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

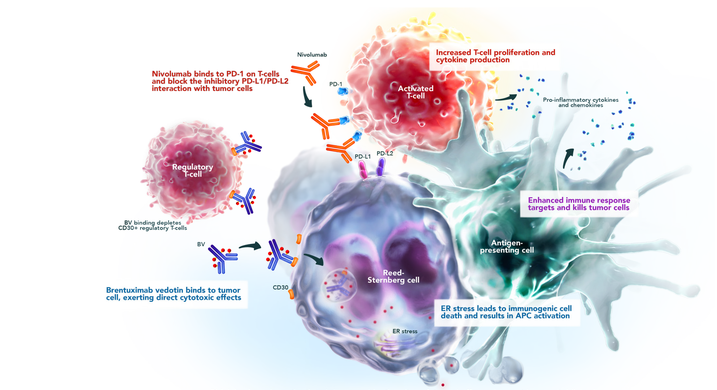
Hun Ju Lee[1], Ian W. Flinn[2], Jason Melear[3], Rod Ramchandren[4], Judah Friedman[5], John M. Burke[3], Yuliya Linhares[3], Matthew R. Peterson[6], Mihir Raval[3], Rangaswamy Chintapatla[7], Tatyana A. Feldman[8], Habte Yimer[3], Miguel Islas-Ohlmayer[3,9], Asad Dean[3], Vishal Rana[10], Mitul D. Gandhi[3], John Renshaw[3], Amanda L. Gillespie-Twardy[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

Background

- BV and nivolumab are both individually active and well tolerated in patients with cHL with distinct and complementary mechanisms of action[1–4]
  - BV is an antibody-drug conjugate directed to CD30, a protein expressed on the Reed-Sternberg cells, and has been shown to have additional mechanisms of action, including the induction of immunogenic cell death.
  - Nivolumab restores antitumor immunity by blocking the PD-1 receptor on activated T-cells, increasing T-cell proliferation and cytokine production.[5]
- The combination of BV plus nivolumab has shown promising activity in first salvage (ORR 85%; CR 67%)[6] and as 1L therapy in older adults (ORR 95%; CR 79%).[7]
- Safety profiles were consistent with that seen with each agent as a monotherapy
- BV+AD in non-bulky Stage I or II cHL resulted in a CR rate of 97% at EOT, as well as a promising 4 year PFS estimate of 91%.[8]
- Importantly, there were no cases of ≥Grade 3 peripheral neuropathy and only 9% were Grade 2.
- Herein, we present initial safety and efficacy results for frontline treatment with AN+AD in patients with 1L advanced cHL.

Rationale for BV+Nivo Combination in cHL Proposed Mechanism of Action

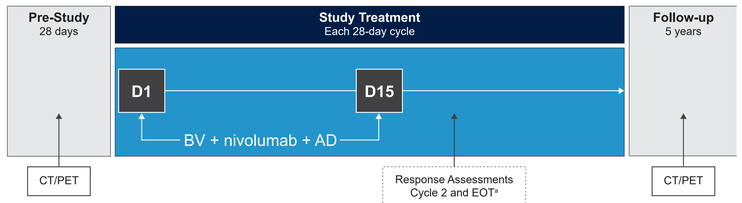


BV+Nivo is an investigational drug combination; its safety and efficacy has not been established.

Methods

- SGN35-027 (NCT03646123) is an open-label, multiple part, multicenter, phase 2 clinical trial.
- Part B enrolled pts with Ann Arbor Stage III/IV cHL, or Stage II with bulky mediastinal disease (≥10 cm).
- 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
- Primary endpoint is CR rate at EOT.
- Key secondary endpoints include safety, tolerability, ORR, and PFS.
- Disease response was assessed by Lugano 2014[9] and LYRIC[10] at Cycle 2 and EOT.

Study Design - Part B



a Response assessments includes PET and diagnostic-quality CT scan on Day 25–28 of Cycle 2, and at EOT.

Results

Demographics

- The majority of patients were younger (median age: 35 years) with Stage III/IV disease (69%, Stage IV 51%).
- Of the 58 patients enrolled, 57 received at least one dose of study treatment.
- Patients received a median of 12 doses of BV (range: 1–12) and nivolumab (range: 1–12)

Demographics	Part B (N=57) n (%)
Age, median (range)	35.0 (19, 78)
Age range, n (%)	
< 65 years	54 (95)
≥65 years	3 (5)
Race, n (%)	
White	50 (88)
Black or African American	2 (4)
Asian	1 (2)
Multiple or Not Reported	4 (7)

a Bulky disease was defined as a mediastinal mass ≥10 cm

Demographics	Part B (N=57) n (%)
Disease stage at diagnosis, n (%)	
II	18 (32)
Bulky[a]	17 (30)
III	10 (18)
IV	29 (51)
Extranodal disease present, n (%)	**27 (47)**
International Prognostic Score, n (%)	
0–1	13 (23)
2–3	32 (57)
4–7	12 (21)

Safety

Treatment-related Adverse Events (>10%)	Part B (N=57) n (%)
Patients with any event	56 (98)
Nausea	37 (65)
Fatigue	26 (46)
Peripheral sensory neuropathy	22 (39)
Alopecia	20 (35)
Diarrhea	17 (30)
Constipation	14 (25)
Headache	10 (18)
Stomatitis	9 (16)
Vomiting	9 (16)
Alanine aminotransferase increased	8 (14)
Bone pain	7 (12)
Decreased appetite	7 (12)
Myalgia	7 (12)
Rash maculo-papular	7 (12)
Aspartate aminotransferase increased	6 (11)
Dyspepsia	6 (11)
Neutropenia	6 (11)

- Peripheral neuropathy was primarily low grade (4% ≥Grade 3), and no patients discontinued due to PN
- No febrile neutropenia was reported and there were no Grade 5 AEs

Treatment-Emergent Grade 3 or Higher Adverse Events by Preferred Term (>2%)	Part B (N=57) n (%)
Patients with any event	30 (53)
Alanine aminotransferase increased	5 (9)
Neutropenia	5 (9)
Colitis	3 (5)
Diarrhea	3 (5)
Anaemia	2 (4)
COVID-19 pneumonia	2 (4)
Fatigue	2 (4)
Hypokalaemia	2 (4)
Neutrophil count decreased	2 (4)
Peripheral sensory neuropathy	2 (4)
Pneumonitis	2 (4)
Rash maculo-papular	2 (4)
Sepsis	2 (4)

Safety: Immune Mediated AEs and SAEs

- Immune-mediated AEs were observed in 18 patients (32%)
  - All cases of pneumonitis resolved fully
  - Eight patients with IMAEs received treatment with a steroid
  - One patient experienced autoimmune hepatitis which resulted in discontinuation of nivolumab
- Eight patients experienced treatment-related SAEs
  - One patient experienced hypophysitis and aseptic meningitis and discontinued treatment after Cycle 1

	Part B (N=57) n (%)
Treatment-Emergent Immune-Mediated Adverse Events (>2%)	
Patients with any event	18 (32)
Hypothyroidism	4 (7)
Alanine aminotransferase increased	2 (4)
Aspartate aminotransferase increased	2 (4)
Colitis	2 (4)
Dermatitis acneiform	2 (4)
Pneumonitis	2 (4)
Rash maculo-papular	2 (4)
Treatment-related Serious Adverse Event (>2%)	
Patients with any event	8 (14)
Pneumonitis	3 (5)
Pyrexia	2 (4)

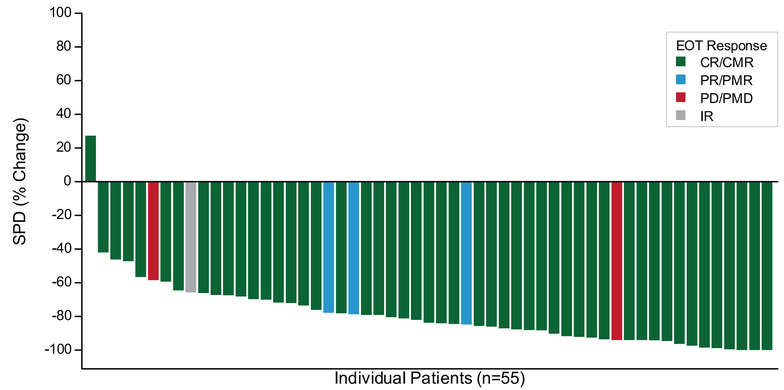
Summary of Initial Response Data at Cycle 2 and EOT

Overall Response at Cycle 2	Part B (N=57) n (%)
ORR (CR+PR)	**55 (96)**
95% CI[a] for objective response rate	(87.9, 99.6)
Complete response (CR)	**42 (74)**
95% CI[a] for CR rate	(60.3, 84.5)
Partial response (PR)	13 (23)
95% CI[a] for PR rate	(12.7, 35.8)
Stable disease (SD)	0
Progression (PD)	0
Indeterminate response (IR)	0
Not evaluable (NE)	2 (4)

Overall Response at EOT	Part B (N=57) n (%)
EOT assessment on or prior to data cutoff[b]	56 (98)
ORR (CR+PR)	**52 (93)**
95% CI for objective response rate	(82.7, 98.0)
CR	**49 (88)**
95% CI for CR rate	(75.9, 94.8)
PR	3 (5)
95% CI for PR rate	(1.1, 14.9)
SD	0
PD	2 (4)
IR	1 (2)
NE[c]	1 (2)

a One patient withdrew following C1. One patient did not have C2 evaluation until after C3 but did have the EOT assessment on schedule.
b One patient had a CMR at EOT after data cutoff.
c Patient withdrew following C1.

Waterfall Plot of Response to AN+AD at EOT (preliminary)



SPD % Change is calculated as the percent change from the baseline SPD to the SPD measured at EOT. 1 patient who achieved CR after data cutoff and 1 patient who discontinued AN+AD prior to EOT assessment are not included. Patient with PD and significant reduction in SPD had new lesions at EOT.

Conclusions

- These preliminary results show promising activity with AN+AD for patients with 1L advanced cHL, with an **ORR of 93%** and a **CR rate of 88%**.
- The use of two active, targeted agents with distinct and complementary MOAs in the 1L setting 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
  - No patients discontinued due to PN
  - 3 of 4 patients who discontinued therapy due to AEs achieved a CR
- AN+AD may provide another active treatment option for patients with 1L advanced cHL. Follow-up is ongoing.
- Enrollment of patients with 1L early stage cHL (Stage I or II, without bulky mediastinal disease) is ongoing in Part C of this study of AN+AD.

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)

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