

A SPECIAL MEETING REVIEW EDITION

Highlights in Relapsed/Refractory Follicular 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:

- Analyzing Efficacy Outcomes From the Phase 2 Study of Single-Agent Tazemetostat as Third-Line Therapy in Patients With Relapsed or Refractory Follicular Lymphoma to Identify Predictors of Response
- Umbralisib, the Once-Daily Dual Inhibitor of PI3K δ and Casein Kinase-1 ϵ Demonstrates Clinical Activity in Patients With Relapsed or Refractory Indolent Non-Hodgkin Lymphoma: Results From the Phase 2 Global UNITY-NHL Trial
- Primary Analysis of ZUMA-5: A Phase 2 Study of Axicabtagene Ciloleucel in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma
- Tazemetostat Is Associated With Lower Risk for Safety Outcomes Versus the PI3-Kinases Idelalisib, Duvelisib, and Copanlisib in Patients With Relapsed/Refractory Follicular Lymphoma Who Have Received at Least 2 Prior Systemic Treatments: A Matching-Adjusted Indirect Comparison of Single-Arm Trials
- Treatment and Outcome of Patients With Follicular Lymphoma Relapsed or Progressed After Frontline Lenalidomide and Rituximab
- Mosunetuzumab Shows Promising Efficacy in Patients With Multiply Relapsed Follicular Lymphoma: Updated Clinical Experience From a Phase 1 Dose-Escalation Trial
- Phase 2 Study Evaluating the Efficacy and Safety of Parsaclisib in Patients With Relapsed or Refractory Follicular Lymphoma (CITADEL-203)
- Efficacy and Safety of Tisagenlecleucel in Adult Patients With Relapsed/Refractory Follicular Lymphoma: Interim Analysis of the Phase 2 ELARA Trial

PLUS Meeting Abstract Summaries

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Analyzing Efficacy Outcomes From the Phase 2 Study of Single-Agent Tazemetostat as Third-Line Therapy in Patients With Relapsed or Refractory Follicular Lymphoma to Identify Predictors of Response

Follicular lymphoma is the most common subtype of non-Hodgkin lymphoma (NHL) and typically follows an indolent course. Tazemetostat is a first-in-class, oral inhibitor of the histone methyltransferase *EZH2*, a gene that is mutated in up to 25% of patients with follicular lymphoma.^{1,2} The US Food and Drug Administration (FDA) recently approved tazemetostat for the treatment of patients with relapsed or refractory follicular lymphoma. The approval includes patients whose tumors are positive for an *EZH2* mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies, as well as patients who lack satisfactory alternative treatment options.

The FDA granted accelerated approval to tazemetostat after positive results from the open-label, single-arm, multicenter phase 2 E7438-G000-101 trial. This study included 99 heavily pretreated patients with follicular lymphoma who had wild-type or mutated *EZH2*.³ Tazemetostat was administered at a dose of 800 mg twice daily, in continuous 28-day cycles.³ Tazemetostat was generally well tolerated and demonstrated clinically meaningful responses. In the entire study population, tazemetostat yielded an objective response rate (ORR) of 51% (95% CI, 40%-61%), a median duration of response of 11 months (95% CI, 7-19 months), and a median progression-free survival (PFS) of 12 months (95% CI, 8-15 months).

The median overall survival (OS) was not reached. The ORR was 69% in patients with the *EZH2* mutation vs 35% in those with wild-type disease. However, patients in the mutated and wild-type cohorts had similar median durations of response (11 months vs 13 months) and PFS (14 months vs 11 months). The median OS was not reached in either cohort.

A post hoc exploratory analysis evaluated whether outcomes were affected by factors such as progression of disease within 24 months after first-line therapy (POD24), prior lines of therapy, and disease that is refractory to rituximab. These factors are known to affect outcomes in patients receiving second- or third-line treatment for follicular lymphoma.⁴⁻⁷ An initial

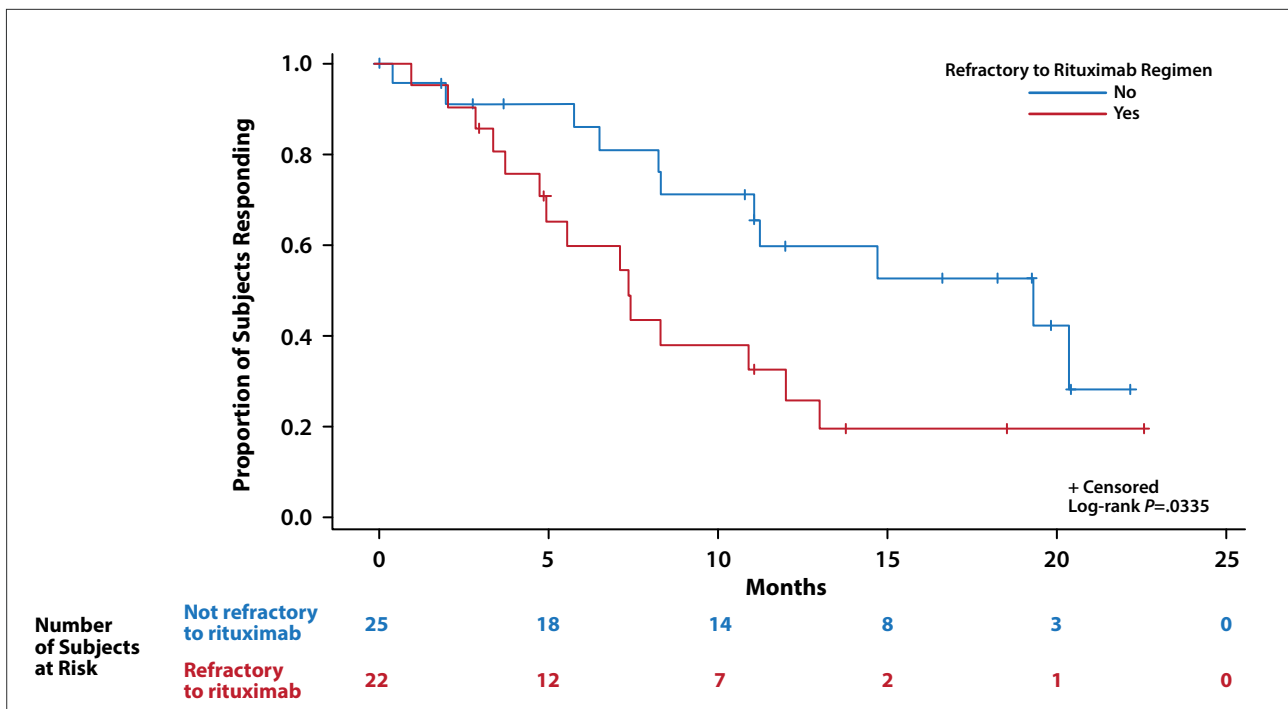


Figure 1. Duration of response to tazemetostat in a phase 2 trial among patients with follicular lymphoma who were or were not refractory to a prior rituximab regimen. Adapted from Salles G et al. ASH abstract 2047. *Blood*. 2020;136(suppl 1).⁷

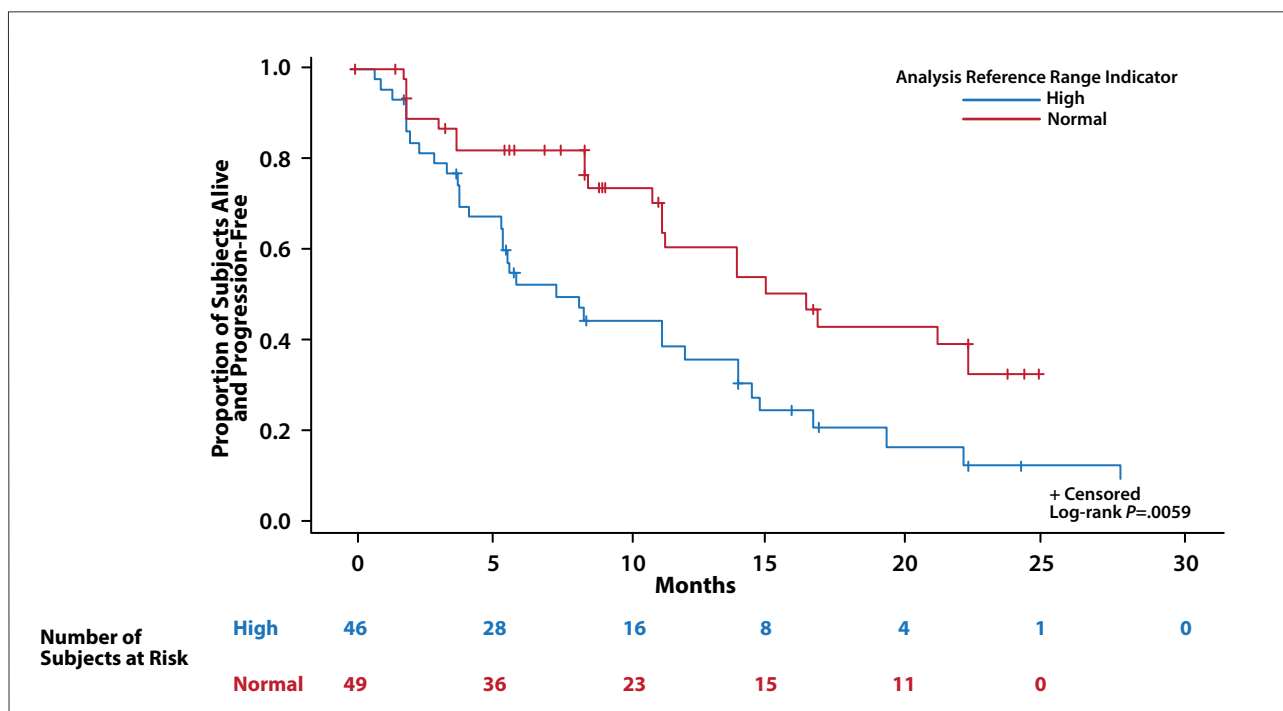


Figure 2. Progression-free survival according to the level of lactate dehydrogenase in a phase 2 trial among patients with follicular lymphoma treated with tazemetostat. Adapted from Salles G et al. ASH abstract 2047. *Blood*. 2020;136(suppl 1).⁷

analysis evaluated data from patients in the phase 2 study with wild-type or mutated *EZH2*. Predictive modeling was used to identify variables that were associated with response. The modeling suggested that a decreased ORR was associated with an increased number of prior therapies (>2) and POD24. Both variables showed a potential correlation with PFS.

An extended exploratory analysis was performed to identify clinical variables that could predict ORR, duration of response, and PFS.⁷ Variables evaluated in the exploratory analysis included levels of lactate dehydrogenase, presence of double-refractory disease, presence of extranodal lesions, number of prior therapies, POD24 status, disease that was refractory to the most recent prior therapy, disease that was refractory to a rituximab regimen, and prior stem cell transplant.

Two variables showed a potential correlation with shorter ORR: increased number of prior therapies (1 or 2 vs >2 prior therapies; odds ratio [OR], 2.81; 95% CI, 1.19-6.61; $P=.02$) and POD24 (OR, 2.46; 95% CI, 1.08-5.61; $P=.04$). Disease that was refractory to rituximab corresponded to a shorter duration of response (Figure 1; hazard ratio [HR], 0.43; $P=.0335$). Variables that correlated with a shorter median PFS included disease that was refractory to rituximab (HR, 0.37; $P=.0006$), a high level of lactate dehydrogenase (HR, 2.10; $P=.007$; Figure 2), and double-refractory disease (HR, 0.52; $P=.03$). Variables that did not show an effect on response outcomes included prior stem cell transplant, disease that was refractory to the most recent prior therapy, and the presence of an extranodal target lesion.

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Umbralisib, the Once-Daily Dual Inhibitor of PI3K δ and Casein Kinase-1 ϵ Demonstrates Clinical Activity in Patients With Relapsed or Refractory Indolent Non-Hodgkin Lymphoma: Results From the Phase 2 Global UNITY-NHL Trial

B-cell receptor signaling plays a key role in normal B-cell development and in the development of B-cell malignancies.¹ A recent mouse model demonstrated that the phosphoinositide 3-kinase (PI3K)/mammalian target of rapamycin pathway drives the pathogenesis of marginal zone lymphoma.² Umbralisib (TGR-1202) is a dual inhibitor of PI3K δ and CK1 ϵ , with a highly selective preference for PI3K δ compared with the α , β , and γ isoforms. The phase 2b UNITY-NHL study evaluated umbralisib monotherapy in previously treated NHL patients.³ The study enrolled adults with histologically confirmed relapsed or refractory marginal zone lymphoma, follicular lymphoma, or small lymphocytic lymphoma (SLL) with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. Patients received umbralisib

(800 mg, twice daily) until disease progression, unacceptable toxicity, or study withdrawal. The first assessment of response was conducted at the end of cycle 3. The primary endpoint was independently assessed ORR. The study included 117 patients with follicular lymphoma, 69 with marginal zone lymphoma, and 22 with SLL. The baseline characteristics were generally well balanced across the 3 arms. The median age was 66 years (range, 29-88 years), and 57% of patients were male. An ECOG performance status of 2 was reported in 3% of patients, and 77% had stage III/IV disease. In the marginal zone lymphoma arm, 55% of patients had the mucosa-associated lymphoid tissue subtype. Patients had received a median of 2 prior therapies (range, 1-10), and all patients had received prior anti-CD20 therapy. Ninety-one percent of patients had

received prior chemoimmunotherapy. Approximately one-third of patients were refractory to their most recent prior therapy, and the median time since the last therapy was 14 months.

The median follow-up was 27.7 months. The median time of exposure to study treatment was 8.4 months (range, 0.2-27 months). Treatment was ongoing in 29% of patients. The most common reasons for discontinuing the study treatment included progressive disease (42%) and adverse events (AEs; 15%). The most common AEs of any grade included diarrhea (59.1%), nausea (39.4%), and fatigue (30.8%). Discontinuation owing to transaminase elevation occurred in 2.9% of patients. Grade 3 diarrhea led to discontinuation in 2.9% of patients. Among 4 patients (1.9%) with noninfectious colitis, symptoms resolved in 3 patients, who continued to receive umbralisib. Grade 3/4 AEs of interest included opportunistic infections (3.4%), rash (1.9%), and pneumonitis (1.0%).

Among patients with follicular lymphoma, the independently assessed ORR was 45.3%, with a complete response (CR) rate of 5% (Figure 3). These rates were 49.3% and 15%, respectively, in patients with marginal zone lymphoma, and 50.0% and 5%, respectively, in SLL patients. Disease reduction was reported in 90.6% of the marginal zone lymphoma patients, 83.5% of those with follicular lymphoma, and 89.5% of those with SLL. The median duration of response was not reached (95% CI, 10.3 months to not evaluable) in marginal zone lymphoma patients, 11.1 months (95% CI, 8.3-15.6 months) in follicular lymphoma patients, and 18.3 months (95% CI, 2.4 months to not evaluable)

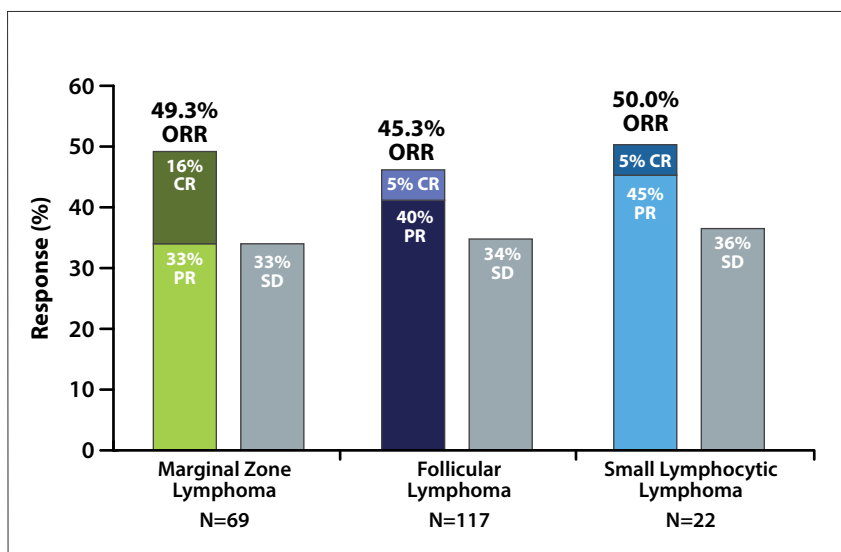


Figure 3. Independently assessed response among patients treated with umbralisib monotherapy in a phase 2 trial. CR, complete response; ORR, overall response rate; PR, partial response; SD, stable disease. Adapted from Zinzani P et al. ASH abstract 2934. *Blood*. 2020;136(suppl 1).³

in SLL patients. PFS was not reached (95% CI, 12.1 months to not evaluable) in the marginal zone lymphoma cohort, 10.6 months (95% CI, 7.2-13.7 months) in those with follicular lymphoma, and 20.9 months (95% CI, 7.4-24.1 months) in those with SLL.

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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

Among patients with indolent NHL who have received 2 or more lines of treatment, approved therapies yield low rates of CR, and the median duration of response is approximately 13 months or less.¹⁻⁵ The phase 2 ZUMA-5 trial evaluated axicabtagene ciloleucel, an autologous chimeric antigen receptor (CAR) T-cell therapy, in patients with follicular lymphoma who had received at least 2 prior lines of therapy. Eligible patients had relapsed or refractory follicular lymphoma of grade 1 to 3a or marginal zone lymphoma.⁶ Prior

treatment included an anti-CD20 monoclonal antibody combined with an alkylating agent. Patients received standard conditioning treatment followed by administration of 2×10^6 CAR-positive cells per kilogram. The primary endpoint was ORR, based on the Lugano criteria.⁷

The trial enrolled 151 patients. All patients underwent leukapheresis, and 146 underwent conditioning chemotherapy. An infusion of axicabtagene ciloleucel was administered to 124 patients with follicular lymphoma and 22 patients with marginal zone lymphoma.

The safety analysis included 146 patients, whereas the efficacy analysis included 104 patients. Axicabtagene ciloleucel therapy was successfully manufactured for all enrolled patients. Delivery to the study site occurred at a median of 17 days after leukapheresis. The patients' median age was 61 years (range, 34-79 years), and 57% of patients were male. Eighty-six percent of patients had stage III/IV disease, and 49% had high tumor bulk. Patients had received a median of 3 prior therapies (range, 1-10), and 68% had refractory disease.

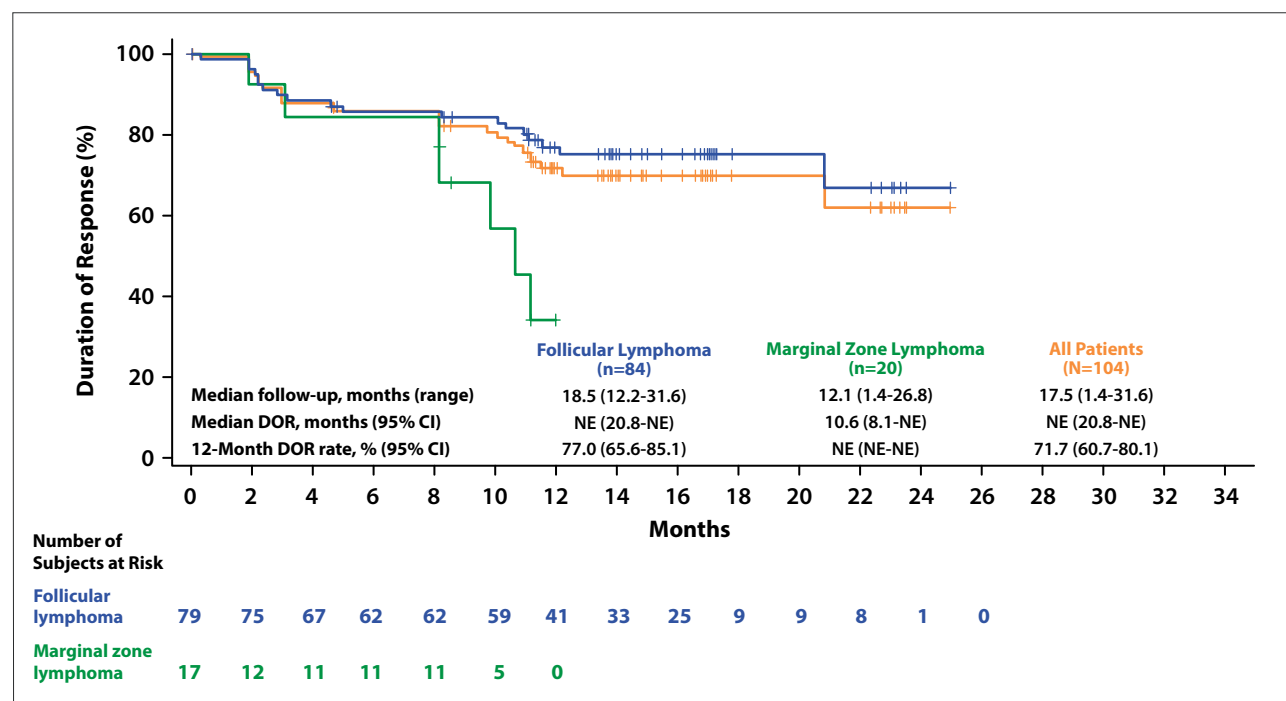


Figure 4. DOR among patients with follicular lymphoma or marginal zone lymphoma treated with axicabtagene ciloleucel in a phase 2 trial. DOR, duration of response; NE, not estimable. Adapted from Jacobson CA et al. ASH abstract 700. *Blood.* 2020;136(suppl 1).⁶

Based on an independent review of the overall study population, the ORR was 92% (95% CI, 85%-97%), with a CR rate of 76% (95% CI, 67%-84%). The ORR was 94% in patients with follicular lymphoma (n=84) and 85% in patients with marginal zone lymphoma (n=20). The median time to first response was 1 month (range, 0.8-3.1 months). Among the 25 patients with follicular lymphoma who had an initial partial response, 13 (52%) subsequently achieved a CR after a median of 2.2 months (range, 1.9-11.2 months).

The ORR was consistent across key subgroups, including patients with high tumor burden (96%), patients who had received 4 or more prior therapies (93%), and those with POD24 following their first anti-CD20 treatment (93%). After a median follow-up of 17.5 months, the median duration of response was not reached for the 104 evaluable patients (Figure 4), and 64% of patients with follicular lymphoma had an ongoing response.

Among the 104 evaluable patients, the median PFS (Figure 5) and OS were not reached. Twelve-month PFS was 73.7%, and 12-month OS was 92.9%.

AEs of grade 3 or higher occurred in 86% of patients, and most commonly consisted of cytopenias (70%) and infections (16%). A grade 5 AE occurred in 3 patients. One death was attributed to multisystem organ failure in a patient with cytokine release syndrome, which was related to treatment with axicabtagene ciloleucel. Overall, 7 patients (10%) experienced grade 3 or higher cytokine release syndrome. The median time to onset of cytokine release syndrome of any grade was 4 days (range, 1-15 days), and the median duration was 6 days (range, 1-27 days). Neurologic events of grade 3 or higher occurred in 28 patients (19%). The median time to onset of neurologic events of any grade was 7 days (range, 1-177 days), and the median duration was 14 days (range, 1-452 days). Neurologic events of any grade resolved in 93% of patients.

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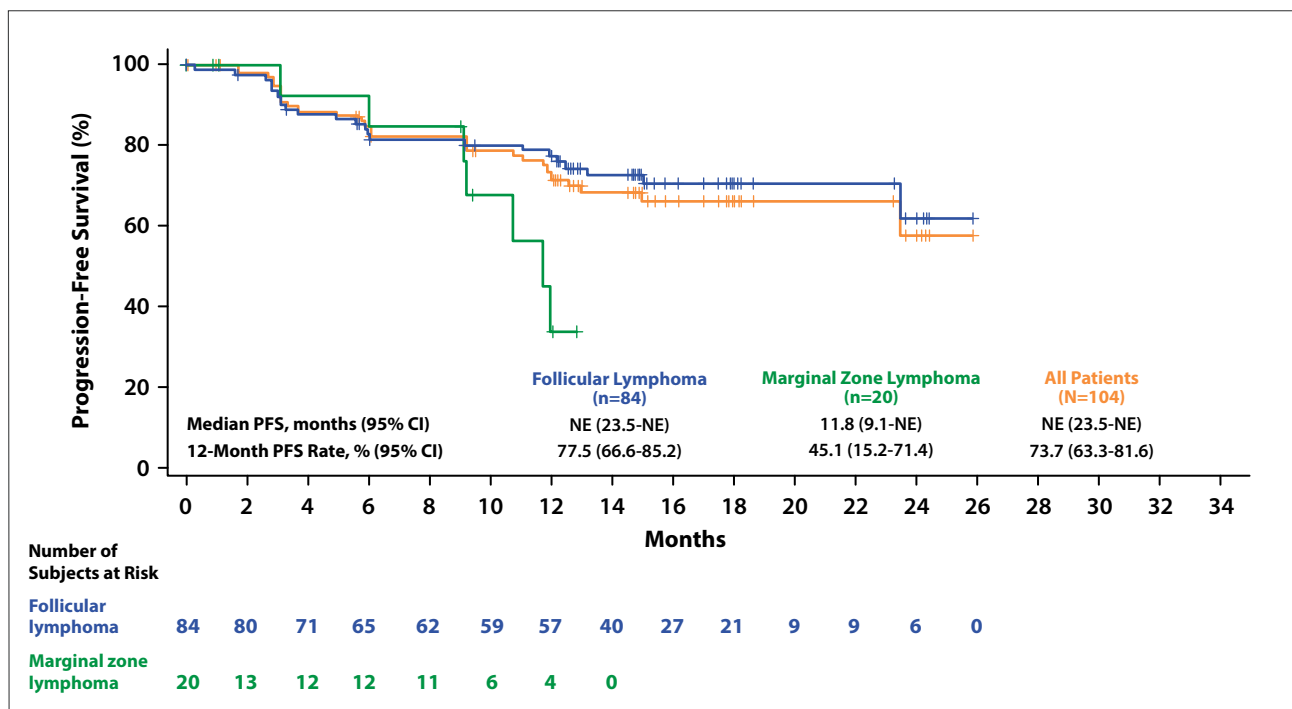


Figure 5. PFS among patients with follicular lymphoma or marginal zone lymphoma treated with axicabtagene ciloleucel in a phase 2 trial. NE, not estimable; PFS, progression-free survival. Adapted from Jacobson CA et al. ASH abstract 700. *Blood*. 2020;136(suppl 1).⁶

Tazemetostat Is Associated With Lower Risk for Safety Outcomes Versus the PI3-Kinases Idelalisib, Duvelisib, and Copanlisib in Patients With Relapsed/Refractory Follicular Lymphoma Who Have Received at Least 2 Prior Systemic Treatments: A Matching-Adjusted Indirect Comparison of Single-Arm Trials

Copanlisib, duvelisib, and idelalisib are approved for the treatment of patients with relapsed or refractory follicular lymphoma after 2 systemic treatments. However, these PI3-kinase inhibitors were approved based on single-arm studies, and they are associated with safety concerns. An indirect treatment comparison was conducted to evaluate tazemetostat vs copanlisib, duvelisib, and idelalisib as third-line or later treatment of patients with relapsed or refractory follicular lymphoma.¹ The investigators conducted a systematic literature review to identify publications of relevant clinical trials (Table 1).²⁻⁶ All of the trials were phase 2, open-label, single-arm studies. Three pairwise analyses were conducted using a matching-adjusted indirect comparison methodology. The patients were matched according to their age, ECOG performance status,

disease stage, histology, number of prior lines of treatment, prior stem cell therapy, refractory status, and POD24. The study evaluated safety and efficacy outcomes.

Baseline characteristics and outcome data for the subpopulation with follicular lymphoma were reported for matching idelalisib (n=72). Full-trial mixed-NHL populations were available for duvelisib (n=129, 64% with follicular lymphoma) and copanlisib (n=142, 73% with follicular lymphoma). Only the trial of tazemetostat included patients with grade 3b or transformed follicular lymphoma.

Grade 3 and higher treatment-emergent AEs are shown in Table 2. After matching for baseline characteristics, tazemetostat was associated with a lower risk of any-grade treatment-emergent AE, any treatment-emergent serious AE, and any treatment-emer-

gent AE leading to dose reduction, drug discontinuation, or treatment interruption. The results were significant ($P<.05$) for all but 2 comparisons (vs idelalisib for any treatment-emergent serious AE, $P=.06$; and vs duvelisib for a treatment-emergent AE that led to discontinuation, $P=.05$). Several treatment-emergent AEs were observed at a significantly lower incidence with tazemetostat compared with the PI3K inhibitors. For example, neutropenia rates varied from 3% to 4% with tazemetostat vs 22% to 25% with the PI3K inhibitors.

Comparisons of ORR showed no statistically significant differences between tazemetostat and each of the comparators. However, the study investigators identified some limitations to the analysis of response. For example, the comparator trial data were not adjusted for the effect modifier of

Table 1. Studies Included in the Indirect Treatment Comparisons

Drug	Study Name	Identifier	Study Title
Tazemetostat	E7438-G000-101 ⁶	NCT01897571	Open-Label, Multicenter, Phase 1/2 Study of Tazemetostat (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Adv. Solid Tumors or With B-Cell Lymphomas and Tazemetostat in Combination With Prednisolone in Subjects With DLBCL
Copanlisib	CHRONOS-1 Part B ²	NCT01660451	Open-Label, Uncontrolled Phase II Trial of Intravenous PI3K Inhibitor BAY80-6946 in Patients With Relapsed, Indolent or Aggressive Non-Hodgkin's Lymphomas
Duvelisib	DYNAMO ⁴	NCT01882803	A Phase 2 Study of Duvelisib in Subjects With Refractory Indolent Non-Hodgkin Lymphoma
Idelalisib	DELTA ⁵	NCT01282424	Efficacy and Safety Study of Idelalisib in Participants With Indolent B-Cell Non-Hodgkin Lymphomas

Data from Proudman D et al. ASH abstract 2064. *Blood*. 2020;136(suppl 1).¹

Table 2. Safety Outcomes for Tazemetostat in a Matching-Adjusted Indirect Comparison of Single-Arm Trials

Grade ≥3 TEAE, % (95% CI)	DELTA ⁵		DYNAMO ⁴		CHRONOS-1 Part B ²	
	Tazemetostat	Idelalisib	Tazemetostat	Duvelisib	Tazemetostat	Copanlisib
Anemia	9 (3-15)	7 (1-13)	6 (1-12)	15 (9-21)	4 (1-7)	5 (1-8)
Asthenia	5 (1-8)	6 (0-11)	3 (2-4)	2 (0-5)	–	–
Diarrhea	0 (0-0)	19 (10-29)	0 (0-0)	15 (9-21)	0 (0-0)	8 (4-13)
Dyspnea	5 (2-9)	4 (0-9)	–	–	–	–
Fatigue	–	–	0 (0-0)	5 (1-8)	2 (0-5)	2 (0-4)
Hyperglycemia	–	–	–	–	1 (0-3)	40 (32-48)
Hypertension	–	–	–	–	2 (0-5)	24 (17-31)
Hypokalemia	5 (1-8)	7 (1-13)	3 (2-4)	3 (0-6)	–	–
Increased ALT	0 (0-0)	13 (5-20)	0 (0-0)	5 (2-9)	1 (0-2)	1 (0-2)
Increased AST	0 (0-0)	10 (3-17)	0 (0-0)	3 (0-6)	0 (0-0)	0 (0-0)
Neutropenia	3 (0-8)	22 (13-32)	3 (0-7)	25 (17-32)	4 (0-8)	24 (17-31)
Pneumonia	0 (0-0)	11 (4-18)	0 (0-0)	5 (2-9)	0 (0-0)	11 (6-16)
Rash	–	–	0 (0-0)	5 (1-8)	0 (0-0)	1 (0-2)
Thrombocytopenia	3 (0-8)	10 (3-17)	3 (0-7)	12 (6-17)	4 (0-8)	5 (1-8)

ALT, alanine aminotransferase; AST, aspartate transaminase; TEAE, treatment-emergent adverse event. Adapted from Proudman D et al. ASH abstract 2064. *Blood*. 2020;136(suppl 1).¹

EZH2 mutation status. The comparator trials also excluded patients with grade 3b tumors or transformed NHL, who may have had a worse prognosis. The authors noted that the efficacy data are not expected to have affected the safety

results. They concluded that tazemetostat was associated with a significantly lower relative risk for adverse events as compared with idelalisib, duvelisib, and copanlisib, while exhibiting similar efficacy outcomes

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ABSTRACT SUMMARY Impaired SARS-CoV-2 Specific Antibody Responses in Patients Treated With Antibodies

This study describes 7 patients with diffuse large B-cell lymphoma or follicular lymphoma who received treatment with rituximab or ocrelizumab within 3 months prior to the onset of COVID-19 disease (Abstract 2140). Testing for the presence of anti-spike and anti-nucleocapsid antibodies to the SARS-CoV-2 virus within 20 days of symptom onset revealed a failure to mount an immune response to the novel coronavirus in these patients. One patient with transformed follicular lymphoma had detectable anti-spike and anti-nucleocapsid antibodies at day +25. Two patients—1 with transformed follicular lymphoma and 1 with follicular lymphoma—were still seronegative for anti-spike and anti-nucleocapsid antibodies at days +133 and +74, respectively, after symptom onset. The results suggest that treatment with an anti-CD20 antibody may adversely affect the immune response to infection in patients with NHL.

Treatment and Outcome of Patients With Follicular Lymphoma Relapsed or Progressed After Frontline Lenalidomide and Rituximab

A retrospective analysis evaluated salvage treatment strategies and survival outcomes in patients with grade 1 to 3a follicular lymphoma after first-line treatment with lenalidomide plus rituximab.¹⁻³ The study included patients with follicular lymphoma who were treated between August 2008 and January 2020 at a single center. Responses were evaluated based on the Lugano 2014 criteria.⁴ Survival results were calculated from the time of second-line therapy. Among 156 patients who met the inclusion criteria, 33 (21%) had relapsed or progressive disease. The 33 patients whose disease had relapsed or progressed included 21 patients (64%) who were 60 years or younger. Eighty-five percent of patients had a hemoglobin level of at least 12 g/dL, and 24% of patients had an elevated level of lactate dehydrogenase. Bone marrow involvement was

observed in 22% of patients, and 9% had grade 3a disease. B symptoms were present in 6% of patients, and 97% had Ann Arbor stage III/IV disease. Thirty percent of patients had more than 4 involved nodal areas, and 27% had a high FLIPI score.

The median time to second-line treatment was 33 months (range, 1-122 months). The POD24 rate was 8%, and no patients developed transformation of follicular lymphoma at the time of the first relapse. The median follow-up after the first relapse was 51 months (95% CI, 27-75 months). The response rate to first salvage therapy after first-line lenalidomide plus rituximab was 78%, including a CR rate of 72%, and the median PFS was 38 months (95% CI, 1-82 months). Treatment with chemoimmunotherapy after progression yielded a superior median PFS compared with biologic therapy

(99 vs 25 months; $P=.004$; Figure 6). Follicular lymphoma transformation occurred in 2 patients (7%), at 2 and 20 months after initiation of second-line therapy. With 4 years of follow-up after failure of first-line therapy, the median OS was not reached.

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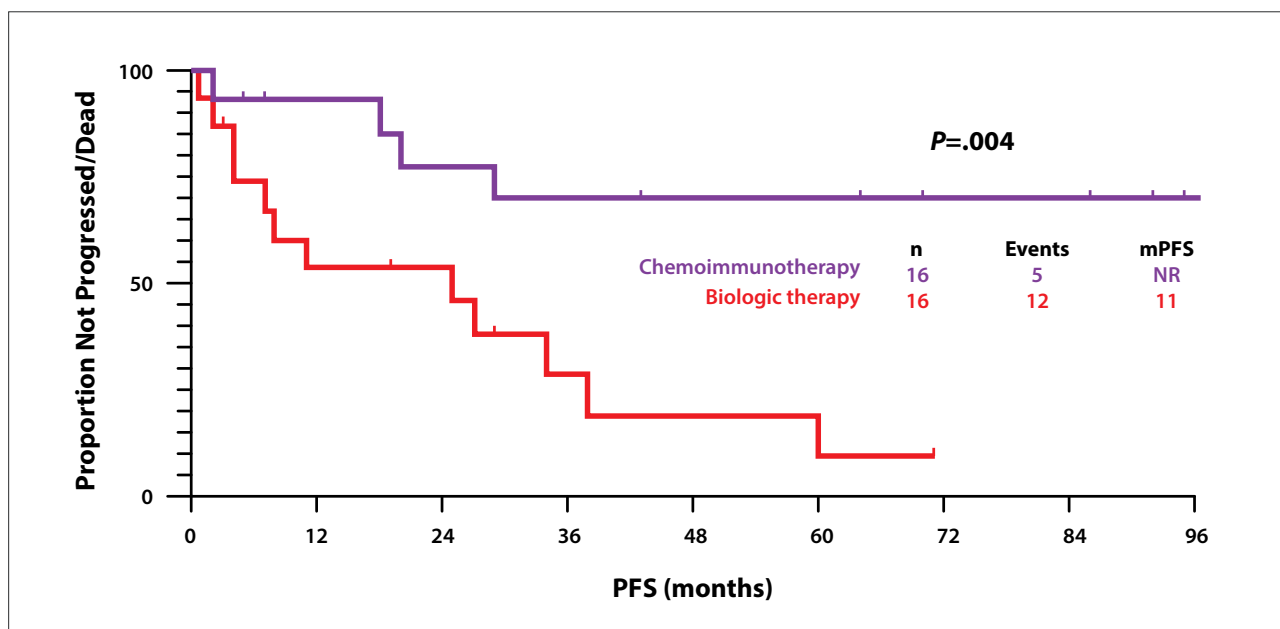


Figure 6. PFS in a retrospective analysis of patients with follicular lymphoma who relapsed or progressed after frontline treatment with lenalidomide and rituximab. NR, not reached; mPFS, median progression-free survival. Adapted from Strati P et al. ASH abstract 1128. *Blood*. 2020;136(suppl 1).³

Mosunetuzumab Shows Promising Efficacy in Patients With Multiply Relapsed Follicular Lymphoma: Updated Clinical Experience From a Phase 1 Dose-Escalation Trial

Mosunetuzumab is a full-length, humanized, bispecific antibody that binds to CD20 and CD3, thus redirecting T cells to target malignant B cells. The ongoing phase 1/1b GO29781 trial is investigating mosunetuzumab monotherapy in patients with relapsed or refractory B-cell NHL.¹ Eligible patients had relapsed or refractory follicular lymphoma of grade 1 to 3a, had received 2 or more prior systemic therapies, and had an ECOG performance status of 0 or 1. Mosunetuzumab was administered in eight 21-day cycles. Dose levels ranged from 0.4 mg to 13.5 mg. Among the 62 patients, the median age was 59 years (range, 27-85 years), and 64.5% were male. High-

risk subgroups included 61.3% with double-refractory disease and 46.8% with POD24. Patients had received a median of 3 prior therapies (range, 2-11), and all patients had received prior anti-CD20 therapy and an alkylating agent.

Across all 62 patients, the ORR was 67.7%, including a CR rate of 51.6% (Figure 7). High response rates were observed in high-risk patients. Among patients with refractory disease or POD24, the ORR ranged from 65.2% to 75.9%. Among 13 patients whose disease was refractory to PI3K inhibitors, the ORR was 92.3%. Four patients had received prior treatment with CAR T-cell therapy, and all of these patients demonstrated a

response. After a median follow-up of 18.4 months (range, 2-34 months), the median duration of response was 20.4 months (95% CI, 9.4-22.7 months). Among patients who achieved a CR, the median duration of response was slightly higher, at 21.0 months (95% CI, 16.0-22.7 months).

Treatment-related AEs of any grade were observed in 72.6% of patients. Treatment-related serious AEs were noted in 14.5% of patients, and treatment-related AEs of grade 3 or higher occurred in 35.5% of patients. Treatment-related AEs of grade 3/4 included hypophosphatemia (21.0%) and neutropenia (15.1%). All cytokine release syndrome events were grade 1 (n=12) or 2 (n=1). These

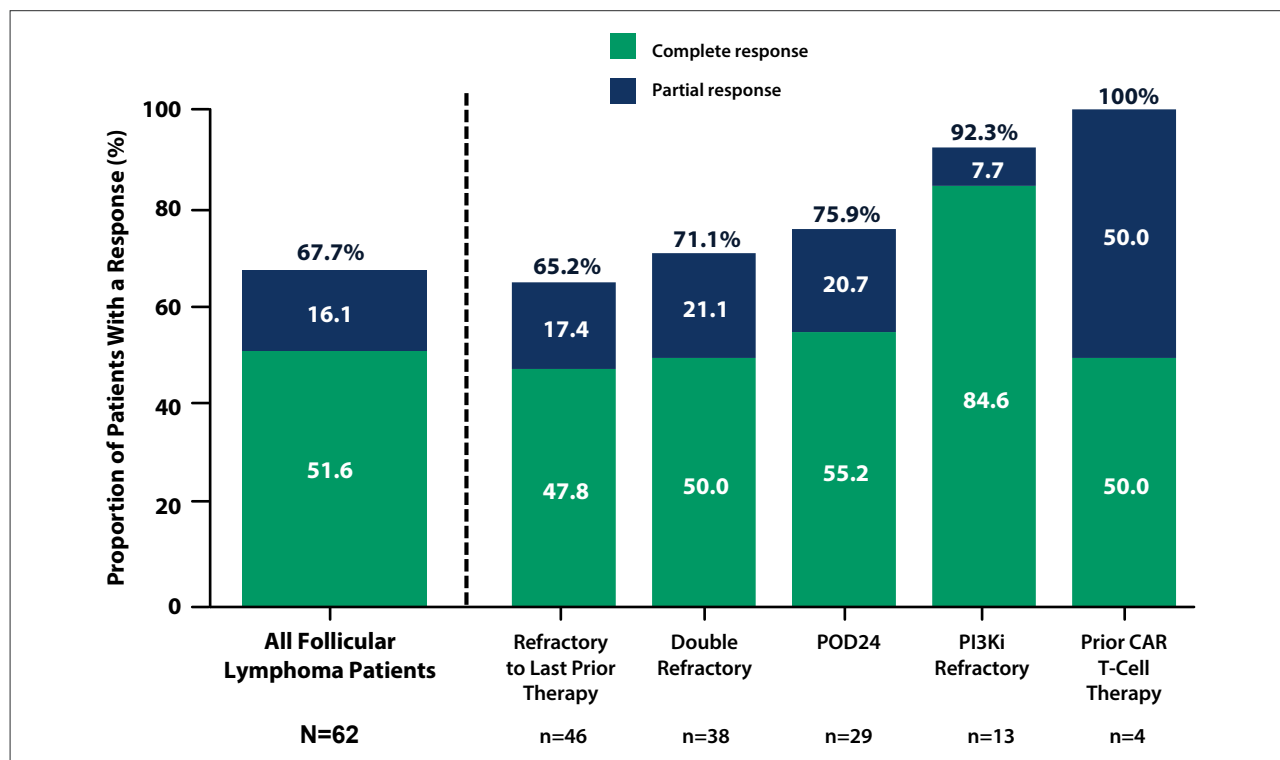


Figure 7. Response rates among patients with multiply-relapsed follicular lymphoma treated with mosunetuzumab monotherapy in a phase 1 trial. CAR, chimeric antigen receptor; PI3Ki, phosphoinositide 3-kinase inhibitor; POD24, progression of disease within 24 months after first-line therapy. Adapted from Assouline S et al. ASH abstract 702. *Blood*. 2020;136(suppl 1).¹

events occurred in 17.7% of patients during dose escalation in the first treatment cycle. Serious cytokine release syndrome events were observed in 4 patients (6.5%). The median time of onset for cytokine release syndrome was 1 day (range, 1-24 days), and the median duration was 2 days (range, 1-8 days). All cytokine release syndrome events resolved without the use of tocilizumab, admission to an intensive care unit, or use of vasopressors. CR rates were similar among patients who developed cytokine release syndrome (45.5%) and those who did not (52.9%). A phase 3 trial will investigate mosunetuzumab combined with lenalidomide in previously treated patients with follicular lymphoma.²

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ABSTRACT SUMMARY A Phase 1b/3 Randomized, Double-Blind, 3-Stage Study of Tazemetostat or Placebo Plus Lenalidomide and Rituximab in Patients With Relapsed/Refractory Follicular Lymphoma

An ongoing 3-stage phase 1b/3 study (NCT04224493) is assessing the efficacy and safety of tazemetostat combined with rituximab and lenalidomide (Abstract 2052). This international, randomized, placebo-controlled study is enrolling adult patients with follicular lymphoma who have received at least 1 prior line of systemic therapy. Patients with mixed or transformed histology will be excluded from enrollment. The primary endpoints are to determine the recommended phase 3 dose, based on a dose-limiting toxicity rate of less than 33%, and to determine investigator-assessed median PFS. Other endpoints include pharmacokinetic parameters and exploratory analyses of *EZH2* mutations, copy number, and expression of mRNA and protein.

Phase 2 Study Evaluating the Efficacy and Safety of Parsaclisib in Patients With Relapsed or Refractory Follicular Lymphoma (CITADEL-203)

The CITADEL-203 study evaluated parsaclisib monotherapy in patients with relapsed or refractory follicular lymphoma.¹ The study enrolled patients with grade 1, 2, or 3a follicular lymphoma who had received 2 or more prior systemic therapies. Patients in the weekly group received parsaclisib at 20 mg once daily for 8 weeks, followed by parsaclisib at 20 mg once weekly. Patients in the daily group received parsaclisib at 20 mg once daily for 8 weeks, followed by parsaclisib at 2.5 mg once daily. During the study, the daily group regimen was chosen as the preferred regimen. The primary endpoint was ORR based on the 2014 Lugano criteria.²

The study enrolled 125 patients: 23 were treated with the weekly regimen and 102 with the daily regimen. Their median age was 68 years (range, 20-88 years). The median time since

the diagnosis of follicular lymphoma was 6 years (range, 0.2-32 years). Seventy-eight percent of patients had Ann Arbor stage III/IV disease, and 46% had a FLIPI risk category of 3 or higher. Patients had received a median of 2 prior therapies (range, 1-8), and 18% of patients had undergone hematopoietic stem cell transplant. The median follow-up was 14.5 months (range, 0.2-28.0 months), and the median duration of parsaclisib therapy was 7.1 months (range, 0.2-21.0 months). The most common reasons for discontinuing parsaclisib were progressive disease (29%) and AEs (19%), followed by patient withdrawal (7%).

Among 118 evaluable patients, the ORR was 73% (95% CI, 64%-81%), with a CR rate of 14%. Among 95 evaluable patients treated in the daily group, the ORR was 75% (95% CI, 65%-83%). A reduction in the target lesion

size was observed in 90% (106/118) of evaluable patients across the entire study group, and in 91% (86/95) of evaluable patients treated with the daily regimen. The median duration of response was 15.9 months (95% CI, 12.0 months to not evaluable) among 86 responders in both treatment arms, and 14.7 months (95% CI, 12.0-17.5 months) among 71 responders treated with the daily regimen (Figure 8). The median PFS was 15.8 months (95% CI, 13.2-19.3 months) among 118 evaluable patients from both arms, and also 15.8 months (95% CI, 13.8-19.1 months) among 95 patients treated with the daily regimen.

Across the entire study cohort of 125 patients, the most common AEs of grade 3 or higher were diarrhea (10%) and neutropenia (10%). The most common serious treatment-emergent AEs were diarrhea (7%) and colitis (6%).

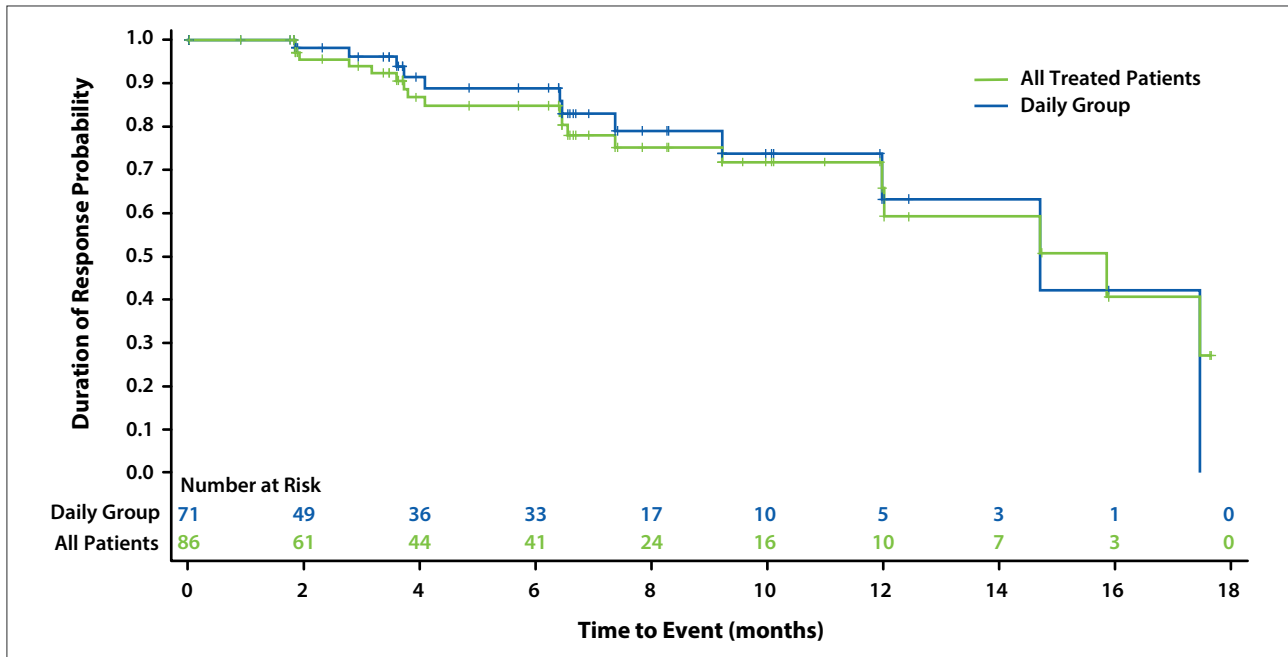


Figure 8. Duration of response among patients with relapsed or refractory follicular lymphoma treated with piasclisib, administered in a daily or a weekly regimen, in a phase 2 trial. Adapted from Lynch RC et al. ASH abstract 2935. *Blood*. 2020;136(suppl 1).¹

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Efficacy and Safety of Tisagenlecleucel in Adult Patients With Relapsed/Refractory Follicular Lymphoma: Interim Analysis of the Phase 2 ELARA Trial

The international phase 2 ELARA trial evaluated the CAR T-cell therapy tisagenlecleucel in adult patients with relapsed or refractory follicular lymphoma.¹ The trial enrolled patients with histologically confirmed follicular lymphoma of grade 1 to 3a. Patients had refractory disease, had relapsed within 6 months of second-line or later therapy, or had relapsed after autologous hematopoietic stem cell transplant. Patients received lymphodepleting chemotherapy followed by a single tisagenlecleucel infusion of 6×10^7 to 6×10^8 CAR T cells. Prior bridging therapy was permitted. The primary endpoint was the CR rate by independent review, based on the 2014 Lugano criteria.²

Among the 97 enrolled patients,

the median age was 57 years (range, 29-73 years). Most patients (83.5%) had stage III/IV disease at baseline, and 59.8% had a FLIPI score of 3 or higher. Patients had received a median of 4 (range, 2-13) prior therapies, and 77.3% were refractory to their most recent prior therapy. The median dose was 2.06×10^8 CAR-positive T cells.

At the first interim analysis, the median follow-up was 9.9 months, and 52 patients were evaluable for efficacy. The ORR was 82.7%, with a CR rate of 65.4%. The median duration of response (Figure 9), median PFS, and median OS were not reached. The 6-month PFS was 73.2% (95% CI, 58.2%-83.5%). At the time of data cutoff, 69% of patients had an ongoing response.

Serious AEs and grade 3/4 AEs that were considered related to study treatment were observed in 26.8% and 38.1% of patients, respectively. There were no cases of grade 3/4 cytokine release syndrome or grade 3/4 tumor lysis syndrome. All reported cases of cytokine release syndrome and neurologic events resolved with appropriate management.

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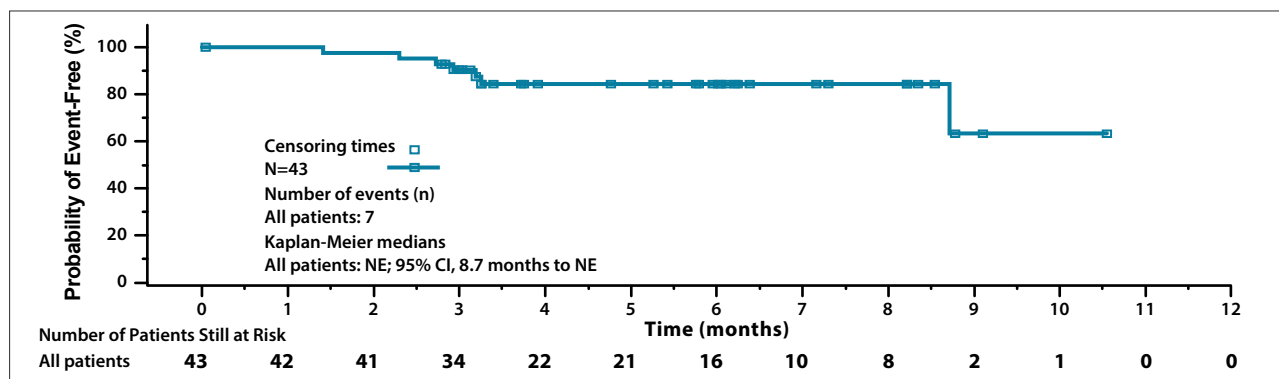


Figure 9. Duration of response among patients with relapsed/refractory follicular lymphoma treated with tisagenlecleucel in a phase 2 trial. NE, not estimable. Adapted from Fowler NH et al. ASH abstract 1149. *Blood*. 2020;136(suppl 1).¹

Highlights in Relapsed/Refractory Follicular Lymphoma From the 62nd American Society of Hematology Annual Meeting and Exposition: Commentary

Gilles Salles, MD, PhD

Among cases of lymphoma, follicular lymphoma is the second most frequent subtype throughout the United States and Europe.¹ The disease is characterized by an indolent course. When follicular lymphoma first manifests, patients usually have few symptoms. Although there are effective first-line treatments, many patients will relapse.² New treatment interventions are needed for disease control, remission, and improved survival.

Studies presented at the 62nd American Society of Hematology (ASH) meeting provided interesting data regarding several types of treatments for these patients. These treatments included a new generation of phosphoinositide 3-kinase (PI3K) inhibitors; immunotherapies; antibody-drug conjugates; and a newer intervention, tazemetostat, which is an EZH2 inhibitor. Tazemetostat is a first-in-class agent approved by the US Food and Drug Administration for the treatment of lymphoid malignancies. Data for new interventions targeting different pathways brought hope for the treatment of relapsed/refractory follicular lymphoma.

PI3K Inhibitors

Among the PI3K inhibitors already approved for patients with follicular lymphoma in the relapsed/refractory setting are idelalisib, duvelisib, and copanlisib. At the ASH meeting, Dr Pier Luigi Zinzani presented data for the PI3K inhibitor umbralisib.³ Unlike other agents, umbralisib specifically targets the PI3K δ isoform, as well as the casein kinase 1 ϵ .⁴ The study enrolled more than 200 patients with indolent disease, including 117 patients with relapsed/refractory follicular lymphoma. Most of the patients had advanced disease. The median number of prior therapies was 3, and approximately one-third of patients were refractory to their previous line of therapy.

The dose of umbralisib was 800 mg/day, and the median duration of exposure was 7.6 months. An interesting finding was that the adverse event (AE) profile of umbralisib appeared to be more limited compared with other PI3K inhibitors.⁵⁻⁷ The main grade 3/4 AEs were diarrhea and neutropenia, each of which occurred in approximately 10% of patients. Grade 3/4 elevated liver enzymes occurred in

approximately 7%, a lower rate than that seen with other drugs from this family. There were a few cases of grade 3/4 opportunistic infection (3.4%), rash (1.9%), and pneumonitis (1.0%). Discontinuations owing to AEs were limited. Approximately 3% of patients discontinued treatment after developing transaminase elevations, and 3% discontinued owing to diarrhea.

Among patients with follicular lymphoma, the overall response rate was 45.3%, with 5% achieving a complete response.³ These outcomes are similar to the other PI3K inhibitors.⁵⁻⁷ The median time to response was 4.6 months. The median duration of response was 11.1 months. Subgroup analysis showed that response was not impacted by clinical characteristics such as the number of prior lines of therapy, chemoresistance, or resistance to anti-CD20 antibodies. These important data confirm that umbralisib is effective in follicular lymphoma, with an acceptable tolerability profile.

Dr Ryan Lynch presented results of the CITADEL-203 study, which evaluated the PI3K inhibitor piasalisib.⁸ This drug is administered in a unique schedule compared with the other PI3K

inhibitors. The CITADEL-203 study evaluated 2 regimens: a weekly schedule, in which parsacalisib was administered at 20 mg once daily for 8 weeks, followed by 20 mg once weekly; and a daily schedule, which consisted of the same loading dose for 8 weeks, followed by 2.5 mg once daily continuously.

The study recruited 125 patients with relapsed/refractory follicular lymphoma. Most patients received the daily regimen. The patients' characteristics were typical for those with this disease. All had received prior chemotherapy and anti-CD20 agents. Approximately 1 out of 5 patients had undergone prior transplant. Approximately half of patients were refractory to their previous line of therapy. The median duration of treatment with parsacalisib was approximately 7 months. The primary reason for discontinuation was disease progression. Among all patients in the study evaluable for efficacy (n=118), the overall response rate was 73%, which is higher than that typically reported for these types of agents. Approximately 14% of patients achieved a complete response. Many patients had good disease control. The median duration of response was 15.9 months, and the median progression-free survival (PFS) was 15.8 months, confirming the efficacy of this drug.

Approximately half of the patients developed a treatment-emergent AE of grade 3 or higher, most commonly, diarrhea and neutropenia. Elevations in transaminase levels occurred in approximately one-quarter of the patients, but most events were grade 1 or 2. Approximately half of patients required dose modification. Overall, this selective PI3K δ inhibitor had promising efficacy in this setting, with an expected safety profile. Further research is needed for parsacalisib, as well as for other agents in this class.

Bispecific Antibodies

The ASH meeting provided data for bispecific antibodies, a promising intervention for patients with follicular lymphoma. Many bispecific antibodies are currently in development. At the

ASH meeting, updates were given for several of these compounds in lymphoma.⁹⁻¹² In these studies, the overall response rates ranged from 67% to 90% in patients with relapsed/refractory follicular lymphoma, and the complete response rates ranged from 50% to 70%. The number of patients in these studies remains small, and these data are preliminary. Some of the agents have not reached their optimal dosing and schedule. Side effects, such as cytokine release syndrome, can occur during the first infusion. Cytokine release syndrome should be managed with hospitalization for a day or more, which can represent a burden for patients in this setting.

Dr Sarit Assouline presented results from a phase 1 dose-escalation trial of mosunetuzumab, an anti-CD20 and anti-CD3 bispecific antibody.¹³ The study recruited 62 patients with relapsed/refractory follicular lymphoma with classic characteristics. Approximately 60% of patients were double refractory, and the median number of prior systemic therapies was 3.

The escalated dose schedule ranged from 0.4 mg to 13.5 mg, administered every 3 weeks. The overall response rate was 67.7%, with a complete response in 51.6%. Interestingly, responses, including complete responses, were reported among patients with an adverse prognosis, such as those who were refractory to the last prior therapy and those who were double refractory. There was a high response rate in patients who were refractory to PI3K inhibitors. Among the 4 patients treated after chimeric antigen receptor (CAR) T-cell therapy, all responded, including 2 patients with a complete response.

The median duration of response was 20 months, suggesting a prolonged efficacy for these patients. The AE profile was similar to that described for other antibodies, but also included neutropenia, infections, and hypophosphatemia. Cytokine release syndrome occurred in 17.7% of patients, with only a few serious cases. The median duration of hospitalization for cytokine release syndrome was 2 days.

CAR T-Cell Therapy

Another category of immunotherapy agents in development for follicular lymphoma are the CAR T-cell therapies. At the ASH meeting, Dr Caron Jacobson presented updated results of the ZUMA-5 study, which evaluated axicabtagene ciloleucel in patients with relapsed/refractory indolent non-Hodgkin lymphoma.¹⁴ Results were previously presented at the European Hematology Association congress in June.¹⁵ The updated analysis reported results for 124 patients with follicular lymphoma and 22 patients with marginal zone lymphoma. These patients were heavily pretreated, with almost two-thirds having received more than 3 lines of prior therapy. In the cohort of patients with follicular lymphoma, the overall response rate was extremely high, at 94%, with 80% of patients achieving a complete response. Among all patients, the median time to a first response was a rapid 1 month. Among the patients with follicular lymphoma who initially had only a partial response, half later converted to a complete response. Responses were seen regardless of the patients' tumor burden, number of prior therapies, and exposure to different agents. The median follow-up was 17.5 months. The median duration of response had not been reached. Among the follicular lymphoma patients with a complete response, 78% were still responding at the time of the analysis. The median PFS had not been reached.

The AEs were typical for CAR T-cell therapies, and included cytopenia, cytokine release syndrome, and neurotoxicity. Frequency and severity were somewhat lower than those seen in patients with diffuse large B-cell lymphoma.¹⁶ Axicabtagene ciloleucel is therefore a promising intervention for patients with follicular lymphoma.

Dr Nathan Fowler presented preliminary results of another CAR T-cell therapy, tisagenlecleucel.¹⁷ The phase 2 ELARA trial enrolled patients with follicular lymphoma from 12 countries. The patients' characteristics were similar to those enrolled in

other studies. The trial recruited 97 patients, but results were reported for 52 patients evaluable for efficacy. The overall response rate was 83%, with 65% of patients achieving a complete response. The median duration of response was not reached.

There was a high rate of conversion from partial remissions to complete remissions, which was also observed frequently in patients treated with 4-1BB CAR T cells. The safety profile was as expected. These results are promising, and longer follow-up is needed.

Antibody-Drug Conjugates

The antibody-drug conjugates in development for follicular lymphoma include polatuzumab vedotin and loncastuximab tesirine. At the ASH meeting, Dr Francisco Hernandez-Ilizaliturri presented data from a phase 1 study of TRPH-222, an antibody-drug conjugate that targets the antigen CD22 with a payload known as maytansine.¹⁸ TRPH-222 incorporates a new type of biochemical linker between the payload and the antibody that allows a stable antibody-drug ratio.

Among the 10 patients with follicular lymphoma, the overall response rate was 50%, with a complete response rate of 40%. In some patients with a complete response, the response was maintained after several cycles. TRPH-222 had a similar safety profile as the other antibody-drug conjugates. There were a few infusion-related reactions. The most common grade 3/4 events included thrombocytopenia and neutropenia. Peripheral neuropathy was infrequent and mostly low grade. As with other antibodies that use maytansine, there were some ocular symptoms, an AE that should be considered in future research.

Tazemetostat

There were several presentations about tazemetostat, which is the first EZH2 inhibitor approved by the US Food and Drug Administration for patients with relapsed or refractory follicular lymphoma.¹⁹ Approval was based on a phase 2 study that recruited 99

patients with follicular lymphoma, either with or without the *EZH2* mutation.²⁰ This mutation occurs in approximately one-quarter of patients with follicular lymphoma.

The recently published results from the phase 2 trial of tazemetostat demonstrated an overall response rate of 69% for patients with the *EZH2* mutation and 35% for patients with wild-type disease.²⁰ The median duration of response was 10.9 months in the *EZH2*-mutated cohort and 13.0 months in the *EZH2*-wild-type cohort. At the ASH meeting, I presented results of an analysis of the phase 2 trial that aimed to better understand the efficacy of tazemetostat in patients with relapsed follicular lymphoma, when the status of the mutation is not known.²¹ This analysis of pooled data examined variables that might influence the overall response rate or the duration of response. The analysis found that the overall response rate was similar in patients with normal or high levels of lactate dehydrogenase (LDH) and was not markedly different for patients who were or were not refractory to rituximab. A significantly lower overall response rate was seen in patients who had received more than 2 lines of therapy; this response rate still remained at 40%. Patients who developed progressive disease within 24 months had an overall response rate of 39% vs 60% for the other patients. The variables that predicted duration of response included refractoriness to rituximab and a high LDH level. The median PFS was 19 months among patients who were not refractory to rituximab vs 8 months in those who were. Among patients with normal LDH levels, the median PFS was 16 months vs 7 months in those with high levels. This analysis confirmed that tazemetostat provides good control of follicular lymphoma, which is prolonged for more than 1 year in the majority of patients. Furthermore, patients with or without the *EZH2* mutation can benefit from treatment.

David Proudman presented data from a matched, indirect comparison

of tazemetostat vs PI3K inhibitors.²² The analysis showed that the response rate did not significantly differ between tazemetostat and the other compounds. The safety of tazemetostat was satisfactory, with less than 20% of patients experiencing mild side effects, such as fatigue or cytopenia, and less than 3% experiencing grade 3/4 events.

Several ongoing studies are evaluating tazemetostat. Dr Krish Patel presented the design of a new study evaluating the combination of tazemetostat plus rituximab for the treatment of relapsed or refractory follicular lymphoma.²³ Dr Connie Batlevi presented the design of a large, ongoing randomized trial that is combining tazemetostat with the recently approved regimen of lenalidomide plus rituximab (known as R²).²⁴ The study consists of different stages. The first stage will identify the recommended phase 3 doses of tazemetostat in combination with R². This stage has almost been completed. The second stage will determine the safety of this combination in a larger number of patients. The randomization will allow patients to receive tazemetostat plus R², and to continue with tazemetostat as a single agent for a 24-month maintenance phase. Therefore, the investigative arm will consist of 6 cycles of the combination followed by 2 years of maintenance, while the control arm will consist of the usual R² regimen. This important study will combine epigenetic modulation with immunotherapy. An interesting recent observation is that tazemetostat is able to enhance the expression of several immunomodulatory molecules on the surface of B cells. Tazemetostat may increase and enhance the activity of the R² regimen. This new study will be a registration trial for this regimen in relapsed/refractory follicular lymphoma.

Rituximab-Based Regimens

Dr Paolo Strati presented a study regarding the efficacy of second-line regimens in patients treated with the R² regimen in the first line.²⁵ The study showed that immunochemotherapy,

rather than biologic therapy, was optimal for this patient group.

A study in newly diagnosed follicular lymphoma compared rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) vs rituximab plus bendamustine with or without rituximab maintenance among patients with high maximum standardized uptake value (SUV_{max}) on positron emission tomography/computed tomography at diagnosis.²⁶ Dr Patrizia Mondello from our institute presented the results. R-CHOP might reduce the risk of early transformation, although this improvement was not statistically significant. Interestingly, in patients with progressive disease at 2 years, the rate of overall survival was approximately 80%, indicating that we have made progress with new treatments in controlling this disease when early progression occurs.

Treatment During the COVID-19 Pandemic

A current concern for patients with follicular lymphoma is how they will respond to vaccinations against COVID-19. Unfortunately, patients with hematologic malignancies treated with an anti-CD20 antibody had a low immune response to the virus in a study by Dr Alessandra Sottini.²⁷ It will be necessary to mitigate the risk of lymphoma progression vs treatment with anti-CD20 antibodies, especially among patients who will be candidates to receive the vaccine.

Disclosure

In the past 12 months, Dr Salles has received financial compensation for participating in advisory boards or consulting fees from AbbVie, BeiGene, BMS/Celgene, Debiopharm, Genmab, Kite/Gilead, Janssen, Miltenyi, MorphoSys, Novartis, Roche, and VelosBio. Dr Salles has received financial compensation for participation in educational events from

BMS/Celgene, Kite/Gilead, MorphoSys, Novartis, and Roche.

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Learn more about TAZVERIK for R/R FL and how it performed in a clinical trial.

Visit [TAZVERIK.com](https://www.tazverik.com) today



Tazemetostat (TAZVERIK®) is recommended in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) as an option for appropriate patients with relapsed or refractory follicular lymphoma.³

Important Safety Information (continued)

• Embryo-Fetal Toxicity (continued)

Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure (area under the plasma concentration time curve [AUC_{0-45h}]) at the 800 mg twice daily dose.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAZVERIK and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for 3 months after the final dose.

Adverse Reactions

In 99 clinical study patients with relapsed or refractory follicular lymphoma receiving TAZVERIK 800 mg twice daily: Serious adverse reactions occurred in 30% of patients who received TAZVERIK. Serious adverse reactions occurring in $\geq 2\%$ were general physical health deterioration, abdominal pain, pneumonia, sepsis, and anemia. The most common ($\geq 20\%$) adverse reactions were fatigue (36%), upper respiratory tract infection (30%), musculoskeletal pain (22%), nausea (24%), and abdominal pain (20%).

Drug Interactions

Avoid coadministration of strong or moderate CYP3A inhibitors with TAZVERIK. If coadministration of moderate CYP3A inhibitors cannot be avoided, reduce TAZVERIK dose.

Avoid coadministration of moderate and strong CYP3A inducers with TAZVERIK, which may decrease the efficacy of TAZVERIK.

Coadministration of TAZVERIK with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and reduced efficacy of CYP3A substrates.

Lactation

Because of the potential risk for serious adverse reactions from TAZVERIK in the breastfed child, advise women not to breastfeed during treatment with TAZVERIK and for one week after the final dose.

Before prescribing TAZVERIK, please read the Brief Summary of the Prescribing Information on the adjacent pages.

EZH2=enhancer of zeste homologue 2; ORR=overall response rate; CI=confidence interval; CR=complete response; PR=partial response; DOR=duration of response; NE=not estimable; IWG-NHL=International Working Group Non-Hodgkin Lymphoma.

References: **1.** TAZVERIK (tazemetostat) Prescribing Information. Cambridge, MA: Epizyme, Inc., July 2020. **2.** Data on file. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-cell Lymphomas V.4.2020. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed August 17, 2020. To view the most recent and complete version of the guideline, go online to [NCCN.org](https://www.nccn.org). NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.



TAZVERIK (tazemetostat) tablets 200mg BRIEF SUMMARY OF PRESCRIBING INFORMATION

CONSULT THE PACKAGE INSERT FOR COMPLETE PRESCRIBING INFORMATION.

INDICATIONS AND USAGE

- TAZVERIK® (tazemetostat) is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies.
- TAZVERIK is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options. These indications are approved under accelerated approval based on overall response rate and duration of response [see *Clinical Studies*]. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

DOSAGE AND ADMINISTRATION

Patient Selection - Select patients with relapsed or refractory (R/R) follicular lymphoma (FL) for treatment with TAZVERIK based on the presence of EZH2 mutation of codons Y646, A682, or A692 in tumor specimens [see *Clinical Studies*]. Information on FDA-approved tests for the detection of EZH2 mutation in relapsed or refractory follicular lymphoma is available at: <http://www.fda.gov/CompanionDiagnostics>.

Recommended Dosage - The recommended dosage of TAZVERIK is 800 mg orally twice daily with or without food until disease progression or unacceptable toxicity. Swallow tablets whole. Do not cut, crush, or chew tablets. Do not take an additional dose if a dose is missed or vomiting occurs after TAZVERIK, but continue with the next scheduled dose.

Dosage Modifications for Adverse Reactions - Table 1 summarizes the recommended dose reductions, and Table 2 summarizes the recommended dosage modifications of TAZVERIK for adverse reactions.

Table 1. Recommended Dose Reductions of TAZVERIK for Adverse Reactions

Dose Reduction	Dosage
First	600 mg orally twice daily
Second	400 mg orally twice daily*

*Permanently discontinue TAZVERIK in patients who are unable to tolerate 400 mg orally twice daily.

Table 2. Recommended Dosage Modifications of TAZVERIK for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Neutropenia [see <i>Adverse Reactions</i>]	Neutrophil count less than $1 \times 10^9/L$	<ul style="list-style-type: none"> • Withhold until neutrophil count is greater than or equal to $1 \times 10^9/L$ or baseline. • For first occurrence, resume at same dose. • For second and third occurrence, resume at reduced dose. • Permanently discontinue after fourth occurrence.
Thrombocytopenia [see <i>Adverse Reactions</i>]	Platelet count less than $50 \times 10^9/L$	<ul style="list-style-type: none"> • Withhold until platelet count is greater than or equal to $75 \times 10^9/L$ or baseline. • For first and second occurrence, resume at reduced dose. • Permanently discontinue after third occurrence.
Anemia [see <i>Adverse Reactions</i>]	Hemoglobin less than 8 g/dL	<ul style="list-style-type: none"> • Withhold until improvement to at least Grade 1 or baseline, then resume at same or reduced dose.
Other adverse reactions [see <i>Adverse Reactions</i>]	Grade 3	<ul style="list-style-type: none"> • Withhold until improvement to at least Grade 1 or baseline. • For first and second occurrence, resume at reduced dose. • Permanently discontinue after third occurrence.
	Grade 4	<ul style="list-style-type: none"> • Withhold until improvement to at least Grade 1 or baseline. • For first occurrence, resume at reduced dose. • Permanently discontinue after second occurrence.

Dosage Modifications for Drug Interactions

Strong and Moderate CYP3A Inhibitors - Avoid coadministration of TAZVERIK with strong or moderate CYP3A inhibitors. If coadministration with a moderate CYP3A inhibitor cannot be avoided, reduce the TAZVERIK dose as shown in Table 3 below. After discontinuation of the moderate CYP3A inhibitor for 3 elimination half-lives, resume the TAZVERIK dose that was taken prior to initiating the inhibitor [see *Drug Interactions, Clinical Pharmacology*].

Table 3. Recommended Dose Reductions of TAZVERIK for Moderate CYP3A Inhibitors

Current Dosage	Adjusted Dosage
800 mg orally twice daily	400 mg orally twice daily
600 mg orally twice daily	400 mg for first dose and 200 mg for second dose
400 mg orally twice daily	200 mg orally twice daily

CONTRAINDICATIONS - None.

WARNINGS AND PRECAUTIONS

Secondary Malignancies - The risk of developing secondary malignancies is increased following treatment with TAZVERIK. Across clinical trials of 729 adults who received TAZVERIK 800 mg twice daily, myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) occurred in 0.7% of patients. One pediatric patient developed T-cell lymphoblastic lymphoma (T-LBL). Monitor patients long-term for the development of secondary malignancies.

Embryo-Fetal Toxicity - Based on findings from animal studies and its mechanism of action, TAZVERIK can cause fetal harm when administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk. Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure (area under the plasma concentration time curve [AUC_{0-48h}]) at the 800 mg twice daily dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAZVERIK and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for 3 months after the final dose [see *Use in Specific Populations*].

ADVERSE REACTIONS - The following clinically significant adverse reactions are described elsewhere in labeling: Secondary Malignancies [see *Warnings and Precautions*].

Clinical Trial Experience - Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of TAZVERIK was evaluated in two cohorts (Cohorts 4 and 5) of Study E7438-G000-101 that enrolled patients with relapsed or refractory follicular lymphoma [see *Clinical Studies*]. Patients received TAZVERIK 800 mg orally twice daily (n=99). Among patients who received TAZVERIK, 68% were exposed for 6 months or longer, 39% were exposed for 12 months or longer, and 21% were exposed for 18 months or longer. The median age was 62 years (range 36 to 87 years), 54% were male, and 95% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. The median number of prior therapies was 3 (range 1 to 11). Patients were required have a creatinine clearance ≥ 40 mL/min per the Cockcroft and Gault formula. Serious adverse reactions occurred in 30% of patients who received TAZVERIK. Serious adverse reactions in $\geq 2\%$ of patients who received TAZVERIK were general physical health deterioration, abdominal pain, pneumonia, sepsis, and anemia. Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received TAZVERIK. Adverse reaction resulting in permanent discontinuation in $\geq 2\%$ of patients was second primary malignancy. Dosage interruptions due to an adverse reaction occurred in 28% of patients who received TAZVERIK. Adverse reactions requiring dosage interruptions in $\geq 3\%$ of patients were thrombocytopenia and fatigue. Dose reduction due to an adverse reaction occurred in 9% of patients who received TAZVERIK. The most common adverse reactions ($\geq 20\%$) were fatigue, upper respiratory tract infection, musculoskeletal pain, nausea, and abdominal pain. Table 6 presents adverse reactions in patients with relapsed or refractory follicular lymphoma in Cohorts 4 and 5 of Study E7438-G000-101.

Table 6. Adverse Reactions ($\geq 10\%$) in Patients with Relapsed or Refractory Follicular Lymphoma Who Received TAZVERIK in Cohorts 4 and 5 of Study E7438-G000-101

Adverse Reaction	TAZVERIK N=99	
	All Grades (%)	Grade 3 or 4 (%)
General		
Fatigue ^a	36	5
Pyrexia	10	0
Infections		
Upper respiratory tract infection ^b	30	0
Lower respiratory tract infection ^c	17	0
Urinary tract infection ^d	11	2
Gastrointestinal		
Nausea	24	1
Abdominal pain ^e	20	3
Diarrhea	18	0
Vomiting	12	1
Musculoskeletal and connective tissue		
Musculoskeletal pain ^f	22	1
Skin and subcutaneous tissue		
Alopecia	17	0
Rash ^g	15	0
Respiratory and mediastinal system		
Cough ^h	17	0
Nervous system		
Headache ⁱ	13	0

Table 6 continues on the next page

Table 6. Adverse Reactions (≥10%) in Patients with Relapsed or Refractory Follicular Lymphoma Who Received TAZVERIK in Cohorts 4 and 5 of Study E7438-G000-101 (continued)

^aIncludes fatigue and asthenia

^bIncludes laryngitis, nasopharyngitis, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection

^cIncludes bronchitis, lower respiratory tract infection, tracheobronchitis

^dIncludes cystitis, urinary tract infection, urinary tract infection staphylococcal

^eIncludes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper

^fIncludes back pain, limb discomfort, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, pain in jaw, spinal pain

^gIncludes erythema, rash, rash erythematous, rash generalized, rash maculo-papular, rash pruritic, rash pustular, skin exfoliation

^hIncludes cough and productive cough

ⁱIncludes headache, migraine, sinus headache

Clinically relevant adverse reactions occurring in <10% of patients who received TAZVERIK included:

- Infection: sepsis (2%), pneumonia (2%), and herpes zoster (2%)

Table 7 summarizes select laboratory abnormalities in patients with follicular lymphoma in Cohorts 4 and 5 of Study E7438-G000-101.

Table 7. Select Laboratory Abnormalities (≥10%) Worsening from Baseline in Patients with Relapsed or Refractory Follicular Lymphoma Who Received TAZVERIK in Cohorts 4 and 5 of Study E7438-G000-101

Laboratory Abnormality	TAZVERIK*	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Decreased lymphocytes	57	18
Decreased hemoglobin	50	8
Decreased platelets	50	7
Decreased white blood cells	41	9
Decreased neutrophils	20	7
Chemistry		
Increased glucose	53	10
Increased aspartate aminotransferase	24	0
Increased alanine aminotransferase	21	2.3
Increased alkaline phosphatase	18	1.0
Increased creatinine	17	0

*The denominator used to calculate the rate varied from 88 to 96 based on the number of patients with a baseline value and at least one post-treatment value.

DRUG INTERACTIONS

Effect of Other Drugs on TAZVERIK - Strong and Moderate CYP3A Inhibitors: Coadministration of TAZVERIK with a strong or moderate CYP3A inhibitor increases tazemetostat plasma concentrations [see *Clinical Pharmacology*], which may increase the frequency or severity of adverse reactions. Avoid coadministration of strong or moderate CYP3A inhibitors with TAZVERIK. If coadministration of moderate CYP3A inhibitors cannot be avoided, reduce TAZVERIK dose [see *Dosage and Administration*]. **Strong and Moderate CYP3A Inducers:** Coadministration of TAZVERIK with a strong or moderate CYP3A inducer may decrease tazemetostat plasma concentrations [see *Clinical Pharmacology*], which may decrease the efficacy of TAZVERIK. Avoid coadministration of moderate and strong CYP3A inducers with TAZVERIK.

Effect of TAZVERIK on Other Drugs - CYP3A Substrates: Coadministration of TAZVERIK with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and reduced efficacy of CYP3A substrates [see *Use in Specific Populations, Clinical Pharmacology*].

USE IN SPECIFIC POPULATIONS

Pregnancy - Risk Summary: Based on findings from animal studies and its mechanism of action [see *Clinical Pharmacology*], TAZVERIK can cause fetal harm when administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk. Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure [AUC_{0-48h}] at the 800 mg twice daily dose (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 pregnant rats, once daily oral administration of tazemetostat during the period of organogenesis from gestation day (GD) 7 through 17 resulted in no maternal adverse effects at doses up to 100 mg/kg/day (approximately 6 times the adult human exposure at 800 mg twice daily). Skeletal malformations and variations occurred in fetuses at doses of ≥50 mg/kg (approximately 2 times the adult human exposure at the 800 mg twice daily dose). At 200 mg/kg (approximately 14 times the adult human exposure at the 800 mg twice daily dose), major findings included increased post implantation loss,

missed digits, fused vertebrae, domed heads and fused bones of the skull, and reduced fetal body weights. In pregnant rabbits, no adverse maternal effects were observed after once daily oral administration of 400 mg/kg/day tazemetostat (approximately 7 times the adult human exposure at the 800 mg twice daily dose) from GD 7 through 19. Skeletal variations were present at doses ≥100 mg/kg/day (approximately 1.5 times the adult human exposure at the 800 mg twice daily dose), with skeletal malformations at ≥200 mg/kg/day (approximately 5.6 times the adult human exposure at the 800 mg twice daily dose). At 400 mg/kg (approximately 7 times the adult human exposure at the 800 mg twice daily dose), major findings included increased post implantation loss and cleft palate and snout.

Lactation - Risk Summary: There are no animal or human data on the presence of tazemetostat in human milk or on its effects on the breastfed child or milk production. Because of the potential risk for serious adverse reactions from TAZVERIK in the breastfed child, advise women not to breastfeed during treatment with TAZVERIK and for one week after the final dose.

Females and Males of Reproductive Potential - Pregnancy Testing: Verify the pregnancy status of females of reproductive potential prior to initiating TAZVERIK [see *Use in Specific Populations*]. **Risk Summary:** TAZVERIK can cause fetal harm when administered to pregnant women [see *Use in Specific Populations*]. **Contraception: Females -** Advise females of reproductive potential to use effective non-hormonal contraception during treatment with TAZVERIK and for 6 months after the final dose. TAZVERIK can render some hormonal contraceptives ineffective [see *Drug Interactions*]. **Males -** Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for at least 3 months after the final dose.

Pediatric Use - The safety and effectiveness of TAZVERIK in pediatric patients aged less than 16 years have not been established.

Juvenile Animal Toxicity Data - In a 13-week juvenile rat toxicology study, animals were dosed daily from post-natal day 7 to day 97 (approximately equivalent to neonate to adulthood). Tazemetostat resulted in:

- T-LBL at doses ≥50 mg/kg (approximately 2.8 times the adult human exposure at the 800 mg twice daily dose)
- Increased trabecular bone at doses ≥100 mg/kg (approximately 10 times the adult human exposure at the 800 mg twice daily dose)
- Increased body weight at doses ≥50 mg/kg (approximately equal to the adult human exposure at the 800 mg twice daily dose)
- Distended testicles in males at doses ≥50 mg/kg (approximately equal to the adult human exposure at the 800 mg twice daily dose)

Geriatric Use - Clinical studies of TAZVERIK did not include sufficient numbers of patients with relapsed or refractory follicular lymphoma aged 65 and over to determine whether they respond differently from younger subjects.

Renal Impairment - No dose adjustment of TAZVERIK is recommended for patients with mild to severe renal impairment or end stage renal disease [see *Clinical Pharmacology*].

Hepatic Impairment - No dose adjustment of TAZVERIK is recommended for patients with mild hepatic impairment (total bilirubin > 1 to 1.5 times upper limit of normal [ULN] or AST > ULN). TAZVERIK has not been studied in patients with moderate (total bilirubin > 1.5 to 3 times ULN) or severe (total bilirubin > 3 times ULN) hepatic impairment [see *Clinical Pharmacology*].

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility - Dedicated carcinogenicity studies were not conducted with tazemetostat, but T-LBL, MDS, and AML have been reported clinically and T-LBL occurred in juvenile and adult rats after ~9 or more weeks of tazemetostat administration during 13-week toxicity studies. Based on nonclinical studies in rats, the risk of T-LBL appears to be greater with longer duration dosing. Tazemetostat did not cause genetic damage in a standard battery of studies including a screening and pivotal bacterial reverse mutation (Ames) assay, an in vitro micronucleus assessment in human peripheral blood lymphocytes, and an in vivo micronucleus assessment in rats after oral administration. Fertility and early embryonic development studies have not been conducted with tazemetostat; however, an assessment of male and female reproductive organs were included in 4- and 13-week repeat-dose toxicity studies in rats and Cynomolgus monkeys. Oral daily administration of tazemetostat did not result in any notable effects in the adult male and female reproductive organs [see *Use in Specific Populations*].

PATIENT COUNSELING INFORMATION - Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Secondary Malignancies - Advise patients of the increased risk of secondary malignancies, including AML, MDS, and T-LBL. Advise patients to inform their healthcare provider if they experience fatigue, easy bruising, fever, bone pain, or paleness [see *Warnings and Precautions*].

Embryo-Fetal Toxicity - Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy [see *Use in Specific Populations*]. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with TAZVERIK and for 6 months after the final dose [see *Use in Specific Populations*]. Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for 3 months after the final dose [see *Use in Specific Populations, Nonclinical Toxicology*].

Lactation - Advise women not to breastfeed during treatment with TAZVERIK and for 1 week after the final dose [see *Use in Special Populations*].

Drug Interactions - Advise patients and caregivers to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid St. John's wort, grapefruit, and grapefruit juice while taking TAZVERIK [see *Drug Interactions*].

Brief Summary [07/2020]

TZ-FL-BR-20-0133

Rx Only

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UNSILENCE AN EXPRESSIVE INSTRUMENT

TAZVERIK® (tazemetostat) is indicated for the treatment of:

- Adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies.
- Adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options.

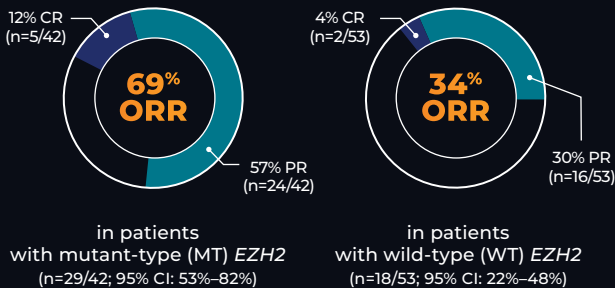
These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).



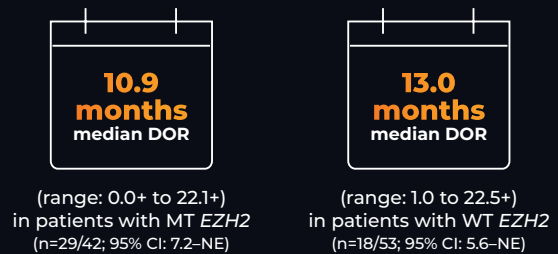
TAZVERIK, the first and only FDA-approved EZH2 inhibitor for relapsed or refractory (R/R) follicular lymphoma (FL)¹

Efficacy results*:

- **FL patients (N=95) responded** to single-agent TAZVERIK in both cohorts^{1,2}



- **Sustained response** demonstrated in patients with both MT and WT EZH2^{1,2}



The data for the MT EZH2 cohort were not yet mature at the time of assessment.

*TAZVERIK was studied in an open-label, single-arm, multicenter, phase 2 trial with 6 cohorts of patients, including 2 cohorts with histologically-confirmed R/R FL. Patients received 800 mg of TAZVERIK orally twice daily until confirmed disease progression or unacceptable toxicity. The major efficacy outcome measures were ORR and DOR according to the IWG-NHL criteria as assessed by independent review committee.^{1,2}

Important Safety Information

Warnings and Precautions

• Secondary Malignancies

The risk of developing secondary malignancies is increased following treatment with TAZVERIK. Across clinical trials of 729 adults who received TAZVERIK 800 mg twice daily, myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) occurred in 0.7% of patients. One pediatric patient developed T-cell lymphoblastic lymphoma (T-LBL). Monitor patients long-term for the development of secondary malignancies.

• Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, TAZVERIK can cause fetal harm when administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk.

Important Safety Information continued on back page of this insert.
Please see Brief Summary of the Prescribing Information on the adjacent pages.