BRENTUXIMAB VEDOTIN IN COMBINATION WITH LENALIDOMIDE AND RITUXIMAB IN PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA: SAFETY AND EFFICACY RESULTS FROM THE SAFETY RUN-IN PERIOD OF THE PHASE 3 ECHELON-3 STUDY

Nancy L. Bartlett[1], Christopher A. Yasenchak[2], Khaleel Ashraf[3], William Harwin[4], James Orcutt[5], Philip Kuriakose[6], Pier Luigi Zinzani[7,8], Adrija Mamidipalli[9], Keenan Fenton[9], Consuelo Glenn[9], Grzegorz Nowakowski[10]

[1]Division of Oncology, Washington University School of Medicine, St. Louis, MO, USA; [2]Willamette Valley Cancer Institute and Research Center/US Oncology Research, Eugene, OR, USA; [3]Hematology and Oncology Associates of Alabama, Birmingham, AL, USA; [4]Sarah Cannon Research Institute, Fort Meyers, FL, USA; [5]Charleston Oncology, Charleston, SC, USA; [6]Henry Ford Health System, Detroit, MI, USA; [7]IRCCS University Hospital of Bologna, Institute of Hematology "Seràgnoli", Bologna, Italy; [8]Department of Specialized Medicine, Diagnostic and Experimental, University of Bologna, Bologna, Italy; [9]Seagen Inc., Bothell, WA, USA; [10]Division of Hematology, Mayo Clinic, Rochester, MN, USA

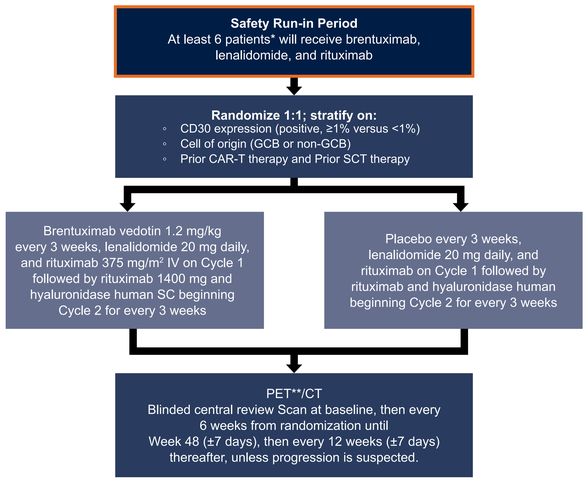
BACKGROUND

- Patients (pts) with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) who relapse after or are ineligible for hematopoietic stem cell transplant (HSCT) or chimeric antigen receptor T cell (CAR-T) therapy generally have poor outcomes
- Rationale exists for combining brentuximab vedotin (BV), lenalidomide (len), and rituximab for the treatment of R/R DLBCL[1]
- BV+len showed promising clinical activity in a Phase 1 trial (N=37) with a 57% overall response rate (ORR), 10.2-month median progression-free survival, and 14.3-month overall survival with similar benefit seen in pts with both CD30+ and CD30- tumors[1]
- We report the results of the open-label safety run-in that was conducted prior to the randomized portion of the ECHELON-3 study

METHODS

- ECHELON-3 (NCT04404283) is a randomized, double-blind, placebo-controlled, active-comparator, multicenter Phase 3 study (Figure 1)
- Prior to randomization phase, an open-label safety run-in was conducted:
  - Treatment
    - Pts received BV (1.2 mg/kg IV) and rituximab (375 mg/m^2 IV; 1400 mg SC) both q3w, and len 20 mg po qd
  - Eligibility Criteria
    - Pts must have received ≥2 prior lines of therapy and be previously treated with or were ineligible for HSCT or CAR-T, ECOG score ≤2, and PET-avid, bidimensional measurable disease (>1.5 cm by CT)
    - Pts with negative CD30 expression (<1%) were eligible
- Response was assessed by the investigator according to the Lugano Classification Revised Staging System[2]

Figure 1. ECHELON-3 Study Design



*Ten pts were enrolled; **Once PET is negative, no further PET scans are required; GCB = germinal center B cell-like; SCT = stem cell transplant; SC = subcutaneous, IV = intravenous; PET = positron emission tomography; CT = computed tomography

References

1.Ward, et al. Blood. 2022;139:1999-2010. doi:10.1182/blood.2021011894.
2.Cheson. J Clin Oncol. 2014;32:3059-3068. doi:10.1200/JCO.2013.54.8800.
3.Clopper, Pearson. Biometrika. 1934;26:404-413. doi:10.1093/biomet/26.4.404.

RESULTS

Disposition

- Ten pts with R/R DLBCL enrolled and were treated
- Nine pts were off treatment
  - Reasons for treatment discontinuation were progressive disease (n=5) and adverse event (n=4)
- Median follow-up was 7.2 months (range, 2 to 14)
- Median duration of exposure was 3.3 months (range, 1 to 12)

Table 1. Patient Disposition

	Safety Run-in (N=10)
Age, median (range)	70.5 (45, 79)
Sex, n (%)	
Male	7 (70)
Female	3 (30)
Ethnicity, n (%)	
Hispanic or Latino/a, or of Spanish Origin	1 (10)
Not of Hispanic or Latino/a, or of Spanish Origin	9 (90)
Race, n (%)	
Asian	1 (10)
Black or African American	2 (20)
White	7 (70)
ECOG Performance Status, n (%)	
0	4 (40)
1	6 (60)

ECOG = Eastern Cooperative Oncology Group

Table 2: Summary of Disease Characteristics

	Safety Run-in (N=10)
Prior lines of therapy, median (range)	3 (2, 6)
CD30 Status, n (%)	
<1%	7 (70)
≥1%	3 (30)
Prior hematopoietic stem cell transplant, n (%)	
Received	0
Not received	10 (100)
Cell of Origin, n (%)	
GCB	5 (50)
Non-GCB	5 (50)
Prior CAR-T therapy, n (%)	
Received	6 (60)
Not received	4 (40)

GCB = Germinal Center B-cell like
CD30 status: positive, ≥1% vs. <1%; IHC results either per central or local lab, at the time of enrollment

Table 3. Treatment-Emergent Adverse Events by Preferred Term Occurring in ≥20% of Patients

	Safety Run-in (N=10)
Patients with any event, n (%)	**10 (100)**
Fatigue	5 (50)
Anaemia	4 (40)
Constipation	4 (40)
Decreased appetite	3 (30)
Diarrhoea	3 (30)
Dyspnoea	3 (30)
Hypokalaemia	3 (30)
Nausea	3 (30)
Oedema peripheral	3 (30)
Pneumonia	3 (30)
Abdominal pain	2 (20)
Back pain	2 (20)
Confusional state	2 (20)
Cough	2 (20)
Dysgeusia	2 (20)
Hypercalcaemia	2 (20)
Infusion related reaction	2 (20)
Neutropenia	2 (20)
Peripheral motor neuropathy	2 (20)
Peripheral sensory neuropathy	2 (20)
Pruritus	2 (20)
Rash maculo-popular	2 (20)
Sinusitis	2 (20)
Stomatitis	2 (20)
Thrombocytopenia	2 (20)
Upper-airway cough syndrome	2 (20)
Vomiting	2 (20)
Weight decreased	2 (20)

Table 4. Treatment-Emergent Serious Adverse Events by Preferred Term

	Safety Run-in (N=10)
Patients with any event, n (%)	7 (70)
Pneumonia	2 (20)
Anaemia	1 (10)
Back pain	1 (10)
Death	1 (10)
Dyspnoea	1 (10)
Hypokalaemia	1 (10)
Pneumonia aspiration	1 (10)
Productive cough	1 (10)
Pulmonary haemorrhage	1 (10)
Pyrexia	1 (10)
Sepsis	1 (10)
Sinusitis	1 (10)
Vomiting	1 (10)

Treatment-emergent adverse events are newly occurring adverse events (not present at baseline) or adverse events that worsen after first dose of investigational product.

Safety

- **Treatment-Emergent Adverse Events > 20% pts:** the events were fatigue (n=5; 50%); anaemia and constipation (n=4 each; 40%); decreased appetite, diarrhoea, dyspnoea, hypokalaemia, nausea, oedema peripheral, and pneumonia (n=3 each; 30%) (Table 3)
- **Treatment-Emergent SAEs:** treatment-emergent SAEs occurred in 7 pts (70%); pneumonia was the most commonly reported event (n=2; 20%)
  - One pt had an unrelated fatal SAE on treatment (died in her sleep)
- **Dose Modifications:** dose modifications of one or more component of the regimen occurred in 8 pts
  - The most common AEs leading to dose modification included anaemia (n=3), neutropenia, peripheral neuropathy, and pneumonia (n=2 each)
- **Discontinuations:** four pts discontinued treatment due to an AE
  - Two deemed treatment related by investigator (Grade 2 fatigue and Grade 3 anaemia)

Efficacy

- The ORR (best response) was 70%, including 5 pts with a complete metabolic response, 2 pts with a partial metabolic response, and 3 pts with progressive disease (Table 5)
- Responses were seen in both CD30 (+) and (-) pts, as well as in 4 of 6 pts who had failed prior CAR-T.
- The median duration of response was 5.6 months (range, 0.9 to 12.6)

Table 5. Summary of Best Overall Response per Investigator

	Safety Run-in (N=10)
Best Overall Response	
Complete Response (CR)	5 (50.0)
95% CI for CR Rate	(18.7, 81.3)
Partial Response (PR)	2 (20.0)
Progressive Disease (PD)	3 (30.0)
Objective Response Rate	7 (70.0)
95% CI for Objective Response Rate	(34.8, 93.3)

Response assessment per Lugano by investigator[2]. CR, PR, and PD include both metabolic and non-metabolic disease assessment. CR, PR, and PD are mutually exclusive. Two-sided 95% exact confidence interval (CI) computed using the Clopper-Pearson method[3].

Table 6. Efficacy Summary (N=10)

Pt. No	No. Prior Systemic Therapies	CD30 Positive* (Y/N)	Prior CAR-T (Y/N)	GCB vs. Non-GCB	Best Response** per PI	DOR† (months)
1	6	N	Y	GCB	CR	5.55
3	5	N	N	GCB	CR	12.65
5	3	N	N	Non-GCB	CR	0.92
8	2	N	Y	Non-GCB	CR	4.4
6	4	Y	N	GCB	CR	9.89
2	4	N	Y	GCB	PR	1.18
7	3	Y	Y	Non-GCB	PR	1.84
9	2	Y	N	Non-GCB	PD	NA
4	3	N	Y	Non-GCB	PD	NA
10	3	N	Y	GCB	PD	NA

* CD30 status: positive, ≥1% vs. <1%; IHC results either per central or local lab, at the time of enrollment;
** Response assessment per Lugano[2];
† DOR = duration of response is time from the earliest occurrence of either CR or PR to the first occurrence of PD or death. Pts without PD or death will be censored at the day after the last disease assessment documenting absence of PD. Pts with ongoing response or who have initiated new subsequent therapy will be censored at most recent prior disease assessment

CONCLUSIONS

- This novel triplet regimen appears active in R/R DLBCL with an acceptable safety profile
- Activity was seen in heavily treated population including in both CD30 (+) and (-) pts and those treated with prior CAR-T therapy
- The randomized portion of the study is currently enrolling

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