Clinical Study Protocol

NCT Number: NCT05673785

Title: A Phase 2, Single-Arm, Open-Label, Multicenter Study of Brentuximab Vedotin in Combination With Cyclophosphamide, Doxorubicin (Hydroxydaunorubicin), Prednisone (CHP) in the Frontline Treatment of Chinese Patients With CD30-Positive (CD30+) Peripheral T-Cell Lymphomas (PTCL)

Study Number: C25024

Document Version and Date: Original Protocol, 13 Dec 2021

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

PROTOCOL

A Phase 2, Single-Arm, Open-Label, Multicenter Study of Brentuximab Vedotin in Combination With Cyclophosphamide, Doxorubicin (Hydroxydaunorubicin), Prednisone (CHP) in the Frontline Treatment of Chinese Patients With CD30-Positive (CD30+) Peripheral T-Cell Lymphomas (PTCL)

A Phase 2, Single-Arm, Open-Label Study of A+CHP as Frontline Treatment of Chinese Patients With CD30+ PTCL

Sponsor:	Takeda Pharma A/S. Takeda Development Center Americas, Inc. has been authorized by Takeda Pharma A/S to conduct this study in the People's Republic of China.
Study Number:	C25024
EudraCT Number:	Not applicable
Compound:	Brentuximab vedotin
Date:	13 December 2021

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Serious adverse event (SAE) and pregnancy reporting information is presented in Section 10.0, as is information on reporting product complaints.

The names and contact information for the medical monitor and responsible medical officer are in the study manual.

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic Signatures may be found on the last page of this document.

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INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure (IB), prescribing information, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study participants in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- ICH E6 GCP: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section 10.0 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the investigator (Appendix B).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

_____
Signature of Investigator Date

_____
Investigator Name (print or type)

_____
Investigator's Title

_____
Location of Facility (City, State/Province)

_____
Location of Facility (Country)

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2.0 STUDY SUMMARY

Name of Sponsor: Takeda Pharma A/S. Takeda Development Center Americas, Inc. has been authorized by Takeda Pharma A/S to conduct this study in the People's Republic of China.	**Compound:** Brentuximab vedotin
Title of Protocol: A Phase 2, Single-Arm, Open-Label, Multicenter Study of Brentuximab Vedotin in Combination With Cyclophosphamide, Doxorubicin (hydroxydaunorubicin), Prednisone (CHP) in the Frontline Treatment of Chinese Patients With CD30-Positive (CD30+) Peripheral T-Cell Lymphomas (PTCL)	**EudraCT No.:** Not applicable
Study Number: C25024	**Phase:** 2
Study Design: Study C25024 is a phase 2, single-arm, open-label, multicenter study designed to evaluate the efficacy, safety, and pharmacokinetics (PK) of brentuximab vedotin (Adcetris) plus cyclophosphamide, doxorubicin (hydroxydaunorubicin), and prednisone (A+CHP) as frontline treatment of Chinese patients with newly diagnosed, CD30-positive (CD30+) PTCL. Eligible histologies include anaplastic lymphoma kinase (ALK)-positive systemic anaplastic large cell lymphoma (sALCL) with an International Prognostic Index (IPI) score of ≥2, ALK-negative sALCL, PTCL-NOS (not otherwise specified), angioimmunoblastic T-cell lymphoma (AITL), enteropathy-associated T-cell lymphoma (EATL), and hepatosplenic T-cell lymphoma (HSTCL).	
Primary Objectives: • To evaluate overall response rate (ORR) (ie, complete response [CR] and partial response [PR]) by independent review facility (IRF) assessment per Revised Response Criteria for Malignant Lymphoma following the completion of study treatment [1]. • To evaluate the safety and tolerability of the A+CHP combination.	
Secondary Objectives: • To evaluate CR rate by IRF assessment per Revised Response Criteria for Malignant Lymphoma criteria following the completion of study treatment. • To evaluate 1-year progression-free survival (PFS) rate by IRF assessment per Revised Response Criteria for Malignant Lymphoma criteria. • To evaluate 1-year overall survival (OS) rate. • To evaluate IRF- and investigator-assessed ORR and CR rate following the completion of study treatment, time to response (TTR), and 1-year PFS rate per 2014 Lugano classification. • To evaluate duration of response (DOR) by investigator assessment per 2014 Lugano classification. • To collect serum/plasma concentration time data to contribute to population PK (popPK) analyses. • To assess immunogenicity.	
Additional Objectives: • To evaluate PFS by investigator assessment. • To evaluate OS.	
Patient Population: Patients aged at least 18 years with previously untreated CD30+ PTCL.	
Number of Patients: Approximately 52 patients, including approximately 36 patients with the primary diagnosis of sALCL.	**Number of Sites:** Estimated total: 15 investigative sites in China.

Doses: Brentuximab vedotin 1.8 mg/kg, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2 on Day 1 of each 21-day treatment cycle; prednisone 100 mg once daily on Days 1 through 5 of each 21-day treatment cycle.	**Route of Administration:** Brentuximab vedotin 1.8 mg/kg is to be administered as an intravenous (IV) infusion over approximately 30 minutes on Day 1 of each 21-day cycle within 1 hour of completing treatment with other agents, ie, cyclophosphamide and doxorubicin administered IV. Prednisone is to be given orally at the dose of 100 mg daily on Days 1 through 5 with ±1 day window.
Duration of Treatment: Six to eight 21-day cycles of A+CHP, which is approximately 18 to 24 weeks, or 4.5 to 6 months of treatment. Patients may receive study treatment until progressive disease (PD), unacceptable toxicity, or completion of the desired 6 to 8 cycles, whichever occurs first.	**Period of Evaluation:** Radiographic disease evaluation will be conducted at baseline, Cycle 4, and at last cycle of study treatment. During the PFS follow-up period, radiographic disease assessment will be performed every 3 months through 24 months after initiation of study treatment and every 6 months, thereafter, until PD per investigator assessment, initiation of new anticancer therapy to treat residual or progressive disease, death, or study closure, whichever occurs first. Once a patient experiences PD per investigator assessment, the patient will be followed for OS every 6 months until death or study closure, whichever occurs first. All patients will have the opportunity to be followed for 36 months after the last patient's first dose of study treatment.

Main Criteria for Inclusion:

Adult patients (Chinese) ≥18 years with previously untreated, CD30+ PTCL per the Revised European American Lymphoma World Health Organization (WHO) 2016 classification by local assessment are eligible for study enrollment. Eligible histologies include ALK-positive sALCL with an IPI score of ≥2, ALK−negative sALCL, PTCL-NOS, AITL, EATL, and HSTCL.

Other main inclusion criteria are:

- An Eastern Cooperative Oncology Group (ECOG) performance status of ≤2.
- Fluorodeoxyglucose-avid disease by positron emission tomography imaging and at least 1 bidimensionally measurable lesion (>1.5 cm in its largest dimension by computed tomography).

Main Criteria for Exclusion:

Patients with a current diagnosis of primary cutaneous CD30+ lymphoproliferative disorders/lymphoma (ie, patients with cutaneous ALCL with extracutaneous tumor spread beyond locoregional lymph nodes are eligible) or mycosis fungoides; and patients with a history of progressive multifocal leukoencephalopathy or known active cerebral/meningeal disease related to the underlying malignancy are excluded from enrollment.

Main Criteria for Evaluation and Analyses:

Primary Endpoints:

- ORR by IRF assessment per Revised Response Criteria for Malignant Lymphoma following the completion of study treatment.
- Adverse events (AEs), assessment of clinical laboratory values, and vital signs measurements.

Secondary Endpoints:

- CR rate by IRF assessment per Revised Response Criteria for Malignant Lymphoma criteria following the completion of study treatment.
- 1-year PFS rate by IRF assessment per Revised Response Criteria for Malignant Lymphoma criteria.
- 1-year OS rate.
- ORR and CR rate following completion of study treatment, TTR, and 1-year PFS rate by IRF and investigator

assessment per 2014 Lugano classification.
- DOR by investigator assessment per 2014 Lugano classification.
- PK (serum antibody-drug conjugate and plasma monomethyl auristatin E concentration time data) to contribute to popPK analyses.
- Immunogenicity assessment; antidrug antibody (ADA) status, including ADA negative, ADA transiently and persistently positive, ADA titer, and neutralizing antidrug antibody (Nab) negative and positive.

Additional Endpoints:

- PFS as assessed by investigator.
- OS.

Statistical Considerations:

Only descriptive summaries and analyses will be performed for all efficacy, safety, and PK endpoints.

Sample Size Justification: It is anticipated that approximately 52 patients will be enrolled in this study. With a target sALCL patient proportion of 70%, approximately 36 sALCL patients need to be enrolled in the study. In ECHELON-2 (ClinicalTrials.gov: NCT01777152), the pivotal phase 3, randomized, double-blind, double-dummy (brentuximab vedotin and vincristine were administered in a double-blinded, double-dummy manner), actively controlled, multicenter study, the observed ORR was 87.65% for sALCL patients and 71.88% for non-sALCL patients. Assuming a true ORR for sALCL and non-sALCL patients are the same as the observed ORR in ECHELON-2, with a sample size of approximately 52 patients, the probability of observing ORR by IRF assessment greater than the lower bound of 95% CI (77.7%-87.8%) of ECHELON-2 is approximately 83%.

Another rationale to determine the sample size is to ensure the lower bound of the observed 95% CI of ORR by IRF is greater than the threshold response rate of 65% [2,3].

With a sample size of approximately 52 patients, the desire is to minimally observe 41 responders (CR or PR) in order for the lower bound of the exact 95% CI of ORR by IRF assessment to be greater than 65%. Using the same assumption as previously described, the probability of observing at least 41 responders is approximately 83%.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities, except for those identified in the clinical supplier list in the study manual. The identified vendors will perform specific study-related activities either in full or in partnership with the sponsor.

3.2 Principal Investigator/Coordinating Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research, and study participation. The signatory coordinating investigator will be required to review and sign the clinical study report (CSR) and, by doing so, agree that it accurately describes the results of the study.

3.3 List of Abbreviations

Abbreviation	Definition
A+CHP	Adcetris plus cyclophosphamide, doxorubicin (hydroxydaunorubicin), and prednisone
ADA	antidrug antibody(ies)
ADC	antibody-drug conjugate
AE	adverse event
AITL	angioimmunoblastic T-cell lymphoma
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
ALK−	anaplastic lymphoma kinase–negative
ALK+	anaplastic lymphoma kinase–positive
ALT	alanine aminotransferase
AST	aspartate aminotransferase
cAC10	CD30-directed monoclonal antibody
CD30+	CD30-positive
cHL	classical Hodgkin lymphoma
CHOEP	cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone
CHOP	cyclophosphamide, doxorubicin (hydroxydaunorubicin), vincristine (Oncovin), and prednisone
CHP	cyclophosphamide, doxorubicin (hydroxydaunorubicin), and prednisone
CR	complete response
CRO	contract research organization
CSF	colony stimulating factor
CSR	clinical study report
CT	computed tomography
CYP	cytochrome P450
DOR	duration of response
EATL	enteropathy associated T-cell lymphoma
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
FAS	full analysis set
FDG	fluorodeoxyglucose
G-CSF	granulocyte colony stimulating factor
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HL	Hodgkin lymphoma

Abbreviation	Definition
HSTCL	hepatosplenic T-cell lymphoma
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IPI	International Prognostic Index
IRB	institutional review board
IRF	independent review facility
IRR	infusion-related reaction
IV	intravenous
IXRS	interactive voice/web response system
JCV	John Cunningham virus
MF	mycosis fungoides
mITT	modified intent-to-treat
MMAE	monomethyl auristatin E
MRI	magnetic resonance imaging
Nab	neutralizing antidrug antibody
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma(s)
NK	natural killer
NMPA	National Medical Product Administration
ORR	overall response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
popPK	population pharmacokinetics
PR	partial response
PTCL	peripheral T-cell lymphoma
PTCL-NOS	peripheral T-cell lymphoma-not otherwise specified
r/r	relapsed or refractory
SAE	serious adverse event
sALCL	systemic anaplastic large cell lymphoma
SAP	statistical analysis plan
SCT	stem cell transplantation
SJS	Stevens-Johnson syndrome
SOE	schedule of events

Abbreviation	Definition
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
TTR	time to response
ULN	upper limit of normal
US	United States
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

4.1.1 Peripheral T-cell Lymphomas

Peripheral T-cell lymphoma (PTCL) is a heterogeneous group of rare lymphoproliferative disorders that originate from clonal expansion of mature, postthymic T cells [4]. Overall, PTCL represents approximately 10% to 15% of non-Hodgkin lymphomas worldwide but is more prevalent in Asia, with PTCL or natural killer (NK)/T-cell lymphoma representing approximately 15% to 20% of all lymphomas in Asian populations [5,6]. In Asia, PTCL incidence is higher due to the endemic occurrence of Epstein-Barr virus–associated extranodal NK/T-cell lymphoma [6]. In China, PTCL accounts for approximately 10% of newly diagnosed lymphomas [7].

Significant advances have occurred in the classification of both nodal and extranodal T-cell and NK-cell neoplasms, which have led to revisions in the classification and introduction of new provisional entities. Many of these changes are the result of genomic studies using approaches to examine gene expression profiling and the genetic landscape of T-cell and NK-cell neoplasms [8]. Various subtypes of T-cell and NK-cell lymphomas are known to express the cell surface marker CD30; of these subtypes, systemic anaplastic large cell lymphoma (sALCL) is most notable, in which CD30 expression is a hallmark of diagnosis.

CD30 expression is well documented in some of the other most common PTCL subtypes, including PTCL-not otherwise specified (PTCL-NOS) with CD30 expression up to 60%; angioimmunoblastic T-cell lymphoma (AITL), CD30 expression up to 60%; enteropathy-associated T-cell lymphoma (EATL), CD30 expression 50% to 80%; adult T-cell leukemia/lymphoma with CD30 expression 30% to 55%; and hepatosplenic T-cell lymphoma (HSTCL) [9,10].

The median age at diagnosis of PTCL is 60 to 70 years, except for ALK-positive anaplastic large cell lymphoma (ALCL), which is diagnosed at the much younger age of 30 to 40 years. While heterogenous, this group of malignancies is generally treated with either CHOP (cyclophosphamide, doxorubicin [hydroxydaunorubicin], vincristine [Oncovin], and prednisone, given for 6 to 8 cycles) or CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone) [6,11-13]; however, treatment guidelines recommend clinical trials as a therapeutic option due to the inadequacy of existing treatment modalities [13,14]. (It should be noted that, before the ECHELON-2 study, no therapy had demonstrated an overall survival (OS) benefit greater than that obtained with CHOP in more than 3 decades.

The sALCL subtype of PTCL is a rare and aggressive T-cell lymphoma that accounts for approximately 2% to 3% of adult non-Hodgkin lymphomas (NHL) [6]. In China, sALCL, including ALK-positive and ALK-negative variants, account for approximately 2.8% of all cases of NHL [7]. The 2016 age-standardized incidence rate of NHL was 4.29 per 100,000 person-years [15], with an approximate annualized incidence of sALCL of 0.12 per 100,000 perso-years. The incidence rate has a slight male predominance (1.2:1 in ALK-positive sALCL and 1.6:1 in

ALK-negative sALCL). The median age is 29 years for patients with ALK-positive sALCL and 45 years for those with ALK-negative sALCL [7].

4.1.2 Brentuximab Vedotin

Brentuximab vedotin is an antibody-drug conjugate (ADC), which consists of a CD30-directed monoclonal antibody (cAC10) covalently linked, via an enzyme-cleavable linker, to the antimitotic small monomethyl auristatin E (MMAE). cAC10 binds to the CD30 antigen, which has very low expression on normal cells, but is found at higher levels of expression on the Hodgkin and Reed-Sternberg cells of Hodgkin lymphoma (HL), on ALCL cells, and on tumor cells of other varied lymphoproliferative disorders. The anticancer activity of brentuximab vedotin is due to the binding of the ADC to CD30-expressing cells, followed by internalization of the ADC-CD30 complex, and the release of MMAE via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic death of the cell.

4.1.3 Clinical Experience With Brentuximab Vedotin

As of 18 August 2021, approximately 3061 patients have received brentuximab vedotin in company-sponsored clinical studies, including 28 completed clinical studies of brentuximab vedotin as a single agent or in combination with other anticancer therapies, and 8 ongoing clinical studies. The 28 completed clinical studies include the pivotal phase 3 study, ECHELON-2 (SGN35-014), which was designed to compare brentuximab vedotin (Adcetris) plus CHP (cyclophosphamide, doxorubicin [hydroxydaunorubicin], and prednisone) (A+CHP) versus CHOP in the frontline treatment of patients with CD30-positive (CD30+) PTCL. The results of ECHELON-2 showed a marked treatment effect of brentuximab vedotin combined with CHP as clinically meaningful, and associated with a positive benefit-risk ratio in the patient population.

Study C25010 (ClinicalTrials.gov: NCT02939014) was the previous local registration study of brentuximab vedotin in Chinese patients with relapsed or refractory (r/r) classical Hodgkin lymphoma (cHL) and r/r sALCL. Study C25010 was a single-arm, open-label, multicenter, phase 2 study designed to evaluate the efficacy, safety, and pharmacokinetics (PK) of brentuximab vedotin as a single agent in Chinese patients with r/r CD30+ HL or sALCL. Brentuximab vedotin was administered as a single, 1.8 mg/kg intravenous (IV) infusion on Day 1 of each 3-week cycle.

A total of 39 patients (30 HL and 9 sALCL patients) were enrolled and received at least 1 dose of brentuximab vedotin. All 39 enrolled patients were included in the safety/modified intent-to-treat (mITT) population.

Brentuximab vedotin showed antitumor activity in Chinese patients with HL and sALCL. The overall response rate (ORR) for the mITT population was 69.2% (95% CI, 52.4%-83.1%). Objective responses were reported for 27 patients, including 11 patients (28.2%) with a best response of a complete response (CR) and 16 patients (41.0%) with a partial response (PR).

Among the 30 patients with HL, the ORR was 70.0% (95% CI, 50.6%-85.3%), with a best response of a CR reported for 6 patients (20%) and a PR reported for 15 patients (50%). A total of 16 patients in the mITT population, including 11 HL patients, achieved a response within

2 months after the first dose, and 7 patients, including 3 HL patients, improved their response over the course of study treatment.

Among the 9 patients with sALCL, the ORR was 66.7% (95% CI, 29.9%-92.5%), with a CR reported for 5 patients (55.6%) and a PR for 1 patient (11.1%). A total of 5 patients with sALCL attained a response within 2 months after the first dose, and 4 patients with sALCL improved their response over the course of study treatment.

The results showed a positive benefit-risk profile for brentuximab vedotin in Chinese patients, consistent with the clinical profile of brentuximab vedotin in the global r/r cHL and sALCL patient populations.

Study SGN35-014 (**ECHELON-2**; ClinicalTrials.gov: NCT01777152**)** was a pivotal phase 3, randomized, double-blind (brentuximab vedotin and vincristine administered in a double-blinded, double-dummy manner), actively controlled, multicenter study to evaluate the efficacy and safety of adding brentuximab vedotin to the standard of care treatment of patients with previously untreated CD30+ PTCL. The study's primary endpoint was progression-free survival (PFS) by independent review facility (IRF) assessment. A total of 452 patients were randomized: 226 patients in experimental arm, A+CHP, and 226 patients in the standard of care arm, CHOP. A total of 449 patients were treated in the study; 223 patients received A+CHP, and 226 patients received CHOP.

The A+CHP regimen was well tolerated and had a manageable safety profile that was similar to that of CHOP. No new safety signals were identified. In both treatment arms, the addition of primary prophylactic granulocyte-colony stimulating factor (G-CSF) (administered to 34% of A+CHP patients and 27% of CHOP patients) reduced the incidence and severity of febrile neutropenia and Grade 3 or higher neutropenia to a similar degree.

In the intent-to-treat population, treatment with A+CHP resulted in statistically significant and clinically meaningful improvements in the primary endpoint of PFS by IRF assessment, with a 29% reduction in the risk of a PFS event versus CHOP (stratified hazard ratio,0.71 [95% CI, 0.54-0.93]; p=0.011). The median PFS with A+CHP was 48.2 months versus 20.8 months with CHOP, and OS was also significantly improved with A+CHP versus CHOP. The stratified hazard ratio was 0.66 (95% CI, 0.46-0.95; p=0.0244), which equates to a 34% reduction in the risk of death for patients treated with A+CHP versus CHOP.

4.1.4 Known or Potential Risks of Brentuximab Vedotin

- Brentuximab vedotin causes both sensory and motor peripheral neuropathy. Brentuximab vedotin-induced peripheral neuropathy is typically cumulative and generally reversible. Monitoring patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, and neuropathic pain or weakness, is required. Patients experiencing new or worsening peripheral neuropathy may require brentuximab vedotin dose modifications, including a dose delay.
- Complete blood counts should be monitored before 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 with dose delays, reductions, or discontinuations.

- Infusion-related reactions (IRRs), including anaphylaxis, have occurred with brentuximab vedotin. 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. Patients who have experienced a prior IRR should be premedicated according to institutional guidelines for subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid.
- 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 through 30 days after the last dose.
- Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) have been reported with brentuximab vedotin. If SJS/TEN occur, brentuximab vedotin must be discontinued and the appropriate medical therapy administered.
- Tumor lysis syndrome may occur. Patients with rapidly proliferating tumors 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.
- Progressive multifocal leukoencephalopathy (PML) has been reported with brentuximab vedotin use. If PML is suspected, a diagnostic work-up should be performed as described in Section 8.7.5.
- 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 and displacement of bile duct stent).
- Hepatotoxicity has been reported in patients treated with brentuximab vedotin and has contributed to fatal outcomes in some cases. The majority of events in the category of hepatobiliary disorders were characterized by asymptomatic mild to moderate transient elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT). Elevated liver enzymes were observed upon rechallenge for some patients. Serious hepatobiliary disorders have also been reported, but causal relationship with brentuximab vedotin could not be established due to confounding by comorbidities and/or concomitant medications with known hepatotoxic potential.
- Gastrointestinal complications, including intestinal obstruction, ileus, enterocolitis, neutropenic colitis, erosion, ulcer, perforation, and hemorrhage, some with fatal outcomes, have been reported in patients treated with brentuximab vedotin. Some cases of gastrointestinal perforations were reported in patients with gastrointestinal involvement of underlying lymphoma. In the event of new or worsening gastrointestinal symptoms, perform a prompt diagnostic evaluation and treat appropriately.

- The PK of brentuximab vedotin was studied in patients with hepatic or renal impairment. Patients with hepatic impairment (Child-Pugh class A to C) and patients with severe renal impairment (creatinine clearance lower than 30 mL/min) exhibited a trend toward moderate decreases in ADC exposure and increases in MMAE exposure; therefore, patients with hepatic impairment and/or severe renal impairment at baseline will not be enrolled in this study. Patients with hepatic or renal impairment during study treatment should be closely monitored for adverse events (AEs) and will be treated based on the local standard of care.
- Coadministration of brentuximab vedotin with ketoconazole, a strong cytochrome P450 (CYP) 3A4 and P-glycoprotein (P-gp) inhibitor, increased the exposure to the antimicrotubule agent, MMAE by approximately 73% and did not alter the plasma exposure to brentuximab vedotin. Therefore, coadministration of brentuximab vedotin with strong CYP3A4 and P-gp inhibitors may increase the incidence of neutropenia.
- Coadministration of brentuximab vedotin with rifampicin, a strong CYP3A4 inducer, did not alter the plasma exposure to brentuximab vedotin; however, it reduced exposure to MMAE by approximately 31%.
- Coadministration of midazolam, a CYP3A4 substrate, with brentuximab vedotin did not alter the metabolism of midazolam; therefore, brentuximab vedotin is not expected to alter the exposure to medicines that are metabolized by CYP3A4 enzymes.
- 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.

Refer to the brentuximab vedotin investigator's brochure (IB) for details.

4.2 Rationale for the Proposed Study

The results of the pivotal phase 3, randomized, double-blind, global, multicenter study, ECHELON-2 (Study SGN35-014) of A+CHP versus CHOP in the frontline treatment of patients with CD30+ PTCL demonstrated a marked treatment effect of brentuximab vedotin plus CHP as both clinically meaningful and associated with a positive benefit-risk ratio in the patient population. In the local registration study, Study C25010, in Chinese patients with r/r cHL and r/r sALCL, the study results showed a positive benefit-risk profile for brentuximab vedotin in Chinese patients with r/r cHL and sALCL consistent with the clinical profile of brentuximab vedotin in the global r/r cHL and sALCL patient populations.

In Chinese patients with untreated CD30+ PTCL, the clinical practice is consistent with the global standard of care and is expected to fill an unmet medical need. This bridging study is designed to determine the efficacy, safety, and PK of A+CHP in the frontline treatment of Chinese patients with CD30+ PTCL.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

The primary objectives are:

- To evaluate ORR (CR and PR) by IRF assessment per Revised Response Criteria for Malignant Lymphoma [1] following the completion of study treatment.
- To evaluate the safety and tolerability of the A+CHP combination.

5.1.2 Secondary Objectives

The secondary objectives are:

- To evaluate CR rate by IRF assessment per Revised Response Criteria for Malignant Lymphoma criteria following the completion of study treatment.
- To evaluate 1-year PFS rate by IRF assessment per Revised Response Criteria for Malignant Lymphoma criteria.
- To evaluate 1-year OS rate.
- To evaluate IRF- and investigator-assessed ORR and CR rate following the completion of study treatment, time to response (TTR), and 1-year PFS rate per 2014 Lugano classification.
- To evaluate duration of response (DOR) by investigator assessment per 2014 Lugano classification.
- To collect serum/plasma concentration time data to contribute to population PK (popPK) analyses.
- To assess immunogenicity.

5.1.3 Additional Objectives

The additional objectives are:

- To evaluate PFS by investigator assessment.
- To evaluate OS.

5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoints are:

- ORR by IRF assessment per Revised Response Criteria for Malignant Lymphoma criteria following the completion of study treatment.

- AEs, assessment of clinical laboratory values, and vital signs measurements.

5.2.2 Secondary Endpoints

The secondary endpoints are:

- CR rate by IRF assessment per Revised Response Criteria for Malignant Lymphoma criteria following the completion of study treatment.
- 1-year PFS rate by IRF assessment per Revised Response Criteria for Malignant Lymphoma criteria.
- 1-year OS rate.
- ORR and CR rate following completion of study treatment, TTR, and 1-year PFS rate by IRF and investigator assessment per 2014 Lugano classification.
- DOR by investigator assessment per 2014 Lugano classification.
- PK (serum ADC and plasma MMAE concentration time data) to contribute to popPK analyses.
- Immunogenicity status; antidrug antibody (ADA) status, including ADA negative, ADA transiently and persistently positive, ADA titer, and neutralizing antidrug antibody (Nab) negative and positive.

5.2.3 Additional Endpoints

The additional endpoints are:

- PFS by investigator assessment.
- OS.

6.0 STUDY DESIGN

6.1 Overview of Study Design

Study C25024 is a phase 2, single-arm, open-label, multicenter study designed to evaluate the efficacy, safety, and PK of A+CHP as frontline treatment of Chinese patients with newly diagnosed CD30+ PTCL. Eligible histologies include ALK-positive sALCL with an International Prognostic Index (IPI) score of ≥2, ALK-negative sALCL, PTCL-NOS, AITL, EATL, and HSTCL.

Enrollment of approximately 52 patients is planned for the study, including approximately 36 patients with the primary diagnosis of sALCL to mimic the proportion of patients with sALCL in ECHELON-2.

Enrolled patients will receive 6 to 8 cycles of A+CHP, each lasting 21 days, as determined by the investigator and based on patient-specific characteristics, including disease stage and IPI score. Patients will receive study treatment until progressive disease (PD), unacceptable toxicity, or completion of the desired 6 to 8 cycles, whichever occurs first. Patients, including those who

discontinue study treatment for any reason other than withdrawal of consent, will have safety follow-up assessments through 30 to 37 days after the last dose of study treatment.

Enrolled patients will undergo radiographic evaluation consisting of fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging and contrast-enhanced computed tomography (CT) scans of the neck, chest, abdomen, and pelvis to monitor and assess disease response. Magnetic resonance imaging (MRI) may be used for patients for whom contrast-enhanced CT scans are contraindicated.

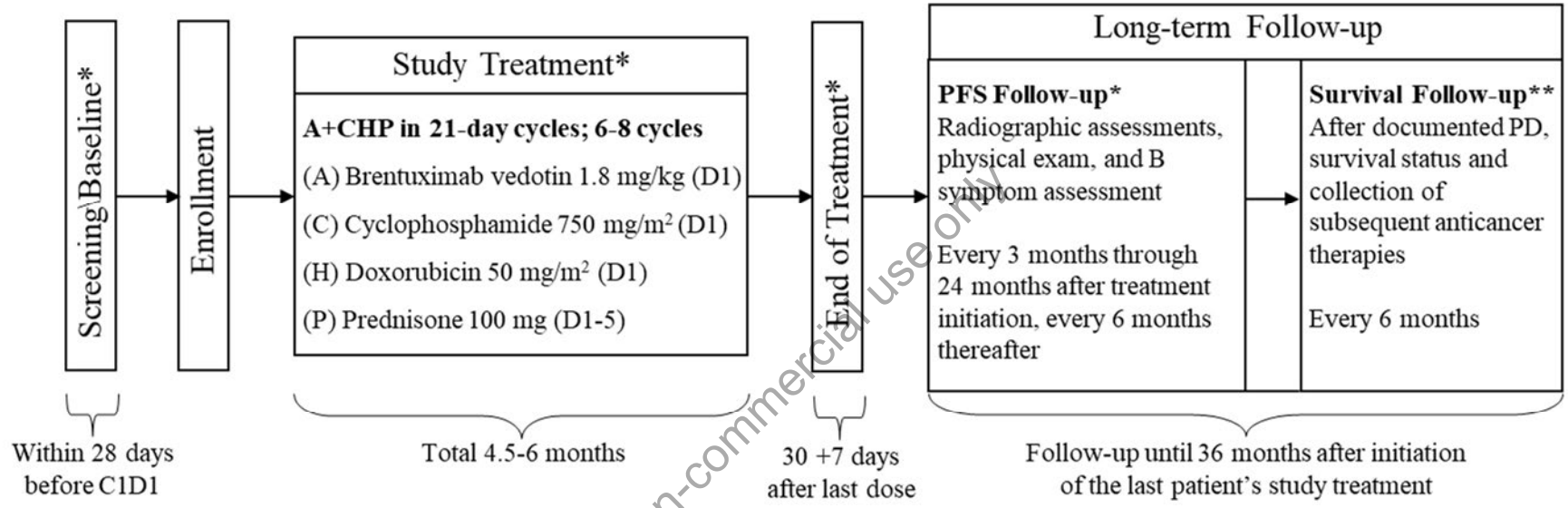
Response will be assessed using Revised Response Criteria for Malignant Lymphoma [1] and the International Working Group 2014 Lugano classification [16]. Radiographic disease evaluation will be conducted at baseline, Cycle 4, and at last cycle of study treatment. During the PFS follow-up period, radiographic disease assessment will be done every 3 months through 24 months after initiation of study treatment and every 6 months thereafter until PD per investigator assessment, initiation of new anticancer therapy to treat residual or progressive disease, death, or study closure, whichever occurs first. The same imaging modality should be used consistently throughout the study to monitor the disease status. Receipt of posttreatment consolidative radiotherapy, posttreatment chemotherapy for the purpose of mobilizing peripheral stem cells, or consolidative autologous or allogeneic stem cell transplantation (SCT) will not be considered PD. Once a patient experiences PD per investigator assessment, the patient will be followed for OS every 6 months until death or study closure, whichever occurs first. All patients will have the opportunity to be followed until 36 months after the last patient's first dose of study treatment.

Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0, effective November 2017 [17]. Clinical laboratory values and vital signs measurements will be obtained to evaluate the safety and tolerability of brentuximab vedotin in combination with CHP. Blood samples will be collected using a sparse PK sampling scheme at prespecified time points for determination of serum and plasma concentrations of PK and immunogenicity endpoints.

The study will end when the last patient completes their last follow-up visit, which will be 36 months after initiation of study treatment.

An overview of the study design is presented graphically in Figure 6.a.

Figure 6.a Study C25024: Overview of Study Design



* Radiographic disease evaluation at baseline, Cycle 4, at last cycle of study treatment, and during PFS follow-up until PD per investigator assessment, initiation of new anticancer therapy to treat residual or progressive disease, death, or study closure, whichever occurs first.
** After PD per investigator assessment, survival follow-up until death or study closure, whichever occurs first.

A+CHP: brentuximab vedotin (Adcetris) plus cyclophosphamide, doxorubicin (hydroxydaunorubicin), and prednisone; C1D1: Cycle 1 Day 1; D: Day; PD: progressive disease; PFS: progression-free survival.

6.2 Number of Patients

Approximately 52 patients with newly diagnosed, previously untreated CD30+ PTCL, including approximately 36 patients with sALCL, will be enrolled in the study, which will be conducted at approximately 15 study centers in China.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Each patient will have a baseline/screening period of up to 28 days (approximately 1 month), a treatment period of up to 8 cycles (6 months) of A+CHP, an end-of-treatment (EOT) visit at 30 days (+7 days) after last dose (ie, approximately 1 month), and a follow-up period through 36 months after the last patient's first dose of study treatment (Figure 6.a).

6.3.2 End of Study/Study Completion Definition and Planned Reporting

Primary Completion/Study Completion

Three analyses of study data are planned. The first analysis will be conducted when all patients have had the opportunity to receive 6 to 8 cycles of A+CHP and have had EOT assessments. The analysis will include the study's primary endpoints, ORR and safety, and secondary endpoints, including CR rate, TTR, PK, and immunogenicity. The results will be presented in a CSR.

The second analysis will be performed when all patients have had the opportunity to be followed for a minimum of 12 months in order to present results of 1-year PFS and OS rates. The third and final analysis will be conducted at the time of study closure. Results of the second and third or final analyses will be presented in addenda to the CSR. The estimated time frame for study completion is 5.5 years.

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

Refer to Table 6.a for disclosures information for all primary and secondary endpoints.

Table 6.a Study C25024: Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame [a]
Primary:		
ORR by IRF assessment per Revised Response Criteria for Malignant Lymphoma criteria following the completion of study treatment.	Percentage of patients in the FAS who achieve an objective response (CR and PR) by IRF assessment following the completion of study treatment.	Approximately 7 months.
AEs, assessment of clinical laboratory values, vital signs measurements.	Percentage of patients in the safety population who experienced TEAEs; changes from baseline in clinical laboratory values and vital signs.	Approximately 7 months.

Table 6.a Study C25024: Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame [a]
Secondary:		
CR rate by IRF assessment per Cheson 2007 Revised Response Criteria following the completion of study treatment.	Percentage of patients who achieve a CR by IRF assessment following the completion of study treatment.	Approximately 7 months.
1-year PFS rate by IRF assessment per Cheson 2007 Revised Response Criteria criteria.	Proportion of patients who are alive and progression free at 1 year; estimated by K-M method.	Approximately 12 months.
1-year OS rate	Proportion of enrolled patients alive at 1 year; estimated by K-M method.	Approximately 12 months.
CR rate by investigator assessment following the completion of study treatment.	Percentage of patients who achieve a CR by investigator assessment following the completion of study treatment.	Approximately 7 months.
TTR by IRF assessment and investigator assessment following the completion of study treatment per 2014 Lugano classification.	Time from the date of first study drug administration to the date of first documented objective response (CR or PR) by IRF and investigator assessment for responders.	Approximately 7 months.
DOR by investigator assessment per 2014 Lugano classification.	Time from start of the first objective response (CR or PR) by investigator assessment to the first subsequent PD or death due to any cause, whichever occurs first.	Approximately 36 months.
PK (serum ADC and plasma MMAE concentration time data) to contribute to popPK analyses, if applicable.	Serum ADC and TAb and plasma MMAE concentrations.	Approximately 7 months.
Immunogenicity; ADA status, including ADA negative, ADA transiently and persistently positive, ADA titer, and Nab status.	Percentage of patients who are ADA negative, ADA transiently and persistently positive, ADA titer, and Nab negative and positive at EOT.	Approximately 7 months.

ADA: antidrug antibody; ADC: antibody-drug conjugate; AE: adverse event; CR: complete response; DOR: duration of response; EOT: end of treatment; FAS: full analysis set; IRF: independent review facility; K-M: Kaplan-Meier; MMAE: monomethyl auristatin E; Nab: neutralizing antidrug antibody; ORR: overall response rate; OS: overall survival; PD: progressive disease; PK: pharmacokinetic(s); popPK: population pharmacokinetic(s); PR: partial response; TAb: total antibody; TEAE: treatment-emergent adverse event; TTR: time to response.

[a] Time to last assessment for that endpoint for the last enrolled patient.

6.3.4 Total Study Duration

As described in Section 6.3.1, each patient will have a screening period of up to 28 days, a treatment period of up to 8 cycles of A+CHP (approximately 6 months), and safety follow-up assessments through 30 days (+7 days) after the last dose of brentuximab vedotin. Follow-up will

be conducted until all patients have had the opportunity to be followed for 36 months after the last patient's initiation of study treatment. The study will be closed when all patients enrolled have completed the required follow-up. It is anticipated that the study will last for approximately 5.5 years.

6.3.5 Posttrial Access

Posttrial access to brentuximab vedotin is not planned for this study because patients will receive study treatment until PD, unacceptable toxicity, or completion of the desired 6 to 8 cycles of study treatment during the study, whichever occurs first.

7.0 STUDY POPULATION

Adult patients aged 18 years or older with newly diagnosed, previously untreated CD30+ PTCL are eligible for study enrollment. (Note that this diagnosis should be made per the Revised European American Lymphoma World Health Organization [WHO] 2016 classification by local assessment.)

7.1 Inclusion Criteria

Each patient must meet all the following inclusion criteria to be enrolled in the study:

1. Patients (Chinese) aged 18 years or older at the time of informed consent.
2. Patients must have newly diagnosed CD30+ PTCL, per the Revised European American Lymphoma 2016 WHO classification, by local assessment. Tumor specimen must be submitted before enrollment for subsequent central pathology review to confirm histology (and ALK status, if applicable), and CD30 expression. Eligible histologies include:
   - ALK-positive sALCL with an IPI score of ≥2.
   - ALK-negative sALCL.
   - PTCL-NOS.
   - AITL.
   - EATL.
   - HSTCL.
3. Eastern Cooperative Oncology Group (ECOG) performance status of less than or equal to 2.
4. FDG-avid disease by PET imaging and measurable disease with at least 1 bidimensionally measurable lesion (>1.5 cm in its largest dimension) by CT.
5. Patients with a uterus and ovary/ovaries 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 1 highly effective method of contraception and 1 additional effective (barrier) method 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 patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

6. Patients with testis/es, 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 drugs, or
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
7. Voluntary written consent must be given before performance of any study-related procedure that is not part of standard medical care. Patient should understand 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 and immunogenicity sampling.
9. Clinical laboratory values as specified below at screening/baseline within 7 days before the first dose of study drug:
   - Total bilirubin must be ≤1.5 times the upper limit of normal (ULN) or ≤3 times the ULN for patients with Gilbert's disease or documented hepatic involvement with lymphoma.
   - ALT and AST must be ≤3 times the ULN or ≤5 times the ULN for patients with an elevation that can be reasonably ascribed to the presence of metastatic disease in liver.
   - Serum creatinine must be <2.0 mg/dL and/or creatinine clearance or calculated creatinine clearance >40 mL/minute. (The Cockcroft-Gault formula is provided in Appendix D.)
   - Hemoglobin must be ≥8 g/dL. (Red blood cell transfusion is allowed ≥14 days before assessment.)
   - Absolute neutrophil count $>1.5\times10^9$/L.
   - Platelet count $\geq75\times10^9$/L (unless documented bone marrow involvement with lymphoma).

7.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study.

1. Patients who are lactating and breastfeeding or have a positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 before the first dose of study drugs.

2. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
3. Treatment with any investigational products within 4 weeks or within at least 5 half-lives before the first dose of study drug, whichever is shorter.
4. Systemic anticancer therapy, including traditional Chinese medicine with antitumor indication for disease under study before the first dose of study drugs.
5. Major surgery within 28 days before the first dose of study drug.
6. Significant active bacterial, fungal, or viral infection within 14 days before the first dose of study drug.
7. Life-threatening illness unrelated to cancer.
8. Known HIV-positive status.
9. Known hepatitis B virus (HBV) surface antigen (HBsAg) seropositivity or active hepatitis C virus infection.

   Note: Patients who have positive HBV core antibody and are HBsAg negative can be enrolled, but must have an undetectable HBV viral load.
10. 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.
11. Any of the following cardiovascular conditions or values within 6 months before the first dose of study drug:
    - Left-ventricular ejection fraction <45%.
    - Myocardial infarction within 6 months of enrollment.
    - New York Heart Association Class III or IV heart failure (Appendix E).
12. Patients with current diagnosis of primary cutaneous CD30+ T-cell lymphoproliferative disorders and lymphomas. Patients with cutaneous ALCL with extracutaneous tumor spread beyond locoregional lymph nodes are eligible (previous single-agent treatment to address cutaneous and locoregional disease is permissible).
13. Patients with mycosis fungoides (MF) (including transformed MF).
14. Uncontrolled diabetes mellitus.
15. Baseline peripheral neuropathy ≥Grade 2 (NCI CTCAE, version 5.0).
16. Known cerebral/meningeal disease related to the underlying malignancy.
17. History of PML.
18. Previous treatment with brentuximab vedotin or CD30 monoclonal antibody.

19. Receipt of any live vaccine within 4 weeks of first dose of study drug.
20. Known hypersensitivity to any excipient contained in the drug formulation.
21. Any kind of disorder that compromises the ability to give written informed consent and/or to comply with study procedures.

8.0 STUDY DRUGS

Investigational medicinal products: brentuximab vedotin+cyclophosphamide, doxorubicin, and prednisone (A+CHP).

8.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented before administration. Study drugs will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

8.1.1 Brentuximab Vedotin

Brentuximab vedotin 1.8 mg/kg will be administered as an IV infusion over approximately 30 minutes on Day 1 of each 21-day cycle within 1 hour of receiving the other agents administered by IV. Starting at Cycle 2, except when it takes longer for the patient to recover from toxicity that is possibly related to brentuximab vedotin after the most recent cycle, an administration window of ±1 day is allowed. A target of 8 cycles of brentuximab vedotin will be administered, per investigator decision, based on patient-specific characteristics, including disease stage and IPI risk score.

Brentuximab vedotin should be given through a dedicated infusion line and should not be mixed with other drug products. Brentuximab vedotin should not be given as a rapid IV dose or bolus injection.

The infusion line should be flushed with saline solution before and after brentuximab vedotin administration to avoid mixing with other drug products.

The dose of brentuximab vedotin will be calculated based on the patient's actual body weight at baseline; the calculated brentuximab vedotin dose will be rounded to the nearest whole number. If the patient experiences a 10% or more change in body weight during the study, the dose should be adjusted. Note that the dose for the patient will be calculated assuming a body weight of 100 kg for patients who weigh more than 100 kg.

Patients will be monitored at bedside from the start of dosing for the first and second doses of brentuximab vedotin. Premedication to prevent IRRs may be used before brentuximab vedotin administration according to investigator discretion and institutional guidelines. If an IRR occurs, continuation of brentuximab vedotin dosing will be determined based on the severity of the event, and at the discretion of the investigator after discussion with the sponsor.

When brentuximab vedotin is administered in combination with CHP, primary prophylaxis with G-CSF, beginning with the first dose, is recommended for all patients.

The following information should be recorded: start/end time of each brentuximab vedotin infusion; stop/restart time if the infusion is interrupted; dose administered (total dose/body) and if dose was reduced; and, potentially, the concentration and/or volume administered.

8.1.2 CHP

8.1.2.1 Cyclophosphamide

Cyclophosphamide is to be administered at the dose of 750 mg/m^2 IV on Day 1 of each 21-day cycle.

8.1.2.2 Doxorubicin

Doxorubicin is to be administered at the dose of 50 mg/m^2 on Day 1 of each 21-day cycle, and may be administered over a period of up to 48 hours per institutional standards.

8.1.2.3 Prednisone

Prednisone is to be given orally at the dose of 100 mg daily on Days 1 through 5 with ±1 day window.

8.2 Reference/Control Therapy

Not applicable.

8.3 Dose Modification Guidelines

8.3.1 Criteria for Dose Modifications

Table 8.a describes the recommended dose modifications for study treatment-associated neuropathy.

Table 8.a Recommended Dose Modifications for Treatment-Associated Neuropathy

Neuropathy Grade	Sensory Neuropathy	Motor Neuropathy
1	Continue study treatment at same dose.	Continue study treatment at same dose.
2	Continue study treatment at same dose.	Reduce dose of brentuximab vedotin to 1.2 mg/kg.
3	Reduce dose of brentuximab vedotin to 1.2 mg/kg.	Discontinue brentuximab vedotin treatment.
4	Discontinue brentuximab vedotin treatment.	Discontinue brentuximab vedotin treatment.

Dose modifications of brentuximab vedotin, cyclophosphamide, doxorubicin, or prednisone due to nonhematologic toxicity (excluding neuropathy) are allowed per institutional standards at the discretion of the investigator. Hematologic toxicity, including anemia and thrombocytopenia, can be managed according to institutional standards and study treatment can be continued at the same

dose. For Grade 3 or Grade 4 neutropenia, G-CSF should be administered in subsequent cycles for patients who are not currently receiving primary G-CSF prophylaxis.

The reduced dose of brentuximab vedotin is 1.2 mg/kg. No further dose reductions of brentuximab vedotin are permitted.

Doses reduced for treatment-related neuropathy should not be re-escalated without discussion with the sponsor.

8.3.2 Criteria for Discontinuation of Study Drugs

A patient's treatment with study drugs may be discontinued due to completion of treatment or for any of the reasons defined in Section 9.8. Patients who discontinue the study treatment will remain in the study for follow-up until withdrawal from the study.

8.4 Excluded Concomitant Medications and Procedures

Patients may not receive other investigational drugs, immunosuppressive medications, radiotherapy, systemic antineoplastic therapy, or traditional Chinese medicine with an antitumor indication from Day 1 through EOT. In addition, other prohibited concomitant therapies should be excluded in accordance with the approved prescribing information for each agent. Exceptions are noted in Section 8.5.

Vaccination with live virus vaccines is not recommended while the patient is being treated on study.

8.5 Permitted Concomitant Medications and Procedures

Routine infectious prophylaxis for *Pneumocystis jiroveci* pneumonia should be considered for all patients.

The use of transfusions, platelet and/or colony-stimulating factors (CSFs) per institutional practice is permitted. Intrathecal prophylactic treatment for cerebral/meningeal disease is permitted at the discretion of the investigator.

The use of CSFs and/or chemotherapy for stem cell collection to enable a future autologous SCT is permitted per institutional standard. Chemomobilization of stem cells is only permitted after EOT procedures are completed.

Consolidative SCTs or radiotherapy may be given at the investigator's discretion after EOT procedures are completed. At least 6 cycles of study treatment should be given before initiating posttreatment consolidative SCT or radiotherapy.

COVID-19 (coronavirus disease 2019) vaccination is permitted according to local regulations and protocols.

8.6 Precautions and Restrictions

It is not known what effects brentuximab vedotin has on human pregnancy or development of the embryo or fetus; therefore, patients participating in this study should avoid becoming pregnant or

avoid impregnating a partner. Nonsterilized patients of reproductive age with a uterus and/or ovaries and nonsterilized patients with testes/testis should use effective methods of contraception through defined periods, during and after study treatment, as specified below.

Reproductively 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 1 highly effective method and 1 additional effective (barrier) method of contraception at the same time, from the time of signing of the informed consent form (ICF) through 6 months after the last dose of study drug (whichever is longer), or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

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

- Agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drugs, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Before starting treatment, patients should be advised to seek counseling on sperm or egg storage.

Patients administered strong CYP3A4 inhibitors concomitantly with brentuximab vedotin should be closely monitored for AEs.

8.7 Management of Clinical Events

If dose modifications are necessary as a result of the events detailed below, please refer to Section 8.3.

8.7.1 Nausea or Vomiting

Routine antiemetic prophylaxis should be administered per institutional standard.

8.7.2 Diarrhea

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

8.7.3 IRRs

IRRs may occur during the infusion of brentuximab vedotin. The infusion should be administered at a site properly equipped and staffed to manage an IRR, including anaphylaxis, should it occur. The patient should be observed for approximately 60 minutes after 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 institutional standards. Medications for IRRs, such as epinephrine and antihistamines, should be available for immediate use.

Patients who experience a Grade 1 or 2 IRR 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 other regimen in accordance with institutional standards, administered 30 to 60 minutes before each 30-minute brentuximab vedotin infusion.

8.7.4 Peripheral Neuropathy

AEs of peripheral neuropathy will be monitored closely throughout the study. These AEs may include, but are not limited to, peripheral sensory neuropathy, peripheral motor neuropathy, paresthesia, hypoesthesia, polyneuropathy, muscular weakness, and demyelinating polyneuropathy. Such AEs, 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 electronic case report form (eCRF). AEs higher than Grade 1 will result in brentuximab vedotin dose modification as shown in Table 8.a.

8.7.5 Suspected Progressive Multifocal Leukoencephalopathy

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. See the IB for further details.

If PML is suspected, hold further dose administration and undertake a diagnostic workup including (but not limited to):

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

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

8.8 Blinding and Unblinding

This is an open-label study; blinding is not applicable.

8.9 Description of Investigational Agents

Brentuximab vedotin for injection, the investigational agent in this study, 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. For further details, see the study manual.

Cyclophosphamide, doxorubicin, and prednisone should be prepared, stored, and handled according to institutional guidelines and instructions in the study manual.

8.10 Preparation, Reconstitution, and Dispensation

Brentuximab vedotin is supplied in single-use glass vials and will be reconstituted in the vial with 10.5 mL of sterile water for injection. The appropriate amount of reconstituted brentuximab vedotin should be withdrawn from the vial and diluted in an infusion bag containing saline solution to produce a final brentuximab vedotin concentration of 0.4 to 1.8 mg/mL. For further details, see the study manual.

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever the solution and container permit.

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

8.11 Packaging and Labeling

Brentuximab vedotin vials will be packaged as single-use cartons. Each carton will contain 1 vial of the investigational product; the vial and carton will be labeled to meet the requirements of the National Medical Product Administration (NMPA).

Table 8.b Investigational Product

Investigational product	Brentuximab vedotin
Content	50 mg/vial
Concentration	5 mg/mL (after reconstitution)
Container	Clear, colorless, glass vial
Packing unit	1 vial/carton
Property	Sterile white to off-white lyophilized cake or powder. Reconstituted products are clear or slightly opaque.
Protection from light	Reconstituted products should be protected from light until preparation.
Storage	Refrigeration (2°C-8°C)
Manufacturer and country	BSP Pharmaceuticals S.P.A.

8.12 Storage, Handling, and Accountability

Vials containing brentuximab vedotin 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.

The specifications and storage conditions of brentuximab vedotin and drug accountability instructions are provided in the study manual.

8.13 Other Protocol-Specified Materials

Cyclophosphamide, doxorubicin, and prednisone will be provided by the sponsor and will be packed in an open fashion. Companion medication will be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. The storage conditions for cyclophosphamide, doxorubicin and prednisone are provided in the study manual. All these medications will remain in their original containers until dispensed.

9.0 STUDY CONDUCT

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), applicable regulatory requirements, and International Council for Harmonisation (ICH) guidelines.

9.1 Study Personnel and Organizations

The contact information for the project clinician for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator for each member state/country, and the IXRS technology provider, ie, 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.

For 24-hour contact information, please refer to the study manual or equivalent.

9.2 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).

9.3 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.

9.4 Treatment Group Assignments

This is a single-arm study with no reference therapy. Treatment group assignments are not applicable.

9.5 Study Procedures

Refer to the schedule of events (SOE; Appendix A) for the timing of assessments. All assessments are shown in Appendix A, Table A-1, and PK and immunogenicity sample collection times are shown in Appendix A, Table A-2.

Additional details are provided as necessary in the sections that follow.

9.5.1 Patient Demographics

The date of birth (or age), race, and sex of the patient are to be recorded during screening (Days -28 to 0).

9.5.2 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, if applicable. In addition, concomitant medications will be recorded as specified in Section 9.5.8.

Medical history will be evaluated for the following categories of clinically significant diseases or procedures that have been or will be completely resolved by at least one day before providing written informed consent.

- Any diseases that meet the exclusion criteria (including all that were resolved before enrollment).
- Any diseases or procedures within the past 3 months that do not meet the exclusion criteria, except transient diseases (eg, upper respiratory inflammation, common cold, headache, diarrhea).
- Any other diseases that are considered to possibly affect the evaluation of drug efficacy.

An IPI score must be determined based on the International NHL Prognostic Factors Project [18] (see Appendix F).

9.5.3 Physical Examination

A physical examination, including evaluation of skin; head, eyes, ears, nose, and throat; lymph nodes; heart; lungs; abdomen; back; extremities; and neurology, will be completed per standard of care at the times specified in the SOE (Appendix A). Any clinically relevant findings are to be documented.

The patient's current signs and symptoms will be reviewed as specified in the SOE (Appendix A), including systemic B symptoms, which include 1 or more of the following:

- Unintentional weight loss of ≥10% of body weight within the previous 6 months.
- Fevers of >100.5°F (>38°C) for ≥2 weeks without evidence of infection.
- Drenching night sweats without evidence of infection.

9.5.4 Patient Height and Weight

Height will be measured only during screening (within 28 days before the first dose of study treatment). Body weight should be recorded as specified in the SOE (Appendix A).

9.5.5 Vital Signs

Vital signs measurements, including measurements of diastolic and systolic blood pressure, heart rate, and body temperature, will be done at times specified in the SOE (Appendix A).

9.5.6 ECOG Performance Status Score

Performance status will be assessed using the ECOG performance status scale (Appendix G) as specified in the SOE (Appendix A).

9.5.7 Pregnancy Test

A serum or urine pregnancy (choriogonadotropin beta) test will be completed for all reproductively female patients of childbearing potential during screening and at the EOT visit; this test must be negative at screening for the patient to be enrolled in the study.

Pregnancy tests may also be repeated during the study if requested by an IEC/IRB or if required by local regulations.

9.5.8 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will recorded in the eCRF from the time of signing informed consent through 30 days after the last dose of study treatment. See Section 8.4 and Section 8.5 for a list of medications and therapies that are prohibited and allowed during the study.

9.5.9 AEs

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the SOE (Appendix A). Refer to Section 10.0 for details regarding definitions, documentation, and reporting of AEs and serious adverse events (SAEs).

9.5.10 Enrollment

Patients are considered to be enrolled in the study when they are entered into the interactive voice/web response system (IXRS) and receive their first dose of study treatment. Eligibility documentation must be submitted to the sponsor and confirmed prior to enrollment. Study treatment must be initiated within 3 days of the patient being entered into IXRS. Procedures for completing enrollment information are described in the study manual.

9.5.11 Electrocardiogram and Echocardiogram

A 12-lead electrocardiogram (ECG) and echocardiogram will be performed at the time points specified in the SOE (Appendix A).

9.5.12 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally. Handling and shipment of clinical laboratory samples will be outlined in the study manual. Clinical laboratory evaluations will be performed as outlined in the following sections.

9.5.12.1 Clinical Chemistry and Hematology

Blood samples for analysis of the clinical chemistry and hematology parameters shown in Table 9.a will be obtained as specified in the SOE (Appendix A).

Table 9.a Clinical Chemistry and Hematology Tests

Hematology	Serum Chemistry	
Hematocrit	Albumin	Creatinine
Hemoglobin	Alkaline phosphatase	Gamma glutamyl transferase
Leukocytes with differential	Alanine aminotransferase	Glucose
Neutrophils (ANC)	Aspartate aminotransferase	Lactate dehydrogenase
Platelet count	Bilirubin (total)	Phosphate
	Blood urea nitrogen	Potassium
	Calcium	Sodium
	Chloride	Urate

ANC: absolute neutrophil count.

If creatinine clearance is to be estimated, the Cockcroft-Gault formula (see Appendix D) will be employed as follows:

$$Estimated\ creatinine\ clearance = [(140 - Age) * Mass(kg)\ ] / [72 * serum\ creatinine(mg/dL)]$$

For female patients, the result of the formula above should be multiplied by 0.85.

Other lab tests: hemoglobin A1c will also be obtained at screening.

9.5.13 Disease Assessment

Appropriate imaging assessments should be performed (eg, CT or MRI, PET). Imaging assessments should be conducted according to the Revised Response Criteria for Malignant Lymphoma (Appendix H) and 2014 Lugano Response Assessment Criteria (Appendix I) [1,16]. IRF-assessed response will be conducted according to both the Revised Response Criteria for Malignant Lymphoma and the 2014 Lugano Response Assessment Criteria, whereas investigator assessment will be conducted according to the 2014 Lugano Response Assessment Criteria.

CT scans with contrast (unless contraindicated) of the neck, chest, abdominal cavity, pelvis, and any other disease sites, and a PET scan, will be obtained at screening. The CT portion of a PET-CT may be submitted in lieu of a dedicated CT; however, certain radiologic requirements are needed for acceptance, provided it is of diagnostic quality. Imaging exams of diagnostic quality performed before the screening consent date may be used as screening tests if performed within the 28 days before the first dose of study treatment. An MRI may be used for patients who are either allergic to CT contrast media or have renal insufficiency that, per institutional guidelines, restricts the use of CT contrast media. Specific disease sites that cannot be adequately imaged by CT may be documented by MRI. Imaging exams should be performed according to the instructions provided in the study manual.

Objective assessments of the disease burden, ie, target, non-target, and potential new lesions, will be performed at each time point. (Note that a ±7-day window is allowed for image tests, as described in the SOE [Appendix A]). Anatomical measurements (summed across target lesions) will be collected at each postscreening evaluation using an imaging modality consistent with that used at screening. A PET scan is required to confirm CR. CT and/or PET scans may also be obtained throughout the study, if clinically indicated; if scans are performed at nonprotocol-specified time points, results will be collected in the patient's eCRF and images will be submitted for central review. Patients who have signs and symptoms of PD outside of the scheduled assessment should be evaluated by the investigator with a physical exam and laboratory assessments to determine if PD is present. Any suspected case of PD should be confirmed with a CT or biopsy. Patients may continue study treatment until PD is confirmed by a serial exam at least 2 weeks later. When possible, the same qualified physician will interpret results to reduce variability. Radiographic images must be submitted to a centralized repository for future centralized review. Radiographic images will be maintained at the site, and test results and physicians' findings will be filed in patient source documents.

A bone marrow biopsy is required at baseline. Information from an assessment performed within 60 days of the first dose of study treatment, as part of clinical care, may be used to satisfy the baseline bone marrow biopsy requirement. Postbaseline biopsies are required to confirm CR, if the screening evaluation was positive and other criteria for CR have been met; this confirmation is to be obtained within 4 weeks of documentation of response by radiographic assessment. Repeat bone marrow biopsies are not required once bone marrow is found to be negative.

If cutaneous lesions are the sole site of PD, a biopsy must be obtained to histologically confirm PD.

9.5.14 Biomarker, Immunogenicity, Pharmacodynamic, and PK Samples

9.5.14.1 Primary Specimen Collection

The primary specimens to be collected are shown in Table 9.b.

Table 9.b Primary Specimen Collection

Specimen Name in Schedule of Procedures	Primary Specimen	Primary Specimen Derivative 1	Description of Intended Use	Sample Collection
Fresh tumor tissue biopsy sample	Fresh tumor tissue	FFPE block/slides	Histology	Mandatory
Blood sample for immunogenicity	Blood	Serum	ADA measurements	Mandatory
Serum sample for PK (ADC)	Blood	Serum	PK measurements	Mandatory
Plasma sample for PK (MMAE)	Blood	Plasma	PK measurements	Mandatory

ADA: antidrug antibody(ies); ADC: antibody drug conjugate; FFPE: formalin-fixed, paraffin-embedded; MMAE: monomethyl auristatin E; PK: pharmacokinetic.

9.5.14.2 Tumor Biopsies

Histologically confirmed CD30+ disease and histologic subtype must be determined by local pathology assessment in a CD30-qualified laboratory to enable enrollment. Local pathology will also assess ALK tumor status for patients with a diagnosis of sALCL.

By local assessment, tissue from the diagnostic biopsy must confirm CD30 positivity by immunohistochemistry. The following 3 criteria must be met to declare CD30 positivity:

- CD30 antigen detected in 10% or greater of neoplastic cells (in cases where enumeration of neoplastic cells is not possible, total lymphocytes may be used).
- CD30 staining at any intensity above background.
- Membranous, cytoplasmic, and/or Golgi pattern of expression of the CD30 antigen.

Submission of the tumor block or unstained slides from a diagnostic biopsy is required before enrollment for subsequent central confirmation of CD30 expression and disease subtype for all patients; for patients with a diagnosis of sALCL only, determination of ALK tumor status is required. The diagnostic specimen must be from a malignant lymph node or extranodal tissue obtained by core or excisional/incisional biopsy. Cutaneous, bone, or bone marrow samples alone are unacceptable. Fine-needle aspirate and cytology samples are also unacceptable.

Detailed handling and shipping instructions for tumor biopsies are provided in the study manual.

9.5.15 PK Measurements

PK samples will be collected at time points specified in the Appendix A, Table A-2 to measure serum ADC-and plasma MMAE concentration versus time data to contribute to popPK analyses. Allowed windows for the PK sample collections are also provided in Appendix A, Table A-2.

Blood samples will be taken either by direct venipuncture or an indwelling cannula inserted in a forearm vein. On the day of brentuximab vedotin administration, samples collected postinfusion

should be collected in the contralateral (opposite) arm from the one being used for drug infusion. The actual date and time (24-hour clock time) of each sample will be recorded in the eCRF. Any sampling problems will be documented in the eCRF. Samples will be collected, labeled, stored, and shipped as detailed in the study manual provided by sponsor or designee.

Samples for the determination of ADC concentrations in serum and MMAE concentrations in plasma will be analyzed on behalf of the sponsor using appropriate validated bioanalytical methods. Full details of the bioanalytical methods will be described in separate bioanalytical reports.

9.5.16 Immunogenicity Sample Collection

Blood samples for the assessment of ADA will be collected at time points specified in the SOE (Appendix A, Table A-2). Samples must be collected before study drug is administered on the day of study drug administration, and, optionally, at unscheduled visits for a patient who experiences an AE that is considered by the investigator to be consistent with hypersensitivity or IRR. Confirmed ADA-positive sample will be assessed for the presence of neutralizing antidrug antibodies (Nab).

9.6 Completion of Study Treatment (for Individual Patients)

Patients will be considered to have completed study treatment if they complete 6 to 8 cycles of treatment with A+CHP, or if they experience PD or death.

9.7 Completion of Study (for Individual Patients)

Patients will be considered to have completed the study if they are discontinued from study drug and 1 or more of the following situations occur:

- Death.
- Withdrawal by patient.
- Study terminated by the sponsor.
- Lost to follow-up.

9.8 Discontinuation of Treatment With Study Drug

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

- Pregnancy.
- PD.

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

- AE.
- Protocol deviation.
- Initiation of new anticancer treatment to treat residual or PD.

- Study terminated by sponsor.
- Withdrawal by patient.
- Investigator decision.
- Lost to follow-up.
- Other.

Once study drugs have been discontinued, all study procedures outlined for the EOT visit will be completed as specified in the SOE (Appendix A). The primary reason for study treatment discontinuation will be recorded on the eCRF.

Note that some patients may discontinue study drugs for reasons other than PD before completing the full treatment course; these patients will remain in the study for posttreatment assessments as outlined in the SOE (Appendix A) and for PFS follow-up as required.

9.9 Withdrawal of Patients From Study

A patient may be withdrawn from the study for any of the following reasons:

- Lost to follow-up.
- Study terminated by sponsor.
- Withdrawal by patient.
- Other.

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

9.10 Study Compliance

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

9.11 Posttreatment Follow-up Assessments (PFS and OS)

Patients will be followed for safety between 30 and 37 days after the last dose of study treatment.

Patients who discontinue study treatment will have PFS follow-up visits every 3 months through 24 months after initiation of study treatment, and every 6 months, thereafter, until the patient experiences PD per investigator assessment, initiates a new anticancer therapy (except autologous SCT or radiotherapy consolidation), death, or study closure, whichever occurs first.

After documented PD, patients will continue to have OS follow-up visits every 6 months until death or study closure, whichever occurs first. Survivor information and death details may be collected by methods that include, but are not limited to, telephone, email, mail, or retrieval from online or other databases. In addition, the start of another anticancer therapy for the disease under study will be collected.

Patient follow-up for PFS/OS will continue until 36 months after initiation of the last patient's study treatment.

Note that related SAEs must be reported to the Global Pharmacovigilance department or designee. This includes deaths that the investigator considers related to study drug that occur during posttreatment follow-up. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of SAEs.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

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

10.1.2 AE Definition

AE means any untoward medical occurrence in a patient 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.

Disease progression of the malignancy under study assessed by measurement of malignant lesions on radiographs or other methods should not be reported as an AE; however, worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the eCRF. Any death, whether due to side effects of the treatment, PD, or other causes, is considered an SAE.

An abnormal clinical 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 SAE Definition

SAE means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening.** (That is, it 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 that hypothetically might have caused death if it were more severe.)

- Requires inpatient **hospitalization or prolongation of an existing hospitalization**. (See clarification in the paragraph in Section 10.2 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, on the basis of appropriate medical judgment, it may jeopardize the patient, require medical or surgical intervention to prevent one 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; the development of drug dependency or drug abuse; and any organism, virus, or infectious particle [eg, prion protein transmitting transmissible spongiform encephalopathy], pathogenic or nonpathogenic, that is considered an infectious agent.)

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 5.0, effective November 2017 [17]. Clarification should be made between an 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). The latter term (severe) is NOT the same as serious, which is based on the 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/mm^3 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 AEs and SAEs

Collection of pretreatment events should be conducted from the time that the patient has signed informed consent to participate in a study, but before administration of any study treatment. The collection of AEs and SAEs will commence at the time the patient signs the informed consent until 30 days after the last dose of study treatment to permit the detection of any delayed treatment-related AEs. For patients who discontinue before the administration of study treatment, AEs will be followed until the patient discontinues study participation.

All AEs spontaneously reported by the patient, 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 (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 a single comprehensive event.

Regardless of causality, SAEs must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee within 24 hours of becoming aware of the event. This will be done by transmitting an electronic data capture (EDC) SAE report. If transmission of an EDC SAE report is not feasible, the safety report form should be completed, signed by the investigator and submitted via email or fax to Takeda Pharmacovigilance Operations contacts included in the form completion instruction. If SAEs are reported via email or by fax, EDC must be updated as soon as possible with the appropriate information. Information in the SAE report or form must be consistent with the data provided on the eCRF.

If information not available at the time of the first report becomes available at a later date, then the investigator will either transmit a follow-up EDC SAE report (or a paper-based SAE form if an EDC SAE report is not feasible) or provide other documentation immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

The SAE reporting contact information is provided below.

SAE Reporting Contact Information	Email	Fax
Cognizant	takedaoncocases@cognizant.com	1-202-315-3560

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

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 severity (toxicity grade) of the event and the relationship of the event to study drug administration.

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 5.0, effective November 2017 [17]. The criteria are provided in the study manual.

Relationship of the event to study drug administration (ie, its causality) will be determined by the investigator responding yes (related) or no (unrelated) to this question: Is there a reasonable possibility that the AE is associated with the study drug?

10.3 Monitoring of AEs and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study:

- AEs will be reported from the signing of informed consent through 30 days after administration of the last dose of study treatment and recorded in the eCRFs.
- SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the signing of informed consent through 30 days after administration of the last dose of study treatment and recorded in the eCRF. After this time, only related SAEs must be reported to the

Takeda Global Pharmacovigilance department or designee. 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).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a reproductively female patient becomes pregnant while participating in this study during administration of study treatment, she must inform the investigator immediately and permanently discontinue the study drugs. The sponsor must also be contacted immediately by sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. The pregnancy must be followed for the final pregnancy outcome.

If a reproductively 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 sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

For pregnancies with live newborns, infants should be followed until 1 year of age or until the study closure, whichever occurs first. Abortions, pregnancy complications, congenital anomalies, or birth defects should all be reported (Section 10.1.3 for SAE definition).

10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)

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 report this via the phone numbers or email addresses provided below.

A medication error is a preventable event that involves an identifiable patient and leads to inappropriate medication use, which may result in patient harm. In contrast, overdoses and underdoses constitute medication errors, while doses missed inadvertently by a patient do not. Individuals who identify a potential medication error (including overdose) situation should immediately report this via the phone numbers or email addresses provided below.

Products	Phone	Email	Fax
Adcetris	1-844-ONC-TKDA (1-844-662-8532) [a]	globaloncologymedinfo@takeda.com	1-800-881-6092

[a] Note that there is a sometimes substantial delay before the welcome message starts due to call forwarding.

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or a medication error results in an SAE, the SAE should be reported.

10.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and IRBs and

IECs, as applicable, and in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by, or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited reports within 7 days for fatal and life-threatening events and within 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues that might materially alter the current benefit-risk assessment of an investigational medicinal product, or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the study. The investigational site also will forward a copy of all expedited reports to its IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be convened for this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the data management plan. If selected for coding, AEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities. Drugs will be coded using the WHO Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each patient who signs an ICF.

The sponsor or its designee will supply investigative sites with access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, CRO partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designee) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for the change.

The principal investigator must review the eCRFs for completeness and accuracy, and sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

The eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor (or designee) will be permitted to review the patient's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The

completed eCRFs are the sole property of the sponsor and should not be made available (in any form) to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities. (It is important to note that these individuals do not need the written permission of the sponsor.)

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include, but are not limited to, study-specific documents; the identification log of all participating patients; medical records; temporary media, such as thermal-sensitive paper, source worksheets, and all original signed and dated ICFs; patient authorization forms regarding the use of personal health information (if separate from the ICFs); electronic copies of eCRFs, including the audit trail; and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and the sponsor (or designees). Any source documentation printed on degradable thermal-sensitive paper should be photocopied by the site and filed with the original in the patient's chart to ensure long-term legibility. The China GCP Section 80 requires the essential documents for new drug application clinical studies to be retained for at least 5 years after the investigational drug is approved for marketing. In addition, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 Section 8 until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements, or for a time specified in the clinical study site agreement between the investigator and sponsor.

Refer to the clinical study site agreement for the sponsor's requirements for record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and approved before enrollment of the first patient. This document will provide further details with regard to handling missing data, the definition of analysis variables, and analysis methodology to address all study objectives.

The analysis of the primary endpoint and previously defined secondary endpoints will be conducted when all enrolled patients have had the opportunity to receive 6 to 8 cycles of study treatment and have had EOT assessments. Results will be presented in a CSR. The analysis of the 1-year PFS and OS rate will be performed after all patients have had the opportunity to be followed for a minimum of 12 months. Final analysis of selected endpoints will be performed at the time of study closure. The results of subsequent analyses after the primary endpoint analysis will be presented in addenda to the CSR.

13.1.1 Analysis Sets

The following analysis sets are defined in the study: full analysis set (FAS), immunogenicity analysis set, and PK analysis set. If a patient will not be included in an analysis set, that determination should be made before database lock.

13.1.1.1 FAS

All demographic, efficacy, and safety analyses will be based on the FAS, which is defined as all enrolled patients (ie, those who are entered into the IXRS and have received at least 1 dose of the study treatment).

13.1.1.2 Response-Evaluable Set

The response-evaluable set will include a subset of the FAS with measurable disease at baseline and with at least 1 postbaseline response assessment. Patients who were discontinue due to death before at least 1 postbaseline evaluation will be included in the analyses of response.

13.1.1.3 Immunogenicity Analysis Set

The immunogenicity analysis set consists of patients who have received at least 1 dose of any of the study drugs and have had an ADA status assessment at baseline and at least 1 postbaseline sample.

13.1.1.4 PK Analysis Set

PK analyses will be based on the PK analysis set, which includes all patients who are in the FAS and are judged by the study team to have adequate dosing records and PK measurements.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Descriptive statistics will be provided on demographics and baseline characteristics, including sex, age, body weight, height, medical history, prior medication, and other parameters, if needed.

13.1.3 Efficacy Analysis

The primary efficacy endpoint is:

- ORR by IRF assessment following the completion of study treatment, defined as the proportion of patients who have achieved a CR or PR by IRF assessment following the completion of study treatment. However, any CR or PR that occurs after receipt of subsequent anticancer therapy to treat residual or PD will not be included in the numerator for the ORR calculation (where the FAS will be the denominator).

The secondary efficacy endpoints are:

- CR rate by IRF assessment following the completion of study treatment, defined as the proportion of patients who have achieved a CR by IRF assessment following the completion of study treatment. Any CR that occurs after receipt of subsequent anticancer therapy to treat

residual or PD will not be included in the numerator for the CR rate calculation (where the FAS will be the denominator).

- The 1-year PFS rate by IRF assessment, defined as the proportion of patients alive and progression free at 1 year, will be estimated by the Kaplan-Meier method. PFS, defined as the time from the start of study treatment to the date of first documentation of PD, death due to any cause, or receipt of subsequent anticancer therapy to treat residual or PD, whichever occurs first. PFS will be censored on the date of last radiographic disease assessment for patients without documentation of PD/relapse, subsequent anticancer therapy for residual disease or PD, or death at the time of analysis.
- The 1-year OS rate, defined as the proportion of patients alive at 1 year, will be estimated by the Kaplan-Meier method. OS is defined as the time from the start of study treatment to the date of death due to any cause. OS will be censored on the date of last contact for patients who are still alive at the time of analysis.
- TTR by IRF assessment, defined as the time from the date of first study drug administration to the date of first documented objective response (CR or PR) by IRF assessment for responders.
- IRF- and/or investigator-assessed ORR, CR rate, TTR, and 1-year PFS rate per Lugano classification will be defined and analyzed as previously described.
- DOR by investigator assessment, defined as the time between the first documentation of objective tumor response (CR or PR) by investigator assessment and the first subsequent documentation of objective tumor progression, death due to any cause, or receipt of subsequent anticancer therapy to treat residual or PD, whichever occurs first. Censoring in the analysis of DOR will be the same as for PFS. The analysis will include responders only.

Additional efficacy endpoints are:

- PFS by investigator assessment, defined as the time from the start of study treatment to the date of first documentation of PD, death due to any cause, or receipt of subsequent anticancer therapy to treat residual or PD, whichever occurs first. PFS will be censored for patients without documentation of PD/relapse, subsequent anticancer therapy for residual or PD, or death at the time of analysis on the date of last radiographic disease assessment. PFS will be summarized per the investigator assessment.

Detailed methodology, including handling rules for missing assessments and censoring approaches for the analysis of PFS, will be provided in the SAP.

- OS, defined as the time from the start of study treatment to the date of death due to any cause. OS will be censored on the date of last contact for patients who are still alive.

Continuous variables will be summarized, including the number of patients, mean, standard deviation, median, minimum, and maximum values; for categorical variables, the frequency and percentage per category will be summarized. Two-sided exact 95% CIs will be computed using appropriate techniques for ORR and CR. The best overall response for each patient will be listed. Time-to-event variables and the 1-year PFS and OS rates will be summarized by the Kaplan-Meier

method with the associated 95% CIs when estimable. In addition, sensitivity analyses may be performed using the response-evaluable analysis set as appropriate.

Note: All patients who do not meet the criteria for an objective response by the completion of treatment date will be considered nonresponders within the response-related analyses.

13.1.4 PK Analysis

13.1.4.1 PK Concentrations

PK concentrations will be summarized using the PK analysis set. Individual study drug concentration-time data will be presented in listings and also tabulated using summary statistics by analyte. Individual and mean concentration-time profiles will be plotted for each analyte, as appropriate.

13.1.4.2 PK Sampling Intended for Population PK Analysis

The PK data collected in this study are intended to contribute to future popPK analyses of brentuximab vedotin. These popPK analyses may additionally include data collected in other brentuximab vedotin clinical studies. The plan for the popPK analysis will be defined separately, and the results reported separately from the CSR.

13.1.5 Immunogenicity Analyses

Immunogenicity will be summarized using the immunogenicity analysis set. Descriptive statistics will be used to summarize patients in the following categories: ADA negative, transiently ADA positive, persistently ADA positive, low or high ADA titer, and Nab positive or negative. The effect of immunogenicity on PK, safety, and efficacy may be examined.

13.1.6 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 clinical laboratory results and vital signs using the FAS. Exposure to study drug, including the number of treated cycles, total amount of doses taken, and dose intensity, will be summarized.

Treatment-emergent adverse events (TEAEs), defined as any AE that occurs after administration of the first dose of study treatment and up through 30 days after the last dose of study treatment, will be tabulated. A listing of deaths and TEAEs resulting in study drug discontinuation will be provided. All reported AEs will be listed along with the date of onset, date of resolution (if resolved), CTCAE grade, and relationship to study treatment.

Summary information (the number and percentage of patients) by System Organ Class, High Level Term, and Preferred Term will be tabulated for the following categories:

- TEAEs.
- Drug-related TEAEs.

- Grade 3 or higher TEAEs.
- Grade 3 or higher drug-related TEAEs.
- TEAEs leading to study drug discontinuation.
- TEAEs leading to study drug modification.
- SAEs.

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. Shift tables for laboratory parameters will be generated based on changes in NCI CTCAE, version 5.0 grade from baseline to the worst postbaseline value.

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs (eg, blood pressure, heart rate, and body temperature) and body weight over time will be tabulated by scheduled time point. ECOG performance status scores over time will also be tabulated.

Additional and unplanned safety analyses may be performed as the study is conducted. Those additional analyses, if deemed necessary, will be presented in a listing and documented in the CSR.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned for this study.

13.3 Determination of Sample Size

It is anticipated that approximately 52 patients will be enrolled in this study. With a target sALCL patient proportion of 70%, approximately 36 sALCL patients need to be enrolled in the study. In ECHELON-2, the observed ORR was 87.65% for sALCL patients and 71.88% for non-sALCL patients. Assuming a true ORR for sALCL and non-sALCL patients is the same as the observed ORR in ECHELON 2, with a sample size of approximately 52 patients, the probability of observing ORR by IRF greater than the lower bound of 95% CI (77.7%-87.8%) of ECHELON-2 is approximately 83%.

Another rationale to determine the sample size is to ensure the lower bound of the observed 95% CI of ORR by IRF is greater than the threshold response rate of 65% [2,3]. With a sample size of approximately 52 patients, the desire is to minimally observe 41 responders (CR or PR) in order for the lower bound of the exact 95% CI of ORR by IRF to be greater than 65%. With the same assumption as previously described, the probability of observing at least 41 responders is approximately 83%.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution are expected to guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including but not limited to the investigator's binder, study medication, patient medical records, informed consent documentation, documentation of patient authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to the study participant. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. No exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria will be allowed.

The site should document all protocol deviations in the patient's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or IEC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the patient, or confound interpretation of the primary study assessment.

The sponsor will assess any protocol deviation; if it is likely to affect, to a significant degree, the safety and rights of a patient, or the reliability and robustness of the data generated, it may be reported to regulatory authorities as a serious breach of GCP and the protocol.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, it is possible that this study may be inspected by regulatory agencies, including the China NMPA and those of foreign governments. If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual study participants (ie, patients) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements, and align his or her conduct in accordance with the responsibilities of the investigator that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and the appendices, which contain requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the IB, a copy of the ICF, and, if applicable, patient recruitment materials and advertisements, in addition to other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and patient informed consent must be obtained and submitted to the sponsor or designee before commencement of the study, ie, before shipment of the sponsor-supplied drug or study-specific screening activity. The IRB or IEC approval must refer to the study by its exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. If required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. The sponsor will ship drug/notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from the competent authority to begin the study. Until the site receives drug/notification, no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by patients, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals, and relevant documentation for these items, must be provided to the sponsor (or designee).

Patient incentives should not exert undue influence for participation. Payments to patients must be approved by the IRB or IEC and sponsor.

15.2 Patient Information, Informed Consent, and Patient Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF patient authorization form (if applicable) and patient information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the patient's personal and personal health information for purposes of conducting the study. The ICF and the patient information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, and the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and, if applicable, the patient authorization form. The ICF patient authorization form (if applicable) and patient information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The ICF patient authorization form (if applicable) and patient information sheet (if applicable) must be written in a language fully comprehensible to the prospective patient. It is the responsibility of the investigator to explain the detailed elements of the ICF and patient authorization form (if applicable) and patient information sheet (if applicable) to the patient. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. An impartial witness may be needed if the patient or patient's legally acceptable representative cannot read. If the patient is not capable of rendering adequate written informed consent, then the patient's legally acceptable representative may provide such consent for the patient in accordance with applicable laws and regulations.

The patient, or the patient's legally acceptable representative, must be given ample opportunity to (1) inquire about details of the study and (2) decide whether to participate in the study. If the patient, or the patient's legally acceptable representative, determines that he or she will participate in the study, then the ICF and patient authorization form (if applicable) must be signed and dated by the patient, or the patient's legally acceptable representative, at the time of consent and before the patient enters into the study. The patient or the patient's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using a ballpoint pen with either blue or black ink. The investigator must also sign and date the ICF and patient authorization (if applicable) at the time of consent, ie, before the patient enters into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, patient authorization form (if applicable), and patient information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date and specific time the patient signs the informed consent in the patient's medical record, and the name of the person responsible for consenting the patient. A signed copy of the ICF, the signed patient authorization form (if applicable), and the patient information sheet (if applicable) shall be given to the patient.

All revised ICFs must be reviewed and signed by relevant patients or the relevant patient's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the patient's medical record, and the patient should receive a copy of the revised ICF.

15.3 Patient Confidentiality

The sponsor and designees affirm and uphold the principle of the patient's right to protection against invasion of privacy. Throughout this study, a patient's source data will be linked to the sponsor's clinical study database or documentation only via a unique identification number. As permitted by all applicable laws and regulations, limited patient attributes, such as sex, age, or date of birth, and patient initials may be used to verify the patient and accuracy of the patient's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, China NMPA), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the patient's original medical records (source data or documents) including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a patient's study participation, and autopsy reports. Access to a patient's original medical records requires the specific authorization of the patient as part of the informed consent process (see Section 15.2).

Copies of any patient source documents that are provided to the sponsor must have certain identifying personal information removed, eg, patient name, address, and other identifier fields not collected on the patient's eCRF.

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the clinical study site agreement. In the event of any discrepancy between the protocol and the clinical study site agreement, the clinical study site agreement will prevail.

15.4.2 Clinical Trial Registration

To ensure that information on clinical trials reach the public in a timely manner and, additionally, comply with applicable laws, regulations, and guidance, Takeda will, at a minimum, register interventional clinical studies it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites on or before start of study, as defined by Takeda policy and standards. Takeda contact information, along with investigator's city, country, and recruiting status will be registered and available for public viewing.

As needed, Takeda and investigator/site contact information may be made public to support participant access to studies via registries. In certain situations/registries, Takeda may assist participants or potential participants in finding a clinical study by helping them locate study sites closest to their homes by providing the investigator name, address, and phone number via email/phone or other methods preferred by callers requesting study information. Once patients receive investigator contact information, they may call the site requesting enrollment into the study. The investigative sites are encouraged to handle the study inquiries according to their established patient screening process. If the caller asks additional questions beyond study enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on National Institute of Health, United States (US) National Library of Medicine, ClinicalTrials.gov, and other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda policy/standards, applicable laws, and/or regulations.

15.4.4 Data Sharing

The sponsor is committed to responsible sharing of clinical data with the goal of advancing medical science and improving patient care. Qualified independent researchers will be permitted to use data collected from patients during the study to conduct additional scientific research, which may be unrelated to the study drug or the patient's disease. The data provided to external researchers will not include information that identifies patients personally.

15.5 Insurance and Compensation for Injury

Each patient in the study must be insured in accordance with the regulations applicable to the site where the patient is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study participants. Refer to the clinical study site agreement regarding the sponsor's policy on participant compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

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Appendix A Schedule of Events

Table A-1 Schedule of Events

	Baseline/Screening [a]		Cycle 1	Cycle 2+	Cycle 4 only	Last Planned Cycle of Tx	EOT Visit [b]	Long-Term Follow-up [c]		
								PFS		Survival
								Mos after first dose		
								≤24	>24	After PD
Visit Window	**Days -28 to 0**	**Days -7 to 0**	**Day 1**	**Day 1 (±1 day)**	**Days 15-21**	**Days 15-21**	**30 days after last dose (+7 days)**	**Every 3 mos (±1 week)**	**Every 6 mos (±1 week)**	**Every 6 mos (±1 week)**
Informed consent	X									
Inclusion/exclusion criteria	X									
Demographics	X									
Medical history	X									
CD30/histology [d]	X									
HgbA1c	X									
Viral tests [e]	X									
IPI score	X									
Vital signs	X		X	X			X			
Height	X									
Weight	X		X	X						
Echocardiogram	X [f]									
12-lead ECG		X								
ECOG performance status		X		X			X			
Serum chemistry		X	X	X			X [g]			
Hematology		X	X	X			X			
Pregnancy test [h]		X					X			
AEs	AEs, including SAEs, will be recorded from the time of signing informed consent through 30 days after last dose of study treatment.							Only related SAEs must be reported.		
Concomitant medications / procedures	Recorded from the time of signing informed consent through 30 days after last dose of study treatment.									

Table A-1 Schedule of Events

	Baseline/Screening [a]		Cycle 1	Cycle 2+	Cycle 4 only	Last Planned Cycle of Tx	EOT Visit [b]	Long-Term Follow-up [c]		
								PFS		Survival
								Mos after first dose		
								≤24	>24	After PD
Visit Window	**Days -28 to 0**	**Days -7 to 0**	**Day 1**	**Day 1 (±1 day)**	**Days 15-21**	**Days 15-21**	**30 days after last dose (+7 days)**	**Every 3 mos (±1 week)**	**Every 6 mos (±1 week)**	**Every 6 mos (±1 week)**
Study treatment administration [i]			X	X						
Response Assessment										
Physical exam and B symptoms [j]	X		X	X		X	X	X [k]	X [k]	X [k]
CT or MRI	X				X	X	X [b]	X [k]	X [k]	X [k]
PET [l]	X				X	X	X [b]	To confirm CR		
Bone marrow biopsy	X [m]				To confirm CR [n]					
Survival status										X [o]
Other Laboratory Samples										
Samples for PK assessment				See Table A-2						
Samples for immunogenicity (ADA, Nab) assessment				See Table A-2						

Table A-1 Schedule of Events

	Baseline/Screening [a]		Cycle 1	Cycle 2+	Cycle 4 only	Last Planned Cycle of Tx	EOT Visit [b]	Long-Term Follow-up [c]		
								PFS		Survival
								Mos after first dose		
								≤24	>24	After PD
Visit Window	**Days -28 to 0**	**Days -7 to 0**	**Day 1**	**Day 1 (±1 day)**	**Days 15-21**	**Days 15-21**	**30 days after last dose (+7 days)**	**Every 3 mos (±1 week)**	**Every 6 mos (±1 week)**	**Every 6 mos (±1 week)**

A+CHP: Adcetris plus cyclophosphamide, doxorubicin (hydroxydaunorubicin), and prednisone; ADA: antidrug antibody; AE: adverse event; ALK: anaplastic lymphoma kinase; CR: complete response; CT: computed tomography; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end of treatment; HbsAg: hepatitis B surface antigen; HBc: hepatitis B core antibody; HBsAb: hepatitis B surface antibody; HBV: hepatitis B virus; HCV-Ab: hepatitis C virus (antibody); HgbA1c: hemoglobin A1c; HIV-Ab: human immunodeficiency virus antibody; IEC: independent ethics committee; IPI: International Prognostic Index; IRB: institutional review board; IXRS: interactive voice/web response system; Mos: months; MRI: magnetic resonanace imaging; PD: progressive disease; PET: positron emission tomography; PFS: progression-free survival; PK: pharmacokinetics; SAE: serious adverse event; sALCL: systemic anaplastic large cell lymphoma; Tx: treatment.

[a] Patients are considered to be enrolled in the study when they are entered into the IXRS and receive their first dose of the study treatment. Eligibility documentation must be submitted to the sponsor and confirmed prior to study start and enrollment. Study treatment must be initiated within 3 days of the patient being entered into the IXRS.

[b] Response assessments at EOT are required if not performed at last cycle of treatment. (A ±7 day window is allowed for image tests.) EOT evaluations should be obtained before the initiation of non-protocol therapy. If EOT evaluations are completed before 30 days following the last study treatment, a phone screen can be done 30 to 37 days following the patient's last study treatment to ensure that there are no changes in AE profile.

[c] Each patient will have the opportunity to be followed for 36 months after initiation of the last patient's treatment.

[d] Locally assessed to enable enrollment (see Section 9.5.14.2 for definition of CD30-positivity); tumor specimen must be submitted before enrollment for subsequent central pathology review to confirm histology (and ALK status, if applicable) and CD30 expression. Submission of the tumor block or unstained slides from a diagnostic biopsy is required before enrollment for subsequent central confirmation of CD30 expression, disease subtype, and ALK status for patients with a diagnosis of sALCL.

[e] HbsAg, HBsAb, anti-HBc, HCV-Ab serology (also HBV-DNA by polymerase chain reaction if anti-HBc positive and HbsAg negative, and HCV-RNA by polymerase chain reaction if HCV-Ab positive), and HIV-Ab.

[f] May be obtained up to 6 months before the first dose of study treatment.

[g] Abnormal liver function tests at EOT will be followed to resolution.

[h] A serum or urine pregnancy (choriogonadotropin beta) test will be completed for all reproductively female patients of childbearing potential during screening and at the EOT visit; this test must be negative at the time of screening for the patient to be enrolled in the study. Pregnancy tests may also be repeated during the study if requested by an IEC/IRB or if required by local regulations.

[i] Patients will receive 6 to 8, 21-day cycles of brentuximab vedotin (Adcetris) plus cyclophosphamide, doxorubicin (hydroxydaunorubicin), and prednisone (A+CHP). Patients may receive study treatment until PD, unacceptable toxicity, or completion of the desired 6 to 8 cycles, whichever occurs first.

[j] Consists of the following: physical examination and a thorough review of the patient's current signs and symptoms, especially B symptoms. See Section 9.5.3.

[k] Obtain disease evaluation until patient experiences PD per investigator assessment, initiation of anticancer therapy to treat residual or PD, death, or study closure, whichever occurs first. A ±7-day window is allowed for image tests.

[l] PET scans will be obtained at any time to confirm CR or if clinically indicated.

[m] Obtained within 60 days of first dose of study treatment.

[n] Bone marrow biopsy is required to confirm CR if bone marrow is positive at baseline and other criteria for CR have been met; this confirmation should be obtained within 4 weeks after documentation of response by radiographic assessment. Repeat bone marrow biopsies are not required once bone marrow is found to be negative.

[o] Once a patient experiences PD per investigator assessment, survival status is monitored every 6 months until death or study closure, whichever occurs first. Survivor information and death details may be collected by methods that include, but are not limited to, telephone, email, mail, or retrieval from online or other databases. Collect information regarding subsequent anticancer therapies.

Table A-2 PK and Immunogenicity Sampling Time Points

Cycle	Study Day	Time	Window	Relative Time [a]	PK	ADA [b]
1	Day 1	Predose	Within prior 24 hr	Start of infusion	X	X
		End of infusion (30 min)	Within 30 min post end of infusion	End of infusion	X	
	Day 3 (Even sites only)	48 hr	±24 hr	Start of infusion	X	
	Day 5 (Odd sites only)	96 hr	±48 hr	Start of infusion	X	
2	Day 1	Predose	Within prior 24 hr	Start of infusion	X	X
		End of infusion (30 min)	Within 30 min post end of infusion	End of infusion	X	
	Day 3 (Odd sites only)	48 hr	±24 hr	Start of infusion	X	
	Day 8 (Even sites only)	168 hr	±72 hr	Start of infusion	X	
3	Day 1	Predose	Within prior 24 hr	Start of infusion	X	X
4	Day 1	Predose	Within prior 24 hr	Start of infusion		X
	Days 15-21	Anytime during visit	Not applicable	Not applicable	X	
5+	Day 1	Predose	Within prior 24 hr	Start of infusion	X	X
Last	Day 1	Predose	Within prior 24 hr	Start of infusion		X
	Days 15-21	Anytime during visit	Not applicable	Not applicable	X	
EOT	30 days (+7 days) after last dose	Anytime during visit	Not applicable	Not applicable		X

ADA: antidrug antibody(ies); AE: adverse event; EOT: end of treatment; PK: pharmacokinetic(s).

All sampling times are relative to the start of the brentuximab vedotin infusion, except for the end of infusion.

[a] Relative to study drug infusion (brentuximab vedotin).

[b] Additional optional samples for immunogenicity may be collected at unscheduled visits for a patient who experiences an AE considered by the investigator to be consistent with hypersensitivity/infusion-related reaction.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study-related procedures, including study-specific (nonroutine/nonstandard panel) screening assessments, are NOT performed on potential study participants before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to ICH and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to study participants. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in ICH and local regulations, are met.
9. Obtain valid informed consent from each patient who participates in the study, and document the date of consent in the patient's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a patient authorization section that describes the uses and disclosures of a patient's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a patient authorization, then the investigator must obtain a separate patient authorization form from each patient or the patient's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of the investigator, including his or her name, address, and other identifying personal information. In addition, the investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, US, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

The investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of the investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details, and results on publicly accessible clinical trial registries, databases, and websites.

The investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in the investigator's own country.

The investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes previously described.

Appendix D Cockcroft-Gault Equation

For male patients:

$$\text{Creatinine clearance} = \frac{(140 - \text{age[years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine[mg/dL]})} \quad \text{OR} \quad \frac{(140 - \text{age[years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine[}\mu\text{mol/L]})}$$

For female patients:

$$\text{Creatinine clearance} = \frac{0.85\ (140 - \text{age[years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine[mg/dL]})} \quad \text{OR} \quad \frac{0.85\ (140 - \text{age[years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine[}\mu\text{mol/L]})}$$

Appendix E 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 (1994) [19].

Appendix F International Prognostic Index For NHL

The International Prognostic Index (IPI) includes the following risk factors shown:

Score

	Score	
Risk Factor	**0 point**	**1 point**
Age	≤60 years	>60 years
Serum LDH	≤1 times the ULN	>1 times the ULN
ECOG performance status	0 or 1	2, 3, or 4
Stage	I or II	III or IV
Extranodal involvement	≤1 site	>1 site

ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; ULN: upper limit of normal.

Each factor is worth 1 point. Based on the IPI score, patients can be categorized as follows:

- Low risk: (0-1 point).
- Low-intermediate risk: (2 points).
- High-intermediate risk: (3 points).
- High risk: (4-5 points).

Appendix G 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 et al (1982) [20].

Appendix H International Working Group Criteria for Response Categories

Tumor response will be assessed by using the International Working Group (IWG) criteria [1].

Table H-1 IWG Revised Response Criteria for Malignant Lymphoma

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease.	FDG-avid or PET positive before therapy; mass of any size permitted if PET negative. Variably FDG-avid or PET negative; regression to normal size on CT. [a]	Not palpable, nodules disappeared.	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative. [b]
PR	Regression of measurable disease and no new sites.	50% decrease in SPD of up to 6 largest dominant nodes or masses [c]; no increase in size of the other nodes. FDG-avid or PET positive before therapy; 1 or more PET positive at previously involved site. Variably FDG-avid or PET negative; regression on CT.	>50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen.	Irrelevant if positive before therapy; cell type should be specified. Patients who achieve CR by the above criteria but have persistent morphologic bone marrow involvement will be considered PR. [d]
Stable disease	Failure to attain CR/PR or PD.	FDG-avid or PET positive before therapy; PET positive at prior sites of disease and no new sites on CT or PET. Variably FDG-avid or PET negative; no change in size of previous lesions on CT.		
Relapsed disease or PD [e]	Any new lesion or increase by >50% of previously involved sites from nadir.	Appearance of a new lesion(s) >1.5 cm in any axis [f], >50% increase in SPD of more than 1 node [g], or >50% increase in longest diameter of a previously identified node >1 cm in short axis. Lesions PET positive if FDG-avid lymphoma or PET positive before therapy.	>50% increase from nadir in the SPD of any previous lesions.	New or recurrent involvement.

Source: Cheson et al (2007) [1].
CR: complete remission; CT: computed tomography, FDG: fluorodeoxyglucose; PET: positron emission tomography, PD: progressive disease; PR: partial response; SPD: sum of the product of the diameters.
[a] ≤1.5 cm in their greatest transverse diameter for nodes >1.5 cm before therapy. Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤1.0 cm in their short axis after treatment.
[b] A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.
[c] These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
[d] When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.
[e] Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes ≤1.0×≤1.0 cm will not be considered as abnormal for relapse or PD.
[f] Increased FDG uptake in a previously unaffected site should only be considered relapsed or PD after confirmation with other modalities. In patients with no history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.
[g] To be considered PD, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥50% and to a size of 1.5×1.5 cm or more than 1.5 cm in the long axis.

Appendix I Lugano Response Assessment Criteria

The Lugano classification for response assessment of non-Hodgkin lymphoma is shown in Table I-1.

Table I-1 Lugano Response Assessment Criteria

Response and Site	PET-CT–Based Response	CT-Based Response
Complete Response	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extra lymphatic sites	Score 1, 2, or 3 [a] with or without a residual mass on 5PS [b]	Target nodes/nodal masses must regress to ≤1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in the marrow	Normal by morphology; if indeterminate, IHC negative.
Partial Response	Partial metabolic response	Partial remission (all of the following).
Lymph nodes and extra lymphatic sites	Score 4 or 5 [b] with reduced uptake compared with baseline and residual mass(es) of any size.	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites.
	At interim, these findings suggest responding disease.	When a lesion is too small to measure on CT, assign 5×5 mm as the default value.
		When no longer visible, 0×0 mm.
	At end of treatment, these findings indicate residual disease.	For a node >5×5 mm, but smaller than the normal, use actual measurement for calculation.
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase.
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal.
New lesions	None	None

Table I-1 Lugano Response Assessment Criteria

Response and Site	PET-CT–Based Response	CT-Based Response
Partial Response (continued)		
Bone marrow	Residual uptake higher than uptake in normal marrow, but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	Not applicable
No Response or Stable Disease	No metabolic response.	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end-of-treatment.	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met.
Nonmeasured lesions	Not applicable	No increase consistent with progression.
Organ enlargement	Not applicable	No increase consistent with progression.
New lesions	None	None
Bone marrow	No change from baseline.	Not applicable
Progressive Disease	Progressive metabolic disease.	Progressive disease requires at least 1 of the following:
Individual target nodes/nodal masses	Score 4 or 5 with increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment.	An individual node/lesion must be abnormal with: • LDi >1.5 cm and • Increase by ≥ 50% from PPD nadir and • An increase in LDi or SDi from nadir: o 0.5 cm for lesions ≤2 cm o 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (eg, a 15 cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions.

Table I-1 Lugano Response Assessment Criteria

Response and Site	PET-CT–Based Response	CT-Based Response
Progressive Disease (continued)		
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma. Assessable disease of any size unequivocally attributable to lymphoma.
Bone marrow	New or recurrent FDG-avid foci.	New or recurrent involvement.

Source: Cheson et al (2014) [16].

5PS: 5-point scale; CT: computed tomography; FDG: fluorodeoxyglucose; IHC: immunohistochemistry; LDi: longest diameter; MRI: magnetic resonance imaging; PET: positron emission tomography; PPD: cross product of the LDi and perpendicular diameter; SDi: shortest axis perpendicular to the LDi; SPD: sum of the product of the perpendicular diameters for multiple lesions.

[a] Score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan; however, in trials involving PET, where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Nonnodal lesions include those in solid organs (eg, liver, spleen, kidneys, and lungs), gastrointestinal involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, gastrointestinal tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

[b] PET 5PS: 1, no uptake above background; 2. Uptake ≤mediastinum; 3, uptake >mediastinum, but ≤liver; 4, uptake moderately >liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Pharmacology Approval	16-Dec-2021 14:26 UTC
[redacted]	Clinical Approval	20-Dec-2021 16:08 UTC
[redacted]	Clinical Approval	21-Dec-2021 00:03 UTC
[redacted]	Biostatistics Approval	21-Dec-2021 02:18 UTC