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A SPECIAL MEETING REVIEW EDITION

Highlights in Leukemia and Lymphoma From the 62nd American Society of Hematology Annual Meeting and Exposition

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

Special Reporting on:

- Umbralisib Plus Ublituximab Is Superior to Obinutuzumab Plus Chlorambucil in Patients With Treatment-Naive and Relapsed/Refractory Chronic Lymphocytic Leukemia: Results From the Phase 3 UNITY-CLL Study
- Primary Analysis of ZUMA-5: A Phase 2 Study of Axicabtagene Ciloleucel in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma
- A Phase 1/2 Study of Umbralisib, Ublituximab, and Venetoclax in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia
- LOXO-305, A Next-Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated CLL/SLL: Results From the Phase 1/2 BRUIN Study
- Umbralisib, the Once Daily Dual Inhibitor of PI3Kδ and Casein Kinase-1ε, Demonstrates Clinical Activity in Patients With Relapsed or Refractory Indolent Non-Hodgkin Lymphoma: Results From the Phase 2 Global UNITY-NHL Trial
- Clinical Activity of TG-1701, as Monotherapy and in Combination With Ublituximab and Umbralisib (U2), in Patients With B-Cell Malignancies
- Phase II Study of Pembrolizumab Plus GVD As Second-Line Therapy for Relapsed or Refractory Classical Hodgkin Lymphoma
- Efficacy and Safety Results From ASCEMBL, a Multicenter, Open-Label, Phase 3 Study of Asciminib, a First-in-Class STAMP Inhibitor, vs Bosutinib in Patients With Chronic Myeloid Leukemia in Chronic Phase Previously Treated With ≥2 Tyrosine Kinase Inhibitors

PLUS Meeting Abstract Summaries

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UKONIQ™

umbralisib 200 mg tablets

THE **FIRST AND ONLY** TARGETED KINASE INHIBITOR OF **PI3K-DELTA** AND **CK1-EPSILON**

INDICATIONS

UKONIQ is indicated for the treatment of adult patients with:

MZL **Relapsed or refractory marginal zone lymphoma (MZL) who have received at least 1 prior anti-CD20-based regimen**

FL **Relapsed or refractory follicular lymphoma (FL) who have received at least 3 prior lines of systemic therapy**

These indications are approved under accelerated approval based on overall response rate. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial.

IMPORTANT SAFETY INFORMATION

Infections: Serious, including fatal, infections occurred in patients treated with UKONIQ. Grade 3 or higher infections occurred in 10% of 335 patients, with fatal infections occurring in <1%. The most frequent Grade ≥3 infections included pneumonia, sepsis, and urinary tract infection. Provide prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP) and consider prophylactic antivirals during treatment with UKONIQ to prevent CMV infection, including CMV reactivation. Monitor for any new or worsening signs and symptoms of infection, including suspected PJP or CMV, during treatment with UKONIQ. For Grade 3 or 4 infection, withhold UKONIQ until infection has resolved. Resume UKONIQ at the same or a reduced dose. Withhold UKONIQ in patients with suspected PJP of any grade and permanently discontinue in patients with confirmed PJP. For clinical CMV infection or viremia, withhold UKONIQ until infection or viremia resolves. If UKONIQ is resumed, administer the same or reduced dose and monitor patients for CMV reactivation by PCR or antigen test at least monthly.

Neutropenia: Serious neutropenia occurred in patients treated with UKONIQ. Grade 3 neutropenia developed in 9% of 335 patients and Grade 4 neutropenia developed in 9%. Monitor neutrophil counts at least every 2 weeks for the first 2 months of UKONIQ and at least weekly in patients with neutrophil count <1 x 10^9/L (Grade 3-4) neutropenia during treatment with UKONIQ. Consider supportive care as appropriate. Withhold, reduce dose, or discontinue UKONIQ depending on the severity and persistence of neutropenia.

Diarrhea or Non-Infectious Colitis: Serious diarrhea or non-infectious colitis occurred in patients treated with UKONIQ. Any grade diarrhea or colitis occurred in 53% of 335 patients and Grade 3 occurred in 9%. For patients with severe diarrhea (Grade 3, i.e., >6 stools per day over baseline) or abdominal pain, stool with mucus or blood, change in bowel habits, or peritoneal signs, withhold UKONIQ until resolved and provide supportive care with antidiarrheals or enteric acting steroids as appropriate. Upon resolution, resume UKONIQ at a reduced dose. For recurrent Grade 3 diarrhea or recurrent colitis of any grade, discontinue UKONIQ. Discontinue UKONIQ for life-threatening diarrhea or colitis.

Hepatotoxicity: Serious hepatotoxicity occurred in patients treated with UKONIQ. Grade 3 and 4 transaminase elevations (ALT and/or AST) occurred in 8% and <1%, respectively, in 335 patients. Monitor hepatic function at baseline and during treatment with UKONIQ. For ALT/AST greater than 5 to less than 20 times ULN, withhold UKONIQ until return to less than 3 times ULN, then resume at a reduced dose. For ALT/AST elevation greater than 20 times ULN, discontinue UKONIQ.

Severe Cutaneous Reactions: Severe cutaneous reactions, including a fatal case of exfoliative dermatitis, occurred in patients treated with UKONIQ. Grade 3 cutaneous reactions occurred in 2% of 335 patients and included exfoliative dermatitis, erythema, and rash (primarily maculo-papular). Monitor patients for new or worsening cutaneous reactions. Review all concomitant medications and discontinue any potentially contributing medications. Withhold UKONIQ for severe (Grade 3) cutaneous reactions until resolution. Monitor at least weekly until resolved. Upon resolution, resume UKONIQ at a reduced dose. Discontinue UKONIQ if severe cutaneous reaction does not improve, worsens, or recurs. Discontinue UKONIQ for life-threatening cutaneous reactions or SJS, TEN, or DRESS of any grade. Provide supportive care as appropriate.

Allergic Reactions Due to Inactive Ingredient FD&C Yellow No. 5: UKONIQ contains FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons, frequently in patients who also have aspirin hypersensitivity.

Embryo-fetal Toxicity: Based on findings in animals and its mechanism of action, UKONIQ can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females and males with female partners of reproductive potential to use effective contraception during treatment and for at least one month after the last dose.

Serious adverse reactions occurred in 18% of 221 patients who received UKONIQ. Serious adverse reactions that occurred in ≥2% of patients were diarrhea-colitis (4%), pneumonia (3%), sepsis (2%), and urinary tract infection (2%). Permanent discontinuation of UKONIQ due to an adverse reaction occurred in 14% of patients. Dose reductions of UKONIQ due to an adverse reaction occurred in 11% of patients. Dosage interruptions of UKONIQ due to an adverse reaction occurred in 43% of patients.

The most common adverse reactions (>15%), including laboratory abnormalities, in 221 patients who received UKONIQ were increased creatinine (79%), diarrhea-colitis (58%, 2%), fatigue (41%), nausea (38%), neutropenia (33%), ALT increase (33%), AST increase (32%), musculoskeletal pain (27%), anemia (27%), thrombocytopenia (26%), upper respiratory tract infection (21%), vomiting (21%), abdominal pain (19%), decreased appetite (19%), and rash (18%).

Lactation: Because of the potential for serious adverse reactions from umbralisib in the breastfed child, advise women not to breastfeed during treatment with UKONIQ and for at least one month after the last dose.

Please see Brief Summary of the full Prescribing Information on the following pages.

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02/2021 US-UMB-2000041

TG Therapeutics

UKONIQ™ (umbralisib) tablets, for oral use

This is a brief summary. Before prescribing, please refer to the full Prescribing Information.

1.1. Marginal Zone Lymphoma

UKONIQ is indicated for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen.

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

1.2. Follicular Lymphoma

UKONIQ is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least three prior lines of systemic therapy.

This indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14.2)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

4. CONTRAINDICATIONS

None.

5. WARNINGS AND PRECAUTIONS

5.1. Infections

Serious, including fatal, infections occurred in patients treated with UKONIQ. Grade 3 or higher infections occurred in 10% of 335 patients, with fatal infections occurring in <1%. The most frequent Grade ≥3 infections included pneumonia, sepsis, and urinary tract infection. The median time to onset of Grade ≥3 infection was 2.4 months (range: 1 day to 21 months) *[see Adverse Reactions (6.1)]*.

Monitor for any new or worsening signs and symptoms of infection. For Grade 3 or 4 infection, withhold UKONIQ until infection has resolved. Resume UKONIQ at the same or a reduced dose *[see Dosage and Administration (2.3)]*.

Provide prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP) during treatment with UKONIQ *[see Dosage and Administration (2.2)]*. Withhold UKONIQ in patients with suspected PJP of any grade and permanently discontinue in patients with confirmed PJP *[see Dosage and Administration (2.2)]*.

Monitor for cytomegalovirus (CMV) infection during treatment with UKONIQ in patients with a history of CMV infection. Consider prophylactic antivirals during treatment with UKONIQ to prevent CMV infection, including CMV reactivation *[see Dosage and Administration (2.2)]*. For clinical CMV infection or viremia, withhold UKONIQ until infection or viremia resolves. If UKONIQ is resumed, administer the same or reduced dose and monitor patients for CMV reactivation by PCR or antigen test at least monthly *[see Dosage and Administration (2.2)]*.

5.2. Neutropenia

Serious neutropenia occurred in patients treated with UKONIQ. Grade 3 neutropenia developed in 9% of 335 patients and Grade 4 neutropenia developed in 9% *[see Adverse Reactions (6.1)]*. The median time to onset of Grade 3 or 4 neutropenia was 45 days.

Monitor neutrophil counts at least every 2 weeks for the first 2 months of UKONIQ and at least weekly in patients with neutrophil counts $<1 \times 10^9$/L (Grade 3-4). Consider supportive care as appropriate. Withhold, reduce dose, or discontinue UKONIQ depending on the severity and persistence of neutropenia *[see Dosage and Administration (2.3)]*.

5.3. Diarrhea or Non-infectious Colitis

Serious diarrhea or non-infectious colitis occurred in patients treated with UKONIQ. Any grade diarrhea or colitis occurred in 53% of 335 patients and Grade 3 occurred in 9% *[see Adverse Reactions (6.1)]*. The median time to onset for any grade diarrhea or colitis was 1 month (range: 1 day to 23 months), with 75% of cases occurring by 2.9 months.

For patients with severe diarrhea (Grade 3, i.e., > 6 stools per day over baseline) or abdominal pain, stool with mucus or blood, change in bowel habits, or peritoneal signs, withhold UKONIQ until resolved and provide supportive care with antidiarrheals or enteric acting steroids as appropriate. Upon resolution, resume UKONIQ at a reduced dose. For recurrent Grade 3 diarrhea or recurrent colitis of any grade, discontinue UKONIQ. Discontinue UKONIQ for life-threatening diarrhea or colitis *[see Dosage and Administration (2.3)]*.

5.4. Hepatotoxicity

Serious hepatotoxicity occurred in patients treated with UKONIQ. Grade 3 and 4 transaminase elevations (ALT and/or AST) occurred in 8% and <1%, respectively, in 335 patients *[see Adverse Reactions (6.1)]*. The median time to onset for Grade 3 or higher transaminase elevations was 2.2 months (range: 15 days to 4.7 months).

Monitor hepatic function at baseline and during treatment with UKONIQ. For ALT/AST greater than 5 to less than 20 times ULN, withhold UKONIQ until return to less than 3 times ULN, then resume at a reduced dose. For ALT/AST elevation greater than 20 times ULN, discontinue UKONIQ *[see Dosage and Administration (2.3)]*.

5.5. Severe Cutaneous Reactions

Severe cutaneous reactions, including a fatal case of exfoliative dermatitis, occurred in patients treated with UKONIQ. Grade 3 cutaneous reactions occurred in 2% of 335 patients and included exfoliative dermatitis, erythema, and rash (primarily maculo-papular) *[see Adverse Reactions (6.1)]*. The median time to onset of Grade 3 or higher cutaneous reaction was 15 days (range: 9 days to 6.4 months). Monitor patients for new or worsening cutaneous reactions. Review all concomitant medications and discontinue any potentially contributing medications. Withhold UKONIQ for severe (Grade 3) cutaneous reactions until resolution. Monitor at least weekly until resolved. Upon resolution, resume UKONIQ at a reduced dose. Discontinue UKONIQ if severe cutaneous reaction does not improve, worsens, or recurs. Discontinue UKONIQ for life-threatening cutaneous reactions or SJS, TEN, or DRESS of any grade *[see Dosage and Administration (2.3)]*. Provide supportive care as appropriate.

5.6 Allergic Reactions Due to Inactive Ingredient FD&C Yellow No. 5

UKONIQ contains FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

5.7 Embryo-Fetal Toxicity

Based on findings in animals and its mechanism of action, UKONIQ can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of umbralisib to pregnant mice during the period of organogenesis caused adverse developmental outcomes including embryo-fetal mortality and fetal malformations at maternal exposures comparable to those in patients at the recommended dose of 800 mg. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment and for one month after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6. ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Infections *[see Warnings and Precautions (5.1)]*
- Neutropenia *[see Warnings and Precautions (5.2)]*
- Diarrhea and Non-infectious Colitis *[see Warnings and Precautions (5.3)]*
- Hepatotoxicity *[see Warnings and Precautions (5.4)]*
- Severe Cutaneous Reactions *[see Warnings and Precautions (5.5)]*

6.1. Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be compared to rates in the clinical trials of another drug and may not reflect the rates observed in the general patient population.

The pooled safety population described in WARNINGS AND PRECAUTIONS reflects exposure to UKONIQ as monotherapy at a dosage of 800 mg orally once daily in 335 adults with hematologic malignancies in studies TGR-1202-101, TGR-1202-202, UTX-TGR-205, and UTX-TGR-501. Among these 335 patients who received UKONIQ, 52% were exposed for 6 months or longer and 30% were exposed for greater than one year.

Relapsed or Refractory Follicular Lymphoma and Marginal Zone Lymphoma

The safety of UKONIQ was evaluated in a pooled safety population that included 221 adults with marginal zone lymphoma (37%) and follicular lymphoma (63%) enrolled in three single-arm, open-label trials (Study TGR-1202-101, TGR-1202-202, and UTX-TGR-205) and one open-label extension trial (Study UTX-TGR-501) *[see Clinical Studies (14.1, 14.2)]*. These trials required hepatic transaminases ≤ 2.5 times upper limit of normal (ULN), total bilirubin ≤ 1.5 times ULN, and creatinine clearance ≥ 30 mL/min. No patients had prior exposure to a PI3K inhibitor. Patients received UKONIQ 800 mg orally once daily. Among these 221 patients who received UKONIQ, 60% were exposed for 6 months or longer and 34% were exposed for greater than one year.

The median age was 66 years (range: 29 to 88 years), 43% were female, and 97% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Race was reported in 92% of patients; of these patients, 89% were White, 6% were Black, and 3% were Asian. Patients had a median of 2 prior therapies (range 1 to 10).

Serious adverse reactions occurred in 18% of patients who received UKONIQ. Serious adverse reactions that occurred in ≥2% of patients were diarrhea-colitis (4%), pneumonia (3%), sepsis (2%), and urinary tract infection (2%). Fatal adverse reactions occurred in <1% of patients who received UKONIQ, including exfoliative dermatitis.

Permanent discontinuation of UKONIQ due to an adverse reaction occurred in 14% of patients. Adverse reactions which resulted in permanent discontinuation of UKONIQ in ≥5% of patients included diarrhea-colitis (6%) and transaminase elevation (5%).

Dose reductions of UKONIQ due to an adverse reaction occurred in 11% of patients. Adverse reactions which required dose reductions in ≥4% of patients included diarrhea-colitis (4%).

Dosage interruptions of UKONIQ due to an adverse reaction occurred in 43% of patients. Adverse reactions which required dosage interruption in ≥5% of patients included diarrhea-colitis (18%), transaminase elevation (7%), neutropenia (5%), vomiting (5%), and upper respiratory tract infection (5%).

The most common (≥15%) adverse reactions, including laboratory abnormalities, were increased creatinine, diarrhea-colitis, fatigue, nausea, neutropenia, transaminase elevation, musculoskeletal pain, anemia, thrombocytopenia, upper respiratory tract infection, vomiting, abdominal pain, decreased appetite, and rash.

Table 3 provides the adverse reactions in the pooled safety population of 221 patients with marginal zone lymphoma and follicular lymphoma who received the recommended dosage.

Table 3: Adverse Reactions Reported (≥10%) in Patients With Marginal Zone Lymphoma and Follicular Lymphoma Who Received UKONIQ in Pooled Safety Population

	UKONIQ N=221	
Adverse Reactions	**All Grades (%)**	**Grade 3 or 4 (%)**
Gastrointestinal Disorders		
Diarrhea	58	10
Nausea	38	<1
Vomiting	21	<1
Abdominal pain[a]	19	3
General Disorders and Administration Site Conditions		
Fatigue[b]	41	3
Edema[c]	14	<1
Pyrexia	10	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[d]	27	2
Infections		
Upper respiratory tract infection[e]	21	<1
Metabolism and Nutrition Disorders		
Decreased appetite	19	2
Skin and Subcutaneous Tissue Disorders		
Rash[f]	18	3
Psychiatric Disorders		
Insomnia	14	<1

[a] Abdominal pain includes Abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort
[b] Fatigue includes Fatigue, asthenia, lethargy
[c] Edema includes Edema peripheral, face edema, pulmonary edema, fluid overload, generalized edema
[d] Musculoskeletal pain includes Back pain, myalgia, pain in extremity, musculoskeletal pain, neck pain, spinal pain, musculoskeletal chest pain, musculoskeletal discomfort
[e] Upper respiratory tract infection includes Upper respiratory tract infection, sinusitis, nasopharyngitis, rhinitis
[f] Rash includes Rash, rash maculo-papular, rash erythematous, rash pruritic, rash macular, exfoliative dermatitis

Clinically relevant adverse reactions in <10% of patients who received UKONIQ included urinary tract infection (9%), dyspnea (7%), pneumonia (6%), sepsis (3%), colitis (2%), pneumonitis (<1%), and exfoliative dermatitis (<1%).

Table 4 provides the laboratory abnormalities in the pooled safety population of 221 patients with marginal zone lymphoma and follicular lymphoma who received the recommended dosage.

Table 4: Select Laboratory Abnormalities (>20%) That Worsened from Baseline in Patients with Marginal Zone Lymphoma and Follicular Lymphoma Who Received UKONIQ in Pooled Safety Population

	UKONIQ N=221	
Laboratory Parameter	**Any Grades[a] (%)**	**Grade 3 or 4[b] (%)**
Hematologic		
Neutrophil decreased	33	16
Hemoglobin decreased	27	3
Platelets decreased	26	4
Chemistry		
Creatinine increased	79	0
Alanine aminotransferase increased	33	8
Aspartate aminotransferase increased	32	7
Potassium decreased	21	4

[a] Laboratory values were categorized using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 grading system.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary

Based on findings from animal studies and the mechanism of action *[see Clinical Pharmacology (12.1)]*, UKONIQ can cause fetal harm when administered to a pregnant woman. There are no available data on UKONIQ use in pregnant women to evaluate for a drug-associated risk. In animal reproduction studies, administration of umbralisib to pregnant mice during organogenesis resulted in adverse developmental outcomes, including alterations to growth, embryo-fetal mortality, and structural abnormalities at maternal exposures (AUC) comparable to those in patients at the recommended dose of 800 mg *(see Data)*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study in mice, pregnant animals

were administered oral doses of umbralisib at 100, 200, and 400 mg/kg/day during the period of organogenesis. Malformations were observed at doses of 200 mg/kg/day (cleft palate) and 400 mg/kg/day (cleft palate and nasopharyngeal fistula). Additional findings occurred starting at the dose of 100 mg/kg/day and included folded retina, delayed ossification of sternebrae and vertebrae, increased resorptions, and increased post-implantation loss. The exposure (AUC) at a dose of 100 mg/kg/day in mice is approximately equivalent to the human exposure at the recommended dose of 800 mg.

In an embryo-fetal development study in rabbits, pregnant animals were administered oral doses of umbralisib at 30, 100, and 300 mg/kg/day during the period of organogenesis. Administration at 300 mg/kg/day resulted in maternal toxicity (decreased food consumption and body weight) and reduced fetal weights. The exposure (AUC) at 300 mg/kg/day in rabbits is approximately 0.03 times the exposure in human patients at the recommended dose of 800 mg.

8.2. Lactation

Risk Summary

There are no data on the presence of umbralisib in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions from umbralisib in the breastfed child, advise women not to breastfeed during treatment with UKONIQ and for one month after the last dose.

8.3. Females and Males of Reproductive Potential

UKONIQ may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating UKONIQ.

Contraception

Females

Advise female patients of reproductive potential to use highly effective contraception during treatment with UKONIQ and for at least 4 months after the last dose.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with UKONIQ and for one month after the last dose.

Infertility

Males

Based on the findings from mice and dogs, UKONIQ may impair male fertility *[see Nonclinical Toxicology (13.1)]*. Trend for reversibility was noted in dogs 30 days after the last dose.

8.4. Pediatric Use

Safety and effectiveness of UKONIQ have not been established in pediatric patients.

8.5. Geriatric Use

Of the 221 patients with MZL or FL who received UKONIQ in clinical studies, 56% of patients were 65 years of age and older, while 19% were 75 years of age and older. No overall differences in effectiveness or pharmacokinetics were observed between these patients and younger patients. In patients 65 years of age and older, 23% experienced serious adverse reactions compared to 12% in patients younger than 65 years of age. There was a higher incidence of infectious serious adverse reactions in patients 65 years of age or older (13%) compared to patients younger than 65 years of age (4%).

8.6. Renal Impairment

No dose adjustment is recommended in patients with mild or moderate renal impairment (creatinine clearance [CLcr] 30 to 89 mL/min estimated by Cockcroft-Gault equation) *[see Clinical Pharmacology (12.3)]*. UKONIQ has not been studied in patients with severe renal impairment ([CLcr] < 30 mL/min).

8.7. Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and AST > ULN or total bilirubin >1 to 1.5 × ULN and any AST) *[see Clinical Pharmacology (12.3)]*. UKONIQ has not been studied in patients with moderate (total bilirubin > 1.5 to 3 × ULN and any AST) or severe hepatic impairment (total bilirubin > 3 × ULN and any AST).

14. CLINICAL STUDIES

14.1. Marginal Zone Lymphoma

The efficacy of UKONIQ was evaluated in a single-arm cohort of Study UTX-TGR-205 (NCT02793583), an open-label, multi-center, multi-cohort trial. Patients with MZL were required to have received at least one prior therapy, including an anti-CD20 containing regimen. The trial excluded patients with prior exposure to a PI3K inhibitor. Patients received UKONIQ 800 mg orally once daily until disease progression or unacceptable toxicity.

A total of 69 patients with MZL [extranodal (N=38), nodal (N=20), and splenic (N=11)] were enrolled in this cohort. The median age was 67 years (range: 34 to 88 years), 52% were female, 83% were White, 7% were Black, 3% were Asian, 7% were Other, and 97% had a baseline ECOG performance status of 0 or 1. Patients had a median number of prior lines of therapy of 2 (range: 1 to 6), with 26% being refractory to their last therapy.

Efficacy was based on overall response rate as assessed by an Independent Review Committee (IRC) using criteria adopted from the International Working Group criteria for malignant lymphoma. The median follow-up time was 20.3 months (range: 15.0 to 28.7 months). Efficacy results are shown in Table 5.

Table 5: Efficacy Results in Patients with MZL (Study 205)

Endpoint	Total (N=69)
ORR, n (%)[a]	34 (49)
95% CI	37.0, 61.6
CR, n (%)	11 (16)
PR, n (%)	23 (33)
DOR	
Median, months (95% CI)[b]	NR (9.3, NE)
Range, months	0.0+, 21.8+

CI, confidence interval; CR, complete response; DOR, duration of response; IRC, Independent Review Committee; ORR, overall response rate; NE, not evaluable; NR, not reached; PR, partial response.
[a]Per IRC according to Revised International Working Group Criteria
[b]Based on Kaplan-Meier estimation
+Denotes censored observation

The median time to response was 2.8 months (range: 1.8 to 21.2 months). Overall response rates were 44.7%, 60.0%, and 45.5% for the 3 MZL sub-types (extranodal, nodal, and splenic, respectively).

14.2. Follicular Lymphoma

The efficacy of UKONIQ was evaluated in a single-arm cohort of Study UTX-TGR-205, an open-label, multi-center, multi-cohort trial (NCT02793583). Patients with relapsed or refractory FL were required to have received at least two prior systemic therapies, including an anti-CD20 monoclonal antibody and an alkylating agent. The trial excluded patients with Grade 3b FL, large cell transformation, prior allogeneic transplant, history of CNS lymphoma, and prior exposure to a PI3K inhibitor. Patients received UKONIQ 800 mg orally once daily until disease progression or unacceptable toxicity.

A total of 117 patients with FL were enrolled in this cohort. The median age was 65 years (range: 29 to 87 years), 38% were female, 80% were White, 4% were Black, 73% had Stage III-IV disease, 38% had bulky disease and 97% had a baseline ECOG performance status of 0 to 1. Patients had a median of 3 prior lines of therapy (range: 1 to 10), with 36% refractory to their last therapy.

Efficacy was based on overall response rate as assessed by an Independent Review Committee (IRC) using criteria adopted from the International Working Group criteria for malignant lymphoma. The median follow-up time was 20.1 months (range: 13.5 to 29.6 months). Efficacy results are shown in Table 6.

Table 6: Efficacy Results in Patients With Relapsed or Refractory FL (Study 205)

Endpoint	Total (N=117)
ORR, n (%)[a]	50 (43)
95% CI	33.6, 52.2
CR, n (%)	4 (3.4)
PR, n (%)	46 (39)
DOR	
Median months (95% CI)[b]	11.1 (8.3, 16.4)
Range, months	0.0+, 20.9+

CI, confidence interval; CR, complete response; DOR, duration of response; IRC, Independent Review Committee; ORR, overall response rate; PR, partial response.
[a]Per IRC according to Revised International Working Group Criteria
[b]Based on Kaplan-Meier estimation
+Denotes censored observation

The median time to response was 4.4 months (range: 2.2 to 15.5 months).

17. PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide).

Infections

Advise patients that UKONIQ can cause serious infections that may be fatal. Advise patients to immediately report any signs or symptoms of infection (e.g., fever, chills, weakness) *[see Warnings and Precautions (5.1)]*.

Neutropenia

Advise patients of the need for periodic monitoring of blood counts and to notify their healthcare provider immediately if they develop a fever or any signs of infection *[see Warnings and Precautions (5.2)]*.

Diarrhea or Non-infectious Colitis

Advise patients that they may experience loose stools or diarrhea and should contact their healthcare provider with any persistent or worsening diarrhea. Advise patients to maintain adequate hydration *[see Warnings and Precautions (5.3)]*.

Advise patients of the possibility of colitis and to notify their healthcare provider of any abdominal pain/distress *[see Warnings and Precautions (5.3)]*.

Hepatotoxicity

Advise patients that UKONIQ may cause significant elevations in liver enzymes and the need for periodic monitoring of liver tests. Advise patients to report symptoms of liver dysfunction including jaundice (yellow eyes or yellow skin), abdominal pain, bruising, or bleeding *[see Warnings and Precautions (5.4)]*.

Severe Cutaneous Reactions

Advise patients that UKONIQ may cause a severe skin rash and to notify their healthcare provider immediately if they develop a new or worsening skin rash *[see Warnings and Precautions (5.5)]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.7), Use in Specific Populations (8.1, 8.3)]*.

Advise females of reproductive potential to use effective contraceptive during treatment with UKONIQ and for one month after the last dose *[see Use in Specific Populations (8.3)]*.

Advise males with female partners of reproductive potential to use effective contraceptive during treatment with UKONIQ and for one month after the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

Advise women not to breastfeed during treatment with UKONIQ and for one month after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise males of reproductive potential that UKONIQ may impair fertility *[see Use in Specific Populations (8.3)]*.

Allergic Reactions Due to Inactive Ingredient FD&C Yellow No. 5

Advise patients that UKONIQ contains FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions in certain susceptible persons *[see Warnings and Precautions (5.6)]*.

Administration

Inform patients to take UKONIQ orally once daily at approximately the same time each day with food and how to make up a missed or vomited dose. Advise patients to swallow tablets whole. Advise patients not to crush, break, cut or chew tablets *[see Dosage and Administration (2.1)]*.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch or call 1-800-FDA-1088.

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umbralisib 200 mg tablets

Umbralisib Plus Ublituximab Is Superior to Obinutuzumab Plus Chlorambucil in Patients With Treatment-Naive and Relapsed/Refractory Chronic Lymphocytic Leukemia: Results From the Phase 3 UNITY-CLL Study

The development of inhibitors of Bruton tyrosine kinase (BTK) and B-cell lymphoma 2 (BCL-2) has dramatically improved outcomes in both treatment-naive and previously treated patients with chronic lymphocytic leukemia (CLL).[1] However, mechanisms of resistance to these agents have been identified. The mechanism of action of drugs that inhibit phosphoinositide 3-kinase delta (PI3Kδ) is distinct from that of BTK and BCL-2 inhibitors, and these drugs have yielded encouraging outcomes in patients with relapsed or refractory CLL.[2,3] Despite promising efficacy, early PI3Kδ inhibitors were associated with high levels of toxicity, and discontinuation rates exceeded 50% in some studies. Umbralisib is a novel dual inhibitor of PI3Kδ and casein kinase 1ε that binds with greater selectivity to the δ isoform of PI3K than to other isoforms, with reduced rates of discontinuation owing to adverse events (AEs) and low rates of immune-mediated toxicities.[4] The affinity of umbralisib for the δ isoform of PI3K is 1000-fold greater than its affinity for the α or β isoform, and its affinity for the δ isoform is 200-fold greater than its affinity for PI3Kγ. Ublituximab is a novel monoclonal antibody that targets CD20 and has been glycoengineered to increase antibody-dependent cellular cytotoxicity.[5]

The UNITY-CLL study evaluated umbralisib monotherapy, ublituximab monotherapy, the combination of umbralisib plus ublituximab (U2), and obinutuzumab plus chlorambucil for the treatment of CLL.[6] Patients with treatment-naive or relapsed or refractory disease requiring treatment according to International Workshop on CLL (iwCLL) criteria were enrolled.[7] They had adequate organ function and an Eastern Cooperative Oncology Group performance status of 2 or lower. Patients were stratified on the basis of chromosome 17 deletion (del[17p]) and prior treatment. Umbralisib (800 mg) was administered once daily until disease progression or cessation for other reasons. Ublituximab (900 mg) was administered as a split dose on days 1 and 2 of cycle 1 and then as a single dose on days 8 and 15 of cycle 1, on day 1 of cycles 2 through 6, and on day 1 of every third cycle after cycle 6. Obinutuzumab (1000 mg) was administered as a split dose on days 1 and 2 and then as a single dose on days 8 and 15 of cycle 1 and on day 1 of cycles 2 through 6. Chlorambucil (0.5 mg/kg) was administered once daily on days 1 and 15 of cycles 1 through 6. Each treatment cycle was 28 days. The primary endpoint was progression-free survival (PFS), assessed by an independent review committee. Secondary endpoints included the objective response rate (ORR), complete response (CR) rate, duration of response (DOR),

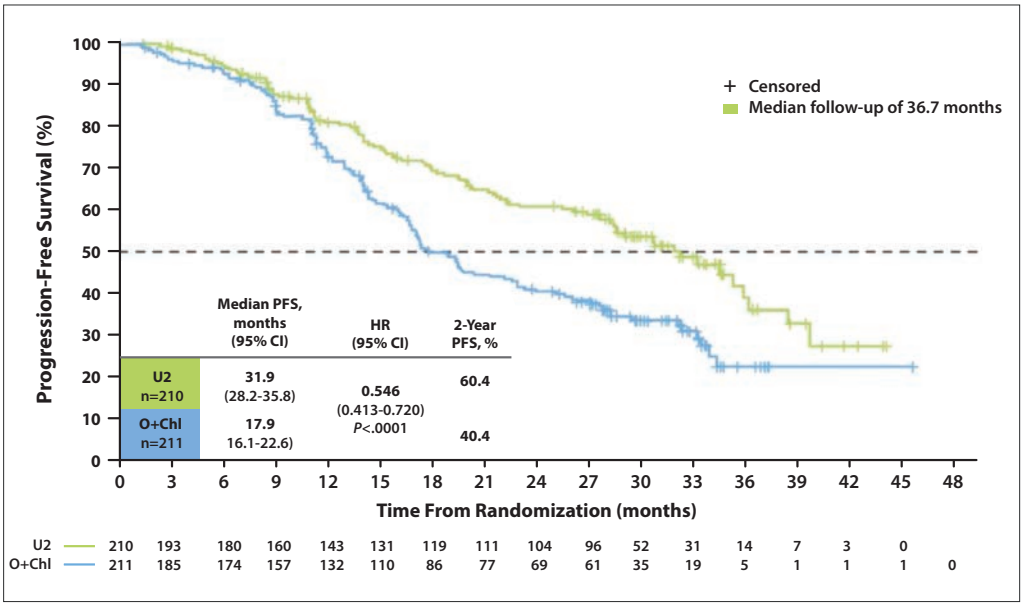

Figure 1. Progression-free survival in the phase 3 UNITY-CLL study, which compared umbralisib plus ublituximab vs obinutuzumab plus chlorambucil in patients with chronic lymphocytic leukemia. HR, hazard ratio; O+Chl, obinutuzumab plus chlorambucil; PFS, progression-free survival; U2, umbralisib plus ublituximab. Adapted from Gribben J et al. ASH abstract 543. *Blood.* 2020;136(suppl 1).[6]

undetectable minimal residual disease (MRD), and safety. Two interim analyses were planned. The first one, for futility only, was performed when 50% of independently assessed PFS events had occurred. The second, to evaluate the superiority of U2 vs obinutuzumab plus chlorambucil, was performed when 75% of those events had occurred. Enrollment into the umbralisib and ublituximab arms was discontinued after the data safety monitoring board determined that the contribution of each agent had been demonstrated.

The study enrolled 210 patients into the U2 arm and 211 patients into the obinutuzumab-plus-chlorambucil arm.[6] In the U2 arm, patients had a median age of 67 years (range, 39-88), and 39% had Rai stage 3/4 disease. High-risk features included the unmutated immunoglobulin heavy chain variable (*IGHV*) region gene in 54%, del(11q) in 22%, and del(17p) in 9%. In the obinutuzumab-plus-chlorambucil arm, patients had a median age of 68 years (range, 36-91), and 35% had Rai stage 3/4 disease. High-risk features included unmutated *IGHV* in 55%, del(11q) in 18%, and del(17p) in 11%. In each arm, 57% of the patients were treatment-naive.

In the U2 arm, the median duration of drug exposure was 21.1 months (range, 0.03-46.3) for ublituximab and 20.5 months (range, 0.03-47.2) for umbralisib. In the comparator arm, the median duration of drug exposure was 4.7 months (range, 0.03-7.4) for obinutuzumab and 5.1 months (range, 0.03-7.4) for chlorambucil. The rate of treatment discontinuation owing to AEs was 17% in the U2 arm vs 8% in the comparator arm.

After a median follow-up of 36.2 months, the median PFS was 31.9 months in the U2 arm vs 17.9 months in the comparator arm (hazard ratio [HR], 0.546; 95% CI, 0.413-0.720; *P*<.0001; Figure 1). Among treatment-naive patients, the median PFS was 38.5 months vs 26.1 months, respectively (HR, 0.482; 95% CI, 0.316-0.736; *P*<.001). Among previously treated patients, the median PFS was 19.5 months in the U2 arm vs 12.9 months in the obinutuzumab-plus-chlorambucil arm (HR, 0.601; 95% CI, 0.415-0.869; *P*<.01). The ORR was 83.3% with the U2 regimen (5% CR rate) vs 68.7% (1% CR rate) with obinutuzumab plus chlorambucil (Figure 2).

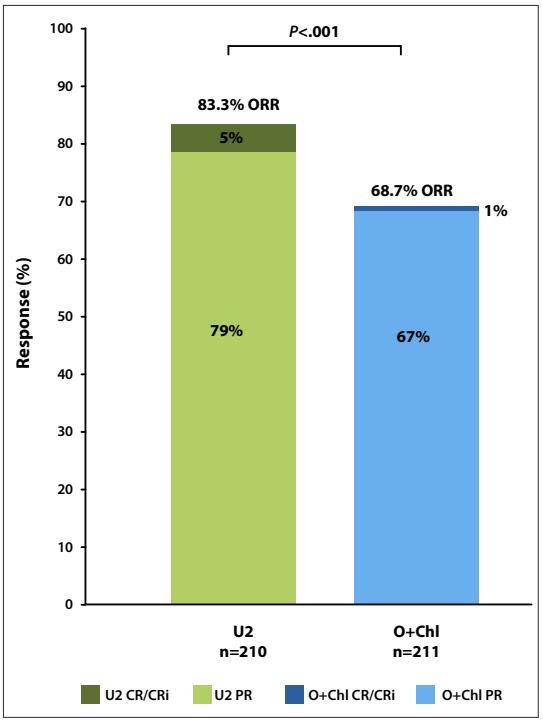

Figure 2. Response rates in the phase 3 UNITY-CLL study, which compared umbralisib plus ublituximab vs obinutuzumab plus chlorambucil in patients with chronic lymphocytic leukemia. CR, complete response; CRi, complete response with incomplete hematologic recovery; HR, hazard ratio; O+Chl, obinutuzumab plus chlorambucil; ORR, overall response rate; PR, partial response; PFS, progression-free survival; U2, umbralisib plus ublituximab. Adapted from Gribben J et al. ASH abstract 543. *Blood.* 2020;136(suppl 1).[6]

Serious AEs were observed in 46.1% of patients in the U2 arm vs 23.5% of patients in the comparator arm. AEs of grade 3 or higher were observed in 82.0% of patients in the U2 arm vs 66.0% of patients in the comparator arm. Grade 5 AEs occurred in 3.9% vs 2.5% of patients, respectively. In the U2 arm, the most common grade 3/4 AEs were neutropenia (31.1%) and diarrhea (12.1%), followed by fatigue (1.9%) and infusion-related reactions (1.9%). The most common PI3K-related AEs of grade 3 or higher were alanine transaminase elevation (8.3%), opportunistic infections (5.8%), and aspartate transaminase elevation (5.3%).

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Primary Analysis of ZUMA-5: A Phase 2 Study of Axicabtagene Ciloleucel in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

In patients with follicular lymphoma who have received 2 or more lines of treatment, CR rates with approved therapies are less than 15%, and the median DORs are 13 months or less.[1-3] Axicabtagene ciloleucel is an autologous chimeric antigen receptor (CAR) T-cell therapy that binds to CD19. It is approved for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy.[4] The single-arm, multicenter phase 2 ZUMA-5 trial evaluated axicabtagene ciloleucel in patients with relapsed or refractory follicular lymphoma or marginal zone lymphoma (MZL) who had previously received 2 or more systemic regimens.[5] Key eligibility criteria included grade 1 to 3a follicular lymphoma or nodal or extranodal MZL and prior treatment with the combination of an anti-CD20 monoclonal antibody and an alkylating agent. The conditioning regimen consisted of fludarabine (30 mg/m^2) plus cyclophosphamide (500 mg/m^2), administered 5, 4, and 3 days before the axicabtagene ciloleucel infusion. The axicabtagene ciloleucel product was infused at a dose of 2 × 10^6 CAR T cells/kg. The study's primary endpoint was the ORR, assessed by independent review according to the Lugano classification.[6]

The manufacture of axicabtagene ciloleucel was successful for the 151 patients enrolled in the trial.[5] The drug was delivered to the study site at a median of 17 days after the patients had undergone leukapheresis. The infusion was administered to 124 patients with follicular lymphoma and 22 patients with MZL. The efficacy analysis included 104 patients, and the safety analysis included 146 patients. The median follow-up was 17.5 months for efficacy and 15.1 months for safety. At baseline, the patients had a median age of 61 years (range, 34-79), 86% had stage 3/4 disease, and 68% had refractory disease. The patients had received a median of 3 prior therapies (range, 1-10).

The independently assessed ORR was 92%, with a CR rate of 76%.[5] The ORR in the patients with follicular lymphoma was 94%, with a CR rate of 80%. The ORR in the patients with MZL was 85%, with a CR rate of 60%. The ORRs with axicabtagene ciloleucel were consistent across key subgroups, such as those based on age and number of prior therapies. The median DOR was not reached, and the 12-month estimated DOR rate was 71.7% (95% CI, 60.7%-80.1%; Figure 3). Ongoing responses were more common among patients who had achieved a CR than in those with a partial response (PR; 78% vs 17%). The median PFS and median overall survival (OS) were not reached. The 12-month PFS rate was 73.7% (Figure 4), and the 12-month OS rate was 92.9%.

Among the 146 patients, the most common treatment-emergent AEs of any grade were pyrexia (84%), neutropenia (64%), and hypotension (49%).[6] AEs of grade 3 or higher were reported in 126 patients (86%). The most common of these events consisted of cytopenias (70%) and infections (16%). Grade 5 AEs were

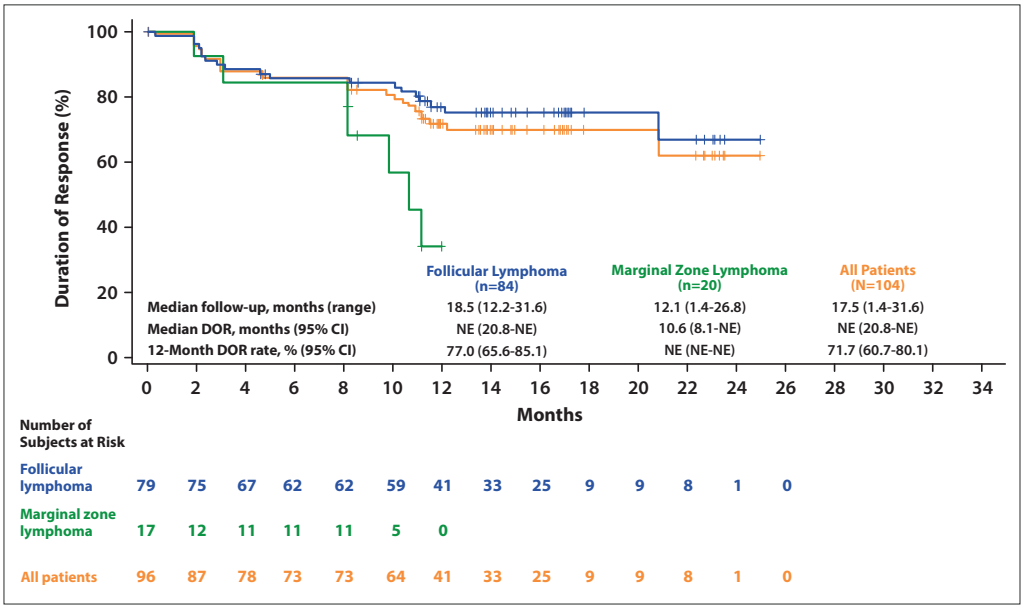

Figure 3. DOR among patients with follicular lymphoma or marginal zone lymphoma in the phase 2 ZUMA-5 trial, which evaluated axicabtagene ciloleucel in patients with relapsed/refractory indolent non-Hodgkin lymphoma. DOR, duration of response; NE, not estimable. Adapted from Jacobson CA et al. ASH abstract 700. *Blood.* 2020;136(suppl 1).[5]

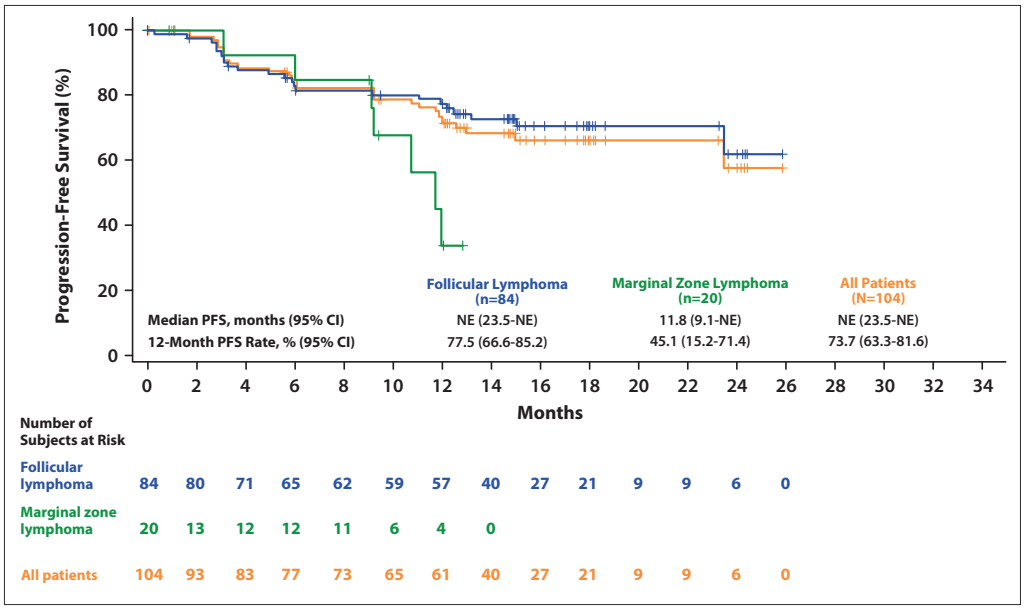

Figure 4. PFS among patients with follicular lymphoma or marginal zone lymphoma in the phase 2 ZUMA-5 trial, which evaluated axicabtagene ciloleucel in patients with relapsed/refractory indolent non-Hodgkin lymphoma. NE, not estimable; PFS, progression-free survival. Adapted from Jacobson CA et al. ASH abstract 700. *Blood.* 2020;136(suppl 1).[5]

reported in 3 patients (2%), including a case of multisystem organ failure, in the context of cytokine release syndrome, that was related to axicabtagene ciloleucel treatment. Cytokine release syndrome of at least grade 3 occurred in 10 patients (7%). Neurologic events of grade 3 or higher were reported in 19% of patients, with no grade 5 neurologic events. The median time to the peak level of engineered CAR T cells was 9 days (range, 8-371) after the axicabtagene ciloleucel infusion.

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A Phase 1/2 Study of Umbralisib, Ublituximab, and Venetoclax in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia

A multicenter phase 1/2 study evaluated the U2 regimen combined with venetoclax in patients with previously treated CLL.[1] The goal was to reduce the risk for venetoclax resistance and tumor lysis syndrome, while increasing the eradication of malignant cells.[2,3] The trial enrolled patients with CLL/small lymphocytic lymphoma (SLL) that had progressed after at least 1 prior regimen and required treatment. During the study, the protocol was amended to limit enrollment to patients who were unable to tolerate BTK inhibition or who had refractory disease. Patients with previous exposure to a PI3K inhibitor or a BCL-2 inhibitor were permitted to enroll. The dose escalation portion of the trial used a standard 3 + 3 design. During the phase 2 portion of the study, patients received 3 infusions of ublituximab (900 mg) during cycle 1, then a single infusion (900 mg) on day 1 of cycles 2 through 6. Umbralisib (800 mg) was administered daily. Venetoclax was initiated with cycle 4; the dose was ramped up to 400 mg in a standard 5-week schedule and was administered once daily through cycle 12. Each cycle was 28 days. The primary objective for phase 2 was the CR rate according to iwCLL criteria.[4]

For the safety analysis, 43 patients were evaluable, and 39 were evaluable for efficacy.[1] Their median age was 64 years (range, 43-83). The median number of prior therapies was 2 (range, 1-6), and 33% had disease that was refractory to the most recent therapy. At least 1 high-risk feature was present in 79% of the patients, such as unmutated *IGHV* in 74%, del(11q) in 30%, *NOTCH1* mutation in 27%, and del(17p) in 26%.

After 3 cycles of U2 therapy, the relative risk for tumor lysis syndrome

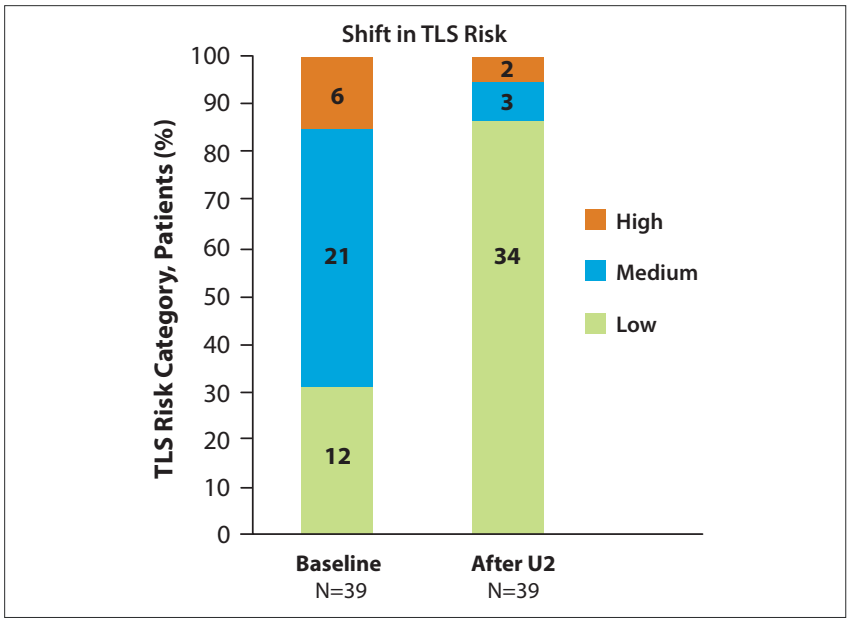

Figure 5. Three cycles of U2 induction reduced the risk of tumor lysis syndrome associated with venetoclax in a phase 1/2 study of patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. TLS, tumor lysis syndrome; U2, umbralisib and ublituximab. Adapted from Barr PM et al. ASH abstract 3137. *Blood.* 2020;136(suppl 1).[1]

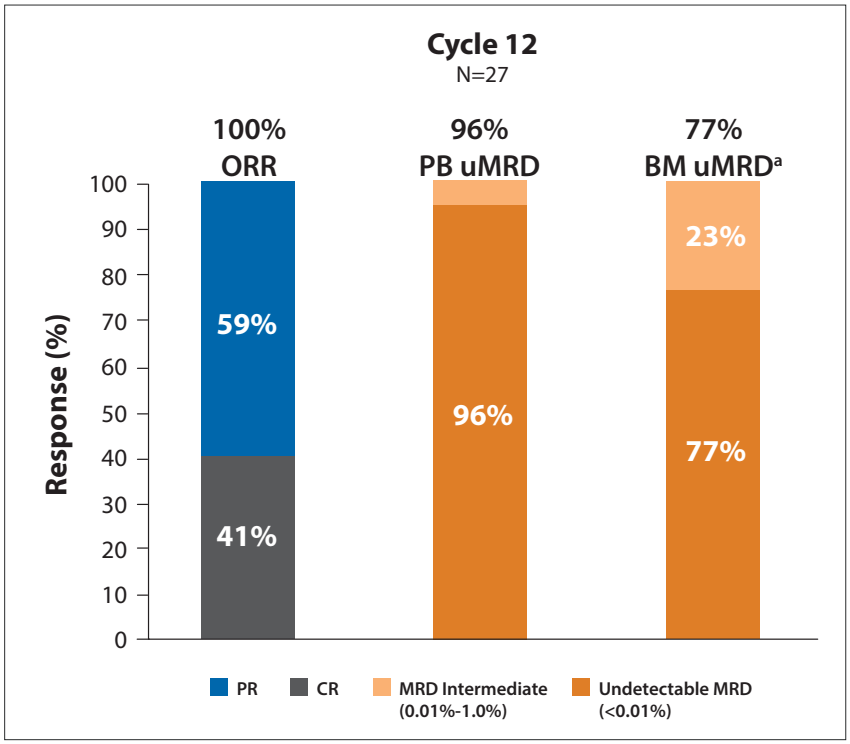

Figure 6. Response rates in a phase 1/2 study of U2 and venetoclax in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. BM, bone marrow; ORR, overall response rate; PB, peripheral blood; uMRD, undetectable minimal residual disease; U2, umbralisib and ublituximab. [a]One BM sample was not analyzed. Adapted from Barr PM et al. ASH abstract 3137. *Blood.* 2020;136(suppl 1).[1]

was reduced by 81% (Figure 5).[1] No cases of tumor lysis syndrome developed during the venetoclax ramp-up. After 12 treatment cycles, the ORR was 100% (59% CR rate/41% PR rate; Figure 6). MRD was undetectable in the peripheral blood in 96% of patients and in the bone marrow in 77%. After a median follow-up of 15.6 months, disease had progressed in only 1 patient. This patient had completed 12 cycles of therapy, with achievement of undetectable MRD in both the peripheral blood and bone marrow; disease progression was noted 10 months later.

The most common AEs of any grade included infusion reaction (60%), anemia (56%), thrombocytopenia (53%), and neutropenia (51%). Grade 3/4 AEs included neutropenia (21%), leukopenia (12%), infusion reaction (7%), anemia (5%), and diarrhea (5%). Grade 3/4 AEs of special interest included lung infection/pneumonia (7%), colitis (5%), tumor lysis syndrome (2%), and rash (2%). The umbralisib dose was reduced in 4% of patients. Umbralisib was discontinued in 9% of patients, and venetoclax was discontinued in 4% of patients. The ongoing phase 2 ULTRA-V study is evaluating U2 plus venetoclax in treatment-naive and previously treated patients.

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LOXO-305, A Next-Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated CLL/SLL: Results From the Phase 1/2 BRUIN Study

Covalent BTK inhibitors have transformed the treatment landscape for CLL, but their use is limited by toxicities and the development of resistance.[1-6] Mutation of the *BTK* gene (cysteine to serine substitution at the 481 residue) is the most common cause of CLL that progresses after treatment with a covalent BTK inhibitor. LOXO-305 is a selective, noncovalent inhibitor of BTK that has nanomolar potency against both wild-type *BTK* and BTK^{C481S} in cell and enzyme assays.[7,8] The phase 1/2 BRUIN study investigated LOXO-305 in patients with non-Hodgkin lymphoma (NHL). During phase 1, LOXO-305 was administered daily in doses ranging from 25 to 300 mg. Each cycle was 28 days. Intrapatient dose escalation was allowed, and cohort expansion was permitted at doses that were considered safe. Eligible patients had previously treated CLL/SLL or another type of B-cell NHL, with active disease that required treatment. Endpoints included efficacy and safety, as well as determinations of the maximum tolerated dose and the recommended phase 2 dose.

The 170 patients with CLL/SLL were a median age of 69 years (range, 36-88).[8] They had received a median of 3 prior systemic therapies (range, 1-11). Unmutated *IGHV* was present in 88% of the patients. At daily doses of 100 mg or higher, the plasma concentration of LOXO-305 exceeded the BTK 90% maximal inhibitory concentration (IC_{90}) throughout the dosing interval. The investigators identified a linear relationship between the dose level and the plasma concentration.

Among the 323 patients with NHL in the study, no dose-limiting toxicities occurred, and the maximum tolerated dose was not reached. Treatment-related AEs led 5 patients (1.5%) to discontinue LOXO-305. The most common treatment-related AEs of any grade, observed in at least 10% of patients, were fatigue (20%), diarrhea (17%), and contusion (13%). AEs of special interest were almost all grade 1/2. Exceptions included hemorrhage (all cases grade 3; <1%) and hypertension (all cases grade 3; 1%). The recommended phase 2 dose was 200 mg daily.

In the cohort of patients with CLL/SLL, the ORR was 63%, including a 50% PR rate and a 14% rate of PR with lymphocytosis.[8] The ORR improved from the end of treatment through 10 months afterward (Figure 7). After a median follow-up of 6 months, 94% of the patients who initially responded to treatment maintained the response. Promising efficacy outcomes were observed in the subgroups of patients with previous exposure to a BTK inhibitor or other therapy, as well as in patients with a BTK^{C481S} mutation.

The BRUIN study also included 61 patients with mantle cell lymphoma, 26 with Waldenström macroglobulinemia, and 66 with another NHL subtype.[9] These patients were a median age of 68 years (range, 27-87). Previous use of BTK therapy was reported among 93% of the patients with mantle cell lymphoma, 69% of those with Waldenström macroglobulinemia, and 37% of those with other NHL subtypes.

In the 56 patients with mantle cell lymphoma evaluable for response, the ORR was 52%, including a CR rate of 25%.[9] Among these patients, a response was maintained in 83% after a median follow-up of 6 months.

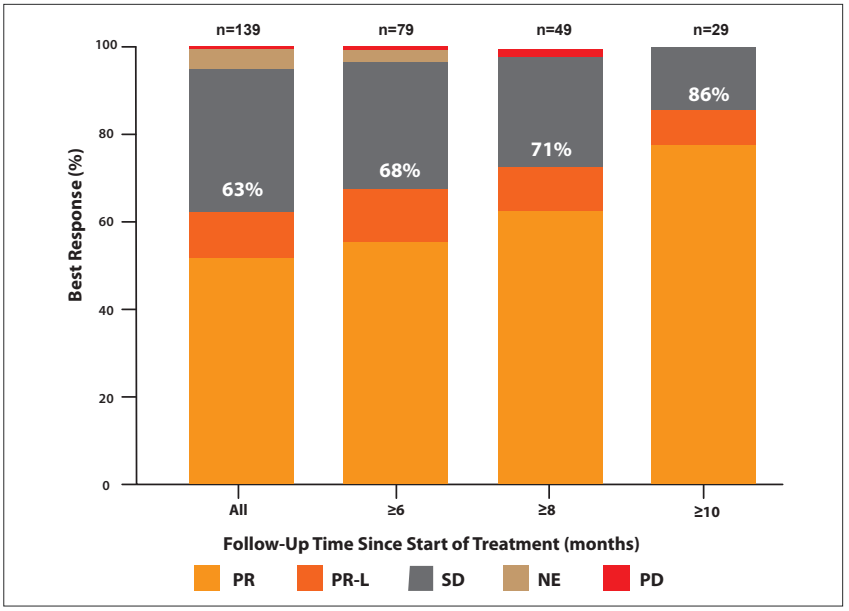

Figure 7. Overall response rates in the phase 1/2 BRUIN trial, which evaluated LOXO-305 in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. The analysis included patients who were evaluable for efficacy at the time of data cutoff. NE, not estimable; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD stable disease. Adapted from Mato A et al. ASH abstract 501. *Blood.* 2019;134(suppl 1).[8]

Among the patients with Waldenström macroglobulinemia, the ORR was 68%, including a PR rate of 47% and a minimal response rate of 21%. Among the patients with other NHL subtypes, the ORR was 22% in those with MZL, 24% in those with diffuse large B-cell lymphoma, 50% in those with follicular lymphoma, and 75% in those with Richter transformation. As of September 27, 2020, responses were ongoing in 77% (10/13) of the patients with Waldenström macroglobulinemia and 83% (5/6) of those with Richter transformation.

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Umbralisib, the Once Daily Dual Inhibitor of PI3Kδ and Casein Kinase-1ε, Demonstrates Clinical Activity in Patients With Relapsed or Refractory Indolent Non-Hodgkin Lymphoma: Results From the Phase 2 Global UNITY-NHL Trial

The international phase 2 UNITY-NHL trial evaluated umbralisib monotherapy in previously treated patients.[1] Eligible patients were adults with histologically confirmed MZL, follicular lymphoma, or SLL that had progressed after at least 2 prior lines of therapy. Umbralisib (800 mg) was administered daily until the patient developed disease progression, experienced unacceptable toxicity, or withdrew from the study. The first response assessment occurred at the end of cycle 3. The primary endpoint was the ORR, assessed by independent review. The study included 69 patients with MZL, 117 with follicular lymphoma, and 22 with SLL. The median age was 66 years (range, 29-88). All patients had received prior treatment with an anti-CD20 agent, 77% had stage 3/4 disease, and 34% had disease that was refractory to the most recent therapy. The median number of prior therapies was 2 (range, 1-10). The median follow-up was 27.7 months.

The ORR was 49.3% (16% CR rate) in patients with MZL, 45.3% (5% CR rate) in those with follicular lymphoma, and 50.0% (5% CR rate) in those with SLL.[1] Across the entire study population of 208 patients,

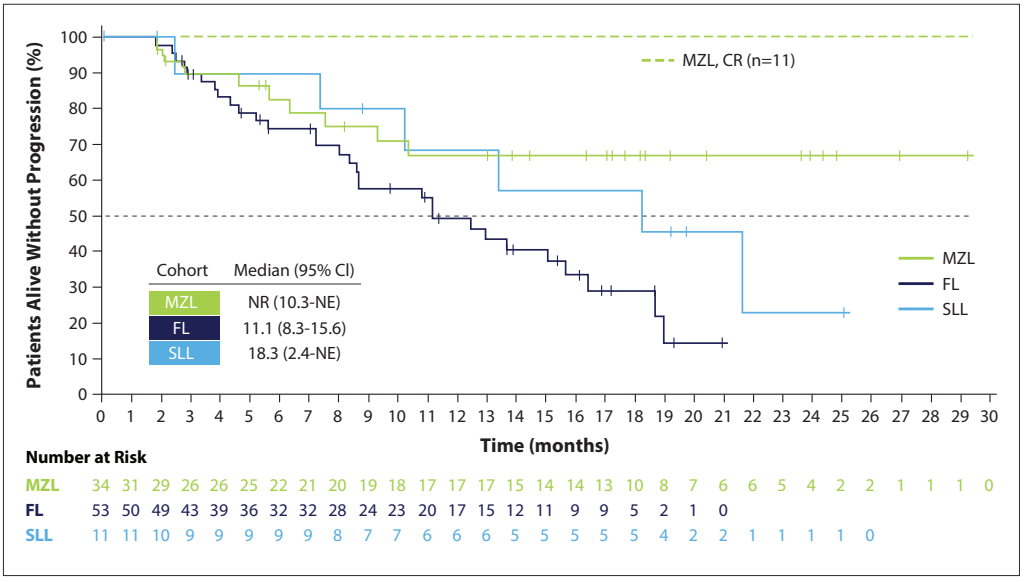

Figure 8. Duration of response in the phase 2 UNITY-NHL trial, which evaluated umbralisib monotherapy in patients with relapsed or refractory indolent non-Hodgkin lymphoma. CR, complete response; FL, follicular lymphoma; MZL, marginal zone lymphoma; NE, not estimable; NR, not reached; SLL, small lymphocytic lymphoma. Adapted from Zinzani P et al. ASH abstract 2934. *Blood.* 2020;136(suppl 1).[1]

umbralisib yielded an ORR of 47.1% and a disease control rate of 81.3%. Encouraging response rates were observed in patients who had received more than 3 prior lines of therapy and in patients with various MZL subtypes. The ORR in patients with follicular lymphoma was 57% for those with grade 1 disease, 45% for those with grade 2 disease, and 34% for those with grade 3A disease. The median decrease in the size of the index lesion was 90.6% in patients with MZL, 83.5% in those with follicular lymphoma, and 89.5% in those with SLL. The median DOR was not reached in the patients with MZL, 11.1 months in those with follicular lymphoma, and 18.3 months in those with SLL (Figure 8). The median PFS was not reached, 10.6 months, and 20.9 months in the 3 cohorts, respectively. Disease progression did not occur in any of the 11 patients with MZL who had a CR.

Umbralisib monotherapy was generally well tolerated in the overall study population.[1] The most common AEs of any grade were diarrhea (59.1%), nausea (39.4%), and fatigue (30.8%). The safety profile of umbralisib was distinct from that of other PI3K inhibitors. AEs of special interest to the investigators were generally uncommon. Transaminase elevations led 2.9% of patients to discontinue therapy, and another 2.9% of patients discontinued treatment after experiencing grade 3 diarrhea. Noninfectious colitis was documented in 4 patients; this event resolved in 3 of them, who continued treatment with umbralisib. Other AEs of special interest included grade 3/4 opportunistic infections (3.4%), grade 3/4 rash (1.9%), and grade 3/4 pneumonitis (1.0%).

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Clinical Activity of TG-1701, as Monotherapy and in Combination With Ublituximab and Umbralisib (U2), in Patients With B-Cell Malignancies

TG-1701 is a covalent inhibitor of BTK with better binding selectivity than ibrutinib.[1] The combination of U2 plus TG-1701 inhibited tumor growth in a mouse model harboring BTK-resistant xenografts.[2] A phase 1 study evaluated TG-1701, alone or in combination with U2, in patients with B-cell NHL or CLL.[3] Key objectives included characterizing the safety profile of TG-1701, determining the recommended phase 2 dose of TG-1701 as monotherapy or in combination with U2, and evaluating pharmacokinetics. Most patients had relapsed or refractory disease. Treatment-naive patients were enrolled if standard frontline chemotherapy was not an option.

Treatment with TG-1701 monotherapy was administered daily in

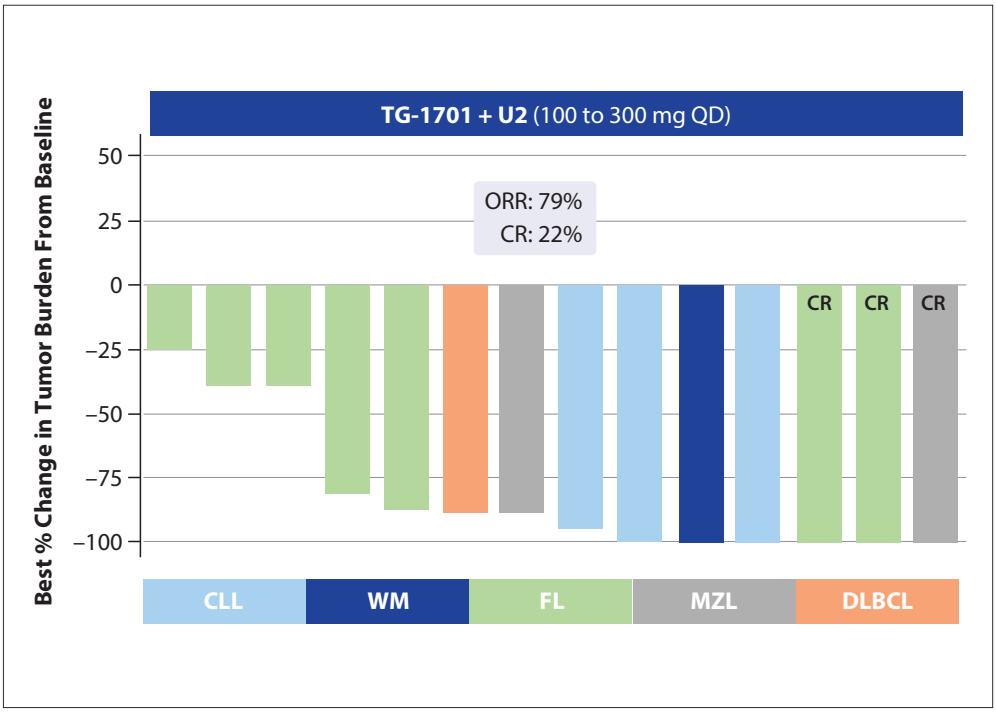

Figure 9. Efficacy of TG-1701 in combination with U2 in a phase 1 trial of patients with B-cell NHL or CLL requiring treatment. One patient with CLL and 2 patients with marginal zone lymphoma did not have target lesions. CLL, chronic lymphocytic leukemia; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; ORR, overall response rate; QD, daily; U2, umbralisib and ublituximab; WM, Waldenström macroglobulinemia. Adapted from Cheah CY et al. ASH abstract 1130. *Blood*. 2020;136(suppl 1).[3]

ABSTRACT SUMMARY Interim Analysis of ZUMA-12: A Phase 2 Study of Axicabtagene Ciloleucel as First-Line Therapy in Patients With High-Risk Large B-Cell Lymphoma

The phase 2 ZUMA-12 trial evaluated axicabtagene ciloleucel as part of first-line therapy in patients with high-risk large B-cell lymphoma (Abstract 405). After leukapheresis and optional bridging therapy, patients received conditioning chemotherapy followed by a single infusion of CAR T cells (2×10^6/kg). The median age of the 32 evaluable patients was 61 years (range, 23-86), and 88% of the patients had stage 3/4 disease. After a median follow-up of 9.3 months (range, 0.9-18.0), the ORR was 85% (23/27), with a CR rate of 75%. The median DOR, median PFS, and median OS were not reached. The most common AEs of grade 3 or higher that were related to axicabtagene ciloleucel included encephalopathy (16%), decreased neutrophil count (9%), and increased alanine transaminase (9%). Grade 3 cytokine release syndrome developed in 3 patients (9%); no grade 4/5 cases occurred. Grade 3/4 neurologic events occurred in 8 patients (25%).

doses ranging from 100 to 400 mg.[3] When TG-1701 was combined with the U2 regimen, the daily dose ranged from 100 to 400 mg. TG-1701 at a daily dose of 200 mg was given to 3 disease-specific cohorts: 20 patients with CLL, 20 with Waldenström macroglobulinemia, and 21 with mantle cell lymphoma; some of these patients were treatment-naive. Seventeen patients with CLL who received TG-1701 at a daily dose of 300 mg comprised another cohort. Intrapatient dose escalation was allowed.

In the monotherapy arm, after a median follow-up of 14 months (range, 1-25), the ORR was 52% (12/23).[3] Across the disease-specific cohorts treated with 200 mg/day of TG-1701, after a median follow-up of 7 months, the ORR was 95% in patients with CLL, 95% in patients with Waldenström macroglobulinemia, and 50% in those with mantle cell lymphoma. In 14 patients treated with the U2 regimen and escalating doses of TG-1701, after a median follow-up of 12 months, the ORR was 79%, with a 22% CR rate (Figure 9). Durable responses were observed with monotherapy and the combination.

The safety profile of TG-1701 monotherapy was manageable, with no grade 4 AEs.[3] The most common AEs of any grade were constipation (32%), respiratory tract infection (28%), and bruising (28%). The most common hematologic and laboratory abnormalities included neutropenia (24%), increased alanine transaminase (24%), and increased aspartate transaminase (20%). Among 16 patients treated with TG-1701 plus U2, the most common AEs diarrhea (44%), infusion-related reaction (38%), and bruising (38%). Grade 4 AEs were rare. The maximum tolerated dose was not reached in the monotherapy arm.

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Phase II Study of Pembrolizumab Plus GVD As Second-Line Therapy for Relapsed or Refractory Classical Hodgkin Lymphoma

Among patients with Hodgkin lymphoma, the goal of second-line therapy is to achieve a CR, according to positron emission tomography (PET), so patients can undergo autologous hematopoietic stem cell transplant (SCT). [1] Autologous SCT is most likely to cure Hodgkin lymphoma when the second-line regimen induces a CR.[2,3] However, second-line therapy fails to achieve a CR in up to half of patients.

A phase 2 trial evaluated pembrolizumab combined with gemcitabine, vinorelbine, and liposomal doxorubicin (GVD) in patients with relapsed or refractory Hodgkin lymphoma after first-line treatment.[4,5] Standard GVD was administered on days 1 and 8, and pembrolizumab (200 mg) was administered on day 1 of each 21-day cycle. Patients with a CR according to PET imaging after 2 cycles were eligible for autologous hematopoietic SCT. Responses were assessed again by PET after cycle 4. The primary endpoint was the CR rate (based on a Deauville score of 3) after 2 or 4 cycles of treatment.[6,7] The 39 enrolled patients were a median age of 38 years (range, 21-71), and 59% had stage 3/4 disease at baseline. A CR had not been achieved with first-line therapy in 41% of the patients, and 38% had experienced a relapse within 1 year of initial treatment. The most common first-line therapy was doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD; 69%), followed by brentuximab vedotin plus AVD (21%).

The median follow-up was 11.2 months (range, 0.95-24).[8] There were 37 evaluable patients. After treatment with pembrolizumab plus GVD for 2 cycles, a CR was reported in 34 patients (92%), and a PR occurred in 3 patients (85%). Among 7 patients who received an additional 2 cycles

of pembrolizumab plus GVD, 4 CRs were maintained, 1 new CR occurred, and 2 PRs were maintained. Overall, a CR was reported in 35 of 37 patients (95%). A total of 35 patients (95%) proceeded to autologous hematopoietic SCT, and 11 of these patients received brentuximab vedotin as part of consolidation treatment.[8] No patients developed progressive disease. The CR rate with pembrolizumab plus GVD was therefore higher than the 67% CR rate reported in the CheckMate 205 study, which evaluated nivolumab plus AVD in previously untreated patients.[9]

Treatment was generally well tolerated, with few high-grade AEs.[8] Grade 3 AEs included elevated transaminase levels in 3 patients (8%), and neutropenia in 3 patients (8%). An additional cohort is being enrolled to evaluate the same regimen followed by pembrolizumab maintenance therapy. Patients with a CR after 4 cycles of pembrolizumab plus GVD will receive up to 13 cycles of pembrolizumab.

ABSTRACT SUMMARY Ibrutinib Plus Venetoclax for First-Line Treatment of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: 1-Year Disease-Free Survival Results From the MRD Cohort of the Phase 2 CAPTIVATE Study

The international phase 2 CAPTIVATE (PCYC-1142) study evaluated ibrutinib (420 mg daily) plus venetoclax (ramped up to 400 mg daily) as first-line therapy in patients with CLL (Abstract 123). After 12 cycles of treatment, patients with confirmed undetectable MRD were randomly assigned in a double-blind manner to receive ibrutinib or placebo, and those with detectable MRD or unconfirmed undetectable MRD were randomly assigned to receive open-label ibrutinib monotherapy or ibrutinib plus venetoclax. The median age of the 164 patients was 58 years (range, 28-69), and the majority had at least 1 high-risk genetic feature. Among the patients with confirmed undetectable MRD before randomization, the rate of disease-free survival at 1 year after randomization was 100.0% in the ibrutinib group vs 95.3% in the placebo group (*P*=.1475). Across all 4 randomized cohorts, the 30-month PFS was between 95% and 100%. No new safety signals arose.

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Efficacy and Safety Results From ASCEMBL, a Multicenter, Open-Label, Phase 3 Study of Asciminib, a First-in-Class STAMP Inhibitor, vs Bosutinib in Patients With Chronic Myeloid Leukemia in Chronic Phase Previously Treated With ≥2 Tyrosine Kinase Inhibitors

Asciminib is a tyrosine kinase inhibitor (TKI) that binds to the myristoyl pocket of ABL1 and the BCR-ABL1 oncoprotein.[1-3] Owing to its unique binding site and mechanism of action, asciminib is predicted to bind with much less affinity to other tyrosine kinase proteins and therefore should have fewer off-target toxicities. Bosutinib binds to the ATP-binding site of ABL1, a mechanism shared by other approved TKIs, and is approved for the treatment of chronic-phase chronic myeloid leukemia.[4-7] Bosutinib has demonstrated efficacy in clinical trials of patients with chronic myeloid leukemia that had been treated with 2 or more TKIs before enrollment.

The phase 2 ASCEMBL study compared asciminib (40 mg twice daily) vs bosutinib (500 mg once daily) in adults with chronic-phase chronic myeloid leukemia.[8] Eligible patients had received prior treatment with at least 2 TKIs, and their most recent TKI had failed or was not tolerable. Patients who could not tolerate their most recent TKI were required to have evidence of the *BCR-ABL1*^{IS} transcript at screening. Patients were stratified by major cytogenetic response and then randomly assigned in a 2:1 ratio to receive asciminib or bosutinib. Patients with a bosutinib-resistant *T315I* or *V299L* mutation were excluded from

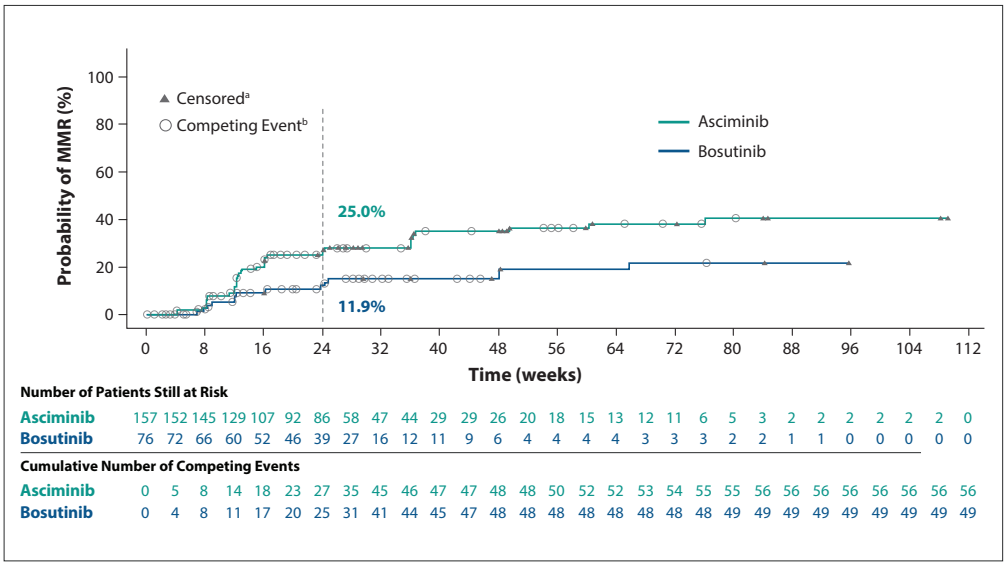

Figure 10. Probability of a major molecular response in a phase 3 study of asciminib vs bosutinib in patients with previously treated chronic myeloid leukemia in chronic phase. MMR, major molecular response. [a]Nonresponders were censored at their last molecular assessment date. [b]Discontinuation from treatment for any reason, without prior achievement of MMR, was considered to be a competing event. Adapted from Hochhaus A et al. ASH abstract LBA-4. *Blood.* 2020;136(suppl 1).[8]

enrollment. When bosutinib failed, patients were able to switch to the asciminib arm at the investigator's discretion. The primary endpoint was major molecular response (MMR) at 24 weeks during treatment in patients who did not meet any treatment failure criteria before 24 weeks.

The trial included 157 patients in the asciminib arm and 76 in the bosutinib arm.[8] The patients had a median age of 52 years (range, 19-83). The most common reasons for discontinuation of the most recent TKI therapy were lack of efficacy (64%) and lack of tolerability (35%). In the asciminib and bosutinib arms, 48% and 61% of patients, respectively, had received 3 or more prior TKI therapies. At cutoff, treatment was ongoing in 62% of patients in the asciminib arm vs 30% of patients in the bosutinib arm. Among the patients randomly assigned to the bosutinib arm, 29% had switched to the asciminib arm.

The median follow-up was 14.9 months after randomization.[8] The MMR rate at 24 weeks was 25.5% with asciminib vs 13.2% with bosutinib, a treatment difference of 12.2% (95% CI, 2.19%-22.3%; *P*=.029) after adjustment for major cytogenetic response status at baseline. The median duration of exposure was 43.4 weeks (range, 0.1-129.9) with asciminib vs 29.2 weeks (range, 1.0-117.0) with bosutinib. The cumulative incidence of MMR is shown in Figure 10. At 24 weeks, the MMR rate was better with asciminib vs bosutinib in most subgroups, including those defined by major cytogenetic response status, sex, outcome with prior TKI treatment, lines of therapy, and *BCR-ABL1* mutation status at baseline.[8] Asciminib was superior to bosutinib after adjustment for patient variables such as major cytogenetic response status (odds ratio, 2.35; 95% CI, 1.08-5.12).

After 12 weeks of study treatment, differences arose between the rates of MMR reported in the 2 arms. Among patients without a complete cytogenetic response at baseline, the complete cytogenetic response rate at 24 weeks was 40.8% with asciminib vs 24.2% with bosutinib (95% CI, 3.62%-31.0%) after adjustment for major cytogenetic response status at baseline.

More patients in the bosutinib arm discontinued treatment owing to an AE (21.1% vs 5.8%).[8] Dose interruptions were also more common in the bosutinib arm (60.5% vs 37.8%), as were AEs requiring additional therapy (88.2% vs 66.0%). Fatal AEs occurred in 1.3% of patients in each arm. AEs of any grade that were more common in the asciminib arm included thrombocytopenia (28.8%) and neutropenia (21.8%). The most common AEs of any grade in the bosutinib arm were observed less frequently in the asciminib arm. These AEs included diarrhea (71.1% vs 11.5%), nausea (46.1% vs 11.5%), and rash (23.7% vs 7.1%). Arterial occlusive events were more common in the asciminib arm (3.2% vs 1.3%).

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

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Many studies presented at the 62nd American Society of Hematology meeting provided important new data on leukemia and lymphoma. Here, I focus on a few abstracts that stand out, acknowledging that this list is not comprehensive.

Umbralisib and Ublituximab

Dr John Gribben presented results from the UNITY-CLL study of umbralisib and ublituximab, a regimen known as U2.[1] This notable abstract provided some of the first randomized, high-level, pivotal phase 2 data for this regimen. Umbralisib is an inhibitor of phosphatidylinositol 3-kinase delta (PI3Kδ) and casein kinase 1 epsilon (CK1ε). Previous data suggested that umbralisib is an efficacious PI3K inhibitor, with perhaps a better safety profile compared with other drugs in this class.[2] The trial enrolled patients with untreated or previously treated chronic lymphocytic leukemia (CLL). The primary outcome was progression-free survival (PFS). The study found a PFS benefit for the investigational U2 arm compared with chlorambucil plus obinutuzumab. The median PFS was 31.9 months vs 17.9 months, respectively (P<.0001). This outcome was unsurprising; many studies have shown that novel agents are superior to chlorambucil-based therapy. The take-home point was that the U2 regimen led to a median PFS of 38.5 months in previously untreated patients and 19.5 months in patients with relapsed/refractory disease. The rate of grade 3 diarrhea was approximately 12% in the U2 arm. Toxicity can be a concern with PI3K inhibitors, which have been associated with high rates in previous trials.[3] In the UNITY-CLL trial, few patients in the U2 arm discontinued treatment after developing diarrhea. The rest of the side effect profile suggested reasonable tolerability.

These data suggest that the combination of umbralisib and ublituximab is efficacious in patients with CLL. Cross-trial comparisons might suggest that the combination does not appear quite as strong as the Bruton tyrosine kinase (BTK) inhibitors.[4,5] Nonetheless, there is a potential role for ublituximab plus umbralisib in CLL, perhaps initially in patients with relapsed disease. The combination might be useful in the community setting, given that the agents are reasonably easy to administer compared with a drug such as venetoclax.

My colleagues and I presented data for a phase 1/2 study of U2 plus venetoclax in patients with relapsed or refractory CLL.[6] This study is being conducted at 3 different centers. More than 40 patients have been enrolled. The idea behind this triplet regimen is to administer therapy for a defined period, rather than subjecting patients to unending treatment. The regimen was evaluated in relapsed patients, given the widespread use of BTK inhibitors in the first-line setting.

Data on 43 patients treated to date were presented. After 12 cycles of therapy, all patients have responded. More than three-quarters of patients have undetectable minimal residual disease in the blood and bone marrow. These early results are promising. In the relapsed setting, this triplet regimen might compare well with regimens such as venetoclax plus rituximab, which was studied in the MURANO trial.[7]

Dr Pier Luigi Zinzani presented the initial results from the UNITY-NHL study, which evaluated umbralisib in patients with relapsed or refractory non-Hodgkin lymphoma (NHL).[8] UNITY-NHL is the pivotal registrational trial for umbralisib in indolent non-Hodgkin lymphoma. The trial enrolled 117 patients with follicular lymphoma, 69 with marginal zone lymphoma, and 22 with small lymphocytic lymphoma (SLL). In the follicular lymphoma cohort, the patients had received a median of 3 prior lines of therapy, and thus were heavily pretreated. Patients with marginal zone lymphoma had received a median of 2 prior therapies. In both of these cohorts, the overall response rate was a little less than 50%. These data are similar to those reported for the other PI3K inhibitors—idelalisib, duvelisib, and copanlisib. A difference is that more patients were able to continue treatment with umbralisib. Toxicity led to low rates of treatment discontinuation, supporting my previous comment that umbralisib appears to have a more favorable safety profile than the other PI3K inhibitors. The rate of grade 3 diarrhea was 10%, but only 2.9% of patients discontinued therapy owing to this event. These rates are similar to those reported in the UNITY-CLL study.[1] Although it will be necessary to monitor for PI3K inhibitor–related side effects during treatment with umbralisib, this drug appears to be well-tolerated overall. Umbralisib could therefore be useful in patients with relapsed/refractory follicular lymphoma, now that the agent is approved by the US Food and Drug Administration in this setting. No other PI3K inhibitors are approved for marginal zone lymphoma, so umbralisib could have an impact here as well.

LOXO-305

The phase 1/2 BRUIN trial is evaluating LOXO-305, an investigational, next-generation BTK inhibitor in patients with previously treated CLL/SLL or NHL. LOXO-305 binds in a noncovalent reversible fashion, which differs from the other BTK inhibitors (ibrutinib, acalabrutinib, and zanubrutinib). Dr Anthony Mato presented data for patients with CLL.[9] The patients with CLL were heavily pretreated. Approximately 86% had already received a covalent BTK inhibitor. When these patients develop resistance, more than half have identifiable BTK or PLCχ mutations.[10] Despite this resistance, the results were impressive, with an overall response rate of 63%. The median follow-up was relatively short, at 6 months. There were low rates of BTK-related side effects, including atrial fibrillation and grade 3 hemorrhage.

The waterfall plot suggests that most of the patients responded. With further follow-up, the response rate may continue to improve, and the duration of response could be significant. Many investigators will monitor this trial closely, given the promising results presented to date.

Dr Michael Wang presented data for LOXO-305 in patients with mantle cell lymphoma, Waldenström macroglobulinemia, and other types of NHL.[11] Most patients had mantle cell lymphoma. The patients were heavily pretreated. They had received a median of 3 prior therapies, including BTK inhibitors in 93%. The response rate was 52%, which is promising given the poor outcomes that patients can experience after treatment with other BTK inhibitors. Responses were ongoing in 83%. Again, the follow-up was short, at approximately 6 months. Among the patients with Waldenström macroglobulinemia, approximately two-thirds had received prior BTK inhibitors. The response rate in this cohort was 68%, with three-quarters of the responses ongoing. Notably, among 8 patients with Richter transformation, there were 6 responses. Based on the data from both of these abstracts, LOXO-305 has promising efficacy across the lymphoma subtypes studied.

Chimeric Antigen Receptor (CAR) T-Cell Therapy

Dr Caron Jacobson presented updated data for the ZUMA-5 study of axicabtagene ciloleucel in patients with relapsed/refractory indolent NHL, specifically follicular lymphoma and marginal zone lymphoma.[12] Earlier data were presented at the 2020 American Society of Clinical Oncology meeting.[13] Axicabtagene ciloleucel is a CAR T-cell product that is approved for the treatment of aggressive lymphomas, including diffuse large B-cell lymphoma and high-grade B-cell lymphoma. This presentation included efficacy data for 104 patients: 84 with follicular lymphoma and 20 with marginal zone lymphoma. The median follow-up was 18 months. These heavily pretreated patients had received a median of 2 prior lines of therapy. More than half had developed progressive disease within 24 months of treatment with an alkylating agent–based regimen. Approximately one-quarter of patients had undergone a prior autologous stem cell transplant.

Among the patients with follicular lymphoma, the complete response rate was 80%. At 1 year, 78% of the patients were without progression and still alive. The complete response rate was 60% among patients with marginal zone lymphoma, but these data are less mature. The side effect profile was mostly similar to that seen in studies of aggressive lymphomas.[14] The rates of grade 3 or higher cytokine release syndrome were somewhat lower, at 7%. Grade 3 or higher neurologic events occurred in 19%.

There are many therapeutic options for patients with follicular lymphoma and marginal zone lymphoma. Overall, these patients have an indolent disease course and therefore a relatively good prognosis. Additionally, CAR T-cell therapy will not be an option for all of these older patients. Nonetheless, axicabtagene ciloleucel—and CAR T-cell therapy in general—could have an impact in high-risk patients with these lymphoma histologies given the potential for long-term remissions. It is possible to envision the use of CAR T-cell therapy in patients with an early relapse or heavily pretreated disease.

The phase 2 ZUMA-12 trial evaluated axicabtagene ciloleucel as first-line therapy in patients with high-risk large B-cell lymphoma.[15] Axicabtagene ciloleucel is approved for the treatment of relapsed/refractory diffuse large B-cell lymphoma and other aggressive lymphoma histologies. Approximately 40% of these patients can develop durable remissions after receiving axicabtagene ciloleucel despite being heavily pretreated.[14] In ZUMA-12, the strategy investigated was to intervene early in patients who appeared to have an inferior response to first-line chemoimmunotherapy. The trial enrolled patients with high-grade B-cell lymphoma; more than half had double-hit or triple-hit lymphoma. Nearly three-quarters of patients had an International Prognostic Index (IPI) score of 3 or higher. All patients had received 2 cycles of induction therapy, which had not led to a complete remission. Their Deauville score was 4 or 5 after treatment with regimens such as rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

The primary endpoint was complete response. Dr Sattva Neelapu presented data for 27 evaluable patients.[15] The evaluable population included all treated patients with centrally confirmed disease (double-hit or triple-hit lymphoma) or an IPI score of 3 who had received at least 1×10^6 CAR T cells/kg and had at least 1 month of follow-up. Treatment with axicabtagene ciloleucel led to a complete response rate of 74%. At a short follow-up of 9 months, 70% of patients had an ongoing response. The toxicity profile was similar to that seen in ZUMA-1, the study that led to the approval of axicabtagene ciloleucel.[14]

The ZUMA-12 study requires additional follow-up. A subsequent

randomized study is also needed to determine if this strategy will improve patient survival in the first-line setting. However, in this population of patients without an adequate response to earlier therapy, a complete remission rate of 74% is promising. Clinicians are excited to see how these data mature over time.

Gemcitabine, Vinorelbine, and Doxorubicin Plus Pembrolizumab

Dr Alison Moskowitz presented results from a phase 2 study of gemcitabine, vinorelbine, and liposomal doxorubicin (GVD) plus pembrolizumab as second-line therapy for relapsed or refractory classical Hodgkin lymphoma.[16] Historically, patients with Hodgkin lymphoma have a relatively good prognosis. Among patients with advanced-stage disease, approximately 70% to 75% are cured with therapy such as doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD).[17] For the patients who relapse, the goal of a second-line regimen is to achieve a complete response or positron emission tomography (PET) negativity. Historically, treatment with chemotherapy has been associated with complete response rates of approximately 50% to 60%.[18,19] More recently, the addition of brentuximab vedotin increased these rates to 65% to 80%.[20,21]

In the study by Dr Moskowitz, GVD plus pembrolizumab could be given for up to 4 cycles.[16] The primary endpoint was PET negativity or complete response. Among the 39 enrolled patients, 41% were primary refractory, meaning they had not achieved a complete remission with ABVD-like therapy. The presentation provided data for 27 patients. After 2 cycles of therapy, 92% of the patients had achieved a complete response. There was 1 additional complete response with another 2 cycles of therapy, for an impressive complete response rate of 95%. Thirty-five of the patients underwent stem cell transplant. After a median follow-up of 11 months, no patients developed progressive disease.

This rate of complete response to a second-line regimen is unprecedented, albeit reported in a relatively small group of patients. It is a higher rate than that seen when programmed death 1 inhibitors were added to first-line therapy in the trial of doxorubicin, vinblastine, and dacarbazine plus nivolumab.[22] These data suggest that the combination of pembrolizumab with gemcitabine-based therapy is worth exploration. The investigators will evaluate this regimen further, perhaps considering a transplant-free approach. Given such a high rate of complete response, it may be possible for these patients to achieve a durable remission with this regimen followed by pembrolizumab maintenance for a year, and thereby avoid stem cell transplant.

Disclosure

Dr Barr has performed consulting for Pharmacyclics/AbbVie, Genentech, Gilead, Merck, TG Therapeutics, AstraZeneca, Celgene/BMS, MorphoSys, Janssen, BeiGene, Seattle Genetics, and Bayer. He has received research funding from AstraZeneca and TG Therapeutics.

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