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FOLLICULAR LYMPHOMA
SEPTEMBER 8, 2022

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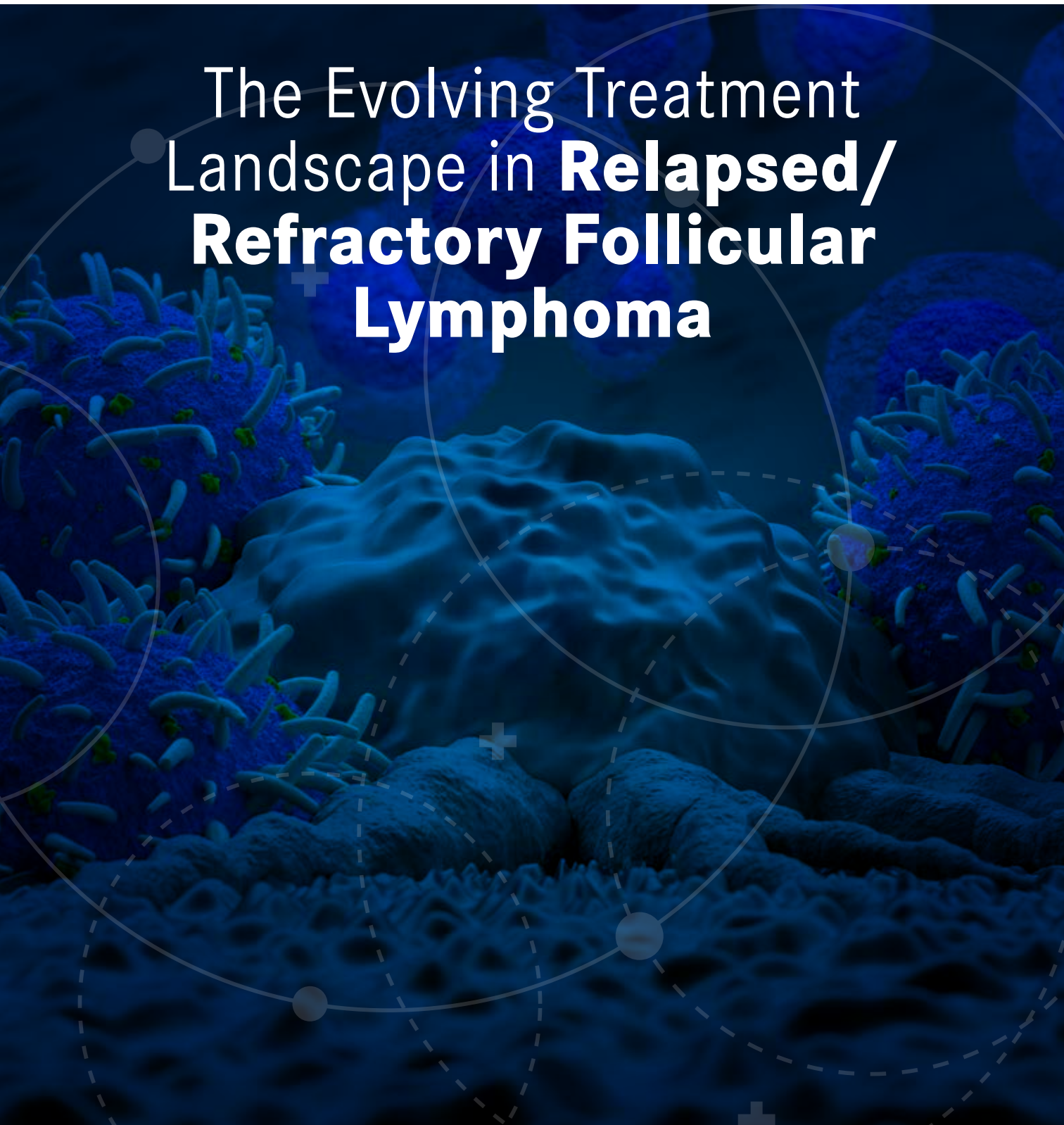

The Evolving Treatment Landscape in **Relapsed/ Refractory Follicular Lymphoma**

OncologyLive®

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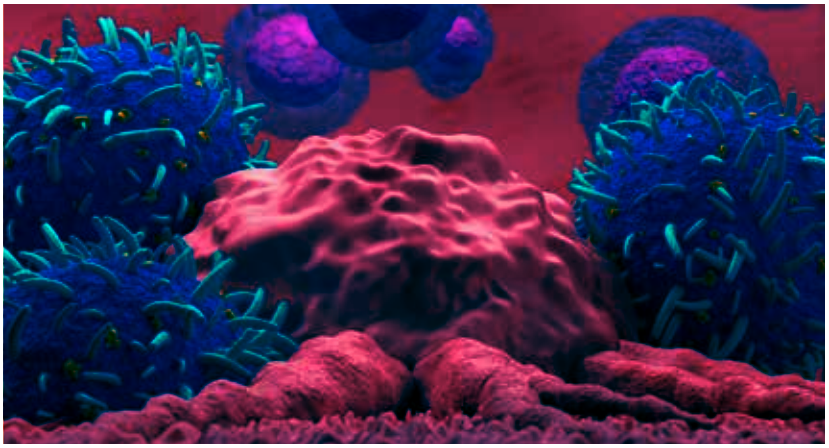


KEY TAKEAWAYS

- Many new therapeutic options are now available to treat relapsed/refractory (R/R) follicular lymphoma (FL), but identification of the ideal therapeutic sequence remains an unmet need.
- The combined use of rituximab plus lenalidomide in patients with R/R disease is common due to its efficacy, manageable toxicity profile, and patient preference.
- Tazemetostat is associated with a favorable adverse effect profile and impressive disease control rate. Given these results, tazemetostat may be an appealing treatment option in the R/R setting.
- Due to harsh toxicities and adverse patient outcomes associated with PI3K inhibitors, faculty expressed limited utility of PI3K inhibitors in patients with R/R FL. Copanlisib is sometimes used as a bridge to chimeric antigen receptor T-cell therapy.
- Although FL remains a disease that is rarely curable, faculty are encouraged by potential treatments for patients with R/R disease.

The Evolving Treatment Landscape in **Relapsed/ Refractory Follicular Lymphoma**

FOLLICULAR LYMPHOMA: UNMET NEEDS IN RELAPSED/REFRACTORY DISEASE

Overview of Follicular Lymphoma

Follicular lymphoma (FL), a lymphoproliferative disorder of transformed germinal center B cells, accounts for 20% to 25% of new non-Hodgkin lymphoma (NHL) cases diagnosed annually in the United States, representing 15,448 to 19,310 of the 77,240 new cases of NHL identified nationally in 2020.[1,2] As with most cancers, the risk of NHL increases with age; the median age at diagnosis is

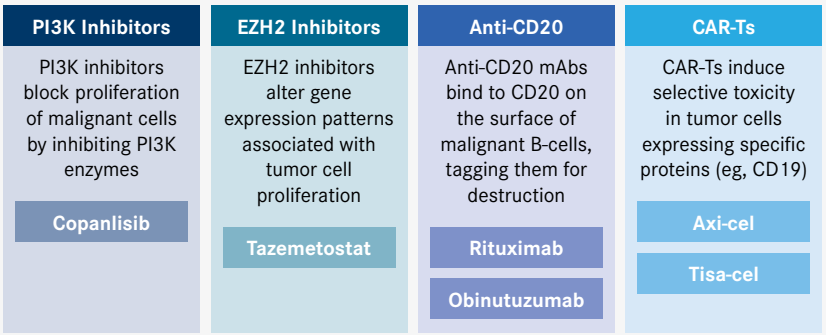
65 years.[3] Since the mid-1990s, the 5-year overall survival (OS) rate has steadily increased, and the 5-year relative survival from 2012-2018 was estimated to be 90.2%.[4] However, FL is considered a chronic and incurable disease, and a need exists for more effective treatment options.

On September 8, 2022, OncLive® brought together physicians who treat FL to participate in a virtual workshop and discuss the treatment landscape and management of patients with relapsed/refractory (R/R) FL. The discussion was led by **Krish Patel, MD**, director of the lymphoma program and director of hematologic malignancies and cellular therapy at the Swedish Center Institute in Seattle, Washington. Perspectives and insights on current treatment options, trial data, and other novel therapies were exchanged. This publication outlines fundamental data on R/R FL and stakeholder insights from the workshop.

First-Line Treatment Options & Outcomes

For the 10% of FL patients who have stage I to II disease at diagnosis, radiotherapy is highly effective; 10-year OS rates of 60% to 80% have been observed, with a median survival of 19 years.[3] However, most patients present with advanced disease. Some of these patients, if asymptomatic, may be observed without ill effects (watchful waiting); others requiring therapy may benefit from the anti-CD20 monoclonal antibody (mAb) rituximab given either alone or in combination with chemotherapy (CT) or lenalidomide (the R² regimen). Overall response rates (ORR) of approximately 70% and complete response (CR) rates of 30% have been observed with rituximab alone in patients with indolent disease. Maintenance use of rituximab after CT improves progression-free survival (PFS) rates, but its effect on OS is unclear, and the risk of toxicities is increased. R² therapy has demonstrated impressive results of increased ORR, PFS, OS, and CR in several trials, and it represents a solid option for both treatment-naive and R/R FL. A list of current therapies based on National Comprehensive Cancer Network guidelines appear in **FIGURE 1**.[5-11]

FIGURE 1.
TREATMENT OF FOLLICULAR LYMPHOMA[5-11]



axi-cel, axicabtagene ciloleucel; CAR-Ts, chimeric antigen receptor T-cells; mAbs, monoclonal antibodies; tisa-cel, tisagenlecleucel.

RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA

Current Treatment Options

Multiple relapses are common in patients with FL, and the length of PFS decreases sharply after the initial relapse (**TABLE 1**).[12]

Approximately 20% of patients relapse and progress after up to 2 years of frontline chemoimmunotherapy; this is associated with a poor prognosis and represents an unmet medical need in FL.[13] Current second- and third-line treatment options in R/R FL are chemotherapy given alone or in combination with anti-CD20 mAbs, the immunomodulatory drug lenalidomide, PI3K inhibitors, *EZH2* inhibitors, or CD-19 directed chimeric antigen receptor (CAR) T-cell therapy. A list of treatment options is depicted in **FIGURE 2**.[11]

TABLE 1.
LENGTH OF PFS WITH SUBSEQUENT LINES OF TREATMENT[12]

Treatment Line	Median PFS Years (95% CI)
First	6.62 (6.10-7.20)
Second	1.50 (1.35-1.70)
Third	0.83 (0.68-1.09)
Fourth	0.69 (0.50-0.97)
Fifth	0.68 (0.43-0.88)

PFS, progression-free survival.

Rituximab Alone or With Lenalidomide: the AUGMENT Trial

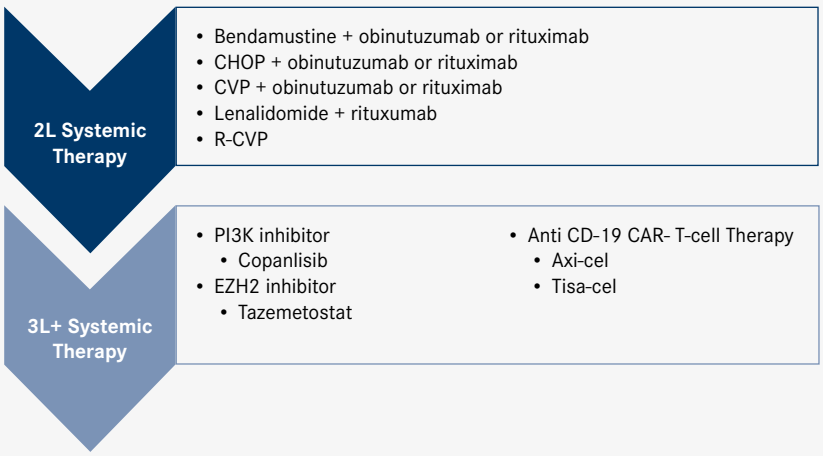
Patients who experience relapse of disease often receive rituximab as single-agent therapy; prior studies have shown that the addition of lenalidomide (R²) enhances the cytotoxic effects of rituximab.[14] The phase 3, multicenter AUGMENT trial (NCT01938001) randomly assigned patients (N = 358) with R/R FL or marginal zone lymphoma (MZL) to R² (n = 178) or placebo plus rituximab (n = 180), with the primary end point of PFS by an independent review committee (IRC).[15] Median PFS was significantly improved for the R² group (39.4 months [95% CI, 22.9 months to not reached]) vs the placebo plus rituximab group (14.1 months [95% CI, 11.4-16.7 months]), with a median follow-up of 28.3 months and a hazard ratio (HR) of 0.46 (95% CI, 0.34-0.62; $P < .0001$).

The 2-year OS rate was 95% for the R² arm and 86% for the placebo plus rituximab arm. Adverse events (AEs) were more common with use of R² vs placebo plus rituximab, respectively (infections, 63% vs 49%; neutropenia, 58% vs 23%; cutaneous reactions, 32% vs 12%). The R² group also saw more grade 3/4 neutropenia (50% vs 13%) and leukopenia (7% vs 2%), but no other grade 3/4 AE differed by 5% or more between groups. Total deaths numbered 11 for the R² arm and 24 for the placebo plus rituximab arm.

Obinutuzumab Plus Bendamustine: the GADOLIN Trial

The activity of the antineoplastic agent bendamustine and the type 2 glycoengineered anti-CD20 antibody obinutuzumab (GA101) were examined in the phase 3 GADOLIN trial (NCT01059630), which enrolled patients with R/R FL that was refractory to rituximab.[16] Patients were randomly assigned to receive bendamustine with or without obinutuzumab and the primary endpoint was PFS.[16] After a median follow-up time of 21.9 months in the bendamustine/obinutuzumab group and of 20.3 months in the bendamustine monotherapy group, the PFS was longer with the combination (median not reached [95% CI, 22.5 months to not estimable (NE)]) than with monotherapy (14.9 months [95% CI,12.8-16.6 months]) (HR, 0.55 [95% CI, 0.40–0.74]; *P* = .0001). Grade 3 to 5 AEs occurred in 68% of patients receiving bendamustine/obinutuzumab and 62% of those receiving bendamustine monotherapy; the most frequent grade 3 or greater AEs were neutropenia (33% vs 26%), thrombocytopenia (11% vs 16%), anemia (8% vs 10%), and infusion-related reactions (11% vs 6%). Serious AEs occurred in 38% of patients in the bendamustine/obinutuzumab group and 33% of those in the bendamustine monotherapy group, and deaths due to AEs occurred in 6% of both groups. An updated analysis of the results at 31.8 months demonstrated a median PFS in the intent-to-treat population of 25.8 months with bendamustine/obinutuzumab compared with 14.1 months with bendamustine alone (HR, 0.57; 95% CI, 0.44-0.73; *P* < .001) and OS was also prolonged (HR, 0.67; 95% CI, 0.47-0.96; *P* = .027).[17] The PFS and OS benefits were similar among patients with FL, confirming the PFS benefit for bendamustine/obinutuzumab in rituximab-refractory FL as found in the primary analysis. As a result of this study, obinutuzumab was FDA-approved in February 2016 for use in combination with bendamustine followed by obinutuzumab monotherapy for the treatment of patients with rituximab-R/R FL.[18]

FIGURE 2.
CURRENT 2L AND 3L TREATMENT OPTIONS IN R/R FL[11]



2L, second line; 3L, third line; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CHOP, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone; CVP, cyclophosphamide, vincristine sulfate, and prednisone; R, rituximab; tisa-cel, tisagenlecleucel.

STAKEHOLDER INSIGHTS

Patients who experience disease progression in the first 2 years after frontline therapy have worse OS than do patients who relapse later and should be considered to be at high risk.[19] Longevity in FL depends on the success of first-line therapy, and subsequent lines of treatment do not appear to improve PFS. The R² regimen is widely used by panelists, but an exacerbation of existing myelosuppression has occurred in some cases.

EZH2 INHIBITORS

Background and Rationale for EZH2 Inhibition

FL is characterized by mutations in histone-modifying enzymes such as the polycomb-group catalytic protein histone-lysine *N*-methyltransferase *EZH2*.[20] Methylation of lysine 27 of histone H3 (H3K27) occurs as a result of *EZH2* activity and represses genes responsible for cell cycle checkpoints and differentiation.[21] Approximately 25% of patients with FL have *EZH2* mutations, most of which are gain-of-function mutations on tyrosine 641.[21,22] Expression of these mutations can synergize with BCL2 deregulation, which ultimately prevents cancer cell death thereby promoting lymphoma development and providing a rationale for *EZH2*-inhibiting agents.[23]

Tazemetostat

The first-in-class oral *EZH2* inhibitor tazemetostat was granted accelerated approval by the FDA in June 2020 for patients with *EZH2* mutation–positive R/R FL who had at least 2 prior therapies or patients with R/R FL with no satisfactory alternative treatment options.[24] A companion diagnostic, the cobas *EZH2* mutation test was approved concurrently; it is required for verifying the presence of an *EZH2* mutation. FDA approval of tazemetostat was based on results of a phase 2 trial (NCT04224493) in patients with R/R FL who had at least 2 prior systemic regimens, including at least 1 anti-CD20–based regimen.[25] Patients were categorized as having an *EZH2* mutation (*EZH2*mut; n = 45) or having wild-type *EZH2* (*EZH2*WT; n = 54). The primary end point was ORR. At data cutoff with a median follow-up of 22.0 months (*EZH2*mut) and 35.9 months (*EZH2*WT), ORR was 69% in the *EZH2*mut cohort and 35% in the *EZH2*WT cohort. The median duration of response (DOR) was 10.9 months (95% CI, 7.2 months to NE) in the *EZH2*mut cohort and 13.0 months (95% CI, 5.6 months to NE) in the *EZH2*WT cohort; median PFS was 13.8 months (95% CI, 10.7-22.0 months) and 11.1 months (95% CI, 3.7-14.6 months). Grade 3 or greater treatment-related AEs (TRAES) included thrombocytopenia (3%), neutropenia (3%), and anemia (2%). Serious TRAEs were reported in 4%, and there were no treatment-related deaths.

Tazemetostat Plus R² (Triplet Therapy): SYMPHONY-1 Trial

At the 2022 Annual Meeting of the American Society of Clinical Oncology, updated results of an interim analysis of the global, multicenter, phase 1b/3 SYMPHONY-1 study (NCT04224493) was presented; the research sought to determine the recommended phase 3 dose, efficacy, and safety of tazemetostat plus R² in patients with R/R FL after at least 1 prior treatment.[26] Patients (N = 43) received 1 of 3 doses of tazemetostat (400, 600, to 800 mg orally twice daily) plus a standard dose of R². The pharmacokinetics of neither tazemetostat nor lenalidomide were altered by concomitant administration of the agents. No dose-limiting toxicities were observed, and no new safety signals were identified as of the January 2022 data cutoff. Serious treatment-emergent AEs (TEAEs) were observed in 32.6% of patients (grade 3/4 TEAEs, 55.8%), with the most common grade 3/4 TEAE being neutrophil count decrease (30.2%). The ORR was 94.7%; of patients evaluable for tumor assessment (n = 38), 50.0% demonstrated a CR, 44.7% had a partial response, and 5.3% had stable disease. These results demonstrated favorable pharmacokinetics, safety profile, and efficacy for the combination of tazemetostat plus R². The 2-arm, randomized, phase 3 portion of the trial is currently underway to further explore the efficacy and safety of tazemetostat 800 mg plus R² in approximately 500 patients with R/R FL.

PI3K INHIBITORS

Background and Rationale for PI3K Inhibition

The PI3K pathway regulates a variety of essential cellular functions; it is aberrantly activated in many cancers, contributing to cellular proliferation, metastasis, and resistance to therapy.[27,28] PI3K inhibition in lymphoma can cause apoptosis of tumor cells, disruption of the tumor microenvironment, and enhancement of antitumor immunity.

Copanlisib

Copanlisib is currently the only PI3K inhibitor approved to treat FL, following the voluntary withdrawal of the indication for duvelisib, idelalisib, and zandelisib.[29-32] Copanlisib was evaluated in the phase 2 CHRONOS-1 trial (NCT01660451) of patients with R/R, indolent, B-cell NHL who had relapsed or were refractory to at least 2 prior treatments, with the primary end point of ORR; secondary end points included DOR, PFS, and OS.[33] The study met its predefined end point with an ORR of 59%, which exceeded the prespecified threshold of 40% (95% CI, 51%-67%; $P < .001$); 17 patients (12%) achieved a CR, and 67 (47%) achieved a partial response. A 2-year follow-up of the study yielded an ORR of 60.6% and a CR of 20% (seven additional CRs since primary analysis).[33] Secondary end points demonstrated a median DOR of 14.1 months (median follow-up, 16.1 months), with a PFS of 12.5 months (median follow-up, 14.0 months) and an OS of 42.6 months (median follow-up, 31.5 months). Of the 142 enrolled patients, 99% experienced TEAEs (grade 3, 53%; grade 4, 27%). The most common TEAEs of all grades, grade 3, and grade 4, respectively, were transient hyperglycemia (50.0%, 33.1%, and 7.0%), diarrhea (35.2%, 8.5%, and 0%), transient hypertension (29.6%, 23.9%, and 0%), and neutropenia (28.9%, 9.2%, and 14.8%). No new TEAEs were reported in the results of the extended analysis compared with the primary results; 4.2% of patients experienced grade 5 events during or within 35 days after permanent discontinuation. Events considered to be related to treatment were lung infection, respiratory failure, and embolism (0.7% each). TEAEs did not increase or worsen following longer exposure in patients treated > 1 year.[33]

STAKEHOLDER INSIGHTS

The EZH2 inhibitor, tazemetostat, demonstrated impressive disease control and has a favorable safety profile. Tazemetostat appealed to clinicians as monotherapy or triplet therapy with R^2; however, as its an epigenetic modifier, results may not be rapidly observed. The clinical utility and availability of the PI3K inhibitors has been limited by disappointing clinical trial results and issues with safety. Furthermore, panelists are hesitant to use the available PI3K inhibitor, copanlisib, except in specific circumstances such as bridging to other treatments.

LOOKING AHEAD

FL remains a disease that is rarely curable, but the faculty were encouraged about future potential treatments for patients with R/R FL. The workshop concluded with a discussion of data from emerging treatment paradigms.

STAKEHOLDER INSIGHTS

The participants concluded that despite advances, patients will still have recurrences and need treatment. Longer relapse-free intervals should be an outcome in the design and investigation of new agents to treat FL. Clear guidelines are needed for sequencing therapies for maximum therapeutic effect and for second-line therapy in patients with disease that relapses within 24 months of initial therapy. ■

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Expert Perspectives: Treatment Approaches for Patients with Relapsed/Refractory Follicular Lymphoma

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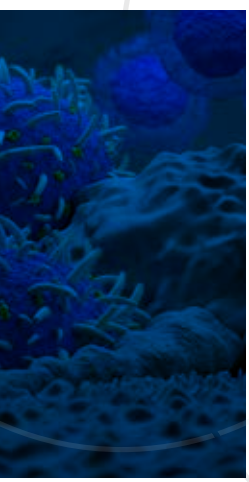
INTRODUCTION

Follicular lymphoma is a chronic and incurable disease. Multiple relapses are common with the disease; with each successive relapse, the length of progression free survival decreases sharply. Treatment options for patients with relapsed/refractory disease are limited. In recent video interviews with OncLive®, oncologists Madan L. Arora, MD; Solly Chedid, MD; and Krish Patel, MD; shared insights into the management of R/R FL. Ahead are the highlights from the interviews.

**Interview transcripts are edited for readability.*

TO WATCH THE VIDEO INTERVIEWS, VISIT **ONCLIVE.COM**



***OncLive*®: What are some of the current treatment considerations for patients with follicular lymphoma (FL)?**

KRISH PATEL, MD: There are lots of different therapies that have been [approved] in the last few years, particularly [in] the relapsed/refractory (R/R) setting. When we think about treatment approaches, there [are] some things [to take into consideration, including the] length of the initial remission after frontline treatment and what kind of frontline treatment patients received. Some clinical factors [to consider are] patient comorbidities, their health status, what risks they are willing to accept, [the] kind of support they have, [and] the duration of therapy. As an example, in the R/R lymphoma setting for [the] third line [of therapy] and beyond, we have oral medications available, [such as] tazemetostat, which can be given for a prolonged [period of time] or until treatment progression. Or we can give what we would consider a fixed-duration treatment, like CAR [chimeric antigen receptor] T-cell therapy, which patients receive as a 1-time therapy, and [they can achieve] long-term remission. [Overall, there are many things] to consider, [which] reflects the fact that there are a diversity of available [therapies] for treating R/R FL.

MADAN L. ARORA, MD: The number 1 [consideration] is deciding whom to treat [and] when to treat. Not everybody needs to be treated

right away. [For] many patients, [the] watch-and-wait [approach] is quite appropriate. Treatment decisions are made based upon GELF [Groupe d'Etude des Lymphomes Folliculaires] criteria. [First-line] treatment [typically] includes the combination of chemotherapy with immunotherapy, commonly, rituximab or obinutuzumab. [For] patients who are not eligible for or willing to take chemotherapy, rituximab alone is reasonable. Most patients respond quite well; good disease control or progression-free survival is generally achieved for 2 or more years. [A] small percentage of patients may [experience] disease progression in less than 24 months, [which suggests] an aggressive disease. [With this type of] patient, I refer them to a tertiary-care center, as the patient may require transplant or even maybe CAR-T therapy [in later lines of treatment].

[For] second-line therapy, we have many treatment options available. We may use the same drug [that was used in the first-line setting] if the interval [of response was] long (typically, > 3 years). We may [use] simpler regimens; lenalidomide plus rituximab is approved by [the] FDA for use [in this setting]. We [also] have the EZH2 drug tazemetostat, which is approved [in the] third-line [setting and] beyond. Beyond that, if the disease progresses for select patients who have a good support system [and a] reasonable performance status, we have CAR T-cell therapy and stem cell transplant available.

OncLive®: Where do PI3K and EZH2 inhibitors fit into the treatment landscape for patients with FL?

ARORA: [EZH2 inhibitors are] FDA-approved in the third line and beyond for [FL], [although] the label gives us some degree of flexibility [such that it] may [be] used in the second-line [setting] if the patient is not a candidate for another treatment. PI3K drugs are gradually disappearing, as the FDA has withdrawn approval [for] 2 of them. Copanlisib is the only [PI3K inhibitor] available at this time, [and it is an intravenously-administered drug]. I was very much hopeful about umbralisib, but that [was] also withdrawn [by the] FDA. I would [say that] bispecifics are going to replace the PIK3 [inhibitors] completely, and tazemetostat is going to stay, considering [it is] well-tolerated [with good] efficacy.

OncLive®: What are some of the benefits of utilizing tazemetostat as a monotherapy?

PATEL: One of the main advantages of tazemetostat is its adverse event (AE) profile; grade 3 and 4 AEs were uncommon in the clinical trial that led to its approval. In my experience, patients [do not] experience a lot of physical symptoms [with it], so that makes it a tool [for use in] broad population. We can give it to patients who have other medical conditions or take other medications without as much concern about the [AEs] they may experience. It is not to say there are not any [AEs]—all medicines have some [AEs]— but [tazemetostat is] generally well-managed, and [it does] not to lead to treatment discontinuation [often].

SOLLY CHEDID, MD: It is extremely well-tolerated. The response rate in patients [with] *EZH2*-mutated [disease] is extremely high—[around] 69%, or something along those lines. It is extremely well-tolerated, so, even after treatment, the patient has a good performance status. In an ideal world, we will be able to combine it with other agents, like rituximab, if necessary.

OncLive®: How could results of the SYMPHONY-1 trial evaluating tazemetostat plus lenalidomide and rituximab affect the utilization of this drug in an earlier-line setting?

PATEL: Tazemetostat is approved in the third line or [a] later setting in *EZH2*-mutated FL or as a therapy when there are no other options in wild-type FL. Patients with FL who have had at least 1 prior line of therapy are [currently] treated with a combination of lenalidomide and rituximab, or [the] so-called R^2 [regimen]. The SYMPHONY-1 trial is [comparing] the addition of tazemetostat to the R^2 regimen with R^2 alone. Tazemetostat [as a monotherapy is well-tolerated], so the [option] to add it to other treatments [is] certainly [possible]. The phase 1 run-in [period] of [the SYMPHONY-1] study demonstrated that in an uncontrolled, dose-escalated cohort [of patients with FL], the overall response rate and the complete response rate with tazemetostat plus R^2 was relatively high. If [the outcomes are similar] in the randomized portion of the trial, then, in the future, we [could] use tazemetostat plus R^2 as an earlier therapy.

ARORA: R^2 is approved [in the second-line setting], and [it is a] well-tolerated regimen. [Tazemetostat] does not seem to add much toxicity [to R^2], and [it has a] different mechanism of action, [so the combination of] R^2 and rituximab [in the] second-line [setting] is going to result [in] the best efficacy without much added toxicity.

OncLive®: What are some of the biggest unmet needs for patients with R/R FL?

CHEDID: As [patients with FL] live for a really long time, [there are several] unmet needs for these patients. [They] go through multiple lines of therapy, and [they can] run out of drugs to use [for treatment]. We are able to recycle the agents, but the time on therapy or the duration of response starts to [decrease] a lot. There is a small percentage of patients that do relatively poorly, and [these patients] are not well served by the current medications we have.

ARORA: Number 1, we do not have any standardized guidelines [for] patients [who experience] disease progression within 24 months [of initial treatment]. Many of them may be treated like a [patients with] diffuse large B-cell lymphoma, and the efficacy is not the greatest. Secondly, [there is still no] cure in sight. At best,

treatment continues to be palliative, [as FL] is a long-term disease. Patients go into remission, eventually relapse, and, ultimately, they succumb to the disease.

PATEL: There is a population of patients we consider to be [at a] high risk of death due to FL—patients with progression of disease within 24 months of initial therapy. This is certainly a population that has an unmet need. [We need] better ways to [identify] these patients up front and incorporate the best treatments in the frontline strategy to avoid early disease progression. Better therapies that improve the outcomes for patients who have had disease progression [are also needed].

OncLive®: What excites you the most about investigational agents for the management of FL from recent conference updates?

PATEL: [Therapeutic agents that are] being evaluated and, perhaps, [that are] close to being available for patients with FL [include] bispecific antibodies [that target C3 and CD20]. [They] have demonstrated very promising activity in patients with R/R FL. We are all eagerly awaiting approval of these agents for broader use outside of clinical trials. Cellular immunotherapies, like CAR T-cell [therapy], are [also] a very good tool [for the treatment of R/R FL]. As we evolve, newer cellular immunotherapies, including allogeneic CAR-T cells, or cellular therapies of different immune cells, like natural killer cell–based therapies, [may be important therapeutic options]. These are tools that, hopefully, will have an impact in R/R FL in the future].

OncLive®: What is your biggest takeaway for colleagues regarding the role of tazemetostat in the management of FL?

CHEDID: For the *EZH2*-mutated patients, [tazemetostat] is [associated] with an extremely high response rate, [and it] can easily be given to patients. Even patients [who] are intolerant to all other therapies and do not have any other good options still have a very good response rate [with tazemetostat].

ARORA: Big progress has been made in treatment options [for FL]. [This malignancy] is also becoming a chronic disease now, with a multitude of treatment options available. Survival is definitely prolonged for [the] majority [of patients], and they are maintaining a reasonable quality of life.

PATEL: Tazemetostat is an important option for us to think about, especially in patients [for whom] a low adverse event profile is desired, because it is a therapy that can be given to a broad range of patients. [Tazemetostat is] potentially usable in patients beyond those with mutated *EZH2*, so [it] can be beneficial in some patients with wild-type *EZH2*, as well. It's an important treatment for us to think about, and, certainly, as the future unfolds, we will find other places to potentially use it. ■

NOTES

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