BRENTUXIMAB VEDOTIN, NIVOLUMAB, DOXORUBICIN, AND DACARBAZINE (AN+AD) FOR ADVANCED-STAGE CLASSICAL HODGKIN LYMPHOMA: UPDATED EFFICACY AND SAFETY RESULTS FROM THE SINGLE-ARM PHASE 2 STUDY (SGN35-027 PART B)

Hun Ju Lee[1], Ian W. Flinn[2], Jason Melear[3], Rod Ramchandren[4], Judah Friedman[5], John M. Burke[3], Yuliya Linhares[3], Paul Gonzales[6], Mihir Raval[3], Rangaswamy Chintapatla[7], Tatyana A. Feldman[8], Habte Yimer[3], Miguel Islas-Ohlmayer[3,9], Asad Dean[3], Vishal Rana[10], Mitul D. Gandhi[3], John Renshaw[3], Linda Ho[11], Michelle A. Fanale[11], Wenchuan Guo[11], Christopher A. Yasenchak[12]

[1]Department of Lymphoma and Myeloma, MD Anderson Cancer Center, Houston, TX, USA; [2]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN, USA; [3]US Oncology Research, The Woodlands, TX, USA; [4]University of Tennessee Medical Center, Knoxville, TN, USA; [5]University Hospitals Seidman Cancer Center, Cleveland, OH, USA; [6]Brooke Army Medical Center, Fort Sam Houston, TX, USA; [7]Kadlec Clinic, Kennewick, WA, USA; [8]Lymphoma Division, John Theurer Cancer Center at Hackensack Meridian Health, Hackensack, NJ, USA; [9]Oncology Hematology Care, Cincinnati, OH; [10]University of Colorado Health Hematology and Oncology, Colorado Springs, CO, USA; [11]Seagen Inc., Bothell, WA, USA; [12]Willamette Valley Cancer Institute and Research Center, Eugene, OR, USA

American Society of Hematology (ASH); New Orleans, Louisiana; December 10-13, 2022; Publication No. 314

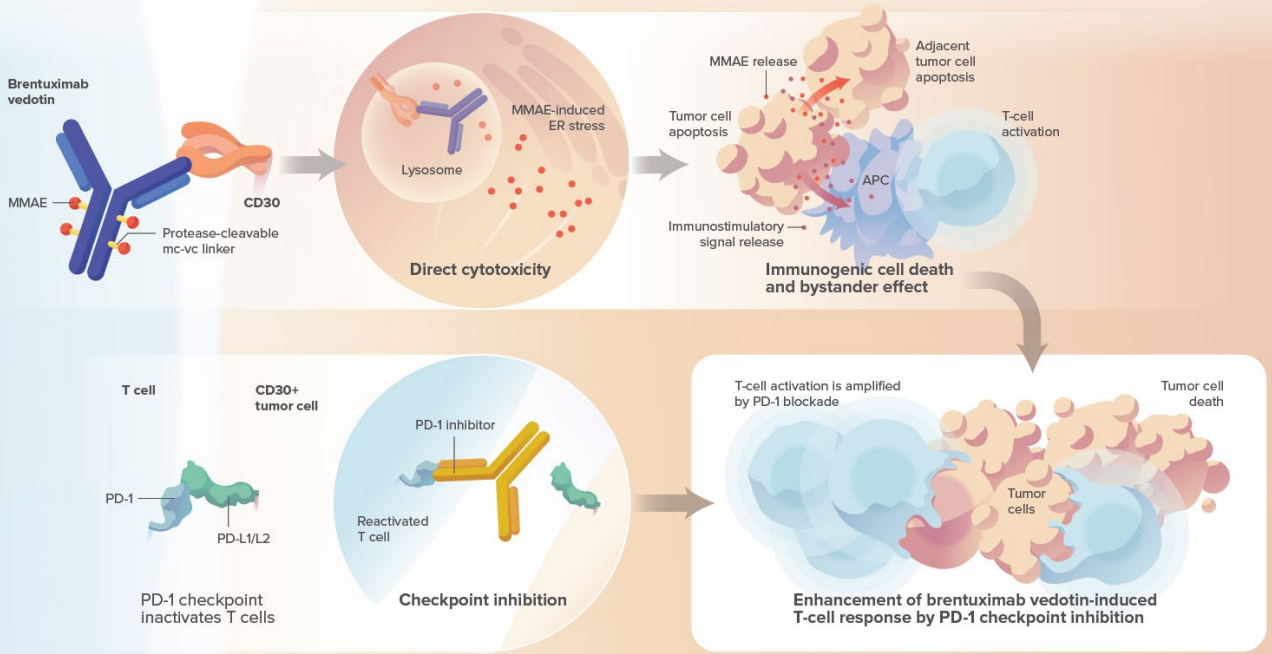
Introduction

- Brentuximab vedotin (BV) is an antibody-drug conjugate approved for multiple cancer types, including previously untreated Stage III or IV classical Hodgkin lymphoma (cHL), in combination with doxorubicin, vinblastine, and dacarbazine (AVD)[1,2]
- BV and nivolumab (N) are both individually active and well tolerated in patients with cHL, and have distinct and complementary mechanisms of action[1-4]
- BV and nivolumab have been previously studied in combination together and with multiagent chemotherapy as BV+AD (omitting vinblastine) and N+AVD
    - BV+AD demonstrated notable and durable activity with low toxicity in patients with previously untreated, non-bulky Stage I or II cHL, suggesting that vinblastine may not be required for efficacy[4]
    - N+AVD was well tolerated and had promising activity in newly diagnosed advanced-stage cHL[5]
    - BV in combination with nivolumab was well-tolerated with favorable efficacy in patients with newly diagnosed cHL who were ineligible for, or declined, conventional chemotherapy[6] and in patients with relapsed/refractory cHL in the first-line salvage setting[7]
- It was hypothesized that the combination of BV and nivolumab with doxorubicin and dacarbazine (AN+AD) would result in high response rates and be well tolerated, with potentially less toxicity than vinblastine-containing regimens
- Preliminary results of this study showed promising efficacy (ORR 93%; CR 88% at EOT) with no cases of febrile neutropenia or Grade 5 adverse events[8]
- Herein, we present updated safety and efficacy results of AN+AD as frontline treatment for patients with advanced-stage cHL

Proposed MOA of BV + a PD-1 Inhibitor in Lymphoma

BRENTUXIMAB VEDOTIN

Proposed mechanism of action
in combination with a PD-1 inhibitor in lymphomas*



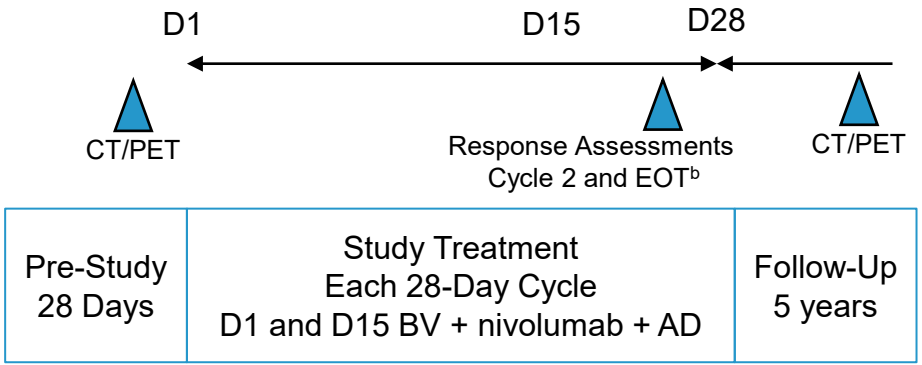
APC: antigen-presenting cell; **CD30:** cluster of differentiation 30; **ER**: endoplasmic reticulum; **mc-vc**: maleimidocaproyl-valine-citrulline; **MMAE**: monomethyl auristatin E; **PD-1**: programmed cell death protein 1; **PD-L1/L2**: programmed cell death-ligands 1 and 2

***Brentuximab vedotin plus a PD-1 inhibitor is an investigational drug combination; the safety and efficacy of the drug combination has not been established.**

Methods

- SGN35-027 (NCT03646123) is an open-label, multiple part, multicenter, phase 2 clinical trial
- Part B enrolled patients with Stage II bulky mediastinal disease (≥10 cm), Stage III, or Stage IV cHL
- Patients received up to 6 cycles of AN+AD
  - BV 1.2 mg/kg, nivolumab 240 mg, doxorubicin 25 mg/m^2, and dacarbazine 375 mg/m^2
  - All study drugs were administered separately by IV infusions on Days 1 and 15 of each 28-day cycle for up to 6 cycles
- Primary endpoint is CR rate at EOT
- Key secondary endpoints include safety, tolerability, ORR, DOR, DOCR, and PFS
- Part B is fully enrolled and long-term follow-up is ongoing

Study Design[a] – Part B



[a]Disease response was assessed by Lugano 2014[9] and LYRIC[10] at Cycle 2 and at EOT.
[b]Response assessments include PET and diagnostic-quality CT scan on Day 25–28 of Cycle 2, and at EOT.

Results: Patient Demographics and Summary of Disposition

Patient Demographics	Part B (N = 57)
Age, median (range)	35.0 (19, 78)
Age range, n (%)[a]	
<65 years	54 (95)
≥65 years	3 (5)
Race, n (%)[a]	
White	50 (88)
Black or African American	2 (4)
Asian	1 (2)
Multiple or Not Reported	4 (7)
Disease stage at diagnosis, n (%)[a]	
Stage II with bulk[b]	17 (30)
III	10 (18)
IV	29 (51)
Extranodal disease, n (%)[a]	28 (49)
International Prognostic Score, n (%)[a]	
0–1	13 (23)
2–3	32 (56)
4–7	12 (21)

[a]Percentages were rounded to the nearest whole number.
[b]Bulky disease was defined as a mass ≥10 cm. No patients with bulky Stage I disease were enrolled. One patient with non-bulky Stage II disease was enrolled per previous protocol amendment.

Summary of Disposition, n (%)[a]	Part B (N = 58)
Patients who received ≥1 dose	57 (98)
Patients on treatment	0
Patients off treatment	57 (98)
Patients in long-term follow-up[b]	55 (95)
Reasons for treatment discontinuation	
Completed treatment	52 (90)
Progressive disease	0
Adverse event	4 (7)
Investigator decision	1 (2)
Patients off study	7 (12)

[a]Percentages were rounded to the nearest whole number.
[b]Patients who completed treatment and entered long-term follow-up.

Results: Overall Response Rate

Overall Response at EOT per Investigator, n (%)	Part B (N = 57)
ORR (CR+PR)[a,b]	53 (93)
95% CI for objective response rate	(83.0, 98.1)
Complete response (CR)[a,b]	50 (88)
95% CI[c] for CR rate	(76.3, 94.9)
Partial response (PR)[a,b]	3 (5)
95% CI[c] for PR rate	(1.1, 14.6)
Stable disease (SD)[a,b]	0
Progressive disease (PD)[a,b]	2 (4)
Indeterminate response (IR)[d]	1 (2)
Not evaluable (NE)[e]	1 (2)

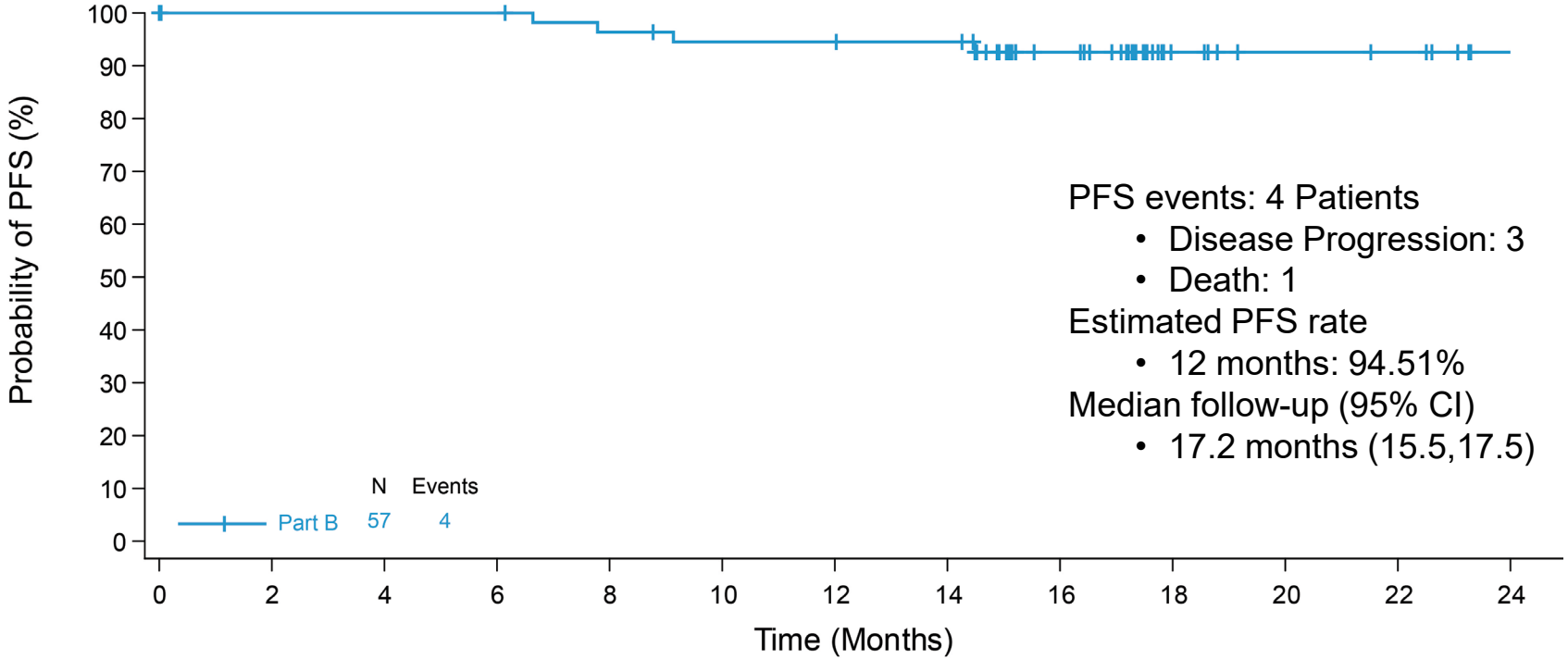
[a]CR, PR, SD and PD per LYRIC per investigator assessment.
[b]CR, PR, SD, PD and NE are mutually exclusive.
[c]Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934).
[d]Confirmatory scan pending.
[e]One patient discontinued after C1D1 due to SAE.

Results: Duration of Objective Response

Duration of Objective Response	Part B (N = 56)
Patients achieved a CR or PR	56
Patients achieved a CR	54
Median DOR[a]	Not reached
Median DOCR[b]	Not reached
Proportion of patients with DOR at least, % (95% CI)	
12 months	94.54 (84.0, 98.2)
Proportion of patients with DOCR at least, % (95% CI)	
12 months	94.30 (83.4, 98.1)

[a]DOR is defined as the time from the first documentation of CR or PR to the first documentation of tumor progression or death, whichever comes first.
[b]DOCR is defined as the time from the first documentation of CR to the first documentation of tumor progression or death, whichever comes first.

Results: Progression-Free Survival



PFS events: 4 Patients
- Disease Progression: 3
- Death: 1

Estimated PFS rate
- 12 months: 94.51%

Median follow-up (95% CI)
- 17.2 months (15.5,17.5)

N at Risk (Events)

Part B	57(0)	56(0)	56(0)	56(0)	53(2)	51(3)	51(3)	50(3)	33(4)	13(4)	9(4)	8(4)	3(4)

Results: Safety

Treatment-Related Treatment-Emergent Adverse Events, n (%)	Part B (N = 57)	
	Any Grade (>10%)	Grade ≥3 (>2%)
Any event	56 (98)	21 (37)
Nausea	37 (65)	–
Fatigue	27 (47)	2 (4)
Peripheral sensory neuropathy	25 (44)	2 (4)
Alopecia	20 (35)	–
Diarrhea	18 (32)	–
Constipation	15 (26)	–
Alanine aminotransferase increased	10 (18)	7 (12)
Headache	10 (18)	–
Vomiting	9 (16)	–
Bone pain	8 (14)	–
Stomatitis	8 (14)	
Aspartate aminotransferase increased	7 (12)	2 (4)
Decreased appetite	7 (12)	–
Myalgia	7 (12)	–
Dyspepsia	6 (11)	–
Neutropenia	6 (11)	5 (9)
Rash maculo-papular	6 (11)	–
Colitis	–	2 (4)
Neutrophil count decreased	–	2 (4)
Pneumonitis	–	2 (4)
Pyrexia	–	2 (4)

- Peripheral sensory neuropathy was primarily low grade (4% TEAEs Grade ≥3 by preferred term)
- No febrile neutropenia was reported and there were no Grade 5 AEs
- Eight patients experienced treatment-related SAEs
  - All cases of pneumonitis and pyrexia resolved fully

Treatment-Related Serious Adverse Events (>2%), n (%)	Part B (N = 57)
Any SAE	8 (14)
Pneumonitis	3 (5)
Pyrexia	3 (5)

Results: Safety – Immune-Mediated AEs

Treatment-Emergent Immune-Mediated Adverse Events[a] (>2%), n (%)	Part B (N = 57)
Any immune-mediated AE	20 (35)
Hypothyroidism	5 (9)
Pneumonitis	3 (5)
Rash maculopapular	3 (5)
Alanine aminotransferase increased	2 (4)
Aspartate aminotransferase increased	2 (4)
Colitis	2 (4)
Dermatitis acneiform	2 (4)
Rash	2 (4)

[a]IMAEs were managed in accordance with the nivolumab Investigator's Brochure

Immune-mediated AEs observed to date are consistent with the individual safety profile of nivolumab

Conclusions

- The use of two active, targeted agents with distinct and complementary MOAs for the 1L treatment of advanced-stage cHL resulted in promising activity and was well tolerated
  - The low rate of PN (including Grade 3) and the absence of febrile neutropenia compare favorably to other 1L regimens, including A+AVD
  - Omitting bleomycin and vinblastine may have contributed to the absence of certain AEs, such as febrile neutropenia
- Updated results confirm initial activity reported for AN+AD as 1L treatment of advanced-stage cHL with an ORR of 93% and a CR rate of 88%
  - The estimated 12-month PFS rate is 95%
- Updated safety results demonstrate continued tolerability with AN+AD and no new safety signals observed
- AN+AD may provide another 1L treatment option for patients with advanced-stage cHL; long-term follow-up is ongoing
- Data from Part C of this study (AN+AD in non-bulky Stage I and II cHL) will be presented as a poster at this meeting (Publication No. 4230)

References

1. Gardai, S.J., A. Epp, and C.L. Law, Brentuximab vedotin-mediated immunogenic cell death. *Cancer Res*, 2015. 75(15 Suppl): p. Abstract 2469.

2. Muller, P., et al., Microtubule-depolymerizing agents used in antibody-drug conjugates induce antitumor immunity by stimulation of dendritic cells. *Cancer Immunol Res*, 2014. 2(8): p. 741-55.

3. Oflazoglu, E., et al., Macrophages contribute to the antitumor activity of the anti-CD30 antibody SGN-30. *Blood*, 2007. 110(13): p. 4370-2.

4. Gardai, S.J., et al., Immune systems engagement results in non-classical antibody-drug conjugate antitumor activity of brentuximab vedotin. *Haematologica*, 2016. 101(Suppl 5): p. 53.

5. OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2021.

6. Advani, R., et al., Brentuximab vedotin in combination with nivolumab in relapsed or refractory Hodgkin lymphoma: 3-year study results. *Blood*, 2021. 138(6): p. 427-38.

7. Yasenchak, C.A., et al., Phase 2 study of frontline brentuximab vedotin plus nivolumab in patients with Hodgkin lymphoma aged ≥60 years. Blood, 2019. 134(Suppl 1): Abstract 237.

8. Lee H, Flinn IW, Melear J, et al. Brentuximab Vedotin, Nivolumab, Doxorubicin, And Dacarbazine (An+ad) For Advanced Stage Classic Hodgkin Lymphoma: Preliminary Safety And Efficacy Results From The Phase 2 Study (SGN35 027 PART B). Hemasphere. 2022 (Suppl) p.979-980.

9. Cheson, B.D., Fisher, R.I., Barrington, S.F., et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014. 32(27): p. 3059-68.

10. Cheson, B.D., Ansell, S., Schwartz, L., et al. Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy. *Blood*. 2016.128(21): p. 2489-96.

11. Clopper, C.J. and Pearson, E.S. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. *Biometrika*, 1934. 26: p. 404-413.

Acknowledgments

Thank you to our patients and their families for their participation in the study, and to all research personnel for their support of this important trial.

Abbreviations

BV (brentuximab vedotin)
AD (doxorubicin and dacarbazine)
AEs (adverse events)
AN+AD (BV, nivolumab, doxorubicin, and dacarbazine)
APC (antigen presenting cell)
AVD (doxorubicin, vinblastine, and dacarbazine)
cHL (classical Hodgkin lymphoma)
CI (confidence interval)
CMR (complete metabolic response)
COVID-19 (coronavirus 19)
CR (complete response)
CT (computed tomography)
D (day)
DCO (data cut-off)
EOT (end of treatment)
ER (endoplasmic reticulum)
IMAE (immune-mediated adverse events)
INV (investigator assessment)
IR (indeterminate response)
LYRIC (Lymphoma Response to Immunomodulatory Therapy Criteria)
NE (not evaluable)
Nivo (nivolumab)
ORR (overall response rate)
PD (progression)
PD-1 (programmed death 1)
PD-L1 (programmed death ligand 1)
PD-L2 (programmed death ligand 2)
PET (positron emission tomography)
PFS (progression free survival)
PN (peripheral neuropathy)
PR (partial response)
pts (patients)
R/R HL (relapsed/refractory Hodgkin lymphoma)
SAEs (serious adverse events)
SD (stable disease)
SPD (sum of the products of the largest diameter)
SUV (standardized uptake value)
TEAEs (treatment-emergent adverse events)