| | |
|---|---|
| **Official Protocol Title:** | Phase 2 Study of Pembrolizumab and Chemotherapy in Patients With Newly Diagnosed Classical Hodgkin Lymphoma (KEYNOTE-C11) |
| **NCT number:** | NCT05008224 |
| **Document Date:** | 15-Dec-2023 |

# TITLE PAGE

**THIS PROTOCOL AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME LLC, RAHWAY, NJ, USA (MSD).**

**Protocol Title:** Phase 2 Study of Pembrolizumab and Chemotherapy in Patients With Newly Diagnosed Classical Hodgkin Lymphoma (KEYNOTE-C11)

**Protocol Number:** C11-06

**Compound Number:** MK-3475

**Sponsor Name:** Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)

**Legal Registered Address:**

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

**Regulatory Agency Identifying Number(s):**

| | |
|---|---|
| NCT | NCT05008224 |
| EU CT | 2022-501615-14 |
| EudraCT | 2021-001244-95 |
| JRCT | Not applicable |
| WHO | Not applicable |
| UTN | Not applicable |
| IND | 118604 |
| | |

**Approval Date:** 15 December 2023

## Sponsor Signatory

| | |
|---|---|
| Typed Name:<br>Title: | Date |

**Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).**

## Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

| | |
|---|---|
| Typed Name:<br>Title: | Date |

## DOCUMENT HISTORY

| Document | Date of Issue | Overall Rationale |
|---|---|---|
| Amendment 6 | 15-DEC-2023 | To add language allowing eligible participants to enroll in an extension study, if available, following the end of MK-3475-C11. |
| Amendment 5 | 06-JUN-2023 | To clarify participants' continuation through the study and into pembrolizumab consolidation regardless of positron emission tomography 2 and 3 response. |
| Amendment 4 | 20-SEP-2022 | Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address. |
| Amendment 3 France-specific | 25-FEB-2022 | Based on France HA feedback, the duration of contraception use in study participants in France was increased to 12 months for females who receive cyclophosphamide and 9 months for males who receive cyclophosphamide. |
| Amendment 2 UK-specific | 01-SEP-2021 | Based on MHRA feedback, the duration of contraception use in UK study participants was increased to 12 months for females who receive cyclophosphamide and was increased to 6 months for males who receive bleomycin, cyclophosphamide, dacarbazine, doxorubicin, etoposide, vincristine, vinblastine, or procarbazine. |
| Amendment 1 | 14-MAY-2021 | To incorporate revisions based on health authority feedback, including modification of sample size, additional safety data monitoring, interim efficacy analysis for futility, only allowing participants <60 years of age to receive escBEACOPP, adding DurCR as a secondary objective, and moving modified PFS and OS from secondary to exploratory objectives. |
| Original Protocol | 11-MAR-2021 | Not applicable |

## PROTOCOL AMENDMENT SUMMARY OF CHANGES

**Amendment:** 06

**Overall Rationale for the Amendment:** To add language allowing eligible participants to enroll in an extension study, if available, following the end of MK-3475-C11.

**Summary of Changes Table:**

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| **Primary Reason for Amendment** | | |
| 4.4 Beginning and End-of-Study Definition | Added language regarding extension study. | Revision to allow eligible participants to enroll in an extension study, if available, following the end of MK-3475-C11. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| **Additional Changes** | | |
| 8.11.4.2 Efficacy Follow-up Visits | Added clarification that an exception to beginning Efficacy Follow-up for participants who discontinue study intervention for a reason other than disease progression is based on investigator assessed disease progression. | To clarify that discontinuation of study intervention for a reason other than disease progression is based on investigator assessed disease progression. |
| 10.1.7 Compliance with Law, Audit, and Debarment | Removed statement on country-specific serious breach reporting. | Text was added in error in previous amendment. |
| Throughout document | Minor administrative, formatting, grammatical, and typographical changes were made throughout the document. | To ensure clarity and accurate interpretation of the intent of the protocol. |

# TABLE OF CONTENTS

**DOCUMENT HISTORY ..... 3**
**PROTOCOL AMENDMENT SUMMARY OF CHANGES ..... 4**
**1 PROTOCOL SUMMARY ..... 14**
**1.1 Synopsis ..... 14**
**1.2 Schema ..... 20**
**1.3 Schedule of Activities ..... 21**
1.3.1 All Participants – Screening, Pembrolizumab Monotherapy (3 Cycles), and AVD (Chemotherapy Phase 1) (2 Cycles) ..... 21
1.3.2 Participants Who are PET-negative at PET3 Scan or PET-positive at PET3 Scan and ≥60 Years of Age – 4 Cycles of AVD (Chemotherapy Phase 2) ..... 28
1.3.3 Participants Who are PET-positive at PET3 Scan and <60 Years of Age – 4 Cycles of escBEACOPP (Chemotherapy Phase 2) ..... 31
1.3.4 All Participants – Pembrolizumab Consolidation and Posttreatment ..... 34
**2 INTRODUCTION ..... 41**
**2.1 Study Rationale ..... 41**
**2.2 Background ..... 42**
2.2.1 Pembrolizumab ..... 42
2.2.1.1 Pharmaceutical and Therapeutic Background ..... 42
2.2.1.2 Preclinical and Clinical Studies ..... 43
2.2.1.3 Ongoing Clinical Studies ..... 43
2.2.2 Treatment of Early Unfavorable and Advanced-stage Hodgkin Lymphoma ..... 43
2.2.3 Role of 2-Fluorodeoxyglucose-positron Emission Tomography ..... 44
2.2.4 Incorporating Anti-PD-1 in Frontline Hodgkin Lymphoma ..... 45
2.2.5 Information on Other Study-related Therapy ..... 46
**2.3 Benefit/Risk Assessment ..... 46**
**3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS ..... 48**
**4 STUDY DESIGN ..... 51**
**4.1 Overall Design ..... 51**
**4.2 Scientific Rationale for Study Design ..... 53**
4.2.1 Rationale for Endpoints ..... 53
4.2.1.1 Efficacy Endpoints ..... 53
4.2.1.2 Safety Endpoints ..... 54
4.2.1.3 Patient-reported Outcomes ..... 54
4.2.1.3.1 EORTC QLQ-C30 ..... 54
4.2.1.3.2 EuroQoL EQ-5D-5L ..... 55
4.2.1.4 Planned Exploratory Biomarker Research ..... 55

4.2.1.5 Future Biomedical Research ....57
**4.3 Justification for Dose ....57**
4.3.1 Pembrolizumab ....57
4.3.2 AVD and escBEACOPP ....58
**4.4 Beginning and End-of-Study Definition ....58**
4.4.1 Clinical Criteria for Early Study Termination ....59
**5 STUDY POPULATION ....60**
**5.1 Inclusion Criteria ....60**
**5.2 Exclusion Criteria ....63**
**5.3 Lifestyle Considerations ....65**
5.3.1 Meals and Dietary Restrictions ....65
**5.4 Screen Failures ....65**
**5.5 Participant Replacement Strategy ....65**
**6 STUDY INTERVENTION ....66**
**6.1 Study Intervention(s) Administered ....66**
6.1.1 Treatment ....70
**6.2 Preparation/Handling/Storage/Accountability ....70**
6.2.1 Dose Preparation ....70
6.2.2 Handling, Storage, and Accountability ....70
**6.3 Measures to Minimize Bias: Randomization and Blinding ....71**
6.3.1 Intervention Assignment ....71
6.3.2 Stratification ....71
6.3.3 Blinding ....71
**6.4 Study Intervention Compliance ....71**
6.4.1 Procarbazine and Prednisone Compliance ....72
**6.5 Concomitant Therapy ....72**
6.5.1 Prohibited Concomitant Medications ....72
6.5.1.1 Systemic Corticosteroid Use ....73
6.5.1.2 Cautions for Use of Chemotherapy ....73
6.5.2 Rescue Medications and Supportive Care ....74
**6.6 Dose Modification (Escalation/Titration/Other) ....74**
6.6.1 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue) ....74
6.6.2 AVD and escBEACOPP Dose Modification ....80
6.6.3 Additional Safety Data Monitoring ....80
**6.7 Intervention After the End of the Study ....81**
**6.8 Clinical Supplies Disclosure ....81**
**6.9 Standard Policies ....81**

**7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL ..... 82**
**7.1 Discontinuation of Study Intervention ..... 82**
**7.2 Participant Withdrawal From the Study ..... 83**
**7.3 Lost to Follow-up ..... 83**
**8 STUDY ASSESSMENTS AND PROCEDURES ..... 84**
**8.1 Administrative and General Procedures ..... 84**
8.1.1 Informed Consent ..... 84
8.1.1.1 General Informed Consent ..... 85
8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research ..... 85
8.1.2 Inclusion/Exclusion Criteria ..... 85
8.1.3 Participant Identification Card ..... 85
8.1.4 Medical History ..... 86
8.1.4.1 Classical Hodgkin Lymphoma Disease History ..... 86
8.1.5 Prior and Concomitant Medications Review ..... 86
8.1.5.1 Prior Medications ..... 86
8.1.5.2 Concomitant Medications ..... 86
8.1.5.3 Subsequent Antineoplastic Therapy Status ..... 86
8.1.6 Assignment of Screening Number ..... 87
8.1.7 Assignment of Treatment/Randomization Number ..... 87
8.1.8 Study Intervention Administration ..... 87
8.1.8.1 Timing of Dose Administration ..... 88
8.1.9 Discontinuation and Withdrawal ..... 89
8.1.9.1 Withdrawal From Future Biomedical Research ..... 89
8.1.10 Participant Blinding/Unblinding ..... 89
8.1.11 Calibration of Equipment ..... 89
8.1.12 Tumor Tissue for Biomarker Status ..... 90
**8.2 Efficacy Assessments ..... 90**
8.2.1 Tumor Imaging and Assessment of Disease ..... 90
8.2.1.1 Initial Tumor Scans ..... 91
8.2.1.2 Tumor Scans During the Study ..... 92
8.2.1.3 End-of-treatment and Follow-up Tumor Scans ..... 92
8.2.1.4 Scan Evaluation ..... 93
8.2.1.5 Bone Marrow Biopsy/Aspirate ..... 93
8.2.2 Patient-reported Outcomes ..... 93
**8.3 Safety Assessments ..... 93**
8.3.1 Physical Examinations ..... 94
8.3.1.1 Full Physical Examination ..... 94

8.3.1.2 Directed Physical Examination....94
8.3.1.3 Assessment of Lymphoma B Symptoms....94
8.3.2 Vital Signs....94
8.3.3 Electrocardiograms....95
8.3.4 Echocardiography or Multigated Acquisition Scan....95
8.3.5 Pulmonary Function Testing....95
8.3.6 Clinical Safety Laboratory Assessments....95
8.3.6.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)....96
8.3.7 Pregnancy Testing....96
8.3.8 International Prognostic Score....97
8.3.9 Unfavorable Risk Factors....97
8.3.10 Performance Assessments: Eastern Cooperative Oncology Group Performance Status....97
**8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events....97**
8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information....98
8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events....100
8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information....100
8.4.4 Regulatory Reporting Requirements for SAE....100
8.4.5 Pregnancy and Exposure During Breastfeeding....100
8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs....101
8.4.7 Events of Clinical Interest....101
**8.5 Treatment of Overdose....102**
8.5.1 Pembrolizumab....102
8.5.2 AVD and escBEACOPP....102
**8.6 Pharmacokinetics....102**
**8.7 Pharmacodynamics....102**
**8.8 Biomarkers....103**
8.8.1 Planned Genetic Analysis Sample Collection....103
**8.9 Future Biomedical Research Sample Collection....103**
**8.10 Medical Resource Utilization and Health Economics....103**
**8.11 Visit Requirements....104**
8.11.1 Screening....104
8.11.2 Treatment Period....104
8.11.3 Discontinued Participants Continuing to be Monitored in the Study....104
8.11.4 Posttreatment Visit....105

8.11.4.1 Safety Follow-up Visit ..... 105
8.11.4.2 Efficacy Follow-up Visits ..... 105
8.11.4.3 Survival Follow-up Contacts ..... 105
8.11.5 Vital Status ..... 105
**9 STATISTICAL ANALYSIS PLAN ..... 106**
**9.1 Statistical Analysis Plan Summary ..... 106**
**9.2 Responsibility for Analyses/In-house Blinding ..... 107**
**9.3 Hypotheses/Estimation ..... 107**
**9.4 Analysis Endpoints ..... 107**
9.4.1 Efficacy Endpoints ..... 107
9.4.2 Safety Endpoints ..... 108
**9.5 Analysis Populations ..... 108**
9.5.1 Efficacy Analysis Populations ..... 108
9.5.2 Safety Analysis Populations ..... 108
**9.6 Statistical Methods ..... 108**
9.6.1 Statistical Methods for Efficacy Analyses ..... 108
9.6.1.1 Complete Response ..... 109
9.6.1.2 PET Negativity ..... 109
9.6.1.3 Duration of Complete Response ..... 109
9.6.1.4 Analysis Strategy for Key Efficacy Variables ..... 110
9.6.2 Statistical Methods for Safety Analyses ..... 111
9.6.3 Demographic and Baseline Characteristics ..... 111
**9.7 Interim Analyses ..... 111**
9.7.1 Interim Efficacy Analysis ..... 111
9.7.2 Ongoing Safety Data Monitoring ..... 112
**9.8 Multiplicity ..... 112**
**9.9 Sample Size and Power Calculations ..... 113**
**9.10 Subgroup Analyses ..... 113**
**9.11 Compliance (Medication Adherence) ..... 113**
**9.12 Extent of Exposure ..... 114**
**10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS ..... 115**
**10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations ..... 115**
10.1.1 Code of Conduct for Clinical Trials ..... 115
10.1.2 Financial Disclosure ..... 118
10.1.3 Data Protection ..... 118
10.1.3.1 Confidentiality of Data ..... 119
10.1.3.2 Confidentiality of Participant Records ..... 119

10.1.3.3 Confidentiality of IRB/IEC Information....119
10.1.4 Committees Structure....119
10.1.4.1 Internal Data Monitoring Committee....119
10.1.5 Publication Policy....119
10.1.6 Compliance with Study Registration and Results Posting Requirements....120
10.1.7 Compliance with Law, Audit, and Debarment....120
10.1.8 Data Quality Assurance....121
10.1.9 Source Documents....122
10.1.10 Study and Site Closure....122
**10.2 Appendix 2: Clinical Laboratory Tests....123**
**10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting....125**
10.3.1 Definitions of Medication Error, Misuse, and Abuse....125
10.3.2 Definition of AE....125
10.3.3 Definition of SAE....126
10.3.4 Additional Events Reported....127
10.3.5 Recording AE and SAE....127
10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor....131
**10.4 Appendix 4: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up....132**
**10.5 Appendix 5: Contraceptive Guidance....133**
10.5.1 Definitions....133
10.5.2 Contraceptive Requirements....134
**10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research....135**
**10.7 Appendix 7: Country-specific Requirements....139**
10.7.1 France-specific Requirements....139
**10.8 Appendix 8: Description of the iRECIST Process for Assessment of Disease Progression....141**
**10.9 Appendix 9: Application of the Lugano Classification for Treatment Response Assessment....142**
10.9.1 Overview....142
10.9.2 Lugano Summary Table....142
10.9.3 Anatomic Disease Assessment....145
10.9.3.1 Screening (Baseline) Assessment....145
10.9.3.2 Post-baseline Assessment....147
10.9.4 Metabolic Response....152
10.9.5 Clinical Data....153

10.9.6 Overall Response ..... 154
**10.10 Appendix 10: International Prognostic Score ..... 156**
**10.11 Appendix 11: Unfavorable Risk Factors – NCCN Guidelines ..... 157**
**10.12 Appendix 12: Eastern Cooperative Performance Status ..... 158**
**10.13 Appendix 13: Abbreviations ..... 159**
**11 REFERENCES ..... 165**

## LIST OF TABLES

Table 1 Adequate Organ Function Laboratory Values ....62
Table 2 Study Interventions ....67
Table 3 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated With Pembrolizumab Monotherapy, Coformulations, or IO Combinations ....75
Table 4 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines ....79
Table 5 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events ....99
Table 6 CCI ....110
Table 7 Analysis Strategy for Key Efficacy Variables ....110
Table 8 CCI ....112
Table 9 Protocol-required Safety Laboratory Assessments ....123

## LIST OF FIGURES

Figure 1 Study Diagram .....20

# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol Title:** Phase 2 Study of Pembrolizumab and Chemotherapy in Patients With Newly Diagnosed Classical Hodgkin Lymphoma (KEYNOTE-C11)

**Short Title:** Pembrolizumab and chemotherapy for newly diagnosed classical Hodgkin Lymphoma

**Acronym:** KEYNOTE-C11

**Hypotheses, Objectives, and Endpoints:**

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In males and females with newly diagnosed early unfavorable or advanced-stage classical Hodgkin Lymphoma:

| **Primary Objective** | **Primary Endpoint** |
|---|---|
| To evaluate complete response (CR) rate at the end of study intervention in participants with newly diagnosed classical Hodgkin Lymphoma (cHL) assessed by independent central review according to Lugano 2014 response criteria | CR |
| CCI [redacted] | |
| **Secondary Objectives** | **Secondary Endpoints** |
| To evaluate the CR rate at the end of study intervention in participants with newly diagnosed cHL by investigator assessment according to Lugano 2014 response criteria | CR |
| CCI [redacted] | |

| | |
|---|---|
| To evaluate the rate of Positron Emission Tomography (PET) negativity at PET2 following 3 cycles of pembrolizumab monotherapy by independent central review according to the 2-fluorodeoxyglucose (FDG)-PET 5-point scale | PET negativity: a score of 1, 2, or 3 on the FDG-PET 5-point scale after 3 cycles of pembrolizumab monotherapy |
| To evaluate the rate of PET negativity at PET3 after completion of 3 cycles of pembrolizumab monotherapy followed by 2 cycles of doxorubicin in combination with vinblastine and dacarbazine (AVD) by independent central review according to the FDG-PET 5-point scale | PET negativity: a score of 1, 2, or 3 on the FDG-PET 5-point scale after 3 cycles of pembrolizumab monotherapy followed by 2 cycles of AVD |
| To evaluate the safety and tolerability of initial pembrolizumab monotherapy followed by chemotherapy and pembrolizumab consolidation in participants with newly diagnosed cHL | -Adverse Events (AEs)<br><br>-Discontinuation of study intervention due to an AE |

## Overall Design:

| | |
|---|---|
| Study Phase | Phase 2 |
| Primary Purpose | Treatment |
| Indication | The treatment of participants with classical Hodgkin's lymphoma |
| Population | Participants with newly diagnosed early unfavorable or advanced-stage cHL |
| Study Type | Interventional |
| Intervention Model | Sequential<br>This is a multi site study. |
| Type of Control | No Treatment Control |
| Study Blinding | Unblinded open-label |
| Blinding Roles | No blinding |
| CCI [redacted] | CCI [redacted] |

## Number of Participants:

Approximately 140 participants will be enrolled in the study.

## Intervention Groups and Duration:

| Arm Name | Intervention Name | Unit Dose Strength(s) | Dosage Level(s) | Route of Administration | Regimen/ Treatment Period/ Vaccination Regimen | Use |
|---|---|---|---|---|---|---|
| All participants | Pembrolizumab | 25 mg/mL | 200 mg | IV Infusion | Day 1 of each cycle, Q3W, 3 cycles | Test Product |
| All participants | Doxorubicin | Variable | 25 mg/m$^2$ | Per Local Guidelines | Days 1 and 15 of each cycle, Q4W, 2 cycles | Test Product |
| All participants | Vinblastine | Variable | 6 mg/m$^2$ | Per Local Guidelines | Days 1 and 15 of each cycle, Q4W, 2 cycles | Test Product |
| All participants | Dacarbazine | Variable | 375 mg/m$^2$ | Per Local Guidelines | Days 1 and 15 of each cycle, Q4W, 2 cycles | Test Product |
| PET3 negative, or PET3 positive and ≥60 years of age | Doxorubicin | Variable | 25 mg/m$^2$ | Per Local Guidelines | Days 1 and 15 of each cycle, Q4W, 4 cycles | Test Product |
| PET3 negative, or PET3 positive and ≥60 years of age | Vinblastine | Variable | 6 mg/m$^2$ | Per Local Guidelines | Days 1 and 15 of each cycle, Q4W, 4 cycles | Test Product |
| PET3 negative, or PET3 positive and ≥60 years of age | Dacarbazine | Variable | 375 mg/m$^2$ | Per Local Guidelines | Days 1 and 15 of each cycle, Q4W, 4 cycles | Test Product |
| PET3 positive and <60 years of age | Bleomycin | Variable | 10 units/m$^2$ | Per Local Guidelines | Day 8 of each cycle, Q3W, 4 cycles | Test Product |

| Arm Name | Intervention Name | Unit Dose Strength(s) | Dosage Level(s) | Route of Administration | Regimen/ Treatment Period/ Vaccination Regimen | Use |
|---|---|---|---|---|---|---|
| PET3 positive and <60 years of age | Etoposide | Variable | 200 mg/m$^2$ | Per Local Guidelines | Days 1 to 3 of each cycle, Q3W, 4 cycles | Test Product |
| PET3 positive and <60 years of age | Doxorubicin | Variable | 35 mg/m$^2$ | Per Local Guidelines | Day 1 of each cycle, Q3W, 4 cycles | Test Product |
| PET3 positive and <60 years of age | Cyclophosphamide | Variable | 1250 mg/m$^2$ | Per Local Guidelines | Day 1 of each cycle, Q3W, 4 cycles | Test Product |
| PET3 positive and <60 years of age | Vincristine | Variable | 1.4 mg/m$^2$ | Per Local Guidelines | Day 8 of each cycle, Q3W, 4 cycles | Test Product |
| PET3 positive and <60 years of age | Procarbazine | Variable | 100 mg/m$^2$ | Oral | Days 1 to 7 of each cycle, Q3W, 4 cycles | Test Product |
| PET3 positive and <60 years of age | Prednisone | Variable | 40 mg/m$^2$ | Oral | Days 1 to 14 of each cycle, Q3W, 4 cycles | Test Product |
| All participants | Pembrolizumab | 25 mg/mL | 400 mg | IV Infusion | Day 1 of each cycle, Q6W, 4 cycles | Test Product |

AVD=doxorubicin in combination with vinblastine and dacarbazine; escBEACOPP=escalated bleomycin in combination with etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; IV=intravenous; PET=positron emission tomography; Q3W=every 3 weeks; Q4W=every 4 weeks; Q6W=every 6 weeks.

Note: Age is based on age at screening.

For vincristine, maximum dose=2 mg.

For participants with early unfavorable, nonbulky disease will receive 2 cycles of AVD if PET3-negative, or if PET3-positive and ≥60 years of age, or 2 cycles of escBEACOPP if PET3-positive and <60 years of age.

Other current or former name(s) or alias(es) for study intervention(s) are as follows: Pembrolizumab is also known as MK-3475. Doxorubicin is also known as adriamycin.

| | |
|---|---|
| Total Number of Intervention Groups/Arms | 1 |
| Duration of Participation | Each participant will participate in the study from the time that the participant provides documented informed consent through the final protocol-specified contact.<br><br>After a screening phase of up to 28 days each participant will be assigned to receive study intervention until one of the conditions for discontinuation of study intervention is met.<br><br>After the end-of-treatment, each participant will be followed for the occurrence of adverse events and spontaneously reported pregnancy.<br><br>Participants who discontinue for any reason will have posttreatment follow-up imaging for disease status until any of the conditions for discontinuation of imaging are met.<br><br>All participants will be followed for overall survival until death, withdrawal of consent, or the end of the study. |

**Study Governance Committees:**

| | |
|---|---|
| Executive Oversight Committee | No |
| Data Monitoring Committee | Yes |
| Clinical Adjudication Committee | No |
| Steering Committee | No |

Study governance considerations are outlined in Appendix 1.

The DMC will be an internal DMC (see Sections 6.6.3 and 10.1.4.1).

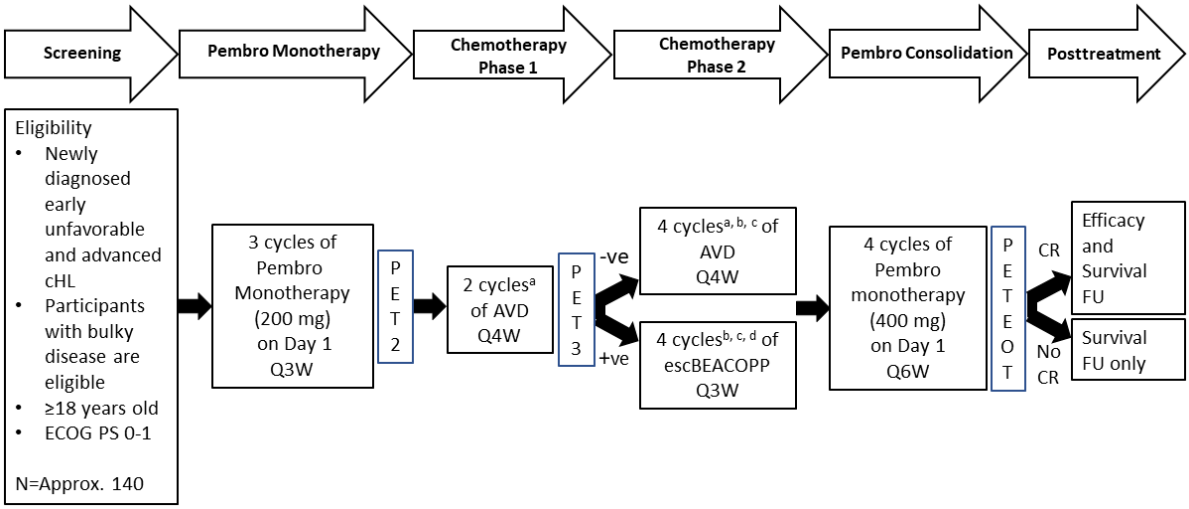
**Study Accepts Healthy Participants: No**

A list of abbreviations is in Appendix 13.

## 1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Diagram




-ve=negative; +ve=positive; AVD=doxorubicin in combination with vinblastine and dacarbazine; cHL=classical Hodgkin Lymphoma; CR=complete response; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOT=end-of-treatment; escBEACOPP=escalated bleomycin in combination with etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; FU=follow-up; N=number of participants; Pembro=pembrolizumab; PET=positron emission tomography; Q3W=every 3 weeks; Q4W=every 4 weeks; Q6W=every 6 weeks.

[a] Each cycle of AVD consists of administration of study intervention on Days 1 and 15.

[b] Participants with early unfavorable, nonbulky disease will receive 2 cycles of AVD (if PET3 -ve or if PET3 +ve and ≥60 years of age) or 2 cycles of escBEACOPP (if PET3 +ve and <60 years of age).

[c] Participants ≥60 years of age will continue to receive AVD in Chemotherapy Phase 2 regardless of their PET3 response, and will not receive escBEACOPP.

[d] Each cycle of escBEACOPP consists of administration of study intervention according to the dosing schedule provided in Section 1.3.3.

Note: Age is based on age at screening.

## 1.3 Schedule of Activities

### 1.3.1 All Participants – Screening, Pembrolizumab Monotherapy (3 Cycles), and AVD (Chemotherapy Phase 1) (2 Cycles)

| **Study Period** | **Screening** | **Intervention (Pembro) (Q3W Cycles)[a]** | | | **PET2** | **Intervention (AVD) (Q4W Cycles)[a,b]** | | | | **PET3** | **Notes** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle** | **Screening** | **Pembro C1** | **Pembro C2** | **Pembro C3** | | **AVD C1** | | **AVD C2** | | | **AVD C1D1 should start 3 weeks (+3 days) after Pembrolizumab C3D1** |
| **Dosing Day** | **-28 to -1** | **D1** | **D1** | **D1** | | **D1** | **D15** | **D1** | **D15** | | |
| **Administrative Procedures** | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | |
| Informed Consent for Future Biomedical Research (optional) | X | | | | | | | | | | Participant may participate in main study without signing Future Biomedical Research consent. |
| Consent for optional tissue collection | X | | | | | | | | | | Optional Consent. |
| Inclusion/Exclusion Criteria | X | | | | | | | | | | |
| Participant Identification Card | X | X | | | | | | | | | Distribute at Screening and add the allocation number at the time of allocation. |
| Demographics and Medical History | X | | | | | | | | | | |
| cHL Disease History | X | | | | | | | | | | |
| Prior/Concomitant Medication Review | X | X | X | X | | X | X | X | X | | Record medications taken within 28 days before the start of study intervention. Concomitant medications will be recorded during the study through the Safety Follow-up Visit (Section 1.3.4). |
| Survival Status | | ← | | | | | | | → | | On Sponsor request, participants may be contacted for survival status at any time during the course of the study. |

| **Study Period** | **Screening** | **Intervention (Pembro) (Q3W Cycles)[a]** | | | **PET2** | **Intervention (AVD) (Q4W Cycles)[a,b]** | | | | **PET3** | **Notes** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle** | **Screening** | **Pembro C1** | **Pembro C2** | **Pembro C3** | | **AVD C1** | | **AVD C2** | | | **AVD C1D1 should start 3 weeks (+3 days) after Pembrolizumab C3D1** |
| **Dosing Day** | **-28 to -1** | **D1** | **D1** | **D1** | | **D1** | **D15** | **D1** | **D15** | | |
| Intervention Allocation in IWRS | | X | | | | | | | | | Treatment number: Obtain after all screening assessments are completed and ensuring participant meets all study-related eligibility criteria. Pembrolizumab C1D1 dose should be administered within 3 days of allocation in IWRS. |
| **Study Intervention Administration (Assessments/procedures to be performed before administration of study intervention at each visit unless otherwise specified)** | | | | | | | | | | | |
| Pembrolizumab | | X | X | X | | | | | | | 200 mg by IV on Day 1 of each Q3W cycle for 3 cycles. |
| Doxorubicin | | | | | | X | X | X | X | | 25 mg/m$^2$ by IV on Days 1 and 15 of each Q4W cycle for 2 cycles |
| Vinblastine | | | | | | X | X | X | X | | 6 mg/m$^2$ by IV on Days 1 and 15 of each Q4W cycle for 2 cycles |
| Dacarbazine | | | | | | X | X | X | X | | 375 mg/m$^2$ by IV on Days 1 and 15 of each Q4W cycle for 2 cycles |
| **Efficacy Procedures** | | | | | | | | | | | |
| FDG-PET scan (Whole body) | X (PET1) | | | | X | | | | | X | PET1 is required for eligibility and must be performed within 28 days before the first dose of study intervention.<br>PET2 must be performed 3 weeks (±3 days) after pembrolizumab C3D1 and before AVD C1D1.<br>PET3 must be performed between AVD C2D26 and C2D29 and before starting additional chemotherapy (AVD or escBEACOPP) (Sections 1.3.2 and 1.3.3).<br>Additional PET scans may be performed as clinically indicated. |

| **Study Period** | **Screening** | **Intervention (Pembro) (Q3W Cycles)[a]** | | | **PET2** | **Intervention (AVD) (Q4W Cycles)[a,b]** | | | | **PET3** | **Notes** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle** | **Screening** | **Pembro C1** | **Pembro C2** | **Pembro C3** | | **AVD C1** | | **AVD C2** | | | **AVD C1D1 should start 3 weeks (+3 days) after Pembrolizumab C3D1** |
| **Dosing Day** | **-28 to -1** | **D1** | **D1** | **D1** | | **D1** | **D15** | **D1** | **D15** | | |
| Diagnostic Quality CT scan (Neck, Chest, Abdominal, Pelvic) | X | | | | | | | | | | CT scan is required for eligibility and must be performed within 28 days before the first dose of study intervention.<br>If PET and CT scans at Screening are positive for disease of the neck, subsequent CT scans must include the neck. If PET and CT scans at Screening are negative for disease in the neck, subsequent CT scans may omit the neck. Additional CT scans may be performed as clinically indicated.<br>If diagnostic quality CT scan cannot be performed due to medical contraindication or local practice, refer to Site Imaging Manual for alternative methods for anatomic imaging. |
| Lymphoma Disease Response Assessment by Lugano Classification 2014 (see Appendix 9) | | | | | X | | | | | X | |
| **Symptom Assessment** | | | | | | | | | | | |
| Assessment of Lymphoma B Symptoms | X | | | | | X | | | | | Perform at screening and within 3 days before AVD C1D1 dosing. |
| **Safety Procedures** | | | | | | | | | | | |
| Full Physical Examination | X | | | | | | | | | | |
| Directed Physical Examination | | X | X | X | | X | | X | | | Perform within 3 days before dosing on Day 1 of each cycle and as clinically indicated. |

| **Study Period** | **Screening** | **Intervention (Pembro) (Q3W Cycles)[a]** | | | **PET2** | **Intervention (AVD) (Q4W Cycles)[a,b]** | | | | **PET3** | **Notes** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle** | **Screening** | **Pembro C1** | **Pembro C2** | **Pembro C3** | | **AVD C1** | | **AVD C2** | | | **AVD C1D1 should start 3 weeks (+3 days) after Pembrolizumab C3D1** |
| **Dosing Day** | **-28 to -1** | **D1** | **D1** | **D1** | | **D1** | **D15** | **D1** | **D15** | | |
| Vital Signs (temperature, blood pressure, respiratory rate, pulse rate, weight, height [height – Screening only]) | X | X | X | X | | X | X | X | X | | Perform at Screening and within 3 days before dosing at each specified time point, and as clinically indicated. |
| 12-lead ECG | X | | | | | | | | | | Additional ECGs may be performed as clinically indicated. |
| ECHO or MUGA | X | | | | | | | | X | | Perform at Screening and at the end of AVD C2 (before starting additional chemotherapy [AVD or escBEACOPP]). |
| ECOG Performance Status | X | | X | X | | X | | X | | | Perform screening assessment within 7 days before C1D1 dose of pembrolizumab and all other assessments within 3 days before dosing on Day 1 of each subsequent cycle. |
| IPS | X | | | | | | | | | | Refer to Appendix 10 for prognostic factors used for scoring. |
| Unfavorable Risk Factors | X | | | | | | | | | | Refer to Appendix 11. Applicable only for participants with Stage I or II disease. |
| HIV / HBV / HCV Eligibility Testing | X | | | | | | | | | | Required only when mandated by local health authority. |
| Adverse Event Monitoring | X | X | X | X | | X | X | X | X | | Report all AEs through 30 days after the last dose. Report SAEs through 90 days after the last dose, or 30 days after the last dose if participant initiates a new anticancer treatment, whichever is earlier. Report SAEs outside the time specified above if considered related to study intervention. |

| Study Period | Screening | Intervention (Pembro) (Q3W Cycles)[a] | | | PET2 | Intervention (AVD) (Q4W Cycles)[a,b] | | | | PET3 | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Cycle | Screening | Pembro C1 | Pembro C2 | Pembro C3 | | AVD C1 | | AVD C2 | | | AVD C1D1 should start 3 weeks (+3 days) after Pembrolizumab C3D1 |
| Dosing Day | -28 to -1 | D1 | D1 | D1 | | D1 | D15 | D1 | D15 | | |
| **Laboratory Procedures/Assessments (Performed by Local Laboratory)** | | | | | | | | | | | |
| Urine or Serum Pregnancy Test – WOCBP Only | X | ← | — | — | — | — | — | — | → | | WOCBP require a negative pregnancy test within 24 hours for urine and 72 hours for serum before C1D1 dose of pembrolizumab.<br>If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required.<br>In case of suspected false positive pregnancy test in participants with fertility preservation, consult Sponsor.<br>A pregnancy test must be performed every cycle (within 24 hours of study visit for urine and 72 hours for serum) during study intervention.<br>More frequent pregnancy testing may be performed if required by local regulations or if clinically indicated. |
| Serum FSH – if needed to confirm postmenopausal state | X | | | | | | | | | | May be used to confirm postmenopausal state in women not currently on HRT or hormonal contraception (see Appendix 5). In absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required. |
| PT/INR and aPTT/PTT | X | | | | | | | | | | Screening: Perform within 7 days before C1D1 dose of pembrolizumab.<br>After Screening: Additional testing may be conducted as clinically indicated. |

| **Study Period** | **Screening** | **Intervention (Pembro) (Q3W Cycles)[a]** | | | **PET2** | **Intervention (AVD) (Q4W Cycles)[a,b]** | | | | **PET3** | **Notes** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle** | **Screening** | **Pembro C1** | **Pembro C2** | **Pembro C3** | | **AVD C1** | | **AVD C2** | | | **AVD C1D1 should start 3 weeks (+3 days) after Pembrolizumab C3D1** |
| **Dosing Day** | **-28 to -1** | **D1** | **D1** | **D1** | | **D1** | **D15** | **D1** | **D15** | | |
| Hematology | X | X | X | X | | X | | X | | | Screening: perform within 7 days before C1D1 dose of pembrolizumab.<br>After Screening: perform within 3 days before dosing on Day 1 of every cycle. There is no need to repeat assessments on pembrolizumab C1D1 if screening assessment is within 3 days before pembrolizumab C1D1 dose.<br>The laboratory criteria in **Table 1** must be met before dosing on Day 1 of every cycle (the requirement for ANC is ≥1000/μL from pembrolizumab C2 onwards), with the exception of hematological parameters for AVD cycles.<br>Perform more frequently as clinically indicated. |
| Chemistry | X | X | X | X | | X | | X | | | |
| Thyroid Function Tests (TSH, T3, T4) | X | X | X | X | | X | | X | | | |
| Urinalysis | X | | | | | | | | | | Perform within 7 days before C1D1 dose of pembrolizumab. |
| ESR | X | | | | | | | | | | |
| LDH | X | | | | | | | | | | |
| Bone Marrow Biopsy/Aspirate | <Perform as clinically indicated > | | | | | | | | | | Refer to Section 8.2.1.5 for details. |
| **Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood (Performed by Central Laboratory)** | | | | | | | | | | | |
| CCI [redacted] | | | | | | | | | | | CCI [redacted] |

| Study Period | Screening | Intervention (Pembro) (Q3W Cycles)[a] | | | PET2 | Intervention (AVD) (Q4W Cycles)[a,b] | | | | PET3 | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Cycle | Screening | Pembro C1 | Pembro C2 | Pembro C3 | | AVD C1 | | AVD C2 | | | AVD C1D1 should start 3 weeks (+3 days) after Pembrolizumab C3D1 |
| Dosing Day | -28 to -1 | D1 | D1 | D1 | | D1 | D15 | D1 | D15 | | |
| CCI | | | | CCI | | | | | | | CCI |
| **Biomarkers** | | | | | | | | | | | |
| CCI | | CCI | | | | | | | | | CCI |
| | | | CCI | CCI | | CCI | | | CCI | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| **Patient-reported Outcomes** | | | | | | | | | | | |
| CCI | | CCI | | CCI | | CCI | | | | | CCI |
| | | | | | | | | | | | |

AE=adverse event; ANC=absolute neutrophil count; aPTT=activated partial thromboplastin time; AVD=doxorubicin in combination with vinblastine and dacarbazine; C=cycle; cHL=classical Hodgkin Lymphoma; CT=computed tomography; CCI; D=day; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; CCI
escBEACOPP=escalated bleomycin in combination with etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; ESR=erythrocyte sedimentation rate; FDG-PET=2-fluorodeoxyglucose positron emission tomography; FSH=follicle-stimulating hormone; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HRT=hormone replacement treatment; INR=international normalized ratio; IPS=international prognostic score; IV=intravenous; IWRS=interactive web response system; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; MUGA=multigated acquisition; PBMC=peripheral blood mononuclear cell; Pembro=pembrolizumab; PET=positron emission tomography; PRO=patient-reported outcome; PT=prothrombin time; PTT=partial thromboplastin time; Q3W=every 3 weeks; Q4W=every 4 weeks; SAE=serious adverse event; T3=triiodothyronine; T4=thyroxine; TCR=T-cell receptor; TSH=thyroid-stimulating hormone; WOCBP=woman of childbearing potential.

[a] A maximum of a 3-day delay is permitted from the scheduled start of each cycle.

[b] For AVD, any delays of more than 3 days beyond the visit window not related to an adverse event should be discussed with Sponsor.

### 1.3.2 Participants Who are PET-negative at PET3 Scan or PET-positive at PET3 Scan and ≥60 Years of Age – 4 Cycles of AVD (Chemotherapy Phase 2)

Note: 2 cycles of AVD in Chemotherapy Phase 2 in participants with early unfavorable, nonbulky disease.
Participants ≥60 years of age who are PET3 positive will continue to receive AVD in Chemotherapy Phase 2.

Age is based on age at screening.

| **Study Period** | **Intervention (AVD Chemotherapy) (Q4W Cycles)[a,b]** | | | | | | | | **Notes** |
|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle** | **AVD C3** | | **AVD C4** | | **AVD C5c** | | **AVD C6c** | | **PET-negative is defined as a score of 1, 2, or 3 on the FDG-PET 5-point scale.** |
| **Dosing Day** | **D1** | **D15** | **D1** | **D15** | **D1** | **D15** | **D1** | **D15** | **AVD C3D1 should start 4 weeks (+3 days) after AVD C2D1 (see Section 1.3.1)** |
| **Administrative Procedures** | | | | | | | | | |
| Concomitant Medication Review | X | X | X | X | X | X | X | X | Concomitant medications will be recorded during the study through the Safety Follow-up Visit (Section 1.3.4). |
| Survival Status | ◄——— | | | | | | | ———► | On Sponsor request, participants may be contacted for survival status at any time during the course of the study. |
| **Study Intervention Administration (Assessments/procedures to be performed before administration of study intervention at each visit unless otherwise specified)** | | | | | | | | | |
| Doxorubicin | X | X | X | X | X | X | X | X | 25 mg/m$^2$ by IV on Days 1 and 15 of each Q4W cycle for 4 cycles[c] |
| Vinblastine | X | X | X | X | X | X | X | X | 6 mg/m$^2$ by IV on Days 1 and 15 of each Q4W cycle for 4 cycles[c] |
| Dacarbazine | X | X | X | X | X | X | X | X | 375 mg/m$^2$ by IV on Days 1 and 15 of each Q4W cycle for 4 cycles[c] |
| **Symptom Assessment** | | | | | | | | | |
| Assessment of Lymphoma B Symptoms | X | | | | | | | | Perform within 3 days before AVD C3D1 dosing. |
| Safety Procedures | | | | | | | | | |
| Directed Physical Examination | X | | X | | X | | X | | Perform within 3 days before dosing on Day 1 of each cycle and as clinically indicated. |
| Vital Signs (temperature, blood pressure, respiratory rate, pulse rate, weight) | X | X | X | X | X | X | X | X | Perform within 3 days before dosing on Day 1 and Day 15 of each cycle and as clinically indicated. |
| 12-lead ECG | <Perform as clinically indicated> | | | | | | | | |

| **Study Period** | **Intervention (AVD Chemotherapy) (Q4W Cycles)[a,b]** | | | | | | | | **Notes** |
|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle** | **AVD C3** | | **AVD C4** | | **AVD C5c** | | **AVD C6c** | | **PET-negative is defined as a score of 1, 2, or 3 on the FDG-PET 5-point scale.** |
| **Dosing Day** | **D1** | **D15** | **D1** | **D15** | **D1** | **D15** | **D1** | **D15** | **AVD C3D1 should start 4 weeks (+3 days) after AVD C2D1 (see Section 1.3.1)** |
| ECHO or MUGA | | | | X* | | | | X | Perform at the end of the last cycle of chemotherapy (before starting pembrolizumab consolidation). Additional testing may be performed as clinically indicated.<br>*Only for participants with early unfavorable nonbulky disease. |
| ECOG Performance Status | X | | X | | X | | X | | Perform within 3 days before dosing on Day 1 of each cycle. |
| Adverse Event Monitoring | X | X | X | X | X | X | X | X | Report all AEs through 30 days after the last dose. Report SAEs through 90 days after the last dose, or 30 days after the last dose if participant initiates a new anticancer treatment, whichever is earlier. Report SAEs outside the time specified above if considered related to study intervention. |
| **Laboratory Procedures/Assessments (Performed by Local Laboratory)** | | | | | | | | | |
| Urine or Serum Pregnancy Test – WOCBP Only | ← | | | | | | | → | A pregnancy test must be performed every cycle (within 24 hours of study visit for urine and 72 hours for serum) during study intervention. More frequent pregnancy testing may be performed if required by local regulations or if clinically indicated.<br>In case of suspected false positive pregnancy test in participants with fertility preservation, consult Sponsor. |
| Hematology | X | | X | | X | | X | | Perform within 3 days before dosing on Day 1 of every cycle.<br>The laboratory criteria in **Table 1** must be met before dosing on Day 1 of every cycle, with the exception of hematological parameters.<br>Perform more frequently as clinically indicated. |
| Chemistry | X | | X | | X | | X | | |
| Thyroid Function Tests (TSH, T3, T4) | X | | X | | X | | X | | |
| Bone Marrow Biopsy/Aspirate | ß Perform as clinically indicated à | | | | | | | | Refer to Section 8.2.1.5 for details. |
| **Patient-reported Outcomes** | | | | | | | | | |
| CCI [redacted] | | | | | CCI [redacted] | | | | CCI [redacted] |

| Study Period | Intervention (AVD Chemotherapy) (Q4W Cycles)[a,b] | | | | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle** | **AVD C3** | | **AVD C4** | | **AVD C5c** | | **AVD C6c** | | **PET-negative is defined as a score of 1, 2, or 3 on the FDG-PET 5-point scale.** |
| **Dosing Day** | **D1** | **D15** | **D1** | **D15** | **D1** | **D15** | **D1** | **D15** | **AVD C3D1 should start 4 weeks (+3 days) after AVD C2D1 (see Section 1.3.1)** |

AE=adverse event; AVD=doxorubicin in combination with vinblastine and dacarbazine; C=cycle; D=day; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; CCI [redacted] CCI [redacted] FDG-PET=2-fluorodeoxyglucose positron emission tomography; IV=intravenous; MUGA=multigated acquisition; PET=positron emission tomography; CCI [redacted]; Q4W=every 4 weeks; SAE=serious adverse event; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WOCBP=woman of childbearing potential.

[a] A maximum of a 3-day delay is permitted from the scheduled start of each cycle.

[b] For AVD, any delays of more than 3 days beyond the visit window not related to an adverse event should be discussed with Sponsor.

[c] Participants with early unfavorable, nonbulky disease will not receive AVD Cycles 5 and 6; therefore, assessments and procedures scheduled during AVD Cycles 5 and 6 are not applicable to these participants.

### 1.3.3 Participants Who are PET-positive at PET3 Scan and <60 Years of Age – 4 Cycles of escBEACOPP (Chemotherapy Phase 2)

Note: 2 cycles of escBEACOPP in Chemotherapy Phase 2 in participants with early unfavorable, nonbulky disease.
Participants ≥60 years of age who are PET3 positive will not receive escBEACOPP in Chemotherapy Phase 2 and should continue to receive AVD according to Section 1.3.2.

Age is based on age at screening.

| **Study Period:** | **Intervention (escBEACOPP Chemotherapy) (Q3W Cycles)[a]** | | | | | | | | **Notes** |
|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle** | **escB C1** | | **escB C2** | | **escB C3b** | | **escB C4b** | | **PET-positive is defined as a score of 4 or 5 on the FDG-PET 5-point scale. escBEACOPP C1D1 should start 4 weeks (+7 days) after AVD C2D1 (see Section 1.3.1)** |
| **Dosing Day** | **D1** | **D8** | **D1** | **D8** | **D1** | **D8** | **D1** | **D8** | |
| **Administrative Procedures** | | | | | | | | | |
| Concomitant Medication Review | X | X | X | X | X | X | X | X | Concomitant medications will be recorded during the study through the Safety Follow-up Visit (Section 1.3.4). |
| Survival Status | ◄——— | | | | | | | ———► | On Sponsor request, participants may be contacted for survival status at any time during the course of the study. |
| **Study Intervention Administration (Assessments/procedures to be performed before administration of study intervention at each visit unless otherwise specified)** | | | | | | | | | |
| Bleomycin | | X | | X | | X | | X | 10 units/$m^2$ by IV on Day 8 of each Q3W cycle for 4 cycles[b] |
| Etoposide | X | | X | | X | | X | | 200 mg/$m^2$ by IV on Days 1 to 3 of each Q3W cycle for 4 cycles[b] |
| Doxorubicin | X | | X | | X | | X | | 35 mg/$m^2$ by IV on Day 1 of each Q3W cycle for 4 cycles[b] |
| Cyclophosphamide | X | | X | | X | | X | | 1250 mg/$m^2$ by IV on Day 1 of each Q3W cycle for 4 cycles[b] |
| Vincristine | | X | | X | | X | | X | 1.4 mg/$m^2$ (maximum 2 mg) by IV on Day 8 of each Q3W cycle for 4 cycles[b] |
| Procarbazine | X | | X | | X | | X | | 100 mg/$m^2$ PO on Days 1 to 7 of each Q3W cycle for 4 cycles[b] |
| Prednisone | X | X | X | X | X | X | X | X | 40 mg/$m^2$ PO on Days 1 to 14 of each Q3W cycle for 4 cycles[b] |
| **Symptom Assessment** | | | | | | | | | |
| Assessment of Lymphoma B Symptoms | X | | | | | | | | Perform within 3 days before escBEACOPP C1D1 dosing. |
| **Safety Procedures** | | | | | | | | | |
| Directed Physical Examination | X | | X | | X | | X | | Perform within 3 days before dosing on Day 1 of each cycle and as clinically indicated. |

| **Study Period:** | **Intervention (escBEACOPP Chemotherapy) (Q3W Cycles)[a]** | | | | | | | | **Notes** |
|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle** | **escB C1** | | **escB C2** | | **escB C3b** | | **escB C4b** | | **PET-positive is defined as a score of 4 or 5 on the FDG-PET 5-point scale. escBEACOPP C1D1 should start 4 weeks (+7 days) after AVD C2D1 (see Section 1.3.1)** |
| **Dosing Day** | **D1** | **D8** | **D1** | **D8** | **D1** | **D8** | **D1** | **D8** | |
| Vital Signs (temperature, blood pressure, respiratory rate, pulse rate, weight) | X | X | X | X | X | X | X | X | Perform within 3 days before dosing on Day 1 and Day 8 of each cycle and as clinically indicated. |
| 12-lead ECG | <Perform as clinically indicated > | | | | | | | | |
| ECHO or MUGA | | | | X* | | | | X | Perform at the end of the last cycle of chemotherapy (before starting pembrolizumab consolidation). Additional testing may be performed as clinically indicated.<br>*Only for participants with early unfavorable nonbulky disease. |
| ECOG Performance Status | X | | X | | X | | X | | Perform within 3 days before dosing on Day 1 of each cycle. |
| Pulmonary function testing | X | | | X* | | | | X | Perform within 7 days before C1D1 dose and at the end of the last cycle of chemotherapy (before starting pembrolizumab consolidation). Additional testing may be performed as clinically indicated.<br>*Only for participants with early unfavorable nonbulky disease. |
| Adverse Event Monitoring | X | X | X | X | X | X | X | X | Report all AEs through 30 days after the last dose. Report SAEs through 90 days after the last dose, or 30 days after the last dose if participant initiates a new anticancer treatment, whichever is earlier. Report SAEs outside the time specified above if considered related to study intervention. |
| **Laboratory Procedures/Assessments (Performed by Local Laboratory)** | | | | | | | | | |
| Urine or Serum Pregnancy Test – WOCBP Only | ◄——— | | | | | | | ———► | A pregnancy test must be performed every cycle (within 24 hours of study visit for urine and 72 hours for serum) during study intervention. More frequent pregnancy testing may be performed if required by local regulations or if clinically indicated.<br>In case of suspected false positive pregnancy test in participants with fertility preservation, consult Sponsor. |
| Hematology | X | | X | | X | | X | | Perform within 3 days before dosing on Day 1 of every cycle.<br>The laboratory criteria in **Table 1** must be met before dosing on Day 1 of every cycle (the requirement for ANC is ≥1000/µL).<br>Perform more frequently as clinically indicated. |
| Chemistry | X | | X | | X | | X | | |
| Thyroid function tests (TSH, T3, T4) | X | | X | | X | | X | | |
| Bone Marrow Biopsy/Aspirate | ß Perform as clinically indicated à | | | | | | | | Refer to Section 8.2.1.5 for details. |

| Study Period: | Intervention (escBEACOPP Chemotherapy) (Q3W Cycles)[a] | | | | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle** | **escB C1** | | **escB C2** | | **escB C3b** | | **escB C4b** | | **PET-positive is defined as a score of 4 or 5 on the FDG-PET 5-point scale. escBEACOPP C1D1 should start 4 weeks (+7 days) after AVD C2D1 (see Section 1.3.1)** |
| **Dosing Day** | **D1** | **D8** | **D1** | **D8** | **D1** | **D8** | **D1** | **D8** | |
| **Patient-reported Outcomes** | | | | | | | | | |
| CCI [redacted] | | | | | CCI [redacted] | | | | CCI [redacted] |
| | | | | | | | | | |

AE=adverse event; ANC=absolute neutrophil count; AVD=doxorubicin in combination with vinblastine and dacarbazine; C=cycle; D=day; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; CCI [redacted]; escB/escBEACOPP=escalated bleomycin in combination with etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; FDG-PET=2-fluorodeoxyglucose positron emission tomography; IV=intravenous; MUGA=multigated acquisition; PET=positron emission tomography; PO=by mouth; CCI [redacted] Q3W=every 3 weeks; SAE=serious adverse event; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WOCBP=woman of childbearing potential.

[a] A maximum of a 7-day delay is permitted from the scheduled start of each cycle.

[b] Participants with early unfavorable, nonbulky disease will not receive escBEACOPP Cycles 3 and 4; therefore, assessments and procedures scheduled during escBEACOPP Cycles 3 and 4 are not applicable to these participants.

### 1.3.4 All Participants – Pembrolizumab Consolidation and Posttreatment

Note: before starting pembrolizumab consolidation, any toxicity from chemotherapy must have resolved to ≤Grade 1 or baseline. Non-clinically significant toxicities (such as: alopecia, low lymphocyte count) may not need dose delays.

| **Study Period** | **Pembro Consolidation (Q6W Cycles)[a]** | | | | **Posttreatment** | | | | **Notes** |
|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle** | **C1** | **C2** | **C3** | **C4** | **Safety Follow-up (by phone)** | **EOT** | **Efficacy Follow-up** | **Survival Follow-up** | **Pembrolizumab consolidation C1D1 should start 4 weeks (+3 days) after Day 1 of the last cycle of chemotherapy (see Sections 1.3.2 and 1.3.3). For participants who complete study intervention, EOT assessments, including imaging, must be performed 6 weeks (±7 days) after the pembrolizumab consolidation C4D1 dose. For participants who discontinue study intervention early, EOT assessments should occur within 7 weeks after the last dose of study intervention.** |
| **Dosing Day** | **D1** | **D1** | **D1** | **D1** | **30 days (+7 d) after last dose** | **6 weeks (±7 d) after last dose** | **Q12W (± 7 d)** | **Q12W (± 14 d)** | |
| **Administrative Procedures** | | | | | | | | | |
| Concomitant Medication Review | X | X | X | X | X | X | | | Concomitant medications will be recorded during the study through the Safety Follow-up Visit. All concomitant medications received within 28 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. |
| Subsequent Anticancer Treatment | | | | | X | X | X | X | Participants should be contacted by telephone to monitor new anticancer treatment if there is no corresponding clinic visit. |
| Survival status | ← | — | — | → | | | | X | On Sponsor request, participants may be contacted for survival status at any time during the course of the study. |
| **Study Intervention Administration (Assessments/procedures to be performed before administration of study intervention at each visit unless otherwise specified)** | | | | | | | | | |
| Pembrolizumab | X | X | X | X | | | | | 400 mg by IV Day 1 of each Q6W cycle for 4 cycles (note different dosing regimen relative to pembrolizumab monotherapy in Section 1.3.1). |

| Study Period | Pembro Consolidation (Q6W Cycles)[a] | | | | Posttreatment | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle** | **C1** | **C2** | **C3** | **C4** | **Safety Follow-up (by phone)** | **EOT** | **Efficacy Follow-up** | **Survival Follow-up** | **Pembrolizumab consolidation C1D1 should start 4 weeks (+3 days) after Day 1 of the last cycle of chemotherapy (see Sections 1.3.2 and 1.3.3). For participants who complete study intervention, EOT assessments, including imaging, must be performed 6 weeks (±7 days) after the pembrolizumab consolidation C4D1 dose. For participants who discontinue study intervention early, EOT assessments should occur within 7 weeks after the last dose of study intervention.** |
| **Dosing Day** | **D1** | **D1** | **D1** | **D1** | **30 days (+7 d) after last dose** | **6 weeks (±7 d) after last dose** | **Q12W (± 7 d)** | **Q12W (± 14 d)** | |
| **Efficacy Procedures** | | | | | | | | | |
| FDG-PET scan (Whole body) | | | | | | X (PET EOT) | X* | | For participants who complete study intervention, the PET EOT scan must be performed 6 weeks (±7 days) after the pembrolizumab consolidation C4D1 dose. For participants who discontinue before completing study intervention, the PET EOT scan should be performed within 6 weeks (±7 days) after the last dose of study intervention.<br>*During Efficacy Follow-up: FDG-PET only required if CT scan suggests progression or clinical suspicion of progression. |

| Study Period | Pembro Consolidation (Q6W Cycles)[a] | | | | Posttreatment | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle** | **C1** | **C2** | **C3** | **C4** | **Safety Follow-up (by phone)** | **EOT** | **Efficacy Follow-up** | **Survival Follow-up** | **Pembrolizumab consolidation C1D1 should start 4 weeks (+3 days) after Day 1 of the last cycle of chemotherapy (see Sections 1.3.2 and 1.3.3). For participants who complete study intervention, EOT assessments, including imaging, must be performed 6 weeks (±7 days) after the pembrolizumab consolidation C4D1 dose. For participants who discontinue study intervention early, EOT assessments should occur within 7 weeks after the last dose of study intervention.** |
| **Dosing Day** | **D1** | **D1** | **D1** | **D1** | **30 days (+7 d) after last dose** | **6 weeks (±7 d) after last dose** | **Q12W (± 7 d)** | **Q12W (± 14 d)** | |
| Diagnostic quality CT scan (Neck, Chest, Abdominal, Pelvic) | | | | | | X (CT EOT) | X* | | For participants who complete study intervention, the CT EOT scan must be performed 6 weeks (±7 days) after the pembrolizumab consolidation C4D1 dose. For participants who discontinue before completing study intervention, the CT EOT scan should be performed within 6 weeks (±7 days) after the last dose of study intervention.<br>*During Efficacy Follow-up: CT scans will be performed Q24W (±7 days) for 2 years after EOT imaging, then at investigator's discretion until the end of the study or meeting other criteria specified in Section 8.2.1.3. MRI can be considered in place of CT if MRI was performed at EOT for comparison. Additional CT scans can be performed as clinically indicated.<br>If PET and CT scans at Screening are positive for disease of the neck, subsequent CT scans must include the neck. If PET and CT scans at Screening are negative for disease in the neck, subsequent CT scans may omit the neck.<br>If diagnostic quality CT scan cannot be performed due to medical contraindication or local practice, refer to Site Imaging Manual for alternative methods for anatomic imaging. |

| Study Period | Pembro Consolidation (Q6W Cycles)[a] | | | | Posttreatment | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle** | **C1** | **C2** | **C3** | **C4** | **Safety Follow-up (by phone)** | **EOT** | **Efficacy Follow-up** | **Survival Follow-up** | **Pembrolizumab consolidation C1D1 should start 4 weeks (+3 days) after Day 1 of the last cycle of chemotherapy (see Sections 1.3.2 and 1.3.3). For participants who complete study intervention, EOT assessments, including imaging, must be performed 6 weeks (±7 days) after the pembrolizumab consolidation C4D1 dose. For participants who discontinue study intervention early, EOT assessments should occur within 7 weeks after the last dose of study intervention.** |
| **Dosing Day** | **D1** | **D1** | **D1** | **D1** | **30 days (+7 d) after last dose** | **6 weeks (±7 d) after last dose** | **Q12W (± 7 d)** | **Q12W (± 14 d)** | |
| Lymphoma Disease Response Assessment by Lugano Classification 2014 (see Appendix 9) | | | | | | X | X* | | *During Efficacy Follow-up: response assessment will be performed Q24W (±7 days) for 2 years after EOT imaging, then at investigator's discretion until the end of the study or meeting other criteria specified in Section 8.2.1.3. |
| **Symptom Assessment** | | | | | | | | | |
| Assessment of Lymphoma B Symptoms | | | | | | X | X* | | *During Efficacy Follow-up: assessment of Lymphoma B symptoms should occur with each disease response assessment. |
| **Safety Procedures** | | | | | | | | | |
| Full Physical Examination | | | | | | X | | | |
| Directed Physical Examination | X | X | X | X | | | X | | During pembrolizumab consolidation: perform within 3 days before dosing on Day 1 of each cycle and as clinically indicated.<br>During Efficacy Follow-up: perform Q12W for 2 years after EOT imaging and then at investigator's discretion. |
| Vital Signs (temperature, blood pressure, respiratory rate, pulse rate, weight) | X | X | X | X | | X | X | | During pembrolizumab consolidation: perform within 3 days before dosing on Day 1 of each cycle and as clinically indicated.<br>During Efficacy Follow-up: perform Q12W for 2 years after EOT imaging and then at investigator's discretion. |
| 12-lead ECG | <Perform as clinically indicated> | | | | | | | | |

| **Study Period** | **Pembro Consolidation (Q6W Cycles)[a]** | | | | **Posttreatment** | | | | **Notes** |
|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle** | **C1** | **C2** | **C3** | **C4** | **Safety Follow-up (by phone)** | **EOT** | **Efficacy Follow-up** | **Survival Follow-up** | **Pembrolizumab consolidation C1D1 should start 4 weeks (+3 days) after Day 1 of the last cycle of chemotherapy (see Sections 1.3.2 and 1.3.3). For participants who complete study intervention, EOT assessments, including imaging, must be performed 6 weeks (±7 days) after the pembrolizumab consolidation C4D1 dose. For participants who discontinue study intervention early, EOT assessments should occur within 7 weeks after the last dose of study intervention.** |
| **Dosing Day** | **D1** | **D1** | **D1** | **D1** | **30 days (+7 d) after last dose** | **6 weeks (±7 d) after last dose** | **Q12W (± 7 d)** | **Q12W (± 14 d)** | |
| ECOG Performance Status | X | X | X | X | | X | | | During pembrolizumab consolidation: perform within 3 days before dosing on Day 1 of each cycle. |
| Adverse Event Monitoring | X | X | X | X | X | X | X | | Report all AEs through 30 days after the last dose. Report SAEs through 90 days after the last dose, or 30 days after the last dose if participant initiates a new anticancer treatment, whichever is earlier. Report SAEs outside the time specified above if considered related to study intervention. |
| CCI [redacted] | | | | | CCI [redacted] | | | | |

| **Study Period** | **Pembro Consolidation (Q6W Cycles)[a]** | | | | **Posttreatment** | | | | **Notes** |
|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle** | **C1** | **C2** | **C3** | **C4** | **Safety Follow-up (by phone)** | **EOT** | **Efficacy Follow-up** | **Survival Follow-up** | **Pembrolizumab consolidation C1D1 should start 4 weeks (+3 days) after Day 1 of the last cycle of chemotherapy (see Sections 1.3.2 and 1.3.3). For participants who complete study intervention, EOT assessments, including imaging, must be performed 6 weeks (±7 days) after the pembrolizumab consolidation C4D1 dose. For participants who discontinue study intervention early, EOT assessments should occur within 7 weeks after the last dose of study intervention.** |
| **Dosing Day** | **D1** | **D1** | **D1** | **D1** | **30 days (+7 d) after last dose** | **6 weeks (±7 d) after last dose** | **Q12W (± 7 d)** | **Q12W (± 14 d)** | |
| **Laboratory Procedures/Assessments (Performed by Local Laboratory)** | | | | | | | | | |
| Urine or Serum Pregnancy Test – WOCBP Only | ← | | | → | | X | X | X | A pregnancy test must be performed every cycle (within 24 hours of study visit for urine and 72 hours for serum) during study intervention. More frequent pregnancy testing may be performed if required by local regulations or if clinically indicated. After discontinuation of study intervention, pregnancy testing should be conducted at the EOT visit and 120 days after the last dose of pembrolizumab or 180 days after the last dose of chemotherapy, whichever comes last. In case of suspected false positive pregnancy test in participants with fertility preservation, consult Sponsor. |
| Hematology | X | X | X | X | | X | X* | | During pembrolizumab consolidation: perform within 3 days before dosing on Day 1 of every cycle. The laboratory criteria in **Table 1** must be met before dosing on Day 1 of every cycle (the requirement for ANC is ≥1000/µL). Perform more frequently as clinically indicated. *During Efficacy Follow-up: perform as clinically indicated. |
| Chemistry | X | X | X | X | | X | X* | | |
| Thyroid function tests (TSH, T3, T4) | X | X | X | X | | X | X* | | |
| Bone Marrow Biopsy/Aspirate | <Perform as clinically indicated> | | | | | | | | Refer to Section 8.2.1.5 for details. |

| Study Period | Pembro Consolidation (Q6W Cycles)[a] | | | | Posttreatment | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|
| Treatment Cycle | C1 | C2 | C3 | C4 | Safety Follow-up (by phone) | EOT | Efficacy Follow-up | Survival Follow-up | Pembrolizumab consolidation C1D1 should start 4 weeks (+3 days) after Day 1 of the last cycle of chemotherapy (see Sections 1.3.2 and 1.3.3). For participants who complete study intervention, EOT assessments, including imaging, must be performed 6 weeks (±7 days) after the pembrolizumab consolidation C4D1 dose. For participants who discontinue study intervention early, EOT assessments should occur within 7 weeks after the last dose of study intervention. |
| Dosing Day | D1 | D1 | D1 | D1 | 30 days (+7 d) after last dose | 6 weeks (±7 d) after last dose | Q12W (± 7 d) | Q12W (± 14 d) | |
| CCI | | | | | | | | | |
| CCI | | | | | | CCI | | | CCI |
| CCI | | | | | | | | | |
| CCI | | | | | | CCI | | | CCI |
| CCI | | | | | | | | | |
| CCI | | | | | | | | | |
| CCI | | | | | | CCI | | | CCI |

AE=adverse event; AVD=doxorubicin in combination with vinblastine and dacarbazine; C=cycle; CT=computed tomography; CCI ; D=day; CCI ECG=electrocardiogram; ECI=event of clinical interest; ECOG=Eastern Cooperative Oncology Group; CCI CCI ; EOT=end-of-treatment; escBEACOPP=escalated bleomycin in combination with etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; EQ-5D-5L=EuroQoL 5-dimension, 5-level scale; FDG-PET=2-fluorodeoxyglucose positron emission tomography; IV=intravenous; MRI= magnetic resonance imaging; PBMC=peripheral blood mononuclear cell; pembro=pembrolizumab; PET=positron emission tomography; CCI ; Q6W=every 6 weeks; Q12W=every 12 weeks; SAE=serious adverse event; SCT=stem cell transplant; T3=triiodothyronine; T4=thyroxine; TCR=T-cell receptor; TSH=thyroid-stimulating hormone; WOCBP=woman of childbearing potential.

[a]. After C1D1 of pembrolizumab consolidation, a ±3-day window is permitted is permitted from the scheduled start of each cycle.

# 2 INTRODUCTION

## 2.1 Study Rationale

cHL has an excellent prognosis with 5-year survival exceeding 75% to 80% [Roy, P., et al 2000] [Brenner, H., et al 2008]. Despite many advances in the field, patients, although often cured of disease, may experience late effects from therapy, reducing length and QoL. As such, multiple efforts have focused on identifying more tolerable treatment combinations or de-escalation of therapy and elimination of the radiotherapy consolidation. Some approaches to limiting toxicity include the elimination of bleomycin from ABVD treatment (doxorubicin in combination with bleomycin, vinblastine, and dacarbazine) [Allen, P. B., et al 2020], treatment with an abbreviated course of chemotherapy [Radford, J., et al 2015], and combining novel drugs with more tolerable side effects. One such class of drugs that has shown promise and tolerability in cHL includes checkpoint inhibitors. The advent of immunotherapy has transformed the therapeutic landscape, changing the standard of care across the field and raising questions of how best to use and assess response to this novel class of drugs. Checkpoint inhibitors, such as pembrolizumab, have shown efficacy and tolerability in relapsed HL, however their efficacy in the frontline setting combined with chemotherapy has not been widely studied.

In a recent study by Allen et al [Allen, P. B., et al 2020], pembrolizumab monotherapy followed by AVD proved both highly effective and safe in patients with newly diagnosed early unfavorable (n=12) or advanced (n=18) stage cHL, including those with bulky disease. In this study, a brief course of pembrolizumab monotherapy, previously unstudied in patients with newly diagnosed cHL, proved to be a powerful induction strategy in early unfavorable and advanced-stage disease. While 37% of patients achieved complete metabolic responses with only 3 doses of pembrolizumab, 100% of patients achieved a complete metabolic response after 2 cycles of chemotherapy, and all patients maintained their responses through the EOT. The complete metabolic response rate was 100%, both at interim PET and at EOT. At a median follow-up of 22.5 months, the PFS and OS were 100%, and no patient required salvage therapy or radiotherapy. No patient was treated with radiation therapy. The authors concluded that sequential administration of a short course of pembrolizumab monotherapy followed by AVD chemotherapy is safe and highly effective in newly diagnosed early unfavorable and advanced-stage cHL, including many patients with bulky disease, with all patients completing the prescribed course of therapy [Allen, P. B., et al 2020].

The study by Allen et al [Allen, P. B., et al 2020] was performed at US sites only, with most patients enrolled at a single institution. KEYNOTE-C11 is built on similar concepts and will use sequential administration of pembrolizumab followed by PET-guided chemotherapy treatment without radiotherapy. With the promising results of sequential pembrolizumab followed by chemotherapy shown by Allen et al [Allen, P. B., et al 2020], this strategy is expected to minimize the treatment toxicity associated with conventional chemotherapy and radiotherapy while improving the therapeutic efficacy. This single-arm study aims to evaluate whether administration of sequential pembrolizumab followed by chemotherapy to participants with newly diagnosed early unfavorable and advanced cHL achieves a CR rate similar to that of Allen et al, in a larger number of participants enrolled across a broader range of institutions. Specifically, it is hypothesized that the study achieves a CR rate of

greater than 80%. A CR rate of 80% was selected as a conservative CR rate based on data from previous studies with conventional chemotherapy [Connors, J. M., et al 2018] [Eichenauer, D. A., et al 2017], in which CR rates ranged from 70% to 86%, and the study of sequential pembrolizumab followed by chemotherapy [Allen, P. B., et al 2020] in which a 100% CR rate was achieved.

## 2.2 Background

### 2.2.1 Pembrolizumab

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across several indications. For more details on specific indications refer to the IB.

#### 2.2.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer, hepatocellular carcinoma, malignant melanoma, and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 that has been shown to negatively regulate antigen receptor signaling on engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an IgV–type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. After T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ, and ZAP70,

which are involved in the CD3 T-cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004] [Riley, J. L. 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005] [Francisco, L. M., et al 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in cHL.

#### 2.2.1.2 Preclinical and Clinical Studies

Refer to the pembrolizumab IB for a summary of preclinical and clinical study data.

#### 2.2.1.3 Ongoing Clinical Studies

Refer to the pembrolizumab IB for a summary of ongoing clinical study data.

### 2.2.2 Treatment of Early Unfavorable and Advanced-stage Hodgkin Lymphoma

Early stage HL is defined as Ann Arbor Stage I to II disease. Patients with bulky mediastinal masses, B symptoms, elevated ESR, or multiple nodal sites are generally classified as early unfavorable HL. Advanced-stage disease generally refers to patients with Ann Arbor Stage III/IV disease [Lister, T. A., et al 1989]. The population in this study will include early unfavorable and advanced disease. Although excellent outcomes in early favorable disease are achieved with existing therapies, there is continued need for therapeutic optimization in early unfavorable and advanced disease.

Combined-modality treatment consisting of chemotherapy and consolidation radiotherapy has been the standard of care for patients with early-stage unfavorable cHL. The most frequently used initial regimen in early unfavorable HL is ABVD × 4 to 6 cycles followed by involved-site radiation therapy to 30 Gy [Engert, A., et al 2003]. However, the use of radiotherapy has long-term sequelae, particularly cardiovascular disease and secondary malignancies. While randomized clinical trials have shown that chemotherapy alone leads to a higher recurrence rate and shorter PFS, this has not translated into an inferior OS compared with addition of radiotherapy to chemotherapy. This is mainly due to a higher number of deaths in patients receiving consolidation radiotherapy. The major focus in frontline cHL is thus the development of various strategies aimed at identifying the optimal balance between maintaining high cure rates and avoiding the long-term toxicity associated with radiation, especially in early-stage disease. Recent studies have been designed to reduce or eliminate radiotherapy, by incorporating novel agents into the treatment and using a PET-guided approach.

The large GHSG HD17 study showed that, in the setting of an appropriate chemotherapy backbone, radiotherapy can be successfully omitted from standard combined-modality treatment without a clinically relevant loss of tumor control in patients with a negative PET after systemic treatment with the 2+2 regimen of ABVD and escBEACOPP [Borchmann, P., et al 2021]. Additionally, in a study examining the use of combination chemotherapy alone in patients perceived to be at low risk of treatment failure but at high risk of radiation-induced toxicity, patients with nonbulky Stage I, II, and IIIA disease receiving 6 cycles of ABVD

with or without consolidation involved-field radiotherapy showed no significant difference in outcome among 152 patients [Straus, D. J., et al 2004].

One of the largest studies to make a direct comparison of chemotherapy alone with a combined modality approach was the intergroup study HD.6 in 399 patients with nonbulky Stage I and II disease. The early report of this study, with a median follow-up of 4.2 years, showed that OS was not significantly different between the combined modality approach and ABVD alone (94% vs 96%, respectively) [Meyer, R. M., et al 2005], but a subsequent reanalysis with median follow-up of 11.3 years showed a different picture, with inferior survival among the patients who had received radiotherapy (87% vs 94%, respectively; $p$=0.04) [Meyer, R. M., et al 2005]. The risk of death from HL was not different between the arms, but the risk of death from other causes was more than 3-fold higher among those irradiated, with much of the excess attributable to second cancers [Meyer, R. M., et al 2012].

The above results suggest that chemotherapy alone may be an appropriate treatment strategy in a subset of patients. In advanced disease, treatment continues to evolve. Guidelines generally recommend treatment with chemotherapy alone, starting with either ABVD or escBEACOPP [Engert, A., et al 2009] [Merli, F., et al 2016]. However, ABVD alone fails to cure 15% to 30% of patients. In contrast to early stage disease in which long-term cure exceeds 90%, only approximately 65% to 75% of patients with advanced-stage HL remain disease free at 10 years [Engert, A., et al 2009] [Carde, P., et al 2016] [Merli, F., et al 2016].

In addition, both ABVD and escBEACOPP are associated with acute and chronic toxicities including bleomycin lung toxicity [Boll, B., et al 2016] [Evens, A. M., et al 2013]. Bleomycin-free strategies that improve long-term remission rates without incorporating radiotherapy are needed.

Although PET-guided approaches might help to individualize chemotherapy and radiotherapy exposure, implementation of novel agents such as the anti–PD-1 therapies will help further optimize the therapy. The investigation of novel drugs is warranted to reduce upfront treatment intensity, achieve PET-negative disease status after systemic therapy in a vast majority of patients to potentially enable omission of radiation therapy, and achieve a PFS superior to that with conventional chemotherapy. Newer trials are designed to exploit the tumor biology with the use of anti-PD-1 agents in both early-stage and late-stage cHL, and attempts are underway to eliminate radiotherapy while maximizing the cure rate.

### 2.2.3 Role of 2-Fluorodeoxyglucose-positron Emission Tomography

FDG-PET has become a standard imaging modality complementing CT scans in the management of HL [Friedberg, J. W., et al 2004] [Jerusalem, G., et al 2003] [Jerusalem, G., et al 2001] [Stumpe, K. D. M., et al 1998]. Efforts over the last decade have focused on tailoring therapy according to risk using an interim PET scan. A major objective of these studies has been to assess if radiotherapy can be omitted in patients with interim PET-negative results and whether intensifying therapy will improve outcomes for patients who are PET-positive.

The data on response-adapted therapy have led to it becoming increasingly accepted as the standard of care, as it supports both de-escalation of therapy for patients with a good early response and intensification of treatment for those with persistent FDG-avid disease early in the course. The findings in early stage disease highlight the utility of interim PET in providing information to patients about the option of omitting consolidation radiotherapy or the advisability of escalating chemotherapy. In advanced-stage disease, a risk-adapted approach combined with a response-adapted approach may be optimal in using more intensive initial therapy for those with the worst disease, but performing interim PET scans to assess the response in all and adjusting subsequent therapy accordingly. The data so far suggest that modulating treatment of advanced-stage HL both upward and downward after interim PET is an effective approach, which may improve the results and reduce morbidity and mortality in the long-term, although longer follow-up is needed to confirm this.

Several large-scale studies with strikingly similar results have now reported the results of treating patients with a positive PET scan with escBEACOPP after 2 cycles of ABVD. In the response-adapted therapy for advanced HL study, which included unfavorable risk Stage II disease as well as Stages III to IV, 16% of patients had a positive interim PET scan, and among 182 patients who went on to receive either 4 cycles of escBEACOPP or 6 dose-dense cycles of BEACOPP-14, there was a subsequent complete metabolic response in 74% of cases, with a 3-year PFS of 68% and OS of 88% [Johnson, P., et al 2016]. Similar results were seen in the Gruppo Italiano Terapie Innovative nei Linfomi/Fondazione Italiana Linfomi (GITIL/FIL) 0607 study, in which treatment was increased to 4 cycles of escBEACOPP followed by 4 cycles of standard BEACOPP with or without rituximab; the 3-year PFS and OS were 57% and 89% in 76 participants treated with escBEACOPP, and 63% and 90% in 72 participants treated with rituximab-supplemented escBEACOPP [Gallamini, A., et al 2018]. In the Southwest Oncology Group S0816 study, in which patients received 6 cycles of escBEACOPP, the 2-year PFS in 60 patients was 64% [Press, O. W., et al 2016].

### 2.2.4 Incorporating Anti-PD-1 in Frontline Hodgkin Lymphoma

Although PET-guided approaches might help to individualize chemotherapy and radiation therapy exposure, implementation of novel agents such as the anti–programmed death 1 antibodies nivolumab or pembrolizumab, approved for the treatment of relapsed or refractory HL, might further optimize therapy [Chen, R., et al 2017]. By exploiting potential synergies (eg, in combination with chemotherapy, radiation therapy, or other targeted agents) and the distinct HL biology with its dependence on a protective immunosuppressive microenvironment [Hude, I., et al 2017], these strategies might also improve outcomes for elderly patients or those with relevant comorbidities. Fueled by the data in relapsed or refractory HL, several Phase 1/2 studies of first-line therapy for HL are planned or actively enrolling patients to investigate combinations of ABVD variants with nivolumab (NCT03004833, NCT03033914), or pembrolizumab (NCT03226249). In addition, studies in elderly patients are studying the combination of brentuximab vedotin, and nivolumab (NCT01716806, NCT02758717) as well as AVD chemotherapy combined with brentuximab vedotin, and nivolumab (NCT03233347).

The results of 2 studies with anti-PD-1 in combination with chemotherapy in frontline cHL has recently been reported: Cohort D of Checkmate 205 in advanced-stage cHL, and the

GHSG Phase 2 NIVAHL study in early unfavorable cHL [Ramchandren, R., et al 2019] [Brockelmann, P. J., et al 2020]. In Checkmate 205, Cohort D, nivolumab was administered as monotherapy for 4 doses followed by 6 cycles of concurrent nivolumab and AVD. The response rate to single-agent nivolumab in this study was identical to that reported previously in the relapsed setting (18% CR). With the addition of AVD chemotherapy, CR rate increased to 51% and 67% at interim and EOT time points [Ramchandren, R., et al 2019]. While these response rates are lower than the CR rate of >80% reported with ABVD alone, the PFS of 83% at 21 months in Cohort D is similar to the historical controls [Domingo-Domenech, E., et al 2019].

The GHSG randomized Phase 2 NIVAHL study for early unfavorable disease compared concurrent nivolumab and AVD to a sequential strategy. All patients were consolidated with radiotherapy. The investigators found no significant differences in outcomes with the concurrent or sequential approaches. Notably, this study showed a CR rate of 51% to frontline single agent nivolumab [Brockelmann, P. J., et al 2020].

### 2.2.5 Information on Other Study-related Therapy

For additional information on doxorubicin, vinblastine, dacarbazine, bleomycin, etoposide, cyclophosphamide, vincristine, procarbazine, and prednisone refer to the respective approved product labels.

## 2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

The investigational agent pembrolizumab is a potent inhibitor of PD-1 signaling that enhances tumor-cell specific T-cell activation and has shown activity in adult patients with rrcHL. Pembrolizumab has been approved in the United States for the treatment of both adult and pediatric patients with rrcHL. Based on current evidence, no difference in mechanism of action and activity are expected in cHL between the frontline and relapsed/refractory settings. Thus, pembrolizumab has the potential to provide therapeutic benefit to patients with newly diagnosed cHL. Pembrolizumab monotherapy has a positive benefit-risk profile and is well tolerated in the approved indications. Most AEOSIs are mild to moderate in severity, and are generally readily manageable with appropriate care in the clinical setting. In combination with chemotherapy, the safety profiles were generally consistent with the known safety profiles of pembrolizumab monotherapy and the chemotherapy regimens administered (refer to the pembrolizumab IB). Preliminary data to support the efficacy and safety of pembrolizumab in combination with chemotherapy in frontline cHL is also available (Section 2.2.4). Thus, pembrolizumab has the potential to offer patients with newly diagnosed cHL a therapy that is expected to be efficacious with a generally tolerable safety profile. Moreover, addition of pembrolizumab to the chemotherapy backbone in cHL may improve disease control and reduce cumulative drug toxicities.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

# 3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In males and females with newly diagnosed early unfavorable or advanced-stage classical Hodgkin Lymphoma:

| **Primary Objective** | **Primary Endpoint** |
|---|---|
| To evaluate complete response (CR) rate at the end of study intervention in participants with newly diagnosed classical Hodgkin Lymphoma (cHL) assessed by independent central review according to Lugano 2014 response criteria | CR |
| CCI [redacted] | |
| **Secondary Objectives** | **Secondary Endpoints** |
| To evaluate the CR rate at the end of study intervention in participants with newly diagnosed cHL by investigator assessment according to Lugano 2014 response criteria | CR |
| CCI [redacted] | |
| To evaluate the rate of Positron Emission Tomography (PET) negativity at PET2 following 3 cycles of pembrolizumab monotherapy by independent central review according to the 2-fluorodeoxyglucose (FDG)-PET 5-point scale | PET negativity: a score of 1, 2, or 3 on the FDG-PET 5-point scale after 3 cycles of pembrolizumab monotherapy |

| | |
|---|---|
| To evaluate the rate of PET negativity at PET3 after completion of 3 cycles of pembrolizumab monotherapy followed by 2 cycles of doxorubicin in combination with vinblastine and dacarbazine (AVD) by independent central review according to the FDG-PET 5-point scale | PET negativity: a score of 1, 2, or 3 on the FDG-PET 5-point scale after 3 cycles of pembrolizumab monotherapy followed by 2 cycles of AVD |
| To evaluate the safety and tolerability of initial pembrolizumab monotherapy followed by chemotherapy and pembrolizumab consolidation in participants with newly diagnosed cHL | -Adverse Events (AEs)<br><br>-Discontinuation of study intervention due to an AE |

CCI

[redacted]

CCI

[redacted]

# 4 STUDY DESIGN

## 4.1 Overall Design

This is a Phase 2, uncontrolled, open-label, multicenter study of sequential pembrolizumab monotherapy followed by chemotherapy and pembrolizumab consolidation in adults ≥18 years of age with newly diagnosed, early unfavorable or advanced-stage cHL.

The study design is depicted in Figure 1 (Section 1.2) and study intervention regimens are described in Table 2 (Section 6.1).

This study will examine the safety and efficacy of 200 mg Q3W pembrolizumab monotherapy, followed by either AVD or escBEACOPP chemotherapy, followed by pembrolizumab consolidation of 400 mg Q6W.

Participants must have newly diagnosed, histologically confirmed, untreated, early unfavorable or advanced-stage cHL. For the purposes of this protocol "early unfavorable" is defined as Stage I or II disease with at least 1 unfavorable NCCN risk factor (Appendix 11) and "advanced" is defined as Stage III or IV disease.

Approximately 140 participants will be enrolled.

Study intervention will be administered as follows:

- Pembrolizumab Monotherapy: all participants will receive 200 mg pembrolizumab monotherapy Q3W for 3 cycles.
  - PET scan (PET2) will be performed after pembrolizumab monotherapy to determine PET response to pembrolizumab alone.
- Chemotherapy Phase 1: all participants will receive AVD on Days 1 and 15 Q4W for 2 cycles.
  - PET scan (PET3) will be performed after 2 cycles of AVD therapy. Investigators will assess PET3 response to determine if participants are PET-negative (a score of 1, 2, or 3 on the FDG-PET 5-point scale) or PET-positive (a score of 4 or 5 on the FDG-PET 5-point scale) (Appendix 9). Participants will receive additional chemotherapy (during Chemotherapy Phase 2) according to their PET3 response and age at screening.
- Chemotherapy Phase 2:
  - If a participant is PET3-negative, they will receive 4 cycles of AVD on Days 1 and 15 Q4W.
  - If a participant is PET3-positive and ≥60 years of age, they will receive 4 cycles of AVD on Days 1 and 15 Q4W.

- If a participant is PET3-positive and <60 years of age, they will receive 4 cycles of escBEACOPP Q3W.

- Participants with early unfavorable, nonbulky disease will receive 2 cycles of AVD OR 2 cycles of escBEACOPP according to the PET3 and age criteria above.

- Pembrolizumab Consolidation: all participants will receive 4 cycles of 400 mg pembrolizumab monotherapy Q6W. Before starting pembrolizumab consolidation, any toxicity from chemotherapy must have resolved to ≤Grade 1 or baseline. Non-clinically significant toxicities (such as: alopecia, low lymphocyte count) may not need dose delays.

  - PET scan (PET EOT) and CT EOT scan will be performed at the end of pembrolizumab consolidation (end of study intervention; 6 weeks [±7 days] after pembrolizumab consolidation Cycle 4 Day 1 dose).

Participants will continue to receive study intervention as defined above until unacceptable AE(s), intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, administrative reasons requiring cessation of treatment, or until the participant has received the maximum duration of treatment specified by the protocol. Additional study intervention discontinuation criteria are outlined in Section 7.1.

Participants with CR at the end of study intervention, or participants who discontinue for reasons other than disease progression, will progress into Efficacy Follow-up. During Efficacy Follow-up, participants will be monitored for disease status every 24 weeks for 2 years after EOT imaging, then at investigator's discretion until the end of the study, or until disease progression, the start of a new anticancer treatment, withdrawal of consent, pregnancy, death, or loss to follow-up, whichever occurs first. When one of these criteria are met, the participant will progress to Survival Follow-up. Participants without CR at the end of study intervention, or participants who discontinue study intervention due to disease progression, will progress immediately to Survival Follow-up. All participants will be followed for OS until death, withdrawal of consent, or the end of the study, whichever occurs first.

Participants with PET-positive residual mass at EOT should not receive radiotherapy as part of study intervention but should be transitioned to Survival Follow-up (see Section 8.11.4.3) before receiving non-study anticancer treatment for residual disease. If at EOT, either anatomic or metabolic imaging shows findings suspicious for residual disease, a biopsy may be obtained, which will contribute to the assessment of disease per Lugano 2014 response criteria (Appendix 9).

AE monitoring will be ongoing throughout the study and graded according to the guidelines outlined in the NCI CTCAE version v5.0. All AEs will be reported through 30 days after the last dose of study intervention. All SAEs will be reported through 90 days after the last dose of study intervention, or 30 days after the last dose if participant initiates a new anticancer treatment, whichever is earlier. For participants who undergo allogeneic stem cell transplant

within 2 years after the last pembrolizumab dose, ECIs will be recorded as detailed in Section 8.4.7. Safety data will be reviewed on a monthly basis by the Sponsor, with additional review of cumulative Grade 3-5 TEAE data for each treatment performed by the Sponsor's study team every 4 months. If the criteria outlined in Section 6.6.3 are met, enrollment will be paused and an internal DMC will review all available safety data.

The primary efficacy endpoint is CR at the end of study intervention, assessed by independent central review according to Lugano 2014 response criteria (Appendix 9).

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 of the SoA. Details of each procedure are provided in Section 8.

## 4.2 Scientific Rationale for Study Design

A Phase 2, uncontrolled, open-label, multicenter study design is considered appropriate for examining the efficacy of sequential pembrolizumab monotherapy followed by chemotherapy and pembrolizumab consolidation in adults ≥18 years of age with newly diagnosed, early unfavorable or advanced-stage cHL.

### 4.2.1 Rationale for Endpoints

#### 4.2.1.1 Efficacy Endpoints

**Complete Response**

The primary efficacy endpoint is CR at the end of study intervention assessed by independent central review according to Lugano 2014 response criteria (Appendix 9).

One secondary efficacy endpoint is CR at the end of study intervention assessed by investigators according to Lugano 2014 response criteria (Appendix 9).

Assessment of CR at the end of study intervention as per the Lugano 2014 response criteria (Appendix 9) will include both PET and CT. As described in Lugano, the PET response, when available, will be the main determinant of the overall visit response.

Treatment effect measured by CR rate can represent direct clinical benefit based on the specific disease, context of use, magnitude of the effect, number of participants with CRs, durability of response, disease setting, location of the tumors, available therapy, and risk-benefit relationship. Treatment effect measured by CR rate can be a surrogate endpoint to support accelerated approval according to FDA guidance [Food and Drug Administration 2018].

**Duration of Complete Response**

CCI [redacted]

**Rate of PET Negativity**

Additional secondary efficacy endpoints include the rate of PET negativity at PET2 after 3 cycles of pembrolizumab monotherapy by independent central review according to the FDG-PET 5-point scale (Appendix 9), and the rate of PET negativity at PET3 after 3 cycles of pembrolizumab monotherapy followed by 2 cycles of AVD (see Section 2.2.3).

**Progression-free Survival and Overall Survival**

CCI [redacted]

#### 4.2.1.2 Safety Endpoints

Safety parameters frequently used for evaluating investigational-systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs, and changes in vital signs and laboratory values. AEs will be assessed as defined by CTCAE, Version 5.0.

#### 4.2.1.3 CCI [redacted]

CCI [redacted]

##### 4.2.1.3.1 CCI [redacted]

CCI [redacted]

CCI [redacted]

#### 4.2.1.3.2 CCI [redacted]

CCI [redacted]

#### 4.2.1.4 CCI [redacted]

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

**4.2.1.5** CCI

CCI

[redacted]

## 4.3 Justification for Dose

### 4.3.1 Pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg Q3W followed by 400 mg Q6W. The current approved dosing regimens of pembrolizumab for IV administration are 200 mg Q3W and 400 mg Q6W for adults.

**200 mg Q3W**

Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is an appropriate dose of pembrolizumab for adults across all indications. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W representing an approximate 5- to 7.5-fold exposure range (refer to IB, Section 5.2.2)
- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from PBPK analysis) at 200 mg Q3W

### 400 mg Q6W

A 400 mg Q6W dosing regimen of pembrolizumab is expected to have a similar benefit-risk profile as 200 mg Q3W, in all treatment settings in which 200 mg Q3W pembrolizumab is currently appropriate [Lala, M., et al 2020]. Specifically, the dosing regimen of 400 mg Q6W for pembrolizumab is considered adequate based on M&S analyses, given the following rationale:

PK simulations demonstrating that in terms of pembrolizumab exposures:

- $C_{avg}$ (or AUC) at 400 mg Q6W is similar to the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.
- Trough concentrations ($C_{min}$) at 400 mg Q6W are generally within the range of those achieved with 2 mg/kg or 200 mg Q3W in the majority (>99%) of patients.
- Peak concentrations ($C_{max}$) at 400 mg Q6W are well below the $C_{max}$ for the highest clinically tested dose of 10 mg/kg Q2W, supporting that the safety profile for 400 mg Q6W should be comparable to the established safety profile of pembrolizumab.
- E-R for pembrolizumab has been shown to be flat across indications, and OS predictions in melanoma and NSCLC show that efficacy at 400 mg Q6W is expected to be similar to 200 mg or 2 mg/kg Q3W, given the similar exposures; thus, 400 mg Q6W is expected to be efficacious across indications.

### 4.3.2 AVD and escBEACOPP

ABVD and escBEACOPP are recommended for newly diagnosed early unfavorable or advanced cHL per NCCN guidelines [National Comprehensive Cancer Network 2019]. However, the omission of bleomycin has been associated with decreased risk of toxicity [Allen, P. B., et al 2020], therefore AVD will be used in this study after pembrolizumab monotherapy in participants who are PET-negative at PET3, and in participants who are PET-positive at PET3 and ≥60 years of age. escBEACOPP will be used in participants who are PET-positive at PET3 and <60 years of age, which is expected to represent a small minority of participants in whom PET3 is performed.

## 4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3). Upon study completion, participants are to be discontinued and may be enrolled in an extension study using pembrolizumab monotherapy, if available. For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

### 4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

# 5 STUDY POPULATION

Male/female participants with newly diagnosed early unfavorable or advanced-stage cHL, who are at least 18 years old will be enrolled in this study.

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

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

## 5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

**Type of Participant and Disease Characteristics**

1. Has a histologically confirmed diagnosis of Ann Arbor Stage III or IV cHL. Stage I and II patients may be enrolled but must have at least one NCCN unfavorable risk factor (see Appendix 11).
   Note: Participants with bulky disease are eligible.
2. Has measurable FDG-avid disease based on investigator assessment according to Lugano 2014 response criteria (Appendix 9).
3. Has not received prior radiation therapy, chemotherapy, immunotherapy, or other systemic therapy (including investigational agents) for the treatment of cHL before the first dose of study intervention.

**Demographics**

4. Is male or female, at least 18 years of age, at the time of providing the informed consent.

**Male Participants**

5. Male participants are eligible to participate if they agree to the following during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. The length of time required to continue contraception for each study intervention is as follows:
   - Pembrolizumab: no contraception requirement
   - Chemotherapy: 90 days

• Refrain from donating sperm

PLUS either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

  OR

- Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]) as detailed below:
  - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.
- Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

Refer to Appendix 7 for country-specific requirements.

**Female Participants**

6. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a WOCBP

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The length of time required to continue contraception for each study intervention is as follows:
  - Chemotherapy: 180 days
  - Pembrolizumab: 120 days

  The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention
  - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 72 hours before the first dose of study intervention.
  - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

- Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.7.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

Refer to Appendix 7 for country-specific requirements.

**Informed Consent**

7. The participant (or legally acceptable representative) has provided documented informed consent for the study. The participant may also provide consent for FBR. However, the participant may participate in the study without participating in FBR.

Additional Categories

8. Has an ECOG Performance Status of 0 to 1 assessed within 7 days before the start of study intervention.
9. Has adequate organ function as defined in the following table (Table 1). Specimens must be collected within 7 days before the start of study intervention. Refer to Appendix 7 for country-specific requirements.

Table 1 Adequate Organ Function Laboratory Values

| System | Laboratory Value |
|---|---|
| Hematological | |
| Absolute neutrophil count (ANC) | ≥1500/µL |
| Platelets | ≥50 000/µL |
| Hemoglobin | ≥8.0 g/dL[a] |
| Renal | |
| Measured or calculated[b] creatinine clearance (GFR can also be used in place of CrCl) | ≥30 mL/min |
| Hepatic | |
| Total bilirubin | ≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN |
| AST (SGOT) and ALT (SGPT) | ≤2.5 × ULN (≤5 × ULN for participants with liver metastases) |

| System | Laboratory Value |
|---|---|
| ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.<br>[a]Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.<br>[b]Creatinine clearance (CrCl) should be calculated using Cockcroft-Gault.<br>$\frac{(140\text{-age [years]} \times \text{weight (kg)}}{\text{Serum creatinine (mg/dL)} \times 72}$ (×F)*<br>*where F = 0.85 for females and F = 1 for males<br>Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies. | |

## 5.2 Exclusion Criteria

An individual must be excluded from the study if the individual meets any of the following criteria:

### Medical Conditions

1. Has confirmed nodular lymphocyte-predominant HL.
2. Has an uncontrolled intercurrent cardiovascular illness including, but not limited to the following:

- Symptomatic congestive heart failure (ejection fraction lower than institutional LLN)
- Unstable angina pectoris
- Cardiac arrythmia

### Prior/Concomitant Therapy

3. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).
4. Has received or is expected to receive a live or live-attenuated vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines are allowed.

### Prior/Concurrent Clinical Study Experience

5. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks before the first dose of study intervention.

   Note: Participants who have entered the follow-up phase of an investigational study will be eligible to participate as long as ≥4 weeks has elapsed since the last dose of an investigational agent administered for a disease/condition other than cHL.

### Diagnostic Assessments

6. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study medication. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
7. Has a known additional malignancy that is progressing or has required active treatment within the past 5 years.

   Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

8. Has radiographically detectable (even if asymptomatic and/or previously treated) central nervous system metastases and/or carcinomatous meningitis as assessed by investigator at the time of diagnosis.
9. Has severe hypersensitivity (≥Grade 3) to any of the study interventions or their excipients.
10. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
11. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
12. Has a history or current evidence of pulmonary fibrosis.
13. Has an active infection requiring systemic therapy.
14. Has a known history of HIV infection. No HIV testing is required unless mandated by local health authority.
15. Has a known history of Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.
    Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.
16. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.
17. Has a known psychiatric or substance abuse disorder that would interfere with the participant’s ability to cooperate with the requirements of the study.

### Other Exclusions

18. Has any contraindication to the use of any of the chemotherapeutic agents used in the study.

19. Has not recovered adequately from surgery and/or any complications from the surgery.
20. Has had an allogenic tissue/solid organ transplant.

## 5.3 Lifestyle Considerations

### 5.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

## 5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently entered in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

Participants who fail screening may be rescreened for eligibility after consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

## 5.5 Participant Replacement Strategy

A participant who discontinues from study intervention OR withdraws from the study will not be replaced.

# 6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

## 6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 2.

Table 2 Study Interventions

| **Arm Name** | **Arm Type** | **Intervention Name** | **Intervention Type** | **Dose Formulation** | **Unit Dose Strength(s)** | **Dosage Level(s)** | **Route of Administration** | **Regimen/ Treatment Period/ Vaccination Regimen** | **Use** | **IMP or NIMP / AxMP** | **Sourcing** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| All participants | Experimental | Pembrolizumab | Biological/Vaccine | Injection, Solution | 25 mg/mL | 200 mg | IV Infusion | Day 1 of each cycle, Q3W, 3 cycles | Test Product | IMP | Central |
| All participants | Experimental | Doxorubicin | Drug | Injection, Solution | Variable | 25 $mg/m^2$ | Per Local Guidelines | Days 1 and 15 of each cycle, Q4W, 2 cycles | Test Product | IMP | Local or Central |
| All participants | Experimental | Vinblastine | Drug | Injection, Solution | Variable | 6 $mg/m^2$ | Per Local Guidelines | Days 1 and 15 of each cycle, Q4W, 2 cycles | Test Product | IMP | Local or Central |
| All participants | Experimental | Dacarbazine | Drug | Injection, Solution | Variable | 375 $mg/m^2$ | Per Local Guidelines | Days 1 and 15 of each cycle, Q4W, 2 cycles | Test Product | IMP | Local or Central |
| PET3 negative, or PET3 positive and ≥60 years of age | Experimental | Doxorubicin | Drug | Injection, Solution | Variable | 25 $mg/m^2$ | Per Local Guidelines | Days 1 and 15 of each cycle, Q4W, 4 cycles | Test Product | IMP | Local or Central |

| Arm Name | Arm Type | Intervention Name | Intervention Type | Dose Formulation | Unit Dose Strength(s) | Dosage Level(s) | Route of Administration | Regimen/ Treatment Period/ Vaccination Regimen | Use | IMP or NIMP / AxMP | Sourcing |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PET3 negative, or PET3 positive and ≥60 years of age | Experimental | Vinblastine | Drug | Injection, Solution | Variable | 6 $mg/m^2$ | Per Local Guidelines | Days 1 and 15 of each cycle, Q4W, 4 cycles | Test Product | IMP | Local or Central |
| PET3 negative, or PET3 positive and ≥60 years of age | Experimental | Dacarbazine | Drug | Injection, Solution | Variable | 375 $mg/m^2$ | Per Local Guidelines | Days 1 and 15 of each cycle, Q4W, 4 cycles | Test Product | IMP | Local or Central |
| PET3 positive and <60 years of age | Experimental | Bleomycin | Drug | Injection, Solution | Variable | 10 $units/m^2$ | Per Local Guidelines | Day 8 of each cycle, Q3W, 4 cycles | Test Product | IMP | Local or Central |
| PET3 positive and <60 years of age | Experimental | Etoposide | Drug | Injection, Solution | Variable | 200 $mg/m^2$ | Per Local Guidelines | Days 1 to 3 of each cycle, Q3W, 4 cycles | Test Product | IMP | Local or Central |
| PET3 positive and <60 years of age | Experimental | Doxorubicin | Drug | Injection, Solution | Variable | 35 $mg/m^2$ | Per Local Guidelines | Day 1 of each cycle, Q3W, 4 cycles | Test Product | IMP | Local or Central |

| Arm Name | Arm Type | Intervention Name | Intervention Type | Dose Formulation | Unit Dose Strength(s) | Dosage Level(s) | Route of Administration | Regimen/ Treatment Period/ Vaccination Regimen | Use | IMP or NIMP / AxMP | Sourcing |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PET3 positive and <60 years of age | Experimental | Cyclophosphamide | Drug | Injection, Solution | Variable | 1250 $mg/m^2$ | Per Local Guidelines | Day 1 of each cycle, Q3W, 4 cycles | Test Product | IMP | Local or Central |
| PET3 positive and <60 years of age | Experimental | Vincristine | Drug | Injection, Solution | Variable | 1.4 $mg/m^2$ | Per Local Guidelines | Day 8 of each cycle, Q3W, 4 cycles | Test Product | IMP | Local or Central |
| PET3 positive and <60 years of age | Experimental | Procarbazine | Drug | Tablet | Variable | 100 $mg/m^2$ | Oral | Days 1 to 7 of each cycle, Q3W, 4 cycles | Test Product | IMP | Local or Central |
| PET3 positive and <60 years of age | Experimental | Prednisone | Drug | Tablet | Variable | 40 $mg/m^2$ | Oral | Days 1 to 14 of each cycle, Q3W, 4 cycles | Test Product | IMP | Local or Central |
| All participants | Experimental | Pembrolizumab | Biological/Vaccine | Injection, Solution | 25 mg/mL | 400 mg | IV Infusion | Day 1 of each cycle, Q6W, 4 cycles | Test Product | IMP | Central |

AVD=doxorubicin in combination with vinblastine and dacarbazine; EEA=European Economic Area; escBEACOPP=escalated bleomycin in combination with etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; IMP=investigational medicinal product; IV=intravenous; NIMP/AxMP=noninvestigational/auxiliary medicinal product; PET=positron emission tomography; Q3W=every 3 weeks; Q4W=every 4 weeks; Q6W=every 6 weeks.
The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.
Note: Age is based on age at screening. Participants ≥60 years of age will continue to receive AVD in Chemotherapy Phase 2 regardless of their PET3 response, and will not receive escBEACOPP.
For vincristine, maximum dose=2 mg.
For participants with early unfavorable, nonbulky disease will receive 2 cycles of AVD if PET3-negative, or if PET3-positive and ≥60 years of age, or 2 cycles of escBEACOPP if PET3-positive and <60 years of age.

All study interventions will be administered on an outpatient basis.

All products indicated in Table 2 will be provided centrally by the Sponsor or locally by the study site, subsidiary, or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the study site, subsidiary, or designee, every attempt will be made to source these supplies from a single lot/batch number. The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

Refer to Section 8.1.8 for details regarding administration of the study intervention.

### 6.1.1 Treatment

The treatment consists of 7 cycles of pembrolizumab and 4 or 6 cycles of chemotherapy (AVD or escBEACOPP). Note: The number of treatments is calculated starting with the first dose.

## 6.2 Preparation/Handling/Storage/Accountability

### 6.2.1 Dose Preparation

Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual. Doxorubicin, vinblastine, dacarbazine, bleomycin, etoposide, cyclophosphamide, vincristine, procarbazine, and prednisone will be prepared and administered as per the approved product label(s) or institutional guidelines.

### 6.2.2 Handling, Storage, and 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 interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions 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).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the

investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

## 6.3 Measures to Minimize Bias: Randomization and Blinding

### 6.3.1 Intervention Assignment

Participants in this study will be allocated by nonrandom assignment. Intervention allocation will occur centrally using an IWRS system.

### 6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

### 6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the intervention administered.

## 6.4 Study Intervention Compliance

If there are interruptions in the study intervention schedule or infusion/injection was stopped, the details of and reason for any interruption or infusion/injection cessation of study intervention will be documented in the participant's medical record.

Refer to Section 6.6.1 for Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations and for other allowed dose interruptions. A delay of more than 7 days in pembrolizumab administration is to be discussed with the Sponsor.

Refer to Section 6.6.2 for dose modification of AVD and escBEACOPP.

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 of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant ID will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

### 6.4.1 Procarbazine and Prednisone Compliance

When participants receiving escBEACOPP self-administer procarbazine and prednisone at home, compliance with study intervention will be assessed at applicable visits. Compliance will be assessed by direct questioning, counting returned tablets/capsules, etc, during the site visits and documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

A record of the number of procarbazine and prednisone tablets/capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

## 6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medications or vaccinations prohibited, the investigator must discuss any questions regarding this with the Sponsor's Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator and the Sponsor.

### 6.5.1 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the screening and intervention phases of this study (unless otherwise noted):

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab, AVD, or escBEACOPP
- Radiation therapy
- Live or live-attenuated vaccines within 30 days before the first dose of study intervention and while participating in the study. Note: Killed vaccines are allowed. Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.
- Systemic glucocorticosteroids, except for the purposes listed in Section 6.5.1.1

CCI [redacted]

CCI

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the eCRF including all prescription, OTC products, herbal supplements, and IV medications, and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 28 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. All concomitant medications administered during SAEs or ECIs are to be recorded. SAEs and ECIs are defined in Section 8.4.

#### 6.5.1.1 Systemic Corticosteroid Use

Systemic corticosteroids are permitted in the following situations:

- Prednisone when administered as part of the escBEACOPP regimen
- To modulate symptoms of an AE that is suspected to have an immunologic etiology
- As needed for the prevention of emesis
- Premedication for IV contrast allergies
- Short-term oral or IV use in doses >10 mg/day prednisone equivalent for chronic obstructive pulmonary disease exacerbations
- For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent

In addition, the following glucocorticoid use is allowed:

- For topical use or ocular use
- Intraarticular joint use
- For inhalation in the management of asthma or chronic obstructive pulmonary disease

#### 6.5.1.2 Cautions for Use of Chemotherapy

Caution should be exercised when AVD/escBEACOPP is concomitantly administered with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index.

Note: a current list of sensitive CYP3A substrates and CYP3A substrates with a narrow therapeutic index can be found at the following website: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

### 6.5.2 Rescue Medications and Supportive Care

Participants receiving escBEACOPP in Chemotherapy Phase 2 should be started on growth factor support on Day 8 of each escBEACOPP cycle and continue during the cycle until ANC returns to normal.

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator.

Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.6.

## 6.6 Dose Modification (Escalation/Titration/Other)

### 6.6.1 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)

**Dose Modification and Toxicity Management for Immune-related AEs Associated With Pembrolizumab**

AEs associated with pembrolizumab exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation.

Dose Modification and Toxicity Management Guidelines for irAEs Associated With Pembrolizumab Monotherapy, Coformulations, or IO Combinations are provided in Table 3.

CCI

[redacted]

CCI

[redacted]

| | | | | |
|---|---|---|---|---|
| T1DM or Hyperglycemia | New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure | Withhold[d] | • Initiate insulin replacement therapy for participants with T1DM<br>• Administer antihyperglycemic in participants with hyperglycemia | • Monitor participants for hyperglycemia or other signs and symptoms of diabetes |
| Hypophysitis | Grade 2 | Withhold | • Administer corticosteroids and initiate hormonal replacements as clinically indicated | • Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency) |
| | Grade 3 or 4 | Withhold or permanently discontinue[d] | | |
| Hyperthyroidism | Grade 2 | Continue | • Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate | • Monitor for signs and symptoms of thyroid disorders |
| | Grade 3 or 4 | Withhold or permanently discontinue[d] | | |
| Hypothyroidism | Grade 2 | Continue | • Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care | • Monitor for signs and symptoms of thyroid disorders |
| | Grade 3 or 4 | Withhold or permanently discontinue[d] | | |

| irAEs | Toxicity Grade (CTCAE v5.0) | Action With Pembrolizumab Monotherapy, Coformulations, or IO Combinations | Corticosteroid and/or Other Therapies | Monitoring and Follow-up |
|---|---|---|---|---|
| Nephritis: grading according to increased creatinine or acute kidney injury | Grade 2 | Withhold | • Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper | • Monitor changes of renal function |
| | Grade 3 or 4 | Permanently discontinue | | |

CCI

[redacted]

CCI

**Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab**

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 4.

Table 4 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

| NCI CTCAE Grade | Treatment | Premedication at Subsequent Dosing |
|---|---|---|
| **Grade 1**<br>Mild reaction; infusion interruption not indicated; intervention not indicated | Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. | None |
| **Grade 2**<br>Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 h | **Stop Infusion.**<br>Additional appropriate medical therapy may include but is not limited to:<br>IV fluids<br>Antihistamines<br>NSAIDs<br>Acetaminophen<br>Narcotics<br>Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.<br>If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose.<br>Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment. | Participant may be premedicated 1.5 h (± 30 minutes) prior to infusion of pembrolizumab with:<br>Diphenhydramine 50 mg po (or equivalent dose of antihistamine).<br>Acetaminophen 500-1000 mg po (or equivalent dose of analgesic). |
| **Grades 3 or 4**<br>Grade 3:<br>Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates)<br>Grade 4:<br>Life-threatening; pressor or ventilatory support indicated | **Stop Infusion.**<br>Additional appropriate medical therapy may include but is not limited to:<br>Epinephrine**<br>IV fluids<br>Antihistamines<br>NSAIDs<br>Acetaminophen<br>Narcotics<br>Oxygen<br>Pressors<br>Corticosteroids<br>Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.<br>Hospitalization may be indicated.<br>**In cases of anaphylaxis, epinephrine should be used immediately.<br>**Participant is permanently discontinued from further study drug treatment.** | No subsequent dosing |

| NCI CTCAE Grade | Treatment | Premedication at Subsequent Dosing |
|---|---|---|
| CTCAE = Common Terminology Criteria for Adverse Event; IV = intravenous; NCI = National Cancer Institute; NSAID = nonsteroidal anti-inflammatory drug; po = orally.<br>Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.<br>For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov | | |

**Other Allowed Dose Interruption for Pembrolizumab**

**Pembrolizumab Monotherapy**

Pembrolizumab C2D1 and C3D1 must occur within +3 days of the scheduled dosing day except in case of AEs as described in Table 3 and Table 4.

**Pembrolizumab Consolidation**

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 6 weeks (42 days) of the originally scheduled dose and within 84 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

### 6.6.2 AVD and escBEACOPP Dose Modification

Dose modifications must follow approved product labeling and institutional guidelines. No dose reduction or modification of AVD should be done for uncomplicated cytopenias.

### 6.6.3 Additional Safety Data Monitoring

Routine medical monitoring of safety data will be performed by the Sponsor on a monthly basis during the study. In addition, every 4 months the Sponsor's study team will review cumulative Grade 3-5 TEAE data for each treatment (pembrolizumab, AVD, or escBEACOPP) for participants who have completed at least 1 cycle of pembrolizumab, 1 cycle of AVD, and 1 cycle of escBEACOPP, respectively. For pembrolizumab, the Grade 3-5 TEAEs occurring during the monotherapy and consolidation phases will be pooled, and for AVD, the Grade 3-5 TEAEs occurring during Chemotherapy Phase 1 and 2 will be pooled. The cumulative Grade 3-5 TEAE data for each treatment will be compared with historical control frequencies of 50% for pembrolizumab (based on the pembrolizumab monotherapy cumulative RSD referenced in the pembrolizumab IB), 70% for AVD (based on the RATHL study [Johnson, P., et al 2016]), and 85% for escBEACOPP (based on the RATHL study [Johnson, P., et al 2016]). If a ≥10% increase is observed in the frequency of Grade 3-5 TEAEs, compared with the specified historical control frequencies, enrollment will be paused and an internal DMC will review all available safety data.

The internal DMC is composed of members of Sponsor staff, none of whom otherwise are directly associated with the conduct of this study. Following internal DMC review, the study

may be discontinued if the totality of the data does not support a favorable risk-benefit trade-off for this study. If the study is discontinued, participants will continue in Survival Follow-up.

## 6.7 Intervention After the End of the Study

There is no study-specified intervention after the end of the study.

## 6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study-site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

## 6.9 Standard Policies

Not applicable.

# 7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

## 7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to be monitored in this study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.11.3 unless the participant has withdrawn from the study Section 7.2.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study intervention, but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Any prolonged interruption of study intervention beyond the permitted periods, for irAE management or other allowed dose interruptions, as noted in Section 6.6.1, require Sponsor consultation prior to restarting treatment. If treatment will not be restarted, the participant will continue to be monitored in the study and the reason for discontinuation of study intervention will be recorded in the medical record.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Any progression or recurrence of malignancy, or any occurrence of another malignancy that requires active treatment.
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.6.

For participants who are discontinued from study intervention, but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

Discontinuation from study intervention is “permanent.” Once a participant is discontinued from study intervention, they shall not be allowed to restart study intervention.

Note: All participants will continue on through the study and into pembrolizumab consolidation regardless of PET2 or PET3 (prior to chemotherapy Phase 1 and Phase 2, respectively) findings.

## 7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant’s legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

## 7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant’s last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant’s medical record.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

# 8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- 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.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before providing documented informed consent may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.
- The maximum amount of blood collected from each participant over the duration of the study will not exceed the amount specified in the Laboratory Manual.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

## 8.1 Administrative and General Procedures

### 8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study or FBR. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

#### 8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

Specifics about the study and the study population are to be included in the study informed consent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

#### 8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

### 8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

### 8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention allocation, site personnel will add the treatment/randomization number to the participant identification card.

The participant ID card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

### 8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically important. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

If a medical condition is diagnosed at the time of screening due to the physical examination, laboratory tests, radiologic assessment, other assessment, and/or a combination of these evaluations, the medical condition is to be recorded as a baseline condition along with the participant's other medical history unless due to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in).

#### 8.1.4.1 Classical Hodgkin Lymphoma Disease History

The investigator or qualified designee will obtain current details regarding cHL disease status.

### 8.1.5 Prior and Concomitant Medications Review

#### 8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the study. Treatment for cancer other than the disease under study will be recorded as prior medication even if taken by the participant more than 28 days before starting the study.

#### 8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up Visit.

#### 8.1.5.3 Subsequent Antineoplastic Therapy Status

The investigator or qualified designee will record all new antineoplastic therapy initiated after the last dose of study intervention, including, but not limited to radiation therapy, systemic therapy, surgery, and stem cell transplant. Stem cell transplant details including date and type of transplant and conditioning regimen will be collected.

If a participant initiates a new antineoplastic therapy within 30 days after the last dose of study intervention, the 30-day Safety Follow-up Visit must occur before the first dose of the

new therapy. Once new antineoplastic therapy has been initiated, the participant will move into Survival Follow-up.

### 8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before intervention allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any individual who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.11.1.

### 8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be allocated, by nonrandom assignment, and will receive a treatment/allocation number. The treatment/allocation number identifies the participant for all procedures occurring after treatment allocation. Once a treatment/allocation number is assigned to a participant, it can never be reassigned to another participant.

A single participant cannot be assigned more than 1 treatment/allocation number.

### 8.1.8 Study Intervention Administration

Pembrolizumab will be administered by the investigator and/or study staff according to the specifications within the Pharmacy Manual. AVD and escBEACOPP will be administered per the approved product label(s) or institutional guidelines; participants will self-administer procarbazine and prednisone according to instructions provided by study staff. Refer to Appendix 7 for country-specific requirements.

After ensuring participants meet study-related inclusion/exclusion criteria, study staff will access IWRS to obtain treatment number.

Study intervention should begin within 3 days of intervention allocation.

Participants will be administered pembrolizumab using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to the planned infusion time possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted.

Note that participants with PET-positive residual mass at EOT should not receive radiotherapy as part of study intervention but should be transitioned to Survival Follow-up (see Section 8.11.4.3) before receiving nonstudy anticancer treatment for residual disease.

#### 8.1.8.1 Timing of Dose Administration

Study interventions will be administered after all predose procedures and assessments have been completed according to the SoAs (Section 1.3).

**Pembrolizumab Monotherapy**

Pembrolizumab will be administered on Day 1 of each 3-week (21-day) cycle for 3 cycles. Each cycle may be administered up to 3 days after the scheduled Day 1 of each cycle due to administrative reasons per the investigator's judgment.

**Chemotherapy**

Following PET2, AVD will be administered on Day 1 and Day 15 of each 4-week (28-day) cycle for 2 cycles. Each cycle may be administered up to 3 days after the scheduled Day 1 of each cycle.

Participants will receive additional chemotherapy according to their PET3 response and age at screening.

If the participant is PET-negative at PET3, or PET-positive at PET3 and ≥60 years of age at the time of Screening, AVD will be administered on Day 1 and Day 15 of each 4-week (28-day) cycle for 4 cycles. However, participants with early unfavorable, nonbulky disease will receive 2 cycles of AVD. Each cycle may be administered up to 3 days after the scheduled Day 1 of each cycle.

If the participant is PET-positive at PET3 and <60 years of age at the time of Screening, escBEACOPP will be administered as follows: doxorubicin (Day 1), cyclophosphamide (Day 1), etoposide (Days 1 to 3), procarbazine (Days 1 to 7), prednisone (Days 1 to 14), bleomycin (Day 8), and vincristine (Day 8) of each 3-week (21-day) cycle for 4 cycles. However, participants with early unfavorable, nonbulky disease will receive 2 cycles of escBEACOPP. Each cycle may be administered up to 7 days after the scheduled Day 1 of each cycle. The maximum dose of vincristine is 2 mg.

**Pembrolizumab Consolidation**

During pembrolizumab consolidation, pembrolizumab will be administered on Day 1 of each 6-week (42-day) cycle for 4 cycles. Before starting pembrolizumab consolidation, any chemotherapy associated toxicity that is deemed clinically significant by the investigator must have resolved to ≤Grade 1 or baseline. Non-clinically significant toxicities (such as: alopecia, low lymphocyte count) may not need dose delays. Cycle 1 may be administered up to 3 days after the scheduled Day 1 and subsequent cycles may be administered up to 3 days before or 3 days after the scheduled Day 1.

The reason for any variability in administration outside the protocol-specified window should be documented in the participant's chart and recorded on the eCRF.

### 8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.11.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the EOT visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

#### 8.1.9.1 CCI

CCI

### 8.1.10 Participant Blinding/Unblinding

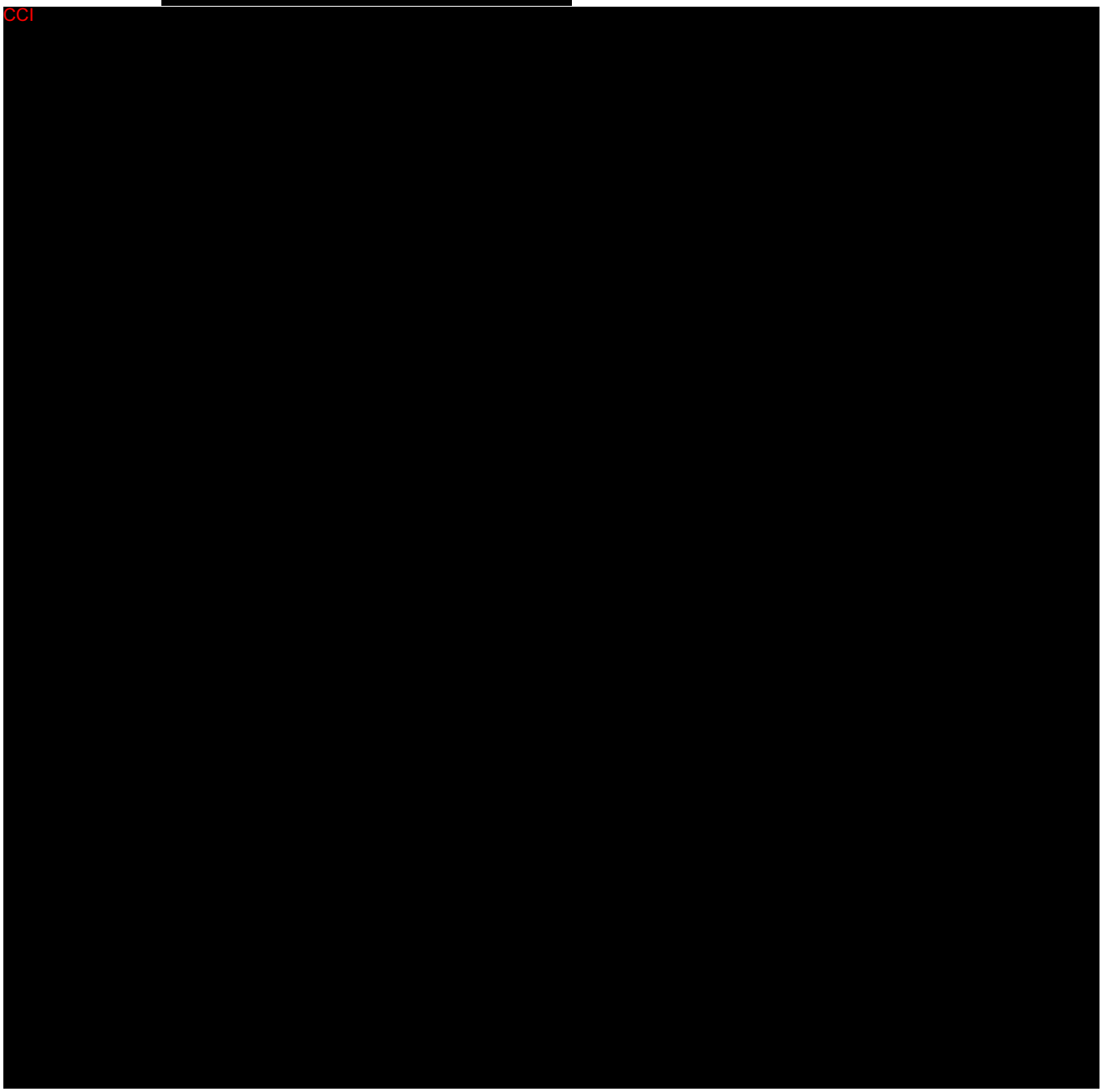
This is an open-label study; there is no blinding for this study. The emergency unblinding call center will be available so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

### 8.1.11 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

### 8.1.12 CCI

CCI



## 8.2 Efficacy Assessments

### 8.2.1 Tumor Imaging and Assessment of Disease

Throughout this section, the term ‘scan’ refers to any medical imaging data used to assess tumor burden and may include cross-sectional imaging (such as CT or MRI), medical photography, or other methods as specified in this protocol.

In addition to survival, efficacy will be assessed based on imaging evaluation of changes in tumor burden over time, until the participant is discontinued from the study or goes into

Survival Follow-up. Disease response assessments may use CT/MRI and/or PET imaging, laboratory studies, physical examination, and biopsy results when a biopsy is performed. The Site Imaging Manual details the scan schedule, anatomic requirements, and imaging methods to be used, as well as the process for scan collection and transmission to the iCRO.

The scheduled imaging time points, and the type of imaging to be performed at each scheduled time point, are specified in the SoA (Section 1.3). All participants require imaging of the neck, chest, abdomen, and pelvis at baseline and all later time points (the neck may be omitted after Screening if no disease is seen in the neck at that time). Anatomic imaging (for this protocol, this term refers to CT or MRI, although CT is preferred) should be of diagnostic quality and acquired with IV contrast. Metabolic imaging (whole body FDG-PET) should be performed with correlative anatomic imaging for attenuation correction. The Site Imaging Manual will provide detailed scan acquisition guidelines, and alternative methods for imaging if the preferred methods cannot be done due to medical contraindication or local practice. The same scan technique should be used in a participant throughout the study.

Other types of medical imaging (such as ultrasound) will not be included in response assessment.

Local assessment (investigator assessment with site radiology reading) will be used to determine participant eligibility and for participant management. Note: For the purposes of assessing tumor scans, the term “investigator” refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility. All scheduled scans for participants will be submitted to the iCRO. In addition, a scan that is obtained at an unscheduled time point, for any reason (including suspicion of progression or other clinical reason), should also be submitted to the iCRO if it shows disease progression, or if it is used to support a response assessment. All scans acquired within the protocol-specified window of time around a scheduled scan visit are to be classified as pertaining to that visit.

Assessment of scans (including classification of lesions before treatment and response determination during treatment) will be performed according to the Lugano Classification [Cheson, B. D., et al 2014], as detailed in Appendix 9.

#### 8.2.1.1 Initial Tumor Scans

Anatomic and metabolic imaging (PET1) must be performed during Screening, within 28 days before the date of the first dose of study intervention. Any imaging obtained after Cycle 1 Day 1 of treatment cannot be included in the screening assessment. The site study team must review screening images to confirm the participant has measurable FDG-avid disease as defined by the Lugano Classification (Appendix 9).

Disease assessments or scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days before the first dose of study intervention.

#### 8.2.1.2 Tumor Scans During the Study

Following Screening, disease response assessments will be performed based on the schedules described below. However, imaging should occur at any time when there is clinical suspicion of progression.

During Pembrolizumab Monotherapy: FDG-PET scan (PET2) must be performed 3 weeks (±3 days) after pembrolizumab Cycle 3 Day 1 and before AVD Cycle 1 Day 1. CT scans are not required during this phase.

During Chemotherapy: PET3 must be performed between AVD Cycle 2 Day 26 and Cycle 2 Day 29 and before starting additional AVD or escBEACOPP chemotherapy (Sections 1.3.2 and 1.3.3). CT scans are not required during this phase.

During Pembrolizumab Consolidation: Imaging should occur at any time when there is clinical suspicion of progression.

#### 8.2.1.3 End-of-treatment and Follow-up Tumor Scans

End-of-Treatment: For participants who complete study intervention, EOT FDG-PET (EOT PET) and CT (EOT CT) scans must be performed 6 weeks (±7 days) after the pembrolizumab consolidation Cycle 4 Day 1 dose. For participants who discontinue before completing study intervention, the EOT PET and EOT CT should be performed within 6 weeks (±7 days) after the last dose of study intervention.

If at EOT, either anatomic or metabolic imaging shows findings suspicious for residual disease, a biopsy may be obtained, which will contribute to the assessment of disease per Lugano 2014 response criteria (Appendix 9).

Efficacy Follow-up: Participants with CR at the end of study intervention, or participants who discontinue for reasons other than investigator discontinuation due to disease progression, will enter Efficacy Follow-up. The first scheduled imaging during Efficacy Follow-up will be performed 24 weeks (±7 days) after EOT imaging. CT scans will then be performed every 24 weeks (±7 days) for 2 years after EOT CT, then at investigator's discretion until one of the following conditions are met:

- Disease progression
- Start of a new anticancer treatment
- Pregnancy
- Death
- Withdrawal of consent
- End of the study

During Efficacy Follow-up, MRI can be considered in place of CT if MRI was performed at EOT for comparison. FDG-PET is only required if CT scan suggests progression or there is clinical suspicion of progression.

Participants without CR at the end of study intervention will progress immediately to Survival Follow-up, and no additional imaging will be performed after EOT imaging.

#### 8.2.1.4 Scan Evaluation

The Lugano Classification [Cheson, B. D., et al 2014] will be used to assess response to treatment including best overall response and date of disease progression, and as a basis for all protocol guidelines related to disease status. Rules for Lugano assessment of response using CT and PET are outlined in Appendix 9.

#### 8.2.1.5 Bone Marrow Biopsy/Aspirate

Bone marrow biopsy and/or aspirate should be obtained as clinically indicated during the study. If bone marrow biopsy is inconclusive, bone marrow aspirate may be substituted. If bone marrow assessment is performed at Screening, subsequent bone marrow assessments will be performed only in subjects who have bone marrow involvement at Screening.

Bone marrow assessments will be performed by the local laboratory according to institutional practice and results will be recorded in the eCRF.

### 8.2.2 CCI

CCI

[redacted]

## 8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood to be drawn/collected over the course of the study, including approximate blood volumes drawn/collected by visit and by sample type per participant, can be found in the Laboratory Manual.

Planned time points for all safety assessments are provided in the SoA.

### 8.3.1 Physical Examinations

#### 8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a full physical examination during the Screening period (consistent with local requirements) as per institutional standard. Clinically significant abnormal findings during Screening should be recorded as medical history. A full physical examination also will be performed at the EOT visit. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs if they fall within the safety reporting period.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

#### 8.3.1.2 Directed Physical Examination

For visits that do not require a full physical examination as defined in Section 1.3, the investigator or qualified designee will perform a directed physical examination. During the treatment period, a directed physical examination will be performed within 3 days before dosing on Day 1 of each cycle and as clinically indicated. During Efficacy Follow-up, a directed physical examination will be performed every 12 weeks for 2 years after EOT imaging, and then at investigator's discretion for the remainder of Efficacy Follow-up. New clinically significant abnormal findings should be recorded as AEs if they fall within the safety reporting period.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

#### 8.3.1.3 Assessment of Lymphoma B Symptoms

Lymphoma B symptoms are a set of clinical criteria assessed during diagnosis and treatment of cHL. Assessment of Lymphoma B symptoms should occur at Screening and as specified in the SoA (Section 1.3). These symptoms include the following:

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

### 8.3.2 Vital Signs

The investigator or qualified designee will assess vital signs at Screening and as specified in the SoA (Section 1.3). Vital signs will include height (at Screening only), weight, temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate.

### 8.3.3 Electrocardiograms

- Single 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) at Screening and as clinically indicated using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals.
- Clinically significant abnormal findings at Screening should be recorded as medical history. Additional ECG(s) should be performed when clinically indicated. Clinically significant abnormal findings on postscreening ECGs should be recorded as AEs.

### 8.3.4 Echocardiography or Multigated Acquisition Scan

An ECHO or MUGA scan will be required at Screening, at the end of AVD Cycle 2 (before starting AVD Cycle 3 or escBEACOPP Cycle 1), and at the end of the last cycle of chemotherapy (before starting pembrolizumab consolidation).

The assessment method will be at the investigator's discretion and per the local standard of care. Additional assessments may be performed as clinically indicated.

### 8.3.5 Pulmonary Function Testing

Pulmonary function testing will be performed according to institutional guidelines within 7 days before escBEACOPP dosing on Day 1 Cycle 1 and at the end of the last cycle of chemotherapy (before starting pembrolizumab consolidation). Additional tests may be performed as clinically indicated.

Pulmonary function testing should include an assessment of FVC, forced expiratory flow between 25 and 75 percent of FVC (FEF25-75), forced expiratory volume in one second, and peak expiratory flow.

### 8.3.6 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are

considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation In the study or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

Details regarding specific laboratory procedures/assessments to be performed in this study are provided below. The total amount of blood to be drawn/collected over the course of the study, including approximate blood volumes drawn/collected by visit and by sample type per participant can be found in the Laboratory Manual. Refer to the SoA (Section 1.3) for the timing of laboratory assessments.

#### 8.3.6.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Details regarding specific laboratory procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in the Laboratory Manual. Refer to the Study Flow Chart (Section 1.3) for the timing of laboratory assessments.

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2.

The laboratory criteria in Table 1 must be met before dosing on Day 1 of every cycle (the requirement for ANC is ≥1000/µL from pembrolizumab Cycle 2 onwards), with the exception of hematological parameters for AVD cycles.

### 8.3.7 Pregnancy Testing

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine or serum) should be conducted at every protocol treatment cycle as per SoA.
  - Pregnancy testing (urine or serum) should be conducted for the time required to eliminate systemic exposure after the last dose of each study intervention and should correspond with the time frame for the participant's contraception, as noted in Section 5.1. The length of time required to continue pregnancy testing for each study intervention is:
    - Pembrolizumab: 120 days
    - Chemotherapy: 180 days

- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

- In case of suspected false positive pregnancy test in participants with fertility preservation, consult Sponsor.

### 8.3.8 International Prognostic Score

The investigator or qualified designee will assess IPS (see Appendix 10) at Screening as specified in the SoA (Section 1.3).

### 8.3.9 Unfavorable Risk Factors

For participants with early stage disease (Ann Arbor Stage I or II), the investigator or qualified designee will assess unfavorable risk factors according to NCCN guidelines (see Appendix 11) at Screening as specified in the SoA (Section 1.3).

### 8.3.10 Performance Assessments: Eastern Cooperative Oncology Group Performance Status

The ECOG Performance Status is standardized criteria to measure how cancer impacts level of functioning (performance status) in terms of ability to care for oneself, daily activity, and physical ability (walking, working, etc) with Grades 0 to 5.

The investigator or qualified designee will assess ECOG status (see Appendix 12) at Screening (within 7 days before the Cycle 1 Day 1 dose of pembrolizumab), before dosing on Day 1 of each subsequent cycle, and at EOT as specified in the SoA (Section 1.3).

## 8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Progression of the cancer under study is not considered an AE as described in Section 8.4.6 and Appendix 3.

Adverse events, SAEs, and other reportable safety 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 reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity, and causality.

### 8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention allocation, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention allocation through 30 days after cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation through 90 days after cessation of study intervention or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of intervention allocation through the time required to eliminate systemic exposure after cessation of study intervention as described in Sections 5.1 and 8.3.7, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside the time specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 5.

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

Table 5 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

| Type of Event | Reporting Time Period: Consent to Randomization/ Allocation | Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period | Reporting Time Period: After the Protocol-specified Follow-up Period | Time Frame to Report Event and Follow-up Information to Sponsor: |
|---|---|---|---|---|
| NSAE | Report if:<br>- due to protocol-specified intervention<br>- causes exclusion<br>- participant is receiving placebo run-in or other run-in treatment | Report all | Not required | Per data entry guidelines |
| SAE including Cancer and Overdose | Report if:<br>- due to protocol-specified intervention<br>- causes exclusion<br>- participant is receiving placebo run-in or other run-in treatment | Report all | Report if:<br>- drug/vaccine related.<br>(Follow ongoing to outcome) | Within 24 hours of learning of event |
| Pregnancy/ Lactation Exposure | Report if:<br>- participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in)<br>Exception: A positive pregnancy test at the time of initial screening is not a reportable event. | Report all | Previously reported – Follow to completion/termination; report outcome | Within 24 hours of learning of event |
| ECI (require regulatory reporting) | Report if:<br>- due to intervention<br>- causes exclusion | Report<br>- potential DILI<br>- require regulatory reporting | Not required | Within 24 hours of learning of event |
| ECI (do not require regulatory reporting) | Report if:<br>- due to intervention<br>- causes exclusion | Report<br>- non-DILI ECIs and those not requiring regulatory reporting | Not required | Within 5 calendar days of learning of event |

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event.

### 8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

### 8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in allocated participants for outcome. Further information on follow-up procedures is given in Appendix 3.

### 8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor 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. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

### 8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee), or a pregnancy that occurs during the study in a nonparticipant whose sexual partner is a participant capable of producing ejaculate is reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing that the fetus will be

born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

### 8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 8.4.1.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will ensure that unblinded aggregated efficacy endpoint events and safety data are monitored to safeguard the participants in the study.

### 8.4.7 Events of Clinical Interest

Selected serious and nonserious AEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5.
2. Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
   *Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

In the event a participant receives an allogeneic SCT within 24 months of the last dose of pembrolizumab, the following events will be collected as ECIs through 18 months from the date of allogeneic SCT: GVHD, febrile syndrome treated with steroids, pulmonary complications, hepatic veno-occlusive disease and/or sinusoidal syndrome, immune-mediated AEs, critical illness, and transplant-related mortality. Additional medically important AEs may be submitted at the investigator’s discretion.

Details to be collected and suggested events to be reported will be provided in the Collection of Stem Cell Transplant (SCT) Details and Post-Allogeneic SCT Events of Clinical Interest (ECI) Guidance Document. Post allogenic SCT ECIs that occur after the normal Safety Follow-up period must be assessed for seriousness and causality and be reported to the Sponsor as follows: within 24 hours if serious regardless of causality or if nonserious and considered to be drug-related; and within 5 calendar days if nonserious and not considered to be drug-related.

If available and relevant to an event post allogeneic SCT, concomitant medications and/or laboratory results may be reported.

## 8.5 Treatment of Overdose

### 8.5.1 Pembrolizumab

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater.

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

### 8.5.2 AVD and escBEACOPP

AVD contains the following medications: doxorubicin, vinblastine, and dacarbazine.

escBEACOPP contains the following medications: doxorubicin, cyclophosphamide, etoposide, procarbazine, prednisone, bleomycin, and vincristine.

In this study, an overdose of any of these agents is any dose exceeding the prescribed dose. In the event of overdose, the administration of the agent should be discontinued, and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

## 8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

## 8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

## 8.8 CCI

CCI

CCI

CCI

CCI

CCI

## 8.10 Medical Resource Utilization and Health Economics

All-cause hospitalizations and emergency room visits must be reported in the eCRF, from the time of treatment allocation through 90 days after cessation of study intervention, or 30 days after cessation of study intervention, if the participant initiates new anticancer therapy, whichever is earlier.

## 8.11 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

### 8.11.1 Screening

Documented informed consent must be provided before performing any protocol-specific procedure. Results of a test performed before the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

Screening procedures are to be completed within 28 days before the first dose of study intervention.

Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria is met. Participants who are rescreened will retain their original screening number.

### 8.11.2 Treatment Period

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 8.

### 8.11.3 Discontinued Participants Continuing to be Monitored in the Study

Discontinuation of treatment does not represent withdrawal from the study.

Participants who discontinue study intervention for reasons other than investigator discontinuation due to disease progression will have a Safety Follow-up Visit by phone and an in-clinic EOT Visit and then proceed to Efficacy Follow-up as described in Section 8.11.4.2.

Participants who discontinue study intervention due to unacceptable AE(s), intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, administrative reasons requiring cessation of treatment, or after the participant has received the maximum duration of treatment specified by the protocol will have a Safety Follow-up Visit by phone and an in-clinic EOT Visit and then proceed to Survival Follow-up as described in Section 8.11.4.3. The Safety Follow-up Visit and the EOT Visit should occur before the start of new anticancer therapy.

For participants who discontinue study intervention early, the EOT Visit should occur within 6 weeks (±7 days) after the last dose of study intervention. If the EOT Visit occurs 30 days from the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, the EOT Visit procedures and assessments should be performed. Additional details regarding participants treatment discontinuation can be found in Section 7.1.

### 8.11.4 Posttreatment Visit

#### 8.11.4.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted 30 days (+7 days) after the last dose of study intervention or before the initiation of a new anticancer treatment, whichever comes first. This visit will be conducted by telephone call.

#### 8.11.4.2 Efficacy Follow-up Visits

Participants who complete the protocol-required cycles of study intervention with CR or who discontinue study intervention for a reason other than investigator discontinuation due to disease progression will begin Efficacy Follow-up. Visits will occur every 12 weeks (±7 days) with imaging assessments for efficacy to be performed every 24 weeks (±7 days) for 2 years after EOT imaging, then at investigator's discretion until end of study, or until the start of new anticancer therapy, disease progression, pregnancy, withdrawal of consent, death, or loss to follow-up, whichever occurs first (imaging as specified in the SoA Section 1.3.4). Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who will not have further efficacy assessments must enter Survival Follow-up.

#### 8.11.4.3 Survival Follow-up Contacts

Participant survival follow-up status will be assessed approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

The first survival follow-up assessment should be scheduled as described below:

1. For participants without CR at the end of study intervention, or who discontinue study intervention due to disease progression, and will not enter Efficacy Follow-up, the first survival follow-up contact will be scheduled 12 weeks after the EOT Visit and/or Safety Follow up Visit (whichever is last).
2. For participants who completed assessments in Efficacy Follow-up, the first survival follow-up contact will be scheduled 12 weeks after the last Efficacy Follow-up Visit has been performed.

### 8.11.5 Vital Status

To ensure current and complete vital status for survival data is available at the time of database locks, updated vital status for survival data may be requested during the study by the Sponsor. For example, updated vital status for survival data may be requested before but not limited to, an eDMC review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their vital status for survival data (excluding participants that have a previously recorded death event in the collection tool).

# 9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any final database lock, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). CCI

CCI

## 9.1 Statistical Analysis Plan Summary

| | |
|---|---|
| Study Design Overview | Phase 2 study of sequential pembrolizumab followed by chemotherapy in patients with newly diagnosed cHL (KEYNOTE-C11) |
| Treatment Assignment | This is an open-label study. |
| Analysis Populations | Efficacy: All Participants as Treated (APaT)<br>Safety: All Participants as Treated (APaT) |
| Primary Endpoint(s) | CR |
| Key Secondary Endpoint(s) | PET Negativity<br>CCI |
| Statistical Methods for Key Efficacy Analyses | The primary hypothesis will be evaluated by comparing CR rate at the end of study intervention to a fixed historical control rate of CCI using a binomial exact test. The point estimate of the CR rate will be provided, together with 95% CI using exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934]. |
| Statistical Methods for Key Safety Analyses | Counts and percentages of participants with AEs will be provided. |

| | |
|---|---|
| CCI | CCI |
| CCI | CCI |
| Sample Size and Power | The planned sample size is 140 participants for the primary analysis. CCI |

## 9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study is being conducted as a nonrandomized, open-label study, ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned.

## 9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

## 9.4 Analysis Endpoints

### 9.4.1 Efficacy Endpoints

**Primary**

- **CR:** having a complete response, assessed by independent central review according to Lugano 2014 response criteria (Appendix 9).

**Secondary**

- **CR:** having a complete response, assessed by investigators according to Lugano 2014 response criteria (Appendix 9).

- **PET negativity:** a score of 1, 2, or 3 assessed by independent central review according to FDG-PET 5-point scale (Appendix 9).

CCI

CCI

CCI

### 9.4.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters, including AEs, laboratory values, and vital signs.

## 9.5 CCI

### 9.5.1 CCI

CCI

### 9.5.2 CCI

CCI

## 9.6 Statistical Methods

### 9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. CCI .

CCI

#### 9.6.1.1 Complete Response

The CR rate is defined as the proportion of participants who have CR at the end of study intervention, after the completion of pembrolizumab consolidation. An exact binomial test will be conducted to test the hypothesis that the CR rate is greater than the fixed control rate of [redacted] The point estimate of CR rate and its 95% CI will be provided using exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934]. Response for the primary analysis will be determined by independent central review according to Lugano 2014 response criteria (Appendix 9). [redacted]

[redacted]

#### 9.6.1.2 PET Negativity

The rate of PET negativity is defined as a score of 1, 2, or 3, assessed by independent central review according to the FDG-PET 5-point scale (Appendix 9). Descriptive statistics will be performed for the rate of PET negativity, (i) after 3 cycles of pembrolizumab monotherapy (PET2); and (ii) after 3 cycles of pembrolizumab monotherapy followed by 2 cycles of AVD (PET3).

#### 9.6.1.3 [redacted]

[redacted]

CCI [redacted]

### 9.6.1.4 Analysis Strategy for Key Efficacy Variables

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 7.

Table 7 Analysis Strategy for Key Efficacy Variables

| Endpoint/Variable | Statistical Method | Analysis Population | Missing Data Approach |
|---|---|---|---|
| **Primary Analyses** | | | |
| CR rate per Lugano 2014 response criteria by independent central review | Testing and estimation: Exact method based on binomial distribution | APaT | Participants with missing data are considered nonresponders |
| CCI [redacted] | | | |

APaT=All Participants as Treated; CR=complete response; DurCR=duration of complete response.

### 9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and laboratory parameters. The broad AE categories consisting of the percentage of participants with any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, a Grade 3 to 5 AE, a drug-related Grade 3 to 5 AE, and who discontinued due to an AE will be summarized. The number and percentage of participants with increased laboratory toxicity grade shift from baseline will also be provided.

The safety analyses will include data after the initial PD at PET2 or PET3 timepoints if participants continued on to the next treatment phase as per Section 7.1 (Note).

### 9.6.3 Demographic and Baseline Characteristics

Each relevant demographic and baseline characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and enrolled and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized either by descriptive statistics or categorical tables.

## 9.7 CCI [redacted]

### 9.7.1 CCI [redacted]

CCI [redacted]

CCI

[redacted]

### 9.7.2 CCI [redacted]

CCI

[redacted]

## 9.8 CCI [redacted]

CCI [redacted]

## 9.9 Sample Size and Power Calculations

Approximately 140 participants will be enrolled in the study. With 140 participants in the primary analysis population, there is CCI (1-sided nominal 2.5% alpha) to detect a CCI or higher CR rate, compared to a fixed control rate of CCI CCI

CCI

## 9.10 Subgroup Analyses

To determine whether the CR rate is consistent across various subgroups, the point estimate of the CR rate (with an exact 95% CI) will be provided within each category of the following classification variables:

CCI

If the observed numbers are too small to make a meaningful clinical interpretation, then that subgroup analysis will not be conducted.

## 9.11 Compliance (Medication Adherence)

Drug accountability data for study intervention will be collected during the study. Any deviation from protocol-directed administration will be reported.

## 9.12 Extent of Exposure

Extent of exposure for a participant is defined as the number of cycles in which the participant receives the study intervention. Summary statistics will be provided on the extent of exposure for the APaT population.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

### 10.1.1 Code of Conduct for Clinical Trials

**Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)**

## I. Introduction

### A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

### B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

## II. Scientific Issues

### A. Trial Conduct

#### 1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Participants must meet protocol entry criteria to be enrolled in the trial.

### 2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

### 3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

## B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

# III. Participant Protection

## A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or

national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

### B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

### C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

### D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

## IV. Financial Considerations

### A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

### B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As

noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

**C. Funding for Travel and Other Requests**

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

**V. Investigator Commitment**

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

### 10.1.2 Financial Disclosure

Financial disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

### 10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

#### 10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee, affiliated institution, and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

#### 10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules, and regulations.

#### 10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

### 10.1.4 Committees Structure

#### 10.1.4.1 Internal Data Monitoring Committee

To supplement the routine monitoring outlined in this protocol, a separate internal DMC will monitor the interim data from this study. The internal DMC is comprised of members of Sponsor Senior Management, none of whom are directly associated with the conduct of this study. The internal DMC will monitor the study progress for evidence of any adverse effects of study intervention. The internal DMC will also make recommendations to the Sponsor study team regarding steps to ensure both participant safety and the continued ethical integrity of the study in the internal DMC charter.

### 10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of

multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

### 10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

### 10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting

from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

### 10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF 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 participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

### 10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF 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/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

### 10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study-site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

## 10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 9 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- The laboratory criteria in Table 1 must be met before dosing on Day 1 of every cycle (the requirement for ANC is ≥1000/µL from pembrolizumab Cycle 2 onwards), with the exception of hematological parameters for AVD cycles.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations. Refer to Appendix 7 for country specific requirements.

Table 9 Protocol-required Safety Laboratory Assessments

| **Laboratory Assessments** | **Parameters** | | | |
|---|---|---|---|---|
| Hematology | Platelet Count<br>RBC Count<br>Hemoglobin<br>Hematocrit | WBC count with Differential[a]:<br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils | | |
| Chemistry | BUN[b] | Potassium | AST/SGOT | Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN) |
| | Albumin | Bicarbonate or $CO_2$[c] | Chloride | Phosphorous |
| | Creatinine | Sodium | ALT/SGPT | Total Protein |
| | Glucose (fasting or nonfasting per institutional standard) | Calcium | Alkaline phosphatase | Magnesium[c]<br>Uric Acid[c] |
| | LDH | CrCl[d] | | |
| Routine Urinalysis | • Specific gravity<br>• pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick]<br>• Microscopic examination (if blood or protein is abnormal) | | | |
| Pregnancy Testing | • hCG pregnancy test (as needed for WOCBP) | | | |
| Other Screening Tests | • Coagulation: PT/INR and aPTT/PTT[e]<br>• ESR<br>• FSH (as needed to confirm postmenopausal state)<br>• Serology (HIV antibody, HBsAg, and HCV antibody) is not required unless mandated by local health authority.<br>Note: If required, testing will be conducted per local regulations and institutional standards. | | | |
| Other Required Tests During Study | • Thyroid function tests: total or free T3, total or free T4, and TSH | | | |

| Laboratory Assessments | Parameters |
|---|---|
| ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; $CO_2$=carbon dioxide; CrCl=creatinine clearance; ESR=erythrocyte sedimentation rate; FSH=follicle-stimulating hormone; GFR=glomerular filtration rate; HBsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HCV=hepatitis C virus; HIV=human immunodeficiency virus; INR=international normalized ratio; LDH=lactate dehydrogenase; PT=prothrombin time; PTT=partial thromboplastin time; RBC=red blood cell; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal; WBC=white blood cell; WOCBP=women of childbearing potential. | |
| [a] Absolute or % acceptable per institutional standard. | |
| [b] BUN is preferred, but if not available then urea may be tested. Record either BUN or urea result, but not both. | |
| [c] Only required if part of standard of care. | |
| [d] Measured or calculated CrCl (GFR can also be used in place of CrCl). Creatinine clearance should be calculated per the Cockcroft-Gault equation (see Table 1). | |
| [e] Coagulation tests must include PT or INR plus aPTT or PTT. | |
| Notes: For laboratory assessments with different testing options, the same test should be performed throughout the duration of the study. | |

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

## 10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

### 10.3.1 Definitions of Medication Error, Misuse, and Abuse

**Medication error**

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

**Misuse**

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

**Abuse**

This corresponds to the persistent or sporadic intentional, excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

### 10.3.2 Definition of AE

**AE definition**

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

**Events meeting the AE definition**

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer (that is not a condition of the study). Progression of the cancer under study is not considered a reportable event unless it results in hospitalization or death.

**Events NOT meeting the AE definition**

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

### 10.3.3 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

**An SAE is defined as any untoward medical occurrence that, at any dose:**

a. Results in death
b. Is life-threatening
   - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization
   - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not

worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. Results in persistent or significant disability/incapacity
   - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
   - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect
   - In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events
   - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
   - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

### 10.3.4 Additional Events Reported

**Additional events that require reporting in the same manner as SAE**

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same time frame as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not the cancer under study) as noted in Section 8.4.1.
- Is associated with an overdose.

### 10.3.5 Recording AE and SAE

**AE and SAE recording**

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

**Assessment of intensity/toxicity**

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 5.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
  - 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 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.

**Assessment of causality**

- Did the study intervention cause the AE?
- The determination of the likelihood that the study intervention caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**
  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with IMP)?
  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
  - **Dechallenge:** Was the study intervention discontinued or dose/exposure/frequency reduced?
    - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
    - If no, this is a negative dechallenge.

    (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the study intervention; (3) the study is a single-dose drug study; or (4) study intervention (s) is/are only used 1 time.)
  - **Rechallenge:** Was the participant reexposed to the study intervention in this study?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

    (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability; (2) the study is a single-dose drug study; or (3) study intervention (s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE STUDY INTERVENTION, OR IF REEXPOSURE TO THE STUDY INTERVENTION POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).
  - Yes, there is a reasonable possibility of study intervention relationship:
    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
  - No, there is not a reasonable possibility of study intervention relationship:
    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.
- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

**Follow-up of AE and SAE**

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

### 10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

**AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool**

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

**SAE reporting to the Sponsor via paper CRF**

- If the EDC tool is not operational, facsimile transmission or secure email of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

## 10.4 Appendix 4: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

## 10.5 Appendix 5: Contraceptive Guidance

### 10.5.1 Definitions

**Women of Childbearing Potential (WOCBP)**

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

## 10.5.2 Contraceptive Requirements

| **Contraceptives allowed during the study include[a]:** |
|---|
| **Highly Effective Contraceptive Methods That Have Low User Dependency**<br>*Failure rate of <1% per year when used consistently and correctly.* |
| • Progestogen-only subdermal contraceptive implant[b,c]<br>• IUS[c,d]<br>• Non-hormonal IUD<br>• Bilateral tubal occlusion |
| • Azoospermic partner (vasectomized or secondary to medical cause)<br>This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.<br><br>Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. |
| **Sexual Abstinence**<br>• Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. |
| [a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.<br>[b] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation.<br>[c] Male condoms must be used in addition to female participant hormonal contraception.<br>[d] IUS is a progestin releasing IUD.<br><br>Note: The following are not acceptable methods of contraception:<br>- Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM.<br>- Male condom with cap, diaphragm, or sponge with spermicide.<br>- Male and female condom should not be used together (due to risk of failure with friction). |

## 10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

### 1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

### 2. Scope of Future Biomedical Research[3, 4]

The specimens consented and/or collected in this study as outlined in Section 8.8 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways with which drugs/vaccines may interact
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease, and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

### 3. Summary of Procedures for Future Biomedical Research[3, 4]

a. Participants for Enrollment
All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent
Informed consent for specimens (ie, DNA, RNA, protein, etc) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens
Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)
Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

**4. Confidential Participant Information for Future Biomedical Research[3, 4]**

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history, and intervention outcomes is critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number that does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

**5. Biorepository Specimen Usage[3, 4]**

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses using the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third-party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

**6. Withdrawal From Future Biomedical Research[3, 4]**

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox

(clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

**7. Retention of Specimens[3, 4]**

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not used in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility, which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

**8. Data Security[3, 4]**

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

**9. Reporting of Future Biomedical Research Data to Participants[3, 4]**

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

## 10. Future Biomedical Research Study Population[3, 4]

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

## 11. Risks Versus Benefits of Future Biomedical Research[3, 4]

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

## 12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@MSD.com.

## 13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618
2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html
3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

## 10.7 Appendix 7: Country-specific Requirements

### 10.7.1 France-specific Requirements

**Section 5.1 Inclusion Criteria**

Criterion #5

**Male Participants**

The length of time required to continue contraception after the last dose of each study intervention is as follows:

- Pembrolizumab: no contraception requirement
- Cyclophosphamide: 9 months
- Other chemotherapy: 90 days

Criterion #6

**Female Participants**

The length of time required to continue contraception after the last dose of each study intervention is as follows:

- Pembrolizumab: 120 days
- Cyclophosphamide: 12 months
- Other chemotherapy: 180 days

Criterion #9

Participants will be included according to the renal function requirement below:

| Renal | |
|---|---|
| Creatinine AND<br>Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl) | ≤1.5 × ULN AND<br>≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN |
| [b] Creatinine clearance (CrCl) should be calculated per institutional standard. | |

**Section 8.1.8 Study Intervention Administration**

Investigators should refer to http://base-donnees-publique.medicaments.gouv.fr for updated Summary of Product Characteristics of the marketing authorization of commercially available products used during the study for participant management, particularly regarding safety monitoring, product contraindications, and precautions.

## Section 10.5.2 Contraception Requirements

List of countries that follow CTFG guidelines (including France):
https://www.hma.eu/nationalcontacts_hum.html

Refer to Appendix 7 for country-specific requirements

## 10.8 Appendix 8: Description of the iRECIST Process for Assessment of Disease Progression

Not applicable.

## 10.9 Appendix 9: Application of the Lugano Classification for Treatment Response Assessment

### 10.9.1 Overview

NOTE: This Lugano appendix defines general rules for the Lugano criteria. Not all requirements will apply to this study. Refer to relevant protocol sections for trial specifics.

This appendix describes the process for assessing treatment response according to the Lugano Classification [Cheson, B. D., et al 2014] ("Lugano" from now on) for malignant lymphoma. This assessment includes anatomic imaging with CT or MRI (size assessments of lymph nodes, extranodal lesions, spleen, and liver), metabolic imaging (whole body assessment with FDG-PET), and clinical findings (physical examination and biopsy results), when these are available and appropriate.

Anatomic imaging may include CT, MRI or some combination of the two, with details specified in the Site Imaging Manual. CT is the most common modality used, and for the purposes of this document the term "CT" will be used to represent all anatomic imaging, no matter which imaging modality is used.

Before treatment ("baseline"), on CT all focal lesions (nodal and extranodal) will be classified as "target" (selected for quantitative assessment) and "non-target" (selected for qualitative assessment). The spleen will be assessed quantitatively (by measuring the vertical length), and the liver will be assessed qualitatively. The FDG-PET will be assessed using the 5-point scale (5PS, a method similar to the older Deauville criteria [Barrington, S. F., et al 2014]). If biopsy is performed, or if there are any physical examination findings that cannot be evaluated by imaging, these should be documented.

After therapy has begun, response assessment will include anatomic response based on CT (when a CT is available), which includes target, non-target, and new focal lesions, as well as spleen and liver size assessment. Metabolic response, when an FDG-PET is available, will be based on the 5PS along with qualitative assessment of changes in FDG uptake from preceding timepoints. Anatomic response, metabolic response, and clinical information will be combined to produce the overall response for each timepoint. The criteria are summarized in the tables below, and detailed in the following sections.

### 10.9.2 Lugano Summary Table

The following tables summarize the assessments based on both CT and PET, as described in the summary table in the original publication [Cheson, B. D., et al 2014]. For details about implementation, please see the sections following the tables.

## Complete Response (CR)

| CR | PET-Based Response – CMR | CT/MRI-Based Response – CR |
|---|---|---|
| Target lesions | Score 1, 2, or 3 with or without a residual mass | Target nodes/nodal masses regress to <1.5 cm in LDi; no extranodal sites of disease remain |
| Non-target lesions | 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, negative by immunohistochemistry |

CMR=complete metabolic response; CR=complete response; CT=computed tomography; FDG=2-fluorodeoxyglucose; LDi=longest diameter; MRI=magnetic resonance imaging; PET=positron emission tomography.

## Partial Response (PR)

| PR | PET-Based Response – PMR | CT/MRI-Based Response – PR |
|---|---|---|
| Target lesions | Score 4 or 5 without new lesions<br>Reduced uptake compared to baseline | ≥50% decrease from baseline in SPD of target lymph nodes and extranodal sites (up to 6) |
| Non-target lesions | Not applicable | Anything other than progression |
| Organ enlargement | Not applicable | Spleen must have regressed by ≥50% in excess length |
| New lesions | None | None |
| Bone marrow | Residual uptake higher than uptake in normal marrow but reduced compared to baseline.<br>If there are persistent focal changes in the marrow in the context of a nodal response and without recent growth factor use, perform biopsy, or consider MRI, or an interval scan. | Not applicable |

CT=computed tomography; MRI=magnetic resonance imaging; PET=positron emission tomography PMR=partial metabolic response; PR=partial response; SPD=sum of products of diameters.

**Stable Disease (SD)**

| SD | PET- Based Response – SMD | CT/MRI-Based Response – SD |
|---|---|---|
| Target lesions | Score 4 or 5 (without new lesions)<br>No significant change in FDG uptake from baseline or nadir | <50% decrease from baseline in SPD of target lesions.<br>No lesion shows progression |
| Non-target 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 |

CT=computed tomography; FDG=2-fluorodeoxyglucose; MRI=magnetic resonance imaging; PET=positron emission tomography; SD=stable disease; SMD=stable metabolic disease; SPD=sum of products of diameters.

**Progressive Disease (PD)**

| PD | PET-Based Response – PMD | CT/MRI-Based Response – PD |
|---|---|---|
| Target lesions | Score 4 or 5 with an increase in intensity of uptake compared to nadir | Growth of any target lesion:<br>Increase ≥50% from nadir PPD and<br>Increase in LDi or SDi from nadir of:<br>≥0.5 cm for lesions <2 cm<br>≥1.0 cm for lesions ≥2 cm<br>and<br>Current LDi >1.5 cm |
| Non-target lesions | Not applicable | Clear progression of pre-existing non-target lesions |
| New lesions | New FDG-avid foci consistent with lymphoma rather than another cause (eg, infection, inflammation).<br>If uncertain regarding cause of new lesions, biopsy or interval scan may be considered. | Regrowth of previously resolved lesions<br>A new node >1.5 cm in LDi<br>A new extranodal site of any size, as long as its presence is unequivocal and attributable to lymphoma |

| PD | PET-Based Response – PMD | CT/MRI-Based Response – PD |
|---|---|---|
| Organ enlargement | Not applicable | When splenomegaly was already present, the excess length must increase by ≥50% (≥1 cm absolute increase) from baseline.<br>If no prior splenomegaly, or prior splenomegaly had resolved, spleen length must increase by ≥2 cm to >13 cm. |
| Bone marrow | New or recurrent FDG-avid foci, confirmed by biopsy | New or recurrent involvement |

CT=computed tomography; FDG=2-fluorodeoxyglucose; LDi=longest diameter; MRI=magnetic resonance imaging; PET=positron emission tomography; PD=progressive disease; PMD=progressive metabolic disease; PPD=product of perpendicular diameters; SDi=short axis diameter.

### 10.9.3 Anatomic Disease Assessment

Anatomic assessment specifically refers to the size of focal lesions or organs, assessed using computed tomography or magnetic resonance imaging. As stated previously, for simplicity the term "CT" will be used to represent all anatomic imaging.

#### 10.9.3.1 Screening (Baseline) Assessment

**Documentation of focal lesions**

All focal lesions caused by lymphoma are identified at screening and classified as measurable or non-measurable. Up to 6 of the measurable lesions are selected to serve as "target" lesions, which are then followed quantitatively throughout the trial. All other focal lesions are documented as "non-target" lesions and evaluated qualitatively thereafter.

**Measurable and non-measurable lesions**

Malignant lymph nodes (nodal lesions) are considered measurable if they are consistent with lymphoma, clearly and reproducibly measurable in 2 dimensions on an axial slice, and measure >1.5 cm in LDi when assessed by CT/MRI scan, irrespective of scanner type and slice thickness/interval. Extranodal lesions are considered measurable if they are consistent with lymphoma, clearly and reproducibly measurable in 2 dimensions on an axial slice and are ≥1.0 cm in both LDi and SDi when assessed by CT/MRI scan, regardless of slice thickness.

Lesions considered non-measurable include:

- Lymph nodes and nodal masses that are PET-positive and considered consistent with lymphoma, but that do not meet the size and reproducibility requirements to be considered measurable, and lesions visible on PET but not CT
- PET-negative lesions which meet the size criteria for measurability, and are considered consistent with lymphoma
- Uni-dimensionally measurable lesions (clearly measurable in only one dimension)
- Extranodal lesions which do not meet the requirements for measurability, but are considered to be clearly due to lymphoma
- Truly non-measurable/assessable sites of disease, including:
  - Effusions and ascites
  - Bone lesions
  - Brain lesions, central nervous system (CNS) lesions, leptomeningeal disease
  - Mucosal lesions in the gastrointestinal tract
  - Pleural, peritoneal or bowel wall thickening

**Target and Non-target Lesions**

Up to 6 target lesions will be selected from among the measurable lesions and documented as target nodal and target extranodal lesions. Target lesions should be selected based on their size (largest lesions preferred) and suitability for reproducible measurements. Measurements of the LDi and SDi should be made in the axial plane on the slice of the tumor with the longest in-plane diameter. Calculate the PPD for each target lesion and the SPD for all target lesions.

Non-target lesions will be all focal (nodal and extranodal) lesions that are consistent with lymphoma, but not chosen as target lesions, whether they were measurable or not.

Once lesions are designated as target or non-target, those designations may not change during later assessments.

**Spleen Assessment at Baseline**

Splenic involvement will be assessed quantitatively, as a separate category from the assessment of measurable or non-measurable focal lesions. The spleen length will be measured from cranial to caudal. All spleen measurements referred to hereafter will refer to this cranio-caudal measurement. The spleen is considered normal if it is less than 13 cm, or if

the spleen has been removed surgically. It is considered enlarged if it is greater than 13 cm in length. The portion of the measurement that exceeds 13 cm will be considered the abnormal portion.

**Liver Assessment at Baseline**

Hepatic enlargement will be assessed qualitatively, separately from the assessment of measurable or non-measurable disease. At baseline, the liver will be assessed qualitatively as either normal or enlarged (qualitatively enlarged based on expert judgment on CT scans, without an explanation of the enlargement from benign causes).

### 10.9.3.2 Post-baseline Assessment

**Target lesions**

At every timepoint after screening, each target lesion is measured. Calculate the PPD for each target lesion and the SPD for all target lesions together. Response categories are as defined below:

- Complete Response (CR): All target lymph nodes must have regressed to normal size defined as ≤1.5 cm in LDi. Target extranodal sites must be absent (0 by 0 cm).
- Partial Response (PR): ≥50% decrease in SPD of target lesions from baseline, and no individual lesion meets the criteria for progression.
- Progressive Disease (PD): Target lesion progression is based on the progression of any single lesion (not a change in the SPD), which meets all of the following requirements:
    - The lesion must have increased by ≥50% from its nadir in PPD.
    - For a lymph node, it must be >1.5 cm in LDi, and for an extranodal lesion it must be ≥1.0 cm in LDi.
    - And one of the following:
        - For lesions <2 cm at nadir, the lesion's LDi or SDi must have increased by ≥0.5 cm at the current timepoint from its nadir.
        - For lesions ≥2 cm at nadir, the lesion's LDi or SDi must have increased by ≥1 cm at the current timepoint from its nadir.
- Stable Disease (SD): A target lesion assessment of SD requires all of the following:
    - Target lesions do not meet the criteria for CR or PR
    - No individual lesion meets the criteria for progression

- Not Evaluable (NE): When a target lesion identified at baseline cannot be evaluated at a post-baseline timepoint due to missing imaging, poor image quality, changes in the lesion or background that precludes assessment, or focal therapy or other procedures that change the lesion size, the target lesion assessment will be NE, unless progression is assessed in another target lesion.

**Non-target lesions**

Non-target lesions will be assessed at each post-baseline timepoint individually and as a group. Response categories are as defined below:

- Absent/Normalized (CR): All individual non-target nodal lesions must have returned to normal size. All extranodal lesions must have disappeared.

- Unequivocal Progression (PD): Any individual non-target lesion must unequivocally progress in the context of the overall disease burden to be assessed as PD. For increased thickening of the wall of a hollow viscus, the reviewer will use their cautious judgment to determine whether the increase is most likely caused by disease progression.

  PD should not be called based on enlarging pleural effusions or ascites, or enlarging lytic bone lesions, and rather, the overall assessment should be based on the rest of the disease burden.

- Stable Disease (SD): At least one non-target lesion is still present, or a node enlarged, without any individual lesions showing unequivocal progression.

- Not Evaluable (NE): When an individual non-target lesion lymph node, extranodal lesion, or non-measurable disease cannot be assessed at a post-baseline timepoint due to missing imaging, poor image quality, changes in the lesion or background that precludes assessment, or focal therapy to a lesion, the individual non-target lesion will be assessed as NE. The assessment of the non-target lesions as a whole will be NE if any of the non-target lesions are NE and none are PD.

**New lesions**

Lesions will be considered new if they were not present at the baseline timepoint, but are visible at the current timepoint.

A node consistent with lymphoma will be recorded as a new lesion if it was previously normal in size and is now >1.5 cm in LDi. An unequivocal, new extranodal lesion consistent with lymphoma of any size is considered a new lesion. If multiple new extranodal lesions are noted, at least one should be recorded as a new lesion.

New lesions must be consistent with lymphoma rather than another etiology (eg, infection, inflammation) and must be PET-positive, if PET is available. New lesions will be treated as PET-positive when PET is not available to confirm avidity.

Some types of truly non-measurable lesions generally require further verification that they are attributable to lymphoma through biopsy or cytology. These include ascites, pleural or pericardial effusions, and lytic bone lesions. They may be recorded as new lesions only when there is other evidence of progression.

Other truly non-measurable lesions will not require verification to be considered a new lesion, as long as their appearance is unequivocal in the judgment of the reviewer:

- Non-measurable lesions such as brain and CNS lesions including leptomeningeal disease attributable to lymphoma
- Non-measurable nodal masses such as infiltrative mesenteric masses or retroperitoneal masses

Extranodal lesions which disappeared and then reappeared at a later timepoint will have the same effect as a new lesion but are not designated "new."

**Spleen response**

The spleen will be measured in the craniocaudal length as at baseline, and the enlarged portion calculated by subtracting 13 cm. Response categories for the spleen are as defined below:

- Normal (CR): Spleen was enlarged at baseline and has regressed to ≤13 cm at the current timepoint, or the spleen was assessed as normal at baseline and is still normal, or there is radiological evidence of splenectomy at baseline, or the spleen was normal at baseline, and there has been a splenectomy since then.
- Partial Resolution (PR): Spleen was assessed as enlarged at baseline, and its excess length has decreased by ≥50%.
- Stable Splenomegaly (SD): No decrease consistent with PR and no increase consistent with progression.
- Unequivocal increase (PD): The spleen is assessed as PD if any of the following are true:
    - Recurrent splenomegaly: A spleen which was abnormal at baseline (>13 cm) first returned to normal, but at the current timepoint the spleen increases by >2 cm from its nadir and the length is >13 cm.
    - New splenomegaly: No prior splenomegaly and spleen increases by >2 cm from baseline and the length is >13 cm.
    - Progression of existing splenomegaly: A spleen which is abnormal at baseline has the enlarged portion increase by ≥50% at the current timepoint from its nadir value.

## Liver response

The liver will be assessed qualitatively. Response categories are as defined below:

- Normal (CR): Liver was assessed as enlarged at baseline and has regressed to a normal size, OR liver was assessed as normal at baseline and continues to be normal in size.
- Stable Disease (SD): Liver is considered stable when it is qualitatively enlarged, without unequivocal increase, on the basis of CT and/or MRI scans.
- Unequivocal increase (PD): New hepatomegaly, recurrent hepatomegaly, or clear progression of existing hepatomegaly.

## Anatomic Response

The anatomic response should be assessed at each post-baseline timepoint based on the criteria below.

### Complete Response (CR)

An anatomic response of complete response (CR) requires one of the following combinations:

| Target Lesion | Non-Target Lesion | Spleen | Liver | New Lesions |
|---|---|---|---|---|
| CR | CR or NA | CR | CR | No |
| CR or NA | CR | CR | CR | No |
| CR or NA | CR or NA | CR and Enlarged at baseline | Normal (CR) | No |

CR=complete response; NA=none identified at baseline.

### Partial Response (PR)

An anatomic response of partial response (PR) requires one of the following combinations:

| Target Lesion | Non-Target Lesion | Spleen | Liver | New Lesions |
|---|---|---|---|---|
| PR | CR or SD or NA | PR or CR | CR or SD | No |
| CR or PR | SD | PR or CR | CR or SD | No |
| CR or PR | SD or CR or NA | PR | CR or SD | No |
| CR, PR | CR, SD, NA | CR or PR | SD | No |

CR=complete response; NA=none identified at baseline; PR=partial response; SD=stable disease.

Stable Disease (SD)

An anatomic response of SD requires one of the following combinations:

| Target Lesion | Non-Target Lesion | Spleen | Liver | New Lesions |
|---|---|---|---|---|
| SD | CR or SD or NE or NA | CR or PR or SD | CR or SD | No |
| CR or PR or SD or NA | CR or SD or NE or NA | SD | CR or SD | No |
| NA | CR or SD or NE or NA | PR | CR or SD | No |

CR=complete response; NA=none identified at baseline; NE=not evaluable; PR=partial response; SD=stable disease.

Progressive Disease (PD)

An anatomic response of PD requires ANY of the following criteria:

| | |
|---|---|
| **Target Lesion** | PD |
| **Non-Target Lesion** | PD |
| **Spleen** | PD |
| **Liver** | PD |
| **New Lesions** | Any new lesions except the following:<br>• New lesions meeting the size requirements for new lesions but PET-negative, when PET is available* and<br>• New ascites, effusion or lytic bone lesions |

*When PET is not available, any unequivocal new lesions will be assumed to be PET-positive and will trigger PD.

Not Evaluable (NE)

An anatomic response of NE during radiology review requires that the criteria for PD are NOT met and any of following criteria are met:

| | |
|---|---|
| **Target Lesion Assessment** | NE |
| **Non-Target Lesion Assessment** | NE<br>Note: If the NE is caused solely by lesions that are not evaluated because scans of the neck and pelvis did not completely cover the anatomic space, the reviewer may base their overall assessment on the remaining lesions. |
| **Spleen** | Enlarged |
| **Liver** | Enlarged |
| **General** | The radiologist determines at any timepoint that a valid timepoint response cannot be made and there is no evidence of progression. As an example, if the radiologist suspects that a lesion was resected, NE may be reported for the anatomic response unless progression was seen in another parameter. |

### 10.9.4 Metabolic Response

In addition to anatomic imaging, metabolic imaging using FDG-PET can contribute to the assessment, if it is available, or may form the sole basis for response if no anatomic imaging is performed at a time point. An FDG-PET is required at screening. Subsequent time points that require PET are shown in the schedule of assessments. If lesions are not FDG-avid at baseline, PET is not required at follow-up timepoints unless clinically indicated.

PET Assessment [Barrington, S. F., et al 2014]

For every FDG-PET scan, a 5PS score is obtained by comparing the maximum standardized uptake value ($SUV_{max}$) of the lesion that shows the greatest tracer uptake (the "hottest" lesion) to surrounding normal tissue, to a region of interest (ROI) placed over blood in the heart or major vessels of the mediastinum (the "mediastinal blood pool") and to an ROI placed over normal liver.

Depending on the uptake, a score between 1-5 will be assigned as follows:

| Score | Definition |
|---|---|
| 1 | No uptake above background |
| 2 | Uptake above background, but below mediastinal blood pool |
| 3 | Uptake > mediastinal blood pool, but ≤ uptake in liver |
| 4 | Uptake moderately higher than liver |
| 5 | Uptake markedly higher than liver ($SUV_{max}$ >2 × normal liver)<br>OR (after treatment has started)<br>New FDG-positive lymphoma lesions |

After screening, in addition to the 5PS score the assessment of the FDG-PET also involves an assessment of the overall uptake (a combination of extent and intensity) by tissue consistent with lymphoma, and comparison of this uptake to the baseline and to the scan on which the overall uptake was lowest (nadir).

Metabolic response determination

Metabolic response categories are defined as follows:

| **Metabolic Response** | **Definition** |
|---|---|
| Complete metabolic response (CMR) | A score of 1, 2, or 3. |
| Partial metabolic response (PMR) | A score of 4 or 5 (without new lesions), AND<br>Overall uptake decreased compared to baseline |
| Stable metabolic disease (SMD) | A score of 4 or 5 (without new lesions), AND<br>Overall uptake unchanged compared to baseline and nadir |
| Progressive metabolic disease (PMD) | A score of 4 or 5 with overall uptake increased compared to nadir, OR with new FDG-positive lesions consistent with lymphoma |

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, CMR 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.

### 10.9.5 Clinical Data

Bone marrow assessment

To allow an overall response of CR, the bone marrow must be clear of lymphoma (negative for lymphoma).

Lugano allows assessment of bone marrow based on FDG-PET, if the lymphoma type is FDG-avid. Bone marrow on FDG-PET may be normal, may show diffuse uptake (compatible with reactive changes due to chemotherapy or colony-stimulating factors), or may show focal increased uptake that is consistent with lymphoma.

A negative PET allows the bone marrow to be declared negative, even without biopsy, and would support a CR overall (diffuse uptake compatible with reactive changes from chemotherapy or growth factor use can fall into this category). A PR may occur with residual uptake higher than uptake in normal marrow but reduced compared with baseline. 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.

Bone marrow aspirate or biopsy is required only as clinically indicated, or if FDG-PET evaluation of bone marrow is judged inconclusive. If bone marrow biopsy is performed and shows lymphoma, the bone marrow is considered positive, regardless of the results of the PET.

Physical examination findings

On rare occasions, lesions may be present on physical examination that are not seen on imaging at all. An example might be lymphadenopathy in the popliteal fossa, when the "whole body" imaging includes only anatomy to the mid-femur. Such lesions should be documented as non-target lesions in study forms. They can contribute to progression if new lesions appear this way, and if any were present at baseline, they must disappear for an overall response of CR.

Other clinical data

Information on the use of hematopoietic growth factors and other medications can affect the response assessment as described above.

At certain protocol-specified time points, additional tissue biopsies may be collected and incorporated into the response assessment.

### 10.9.6 Overall Response

Overall response at each timepoint is determined by combining the anatomic response, metabolic response, and clinical data.

When both CT and FDG-PET are available, the overall response is driven primarily by the metabolic response. When only one imaging modality is available at a given timepoint, that modality is the main determinant of overall response.

| Metabolic Response | Anatomic Response | Bone Marrow | Physical Exam | Overall Response |
|---|---|---|---|---|
| CMR | CR, PR, or SD | Negative | No lesions | CR |
| PMR | CR, PR, or SD | Any | No new lesions | PR |
| SMD | CR, PR, or SD | Any | No new lesions | SD |
| PMD | Any | Any | Any | PD |
| Any | PD | Any | Any | PD |

CMR=complete metabolic response; CR=complete response; PD=progressive disease; PMD=progressive metabolic disease; PMR=partial metabolic response; PR=partial response; SD=stable disease; SMD=stable metabolic disease.

During determination of overall response, if no FDG-PET was performed at the timepoint in question, the results of a preceding PET may be "carried forward," unless there has been worsening of disease on the CT. For example, if a post-baseline assessment shows a CMR on the PET, and PR on the CT, the overall response is CR. If the next timepoint shows continued PR on the CT, but there is no PET available, the overall response for that visit is still CR.

If there is PR based on either anatomic or metabolic imaging, but a biopsy demonstrates that the tissue in question is not malignant, the response can be upgraded to a CR.

Lugano Classification 2014 [Cheson, B. D., et al 2014].

## 10.10 Appendix 10: International Prognostic Score

**IPS 1 Point per Factor**

| |
|---|
| Albumin <4 g/dL |
| Hemoglobin <10.5 g/dL |
| Male |
| Age ≥45 years |
| Stage IV disease (according to the Ann Arbor classification) |
| Leukocytosis (white blood cell count at least 15,000/$mm^3$) |
| Lymphocytopenia (lymphocyte count less than 8% of white blood cell count, and/or lymphocyte count less than 600/$mm^3$) |

Source: [Hasenclever, D. 1998]

## 10.11 Appendix 11: Unfavorable Risk Factors – NCCN Guidelines

### Unfavorable Risk Factors for Stage I-II Classical Hodgkin Lymphoma

| Risk factor | NCCN |
|---|---|
| Age | - |
| Histology | - |
| ESR and B symptoms | ≥50 or any B symptoms |
| Mediastinal mass | MMR >0.33 |
| Number of nodal sites | >3 |
| E lesion | - |
| Bulky | >10 cm |

ESR=erythrocyte sedimentation rate; MMR=mediastinal mass ratio, maximum width of mass/maximum intrathoracic diameter; NCCN=National Comprehensive Cancer Network.

Source: [National Comprehensive Cancer Network 2020]

Under NCCN criteria, lymph node regions are defined using Ann Arbor definitions listed below.

### Ann Arbor Definitions of Lymph Node Regions

| | | Ann Arbor |
|---|---|---|
| Supradiaphragmatic Nodal Regions | R Cervical/SCL | |
| | R ICL/Subpectoral | |
| | R Axilla | |
| | L Cervical/SCL | |
| | L ICL/Subpectoral | |
| | L Axilla | |
| | Mediastinum | |
| | R Hilum | |
| | L Hilum | |
| Infradiaphragmatic Nodal Regions | Celiac/Spleen hilar | |
| | Paraortic | |
| | Mesenteric | |
| | R Iliac | |
| | L Iliac | |
| | R Inguinal/Femoral | |
| | L Inguinal/Femoral | |

Source: [National Comprehensive Cancer Network 2020]

## 10.12 Appendix 12: Eastern Cooperative Performance Status

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

[ECOG ACRIN Cancer Research Group 2016]

## 10.13 Appendix 13: Abbreviations

| Abbreviation | Expanded Term |
|---|---|
| 5PS | 5-point scale |
| ABVD | doxorubicin in combination with bleomycin, vinblastine, and dacarbazine |
| AE | adverse event |
| AEOSI | adverse events of special interest |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| APaT | All Participants as Treated |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| AVD | doxorubicin in combination with vinblastine and dacarbazine |
| BEACOPP | bleomycin in combination with etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone |
| $C_{avg}$ | average plasma concentration |
| CD28 | cluster of differentiation 28 |
| CD3ζ | CD3 zeta |
| CFR | Code of Federal Regulations |
| cHL | classical Hodgkin Lymphoma |
| CI | confidence interval |
| $C_{max}$ | peak plasma concentration |
| $C_{min}$ | trough plasma concentration |
| CMR | complete metabolic response |
| CNS | central nervous system |
| CONSORT | Consolidated Standards of Reporting Trials |
| COVID-19 | coronavirus disease 2019 |
| CR | complete response |
| CRF | Case Report Form |
| CSR | Clinical Study Report |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |

| Abbreviation | Expanded Term |
|---|---|
| CTCAE 5.0 | Common Terminology Criteria for Adverse Events, Version 5.0 |
| ctDNA | circulating tumor deoxyribonucleic acid |
| CTFG | Clinical Trial Facilitation Group |
| CTLA-4 | cytotoxic T-lymphocyte-associated protein 4 |
| CYP | cytochrome P450 |
| DMC | Data Monitoring Committee |
| DNA | deoxyribonucleic acid |
| DurCR | duration of complete response |
| ECG | electrocardiogram |
| ECHO | echocardiogram |
| ECI | event of clinical interest |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EDC | electronic data collection |
| ELISA | enzyme-linked immunosorbent assay |
| EMA | European Medicines Agency |
| EORTC QLQ-C30 | European Organisation for Research and Treatment of Cancer quality of life questionnaire C30 |
| EOT | end-of-treatment |
| ePROs | electronic patient-reported outcomes |
| escBEACOPP | escalated bleomycin in combination with etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone |
| ESR | erythrocyte sedimentation rate |
| EU CT | European Union Clinical Trial |
| EU CTR | European Union Clinical Trial Regulations |
| EudraCT | European Union Drug Regulating Authorities Clinical Trials |
| EuroQoL EQ-5D-5L | 5-level EQ-5D questionnaire |
| FBR | future biomedical research |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act |

| Abbreviation | Expanded Term |
|---|---|
| FDG | 2-fluorodeoxyglucose |
| FFPE | formalin-fixed paraffin-embedded |
| FSH | follicle-stimulating hormone |
| FVC | forced vital capacity |
| GCP | Good Clinical Practice |
| GHSG | German Hodgkin Study Group |
| HA | Health Authority |
| HBsAg | hepatitis B surface antigen |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| HL | Hodgkin Lymphoma |
| HRQoL | health-related quality of life |
| HRT | hormone replacement therapy |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| ICMJE | International Committee of Medical Journal Editors |
| iCRO | imaging CRO |
| ID | identification |
| IEC | Independent Ethics Committee |
| Ig | immunoglobulin |
| IgG4 | immunoglobulin G4 |
| IgV | immunoglobulin-variable |
| IHC | immunohistochemistry |
| IMP | investigational medicinal product |
| IND | Investigational New Drug |
| IO | immuno-oncology |
| IPS | International Prognostic Score |
| irAEs | immune-related AEs |
| IRB | Institutional Review Board |

| Abbreviation | Expanded Term |
|---|---|
| IUD | intrauterine device |
| IUS | intrauterine hormone-releasing system |
| IV | intravenous |
| IVD | in vitro diagnostic |
| IWRS | integrated web response system |
| LAM | lactational amenorrhea method |
| LDi | longest diameter |
| LLN | lower limit of normal |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MRI | magnetic resonance imaging |
| mRNA | messenger RNA |
| MSI | microsatellite instability |
| MUGA | multigated acquisition |
| NCCN | National Comprehensive Cancer Network |
| NCI | National Cancer Institute |
| NE | not evaluable |
| NIVAHL | nivolumab and doxorubicin, vinblastine, and dacarbazine for early stage unfavorable Hodgkin Lymphoma |
| NSCLC | non–small cell lung cancer |
| OS | overall survival |
| OTC | over-the-counter |
| PBMC | peripheral blood mononuclear cell |
| PBPK | physiological based pharmacokinetic modeling and simulation |
| PD | progressive disease |
| PD-1 | programmed cell death 1 protein |
| PD-L1 | programmed cell death ligand 1 |
| PD-L2 | programmed cell death ligand 2 |
| PET | positron emission tomography |
| PFS | progression-free survival |
| P-gp | P-glycoprotein |
| PK | pharmacokinetic |

| Abbreviation | Expanded Term |
|---|---|
| PKCθ | protein kinase C-theta |
| PMD | progressive metabolic disease |
| PMR | partial metabolic responses |
| po | by mouth |
| PPD | product of perpendicular diameters |
| PR | partial response |
| PRO | patient-reported outcome |
| Q3W | every 3 weeks |
| Q4W | every 4 weeks |
| Q6W | every 6 weeks |
| QoL | quality of life |
| RNA | ribonucleic acid |
| rrcHL | relapsed or refractory classical Hodgkin Lymphoma |
| RSD | Reference Safety Dataset |
| SAE | serious adverse event |
| SCT | stem cell transplantation |
| SD | stable disease |
| SDi | short axis diameter |
| SLAB | Supplemental laboratory test(s) |
| SMD | stable metabolic disease |
| SoA | schedule of activities |
| SPD | sum of products of diameters |
| sSAP | supplemental Statistical Analysis Plan |
| SUSAR | suspected unexpected serious adverse reaction |
| $SUV_{max}$ | maximum standardized uptake value |
| TCR | T-cell receptor |
| TEAE | treatment-emergent adverse event |
| UK | United Kingdom |
| US | United States |
| WOCBP | woman/women of childbearing potential |

| Abbreviation | Expanded Term |
|---|---|
| ZAP70 | zeta-chain-associated protein kinase |

# 11 REFERENCES


| | | |
|---|---|---|
| [Aaronson, N. K., 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. | [03Q3QL] |
| [Allen, P. B., et al 2020] | Allen PB, Savas H, Evens AM, Advani R, Palmer B, Pro B, et al. Pembrolizumab followed by AVD in untreated early unfavorable and advanced stage classical Hodgkin lymphoma [manuscript]. Blood. 2020. 26 p. | [05NJBB] |
| [Barrington, S. F., et al 2014] | Barrington SF, Mikhaeel NG, Kostakoglu L, Meignan M, Hutchings M, Mueller SP, 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 Sep 20;32(27):3048-58. Erratum in: J Clin Oncol. 2016 Jul 20;34(21):2562. | [05QDSG] |
| [Boll, B., et al 2016] | Boll B, Goergen H, Behringer K, Brockelmann PJ, Hitz F, Kerkhoff A, et al. Bleomycin in older early-stage favorable Hodgkin lymphoma patients: analysis of the German Hodgkin Study Group (GHSG) HD10 and HD13 trials. Blood. 2016 May 5;127(18):2189-92. | [05NJC5] |
| [Borchmann, P., et al 2021] | Borchmann P, Plutschow A, Kobe C, Greil R, Meissner J, Topp MS, et al. PET-guided omission of radiotherapy in early-stage unfavourable Hodgkin lymphoma (GHSG HD17): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2021 Feb;22:223-34. | [06C892] |

| | | |
|---|---|---|
| [Brenner, H., et al 2008] | Brenner H, Gondos A, Pulte D. Ongoing improvement in long-term survival of patients with Hodgkin disease at all ages and recent catch-up of older patients. Blood. 2008 Mar 15;111(6):2977-83. | [05NFF3] |
| [Brockelmann, P. J., et al 2020] | Brockelmann PJ, Goergen H, Keller U, Meissner J, Ordemann R, Halbsguth TV, et al. Efficacy of nivolumab and AVD in early-stage unfavorable classic Hodgkin lymphoma: the randomized phase 2 German Hodgkin Study Group NIVAHL trial. JAMA Oncol. 2020 Jun;6(6):872-80. | [05NJCG] |
| [Carde, P., et al 2016] | Carde P, Karrasch M, Fortpied C, Brice P, Khaled H, Casasnovas O, et al. Eight cycles of ABVD versus four cycles of BEACOPP(escalated) plus four cycles of BEACOPP(baseline) in stage III to IV, International Prognostic Score >= 3, high-risk Hodgkin lymphoma: first results of the phase III EORTC 20012 intergroup trial. J Clin Oncol. 2016 Jun 10;34(17):2028-36. | [05NK9D] |
| [Chemnitz, J. M., et al 2004] | Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173:945-54. | [00VMPN] |
| [Chen, R., et al 2017] | Chen R, Zinzani PL, Fanale MA, Armand P, Johnson NA, Brice P, et al. Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. J Clin Oncol. 2017 Jul 1;35(19):2125-32. | [0537CD] |
| [Cheson, B. D., et al 2014] | Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014 Sep 20;32(27):3059-67. | [045PKM] |

| | | |
|---|---|---|
| [Clopper, C. J. and Pearson, E. S. 1934] | Clopper CJ and Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26(4):404-13. | [03Y75Y] |
| [Connors, J. M., et al 2018] | Connors JM, Jurczak W, Straus DJ, Ansell SM, Kim WS, Gallamini A, et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. N Engl J Med. 2018 Jan 25;378(4):331-44. Erratum in: N Engl J Med. 2018 Mar 1;378(9):878. | [05GLPK] |
| [Disis, M. L. 2010] | Disis ML. Immune regulation of cancer. J Clin Oncol 2010;28(29):4531-8. | [058SQL] |
| [Domingo-Domenech, E., et al 2019] | Domingo-Domenech E, Ramchandren R, Rueda A, Trneny M, Feldman T, Lee HJ, et al. Nivolumab plus doxorubicin, vinblastine and dacarbazine for newly diagnosed advanced-stage classical Hodgkin lymphoma: 2-year extended follow-up from Cohort D of the phase 2 checkmate 205 study [abstract]. Presented at: 24th Congress of European Hematology Association (EHA); 2019 Jun 13-16; Amsterdam (Netherlands). Abstract no. S821. | [05QSZM] |
| [Dudley, M. E., et al 2005] | Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57. | [00VMPR] |
| [ECOG ACRIN Cancer Research Group 2016] | ECOG-ACRIN Cancer Research Group. ECOG Performance Status [Internet]. Philadelphia: ECOG-ACRIN Cancer Research Group; 2016. Available from: http://ecog-acrin.org/resources/ecog performance-status. | [04JT28] |

| | | |
|---|---|---|
| [Eichenauer, D. A., et al 2017] | Eichenauer DA, Plutschow A, Kreissl S, Sokler M, Hellmuth JC, Meissner J, et al. Incorporation of brentuximab vedotin into first-line treatment of advanced classical Hodgkin's lymphoma: final analysis of a phase 2 randomised trial by the German Hodgkin Study Group. Lancet Oncol. 2017 Dec;18:1680-7 | [05PJTL] |
| [Engert, A., et al 2003] | Engert A, Schiller P, Josting A, Herrmann R, Koch P, Sieber M, et al. Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherapy in patients with early-stage unfavorable Hodgkin's lymphoma: results of the HD8 trial of the German Hodgkin's Lymphoma Study Group. J Clin Oncol. 2003 Oct 1;21(19):3601-8. | [05NK9H] |
| [Engert, A., et al 2009] | Engert A, Diehl V, Franklin J, Lohri A, Dorken B, Ludwig WD, et al. Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSG HD9 study. J Clin Oncol. 2009 Sep 20;27(27):4548-54. | [05NK9K] |
| [European Medicines Agency 2017] | European Medicines Agency. Guideline on the evaluation of anticancer medicinal products in man. London: European Medicines Agency; 2017. 43 p. EMA/CHMP/205/95 Rev.5. | [04XQP6] |
| [Evens, A. M., et al 2013] | Evens AM, Hong F, Gordon LI, Fisher RI, Bartlett NL, Connors JM, et al. The efficacy and tolerability of adriamycin, bleomycin, vinblastine, dacarbazine and Stanford V in older Hodgkin lymphoma patients: a comprehensive analysis from the North American intergroup trial E2496. Br J Haematol. 2013;161:76-86. | [05NK9V] |

| | | |
|---|---|---|
| [Food and Drug Administration 2018] | Food and Drug Administration. Clinical trial endpoints for the approval of cancer drugs and biologics: guidance for industry. Silver Spring, MD. Dec 2018. | [054RV4] |
| [Francisco, L. M., et al 2010] | Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42. | [058SQP] |
| [Friedberg, J. W., et al 2004] | Friedberg JW, Fischman A, Neuberg D, Kim H, Takvorian T, Ng AK, et al. FDG-PET is superior to gallium scintigraphy in staging and more sensitive in the follow-up of patients with de novo Hodgkin lymphoma: a blinded comparison. Leuk Lymphoma. 2004 Jan;45(1):85-92. | [05NFGV] |
| [Gallamini, A., et al 2018] | Gallamini A, Tarella C, Viviani S, Rossi A, Patti C, Mule A, et al. Early chemotherapy intensification with escalated BEACOPP in patients with advanced-stage Hodgkin lymphoma with a positive interim positron emission tomography/computed tomography scan after two ABVD cycles: long-term results of the GITIL/FIL HD 0607 trial. J Clin Oncol. 2018 Feb 10;36(5):454-62. | [05PP9Z] |
| [Greenwald, R. J., et al 2005] | Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005;23:515-48. | [00VMQL] |
| [Hasenclever, D. 1998] | Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. N Engl J Med. 1998 Nov 19;339(21):1506-14. | [0534XK] |
| [Hude, I., et al 2017] | Hude I, Sasse S, Engert A, Brockelmann PJ. The emerging role of immune checkpoint inhibition in malignant lymphoma. Haematologica. 2017;102(1):30-42. | [05NKDD] |

| | | |
|---|---|---|
| [Hunder, N. N., et al 2008] | Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703. | [00VMPX] |
| [Jerusalem, G., et al 2001] | Jerusalem G, Beguin Y, Fassotte MF, Najjar F, Paulus P, Rigo P, et al. Whole-body positron emission tomography using (18)F-fluorodeoxyglucose compared to standard procedures for staging patients with Hodgkin's disease. Haematologica. 2001 Mar;86(3):266-73. | [05NFGT] |
| [Jerusalem, G., et al 2003] | Jerusalem G, Beguin Y, Fassotte MF, Belhocine T, Hustinx R, Rigo P, et al. Early detection of relapse by whole-body positron emission tomography in the follow-up of patients with Hodgkin's disease. Ann Oncol. 2003;14:123-30. | [05NFF4] |
| [Johnson, P., et al 2016] | Johnson P, Federico M, Kirkwood A, Fossa A, Berkahn L, Carella A, et al. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. N Engl J Med. 2016 Jun 23;374(25):2419-29. | [05PPB4] |
| [Lala, M., et al 2020] | Lala M, Li TR, de Alwis DP, Sinha V, Mayawala K, Yamamoto N, et al. A six-weekly dosing schedule for pembrolizumab in patients with cancer based on evaluation using modelling and simulation. Eur J Cancer. 2020;131:68-75. | [05GNZM] |
| [Lister, T. A., et al 1989] | Lister TA, Crowther D, Sutcliffe SB, Glatstein E, Canellos GP, Young RC, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 1989;7(11):1630-6. | [03QQXQ] |

| | | |
|---|---|---|
| [Merli, F., et al 2016] | Merli F, Luminari S, Gobbi PG, Cascavilla N, Mammi C, Ilariucci F, et al. Long-term results of the HD2000 trial comparing ABVD versus BEACOPP versus COPP-EBV-CAD in untreated patients with advanced Hodgkin lymphoma: a study by Fondazione Italiana Linfomi. J Clin Oncol. 2016 Apr 10;34(11):1175-81. | [05NKD4] |
| [Meyer, R. M., et al 2005] | Meyer RM, Gospodarowicz MK, Connors JM, Pearcey RG, Bezjak A, Wells WA, et al. Randomized comparison of ABVD chemotherapy with a strategy that includes radiation therapy in patients with limited-stage Hodgkin's lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group. J Clin Oncol. 2005 Jul 20;23(21):4634-42. | [06C894] |
| [Meyer, R. M., et al 2012] | Meyer RM, Gospodarowicz MK, Connors JM, Pearcey RG, Wells WA, Winter JN, et al. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. N Engl J Med. 2012 Feb 2;366(5):399-408. | [04QPK8] |
| [National Comprehensive Cancer Network 2019] | National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: Hodgkin lymphoma; version 2.2019. Plymouth Meeting (PA): National Comprehensive Cancer Network (NCCN); 2019. 86 p. | [05DMDL] |
| [National Comprehensive Cancer Network 2020] | National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: NCCN clinical practice guidelines in oncology: Hodgkin lymphoma; version 1.2021. Plymouth Meeting (PA): National Comprehensive Cancer Network (NCCN); 2020. 80 p. | [05PGX0] |

| | | |
|---|---|---|
| [Okazaki, T., et al 2001] | Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A 2001;98(24):13866-71. | [00VMQ6] |
| [Parry, R. V., et al 2005] | Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol 2005;25(21):9543-53. | [00VMQ7] |
| [Pickard, A. S., et al 2007] | Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes 2007;5:1-8. | [00W0FM] |
| [Press, O. W., et al 2016] | Press OW, Li H, Schoder H, Straus DJ, Moskowitz CH, LeBlanc M, et al. US intergroup trial of response-adapted therapy for stage III to IV Hodgkin lymphoma using early interim fluorodeoxyglucose-positron emission tomography imaging: Southwest Oncology Group S0816. J Clin Oncol. 2016 Jun 10;34(17):2020-7. | [05P0K5] |
| [Rabin, R. and de Charro, F. 2001] | Rabin R and de Charro F. EQ-5D: a measure of health status from the EuroQol group. Ann Med 2001;33:337-43. | [03QM46] |
| [Radford, J., et al 2015] | Radford J, Illidge T, Counsell N, Hancock B, Pettengell R, Johnson P, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. N Engl J Med. 2015 Apr 23;372(17):1598-607. | [05NFF5] |

| | | |
|---|---|---|
| [Ramchandren, R., et al 2019] | Ramchandren R, Domingo-Domenech E, Rueda A, Trneny M, Feldman TA, Lee HJ, et al. Nivolumab for newly diagnosed advanced-stage classic Hodgkin lymphoma: safety and efficacy in the phase II CheckMate 205 study. J Clin Oncol. 2019;37(23):1997-2007. | [05NKD6] |
| [Riley, J. L. 2009] | Riley JL. PD-1 signaling in primary T cells. Immunol Rev 2009;229:114-25. | [00VMQ9] |
| [Roy, P., et al 2000] | Roy P, Vaughan Hudson G, Vaughan Hudson B, Esteve J, Swerdlow AJ. Long-term survival in Hodgkin's disease patients: a comparison of relative survival in patients in trials and those recorded in population-based cancer registries. Eur J Cancer. 2000;36:384-9. | [05NFGW] |
| [Sheppard, K-A, et al 2004] | Sheppard K-A, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett. 2004;574:37-41. | [00VMQC] |
| [Straus, D. J., et al 2004] | Straus DJ, Portlock CS, Qin J, Myers J, Zelenetz AD, Moskowitz C, et al. Results of a prospective randomized clinical trial of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by radiation therapy (RT) versus ABVD alone for stages I, II, and IIIA nonbulky Hodgkin disease. Blood. 2004 Dec 1;104(12):3483-9. | [06C896] |
| [Stumpe, K. D. M., et al 1998] | Stumpe KDM, Urbinelli M, Steinert HC, Glanzmann C, Buck A, von Schulthess GK. Whole-body positron emission tomography using fluorodeoxyglucose for staging of lymphoma: effectiveness and comparison with computed tomography. Eur J Nucl Med. 1998 Jul;25(7):721-8. | [05NFF8] |

| | | |
|---|---|---|
| [Zhang, X., et al 2004] | Zhang X, Schwartz J-CD, Guo X, Bhatia S, Cao E, Chen L, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity 2004;20:337-47. | [00VMQJ] |