

A SPECIAL MEETING REVIEW EDITION

**Advances in Aggressive Lymphoma From the 2019
American Society of Clinical Oncology Annual Meeting**

A Review of Selected Presentations From the 2019 ASCO Annual Meeting

• May 31-June 4, 2019 • Chicago, Illinois

Special Reporting on:

- Rituximab Maintenance for Patients With Diffuse Large B-Cell Lymphoma in First Complete Remission: Results From a Randomized HOVON-Nordic Lymphoma Group Phase III Study
- Safety and Preliminary Efficacy in Patients With Relapsed/Refractory Mantle Cell Lymphoma Receiving Lisocabtagene Maraleucel (Liso-Cel) in TRANSCEND NHL 001
- Phase 1/2 Trial of Acalabrutinib Plus Pembrolizumab in Relapsed/Refractory Diffuse Large B-Cell Lymphoma
- Ibrutinib Maintenance Following Induction for Untreated Mantle Cell Lymphoma: Initial Safety Report
- Smart Start: Final Results of Rituximab, Lenalidomide, and Ibrutinib Lead-In Prior to Combination With Chemotherapy for Patients With Newly Diagnosed Diffuse Large B-Cell Lymphoma
- Allogeneic Stem Cell Transplantation for Patients With Lymphoma and Chronic Lymphocytic Leukemia Following Targeted Small-Molecule Inhibitors
- First-Line Therapy of T-Cell Lymphoma: Allogeneic or Autologous Transplantation for Consolidation—Final Results of the AATT Study
- Frontline Therapy for Mantle Cell Lymphoma: To Transplant or Not to Transplant
- Sintilimab for Relapsed/Refractory Extranodal NK/T Cell Lymphoma: A Multicenter, Single-Arm, Phase 2 Trial (ORIENT-4)

PLUS Meeting Abstract Summaries

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A BTKi for adult patients with MCL after at least one prior therapy¹CALQUENCE
GO STRONG

STRONG EFFICACY PROVEN OVER TIME IN PATIENTS WITH R/R MCL

At median follow-up of 15.2 months*[†]

- ♦ 80% ORR (n=99) [95% CI: 72, 87]¹
- ♦ 40% CR (n=49) [95% CI: 31, 49]¹

At median follow-up of 26.3 months[‡]

- ♦ 81% ORR (n=100) [95% CI: 73, 87]²
- ♦ 43% CR (n=53) [95% CI: 34, 52]²
- ♦ Median DoR of 25.7 months^{§||2}
- ♦ Median PFS of 19.5 months²

Trial LY-004, a Phase 2, open-label, single-arm, multicenter trial enrolled 124 patients (≥18 years) with MCL who had received ≥1 prior therapy. Patients received CALQUENCE 100 mg BID until disease progression or unacceptable toxicity. The primary endpoint was ORR; secondary endpoints were DoR, PFS, and OS.^{1,3}

Initial data analysis was based on efficacy and safety endpoints that occurred from March 12, 2015, through approximately 14 months after the last subject was enrolled.² 24-month update analysis was based on the cumulative efficacy and safety endpoints that occurred from March 12, 2015, until data cutoff on February 12, 2018 (24-month update).²

*Independent Review Committee-assessed per 2014 Lugano Classification response criteria for non-Hodgkin's lymphoma (NHL).¹

[†]Investigator-assessed response rates were ORR: 81%; CR: 40%; PR: 41%.¹

[‡]Investigator-assessed per 2014 Lugano Classification response criteria for NHL.²

[§]Median follow-up for DoR was 26.3 months (range: 0.3 to 35.1 months).²

^{||}Duration of response was measured in the 100 subjects who achieved a CR or PR.²

DEMONSTRATED SAFETY PROFILE FROM INITIAL DATA ANALYSIS

- ♦ Warnings and precautions include hemorrhage, infections, cytopenias, second primary malignancies, and atrial fibrillation/flutter¹
- ♦ The most common adverse drug reactions (≥20%) were anemia, thrombocytopenia, headache, neutropenia, diarrhea, fatigue, myalgia, and bruising¹

SAFETY PROFILE FROM 24-MONTH UPDATE ANALYSIS CONSISTENT WITH INITIAL DATA ANALYSIS

- ♦ Most common treatment-emergent adverse events ≥20%: headache (37.9%), diarrhea (36.3%), fatigue (28.2%), myalgia (21.0%), and cough (21.8%)²

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.

SELECT SAFETY INFORMATION

Hemorrhage

Serious hemorrhagic events, including fatal events, have occurred in the combined safety database of 612 patients with hematologic malignancies treated with CALQUENCE monotherapy. Grade 3 or higher bleeding events, including gastrointestinal, intracranial, and epistaxis, have been reported in 2% of patients. Overall, bleeding events, including bruising and petechiae of any grade, occurred in approximately 50% of patients with hematological malignancies. The mechanism for the bleeding events is not well understood.

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

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

Infection

Serious infections (bacterial, viral, or fungal), including fatal events and opportunistic infections, have occurred in the combined safety database of 612 patients with hematologic malignancies treated with CALQUENCE monotherapy. Grade 3 or higher infections occurred in 18% of these patients. The most frequently reported Grade 3 or 4 infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation and progressive multifocal leukoencephalopathy (PML) have occurred.

Monitor patients for signs and symptoms of infection and treat as medically appropriate. Consider prophylaxis in patients who are at increased risk for opportunistic infections.

Cytopenias

In the combined safety database of 612 patients with hematologic malignancies, patients treated with CALQUENCE monotherapy experienced Grade 3 or 4 cytopenias, including neutropenia (23%), anemia (11%), and thrombocytopenia (8%), based on laboratory measurements. Monitor complete blood counts monthly during treatment.

Second Primary Malignancies

Second primary malignancies, including non-skin carcinomas, have occurred in 11% of patients with hematologic malignancies treated with CALQUENCE monotherapy in the combined safety database of 612 patients. The most frequent second primary malignancy was skin cancer, reported in 7% of patients. Advise protection from sun exposure.

Atrial Fibrillation and Flutter

In the combined safety database of 612 patients with hematologic malignancies treated with CALQUENCE monotherapy, atrial fibrillation and atrial flutter of any grade occurred in 3% of patients, and Grade 3 in 1% of patients. Monitor for atrial fibrillation and atrial flutter and manage as appropriate.

ADVERSE REACTIONS

The most common adverse reactions (≥20%) of any grade were anemia,* thrombocytopenia,* headache (39%), neutropenia,* diarrhea (31%), fatigue (28%), myalgia (21%), and bruising (21%).

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

The most common Grade ≥ 3 non-hematological adverse reaction (reported in at least 2% of patients) was diarrhea (3.2%).

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.

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.

CR=complete response; DoR=duration of response; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; R/R=relapsed/refractory. **References:** 1. CALQUENCE [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2017. 2. Data on File, REF-43179. AstraZeneca Pharmaceuticals LP. 3. Wang M, Rule S, Zinzani PL, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY004): a single-arm, multicentre, phase 2 trial. *Lancet*. 2018;391(10121):659-667.

Please see Brief Summary of complete Prescribing Information on adjacent pages.



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CALQUENCE[®]
(acalabrutinib) 100 mg capsules

VISIT CALQUENCE.COM/PHYSICIAN

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

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)* 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

The recommended dose of CALQUENCE is 100 mg taken orally approximately every twelve 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.

Dose Modifications

Adverse Reactions

Recommended dose modifications of CALQUENCE for Grade 3 or greater adverse reactions are provided in Table 1.

Table 1: Recommended Dose Modifications for Adverse Reactions

Event	Adverse Reaction Occurrence	Dose Modification (Starting dose = 100 mg twice daily)
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 therapy may be resumed at 100 mg twice daily.
	Third	Interrupt CALQUENCE. Once toxicity has resolved to Grade 1 or baseline level, CALQUENCE therapy may be resumed at 100 mg daily.
	Fourth	Discontinue CALQUENCE.

Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

Dose Modifications for Use with CYP3A Inhibitors or Inducers

Recommended dose modifications are described below [see *Drug Interactions (7)* in the full Prescribing Information].

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 twice daily.

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].

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Hemorrhage

Serious hemorrhagic events, including fatal events, have occurred in the combined safety database of 612 patients with hematologic malignancies treated with CALQUENCE monotherapy. Grade 3 or higher bleeding events, including gastrointestinal, intracranial, and epistaxis have been reported in 2% of patients. Overall, bleeding events including bruising and petechiae of any grade occurred in approximately 50% of patients with hematologic malignancies.

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

Infection

Serious infections (bacterial, viral or fungal), including fatal events and opportunistic infections have occurred in the combined safety database of 612 patients with hematologic malignancies treated with CALQUENCE monotherapy. Consider prophylaxis in patients who are at increased risk for opportunistic infections.

Grade 3 or higher infections occurred in 18% of these patients. The most frequently reported Grade 3 or 4 infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation and progressive multifocal leukoencephalopathy (PML) have occurred. Monitor patients for signs and symptoms of infection and treat as medically appropriate.

Cytopenias

In the combined safety database of 612 patients with hematologic malignancies, patients treated with CALQUENCE monotherapy experienced Grade 3 or 4 cytopenias, including neutropenia (23%), anemia (11%) and thrombocytopenia (8%) based on laboratory measurements. In the CALQUENCE clinical Trial LY-004, patients' complete blood counts were assessed monthly during treatment.

Second Primary Malignancies

Second primary malignancies, including non-skin carcinomas, have occurred in 11% of patients with hematologic malignancies treated with CALQUENCE monotherapy in the combined safety database of 612 patients. The most frequent second primary malignancy was skin cancer, reported in 7% of patients. Advise protection from sun exposure.

Atrial Fibrillation and Flutter

In the combined safety database of 612 patients with hematologic malignancies treated with CALQUENCE monotherapy, atrial fibrillation and atrial flutter of any grade occurred in 3% of patients, and Grade 3 in 1% of patients. Monitor for atrial fibrillation and atrial flutter and manage as appropriate.

ADVERSE REACTIONS

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

- Hemorrhage [see *Warnings and Precautions (5.1)* in the full Prescribing Information]
- Infection [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 safety data described in this section reflect exposure to CALQUENCE (100 mg twice daily) in 124 patients with previously treated MCL in Trial LY-004 [see *Clinical Studies (14)* 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 ($\geq 20\%$) 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 or discontinuation due to any adverse reaction were reported in 1.6% and 6.5% of patients, respectively.

Tables 2 and 3 present the frequency category of adverse reactions observed in patients with MCL treated with CALQUENCE.

Table 2: Non-Hematologic Adverse Reactions* in $\geq 5\%$ (All Grades) of Patients with MCL in Trial LY-004

Body System Adverse Reactions	CALQUENCE 100 mg twice daily 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 & subcutaneous tissue disorders		
Bruising†	21	-
Rash†	18	0.8
Vascular disorders		
Hemorrhage/Hematoma†	8	0.8
Respiratory, thoracic & mediastinal disorders		
Epistaxis	6	-

* Per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

† Bruising: Includes all preferred terms (PTs) containing 'bruise,' 'contusion,' 'petechiae,' or 'ecchymosis'

Rash: Includes all PTs containing 'rash'

Hemorrhage/hematoma: Includes all PTs containing 'hemorrhage' or 'hematoma'

Table 3: Hematologic Adverse Reactions Reported* in ≥ 20% of Patients with MCL in Trial LY-004

Hematologic Adverse Reactions	CALQUENCE 100 mg twice daily N=124	
	All Grades (%)	Grade ≥ 3 (%)
Hemoglobin decreased	46	10
Platelets decreased	44	12
Neutrophils decreased	36	15

* Per National Cancer Institute Common Terminology Criteria for Adverse Events (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	<ul style="list-style-type: none">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	<ul style="list-style-type: none">Avoid co-administration of strong CYP3A inhibitors with CALQUENCE.Alternatively, if the inhibitor will be used short-term, interrupt CALQUENCE [see Dosage and Administration (2.2) in the full Prescribing Information].	
Moderate CYP3A Inhibitors		
Clinical Impact	<ul style="list-style-type: none">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	<ul style="list-style-type: none">When CALQUENCE is co-administered with moderate CYP3A inhibitors, reduce acalabrutinib dose to 100 mg once daily.	
Strong CYP3A Inducers		
Clinical Impact	<ul style="list-style-type: none">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	<ul style="list-style-type: none">Avoid co-administration of strong CYP3A inducers with CALQUENCE.If a strong CYP3A inducer cannot be avoided, increase the acalabrutinib dose to 200 mg twice daily.	
Gastric Acid Reducing Agents		
Clinical Impact	<ul style="list-style-type: none">Co-administration of CALQUENCE with a proton pump inhibitor, H2-receptor antagonist, or antacid may decrease acalabrutinib plasma concentrations [see 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 Dosage and Administration (2.2) in the full Prescribing Information].
	H2-receptor antagonists	Take CALQUENCE 2 hours before taking the H2-receptor antagonist [see Dosage and Administration (2.2) 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 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 pregnant rabbits during organogenesis resulted in reduced fetal growth at maternal exposures (AUC) approximately 4 times exposures in patients at the recommended dose of 100 mg twice daily (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 16-times the AUC in patients at the recommended dose of 100 mg twice daily. 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 4-times the AUC in patients at 100 mg twice daily.

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.

Pediatric Use

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

Geriatric Use

Eighty (64.5%) of the 124 MCL patients in clinical trials of CALQUENCE were 65 years of age or older, and 32 patients (25.8%) were 75 years of age or older. No clinically relevant differences in safety or efficacy were observed between patients ≥ 65 years and younger.

PATIENT COUNSELING INFORMATION

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

Hemorrhage

Inform patients to report signs or symptoms of severe bleeding. Inform patients that CALQUENCE may need to be interrupted for major surgeries [see *Warnings and Precautions* (5.1) in the full Prescribing Information].

Infections

Inform patients to report signs or symptoms suggestive of infection [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. 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, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort [see *Warnings and Precautions* (5.5) 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].

Lactation

Advise women 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].

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Rituximab Maintenance for Patients With Diffuse Large B-Cell Lymphoma in First Complete Remission: Results From a Randomized HOVON-Nordic Lymphoma Group Phase III Study

The Haemato Oncology Foundation for Adults in the Netherlands (HOVON) and the Nordic Lymphoma Group conducted a phase 3 study that evaluated the addition of 4 extra doses of rituximab to the standard regimen of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in patients with diffuse large B-cell lymphoma (DLBCL).^{1,2} Patients with stage 2, 3, or 4 DLBCL were randomly assigned to receive standard R-CHOP, administered in 14-day cycles, with or without an extra dose of rituximab (375 mg/m²) administered on day 8 of the first 4 cycles. After a maximum

of 8 treatment cycles, patients with a complete response (CR) were randomly assigned to receive rituximab maintenance or undergo observation. Maintenance rituximab was administered every 8 weeks for a total of 12 doses. Responses were assessed by positron emission tomography/computed tomography imaging and were evaluated by central review according to the Lugano 2014 criteria.³ A Deauville score of at least 3 was considered a CR.⁴

For the maintenance portion of the trial, the statistical design assumed 395 patients and 126 events for an 80% power to detect a hazard ratio (HR) of

0.60 for disease-free survival between the 2 arms. The second randomization included patients who had been in a CR for at least 4 weeks after the last cycle of chemoimmunotherapy. Inclusion criteria also required that 4 to 8 weeks had elapsed since the patient's last cycle of R-CHOP (including the last rituximab dose). Patients who experienced an adverse event (AE) that led to discontinuation of rituximab were excluded. The primary endpoint was efficacy.

The trial enrolled 575 patients with DLBCL. Their median age was 65 years (range, 18-80 years). Most patients scored high-intermediate or

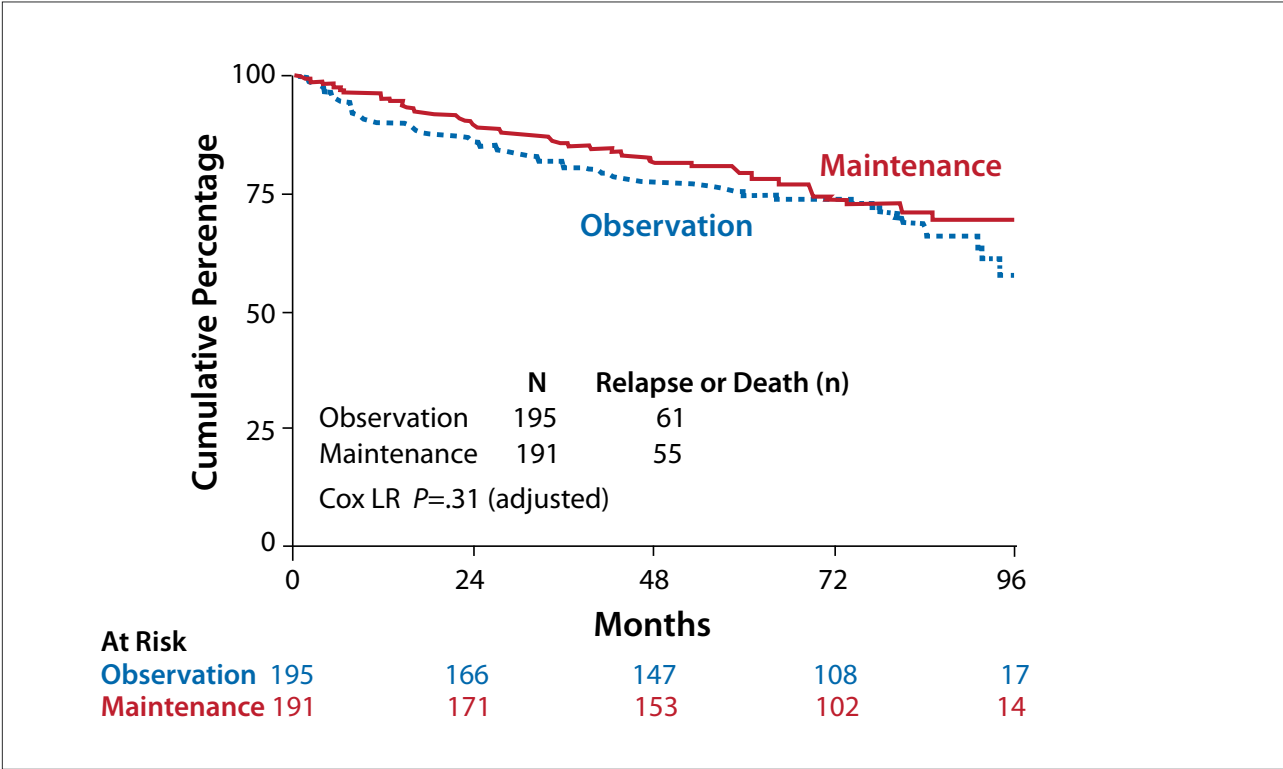


Figure 1. Disease-free survival in the HOVON-Nordic Lymphoma Group phase 3 study of rituximab maintenance in patients with DLBCL. DLBCL, diffuse large B-cell lymphoma; HOVON, Haemato Oncology Foundation for Adults in the Netherlands; LR, likelihood ratio. Adapted from Lugtenburg PJ et al. ASCO abstract 7507. *J Clin Oncol*. 2019;37(suppl).²

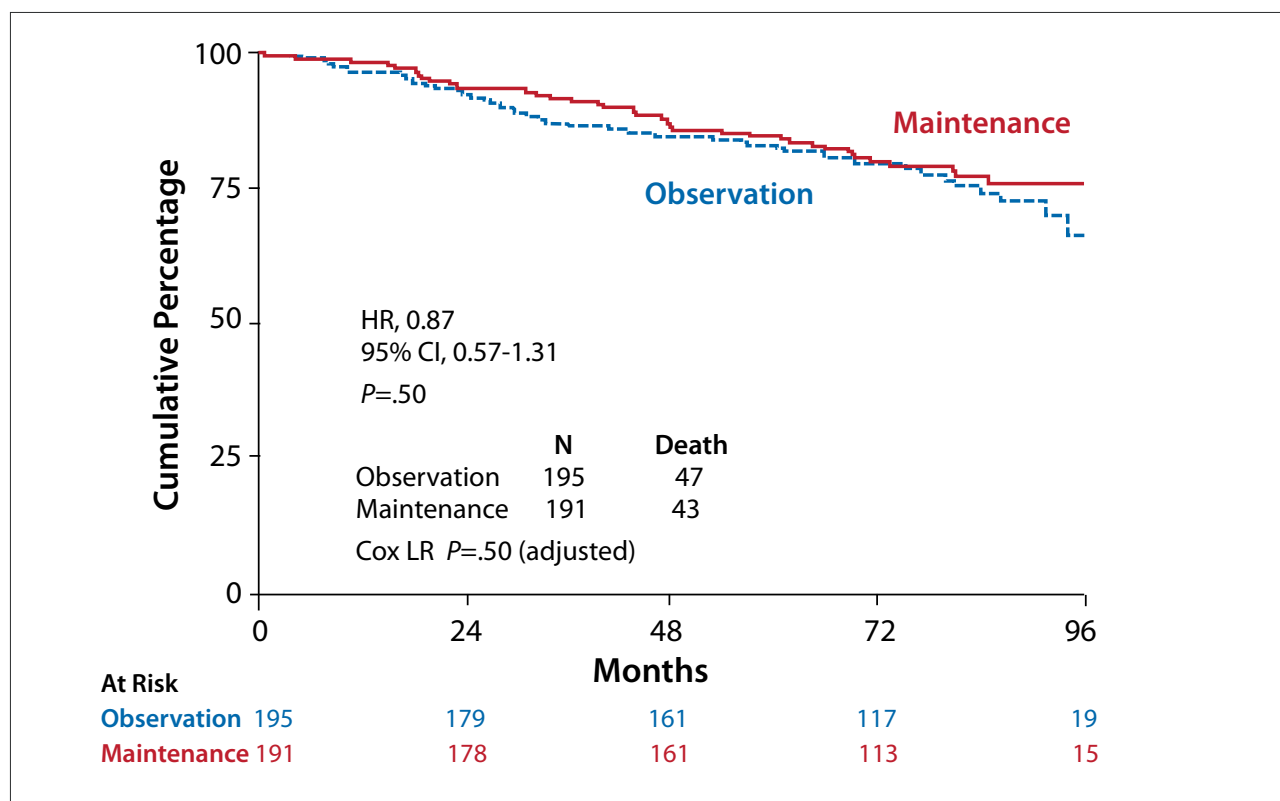


Figure 2. Overall survival in the HOVON-Nordic Lymphoma Group phase 3 study of rituximab maintenance in patients with DLBCL. DLBCL, diffuse large B-cell lymphoma; HOVON, Haemato Oncology Foundation for Adults in the Netherlands; LR, likelihood ratio. Adapted from Lugtenburg PJ et al. ASCO abstract 7507. *J Clin Oncol.* 2019;37(suppl).²

high on the age-adjusted International Prognostic Index (IPI).

In the first portion of the trial, the treatment arms yielded similar rates of CR ($P=.40$) and 3-year progression-free survival (PFS; $P=.17$).¹ No significant differences in PFS emerged in subgroup analyses based on age, sex, or age-adjusted IPI score.

In the second portion of the trial, 191 patients were randomly assigned to rituximab maintenance and 195 to observation.² More than three-fourths of patients in each arm had Ann Arbor stage 3/4 disease, and one-fourth had bulky disease of at least 10 cm. In each arm, 12% of patients had bone marrow involvement, and more than half had a high-intermediate or high age-adjusted IPI score. More than 6 cycles of induction R-CHOP treatment were administered to 57% of patients in the rituximab maintenance

arm and 61% in the observation arm.

After a median follow-up of 79.9 months, the median disease-free survival was not reached in either arm. Five-year disease-free survival was 79% in the rituximab maintenance arm vs 74% in the observation arm (HR, 0.83; 95% CI, 0.57%-1.19%; $P=.31$; Figure 1). Both treatment arms also had similar times to relapse ($P=.42$) and death ($P=.66$). Subgroup analysis of disease-free survival yielded similar outcomes for rituximab maintenance vs observation. The median overall survival (OS) was also similar for both arms (HR, 0.87; 95% CI, 0.57-1.31; $P=.50$; Figure 2).

In the maintenance arm, 81% of patients received all 12 doses of rituximab after completing induction therapy. The median duration of exposure to maintenance rituximab was 22.5 months (range, 0.8-28.1 months). The

most common reasons for discontinuation of rituximab maintenance were disease progression (8%) and toxicity (8%). A grade 3/4 AE occurred in 23% of patients. At least 1 serious AE was reported in 19% of patients, and 8% had a serious AE that was considered probably or possibly related to study treatment. Grade 4 AEs of interest included neutropenia (3%), neurologic AEs (1%), and AEs affecting the lungs and/or upper respiratory tract (1%). The most common grade 3 AEs were infection (6%), cardiac disorders (4%), gastrointestinal AEs (2%), and neurologic AEs (2%). No patient died from an AE.

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Safety and Preliminary Efficacy in Patients With Relapsed/Refractory Mantle Cell Lymphoma Receiving Lisocabtagene Maraleucel (Liso-Cel) in TRANSCEND NHL 001

Lisocabtagene maraleucel is a chimeric antigen receptor (CAR) T-cell therapy directed against the CD19 antigen.¹ This product is administered as a defined composition of CD4-positive and CD8-positive T cells. The open-label, multicenter phase 1 TRANSCEND NHL 001 trial (Study Evaluating the Safety and Pharmacokinetics of JCAR017 in B-Cell Non-Hodgkin Lymphoma) evaluated lisocabtagene maraleucel in patients with mantle cell lymphoma that was refractory or had relapsed after at least 1 line of therapy.² Patients had confirmed expression of cyclin D1 or evidence of t(11;14) translocation. Their Eastern Cooperative Oncology Group (ECOG) performance status was

0, 1, or 2. The eligibility criteria included patients who had undergone prior stem cell transplant (SCT) or who had secondary involvement of the central nervous system. After leukapheresis, lymphodepletion was achieved with fludarabine (30 mg/m²) and cyclophosphamide (300 mg/m²) given for 3 days. Within 2 to 7 days after lymphodepletion, patients received the infusion of lisocabtagene maraleucel. The CAR T-cell product was given at 2 dose levels: 50 × 10⁶ CAR T cells or 100 × 10⁶ CAR T cells. The primary endpoints included AEs and dose-limiting toxicities. Efficacy was evaluated according to the 2014 Lugano criteria.³

Seventeen patients received treatment with lisocabtagene maraleucel

and were included in the safety and efficacy analyses. The patients' median age was 66 years (range, 53-80 years), and they had received a median of 4 prior therapies (range, 1-8). Ten patients (59%) received bridging chemotherapy. The median follow-up was 8.4 months (range, 0.4 to 18.2+ months).

Twelve patients (71%) achieved a response, including 9 patients (53%) with a CR. The median time to a CR was 1 month (range, 0.9-6.3 months). The median PFS was 5.8 months (range, 0.4 to 18.2+ months), and the median OS was 11.1 months (range, 0.4 to 18.2+ months). At the time of their most recent visit, 7 patients (41%) had an ongoing CR, including 2 patients treated with the lower dose and 5 treated with the higher dose. The median duration of response was not reached; however, the duration of CR in 7 patients ranged from 90 days to 545 days. Five patients did not respond to study treatment, including 1 patient with secondary central nervous system involvement. Two patients had central nervous system involvement at relapse.

Cytopenias were the most common grade 3/4 treatment-emergent AEs. Grade 4 cytokine release syndrome was reported in 1 patient (6%), and grade 3/4 neurologic events were observed in 2 patients (12%). All 3 of these patients had received the higher dose of lisocabtagene maraleucel (Table 1). One dose-limiting toxicity of grade 5 tumor lysis syndrome occurred in a patient who declined intubation. This

ABSTRACT SUMMARY Update of the Single-Arm Phase II L-MIND Study of MOR208 + Lenalidomide in Relapsed/Refractory Diffuse Large B-Cell Lymphoma: Response Rates in Patient Subgroups With Poor Prognosis

The single-arm, multicenter phase 2 MIND study (A Study to Evaluate the Safety and Efficacy of Lenalidomide With MOR00208 in Patients With R-R DLBCL) evaluated lenalidomide plus tafasitamab (MOR208) in patients with relapsed or refractory DLBCL (Abstract 7521). After a median follow-up of 12 months, the ORR was 54%, with a CR rate of 32%, as assessed by an independent review committee. The median time to response was 1.8 months, and the median time to CR was 3.4 months. The median duration of response was not reached. The ORR was 46% in patients who had received 2 or more prior lines of therapy, 53% in patients with GCB-DLBCL, 64% in patients with primary refractory disease, and 59% in patients who were refractory to rituximab. The combination was generally well tolerated, with no unexpected toxicities based on the safety profiles of the individual drugs.

Table 1. Adverse Events of Specific Interest to Lisocabtagene Maraleucel

	Dose Level 1 (n=6)	Dose Level 2 (n=11)	All Patients (N=17)
Any-grade CRS, n	1	6	7 (41%)
Grade 3 or 4 CRS, n	0	1	1 (6%)
Median time to CRS onset, days (range)	6 (6-6)	7 (2-10)	7 (2-10)
Median time to CRS resolution, days (range)	2 (2-2)	5 (2-8)	4 (2-8)
Any-grade NEs, n	0	3	3 (18%)
Grade 3 or 4 NEs, n	0	2	2 (12%)
Median time to NE onset, days (range)	NA	9 (7-25)	9 (7-25)
Median time to NE resolution, days (range)	NA	3 (1-3)	3 (1-3)
Tocilizumab use, n	0	3	3 (18%)
Corticosteroid use, n	0	3	3 (18%)

CRS, cytokine release syndrome; NA, not applicable; NE, neurologic event.

Adapted from Wang M et al. ASCO abstract 7516. *J Clin Oncol*. 2019;37(18 suppl).²

patient had a high tumor burden and pleural effusions, as well as bone marrow and gastric involvement, and had received the higher dose of lisocabtagene maraleucel.

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Phase 1/2 Trial of Acalabrutinib Plus Pembrolizumab in Relapsed/Refractory Diffuse Large B-Cell Lymphoma

The combination of acalabrutinib plus pembrolizumab was evaluated among patients with B-cell malignancies enrolled in the phase 1/2 ACE-LY-005 trial (ACP-196 [Acalabrutinib] in Combination With Pembrolizumab, for Treatment of Hematologic Malignancies).¹ The study enrolled patients with DLBCL who had received at least 1 prior chemotherapeutic regimen. Patients had a confirmed diagnosis of de novo DLBCL with measurable disease and an ECOG performance status of 0 or 1. Study treatment consisted of acalabrutinib at 100 mg twice daily plus pembrolizumab at 2 mg/kg every 3 weeks. Tumor assessments were based on Lugano 2014 criteria.² The primary endpoint was safety.

The study enrolled and treated 61 patients with DLBCL, including 30 with the germinal center B-cell (GCB) subtype and 31 with the non-GCB subtype. The patients had a median age of 67 years (range, 30-85 years). Most patients (84%) had Ann Arbor stage 3/4 disease at enrollment, 39% had bulky lymph nodes, and 36%

had extranodal disease. Patients had received a median of 3 prior therapies (range, 1-8), including CAR T-cell therapy in 5% and SCT in 14%. The median follow-up was 5.2 months (range, 0.4-38.5 months).

The overall response rate (ORR) was 23% among the intention-to-treat

population. The ORR was 29% in patients with non-GCB DLBCL vs 17% in patients with GCB DLBCL (Figure 3). The median duration of response was 8.0 months for the 61 patients. In 2 patients, the duration of response lasted beyond 24 months. The median PFS was 2.1 months (95%

ABSTRACT SUMMARY A Phase I Study of the Selective PI3Kδ Inhibitor YY-20394 in Patients With Relapsed or Refractory B-Cell Malignancies

YY-20394 is a selective inhibitor of phosphoinositide 3-kinase delta that was evaluated in a phase 1 trial of 25 heavily pretreated patients with B-cell malignancies (Abstract 7563). Using a 3 + 3 design, patients received up to 200 mg daily in 28-day cycles. The disease subtypes included follicular lymphoma in 40%, CLL/small lymphocytic lymphoma in 16%, and mantle cell lymphoma in 16%. Prior treatment with 3 or more systemic regimens was reported in 64%. Responses were observed in patients with all represented malignancies. ORR was 89% in those with follicular lymphoma, 75% in those with CLL/small lymphocytic lymphoma, and 25% in those with mantle cell lymphoma. Grade 3/4 hematologic AEs included neutropenia (20%), leukopenia (8%), and lymphocytosis (8%). Grade 3/4 nonhematologic AEs included pneumonia (20%) and hyperuricemia (8%). At the time of the analysis, 10 patients were continuing treatment. The median duration of response had not been reached. In 4 patients, the response duration was longer than 1 year.

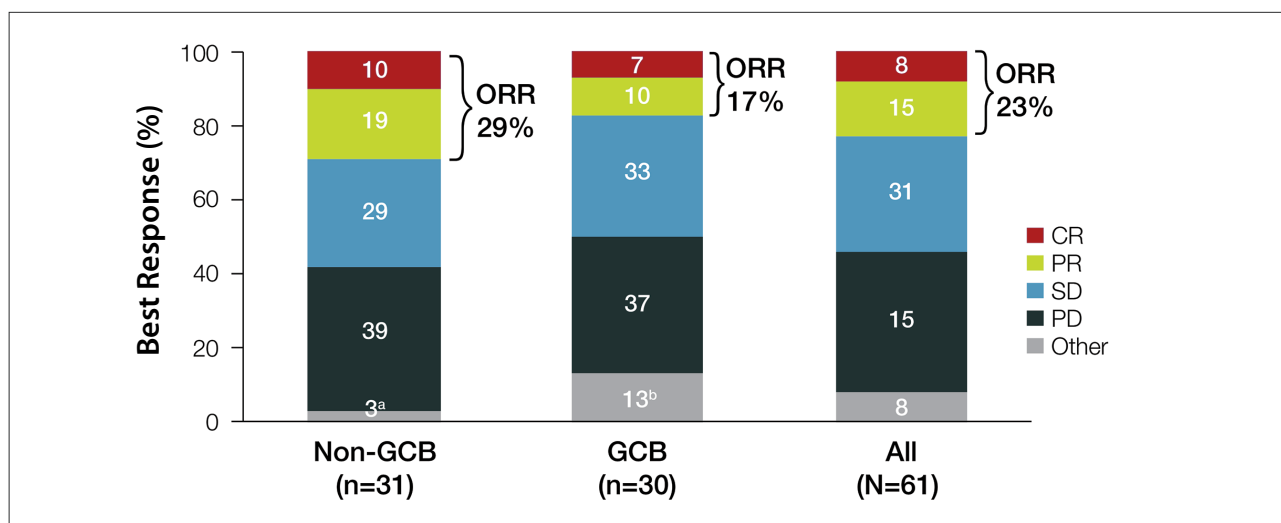


Figure 3. Best response among patients with relapsed/refractory DLBCL treated with acalabrutinib plus pembrolizumab in the phase 1/2 ACE-LY-005 trial. ACE-LY-005, ACP-196 (Acalabrutinib) in Combination With Pembrolizumab, for Treatment of Hematologic Malignancies; CR, complete response; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease. ^aAmong patients with the non-GCB subtype, 1 did not reach the first assessment owing to death (from abdominal abscess). ^bAmong patients with the GCB subtype, 4 did not reach the first assessment owing to death (from progressive disease and clinical progressive disease [n=1 each]) and withdrawal of consent owing to AEs (thrombocytopenia, altered mental status). Adapted from Witzig TE et al. ASCO abstract 7519. *J Clin Oncol.* 2019;37(suppl).¹

ABSTRACT SUMMARY Outcomes of Lenalidomide in Diffuse Large B-Cell and High-Grade NHL: A Single-Center Retrospective Analysis

A retrospective study evaluated outcomes in patients with DLBCL or high-grade B-cell lymphoma who received treatment with lenalidomide, with or without rituximab, at a single institution between 2011 and 2018 (Abstract 7547). The cell of origin was determined by the Hans algorithm. The study included 23 patients with non-GCB DLBCL, 18 with de novo GCB-type DLBCL, and 16 with transformed follicular lymphoma. The median age was 73 years (range, 52-102 years). All patients had received previous treatment; 29% had received 3 or more prior therapies. The ORR was 39% among non-GCB and de novo GCB DLBCL patients vs 62.5% in patients with transformed follicular lymphoma. The median PFS was 5 months in the non-GCB group, 4 months in the GCB group, and 24 months in the transformed follicular lymphoma group. OS was 8.8 months, 7.8 months, and 46.7 months, respectively. Among patients with a *MYC* translocation, 3 had a CR, 3 had a PR, and 1 had stable disease. In 3 patients with high-grade B-cell lymphoma, there was 1 CR and 2 PRs.

CI, 1.6-3.7), and the median OS was 8.7 months (95% CI, 4.8-12.9). The median duration of response was 8.0 months in patients with the non-GCB subtype vs 9.0 months in those with the GCB subtype. The median PFS was 2.5 months vs 1.9 months, respectively, and the median OS was 7.8 months vs 11.7 months.

Among the 93% of patients who discontinued acalabrutinib, 70% did so after disease progression. Pembrolizumab was discontinued by 98%, including 62% after disease progression. Discontinuation of both study drugs was reported in 93% of patients.

The most common AEs of any grade included diarrhea (41%), fatigue

(33%), decreased appetite (30%), and nausea (30%). The most common grade 3/4 AEs included neutropenia (15%), anemia (11%), and hypokalemia (8%). The most common serious AEs included sepsis (7%) and pleural effusions (5%). Six patients died from AEs. AEs led to discontinuation of the study drug in 17 patients (28%), most commonly owing to elevated transaminase levels (10%) or pneumonitis (3%). Three patients developed 7 cases of grade 3/4 transaminase elevation, indicating a risk for the combination of acalabrutinib plus pembrolizumab. Rates of atrial fibrillation and hypertension were consistent with those observed in studies of acalabrutinib monotherapy.

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Ibrutinib Maintenance Following Induction for Untreated Mantle Cell Lymphoma: Initial Safety Report

The multicenter phase 2 trial known as Ibrutinib After Intensive Induction in Treating Patients With Previously Untreated Mantle Cell Lymphoma evaluated the efficacy and safety of ibrutinib maintenance therapy after first-line induction treatment in patients with mantle cell lymphoma.¹ Patients with a CR or partial response (PR) after first-line intensive chemoimmunotherapy were enrolled. First-line treatment was chosen by the investigator but had to include at least 4 cycles of 1 of the following regimens: R-CHOP (with or without cytarabine); rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyperCVAD); or rituximab plus bendamustine. Autologous SCT consolidation prior to maintenance treatment was allowed.

Maintenance therapy consisted of ibrutinib at 560 mg given every day of each 28-day cycle for a maximum of 4 years. The primary endpoint was to evaluate the efficacy of ibrutinib maintenance (based on 3-year PFS) among patients with mantle cell lymphoma who achieved a CR or PR after intensive induction therapy. This report provided data from the initial safety analysis.¹

The study enrolled 36 treatment-naïve patients with mantle cell lymphoma. Their median age was 60 years (range, 46-90 years). The disease was stage 3/4 in 78% of patients, 50% had a low mantle cell lymphoma IPI score, and 25% had extranodal disease at their initial diagnosis.² Among 20 patients who were evaluated for Ki67 expression, 8 (40%) had a Ki67 expression value of 30% or higher. The most common induction regimens were rituximab plus bendamustine (47%) and rituximab plus hyperCVAD (25%). Prior to enrollment, half of the patients had undergone consolidation by autologous SCT, and 92%

Table 2. Treatment Exposure and Summary of Adverse Events (n=36) in a Study of Ibrutinib Maintenance

Median cycles of treatment (range)	15 (1-49)
Duration on drug at time of data analysis (cycles, n [%]) ^a	
1-12	8 (22)
13-24	19 (53)
25-36	7 (19)
37-49	2 (6)
Adverse events resulting in dose modifications, n (%)	25 (69)
Permanent reduction ^b	7 (19)
Permanent discontinuation ^c	9 (25)
Drug-related adverse events, total events in 36 patients	
Any grade	361
Grade ≥3, n (%)	63 (17)

^aAt the time of the study report, 24 patients remained on maintenance therapy, with 2 patients on their last cycle.

^b3 for neutropenia, 2 for fatigue, 1 for diarrhea, and 1 for muscle cramps.

^c5 for atrial fibrillation/flutter, 1 for rash, 1 for pericardial effusion, 1 for mucositis, and 1 for intracerebral hemorrhage/bleed.

Adapted from Karmali R et al. ASCO abstract 7542. *J Clin Oncol*. 2019;37(18 suppl).¹

ABSTRACT SUMMARY Safety and Efficacy of PD-L1 Inhibitor Durvalumab With R-CHOP or R²-CHOP in Subjects With Previously Untreated, High-Risk DLBCL

An open-label phase 2 study evaluated the programmed death ligand 1 inhibitor durvalumab, with or without lenalidomide, in combination with R-CHOP in patients with treatment-naïve, high-risk DLBCL (Abstract 7520). Forty-three patients were treated with durvalumab plus R-CHOP, and 3 patients also received lenalidomide. After completion of 6 or 8 cycles of R-CHOP, with or without lenalidomide, administration of durvalumab monotherapy continued for a total of 12 months. Twenty-five patients (68%) who received durvalumab plus R-CHOP and 2 patients (67%) who also received lenalidomide continued to consolidation therapy with single-agent durvalumab and were progression-free at month 12. Responses were observed in all 19 patients with double- or triple-hit disease (n=17 in the durvalumab plus R-CHOP arm and n=2 in the lenalidomide-containing arm). No new safety signals were observed. Grade 3/4 treatment-related, treatment-emergent AEs occurred in 31 of 43 patients (72%) in the durvalumab plus R-CHOP arm and in all 3 patients (100%) in the lenalidomide-containing arm.

had achieved a CR. After a median follow-up of 19 months, patients had received a median of 15 cycles of treat-

ment (range, 1-49 cycles), and 25% of patients had received between 25 and 49 cycles of treatment.

One patient developed disease progression, and 1 death occurred. AEs that resulted in dose modification occurred in 69% of patients, including 19% who had a permanent dose reduction and 25% who discontinued treatment permanently (Table 2). A total of 361 drug-related AEs of any grade were observed, including 63 that

were grade 3/4. The most common treatment-related AEs of any grade were lymphopenia (7%), leukopenia (6%), diarrhea (6%), and thrombocytopenia (6%).

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Smart Start: Final Results of Rituximab, Lenalidomide, and Ibrutinib Lead-In Prior to Combination With Chemotherapy for Patients With Newly Diagnosed Diffuse Large B-Cell Lymphoma

The single-center, single-arm phase 2 Smart Start trial (A Phase II Study of Rituximab, Lenalidomide, and Ibrutinib) evaluated 2 cycles of rituximab, lenalidomide, and ibrutinib followed by 6 cycles of this regimen plus chemotherapy in patients with newly diagnosed non-GCB DLBCL.¹ The treatment was administered in 21-day cycles and consisted of rituximab at 375 mg/m² on day 1, lenalidomide at 25 mg on days 1 to 10, and ibrutinib at 560 mg daily. For cycles 3 to 8, the regimen was combined with either CHOP or etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH), also in 21-day cycles. EPOCH chemotherapy was selected by the treating physician based on disease characteristics, such as a high Ki67 value, the presence of bulky masses, or IPI. All patients received mandatory treatment with granulocyte colony-stimulating factor and prophylaxis for prevention of *Varicella zoster* and *Pneumocystis jirovecii* infection. In July 2018, the protocol was amended to reduce the dose of ibrutinib to 420 mg for patients ages 65 years or older, and 9 patients were treated with the reduced dose.

The primary objectives were to determine the ORR at the end of the first 2 cycles of rituximab, lenalido-

mid, and ibrutinib, and to determine the CR rate after completion of all 8 treatment cycles. The study enrolled treatment-naïve patients with non-GCB DLBCL based on the Hans immunohistochemistry algorithm.²

Among the 60 enrolled patients, 58 completed 2 cycles of rituximab, lenalidomide, and ibrutinib, and 49 completed all 8 treatment cycles and were evaluable. The 60 patients had a median age of 63.5 years (range, 29-83 years), and 28% were older than 70 years. The IPI score was 3, 4, or 5 in 83%. The Ki67 value was greater than 80% in 77% of patients, and exceeded 90% in 49% of patients. Two-thirds of patients had stage 3/4 disease. Among 35 patients tested, 19 (54%) had expression of both MYC and BCL2 according to immunohistochemistry, and 1 of 37 patients (2.7%) had MYC and BCL6 translocation according to fluorescence in situ hybridization, indicating aggressive disease.

In addition to treatment with rituximab, lenalidomide, and ibrutinib, 43% of patients received CHOP and 55% received EPOCH. One patient received rituximab, lenalidomide, and ibrutinib only. The dose intensities were 95.4% for ibrutinib and 90.1% for lenalidomide. Seven patients received 5 cycles of chemo-

therapy, and 4 patients received 4 cycles.

After 2 cycles of rituximab, lenalidomide, and ibrutinib alone, the ORR was 86%, including a CR rate of 36%. After 2 cycles of this regimen alone followed by 2 cycles of this regimen plus chemotherapy, the ORR was 100%, including a CR rate of 73%. At the end of all 8 treatment cycles, the ORR in 49 patients was 100%, with a CR rate of 96%. Most patients showed a dramatic reduction in disease burden after the first 2 cycles of rituximab, lenalidomide, and ibrutinib, with continuing reductions in disease burden during subsequent treatment cycles. In the subgroup of 29 patients with a PR after 2 cycles of rituximab, lenalidomide, and ibrutinib alone, the median reduction in disease burden was 81%. The median OS was not reached (range, 74-938 days), and 1-year OS was 96%. In the subgroup of patients with double-expressor disease, 1-year PFS was 94%.

The most common AEs of any grade consisted of nausea, peripheral sensory neuropathy, and diarrhea. The most common grade 3 AEs were anemia, febrile neutropenia, and thrombocytopenia, and the most common grade 4 AEs were neutropenia and thrombocytopenia. One patient died

from febrile neutropenia. Another patient developed a fatal fungal infection—specifically, central nervous system aspergillosis—that was attributed to the combination of a high-dose corticosteroid plus rituximab, lenalidomide, and ibrutinib. This patient had prominent splenic and pancreatic

disease at screening and was receiving dexamethasone (4 mg twice daily) to control symptoms. As a result, the use of corticosteroids was subsequently prohibited during the first 2 cycles of rituximab, lenalidomide, and ibrutinib. No further fungal infections were observed.

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Allogeneic Stem Cell Transplantation for Patients With Lymphoma and Chronic Lymphocytic Leukemia Following Targeted Small-Molecule Inhibitors

With the availability of small-molecule inhibitors that target key cancer signaling pathways, outcomes have improved in patients with chronic lymphocytic leukemia (CLL) and other types of lymphoma.¹⁻³ A single-center, retrospective study evaluated safety and efficacy in patients with CLL or lymphoma who received treatment with a small-molecule inhibitor followed by allogeneic SCT.⁴ The study included 49 patients with CLL, mantle cell lymphoma, or follicular lymphoma who underwent allogeneic SCT between 2013 and 2018. At any time prior to SCT, these patients had developed progressive disease during treatment that included venetoclax, idelalisib, or ibrutinib or had received bridging chemotherapy with any of these drugs. Patients had a median age of 51 years (range, 24-69 years). Histologic subtypes included CLL (63%), mantle cell lymphoma (27%), and follicular lymphoma (10%). Prior treatment included ibrutinib in 94%, venetoclax in 39%, and idelalisib in 12%. Patients had received a median of 4 prior lines of therapy (range, 1-11). The median duration of small-molecule inhibitor therapy was 4.6 months (range, 1-61 months). Most patients had high-risk features.

Stem cell engraftment was suc-

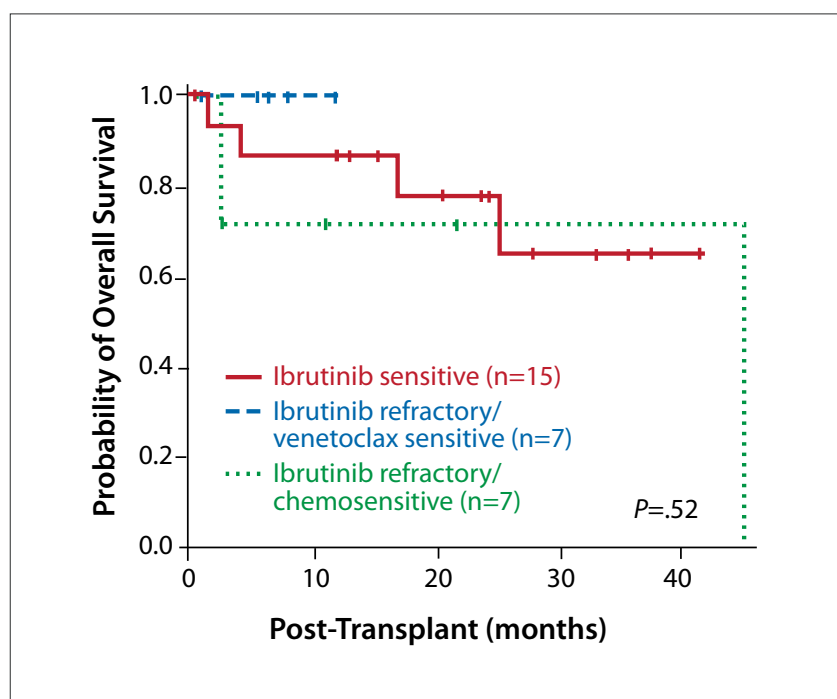


Figure 4. Overall survival based on sensitivity to ibrutinib or venetoclax in a retrospective study of patients with CLL or lymphoma who received treatment with a small-molecule inhibitor followed by allogeneic stem cell transplant. CLL, chronic lymphocytic leukemia. Adapted from Mukherjee A et al. ASCO abstract 7550. *J Clin Oncol*. 2019;37(suppl).⁴

cessful in all patients, with no evidence of engraftment delay or failure. After a median follow-up of 12.4 months for survivors, the 1-year rate of PFS was 68% and the 1-year rate of OS was 77% (Figure 4). The median OS was similar among the subgroups

of patients with CLL, mantle cell lymphoma, or follicular lymphoma ($P=.79$). Similar OS probabilities were observed in patient subgroups based on remission status or sensitivity to ibrutinib and/or venetoclax. Based on multivariate analysis, factors that

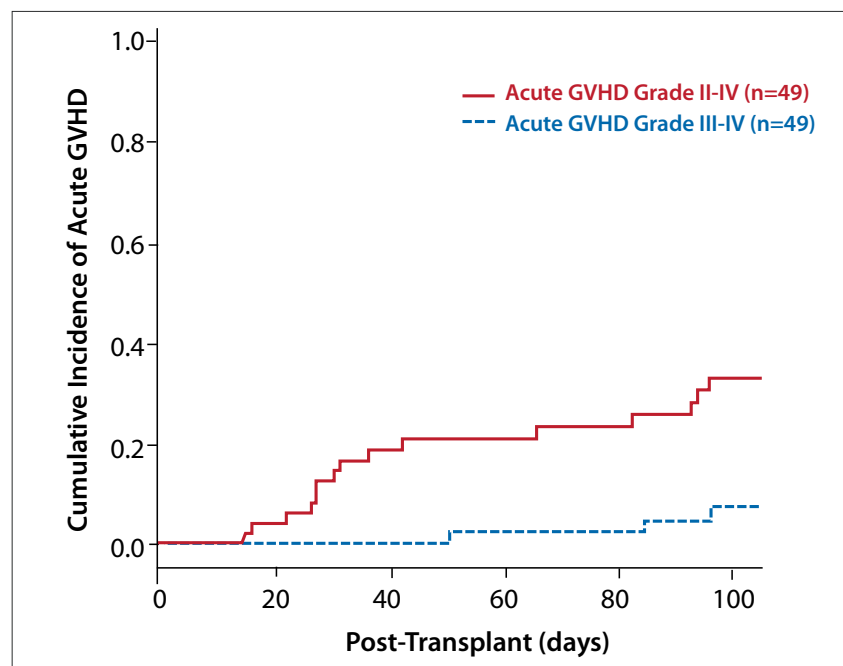


Figure 5. The incidence of acute GVHD in a retrospective study of patients with CLL or lymphoma who received treatment with a small-molecule inhibitor followed by allogeneic stem cell transplant. CLL, chronic lymphocytic leukemia; GVHD, graft-vs-host disease. Adapted from Mukherjee A et al. ASCO abstract 7550. *J Clin Oncol*. 2019;37(suppl).⁴

affected survival included refractory disease and acute grade 3/4 graft-vs-host disease. The presence or absence of high-risk mutations did not affect survival. The 14 deaths in the study were attributed to disease progression (9 patients), acute or chronic graft-vs-host disease (3 patients), and infection (2 patients). The incidence of acute graft-vs-host disease is shown in Figure 5.

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First-Line Therapy of T-Cell Lymphoma: Allogeneic or Autologous Transplantation for Consolidation—Final Results of the AATT Study

The AATT trial (Autologous or Allogeneic Transplantation in T-Cell Lymphoma) compared autologous vs allogeneic SCT in newly diagnosed patients with T-cell lymphoma.¹ Eligible patients were ages 18 to 60 years and had an ECOG performance status of 0 to 3. Most enrolled patients had a diagnosis of peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), or anaplastic lymphoma kinase-negative angioimmunoblastic T-cell lymphoma. The study excluded patients with stage 1 disease and those with an age-adjusted IPI of 0.

Patients were randomly assigned to treatment after study enrollment.¹ The patients initially received 4 cycles of CHOP plus etoposide in 2-week

cycles. Patients then received dexamethasone, cytarabine, and cisplatin (DHAP) as a stem cell mobilization regimen. For patients who had been randomly assigned to the autologous SCT arm, peripheral blood stem cells were harvested; patients then received carmustine, etoposide, cytarabine, and melphalan followed by autologous SCT. Patients in the allogeneic SCT arm received myeloablative treatment with fludarabine, busulfan, and cyclophosphamide prior to SCT. For cases in which no donor was available, patients could switch to the autologous SCT arm.

The AATT study was based on the hypothesis that allogeneic SCT would improve 3-year event-free survival from 35% to 60%, with an α of 5%

and a power of 80%. The statistical power was predicated on an enrollment of 140 patients. In 2015, a planned interim analysis of 58 patients revealed a low probability of detecting a 25% difference in event-free survival.¹ As a result, the data safety monitoring committee stopped the study after 104 patients had been accrued. The final analysis included 54 patients in the autologous SCT arm and 49 in the allogeneic SCT arm.²

Patient characteristics were well balanced between the 2 arms. Patients had a median age of 50 years (range, 24-60 years). A high level of lactate dehydrogenase was seen in 61%. ECOG performance status was 2 or 3 in 20%, and 42% had an age-adjusted IPI of 0 or 1. Disease stage

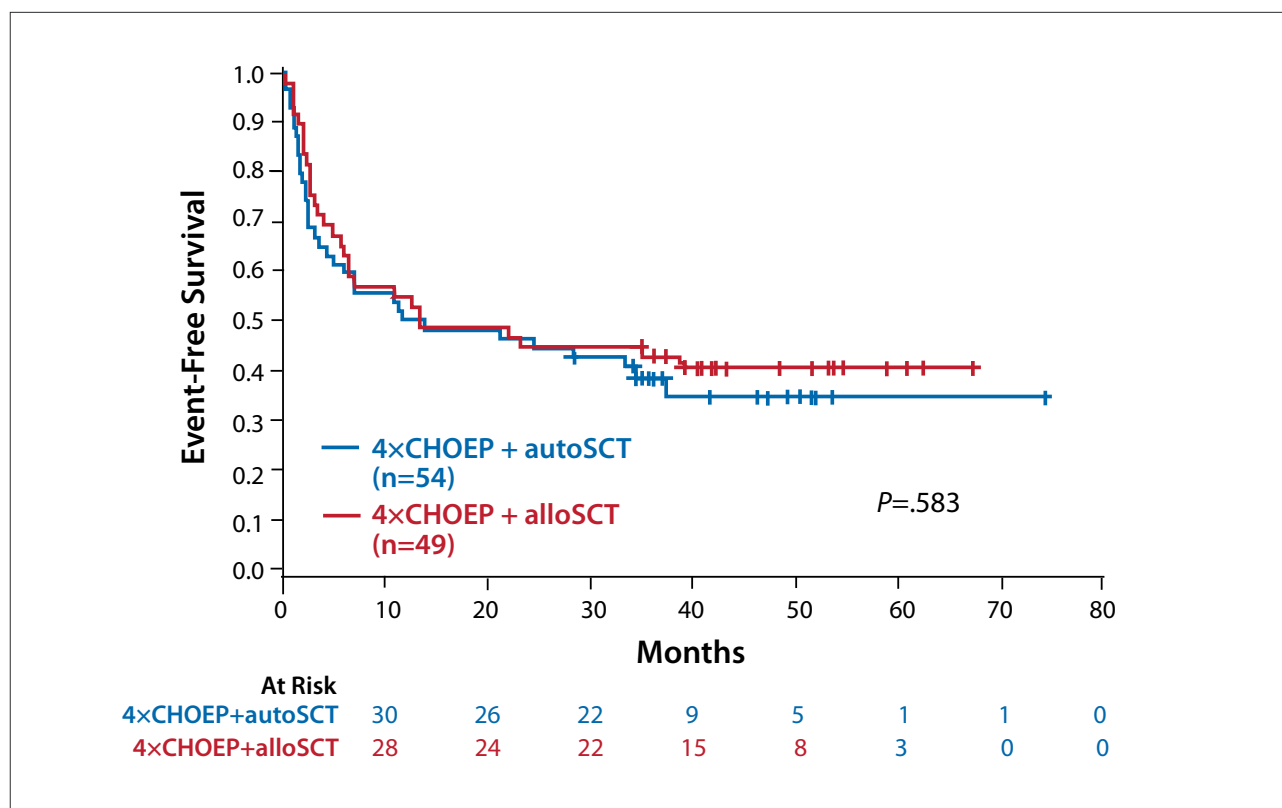


Figure 6. Rates of 3-year event-free survival in the AATT trial, which compared autologous SCT vs allogeneic SCT in newly diagnosed patients with T-cell lymphoma. AATT, Autologous or Allogeneic Transplantation in T-Cell Lymphoma; alloSCT, allogeneic stem cell transplant; autoSCT, autologous stem cell transplant; CHOEP, cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone; SCT, stem cell transplant. Adapted from Shmitz N et al. ASCO abstract 7503. *J Clin Oncol.* 2019;37(suppl).²

was 3/4 in 88% of patients, and disease involvement in 2 or more nodes was observed in 61%. The T-cell lymphoma subtypes included angioimmunoblastic T-cell lymphoma (38%), PTCL-NOS (29%), and anaplastic lymphoma kinase–negative anaplastic large cell lymphoma (14%). Seven patients (14%) originally randomly assigned to allogeneic SCT instead underwent autologous SCT. Twenty patients (37%) in the autologous SCT arm and 16 patients (33%) in the allogeneic SCT arm discontinued from the study prior to SCT, mainly owing to refractory disease or early relapse.

In the intention-to-treat population of 103 patients, rates of event-free survival at 3 years were 38% (95% CI, 25%-52%) in the autologous SCT arm vs 43% (95% CI, 29%-57%) in the allogeneic SCT arm ($P=.583$;

Figure 6). Forty-one patients underwent autologous SCT, and 26 underwent allogeneic SCT. The rates of 3-year event-free survival were also similar among these patients, at 61% vs 65%, respectively ($P=.430$). In the intention-to-treat population, rates of OS at 3 years were 70% in the autologous SCT arm vs 57% in the allogeneic SCT arm ($P=.408$). OS was superior among patients with an age-adjusted IPI of 0 or 1 vs 2 or 3 ($P=.012$). A CR/unconfirmed CR was seen in 39% of the autologous SCT arm vs 51% of the allogeneic SCT arm. The PR rate was 17% vs 8%.

Among the intention-to-treat population, the study treatment led to death in 0 patients in the autologous SCT arm vs 8 patients in the allogeneic SCT arm. Treatment-related mortality from salvage therapy occurred in

4 vs 2 patients, respectively. Among patients who underwent SCT, lymphoma was the cause of death in 7 patients in the autologous arm vs 1 patient in the allogeneic arm. One patient, in the autologous SCT arm, died from secondary neoplasia after the procedure. Transplant-related mortality caused by the study treatment was reported in 0 patients in the autologous SCT arm vs 8 patients in the allogeneic SCT arm.

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Frontline Therapy for Mantle Cell Lymphoma: To Transplant or Not to Transplant

During an Interactive Case-Based Session, Drs Nilanjan Ghosh, Tycel Jovelle Phillips, and Timothy Fenske discussed the role of transplant in the frontline management of patients with mantle cell lymphoma.¹ Dr Ghosh began with some background on the disease.¹ Mantle cell lymphoma is a heterogeneous disease with a variety of underlying genetic aberrancies, and patients can present in different ways.² Indolent disease can have few or no symptoms, and aggressive disease can be associated with obvious symptoms. Disease characteristics and patient characteristics (eg, age, comorbidities) must be considered when choosing a first-line regimen.³ There is currently no single agreed-upon first-line treatment approach for mantle cell lymphoma. Despite the existence of risk assessment tools, such as the mantle cell lymphoma IPI score and proliferation index, the results of these tests do not determine treatment.

Intensive Induction Regimens

Patients with mantle cell lymphoma most often present with aggressive, advanced-stage disease. Intensive induction regimens followed by autologous SCT is appropriate for many patients, such as younger patients and those without significant comorbidities. The Nordic MCL2 and MCL3 trials evaluated a regimen consisting of an induction phase of alternating rituximab plus maxi-CHOP and rituximab plus high-dose cytarabine; followed by high-dose chemotherapy consisting of carmustine, etoposide, cytarabine, and melphalan (BEAM) or carmustine, etoposide, cytarabine, and cyclophosphamide (BEAC); and autologous SCT.^{4,5} The Nordic MCL2 trial enrolled 160 patients, ages 65 years or younger, with previously untreated mantle cell lymphoma. The ORR was 96%, and the CR rate was 54%. Patients who demonstrated a response

after induction therapy could proceed to autologous SCT. After a median follow-up of 11.4 years, the median OS was 12.7 years, and the median PFS was 8.5 years in the intention-to-treat population. Patients with a CR after induction treatment had a superior OS ($P=.0038$) and PFS ($P<.0001$) compared with patients whose best response was a PR. However, the rate of nonrelapse mortality was 7.5%. In addition, 6 patients developed relapsed disease more than 10 years after the end of treatment, and the risk of treatment-related myeloid neoplasms was 3.1%. A follow-up analysis of data from the Nordic MCL2 and MCL3 trials showed improved OS among patients without the *TP53* deletion (Figure 7).⁵

An open-label, parallel-group phase 3 study by the European MCL Network evaluated 6 courses of R-CHOP or 6 courses of alternating R-CHOP and rituximab plus DHAP (R-DHAP) followed by autologous SCT among patients ages 65 years or younger with newly diagnosed, stage 2 to 4 mantle cell lymphoma.⁶ Prior to autologous SCT, patients in the R-CHOP arm received myeloablative radiochemotherapy, whereas those in the R-CHOP/R-DHAP arm received a conditioning regimen that contained high-dose cytarabine. After a median follow-up of 6.1 years, the median time to treatment failure was 9.1 years in the R-CHOP/R-DHAP group vs 3.9 years in the control group ($P=.038$). Median OS for patients in the alternating therapy arm was 9.8 years. The rate of nonrelapse mortality was 3.4%, and the rate of myelodysplastic syndrome/acute myeloid leukemia was 2.4%.

A retrospective study from the Center for International Blood and Marrow Transplant Research compared outcomes in 519 patients with mantle cell lymphoma who had received autologous or allogeneic SCT.⁷ Patients who underwent autologous SCT had

received any induction regimen prior to transplant. For the cohort of patients who received autologous SCT, 5-year OS was 61%, 5-year PFS was 52%, and the rate of nonrelapse mortality was 3%. Patients who underwent allogeneic SCT had a lower rate of disease progression and relapse, whereas the rate of nonrelapse mortality was higher.

A phase 2 study evaluated a regimen of intense chemoimmunotherapy without subsequent SCT among 97 treatment-naïve patients with mantle cell lymphoma.⁸ Patients received rituximab in combination with hyper-CVAD, alternating with rituximab in combination with high-dose methotrexate and cytarabine. The ORR was 97%, including a CR rate of 87%. After a median follow-up of 8 years, the median OS was not reached. The median PFS was 4.6 years, and the rate of 10-year OS was 64%. The rate of nonrelapse mortality was 8%, and 5% of patients were diagnosed with myelodysplastic syndrome/acute myeloid leukemia.

In a phase 3 study of patients with mantle cell lymphoma, PFS was better with rituximab maintenance vs observation in patients who had received R-DHAP intensive treatment followed by autologous SCT.⁹ Patients were younger than 66 years at diagnosis. If a patient did not experience a reduction of at least 75% in lymph node size after induction with R-DHAP, he or she could then receive treatment with 4 cycles of R-CHOP. The trial randomly assigned 240 patients to receive rituximab maintenance therapy vs observation. After 4 cycles of R-DHAP, the ORR was 89%, with a CR rate of 77%. After a median follow-up of 50.2 months, the rate of event-free survival at 4 years was 79% in the rituximab maintenance arm vs 61% in the observation arm ($P=.001$). Four-year PFS was 83% with rituximab maintenance vs 64% with observation ($P<.001$).

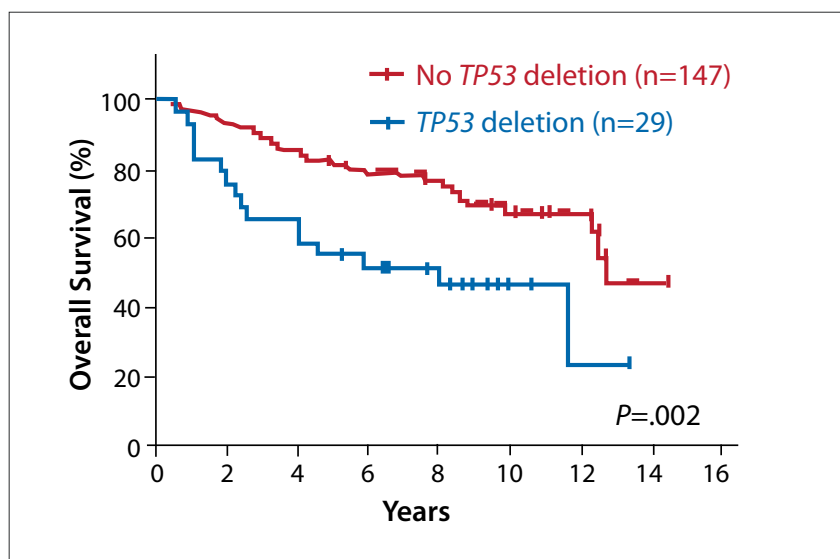


Figure 7. Overall survival according to *TP53* deletion status among patients with previously untreated mantle cell lymphoma who received dose-intensive therapy in an analysis of data from the Nordic MCL2 and MCL3 trials. Adapted from Eskelund CW et al. *Blood*. 2017;130(17):1903-1910.⁵

Based on unadjusted Cox regression analysis, 4-year OS was superior in patients who received rituximab maintenance (HR, 0.50; 95% CI, 0.26-0.99; $P=.04$).

Nonintensive Induction Regimens

Dr Phillips discussed nonintensive induction regimens.¹ Two studies of mantle cell lymphoma patients who were not eligible for high-dose induction therapy demonstrated a benefit with rituximab maintenance. A German study enrolled patients with stage 2 to 4 mantle cell lymphoma who were older than 60 years.^{10,11} Patients were randomly assigned to receive either 6 cycles of rituximab, fludarabine, and cyclophosphamide every 28 days; or 8 cycles of R-CHOP, every 21 days. Patients who responded to therapy were randomly assigned a second time to receive maintenance treatment with either rituximab or interferon- α . Among the patients who responded to R-CHOP and were randomly assigned to maintenance therapy, rituximab yielded a superior 5-year PFS (51% vs

22%; $P<.0001$) and 5-year OS (79% vs 59%; $P=.0026$) compared with interferon- α . Rituximab maintenance was associated with a low rate of treatment-emergent AEs.

Another German study evaluated rituximab plus bendamustine in a similar patient population.¹² Patients who responded to induction treatment with up to 6 cycles of rituximab plus bendamustine were randomly assigned to receive subsequent treatment with rituximab maintenance vs observation. Among 120 evaluable patients, rituximab plus bendamustine induction yielded an ORR of 85%, with a CR rate of 27%. However, after a median observation duration of 4.5 years, the median PFS did not significantly differ between rituximab maintenance vs observation (72 vs 55 months; HR, 0.71; 95% CI, 0.41-1.23; $P=.2267$). The median OS was also similar for both groups (HR, 1.51; 95% CI, 0.7-3.25; $P=.2974$). Dr Phillips noted that in the future, a risk-adapted approach to inform treatment may improve outcomes for patients with mantle cell lymphoma.

A recent retrospective study evaluated the impact of autologous SCT consolidation on survival among 1029 patients with newly diagnosed mantle cell lymphoma. Patients were ages 65 years or younger. The median PFS was 62 months, and the median OS was 139 months. The study found that autologous SCT consolidation after induction was associated with significantly improved PFS but not OS after propensity score-weighted analysis (Figure 8).¹³

The Role of Minimal Residual Disease

Dr Fenske discussed how to select patients for autologous SCT, with a focus on the role of minimal residual disease (MRD).¹ Achievement of negative MRD in the bone marrow or peripheral blood is associated with a superior PFS and OS in patients with mantle cell lymphoma.^{14,15} The phase 3 ECOG 4151 study (Rituximab With or Without Stem Cell Transplant in Treating Patients With Minimal Residual Disease-Negative Mantle Cell Lymphoma in First Complete Remission) is currently recruiting patients with mantle cell lymphoma to evaluate outcomes when different consolidation treatments are selected based on MRD status after induction.¹⁶ Patients are not required to be enrolled at the time they are diagnosed with mantle cell lymphoma, and they may receive treatment with any induction regimen. After completing induction therapy, patients will be restaged by imaging, bone marrow biopsy, and MRD analysis of the peripheral blood. Patients who achieve a CR with negative MRD will be randomly assigned to undergo autologous SCT followed by 3 years of rituximab or 3 years of rituximab with deferral of autologous SCT. All other patients with a response will undergo autologous SCT followed by 3 years of rituximab maintenance. The primary objective is to compare 6-year OS. Because mantle cell lymphoma comprises such a wide range of biologic

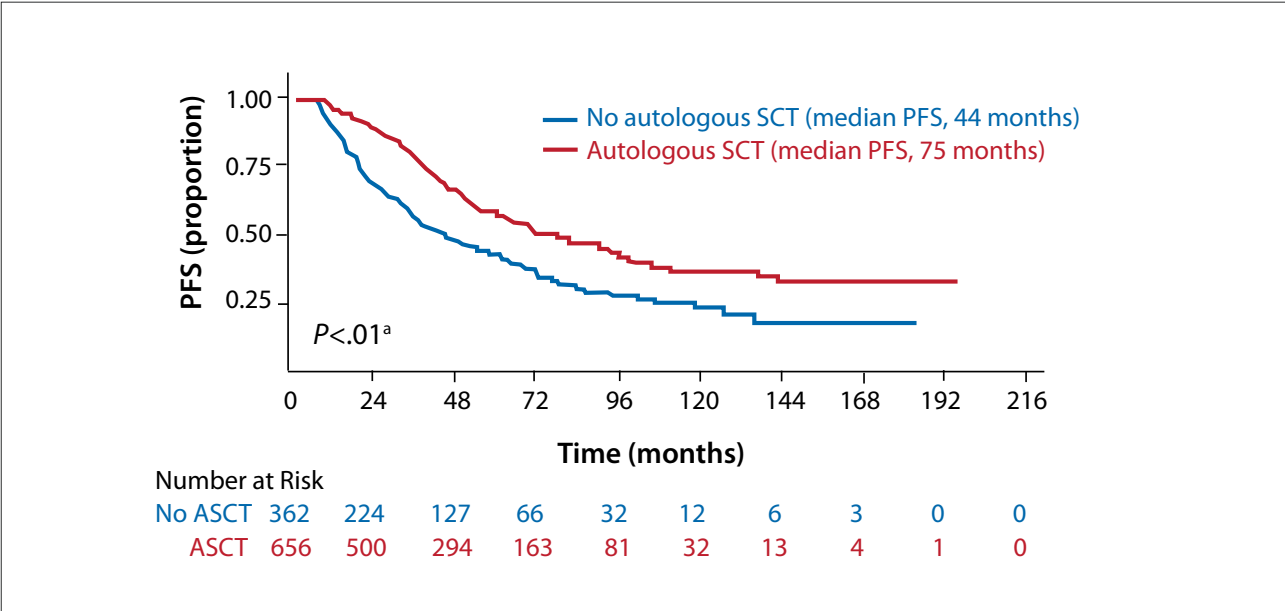


Figure 8. Progression-free survival in a retrospective study of patients with newly diagnosed mantle cell lymphoma who received treatment with autologous SCT consolidation after induction. ASCT, autologous stem cell transplant; PFS, progression-free survival; SCT, stem cell transplant. ^aLog-rank test. Adapted from Gerson JN et al. *J Clin Oncol.* 2019;37(6):471-480.¹³

and clinical behaviors, this population is particularly suited for evaluation of a risk-adapted treatment approach.

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Sintilimab for Relapsed/Refractory Extranodal NK/T Cell Lymphoma: A Multicenter, Single-Arm, Phase 2 Trial (ORIENT-4)

Sintilimab (IBI308) is a fully human antibody that binds to programmed cell death receptor 1 (PD-1) with high affinity, thus preventing interaction with its ligands and restoring the ability of T cells to recognize and attack tumor cells. The antibody is approved in China for the treatment of relapsed or refractory classical Hodgkin lymphoma in patients who have received at least 2 lines of systemic chemotherapy.¹ Approval was based on results from the single-arm, phase 2 ORIENT-1 study of 96 patients. All patients were treated with sintilimab (200 mg, once every 3 weeks). After a median follow-up of 10.5 months, the ORR was 80.4% (95% CI, 70.9%-88.0%). Eighteen percent of patients had grade 3/4 treatment-related AEs, most commonly pyrexia (3%), and 15% had serious AEs.

Extranodal natural killer/T-cell lymphoma is a type of non-Hodgkin lymphoma that accounts for more than 20% of cases of PTCL in Asia.^{2,3} Chemotherapy that includes L-asparaginase has improved outcomes, but relapse remains common. In a retrospective study of 179 patients with relapsed or progressive extranodal natural killer/T-cell lymphoma who were diagnosed between 1997 and 2015, the median second PFS was 4.1 months (95% CI, 3.04-5.16), and the median OS was 6.4 months (95% CI, 4.36-8.51). In a recent study of 7 patients with extranodal natural killer/T-cell lymphoma, PD-1 blockade with pembrolizumab induced responses in all patients, including 2 patients who achieved a CR in all tested parameters.⁴

The multicenter, single-arm, phase 2 ORIENT-4 trial (Efficacy and Safety Evaluation of IBI308 in Patients With Relapsed/Refractory Extranodal NK/T Cell Lymphoma, Nasal Type: A Multicenter, Single Arm, Phase 2 Study)

evaluated the safety and efficacy of sintilimab in patients with relapsed or refractory extranodal natural killer/T-cell lymphoma.⁵ Eligible patients had pathologically confirmed, measurable disease; had already received an asparaginase-based regimen; and had an ECOG performance status of 0 to 2. Sintilimab at 200 mg was administered every 3 weeks until disease progression, unacceptable toxicity, death, or study withdrawal. Continuing treatment was allowed in patients whose disease progressed during the study. The primary endpoint was the investigator-assessed ORR, based on Lugano criteria.⁶ Patient quality of life was assessed with the EQ-5D-5L questionnaire, the EQ-5D-5L visual analogue scale, and the QLQ-C30 questionnaire.

The study enrolled 28 patients, with a mean age of 39.8 years (range, 19-65 years). The median time from the initial diagnosis was 22.0 months.

Patients had received a median of 3 prior lines of chemotherapy, and 53.6% had received at least 3 prior treatments. Following asparaginase-based treatment, 42.9% of patients had refractory disease, and 57.1% had relapsed disease. B symptoms were present in 85.7% of patients, and bone marrow involvement was noted in 21.4% of patients. Elevated levels of lactate dehydrogenase were observed in 64.3% of patients, and 67.9% of patients had Ann Arbor stage IV disease. Epstein-Barr virus was detected in the plasma of 28.6% of patients. The median duration of treatment was 14 months (range, 1.4-17.3 months).

A response was seen in 19 patients (67.9%), including 4 patients who initially had disease progression. An additional 17.9% of patients had stable disease. The median time to response was 1.3 months (range,

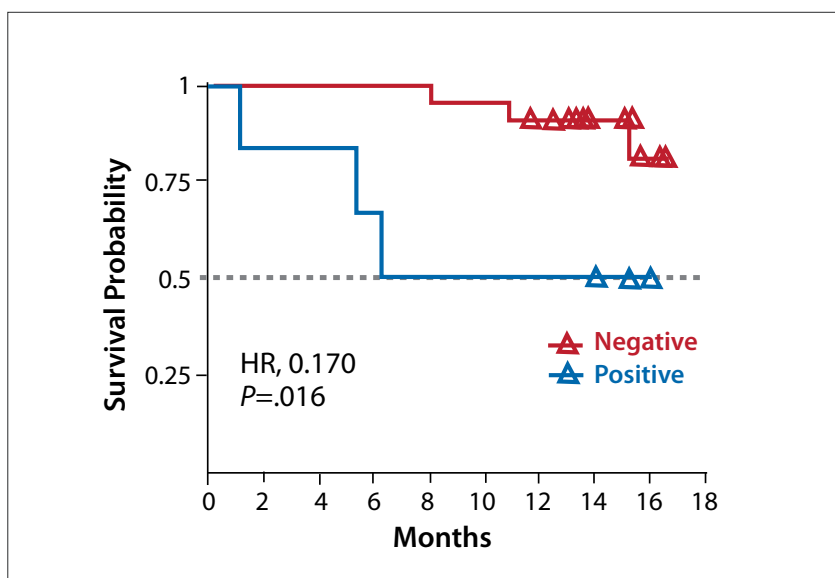


Figure 9. Overall survival according to bone marrow involvement among patients treated with sintilimab in the phase 2 ORIENT-4 trial. ORIENT-4, Efficacy and Safety Evaluation of IBI308 in Patients With Relapsed/Refractory Extranodal NK/T Cell Lymphoma, Nasal Type: A Multicenter, Single Arm, Phase 2 Study. Adapted from Tao R et al. ASCO abstract 7504. *J Clin Oncol.* 2019;37(suppl 15).⁵

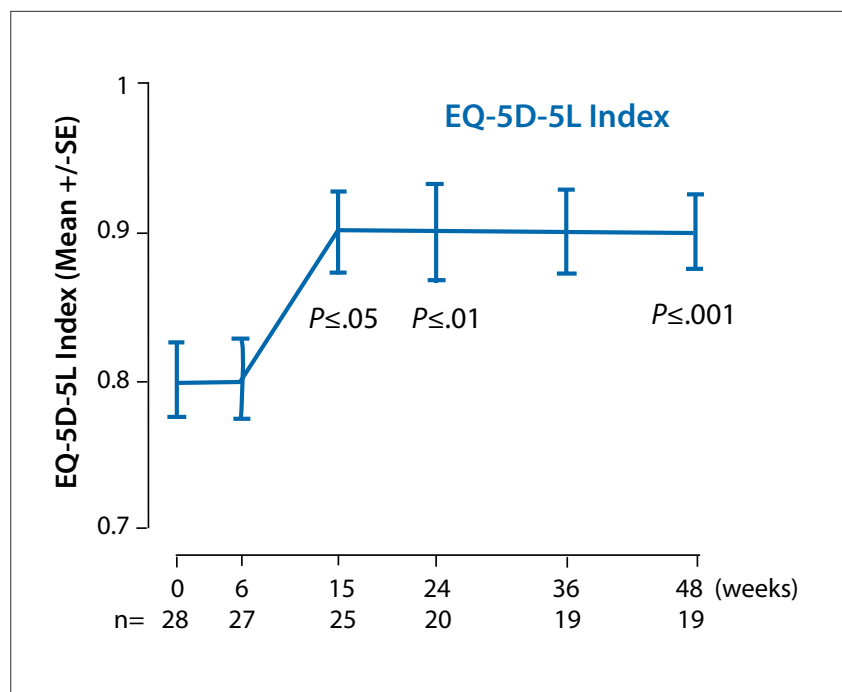


Figure 10. Quality of life as assessed by the EQ-5D-5L Index among patients treated with sintilimab in the phase 2 ORIENT-4 trial. Quality of life was measured at baseline and at each subsequent evaluation of tumor response. EQ-5D-5L, European Quality of Life 5-Dimensions; ORIENT-4, Efficacy and Safety Evaluation of IBI308 in Patients With Relapsed/Refractory Extranodal NK/T Cell Lymphoma, Nasal Type: A Multicenter, Single Arm, Phase 2 Study; SE, standard error. Adapted from Tao R et al. ASCO abstract 7504. *J Clin Oncol*. 2019;37(suppl 15).⁵

1.2-5.5 months) and the median duration of response was 4.1 months (range, 0+ to 4.+ months). After a median follow-up of 15.4 months (range, 11.8 to 17.1 months), the median OS was not reached; 6 patients had died, and the 1-year OS rate was 82.1%. Based on subgroup analysis, patients with no evidence of Epstein-Barr virus infection, no B symptoms,

normal levels of lactate dehydrogenase, and no bone marrow involvement were more likely to achieve a response (Figure 9). Patients who did not have bone marrow involvement had a superior OS compared with patients who did (HR, 0.170; $P=.016$).

Treatment with sintilimab was generally well tolerated. All of the patients in the study experienced at

least 1 treatment-emergent AE, the majority of which were grade 1/2. No grade 4/5 AEs were observed. The most common grade 1 to 3 treatment-emergent AEs were decreased lymphocyte count (46.4%), fever (42.9%), and leukocytopenia (39.3%). Serious AEs were observed in 21.4% of patients, but none of these events were considered related to treatment. No infusion-related AEs occurred. None of the patients developed antidrug antibodies. Quality of life improved significantly after 15 weeks of treatment with sintilimab and remained superior to baseline values throughout the remainder of the study (Figure 10).

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Advances in Aggressive Lymphoma From the 2019 American Society of Clinical Oncology Annual Meeting: Commentary

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Important data on aggressive lymphomas were presented at the 2019 American Society of Clinical Oncology (ASCO) annual meeting. Although major advances in this field are typically reported at the American Society of Hematology (ASH) meeting, several sessions at this year's ASCO meeting have the potential to impact clinical care of patients with diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma.

Newly Diagnosed Disease

The single-center, investigator-initiated Smart Start trial evaluated lead-in treatment with rituximab, lenalidomide, and the Bruton tyrosine kinase (BTK) inhibitor ibrutinib in patients with newly diagnosed DLBCL.¹ The lead-in regimen was administered for 2 cycles, and then combined with standard chemotherapy consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) for an additional 6 cycles. This trial builds on prior data presented at the 2018 ASH meeting, which showed that the combination of ibrutinib, lenalidomide, and rituximab was associated with a response rate of over 50% among relapsed/refractory patients with the non-germinal center B-cell (GCB) subtype.² The Smart Start trial enrolled 60 patients, and many were older and had comorbidities. After the first 2 cycles of rituximab, lenalidomide, and ibrutinib, the overall

response rate was approximately 85%, with a complete response rate of 36%. This study provides early data suggesting that rituximab, lenalidomide, and ibrutinib might be an important upfront regimen for patients who are not candidates for chemotherapy or who cannot tolerate standard induction therapies. Additional studies will likely evaluate whether the use of this regimen up front will allow these patients to receive less chemotherapy afterward.

Dr Grzegorz Nowakowski and colleagues presented an interesting prospective study evaluating durvalumab, an inhibitor of the programmed death ligand 1 (PD-L1), combined with either rituximab plus CHOP or rituximab and lenalidomide plus CHOP, among patients with previously untreated, high-risk DLBCL.³ The rituximab/lenalidomide plus CHOP regimen was originally designed for patients with the non-GCB subtype of DLBCL. The idea behind the study was that the addition of a PD-L1 inhibitor might improve the cure rate for these patients. A similar trial, known as ROBUST (Efficacy and Safety Study of Lenalidomide Plus R-CHOP Chemotherapy Versus Placebo Plus R-CHOP Chemotherapy in Untreated ABC Type Diffuse Large B-Cell Lymphoma), was presented at the 2019 International Conference on Malignant Lymphoma.⁴ The ROBUST trial compared lenalidomide and rituximab plus CHOP with standard R-CHOP in these non-

GCB patients. Previous studies began to show significant toxicity when patients were treated with lenalidomide in combination with a checkpoint inhibitor, and the US Food and Drug Administration put clinical holds on several trials of checkpoint inhibitors and immunomodulatory agents.⁵ The toxicity was significant, and primarily consisted of increased immune-mediated toxicities. This trial then stopped enrolling patients with the non-GCB subtype into the lenalidomide arm.

The response rate reported with durvalumab plus R-CHOP exceeded 50%. This finding is encouraging, particularly when considering that approximately one-third of patients in the study had double-hit or triple-hit lymphomas. Two-thirds of the patients in the study were able to receive consolidation therapy with durvalumab, and were progression-free a year after treatment. R-CHOP plus durvalumab might represent an advance for patients who are difficult to treat, particularly those with double-hit or triple-hit disease. A next step might be to evaluate this regimen in a randomized trial.

Maintenance Therapy

Perhaps the strongest data in aggressive lymphoma presented at the 2019 ASCO meeting came from a randomized phase 3 trial performed by the Haemato Oncology Foundation for Adults in the Netherlands (HOVON) and the Nordic Lymphoma Group.⁶

This trial explored the idea of using maintenance rituximab in patients with DLBCL. The trial enrolled patients with DLBCL in first remission who received CHOP as their backbone induction therapy.

Previously, it had been shown that maintenance rituximab likely does not have a significant role in patients with DLBCL who achieved a first remission after frontline treatment with rituximab combined with standard CHOP chemotherapy.⁷ This earlier observation was confirmed in the HOVON trial. For the first 4 cycles, the trial compared standard R-CHOP vs an R-CHOP regimen that used an intensified dose of rituximab. Patients in first remission entered the phase 3 portion of the trial, and were randomly assigned to treatment with rituximab maintenance or observation. A previous report of this trial focused on whether the intensive rituximab regimen improved outcomes. The analysis identified no differences in the rates of complete remission and progression-free survival with intensification of rituximab plus CHOP vs standard R-CHOP.⁸ The presentation at ASCO provided data for the maintenance phase. Patients received rituximab every 8 weeks for 2 years or underwent observation. The median follow-up was an appropriate duration of almost 80 months. The analysis found no statistically significant difference in the rate of 5-year disease-free survival between the 2 different arms, at 79% for rituximab maintenance vs 74% for observation. The hazard ratio was 0.83, and the confidence interval crossed 1. Not surprisingly, there was also no significant difference in the secondary endpoint of overall survival.

The results of this study provide further confirmation that rituximab maintenance provides little to no additional benefit for patients with DLBCL who achieved a first complete remission after standard R-CHOP chemoimmunotherapy. Importantly, the majority of patients will be cured with standard R-CHOP chemoim-

muno-therapy, and there is a limited role in 2019 for maintenance rituximab in these patients.

Several studies presented at ASCO evaluated BTK inhibitors in patients with mantle cell lymphoma. Ibrutinib and acalabrutinib have been effective in patients with relapsed mantle cell lymphoma.^{9,10} The therapies are now being evaluated in untreated mantle cell lymphoma. A study presented by Dr Reem Karmali and colleagues investigated the use of ibrutinib as a maintenance therapy in patients with mantle cell lymphoma who achieved remission following induction therapy.¹¹ This analysis focused on safety, and it did not provide data on progression-free survival or overall survival. The regimen was very tolerable. Should this treatment improve progression-free survival, it might help avoid the use of consolidative autologous stem cell transplant in these patients.

Relapsed/Refractory Disease

Several studies explored novel therapies to improve outcomes for patients with relapsed, aggressive DLBCL, a population that is difficult to treat. Dr Thomas Rodgers and colleagues presented the results of a retrospective, single-center analysis examining the role of lenalidomide in patients with relapsed DLBCL.¹² The study included 62 patients, a relatively small number, who had been treated with lenalidomide as a single agent or in combination with rituximab.

As always, there are limitations and caveats to the interpretation of data from a retrospective analysis. It appeared, however, that single-agent lenalidomide had significant benefit to many of these very high-risk, difficult-to-treat patients. The overall response rate was higher than 40%. A significant amount of patients, 14 of 62 (23%), achieved a complete remission. The median progression-free survival was not particularly long, at 4.6 months. In nearly 20 patients, however, progression-free survival

lasted longer than 1 year. The median overall survival was approximately 14 months. This retrospective, single-center experience therefore suggests that lenalidomide with or without rituximab might be an appropriate regimen for patients with relapsed disease, even after autologous transplant. This regimen might serve as a bridge to other treatments, particularly other consolidative cellular therapies, such as chimeric antigen receptor (CAR) T-cell therapy.

This study and other retrospective studies suggest that lenalidomide might be active in patients with more aggressive disease, including those with double-hit or triple-hit disease and those with overexpression of the *MYC* gene. The study by Dr Rodgers included 7 patients with *MYC* translocation, and their response rates were notable (albeit based on a small number), with 3 complete responses and 3 partial responses.¹² The 3 patients with double-hit or triple-hit disease all had an objective response.

Lenalidomide was also combined with a new Fc-enhanced, humanized, anti-CD19 monoclonal antibody, known as MOR208, in a single-arm, phase 2 study of patients with relapsed/refractory DLBCL.¹³ The trial enrolled approximately 80 patients, whose median age was 72. Approximately one-third of patients were refractory to rituximab. The regimen appeared to be highly active in these patients, who had a poor prognosis and were difficult to treat. Among the patients who were refractory to rituximab, almost 60% responded to this regimen. Progression-free survival was approximately a year and a half. These findings suggest that this encouraging activity could lead to durable progression-free survival. The regimen could provide an opportunity to overcome rituximab resistance and improve response rates. It might also act as a bridge to allow a more definitive treatment—perhaps cellular therapy—to be implemented at a later time.

The dose-finding, phase 1 TRANSCEND NHL 001 trial (Study Evaluating the Safety and Pharmacokinetics of JCAR017 in B-Cell Non-Hodgkin Lymphoma) evaluated lisocabtagene maraleucel (also known as liso-cel and JCAR017) in patients with relapsed/refractory mantle cell lymphoma.¹⁴ Lisocabtagene maraleucel is a CAR T-cell therapy. The TRANSCEND NHL 001 trial found that the toxicity profile was tolerable and predictable. Approximately one-third of patients developed cytokine release syndrome; importantly, all cases were grade 1.

At the time of this analysis, 17 patients had received treatment. Although longer follow-up is needed, the response rates were outstanding. The rate of best overall response was 71%. Among the 9 patients with a complete response, the response was durable in 7: lasting through day 90 in 3 patients, through day 180 in 2 patients, through day 365 in 1 patient, and through day 545 in 1 patient. It will be necessary to treat more patients and define the exact cellular dose, as well as to closely monitor for adverse events. However, based on this study and others, it appears that CAR T-cell therapy is an important advance in patients with very aggressive, relapsed mantle cell lymphoma.

Disclosure

Dr Pagel is a consultant for Pharmacy-clics, AstraZeneca, Gilead, and Actinium Pharmaceuticals.

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