Protocol Number:	SGN35-031
Version:	"Amendment 1" ; 24-Apr-2020
Protocol Title:	A Randomized, Double-blind, Placebo-Controlled, Active-Comparator, Multicenter, Phase 3 Study of Brentuximab Vedotin or Placebo in Combination With Lenalidomide and Rituximab in Subjects with Relapsed or Refractory Diffuse Large B-cell Lymphoma (DLBCL)
Investigational Product:	Brentuximab vedotin
Brief Title:	Brentuximab Vedotin plus Lenalidomide and Rituximab for the Treatment of Relapsed/Refractory DLBCL
Phase:	3
IND Number:	071634
Sponsor:	Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA
Medical Monitor:	Robert Sims, MD Seattle Genetics, Inc. Tel: 425-527-2806 E-mail: rsims@seagen.com
SAE Email or Fax:	See email or fax number specified on the SAE report form.

PROTOCOL SYNOPSIS

Protocol Number SGN35-031 **Version** 2 **Phase** 3	**Product Name** Brentuximab vedotin **Sponsor** Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA

Protocol Title

A randomized, double-blind, placebo-controlled, active-comparator, multicenter, phase 3 study of brentuximab vedotin or placebo in combination with lenalidomide and rituximab in subjects with relapsed or refractory diffuse large B-cell lymphoma (DLBCL)

Study Objectives and Endpoints

Primary Objectives	**Corresponding Dual Primary Endpoints**
• Evaluate and compare progression-free survival (PFS) between the 2 treatment arms in the intent-to-treat (ITT) population • Evaluate and compare PFS between the 2 treatment arms in the CD30-positive population	• PFS[a] per blinded independent central review (BICR) in the ITT population • PFS per BICR in the CD30-positive population.
Key Secondary Objectives	**Corresponding Key Secondary Endpoints**
• Evaluate and compare the objective response rate (ORR) between the 2 treatment arms in the ITT population	• ORR per BICR
• Evaluate and compare overall survival (OS) between the 2 treatment arms in the ITT population • Evaluate and compare OS between the 2 treatment arms in the CD30-positive population	• OS in the ITT population • OS in the CD30+ population
Other Secondary Objectives	**Corresponding Other Secondary Endpoints**
• Evaluate and compare the complete response (CR) rate between the 2 treatment arms	• CR rate
• Evaluate and compare duration of response between the 2 treatment arms	• Duration of objective response
• Evaluate the safety and tolerability of the 2 treatment arms	• Incidence, severity, and seriousness of adverse events (AEs) per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0
Exploratory Objectives	**Corresponding Exploratory Endpoints**
• To characterize the relationship of CD30 expression with clinical responses to brentuximab vedotin, lenalidomide, and rituximab	• Association of CD30 expression with ORR and PFS

• To evaluate the utility of RECIL 2017 response assessments in DLBCL	• ORR and PFS based on RECIL 2017 response criteria
• To assess the serum pharmacokinetic (PK) and immunogenicity of brentuximab vedotin	• Brentuximab vedotin serum concentrations and incidence of antidrug antibody (ADA) to brentuximab vedotin
• To explore the relationship between prognostic molecular phenotype markers and clinical responses to brentuximab vedotin, lenalidomide, and rituximab	• Association of molecular biomarkers with ORR and PFS.
• To explore the relationship of responses to patient-reported outcomes (PROs) and healthcare utilization between the 2 treatment arms	• EuroQol-5 dimension-5 level (EQ-5D-5L), National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy-Lymphoma (NCCN FACT-Lym), and healthcare utilization

a The dual-primary efficacy endpoints of this study are PFS by BICR in the ITT population and in the CD30-positive population. PFS is defined as the time from the date of randomization to the date of first documentation of progressive disease (PD), or death due to any cause, whichever occurs first.

Study Population

Key eligibility criteria include subjects aged 18 and older with relapsed/refractory (R/R) DLBCL with an eligible subtype; subjects must have ≥2 prior lines of therapy and must be ineligible for, or have declined, stem cell transplant and CAR-T therapy; subjects must have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2; subjects must have a fluorodeoxyglucose (FDG)-avid disease by positron emission tomography (PET) and bidimensional measurable disease of at least 1.5 cm by computed tomography (CT), as assessed by the site radiologist.

Number of Planned Subjects

Approximately 400 subjects (approximately 200 subjects per arm) will be randomized in this study. At least 200 CD30-positive subjects will be enrolled in this study.

Study Design

This is a randomized, double-blind, placebo-controlled, active-comparator, multicenter phase 3 study designed to evaluate the efficacy of brentuximab vedotin in combination with lenalidomide and rituximab versus placebo in combination with lenalidomide and rituximab for the treatment of subjects with R/R DLBCL. All subjects will receive primary granulocyte-colony stimulating factor (G-CSF) prophylaxis.

There will be a safety and PK run-in period prior to the randomized portion of the study. Approximately 6 subjects will receive brentuximab vedotin, lenalidomide, and rituximab. The safety data for at least 6 subjects and the PK data for at least 3 subjects from this run-in period (including a Ctrough sample prior to Cycle 2) will be evaluated after these subjects have completed the first cycle of treatment and prior to proceeding with the randomized portion of the study ..

After completion of the safety run-in period, subsequent subjects will be randomized in a 1:1 manner to receive either brentuximab vedotin or placebo in combination with lenalidomide and rituximab and will be stratified by CD30 expression (positive, ≥1% versus <1%), prior allogenic or autologous SCT therapy (received or not), prior CAR-T therapy (received or not), and cell of origin (GCB or non-GCB). DLBCL and cell of origin (GCB or non-GCB) will be histologically determined by local pathology assessment.

Subjects will have central pathology lab determination of CD30 expression by visual assessment of CD30 on tumor cells from a recent biopsy specimen by immunohistochemistry (IHC; using anti-CD30 BerH2 antibody) for stratification purposes. If, in the determination of the investigator, it is not medically feasible for the subject to undergo central pathology evaluation prior to randomization, and after discussion with the Medical Monitor, the subject may be stratified based on CD30 expression from the local pathology lab. Expression of ≥1% CD30 tumor expression will be considered CD30-positive while expression of <1% CD30 tumor expression will be considered CD30-negative but referred to as CD30 <1%.

Subjects who are stratified based on local pathology lab results must send in archived tumor tissue for central CD30 evaluation within 2 weeks of enrollment. To ensure sufficient power in the CD30-positive population, at least 200 CD30-positive subjects will be enrolled in this study. The percentage of total subjects in each CD30 strata will be approximately 50%.

Investigational Product, Dose, and Mode of Administration

Brentuximab vedotin, 1.2 mg/kg via intravenous infusion every 3 weeks

Lenalidomide, 20 mg orally daily

Rituximab, 375 mg/m^2, via intravenous infusion on Cycle 1 Day 1

Rituximab, 1400 mg, via subcutaneous injection permitted every 3 weeks from Cycle 2 Day 1 through end of treatment.

Control Product, Dose, and Mode of Administration

Placebo replacement for brentuximab vedotin will be administered via intravenous infusion every 3 weeks in the same manner as brentuximab vedotin

Lenalidomide, 20 mg orally daily

Rituximab, 375 mg/m^2, via intravenous infusion on Cycle 1 Day 1

Rituximab, 1400 mg, via subcutaneous injection permitted every 3 weeks from Cycle 2 Day 1 through end of treatment.

Duration of Treatment

Treatment may continue as long as there is clinical benefit (stable disease [SD] or better) without progression or unacceptable toxicity.

Efficacy Assessments

Subjects will be assigned a response status based on imaging and lymphoma assessments. Disease response will be assessed by a BICR and the investigator according to the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas. Radiographic disease evaluations, including contrast-enhanced CT scans of neck, chest, abdomen and pelvis, will be assessed at baseline, then every 6 weeks from randomization for 12 months, then every 12 weeks (±3 days). A PET scan is required at baseline and every 6 weeks thereafter. Once the PET is negative per the investigator, no further PET scans are required. A diagnostic quality CT-PET scan should also be performed at the time of suspected clinical progression.

Pharmacokinetic and Immunogenicity Assessments

Blood samples will be obtained for PK and immunogenicity evaluation at protocol-defined time points. PK parameters to be estimated include maximum plasma concentration (C_{max}), the time C_{max} occurred (T_{max}), concentration at the end of infusion for brentuximab vedotin (C_{eoi}), and trough concentration (C_{trough}). Immunogenicity will be evaluated with measurements of ADA in serum.

Blood will be collected for ADA to brentuximab vedotin, brentuximab vedotin and monomethyl auristatin E (MMAE) exposures, and pharmacodynamic assessments.

Biomarker Assessments

Tumor samples will be collected for biomarker assessment including, but not limited to CD30 expression by IHC, prognostic molecular phenotypes, and gene expression profiling. Blood will be collected for chemokines/cytokines of interest.

Safety Assessments

Safety assessments will include the surveillance and recording of adverse events (AEs), physical examination findings, and laboratory tests.

Other Assessments

Patient-Reported Outcomes and Health Economics: Health outcomes assessments will include health-related quality of life and healthcare utilization, which will be described in the statistical analysis plan (SAP).

Statistical Methods

Stratification:

Subjects will be stratified by CD30 status (positive or <1%) by central pathology review, cell of origin (GCB or non-GCB), prior treatment with CAR-T (received or not), and prior SCT therapy (received or not).

Sample Size Considerations:

In order to evaluate the dual primary endpoint of PFS in the ITT population and in CD30-positive population, an exhaustive fallback testing approach will be used to control overall type I error rate. PFS in the ITT population will be tested at a 2-sided alpha of 0.03 and PFS in the CD30-positive population will be tested at a 2-sided alpha of 0.02. If 1 of the 2 endpoints meets statistical significance, the other can be tested again at an alpha level of 0.05.

Under this testing strategy, assuming a hazard ratio (HR) of 0.62 for both the ITT population and the CD30-positive population, approximately 280 PFS events are required to achieve at least 90% power in the ITT population. Under these assumptions approximately 140 events are expected to be observed for the CD30-positive population, which will provide at least 80% power. Calculations are based on a 2-sided alpha level of 0.05 using the log-rank test.

The accrual period is expected to be approximately 24 months, with additional follow up to reach the specified number of events. The PFS rates in the control arm are based on Czuczman et al and Wang et al: 50% at 3 months, 20% at 6 months, and 18% at 12 months. Assuming a HR of 0.62, and a 5% annual dropout rate, approximately 400 subjects will be randomized.

An interim analysis of ORR may be performed after completion of enrollment. The analysis will include a minimum of 250 subjects (125 per arm) who have completed 6 months of follow-up or have discontinued from the study. Assuming an ORR of 57% in the experimental arm and an ORR of 28% in the control arm, this will provide at least 90% power to detect a difference in ORR between the 2 arms, based on Fisher's exact test at a 2-sided alpha of 0.005.

The key secondary endpoint of OS will be tested in the ITT population and the CD30-positive population at 2 time points. An interim analysis will be conducted at the time of the PFS analysis and a final analysis will be conducted after approximately 300 OS events have been observed. Power for the ITT population and CD30-positive group are similar to those for the PFS analysis described above.

Analysis Methods:

For the primary efficacy analyses of PFS per BICR in the ITT population and in CD30-positive subjects, the stratified log-rank test will be used to compare PFS between the 2 treatment groups. The HR will be estimated using a stratified Cox regression model. PFS will also be summarized using the Kaplan-Meier method. Similar methods will be used for the secondary efficacy endpoint of OS, and other time-to-event efficacy endpoints.

Strata levels may be combined for stratified analyses if too few subjects are included in certain strata levels; details for combining strata will be provided in the SAP.

Analysis Timing:

The estimated duration of the study through final primary analysis is approximately 2.5 years from the randomization of the first subject (including approximately 2 years of enrollment and an additional 6 months of follow-up to reach the specified number of PFS events). If performed, an interim analysis of ORR will occur after the completion of enrollment. The final analysis of OS is expected to occur approximately 1 year from the final primary analysis.