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A SPECIAL MEETING REVIEW EDITION

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

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

Special Reporting on:

- The Combination of Umbralisib Plus Ublituximab Is Active in Patients With Relapsed or Refractory Marginal Zone Lymphoma: Results From the Phase 2 Global UNITY-NHL Trial
- SEQUOIA: Results of a Phase 3 Randomized Study of Zanubrutinib vs Bendamustine + Rituximab in Patients With Treatment-Naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
- Efficacy and Safety of Umbralisib, Ublituximab (U2), and U2 Plus Bendamustine in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma
- Tisagenlecleucel vs Standard of Care as Second-Line Therapy of Primary Refractory or Relapsed Aggressive B-Cell Non-Hodgkin Lymphoma: Analysis of the Phase III BELINDA Study
- A Phase 2 Study Evaluating the Addition of Ublituximab and Umbralisib (U2) to Ibrutinib in Patients With Chronic Lymphocytic Leukemia: A Minimal Residual Disease–Driven, Time-Limited Approach
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PLUS Meeting Abstract Summaries

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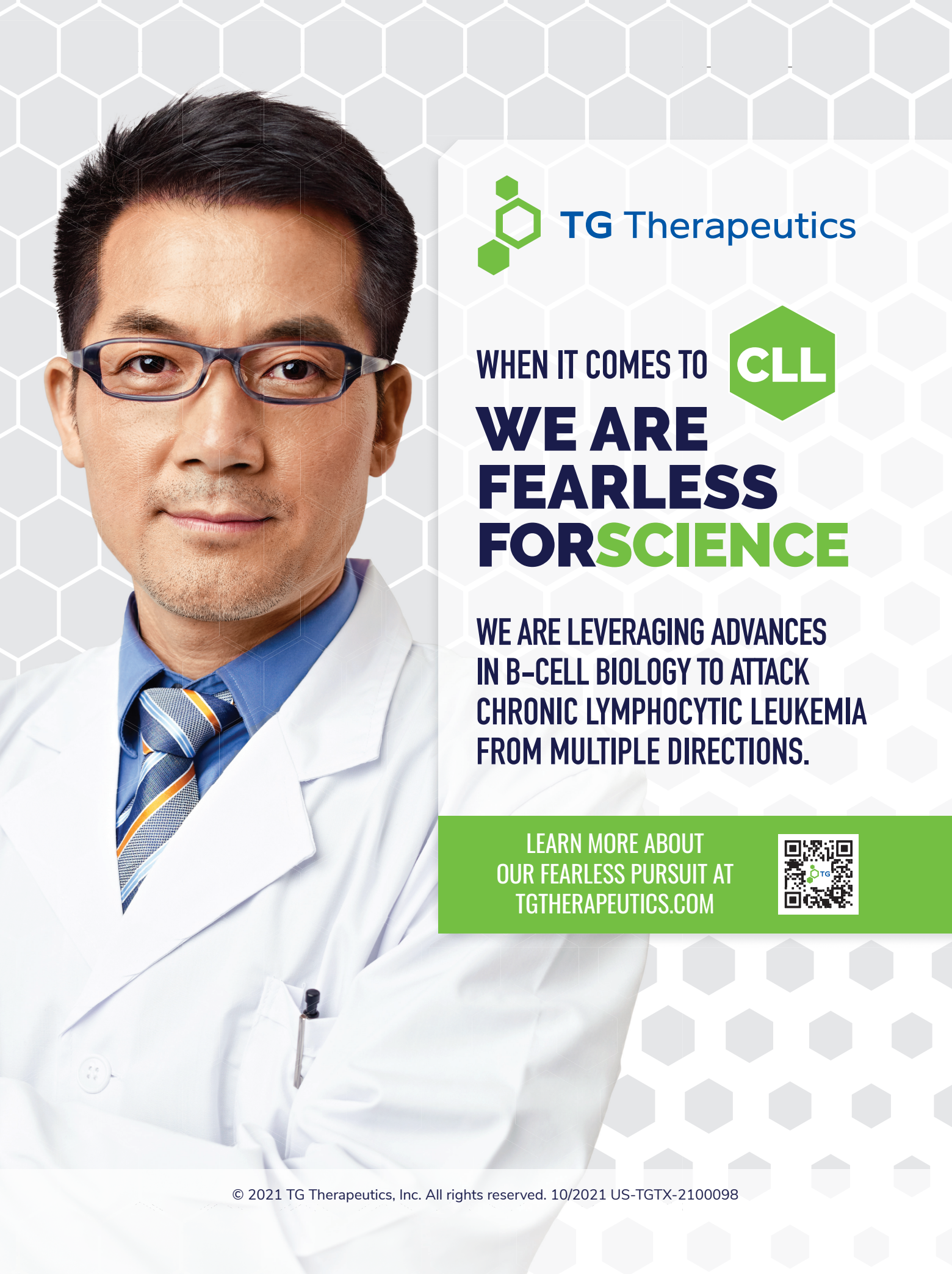

The Combination of Umbralisib Plus Ublituximab Is Active in Patients With Relapsed or Refractory Marginal Zone Lymphoma: Results From the Phase 2 Global UNITY-NHL Trial

A genetically engineered mouse model suggested that increased activity of the phosphoinositide 3-kinase-δ (PI3Kδ)/mammalian target of rapamycin pathway is sufficient for the development of marginal zone lymphoma (MZL).[1] Umbralisib is an inhibitor of both PI3Kδ and casein kinase-1ε that is approved for the treatment of patients with relapsed or refractory MZL or follicular lymphoma.[2] Ublituximab is a monoclonal antibody that targets a unique CD20 epitope and has been glycoengineered to enhance antibody-directed cellular cytotoxicity.[3] In a phase 1 study, the combination of umbralisib plus ublituximab (U2) was active and generally well tolerated among patients with relapsed or refractory non-Hodgkin lymphoma.[4]

The phase 2 UNITY-NHL trial evaluated the efficacy and safety of U2 in patients with previously treated non-Hodgkin lymphoma. At the 2021 American Society of Hematology annual meeting, Dr Julio Chavez presented results for the cohort of patients with relapsed/refractory MZL (n=72).[5] Eligible patients had histologically confirmed, relapsed or refractory MZL requiring treatment and had received at least 1 prior anti-CD20 therapy. Umbralisib (800 mg) was administered continuously until disease progression, unacceptable toxicity, or study withdrawal. Ublituximab (900 mg) was administered on days 1, 8, and 15 of cycle 1, on day 1 of cycles 2 through 6, and then on day 1 of every third cycle. The first response assessment occurred at the end of cycle 3. The primary endpoint was the objective response rate (ORR) as assessed by independent review.

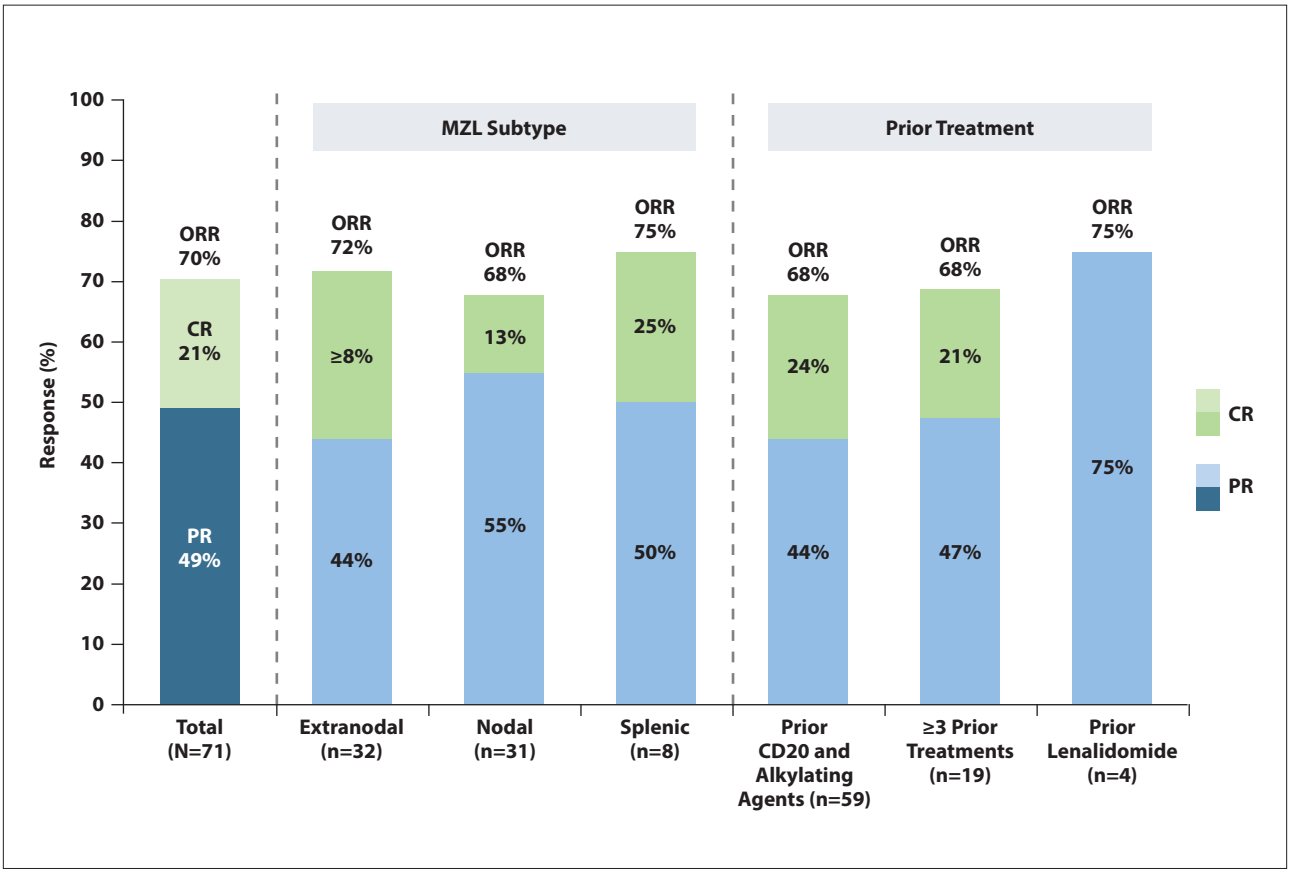

Figure 1. Responses among patients with previously treated marginal zone lymphoma who received umbralisib plus ublituximab in the phase 2 UNITY-NHL trial. CR, complete response; MZL, marginal zone lymphoma; ORR, overall response rate; PR, partial response. Adapted from Chavez JC et al. ASH abstract 45. *Blood*. 2021;138(suppl 1).[5]

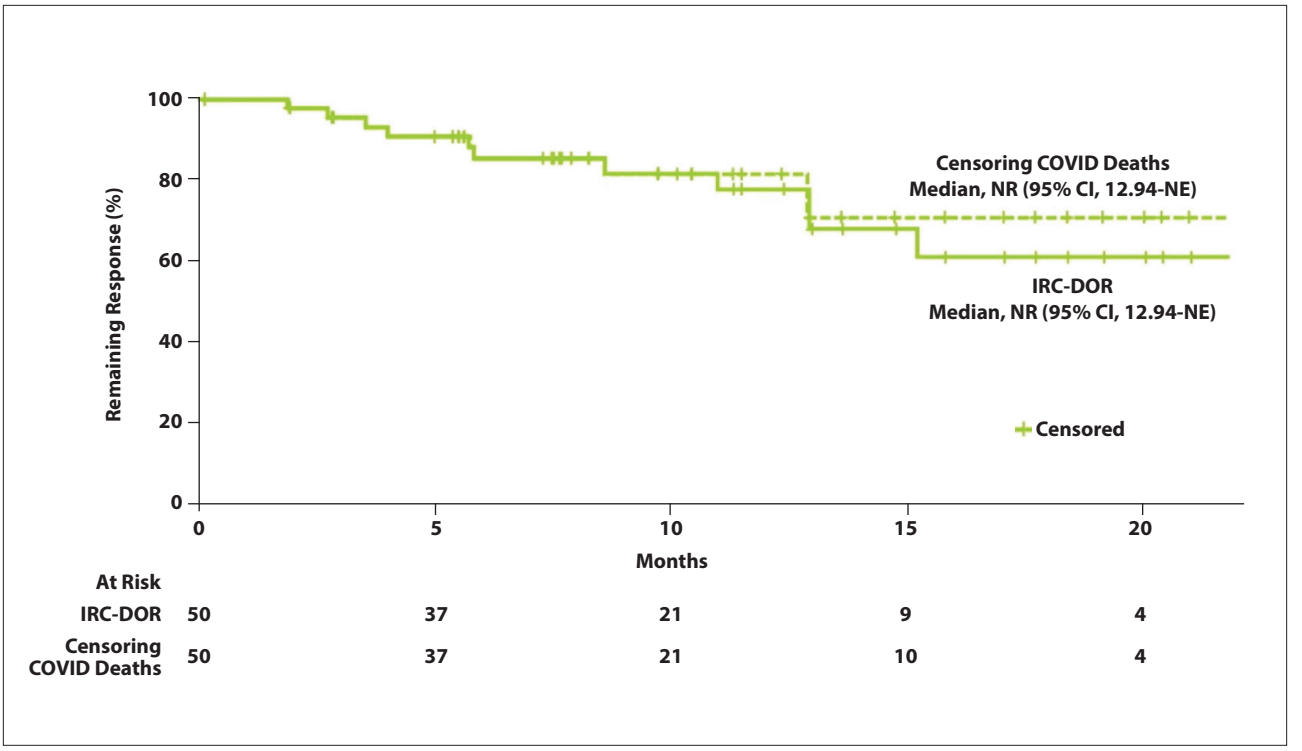

Figure 2. Duration of response among patients with previously treated marginal zone lymphoma who received umbralisib plus ublituximab in the phase 2 UNITY-NHL trial. DOR, duration of response; IRC, independent review committee; NE, not estimable; NR, not reached. Adapted from Chavez JC et al. ASH abstract 45. *Blood*. 2021;138(suppl 1).[5]

Patients in the MZL cohort were a median age of 70 years (range, 40-89). Seventy-four percent of patients had stage 3/4 disease. MZL subtypes included extranodal in 46%, nodal in 43%, and splenic in 11%. Patients had received a median of 2 prior therapies (range, 1-9). The median number of prior regimens containing anti-CD20 therapy was 2 (range, 1-7).

The independently assessed ORR was 70%, with a complete response (CR) rate of 21% (Figure 1). In 88% of patients in the MZL cohort, U2 therapy reduced the index lesion size. Responses were observed across the 3 MZL subtypes (ORR range, 68%-75%). The median duration of response was not reached (95% CI, 12.94 months to not estimable; Figure 2), and the median progression-free survival (PFS) was 17.61 months (95% CI, 15.47 months to not estimable).

After a median follow-up of 20 months (range, 9-29), treatment was ongoing in 47% of patients. The most common reasons for discontinuation of study therapy were disease progression (22%), adverse events (AEs; 10%), and death (10%). There were 6 deaths: 4 from COVID-19, 1 from septic shock, and 1 from pneumonia.

Events of special interest in the context of PI3K inhibition include diarrhea, neutropenia, elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), rash, noninfectious colitis, and pneumonitis. The most common AEs of any grade were diarrhea (49%), nausea (42%), and fatigue (38%). The most common grade 3/4 AEs were neutropenia (18%), increased levels of ALT or AST (15%), and diarrhea (13%). AEs that led to discontinuation of study treatment included diarrhea (2.8%), elevated levels of ALT/AST (2.8%), and increased neutropenia (1.4%).

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SEQUOIA: Results of a Phase 3 Randomized Study of Zanubrutinib vs Bendamustine + Rituximab in Patients With Treatment-Naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

The use of Bruton's tyrosine kinase (BTK) inhibitors has dramatically improved outcomes in patients with B-cell malignancies.[1] The second-generation BTK inhibitor zanubrutinib was designed to maximize BTK occupancy while limiting the toxicities associated with off-target binding. The open-label phase 3 SEQUOIA trial investigated zanubrutinib therapy in patients with treatment-naive chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).[2] The study enrolled patients who were unsuitable for treatment with standard immunochemotherapy or were ages 65 years or older. Treatment with CYP3A inhibitors or anticoagulants was allowed. Patients were screened for chromosome 17p deletion (del[17p]), and those without del(17p) were enrolled in cohort 1. Stratification factors included age, Binet stage, immunoglobulin heavy chain variable region (IGHV) status, and geographic region. Patients in cohort 1 were randomly assigned to receive zanubrutinib (160 mg, twice daily) in arm A or 6 cycles of bendamustine (90 mg/m^2, days 1 and 2) plus rituximab (375 mg/m^2 on day 1 of cycle 1, then 500 mg/m^2 on day 1 of cycles 2-6) in arm B. Patients in arm B were allowed to cross over into the zanubrutinib monotherapy arm. The primary endpoint for cohort 1 was PFS according to independent review.

The trial randomly assigned 479 patients without del(17p) into the 2 arms of cohort 1. The patient characteristics were well balanced between the 2 treatment arms. The patients' median age was 70 years (range, 66-75), 29% had Binet stage C disease, and 30% had bulky disease (≥5 cm). More than half of patients (52%-53%) had unmutated *IGHV*, approximately 18% had del(11q), and 6% had the *TP53* mutation.

The median 24-month rate of PFS was 85.5% with zanubrutinib vs 69.5% with bendamustine plus rituximab (hazard ratio [HR], 0.42; 95% CI, 0.27-0.63; *P*<.0001; Figure 3). The median PFS was superior with zanubrutinib vs bendamustine plus rituximab in nearly all patient subgroups,

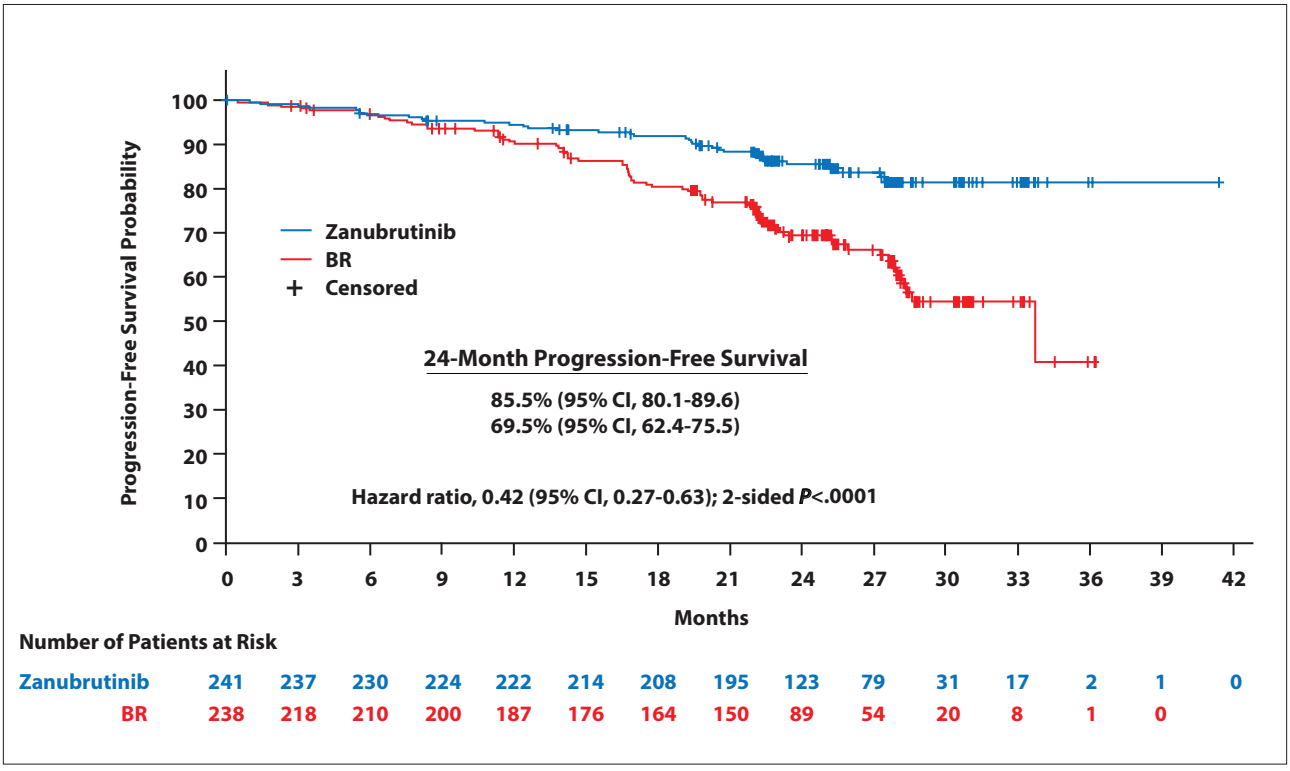

Figure 3. Median progression-free survival at 24 months among patients with treatment-naive chronic lymphocytic leukemia or small lymphocytic lymphoma treated with zanubrutinib or bendamustine plus rituximab in the phase 3 SEQUOIA trial. BR, bendamustine plus rituximab. Adapted from Tam CS et al. ASH abstract 396. *Blood*. 2021;138(suppl 1).[2]

including patients with unmutated *IGHV* (HR, 0.24; 95% CI, 0.13-0.43) and those with chromosome 11q deletion (del[11q]; HR, 0.21; 95% CI, 0.09-0.50).

Grade 3/4 AEs were reported in 52.5% of the zanubrutinib arm vs 79.7% of the bendamustine/rituximab arm. AEs required a dose reduction in 7.5% vs 37.4% of patients, respectively. A dose interruption or delay owing to an AE was reported in 46.3% vs 67.8%. AEs led to treatment discontinuation in 8.3% vs 13.7%. Rates of atrial fibrillation were similar in the 2 arms.

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Efficacy and Safety of Umbralisib, Ublituximab (U2), and U2 Plus Bendamustine in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma

The phase 2 UNITY-NHL trial enrolled 226 patients with diffuse large B-cell lymphoma (DLBCL). The patients were randomly assigned to treatment with umbralisib monotherapy (n=30), U2 (n=66), or U2 plus bendamustine (n=130).[1] The trial enrolled adults with histologically confirmed relapsed or refractory DLBCL who had already received or were ineligible to receive autologous stem cell transplant. There was no limit to the number of prior therapies, and prior treatment with bendamustine, anti-CD20 therapy, and chimeric antigen receptor (CAR) T-cell therapy was permitted. The primary endpoint was the ORR based on independent review.

Across the 3 arms, the patients' median ages ranged from 71 to 74 years. The proportion of patients with stage 3/4 disease ranged from 60% to 80%. The median number of prior therapies was 2 in each arm (range, 1-8). The proportion of patients who were refractory to their most recent prior therapy ranged from 43% to 65%, and 37% to 55% were refractory to prior anti-CD20 therapy. The median follow-up was 54 months in the umbralisib monotherapy arm, 50 months in the U2 arm, and 43 months in the U2-plus-bendamustine arm. More than 90% of patients in each arm discontinued therapy (range, 92%-100%). The most common reason for treatment discontinuation was progressive disease, reported in 61% of the U2 arm, 66% of the U2-plus-bendamustine arm, and 87% of the umbralisib arm.

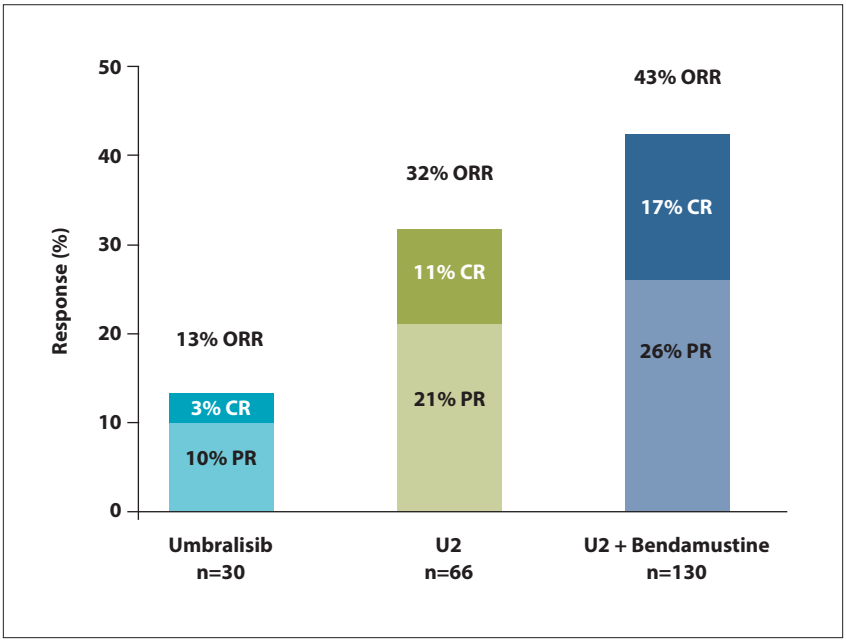

Figure 4. Responses among patients with relapsed or refractory DLBCL treated with umbralisib monotherapy, umbralisib and ublituximab, or umbralisib and ublituximab plus bendamustine in the phase 2 UNITY-NHL trial. CR, complete response; DLBCL, diffuse large B-cell lymphoma; ORR, overall response rate; PR, partial response; U2, umbralisib and ublituximab. Adapted from Burke JM et al. ASH abstract 527. *Blood*. 2021;138(suppl 1).[1]

The ORR was 13% with umbralisib monotherapy, 32% with U2, and 43% with U2 plus bendamustine (Figure 4). The CR rates were 3%, 11%, and 17%, respectively. The median PFS was 2 months (95% CI, 1.8-3.8 months) with umbralisib, 2 months (95% CI, 1.9-3.1 months) with U2, and 5 months (95% CI, 4.2-5.7 months) with U2 plus bendamustine. The median overall survival (OS) was 8 months (95% CI, 4.0-12.3 months) with umbralisib monotherapy, 9 months (95% CI, 4.8-29.9 months) with U2, and 10 months (95% CI, 7.0-13.4 months) with U2 plus bendamustine.

The median duration of treatment was 2.0 months with umbralisib monotherapy, 2.1 months with U2, and 4.5 months with U2 plus bendamustine

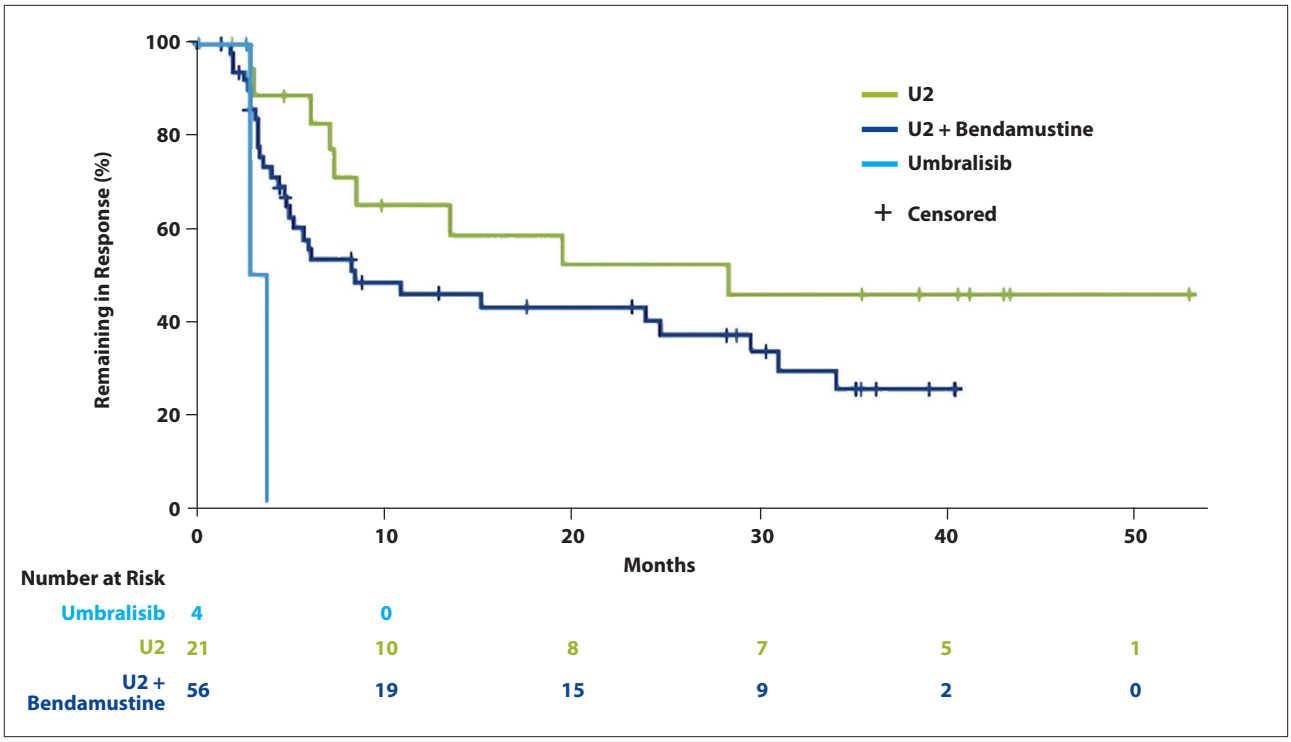

Figure 5. Duration of response among patients with relapsed or refractory DLBCL treated with umbralisib monotherapy, umbralisib and ublituximab, or umbralisib and ublituximab plus bendamustine in the phase 2 UNITY-NHL trial. DLBCL, diffuse large B-cell lymphoma; U2, umbralisib and ublituximab. Adapted from Burke JM et al. ASH abstract 527. *Blood*. 2021;138(suppl 1).[1]

(Figure 5). AEs led to treatment discontinuation among 10% of patients treated with umbralisib monotherapy, 11% of patients who received U2, and 7% of those who received U2 plus bendamustine. The rates of grade 3/4 AEs were 53%, 62%, and 80%, respectively, and the rates of serious AEs were 30%, 38%, and 49%. There were 2 deaths possibly related to AEs, 1 in the U2 arm and 1 in the U2-plus-bendamustine arm. Both of the deaths were attributed to pneumonia.

Rates of any-grade diarrhea were similar across the 3 arms (41%-48%). Grade 3/4 AEs related to PI3K inhibition included elevations in ALT/AST (range, 3%-12%) and diarrhea (range, 2%-7%). Grade 3/4 neutropenia occurred in 3% of patients in the umbralisib arm, 11% in the U2 arm, and 27% in the U2-plus-bendamustine arm.

Reference

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Tisagenlecleucel vs Standard of Care as Second-Line Therapy of Primary Refractory or Relapsed Aggressive B-Cell Non-Hodgkin Lymphoma: Analysis of the Phase III BELINDA Study

Tisagenlecleucel is an autologous CD19-directed CAR T-cell therapy approved for the treatment of DLBCL after 2 or more lines of therapy. The randomized phase 3 BELINDA trial compared tisagenlecleucel vs the second-line standard of care among patients with aggressive non-Hodgkin lymphoma who had developed relapsed or refractory disease within 12 months of first-line treatment.[1] The patients were eligible for autologous transplant, and they had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Stratification factors included region, duration of remission after the most recent treatment, and International Prognostic Index (IPI) score.

Patients in the tisagenlecleucel arm (arm A) were permitted to receive bridging therapy. After lymphodepletion chemotherapy, patients in the tisagenlecleucel arm received CAR T cells

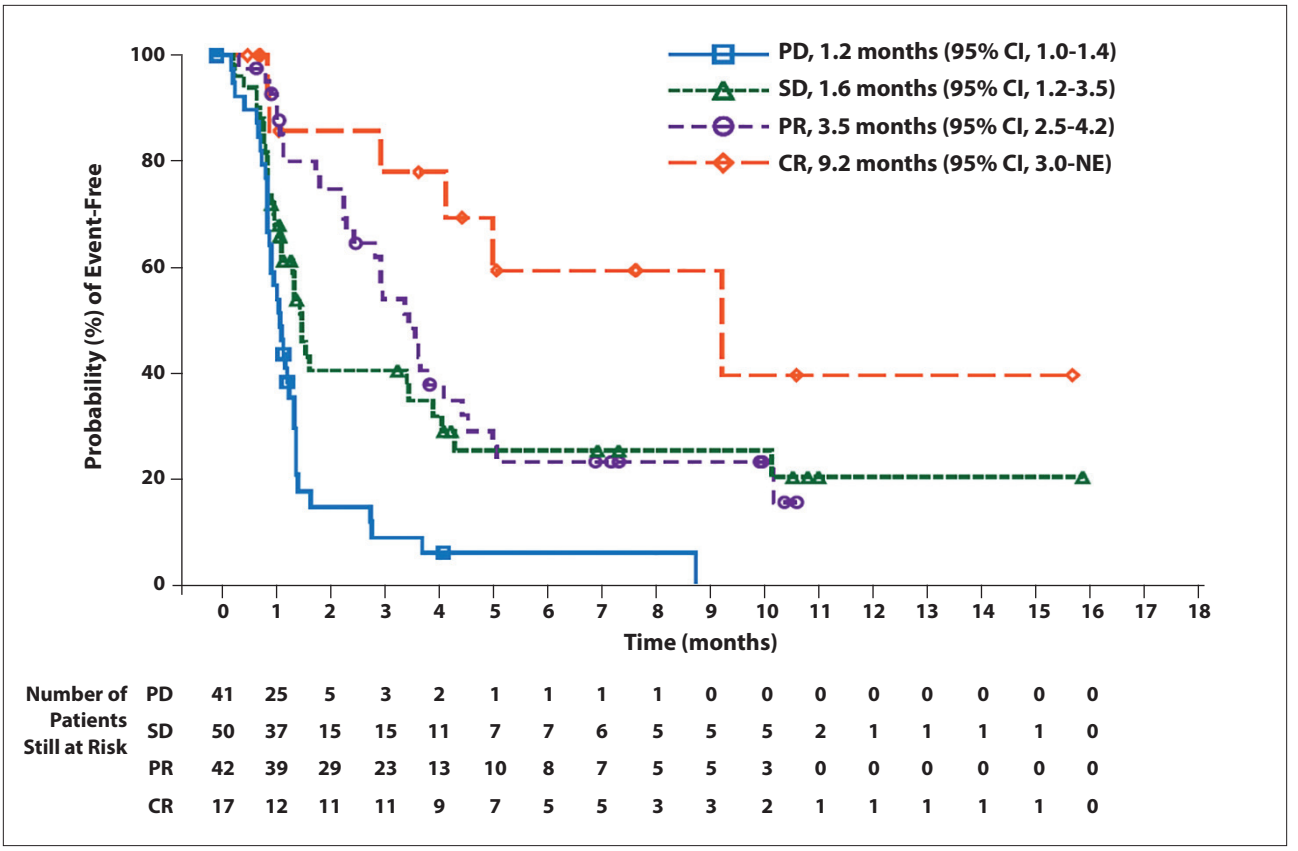

Figure 6. Event-free survival according to response before infusion of tisagenlecleucel among patients with relapsed/refractory aggressive non-Hodgkin lymphoma in the phase 3 BELINDA trial. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease. Adapted from Bishop MR et al. ASH abstract LBA6. *Blood*. 2021;138(suppl 1).[1]

in a single intravenous dose ranging from 0.6×10^8 to 6.0×10^8. Patients in the control arm (arm B) were first treated with the investigator's choice of 4 predefined chemotherapy regimens. Patients with a CR or partial response after treatment received high-dose chemotherapy and autologous stem cell transplant. The primary endpoint was event-free survival (EFS).

The BELINDA study randomly assigned 162 patients to receive tisagenlecleucel and 160 patients to receive the investigator's choice of therapy. In the 2 arms, 33% and 29% of patients, respectively, were ages 65 years or older. Refractory disease was reported in 66.0% and 66.9% of patients. In each arm, 18.5% and 20% of patients had relapsed within 6 months of their treatment prior to study entry. High-grade B-cell lymphoma with a high-risk mutation in *MYC* and *BCL2* and/or *BCL6* was reported in 20% of patients treated with tisagenlecleucel vs 12% of those treated with the standard of care. The IPI score was 2 or higher in 65% vs 58%, respectively.

The median EFS was 3.0 months in both arms (HR, 1.07; 95% CI, 0.82-1.40; *P*=.69). In the tisagenlecleucel arm, 6 patients had stable or progressive disease that was considered an EFS event, but subsequently responded to therapy. The ORR was 46.3% in the tisagenlecleucel arm vs 42.5% in the standard-of-care arm. The median PFS was 9.2 months in patients with a CR prior to receiving the tisagenlecleucel infusion vs 1.2 months in those with progressive disease (Figure 6), suggesting that strategies to mitigate disease progression before the infusion of tisagenlecleucel may improve outcomes.

No new safety signals were raised in either arm. Serious treatment-related grade 3 or higher AEs occurred in 27.2% of the tisagenlecleucel arm vs 31.3% of the standard-of-care arm. The most common grade 3 or higher AEs in the tisagenlecleucel arm were neutropenia (40.1% vs 39.4% in the control arm), anemia (33.3% vs 57.5%), and thrombocytopenia (32.1% vs 47.5%). In the tisagenlecleucel arm, grade 3 or higher cytokine-release syndrome occurred in 4.9% of patients, and grade 3 or higher neurologic events occurred in 1.9% of patients.

Reference

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A Phase 2 Study Evaluating the Addition of Ublituximab and Umbralisib (U2) to Ibrutinib in Patients With Chronic Lymphocytic Leukemia: A Minimal Residual Disease–Driven, Time-Limited Approach

High rates of overall response and durable response have been seen in patients with CLL treated with continuous administration of newer agents.[1] Among patients with favorable outcomes, a limited duration of treatment could prevent overtreatment and reduce cumulative toxicity, while preventing resistance. A phase 2 study of patients with CLL investigated the addition of U2 to ibrutinib based on minimal residual disease (MRD) status.[2] Patients who had received ibrutinib monotherapy for at least 6 months as any line of therapy and who had detectable MRD were enrolled to receive "add-on" U2 therapy. MRD was assessed in the peripheral blood every 3 treatment cycles. Patients with undetectable MRD were assessed again after 28 days. Those with undetectable MRD in 2 sequential tests underwent observation without further treatment. If patients were free of disease progression for 6 months but then relapsed, retreatment with ibrutinib plus U2 was initiated. The rate of undetectable MRD was the primary endpoint, with a target rate of 25% converting from detectable to undetectable MRD.

The analysis provided data for 28 patients evaluable for safety and 27 patients evaluable for efficacy. The patients' median age was 64 years (range, 48-81). Prior to the addition of U2, the median duration of ibrutinib therapy was 21 months (range, 7-67 months). The majority of patients (68%) had received ibrutinib monotherapy as first-line treatment. Two-thirds of patients had unmutated *IGHV*, 21% had del(11q), and 7% had del(17p). Two patients discontinued all study treatment after developing rash and/or arthralgia. Both of these patients had undetectable MRD at the time of treatment discontinuation. One patient died from complications of COVID-19 103 days after discontinuation of U2 therapy. This patient was excluded from the efficacy analysis.

With the addition of U2 therapy to ibrutinib, 77% of patients achieved undetectable MRD. The median time to undetectable MRD was 7.4 months

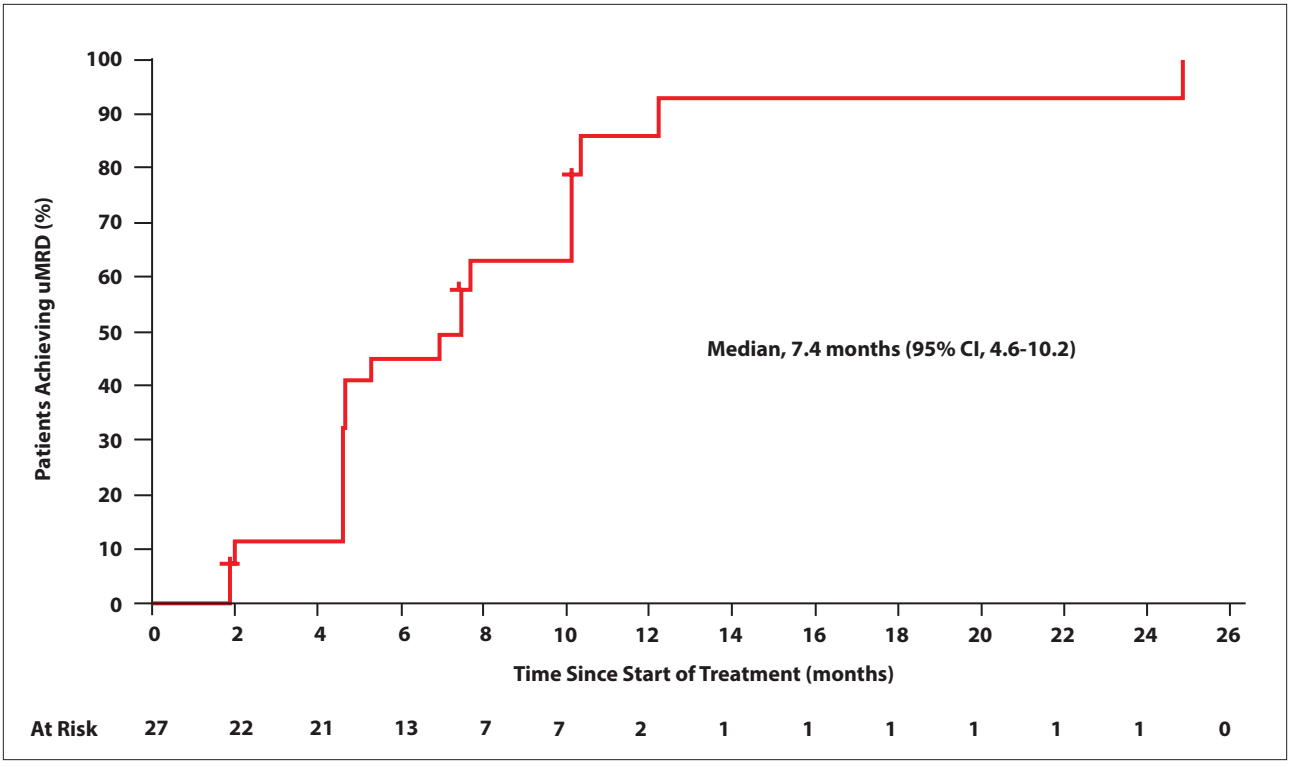

Figure 7. Rates of uMRD in patients with chronic lymphocytic leukemia who received ublituximab, umbralisib, and ibrutinib in a phase 2 trial. uMRD, undetectable minimal residual disease. Adapted from Roeker LE et al. ASH abstract 395. *Blood*. 2021;138(suppl 1).[2]

(95% CI, 4.6-10.2 months; Figure 7).

Grade 3/4 AEs included hypertension in 7%, ALT/AST elevations in 4%, COVID-19 in 4%, and diarrhea in 4%. Two patients discontinued all treatment owing to AEs that consisted of rash in one case and rash plus arthralgias in the other.

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

A randomized phase 3 trial evaluated rituximab, high-dose cytarabine, and dexamethasone (R-HAD) with or without bortezomib, in elderly MCL patients who had relapsed or progressed after 1 to 3 prior lines of therapy (Abstract 383). The study was closed early owing to poor recruitment. The trial enrolled 128 patients, whose median age was 70 years. Most patients (82%) had Ann Arbor stage IV disease. After a median follow-up of 41.3 months, the primary endpoint of time to treatment failure in the intention-to-treat population was 12.0 months with bortezomib plus R-HAD vs 2.6 months with R-HAD alone (HR, 0.68; *P*=.045, corrected for sequential design). The CR rates were significantly increased in the bortezomib arm compared with the R-HAD arm (28% vs 12%; *P*=.043). The most common serious AEs in the bortezomib arm were infections (26%) and fever (18%).

The POLARIX Study: Polatuzumab Vedotin With Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone vs Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Therapy in Patients With Previously Untreated Diffuse Large B-Cell Lymphoma

For more than 2 decades, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) has been the standard of care for first-line treatment of patients with DLBCL.[1,2] However, up to 40% of patients relapse after treatment or are refractory to this regimen. Polatuzumab vedotin is an antibody-drug conjugate directed at CD79b, which is universally expressed on DLBCL cells. In a phase 2 trial of patients with treatment-naive DLBCL, polatuzumab vedotin was combined with R-CHP, a regimen that omits vincristine to avoid the associated neurotoxicities.[3] The novel drug combination demonstrated efficacy and acceptable tolerability.

The international, double-blind phase 3 POLARIX study compared polatuzumab vedotin plus R-CHP vs standard R-CHOP among previously untreated patients with intermediate- or high-risk DLBCL.[4,5] Patients in the R-CHOP arm received a placebo in place of polatuzumab vedotin. Both regimens were administered in 21-day cycles for up to 6 cycles, followed by 2 cycles of rituximab monotherapy. The patients were ages 18 to 80 years, with an IPI score of 2 to 5 and an ECOG performance status of 0 to 2. Stratification factors included the IPI score, bulky disease, and geographic region. The primary endpoint was investigator-assessed PFS.

The trial randomly assigned 440 patients to receive polatuzumab vedotin plus R-CHP and 439 to receive R-CHOP. The baseline characteristics were well balanced between the 2 arms. The patients' median age was 65.5 years (range, 19-80). Bulky disease (≥7.5 cm) was present in 44% of patients, 88% to 89% of patients had Ann Arbor stage III/IV disease, and 48% to 49% of patients had 2 or more extranodal sites. Sixty-two percent of patients had an IPI score of 3 to 5, and approximately 40% had expression of both MYC and BCL2.

After a median follow-up of 28.2 months, the 24-month PFS was 76.7% with polatuzumab vedotin plus R-CHP vs 70.2% with R-CHOP (HR, 0.73; 95% CI, 0.57-0.95; *P*<.02; Figure 8). The median EFS was also superior with polatuzumab vedotin vs R-CHOP (HR, 0.75; 95% CI, 0.58-0.96; *P*=.02). There was no difference in OS (HR, 0.94; 95% CI, 0.65-1.37; *P*=.75).

The safety profile of polatuzumab vedotin plus R-CHP was similar to that of R-CHOP in terms of grade 3/4 AEs (58% in both arms), serious AEs (34% vs 31%), AEs leading to discontinuation of any study drug (6.2% vs 6.6%), and AEs leading to discontinuation of polatuzumab vedotin or vincristine (4.4% vs 5.0%). AEs led to dose reductions in 9.2% of patients treated with polatuzumab vedotin plus R-CHP vs 13.0% of those treated with R-CHOP.

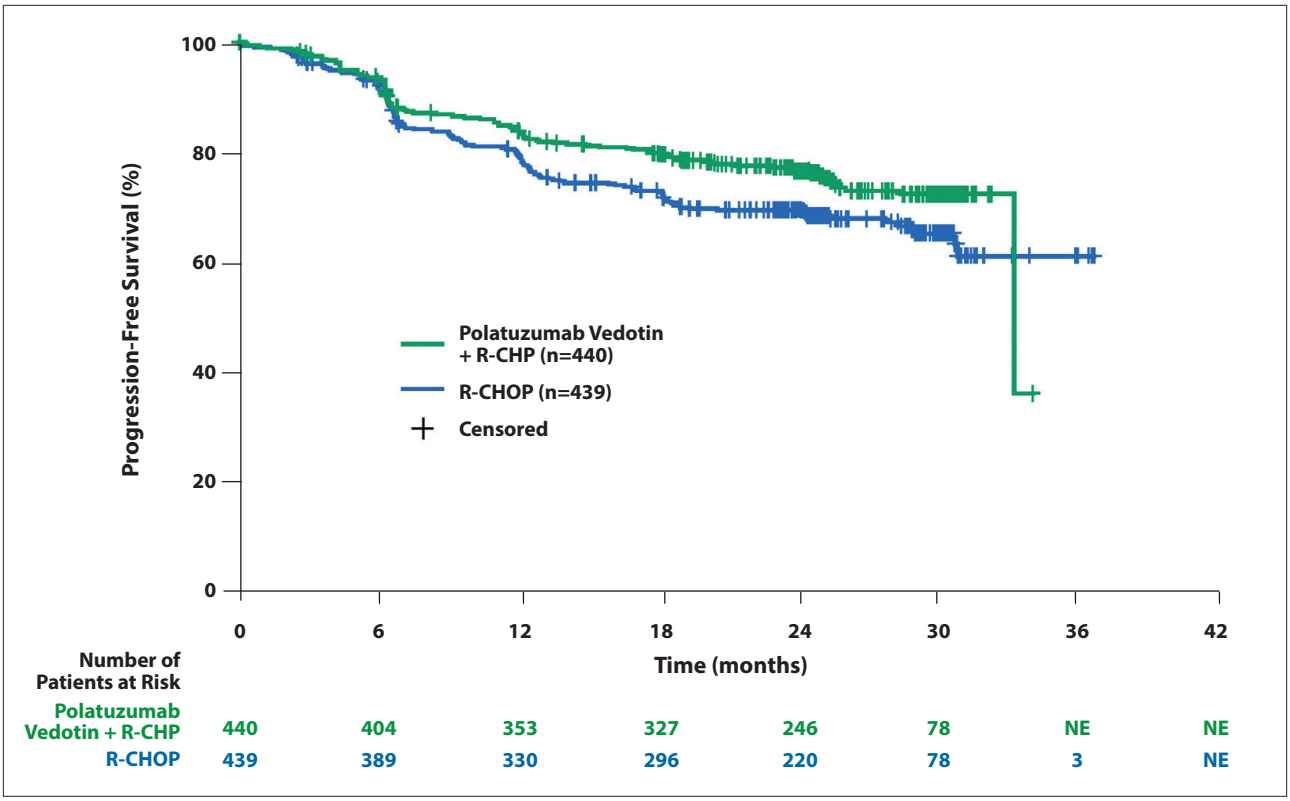

Figure 8. Progression-free survival at 24 months among patients with previously untreated intermediate- or high-risk DLBCL who received polatuzumab vedotin plus R-CHP or standard R-CHOP in the phase 3 POLARIX trial. DLBCL, diffuse large B-cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHP, rituximab, cyclophosphamide, doxorubicin, and prednisone. Adapted from Tilly H et al. ASH abstract LBA-1. *Blood*. 2021;138(suppl 1).[4]

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The Selective Bruton Tyrosine Kinase Inhibitor TG-1701 as Monotherapy and in Combination With Ublituximab and Umbralisib (U2) in Patients With B-Cell Malignancies

A phase 1 study evaluated the irreversible, selective, novel BTK inhibitor TG-1701, with or without U2.[1] The trial enrolled patients with CLL, Waldenström macroglobulinemia, follicular lymphoma, or mantle cell lymphoma (MCL).[1] TG-1701 monotherapy was administered at a daily dose of 200 mg to 300 mg. When combined with U2, the TG-1701 dose ranged from 100 mg/day to 300 mg/day. In the TG-1701/U2 dose-escalation cohort, patients who received TG-1701 at 300 mg/day received umbralisib at a daily dose of 600 mg. In the TG-1701/U2 dose-expansion cohort, patients received TG-1701 at 100 mg/day, and the dose of umbralisib was reduced to 400 mg/day. All patients were treated until disease progression, unacceptable toxicity, or withdrawal from the study.

The trial enrolled 135 patients across 4 treatment arms, which consisted of TG-1701 at 200 mg (arm A), TG-1701 at 300 mg (arm B), TG-1701 at 100 mg to 300 mg plus U2 (arm C), and TG-1701 at 100 mg plus U2 (arm D). The median follow-up ranged from 3 months in arm D to

Table 1. Grade 3 or Higher Hematologic AEs From a Phase 1 Study of TG-1701 With or Without U2

	Arm A (%)	Arm B (%)	Arm C (%)	Arm D (%)
Neutropenia	8	20	19	16
ALT increase	3	5	19	5
AST increase	2	5	14	5
Anemia	5	0	0	0

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; U2, umbralisib plus ublituximab. Adapted from Cheah CY et al. ASH abstract 1549. *Blood*. 2021;138(suppl 1).[1]

20 months in arm C.

The changes in tumor burden are shown in Figure 9. Among 20 patients with CLL treated with TG-1701 at 200 mg/day in arm A, the ORR was 95% after a median follow-up of 20 months (range, 17-23.7 months). One patient died of COVID-19, and 1 patient developed disease progression. Among 19 CLL patients treated with TG-1701 at 300 mg/day in arm B, the ORR was 100% after a median follow-up of 13.8 months (range, 10.3-15.9 months). One patient died from COVID-19. No patient developed disease progression. Twenty-one patients with MCL were treated in arm A. After a median follow-up of 17.2 months (range, 12.4-22 months), these patients had an ORR of 71% and demonstrated a median PFS of 15.6 months (95% CI, 3.7 months to not estimable). Arms C and D included patients with CLL, MCL, follicular lymphoma, and Waldenström macroglobulinemia. In arm C, after a median follow-up of 20.2 months (range, 2.6-29.6 months), the ORR was 86% (18/21), with a CR rate of 19% (4/21). In arm D, after a median follow-up of 2.7 months (range, 0.2-5.5 months), the ORR was 83% (15/18), with a CR rate of 6% (1/18).

The proportion of patients who discontinued study treatment was 31% in arm A, 10% in arm B, 14% in arm C, and 0% in arm D. No dose-limiting toxicities were observed, and AEs were generally manageable. The most common nonhematologic AEs of grade 3 or higher were diarrhea (10%), nausea (5%), and infusion-related reaction (5%), all of which occurred in arm 3. Hematologic AEs included neutropenia and elevations in ALT and AST (Table 1). One patient in arm A developed atrial fibrillation of grade 3 or higher. Hypertension of grade 3 or higher was observed in 5% of patients in arm A, arm B, and arm C, with no cases in arm D.

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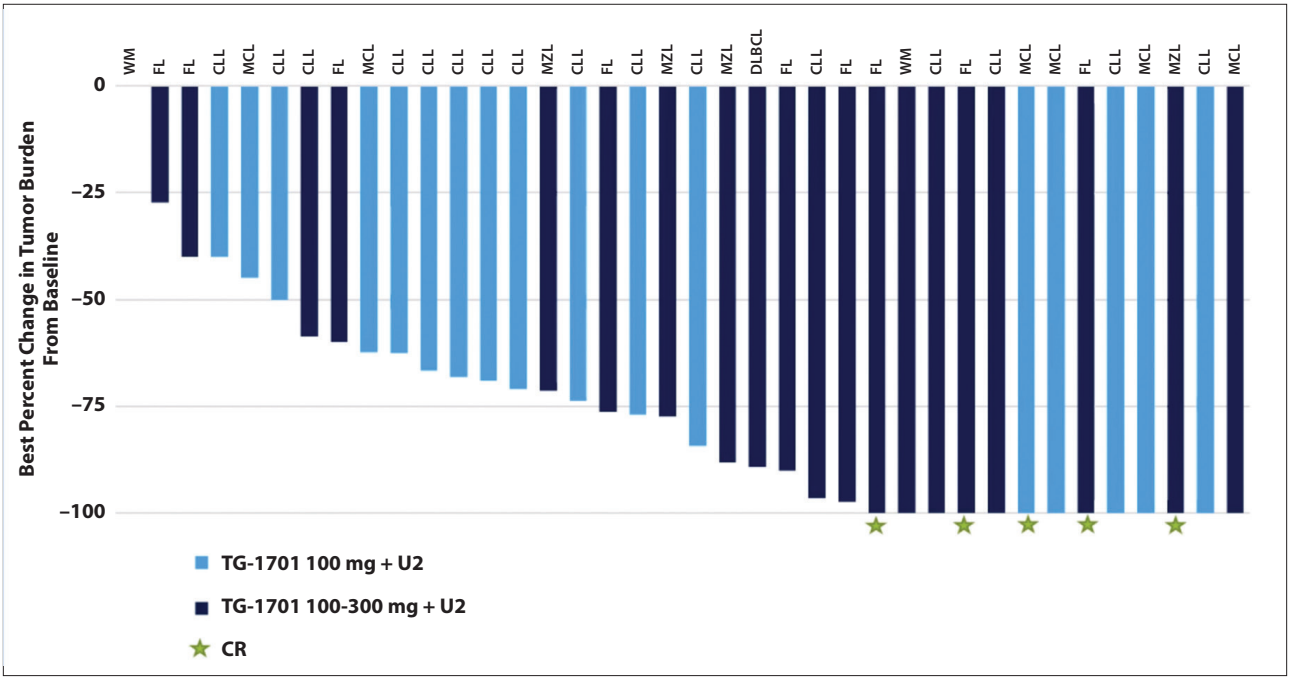

Figure 9. Changes in tumor burden from baseline among patients with B-cell malignancies who received TG-1701 in combination with ublituximab and umbralisib in a phase 1 study. CLL, chronic lymphocytic leukemia; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL mantle cell lymphoma; MZL, marginal zone lymphoma; U2, umbralisib and ublituximab; WM, Waldenström macroglobulinemia. Adapted from Cheah CY et al. ASH abstract 1549. *Blood*. 2021;138(suppl 1).[1]

Favorable Outcomes for Patients Treated With U2 With Comorbidities or Concomitant Medications: A Retrospective Analysis of the UNITY-CLL Phase 3 Trial

To improve outcomes among patients with CLL who have comorbidities, chemotherapy-free regimens that do not exacerbate these comorbidities or interact with medications are needed. The phase 3 UNITY-CLL study compared U2 vs obinutuzumab plus chlorambucil in patients with CLL who were treatment-naive or who had received prior therapy and required treatment per criteria from the International Workshop on CLL.[1-3] A retrospective analysis evaluated efficacy and safety among patients from the UNITY-CLL trial who had a preexisting comorbidity or who were receiving a medication that could preclude treatment with a BTK inhibitor.[1] Among 210 patients originally included in the U2 arm, 131 patients (64%) met these criteria. Comorbidities included cardiovascular dysfunction (n=50), arthritis/arthralgia (n=46), hypertension with use of 2 antihypertensive agents (n=45), arrhythmia (n=31), and history of hemorrhage (n=5). The most commonly used concomitant medications were proton pump inhibitors (n=37), anticoagulants (n=9), and a CYP3A4 moderate inhibitor (n=7).

The baseline characteristics were similar in the U2 cohort of 210 patients (cohort A), the 79 patients with no comorbidities or concomitant medications (cohort B), and the 131 patients with any comorbidity or concomitant medication (cohort C). Across the 3 cohorts, 56% to 57% of patients were treatment-naive, and high-risk features included del(11q) in 22% to 23%, del(17p) in 6% to 11%, and unmutated *IGHV* in 51% to 56%. Rates of treatment discontinuation were similar in the 3 cohorts (60%-63%).

An independent review reported an ORR of 83% in the overall population, 76% in patients without comorbidities or use of concomitant medications, and 88% in patients with comorbidities or use of concomitant

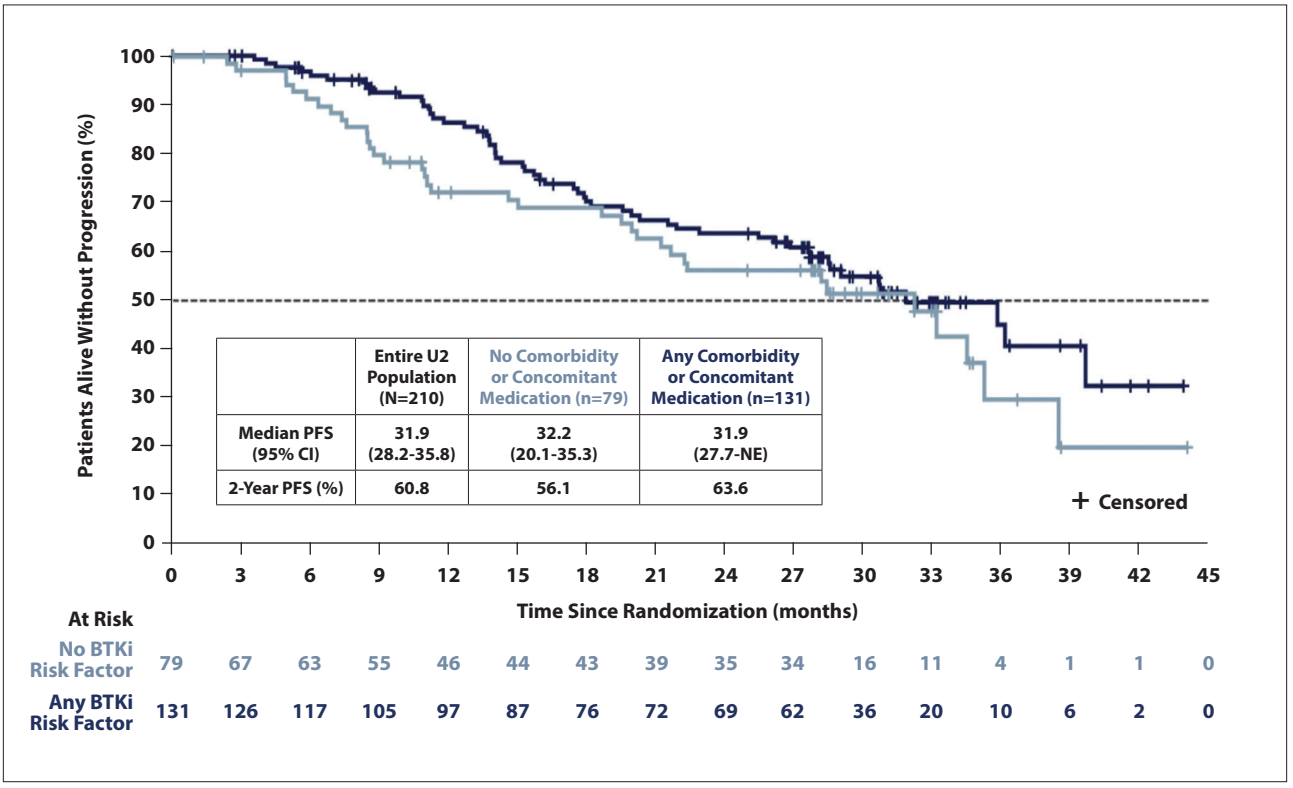

Figure 10. Progression-free survival among patients treated with umbralisib plus ublituximab in the phase 3 UNITY-CLL in a retrospective analysis that focused on those who had a preexisting comorbidity or who were receiving a medication that could preclude treatment with a BTK inhibitor. BTKi, Bruton's tyrosine kinase inhibitor; NE, not estimable; PFS, progression-free survival; U2, umbralisib and ublituximab. Adapted from Pinilla-Ibarz J et al. ASH abstract 3748. *Blood*. 2021;138(suppl 1).[1]

medications. The CR rate was 5% in each group. No difference was observed in PFS across the 3 cohorts (Figure 10).

The 3 groups had similar safety profiles. Serious AEs occurred in 46% of the entire U2 population, 39% of patients without comorbidities or concomitant medications, and 50% of those with comorbidities or concomitant medications. Grade 3 or higher AEs occurred in 82%, 80%, and 83%, respectively. Rates of PI3K-related AEs were also similar among the 3 groups.

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Efficacy and Safety of Ublituximab in Combination With Umbralisib (U2) in Patients With Chronic Lymphocytic Leukemia by Treatment Status: A Subanalysis of the Phase 3 UNITY-CLL Study

A post hoc analysis of the UNITY-CLL trial evaluated outcomes with U2 according to whether the patient had received prior treatment.[1,2] The U2 arm of the UNITY-CLL trial included 119 patients who were treatment-naive and 91 who were previously treated. The median age of patients in the treatment-naive group was 68 years (range, 39-88 years). High-risk genetic features included del(11q) in 21%, del(17p) in 5%, and unmutated *IGHV* in 51%. The median age of patients in the previously treated group was 65 years (range, 43-87 years). High-risk genetic features included del(11q) in 24%, del(17p) in 14%, and unmutated

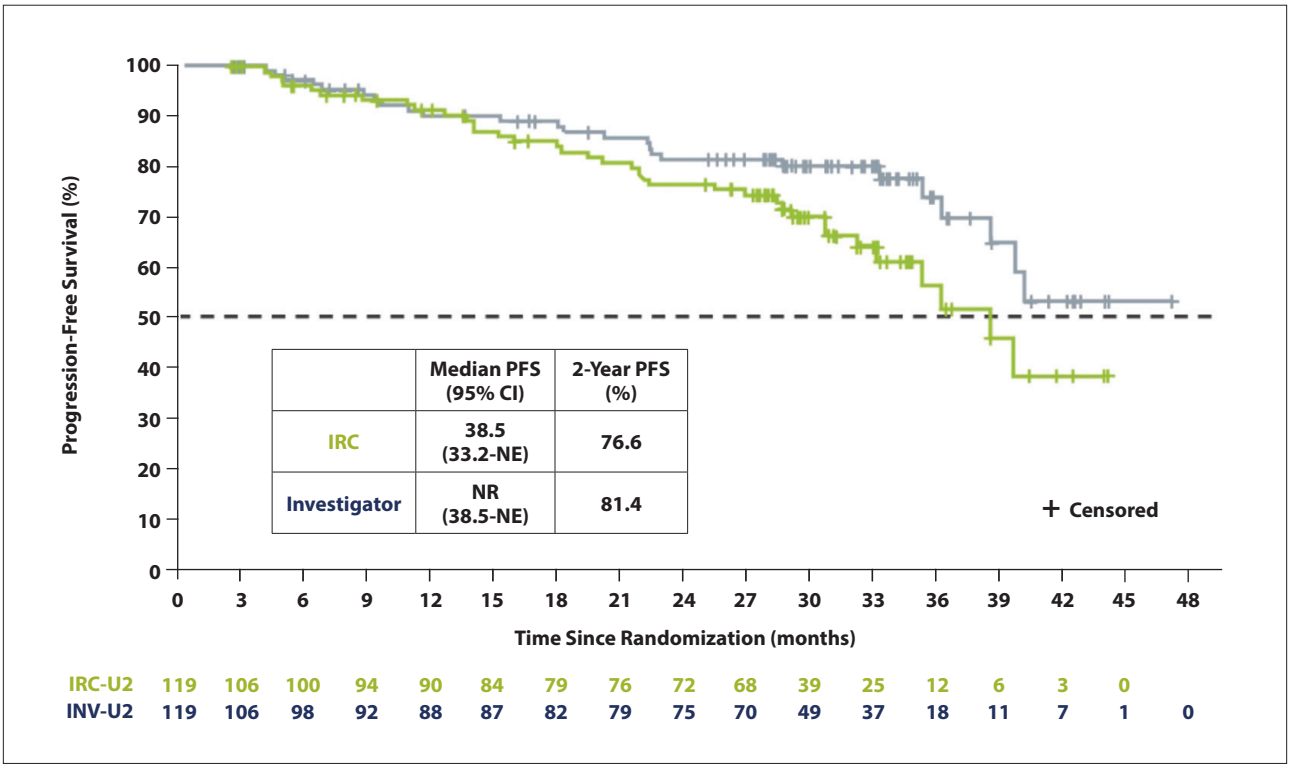

Figure 11. Progression-free survival according to an independent review committee vs investigator assessment in patients with treatment-naive chronic lymphocytic leukemia who received ublituximab and umbralisib in a subanalysis of the phase 3 UNITY-CLL study. INV, investigator; IRC, independent review committee; NE, not estimable; NR, not reached; PFS, progression-free survival. Adapted from Jacobs R et al. ASH abstract 3726. *Blood*. 2021;138(suppl 1).[2]

IGHV in 57%. The median number of prior therapies was 2 (range, 1-9). The median exposure to study drug was longer in the treatment-naive group, at 30 months with ublituximab and 27 months with umbralisib. In the previously treated group, these durations were 15 months with ublituximab and 16 months with umbralisib. The proportion of patients who discontinued therapy owing to an AE was 21% in the treatment-naive group vs 11% in the previously treated group.

Based on independent review, the median PFS was 38.5 months (95% CI, 33.2 to not estimable) in the treatment-naive patients vs 19.5 months (95% CI, 14.6-27.7) in previously treated patients. Two-year PFS rates were 76.6% vs 41.3%, respectively. PFS among patients with treatment-naive CLL as assessed by the independent review committee vs investigators is shown in Figure 11. The ORR was 84%, with a 5% CR rate, in the treatment-naive group vs 82%, with a 4% CR rate, in the previously treated group.

The most common AEs of grade 3 or higher related to PI3K inhibition included ALT elevation (12%), AST elevation (8%), and pneumonia (7%) in the treatment-naive group and pneumonia (11%), ALT elevation (3%) and AST elevation (2%) in the previously treated group.

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Advances in Chronic Lymphocytic Leukemia From the 63rd American Society of Hematology Annual Meeting and Exposition: Commentary

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Novel treatments for patients with chronic lymphocytic leukemia include the combination of ublituximab and umbralisib (also known as U2),* next-generation Bruton's tyrosine kinase (BTK) inhibitors, and venetoclax-based combinations. Presentations at the 63rd American Society of Hematology (ASH) meeting provided data from clinical trials of these promising therapies.

Ublituximab and Umbralisib

Dr Lindsey Roeker presented results from a unique phase 2 study that evaluated the addition of the anti-CD20 monoclonal antibody ublituximab and the phosphoinositide 3-kinase (PI3K) inhibitor umbralisib to ibrutinib for patients with CLL.[1] Patients who receive ibrutinib are unlikely to attain deep remissions.[2]

The concept behind this study was that add-on therapy might lead to minimal residual disease (MRD) negativity in patients who achieved stable disease, but not deep remissions, after treatment with ibrutinib. As a result, it might be possible to convert treatment to a time-limited approach, which could allow time off therapy. The study enrolled patients who had received ibrutinib, during any line of therapy, for a minimum duration of 6 months.[1] The patients had detectable residual CLL in the peripheral blood. The combination of umbralisib plus ublituximab was added to the existing ibrutinib regimen. Patients were serially monitored for MRD with peripheral blood testing, starting at the third cycle. Among patients with undetectable MRD (10^{-4}), the test was repeated 4 weeks later. When undetectable MRD was confirmed on the subsequent test, the patient began a period of treatment-free observation. Sixty-seven percent of the patients entered the treatment-free observation period.

The study investigators hypothesized that the trial would be successful if the treatment strategy achieved a prespecified MRD conversion rate of 25%, which they considered promising. The results were much higher. Undetectable MRD was reported at least once in 77% of patients.[1] The median time to the first measurement of undetectable MRD was 7.4 months.

The study explored an interesting concept. Among patients receiving ibrutinib, the addition of ublituximab and umbralisib led to deep remissions that allowed discontinuation of therapy. The ability to have some time off therapy likely had important positive quality-of-life implications for the patients.

The study did not identify whether the rate of undetectable MRD was driven by ublituximab, umbralisib, or both. In response to a question from the audience, Dr Roeker noted that ublituximab alone was unlikely to confer this level of improvement, given the lower rates of MRD negativity seen in other studies of a BTK inhibitor plus an anti-CD20 monoclonal antibody, such as the iLLUMINATE trial.[1,3] The addition of umbralisib might have increased efficacy. It is difficult to say, however, because the trial did not evaluate ublituximab alone in a separate arm.

Another question is whether assessment of the bone marrow would have led to the high rates of MRD negativity reported with testing in the peripheral blood. There is a strong correlation between MRD testing in bone marrow and peripheral blood, although it is somewhat dependent on the treatment regimen. The study by Dr Roeker was designed to be minimally invasive and convenient to patients, so peripheral blood was selected as the means of MRD testing.[1] Further follow-up will be needed to determine how long the patients are able to remain treatment-free, given that MRD was assessed only in the blood.

Updated analyses were presented for the phase 3 UNITY-CLL trial. Results of this study were first presented at the 2020 ASH annual meeting.[4] The trial compared U2 vs chlorambucil plus obinutuzumab. The results were positive, showing that progression-free survival (PFS) was superior among patients treated with the U2 regimen. This study included patients with both treatment-naive and relapsed/refractory disease. At the 2021 ASH annual meeting, Dr Ryan Jacobs presented a subanalysis of the UNITY-CLL trial that examined data in the treatment-naive and relapsed/refractory arms.[5] This analysis reiterated the previous finding for PFS among the treatment-naive patients, which was a median of 38.5 months. The estimated 24-month PFS was 76.6%. Dr Jacobs provided a closer look at side effects among treatment-naive patients. This analysis is important because with other PI3K inhibitors, adverse events are more common among treatment-naive patients, given that these patients are more prone to immune-mediated toxicities. Umbralisib is a newer-generation PI3K inhibitor that has shown favorable safety compared with the older agents idelalisib and duvelisib. UNITY-CLL is the first phase 3 trial of umbralisib completed in patients who were treatment-naive. Data for AEs were provided separately for treatment-naive patients and previously treated patients. Rates of immune-mediated toxicities are often lower in previously treated patients, who may be less vulnerable owing to their prior treatments. The rate of grade 3/4 neutropenia was 25% in treatment-naive patients vs 40% in previously treated patients. Grade 3 diarrhea occurred in 14% vs 10%, respectively. Grade 3 or higher elevations in ALT occurred in 12% vs 3%. Grade 3 or higher elevations in AST were reported in 8% vs 2%. Overall, toxicity and efficacy were favorable for this newer-generation PI3K inhibitor.

Dr Javier Pinilla-Ibarz presented an analysis of the UNITY-CLL trial that evaluated where the U2 regimen might fit into the current therapeutic landscape,[6] which is a crowded field that includes BTK inhibitors and venetoclax. The BTK inhibitors are the most frequently used among the new targeted agents. This analysis evaluated how many patients in the UNITY-CLL trial had comorbidities or were receiving concomitant medications that might preclude the use of BTK inhibitors. Presumably, these patients might benefit from a treatment with a different adverse event profile and drug-drug interactions than those reported with BTK inhibitors. This analysis

ABSTRACT SUMMARY A Randomized Phase III Study of Venetoclax-Based Time-Limited Combination Treatments vs Standard Chemoimmunotherapy in Frontline Chronic Lymphocytic Leukemia of Fit Patients: First Co–Primary Endpoint Analysis of the International Intergroup GAIA (CLL13) Trial

The phase 3 CLL13 study compared venetoclax-based therapy, administered for a limited number of cycles, vs chemoimmunotherapy in fit, treatment-naive patients with CLL (Abstract 71). The trial randomly assigned 926 patients to chemoimmunotherapy (CIT; n=229), rituximab plus venetoclax (RVe; n=237), obinutuzumab plus venetoclax (GVe; n=229), or obinutuzumab, ibrutinib, and venetoclax (GIVe; n=231). Treatment was administered for 6 cycles, with the exception of ibrutinib, which could be administered for up to 36 cycles. At month 15, the rate of undetectable MRD was 52.0% in the CIT arm, 57.0% in the RVe arm, 86.5% in the GVe arm, and 92.2% in the GIVe arm. The trial met its first co–primary endpoint of undetectable MRD with GVe vs the CIT arm (P<.0001). Across the 4 arms, grade 3 or higher AEs of special interest included infections (11.4%-22.1%), tumor lysis syndrome (4.2%-10.1%), and febrile neutropenia (3.1%-11.1%). Rates of treatment discontinuation were less than 15% in the 3 experimental arms.

focused on the patients who received U2. These patients were subdivided into those with or without comorbidities and/or risk factors associated with BTK inhibitors, which included use of a concomitant medication, such as an anticoagulant, that could lead to increased complications. The comorbidities included cardiovascular dysfunction, arrhythmias, hypertension, and history of major bleeding. Among the study population, 64% of patients met the criteria for comorbidities or risk factors. These patients were older than the overall population treated with U2. The patients' median age was 69 years vs 67 years, respectively.

The median PFS for patients with BTK-inhibitor risk factors was equivalent to the entire population of patients in the U2 arm, at 31.9 months for each group. The overall response rates were also similar, at 88% vs 83%, respectively. These findings suggest that among patients who may not be optimal candidates for BTK inhibitors, the U2 regimen can be similarly effective as in patients without these risk factors. There may be a role for the U2 regimen in the treatment of CLL should the agents receive approval in this setting from the US Food and Drug Administration (FDA).

ABSTRACT SUMMARY Pirtobrutinib, a Next-Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated CLL/SLL: Updated Results From the Phase 1/2 BRUIN Study

The multicenter phase 1/2 BRUIN study evaluated single-agent pirtobrutinib, a noncovalent inhibitor of BTK, in previously treated patients with CLL/SLL (Abstract 391). The trial enrolled 261 patients, whose median age was 69 years. The patients had received a median of 3 lines of prior therapy (range, 1-11). All patients had prior exposure to a BTK inhibitor. After a median follow-up of 9.4 months, the ORR was 68% (95% CI, 62%-74%), with a CR rate of 1%. Most patients (74%) were receiving pirtobrutinib at the time of the report. Responses were observed in patients who discontinued prior BTK inhibitor therapy owing to disease progression or toxicity. The efficacy of pirtobrutinib was not associated with BTK C481 status. AEs were generally manageable, and no dose-limiting toxicities were reported. Phase 3 studies of pirtobrutinib in CLL/SLL are ongoing.

BTK Inhibitors

The phase 3 SEQUOIA trial evaluated the BTK inhibitor zanubrutinib in patients with treatment-naive CLL or small lymphocytic lymphoma (SLL).[7] The trial had several different patient cohorts and treatment arms. The largest cohort compared zanubrutinib monotherapy vs bendamustine plus rituximab in patients without deletion 17p (del[17p]). Patients with del(17p) were enrolled in different cohorts of either zanubrutinib monotherapy or zanubrutinib with venetoclax, and these results were presented separately.[8,9] Dr Constantine Tam presented data for patients without del(17p), who received treatment with zanubrutinib or bendamustine plus rituximab.[7] The trial showed favorable activity of zanubrutinib in the frontline setting. The efficacy of zanubrutinib was clearly superior to that of bendamustine plus rituximab. At 24 months, the rate of PFS was 85.5% for zanubrutinib vs 69.5% for bendamustine plus rituximab. The analysis also suggested that the toxicity of zanubrutinib compares favorably with the other covalent BTK inhibitors. Zanubrutinib was associated with a low rate of cardiac side effects, such as atrial fibrillation and flutter. The rate of any-grade atrial fibrillation was 3.3%, which compares favorably with the rates reported for ibrutinib and acalabrutinib.[10,11]

Overall, this analysis of the SEQUOIA trial showed that zanubrutinib is a well-tolerated, highly effective agent in the frontline setting.[7] The results of the trial may lead to FDA approval in the coming months, which would provide another frontline option for patients with CLL.

Dr Chan Cheah presented the results of a phase 1 study evaluating a new BTK inhibitor, TG-1701, as monotherapy and in combination with ublituximab and umbralisib.[12] The trial population consisted of patients with different types of B-cell malignancies. The trial enrolled 36 patients in the combination arm. Among these patients, 19 were evaluable for efficacy and safety. Treatment with TG-1701, ublituximab, and umbralisib led to a high overall response rate of 84%, which included complete responses in 4 patients and partial responses in 12 patients. The remaining patients were awaiting postbaseline assessment at the time of the report.

Among the CLL population who received monotherapy, 40 patients were evaluated for safety and 39 for efficacy. The overall response rate for the CLL group was very high, at 97%. As is typical for BTK inhibitors and PI3K inhibitors, the responses were all partial remissions or partial remissions with lymphocytosis.

The safety of this regimen appeared reasonable. Within the CLL monotherapy subset, the most common any-grade treatment-emergent adverse events consisted of increased transaminases in 18% (although grade 3 or higher events were rare, at 3%), followed by diarrhea in 15% (no grade 3 or higher events), and neutropenia in 13% (with grade 3 or higher events in 13%). Fortunately, there were no cases of atrial fibrillation, bleeding, or ventricular tachyarrhythmias in the cohort of patients with CLL, with a follow-up of just over a year. These results are

ABSTRACT SUMMARY Rituximab-Lenalidomide (R2) Maintenance Is Superior to Rituximab Maintenance After First-Line Immunochemotherapy in Mantle Cell Lymphoma: Results of the MCL R2 Elderly Clinical Trial

The open-label MCL R2 Elderly trial evaluated maintenance therapy consisting of rituximab with or without lenalidomide in elderly MCL patients (Abstract 379). The trial enrolled treatment-naive patients ages 60 years or older who were ineligible for autologous transplant. Patients were first randomly assigned to receive 8 cycles of R-CHOP or 6 cycles of alternating R-CHOP/R-HAD. Patients with a response were then randomly assigned to 24 months of rituximab or rituximab plus lenalidomide for maintenance. The trial randomly assigned 447 patients to maintenance therapy. Their median age was 71 years, and 89.5% had Ann Arbor stage IV disease. At 2 years, the median PFS was 76.6% with lenalidomide plus rituximab vs 60.8% with rituximab alone (*P*=.0003). No difference in OS was observed. One patient who received rituximab plus lenalidomide died of treatment-related toxicity. Hematologic AEs were more common with the lenalidomide combination.

encouraging. Further registrational trials of TG-1701 in CLL are being planned.[13]

Data were presented for 2 noncovalent BTK inhibitors, pirtobrutinib and nemtabrutinib (formerly ARQ 531). Pirtobrutinib is a noncovalent reversible BTK inhibitor that binds at a different site from the C481 residue, which when mutated leads to covalent BTK inhibitor resistance. Dr Anthony Mato presented an updated analysis for patients with CLL or SLL in the phase 1/2 BRUIN trial, which evaluated pirtobrutinib.[14] The analysis included data for approximately 100 new patients with CLL (bringing the CLL/SLL population to 252) and 10 additional months of follow-up. Pirtobrutinib continued to exhibit favorable safety, with only 1% of patients discontinuing therapy owing to treatment-related AEs. The efficacy of pirtobrutinib persisted, with an overall response rate of 68% and a median PFS that had not yet been reached for patients with prior BTK treatment. In patients who had received a prior BTK inhibitor and venetoclax, the median PFS was 18 months.

Nemtabrutinib (also known as MK-1026) is another noncovalent inhibitor of both wild-type and C481-mutant BTK. Dr Jennifer Woyach presented data for 68 patients with CLL or SLL.[15] Nemtabrutinib had activity among the CLL/SLL patient population, with an overall response rate of 57.9% among the patients evaluable for efficacy who received the recommended phase 2 dose. One difference between nemtabrutinib and pirtobrutinib is that nemtabrutinib appears to have a bit higher rate of grade 3 or higher treatment-emergent AEs, which occurred in 68% of participants, leading to treatment discontinuation in 7.6%. Overall, nemtabrutinib appears to be active in relapsed/refractory CLL, with a manageable safety profile. Further evaluation is ongoing.

Venetoclax Combinations

Dr Barbara Eichhorst presented results of CLL13, a large, long-anticipated trial from the German CLL Study Group.[16] This randomized phase 3 trial compared 3 venetoclax-based combination regimens to standard chemoimmunotherapy as frontline treatment in fit patients with CLL. Venetoclax was administered with rituximab, with obinutuzumab, or with ibrutinib and obinutuzumab. The chemoimmunotherapy arm was either fludarabine, cyclophosphamide, and rituximab or bendamustine plus rituximab, based on the patient's age. The patients were randomly assigned in a 1-to-1-to-1-to-1 ratio to receive a standard 6 courses of chemoimmunotherapy or 1 of the 3 venetoclax-based combinations. Notably, venetoclax was administered throughout the course of 12 cycles, as opposed to a longer duration. A co–primary endpoint was the rate of undetectable MRD at 15 months.

The interesting results showed that the regimens containing obinutuzumab led to superior rates of undetectable MRD compared with chemoimmunotherapy, but the rituximab regimen did not. Rituximab is not typically used in the frontline setting, based on the results of a predecessor to this study that showed that obinutuzumab was superior to rituximab, albeit when combined with chlorambucil.[17] Rates of undetectable MRD ($<10^{-4}$) in the peripheral blood were 52.0% for chemoimmunotherapy, 57.0% for rituximab plus venetoclax, 86.5% for obinutuzumab plus venetoclax, and 92.2% for obinutuzumab, ibrutinib, and venetoclax. These data provide further evidence of the inferiority of rituximab to obinutuzumab when combined with venetoclax given for 12 cycles in the frontline setting. These results are not necessarily applicable to the relapsed setting. It is known that rituximab administered with 2 years of venetoclax is highly efficacious in the relapsed setting.[18] This analysis of the CLL13 trial suggests that it would not be appropriate to use rituximab combined with venetoclax in the frontline setting, and provides strong support for time-limited therapy with venetoclax plus obinutuzumab in younger, fitter patients. This regimen was previously studied in an older, unfit patient population.[19]

Disclosure

Dr Coombs has served as a consultant for AbbVie. She has served on steering committees for AbbVie and Loxo Oncology, and on independent review committees for AbbVie and Octapharma. She has received honoraria from AbbVie, AstraZeneca, BeiGene, Genentech, Loxo Oncology, MEI Pharma, Novartis, and TG Therapeutics. She has received research funding (paid to her institution) from AbbVie, H3 Biomedicine, Incyte, and Loxo Oncology.

Note

**In February 2022, the US Food and Drug Administration placed a partial clinical hold on trials evaluating umbralisib and ublituximab as a treatment for chronic lymphocytic leukemia and non-Hodgkin lymphoma.*

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