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)

Christopher A. Yasenchak[1]; Ian W. Flinn[2]; Jason Melear[3]; Rod Ramchandren[4]; Judah Friedman[5]; John M. Burke[3]; Yuliya Linhares[6]; Paul Gonzales[7]; Mihir Raval[3]; Rangaswamy Chintapatla[8]; Tatyana A. Feldman[9]; Habte Yimer[3]; Migue Islas-Ohlmayer[3,10]; Asad Dean[3]; Vishal Rana[11]; Mitul D. Gandhi[3]; John Renshaw[3]; Linda Ho[12]; Michelle A. Fanale[12]; Wenchuan Guo[12]; Hun Ju Lee[13]

[1]Williamette Valley Cancer Institute and Research Center, Eugene OR, 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]Florida Cancer Specialists & Research Institute, Palm Springs FL, USA; [6]Miami Cancer Institute, Baptist Health South Florida, Miami FL, USA; [7]Brooke Army Medical Center Fort Sam Houston TX, USA; [8]Kadlec Clinic, Kennewick WA, USA; [9]John Theurer Cancer Center at Hackensack Meridian Health, Hackensack NJ, USA; [10]Oncology Hematology Care, Cincinnati OH, USA; [11]University of Colorado Health Hematology and Oncology, Colorado Springs CO, USA; [12]Seagen Inc., Bothell WA, USA; [13]MD Anderson Cancer Center, Houston TX, USA

Objectives

The primary objective of Part B is to assess the CR rate at EOT with brentuximab vedotin, nivolumab, doxorubicin, and dacarbazine (AN+AD) in patients with previously untreated cHL

- Secondary objectives are the evaluation of the safety and tolerability of AN+AD, ORR, DOR, DOCR, EFS, PFS, and OS

Herein, we present updated (18-month) safety and efficacy results of AN+AD as frontline treatment for patients with advanced stage cHL

Conclusions

Brentuximab vedotin + nivolumab, two targeted agents with distinct and complementary MOAs, in combination with AD, demonstrated promising activity and were well tolerated in the treatment of patients with advanced-stage cHL

- The low rate of PSN (including grade 3) and the absence of febrile neutropenia compare favorably to other 1L regimens, including A+AVD[8,10,11]
- Omitting bleomycin and vinblastine may have contributed to the absence of certain AEs, such as febrile neutropenia

Updated results presented here confirm initial activity reported[8] for AN+AD as 1L treatment in patients with advanced-stage cHL with an ORR of 95% and a CR rate of 89% at EOT

The estimated 18-month PFS rate was 93%

Updated safety results demonstrate continued tolerability with AN+AD and no new safety signals observed

AN+AD may provide another potential 1L treatment option for patients with advanced-stage cHL; long-term follow-up is ongoing

Abbreviations

ABVD: doxorubicin, bleomycin, vinblastine,and dacarbazine; AD: doxorubicin and dacarbazine; ADC: antibody drug conjugate; AEs: adverse events; ALT: alanine aminotransferase; AN+AD: BV and nivolumab with doxorubicin, and dacarbazine; APC: antigen-presenting cell; AST: aspartate aminotransferase; AVD: doxorubicin, vinblastine, and dacarbazine; BV: brentuximab vedotin; CD30: cluster of differentiation; cHL: classical Hodgkin lymphoma; CMR: complete metabolic response; COVID-19: coronavirus 19; CR: complete response; CT: computed tomography; D: day; DOR: duration of response; EOT: end of treatment; ER: endoplasmic reticulum; IB: Investigator's Brochure; IMAE: immune-mediated AE; INV: investigator assessment; IR: indeterminate response; LYRIC: Lymphoma Response to Immunomodulatory Therapy Criteria; mc-vc: maleimidocaproyl-valine-citrulline; MMAE: monomethyl auristatin E; N: nivolumab; NE: not evaluable; NR: not reached; ORR: overall response rate; PD: progressive disease; PD-1: programmed cell death 1; PD-L1: programmed cell death ligand 1; PD-L2: programmed cell death ligand 2; PET: positron emission tomography; PFS: progression-free survival; PSN: peripheral sensory neuropathy; PR: partial response; PSN: peripheral sensory neuropathy; pts: patients; SAEs: serious adverse events; SD: stable disease; TEAE: treatment-emergent adverse events

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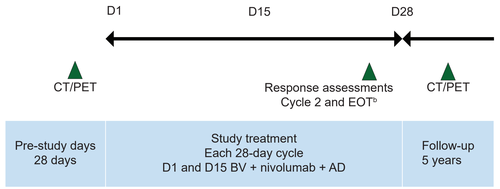
Background

- Brentuximab vedotin (BV) is an ADC approved for multiple cancer types, including previously untreated stage III or IV cHL in combination with doxorubicin, vinblastine, and dacarbazine (AVD),[1-4] based on improved efficacy and overall survival benefit versus doxorubicin, bleomycin, vinblastine,and dacarbazine (ABVD) (0.59 [95% CI: 0.40, 0.88]; P = 0.009), as demonstrated in ECHELON-1[13]
- 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, 6]
- 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 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 patients with 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
- 12-month initial analysis showed promising efficacy (ORR 93%; CR rate 88% at EOT) with no cases of febrile neutropenia or grade 5 adverse events[8]

Methods

- SGN35-027 (NCT03646123) is an open-label, multiple part, multicenter, phase 2 clinical trial
- Part B enrolled patients with stage II bulky mediastinal (≥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 to 28 of Cycle 2, and at EOT.

Results

Patient Demographics and Summary of Disposition

Patient demographics	Part B (N = 57)
Age, median (range)	35 (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 unknown	4 (7)
Disease stage at initial 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. 1 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]	51 (88)
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.

Overall Response Rate

Overall response at EOT per investigator, n (%)	Part B (N = 56)[a]
ORR (CR+PR)[b,c]	53 (95)
95% CI[d] for objective response rate	(85.1, 98.9)
CR[b,c]	50 (89)
95% CI[d] for CR rate	(78.1, 96.0)
PR[b,c]	3 (5)
SD[b,c]	0
PD[b,c]	2 (4)
IR[e]	1 (2)
NE	0

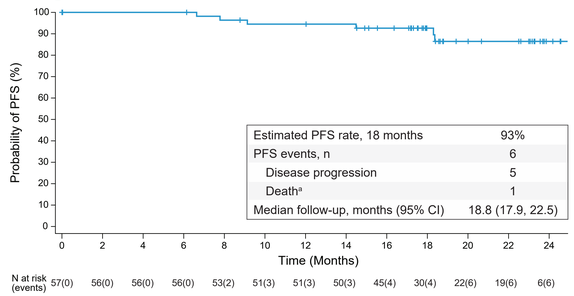
[a]Patients who completed EOT assessment.
[b]CR, PR, SD and PD per LYRIC[10] per investigator assessment.
[c]CR, PR, SD, PD and NE are mutually exclusive.
[d]Two-sided 95% exact CI, computed using the Clopper-Pearson method (1934).
[e]IR converted to CMR in long-term follow-up.

Duration of Response

Results: Duration of Response[a]	Part B
Median DOR, months[b]	NR
Median DOCR, months[c]	NR
Patients with DOR of ≥18 months, % (95% CI)[d]	86 (71.2, 93.9)
Patients with DOCR of ≥18 months, % (95% CI)[d]	88 (75.8, 94.6)

[a]DOR analysis performed in patients who achieved a CR or PR at any visit (n=56). DOCR analysis performed in patients who achieved a CR at any visit (n=54).
[b]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.
[c]DOCR is defined as the time from the first documentation of CR to the first documentation of tumor progression or death, whichever comes first.
[d]DOR/DOCR are estimated using Kaplan-Meier method and CI are computed using complementary log-log transformation.

Progression-Free Survival



[a]Patient died from sepsis secondary to aspiration pneumonia and bacteremia after safety reporting period.

Safety

Treatment-related treatment-emergent AEs, n (%)	Part B (N = 57) Any grade (>10%)	Part B (N = 57) Grade ≥3 (>2%)
Any event	56 (98)	19 (33)
Nausea	37 (65)	–
Fatigue	28 (49)	2 (4)
Peripheral sensory neuropathy	25 (44)	2 (4)
Alopecia	20 (35)	–
Diarrhoea	17 (30)	–
Constipation	15 (26)	–
Alanine aminotransferase increased	9 (16)	6 (11)
Headache	9 (16)	–
Vomiting	9 (16)	–
Bone pain	8 (14)	–
Stomatitis	8 (14)	–
Aspartate aminotransferase increased	7 (12)	2 (4)
Decreased appetite	7 (12)	–
Myalgia	7 (12)	–
Rash maculo-popular	7 (12)	–
Dyspepsia	6 (11)	–
Neutropenia	6 (11)	5 (9)
Colitis	–	2 (4)
Anaemia	–	2 (4)
Pneumonitis	–	2 (4)
Pyrexia	–	2 (4)

Note: "–" indicates TEAEs below 10% (all grade) or 2% (grade ≥3) threshold

- PSN events were primarily low grade (4% TEAEs grade ≥3 by preferred term)
- No events of febrile neutropenia were reported
- 8 (14%) patients experienced treatment-related SAEs
  - Treatment-related SAEs that occurred in >2% of patients were pneumonitis and pyrexia (3 [5%] each)
  - All cases of pneumonitis and pyrexia resolved fully
- No grade 5 AEs

Immune-Mediated AEs

Treatment-emergent immune-mediated AEs[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]Immune-mediated AEs were managed in accordance with the nivolumab Investigator's Brochure

- IMAEs observed to date are consistent with the individual safety profile of nivolumab.[12]
- Grade 3 or higher IMAEs occurred in 8 (14%) patients, with one event each of ALT increased, AST increased, autoimmune hepatitis, colitis, hypophysitis, pneumonitis, rash maculo-popular, rash morbilliform, and transaminases increased.