Loncastuximab Tesirine Dosing & Administration

THERAPEUTICS
Innovating Science. Inspiring Hope.

Disclaimer

This material is intended for field medical use in scientific exchange and/or in response to unsolicited requests for medical information.

Please note that sharing, copying, or disseminating the following material(s) outside of ADCT may be in violation of copyright law. Please do not share, copy, or disseminate the following material(s).

LONCA

Table of Contents

Indication and Usage

Loncastuximab tesirine (Lonca) is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma.

This indication is approved under accelerated approval based on the overall response rate. Continued approval for this indication may be contingent upon the verification and description of the clinical benefit in a confirmatory trial(s).

Lonca Dosing and Administration Overview

Recommended Dose

0.15 mg/kg first 2 cycles

0.075 mg/kg subsequent cycles

In LOTIS-2, Lonca was administered until progressive disease or unacceptable toxicity

Premedication

Dexamethasone 4 mg (oral or intravenous) twice daily for 3 days beginning the day before Lonca infusion (unless contraindicated)

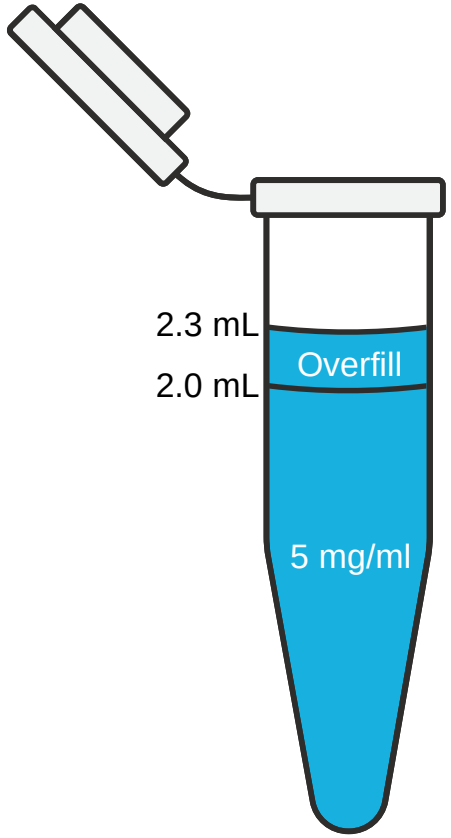
If dexamethasone administration does not begin the day before Lonca, it should begin at least 2 hours prior to Lonca infusion

Administration

Administer by intravenous infusion over 30 minutes every 3 weeks

Lonca Reconstitution and Dilution

- Lonca is supplied as a lyophilized powder in a 10-mg single-dose vial for reconstitution and further dilution[1]
- Reconstitute each Lonca vial using 2.2 mL of sterile water for injection to obtain a final concentration of 5 mg/mL[1]
  - The overfill amount of Lonca is approximately 0.3 mL after reconstitution[2]
  - The overfill ensures that approximately 2 mL of the drug at a concentration of 5 mg/mL can be extracted from the vial
- Withdraw the required volume of the reconstituted solution from the Lonca vial using a sterile syringe[1]
- Add the calculated dose volume of the Lonca solution into a 50-mL infusion bag of 5% dextrose injection, USP[1]



Dosing & Administration

Lonca Dose Calculation

- Calculate the total dose (mg) required based on the patient's weight and prescribed dose
- For patients with a body mass index ≥35 kg/m^2, calculate the dose based on an adjusted body weight (ABW) as follows:
  - ABW in kg = 35 kg/m^2 × (height in meters)^2
- More than one vial may be needed to achieve the calculated dose
- Convert the calculated dose (mg) to volume using 5 mg/mL, which is the concentration of Lonca after reconstitution

Lonca Administration

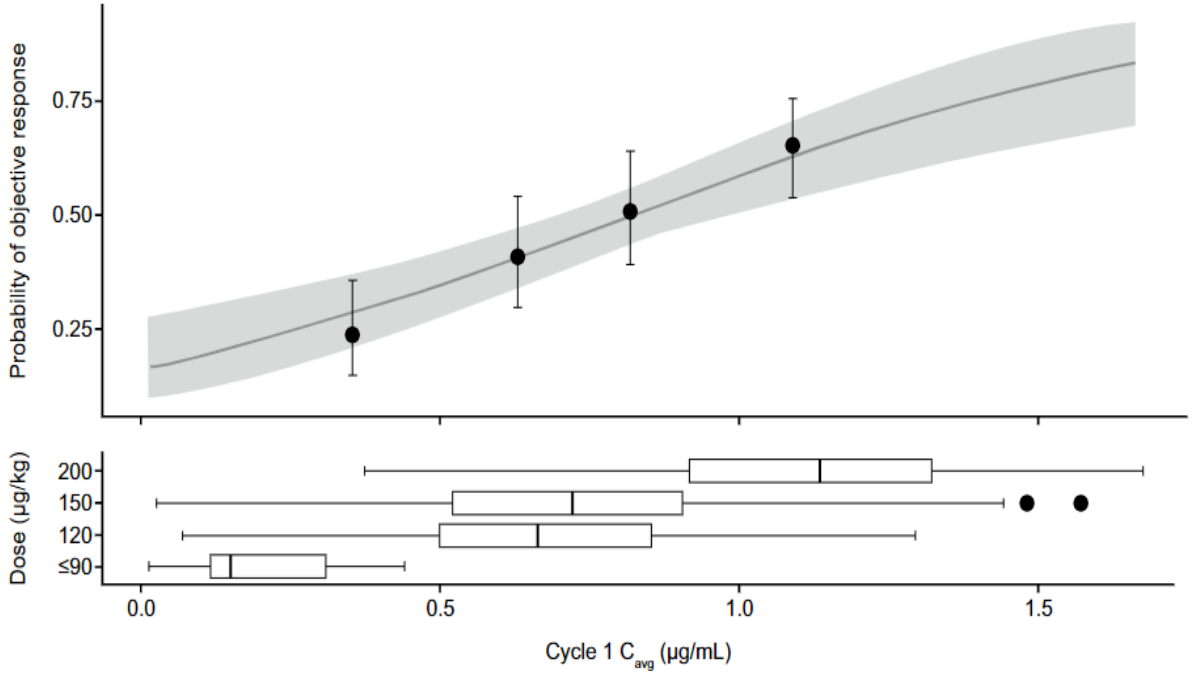
- Administer Lonca as an infusion over 30 minutes on Day 1 of each cycle (every 3 weeks); recommended dosage:
  - 0.15 mg/kg every 3 weeks for 2 cycles
  - 0.075 mg/kg every 3 weeks for subsequent cycles
- Administer using a dedicated infusion line equipped with a sterile, non-pyrogenic, low-protein binding in-line or add-on filter (0.2- or 0.22-micron pore size) and catheter
- Do not mix Lonca or administer as an infusion with other drugs

Rationale for Dose Selection

- The 150 µg/kg dose was selected as a dose with encouraging responses but lower frequency of AEs than those observed at the 200 µg/kg dose in the phase 1 LOTIS-1 study[1]
- Moderate accumulation of Lonca together with frequent dose delays and 50% dose reductions after prolonged delays required during the phase 1 LOTIS-1 study supported a strategy of planned dose reduction of 50% after 2 cycles to mitigate onset of late-developing and difficult-to-manage toxicities, such as edema, which generally developed after ≥2 cycles[1]
- Selection of this dosing regimen was further supported by the rapid onset of response (median, 2 cycles)[1]

Initial dosing at 150 µg/kg for 2 cycles is expected to optimize the frequency of objective response whereas dose reduction in subsequent cycles to 75 µg/kg enables continued exposure with manageable toxicity to optimize the durability of response while reducing the need for dose delay or further dose reduction[1,2]

ORR Increases With Increasing Lonca Exposure



The dose and cycle 1 C_{avg} of Lonca (bottom graph) correlate with the predicted ORR (top graph).

The solid black circles (vertical line segments) represent the observed objective response rate (95% CI, Clopper-Pearson method) for each quartile of cycle 1 C_{avg}. The solid black line and shaded grey area represent the predicted objective response rate (95% CI) from a univariate logistic regression using individual patient level cycle 1 C_{avg}.

An increasing ORR was observed with increasing PBD-conjugated antibody drug exposure.

Additionally, the occurrence of grade ≥2 increased GGT, skin and nail, and liver function test treatment-emergent adverse events consistently showed significant relationships with C_{avg} and C_{min} in cycles 1, 2, and 3.

Cycle 1 C_{avg} Quartiles	
1st quartile	0.0120 to 0.504 µg/mL
2nd quartile	0.506 to 0.723 µg/mL
3rd quartile	0.727 to 0.941 µg/mL
4th quartile	0.943 to 1.68 µg/mL

Initial dosing at 150 µg/kg dose for 2 cycles is expected to optimize the frequency of objective response whereas dose reduction in subsequent cycles to 75 µg/kg per dose enables continued exposure to Lonca with manageable toxicity.

This optimizes the durability of response to Lonca while reducing the need for dose delay or further dose reduction

Cycle 1 Average Concentration, Baseline Tumor Sum of Area, and Disease Phenotype Are Predictors of ORR

Estimates of Odds Ratio (95% CI) from the Final Logistic Regression Model for ORR with PBD-Conjugated Ab Cycle 1 C_{avg}

	Estimate	Odds Ratio (95% CI)	p-value
Cycle 1 C_{avg} (µg/mL)	1.807	6.095 (2.647, 14.749)	3.50E-05
Baseline tumor sum of area (cm^2)	-0.015	0.985 (0.977, 0.992)	8.13E-05
Selected high risk disease type	-0.733	0.48 (0.268, 0.847)	0.01218

Note: AIC = 346.

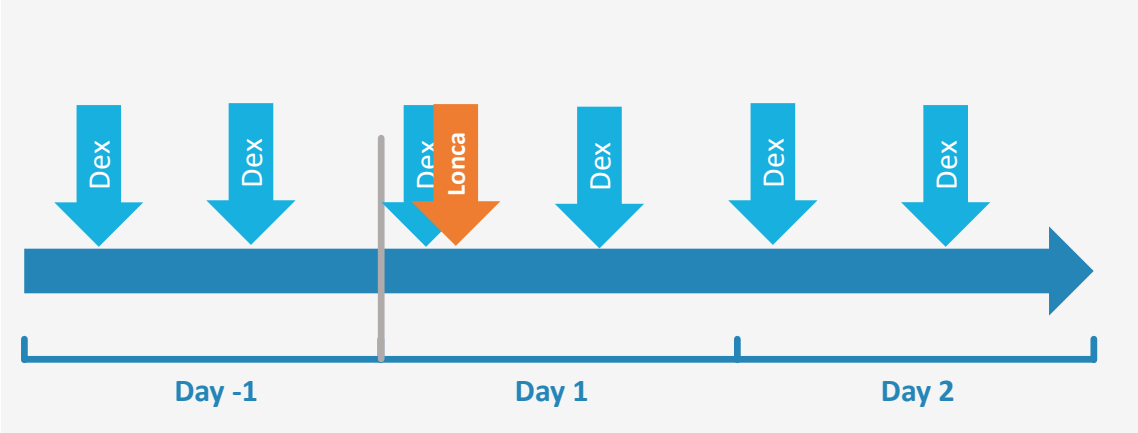
- The odds of objective response increased by 6.095-fold and 1.198-fold for 1 µg/mL and 0.1 µg/mL increase, respectively, in Cycle 1 C_{avg}
- The odds of objective response decreased by 0.985-fold for 1 cm^2 increase in baseline tumor sum of area and 0.48-fold for selected high-risk disease phenotypes

Premedication

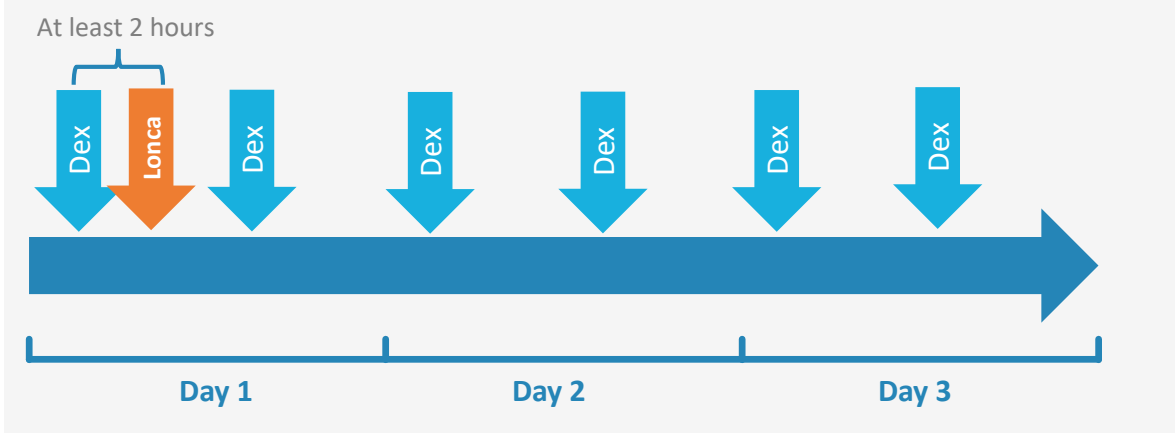
- Unless contraindicated, administer dexamethasone 4 mg orally or intravenously twice daily for 3 days beginning the day before administering Lonca. If dexamethasone administration does not begin the day before Lonca, dexamethasone should begin at least 2 hours prior to administration of Lonca[1,a]
- The rationale is based on the use of this premedication regimen in the phase 2 clinical trial LOTIS-2 to reduce PBD-related dimer adverse events (i.e., edema, effusion)[2,3]

Dexamethasone Premedication Administration

If dexamethasone administration begins the day before Lonca:



If dexamethasone administration does not begin the day before Lonca:



[a]ADC Therapeutics does not have data on alternative premedication regimens and does not make recommendations outside of what is stated in the Prescribing Information.[1] If premedication with dexamethasone is not administered according to the recommendations within the ZYNLONTA prescribing information, alternative dosing regimens are at the clinical discretion of the practitioner. See relevant Prescribing Information for additional information.

Dose Delays and Modifications

Adverse Reactions	Severity[a]	Dosage Modification
Hematologic Adverse Reactions		
Neutropenia	Absolute neutrophil count <1 × 10^9/L	Withhold Lonca until neutrophil counts returns to 1 × 10^9/L or higher
Thrombocytopenia	Platelet count <50,000/mcL	Withhold Lonca until platelet count returns to 50,000/mcL or higher
Nonhematologic Adverse Reactions		
Edema or Effusion	Grade 2[a] or higher	Withhold Lonca until the toxicity resolves to grade 1 or less
Other Adverse Reactions	Grade 3[a] or higher	Withhold Lonca until the toxicity resolves to grade 1 or less

[a]National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

If dosing is delayed by more than 3 weeks due to toxicity related to Lonca, reduce subsequent doses by 50%. If toxicity reoccurs following dose reduction, consider discontinuation.

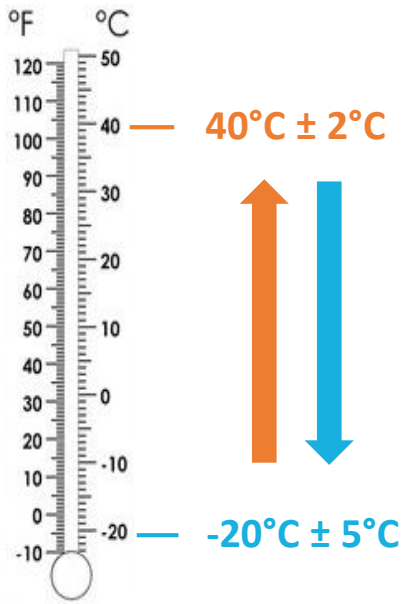
Note: If toxicity requires dose reduction following the second dose of 0.15 mg/kg (Cycle 2), the patient should receive the dose of 0.075 mg/kg for Cycle 3.

Storage and Stability

Lyophilized Lonca

- Lonca is supplied as a lyophilized powder in a 10-mg single-dose vial for reconstitution and further dilution[1]
- Lonca should be stored refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect it from light. Do not use the medication beyond the expiration date shown on the carton. Do not freeze the medication. Do not shake the medication[1]
- Temperature excursion studies found that the lyophilized Lonca powder may be stored at a temperature range of -20°C to 40°C (-4°F to 104°F) for up to 48 hours[2]

Temperature cycling stability study



- Lonca lyophilized powder underwent 3 rounds of cycling (-20°C ± 5°C to 40°C ± 2°C/75 ± 5% relative humidity)
- Samples were exposed to high and low temperatures for 2 days at each cycle
- Lonca lyophilized powder remained stable after 3 temperature cycles[2]

ADC Therapeutics does not recommend any practices, procedures, or storage conditions that are not aligned with the ZYNLONTA product labeling and are not approved by the US Food and Drug Administration. The information provided above is outside of the approved storage recommendations as per the label. Please defer to your clinical judgement regarding use of the product.

Storage and Stability (cont'd)

Reconstituted or diluted Lonca

- ADC Therapeutics has not conducted any studies that evaluate acceptable temperature excursion data for reconstituted or diluted Lonca
- After reconstitution, the vials may be stored for up to 4 hours[1]
  - Refrigerated (2°C to 8°C; 36°F to 46°F)
  - Room temperature (20°C to 25°C; 68°F to 77°F)
- After dilution, the preparation may be stored as follows:[1]
  - Refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours
  - Room temperature at 20°C to 25°C (68°F to 77°F) for up to 8 hours
  - Discard if storage time exceeds these limits
- Please follow the proper aseptic technique and align with local or institutional policies for compounding sterile preparations as highlighted by the ASHP[2]

Summary

- Lonca is administered as an IV infusion over 30 minutes on Day 1, every 3 weeks
- Lonca should be reconstituted to obtain a final concentration of 5 mg/mL
  - The overfill amount of Lonca is approximately 0.3 mL after reconstitution
- Initial dosing of 150 µg/kg for 2 cycles is given to optimize objective responses while dose reduction in subsequent cycles to 75 µg/kg enables continued exposure with manageable toxicity
  - If dosing is delayed by more than 3 weeks due to toxicity related to Lonca, reduce subsequent doses by 50%. If toxicity reoccurs following dose reduction, consider discontinuation
- Patients should receive dexamethasone premedication for 3 days beginning the day before Lonca administration to reduce PBD-related adverse events
- Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect it from light. Do not use it beyond the expiration date shown on the carton. Do not freeze. Do not shake
  - Lonca is supplied as a lyophilized powder that may be stored at a temperature range of -20°C to 40°C (-4°F to 104°F) for up to 48 hours
- Reconstituted Lonca may be stored refrigerated (up to 24 hours) or at room temperature (≤ 8 hours)