Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Connors JM, Jurczak W, Straus DJ, et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. N Engl J Med 2018;378:331-44. DOI: 10.1056/NEJMoa1708984

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes
2. Original statistical analysis plan, final statistical analysis plan, summary of changes

CLINICAL STUDY PROTOCOL C25003

Brentuximab vedotin

A Randomized, Open-label, Phase 3 Trial of A+AVD Versus ABVD as Frontline Therapy in Patients With Advanced Classical Hodgkin Lymphoma

Protocol Number:	C25003
Indication:	Treatment-naïve advanced Hodgkin lymphoma
Phase:	3
Sponsor:	Millennium Pharmaceuticals, Inc.
EudraCT Number:	2011-005450-60
Therapeutic Area:	Oncology

Protocol History
Original 29 March 2012

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[redacted]

[redacted]

Date DD Month YYYY

[redacted]

Date DD Month YYYY

PROTOCOL SUMMARY

Study Title: A Randomized, Open-label, Phase 3 Trial of A+AVD Versus ABVD as Frontline Therapy in Patients With Advanced Classical Hodgkin Lymphoma

Number of Patients: 520 patients randomized to each treatment arm, for 1040 patients total

Study Objectives

Primary

- To compare the modified progression-free survival (mPFS) obtained with brentuximab vedotin (ADCETRIS™) plus AVD (doxorubicin [Adriamycin], vinblastine, and dacarbazine; abbreviated A+AVD) versus that obtained with ABVD (doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine) for the frontline treatment of advanced classical Hodgkin lymphoma (HL)

Key Secondary

- To determine if A+AVD improves overall survival (OS) versus that obtained with ABVD

Other Secondary

- To determine if A+AVD improves complete remission (CR) rate versus that obtained with ABVD
- To determine the safety profile of A+AVD relative to that of ABVD
- To determine the event-free survival (EFS) obtained with A+AVD and ABVD
- To determine the disease-free survival (DFS) rate obtained with A+AVD and ABVD
- To determine if A+AVD improves overall objective response rate (ORR, defined as CR + partial response [PR]) versus that obtained with ABVD
- To determine the duration of response (DOR) and duration of complete remission (DOCR) obtained in the A+AVD and ABVD arms
- To determine the rate of patients receiving irradiation for HL not in complete remission in the A+AVD and ABVD arms
- To determine the rate of patients in CR at the end of frontline therapy in the A+AVD and ABVD arms
- To determine the rate of Cycle 2 positron emission tomography (PET) negativity in patients treated with A+AVD versus those treated with ABVD
- To determine if A+AVD improves health-related quality of life (HRQoL) versus ABVD
- To describe the pharmacokinetics (PK) of brentuximab vedotin, monomethyl auristatin E (MMAE), and total antibody (TAb) in blood
- To determine the immunogenicity of brentuximab vedotin

Exploratory

- To investigate any differences in lung-specific patient reported outcomes (PROs) between the treatment arms

- To assess any impact of brentuximab vedotin dosing on serum concentrations of AVD
- To investigate any differences between the treatment arms in the rate of patients alive without HL at 3 and 5 years (see Section 8.1.6.3 for definition)
- To assess changes in tumor biomarker expression before and after treatment

[redacted]

- To assess other PROs
- To assess medical resource utilization
- To assess fertility

Overview of Study Design:

This open-label, randomized, 2-arm, multicenter, phase 3 study has the primary objective of comparing the mPFS obtained with A+AVD against that obtained with ABVD.

- A+AVD: Brentuximab vedotin 1.2 mg/kg, plus doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, dacarbazine (DTIC) 375 mg/m^2.
- ABVD: Doxorubicin 25 mg/m^2, bleomycin 10 units/m^2, vinblastine 6 mg/m^2, DTIC 375 mg/m^2.

For this study, the definition of PFS has been modified to include the receipt of anticancer chemotherapy or radiotherapy for patients not in CR after the completion of frontline therapy as a progression event in addition to the customary events of disease progression or death due to any cause. Computed tomography (CT) and PET scans for mPFS disease assessment will be read by a blinded independent review facility (IRF).

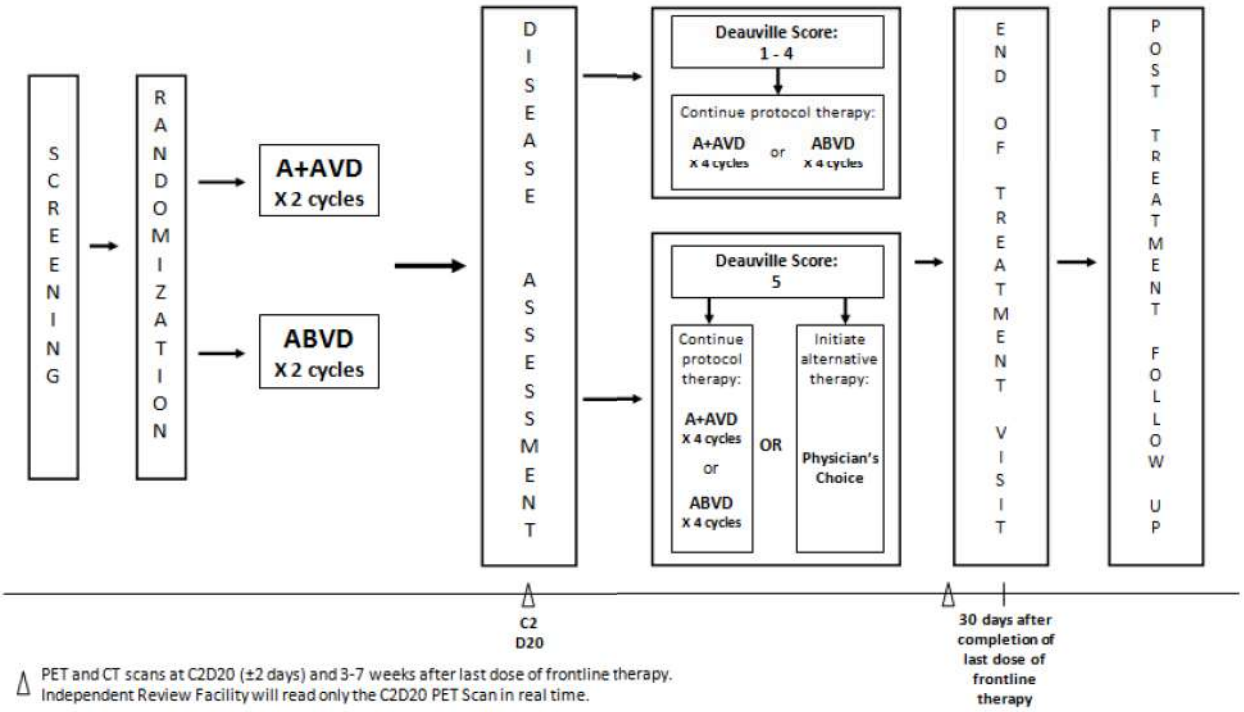
The study will enroll approximately 1040 patients; enrollment is anticipated to last 2 years. All enrolled patients must have a histologically confirmed diagnosis of Stage III or IV classical HL that has not been previously treated with systemic chemotherapy or radiotherapy. Patients will be stratified by region (Americas vs Europe vs Asia) and number of International Prognostic Factor Project (IPFP) risk factors (0-1 vs 2-3 vs 4-7).

Patients will be randomized 1:1 into 1 of 2 treatment arms, for a total of approximately 520 patients per arm. A+AVD and ABVD will be administered intravenously on Days 1 and 15 of each 28-day cycle. Brentuximab vedotin will be administered intravenously over 30 minutes at a dose of 1.2 mg/kg; the brentuximab vedotin infusion is to be started within approximately 1 hour after completion of AVD therapy. PET scan results at Cycle 2 Day 20 will be used to guide an optional switch to physician's choice of alternative therapy for those patients with a Deauville score of 5. Patients may receive up to 6 cycles of planned study therapy (A+AVD or ABVD). Radiotherapy is permitted for those patients in partial remission at conclusion of frontline therapy with a persistent mass measuring 2.5 cm or more that is PET-positive per central review; however, receipt of such radiotherapy will be counted as an mPFS progression event.

An interim futility analysis will be conducted when the first approximately 348 patients have completed the regimen to which they were randomized (ie, received the planned study drug regimen with no more than 2 missed doses of A+AVD or ABVD) or have discontinued treatment prior to completion. The study will use an independent data monitoring committee (IDMC); recommendation to terminate the study would be based on evaluation of the overall safety information and efficacy data (CR rate per IRF for the A+AVD arm at least 5% lower than that of

the ABVD arm, with trends toward inferior A+AVD efficacy for mPFS and other efficacy parameters). The final analysis of the mPFS primary endpoint will be conducted when 260 mPFS events occur, approximately 3 years after randomization of the last patient; an interim efficacy analysis of OS will also be conducted at that time. The final analysis of OS will be conducted when 112 deaths occur, approximately 5 years after randomization of the last patient.
Study Population: Treatment-naïve, HL patients with Ann Arbor Stage III or IV disease are eligible for the study. Patients must have histologically confirmed classical HL according to the current World Health Organisation Classification (nodular sclerosis, mixed cellularity, lymphocyte rich, lymphocyte depleted, or classical Hodgkin lymphoma, NOS [not otherwise specified]). Patients with any sensory or motor peripheral neuropathy are excluded, as are those with nodular lymphocyte predominant HL.
Duration of Study: The study will last approximately 60 months to reach the final analysis of the mPFS endpoint (approximately 24 months of enrollment plus 36 months of additional follow-up after the last patient is randomized). Patients will be followed for survival until death or the end of long-term follow-up (when 112 deaths occur, approximately 5 years from the date of the last patient randomized), whichever occurs first. The total study duration is approximately 7 years.

STUDY OVERVIEW DIAGRAM



Δ PET and CT scans at C2D20 (±2 days) and 3-7 weeks after last dose of frontline therapy. Independent Review Facility will read only the C2D20 PET Scan in real time.

SCHEDULE OF EVENTS

				Cycle (C) Every 28 Days																	
		Screening	Enrollment	Cycle 1				Cycle 2			Cycle 3				Cycle 4		Cycle 5		Cycle 6		EOT	PTFU [a]
	Day (D)	-28 to D1	Within 24 hours of first dose	D1	D2	D3	D 15	D1	D 15	D 20	D1	D2	D3	D 15	D1	D 15	D1	D 15	D1	D 15	30 ± 7 days after last dose of frontline therapy	Every 3 months for 36 months and then every 6 months until study closure
Screening/ Baseline	Informed consent	X	Randomization																			
	Inclusion/ exclusion	X																				
	Demographics	X																				
	Medical History	X																				
	Tumor specimen	X[b]																				
	IPFP	X																				
Safety Assessments	Height	X																				
	Weight	X		X			X	X	X		X			X	X	X	X	X	X	X		
	Physical exam including focused lymphoma assessment	X		X[c]				X			X				X		X		X		X	X
	Pregnancy test [d]	X		X[d]																		
	Vital signs [e]	X		X[e]			X[e]	X	X		X			X	X	X	X	X	X	X	X	X	
	ECOG performance status	X						X			X				X		X		X		X	
	Hematology and serum chemistry [f]	X[f]		X[f]			X[f]	X	X		X			X	X	X	X	X	X	X	X	
	Urinalysis	X																				
	12-lead ECG	X																				
	Quality of Life (QoL) Assessments[g]	X		X[g]				X			X				X		X		X		X	X[g]
	Medical Resource Utilization			X				X			X				X		X		X		X	X
	Monitoring of concomitant	Concomitant medications will be recorded from signing the informed consent through 30 days after the last dose of Frontline Therapy																				

		Screening	Enrollment	Cycle (C) Every 28 Days																EOT	PTFU [a]
				Cycle 1				Cycle 2			Cycle 3				Cycle 4		Cycle 5		Cycle 6		
	Day (D)	-28 to D1	Within 24 hours of first dose	D1	D2	D3	D 15	D1	D 15	D 20	D1	D2	D3	D 15	D1	D 15	D1	D 15	D1	D 15	30 ± 7 days after last dose of frontline therapy	Every 3 months for 36 months and then every 6 months until study closure
	medications																				
	Adverse event reporting			Recorded from first dose of study drugs through 30 days after the last dose of Frontline Therapy (**Treatment-related** adverse events must be followed until the sooner of resolution or study closure.)																	
	Serious adverse events[h]	Serious adverse events will be collected from signing of the informed consent through 30 days after the last dose of Frontline Therapy																			
Disease Assessment	Tumor Biopsy[i]	X																		X[i]	
	CT of chest, neck, abdomen, pelvis[j]	X								X[j]										X[j]	X[j]
	PET[k]	X								X[k]										X[k]	
	Survival/ disease status and concomitant treatments																				X[l]
Fertility Assessment	Fertility Assessment[m]			Dates and outcomes of all pregnancies to be recorded from first dose of study drugs through end of study																	
Study Drug Administration	ABVD or A+AVD[n]			X			X	X	X		X			X	X	X	X	X	X	X	
PK/PD	PK Sample[o]			X	X	X		X			X	X	X		X		X		X		
	Serum Biomarkers such as [redacted]			X				X			X				X		X		X		X
	Immunogenicity[q]	X		X				X											X		X
	Germline DNA[r]			X																	

Abbreviations: ATA = antitherapeutic antibodies; A+AVD = brentuximab vedotin (ADCETRIS™) plus doxorubicin, vinblastine and dacarbazine; ABVD = doxorubicin, bleomycin, vinblastine,

and dacarbazine; CT = computed tomography; CTACK = cutaneous T-cell-attracting chemokine; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; EOT = end of treatment; FDG = fluorodeoxyglucose; IL-6 = interleukin-6; PD = pharmacodynamics; PET = positron emission tomography; IPFP = International Prognostic Factor Project; PK = pharmacokinetics; PTFU = post-treatment follow-up; TARC = thymus and activation-regulated chemokine.

Tests and procedures should be performed on schedule, but occasional changes are allowable (± 3 days) for administrative reasons unless indicated otherwise.

a. All treated patients will be followed for progression-free survival disease status, event-free survival and overall survival every 12 weeks (± 1 week) until 36 months of PTFU and then every 6 months until study closure. For patients who have progressive disease, survival/disease status and information regarding the initiation of an alternative lymphoma treatment may be obtained by phone call. Note: Radiological assessments are only required every 12 weeks (± 1 week) until 12 months of PTFU and then every 6 months until study closure.

b. Tumor tissue collected at the time of original diagnosis or subsequent procedures (unstained slides or a paraffin-embedded block) will be obtained after the patient has signed the informed consent form. This will be used to assess biomarkers implicated in sensitivity or resistance to brentuximab vedotin or vinca alkyloids and taxanes (eg, p53, beta 3 tubulin, and ABCC transporters). If archived tissue cannot be obtained, a biopsy should be performed at screening; refer to footnote "i".

c. The Cycle 1 Day 1 physical examination is not required if the screening physical examination was conducted within 4 days before administration of the first dose of study drug. A limited physical exam may be administered at the treating physician's discretion.

d. A serum β-hCG pregnancy test will be performed for women of childbearing potential during screening and again at Cycle 1, Day 1 (baseline). A urine pregnancy test is required if the serum pregnancy test was not done within 4 days of the first dose of study drug. The results must be negative within 4 days prior to the first dose of brentuximab vedotin.

   Additional pregnancy testing may be performed during the study at the discretion of the investigator, upon request of the IEC/IRB, or if required by local regulations.

e. Vital signs should be measured at screening *and within 1 hour prior* to infusion of ABVD and AVD on Days 1 and 15 of each cycle and EOT. *All vital sign measurements include: systolic* and diastolic orthostatic blood pressure (sitting 3-5 minutes and standing 3-5 minutes), heart rate and oral temperature. <u>In Cycle 1 only</u> (Days 1 and 15), vital signs should be recorded pre-dose and 1 hour post-dose (± 10 minutes).

f. A blood sample for hematology and serum chemistry will be obtained at screening and pre-dose at Days 1 and 15 of each cycle and EOT.

   Hematology and chemistry blood samples for Cycle 1, Day 1 may be collected within 4 days prior to dosing to ensure patient eligibility on study Day 1. In this situation it need not be repeated on Cycle 1, Day 1.

   Hematology includes complete blood count (CBC) with differential consisting of the following: hemoglobin, hematocrit, total white blood cell count (WBC), differential WBC count, absolute neutrophil count (ANC), and platelet count. Machine counts are acceptable.

   Serum chemistry includes sodium, potassium, carbon dioxide, chloride, blood urea nitrogen (BUN), serum creatinine, bilirubin (total, direct, indirect), alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), Gamma glutamyl transferase, albumin, glucose, urate, calcium, phosphate, and magnesium. A fasting A1C Hb will be obtained at screening and Day 1 every cycle.

g. All questionnaires should be completed on screening, Day 1 of every cycle (before any other study procedures are performed), 30 days after last dose of Frontline Therapy, and during post treatment follow up unless indicated otherwise (see table below). If screening questionnaires were completed within 4 days before Cycle 1 Day 1, they do not need to be repeated on Cycle 1 Day 1.
   Patient-reported outcomes will be evaluated using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, the FACIT-Dyspnea 10 questionnaire, the EQ-5D questionnaire, and the Functional Assessment of Cancer Therapy—Neurotoxicity (FACT-Ntx).

   Questionnaires may be collected by phone for patients with stable disease or progressive disease during post treatment follow-up.

Patient Reported Outcome	End of Collection Period
FACIT-Dyspnea 10 Item Short Form	Collected until EOT
FACT-Ntx	Collected until EOT
EuroQOL EQ-5D (Utility Measurement)	Collected until 3 years post last dose of frontline therapy or development of confirmed progressive disease (PD), whichever occurs first
EORTC QLQ-C30	Collected at all patient visits (as outlined in the SOE table), including visits during the PTFU, until the final visit by the patient

h. Includes serious pretreatment events. Serious pretreatment events will be reported to Millennium Pharmacovigilance & Risk Management or designee from the time of signing ICF up to first dose of study drug, but will not be recorded in the eCRF.

i. Patients who cannot provide at least 10 histological slides from their diagnostic biopsy will undergo a new tumor biopsy during screening, which may be obtained up to 14 days prior to the first dose of study drug. Patients who have an archived tumor specimen/ histological slides as previously mentioned, will not need to undergo a biopsy at the time of screening.

Efforts should be made to obtain a tumor biopsy at the time of disease progression. Additional on-study biopsies will be optional and may be used to test for other salient pharmacodynamic and genomic markers related to [redacted]

j. Response to treatment and disease status assessments will be evaluated according to the Revised Response Criteria for Malignant Lymphomas *(Cheson 2007) and confirmed by an* independent review facility.

During the treatment phase CT scans will be performed at:

- Screening
- After Cycle 2: On C2D20 (± 2 days). This corresponds to 5 days (± 2 days) after the 4th dose (after C2D15) of study drug administration
- After last dose of frontline therapy (usually Cycle 6): between 3 and 7 weeks following last dose of frontline therapy. In addition, patients who switch therapy prior to completion of frontline therapy must have a scan performed prior to the first dose of alternative treatment.
- During the follow-up period: every 3 months for the first year and then every 6 months thereafter.

*The actual time points for CT scans during PTFU will be based on calendar days.

PTFU Scan Number	CT Scan Time Points (Calendar days)	Corresponding Year
1	Day 302 ± 7 days	Year 1
2	Day 382 ± 7 days	
3	Day 473 ± 7 days	
4	Day 564 ± 7 days	
5	Day 655 ± 14 days	Year 2
6	Day 837 ± 14 days	

7	Day 1018 ± 14 days	Year 3
8	Day 1200 ± 14 days	
9	Day 1381 ± 14 days	Year 4
10	Day 1563 ± 14 days	
11	Day 1744± 14 days	Year 5
12	Day 1926 ± 14 days	

k. During the treatment phase PET scans will be performed at:

- Screening
- After Cycle 2: On C2D20 (± 2 days). This corresponds to 5 days (± 2 days) after the 4th dose (after C2D15) of study drug administration
- After last dose of frontline therapy (usually Cycle 6): between 3 and 7 weeks following last dose of frontline therapy. In addition, patients who switch therapy prior to completion of frontline therapy must have a scan performed prior to the first dose of alternative treatment.

l. Subjects will be followed for survival disease status every 3 months for 36 months and then every 6 months until death /study closure

m. Fertility is being assessed as an exploratory endpoint independent of safety reporting.

n. Brentuximab vedotin will be administered intravenously at a dose of 1.2 mg/kg within approximately 1 hour after completion of AVD therapy.

o. Pharmacokinetics will be assessed as indicated in the tables below.

Pharmacokinetic Sampling Time Points for All Patients

Full A+AVD Arm				
Cycle	**Study Day**	**Time**	**Window**	**Relative Time**
1-6	1	Predose	Within prior 4 hr	Start of brentuximab vedotin infusion
		EOI (~30 min)	Within 1 hour post EOI	End of brentuximab vedotin infusion
	15	Predose	Within prior 4 hr	Start of brentuximab vedotin infusion
		EOI (~30 min)	Within 1 hour post EOI	End of brentuximab vedotin infusion
1 and 3, in addition	2	24 hr	± 4 hr	Start of brentuximab vedotin infusion
	3	48 hr	± 4 hr	Start of brentuximab vedotin infusion

Pharmacokinetic Sampling Time Points for All Patients

Full A+AVD Arm				
Cycle	**Study Day**	**Time**	**Window**	**Relative Time**
50 Patient Subset Arm: In addition to the above time points, the below pharmacokinetic time points will be drawn from 50 recruited patients from each treatment arm (total of 100 patients).				
A.	**PK Sampling Time Points for the 50-patient Subset of A+AVD Arm Group.**			
1 and 3	1	2 min	± 2 min	End of doxorubicin infusion
		2 min	± 2 min	End of vinblastine infusion
		2 min	± 2 min	End of dacarbazine infusion
		1 hr	± 5 min	End of brentuximab vedotin infusion
		6 hr	± 10 min	End of brentuximab vedotin infusion
	7	168 hr	± 24 hr	End of brentuximab vedotin infusion
B.	**Additional PK Sampling Time Points for the 50-patient Subset of ABVD Arm Group.**			
1 and 3	1	Predose	Within prior 4 hr	Start of doxorubicin infusion
		2 min	± 2 min	End of doxorubicin infusion
		2 min	± 2 min	End of vinblastine infusion
		2 min	± 2 min	End of dacarbazine infusion
		1 hr	± 5 min	End of dacarbazine infusion
		6 hr	± 10 min	End of dacarbazine infusion
	2	24 hr	± 4 hr	End of dacarbazine infusion
	7	168 hr	± 24 hr	End of dacarbazine infusion

Abbreviations: A+AVD = brentuximab vedotin (ADCETRIS™) plus doxorubicin, vinblastine, and dacarbazine; ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; EOI = end of infusion; hr = hour; min = minutes.

*These 50 patients in each treatment arm from whom additional PK samples are drawn will be recruited from sites that agree to participate. In addition, approximately 20 patients in each 50-patient intensive-sampling group must be of Asian race.

p. Serum samples will be collected predose on Day 1 of each cycle, and at EOT in all patients to evaluate protein markers such as [redacted] (circulating protein markers).

q. Immunogenicity samples will all be collected at screening, and before dosing on Day 1 of Cycle 1, Cycle 2, and Cycle 6; or at termination if treatment is terminated before Cycle 6.

r. Optional germline DNA will be collected on Cycle1 Day1 pre-dose.

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
A+AVD	brentuximab vedotin (ADCETRIS™) plus doxorubicin (Adriamycin), vinblastine, dacarbazine
ABVD	doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine
ADC	antibody-drug conjugate
AE	adverse event
ALCL	anaplastic large cell lymphoma
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
AVD	doxorubicin (Adriamycin), vinblastine, and dacarbazine
BEACOPP	bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine, procarbazine, and prednisone
βhCG	beta-human chorionic gonadotropin
BPT	bleomycin pulmonary toxicity
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CL	clearance
C_{max}	maximum plasma concentration
CO_2	carbon dioxide
CR	complete remission
CR(u)	unconfirmed complete response
CT	computed tomography
CTACK	cutaneous T-cell-attracting chemokine
CYP	cytochrome P_{450}
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOCR	duration of complete remission
DOR	duration of response

Abbreviation	Term
DTIC	dacarbazine
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End of Study (visit)
EOT	End of Treatment (visit)
ESMO	European Society for Medical Oncology
EU	European Union
FDA	United States Food and Drug Administration
FDG	fluorodeoxyglucose
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
GHSG	German Hodgkin Study Group
GI	gastrointestinal
GLP	Good Laboratory Practices
GM-CSF	granulocyte macrophage-colony stimulating factor
GMP	Good Manufacturing Practice
Hb	hemoglobin
Hct	hematocrit
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HNSTD	highest nonseverely toxic dose
HRQoL	health-related quality of life
HRS	Hodgkin Reed-Sternberg
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IgG1	immunoglobulin G1

Abbreviation	Term
IL-6	interleukin-6
IPS	(Hasenclever) International Prognostic Score
IRB	institutional review board
IRF	independent review facility
ITT	intent-to-treat
IV	intravenous; intravenously
IVRS	interactive voice response system
JCV	John Cunningham virus
LDH	lactate dehydrogenase
LFT	liver function test(s)
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
mPFS	modified progression-free survival
MRI	magnetic resonance imaging
MRU	medical resource utilization
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease (disease progression)
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PR	partial response
PRO	patient-reported outcome
QALY	quality-adjusted life year
QOL	quality of life
QTc	rate-corrected QT interval (millisec) of electrocardiograph
RBC	red blood cell
SAE	serious adverse event

Abbreviation	Term
SD	stable disease
SmPC	Summary of Product Characteristics
SPD	sum of the product of the (tumor) diameters
$t_{1/2}$	half-life
TARC	thymus- and activation-regulated chemokine
TGD	tumor growth delay
TGI	tumor growth inhibition
T_{max}	first time to maximum plasma concentration
UK	United Kingdom
ULN	upper limit of the normal range
US	United States
WBC	white blood cell
WHO	World Health Organization

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Disease Under Treatment

Hodgkin lymphoma (HL), a neoplasm of lymphoid tissue, is histopathologically defined by the presence of malignant Hodgkin Reed-Sternberg (HRS) cells in a background of inflammatory cells. The characteristic surface antigen expressed on HRS cells is CD30. In 2008 alone, it was estimated that approximately 8220 new cases of HL were diagnosed in the United States,[(1)] approximately 7709 new cases of HL were diagnosed in the 5 major EU countries (UK, France, Germany, Italy, and Spain),[(2)] and approximately 890 new cases of HL were diagnosed in Canada.[(3)]

Advanced HL, here defined as Ann Arbor Stage III or IV disease, is characterized by supra- and sub-diaphragmatic or more widespread disease and is associated with diminished survival. Median overall survival (OS) in the more than 14,000-patient International Hodgkin Lymphoma Database[(4)] is approximately 9 years for patients with Stage IV disease and approximately 18 years for patients with Stage III disease. The Stage III and IV populations typically receive homogenous treatment modalities, providing fewer confounding factors for time-to-event endpoints.

1.1.2 Study Drug

Brentuximab vedotin (ADCETRIS™, the first "A" of the experimental arm acronym) is an antibody-drug conjugate (ADC) composed of the anti-CD30 chimeric immunoglobulin G1 (IgG1) monoclonal antibody cAC10 and the potent antimicrotubule drug monomethyl auristatin E connected by a protease-cleavable linker. cAC10 binds to the CD30 antigen, which has a very low expression on normal cells but is found on the HRS cells of HL, on anaplastic large cell lymphoma (ALCL) cells, and on tumor cells of other varied lymphoproliferative disorders.

Brentuximab vedotin in approved in the United States as ADCETRIS™ for the treatment of patients with HL after failure of autologous stem cell transplant (ASCT) or after failure of at least 2 prior multi-agent chemotherapy regimens in patients who are not ASCT candidates and for the treatment of patients with systemic ALCL after failure of at least 1 prior multi-agent chemotherapy regimen.

1.2 Nonclinical Experience

Brentuximab vedotin has the potential to target and selectively deliver a potent cytotoxic to tumor cells. It induces cell death of both HL and ALCL cell lines in vitro with subnanomolar concentrations producing 50% inhibition (IC_{50}) and has demonstrated antitumor activity in xenograft models of the same tumors.

Multiple-dose brentuximab vedotin toxicity studies have been performed in monkeys and rats. In both species, hypocellularity of the bone marrow and lymphoid depletion of the thymus were observed. In addition, lesions were seen in the kidneys, liver, and spleen in monkeys and in the liver and testes in rats. Reversibility of toxicity was demonstrated for all of the findings with the exception of the testicular changes in rats. At the recovery sacrifice 4 weeks following the last dose of brentuximab vedotin, testicular changes (diffuse seminiferous tubule degeneration) were still evident. The no observed adverse effect level for brentuximab vedotin was defined at 1.0 mg/kg in monkeys and 0.5 mg/kg in rats. Human equivalent doses are 0.32 and 0.08 mg/kg, respectively.

In the L450cy tumor model,[5] administration of doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine (ABVD) plus brentuximab vedotin in tumor-bearing mice demonstrated significantly increased antitumor activity as compared to the mice treated with ABVD or brentuximab vedotin alone, suggesting a synergistic effect.[6] ABVD and brentuximab vedotin-treated animals demonstrated 0/8 and 4/9 durable responses, respectively, while the combination of brentuximab vedotin and ABVD resulted in 9/9 durable tumor regressions in all experimental animals. In addition, combination therapy was associated with a statistically significant tumor growth delay (TGD) relative to each treatment arm alone (combination vs brentuximab vedotin: $P < 0.0101$, combination versus ABVD: $P < 0.0001$). Improved efficacy in high tumor burden models suggests that combining brentuximab vedotin with ABVD may be associated with greater efficacy.

Similarly, when treatment was initiated when tumors reached 300 mm^3 volume, the combination of brentuximab vedotin with ABVD significantly increased the TGD, resulting in durable responses in 5 of 10 animals. The delay in tumor growth induced by the combination treatment was highly significant relative to each individual treatment arm alone (combination versus brentuximab vedotin: $P < 0.05$, combination versus ABVD: $P < 0.001$).

Doxorubicin, vinblastine, and bleomycin had little if any single-agent antitumor activity in L540cy xenograft models and did not significantly improve antitumor activity of

brentuximab vedotin when used in combination with the single-agent chemotherapy drugs (data on file, Seattle Genetics). Specifically, vinblastine had neither a synergistic nor an antagonistic effect when used in combination with brentuximab vedotin. Although vinblastine and auristatins are cell-cycle specific agents belonging to the vinca alkaloid family, they have slightly different mechanisms of action due to their interactions with different microtubule-associated proteins.[7]

Detailed information regarding the nonclinical pharmacology and toxicology of brentuximab vedotin may be found in the Investigator's Brochure (IB).

1.3 Clinical Experience

The safety and efficacy of brentuximab vedotin has been evaluated in more than 450 patients with HL, sALCL, and other CD30+ hematologic malignancies in 11 clinical studies. Clinical data have been collected from 2 completed phase 1 dose-escalation studies (SG035-0001 and SG035-0002), a pivotal phase 2 study in relapsed or refractory HL after ASCT (SG035-0003), a pivotal phase 2 study in relapsed or refractory systemic ALCL (sALCL) (SG035-0004), and a phase 1 drug-drug interaction study (SGN35-008A). Preliminary and final analyses of safety data indicate that brentuximab vedotin has a manageable safety profile in the studied populations.

In Study SG035-0001, a total of 45 patients with CD30+ hematologic malignancies (42 with HL, 2 with sALCL, 1 with angioimmunoblastic T-cell lymphoma) were treated with brentuximab vedotin at dose levels of 0.1 to 3.6 mg/kg administered intravenously (IV) every 3 weeks. The primary objectives of the study were to establish a maximum tolerated dose (MTD) of brentuximab vedotin and to assess the associated toxicity profile. The most common adverse events (AEs) were fatigue (36%), pyrexia (33%), diarrhea, nausea, peripheral neuropathy, and neutropenia (22% each). Notable serious adverse events (SAEs) considered at least possibly related to treatment included anaphylaxis, myocardial infarction, and peripheral neuropathy. Numerous responses, including complete remissions (CRs), were observed. The maximum tolerated dose (MTD) was determined to be 1.8 mg/kg administered IV over 30 minutes every 3 weeks.

In Study SG035-0002, a total of 44 patients with CD30-positive hematologic malignancies (including 38 with HL) were treated with brentuximab vedotin at dose levels of 0.4 to 1.4 mg/kg administered IV weekly for 3 of 4 weeks. The primary objectives explored in this study were to establish the safety profile and MTD of weekly brentuximab vedotin monotherapy in patients with relapsed/refractory CD30+ hematologic malignancies.

Although this weekly regimen was designed to enable combination use with gemcitabine, efficacy with brentuximab vedotin monotherapy was deemed sufficient and the planned brentuximab vedotin/gemcitabine combination was not pursued. The most common AEs were peripheral sensory neuropathy (66%); fatigue (52%); nausea (50%); diarrhea (32%); arthralgia (27%); pyrexia (25%); and decreased appetite, myalgia, and upper respiratory tract infection (23% each). Treatment discontinuations due to AEs were observed in 30% of patients. The most frequent AE that led to dose modification or delay was peripheral sensory neuropathy. Acute infusion reaction AEs occurred in a total of 6 patients. Overall, these acute infusion reaction AEs were reported as less than Grade 2 in severity and resolved. Overall, 2 patients (14%) who had an acute infusion reaction also had antitherapeutic antibodies at any postbaseline visit.

In SG035-0003, a phase 2 single-arm, open-label study in patients with relapsed or refractory HL after ASCT, and SG035-0004, a phase 2 trial conducted in patients with relapsed or refractory sALCL, brentuximab vedotin was administered at a dose of 1.8 mg/kg every 3 weeks. One hundred two patients with relapsed and refractory HL and 58 patients with relapsed and refractory sALCL were exposed for a median duration of approximately 27weeks (9 cycles) and 20 weeks (6 cycles), respectively. Most patients (89%) in the 2 phase 2 studies were between the ages of 18 and 65 years. The primary endpoint of both studies was overall response rate (ORR) as assessed by an independent review facility (IRF). Key secondary endpoints included duration of response, CR rate per IRF, OS, and progression free survival (PFS). The key efficacy results in HL (SG035-0003) include ORR per IRF (75% [95% confidence interval (CI): 64.9-82.6%]), CR rate per IRF (34% [95% CI: 25.2 44.6%]), B symptom resolution rate (77%), and duration of response (DOR; 6.7 months). Of interest, for those patients achieving a CR, the median DOR was 20.5 months. Key efficacy endpoints in sALCL (SG035-0004) include ORR per IRF (88% [95% CI: 74.6-93.9%]), CR rate per IRF (53% [95% CI: 39.6-66.7%]), and B symptom resolution rate (82%).

Treatment-emergent AEs (TEAEs) occurring in ≥ 20% of patients in phase 2 were peripheral sensory neuropathy (44%), fatigue (42%), nausea (41%), diarrhea (34%), pyrexia (31%), upper respiratory tract infection (28%), neutropenia (21%), and vomiting (20%). These events were primarily mild to moderate in severity and reversible. Approximately half of patients had treatment-emergent peripheral neuropathy, predominantly sensory neuropathy, with an onset and severity pattern consistent with a cumulative effect. Dose delay and subsequent reduction to 1.2 mg/kg was generally effective in managing peripheral neuropathy. Grade 3 and 4 neutropenia occurred in 13% and 7% of patients, respectively;

these events were typically of short duration and well managed by brief dose delays with growth factor support in some cases. Infusion-related reactions occurred in approximately 10% of patients and were typically managed by dose interruption. Infusion-related reaction prophylaxis in subsequent treatment cycles was instituted at the discretion of the investigator. The clinical laboratory parameters for which the most patients had new or worsening shifts to ≥ Grade 3 were low neutrophils (11%), lymphocytes (11%), platelets (6%), leukocytes (5%), and high glucose (6%). Only 1 patient in the phase 2 studies had Grade 3 ALT and aspartate aminotransferase (AST).

In the phase 2 studies, 31% of patients had an SAE, 28% had an SAE of Grade 3 or higher, and 15% had an SAE that was determined by the investigator to be related to brentuximab vedotin. The most common SAE preferred terms (2%) were abdominal pain, disease progression (recurrent sALCL), pulmonary embolism, and septic shock. A higher proportion of sALCL patients experienced SAEs, including deaths within 30 days of last dose, relative to HL patients, likely due to the older age and more aggressive nature of the malignancy in this patient population.

A total of 9 deaths were reported within the safety evaluation period (within 30 days of the last dose of brentuximab vedotin) in 357 patients across the 6 phase 1 and phase 2 studies for which data are available. Two patient deaths (0.6%) were considered related to study treatment. One patient in Study SG035-0001 who received 3.6 mg/kg in phase 1 died due to febrile neutropenia and presumed septic shock. A second treatment-related death in Study SGN35-008A was attributed to pancytopenia, cytomegalovirus (CMV) infection, and intracranial hemorrhage. The remaining on-study deaths were primarily related to disease progression in sALCL patients.

Brentuximab vedotin has been shown to induce durable remissions in patients with HL both pre- and post-ASCT, and in patients with relapsed or refractory sALCL. PFS results comparing PFS with brentuximab vedotin to PFS from prior systemic therapy indicate that PFS is significantly prolonged with brentuximab vedotin for both HL and sALCL. A substantial number of HL and sALCL patients with B symptoms at baseline saw these symptoms resolve during treatment with brentuximab vedotin. In addition, the large majority of sALCL patients presenting with cutaneous lesions at baseline experienced resolution of these symptoms after receiving brentuximab vedotin.

Study SGN35-009 is a phase 1, 2-arm, open label, multicenter study to evaluate the safety of brentuximab vedotin when administered in combination with standard therapy (ABVD) or a

modified standard (doxorubicin (Adriamycin), vinblastine, dacarbazine [AVD]). To date, patients have received doses of 0.6, 0.9, or 1.2 mg/kg brentuximab vedotin with standard doses of ABVD or 1.2 mg/kg brentuximab vedotin with AVD, depending upon cohort assignment. The combination regimens are administered on Days 1 and 15 of each 28-day cycle for up to 6 cycles of therapy. Each regimen evaluated a dose limiting toxicity (DLT) period, defined as any Cycle 1 toxicity requiring a delay of ≥ 7 days in standard ABVD or AVD therapy. No DLTs were observed. Enrollment of an expansion cohort further testing 1.2 mg/kg brentuximab vedotin plus AVD is now complete and treatment of enrolled patients is ongoing within this cohort.

Of the 51 patients enrolled in Study SGN35-009, the mean age was 34.8 (range 18-59); 47% of patients had Stage IV disease at diagnosis, and 25% had a Hasenclever Hodgkin's Prognosis Score (IPS) ≥ 4. A recent review of interim safety data as of 07 February 2012 for all 51 enrolled patients included data from 25 patients in the brentuximab vedotin plus ABVD cohorts and 26 patients in the brentuximab vedotin plus AVD cohorts. The most commonly reported TEAEs were nausea, neutropenia, peripheral sensory neuropathy, fatigue, vomiting, constipation, alopecia, pyrexia, bone pain, decreased appetite, diarrhea, and insomnia, each reported in 25% or more patients. Peripheral neuropathy events have been reported in 25 patients (49%); 1 patient had Grade 3 peripheral motor and sensory neuropathy, but no other patient's peripheral neuropathy event exceeded Grade 2. In the brentuximab vedotin plus ABVD cohorts, Grade ≥ 3 events included neutropenia (n = 20, 80%), febrile neutropenia (n = 5), pulmonary toxicity (n = 5), anemia (n = 4), dyspnea (n = 3), pulmonary embolism (n = 3), syncope (n = 3), and anorectal cellulitis, cough, fatigue, hypokalemia, hyponatremia, leukopenia, pericardial effusion, rash, and respiratory failure (n = 1 each). In the brentuximab vedotin plus AVD cohorts, Grade ≥ 3 events included neutropenia (n = 17, 65%), anemia (n = 3), febrile neutropenia (n = 2), and decreased appetite, dyspnea, elevated ALT, fatigue, leukopenia, peripheral sensory and motor neuropathy, *Pneumocystis jiroveci* pneumonia, SIADH, syncope, and tooth abscess (n = 1 each).

Interim efficacy data as of 07 February 2012 demonstrate that all patients who completed frontline therapy on study for whom response assessment results are available achieved a CR at the end of treatment, including 18 patients from the ABVD cohorts and 6 patients from the AVD cohorts. Additionally, an exploratory analysis of interim fluorodeoxyglucose (FDG) positron emission tomography (PET) results after 2 cycles of therapy was performed by independent radiology review using the Deauville criteria.[8] Of 37 patients, 36 (97%)

had a negative interim PET after cycle 2 by central review, including 22 of 22 (100%) negative in the ABVD cohorts and 14 of 15 (93%) negative in the AVD cohorts.

Further details on these studies are provided in the IB.

1.4 Study Rationale

Advances in the use of combined chemotherapy and radiotherapy over the past half century have dramatically improved outcomes for HL patients. The most commonly used frontline therapies, ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) and BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone), result in CRs in 72% to 90% of patients.[9, 10, 11] However, following frontline treatment with multimodality therapy, including combination chemotherapy and radiation, relapse is observed in up to 35% of advanced-stage cases. Also, 10% to 20% of patients are refractory to frontline treatment.[12, 13, 14]

The high CR rate and ORR obtained with brentuximab vedotin in 2 single-arm phase 2 studies in relapsed or refractory HL (SG035-0003) and relapsed or refractory sALCL (SG035-0004) suggest that its addition to frontline therapy may enhance efficacy in newly diagnosed HL.

Of the 4 agents in ABVD, bleomycin is the agent most associated with unpredictable, life-threatening toxicity and is thought to have the lowest single-agent activity.[15] Standard practice in patients who develop bleomycin pulmonary toxicity (BPT) is to continue frontline therapy with AVD while omitting bleomycin. Retrospective analyses of the Cancer and Leukemia Group B (CALGB) 8251 and 8952 studies have shown no difference in response or relapse rates for patients who had bleomycin discontinued at any point in their frontline therapy.[16] Furthermore, noninfectious pulmonary toxicity was observed in some patients treated with brentuximab vedotin in combination with bleomycin within the ABVD cohorts of Study SGN35-009. The incidence of pulmonary toxicity in the brentuximab vedotin plus ABVD cohorts of the trial was approximately 44% (11 of 25 patients), compared with an incidence of 10% to 25% most commonly reported in the literature for bleomycin-based regimens.[17, 18, 19] Patients presented with cough and dyspnea. Interstitial infiltration and/or inflammation were observed on X-ray and computed tomography (CT) of the chest. Six patients had a maximum severity ≥ Grade 3 (3 with Grade 3, 2 with Grade 4, and 1 with Grade 5). It was determined that concomitant administration of brentuximab vedotin and bleomycin is contraindicated due to pulmonary toxicity. Of note, Study SGN35-009 patients who experienced pulmonary toxicity with brentuximab vedotin plus

ABVD were permitted to discontinue bleomycin but resume therapy with brentuximab vedotin plus AVD. Due to the proven antitumor activity and tolerability with single-agent treatment, evaluation of brentuximab vedotin as a replacement for bleomycin in the AVD combination regimen is hypothesized to provide an improvement in PFS over the standard ABVD regimen, and eliminate the risk of bleomycin-associated pulmonary toxicity.

In ongoing Study SGN35-009, brentuximab vedotin is administered in combination with ABVD (doxorubicin 25 mg/m^2, bleomycin 10 units/m^2, vinblastine 6 mg/m^2, dacarbazine [DTIC] 275 mg/m^2) or in combination with AVD (doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, DTIC 275 mg/m^2) in 28-day cycles, with brentuximab vedotin administered on Days 1 and 15 of each cycle for up to 6 cycles of therapy. Brentuximab vedotin was administered in combination with ABVD at 0.6, 0.9, and 1.2 mg/kg (total N = 25) and was administered in combination with AVD at 1.2 mg/kg in dose cohorts of 6 or more patients (total N = 26). No DLTs were observed in any of the cohorts. Brentuximab vedotin monotherapy has previously been shown to be reasonably well tolerated in a phase 1 study and a phase 2 pivotal trial at 1.8 mg/kg in every 3 week dosing. Because the pharmacokinetics (PK) of brentuximab vedotin are linear, PK modeling has shown that the administration of 1.2 mg/kg IV every 2 weeks or 1.8 mg/kg IV every 3 weeks should result in similar exposures (area under the plasma concentration versus time curve [AUC]). Therefore, given the tolerability and the expected PK profiles, it was determined that an appropriate dose level of brentuximab vedotin is 1.2 mg/kg delivered IV every 2 weeks and the recommended combination for further clinical development in phase 3 is with AVD (hereafter called A+AVD). Furthermore, additional PK samples will be taken in the current study to allow further understanding of the PK of brentuximab vedotin and AVD when coadministered in frontline HL setting.

Regarding patients' duration of therapy, functional imaging has recently changed how physicians determine the number of cycles of chemotherapy newly diagnosed HL patients receive. Prior to the widespread use of PET scanning, many patients with advanced stage HL appeared to have partial responses due to residual masses visible upon CT. This large category of partial responses or "complete responses, unconfirmed" (CRu) is now mostly eliminated with the use of PET scanning, which has shown that at least 75% of such patients assessed by CT actually have a CR when PET scanning is added,[20] and such patients with PET-negative residual masses have the same prognosis as patients with no residual mass.[21] As there is no known benefit to continued chemotherapy for HL after achievement of CR, most patients will be assessable after 6 cycles and the very large majority will have reached a CR. For those patients with a PET-positive residual mass after 6 cycles of chemotherapy,

most clinicians would prefer to switch to radiation, thus also concluding frontline chemotherapy after 6 cycles. Therefore, information obtained by functional imaging typically obviates the need for a flexible number of cycles (6-8), and European Society for Medical Oncology (ESMO) and other guidelines are in the process of being updated to reflect this evolving information. Six cycles was thus selected as the duration of frontline therapy in this study.

Notably, this trial does not prospectively plan for patients, even those with bulky disease, to receive radiation therapy. It instead follows the model recently presented by Engert et al as used in the German Hodgkin Study Group (GHSG) HD15 trial.[21] In that study, patients in partial response (PR) with a persistent mass measuring 2.5 cm or more upon completion of frontline chemotherapy were assessed by PET. Only patients who were positive on centrally-reviewed PET scan received additional radiotherapy with 30Gy, yet these data show that frontline therapy was successful. Although the GHSG HD15 study investigated 3 various BEACOPP regimens, this approach to radiotherapy has also been recommended for use with ABVD[22] and seems to strike an appropriate compromise between therapeutic benefit and reducing the risk of later malignancy secondary to radiation exposure.

1.5 Potential Risks and Benefits

As detailed in Section 1.3, brentuximab vedotin monotherapy has demonstrated therapeutic activity in CD30+ hematological malignancies.

Brentuximab vedotin treatment causes a peripheral neuropathy that is predominantly sensory. Cases of peripheral motor neuropathy have also been reported. Brentuximab vedotin-induced peripheral neuropathy is typically cumulative and generally reversible. In the SG035-0003 and SG035-0004 clinical trials, 54% of patients experienced any grade of neuropathy. Of these patients, 49% had complete resolution, 31% had partial improvement, and 20% had no improvement. Of the patients who reported neuropathy, 51% had residual neuropathy at the time of their last evaluation. Monitoring patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness is required. Patients experiencing new or worsening peripheral neuropathy may require brentuximab vedotin dose modifications, including a dose delay (see Table 6-1).

Infusion-related reactions, including anaphylaxis, have occurred with brentuximab vedotin.[23] Monitoring of patients during infusion is required. If anaphylaxis occurs, the administration of brentuximab vedotin should be immediately and permanently discontinued

and appropriate medical therapy administered. If an infusion-related reaction occurs, the infusion should be interrupted and appropriate medical management instituted. Patients who have experienced a prior infusion-related reaction should be premedicated according to institutional guidelines for subsequent infusions. Premedication may include acetaminophen, an antihistamine and a corticosteroid.

Clinically significant laboratory abnormalities were to be reported as adverse events per the phase 2 study protocols. Central laboratory data were collected only predose for each treatment cycle. Few patients overall had postbaseline worsening to Grade 3 or higher in clinical laboratory values. The clinical laboratory parameters for which the most patients had new or worsening shifts to ≥ Grade 3 were low neutrophils (11%), lymphocytes (11%), platelets (6%), leukocytes (5%), and high glucose (6%). Only 1 patient in the phase 2 studies had Grade 3 ALT and AST.

Any treatment that can decrease immune function may contribute to malignancy and infections; patients are to be monitored for these events during the treatment period and up to and including 30 days after the last dose of frontline therapy.

Complete blood counts should be monitored prior to each dose of brentuximab vedotin and more frequent monitoring should be considered for patients with Grade 3 or 4 neutropenia. Prolonged (≥ 1 week) severe neutropenia can occur. If Grade 3 or 4 neutropenia develops, manage by dose delays, reductions, or discontinuations (see Table 6-1).

Tumor lysis syndrome may occur. Patients with rapidly proliferating tumor and high tumor burden are at risk of tumor lysis syndrome and should be closely monitored. If tumor lysis syndrome occurs, take medically appropriate measures.

Stevens-Johnson syndrome has been reported with brentuximab vedotin. If Stevens-Johnson syndrome occurs, brentuximab vedotin must be discontinued and the appropriate medical therapy administered.

Progressive multifocal leukoencephalopathy (PML), including 1 case with a fatal outcome in a patient who had received multiple prior antineoplastic treatments, has been reported with brentuximab vedotin use. PML is a rare demyelinating disease of the brain that is caused by the John Cunningham virus (JCV). It typically occurs in immunocompromised individuals and can be fatal. Presenting features may include altered mental status, motor deficits such as hemiparesis or ataxia, visual disturbances, or higher cortical dysfunction such as dysphasia or agnosia. Seizures have also been reported in PML patients

(approximately 20%). The onset of neurological deficits may occur over weeks to months. Cognitive decline without accompanying deficits in motor or sensory function is uncommon. Optic nerve involvement, fever, and spinal cord disease are not typically associated with PML. In addition, peripheral neuropathy, which has been reported with brentuximab vedotin treatment, is not commonly reported with PML. If PML is suspected, a diagnostic work-up should be performed, as described in Section 6.6.

Preliminary population PK analyses of the effects of renal impairment on brentuximab vedotin metabolism suggest that no dose adjustments are necessary for patients with moderate renal impairment. Additional analysis is planned to more fully characterize the pharmacokinetics in these patient populations.

Monomethyl auristatin E (MMAE) is primarily metabolized by CYP3A. Co-administration of brentuximab vedotin with ketoconazole, a potent CYP3A4 inhibitor, increased exposure to MMAE by approximately 34%. Patients who are receiving strong CYP3A4 inhibitors concomitantly with brentuximab vedotin should be closely monitored for adverse reactions. Co-administration of brentuximab vedotin with rifampin, a potent CYP3A4 inducer, reduced exposure to MMAE by approximately 46%.

The effects of brentuximab vedotin on embryogenesis, reproduction, and spermatogenesis in humans are unknown. In addition, data about the effects of brentuximab vedotin in pregnant women are unavailable. Please see Section 6.5 for appropriate precautions triggered by the administration of study medication.

2. STUDY OBJECTIVES

2.1 Primary Objective

- To compare the modified progression-free survival (mPFS) obtained with brentuximab vedotin (ADCETRIS™) plus AVD (abbreviated A+AVD) versus that obtained with ABVD for the frontline treatment of advanced classical HL

2.2 Secondary Objectives

The key secondary objectives are:

- To determine if A+AVD improves OS versus that obtained with ABVD

Other secondary objectives include:

- To determine if A+AVD improves CR rate versus that obtained with ABVD
- To determine the safety profile of A+AVD relative to that of ABVD
- To determine the event-free survival (EFS) obtained with A+AVD and ABVD
- To determine the disease-free survival (DFS) rate obtained with A+AVD and ABVD
- To determine if A+AVD improves overall ORR (defined as CR + PR) versus that obtained with ABVD
- To determine the DOR and duration of complete remission (DOCR) obtained in the A+AVD and ABVD arms
- To determine the rate of patients receiving irradiation for HL not in CR in the A+AVD and ABVD arms
- To determine the rate of patients in CR at the end of frontline therapy in the A+AVD and ABVD arms
- To determine the rate of Cycle 2 PET negativity in patients treated with A+AVD versus those treated with ABVD
- To determine if A+AVD improves health-related quality of life (HRQoL) versus ABVD
- To describe the PK of brentuximab vedotin, MMAE, and total antibody (TAb) in blood
- To determine the immunogenicity of brentuximab vedotin

2.3 Exploratory Objectives

The exploratory objectives include:

- To investigate any differences in lung-specific patient-reported outcomes (PROs) between the treatment arms

- To assess any impact of brentuximab vedotin dosing on serum concentrations of AVD
- To investigate any differences between the treatment arms in the rate of patients alive without HL at 3 and 5 years (see Section 8.1.6.3 for definition)
- To assess changes in tumor biomarker expression before and after treatment

[redacted]

- To assess other PROs
- To assess medical resource utilization
- To assess fertility

3. STUDY ENDPOINTS

3.1 Primary Endpoints

The primary endpoint is

- Modified PFS per IRF assessment using the Revised Response Criteria for Malignant Lymphoma

3.2 Secondary Endpoints

The key secondary endpoints are:

- OS

Other secondary endpoints include:

- Rate of CR as best overall response achieved at the end of randomized regimen (A+AVD or ABVD) per IRF assessment using the Revised Response Criteria for Malignant Lymphoma
- AEs, SAEs, assessments of clinical laboratory values, and vital sign measurements

- EFS
- DFS
- ORR
- DOR per IRF
- DOCR per IRF
- The rate of patients not in CR that received irradiation
- CR rate per IRF at the end of frontline therapy
- The rate of Cycle 2 PET negativity
- PRO per European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30
- PK parameters for brentuximab vedotin, MMAE, and TAb
- The presence of antitherapeutic antibodies (ATA) to brentuximab vedotin

3.3 Exploratory Endpoints

The exploratory endpoints include:

- PRO per FACIT-Dyspnea 10
- Serum concentrations of AVD in a subset of ABVD- and A+AVD-treated patients, respectively
- Percent of patients alive without HL at 3 and 5 years
- Percent of patients switching therapy post Cycle 2 pre-End of Treatment (EOT)
- [redacted]

- [redacted]
- PRO per FACT-Ntx
- Patient-reported health utility values per EQ-5D
- Utilization of medical resources
- Incidence of pregnancy (patients or partners of patients) in each treatment arm at time of study closure

4. STUDY DESIGN

4.1 Overview of Study Design

This open-label, randomized, 2-arm, multicenter, phase 3 study has the primary objective of comparing the mPFS obtained with A+AVD against that obtained with ABVD. For this study, the definition of PFS has been modified to include the receipt of anticancer chemotherapy or radiotherapy for patients not in CR after the completion of frontline therapy as a progression event in addition to the customary events of disease progression or death due to any cause (a definition of completion of frontline therapy is provided in Table 8-1).

The study will enroll approximately 1040 patients; enrollment is anticipated to last 2 years. All enrolled patients must have a histologically-confirmed diagnosis of Stage III or IV classical HL that has not been previously treated with systemic chemotherapy or radiotherapy. Patients will be stratified by region (Americas vs Europe vs Asia) and number of International Prognostic Factor Project (IPFP) risk factors (0-1 vs 2-3 vs 4-7). (IPFP risk factors are listed in Section 15.5.)

Patients will be randomized 1:1 into 1 of 2 treatment arms, for a total of approximately 520 patients per arm:

- A+AVD: Brentuximab vedotin 1.2 mg/kg plus doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, dacarbazine (DTIC) 375 mg/m^2.

- ABVD: Doxorubicin 25 mg/m^2, bleomycin 10 units/m^2, vinblastine 6 mg/m^2, dacarbazine (DTIC) 375 mg/m^2.

A+AVD and ABVD will be administered intravenously on Days 1 and 15 of each 28-day cycle. Brentuximab vedotin will be administered intravenously over 30 minutes at a dose of 1.2 mg/kg; the brentuximab vedotin infusion is to be started within approximately 1 hour after completion of AVD therapy. Patients may receive up to 6 cycles of therapy (A+AVD or ABVD).

Response to treatment and disease status assessments will be evaluated according to the Revised Response Criteria for Malignant Lymphoma[24] by an IRF that will be blinded to patients' treatment. Tumor measurements will be assessed (CT and PET scans) at Screening, after completion of Cycle 2 (Cycle 2 Day 20 ± 2 days), and at 3-7 weeks after the last dose of frontline therapy. CT scans only will be used for the disease assessment follow-up, performed every 3 months during the first year of posttreatment disease follow-up, then every 6 months until study closure (5 years after last patient enrolled). If, for any reason other than death or documented disease progression, a patient discontinues randomization therapy (A+AVD or ABVD) after Cycle 2 Day 20 but before completion of randomization therapy, every effort must be made to obtain PET and CT scans prior to initiation of subsequent therapy for HL. Responses and relapses will be assessed by an IRF. Evaluations will be performed until progressive disease (PD) is documented, receipt of second-line anticancer therapy for HL (including chemotherapy or radiation), death occurs, or the end of study. Patients will be followed for survival until death or for a minimum of 5 years after enrollment of the last patient.

Deauville scoring (see Section 15.6) per IRF will be used to evaluate the results of patients' Cycle 2 Day 20 PET-CT. Patients whose disease earns a Deauville score of 4 or less will continue study drug treatment according to their randomized arm (ABVD or A+AVD). Patients whose PET-positive disease earns a score of 5 may, at the investigator's discretion, receive an alternative regimen (physician's choice) for the remainder of planned frontline therapy. Patients with a Deauville score of 5 who, at investigator's discretion, are taken off study drug will be continue to be followed for response assessment; switching therapy prior to completion of frontline therapy will not be considered an mPFS progression event. Of further note, any switch in therapy prior to completion of frontline therapy will not be considered an mPFS event.

An interim futility analysis will be conducted when the first approximately 348 patients (1/3 of overall sample size 1040) have completed the regimen to which they were randomized (ie, received the planned study drug regimen with no more than 2 missed doses of A+AVD or ABVD) or have discontinued treatment prior to completion. The final analysis of the mPFS primary endpoint will be conducted when 260 mPFS events occur, approximately 3 years after randomization of the last patient; an interim analysis of OS will also be conducted at that time. The final analysis of OS will be conducted when 112 deaths occur, approximately 5 years after randomization of the last patient.

Safety will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, effective date 14 June 2010,[25] as well as by measuring changes from baseline in the patient's vital signs, ECOG performance status, electrocardiogram (ECG), and clinical laboratory results. Safety data will be periodically reviewed by an independent data monitoring committee (IDMC) per the IDMC charter.

Patient-reported outcomes will be evaluated using the EORTC QLQ-C30, the FACIT-Dyspnea 10 questionnaire, the EQ-5D questionnaire, and the Functional Assessment of Cancer Therapy—Neurotoxicity (FACT-Ntx).

Relationships between plasma levels of brentuximab vedotin, soluble CD30, and CD30 expression on lymphoma cells will be assessed. A possible dose response for any such effects as well as the presence of ATAs may be subsequently examined.

Patients may discontinue therapy at any time. Patients will attend the EOT visit 30 (±7) days after completion of their last dose of frontline therapy.

4.2 Number of Patients

Approximately 1040 patients (approximately 520 patients per treatment arm) will be randomized in this study from approximately 150 study centers globally, including centers in North America, Europe, and Asia.

4.3 Duration of Study

Patients will be screened within 4 weeks of randomization, receive a maximum of six 28-day cycles of A + AVD or ABVD treatment (approximately 6 months), and will have follow-up disease assessments performed until study closure for a minimum of 5 years.

It is expected that the study will last approximately 60 months to reach the final analysis of the mPFS endpoint (approximately 24 months of enrollment plus 36 months of additional follow-up after the last patient is randomized). Patients will be followed for survival until death or the end of long-term follow-up (when 112 deaths occur, approximately 5 years from the date of the last patient randomized), whichever occurs first. The total study duration is approximately 7 years.

5. STUDY POPULATION

Eligible patients with treatment-naïve advanced classical HL will be randomized to receive either A + AVD or ABVD.

5.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be randomized to treatment:

1. Male or female patients 18 years or older.
2. Treatment-naïve, HL patients with Ann Arbor Stage III or IV disease (refer to Section 15.1).
3. Patients must have histologically confirmed classical HL according to the current World Health Organisation Classification (nodular sclerosis, mixed cellularity, lymphocyte rich, lymphocyte depleted, or classical Hodgkin lymphoma, NOS [not otherwise specified]).
4. ECOG performance status ≤ 2 (refer to Section 15.2).
5. Patients must have bidimensional measurable disease as documented by radiographic technique (spiral CT preferred) per the International Working Group Revised Criteria for Response Assessment for Malignant Lymphoma (Cheson 2007).[24]
6. Female patients who:
   - Are postmenopausal for at least 1 year before the screening visit, OR
   - Are surgically sterile, OR

- If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 6 months after the last dose of study drug, or agree to completely abstain from heterosexual intercourse

Male patients, even if surgically sterilized (ie, status postvasectomy), who:

- Agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, or
- Agree to completely abstain from heterosexual intercourse

7. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

8. Suitable venous access for the study-required blood sampling, including PK sampling.

9. Clinical laboratory values as specified below within 7 days before the first dose of study drug:

   - Absolute neutrophil count ≥ 1,500/μL unless there is known HL marrow involvement
   - Platelet count ≥ 75,000/μL unless there is known HL marrow involvement
   - Total bilirubin must be < 1.5 × the upper limit of normal (ULN) unless the elevation is known to be due to Gilbert syndrome.
   - ALT or AST must be < 3 × the upper limit of the normal range. AST and ALT may be elevated up to 5 times the ULN if their elevation can be reasonably ascribed to the presence of HL in liver.
   - Serum creatinine must be < 2.0 mg/dL and/or creatinine clearance or calculated creatinine clearance > 40 mL/minute (refer to Section 15.3).
   - Hemoglobin must be ≥ 8 g/dL.

5.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be randomized to treatment.

1. Nodular lymphocyte predominant Hodgkin lymphoma
2. Female patients who are both lactating and breastfeeding or who have a positive serum pregnancy test during the screening period or a positive pregnancy test on Day 1 before first dose of study drug
3. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol
4. Known cerebral or meningeal disease (HL or any other etiology), including signs or symptoms of PML
5. Pulmonary diffusion capacity > 25% lower than normal predicted value
6. Symptomatic neurologic disease compromising normal activities of daily living or requiring medications
7. Any sensory or motor peripheral neuropathy
8. Any active systemic viral, bacterial, or fungal infection requiring systemic antibiotics within 2 weeks prior to first study drug dose
9. Prior immunosuppressive chemotherapy, therapeutic radiation, or any immunotherapy (eg, immunoglobulin replacement, other monoclonal antibody therapies) within 12 weeks of first study drug dose
10. Known hypersensitivity to recombinant proteins, murine proteins, or to any excipient contained in the drug formulation of brentuximab vedotin or any component of ABVD
11. Known human immunodeficiency virus (HIV) positive
12. Known hepatitis B surface antigen-positive, or known or suspected active hepatitis C infection

13. Diagnosed or treated for another malignancy within 3 years before the first dose or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

14. Any of the following cardiovascular conditions or values within 6 months before the first dose of study drug:

    - A left-ventricular ejection fraction < 50%
    - Myocardial infarction within 2 years of randomization
    - New York Heart Association (NYHA) Class III or IV heart failure (see Section 15.4).
    - Evidence of current uncontrolled cardiovascular conditions, including cardiac arrhythmias, congestive heart failure (CHF), angina, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities

6. STUDY DRUG

All protocol-specific criteria for administration of study drug must be met and documented prior to drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The components of ABVD used in this study will be supplied by the study site and will be billed to patients and/or their third-party payer (insurance) and/or the sponsor according to local regulations. Brentuximab vedotin will be supplied by the study sponsor.

Treatment for advanced HL has improved over the past 30 years with combination chemotherapy regimens. The current anthracycline-containing regimen of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) has proven superior to alkylating agent regimens and results in a long-term cure rate of approximately 70% in patients with advanced disease. Although combination regimens have successfully been expanded to up to 8 chemotherapeutic agents in attempts to increase overall response, these additional agents have also produced increased toxicity. ABVD thus remains the standard of care.

However, of the four agents in ABVD, bleomycin is the agent most associated with unpredictable, life-threatening toxicity, and is thought to have the lowest single-agent activity.[15] Standard practice in patients who develop BPT is to continue frontline therapy with AVD while omitting bleomycin. Retrospective analyses of CALGB 8251 and 8952 have shown no difference in response or relapse rates for patients who had bleomycin discontinued at any point in their frontline therapy.[16] Due to the proven antitumor activity and manageable safety profile of brentuximab vedotin monotherapy, substituting brentuximab vedotin for bleomycin (A+AVD) is hypothesized to provide a PFS improvement over the standard ABVD regimen and eliminate the risk of BPT.

6.1 ABVD Administration

ABVD consists of doxorubicin 25 mg/m^2, bleomycin 10 units/m^2, vinblastine 6 mg/m^2, and dacarbazine (DTIC) 375 mg/m^2.

- **A**: Doxorubicin: 25 mg/m^2 will be administered by IV infusion on Days 1 and 15 of each 28-day cycle
- **B**: Bleomycin: 10 units/m^2 will be administered by IV infusion on Days 1 and 15 of each 28-day cycle
- **V**: Vinblastine: 6 mg/m^2 will be administered by IV infusion on Days 1 and 15 of each 28-day cycle
- **D**: Dacarbazine (DTIC): 375 mg/m^2 will be administered by IV infusion on Days 1 and 15 of each 28-day cycle

  ABVD is to be administered in the above-stated order at administration times per institutional guidelines.

6.2 A+AVD Administration

A+AVD consists of brentuximab vedotin (ADCETRIS™) 1.2 mg/kg plus doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, and dacarbazine (DTIC) 375 mg/m^2.

- **A**: Doxorubicin: 25 mg/m^2 will be administered by IV infusion on Days 1 and 15 of each 28-day cycle
- **V**: Vinblastine: 6 mg/m^2 will be administered by IV infusion on Days 1 and 15 of each 28-day cycle

- **D**: Dacarbazine (DTIC): 375 mg/m^2 will be administered by IV infusion on Days 1 and 15 of each 28-day cycle

AVD is to be administered first, in the above-stated order at administration times per institutional guidelines. Brentuximab vedotin is to be administered after AVD:

- **A**: brentuximab vedotin (ADCETRIS): 1.2 mg/kg will be administered by IV infusion over approximately 30 minutes on Days 1 and 15 of each 28-day cycle; the infusion is to start approximately 1 hour after the conclusion of the dacarbazine administration.

  In the absence of infusion toxicities, the infusion rate for all patients must be calculated in order to achieve a 30-minute (approximate) brentuximab vedotin infusion period.

  Brentuximab vedotin must not be administered as an IV push or bolus. It must be administered through a dedicated IV line and cannot be mixed with other medications.

  The dose of brentuximab vedotin is 1.2 mg/kg. Dosing is based on patients' weight according to the institutional standard; however, doses will be adjusted for patients who experience a ≥ 10% change in weight from baseline. Actual weight will be used except for patients weighing greater than 100 kg; dose will be calculated based on 100 kg for these individuals. The dose will be rounded to the nearest whole number of milligrams.

  Further brentuximab vedotin administration information can be found in the Pharmacy Manual.

No routine pre or post medications are required for A+AVD therapy.

6.3 Dose-Modification Guidelines

6.3.1 Recommended Brentuximab Vedotin Dose Modifications for Treatment-Associated Toxicity

Table 6-1 details the recommended brentuximab vedotin dose modifications to be enacted in the event of treatment-associated toxicity. Please also refer to Section 6.3.2 for criteria pertinent to ABVD and AVD dose modifications.

Table 6-1 Recommended A+ AVD Dose Modifications for Treatment-Associated Toxicity

Toxicity	≤ Grade 2		≥ Grade 3	
Nonhematologic (excluding neuropathy)	Continue at same dose level.		Hold A+AVD dosing until toxicity has resolved to ≤ Grade 2 or has returned to baseline.[a]	
Hematologic	Continue at same dose level.		For neutropenia, manage with growth factors (granulocyte colony stimulating factor [G-CSF] or granulocyte-macrophage colony stimulating factor [GM-CSF]) per institutional guidelines. For thrombocytopenia, consider platelet transfusion and/or proceed according to institutional guidelines. For anemia, manage per institutional guidelines.	
Peripheral neuropathy	**Grade 1** Continue at same dose level.	**Grade 2** Reduce dose to 0.9 mg/kg and resume treatment; if already at 0.9 mg/kg, continue dosing at that level.	**Grade 3** Withhold brentuximab vedotin until toxicity is ≤ Grade 2, then reduce dose to 0.9 mg/kg and resume treatment. If already at 0.9 mg/kg, consult with sponsor (AVD may be continued or held concurrently at physician's discretion.)	**Grade 4** Discontinue brentuximab vedotin

a Patients who develop clinically insignificant Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption.

6.3.2 Reference Therapy Dose Modifications

ABVD or AVD treatment should be modified or discontinued per applicable label/Summary of Product Characteristics (SmPC) instructions.

6.3.3 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Any investigational agent other than brentuximab vedotin.

- Any frontline anticancer treatment for remission induction other than ABVD or AVD (unless on the basis of a Cycle 2 Day 20 PET Deauville score of 5 as noted in Section 6.4).

- The concomitant use of brentuximab vedotin and bleomycin has resulted in increased pulmonary toxicity versus bleomycin alone. Coadministration of brentuximab vedotin and bleomycin is a contraindication.

6.4 Permitted Concomitant Medications and Procedures

The following medications and procedures are allowed during the study:

- For patients with a Deauville score of 5 upon Cycle 2 Day 20 PET scanning, physician's choice of alternative therapy is permitted, but not required, for the remainder of frontline treatment.

- Radiotherapy based on end-of-frontline therapy PET scanning: Patients in PR with a persistent mass measuring 2.5 cm or more upon completion of frontline chemotherapy with PET-positive disease per IRF may receive radiotherapy with 30Gy.

- The use of topical, inhalational and ophthalmic steroids is permitted. Corticosteroids are permitted as part of a chemotherapy premedication regimen or for the treatment of HL per institutional standards.

- Patients may receive concomitant hormonal therapy provided they have been on a stable dosage for at least 1 month prior to enrollment. No restrictions are placed upon the use of birth control.

- The use of platelet and/or red blood cell supportive growth factors or transfusions when applicable is allowed.

- The use of colony stimulating factors for the treatment of neutropenia per institutional practice is permitted during therapy.

6.5 Precautions and Restrictions

Infusion-Related Reactions

All infusions should be administered at a site properly equipped and staffed for anaphylaxis should it occur. Medications for treatment of hypersensitivity reactions, such as epinephrine, antihistamines, and steroids, should be available for immediate use in the event of a reaction during administration and also during the observation period following the first brentuximab vedotin infusion.

Pregnancy

It is not known what effects brentuximab vedotin has on human pregnancy or development of the embryo or fetus, and ABVD is known to have deleterious effects on pregnancy. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing of the informed consent form through 6 months after the last dose of study drug, or agree to completely abstain from heterosexual intercourse

Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, or completely abstain from heterosexual intercourse

6.6 Management of Clinical Events

Nausea and/or Vomiting

Although this study will not initially employ prophylactic anti-emetics, there is no prohibition against their use in the management of a patient who develops nausea and/or vomiting. As in the prophylactic setting, 5-HT_3 receptor antagonists and corticosteroids should be tried first.

Diarrhea

Prophylactic antidiarrheals will not be used in this protocol; however, patients will be instructed to take antidiarrheal medication(s) at physician's discretion until they are diarrhea-free for at least 12 hours. Fluid intake should be maintained to avoid dehydration.

Infusion-Related Reactions

Infusion-related reactions may occur during the infusion of brentuximab vedotin. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. The patient should be observed for 60 minutes following the first infusion of brentuximab vedotin. During this observation period, the IV line should remain open for at least 1 hour to allow administration of IV drugs if necessary. All supportive measures consistent with optimal patient care will be given throughout the study according to institution standards. Medications for infusion-related reactions, such as epinephrine and antihistamines should be available for immediate use.

Patients who experience a Grade 1 or 2 infusion-related reaction may receive subsequent brentuximab vedotin infusions with premedication consisting of acetaminophen (650 mg orally) and diphenhydramine (25-50 mg orally or 10-25 mg IV) or according to institutional standards, administered 30 to 60 minutes prior to each 30-minute brentuximab vedotin infusion.

Peripheral Neuropathy

AEs of peripheral neuropathy will be monitored closely throughout the study. Events that are greater than Grade 1 in severity will result in brentuximab vedotin dose modification as shown in Table 6-1.

Suspected Progressive Multifocal Leukoencephalopathy (PML)

Signs and symptoms of PML may include altered mental status; motor deficits, such as hemiparesis or ataxia; visual disturbances; or higher cortical dysfunction, such as dysphasia or agnosia. Seizures have also been reported in PML patients (approximately 20%). The onset of neurological deficits may occur over weeks to months. See the IB for further details.

If PML is suspected, hold further brentuximab vedotin dosing and undertake a diagnostic workup that may include (but is not limited to):

- Neurologic examinations, as warranted.
- Brain magnetic resonance imaging (MRI): Features suggestive of PML include presence of unifocal or multifocal lesions, mainly of the white matter, which are typically nonenhancing and do not have mass effect.
- Polymerase chain reaction (PCR) analysis: JCV DNA detectable in cerebrospinal fluid or there is evidence of JCV in a brain biopsy.
- Neurology consultation.

If PML is confirmed, permanently discontinue treatment with brentuximab vedotin.

6.7 Blinding and Unblinding

This is an open-label study; investigators and patients will know the individual treatment assignments. However, aggregate efficacy data will be blinded to the sponsor's study team, investigators, and patients throughout the study conduct. The IRF will be blinded to treatment assignments.

6.8 Description of Investigational Agents

Brentuximab vedotin for Injection is a sterile, preservative-free, white to off-white lyophilized cake for reconstitution for IV administration. Brentuximab vedotin for Injection is supplied in single-use, Type 1 borosilicate glass vials with FluroTec®-coated butyl rubber stoppers and aluminum seals. Each vial of the product contains brentuximab vedotin, trehalose, sodium citrate, and polysorbate 80. The lyophilized product, after reconstitution with 10.5 mL sterile Water for Injection, USP, yields 11 mL of brentuximab vedotin solution (5 mg/mL).

6.9 Preparation, Reconstitution, and Dispensation

Brentuximab vedotin is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling brentuximab vedotin.

Recommended safety measures for handling and preparation include masks, protective clothing, gloves, and vertical laminar airflow safety cabinets.

Study treatment vials are single-use containers. Any partially used vials or diluted dosing solutions are to be discarded using appropriate institutional drug disposal procedures according to the guidelines in the Study Manual.

Study treatment must be reconstituted with the appropriate amount of sterile water for injection (see the Pharmacy Manual for details). GENTLY swirl the vial until the contents are completely dissolved. **The vial must not be shaken or vigorously swirled**; excess agitation may cause aggregate formation. Visually inspect the reconstituted drug product for any particulate matter and discoloration.

The appropriate amount of reconstituted study treatment will be withdrawn from the vial(s) and diluted in a 150 to 250 mL infusion bag containing 0.9% Sodium Chloride Injection, USP.

There are no known incompatibilities between study treatment and polyvinyl chloride (PVC), ethyl vinyl acetate (EVA), polyolefin, or polyethylene (PE) bags. The bag should be gently inverted to mix the solution. **The bag must not be shaken**; excess agitation may cause aggregate formation. Prior to administration, the reconstituted and diluted drug product should be inspected visually for any particulate matter and discoloration.

The formulation contains no preservative and is intended for single use only; infusion solutions should be prepared and transferred using aseptic technique in a biosafety hood.

Refer to the Directions for Use/Pharmacy Manual for more specific instructions on reconstitution and use.

6.10 Packaging and Labeling

Vials of study treatment will be packaged in cardboard kits. Each kit will contain 1 vial of investigational product. Vials and kits will be labeled to meet country-specific regulatory requirements.

6.11 Storage, Handling, and Accountability

Brentuximab vedotin

Vials containing study treatment must be refrigerated at 2°C to 8°C in a secure location (eg, locked room) accessible only to the pharmacist, the investigator, or a duly designated person.

Study treatment does not contain preservatives; therefore, opened and reconstituted vials of study treatment must be used within 24 hours when stored under refrigeration at 2°C to 8°C. Reconstituted study treatment should not be stored at room temperature. It is recommended that study treatment vials and solutions be protected from direct sunlight until the time of use. **Reconstituted vials must not be shaken**.

Drug accountability instructions are provided in the Pharmacy Manual.

Bleomycin (If Investigational Medicinal Product)

Please refer to the appropriate package insert for information regarding the proper storage and handling of bleomycin.

Report all investigational product events, including complaints and issues, using the Investigational Product Complaints and reporting information listed in Section 11.11 in the protocol.

Bleomycin must be kept in an appropriate, limited-access, secure place until it is dispensed to study enrollees, returned to the sponsor, or forwarded to the sponsor's designee for destruction. Drug supplies will be counted and reconciled at the site before being returned.

The investigator must maintain 100% accountability for all bleomycin received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if retest date is provided to the investigator
- Frequently verifying that actual inventory matches documented inventory
- Verifying that the drug accountability log is completed for the drug lot used to prepare each dose
- Verifying that all containers used are documented accurately on the log

- Verifying that required fields are completed accurately and legibly

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The investigator must maintain a current inventory (drug accountability log) of all bleomycin delivered to the site, inventory at the site, and patients' use records. This log must accurately reflect the drug accountability of the study medication at all times. The following information will be recorded at a minimum: protocol number and title, name of the investigator, site identifier and number, description of the study medication, expiry and/or retest date, date and amount dispensed, including the initials of the person dispensing and receiving the study medication. The log should include all required information as a separate entry for each patient to whom study medication is dispensed.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform clinical study material accountability and reconciliation before clinical study materials are destroyed or returned to the sponsor or its designee for destruction. The investigator will retain the original documentation regarding clinical study material accountability, return, and/or destruction, and copies will be sent to the sponsor.

The investigator will be notified of any expiry date or retest date extension of clinical study material during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired clinical study materials for return to the sponsor or its designee for destruction. In the event of expiry date extension of supplies already at the study site, supplies will be relabeled with the new expiry date at the site. In such cases, the sponsor or its designee will prepare additional labels, certificates of analysis, and all necessary documentation for completion of the procedure at the sites.

Do not use or destroy the investigational product until you receive documented confirmation from Millennium stating the drug may be used or destroyed.

Drug accountability instructions are also provided in the Pharmacy Manual.

7. STUDY CONDUCT

This trial will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

7.1 Study Personnel and Organizations

The contact information for the Millennium Study Monitor for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator for each member state/country, the independent radiologic review facility, and the interactive voice response system (IVRS) provider, and the contract research organization (CRO) team may be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

7.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/independent ethics committee (IEC). It is not envisioned that prisoners (or other populations that might be subject to coercion or exploitation) will be enrolled into this study.

7.3 Treatment Group Assignments

Patients will be randomized to receive either A+AVD or ABVD. Patients will be stratified by region (Americas vs Europe vs Asia), and number of IPFP risk factors (0-1 vs 2-3 vs 4-7).

7.4 Study Procedures

Refer to the Schedule of Events for timing of assessments. Additional details are provided as necessary in the sections that follow.

7.4.1 Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

7.4.2 Patient Demographics

The date of birth, race, ethnicity, and sex of the patient are to be recorded during screening.

7.4.3 Medical History

During the Screening period, a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy and include a description of prior therapies for it. In addition, concomitant medications will be recorded as specified in Section 7.4.8.

7.4.4 Physical Examination

A physical examination will be completed per standard of care at the times specified in the Schedule of Events.

7.4.5 Patient Height, Weight, and Body Surface Area

Height will be measured only during screening (within 28 days before the first dose of study drug). Weight and body surface area (BSA) will be determined to support dosing at the times specified in the Schedule of Events.

7.4.6 Vital Signs

Vital sign measurements include supine (after 3-5 minutes in this position) and standing (after 3-5 minutes in this position) measurements of diastolic and systolic blood pressure, heart rate, and oral temperature.

7.4.7 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at screening. The results from this test must be available and negative before the first dose of study drug is administered. If Cycle 1 Day 1 serum pregnancy results will not be available before dosing, a urine pregnancy test may be performed.

7.4.8 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will recorded in the electronic case report form (eCRF) from date of informed consent through 30 days after completion of frontline therapy. See Section 6.3.3 and Section 6.4 for a list of medications and therapies that are prohibited and/or allowed during the study.

7.4.9 Adverse events

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the Schedule of Events. Refer to Section 10 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs.

7.4.10 Enrollment

A patient is considered to be enrolled in the study when randomized to a treatment arm.

Procedures for completion of the enrollment information are described in the Study Manual.

7.4.11 Electrocardiograms

A 12-lead ECG will be administered at the time points specified in the Schedule of Events.

7.4.12 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed centrally. Decisions regarding eligibility for this study may be made using local laboratory determinations. For dosing decisions, local hematology and chemistry laboratory results may be used.

Handling and shipment of clinical laboratory samples will be outlined in the study manual.

Clinical laboratory evaluations will be performed as outlined below.

Clinical Chemistry and Hematology

Blood samples for analysis of the following clinical chemistry and hematological parameters will be obtained as specified in the Schedule of Events.

Hematology

- Hemoglobin
- Hematocrit
- Platelet (count)
- Leukocytes with Differential
- Neutrophils (absolute neutrophil count [ANC])

Serum Chemistry

- Blood urea nitrogen (BUN)
- Creatinine
- Bilirubin (total)
- Albumin
- Alkaline phosphatase (ALP)
- AST
- Calcium
- Chloride
- Carbon dioxide (CO_2)

- Urate
- Lactate dehydrogenase (LDH)
- Gamma glutamyl transferase (GGT)
- Phosphate
- ALT
- Glucose
- Sodium
- Potassium
- Magnesium

Other

- Hemoglobin A1C

7.4.13 Disease Assessment

Response to treatment and disease status assessments will be evaluated following the completion of frontline therapy according to the Revised Response Criteria for Malignant Lymphomas.[24] Disease assessments will be performed at times specified in the Schedule of Events. Patients' disease status following Cycle 2 will be assessed by PET scan using the Deauville criteria (Section 15.6). All disease and response assessments will be performed by investigators and a blinded IRF. If, for any reason other than death or documented disease progression, a patient discontinues randomization therapy (A+AVD or ABVD) after Cycle 2 Day 20 but before completion of randomization therapy, every effort must be made to obtain PET and CT scans prior to initiation of subsequent therapy for HL.

7.4.14 Patient-Reported Outcomes

Questionnaires (FACIT-Dyspnea 10-item short form, FACT-Ntx, EORTC QLQ-C30) will be administered as specified in the Schedule of Events and must be completed before study drug is administered. For patients who discontinue study drug, the scheduled collection of patient-reported outcome (PRO) data should continue until the patient discontinues scheduled study visits.

7.4.15 Utility Measurement

The EuroQOL EQ-5D is a 5-item questionnaire with a "thermometer" visual analog scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state) that will be administered as specified in the Schedule of Events. The utility measurement should be collected until the sooner of development of confirmed PD or 3 years after the last dose of frontline therapy.

7.4.16 Medical Resource Utilization Data Collection

All medical care encounters will be collected for all patients until study closure. Each time an AE or unscheduled physician visit occurs, medical resource utilization (MRU) data will be captured. Examples of data to be collected are number of medical care encounters, such as hospital admissions or major diagnostic procedures.

7.4.17 Cost Assessment

The cost of treatment in each arm of the study will be assessed through the collection of MRU in each arm in terms of medical resource utilization frequency. Valuation of the costs will be undertaken separately.

7.4.18 Tumor Biopsies

Banked formalin fixed paraffin-embedded tumor tissue or a minimum of 10 unstained slides of the tumor tissue (ie, tumor tissue obtained at the time of the patient's original diagnosis and/or at the time of subsequent procedures conducted as part of the patient's standard care) will be collected at screening to assess biomarkers implicated in sensitivity or resistance to brentuximab vedotin or vinca alkyloids and taxanes (eg, p53, beta 3 tubulin, and ABCC transporters). The tumor pathology block will be returned to the original site by the sponsor or designee. If the pathology block is not provided, submission of 10 unstained slides that have been immersed in paraffin after sectioning will be accepted. See the Laboratory Manual for details. Patients who cannot provide at least 10 histological slides from their diagnostic biopsy will undergo a new tumor biopsy during screening (may be obtained up to 14 days prior to the first dose of study drug).

Efforts should be made to take an additional biopsy when patients randomized to A+AVD have relapsed. These samples are to be tested for the expression of CD30 and other potential markers of tumor resistance.

7.4.19 Pharmacokinetic Measurements

PK measurements will be made in all brentuximab vedotin-treated patients. PK parameters to be estimated may include the maximum concentration for MMAE (maximum plasma concentration [C_{max}]) and concentration at the end of infusion for brentuximab vedotin (C_{eoi}). Concentrations will be measured and PK parameters also estimated for the intact brentuximab vedotin ADC and TAb. Population PK methodologies will be used to

determine PK parameters and covariates in this population. Efficacy parameters will be related to brentuximab vedotin exposure in the patients.

The incidence of ATA to brentuximab vedotin will also be assessed (see Section 7.4.21).

The Schedule of Events presents the sample collection time points. All sampling times are relative to the start of the brentuximab vedotin infusion. Refer to the Research Specimen Manual for information on collection, processing, storage, and shipment of samples.

ATA samples will be taken only at predose Cycle 1, Cycle 2, and Cycle 6 or at termination if treatment is terminated before Cycle 6.

Table 7-1 Pharmacokinetic Sampling Time Points

Cycle	Study Day	Time	Window	Relative Time
Full A+AVD Arm				
1-6	1	Predose	Within prior 4 hr	Start of brentuximab vedotin infusion
		EOI (~30 min)	Within 1 hour post EOI	End of brentuximab vedotin infusion
	15	Predose	Within prior 4 hr	Start of brentuximab vedotin infusion
		EOI (~30 min)	Within 1 hour post EOI	End of brentuximab vedotin infusion
1 and 3, in addition	2	24 hr	± 4 hr	Start of brentuximab vedotin infusion
	3	48 hr	± 4 hr	Start of brentuximab vedotin infusion
Additional Sampling for 50-patient Subset of A+AVD Arm				
1 and 3	1	2 min	± 2 min	End of doxorubicin infusion
		2 min	± 2 min	End of vinblastine infusion
		2 min	± 2 min	End of dacarbazine infusion
		1 hr	± 5 min	End of brentuximab vedotin infusion
		6 hr	± 10 min	End of brentuximab vedotin infusion
	7	168 hr	± 24 hr	End of brentuximab vedotin infusion
Additional Sampling for 50-patient Subset of ABVD Arm				
1 and 3	1	Predose	Within prior 4 hr	Start of doxorubicin infusion
		2 min	± 2 min	End of doxorubicin infusion
		2 min	± 2 min	End of vinblastine infusion
		2 min	± 2 min	End of dacarbazine infusion
		1 hr	± 5 min	End of dacarbazine infusion
		6 hr	± 10 min	End of dacarbazine infusion
	2	24 hr	± 4 hr	End of dacarbazine infusion
	7	168 hr	± 24 hr	End of dacarbazine infusion

Abbreviations: A+AVD = brentuximab vedotin (ADCETRIS™) plus doxorubicin, vinblastine, and dacarbazine; ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; EOI = end of infusion; hr = hour; min = minutes.

These 50 patients in each treatment arm from whom additional PK samples are drawn will be recruited from sites that agree to participate. Further, approximately 20 patients in each 50-patient intensive-sampling group must be of Asian race.

7.4.20 Serum Biomarkers

Blood (5 mL) for serum samples will be collected as specified in the Schedule of Events to measure circulating biomarkers such as soluble CD30 (sCD30), thymus- and activation-regulated chemokine (TARC), cutaneous T-cell-attracting chemokine (CTACK), and interleukin-6 (IL-6). Previous research has demonstrated a relationship between circulating sCD30 concentration and overall tumor burden.[26] A decrease in sCD30 may reflect a decrease in overall tumor burden. The Reed-Sternberg cells characteristic of classical HL produce high concentrations of TARC that correlate with increased T-cell infiltration of tumor tissue.[27] Further, previous phase 2 clinical studies of brentuximab vedotin showed [redacted]

Biomarkers such as sCD30, TARC, and IL-6 will be measured at baseline, on Day 1 of all cycles, and at the EOT visit. Baseline values and changes in these markers will be compared to efficacy. In addition, the possible impact of sCD30 concentrations on PK will be explored.

The maximum amount of blood collected from each patient for this analysis throughout the study will not exceed 200 mL. The timing of the blood samples may be changed and/or the number of samples reduced if emerging data indicate that changes to the sampling scheme are needed to better characterize the effects of brentuximab vedotin. Details regarding the preparation, handling, and shipping of samples are provided in the Study Manual.

7.4.21 Immunogenicity Measurements

Blood (5 mL) for serum samples will be collected as specified in the Schedule of Events to evaluate antitherapeutic antibody (ATA) and neutralizing ATA as a PK and safety assessment. On dosing days, the blood samples for ATA and neutralizing ATA assessment must be collected before dosing. The maximum volume of blood collected for immunogenicity will be 5 mL per cycle. Neutralizing ATA assessment will be performed only for ATA-positive samples. Immunogenicity parameters will be assayed only for patients who receive at least 1 brentuximab vedotin dose.

7.4.22 Germline DNA Polymorphism Assessment

An optional blood sample (5 mL) will be collected on Day 1 of Cycle 1, before dosing, to examine genotyping variations in the germ line genes of the disease pathway, drug mechanism, and drug clearance proteins, such as CD30, tubulin, Fc_{neo}, and Fcγ receptors.

7.4.23 Fertility Assessment

The incidence of pregnancy in each treatment arm will be assessed at the time of study closure. Any pregnancy occurring in patients or their partners from the date of first dose until the date of study closure should be reported.

7.5 Completion of Treatment

Patients will be considered to have completed study treatment if they:

- Complete frontline treatment (see Table 8-1) or
- Experience PD or die prior to completion of frontline treatment

7.6 Completion of Study

Patients will be considered to have completed the study if they meet both of the following criteria:

- Complete 6 cycles of frontline treatment
- Have 5 years of follow-up or have died

Regardless of the duration of treatment, all patients will remain on study for follow-up following the last dose of study treatment until they withdraw consent for further follow-up, are lost to follow-up, have been followed for 5 years from randomization, or until study closure. The study is expected to close approximately 7 years after the first patient starts study treatment. Posttreatment follow-up is further described in Section 7.10.

For patients who do not complete 6 treatment cycles, please see the Schedule of Events for details of follow-up assessments performed between EOT and 24 months.

7.7 Discontinuation of Treatment With Study Drug, and Patient Replacement

Study drug must be permanently discontinued for patients meeting any of the following criteria:

- Completed 6 cycles of A+AVD or ABVD
- Investigator or patient deems it is in the patient's best interest to discontinue

The primary reason for study treatment withdrawal must be documented.

Patients who discontinue from study treatment will remain on study for follow-up unless they withdraw consent for the follow-up phase of the study. All randomized patients will be followed until study closure (see Section 7.6).

Patients who are randomized to a treatment arm but do not receive study drug for any reason will not be replaced.

Treatment with study drug may also be discontinued for any of the following reasons:

- AE
- Protocol violation
- PD
- Unsatisfactory therapeutic response
- Study terminated by sponsor
- Withdrawal by subject
- Lost to follow-up
- Other

At the time of study drug discontinuation, all study procedures outlined for the EOT visit will be completed as specified in the Schedule of Events. The primary reason for study drug discontinuation will be recorded on the eCRF.

Note that some patients may discontinue study drug for reasons other than PD before completing the full treatment course (eg, after Cycle 2 based on a Deauville score of 5); these patients will remain in the study for posttreatment assessments as outlined in the Schedule of Events until disease progression occurs.

7.8 Withdrawal of Patients from Study

A patient may be discontinued from the study (during treatment cycle or follow-up) for any of the following reasons:

- Lost to follow-up
- Study terminated by sponsor
- Withdrawal by subject
- Death
- Other

The consequence of study withdrawal is that no new information will be collected from the withdrawn patient and added to the existing data or any database.

Millennium or their designee must be notified in writing if a patient is withdrawn from study treatment or from the study. The reason(s) for withdrawal must be documented in the patient's medical records. The investigators will make every reasonable effort to keep each patient on the study until all planned treatments and assessments have been performed. If a patient withdraws from study treatment, every attempt should be made to follow the patient until death or administrative study closure. Final treatment assessments will be performed before any other therapeutic intervention if possible. Additionally, any planned alternative treatments should be documented on the patient's medical records and CRF.

7.9 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

7.10 Posttreatment Follow-up Assessments

Posttreatment follow-up for all patients consists of a physical exam, disease assessment, and radiological assessment if indicated (see note below), performed every 3 months until 36 months after the EOT and then every 6 months until the first of disease progression or study closure. Note: Radiological assessments are only required every 12 weeks (± 1 week) until 12 months of PTFU and then every 6 months (± 2 weeks) until study closure. Information regarding the initiation of an alternative form of treatment for lymphoma will also be collected. For patients who have PD, survival/disease status and information regarding the initiation of an alternative lymphoma treatment may be obtained by phone call. To support fertility assessment, any pregnancy occurring in patients or their partners from the date of first dose until the date of study closure should be reported.

Patients who stop treatment for any reason other than PD will continue to have mPFS follow-up visits until the occurrence of PD; the patient withdraws consent for further follow-up; or, after completion of frontline therapy, the start of anticancer therapy.

Patients will be followed for survival until 5 years from the date of the last patient randomized, or death, whichever occurs first. Survivor information may be collected by methods that include, but are not limited to, telephone, e-mail, mail, or retrieved from online or other databases (eg, social security indexes). In addition, the start of another anticancer therapy will be collected.

See the Schedule of Events for appropriate assessments during follow-up.

NOTE: Related SAEs must be reported to the Millennium Department of Pharmacovigilance & Risk Management or designee. This includes deaths that the investigator considers related to study drug that occur during the posttreatment follow-up. Refer to Section 10 for details regarding definitions, documentation, and reporting of SAEs.

8. STATISTICAL AND QUANTITATIVE ANALYSES

8.1 Statistical Methods

In general, summary tabulations will be presented by treatment arm and will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent per category for categorical data. The

Kaplan-Meier survival curves and 25th, 50th (median), and 75th percentiles will be provided along with their 2-sided 95% CIs for time-to-event data.

The statistical methods are outlined below; analysis details will be provided in the statistical analysis plan (SAP). The SAP will be written by Millennium and will be finalized prior to the formal interim analysis.

Deviations from the statistical analyses outlined in this protocol will be indicated in the SAP; any further modifications will be noted in the final clinical study report.

8.1.1 Determination of Sample Size

The primary endpoint of the study is mPFS, and the study is powered on the following assumption: a 3-year mPFS of 82.5% for patients in the A+AVD treatment group versus 75% for patients in the ABVD treatment group (HR = 0.67 assuming exponential distribution). A total of 260 mPFS events will provide 90% power to detect a hazard ratio of 0.67 at a 1-sided significance level of 0.025. Approximately 1040 patients will be randomized to achieve 260 mPFS events in about 60 months, assuming 24 months of accrual, a 5% annual dropout rate, and 36 months of mPFS follow-up after last patient in.

8.1.2 Randomization and Stratification

The randomization scheme will be generated by Millennium. Prior to dosing, a randomization number will be assigned to each patient. The randomization schedule also includes the study specific identifiers (company name, protocol name, and protocol number) and the date and time the schedule was generated.

Patients will be randomized in an overall ratio 1:1 to A+AVD or ABVD. Patients will be stratified by region (Americas vs Europe vs Asia) and number of IPFP risk factors (0-1 vs 2-3 vs 4-7).

8.1.3 Populations for Analysis

The populations used for analysis will include the following:

- Safety population: patients who receive at least 1 dose of study drug will be used for all safety analyses. All patients in the safety population will be analyzed according to the actual treatment received.

- Intent-to-Treat (ITT) population: all patients randomized to treatment. All patients in the ITT population will be analyzed according to the treatment they were randomized to receive and not according to what they actually received, if different.

- Per-Protocol (PP) population: a subset of ITT patients who do not have a major protocol violation as determined by the project clinician. All decisions to exclude patients from the PP population will be made prior to database lock.

- Response-Evaluable population: all patients with diagnosis as confirmed by an independent pathology review facility, with measurable disease at baseline, who receive at least 1 dose of study drug, and have at least 1 postbaseline response assessment.

- PK population: patients with sufficient dosing and PK data to reliably estimate PK parameters as determined by a clinical pharmacologist. The PK population will be used for PK analyses.

- Pharmacodynamics population: patients with sufficient dosing and sufficient pharmacodynamics data to reliably measure pharmacodynamics parameters will be used for pharmacodynamics analyses.

8.1.4 Procedures for Handling Missing, Unused, and Spurious Data

All available efficacy and safety data will be included in data listings and tabulations. The relevance of missing sample data will be assessed. Details on any sensitivity analyses and data handling details regarding issues such as missing data will be discussed in the SAP.

Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

8.1.5 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized, including gender, age, race, weight, height, BSA, primary diagnosis, and other parameters as appropriate. No inferential statistics will be carried out.

8.1.6 Efficacy Analysis

All efficacy evaluations will be conducted using the ITT population unless otherwise specified.

8.1.6.1 Analysis of Primary Efficacy Endpoint

Modified PFS per IRF will be used for the primary efficacy analysis.

Modified Progression-Free Survival

As PET-negative CR is the expected therapeutic outcome in frontline HL, the definition of PFS has been modified to reflect current standards of care. Modified PFS per IRF will be analyzed based on the ITT population using a stratified log-rank test. Modified PFS is defined as the time from the date of randomization to the date of the first of (1) documentation of PD; (2) death due to any cause; (3) for patients who are confirmed noncomplete responders per IRF, receipt of anticancer chemotherapy or radiotherapy for HL after completion of frontline therapy, as defined in Table 8-1; these patients' mPFS event date will be the date of receipt of first dose of second-line therapy.

Table 8-1 Completion of Frontline Therapy

Treatment History	Completion of Frontline Therapy
Did not switch therapy	Upon receipt of planned study drug regimen with no more than 2 missed doses of A+AVD or ABVD[a]
Switched therapy before completion of A+AVD or ABVD	Upon conclusion of 1 alternative anticancer regimen[b] for HL subsequent to A+AVD or ABVD discontinuation

a ABVD-randomized patients experiencing bleomycin-associated pulmonary toxicity may discontinue bleomycin and continue on AVD without this counting as a missed dose.
b Receipt of chemotherapy OR radiation.

Patients without a documented mPFS event at the time of analysis (defined as PD/relapse, subsequent anticancer therapy for residual disease after completion of planned frontline therapy for HL, or death) will be censored at the date of last response assessment.

Patients who are lost to follow-up, withdraw consent, or who discontinue treatment due to undocumented disease progression after the last adequate disease assessment will be censored at last disease assessment. If death or disease progression occurs after more than 1 missed visit, then this will be deemed PD at the date of death or the date of the first disease assessment documenting disease progression. Patients without baseline and/or with insufficient postbaseline data for disease assessment, without subsequent anticancer therapy after completion of planned frontline therapy for HL, and with no death recorded will be censored at the date of randomization. If the disease progression is documented between scheduled visits, then the date of the documented disease progression is the date of

progression. Detailed handling rules for missing assessments and censoring for the analysis of mPFS will be described in the SAP.

Modified PFS will be tested at a 1-sided 0.025 level at the final analysis.

In addition, a stratified Cox regression model will be used to estimate the hazard ratio and the 95% CI for the treatment effect. The Kaplan-Meier survival curves, 25th, 50th (median), and 75th percentiles (if estimable), along with their 2-sided 95% CIs, will also be presented for each treatment arm.

Sensitivity analyses for mPFS per IRF will be performed using the PP population. Modified PFS per IRF using different censoring approaches will be also analyzed in the ITT population. Details of different censoring approaches will be included in the SAP. Modified PFS per investigator will also be analyzed similarly using the ITT population.

8.1.6.2 Analyses of Secondary Efficacy Endpoints

CR rate and OS are designated as key secondary endpoints. Key secondary endpoints will be tested at 1-sided 0.025 level when the test of mPFS is statistically significant at the final analysis. A closed sequential testing procedure will be used to ensure type I error control for key secondary endpoints. The testing order is 1) CR rate, and 2) OS.

Complete Remission Rate

CR per IRF will be analyzed based on the ITT population. CR rate per IRF is defined as the proportion of patients who achieve CR as the end of treatment with randomized regimen (A+AVD or ABVD) as determined by an IRF. CR rates between the 2 treatment arms will be compared using a stratified Cochran-Mantel-Haenszel (CMH) test.

A logistic regression model will be used to estimate the treatment effect in terms of odds ratio. The odds ratio and its associated 95% CIs will be presented.

Sensitivity analyses for CR per IRF will be performed using the response-evaluable population. CR rate per investigator will also be analyzed similarly using the ITT population.

Overall Survival

OS is defined as the time from the date of randomization to the date of death. Patients without documented death at the time of analysis will be censored at the date last known to be alive.

There will be 2 formal analyses performed for OS. An OS interim analysis will be performed at the time of the final mPFS analysis (approximately 3 years after the last patient is enrolled), and the final analysis of OS will be performed when 112 deaths have occurred, assuming 5-year OS rates for the A+AVD and ABVD arms are 91% and 88% and, respectively (HR=0.75). Overall type I error will be controlled using the O'Brien-Fleming method with a Lan-DeMets alpha-spending function.

Stratified log-rank testing will be used to compare OS between the 2 treatment arms. The hazard ratios along with the 95% CIs will be estimated using a stratified Cox regression model. The Kaplan-Meier method will be used to estimate the distribution of the OS endpoint for each treatment. Median survival times (if estimable), along with the 2-sided 95% CIs will be presented. Analysis of OS will be performed based on the ITT population.

Other Secondary Efficacy Endpoints

Comparison of the ORR between the 2 treatment groups will be conducted using the stratified Cochran-Mantel-Haenszel test. The 95% CI of the difference of the response rates between the 2 treatments will also be provided. ORR per IRF will be analyzed based on the ITT population.

Similar analyses will be conducted to compare the rate of patients that received consolidating irradiation between the 2 treatment arms.

DOR in subjects with confirmed response is the time between first documentation of response and disease progression. DOCR in subjects with confirmed CR is the time between first documentation of CR and disease progression. DOR and DOCR per IRF will be analyzed based on the ITT population.

EFS is defined as the time from randomization until any cause of treatment failure: disease progression, premature discontinuation of treatment for any reason, or death due to any cause, whichever occurs first. Analyses of EFS will be performed based on the ITT population.

DFS is defined as the time from CR to disease progression or to death from lymphoma or acute toxicity from treatment. Analyses of DFS will be performed based on the subset of the ITT population achieving a CR.

The same analyses will be applied to these time-to-event endpoints as those described for OS above.

8.1.6.3 Exploratory Endpoints

Alive without HL rate at 3 years and 5 years is defined as the proportion of patients who are alive without classical Hodgkin lymphoma at 3 years or 5 years after the patient's randomization date.

Alive without lymphoma rates between the 2 treatment arms will be compared using a stratified Cochran-Mantel-Haenszel (CMH) test.

8.1.7 Analyses of Patient-Reported Outcomes and Health Economics

Analyses of PROs and health economics will be performed using the ITT population.

8.1.7.1 Patient-Reported Outcomes Analysis

PRO assessments based on the QLQ-C30 will be analyzed to determine if treatments affect PRO scores. Analyses of PRO scores including global health status will be performed using longitudinal models. All subscales and individual item scores will be tabulated. Descriptive summaries of observed data will be provided at each scheduled assessment time point. PRO assessments based on FACIT Dyspnea 10 and Fact-Ntx will be analyzed using the same methods as QLQ-C30.

Initially, the manuals for scoring and handling missing data published for QLQ-C30, FACIT Dyspnea 10, and Fact-Ntx will be used. Further investigation of missing patterns and details of imputation will be discussed in SAP.

8.1.7.2 Health Economics Analysis Using Medical Resource Utilization and Utility

EQ-5D-3L scores will be summarized in descriptive statistics for treatment groups.

MRU data will be summarized in descriptive statistics for hospitalization (length of stay, inpatient, outpatient, and reason), number of missing days from work or other activities by patient, and care-giver, by treatment group.

8.1.8 Pharmacokinetics/Pharmacodynamics/Biomarkers

Pharmacokinetic Analysis

The PK of the antibody-drug conjugate (brentuximab vedotin), total antibody, and unconjugated drug (MMAE) will be based on serum or plasma samples collected from patients who meet study inclusion criteria, received study drug, and provided evaluable PK data. Population PK parameters will be calculated with an appropriate method based on a validated PK analysis program. Exploratory safety-PK, efficacy-PK, and if possible, PK-pharmacodynamic relationships will be determined.

Descriptive statistics (eg, number of patients, mean, standard deviation, median, minimum, and maximum) will be used to summarize concentrations of analyte for brentuximab vedotin-treated patients.

The pharmacokinetics of doxorubicin, vinblastine, and dacarbazine will be compared between the treatment arms. Descriptive statistics (eg, number of patients, mean, standard deviation, median, minimum, and maximum) will be used to summarize concentrations of analyte. Geometric mean ratios of the AUC will be calculated for each AVD component (doxorubicin, vinblastine, and dacarbazine).

Immunogenicity Analysis

All patients who were administered at least 1 dose of brentuximab vedotin will be evaluated for antitherapeutic antibody (ATA) development. A list/table of ATA status will be provided. Antibody neutralizing status (neutralizing or not neutralizing) will also be listed for patients who have positive antibody status.

Immunogenicity information, including ATA and neutralizing ATA, will be summarized in descriptive statistics as applicable.

Relationships between ATA development and safety and efficacy will be explored.

Biomarkers

Absolute and change from baseline value of circulating biomarkers will be summarized by time point using descriptive statistics, as applicable. Descriptive statistics (eg, number of patients, mean, standard deviation, median, minimum, maximum) will also be provided to summarize disease markers [redacted]), tissue levels of potential resistance markers [redacted].

[redacted]), and qualitative and semiquantitative measures of markers [redacted], and change from baseline values of these markers, as applicable. The association between these and clinical response or safety endpoints might be explored. These analyses will be detailed in the SAP.

8.1.9 Safety Analysis

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the safety population. Exposure to frontline therapy and reasons for discontinuation will be tabulated.

Treatment-emergent AEs that occur after administration of the first dose of study drug and through 30 days after the last dose of frontline therapy will be tabulated.

AEs will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) and will include the following categories:

- Treatment-emergent AEs
- Drug-related treatment-emergent AEs
- Grade 3 or higher treatment-emergent AEs
- Grade 3 or higher drug-related treatment-emergent AEs
- The most commonly reported treatment-emergent AEs (ie, those events reported by ≥ 10% of all patients)
- SAEs

A listing of treatment-emergent AEs resulting in frontline therapy discontinuation will be provided.

Descriptive statistics for the actual values of clinical laboratory parameters (and/or change from baseline in clinical laboratory parameters) will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters.

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs and weight over time will be tabulated by scheduled time point.

Shift tables for laboratory parameters will be generated based on changes in NCI CTCAE grade from baseline to the worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst postbaseline values, may be used to understand the safety profile of patients' frontline therapies.

All concomitant medications collected from screening through the study period will be classified to preferred terms according to the World Health Organization (WHO) drug dictionary.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of patients' frontline therapies.

Electrocardiogram Analysis

Investigators' assessments of ECG monitoring (normal, abnormal and clinically significant, or abnormal and not clinically significant), including unscheduled or retested measurements, will be presented in a listing.

8.1.10 Interim Analyses

Two formal interim analyses (IAs) are planned for this study.

The first IA to be performed is a futility analysis. CR rate will be analyzed when the first approximately 348 patients (1/3 of overall sample size 1040) have completed the regimen to which they were randomized (ie, received the planned study drug regimen with no more than 2 missed doses of A+AVD or ABVD) or have discontinued treatment prior to completion.

Recommendation by the IDMC whether to terminate the study based on this IA will be determined upon evaluation of the overall safety information and efficacy data, specifically if the CR rate per IRF for the A+AVD arm is at least 5% lower than that of the ABVD arm, and trends in mPFS and other efficacy endpoints suggest inferior efficacy in the A+AVD arm.

Enrollment will continue during the first IA.

An IA for OS is also planned to occur at the time of the final mPFS analysis (approximately 3 years after the last patient enrolls). Overall type I error for OS will be controlled using the O'Brien-Fleming method with a Lan-DeMets alpha-spending function.

9. STUDY COMMITTEES

9.1 Data Safety Monitoring Board

An IDMC will review safety and efficacy data at the interim analysis. The IDMC will provide a recommendation regarding study continuation based on the safety and efficacy parameters. In the event that the study is terminated early based on an IDMC recommendation, Millennium will notify the appropriate regulatory authorities.

Additionally, the IDMC will periodically review safety data per the IDMC charter. The first formal safety review will occur after the first 100 patients have completed 2 cycles (8 weeks) of treatment or discontinued prior to completing 2 cycles of treatment. Subsequently, IDMC safety reviews will be performed periodically per the IDMC charter.

10. ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a

previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

10.1.3 Serious Adverse Event Definition

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE v4.03, effective date 14 June 2010.[25] Clarification should be made

between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs and serious pretreatment events (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Millennium Pharmacovigilance & Risk Management or designee (contact information provided below) by faxing the SAE Form within 1 working day after becoming aware of the event. All SAEs and serious pretreatment events (which include all deaths) must be reported whether or not considered causally related to the study drug or study procedures. The SAE Form, created specifically by Millennium, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious pretreatment event may be requested by Millennium or designee. SAE report information must be consistent with the data provided on the eCRF.

For SAE and Pregnancy Reporting Contact Information, please refer to Section 15.7

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

Intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE v4.03, effective date 14 June 2010.[25] The criteria are provided in the Study Manual.

Relationship to study drug administration will be determined by the investigator responding yes or no to this question: Is there a reasonable possibility that the AE is associated with the study drug?

10.3 Monitoring of Adverse Events and Period of Observation

AEs, both nonserious and serious (which include all deaths), will be monitored throughout the study as follows:

- AEs will be reported from first dose of frontline therapy through 30 days after administration of the last dose of frontline therapy and recorded in the eCRFs.
- Treatment-related AEs will be reported from first dose of frontline therapy through 30 days after administration of the last dose of frontline therapy and monitored for resolution through event resolution or study closure, and recorded in the eCRFs.
- Serious pretreatment events will be reported to Millennium Pharmacovigilance & Risk Management or designee from the time of the signing of the ICF up to first dose of frontline therapy, but will not be recorded in the eCRF.
- Related and unrelated SAEs will be reported to Millennium Pharmacovigilance & Risk Management or designee from the first dose of frontline therapy through 30 days after administration of the last dose of frontline therapy and recorded in the eCRF. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent

illness(es). Any SAE that occurs at any time after completion of the study and the designated follow-up period that the investigator considers to be related to frontline therapy must be reported to the Millennium Department of Pharmacovigilance & Risk Management or designee.

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance & Risk Management or designee (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance & Risk Management or designee (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

For safety purposes, pregnancies must be reported for 6 months following EOT. (This is distinct from the fertility assessment collection of pregnancy data, which is to continue until study closure.)

11. ADMINISTRATIVE REQUIREMENTS

11.1 Good Clinical Practice

The study will be conducted in accordance with the ICH-GCP and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and the IB.

11.2 Data Quality Assurance

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study patient. Study data will be entered into an eCRF by site personnel using a secure, validated, web-based electronic data capture (EDC) application. Millennium will have access to all data upon entry in the EDC application.

Study monitors will discuss instances of missing or uninterpretable data with the investigator for resolution. Any changes to study data will be made to the eCRF and documented via an electronic audit trail associated with the affected eCRF.

11.3 Electronic Case Report Form Completion

Millennium or designee will provide the study sites with secure access to and training on the EDC application, sufficient to permit site personnel to enter or correct information in the eCRFs for the patients for whom they are responsible.

eCRFs will be completed for each study patient. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the patient's eCRF.

The investigator, or designated representative, should complete the eCRF as soon as possible after information is collected.

The investigator must provide through the EDC application formal approval of all the information in the eCRFs and changes to the eCRFs to endorse the final submitted data for the patients for which he or she is responsible. The audit trail entry will show the user's identification information and the date and time of the correction.

Millennium, or a designee, will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disk (CD) or other electronic media will be placed in the investigator's study file.

11.4 Study Monitoring

Monitoring and auditing procedures developed or approved by Millennium will be followed to comply with GCP guidelines.

All information recorded on the eCRFs for this study must be consistent with the patient's source documentation. During the course of the study, the study monitor will make study site visits to review protocol compliance, verify eCRFs against source documentation, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The review of medical records will be performed in a manner that ensures that patient confidentiality is maintained.

11.5 Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirement(s) and will adhere to GCP standards. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the patients. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or the sponsor, as allowed by local regulations.

11.6 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

11.7 Patient Confidentiality

To maintain patient privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the patient by initials where permitted and/or by the assigned patient number. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

11.8 Investigator Compliance

The investigator will conduct the trial in compliance with the protocol provided by Millennium and given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Modifications to the protocol are not to be made without agreement of both the investigator and Millennium. Changes to the protocol will require written IRB/IEC approval/favorable opinion before implementation, except when the modification is needed to eliminate an immediate hazard or hazards to patients. Millennium, or a designee, will submit all protocol modifications to the appropriate regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard or hazards to patients, the investigator will contact Millennium, or a designee, if

circumstances permit, to discuss the planned course of action. Any departures from the protocol must be documented.

11.9 On-site Audits

Regulatory authorities, the IEC/IRB, and/or Millennium may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

11.10 Investigator and Site Responsibility for Drug Accountability

Accountability for investigational medicinal product at the trial site is the responsibility of the investigator. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and amount returned to Millennium, or a designee (or disposal of the drug, if approved by Millennium) will be maintained by the clinical site. Millennium or its designee will review drug accountability at the site on an ongoing basis.

All material containing study drug will be treated and disposed of in accordance with governing regulations.

11.11 Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact [redacted] (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

For Product Complaints,
call [redacted]
(US and International)

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to PPD (refer to Section 10.2).

11.12 Closure of the Study

Within 90 days of the end of the study, the sponsor will notify the competent authorities and the IECs in all member states where the study is being carried out that the study has ended.

Within 1 year of the end of the study, a summary of the clinical trial results will be submitted to the competent authorities and IECs in all member states involved in the study.

Study participation by individual sites or the entire study may be prematurely terminated if, in the opinion of the investigator or Millennium, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Millennium by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete, and/or unevaluable data
- Determination of efficacy based on interim analysis
- Plans to modify, suspend or discontinue the development of the study drug

Should the study be closed prematurely, the site will no longer be able to access the EDC application, will not have a right to use the EDC application, and will cease using the password or access materials once their participation in the study has concluded. In the event that any access devices for the EDC application have been provided, these will be returned to Millennium once the site's participation in the study has concluded.

Within 15 days of premature closure, Millennium must notify the competent authorities and IECs of any member state where the study is being conducted, providing the reasons for study closure.

11.13 Record Retention

The investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last

marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and Millennium notified.

12. USE OF INFORMATION

All information regarding brentuximab vedotin supplied by Millennium to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from Millennium. It is understood that there is an obligation to provide Millennium with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of brentuximab vedotin and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

Upon completion of the clinical study and evaluation of results by Millennium, the hospital or institution and/or investigator may publish or disclose the clinical trial results pursuant to the terms contained in the applicable Clinical Trial Agreement.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer-reviewed scientific or medical journal. A Publications Group comprising Millennium employees and study investigators will be formed to oversee the publication of the study results, which will reflect the experience of all participating study centers. Subsequently, individual investigators may publish results from the study in compliance with their agreements with Millennium.

A prepublication manuscript or abstract is to be provided to Millennium a minimum of 30 days before the intended submission date of the manuscript or abstract to a publisher. Within 30 days after receipt by Millennium of the notification, Millennium shall inform the study centers whether it has objections to the publication for reasons including, but not limited to, those defined below:

- If patentable subject matter is disclosed, the publication shall be delayed for a period not to exceed 90 days from Millennium's receipt of the proposed publication to allow time for the filing of patent applications covering patentable subject matter.

- If confidential information is contained in any proposed publication or public disclosure, such confidential information will be removed at Millennium's request.

The overall principal investigator will be the last author on abstracts and publications of the data generated from this study. Other authors will be listed according to number of patients enrolled to the study. If the principal investigator has the highest enrollment, he/she may choose to be either first or last author. This policy may be changed with the agreement of both the investigators and Millennium.

13. INVESTIGATOR AGREEMENT

I have read Protocol C25003: A Randomized, Open-label, Phase 3 Trial of A+AVD Versus ABVD as Frontline Therapy in Patients With Advanced Classical Hodgkin Lymphoma.

I agree to conduct the study as detailed herein and in compliance with International Conference on Harmonisation Guidelines for Good Clinical Practice and applicable regulatory requirements and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____
Principal investigator printed name

_____ _____
Principal investigator signature Date

_____

_____

_____
Investigational site or name of institution and location (printed)

14. REFERENCES

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15. APPENDICES

15.1 Ann Arbor Staging System for Hodgkin Lymphoma

Stage	Definition
I	Involvement of a single lymph node region or lymphoid structure (eg, spleen, thymus, Waldeyer's ring)
II	Involvement of 2 or more lymph node regions on the same side of the diaphragm (the mediastinum is a single site; hilar lymph nodes should be considered "lateralized" and, when involved on both sides, constitute Stage II disease)
III	Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm
III_1	Subdiaphragmatic involvement limited to spleen, splenic hilar nodes, celiac nodes, or portal nodes
III_2	Subdiaphragmatic involvement includes paraaortic, iliac, or mesenteric nodes plus structures in III_1
IV	Involvement of extranodal site(s) beyond that designated as "E" More than 1 extranodal deposit at any location Any involvement of liver or bone marrow
A	No symptoms
B	Unexplained weight loss of >10% of the body weight during the 6 months before staging investigation Unexplained, persistent, or recurrent fever with temperatures >38°C during the previous month Recurrent drenching night sweats during the previous month
E	Localized, solitary involvement of extralymphatic tissue, excluding liver and bone marrow

Source: Harrison's Manual of Medicine, 17th Edition.[28]

15.2 Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.[29]

15.3 Cockcroft-Gault Equation

For male patients:

Creatinine Clearance = [(140-age) (body weight in kg) / (72 × serum creatinine in mg/dL)]

For female patients:

Creatinine Clearance = [(140-age) (body weight in kg) / (72 × serum creatinine in mg/dL)] × 0.85

15.4 New York Heart Association Classification of Cardiac Disease

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.[30]

15.5 International Prognostic Factors Scoring for Advanced Hodgkin Lymphoma

One Point To Be Assigned for Each Prognostic Factor:
Serum albumin < 4 g/dL
Hemoglobin < 10.5 g/dL
Male sex
Stage IV disease
Age ≥ 45 years
White cell count ≥ 15,000 mm^3
Lymphocyte count < 600 mm^3 or < 8% of white-cell count

Source: A Prognostic Score for Advanced Hodgkin's Disease. Hasenclever D and Diehl V for the International Prognostic Factors Project on Advanced Hodgkin's Disease. NEJM 339; 1998: 1506-15.[31]

15.6 Deauville Criteria for PET

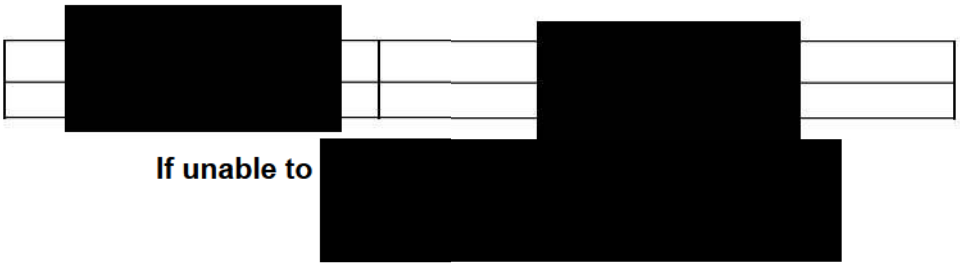
Score	
1	no uptake
2*	uptake ≤ mediastinum
3*	uptake > mediastinum but ≤ liver
4	Uptake moderately increased compared to the liver at any site.
5	Uptake markedly increased compared to the liver at any site or/and new sites of disease.

* If mediastinal blood pool activity is equal or greater than liver then the uptake within the lesion should be compared with liver (lesion uptake less than liver = score 2; lesion uptake equal to liver = score 3).

Source: Report on the Second International Workshop on interim positron emission tomography in lymphoma held in Menton, France, 8-9 April 2010. Meignan M, Gallamini A, Haioun C, Polliack A. Leuk Lymphoma 51; 2010:2171-80.[32]

15.7 Serious Adverse Event and Pregnancy Reporting Contact Information

United States and Canada
(24 hours/7 days a week)



Please refer to Section 10 of the study protocol for complete details on AE/SAE definitions and reporting (including pregnancy and birth defects).

International (Countries Outside United States and Canada)
(24 hours/7 days a week)

Phone/ Helpline Instructions

To place a call using World Phone (WP)

1. Get a line with dial tone
2. Dial the Worldwide access number (international toll free number listed below)
3. Listen for tone/chime and menu; enter five digit WP access code listed beside applicable Worldwide access number below.

American Samoa	[redacted]

Uzbekistan	8641-998-0001 Access Code 18726

International
(Countries Outside United States & Canada)

Reporting via Fax

All SAEs (regardless of their relationship to study drug), **must be reported within 1 working day of knowledge of the event** by FAX to the appropriate PPD PVG safety fax number:

To fax using World Phone (WP)

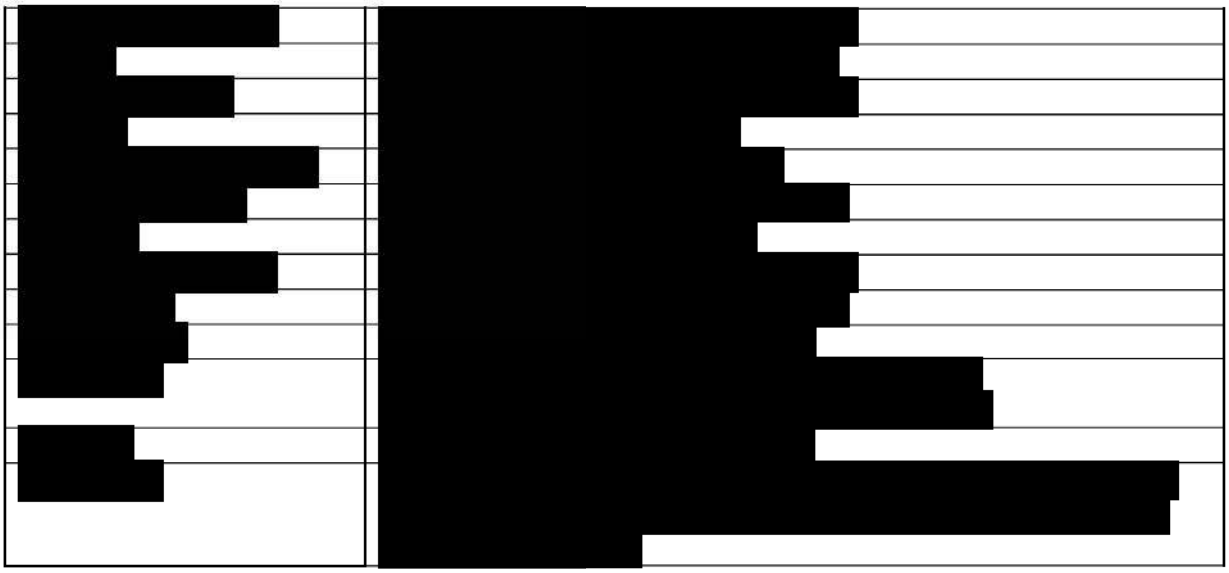
1. Get a line with a dial tone
2. Dial the Worldwide access number (international toll free number listed below)
3. Listen for tone/chime and menu; enter five digit WP access code listed beside applicable worldwide access number below.
4. Note: Some fax machines may require pushing the “pause” or “add digit” or “star” button either 2 or 3 times before entering the 5 digit access code.

American Samoa	633-2624 Access Code 79697

	Call using ENTEL 800-360-180 Access Code 79697
China	[redacted]


Collect access (Creole) 190 Access Code 79697


Nicaragua



If there are difficulties using the international toll free access, please fax SAEs to the back-up RightFax number below. Note that this number is dialed direct and not toll free.

If unable to fax, please report SAEs via email:

Please refer to Section 10 of the study protocol for complete details on AE/SAE definitions and reporting (including pregnancy and birth defects).

CLINICAL STUDY PROTOCOL C25003 AMENDMENT 7

Brentuximab vedotin

A Randomized, Open-label, Phase 3 Trial of A+AVD Versus ABVD as Frontline Therapy in Patients With Advanced Classical Hodgkin Lymphoma

Protocol Number:	C25003
Indication:	Treatment-naïve advanced Hodgkin lymphoma
Phase:	3
Sponsor:	Millennium Pharmaceuticals, Inc.
EudraCT Number:	2011-005450-60
Therapeutic Area:	Oncology

Protocol History

Original	29 March 2012
Amendment 1	14 May 2012
Amendment 2	01 June 2012
Amendment 3	13 July 2012
Amendment 4	03 August 2012
Amendment 5	06 February 2014
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Amendment 7	02 March 2015

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Rationale for Amendment 7

Amendment 7 facilitates the enrollment of an additional 200 patients into the study to increase the likelihood of observing 260 modified progression-free survival (mPFS) events. The increased enrollment is predicated upon revised estimates of mPFS event rates for both treatment arms in the study. This amendment also contains minor revisions and updates to improve protocol clarity and compliance and align study conduct with the sponsor's current guidelines and practices.

Purposes for Amendment 7

The purposes of this amendment are to:

- Increase study enrollment.
  - Increase the sample size by 200 patients to a total of approximately 1240 enrolled patients, and increase the anticipated enrollment period.
  - Increase enrollment to 620 patients per treatment arm, and increase the estimated number of sites to 250 study sites globally.
  - Delete reference to the percentage of the original sample size that was planned for inclusion in the interim futility analysis.
  - Revise the projected length of enrollment and follow-up periods.
- Revise the statistical assumptions of mPFS rates for both treatment arms in the study.
  - Align the timing of the interim overall survival analysis with that for the final mPFS analysis.
  - Revise the timing for the final analysis of overall survival.
- Institute minor modifications in protocol language to improve protocol clarity and compliance, and align study conduct with the sponsor's current guidelines and practices.
  - Clarify and align the posttreatment follow-up assessments for PFS disease status, event-free survival, and overall survival.
  - Clarify the PK sampling time points for the 50-patient subset in both treatment arms by correcting the study day stated in the protocol.
  - Update the contact information for product complaints and medication errors.
  - Add the Global Statistical Lead to the list of approvers for the amended protocol.
- Correct typographical errors, punctuation, grammar, and formatting, as applicable.

For specific examples of changes in text and where the changes are located, see Section 15.14.

PROTOCOL SUMMARY

Study Title: A Randomized, Open-label, Phase 3 Trial of A+AVD Versus ABVD as Frontline Therapy in Patients With Advanced Classical Hodgkin Lymphoma

Number of Patients: 620 patients randomized to each treatment arm, for 1240 patients total

Study Objectives

Primary

- To compare the modified progression-free survival (mPFS) obtained with brentuximab vedotin (ADCETRIS®) plus AVD (doxorubicin [Adriamycin], vinblastine, and dacarbazine; abbreviated A+AVD) versus that obtained with ABVD (doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine) for the frontline treatment of advanced classical Hodgkin lymphoma (HL)

Key Secondary

- To determine if A+AVD improves overall survival (OS) versus that obtained with ABVD

Other Secondary

- To determine if A+AVD improves complete remission (CR) rate versus that obtained with ABVD
- To determine the safety profile of A+AVD relative to that of ABVD
- To determine the event-free survival (EFS) obtained with A+AVD and ABVD
- To determine the disease-free survival (DFS) rate obtained with A+AVD and ABVD
- To determine if A+AVD improves overall objective response rate (ORR, defined as CR + partial response [PR]) versus that obtained with ABVD
- To determine the duration of response (DOR) and duration of complete remission (DOCR) obtained in the A+AVD and ABVD arms
- To determine the rate of patients receiving irradiation for HL not in complete remission in the A+AVD and ABVD arms
- To determine the rate of patients in CR at the end of frontline therapy in the A+AVD and ABVD arms
- To determine the rate of Cycle 2 positron emission tomography (PET) negativity in patients treated with A+AVD versus those treated with ABVD
- To determine if A+AVD improves health-related quality of life (HRQOL) versus ABVD
- To describe the pharmacokinetics (PK) of brentuximab vedotin, monomethyl auristatin E (MMAE), and total antibody (TAb) in blood
- To determine the immunogenicity of brentuximab vedotin

Exploratory

- To investigate any differences in lung-specific patient reported outcomes (PROs) between the treatment arms

- To assess any impact of brentuximab vedotin dosing on serum concentrations of AVD
- To investigate any differences between the treatment arms in the rate of patients alive without HL at 3 and 5 years (see Section 8.1.6.3 for definition)
- To assess changes in tumor biomarker expression before and after treatment

[redacted]

- To assess other PROs
- To assess medical resource utilization
- To assess fertility

Overview of Study Design:

This open-label, randomized, 2-arm, multicenter, phase 3 study has the primary objective of comparing the mPFS obtained with A+AVD against that obtained with ABVD.

- A+AVD: Brentuximab vedotin 1.2 mg/kg, plus doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, dacarbazine (DTIC) 375 mg/m^2.
- ABVD: Doxorubicin 25 mg/m^2, bleomycin 10 units/m^2, vinblastine 6 mg/m^2, DTIC 375 mg/m^2.

For this study, the definition of PFS has been modified to include the receipt of anticancer chemotherapy or radiotherapy for patients not in CR after the completion of frontline therapy as a progression event in addition to the customary events of disease progression or death due to any cause. Computed tomography (CT) and PET scans for mPFS disease assessment will be read by a blinded independent review facility (IRF).

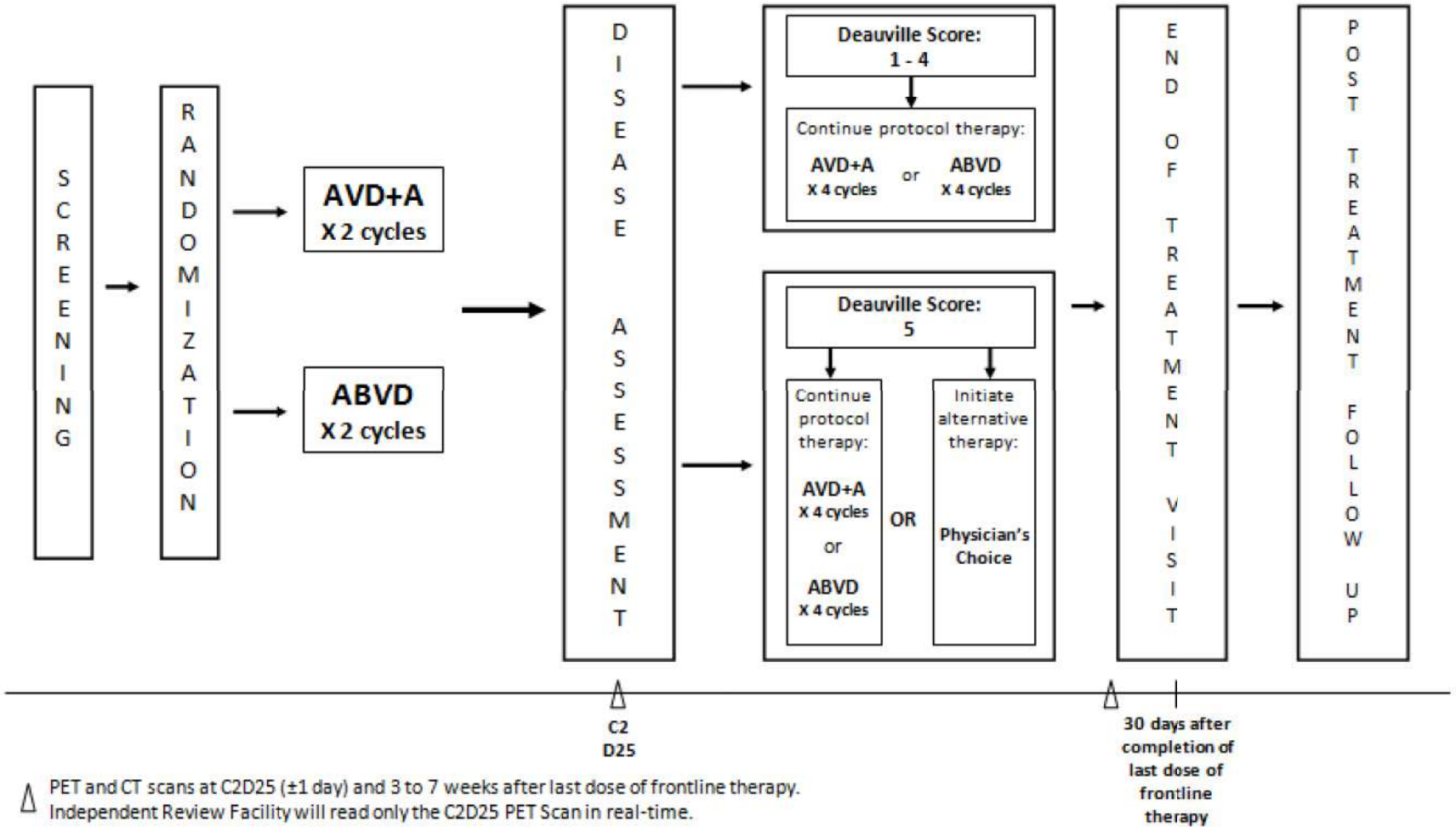
The study will enroll approximately 1240 patients; enrollment is anticipated to last 3 years. All enrolled patients must have a histologically confirmed diagnosis of Stage III or IV classical HL that has not been previously treated with systemic chemotherapy or radiotherapy. Patients will be stratified by region (Americas vs Europe vs Asia) and number of International Prognostic Factor Project (IPFP) risk factors (0-1 vs 2-3 vs 4-7).

Patients will be randomized 1:1 into 1 of 2 treatment arms, for a total of approximately 620 patients per arm. A+AVD and ABVD will be administered intravenously on Days 1 and 15 of each 28-day cycle. Brentuximab vedotin will be administered intravenously over 30 minutes at a dose of 1.2 mg/kg; the brentuximab vedotin infusion is to be started within approximately 1 hour after completion of AVD therapy. PET scan results at Cycle 2 Day 25 will be used to guide an optional switch to physician's choice of alternative therapy for those patients with a Deauville score of 5. Patients may receive up to 6 cycles of planned study therapy (A+AVD or ABVD). Radiotherapy is permitted for those patients in partial remission at conclusion of frontline therapy with a persistent PET-positive mass, however, receipt of such radiotherapy will be counted as an mPFS progression event for patients who are confirmed noncomplete responders per IRF.

An interim futility analysis will be conducted when the first approximately 348 patients have completed the regimen to which they were randomized (ie, received the planned study drug regimen with no more than 2 missed doses of A+AVD or ABVD) or have discontinued treatment prior to completion. The study will use an independent data monitoring committee (IDMC); recommendation to terminate the study would be based on evaluation of the overall safety

information and efficacy data (CR rate per IRF for the A+AVD arm at least 5% lower than that of the ABVD arm, with trends toward inferior A+AVD efficacy for mPFS and other efficacy parameters). The final analysis of the mPFS primary endpoint will be conducted when 260 mPFS events occur, approximately 2 years after randomization of the last patient; an interim efficacy analysis of OS will also be conducted at that time. The final analysis of OS will be conducted when 112 deaths occur, approximately 4 years after randomization of the last patient.
Study Population: Treatment-naïve patients with HL and Ann Arbor Stage III or IV disease are eligible for the study. Patients must have histologically confirmed classical HL according to the current World Health Organisation Classification (nodular sclerosis, mixed cellularity, lymphocyte rich, lymphocyte depleted, or classical Hodgkin lymphoma, NOS [not otherwise specified]). Patients with any sensory or motor peripheral neuropathy are excluded, as are those with nodular lymphocyte predominant HL.
Duration of Study: The study will last approximately 60 months to reach the final analysis of the mPFS endpoint (approximately 36 months of enrollment plus 24 months of additional follow-up after the last patient is randomized). Patients will be followed for survival until death or the end of posttreatment follow-up (when 112 deaths occur, approximately 4 years from the date of the last patient randomized), whichever occurs first. The total study duration is approximately 7 years.

STUDY OVERVIEW DIAGRAM



△ PET and CT scans at C2D25 (±1 day) and 3 to 7 weeks after last dose of frontline therapy. Independent Review Facility will read only the C2D25 PET Scan in real-time.

SCHEDULE OF EVENTS

				Cycle (C) Every 28 Days																	
		Screening	Enrollment	Cycle 1				Cycle 2			Cycle 3				Cycle 4		Cycle 5		Cycle 6		EOT	PTFU [a]
	Day (D)	-28 to D1	Within 24 hours of first dose	D1	D2	D3	D 15	D1	D 15	D 25	D1	D2	D3	D 15	D1	D 15	D1	D 15	D1	D 15	30 ± 7 days after last dose of frontline therapy	Every 3 months for 36 months and then every 6 months until study closure
Screening/ Baseline	Informed consent	X																				
	Inclusion/ exclusion	X																				
	Demographics	X																				
	Medical history	X																				
	Tumor specimen	X[b]																				
	IPFP	X																				
Safety Assessments	Height	X																				
	Weight and BSA	X		X			X	X	X		X			X	X	X	X	X	X	X		
	Physical exam including focused lymphoma assessment	X		X[c]				X			X				X		X		X		X	X
	Pregnancy test [d]	X		X[d]																		
	Vital signs [e]	X		X[e]			X[e]	X	X		X			X	X	X	X	X	X	X	X	
	ECOG performance status	X						X			X				X		X		X		X	
	Hematology and serum chemistry [f]	X[f]		X[f]			X[f]	X	X		X			X	X	X	X	X	X	X	X	
	12-lead ECG	X																				
	Quality of life (QOL) assessments[g]	X		X[g]				X			X				X		X		X		X	X[g]
	Medical resource utilization			X				X			X				X		X		X		X	X

		Screening	Enrollment	Cycle (C) Every 28 Days																	EOT	PTFU [a]
				Cycle 1				Cycle 2			Cycle 3				Cycle 4		Cycle 5		Cycle 6			
	Day (D)	-28 to D1	Within 24 hours of first dose	D1	D2	D3	D 15	D1	D 15	D 25	D1	D2	D3	D 15	D1	D 15	D1	D 15	D1	D 15	30 ± 7 days after last dose of frontline therapy	Every 3 months for 36 months and then every 6 months until study closure
	Monitoring of concomitant medications and procedures	Concomitant medications and procedures will be recorded from signing the informed consent through 30 days after the last dose of Frontline Therapy																				
	Adverse event reporting		Recorded from first dose of study drugs through 30 days after the last dose of Frontline Therapy (**Treatment-related** adverse events must be followed until the sooner of resolution or study closure. However, these AEs will only be recorded in the eCRF from first dose of study drugs through 30 days after the last dose of Frontline Therapy.) All events related to peripheral neuropathy, regardless of seriousness, will be followed for all changes in severity until resolution to baseline or study closure, whichever occurs first, and recorded in the eCRF.																	
	Serious adverse events[h]	Serious adverse events will be collected from signing of the informed consent through 30 days after the last dose of Frontline Therapy																				
Disease Assessment	Tumor biopsy[i]	X																			X[i]	
	CT of chest, neck, abdomen, pelvis[j]	X								X[j]											X[j]	X[j]
	PET[k]	X								X[k]											X[k]	
	B symptom assessment	X		X				X			X				X		X		X		X	X
	Survival/ disease status and anticancer treatments for HL																					X[l]
Fertility Assessment	Fertility assessment[m]			Dates and outcomes of all pregnancies to be recorded from first dose of study drugs through end of study																		
Study Drug Administration	ABVD or A+AVD[n]			X			X	X	X		X			X	X	X	X	X	X	X		

				Cycle (C) Every 28 Days																	
		Screening	Enrollment	Cycle 1				Cycle 2			Cycle 3				Cycle 4		Cycle 5		Cycle 6		EOT	PTFU [a]
	Day (D)	-28 to D1	Within 24 hours of first dose	D1	D2	D3	D 15	D1	D 15	D 25	D1	D2	D3	D 15	D1	D 15	D1	D 15	D1	D 15	30 ± 7 days after last dose of frontline therapy	Every 3 months for 36 months and then every 6 months until study closure
PK/PD	PK Sample[o]			X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
	Serum biomarkers such as [redacted]			X				X			X				X		X		X		X	
	Immunogenicity[q]			X				X											X		X	
	Germline DNA[r]			X																		

Abbreviations: ATA=antitherapeutic antibodies; A+AVD=brentuximab vedotin (ADCETRIS®) plus doxorubicin, vinblastine and dacarbazine; ABVD=doxorubicin, bleomycin, vinblastine, and dacarbazine; BSA=body surface area; CT=computed tomography; CTACK=cutaneous T-cell-attracting chemokine; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOI=end of infusion; EOT=end of treatment; FDG=fluorodeoxyglucose; IL-6=interleukin-6; IPFP=International Prognostic Factor Project; PD=pharmacodynamics; PET=positron emission tomography; PK=pharmacokinetics; PTFU=posttreatment follow-up; TARC=thymus and activation-regulated chemokine.

Tests and procedures should be performed on schedule, but occasional changes are allowable (±3 days) for logistic reasons unless indicated otherwise.

a. All treated patients will be followed for progression-free survival disease status, event-free survival and overall survival every 12 weeks (±1 week) until 36 months of PTFU and then every 6 months until study closure. For patients who have progressive disease, survival/disease status and information regarding the initiation of an alternative lymphoma treatment may be obtained by phone call. Note: Radiological assessments are only required every 12 weeks (±1 week) until 12 months of PTFU and then every 6 months until study closure. To assist with scheduling of visits, patients may begin to align the timing of their follow-up visits with the timing of the CT scans during PTFU, when applicable.

b. Tumor tissue collected at the time of original diagnosis or subsequent procedures (unstained slides or a formalin-fixed paraffin-embedded block) will be obtained after the patient has signed the informed consent form. This will be used to assess biomarkers implicated in sensitivity or resistance to brentuximab vedotin or vinca alkyloids and taxanes (eg, p53, beta 3 tubulin, and ABCC transporters). If archived tissue cannot be obtained, a biopsy should be performed at screening; refer to footnote "i."

c. The Cycle 1 Day 1 physical examination is not required if the screening physical examination was conducted within 4 days before administration of the first dose

of study drug. A limited physical exam may be administered at the treating physician's discretion.

d. A serum pregnancy test will be performed for women of childbearing potential during screening and again at Cycle 1, Day 1 (baseline). A urine pregnancy test is required if the serum pregnancy test was not done within 4 days of the first dose of study drug. The results must be negative within 4 days prior to the first dose of brentuximab vedotin. Additional pregnancy testing may be performed during the study at the discretion of the investigator, upon request of the IEC/IRB, or if required by local regulations.

e. Vital signs should be measured at screening and within 1 hour prior to infusion of ABVD and AVD on Days 1 and 15 of each cycle and EOT. All vital sign measurements include: systolic and diastolic blood pressure (sitting 3-5 minutes), heart rate and body temperature. In Cycle 1 only (Days 1 and 15), vital signs should be recorded pre-dose and 1 hour post-dose (± 10 minutes).

f. A blood sample for hematology and serum chemistry will be obtained at screening and predose at Days 1 and 15 of each cycle and EOT.

   Hematology and chemistry blood samples for Cycle 1, Day 1 may be collected within 4 days prior to dosing to ensure patient eligibility on study Day 1. In this situation it need not be repeated on Cycle 1, Day 1.

   Hematology includes complete blood count (CBC) with differential consisting of the following: hemoglobin, hematocrit, total white blood cell count (WBC), differential WBC count, absolute neutrophil count (ANC), and platelet count. Machine counts are acceptable.

   Serum chemistry includes sodium, potassium, carbon dioxide, chloride, blood urea nitrogen (BUN), serum creatinine, bilirubin (total), alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), gamma glutamyl transferase, albumin, fasting glucose, urate, calcium, phosphate, and magnesium. An Hb A1C measurement will be obtained at screening and at EOT.

g. All questionnaires should be completed on screening, Day 1 of every cycle (before any other study procedures are performed), 30 days after last dose of Frontline Therapy, and during posttreatment follow-up unless indicated otherwise (see table below). If screening questionnaires were completed within 4 days before Cycle 1 Day 1, they do not need to be repeated on Cycle 1 Day 1.
   Patient-reported outcomes will be evaluated using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, the FACIT-Dyspnea 10 questionnaire, the EQ-5D questionnaire, and the Functional Assessment of Cancer Therapy—Neurotoxicity (FACT-Ntx; Abbreviated).

Patient Reported Outcomes	End of Collection Period
FACIT-Dyspnea 10 Item Short Form	Collected until EOT
FACT-Ntx Abbreviated	Collected until EOT
EuroQOL EQ-5D (Utility Measurement)	Collected until 3 years post last dose of frontline therapy or development of confirmed progressive disease (PD), whichever occurs first
EORTC QLQ-C30	Collected at all patient visits (as outlined in the SOE table), including visits during the PTFU, until the final visit by the patient

h. Includes serious pretreatment events. Serious pretreatment events will be reported to Millennium Department of Pharmacovigilance & Risk Management or designee from the time of signing ICF up to first dose of study drug, but will not be recorded in the eCRF.

i. Patients who cannot provide at least 10 histological slides from their diagnostic biopsy will undergo a new tumor biopsy during screening, which may be obtained up to 14 days prior to the first dose of study drug. Patients who have an archived tumor specimen/ histological slides as previously mentioned, will not need to undergo a biopsy at the time of screening.
Efforts should be made to obtain a tumor biopsy at the time of disease progression for patients in the A+AVD arm. Additional on-study biopsies will be optional and may be used to test for other salient pharmacodynamic and genomic markers related to the [redacted]

j. Response to treatment and disease status assessments will be evaluated according to the Revised Response Criteria for Malignant Lymphomas (Cheson 2007) and confirmed by an independent review facility. MRI scans may be substituted for CT scans only if a patient 1) has a glomerular filtration rate of less than 60 mL/min such that IV contrast presents a risk of renal failure, 2) develops anaphylaxis to IV contrast, or 3) becomes pregnant during posttreatment follow-up. If use of MRI is required, a consistent scanning modality must be maintained.

During the treatment phase CT scans will be performed at:

- Screening
- After Cycle 2: On C2D25 (±1 day). This corresponds to 10 days (±1 day) after the 4th dose (after C2D15) of study drug administration
- After last dose of frontline therapy (usually Cycle 6): between 3 and 7 weeks following last dose of frontline therapy. In addition, patients who switch therapy prior to completion of frontline therapy must have a scan performed prior to the first dose of alternative treatment.
- During the follow-up period: every 3 months for the first year and then every 6 months thereafter. The CT scan time points are calculated from C1D1.

*The actual time points for CT scans during PTFU will be based on calendar days.

PTFU Scan Number	CT Scan Time Points (Calendar days)	Corresponding Year
1	Day 302 ±7 days	Year 1
2	Day 393 ±7 days	
3	Day 484 ±7 days	
4	Day 575 ±7 days	
5	Day 757 ±14 days	Year 2
6	Day 939 ±14 days	
7	Day 1121 ±14 days	Year 3
8	Day 1303 ±14 days	
9	Day 1485 ±14 days	Year 4
10	Day 1667 ±14 days	
11	Day 1849 ±14 days	Year 5
12	Day 2031 ±14 days	

k. During the treatment phase PET scans will be performed at:

- Screening
- After Cycle 2: On C2D25 (±1 day). This corresponds to 10 days (±1 day) after the 4th dose (after C2D15) of study drug administration

- After last dose of frontline therapy (usually Cycle 6): between 3 and 7 weeks following last dose of frontline therapy. In addition, patients who switch therapy prior to completion of randomized treatment must have a scan performed prior to the first dose of alternative treatment.

l. Subjects will be followed for survival disease status every 3 months for 36 months and then every 6 months until death /study closure

m. Fertility is being assessed as an exploratory endpoint independent of safety reporting.

n. Brentuximab vedotin will be administered intravenously at a dose of 1.2 mg/kg within approximately 1 hour after completion of AVD therapy. For patients whose frontline therapy is switched to physician's choice, regimen details will be recorded.

o. Pharmacokinetics will be assessed as indicated in the tables below.

Pharmacokinetic Sampling Time Points

Cycle	Study Day	Time	Window	Relative Time
			Full A+AVD Arm	
1-6	1	Predose	Within prior 4 hr	Start of brentuximab vedotin infusion
		EOI (~30 min)	Within 1 hour post EOI	End of brentuximab vedotin infusion
	15	Predose	Within prior 4 hr	Start of brentuximab vedotin infusion
		EOI (~30 min)	Within 1 hour post EOI	End of brentuximab vedotin infusion
1 and 3, in addition	2	24 hr	±4 hr	Start of brentuximab vedotin infusion
	3	48 hr	±4 hr	Start of brentuximab vedotin infusion
50 Patient Subset Arm: In addition to the above time points, the below pharmacokinetic time points will be drawn from 50 recruited patients from each treatment arm (total of 100 patients).				
A.	**PK Sampling Time Points for the 50-patient Subset of A+AVD Arm Group.**			
1 and 3	1	2 min	±2 min	End of doxorubicin infusion
		2 min	±2 min	End of vinblastine infusion
		2 min	±2 min	End of dacarbazine infusion
		1 hr	±5 min	End of brentuximab vedotin infusion
		6 hr	±10 min	End of brentuximab vedotin infusion
	8	168 hr	±24 hr	End of brentuximab vedotin infusion

Pharmacokinetic Sampling Time Points

Cycle	Study Day	Time	Window	Relative Time
B.	**Additional PK Sampling Time Points for the 50-patient Subset of ABVD Arm Group.**			
1 and 3	1	Predose	Within prior 4 hr	Start of doxorubicin infusion
		2 min	±2 min	End of doxorubicin infusion
		2 min	±2 min	End of vinblastine infusion
		2 min	±2 min	End of dacarbazine infusion
		1 hr	±5 min	End of dacarbazine infusion
		6 hr	±10 min	End of dacarbazine infusion
	2	24 hr	±4 hr	End of dacarbazine infusion
	8	168 hr	±24 hr	End of dacarbazine infusion

Abbreviations: A+AVD = brentuximab vedotin (ADCETRIS®) plus doxorubicin, vinblastine, and dacarbazine; ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; EOI = end of infusion; hr = hour; min = minutes.

*The 50 patients in each treatment arm from whom additional PK samples are drawn will be recruited from sites that agree to participate. In addition, approximately 20 patients in each 50-patient intensive-sampling group must be of Asian race.

p. Serum samples will be collected predose on Day 1 of each cycle, and at EOT in all patients to evaluate protein markers such as [redacted] (circulating protein markers).

q. Immunogenicity samples will be collected for patients in the A+AVD arm only before dosing on Day 1 of Cycle 1, Cycle 2, and Cycle 6; or at termination if treatment is terminated before Cycle 6.

r. Optional germline DNA will be collected on Cycle 1 Day 1 predose for patients in the A+AVD arm only.

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
A+AVD	brentuximab vedotin (ADCETRIS®) plus doxorubicin (Adriamycin), vinblastine, dacarbazine
ABVD	doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine
ADC	antibody-drug conjugate
AE	adverse event
ALCL	anaplastic large cell lymphoma
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
AVD	doxorubicin (Adriamycin), vinblastine, and dacarbazine
BEACOPP	bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine, procarbazine, and prednisone
BPT	bleomycin pulmonary toxicity
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CL	clearance
C_{max}	maximum plasma concentration
CO_2	carbon dioxide
CR	complete remission
CR(u)	unconfirmed complete response

Abbreviation	Term
CT	computed tomography
CTACK	cutaneous T-cell-attracting chemokine
CYP	cytochrome P_{450}
DLCO	carbon monoxide diffusion capacity
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOCR	duration of complete remission
DOR	duration of response
DTIC	dacarbazine
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End of Study (visit)
EOT	End of Treatment (visit)
ESMO	European Society for Medical Oncology
EU	European Union
FDA	(United States) Food and Drug Administration
FDG	fluorodeoxyglucose
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
GHSG	German Hodgkin Study Group
GI	gastrointestinal
GLP	Good Laboratory Practices
GM-CSF	granulocyte macrophage-colony stimulating factor
GMP	Good Manufacturing Practice
Hb	hemoglobin
Hct	hematocrit
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HNSTD	highest nonseverely toxic dose
HRQOL	health-related quality of life

Abbreviation	Term
HRS	Hodgkin Reed-Sternberg
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IgG1	immunoglobulin G1
IL-6	interleukin-6
IPS	(Hasenclever) International Prognostic Score
IRB	institutional review board
IRF	independent review facility
ITT	intent-to-treat
IV	intravenous; intravenously
IXRS® (IVRS/IWRS)	interactive voice response system and/or interactive web response system
JCV	John Cunningham virus
LDH	lactate dehydrogenase
LFT	liver function test(s)
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
mPFS	modified progression-free survival
MRI	magnetic resonance imaging
MRU	medical resource utilization
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease (disease progression)
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)

Abbreviation	Term
PML	progressive multifocal leukoencephalopathy
PN	peripheral neuropathy
PR	partial response
PRO	patient-reported outcomes
QALY	quality-adjusted life year
QOL	quality of life
QTc	rate-corrected QT interval (millisec) of electrocardiograph
RBC	red blood cell
SAE	serious adverse event
SD	stable disease
SmPC	Summary of Product Characteristics
SPD	sum of the product of the (tumor) diameters
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TARC	thymus- and activation-regulated chemokine
TGD	tumor growth delay
TGI	tumor growth inhibition
T_{max}	first time to maximum plasma concentration
UK	United Kingdom
ULN	upper limit of the normal range
US	United States
WBC	white blood cell
WHO	World Health Organization

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Disease Under Treatment

Hodgkin lymphoma (HL), a neoplasm of lymphoid tissue, is histopathologically defined by the presence of malignant Hodgkin Reed-Sternberg (HRS) cells in a background of inflammatory cells. The characteristic surface antigen expressed on HRS cells is CD30. In 2008 alone, it was estimated that approximately 8220 new cases of HL were diagnosed in the United States,[(1)] approximately 7709 new cases of HL were diagnosed in the 5 major EU countries (UK, France, Germany, Italy, and Spain),[(2)] and approximately 890 new cases of HL were diagnosed in Canada.[(3)]

Advanced HL, here defined as Ann Arbor Stage III or IV disease, is characterized by supra- and sub-diaphragmatic or more widespread disease and is associated with diminished survival. Median overall survival (OS) in the more than 14,000-patient International Hodgkin Lymphoma Database[(4)] is approximately 9 years for patients with Stage IV disease and approximately 18 years for patients with Stage III disease. The Stage III and IV populations typically receive homogenous treatment modalities, providing fewer confounding factors for time-to-event endpoints.

1.1.2 Study Drug

Brentuximab vedotin (ADCETRIS®, the first "A" of the experimental arm acronym) is an antibody-drug conjugate (ADC) composed of the anti-CD30 chimeric immunoglobulin G1 (IgG1) monoclonal antibody cAC10 and the potent antimicrotubule drug monomethyl auristatin E connected by a protease-cleavable linker. cAC10 binds to the CD30 antigen, which has a very low expression on normal cells but is found on the HRS cells of HL, on anaplastic large cell lymphoma (ALCL) cells, and on tumor cells of other varied lymphoproliferative disorders.

Brentuximab vedotin in approved in the United States as ADCETRIS® for the treatment of patients with HL after failure of autologous stem cell transplant (ASCT) or after failure of at least 2 prior multi-agent chemotherapy regimens in patients who are not ASCT candidates and for the treatment of patients with systemic ALCL after failure of at least 1 prior multi-agent chemotherapy regimen.

1.2 Nonclinical Experience

Brentuximab vedotin has the potential to target and selectively deliver a potent cytotoxic to tumor cells. It induces cell death of both HL and ALCL cell lines in vitro with subnanomolar concentrations producing 50% inhibition (IC_{50}) and has demonstrated antitumor activity in xenograft models of the same tumors.

Multiple-dose brentuximab vedotin toxicity studies have been performed in monkeys and rats. In both species, hypocellularity of the bone marrow and lymphoid depletion of the thymus were observed. In addition, lesions were seen in the kidneys, liver, and spleen in monkeys and in the liver and testes in rats. Reversibility of toxicity was demonstrated for all of the findings with the exception of the testicular changes in rats. At the recovery sacrifice 4 weeks following the last dose of brentuximab vedotin, testicular changes (diffuse seminiferous tubule degeneration) were still evident. The no observed adverse effect level for brentuximab vedotin was defined at 1.0 mg/kg in monkeys and 0.5 mg/kg in rats. Human equivalent doses are 0.32 and 0.08 mg/kg, respectively.

In the L540cy tumor model,[5] administration of doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine (ABVD) plus brentuximab vedotin in tumor-bearing mice demonstrated significantly increased antitumor activity as compared to the mice treated with ABVD or brentuximab vedotin alone, suggesting a synergistic effect.[6] ABVD and brentuximab vedotin-treated animals demonstrated 0/8 and 4/9 durable responses, respectively, while the combination of brentuximab vedotin and ABVD resulted in 9/9 durable tumor regressions in all experimental animals. In addition, combination therapy was associated with a statistically significant tumor growth delay (TGD) relative to each treatment arm alone (combination vs brentuximab vedotin: $P < 0.0101$, combination versus ABVD: $P < 0.0001$). Improved efficacy in high tumor burden models suggests that combining brentuximab vedotin with ABVD may be associated with greater efficacy.

Similarly, when treatment was initiated when tumors reached 300 mm^3 volume, the combination of brentuximab vedotin with ABVD significantly increased the TGD, resulting in durable responses in 5 of 10 animals. The delay in tumor growth induced by the combination treatment was highly significant relative to each individual treatment arm alone (combination versus brentuximab vedotin: $P < 0.05$, combination versus ABVD: $P < 0.001$).

Doxorubicin, vinblastine, and bleomycin had little if any single-agent antitumor activity in L540cy xenograft models and did not significantly improve antitumor activity of brentuximab vedotin when used in combination with the single-agent chemotherapy drugs

(data on file, Seattle Genetics). Specifically, vinblastine had neither a synergistic nor an antagonistic effect when used in combination with brentuximab vedotin. Although vinblastine and auristatins are cell-cycle specific agents belonging to the vinca alkaloid family, they have slightly different mechanisms of action due to their interactions with different microtubule-associated proteins.[7]

Detailed information regarding the nonclinical pharmacology and toxicology of brentuximab vedotin may be found in the Investigator's Brochure (IB).

1.3 Clinical Experience

The safety and efficacy of brentuximab vedotin has been evaluated in more than 450 patients with HL, sALCL, and other CD30+ hematologic malignancies in 11 clinical studies. Clinical data have been collected from 2 completed phase 1 dose-escalation studies (SG035-0001 and SG035-0002), a pivotal phase 2 study in relapsed or refractory HL after ASCT (SG035-0003), a pivotal phase 2 study in relapsed or refractory systemic ALCL (sALCL) (SG035-0004), and a phase 1, drug-drug interaction study (SGN35-008A). Preliminary and final analyses of safety data indicate that brentuximab vedotin has a manageable safety profile in the studied populations.

In Study SG035-0001, a total of 45 patients with CD30+ hematologic malignancies (42 with HL, 2 with sALCL, 1 with angioimmunoblastic T-cell lymphoma) were treated with brentuximab vedotin at doses of 0.1 to 3.6 mg/kg administered intravenously (IV) every 3 weeks. The primary objectives of the study were to establish a maximum tolerated dose (MTD) of brentuximab vedotin and to assess the associated toxicity profile. The most common adverse events (AEs) were fatigue (36% of patients), pyrexia (33%), diarrhea, nausea, peripheral neuropathy, and neutropenia (22% each). Notable serious adverse events (SAEs) considered at least possibly related to treatment included anaphylaxis, myocardial infarction, and peripheral neuropathy. Numerous responses, including complete remissions (CRs), were observed. The MTD was determined to be 1.8 mg/kg administered IV over 30 minutes every 3 weeks.

In Study SG035-0002, a total of 44 patients with CD30-positive hematologic malignancies (including 38 with HL) were treated with brentuximab vedotin at doses of 0.4 to 1.4 mg/kg administered IV weekly for 3 of 4 weeks. The primary objectives explored in this study were to establish the safety profile and MTD of weekly brentuximab vedotin monotherapy in patients with relapsed/refractory CD30+ hematologic malignancies. Although this weekly regimen was designed to enable combination use with gemcitabine, efficacy with

brentuximab vedotin monotherapy was deemed sufficient and the planned brentuximab vedotin/gemcitabine combination was not pursued. The most common AEs were peripheral sensory neuropathy (66% of patients); fatigue (52%); nausea (50%); diarrhea (32%); arthralgia (27%); pyrexia (25%); and decreased appetite, myalgia, and upper respiratory tract infection (23% each). Treatment discontinuations due to AEs were observed in 30% of patients. The most frequent AE that led to dose modification or delay was peripheral sensory neuropathy. Acute infusion reaction AEs occurred in a total of 6 patients. Overall, these acute infusion reaction AEs were reported as less than Grade 2 and resolved. Overall, 2 patients (14%) who had an acute infusion reaction also had antitherapeutic antibodies at any postbaseline visit.

In Study SG035-0003, a phase 2, single-arm, open-label study in patients with relapsed or refractory HL after ASCT, and Study SG035-0004, a phase 2 study conducted in patients with relapsed or refractory sALCL, brentuximab vedotin was administered at a dose of 1.8 mg/kg every 3 weeks. One hundred two patients with relapsed and refractory HL and 58 patients with relapsed and refractory sALCL were exposed for a median duration of approximately 27 weeks (9 cycles) and 20 weeks (6 cycles), respectively. Most patients (89%) in the 2 phase 2 studies were between the ages of 18 and 65 years. The primary endpoint of both studies was overall response rate (ORR) as assessed by an independent review facility (IRF). Key secondary endpoints included duration of response, CR rate per IRF, OS, and progression-free survival (PFS). The key efficacy results in HL (SG035-0003) include ORR per IRF (75% [95% confidence interval (CI): 64.9-82.6%]), CR rate per IRF (34% [95% CI: 25.2 44.6%]), B symptom resolution rate (77%), and duration of response (DOR; 6.7 months). Of interest, for those patients achieving a CR, the median DOR was 20.5 months. Key efficacy endpoints in sALCL (SG035-0004) include ORR per IRF (88% [95% CI: 74.6-93.9%]), CR rate per IRF (53% [95% CI: 39.6-66.7%]), and B symptom resolution rate (82%).

Treatment-emergent AEs (TEAEs) occurring in ≥20% of patients in the phase 2 studies were peripheral sensory neuropathy (44%), fatigue (42%), nausea (41%), diarrhea (34%), pyrexia (31%), upper respiratory tract infection (28%), neutropenia (21%), and vomiting (20%). These events were primarily mild to moderate and reversible. Approximately half of patients had treatment-emergent peripheral neuropathy, predominantly sensory neuropathy, with an onset and severity pattern consistent with a cumulative effect. Dose delay and subsequent reduction to 1.2 mg/kg was generally effective in managing peripheral neuropathy. Grade 3 and 4 neutropenia occurred in 13% and 7% of patients, respectively; these events were typically of short duration and well managed by brief dose delays with

growth factor support in some cases. Infusion-related reactions occurred in approximately 10% of patients and were typically managed by dose interruption. Infusion-related reaction prophylaxis in subsequent treatment cycles was instituted at the discretion of the investigator. The clinical laboratory parameters for which the most patients had new or worsening shifts to ≥Grade 3 were low neutrophils (11%), lymphocytes (11%), platelets (6%), leukocytes (5%), and high glucose (6%). Only 1 patient in the phase 2 studies had Grade 3 alanine aminotransferase (ALT) and Grade 3 aspartate aminotransferase (AST).

In the phase 2 studies, 31% of patients had an SAE, 28% had a Grade 3 or higher SAE, and 15% had an SAE that was determined by the investigator to be related to brentuximab vedotin. The most common SAE preferred terms (2%) were abdominal pain, disease progression (recurrent sALCL), pulmonary embolism, and septic shock. A higher proportion of patients with sALCL experienced SAEs, including deaths within 30 days of last dose, relative to patients with HL, likely due to the older age and more aggressive nature of the malignancy in this patient population.

A total of 9 deaths were reported within the safety evaluation period (within 30 days of the last dose of brentuximab vedotin) in 357 patients across the six phase 1 and phase 2 studies for which data are available. Two patient deaths (0.6%) were considered related to study treatment. One patient in Study SG035-0001 who received 3.6 mg/kg in phase 1 died due to febrile neutropenia and presumed septic shock. A second treatment-related death in Study SGN35-008A was attributed to pancytopenia, cytomegalovirus (CMV) infection, and intracranial hemorrhage. The remaining on-study deaths were primarily related to disease progression in patients with sALCL.

Brentuximab vedotin has been shown to induce durable remissions in patients with HL both pre- and post-ASCT, and in patients with relapsed or refractory sALCL. PFS results comparing PFS after brentuximab vedotin with PFS from prior systemic therapy indicate that PFS is significantly prolonged with brentuximab vedotin for both HL and sALCL. A substantial number of patients with HL and sALCL and B symptoms at baseline saw these symptoms resolve during treatment with brentuximab vedotin. In addition, the large majority of patients with sALCL presenting with cutaneous lesions at baseline experienced resolution of these symptoms after receiving brentuximab vedotin.

Study SGN35-009 is a phase 1, 2-arm, open-label, multicenter study to evaluate the safety of brentuximab vedotin when administered in combination with standard therapy (ABVD) or a modified standard (doxorubicin [Adriamycin], vinblastine, dacarbazine [AVD]). To date,

patients have received doses of 0.6, 0.9, or 1.2 mg/kg brentuximab vedotin with standard doses of ABVD or 1.2 mg/kg brentuximab vedotin with AVD, depending upon cohort assignment. The combination regimens are administered on Days 1 and 15 of each 28-day cycle for up to 6 cycles of therapy. Each regimen evaluated a dose-limiting toxicity (DLT) period, defined as any Cycle 1 toxicity requiring a delay of ≥7 days in standard ABVD or AVD therapy. No DLTs were observed. Enrollment of an expansion cohort further testing 1.2 mg/kg brentuximab vedotin plus AVD is now complete and treatment of enrolled patients is ongoing within this cohort.

Of the 51 patients enrolled in Study SGN35-009, the mean age was 34.8 (range 18-59); 47% of patients had Stage IV disease at diagnosis, and 25% had a Hasenclever Hodgkin's Prognosis Score (IPS) ≥4. A recent review of interim safety data as of 07 February 2012 for all 51 enrolled patients included data from 25 patients in the brentuximab vedotin plus ABVD cohorts and 26 patients in the brentuximab vedotin plus AVD cohorts. The most commonly reported TEAEs were nausea, neutropenia, peripheral sensory neuropathy, fatigue, vomiting, constipation, alopecia, pyrexia, bone pain, decreased appetite, diarrhea, and insomnia, each reported in 25% or more patients. Peripheral neuropathy events have been reported in 25 patients (49%); 1 patient had Grade 3 peripheral motor and sensory neuropathy, but no other patient's peripheral neuropathy event exceeded Grade 2. In the brentuximab vedotin plus ABVD cohorts, Grade ≥3 events included neutropenia (n=20, 80%), febrile neutropenia (n=5), pulmonary toxicity (n=5), anemia (n=4), dyspnea (n=3), pulmonary embolism (n=3), syncope (n=3), and anorectal cellulitis, cough, fatigue, hypokalemia, hyponatremia, leukopenia, pericardial effusion, rash, and respiratory failure (n=1 each). In the brentuximab vedotin plus AVD cohorts, Grade ≥3 events included neutropenia (n=17, 65%), anemia (n=3), febrile neutropenia (n=2), and decreased appetite, dyspnea, elevated ALT, fatigue, leukopenia, peripheral sensory and motor neuropathy, *Pneumocystis jiroveci* pneumonia, SIADH, syncope, and tooth abscess (n=1 each).

Interim efficacy data as of 07 February 2012 demonstrate that all patients who completed frontline therapy on study for whom response assessment results are available achieved a CR at the end of treatment, including 18 patients from the ABVD cohorts and 6 patients from the AVD cohorts. Additionally, an exploratory analysis of interim fluorodeoxyglucose (FDG) positron emission tomography (PET) results after 2 cycles of therapy was performed by independent radiology review using the Deauville criteria.[8] Of 37 patients, 36 (97%) had a negative interim PET after Cycle 2 by central review, including 22 of 22 (100%) negative in the ABVD cohorts and 14 of 15 (93%) negative in the AVD cohorts.

Further details on these studies are provided in the IB.

1.4 Study Rationale

Advances in the use of combined chemotherapy and radiotherapy over the past half century have dramatically improved outcomes for patients with HL. The most commonly used frontline therapies, ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) and BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone), result in CRs in 72% to 90% of patients.[9, 10, 11] However, following frontline treatment with multimodality therapy, including combination chemotherapy and radiation, relapse is observed in up to 35% of advanced-stage cases. Also, 10% to 20% of patients are refractory to frontline treatment.[12, 13, 14]

The high CR rate and ORR obtained with brentuximab vedotin in 2 single-arm, phase 2 studies in relapsed or refractory HL (SG035-0003) and relapsed or refractory sALCL (SG035-0004) suggest that its addition to frontline therapy may enhance efficacy in newly diagnosed HL.

Of the 4 agents in ABVD, bleomycin is the agent most associated with unpredictable, life-threatening toxicity and is thought to have the lowest single-agent activity.[15] Standard practice in patients who develop bleomycin pulmonary toxicity (BPT) is to continue frontline therapy with AVD while omitting bleomycin. Retrospective analyses of the Cancer and Leukemia Group B (CALGB) 8251 and 8952 studies have shown no difference in response or relapse rates for patients who had bleomycin discontinued at any point in their frontline therapy.[16] Furthermore, noninfectious pulmonary toxicity was observed in some patients treated with brentuximab vedotin in combination with bleomycin within the ABVD cohorts of Study SGN35-009. The incidence of pulmonary toxicity in the brentuximab vedotin plus ABVD cohorts of the trial was approximately 44% (11 of 25 patients), compared with an incidence of 10% to 25% most commonly reported in the literature for bleomycin-based regimens.[17, 18, 19] Patients presented with cough and dyspnea. Interstitial infiltration and/or inflammation were observed on radiographs and computed tomography (CT) scans of the chest. Six patients had a Grade 3 or higher event (3 with Grade 3, 2 with Grade 4, and 1 with Grade 5). It was determined that concomitant administration of brentuximab vedotin and bleomycin is contraindicated due to pulmonary toxicity. Of note, Study SGN35-009 patients who experienced pulmonary toxicity with brentuximab vedotin plus ABVD were permitted to discontinue bleomycin but resume therapy with brentuximab vedotin plus AVD. Due to the proven antitumor activity and tolerability with single-agent

treatment, evaluation of brentuximab vedotin as a replacement for bleomycin in the AVD combination regimen is hypothesized to provide an improvement in PFS over the standard ABVD regimen, and eliminate the risk of bleomycin-associated pulmonary toxicity.

In ongoing Study SGN35-009, brentuximab vedotin is administered in combination with ABVD (doxorubicin 25 mg/m^2, bleomycin 10 units/m^2, vinblastine 6 mg/m^2, dacarbazine [DTIC] 375 mg/m^2) or in combination with AVD (doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, DTIC 375 mg/m^2) in 28-day cycles, with brentuximab vedotin administered on Days 1 and 15 of each cycle for up to 6 cycles of therapy. Brentuximab vedotin was administered in combination with ABVD at doses of 0.6, 0.9, and 1.2 mg/kg (N=25) and was administered in combination with AVD at 1.2 mg/kg in dose cohorts of 6 or more patients (N=26). No DLTs were observed in any of the cohorts. Brentuximab vedotin monotherapy has previously been shown to be reasonably well tolerated in a phase 1 study and a phase 2 pivotal trial at 1.8 mg/kg in every-3-week dosing. Because the pharmacokinetics (PK) of brentuximab vedotin are linear, PK modeling has shown that the administration of 1.2 mg/kg IV every 2 weeks or 1.8 mg/kg IV every 3 weeks should result in similar exposures (area under the plasma concentration versus time curve [AUC]). Therefore, given the tolerability and the expected PK profiles, it was determined that an appropriate dose level of brentuximab vedotin is 1.2 mg/kg delivered IV every 2 weeks and the recommended combination for further clinical development in phase 3 is with AVD (hereafter called A+AVD). Furthermore, additional PK samples will be taken in the current study to allow further understanding of the PK of brentuximab vedotin and AVD when coadministered in frontline HL setting.

Regarding patients' duration of therapy, functional imaging has recently changed how physicians determine the number of cycles of chemotherapy that patients with newly diagnosed HL receive. Prior to the widespread use of PET scanning, many patients with advanced stage HL appeared to have partial responses due to residual masses visible upon CT. This large category of partial responses or "complete responses, unconfirmed" (CRu) is now mostly eliminated with the use of PET scanning, which has shown that at least 75% of such patients assessed by CT actually have a CR when PET scanning is added,[(20)] and such patients with PET-negative residual masses have the same prognosis as patients with no residual mass.[(21)] As there is no known benefit to continued chemotherapy for HL after achievement of CR, most patients will be assessable after 6 cycles and the very large majority will have reached a CR. For those patients with a PET-positive residual mass after 6 cycles of chemotherapy, most clinicians would prefer to switch to radiation, thus also concluding frontline chemotherapy after 6 cycles. Therefore, information obtained by

functional imaging typically obviates the need for a flexible number of cycles (6-8), and European Society for Medical Oncology (ESMO) and other guidelines are in the process of being updated to reflect this evolving information. Six cycles was thus selected as the duration of frontline therapy in this study.

Notably, this trial does not prospectively plan for patients, even those with bulky disease, to receive radiation therapy. It instead follows the model recently presented by Engert et al as used in the German Hodgkin Study Group (GHSG) HD15 trial.[21] In that study, patients in partial response (PR) with a persistent mass measuring 2.5 cm or more upon completion of frontline chemotherapy were assessed by PET. Only patients who were positive on centrally-reviewed PET scan received additional radiotherapy with 30Gy, yet these data show that frontline therapy was successful. Although the GHSG HD15 study investigated 3 various BEACOPP regimens, this approach to radiotherapy has also been recommended for use with ABVD[22] and seems to strike an appropriate compromise between therapeutic benefit and reducing the risk of later malignancy secondary to radiation exposure.

1.5 Potential Risks and Benefits

As detailed in Section 1.3, brentuximab vedotin monotherapy has demonstrated therapeutic activity in CD30+ hematological malignancies.

Brentuximab vedotin treatment causes a peripheral neuropathy that is predominantly sensory. Cases of peripheral motor neuropathy have also been reported. Brentuximab vedotin-induced peripheral neuropathy is typically cumulative and generally reversible. In the SG035-0003 and SG035-0004 clinical studies, 54% of patients experienced neuropathy of any grade. Of these patients, 49% had complete resolution, 31% had partial improvement, and 20% had no improvement. Of the patients who reported neuropathy, 51% had residual neuropathy at the time of their last evaluation. Monitoring patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness is required. Patients experiencing new or worsening peripheral neuropathy may require brentuximab vedotin dose modifications, including a dose delay (see Table 6-1).

Infusion-related reactions, including anaphylaxis, have occurred with brentuximab vedotin.[23] Monitoring of patients during infusion is required. If anaphylaxis occurs, the administration of brentuximab vedotin should be immediately and permanently discontinued and appropriate medical therapy administered. If an infusion-related reaction occurs, the infusion should be interrupted and appropriate medical management instituted. Patients who

have experienced a prior infusion-related reaction should be premedicated according to institutional guidelines for subsequent infusions. Premedication may include acetaminophen, an antihistamine and a corticosteroid.

Clinically significant laboratory abnormalities were to be reported as adverse events per the phase 2 study protocols. Central laboratory data were collected only predose for each treatment cycle. Few patients overall had postbaseline worsening to Grade 3 or higher in clinical laboratory values. The clinical laboratory parameters for which the most patients had new or worsening shifts to ≥Grade 3 were low neutrophils (11%), lymphocytes (11%), platelets (6%), leukocytes (5%), and high glucose (6%). Only 1 patient in the phase 2 studies had Grade 3 ALT and AST.

Any treatment that can decrease immune function may contribute to malignancy and infections; patients are to be monitored for these events during the treatment period and up to and including 30 days after the last dose of frontline therapy.

Complete blood counts should be monitored prior to each dose of brentuximab vedotin and more frequent monitoring should be considered for patients with Grade 3 or 4 neutropenia. Prolonged (≥1 week) severe neutropenia can occur. If Grade 3 or 4 neutropenia develops, manage by dose delays, reductions, or discontinuations (see Table 6-1).

Tumor lysis syndrome may occur. Patients with rapidly proliferating tumor and high tumor burden are at risk of tumor lysis syndrome and should be closely monitored. If tumor lysis syndrome occurs, take medically appropriate measures.

Stevens-Johnson syndrome has been reported with brentuximab vedotin. If Stevens-Johnson syndrome occurs, brentuximab vedotin must be discontinued and the appropriate medical therapy administered.

Progressive multifocal leukoencephalopathy (PML) has been reported with brentuximab vedotin use. PML is a rare demyelinating disease of the brain that is caused by the John Cunningham virus (JCV). It typically occurs in immunocompromised individuals and can be fatal. Presenting features may include altered mental status, motor deficits such as hemiparesis or ataxia, visual disturbances, or higher cortical dysfunction such as dysphasia or agnosia. Seizures have also been reported in patients with PML (approximately 20%). The onset of neurological deficits may occur over weeks to months. Cognitive decline without accompanying deficits in motor or sensory function is uncommon. Optic nerve involvement, fever, and spinal cord disease are not typically associated with PML. In

addition, peripheral neuropathy, which has been reported with brentuximab vedotin treatment, is not commonly reported with PML. If PML is suspected, a diagnostic work-up should be performed, as described in Section 6.6.

Acute pancreatitis has been reported in patients treated with brentuximab vedotin and has contributed to fatal outcomes in some cases. Onset typically occurred after 1 to 2 doses of brentuximab vedotin. Early symptoms included severe abdominal pain, nausea, and vomiting. The majority of pancreatitis cases were complicated by other possible contributory factors, including cholelithiasis and alternate etiologies (eg, pancreatic lymphoma progression, displacement of bile duct stent, etc.).

Approximately 1% of patients treated with brentuximab vedotin in the investigational or commercial setting have had an AE that was suggestive of a hepatobiliary disorder. The majority of events occurred after 1 to 2 treatment cycles and they were characterized by asymptomatic mild to moderate transient elevations in ALT and AST. Elevated liver enzymes were observed upon rechallenge for some patients.

Preliminary population PK analyses of the effects of renal impairment on brentuximab vedotin metabolism suggest that no dose adjustments are necessary for patients with moderate renal impairment. Additional analysis is planned to more fully characterize the pharmacokinetics in these patient populations.

Monomethyl auristatin E (MMAE) is primarily metabolized by CYP3A. Coadministration of brentuximab vedotin with ketoconazole, a potent CYP3A4 inhibitor, increased exposure to MMAE by approximately 34%. Patients who are receiving strong CYP3A4 inhibitors concomitantly with brentuximab vedotin should be closely monitored for adverse reactions. Coadministration of brentuximab vedotin with rifampin, a potent CYP3A4 inducer, reduced exposure to MMAE by approximately 46%.

The effects of brentuximab vedotin on embryogenesis, reproduction, and spermatogenesis in humans are unknown. In addition, data about the effects of brentuximab vedotin in pregnant women are unavailable. Please see Section 6.5 for appropriate precautions triggered by the administration of study medication.

2. STUDY OBJECTIVES

2.1 Primary Objective

- To compare the modified progression-free survival (mPFS) obtained with brentuximab vedotin (ADCETRIS®) plus AVD (abbreviated A+AVD) versus that obtained with ABVD for the frontline treatment of advanced classical HL

2.2 Secondary Objectives

The key secondary objective is

- To determine if A+AVD improves OS versus that obtained with ABVD

Other secondary objectives are:

- To determine if A+AVD improves CR rate versus that obtained with ABVD
- To determine the safety profile of A+AVD relative to that of ABVD
- To determine the event-free survival (EFS) obtained with A+AVD and ABVD
- To determine the disease-free survival (DFS) rate obtained with A+AVD and ABVD
- To determine if A+AVD improves overall ORR (defined as CR + PR) versus that obtained with ABVD
- To determine the DOR and duration of complete remission (DOCR) obtained in the A+AVD and ABVD arms
- To determine the rate of patients receiving irradiation for HL not in CR in the A+AVD and ABVD arms
- To determine the rate of patients in CR at the end of frontline therapy in the A+AVD and ABVD arms
- To determine the rate of Cycle 2 PET negativity in patients treated with A+AVD versus those treated with ABVD
- To determine if A+AVD improves health-related quality of life (HRQOL) versus ABVD

- To describe the PK of brentuximab vedotin, MMAE, and total antibody (TAb) in blood
- To determine the immunogenicity of brentuximab vedotin

2.3 Exploratory Objectives

The exploratory objectives are:

- To investigate any differences in lung-specific patient-reported outcomes (PROs) between the treatment arms
- To assess any impact of brentuximab vedotin dosing on serum concentrations of AVD
- To investigate any differences between the treatment arms in the rate of patients alive without HL at 3 and 5 years (see Section 8.1.6.3 for definition)
- To assess changes in tumor biomarker expression before and after treatment

[redacted]

- To assess other PROs
- To assess medical resource utilization
- To assess fertility

3. STUDY ENDPOINTS

3.1 Primary Endpoints

The primary endpoint is

- Modified PFS per IRF assessment using the Revised Response Criteria for Malignant Lymphoma

3.2 Secondary Endpoints

The key secondary endpoint is

- OS

Other secondary endpoints are:

- Rate of CR as best overall response achieved at the end of randomized regimen (A+AVD or ABVD) per IRF assessment using the Revised Response Criteria for Malignant Lymphoma
- AEs, SAEs, assessments of clinical laboratory values, and vital sign measurements
- EFS
- DFS
- ORR
- DOR per IRF
- DOCR per IRF
- The rate of patients not in CR that received irradiation
- CR rate per IRF at the end of frontline therapy
- The rate of Cycle 2 PET negativity
- PRO per European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30

- PK parameters for brentuximab vedotin, MMAE, and TAb
- The presence of antitherapeutic antibodies (ATA) to brentuximab vedotin

3.3 Exploratory Endpoints

The exploratory endpoints are:

- PRO per FACIT-Dyspnea 10
- Serum concentrations of AVD in a subset of ABVD- and A+AVD-treated patients, respectively
- Percent of patients alive without HL at 3 and 5 years
- Percent of patients switching therapy post Cycle 2 pre-End of Treatment (EOT)

- PRO per FACT-Ntx (Abbreviated)
- Patient-reported health utility values per EQ-5D
- Utilization of medical resources
- Incidence of pregnancy (patients or partners of patients) in each treatment arm at time of study closure

4. STUDY DESIGN

4.1 Overview of Study Design

This open-label, randomized, 2-arm, multicenter, phase 3 study has the primary objective of comparing the mPFS obtained with A+AVD against that obtained with ABVD. For this study, the definition of PFS has been modified to include the receipt of anticancer chemotherapy or radiotherapy for patients not in CR after the completion of frontline therapy as a progression event in addition to the customary events of disease progression or death due to any cause (a definition of completion of frontline therapy is provided in Table 8-1).

The study will enroll approximately 1240 patients; enrollment is anticipated to last 3 years. All enrolled patients must have a histologically-confirmed diagnosis of Stage III or IV classical HL that has not been previously treated with systemic chemotherapy or radiotherapy. Patients will be stratified by region (Americas vs Europe vs Asia) and number of International Prognostic Factor Project (IPFP) risk factors (0-1 vs 2-3 vs 4-7). (IPFP risk factors are listed in Section 15.5.)

Patients will be randomized 1:1 into 1 of 2 treatment arms, for a total of approximately 620 patients per arm:

- A+AVD: Brentuximab vedotin 1.2 mg/kg plus doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, dacarbazine (DTIC) 375 mg/m^2.
- ABVD: Doxorubicin 25 mg/m^2, bleomycin 10 units/m^2, vinblastine 6 mg/m^2, dacarbazine (DTIC) 375 mg/m^2.

A+AVD and ABVD will be administered intravenously on Days 1 and 15 of each 28-day cycle. Brentuximab vedotin will be administered intravenously over 30 minutes at a dose of 1.2 mg/kg; the brentuximab vedotin infusion is to be started within approximately 1 hour after completion of AVD therapy. Patients may receive up to 6 cycles of therapy (A+AVD or ABVD).

Response to treatment and disease status assessments will be evaluated according to the Revised Response Criteria for Malignant Lymphoma[25] by an IRF that will be blinded to patients' treatment. Tumor measurements will be assessed (CT and PET scans) at screening, after completion of Cycle 2 (Cycle 2 Day 25 ±1 day), and at 3 to 7 weeks after the last dose of frontline therapy. CT scans only will be used for the disease assessment follow-up,

performed every 3 months during the first year of posttreatment disease follow-up, then every 6 months until study closure (5 years after the last patient is enrolled). If, for any reason other than death or documented disease progression, a patient discontinues randomization therapy (A+AVD or ABVD) after Cycle 2 Day 25 but before completion of randomization therapy, every effort must be made to obtain PET and CT scans prior to initiation of subsequent therapy for HL. Responses and relapses will be assessed by an IRF. Evaluations will be performed until progressive disease (PD) is documented, receipt of second-line anticancer therapy for HL (including chemotherapy or radiation), death occurs, or the end of study. Patients will be followed for survival until death or for a minimum of 5 years after enrollment of the last patient.

Deauville scoring (see Section 15.6) per IRF will be used to evaluate the results of patients' Cycle 2 Day 25 PET/CT. Patients whose disease earns a Deauville score of 4 or less will continue study drug treatment according to their randomized arm (ABVD or A+AVD). Patients whose PET-positive disease earns a score of 5 may, at the investigator's discretion, receive an alternative regimen (physician's choice) for the remainder of planned frontline therapy. Patients with a Deauville score of 5 who, at investigator's discretion, are taken off study drug will be continue to be followed for response assessment; switching therapy prior to completion of frontline therapy will not be considered an mPFS progression event. Of further note, any switch in therapy prior to completion of frontline therapy will not be considered an mPFS event.

An interim futility analysis will be conducted when the first approximately 348 patients have completed the regimen to which they were randomized (ie, received the planned study drug regimen with no more than 2 missed doses of A+AVD or ABVD) or have discontinued treatment prior to completion. The final analysis of the mPFS primary endpoint will be conducted when 260 mPFS events occur; an interim analysis of OS will also be conducted at that time. The final analysis of OS will be conducted when 112 deaths occur, approximately 4 years after randomization of the last patient.

Safety will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03, effective 14 June 2010,[26] and by measuring changes from baseline in the patient's vital signs, ECOG performance status, electrocardiogram (ECG), and clinical laboratory results. Safety data will be periodically reviewed by an independent data monitoring committee (IDMC) per the IDMC charter.

Patient-reported outcomes will be evaluated using the EORTC QLQ-C30, the FACIT-Dyspnea 10 questionnaire, the EQ-5D questionnaire, and the abbreviated Functional Assessment of Cancer Therapy—Neurotoxicity (FACT-Ntx; Abbreviated).

Relationships between plasma levels of brentuximab vedotin, soluble CD30, and CD30 expression on lymphoma cells will be assessed. A possible dose response for any such effects as well as the presence of ATAs may be subsequently examined.

Patients may discontinue therapy at any time. Patients will attend the EOT visit 30 (±7) days after completion of their last dose of frontline therapy.

4.2 Number of Patients

Approximately 1240 patients (approximately 620 patients per treatment arm) will be randomized in this study from approximately 250 study centers globally.

4.3 Duration of Study

Patients will be screened within 4 weeks of randomization, receive a maximum of six 28-day cycles of A +AVD or ABVD treatment (approximately 6 months), and will have follow-up disease assessments performed until study closure for a minimum of 5 years.

It is expected that the study will last approximately 60 months to reach the final analysis of the mPFS endpoint (approximately 36 months of enrollment plus 24 months of additional follow-up after the last patient is randomized). Patients will be followed for survival until death or the end of posttreatment follow-up (when 112 deaths occur, approximately 4 years from the date of the last patient randomized), whichever occurs first. The total study duration is approximately 7 years.

5. STUDY POPULATION

Eligible patients with treatment-naïve advanced classical HL will be randomized to receive either A +AVD or ABVD.

5.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be randomized to treatment:

1. Male or female patients 18 years or older.

2. Treatment-naïve, HL patients with Ann Arbor Stage III or IV disease (refer to Section 15.1).

3. Patients must have histologically confirmed classical HL according to the current World Health Organisation Classification (nodular sclerosis, mixed cellularity, lymphocyte rich, lymphocyte depleted, or classical Hodgkin lymphoma, NOS [not otherwise specified]).

4. ECOG performance status ≤2 (refer to Section 15.2).

5. Patients must have bidimensional measurable disease as documented by radiographic technique (spiral CT preferred) per the International Working Group Revised Criteria for Response Assessment for Malignant Lymphoma (Cheson 2007).[25]

6. Female patients who:

   - Are postmenopausal for at least 1 year before the screening visit, OR
   - Are surgically sterile, OR
   - If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 6 months after the last dose of study drug, or
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

   Male patients, even if surgically sterilized (ie, status postvasectomy), who:

   - Agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

7. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

8. Suitable venous access for the study-required blood sampling, including PK sampling.

9. Clinical laboratory values as specified below within 7 days before the first dose of study drug:

   - Absolute neutrophil count ≥1,500/µL unless there is known HL marrow involvement
   - Platelet count ≥75,000/µL unless there is known HL marrow involvement
   - Total bilirubin must be <1.5 × the upper limit of normal (ULN) unless the elevation is known to be due to Gilbert syndrome.
   - ALT or AST must be <3 × the upper limit of the normal range. AST and ALT may be elevated up to 5 times the ULN if their elevation can be reasonably ascribed to the presence of HL in liver.
   - Serum creatinine must be <2.0 mg/dL and/or creatinine clearance or calculated creatinine clearance >40 mL/minute (refer to Section 15.3).
   - Hemoglobin must be ≥8 g/dL.

5.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be randomized to treatment.

1. Nodular lymphocyte predominant Hodgkin lymphoma

2. Female patients who are both lactating and breastfeeding or who have a positive serum pregnancy test during the screening period or a positive pregnancy test on Day 1 before first dose of study drug

3. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol

4. Known cerebral or meningeal disease (HL or any other etiology), including signs or symptoms of PML

5. Symptomatic neurologic disease compromising normal activities of daily living or requiring medications

6. Any sensory or motor peripheral neuropathy

7. Any active systemic viral, bacterial, or fungal infection requiring systemic antibiotics within 2 weeks prior to first study drug dose

8. Prior immunosuppressive chemotherapy, therapeutic radiation, or any immunotherapy (eg, immunoglobulin replacement, other monoclonal antibody therapies) within 12 weeks of first study drug dose

9. Known hypersensitivity to recombinant proteins, murine proteins, or to any excipient contained in the drug formulation of brentuximab vedotin or any component of ABVD

10. Known human immunodeficiency virus (HIV) positive

11. Known hepatitis B surface antigen-positive, or known or suspected active hepatitis C infection

12. Diagnosed or treated for another malignancy within 3 years before the first dose or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

13. Any of the following cardiovascular conditions or values within 6 months before the first dose of study drug:

    - A left-ventricular ejection fraction <50%
    - Myocardial infarction within 2 years of randomization
    - New York Heart Association (NYHA) Class III or IV heart failure (see Section 15.4).

- Evidence of current uncontrolled cardiovascular conditions, including cardiac arrhythmias, congestive heart failure (CHF), angina, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities

6. STUDY DRUG

All protocol-specific criteria for administration of study drug must be met and documented prior to drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The components of ABVD used in this study will be supplied by the study site and will be billed to patients and/or their third-party payer (insurance) and/or the sponsor according to local regulations unless otherwise arranged between the study site and sponsor. Brentuximab vedotin will be supplied by the study sponsor.

Treatment for advanced HL has improved over the past 30 years with combination chemotherapy regimens. The current anthracycline-containing regimen of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) has been proven superior to alkylating agent regimens and results in a long-term cure rate of approximately 70% in patients with advanced disease. Although combination regimens have successfully been expanded to up to 8 chemotherapeutic agents in attempts to increase overall response, these additional agents have also produced increased toxicity. ABVD thus remains the standard of care in many regions.

However, of the four agents in ABVD, bleomycin is the agent most associated with unpredictable, life-threatening toxicity, and is thought to have the lowest single-agent activity.[15] Standard practice in patients who develop BPT is to continue frontline therapy with AVD while omitting bleomycin. Retrospective analyses of CALGB 8251 and 8952 have shown no difference in response or relapse rates for patients who had bleomycin discontinued at any point in their frontline therapy.[16] Due to the proven antitumor activity and manageable safety profile of brentuximab vedotin monotherapy, substituting brentuximab vedotin for bleomycin (A+AVD) is hypothesized to provide a PFS improvement over the standard ABVD regimen and eliminate the risk of BPT.

6.1 ABVD Administration

ABVD consists of doxorubicin 25 mg/m^2, bleomycin 10 units/m^2, vinblastine 6 mg/m^2, and dacarbazine (DTIC) 375 mg/m^2.

- **A**: Doxorubicin: 25 mg/m^2 will be administered by IV infusion on Days 1 and 15 of each 28-day cycle
- **B**: Bleomycin: 10 units/m^2 will be administered by IV infusion on Days 1 and 15 of each 28-day cycle
- **V**: Vinblastine: 6 mg/m^2 will be administered by IV infusion on Days 1 and 15 of each 28-day cycle
- **D**: Dacarbazine (DTIC): 375 mg/m^2 will be administered by IV infusion on Days 1 and 15 of each 28-day cycle

  ABVD is to be administered in the stated order, per institutional guidelines. If an investigator needs to choose a different order of administration of the study drugs, this must first be discussed with the CRO and/or the Millennium project clinician. The order of administration must not be changed for the 50-patient subset in each treatment arm from whom additional PK samples are to be obtained (see Section 7.4.19).

6.2 A+AVD Administration

A+AVD consists of brentuximab vedotin (ADCETRIS®) 1.2 mg/kg plus doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, and dacarbazine (DTIC) 375 mg/m^2.

- **A**: Doxorubicin: 25 mg/m^2 will be administered by IV infusion on Days 1 and 15 of each 28-day cycle
- **V**: Vinblastine: 6 mg/m^2 will be administered by IV infusion on Days 1 and 15 of each 28-day cycle
- **D**: Dacarbazine (DTIC): 375 mg/m^2 will be administered by IV infusion on Days 1 and 15 of each 28-day cycle

AVD is to be administered first, in the stated order, per institutional guidelines. If an investigator needs to choose a different order of administration of the study drugs, this must

first be discussed with the CRO and/or the Millennium project clinician. The order of administration must not be changed for the 50-patient subset in each treatment arm from whom additional PK samples are obtained (see Section 7.4.19).

Brentuximab vedotin is to be administered after AVD:

- **A**: brentuximab vedotin (ADCETRIS): 1.2 mg/kg will be administered by IV infusion over approximately 30 minutes on Days 1 and 15 of each 28-day cycle; the infusion is to start approximately 1 hour after the conclusion of the dacarbazine administration.

  In the absence of infusion toxicities, the infusion rate for all patients must be calculated in order to achieve a 30-minute (approximate) brentuximab vedotin infusion period.

  Brentuximab vedotin must not be administered as an IV push or bolus. It must be administered through a dedicated IV line and cannot be mixed with other medications.

  The dose of brentuximab vedotin is 1.2 mg/kg. Dosing is based on patients' weight according to the institutional standard; however, doses will be adjusted for patients who experience a ≥10% change in weight from baseline. Actual weight will be used except for patients weighing greater than 100 kg; dose will be calculated based on 100 kg for these individuals. The dose will be rounded to the nearest whole number of milligrams.

  Further brentuximab vedotin administration information can be found in the Pharmacy Binder.

No routine pre- or post-medications are required for A+AVD therapy.

6.3 Dose-Modification Guidelines

6.3.1 Recommended Brentuximab Vedotin Dose Modifications for Treatment-Associated Toxicity

Table 6-1 details the recommended brentuximab vedotin dose modifications to be enacted in the event of treatment-associated toxicity. Please also refer to Section 6.3.2 for criteria pertinent to ABVD and AVD dose modifications.

Table 6-1 Recommended A+AVD Dose Modifications for Treatment-Associated Toxicity

Toxicity	≤Grade 2		≥Grade 3	
Nonhematologic (excluding neuropathy)	Continue at same dose level.		Hold A+AVD dosing until toxicity has resolved to ≤Grade 2 or has returned to baseline.[a]	
Hematologic	Continue at same dose level.		For neutropenia, manage with growth factors (granulocyte colony stimulating factor [G-CSF] or granulocyte-macrophage colony stimulating factor [GM-CSF]) per institutional guidelines. For thrombocytopenia, consider platelet transfusion and/or proceed according to institutional guidelines. For anemia, manage per institutional guidelines.	
Peripheral neuropathy	**Grade 1** Continue at same dose level.	**Grade 2** Reduce dose to 0.9 mg/kg and resume treatment; if already at 0.9 mg/kg, continue dosing at that level.	**Grade 3** Withhold brentuximab vedotin until toxicity is ≤Grade 2, then reduce dose to 0.9 mg/kg and resume treatment. If already at 0.9 mg/kg, consult with sponsor (AVD may be continued or held concurrently at physician's discretion.)	**Grade 4** Discontinue brentuximab vedotin

a Patients who develop clinically insignificant Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption.

6.3.2 Reference Therapy Dose Modifications

ABVD or AVD treatment should be modified or discontinued per applicable label/Summary of Product Characteristics (SmPC) instructions.

6.3.3 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Any investigational agent other than brentuximab vedotin.

- Any frontline anticancer treatment for remission induction other than ABVD or AVD (unless on the basis of a Cycle 2 Day 25 PET Deauville score of 5 as noted in Section 6.4).

- The concomitant use of brentuximab vedotin and bleomycin has resulted in increased pulmonary toxicity versus bleomycin alone. Coadministration of brentuximab vedotin and bleomycin is contraindicated.

6.4 Permitted Concomitant Medications and Procedures

The following medications and procedures are allowed during the study:

- For patients with a Deauville score of 5 upon Cycle 2 Day 25 PET scanning, physician's choice of alternative therapy is permitted, but not required, for the remainder of frontline treatment.

- Radiotherapy based on end-of-frontline therapy PET scanning: Patients in PR upon completion of frontline chemotherapy with PET-positive disease may receive radiotherapy.

- The use of topical, inhalational and ophthalmic steroids is permitted. Corticosteroids are permitted as part of a chemotherapy premedication regimen or for the treatment of HL per institutional standards.

- Patients may receive concomitant hormonal therapy provided they have been on a stable dosage for at least 1 month prior to enrollment. No restrictions are placed upon the use of birth control.

- The use of platelet and/or red blood cell supportive growth factors or transfusions when applicable is allowed.

- The use of colony stimulating factors for the treatment of neutropenia per institutional practice is permitted during therapy.

6.5 Precautions and Restrictions

Infusion-Related Reactions

All infusions should be administered at a site properly equipped and staffed for anaphylaxis should it occur. Medications for treatment of hypersensitivity reactions, such as

epinephrine, antihistamines, and steroids, should be available for immediate use in the event of a reaction during administration and also during the observation period following the first brentuximab vedotin infusion.

Pregnancy

It is not known what effects brentuximab vedotin has on human pregnancy or development of the embryo or fetus, and ABVD is known to have deleterious effects on pregnancy. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing of the informed consent form through 6 months after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

6.6 Management of Clinical Events

Nausea and/or Vomiting

Although this study will not require prophylactic antiemetics, there is no prohibition against their use.

Diarrhea

Prophylactic antidiarrheals will not be used in this protocol; however, patients will be instructed to take antidiarrheal medication(s) at physician's discretion until they are diarrhea-free for at least 12 hours. Fluid intake should be maintained to avoid dehydration.

Infusion-Related Reactions

Infusion-related reactions may occur during the infusion of brentuximab vedotin. The infusion should be administered at a site properly equipped and staffed to manage an infusion-related reaction, including anaphylaxis should it occur. The patient should be observed for approximately 60 minutes following the first infusion of brentuximab vedotin. During this observation period, the IV line should remain open for at least 1 hour to allow administration of IV drugs if necessary. All supportive measures consistent with optimal patient care will be given throughout the study according to institution standards. Medications for infusion-related reactions, such as epinephrine and antihistamines should be available for immediate use.

Patients who experience a Grade 1 or 2 infusion-related reaction may receive subsequent brentuximab vedotin infusions with premedication consisting of acetaminophen (650 mg orally) and diphenhydramine (25-50 mg orally or 10-25 mg IV) or according to institutional standards, administered 30 to 60 minutes prior to each 30-minute brentuximab vedotin infusion.

Peripheral Neuropathy

AEs of peripheral neuropathy will be monitored closely throughout the study. These events may include, but are not limited to peripheral sensory neuropathy, peripheral motor neuropathy, paresthesia, hypoesthesia, polyneuropathy, muscular weakness, and demyelinating polyneuropathy. Such events, regardless of seriousness, will be followed for all changes in severity until the sooner of resolution to baseline or study closure, and recorded in the eCRF. Events that are higher than Grade 1 will result in brentuximab vedotin dose modification as shown in Table 6-1.

Suspected Progressive Multifocal Leukoencephalopathy (PML)

Signs and symptoms of PML may include altered mental status; motor deficits, such as hemiparesis or ataxia; visual disturbances; or higher cortical dysfunction, such as dysphasia or agnosia. Seizures have also been reported in patients with PML (approximately 20%). The onset of neurological deficits may occur over weeks to months. See the IB for further details.

If PML is suspected, hold further brentuximab vedotin dosing and undertake a diagnostic workup that may include (but is not limited to):

- Neurologic examinations, as warranted.
- Brain magnetic resonance imaging (MRI): Features suggestive of PML include presence of unifocal or multifocal lesions, mainly of the white matter, which are typically nonenhancing and do not have mass effect.
- Polymerase chain reaction (PCR) analysis: JCV DNA detectable in cerebrospinal fluid or there is evidence of JCV in a brain biopsy.
- Neurology consultation.

If PML is confirmed, permanently discontinue treatment with brentuximab vedotin.

6.7 Blinding and Unblinding

This is an open-label study; investigators and patients will know the individual treatment assignments. However, aggregate efficacy data will be blinded to the sponsor's study team, investigators, and patients throughout the study conduct. The IRF will be blinded to treatment assignments.

6.8 Description of Investigational Agents

Brentuximab vedotin for Injection is a sterile, preservative-free, white to off-white lyophilized cake for reconstitution for IV administration. Brentuximab vedotin for Injection is supplied in single-use, Type 1 borosilicate glass vials with FluroTec®-coated butyl rubber stoppers and aluminum seals. Each vial of the product contains brentuximab vedotin, trehalose, sodium citrate, and polysorbate 80. The lyophilized product, after reconstitution with 10.5 mL sterile Water for Injection, United States Pharmacopeia (USP) or an equivalent standard, yields 11 mL of brentuximab vedotin solution (5 mg/mL).

6.9 Preparation, Reconstitution, and Dispensation

Brentuximab vedotin is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling brentuximab vedotin.

Recommended safety measures for handling and preparation include masks, protective clothing, gloves, and vertical laminar airflow safety cabinets.

Study treatment vials are single-use containers. Any partially used vials or diluted dosing solutions are to be discarded using appropriate institutional drug disposal procedures.

Study treatment must be reconstituted with the appropriate amount of sterile water for injection (see the Pharmacy Manual for details). GENTLY swirl the vial until the contents are completely dissolved. **The vial must not be shaken or vigorously swirled**; excess agitation may cause aggregate formation. Visually inspect the reconstituted drug product for any particulate matter and discoloration.

The appropriate amount of reconstituted study treatment will be withdrawn from the vial(s) and diluted in an infusion bag according to the instructions provided in the Pharmacy Manual. Refer to the Pharmacy Manual for more specific instructions on drug preparation.

6.10 Packaging and Labeling

Vials of study treatment will be packaged in cardboard kits. Each kit will contain 1 vial of investigational product. Vials and kits will be labeled to meet country-specific regulatory requirements.

6.11 Storage, Handling, and Accountability

Brentuximab vedotin

Vials containing study treatment must be refrigerated at 2°C to 8°C in a secure location (eg, locked room) accessible only to the pharmacist, the investigator, or a duly designated person.

Study treatment does not contain preservatives; therefore, opened and reconstituted vials of study treatment must be used within 24 hours when stored under refrigeration at 2°C to 8°C. Reconstituted study treatment should not be stored at room temperature. It is recommended that study treatment vials and solutions be protected from direct sunlight until the time of use. **Reconstituted vials must not be shaken**.

Drug accountability instructions are provided in the Pharmacy Binder.

Bleomycin

Bleomycin may be sourced locally by the clinical sites when 1) arrangements have been made and agreed to by Millennium and the clinical sites and 2) local and regional regulations are met.

Please refer to the appropriate package insert for information regarding the proper storage and handling of bleomycin.

Bleomycin must be kept in an appropriate, limited-access, secure place until it is dispensed to study enrollees, returned to the sponsor, or forwarded to the sponsor's designee for destruction.

The investigator must maintain 100% accountability for all bleomycin received from the study sponsor and dispensed during his or her entire participation in the study. Drug accountability instructions can be found in the Pharmacy Binder. Drug supplies will be counted and reconciled at the site before being returned.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

7. STUDY CONDUCT

This trial will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

7.1 Study Personnel and Organizations

The contact information for the Millennium project clinician for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator for each member state/country, the independent radiologic review facility, the interactive voice response system (IVRS) / interactive web response system (IWRS) provider, known as IXRS®, and the contract research organization (CRO) team may be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

7.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/independent ethics committee (IEC). It is not envisioned that prisoners (or other populations that might be subject to coercion or exploitation) will be enrolled into this study.

7.3 Treatment Group Assignments

Patients will be randomized to receive either A+AVD or ABVD. Patients will be stratified by region (Americas vs Europe vs Asia), and number of IPFP risk factors (0-1 vs 2-3 vs 4-7).

7.4 Study Procedures

Refer to the Schedule of Events for timing of assessments. Additional details are provided as necessary in the sections that follow.

7.4.1 Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

7.4.2 Patient Demographics

The date of birth, race, ethnicity, and sex of the patient are to be recorded during screening.

7.4.3 Medical History

During the Screening period, a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy and include a description of prior therapies for it. In addition, concomitant medications will be recorded as specified in Section 7.4.8.

7.4.4 Physical Examination

A physical examination will be completed per standard of care at the times specified in the Schedule of Events.

7.4.5 Patient Height, Weight, and Body Surface Area

Height will be measured only during screening (within 28 days before the first dose of study drug). Weight and body surface area (BSA) will be determined to support dosing at the times specified in the Schedule of Events (see Section 15.7).

7.4.6 Vital Signs

Vital sign measurements include seated (after 3-5 minutes in this position) measurements of diastolic and systolic blood pressure, heart rate, and body temperature.

7.4.7 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at screening and at Cycle 1 Day 1. The results from this test must be available and negative before the first dose of study drug is administered. If Cycle 1 Day 1 serum pregnancy results will not be available before dosing, a urine pregnancy test must be performed. Pregnancy tests may also be repeated during the study if requested by an IEC/IRB or if required by local regulations.

7.4.8 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will recorded in the electronic case report form (eCRF) from date of informed consent through 30 days after completion of frontline therapy. See Section 6.3.3 and Section 6.4 for a list of medications and therapies that are prohibited and/or allowed during the study.

7.4.9 Adverse events

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the Schedule of Events. All events relating to peripheral neuropathy, regardless of seriousness, will be followed for all changes in severity until the resolution to baseline or study closure, whichever occurs first, and recorded in the eCRF. Refer to Section 10 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs.

The occurrence of PML, malignancies other than classical HL, and changes in severity of events related to peripheral neuropathy will be recorded as described in Section 10.

7.4.10 Enrollment

A patient is considered to be enrolled in the study when randomized to a treatment arm.

Procedures for completion of the enrollment information are described in the Study Manual.

7.4.11 Electrocardiograms

A 12-lead ECG will be administered at the time points specified in the Schedule of Events.

7.4.12 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed centrally. Decisions regarding eligibility for this study may be made using local laboratory determinations. For dosing decisions, local hematology and chemistry laboratory results may be used.

Handling and shipment of clinical laboratory samples will be outlined in the Study Manual.

Clinical laboratory evaluations will be performed as outlined below.

Clinical Chemistry and Hematology

Blood samples for analysis of the following clinical chemistry and hematological parameters will be obtained as specified in the Schedule of Events.

Hematology

- Hemoglobin
- Hematocrit
- Platelet (count)
- Leukocytes with Differential
- Neutrophils (absolute neutrophil count [ANC])

Serum Chemistry

- Blood urea nitrogen (BUN)
- Creatinine
- Bilirubin (total)
- Urate
- Lactate dehydrogenase (LDH)
- Gamma glutamyl transferase (GGT)
- Phosphate
- Albumin
- Alkaline phosphatase (ALP)
- AST
- ALT
- Glucose
- Sodium
- Potassium
- Calcium
- Chloride
- Carbon dioxide (CO_2)
- Magnesium

Other

- Hemoglobin A1C

7.4.13 Disease Assessment

Response to treatment and disease status assessments will be evaluated according to the Revised Response Criteria for Malignant Lymphomas.[25] These disease assessments will be performed by investigators and a blinded IRF at times specified in the Schedule of Events. In addition, patients' disease status following Cycle 2 and at EOT will be assessed per IRF by PET scan using the Deauville criteria (Section 15.6); an IRF assessment using the Deauville criteria will also be made if an unscheduled PET scan is obtained. Investigator assessments using the Deauville criteria are not required.

If, for any reason other than death or documented disease progression, a patient discontinues randomization therapy (A+AVD or ABVD) after Cycle 2 Day 25 but before completion of randomization therapy, every effort must be made to obtain PET and CT scans prior to initiation of subsequent therapy for HL.

MRI scans may be substituted for CT scans only if a patient 1) has a glomerular filtration rate of less than 60 mL/min such that IV contrast presents a risk of renal failure, 2) develops anaphylaxis to IV contrast, or 3) becomes pregnant during posttreatment follow-up. If use of MRI is required, a consistent scanning modality must be maintained. Further detail may be found in the Imaging Manual.

All subsequent anticancer therapies will be recorded, regardless if they are initiated before or after progressive disease. For patients whose frontline therapy is switched to physician's choice, regimen details will be recorded. Subsequent anticancer therapy during the posttreatment follow-up is discussed in Section 7.10.

B symptom assessments, including fever, night sweats, and weight loss, will be evaluated at the time points indicated in the Schedule of Events.

Bone marrow assessments are not required for this study. However, if bone marrow biopsies are obtained at baseline or during the course of the study, the results of each bone marrow assessment should be recorded. Similarly, if cytology results of any kind are obtained (eg, from malignant ascites) they should be recorded.

7.4.14 Patient-Reported Outcomes

Questionnaires (FACIT-Dyspnea 10-item short form, FACT-Ntx; Abbreviated, EORTC QLQ-C30) will be administered as specified in the Schedule of Events and must be completed before study drug is administered. For patients who discontinue study drug, the scheduled collection of patient-reported outcomes (PRO) data should continue until the patient discontinues scheduled study visits.

7.4.15 Utility Measurement

The EuroQOL EQ-5D is a 5-item questionnaire with a "thermometer" visual analog scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state) that will be administered as specified in the Schedule of Events. The utility measurement should be collected until the sooner of development of confirmed PD or 3 years after the last dose of frontline therapy.

7.4.16 Medical Resource Utilization Data Collection

All medical care encounters will be collected for all patients until study closure. Each time an AE or unscheduled physician visit occurs, medical resource utilization (MRU) data will be captured. Examples of data to be collected are number of medical care encounters, such as hospital admissions or major diagnostic procedures.

7.4.17 Cost Assessment

The cost of treatment in each arm of the study will be assessed through the collection of MRU in each arm in terms of medical resource utilization frequency. Valuation of the costs will be undertaken separately.

7.4.18 Tumor Biopsies

Banked formalin-fixed paraffin-embedded tumor tissue or a minimum of 10 unstained slides of the tumor tissue (ie, tumor tissue obtained at the time of the patient's original diagnosis and/or at the time of subsequent procedures conducted as part of the patient's standard care) will be collected at screening to assess biomarkers implicated in sensitivity or resistance to brentuximab vedotin or vinca alkyloids and taxanes (eg, p53, beta 3 tubulin, and ABCC transporters). The tumor pathology block will be returned to the original site by the sponsor or designee if requested. If the pathology block is not provided, submission of 10 unstained slides will be accepted. See the Laboratory Manual for details. Patients who cannot provide at least 10 histological slides from their diagnostic biopsy will undergo a new tumor biopsy during screening (may be obtained up to 14 days prior to the first dose of study drug).

Efforts should be made to take an additional biopsy when patients randomized to the A+AVD treatment arm have disease relapse. These samples are to be tested for the expression of CD30 and other potential markers of tumor resistance.

7.4.19 Pharmacokinetic Measurements

PK measurements will be made in all brentuximab vedotin-treated patients and a subset of patients in the ABVD arm. PK parameters to be estimated may include the maximum concentration for MMAE (maximum plasma concentration [C_{max}]) and concentration at the end of infusion for brentuximab vedotin (C_{eoi}). Concentrations will be measured and PK parameters also estimated for the intact brentuximab vedotin ADC and TAb. Population PK methodologies will be used to determine PK parameters and covariates in this population. Efficacy parameters will be related to brentuximab vedotin exposure in the patients.

The incidence of ATA to brentuximab vedotin will also be assessed (see Section 7.4.21).

The Schedule of Events presents the sample collection time points. Refer to the Laboratory Manual for information on collection, processing, storage, and shipment of samples.

ATA samples will be taken only at predose Cycle 1, Cycle 2, and Cycle 6 or at termination if treatment is terminated before Cycle 6 (see Section 7.4.21).

Table 7-1 Pharmacokinetic Sampling Time Points

Cycle	Study Day	Time	Window	Relative Time
Full A+AVD Arm				
1-6	1	Predose	Within prior 4 hr	Start of brentuximab vedotin infusion
		EOI (~30 min)	Within 1 hour post EOI	End of brentuximab vedotin infusion
	15	Predose	Within prior 4 hr	Start of brentuximab vedotin infusion
		EOI (~30 min)	Within 1 hour post EOI	End of brentuximab vedotin infusion
1 and 3, in addition	2	24 hr	±4 hr	Start of brentuximab vedotin infusion
	3	48 hr	±4 hr	Start of brentuximab vedotin infusion
Additional Sampling for 50-Patient Subset of A+AVD Arm				
1 and 3	1	2 min	±2 min	End of doxorubicin infusion
		2 min	±2 min	End of vinblastine infusion
		2 min	±2 min	End of dacarbazine infusion
		1 hr	±5 min	End of brentuximab vedotin infusion
		6 hr	±10 min	End of brentuximab vedotin infusion
	8	168 hr	±24 hr	End of brentuximab vedotin infusion
Additional Sampling for 50-Patient Subset of ABVD Arm				
1 and 3	1	Predose	Within prior 4 hr	Start of doxorubicin infusion
		2 min	±2 min	End of doxorubicin infusion
		2 min	±2 min	End of vinblastine infusion
		2 min	±2 min	End of dacarbazine infusion
		1 hr	±5 min	End of dacarbazine infusion
		6 hr	±10 min	End of dacarbazine infusion
	2	24 hr	±4 hr	End of dacarbazine infusion
	8	168 hr	±24 hr	End of dacarbazine infusion

Abbreviations: A+AVD=brentuximab vedotin (ADCETRIS®) plus doxorubicin, vinblastine, and dacarbazine; ABVD=doxorubicin, bleomycin, vinblastine, and dacarbazine; EOI=end of infusion; hr=hour; min=minutes.

The 50 patients in each treatment arm from whom additional PK samples are obtained will be recruited from sites that agree to participate. Further, approximately 20 patients in each 50-patient intensive-sampling group must be Asian.

7.4.20 Serum Biomarkers

Blood for serum samples will be collected as specified in the Schedule of Events to measure circulating biomarkers such as soluble CD30 (sCD30), thymus- and activation-regulated chemokine (TARC), cutaneous T-cell-attracting chemokine (CTACK), and interleukin-6 (IL-6). Previous research has demonstrated a relationship between circulating sCD30 concentration and overall tumor burden.[27] A decrease in sCD30 may reflect a decrease in overall tumor burden. The Reed-Sternberg cells characteristic of classical HL produce high concentrations of TARC that correlate with increased T-cell infiltration of tumor tissue.[28] Further, previous phase 2 clinical studies of brentuximab vedotin showed [redacted]

Biomarkers such as sCD30, TARC, and IL-6 may be measured on Day 1 of all cycles and at the EOT visit. Baseline values and changes in these markers may be compared to efficacy. In addition, the possible impact of sCD30 concentrations on PK will be explored.

The timing of the blood samples may be changed and/or the number of samples reduced if emerging data indicate that changes to the sampling scheme are needed to better characterize the effects of brentuximab vedotin. Details regarding the preparation, handling, and shipping of samples are provided in the Study Manual.

7.4.21 Immunogenicity Measurements

Blood for serum samples will be collected as specified in the Schedule of Events to evaluate antitherapeutic antibody (ATA) and neutralizing ATA as a PK and safety assessment. On dosing days, the blood samples for ATA and neutralizing ATA assessment must be collected before dosing. Neutralizing ATA assessment will be performed only for ATA-positive samples. Immunogenicity parameters will be assayed only for patients who receive at least 1 brentuximab vedotin dose.

7.4.22 Germline DNA Polymorphism Assessment

For patients on the A+AVD arm only, an optional blood sample will be collected on Day 1 of Cycle 1, before dosing, to examine genotyping variations in the germ line genes of the disease pathway, drug mechanism, and drug clearance proteins, such as CD30, tubulin, Fc_{neo}, and Fcγ receptors.

7.4.23 Fertility Assessment

The incidence of pregnancy in each treatment arm will be assessed at the time of study closure. Any pregnancy occurring in patients or their partners from the date of first dose until the date of study closure should be reported.

7.5 Completion of Treatment

Patients will be considered to have completed study treatment if they:

- Complete frontline treatment (see Table 8-1), or
- Experience PD or die prior to completion of frontline treatment

7.6 Completion of Study

Patients will be considered to have completed the study if they meet both of the following criteria:

- Complete 6 cycles of frontline treatment
- Have 5 years of follow-up or have died

Regardless of the duration of treatment, all patients will remain on study for follow-up following the last dose of study treatment until they withdraw consent for further follow-up, are lost to follow-up, have been followed for 5 years from randomization, or until study closure. The study is expected to close approximately 7 years after the first patient starts study treatment. Posttreatment follow-up is further described in Section 7.10.

For patients who do not complete 6 treatment cycles, please see the Schedule of Events for details of follow-up assessments.

7.7 Discontinuation of Treatment With Study Drug, and Patient Replacement

Study drug must be permanently discontinued for patients meeting any of the following criteria:

- Completed 6 cycles of A+AVD or ABVD
- Investigator deems it is in the patient's best interest to discontinue

The primary reason for study treatment withdrawal must be documented.

Patients who discontinue from study treatment will remain on study for follow-up unless they withdraw consent for the follow-up phase of the study. All randomized patients will be followed until study closure (see Section 7.6).

Patients who are randomized to a treatment arm but do not receive study drug for any reason will not be replaced.

Treatment with study drug may also be discontinued for any of the following reasons:

- AE
- Protocol violation
- PD
- Unsatisfactory therapeutic response
- Study terminated by sponsor
- Withdrawal by subject
- Lost to follow-up
- Other

Once study drug has been discontinued, all study procedures outlined for the EOT visit will be completed as specified in the Schedule of Events. The primary reason for study drug discontinuation will be recorded on the eCRF.

Note that some patients may discontinue study drug for reasons other than PD before completing the full treatment course (eg, after Cycle 2 based on a Deauville score of 5); these patients will remain in the study for posttreatment assessments as outlined in the Schedule of Events until disease progression occurs.

7.8 Withdrawal of Patients From Study

A patient may be discontinued from the study (during treatment cycle or follow-up) for any of the following reasons:

- Lost to follow-up
- Study terminated by sponsor
- Withdrawal by subject
- Death
- Other

The consequence of study withdrawal is that no new information will be collected from the withdrawn patient and added to the existing data or any database.

Millennium or their designee must be notified in writing if a patient is withdrawn from study treatment or from the study. The reason(s) for withdrawal must be documented in the patient's medical records. The investigators will make every reasonable effort to keep each patient on the study until all planned treatments and assessments have been performed. If a patient withdraws from study treatment, every attempt should be made to follow the patient until death or administrative study closure. Final treatment assessments will be performed before any other therapeutic intervention if possible. Additionally, any planned alternative treatments should be documented on the patient's medical records and CRF.

7.9 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

7.10 Posttreatment Follow-up Assessments

Posttreatment follow-up for all patients consists of a physical exam, B symptom assessment, selected QOL assessments as specified in the Schedule of Events, medical resource utilization, CT scan, and collection of survival/disease status and anticancer treatment for HL. Information regarding new primary malignancies will be recorded. All assessments except CT scans are to be performed every 3 months until 36 months after the EOT and then

every 6 months until the first of disease progression or study closure. CT scans are required every 12 weeks (±1 week) until 12 months of PTFU and then every 6 months (±2 weeks) until study closure. For patients who have PD, survival/disease status and information regarding the initiation of an alternative lymphoma treatment may be obtained by phone call. To support fertility assessment, any pregnancy occurring in patients or their partners from the date of first dose until the date of study closure should be reported.

Patients who stop treatment for any reason other than PD will continue to have mPFS follow-up visits until the occurrence of PD; the patient withdraws consent for further follow-up; or, the start of another anticancer therapy for patients not in CR after completion of frontline therapy.

Patients will be followed for survival until 5 years from the date of the last patient randomized, or death, whichever occurs first. Survivor information may be collected by methods that include, but are not limited to, telephone, e-mail, mail, or retrieved from online or other databases (eg, social security indexes). In addition, the start of another anticancer therapy will be collected.

See the Schedule of Events for appropriate assessments during follow-up.

NOTE: Related SAEs must be reported to the Millennium Department of Pharmacovigilance & Risk Management or designee. This includes deaths that the investigator considers related to study drug that occur during the posttreatment follow-up. Refer to Section 10 for details regarding definitions, documentation, and reporting of SAEs.

8. STATISTICAL AND QUANTITATIVE ANALYSES

8.1 Statistical Methods

In general, summary tabulations will be presented by treatment arm and will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent per category for categorical data. The Kaplan-Meier survival curves and 25th, 50th (median), and 75th percentiles will be provided along with their 2-sided 95% CIs for time-to-event data.

The statistical methods are outlined below; analysis details will be provided in the statistical analysis plan (SAP). The SAP will be written by Millennium and will be finalized prior to the formal interim analysis.

Deviations from the statistical analyses outlined in this protocol will be indicated in the SAP; any further modifications will be noted in the final clinical study report.

8.1.1 Determination of Sample Size

The primary endpoint of the study is mPFS, and the study is powered on the following assumption: a 2-year mPFS of 81% for patients in the A+AVD treatment group versus 73% for patients in the ABVD treatment group (HR=0.67; assuming a decrease in the PFS event rate after 2 years). A total of 260 mPFS events will provide 90% power to detect a hazard ratio of 0.67 at a 1-sided significance level of 0.025 using a log-rank test. Approximately 1240 patients will be randomized to achieve (with 95% probability) 260 mPFS events in approximately 60 months, assuming 36 months of accrual, a 5% annual dropout rate, and 24 months of mPFS follow-up after last patient in.

8.1.2 Randomization and Stratification

The randomization scheme will be generated by Millennium. Prior to dosing, a randomization number will be assigned to each patient. The randomization schedule also includes the study specific identifiers (company name, protocol name, and protocol number) and the date and time the schedule was generated.

Patients will be randomized in an overall ratio 1:1 to A+AVD or ABVD. Patients will be stratified by region (Americas vs Europe vs Asia) and number of IPFP risk factors (0-1 vs 2-3 vs 4-7).

8.1.3 Populations for Analysis

The populations used for analysis will include the following:

- Safety population: patients who receive at least 1 dose of study drug will be used for all safety analyses. All patients in the safety population will be analyzed according to the actual treatment received.

- Intent-to-Treat (ITT) population: all patients randomized to treatment. All patients in the ITT population will be analyzed according to the treatment they were randomized to receive and not according to what they actually received, if different.

- Per-Protocol (PP) population: a subset of ITT patients who do not have a major protocol violation as determined by the project clinician. All decisions to exclude patients from the PP population will be made prior to database lock.

- Response-Evaluable population: all patients with diagnosis as confirmed by an independent pathology review facility, with measurable disease at baseline, who receive at least 1 dose of study drug, and have at least 1 postbaseline response assessment.

- PK population: patients with sufficient dosing and PK data to reliably estimate PK parameters as determined by a clinical pharmacologist. The PK population will be used for PK analyses.

- Pharmacodynamics population: patients with sufficient dosing and sufficient pharmacodynamics data to reliably measure pharmacodynamics parameters will be used for pharmacodynamics analyses.

8.1.4 Procedures for Handling Missing, Unused, and Spurious Data

All available efficacy and safety data will be included in data listings and tabulations. The relevance of missing sample data will be assessed. Details on any sensitivity analyses and data handling details regarding issues such as missing data will be discussed in the SAP.

Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

8.1.5 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized, including gender, age, race, weight, height, BSA, primary diagnosis, and other parameters as appropriate. No inferential statistics will be carried out.

8.1.6 Efficacy Analysis

All efficacy evaluations will be conducted using the ITT population unless otherwise specified.

8.1.6.1 Analysis of Primary Efficacy Endpoint

Modified PFS per IRF will be used for the primary efficacy analysis.

Modified Progression-Free Survival

As PET-negative CR is the expected therapeutic outcome in frontline HL, the definition of PFS has been modified to reflect current standards of care. Modified PFS per IRF will be analyzed based on the ITT population using a stratified log-rank test. Modified PFS is defined as the time from the date of randomization to the date of the first of (1) documentation of PD; (2) death due to any cause; (3) for patients who are confirmed noncomplete responders per IRF, receipt of anticancer chemotherapy or radiotherapy for HL after completion of frontline therapy, as defined in Table 8-1; these patients' mPFS event date will be the date of the first PET scan post completion of frontline therapy demonstrating the absence of a CR, defined as a Deauville score of ≥3.

Table 8-1 Completion of Frontline Therapy

Treatment History	Completion of Frontline Therapy
Did not switch therapy	Upon receipt of planned study drug regimen with no more than 2 missed doses of A+AVD or ABVD[a]
Switched therapy before completion of A+AVD or ABVD	Upon conclusion of 1 alternative anticancer regimen[b] for HL subsequent to A+AVD or ABVD discontinuation

a A "missed dose" refers to administration of the full study regimen of either A+AVD or ABVD. Patients may miss individual agents within the A+AVD or ABVD regimen (such as patients who discontinue bleomycin for pulmonary toxicity) without this counting as a missed dose.

b Receipt of chemotherapy OR radiation.

Patients without a documented mPFS event at the time of analysis (defined as PD/relapse, subsequent anticancer therapy for residual disease after completion of planned frontline therapy for HL, or death) will be censored at the date of last response assessment. Detailed handling rules for missing assessments and censoring for the analysis of mPFS will be described in Section 5.8.1.2 of the SAP.

Modified PFS will be tested at a 1-sided 0.025 level at the final analysis.

In addition, a stratified Cox regression model will be used to estimate the hazard ratio and the 95% CI for the treatment effect. The Kaplan-Meier survival curves, 25th, 50th (median), and 75th percentiles (if estimable), along with their 2-sided 95% CIs, will also be presented for each treatment arm.

Sensitivity analyses for mPFS per IRF will be performed using the PP population. Modified PFS per IRF using different censoring approaches will be also analyzed in the ITT population. Details of different censoring approaches and further sensitivity analyses of

mPFS will be included in the SAP. Modified PFS per investigator will also be analyzed similarly using the ITT population.

8.1.6.2 Analyses of Secondary Efficacy Endpoints

Overall survival is designated as a key secondary endpoint. It will be tested at 1-sided 0.025 level when the test of mPFS is statistically significant at the final analysis.

Overall Survival

OS is defined as the time from the date of randomization to the date of death. Patients without documented death at the time of analysis will be censored at the date last known to be alive.

Two formal analyses will be performed for OS. An OS interim analysis will be performed at the time of the final mPFS analysis, and the final analysis of OS will be performed when 112 deaths have occurred, assuming 5-year OS rates for the A+AVD and ABVD arms are 91% and 88%, respectively (HR=0.75). Overall type I error will be controlled using the O'Brien-Fleming method with a Lan-DeMets alpha-spending function.

Stratified log-rank testing will be used to compare OS between the 2 treatment arms. The hazard ratios along with the 95% CIs will be estimated using a stratified Cox regression model. The Kaplan-Meier method will be used to estimate the distribution of the OS endpoint for each treatment. Median survival times (if estimable), along with the 2-sided 95% CIs will be presented. Analysis of OS will be performed based on the ITT population.

Other Secondary Efficacy Endpoints

CR per IRF will be analyzed based on the ITT population. CR rate per IRF is defined as the proportion of patients who achieve CR at the end of treatment with randomized regimen (A+AVD or ABVD) as determined by an IRF. CR rates between the 2 treatment arms will be compared using a stratified Cochran-Mantel-Haenszel (CMH) test. A logistic regression model will be used to estimate the treatment effect in terms of odds ratio. The odds ratio and its associated 95% CIs will be presented. Sensitivity analyses for CR per IRF will be performed using the response-evaluable population. CR rate per investigator will also be analyzed similarly using the ITT population.

Comparison of the ORR between the 2 treatment groups will be conducted using the stratified Cochran-Mantel-Haenszel test. The 95% CI of the difference of the response rates

between the 2 treatments will also be provided. ORR per IRF will be analyzed based on the ITT population.

Similar analyses will be conducted to compare the rate of patients that received consolidating irradiation between the 2 treatment arms.

CR rate at the end of frontline therapy will be assessed similarly to CR rate at the end of treatment with randomized regimen.

DOR in subjects with confirmed response is the time between first documentation of response and disease progression. DOCR in subjects with confirmed CR is the time between first documentation of CR and disease progression. DOR and DOCR per IRF will be analyzed based on the ITT population.

EFS is defined as the time from randomization until any cause of treatment failure: disease progression, premature discontinuation of treatment for any reason, or death due to any cause, whichever occurs first. Analyses of EFS will be performed based on the ITT population.

DFS is defined as the time from CR to disease progression or to death from lymphoma or acute toxicity from treatment. Analyses of DFS will be performed based on the subset of the ITT population achieving a CR.

The same analyses will be applied to these time-to-event endpoints as those described for OS above.

8.1.6.3 Exploratory Endpoints

Alive without HL rate at 3 years and 5 years is defined as the proportion of patients who are alive without classical Hodgkin lymphoma at 3 years or 5 years after the patient's randomization date.

Alive without lymphoma rates between the 2 treatment arms will be compared using a stratified Cochran-Mantel-Haenszel (CMH) test.

8.1.7 Analyses of Patient-Reported Outcomes and Health Economics

Analyses of PROs and health economics will be performed using the ITT population.

8.1.7.1 Patient-Reported Outcomes Analysis

PRO assessments based on the QLQ-C30 will be analyzed to determine if treatments affect PRO scores. Analyses of PRO scores including global health status will be performed using longitudinal models. All subscales and individual item scores will be tabulated. Descriptive summaries of observed data will be provided at each scheduled assessment time point. PRO assessments based on FACIT Dyspnea 10 and FACT-Ntx Abbreviated; will be analyzed using the same methods as QLQ-C30.

Initially, the manuals for scoring and handling missing data published for QLQ-C30, FACIT Dyspnea 10, and FACT-Ntx Abbreviated; will be used. Further investigation of missing patterns and details of imputation will be discussed in SAP.

8.1.7.2 Health Economics Analysis Using Medical Resource Utilization and Utility

EQ-5D-3L scores will be summarized in descriptive statistics for treatment groups.

MRU data will be summarized in descriptive statistics for hospitalization (length of stay, inpatient, outpatient, and reason), number of missing days from work or other activities by patient, and care-giver, by treatment group.

8.1.8 Pharmacokinetics/Pharmacodynamics/Biomarkers

Pharmacokinetic Analysis

The PK of the antibody-drug conjugate (brentuximab vedotin), total antibody, and unconjugated drug (MMAE) will be based on serum or plasma samples collected from patients who meet study inclusion criteria, received study drug, and provided evaluable PK data. Population PK parameters will be calculated with an appropriate method based on a validated PK analysis program. Exploratory safety-PK, efficacy-PK, and if possible, PK-pharmacodynamic relationships will be determined.

Descriptive statistics (eg, number of patients, mean, standard deviation, median, minimum, and maximum) will be used to summarize concentrations of analyte for brentuximab vedotin-treated patients.

The pharmacokinetics of doxorubicin, vinblastine, and dacarbazine will be compared between the treatment arms. Descriptive statistics (eg, number of patients, mean, standard deviation, median, minimum, and maximum) will be used to summarize concentrations of

analyte. Geometric mean ratios of the AUC will be calculated for each AVD component (doxorubicin, vinblastine, and dacarbazine).

Immunogenicity Analysis

All patients who were administered at least 1 dose of brentuximab vedotin will be evaluated for antitherapeutic antibody (ATA) development. A list/table of ATA status will be provided. Antibody neutralizing status (neutralizing or not neutralizing) will also be listed for patients who have positive antibody status.

Immunogenicity information, including ATA and neutralizing ATA, will be summarized in descriptive statistics as applicable.

Relationships between ATA development and safety and efficacy will be explored.

Biomarkers

Absolute and change from baseline value of circulating biomarkers will be summarized by time point using descriptive statistics, as applicable. Descriptive statistics (eg, number of patients, mean, standard deviation, median, minimum, maximum) will also be provided to summarize disease markers [redacted]), tissue levels of potential resistance markers [redacted], and qualitative and semiquantitative measures of markers [redacted]), and change from baseline values of these markers, as applicable. The association between these and clinical response or safety endpoints might be explored. These analyses will be detailed in the SAP.

8.1.9 Safety Analysis

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the safety population. Exposure to frontline therapy and reasons for discontinuation will be tabulated.

Treatment-emergent AEs that occur after administration of the first dose of study drug and through 30 days after the last dose of frontline therapy will be tabulated.

AEs will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) and will include the following categories:

- Treatment-emergent AEs
- Drug-related treatment-emergent AEs
- Grade 3 or higher treatment-emergent AEs
- Grade 3 or higher drug-related treatment-emergent AEs
- The most commonly reported treatment-emergent AEs (ie, those events reported by ≥10% of all patients)
- SAEs

A listing of treatment-emergent AEs resulting in frontline therapy discontinuation will be provided.

Descriptive statistics for the actual values of clinical laboratory parameters (and/or change from baseline in clinical laboratory parameters) will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters.

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs and weight over time will be tabulated by scheduled time point.

Shift tables for laboratory parameters will be generated based on changes in NCI CTCAE grade from baseline to the worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst postbaseline values, may be used to understand the safety profile of patients' frontline therapies.

All concomitant medications collected from screening through the study period will be classified to preferred terms according to the World Health Organization (WHO) drug dictionary.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of patients' frontline therapies.

Electrocardiogram Analysis

Investigators' assessments of ECG monitoring (normal, abnormal and clinically significant, or abnormal and not clinically significant), including unscheduled or retested measurements, will be presented in a listing.

8.1.10 Interim Analyses

Two formal interim analyses (IAs) are planned for this study.

The first IA to be performed is a futility analysis. CR rate will be analyzed when the first approximately 348 patients have completed the regimen to which they were randomized (ie, received the planned study drug regimen with no more than 2 missed doses of A+AVD or ABVD) or have discontinued treatment prior to completion.

Recommendation by the IDMC whether to terminate the study based on this IA will be determined upon evaluation of the overall safety information and efficacy data, specifically if the CR rate per IRF for the A+AVD arm is at least 5% lower than that of the ABVD arm, and trends in mPFS and other efficacy endpoints suggest inferior efficacy in the A+AVD arm.

Enrollment will continue during the first IA.

An IA for OS is also planned to occur at the time of the final mPFS analysis. Overall type I error for OS will be controlled using the O'Brien-Fleming method with a Lan-DeMets alpha-spending function.

9. STUDY COMMITTEES

9.1 Data Safety Monitoring Board

An IDMC will review safety and efficacy data at the interim analysis. The IDMC will provide a recommendation regarding study continuation based on the safety and efficacy parameters. In the event that the study is terminated early based on an IDMC recommendation, Millennium will notify the appropriate regulatory authorities.

Additionally, the IDMC will periodically review safety data per the IDMC charter. The first formal safety review will occur after the first 100 patients have completed 2 cycles

(8 weeks) of treatment or discontinued prior to completing 2 cycles of treatment. Subsequently, IDMC safety reviews will be performed periodically per the IDMC charter.

10. ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

10.1.3 Serious Adverse Event Definition

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).

- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).

- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).

- Is a **congenital anomaly/birth defect**.

- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE v4.03, effective 14 June 2010.[26] Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic

procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs and serious pretreatment events (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Millennium Department of Pharmacovigilance & Risk Management or designee (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. All SAEs and serious pretreatment events (which include all deaths) must be reported whether or not considered causally related to the study drug or study procedures. The SAE Form, created specifically by Millennium, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious pretreatment event may be requested by Millennium or designee. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information

[redacted]

US and Canada

Toll-Free Fax #: [redacted]
E-mail: [redacted]

All Other Countries (Rest of World)

Fax #: [redacted]
E-mail: [redacted]

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

Intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE v4.03, effective 14 June 2010.[26] The criteria are provided in the Study Manual.

Relationship to study drug administration will be determined by the investigator responding yes or no to this question: Is there a reasonable possibility that the AE is associated with the study drug?

Sponsor Responsibilities

The IB will be used as the resource for determining expectedness of SAEs for brentuximab vedotin.

Millennium will ensure that all relevant information regarding suspected, unexpected serious adverse reactions (SUSARs) that are fatal or life threatening is recorded and reported as soon as possible to the competent authorities in all the member states concerned, and to the IEC, and in any case no later than 7 days after knowledge by Millennium of such a case. The relevant follow-up information will subsequently be communicated within an additional 8 days or as required by country regulations.

All other SUSARs will be reported as required to the competent authorities and IEC as soon as possible but within a maximum of 15 days after Millennium becomes aware of the event.

10.3 Monitoring of Adverse Events and Period of Observation

AEs, both nonserious and serious (which include all deaths), will be monitored throughout the study as follows:

- AEs will be reported from first dose of frontline therapy through 30 days after administration of the last dose of frontline therapy and recorded in the eCRFs. A diagnosis of a malignancy other than classical HL that occurs at any time prior to study closure must be recorded in the eCRF regardless of causality. Additionally, events of malignancy occurring more than 30 days post the last dose of frontline therapy that are deemed serious and related to study drug must be reported to Millennium Department of Pharmacovigilance & Risk Management or designee on an SAE form. All events relating to peripheral neuropathy, regardless of seriousness, will be followed for all changes in severity until resolution to baseline or study closure, whichever occurs first, and recorded in the eCRF.

- Treatment-related AEs will be reported from first dose of frontline therapy through 30 days after administration of the last dose of frontline therapy and recorded in the eCRFs. Treatment-related AEs must be monitored for resolution through event resolution or study closure.

- Serious pretreatment events will be reported to Millennium Department of Pharmacovigilance & Risk Management or designee from the time of the signing of the ICF up to first dose of frontline therapy, but will not be recorded in the eCRF.

- Related and unrelated SAEs will be reported to Millennium Department of Pharmacovigilance & Risk Management or designee from the first dose of frontline therapy through 30 days after administration of the last dose of frontline therapy and recorded in the eCRF. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). Any SAE that occurs between 30 days post last dose of frontline therapy and study closure that the investigator considers related to study drug must be reported to the Millennium Department of Pharmacovigilance & Risk Management or designee. In addition, events of PML must be reported on an SAE form, regardless of treatment arm or causal relationship, from the first dose of study drug through death or termination of the study by the sponsor.

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance & Risk Management or designee. The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance & Risk Management or designee. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Pregnancy follow-up will continue throughout the posttreatment follow-up period until study closure.

11. ADMINISTRATIVE REQUIREMENTS

11.1 Good Clinical Practice

The study will be conducted in accordance with the ICH-GCP and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and the IB.

11.2 Data Quality Assurance

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study patient. Study data will be entered into an eCRF by site personnel using a secure, validated, web-based electronic data capture (EDC) application. Millennium will have access to all data upon entry in the EDC application.

Study monitors will discuss instances of missing or uninterpretable data with the investigator for resolution. Any changes to study data will be made to the eCRF and documented via an electronic audit trail associated with the affected eCRF.

11.3 Electronic Case Report Form Completion

Millennium or designee will provide the study sites with secure access to and training on the EDC application, sufficient to permit site personnel to enter or correct information in the eCRFs for the patients for whom they are responsible.

eCRFs will be completed for each study patient. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the patient's eCRF.

The investigator, or designated representative, should complete the eCRF as soon as possible after information is collected.

The investigator must provide through the EDC application formal approval of all the information in the eCRFs and changes to the eCRFs to endorse the final submitted data for the patients for which he or she is responsible. The audit trail entry will show the user's identification information and the date and time of the correction.

Millennium, or a designee, will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disk (CD) or other electronic media will be placed in the investigator's study file.

11.4 Study Monitoring

Monitoring and auditing procedures developed or approved by Millennium will be followed to comply with GCP guidelines.

All information recorded on the eCRFs for this study must be consistent with the patient's source documentation. During the course of the study, the study monitor will make study site visits to review protocol compliance, verify eCRFs against source documentation, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The review of medical records will be performed in a manner that ensures that patient confidentiality is maintained.

11.5 Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirement(s) and will adhere to GCP standards. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the patients. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or the sponsor, as allowed by local regulations.

11.6 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

11.7 Patient Confidentiality

To maintain patient privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the patient by initials where permitted and/or by the assigned patient number. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

11.8 Investigator Compliance

The investigator will conduct the trial in compliance with the protocol provided by Millennium and given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Modifications to the protocol are not to be made without agreement of both the investigator and Millennium. Changes to the protocol will require written IRB/IEC approval/favorable opinion before implementation, except when the modification is needed to eliminate an immediate hazard or hazards to patients. Millennium, or a designee, will submit all protocol modifications to the appropriate regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard or hazards to patients, the investigator will contact Millennium, or a designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be documented.

11.9 On-site Audits

Regulatory authorities, the IEC/IRB, and/or Millennium may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

11.10 Investigator and Site Responsibility for Drug Accountability

Accountability for investigational medicinal product at the trial site is the responsibility of the investigator. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and amount returned to Millennium, or a designee (or disposal of the drug, if approved by Millennium) will be maintained by the clinical site. Millennium or its designee will review drug accountability at the site on an ongoing basis.

All material containing study drug will be treated and disposed of in accordance with governing regulations.

11.11 Product Complaints and Medication Errors

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact [redacted] (formerly [redacted]) (see below) and report the

event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error situation should immediately contact [redacted] (see below) and report the event.

For Product Complaints or Medication Errors,
call [redacted] at
[redacted]; Option 1 (toll free)
or
[redacted] (non-toll free)

Product complaints and medication errors in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to [redacted] (refer to Section 10.2).

11.12 Closure of the Study

Within 90 days of the end of the study, the sponsor will notify the competent authorities and the IECs in all member states where the study is being carried out that the study has ended.

Within 1 year of the end of the study, a summary of the clinical trial results will be submitted to the competent authorities and IECs in all member states involved in the study.

Study participation by individual sites or the entire study may be prematurely terminated if, in the opinion of the investigator or Millennium, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Millennium by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements

- Insufficient, incomplete, and/or unevaluable data
- Determination of efficacy based on interim analysis
- Plans to modify, suspend or discontinue the development of the study drug

Should the study be closed prematurely, the site will no longer be able to access the EDC application, will not have a right to use the EDC application, and will cease using the password or access materials once their participation in the study has concluded. In the event that any access devices for the EDC application have been provided, these will be returned to Millennium once the site's participation in the study has concluded.

Within 15 days of premature closure, Millennium must notify the competent authorities and IECs of any member state where the study is being conducted, providing the reasons for study closure.

11.13 Record Retention

The investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and Millennium notified.

12. USE OF INFORMATION

All information regarding brentuximab vedotin supplied by Millennium to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from Millennium. It is understood that there is an obligation to provide Millennium with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of brentuximab vedotin and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

Upon completion of the clinical study and evaluation of results by Millennium, the hospital or institution and/or investigator may publish or disclose the clinical trial results pursuant to the terms contained in the applicable Clinical Trial Agreement.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer-reviewed scientific or medical journal. A Publications Group comprising Millennium employees and study investigators will be formed to oversee the publication of the study results, which will reflect the experience of all participating study centers. Subsequently, individual investigators may publish results from the study in compliance with their agreements with Millennium.

A prepublication manuscript or abstract is to be provided to Millennium a minimum of 30 days before the intended submission date of the manuscript or abstract to a publisher. Within 30 days after receipt by Millennium of the notification, Millennium shall inform the study centers whether it has objections to the publication for reasons including, but not limited to, those defined below:

- If patentable subject matter is disclosed, the publication shall be delayed for a period not to exceed 90 days from Millennium's receipt of the proposed publication to allow time for the filing of patent applications covering patentable subject matter.

- If confidential information is contained in any proposed publication or public disclosure, such confidential information will be removed at Millennium's request.

The overall principal investigator will be the last author on abstracts and publications of the data generated from this study. Other authors will be listed according to number of patients enrolled to the study. If the principal investigator has the highest enrollment, he/she may choose to be either first or last author. This policy may be changed with the agreement of both the investigators and Millennium.

13. INVESTIGATOR AGREEMENT

I have read Protocol C25003 Amendment 7: A Randomized, Open-label, Phase 3 Trial of A+AVD Versus ABVD as Frontline Therapy in Patients With Advanced Classical Hodgkin Lymphoma.

I agree to conduct the study as detailed herein and in compliance with International Conference on Harmonisation Guidelines for Good Clinical Practice and applicable regulatory requirements and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____
Principal investigator printed name

_____ _____
Principal investigator signature Date

_____

_____

_____
Investigational site or name of institution and location (printed)

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15. APPENDICES

15.1 Ann Arbor Staging System for Hodgkin Lymphoma

Stage	Definition
I	Involvement of a single lymph node region or lymphoid structure (eg, spleen, thymus, Waldeyer's ring)
II	Involvement of 2 or more lymph node regions on the same side of the diaphragm (the mediastinum is a single site; hilar lymph nodes should be considered "lateralized" and, when involved on both sides, constitute Stage II disease)
III	Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm
III_1	Subdiaphragmatic involvement limited to spleen, splenic hilar nodes, celiac nodes, or portal nodes
III_2	Subdiaphragmatic involvement includes paraaortic, iliac, or mesenteric nodes plus structures in III_1
IV	Involvement of extranodal site(s) beyond that designated as "E" More than 1 extranodal deposit at any location Any involvement of liver or bone marrow
A	No symptoms
B	Unexplained weight loss of >10% of the body weight during the 6 months before staging investigation Unexplained, persistent, or recurrent fever with temperatures >38°C during the previous month Recurrent drenching night sweats during the previous month
E	Localized, solitary involvement of extralymphatic tissue, excluding liver and bone marrow

Source: Harrison's Manual of Medicine, 17th Edition.[29]

15.2 Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.[30]

15.3 Cockcroft-Gault Equation

For male patients:

Creatinine Clearance=[(140-age) (body weight in kg) / (72 × serum creatinine in mg/dL)]

For female patients:

Creatinine Clearance=[(140-age) (body weight in kg) / (72 × serum creatinine in mg/dL)] × 0.85

15.4 New York Heart Association Classification of Cardiac Disease

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.[31]

15.5 International Prognostic Factors Scoring for Advanced Hodgkin Lymphoma

One Point To Be Assigned for Each Prognostic Factor:
Serum albumin <4 g/dL
Hemoglobin <10.5 g/dL
Male sex
Stage IV disease
Age ≥45 years
White cell count ≥15,000 mm^3
Lymphocyte count <600 mm^3 or <8% of white-cell count

Source: A Prognostic Score for Advanced Hodgkin's Disease. Hasenclever D and Diehl V for the International Prognostic Factors Project on Advanced Hodgkin's Disease. NEJM 339; 1998: 1506-15.[32]

15.6 Deauville Criteria for PET

Score	
1	no uptake
2*	uptake ≤mediastinum
3*	uptake >mediastinum but ≤ liver
4	Uptake moderately increased compared to the liver at any site.
5	Uptake markedly increased compared to the liver at any site or/and new sites of disease.

Source: Report on the Second International Workshop on interim positron emission tomography in lymphoma held in Menton, France, 8-9 April 2010. Meignan M, Gallamini A, Haioun C, Polliack A. Leuk Lymphoma 51; 2010:2171-80.[33]

* If mediastinal blood pool activity is equal or greater than liver then the uptake within the lesion should be compared with liver (lesion uptake less than liver=score 2; lesion uptake equal to liver=score 3).

15.7 Body Surface Area Nomogram

Body surface area should be calculated according to institutional guidelines, preferably by using the Mosteller formula standard nomogram.

The Mosteller Formula

$$BSA\ (m^2) = \left([Height(cm) \times Weight(kg)\ ] / 3600 \right)^{1/2}$$

eg, BSA=SQRT([cm*kg]/3600)

or in inches and pounds: $BSA\ (m^2) = \left([Height(in) \times Weight(lbs)\ ] / 3131 \right)^{1/2}$

Adapted from: Mosteller RD. Simplified calculation of body-surface area. N Engl J Med 1987;317(17):1098.[34]

15.8 Amendment 1 Rationale and Purposes

Rationale for Amendment 1

This amendment reduces subjectivity in the assessment of the study's modified progression-free survival (mPFS) primary endpoint and clarifies the sourcing of bleomycin, corrects the posttreatment follow-up disease assessment scanning schedule, and clarifies the sampling schema for serum chemistry, PK, urinalysis, fasting A1C Hb, immunogenicity, and germline DNA.

Purposes for Amendment 1

The purposes of this amendment are to:

- Change the mPFS event date for patients who receive subsequent anticancer chemotherapy in the absence of disease progression. The mPFS event will be recorded as occurring on the date of the first positron emission tomography (PET) scan post completion of frontline therapy demonstrating the absence of a complete remission (CR), defined as a Deauville score of ≥3.
- Specify that Deauville scoring must be performed for the End of Treatment (EOT) PET scan and any unscheduled PET scan to support objective determination of mPFS.
- Clarify that sensitivity analyses around the mPFS endpoint and censoring rules will be described in the Statistical Analysis Plan (SAP).
- Align Section 8.1, Statistical Methods, with Sections 2 (objectives) and 3 (endpoints) with regard to key secondary versus other secondary objectives and endpoints.
- Simplify the bleomycin Storage, Handling, and Accountability rules and permit local sourcing of bleomycin as agreed by the site and sponsor if applicable regulations are met.
- Delete bilirubin subtypes from the Schedule of Events to align with Section 7.4, Study Procedures.
- Add Day 15 PK sampling in the Schedule of Events as already specified in Section 7.4, Study Procedures.
- Delete urinalysis from the Schedule of Events to align with Section 7.4, Study Procedures.
- Remove the option for patients with stable disease to have patient-reported outcomes (PRO) collection via phone from the Schedule of Events to align with Section 7.10.
- Reflect collection of a fasting Day 15 A1C Hb in the footnote accompanying the Schedule of Events table as specified in the table body.
- Remove immunogenicity sampling at screening and restrict immunogenicity sampling at all other time points to patients in the A+AVD arm, only.
- Restrict germline DNA sampling only to patients in the A+AVD arm.
- Restrict post-progression tumor biopsies only to patients in the A+AVD arm in the Schedule of Events to align with Section 7.4.18.

- Correct calendar days of posttreatment follow-up computed tomography (CT) scanning.
- Align pregnancy testing in Section 7.4.7 with the Schedule of Events.
- Clarify collection of and populations for PK sampling.
- Remove requirement for baseline biomarker sampling.
- Correct typographical errors, punctuation, grammar, and formatting.

15.9 Amendment 2 Rationale and Purposes

Rationale for Amendment 2

This amendment seeks to clarify the modified progression-free survival (mPFS) censoring rules, clarify the content and timing of disease and other assessments, and to further align the biostatistical analysis methods section with the existing "other secondary" objectives and endpoints.

Purposes for Amendment 2

The purposes of this amendment are to:

- Refer the reader to the Statistical Analysis Plan (SAP) for censoring rules for the mPFS primary endpoint in the event of missing information
- Describe the biostatistical analysis of complete remission (CR) rate at the end of frontline therapy
- Specify that B symptoms will be assessed
- Clarify that concomitant procedure data will be collected
- Clarify that the "concomitant treatments" recorded during long-term follow-up are anticancer treatments for Hodgkin lymphoma
- Clarify language describing the frequency of posttreatment follow-up assessments, including radiological assessments
- Specify that MRI may be substituted for CT in select circumstances
- Correct typographical errors, punctuation, grammar, and formatting

15.10 Amendment 3 Rationale and Purposes

Rationale for Amendment 3

This amendment seeks to improve the accuracy of the Cycle 2 positron emission tomography (PET)/computed tomography (CT) scan. The timing of the Cycle 2 PET/CT scan was originally scheduled for Cycle 2 Day 20 (±2 days). The scheduled assessment time has been revised to Cycle 2 Day 25 (±1 day) to allow for additional recovery time following the second Cycle 2 dose to decrease the likelihood of a false-positive result related to posttreatment inflammation.

Purposes for Amendment 3

The purposes of this amendment are to:

- Change the scheduled timing of the Cycle 2 PET/CT scan to Day 25 (±1 day)
- Correct typographical errors, punctuation, grammar, and formatting

15.11 Amendment 4 Rationale and Purposes

Rationale for Amendment 4

This amendment seeks to align sites' choice to administer radiotherapy to noncomplete responders at the conclusion of frontline therapy with current clinical practice. It also reduces variation in dose calculations by specifying a single formula for body surface area (BSA) and simplifies blood pressure measurements for ease and increased compliance. It clarifies multiple types of data recording to reduce potential reporting errors and improve the resulting understanding of the studied treatments' safety and efficacy profiles. Last, it aligns certain protocol language with the sponsor's other clinical protocols investigating brentuximab vedotin for greater consistency and ease of use.

Purposes for Amendment 4

The purposes of this amendment are to:

- Allow sites' determination of positron emission tomography (PET) positivity to guide additional radiotherapy for noncomplete responders at the conclusion of frontline therapy, allow radiation to be given for patients with PET-positive residual masses of any size instead of only those with masses of 2.5 cm or larger, and allow sites to select radiation doses as medically appropriate.
- Specify Mosteller's nomogram for calculating BSA
- Require only seated measurements of blood pressure
- Align progressive multifocal leukoencephalopathy (PML) descriptive text across the sponsor's clinical protocols
- Clarify that sites need not perform Deauville assessments of PET scans, which will be performed by an independent review facility
- Specifically describe the recording of data regarding the incidence PML or malignancies other than classical Hodgkin lymphoma (HL), data regarding a switch in frontline therapy, and data regarding unscheduled bone marrow or cytology results
- Remove specific limits on blood sampling volumes for serum biomarkers, immunogenicity, and germline DNA to accommodate small variations among sampling kits
- Remove patient decision as a reason for discontinuing study drug as it is already a reason for study withdrawal
- Clarify that, unless otherwise specified, only those serious adverse events that occur during long term follow-up that are considered related to study drug (instead of "frontline therapy") will be reported.
- Further clarify that pregnancy data will be collected until study closure
- Correct typographical errors, punctuation, grammar, and formatting.

15.12 Amendment 5 Rationale and Purpose

Rationale for Amendment 5

Amendment 5 seeks to eliminate a potential bias in favor of the experimental treatment arm by providing symmetry across the 2 treatment arms in the definition of completion of frontline therapy, which might affect the modified progression-free survival (mPFS) primary endpoint of the study. The amendment also contains minor updates to enhance patient safety, improve protocol clarity and compliance, and align study conduct with the sponsor's current guidelines and practices.

Purposes for Amendment 5

The purposes of this amendment are to:

- **Provide symmetry across the 2 treatment arms in the definition of completion of frontline therapy**:
  - Standardize the definition of a missed dose across the 2 treatment arms to permit investigators, who are best able to determine the adequacy of the delivered regimen and the need to make adjustments for treatment-related toxicity, to omit individual agents from the randomized treatment regimen without this counting as a missed dose.
- **Enhance patient safety**:
  - Add acute pancreatitis and hepatotoxicity to the discussion of potential risks associated with brentuximab vedotin.
  - Require consultation with the contract research organization (CRO) and/or sponsor's project clinician as prerequisite for changing the order of administration of the study drugs and specify that the order of administration must not be changed for the subset of patients from whom additional pharmacokinetic (PK) samples are to be obtained.
  - Permit the prophylactic use of antiemetics during the treatment period of the study.
  - Allow for the use of alternate methods other than the Mosteller formula standard nomogram for the calculation of body surface area (BSA) to ensure that sites using electronic chemotherapy order entry systems are able to comply with the protocol. Electronic chemotherapy order entry systems enhance patient safety by eliminating the potential for manual calculation errors, and should be supported where available.
- **Institute minor modifications in study procedures to enhance clarity and/or facilitate greater compliance with the protocol**:
  - Clarify that the abbreviated version of Functional Assessment of Cancer Therapy-Neurotoxicity (FACT-Ntx Abbreviated) is being used in the study.
  - Revise the anticipated number of study sites globally.
  - Clarify the exclusion criterion pertaining to pulmonary diffusion capacity.
  - Clarify the procedure for supply of study drugs.
  - Clarify the guidelines for reconstitution and disposal of brentuximab vedotin.

  - Clarify the accountability requirements for bleomycin.
  - Remove the requirement for body temperature to be measured orally.
  - Align the pregnancy testing guideline with that in the Schedule of Events.
  - Clarify the guidelines for preparation of unstained slides of tumor tissue to be used for assessment of biomarkers to reflect current practice at some diagnostic facilities.
  - Clarify posttreatment follow-up assessments for patients who do not complete 6 treatment cycles.
  - Clarify the guideline for posttreatment follow-up assessments for mPFS.
  - Stipulate fasting for patients before measurement of blood glucose concentrations; remove the requirement for the patient to fast before measurement of hemoglobin A1C (Hb A1C) concentrations and revise the timing of these measurements to optimize the clinical value of these measurements.
  - Specify that posttreatment patient-reported outcomes (PRO) assessments will not be performed by telephone.
  - Clarify the timing between screening and administration of first dose of study drugs.
  - Clarify that a computed tomography (CT) scan must be performed when patients start an alternate therapy before completion of the randomized treatment regimen (either A+AVD or ABVD).
- **Align study conduct with the sponsor's current guidelines and practices**:
  - Modify contraception language.
  - Define peripheral neuropathy (PN) and PN-related adverse events (AEs) and align the monitoring guidelines for these AEs across the brentuximab vedotin clinical development program.
  - Update the reporting period for serious adverse events (SAEs) to Millennium from 1 working day to 24 hours.
  - Update SAE reporting language to meet regulatory requirements in the European Union (EU) Directive, 2001/20/EC Article 17 parts (a) and (b).
  - Clarify the monitoring and reporting guidelines for treatment-related AEs.
  - Update text pertaining to product complaints and medication errors for commercial products.
  - Revise and update the Serious Adverse Event and Pregnancy Contact Information.
- **Correct typographical errors, punctuation, grammar, and formatting**.

For specific examples of changes in text and where the changes are located, see Section 15.13.

15.13 Amendment 6 Rationale and Purpose

Rationale for Amendment 6

Amendment 6 removes the exclusion criterion pertaining to pulmonary diffusion capacity on the basis of input from study investigators and the study's Steering Committee to better align with standard practice in the treatment of patients with advanced classical Hodgkin lymphoma (HL) and increase the generalizability of the study. Pulmonary carbon monoxide diffusion capacity (DLCO) does not accurately reflect pulmonary reserve, particularly in patients with advanced HL who may have mediastinal and/or pulmonary involvement. Patients who have been excluded from this study on the basis of DLCO have generally been treated with ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine, and dacarbazine), indicating that the exclusion criterion does not reflect current standard practice.

The amendment also contains revised and updated serious adverse event (SAE) reporting contact information.

Purposes for Amendment 6

The purposes of this amendment are to:

- Remove the exclusion criterion pertaining to pulmonary diffusion capacity
- Revise and update the SAE Reporting Contact Information to reflect the change in the sponsor's vendor
- Correct typographical errors, punctuation, grammar, and formatting

For specific examples of changes in text and where the changes are located, see Section 15.14.

15.14 Amendment 7 Detailed Summary of Changes

THE PRIMARY SECTIONS OF THE PROTOCOL AFFECTED BY THE CHANGES IN AMENDMENT 7 ARE INDICATED. THE CORRESPONDING TEXT HAS BEEN REVISED THROUGHOUT THE PROTOCOL.

Purpose: Increase study enrollment.

- Increase the sample size by 200 patients to a total of approximately 1240 enrolled patients, and increase the anticipated enrollment period.

The primary change occurs in Section 4.1, Overview of Study Design:

Formerly read:	The study will enroll approximately ~~1040~~ patients; enrollment is anticipated to last ~~2~~ years.
Now reads:	The study will enroll approximately **1240** patients; enrollment is anticipated to last **3** years.

Sections that also contain this change are:

- Section 4.2, Number of Patients
- Section 8.1.1, Determination of Sample Size
- Protocol Summary

- Increase enrollment to 620 patients per treatment arm, and increase the estimated number of sites to 250 study sites globally.

The primary change occurs in Section 4.2, Number of Patients:

Formerly read:	Approximately ~~1040~~ patients (approximately ~~520~~ patients per treatment arm) will be randomized in this study from approximately ~~200~~ study centers globally~~, including centers in North America, Europe, and Asia~~.
Now reads:	Approximately **1240** patients (approximately **620** patients per treatment arm) will be randomized in this study from approximately **250** study centers globally.

Sections that also contain this change are:

- Section 4.1, Overview of Study Design
- Protocol Summary

- Delete reference to the percentage of the original sample size that was planned for inclusion in the interim futility analysis.

The primary change occurs in Section 4.1, Overview of Study Design:

Deleted text:	An interim futility analysis will be conducted when the first approximately 348 patients ~~(1/3 of overall sample size of 1040 patients)~~ have completed the regimen to which they were randomized (ie, received the planned study drug regimen with no more than 2 missed doses of A+AVD or ABVD) or have discontinued treatment prior to completion.

Section 8.1.10, Interim Analyses also contains this change.

- Revise the projected length of enrollment and follow-up periods.

The primary change occurs in Section 4.3, Duration of Study:

Formerly read:	It is expected that the study will last approximately 60 months to reach the final analysis of the mPFS endpoint (approximately ~~24~~ months of enrollment plus ~~36~~ months of additional follow-up after the last patient is randomized).
Now reads:	It is expected that the study will last approximately 60 months to reach the final analysis of the mPFS endpoint (approximately **36** months of enrollment plus **24** months of additional follow-up after the last patient is randomized).

Sections that also contain this change are:

- Section 8.1.1, Determination of Sample Size
- Protocol Summary

Purpose: Revise the statistical assumptions of mPFS rates for both treatment arms in the study.

The change occurs in Section 8.1.1, Determination of Sample Size:

Formerly read:	The primary endpoint of the study is mPFS, and the study is powered on the following assumption: a ~~3~~-year mPFS of ~~82.5~~% for patients in the A+AVD treatment group versus ~~75~~% for patients in the ABVD treatment group (HR=0.67 assuming ~~exponential distribution~~). A total of 260 mPFS events will provide 90% power to detect a hazard ratio ~~(HR)~~ of 0.67 at a 1-sided significance level of 0.025. Approximately ~~1040~~ patients will be randomized to achieve 260 mPFS events in ~~about~~ 60 months, assuming ~~24~~ months of accrual, a 5% annual dropout rate, and ~~36~~ months of mPFS follow-up after last patient in.

Now reads:	The primary endpoint of the study is mPFS, and the study is powered on the following assumption: a **2**-year mPFS of **81**% for patients in the A+AVD treatment group versus **73**% for patients in the ABVD treatment group (HR=0.67**;** assuming **a decrease in the PFS event rate after 2 years**). A total of 260 mPFS events will provide 90% power to detect a hazard ratio of 0.67 at a 1-sided significance level of 0.025 **using a log-rank test**. Approximately **1240** patients will be randomized to achieve (**with 95% probability**) 260 mPFS events in **approximately** 60 months, assuming **36** months of accrual, a 5% annual dropout rate, and **24** months of mPFS follow-up after last patient in.

- Align the timing of the interim overall survival analysis with that for the final mPFS analysis.

The primary change occurs in Section 8.1.6.2, Analyses of Secondary Efficacy Endpoints:

Deleted text:	An OS interim analysis will be performed at the time of the final mPFS analysis ~~(approximately 3 years after the last patient is enrolled)~~, and the final analysis of OS will be performed when 112 deaths have occurred, assuming 5-year OS rates for the A+AVD and ABVD arms are 91% and 88%, respectively (HR=0.75).

Section 8.1.10, Interim Analyses also contains this change.

- Revise the timing for the final analysis of overall survival.

The primary change occurs in Section 4.1, Overview of Study Design:

Formerly read:	The final analysis of OS will be conducted when 112 deaths occur, approximately ~~5~~ years after randomization of the last patient.
Now reads:	The final analysis of OS will be conducted when 112 deaths occur, approximately **4** years after randomization of the last patient.

Sections that also contain this change are:

- Section 4.3, Duration of Study
- Protocol Summary

Purpose: Institute minor modifications in protocol language to improve protocol clarity and compliance, and align study conduct with the sponsor's current guidelines and practices.

- Clarify and align the posttreatment follow-up assessments for PFS disease status, event-free survival, and overall survival.

The change occurs in the Schedule of Events, footnotes a and j:

Added text:

a. Note: Radiological assessments are only required every 12 weeks (± 1 week) until 12 months of PTFU and then every 6 months until study closure. **To assist with scheduling of visits, patients may begin to align the timing of their follow-up visits with the timing of CT scans during PTFU, when applicable.**

…

j. Response to treatment and disease assessments…

…

- During the follow-up period: every 3 months for the first year and then every 6 months thereafter. **The CT scan time points are calculated from C1D1.**

- Clarify the PK sampling time points for the 50-patient subset in both treatment arms by correcting the study day stated in the protocol.

The primary change occurs in Section 7.4.19, Pharmacokinetic Measurements; Table 7-1.

Formerly read:

Cycle	Study Day	Time	Window	Relative Time
	~~7~~	168 hr	± 24 hr	End of brentuximab vedotin infusion

Now reads:

Cycle	Study Day	Time	Window	Relative Time
	8	168 hr	± 24 hr	End of brentuximab vedotin infusion or End of dacarbazine infusion

The Schedule of Events also contains this change.

- Update the contact information for product complaints and medication errors.

The change occurs in Section 11.11, Product Complaints and Medication Errors:

Formerly read:

Individuals who identify a potential product complaint situation should immediately contact [redacted] (see below) and report the event.

…

Individuals who identify a potential medication error situation should immediately contact [redacted] (see below) and report the event.

For Product Complaints or Medication Errors, call [redacted] at [redacted] ~~(US and International)~~

Now reads:	Individuals who identify a potential product complaint situation should immediately contact [redacted] **(formerly** [redacted]**)** (see below) and report the event. … Individuals who identify a potential medication error situation should immediately contact [redacted] (see below) and report the event. For Product Complaints or Medication Errors, call [redacted] at [redacted] **Option 1 (toll free)** **or** [redacted] **(non-toll free)**

- Add the Global Statistical Lead to the list of approvers for the amended protocol.

The change occurs on the Title Page:

Added text:	[redacted], **Biostatistics Global Statistics**	**Signature**	**Date**

Purpose: Correct typographical errors, punctuation, grammar, and formatting, as applicable.

These changes are not listed individually.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Biostatistics Approval	05-Mar-2015 22:14
[redacted]	Clinical Science Approval	05-Mar-2015 23:32
[redacted]	Clinical Approval	09-Mar-2015 23:27

Protocol Version & Date	Changes (Summarized)
Original Protocol, 29March2012	Not applicable
Amendment 1, 14May2012	• Change the modified progression-free survival (PFS) event date for patients who receive subsequent anticancer chemotherapy in the absence of disease progression. The modified PFS event will be recorded as occurring on the date of the first positron emission tomography (PET) scan post completion of frontline therapy demonstrating the absence of a complete remission (CR), defined as a Deauville score of ≥3 • Specify that Deauville scoring must be performed for the End of Treatment PET scan and any unscheduled PET scan to support objective determination of modified PFS • Clarify that sensitivity analyses around the modified PFS endpoint and censoring rules will be described in the Statistical Analysis Plan (SAP) • Align Section 8.1, Statistical Methods, with Sections 2 (objectives) and 3 (endpoints) with regard to key secondary versus other secondary objectives and endpoints • Simplify the bleomycin Storage, Handling, and Accountability rules and permit local sourcing of bleomycin as agreed by the site and sponsor if applicable regulations are met • Delete bilirubin subtypes from the Schedule of Events to align with Section 7.4, Study Procedures • Add Day 15 pharmacokinetic (PK) sampling in the Schedule of Events as already specified in Section 7.4, Study Procedures • Delete urinalysis from the Schedule of Events to align with Section 7.4, Study Procedures • Remove the option for patients with stable disease to have patient-reported outcomes (PRO) collection via phone from the Schedule of Events to align with Section 7.10 • Reflect collection of a fasting Day 15 haemoglobin A1C (Hb A1C) in the footnote accompanying the Schedule of Events table as specified in the table body • Remove immunogenicity sampling at screening and restrict immunogenicity sampling at all other time points to patients in the A+AVD arm, only • Restrict germline DNA sampling only to patients in the A+AVD arm • Restrict post-progression tumor biopsies only to patients in the A+AVD arm in the Schedule of Events to align with Section 7.4.18 • Correct calendar days of posttreatment follow-up computed tomography (CT) scanning • Align pregnancy testing in Section 7.4.7 with the Schedule of Events • Clarify collection of and populations for PK sampling • Remove requirement for baseline biomarker sampling • Correct typographical errors, punctuation, grammar, and formatting

Amendment 2, 01June2012	• Refer the reader to the SAP for censoring rules for the modified PFS primary endpoint in the event of missing information • Describe the biostatistical analysis of CR rate at the end of frontline therapy • Specify that B symptoms will be assessed • Clarify that concomitant procedure data will be collected • Clarify that the "concomitant treatments" recorded during long-term follow-up are anticancer treatments for Hodgkin lymphoma (HL) • Clarify language describing the frequency of posttreatment follow-up assessments, including radiological assessments • Specify that magnetic resonance imaging may be substituted for CT in select circumstances • Correct typographical errors, punctuation, grammar, and formatting
Amendment 3, 13July2012	• Change the scheduled timing of the Cycle 2 PET/CT scan to Day 25 (±1 day) • Correct typographical errors, punctuation, grammar, and formatting
Amendment 4, 03August2012	• Allow sites' determination of PET positivity to guide additional radiotherapy for noncomplete responders at the conclusion of frontline therapy, allow radiation to be given for patients with PET-positive residual masses of any size instead of only those with masses of 2.5 cm or larger, and allow sites to select radiation doses as medically appropriate • Specify Mosteller's nomogram for calculating body surface area (BSA) • Require only seated measurements of blood pressure • Align progressive multifocal leukoencephalopathy (PML) descriptive text across the sponsor's clinical protocols • Clarify that sites need not perform Deauville assessments of PET scans, which will be performed by an independent review facility • Specifically describe the recording of data regarding the incidence PML or malignancies other than classical HL, data regarding a switch in frontline therapy, and data regarding unscheduled bone marrow or cytology results • Remove specific limits on blood sampling volumes for serum biomarkers, immunogenicity, and germline DNA to accommodate small variations among sampling kits • Remove patient decision as a reason for discontinuing study drug as it is already a reason for study withdrawal • Clarify that, unless otherwise specified, only those serious adverse events (SAEs) that occur during long term follow-up that are considered related to study drug (instead of "frontline therapy") will be reported. • Further clarify that pregnancy data will be collected until study closure • Correct typographical errors, punctuation, grammar, and formatting
Amendment 5, 06February2014	• Provide symmetry across the 2 treatment arms in the definition of completion of frontline therapy: ○ Standardize the definition of a missed dose across the 2 treatment arms to permit investigators, who are best able to determine the adequacy of the delivered regimen and the need to make adjustments for treatment-

	related toxicity, to omit individual agents from the randomized treatment regimen without this counting as a missed dose • Enhance patient safety: o Add acute pancreatitis and hepatotoxicity to the discussion of potential risks associated with brentuximab vedotin o Require consultation with the contract research organization (CRO) and/or sponsor's project clinician as prerequisite for changing the order of administration of the study drugs and specify that the order of administration must not be changed for the subset of patients from whom additional PK samples are to be obtained o Permit the prophylactic use of antiemetics during the treatment period of the study o Allow for the use of alternate methods other than the Mosteller formula standard nomogram for the calculation of BSA to ensure that sites using electronic chemotherapy order entry systems are able to comply with the protocol. Electronic chemotherapy order entry systems enhance patient safety by eliminating the potential for manual calculation errors, and should be supported where available • Institute minor modifications in study procedures to enhance clarity and/or facilitate greater compliance with the protocol: o Clarify that the abbreviated version of Functional Assessment of Cancer Therapy-Neurotoxicity (FACT-Ntx Abbreviated) is being used in the study o Revise the anticipated number of study sites globally o Clarify the exclusion criterion pertaining to pulmonary diffusion capacity o Clarify the procedure for supply of study drugs o Clarify the guidelines for reconstitution and disposal of brentuximab vedotin o Clarify the accountability requirements for bleomycin o Remove the requirement for body temperature to be measured orally o Align the pregnancy testing guideline with that in the Schedule of Events o Clarify the guidelines for preparation of unstained slides of tumor tissue to be used for assessment of biomarkers to reflect current practice at some diagnostic facilities o Clarify posttreatment follow-up assessments for patients who do not complete 6 treatment cycles. o Clarify the guideline for posttreatment follow-up assessments for modified PFS o Stipulate fasting for patients before measurement of blood glucose concentrations; remove the requirement for the patient to fast before measurement of Hb A1C concentrations and revise the timing of these measurements to optimize the clinical value of these measurements o Specify that posttreatment PRO assessments will not be performed by telephone o Clarify the timing between screening and administration of first dose of study drugs

	○ Clarify that a CT scan must be performed when patients start an alternate therapy before completion of the randomized treatment regimen (either A+AVD or ABVD) • Align study conduct with the sponsor's current guidelines and practices: ○ Modify contraception language ○ Define peripheral neuropathy (PN) and PN-related adverse events (AEs) and align the monitoring guidelines for these AEs across the brentuximab vedotin clinical development program ○ Update the reporting period for SAEs to Millennium from 1 working day to 24 hours ○ Update SAE reporting language to meet regulatory requirements in the European Union (EU) Directive, 2001/20/EC Article 17 parts (a) and (b) ○ Clarify the monitoring and reporting guidelines for treatment-related AEs ○ Update text pertaining to product complaints and medication errors for commercial products ○ Revise and update the SAE and Pregnancy Contact Information • Correct typographical errors, punctuation, grammar, and formatting
Amendment 6, 27May2014	• Remove the exclusion criterion pertaining to pulmonary diffusion capacity • Revise and update the SAE Reporting Contact Information to reflect the change in the sponsor's vendor • Correct typographical errors, punctuation, grammar, and formatting
Amendment 7, 02March2015	• Increase study enrollment ○ Increase the sample size by 200 patients to a total of approximately 1240 enrolled patients, and increase the anticipated enrollment period ○ Increase enrollment to 620 patients per treatment arm, and increase the estimated number of sites to 250 study sites globally ○ Delete reference to the percentage of the original sample size that was planned for inclusion in the interim futility analysis ○ Revise the projected length of enrollment and follow-up periods • Revise the statistical assumptions of modified PFS rates for both treatment arms in the study ○ Align the timing of the interim overall survival analysis with that for the final modified PFS analysis ○ Revise the timing for the final analysis of overall survival • Institute minor modifications in protocol language to improve protocol clarity and compliance, and align study conduct with the sponsor's current guidelines and practices ○ Clarify and align the posttreatment follow-up assessments for PFS disease status, event-free survival, and overall survival ○ Clarify the PK sampling time points for the 50-patient subset in both treatment arms by correcting the study day stated in the protocol ○ Update the contact information for product complaints and medication errors ○ Add the Global Statistical Lead to the list of approvers for the amended protocol

	• Correct typographical errors, punctuation, grammar, and formatting, as applicable

STATISTICAL ANALYSIS PLAN

CLINICAL STUDY PROTOCOL C25003
Brentuximab vedotin
A Randomized, Open-label, Phase 3 Trial of A+AVD Versus ABVD as Frontline Therapy in Patients With Advanced Classical Hodgkin Lymphoma

Protocol #: C25003

SAP Version:	Date of Statistical Analysis Plan:
Draft	22 May 2012
Draft	03 March 2015

Approval Signatures

Date	Prepared by: [redacted], Clinical Biostatistics
Date	Reviewed by: [redacted] Clinical Biostatistics
Date	Approved by: [redacted], Oncology Clinical Research

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
A	ADCETRIS™
ABVD	doxorubicin [Adriamycin], bleomycin, vinblastine, dacarbazine
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AUC	area under the plasma concentration versus time curve
AVD	doxorubicin [Adriamycin], vinblastine, dacarbazine
A+AVD	doxorubicin [Adriamycin], vinblastine, dacarbazine, brentuximab vedotin [ADCETRIS™]
BPT	bleomycin pulmonary toxicity
BSA	body surface area
C_{max}	maximum plasma concentration
CO_2	carbon dioxide
CR	complete response
CR(u)	unconfirmed complete response
CT	computed tomography
DNA	deoxyribonucleic acid
DOCR	duration of complete response
DOR	duration of response
ECG	electrocardiogram

Abbreviation	Term
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOS	End of Study (visit)
EOT	End of Treatment (visit)
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IPFP	International Prognostic Factor Project
IPS	[Hasenclever] International Prognostic Score
IRB	institutional review board
IRF	independent review facility
ITT	intent-to-treat
IV	intravenous; intravenously
IVRS	interactive voice response system
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
mPFS	modified progression-free survival
MRI	magnetic resonance imaging
MRU	medical resource utilization
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OS	overall survival
PD	progressive disease (disease progression)
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
QALY	quality-adjusted life year
QOL	quality of life
QTc	rate-corrected QT interval (millisec) of electrocardiograph
SAE	serious adverse event
SD	stable disease
$t_{1/2}$	half-life
T_{max}	first time to maximum plasma concentration
ULN	upper limit of the normal range
V_z	volume of distribution in the terminal phase
WHO	World Health Organization

1. INTRODUCTION

In general, the purpose of the Statistical Analysis Plan (SAP) is to provide a framework that addresses the protocol objectives in a statistically rigorous fashion, with minimized bias or analytical deficiencies. Specifically, this plan has the following purpose:

To prospectively (a priori) outline the types of analyses and data presentations that will addresses the study objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the pharmaceutical industry.

1.1 Study Design

This open-label, randomized, 2-arm, multicenter, phase 3 study has the primary objective of comparing the modified progression-free survival (mPFS) obtained with A+AVD against that obtained with ABVD.

Approximately 1040 patients will be randomized 1:1 into 2 treatment arms:

- A+AVD: Doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, dacarbazine (DTIC) 375 mg/m^2, brentuximab vedotin 1.2 mg/kg
- ABVD: Doxorubicin 25 mg/m^2, bleomycin 10 units/m^2, vinblastine 6 mg/m^2, dacarbazine (DTIC) 375 mg/m^2

ABVD and A+AVD will be administered intravenously on Days 1 and 15 of each 28-day cycle. Brentuximab vedotin will be administered intravenously over 30 minutes at a dose of 1.2 mg/kg; the brentuximab vedotin infusion is to be started within approximately 1 hour after completion of AVD therapy. Patients may receive up to 6 cycles of therapy (ABVD or A+AVD).

Randomization will be stratified by region (Americas versus Europe versus Asia), and number of International Prognostic Factor Project(IPFP) risk factors (0-1 versus 2-3 versus 4-7).

1.2 Study Objectives

Primary Objective:

- To compare the modified progression-free survival (mPFS) obtained with brentuximab vedotin plus AVD (abbreviated A+AVD) versus that obtained with ABVD for the frontline treatment of advanced classical HL

Key secondary objective:

- To determine if A+AVD improves overall survival (OS) versus that obtained with ABVD

Other secondary objectives:

- To determine if A+AVD improves complete remission (CR) rate at the end of randomized regimen versus that obtained with ABVD
- To determine the safety profile of A+AVD relative to that of ABVD
- To determine the event-free survival (EFS) obtained with A+AVD and ABVD
- To determine the disease-free survival (DFS) obtained with A+AVD and ABVD
- To determine if A+AVD improves overall objective response rate (ORR, defined as CR + PR) versus that obtained with ABVD
- To determine the duration of response (DOR) and duration of complete response (DOCR) obtained in the A+AVD and ABVD arms
- To determine the rate of patients receiving irradiation for HL not in CR in the A+AVD and ABVD arms
- To determine the rate of patients in CR at the end of frontline therapy in the A+AVD and ABVD arms
- To determine the rate of Cycle 2 PET negativity in patients treated with A+AVD versus those treated with ABVD

- To determine if A+AVD improves health-related quality of life (HRQoL) versus ABVD
- To describe the PK of brentuximab vedotin, MMAE, and total antibody (TAb) in blood
- To determine the immunogenicity of brentuximab vedotin

Exploratory objectives:

- To investigate any differences in lung-specific patient reported outcomes (PRO) between the treatment arms
- To assess any impact of brentuximab vedotin dosing on serum concentrations of AVD
- To investigate any differences between the treatment arms in the rate of patients alive without HL at 3 and 5 years
- To assess changes in tumor biomarker expression before and after treatment

[redacted]

- To assess other PROs
- To assess medical resource utilization
- To assess fertility

2. POPULATIONS FOR ANALYSIS

2.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population will include all patients randomized to treatment. All patients in the ITT population will be analyzed according to the treatment they were randomized to receive and not according to what they actually received, if different. The

ITT population will be used for all efficacy analyses of efficacy endpoints unless specified otherwise.

2.2 Per-Protocol Population

The Per-Protocol (PP) population will include all randomized patients who do not have major protocol violation as determined by the project clinician. All decisions to exclude patients from the PP population will be made prior to database lock.

The PP population will be used as a supplement to the analysis of the ITT population for the primary efficacy endpoint.

All patients in the PP population will be analyzed according to the actual treatment received. The PP population will be used as supportive analysis for the primary efficacy endpoint mPFS.

2.3 Response-Evaluable Population

The response-evaluable population is defined as a subset of the ITT population with diagnosis as confirmed by an independent pathology review facility, with measurable disease at baseline, who receive at least 1 dose of study drug, and have at least 1 postbaseline response assessment. The response-evaluable population will be used for the analyses of CR rate, overall response rate, and duration of response.

2.4 Safety Population

The safety population will include all enrolled patients who have received at least 1 dose of study medication. All patients in the safety population will be analyzed according to the actual treatment received.

All safety analyses will be performed using the safety population.

2.5 Pharmacokinetics Population

The PK population will include enrolled patients with sufficient dosing and PK data to reliably estimate PK parameters as determined by a clinical pharmacologist. The PK population will be used for PK analyses.

2.6 Pharmacodynamics Population

The pharmacodynamics population will include enrolled patients with sufficient dosing and sufficient pharmacodynamics data to reliably measure pharmacodynamics parameters. The PHARMACODYNAMICS population will be used for pharmacodynamics analyses.

3. HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

Primary hypothesis to be tested:

> The primary null hypothesis is that there is no difference in modified progression-free survival (mPFS) between the 2 treatments of A+AVD and ABVD. The alternative hypothesis is that A+AVD improves mPFS.

Key secondary hypothesis to be tested:

> The null hypothesis is that there is no difference in overall survival (OS) between the 2 treatments of A+AVD and ABVD. The alternative hypothesis is that A+AVD improves OS.

Hypotheses for the secondary endpoints will also be tested.

3.2 Statistical Decision Rules

3.2.1 Testing Significance for Primary Endpoint

Modified PFS will be tested at a 1-sided significance level of 0.025. We will conclude that the A+AVD treatment can improve mPFS compared with the ABVD treatment if the test is statistically significant.

3.2.2 Testing Process and Significance for Key Secondary Efficacy Endpoint

Key secondary endpoint will be tested at 1-sided, 0.025 level only when the test of the primary endpoint (mPFS) is statistically significant. If the test is statistically significant, we will conclude that the A+AVD treatment can make improvement in OS compared with the ABVD treatment.

4. INTERIM ANALYSIS

4.1 Interim Analysis

There will be 2 formal interim analyses in this study.

The first formal interim analysis to be performed is a futility analysis. The CR rate at the end of frontline therapy will be analyzed when the first approximately 348 patients (1/3 of the overall sample size of 1040 patients) have completed the regimen to which they were randomized (ie, received the planned study drug regimen with no more than 2 missed doses of A+AVD or ABVD) or have discontinued treatment prior to completion. Recommendation by the independent data monitoring committee (IDMC) whether to terminate the study based on this interim analysis will be determined upon evaluation of the overall safety information and efficacy data, specifically if the CR rate per independent review facility (IRF) for the A+AVD arm is at least 5% lower than that of the ABVD arm and trends in mPFS and other efficacy endpoints suggest inferior efficacy in the A+AVD arm. This futility analysis does not require adjustment of the type I error.

The second formal interim analysis is for OS to be performed at the time of the final mPFS analysis (260 mPFS events observed, approximately 3 years after the last patient is enrolled). Overall type-I error for OS will be controlled using the O'Brien-Fleming method with a Lan-DeMets alpha spending function, with final OS analysis scheduled forwhen 112 deaths have occurred.

4.2 Independent Data Monitoring Committee (IDMC)

An IDMC will review safety and efficacy data at the interim analyses. The IDMC will provide a recommendation regarding study continuation based on the safety and efficacy parameters. In the event that the study is terminated early based on an IDMC recommendation, Millennium will notify the appropriate regulatory authorities. Detailed information regarding the composition of the IDMC and detailed IDMC procedures will be provided in the IDMC charter.

The first formal safety review will occur after the first 100 patients have completed 2 cycles (8 weeks) of treatment or discontinued prior to completing 2 cycles of treatment. Subsequently, IDMC safety reviews will be performed periodically per the IDMC charter.

5. STATISTICAL METHODOLOGY

In general, summary tabulations will be presented that display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent (of non-missing) per category for categorical data, unless specified otherwise.

5.1 Sample Size Justification

The primary endpoint of the study is mPFS, and the study is powered on the following assumption: a 3-year mPFS of 82.5% for patients in the A+AVD treatment group versus 75% for patients in the ABVD treatment group (HR = 0.67 assuming exponential distribution). A total of 260 mPFS events will provide 90% power to detect a hazard ratio of 0.67 at a 1-sided significance level of 0.025 using a log-rank test. Approximately 1040 patients will be randomized to achieve 260 mPFS events in about 60 months assuming 24 months of accrual, a 5% annual dropout rate, and 36 months of mPFS follow-up after last patient in.

5.2 Randomization and Stratification

The randomization scheme will be generated by Millennium. Prior to dosing, a randomization number will be assigned to each patient. The randomization schedule also includes the study specific identifiers (company name, protocol name, and protocol number) and the date and time the schedule was generated.

Patients will be randomized in an overall ratio of 1:1 to A+AVD or ABVD. Patients will be stratified by region (Americas versus Europe versus Asia), and number of IPFP risk factors (0-1 versus 2-3 versus 4-7).

5.3 Unblinding

This is an open-label study; investigators and patients will know the individual treatment assignments. However, aggregate efficacy data will be blinded to the sponsor's study team, investigators, and patients throughout the study conduct. The IRF will be blinded to treatment assignments.

5.4 Data Handling

5.4.1 Methods for Handling Missing Data

All available efficacy and safety data will be included in data listings and tabulations. Data that are potentially spurious or erroneous will be examined under the auspices of standard data management operating procedures.

In general, missing data will be treated as missing and no data imputation will be applied, unless otherwise specified. For Quality of Life Data, missing elements may be substituted with the average of non-missing items per published methods of analysis.

Last observation carried forward method and multiple imputation method may be considered for some clinical outcomes as deemed appropriate.

5.4.1.1 Missing/Partial Dates in Screening Visit

The following rules apply to dates recorded in the screening visits, with the exception of prior therapies (Section 5.4.1.2).

- If only the day-component is missing, the first day of the month will be used if the year and the month are the same as those for the first treatment. Otherwise, the 15th will be used.

- If only a year is present, and it is the same as the year of the first treatment, the 15th of January will be used unless it is later than the first treatment, in which case the date of the first of January will be used.

- If only a year is present, and it is not the same as the year of the first treatment, the 15th of June will be used, unless other data indicates that the date is earlier.

5.4.1.2 Missing/Partial Dates in Adverse Events/Concomitant Therapies/Subsequent Therapies

Every effort will be made to avoid missing/partial dates in on-study data. If the resolution date of a resolved adverse event (AE) or the stop date of a concomitant therapy is missing, the following rules are to be used unless conflicting data exists: if month and year are present and the day of the month is missing, the last day of the month is imputed. If only a year is present, the 31st of December is used. After imputation, the imputed dates will be

compared against the date of death, if available. If the date is later than the date of death, the date of death will be used as the imputed date instead.

In cases where the onset date of an adverse event is completely or partially missing, the following imputation rules will be used:

1. When month and year are present and the day of the month is missing,
    - If the onset month and year are the same as the month and year of first treatment with study drug, the day of first treatment or the day-component of the resolution date are imputed, whichever is earliest.
    - If the onset month and year are not the same as the month and year of first treatment with study drug, the first day of the month is imputed.
2. When only a year is present, or no components of the onset date are present,
    - If the resolution date is available, the earlier of the resolution date (possibly imputed) and the date of first treatment will be used.
    - If the resolution date is missing, and the onset-year is the same as the year of first treatment with study drug, then the date of first treatment with study drug is used.
    - Otherwise if only a year is present, the 1st of January of that year is imputed.
3. If none of the previous rules can be applied, then the date of first treatment with study drug is imputed as the onset date.

The imputation rules for missing/partial start dates of concomitant therapies will be the same as the above with the exception as follows:

For prior therapy data, no imputation will be done for start dates.

The imputation rules for missing/partial start dates of subsequent therapies recorded as concomitant medications will be the same as the above with exceptions as follows.

1. When month and year are present and the day of the month is missing,
    a. If the month and year of the start date are the same as the month and year of treatment termination, the day of treatment termination or the day-component of the stop date is imputed, whichever is earliest.

b. If the start month and year are not the same as the month and year of treatment termination, the first day of the month is imputed.

2. When only a year is present, or no components of the start date are present, the date will not be imputed.

5.4.1.3 Lab Values Below the Lower Limit of Quantification

If the numeric value of a laboratory test (excluding PK analyses) is not available because it is below the lower limit of quantification (LLOQ), a logical value of < LLOQ should be used whenever applicable. In cases where a numeric value is required, eg, calculating the mean, the LLOQ will be used.

5.4.2 Definition of Baseline Values

Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, but prior to, the start of study drug administration. If a patient is not dosed, the date of randomization will be used.

In the case that laboratory values from both the central lab and local lab are available before randomization, the most recent value from the central lab will be used as baseline, even if the sample date of the central lab result is prior to that of any local lab value.

5.4.3 Windowing of Visits

All data will be categorized based on the scheduled visit at which it was collected. These visit designators are predefined values that appear as part of the visit tab in the eCRF.

5.4.4 Justification of Pooling

All data from all sites will be pooled. Study center or treatment-by-center interaction will not be included in any statistical analysis.

5.4.5 Withdrawals, Dropouts, Lost to Follow-up

No patients will be replaced in this study.

5.5 Patient Disposition

A disposition of patients includes the number and percentage of patients for the following categories: patients in each of the study population, primary reason to discontinue from the

treatment, patients discontinued from the study, and primary reason to discontinue from the study. All percentages will be based on the number of patients in the ITT population.

A listing will present data concerning patient disposition.

5.6 Demographics and Baseline Disease Characteristics

5.6.1 Demographics

Demographic and baseline characteristics will be summarized, including gender, age, race, weight, height, BSA, primary diagnosis, and other parameters as appropriate. No inferential statistics will be carried out.

The formulation for BSA is:

BSA = sqrt(height(cm) x weight (kg) / 3600).

5.6.2 Medical History

Medical history will be listed for all patients.

5.6.3 Baseline Disease Status

Baseline disease status will be summarized by the treatment groups, including disease primary diagnosis, time since initial diagnosis (months), IPFP risk factors, Ann Arbor stage, and baseline Eastern Cooperative Oncology Group (ECOG) performance status.

Patient distribution by stratification factors will also be summarized.

5.7 Treatments and Medications

5.7.1 Concomitant Medications

Concomitant medications will be coded by preferred term using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking concomitant medications will be tabulated.

Concomitant procedures will not be coded, but will be presented in a data listing in the clinical study report (CSR).

5.7.2 Study Treatments

The study treatments for this study are A+AVD and ABVD. ABVD consists of doxorubicin 25 mg/m^2, bleomycin 10 units/m^2, vinblastine 6 mg/m^2, and dacarbazine (DTIC) 375 mg/m^2. A+AVD consists of doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, dacarbazine (DTIC) 375 mg/m^2, and brentuximab vedotin (ADCETRIS) 1.2 mg/kg. A+AVD and ABVD will be administered by IV infusion on Days 1 and 15 of each 28-day cycle, for a total of 6 cycles. Details of study treatments administration is described in the protocol.

5.7.2.1 Extent of Exposure

The exposure to each component of study treatments A+AVD and ABVD will be characterized by total amount of dose taken (mg or units), total number of doses taken, number of treated cycles, numbers and percentages of patients who had 1, 2, …, and 6 treated cycles, and treatment compliance (%) for each treatment group.

A treated cycle is defined as a cycle in which the patient received any amount of study drug.

Prescribed dose is determined by the dose level to which a patient is enrolled at the onset of the study.

Treatment compliance (%) is defined as 100 x (total dose received) / (prescribed dose per cycle x number of treated cycle).

Dosing data will also be presented in a by-patient listing.

5.7.2.2 Treatment Modifications

Action on each component of study treatments A+AVD and ABVD will be summarized by Cycles 1 through 6.

Patients who switch to another frontline therapy before completing A+AVD and ABVD will be summarized by time of switch and by treatment to which they switch.

5.8 Efficacy Analyses

All efficacy evaluations will be conducted using the ITT population unless otherwise specified.

5.8.1 Primary Efficacy Endpoint

The primary endpoint is mPFS (modified progression-free survival) per IRF assessment using the Revised Response Criteria for Malignant Lymphoma.

5.8.1.1 Definition

mPFS is defined as :

The time from the date of randomization to the date of the first of (1) documentation of progressive disease (PD); (2) death due to any cause; (3) for patients who are confirmed non-complete responders per IRF, receipt of anticancer chemotherapy or radiotherapy for HL after completion of frontline therapy, as defined in Table 5-1; these patients' mPFS event date will be the date of the first PET scan post completion of frontline therapy demonstrating the absence of a CR, defined as a Deauville score of ≥ 3.

Table 5-1 Completion of Frontline Therapy

Treatment History	Completion of Frontline Therapy
Did not switch therapy	Upon receipt of planned study drug regimen with no more than 2 missed doses of A+AVD or ABVD[a]
Switched therapy before completion of A+AVD or ABVD	Upon conclusion of 1 alternative anticancer regimen[b] for HL subsequent to A+AVD or ABVD discontinuation

a ABVD-randomized patients experiencing bleomycin-associated pulmonary toxicity may discontinue bleomycin and continue on AVD without this counting as a missed dose.

b Receipt of chemotherapy OR radiation.

5.8.1.2 Handling of Missing Assessment and Censoring for mPFS Primary Analysis

The determination of the date of progression by the IRF will be used for the primary analysis. Sensitivity analyses will also be performed to evaluate the robustness of results.

For the mPFS primary analysis, disease assessment data should be collected according to the intended schedule of assessment, and the date of progression should be assigned based on the time of the first evidence of disease progression regardless of violations and discontinuation of study drug. For those patients who receive new anticancer chemotherapy or radiotherapy for HL after completion of frontline therapy without confirmed noncomplete-response, mPFS will be determined by PD or death. Detailed handling rules for missing assessments and censoring for the analysis of mPFS are presented in **Error! Reference source not found.**.

Table 5-2 Handling of Missing Assessments and Censoring for mPFS Primary Analysis

Situation	Date of Progression or Censoring	Outcome
No baseline and/or no postbaseline assessment, no subsequent anticancer therapy after frontline therapy, no death	Date of Randomization	Censored
Disease progression documented between scheduled visits	Date of next scheduled visit	Progressed
No documented mPFS event	Date of last adequate assessment[a]	Censored
Lost to follow-up, withdraw consent before any documented mPFS event	Date of last adequate assessment[a]	Censored
Treatment discontinuation for undocumented disease progression after the last adequate assessment	Date of last adequate assessment[a]	Censored
mPFS event after more than one missed visit	Date of last adequate assessment[a]	Censored

a Adequate assessment is defined as there is sufficient data to evaluate a patient's disease status.

5.8.2 Primary Efficacy Analysis

Final analysis of mPFS will be performed when approximately 260 mPFS events have been observed, which is estimated to occur around 36 months after the last patient is randomized.

Stratified log-rank testing will be used to compare mPFS between the 2 treatment arms as the primary analysis. The stratification factors include region and number of IPFP risk factors at baseline (Section 5.2). The hazard ratios along with the 95% confidence interval (CI; 2-sided) will be estimated using the stratified Cox model with treatment as the explanatory variable. The Kaplan-Meier (K-M) survival curves and K-M 25th, 50th (median), and 75th percentiles (if estimable) along with the 2-sided 95% CIs will also be provided for each treatment group.

In addition, a stratified Cox regression model will be used to further evaluate the treatment effects on mPFS after adjusting for some prognostic factors. Besides treatment and the stratification factors (Section 5.2), the following prognostic factors will be included in the model simultaneously: age, race (white, non-white), baseline ECOG score, baseline cancer stage, baseline B symptoms, and PET results from Cycle 2. Additional exploratory analyses may be performed if deemed necessary.

For patients with mPFS events, the reasons leading to the determination of mPFS will be tabulated. For patients without mPFS events, the main reason for censoring will also be tabulated.

The proportional hazard assumptions will be examined and sensitivity analysis may be conducted if appropriate.

5.8.2.1 mPFS Sensitivity Analyses

Sensitivity analyses will be performed for mPFS to evaluate the robustness of treatment effects. In the first sensitivity analysis, mPFS based on the investigators' determinations of disease progression will be analyzed in the same manner as the primary analysis. In the second sensitivity analysis, if confirmed non-complete response constitutes the mPFS event, the mPFS event date will be the date of receipt of first dose of second-line therapy. Additional sensitivity analyses for mPFS will be performed based on the alterations of the handling of missing assessment and censoring in Table 5-3, on the basis of 1 alteration at a time, not on combined alterations unless otherwise specified.

Table 5-3 Handling of Missing Assessments and Censoring for mPFS Sensitivity Analysis

Situation	Date of Progression or Censoring	Outcome
Disease progression documented between scheduled visits	Date of documented disease progression	Progressed
Treatment discontinuation for undocumented disease progression after the last adequate assessment	Date of last adequate assessment	Progressed
New anticancer chemotherapy or radiotherapy after completion of frontline therapy without confirmed non-complete-response	Date of first dose of second-line therapy	Progressed
New anticancer chemotherapy or radiotherapy after completion of frontline therapy without confirmed non-complete-response	Date of first dose of second-line therapy	Censored
mPFS event after more than one missed visit	Date of mPFS event	Progressed
Lost to follow-up before any documented mPFS event	Next scheduled assessment	Progressed
Lost to follow-up before any documented mPFS event	A+AVD: Next scheduled assessment	progressed
	ABVD: Last adequate assessment	Censored
Lost to follow-up before any documented	A+AVD: Last adequate assessment	Censored

mPFS event	ABVD: Next scheduled assessment	Progressed

5.8.2.2 Other Analysis

In addition, the primary analysis of mPFS will be performed for the PP population, as well as for the subgroups specified below. The statistical model will be adjusted accordingly to fit the subgroup analyses.

Table 5-4 Subgroups for subgroup analysis

Subgroup	Definition of Group
Age	< 70 years; ≥ 70 years
Region	North American, Europe, Asia
Number of IPFP risk factors	0-1; 2-3; 4-7
Baseline cancer stage	stage III; Stage IV
Baseline B symptoms	Present; absent
Cycle 2 PET	Positive; negative
Cycle 2 PET Deauville Score	< 5; 5
Receipt of alternative frontline therapy	Yes; No

Two exploratory analyses will also be performed. One for mPFS with definition of frontline therapy restricted to no-switch in therapy. The other for PFS, which is defined as the earlier of (1) documentation of PD or (2) death due to any cause. The statistical methods will be similar to those used for mPFS.

5.8.3 Key Secondary Efficacy Endpoint

OS is designated as a key secondary endpoint. The key secondary endpoint will be tested at a 1-sided 0.025 level when the test of mPFS is statistically significant.

OS is defined as the time from the date of randomization to the date of death. Patients without documented death at the time of analysis will be censored at the date last known to be alive.

There will be 2 formal analyses for OS, an OS interim analysis at the time of the final mPFS analysis, and the OS final analysis when 112 deaths have occurred. Overall type I error will be controlled using the O'Brien-Fleming method with a Lan-DeMets alpha spending function.

Stratified log-rank testing will be used to compare OS between the 2 treatment arms. The stratification factors include region and number of IPFP risk factors at baseline (Section 5.2). The hazard ratios along with the 95% CIs (2-sided) will be estimated using a stratified Cox regression model. The Kaplan-Meier method will be used to estimate the distribution of the OS endpoint for each treatment. The 25th, 50th (median), 75th percentiles of survival times (if estimable), and the 2-sided 95% CIs will be presented. Analysis of OS will be performed based on the ITT population.

In addition, a stratified Cox regression model will be used to further evaluate the treatment effects on OS after adjusting for some prognostic factors. Besides treatment and the stratification factors (Section 5.2), the following prognostic factors will be included in the model simultaneously: age, race (white, non-white), baseline ECOG score, baseline cancer stage, baseline B symptoms, and PET results from Cycle 2. Additional exploratory analyses may be performed if deemed necessary.

Subgroup analyses may be performed using subgroups defined for mPFS analyses. Additional analyses of OS may be performed if deemed necessary.

5.8.4 Other Secondary Efficacy Endpoints

5.8.4.1 Overview of Statistical methods

Other secondary efficacy endpoints mainly consist of 2 types of variables: time to event variables (eg, event-free survival) and binary outcome variables (eg, CR). For time to event variables, the statistical methods will be the same as that for time to death outlined in Section 5.8.3. For binary outcome variables, the statistical methods will be the same as that for CR outlined in Section 5.8.4.2. Other endpoints that don't belong to these 2 categories will be addressed separately.

5.8.4.2 Complete Remission Rate at the End of Randomized Regimen per IRF

CR rate per IRF is defined as the proportion of patients who achieve CR at the end of treatment with randomized regimen (ABVD or A+AVD) as determined by an IRF.

The number and percentage of patients who experienced a CR at the end of treatment with ABVD/A+AVD will be summarized by treatment groups. The response rates between the 2 treatment groups will be tested using Cochran-Mantel-Haenszel (CMH) chi-square test, stratified by the stratification factors (Section 5.2). The CMH chi-square p-value and the relative risk (and odds ratio), along with its 95% 2-sided CI will also be provided. In

addition, the absolute treatment difference in CR response rates will be provided along with the 95% 2-sided CI.

In addition, a logistic regression model will be used to further evaluate the treatment effects on CR rate after adjusting for some prognostic factors. Besides treatment and the stratification factors (Section 5.2), the following prognostic factors will be included in the model simultaneously: age, race (white, non-white), baseline ECOG score, baseline cancer stage, baseline B symptoms, and PET results from Cycle 2. The odds ratio and its associated 95% CIs will be presented. Subgroup analyses may be performed using subgroups defined for mPFS analyses. Additional exploratory analyses may be performed if deemed necessary.

In the primary analysis of CR using ITT population, nonevaluable patients will be treated as nonCR. Sensitivity analyses for CR per IRF will be performed using the response-evaluable population. CR rate per investigator will also be analyzed similarly using the ITT population.

5.8.4.3 Complete Remission Rate at the End of Frontline Therapy

CR rate at the end of frontline therapy per IRF is defined as the proportion of patients who achieve CR at the end of frontline therapy as determined by an IRF. CR at the end of frontline therapy is a binary outcome variable.

5.8.4.4 Event-Free Survival

EFS is defined as the time from randomization until any cause of treatment failure: disease progression, premature discontinuation of treatment for any reason, or death due to any cause, whichever occurs first. EFS is a time-to-event variable.

5.8.4.5 Disease-Free Survival

DFS is defined as the time from CR to disease progression or to death from lymphoma or acute toxicity from treatment. Analyses of DFS will be performed based on the subset of the ITT population achieving a CR. DFS is a time-to-event variable.

5.8.4.6 Overall response rate

Overall response rate (ORR) is defined as the proportion of patients who achieve CR or PR at the end of treatment with randomized regimen (ABVD or A+AVD) as determined by an IRF.

ORR is a binary outcome variable.

5.8.4.7 Duration of Response (DOR) or Complete Response (DOCR)

DOR in subjects with confirmed response is the time between first documentation of response (PR or CR) and disease progression. DOCR in subjects with confirmed CR is the time between first documentation of CR and disease progression. DOR and DOCR per IRF will be analyzed based on the subset of ITT population who had response. DOR and DOCR are time-to event-variables.

5.8.4.8 PET Negativity Rate

PET negativity rate at Cycle 2 is defined as the proportion of patients with negative Cycle 2 PET results. PET negativity is a binary outcome variable.

5.8.5 Other Efficacy Endpoints

Alive without HL rate at 3 years and 5 years is defined as the proportion of patients who are alive without classical Hodgkin lymphoma at 3 years or 5 years after the patient's randomization date.

Alive without lymphoma rates between the 2 treatment arms will be compared using a stratified Cochran-Mantel-Haenszel (CMH) test.

5.9 Pharmacokinetic, Pharmacodynamic, and Biomarker Analysis

5.9.1 Pharmacokinetic Analyses

The PK of the antibody-drug conjugate (brentuximab vedotin), total antibody, and unconjugated drug (MMAE) will be based on serum or plasma samples collected from patients who meet study inclusion criteria, received study drug, and provided evaluable PK data. Population PK parameters will be calculated with an appropriate method based on a validated PK analysis program. Exploratory safety-PK, efficacy-PK, and if possible, PK-pharmacodynamic relationships will be determined.

Descriptive statistics (eg, number of patients, mean, standard deviation, median, minimum, and maximum) will be used to summarize concentrations of analyte for brentuximab vedotin-treated patients.

The pharmacokinetics of doxorubicin, vinblastine, and dacarbazine will be compared between the treatment arms. Descriptive statistics (eg, number of patients, mean, standard deviation, median, minimum, and maximum) will be used to summarize concentrations of analyte. Geometric mean ratios of the AUC will be calculated for each AVD component (doxorubicin, vinblastine, and dacarbazine).

5.9.2 Immunogenicity Analysis

All patients who were administered at least 1 dose of brentuximab vedotin will be evaluated for antitherapeutic antibody (ATA) development. A list/table of ATA status will be provided. Antibody neutralizing status (neutralizing or not neutralizing) will also be listed for patients who have positive antibody status.

Immunogenicity information, including ATA and neutralizing ATA, will be summarized in descriptive statistics as applicable.

Relationships between ATA development and safety and efficacy will be explored.

5.9.3 Biomarker Analysis

Absolute and change from baseline value of circulating biomarkers will be summarized by time point using descriptive statistics, as applicable. Descriptive statistics (eg, number of patients, mean, standard deviation, median, minimum, and maximum) will also be provided to summarize disease markers [redacted]), tissue levels of potential resistance markers ([redacted]), and qualitative and semiquantitative measures of markers ([redacted]), and change from baseline values of these markers, as applicable. The association between these and clinical response or safety endpoints might be explored.

5.10 Resource Utilization and Patient-Reported Outcome Analysis

Analyses of patient-reported outcomes (PROs) and health economics will be performed using the ITT population.

5.10.1 Patient-Reported Outcomes Analysis

Patient-reported outcome (PRO) assessments based on EORTC QLQ-C30, FACIT Dyspnea 10, and FACT/GOG-NTX Additional scale will be analyzed to determine if response to therapy is accompanied by changes in the quality of life.

The analysis will be based on scores from the global health status/QoL scale of QLQ-C30, shortness of breath scale of FACIT DYSPNEA 10, and the sensory scale of FACT/GOG-NTX. The analysis of change of scores from baseline will use mixed-effects models with repeated measures at each time point specified in the Schedule of Events of the protocol and the 95% CIs of the estimates will be provided.

Descriptive summaries of all the scales and individual item scores observed will be generated at each scheduled assessment time point by treatment.

Missing data will be summarized with the proportion of missing responses for each item over time. Manuals for scoring and handling missing data published for QLQ-C30, FACIT Dyspnea 10, and Fact-Ntx will be used to impute missing data initially.

A sensitivity analysis will be performed to evaluate the impact on the analysis results from missing data imputation. Conditional on the patterns of missing data, multiple imputation methods, including a pattern-mixture model, will be considered. Any deaths that occur before the end of treatment (EOT) are to be imputed by a value zero and will be considered missing otherwise.

5.10.2 Health Economics Analysis Using Medical Resource Utilization and Utility

EQ-5D scores will be summarized in descriptive statistics for treatment arms.

MRU data will be summarized in descriptive statistics of medical encounters (length of stay, inpatient, outpatient, and reason), number of missing days from work or other activities by patient and care-giver for treatment arms.

Further modeling will be performed separately at post hoc analyses.

5.11 Safety Analyses

Safety will be evaluated by the incidence of TEAEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, ECOG performance status, ECG, and

clinical laboratory results using the safety population. Exposure to study drug and reasons for discontinuation will be tabulated.

These analyses will be performed using the safety population.

5.11.1 Adverse Events

Treatment-emergent adverse events are defined as any AE that occurs after administration of the first dose of study drug and up through 30 days after the last dose of frontline therapy or EOT (whichever is later), any event that is considered drug-related regardless of the start date of the event, or any event that is present at the baseline assessment but worsens in severity after that assessment or is subsequently considered drug related by the investigator.

The MedDRA dictionary will be used to code the investigator's adverse event terms. Adverse event tables will summarize subject incidence by treatment group actually received. The severity of adverse events will be assessed using NCI CTCAE version 4.03.

5.11.1.1 Adverse Events

The number and percentage of patients experiencing at least 1 treatment emergent adverse event will be tabulated by MedDRA primary system organ class, high level term, preferred term, and treatment group. For the number of patients with AEs, patients reporting the same event more than once will have that event counted only once within each body system, once within each high level term, and once within each preferred term. AEs will be coded using the MedDRA dictionary.

The number and percentage of patients experiencing at least 1 treatment emergent AE considered related to treatment will also be summarized. If the event is missing relationship data, the event will be included in the total column for the corresponding treatment group. Multiple occurrences of the same event are counted once per subject using the most related event.

AEs will also be summarized by intensity grade. Again, multiple occurrences of the same event are counted once per subject using the maximum intensity. If the intensity of an AE is missing, the event will be included in the total column for the corresponding treatment group.

The following tabulations will also be presented:

- Incidence of treatment-emergent adverse events by System Organ Class (SOC), high-level term, and preferred term

- Incidence of treatment-emergent adverse events reported by at least 10% of patients in either treatment group by MedDRA preferred term

- Incidence of treatment-emergent adverse events considered by the investigator to be related to study drug by MedDRA SOC and preferred term

- Incidence of treatment-emergent adverse events that caused study drug dose modification by MedDRA SOC and preferred term

For treatment-emergent adverse events with NCI CTCAE toxicity Grade 3 or higher, the following summaries are to be produced:

- Incidence of Grade $\geq$ 3 treatment-emergent adverse events, by SOC and preferred term

- Incidence of Grade $\geq$ 3 treatment-emergent adverse events considered by the investigator to be related to study drug, by SOC and preferred term

- Incidence of Grade $\geq$ 3 treatment-emergent adverse events that caused study drug dose modification

5.11.1.2 Serious Adverse Events

The number and percentage of patients experiencing at least 1 treatment-emergent serious AE (SAE) will be summarized by MedDRA primary system organ class, high-level term, and preferred term. The following summaries are to be produced:

- Incidence of treatment-emergent serious adverse events, by SOC and preferred term

- Incidence of treatment-emergent serious adverse events considered by the investigator to be related to study drug, by SOC and preferred term

In addition, a by-subject listing of the SAEs will be presented (the subject listing will contain all SAEs regardless of treatment emergent AE status).

5.11.1.3 Deaths

All deaths occurring on-study and during follow-up will be summarized. Cause of death will be summarized as well in this table. Frequencies of deaths due to study treatment-related adverse events will also be reported.

A by-subject listing of the deaths will be presented. All deaths occurring on-study and during follow-up will be displayed (regardless of treatment emergent AE status).

5.11.1.4 Adverse Events Resulting in Discontinuation of Study Drug

Adverse events results in discontinuation of study drug will be tabulated by treatment. A by-subject listing of AEs resulting in discontinuation of study drug will be presented.

5.11.2 Laboratory Data

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units. If a lab value is reported using a non-numeric qualifier (eg, less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier.

If a subject has repeated laboratory values for a given time point, the value from the last evaluation will be used.

The parameters to be analyzed are as follows:

- Hematology: hemoglobin, hematocrit, platelet count, leukocytes with differential, neutrophils (absolute neutrophil count [ANC])
- Serum chemistry: Blood urea nitrogen, Creatinine, Total bilirubin, Urate, Lactate dehydrogenase, Gamma-glutamyl transpeptidase (GGT), Phosphate, Albumin, Alkaline phosphatase (ALP), AST, ALT, Glucose, Sodium, Potassium, Calcium, Chloride, Carbon dioxide, Magnesium.
- Other: Hemoglobin A1C

Laboratory data of hematology and clinical chemistry up to 30 days after last dose or the End of Treatment visit date, whichever is later, will be reported in SI units. Normal ranges from the central and local laboratories used in this study will be listed.

Summary statistics (mean, standard deviation, median, and range) will be calculated for the raw data and for their percentage changes from baseline at each time point of assessment and for the percentage changes from baseline to the last value. Individual values outside the normal ranges will be identified (by "H" for high and "L" for low) in the data listings displaying the absolute values for each subject.

Graphical displays of over-time summaries will be presented for the following key laboratory parameters: hemoglobin, neutrophils, platelets, bilirubin, creatinine, alkaline phosphatase, glucose, and electrolytes (sodium, potassium, chloride, calcium, and phosphate).

Shift tables for each cycle will be produced for selected laboratory parameters, to include hemoglobin, neutrophils, platelets, bilirubin, creatinine, alkaline phosphatase, glucose, and electrolytes (sodium, potassium, chloride, calcium, and phosphate). These tables will summarize, by cycle, the number of patients with each baseline NCI CTCAE grade and changes to the maximum NCI CTCAE grade in the cycle.

Shift tables from baseline to worst value (ie, worst grade) on study (from treatment start to 30 days after last dose or the End of Treatment visit date, whichever is later) will also be provided. The worst toxicity grade during the study will be tabulated.

Summary statistics will also be presented for shift from baseline urinalysis values.

5.11.3 Electrocardiograms

Investigators' assessments of ECG monitoring (normal, abnormal and clinically significant, or abnormal and not clinically significant), including unscheduled or retested measurements, will be presented in a listing.

5.11.4 Vital Signs

The actual values of vital sign parameters including temperature, pulse rate, and systolic and diastolic blood pressure when available, will be summarized over time.

6. CHANGES TO PLANNED ANALYSES FROM PROTOCOL

Not applicable.

7. PROGRAMMING CONSIDERATIONS

7.1 Statistical Software

SAS version 9.1 (or higher) will be used for all analyses.

7.2 Rules and Definitions

Subject populations are defined in Section 2.

Baseline values are defined in Section 5.4.2.

Treatment-emergent AEs are defined in Section 5.11.1.1.

8. REFERENCES

Not applicable.

STATISTICAL ANALYSIS PLAN

CLINICAL STUDY PROTOCOL C25003
Brentuximab vedotin
A Randomized, Open-label, Phase 3 Trial of A+AVD Versus ABVD as Frontline Therapy in Patients With Advanced Classical Hodgkin Lymphoma

Protocol #: C25003

SAP Version:	Date of Statistical Analysis Plan:
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Date	Prepared by: [redacted] Clinical Biostatistics
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Date	Approved by: [redacted], Oncology Clinical Research

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
A	ADCETRIS™
ABVD	doxorubicin [Adriamycin], bleomycin, vinblastine, dacarbazine
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AUC	area under the plasma concentration versus time curve
AVD	doxorubicin [Adriamycin], vinblastine, dacarbazine
A+AVD	doxorubicin [Adriamycin], vinblastine, dacarbazine, brentuximab vedotin [ADCETRIS™]
BPT	bleomycin pulmonary toxicity
BSA	body surface area
C_{max}	maximum plasma concentration
CO_2	carbon dioxide
CR	complete response
CR(u)	unconfirmed complete response
CT	computed tomography
DNA	deoxyribonucleic acid
DOCR	duration of complete response
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture

Abbreviation	Term
EOS	End of Study (visit)
EOT	End of Treatment (visit)
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IPFP	International Prognostic Factor Project
IPS	[Hasenclever] International Prognostic Score
IRB	institutional review board
IRF	independent review facility
ITT	intent-to-treat
IV	intravenous; intravenously
IVRS	interactive voice response system
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
mPFS	modified progression-free survival
MRI	magnetic resonance imaging
MRU	medical resource utilization
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OS	overall survival
PD	progressive disease (disease progression)
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
QALY	quality-adjusted life year
QOL	quality of life
QTc	rate-corrected QT interval (millisec) of electrocardiograph
SAE	serious adverse event
SD	stable disease
$t_{1/2}$	half-life
T_{max}	first time to maximum plasma concentration
ULN	upper limit of the normal range
V_z	volume of distribution in the terminal phase
WHO	World Health Organization

1. INTRODUCTION

In general, the purpose of the Statistical Analysis Plan (SAP) is to provide a framework that addresses the protocol objectives in a statistically rigorous fashion, with minimized bias or analytical deficiencies. Specifically, this plan has the following purpose:

To prospectively (a priori) outline the types of analyses and data presentations that will addresses the study objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the pharmaceutical industry.

1.1 Study Design

This open-label, randomized, 2-arm, multicenter, phase 3 study has the primary objective of comparing the modified progression-free survival (mPFS) obtained with A+AVD against that obtained with ABVD.

Approximately 1240 patients will be randomized 1:1 into 2 treatment arms:

- A+AVD: Doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, dacarbazine (DTIC) 375 mg/m^2, brentuximab vedotin 1.2 mg/kg
- ABVD: Doxorubicin 25 mg/m^2, bleomycin 10 units/m^2, vinblastine 6 mg/m^2, dacarbazine (DTIC) 375 mg/m^2

ABVD and A+AVD will be administered intravenously on Days 1 and 15 of each 28-day cycle. Brentuximab vedotin will be administered intravenously over 30 minutes at a dose of 1.2 mg/kg; the brentuximab vedotin infusion is to be started within approximately 1 hour after completion of AVD therapy. Patients may receive up to 6 cycles of therapy (ABVD or A+AVD).

Randomization will be stratified by region (Americas versus Europe versus Asia), and number of International Prognostic Factor Project(IPFP) risk factors (0-1 versus 2-3 versus 4-7).

1.2 Study Objectives

Primary Objective:

- To compare the modified progression-free survival (mPFS) obtained with brentuximab vedotin plus AVD (abbreviated A+AVD) versus that obtained with ABVD for the frontline treatment of advanced classical HL

Key secondary objective:

- To determine if A+AVD improves overall survival (OS) versus that obtained with ABVD

Other secondary objectives:

- To determine if A+AVD improves complete remission (CR) rate at the end of randomized regimen versus that obtained with ABVD
- To determine the safety profile of A+AVD relative to that of ABVD
- To determine the event-free survival (EFS) obtained with A+AVD and ABVD
- To determine the disease-free survival (DFS) obtained with A+AVD and ABVD
- To determine if A+AVD improves overall objective response rate (ORR, defined as CR + PR) versus that obtained with ABVD
- To determine the duration of response (DOR) and duration of complete response (DOCR) obtained in the A+AVD and ABVD arms
- To determine the rate of patients receiving irradiation for HL not in CR in the A+AVD and ABVD arms
- To determine the rate of patients in CR at the end of frontline therapy in the A+AVD and ABVD arms
- To determine the rate of Cycle 2 PET negativity in patients treated with A+AVD versus those treated with ABVD

- To determine if A+AVD improves health-related quality of life (HRQoL) versus ABVD
- To describe the PK of brentuximab vedotin, MMAE, and total antibody (TAb) in blood
- To determine the immunogenicity of brentuximab vedotin

Exploratory objectives:

- To investigate any differences in lung-specific patient reported outcomes (PRO) between the treatment arms
- To assess any impact of brentuximab vedotin dosing on serum concentrations of AVD
- To investigate any differences between the treatment arms in the rate of patients alive without HL at 3 and 5 years
- To assess changes in tumor biomarker expression before and after treatment
- [redacted]
- To assess other PROs
- To assess medical resource utilization
- To assess fertility

2. POPULATIONS FOR ANALYSIS

2.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population will include all patients randomized to treatment. All patients in the ITT population will be analyzed according to the treatment they were randomized to receive and not according to what they actually received, if different. The

ITT population will be used for all efficacy analyses of efficacy endpoints unless specified otherwise.

2.2 Per-Protocol Population

The Per-Protocol (PP) population will include all randomized patients who do not have major protocol violation as determined by the project clinician. All decisions to exclude patients from the PP population will be made prior to database lock.

The PP population will be used as a supplement to the analysis of the ITT population for the primary efficacy endpoint.

All patients in the PP population will be analyzed according to the actual treatment received. The PP population will be used as supportive analysis for the primary efficacy endpoint mPFS.

2.3 Response-Evaluable Population

The response-evaluable population is defined as the subset of the ITT population with diagnosis as confirmed by an independent pathology review facility, with measurable disease at baseline, who receive at least 1 dose of study drug, and have at least 1 postbaseline response assessment. The response-evaluable population will be used for the analyses of CR rate, overall response rate, and duration of response.

2.4 Safety Population

The safety population will include all enrolled patients who have received at least 1 dose of study medication. All patients in the safety population will be analyzed according to the actual treatment received.

All safety analyses will be performed using the safety population.

2.5 Pharmacokinetics Population

The PK population will include enrolled patients with sufficient dosing and PK data to reliably estimate PK parameters as determined by a clinical pharmacologist. The PK population will be used for PK analyses.

2.6 Pharmacodynamics Population

The pharmacodynamics population will include enrolled patients with sufficient dosing and sufficient pharmacodynamics data to reliably measure pharmacodynamics parameters. The pharmacodynamics population will be used for pharmacodynamics analyses.

3. HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

Primary hypothesis to be tested:

> The primary null hypothesis is that there is no difference in modified progression-free survival (mPFS) between the 2 treatments of A+AVD and ABVD. The alternative hypothesis is that A+AVD improves mPFS.

Key secondary hypothesis to be tested:

> The null hypothesis is that there is no difference in overall survival (OS) between the 2 treatments of A+AVD and ABVD. The alternative hypothesis is that A+AVD improves OS.

Hypotheses for the secondary endpoints will also be tested.

3.2 Statistical Decision Rules

3.2.1 Testing Significance for Primary Endpoint

Modified PFS will be tested at a 1-sided significance level of 0.025. We will conclude that the A+AVD treatment can improve mPFS compared with the ABVD treatment if the test is statistically significant.

3.2.2 Testing Process and Significance for Key Secondary Efficacy Endpoint

Key secondary endpoint will be tested at 1-sided, 0.025 level only when the test of the primary endpoint (mPFS) is statistically significant. If the test is statistically significant, we will conclude that the A+AVD treatment can make improvement in OS compared with the ABVD treatment.

4. INTERIM ANALYSIS

4.1 Interim Analysis

There will be 2 formal interim analyses in this study.

The first formal interim analysis to be performed is a futility analysis. The CR rate at the end of frontline therapy will be analyzed when the first approximately 348 patients have completed the regimen to which they were randomized (ie, received the planned study drug regimen with no more than 2 missed doses of A+AVD or ABVD) or have discontinued treatment prior to completion. Recommendation by the independent data monitoring committee (IDMC) whether to terminate the study based on this interim analysis will be determined upon evaluation of the overall safety information and efficacy data, specifically if the CR rate per independent review facility (IRF) for the A+AVD arm is at least 5% lower than that of the ABVD arm and trends in mPFS and other efficacy endpoints suggest inferior efficacy in the A+AVD arm. This futility analysis does not require adjustment of the type I error.

The second formal interim analysis is for OS to be performed at the time of the final mPFS analysis. Overall type-I error for OS will be controlled using the O'Brien-Fleming method with a Lan-DeMets alpha spending function, with final OS analysis scheduled for when 112 deaths have occurred.

4.2 Independent Data Monitoring Committee (IDMC)

An IDMC will review safety and efficacy data at the interim analyses. The IDMC will provide a recommendation regarding study continuation based on the safety and efficacy parameters. In the event that the study is terminated early based on an IDMC recommendation, Millennium will notify the appropriate regulatory authorities. Detailed information regarding the composition of the IDMC and detailed IDMC procedures will be provided in the IDMC charter.

The first formal safety review will occur after the first 100 patients have completed 2 cycles (8 weeks) of treatment or discontinued prior to completing 2 cycles of treatment. Subsequently, IDMC safety reviews will be performed periodically per the IDMC charter.

5. STATISTICAL METHODOLOGY

In general, summary tabulations will be presented that display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent (of non-missing) per category for categorical data, unless specified otherwise.

5.1 Sample Size Justification

The primary endpoint of the study is mPFS, and the study is powered on the following assumption: a 2-year mPFS of 81% for patients in the A+AVD treatment group versus 73% for patients in the ABVD treatment group (HR = 0.67, assuming an emergent plateau in the PFS event rate after 2 years). A total of 260 mPFS events will provide 90% power to detect a hazard ratio of 0.67 at a 1-sided significance level of 0.025 using a log-rank test. Approximately 1240 patients will be randomized to achieve (with 95% probability) 260 mPFS events in about 60 months assuming 36 months of accrual, a 5% annual dropout rate, and 24 months of mPFS follow-up after last patient in.

5.2 Randomization and Stratification

The randomization scheme will be generated by Millennium. Prior to dosing, a randomization number will be assigned to each patient. The randomization schedule also includes the study specific identifiers (company name, protocol name, and protocol number) and the date and time the schedule was generated.

Patients will be randomized in an overall ratio of 1:1 to A+AVD or ABVD. Patients will be stratified by region (Americas versus Europe versus Asia), and number of IPFP risk factors (0-1 versus 2-3 versus 4-7).

5.3 Unblinding

This is an open-label study; investigators and patients will know the individual treatment assignments. However, aggregate efficacy data will be blinded to the sponsor's study team, investigators, and patients throughout the study conduct. The IRF will be blinded to treatment assignments.

5.4 Data Handling

5.4.1 Methods for Handling Missing Data

All available efficacy and safety data will be included in data listings and tabulations. Data that are potentially spurious or erroneous will be examined under the auspices of standard data management operating procedures.

In general, missing data will be treated as missing and no data imputation will be applied, unless otherwise specified. For Quality of Life Data, missing elements may be substituted with the average of non-missing items per published methods of analysis.

Last observation carried forward method and multiple imputation method may be considered for some clinical outcomes as deemed appropriate.

5.4.1.1 Missing/Partial Dates in Screening Visit

The following rules apply to dates recorded in the screening visits, with the exception of prior therapies (Section 5.4.1.2).

- If only the day-component is missing, the first day of the month will be used if the year and the month are the same as those for the first treatment. Otherwise, the 15th will be used.

- If only a year is present, and it is the same as the year of the first treatment, the 15th of January will be used unless it is later than the first treatment, in which case the date of the first of January will be used.

- If only a year is present, and it is not the same as the year of the first treatment, the 15th of June will be used, unless other data indicates that the date is earlier, in which case the 15th of January will be used. .

5.4.1.2 Missing/Partial Dates in Adverse Events/Concomitant Therapies/Subsequent Therapies

Every effort will be made to avoid missing/partial dates in on-study data. If the resolution date of a resolved adverse event (AE) or the stop date of a concomitant therapy is missing, the following rules are to be used unless conflicting data exists: if month and year are present and the day of the month is missing, the last day of the month is imputed. If only a

year is present, the 31st of December is used. After imputation, the imputed dates will be compared against the date of death, if available. If the date is later than the date of death, the date of death will be used as the imputed date instead.

In cases where the onset date of an adverse event is completely or partially missing, the following imputation rules will be used:

1. When month and year are present and the day of the month is missing,
    - If the onset month and year are the same as the month and year of first treatment with study drug, the day of first treatment or the day-component of the resolution date are imputed, whichever is earliest.
    - If the onset month and year are not the same as the month and year of first treatment with study drug, the first day of the month is imputed.
2. When only a year is present, or no components of the onset date are present,
    - If the resolution date is available, the earlier of the resolution date (possibly imputed) and the date of first treatment will be used.
    - If the resolution date is missing, and the onset-year is the same as the year of first treatment with study drug, then the date of first treatment with study drug is used.
    - Otherwise if only a year is present, the 1st of January of that year is imputed.
3. If none of the previous rules can be applied, then the date of first treatment with study drug is imputed as the onset date.

The imputation rules for missing/partial start dates of concomitant therapies will be the same as the above with the exception as follows:

For prior therapy data, no imputation will be done for start dates.

The imputation rules for missing/partial start dates of subsequent therapies recorded as concomitant medications will be the same as the above with exceptions as follows.

1. When month and year are present and the day of the month is missing,

a. If the month and year of the start date are the same as the month and year of treatment termination, the day of treatment termination or the day-component of the stop date is imputed, whichever is earliest.

b. If the start month and year are not the same as the month and year of treatment termination, the first day of the month is imputed.

2. When only a year is present, or no components of the start date are present, the date will not be imputed.

5.4.1.3 Lab Values Below the Lower Limit of Quantification

If the numeric value of a laboratory test (excluding PK analyses) is not available because it is below the lower limit of quantification (LLOQ), a logical value of < LLOQ should be used whenever applicable. In cases where a numeric value is required, eg, calculating the mean, the LLOQ will be used.

5.4.2 Definition of Baseline Values

Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, but prior to, the start of study drug administration. If a patient is not dosed, the date of randomization will be used.

In the case that laboratory values from both the central lab and local lab are available before randomization, the most recent value from the central lab will be used as baseline, even if the sample date of the central lab result is prior to that of any local lab value.

5.4.3 Windowing of Visits

All data will be categorized based on the scheduled visit at which it was collected. These visit designators are predefined values that appear as part of the visit tab in the eCRF.

5.4.4 Justification of Pooling

All data from all sites will be pooled. Study center or treatment-by-center interaction will not be included in any statistical analysis.

5.4.5 Withdrawals, Dropouts, Lost to Follow-up

No patients will be replaced in this study.

5.5 Patient Disposition

A disposition of patients includes the number and percentage of patients for the following categories: patients in each of the study population, primary reason to discontinue from the treatment, patients discontinued from the study, and primary reason to discontinue from the study. All percentages will be based on the number of patients in the ITT population.

A listing will present data concerning patient disposition.

5.6 Demographics and Baseline Disease Characteristics

5.6.1 Demographics

Demographic and baseline characteristics will be summarized, including gender, age, race, weight, height, BSA, primary diagnosis, and other parameters as appropriate. No inferential statistics will be carried out.

The formulation for BSA is:

BSA = sqrt(height(cm) x weight (kg) / 3600).

5.6.2 Medical History

Medical history will be listed for all patients.

5.6.3 Baseline Disease Status

Baseline disease status will be summarized by the treatment groups, including disease primary diagnosis, time since initial diagnosis (months), IPFP risk factors, Ann Arbor stage, and baseline Eastern Cooperative Oncology Group (ECOG) performance status.

Patient distribution by stratification factors will also be summarized.

5.7 Treatments and Medications

5.7.1 Concomitant Medications

Concomitant medications will be coded by preferred term using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking concomitant medications will be tabulated.

Concomitant procedures will not be coded, but will be presented in a data listing in the clinical study report (CSR).

5.7.2 Study Treatments

The study treatments for this study are A+AVD and ABVD. ABVD consists of doxorubicin 25 mg/m^2, bleomycin 10 units/m^2, vinblastine 6 mg/m^2, and dacarbazine (DTIC) 375 mg/m^2. A+AVD consists of doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, dacarbazine (DTIC) 375 mg/m^2, and brentuximab vedotin (ADCETRIS) 1.2 mg/kg. A+AVD and ABVD will be administered by IV infusion on Days 1 and 15 of each 28-day cycle, for a total of 6 cycles. Details of study treatments administration is described in the protocol.

5.7.2.1 Extent of Exposure

The exposure to each component of study treatments A+AVD and ABVD will be characterized by total amount of dose received (mg or units), total number of doses received, number of treatment cycles, numbers and percentages of patients by maximum number of treatment cycles completed(1, 2, … , 6).

A treatment cycle is defined as a cycle in which the patient received any amount of study drug.

Relative dose intensity (%) is defined as: 100 x (total dose received)/(total dose intended). Total dose intended is the summation of the intended doses in all treatment cycles. The intended dose in each cycle is determined by the dose level when the patient was randomized.

Dosing data will also be presented in a by-patient listing.

5.7.2.2 Treatment Modifications

Action on each component of study treatments A+AVD and ABVD will be summarized by Cycles 1 through 6.

Patients who switch to another frontline therapy before completing A+AVD and ABVD will be summarized by time of switch and by treatment to which they switch.

5.8 Efficacy Analyses

All efficacy evaluations will be conducted using the ITT population unless otherwise specified.

5.8.1 Primary Efficacy Endpoint

The primary endpoint is mPFS (modified progression-free survival) per IRF assessment using the Revised Response Criteria for Malignant Lymphoma.

5.8.1.1 Definition

mPFS is defined as:

The time from the date of randomization to the date of the first of (1) documentation of progressive disease (PD); (2) death due to any cause; (3) for patients who are confirmed non-complete responders per IRF, receipt of anticancer chemotherapy or radiotherapy for HL after completion of frontline therapy, as defined in Table 5-1; these patients' mPFS event date will be the date of the first PET scan post completion of frontline therapy demonstrating the absence of a CR, defined as a Deauville score of ≥ 3.

Table 5-1 Completion of Frontline Therapy

Treatment History	Completion of Frontline Therapy
Did not switch therapy	Upon receipt of planned study drug regimen with no more than 2 missed doses of A+AVD or ABVD[a]
Switched therapy before completion of A+AVD or ABVD	Upon conclusion of 1 alternative anticancer regimen[b] for HL subsequent to A+AVD or ABVD discontinuation

a A "missed dose" refers to administration of the full study regimen of either A+AVD or ABVD. Patients may miss individual agents within the A+AVD or ABVD regimen (such as patients who discontinue bleomycin for pulmonary toxicity)without this counting as a missed dose.

b Receipt of chemotherapy OR radiation.

5.8.1.2 Handling of Missing Assessment and Censoring for mPFS Primary Analysis

The determination of the date of progression by the IRF will be used for the primary analysis. Sensitivity analyses will also be performed to evaluate the robustness of results.

For the mPFS primary analysis, disease assessment data should be collected according to the intended schedule of assessment, and the date of progression should be assigned based on the time of the first evidence of disease progression regardless of violations and

discontinuation of study drug. For those patients who receive new anticancer chemotherapy or radiotherapy for HL after completion of frontline therapy without confirmed noncomplete-response, mPFS will be determined by PD or death. Detailed handling rules for missing assessments and censoring for the analysis of mPFS are presented in Table 5-2.

Table 5-2 Handling of Missing Assessments and Censoring for mPFS Primary Analysis

Situation	Date of Progression or Censoring	Outcome
No baseline and/or no postbaseline assessment, no subsequent anticancer therapy after frontline therapy, no death	Date of Randomization	Censored
Disease progression documented between scheduled visits	Date of next scheduled visit	Progressed
No documented mPFS event	Date of last adequate assessment[a]	Censored
Lost to follow-up, withdraw consent before any documented mPFS event	Date of last adequate assessment[a]	Censored
Treatment discontinuation for undocumented disease progression after the last adequate assessment	Date of last adequate assessment[a]	Censored
mPFS event after more than one missed visit	Date of last adequate assessment[a]	Censored

a Adequate assessment is defined as there is sufficient data to evaluate a patient's disease status.

5.8.2 Primary Efficacy Analysis

Final analysis of mPFS will be performed when 260 mPFS events have been observed, which is estimated to occur by 24 months after the last patient is randomized.

Stratified log-rank testing will be used to compare mPFS between the 2 treatment arms as the primary analysis. The stratification factors include region and number of IPFP risk factors at baseline (Section 5.2). The hazard ratios along with the 95% confidence interval (CI; 2-sided) will be estimated using the stratified Cox model with treatment as the explanatory variable. The Kaplan-Meier (K-M) survival curves and survival probability at 2 and 3 years along with the 2-sided 95% CIs will also be provided for each treatment group.

In addition, a stratified Cox regression model will be used to further evaluate the treatment effects on mPFS after adjusting for some prognostic factors. Besides treatment and the stratification factors (Section 5.2), the following prognostic factors will be included in the model simultaneously: age, race (white, non-white), baseline ECOG score, baseline cancer

stage, baseline B symptoms, and PET results from Cycle 2. Additional exploratory analyses may be performed if deemed necessary.

For patients with mPFS events, the reasons leading to the determination of mPFS will be tabulated. For patients without mPFS events, the main reason for censoring will also be tabulated.

The proportional hazard assumptions will be examined and sensitivity analysis may be conducted if appropriate.

5.8.2.1 mPFS Sensitivity Analyses

Sensitivity analyses will be performed for mPFS to evaluate the robustness of treatment effects. To satisfy EMA requirements, a sensitivity analysis will be performed by treating the last two categories of Table 5-2 as events, the events time will follow the description provided in Table 5-3. In the second sensitivity analysis, mPFS based on the investigators' determinations of disease progression will be analyzed in the same manner as the primary analysis. In the third sensitivity analysis, if confirmed non-complete response constitutes the mPFS event, the mPFS event date will be the date of receipt of first dose of second-line therapy. Additional sensitivity analyses for mPFS will be performed based on the alterations of the handling of missing assessment and censoring in Table 5-3, on the basis of 1 alteration at a time, not on combined alterations unless otherwise specified.

Table 5-3 Handling of Missing Assessments and Censoring for mPFS Sensitivity Analysis

Situation	Date of Progression or Censoring	Outcome
Disease progression documented between scheduled visits	Date of documented disease progression	Progressed
Treatment discontinuation for undocumented disease progression after the last adequate assessment	Date of last adequate assessment	Progressed
New anticancer chemotherapy or radiotherapy after completion of frontline therapy without confirmed non-complete-response	Date of first dose of second-line therapy	Progressed
New anticancer chemotherapy or radiotherapy after completion of frontline therapy without confirmed non-complete-response	Date of first dose of second-line therapy	Censored
mPFS event after more than one missed visit	Date of mPFS event	Progressed
Lost to follow-up before any documented mPFS event	Next scheduled assessment	Progressed
Lost to follow-up before any documented mPFS event	A+AVD: Next scheduled assessment	progressed
	ABVD: Last adequate assessment	Censored
Lost to follow-up before any documented mPFS event	A+AVD: Last adequate assessment	Censored
	ABVD: Next scheduled assessment	Progressed

5.8.2.2 Other Analysis

In addition, the primary analysis of mPFS will be performed for the PP population, as well as for the subgroups specified below. The statistical model will be adjusted accordingly to fit the subgroup analyses.

Table 5-4 Subgroups for Subgroup Analysis

Subgroup	Definition of Group
Age	< 60 years; ≥ 60 years
Region	North American, Europe, Asia
Number of IPFP risk factors	0-1; 2-3; 4-7
Baseline cancer stage	stage III; Stage IV
Baseline B symptoms	Present; absent
Cycle 2 PET	Positive; negative
Cycle 2 PET Deauville Score	< 5; 5
Receipt of alternative frontline therapy	Yes; No
Baseline extra nodal sites	0, 1, >1

As HL is a curable disease, a mixture cure survival model will be performed:

$$Survival_i = P_i + (1-P_i)S_i$$

where P_i denotes the fraction of patients cured in each arm, S_i is the mPFS survival function for those who are not cured. S_i is assumed to follow Weibull distribution with the same shape parameter for both treatment arms. If Weibull distribution assumption for S_i is not appropriate, other parametric distributions will be considered. Two additional exploratory analyses will also be performed. One for mPFS with definition of frontline therapy restricted to no-switch in therapy. The other for PFS, which is defined as the earlier of (1) documentation of PD or (2) death due to any cause. The statistical methods will be similar to those used for mPFS.

5.8.3 Key Secondary Efficacy Endpoint

OS is designated as a key secondary endpoint. The key secondary endpoint will be tested at a 1-sided 0.025 level when the test of mPFS is statistically significant.

OS is defined as the time from the date of randomization to the date of death. Patients without documented death at the time of analysis will be censored at the date last known to be alive.

There will be 2 formal analyses for OS, an OS interim analysis at the time of the final mPFS analysis, and the OS final analysis when 112 deaths have occurred. Overall type I error will be controlled using the O'Brien-Fleming method with a Lan-DeMets alpha spending function.

Stratified log-rank testing will be used to compare OS between the 2 treatment arms. The stratification factors include region and number of IPFP risk factors at baseline (Section 5.2). The hazard ratios along with the 95% CIs (2-sided) will be estimated using a stratified Cox regression model. The Kaplan-Meier method will be used to estimate the distribution of the OS endpoint for each treatment. The 25th, 50th (median), 75th percentiles of survival times (if estimable), and the 2-sided 95% CIs will be presented. Analysis of OS will be performed based on the ITT population.

In addition, a stratified Cox regression model will be used to further evaluate the treatment effects on OS after adjusting for some prognostic factors. Besides treatment and the stratification factors (Section 5.2), the following prognostic factors will be included in the model simultaneously: age, race (white, non-white), baseline ECOG score, baseline cancer stage, baseline B symptoms, and PET results from Cycle 2. Additional exploratory analyses may be performed if deemed necessary.

Subgroup analyses may be performed using subgroups defined for mPFS analyses. Additional analyses of OS may be performed if deemed necessary.

5.8.4 Other Secondary Efficacy Endpoints

5.8.4.1 Overview of Statistical methods

Other secondary efficacy endpoints mainly consist of 2 types of variables: time to event variables (eg, event-free survival) and binary outcome variables (eg, CR). For time to event variables, the statistical methods will be the same as that for time to death outlined in Section 5.8.3. For binary outcome variables, the statistical methods will be the same as that for CR outlined in Section 5.8.4.2. Other endpoints that don't belong to these 2 categories will be addressed separately.

5.8.4.2 Complete Remission Rate at the End of Randomized Regimen per IRF

CR rate per IRF is defined as the proportion of patients who achieve CR at the end of treatment with randomized regimen (ABVD or A+AVD) as determined by an IRF.

The number and percentage of patients who experienced a CR at the end of treatment with ABVD/A+AVD will be summarized by treatment groups. The response rates between the 2 treatment groups will be tested using Cochran-Mantel-Haenszel (CMH) chi-square test, stratified by the stratification factors (Section 5.2). The CMH chi-square p-value and the relative risk (and odds ratio), along with its 95% 2-sided CI will also be provided. In

addition, the absolute treatment difference in CR response rates will be provided along with the 95% 2-sided CI.

In addition, a logistic regression model will be used to further evaluate the treatment effects on CR rate after adjusting for some prognostic factors. Besides treatment and the stratification factors (Section 5.2), the following prognostic factors will be included in the model simultaneously: age, race (white, non-white), baseline ECOG score, baseline cancer stage, baseline B symptoms, and PET results from Cycle 2. The odds ratio and its associated 95% CIs will be presented. Subgroup analyses may be performed using subgroups defined for mPFS analyses. Additional exploratory analyses may be performed if deemed necessary.

In the primary analysis of CR using ITT population, nonevaluable patients will be treated as nonCR. Sensitivity analyses for CR per IRF will be performed using the response-evaluable population. CR rate per investigator will also be analyzed similarly using the ITT population.

5.8.4.3 Complete Remission Rate at the End of Frontline Therapy

CR rate at the end of frontline therapy per IRF is defined as the proportion of patients who achieve CR at the end of frontline therapy as determined by an IRF. CR at the end of frontline therapy is a binary outcome variable.

5.8.4.4 Event-Free Survival

EFS is defined as the time from randomization until any cause of treatment failure: disease progression, premature discontinuation of randomized treatment for any reason, or death due to any cause, whichever occurs first. EFS is a time-to-event variable.

5.8.4.5 Disease-Free Survival

DFS is defined as the time from CR to disease progression or to death from lymphoma or acute toxicity from treatment. Analyses of DFS will be performed based on the subset of the ITT population achieving a CR. DFS is a time-to-event variable.

5.8.4.6 Overall response rate

Overall response rate (ORR) is defined as the proportion of patients who achieve CR or PR at the end of treatment with randomized regimen (ABVD or A+AVD) as determined by an IRF.

ORR is a binary outcome variable.

5.8.4.7 Duration of Response (DOR) or Complete Response (DOCR)

DOR in subjects with confirmed response is the time between first documentation of response (PR or CR) and disease progression. DOCR in subjects with confirmed CR is the time between first documentation of CR and disease progression. DOR and DOCR per IRF will be analyzed based on the subset of ITT population who had response. DOR and DOCR are time-to event-variables.

5.8.4.8 PET Negativity Rate

PET negativity rate at Cycle 2 is defined as the proportion of patients with negative Cycle 2 PET results. PET negativity is a binary outcome variable.

5.8.5 Other Efficacy Endpoints

Alive without HL rate at 3 years and 5 years is defined as the proportion of patients who are alive without classical Hodgkin lymphoma at 3 years or 5 years after the patient's randomization date.

Alive without HL rates between the 2 treatment arms will be compared using a stratified Cochran-Mantel-Haenszel (CMH) test.

5.9 Pharmacokinetic, Pharmacodynamic, and Biomarker Analysis

5.9.1 Pharmacokinetic Analyses

The PK of the antibody-drug conjugate (brentuximab vedotin), total antibody, and unconjugated drug (MMAE) will be based on serum or plasma samples collected from patients who meet study inclusion criteria, received study drug, and provided evaluable PK data. Population PK parameters will be calculated with an appropriate method based on a validated PK analysis program. Exploratory safety-PK, efficacy-PK, and if possible, PK-pharmacodynamic relationships will be determined.

Descriptive statistics (eg, number of patients, mean, standard deviation, median, minimum, and maximum) will be used to summarize concentrations of analyte for brentuximab vedotin-treated patients.

The pharmacokinetics of doxorubicin, vinblastine, and dacarbazine will be compared between the treatment arms. Descriptive statistics (eg, number of patients, mean, standard deviation, median, minimum, and maximum) will be used to summarize concentrations of analyte. Geometric mean ratios of the AUC will be calculated for each AVD component (doxorubicin, vinblastine, and dacarbazine).

5.9.2 Immunogenicity Analysis

All patients who were administered at least 1 dose of brentuximab vedotin will be evaluated for antitherapeutic antibody (ATA) development. A list/table of ATA status will be provided. Antibody neutralizing status (neutralizing or not neutralizing) will also be listed for patients who have positive antibody status.

Immunogenicity information, including ATA and neutralizing ATA, will be summarized in descriptive statistics as applicable.

Relationships between ATA development and safety and efficacy will be explored.

5.9.3 Biomarker Analysis

Absolute and change from baseline value of circulating biomarkers will be summarized by time point using descriptive statistics, as applicable. Descriptive statistics (eg, number of patients, mean, standard deviation, median, minimum, and maximum) will also be provided to summarize disease markers [redacted]), tissue levels of potential resistance markers ([redacted]), and qualitative and semiquantitative measures of markers [redacted]), and change from baseline values of these markers, as applicable. The association between these and clinical response or safety endpoints might be explored.

5.10 Resource Utilization and Patient-Reported Outcome Analysis

Analyses of patient-reported outcomes (PROs) and health economics will be performed using the ITT population.

5.10.1 Patient-Reported Outcomes Analysis

Patient-reported outcome (PRO) assessments based on EORTC QLQ-C30, FACIT Dyspnea 10, and FACT/GOG-NTX Additional scale will be analyzed to determine if response to therapy is accompanied by changes in the quality of life.

The analysis will be based on scores from the global health status/QoL scale of QLQ-C30, shortness of breath scale of FACIT Dyspnea 10, and the sensory scale of FACT/GOG-NTX. The analysis of change of scores from baseline will use mixed-effects models with repeated measures at each time point specified in the Schedule of Events of the protocol and the 95% CIs of the estimates will be provided.

Descriptive summaries of all the scales and individual item scores observed will be generated at each scheduled assessment time point by treatment.

Missing data will be summarized with the proportion of missing responses for each item over time. Manuals for scoring and handling missing data published for QLQ-C30, FACIT Dyspnea 10, and FACT/GOG-NTX will be used to impute missing data initially.

A sensitivity analysis will be performed to evaluate the impact on the analysis results from missing data imputation. Conditional on the patterns of missing data, multiple imputation methods, including a pattern-mixture model, will be considered. Any deaths that occur before the end of treatment (EOT) are to be imputed by a value zero and will be considered missing otherwise.

5.10.2 Health Economics Analysis Using Medical Resource Utilization and Utility

EQ-5D scores will be summarized in descriptive statistics for treatment arms.

MRU data will be summarized in descriptive statistics of medical encounters (length of stay, inpatient, outpatient, and reason), number of missing days from work or other activities by patient and care-giver for treatment arms.

Further modeling will be performed separately at post hoc analyses.

5.11 Safety Analyses

Safety will be evaluated by the incidence of TEAEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, ECOG performance status, ECG, and

clinical laboratory results. Exposure to study drug and reasons for discontinuation will be tabulated.

These analyses will be performed using the safety population.

5.11.1 Adverse Events

Treatment-emergent adverse events are defined as any AE that occurs after administration of the first dose of study drug and through 30 days after the last dose of frontline therapy.

The MedDRA dictionary will be used to code the investigator's adverse event terms. Adverse event tables will summarize subject incidence by treatment group actually received. The severity of adverse events will be assessed using NCI CTCAE version 4.03.

5.11.1.1 Adverse Events

The number and percentage of patients experiencing at least 1 treatment emergent adverse event will be tabulated by MedDRA primary system organ class, high level term, preferred term, and treatment group. For the number of patients with AEs, patients reporting the same event more than once will have that event counted only once within each body system, once within each high level term, and once within each preferred term. AEs will be coded using the MedDRA dictionary.

The number and percentage of patients experiencing at least 1 treatment emergent AE considered related to treatment will also be summarized. If the event is missing relationship data, the event will be included in the total column for the corresponding treatment group. Multiple occurrences of the same event are counted once per subject using the most related event.

AEs will also be summarized by intensity grade. Again, multiple occurrences of the same event are counted once per subject using the maximum intensity. If the intensity of an AE is missing, the event will be included in the total column for the corresponding treatment group.

The following tabulations will also be presented:

- Incidence of treatment-emergent adverse events by System Organ Class (SOC), high-level term, and preferred term

- Incidence of treatment-emergent adverse events reported by at least 10% of patients in either treatment group by MedDRA preferred term

- Incidence of treatment-emergent adverse events considered by the investigator to be related to study drug by MedDRA SOC, high-level term and preferred term

- Incidence of treatment-emergent adverse events that caused study drug dose modification by MedDRA SOC, high-level term and preferred term

For treatment-emergent adverse events with NCI CTCAE toxicity Grade 3 or higher, the following summaries are to be produced:

- Incidence of Grade ≥ 3 treatment-emergent adverse events, by SOC, high-level term and preferred term

- Incidence of Grade ≥ 3 treatment-emergent adverse events considered by the investigator to be related to study drug, by SOC, high-level term and preferred term

5.11.1.2 Serious Adverse Events

The number and percentage of patients experiencing at least 1 treatment-emergent serious AE (SAE) will be summarized by MedDRA primary system organ class, high-level term, and preferred term. The following summaries are to be produced:

- Incidence of treatment-emergent serious adverse events, by SOC, high-level term and preferred term

- Incidence of treatment-emergent serious adverse events considered by the investigator to be related to study drug, by SOC, high-level term and preferred term

In addition, a by-subject listing of the SAEs will be presented (the subject listing will contain all SAEs regardless of treatment emergent AE status).

5.11.1.3 Deaths

All deaths occurring on-study and during follow-up will be summarized. Cause of death will be summarized as well in this table. Frequencies of deaths due to study treatment-related adverse events will also be reported.

A by-subject listing of the deaths will be presented. All deaths occurring on-study and during follow-up will be displayed (regardless of treatment emergent AE status).

5.11.1.4 Adverse Events Resulting in Discontinuation of Study Drug

Adverse events results in discontinuation of study drug will be tabulated by treatment. A by-subject listing of AEs resulting in discontinuation of study drug will be presented.

5.11.2 Laboratory Data

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units. If a lab value is reported using a non-numeric qualifier (eg, less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier. In case a central lab value is missing, the local lab, if available, will be used.

If a subject has repeated laboratory values for a given time point, the value from the last evaluation will be used.

The parameters to be analyzed are as follows:

- Hematology: hemoglobin, hematocrit, platelet count, leukocytes with differential, neutrophils (absolute neutrophil count [ANC])
- Serum chemistry: Blood urea nitrogen, Creatinine, Total bilirubin, Urate, Lactate dehydrogenase, Gamma-glutamyl transpeptidase (GGT), Phosphate, Albumin, Alkaline phosphatase (ALP), AST, ALT, Glucose, Sodium, Potassium, Calcium, Chloride, Carbon dioxide, Magnesium.
- Other: Hemoglobin A1C

Laboratory data of hematology and clinical chemistry up to 30 days after last dose or the End of Treatment visit date, whichever is later, will be reported in SI units. Normal ranges from the central and local laboratories used in this study will be listed.

Summary statistics (mean, standard deviation, median, and range) will be calculated for the raw data and for their percentage changes from baseline at each time point of assessment and for the percentage changes from baseline to the last value. Individual values outside the

normal ranges will be identified (by "H" for high and "L" for low) in the data listings displaying the absolute values for each subject.

Shift tables from baseline to worst value (ie, worst grade) on study (from treatment start to 30 days after last dose or the End of Treatment visit date, whichever is later) will be provided for the following laboratory parameters: hemoglobin, ANC, WBC, platelets, AST, ALT, bilirubin and HbA1C.

5.11.3 Electrocardiograms

Investigators' assessments of ECG monitoring (normal, abnormal and clinically significant, or abnormal and not clinically significant), including unscheduled or retested measurements, will be presented in a listing.

5.11.4 Vital Signs

The actual values of vital sign parameters including temperature, pulse rate, and systolic and diastolic blood pressure when available, will be summarized over time.

6. CHANGES TO PLANNED ANALYSES FROM PROTOCOL

Not applicable

7. PROGRAMMING CONSIDERATIONS

7.1 Statistical Software

SAS version 9.1 (or higher) will be used for all analyses.

7.2 Rules and Definitions

Subject populations are defined in Section 2.

Baseline values are defined in Section 5.4.2.

Treatment-emergent AEs are defined in Section 5.11.1.1.

8. REFERENCES

Not applicable.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Biostatistics Approval	10-Mar-2015 18:13
[redacted]	Biostatistics Approval	10-Mar-2015 19:17
[redacted]	Clinical Approval	10-Mar-2015 20:30

Statistical Analysis Plan Version & Date	Changes (Summarized)
Draft Version 1.0, 22May2012	Not applicable
Draft Version 2.0, 10March2015	• Increase the sample size by 200 patients to a total of approximately 1240 enrolled patients (section 1.1) • Delete reference to the percentage of the original sample size that was planned for inclusion in the interim futility analysis (section 4.1) • Align the timing of the interim overall survival analysis with that for the final modified PFS analysis (section 4.1) • Revise the statistical assumptions of modified PFS rates for both treatment arms in the study (section 5.1 and 5.8.2) • Add language to clarify rules to apply to dates recorded in the screening visits (section 5.4.1.1) • Add language to define relative dose intensity (section 5.7.2.1) • Provide symmetry across the 2 treatment arms in the definition of completion of frontline therapy (section 5.8.1.1): o Standardize the definition of a missed dose across the 2 treatment arms to permit investigators, who are best able to determine the adequacy of the delivered regimen and the need to make adjustments for treatment-related toxicity, to omit individual agents from the randomized treatment regimen without this counting as a missed dose • Further clarify the sensitivity analyses around the modified PFS endpoint (section 5.8.2.1) • Revise the 'Age' and add the 'Baseline extranodal site' subgroups for subgroup analyses (section 5.8.2.2, Table 5-4) • Add language describing the mixture cure survival model (section 5.8.2.2) • Remove requirement for graphical displays of over time summaries for laboratory data and clarify shift tables that will be produced for laboratory data (section 5.11.2) • Institute minor modifications in protocol language to improve protocol clarity and compliance, and align study conduct with the sponsor's current guidelines and practices • Correct typographical errors, punctuation, grammar, and formatting