Poster: ABCL-711

Brentuximab vedotin in combination with lenalidomide and rituximab in patients with relapsed/refractory diffuse large B-cell lymphoma: results from the phase 3 ECHELON-3 study

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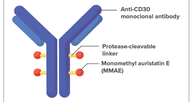
Key takeaways

- ECHELON-3 (NCT04404283) is the first randomized, placebo-controlled, phase 3 study to demonstrate overall survival (OS) benefit in a contemporary population of patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) who have received ≥2 prior lines of systemic therapy
- This study met its primary objective of demonstrating a significant improvement in OS for brentuximab vedotin (BV) + lenalidomide (Len) + rituximab (R) compared with placebo+Len+R
- Key secondary endpoints of progression-free survival (PFS) and objective response rate (ORR) were also significantly improved with BV+Len+R
- Consistent benefit of BV+Len+R for OS, PFS, and ORR was observed in tumors with or without CD30 expression
- This triplet combination, with its promising OS benefit, has the potential to address the high unmet need in patients with R/R DLBCL, particularly those who are not able to receive chimeric antigen receptor (CAR) T-cell therapy or bispecific antibodies or have R/R disease following these treatments

Background and rationale

- BV is an antibody-drug conjugate targeting CD30[1]
- In patients with R/R DLBCL:
  - ORR with BV (n=49) was 44%[2]
  - ORR with BV+R (n=13) was 46%[2]
  - ORR with Len+R (n=32) was 28%[3]
  - ORR with BV+Len (n=37) was 57%, and complete response (CR) rate was 35%[4]
    - Responses were observed in patients regardless of CD30 status
- Despite recent advances, including T-cell–directed therapies, there remains a high unmet need for readily available and tolerable regimens for patients with later-line DLBCL
  - Real-world data has shown that real-world OS in the third-line or later setting is <1 year[5,6]
- ECHELON-3 is a randomized, double-blind, placebo-controlled, active comparator, multicenter, phase 3 study comparing BV or placebo in combination with Len+R (BV+Len+R vs placebo+Len+R) in patients with R/R DLBCL[7,8]
- Here we report safety and efficacy results from the interim analysis of the ECHELON-3 study

Figure 1. BV



Methods

ECHELON-3 trial design

Phase 3 in R/R DLBCL

Figure 2. ECHELON-3 Trial Design

- Per protocol, G-CSF prophylaxis was required

Key inclusion criteria
- R/R DLBCL with eligible subtypes[a]
- Age ≥18 years
- **≥2 prior lines of therapy**
- **Ineligibility for or disease relapse following HSCT or CAR T-cell therapy**
- ECOG PS 0-2
- FDG-avid, measurable disease

Key exclusion criteria
- Prior BV or Len
- Active cerebral/meningeal disease
- Grade ≥2 peripheral neuropathy

Randomization 1:1

BV+Len+R (n=112)
BV 1.2 mg/kg IV Q3W + Len 20 mg PO QD + R 375 mg/m^2 IV Q3W[b]

Placebo+Len+R (n=118)
Placebo IV Q3W + Len 20 mg PO QD + R 375 mg/m^2 IV Q3W[b]

Treatment groups[c]

Primary endpoint
- OS in ITT population

Secondary endpoints
- PFS_{IWG} and ORR_{IWG} using the response criteria per Lugano 2014 in ITT population
- $CR\ rate_{IWG}$
- DOR_{IWG}
- OS in CD30-positive population
- Safety and tolerability

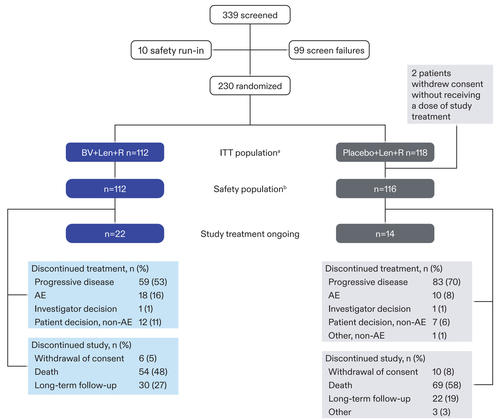
Stratification
- CD30 status (≥1% vs <1%)
- Cell of origin (GCB or non-GCB)
- Prior treatment with CAR-T therapy (received or not)
- Prior treatment with SCT (received or not)

BV, brentuximab vedotin; CAR, chimeric antigen receptor; CD, cluster of differentiation; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FDG, fluorodeoxyglucose; GCB, germinal center B cell; G-CSF, granulocyte colony-stimulating factor; HSCT, hematopoietic stem cell transplant; INV, investigator; ITT, intention to treat; IV, intravenous; Len, lenalidomide; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, oral; Q3W, every 3 weeks; QD, once daily; R, rituximab; R/R, relapsed or refractory; SCT, stem cell transplant.
[a]Eligible subtypes include but are not limited to transformed DLCBL, high-grade double-/triple-hit lymphoma, and not otherwise specified.
[b]Starting with cycle 2, R can be administered intravenously or subcutaneously (1400 mg subcutaneously Q3W).
[c]Treatment was allowed to continue until disease progression or unacceptable toxicity.

Results

Patient disposition

Figure 3. Patient Disposition



- Median duration of treatment was 3.6 months (range: 0.5-26.4) for BV+Len+R and 2.0 months (range: 0.1-26.6) for placebo+Len+R

AE, adverse event; BV, brentuximab vedotin; ITT, intention to treat; Len, lenalidomide; R, rituximab.
[a]Includes all randomized patients regardless of actual treatment received.
[b]Patients who received ≥1 dose of study treatment. Patients who received any BV dose were put in the experimental group. Patients who did not receive BV but received either Len or R were put into the control group.

Patient characteristics were well balanced between groups

Table 1. Patient Characteristics

	BV+Len+R (n=112)	Placebo+Len+R (n=118)
Patient characteristics		
Age, median (range), years	74.0 (29-87)	70.0 (21-89)
Age, n (%)		
≥65 years	79 (71)	76 (64)
≥80 years	23 (21)	15 (13)
Male, n (%)	60 (54)	70 (59)
ECOG PS 2, n (%)[a]	12 (11)	13 (11)
Race, n (%)		
White	65 (58)	56 (47)
Asian	28 (25)	32 (27)
Other or unknown	19 (17)	30 (25)
Prior treatments		
Lines of systemic therapies, median (range)	3 (2-8)	3 (2-7)
Systemic therapies received, n (%)		
Previous anthracycline	110 (98)	115 (97)
Previous anti-CD20 antibody	110 (98)	114 (97)
CAR T-cell therapy	32 (29)	35 (30)
Bispecific antibody	14 (13)	20 (17)
HSCT	10 (9)	18 (15)

BV, brentuximab vedotin; CAR, chimeric antigen receptor; CD, cluster of differentiation; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; HSCT, hematopoietic stem cell transplant; Len, lenalidomide; PS, performance status; R, rituximab.
[a]Values presented are the last non-missing value on or before the first dose date. If a patient did not receive any dose, the randomization/enrollment date is used in place of the first dose date.

Disease characteristics were well balanced between groups

Table 2. Disease Characteristics

n (%)	BV+Len+R (n=112)	Placebo+Len+R (n=118)
DLBCL NOS	63 (56)	64 (54)
Transformed DLBCL	32 (29)	27 (23)
Cell of origin[a]		
GCB	51 (46)	54 (46)
Non-GCB	61 (54)	64 (54)
CD30 status[b]		
≥1%	36 (32)	38 (32)
<1%	76 (68)	80 (68)
Other disease characteristics		
Ann Arbor stage III/IV at study entry[c]	83 (74)	98 (83)
IPI score ≥3 at time of enrollment	67 (60)	71 (60)
Primary refractory[c]	64 (57)	64 (54)
Refractory to last prior DLBCL therapy[c]	98 (88)	96 (81)

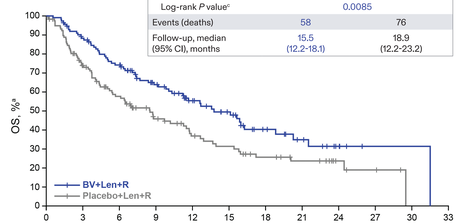
BV, brentuximab vedotin; CD, cluster of differentiation; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B cell; IPI, International Prognostic Index; Len, lenalidomide; NOS, not otherwise specified; R, rituximab.
[a]Based on post randomization corrected values.
[b]CD30 status per central result. When central result is not available, local result is used.
[c]Relapsed or refractory status is derived from prior therapy data. Refractory was defined as no response or a response lasting <6 months from the last treatment end date. Relapsed was defined as a response lasting ≥6 months from the last treatment end date.

Primary endpoint met with significant improvement in OS

BV+Len+R reduced risk of death by 37% compared with placebo+Len+R

Figure 3. OS

	BV+Len+R (n=112)	Placebo+Len+R (n=118)
OS, median (95% CI), months	13.8 (10.3-18.8)	8.5 (5.4-11.7)
HR (95% CI)[b]	0.629 (0.445-0.891)	
Log-rank *P* value[c]	0.0085	
Events (deaths)	58	76
Follow-up, median (95% CI), months	15.5 (12.2-18.1)	18.9 (12.2-23.2)



No. at risk

BV+Len+R	112	96	79	57	40	30	17	11	5	1	1	0
Placebo+Len+R	118	81	58	39	28	23	16	12	5	3	0	0

- BV+Len+R prolonged median OS by 5.3 months compared with placebo+Len+R
- Prespecified O'Brien-Fleming efficacy boundary was crossed at this interim analysis

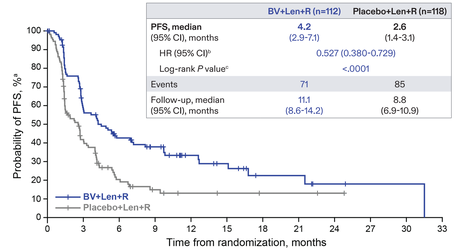
BV, brentuximab vedotin; CD, cluster of differentiation; GCB, germinal center B cell; HR, hazard ratio; Len, lenalidomide; OS, overall survival; R, rituximab.
[a]OS is time from randomization to death due to any cause. OS is estimated using Kaplan-Meier method.
[b]HR and 95% CI are based on a stratified Cox regression model with stratification factors (GCB or non-GCB) and CD30 status (≥1% or <1%) at randomization. HR of <1 favors BV+Len+R. Nonbinding futility boundary HR is 1.1.
[c]Two-sided *P* value from a stratified log-rank test with stratification factors of cell origin and CD30 status at randomization. O'Brien-Fleming efficacy boundary 2-sided *P* value is .0232.

Key secondary endpoint met with significant improvement in PFS

BV+Len+R reduced risk of disease progression or death by 47% compared with placebo+Len+R

Figure 4. PFS

	BV+Len+R (n=112)	Placebo+Len+R (n=118)
PFS, median (95% CI), months	4.2 (2.9-7.1)	2.6 (1.4-3.1)
HR (95% CI)[a]	0.527 (0.380-0.729)	
Log-rank *P* value[c]	<.0001	
Events	71	85
Follow-up, median (95% CI), months	11.1 (8.6-14.2)	8.8 (6.9-10.9)



No. at risk

BV+Len+R	112	58	38	27	15	11	5	5	2	1	1	0
Placebo+Len+R	118	40	16	8	4	3	2	2	1	0	0	0

- PFS was an alpha controlled key secondary endpoint

BV, brentuximab vedotin; CD, cluster of differentiation; GCB, germinal center B cell; HR, hazard ratio; Len, lenalidomide; PFS, progression-free survival; R, rituximab.
[a]PFS is time from randomization to earliest occurrence or progressive disease per Lugano 2014 or death. PFS is estimated using Kaplan-Meier method.
[b]HR and 95% CI are based on a stratified Cox regression model with stratification factors (GCB or non-GCB) and CD30 status (≥1% or <1%) at randomization. HR of <1 favors BV+Len+R.
[c]Two-sided *P* value from a stratified log-rank test based on stratification factors of cell origin (GCB or non-GCB) and CD30 status (≥1% or <1%) at randomization.

Median OS was longer with BV+Len+R across subgroups[a]

Figure 5. OS Across Key Subgroups

Subgroups		Median OS, months (events/n) BV+Len+R	Placebo+Len+R	HR for death	HR (95% CI)
All patients		**13.8 (58/112)**	**8.5 (76/118)**		**0.63 (0.44-0.89)**
Age	<65 Years	11.2 (20/33)	8.7 (28/42)		0.88 (0.49-1.56)
	≥65 Years	15.9 (38/79)	8.5 (48/76)		0.54 (0.35-0.83)
CD30	<1%	15.6 (42/76)	6.5 (55/80)		0.56 (0.37-0.84)
expression	≥1%	13.6 (16/36)	11.7 (21/38)		0.83 (0.43-1.60)
Cell of	GCB	13.6 (28/51)	8.5 (32/54)		0.77 (0.46-1.29)
origin	Non-GCB	18.8 (30/61)	8.5 (44/64)		0.55 (0.34-0.88)
Prior	Received	15.6 (16/32)	4.4 (25/35)		0.38 (0.20-0.75)
CAR-T	Not Received	13.8 (42/80)	9.7 (51/83)		0.74 (0.49-1.11)
Baseline	<3	18.8 (20/45)	15.4 (24/47)		0.75 (0.41-1.37)
IPI score	≥3	11.7 (38/67)	5.2 (52/71)		0.55 (0.36-0.84)
Status after last prior therapy	Refractory	11.7 (55/98)	5.5 (70/96)		0.57 (0.40-0.81)
	Relapsed	NA (3/13)	20.1 (6/21)		0.76 (0.19-3.09)
Region	North America	15.1 (18/30)	11.8 (12/19)		0.83 (0.39-1.74)
	Europe	11.3 (26/50)	6.5 (42/60)		0.57 (0.35-0.93)
	Asia-Pacific	20.3 (14/32)	11.3 (22/39)		0.58 (0.30-1.15)
Double-/ triple-hit lymphoma	Yes	16.3 (8/15)	4.4 (10/14)		0.49 (0.19-1.24)
	No	13.6 (50/97)	8.7 (66/104)		0.63 (0.44-0.92)

0.0 0.5 1.0 1.5 2.0
Favors BV+Len+R | Favors placebo+Len+R

BV, brentuximab vedotin; CAR, chimeric antigen receptor; CD, cluster of differentiation; GCB, germinal center B cell; HR, hazard ratio; IPI, International Prognostic Index; Len, lenalidomide; NA, not available; OS, overall survival; R, rituximab.
[a]The subgroups shown here had a HR of <1.

Median PFS was longer with BV+Len+R across subgroups[a]

Figure 6. PFS per Investigator Across Key Subgroups

Subgroups		Median PFS, months (events/n) BV+Len+R	Placebo+Len+R	HR for disease progression or death	HR (95% CI)
All patients		**4.2 (71/112)**	**2.6 (85/118)**		**0.53 (0.38-0.73)**
Age	<65 Years	2.9 (25/33)	1.4 (33/42)		0.69 (0.41-1.17)
	≥65 Years	5.7 (46/79)	2.8 (52/76)		0.48 (0.32-0.72)
CD30	<1%	3.1 (49/76)	1.9 (57/80)		0.57 (0.38-0.84)
expression	≥1%	6.9 (22/36)	2.7 (28/38)		0.49 (0.28-0.86)
Cell of	GCB	4.2 (33/51)	2.8 (38/54)		0.55 (0.34-0.89)
origin	Non-GCB	4.5 (38/61)	1.9 (47/64)		0.52 (0.33-0.80)
Prior	Received	3.0 (21/32)	1.4 (25/35)		0.41 (0.22-0.76)
CAR-T	Not Received	5.1 (50/80)	2.8 (60/83)		0.58 (0.40-0.85)
Baseline	<3	5.4 (29/45)	2.8 (32/47)		0.60 (0.36-1.00)
IPI score	≥3	3.6 (42/67)	1.5 (53/71)		0.49 (0.32-0.73)
Status after last prior therapy	Refractory	4.1 (66/98)	1.5 (74/96)		0.51 (0.36-0.71)
	Relapsed	15.1 (5/13)	5.6 (10/21)		0.29 (0.08-0.98)
Region	North America	4.1 (22/30)	1.4 (12/19)		0.65 (0.32-1.34)
	Europe	3.6 (31/50)	1.5 (44/60)		0.48 (0.30-0.77)
	Asia-Pacific	9.7 (18/32)	3.0 (29/39)		0.50 (0.28-0.91)
Double-/ triple-hit lymphoma	Yes	4.1 (9/15)	1.5 (9/14)		0.36 (0.13-0.97)
	No	4.5 (62/97)	2.6 (76/104)		0.56 (0.40-0.78)

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Favors BV+Len+R | Favors placebo+Len+R

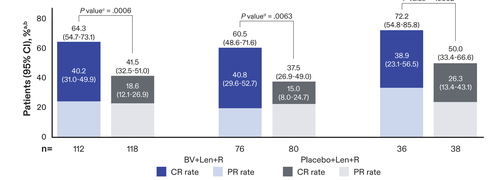
BV, brentuximab vedotin; CAR, chimeric antigen receptor; CD, cluster of differentiation; GCB, germinal center B cell; HR, hazard ratio; IPI, International Prognostic Index; Len, lenalidomide; PFS, progression-free survival; R, rituximab.
[a]The subgroups shown here had a HR of <1.

ORR was significantly higher with BV+Len+R

40% CR rate with BV+Len+R and ORR improvement regardless of CD30 expression

- In the total population, the median duration of response (DOR; 95% CI) was longer with BV+Len+R: 8.3 months (4.2-15.3 months) vs 3.0 months (2.8-5.4 months)
  - In patients who had a CR, the median DOR (95% CI) was 18.9 months (11.1 months-not reached [NR]) with BV+Len+R and NR (2.8 months-NR) with placebo+Len+R
  - The median time to CR onset (range) was 1.58 months (1.2-7.3 months) with BV+Len+R and 1.61 months (0.7-4.6 months) with placebo+Len+R

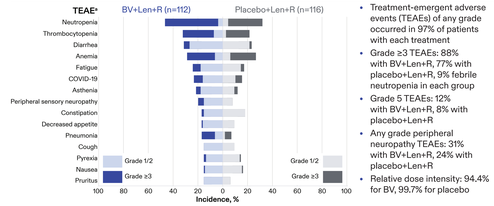
Figure 7. ORR per Investigator



BV, brentuximab vedotin; CD, cluster of differentiation; CR, complete response; DOR, duration of response; GCB, germinal center B cell; Len, lenalidomide; NR, not reached; ORR, objective response rate; PR, partial response; R, rituximab.
[a]Exact 95% CI computed using the Clopper-Pearson method (Clopper 1934).
[b]Best response per Lugano 2014 by investigator assessment. Includes metabolic and nonmetabolic response. Response assessments after progressive disease or start of new anticancer therapy are excluded.
[c]Two-sided *P* value based on Cochran-Mantel-Haenszel test controlling for stratification factors cell of origin (GCB or non-GCB) and CD30 status (≥1% or <1%) at randomization.
[d]Two-sided *P* value based on Fisher exact test.

No new safety signals were observed with addition of BV to Len+R

Figure 8. Adverse Events (≥15%) Observed in ECHELON-3



- Treatment-emergent adverse events (TEAEs) of any grade occurred in 97% of patients with each treatment
- Grade ≥3 TEAEs: 88% with BV+Len+R, 77% with placebo+Len+R, 9% febrile neutropenia in each group
- Grade 5 TEAEs: 12% with BV+Len+R, 8% with placebo+Len+R
- Any grade peripheral neuropathy TEAEs: 31% with BV+Len+R, 24% with placebo+Len+R
- Relative dose intensity: 94.4% for BV, 99.7% for placebo

BV, brentuximab vedotin; Len, lenalidomide; R, rituximab; TEAE, treatment-emergent adverse event.
[a]TEAEs listed are those occurring in ≥15% of patients on either arm. TEAEs are newly occurring or worsening within the safety reporting period (after first dose of study treatment and within 30 days after last dose of BV or Len or 110 days after last dose of R, whichever is later). TEAEs are organized by decreasing frequency in the BV+Len+R group.

Subsequent anticancer therapies received were balanced across both groups

Table 3. Subsequent Anticancer Therapies

n (%)	BV+Len+R (n=112)	Placebo+Len+R (n=116)
Received any subsequent therapy[a]	38 (34)	55 (47)
For progressive disease	30 (27)	44 (38)
For relapsed disease	6 (5)	5 (4)
Secondary malignancy	0	2 (2)
Other	5 (4)	8 (7)
Subsequent therapies		
Anti-CD20	9 (8)	10 (9)
Antibody-drug conjugate	7 (6)	6 (5)
Bispecific	5 (4)	10 (9)
CAR T-cell therapy	5 (4)	5 (4)
Tafasitamab	4 (4)	1 (1)
Other	12 (11)	27 (23)

BV, brentuximab vedotin; CAR, chimeric antigen receptor; CD, cluster of differentiation; Len, lenalidomide; R, rituximab.
[a]Patients receiving multiple therapies were counted once for each type of therapy and specific therapy received.

Conclusions

- ECHELON-3 is the first randomized, placebo-controlled, phase 3 study to demonstrate OS benefit in a contemporary population of patients with R/R DLBCL who have received ≥2 prior lines of systemic therapy
- BV+Len+R met its primary objective, showing a statistically significant and clinically meaningful improvement in OS
  - Reduction in risk of death by 37% with median OS of 13.8 months
- Significant improvement was also observed for key secondary endpoints of PFS and ORR with BV+Len+R
  - Risk of progression or death was 47% lower with median PFS of 4.2 months
  - Significant benefit in ORR of 64% and a 40% CR rate
- Consistent benefit of BV+Len+R for OS, PFS, and ORR was observed regardless of CD30 expression
- BV+Len+R was well tolerated
  - Adverse events were manageable with dose modifications and consistent with the known safety profile of each individual drug[2,9,10]
- This triplet combination, with its promising OS benefit, has the potential to address the high unmet need in patients with R/R DLBCL, particularly those who are not able to receive CAR T-cell therapy or bispecific antibodies or have R/R disease following these treatments

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- Patient enrollment was diverse, with global involvement
- Medical writing support was provided by Caitlin Cash, PhD, of Nucleus Global and funded by Pfizer

ECHELON-3 Site Footprint



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