Clinical Study Protocol	
Study Intervention	Sabestomig (AZD7789)
Study Code	D9571C00001
Version	5
Date	07 May 2024

A Phase I/II Open-label, Multi-center Study to Assess Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of AZD7789, an anti-PD-1 and anti-TIM-3 Bispecific Antibody, in Patients with Relapsed or Refractory Classical Hodgkin Lymphoma

Sponsor Name: AstraZeneca

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This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered, and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number: D9571C00001

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Study Intervention: Sabestomig (AZD7789)

Study Phase: Phase I/II

Short Title: Open-label, Multi-center Study to Assess the Safety and Preliminary Efficacy of AZD7789 in Patients with Relapsed or Refractory Classical Hodgkin Lymphoma (cHL)

SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Protocol Version 5	07 May 2024
Protocol Version 4	11 July 2023
Protocol Version 3	1 November 2022
Protocol Version 2	24 September 2021
Original Protocol	23 July 2021

Version 5 (07 May 2024)

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trials Regulation Article 2, 2 (13).

Overall Rationale for the Modification:

The primary rationale for the changes implemented in this protocol modification is to provide continued access to sabestomig (AZD7789) through a post-trial access program for participants who are deriving clinical benefit at the time of data cut-off for the final analysis of the study. Assessment of these participants will revert to standard of care at the investigational site, with the exception of safety reporting. Further changes were made for clarification and to address inconsistencies.

Summary of Changes:

List of Substantial Modifications

Section # and name	Description of change	Brief rationale
Section 1.3 Schedule of Activities Tables 2 and 4 6.9 Continued Access to Study Intervention After the End of the Study 8 Study Assessments and Procedures 8.9 Assessments for Participants Who Transition to PTAP	Added PTAP guidance including test assessments and samples at last study visit prior to the final study DCO Added requirement for safety reporting to continue during PTAP Clarified that the EoT visit would not be required for participants entering the PTAP	To provide continued access to sabestomig (AZD7789) to participants who continue to derive clinical benefit from treatment beyond the end of study. Final assessments at last study visit prior to PTAP initiation (at the time of DCO) was added to further inform on exploratory endpoints. EoT visit is not required for participants continuing on PTAP because patients are continuing on treatment; this will avoid confusion with sample labeling.
5.1 Inclusion Criteria (15b, 15c, 16, 17a, 17c) 8.3.10.2 Paternal Exposure	Revised time period for use of contraception and donation of sperm and ova to 90 days after last dose of sabestomig	To align with updated pharmacokinetic data that shows a mean half-life for sabestomig of approximately 10 to 11 days

DCO = data cut-off; EoT = end of treatment; PTAP = Post-trial Access Program.

List of Non-substantial Modifications

Section # and name	Description of change	Brief rationale
Throughout the document	Administrative change: The version numbering was updated. Typographical errors were corrected, and minor clarifications were made.	Editorial updates
Throughout the document	Added investigational product name sabestomig	To provide the nonproprietary name of the investigational product
Section 1.3 Schedule of Activities - Tables 1, 2, 3, and 48.6.1 Collection of Mandatory Samples for Biomarker Analysis	Corrected matrix from plasma to whole blood for collection of circulating tumor DNA and circulating biomarkers	To clarify the correct matrix for the sample collection, reflecting the sample collected at the study site and the subsequent samples that are analyzed

Section # and name	Description of change	Brief rationale
Section 1.3 Schedule of Activities - Tables 2 and 3	Deleted footnote regarding additional glycated hemoglobin assessments for participants with evidence or suspicion of diabetes mellitus development	To reduce burden of additional test for participants
Section 1.3 Schedule of Activities - Table 4	Clarified text for sample collection/assessments at combined EoT visit and Day 30 post-last dose follow-up visit when timelines/windows overlap. Clarified that if a participant begins a new treatment shortly after discontinuation and within the EoT biopsy window, a biopsy should not be collected	To clarify which tests and data should be obtained when EoT and Day 30 post-last dose visit are combined to limit sample/assessment duplication and ensure samples from both visits are collected at one timepoint To ensure accurate interpretation of biopsy results
4.4 End of Study Definition	Revised cross-reference to Section 6.7 to correct section heading Section 6.6.7	Linking error
6.9 Continued Access to Study Intervention After the End of the Study 8.3.1 Time Period and Frequency for Collecting AE and SAE Information	Added text regarding AE and SAE collection time period following discontinuation of sabestomig	To provide timing for collection of AEs and SAEs during the PTAP and to clarify that AEs and SAEs will be collected regardless of participants' initiation of new anticancer treatment up to required timelines in protocol
Section 1.3 Schedule of Activities – Table 4 7.1 Discontinuation of Study Intervention	Added text regarding last study contact for participants in safety or survival follow-up	To clarify last study-related contact and documentation during safety or survival follow-up
8.3.6 Adverse Events of Special Interest	Updated AESI terminology	To align AESI terminology with updates from current MedDRA coding and to align the PT terms coded to the medical concepts across the Sponsor bispecifics platform/program development
Appendix A1 Regulatory and Ethical Considerations	Added text regarding reporting of SUSARs in the EudraVigilance database	To comply with EU CTR language standards on reporting of SUSARs
Appendix B2 Contraception Methods	Added statement regarding acceptable use of oral contraceptives (only highly effective when associated with inhibition of ovulation).	To comply with CTFG guidance on the recommendations related to contraception and pregnancy testing

Section # and name	Description of change	Brief rationale
Appendix C3 International WG Consensus Response evaluation Criteria in Lymphoma (Younes et al 2017 [RECIL 2017])	Added definitions of response per RECIL criteria	To provide further definitions of RECIL response to align with AstraZeneca clinical study protocol template language

AE = adverse event; AESI = adverse event of special interest; CTFG = Clinical Trials Facilitation Group; EoT = end of treatment; EU CTR = European Union Clinical Trials Regulation; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; PTAP = Post-trial Access Program; RECIL = Response-evaluation Criteria in Lymphoma; SAE = serious adverse event; SUSAR = suspected unexpected serious adverse reaction; WG = Working Group.

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1. PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A Phase I/II Open-label, Multi-center Study to Assess Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of AZD7789, an Anti-PD-1 and Anti-TIM-3 Bispecific Antibody, in Patients with Relapsed or Refractory Classical Hodgkin Lymphoma

Short Title:

Open-label, Multi-center Study to Assess the Safety and Preliminary Efficacy of AZD7789 in Patients with Relapsed or Refractory Classical Hodgkin Lymphoma (cHL)

Rationale:

The cellular microenvironment of classical Hodgkin Lymphoma (cHL) is characterized by a paucity of B cell-derived malignant Hodgkin Reed-Sternberg (HRS) cells within a tumor microenvironment (TME) comprised of non-malignant stromal and immune cells. Despite extensive immune cell infiltration, the antitumor immune response is ineffective. It is hypothesized that this is due to the ability CCI CCI .

Hodgkin Reed-Sternberg cells co-opt the programmed cell death protein-1 (PD-1) pathway and upregulate PD-1 ligands by several mechanisms including copy gain alterations of 9p24.1. Topographical analysis of cHL TME demonstrated that HRS cells with programmed cell death-ligand 1 (PD-L1) overexpression were in close proximity to PD-1^+ $CD4^+$ T cells within the TME. Furthermore, reports demonstrated that PD-1 expression on $CD4^+$ T cells, within the cHL TME, is more frequently observed on the T helper 1 (Th1) effector cells compared to $CD4^+$ Tregs, which are in turn largely PD-1 negative. Consequently, a double immune evasion strategy exists within cHL, whereby Th1-mediated immune responses are likely dysfunctional while the immunosuppressive Treg cells retain functionality.

Due to the strong scientific rationale, anti-PD-1/PD-L1 therapy entered clinical trials and yielded a breakthrough in relapsed or refractory (r/r) cHL. However, as monotherapy, less than 20% of patients achieved a complete response (CR) and results were not durable.

CCI , the relative CCI CCI suggests CCI contribute to promote CCI . CCI CCI and CCI is an immune checkpoint (IC) that has been associated with CCI and has recently been implicated as a resistance mechanism following PD-1 therapy. While data in cHL is limited, CCI expression has been observed in cHL. Therefore, co-targeting both PD-1 and CCI may reinvigorate CCI and lead to more durable CCI .

This study will investigate the safety, tolerability, pharmacokinetics (PK), and antitumor activity of sabestomig (AZD7789), a PD-1/TIM-3 bispecific monoclonal antibody (mAb), in the r/r cHL population. The study design comprises of two parts: Part A consists of a dose escalation that will enroll r/r cHL participants and Part B a dose expansion, which will enroll in Cohort B1 r/r cHL participants who were previously exposed to anti-PD-1/PD-L1 based therapy and in Cohort B2 r/r cHL participants who are naïve to anti-PD-1/PD-L1 therapy.

Objectives and Endpoints:

Primary	
Objectives	**Endpoints**
Part A Dose Escalation	
• To assess the safety and tolerability of sabestomig in participants with r/r cHL • To establish the maximum tolerated dose, or optimal biological dose, and recommended Phase 2 dose	• Incidence of AEs, imAEs, and SAEs • Incidence of AEs leading to discontinuation of sabestomig • Changes from baseline and clinically significant alterations in vital signs, laboratory parameters, and ECG results • Incidence of dose-limiting toxicities
Part B Dose Expansion (all)	
• To assess the safety and tolerability of sabestomig in participants with r/r cHL	• Incidence of AEs, imAEs, and SAEs • Incidence of AEs leading to discontinuation of sabestomig • Changes from baseline and clinically significant alterations in vital signs, laboratory parameters, and ECG results
Part B Dose Expansion (B1)	
• To assess the preliminary antitumor activity of sabestomig in participants with r/r cHL (anti-PD-1/PD-L1 exposed)	• Objective Response Rate (defined as the proportion of patients with complete remission or partial remission) [a]
Part B Dose Expansion (B2)	
• To assess the preliminary antitumor activity of sabestomig in participants with r/r cHL (anti-PD-1/PD-L1 naïve)	• Complete Response Rate (defined as the proportion of patients with complete remission) [a]

[a] Disease response will be assessed according to Blinded Independent Central Review using Modified Lugano Criteria (2014) [1]

Abbreviations: AE: adverse event; cHL: classical Hodgkin Lymphoma; ECG: electrocardiogram; imAE: immune-mediated adverse event; PD-1: programmed cell death protein-1 and PD-L1: programmed cell death-ligand 1; r/r cHL: relapsed/refractory classical Hodgkin Lymphoma; SAE: serious adverse event.

[1] Reference: Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, Lister TA. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. American Society of Clinical Oncology. J Clin Oncol. 201432(27):3059-67.

Secondary	
Objectives	**Endpoints**
Part A Dose Escalation	
• To assess the preliminary antitumor activity of sabestomig in participants with r/r cHL	• Complete Response Rate, Objective Response Rate, DoR, and DoCR, and PFS including landmarks at 12 and 24 months [a] • OS including landmarks at 12 and 24 months
Part B Dose Expansion	
• To further assess the preliminary antitumor activity of sabestomig in participants with r/r cHL	• DoR, DoCR, and PFS including landmarks at 12 and 24 months [b] • OS including landmarks at 12 and 24 months
• To evaluate Patient Reported Outcomes (PROs) and Quality of Life (QoL) while on sabestomig.	• Proportion of dosed subjects over time with: ° diarrhea, rash, and fatigue (PRO-CTCAE or Peds-PRO-CTCAE) ° overall side-effect bother (PGI-TT) ° quality of life/health (EORTC ILXX QL2)
Part A Dose Escalation and Part B Dose Expansion	
• To assess the PK of sabestomig in participants with r/r cHL	• PK parameters including the maximum observed concentration, area under the concentration-time curve, clearance, and terminal elimination half-life
• To assess the immunogenicity of sabestomig in participants with r/r cHL	• Incidence of anti-drug antibodies against sabestomig in serum

[a] Disease response will be assessed according to Investigator assessment using Modified Lugano (2014) [1] and RECIL criteria [2].

[b] Disease response will be assessed according to Blinded Independent Central Review using Modified Lugano (2014) [1].

Abbreviations: DoR: Duration of Response; DoCR: Duration of Complete Response; EORTC IL: European Organization for Research and Treatment of Cancer Item List; OS: Overall Survival; Peds: pediatric; PFS: Progression-free Survival; PGI-TT: Patient Global Impression of Treatment Tolerability; PK: pharmacokinetic(s); PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QoL: quality of life; RECIL: Response-evaluation Criteria in Lymphoma; r/r cHL: relapsed/refractory classical Hodgkin Lymphoma.

Overall Design:

This Phase I/II, open-label multi-center, dose escalation and dose expansion study will evaluate the safety, tolerability, PK, pharmacodynamics, and antitumor activity of sabestomig in adult/young adult participants with r/r cHL. The study includes two parts: Part A Dose Escalation and Part B Dose Expansion. Part A will enroll participants with r/r cHL previously treated with anti-PD-1/PD-L1 based therapy. Part B will be subdivided into Cohort B1, enrolling a patient population identical to Part A, and Cohort B2 enrolling participants who

[2] Younes A, Hilden P, Coiffier B, Hagenbeek A, Salles G, Wilson W, et al. International Working Group consensus response-evaluation criteria in lymphoma (RECIL 2017). Ann Oncol 2017;28:1436-47.

never received an anti-PD-1/PD-L1 therapy previously. Approximately 180 participants will receive treatment with sabestomig in the study at up to approximately [redacted] sites globally.

Part A Dose Escalation will evaluate up to 8 dose levels of sabestomig and consist of up to [redacted] participants with r/r cHL. Cohorts A1 to A4 will be single participant cohorts with 4 dose levels of sabestomig (2, 7, 22.5, and 75 mg) based on an accelerated titration design (ATD). However, the operating model will switch to a modified toxicity probability interval-2 (mTPI-2) algorithm should a DLT or Grade 2 or greater treatment-emergent adverse event (TEAE) occur.

Cohorts A5, A6, and A7 for subsequent dose levels of sabestomig (225, 750, and 1500 mg) will enroll 3 participants based on the mTPI-2 algorithm to establish the safety of sabestomig. Based on emerging data, the optional Cohort A8 (at 2000 mg) may open and may also enroll up to [redacted] participants. After a cohort is declared safe (eg, Cohort A5, A6, A7 or A8) and based on emerging safety, efficacy, PK and biomarker data, the cohort may be expanded (up to [redacted] participants); the cohorts may be opened in parallel to fill their rosters of up to [redacted] participants each (mini dose expansion). Intermediate dose levels (50, 150, 450, 1000, 1250, and 1750 mg) may be explored if warranted by emerging safety, PK, pharmacodynamics, biomarker, and response data.

The planned starting dose will be 2 mg (dose level 1). Participants will be evaluated for DLTs during a 28-day DLT evaluation period.

Part B Dose Expansion may be considered once a recommended Phase 2 dose (RP2D) is determined in Part A Dose Escalation and will evaluate the safety, tolerability, PK, pharmacodynamic, and antitumor activity of sabestomig at the determined RP2D in 2 cohorts (Cohorts B1 and B2) described below.

Cohort B1: Approximately [redacted] participants with cHL who have received at least 2 prior lines of systemic treatment and have subsequently relapsed or become refractory to treatment and have been previously treated with at least 2 cycles of anti-PD-1/PD-L1 based therapy. Participants in Cohort B1 will be identical to those of the dose escalation stage. For this reason, enrolment of a larger sample size will provide a clearer confirmatory efficacy signal. [redacted].

Cohort B2: Approximately [redacted] participants with cHL who have received at least 2 prior lines of systemic treatment and have subsequently relapsed or become refractory to treatment, but have not received an anti-PD-1/PD-L1 based therapy.

Disclosure Statement:

This is a dose escalation and expansion study in which treatment is not blinded.

Number of Participants:

Approximately 180 participants will be treated with sabestomig, with up to CCI participants in Part A (Dose Escalation) and CCI participants in Part B (Dose Expansion). Additional participants may be enrolled if additional dose levels, expansion cohorts, treatment schedules are explored, or participants require replacement for any reason.

Note: "Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study but are not assigned in the study, are considered "screen failures" unless otherwise specified by the protocol.

Intervention Groups and Duration:

Following an initial screening period of up to 4 weeks, eligible participants will receive sabestomig every 3 weeks (Q3W) administered via intravenous infusion at the selected dose starting on Cycle 1 Day 1. Participants will be treated with study intervention for a maximum of 35 cycles, or until disease progression, unacceptable toxicity, withdrawal of consent, or if other reasons to discontinue treatment occur. All participants will be followed for survival until the end of study, regardless of whether treatment was discontinued.

No dose reductions of sabestomig will be allowed. Dose modification (hold or delay) and toxicity management for sabestomig-related toxicity, including management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions are provided in the Toxicity Management Guidelines (Appendix I).

Safety Review Committee:

A study-specific Safety Review Committee will provide ongoing safety surveillance of the study, with regularly scheduled reviews of safety, PK, and other relevant data. This committee will be responsible for making recommendations for dose escalation or dose de-escalation decisions and making recommendations regarding further conduct of the study during all phases of the study.

Statistical Methods:

The efficacy endpoints of Complete Response Rate (CRR), Objective Response Rate (ORR), Duration of Response (DoR), and Duration of Complete Response (DoCR) will be summarized on the response-evaluable analysis set (defined as all dosed participants who had measurable disease at baseline). The efficacy endpoints of Progression-free survival (PFS), and overall survival (OS) will be summarized on the full analysis set (defined as all

participants who received any amount of study intervention). The CRR/ORR and its confidence intervals will be summarized by dose level. The DoR/DoCR will be summarized using descriptive statistics and Kaplan-Meier plots, where there are sufficient numbers of responders. The PFS and OS will be summarized by dose level, and Kaplan-Meier plots will be provided.

Safety and tolerability will be assessed in terms of DLTs, adverse events (AEs)/serious AEs (SAEs), immune-mediated adverse events (imAEs), vital signs, clinical chemistry/hematology parameters, and clinically significant abnormalities in electrocardiograms (ECGs). All safety analyses will be performed on the safety analysis set (defined as all participants who received any amount of study intervention). The number and percentage of participants with AEs in different categories (eg, causally related, Common Terminology Criteria for Adverse Events Grade ≥ 3, etc.) will be summarized by dose level; events in each category will be further summarized by Medical Dictionary for Regulatory Activities system organ class and preferred term. The SAEs will be summarized separately. All safety data including clinical chemistry, hematology, coagulation, urinalysis, vital signs, and clinically significant abnormalities in ECGs will be listed individually by participant and appropriately summarized.

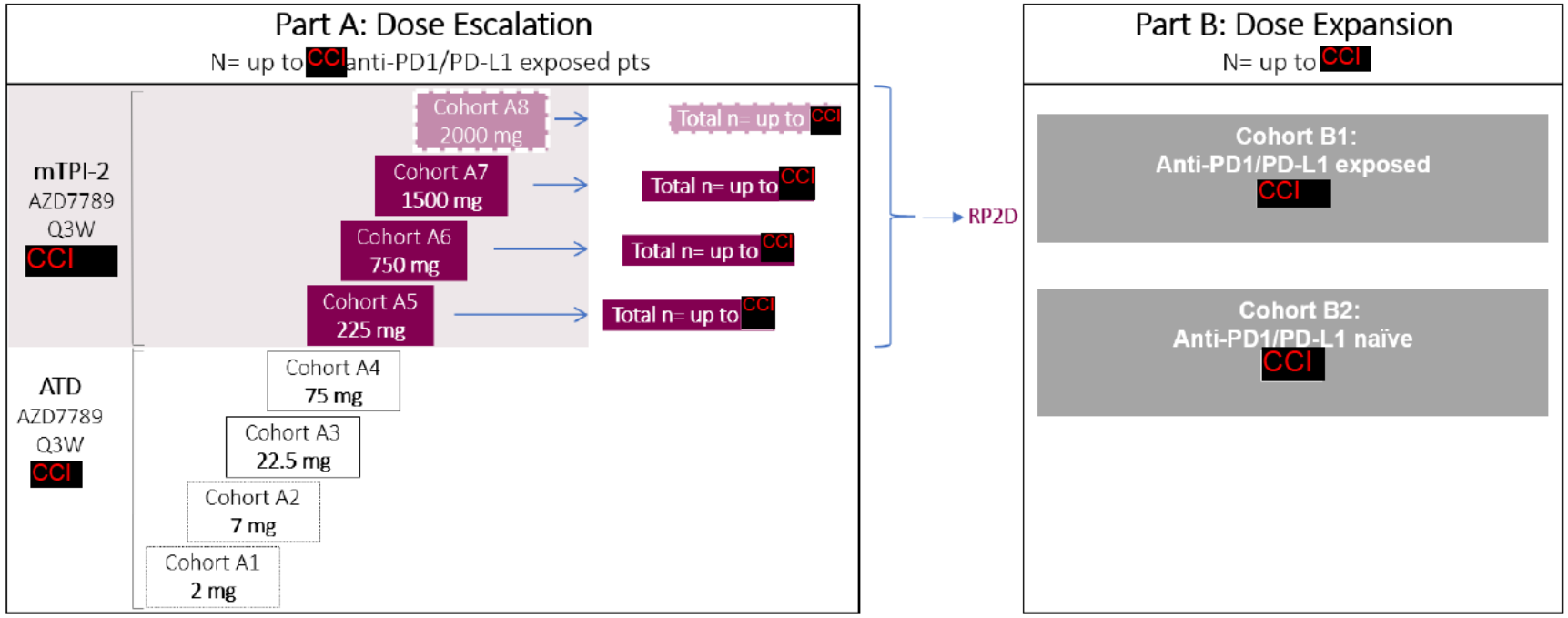
Individual sabestomig concentrations will be tabulated by dose level along with descriptive statistics. Relevant descriptive statistics of non-compartmental PK parameters will be provided if data allow and may include AUC, C_{max}, clearance, and t½ if data allow. Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of participants who develop detectable ADAs to sabestomig.

Interim safety analysis will be conducted in Part B after approximately CCI participants have received the first dose at least CCI to data cut-off, using the interim safety population (defined as all participants who received the first dose at least CCI to data cut-off). For both Cohorts (B1 and B2) in Part B, interim efficacy analyses to assess futility will be performed in a continuous manner using CCI and will begin after approximately CCI participants in each respective cohort are included in the interim response-evaluable population (defined as all dosed participants who had measurable disease at baseline and received first dose at least CCI prior to data cut-off). Following this initial interim efficacy analysis, subsequent interim efficacy analyses may be performed after every CCI additional participants for Cohort B1 and every CCI additional participants for Cohort B2 that gets included in the interim response-evaluable population, until all participants are enrolled and evaluated. For any interim futility analyses, an objective response is defined as either a CR or PR as per Modified Lugano criteria, and a complete response is defined as a CR as per Modified Lugano Criteria. For any interim analysis of Cohort B1, participants dosed at RP2D in Part A will be included.

1.2 Schema

The study flow is presented in Figure 1.

Figure 1 Study Flow Diagram



Abbreviations: ATD: accelerated titration design; mTPI-2: modified toxicity probability interval-2; n: number of participants; PD-1: programmed cell death protein-1; PD-L1: programmed cell death-ligand 1; Q3W: every 3 weeks; RP2D: recommended phase 2 dose

1.3 Schedule of Activities

The SoA to be performed during the screening period is presented in Table 1. The SoA to be performed during the intervention period is presented in Table 2 for Part A Dose Escalation and Table 3 for Part B Dose Expansion. The SoA to be performed at disease progression, at EoT, and during the follow-up period is presented in Table 4.

Table 1 Schedule of Activities for Screening Period (Parts A and B)

Study Period	**Screening**
Visit	**V1**
Procedure/Study Day	**Day -28 to -1**
Informed consent and assignment of participant identification number (Section 5.1 and Appendix A)	X
Demography (including race and ethnicity, per local regulations)	X
Medical/surgical history and comorbid conditions (includes substance usage; Section 8.2.1)	X
Full physical examination including height and weight (Section 8.2.2)	X
12-lead ECG (triplicate; Section 8.2.4) [a]	X
Left ventricular ejection fraction by echocardiogram/ multiple-gated acquisition scan (Section 8.2.5)	X
Vital signs including pulse oximetry (Section 8.2.3)	X
Pulmonary function test (FEV_1), restricted to eligible participants with pre-existing obstructive or fibrotic lung conditions (Section 8.2.8) [b]	X
Eastern Cooperative Oncology Group performance status (Section 8.2.6)	X
Assessment of B-symptoms (Section 8.1.1)	X
Assessment of AEs/SAEs (Section 8.3)	X
Concomitant medications (Section 6.5)	X
Verify eligibility criteria (Sections 5.1 and 5.2)	X
COVID-19 testing [c]	X
Blood and Urine Tests for Safety	
Clinical Chemistry (Section 8.2.7)	X
Hematology (Section 8.2.7)	X
Cardiac troponin (Section 8.2.7)	X
Glycated hemoglobin (Section 8.2.7)	X
Thyroid function (thyroid-stimulating hormone, and free thyroxine and free triiodothyronine as indicated; Section 8.2.7) [d]	X
Anti-thyroid antibodies (anti-thyroid peroxidase antibodies, thyroglobulin antibodies, thyrotropin receptor antibodies; Section 8.2.7)	X
Coagulation parameters (Section 8.2.7)	X

Table 1 Schedule of Activities for Screening Period (Parts A and B)

Study Period	**Screening**
Visit	**V1**
Procedure/Study Day	**Day -28 to -1**
Cortisol stimulation test, if adrenal insufficiency is suspected (Section 8.2.7)	X
Hepatitis A, B, and C; HIV-1 and HIV-2 virology (Sections 5.1 and 8.2.7) [e]	X
Pregnancy test (serum or urine; women of childbearing potential only; Section 8.2.7) [f]	X
Urinalysis (Section 8.2.7)	X
Biomarker Evaluations [g]	
Whole blood for CCI (Section 8.6.1)	X
Whole blood for CCI (flow; Section 8.6.1)	X
Serum for CCI (Section 8.6.1)	X
Whole blood for CCI and CCI (Section 8.6.1)	X
Whole blood for CCI (Section 8.6.1)	X
Tumor Tissue Sample [g]	
Archival tumor tissue sample from first diagnosis, if available (all participants; Section 8.6.2.1)	X
Mandatory archival or fresh tumor tissue biopsy collected within 4 months prior to enrolling in this study (for participants in Part A mini-expansion and Part B; Section 8.6.2.1) [h]	X
Disease Assessments	
Disease assessment scans; positron emission tomography computed tomography scan [i]	X
Collection of relevant tumor marker data, if available	X

[a] All ECGs will be obtained in triplicate (all within a 5-minute time period). Whenever ECGs and blood draws are scheduled for the same nominal time, the blood draws should occur last.

[b] The FEV1 should be greater than 50% of predicted value or for FEV/FVC ratio, the fifth percentile of the lower limit of normal (American Thoracic Society definition of moderately severe).

[c] For all participants in the study, all local institutional standards for COVID-19 must be followed for testing. For participants with a known previous COVID-19 infection in the last 3 months, a negative PCR test must be documented within 72 hours prior to the first dose.

[d] Free thyroxine and triiodothyronine only to be measured if thyroid-stimulating hormone is abnormal or if suspicion of an adverse event related to the endocrine system.

[e] Participants with active hepatitis A, B, or C are excluded. Participants who have chronic hepatitis B and receiving suppressive antiviral therapy are allowed on study if ALT is normal and viral load is controlled; controlled hepatitis B viral load is defined as serum hepatitis B virus DNA < 100 IU/mL by PCR. Participants who have chronic hepatitis C are allowed to be enrolled if ALT is normal and hepatitis C virus RNA is undetectable by PCR, either spontaneously or in response to a successful prior course of anti-hepatitis C therapy.

[f] A urine or serum pregnancy test is acceptable; if urine test is positive or equivocal, then serum β-hCG testing should be performed for confirmation.

[g] For participants in mainland China only, samples will not be collected.

[h] Recent biopsy within the last 4 months is required for participants in Part A mini-expansion and Part B unless medically contraindicated. Within that time period, participant must not have received any anti-cHL treatment since the last line of therapy, otherwise fresh tissue is required. For participants in Part A Dose Escalation, tumor tissues biopsy within prior 4 months is optional.

[i] AstraZeneca may request prior images/scans performed up to 6 months prior to start of study intervention.

Abbreviations: AE: adverse event; ALT: alanine transaminase; COVID-19: coronavirus disease 2019; ECG: electrocardiogram; FEV1: forced expiratory volume over 1 second; FVC: forced vital capacity; HIV: Human immunodeficiency virus; PCR: polymerase chain reaction; SAE: serious adverse event.

Table 2 Schedule of Activities for the Intervention Period (Part A Dose Escalation)

Study Period	**Intervention Period**						
Visit	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8-Vn**
Cycle Number and Day	**C1D1**	**C1D3**	**C1D8**	**C1D15**	**C2D1**	**C2D8**	**C3D1-CnD1** [a]
Procedure/Window			**± 1 D**	**± 3 D**	**± 1 D**	**± 3 D**	**± 3 D**
Abbreviated (symptom-directed) physical examination including weight (Section 8.2.2) [b]	X		X	X	X [b]	X	X [b]
12-lead ECG (triplicate) (Section 8.2.4) [c]	X [c]		X		X [c]	X	C3D1 [c], C4D1 [c], and as clinically indicated thereafter
Left ventricular ejection fraction by echocardiogram/ multiple-gated acquisition scan (Section 8.2.5) [d]	As clinically indicated						
Vital signs including pulse oximetry (Section 8.2.3) [e]	X [e]		X	X	X [e]	X	X [e]
Eastern Cooperative Oncology Group performance status (Section 8.2.6)	X				X		X
Assessment of B-symptoms (Section 8.1.1)	X				X		X
Assessment of adverse events and serious adverse events (Section 8.3)	←----------X----------→						
Concomitant medications (Section 6.5)	←----------X----------→						
Blood and Urine Tests for Safety							
Chemistry (Section 8.2.7) [f]	X [g]	X	X	X	X		X
Hematology (Section 8.2.7) [f]	X [g]	X	X	X	X		X
Cardiac troponin (Section 8.2.7) [f]	If clinically indicated						
Glycated hemoglobin (Section 8.2.7)							C3D1, C5D1, C7D1, C9D1, C11D1, C13D1, C15D1, C17D1, C19D1, C21D1, C23D1, C25D1, C27D1, C29D1, C31D1, C33D1, and C35D1

Table 2 Schedule of Activities for the Intervention Period (Part A Dose Escalation)

Study Period	**Intervention Period**						
Visit	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8-Vn**
Cycle Number and Day	**C1D1**	**C1D3**	**C1D8**	**C1D15**	**C2D1**	**C2D8**	**C3D1-CnD1** [a]
Procedure/Window			**± 1 D**	**± 3 D**	**± 1 D**	**± 3 D**	**± 3 D**
Thyroid function (thyroid-stimulating hormone, and free thyroxine and free triiodothyronine as indicated [h]; Section 8.2.7) [f]	X [g]			X	X		X
Anti-thyroid antibodies (anti-thyroid peroxidase antibodies, thyrotropin receptor antibodies, thyroglobulin antibodies; Section 8.2.7)	As clinically indicated						
Coagulation parameters (Section 8.2.7) [f]	X [g]		X	X	X		X
Hepatitis B and C virology (Section 8.2.7) [i]							C5D1, C9D1, C13D1, C17D1, C21D1, C25D1, C29D1, and C33D1
Pregnancy test (urine or serum; women of child-bearing potential only; Section 8.2.7) [f]	X [g]				X		X
Urinalysis (Section 8.2.7)	As clinically indicated						
Blood Tests for PK and Immunogenicity							
Serum for sabestomig PK (Section 8.5) [j]	X [j]	X	X	X	X	X	C3D1, C4D1, C5D1, C6D1, then C8D1, C10D1, C14D1, C18D1, C26D1, C34D1, and CnD1[a]
Serum for sabestomig ADA (Section 8.5) [k]	X				X	X	C3D1, C4D1, C5D1, C6D1, then C8D1, C10D1, C14D1, C18D1, C26D1, C34D1, and CnD1[a]
Biomarker Evaluations							
Whole blood for CCI CCI (Section 8.6.1) [l]	X		X [m]		X	X	C3D1, C4D1, C5D1, C6D1, then C10D1, C14D1, C18D1, C22D1, C26D1, C30D1, and C34D1

Table 2 Schedule of Activities for the Intervention Period (Part A Dose Escalation)

Study Period	**Intervention Period**						
Visit	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8-Vn**
Cycle Number and Day	**C1D1**	**C1D3**	**C1D8**	**C1D15**	**C2D1**	**C2D8**	**C3D1-CnD1** [a]
Procedure/Window			**± 1 D**	**± 3 D**	**± 1 D**	**± 3 D**	**± 3 D**
Whole blood for CCI (flow) (Section 8.6.1) [l]	X		X [m]	X	X	X	C3D1, C4D1, C5D1, C6D1, C10D1, C14D1, C18D1, and CnD1[a]
Serum for CCI (Section 8.6.1) [l]	X		X [m]	X	X	X	X
Serum for CCI analysis (Section 8.6.1) [l]	X		X [m]	X	X	X	X and CnD1[a]
Whole blood for CCI and circulating biomarkers (Section 8.6.1) [l]	X		X [m]	X	X	X	C3D1, C4D1, C5D1, C6D1, then C10D1, C14D1, C18D1, C22D1, C26D1, C30D1, C34D1, and CnD1[a]
Whole blood for CCI (Section 8.6.1) [l]	X		X [m]	X	X	X	C3D1, C4D1, C5D1, and C6D1
Genomics Initiative (optional, exploratory genetic saliva sample; Section 8.7 and Appendix F) [n]	X						
Biopsies							
Optional Tumor tissue biopsy (Section 8.6.2.1)			X (± 2 D) [m]				
Optional non-tumor tissue biopsy (Section 8.6.2.2)	At toxicity; if clinically indicated						
Study Intervention Administration							
Premedication (Section 6.5.1)	X				X		X
Sabestomig administration [o] (Section 6)	X				X		X

Table 2 Schedule of Activities for the Intervention Period (Part A Dose Escalation)

Study Period	Intervention Period						
Visit	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8-Vn**
Cycle Number and Day	**C1D1**	**C1D3**	**C1D8**	**C1D15**	**C2D1**	**C2D8**	**C3D1-CnD1** [a]
Procedure/Window			**± 1 D**	**± 3 D**	**± 1 D**	**± 3 D**	**± 3 D**
Disease Assessments							
Imaging disease assessment (Section 8.1, Table 16) [p]	At least 10 days after sabestomig administration in Cycle CCI and CCI then thereafter at Year 1 from the date of the first infusion, then Q6M until PD, start of new anti-cHL therapy or EoS (whichever occurs first). Of note: if a participant in CR receives radiotherapy alone as consolidation, imaging for disease assessment should continue until the participant meets the criteria mentioned above.						

[a] If the participant is deriving clinical benefit per investigator assessment at the time of final study DCO and is planned to continue treatment if the study transitions to PTAP, the participant will complete their last planned dosing visit before the final study DCO. The following samples will need to be collected if they are not planned as scheduled assessments during this visit: serum for PK, ADA, and CCI analysis; whole blood for CCI and CCI and circulating biomarkers. During the treatment visits after the final DCO, participants will continue to receive sabestomig per the dosing schedule (Q3W) and should be followed according to the institution's standard-of-care assessments. No further data collection is required except for safety reporting (see Section 6.9).

[b] On dosing days, the physical examination will be conducted prior to sabestomig administration.

[c] All ECGs will be obtained in triplicate (all within a 5-minute time period). Collection times for ECGs on days of sabestomig administration are shown below. Whenever ECGs and blood draws (eg, PK/ADA) are scheduled for the same nominal time, the blood draws should occur last. The timing of the ECG should be such that it allows the blood draw to occur at the proper nominal time.

Collection Times for ECGs on Sabestomig Dosing Days				
Cycle Number and Day	**Prior to SOI (within 30 min prior to SOI)**	**Post EOI**		
		30 min (± 5 min)	**1 h (± 5 min)**	**4 h (± 15 min)**
C1D1	X	X		X
C2D1, C3D1, and C4D1	X		X	
C5D1, C6D1, etc.	As clinically indicated			

[d] If clinically indicated, and at the Investigator's discretion, a consultation with a cardiologist is recommended for follow-up.

[e] Collection times for vital signs and pulse oximetry on days of sabestomig administration are shown below. Whenever vital signs and blood draws (eg, PK/ADA) are scheduled for the same nominal time, the blood draws should occur last. The timing of the vital signs assessment should be such that it allows the blood draw to occur at the proper nominal time.

Collection Times for Vital Signs and Pulse Oximetry on Sabestomig Dosing Days								
Cycle Number and Day	**Prior to SOI (within 30 min prior to SOI)**	**Every 15 min (± 5 min) During Infusion**	**EOI (± 5 min)**	**Post EOI**				
				30 min (± 5 min)	**1 h (± 10 min)**	**2 h (± 10 min)**	**3 h (± 10 min)**	**4 h (± 15 min)**
C1D1	X	X	X	X	X	X	X	X
C2D1, C3D1, and C4D1	X	X	X	X	X			
C5D1, C6D1, etc.	X			X				

f All safety laboratory results must be reviewed by the Investigator or designee prior to sabestomig administration.

g If screening assessment was performed within the 5 days prior to C1D1 (Days -5 to -1), then the assessment does not need to be performed prior to SOI on C1D1.

h Free thyroxine and triiodothyronine only to be measured if thyroid-stimulating hormone is abnormal or if suspicion of an adverse event related to the endocrine system.

i Hepatitis B virology testing during treatment and follow-up is required for participants with positive HbsAg or isolated positive anti-hepatitis B core antibody (negative HbsAg and negative antibody to hepatitis B surface antigen) at screening and for any participant where clinically indicated. Participants with positive HbsAg must remain on antiviral therapy, per institutional practice, to ensure adequate viral suppression during the study intervention and follow-up periods. Controlled hepatitis B viral load is defined as serum hepatitis B virus DNA < 100 IU/mL by PCR.
Hepatitis C virology testing during treatment and follow-up is only required for participants with positive hepatitis C antibody at screening and for any participant where clinically indicated. Controlled hepatitis C viral load is defined as undetectable hepatitis C virus RNA by PCR either spontaneously or in response to a successful prior course of anti-hepatitis C therapy.

j Collection times for serum samples for PK on days of sabestomig administration are shown below. On days when sabestomig is not administered (C1D8, C1D15, and C2D8), only one serum sample for PK is required during the visit.

Collection Times for Serum Samples for PK on Sabestomig Dosing Days				
Cycle Number and Day	**Prior to SOI (within 30 min prior to SOI)**	**EOI (+15 min)**	**Post EOI**	
			4 h (± 15 min)	**48 h (± 2 h)**
C1D1	X	X	X	X (collected at C1D3 visit)
C2D1, C3D1, C4D1, C5D1, C6D1, C8D1, C10D1, C14D1, C18D1, C26D1, C34D1, and CnD1[a]	X	X		

k On sabestomig dosing days, serum samples for ADA will be collected within 30 minutes prior to SOI and may be collected at the same time as the prior to SOI serum sample for PK.

l On sabestomig dosing days, the sample should be collected prior to start of sabestomig administration.

m If tumor biopsy will be collected on C1D8 (± 2 D) then C1D8 Biomarker Evaluation samples should be collected prior to surgery on the same day as the biopsy (to coincide with the biopsy).

[n] If, for any reason, the sample is not drawn at screening, it may be collected at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study. The genetic informed consent addendum must be signed prior to sample collection. Refer to Appendix F for inclusion/exclusion criteria specific to the Genomics Initiative and further details on the optional Genomics Initiative sample.

[o] Each dose of sabestomig will be infused over approximately 60 minutes (-5 min to +15 min). Participants should be closely monitored during and after infusions, as described in Section 6.2.1.2. Following completion of the first treatment cycle, participants may receive additional treatment with sabestomig if dosing criteria defined in Section 6.1.2 are met. For participants with a known previous COVID-19 infection in the last 3 months, a negative PCR test must be documented within 72 hours prior to the first dose of sabestomig. In the event of a COVID-19 infection while on active treatment with sabestomig, the investigatory should use their judgement to delay treatment depending on the clinical situation of the participant (see also Section 6.7).

[p] At least 10 days post infusion, but prior to the next infusion. Disease response should be assessed by PET-CT as per Modified Lugano criteria (2014) until participant achieves CR. Once CR is achieved, contrast CT may replace PET-CT to monitor disease response until PD is suspected. If PD is suspected, PD must be confirmed by PET scan. Disease response assessments will be according to the Investigator evaluation using Modified Lugano (Cheson et al, 2014) and RECIL (Younes et al, 2017) criteria. In the event pseudo progression is suspected by imaging, a PET-CT scan should be repeated at least 4 weeks after the previous assessment to confirm progression or response.

Abbreviations: ADA: anti-drug antibody; C: cycle; cHL: classical Hodgkin Lymphoma; CR: complete response; CT: computed tomography; D: day(s); DCO: data cut-off; ECG: electrocardiogram; EOI: end of infusion; EoS: End of Study; HbsAg: hepatitis B surface antigen; h: hour; min: minute; PCR: polymerase chain reaction; PD: progressive disease; PET-CT: positron emission tomography-CT; PK: pharmacokinetic(s); PTAP: post-trial Access Program; Q3W: every 3 weeks; Q6M: every 6 months; SOI: start of infusion; TIM-3: T cell immunoglobulin and mucin domain-containing protein-3; V: visit.

Table 3 Schedule of Activities for the Intervention Period (Part B Dose Expansion)

Study Period	**Intervention Period**					
Visit	**V2**	**V3**	**V4**	**V5**	**V6**	**V7-Vn**
Cycle Number and Day	**C1D1**	**C1D8**	**C1D15**	**C2D1**	**C2D8**	**C3D1-CnD1**
Procedure/Window		**± 1 D**	**± 3 D**	**± 1 D**	**± 3 D**	**± 3 D**
Abbreviated (symptom-directed) physical examination including weight (Section 8.2.2) [a]	X	X	X	X [a]	X	X [a]
12-lead ECG (triplicate) (Section 8.2.4) [b]	X [b]	X [b]		X [b]	X [b]	C3D1 [b], C4D1 [b], and as clinically indicated thereafter
Left ventricular ejection fraction by echocardiogram/ multiple-gated acquisition scan (Section 8.2.5) [c]	As clinically indicated					
Vital signs including pulse oximetry (Section 8.2.3) [d]	X [d]	X	X	X [d]	X	X [d]
Eastern Cooperative Oncology Group performance status (Section 8.2.6)	X			X		X
Assessment of B-symptoms (Section 8.1.1)	X			X		X
Assessment of AEs/SAEs (Section 8.3)	←----------X----------→					
Concomitant medications (Section 6.5)	←----------X----------→					
Blood and Urine Tests for Safety						
Clinical Chemistry (Section 8.2.7) [e]	X [f]	X	X	X		X
Hematology (Section 8.2.7) [e]	X [f]	X	X	X		X
Cardiac troponin (Section 8.2.7) [e]	If clinically indicated					
Glycated hemoglobin (Section 8.2.7)						C3D1, C5D1, C7D1, C9D1, C11D1, C13D1, C15D1, C17D1, C19D1, C21D1, C23D1, C25D1, C27D1, C29D1, C31D1, C33D1 and C35D1
Thyroid function (thyroid-stimulating hormone, free thyroxine, and free triiodothyronine as indicated [g]; Section 8.2.7) [e]	X [f]		X	X		X

Table 3 Schedule of Activities for the Intervention Period (Part B Dose Expansion)

Study Period	**Intervention Period**					
Visit	**V2**	**V3**	**V4**	**V5**	**V6**	**V7-Vn**
Cycle Number and Day	**C1D1**	**C1D8**	**C1D15**	**C2D1**	**C2D8**	**C3D1-CnD1**
Procedure/Window		**± 1 D**	**± 3 D**	**± 1 D**	**± 3 D**	**± 3 D**
Anti-thyroid antibodies (anti-thyroid peroxidase antibodies, thyroglobulin antibodies, thyrotropin receptor antibodies; Section 8.2.7)	As clinically indicated					
Coagulation parameters (Section 8.2.7) [e]	X [f]	X	X	X		X
Hepatitis B and C virology (Section 8.2.7) [h]						C5D1, C9D1, C13D1, C17D1, C21D1, C25D1, C29D1 and C33D1
Pregnancy test (urine or serum; women of childbearing potential only; Section 8.2.7) [e]	X [f]			X		X
Urinalysis (Section 8.2.7)	As clinically indicated					
Blood Tests for PK and Immunogenicity						
Serum for sabestomig PK (Section 8.5) [i, j]	X	X	X	X	X [k]	C4D1 and C6D1 only [j]
Serum for sabestomig ADA (Section 8.5) [l]	X			X		C4D1, C6D1, C8D1, C10D1, C14D1, C18D1, C26D1 and C34D1
Biomarker Evaluations [m]						
Whole blood for CCI [redacted] l (Section 8.6.1) [m,n]	X	X [o]		X	X	C3D1, C4D1, C5D1, C6D1, then C10D1, C14D1, C18D1, C22D1, C26D1, C30D1 and C34D1
Whole blood for CCI [redacted] (flow) (Section 8.6.1) [m,n]	X	X [o]	X	X	X	C3D1, C4D1, C5D1, C6D1, then C10D1, C14D1 and C18D1
Serum for CCI [redacted] (Section 8.6.1) [m,n]	X	X [o]	X	X	X	X
Serum for CCI [redacted] analysis (Section 8.6.1) [m,n]	X	X [o]	X	X	X	X

Table 3 Schedule of Activities for the Intervention Period (Part B Dose Expansion)

Study Period	**Intervention Period**					
Visit	**V2**	**V3**	**V4**	**V5**	**V6**	**V7-Vn**
Cycle Number and Day	**C1D1**	**C1D8**	**C1D15**	**C2D1**	**C2D8**	**C3D1-CnD1**
Procedure/Window		**± 1 D**	**± 3 D**	**± 1 D**	**± 3 D**	**± 3 D**
Whole blood for CCI and circulating biomarkers (Section 8.6.1) [m,n]	X	X [o]	X	X	X	C3D1, C4D1, C5D1, C6D1, then C10D1, C14D1, C18D1, C22D1, C26D1, C30D1 and C34D1
Whole blood for CCI (Section 8.6.1) [m,n]	X	X [o]	X	X	X	C3D1, C4D1 C5D1 and C6D1
Genomics Initiative (optional, exploratory genetic saliva sample; Section 8.7 and Appendix F) [p]	X					
Biopsies [q,m]						
Tumor tissue biopsy (Section 8.6.2.1) [q]		X (± 2D) [o]				
Optional non-tumor tissue biopsy (Section 8.6.2.2)	At toxicity, if clinically indicated					
PRO Collection [r]						
Tolerability [Adults: PRO-CTCAE + PGI-TT Adolescents: Peds-PRO-CTCAE]	C1D1 as baseline then Q1W from Week 1 until Week 6, then Q3W from Week 7 until Week 18, then Q6W from Week 19 until EoT or disease progression. Refer to Vendor's Study Information Guide and training for window of completion.					
Physical function [Adults CCI Adolescents: CCI]	C1D1 as baseline then Q3W from Week 1 until Week 18, then Q6W from Week 19 until EoT or disease progression. Refer to Vendor's Study Information Guide and training for window of completion.					
Disease symptoms and health status [Adults: CCI]	C1D1 as baseline then Q6W from Week 1 until EoT or disease progression. Refer to Vendor's Study Information Guide and training for window of completion.					
Change [Adults: PGIC]	At Week 10, 19, 37, 67, and 103. Refer to Vendor's Study Information Guide and training for window of completion.					
Study Intervention Administration						
Premedication (Section 6.5.1)	X			X		X
Sabestomig administration (Section 6) [s]	X			X		X

Table 3 Schedule of Activities for the Intervention Period (Part B Dose Expansion)

Study Period	**Intervention Period**					
Visit	**V2**	**V3**	**V4**	**V5**	**V6**	**V7-Vn**
Cycle Number and Day	**C1D1**	**C1D8**	**C1D15**	**C2D1**	**C2D8**	**C3D1-CnD1**
Procedure/Window		**± 1 D**	**± 3 D**	**± 1 D**	**± 3 D**	**± 3 D**
Disease Assessments						
Imaging disease assessment (Section 8.1, Table 16) [t]	At least 10 days after sabestomig administration in Cycle CCI and CCI then thereafter at Year 1 from the date of the first infusion, then Q6M until PD, start of new treatment for HL or EoS (whichever occurs first). Of Note: if a participant in CR receives RT as consolidation, imaging disease assessment should continue until the participant meet the criteria mentioned in the paragraph above.					

[a] On dosing days, the physical examination will be conducted prior to sabestomig administration.

[b] All ECGs will be obtained in triplicate (all within a 5-minute time period). Collection times for ECGs on days of sabestomig administration are shown below. Whenever ECGs and blood draws (eg, PK/ADA) are scheduled for the same nominal time, the blood draws should occur last. The timing of the ECG should be such that it allows the blood draw to occur at the proper nominal time. Day 8 assessment only to be performed if cardiac signal is detected in Part A.

Collection Times for ECGs on Sabestomig Dosing Days		
Cycle Number and Day	**Prior to SOI (within 30 mins prior to SOI)**	**1 h (± 5 mins) Post EOI**
C1D1, C2D1, C3D1, and C4D1	X	X
C5D1, C6D1, etc.	As clinically indicated	

[c] If clinically indicated, and at the Investigator's discretion, a consultation with a cardiologist is recommended for follow-up.

[d] Collection times for vital signs and pulse oximetry on days of sabestomig administration are shown below. Whenever vital signs and blood draws (eg, PK/ADA) are scheduled for the same nominal time, the blood draws should occur last. The timing of the vital signs assessment should be such that it allows the blood draw to occur at the proper nominal time.

Collection Times for Vital Signs and Pulse Oximetry on Sabestomig Dosing Days			
Cycle Number and Day	**Prior to SOI (within 30 mins prior to SOI)**	**EOI (± 5 min)**	**30 mins (± 10 min) Post EOI**
C1D1	X	X	X
C2D1, C3D1, C4D1, etc.	X		X

[e] All safety laboratory results must be reviewed by the Investigator or designee prior to sabestomig administration.

[f] If screening assessment was performed within the 5 days prior to C1D1 (Days -5 to -1), then the assessment does not need to be performed prior to SOI on C1D1.

[g] Free thyroxine and triiodothyronine only to be measured if thyroid-stimulating hormone is abnormal or if suspicion of an adverse event related to the endocrine system.

[h] Hepatitis B virology testing during treatment and follow-up is required for participants with positive HbsAg or isolated positive anti-HBc (negative HbsAg and negative antiHBs) at screening and for any participant where clinically indicated. Participants with positive HbsAg must remain on antiviral therapy, per institutional practice, to ensure adequate viral suppression during the study intervention and follow-up periods. Controlled hepatitis B viral load is defined as serum hepatitis B virus DNA < 100 IU/mL by PCR.
Hepatitis C virology testing during treatment and follow-up is only required for participants with positive hepatitis C antibody at screening and for any participant where clinically indicated. Controlled hepatitis C viral load is defined as undetectable hepatitis C virus RNA by PCR either spontaneously or in response to a successful prior course of anti-hepatitis C therapy.

[i] Collection times for serum samples for PK on days of sabestomig administration are shown below. On days when sabestomig is not administered (C1D8 and C1D15), only one serum sample for PK is required during the visit.

Collection Times for Serum Samples for PK on Sabestomig Dosing Days		
Cycle Number and Day	**Prior to SOI (within 30 mins prior to SOI)**	**EOI (+15 mins)**
C1D1, C2D1, C4D1, C6D1	X	X

[j] For participants in mainland China, collection times for serum samples for PK on days of sabestomig administration are shown below. One serum sample for PK is required on days when sabestomig is not administered (C1D8, C1D15, C2D8) and is to be collected during the visit.

Collection Times for Serum Samples for PK on Sabestomig Dosing Days				
Cycle Number and Day	**Prior to SOI (within 30 min prior to SOI)**	**EOI (+15 min)**	**Post EOI**	
			4 h (± 15 min)	**48 h (± 2 h)**
C1D1	X	X	X	X (collected at visit)
C2D1, C4D1, C6D1, C8D1, C10D1, C14D1, C18D1, C26D1, C34D1	X	X		

[k] Sample to be collected only in mainland China.

[l] On sabestomig dosing days, serum samples for ADA will be collected within 30 minutes prior to SOI and may be collected at the same time as the prior to SOI serum sample for PK.

[m] These samples will not be collected in mainland China.

[n] On sabestomig dosing days, the sample should be collected prior to start of sabestomig administration.

[o] If tumor biopsy will be collected on C1D8 (± 2 D) then C1D8 Biomarker Evaluation samples should be collected prior to surgery on the same day as the biopsy (to coincide with the biopsy)

[p] If, for any reason, the sample is not drawn at screening, it may be collected at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study. The genetic informed consent addendum must be signed prior to sample collection. Refer to Appendix F for inclusion/exclusion criteria specific to the Genomics Initiative and further details on the optional Genomics Initiative sample.

[q] Biopsy is mandatory unless medically contraindicated.

[r] PRO questionnaires will be implemented in Part B once available at the site. Baseline PRO questionnaires must be administered after informed consent and before the first dose of study drug. Subsequent PRO questionnaires may be completed at home or at the site. If PRO questionnaires are completed at the site on dosing dates, then they must be completed prior to treatment administration.

[s] Each dose of sabestomig will be infused over approximately 60 minutes (-5 min to +15 min). Participants should be closely monitored during and after infusions, as described in Section 6.2.1.2. Following completion of the first treatment cycle, participants may receive additional treatment with sabestomig if dosing criteria defined in Section 6.1.2 are met. For participants with a known previous COVID-19 infection in the last 3 months, a negative PCR test must be documented within 72 hours prior to the first dose of sabestomig. In the event of a COVID-19 infection while on active treatment with sabestomig, the investigator should use their judgement to delay treatment depending on the clinical situation of the participant (see also Section 6.7).

[t] At least 10 days post infusion, but prior to the next infusion. Disease response should be assessed by PET-CT as per Modified Lugano criteria (2014) until participant achieves CR. Once CR is achieved, contrast CT may replace PET-CT to monitor disease response until PD is suspected. If PD suspected, PD must be confirmed by PET CT scan. Disease response assessments will be assessed by both the Investigator according to Modified Lugano (Cheson et al, 2014) and RECIL (Younes et al, 2017) criteria and Blinded Independent Central Review according to Modified Lugano.

Abbreviations: ADA: anti-drug antibody; AE: adverse event; anti-HBc: hepatitis B core antibody; anti-HBs: antibody to hepatitis B surface antigen; C: cycle; COVID-19: coronavirus disease; CR: complete response; CT: computed tomography; D: day(s); ECG: electrocardiogram; EOI: end of infusion; CCI [redacted]; EoS: end of study; EoT: end of treatment; CCI [redacted]; HbsAg: hepatitis B surface antigen; h: hour; HL: Hodgkin lymphoma; min: minute; PCR: polymerase chain reaction; PD: progressive disease; CCI [redacted]; PET-CT: positron emission tomography-CT; PF: pediatric short form; PGI-TT: Patient Global Impression of Treatment Tolerability; PGIC: Patient Global Impression of Change; CCI [redacted]; PK: pharmacokinetic(s); PRO: patient-reported outcomes; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; Q1W: every week; Q3W: every 3 weeks; Q6M: every 6 months; Q6W: every 6 weeks; RECIL: Response Evaluation Criteria in Lymphoma; RT: radiation therapy; SAE: serious adverse event; SF: short form; SOI: start of infusion; TIM-3: T cell immunoglobulin and mucin domain-containing protein-3; V: visit.

Table 4 Schedule of Activities for Disease Progression, End of Treatment, and Follow-up Period (Parts A and B)

Procedure/Visit (Window)	At Disease Progression [a]	EoT [b]	Post-treatment Safety Follow-up [c]		Survival Follow-up [c]
		+ 14 D	Day 30 Post Last Dose (± 7 D)	Day 90 Post Last Dose (± 7 D)	Q6M Post Last Disease Assessment (± 14 D)
Abbreviated (symptom-directed) physical examination including weight (Section 8.2.2)		X	X	X	
12-lead ECG (triplicate) (Section 8.2.4)		X			
Left ventricular ejection fraction by echocardiogram/ multiple-gated acquisition scan (Section 8.2.5) [d]		X	If clinically indicated.		
Vital signs including pulse oximetry (Section 8.2.3)		X	X	X	
Eastern Cooperative Oncology Group performance status (Section 8.2.6)		X	X	X	
Assessment of B-Symptoms (Section 8.1.1)		X	X	X	
Assessment of AEs/SAEs (Section 8.3)		←----------X----------→			
Concomitant medications (Section 6.5)		←----------X----------→			
Subsequent anticancer therapy	X	X	X	X	X
Survival status (by telephone, email, or clinic visit)	X	X	X	X	X
Disease status post HSCT if applicable (by telephone, email, or clinic visit) [e]					X
Blood and Urine Tests					
Clinical Chemistry (Section 8.2.7)		X	X	X	
Hematology (Section 8.2.7)		X	X	X	
Glycated hemoglobin (Section 8.2.7)		X		X	
Thyroid function (thyroid-stimulating hormone, free thyroxine, and free triiodothyronine as indicated [f]; Section 8.2.7)		X	X	X	
Anti-thyroid antibodies (anti-thyroid peroxidase antibodies, thyroglobulin antibodies, thyrotropin receptor antibodies; Section 8.2.7)		X	X	X	
Hepatitis B and C virology (Section 8.2.7) [g]			X		

Table 4 Schedule of Activities for Disease Progression, End of Treatment, and Follow-up Period (Parts A and B)

Procedure/Visit (Window)	At Disease Progression [a]	EoT [b]	Post-treatment Safety Follow-up [c]		Survival Follow-up [c]
		+ 14 D	Day 30 Post Last Dose (± 7 D)	Day 90 Post Last Dose (± 7 D)	Q6M Post Last Disease Assessment (± 14 D)
Pregnancy test (urine or serum; women of child-bearing potential only; Section 8.2.7)		X	X	X	
Urinalysis (Section 8.2.7)		X	X		
Blood Tests for PK and Immunogenicity					
Part A Dose Escalation and Part B for patients from mainland China: Serum for sabestomig PK (Section 8.5)		X	X		
Part A Dose Escalation and Part B for patients from mainland China: Serum for sabestomig ADA (Section 8.5)		X	X	X	
Blood Tests for Biomarker Evaluations [h]					
Whole blood for CCI (Section 8.6.1) [i]	X	X	X		
Whole blood for CCI (flow) (Section 8.6.1) [i]	X	X			
Serum for CCI (Section 8.6.1) [i]	X	X	X		
Serum for CCI analysis (Section 8.6.1) [i]	X	X	X	X	
Whole blood for CCI and circulating biomarkers (Section 8.6.1) [i]	X	X	X	X	
Whole blood for CCI (Section 8.6.1) [i]	X	X	X		
PRO Collection (Part B only)					
Tolerability [Adults: PRO-CTCAE + PGI-TT Adolescents: Peds-PRO-CTCAE]		X[j]			
Physical function [Adults CCI Adolescents: CCI]		X[j]			

Table 4 Schedule of Activities for Disease Progression, End of Treatment, and Follow-up Period (Parts A and B)

Procedure/Visit (Window)	At Disease Progression [a]	EoT [b]	Post-treatment Safety Follow-up [c]		Survival Follow-up [c]
		+ 14 D	Day 30 Post Last Dose (± 7 D)	Day 90 Post Last Dose (± 7 D)	Q6M Post Last Disease Assessment (± 14 D)
Disease symptoms and health status [Adults: CCI Adolescents: CCI]		X[j]			
Biopsies [j, h]					
Optional tumor tissue biopsy (Section 8.6.2.1) [k]	X	X[k]			
Non-tumor tissue biopsy (Section 8.6.2.2)		At toxicity, if clinically indicated			
Disease Assessments					
Imaging disease assessment (Section 8.1, Table 16) [l]	At least 10 days after sabestomig administration in Cycle CCI and CCI then thereafter at Year 1 then Q6M **to be continued beyond the Day 90 post last dose visit** if participant still in response, until PD, start of new treatment for cHL or EoS (whichever occurs first)				

[a] This visit is only required for participants who discontinued for disease progression.

[b] The EoT visit can be combined with the Day 30 post-last dose follow-up visit if timelines/windows overlap. At this combined visit, required tests and assessments between both the EoT and Day 30 post last dose visit must be performed, ensuring there are no duplicates. If the participant is planned to continue on sabestomig treatment at the time of the final study DCO and as the study transitions to PTAP, the EoT visit will not be performed. The participant will complete the last dosing visit per SoA Table 2 before the final DCO.

[c] All participants in Safety or Survival follow-up at the time of final study DCO will be contacted by the study site prior to the final study DCO to confirm their survival status and to inform participants that this was the last study-related contact, and no further survival data will be collected in respect to the study. Sites are requested to document this last contact in the source records.

[d] If clinically indicated, and at the Investigator's discretion, a consultation with a cardiologist is recommended for follow-up.

[e] To be collected only for participant who received any dose of the study drug and underwent HSCT while in response (CR or PR) without any other treatment between last dose of sabestomig and start of pre-conditioning for HSCT.

[f] Free thyroxine and triiodothyronine only to be measured if thyroid-stimulating hormone is abnormal or if suspicion of an adverse event related to the endocrine system.

[g] Hepatitis B virology testing during treatment and follow-up is required for participants with positive HbsAg or isolated positive anti-HBc (negative HbsAg and negative anti HBs) at screening and for any participant where clinically indicated. Participants with positive HbsAg must remain on antiviral therapy, per institutional practice, to ensure adequate viral suppression during the study intervention and follow-up periods. Controlled hepatitis B viral load is defined as serum hepatitis B virus DNA < 100 IU/mL by PCR.
Hepatitis C virology testing during treatment and follow-up is only required for participants with positive hepatitis C antibody at screening and for any participant where clinically indicated. Controlled hepatitis C viral load is defined as undetectable hepatitis C virus RNA by PCR either spontaneously or in response to a successful prior course of anti-hepatitis C therapy.

[h] These samples will not be collected in mainland China.

[i] All ECGs will be obtained in triplicate (all within a 5-minute time period). Whenever ECGs and blood draws (eg, PK/ADA) are scheduled for the same nominal time, the blood draws should occur last. The timing of the ECG should be such that it allows the blood draw to occur at the proper nominal time.

[j] Refer to Vendor's Study Information Guide and training for window of completion.

[k] Optional biopsy at EoT is to be performed only for participants who discontinue treatment due to disease progression and if participant has consented for the optional procedure. If the participant begins a new treatment shortly after discontinuation and within the 14-day allowable EoT biopsy window, a biopsy should not be collected.

[l] During the intervention period, the imaging to be performed at least 10 days post infusion. Disease response should be assessed by PET-CT as per Modified Lugano criteria (2014) until participant achieves CR. Once CR is achieved, contrast CT may replace PET-CT to monitor disease response until PD is suspected. If PD is suspected, PD must be confirmed by PET. Disease response assessments will be assessed by both the Investigator according to Modified Lugano (Cheson et al, 2014) and RECIL (Younes et al, 2017) criteria and Blinded Independent Central Review according to Modified Lugano. Schedule is detailed in Table 16.

Abbreviations: ADA: anti-drug antibody; AE: adverse event; anti-HBc: hepatitis B core antibody; anti-HBs: antibody to hepatitis B surface antigen; cHL: classical Hodgkin disease; CR: complete response; CT: computed tomography; D day(s); DCO: data cut-off; ECG: electrocardiogram; CCI [redacted]; EoS: end of study; EoT: end of treatment; CCI [redacted]; HbsAg: hepatitis B surface antigen; HSCT: hematopoietic stem cell transplantation; PCR: polymerase chain reaction; PD: progressive disease; Peds: Pediatric; PET-CT: positron emission tomography-CT; PF: pediatric short form; PGI-TT: Patient Global Impression of Treatment Tolerability; CCI [redacted] PK: pharmacokinetic(s); PR: partial response; PRO: patient-reported outcomes; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PTAP: post-trial Access Program; Q6M: every 6 months; RECIL: Response Evaluation Criteria in Lymphoma; SAE: serious adverse event; SF: short form; SoA: Schedule of Activities; CCI [redacted]

2. INTRODUCTION

Sabestomig (AZD7789) is a [redacted]. Programmed cell death protein-1 and TIM-3 are part of a complex system of cell surface receptors that, when bound to their cognate ligands, provide co-inhibitory signals to T cells to modulate their activity. [redacted] and [redacted] is [redacted]. AstraZeneca is developing sabestomig for the treatment of r/r cHL in patients having either refractory or have developed a resistance to PD-1 selective treatment or are anti-PD-1/PD-L1-naïve.

2.1 Study Rationale

Multiple reports have identified a high correlation in PD-1 and TIM-3 expression on tumor infiltrating lymphocytes across multiple indications with dual receptor expression associated with diminished functionality (Biton et al, 2018, Fourcade et al, 2010, Thommen et al, 2015). [redacted].

2.2 Background

2.2.1 Programmed Cell Death Protein-1 and T Cell Immunoglobulin and Mucin Domain-containing Protein-3

Programmed cell death protein-1 and TIM-3 are immunoregulatory proteins associated with diminished T cell functionality (Jones et al, 2008, Monney et al, 2002). The PD-1 receptor was one of the first co-inhibitory cell surface molecules identified to regulate T cell activation and function (Ishida et al, 1992). Programmed cell death protein-1 is transiently upregulated upon TCR stimulation, with the highest cell surface expression observed on T cells experiencing chronic antigen exposure (Wherry et al, 2015), and mediates inhibitory effects on T cell activation upon engagement with its ligands, PD-L1 or PD-L2 (Freeman et al, 2000, Hui et al, 2017, Latchman et al, 2001). Agents that inhibit the PD-1/PD-L1 pathway demonstrate clinical activity in a wide range of cancers relative to the previous SoC and have led to several regulatory approvals by the US FDA and/or the EMA for the treatment of various malignancies (Chai et al, 2020).

The TIM-3 receptor is an immunoregulatory protein associated with diminished T cell functionality (Monney et al, 2002, Wolf et al, 2020). Although generally undetectable on

peripheral blood T cells, cell surface levels of TIM-3 are upregulated upon TCR stimulation of $CD4^+$ and $CD8^+$ T cells, with highest expression observed upon chronic antigen exposure or within the TME (Fourcade et al, 2010, Jones et al, 2008). Unlike other known IC receptors, TIM-3 does not contain an immunoreceptor tyrosine-based inhibitory motif within its cytoplasmic tail (Rangachari et al, 2012). However, TIM-3 has been shown to regulate T cell responses through mediating effects on the TCR signaling cascade (Lee et al, 2011, van de Weyer et al, 2006). Multiple reports have highlighted a role for TIM-3 in diminishing T cell responses within nonclinical cancer models, with blockade of TIM-3 to its putative ligands reversing immune-inhibitory effects (Fourcade et al, 2010, Ngiow et al, 2011, Sakuishi et al, 2010). In addition to conventional T cells, TIM-3 can be expressed by regulatory T cells, natural killer cells and myeloid cell subsets, and has been shown to modulate activity within these cellular subsets (Chiba et al, 2012, Gao et al, 2012, Ndhlovu et al, 2012, Sakuishi et al, 2010).

2.2.2 Disease Background and Current Landscape

Classical Hodgkin lymphoma is an uncommon malignancy, accounting for less than 1% of all cancers but is amongst the most common in young adults. The disease has a bimodal distribution with an increased incidence in young adults as well as in patients 65 years and older. There are no clearly defined risk factors for the development of this disease and the cause of Hodgkin lymphoma remains unknown. Factors shown to be associated with cHL include familial factors, viral exposures, and immune suppression.

Despite the high cure rate with initial therapy, approximately 5% to 10% of patients with Hodgkin lymphoma are refractory to initial treatment and 10% to 30% of patients will relapse after achieving an initial complete remission. High dose chemotherapy followed by an ASCT is the SoC for many patients who relapse following a response to initial chemotherapy. Patients with r/r cHL who progress after ASCT have poor prognosis, with a median OS of 2 to 4 years in the pre-PD-1 blockade era. Overall survival is similarly poor in patients with primary refractory disease and those ineligible for ASCT.

Inhibitors of PD-1, nivolumab and pembrolizumab, have demonstrated effective antitumor activity and tolerable safety in patients with cHL that progressed after ASCT and/or brentuximab vedotin, an antibody–drug conjugate targeting CD30. Programmed cell death protein-1 inhibitors can also be considered for the treatment of patients with refractory cHL who are ineligible for ASCT because of comorbidities. Although there is a high initial response with an ORR above 70%, CR is only achieved in 25% to 40% of patients with many ultimately relapsing (Armand et al, 2018, Younes et al, 2016, Zinzani et al, 2020).

An unmet medical need exists for both r/r cHL patients with IO acquired resistance, specifically to anti-PD-1/PD-L1 based therapy and also for patients with r/r cHL post ASCT/ASCT ineligible given the high risk of relapse with single agent PD-1 blockade.

2.2.3 Clinical Development Rationale for Dual PD-1 and TIM-3 Blockade

The cellular microenvironment of cHL is characterized by a paucity of B cell-derived malignant HRS cells within a TME comprised of non-malignant stromal and immune cells (Connors et al, 2020). Despite extensive immune cell infiltration, the antitumor immune response is ineffective. It is hypothesized that this is due to the ability of HRS cells modulate the TME to avoid immune cell recognition and killing (Weniger and Küppers, 2021).

Hodgkin Reed-Sternberg cells co-opt the PD-1 pathway and upregulate PD-1 ligands by several mechanisms including copy gain alterations of 9p24.1. Topographical analysis of cHL TME demonstrated that HRS cells with PD-L1 overexpression were in close proximity to PD-1$^+$ CD4$^+$ T cells, within the TME, (Carey et al, 2017). Furthermore, reports demonstrated that PD-1 expression on CD4$^+$ T cells, within the cHL TME, is more frequently observed on Th1 effector cells compared to CD4$^+$ Tregs, which are in turn largely PD-1 negative. Consequently, a double immune evasion strategy exists in cHL, whereby Th1-mediated immune responses are likely dysfunctional while the immunosuppressive Treg cells retain functionality (Cader et al, 2018).

Although the targeting of the PD-1 axis shows clinical potential, the relative lack of complete responders suggests additional mechanisms contribute to promote HRS survival (Ansell et al, 2015). T cell immunoglobulin and mucin domain-containing protein-3, is an IC that has been associated with dysfunctional T cells (Jones et al, 2008, Sakuishi et al, 2010) and has recently been implicated as a resistance mechanism following PD-1 therapy. While data in cHL is limited, TIM-3 expression has been observed in cHL (El Halabi et at, 2020). Therefore, co-targeting both PD-1 and TIM-3 in cHL [redacted]. This study will investigate the safety, tolerability, PK, and antitumor activity of sabestomig, a PD-1/TIM-3 bispecific mAb, in the r/r cHL population. The study design comprises of two parts: Part A consists of a dose escalation that will enroll r/r cHL participants and Part B a dose expansion, which will enroll in Cohort B1 r/r cHL participants who were previously exposed to anti-PD-1/PD-L1 based therapy and in Cohort B2 r/r cHL participants who are naïve to anti-PD-1/PD-L1 therapy.

2.2.4 Sabestomig Background

Sabestomig is briefly summarized below. A detailed description of the chemistry, pharmacology, and nonclinical data for sabestomig is provided in the Investigator's Brochure.

Sabestomig is a [redacted] with an engineered Fc domain to reduce Fc effector function that specifically binds PD-1 and TIM-3. Programmed cell death protein-1 and TIM-3 are part of a complex system of cell surface receptors that when bound to their cognate ligands, provide co-inhibitory signals to T cells to modulate their activity. Dual blockade of PD-1 and TIM-3 is expected to restore the [redacted] of [redacted] within the [redacted].

2.2.4.1 Sabestomig Nonclinical Pharmacology

The ability of sabestomig to engage TIM-3 and PD-1 receptors and thereby promote immune-mediated antitumor responses was evaluated in in vitro and in vivo studies. Sabestomig demonstrated binding to human PD-1 and human TIM-3 receptors, in addition to CCI PD-1 and TIM-3 receptors. In in vitro functional assays utilizing CCI from healthy human donors, sabestomig promoted increased antigen-driven CCI CCI and CCI of a human tumor cell line over an isotype control and the parental CCI, the variable domains of which were used for generation of the CCI binding fragment of sabestomig. Sabestomig was also evaluated in 2 distinct xenograft CCI and an CCI CCI model of human cancer. Across multiple donors and model systems, sabestomig demonstrated an CCI burden compared to CCI alone.

2.2.4.2 Sabestomig Nonclinical Pharmacokinetics

In the non-GLP CCI PK/pharmacodynamic and toxicity study, CCI CCI received a CCI of CCI mg/kg of sabestomig. The dose was well tolerated but in CCI of CCI was detected after a CCI of sabestomig. The presence of CCI correlated with accelerated sabestomig clearance after Day 11.

In the GLP CCI toxicity study of sabestomig administered IV in CCI with a CCI, the increases in sabestomig mean Cmax and the AUCτ values were approximately proportional to the increase in dose level from CCI mg/kg/dose. The clearance was CCI across all dose groups. CCI PK exposure was observed for a total of CCI, including CCI and CCI at CCI mg/kg, CCI males and CCI females at CCI mg/kg, and CCI males at CCI mg/kg. In the other CCI monkeys administered sabestomig whose PK exposures were not impacted by CCI, any CCI results did not produce reduced PK exposure. These events did not impact the overall inferences and conclusions drawn from the PK analysis for this study.

2.2.4.3 Sabestomig Nonclinical Toxicology

A nonclinical safety assessment package was conducted in support of the FTIH clinical study with sabestomig and included:

1 A non-GLP CCI PK/pharmacodynamic study evaluating a CCI IV dose of CCI mg/kg,

2 A 4-week repeated dose GLP toxicology study in CCI evaluating repeated weekly IV doses of CCI, and CCI mg/kg with a 12-week recovery period, and

3 An in vitro assessment of [redacted] and [redacted] for the production of [redacted] including [redacted] and [redacted], when stimulated for 24 hours with sabestomig in a [redacted] and [redacted] format.

A summary of main findings is detailed below:

- Sabestomig was well tolerated after [redacted] IV dose of [redacted] mg/kg but [redacted] and [redacted] was observed after a [redacted] in [redacted] out of [redacted] from Day [redacted] after the EOI.
- In the [redacted] GLP toxicology study, as observed in the [redacted] study, [redacted] and [redacted] was observed in [redacted] in all dose groups.
- In the affected animals, a consistent range of effects were observed which were all considered to be related to [redacted], and development of [redacted]. These effects included reduced exposure due to [redacted] [redacted], [redacted], and [redacted] in several organs in medium to large vessels in the mid and high dose animals, formation of aggregate deposits of [redacted] in the [redacted], and [redacted] in the [redacted] of the brain.
- [redacted] and [redacted] in the spleen was seen in [redacted] at the high dose.
- Increased [redacted] and [redacted] were observed in mid- and high-dosed animals displaying [redacted], reflecting the [redacted] [redacted].
- [redacted] in a high dose male on Day 25 of the study was observed as well as adverse clinical signs of [redacted] and [redacted] in one [redacted] and [redacted] [redacted]. The [redacted] and the [redacted] were considered to be downstream effects of the high levels of [redacted] and [redacted] observed in these [redacted].
- No effects on body weights, food consumption, ophthalmology, cardiovascular respiratory, or CNS safety pharmacology, hematology, or clinical pathology were observed.
- As outlined above, the findings observed in the 4-week GLP study were all considered to be related to [redacted] and [redacted], in response to treatment with a human antibody. These findings are not considered representative of expected findings in humans treated with sabestomig. Despite the effects not considered relevant to humans, a NOAEL of 100 mg/kg was defined based on the absence of [redacted], [redacted], and [redacted] in the low dose [redacted] mg/kg group.
- In the in vitro assessment of [redacted], [redacted] and [redacted] from [redacted] were assessed. Sabestomig induced a [redacted] compared to its isotype control. However, the [redacted] was more than 20-fold lower than in positive controls using strong [redacted]. No signs of activation of release of the [redacted], [redacted], and [redacted] were observed. This indicates no or low risk for sabestomig to stimulate [redacted] in clinical studies.

The full details of the chemistry, pharmacology, efficacy, and safety of sabestomig is provided in the Investigator's Brochure.

2.3 Benefit/Risk Assessment

More detailed information about the known and anticipated benefits and potential risks of sabestomig may be found in the Investigator's Brochure.

2.3.1 Risk Assessment

This is the second trial in humans for sabestomig (the first study will be ongoing at the start of the current study). There are no identified risks based on human clinical data of sabestomig at this time.

Cell surface levels of PD-1 and TIM-3 are transiently upregulated upon TCR stimulation on $CD4^+$ and $CD8^+$ T cells in the TME (Fourcade et al, 2010, Jones et al, 2008). In addition to conventional T cells, TIM-3 can be expressed on the cell surface of regulatory T cells, natural killer cells, and myeloid cell subsets and has been shown to modulate activity within these cellular subsets (Chiba et al, 2012, Gao et al, 2012, Ndhlovu et al, 2012, Sakuishi et al, 2010). Checkpoint blockade of PD-1 and TIM-3 predominantly inhibits their negative regulatory mechanisms and subsequently invigorates T cells to unleash antitumor responses (ie, cytotoxicity, proliferation, and cytokine secretion). Neither for the individual blockade of each receptor nor for dual blockage are super agonistic or cascade effects anticipated.

The observed effects in the 4-week GLP study were considered to be related to the immunogenicity and associated ADA formation and its downstream effects. Such reactions are considered specific to monkeys as a reaction to a foreign human protein and not considered predictive of potential immunogenicity reactions in humans (Brennan et al, 2010).

The potential for sabestomig to induce cytokine production was assessed using human whole blood and human PBMCs (Section 2.2.4.3). Sabestomig induced mild [redacted] compared to its isotype control. The [redacted] was more than [redacted] lower than in positive controls using strong T cell activating antibodies. In this assay, sabestomig did not cause release of any other measured cytokines. Based on these data, sabestomig is considered low risk for inducing cytokine release syndrome.

Programmed cell death protein-1 targeting the checkpoint inhibitor axis, PD-1/PD-L1, has a well characterized safety profile with adverse reactions consisting predominantly of imAEs. Such imAEs are well characterized and various internationally recognized management guidelines are available to treat patients experiencing imAEs (Brahmer et al, 2018, Puzanov et al, 2017). The majority of imAEs are low-grade, monitorable, manageable, and reversible with immunosuppressive treatment. Publicly available safety information on anti-TIM-3 antibodies currently in clinical trials indicate- that monotherapy as well as

combination therapy with anti-PD-1 antibodies lead to imAEs which were mainly mild (Grade ≤ 2). Grade 3 to 4 AEs were reported in approximately 4% to 11% of participants (Borate et al, 2019, Curigliano et al, 2019).

Therefore, imAEs are an important potential risk of sabestomig and include, but are not limited to, pneumonitis, gastrointestinal disorders (especially diarrhea and colitis), hepatitis, endocrinopathies, nephritis and renal dysfunction, skin disorders, encephalitis, myocarditis, and neurological and musculoskeletal inflammatory disorders. Other potential risks include abnormal investigations (changes in laboratory parameters [eg, elevation of amylase, lipase], increased triglycerides and cholesterol, hyperkalemia, hyponatremia), and worsening of existing autoimmune inflammatory conditions.

Further potential risks of sabestomig are immune reactivity (ADA formation potentially leading to development of immune complex disease and vasculitis) and cytokine release syndrome. Like with any other biologic, there are potential risks of IRRs and hypersensitivity reactions.

For more information on the risks of sabestomig administration please refer to the Investigator's Brochure and current version of the TMGs in Appendix I.

2.3.2 Benefit Assessment

Agents that competitively inhibit the PD-1/PD-L1 pathway demonstrated improved clinical activity including clinical meaningful improvements of survival in a wide range of cancers, including cHL, relative to the previous SoC and have led to several regulatory approvals by the US FDA and the EMA for the treatment of various malignancies (Chai et al, 2020).

However, patients who initially respond to anti-PD-1/PD-L1 based therapy may experience disease progression due to acquired resistance mediated by exhausted T cells overexpressing inhibitory receptors including PD-1 and TIM-3 (Bai et al, 2017, Thommen et al, 2015). In vitro and in vivo studies have demonstrated the ability of sabestomig to engage both TIM-3 and PD-1 and thereby promote enhanced immune-mediated antitumor responses compared to targeting PD-1 alone (Section 2.2.4). CCI

2.3.3 Overall Benefit: Risk Conclusion

To minimize potential risks to participants, the study design integrates guidelines for inclusion and exclusion criteria (Sections 5.1 and 5.2), safety monitoring (Sections 8.1.4 and 8.3), TMGs (Section 6.6.8), starting dose, dose escalation scheme, stopping criteria (Section 6.6.1), and review of safety, PK, and pharmacodynamic data by the SRC (Section 6.6.7).

Taking into account the measures to minimize risk to participants in the study, the potential risks identified in association with sabestomig are justified by the anticipated benefits that may be afforded to participants with r/r cHL.

For details on study conduct during civil crisis, natural disaster, or public health crisis, eg, during the COVID-19 pandemic, refer to Appendix H.

3. OBJECTIVES AND ENDPOINTS

The objectives and endpoints for the study are presented in Table 5 (primary), Table 6 (secondary), and Table 7 (exploratory).

Table 5 Primary Objectives and Endpoints

Type	Objectives	Endpoints
Part A Dose Escalation		
Safety	• To assess the safety and tolerability of sabestomig in participants with r/r cHL • To establish the maximum tolerated dose, or optimal biological dose, and recommended Phase 2 dose	• Incidence of AEs, imAEs, and SAEs • Incidence of AEs leading to discontinuation of sabestomig • Changes from baseline and clinically significant alterations in vital signs, laboratory parameters, and ECG results • Incidence of dose-limiting toxicities
Part B Dose Expansion (all)		
Safety	• To assess the safety and tolerability of sabestomig in participants with r/r cHL	• Incidence of AEs, imAEs, and SAEs • Incidence of AEs leading to discontinuation of sabestomig • Changes from baseline and clinically significant alterations in vital signs, laboratory parameters, and ECG results
Part B Dose Expansion (B1)		
Efficacy	• To assess the preliminary antitumor activity of sabestomig in participants with r/r cHL (anti-PD-1/PD-L1 exposed)	• Objective Response Rate (defined as the proportion of patients with complete remission or partial remission) [a]
Part B Dose Expansion (B2)		
Efficacy	• To assess the preliminary antitumor activity of sabestomig in participants with r/r cHL (anti-PD-1/PD-L1 naïve)	• Complete Response Rate (defined as the proportion of patients with complete remission) [a]

[a] Disease response will be assessed according to Blinded Independent Central Review using Modified Lugano Criteria 2014 (Cheson et al, 2014)

Abbreviations: AE: adverse event; cHL: classical Hodgkin Lymphoma; ECG: electrocardiogram; imAE: immune-mediated adverse event; PD-1: programmed cell death protein-1; PD-L1: programmed cell death-ligand 1; r/r cHL: relapsed/refractory cHL; SAE: serious adverse event.

Table 6 Secondary Objectives and Endpoints

Type	Objectives	Endpoints
Part A Dose Escalation		
Efficacy	• To assess the preliminary antitumor activity of sabestomig in participants with r/r cHL	• Complete Response Rate, Objective Response Rate, DoR, and DoCR, and PFS including landmarks at 12 and 24 months [a] • OS including landmarks at 12 and 24 months
Part B Dose Expansion		
Efficacy	• To further assess the preliminary antitumor activity of sabestomig in participants with r/r cHL	• DoR, DoCR, and PFS including landmarks at 12 and 24 months [b] • OS including landmarks at 12 and 24 months
Patient-Reported Outcomes	• To assess patient-reported treatment-related symptoms, overall side-effect bother, and overall global health status while on sabestomig	• Proportion of participants reporting different levels of presence/magnitude/interference (as applicable) of diarrhea, rash, and fatigue over time based on PRO-CTCAE or Peds-PRO-CTCAE. • Proportion of participants reporting different levels of overall side-effect bother over time based on the PGI-TT. • Proportion of participants reporting different levels of quality of life/health over time based on the EORTC ILXX QL2 items.
Part A Dose Escalation and Part B Dose Expansion		
PK	• To assess the PK of sabestomig in participants with r/r cHL	• PK parameters including the maximum observed concentration, area under the concentration-time curve, clearance, and terminal elimination half-life
Immunogenicity	• To assess the immunogenicity of sabestomig in participants with r/r cHL	• Incidence of anti-drug antibodies against sabestomig in serum

[a] Disease response will be assessed according to Investigator assessment using Modified Lugano (2014) (Cheson et al, 2014) and RECIL criteria (Younes et al, 2017).

[b] Disease response will be assessed according to Blinded Independent Central Review using Modified Lugano (2014) (Cheson et al, 2014).

Abbreviations: cHL: classical Hodgkin Lymphoma; DoR: Duration of Response; DoCR: Duration of Complete Response; EORTC IL: European Organization for Research and Treatment of Cancer Item List; OS: Overall Survival; Peds: pediatric; PFS: Progression-free Survival; PGI-TT: Patient Global Impression of Treatment Tolerability; PK: pharmacokinetic(s); PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; RECIL: Response-evaluation Criteria in Lymphoma; r/r cHL: relapsed/refractory cHL.

Table 7 Exploratory Objectives and Endpoints

Type	Objectives	Endpoints
Part A Dose Escalation and Part B Dose Expansion		
Efficacy	• To assess the preliminary antitumor activity of sabestomig via CCI	• Changes in CCI and profile between CCI
Pharmacodynamic	• To assess CCI associated effects of sabestomig	• Measures of CCI and CCI , including but not limited to, levels of CCI and CCI and CCI , and CCI in peripheral blood and measures of changes in CCI and CCI CCI in tumor and non-tumor tissue samples
Predictive Biomarker	• To assess the association of CCI CCI with the antitumor activity of sabestomig	• Measures of CCI and CCI CCI , including but not limited to, CCI and expression of CCI (eg, CCI) and/or CCI and/or CCI
Patient-Reported Outcomes	• To further assess patient-reported CCI as well as the CCI CCI while on sabestomig	• Proportion of participants reporting different levels of CCI (as applicable) of other symptoms over time based on CCI or CCI CCI • Proportion of participants reporting different levels of impact on CCI over time based on CCI .
	• To assess patient-reported CCI of CCI	• Change from baseline in scores on CCI CCI .
	• To assess CCI CCI and change in overall CCI as well as impact on CCI CCI while on sabestomig	• Change from baseline in CCI CCI based on the CCI • Proportion of participants reporting different levels of change in overall CCI based on the CCI . • Change from baseline in physical function over time CCI CCI • Change from CCI on CCI CCI CCI).

Table 7 Exploratory Objectives and Endpoints

Type	Objectives	Endpoints
	• To assess patient-reported CCI while on sabestomig	• CCI and CCI • Proportion of participants reporting CCI CCI as measured by CCI .

Abbreviations: CCI ; CCI : CCI CCI CCI CCI .

4. STUDY DESIGN

4.1 Overall Design

This Phase I/II, open-label, multi-center, dose escalation and dose expansion study will evaluate the safety, tolerability, PK, pharmacodynamics, and antitumor activity of sabestomig in adult/young adult participants with r/r cHL. The study includes two parts: Part A Dose Escalation and Part B Dose Expansion.

Part A Dose Escalation will enroll participants with r/r cHL previously treated with anti-PD-1/PD-L1 based therapy.

Part B Dose Expansion will be subdivided into Cohort B1, enrolling a patient population identical to Part A, and Cohort B2 enrolling participants who never received an anti-PD-1/PD-L1 therapy previously.

Approximately 180 participants ([CCI] participants in Part A Dose Escalation and [CCI] participants in Part B Dose Expansion) will receive treatment with sabestomig at approximately [CCI] sites globally.

All participants will be followed for survival until the end of study as defined in Section 4.4, regardless of whether treatment was discontinued.

The overall study flow is presented in Figure 1 and further details can be found in Section 4.1.1 for Part A (Dose Escalation) and Section 4.1.2 for Part B (Dose Expansion).

4.1.1 Part A: Dose Escalation

Part A Dose Escalation will evaluate up to 8 dose levels of sabestomig and consist of up to [CCI] participants with r/r cHL in order to determine a RP2D. Cohorts A1 to A4 will be single participant cohorts with 4 dose levels of sabestomig (2, 7, 22.5, and 75 mg) based on an ATD (Section 6.6.1.1). However, the operating model will switch to a mTPI-2 algorithm should a Grade 2 or greater TEAE occur during the DLT period (Section 6.6.1.2).

Cohorts A5, A6, and A7 for subsequent dose levels of sabestomig (225, 750, and 1500 mg) will enroll [CCI] participants based on the mTPI-2 algorithm to establish the safety of sabestomig (Section 6.6.1.1). Based on emerging data, the optional Cohort A8 (at 2000 mg) may open and may also enroll up to [CCI] participants. After a cohort is declared safe (eg, Cohort A5, A6, A7 or A8) and based on emerging safety, efficacy, PK and biomarker data, the cohort may be expanded (up to [CCI] participants); the cohorts may be opened in parallel to fill their rosters of up to [CCI] participants each (mini dose expansion).Intermediate dose levels (50, 150, 450, 1000, 1250, and 1750 mg) may be explored if warranted by emerging safety, PK, pharmacodynamic, biomarker, and response data (Section 6.6.1 and Table 14).

The planned starting dose will be 2 mg (dose level 1). Participants will be evaluated for DLTs during a 28-day DLT evaluation period. Refer to Section 6.6 for further details regarding the ATD, mTPI-2 algorithm, and DLT definitions.

Participants will receive sabestomig Q3W administered via IV infusion at the selected dose starting on Cycle 1 Day 1. All participants will be treated for a maximum of 35 cycles, until disease progression, unacceptable toxicity, withdrawal of consent, or other reason for discontinuation (Section 7).

4.1.2 Part B: Dose Expansion

Part B Dose Expansion may be considered once the RP2D is determined in Part A Dose Escalation and will evaluate the safety, tolerability, PK, pharmacodynamic, and antitumor activity of sabestomig at the determined RP2D in 2 cohorts (Cohorts B1 and B2) described below.

Cohort B1: Approximately up to CCI participants with cHL who have received at least 2 prior lines of systemic treatment and have subsequently relapsed or become refractory to treatment and have been previously treated with at least 2 cycles of anti-PD-1/PD-L1 based therapy. Participants in Cohort B1 will be identical to those of the dose escalation stage. For this reason, enrolment of a larger sample size will provide a clearer confirmatory efficacy signal. For the analysis in Cohort B1, participants treated at the RP2D in Part A (N=CCI) will be combined with participants enrolled in Part B, which gives a total sample size of approximately up to CCI.

Cohort B2: Approximately up to CCI participants with cHL who have received at least 2 prior lines of systemic treatment and have subsequently relapsed or become refractory to treatment but have not received an anti-PD-1/PD-L1 based therapy.

Participants will receive sabestomig Q3W administered via IV infusion at the RP2D (determined during Part A Dose Escalation) starting on Cycle 1 Day 1. All participants will be treated for a maximum of 35 cycles until disease progression, unacceptable toxicity, withdrawal of consent, or other reason for discontinuation (Section 7).

The opening of Part B is dependent on emerging data from Part A. Cohorts B1 and B2 may open for enrollment either in parallel or sequentially at the discretion of AstraZeneca.

4.1.3 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic

infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study-site staff or the participant's ability to conduct the study. The Investigator or designee should contact AstraZeneca to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with GCP, and minimize risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies), or local government, these changes may include the following options:

- Rescreening: Rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants; refer to Section 5.4. The Investigator should confirm this with AstraZeneca.
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- Exploratory sample collection: AstraZeneca may provide sample collection strategy guidance for exploratory samples.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix H.

4.2 Scientific Rationale for Study Design

Sabestomig will be evaluated in adult/young adult participants with r/r cHL. Classical Hodgkin Lymphoma is considered to be sensitive to IC blockade achieving an ORR of over 70%. However, patients who initially respond to an anti-PD-1/PD-L1 based therapy may experience disease progression due to acquired resistance mediated by exhausted T cells overexpressing inhibitory receptors including PD-1 and TIM-3. Therefore, targeting both PD-1 and TIM-3 with sabestomig represents a promising therapeutic approach CCI CCI .

The CSP includes two parts: Part A Dose Escalation and Part B Dose Expansion. The proposed population for dose escalation is comprised of adult/young adult participants with r/r cHL with at least 2 prior lines of systemic therapy. Sabestomig also targets PD-1 and therefore is anticipated to provide clinical benefit from the PD-1 blockade mediated anticancer response. Inclusion of, anti-PD-1/PD-L1-naïve in the expansion Cohort B2 provides an CCI CCI CCI

4.2.1 Rationale for Endpoints

The primary objective of the study is to assess safety and tolerability and to identify the MTD or OBD, and a RP2D of sabestomig. The MTD will be determined by DLTs during the dose escalation phase (Sections 6.6.4 and 9.4.3.1). The rate of any observed DLTs will be used to establish the MTD in Part A Dose Escalation, and standard safety endpoints, such as AEs, SAEs, abnormal laboratory parameters, vital signs, and ECGs, will be used to assess the safety profile of sabestomig throughout the study. The RP2D will be selected by the Steering Committee and AstraZeneca based on the OBD determined by pooling and evaluating all available PK, pharmacodynamic, target engagement, efficacy, safety, and tolerability data.

To understand the efficacy of sabestomig in r/r cHL, this study will incorporate response assessment parameters during dose escalation (Part A) and dose expansion (Part B). To evaluate the antitumor activity of sabestomig the ORR, DoR, and PFS will be assessed. Participants will be evaluated by the Investigator, for disease response using the Modified Lugano and RECIL criteria as secondary endpoints. Additionally, in Part B only, disease response will be evaluated by a blind independent review committee using Modified Lugano Criteria. All participants will be followed up to evaluate OS. Of note, in the Part A, imaging must be archived and transferred to the BICR to allow retrospective disease response assessment in participants treated at a potential RP2D.

The study will also characterize the PK of sabestomig to determine drug exposure. Immunogenicity will be examined to assess its impact on PK, safety, and preliminary efficacy of sabestomig. Potential biological activity will also be explored by assessing pharmacodynamic and exploratory biomarkers and antitumor activity.

4.3 Justification for Dose

The rationale for selecting the starting dose of 2 mg Q3W for the proposed study (D9571C00001) is based on modeling and simulation of the PK/pharmacodynamic data and the prior clinical experience reported on PD-1 and TIM-3 targeting checkpoint inhibitors, the PD-1 inhibitors nivolumab and pembrolizumab (USPI OPDIVO® and USPI KEYTRUDA®) and the TIM-3 targeting mAbs MBG543 and TSR-022 (Curigliano et al, 2019, Davar et al, 2018), in conjunction with the safety margin calculated from the NOAEL of CCI mg/kg sabestomig in CCI [redacted] from the GLP toxicology study.

In addition, an unnecessary low starting dose would expose an excess of participants with high unmet medical need to exposure levels of sabestomig unable to drive pharmacodynamic effects in the tumor, thereby preventing the possibility to derive benefit from sabestomig treatment and to generate data useful for clinical development of sabestomig.

4.3.1 Rationale for Calculation of the Starting Dose in the Ongoing First-In-Human Study (D9570C00001)

The release of cytokine in the systemic circulation is one of the most important toxicities for immune-stimulating agents. For this reason, the most conservative approach to calculate the FIH starting dose relies on a minimum anticipated biological effect level tailored on the most sensitive in vitro assay (FDA 2020). Based on these principles (the lowest EC^{50} of CCI nM from the most sensitive in vitro assay), the FIH dose for sabestomig would be approximately CCI mg. At this dose, there would be minimal peripheral receptor occupancy, even less occupancy in the tumor, and therefore, little or no pharmacodynamic activity is expected. This approach is deemed not appropriate for sabestomig for the following reasons:

- CCI CCI data. Noteworthy, IC inhibitors are not direct immune cell agonists (eg, T cell engagers, CAR-T cell therapies) able to stimulate cytokine production via direct receptor engagement.
- In keeping with the absence of cytokine release via direct receptor engagement, the results of a human whole blood and human PBMC assays to test cytokine release did not raise any concerns regarding a potential for sabestomig to induce a cytokine release in clinical settings (see Section 2.3.1 for further details).
- No signs of CCI or CCI were observed in the CCI GLP toxicology study in CCI taking into account the CCI of CCI and CCI for both targets.
- A clinical review of available safety data for agents targeting PD-1 and TIM-3 implies that cytokine release does not occur in the clinic when these targets are engaged. In this sense, PD-1 is a clinically validated target and the occurrence of systemic cytokine release is extremely rare and, in these rare instances, possibly mediated by hypersensitivity reactions whose nature is not dose-dependent by definition. Safety clinical data from TIM-3 targeting agents either administered as monotherapy or in combination with PD-1 targeting mAbs indicate a safety profile in line with what is expected for PD-1 checkpoint inhibitors without the occurrence of cytokine release.
- An unnecessary low starting dose would expose an excess of participants with high unmet medical need to exposure levels of sabestomig unable to drive pharmacodynamic effects in the tumor, thereby preventing the possibility to derive benefit from sabestomig treatment and to generate data useful for clinical development of sabestomig.

Based on the above data and the consequent low risk of systemic cytokine release, the adoption of an alternative FIH dose calculation for a higher starting dose (2 mg) was chosen for administration of sabestomig.

4.3.2 Calculation of the First-In-Human Dose Based on Pharmacokinetic and Pharmacodynamic Modelling and Simulation

For the PK/pharmacodynamic modeling and simulation approach, a population PK model was developed to describe the PK of sabestomig in CCI. By extrapolating to humans from monkey PK data in sabestomig, the predicted PK parameters in humans were comparable with observed human PK of MEDI5752, which is an AstraZeneca developed anti-PD-1/CTLA-4 bispecific CCI CCI as sabestomig. MEDI5752 is currently in Phase I/Ib development; dose escalation has been completed and expansion cohorts in solid tumors including NSCLC are ongoing (D7980C00001 [NCT03530397] and D7980C00003 [NCT04522323]). The half-life of sabestomig in human is projected to be about CCI; hence, a dosing interval of Q3W is proposed for this study.

A PK/pharmacodynamic model was developed to describe the dual TMDD of sabestomig in humans. Taking into consideration the similarities between MEDI5752 and sabestomig described above, the linear PK parameters were set at typical human values for MEDI5752. The saturable component of the TMDD model was assumed to be due to the binding of sabestomig to the cell-surface PD-1 and TIM-3 as well as soluble TIM-3 in the periphery. For human simulations, the in vitro binding data including antibody affinity and antigen density as well as the antigen internalization data were incorporated in the model to predict the receptor occupancy of PD-1 and TIM-3 in the periphery following IV administration of sabestomig at various dose levels. The starting dose of 2 mg sabestomig corresponded to predicted levels of occupancy of PD-1 of approximately CCI% and CCI% of baseline at steady state Cmin and Cmax of sabestomig, and TIM-3 occupancy of CCI% and CCI% of baseline at steady state Cmin and Cmax of sabestomig.

The predicted receptor occupancy levels were in line with data in the public domain with the observed full PD-1 saturation levels for the PD-1 targeting antibodies, nivolumab and pembrolizumab, in the periphery at the starting doses of 0.3 mg/kg nivolumab (Agrawal et al, 2016, Brahmer et al, 2010) and 1.0 mg/kg pembrolizumab (Patnaik et al, 2015) in the Phase I studies, as well as the predicted full TIM-3 occupancy at the RP2D of TIM-3 targeting antibodies, 400 mg Q2W/800 mg Q4W MBG453 (Wei et al, 2020) in the bone marrow and the observed 80% peripheral TIM-3 occupancy at Cmin at 900 mg Q3W TSR-022 (Davar et al, 2018).

4.3.3 Clinical References for PD-1 and TIM-3 Targeting Agents to Support Starting Dose Selection for Sabestomig

Several PD-1 targeting agents have been approved for a broad range of both solid tumor and hematological indications and are established as SoC treatments. Pembrolizumab (KEYTRUDA®) and nivolumab (OPDIVO®) have been the first PD-1 targeting agents to be approved for the treatment of adult patients with cHL that has relapsed or progressed after

SoC treatment including autologous hematopoietic stem cell transplantation and brentuximab vedotin. Both PD-1 targeting agents have a well characterized benefit-risk profile (USPI OPDIVO® and USPI KEYTRUDA®) across solid and hematologic indications.

Publicly available data regarding AEs of TIM-3 in combination with PD-1 targeting agents (Curigliano et al, 2019, Weiss et al, 2017, Lakhani et al, 2020) indicate a safety profile consistent with what has been shown for other PD-1 checkpoint targeting inhibitors (Wang et al, 2019). Immune-mediated AEs associated with these agents are monitorable and manageable based on well-established TMGs (Brahmer et al, 2018, Puzanov et al, 2017).

Sym021 is a humanized IgG1 mAB targeting PD-1 and Sym023 is a recombinant, fully human antibody that binds TIM-3 (Lakhani et al, 2020). A FIH Phase 1 dose escalation study combining Sym021 with Sym022 (anti-LAG) or Sym021 with Sym023 (anti-TIM-3) in advanced or metastatic solid tumor malignancies or lymphomas is ongoing (NCT03311412). The dose escalation studies of Sym021, Sym022, and Sym023 as singe agents has been completed. The MTD was not reached for any single agent. The Sym021 dose was fixed at 3 mg/kg based on PK/pharmacodynamic analysis for subsequent combination with Sym022 or Sym023. The MTD was not reached for any combination. Part 2 Arm B combining Sym021 RP2D with Sym023 enrolled 17 patients and was well tolerated with AE profiles typical of IC inhibitors. The most commonly observed Grade 3 or Grade 4 treatment-related adverse events included 5 events: ALT increase (5.9%), lymphopenia/lymphocytes decreased (5.9%), fatigue (5.9%), cough (5.9%) and rash (5.9%). Objective responses in the Part 2 Arm B combination of Sym021+Sym023 included 2 PRs. Evaluation of antitumor activity of Sym021+023 doublets in select tumor types post-PD-1/PD-L1 treatment are planned.

In a phase Ib study of MBG543, a humanized IgG4 TIM-3 mAb, clinical trial conducted in patients (n=155) with HR-MDS/AML, TIM-3 receptor occupancy in bone marrow > 95% in ≥ 95% of patients was predicted at steady state for doses of 400 mg Q2W and 800 mg Q4W (Wei et al, 2020). Given the free blood flow of bone marrow with peripheral circulation, similarly high receptor occupancy in the periphery can be assumed. Overall, MBG453 + hypomethylating agent (decitabine or azacitidine) was safe and well tolerated with a low rate of study discontinuation due to AEs (3.4% [4/116]). Rates of most common grade ≥ 3 TEAEs and rates of Grade ≥ 3 possible imAEs related to study intervention did not appear to be dose dependent. Among 35 evaluable patients with HR-MDS, CR/metabolic CR/PR rates were 50.0%, 33.3% and 54.5% at MBG453 doses of 240 mg Q2W, 400 mg Q2W and 800 mg Q4W. Among 60 evaluable patients with AML, CR/CR without hematologic recovery/PR rates were 35.3%, 37.5% and 31.6%, respectively. There were no notable differences in responses across the 3 doses.

TSR-022 is a humanized IgG4 mAb targeting TIM-3. Phase I AMBER is a dose escalation study with expansion cohorts that investigates TSR-022 as a single agent and in combination

with the anti-PD-1 mAb TSR-042 (NCT02817633) in advanced solid tumors. Part 1a of this study investigated single -agent dose escalation in patients with solid tumors at dose ranges from 0.03 up to 10 mg/kg (Weiss et al, 2017). The MTD was not reached and only one DLT was observed at the highest dose level, Grade 3 immune-related lipase elevation without symptoms. The drug was well tolerated with mainly Grade ≤ 2 treatment-related toxicities. In addition to the reported DLT there was only one treatment-related AE Grade 3 at dose level 1 mg/kg, dyspnea in conjunction with Grade 2 pneumonitis in a patient with extensive mediastinal disease and vena cava syndrome. Preliminary signs of a clinical antitumor effect were observed at the dose of 10 mg/kg. In an additional dose escalation, Part 1c investigated the combination of TSR-022 in 54 patients with solid tumors at dose levels of 100 mg, 300 mg and 900 mg with the anti-PD-1 mAb TSR-042, which was administered at 500 mg (Davar et al, 2018).

There was approximately 50%, 70%, and 80% peripheral TIM-3 saturation at Cmin at 100 mg, 300 mg and 900 mg Q3W, respectively. No DLTs were observed for the combination. The highest treatment-related toxicities reported were one Grade 3 event of rash at the 100 mg dose level and one Grade 4 event of hypothyroidism at 900 mg dose level. The reported data indicate a trend for dose-dependent antitumor activity with one PR observed for the combination at a TSR-022 dose of 100 mg and 3 PRs at a dose of 300 mg. No efficacy data has been provided for the highest dose level. Part 2 expansion cohorts included patients treated at the same 3 dose levels of TSR-022 in combination with TSR-042 administered at 500 mg (100 mg, n=41; 300 mg, n=110; 900 mg, n=22), both agents administered on a Q3W schedule. For the overall cohort, the rate of patients with treatment-related Grade 3 AEs at each dose level was below 10% (9.2%, 8.2%, 0%), observed AEs consisted predominantly of rash, including 1 participant with Grade 4 lipase increase and 2 participants with immune-related AEs of hypothyroidism and pancreatitis.

Most recently, clinical safety data have been disclosed regarding the PD-L1/TIM-3 bispecific antibody LY3415244. The Phase I study evaluating safety and efficacy of this molecule in participants with advanced cancer was terminated early during the escalation phase due to significant immunogenicity to both arms of the molecule leading to loss of target engagement. In addition, 2 out of 12 participants with high ADA levels developed hypersensitivity reactions (Hellmann et al, 2021).

No clinical safety data have been disclosed regarding the bispecific antibody RG7769. However, based on information in the public domain the compound has completed dose escalation and the RP2D has been set to 2100 mg Q2W.

Overall, the reported AEs of anti-TIM-3 in combination with PD-1 targeting agents indicate that the safety profile is consistent with what has been shown for other PD-1 checkpoint targeting inhibitors and similar across tumor types.

4.3.4 Calculation of Safety Margins for the First-In-Human Dose of Sabestomig

In the completed 4-week GLP toxicology study with weekly IV dosing of CCI mg, CCI mg, and CCI mg/kg, the NOAEL was determined to be CCI mg/kg based on the absence of CCI and CCI. Mean plasma AUC data obtained after 4-week repeat dosing at the NOAEL (CCI mg/kg/week) provide a CCI safety margin to the predicted AUC at the proposed FIH starting dose of 2 mg Q3W while the mean Cmax gives a 7000-fold safety margin to the predicted Cmax at the starting dose of 2 mg Q3W (Table 8).

Sabestomig will be administered at escalating dose intervals with a starting dose of 2 mg (dose level 1). The proposed dose escalation scheme is 2, 7, 22.5, 75, 225, 750, 1500 to 2000 mg Q3W. Dose escalation for the first 4 dose levels of sabestomig (ie, 2, 7, 22.5, and 75 mg Q3W) is planned to follow an ATD with Cohorts 1 to 4 as single participant cohorts. Dose escalation for the subsequent 4 dose levels of sabestomig (225, 750, 1500, and 2000 mg) will follow the mTPI-2 algorithm with Cohorts 5, 6, and 7 with up to CCI participants each, with the optional last cohort, Cohort 8 that will also consist of up to CCI participants. If predefined safety criteria are met in an ATD cohort, dose escalation will switch to the mTPI-2 algorithm for all subsequent dose levels (Section 6.6.1).

Table 8 Safety Margins of Doses of Sabestomig Used in the Proposed Dose Escalation Scheme

Dose of Sabestomig (mg/75 kg)	AUCcyno (µg·day/mL)	Predicted Human AUCh (µg·day/mL)	Safety Margin (AUCcyno/ AUCh)	Cmax,cyno (µg/mL)	Predicted Human Cmax,h (µg/mL)	Safety Margin (Cmax,cyno/ Cmax,h)
2	CCI	CCI	CCI	CCI	CCI	CCI
7		CCI	CCI		CCI	CCI
22.5		CCI	CCI		CCI	CCI
75		CCI	CCI		CCI	CCI
225		CCI	CCI		CCI	CCI
750		CCI	CCI		CCI	CCI
1500		CCI	CCI		CCI	CCI
2000		CCI	CCI		CCI	CCI

Safety margins were calculated based on predicted AUCh and Cmax,h relative to the AUCcyno (43626 µg·day/mL) and Cmax,cyno (3500 µg/mL) following administration of a 100 mg/kg dose in CCI (Study 8419789).
Abbreviations: AUCcyno: area under the concentration-time curve from time zero to Day 21 at steady state in CCI AUCh: area under the concentration-time curve from time zero to Day 21 at steady state in humans; Cmax,h: maximal concentration in humans at steady state; Cmax,cyno: maximal concentration in CCI at steady state.

4.4 End of Study Definition

For the purpose of Clinical Trial Transparency (CTT) the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol related activity.

Food and Drug Administration requirements defines two completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if the participant has completed all phases of the study including the last visit or the last scheduled procedure shown in the SoA (Table 4), including survival follow-ups.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA (Table 4) for the last participant in the study globally.

Participants may be withdrawn from the study if the study itself is stopped (see Section 4.5, Section 6.6.7 and Appendix A 9).

See Section 6.9 for details on participant management following the final DCO as well as following the end of study.

4.5 Study Stopping Criteria

Part A and Part B Study Stopping Criteria:

AstraZeneca reserves the right to pause recruitment, temporarily suspend or permanently terminate this study or components of the study at any time. The reasons for temporarily suspending or permanently terminating the study may include, at least one of the following:

- A fatal event (Grade 5) deemed related to study therapy by AstraZeneca and in discussion with the SRC (probable or certain causality based on WHO-UMC after full etiological work-up). This will also result in a comprehensive review of safety.
- Any unexpected and Grade 4 life-threatening events deemed related to study therapy that exposed participants to unacceptable risk as assessed by the SRC in discussion with AstraZeneca.
- One or more Grade 4 immune related AEs unmanageable with implementation of the current toxicity management guidelines instituted in the protocol and/or as per institution of local practice as assessed by the SRC in discussion with AstraZeneca.
  Note: As immune-mediated AEs such as pneumonitis and myocarditis are important potential risks, these events will be further addressed at time of the safety interim analysis described below and will not be considered as stopping criteria.
- AstraZeneca decision that study participants are placed at undue safety risk.

Part A Mini Expansion Study Stopping Criteria:

Of note, during the mini expansion in the Part A portion of the study, if one or more mini expansions occur in parallel with different dose levels being evaluated (as per protocol design, see Section 4.1.1); the stopping criteria described above will apply independently to each individual cohort. The enrollment would be paused in the impacted dose level cohort but would not affect the other ongoing dose level cohorts if no stopping criterion was met.

Part B Study Stopping Criteria:

During the conduct of Part B, in addition to the stopping criteria applicable for Part A and Part B, the following criteria apply to participants treated at RP2D regardless of the cohort they are enrolled in (Cohort B1, B2 as well as participants treated in Part A mini expansion):

- At the time of interim safety analysis during Part B (after approximately CCI participants have received the first dose at least 3 months prior to data cut-off), the study recruitment may be paused, pending investigation by AstraZeneca in discussion with SRC, if at least one of the following events occur:

  - Incidence of Grade ≥ 3 immune-mediated AEs deemed to be related to study drug, above the following limits:
    - ≥ 10 % participants experiencing Grade ≥ 3 pneumonitis
    - ≥ 10 % participants experiencing Grade ≥ 3 myocarditis
    - ≥ 10 % participants experiencing Grade ≥ 3 immune complex disease and vasculitis
    - ≥ 10 % participants experiencing Grade ≥ 3 rash
    - ≥ 10 % participants experiencing Grade ≥ 3 colitis
    - ≥ 10% participants experiencing systemic drug hypersensitivity reactions

- 25% participants discontinuing study treatment due to any grade, treatment-related AE

Additional reasons to stop the study at any time may also include:

- Participant enrollment is unsatisfactory.
- Noncompliance that might significantly jeopardize the validity or integrity of the study.
- AstraZeneca decision to terminate development of the study intervention.
- AstraZeneca decision to terminate the study based on a planned futility analysis.
- AstraZeneca decision to discontinue the development of the study treatment in the proposed indications (see Section 7.1).

If AstraZeneca determines that temporary suspension or permanent termination of the study or components of the study is required, AstraZeneca will discuss the reasons for taking such action with all participating Investigators. When feasible, AstraZeneca will provide advance notice to all participating Investigators of the impending action.

If the study or components of the study is suspended or terminated for safety reasons, AstraZeneca will promptly inform all Investigators and/or institutions conducting the study. AstraZeneca will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the Investigator must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination. If the study or components of the study is suspended for safety reasons and it is deemed appropriate by AstraZeneca to resume the study or components of the study, approval from the relevant regulatory authorities (and IRBs/IECs when applicable) will be obtained prior to resuming the study.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria are met:

Informed Consent

1 Capable of giving signed informed consent or assent, if required per local regulations, as described in Appendix A, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

2 Written informed consent and any locally required authorization obtained from the participant prior to performing any protocol-related procedures. For participants from 16 to < 18 years of age, their legally authorized representative must give their signed

written informed consent, as appropriate, and participants will sign an assent form, if required per local regulations.

3 Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of samples for optional genetic research that supports Genomic Initiative (Section 8.7 and Appendix F). Participants who decline participation in genomic initiative are still eligible for the main study.

Age

4 Must be ≥ 16 years of age at the time of signing the ICF.

Type of Participant and Disease Characteristics

5 Eastern Cooperative Oncology Group performance status of 0 or 1 at screening.

6 Predicted life expectancy of ≥ 12 weeks.

7 Must have at least one PET-avid measurable lesion according to Modified Lugano Criteria after the last line of therapy. A measurable lesion is a lesion that can be clearly measured in at least 2 perpendicular dimensions (LDi and SDi). The LDi must be:

(a) For nodal lesions: LDi > 1.5 cm,

(b) For extranodal lesions (eg, Hepatic, lung nodules): LDi > 1 cm,

(c) The LDi and the SDi should be measured on the same slice.

8 Adequate organ and bone marrow function as defined in Table 9.

Table 9 Criteria for Adequate Organ and Marrow Function

Type	Parameter	Value
Hematological [a]	Hemoglobin	≥ 8.0 g/dL (4.96 mmol/L) Blood transfusions (packed red blood cells) permitted 10 days prior to first dose
	Absolute neutrophil count	≥ 1.0 x 10^9/L (1,000 per mm^3) Granulocyte colony-stimulating factor permitted 7 days prior to first dose
	Platelet count	≥ 75 x 10^9/L (75,000 per mm^3) Platelet transfusions permitted 5 days prior to first dose
Hepatic [a]	Total bilirubin	≤ 1.5 x ULN in the absence of Gilbert's syndrome
		≤ 3 x ULN and direct bilirubin < 30% of TBL in the absence of hemolysis if the participant has Gilbert's syndrome
	Alanine transaminase and aspartate transaminase	≤ 2.5 x ULN
		≤ 5 x ULN in the case of liver involvement
Renal [a]	Calculated creatinine clearance by modified Cockcroft Gault [b]	≥ 45 mL/minute
Cardiac [c]	LVEF	LVEF ≥ 45% (or ≥ institutes' lower limit of normal) confirmed by ECHO or MUGA.
Pulmonary [d]	FEV_1	FEV_1 >50% of predicted value

Abbreviations: ECHO: echocardiogram; FEV_1: forced expiratory volume over 1 second; LVEF: Left ventricular ejection fraction; MUGA: multigated acquisition scan; ULN: upper limit normal.

[a] To receive subsequent cycles of sabestomig (from cycle 2 onwards) thresholds for adequate marrow, renal, and liver function must be met. Laboratory evaluations must be performed up to 3 days prior to initiation of each cycle of treatment; transfusion and granulocyte colony stimulating factor support is permissible.

[b] Rostoker et al, 2007.

[c] If clinically indicated, and at the Investigator's discretion, a consultation with a cardiologist is recommended for follow-up.

[d] If assessed – pulmonary function testing is only required for those eligible participants with pre-existing obstructive or fibrotic lung conditions.

9 Part A Dose Escalation:

Must have a diagnosis of cHL histologically proven based on criteria established by the World Health Organization as documented in medical records.

(a) Documented active disease requiring treatment that is r/r defined as:

- Recurrence/relapse of disease after response to prior line(s) of therapy.
- Progressive Disease (refractory) during the treatment regimen preceding entry into the study.

(b) Failed at least 2 prior lines of systemic therapy.

(c) Have had at least 3 cycles of an anti-PD-1/PD-L1 based therapy.

(d) No previous treatment with anti-TIM-3.

(e) Previous anti-CTLA-4 treatment is allowed, however, only up to 2 months prior to study entry.

10 Part B Dose Expansion:

(a) Cohort B1: Meets all Part A criteria; 9(a), 9(b), 9(d), 9(e), and have had at least 2 cycles of an anti-PD-1/PD-L1 based therapy.

(b) Cohort B2: Meets Part A criteria; 9(a), 9(b), 9(d), 9(e), and have never previously received an anti-PD-1/PD-L1 based therapy.

Tissue Requirements (see Section 8.6.2.1 for additional details)

11 Participants enrolled in Part A dose escalation: If available, provision of sufficient tumor material from an archival tissue at time of first diagnosis and/or within 4 months prior to initiating study intervention.

12 Participants in Part A mini expansion: Provision of sufficient tumor material at screening from an archival tissue sample collected at first diagnosis and an archival tissue sample collected within the prior 4 months. If archival tissue sample is not available within prior 4 months, or when participant received any anti-cHL treatment since biopsy was taken, provision of sufficient tumor material at screening from a fresh tissue sample (core or excisional biopsy), unless medically contraindicated.

13 Participants enrolled in Part B Dose expansion cohorts (Cohorts B1 and B2): Provision of sufficient tumor material at screening from an archival tissue sample collected at first diagnosis and an archival tissue sample collected within the prior ≤ 4 months. If archival tissue sample is not available within prior 4 months, or when participant received any anti-cHL treatment since biopsy was taken, provision of sufficient tumor material at screening from a fresh tissue sample (core or excisional biopsy) unless medically contraindicated.

Note: On-treatment biopsy is mandatory in Part B, unless medically contraindicated. Tumor biopsy will not be collected in mainland China.

Reproduction and Contraception

14 Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Refer to Appendix B for definitions of women of childbearing potential and highly effective methods of contraception.

15 Female participants of childbearing potential:

(a) Must have negative pregnancy test at screening and prior to any administration of sabestomig.

(b) If sexually active with a non-sterilized male partner, must use at least one highly effective method of birth control from screening to 90 days after the last dose of sabestomig.

(c) It is strongly recommended that non-sterilized male partners of female participants of childbearing potential use a male condom plus spermicide, from screening to 90 days after the last dose of sabestomig.
NOTE: Male condoms are not reliable as a sole contraception method.

16 Female participants must not breastfeed and must not donate, or retrieve for their own use, ova, or plan to get pregnant from screening to 90 days after the last dose of sabestomig.

17 Non-sterilized male participants who are sexually active with a female partner of childbearing potential:

(a) Must use a condom with spermicide from screening to 90 days after the last dose of sabestomig.
NOTE: Male condoms are not reliable as a sole contraception method).

(b) It is strongly recommended that female partners of a male participant also use at least one highly effective method of contraception throughout this period.

(c) Male participants must refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of sabestomig.

Other

18 Minimum body weight ≥ 40 kg for all participants.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1 Participants with either of the following are excluded:

(a) Previous history of allogeneic stem cell transplant.

(b) Previous history of organ transplant

(c) Autologous stem cell transplant ≤ 3 months prior to study entry

(d) CAR-T based therapies ≤ 3 months prior to study entry

2 Unresolved toxicities of ≥ Grade 2 (NCI CTCAE v5.0) from prior therapy (excluding peripheral neuropathy, vitiligo, alopecia, and endocrine disorders that are controlled with replacement hormone therapy, and asymptomatic laboratory abnormalities), unless immune-mediated then refer to Exclusion criteria 3.

3 Any prior ≥ Grade 3 imAE while receiving prior checkpoint inhibitor immunotherapy or any unresolved imAE ≥ Grade 2 (excluding Grade 2 vitiligo, alopecia, and endocrine disorders that are controlled with replacement hormone therapy).

4 Must not have experienced a toxicity that led to permanent discontinuation of prior immunotherapy.

5 Participants with CNS involvement or leptomeningeal disease.

6 Any venous or arterial thromboembolic event within ≤ 6 months prior to the first dose of study intervention.

7 Infectious disease exclusions:

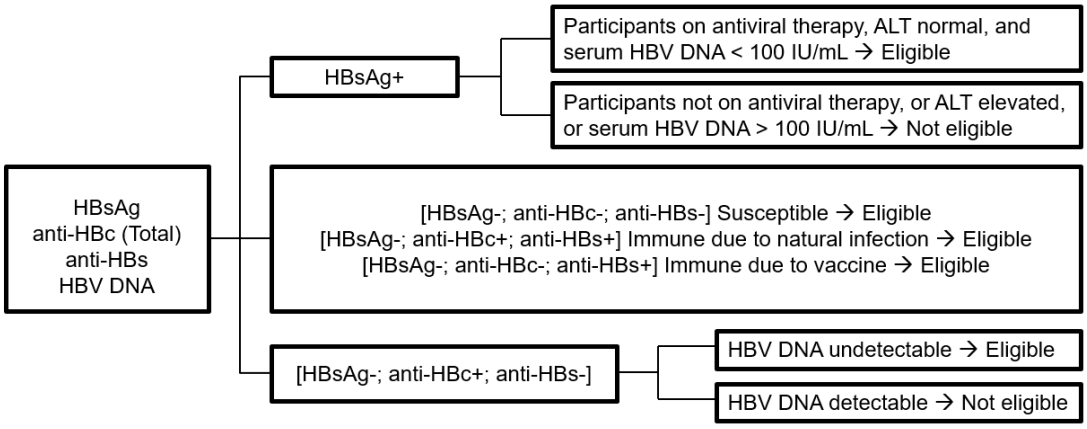
(a) Active infection including TB (clinical evaluation that includes clinical history, physical examination, and radiographic findings and TB testing in line with local practice).

(b) HIV (positive for HIV-1 or HIV-2 antibodies).

(c) Active hepatitis A.

(d) Chronic or active hepatitis B, however, participants who have chronic hepatitis B and are receiving suppressive antiviral therapy are allowed to be enrolled if ALT is normal and viral load is controlled. Controlled hepatitis B viral load is defined as serum HBV DNA < 100 IU/mL by PCR (Regev et al, 2020); see Figure 2.
NOTE: Participants with controlled hepatitis B viral load must remain on antiviral therapy, per institutional practice, during the study intervention and follow-up periods to ensure adequate viral suppression.

Figure 2 Hepatitis B Screening Tests and Eligibility Algorithm



Abbreviations: -: negative; +: positive; ALT: alanine transaminase; anti-HBs: antibody to hepatitis B surface antigen; anti-HBc: hepatitis B core antibody; HbsAg: hepatitis B surface antigen; HBV: hepatitis B virus.

(e) Chronic or active hepatitis C; however, participants who have chronic hepatitis C are allowed to be enrolled if ALT is normal and HCV RNA undetectable by PCR, either spontaneously or in response to a successful prior course of anti-hepatitis C therapy (Regev et al, 2020).

(f) For all participants in the study, all local institutional standards for COVID-19 must be followed for testing. For participants with a known previous COVID-19 infection in the last 3 months, a negative PCR test must be documented within 72 hours prior to the first dose. For timing of COVID-19 vaccination, see Section 6.5.

8 History of arrhythmia (such as multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia), which requires treatment (NCI CTCAE v5.0 Grade 3); symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia.

9 Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection requiring IV antibiotics, cardiomyopathy of any etiology, symptomatic congestive heart failure (as defined by New York Heart Association class ≥ 3), uncontrolled hypertension, uncontrolled diabetes mellitus, unstable angina pectoris, history of myocardial infarction within the past ≤ 6 months, history of myocarditis, serious chronic gastrointestinal conditions associated with diarrhea, active noninfectious skin disease (including ≥ Grade 2 (CTCAE v5), rash urticarial, dermatitis, ulceration, or psoriasis, but excluding stable plaque psoriasis from the definition of active disease).

10 Psychiatric illness/social situations/substance abuse disorders that would limit compliance with study requirements, substantially increase risk of incurring AEs, or compromise the ability of the participant to give written informed consent.

11 Active or prior documented **pathologically confirmed** autoimmune or inflammatory disorders, including inflammatory bowel disease (eg, colitis or Crohn's disease), diverticulitis (with the exception of diverticulosis), systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome (granulomatosis with polyangiitis), Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc. The following are exceptions to this criterion:

(a) Vitiligo or alopecia.

(b) Hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement.

(c) Any chronic skin condition that does not require systemic therapy.

(d) Participants without active disease in the last 5 years may be included but only after consultation with the Study Physician.

(e) Celiac disease controlled by diet alone.

12 Past medical history of confirmed ILD, drug-induced ILD, radiation pneumonitis requiring steroid treatment, or any evidence of clinically active ILD or active pneumonitis.

13 Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of study intervention or still recovering from prior surgery.
NOTE: Local surgery of isolated lesions for palliative intent is acceptable.

14 Radiotherapy within ≤ 3weeks of the first dose of sabestomig exceptions are:
   (a) Local treatment of isolated lesions, excluding target lesions (for palliative intent is acceptable).
   (b) Mediastinal irradiation not permissible < 3 months of the first dose of sabestomig.
15 Other invasive malignancy within 2 years prior to screening with the exception of:
   (a) Malignancy treated with curative intent and with no evidence of active disease present for more than 2 years before screening and considered to be at low risk of recurrence by the treating physician.
   (b) Adequately treated lentigo malignant melanoma without current evidence of disease or adequately controlled non-melanomatous skin cancer.
16 Congenital long QT syndrome or history of QT prolongation associated with other medications that cannot be changed or discontinued based on a cardiologist assessment.

Current or Prior Therapy

17 Current or prior use of immunosuppressive medication within 14 days prior to the first dose of study intervention. The following are exceptions to this criterion:
   (a) Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection).
   (b) Systemic corticosteroids at physiological doses not to exceed 10 mg/day of prednisone or its equivalent.
   (c) Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).
18 Any concurrent chemotherapy, radiotherapy, investigational, biologic, or hormonal therapy for cancer treatment.
   (a) Concurrent use of hormonal therapy for noncancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable.
   (b) A washout period of at least 28 days after the last chemotherapy, radiotherapy, investigational, biologic, or hormonal therapy for cancer treatment must be followed before the administration of sabestomig.
19 Receipt of live attenuated vaccine within 30 days prior to the first dose of study intervention.
   NOTE: Participants should not receive live vaccine while receiving study intervention and up to 30 days after the last dose of study intervention.

Concurrent or Prior Clinical Study Experience

20 Concurrent enrollment into another interventional clinical trial, unless it is an observational (noninterventional) clinical study or during the follow-up period of an interventional study.
21 Known allergy or hypersensitivity to sabestomig or any of the excipients of sabestomig.

Other Exclusions

22 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

23 Judgment by the Investigator that the individual should not participate in the study if they are unlikely to comply with study procedures, restrictions, and requirements.

24 Previous dosing with sabestomig initiated in this study.

5.3 Lifestyle Considerations

Due to the nature of sabestomig (Section 2), no interactions are foreseen with the consumption of meals, caffeine, alcohol, the use of tobacco or nicotine containing products, or strenuous (more than usual) activity. Normal lifestyle activities may continue while participating in this study.

The requirements and restrictions pertaining to reproduction and contraception use for both female and male participants and their partners are further detailed in the inclusion criteria (Section 5.1) and Appendix B.

Restrictions for concomitant medications are described in Section 6.5.

For further details about considerations for the COVID-19 pandemic and mitigation strategies for study disruption due to civil unrest, natural disaster, and Public Health Crisis, please refer to Appendix H.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study intervention/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once if confirmed by AstraZeneca. Rescreened participants should be assigned the same participant number as for the initial screening.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention intended to be administered to a study participant according to the study protocol.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

Sabestomig (AZD7789) will be supplied by AstraZeneca as either a CCI or CCI product as described in Table 10. Commercially available CCI for injection will be supplied by each site.

Table 10 Investigational Product

Study intervention	Sabestomig (AZD7789)
Type	Biologic
Dosage Form	Sabestomig is supplied as either a CCI or CCI. Sabestomig CCI mg: CCI for CCI for infusion Sabestomig CCI mg: CCI for CCI for infusion
Unit dose strength(s)	CCI mg CCI) or CCI mg (CCI CCI mg/mL
Dosage level(s)	Part A (Dose Escalation): • Planned dose levels: 2, 7, 22.5, 75, 225, 750, 1500, and 2000 mg Q3W. • Intermediate dose levels: 50, 150, 450, 1000, 1250, and 1750 mg Q3W. Part B (Dose Expansion): • Recommended Phase 2 dose determined in Part A Dose Escalation administered Q3W.
Route of administration	Intravenous infusion
Use	Experimental
IMP or non-investigational medicinal product	IMP (study intervention)
Sourcing	Provided centrally by AstraZeneca.
Packaging and labeling	Study intervention will be provided in vials in a carton. Each vial and carton will be labeled in accordance with country regulatory requirements.

Abbreviations: IMP: investigational medicinal product; Q3W: every 3 weeks; w/v: weight/volume.

6.1.2 Identity of Investigational Product(s)

Sabestomig will be supplied as either a CCI or a CCI.

Sabestomig CCI Product

Sabestomig will be supplied in a vial as a CCI mg CCI product for CCI CCI for infusion. The reconstituted solution contains CCI mg/mL sabestomig in CCI

CCI [redacted] it has a pH 6.0 and a density of 1.045 g/mL. The post-reconstitution label-claim volume is CCI [redacted] mL.

Sabestomig CCI [redacted] Product

Sabestomig will be supplied as a concentrate for solution for infusion. Sabestomig CCI [redacted] mg will be supplied in vials containing CCI [redacted] mg/mL sabestomig in CCI [redacted] it has a pH CCI [redacted] and a density of CCI [redacted] g/mL. The label-claim volume is CCI [redacted] mL.

The investigational product kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of each container within the carton). Each carton and vial are labeled with the same unique sequence number range.

Dosing Criteria for Cycles ≥ 2

Following completion of the first treatment cycle, participants may receive additional treatment with sabestomig when the following conditions are met:

- The participant does not meet any criteria for discontinuation of IMP as listed in Section 7.1
- The participant has adequate marrow, renal, and liver function, outlined in Table 9. Note: Laboratory evaluations must be performed up to 3 days prior to initiation of each cycle of treatment; transfusion and granulocyte colony stimulating factor support is permissible.
- If the participant experiences an AE following administration of study intervention in the previous dosing cycle, the participant must not meet criteria for dose omission or permanent discontinuation and must meet retreatment guidelines as outlined in the toxicity management guidelines as defined in Appendix I.

6.2 Preparation/Handling/Storage/Accountability

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled CCI [redacted] CCI [redacted]) with access limited to the Investigator and authorized site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the Investigational Product Manual.

6.2.1 Sabestomig Infusion Preparation and Administration

6.2.1.1 Preparation

Sabestomig is a CCI product, CCI. The reconstituted Drug Product is a CCI CCI.

Sabestomig CCI Drug Product is a CCI CCI.

Each vial selected for dose preparation should be inspected. If any defects are noted with the investigational product(s), the Investigator and site monitor should be notified immediately.

The dose of sabestomig for administration must be prepared by the pharmacy staff members (or an appropriate designee trained in study drug preparation), using aseptic technique in compliance with local regulations and site requirements.

The total time from needle puncture of the sabestomig vial to the start of administration must not exceed 24 hours. Of this time, not more than CCI hours may be at room temperature, with the remaining time at CCI, otherwise a new dose must be prepared from new vials.

The volume of sabestomig (in mL) to add to the IV bag is calculated as follows:

$$\text{CCI} \quad \frac{\text{CCI}}{\text{CCI}}$$

where CCI.

Sabestomig does not contain preservatives; any unused portion of the vial must be discarded immediately after use.

Sabestomig CCI Product

No incompatibilities between sabestomig CCI product and the following component materials of construction have been observed when diluted in 0.9% sodium chloride for injection:

- CCI
- CCI
- CCI
- CCI

To reconstitute, slowly add CCI mL of sWFI by tilting the vial to one side such that the liquid stream is directed along the wall of the vial and not directly upon the CCI product.

Gently swirl the solution until all solids are dissolved. Gently invert the vial to dissolve any solids that may be present at the neck of the vial or on the stopper. DO NOT SHAKE OR VIGOROUSLY AGITATE THE VIAL. Visually inspect the solution to ensure that the entire content of the CCI product is completely reconstituted. A thin layer of bubbles on the surface of the CCI is normal.

If a closed system transfer device (CSTD) must be used to withdraw the sWFI for reconstitution, then a new syringe and syringe adapter must be used to withdraw the reconstituted product, ie, do not re-use the same syringe and syringe adapter that was used for withdrawal of sWFI to withdraw the product. This will prevent additional dilution resulting from addition of residual sWFI contained in the syringe and syringe adapter.

Doses of sabestomig less than or equal to CCI mg will be prepared using a polypropylene syringe containing CCI for injection. Dose preparation will be achieved using the following method:

1. Dilute sabestomig drug product with CCI for injection in a polypropylene syringe according to the appropriate dose level, as shown in Table 11.
2. Gently invert the syringe several times until the solution is completely mixed.

Table 11 Preparation of Diluted Sabestomig for IV Administration Using a Syringe Pump

Dose (mg)	Volume of sabestomig (mL)	Volume of 0.9% (w/v) saline (mL)	Concentration of diluted sabestomig (mg/mL)	Dose volume of diluted sabestomig to be administered (mL)
CCI	CCI	CCI	CCI	CCI
CCI	CCI	CCI	CCI	CCI
CCI	CCI	CCI	CCI	CCI

Abbreviations: IV: intravenous; w/v: weight/volume.

Doses of sabestomig between CCI mg and CCI mg will be prepared using an IV bag containing CCI for injection. Add the calculated volume of sabestomig for each dose level to the IV bag. The IV bag size should be selected such that the final concentration is within CCI mg/mL, however the selected IV bag size must not be CCI CCI for patients CCI. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag. Additional details regarding dose preparation are provided in the IP Handling Instructions.

Sabestomig [redacted] Product

No incompatibilities between sabestomig [redacted] product and the following component materials of construction have been observed at [redacted] mg/mL in [redacted] or [redacted] for injection:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Sabestomig will be prepared using an IV bag containing [redacted] or [redacted] for injection. Add the calculated volume of sabestomig for each dose level to the IV bag. The IV bag size should be selected such that the final concentration is within [redacted] to [redacted] mg/mL, however the selected IV bag size must not be [redacted]. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag. Additional details regarding dose preparation are provided in the IP Handling Instructions.

6.2.1.2 Administration

All participants will be observed for fever, chills, or other infusion-associated symptoms after sabestomig is infused. All participants will be evaluated clinically post-infusion with vital signs checked at indicated timepoints as per schedule of assessments (Table 2, Table 3 and Section 8.2.3). The infusion may be slowed or interrupted for participants experiencing infusion associated symptoms.

Administration with Syringe Pump

Administer the appropriate dose volume of diluted sabestomig, as shown in Table 11, using a syringe pump. Discard excess sabestomig remaining in the syringe after administration.

Prior to the start of the infusion, the full set of tubing (line) will be primed with the sabestomig solution out to the distal end of the tubing.

Sabestomig infusion time is 1 hour (-5 minutes to + 15 minutes); however, if there are interruptions, the total allowed time must not exceed 4 hours with the infusion syringe kept at room temperature, otherwise a new dose must be prepared from new vials.

Do not co-administer other drugs through the same infusion line.

The tubing will be flushed with a volume equal to the tubing volume, according to local practices, to ensure the full dose is administered. Infusion time does not include the final flush time.

Administration from IV Bag

Sabestomig infusions are to be administered through an IV administration set with a CCI or CCI µm filter; acceptable configurations include an IV set containing an in-line filter or the attachment of a separate filter to the distal end of the IV tubing.

The sabestomig infusion time is 1 hour (-5 minutes to + 15 minutes); however, if there are interruptions, the total allowed time must not exceed 4 hours with the infusion bag kept at room temperature, otherwise a new dose must be prepared from new vials.

Do not co-administer other drugs through the same infusion line.

The IV line will be flushed with a volume equal to the IV line volume, according to local practices, to ensure the full dose is administered. Infusion time does not include the final flush time.

6.3 Measures to Minimize Bias: Randomization and Blinding

This study does not include blinding or randomization in order to minimize bias. However, participants will be assigned to dosing cohorts (or dose levels) on a “first come, first served” basis. When cohorts are opened in parallel for mini expansion Cohorts A5 to A8, participants will be assigned in such a way as to fill the cohorts equally, starting with the highest dose that has been declared safe by the SRC. However, prioritization may be given to cohorts where potential clinical activity has been observed.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study-site staff other than the person administering the study intervention.

6.5 Concomitant Therapy

Any medication or vaccine or supplement (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose, frequency, and route of administration.

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

Use of concomitant medications including over-the-counter medications, herbal supplements, vitamins, etc., from time of screening until the final study visit is not permitted without first consulting with the Investigator or delegate.

Prohibited concomitant medications are detailed in Table 12 and permitted concomitant medications are detailed in Table 13.

6.5.1 Premedication

Thirty minutes prior to each dose of sabestomig, participants will receive diphenhydramine 25 to 50 mg PO and acetaminophen/paracetamol 500 mg PO.

Post-infusion, acetaminophen/paracetamol may be given at 4, 8, and 12 hours. All participants should be well hydrated prior to all doses of sabestomig.

The addition of steroid premedication (prednisone equivalent dose is ≤ 10 mg/day) may be warranted if CRS or significant IRRs are observed with diphenhydramine and an antipyretic alone. Refer to Appendix I for CRS/IRR toxicity management guidelines.

Following completion of Part A, if there are no or minimal occurrences of CRS or IRRs, the need for premedication will be made optional through a future protocol version.

6.5.2 Rescue Medicine

The study site will supply rescue medication that will be obtained locally. For example, the following rescue medications may be used (list not exhaustive):

1 Tumor Necrosis Factor inhibitors (infliximab).
2 Anti-IL-6 (tocilizumab).
3 Nonselective adrenergic agonist (epinephrine).

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

Table 12 Prohibited Concomitant Medications

Prohibited Medication/Class of Drug	Usage
Any investigational therapy including anticancer therapy other than those under investigation in this study.	Should not be given concomitantly while the participant is on study intervention.
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study.	Should not be given concomitantly while the participant is on study intervention (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy]).
Live attenuated vaccines.	Should not be given within 30 days prior to the first dose through 30 days after the last dose of study intervention.
Immunosuppressive medications, including but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers.	Should not be given concomitantly or used for premedication prior to the immunotherapy infusions. The following are allowed exceptions: Premedication prior to infusion of sabestomig as outlined in Section 6.5.1. Use of immunosuppressive medications for the management of study intervention-related AEs. For ≥ Grade 2 IRRs after Cycle 1 Day 1 per institutional standards and at the Investigator's discretion; however, steroids should not be used as routine premedication for Grade 1 or 2 IRRs (refer to Section 6.6.8 and Toxicity Management Guidelines [Appendix I]). Use in participants with contrast allergies. In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy-related events experienced by the participant (eg, chronic obstructive pulmonary disease, radiation, nausea, etc.).
Herbal and natural remedies which may have immune-modulating effects.	Should not be given concomitantly.

Abbreviation: IRR: infusion-related reaction.

Table 13 Permitted Concomitant Medications

Supportive Medication/Class of Drug	Usage
Premedication for management of diarrhea, nausea, and vomiting.	Permitted after but not before the first dose of study intervention.
Blood transfusions	Permitted at any time after Cycle 1 Day 1.
Erythropoietin	Prophylactic erythropoietin should not be started during Cycle 1 of the study but may be started during Cycle 2 and after.
G-CSF	G-CSF should not be used prophylactically during Cycle 1, but may be considered after Cycle 1 following discussion with the Study Physician.
Megestrol acetate	Permitted for appetite stimulation.
Bisphosphonates	Permitted for treatment of bone metastases.
Concomitant medications or treatments (eg, paracetamol/acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed in Table 12.	To be administered as prescribed by the Investigator.
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc.]).	Should be used, when necessary, for all participants.
Inactivated viruses, such as those in the influenza vaccine.	Permitted
COVID-19 vaccine.	COVID-19 vaccine is permitted as per local standards/guidance, while following the recommended guidance below: Part A (Dose Escalation): Cycle 1: It is strongly advised to avoid vaccination for at least 72 hours prior to administration of the first dose of sabestomig and during the dose-limiting toxicity evaluation period. Cycle 3 and beyond: It is strongly advised to avoid vaccination for at least 72 hours prior to or after administration of sabestomig. Part B (Dose Expansion): Cycle 1 and beyond: It is strongly advised to avoid vaccination for at least 72 hours prior to or after administration of sabestomig.

Abbreviations: COVID-19: coronavirus disease 2019; G-CSF: granulocyte colony stimulating factor.

6.6 Dose Modification

6.6.1 Starting Dose, Dose Escalation Scheme, and Stopping Criteria

Dosing will begin at 2 mg sabestomig. The justification for the starting dose and the dose escalation scheme is discussed in Section 4.3.

The dose for subsequent cohorts or a decision to stop recruitment to Part A (Dose Escalation) will be agreed by the SRC after review of the data from each cohort (Section 6.6.7).

Rules for dose escalation will be initiated using an ATD (Simon et al, 1997) for the first 4 dose levels (Section 6.6.1.1). If predefined safety criteria are met, dose escalation will switch to the mTPI-2 algorithm (Guo et al, 2017, Ji et al, 2010). After the first 4 dose levels, rules for dose escalation will be conducted using the mTPI-2 algorithm (Section 6.6.1.2). Once the mTPI-2 algorithm is triggered, all future dose escalations will follow the mTPI-2 algorithm. The maximum dose increments will be modified from shown in the study schema (Figure 1) as follows:

- Limit the maximum dose increment to 100% if participants of a given cohort experience 1 Grade ≥ 2 imAE during the DLT period that does not decrease to Grade 1 within 72 hours.
- Limit the maximum dose increment to 50% if participants of a given cohort experience 2 or more Grade ≥ 2 imAEs during the DLT period that do not decrease to Grade 1 within 72 hours.
- Limit the maximum dose increment to 50% if participants of a given cohort experience 1 imAE DLT during the DLT period.
- Limit the maximum dose increment to 30% if participants of a given cohort experience 2 DLTs during the DLT period.

In each cohort, participant dosing will be staggered such that administration of the first dose is separated by at least 24 hours before the second participant is dosed. Provided there are no serious or unexplained safety issues, as determined by the SRC, dosing of the remainder of the cohort will continue as suitable participants are identified. However, should ambiguous findings occur, the SRC may choose to stagger the start of dosing for the remainder of the cohort of participants.

The sabestomig planned and intermediate dose levels that may be studied during dose escalation are shown in Table 14.

Table 14 Sabestomig Planned and Intermediate Dose Levels

Planned Cohort	Planned Dose Levels
Cohort A1	2 mg
Cohort A2	7 mg
Cohort A3	22.5 mg
Cohort A4	75 mg
Cohort A5	225 mg
Cohort A6	750 mg
Cohort A7	1500 mg
Cohort A8	2000 mg
Intermediate Cohort	**Intermediate Dose Levels [a]**
Cohort A3.5	50 mg
Cohort A4.5	150 mg
Cohort A5.5	450 mg
Cohort A6.25	1000 mg
Cohort A6.5	1250 mg
Cohort A7.5	1750 mg

[a] Only to be considered by decision of the Safety Review Committee in consideration of the totality of the data available. Other intermediate dose levels may be evaluated prior to declaring the recommended Phase 2 dose.

Abbreviation: mTPI-2: modified toxicity probability interval-2.

6.6.1.1 Accelerated Titration Design

For dose levels < 225 mg (Cohorts 1 to 4), dose escalation will follow an ATD and will be CCI participant cohorts. Cohorts 5, 6, 7, and the optional last cohort, Cohort 8, will follow an mTPI-2 and will consist of CCI participants. The enrolled participants must complete the DLT evaluation period before a dose escalation decision is made by the SRC.

At any ATD dose level, dose escalation will switch from ATD dose escalation to the mTPI-2 dose escalation algorithm if the initially enrolled participant has any of the following during the DLT evaluation period:

- Any DLT.
- Any ≥ Grade 2 TEAE.

Once the mTPI-2 algorithm is triggered, all further dose escalation will follow mTPI-2 algorithm.

Intra-participant Dose Escalation

Participants in the ATD cohorts (Part A, Cohorts A1-A4) are allowed to escalate at any higher dose level considered to be safe after they have completed a minimum of 2 cycles of the

protocol, and provided they did not present any DLT or unacceptable toxicity since the treatment onset and have not met any of the criteria for treatment discontinuation in Section 7.1 (Ribas et al, 2005). The objective is to provide the above-defined participants the opportunity to be treated at higher and presumably more effective doses.

6.6.1.2 Modified Toxicity Probability Interval

A minimum of [redacted] and a maximum of [redacted] participants will be enrolled at a given dose level for Part A. Dose escalation to the next dose level will be conducted using the mTPI-2 algorithm with a target DLT rate of 30% and an equivalence interval (25%, 33%). A minimum of [redacted] participants must complete the DLT evaluation period before making an escalation decision. Dose escalation will consist of 4 planned dose levels of sabestomig. Intermediate dose levels may be explored if warranted by emerging safety, PK, pharmacodynamic, biomarker, and efficacy data. Dose escalation and de-escalation recommendations will follow the mTPI-2 algorithm schema below:

1 A minimum of [redacted] evaluable participants are required in each dose level unless unacceptable toxicity is encountered in the first [redacted] participants prior to enrollment of the third participant, which would require dose de-escalation per the mTPI-2 algorithm. For a dose level that has fewer than [redacted] participants who are DLT-evaluable, participants will be replaced.

2 If a de-escalation decision is made, choice of de-escalation to the previous dose level will be at the discretion of the SRC. In the eventuality that a decision is made to de-escalate back to a dose escalation level that was previously deemed safe, and into which mini expansion cohort participants have since been enrolled at that dose level, these mini-expansion cohort participants may be included in further dose escalation decisions.

3 If a stay (“S”) decision is made, additional participants will be enrolled up to a maximum of [redacted] participants for a given dose level.

4 Administration of the first dose of sabestomig will be staggered by a minimum of 24 hours between the first and second participants in each dose escalation cohort. Intra-participant dose escalation will not be allowed during the mTPI-2 part of dose escalation.

5 At the discretion of AstraZeneca, dose escalation may be stopped before an MTD is reached.

6 The MTD will be determined by isotonic regression analysis applied to DLT rates observed during dose escalation using the mTPI-2 method (Ji et al, 2010).

Participants enrolled into ATD dose escalation cohorts may be considered evaluable for dose escalation decision-making purposes using mTPI-2 algorithm if the dose under investigation is identical to one previously assessed by ATD dose escalation.

Description of the Modified Toxicity Probability Interval-2 Algorithm

The mTPI-2 algorithm employs a simple beta-binomial Bayesian model. The prior distribution for all dose levels is Beta(1,1). The posterior distribution for all dose levels is Beta(1+*a*, 1+*b*), where *a* and *b* are the number of participants with and without a DLT at the current dose level, respectively. The posterior density of the toxicity probability is divided into multiple intervals with equal length. These intervals are categorized as underdosing, proper dosing, and overdosing in terms of toxicity. The underdosing interval corresponds to a dose escalation, overdosing corresponds to a dose de-escalation, and proper dosing corresponds to staying at the current dose. Given an interval and a probability distribution, the unit probability mass of that interval is defined as the probability of the interval divided by the length of the interval. The design for the dose escalation phase of the study uses a target DLT rate of 30% and an equivalence interval (25%, 33%) for dose escalation/de-escalation decisions as well as MTD determination. A dose level will be considered unsafe, with no additional participants enrolled at that dose level, if it has an estimated 80% or more probability of exceeding the target DLT rate of 30% (ie, Probability [DLT > 30% data] ≥ 80%) with at least [redacted] participants treated and evaluated at that dose level. In Table 15, dose escalation/de-escalation decision rules are computed based on the above information.

Table 15 Modified Toxicity Probability Interval-2 Algorithm

Number of DLTs	Number of Evaluable Participants Treated at Current Dose Level											
	1	2	3	4	5	6	7	8	9	10	11	12 [c]
0	S [a]	S [a]	E	E	E	E	E	E	E	E	E	E
1	S [b]	S [b]	S [e]	S	E	E	E	E	E	E	E	E
2		DU [d]	DU	DU	D	D	S	S	E	E	E	E
3			DU	DU	DU	DU	DU	D	D	S	S	E
4				DU	DU	DU	DU	DU	DU	D	D	D
5					DU	DU	DU	DU	DU	DU	DU	DU

[a] Changed from "E" to "S" as a minimum of [redacted] evaluable participants are needed to make a dose escalation decision.

[b] Changed from "D" to "S" as a minimum of [redacted] evaluable participants are needed to make a dose escalation decision.

[c] The "S" cells in original modified toxicity probability interval-2 algorithm are modified to either E or D according to whether the observed DLT rate is < or ≥ the target toxicity of 30%, respectively.

[d] If at the first dose level, participants can choose to early terminate the trial or not based on their own discretion.

[e] Changed from "D" to "S" to ensure the mTPI-2 algorithm performs as conservatively as the standard 3+3 design if a single DLT is observed among the first 3 participants at a new dose level.

Note: Target toxicity (%) is 30% and equivalence interval (25%, 33%). The sample size cap for each dose level will be [redacted] participants.

Abbreviations: D: de-escalate to the next lower-dose level; DLT: dose-limiting toxicity; DU: current dose is unacceptably toxic; E: escalate to the next higher dose level; S: stay at the current dose level.

Sources: Modified from Guo et al, 2017 and Ji et al, 2010.

6.6.2 Dose Expansion

Participants enrolled in Part B Dose Expansion will receive sabestomig Q3W administered via IV infusion at the RP2D determined during Part A Dose Escalation.

The opening of Part B is dependent on emerging data from Part A. Cohorts B1 and B2 may open for enrollment either in parallel or sequentially at the discretion of AstraZeneca. The opening of Cohort B2 will be gated on emerging antitumor activity data from participants enrolled in Part A and/or Cohort B1.

6.6.3 Definition of Dose-limiting Toxicity

The DLTs will be evaluated during Part A Dose Escalation. The DLT evaluation period will be 28 days from the first dose of sabestomig on Cycle 1 Day 1. Participants who do not remain in the study for the entire duration of the DLT evaluation period, for reasons other than DLT, will be considered non-evaluable for DLT evaluation and will be replaced with another participant at the same dose level if needed to ensure a minimum of [redacted] evaluable participants in the ATD and mTPI-2 cohorts, respectively.

A DLT will be defined during Part A Dose Escalation as any ≥ Grade 3 AE as per NCI CTCAE version 5 unless unequivocally due to underlying malignancy or an extraneous cause. The modifications and exceptions to this are detailed below.

The following conditions will be considered as DLTs:

- Any death not clearly due to the underlying disease or extraneous causes.
- Grade 4 imAE.
- Any ≥ Grade 3 non-infectious pneumonitis irrespective of duration.
- Any ≥ Grade 3 non-infectious colitis irrespective of duration.
- Liver transaminase elevation:
  - Isolated liver transaminase elevation > 5 x but ≤ 10 x ULN that does not downgrade to AST/ALT ≤ 3 x ULN or less within 7 days after onset with optimal medical management including systemic corticosteroids.
  - Transaminase elevation > 10 x ULN regardless of duration or reversibility.
  - Isolated TBL elevation > 3 x ULN that does not downgrade to ≤ 1.5 x ULN within 7 days after onset with optimal medical management (for participants with Gilbert's syndrome: TBL > 3 x ULN and doubling of direct bilirubin that does not downgrade to baseline value within 7 days).
  - Any increase in AST/ALT > 3 x ULN and concurrent increase in TBL ≥ 2 x ULN, regardless or duration or reversibility, where no other reason, other than the investigational product(s), can be found to explain the combination of increases (for participants with Gilbert's syndrome: TBL > 3 x ULN and doubling of direct bilirubin that does not downgrade to baseline value within 7 days).
- Any Grade 3 imAE, including rash, pruritus, or diarrhea (NOTE: this excludes colitis or pneumonitis, as these AEs are already defined above), that does not downgrade to Grade 2 or less within 7 days after onset of the event despite maximal supportive care including systemic corticosteroids.
- Grade 3 nausea, vomiting, or diarrhea that does not resolve to Grade 2 or less within 3 days of initiation of maximal supportive care.
- Neutropenia.
  - ≥ Grade 3 neutropenia, without associated fever or systemic infection, which does not improve by at least one grade within 7 days of onset.
- Thrombocytopenia:
  - Grade 4 thrombocytopenia lasting more than 7 days.
  - ≥ Grade 3 thrombocytopenia associated with a Grade ≥ 2 bleeding, which in the opinion of the Investigator, is related to study intervention.
- Grade 4 anemia not related to the underlying disease or any extraneous cause.

- Cytokine Release Syndrome (CRS):
  - Grade 4 CRS of any duration.
  - Grade 3 CRS that does not improve to Grade ≤ 2 within 72 hours.

The following conditions will not be considered as DLTs:

- Grade 3 fatigue lasting ≤ 7 days.
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy with resolution of the symptoms within 14 days after treatment onset.
- Grade 3 inflammatory reaction attributed to a local antitumor response (eg, inflammatory reaction at sites of metastatic disease, lymph nodes) that resolves to ≤ Grade 1 within 7 days after onset.
- Vitiligo or alopecia of any AE Grade.
- Grade 3 or Grade 4 lymphopenia (unless associated with clinical sequelae).
- Grade 3 laboratory abnormalities that are not associated with clinical signs or symptoms (eg, hyperlipasemia or hyperamylasemia not associated with clinical signs or symptoms or radiographic features suggestive of pancreatitis) and are reversed with appropriate maximal medical intervention within 7 days.

Immune-mediated AEs are defined as AEs of an immune nature (ie, inflammatory) in the absence of a clear alternative etiology. In the absence of clinical abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT.

An AE not listed above or an AE meeting the DLT criteria above but occurring outside of the DLT-evaluation period, may be defined as a DLT after consultation with AstraZeneca and Investigators based on the emerging safety profile.

6.6.4 Definition of Maximum Tolerated Dose

The MTD will be selected from all tried dose levels that have not been previously declared to be unsafe with a DU decision according to the mTPI-2 algorithm. With this constraint, the MTD will be determined as the dose level with the DLT estimate closest to the target toxicity level of 30%.

In the case of dose levels with estimated toxicity of equal distance (tied dose levels) from the target toxicity of 30%, the following approach will be used (Ji et al, 2010): among all tied dose levels the highest dose level with target toxicity ≤ 30% will be selected, unless all tied dose levels have estimated toxicity > 30%, in which case the lowest dose level will be selected.

6.6.5 Definition of Optimal Biological Dose

The OBD will be determined from the safety, efficacy, PK, pharmacodynamic, and biomarker data during the dose escalation phase. The RP2D will be selected by AstraZeneca in discussion with the members of the Study Steering Committee, based on the totality of the data from the dose escalation phase of the study.

Pharmacokinetic and pharmacodynamic data collected in Parts A and B will provide demonstration of adequate drug exposure and high target binding level. Data demonstrate that clinical efficacy of the approved anti-PD-1 agents, pembrolizumab and nivolumab, is associated with PD-1 receptor occupancy (RO) > 90%, thereby suggesting that a similar level of PD-1 inhibition by sabestomig will confer clinical benefit at least equivalent to that of pembrolizumab and nivolumab.

6.6.6 Definition of DLT-evaluable Participants

For decisions on dose escalation, an evaluable participant is defined as a participant who has received sabestomig and has completed the DLT period (28 days after receiving 1st dose of sabestomig) or has experienced a DLT during the DLT period.

6.6.7 Safety Review Committee

To ensure safety surveillance of developmental compounds in line with regulatory expectations for safety assessment committees, AstraZeneca has systematic and robust internal processes in place. This includes processes with clearly described roles and responsibilities that are owned by AstraZeneca's Patient Safety organization. These processes are designed to monitor the evolving safety profile (ie, review of cumulative SAEs, or other important safety information) by designated cross-functional teams in a timely manner at predefined intervals or on an ad-hoc basis.

In addition to AstraZeneca's internal processes, a study-specific SRC, in accordance with its charter, will provide ongoing safety surveillance of the study, with regularly scheduled reviews of safety, PK, and other relevant data. The SRC comprises of members of AstraZeneca and investigators. This committee may also meet to review data at other time points (eg, in response to AEs assessed as medically relevant by the Study Physician). This committee will be responsible for making recommendations for dose escalation or dose de-escalation decisions and making recommendations regarding further conduct of the study during all phases of the study including suspension or stopping of the trial. The SRC will review the totality of all available clinical, laboratory safety and all other relevant data prior to adjudicating on dose escalation/de-escalation decisions based on the dose escalation rules. All decisions by this committee will be documented and shared in writing with all participating sites.

During Part A, in addition to continuous monitoring as per AstraZeneca pharmacovigilance process, the SRC will evaluate toxicities occurring study wide. In addition, to assess potential late toxicity occurring beyond the DLT window, an analysis of cumulative safety data will be performed and shared with the SRC when 1) once at least 6 participants have completed at least 2 cycles of study drug, and 2) after completion of Part A (Dose Escalation) and prior to moving to Part B (Dose Expansion).

The membership, roles, responsibilities, and decision-making process will be detailed in the SRC charter.

6.6.8 Dose Modification and Toxicity Management

If a participant experiences a clinically significant and/or unacceptable toxicity including a DLT not attributable to the disease or disease-related processes under investigation, dosing will be interrupted, and supportive therapy will be administered.

All toxicities will be graded according to NCI CTCAE v5.0.

The following general guidance should be followed for management of toxicities:

- Treat each of the toxicities with maximum supportive care (including withholding the agent suspected of causing the toxicity if required).
- If the symptoms promptly resolve with supportive care, consideration should be given to resuming the assigned study intervention along with appropriate continuing supportive care. If medically appropriate, dose modifications (eg, dose interruption) are permitted.
- All dose modifications (eg, dose interruption, discontinuation) should be documented with clear reasoning and documentation of the approach taken.
- Dose reductions are not permitted.

Toxicity Management Guidelines have been developed to assist Investigators with the recognition and management of toxicities associated with use of the IC inhibitor sabestomig. The TMGs are provided in Appendix I.

These TMGs are applicable to the management of participants receiving sabestomig as specified in the CSP. The TMGs provide information for the management of immune-mediated reactions, IRRs, and non-immune-mediated reactions that may be observed with monotherapy or combination checkpoint inhibitor regimens, with specific instructions for checkpoint inhibitor-specific dose modifications (including permanent discontinuation) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other anticancer treatment.

6.7 Dose Delay

In the event of treatment-related toxicities, study intervention should be permanently discontinued if sabestomig is not given for more than 12 weeks.

If treatment interruption is caused by intercurrent illness that is not a direct consequence of sabestomig-related toxicity (ie, COVID-19 infection), the option to restart treatment can be offered beyond 12 weeks following discussion with the AstraZeneca representative. In the event of a COVID-19 infection, the investigator should use their judgment to delay treatment with sabestomig depending on the clinical situation of the participant.

6.8 Treatment Beyond Progression

Participants may continue to be treated with the scheduled regimen and dose assigned at the discretion of the Investigator until one of the following criteria is met:

- Disease progression based on the Modified Lugano criteria assessed by the Investigator or pathological progression confirmed by biopsy. The assessment of PD must be confirmed by a repeat evaluation made by PET.
- Any of the study intervention discontinuation criteria is met.
- Clinical symptoms or signs indicating clinically significant PD such that the benefit-risk ratio of continuing therapy is no longer justified based on Investigator judgment.
- Decline in ECOG performance status compared to baseline.
- Rapid PD or threat to vital organs/critical anatomical sites (eg, spinal cord compression) requiring urgent alternative medical intervention, and/or continuation of study therapy would prevent institution of such intervention.

Pseudo progression:

During immunomodulatory agent therapy (eg, checkpoint inhibitors, BTK inhibitors, CAR T-cell therapy, bi-specific antibody, lenalidomide, brentuximab-vedotin), imaging findings suggestive of PD without clinical deterioration may instead represent a tumor flare (also called pseudo-progression). To avoid early termination of the study treatment, if a pseudo-progression is suspected (eg, in presence of tumor flare with no clinical deterioration), it is recommended that a lymph node biopsy (if applicable) and a subsequent imaging at least 4 weeks apart from the initial assessment (and within a maximum of 12 weeks) is done, to confirm true PD versus a tumor flare/pseudo-progression.

6.9 Continued Access to Study Intervention After the End of the Study

AstraZeneca will continue to supply sabestomig in the continued access phase of the study (ie, PTAP), if the participant consents to this, and while in the opinion of the investigator and in agreement with the medical monitor, the participant is benefiting from the treatment.

Treatment will continue until PD occurs as judged by the investigator, completion of a participant's current 35-cycle treatment period, or until meeting any other discontinuation criteria defined in Section 7.1. Participants should be followed according to the institution's SoC assessments and as deemed appropriate by the investigators. It is recommended that investigators continue to observe ongoing participants at the frequency employed prior to the final DCO. No further data collection is required, except for safety reporting. The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of AE and SAE and special situations (see Sections 8.3, 8.4, and Appendix D). Adverse events will be collected from time of signature of ICF throughout the PTAP until 90 days after the last dose of sabestomig, regardless of whether the participant has initiated a new anticancer treatment.

Protocol dose modification and stopping criteria are to be followed while a participant is receiving sabestomig. A change in the dose/schedule of sabestomig should only occur for safety reasons, based on the investigator's judgment, and should follow the approach for dose reduction and discontinuation as described in this protocol.

In the event that product development reaches a point where alternative product supply options become available, then these alternative product supply options will be discussed by AstraZeneca with the investigator. AstraZeneca will work with the investigator to transition the participant(s) to alternative supply, where possible. In the event that AstraZeneca terminates further development of the study intervention, AstraZeneca will continue to supply study intervention where possible, however the supply may become unavailable. AstraZeneca will notify investigators in advance if supply of study intervention must be discontinued.

In the event that a rollover or safety extension study is available at the time of the final DCO and database closure, participant(s) currently receiving treatment with sabestomig may be transitioned to such a study, and the current study would reach its end. The rollover or safety extension study would ensure treatment continuation with visits and assessments per its protocol, as applicable. Any participant who would be proposed to move to such a study would be asked to sign a new ICF, as applicable.

6.10 Treatment of Overdose

For this study, any dose of study intervention in excess of that specified in this CSP will be considered an overdose.

In the event of an overdose, the Investigator should:

- Evaluate the participant to determine, in consultation with the Study Clinical Lead, if possible, whether study intervention should be interrupted or whether the dose should be reduced.

- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up. Refer to Section 8.4 for details of AE/SAE reporting related to overdose.
- Obtain a plasma sample for PK analysis if requested by the Study Clinical Lead (determined on a case-by-case basis) on day of visit (after end of infusion) if no other PK samples are scheduled; alternatively, up to 3 days from the date of the last dose of study intervention.
- Document the quantity of the excess dose as well as the duration of the overdose.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study drug. Note that discontinuation from study drug is NOT the same thing as discontinuation from the study.

Participants may be discontinued from study drug in the following situations:

- Confirmed disease progression by PET-CT.
- An AE that meets criteria for discontinuation of study drug (as defined in Sections 6.6.3 and 6.6.8 and the Toxicity Management Guidelines, Appendix I) or in the opinion of the Investigator or AstraZeneca warrants discontinuation of further dosing.
- Investigator determination that the participant is no longer benefiting from study intervention.
- Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment.
- Pregnancy or intent to become pregnant (Section 8.3.10).
- Non-compliance with the CSP (Investigator or participant).
- Participant incorrectly initiated on study intervention.
  - When the reason does not impact safety consider the risk/benefit to the participant of stopping treatment.
- Unexpected, significant, or unacceptable risk to the participants enrolled in the study.
- AstraZeneca termination of study for reasons including but not limited to unfavorable risk/benefit or change in drug development plan.

If study drug is permanently discontinued, the participant will remain on study to be evaluated for protocol-specified assessments including follow-up of any AEs and survival follow-up. At the time of study drug discontinuation, the participant will be followed-up for safety and a visit will be performed 30 and 90 days after receiving the last dose of sabestomig.

Participants discontinuing study treatment due to PD:

Imaging for disease assessment will stop and participants will enter the safety and survival follow-up.

Participants discontinuing study treatment while in response (PR/CR) or with SD:

Participants will enter the safety follow-up and will carry on with efficacy assessments by imaging until PD, start of a new anti-cHL therapy or EoS, whichever comes first (Table 4 and Table 16).

Note:

- Radiotherapy administered alone after the last dose of sabestomig while a participant is in CR, with a consolidation intent will not be considered as a new anti-cHL line of therapy. Therefore, the participant should carry on the efficacy follow-up and perform disease assessment by imaging as per SoA (Table 16).
- Participant in CR/PR who proceeds to HSCT without any treatment between the last dose of sabestomig and the start of the conditioning regimen will be followed-up for disease assessment post-transplant as per SoC and data on their disease status will be collected in the EDC as part of the survival follow-up.

See the SoA (Table 1, Table 2, Table 3, and Table 4) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

If the participant does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This could be a telephone contact with the participant, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A participant who agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

All participants in Safety or Survival follow-up at the time of final study DCO will be contacted by the study site prior to the final study DCO to confirm their survival status and to inform participants that this was the last study-related contact, and no further survival data will be collected in respect to the study. Sites are requested to document this last contact in the source records.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at their own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

- A participant who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records). If a participant agrees to modified follow-up options, the participant will not be considered to have withdrawn from the study (see Section 7.1).
- At the time of withdrawal from the study, if possible, an EoT visit should be conducted, as shown in the SoA. See the SoA (Table 4) for data to be collected at the time of the EoT Visit.
- If the participant withdraws consent for disclosure of future information, AstraZeneca may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if they still agree for existing samples to be used in line with the original consent. If they request withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

Site personnel, or an independent third-party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants who received any dose of study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. AstraZeneca personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Table 1, Table 2, Table 3, and Table 4). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with AstraZeneca immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- AstraZeneca will continue to supply sabestomig in the continued access phase of the study (ie, PTAP) if the participant provides consent and while the participant is benefiting from the treatment, in the opinion of the investigator and in agreement with the medical monitor (see Section 6.9 and Section 8.9 for further details).
- Adherence to the study design requirements, including those specified in the SoA (Table 1, Table 2, Table 3, and Table 4), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
  - Retesting of laboratory values during the screening period is allowed.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count and imaging assessments) and obtained before signing of the ICF, may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 1, Table 2, Table 3, and Table 4).

A total of approximately 110 mL of blood will be required for all screening tests, which will be conducted during the 28-day screening period. No more than approximately 300 mL of blood will be collected between Days 1 and 21 after the first dose of study intervention within any cohort. No more than approximately 100 mL of blood will be drawn on any visit day after Cycle 1. The total volume to be collected will depend on the number of doses administered and the length of follow-up.

8.1 Disease Response Assessment

Sites will be required to store electronic copies of all scans, and AstraZeneca will arrange for centralized storage of all imaging data. All imaging assessments, including unscheduled visit scans, will be collected on an ongoing basis and sent to AstraZeneca or designee for storage. The centralized storage of imaging data would allow independent centralized third-party blinded review of disease assessments. In this regard, and at the discretion of AstraZeneca, an independent central review of all scans used in disease assessment guidelines for imaging collection and storage will be provided in a separate document.

Participants will be evaluated by the Investigator for disease response using the Modified Lugano and RECIL criteria as secondary endpoints. Additionally, in Part B only, disease response will be evaluated by a BICR using Modified Lugano criteria. All participants will be followed up to evaluate OS. In the Part A of the study, imaging must be archived and transferred to the BICR to allow retrospective disease response assessment in participants treated at RP2D.

Efficacy assessments will be performed until PD/relapse, death, lost to follow-up, start of new treatment for cHL or withdrawal of the consent (whichever comes first). For participants discontinuing the study intervention due to other causes (eg, due to toxicities), disease follow-up will continue as per SoA until PD/relapse or start of new treatment for cHL is documented.

In the event pseudo progression is suspected by imaging, a PET-CT scan should be repeated at least 4 weeks after the previous assessment to confirm progression or response (Section 6.7) provided that the participants' clinical condition is stable. However, repeat imaging must be performed earlier than the next 12-week assessment where there is clinical suspicion of progression. The assessment of "clinically stable" must meet the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression.
- No decline in ECOG performance status.
- Absence of rapid progression of disease.
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical attention.

Radiological response should be integrated with clinical data and pathological findings, where available. Regardless of the radiological response, new or worsening of clinical findings indicative of lymphoma progression will result in an overall response of PD.

Unless unequivocally attributed to the disease, whenever possible the presence of a new lesion should be confirmed by biopsy. Biopsies at PD/relapse are not mandatory but recommended. If clinically indicated, unscheduled assessments can be performed at any time during the study.

8.1.1 B-symptoms

B-symptoms are constitutional symptoms defined as any one or more of the following disease-related symptoms or signs:

- Unintentional weight loss of 10% or more within the previous 6 months,
- Fevers > 100.5°F or 38.0°C for ≥ 2 weeks without other evidence of infection, or
- Night sweats for > 1 month without evidence of infection.

B-symptoms should not be reported as AEs and will be collected when a disease response assessment is performed during treatment and as clinically indicated.

The presence of B-symptoms should not be used in the overall response assessment as per Lugano 2014 criteria. In fact, the presence of residual symptoms in the absence of detectable disease by imaging does not preclude the designation of complete response.

8.1.2 Efficacy Assessment Types

All efficacy assessments captured at baseline and during the study will include the following evaluations: Physical examination and imaging by PET-CT scan (preferred modality).

Physical Examination

Lesions detected by physical examination will only be considered measurable if superficial, eg, skin nodules, and palpable lymph nodes and spleen. Documentation by color photography including ruler is recommended for estimating the size of skin lesions and photographic documentation should be submitted to BICR and kept in medical records. Unless unequivocally related to lymphoma, new or worsened abnormalities should be reported as AE.

Radiological Assessments

Imaging is required for all participants, PET, and contrast CT scans to be performed as indicated in the SoA and in Table 16. If the study treatment is discontinued prior to PD, participant in response PR or CR (including participant in CR who received radiotherapy with consolidation intent) or stable disease will continue to be monitored for efficacy until PD, death, start of a new anti-cHL treatment, whichever comes first as per Table 16. If the treatment is discontinued prior to Year 1, the timepoints for disease assessment should follow approximately those of regular treatment administration.

Note: participant in CR/PR who proceeds to HSCT without any treatment between the last dose of sabestomig and the start of the conditioning regimen will be followed-up for disease assessment post-transplant as per SoC and data on their disease status will be collected in the EDC as part of the survival follow-up.

Table 16 Radiology Scans for Tumor Assessments

Timepoints		Radiologic Scans [a]	
Screening		Contrast CT	PET
During the study [b]	CCI	Contrast CT	PET
	CCI	Contrast CT	PET

Timepoints		Radiologic Scans [a]	
	CCI	Contrast CT	PET
	Year [c] 1	Contrast CT	PET
	Q6M until EoS [c]	Contrast CT	PET

[a] Disease response should be assessed by PET-CT as per Modified Lugano criteria (2014) until participant achieves CR. Once CR is achieved, contrast CT may replace PET-CT until PD is suspected. If PD is suspected, PD must be confirmed by PET scan.
[b] At least 10 days post infusion, but prior to the next infusion.
[c] Calculated from the time of first dose (± 2 weeks).
Abbreviations: CT computed tomography; EoS: end of study; PD: progressive disease; PET-CT: positron emission tomography-CT.

Imaging modalities selected at baseline should remain consistent during the study; participants should have imaging assessments done at the participating study center or an acceptable alternate imaging facility using an identical imaging protocol and similar equipment.

The following options can be used:

- If PET-CT is of diagnostic quality with contrast, a separate CT/MRI with contrast is not required.
- If PET-CT is of diagnostic quality BUT without contrast, a separate CT/MRI with contrast is preferred but not mandatory.
- If PET-CT is not of diagnostic quality, a separate diagnostic-quality CT should be performed per SoC practices. In the event of contrast shortage, if a change in modality from CT to MRI is necessary, consider following the participant with MRI at least until the shortage is over.

Note: Diagnostic quality CT means that acquisition parameters, such as tube current, voltage, and exposure, of CT portion of PET are similar/comparable to a routine abdominal/pelvic CT scan done for diagnostic purposes, as per site's SoC.

Brain MRI or brain CT with contrast (if possible) will be performed at baseline only if there is a prior history of CNS involvement or if there are neurologic signs or symptoms present and as clinically indicated during the study.

- CT scans:
  - CT scans should be performed with contiguous cuts in slice thickness of 5 mm or less. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm.
  - The CT scans should cover the neck, chest, abdomen, and pelvis and any other disease sites as clinically indicated.
  - If the use of CT IV contrast is clinically contraindicated or frequent contrast CT scans are not allowed by the local IRB/Ethics Committee, an MRI may be used for

imaging assessments. In cases where MRI is desirable, the MRI must be obtained at screening and at all subsequent response-evaluations.

- Disease response should be assessed by PET-CT as per Modified Lugano criteria (2014) until participant achieves CR.
- For all participants who achieve CR, a CT with contrast may replace PET-CT to monitor disease response until PD is suspected. If PD suspected, PD must be confirmed by PET.
- If PET and CT scans are performed on the same day, PET must be performed prior to contrast-enhanced CT.
- For participants who require both a CT with contrast and a PET together, a CT without contrast is permissible during the Investigator assessed response period (Part A only) provided that the institution can provide accurate measurement without contrast for the CT portion per the Investigator.

- MRI scans:
  - MRI scan is acceptable for measurement of lesions provided that the same anatomical plane is used for serial assessments. If possible, the same imaging device should be used for serial evaluations.
- PET:
  - The PET scans should cover the whole body from base of skull to mid-thigh. The visual interpretation of PET scans will be performed using the 5-point scale Deauville criteria (Appendix C 2). Target lesions selected at baseline (max 6) must meet the measurability criteria and show FDG-avid uptake. Lesions visible on PET but not measurable on CT/MRI should be assigned as non-target lesions. Refer to Appendix C Lugano for additional details.

8.1.3 Blinded Independent Central Review Assessment

For Part B of the study, radiological imaging, including unscheduled disease assessments, will be transmitted by the sites to the vendor designated by AstraZeneca for central review by BICR. Of note, in Part A, imaging must be archived and transferred to the BICR vendor to allow retrospective disease response assessment in participants treated at a potential RP2D. All imaging assessments submitted for BICR should have a corresponding local efficacy assessment completed in eCRFs. De-identified copies of all radiology results may be requested by AstraZeneca. If PET scans are submitted to the BICR vendor, information including participant height, weight, administered dose, time between dose administration and imaging, and glucose level are required for each time point. Further details will be provided in the Imaging BICR charter and imaging acquisition guideline.

8.1.4 Patient-reported Outcomes

For Part B, assessment of patient-reported outcomes (PROs) will be undertaken to examine the impact of treatment on symptoms and function, as well as assessment of lymphoma ‘B’

symptoms and impact of cancer on health-related quality of life (HRQoL) and overall health status. Patient-reported outcomes have become increasingly important in evaluating the efficacy and tolerability of study treatments in clinical studies as part of the overall benefit/risk evaluation (Kluetz et al, 2016).

Importantly, cognitive, linguistic, and other developmental differences between adults and children often lead to different approaches to PRO assessment being needed within different pediatric age groups (Matza et al, 2013). Many standard PRO questionnaires are designed for and validated with adults only and therefore specific consideration is needed to determine the most suitable approach to PRO administration in a given context. In this study, well-established questionnaires designed for pediatric use are selected for trial participants < 18 years, based on the target concepts of interest and context of use.

In summary, health-related quality of life and health status measures will be used to evaluate PROs, including (refer to SoA):

- Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE): Appendix J 1
    - or Pediatric Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (Peds-PRO-CTCAE): Appendix J 2
- CCI [redacted]
- CCI [redacted]
- Patient Global Impression of Treatment Tolerability (PGI-TT): Appendix J 6
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

By combining PRO-CTCAE with questions selected from the EORTC Item Library as well as the static CCI [redacted] measures, this pragmatic and patient-centered approach will be focusing on what matters most to patients while helping to minimize participant burden. In addition, global impression measures will be used to CCI [redacted] and overall tolerability of treatment (PGI-TT). Participants aged < 18 years will complete two pediatric-specific measures, the Peds-PRO-CTCAE and CCI [redacted]

8.1.4.1 Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

PRO-CTCAE is a PRO measurement system developed to evaluate symptomatic toxicity in participants on cancer clinical trials. The PRO-CTCAE Item Library includes 124 items representing 78 symptomatic toxicities drawn from the CTCAE. PRO-CTCAE items evaluate the symptom attributes of frequency, severity, interference, amount, presence/absence. Each symptomatic AE is assessed by 1 to 3 attributes. Conditional branching logic is used with electronic data capture, thereby reducing respondent burden. The recall period is the past 7 days and PRO-CTCAE responses are scored from 0 to 4 (or 0/1 for absent/present).

In this study, 19 symptomatic toxicities are selected based upon anticipated AEs from previous preclinical data and regimen-specific information about the anticipated profile of symptomatic AEs. Thus, the total number of questions that participants will answer will range from 19 (assuming that no branching questions are triggered ie, the participant answers '0' to the initial question for each symptom) to 37 items (assuming that all possible branching questions are triggered for every symptom posed to the participant).

8.1.4.2 Pediatric Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (Peds-PRO-CTCAE)

The pediatric module includes 130 items representing 62 symptomatic toxicities and permits self-reporting by children and adolescents ages 7 to 17 years. In this study, 17 symptomatic toxicities are selected. Two symptoms included in the adult version are missing from the pediatric module and therefore cannot be included in the pediatric tool; these are 'rash' and 'sweating.' Thus, the total number of questions that participants will answer will range from 17 (assuming that no branching questions are triggered, ie, the participant answers '0' to the initial question for each symptom) to 42 items (assuming that all possible branching questions are triggered for every symptom posed to the participant).

8.1.4.3 European Organization for Research and Treatment of Cancer (EORTC) Item List (IL)XX

The EORTC Item Library is an online platform comprising more than 1000 individual items from over 70 EORTC questionnaires. As static questionnaires might not always be sufficient to meet the demands of quickly evolving treatment modalities, selecting items from EORTC Item Library offers new opportunities to leverage existing EORTC items and capture additional constructs (eg, symptoms, functioning, and global health status/quality of life) that are relevant to a given study.

The EORTC QLQ-C30 was developed by the EORTC Quality of Life Group to assess cancer-specific HRQoL, functioning, and symptoms for use in cancer clinical studies. It has undergone extensive testing and validation as well as detailed cross-cultural testing and validation (Aaronson et al, 1993). The EORTC QLQ-C30 is a 30-item self-administered questionnaire designed for all cancer types. Questions are grouped into 5 multi-item functional

scales (physical, role, emotional, cognitive, and social), 3 multi-item symptom scales (fatigue, pain, and nausea/vomiting), a 2-item global HRQoL (QL2) scale, 5 single items assessing additional symptoms commonly reported by patients with cancer (dyspnea, loss of appetite, insomnia, constipation, and diarrhea), and 1 item on the financial impact of the disease. All but 2 questions have 4-point scales: "Not at All," "A Little," "Quite a Bit," and "Very Much." The QL2 items have 7-point scales with ratings ranging from "Very poor" to "Excellent." Participants answer the QLQ-C30 questions in reference to how they have been over the past week. For each of the 15 domains, final scores are transformed such that they range from 0 to 100, where higher scores indicate better functioning, better HRQoL, or greater level of symptoms (Aaronson et al, 1993).

For adult participants only in this study, EORTC ILXX combines three single items from the Item Library to assess night sweats, fevers, and weight loss, plus the two QL2 items assessing overall HRQL and overall health.

8.1.4.4 CCI

The PROMIS Physical Function (PF) item bank (CCI) is an assessment tool that was designed using well-specified instrument development protocols with an item bank that allows for assessment across a wide range of activities and levels of ability (Cella et al, 2010).

The CCI – CCI is currently under qualification as an indicator of treatment benefit in PF among adults with advanced or metastatic cancer and will provide the primary support for the assessment of PF in the current trial. Data from CCI CCI will capture participants' perceived ability to perform specific activities over the past CCI days.

8.1.4.5 CCI

The CCI was designed to assess physical functioning and mobility in a pediatric population (DeWitt et al, 2011). It was developed based on the CCI. The measure includes CCI items asking about functional tasks such as standing independently, standing on tiptoes, using stairs etc. All questions use a CCI recall period, are written in the past tense, and have a standard CCI response scale from "CCI " to "CCI

8.1.4.6 Patient Global Impression of Treatment Tolerability

For adult participants only, the PGI-TT item is included to assess how a participant perceives the overall burden of treatment-related side effects of cancer treatment over the past 7 days. Participants will be asked to choose the response that best describes the level of burden by the side effect of their cancer treatment over the past week. The response options are: "not at all", "a little bit", "somewhat", "quite a bit", and "very much". This item is included to aid in the interpretation of other PRO measures and to evaluate the overall impact of treatment-related side effects.

8.1.4.7 CCI

For adult participants only, the CCI is a CCI questionnaire assessing how a participant perceives the overall severity of cancer symptoms over the past CCI. The response options are: CCI". This item is included to aid in the interpretation of other PRO measures and to evaluate the overall impact of treatment on the global severity of cancer symptoms.

8.1.4.8 CCI

For adult participants only, the CCI is a single-item questionnaire assessing how a participant perceives overall change in health status since the start of study intervention. The response options are "CCI".

8.1.4.9 CCI

The CCI will be used to explore the impact of treatment and disease state on health state utility. The CCI, developed by the CCI, is a generic questionnaire that provides a simple descriptive profile of health and a single index value for health status used for economic appraisal (EuroQol, 2019). The CCI questionnaire is comprised of CCI that cover CCI dimensions of health (eg, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Participants assess their health today using the CCI CCI, which ranges from 0 (CCI). The CCI is validated for use by respondents aged CCI

8.1.4.10 Administration of Patient-Reported Outcome Questionnaires

PRO will be implemented in Part B once approved and available at the site. Baseline PRO questions should be completed after informed consent and before the first dose of the study drug. PRO questionnaires that are completed at study sites must be completed prior to treatment administration performed at the site and ideally before any discussions of health status to avoid biasing the participant's responses to the questions. As feasible, site staff should also ensure PRO questionnaires are completed prior to other study procedures, such as collection of laboratory samples, to further minimize bias. Each site must allocate the responsibility for the administration of the electronic device and PRO instruments (subsequently referred to as "ePRO") to a specific individual (eg, a research nurse or study coordinator) and, if possible, assign a backup person to cover if that individual is absent. A web back-up may be available to answer the questionnaires if there are technical problems with the device or if preferred by the participant.

PRO questionnaires that will be self-administered electronically at home by the participants will be completed by using an application installed on handheld devices (participant's own device or provisioned device) at the time points indicated in the SoA. The device may either belong to the participant ("bring your own device") or be provisioned for the study by the

Sponsor. Participants should complete the ePROs prior to or at the site if the assessment time point coincides with a scheduled site visit. Alerts will remind participants when ePRO assessments should be completed. Participants should be instructed to bring the device to all visits. The amount of time needed to complete questionnaires at each time point will vary based on the specific questionnaires being administered. At Cycle 1 Day 1, adult participants will need approximately 12 to 17 minutes for questionnaire completion; adolescent participants will need approximately 9 to 14 minutes. For subsequent completions, including EoT, approximately 8 to 17 minutes will be required for adults to complete questionnaires at each timepoint; adolescent participants will require 7 to 15 minutes for subsequent completions.

The below instructions should be followed when collecting PRO data:

- The research nurse or appointed site staff should explain to participants the value and relevance of these data, so participants are motivated to comply with questionnaire completion.
- Participants should be informed that these questions are being asked to find out, directly from them, how they feel.
- The research nurse or appointed site staff must train the participant on how to use the ePRO device using the materials and training provided by the ePRO vendor.
- The research nurse or appointed site staff must provide guidance on who to call if there are problems with the device when the participant is completing the ePRO at home.
- Participants should be instructed to bring visual aids for reading (eg, glasses or contact lenses) to the baseline visit and all subsequent visits. If visual aids are not available at the visit, PRO questionnaires may be completed after the visit during the available window.
- It is vital that the ePRO reporting is initiated at Cycle 1 Day 1, as specified in the module-specific SoA to capture the effect of study intervention. The ePRO device must be charged and fully functional at the beginning of the baseline visit to ensure that the PROs can be completed at the start of the visit.
- PRO questionnaires should be completed by the participant in a quiet and private location whether completing the questionnaires at home or at a site visit. If completing at a site visit, the participant should be given sufficient time to complete the PRO questionnaires at their own speed.
- The order in which PRO questionnaires are to be completed will be pre-programmed into the ePRO device. Not all PRO questionnaires will be administered at every time point. Please refer to the SoA. PRO questionnaires will be completed in the following order: PRO-CTCAE/Peds-PRO-CTCAE, PGI-TT, CCI [redacted] CCI [redacted] CCI [redacted], CCI [redacted].
- The research nurse or appointed site staff should stress that the information is not routinely shared with study staff. Therefore, if the participant has any medical problems, they should discuss them with the doctor or research nurse separately from the ePRO assessment.

- The research nurse or appointed site staff must remind participants that there are no right or wrong answers and avoid introducing bias by not clarifying items.
- The participant should be instructed not to receive help from relatives, friends, or clinic staff when responding to the PRO questionnaires.
- Site staff should not read or complete the PRO questionnaires on behalf of the participant.
- The participant should bring the ePRO device to each site visit so the research nurse or appointed site staff can check if there are available PRO questionnaires to be completed and that the device is functioning properly.
- All questionnaires must be completed electronically via application on a handheld device or via web; paper questionnaires are not allowed in this study.
- If the participant is unable to complete the questionnaire (eg, being blind, illiterate, not fluent in the available language), that participant is exempted from completing PRO questionnaires but may still participate in the study. If the ePRO system is not ready, the participant is exempt from completing the PRO questionnaires during that time only but may still participate in the study. When the ePRO system is available, the participant is required to complete the PRO questionnaires. If the participant cannot complete the PRO questionnaires due to reasons other than being blind, illiterate, not fluent in the available language, or the ePRO system is not ready, the Sponsor's study team must be contacted to determine if the participant can be exempted. Participants exempted in this regard should be flagged appropriately by the site staff in the source documents and in the designated eCRF.
- Site staff must administer questionnaires available in the language that the participant speaks and understands. Questions must not be read in an available language and translated into another language for the participant.
- Reminders should be provided to participants, as needed to ensure compliance with the assessment schedules.
- The research nurse or appointed site staff should monitor compliance since minimizing missing data is a key aspect of study success.
- The research nurse or appointed site staff will review the completion status of questionnaires throughout the study and during site visits and document the reason(s) why a participant could not complete assessments, in the source documents and in the designated eCRF. If the site receives an email notification regarding the participant's compliance, appropriate action will be taken (eg, discussion with participant to improve compliance, a check-in call from the site to ask the participant if they have any difficulties in completing questionnaires on schedule). A solution to enhance/resolve compliance should be discussed with the participant. Discussions and compliance review should be reflected in source documents.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1, Table 2, Table 3, and Table 4).

8.2.1 Medical History

A medical and surgical history, including but not limited to, substance usage (eg, smoking and alcohol consumption history), comorbid conditions, tumor diagnosis and histology, PD-L1 status, EBV status, and prior cancer therapies, will be obtained at screening. Based on findings from medical history, ongoing current conditions will be given a baseline grade (NCI CTCAE v5.0). Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the baseline grade or below.

8.2.2 Physical Examinations

A complete physical examination will be performed at screening and will include assessments of the head, eyes, ears, nose, and throat, respiratory, cardiovascular, gastrointestinal, urogenital, musculoskeletal, neurological, psychiatric, dermatological, hematologic/lymphatic systems, and weight and height.

An abbreviated symptom-directed physical examination (including weight) will be conducted during the intervention and follow up periods.

Physical examinations will be performed at time points specified in the SoA (Table 1, Table 2, Table 3, and Table 4). On dosing days, the physical examination will be conducted prior to sabestomig administration.

8.2.3 Vital Signs

Vital signs (body temperature, blood pressure, pulse rate, and respiratory rate) and pulse oximetry will be measured at time points specified in the SoA (Table 1, Table 2, Table 3, and Table 4).

In addition, oxygen saturation by pulse oximetry should be obtained at any time if a participant has any new or worsening respiratory symptoms. A reading at rest and on exertion should be obtained at each time point. The extent of the exertion should be based on the judgment of the Investigator but should remain consistent for each participant throughout the study. If a participant's status changes, the Investigator can alter the extent of the exertion based on their medical judgment. If a participant shows changes on the pulse oximetry or other pulmonary-related signs (eg, hypoxia, fever) or symptoms (eg, dyspnea, cough) consistent with the possible pulmonary AE, the participant should be immediately evaluated to rule out pulmonary toxicity.

8.2.4 Electrocardiograms

The ECGs will be performed at time points specified in the SoA (Table 1, Table 2, Table 3, and Table 4).Whenever ECGs and blood draws (eg, PK/ADA) are scheduled for the same

nominal time, the blood draws should occur last. The timing of the ECG should be such that it allows the blood draw to occur at the proper nominal time.

The ECGs will be performed in triplicate (all 3 ECGs to be performed within a 5-minute time period, at least 1 minute apart) and the mean value of the triplicate measurement will be recorded at the local site as the baseline value.

All ECG recordings will be made with the participant in a supine position having rested in this position for at least 5 minutes before the start of the ECG.

Digital copies of ECGs may be held centrally by a central ECG provider and stored for potential independent analysis during, or at the end of, the study at AstraZeneca's discretion. The central independent review will not replace the local review by the Investigator or other medically qualified designee.

Electronic software will be used to assess the following parameters: pulse rate, QRS, QT, and QTcF time intervals. All ECGs must be reviewed by the Principal Investigator or a medically qualified designee before the SOI (for time points prior to the SOI) and before the participant is permitted to leave the clinic (for post infusion time points). In case of a clinically significant ECG abnormality (eg, occurrence of de- or re-polarization disorders, arrhythmic disorders), including QTcF of > 500 milliseconds, a minimum of 2 additional 12-lead ECGs should be obtained over a brief interval (eg, 30 minutes) to confirm the abnormality based on manual over-read by a medically qualified person. Such abnormalities and any obvious changes in ECG parameters from baseline will be assessed by the Principal Investigator for clinical significance. If clinically significant, the ECG abnormality should be recorded as an AE in the eCRF.

Clinical interpretation and any associated management of participants related to ECG abnormalities will be done locally and will be based on interpretation by a medically qualified person at the site.

8.2.5 Echocardiogram/Multiple-gated Acquisition Scan

Left ventricular ejection fraction will be measured by ECHO or MUGA scan at screening, EoT, and as clinically indicated during the study, eg, if the participant exhibits any symptoms indicative of myocarditis (eg, chest pain, dyspnea, palpitations, etc.) or other cardiac AEs (Section 1.3).

8.2.6 Eastern Cooperative Oncology Group Performance Status

The ECOG performance status will be assessed at time points specified in the SoA (Table 1, Table 2, Table 3, and Table 4) based on the following (Oken et al, 1982):

0 – Fully active, able to carry on all pre-disease performance without restriction.

1 – 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 – 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 – Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

4 – Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

5 – Dead.

8.2.7 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, hematology, coagulation, and urinalysis will be collected at time points specified in the SoA (Table 1, Table 2, Table 3, and Table 4).

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

The clinical chemistry, hematology, and urinalysis will be performed at a local laboratory at or near to the Investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The clinical safety laboratory variables will be measured as described in Table 17 below.

Table 17 Clinical Safety Laboratory Variables

Hematology	White blood cell count (total and differential); Absolute and differential % lymphocyte count; Absolute and differential % monocyte count; Absolute and differential % neutrophil count; Absolute and differential % eosinophil count; Absolute and differential % basophil count; Red blood cell count; Platelet count; Hemoglobin; Hematocrit; Erythrocyte sedimentation rate; Mean corpuscular volume; Ferritin.
Clinical Chemistry	Sodium; Potassium; Phosphorous; Blood urea nitrogen or urea; Creatinine; Creatinine clearance, Glucose; Chloride; Bicarbonate; Magnesium; ALT, AST, ALP [a]; GGT; TBL (direct and indirect); Total protein; Albumin; Lipase; Amylase; Uric acid; C-reactive protein; Lactate Dehydrogenase, Creatinine phosphokinase; Lipids (triglycerides, cholesterol).
Glycated hemoglobin	Glycated hemoglobin.
Cardiac troponin	Cardiac Troponin.
Urinalysis [b]	Color; Appearance; specific gravity; pH; Protein; Glucose; Ketones; Blood; Bilirubin.
Pregnancy test [c]	Urine hCG or serum β-hCG.

Table 17 Clinical Safety Laboratory Variables

Hematology	White blood cell count (total and differential); Absolute and differential % lymphocyte count; Absolute and differential % monocyte count; Absolute and differential % neutrophil count; Absolute and differential % eosinophil count; Absolute and differential % basophil count; Red blood cell count; Platelet count; Hemoglobin; Hematocrit; Erythrocyte sedimentation rate; Mean corpuscular volume; Ferritin.
Coagulation parameters	Prothrombin time; PTT (or activated PTT); international normalized ratio; Fibrinogen. Additional testing, including but not limited to, D-dimer, fibrin split products, and further evaluation for hypercoagulable condition may be considered as needed per clinical assessment.
Thyroid function tests	Thyroid function tests: TSH, and free T4 and free T3 if indicated (free T3 and T4 only be measured if TSH is abnormal or suspicion of an adverse event related to the endocrine system); Anti-thyroid antibodies (anti-thyroid peroxidase antibodies, thyrotropin receptor antibodies, and thyroglobulin antibodies) measured at screening and as clinically indicated.
Hepatitis and HIV virology	Hepatitis A virus immunoglobulin M; HbsAg, hepatitis B core antibody total, antibody to HbsAg, quantitative PCR for hepatitis B virus DNA; HCV antibody, PCR for HCV RNA; HIV-1 or HIV-2 antibodies.
Cortisol stimulation test (ACTH)	Cortisol stimulation test, if adrenal insufficiency is suspected.

[a] Tests for AST, ALT, ALP, and TBL must be conducted concurrently and assessed concurrently. If TBL is ≥ 2 x ULN, indirect bilirubin should be assessed unless previously documented Gilbert's disease.

[b] Urinalysis (dipstick acceptable). Urine microscopy (including white blood cells/high power field, red blood cells/high power field) is to be assessed if other urinalysis measurements are abnormal or if clinically indicated.

[c] A urine or serum pregnancy test is acceptable; if urine test is positive or equivocal, then serum β-hCG testing should be performed for confirmation.

Note: In case a participant shows an AST or ALT ≥ 3 x ULN together with TBL ≥ 2 x ULN, refer to Appendix G "Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law," for further instructions.

Abbreviations: ACTH: adrenocorticotropic hormone; ALP: alkaline phosphatase; ALT: alanine transaminase; AST: aspartate transaminase; GGT: Gamma-glutamyl transpeptidase; HbsAg: hepatitis B surface antigen; hCG: human chorionic gonadotropin; HCV: hepatitis C virus; HIV: human immunodeficiency virus; PCR: polymerase chain reaction; PTT: Partial Thromboplastin Time; T3: triiodothyronine; T4: thyroxine; TBL: total bilirubin; TSH: thyroid-stimulating hormone; ULN: upper limit of normal.

8.2.8 Pulmonary Lung Function Tests

Evaluation of pulmonary lung function will only be required during screening for eligible participants with pre-existing obstructive or fibrotic lung conditions. Testing will be done locally according to the recommendation of the Official Statement of the European Respiratory Society and American Thoracic Society [Miller et al, 2005].

Forced Expiratory Volume in the 1st second will be assessed at screening under medical supervision from a FVC maneuver. The highest value from 3 technically satisfactory attempts will be recorded (irrespective of the curve they come from). The chosen value should not exceed the next one by more than 150 mL. If the difference is larger, up to 8 measurements will be made and the largest value be reported. The ratio FEV/FVC will be derived from these highest values of each parameter. The FEV1 should be greater than 50% of predicted value or for FEV/FVC ratio, the fifth percentile LLN. Lung function measurements will be done with patients either standing or sitting with the nose clipped after at least 10 minutes rest.

All sites will use local equipment and local spirometry lab will be used.

8.3 Adverse Events and Serious Adverse Events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix D.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from time of signature of ICF throughout the treatment period and including the follow-up period until 90 days after the last dose of study intervention.

Serious AEs will be collected from the time of signing of ICF until the end of the study.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant treated by him or her, the Investigator shall, without undue delay, report the SAE to AstraZeneca.

Adverse event and SAE collection will be performed per specified timelines regardless of whether the participant has initiated a new anticancer treatment. See Section 6.9 for reporting of AEs and SAEs during PTAP.

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse Event Variables

The following variables will be collected for each AE:

- Adverse Event (verbatim),
- The date and time when the AE started and stopped,
- NCI CTCAE v.5.0 grade and grade changes, with the date of change,

- Whether the AE is serious or not,
- Investigator causality rating against the Investigational product(s) (yes or no),
- Action taken with regard to investigational product(s),
- Adverse Event caused participant's withdrawal from study (yes or no), and
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE,
- Date Investigator became aware of SAE,
- Seriousness criteria,
- Date of hospitalization,
- Date of discharge,
- Probable cause of death,
- Date of death,
- Autopsy performed,
- Causality assessment in relation to study procedure(s), and
- Causality assessment to other medication.

8.3.3 Causality Collection

The Investigator should assess causal relationship between investigational product and each AE, and answer 'yes' or 'no' to the question: 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes.'

A guide to the interpretation of the causality question is found in Appendix D.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study-site staff: "Have you had any health problems since the previous visit or since you were last asked?," or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately. When/if a diagnosis is confirmed, the eCRF should be updated to record the diagnosis and remove the associated signs and symptoms.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the CSP mandated laboratory tests, vital signs, and clinically significant abnormalities in ECGs will be summarized in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, and ECGs should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the investigational product, or are considered to be clinically relevant as judged by the Investigator (which may include but is not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting Investigator uses the clinical rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.6 Adverse Events of Special Interest

An AESI is an AE of scientific and medical interest specific to understanding of a study intervention and may require close monitoring and rapid communication to AstraZeneca by the Investigator. An AESI may be serious or non-serious. The reporting of AESIs allows ongoing surveillance of these events to characterize and understand them in association with the use of a study intervention.

The AESIs will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. The AEs will be assessed by the Investigator for severity, relationship to the study intervention, possible etiologies, and whether the event meets criteria for an SAE and therefore requires immediate notification to AstraZeneca. If an AE evolves into a condition that meets the regulatory definition of “serious,” it will be reported as described in Section 8.3.9.

The AESIs for sabestomig include events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. Additionally, IRRs and

events of similar presentation are considered AESIs for sabestomig. These AESIs are being closely monitored in clinical studies with sabestomig.

An imAE is an event that is associated with drug exposure, is consistent with an immune-mediated mechanism of action and has no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

The imAEs that may be observed with sabestomig (based on the available nonclinical and clinical data, review of the cumulative literature, reported toxicities for the same class of agents, and biological plausibility) and are considered AESIs for this study include, but are not limited to:

- Respiratory disorders: Pneumonitis, ILD
- Gastrointestinal disorders: Diarrhea, colitis, intestinal perforation
- Endocrinopathies: Hyperthyroidism and hypothyroidism (including thyrotoxicosis), adrenal insufficiency, diabetes mellitus, pituitary inflammation (hypophysitis), and hyperpituitarism and hypopituitarism
- Hepatic disorders: Elevated transaminases and hepatitis
- Renal disorders: Nephritis, nephropathy, elevated serum creatinine, and glomerulonephritis/sclerosis
- Cardiac disorders: Myocarditis and pericarditis
- Skin disorders: Rash, pruritus, dermatitis, vitiligo, psoriasis, SJS/TEN, pemphigus, and lichen planus
- Other rare imAEs including encephalitis, hemophagocytic lymphohistiocytosis, myositis/polymyositis, uveitis, iridiocyclitis, arthritis, Guillain-Barre syndrome, myasthenia gravis, vasculitis, hemolytic anemia, aplastic anemia, anemia, and sarcoidosis

Other aEs which are considered to be AESIs with sabestomig include but are not limited to:

- Infusion-related reactions; hypersensitivity including anaphylactic/anaphylactoid and other allergic reactions
- Immune complex disease and vasculitis
- Cytokine release syndrome

8.3.7 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 x ULN together with TBL ≥ 2 x ULN may need to be reported as SAEs. Refer to Appendix G for further instruction on cases of increases in liver biochemistry, evaluation of HL, and participants with pre-existing liver metastases.

8.3.8 Disease Progression

Disease progression can be considered as a worsening of a participant's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study, unless the disease progression worsens in terms of time-course or severity compared to what would normally be expected for that participant, or if the Investigator considers that there was a causal relationship between treatment with the study medication(s) or protocol design/procedures and the disease progression in which case must be reported as an SAE/SUSAR, due to the medical significance of the event.

8.3.9 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening aEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative. If the EDC system is not available, then the Investigator or other study-site staff reports an SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the Investigator/study-site staff how to proceed.

For further guidance on the definition of an SAE, see Appendix D.

The reference document for definition of expectedness/listedness is the Investigator's Brochure for the AstraZeneca drug.

8.3.10 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study intervention.

8.3.10.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as aEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **one day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within **one** (initial fatal/life-threatening or follow-up fatal/life-threatening) **or 5** (other serious initial and follow-up) **calendar days** for SAEs (see Section 8.3.9) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The pregnancy reporting module in the eCRF is used to report the pregnancy and the pregnancy outcome module is used to report the outcome of the pregnancy.

8.3.10.2 Paternal Exposure

Male participants should refrain from fathering a child or donating sperm during the study and for 90 days following the last dose of study intervention.

Pregnancy of the participant's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly), occurring from the date of the first dose until 90 days after the last dose of study intervention should, if possible, be followed up and documented in the

Pregnancy Report Form. Consent from the partner must be obtained before the Pregnancy Report Form is completed.

8.3.11 New Cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the study intervention and have been identified after the participant's inclusion in this study. They do not include metastases of the original cancer.

8.3.12 Deaths

All deaths that occur during the study intervention period, or within the protocol-defined follow-up period after the administration of the last dose of study intervention, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported as an SAE within 24 hours. It should also be documented in the eCRF. The report should contain a comment regarding the coinvolvement of PD, if appropriate, and should assign main and contributory causes of death.
- Death with an unknown cause should always be reported as an SAE. It should also be documented in the eCRF. A postmortem may be helpful in the assessment of the cause of death, and if performed, a copy of the postmortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual time frames.

Deaths occurring after the protocol-defined safety follow-up period (90 days after the administration of the last dose of study intervention) should be documented in the eCRF. If the death occurred as a result of an event that started after the defined safety follow-up period and the event is considered to be due to a late-onset toxicity to study intervention, then it should also be reported as an SAE.

8.3.13 Medication Error, Drug Abuse and Drug Misuse

8.3.13.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **one calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within **one** (initial fatal/life-threatening or follow-up

fatal/life-threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the medication error, drug abuse, or misuse (see Section 8.3.9) and **within 30 days** for all other events.

8.3.13.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication error can be found in Appendix D 4.

8.3.13.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix D 4.

8.3.13.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix D 4.

8.4 Reporting of Overdose

For this study, any dose of study intervention in excess of that specified in this CSP will be considered an overdose.

- An overdose with associated aEs is recorded as the AE diagnoses/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an IMP or AstraZeneca NIMP occurs in the course of the study, the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she become aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.9) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study-specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples, see Appendix E.

Note: In mainland China, all human biological samples will only be collected or analyzed after approval by relevant local authorities. For additional details regarding sample and data collection/test/disposal in China, please refer to the China specific Human Genetic Resource management plan.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated. Samples collected from participants in China will be destroyed or repatriated within one year of the CSR.

- The PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - The PK samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterization of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR. ADA samples collected from participants in China will be disposed of within one year of the CSR.

8.5.1 Pharmacokinetics

Blood samples will be collected for measurement of serum concentrations of sabestomig at time points specified in the SoA (Table 1, Table 2, Table 3, and Table 4).

Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and AstraZeneca, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

Serum samples will be used to analyze the PK of sabestomig. Samples collected for analyses of sabestomig serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentration in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

8.5.2 Immunogenicity Assessments

Blood samples for determination of ADA responses in serum to sabestomig will be collected at time points specified in the SoA (Table 1, Table 2, Table 3, and Table 4) and will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the methods used will be described in a separate report. ADA samples may also be further tested for characterization of the ADA response (eg, neutralizing antibodies). Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

8.5.3 Pharmacodynamics

Blood (including serum and plasma) and tumor samples will be collected at time points specified in the SoA (Table 1, Table 2, Table 3, and Table 4) and will be evaluated to determine changes in immune and tumor–associated profile following sabestomig treatment and characterize pharmacodynamic biomarkers associated with sabestomig clinical outcomes. Pharmacodynamic evaluation includes but is not limited to CCI changes and CCI CCI between baseline and following treatment.

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of Mandatory Samples for Biomarker Analysis

By consenting to participate in the study the participant consents to participate in the mandatory research components of the study.

Samples for biomarker research are required and will be collected from all participants in this study at time points specified in the SoA (Table 1, Table 2, Table 3, and Table 4).

[redacted] and [redacted] will be evaluated for exploratory protein, RNA and DNA biomarkers associated with [redacted] to assess correlations with disease activity, effects of study intervention, clinical outcomes, and toxicity. These biomarker measurements will support understanding of the mechanism of action of sabestomig and may guide the identification of participants who are most likely to respond to sabestomig.

The following samples are mandatory and will be collected from all participants (unless otherwise noted) at time points specified in the SoA (Table 1, Table 2, Table 3, and Table 4):

- Tumor tissue samples, see Table 18 (Section 8.6.2).
- Whole blood for [redacted]).
- Whole blood for [redacted]
- Whole blood for [redacted] and circulating biomarkers.
- Serum for [redacted] and [redacted]
- Whole blood for [redacted].

Note: The above collection of biomarker samples is not applicable in mainland China.

8.6.2 Tissue Samples

8.6.2.1 Tumor Tissue Samples

Tumor sample requirements for all participants in this study are described in Table 18. Tumor samples are defined as either archival or fresh tumor samples.

Note: The above collection of tumor tissue samples is not applicable in mainland China.

Table 18 Tumor Sample Requirement at Each Time Point

Part of Study/Cohort	At Screening		Cycle 1 Day 8 (Study Day 8) (± 2 days)	At Progression
	Archival from first diagnosis	Fresh or archival biopsy within 4 months prior to initiating study intervention	Fresh	Fresh
Part A Cohorts A1-A4	If available	If available [a]	Optional	Optional
Part A Cohorts A5-A8	If available	Fresh biopsy mandatory if archival tissue collected within prior 4 months prior is not available [a, b]	Optional	Optional
Part B Dose Expansion Cohorts B1 and B2	If available	Fresh biopsy mandatory if archival tissue collected within prior 4 months is not available [a, b]	Mandatory [b]	Optional

[a] For archival biopsy within 4 months prior to initiating study intervention, participant must not have received any anti-cHL treatment within that time period otherwise fresh tissue required.
[b] Unless medically contraindicated.

Samples will be assessed for:

- Predictive and/or pharmacodynamic biomarkers associated with immune modulation and TME using assays which may include, but are not limited to, CCI [redacted] CCI [redacted].

Archival and fresh tumor tissue samples will be stored at AstraZeneca or a vendor selected by AstraZeneca. Details for archival and fresh tumor sample collection, processing, storage, and shipment are provided in the Laboratory Manual. The associated pathology report(s) will be requested (see details in the Laboratory Manual).

Archival Tumor Tissue Samples

Archival tumor biopsy samples can be obtained from the FFPE tissue block or FFPE unstained slides. Formalin-Fixed Paraffin-Embedded archival tumor biopsies must meet the following criteria to be an acceptable sample:

- With the exception of the archival sample from first diagnosis, the FFPE tissue tumor blocks must have been obtained within ≤ 4 months of the first dose of study intervention. Of note, the participant must not have received any anti-cHL treatment within that time period otherwise fresh tissue is required.

- If archival tumor tissue FFPE blocks are not available for sectioning at screening, then archival tumor FFPE unstained slides are acceptable if sectioned less than 4 months prior to the first dose of study intervention.
  - A minimum of 10 unstained slides is required for biomarker determination and an additional 5 to 10 unstained slides for exploratory biomarker analysis.
- If archival tumor tissues are greater than 4 months prior to first dose of study intervention, then an additional fresh tumor tissues biopsy is required.

Fresh Tumor Tissue Samples

Fresh tumor tissue biopsies must meet the following criteria to be acceptable samples:

- Only core biopsies or excisional biopsies are acceptable. Samples from fine-needle aspiration are not acceptable.
- Part A Dose Escalation cohorts: For participants who undergo tumor biopsies at screening and/or on treatment, it is preferred, though not required, that the biopsied lesion be distinct from any target lesion used in the Modified Lugano criteria.
- Part B Dose Expansion cohorts: For participants who undergo biopsies at screening and/or on treatment, the biopsied lesion must be distinct from any target lesion used in the Modified Lugano criteria.

Time points for sample collection are presented in Table 18. For all participants in the study, additional fresh tumor biopsies may also be considered if clinically indicated and feasible, eg, at disease progression or for mixed responses or pseudo-progression.

If clinically feasible, at each fresh tumor sample time point, participants will undergo core image-guided needle biopsies. Per institutional practice, image-guided fresh core needle tumor biopsies (preferably 18 gauge or larger needle) should be preferentially obtained from tumor tissues that are safely accessible, as determined by the Investigator. If possible, sample same site for pre-treatment and C1D8 biopsies. Sites should confirm adequacy of tumor biopsy material at the time of the procedure.

8.6.2.2 Non-tumor Tissue Biopsy at Toxicity

For all participants in the study who undergo non-tumor tissue biopsies (eg, skin, liver, or kidney) to evaluate toxicity, involved tissue should be biopsied if clinically indicated and feasible and following the participant's consent. Adjacent uninvolved tissue should also be biopsied if the participant consents.

Samples will be assessed for predictive and/or pharmacodynamic immune-related biomarkers associated with toxicity profile using assays, including but not limited to, IHC, multiplex immunofluorescence, RNA expression, and proteomic analyses. Details for fresh non-tumor tissue biopsy sample collection, processing, storage, and shipment are provided in the Laboratory Manual.

Note: The above collection of tissue biopsy samples is not applicable in mainland China.

8.6.3 Collection of Optional Biomarker Samples

Collection of optional samples for biomarker research is also part of this study as specified in the SoA (Table 1, Table 2, Table 3, and Table 4) and is subject to agreement to optional consent. Refer to Section 8.6.2 for additional details for optional tissue samples collected during the study.

Note: The above collection of biomarker samples is not applicable in mainland China.

8.7 Optional Genomics Initiative Sample

Collection of optional samples for Genomics Initiative research is also part of this study as specified in the SoA (Table 1) and is subject to agreement in the ICF addendum.

A saliva sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

See Appendix F for information regarding the Genomics Initiative genetic sample. Details on processes for collection and shipment and destruction of these samples can be found either in the appendices or in the Laboratory Manual. For storage and destruction of genetic samples see Appendix F.

Note: Optional Genomics Initiative Samples will not be collected in mainland China.

8.8 Health Economics/Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.9 Assessments for Participants Who Transition to PTAP

Participants who continue to derive clinical benefit from treatment with sabestomig per investigator assessment and are still enrolled at the time of the final DCO, will proceed with the continued planned 21-day dosing schedule of sabestomig in the PTAP for this study.

AstraZeneca will inform investigators of planned and activated PTAP initiation timelines within each country, if available. The participant's last scheduled dosing visit prior to the final study DCO will include collection of samples indicated in the SoA Table 2 in addition to planned assessments for the scheduled dosing visit, ensuring no duplicates. See Section 6.9 for further details about PTAP.

9. STATISTICAL CONSIDERATIONS

The statistical analyses will be performed by AstraZeneca or its representatives. A comprehensive SAP will be prepared.

9.1 Statistical Hypotheses

There are no planned formal statistical hypotheses to be tested in this study.

9.2 Sample Size Determination

Approximately 180 participants will be treated with sabestomig, with up to CCI participants in Part A (Dose Escalation) and CCI participants in Part B (Dose Expansion). Additional participants may be enrolled if additional dose levels, expansion cohorts, treatment schedules are explored, or participants require replacement for any reason.

Note: "Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but are not assigned in the study, are considered "screen failures" unless otherwise specified by the protocol.

Part A Dose Escalation

The primary objective of this study is to investigate the safety and tolerability and estimate a RP2D of sabestomig for further evaluation. Hence the number of participants has been based on the desire to obtain adequate tolerability, safety, PK, efficacy, and biological data while exposing as few participants as possible to the study intervention and study procedures.

The number of participants treated during Part A Dose Escalation will depend upon the toxicities observed as the study progresses. With participants treated at each ATD dose level (single participants each for Cohorts 1 to 4) and a maximum of CCI participants treated at each mTPI-2 dose level (with CCI participants each for Cohorts 5, 6, 7, and 8 [optional cohort]), up to CCI participants may be treated for the 8 planned sabestomig dose levels (4 dose levels for ATD and 4 dose levels for mTPI-2). Additional participants may be required if additional dose levels or dosing schedules are explored. Given that the mTPI-2 algorithm leads to a dose escalation decision if there is no DLT in the first CCI participants treated in a dose level cohort, the actual sample size evaluated may be smaller than CCI participants.

Part B Dose Expansion

In Part B Dose Expansion, CCI participants may be treated, which may include up to 2 cohorts, Cohorts B1 (anti-PD-1/PD-L1-exposed; CCI participants) and B2 (anti-PD-1/PD-L1-naïve; CCI participants). For analysis in Cohort B1, participants treated at the RP2D in Part A (N=CCI) will be combined with participants enrolled in Part B, which gives a total sample size of approximately up to 100. The sample size of CCI participants is primarily chosen to maintain the accuracy of a No-Go decision based on efficacy signals. Observable exact binomial two-sided 80% cIs are presented in Table 19 and Table 20.

Table 19 Estimated Response Rate and 80% Two-sided Confidence Interval Out of CCI Participants (Cohort B1)

Number (%) of Objective Responses [a]	CCI (20%)	CCI (25%)	CCI (30%)	CCI (35%)	CCI (40%)	CCI (45%)
CCI	CCI	CCI	CCI	CCI	CCI	CCI
CCI	CCI	CCI	CCI	CCI	CCI	CCI

[a] Objective response per Modified Lugano Criteria (objective response rate for Cohort B1).
[b] CI obtained from exact binomial distribution.
Abbreviation: CI: confidence interval.

Table 20 Estimated Response Rate and 80% Two-sided Confidence Interval Out of CCI Participants (Cohort B2)

Number (%) of Complete Responses [a]	CCI (20%)	CCI (25%)	CCI (30%)	CCI (35%)	CCI (40%)	CCI (45%)
C	CCI	CCI	CCI	CCI	CCI	CCI
CCI	CCI	CCI	CCI	CCI	CCI	CCI

[a] Complete response per Modified Lugano Criteria (Complete Response Rate for Cohort B2).
[b] CI obtained from exact binomial distribution.
Abbreviation: CI: confidence interval.

9.3 Populations for Analyses

For purposes of analysis, the study populations are defined as provided in Table 21. For the safety and PK analyses, participants will be classified according to the dose level they actually received. For all efficacy analyses, and for baseline and demography, participants will be classified according to the dose they were assigned to (ie, the planned treatment/dose level/dose schedule).

Table 21 Study Populations

Population/Analysis set	Description	Endpoint/Output
Enrolled	All participants who sign the Informed Consent Form, or whose legally authorized representative [a] sign the Informed Consent Form.	Disposition
Full / Safety	All participants who received any amount of study intervention	Exposure Safety Baseline and demography PFS OS
Interim safety	All participants who received the first dose at least 6 weeks prior to data cut-off	Safety at interim
DLT-evaluable	Participants enrolled in the dose escalation phase who have received sabestomig and completed the DLT evaluation period (defined as 28 days after the start of study intervention) or who experience any DLT	DLT
Response-evaluable	All dosed participants who had measurable disease at baseline	ORR CRR BOR Duration of response Duration of complete response
Interim response-evaluable	All dosed participants who had measurable disease at baseline and received first dose at least 10 weeks prior to data cut-off	Efficacy at interim
PK	All participants who received at least 1 dose of study intervention with at least 1 reportable concentration	PK concentrations PK parameters
Pharmacodynamics	All participants who received at least 1 dose of study intervention with at least 1 reportable pharmacodynamic measurement	Pharmacodynamic endpoints
Immunogenicity	All participants who received at least 1 dose of study intervention with at least 1 reportable immunogenicity measurement	Immunogenicity endpoints
Exploratory biomarkers	All participants that participate in the exploratory biomarker research	Biomarker endpoints

[a] Legally authorized representative will be required to sign a statement of informed consent and informed assent from the participant (as appropriate) that meets the requirements of 21 CFR 50, local regulations, ICH guidelines Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

Individual PK concentration and parameter data for any participants not included in the PK analysis set or excluded from the descriptive summary tables, figures, and/or inferential statistical analyses will be included in the listings and flagged with an appropriate footnote.

DoR is reported for the subset of participants with objective response.

DoCR is reported for the subset of participants with complete response.

Abbreviations: BOR: best overall response; CRR: Complete Response Rate; DLT: dose-limiting toxicity; DoR: Duration of Response; DoCR: Duration of Complete Response; ORR: Objective Response Rate; OS: Overall Survival; PFS: Progression-free Survival; PK: pharmacokinetic(s).

9.4 Statistical Analyses

The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. Any deviations from this plan will be reported in the CSR.

9.4.1 General Considerations

Analysis will be performed by AstraZeneca or its representatives, including CROs. A comprehensive SAP will be developed and will describe the patient populations to be included in the analyses, the analyses including any subgroup analyses or sensitivity analyses, and the procedures to account for missing, unused, and spurious data.

Data will be presented by dose level in Part A and cohorts in Part B; no direct statistical comparisons will be made between any 2 dose levels or cohorts. For Cohort B1, participants treated at the RP2D in Part A will be included.

Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Geometric mean and coefficient of variation may be presented as applicable. Categorical variables will be summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated based on the population total, by dose level or cohort and by time point as appropriate. Time to event variables will be presented using the Kaplan-Meier methodology including median time calculated from the Kaplan-Meier curves.

An interim analysis will be performed as detailed in Section 9.5.

The primary analysis for Part B will be conducted at least 3 months after the final enrolled participant has received their first dose of sabestomig.

A final analysis may be performed 6 months after the last participant begins treatment or when AstraZeneca stops the study, whichever occurs first.

SAS® version 9.4 (as a minimum) will be used for analyses presented in CSR.

Baseline will be considered the last non-missing value obtained prior to the first dose of study intervention. Any information taken after first dose of study intervention will be regarded as post-baseline information. Detailed rules for deriving baseline values are described in the SAP.

Unless stated otherwise, two-sided cIs will be produced at 95%.

As appropriate, time windows will be defined for data summaries presented by visit. Time windows are described in the SAP.

Depending on the extent of any impact, summaries of data relating to participants diagnosed with COVID-19, and impact of COVID-19 on study conduct (in particular, missed visits, delayed or discontinued study intervention, and other protocol deviations) may be generated. Further details will be provided in the SAP.

9.4.2 Efficacy Analyses

The efficacy endpoints of ORR, CRR, DoR and DoCR will be summarized on the response-evaluable analysis set. The efficacy endpoints of, PFS, and OS will be summarized on the full analysis set. Additional subgroup analysis of efficacy may be performed as specified in the SAP.

9.4.2.1 Primary Endpoint(s)

Objective Response Rate

The ORR is defined as the percentage of participants with a CR or PR, with the denominator defined as the number of participants in the response-evaluable analysis set.

Data obtained until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR, regardless of whether the participant withdraws from therapy. Participants who discontinue treatment without a response, receive subsequent anti-lymphoma therapy and then respond will not be included as responders in the ORR.

The ORR will include data of all scans, regardless of whether it was scheduled or not.

The ORR will be presented by the number and percentage of participants with a response (CR/PR) including 95% cIs based on exact binomial proportions.

Best overall response will also be summarized by n (%) for each category, with no formal statistical analysis presented.

The ORR as assessed by BICR based on Modified Lugano criteria for lymphoma is the primary efficacy endpoint in Cohort B1 in Dose Expansion. The ORR is a secondary endpoint for Part A Dose Escalation assessed by Investigator based on Modified Lugano criteria and RECIL criteria.

Complete Response Rate

The CRR is defined as the percentage of participants with a CR, with the denominator defined as the number of participants in the response-evaluable analysis set.

Data obtained until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of CRR, regardless of whether the participant withdraws from therapy. Participants who discontinue treatment without a response, receive subsequent anti-lymphoma therapy and then respond will not be included as responders in the CRR.

The CRR will include data of all scans, regardless of whether it was scheduled or not.

The CRR will be presented by the number and percentage of participants with CR including 95% cIs based on exact binomial proportions.

The CRR as assessed by BICR based on Modified Lugano criteria for lymphoma is the primary efficacy endpoint in Cohort B2 in Dose Expansion. The CRR is a secondary endpoint for Part A Dose Escalation assessed by Investigator based on Modified Lugano criteria and RECIL criteria.

9.4.2.2 Secondary Endpoint(s)

Duration of Response

The DoR is defined as the time from the date of first documented response, assessed by Investigator for Part A and by BICR for Cohorts B1 and B2, using the Modified Lugano criteria, until the date of documented progression or death due to any cause (in the absence of disease progression). The end of response should coincide with date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit that was CR or PR.

The analysis will include all participants in the response-evaluable analysis set who had a response, regardless of whether the participant withdraws from therapy.

If a participant does not progress following a response, then the DoR will use the PFS censoring time.

Kaplan-Meier plots of DoR will be presented if data permitted. Median DoR, including 95% CIs, will also be presented, calculated from the Kaplan-Meier curve. In addition, the number of participants still responding at 3, 6, and 12 months after initial response will also be presented. Swimmer plots that clearly show the profile of each participant who responds will also be produced.

Duration of Complete Response

The DoCR is defined as the time from first documented CR, assessed by the Investigator for Part A and by BICR for Cohorts B1 and B2, using Modified Lugano criteria, until the date of documented relapse/progression or death due to any cause (in the absence of disease progression).

The analysis will include all participants in the response-evaluable analysis set who had a response, regardless of whether the participant withdraws from therapy.

If a participant does not progress following a response of CR, then the DoCR will use the PFS censoring time.

Kaplan-Meier plots of DoCR will be presented if data permitted. Median DoCR, including 95% CIs, will also be presented, calculated from the Kaplan-Meier curve. In addition, the number of participants still responding at 3, 6, and 12 months after initial response will also be presented. Swimmer plots that clearly show the profile of each participant who responds will also be produced.

Progression-free Survival

PFS is defined as the time from first dose until the earlier of the date of first documented disease progression, per Lugano classification as assessed by the Investigator for Part A (by BICR for Cohorts B1 and B2), or death (by any cause in the absence of disease progression or subsequent anticancer treatment). Participants who have not progressed or died at the time of analysis, or have unknown status, will be censored at the time of the latest date of assessment from their last evaluable assessment. Additional information and supportive/sensitivity analyses will be provided in the SAP.

The PFS time will always be derived, based on scan/assessment dates, not visit dates.

Disease assessments/scans contributing toward a particular visit may be performed on different dates. The following rules will be applied:

- Date of progression will be determined, based on the earliest of the dates of the component that triggered the progression.
- When censoring a participant for PFS, the participant will be censored at the latest of the dates contributing to a particular overall visit assessment.

Kaplan-Meier plots of PFS will be presented. Summaries of the number and percentage of participants experiencing a PFS event, and type of event (progression or death) will be provided along with the median PFS, its 95% CI and the proportion of participants who were progression free at 3, 6, 12, 18, and 24 months.

The treatment status at progression of participants at the time of the analysis will be summarized. This will include the number and percentage of participants who were on treatment at the time progression, the number and percentage of participants who discontinued study intervention prior to progression, the number and percentage of participants who have not progressed and were on treatment or discontinued treatment. This will also provide a

distribution of number days prior to progression for participants who have discontinued treatment.

Overall Survival

The OS is defined as the time from the start of treatment until death due to any cause regardless of whether participant withdraws from treatment or receives another anti-lymphoma therapy. Any participant not known to have died at the time of analysis will be censored based on the last recorded date on which the participant was known to be alive.

Note: Survival follow-up phone calls will be made in the week following the date of DCO for the analysis, if participants are confirmed to be alive or if the death date is after the DCO date the participants will be censored at the date of DCO.

The OS data will be presented similarly to the presentation described for PFS.

9.4.3 Safety Analyses

Safety and tolerability will be assessed in terms of DLTs, AEs/SAEs, imAEs, vital signs, clinical chemistry/hematology parameters, and clinically significant abnormalities in ECGs. These variables will be collected for all participants where applicable. All safety analyses will be performed on the safety analysis set. Additional subgroup analysis of safety may be performed, as specified in the SAP.

9.4.3.1 Maximum Tolerated Dose Evaluation

The MTD evaluation will be based on the DLT-evaluable population. After each escalation stage is completed, final DLT rates at each dose level will be estimated by isotonic regression (Ji et al, 2010). The weighted least squares regression model will assume monotonic non-decreasing DLT rates with increasing dose, and use the empirical (observed) DLT rates at each dose level as responses and dose level sample sizes as weights, along with the pool adjacent violators algorithm to estimate the DLT rate at each dose level using available software such as EAST® and R. Given the DLT estimates for each dose level, the MTD will be selected from all tried dose levels that have not been previously declared to be unsafe (Probability [DLT > 30% data] ≥ 80%) with a DU decision according to the mTPI-2 decision table. With this constraint, the MTD will be determined as the dose level with the DLT estimate closest to the target toxicity level of 30%.

In the case of dose levels with estimated toxicity of equal distance (tied dose levels) from the target toxicity of 30%, the following approach will be used (Ji et al, 2010): among all tied dose levels, the highest dose level with target toxicity ≤ 30% will be selected, unless all tied dose levels have estimated toxicity > 30%, in which case the lowest dose level will be selected.

The number and percentage of participants with a DLT will also be presented by dose level.

9.4.3.2 Analysis of Adverse Events

The MedDRA will be used to code AEs. All AEs will be graded according to the NCI CTCAE v5.0. The number of participants in each dose level experiencing each AE will be summarized by MedDRA system organ class and preferred term. The number and percentage of participants with AEs in different categories (eg, causally related, NCI CTCAE Grade ≥ 3, etc.) will be summarized by dose level; events in each category will be further summarized by MedDRA system organ class and preferred term. The SAEs and imAEs will be summarized separately.

Any AE occurring before the first dose of study intervention will be included in the data listings but not in the summary tables of AEs. The AE summary tables will include only treatment-emergent AEs. Adverse events will be defined as treatment-emergent if they have an onset or worsen (by Investigator report of a change in intensity/severity) during the study intervention or safety follow-up periods, ie, from the date of first dose of study intervention up to 90 days after the last dose of study intervention. Any AEs in the safety follow-up period that occur after a participant has received further therapy for cancer (following discontinuation of study intervention) will be flagged in the data listings and will not be defined as treatment-emergent.

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation. Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the CSR. A similar review of laboratory/vital signs (pulse and blood pressure)/clinically significant abnormalities in ECGs will be performed for identification of OAEs. Examples of these could be marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction, or significant additional treatment.

9.4.3.3 Analysis of Other Safety Data

All safety data including clinical chemistry, hematology, coagulation, urinalysis, vital signs, and clinically significant abnormalities in ECGs will be listed individually by participant and appropriately summarized. For all laboratory variables that are included in NCI CTCAE v5.0, the CTCAE grade will be calculated. Details of any deaths will be listed for all participants. Graphical presentations of safety data will be presented as appropriate. The DLTs will be displayed in a listing.

Duration of exposure will be summarized.

Clinical Laboratory Parameters

Laboratory parameters will be assessed at baseline as well as throughout the study. Frequencies of worst observed Grade 0 to 4 toxicity, as defined by NCI CTCAE v5.0, will be presented for each laboratory parameter. The analysis will present worst grade observed and the rates of participants with Grade 3 or 4 toxicity. Also, laboratory parameters will be assessed by presenting tables containing information related to 2-grade (or greater) laboratory shifts from baseline as well as descriptively over time.

Vital Signs

Descriptive statistics will be provided for the vital signs measurements and changes from baseline by scheduled time of evaluation and by treatment part, including the EoT visit as well as for the maximum and minimum post-baseline values.

Electrocardiograms

The ECG parameters will be assessed at baseline by the Investigator as well as throughout the study and an overall ECG evaluation will be recorded. Overall ECG evaluation at baseline and throughout the study may be summarized.

9.4.4 Other Analyses

9.4.4.1 Pharmacokinetics and Pharmacodynamics

Individual sabestomig concentrations will be tabulated by dose level along with descriptive statistics. Relevant descriptive statistics of non-compartmental PK parameters will be provided if data allow and may include AUC, Cmax, clearance, and t½ if data allow. If the data merit, population PK, PK/pharmacodynamic relationships, and/or exposure response/safety analyses will be performed, and details of the analyses will be described in a separate document.

9.4.4.2 Immunogenicity

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of participants who develop detectable ADAs to sabestomig. The potential impact of ADAs on PK, pharmacodynamics, and safety will be assessed if data allow. Samples confirmed positive for ADAs may also be evaluated for neutralizing antibody activity.

9.4.4.3 Biomarkers

Biomarker analysis at baseline and/or on treatment (pharmacodynamics) will be assessed for participants in each cohort that may be detailed in the SAP. The relationship of exploratory biomarkers to clinical outcomes may be presented. Biomarker exploratory analyses may be described in a separate analysis plan and may be reported outside the CSR in a separate report as an addendum, or separately in a scientific report or publication. The results of this

biomarker assessment may be pooled with biomarker data from other studies with the study intervention to generate hypotheses to be tested in future research.

Antitumor activity will be also evaluated by measuring changes in CCI level and profile following administration of sabestomig.

9.4.4.4 Patient-Reported Outcomes

All PRO tolerability-related analyses will use the safety analysis set. PROs will be scored according to the relevant scoring manuals. Full detail of PRO endpoint derivation will be documented in the SAP along with the analysis methodology.

The secondary PRO endpoints include the following:

- Proportion of participants reporting different levels of presence/magnitude/interference (as applicable) of diarrhea, rash, and fatigue, over time based on PRO-CTCAE or Peds-PRO-CTCAE
- Proportion of participants reporting different levels of overall side-effect bother over time based on the PGI-TT
- Proportion of participants reporting different levels of quality of life/health over time based on the EORTC ILXX QL2 items

Single items and subscales from the PRO questionnaires and health status measures to be used are described in Section 8.1.4. Details of all statistical analyses, including analyses for other exploratory PRO endpoints, will be described in full in the SAP.

9.5 Interim Analyses

Efficacy Interim Analyses

Interim analyses will be performed in a continuous manner for Part B using CCI CCI (Lee and Liu, 2008). The prior distribution of the ORR is Beta(1,1). For each cohort, interim analyses will begin after approximately CCI participants in each respective cohort are included in the interim response-evaluable population (Section 9.3). For Cohort B1, participants treated at the RP2D in Part A will be included.

Following this initial interim analysis, subsequent interim analyses may be performed after every CCI additional participants in Cohort B1 and every CCI additional participants in Cohort B2 get included in the interim response-evaluable population, until all participants are enrolled and evaluated. The interim analyses will be conducted to determine futility, where the stopping criteria for futility will be based on the interim response-evaluable set. For any interim futility analyses, an objective response is defined as either a CR or PR as per the

Modified Lugano criteria (Appendix C), and a complete response is defined as a CR as per the Modified Lugano criteria (Appendix C).

The ORR as assessed by Investigator based on Modified Lugano criteria for lymphoma is the interim efficacy endpoint. As appropriate, the ORR as assessed by BICR based on Modified Lugano criteria may also be considered. Recruitment will not be paused while the participants required for the interim analysis are evaluated. Any decision to stop recruitment in a specific cohort will be at the discretion of AstraZeneca and will be based on emerging efficacy, safety, and tolerability.

Further details will be included in the SAP.

Interim Safety Analyses

Interim safety analysis will be conducted in Part B after approximately CCI participants have received the first dose at least 3 months prior to data-cut off, using the interim safety population. The study recruitment may be paused, pending investigation by AstraZeneca in discussion with SRC, if at least one of the safety events described in Section 4.5 (Part B Study Stopping Criteria) occur.

For safety stopping purposes, data from both B1 and B2 will be combined. Safety data from subjects in Part A who are treated at the RP2D will also be included analysis of data from Part B.

Further details will be included in the SAP.

9.5.1 Relapsed or Refractory cHL, Anti-PD-1/PD-L1 Exposed

The prior distribution of the ORR is Beta (1,1). The Target Value (TV) is set to demonstrate a CCI over the benchmark CCI

At final analysis:

- No-Go criterion is met if the probability that the true ORR exceeds the pre-specified TV of CCI

Given the observed data during the continuous monitoring stage, the Bayesian predictive probability is calculated as the probability of reaching a No-Go decision should the treatment group be enrolled and evaluated to the planned final sample size of CCI Further enrolment may be terminated if futility is met at any interim looks, which is defined as a > 95% predicted probability of meeting the No-Go criterion upon full enrolment of CCI participants given the currently observed data.

The decision matrix for continuous monitoring of ORR is provided in Figure 3 below. Operating characteristics are presented in Table 22 and are based on 10000 simulations using the prespecified TV, No-Go, and Futility definitions.

- A false No-Go is defined as observing either futility during the continuous monitoring stage or No-Go at final analysis when the true ORR is greater than or equal to the TV (ie, False No-Go: P[Futility or No-Go Decision | true ORR ≥ TV]). As shown in Table 22, CCI

Figure 3 Continuous Objective Response Rate Monitoring for Anti-PD-1/PD-L1 Exposed Participants

Table 22 Operating Characteristics of Bayesian Continuous Monitoring of Cohort B1

True ORR	%No-Go (Anytime)	% Early Futility Decision	% Concordance (IA and FA)
CCI	CCI	CCI	CCI
CCI	CCI	CCI	CCI
CCI	CCI	CCI	CCI
CCI	CCI	CCI	CCI

Target Value (TV) ORR = 40%; No-Go: P(ORR > TV) < 10%; Futility: PP(No-Go) > 95%)

9.5.2 Relapsed or Refractory cHL, Anti-PD-1/PD-L1-naïve

The prior distribution of the CRR is Beta (1,1). The Target Value (TV) is set to demonstrate a CCI

At final analysis:

- No-Go criterion is met if the probability that the true CRR exceeds the pre-specified TV of CCI

Given the observed data during the continuous monitoring stage, the Bayesian predictive probability is calculated as the probability of reaching a No-Go decision should the treatment group be enrolled and evaluated to the planned final sample size of CCI. Further enrolment may be terminated if futility is met at any interim looks, which is defined as a > 95% predicted

probability of meeting the No-Go criterion upon full enrolment of CCI participants given the currently observed data.

The decision matrix for continuous monitoring of CRR is provided in Figure 4 below. Operating characteristics are presented in Table 23 and are based on 10000 simulations using the prespecified TV, No-Go, and Futility definitions.

- A false No-Go is defined as observing either futility during the continuous monitoring stage or No-Go at final analysis when the true CRR is greater than or equal to the TV (ie, False No-Go: P[Futility or No-Go Decision | true CRR ≥ TV]). As shown in the table below, CCI

Figure 4 **Continuous Objective Response Rate Monitoring for Anti-PD-1/PD-L1 Naïve Participants**

Table 23 **Operating Characteristics of Bayesian Continuous Monitoring of Cohort B2**

True CRR	%No-Go (Anytime)	% Early Futility Decision	% Concordance (IA and FA)
CCI	CCI	CCI	CCI
CCI	CCI	CCI	CCI
CCI	CCI	CCI	CCI
CCI	CCI	CCI	CCI

CCI

9.6 Data Monitoring Committee

There will be no Data Monitoring Committee for this study. A study-specific SRC will review the emerging data from the study and will continue to monitor safety data on an ongoing basis (see Section 6.6.7).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to AstraZeneca of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. AstraZeneca will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- For all studies except those utilizing medical devices Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and AstraZeneca policy and forwarded to Investigators as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from AstraZeneca will review and then file it along with the [Investigator's Brochure or state other documents] and will notify the IRB/IEC, if appropriate according to local requirements.

- In the EU, the Sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU CTR) No. 536/2014. All SUSARs to investigational medicinal product will be reported to the EudraVigilance database within the required regulatory timelines.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency (EMA) Clinical Trial Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

A 2 Financial Disclosure

Investigators and sub-Investigators will provide AstraZeneca with sufficient, accurate financial information as requested to allow AstraZeneca to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

A 3 Informed Consent Process

- The Investigator or their representative will explain the nature of the study to the participant or their legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants below the age of 18 years will be required to provide their assent, if required by local regulations, and participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The Investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

A 4 Data Protection

- Participants will be assigned a unique identifier by AstraZeneca. Any participant records or datasets that are transferred to AstraZeneca will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by AstraZeneca in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by AstraZeneca, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be

addressed; for instance, this could involve amendments to the Clinical Study Protocol and letters to Investigators.

A 6 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on an electronic case report form (eCRF) unless transmitted to AstraZeneca or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections, and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Monitoring Plan.
- AstraZeneca or designee is responsible for the data management of this study including quality checking of the data.
- AstraZeneca assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification as per the Monitoring Plan(s) to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in

accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a minimum of 25 years after study completion or as required by local regulations or institutional policies, according to the AstraZeneca Global Retention and Disposal (GRAD) Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study are defined as source documents. Source data are contained in source documents (original records or certified copies).
- A digital copy of all imaging scans should be stored as source documents.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

AstraZeneca designee reserves the right to close the study site, temporarily suspend, or permanently terminate the study or any component of the study at any time for any reason at the sole discretion of AstraZeneca (see Section 4.5). Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by AstraZeneca or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, AstraZeneca's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, AstraZeneca shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to AstraZeneca before submission. This allows AstraZeneca to protect proprietary information and to provide comments.
- AstraZeneca will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, AstraZeneca will generally support publication of multi-center studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Contraception Guidance

B 1 Definitions

- Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or who are post-menopausal.
- Women will be considered post-menopausal if they have been amenorrhoeic for 12 months prior to the planned date of first dose of study intervention without an alternative medical cause. The following age-specific requirements apply:
  - Women < 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range.
  - Women ≥ 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments.
- A highly effective method of contraception is defined as one that can achieve a failure rate of < 1% per year when used consistently and correctly.

B 2 Contraception Methods

The highly effective methods of contraception are described in the table below.

Highly Effective Methods of Contraception

Barrier/Intrauterine Methods	Hormonal Methods
• Intrauterine device • Intrauterine hormone-releasing system (IUS) [a] • Bilateral tubal occlusion • Vasectomized partner [b] • Sexual abstinence [c]	Combined (estrogen and progestogen containing hormonal contraception) • Oral (combined pill) • Injectable • Transdermal (patch) Progestogen-only hormonal contraception associated with inhibition of ovulation [d] • Injectable • Implantable

[a] This is also considered a hormonal method.

[b] With appropriate post-vasectomy documentation of surgical success (absence of sperm in ejaculate).

[c] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study and if it is the preferred and usual lifestyle of the participant. However, periodic or occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

[d] Progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action (eg, minipill), is not accepted as a highly effective method. In line with the Clinical Trials Facilitation Group guidance on the recommendations related to contraception and pregnancy testing in clinical trials, oral contraceptives are only highly effective when associated with inhibition of ovulation.

Appendix C Response Evaluation Using the Modified Lugano (Cheson et al, JCO 2014) and RECIL (Younes et al, Ann Oncol 2017) Criteria

C 1 Modified Lugano (Cheson et al, 2014)

The purpose of this document is to provide guidance to the Investigators on the assessment of efficacy in Hodgkin and Non-Hodgkin lymphoma studies conducted by AstraZeneca.

General definitions

Tumor lesions will be categorized as follows:

- **Baseline:** Baseline assessments are those assessments performed as close as possible to the start of study treatment. Baseline scans will be used to confirm eligibility based on the presence of measurable disease and as reference to assess disease response to study treatment. No anti-lymphoma treatment (including palliative RT) should be implemented between the baseline scans and the first planned dose.
- **Nodal vs Extranodal**: a lesion can be categorized as:
    - Nodal (a lymph node or a nodal mass), or
    - Extranodal (a lesion located in other organs, including liver and bone marrow; Tonsils, Waldever's ring, and spleen are considered nodal tissue).

- **Measurable Lesions –** a measurable lesion is a lesion that can be clearly measured in at least two perpendicular dimensions by CT/MRI (longest diameter [LDi] and shortest diameter [sDi]). The LDi and SDi will be measured in the transverse plane. A lesion is considered measurable if:
    - For nodal lesions: LDi > 1.5 cm,
    - For extranodal lesion (eg hepatic, lung nodules): LDi > 1 cm,
    - The Ldi and the SDi should be measured on the same slice.

- **Bulky disease –** the presence of a bulky disease is captured by the LDi on CT scan. For HL, bulky is defined as a single nodal mass, of 10cm or greater than a third of the transthoracic diameter at any level of thoracic vertebrae.

- **Target Lesions –** At baseline, all lesions up to a maximum of 6 measurable nodal or extranodal lesions should be identified as target lesions at baseline and followed throughout the study. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. Target lesions should be identified from different body regions representative of the patient's overall disease burden and include mediastinal and retroperitoneal disease, if involved. A bulky lesion can also be selected as target lesion. Target lesions must meet the measurability criteria and show FDG-avid

uptake. Lesions visible on PET but not measurable on CT/MRI should be assigned as non-target lesions. When selecting the target lesions, consider the following:

- Target lesions should be identified from different body regions representative of the participant's overall disease burden and include mediastinal and retroperitoneal disease, if involved.
- A bulky lesion can also be selected as target lesion.
- Target lesions should be selected from those of the largest size that can be measured reproducibly.
- In certain anatomical sites (inguinal, axillary, and portocaval), normal lymph nodes may exist in a very narrow, elongated form. Clinical judgment should be used when selecting these lesions are target lesions.
- Because of the variable anatomical coverage of scans at different timepoints, it is preferrable not to select as target lesions nodal lesions located in the higher cervical and/or lower inguinal districts.

For the selected target lesions, the sum of the product of the perpendicular diameters (SPD) will be calculated with the percentage change from baseline for assessment of response and nadir for assessment of progression.

- **Non-target Lesions –** All other lesions (including nodal, extranodal, and assessable disease) not selected as target lesions, as well as truly non-measurable sites of disease should be followed as non-measurable disease (eg, Cutaneous, gastrointestinal, bone, spleen, liver, kidney, pleural or pericardial effusions, ascites) and should be factored into the overall response assessment. Non-target lesions will be documented at baseline and throughout the study qualitatively (for example: present, absent/normalized /clear progression). Measurement of these lesions is not required to be documented in the eCRF.

- **Organ Involvement**
  - **Spleen involvement**: Spleen will be considered to be normal if size of its vertical length (cranial-caudal measurement) is ≤ 13 cm. Spleen vertical length will be assessed at screening and all subsequent response-evaluations. Splenic nodules should be considered as extra-nodal lesions and treated as target, non-target or new lesions are appropriate.
  - **Liver involvement**: Given variability in body habitus and the impact of numerous medical conditions, liver size by physical examination or CT scan is not a reliable measure of hepatic involvement by lymphoma. For these reasons, liver size will not be collected in eCRFs. The presence of a diffuse or focal uptake with or without focal or disseminated nodules support liver involvement. Intrahepatic lesions should be considered as target, non-target, or new lesion as applicable.

- **Bone Marrow involvement:** Bone marrow involvement by lymphoma documented by biopsy and/or aspirate or by PET will be reported on the eCRF as positive, negative or unknown.

- **Other, skin and soft tissue lesions:** Skin lesions histologically proven for lymphoma should be preferably selected as Non-target lesions due to variability in measurement on skin photography**.** If skin is the only site of measurable disease, colour photographs including a ruler should be submitted to BICR (as applicable) and stored in medical records. Measurements should be reported in eCRFs at each disease response assessment if these lesions are selected as target lesions.

- **New Lesions** – Lesions which were not present at the baseline, but are visible at a subsequent timepoint:
  - Nodal lesion of > 1.5 cm in any axis,
  - Extranodal lesion of > 1 cm in any axis.
  - In case of appearance of a new extranodal lesion ≤ 1 cm, a biopsy confirmation of lymphoma is always preferable to rule out a benign origin, unless not feasible (lesions too small) or if the procedure is medically contraindicated.

  The appearance of a new lesion, even if all other lesions are decreasing should be considered progression.

- **Staging and Classification**
  - Stage: Extent of disease should be described at baseline using the Revised Ann Arbor classification (Table 2).
  - Symptoms: according to the absence (A) or presence (B) of disease related symptoms. Only patients with HL need to be assigned the designations A or B because symptoms only direct treatment in that disease.

Table 2. Revised Staging System for Primary Nodal Lymphomas

Stage	Involvement	Extranodal (E) Status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky*	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

NOTE. Extent of disease is determined by positron emission tomography–computed tomography for avid lymphomas and computed tomography for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

*Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

C 2 Modified Lugano Response-evaluation Criteria (Cheson et al, 2014)

Table 3. Revised Criteria for Response Assessment

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	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 marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† 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 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than 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
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 an 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 0.5 cm for lesions ≤ 2 cm 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

(continued on following page)

Table 3. Revised Criteria for Response Assessment (continued)

Response and Site	PET-CT–Based Response	CT-Based Response
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

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; 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 six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI 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, GI 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).
†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.

Deauville 5-point scale: The use of PET/CT is standard for FDG-avid lymphomas and whenever aggressive transformation is suspected. Variation in FDG uptake in a nodal or extranodal sites indicative for lymphoma will be visually assessed using the Deauville 5-point scale. The scale ranges from 1 to 5, where 1 is best and 5 is the worst. Each FDG-avid (or previously FDG-avid) lesion is rated independently.

Deauville 5-point scale

Score	Description
Score 1	No uptake above background
Score 2	Uptake ≤ mediastinum
Score 3	Uptake > mediastinum, but ≤ liver
Score 4	Uptake moderately > liver [a]
Score 5	Uptake markedly higher than liver and/or new lesion [a]
X (New)	Areas of uptake unlikely to be related to lymphoma [b]

[a] Barrington et al (2014) suggest the following: "The terms moderately and markedly were not defined initially, because there were insufficient data to define scores quantitatively. Meanwhile, it is suggested according to published data that score 4 be applied to uptake greater than the maximum SUV in a large region of normal liver and score 5 to uptake 2 × to 3 × greater than the maximum SUV in the liver."

[b] Barrington SF, Mikhaeel NG, Kostakoglu L, et al: Role of imaging in the staging and response assessment of lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol 32:3048-3058, 2014

Abbreviation: SUV: standardized uptake value.

It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or bone marrow (eg, following chemotherapy or G-CSF treatment), the uptake may be greater than normal mediastinum and/or liver. In this

circumstance, complete CR 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.
In presence of new areas of FDG uptake that are unlikely to be related to lymphoma but are thought to be of inflammatory or infectious origin by the Investigator, the reporter should assign 'X' in addition to the Deauville score. For example, if there is a complete resolution of all uptake with no abnormal nodes but new lesions likely to be related to another etiology occur, the total score should be of DS 1X rather than DS 5. Additionally, these lesions should be tracked and should not be used to determine the PET response at subsequent assessments.

Evaluation of Overall Response

The possible outcomes for Overall Response Assessment are: CR, PR, SD, PD or Unknown.

Any clinical, laboratory, histopathologic or cytologic findings accounting for a discrepancy between the radiological response and the oncologic overall disease response, should be appropriately documented in eCRFs.

The following tables are intended as general guidance only for Investigators and do not cover all possible scenarios. Clinical judgment should be applied.

The Investigator-assessed Overall Response Assessment and respective date will be captured on the eCRF. In presence of an overall response of PD, the overall disease response date is the earliest date when PD was documented by any method (eg, bone marrow, CT/MRI or PET scan). In presence of an overall response of CR/PR/SD/Unknown, the overall disease response date is the latest date when the response was documented/confirmed.

The table below provides overall responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions.

Evaluation of Overall Response Using the Modified Lugano Criteria

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
No target lesion [a]	CR	No	CR
CR	Not evaluable [b]	No	PR
CR	Non-CR/ non-PD	No	PR
PR	Non-PD and not evaluable [b]	No	PR
Stable disease	Non-PD and not evaluable [b]	No	Stable disease
Not all evaluated	Non-PD	No	Not evaluable
No target lesion [a]	Not all evaluated	No	Not evaluable
No target lesion [a]	Non-CR/ non-PD	No	Non-CR/ non-PD

Evaluation of Overall Response Using the Modified Lugano Criteria

Target Lesions	Non-target Lesions	New Lesions	Overall Response
PD	Any	Yes/No	PD
Any	Unequivocal PD	Yes/No	PD
Any	Any	Yes	PD
No target lesion [a]	Unequivocal PD	Yes/No	PD
No target lesion [a]	Any	Yes	PD

[a] Defined as no target lesion at baseline.
[b] Not evaluable is defined as either when no or only a subset of lesion measurements are made at an assessment.

Abbreviation: CR: complete response; PD: progressive disease; PR: partial response.
Modified Lugano: Response-evaluated Criteria

Integrated Radiological Overall Response

PET-based Overall Response	CT/MRI-based Overall Response	Radiological Overall Response
CMR	Any [b]	CR
PMR	Any [b]	PR
NMR	Any [b]	SD
UNK [a]	CR/PR/SD + prior PET response of CMR (as long as the CT response remains stable/improves as compared to the previous timepoint when PET was available)	CR
UNK [a]	CR/PR + prior PET PMR or no PET (as long as the CT response remains stable/improves as compared to the previous timepoint when PET was available)	PR
UNK [a]	CR/PR + prior PET NMR	SD
UNK [a]	Any response except for PD (but has worsened from the previous timepoint when PET was available)	UNK
UNK [a]	UNK	UNK
UNK [a]	PD	PD
PMD	Any	PD

[a] PET not done/not available.
[b] Depending on the histology of the lymphoma. For lymphomas with variable avidity, CT PD could lead to an overall assessment of PD.

CMR: complete metabolic response; CR: complete response; NMR: no metabolic response; PD: progressive disease; PMD: progressive metabolic disease; PR: partial response; SD: stable disease; UNK: unknown.

Overall Response Assessment

Radiological Overall Response	Bone Marrow Aspirate/Biopsy	Clinical findings (Physical Examination/ Lesion Biopsy)	Overall Response Assessment
CR	Negative (+ 28 days from radiological assessment) or negative at baseline	No evidence of PD	CR

CR	Positive at baseline and positive (no new involvement) + 28 days from radiological assessment; or positive at the previous timepoint and not repeated	No evidence of PD	PR
PR/SD	Any but new or recurrent involvement	No evidence of PD	PR/SD
PD	Any	Any	PD
Any	New or recurrent BM involvement	Any	PD
Any	Any	New or recurrent lymphoma manifestation	PD

BM: bone marrow; CR: complete response; PD: progressive disease; PR: partial response; SD: stable disease; UNK: unknown.

Additional response assessment guidelines:

- Nodes or Extranodal lesions that split when disease is responding: If a confluent nodal mass splits into several discrete nodes, the individual product of the perpendicular diameters (PPDs) of the nodes should be summed together to represent the PPD of the split lesion; this PPD is added to the sum of the PPDs of the remaining lesions to measure response. If subsequent growth of any or all of these discrete nodes occurs, the nadir of each individual node is used to determine progression (as if each individual node was selected as a target lesion at baseline).
- Nodes or extranodal lesions that become confluent: If a group of target lymph nodes becomes confluent, the PPD of the current confluent mass should be compared with the sum of the PPDs of the individual nodes, with more than 50% increase in the PPD of the confluent mass compared with the sum of individual nodes necessary to indicate progressive disease. The LDi and shortest diameter are no longer needed to determine progression.
- The presence of residual symptoms in the absence of detectable disease by imaging does not preclude the designation CR.

C 3 International WG Consensus Response evaluation Criteria in Lymphoma (Younes et al 2017 [RECIL 2017])

The purpose of this document is to provide guidance to the Investigators on the assessment of efficacy in Hodgkin and Non-Hodgkin lymphoma studies conducted by AstraZeneca.

Complete response:

- Complete response is defined as a complete resolution of all target lesions by CT scans with complete normalization of FDG-PET uptake in all areas (Deauville score of 1–3), and bone marrow biopsy negativity (if it was positive or unknown at baseline). If pre-treatment PET scan was negative, lymph nodes that measured ≥ 15mm in the long axis should regress to < 10 mm. CR is also defined as achievement of a partial remission

by CT scan criteria (reduction in sum of longest diameters by CT imaging by > 30%) with normalization (Deauville score 1–3) of FDG-PET activity in FDG-avid lymphoma. However, because targeted agents may alter glucose uptake and/or metabolism, normalizing of FDG-PET imaging alone is not sufficient by itself to determine CR status unless accompanied with a significant (> 30%) decrease in the sum of diameters. Accordingly, a reduction in the sum of diameters by ≤ 30% with normalization of FDG-PET uptake should not be considered a CR unless documented by a negative tissue biopsy.

Partial response:

- Partial response is defined as a reduction of the sum of longest diameters of target lesions by ≥ 30%.

Minor response:

- This is a provisional category. Minor response is defined as a reduction in the SLD of target lesions by ≥ 10% but < 30%, without the appearance of any new lesions, and irrespective of PET scan results.

Stable disease:

- Stable disease is defined as changes in the SLD of targeted lesions ranging between reduction of < 10% to an increase by ≤ 20% without the appearance of a new lesion, and irrespective of PET results.

Progressive disease:

- Progressive disease is defined as an increase in the SLD of target lesions by > 20%, and/or appearance of a new lesion (≥ 10mmof the longest diameter) irrespective of FDG-PET results. In case of small FDG-PET avid lesions, a biopsy is recommended whenever possible. PD per RECIL is based on imaging findings only.

Table 1: RECIL 2017 Response categories based on assessment of target lesions

Table 1. RECIL 2017: Response categories based on assessment of target lesions

	% Change in sum of diameters of target lesions from nadir				
	CR	**PR**	**MR[a]**	**SD**	**PD**
% change from baseline	• Complete disappearance of all target lesions and all nodes with long axis <10mm. • ≥30% decrease in the sum of longest diameters of target lesions (PR) with normalization of FDG-PET	≥30% decrease in the sum of longest diameters of target lesions but not a CR	≥10% decrease in the sum of longest diameters of target lesions but not a PR (<30%)	<10% decrease or ≤ 20% increase in the sum of longest diameters of target lesions	• >20% increase in the sum of longest diameters of target lesions • For small lymph nodes measuring <15 mm post therapy, a minimum absolute increase of 5 mm and the long diameter should exceed 15 mm • Appearance of a new lesion
FDG-PET	Normalization of FDG-PET (Deauvile score 1-3)	Positive (Deauville score 4-5)	Any	Any	Any
Bone marrow involvement	Not involved	Any	Any	Any	Any
New lesions	No	No	No	No	Yes or No

CR, complete response; CT, computerized tomography; FDG-PET, [^{18}F]2-fluoro-2-deoxy-D-glucose; MR, minor response; PD, progression of disease; PR, partial response; SD, stable disease.
[a]A provisional category.

Table 2. Calculating sum of diameters to include small responsive lymph nodes

Target lesions	Baseline measurement (long axis; cm)	Nadir actual measurement (cm) method 1	Nadir normalized measurement (cm) method 2
Lesion 1	1.6	0.9	0 (resolved)
Lesion 2	1.7	1.4	1.4
Lesion 3	2	1.8	1.8
Sum of diameters	5.3	4.1	3.2
% change from baseline	N/a	23	40
Response designation	N/A	Minor response	Partial response (or CR if PET is negative)

CR, complete response; PET, positron emission tomography.

Key Differences Between RECIL 2017 and Lugano 2014

Parameter	Lugano 2014	RECIL 2017
Number of target lesions	Max. 6	Max. 3
Measurement method	Bi-dimensional: perpendicular Diameters (LDi, SDi)	Uni-dimensional: LDi
Extranodal lesion measurability criteria	LDi ≥ 10 mm	LDi ≥ 15 mm
Spleen assessment integration in the Overall Response	Present	Absent
Complete Response	Regression of all nodal masses to LDi ≤ 15 mm. No extralymphatic sites of disease	Regression of all target lesions and all nodes with LDi < 10 mm.
Minor Response	No	Yes, reduction in sum of long diameters between ≥ 10% and < 30%
Stable Disease	- 50% to + 50%	decrease < 10% to increase ≤ 20%
Progressive Disease	Increase in the sum of products of perpendicular diameters by > 50%, or any single lesion by > 50%	Increase in sum of the longest diameters by 20%. For relapse from CR, at least one lesion should measure 2 cm in the long axis with or without PET activity

Abbreviations: CR: complete response; LDi: long diameter of any target lesion; Max: maximum; PET: positron emission tomography; SDi: short diameter of any target lesion.

Appendix D Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

D 1 Definition of Adverse Events

An adverse event (AE) is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Note: B-Symptoms (Section 8.1.1) will not be reported as AEs.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

D 2 Definitions of Serious Adverse Event

A serious adverse event (SAE) is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse Events for **malignant tumors** reported during a study should generally be assessed as **Serious** AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **non-serious** AE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumor event in question is a new malignant tumor (ie, it is **not** the tumor for which entry into the study is a criterion and that is being treated by the investigational product under study and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors that – as part of normal, if rare, progression – undergo transformation (eg, Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumor.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment.
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine.
- Intensive treatment in an emergency room or at home for allergic bronchospasm.
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization.
- Development of drug dependency or drug abuse.

Intensity Rating Scale:

- Mild (awareness of sign or symptom, but easily tolerated),
- Moderate (discomfort sufficient to cause interference with normal activities),
- Severe (incapacitating, with inability to perform normal activities).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix D 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix D 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix D 2.

The grading scales found in the revised National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

- **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2** Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL)#.
- **Grade 3** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL##.
- **Grade 4** Life-threatening consequences; urgent intervention indicated.
- **Grade 5** Death related to AE.

A semicolon indicates ‘or’ within the description of the grade.

Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

Self-care ADL refer to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

D 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

D 4 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study-site staff or participant.

Medication error includes situations where an error:

- Occurred
- **Was identified and** participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, eg, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding Interactive Response Technology/Randomization and Trial Supply Management [IRT/RTSM] errors)
- Wrong drug administered to participant (excluding IRT/RTMS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTMS – including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AstraZeneca product.

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the Data Entry Site (DES) using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

Appendix E Handling of Human Biological Samples

E 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each center keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples while at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire lifecycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample lifecycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

E 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures participant’s withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.

- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action documented, and study site notified.

E 3 International Airline Transportation Association 6.2 Guidance Document

LABELING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900:

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name

- UN 3373 – Biological Substance, Category B are to be packed in accordance with UN 3373 and IATA 650.

Exempt – Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations.
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content.

Appendix F Optional Genomics Initiative Sample

F 1 Use/Analysis of DNA

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments, or medications. Therefore, where local regulations and Institutional Review Board/Independent Ethics committee allow, a saliva sample will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant´s DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- AstraZeneca will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

F 2 Genetic Research Plan and Procedures

Selection of Genetic Research Population

- All participants will be asked to participate in this genetic research. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion Criteria

For inclusion in this genetic research, participants must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol (CSP) and: Provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

- Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:
  - Previous allogeneic bone marrow transplant.
  - Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection.

Withdrawal of Consent for Genetic Research

- Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the main CSP.

Collection of Samples for Genetic Research

- The saliva sample for this genetic research will be obtained from the participants at screening. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an adverse event (AE). If for any reason the sample is not drawn at screening, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

Coding and Storage of DNA Samples

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years, from the date of last participant last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
- An additional second code will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).
- The link between the participant enrolment organization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

- The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed Consent

- The genetic component of this study is optional and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study the participant must sign and date both the consent form for the main study and the addendum for the Genomics Initiative component of the study. Copies of both signed and dated consent forms must be given to the participant and the original filed at the study center. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the participant understands that they may freely withdrawal from the genetic aspect of the study at any time.

Participant Data Protection

- AstraZeneca will not provide individual genotype results to participants, any insurance company, any employer, their family members, general physician unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a participant's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Data Management

- Any genetic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyses the samples.
- AstraZeneca and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organizations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results, but they will not be able to see individual participant data or any personal identifiers.
- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Appendix G Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

G 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

Specific guidance on managing liver abnormalities can be found in Section 6.6.8 and Appendix I.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated alanine aminotransferase (ALT) from a central laboratory and/or elevated total bilirubin (TBL) from a local laboratory.

The Investigator will also review adverse event (AE) data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug-Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting serious adverse events (SAEs) and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

G 2 Definitions

Potential Hy's Law

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3 x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2 x ULN at any point during the study following the start of study intervention irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law

AST or ALT ≥ 3 x ULN **together with** TBL ≥ 2 x ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

G 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 x ULN
- AST ≥ 3 x ULN
- TBL ≥ 2 x ULN

Central Laboratories Being Used:

When a participant meets any of the PHL identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the PHL identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca.
- Request a repeat of the test (new blood draw) by the central laboratory without delay.
- Complete the appropriate unscheduled laboratory eCRF module(s) with the original local laboratory test result.

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the participant meets PHL criteria (see Section G 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results).

Local Laboratories Being Used:

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative.
- Determine whether the participant meets PHL criteria (see Section G 2 for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory eCRF.

G 4 Follow-up

G 4.1 Potential Hy's Law Criteria Not Met

If the participant does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

G 4.2 Potential Hy's Law Criteria Met

If the participant does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study intervention (see Section G 6).
- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within one day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For participants who met PHL criteria prior to starting IMP, the Investigator is not required to submit a PHL SAE unless there is a significant change# in the participant's condition.
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the Investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. If central laboratories are used, this includes deciding which tests available in the HL laboratory kit should be used.

- Complete the 3 Liver eCRF Modules as information becomes available.

#A 'significant' change in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

G 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

G 6 Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Intervention

This section is applicable to participants with liver infiltration/involvement who meet PHL criteria on study intervention, having previously met PHL criteria at a study visit prior to starting study intervention.

At the first on study intervention occurrence of PHL criteria being met the Investigator will determine if there has been a **significant change** in the participants' condition[#] compared with the last visit where PHL criteria were met[#]

- If there is no significant change no action is required.
- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Section G 4.2.

#A 'significant' change in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

G 7 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a participant meets PHL criteria on study intervention and has already met PHL criteria at a previous on study intervention visit (see Section G 6).

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study, eg, chronic or progressing malignant disease, severe infection, or liver disease or did the participant meet PHL criteria prior to starting study intervention and at their first on study intervention visit as described in Section G 6 of this Appendix.

If **No**: follow the process described in Section G 4.2 for reporting PHL as an SAE

If **Yes**: Determine if there has been a significant change in the participant's condition[#] compared with when PHL criteria were previously met:

- If there is no significant change no action is required.
- If there is a significant change follow the process described in Section G 4.2 for reporting PHL as an SAE.

A 'significant' change in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

G 8 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended. When using a central laboratory, all recommended tests will be completed. When using a local laboratory, the list may be modified based on clinical judgment.

Hy's Law Laboratory Kit for Central Laboratories	
Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV HbsAg IgM and IgG anti-HBc HBV DNA [a] IgG anti-HCV HCV RNA [b] IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-Epstein-Barr virus
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin)[c]
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin [c] Transferrin saturation

[a] HBV DNA is only recommended when IgG anti-HBc is positive
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive
[c] CD-transferrin and Transferrin are not available in China. Study teams should amend this list accordingly

CMV: cytomegalovirus; GGT: gamma-glutamyl transferase; HAV: hepatitis A virus; HBc: hepatitis B core antigen; HbsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCV: hepatitis C virus; HEV: hepatitis E virus; HSV: herpes simplex virus; IgG: immunoglobulin G; IgM: immunoglobulin M; INR: international normalized ratio; LDH: lactate dehydrogenase.

G 9 References

(Aithal et al 2011, FDA 2009)

Aithal et al, 2011A ithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

Appendix H Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following agreement from AstraZeneca.

H 1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on-site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Consent for the alternative means of carrying our visits and assessments will be obtained at study entry.

H 2 Rescreening of Participants to Reconfirm Study Eligibility

Rescreening for screen failure due to study disruption can be performed in previously screened participants; refer to Section 5.4. The Investigator should confirm this with the designated Study Physician.

H 3 Telemedicine Visit to Replace On-site Visit (Where Applicable)

In this appendix, the term telemedicine visit refers to remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow adverse events and concomitant medications to be reported and documented.

H 4 Data Capture During Telemedicine or Home/Remote Visits

Data collected during telemedicine or home/remote visits will be captured by the qualified healthcare professional from the study site or third-party vendor service in the source documents, or by the participant themselves.

H 5 Schedule of Activities

For further details on the Schedule of Activities, refer to Section 1.3.

Appendix I Dosing Modification and Toxicity Management Guidelines for Sabestomig Monotherapy

Version 24 March 2022

The Toxicity Management Guidelines (TMGs) have been developed to assist Investigators with the recognition and management of toxicities associated with use of sabestomig in monotherapy and in combination with other anticancer drugs (ie, antineoplastic chemotherapy, targeted agents) which are administered concurrently or sequentially as part of a protocol-specific treatment regimen. The TMGs provide information for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions that may be observed with monotherapy or combination checkpoint inhibitor regimens, with specific instructions for checkpoint inhibitor-specific treatment modifications (including discontinuation) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references, incl. the product labels for the management of toxicities observed with other anticancer treatment.

Toxicity management for immune-mediated, infusion-related, and non-immune–mediated reactions associated with the use of sabestomig in monotherapy and in combination with other anticancer drugs (ie, antineoplastic chemotherapy, targeted agents) administered concurrently or sequentially – should therefore be performed in accordance with this Annex to Protocol, which for the purposes of submission and approval of substantial updates is maintained as a standalone document. The TMG updates are iterated by date and should be used in accordance with the CTCAE version specified in the Clinical Study Protocol (CSP).

Although the TMG versioning is independent of the CSP, the TMG Annex to the CSP should be read in conjunction with the CSP, where if applicable additional references for the management of toxicities observed with other anticancer treatment are included in the specific section of the CSP.

Dosing Modification and Toxicity Management Guidelines (TMGs) for Sabestomig

General Considerations Regarding Immune-Mediated Reactions

These guidelines are provided as a recommendation to support Investigators in the management of potential imAEs.

Immune-mediated events can occur in nearly any organ or tissue, therefore, these guidelines may not include all the possible immune-mediated reactions. Investigators are advised to take into consideration the appropriate practice guidelines and other society guidelines (eg, NCCN, ESMO) in the management of these events. Refer to the section of the table titled "Other -Immune-Mediated Reactions" for general guidance on imAEs not noted in the "Specific Immune-Mediated Reactions" section.
Early identification and management of imAEs are essential to ensure safe use of the study intervention. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying imAEs. Patients with suspected imAEs should be thoroughly evaluated to rule out any alternative etiologies (eg, disease progression, concomitant medications, infections). In the absence of a clear alternative etiology, all such events should be managed as if they were immune-mediated. Institute medical management promptly, including specialty consultation as appropriate. In general, withhold investigational drug(s) for severe (Grade 3) imAEs. Permanently discontinue investigational drug(s) for life-threatening (Grade 4) imAEs, recurrent severe (Grade 3) imAEs that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

Based on the severity of the imAE, treatment with sabestomig should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 28 days. More potent immunosuppressive agents such as TNF inhibitors (eg, infliximab) should be considered for events not responding to systemic steroids. Alternative immunosuppressive agents not listed in this guideline may be considered at the discretion of the Investigator based on clinical practice and relevant guidelines. With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring.

AE: Adverse event; ESMO: European Society for Medical Oncology; imAE: immune-mediated adverse event; NCCN: National Comprehensive Cancer Network; TNF: tumor necrosis factor.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Evaluate patients with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related aetiologies excluded and managed as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high-resolution CT scan. – Consider Pulmonary and Infectious Diseases consults. – For diagnosis of pneumonitis/ILD follow local clinical guidance in consultation with pulmonologist.
	Grade 1	No dose modifications required. However, consider holding investigational drug(s) as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up, and then as clinically indicated.
	Grade 2	Hold investigational drug(s) until Grade 2 resolution to Grade ≤ 1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤ 1, then the decision to reinitiate investigational drug(s) will be based upon treating physician's clinical judgment	**For Grade 2** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (eg, prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated, consider chest CT with contrast and repeat in 3 to 4 weeks. – If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
		and after completion of steroid taper.	– If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Consider, as necessary, discussing with study physician.
	Grade 3 or 4	Permanently discontinue investigational drug(s).	**For Grade 3 or 4** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious Diseases Consults; consider discussing with study physician, as needed. – Hospitalize the patient. – Supportive care (eg, oxygen). – If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab.
Diarrhea/Colitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – **WHEN SYMPTOMS OR EVALUATION INDICATE AN INTESTINAL PERFORATION IS SUSPECTED, CONSULT A SURGEON**

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			EXPERIENCED IN ABDOMINAL SURGERY IMMEDIATELY WITHOUT ANY DELAY. – **PERMANENTLY DISCONTINUE STUDY INTERVENTION FOR ANY GRADE OF INTESTINAL PERFORATION.** – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections), including testing for *Clostridium difficile* toxin, etc. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade events, including intestinal perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1	No dose modifications.	**For Grade 1** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), loperamide, and other supportive care measures. – If symptoms persist, consider checking lactoferrin; if positive, treat as Grade 2 below. If negative and no infection, continue Grade 1 management.
	Grade 2	Hold investigational drug(s) until resolution to Grade ≤ 1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤ 1, then investigational drug(s) can be resumed after completion of steroid taper.	**For Grade 2** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 2 to 3 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consult a GI specialist for consideration of further workup, such as imaging

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			and/or colonoscopy, to confirm colitis and rule out perforation. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg IV methylprednisolone, promptly start immunosuppressants such as infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider. [a] **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days.
	Grade 3 or 4	**Grade 3** • Hold investigational drug(s) until resolution to Grade ≤ 1; investigational drug(s) can be resumed after completion of steroid taper. Permanently discontinue investigational drug(s) for Grade 3 if toxicity does not improve to Grade ≤ 1 within 14 days. • Permanently discontinue investigational drug(s) for any grade of intestinal perforation in any patient treated with study intervention.	**For Grade 3 or 4** – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 2 days, continue steroids and promptly add further immunosuppressants (eg, infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – **If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.**

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
		• Permanently discontinue investigational drug(s) for recurrent ≥ Grade 3 colitis **Grade 4** Permanently discontinue investigational drug(s).	
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – Consult a nephrologist. – Monitor for signs and symptoms that may be related to changes in renal function (eg, routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decreased urine output, or proteinuria). – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, infections, recent IV contrast, medications, fluid status). – Consider using steroids in the absence of a clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade events.
	Grade 1	No dose modifications.	**For Grade 1** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			– Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.
	Grade 2	Hold investigational drug(s) until resolution to Grade ≤ 1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤ 1 or baseline, then resume investigational drug(s) after completion of steroid taper.	**For Grade 2** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent beyond 3 to 5 days or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup. When event returns to baseline, resume investigational drug(s) and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4	Permanently discontinue investigational drug(s).	**For Grade 3 or 4** – Carefully monitor serum creatinine daily. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup and prompt treatment with an immunosuppressant in consultation with a nephrologist.
Rash or Dermatitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for	**General Guidance**	**For Any Grade** – Monitor for signs and symptoms of dermatitis (rash and pruritus).

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
(Including Pemphigoid)	definition of severity/grade depending on type of skin rash)		– **HOLD INVESTIGATIONAL DRUG(S) IF STEVENS-JOHNSON SYNDROME (SJS), TOXIC EPIDERMAL NECROLYSIS (TEN), OR OTHER SEVERE CUTANEOUS ADVERSE REACTION (SCAR) IS SUSPECTED.** – **PERMANENTLY DISCONTINUE INVESTIGATIONAL DRUG(S) FOR ANY GRADE OF CONFIRMED SJS, TEN, OR SCAR.**
	Grade 1	No dose modifications.	**For Grade 1** – Consider symptomatic treatment, including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, normalize, lotion, or institutional standard).
	Grade 2	For persistent (> 1 week) Grade 2 events, hold investigational drug(s) until resolution to Grade ≤ 1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤ 1 or baseline, then resume investigational drug(s) after completion of steroid taper.	**For Grade 2** – Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy. – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider discussing with study physician, as needed, and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event persists for >1 week or recurs.
	Grade 3 or 4	**For Grade 3** • Hold investigational drug(s) until resolution to Grade ≤ 1 or baseline.	**For Grade 3 or 4** – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines].

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
		• If toxicity improves to Grade ≤ 1 or baseline, then resume investigational drug(s) after completion of steroid taper. • If toxicity worsens, then treat as Grade 4. **For Grade 4** Permanently discontinue investigational drug(s).	– Consider skin biopsy (preferably more than 1) as clinically feasible. Consider, as necessary, discussing with study physician.
Endocrinopathy (eg, hyperthyroidism, thyroiditis, hypothyroidism, type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency)	**Any Grade** (Depending on the type of endocrinopathy, refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – Consider consulting an endocrinologist for endocrine events. – Consider discussing with study physician, as needed. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behaviour changes, mental status changes, photophobia, visual field cuts, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (eg, blood glucose and ketone levels, HgA1c).If a patient experiences an AE that is thought to be possibly of autoimmune nature (eg, thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the Investigator should send a blood sample for appropriate autoimmune antibody testing.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			– Investigators should ask participants with endocrinopathies who may require prolonged or continued hormonal replacement, to consult their primary care physicians or endocrinologists about further monitoring and treatment after completion of the study.
	Grade 1	No dose modifications.	**For Grade 1** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consulting an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
	Grade 2, 3, or 4	• For Grade 2 to 4 endocrinopathies other than hypothyroidism and type 1 diabetes mellitus, consider holding investigational drug(s) dose until acute symptoms resolve. • Investigational drug(s) can be resumed once patient stabilizes and after completion of steroid taper.	**For Grade 2, 3, or 4** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (eg, 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (eg, hydrocortisone, sex hormones).

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
		• Patients with endocrinopathies who may require prolonged or continued steroid replacement (eg, adrenal insufficiency) can be retreated with investigational drug(s) if the patient is clinically stable as per Investigator or treating physician's clinical judgement. • If toxicity worsens, then treat based on severity.	– Isolated hypothyroidism may be treated with replacement therapy, without investigational drugs interruption, and without corticosteroids. – Isolated type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, and without corticosteroids. **Only hold investigational drug(s) in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis**. – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
Amylase/Lipase increased	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – Assess for signs/symptoms of pancreatitis. – Consider appropriate diagnostic testing (eg, abdominal CT with contrast, MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT). – If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy. Consider other causes of elevated amylase/lipase. – If evidence of pancreatitis, manage according to pancreatitis recommendations.
	Grade 1	No dose modifications.	
	Grade 2, 3, or 4	**For Grade 2, 3, or 4** In consultation with relevant pancreatic specialist consider continuing investigational drug(s) if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase.	
Acute Pancreatitis	**Any Grade**	**General Guidance**	**For Any Grade** – Consider Gastroenterology referral.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
	(Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)		
	Grade 1	No dose modifications.	**For Grade 1** – IV hydration. – Manage as per amylase/lipase increased (asymptomatic).
	Grade 2, 3, or 4	**For Grade 2** Hold investigational drug(s) until resolution to Grade ≤ 1. **For Grade 3 or 4** Permanently discontinue investigational drug(s).	**For Grade 2, 3, or 4** – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – IV hydration.
Neurotoxicity (to include but not limited to non-infectious meningitis, non-infectious encephalitis, and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (Depending on the type of neurotoxicity, refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (eg, electromyogram and nerve conduction investigations). – Perform symptomatic treatment with neurological consult as appropriate. – **FOR TRANSVERSE MYELITIS OR MENINGOENCEPHALITIS, PERMANENTLY DISCONTINUE INVESTIGATIONAL DRUG(S) FOR ANY GRADE.**

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
	Grade 1	No dose modifications.	**For Grade 1** – See "Any Grade" recommendations above.
	Grade 2	• For acute motor neuropathies or neurotoxicity, hold investigational drug(s) until resolution to Grade ≤ 1. • For sensory neuropathy/neuropathic pain, consider holding investigational drug(s) until resolution to Grade ≤ 1. • Permanently discontinue investigational drug(s) if Grade 2 imAE does not resolve to Grade ≤ 1 within 30 days. • If toxicity worsens, then treat as Grade 3 or 4.	**For Grade 2** – Consider, as necessary, discussing with the study physician. – Obtain neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with an additional immunosuppressant (eg, IV IG or other immunosuppressant depending on the specific imAE).
	Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue investigational drug(s).	**For Grade 3 or 4** – Consider, as necessary, discussing with study physician. – Obtain neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite IV corticosteroids, consider additional workup and promptly treat with an additional immunosuppressant (eg, IV IG or other immunosuppressant depending on the specific imAE).

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			– Once stable, gradually taper steroids over ≥ 28 days.
Peripheral neuromotor syndromes	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. – Neurophysiologic diagnostic testing (eg, electromyogram and nerve conduction investigations, and “repetitive stimulation” if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG. – **FOR CONFIRMED MYASTENIC SYNDROME/MYASTHENIA GRAVIS, GUILLAIN-BARRE SYNDROME**

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			PERMANENTLY DISCONTINUE INVESTIGATIONAL DRUG(S) FOR ANY GRADE.
	Grade 1	No dose modifications.	**For Grade 1** – Consider discussing with the study physician, as needed. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Consult a neurologist.
	Grade 2	Hold investigational drug(s) until resolution to Grade ≤ 1. Permanently discontinue investigational drug(s) if it does not resolve to Grade ≤ 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **PERMANENTLY DISCONTINUE INVESTIGATIONAL DRUG(S) FOR CONFIRMED MYASTENIC SYNDROME/MYASTHENIA GRAVIS OR GUILLAIN-BARRE OF ANY GRADE.**	**For Grade 2** – Consider discussing with the study physician, as needed. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Consult a neurologist. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine). MYASTHENIA GRAVIS: o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AchE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. o Avoid medications that can worsen myasthenia gravis. GUILLAIN-BARRE: o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 3 or 4	**For Grade 3** • Hold investigational drug(s) until resolution to Grade ≤ 1. • Permanently discontinue investigational drug(s) if Grade 3 imAE does not resolve to Grade ≤ 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4**	**For Grade 3 or 4** – Consider discussing with study physician, as needed. – Recommend hospitalization. – Monitor symptoms and consult a neurologist. MYASTHENIA GRAVIS: o Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. o If myasthenia gravis-like neurotoxicity present, consider starting AchE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
		Permanently discontinue investigational drug(s). **PERMANENTLY DISCONTINUE INVESTIGATIONAL DRUG(S) FOR CONFIRMED MYASTENIC SYNDROME/MYASTHENIA GRAVIS OR GUILLAIN-BARRE OF ANY GRADE.**	o Avoid medications that can worsen myasthenia gravis. GUILLAIN-BARRE: o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Myocarditis For patients with asymptomatic laboratory (eg, elevated troponin or N-terminal pro-hormone BNP (NT-proBNP) / brain natriuretic peptide (BNP) > ULN) or cardiac imaging abnormalities (including patients with elevated troponin at baseline who have any further increase after dosing), follow the guidelines as for Grade 1.	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider discussing with the study physician/medical monitor, as needed. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (eg, pulmonary embolism, congestive heart failure, malignant pericardial effusion). – Consult a cardiologist early, to promptly assess whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, troponin, NT-proBNP/BNP, CPK, CK-MB, ECG, ECHO, monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Consider cardiac MRI with

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			T1/T2 mapping to assess for the presence of myocardial edema, and/or endomyocardial biopsy to make an accurate diagnosis when it is possible, and the clinical condition of the patient allows. – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections).
	Grade 1	Hold investigational drug during diagnostic work-up for other etiologies. If investigational drug is held, resume if all diagnostic work-up is negative and no persistent worsening of elevated troponin is noted.	**For Grade 1 (no definitive findings)** - Consider cardiology consult. - Consider diagnostic work-up coordinated with cardiologist that may include evaluation for clinical symptoms, NT-proBNP/BNP, serial measurement of CPK, CK-MB, and troponin at 6 and 12 hours to evaluate for acute coronary syndrome, ECG, ECHO and/or cardiac MRI, pulse oximetry (resting and exertion), and other laboratory work-up as clinically indicated. - Consider using steroids if clinical suspicion is high. - Monitor and closely follow up in 24 to 48 hours with repeat NT-proBNP, CPK, CK-MB, troponin, ECG, and other work-up as clinically indicated.
	Grade 2	Hold investigational drug during diagnostic workup. If immune mediated myocarditis is confirmed, therapy may be re-initiated once the participant has recovered and where the benefit risk balance is deemed positive following consultation between Investigator and cardiologist. Upon re-initiation it is highly recommended that the	– Monitor symptoms daily, hospitalize. – Supportive care (eg, oxygen). – Consider laboratory workup and imaging as described under general guidance for all grades of myocarditis. – Consider cardiology consult to determine if and when to complete diagnostic procedures including a cardiac biopsy. – Promptly start high-dose pulse IV methylprednisolone 1 gram/day for 3 days and then 2 mg/kg prednisone daily. – If no improvement within 2 to 3 days despite IV methylprednisolone at 1 gram/day, promptly start additional immunosuppressives (eg, tacrolimus, mycophenolate mofetil, or TNF inhibitors such as

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
		participant is assessed by a cardiologist on a regular basis.	infliximab at 5 mg/kg IV which may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Infliximab is contraindicated for patients who have heart failure. – Close monitoring for worsening symptoms or signs of myocarditis needs to be performed before and during the tapering of corticosteroid or other immunosuppressive. – If patient continues to worsen, treat as Grade 3/4.
	Grade 3 or 4	• Permanently discontinue investigational drug.	– Monitor symptoms daily, hospitalize. – Supportive intensive care (eg, oxygen, circulatory support including hemodynamic, temporary pacing, arrhythmia treatment as needed). – Consider laboratory workup and imaging as described under general guidance for all grades of myocarditis. – Consider urgent cardiology consultation to determine if and when to complete diagnostic procedures, including a cardiac biopsy. – Promptly start high-dose pulse high-dose IV methylprednisolone 1 gram/day for 3 days and then 2 mg/kg prednisone daily. Consider initiation ACE inhibitors or ARBs for LV dysfunction, if clinically appropriate. – If no improvement within 3 to 5 days despite IV methylprednisolone, consider starting additional immunosuppressives such as tacrolimus or mycophenolate mofetil. In unstable patients who do not respond to corticosteroids, consider antithymocyte globulin or IV immunoglobulin. – Close monitoring for worsening symptoms or signs of myocarditis needs to be performed before and during the tapering of corticosteroid or other immunosuppressive.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
Myositis/ Polymyositis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (ie, consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			Barium swallow for evaluation of dysphagia or dysphonia. – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections).
	Grade 1	• No dose modifications.	**For Grade 1** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
	Grade 2	• Hold investigational drug(s) until resolution to Grade ≤ 1. • Permanently discontinue investigational drug(s) if it does not resolve to Grade ≤ 1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If clinical course is **not** rapidly progressive, start systemic steroids (eg, prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 2 to 3 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (eg, infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider).

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.
	Grade 3 or 4	**For Grade 3** • Hold investigational drug(s) until resolution to Grade ≤ 1. • Permanently discontinue investigational drug(s) if Grade 3 imAE does not resolve to Grade ≤ 1 within 30 days or if there are signs of respiratory insufficiency. • Permanently discontinue investigational drug(s) for recurrent ≥ Grade 3 myositis **For Grade 4** • Permanently discontinue investigational drug(s).	**For Grade 3 or 4** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult – Consider discussing with the study physician, as needed. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (eg, infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.** – Consider whether patient may require IV IG, plasmapheresis.

[a] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD.
[b] FDA Liver Guidance Document 2009 Guidance for Industry: Drug-induced Liver Injury – Premarketing Clinical Evaluation.
[c] NCCN Clinical Practice Guidelines in Oncology "Management of Immunotherapy-Related Toxicities" Version 1.2020 – December 2019.
AchE: Acetylcholine esterase; ACTH: adrenocorticotropic hormone; ADL: Activities of daily living; AE: Adverse event; ALP: Alkaline phosphatase test; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CK-MB: creatinine kinase isoenzyme MB; CT: Computed tomography; CTC: Common Terminology Criteria; CTCAE: Common Terminology Criteria for Adverse Events; ILD: Interstitial lung disease; imAE: immune-mediated adverse event; IG: Immunoglobulin; IV: Intravenous; GI: Gastrointestinal; LFT: Liver function tests; LLN: Lower limit of normal; MRI: Magnetic resonance imaging; NCI: National Cancer Institute; NCCN: National Comprehensive Cancer Network; PJP: *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO: per os (taken orally); T3: Triiodothyronine; T4: Thyroxine; TBL: Total bilirubin; TNF: Tumor necrosis factor; TSH: Thyroid-stimulating hormone; ULN: Upper limit of normal.

Management of immune-mediated liver injury caused by immune checkpoint inhibitors (ILICI)

Recommended management of treatment-emergent abnormal hepatic biochemical tests in clinical trials with sabestomig (patients with normal baseline ALT, AST[a])

Treatment Emergent ALT/AST Elevations	TBL[b] Values at Time of Treatment Emergent ALT Elevation	Investigational drugs treatment adjustment and additional therapy	Monitoring and evaluation
Normal	Isolated total blood bilirubin elevation > 3 × ULN	Discontinue investigational drug.	Repeat blood tests[d] within 2 to 3 days. Initiate close monitoring and evaluation[e].
≤ 3 x ULN	Normal. Patients with Gilbert's syndrome: No change in baseline TBL.	Continue treatment.	Repeat blood tests[c] within 1 to 2 weeks.
> 3 x ULN	Normal. Patients with Gilbert's syndrome: No change in baseline TBL.	Withhold investigational drug. If rising ALT/AST when re-checked, start prednisone/prednisolone 1 mg/kg/d[f]. If ALT/AST improve to ≤ 3.0 x ULN, resume treatment after completion of steroid taper to equivalent of prednisone ≤ 10 mg/day.	Repeat blood tests[d] within 2 to5 days. Initiate close monitoring and evaluation[e].
	TBL ≥ 2 x ULN. Patients with Gilbert's syndrome: Doubling of direct bilirubin.	Discontinue investigational drug. Start prednisone/prednisolone 1 to 2 mg/kg/d[f].	Repeat blood tests[d] within 2 to 3 days. Initiate close monitoring and evaluation[e].
> 5 x ULN	Normal. Patients with Gilbert's syndrome: No change in baseline TBL.	Withhold investigational drug. Start prednisone/prednisolone 1 to 2 mg/kg/d[f]. Resume treatment if elevations downgrade to AST and ALT ≤ 3.0 x ULN within 14 days, and after completion of steroid taper to equivalent of prednisone ≤ 10 mg/day. Otherwise discontinue investigational drug permanently.	Repeat blood tests[d] within 2 to 3 days. Initiate close monitoring and evaluation[e]. Treatment shall only resume following consultation with a hepatologist and based on a benefit/risk assessment for the affected participant.
> 10 x ULN	Normal or elevated.	Discontinue investigational drug. Start prednisone/prednisolone 1 to 2 mg/kg/d[g].	Repeat blood tests[d] within 2 to 3 days. Initiate close monitoring and evaluation[e].

Recommended management of treatment-emergent abnormal hepatic biochemical tests in clinical trials with sabestomig (patients with abnormal baseline ALT, AST[a])

Treatment Emergent ALT/AST Elevations	TBL[b] Values at Time of Treatment Emergent ALT Elevation	Investigational drugs treatment adjustment and additional therapy	Monitoring and evaluation
> bsl	Normal. Patients with Gilbert's syndrome: No change in baseline TBL.	Continue treatment.	Repeat blood tests[c] within 1 to 2 weeks.
> 2 x bsl	Normal. Patients with Gilbert's syndrome: No change in baseline TBL.	Withhold investigational drug. If rising ALT/AST when re-checked, start prednisone/prednisolone 1 mg/kg/d[f]. If ALT/AST improve to ≤ 2 x bsl, resume treatment after completion of steroid taper to equivalent of prednisone ≤ 10 mg/day.	Repeat blood tests[d] within 2 to 5 days. Initiate close monitoring and evaluation[e].
	TBL ≥2 x ULN. Patients with Gilbert's syndrome: Doubling of direct bilirubin	Discontinue investigational drug. Start prednisone/prednisolone 1 to 2 mg/kg/d[f].	Repeat blood tests[d] within 2 to 3 days. Initiate close monitoring and evaluation[e].
> 3 x bsl	Normal. Patients with Gilbert's syndrome: No change in baseline TBL.	Withhold investigational drug. Start prednisone/prednisolone 1 to 2 mg/kg/d[f]. Resume treatment if elevations downgrade to AST and ALT ≤ 2 x bsl within 14 days, and after completion of steroid taper to equivalent of prednisone ≤ 10 mg/day. Otherwise discontinue investigational drug permanently.	Repeat blood tests[d] within 2 to 3 days. Initiate close monitoring and evaluation[e].
> 5 x bsl	Normal or elevated.	Discontinue investigational drug. Start prednisone/prednisolone 1 to 2 mg/kg/d[g].	Repeat blood tests[d] within 2 to 3 days. Initiate close monitoring and evaluation[e].

a. Use of serum ALT is preferred over AST due to its higher hepatic specificity. ALP is not included in this table as isolated ALP elevation is often related to the underlying malignancy and uncommonly related to ILICI. Furthermore, there are limited published data regarding management of ILICI in patients who develop isolated ALP elevation during ICI treatment.
b. Measurement of total and conjugated (or direct) bilirubin is recommended to help identify patients with indirect hyperbilirubinemia due to Gilbert's syndrome or hemolysis versus liver injury.
c. Recommended blood tests include ALT, AST, ALP, GGT, TBL.
d. Recommended blood tests include: ALT, AST, ALP, GGT, TBL, DBL, CK, INR.
e. Initial monitoring should be 2–3 times a week. Frequency of monitoring may be adjusted based on clinical scenario and severity of injury. Monitoring should continue until ALT/AST levels return to ≤ 3 x ULN, regardless of whether or not the investigational drugs have been discontinued. For recommendations on diagnostic follow-up and evaluation of potential alternative etiologies see Table 1 below.
f. Oral prednisone/prednisolone: if hepatic biochemical tests worsen on oral prednisone/prednisolone, change to IV (methyl)prednisolone. Once ALT/AST return to ≤ 3 x ULN, corticosteroids can be weaned over 2–4 weeks. Treatment with investigational drug(s) may be resumed with close monitoring, once prednisone/ prednisolone dose ≤ 10 mg/day.
g. IV (methyl)prednisolone: if worsening continues on IV (methyl)prednisolone, consider adding MMF 500–1000 mg twice daily. Once hepatic biochemical tests return to Grade 1, corticosteroids can be weaned over 4 weeks. Treatment with investigational drug(s) may be resumed with close monitoring, once prednisone/prednisolone dose ≤ 10 mg/day.

Abbreviations: bsl: baseline; CK creatinine kinase; DBL direct Bilirubin; GGT Gamma-glutamyl transferase; INR international normalized ratio; IV: intravenous; PO: per os (taken orally); ULN upper limit of normal

Table 1 – Recommended evaluation of patients with treatment-emergent ALT elevation during a clinical trial with immune checkpoint inhibitors[a]

Recommended evaluation	Competing causes of abnormal liver tests
1st Line Testing	
Thorough history of symptoms, co-existing medical conditions, concomitant medications, dietary and nutritional supplements, excessive exercise or muscle injury, alcohol consumption, illicit substances.	Systemic infection/sepsis; ischemic/congestive hepatic injury; gallstone disease; alcoholic liver disease; muscle injury/rhabdomyolysis; acetaminophen toxicity; DILI due to another drug, herbal or dietary supplement.
Serum CK	Muscle injury/rhabdomyolysis[b]
Anti-HAV (IgM)	Acute HAV infection
HbsAg • Anti-HBc IgG, IgM, HBV DNA	Acute hepatitis B; Exacerbation of chronic hepatitis B
Anti-HCV • HCV RNA (PCR)	Acute hepatitis C Exacerbation of chronic hepatitis C[c]

Anti-HEV (IgG, IgM); HEV RNA[d]	Acute hepatitis E
ANA, ASMA • Quantitative immunoglobulins (IgG, IgM, IgA)	Autoimmune hepatitis[e]
Hepatobiliary imaging (ultrasonography, CT scan, MRI, MRCP)[f]	Biliary obstruction; pancreatitis; gallstones; portal-vein/hepatic vein thrombosis; hepatic metastasis
2nd Line Testing	
Serological tests for EBV, CMV, HSV. • May need to obtain acute and convalescent serological tests • EBV-DNA, CMV-DNA, HSV-DNA by PCR. Liver biopsy needed to confirm HSV	Hepatic injury caused by CMV, EBV, HSV
Additional Tests[g]	
Anti-LKM-1	Autoimmune hepatitis
Serum EtOH • Urinary ethyl-glucuronide and ethyl-sulfate[h], Serum phosphatidylethanol[i]	Alcohol related liver disease
Serum acetaminophen level; Acetaminophen protein adducts	Acetaminophen toxicity
Review of blood pressure, pulse, electrocardiogram, echocardiogram, cardiology consult	Ischemic or congestive hepatic injury
Urine toxicology screen	Hepatotoxicity due to cocaine, amphetamines, opiates and other illicit substances
Anti-HDV	Hepatitis D
Blood or urine cultures	Systemic infection, sepsis
Blood ceruloplasmin, serum copper • Slit lamp eye examination for Kayser-Fleischer rings, genetic testing	Wilson's disease

Abbreviations used: CMV, Cytomegalovirus; CK, creatine kinase; DILI, drug-induced liver injury; EBV, Epstein Bar Virus; HBV, hepatitis B virus, HbsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; HSV; Herpes Simplex Virus; LKM-1, liver kidney microsomal type 1.

Adapted from Arie Regev, et al., Journal of Autoimmunity, https://doi.org/10.1016/j.jaut.2020.102514

a Extent and type of work-up may vary by patient's history, severity of liver injury, underlying disease, and geography.
b Serum AST typically (although not always) is higher than ALT.
c Acute hepatitis C may be anti-HCV negative but HCV RNA positive.
d If anti-HEV IgM positive, consider confirmation with HEV RNA by nested PCR.
e A liver biopsy is needed to confirm a diagnosis of AIH.
f If cholestatic injury, magnetic resonance cholangiopancreatography may be recommended.
g Based on medical history and clinical judgment.
h Alcohol consumption in past 3 to 5 days.
i Alcohol consumption in past 3 weeks.

Other–Immune-Mediated Reactions (incl. hypersensitivity reactions)

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	Dose Modifications	Toxicity Management
Any Grade	Note: It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them are not noted specifically in these guidelines (eg, immune thrombocytopenia, haemolytic anaemia, uveitis, vasculitis).	– The study physician may be contacted for immune-mediated reactions not listed in the "specific immune-mediated reactions" section. – Thorough evaluation to rule out any alternative etiology (eg,, disease progression, concomitant medications, and infections). – Consultation with relevant specialist. – Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Monitor as clinically indicated
Grade 2	• Hold investigational drug(s) until resolution to ≤ Grade 1 or baseline. • If toxicity worsens, then treat as Grade 3 or Grade 4. • Investigational drug(s) can be resumed once event stabilizes to Grade ≤ 1 after completion of steroid taper. • Consider whether investigational drug(s) should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality when they do not rapidly improve to Grade < 1 upon treatment with systemic steroids and following full taper.	**For Grade 2, 3, or 4** Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and other society guidelines (eg, NCCN, ESMO).
Grade 3	Hold investigational drug(s).	
Grade 4	Permanently discontinue investigational drug(s).	

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."
AE: Adverse event; CTCAE: Common Terminology Criteria for Adverse Events; NCI: National Cancer Institute.

Infusion-Related Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	Dose Modifications	Toxicity Management
Any Grade	General Guidance.	**For Any Grade** – Manage per institutional standard at the discretion of Investigator. – Monitor patients for signs and symptoms of infusion-related reactions (eg, fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (eg, generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1** The infusion rate of investigational drug(s) may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2** • The infusion rate of investigational drug(s) may be decreased 50% or temporarily interrupted until resolution of the event. • Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2** – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the Investigator. – Consider premedication per institutional standard prior to subsequent doses. – Steroids should not be used for routine premedication of Grade ≤ 2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue investigational drug(s).	**For Grade 3 or 4** – Manage severe infusion-related reactions per institutional standards (eg, IM epinephrine, followed by IV diphenhydramine and famotidine, and IV glucocorticoid).

CTCAE: Common Terminology Criteria for Adverse Events; IM: intramuscular; IV: intravenous; NCI: National Cancer Institute.

Cytokine Release Syndrome (CRS)

NOTE: Dose modification (ie, hold and discontinuation) and toxicity management guidelines for CRS are provided based on 2018 CRS Consensus Grading by Lee et al[1].

CRS is a systemic inflammatory response caused by the release of cytokines, chemokines and interferon (IFN)-inducible genes that are expected to induce both innate and adaptive immunity. Clinically, CRS consists of a constellation of symptoms that may include fever, nausea, headaches, flushing, flu-like symptoms, tachypnea, hypoxemia, tachycardia, hypotension, confusion, etc, along with possible laboratory changes in the cell blood count, liver function tests, C-reactive protein, and ferritin. Because these symptoms can progress quickly to become potentially life-threatening, suggested guidelines for the management of sabestomig-related CRS are provided below. These general guidelines are to assist the investigator in the diagnosis and management of the potential immune-mediated/CRS events and are not meant to supplant discussions with the Medical Monitor. Accordingly, please notify the Medical Monitor as soon as possible for all AEs consistent with CRS.

1 Riegler LL, Jones GP, Lee DW. Current approaches in the grading and management of cytokine release syndrome after chimeric antigen receptor T-cell therapy. Ther Clin Risk Manag. 2019;15:323-35.

Cytokine Release Syndrome

Severity Grade of the Event	Dose Modifications	Toxicity Management
Grade 1 Fever (≥ 100 ºF or ≥ 38ºC)*	No dose modifications.	Immediately inform Medical Monitor. – Patients should be thoroughly evaluated to rule out any alternative etiology. – Symptomatic treatment (eg, antipyretics). – Close monitoring of the vital parameters and of biologic lab tests (including CBC, LFTs, CRP, and ferritin) should be performed until resolution of symptoms.
Grade 2 Fever (≥ 100 ºF or ≥ 38ºC)* with hypotension not requiring vasopressors and/or hypoxia requiring low-flow nasal cannula or blow-by oxygen	Hold sabestomig until resolution to Grade ≤ 1. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity does not improve to Grade ≤ 1 within 48 hours, then permanently discontinue sabestomig. • If toxicity improves to Grade ≤ 1 within 48 hours, then sabestomig can be resumed under the following conditions: – The event stabilizes and is controlled. – The patient is clinically stable as per investigator or treating physician's clinical judgement. – Prednisone equivalent dose is ≤ 10 mg/day.	– Immediately inform Medical Monitor. – Recommend hospitalization for management and observation until recovery. – Close monitoring of the vital parameters and of biologic lab tests including CBC, LFTs, CRP and ferritin should be performed until the resolution of the symptoms. – Aggressive supportive care including fluid and electrolyte replacement. – Systemic corticosteroids (1-2 mg/kg/day of methylprednisolone IV) should be considered. – Tocilizumab may be considered per the Investigator's institutional SOPs. – If the symptoms do not improve within 48 hours despite appropriate medical management, proceed with measures applicable to Grade 3.
Grade 3 Fever (≥ 100 ºF or ≥ 38ºC)* with hypotension requiring one vasopressor with or without vasopressin and/or hypoxia requiring high-flow nasal cannula, facemask, non-rebreather mask, or Venturi mask not attributable to any other cause	Permanently discontinue investigational drug(s).	- Immediately inform Medical Monitor. - Proceed with the CRS management related to Grade 2. - Consider higher dose corticosteroids of 1-2 mg/kg every 12 hours of methylprednisolone IV (ie, 2-4 mg/kg/day).

Cytokine Release Syndrome

Severity Grade of the Event	Dose Modifications	Toxicity Management
Grade 4 Fever (≥ 100 ºF or ≥ 38ºC)* with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation) not attributable to any other cause	Permanently discontinue sabestomig.	Immediately inform Medical Monitor. Proceed with the CRS management related to Grade 3.

*In patients who have CRS then receive tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia. BiPAP, bilevel positive airway pressure; CBC, complete blood count; CPAP, continuous positive airway pressure; CRP, C-reactive protein; CRS, cytokine release syndrome; IV, intravenous; LFT, liver function test; SOP, standard operating procedure.

Non-Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study intervention (ie, events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold investigational drug(s) until resolution to ≤ Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold investigational drug(s) until resolution to ≤ Grade 1 or baseline. For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume investigational drug(s) administration. Otherwise, discontinue investigational drug(s).	Treat accordingly, as per institutional standard.
Grade 4	Discontinue investigational drugs (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with AstraZeneca).	Treat accordingly, as per institutional standard.

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."
AE: Adverse event; CTCAE: Common Terminology Criteria for Adverse Events; NCI: National Cancer Institute.

Appendix J Clinical Outcome Assessment Questionnaires

This appendix includes example copies of the following patient-reported outcome assessment questionnaires:

Sub-Appendix	Clinical Outcome Assessment	Figure
J 1	National Cancer Institute (NCI) Patient Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE)	Figure 5
J 2	National Cancer Institute (NCI) Pediatric Patient Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE)	Figure 6
J 3	CCI	CCI
J 4	CCI	CCI
J 5	CCI	CCI
J 6	Patient Global Impression of Treatment Tolerability (PGI-TT)	Figure 10
J 7	CCI	CCI
J 8	CCI	CCI
J 9	CCI	CCI

J 1 National Cancer Institute Patient Reported Outcomes-Common Terminology Criteria for Adverse Events

Figure 5 NCI PRO-CTCAE Questionnaire Example

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 27 January 2020

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days...

1.	In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much
2.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
3.	In the last 7 days, how OFTEN did you have VOMITING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
4.	In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
5.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 27 January 2020

6.	In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

7.	In the last 7 days, what was the SEVERITY of your COUGH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did COUGH INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

8.	In the last 7 days, how OFTEN did you feel a POUNDING OR RACING HEARTBEAT (PALPITATIONS)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your POUNDING OR RACING HEARTBEAT (PALPITATIONS)? at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

9.	In the last 7 days, did you have any RASH?	
	○ Yes	○ No

10.	In the last 7 days, what was the SEVERITY of your ITCHY SKIN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 27 January 2020

11.	In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

12.	In the last 7 days, how OFTEN did you have a HEADACHE?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your HEADACHE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did your HEADACHE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

13.	In the last 7 days, how OFTEN did you have ACHING MUSCLES?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your ACHING MUSCLES at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did ACHING MUSCLES INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

14.	In the last 7 days, how OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 27 January 2020

15.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

16.	In the last 7 days, did you BRUISE EASILY (BLACK AND BLUE MARKS)?				
	○ Yes		○ No		

17.	In the last 7 days, how OFTEN did you have SHIVERING OR SHAKING CHILLS?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your SHIVERING OR SHAKING CHILLS at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

18.	In the last 7 days, how OFTEN did you have NOSEBLEEDS?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NOSEBLEEDS at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

Basch E, Reeve BB, Mitchell SA, et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). J Natl Cancer Inst 2014;106(9). Available at: https://healthcaredelivery.cancer.gov/pro-ctcae/. Accessed 27 January 2020.

J 2 National Cancer Institute Pediatric Patient Reported Outcomes-Common Terminology Criteria for Adverse Events

Figure 6 NCI Peds-PRO-CTCAE Questionnaire Example

NCI Ped-PRO-CTCAE® CUSTOM SURVEY

Item subset derived from Ped-PRO-CTCAE® Item Library Version 1.0
English
Form Created on 19-June-2023
https://healthcaredelivery.cancer.gov/pro-ctcae/builder-ped.html

Please answer the following questions:

1.	a. In the past 7 days, how often did you feel sick to your stomach (nausea)?
	○ Never
	○ Sometimes
	○ Most of the time
	○ Almost all the time
	b. In the past 7 days, how bad was your feeling sick to your stomach (nausea)?
	○ Did not have any
	○ A little bad
	○ Bad
	○ Very bad
	c. In the past 7 days, how much did feeling sick to your stomach (nausea) keep you from doing things you usually do?
	○ Not at all
	○ Some
	○ A lot
	○ A whole lot

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2.	a. In the past 7 days, how often did you throw up?
	○ Never
	○ Sometimes
	○ Most of the time
	○ Almost all the time
	b. In the past 7 days, how much did throwing up keep you from doing things you usually do?
	○ Not at all
	○ Some
	○ A lot
	○ A whole lot

3.	
	a. In the past 7 days, how often did you have problems with not being able to poop?
	○ Never
	○ Sometimes
	○ Most of the time
	○ Almost all the time
	b. In the past 7 days, how bad were your problems with not being able to poop?
	○ Did not have any
	○ A little bad
	○ Bad
	○ Very bad
	c. In the past 7 days, how much did problems with not being able to poop keep you from doing things you usually do?
	○ Not at all
	○ Some
	○ A lot
	○ A whole lot

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4.	
	a. In the past 7 days, how often did you have runny or watery poop?
	○ Never
	○ Sometimes
	○ Most of the time
	○ Almost all the time
	b. In the past 7 days, how much did having runny or watery poop keep you from doing things you usually do?
	○ Not at all
	○ Some
	○ A lot
	○ A whole lot

5.	
	a. In the past 7 days, how often did you have stomach pain?
	○ Never
	○ Sometimes
	○ Most of the time
	○ Almost all the time
	b. In the past 7 days, how bad was your stomach pain?
	○ Did not have any
	○ A little bad
	○ Bad
	○ Very bad
	c. In the past 7 days, how much did stomach pain keep you from doing things you usually do?
	○ Not at all
	○ Some
	○ A lot
	○ A whole lot

6.	
	a. In the past 7 days, how often did you have problems breathing (shortness of breath)?
	○ Never
	○ Sometimes
	○ Most of the time
	○ Almost all the time
	b. In the past 7 days, how bad were your problems breathing (shortness of breath)?
	○ Did not have any
	○ A little bad
	○ Bad
	○ Very bad
	c. In the past 7 days, how much did your problems breathing (shortness of breath) keep you from doing things you usually do?
	○ Not at all
	○ Some
	○ A lot
	○ A whole lot

7.	a. In the past 7 days, how often did you cough?
	○ Never
	○ Sometimes
	○ Most of the time
	○ Almost all the time
	b. In the past 7 days, how bad was your coughing?
	○ Did not have any
	○ A little bad
	○ Bad
	○ Very bad
	c. In the past 7 days, how much did coughing keep you from doing things you usually do?
	○ Not at all
	○ Some
	○ A lot
	○ A whole lot

8.	a. In the past 7 days, how often did you have a racing heart beat?
	○ Never
	○ Sometimes
	○ Most of the time
	○ Almost all the time
	b. In the past 7 days, how bad was your racing heart beat?
	○ Did not have any
	○ A little bad
	○ Bad
	○ Very bad

9.	a. In the past 7 days, how bad was your itchy skin?
	○ Did not have any
	○ A little bad
	○ Bad
	○ Very bad
	b. In the past 7 days, how much did your itchy skin keep you from doing things you usually do?
	○ Not at all
	○ Some
	○ A lot
	○ A whole lot

10.	a. In the past 7 days, how bad was your dizziness?
	○ Did not have any
	○ A little bad
	○ Bad
	○ Very bad
	b. In the past 7 days, how much did dizziness keep you from doing things you usually do?
	○ Not at all
	○ Some
	○ A lot
	○ A whole lot

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11.	a. In the past 7 days, how bad were your problems with paying attention (focusing on TV, reading, or school work)?
	○ Did not have any
	○ A little bad
	○ Bad
	○ Very bad
	b. In the past 7 days, how much did problems with paying attention (focusing on TV, reading, or school work) keep you from doing things you usually do?
	○ Not at all
	○ Some
	○ A lot
	○ A whole lot

12.	
	a. In the past 7 days, how often did you have pain?
	○ Never
	○ Sometimes
	○ Most of the time
	○ Almost all the time
	b. In the past 7 days, how bad was your pain?
	○ Did not have any
	○ A little bad
	○ Bad
	○ Very bad
	c. In the past 7 days, how much did pain keep you from doing things you usually do?
	○ Not at all
	○ Some
	○ A lot
	○ A whole lot

13.	
	a. In the past 7 days, how often did your muscles hurt?
	○ Never
	○ Sometimes
	○ Most of the time
	○ Almost all the time
	b. In the past 7 days, how bad did your muscles hurt?
	○ Did not have any
	○ A little bad
	○ Bad
	○ Very bad
	c. In the past 7 days, how much did your muscles hurting keep you from doing things you usually do?
	○ Not at all
	○ Some
	○ A lot
	○ A whole lot

14.	a. In the past 7 days, how often did you have pain in any bendable part of your body (knees, ankles, shoulders, or fingers)?
	○ Never
	○ Sometimes
	○ Most of the time
	○ Almost all the time
	b. In the past 7 days, how bad was the pain in any bendable part of your body (knees, ankles, shoulders, or fingers)?
	○ Did not have any
	○ A little bad
	○ Bad
	○ Very bad
	c. In the past 7 days, how much did pain in any bendable part of your body (knees, ankles, shoulders, or fingers) keep you from doing things you usually do?
	○ Not at all
	○ Some
	○ A lot
	○ A whole lot

15.	
	a. In the past 7 days, how bad was your feeling tired?
	○ Did not have any
	○ A little bad
	○ Bad
	○ Very bad
	b. In the past 7 days, how much did feeling tired keep you from doing things you usually do?
	○ Not at all
	○ Some
	○ A lot
	○ A whole lot

16.	
	a. In the past 7 days, how bad was the pain or burning when you pee?
	○ Did not have any
	○ A little bad
	○ Bad
	○ Very bad
	b. In the past 7 days, how much did pain or burning when peeing keep you from doing things you usually do?
	○ Not at all
	○ Some
	○ A lot
	○ A whole lot

17.	a. In the past 7 days, how often did you have to pee more than usual?
	○ Never
	○ Sometimes
	○ Most of the time
	○ Almost all the time
	b. In the past 7 days, how much did peeing more than usual keep you from doing things you usually do?
	○ Not at all
	○ Some
	○ A lot
	○ A whole lot

18.	
	a. In the past 7 days, how often did you sweat more than usual or sweat for no reason?
	○ Never
	○ Sometimes
	○ Most of the time
	○ Almost all the time
	b. In the past 7 days, how bad was your sweating more than usual or sweating for no reason?
	○ Did not have any
	○ A little bad
	○ Bad
	○ Very bad
	c. In the past 7 days, how much did sweating more than usual or sweating for no reason keep you from doing things you usually do?
	○ Not at all
	○ Some
	○ A lot
	○ A whole lot

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Appendix J 3 European Organization for Research and Treatment of Cancer Item List XX removed due to copyrights (Page 232)

Appendix J 4 Patient-reported Outcomes questionnaires: PROMIS Short Form v2.0 – Physical Function 8c removed due to copyrights (Page 233)

Appendix J 5 Patient-reported Outcomes questionnaires: PROMIS Pediatric Short Form v3.0 — Mobility 7a removed due to copyrights (Page 234)

J 6 Patient Global Impression of Treatment Tolerability

Figure 10 PGI-TT questionnaire

Study Number:		Site Number:
Subject Number:	Visit Number:	Assessment Date:

PATIENT GLOBAL IMPRESSION OF TREATMENT TOLERABILITY (PGI-TT)

In the last 7 days, how bothered were you by the side effects of your cancer treatment?

- ☐ Not at all
- ☐ A little bit
- ☐ Somewhat
- ☐ Quite a bit
- ☐ Very much

Appendix J 7 Patient-reported Outcomes questionnaires: Patient Global Impression of Cancer Severity removed due to copyrights (Page 236)

Appendix J 8 Patient Global Impression of Change removed due to copyrights (Page 237)

Appendix J 9 Patient-reported Outcomes questionnaires: EuroQol 5-Dimension, 5-Level Health- State Utility Index removed due to copyright (pages 238-240)

Appendix K Abbreviations

Abbreviation or special term	Explanation
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibody
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine transaminase
AML	acute myeloid leukemia
ANSM	French National Agency for the Safety of Medicines and Health Products
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
ATD	accelerated titration design
AUC	area under the concentration curve
BICR	blinded independent central review
BOR	best overall response
BUN	blood urea nitrogen
CAPA	corrective and preventive action
CAR-T	Chimeric Antigen Receptor T cell
cHL	Classical Hodgkin Lymphoma
CI	confidence interval
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	Complete Response
CRO	Contract Research Organization
CRR	Complete Response Rate
CRS	Cytokine Release Syndrome
CSP	clinical study protocol
CSTD	closed system transfer device
CSR	clinical study report
CT	computed tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CCI	CCI
CTFG	Clinical Trials Facilitation Group

Abbreviation or special term	Explanation
CTIS	Clinical Trials Information System
CTLA-4	cytotoxic T-lymphocyte associated protein 4
CTR	Clinical Trials Regulation
CTT	Clinical Trial Transparency
DCO	data cut-off
DEHP	Di (2-ethylhexyl) phthalate
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DoCR	Duration of Complete Response
DoR	Duration of Response
DU	current dose is unacceptably toxic
EBV	Epstein Bar Virus
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
CCI	CCI
CCI	CCI
EMA	European Medicines Agency
EOI	end of infusion
EORTC IL	European Organization for Research and Treatment of Cancer Item List
EoS	end of study
EoT	end of treatment
ePRO	electronic device and patient-reported outcome instruments
ESMO	European Society for Medical Oncology
EU	European Union
FAS	full analysis set
Fc	fragment crystallizable
FDA	US Food and Drug Administration
FDG	^{18}F-fluorodeoxyglucose
FEV_1	Forced Expiratory Volume in the 1st second
FFPE	Formalin-Fixed Paraffin-Embedded
FIH	first-in-human
FVC	forced vital capacity

Abbreviation or special term	Explanation
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
GRAD	Global Retention and Disposal
HAV	hepatitis A virus
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HEV	hepatitis E virus
HIV	human immunodeficiency virus
HL	Hy's Law
HR-MDS	high risk myelodysplastic syndrome
HRQoL	health-related quality of life
HRS	Hodgkin Reed-Sternberg
HSCT	hematopoietic stem cell transplantation
HSV	herpes simplex virus
IC	immune checkpoint
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG1	immunoglobulin G1
IgM	Immunoglobulin M
IHC	immunohistochemistry
IL	Interleukin
ILD	Interstitial Lung Disease
ILICI	immune-mediated liver injury caused by immune checkpoint inhibitors
IM	intramuscular
imAE	immune-mediated adverse event
IMP	investigational medicinal product
IO	Immuno-oncology
IRB	Institutional Review Board
IRR	infusion-related reaction
IRT/RTSM	Interactive Response Technology System/ Randomization and Trial Supply Management
IV	intravenous(ly)

Abbreviation or special term	Explanation
LDH	lactate dehydrogenase
LDi	longest diameter
LFT	liver function test
LLN	lower limit of normal
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
MUGA	multiple-gated acquisition scan
NCI	National Cancer Institute
NOAEL	no-observed adverse event level
NSCLC	non-small-cell lung carcinoma
OAE	ontology of adverse events
OBD	optimal biological dose
ORR	Objective Response Rate
OS	Overall Survival
PBMC	peripheral blood mononuclear cell
PC	polycarbonate
PCR	polymerase chain reaction
PD	progressive disease
PD-1	Programmed cell death protein-1
PD-L1	Programmed cell death-ligand 1
PET	positron emission tomography
PET-CT	positron emission tomography-computed tomography
PGI-TT	Patient Global Impression of Treatment Tolerability
PGIC	Patient Global Impression of Change
CCI	CCI
PHL	Potential Hy's Law
PE	polyethylene
CCI	CCI
PF	physical function
PFS	Progression-free Survival
PK	pharmacokinetics

Abbreviation or special term	Explanation
PK/PD	pharmacokinetics / pharmacodynamics
PO	per os (taken orally)
PP	polypropylene
PVC	polyvinylchloride
PR	partial response
PRO	patient-reported outcomes
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
PTAP	Post-trial Access Program
Q1W	every week
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
Q6W	every 6 weeks
QL2	2-item global HRQoL
QTcF	Corrected QT interval, using Fridericia's formula
RECIL	Response-evaluation Criteria in Lymphoma
RNA	ribonucleic acid
RP2D	recommended phase 2 dose
r/r	relapsed/refractory
RT	radiation therapy
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SDi	shortest diameter
SLD	sum of longest diameters
SJS	Stevens-Johnson syndrome
SoA	schedule of activities
SoC	standard of care
SOI	start of infusion
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
sWFI	sterile water for injection
t½	terminal elimination half-life
TB	Tuberculosis
TBL	total bilirubin

Abbreviation or special term	Explanation
TCR	T cell receptor
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
TH1	T helper 1
TIM-3	T cell immunoglobulin and mucin domain-containing protein-3
TMDD	Target-mediated drug disposition
TME	tumor microenvironment
TMG	toxicity management guidelines
TNF	Tumor Necrosis Factor
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
V	Visit
w/v	Weight/volume

Appendix L Protocol Version History

The Protocol Version Summary of Changes Table for the current version is located directly before the Table of Contents in this document.

Version 4 (11 July 2023)

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

Overall Rationale for the Modification:

The primary rationale for the changes implemented in this protocol modification was to introduce the new liquid formulation, implement EU CTR language, and introduce the endpoint of quality of life. Further changes were made for clarification and to address inconsistencies.

List of Substantial Modifications

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, Section 3 Objectives and Endpoints – Table 6 and Table 7	Included objectives for quality of life / PRO assessments.	Additional metrics assessing impact of AZD7789 on quality of life/patient reported outcomes to further improve the risk/benefit assessment.
Section 1.1 Synopsis, Section 4.1.2 Part B: Dose Expansion, and Section 5.1 Inclusion Criteria #10a	Changed eligibility of Cohort B1 from at least 3 to 2 prior cycles of anti-PD-1/ PD-L1 based therapy.	To expand the participant population
Section 1.3 Schedule of Activities – Tables 3 and 4	Added PRO-CTCAE (or Peds-PRO-CTCAE), PGI-TT, CCI [redacted] (or CCI [redacted] a), CCI [redacted]	To provide schedule of quality of life / patient reported outcomes assessments
Section 5.2 Exclusion criteria #2	Added peripheral neuropathy to the list of acceptable ongoing ≥ Grade 2 toxicities from prior therapies unless immune-mediated.	Accounting for propensity for participants to have peripheral neuropathy based on prior treatment.
Section 5.2 Exclusion criteria #3	Added list of acceptable unresolved imAE ≥ Grade 2	To account for immune-mediated conditions where there would be an unreasonable expectation for resolution to < Grade 2 given pathophysiology of conditions.
Section 5.2 Exclusion Criteria #18b	Modified the definition of washout period to 28 days.	To account for extended half-lives of certain monoclonal antibodies while ensuring agents with short-

Section # and Name	Description of Change	Brief Rationale
		half lives have shorter washout periods.
Section 6.1.1 Investigational Products – Table 10, and Section 6.1.2 Identity of Investigational Product(s)	Added description of CCI formulation.	New CCI formulation added.
Section 6.2.1 AZD7789 Infusion Preparation and Administration	Added preparation and administration guidance for CCI formulation.	New CCI formulation added.
Section 8.1.4 Patient-Reported Outcomes, Section 9.4.3 Safety Analyses, and Section 9.4.4.4 Patient-Reported Outcomes	Added description of quality of life / PRO secondary and exploratory endpoints to be included in Part B of study.	To acquire additional information regarding the impact of AZD7789 on PRO to support development of therapy for r/r cHL population.

cHL: classical Hodgkin Lymphoma; CCI [redacted]; CCI [redacted]; imAE: immune-mediated adverse event; PD-1: programmed cell death protein-1; PD-L1: programmed cell death ligand-1; r/r: relapsed or refractory; Peds: Pediatric; PGI-TT: Patient Global Impression of Treatment Tolerability; CCI [redacted]; PRO: patient-reported outcomes; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events.

List of Non-substantial Modifications

Section # and Name	Description of Change	Brief Rationale
Throughout	Administrative change: The version numbering was updated. Typos were corrected and minor clarifications made.	Editorial updates
Title Page	Added EU CT number	Update required to comply with EU CTR.
Section 1.1 Synopsis, and Section 9.3 Populations for Analyses – Table 21	Updated definition of interim response-evaluable population.	Update to be in consistent with planned response assessment for Cycle 3.
Section 1.3 Schedule of Activities – Table 1	COVID-19 testing added to screening procedures and footnote added.	COVID testing is required at screening per eligibility criteria; updating SoA to align.
Section 1.3 Schedule of Activities – Tables 1, 2, 3	Moved biomarker evaluation for Genomics Initiative from Screening to Cycle 1 Day 1	Participants must fulfill eligibility criteria for inclusion in the genetic research
Section 1.3 Schedule of Activities – Tables 1, 2, 3, 4, and Section 8.2.7 Clinical	Clarified when free thyroxine and free triiodothyronine testing is indicated and footnote added.	For consistency with description of clinical safety laboratory variables

Section # and Name	Description of Change	Brief Rationale
Safety Laboratory Assessments – Table 17		
Section 1.3 Schedule of Activities – Tables 2, 3, 4	Clarified timing of imaging disease assessment relative to AZD7789 administration.	Improve consistency and provide clearer guidance
Section 1.3 Schedule of Activities – Table 2	Aligned PK schedule and footnote to ADA sampling cycle 8 onwards in Part A	Match PK sampling to ADA scheduling
Section 1.3 Schedule of Activities – Table 3	Added footnote b to C2D8.	Improve clarity of ECG schedule
Section 1.3 Schedule of Activities – Table 3	Clarified in footnotes that Day 8 ECG assessment is only to be performed if cardiac signal is detected in Part A.	Corrected error
Section 1.3 Schedule of Activities – Table 3	Footnotes and text added to clarify PK sample collection for mainland China.	To correct the PK sampling frequency to match Part A
Section 1.3 Schedule of Activities – Table 3	Clarified in footnotes differences in disease response assessment between Investigator and BICR review.	BICR will only assess according to Modified Lugano.
Section 1.3 Schedule of Activities – Table 4	Table formatting mistake fixed.	No ECHO/MUGA testing during remote survival follow-up.
Section 1.3 Schedule of Activities – Table 4	PK timepoint removed at Day 90 post treatment	Reduce sampling where appropriate.
Section 4.2.1 Rationale for Endpoints, and Section 8.1 Disease Response Assessment	Clarified that Investigator response assessment using the Modified Lugano and RECIL criteria during Parts A and B were secondary endpoints.	Correcting description of analysis.
Section 4.4 End of Study Definition	Clarified definition of the end of study according to European Union and Food and Drug Administration requirements.	For consistency and alignment with how study results are shared.
Section 6.1 Study Intervention(s) Administered, and Section 6.2 Preparation/Handling/Storage/ Accountability	Updated language for lyophilized product to match current lyophilized product template	For consistency and alignment across development program.
Section 6.1.1 Investigational Products	Added CCI to list of commercially available products to be supplied by each site.	Clarified study resourcing
Section 6.2.1 AZD7789 Infusion Preparation for Administration	Updated description of AZD7789 product preparation and administration.	Guidance provided for new CCI formulation.
Section 6.10 Treatment of Overdose	Update of AstraZeneca standard text to include new section on the treatment of overdose	Update of AstraZeneca standard text

Section # and Name	Description of Change	Brief Rationale
Section 8.1.1 B-symptoms	B-symptoms moved from the safety section to efficacy assessments	B-symptoms assessment is not a safety measure but is part of the disease assessment
Section 8.1.2 Efficacy Assessment Types	Added description of radiological assessment schedule if treatment discontinued prior to Year 1	Clarified assessment schedule
Section 8.3.13 Medication Error, Drug Abuse and Drug Misuse	Added Drug Abuse and Drug Misuse definition.	Update required due to CT-3 Regulation and corporate safety CAPA.
Section 8.4 Reporting of Overdose	Update of AstraZeneca standard text to include new section on the treatment of overdose.	Update of AstraZeneca standard text.
Section 8.6.2.1 Tumor Tissue Sample – Table 18	Adjusted labeling in rows for Part A of the study	To clarify that baseline biopsies are required in the mTPI portion of the study
Appendix A 1 Regulatory and Ethical Considerations	Added sub-heading “Regulatory Reporting Requirements for Serious Breaches.”	Update required to comply with regulatory requirement (eg, EU CTR) and global company requirement.
Appendix A 6 Dissemination of Clinical Study Data	Updated information about timelines for submission of trial results summaries to EU CTIS.	Update required to comply with EU CTR.
Appendix A 7 Data Quality Assurance	Updated information about retention timelines of records and documents to minimum of 25 years after study archiving or as required by local regulations.	Update required to comply with EU CTR and global company requirement.
Appendix D 4 Medication Error, Drug Abuse, and Drug Misuse	Added detailed Drug Abuse and Drug Misuse definition and examples.	Update required due to CT-3 Regulation and corporate safety CAPA.
Appendix J Clinical Outcome Assessment Questionnaires	Added example copies of PRO assessment questionnaires	To provide information on content of questionnaires.

BICR: blinded independent central review; C: cycle; CAPA: corrective and preventive action; COVID-19: coronavirus disease 2019; CTIS: Clinical Trials Information System; CTR: Clinical Trials Regulation; D: day; ECG: electrocardiogram; ECHO: echocardiogram; EU: European Union; IV: intravenous; mTPI: modified toxicity probability interval; MUGA: multigated acquisition scan; PK: pharmacokinetic; PRO: patient-reported outcomes; RECIL: Response evaluation Criteria in Lymphoma; SoA: schedule of activities.

Version 3 (1 November 2022)

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Summary of Changes:

List of Substantial Modifications

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, and 4.1.1 Part A: Dose Escalation	Amended to clarify when a cohort (eg, Cohort A5, A6, A7 or A8) could fill their roster of up to 12 participants independently of each other.	To clarify the timing of opening a mini expansion once a dose level cohort is declared safe.
Section 1.1 Synopsis, 4.1 Overall Design, and 4.2 Scientific Rationale for Study Design, 9.2 Sample Size Determination, 9.3 Populations for Analysis, and Appendix A 3 Informed Consent Process	Added wording associated with collecting agreement from a young adult participant or their legally authorized representative for participation in the study, and updated instances of “adult” to adult/young adult".	To align with changes in Section 5.1 Inclusion Criteria to lower the age range of participants from 18 to 16 years.
Section 1.3 Schedule of Activities – Table 2	Reduction of PK sampling at later timepoints in Part A Dose Escalation.	To reduce participant burden of PK sampling at later timepoints.
Section 1.3 Schedule of Activities – Table 4	Addition of AZD7789 PK and ADA samples at EoT.	To align with collection of other samples at EoT.
Section 4.5 Study Stopping Criteria	The study stopping criteria were further clarified for each phase of the study by adding frequency and severity of the AEs. Some details in this section were also removed to avoid redundancy while a paragraph was moved to the more relevant Section 6.6.7 "Safety Review Committee" as the information was related to the SRC meeting schedule.	To address a request from the ANSM - amended to clarify the study stopping rules, applying to the study as a whole and to its different phases.
Section 5.1 Inclusion Criteria - #1, #2, and #4.	Age range of participants lowered from 18 to 16 years. Addition of text specifying that participants between 16 and 18 years old need to provide assent, if required per local regulations, and their legally authorized representative must give signed written informed consent.	To increase the therapeutic options available for young adults with r/r cHL, who otherwise have limited treatment alternatives.
Section 5.1 Inclusion Criteria - #7	“after the last line of therapy” was added.	Amended to clarify when measurable disease was required.
Section 5.1 Inclusion Criteria - #8	Amended the minimum threshold left ventricular ejection fraction as part of the inclusion criteria. Added a footnote to Table 9 to state that if clinically indicated, and at the Investigator’s discretion, a consultation with cardiologist is recommended for follow-up.	Allow patients with mild cardiac dysfunction to be included in this trial so as not to exclude previous heavily pre-treated patients who might have mild cardiac dysfunction but who could have clinical benefit being treated with the study drug.

Section # and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion Criteria - #18	Addition of criterion for minimum body weight ≥ 40 kg for all participants.	Introducing a minimum weight will guarantee that participants will receive an adequate flat dose per current protocol, as 40 kg is considered the girls' 0.4th percentile weight at 18 years, which means a ≥ 16-year-old participant weighing at least 40kg will have similar PK/PD and metabolism to the adult population (≥ 18 years old) already being studied in this trial. Additionally, the minimum threshold weight of 40kg is aligned with the inclusion of young adult participants per 2019 FDA guidance (Inclusion of Adolescent Patients in Adult Oncology Clinical Trials), which states that adolescent participants weighing at least 40 kg can receive the same fixed dose administered in adults.
Section 5.2 Exclusion Criteria - #11	Bold text was added to the exclusion criteria as follows: "Active or prior documented pathologically confirmed autoimmune or inflammatory disorders, including inflammatory bowel disease (eg, colitis or Crohn's disease), diverticulitis (with the exception of diverticulosis)"	Clarification of the exclusion criterion specifying participants with pathologically confirmed autoimmune or inflammatory disorders will be excluded from this trial.
Section 5.2 Exclusion Criteria - #3	Addition of "prior checkpoint inhibitor" to clarify which immunotherapy.	To limit the type of immunotherapy to checkpoint inhibitors.
Section 5.2 – Exclusion Criteria - #7f	Specified for participants with COVID-19 infection in the last 3 months, a negative PCR test is needed within 72 hours prior to first dose.	Clarification on timeframe regarding testing requirement in the event of previous COVID-19 infection prior to dosing.
Section 5.2 – Exclusion Criteria - #18b	Washout period timeframe "whichever is shorter" updated to "whichever is longer".	Correction
Section 6.6.1.2 Modified Toxicity Probability Interval, and Table 15	Decreased the upper limit of the target toxicity interval from 35% to 33%. Table 15 was updated to align with the new upper limit and include an	To address a request from the MHRA - amended to provide a more conservative Modified

Section # and Name	Description of Change	Brief Rationale
	additional rule of exception when a single dose-limiting toxicity is observed among the first 3 participants.	Toxicity Probability Interval dose setting design.
Section 6.6.3 Definition of Dose-limiting Toxicity	The DLT definition was amended to include Grade 4 anemia not related to the underlying disease or any extraneous cause (eg, bleeding).	To address a request from the ANSM - amended as Grade 4 anemia is with life-threatening consequences and needs urgent intervention as per CTCAE v5.0.
Section 6.7 Dose Delay	Consideration added as regards dose delay.	Clarification on acceptable timing to delay/resume AZD7789 dosing.
Section 6.8 Treatment Beyond Progression	A subsection was added to provide guidance in case pseudo-progression (eg, tumor flare due to immunomodulatory agent therapy) occurs during treatment with the study drug.	Additional guidance was provided to prevent premature treatment discontinuation.
Section 7.1 Discontinuation of Study Intervention	Additional text in terms of efficacy assessments during follow-up for participants discontinuing study intervention due to PD versus participant discontinuing the study drug while in response (CR, PR) or with stable disease.	Further clarification to clearly specify participants in response who discontinue treatment should continue efficacy assessments until death, PD or start of new treatment (whichever occurs first).
Section 8.1.1 Efficacy Assessment Types, Table 16, Section 1.3 Schedule of Activities Table 2, 3 and 4	Text was added and Table 16 modified to clarify timing of imaging based on disease response.	Modification of PET-CT frequency requirement to limit the exposure of the participant to unnecessary radiation.
Section 8.3.8 Disease Progression	Added text to specify when disease progression should be reported as a SAE/ SUSAR.	To address a request from the MHRA - amended to include the possibility that an IMP enhances disease progression, and that an investigator may consider that disease progression is IMP related and as such should be a SAE/SUSAR.
Appendix I Dosing Modification and Toxicity Management Guidelines for AZD7789 Monotherapy	Revision of the study drug discontinuation criteria in the following sections: colitis; rash/dermatitis; neurotoxicity; peripheral neuromotor syndromes; myositis; immune-mediated liver injury; cytokine release syndrome	To address a request from the MHRA - amended to add permanent study drug discontinuation guidance for selected high-grade AEs.

AE: adverse event; ADA: anti-drug antibodies; ANSM: Agence Nationale de Sécurité du Médicament et des Produits de Santé (National Security Agency of Medicines and Health Products); cHL: classical Hodgkin Lymphoma; CR: complete response; COVID-19: coronavirus disease 2019; CTCAE: Common Terminology Criteria for Adverse Events; DLT: dose-limiting toxicity; EoT: end of treatment; FDA: United States Food and Drug Administration; IMP: investigational medicinal product; MHRA: Medicines and Healthcare products Regulatory Agency; PCR: polymerase chain reaction; PD: progressive disease; PET-CT: positron

Section # and Name	Description of Change	Brief Rationale

emission tomography-computed tomography; PK: pharmacokinetic; PK/PD: pharmacokinetics/ pharmacodynamics; PR: partial response; r/r: relapsed or refractory; SAE: serious adverse event; SRC: Safety Review Committee; SUSAR: suspected unexpected serious adverse reaction.

List of Non-substantial Modifications

Section # and Name	Description of Change	Brief Rationale
Throughout	Administrative change: The version numbering was updated. Typos were corrected and minor clarifications made. 'The Sponsor' has been changed to 'AstraZeneca'.	Editorial updates. Update of AstraZeneca standard text and changed globally for consistency.
Section 1.1 Synopsis, and Section 9.5 Interim Analysis	Clarification of timing and details of interim safety and efficacy analysis.	Amended to differentiate timepoints for interim safety and efficacy analysis (previously described in Section 4.5 only) as not necessarily both analyses will occur at the same time.
Section 1.1 Synopsis, and Section 9.3 Populations for Analyses	Clarified the definition of the interim safety and efficacy evaluable populations.	Amended to remove ambiguity of analysis set definition.
Section 1.1 Synopsis, and Section 9.5 Interim Analyses	Updated text for subsequent interim analyses from "will be performed after every 20 additional participants" to "may be performed after every 20 additional participants". Clarified role of Part A participants for interim efficacy analyses in synopsis per Section 9.5.	For operational flexibility, and clarification in the synopsis.
Section 1.1 Synopsis – Figure 1	Figure updated to amend "total n = [redacted]" to "total n = up to [redacted]" for cohorts A5-A8, and text added to clarify total numbers of participants in Parts A and B.	For clarification and consistency with updates in other sections of the protocol.
Section 1.3 Schedule of Activities – Table 1, Table 3; Section 5.1 Inclusion criteria - #13; Section 8.5 Human Biological Samples; Section 8.6. Collection of Mandatory Samples for Biomarker Analysis1; Section 8.6.2.1 Tumor Tissue Samples; Section 8.6.2.2 Non-tumor Tissue Biopsy at Toxicity;	Footnotes and text added to clarify sample collection requirements for mainland China.	To conform with country-specific sample collection requirements

Section # and Name	Description of Change	Brief Rationale
Section 8.6.3 Collection of Optional Biomarker Samples; Section 8.7 Optional Genomics Initiative Sample		
Section 1.3 Schedule of Activities – Table 1	Urine pregnancy test added to the screening procedure with footnote specifying that in the event of a positive urine test, a serum test should be performed for confirmation.	Alignment with Section 8.2.8
Section 1.3 Schedule of Activities – Table 1	Additional instructions provided for the collection of tumor archival tissue to be obtained within 4 months of study participation.	Alignment with Section 8.6.2.1
Section 1.3 Schedule of Activities – Table 2 and Table 3	Removed "Study Day" row from the SoA.	Removed to simplify as "Cycle Number and Day" are already provided in the table.
Section 1.3 Schedule of Activities – Table 2 and Table 3	Removed column for "After EOI" at C1D1 and added footnotes in ECG and vital signs rows.	For clarity, as EOI collection of ECGs, vital signs and PK samples are already detailed in the footnotes of the table. The hematology EOI sample was removed as it was not an informative assessment.
Section 1.3 Schedule of Activities – Table 2	Anti-drug antibody sample collection added in the schedule of activities for C2D8.	Alignment between the clinical study protocol and the laboratory manual
Section 1.3 Schedule of Activities – Table 2, Table 3, Table 4	Clarifications made for assessment and sampling timepoints.	To avoid confusion around collection timings for samples.
Section 1.3 Schedule of Activities – Table 3, Table 4	Addition of soluble TIM-3 assessments to Tables 3 and 4.	To correct previous omission of TIM-3 assessments in Tables 3 and 4.
Section 3 Objectives and Endpoints – Table 7	Exploratory endpoint CCI [redacted]. Formatting of list of secondary endpoints for Part A Dose Escalation and Part B Dose Expansion updated.	Removed as this was a duplication of the secondary endpoint for Part A and Part B. Formatting improved to clarify which footnotes pertain to which endpoints.
Section 4.2 Scientific Rationale for Study Design	Update from 1 to 2 prior lines of therapy.	Correction of typo to be aligned with inclusion criterion #9
Section 4.5 Study Stopping Criteria, and Section 6.6.7 Safety Review Committee	The paragraph describing SRC safety review milestones during Part A of the study was moved for clarity from Section	Moved for clarity since the paragraph pertains to SRC safety review milestones

Section # and Name	Description of Change	Brief Rationale
	4.5 "Study Stopping Criteria" to the more relevant Section 6.6.7 "Safety Review Committee".	during Part A of the study and not to study stopping criteria.
Section 5.1 Inclusion Criteria - #8	Removed “measured within 7 days prior to first dose”	The values in Table 9 pertain to study entry levels, so this text is not needed.
	Addition of a footnote to Table 9 to explain that from cycle 2 onwards, thresholds for adequate marrow, renal and liver function must be met.	For clarification and completeness.
Section 6.1.1 Investigational Products	“within 1 to 3 days prior to infusion” amended to “within 3 days prior to infusion”	Amended to provide flexibility in logistics and scheduling at site
Section 6.2.3 AZD7789 IV Bag or Syringe Preparation for IV Administration	Timepoints for vital signs checks replaced by reference to schedule of assessments Table 2 and Table 3	Clarification to provide all timepoints in one single place
Section 6.3 Measures to Minimize Bias: Randomization and Blinding	Text “or B1 and B2” removed. Text “starting with the highest dose that has been declared safe by the SRC. However, prioritization may be given to cohorts where potential clinical activity has been observed” added.	Cohort assignment was inaccurately defined, and clarification was provided as follows for: • Cohorts B1 and B2, text was not applicable as study entry is not randomly assigned but is dependent on prior anti-PD-1 exposure • Cohorts A5 to A8, clarification on cohort assignment in the event mini dose expansions are opened in parallel.
Section 6.5.1 Premedication	Removed dose specification for acetaminophen.	Clarification.
Section 6.5.2 Rescue Medicine – Table 13	The recommended timing for COVID-19 vaccination was clarified for the first 2 cycles. Text related to cycle 2 was removed.	Clarification as cycle 2 occurs within the 28 days DLT period, during which COVID-19 vaccination is not recommended.
Section 6.6.1 Starting Dose, Dose Escalation Scheme, and Stopping Criteria – Table 14	Removed footnote “a”.	Correction – footnote was not required in the table.
Section 6.6.5 Definition of Optimal Biological Dose	Clarified that RP2D will be selected by AstraZeneca in discussion with members of the Study Steering Committee.	Clarification.

Section # and Name	Description of Change	Brief Rationale
Section 6.6.6 Definition of DLT-evaluable Participants	Re-wording to indicate 28 days is the DLT-evaluation period.	Clarification and to align with other sections of the protocol
Section 8.1.1 Efficacy Assessment Types – Table 16, and Section 1.3 Schedule of Activities Tables 2, 3, and 4	Text added to describe options for imaging modalities and that the modality selected at baseline should remain consistent during the study.	To clarify the definition of diagnostic quality and what to do in the event of contrast shortage.
Section 8.1.2 Blinded Independent Review Committee Assessment	Addition of subsection describing central review of radiological imaging by BICR in Part B of the study, and that in Part A, imaging must be archived and transferred to the BICR vendor to allow retrospective disease response assessment in participants treated at a potential RP2D.	Guidelines on transfer and archiving of disease assessment imaging reports were added because participants treated with the RP2D at Part A will be included in the Part B analysis.
Section 8.2.7 B-symptoms	Clarification that presence of B-symptoms should not be used in the overall response assessment as per Lugano 2014.	B-symptoms assessment is not part of the overall disease response criteria as per Lugano 2014.
Section 8.2.8 Clinical Safety Laboratory Assessment Table 17	Creatinine clearance added to the list of parameters to tested for biochemistry	To be consistent with inclusion criterion #8, Table 9.
Section 8.3.1 Time Period and Frequency for Collecting AE and SAE Information	"Serious AEs will be recorded from the time of signing of ICF." was modified to "Serious AEs will be collected from the time of signing of ICF until the end of the study."	To address a request from the German Clinical Ethics Committee - amended to clarify that SAEs are recorded throughout the entire duration of the clinical trial.
Section 8.6.1 Collection of Mandatory Samples for Biomarker Analysis	Sampling timepoints for tumor tissue samples removed, and text mentioning CCI serum samples added.	Alignment with timeframes outlined in Table 18, and to clarify there are 2 serum biomarker samples (exploratory analysis and CCI).

Section # and Name	Description of Change	Brief Rationale
Section 8.6.2.1 Tumor Tissue Samples, and Table 18	The following instructions were added to the section for the collection of tumor archival tissue to be obtained within 4 months prior to initiating of study intervention: "participant must not have received any anti-cHL treatment within that time period otherwise fresh tissue required". Additionally, in Table 18 it was clarified that the instructions for tumor tissue collection apply to the entire dose escalation regardless of the design and therefore "accelerated titration design segment" was removed to avoid confusion.	Additional instruction provided as archival tissue prior to study entry will utilised as baseline and any treatment intervention in-between will interfere with the biology of the tumor.
Section 9 Statistical Considerations	Clarification of interim safety population, timing of primary, safety, and efficacy analysis, other minor clarifications, and a correction to the heading of Table 23.	Amended for clarification and consistency with other protocol sections. Table 23 heading corrected to refer to Cohort B2.
Section 9.4.4.1 Pharmacokinetics and Pharmacodynamics	Updated text to indicate analysis of PK/PD data will be described in a separate document.	Clarification of potential exploratory analysis of PK/PD.
Section 9.5 Interim Analyses	Language amended to specify Investigator assessment will be used for interim analysis assessment and, as appropriate, BICR assessment may complement.	For clarification of endpoints considered for interim efficacy analyses to enable timely evaluation of emerging data.
Appendix C Response Evaluation Using the Modified Lugano (Cheson et al, JCO 2014) and RECIL (Younes et al, Ann Oncol 2017) Criteria	Additional guidance provided in the appendix to perform disease assessment as per Modified Lugano 2014 and as per RECIL. The Deauville 5-point scale was updated per Cheson et al 2014.	For clarification and completeness.
Appendix K Protocol Version History	Added Protocol Version History Appendix	Appendix was added to include previous version summaries of changes.
Appendix J Abbreviations	Abbreviations added/removed.	To align with revisions. Missing abbreviations added.

AE: adverse event; BICR: blinded independent central review; C: cycle; cHL: classical Hodgkin Lymphoma; COVID-19: coronavirus disease 2019; D: day; DLT: dose-limiting toxicity; ECG: electrocardiogram; EOI: end of infusion; ICF: informed consent form; IV: intravenous; PD-1: programmed cell death protein-1; PK: pharmacokinetic; PK/PD: pharmacokinetics/pharmacodynamics; RECIL: Response Evaluation Criteria in Lymphoma; RP2D: recommended phase 2 dose; SAE: serious adverse event; SOA: Summary of Assessments; SRC: Safety Review Committee; TIM-3: T cell immunoglobulin and mucin domain-containing protein-3.

Version 2 (24 September 2021)

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Modification:

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.1 Synopsis	The synopsis was revised to align with revisions in the CSP sections.	Revisions were made for consistency.	Non-substantial
Section 1.2 Schema	The schema was revised to align with revisions in Sections 6.6.1 and 9.2.	Revisions were made for consistency.	Non-substantial
Section 1.3 Schedule of Activities	In Table 2 and Table 3, ADA sample timepoints were revised.	Amended in response to request from FDA.	Non-substantial
	Table 2 and Table 3 were aligned with revisions in Sections 6.2.3, 6.5.1 (newly added) and 6.6.1.1.	Revisions were made for consistency.	Non-substantial
Section 4.1 Overall Design	Part A and Part B were described in more detail and the number of participants to be enrolled was updated. The participants to be included in the analysis in Cohort B1 was clarified.	Amended in response to request from FDA.	Non-substantial
Section 4.2.1 Rationale for Endpoints	Added text to clarify that the selection of the RP2D will be made by the Study Steering Committee, based on the OBD.	Amended in response to request from FDA.	Non-substantial
Section 4.5 Study Stopping Criteria	The stopping criteria were expanded and described in more detail.	Amended in response to request from FDA.	Substantial
Section 5.1 Inclusion criteria	Inclusion criterion 9 for Part A was modified to require that participants failed at least 2 prior lines of systemic therapy (instead of 2 prior lines of therapy) and received at least 3 cycles of anti-PD-1/PD-L1 based therapy (instead of 1 cycle)	Amended in response to request from FDA.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 6.1.1 Investigational Products	Added text to describe dosing criteria for Cycles ≥ 2.	Amended in response to request from FDA.	Substantial
Section 6.2.3 AZD7789 IV Bag or Syringe Preparation for IV Administration	Added text to clarify how participants will be monitored during and after infusions, on Cycle 1 Day 1 and for subsequent doses.	Amended in response to request from FDA.	Substantial
Section 6.5.1 (Premedication)	This section was added to discuss premedication to be administered 30 minutes prior to each dose.	Amended in response to request from FDA.	Substantial
Section 6.5.2 Rescue Medication (previously Section 6.5.1)	Table 12 was updated to include a reference to the text added in Section 6.5.1. In addition, existing text was updated for clarification.	Revisions were made for consistency.	Non-substantial
Section 6.6.1 Starting Dose, Dose Escalation Scheme, and Stopping Criteria	Added text to explain that the planned dose levels may need to be adjusted depending on reported AEs and DLTs.	Amended in response to request from FDA.	Substantial
Section 6.6.1.2 Modified Toxicity Probability Interval	Added text to specify that the posterior distribution for all dose levels is Beta(1+a, 1+b), where a and b are the number of participants with and without a DLT at the current dose level, respectively. The criteria for an unsafe dose level and dose escalation/de-escalation decision rules were adjusted.	Amended in response to request from FDA.	Substantial
Section 6.6.3 Definition of Dose-limiting Toxicity	The DLT evaluation period was changed from 21 to 28 days from the first dose of AZD7789 on Cycle 1 Day 1.	Amended in response to request from FDA.	Substantial
	Updated conditions to be considered as DLTs: Conditions for thrombocytopenia were updated and conditions for CRS were added.	Amended in response to request from FDA.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 6.6.6 Definition of DLT-evaluable Participants	The definition for an evaluable participant was aligned with revised definition of the DLT evaluation period in Section 6.6.3.	Revisions were made for consistency.	Substantial
Section 8.6.2.1 Tumor Tissue Samples	Table 18 was corrected to indicate that Cycle 1 Day 8 biopsy during Part B is not mandatory if medically contraindicated.	Correction of a typo.	Non-substantial
Section 9.2 Sample Size Determination	The total number of participants to be enrolled in the study and the number of participants to be enrolled in Part B were updated.	Amended in response to request from FDA.	Substantial
Section 9.3 Populations for Analyses	In Table 21, the definition for an evaluable participant was aligned with revised definition of the DLT evaluation period in Section 6.6.3.	Revisions were made for consistency.	Substantial
Section 9.4.2.2 Secondary Endpoint(s)	It was clarified that, for progression-free survival, additional supportive/sensitivity analyses will be provided in the SAP.	Amended in response to request from FDA.	Non-substantial
Section 9.4.3.1 Maximum Tolerated Dose Evaluation	Changed the probability percentage for dose level considered to be unsafe.	Amended in response to request from FDA.	Substantial
Section 9.5 Interim Analyses	It was clarified that participants treated at the RP2D in Part A will be included in Cohort B1.	Amended in response to request from FDA.	Substantial
Section 9.5.1 Relapsed or Refractory cHL, Anti-PD-1/PD-L1 Exposed	Defined No-Go and false No-Go criteria.	Amended in response to request from FDA.	Substantial
Section 9.5.2 Relapsed or Refractory cHL, Anti-PD-1/PD-L1-naïve	Defined No-Go and false No-Go criteria.	Amended in response to request from FDA.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Appendix I	Added section for Cytokine Release Syndrome (CRS).	Amended in response to request from FDA.	Substantial
Appendix J	Added abbreviations to align with revisions.	Revisions were made for consistency.	Non-substantial
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarized.	Non-substantial

11. REFERENCES

Aaronson et al, 1993
Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.

Agrawal et al, 2016
Agrawal S, Feng Y, Roy A, Kollia G, Lestini B. Nivolumab dose selection: challenges, opportunities, and lessons learned for cancer immunotherapy. J Immunother Cancer. 2016;4:72.

Aithal et al, 2011
Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther. 2011;89(6):806-15.

American Cancer Society
American Cancer Society. Cancer Facts & Figures. Available at https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf. 2020.

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[redacted]

Armand et al, 2018
Armand P, Engert A, Younes A, Fanale M, Santoro A, Zinzani PL, et al. Nivolumab for Relapsed/Refractory Classic Hodgkin Lymphoma After Failure of Autologous Hematopoietic Cell Transplantation: Extended Follow-Up of the Multicohort Single-Arm Phase II CheckMate 205 Trial. J Clin Oncol. 2018;36(14):1428-39.

Bai et al, 2017
Bai J, Gao Z, Li X, Dong L, Han W, Nie J. Regulation of PD-1/PD-L1 pathway and resistance to PD-1/PD-L1 blockade. Oncotarget. 2017;8(66):110693-707.

Baine et al, 2015
Baine MK, Turcu G, Zito CR, Adeniran AJ, Camp RL, Chen L, et al. Characterization of tumor infiltrating lymphocytes in paired primary and metastatic renal cell carcinoma specimens. Oncotarget. 2015;6(28):24990-5002.

Barrington et al, 2014
Barrington SF, Mikhael NG, Kostakoglu L, Hutchings M, Mueller SP, Schwartz LH, et al. Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol. 2014;32(27): 3048-58.

Biton et al, 2018
Biton J, Mansuet-Lupo A, Pecuchet N, Alifano M, Ouakrim H, Arrondeau J, et al. TP53, STK11, and EGFR mutations predict tumor immune profile and the response to anti-PD-1 in lung adenocarcinoma. Clin Cancer Res. 2018;24(22):5710-23.

Borate et al, 2019
Borate U, Esteve J, Porkka K, Knapper S, Vey N, Scholl S, et al. Phase Ib Study of the anti-TIM-3 Antibody MBG453 in combination with decitabine in patients with high-risk myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Blood. 2019;134(Suppl 1):570.

Brahmer et al, 2010
Brahmer JR, Drake CG, Wollner I, Powderly JD, Picus J, Sharfman WH, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol. 2010;28(19):3167-75.

Brahmer et al, 2018
Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018;36(17):1714-68.

Bray et al, 2018
Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.

Brennan et al, 2010
Brennan FR, Morton LD, Spindeldreher S, Kiessling A, Allenspach R, Hey A, et al. Safety and immunotoxicity assessment of immunomodulatory monoclonal antibodies. MAbs. 2010;2(3):233-55.

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[redacted]

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CCI

Chai et al, 2020
Chai LF, Prince E, Pillarisetty VG, Katz SC. Challenges in assessing solid tumor responses to immunotherapy. Cancer Gene Ther. 2020;27(7-8):528-38.

Cheson et al, 2014
Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, Lister TA. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. American Society of Clinical Oncology. J Clin Oncol. 201432(27):3059-67.

Chiba et al, 2012
Chiba S, Baghdadi M, Akiba H, Yoshiyama H, Kinoshita I, Dosaka-Akita H, et al. Tumor-infiltrating DCs suppress nucleic acid-mediated innate immune responses through interactions between the receptor TIM-3 and the alarmin HMGB1. Nat Immunol. 2012;13(9):832-42.

CCI
CCI
.

Curigliano et al, 2019
Curigliano G, Gelderblom H, Mach N, Doi T, Tai WMD, Forde P, et al. Abstract CT183: Phase (Ph) I/II study of MBG453± spartalizumab (PDR001) in patients (pts) with advanced malignancies. Cancer Research. 2019;79(Suppl 13):CT183.

Davar et al, 2018
Davar D, Boasberg PD, Eroglu Z, Falchook GS, Gainor JF, Hamiliton EP, et al. A phase 1 study of TSR-022, an anti-TIM-3 monoclonal antibody, in combination with TSR-042 (anti-PD-1) in patients with colorectal cancer and post-PD-1 NSCLC and melanoma. SITC 2018 Annual Conference Proceedings. 2018:O21.

Davies et al, 2017
Davies J, Patel M, Gridelli C, de Marinis F, Waterkamp D, McCusker ME. Real-world treatment patterns for patients receiving second-line and third-line treatment for advanced

non-small cell lung cancer: A systematic review of recently published studies. PLoS One. 2017;12(4):e0175679.

CCI
CCI

Eisenhauer et al, 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response-evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

CCI
CCI

ESMO, Metastatic non-small cell lung cancer
ESMO. Metastatic non-small cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol.2018;29(Suppl 4):iv192-237. 2020;29(Suppl 4):iv192-iv237. Available at https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer.

CCI
CCI

Fares et al, 2019
Fares CM, Van Allen EM, Drake CG, Allison JP, Hu-Lieskovan S. Mechanisms of resistance to immune checkpoint blockade: why does checkpoint inhibitor immunotherapy not work for all patients? Am Soc Clin Oncol Educ Book. 2019;39:147-64.

FDA 2009
FDA. Guidance for industry: Drug-induced liver injury: premarketing clinical evaluation. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). 2009.

FDA 2020
FDA. Guidance for industry: Nonclinical safety evaluation of the immunotoxic potential of drugs and biologics. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). 2020.

Fourcade et al, 2010
Fourcade J, Sun Z, Benallaoua M, Guillaume P, Luescher IF, Sander C, et al. Upregulation of TIM-3 and PD-1 expression is associated with tumor antigen-specific $CD8^+$ T cell dysfunction in melanoma patients. J Exp Med. 2010;207(10):2175-86.

Freeman et al, 2000
Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, et al. Engagement of the Pd-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med. 2000;192(7):1027-34.

Fu et al, 2019
Fu Q, Chen N, Ge C, Li R, Li Z, Zeng B, et al. Prognostic value of tumor-infiltrating lymphocytes in melanoma: a systematic review and meta-analysis. Oncoimmunology. 2019;8(7):1593806.

Gao et al, 2012
Gao X, Zhu Y, Li G, Huang H, Zhang G, Wang F, et al. TIM-3 expression characterizes regulatory T cells in tumor tissues and is associated with lung cancer progression. PLoS One. 2012;7(2):e30676.

Guo et al, 2017
Guo W, Wang SJ, Yang S, Lynn H, Ji Y. A Bayesian interval dose-finding design addressing Ockham's razor: mTPI-2. Contemp Clin Trials. 2017;58:23-33.

Hanna et al, 2020
Hanna NH, Schneider BJ, Temin S, Baker S, Jr., Brahmer J, Ellis PM, et al. Therapy for Stage IV Non-Small-Cell Lung Cancer Without Driver Alterations: ASCO and OH (CCO) Joint Guideline Update. J Clin Oncol. 2020;38(14):1608-32.

Hellmann et al, 2021
Hellmann MD, Bivi N, Calderon B, Shimizu T, Delafontaine B, Liu ZT, et al. Safety and immunogenicity of LY3415244, a bispecific antibody against TIM-3 and PD-L1, in patients with advanced solid tumors. Clin Cancer Res. 2021:clincanres.3716.2020.

Herdman et al, 2011
Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20(10):1727-36.

Howlader et al, 2020
Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, et al. SEER cancer statistics review, 1975-2017, National Cancer Institute. Bethesda, MD, based on November 2019 SEER data submission, posted to the SEER web site, April 2020. Available at https://seer.cancer.gov/csr/1975_2017/.

Hui et al, 2017
Hui E, Cheung J, Zhu J, Su X, Taylor MJ, Wallweber HA, et al. T cell costimulatory receptor CD28 is a primary target for PD-1–mediated inhibition. Science. 2017;355(6332):1428-33.

Ishida et al, 1992
Ishida Y, Agata Y, Shibahara K, Honjo T. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. EMBO J. 1992;11(11):3887-95.

Ji et al, 2010
Ji Y, Liu P, Li Y, Bekele BN. A modified toxicity probability interval method for dose-finding trials. Clin Trials. 2010;7(6):653-63.

Jia et al 2019
Jia K, He Y, Dziadziuszko R, Zhao S, Zhang X, Deng J, et al. T cell immunoglobulin and mucin-domain containing-3 in non-small cell lung cancer. Transl Lung Cancer Res. 2019;8(6):895-906.

CCI
CCI
[redacted]

Klein et al, 2019
Klein C, Schaefer W, Regula JT, Dumontet C, Brinkmann U, Bacac M, et al. Engineering therapeutic bispecific antibodies using CrossMab technology. Methods. 2019;154:21-31.

Kluetz et al, 2016
Kluetz PG, Chingos DT, Basch EM, Mitchell SA. Patient-Reported Outcomes in Cancer Clinical Trials: Measuring Symptomatic Adverse Events With the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Am Soc Clin Oncol Educ Book. 2016;35:67-73.

Kluger et al, 2020
Kluger HM, Tawbi HA, Ascierto ML, Bowden M, Callahan MK, Cha E, et al. Defining tumor resistance to PD-1 pathway blockade: recommendations from the first meeting of the SITC Immunotherapy Resistance Taskforce. J Immunother Cancer. 2020;8(1).

Kong et al, 2019
Kong JC, Guerra GR, Pham T, Mitchell C, Lynch AC, Warrier SK, et al. Prognostic Impact of Tumor-Infiltrating Lymphocytes in Primary and Metastatic Colorectal Cancer: A Systematic Review and Meta-analysis. Dis Colon Rectum. 2019;62(4):498-508.

Koyama et al, 2016
Koyama S, Akbay EA, Li YY, Herter-Sprie GS, Buczkowski KA, Richards WG, et al. Adaptive resistance to therapeutic PD-1 blockade is associated with upregulation of alternative immune checkpoints. Nat Commun. 2016;7:10501.

Lakhani et al, 2020
Lakhani N, Spreafico A, Tolcher AW, Rodon J, Janku F, Chandana SR et al. 1019O - Phase I Studies of Sym021, an anti-PD-1 antibody, Alone and in Combination with Sym022 (anti-LAG-3) or Sym023 (anti-TIM-3). Annals of Oncology. 2020; 31(4)645-71.

Latchman et al, 2001
Latchman Y, Wood CR, Chernova T, Chaudhary D, Borde M, Chernova I, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. Nat Immunol. 2001;2(3):261-8.

Lazzari et al, 2017
Lazzari C, Bulotta A, Ducceschi M, Vigano MG, Brioschi E, Corti F, et al. Historical evolution of second-line therapy in non-small cell lung cancer. Front Med (Lausanne). 2017;4:4.

Lee and Liu, 2008
Lee JJ, Liu DD. A predictive probability design for phase II cancer clinical trials. Clin Trials. 2008;5(2):93-106.

Lee et al, 2011
Lee J, Su EW, Zhu C, Hainline S, Phuah J, Moroco JA, et al. Phosphotyrosine-dependent coupling of TIM-3 to T-cell receptor signaling pathways. Mol Cell Biol. 2011;31(19):3963-74.

Matza et al, 2013
Matza LS, Patrick D, Riley AW, Alexander J, Rajmil L, Pleil AM, et al. Pediatric patient-reported outcome instruments for research to support medical product labeling: report of the ISPOR PRO Good Research Practices for the Assessment of Children and Adolescents Task Force. Value Health. 2013;16(4):461-79.

Miller et al, 2005
Miller MR et al. Standardisation of spirometry. Eur Respir J 2005;26(2):319-538

Monney et al, 2002
Monney L, Sabatos CA, Gaglia JL, Ryu A, Waldner H, Chernova T, et al. Th1-specific cell surface protein TIM-3 regulates macrophage activation and severity of an autoimmune disease. Nature. 2002;415(6871):536-41.

NCCN. Clinical Practice Guidelines in Oncology
NCCN. Clinical Practice Guidelines in Oncology: Non-small Cell Lung Cancer. Version 8.2020. 15 September 2020.2020 [cited ID/VAC. Available from: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.

Ndhlovu et al, 2012
Ndhlovu LC, Lopez-Verges S, Barbour JD, Jones RB, Jha AR, Long BR, et al. TIM-3 marks human natural killer cell maturation and suppresses cell-mediated cytotoxicity. Blood. 2012;119(16):3734-43.

Ngiow et al, 2011
Ngiow SF, von Scheidt B, Akiba H, Yagita H, Teng MW, Smyth MJ. Anti-TIM-3 antibody promotes T cell IFN-gamma-mediated antitumor immunity and suppresses established tumors. Cancer Res. 2011;71(10):3540-51.

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

Patnaik et al, 2015
Patnaik A, Kang SP, Rasco D, Papadopoulos KP, Elassaiss-Schaap J, Beeram M, et al. Phase I Study of pembrolizumab (MK-3475; anti-PD-1 monoclonal antibody) in patients with advanced solid tumors. Clin Cancer Res. 2015;21(19):4286-93.

Puzanov et al, 2017
Puzanov I, Diab A, Abdallah K, Bingham CO, Brogdon C, Dadu R, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer. 2017;5(1):95.

Rami-Porta et al, 2016
Rami-Porta R. Staging manual in thoracic oncology (2nd ed; includes 8th ed): tumor, node, and metastasis classification (TNM) information for lung cancer, plural mesothelioma, thymic malignancies, and carcinoma of the oesophagus and of oesophagogastric junction). 2016.

Rangachari et al, 2012
Rangachari M, Zhu C, Sakuishi K, Xiao S, Karman J, Chen A, et al. Bat3 promotes T cell responses and autoimmunity by repressing TIM-3-mediated cell death and exhaustion. Nat Med. 2012;18(9):1394-400.

Regev et al, 2020
Regev A, Avigan MI, Kiazand A, Vierling JM, Lewis JH, Omokaro SO, et al. Best practices for detection, assessment and management of suspected immune-mediated liver injury caused by immune checkpoint inhibitors during drug development. J Autoimmun. 2020;114:102514.

Ribas et al, 2005
Ribas A, Camacho LH, Lopez-Berestein G, Pavlov D, Bulanhagui CA, Millham R, et al. Antitumor activity in melanoma and anti-self responses in a phase I trial with the anti-cytotoxic T lymphocyte-associated antigen 4 monoclonal antibody CP-675,206. J Clin Oncol. 2005;23(35):8968-77.

Rostoker et al, 2007
Rostoker G, Andrivet P, Pham I, Griuncelli M, Adnot S. A modified Cockcroft-Gault formula taking into account the body surface area gives a more accurate estimation of the glomerular filtration rate. J Nephrol. 2007;20(5):576-85.

CCI
CCI
[redacted]
.

Seymour et al, 2017
Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017;18(3):e143-e52.

Sharma et al, 2017
Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, adaptive, and acquired resistance to cancer immunotherapy. Cell. 2017;168(4):707-23.

Shayan et al, 2017
Shayan G, Srivastava R, Li J, Schmitt N, Kane LP, Ferris RL. Adaptive resistance to anti-PD-1 therapy by TIM-3 upregulation is mediated by the PI3K-Akt pathway in head and neck cancer. Oncoimmunology. 2017;6(1):e1261779.

Siegel et al, 2020
Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7-30.

Simon et al, 1997
Simon R, Freidlin B, Rubinstein L, Arbuck SG, Collins J, Christian MC. Accelerated titration designs for phase I clinical trials in oncology. J Natl Cancer Inst. 1997;89(15):1138-47.

Thommen et al, 2015
Thommen DS, Schreiner J, Muller P, Herzig P, Roller A, Belousov A, et al. Progression of lung cancer is associated with increased dysfunction of T cells defined by coexpression of multiple inhibitory receptors. Cancer Immunol Res. 2015;3(12):1344-55.

van de Weyer et al, 2006
van de Weyer PS, Muehlfeit M, Klose C, Bonventre JV, Walz G, Kuehn EW. A highly conserved tyrosine of TIM-3 is phosphorylated upon stimulation by its ligand galectin-9. Biochem Biophys Res Commun. 2006;351(2):571-6.

Wang et al, 2019
Wang Y, Zhou S, Yang F, Qi X, Wang X, Guan X, et al. Treatment-related adverse events of PD-1 and PD-L1 inhibitors in clinical trials: a systematic review and meta-analysis. JAMA Oncol. 2019;5(7):1008-19.

Wei et al, 2020
Wei AH, Esteve J, Porkka K, Knapper S, Vey N, Scholl S, et al. Sabatolimab (MBG453) dose selection and dose-response analysis in myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML): population pharmacokinetics (PK) modeling and evaluation of clinical efficacy/safety by dose. Blood. 2020;136(Suppl 1):40-2.

Weiss et al, 2017
Weiss GJ, Luke JJ, Falchook G, Eroglu Z, Wang J, Hamilton E, et al. A phase 1 study of TSR-022, an anti-TIM-3 monoclonal antibody, in patients (pts) with advanced solid tumors. SITC 2018 Annual Conference Proceedings. 2017:O13.

Weniger and Küppers, 2021
Weniger A, and Küppers R. Molecular biology of Hodgkin lymphoma. Nature, Leukemia 2021;35:968–981.

CCI
CCI
[redacted]
.

Wolf et al, 2020
Wolf Y, Anderson AC, Kuchroo VK. TIM-3 comes of age as an inhibitory receptor. Nat Rev Immunol. 2020;20(3):173-85.

Younes et al, 2016
Younes A, Santoro A, Shipp M, Zinzani PL, Timmerman JM, Armand P, et al. Nivolumab for classical Hodgkin lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. Lancet Oncol 2016;17:1283-94.

Younes et al, 2017
Younes A, Hilden P, Coiffier B, Hagenbeek A, Salles G, Wilson W, et al. International Working Group consensus response-evaluation criteria in lymphoma (RECIL 2017). Ann Oncol 2017;28:1436-47.

Zinzani et al, 2020
Zinzani PL, Chen R, Armand P, Johnson NA, Brice P, Radford J, et al. Pembrolizumab monotherapy in patients with primary refractory classic Hodgkin lymphoma: KEYNOTE-087 subgroup analysis. Leuk Lymphoma 2020;61(4):950-954.