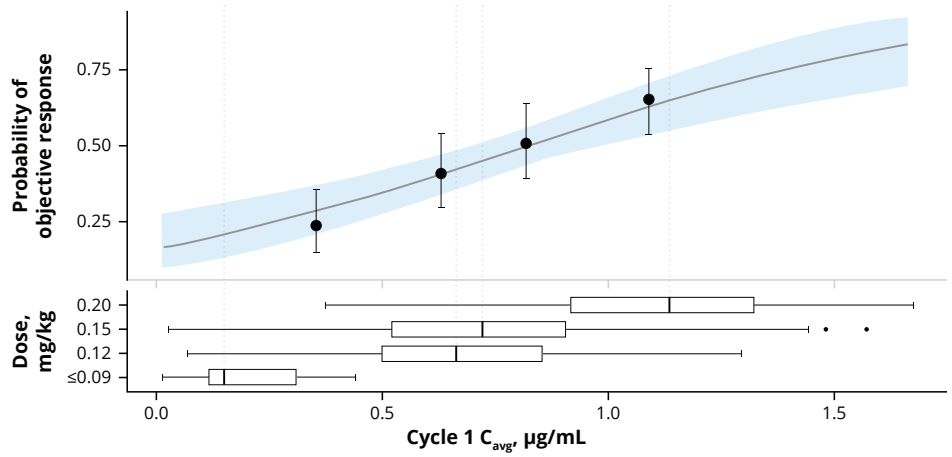
Dose Exposure–Response Analysis of Loncastuximab Tesirine in Patients With B-cell Non-Hodgkin Lymphoma

Population pharmacokinetic modeling and exposure–response analyses are crucial tools in drug development and clinical research because they provide a way to understand better how drugs work in different populations and how they affect different patient outcomes. Loncastuximab tesirine (loncastuximab tesirine-lpyl [Lonca]) is an antibody–drug conjugate comprising a humanized anti-CD19 antibody (Ab) conjugated to a pyrrolobenzodiazepine (PBD) dimer cytotoxin that is indicated for patients with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL) after ≥2 lines of prior systemic therapy at 0.15 mg/kg every 3 weeks (Q3W) for the first 2 cycles and then 0.075 mg/kg Q3W for subsequent cycles.[1]

METHODS

Relationships between exposure (PBD-conjugated antibody [cAb] cycle 1 average concentration [C_{avg}]) and efficacy (objective response rate [ORR]) events were explored with univariate and multivariate logistic regression analyses.

Relationship of ORR to Lonca Exposure*[2]



Top graph: the relationship between the level of exposure to the PBD-conjugated antibody and the probability of response. The solid circles with vertical lines are the observed ORR (95% CI) values for each quartile of cycle 1 C_{avg}; the middle line and shaded blue area represent the predicted ORR (95% CI).

Bottom graph: loncastuximab tesirine cycle 1 C_{avg} across 4 doses. The black circles on the box and whisker plot represent patients whose C_{avg} concentrations were outside of the 95% CI.

ORR increases with increasing Lonca exposure

HOW TO INTERPRET THE GRAPH

To find the probability of an objective response (top graph) for a patient:

- Find the patient's dose from the y-axis of the bottom graph (eg, 0.15 mg/kg)
- Identify the median cycle 1 C_{avg} concentration value from the dose's corresponding box and whisker plot (eg, ~0.75 µg/mL)
- Follow the median value vertically until it intersects with the plot line of the top graph to find the objective response (eg, ~47%)

Cycle 1 C_{avg}, Baseline Tumor Sum of Area, and Disease Phenotype Are Predictors of ORR[3]

	Estimate	Odds ratio (95% CI)	p-value
Cycle 1 C_{avg} (µg/mL)	1.807	6.095 (2.647, 14.749)	0.000035
Baseline tumor sum of area (cm^2)	-0.015	0.985 (0.977, 0.992)	0.0000813
Selected high-risk disease phenotype	-0.733	0.48 (0.268, 0.847)	0.01218

- Upon further refinement, the average concentration at cycle 1 maintained a statistically significant relationship that positively correlated with the ORR.
  - The odds of the objective response increased by 1.198-fold for every 0.1 µg/mL–increase in cycle 1 C_{avg}.
  - There was a higher frequency of TEAEs, including hematologic abnormalities, peripheral edema, and liver test abnormalities, in the 0.20 mg/kg–dose group than in lower-dose groups.[4]
- A higher baseline tumor sum of area and the presence of a high-risk disease phenotype could cause the predictive probability to be lower than what is depicted in the univariate analysis.
  - The odds of the objective response decreased by 0.985-fold for a 1 cm^2–increase in the baseline tumor sum of area and 0.48-fold for selected high-risk phenotypes.

KEY TAKEAWAY

In this study, a statistically significant relationship was found between a patient's objective response and their average circulating dose concentration of Lonca at cycle 1. Therefore, administering the labeled dose (0.15 mg/kg for the first 2 cycles and 0.075 mg/kg Q3W for subsequent cycles) optimized objective responses while reducing toxicity.

*Based on the cycle 1 circulating dose concentration.
C_{avg}, average serum concentration; DLBCL, diffuse large B-cell lymphoma; Lonca, loncastuximab tesirine; ORR, objective response rate; Q3W, every 3 weeks; R/R, relapsed/refractory; TEAEs, treatment-emergent adverse events.
1. ZYNLONTA® (loncastuximab tesirine-lpyl) prescribing information. Murray Hill, NJ; ADC Therapeutics; October 2022. 2. Hess B, et al. *AAPS J*. 2021;24:11. 3. Data on file, ADC Therapeutics. 4. Hamadani M, et al. *Blood*. 2021;137:2634-2645.

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SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Effusion and Edema

Serious effusion and edema occurred in patients treated with ZYNLONTA®. Grade 3 edema occurred in 3% (primarily peripheral edema or ascites) and Grade 3 pleural effusion occurred in 3% and Grade 3 or 4 pericardial effusion occurred in 1%.

Monitor patients for new or worsening edema or effusions. Withhold ZYNLONTA® for Grade 2 or greater edema or effusion until the toxicity resolves. Consider diagnostic imaging in patients who develop symptoms of pleural effusion or pericardial effusion, such as new or worsened dyspnea, chest pain, and/or ascites such as swelling in the abdomen and bloating. Institute appropriate medical management for edema or effusions.

Myelosuppression

Treatment with ZYNLONTA® can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia. Grade 3 or 4 neutropenia occurred in 32%, thrombocytopenia in 20%, and anemia in 12% of patients. Grade 4 neutropenia occurred in 21% and thrombocytopenia in 7% of patients. Febrile neutropenia occurred in 3%.

Monitor complete blood counts throughout treatment. Cytopenias may require interruption, dose reduction, or discontinuation of ZYNLONTA®. Consider prophylactic granulocyte colony-stimulating factor administration as applicable.

Infections

Fatal and serious infections, including opportunistic infections, occurred in patients treated with ZYNLONTA®. Grade 3 or higher infections occurred in 10% of patients, with fatal infections occurring in 2%. The most frequent Grade ≥3 infections included sepsis and pneumonia.

Monitor for any new or worsening signs or symptoms consistent with infection. For Grade 3 or 4 infection, withhold ZYNLONTA® until infection has resolved.

Cutaneous Reactions

Serious cutaneous reactions occurred in patients treated with ZYNLONTA®. Grade 3 cutaneous reactions occurred in 4% and included photosensitivity reaction, rash (including exfoliative and maculo-papular), and erythema.

Monitor patients for new or worsening cutaneous reactions, including photosensitivity reactions. Withhold ZYNLONTA® for severe (Grade 3) cutaneous reactions until resolution. Advise patients to minimize or avoid exposure to direct natural or artificial sunlight including exposure through glass windows. Instruct patients to protect skin from exposure to sunlight by wearing sun-protective clothing and/or the use of sunscreen products. If a skin reaction or rash develops, dermatologic consultation should be considered.

Embryo-Fetal Toxicity

Based on its mechanism of action, ZYNLONTA® can cause embryo-fetal harm when administered to a pregnant woman because it contains a genotoxic compound (SG3199) and affects actively dividing cells.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ZYNLONTA® and for 10 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ZYNLONTA®, and for 7 months after the last dose.

ADVERSE REACTIONS

In a pooled safety population of 215 patients (Phase 1 and LOTIS-2), the most common (>20%) adverse reactions, including laboratory abnormalities, were thrombocytopenia, increased gamma-glutamyltransferase, neutropenia, anemia, hyperglycemia, transaminase elevation, fatigue, hypoalbuminemia, rash, edema, nausea, and musculoskeletal pain.

In LOTIS-2, serious adverse reactions occurred in 28% of patients receiving ZYNLONTA®. The most common serious adverse reactions that occurred in ≥2% receiving ZYNLONTA® were febrile neutropenia, pneumonia, edema, pleural effusion, and sepsis. Fatal adverse reactions occurred in 1%, due to infection.

Permanent treatment discontinuation due to an adverse reaction of ZYNLONTA® occurred in 19% of patients. Adverse reactions resulting in permanent discontinuation of ZYNLONTA® in ≥2% were gamma-glutamyltransferase increased, edema, and effusion.

Dose reductions due to an adverse reaction of ZYNLONTA® occurred in 8% of patients. Adverse reactions resulting in dose reduction of ZYNLONTA® in ≥4% was gamma-glutamyltransferase increased.

Dosage interruptions due to an adverse reaction occurred in 49% of patients receiving ZYNLONTA®. Adverse reactions leading to interruption of ZYNLONTA® in ≥5% were gamma-glutamyltransferase increased, neutropenia, thrombocytopenia, and edema.

DOSAGE MODIFICATIONS AND DELAYS

Recommended Dosage Modifications for Adverse Reactions

For any Grade 3 or greater nonhematologic toxicity, ZYNLONTA® should be held until the toxicity resolves to Grade 1 or less. For neutropenia: if absolute neutrophil count is <1 x 10^9/L, withhold ZYNLONTA® until the neutrophil count returns to 1 x 10^9/L or higher. For thrombocytopenia: if platelet count is <50,000/mcL, withhold ZYNLONTA® until the platelet count returns to 50,000/mcL or higher. For Grade 2 or greater edema or effusion, ZYNLONTA® should be held until the toxicity resolves to Grade 1 or less.

Recommendations for Dosage Delays

If dosing is delayed by more than 3 weeks due to toxicity related to ZYNLONTA®, reduce subsequent doses by 50%. If toxicity reoccurs following dose reduction, consider discontinuation. Note: If toxicity requires dose reduction following the second dose of 0.15 mg/kg (Cycle 2), the patient should receive the dose of 0.075 mg/kg for Cycle 3.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to ADC Therapeutics at 1-855-690-0340.

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