Loncastuximab Tesirine in Combination with Venetoclax Is Safe and Shows Efficacy in Patients with Relapsed/Refractory Non-Hodgkin Lymphoma

Paolo F. Caimi, MD, Allison M. Winter, MD, Robert M. Dean, MD, Taylor R. Brooks, MD, Deepa Jagadeesh, MD, Craig S. Sauter, MD and Brian T. Hill, MD, PhD
Department of Hematology and Medical Oncology, Cleveland Clinic Taussig Cancer Institute, Cleveland, Ohio and Case Comprehensive Cancer Center, Cleveland, Ohio.

Cleveland Clinic Cancer Institute

BACKGROUND

- Loncastuximab tesirine (lonca) is an antibody drug conjugate targeting CD19, active against aggressive and indolent B cell malignancies.
- Venetoclax (VEN) is a potent BCL2 inhibitor with demonstrated single agent activity in CLL, but modest single agent activity against other B cell malignancies.
- The antineoplastic activity of VEN in B cell non-Hodgkin lymphoma (NHL) appears to be increased when combined with other agents.
- The combination of lonca and VEN has been shown to have synergistic activity against NHL models in vivo and in vitro (Tarantelli C, et al. Haematologica. 2024).

OBJECTIVES

- To determine the safety and tolerability of the combination of lonca and VEN and identify the recommended phase 2 dose (RP2D) of lonca in this combination.

METHODS

Eligibility

- Adults ≥18years
- Relapsed/refractory B-NHL (except CLL & MCL)
- Two or more prior systemic therapies
- Measurable disease by PET or CT imaging

Treatment (figure 1)

- 6 cycles of therapy
- Lonca: IV over 30 minutes on day 1
  - 3 dose levels: 50, 100, 150µg/kg
  - Cycles 3-6: 50% dose if C1-2 ≥ 100µg/kg
- Venetoclax: orally on days 1 - 5 (Ramp up cycle 1)

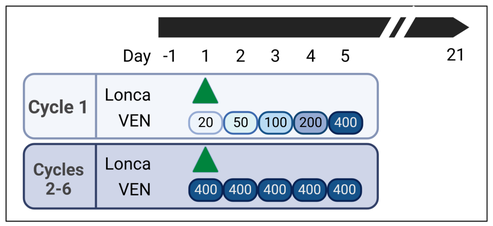

Figure 1. Treatment schedule for combination of loncastuximab (lonca) and venetoclax (VEN)

Supportive care

- Dexamethasone 4mg/d orally on days -1 - 2 of each cycles
- Allopurinol 300mg/d orally on day -1 to 7 of each cycle

Dose escalation

Following the Bayesian Optimized Interval (BOIN) design.

Dose limiting toxicities (DLTs) included grade ≥3 non hematologic toxicities and persistent grade ≥3 hematologic toxicities.

RESULTS

Patients

- 16 patients have enrolled and received at least one cycle of therapy.

Table 1. Baseline patient characteristics

Characteristic	N (%)
Age, years, median (range)	67 (48 - 84)
Gender (Female/Male)	(5/11)
Race/ethnicity White/non-Hispanic	 16 (100)
Diagnoses Diffuse large B cell lymphoma High grade B cell lymphoma Follicular lymphoma LPL / Waldenström macroglobulinemia	 7 (44) 2 (13) 4 (25) 3 (19)
Extranodal involvement (at enrollment)	7 (44)
Median number of prior therapies (range)	4 (2 - 9)
Disease refractory to prior line of therapy	12 (75)
Prior autologous stem cell transplant	3 (16)
Prior CAR T-cell therapy	9 (47)

Safety

- Two DLTs were observed (dose level 1 and 3)
  - Grade ≥ 3 neutropenia without fever, resolved >7 days after cycle 2 day 1 (both resolved in 8 days)
  - 3 patients experienced TEAEs that lead to death:
    - COVID lung infection
    - Ileal obstruction with multiorgan failure
    - Drug-induced cholestasis and hemolysis.

- All patients experienced at least one treatment emergent adverse event (table 2).

Table 2. All Grade Treatment Emergent Adverse Events

CTCAE Category	N (%)
Anemia	9 (56)
White blood cell decreased	8 (50)
Alkaline phosphatase increased	6 (38)
Creatinine increased	6 (38)
Gamma glutamyl transferase increased	6 (38)
Hyponatremia	6 (38)
Hypophosphatemia	6 (38)
Platelet count decreased	6 (38)
Hypocalcemia	5 (31)
Hypokalemia	5 (31)
Neutrophil count decreased	5 (31)

- 12 (75%) patients experienced at least one grade ≥ 3 treatment emergent adverse event (table 3).

Table 3. Grade ≥ 3 Treatment Emergent Adverse Events

CTCAE Category	N (%)
White blood cell decreased	5 (31)
Neutrophil count decreased	4 (25)
Blood bilirubin increased	3 (18)
Atrial fibrillation	2 (12.5)
Hypotension	2 (12.5)
Generalized muscle weakness	2 (12.5)
Alanine aminotransferase increased	1 (6)
Aspartate aminotransferase increase	1 (6)
Alkaline phosphatase increased	1 (6)
Ileal obstruction	1 (6)
Lung infection	1 (6)

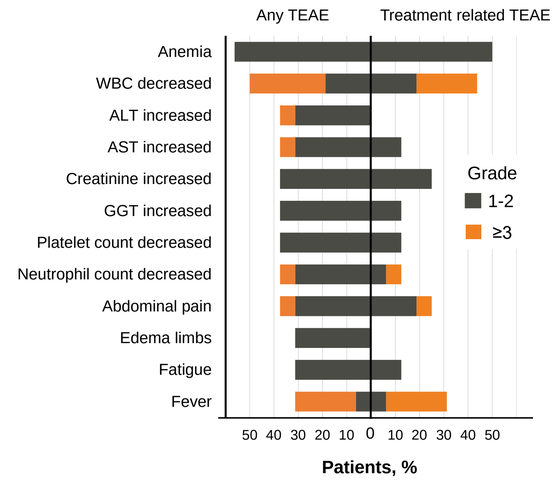

Figure 2. Treatment emergent adverse events and treatment related adverse events for lonca + VEN. (ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; TEAE: treatment emergent adverse event; WBC: white blood cell count)

- Adverse events of special interest included increase in GGT, edema (including ascites or effusions) and cutaneous TEAEs

Table 4. All-grade adverse events of special interest

CTCAE Category	N (%)
Gamma glutamyl transferase increased	6 (38)
Edema of limbs or trunk	5 (31)
Rash / skin disorders	5 (31)

Response

- 14 patients were evaluable for response (figure 3)
- 8/14 (57%) evaluable patients had disease response; 6 patients (43%) had complete response by ICML-14 criteria.
- 2 patients died prior to restaging imaging on cycle 3, day 1 (COVID-19 pneumonia and cholestatic hepatic failure /preexisting autoimmune hemolytic anemia).

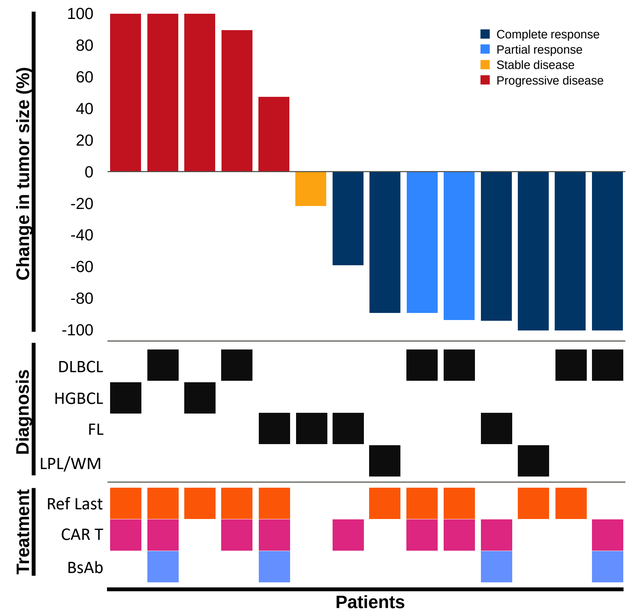

Figure 3. Waterfall plot showing best response to lonca + VEN according to ICML14 criteria – WM patients achieved VGPR per IWMF criteria), matrix represents patient diagnoses and prior therapy. (BsAb: Bispecific antibody; CAR T: chimeric antigen receptor T cell; DLBCL: diffuse large B cell lymphoma; FL: follicular lymphoma; HGBCL: high grade B cell lymphoma; LPL/WM: Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia; Ref Last: refractory to last therapy).

- All patients (n=3) with Waldenstrom macroglobulinemia had >80% decrease in IgM monoclonal protein concentration.
- Per IWMF criteria, 2 measurable patients have achieved very good partial remission, both sustained > 12 months.

CONCLUSIONS

- Loncastuximab combined with intermittent-dose venetoclax appears to be well tolerated, without new toxicities identified in relapsed / refractory NHL.
- The maximum tolerated dose of loncastuximab was 150µg/kg.
- Responses were observed in patients with aggressive and indolent NHL with extensive prior therapies, including CAR T cell therapy and bispecific antibodies.
- Enrollment expansion at the MTD continues to further evaluate the safety and preliminary efficacy of this combination.