Lisocabtagene maraleucel is a CAR T-cell therapy that uses the 4-1BB construct.<sup>13</sup> Dr M. Lia Palomba presented safety and preliminary efficacy results for patients with relapsed/refractory mantle cell lymphoma treated with lisocabtagene maraleucel in the phase 1 TRANSCEND trial.<sup>14</sup> The trial evaluated 2 different dose levels. The patients had received 2 or more lines of prior therapy, including a BTK inhibitor and an anti-CD20 agent. The eligibility criteria were similar to those in ZUMA-2.

The analysis provided data for 32 treated patients. The high response rates were similar to those reported in ZUMA-2.<sup>12</sup> The overall response rate was 84%, including a response rate of 66%.<sup>14</sup> The follow-up was relatively short, at a median of 5.9 months. It appeared that the adverse event profile was somewhat better than that for brexucabtagene autoleucel.<sup>15</sup> The improvement in adverse events is important among these patients, who are often ill and difficult to treat. A therapy with fewer adverse events will permit treatment of more patients. There is also the possibility of moving treatment earlier in the natural history of the disease, which would have the greatest impact.

The data from these 2 trials are exciting. Confirmation of the results in follow-up analyses may change treatment of patients with mantle cell lymphoma.

### LOXO-305

Treatment is currently unclear for patients with mantle cell lymphoma who develop progressive disease during second-line therapy with a BTK inhibitor. This question is a recent one, as it was not too long ago that the median survival of patients with mantle cell lymphoma was just a few years. Treatment with first-line and second-line therapies now leads to much longer median survival. There are several potential options for third-line therapy. LOXO-305 is a next-

generation BTK inhibitor that is not covalently bound,<sup>16,17</sup> in contrast to the BTK inhibitors approved by the FDA. Patients can develop mutations that render those BTK inhibitors ineffective. These mutations are most common among patients with chronic lymphocytic leukemia. They also arise in mantle cell lymphoma, even though these patients do not develop the same cysteine 481 mutation that occurs in chronic lymphocytic leukemia. The mutations are likely attributable to multiple mechanisms.

Dr Michael Wang presented results for patients with previously treated non-Hodgkin lymphoma who received LOXO-305 in a phase 1/2 trial.<sup>18</sup> The study enrolled 61 patients with mantle cell lymphoma, 93% of whom had received prior treatment with a BTK inhibitor. Among patients with mantle cell lymphoma, the overall response rate was 52% in the entire cohort and also 52% among those patients who had previously received a BTK inhibitor. It was exciting to see these results. In general, when ibrutinib fails to achieve a response, a switch to zanubrutinib or acalabrutinib will not be successful. These drugs share the same mechanism of action and binding site. A response would be likely if treatment with ibrutinib was discontinued owing to intolerance, but not resistance.

More research is required to determine why LOXO-305 is effective in these patients. The trial did not report the reasons why patients had discontinued their previous BTK treatment, whether it was owing to resistance or adverse events. Further follow-up is needed to determine the median progression-free survival. However, it is important that there may be another BTK inhibitor for these patients. LOXO-305 is currently in trials that will hopefully lead to FDA approval.

### Venetoclax, Lenalidomide, and Rituximab

Dr Mats Jerkeman presented the results of a phase 1 study of venetoclax,

lenalidomide, and rituximab in patients with relapsed or refractory mantle cell lymphoma.<sup>19</sup> As monotherapies, venetoclax and lenalidomide each have substantial activity in patients with mantle cell lymphoma.<sup>20,21</sup> However, single agents are not appealing in this setting.

The trial by Dr Jerkeman established doses for these drugs.<sup>19</sup> The preliminary results showed high efficacy for the triplet regimen. A caveat is that only 18% of patients had received previous treatment with a BTK inhibitor (ibrutinib). This regimen would need to be evaluated in a population with a higher rate of prior treatment with BTK inhibitors. These initial data should not lead to widespread adoption of this regimen in the community. Further follow-up is needed as more patients are accrued to the trial. However, it is important to continue to explore later-line treatment strategies for this difficult-to-manage patient population.

#### Disclosure

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