Brentuximab Vedotin, Nivolumab, Doxorubicin, and Dacarbazine for Early-Stage Classical Hodgkin Lymphoma: Updated Results From an Ongoing Phase 2 Study (SGN35-027 Part C)

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Objectives

To present updated efficacy and safety results from an ongoing phase 2 study of the novel combination of BV+nivolumab with AD for patients with early-stage cHL (SGN35-027 Part C)

Conclusions

BV+nivolumab, 2 targeted agents with distinct and complementary MOAs, in combination with AD, demonstrated promising activity and were well tolerated in the first-line treatment of early-stage cHL

- The low rate of peripheral sensory 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

AN+AD is well tolerated and demonstrated notable efficacy as a first-line therapy in early-stage cHL with an ORR of 98% and CR rate of 93% in the efficacy evaluable population at EOT

Interim safety results at EOT indicate that AN+AD is well tolerated

This study is ongoing and updated results with additional follow-up will be reported in the future

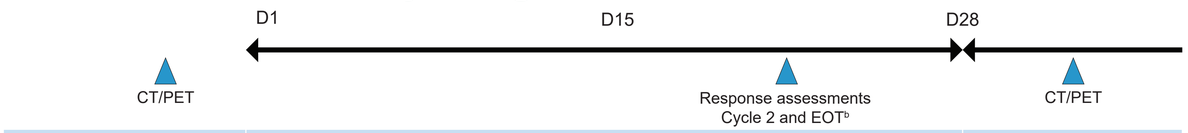
Background

- BV is an antibody-drug conjugate approved for multiple cancer types, including previously untreated stage III or IV cHL, in combination with AVD[1,2]
- BV and nivolumab are both individually active and well tolerated in patients with cHL, and have distinct and complementary MOA[1-5]
- BV and nivolumab have been previously studied in combination together and with multiagent chemotherapy as BV+AD (omitting vinblastine) and nivolumab+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]
  - Nivolumab+AVD was well tolerated and had promising activity in newly diagnosed advanced-stage cHL[6]
  - 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[7] 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 AN+AD would result in high response rates and be well tolerated, with potentially less toxicity than vinblastine-containing regimens
  - In patients enrolled with Ann Arbor stage I/II cHL, without bulky mediastinal disease (<10 cm), 12-month follow-up showed promising efficacy (ORR 95%; CR rate 92% at EOT) with no cases of febrile neutropenia or grade 5 adverse events[8]
  - Here, the efficacy and safety of AN+AD for the treatment of early-stage cHL with an additional 3 months of follow-up is reported

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 CR rate at EOT
- Key secondary endpoints include safety, tolerability, ORR, DOR, DOCR, and PFS
- Use of G-CSF for the treatment of neutropenia was permitted during therapy per institutional practice

SGN35-027 Part C Study Design



Pre-study days	Study treatment	Follow-up
28 days	Each 28-day cycle D1 and D15 BV + nivolumab + AD	5 years

[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

Patient Demographics and Disease Characteristics

- As of February 24, 2023, 156 patients were enrolled
  - Of the 156 patients enrolled, 154 patients received at least 1 dose of study treatment with a median follow-up of 15.6 months
  - At the time of this analysis, no patients were still on treatment

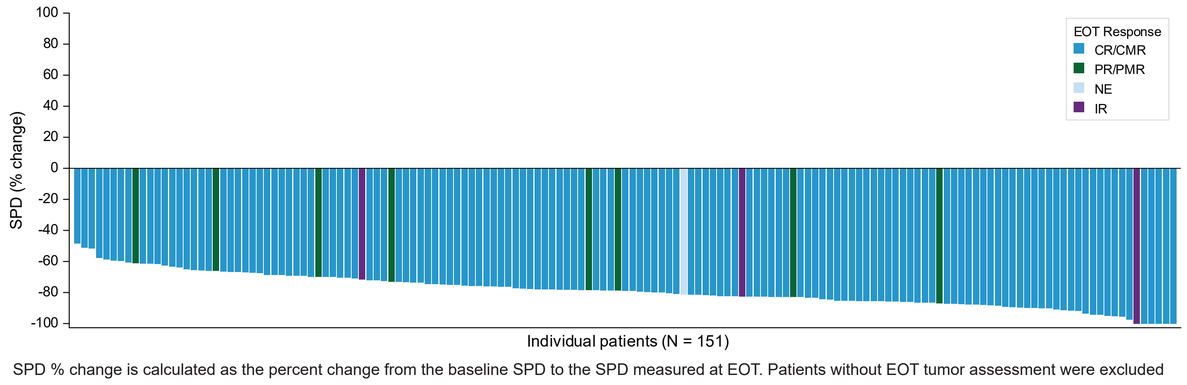
Demographics	Part C N = 154
Age, median (range)	31 (18, 77)
Age range, n (%)	
<65 years	142 (92)
≥65 years	12 (8)
Race, n (%)	
White	129 (84)
Black or African American	1 (1)
Asian	6 (4)
American Indian or Alaska Native	1 (1)
Other	1 (1)
Unknown	16 (10)
Disease stage at initial diagnosis, n (%)	
I	17 (11)
II	137 (89)

Summary of Responses at EOT

	All treated patients N = 154	Efficacy evaluable patients N = 150
Overall Response at EOT[a,b]		
CR, n (% [95% CI])[c]	139 (90 [84.4, 94.4])	139 (93 [87.3, 96.3])
PR, n (%)	8 (5)	8 (5)
SD	0	0
PD	0	0
IR[d], n (%)	3 (2)	3 (2)
NE, n (%)	4 (3)	0
ORR at EOT (CR+PR), n (% [95% CI])[c]	147 (95 [90.9, 98.2])	147 (98 [94.3, 99.6])

Efficacy evaluable patients includes patients who completed EOT response assessments
[a]CR, PR, SD and PD per LYRIC 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 (1934)
[d]Confirmatory Scan is pending at time of DCO

Change from Baseline SPD at EOT



SPD % change is calculated as the percent change from the baseline SPD to the SPD measured at EOT. Patients without EOT tumor assessment were excluded

Safety: Treatment-Related Treatment-Emergent Adverse Events

Treatment-related treatment-emergent AEs	Part C N = 154 n (%)	
	Any grade	Grade ≥3
Patients with any event	149 (97)	52 (34)
Nausea	100 (65)	–
Peripheral sensory neuropathy	72 (47)	4 (3)
Fatigue	67 (44)	–
Constipation	44 (29)	–
Alopecia	34 (22)	–
Alanine aminotransferase increased	32 (21)	11 (7)
Diarrhoea	30 (19)	–
Aspartate aminotransferase increased	27 (18)	8 (5)
Decreased appetite	19 (12)	–
Vomiting	19 (12)	–
Stomatitis	19 (12)	–
Neutropenia	18 (12)	14 (9)
Rash maculo-papular	16 (10)	–
Dyspnea	15 (10)	–
Lipase increased	–	4 (3)
Amylase increased	–	3 (2)

Treatment-related treatment-emergent AEs are shown for ≥10% any grade or ≥2% grade ≥3 thresholds are not reported herein (–)

- AEs and SAEs observed to date with this AN+AD combination regimen are consistent with individual safety profiles of the components of this regimen[9-10]
- There were no cases of febrile neutropenia
- All cases treatment-related treatment-emergent SAEs of pyrexia fully resolved
- There was a low incidence of grade ≥3 peripheral sensory neuropathy with a median treatment duration of 14.1 weeks
- There were no grade 5 events

Treatment-related treatment-emergent SAEs	Part C N = 154 n (%)
Patients with any event	21 (14)
Pyrexia	5 (3)

Treatment-related treatment-emergent AEs are shown for >1%

Immune-Mediated AEs

- Immune-mediated AEs observed to date are consistent with the individual safety profile of nivolumab[11]
  - Immune-mediated AEs were managed in adherence with the nivolumab Investigator's Brochure

Treatment-emergent immune-mediated AEs (≥2%)	Part C N = 154 n (%)
Patients with any event	34 (22)
Hypothyroidism	9 (6)
Hyperthyroidism	7 (5)
Rash maculo-papular	6 (4)
Alanine aminotransferase increased	4 (3)
Pneumonitis	3 (2)

Treatment-emergent adverse events are newly occurring adverse events (not present at baseline) or adverse events that worsen after first dose of investigational product

Treatment-emergent grade ≥3 immune-mediated AEs	Part C N = 154 n (%)
Patients with any event	11 (7)
Alanine aminotransferase increased	3 (2)
Rash maculo-papular	2 (1)
Aspartate aminotransferase increased	1 (1)
Immune-mediated hepatitis	1 (1)
Pneumonitis	1 (1)
Rash macular	1 (1)
Thyroiditis	1 (1)
Type 1 diabetes mellitus	1 (1)

Disclosures
JSA has consultancy for Allogene, Astra-Zeneca, BeiGene, Bluebird Bio, Bristol-Myers Squibb, C4 Therapeutics, Celgene, Century Therapeutics, Epizyme, Genentech, Regeneron, Genmab, Incyte, Karyopharm Kite Pharma, Kymera, MorphoSys, Mustang Bio, and Ono Pharma; and research funding with Bristol-Myers Squibb, and Seagen. DS has constantancy for Seagen and Takeda; and research funding from Seagen. NB has consultancy for ADC Therapeutics, Roche/Genentech, and Seagen; and research funding from ADC Therapeutics, Autolus, Bristol-Myers Squibb, Celgene, Forty Seven, Genentech, Janssen, Kite, Merck, Millennium, Pharmacyclics, and Seagen. JMB has consultancy for Abbvie, Adaptive Bio, AstraZeneca, BeiGene, Bristol-Myers Squibb, Epizyme, Kura, Kymera, MorphoSys, Roche/Genentech, Seagen, and Verastem; and research funding from BeiGene and Seagen. EDD has consultancy for Takeda; and other remuneration with Takeda. YL has consultancy for Abbvie, ADC, Alexion, AstraZeneca, BeiGene, Celgene, Genentech, GSK, Incyte, Janssen, Kyowa, Novartis, and Seagen; research funding from BeiGene and Seagen; and other remuneration with Kyowa Kirin, and Curio Science Workshop Participation and Moderation. RR has consultancy for Bristol-Myers Squibb, Merck, Pharmacyclics, and Seagen; and research funding from Curis, Merck, Pharmacyclics, Seagen, and Trillium. MG has honoraria from GlaxoSmithKline, Karyopharm, and TG Therapeutics. WJ has an employment or leadership position with Abbvie, Astra Zeneca, BeiGene, Janssen, Lilly, Merck, Morphosys, Roche, Seagen, and Takeda; and consultancy for Abbvie, Astra Zeneca, BeiGene, Lilly, Roche, and Takeda. AR has consultancy for Takeda, Incyte, Servier, and Italfarmaco. LH has an employment or leadership position with Seagen; stock ownership with Seagen; and travel grants from Seagen. WG has an employment or leadership position with Seagen; and stock ownership with Seagen. CY has research funding from Seagen. HJL has consultancy for Century Therapeutics, Bristol-Myers Squibb, Deloitte, and Guidepoint Global; honoraria from Aptitude Health, Cancer Experts, Curio Science, Korean Society of Cardiology, and Olson Research; and research funding from Bristol-Myers Squibb, Celgene, Octernal Therapeutics, Seagen, Takeda, and Pharmacyclics.

Abbreviations
AE, adverse event; AN+AD, doxorubicin and dacarbazine; AVD, doxorubicin, vinblastine, and dacarbazine; BV, brentuximab vedotin; cHL, classical Hodgkin lymphoma; CI, confidence interval; CR, complete response; CMR, Complete Metabolic Response; CT, computed tomography; ctDNA, circulating tumor DNA; D, day; DCO, data cut off; DOR, duration of response; DOCR, duration of complete response; EOT, end of treatment; G-CSF, granulocyte-colony stimulating factor; IR, indeterminate response; LYRIC, Lymphoma Response to Immunomodulatory Therapy Criteria; MOA, mechanism of action; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PET, positron emission tomography; PFS, progression-free survival; PR, partial response; PMR, Partial Metabolic Response; SAE, serious adverse event; SD, stable disease; SPD, sum of the products of the largest diameter

Acknowledgements
The authors wish to thank the patients and their families and the co-investigators and study teams at the various sites for their participation in this study.
Direct funding for this research was issued by Seagen Inc. through the joint financial support of Seagen Inc. and Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceuticals Limited.
Medical writing support was provided by Natalie Pizzimenti (MMS Holdings) with funding from Seagen Inc.

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