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A SPECIAL MEETING REVIEW EDITION

Highlights in Mantle Cell Lymphoma From the 63rd American Society of Hematology Annual Meeting and Exposition

A Review of Selected Presentations From the 63rd ASH Meeting and Exposition • December 11-14, 2021 • Atlanta, Georgia

Special Reporting on:

- Safety and Efficacy of Acalabrutinib Plus Venetoclax and Rituximab in Patients With Treatment-Naive Mantle Cell Lymphoma
- Addition of High-Dose Cytarabine to Immunochemotherapy Before Autologous Stem-Cell Transplantation in Patients Ages 65 Years or Younger With Mantle Cell Lymphoma (MCL Younger): A Long-Term Follow-Up of the Randomized, Open-Label, Phase 3 Trial of the European Mantle Cell Lymphoma Network
- Rituximab-Lenalidomide (R^2) Maintenance Is Superior to Rituximab Maintenance After First-Line Immunochemotherapy in Mantle Cell Lymphoma: Results of the MCL R^2 Elderly Clinical Trial
- Pirtobrutinib, a Next-Generation, Highly Selective, Noncovalent BTK Inhibitor in Previously Treated Mantle Cell Lymphoma: Updated Results From the Phase 1/2 BRUIN Study
- Efficacy and Safety of Parsaclisib in Patients With Relapsed or Refractory Mantle Cell Lymphoma Not Previously Treated With a BTK Inhibitor: Primary Analysis From a Phase 2 Study (CITADEL-205)
- Rituximab and High-Dose Cytarabine/Dexamethasone (R-HAD) Plus Bortezomib Is Superior to R-HAD Only in Relapsed Mantle Cell Lymphoma: A Randomized Phase 3 Trial of the European MCL Network
- KTE-X19 in Relapsed or Refractory Mantle-Cell Lymphoma, a "Real-Life" Study From the DESCAR-T Registry and LYSA Group
- Brexucabtagene Autoleucel for Relapsed/Refractory Mantle Cell Lymphoma: Real-World Experience From the US Lymphoma CAR T Consortium

PLUS Meeting Abstract Summaries

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(PubMed/MEDLINE), PubMed Central (PMC), and EMBASE

A BTKi for adult patients with previously treated mantle cell lymphoma (MCL)[1]

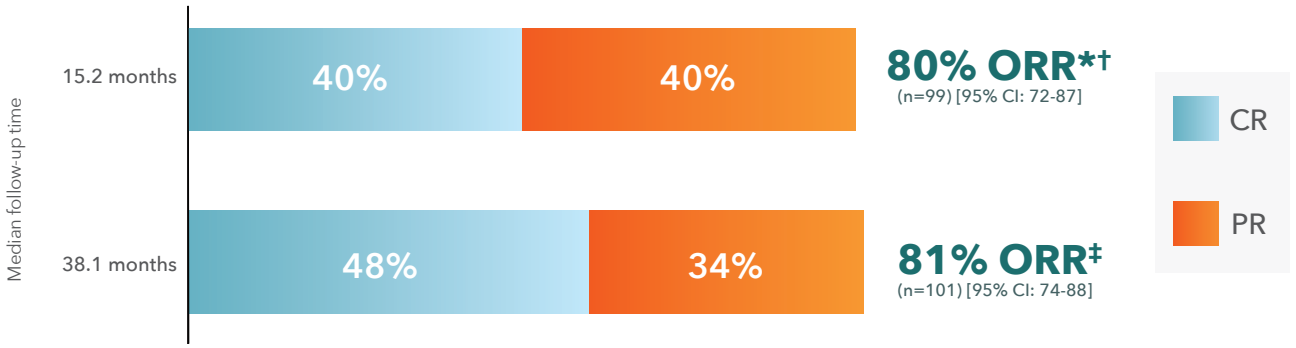
CALQUENCE CONFIDENCE

WITH MEDIAN 38-MONTH LONG-TERM DATA[2]

Median follow-up of 38.1 months (range: 0.3 to 59.5 months).[2]

CALQUENCE HAS CONTINUED TO SHOW STRONG EFFICACY AND DEEP RESPONSES FOR OVER 3 YEARS IN PATIENTS WITH R/R MCL[2]

RESPONSE RATES OVER TIME (N=124)[1-3]



Median DoR: 29 months‡[2]
(95% CI: 17.5-39.1)

Median PFS: 22 months‡[2]
(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).[2]

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

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.[2]

*Independent Review Committee-assessed per 2014 Lugano Classification. Median follow-up of 15.2 months.[1]
†Investigator-assessed response rates were ORR: 81%; CR: 40%; PR: 41%.[1]
‡Investigator-assessed per 2014 Lugano Classification.[2,5]

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.

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 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.

CALQUENCE®
(acalabrutinib) 100 mg capsules

THE 38-MONTH SAFETY PROFILE WAS CONSISTENT WITH INITIAL ANALYSIS[2]

Initial data analysis*

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

*Median duration of therapy was 16.6 months (range: 0.1 to 26.6 months).[1]

38-month analysis

- The most common non-hematological adverse events (≥20%) were headache, diarrhea, fatigue, cough, myalgia, and nausea[5]
- 2% dose reduction rate and 11% discontinuation rate due to adverse events[2,5]
- 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%)[2]

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.[3]

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.[3]

The 38-month analysis represents an additional year of follow-up succeeding the 26-month update from March 12, 2015, to February 12, 2018.[2-4]

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.

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 prescription drugs to the FDA. Visit 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. Acalabrutinib 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. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): 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.

AstraZeneca

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		
Clinical Impact	• Co-administration of CALQUENCE with a strong CYP3A inhibitor (itraconazole) increased acalabrutinib plasma concentrations *[see Clinical Pharmacology (12.3) in the full Prescribing Information].* • Increased acalabrutinib concentrations may result in increased toxicity.	
Prevention or Management	• Avoid co-administration of strong CYP3A inhibitors with CALQUENCE. • Alternatively, if the inhibitor will be used short-term, interrupt CALQUENCE *[see Recommended Dosage for Drug Interactions (2.3) in the full Prescribing Information].*	
Moderate CYP3A Inhibitors		
Clinical Impact	• Co-administration of CALQUENCE with a moderate CYP3A inhibitor may increase acalabrutinib plasma concentrations *[see Clinical Pharmacology (12.3) in the full Prescribing Information].* • Increased acalabrutinib concentrations may result in increased toxicity.	
Prevention or Management	• When CALQUENCE is co-administered with moderate CYP3A inhibitors, reduce acalabrutinib dose to 100 mg once daily.	
Strong CYP3A Inducers		
Clinical Impact	• Co-administration of CALQUENCE with a strong CYP3A inducer (rifampin) decreased acalabrutinib plasma concentrations *[see Clinical Pharmacology (12.3) in the full Prescribing Information].* • Decreased acalabrutinib concentrations may reduce CALQUENCE activity.	
Prevention or Management	• 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		
Clinical Impact	• Co-administration of CALQUENCE with a proton pump inhibitor, H2-receptor antagonist, or antacid may decrease acalabrutinib plasma concentrations *[see Clinical Pharmacology (12.3)] in the full Prescribing Information.* • 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).	
Prevention or Management	Antacids	Separate dosing by at least 2 hours *[see Recommended Dosage for Drug Interactions (2.3) in the full Prescribing Information].*
	H2-receptor antagonists	Take CALQUENCE 2 hours before taking the H2-receptor antagonist *[see Recommended Dosage for Drug Interactions (2.3) in the full Prescribing Information].*
	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.

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 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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Safety and Efficacy of Acalabrutinib Plus Venetoclax and Rituximab in Patients With Treatment-Naive Mantle Cell Lymphoma

Although chemoimmunotherapy is the standard initial treatment for patients with mantle cell lymphoma (MCL), the benefit of this approach is limited by a suboptimal response duration and excessive toxicity. The US Food and Drug Administration (FDA) approved the second-generation Bruton's tyrosine kinase (BTK) inhibitor acalabrutinib as a single agent for the treatment of relapsed/refractory MCL. To further improve outcomes in MCL, various targeted therapy combinations are being explored in different treatment settings. The combination of the first-generation BTK inhibitor ibrutinib, the BCL-2 inhibitor venetoclax, and the anti-CD20 monoclonal antibody obinutuzumab has demonstrated sustained responses in both the frontline and relapsed/refractory settings.[1] At the 2021 American Society of Hematology (ASH) annual meeting, Michael Wang, MD, presented results of a phase 1/2 trial evaluating the safety and activity of the combination of acalabrutinib, venetoclax, and rituximab in patients with previously untreated MCL.[2]

The ongoing trial is enrolling adults with treatment-naive MCL and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2, with no history of central nervous system (CNS) lymphoma or leptomeningeal disease, as well as no significant cardiovascular disease.[2] The treatment regimen consists of acalabrutinib administered at 100 mg twice daily starting on cycle 1 and continued until the patient develops progressive disease or has another reason for discontinuation; venetoclax starting on day 1 of cycle 2, with an initial 5-week ramp-up from 20 mg to 400 mg daily, through cycle 25; and rituximab given at 375 mg/m^2 on day 1 of each 28-day cycle for 6 cycles, followed by maintenance therapy every other cycle for patients who attain a complete response (CR) or partial response (PR) through cycle 24.

The analysis provided data for 21 enrolled patients. Their median age was 66 years (range, 51-85 years). Bone marrow involvement was observed in 71% of patients, and 90% had Ann Arbor stage IV disease.[2] The patients received a median of 19 cycles of acalabrutinib, 18 cycles of venetoclax, and 13 cycles of rituximab. Among the 6 patients (29%) who discontinued therapy early, the reasons were adverse events (AEs) in 19% and disease progression in 10%.

The combination of acalabrutinib, venetoclax, and rituximab was associated with an overall response rate (ORR) of 100%, including CRs in 71% and PRs in 29%, as evaluated per the Lugano criteria.[2] Assessment with positron emission tomography/computed tomography also identified an ORR of 100%, with CRs in 90% and PRs in 10%. The maximum change in baseline lesions is shown in Figure 1. After a median follow-up of 20.5 months, the rates of 1-year progression-free survival (PFS; Figure 2) and overall survival (OS) were 90% and 95%, respectively. These rates increased to 95% and 100%, respectively, after censoring 4 patients who died from COVID-19. Analyses of minimal residual disease showed a high rate of complete molecular response.

The most common any-grade treatment-emergent AEs were diarrhea (71%), headache (52%), fatigue

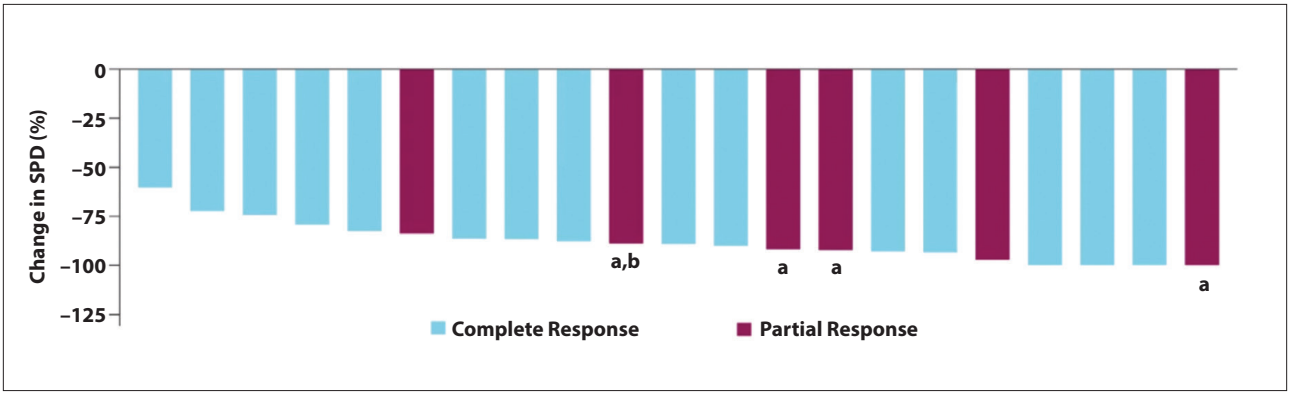

Figure 1. Maximum change from baseline in the sum of product diameters in a phase 1/2 trial evaluating acalabrutinib, venetoclax, and rituximab in patients with previously untreated mantle cell lymphoma. [a]Complete response according to PET (bone marrow biopsy is missing to confirm complete response by Lugano criteria). [b]Patient had missing postscreening measurements for 2 out of 6 target lesions. Only 4 of the 6 target lesions were calculated for SPD. PET, positron emission tomography; SPD, sum of product diameters. Adapted from Wang M et al. ASH abstract 2416. *Blood*. 2021;138(suppl 1).[2]

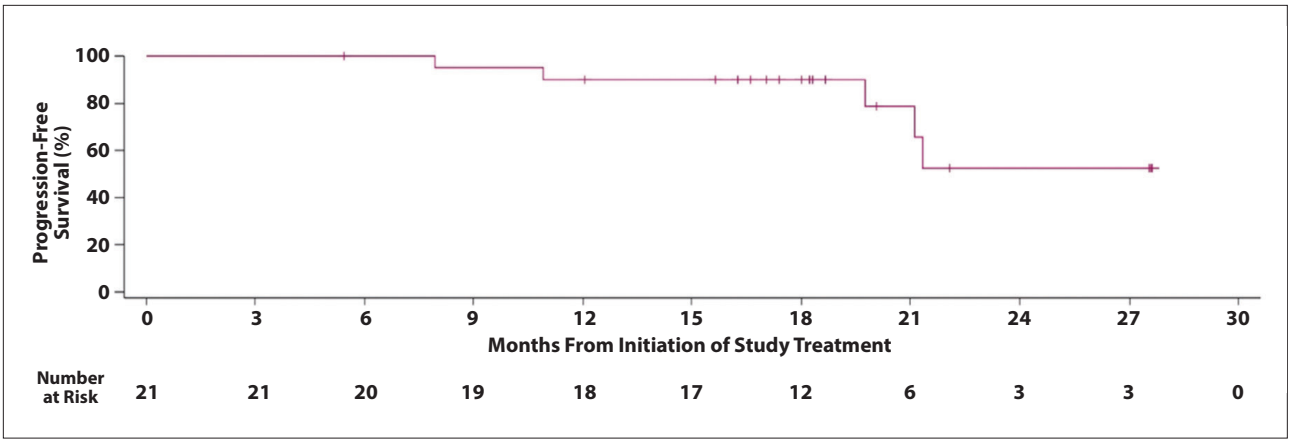

Figure 2. Progression-free survival in a phase 1/2 trial evaluating acalabrutinib, venetoclax, and rituximab in patients with previously untreated mantle cell lymphoma. Adapted from Wang M et al. ASH abstract 2416. *Blood*. 2021;138(suppl 1).[2]

(48%), neutropenia (38%), and dizziness (33%). Grade 3/4 treatment-emergent neutropenia were reported in 33% of patients. Four patients died, all from COVID-19.[2] Adverse events of clinical interest included cardiac events (19%; no grade 3/4), leukopenia (48%; 38% grade 3/4), hemorrhage (33%; no grade 3/4), and infection (57%). Grade 3 or higher infections were reported in 7 patients (33%). Five of these infections were from the SARS-CoV-2 virus. There were no cases of atrial fibrillation or major hemorrhage. Grade 1 hypertension was reported in one patient.

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Addition of High-Dose Cytarabine to Immunochemotherapy Before Autologous Stem-Cell Transplantation in Patients Ages 65 Years or Younger With Mantle Cell Lymphoma (MCL Younger): A Long-Term Follow-Up of the Randomized, Open-Label, Phase 3 Trial of the European Mantle Cell Lymphoma Network

The randomized, open-label phase 3 MCL Younger trial, conducted by the European Mantle Cell Lymphoma Network, assessed the benefit of adding high-dose cytarabine to immunochemotherapy before autologous stem cell transplant (ASCT) in patients with MCL younger than 65 years.[1] Between July 2004 and March 2010, the trial enrolled 497 patients with previously untreated advanced MCL (Ann Arbor stages II-IV) and a World Health Organization performance status of 0 to 2. The trial randomly assigned patients to receive 6 courses of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) followed by myeloablative radiochemotherapy and ASCT (n=249), or 6 courses of alternating R-CHOP and rituximab plus dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP) followed by a high-dose cytarabine–containing conditioning regimen and ASCT (n=248).

Results after a median follow-up of 6.1 years were published in 2016. The median time to treatment failure (TTF) was 9.1 years with R-DHAP/R-CHOP vs 3.9 years with R-CHOP alone (hazard ratio [HR], 0.56; *P*=.038).[1] The median PFS was not reached vs 4.5 years, respectively (HR, 0.45; *P*<.0001). However, there was no significant difference in OS between the arms (HR, 0.78; *P*=.12). Cytarabine was associated with increased rates of grade 3/4 hematologic toxicities.

At the 2021 ASH annual meeting, Olivier Hermine, MD, presented long-term results from the MCL Younger trial.[2] After a median follow-up of 10.6 years, the median TTF in a per-protocol analysis was 8.4 years with R-DHAP/R-CHOP vs 3.9 years with R-CHOP (HR, 0.59; *P*=.038; Figure 3). The 10-year TTF rates were 46% vs 25%, respectively.[2] In an intention-to-treat analysis, the median TTF was 7.7 years with R-DHAP/R-CHOP vs 4.1 years with R-CHOP (HR, 0.60; *P*<.0001). The 10-year TTF rates were 43% vs 27%, respectively. In an

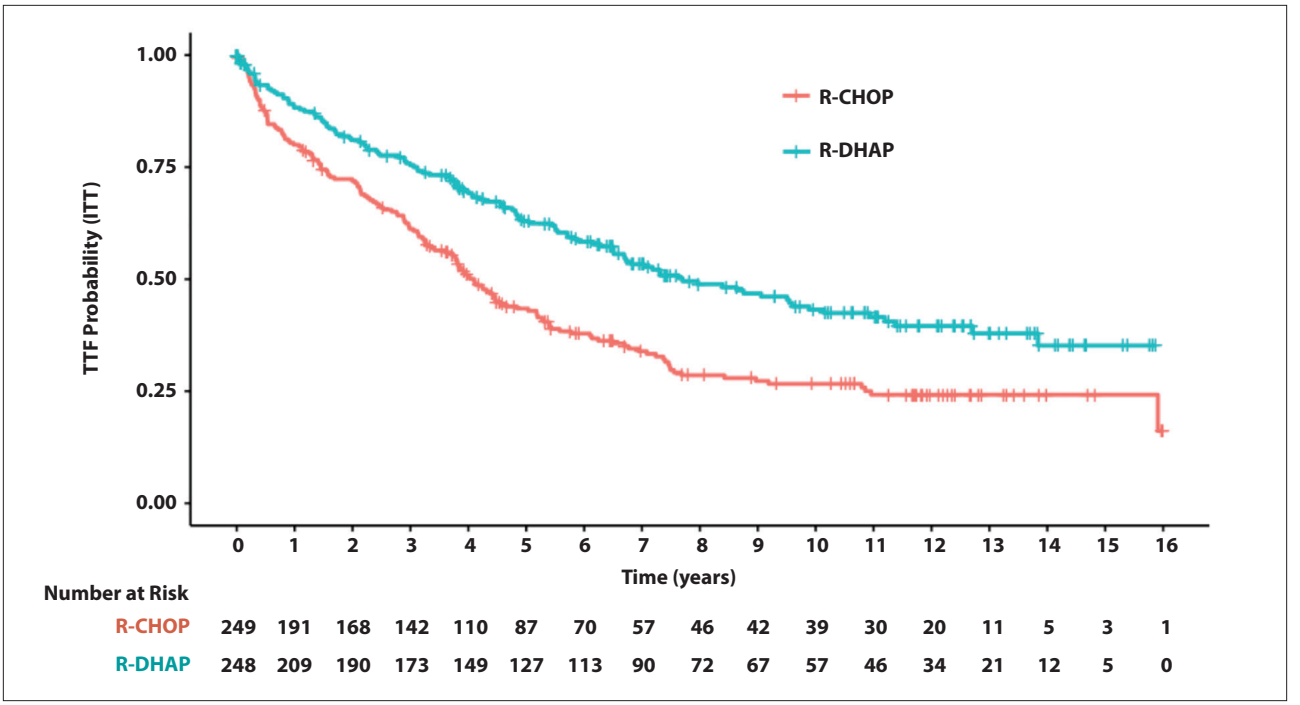

Figure 3. Time to treatment failure in a phase 3 trial that evaluated the addition of high-dose cytarabine to immunochemotherapy before autologous stem-cell transplant in patients ages 65 years or younger with mantle cell lymphoma. ITT, intention-to-treat; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DHAP, dexamethasone, high-dose cytarabine, and cisplatin; TTF, time to treatment failure. Adapted from Hermine O et al. ASH abstract 380. *Blood*. 2021;138(suppl 1).[2]

adjusted analysis, the HR for TTF was 0.56 (*P*<.0001) after adjusting for the Mantle Cell Lymphoma International Prognostic Index (MIPI) score and 0.52 (*P*<.0001) after adjusting for the MIPI score and Ki-67 score (measured in 297 patients).

The report also provided updated PFS results calculated at various times throughout the study.[2] In each analysis, the median PFS was significantly longer with R-DHAP/R-CHOP vs R-CHOP alone, including at the time from randomization (8.0 vs 4.3 years; HR, 0.61; *P*<.0001), the time from end of induction (8.5 vs 4.2 years; HR, 0.60; *P*<.0001), and the time from ASCT (10.8 vs 4.7 years; HR, 0.53; *P*<.0001).

The study was not powered to detect statistically significant differences in OS. After a median follow-up of 11.0 years, the median OS was not reached in the R-DHAP/R-CHOP arm vs 11.3 years in the R-CHOP arm (*P*=.12). The 10-year OS rates were 60% vs 55%, respectively (*P*=.12). The HR for OS was 0.74 (*P*=.038) after adjusting for the MIPI score and 0.60 (*P*=.0066) after adjusting for both the MIPI score and the Ki-67 score, indicating a significant improvement in OS with the addition of high-dose cytarabine in these analyses.

The study included subgroup analyses based on risk. High-risk MCL was defined as high-intermediate or high combined MIPI, high *TP53*, or blastoid morphology. Low-risk MCL was defined as low-intermediate or low combined MIPI, low *TP53*, or nonblastoid morphology. The median TTF in patients with high-risk MCL was 7.6 years with R-DHAP/R-CHOP vs 2.8 years with R-CHOP (HR, 0.49; *P*=.00078).[2] The median TTF in patients with low-risk MCL was not reached in the cytarabine arm vs 5.3 years in the control arm (HR, 0.56; *P*=.11). Among patients at high risk, the median OS was 10.4 years with R-DHAP/R-CHOP vs 5.0 years with R-CHOP (HR, 0.55; *P*=.013). Among low-risk patients, the median OS was not reached vs 14.4 years, respectively (HR, 0.37; *P*=.064). There was no significant difference between the arms in the 10-year probability of secondary hematologic malignancy (4.5% vs 1.4%; *P*=.14) or secondary nonhematologic malignancy (7.4% vs 9.0%; *P*=.42). There were no significant differences in long-term toxicities between the arms.

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Rituximab-Lenalidomide (R^2) Maintenance Is Superior to Rituximab Maintenance After First-Line Immunochemotherapy in Mantle Cell Lymphoma: Results of the MCL R^2 Elderly Clinical Trial

A standard of care is lacking for older patients with MCL who are not fit for high-dose therapy and ASCT. Although chemoimmunotherapy is the backbone of treatment, the benefit of cytarabine in elderly patients has not been evaluated. The MCL R^2 Elderly study established the role of R-CHOP induction therapy followed by rituximab maintenance in older adults with MCL.[1] The combination of rituximab and the immunomodulatory drug lenalidomide (R^2) has demonstrated activity in MCL, both in the frontline setting and in relapsed/refractory disease.[2,3] However, the potential role of this regimen as maintenance therapy after immunochemotherapy has not been evaluated.

Vincent Ribrag, MD, presented results from the MCL R^2 Elderly trial, which compared lenalidomide plus rituximab vs rituximab alone as maintenance therapy in patients with previously untreated MCL.[4] The patients were ages 60 years or older and were ineligible for high-dose therapy.[4] The trial was also designed to evaluate the benefit of adding cytarabine to R-CHOP induction therapy. The trial randomly assigned 620 patients to receive 8 cycles of R-CHOP given 3 times a week or 6 cycles of alternating treatment with R-CHOP given 3 times weekly and rituximab, cytarabine, and dexamethasone (R-HAD) given 4 times weekly. The patients' median age was 71 years, 72% were male, and 90% had Ann Arbor stage IV disease. Patients with a CR or PR after induction therapy (n=447) underwent a second randomization to 2 years of maintenance therapy with either rituximab given every 2 months or rituximab plus lenalidomide administered at 10 mg or 15 mg for 3 of every 4 weeks.

The combination of rituximab plus lenalidomide was associated with a significant improvement vs rituximab in PFS since maintenance randomization. The median PFS was 5.1 years with rituximab plus lenalidomide vs 3 years with rituximab alone (relative risk, 0.579; 95% CI, 0.429-0.781; *P*=.0003).[4] After a median follow-up of 32.4 months since induction randomization and 25.2 months since maintenance randomization, there was no difference between the arms in OS as assessed from either time.

Treatment with rituximab plus lenalidomide was associated with more blood and lymphatic system disorders (59% vs 27% with rituximab alone), including grade 3 or higher neutropenia (50% vs 19%) and grade 3 or higher anemia (2.9% vs 0.4%). The combination also led to more infections and infestations (10.9% vs 2.4%) and secondary primary malignancies (13.4% vs 10.4%).[4] During the maintenance phase, the mortality rate was 18% in the combination arm vs 19% in the monotherapy arm. Most deaths were attributable to lymphoma (12% and 12.4%, respectively). One patient in the combination arm died from toxicity.

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ABSTRACT SUMMARY Combination Therapy of BCL-2/X_L Dual Inhibitor AZD0466 With Acalabrutinib to Overcome Therapeutic Resistance in Aggressive R/R Mantle Cell Lymphoma

AZD0466 is a novel BCL-2/X_L dual inhibitor with an active moiety, AZD4320, that demonstrated activity against MCL cells in preclinical studies. Preclinical studies have evaluated the combination of AZD4320/AZD0466 and acalabrutinib (Abstract 1867). AZD4320 was used to assess in vitro activity. However, owing to the physiochemical properties of AZD4320 and its dose-limiting toxicity, the drug-dendrimer conjugate of AZD4320, AZD0466, was used for the in vivo animal studies. The researchers found that the combination of AZD4320 and acalabrutinib was synergistic in MCL cell lines, significantly inhibiting cell viability and enhancing apoptosis in cells that were sensitive or resistant to ibrutinib and venetoclax. The combination was also synergistic in vivo and appeared to have the potential to overcome venetoclax resistance. The activity was retained in a model with resistance to ibrutinib and CAR T-cell therapy. Researchers suggested that combined targeting of BCL-2/X_L and BTK may have the potential to overcome multiple acquired resistance phenotypes.

Pirtobrutinib, a Next-Generation, Highly Selective, Noncovalent BTK Inhibitor in Previously Treated Mantle Cell Lymphoma: Updated Results From the Phase 1/2 BRUIN Study

The covalent BTK inhibitors ibrutinib, acalabrutinib, and zanubrutinib are approved by the FDA for the treatment of patients with relapsed/refractory MCL. Among patients who develop disease progression after treatment with a covalent BTK inhibitor, outcomes are poor, with a reported median OS of less than 9 months.[1,2] Mechanisms of resistance to covalent BTK inhibitors in patients with MCL are not fully understood. *BTK C481* mutations are uncommon in MCL; bypass alterations and epigenetic changes may be alternative mechanisms of resistance.[3]

Pirtobrutinib is a novel, highly potent, selective, noncovalent BTK inhibitor that has high selectivity for BTK. In preclinical studies, pirtobrutinib demonstrated activity against wild-type and *BTK C481*–mutated cells. Because pirtobrutinib binds reversibly, its binding is not affected by BTK turnover. Moreover, pirtobrutinib has sustained BTK inhibition throughout the dosing interval.[4]

The phase 1/2 BRUIN study is evaluating the efficacy and safety of pirtobrutinib in patients with hematologic malignancies, including MCL. In the phase 1 portion of the study, patients received pirtobrutinib at escalating doses of 25 mg to 300 mg once daily, with cohort expansion permitted at doses considered safe. In the phase 2 study, pirtobrutinib was administered at 200 mg once daily.[4]

At the 2021 ASH annual meeting, Michael Wang, MD, and colleagues presented updated results from the cohort of 134 patients with MCL in the BRUIN study.[5] The patients' median age was 70 years (range, 46-88 years), 78% were male, and 81% had classic morphology. Patients had received a median of 3 prior lines of systemic therapy (range, 1-9 prior lines). The most frequent prior therapies included anti-CD20 antibodies in 97%, chemotherapy in 91%, a BTK inhibitor in 90%, stem cell transplant (SCT) in 22%, an immunomodulatory drug in 17%, a BCL-2 inhibitor in 15%, and a proteasome inhibitor in 13%. Among the patients who discontinued BTK inhibitors, the cause was progressive disease in 83% of cases.

Among the 100 evaluable patients with MCL who had received previous treatment with a BTK inhibitor, pirtobrutinib led to an ORR of 51%,

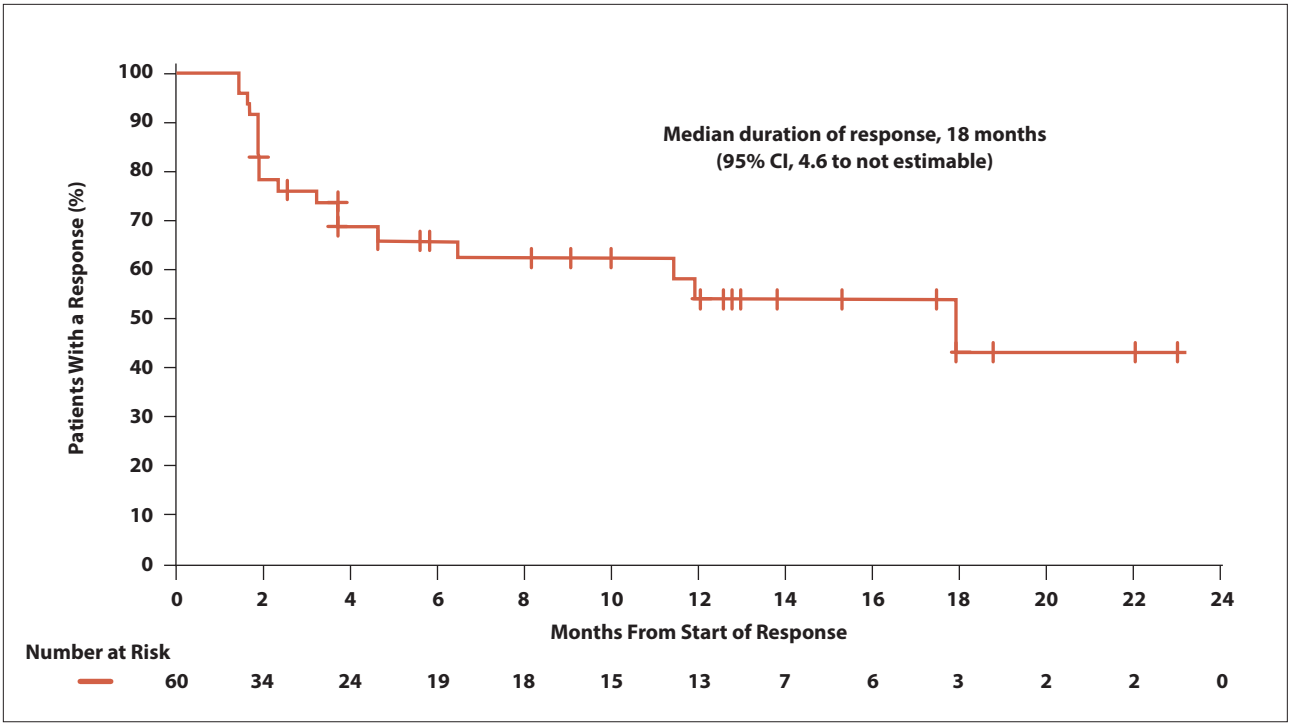

Figure 4. Duration of response among patients with previously treated mantle cell lymphoma treated with pirtobrutinib in the phase 1/2 BRUIN study. Adapted from Wang M et al. ASH abstract 381. *Blood*. 2021;138(suppl 1).[5]

which consisted of CRs in 25% and PRs in 26%. Stable disease was reported in 16% of patients.[5] Among the 11 evaluable patients who were naive to BTK inhibitors, pirtobrutinib led to an ORR of 82%, including CRs in 18% and PRs in 64%. Stable disease occurred in 9%. In subgroup analyses, the ORR was 64% among patients previously treated with SCT (n=28) and 50% in those previously treated with chimeric antigen receptor (CAR) T-cell therapy. After a median follow-up of 8.2 months in patients with a response, the median duration of response was 18 months (Figure 4). At the time of the analysis, 60% of responses were ongoing.

No dose-limiting toxicities were noted, and the maximum tolerated dose was not reached.[5] The most common treatment-emergent AEs were fatigue (23%), bruising (22%), diarrhea (19%), neutropenia (18%), and contusion (17%). The most frequent AEs deemed treatment-related were bruising (15%), contusion (12%), and neutropenia (10%; 8% were grade 3/4). Six patients (1%) permanently discontinued pirtobrutinib owing to treatment-related AEs. The incidence of treatment-related atrial fibrillation/flutter was less than 1%. The randomized phase 3 BRUIN MCL-321 trial is comparing pirtobrutinib against an investigator's choice of covalent BTK inhibitor in patients with BTK inhibitor-naive relapsed MCL.[6]

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Efficacy and Safety of Parsaclisib in Patients With Relapsed or Refractory Mantle Cell Lymphoma Not Previously Treated With a BTK Inhibitor: Primary Analysis From a Phase 2 Study (CITADEL-205)

Parsaclisib is a potent, selective next-generation phosphoinositide 3-kinase (PI3K) δ inhibitor that is being evaluated in patients with various hematologic malignancies. The phase 2 CITADEL-205 trial evaluated the efficacy and safety of parsaclisib in patients with relapsed/refractory MCL.[1] Previous treatment with BTK inhibitors was permitted.

Amitkumar Mehta, MD, presented the primary efficacy and safety analyses for the BTK inhibitor–naive cohort of the CITADEL-205 trial.[1] The cohort enrolled patients with relapsed or refractory MCL who had received 1 to 3 prior systemic regimens (that did not include PI3K or BTK inhibitors). The patients had an ECOG PS of 0 to 2, and documented cyclin D1 overexpression or a t(11;14) translocation.

A total of 108 patients were randomly assigned to receive parsaclisib at a weekly dose or a daily dose. Patients in the weekly dosing group (n=31)

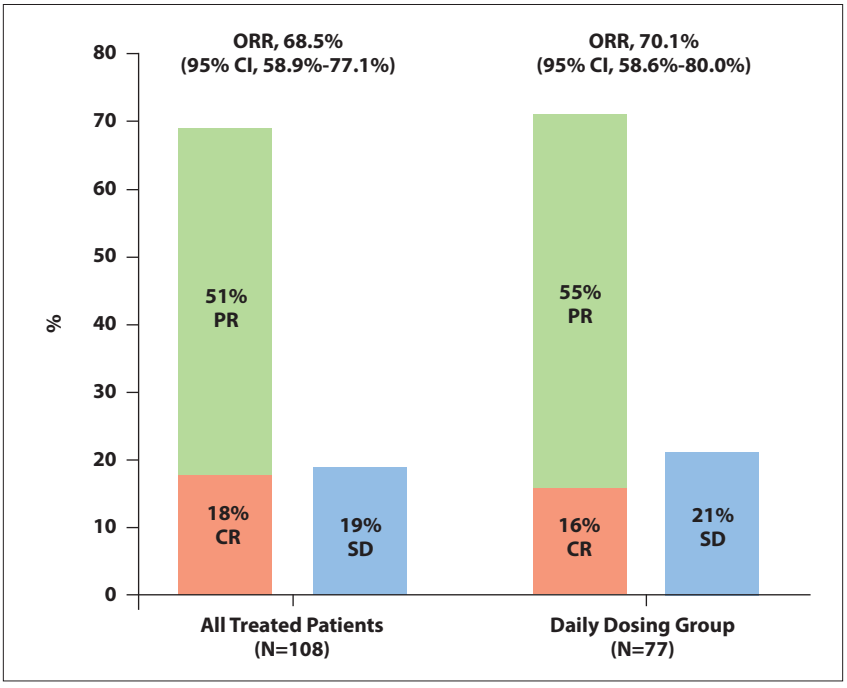

Figure 5. Response rates among patients with relapsed or refractory mantle cell lymphoma not previously treated with a BTK inhibitor who received parsaclisib in the phase 2 CITADEL-205 trial. BTK, Bruton's tyrosine kinase; CR, complete response; ORR, objective response rate; PR, partial response; SD stable disease. Adapted from Mehta A et al. ASH abstract 382. *Blood*. 2021;138(suppl 1).[1]

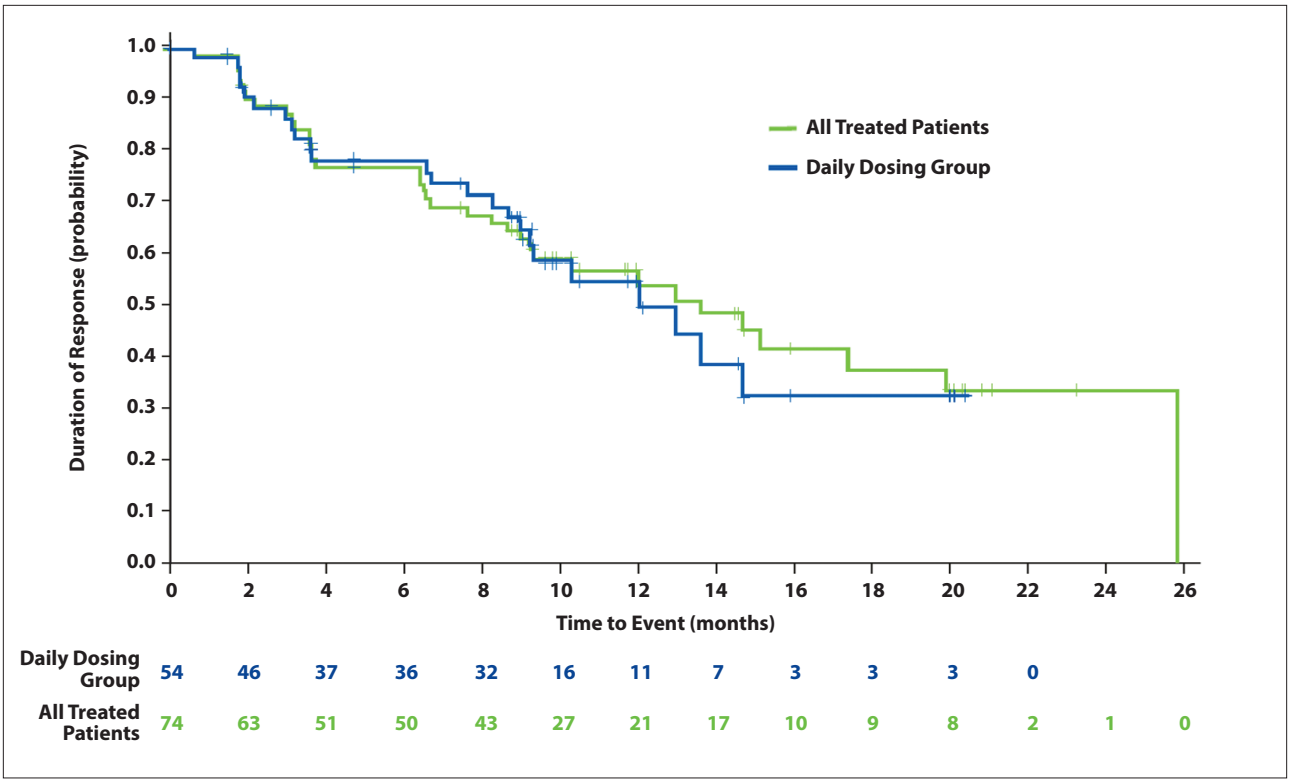

Figure 6. Duration of response among patients with relapsed or refractory mantle cell lymphoma not previously treated with a BTK inhibitor who received parsaclisib in the phase 2 CITADEL-205 trial. BTK, Bruton's tyrosine kinase. Adapted from Mehta A et al. ASH abstract 382. *Blood*. 2021;138(suppl 1).[1]

received parsaclisib at 20 mg once daily for 8 weeks followed by parsaclisib at 20 mg once weekly. Patients in the daily dosing group (n=77) received parsaclisib at 20 mg once daily, followed by 2.5 mg once daily given continuously. Following an interim analysis, enrollment was closed in the weekly dosing group, but continued in the daily dosing group. Daily dosing was selected as the recommended strategy. The CITADEL-205 analysis included patients in the daily dosing group and those initially assigned to weekly dosing who switched to daily dosing.

The patients' median age was 72.0 years, and 79% were ages 65 or older.[1] Most patients (80%) were male. The median time since MCL diagnosis was 3.6 years (range, 0.1-20.9 months), and 56% of patients had a high-risk MIPI score. At the data cutoff, 72% of patients had discontinued treatment, primarily owing to progressive disease (45%) or AEs (23%). The median treatment duration was 8.3 months (range, 0.1-30.0 months), and the median duration of follow-up was 22.9 months (range, 11.6-35.9 months).

According to an independent review committee, the ORR was 68.5% (with CRs in 18%) in all treated patients (N=108; Figure 5). The ORR was 70.1% (with CRs in 16%) in the daily dosing group (n=77).[1] Assessment by investigators reported ORRs of 79.6% and 81.8%, respectively. Most first responses (89%) occurred by the time of the first disease assessment at 8 weeks. Regression of the target lesions was documented in 96% of evaluable patients (90 of 94). A reduction in the best percentage change from baseline of more than 50% was reported in 84% of patients. The median duration of response was 13.7 months in all treated patients and 12.1 months in the daily dosing group (Figure 6). The median PFS was 12.0 months vs 13.6 months, respectively. The median OS had not been reached. The overall OS rate was 90% at 6 months and 80% at 12 months.

The most frequent treatment-emergent AEs was diarrhea, reported in 34% of all treated patients and 40% in the daily dosing group. Other treatment-emergent AEs included pyrexia (18% and 17%, respectively), constipation (13% and 14%), rash (11% and 14%), asthenia (11% and 13%), neutropenia (11% and 12%), and cough (10% and 12%).[1] The most common grade 3 or higher AEs was diarrhea, reported in 14% of all treated patients and 18% in the daily dosing group. Other grade 3 or higher AEs included neutropenia (8% and 9%, respectively), rash (3% and 4%), and nausea (2% and 3%). The most common grade 3/4 laboratory abnormalities included decreased neutrophils

(11% in all treated patients and 11.5% in the daily dosing group), decreased platelets (9% and 7%, respectively), decreased hemoglobin (3% and 4%, respectively), alanine aminotransferase elevations (5% and 3%, respectively), and aspartate aminotransferase elevations (3% in both groups). Serious treatment-emergent AEs included diarrhea (9% in all treated patients and 13% in the daily dosing group), colitis (5% and 6.5%, respectively), hypokalemia (3% in each group), pyrexia (3% in each group), and rash (2% and 3%, respectively).[1]

The median time to onset of grade 3 or higher diarrhea was 4.3 months in all treated patients and 5.1 months in the daily dosing group. Diarrhea improved to grade 0 to 2 after a median of 11 days. The median time to onset of colitis was 3.1 months, and the median time to improvement to grade 0 to 2 was 20 days. In the daily dosing group, the most frequently occurring treatment-emergent AEs leading to dose modifications consisted of interruptions owing to diarrhea (14%) or neutropenia (9%), reductions owing to rash (3%), and discontinuations owing to diarrhea (16%) and colitis (6.5%). One death owing to a treatment-emergent AE was deemed related to parsaclisib by the investigator. This patient had leukocytosis, acute myelomonocytic leukemia, and acute kidney injury.

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Rituximab and High-Dose Cytarabine/Dexamethasone (R-HAD) Plus Bortezomib Is Superior to R-HAD Only in Relapsed Mantle Cell Lymphoma: A Randomized Phase 3 Trial of the European MCL Network

The addition of cytarabine to standard chemotherapy improved PFS in the MCL Younger trial.[1] Data have also shown significant PFS and OS benefits with the frontline administration of bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone compared with R-CHOP in patients with MCL who are ineligible for transplant.[2] Martin Dreyling, MD, presented results of a phase 3 trial from the European MCL Network that evaluated the inclusion of both bortezomib and high-dose cytarabine in the treatment of older patients with MCL.[3] The trial enrolled 128 patients with relapsed or progressive disease following 1 to 3 prior lines of therapy. The patients were randomly assigned to treatment with 4 cycles of rituximab, high-dose cytarabine, and dexamethasone either with bortezomib (administered at 1.5 mg/m^2 subcutaneously on days 1 and 4 [R-HAD plus bortezomib]) or without bortezomib (R-HAD).[3] Although the original plan was to allow patients with stable disease after 2 cycles to withdraw from the study, some patients with minor responses were permitted to receive the full 4 cycles.

The trial enrolled 63 patients to receive R-HAD plus bortezomib and 64 patients to receive R-HAD.[3] Their median age was 69 years vs 71 years, respectively. In both groups, most patients were male (71% vs 80%). Ann Arbor stage IV MCL was reported in 65% of patients treated with R-HAD plus bortezomib and 77% of those in the R-HAD alone group. At study entry, 37% and 48% of patients, respectively, had high-risk disease according to their MIPI score. The median time since diagnosis was 3.9 years and 3.7 years, respectively. Previous treatment with only 1 prior line of therapy was reported in 79% and 62% of patients. Prior treatment with high-dose cytarabine was reported in 38% and 34% of patients.

The ORR was 63% with R-HAD plus bortezomib vs 45% with R-HAD (P=.049). The rate of CR was 28% vs 12% (P=.043), respectively. The rate of CR/unconfirmed CR was 42% vs 19% (P=.0062).[3] The primary endpoint was TTF. In most cases, TTF was defined as nonachievement of PR after 2 cycles of treatment, which Dr Dreyling considered a limitation of the study design. In an intention-to-treat analysis, the median TTF after a median follow-up of 41 months was 12.0 months with R-HAD plus bortezomib vs 2.6 months with R-HAD (Figure 7). In an adjusted analysis to correct for the sequential study design, the HR was 0.68 (P=.045). In a secondary per-protocol analysis, the median TTF was 12.9 months with R-HAD plus bortezomib vs 2.6 months with R-HAD alone (HR, 0.60; P=.017).

Subgroup analyses suggested a differential benefit with bortezomib based on the MIPI risk group (P value for interaction, .024).[3] There were insufficient patient numbers in the low-risk group (n=26) to draw major conclusions. However, there appeared to be a potential benefit with R-HAD plus bortezomib vs R-HAD alone in the intermediate-risk and high-risk groups. An analysis of TTF based on cytarabine exposure showed a benefit of bortezomib in patients who had not

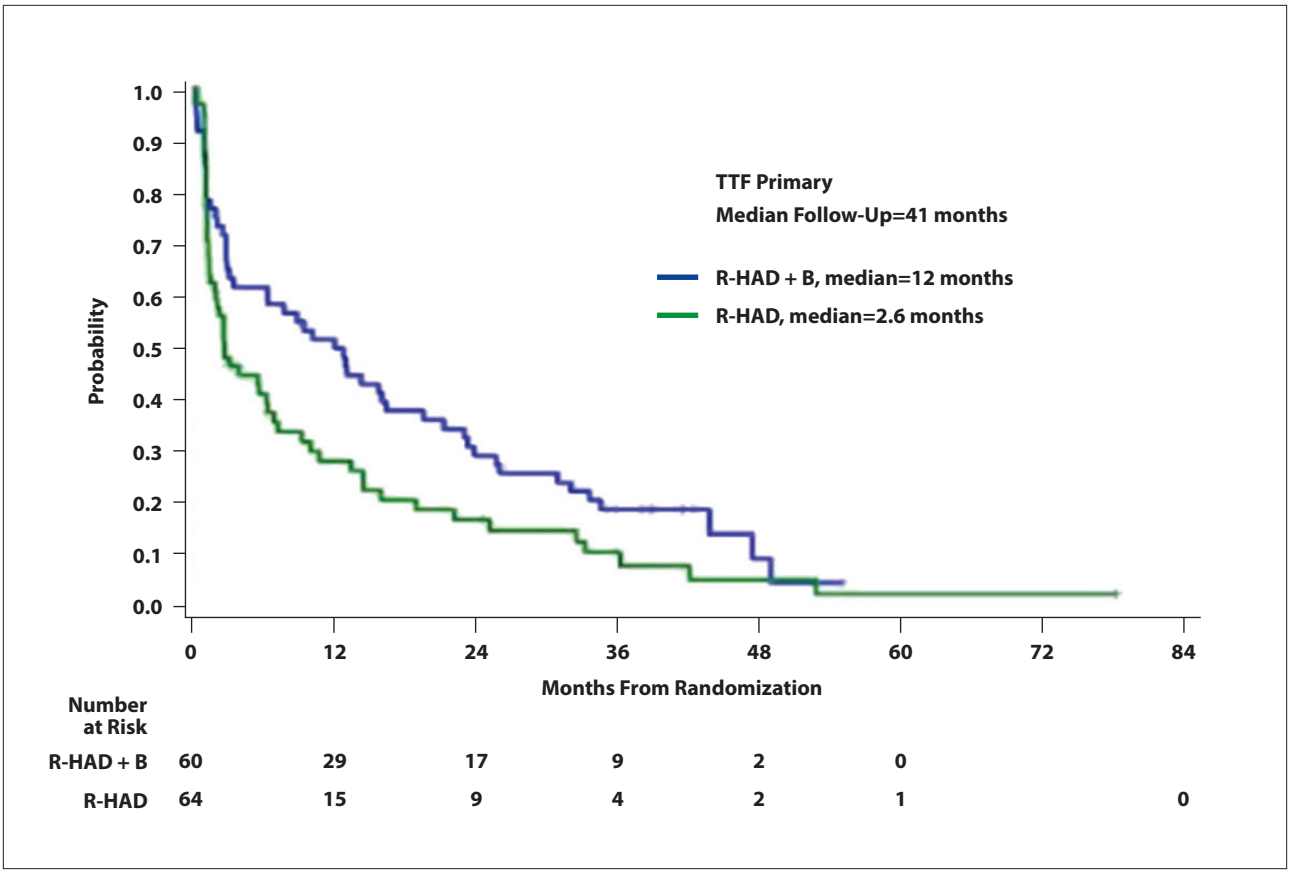

Figure 7. Time to treatment failure among patients with relapsed or progressive mantle cell lymphoma who received rituximab, high-dose cytarabine, and dexamethasone, with or without bortezomib, in a phase 3 trial. Data are shown for the primary intention-to-treat population. R-HAD + B, rituximab, high-dose cytarabine, and dexamethasone with bortezomib; R-HAD, rituximab, high-dose cytarabine, and dexamethasone; TTF, time to treatment failure. Adapted from Dreyling M et al. ASH abstract 383. *Blood*. 2021;138(suppl 1).[3]

previously received cytarabine (median TTF, 16.0 vs 2.2 months; HR, 0.58; *P*=.031).

The median PFS was 15.4 months with R-HAD plus bortezomib vs 9.2 months with R-HAD, although this difference did not reach statistical significance (HR, 0.78; *P*=.21).[3] There was no significant difference in the duration of response between the arms. Dr Dreyling noted that this trial was initiated 15 years ago, and it is now recognized that chemotherapy-based regimens have only modest activity in relapsed MCL. Although the sample size was small, the addition of bortezomib to R-HAD was associated with an extended TTF that was driven primarily by higher response rates. There were no significant differences in survival or toxicity.

Serious AEs occurred in 34% of patients treated with R-HAD plus bortezomib vs 50% of those treated with R-HAD. Dr Dreyling suggested that this finding indicated that the dose of bortezomib was well tolerated. Infections occurred in 9% of patients in each arm.[3] The rates of grade 3/4 neurotoxicity were low and therefore not included in the presented data for serious AEs.

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KTE-X19 in Relapsed or Refractory Mantle-Cell Lymphoma, a "Real-Life" Study From the DESCAR-T Registry and LYSA Group

Brexucabtagene autoleucel is a CD19-directed CAR T-cell therapy that is approved by the FDA for patients with relapsed/refractory MCL. The approval was based on results from the ZUMA-2 trial, in which brexucabtagene autoleucel demonstrated a higher rate of durable remissions among patients previously treated with up to 5 previous therapies, including a BTK inhibitor.[1] At 12 months, the estimated rates of PFS and OS were 61% and 83%, respectively.

Charles Herbaux, MD, presented results of a real-world analysis of outcomes with brexucabtagene autoleucel in patients with MCL from the DESCAR-T registry.[2] Patients in this registry had received treatment with commercial CAR T cells.[2] The study included 57 registered patients with MCL, 51 of whom were enrolled in a French early access program (starting in January 2020) and 6 of whom enrolled after the end of this program. At the time of the analysis, CAR T-cell therapy had been ordered for 55 patients and administered to 48 patients. The median age of the enrolled patients was 67 years (range, 45-79 years), 89.5% were male, and 31.9% had high-risk disease (per MIPI) at diagnosis. Patients had received a median of 3 prior lines of treatment (range, 2-9 prior lines), and 38.2% had undergone a prior ASCT. In the treated set of 48 patients, 93.8% were male, 30.0% had high-risk disease (per MIPI), and 33.3% had undergone a prior ASCT.

Among patients who had received a CAR T-cell infusion, the median time from the CAR T-cell order to infusion was 56 days (range, 35-134 days).[2] Bridging therapy was administered to 87.2% of patients. Bridging therapies consisted of anti-CD20 monoclonal antibodies in 64.3%, chemotherapy in 57.1%, BTK inhibitors in 26.2%, and immunomodulatory drugs in 14.3%. These therapies led to an ORR of 45.3%. After a median follow-up of 6 months since administration of CAR T-cell therapy (range, 3.3-6.2 months), the median OS was not reached in the treated set of patients (n=48) vs 1.5 months in the untreated set (n=7; Figure 8). Among patients who received brexucabtagene autoleucel and were evaluated for efficacy, the best ORR was 87.2%, including a CR in 63.8%. The median PFS was 6.3 months.

Cytokine release syndrome (CRS) was reported in 84.8% of patients (grade ≥3, 8.7%) and neurotoxicity occurred in 52.2% (grade ≥3, 8.7%).[2] Treatment in an intensive care

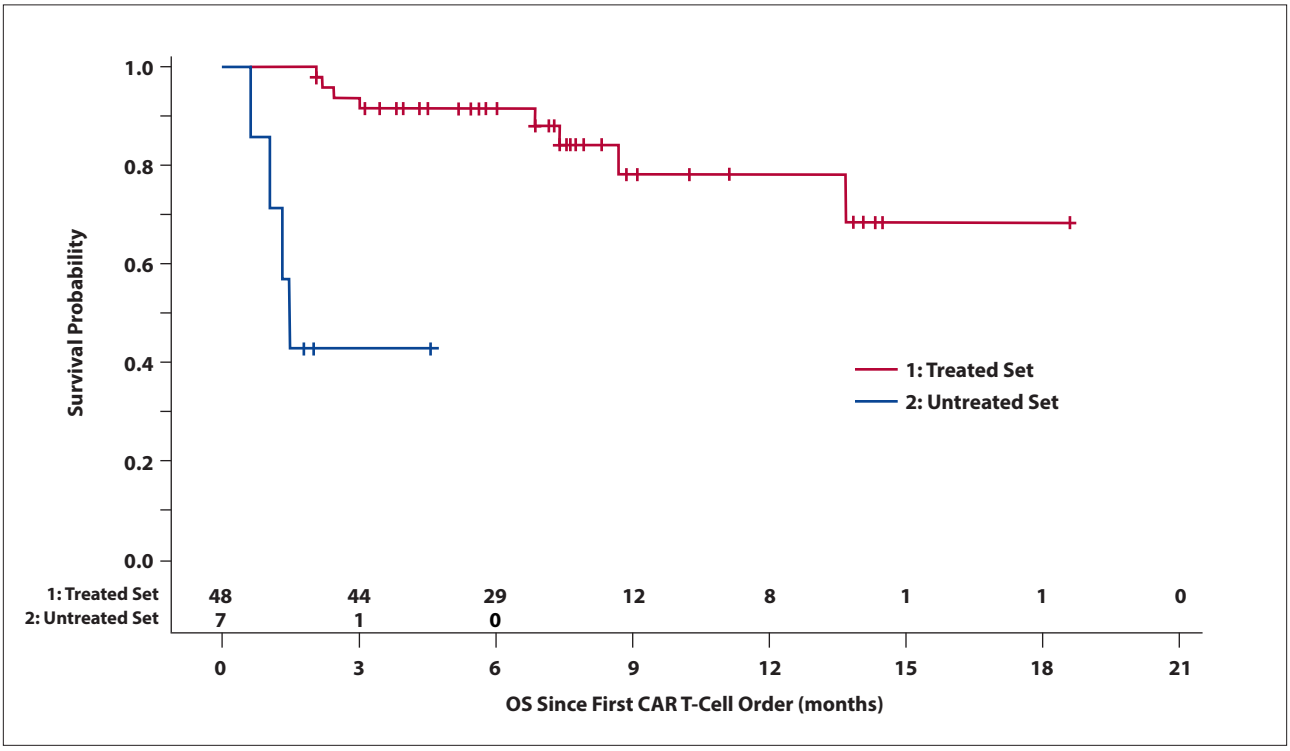

Figure 8. Overall survival since the first order of CAR T-cell therapy by treatment set in a real-world analysis of brexucabtagene autoleucel in patients with relapsed or refractory mantle cell lymphoma. CAR, chimeric antigen receptor; OS, overall survival. Adapted from Herbaux C et al. ASH abstract 743. *Blood*. 2021;138(suppl 1).[2]

unit (ICU) was required by 28.3% of patients. The median duration of hospitalization was 4.5 days.[2] Treatment included tocilizumab in 69.2 of patients and corticosteroids in 59%. Among the 48 treated patients, 8 patients died, including 6 from progressive disease, 1 from CRS, and 1 from candida septic shock. Cytopenias in the first month included neutropenia (69.6%), thrombocytopenia (67.4%), and anemia (67.4%). Cellular kinetics assessed in a subset of patients (n=14) showed a statistical trend toward a shorter time to maximal expansion in those with a response vs those without a response (*P*=.046).

Dr Herbaux concluded that in this real-world analysis of brexucabtagene autoleucel, the safety profile and ORR were in line with previously published data.[2] There was, however, increased use of bridging therapy and possibly a shorter median PFS.[2] He added that the findings support the use of brexucabtagene autoleucel in patients with relapsed/refractory MCL after unsuccessful treatment with chemotherapy and a BTK inhibitor.

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Brexucabtagene Autoleucel for Relapsed/Refractory Mantle Cell Lymphoma: Real-World Experience From the US Lymphoma CAR T Consortium

A real-world analysis reported data for the patterns of use, safety, and efficacy of brexucabtagene autoleucel among patients with MCL enrolled in the US Lymphoma CAR T Consortium.[1] The analysis included 107 patients from 14 centers in the United States who underwent leukapheresis between August 2020 and June 2021, with the intent of manufacturing brexucabtagene autoleucel. CAR T cells were administered to 95 patients. The remaining 12 patients did not receive infusions owing to manufacturing failure (n=6), death (n=5), or organ dysfunction (n=1).

Among the 95 treated patients, the median age was 67 years (range, 34-89 years). Most patients (80%) were male, and 12% had high-risk disease according to the simplified MIPI.[1] Other factors included a Ki-67 score of 50% or higher in 57% of patients, a

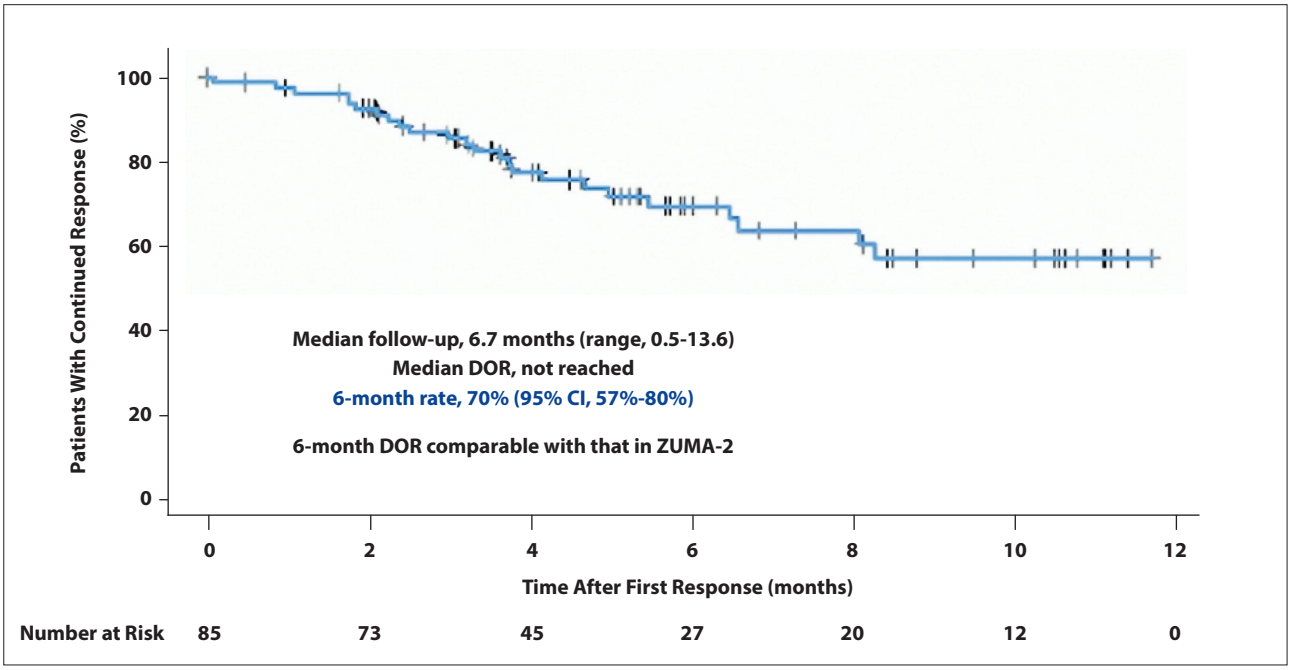

Figure 9. Duration of response among patients with relapsed/refractory mantle cell lymphoma treated with brexucabtagene autoleucel in a real-world analysis. DOR, duration of response. Adapted from Wang Y et al. ASH abstract 744. *Blood*. 2021;138(suppl 1).[1]

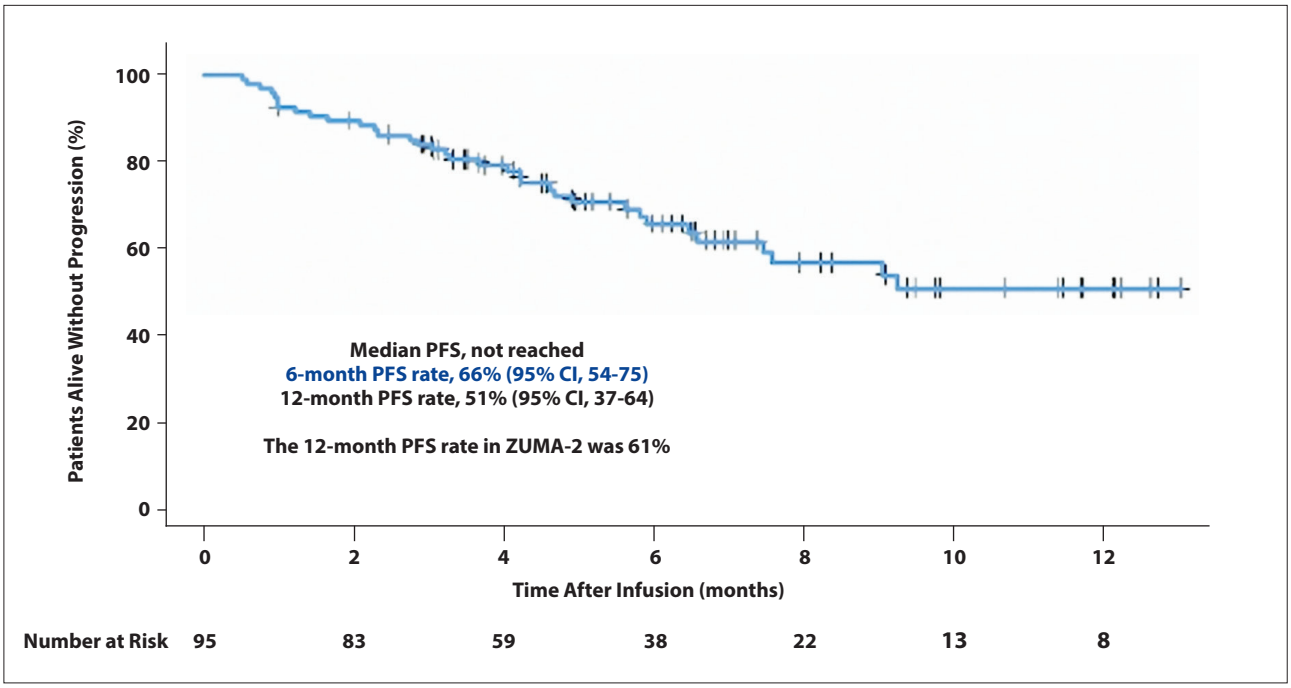

Figure 10. Progression-free survival among patients with relapsed/refractory mantle cell lymphoma treated with brexucabtagene autoleucel in a real-world analysis. PFS, progression-free survival. Adapted from Wang Y et al. ASH abstract 744. *Blood.* 2021;138(suppl 1).[1]

blastoid or pleomorphic morphology in 41%, *TP53* mutation or deletion in 44%, and a complex karyotype in 29%. CNS involvement was present in 7% of patients, and 11% had bulky disease (≥10 cm). The patients had received a median of 3 prior lines of therapy (range, 1-10). Previous treatments included a BTK inhibitor in 82% and venetoclax in 35%. Most patients (78%) would not have met the ZUMA-2 eligibility criteria, primarily owing to their number and types of prior therapies, renal dysfunction, cytopenias, ECOG PS, and CNS involvement.

Bridging therapy was administered to 67% of patients, and most often consisted of BTK inhibitor–based therapy (n=20), rituximab plus chemotherapy with or without a corticosteroid (n=16), and a BTK inhibitor plus venetoclax-based therapy (n=9).[1] The median time from leukapheresis to lymphodepletion chemotherapy was 23 days (range, 12-54 days). The median time from lymphodepletion to infusion with CAR T cells was 5 days (range, 4-12 days).

CRS was reported in 91% of patients (grade 3/4, 8%). Immune effector cell–associated neurotoxicity syndrome (ICANS) occurred in 60% (grade 3/4, 35%).[1] The median time to onset of CRS was 4 days (range, 0-11 days), and the median duration was 5 days (range, 1-33+ days). The median time to ICANS was 6 days (range, 1-15 days), and the median duration was 6 days (range, 2-144+ days). The maximum grade of CRS occurred at day 5. The maximum grade of ICANS was reported at day 7. Prior treatments included tocilizumab in 79% of patients and corticosteroids in 69% of patients. Admission to an ICU was required by 21% of patients, for a median of 3 days (range, 1-12 days). The investigators noted that the incidences of CRS and ICANS were comparable with those reported in the ZUMA-2 trial (91% and 63%, respectively).[2] The use of tocilizumab and corticosteroids appeared to be more common in the real-world cohort.

The best ORR was 89%, which included CRs in 81%.[1] The median time to an initial response was 30 days (range, 16-104 days). At day 30, the ORR (n=92) was 88%, including CRs in 66%. Responses deepened over time. After a median of 64 days (range, 22-135 days), a CR was reported in 12 of 20 patients with an initial PR and in 1 of 2 patients with stable disease. The median time to best response was 30 days (range, 16-168 days). Dr Wang noted that the best ORR was comparable with that reported in the ZUMA-2 trial (93%).[2] In subgroup analyses, brexucabtagene autoleucel was active even in high-risk groups, including patients with a blastoid or pleomorphic morphology, *TP53* alterations, high Ki-67, and CNS involvement. After a median follow-up of 6.7 months, the median duration of response was not reached, and the 6-month response rate was 70% (Figure 9). The median PFS was not reached (Figure 10). The rates of PFS were 66% at 6 months and 51%

at 12 months. The 12-month PFS rate in the ZUMA-2 trial was 61%.[2] The rates of OS were 81% at 6 months and 72% at 12 months. In ZUMA-2, the 12-month OS rate was 83%.[2]

Dr Wang noted that the patients in this real-world analysis are representative of the types of patients who receive brexucabtagene autoleucel in standard practice, with more high-risk features and broader characteristics. He concluded that treatment with brexucabtagene autoleucel was feasible and demonstrated similar safety and efficacy as reported in the ZUMA-2 trial.[1]

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Highlights in Mantle Cell Lymphoma From the 63rd American Society of Hematology Annual Meeting and Exposition: Commentary

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A rich data set covering multiple aspects of the management of mantle cell lymphoma (MCL) was presented at the 63rd American Society of Hematology (ASH) annual meeting, held in December 2021. This article will review how these findings might impact the different settings of MCL therapy from frontline to maintenance, as well as relapsed/refractory disease.

Frontline Treatment

Dr Olivier Hermine presented the results of a large, randomized trial from the European MCL Network that evaluated the addition of high-dose cytarabine to immunochemotherapy before autologous stem cell transplant (ASCT) in patients ages 65 years or younger.[1] Of note, patients did not receive any maintenance therapy in this trial. The primary endpoint was time to treatment failure (TTF). In the original report, at a median follow-up of 6 years, treatment with rituximab plus dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP) was associated with significant improvement in TTF and progression-free survival (PFS) compared with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP),[2] which confirmed the original observation from the phase 2 NORDIC 2 trial.[3] Now, with the median follow-up nearly doubled at 11 years, the benefits with R-DHAP vs R-CHOP were sustained for both TTF (7.7 years vs 4.1 years; $P<.0001$) and PFS (8.0 years vs 4.3 years; $P<.0001$). The 10-year rate of overall survival was not significantly different (60% with R-DHAP vs 55% with R-CHOP; $P=.12$). Interestingly, the benefit of cytarabine was most pronounced in high-risk patients (defined as those with an intermediate/high-risk Mantle Cell Lymphoma International Prognostic Index [MIPI] score, high *TP53*, or the blastoid variant), in whom the median TTF was 7.6 years with R-DHAP vs 2.8 years with R-CHOP ($P<.0001$). Among these patients, R-DHAP doubled the median overall survival (10 years for R-DHAP vs 5 years for R-CHOP; $P=.013$). For a trial with no maintenance therapy, these results are impressive, even given the caveat of potential selection bias inherent to clinical trials, as suggested by real-world MCL series.[4]

This large, randomized trial established the importance of cytarabine-containing regimens as induction in younger MCL patients.[2] The updated analysis, with close to 12 years of follow-up, confirmed the benefit of cytarabine, particularly in high-risk patients.[1] This regimen (R-CHOP alternating with R-DHAP followed by ASCT) became the de facto control arm for subsequent studies, in particular the ongoing European TRIANGLE trial, which is evaluating whether the addition of ibrutinib can improve outcome in younger MCL patients.[5] This trial includes a maintenance ibrutinib arm post-ASCT and one arm in which patients will proceed straight to

maintenance after induction, without ASCT consolation. Results from this trial will continue to help to reshape the frontline management of younger MCL patients.

MCL patients who are elderly and/or ineligible for intensive therapy represent approximately two-thirds of the population. Dr Maria Chiara Tisi presented the long-term update of a phase 2 trial that evaluated rituximab, bendamustine, and low-dose cytarabine as induction therapy in elderly patients.[6] The dose of cytarabine was 500 mg/m^2 instead of 800 mg/m^2 because of the toxicity reported with the higher dose in the original R-BAC trial.[7] Previous data for this multicenter Italian study, which enrolled 58 patients with a median age of 71 years, was reported after a median of 3 years of follow-up. The objective response rate (ORR) was 91%, all complete responses (CRs), and the 2-year PFS rate was 81%.[7] This recent update provided results after a median follow-up of 7 years. The PFS was 56% and the overall survival was 63%, including a high proportion (78%) of minimal residual disease (MRD)-negative patients at the end of induction, which dramatically impacted outcome. The median PFS was 12 months for MRD-positive patients vs not reached in MRD-negative patients (P=.05). At 8 years, 70% of patients were still disease-free in the MRD-negative group.

Results for the R-BAC500 regimen, although from a small phase 2 trial, are very promising. The data appear superior to those reported for bendamustine plus rituximab (BR), which had a CR rate of approximately 30% to 40% in several studies.[8] A recent large, randomized Eastern Cooperative Oncology Group E1411 trial, which was presented at the 2021 American Society of Clinical Oncology annual meeting, compared BR vs BR plus bortezomib (BVR), followed by maintenance with rituximab alone or rituximab plus lenalidomide (R^2).[9] In this trial, the CR rate was higher for both treatment arms, at 59.7% with BR vs 66.3% with BVR. The median PFS was approximately 5 years. Of note, the R-BAC500 regimen also showed very durable responses, although the trial did not include maintenance. Outside of a clinical trial, R-BAC seems to be a very appropriate regimen, particularly in patients without high-risk molecular features and who are not candidates for high-dose or dose-intensive therapy. This regimen is now undergoing evaluation in combination with other agents, such as venetoclax (VR-BAC), using a stratification strategy from low risk to high risk based on the following factors: morphology (blastoid vs others), Ki-67 expression (≥30% vs <30%, and *TP53* mutation/*TP53* deletion (found in 21% and 13% of cases, respectively).[10] Patients with low risk received 6 cycles of R-BAC, whereas high-risk patients received a maximum of 4 cycles of R-BAC followed by consolidation (4 months, 800 mg/day) and maintenance (20 months, 400 mg/day) with venetoclax. The trial is ongoing.

When treating with chemoimmunotherapy, high-risk features, such as high Ki-67, the blastoid variant, *TP53* mutation/*TP53* deletion, and/or complex karyotype, are associated with poor outcome regardless of the treatment regimen used.[11] Although a 17p deletion is not common at baseline, the presence of *TP53* mutations can be found in up to 20% to 25% of MCL patients at diagnosis. Numerous studies have shown the impact of *TP53* mutations on outcome, even after high-dose therapy and ASCT.[12,13] In the setting of relapsed/refractory MCL, *TP53* aberrations are much more common and therefore justify a repeat biopsy when disease progresses. These patients do very poorly with all standard therapies, with the exception of Bruton's tyrosine kinase (BTK) inhibitors and chimeric antigen receptor (CAR) T-cell therapy, which have shown durable responses. Combinations of biologic agents, such as R^2 plus ibrutinib and venetoclax plus ibrutinib showed high CR rates (70%-80%) and durable responses, even in patients who were heavily pretreated and who had high-risk molecular features.[14,15] These results have prompted efforts to bring novel therapies into the frontline management of MCL. Small phase 2 studies using doublets, such as R^2 and rituximab plus ibrutinib, showed impressive rates of CRs and durable responses, as well.[16,17] Building on these data, triplet therapy, particularly, R^2

ABSTRACT SUMMARY Real-World Bruton Tyrosine Kinase Inhibitor Treatment Patterns, Compliance, Costs, and Hospitalizations in Patients With Mantle Cell Lymphoma in the United States

A retrospective analysis evaluated the real-world use of BTK inhibitors, including ibrutinib (n=1242), acalabrutinib (n=485), and zanubrutinib (n=67), in patients with MCL in the United States (Abstract 3046). The patients' median age was 64 to 71 years (range, 59-74 years), and 50% to 55% of patients were ages 75 years or older. The most common comorbidities were hypertension (41.1%), dyslipidemia (28.6%), diabetes (17.5%), cardiac arrhythmia (15.6%), and gastroesophageal reflux disease (14.5%). Ibrutinib was most often used in the frontline setting (68.4%). Acalabrutinib and zanubrutinib were more commonly used in relapsed/refractory MCL (68.9% and 80.6%, respectively). The adherence rates were 65% with zanubrutinib, 62% with acalabrutinib, and 59% with ibrutinib. Among patients who were hospitalized at least once, the average length of the stay was 5.9 days with ibrutinib, 5.8 days with acalabrutinib, and 4.0 days with zanubrutinib. Average inpatient charges per stay were $79,482, $74,546, and $51,051, respectively.

plus ibrutinib; lenalidomide, venetoclax, and rituximab; and ibrutinib, venetoclax, and obinutuzumab (in the OASIS trial[18]), showed remarkable activity, including high rates of MRD-negativity, even in patients with the *TP53* mutation at study entry. At the 2021 ASH annual meeting, Dr Michael Wang presented the results of a small phase 1b study of acalabrutinib, venetoclax, and rituximab in 21 patients with treatment-naive MCL.[19] An interesting finding from this trial was that the CR rate was 90%, and all CRs occurred in patients who were MRD negative. Although the follow-up is short, early MRD-negative CRs typically translate into very favorable long-term outcome in MCL. As in the field of chronic lymphocytic leukemia, the management of MCL will continue to evolve, relying less on chemotherapy to encompass nonchemotherapy options or the sequential use of nonchemotherapy agents followed by chemotherapy.

The WINDOW-1 trial explored a "window" with ibrutinib and rituximab, followed by a reduced number of cycles of rituximab plus cyclophosphamide, vincristine, doxorubicin, and dexamethasone (R-hyper-CVAD), with very promising results.[20] The overall best response in part A of therapy (which was the ibrutinib and rituximab "window" before chemotherapy) was 100%, with a CR rate of 88%. At the end of induction therapy, the ORR was 100%, with CRs in 94%, and 78% of patients overall were MRD-negative.[21] (There was no maintenance arm in this trial.) The WINDOW-2 trial is evaluating ibrutinib plus rituximab followed by venetoclax in the nonchemotherapy "window," followed by R-hyper-CVAD consolidation, with stratification based on the extent of high-risk features.[22] In current practice, next-generation sequencing can identify patients with high-risk features more easily than standard immunohistochemistry and/or fluorescence in situ hybridization. As we continue to reshape the management of MCL, it is likely we will use more nonchemotherapy options. Among the remaining questions is whether the patients still need chemotherapy afterward. Ongoing studies will help stratify patients based on the degree of high-risk molecular features. Finally, CAR T-cell therapy will be explored early on in very high-risk patients and/or those who are still MRD-positive after induction therapy.

Maintenance

The benefit of maintenance therapy was first established with rituximab after R-CHOP in elderly patients.[23] These benefits are now recognized in both younger and elderly patients with MCL.[24] Two studies at the 2021 ASH annual meeting evaluated data from the MCL R^2 Elderly clinical trial from the European MCL Network. A presentation by Dr Vincent Ribrag reported on the maintenance phase of the trial, which compared R^2 vs rituximab.[25] This trial first randomly assigned patients to treatment with R-CHOP vs R-CHOP combined with cytarabine. Patients achieving a CR or partial response (PR) underwent a second randomization to receive maintenance therapy with rituximab vs R^2 every 2 months for 2 years. The trial enrolled approximately 600 patients, 500 of whom received maintenance therapy. The 2-year rate of PFS was 76% in the R^2 arm vs 60% in the rituximab arm. The improvement in the R^2 arm might be attributable to the immunomodulatory effects of lenalidomide, which improves antibody-dependent cellular cytotoxicity and potentially clears further residual MCL cells. However, there was no difference in overall survival, partly owing to the use of novel agents that provide better salvage therapy in MCL. As expected, the rates of neutropenia and infection were higher in the R^2 arm, but manageable.

Although the benefit of maintenance with rituximab has been extensively confirmed, there are remaining questions, such as the optimal duration of maintenance (2-3 years in most trials vs until disease progression in the original MCL study in elderly patients[23]) and how to improve on rituximab maintenance alone. The trial by Dr Ribrag explored the latter question, by adding lenalidomide to rituximab.[25] The R^2 regimen seemed superior in delaying progression, but it did not improve overall survival. In practice, rituximab is administered for 2 years to mitigate the potential cumulative toxicity that can occur over time, which includes hypogammaglobulinemia and increased risk of infections (eg, upper respiratory and sinus infections). The most important question is whether it will be possible to customize the need for and/or duration of maintenance. Without a doubt, patients with early CRs who are MRD-negative do better overall, but do patients who are MRD-negative after induction still benefit from maintenance?

Dr Marie-Helene Delfau provided interesting data at the 2021 ASH annual meeting regarding the impact of MRD on maintenance status in the MCL R^2 Elderly trial.[26] This trial nicely collected prospective data for MRD at multiple time points, with centralized processing of MRD via quantitative polymerase chain reaction, focusing on rearrangements in the immunoglobulin heavy chain VDJ junction (IGH) or IGH-BCL1. As mentioned previously, this trial compared R-CHOP vs R-CHOP alternating with high-dose cytarabine in elderly patients. At the end of induction, both arms had similar rates of MRD negativity: 42% with R-CHOP vs 36% with R-CHOP/R-HAD. Of note, these results differ from those reported with high-dose cytarabine in younger patients, which showed much higher rates of CR and MRD negativity that were achieved at earlier time points, thus explaining why TTF and PFS were superior in the high-dose cytarabine arm.[2] Whether

this difference is attributable to the intensity of the cytarabine is unclear. As expected, outcomes were worse in patients with detectable MRD at the end of treatment. The median PFS was 2.7 years in patients with detectable MRD vs 4.7 years in patients who were MRD-negative. Maintenance with rituximab alone had no impact on outcome, regardless of whether the patient was MRD-positive or MRD-negative after induction. In the R^2 arm, only the MRD-negative patients benefited from maintenance therapy. Hypothetically, lenalidomide might help clear additional cells through its immunomodulatory effects and thereby improve outcome. Additional ongoing trials exploring the integration of other biologic agents, in particular BTK inhibitors, might help build better maintenance regimens, ideally guided by MRD status, to further delay recurrence and to continue to improve survival.[27]

Relapsed/Refractory Disease

The US Food and Drug Administration granted accelerated approval to brexucabtagene autoleucel in relapsed/refractory MCL based on results of the ZUMA-2 trial.[28] The indication does not limit treatment to patients who had previously received BTK inhibitors, but encompasses patients with relapsed/refractory MCL after at least one line of therapy. Dr Yucai Wang presented results from a real-world study of brexucabtagene autoleucel in approximately 100 patients in the United States.[29] A similar European study included 57 patients.[30] Both of these studies enrolled heavily pretreated patients, who had received a median of 3 prior therapies. In the US series, in which patients had received up to 10 prior therapies, almost half of the patients had high-risk features (either high Ki-67 level, mutation and/or deletion of *TP53*, blastoid variant, or complex karyotype), and almost 80% would not have qualified for the ZUMA-2 trial based on eligibility criteria. Grade 3/4 cytokine release syndrome (CRS) occurred in 8% of patients, and grade 3/4 immune effector cell–associated neurotoxicity syndrome occurred in 35% of patients in the US real-world study. In comparison, in the ZUMA-2 trial, grade 3/4 CRS occurred in 15% of patients, and grade 3/4 neurotoxicity occurred in 31%. These adverse events are now better managed thanks to preemptive treatment with tocilizumab and/or corticosteroids, which were administered more frequently to patients in the real-world data series compared with those in the ZUMA-2 trial. The ORR at day 30 was 88%, with a CR rate of 66% in the US series, results that were similar to those reported in the ZUMA-2 trial, which showed an ORR of 93% and a CR rate of 67%. Early data for the duration of response appear similar to those reported in the ZUMA-2 trial, as well. Finally, as seen in the pivotal trial, a significant proportion of patients (12/20 in the US series) with an initial PR achieved a CR over time.

In the real-world analysis of brexucabtagene autoleucel conducted in Europe, 87% of patients had received bridging therapy.[30] The best ORR was 87%, which included CRs in 64%. The rate of grade 3 or higher CRS was 8.7%, and the rate of grade 3 or higher neurotoxicity was also 8.7%. As in the US series, patients received higher amounts of tocilizumab and corticosteroids. Hypothetically, the lower rates of CRS and neurotoxicity might be related to the higher rates of bridging therapy. The take-home message from these real-world analyses is that CAR T-cell therapy with brexucabtagene autoleucel showed similar activity in real-world data as in the ZUMA-2 trial, in a very heavily pretreated population of patients who, in many cases, would not have qualified for the clinical trial based on eligibility criteria. CAR T-cell therapy is transforming the management of relapsed/refractory MCL, even in patients with high-risk disease, who have achieved robust and durable responses.[28-30]

Future research will focus on how to optimize the timing of CAR T-cell therapy in MCL, based on T-cell fitness (which is improved in patients who have received fewer prior therapies and no bendamustine). There is the potential that CAR T-cell therapy could be administered earlier in high-risk patients after induction. Other types of CAR T-cell therapy

ABSTRACT SUMMARY Rituximab Plus Bendamustine and Cytarabine in Elderly Patients With Newly Diagnosed Mantle Cell Lymphoma: Long-Term Follow-Up and MRD Results of a Phase 2 Study From the Fondazione Italiana Linfomi

Maria Chiara Tisi, MD, presented long-term follow-up from a phase 2 study evaluating rituximab, bendamustine, and low-dose cytarabine as induction therapy in 57 previously untreated patients with MCL not eligible for ASCT (Abstract 384). The patients' median age was 71 years (range, 61-79 years). The regimen led to a CR rate of 91%. The most frequent grade 3/4 toxicities were thrombocytopenia (52%), neutropenia (49%), and leukopenia (44%). In the primary analysis, after a median follow-up of 35 months, the 2-year rates of PFS and OS were 81% and 86%, respectively. After a median follow-up of 7 years (86 months), the median OS and PFS were not reached. At 7 years, the rates of PFS and OS were 56% and 63%, respectively. Eight patients (14%) developed secondary neoplasias. Minimal residual disease positivity was associated with a high risk of relapse.

are also undergoing evaluation in MCL, including dual CAR T-cell therapy (targeting 19/20 and 20/22). Reports on bispecific antibodies at the 2021 ASH annual meeting are clearly showing the expanding potential of this newer form of T cell–engaging therapy. Glofitamab, for example, is a CD20 × CD3 bispecific antibody that showed an impressive ORR at 81%, with a CR rate at 66%, in patients with relapsed/refractory MCL, most of whom had received prior unsuccessful treatment with a BTK inhibitor.[31]

Several years ago, studies of PI3Kδ inhibitors in MCL showed a modest response rate with limited durability, and raised concern regarding toxicities, particularly liver toxicity.[32] The phase 2 CITADEL trial evaluated parsaclisib, a PI3Kδ inhibitor that is 1000 times more selective than previous agents.[33] Such higher selectivity may potentially lead to fewer off-target effects and immune-based interactions, and therefore less toxicity. Study results were presented by Dr Amitkumar Mehta for the subset of patients who had not received previous treatment with a BTK inhibitor, using parsaclisib at a weekly dose (n=31) or a daily dose (n=77) for 8 weeks.[34] The ORR was promising, at 68.5% for all treated patients and 70.1% for the daily dosing group. The CR rates, however, were rather low, at 18% and 16%, respectively, and the median duration of response was 13.7 months and 12.1 months. These results are more promising than those reported for other PI3Kδ inhibitors, and tolerability was also improved. Future studies will explore combination regimens, although in the past, observed toxicity was a limiting factor for other combinations of PI3Kδ inhibitors, particularly those that use other biologic agents.

Covalent BTK inhibitors have transformed the management of chronic lymphocytic leukemia and MCL, but these treatments are not curative, and many patients will eventually relapse with a typically poor outcome. The mechanisms of resistance to BTK inhibition are still poorly understood; mutations of BTK binding site C481S have been described in chronic lymphocytic leukemia but seem less common in MCL. Downstream mutations in genes such as *PLCG2* and other bypass changes are not well identified. Progression after BTK inhibitors in MCL is associated with dismal overall survival, except in patients treated with CAR T-cell therapy. Covalent BTK inhibitors share pharmacologic liabilities (eg, low oral bioavailability, short half-life) that collectively may lead to suboptimal BTK target coverage, for example in rapidly proliferating tumors with high BTK protein turnover, and can ultimately manifest as acquired resistance in some patients.[35] To address these limitations, pirtobrutinib, a highly selective, noncovalent BTK inhibitor of both wild-type and C481-mutated BTK with equal low nM potency was developed. Dr Michael Wang presented data for pirtobrutinib, focusing on patients with relapsed/refractory MCL enrolled in the phase 1/2 BRUIN study.[36] Among patients who had received a previous BTK inhibitor, the ORR rate was 51%, with a CR rate of 25%, whereas in the BTK inhibitor–naive population, the ORR was 82%, with a CR rate of only 18%. For all patients, the median duration of response was impressive, at 18 months. Across studies of BTK inhibitors, the rates of ORR and CR differ,[37] which might reflect differences in patient populations, such as the number of prior therapies. Overall, however, the efficacy among the 3 first-generation agents is rather similar. An ongoing phase 3 trial is comparing pirtobrutinib with the investigator's choice of a covalent BTK inhibitor in patients with relapsed MCL who have not received prior treatment with a BTK inhibitor.[38]

Conclusion and Summary

In summary, the challenges and poor outcomes observed with MCL since the early 1990s led to rewarding clinical research endeavors, which helped establish current standards and translated into improvements in both median PFS (>7-8 years) and median overall survival (>10-12 years). In spite of these advances, patients who have high risk according to the MIPI score, high Ki-67 (≥30%), or the blastoid variant still have a worse outcome, with a median overall survival of approximately 3 years. Furthermore, patients with high-risk molecular features, in particular *TP53* mutations, experience a dismal outcome even after high-dose therapy, with a median overall survival of 1.8 years.

Acceleration in the development of novel therapies led to 6 newly approved drugs in relapsed/refractory MCL in the last 15 years (5 of them in the last 7 years), which translated into improved survival, thanks to their efficacy in patients who are refractory to chemoimmunotherapy and/or carry high-risk features.

Presentations at the 2021 ASH annual meeting provided data for different phases of MCL management that will continue to help refine the field, from frontline treatment to maintenance and/or consolidation, and to the relapsed/refractory setting. Meanwhile, progress in understanding the clinical, biologic, and molecular heterogeneity of MCL has expanded our appreciation of the spectrum of subentities across MCL. Combined with a growing number of additional molecular features that impact outcome—well beyond *TP53* abnormalities—a new paradigm is emerging that turns away from a dichotomy based on dose intensity and age and turns toward less or no chemotherapy at all, in a growing number of MCL patients.

Improved access to routine diagnostics (in particular, next-generation sequencing) has the potential to impactfully guide treatment decisions across the different phases of therapy for each patient with MCL. Finally,

real-world data at scale are needed to refine choices among the increasing number of options available in MCL and to identify the best sequence of care, an emerging critical question across oncology.

Disclosure

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