AHFS Final Determination of Medical Acceptance: Off-label Use of Loncastuximab tesirine plus Rituximab in Follicular Lymphoma

Drug: Loncastuximab tesirine

Off-label Use: Follicular lymphoma

Off-label Use for Review:

- Results from an ongoing, single-arm, phase 2 study

Strength of Evidence: Level 2 (moderate strength/quality)

Grade of Recommendation: Reasonable choice (accepted, with possible conditions)

Narrative Summary:

Follicular lymphoma, an indolent subtype of B-cell non-Hodkin lymphoma (NHL), comprises approximately 20% of all NHLs.[10001] The majority of patients with follicular lymphoma are ≥50 years of age and present with extensive disease upon diagnosis; median survival ranges from 8 to 15 years, even with advanced disease.[10001] Watchful waiting remains standard care for follicular lymphoma initially and for patients with slow asymptomatic relapsing disease.[10001] Per the National Cancer Institute (NCI), there are numerous therapeutic options, administered in varying sequences, when therapy is required.[10001] For those with advanced disease, first-line therapy is composed of a chemotherapy backbone or lenalidomide in combination with an anti-CD20 antibody.[10002] In patients with relapsed or refractory follicular lymphoma, no standard-of-care treatment currently exists.[10002]

A single-arm, investigator-initiated, phase 2 trial evaluated the use of loncastuximab tesirine plus rituximab in patients with relapsed or refractory follicular lymphoma.[10002] This ongoing study was performed at the Sylvester Comprehensive Cancer Center in Miami, FL and enrolled adults (≥18 years of age) with histologically confirmed follicular lymphoma (grade 1, 2, or 3A) and relapsed or refractory disease treated prior with ≥1 lines of systemic therapy.[10002] Eligible patients also had an Eastern Cooperative Oncology Group (ECOG) performance status

of 0 to 2, life expectancy of >6 weeks, and appropriate organ function.[10002] A total of 39 patients were enrolled.[10002] Loncastuximab tesirine 0.15 mg/kg IV over 30 minutes was administered once every 3 weeks on Day 1 of a 21-day cycle for the initial 2 cycles, followed by 0.075 mg/kg for subsequent cycles. [10002] Rituximab 375 mg/m^2 IV was administered on Day 1 of Cycle 1 for four weekly doses during induction (Cycles 1-4), followed by a single dose every 8 weeks during maintenance (Cycles 5 to 7). [10002] During the induction and first maintenance phases (cycles 1 to 5; 21 weeks), a total of 7 doses of loncastuximab tesirine and 5 doses of rituximab were administered. [10002] The use of subcutaneous rituximab 1400 mg/hyaluronidase 23,400 units was permissible at any stage. [10002] If a patient experienced a complete response at week 21 (the beginning of the second maintenance phase), loncastuximab tesirine was discontinued and two more rituximab doses were administered every 8 weeks. [10002] If a partial response was observed at week 21, patients continued loncastuximab tesirine every 21 days and rituximab every 8 weeks for 18 additional weeks. [10002] Upon the end of study treatment, patients were followed for 2 years to obtain disease progression and survival data.[10002] Patients who experienced stable disease or disease progression on imaging at week 12 or 21 were dismissed from study treatment. [10002] The primary study endpoint was complete response via [^{18}F]FDG-PET-CT at week 12 as assessed by Lugano 2014 criteria.[10002] Key secondary endpoints included overall response rate at week 12, safety and tolerability of the combination, and progression-free survival and overall survival at 2 years.[10002]

At baseline, the median age of patients was 68 years (range: 58 to 77 years), 54% were male, and the majority were white (95%).[10002] Enrolled patients had an ECOG performance status of 0 (74%) or 1 (26%) and most experienced grade 1-2 disease (72%).[10002] Refractory disease was present in 51% of patients; 49% had relapse.[10002] The number of prior lines of therapy was 1 in 26 patients, 2 in 2 patients, and 3 to 6 in 11 patients.[10002]

The overall response rate at week 12 was 97% (38 of 39 patients).[10002] A complete response rate of 67% (n=26) was observed at week 12, with 23 of these 26 patients maintaining a complete response at week 21.[10002] Of note, 4 of 12 patients with a partial response at week 12 improved to a complete response at week 21.[10002] This translated to an overall best complete response rate across weeks 12 and 21 of 77%.[10002] The median time to overall response was 2.7 months.[10002] Post hoc, responses were observed across all high risk subgroups.[10002]

At the time of data cutoff for this analysis, the median follow-up was 18.2 months.[10002] The median duration of a complete or partial response as a “best response” was 16.2 and 6 months, respectively.[10002] Progression-free and overall survival at 12 months were similar: 94.6% and 94.1%, respectively (median progression-free survival and overall survival not yet reached).[10002] Three events were recorded up to the data cutoff.[10002] These included 2 patients with disease progression (biopsy-proven transformation to diffuse large B-cell lymphoma with subsequent death) and a single patient with relapsed follicular lymphoma under observation due to asymptomatic and localized disease.[10002]

The most common treatment-emergent adverse events (TEAEs) in the safety set included hyperglycemia (44%), increased alkaline phosphatase (41%), and neutropenia, fatigue, and

increased AST and ALT (38% each).[10002] The most common grade 3 or worse TEAE was lymphopenia (21%).[10002] Permanent discontinuation of loncastuximab tesirine due to a TEAE occurred in a single patient.[10002] Dose reduction of loncastuximab tesirine was necessary in 4 patients due to grade 2 generalized edema, grade 3 dyspnea, grade 3 skin infection, and grade 3 ɣ-glutamyltransferase elevation.[10002] Four serious TEAEs were considered to be related to the study drugs (grade 3 febrile neutropenia, grade 3 dyspnea, grade 3 generalized edema, grade 3 skin infection).[10002] No fatal TEAEs were recorded.[10002]

Based on current evidence, loncastuximab tesirine, in combination with rituximab, as a third-line and subsequent treatment in follicular lymphoma, has Level 2 (moderate strength/quality) evidence supporting its use.[10002] This combination results in clinically meaningful activity in relapsed or refractory disease with a manageable safety profile.[10002] However, it is important to note that this limited sample size study is still enrolling patients, is occurring at a single center only, and enrolled patients lack racial diversity.[10002] In addition, many patients were administered loncastuximab tesirine with rituximab as a second-line option in the study.[10002]

Dosage

When loncastuximab tesirine is used in combination with rituximab as a third-line and subsequent treatment in follicular lymphoma, the usual dosage of loncastuximab tesirine is 0.15 mg/kg IV over 30 minutes once every 3 weeks on Day 1 of a 21-day cycle for the initial 2 cycles, followed by 0.075 mg/kg for subsequent cycles.[10002] Rituximab 375 mg/m^2 IV was administered on Day 1 of Cycle 1 for 4 once weekly doses during the induction phase (Cycles 1-4), followed by a single dose every 8 weeks during the 9-week maintenance cycles (Cycles 5-7), for a total of 7 doses of loncastuximab tesirine and 5 doses of rituximab during the initial 21 weeks (induction and first maintenance phase).[10002] In the second maintenance phase, patients with a complete response were administered 2 more rituximab doses every 8 weeks while those with a partial response continued loncastuximab tesirine every 21 days and rituximab every 8 weeks for 18 more weeks, for a total of 13 doses of loncastuximab tesirine and 7 doses of rituximab.[10002]

References:

10001. National Cancer Institute. Indolent B-cell non-Hodgkin lymphoma (PDQ®) Health Professional Version. Indolent B-Cell Non-Hodgkin Lymphoma Treatment (PDQ®) NCI. Updated May 14, 2025.

10002. Alderuccio JP, Alencar AJ, Schatz JH, et al. Loncastuximab tesirine with rituximab in patients with relapsed or refractory follicular lymphoma: a single-centre, single arm, phase 2 trial. *Lancet Haematol*. 2025;12:e23-34.

Oncology Expert Committee Voting Results and Comments:

First-Round Vote (6 of 7 committee members returned the initial ballot):

Proposed Level of Evidence: Level 2 (Moderate strength/quality)

Concur with rating: 5 votes

Do not concur with rating: 1 vote

One committee member disagreed and voted for a **Level 3: Low Strength/Quality Evidence** rating.

Grade of Recommendation:

Recommended use (Accepted): 0 votes

Reasonable choice (Accepted, with possible conditions): 5 respondents

Not fully established (Equivocal): 1 respondent

Not recommended (Unaccepted): 0 respondent

Reviewer Comments on Level of Evidence and Grade of Recommendation

While most of the patients in this study were treated in the second-line setting, it is reasonable to limit this recommendation to the third-line+ of treatment given the very small sample size and abundance of better-established treatment options already available in the second-line setting. The low rates of grades 3-4 non-hematological TEAEs are encouraging but it should be noted that patients enrolled were all ECOG 0-1 (although the protocol allowed for up to ECOG 2). The high CR rates and relatively low toxicity could also make loncastuximab tesirine + rituximab a useful option in the rare case that a patient with FL proceeds to an allogeneic HSCT.

Based on excellent clinical summary, that included the investigator-initiated phase 2 trial conducted at the Sylvester Comprehensive Cancer Center, the combination of loncastuximab tesirine and rituximab demonstrates promising activity with a manageable safety profile in patients with relapsed or refractory follicular lymphoma, particularly in the third-line and later settings. The high overall and complete response rates observed, even among high-risk subgroups, support its potential role as a chemotherapy-free, targeted treatment option for patients who have exhausted conventional therapies. Given the single-arm nature of the study, further validation in randomized settings—such as the ongoing LOTIS-5 Phase 3 trial—is warranted to establish this combination as a standard therapeutic strategy.

While I agree with the level 2 rating of the evidence, it is worth noting that the study is not completed with enrollment, and our analysis is based on patients accrued up to a certain point (September 2024)

The study enrolled mainly patients undergoing second-line treatment, so it was not carried out to support a third-line option. It was single-center with a very small study population. Although it is thought-provoking, it is not practice-changing and requires further investigation.

The narrative summary indicates that this combination is an option for 3rd line and subsequent therapy. From the footnote, this is likely due to being in alignment with the NCCN guidelines which lists loncastuximab and rituximab under the "THIRD-LINE AND SUBSEQUENT THERAPY" section for Follicular Lymphoma. However, in the NCCN Guidelines it designates that "Subsequent systemic therapy options include second-line therapy regimens (FOLL-B 2 of 6) that were not previously given." This trial was designed in a way that patients that progressed after 1 line of therapy would be eligible for this treatment - in fact a majority of patients (26/39) were only on 1 line of therapy prior to starting this treatment. Therefore, designating this regimen as a 2nd line treatment would be more appropriate. I would propose to edit the lines to the following: "Based on current evidence, loncastuximab tesirine, in combination with rituximab, as a third-line..." --&; "Based on current evidence, loncastuximab tesirine, in combination with rituximab, as a second-line..." "When loncastuximab tesirine is used in combination with rituximab as a third-line and subsequent treatment in follicular lymphoma..." --&; "When loncastuximab tesirine is used in combination with rituximab as a second-line and subsequent treatment in follicular lymphoma..."

Consensus Vote (6 of 7 committee members returned the consensus ballot):

Proposed Level of Evidence: Level 2 (Low strength/quality)

Concur with rating: 6 votes

Do not concur with rating: 0 votes

Grade of Recommendation:

Recommended use (Accepted): 0 votes

Reasonable choice (Accepted, with possible conditions): 5 votes

Not fully established (Equivocal): 1 vote

Not recommended (Unaccepted): 0 votes

Final Grade of Recommendation: Reasonable choice (accepted, with possible conditions)

Participants:

AHFS Staff Members (writing and editing): Michael Gabay PharmD, JD, BCPS

AHFS Oncology Expert Committee Members (reviewing and voting): Chase Ayres PharmD, BCOP; Sandra Cuellar PharmD, BCOP; Chelsea Gustafson PharmD, BCOP; Isabel Houlzet PharmD, BCOP; Kathleen Wiley MSN, RN; Andrew Li PharmD, BCOP; John Villano MD, PhD

Conflict of Interest Disclosures:

Individuals who substantively participated in the development, review, and/or disposition of this off-label oncology determination were screened for direct and indirect conflicts of interests involving themselves, their spouse, and minor children. No conflicts of interest were identified for this determination.

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