Title: An international, multi-centre, non-interventional retrospective study to describe treatment pathways, outcomes, and resource use in patients with classical Hodgkin lymphoma (B-HOLISTIC)

NCT Number: NCT03327571

SAP Approve Date: 24FEB2020

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- Named persons or organizations associated with the study.

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Please note that the statistical output shells have been removed for brevity, since they are not a requirement of the statistical analysis plan.

STATISTICAL ANALYSIS PLAN

PROTOCOL ID: CHL-5001 (PROTOCOL VERSION NO. 1.0 DATED 04 MAY 2017)

AN INTERNATIONAL, MULTI-CENTRE, NON-INTERVENTIONAL RETROSPECTIVE STUDY TO DESCRIBE TREATMENT PATHWAYS, OUTCOMES, AND RESOURCE USE IN PATIENTS WITH CLASSICAL HODGKIN LYMPHOMA (B-HOLISTIC)

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VERSION NUMBER AND DATE: V2.0, 24FEB2020

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V2.0 (Dated 24FEB2020) for Protocol CHL-5001 (version No. 1.0, dated 04 May 2017).

	Name	Signature	Date
Author:	PPD		
Position:			
Company:			

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
0.1	25AUG2017	PPD	Not Applicable – First Version
0.2	24OCT2017		Changes made to address Takeda comments and CRF V1.0 dated 29SEP2017
0.3	13DEC2017		Changes made to address Takeda comments and CRF V2.0 dated 29NOV2017
0.4	30JAN2018		Changes made to address Takeda comments on SAP v0.3 dated 13DEC2017
0.5	08FEB2018		Changes made to address Takeda comments on SAP v0.4 dated 30JAN2018
0.6	20MAR2018		Changes made after discussion with Takeda of some pending comments on SAP v0.5 dated 08FEB2018
1.0	17MAY2018		Changes made after updates discussed in the meeting on 19APR2018 with Takeda Description of outputs produced for Interim analysis
1.1	22OCT2019		Changes made to address Takeda comments during the dry-run and CRF V6.0 dated 27AUG2019
1.2	23DEC2019		Changes made to address comments from Takeda on SAP v1.1, dated 22OCT2019 and from Steering Committee held on 06DEC2019
1.3	20FEB2020		Changes made to address comments from Takeda on SAP v1.2, dated 23DEC2019

			and other comments received during SAP discussion meetings on 30JAN2020 and 03FEB2020
2.0	24FEB2020	PPD	Changes made to address comments from Takeda on SAP v1.3, dated 20FEB2020

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1. ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse Event
Allo-SCT	Allogeneic Haematopoietic Stem Cell Transplantation
ASCT	Autologous Stem Cell Transplantation
BMT	Bone Marrow transplant
cHL	Classical Hodgkin Lymphoma
CI	Confidence Interval
CL	Confidence Limits
CR	Complete Remission
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computerised Tomography
dL	Decilitre
ECOG	Eastern Cooperative Oncology Group
FDG	Fluorodeoxyglucose
FAS	Full Analysis Set
G	Gram
G-CSF	Granulocyte-colony Stimulating Factor
High-risk stage IIb–IV cHL	HL is staged using the Ann Arbor staging classification (1). Patients with stage IIb HL are classified as 'high risk' if they have a large mediastinal mass (measuring at least one-third of the transverse diameter of the thorax) or extranodal disease (any tumour spread involving other tissues than those of the lymph nodes, spleen, thymus, Waldeyer's tonsillar ring, appendix, and Peyer's patches)
HIV	Human Immunodeficiency Virus
HL	Hodgkin Lymphoma
HR	Hazard Ratio
ICU	Intensive Care Unit
IPS	International Prognostic Score
Kg	Kilogram
KM	Kaplan-Meier
L	Litre
LatAm	Latin America
LCL	Lower Confidence Limit
LOT	Line of Treatment

OS	Overall Survival
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PN	Peripheral Neuropathy
PR	Partial Remission
Q1	First Quartile
Q3	Third Quartile
Risk factors for relapse	Risk factors for relapse are defined using the International Prognostic Score for newly diagnosed advanced stage cHL (2) and the Josting score for RRHL (3)
RRHL	Relapsed or refractory classical Hodgkin lymphoma. RRHL includes patients with primary refractory HL (those who have failed to achieve a complete remission [CR] with frontline therapy or relapse within 3 months after end of frontline therapy) and patients with relapsed HL (those who have a recurrence >3 months after end of frontline treatment [early relapsers: recurrence within 3–12 months; late relapsers: recurrence >12 months])
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCT	Stem Cell Transplantation
SD	Stable Disease
StDev	Standard Deviation
TB	Tuberculosis
TLFs	Tables, Listings, and Figures
UCL	Upper Confidence Limit
uCR	Unconfirmed Complete Remission
WBC	White Blood Cells

2. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of data for the B-HOLISTIC study. This SAP is based on the study Protocol (CHL-5001) No. 1.0, dated 04 May 2017 and the Case Report Form (CRF) Version 6.0, dated 27AUG2019. The SAP describes the study population, the variables that will be analysed and the statistical methods that will be used.
The final study report will detail all analyses, including any deviations from the planned ones, and any other analyses that may be included in future abstracts and manuscripts.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The primary objective is to describe the progression-free survival (PFS) in patients with relapsed or refractory classical Hodgkin lymphoma (RRHL), defined as the time from initiation of first treatment for RRHL to the first documentation of relapse or disease progression or death.

3.2. SECONDARY OBJECTIVES

The secondary objectives will be described in two populations of patients with Hodgkin lymphoma (HL): in those receiving frontline treatment for high-risk stage IIb–IV classical Hodgkin lymphoma (cHL – Group 1) and in those with RRHL (Group 2). These objectives are:
1. Patient demographic and clinical characteristics (including known risk factors for relapse, prior therapies, and clinical staging).
2. HL treatment pathways (treatments and treatment sequences received for cHL or RRHL and imaging tests used to evaluate response).
3. Clinical outcomes:
    a) Overall survival (OS).
    b) 1- and 5-year survival rates.

For each line of therapy:
    c) Best clinical response after completion of treatment, as defined by the International Working Group 2007 Revised Response Criteria for Malignant Lymphoma (4).

d) Response duration.

e) PFS (Group 1).

4. Adverse events (AEs) associated with each line of therapy.
5. HL-related healthcare resource use associated with each line of therapy.
6. HL-related healthcare costs associated with each line of therapy[†].

[†] It is expected that all participating countries will collect data on patient characteristics, treatment pathways, clinical outcomes, AEs, and resource use (for the primary objective and secondary objectives 1–5). Allocation of costs (for secondary objective 6) is optional and country dependent.

4. STUDY DESIGN

4.1. GENERAL DESCRIPTION

The study is an international, multi-centre, retrospective observational research study, involving retrospective review of medical records (paper and/or electronic, as applicable locally) of patients with a diagnosis of high-risk stage IIb–IV cHL, who have received frontline treatment with chemotherapy with or without radiotherapy (Group 1) and/or patients with a diagnosis of RRHL (Group 2). Patients who are diagnosed with high-risk stage IIb–IV classical HL and/or RRHL between 01st of January, 2010 and 31st of December, 2013 will be included.

For each patient included in the newly diagnosed cHL group (Group 1), data on treatments received for cHL, the associated AEs and resource use will be collected from the date of cHL diagnosis until the date of first documented relapse or disease progression after frontline therapy. Patients will continue to be observed until the date of death (or the date when the patient was last known to be alive, whichever occurs first) for collection of OS data.

For patients in the RRHL group (Group 2), a summary of treatments received prior to diagnosis of RRHL will be collected; detailed data on treatment pathways, clinical outcomes, AEs, and healthcare resource use will be collected from the date of RRHL diagnosis until the death of the patient or the date when the patient was last known to be alive (whichever occurs first).

In both groups, healthcare resource use data will be collected for periods when the patient is receiving active treatment for cHL or RRHL, to enable the resource use associated with each line of treatment to be determined.

4.2. SELECTION OF STUDY POPULATION

The plan is that the study will be conducted in approximately 100 sites across 13 countries within the emerging market regions (Argentina, Australia, China, Colombia, Hong Kong, Mexico, Republic of Korea, Russia, Saudi Arabia, Singapore, South Africa, Taiwan, and Turkey).
To take account of different population sizes, approximately 50–200 patients with cHL (Group 1) and 50–200 patients with RRHL (Group 2) will be included in the study in each participating country.

Patients will be identified at each centre using hospital central management information systems, local department databases, pharmacy databases, or multidisciplinary team records (as applicable locally), and screened for eligibility by a member of the direct care team at each site. Physicians will be asked to select patients for inclusion in the study, according to study-specific inclusion/exclusion criteria (see below) consecutively, according to the date of cHL or RRHL diagnosis, until the target sample size has been met. Written informed consent will be obtained from each patient prior to participation (where required by local regulations).

Inclusion criteria:

Patients who meet **all** of the following criteria are eligible for this study.

1. Patients newly diagnosed with high-risk stage IIb–IV cHL (for Group 1) or RRHL (for Group 2) between 01st of January, 2010 and 31st of December, 2013.
2. Age ≥18 years at diagnosis of cHL (Group 1) or RRHL (Group 2).
3. Alive or deceased.
4. Written informed consent is obtained for study data collection, where necessary according to local regulations.

Exclusion criteria:

Patients who meet **any** of the follow criteria are not eligible for this study.

1. Patients for whom the minimum study dataset (see Appendix 1 and Table 4 of Protocol and further specified in the Appendix 1 of this SAP) is not available from their hospital medical records.
2. Patients who have participated in an interventional clinical trial at any stage of their cHL (Group 1) or RRHL (Group 2) management.

Patients diagnosed with high-risk stage IIb–IV cHL between 2010 and 2013, who are

subsequently diagnosed with RRHL, can be included in both groups, provided that the RRHL diagnosis was also between 2010 and 2013. Examples of study eligibility are shown in **Table *1***.

Table 1: **Patient eligibility for study cHL group and RRHL group – examples**

Example	Date of HL diagnosis	Date of RRHL diagnosis	Study eligibility
1	01 March 2013	01 March 2014	Include in cHL group (Group 1) only
2	01 May 2008	01 May 2010	Include in RRHL group (Group 2) only
3	01 February 2011	01 February 2013	Include in both cHL and RRHL groups
4	01 November 2009	01 November 2014	Exclude – patient not eligible

4.3. SAMPLE SIZE

For both, the mean and median PFS time outcomes (for the primary outcome); samples of 50 or more patients give reliable outcomes as they generate reasonably reliable country-level estimates of the standard deviation of the PFS distribution. Therefore, a sample of at least 50 (50–200) patients with cHL and at least 50 (50–200) patients with RRHL per country will be used in this study. Whilst it is hoped that each country will be able to include 100 patients in each group (approximately 1300 per group in total across all 13 countries) to allow description of PFS in different subgroups and for different treatments, it is recognised that this may not be possible in every country and therefore oversampling may be performed in countries with larger populations of eligible patients to enable the overall sample to be achieved.

The reliability of a range of mean and median PFS estimates for various sample/subgroup sizes are shown in **Table 2** and **Table 3**.

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Table 2 Reliability of the mean progression-free survival at various sample sizes

| Observed mean PFS (months) | 95% Confidence Limits (CLs) | | | | | | | |
| | n = 25 | | n = 50 | | n = 100 | | n = 200 | |
	LCL	UCL	LCL	UCL	LCL	UCL	LCL	UCL
18	15.6	20.4	16.3	19.7	16.8	19.2	17.2	18.8
21	18.2	23.8	19.0	23.0	19.6	22.4	20.0	22.0
24	20.8	27.2	21.7	26.3	22.4	25.6	22.9	25.1
27	23.4	30.6	24.5	29.5	25.2	28.8	25.7	28.3
30	26.0	34.0	27.2	32.8	28.0	32.0	28.6	31.4
33	28.6	37.4	29.9	36.1	30.8	35.2	31.4	34.6
36	31.2	40.8	32.6	39.4	33.6	38.4	34.3	37.7

PFS = Progression Free Survival; LCL = Lower Confidence Limit; UCL = Upper Confidence Limit.

Table 3: Reliability of the median progression-free survival at various sample sizes

| Observed median PFS (months) | 95% Confidence Limits (CLs) | | | | | | | |
| | n = 25 | | n = 50 | | n = 100 | | n = 200 | |
	LCL	UCL	LCL	UCL	LCL	UCL	LCL	UCL
18	14.3	21.7	15.0	21.0	15.4	20.6	15.7	20.3
20	15.9	24.1	16.6	23.4	17.1	22.9	17.4	22.6
24	19.1	28.9	20.0	28.0	20.5	27.5	20.9	27.1
27	21.5	32.5	22.5	31.5	23.1	30.9	23.5	30.5
30	23.8	36.2	25.0	35.0	25.6	34.4	26.1	33.9
33	26.2	39.8	27.5	38.5	28.2	37.8	28.7	37.3
36	28.6	43.4	30.0	42.0	30.8	41.2	31.3	40.7

PFS = Progression Free Survival; LCL = Lower Confidence Limit; UCL = Upper Confidence Limit.

4.4. CHANGES TO ANALYSIS FROM PROTOCOL

There were changes in the definition of International Prognostic Score (IPS) risk factors, regarding the units to be presented for albumin results and haemoglobin values at diagnosis, from those planned in the protocol. The reason of these changes is to be aligned with the literature (2). Date of agreement of change is 06FEB2018.

- Albumin results at diagnosis was defined in the protocol as "Albumin <4 g/L". This has been updated in Section 8.4 and Section 9.3 of this SAP to be "Albumin <4 g/dl".
- Haemoglobin results at diagnosis was defined in the protocol as "Haemoglobin <10.5 g/L". This has been updated in Section 8.4 and Section 9.3 of this SAP to be

"Haemoglobin <10.5 g/dl".

An additional definition of OS, for the RRHL set, was considered from those planned in the protocol. The reason of this change is to compare the OS with cHL set. This has been updated in Section 7.7.

The "date of most recent follow-up contact" as mentioned in protocol will be considered the "date when the patient was last known to be alive" and has been updated in Section 7 and in Section 9 of this SAP.

Note that, based on Cheson 2007, the updated definitions for CR and PR have eliminated the category of unconfirmed CR (uCR). In case uCR category is still used by sites, to be conservative, these patients will be grouped under PR since we cannot be certain that these patients have achieved a CR.

The definitions of "Best Response", "Time to response" and "Duration of response" were better defined in Section 9.9.1 of this SAP for both groups, as presented in the **Table 4** below:

Table 4: "Time to response" and "Duration of response definitions"

Definition per protocol	Change in protocol definition
cHL group: Best clinical response after completion of frontline treatment (CR, PR, SD, PD), as defined by the International Working Group 2007 Revised Response Criteria for Malignant Lymphoma (4) **RRHL group:** Best clinical response after completion of each line of treatment (CR, PR, SD, PD)	**cHL group**: Best clinical response after completion of frontline treatment is defined as the response (CR, uCR*, PR, SD, PD) that one patient achieves, at last therapy regimen of frontline treatment (by *Chemotherapy Details* CRF page) **RRHL group**: Best clinical response after completion of each line of treatment is defined as the response (CR, uCR*, PR,SD, PD) that one patient achieves, at last therapy regimen of each line of treatment (by *Chemotherapy Details* CRF page).
cHL group: Time to best response	**cHL group:** "Time to response, (in months) among patients who achieve clinical

RRHL group: Time to best response No definition is provided in the protocol.	response, defined as the time from initiation of frontline treatment to the first documentation of PR, uCR* or CR, whichever occurs first". **RRHL group**: "Time to response, among patients who achieve clinical response, defined as the time from initiation of first treatment for RRHL to the first documentation of PR, uCR* or CR, whichever occurs first". The reason of this change is to define "Time to response" and also consider uCR as a clinical response (4) (5).
cHL group: "Duration of best response", defined as the time from when the criteria for response (CR or PR) are met to first documentation of relapse or disease progression. **RRHL group:** "Duration of best response" (as previously defined)	**cHL group:** "Duration of response (in months), among patients who achieved clinical response (CR, uCR* or PR) after initiation of frontline treatment, defined as the time from the date of first documented response (CR, uCR* or PR) after initiation of frontline treatment to the first documented relapse, disease progression or death from any cause". **RRHL group:** "Duration of response (in months), among patients who achieved clinical response (CR, uCR* or PR) after initiation of first treatment for RRHL, defined as the time from the date of first documented response (PR, uCR*, or CR) after initiation of first treatment for RRHL to the first documented relapse, disease progression, or death from any cause". Patients with a CR, uCR, or PR who did not have a relapse, disease progression or did not die, will be censored at the date when the

	patient was last known to be alive".
	"Duration of response" definition was changed to consider uCR as a clinical response (4) (5), and since it is not expected to observe relapse or progression disease after response, in a considerable number of patients during the follow-up period, the Kaplan-Meier method will be the most appropriate.

* uCR response will be reported and summarized under PR.

In addition to the "Time to response" definition, "The number of lines of treatment needed to achieve a first response (CR, uCR or PR)" will be provided to complement information which we obtain from "Time to response". An algorithm describing the way this variable will be calculated for cHL and RRLH group is presented in **Appendix 2**.

An exploratory analysis for PFS and OS will be performed for RRHL set only, i.e. removing the overlapping group from RRHL set. Details of this analysis are presented in Section 9.10.

5. PLANNED ANALYSES

The following analyses will be performed for this study:

- Interim Analysis

- Final Analysis

5.1. INTERIM ANALYSIS

There will be two interim analyses for this study. The first interim analysis will be based on all patients' data collected up to 11 May 2018 and the second interim analysis will be based on all LatAm (Latin America) and East Asia patients' data collected up to 31 October 2019. It is expected that the results of each interim analysis will be published, if possible as a conference abstract.

Derivations and definitions for the interim analyses will be based on those required for the final analysis contained in this analysis plan, unless deviations are stated as footnotes for the respective tables.

First interim analysis will include the following outputs: Figure 1, Figure 2, Table 1, Table 2, Table 3, Table 7, Table 8, Table 16, Table 17, Table 18, Table 19, Table 20, Table 21, Table 22, Table 23, Table 46, Table 47, Table 50 and Table 51.
Second interim analysis will include all, or a subset, of the following outputs: Figure 1.2, Figure 1.3, Figure 2.2, Figure 2.3, Figure 4.2, Figure 4.3, Figure 6.2, Figure 6.3, Table 1.1, Table 1.2, Table 2.1, Table 2.2, Table 3.1, Table 3.2, Table 7.1, Table 7.2, Table 8.1, Table 8.2, Table 14.1, Table 14.2, Table 15.1, Table 15.2, Table 17.1, Table 17.2, Table 18.1, Table 18.2, Table 19.1, Table 19.2, Table 20.1, Table 20.2, Table 21.1, Table 21.2, Table 22.1, Table 22.2, Table 23.1, Table 23.2, Table 24.1, Table 24.2, Table 25.1, Table 25.2, Table 27.1, Table 27.2, Table 30.1, Table 30.2, Table 46.1, Table 46.2, Table 47.1, Table 47.2, Table 50.1, Table 50.2, Table 60.1 and Table 60.2.

5.2. FINAL ANALYSIS

The final analysis will include the full study population and all analyses outlined in Section 9 (see below). This analysis will be delivered in the form of populated data tables, listings and figures (TLFs) and a final Clinical Study Report (CSR). Any known deviations from the planned analyses, the reason for such deviations, and all alternative/additional statistical analyses that may be performed, as well as the final statistical analysis, must be described in a revised SAP before the completion of data collection. All later deviations and/or alterations will be summarised in the CSR.
The final analysis will be performed in a timely manner after the database has been locked.

All analyses (interim and final) will be performed by IQVIA – Real World Solutions Biostatistics, following Takeda's approval of this SAP.

6. ANALYSIS SETS

6.1. FULL ANALYSIS SET (FAS)

The full analysis set (FAS) will contain all patients who were diagnosed with high-risk stage IIb-

IV classical HL and/or RRHL between the 01st of January 2010 and the 31st of December 2013, provide written informed consent for this study (where required by local regulations), fulfil all inclusion and exclusion criteria, and meet minimum dataset requirements.

6.2. CLASSICAL HODGKIN LYMPHOMA (CHL) SET (GROUP 1)

The cHL set will contain all patients in the FAS who were diagnosed with high-risk stage IIb–IV cHL between 01st of January, 2010 and 31st of December, 2013 and received frontline treatment with chemotherapy with or without radiotherapy.

6.3. RELAPSED OR REFRACTORY CLASSICAL HODGKIN LYMPHOMA (RRHL) SET (GROUP 2)

The RRHL set will contain all patients in FAS who were diagnosed with RRHL between 01st of January, 2010 and 31st of December, 2013.

7. GENERAL CONSIDERATIONS

7.1. OBSERVATION PERIOD

For each patient included in cHL set, the observation period is defined as the period from the date of cHL diagnosis, between 01st of January, 2010 and 31st of December, 2013, until the date of death or the date when the patient was last known to be alive, whichever occurs first.

For patients in the RRHL set, the observational period is defined as the period from the date of RRHL diagnosis, until the date of death or the date when the patient was last known to be alive, whichever occurs first. It is possible to enter the study if RRHL happened before 2010.

7.2. DATA ABSTRACTION START DATE

The data abstraction start date refers to the first day of data abstraction, in which the patient is screened, and included in the study if fully compliant with the inclusion and exclusion criteria.

7.3. cHL/RRHL Diagnosis Date

The cHL and RRHL diagnosis date will be defined as the date of cHL or RRHL diagnosis entered in the CRF for cHL and RRHL patients, respectively.

7.4. Initiation Date of cHL/RRHL Therapy

The initiation date of cHL and RRHL therapy will be defined as the date of first treatment after diagnosis of cHL or RRHL, respectively.

7.5. First Relapse/Refractory/Disease Progression Date

The date of first relapse, refractory, or disease progression will be defined as the date of first documentation of relapse, refractory, or disease progression after initiation of frontline therapy, respectively.

7.6. Progression Free Survival (PFS)

For the RRHL set, PFS is defined as the time (in months) from initiation of the first treatment for RRHL to the first documentation of relapse or disease progression or death. Patients who did not have a relapse or disease progression and did not die will be censored on the date when the patient was last known to be alive.

For cHL set, PFS is defined as the time (in months) from initiation of frontline regimen for cHL to the first documentation of relapse or disease progression or death. Patients who did not have a relapse or disease progression and did not die will be censored on the date when the patient was last known to be alive.

7.7. Overall Survival (OS)

For cHL set, OS is defined as the time from diagnosis of cHL to death. Patients who did not die will be censored on the date when the patient was last known to be alive.

For RRHL set, OS is defined as the time from the first relapse after frontline treatment to death. Patients who did not die will be censored on the date when the patient was last known to be alive.

In addition, for RRHL set, OS will also be defined as the time from diagnosis of cHL to death. Patients who did not die will be censored on the date when the patient was last known to be alive.

7.8. WINDOWING CONVENTIONS

No visit windowing will be performed for this study.

7.9. STATISTICAL TESTS

Unless otherwise specified in the description of the analysis, the default confidence interval (CI) will be 95% and significance level will be 5%.

7.10. SOFTWARE VERSION

All analyses will be conducted using SAS® Software, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

8. STATISTICAL CONSIDERATIONS

8.1. DESCRIPTIVE ANALYSIS

All analyses will be conducted separately for the cHL set and the RRHL set. Data will be presented for the overall sample (aggregated across all countries), at regional level (East Asia, Latin America, Middle East and South Africa, Australia and Russia), and separately for each participating country (Argentina, China, Colombia, Hong Kong, Mexico, Republic of Korea, Saudi Arabia, Singapore, South Africa, Taiwan and Turkey) as presented in the **Table 5** below. Australia and Russia will be presented at regional level, thus they will not be presented at country level.

Table 5: Regional and Country split

Overall and Regions	East Asia (Countries)	Latin America (Countries)	Middle East and South Africa (Countries)
Overall	Overall	Overall	Overall
East Asia	Republic of Korea	Argentina	Saudi Arabia
Latin America	Singapore	Colombia	South Africa
Middle East and South Africa	Taiwan	Mexico	Turkey
Australia	China		
Russia	Hong Kong		

Summary statistics will be used to describe patient demographics and clinical characteristics, treatment patterns, clinical outcomes, AEs and healthcare resource utilisation.

Categorical endpoints
Key categorical endpoints will be summarised using both the number (n) and percentage (%) of patients in each category, otherwise it will be stated as number of "events", "procedures", "radiotherapies", *etc.* when does not refer to subjects. Only patients with data available (non-missing) for a particular variable will be included in the calculation of a percentage. The count of missing observations will be provided in all Tables for information only. Computed percentages will be presented with one decimal place.
The population size (N) will also be presented in the header of the Tables.

Continuous endpoints
Key continuous endpoints (e.g. duration of treatment, healthcare resource utilisation) will be summarised using the summary statistics of mean, standard deviation (StDev), median, first and third quartiles (Q1, Q3), minimum, maximum, number of non-missing observations and the number of missing observations. Mean and median will be rounded to 1 decimal place, StDev will be rounded to 2 decimals.

If there is no observation, a hyphen '-' will be displayed with no other statistics. If there is only one observation, the StDev will be displayed as a hyphen '-'.

The following categories presented in the CRF and in the respective tables, for a certain field, are defined as:
"Unknown": when there is no entry in the medical record or patient chart relating to an item as confirmed by the site,
"Not available": something was done but the result is not available,

"Not applicable": something that is not expected to be collected,

"Missing": when none of the categories of a field is selected.

If in the final database a "Missing" is reported and the site confirmed that the answer is "Unknown" to that specific field, those missing values will be presented as "Unknown" in the Tables.

8.2. TIME TO EVENT ANALYSIS

Time to event endpoints

Key time to event endpoints (e.g. PFS, OS) will be analysed using the Kaplan-Meier (KM) method. Data will be presented as: number of patients at risk, with the event and censored, PFS and OS times (median, Q3 and Q1). Two-sided 95% CI, using Brookmeyer and Crowley method, will be provided for the main statistical estimators. In addition, the KM curves of PFS and OS will be presented graphically.

Survival analyses will be performed and presented in tables even if the number of events is lower than 10, however, these results will only serve for informative purpose.

PFS and OS rates at 1-, 3- and 5 years will also be presented after accounting for censoring using KM method. Five-year PFS and OS rates will be reported only for patients with > 5-year observation periods.

8.3. PROPORTIONAL HAZARD COX MODEL

In addition to the descriptive analyses, multivariable analyses, as Proportional Hazards Cox models will be used for key time to event analyses (PFS and OS), when treatment cohorts will be compared within the RRHL or frontline setting. Adjustment for patient demographic, clinical, treatment characteristics, and other potential factors will be considered.

Proportional hazard assumption methods of verification will be performed as described below:

- plot of the log of the cumulative hazard functions against time (curves on the plot should be parallel with distance that is constant over time),
- plot of Schoenfeld residuals as function of time (residuals should not show any trend),
- adding interaction of a covariate with function of time variable (newly added variable should not be statistically significant)

If the proportional hazard assumption is not satisfied for a covariate/factor, the following non-proportional Cox extension methods could be considered:

- adding interaction term of selected covariate(s)/factor(s) with function of time,
- stratification model by the covariate/factor

If the proportional hazard assumption methods are verified, the Proportional Hazards Cox model will be used to describe the relationship between time to first event (relapse or disease progression or death) and the potential covariates/factors.

The model will be adjusted for the covariates/factors described in Section 8.4. Continuous variables may be categorized for clinical interpretation of the coefficients. Categorical variables will be defined according to the data reported and will be defined prior to modelling the data, if needed categories will be combined into larger categories, depending on the number of patients per category.

Potential covariates/factors for inclusion in the final multivariable model will be determined using an iterative process as described below:
- Univariate proportional hazards Cox models will be fitted to the data to explore the association of each covariate/factor and time to first event (relapse, disease progression or dead). Any covariate/factor considered clinically relevant or with univariate test p-value <0.20 will be a candidate for the multivariable model.
- All candidate covariates/factors identified in the above item will be entered together in a multivariable adjusted proportional hazard Cox model.

Results will be presented as hazard ratios (HRs) and 95% CIs. Two-sided 95% CIs will be computed using the Brookmeyer-Crowley method.
Patient records with missing data in the outcome, covariates/factors will be excluded from the model.

8.4. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The following covariates and factors will be used in the analyses of Proportional Hazards Cox models. For details of their inclusion in the models, see Section 8.3.

Patient Demography:

- Gender (male, female),

- Ethnicity/Race (Asian, White or Caucasian, Other). The 'Other' category, combines the following categories: Black or African American, American Indian or Alaska Native, Native Hawaiian or another Pacific Islander, Not reported or Other.

Clinical Characteristics:

For cHL group:

- IPS risk factors[1]:

    o Age at cHL diagnosis,
    o Clinical stage IV at diagnosis (yes, no),
    o Albumin results at diagnosis (Albumin <4 g/dl, Albumin ≥4 g/dl),
    o White Blood Cells (WBC) results at diagnosis (WBC <15 × 10^9/L, WBC ≥15 × 10^9/L),
    o Haemoglobin values at diagnosis (Haemoglobin <10.5 g/dl, Haemoglobin ≥10.5 g/dl),
    o Lymphocyte count <0.6 x 10^9/L or <8% of differential at diagnosis (yes, no),

- Extranodal involvement at initial diagnosis (yes, no),

- Presence of B symptoms at diagnosis (yes, no),

- Comorbid conditions (yes, no).

For RRHL group:

- Age at RRHL diagnosis,

- Bulky disease (≥ 5 cm) at first relapse/refractory diagnosis (yes, no),

- Josting Risk factors:

    o Time to recurrence within 3–12 months after end of frontline treatment (yes, no),
    o Clinical Stage III or IV at first RRHL diagnosis (yes, no),
    o Haemoglobin at first relapse/refractory diagnosis <10.5 g/dL for females and <12 g/dL for males (yes, no),

- Inadequate response to salvage chemotherapy [<PR (partial remission) or Positron Emission Tomography (PET) positivity] (yes, no),

- Performance status (Eastern Cooperative Oncology Group [ECOG]) ≥ 1 (yes, no),

- Extranodal involvement at first relapse/refractory diagnosis (yes, no),

- Presence of B symptoms at first RRHL diagnosis (yes, no),

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[1] Male gender is a IPS risk factor and is already described in patient demography.

- Comorbid conditions (yes, no).

Treatment Characteristics:

- Type of Stem Cell Transplantation (SCT) (no transplant, allogeneic only, autologous only, or both).

For cHL group:

- Positron Emission Tomography-Computerised Tomography (PET, PET-CT, CT) scan performed at baseline or frontline (yes, no),

For RRHL group:

- Positron Emission Tomography-Computerised Tomography (PET, PET-CT, CT) scan performed at relapse/ refractory (yes, no).

8.5. RULES FOR HANDLING MISSING DATA

As data are collected retrospectively in medical charts, a high frequency of partial dates is expected.
Partial missing dates will be handled as detailed below. For the minimum study dataset requirements, the month and the year are mandatory, in case the month and the year are missing no imputation rule will be done, otherwise the minimum dataset requirements will not be satisfied. Any other missing data will not be imputed.
In Listings the dates will be reported in their original format before imputation.

For cHL diagnosis date: if only the day is missing, the 1st day of the month will be imputed.

For death date and date of last known to be alive: if only the day is missing, the last day of the month will be imputed.

For SCT date: if only the day is missing, the 1st day of the month will be imputed, unless this is before the end date of frontline treatment; in this case the end date of frontline treatment + 1 day will be imputed.

For date of assessment of refractory disease: if only the day is missing, the first day of the month (01) will be used, unless this is before the start date of frontline treatment; in this case, the start date of frontline treatment + 1 day will be imputed.

For date of first relapse after start of frontline treatment: if only the day is missing, the first day of the month (01) will be used, unless this is before the start date of frontline treatment; in this case, the start date of frontline treatment + 1 day will be imputed.

For date of relapse (after 1st relapse): if only the day is missing, the first day of the month (01) will be imputed, unless this is before the date of previous relapse; in this case, the date of previous relapse + 1 day will be imputed.

For date of radiotherapy: if only the day is missing, the first day of the month (01) will be imputed, unless this is before the date of cHL diagnosis; in this case, the date of cHL diagnosis + 1 day will be used.

For chemotherapy regimens start and stop dates: if only the day is missing:

- For the <u>start date</u>, the first day of the month (01) will be used, unless:
    - this is before the date of cHL diagnosis for the 1st regimen; in this case, the date of cHL diagnosis + 1 day will be used, or
    - this is before the end date of the previous treatment regimen; in this case, the end date of the previous treatment regimen + 1 day will be used.
- For the <u>stop date</u>, the last day of the month will be used, unless
    - this is after the patient's death date; in this case or if the regimen is ongoing, the death date will be used for the imputation, or,
    - this is after the last date the patient is known to be alive; in this case and if the regimen is ongoing, the last date the patient was known to be alive will be used for the imputation, or,
    - this is after the start date of a subsequent treatment regimen; in this case, or, if the regimen is not ongoing, the start date of the subsequent regimen – 1 day will be used.

For healthcare resource utilisation dates (e.g. inpatient hospitalisation admission date, date of emergency visit, etc. not required by the minimum dataset): if only the day is missing, it will be imputed as the first day of the month. If either the month or the year are missing, then the date will not be imputed and will be assigned a missing value.

When performing multivariable analyses, patients with missing data on any covariate will be excluded and this will be reported in the corresponding table.

8.6. EXAMINATION OF SUBGROUPS

All analysis will be performed separately for the cHL set and the RRHL set. Within each group,

the analysis will be presented for the overall sample, at a regional level and separately for each participating country.

Regions will be defined as follows:

- East Asia: Republic of Korea, Singapore, Taiwan, China and Hong Kong,

- Latin America (LatAm): Argentina, Colombia and Mexico,

- Middle East and South Africa: Saudi Arabia, South Africa and Turkey,

- Australia,

- Russia.

Australia and Russia will be analysed as single countries within regional level analysis. As a consequence, these countries will not be presented at country level analysis.

Clinical outcomes will also be presented separately for the following subgroups:

- Patients with Human Immunodeficiency Virus (HIV)/ Hepatitis B or C *versus* without HIV, Hepatitis B and C,

- Patients who receive PET or PET-CT *versus* CT only for evaluation of treatment response.

- In the RRHL set:

  o SCT patients,
  o each salvage regimen used pre-SCT,
  o each salvage regimen used post-SCT,
  o each treatment regimen received by non-SCT patients,
  o each post SCT regimen in patients who relapse after SCT,
  o Patients with primary refractory HL (those who have failed to achieve a complete remission (CR) with frontline therapy or relapse within 3 months after end of frontline therapy) *versus* patients with relapsed HL (relapse >3 months after end of frontline therapy),
  o Early *versus* late relapsers (early: relapse within 3–12 months after end of frontline therapy; late: relapse >12 months after end of frontline therapy),
  o Patients undergoing SCT *versus* non-SCT patients,
  o Patients who receive brentuximab vedotin *versus* other treatments in the non-SCT setting,
  o Patients who receive brentuximab vedotin *versus* other treatments in the post-SCT setting.

For the final analysis and if there is a sufficient number of patients, the items above related with SCT may be repeated for Autologous Stem Cell Transplantation (ASCT) only, overall and by region.

Patient demographic and disease characteristics will be presented overall and by:

- SCT type (Allo-SCT only, ASCT only and both).

- Non-SCT patients receiving brentuximab vedotin (yes/no),

- Post-SCT patients receiving brentuximab vedotin post-relapse (yes/no).

Pre-SCT and post-SCT are defined as follows:
"Pre-SCT": Preparatory or conditioning regimens used in patients preparing for a stem cell transplant,
"Post-SCT": Consolidation or salvage regimen used in patients after receiving a stem cell transplant.

9. STATISTICAL ANALYSIS

9.1. PATIENT DISPOSITION

All patients diagnosed with high-risk stage IIb-IV cHL and/or RRHL between 01st of January, 2010 and 31st of December, 2013 who provide written informed consent for this study (where required by local regulations) will be accounted for in this study.

Patient disposition will be summarized descriptively for FAS overall, by region and by country as follows:
- Number of enrolled patients,
- Number of non-eligible patients in the study,
- Number of non-eligible patients by reason for non-eligibility,
- Number of cHL and RRHL enrolled patients in the study,
- Number of enrolled patients in cHL set that are refractory or relapsed between 01st of January 2010 and 31st of December 2013,
- Number and percentage of cHL and RRHL enrolled patients alive or dead at the time of the abstraction date,
- Number and percentage of cHL and RRHL patients who died, by cause of death: HL-

related, adverse event, treatment-related, unknown and other.

9.2. PATIENT DEMOGRAPHIC CHARACTERISTICS

The following demographic data will be described for cHL and RRHL sets overall, by region and by country:
- Number and percentage of patients by gender,
- Number and percentage of patients by ethnicity/race.

For the RRHL set, demographic characteristics will also be described overall, by region and by country for the following subgroups:

- SCT type (allo-SCT only, ASCT only and both),

- Non-SCT patients receiving brentuximab vedotin (yes, no),

- Post-SCT patients receiving brentuximab vedotin post-relapse (yes, no).

9.3. DISEASE CHARACTERISTICS

The following clinical data will be described for the cHL set overall, by region and by country:
- Mean age (StDev) at cHL diagnosis (years),
- Number and percentage of patients by age group (<60 years and ≥60 years) at cHL diagnosis,
- Number and percentage of patients by clinical staging at cHL diagnosis,
- Proportion of patients with B symptoms at cHL diagnosis,
- Number and percentage of patients with any Bulky disease greater than or equal to 5 cm at initial diagnosis,
- Number and percentage of patients with any extranodal involvement at initial diagnosis,
- Mean (StDev) body weight at diagnosis (kg),
- Number and percentage of patients by histological subtype of cHL (Nodular Sclerosis cHL, Mixed Cellularity cHL, Lymphocyte-depleted cHL, Lymphocyte-rich cHL, Unknown)
- Number and percentage of patients with the following risk factors for relapse [International Prognostic Score (IPS) factors] at diagnosis:
  - Age at diagnosis (age ≥45 years*, age <45 years),
  - Gender (male*, female),
  - Stage IV disease (yes*, no),

- - o Albumin results (Albumin <4 g/dl*, Albumin ≥4 g/dl),
    - o WBC results (WBC ≥15 × 10^9/L*, WBC <15 × 10^9/L),
    - o Haemoglobin values (Haemoglobin <10.5 g/dl*, Haemoglobin ≥10.5 g/dl),
    - o Lymphocyte count <0.6 × 10^9/L or <8% of differential (yes*, no),
- * Increased risk category.
- Mean (StDev) and median (range) of IPS score and number and percentage of patients by IPS score categories,

The following clinical data will be described for the RRHL set overall by region and country:
- Mean (StDev) age at RRHL diagnosis (years),
- Number and percentage of patients by age group (<60 years and ≥60 years) at RRHL diagnosis,
- Number and percentage of patients with any record of relapse, refractory disease or both,
- Number and percentage of patients with any relapse after first relapse following start of frontline treatment and mean (StDev) number of those relapses,
- Number and percentage of patients with first relapse and with subsequent relapses following frontline treatment,
- Number and percentage of patients by clinical staging at first RRHL diagnosis, and subsequent relapses, and at start of treatment with brentuximab vedotin (if used),
- Proportion of patients with B symptoms at RRHL diagnosis and subsequent relapses,
- Mean (StDev) body weight at first relapse/refractory diagnosis and subsequent relapses (kg),
- Number and percentage of patients by histological subtype of cHL (Nodular Sclerosis cHL, Mixed Cellularity cHL, Lymphocyte-depleted cHL, Lymphocyte-rich cHL, Unknown),
- Number and percentage of patients by haemoglobin clinical assessment (normal, abnormal: low and high abnormal) at first relapse/refractory and subsequent relapses. "Abnormal" clinical assessment will be derived pooling the 3 categories: "Abnormal, significant unknown", "Abnormal, not clinically significant" and "Abnormal, clinically significant" of the respective Laboratory Parameter, Clinical Assessment
- Mean (StDev) and median (range) of haemoglobin normal and abnormal (low/high) results at first relapse/refractory and subsequent relapses. The classification of laboratory results (normal vs abnormal) will be based on local laboratory reference ranges as reported by the sites and normal values vary between sites. The high/low abnormal values will be defined as:
    - o Haemoglobin: low abnormal (< 14 g/dl); high abnormal (>= 14 g/dl),
- Number and percentage of patients with any Bulky disease greater than or equal to 5 cm at first relapse/refractory diagnosis and subsequent relapses,
- Number and percentage of patients with the following risk factors for relapse (Josting

factors):

  o Time to recurrence within 3–12 months after end of frontline treatment (yes*, no),
  o Stage III or IV relapse (yes*, no),
  o Haemoglobin at relapse <10.5 g/dL for females and <12 g/dL for males (yes*, no),
  *Increased risk category
- Number and percentage of patients by Josting score (0, 1, 2, 3) categories.

The following derived and conversion values will be used:

- *Age at cHL diagnosis (years) = (date of cHL diagnosis – date of birth[a) + 1) / 365.25.*

- *Age at RRHL diagnosis (years) = (min (date of assessment of refractory disease, date of first relapse after start of frontline treatment) – date of birth[a) + 1) / 365.25.*

[a) *The day of birth will not be collected, as some sites do not collect the day due to ethical reasons. Thus, the day of birth will be imputed as the 1st day of the month.*

- *Patients with clinical stage I-B, II-B, III-B or IV-B at initial cHL diagnosis, will be considered as patients with "presence of B symptoms" and patients with clinical stage I-A, II-A, III-A or IV-A at initial cHL diagnosis, will be considered as patients without B symptoms.*

- *Patients with clinical stage I-B, II-B, III-B or IV-B at first RRHL diagnosis, will be considered as patients with "presence of B symptoms" and patients with clinical stage I-A, II-A, III-A or IV-A at first RRHL diagnosis and at each subsequent relapse, will be considered as patients without B symptoms.*

- *For patients reporting weight in pounds in the CRF, the following conversion will be applied: weight in kg is 0.45 times the weight in lb.*

- *One point will be given for each of the risk factors selected below:*
  o *age at diagnosis ≥ 45years,*
  o *male gender,*
  o *stage IV at disease diagnosis,*
  o *albumin results at diagnosis < 4 g/dl,*
  o *WBC results at diagnosis ≥15 × 10^9/L,*
  o *haemoglobin results at diagnosis< 10.5 g/dl,*
  o *lymphocyte count <0.6 × 10^9/L or <8% of differential at diagnosis,*

The sum of all the points will be the IPS score.

- *Based on the IPS score (sum of the above selected risk factors), patients with advanced disease can be categorised as follows:*
  - o good risk (IPS 0-1),
  - o fair risk (IPS 2-3),
  - o poor risk (IPS 4-7).

- *One point will be given for each of the risk factor selected below:*
  - o *time to recurrence within 3–12 months after end of frontline treatment,*
  - o *stage III or IV at first RRHL diagnosis,*
  - o *haemoglobin at first relapse/refractory diagnosis <10.5 g/dl for females and <12 g/dl for males,*

  The sum of all the points will be the Josting score.

For the RRHL set, disease characteristics will also be described overall, by region and by country for the following subgroups:

- SCT type (allo-SCT only, ASCT only and both),

- Non-SCT patients receiving brentuximab vedotin (yes, no),

- Post-SCT patients receiving brentuximab vedotin post-relapse (yes, no).

9.4. MEDICAL HISTORY

The following medical history data will be described for the cHL and the RRHL sets overall, by region and by country:
- Number and percentage of patients with presence of comorbid conditions and with any of the following relevant comorbid conditions:
  - o Lung disease [including Tuberculosis (TB)],
  - o Cardiovascular disease,
  - o HIV Infection,
  - o Hepatitis B,
  - o Hepatitis C and
  - o Other.

9.5. DIAGNOSTIC TEST AT INITIAL DIAGNOSIS

The following patient diagnosis tests results and respective clinical assessment (normal and abnormal) at initial diagnosis will be presented descriptively for cHL and RRHL sets overall, by region and by country:
- Bone marrow involvement (negative lymphoma infiltration, positive lymphoma infiltration, not done)
- ECOG (0, 1, 2, 3, 4),
- Albumin (g/dl),
- WBC count (10^9/L),
- Haemoglobin (g/dl),
- Lymphocyte (10^9/L).
-

"Abnormal" in clinical assessment will be derived pooling the 3 categories: "Abnormal, significant unknown", "Abnormal, not clinically significant" and "Abnormal, clinically significant" of the respective Laboratory Parameter, Clinical Assessment. The classification of laboratory results (normal vs abnormal) will be based on local laboratory reference ranges as reported by the sites and normal values vary between sites. High/low abnormal values will be defined as:
- Albumin: low abnormal (< 4 g/dl); high abnormal (>= 4 g/dl),
- White Blood Count: low abnormal (< 7.5 x 10^9/L); high abnormal (>= 7.5 x 10^9/L),
- Haemoglobin: low abnormal (< 14 g/dl); high abnormal (>= 14 g/dl),
- Lymphocyte count: low abnormal (< 1.0 x 10^9/L); high abnormal (>= 1.0 x 10^9/L).

9.6. PREVIOUS THERAPIES FOR HL

The following data for previous therapies for HL will be presented descriptively for RRHL set overall, by region and by country:
- Number and percentage of patients by any prior therapies for HL and at each line of treatment
- Median (range) number of previous treatment regimens
- Mean (StDev) and median (range) time from end of frontline treatment to first relapse (in months).

The therapy regimens will be presented by line of therapy and will be abbreviated in the TLFs shells by "Therapy Regimen #" as follows:

Therapy regimen 1	Doxorubicin + Bleomycin + Vinblastine + Dacarbazine (ABVD)

Therapy regimen 2	ABVD followed by escalated BEACOPP (Doxo + Bleo + Vinbl + Dacar then Bleo + Etop + Doxo + Cycl + Vinc + Procar + Pred)
Therapy regimen 3	Doxorubicin + Vinblastine + Mechlorethamine + Etoposide + Vincristine + Bleomycin + Prednisone (Stanford V)
Therapy regimen 4	Bleo + Eto + Doxo + Cyclo + Vincri + Procarb + Pred (BEACOPP)
Therapy regimen 5	Escalated BEACOPP followed by ABVD with ISRT
Therapy regimen 6	Cyclophosphamide + Vincristine + Procarbazine + Prednisone (C-MOPP)
Therapy regimen 7	Dexamethasone + Cytarabine + Cisplatin (DHAP)
Therapy regimen 8	Etoposide + Methylprednisolone + Cytarabine + Cisplatin (ESHAP)
Therapy regimen 9	Gemcitabine + Carboplatin + Dexamethasone (GCD)
Therapy regimen 10	Ifosfamide + Carboplatin + Etoposide (ICE)
Therapy regimen 11	Ifosfamide + Gemcitabine + Vinorelbine + Prednisone (IGEV)
Therapy regimen 12	Carmustine + Cytarabine + Etoposide + Melphalan (Mini- BEAM)
Therapy regimen 13	Etoposide + Ifosfamide + Mesna + Mitoxantrone (MINE)
Therapy regimen 14	Cyclophosphamide + Doxorubicin + Vincristine + Prednisone (CHOP)
Therapy regimen 15	Cyclophosphamide + Vincristine + Prednisone (CVP)
Therapy regimen 16	Gemcitabine + Vinorelbine + Pegylated liposomal doxorubicin (GVD)
Therapy regimen 17	Rituximab
Therapy regimen 18	Brentuximab vedotin
Therapy regimen 19	Bendamustine
Therapy regimen 20	Everolimus
Therapy regimen 21	Lenalidomide
Therapy regimen 22	Nivolumab
Therapy regimen 23	Pembrolizumab
Therapy regimen 24	Other

If applicable, the therapy regimens reported as "Other" will be re-classified by medical team and included in the analysis as therapy regimens ABVD, ABVD followed by escalated BEACOPP and BEACOPP.

The following derived values will be used:

- *Prior therapies for HL = therapies with the start date before the date of first relapse or before the date of diagnosis of refractory disease.*

- *Time from end of frontline treatment to 1st relapse (months) = (date of 1st of relapse – end date of frontline treatment + 1) / 30.44.*

9.7. TREATMENT PATHWAYS

The proportion of treated patients will be presented by treatment pathway: PET, PET-CT and/or CT scan, chemotherapy, radiotherapy and SCT.

The following data will be described for the cHL set, overall, by region and by country:
- Number and percentage of patients that performed PET or PET-CT and CT scan,
- Median (range) frequency of PET or PET-CT and CT assessment and when performed (baseline and frontline),
- Distribution of PET or PET-CT and CT scan results (if available) at baseline and at frontline in each cycle (after 1-2 cycles, 3-4 cycles and 5-6 cycles) and at surveillance,
- Distribution of PET or PET-CT scans rating [assessed by Deauville rating as: 1 - no uptake or no residual uptake (when used interim); 2 – slight uptake, but equal to or below blood pool (mediastinum); 3 - uptake above mediastinal, but below or equal to uptake in the liver; 4 - uptake slightly to moderately higher than liver; 5 - markedly increased uptake or any new lesion (on response evaluation); Not Applicable and Unknown] at baseline and frontline,
- Number and percentage of patients by frontline treatment regimens,
- Median (range) number of treatment cycles per patient associated with each regimen,
- Number and percentage of patients with any treatments received for HL after completion of frontline therapy (but before relapse, if this occurred),
- Number and percentage of patients that performed radiotherapy at frontline,
- Distribution of type, anatomical site (if used) and intent of radiotherapy treatment (radical/cure intent, palliative intent and other), at frontline and whether used for pre-planned frontline treatment or for residual fluorodeoxyglucose (FDG)-avid disease,
- Median (range) dosing of Radiotherapy (if used).

The following data will be described for the RRHL set, overall, by region and by country:
- Number and percentage of patients that performed PET or PET-CT and CT scan,
- Median (range) frequency of PET or PET-CT and CT assessment and when performed (baseline, frontline and relapse/refractory),
- Distribution of PET or PET-CT and CT scan results (if available) at baseline, at frontline and refractory/relapse after treatment cycles cycle (after 1-2 cycles, 3-4 cycles and 5-6 cycles) and at surveillance,
- Distribution of PET or PET-CT scans rating [assessed by Deauville rating as: 1 - no uptake or no residual uptake (when used interim); 2 – slight uptake, but equal to or below blood pool (mediastinum); 3 - uptake above mediastinal, but below or equal to uptake in the liver; 4 - uptake slightly to moderately higher than liver; 5 - markedly increased uptake or

any new lesion (on response evaluation); Not Applicable and Unknown] at baseline, at frontline and at relapse/refractory.
- Number and percentage of patients that performed radiotherapy at frontline and at relapse/refractory,
- Distribution of type, anatomical site (if used) and intent of radiotherapy treatment (radical/cure intent, palliative intent and other), when used (frontline or relapse) and whether used for pre-planned frontline treatment or for residual fluorodeoxyglucose (FDG)-avid disease,
- Median (range) dosing of Radiotherapy (if used).

The following treatment pathways data will also be described for all patients of RRHL set and for each of the following subgroups of RRHL set: non-SCT patients, patients undergoing SCT and patients who relapse after SCT overall, by region and by country:

All patients with RRHL:
- Number and proportion of patients who were considered eligible/ineligible for SCT at relapse/refractory,
- Number and proportion of patients initially considered ineligible for SCT who subsequently became eligible and received SCT:
  - o Treatment received, including median (range) number of doses or treatment cycles associated with each therapy regimen,
  - o Median (range) of PET, PET-CT and/or CT assessment and when used (e.g. baseline, frontline and relapse/refractory).
- Number and proportion of eligible patients who received/did not receive SCT and type of SCT performed,
- Distribution of clinical stage of SCT and type of SCT (allo-SCT and ASCT)

Non-SCT patients (patients considered ineligible for SCT or subsequently become SCT eligible but not undergoing SCT):
- Number and percentage of patients by reasons for not undergoing SCT in patients who were SCT-eligible (advanced age, comorbid conditions, cumulative toxicities, patient refusal, inability to mobilise stem cells, loss of response to chemotherapy, financial reasons, other, unknown),
- Number and percentage of patients by reasons for SCT ineligibility (advanced age, comorbid conditions, chemo-resistant disease, cumulative toxicities, patient refusal, inability to mobilise stem cells, loss of response to chemotherapy, other, unknown),

- Distribution of treatment regimens received at each line of treatment and proportion of patients for whom treatment is palliative,
- Mean (StDev) and median (range) duration of each line of treatment (in months),
- Median (range) number of treatment cycles received at each line of treatment, for each treatment regimen,
- Number and proportion of patients with dose delays at each line of treatment for each treatment regimen,
- Mean (StDev) and median (range) time from relapse (after frontline treatment) to first treatment post-relapse (in days),
- Mean (StDev) and median (range) time to initiation of each subsequent treatment, both from relapse and from completion of previous treatment (in days),
- Number and proportion of patients receiving at least one PET or PET-CT and/or CT scan at baseline, frontline and relapse/refractory and frequency of assessment,
- Number and proportion of patients receiving at least one radiotherapy at each stage (at frontline and at relapse/refractory) of the treatment pathway,
- Distribution of type, anatomical site and intent of radiotherapy treatment at each stage (frontline and relapse/refractory),
- Mean (StDev) and median (range) dosing of radiotherapy (if used).

The following derived values will be used:

- *Duration of a line of treatment (months) = (end date of the line of treatment – start date of the line of treatment + 1) / 30.44*

- *Time from relapse (after frontline treatment) to 1st treatment post relapse (days) = (date of 1st treatment post relapse – date of relapse after frontline treatment + 1)*

- *Time from 2nd relapse to initiation of the subsequent treatment post relapse (days) = (start date of subsequent treatment post relapse – date of 2nd relapse + 1)*

- *Time from 3rd relapse to initiation of the subsequent treatment post relapse (days) = (start date of subsequent treatment post relapse – date of 3rd relapse + 1)*
  ...

- *Time from completion of frontline treatment to initiation of the subsequent treatment (days) = (start date of subsequent treatment – end date of frontline treatment + 1)*

- *Time from completion of 1st treatment after 1st relapse to initiation of the subsequent treatment (days) = (start date of subsequent treatment - end date of 1st treatment after 1st relapse + 1)*

- *Time from completion of 2nd treatment after 1st relapse to initiation of the subsequent treatment (days) = (start date of subsequent treatment - end date of 2nd treatment after 1st relapse+ 1)*

...

Patients undergoing SCT (patients eligible for SCT or initially considered ineligible but subsequently become eligible, and who performed SCT):
- Number and percentage of patients by chemotherapeutic salvage regimens used pre- and post-SCT,
- Median (range) number of cycles associated with each salvage regimen,
- Distribution of chemotherapy conditioning regimens used,
- Proportion of patients receiving consolidation therapy post-SCT,
- Number and percentage of patients by consolidation therapies used, and mean (StDev) and median (range) duration of treatment (in months),
- Time from relapse (after end of frontline treatment) to SCT (in days),
- Number and percentage of SCT by source of SCT (bone marrow, peripheral and cord blood),
- Mean (StDev) and median (interquartile range) CD34+ count administered,
- Number and percentage of patients by known risk factors for relapse after SCT:
  - time to first relapse ≤3 months (yes, no),
  - stage IV disease at relapse (yes, no),
  - bulky disease ≥5 cm at relapse (yes, no),
  - extranodal disease (yes, no),
  - inadequate response to salvage chemotherapy (<PR or PET positivity) (yes, no),
  - performance status (ECOG) ≥1 (yes, no).

The following derived values will be used:

- *Duration of consolidation therapy treatment (months) = (end date of consolidation therapy treatment – start date of consolidation therapy treatment + 1) / 30.44*

- *Time from relapse (after end of frontline treatment) to SCT (days) = (date of SCT – date of relapse after end of frontline treatment + 1)*

Patients who relapse after SCT:
- Mean (StDev) and median (range) time from SCT to first relapse post-SCT (in months),
- Number and percentage of patients by post-SCT therapy regimens received and proportion of patients for whom treatment is palliative,
- Mean (StDev) and median (range) duration of each line of treatment (months),
- Median (range) number of cycles received at each line of treatment, for each treatment regimen,
- Mean (StDev) and median (range) time from SCT to first treatment after relapse post-SCT (months),
- Mean (StDev) and median (range) time to initiation of each subsequent treatment, both from SCT (in months) and from completion of previous treatment (in days),
- Number and proportion of patients receiving PET or PET-CT and/or CT scan at each stage of treatment pathway (baseline, frontline and relapse/refractory),
- Mean (StDev) and median (range) frequency of assessment in patients receiving PET or PET-CT and/or CT scan at baseline, frontline and relapse/refractory,
- Number and proportion of patients receiving at least one radiotherapy at each stage of the treatment pathway (frontline and relapse/refractory),
- Distribution of type, anatomical site and intent of radiotherapy (if used) at each stage of treatment pathway (frontline and relapse/refractory)
- Mean (StDev) and median (range) dosing, and frequency of radiotherapy (if used) at each stage of the treatment pathway (frontline and relapse/refractory),
- Number and proportion of patients undergoing subsequent SCTs and median (range) number of SCTs per patient,
- Number and proportion of patients undergoing allogeneic stem cell transplantation (Allo-SCT).

The following derived values will be used:
- *Time from SCT to first relapse post-SCT (months) = (date of 1ˢᵗ relapse post-SCT – date of SCT + 1) / 30.44*

- *Duration of a line of treatment (months) = (end date of the line of treatment – start date of the line of treatment + 1) / 30.44*

- *Time from SCT to 1ˢᵗ treatment after relapse post-SCT (months) = (date of 1ˢᵗ treatment after relapse post-SCT - date of SCT + 1) / 30.44*

- *Time from SCT to initiation of 2nd treatment after relapse post-SCT (months) = (start date of 2nd treatment after relapse post-SCT – date of SCT + 1) / 30.44*

- *Time from SCT to initiation of 3rd treatment after relapse post-SCT (months) = (start date of 3rd treatment after relapse post-SCT – date of SCT + 1) / 30.44*

...

- *Time from completion of 1st treatment after relapse (post-SCT) to initiation of subsequent treatment (days) = (start date of subsequent treatment – end date of 1st treatment after relapse post-SCT + 1)*

- *Time from completion of 2nd treatment after relapse (post-SCT) to initiation of subsequent treatment (days) = (start date of subsequent treatment – end date of 2nd treatment after relapse post-SCT + 1)*

...

For the final analysis, the items above may be repeated for ASCT.

9.8. PRIMARY ENDPOINT ANALYSIS

9.8.1. PROGRESSION-FREE SURVIVAL

The primary effectiveness variable in the study is PFS in patients with RRHL, defined as the time (in months) from initiation of first treatment for RRHL to first documentation of relapse or disease progression or death. Patients who did not have a relapse or disease progression and did not die will be censored on the date when the patient was last known to be alive.

The following derived value will be used:

- *PFS duration (months) = (min (date of 1st documentation of relapse/disease progression/death/date when the patient was last known to be alive after initiation of 1st treatment for RRHL) – date of initiation of 1st treatment for RRHL + 1) / 30.44*

PFS duration will be summarized descriptively by: number of patients at risk, number of patients with event, number of patients censored, median, Q3 and Q1 and respective 95% CI using the estimates of KM method. In addition, the KM curve of PFS will be presented graphically, overall and for each region and country.

A Proportional Hazards Cox model will be used to describe the relationship between time to first documentation of relapse or disease progression or death overtime and the potential covariates/factors.

The model will be adjusted for the covariates and factors described in Section 8.4. Results will be presented as HRs and the respective 95% CIs.

The RRHL set will be considered for the primary analysis.

9.9. SECONDARY ENDPOINT ANALYSIS

9.9.1. CLINICAL OUTCOMES

The following clinical outcomes data will be described for the cHL set overall, by region and by country:
- Median PFS (in months). Patients who did not have a relapse or disease progression and did not die will be censored on the date when the patient was last known to be alive,
- Number and percentage of patients by best clinical response after completion of frontline treatment [CR, Unconfirmed CR (uCR), PR, Stable Disease (SD) and PD], as defined by the International Working Group 2007 Revised Response Criteria for Malignant Lymphoma (4),
- Mean (StDev) and median (range) time to response, among patients who achieved clinical response (CR, uCR, or PR), defined as the time from initiation of frontline treatment to the first documentation of PR, uCR or CR, whichever occurs first (in months),
- Mean (StDev) and median (range) number of lines of treatment needed to achieve a first response (CR, uCR or PR) after initiation of frontline treatment,
- Number and proportion of patients with documented relapse or disease progression at any point after completion of frontline treatment,
- Median duration of response, among patients who achieved clinical response (CR, uCR or PR) after initiation of frontline treatment, defined as the time (in months) from the date of first documented response (CR, uCR or PR) after initiation of frontline treatment to the first documented relapse, disease progression or death from any cause. Patients with a CR, uCR, or PR who did not have a relapse, disease progression or did not die, will be censored at the date when the patient was last known to be alive,
- 1-, 3-, and 5-year PFS rates, estimated from Kaplan-Meier estimate,
- Median OS (in months). Patients who did not die will be censored on the date when the patient was last known to be alive,
- Proportion of patients alive at 1, 3 and 5 years after diagnosis, estimated from KM

estimate.
- For deceased patients:
  o Mean (StDev) and median (range) time to death (from diagnosis and from completion of frontline therapy) in months,
  o Number and percentage of patients by cause of death (HL-related/AE/treatment-related/unknown/other).

The following derived values will be used:

- *PFS duration (months) = (min (date of 1st documentation of relapse/disease progression/death/date when the patient was last known to be alive after initiation of frontline treatment) – date of initiation of frontline treatment + 1) / 30.44*

- *Best clinical response after completion of frontline treatment = Best response (CR, uCR, PR, SD, PD) that one patient achieves after completion of last regimen of frontline treatment (by Chemotherapy Details eCRF page)*

- *Time to response after initiation of frontline treatment (months) = (min (date of CR, uCR or PR achievement after initiation of frontline treatment) – start date of frontline treatment + 1) / 30.44*

- *Duration of response, after initiation of frontline treatment (months) = (min (date of 1st documentation of relapse/disease progression/death/date when patient was last known to be alive, after initiation of frontline treatment – min (date of documented CR, uCR or PR after initiation of frontline treatment) + 1) / 30.44*

- *OS (months) = (date of death/date when the patient was last known to be alive– date of cHL diagnosis + 1) / 30.44*

- *Time from cHL diagnosis to death (months) = (date of death – date of cHL diagnosis + 1) / 30.44*

- *Time from completion of frontline therapy to death (months) = (date of death – end date of frontline therapy + 1) / 30.44*

For cHL set, PFS and OS will be summarized descriptively as in the primary effectiveness analysis. The KM curves of PFS and OS will be presented graphically, overall, by region and by country.

For cHL set, Proportional Hazard Cox Model will be used to identify the various patient or disease risk factors for PFS and OS, using the same methodology described in the primary effectiveness analysis (Section 9.8.1).

The following clinical outcomes data will be described for the RRHL set and for each of the following subgroups: for SCT, each salvage regimen used pre- and post-SCT, each treatment regimen received by non-SCT patients, and each post-SCT regimen in patients who relapse after SCT, by overall, region and country.

- Median PFS (in months). Patients who did not have a relapse or disease progression and did not die will be censored on the date when the patient was last known to be alive,
- Number and percentage of patients by best clinical response (CR, uCR, PR, SD and PD) after completion of each line of treatment,
- Mean (StDev) and median (range) time to response, among patients who achieved clinical response (CR, uCR or PR), defined as the time (in months) from initiation of first treatment for RRHL to the first documentation of PR, uCR or CR, whichever occurs first (in months),
- Mean (StDev) and median (range) number of lines of treatment needed to achieve a first response (CR, uCR or PR) after initiation of second line of treatment,**For SCT patients:** number and proportion of patients in response (CR, or PR, or SD) who are assessed as high risk of relapse pre-SCT (risk factors defined in Section 9.7. above),
- Number and proportion of patients with documented relapse or disease progression at any time after completion of line of treatment,
- Median duration of response, among patients who achieved clinical response (CR, uCR or PR) after initiation of first treatment for RRHL defined as the time (in months) from the date of first documented response (CR, uCR or PR) after initiation of first treatment for RRHL, to first documentation of relapse, disease progression or death from any cause. Patients with a CR, uCR, or PR who did not have a relapse, disease progression or did not die, will be censored at the date when the patient was last known to be alive,
- 1-, 3-, and 5-year PFS rates, estimated from KM estimate,
- Median OS (in months). Patients who did not die will be censored on the date when the patient was last known to be alive,
- Proportion of patients alive at 1, 3 and 5 years after first relapse, estimated from KM estimate.
- Proportion of patients alive at 1, 3 and 5 years after cHL diagnosis, estimated from KM estimate.

- For deceased patients:

o Mean (StDev) and median (range) time to death (from initial diagnosis, from first relapse, from SCT, and from relapse after SCT) in months,

o Number and percentage of patients by cause of death (HL-related/AE/treatment-related/unknown/other).

The following derived values will be used:

- *PFS duration (months) = (min (date of 1ˢᵗ documentation of relapse/ disease progression/ death/ date when the patient was last known to be alive, after initiation of 1ˢᵗ treatment for RRHL) – date of initiation of 1ˢᵗ treatment for RRHL + 1) / 30.44*

- *Best clinical response after completion of each line of treatment = Best response (CR, uCR, PR, SD, PD) that one patient achieves after completion of last regimen of each line of treatment (by Chemotherapy Details eCRF page),*

- *Time to response after initiation of 1ˢᵗ treatment of RRHL (months) = (min (date of CR, uCR or PR achievement after initiation of 1ˢᵗ treatment for RRHL) – start date of 1ˢᵗ treatment for RRHL + 1) / 30.44*

- *Duration of response, after initiation of 1ˢᵗ treatment of RRHL (months) = (min (date of 1ˢᵗ documentation of relapse/disease progression/death/ date when patient was last known to be alive, after initiation of 1ˢᵗ treatment for RRHL – min (date of documented CR, uCR orPR after initiation of 1ˢᵗ treatment of RRHL) + 1) / 30.44*

- *OS from 1ˢᵗ relapse after frontline therapy (months) = (date of death/date when the patient was last known to be alive – date of 1ˢᵗ relapse after frontline therapy + 1) / 30.44*

- *OS from cHL diagnosis (months) = (date of death/date when the patient was last known to be alive– date of cHL diagnosis + 1) / 30.44*

- *Time from diagnosis of cHL to death (months) = (date of death –date of cHL diagnosis + 1) / 30.44*

- *Time from 1ˢᵗ relapse to death (months) = (date of death – date of 1ˢᵗ relapse + 1) / 30.44*

- *Time from SCT to death (months) = (date of death – date of SCT + 1) / 30.44*

- *Time from relapse after SCT to death (months) = (date of death – date of relapse after SCT + 1) / 30.44*

For RRHL set, PFS and OS will be summarized descriptively as in the primary effectiveness analysis. The KM curves of PFS and OS will be presented graphically, overall, by region and by country.

For RRHL set, Proportional Hazard Cox Model will be used to identify the various patient or disease risk factors for PFS and OS, using the same methodology described in the primary effectiveness analysis ([Section 9.8.1](#))

Clinical outcomes will also be presented overall, for the following subgroups:

In the cHL and RRHL sets:
- Patients with HIV/ Hepatitis B or C *versus* without HIV, Hepatitis B and C,

In the RRHL set:
- Patients with primary refractory HL (those who have failed to achieve a CR with frontline therapy or relapse within 3 months after end of frontline therapy) *versus* patients with relapsed HL (relapse >3 months after end of frontline therapy),
- Early *versus* late relapsers (early: relapse within 3–12 months after end of frontline therapy; late: relapse >12 months after end of frontline therapy),
- Patients undergoing SCT *versus* non-SCT patients,
- Patients who receive brentuximab vedotin *versus* other treatments in the non-SCT setting,
- Patients who receive brentuximab vedotin *versus* other treatments in the post-SCT setting.

9.10. EXPLORATORY ANALYSIS

Additionally, to the primary and secondary endpoint analysis, an exploratory analysis for PFS and OS will be performed for RRHL set only, i.e. subjects counted under both, cHL group and RRHL group, will not be included.

9.10.1. PROGRESSION-FREE SURVIVAL

The PFS in patients with RRHL only will be analysed in the same way as the primary variable, defined as the time (in months) from initiation of first treatment for RRHL to first documentation of relapse or disease progression or death. Patients who did not have a relapse or disease progression and did not die will be censored on the date when the patient was last known to be

alive.

The following derived value will be used:

- *PFS duration (months) = (min (date of 1st documentation of relapse/disease progression/death/date when the patient was last known to be alive, after initiation of 1st treatment for RRHL) – date of initiation of 1st treatment for RRHL + 1) / 30.44*

PFS duration will be summarized descriptively by: number of patients at risk, number of patients with event, number of patients censored, median, Q3 and Q1 and respective 95% CI using the estimates of KM method. In addition, the KM curve of PFS will be presented graphically, overall and for each region and country.

- The 1-, 3-, and 5-year PFS rates, will also be estimated from KM estimate.

9.10.2. OVERALL SURVIVAL

The OS in patients with RRHL only will be defined as the time from the first relapse after frontline treatment to death. Patients who did not die will be censored on the date when the patient was last known to be alive.

In addition, OS will also be defined as the time from diagnosis of cHL to death. Patients who did not die will be censored on the date when the patient was last known to be alive.

The following derived values will be used:
- *OS from 1st relapse after frontline therapy (months) = (date of death/date when the patient was last known to be alive – date of 1st relapse after frontline therapy + 1) / 30.44*

- *OS from cHL diagnosis (months) = (date of death/date when the patient was last known to be alive – date of cHL diagnosis + 1) / 30.44*

OS will be summarized descriptively as in the previous section (Section 9.10.1). The KM curves of OS will be presented graphically, overall, by region and by country.

The proportion of patients alive at 1, 3 and 5 years after first relapse, and after cHL diagnosis, will be estimated from KM estimate.

9.11. ADVERSE EVENTS

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary, Version 22.0 and grouped by System Organ Class (SOC) and Preferred Term (PT). The number and percentage of patients having at least one adverse event will be presented by SOC and PT. Separate summaries will be given for all AEs, treatment-related AEs, Serious Adverse Events (SAE), treatment-related SAE, non-SAE and treatment-related non-SAE.

The following AEs data will be described for cHL set and presented overall and separately for AEs considered by the treating clinician as treatment-related, overall, by region and by country:
- Number and percentage of patients with at least one AE associated with frontline treatment, including haematological malignancies, and peripheral neuropathy (PN). In addition, the number of AEs will also be described,
- Number and percentage of patients with at least one AE by seriousness (serious/non-serious).
- Number of AEs by duration of exposure in the line of treatment

The following AEs data will be described for RRHL set and presented overall and separately for AEs considered by the treating clinician as treatment-related and will be described, overall, by region and by country:
- Number and percentage of patients with at least one AE (including haematological malignancies and PN) associated with:

    o SCT
    o Each treatment regimen received by non-SCT patients
    o Each post-SCT treatment regimen

- Number and percentage of patients with at least one AE by seriousness (serious/non-serious)
- Number of AEs by duration of exposure in the line of treatment

9.12. HEALTHCARE RESOURCE USE

The following resource use data will be described for cHL set overall, by region and by country and will be reported for:

    o Frontline chemotherapy ± Radiotherapy treatment (per patient per cycle)

Overall HL-related resource use will be reported, as well as the resource use associated with AE management:
- Number and proportion of patients with any inpatient hospitalisation admission
- Mean (StDev) number of inpatient hospital admissions
- Number and proportion of patients by type and reasons of inpatient hospitalization (if available)
- For inpatient hospital admissions; mean (StDev) length of stay, overall and by unit/ward [general, high dependency/intermediate, Intensive Care Unit (ICU), bone marrow transplant (BMT) unit]
- Number and proportion of patients with any emergency room visit
- Mean (StDev) number of emergency room visits
- Number and proportion of patients with any outpatient visits
- Mean (StDev) number of outpatient visits by healthcare professional seen
- Number and proportion of patients that received any radiotherapy
- Mean (StDev) number of episodes of radiotherapy received
- Number and proportion of patients that received any type of scan/procedure
- Mean (StDev) number of each type of scan/procedure
- Number and proportion of patients that received Granulocyte-colony Stimulating Factor (G-CSF)/pegylated G-CSF or other high-cost medicines
- Mean (StDev) number of days of treatment with G-CSF/pegylated G-CSF or other high-cost medicines
- Mean (StDev) number of courses of treatment with G-CSF/pegylated G-CSF or other high-cost medicines

The above resource use data will also be described for RRHL set, by overall, region and country and reported for:
- Salvage therapy (per patient per cycle)
- ASCT (per patient)
- Allo-SCT (per patient)
- Brentuximab vedotin in the non-SCT setting (per patient per cycle)
- Brentuximab vedotin in the post-SCT setting (per patient per cycle)
- Each post-SCT chemotherapy regimen (per patient per cycle)

For each treatment, overall HL-related resource use will be reported, as well as the resource use associated with AE management.

The following derived values will be used:

- *Duration of G-CSF/ pegylated G-CFS or other high-cost medicines (days) = (end date of medication – start date of medication + 1)*

9.13. COSTS ASSOCIATED WITH EACH LINE OF THERAPY

Estimates for costs associated with each line of therapy is optional and will be calculated based on health resource use and country level costs.

Statistical Analysis Plan

10. REFERENCES

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