Liver Enzyme Elevation

Incidence and Management

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Objectives

Liver Enzyme Elevations

- Review premedication and dose modification recommendations for liver enzyme elevation based on the loncastuximab tesirine prescribing information
- Review the incidence, onset, duration, and dose modification for liver enzyme elevation in the LOTIS-2 study

Table of Contents

Indication and Usage

Indication for Loncastuximab Tesirine

Loncastuximab tesirine 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 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 overall response. Continued approval for this indication may be contingent upon verification and description of the clinical benefit in a confirmatory trial(s).

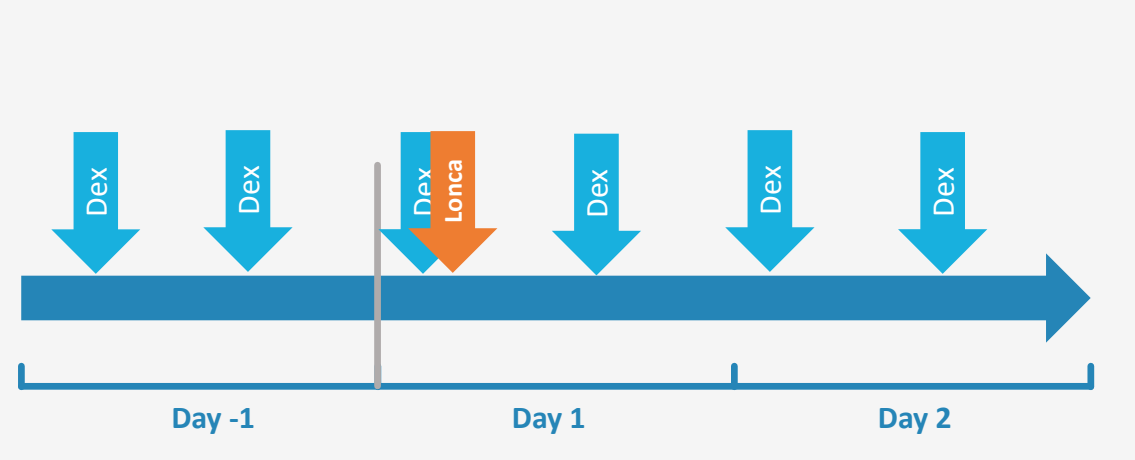
Premedication Recommendation

The loncastuximab tesirine prescribing information recommends dexamethasone premedication[1]

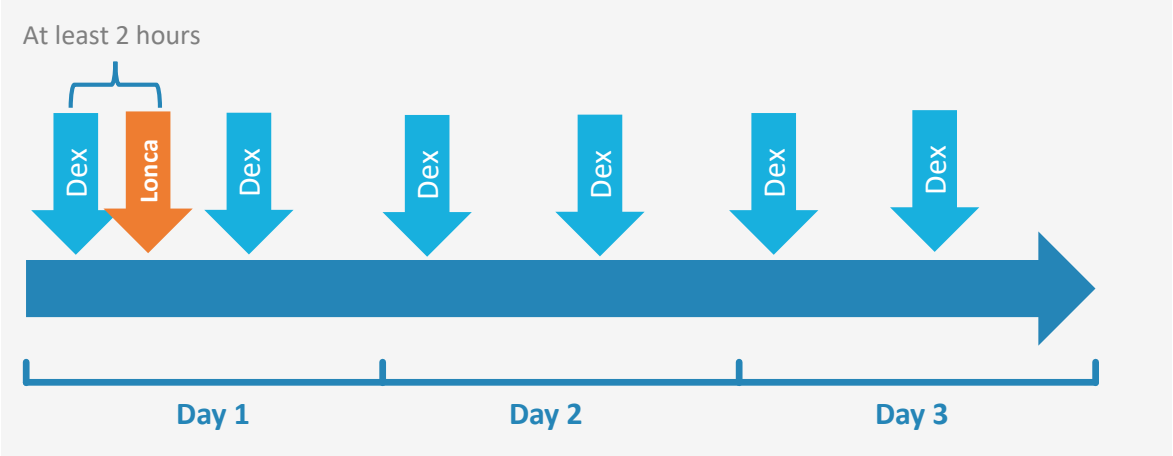
- Dexamethasone premedication is recommended to reduce the incidence and severity of pyrrolobenzodiazepine (PBD)-related adverse reactions[2]

Dexamethasone Premedication Administration

If dexamethasone administration begins the day before Lonca:



If dexamethasone administration does not begin the day before Lonca:



REFERENCES

Incidence, Onset, Duration, and Dose Modification for GGT Elevation (LOTIS-2)

All-Treated Population (N=145)[1,a,b]

GGT Elevation

	Incidence	Onset (median)	Duration[c] (median)
Any grade	**72.4%** (n=105)	**36.0 Days** Range: 1–245 (n=59)	**70.0 Days** Range: 6–526 (n=59)
Grade ≥3	**22.1%** (n=32)	**54.5 Days** Range: 8–136 (n=24)	**49 Days** Range: 3–335 (n=24)

Eligibility: To be eligible for treatment with Lonca in LOTIS-2, patients were required to have GGT ≤2.5 × ULN (grade ≤1)[2]

Severe events: Increased GGT was not associated with synthetic dysfunction or severe hepatic events[3]

Dose Modification due to GGT Elevation

Subset of Patients with GGT Elevation (n=105)[1,a,b]

Delayed	Reduced	Discontinued
28.6% (n=30)	**5.7% (n=6)**	**14.3% (n=15)**

Management: In LOTIS-2, Lonca was held for patients with grade ≥2 increased GGT until it resolved to grade ≤1[2]

[a]Data cut-off: April 6, 2020. Post hoc analysis.

[b]Incidence of biochemistry abnormalities was based on laboratory reporting, while dose modifications and time to onset were based on adverse event reporting.

[c]Missing end dates were imputed using the date of new anticancer therapy (NAT) for patients who received NAT or end of study (EOS) or data cut-off date for patients who did not receive NAT for the calculation of the duration of adverse events. Partial end dates were imputed using the last month or day of a month bounded by EOS. Grade ≥3 duration calculated at the time of first occurrence until adverse event resolved to grade ≤2.

Incidence and Dose Modification for Additional Liver Enzyme Elevations (LOTIS-2)

All-Treated Population (N=145)[a,b]

Grade ≥3 Liver Enzyme Elevations

	Incidence
AST Elevation	**0.7%** (n=1)
ALT Elevation	**3.4%** (n=5)
ALP Elevation	**2.1%** (n=3)
GGT Elevation	**22.1%** (n=32)

Grade ≥3 GGT elevation occurred in 22.1% of patients; however, elevations of other liver enzymes, including AST and ALT, were less frequent

Dose Modification due to Liver Enzyme Elevations

All-Treated Population (N=145)[a,b,c]

	Delayed	Reduced	Discontinued
AST Elevation	**2.1%** (n=3)	**0%** (n=0)	**0%** (n=0)
ALT Elevation	**3.4%** (n=5)	**0%** (n=0)	**0%** (n=0)
ALP Elevation	**4.1%** (n=6)	**0%** (n=0)	**0.7%** (n=1)

[a]Data cut-off: April 6, 2020. Post hoc analysis.
[b]Incidence of biochemistry abnormalities was based on laboratory reporting, while dose modifications and time to onset were based on adverse event reporting.
[c]Dose modification percentages are reported out of the number of patients from the all-treated population, rather than the subsets of patients who experienced liver enzyme elevations.

Dose Modification Recommendation

Dose Modification Recommendation in the Lonca Prescribing Information
Other Adverse Reactions (e.g., GGT Elevation)
For grade ≥3 GGT elevation[a], withhold loncastuximab tesirine until toxicity resolves to grade ≤1[1,b]
If dosing is delayed by more than 3 weeks due to toxicity related to loncastuximab tesirine, reduce subsequent doses by 50%. If toxicity reoccurs following dose reduction, consider discontinuation[1]

Monitoring: The loncastuximab tesirine prescribing information does not make any statements or recommendations regarding monitoring of GGT levels[1]

[a]Grade 3 GGT elevation is defined as >5.0 to 20.0 × ULN for patients with normal baseline GGT, or >5.0 to 20.0 × baseline for patients with abnormal baseline.[2]
[b]Grade 1 GGT elevation is defined as >ULN to 2.5 × ULN for patients with normal baseline GGT, or 2.0 to 2.5 × baseline for patients with abnormal baseline.[2]

Summary

- Though monitoring of GGT elevation is not specified by the prescribing information, for those patients with grade ≥3 GGT elevation, Lonca should be withheld until toxicity resolves to grade ≤1[3]
- Dexamethasone premedication is recommended to reduce the incidence and severity of pyrrolobenzodiazepine (PBD)-related adverse reactions[1]
- In the LOTIS-2 trial, grade ≥3 GGT elevation occurred in 22.1% (n=32) of patients[2]
  - Dose delays, reductions, and discontinuations occurred due to GGT elevation in 28.6%, 5.7%, and 14.3% of patients who experienced GGT elevation (n=105), respectively[2]

Appendix

GGT Background

- GGT is elevated in all forms of liver disease (cirrhosis, cholangitis, cholecystitis, etc.)[1]
- Baseline GGT levels vary by patient age[1]
- GGT is not included in the liver function panel of tests for most labs[2]
- GGT has a half-life of 10 days[1]

Population	GGT Reference Range[1]
Male/Female (≥45 years)	8–38 units/L
Female (<45 years)	5–27 units/L
Elderly	Slightly higher than adults
Child	Similar to adult level
Newborn	5× higher than adult level