BRENTUXIMAB VEDOTIN, NIVOLUMAB, DOXORUBICIN, AND DACARBAZINE (AN+AD) FOR EARLY STAGE CLASSIC HODGKIN LYMPHOMA: INTERIM EFFICACY AND SAFETY RESULTS FROM THE SINGLE-ARM PHASE 2 STUDY (SGN35-027 PART C)

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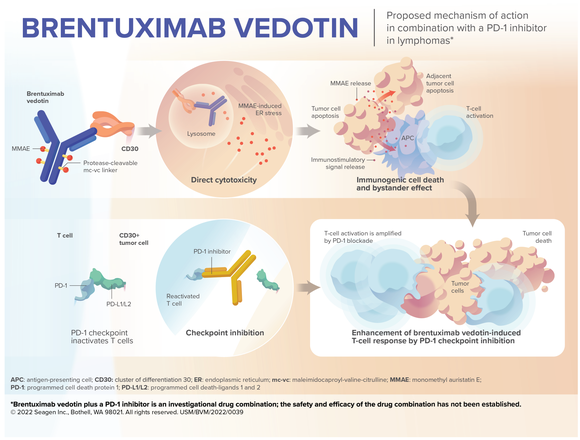
Introduction

- Brentuximab vedotin (BV) is an antibody-drug conjugate approved in multiple cancer types, including as frontline therapy in advanced classical Hodgkin lymphoma (cHL) in combination with doxorubicin, vinblastine, and dacarbazine (AVD).[1,2]
- BV and checkpoint inhibitor, nivolumab, are both individually active and well-tolerated in patients with cHL with distinct and complementary mechanisms of action (MOAs).[1-4]
- BV and nivolumab have been previously studied in combination together and with multiagent chemotherapy, BV with doxorubicin and dacarbazine (BV+AD) and nivolumab with AVD (N+AVD), respectively.
  - BV+AD demonstrated notable and durable activity with low toxicity in frontline patients with 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 combined 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 is hypothesized that the combination of BV and nivolumab (**Figure 1**) with doxorubicin and dacarbazine (AN+AD) would result in high response rates and be well-tolerated, with potentially less toxicity than vinblastine-containing regimens.
- Herein, we present interim safety and efficacy results for frontline treatment with AN+AD in patients with early stage cHL.

Figure 1. Brentuximab Vedotin + PD-1 Inhibitor Combination Proposed Mechanism of Action



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.

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Methods

- SGN35-027 (NCT03646123; EudraCT 2020-004027-17) is an open-label, multiple part, multicenter, phase 2 trial.
- Part C enrolled patients with Ann Arbor Stage I/II cHL, without bulky mediastinal disease (<10 cm).
- Patients received 4 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 administered separately by intravenous infusions on Days 1 and 15 of each 28-day cycle.
- Primary endpoint is complete response (CR) rate at end of treatment (EOT).
- Key secondary endpoints include safety, tolerability, overall response rate (ORR), duration of response (DOR), duration of complete response (DOCR), and progression-free survival (PFS).

Figure 2. SGN35-027 Part C Study Design

Pre-Study	Study Treatment	Follow-up
28 days	Every 28-day cycle D1 and D15 BV + Nivolumab + AD	5 years

AD = doxorubicin and dacarbazine; BV = brentuximab vedotin; CT = computed tomography; D = Day; EOT = end of treatment; PET = positron emission tomography.
a Disease response was assessed by Lugano 2014[8] and LYRIC[9] at Cycle 2 and EOT.
b Response assessments includes PET and diagnostic-quality CT scan on Day 25–28 of Cycle 2, and at EOT.

Results

Demographics and Disease Characteristics

- This interim analysis (data cutoff 16-Mar-2022) presents safety data from 125 patients that received study drug and efficacy data from 76 patients who completed EOT assessment or discontinued without EOT assessment.
  - Of the 129 patients enrolled, 125 received at least 1 dose of study treatment.
  - At the time of this analysis, 50 patients were still on treatment.

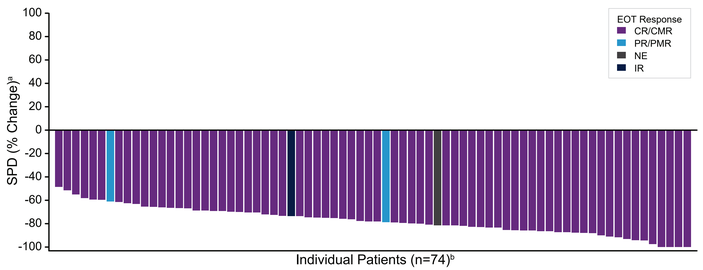
Demographics	Part C (N=125)
Age, median (range)	33.0 (18, 77)
Age range, n (%)	
<65 years	114 (91)
≥65 years	11 (9)
Race, n (%)	
White	106 (85)
Black or African American	1 (1)
Asian	3 (2)
American Indian or Alaska Native	1 (1)
Unknown	14 (11)
Disease stage at diagnosis, n (%)	
I	14 (11)
II	111 (89)

Summary of Response at EOT

Overall Response at EOT[a,b]	Part C (N=76) n (%)
Overall response rate at EOT (CR+PR)	72 (95)
95% CI[c] for overall response rate	(87.1, 98.5)
Complete response (CR)	70 (92)
95% CI[c] for CR rate	(83.6, 97.0)
Partial response (PR)	2 (3)
95% CI[c] for PR rate	(0.3, 9.2)
Stable disease (SD)	0
Progression (PD)	0
Indeterminate response (IR)	1 (1)
Not evaluable (NE)	3 (4)

Efficacy evaluable patients include all patients who completed EOT response assessment or discontinued treatment/study without EOT assessment.
a CR, PR, SD and PD per LYRIC[9] per investigator.
b CR, PR, SD, PD and NE are mutually exclusive.
c Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method.[10]

Waterfall Plot: Change from Baseline SPD at EOT



CR/CMR = complete response/complete metabolic response; PR/PMR = partial response/partial metabolic response; SPD = sum of the products of the largest diameter
a SPD % Change is calculated as the percent change from the baseline SPD to the SPD measured at EOT.
b Two patients without EOT tumor assessment are excluded (n=74 versus n=76 for efficacy). One patient who was Not Evaluable received a PET but not a CT at EOT and is included in the SPD analysis.

Safety: Treatment-Related Treatment-Emergent Adverse Events

Treatment-Related Treatment-Emergent Adverse Events (>10% Any Grade or >2% Grade ≥3)	Part C (N=125) n (%)	
	Any Grade	Grade ≥3
Patients with any event	122 (98)	33 (26)
Nausea	85 (68)	–
Peripheral sensory neuropathy	53 (42)	2 (2)
Fatigue	47 (38)	–
Constipation	33 (26)	–
Alopecia	25 (20)	–
Diarrhoea	25 (20)	2 (2)
Alanine aminotransferase increased	19 (15)	6 (5)
Decreased appetite	18 (14)	–
Aspartate aminotransferase increased	15 (12)	4 (3)
Stomatitis	15 (12)	–
Neutropenia	11 (9)	8 (6)

- Adverse events (AEs) and serious AEs (SAEs) observed to date with this combination regimen are consistent with individual safety profiles of the components of this regimen.
- All cases of pyrexia and pneumonitis treatment-related treatment-emergent SAEs were fully resolved.
- Low incidence of peripheral sensory neuropathy, primarily low grade (2% Grade ≥3).

Treatment-Related Treatment-Emergent Serious Adverse Events (>1%)	Part C (N=125) n (%)
Patients with any event	10 (8)
Pyrexia	3 (2)
Pneumonitis	2 (2)

Immune-Mediated AEs

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

Treatment-Emergent Immune-Mediated Adverse Events (>2%)	Part C (N=125) n (%)
Patients with any event	22 (18)
Hyperthyroidism	7 (6)
Hypothyroidism	7 (6)
Rash maculo-papular	4 (3)

Treatment-Emergent Grade ≥3 Immune-Mediated Adverse Events	Part C (N=125) n (%)
Patients with any event	5 (4)
Rash maculo-papular	2 (2)
Alanine aminotransferase increased	1 (1)
Pneumonitis	1 (1)
Rash macular	1 (1)

*Immune-mediated AEs were managed in adherence with the nivolumab Investigator's Brochure.

Conclusions

- The use of 2 active, targeted agents with distinct and complementary MOAs in the first-line setting resulted in promising activity and was well-tolerated.
  - The low rate of peripheral neuropathy (including Grade 3) and the absence of febrile neutropenia compare favorably to other first-line regimens.
  - Omitting bleomycin and vinblastine may have contributed to the absence of certain AEs, such as febrile neutropenia.
- Interim efficacy reported for AN+AD in first-line early stage cHL with an **ORR of 95%** and a **CR rate of 92%**.
- Interim safety results at EOT indicate that AN+AD is well-tolerated by patients with early stage cHL with no patient discontinuation due to an AE.
- This study is ongoing and 2-year PFS will be disclosed once available.
- Data from Part B of this study (AN+AD in advanced stage and bulky Stage I to II cHL) will be presented in an oral presentation at this meeting (Publication Number 314).

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