Protocol Number: ADCT-402-203

Official Title: A Phase 2 Open-label Study of Loncastuximab Tesirine in Combination with Rituximab (Lonca-R) in Previously Untreated Unfit/Frail Patients with Diffuse Large B-cell Lymphoma (DLBCL) (LOTIS-9)

NCT Number: NCT05144009

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Statistical Analysis Plan

A Phase 2 Open-label Study of Loncastuximab Tesirine in Combination with Rituximab (Lonca-R) in Previously Untreated Unfit/Frail Patients with Diffuse Large B-cell Lymphoma (DLBCL) (LOTIS-9)

PROTOCOL NO.: ADCT-402-203 Phase 2

SAP Version No./ Date: V1.0, 11, Jan 2024

Statistician: [redacted]

Confidentiality Statement

SAP Approval – Sponsor Signatory

Study Title	A Phase 2 Open-label Study of Loncastuximab Tesirine in Combination with Rituximab (Lonca-R) in Previously Untreated Unfit/Frail Patients with Diffuse Large B-cell Lymphoma (DLBCL) (LOTIS-9)
Protocol Number	ADCT-402-203 Amendment 3
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SAP accepted and approved by:

[redacted]

11-Jan-2024

Signature | Date

[redacted]

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Signature | Date

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List of Abbreviations

Abbreviation	Definition
ADA	anti-drug antibody
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice daily
BOR	best overall response
C1D1	Cycle 1, Day 1
CCI [redacted]	
CI	confidence interval
CIRS-G	Cumulative Illness Rating Scale for Geriatrics
CR	complete response
CRF	case report form
CRR	complete response rate
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	diffuse large B-cell lymphoma
DNA	deoxyribonucleic acid
DoR	duration of response
ECG	electrocardiogram(s)
ECOG	Eastern Cooperative Oncology Group
EoS	end of study
EoT	end of treatment
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
CCI [redacted]	
FIL	Fondazione Italiana Linfomi
CCI [redacted]	
GGT	gamma glutamyl transferase
HBV	hepatitis B virus
HCV	hepatitis C virus
HGBCL	high-grade B cell lymphoma
HIV	human immunodeficiency virus
IADL	instrumental activities of daily living
ICF	informed consent form
IPI	International Prognostic Index
Lonca	loncastuximab tesirine
Lonca-R	loncastuximab tesirine and rituximab
LVEF	left ventricular ejection fraction
NHL	non-Hodgkin's lymphoma
ORR	overall response rate
OS	overall survival
PBD	pyrrolobenzodiazepine

Abbreviation	Definition
PD	progressive disease
PET-CT	positron emission tomography-computed tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient reported outcome
PS	performance status
QT	measure between Q wave and T wave in the electrocardiogram
QTcF	Fridericia correction of the QT measure
RBC	red blood cell
R-CHOP	combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
sGA	simplified geriatric assessment
SoC	standard of care
SoE	schedule of events
TEAE	treatment-emergent adverse event

1 Introduction

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analysis of data collected under ADC Therapeutics Protocol ADCT-402-203. The company decided to discontinue the study on 20 Jul 2023. Given the challenges of defining the addressable segment of this difficult-to-treat patient population, the benefit-risk profile does not support continuation of the LOTIS-9 trial. So not all the analyses specified in study protocol are covered by the SAP. Analyese of PK/Biomarker data will be covered in separate SAP if needed.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the Protocol Amendment 3 08 August 2022 and CRF version dated 02 Feb 2023.

2 Study Objectives

2.1 Primary Objectives

Cohort A

- To assess the efficacy of a response-adapted treatment of Lonca-R in unfit patients with previously untreated DLBC, or HGBCL, or Grade 3b FL

Cohort B

- To assess the tolerability and efficacy of a response-adapted treatment of Lonca-R in frail patients or patients with cardiac comorbidities with previously untreated DLBCL who are ineligible for standard R-mini-CHOP

2.2 Secondary Objectives

Cohort A and Cohort B

- Further evaluate the efficacy of Lonca-R
- To characterize the safety profile of Lonca-R
- To characterize the PK profile of Lonca when given in combination with rituximab
- To evaluate the immunogenicity of Lonca when given in combination with rituximab
- To evaluate the impact of Lonca-R treatment on treatment-related and disease-related symptoms, patient-reported functions, and overall health status

Due to early termination of the study, patients are not followed up for sufficient time. Some endpoints for secondary objectives,such as progression-free survival (PFS), overall survival (OS) and patient reported outcome (PRO), will not be analyzed because of lack of sufficient follow up.

[redacted]

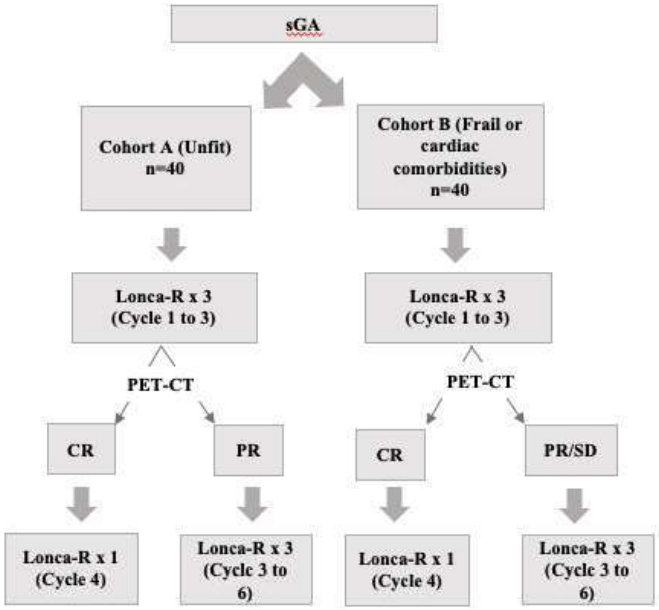
3 Study Design

3.1 Overview

This is a Phase 2, multicenter, multi-cohort, open-label study of Lonca-R in unfit/frail patients with previously untreated DLBCL. Fitness and frailty of the patients will be assessed using the sGA tool developed by the FIL. A response-adapted approach will be used in this study. Two parallel cohorts will enroll patients; Cohort A will enroll unfit patients and Cohort B will enroll frail patients or patients with cardiac comorbidities (Figure 1).

A treatment cycle in the study is defined as 3 weeks (i.e., 21 days). Cohort A will assess efficacy and Cohort B will assess the efficacy and tolerability of Lonca-R. After completion of 3 cycles of Lonca-R treatment, patients who achieve CR or PR will continue to receive 1 additional cycle or 3 cycles of Lonca-R, respectively. Patients in Cohort A who do not achieve a CR or PR will discontinue study treatment. For Cohort B only, patients who achieve stable disease (SD) and derive clinical benefit per the treating physician may continue to receive additional 3 cycles of Lonca-R.

Eligible patients will be administered through IV with loncastuximab tesirine 150mcg/kg for the first 2 cycles starting at C1D2. For subsequent cycles, the dose level will be reduced to 75mg/kg. Rituxinmab will be dosed through IV with dose level of 375 mg/m2 starting at C1D1.



Abbreviations: CR, complete response; Lonca-R, loncastuximab tesirine in combination with rituximab; PET-CT, positron emission tomography-computed tomography; PR, partial response; SD, stable disease; sGA, simplified geriatric assessment.

3.2 Sample Size Consideration

A sample size of 40 patients for each cohort is considered adequate to assess safety and efficacy in the corresponding study population. The percentage of ORR and CR rate with its 95% CI will be presented

descriptively. The primary endpoint, CRR, will be calculated based on the exact Clopper-Pearson Method.

Number of Patients	Number of CRs	CRR	Confidence intervals based on exact Clopper-Pearson method		
			90% CI for CRR	95% CI for CRR	99% CI for CRR
40	12	30%	(18.3, 44.0)	(16.6, 46.5)	(13.4, 51.4)
40	16	40%	(26.9, 54.2)	(24.9, 56.7)	(21.0, 61.4)
40	20	50%	(36.1, 63.9)	(33.8, 66.2)	(29.5, 70.5)
40	24	60%	(45.8, 73.1)	(43.3, 75.1)	(38.6, 79.0)

As of 20 Jul 2023 when decision was made to discontinue the study, 41 patients were enrolled an treated in total.

3.3 Randomization

Not applicable.

3.4 Modifications to the statistical section of the protocol

Not applicable

4 Statistical Methods

All analyses will use SAS® version 9.4 or higher.

Categorical data will be presented using counts and percentages, with the number of patients in the analysis population as the denominator for percentages. Percentages will be rounded to 1 decimal place and not be displayed for zero counts.

Continuous data will be summarized using the number of observations (n), mean, standard deviation (std), median, minimum, and maximum. Minima and maxima will be rounded to the precision of the original value, and means, medians, and 95% confidence intervals (CIs) if presented will be rounded to 1 decimal place greater than the precision of the original value. The std will be rounded to 2 decimal places greater than the precision of the original value, up to a maximum of 3 decimal places.

4.1 Analysis Populations

4.1.1 All-Treated Population

All patients who receive at least 1 dose of study drug. This population will be used in the primary analyses of efficacy and safety for both cohorts.

4.1.2 Patient-reported Outcomes Population

All patients who receive at least one dose of study treatment and complete at least one questionnaire at baseline and at one post baseline visit.

4.1.3 PK Population

All patients who receive study drug and have at least 1 pre- (C1D1) and 1 post-dose valid PK assessment.

4.1.4 Immunogenicity Population

All patients who receive study drug and have at least 1 valid anti-drug antibody assessment.

[redacted]

4.2 Patient Disposition

The number and percentage of patients enrolled and treated in the study will be presented. In addition, the number and percentage of patients who withdrew from study treatment and who discontinued the study for each reason will be tabulated..

Patient disposition data will be listed in patient level.

4.3 Protocol Deviations

All protocol deviations will be determined prior to database lock and will be agreed upon by a review of individual subject data.

The pre-defined important CSR-reportable protocol deviations are listed below; in addition, any other protocol deviations deemed by ADCT medical to be important CSR-reportable deviations will be included in the summary.

1. Patient entered the study even though they did not satisfy the entry criteria.
2. Patient received a prohibited concomitant treatment during the study.
3. Patient who met criteria for mandatory study drug discontinuation during the study but did not have study drug withdrawn.
4. Patient who received the wrong treatment or incorrect dose, specifically:
   - Actual dose of study drug was greater than 15% more or less than protocol defined planned dose level.
   - Patient started next cycle less than 18 days after Day 1 of the most recent treatment cycle.

Important protocol deviations will be listed in patient level.

4.4 Demographic and Baseline Characteristics

Demographic information will be summarized. The summary will include age and age groups (≥ 65, <80), (≥ 80), sex, Ethnicity, race and race groups.

The baseline characteristics will be summarized. The baseline characteristics will include cumulative illness rating scale for geriatrics (CIRS-G), Katz activities of daily living (ADL scales), and Lawton- Brody instrumental activities of daily living scale (IADL scales). The three categories of fit, unfit, and frail will be derived from the three rating scales. The patient level rating scales and derived sGA categories will be listed.

Demographic and baseline characteristics data will also be listed at patient level.

4.5 Cancer History and Medical History

Cancer history, including primary category per WHO 2016 classification, method used to designate cell of orgin for DLBCL subtype, diseae staging, and additional subtype information will be summarized.

Prior systemic treatments for iNHL, including number of lines, response to the first/most recent line, prior radiotherapy will be summarized.

Cancer history and medical history will be listed.

Prior systemic therapy and radiotherapy will be listed.

4.6 Prior and Concomitant Medications (other than anticancer therapies)

All medications will be recorded in the CRF starting from the ICF signature date or from 14 days prior to C1D1, whichever is earlier, and continuing until 30 days after last dose of study drug.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD).

- Prior medications are those the patient used prior to the first dose. Prior medications can be discontinued before the first dose or can be ongoing during the treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to any loncastuximab tesirine from the first dose to the last dose + 30 days. A given medication can be classified both as a prior medication and as a concomitant medication. Concomitant medications do not include medications started 30 days after the last dose.

Prior and concomitant medications will be listed in patient level.

4.7 Exposure to Treatment

4.7.1 Extent of Study Drug Exposure

Study drug exposures will be based on the All-treated population.

A treatment cycle is defined as 3 weeks (i.e., 21 days).

Duration of treatment, total number of cycles dosed, total dose received), average dose per cycle, and relative dose intensity (actual dose taken / planned dose) will be summarized. Dose administered at each infusion is calculated by concentrated investigational product (IP) volume (in mL)* concentration. For incomplete infusion, actual dose will be adjusted by proportion of volume of dosing solution administered.

Relative dose intensity will be additionally presented categorized (<60%, >=60 - <80%, >=80 - <90%, >=90 - <110%, >=110%).

Exposure data and infusion details will be listed together.

4.7.2 Prophylactic Medications for Hypersensitivity

Prophylactic medications for hypersensitivity will be listed only.

4.7.3 Subsequent Anticancer Therapy or Procedure

Patients' subsequent anticancer therapies or procedures including systemic therapy, radiation, transplant, or other, along with the start date of new anticancer therapy or procedure will be collected and listed only.

4.8 Efficacy Analyses

Efficacy analyses will be based on response as determined by investigator with the All-treatmed population. The endpoints for efficacy include Complete Response Rate (CRR), Overall Response Rate (ORR) according to the 2014 Lugano classification as determined by investigator (See Lugano classification in Appendix x), Duration of Response (DoR).

All efficacy endpoints and tumor assessment data will be listed in patient level.

4.8.1 Overall Response Rate

Overall response rate (ORR) is defined as the proportion of patients with a BOR of complete response (CR) or partial response (PR) as determined by the investigator according to the 2014 Lugano classification criteria before the start of subsequent anticancer therapy or procedure. For the ORR analysis in the all-treated population, patients with a CR or PR will be counted as successes and all other patients (including those with missing response information) will be counted as failures.

A BOR of SD can only be made after the patient is on-study for a minimum of 35 days after the first dose of study drug. Any tumor assessment indicating SD before this time period will be considered as NE for BOR if no assessment after this time period is available.

The overall response rate and the corresponding 95% two-sided exact confidence interval will be presented.

4.8.2 Complete Response Rate

Complete response rate (CRR) is defined as the proportion of patients with a BOR of complete response (CR) as determined by the investigator according to the 2014 Lugano classification. The percentage of CRR with its 95% CI will be presented

4.8.3 Duration of Response

Duration of response (DoR) is defined for patients with CR or PR only as the interval between the date of initial documentation of a response and the date of the first documented evidence of progressive disease (based on radiographic or clinical progression at end of treatment [EOT]/end of study [EOS]) or death due to any cause, whichever occurs first. Patients who have the event after the start of subsequent anticancer therapy/procedure, or are progression-free and alive at the time of clinical cut-off, or have unknown status, will be censored at the last valid tumor assessment on or before the start of subsequent anticancer therapy/procedure or clinical cut-off time. When a subsequent anticancer therapy is used and progressive disease

(based on radiographic or clinical progression at EOT/EOS) is observed within 6 days, they will be considered as the same visit (within the protocol specified +/-6 days visit window) and the patient will be counted as having an event (losing the response).

Patients with no post-baseline disease assessment will be censored on Day 1.

Duration of response will be estimated and displayed for the all-treated population using Kaplan-Meier methods (SAS® PROC LIFETEST). A Kaplan-Meier plot will be presented.

4.9 Safety Analyses

All safety analyses will be based on the all-treated population.

General common rules

All safety analyses will be performed on the all-treated population, unless otherwise specified, using the following common rules:

- The baseline value is defined as the last non-missing value or measurement taken up to the first dose in the study.
- The analyses of the safety variables will be essentially descriptive and no systematic testing is planned.

4.9.1 Adverse Events, Serious Adverse Events, and Deaths

4.9.1.1 Analyses of Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this study treatment.

A treatment-emergent AE (TEAE) is defined as an AE that occurs or worsens in the period extending from the first dose of study drug to 15 weeks after the last dose of study drugs in this study (either loncastuximab or Rituximab) or start of a new anticancer therapy, whichever is earlier. The primary focus of adverse event reporting will be on TEAEs.

AEs will be coded according to MedDRA Version 24.1, and the severity of the toxicities will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, where applicable.

The summary of overall TEAEs includes:

- TEAEs
- Drug-related TEAEs (loncastuximab tesirine or Rituximab)
- Grade ≥3 TEAEs
- Drug-related Grade ≥3 TEAEs (loncastuximab tesirine or Rituximab)
- Serious Adverse Events (SAEs)

- TEAEs leading to dose delayed, reduced or interrupted (loncastuximab tesirine or Rituximab)
- TEAEs leading to discontinuation of loncastuximab tesirine or Rituximab
- TEAEs leading to death
- Infusion related reaction

The incidence of TEAEs will be summarized by system organ class (SOC) and preferred term (PT). A patient will be counted only once within a SOC and PT, even if the patient experienced more than one AE within a specific SOC and PT.

- All TEAEs ≥Grade 3 by PT, showing number (%) of patients with at least one TEAE, sorted by decreasing incidence of PTs
- All TEAEs by primary System Organ Class (SOC) and PT, showing number (%) of patients with at least one TEAE, sorted by SOC in alphabetic agreed order and decreasing incidence of PTs within SOC. This sorting order will be applied to all other tables, unless otherwise specified.
- All TEAEs by primary SOC, PT and Maximal CTCAE grade, showing number (%) of patients with at least one TEAE, sorted by SOC and PT in alphabetic order. This sorting order will be applied to all other tables, unless otherwise specified.
- All TEAEs ≥Grade 3 by primary SOC, PT and Maximal CTCAE grade
- All related TEAEs by primary SOC, PT and Maximal CTCAE grade (including possibly related, probably related, or related)
- All TEAEs leading to treatment withdrawal by primary SOC, PT and Maximal CTCAE grade
- All TEAEs leading to dose delay by primary SOC, PT and Maximal CTCAE grade
- All TEAEs leading to dose reduction by primary SOC, PT and Maximal CTCAE grade
- All TEAEs leading to infusion interruption by primary SOC, PT and Maximal CTCAE grade
- All TEAEs with fatal outcome by primary SOC, PT and Maximal CTCAE grade
- All Serious TEAEs by primary SOC, PT and Maximal CTCAE grade
- All infusion related reaction TEAEs by primary SOC, PT and Maximal CTCAE grade
- Summary of grouped TEAEs selected by Standardised MedDRA Query (SMQ), ADCT modified SMQ will also be provided by primary Grouped terms, PT and Maximal CTCAE grade.

Listing of all AEs, including non-TEAEs, will be provided. Besides, TEAEs leading to dose reduced, delayed or interrupted (loncastuximab tesirine or Rituximab), TEAEs leading to

discontinuation of loncastuximab tesirine or Rituximab, and TEAEs leading to death will also be provided.

4.9.1.2 Deaths

The following deaths summaries will be generated on the all-treated population.

- Number (%) of patients who died during the study and reasons for death
- Number (%) of patients who died within 15 weeks after the last dose of study drug (excluding those who died after taking any subsequent anticancer therapy/procedure) and reasons for deathListing of deaths will be provided.

4.9.2 Laboratory Data

Laboratory data of hematology, chemistry will be summarized for the raw data and the change from baseline value at each scheduled assessment. Descriptive statistics (mean, standard deviation, median, and range) will be calculated for the actual data and for their changes from baseline at each scheduled assessment.

All results will be graded according to CTCAE version 5.0. Shift tables will summarize the shift from baseline grade to maximum post-baseline CTCAE grade.

Summaries by visit will include data from scheduled assessments, and all data will be reported according to the nominal visit date for which it was recorded. Unscheduled data will be included in “worst case post-baseline” summaries, which will capture a worst case across all scheduled and unscheduled visits after the first dose of study treatment.

All laboratory data, including urinalysis and serology, will be listed.

4.9.3 Electrocardiogram Data

Electrocardiogram (ECG) parameters (e.g., corrected QT interval [QTc] in ms) will not be converted or derived, but will be reported as provided by investigational sites.

Descriptive statistics (mean, standard deviation, median and range) will be calculated for the raw data and for their changes from baseline at each scheduled assessment.

The following abnormal QTcF will be reported by a frequency table:

At any post-baseline with absolute value

>450 - <=480 ms

>480 - <=500 ms

> 500 ms

Change from Baseline

>30 – <=60 ms

>60 ms

All ECG data will be listed, both for quantitative data and for overall impression.

4.9.4 Vital Signs

Descriptive statistics (mean, standard deviation, median, and range) for vital signs data, including systolic and diastolic blood pressure, heart rate, respiration rate, and body temperature will be calculated for the raw data and for their changes from baseline at each scheduled assessment.

All vital signs data will be listed together with body weight.

4.9.5 ECOG Performance Status

Descriptive statistics (mean, standard deviation, median and range) will be calculated for the raw data and for their changes from baseline at each scheduled assessment.

ECOG performance score data will be listed.

4.9.6 Physical Examinations

Listing of physical examinations will be provided.

4.9.7 Pregnancy Test

Listing of pregnancy test, if applicable, will be provided.

5 Data handling conventions

6.1 General conventions

6.1.1 Missing data

In general, imputation of missing dates will be made for AE onset date, AE resolution date, date of death, medication start/end dates, start and end dates of prior and subsequent therapies, and date of initial diagnosis for reporting. No imputation should be done at the data level.

- If dates are completely missing, no imputation will be made.
- For any partial date with missing year, no imputation will be made.
- For missing initial diagnosis date, if only day is missing, then the first day of the month will be used; if only year is present, then Jan 1st will be used. If such imputed date for initial diagnosis is on or after date of first dose, then date of first dose - 1 will be used.
- If the imputed date is for an AE start date and is in the same year and month as but before the first dose date, then the first dose date will be used, or if the imputed AE start date is after the AE end date, then the AE end date will be used. If the imputed date is for an AE start date and is in the same year and month as but after the last dose date + 15 weeks, then the last dose date + 15 weeks will be used.
- If a medication date or time is missing or partially missing, so it cannot be determined whether it was taken prior or concomitantly, it will be considered as a prior and concomitant medication.
- If the imputed date is for a date of death and is before the last date that the patient is known to be alive, the latter date will be used.
- If the date part is missing for new anticancer therapy, the month and year will be used for comparison with disease assessment.

Handling of missing relationship to investigational product of TEAEs
If the assessment of the relationship to IP is missing, then the relationship to IP has to be assumed and the TEAE considered as such in the frequency tables of possibly related TEAEs, but no imputation should be done at the data level.

Handling of missing severity/grades of AEs
If the severity/grade is missing for one of the treatment emergent occurrences of an AE, the maximal severity of the remaining occurrences will be considered. If the severity is missing for all the occurrences a “missing” category will be added in summary table.

No other imputation of values for missing data will be performed.

6.1.2 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will be used for computation of baseline and worst values and/or grades. Re-windowing for unscheduled visits will not be performed.

6.1.3 Duplicated visits

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value per visit. Unless otherwise noted throughout the rest of this document, when a single value is needed, the following rule(s) will be used:

- If more than 1 assessment occurs during the same nominal visit, select the record closest to the nominal day for that visit.
- If there are 2 assessments that are equidistant from the nominal day, the data of the assessment after the scheduled study day will be used.
- The last measurement will be used if multiple measurements are taken on the same day.

6 Reference List

Zimmer AJ, Freifeld AG, et al. Optimal Management of Neutropenic Fever in Patients With Cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2019;15:19-24. Available from: Optimal Management of Neutropenic Fever in Patients With Cancer | JCO Oncology Practice (ascopubs.org)

John Crowley, Donna Pauler Ankerst. Handbook of Statistics in Clinical Oncology. *Chapman & Hall/CRC.* 2006.

Carter RH and Barrington RA. Signaling by the CD19/CD21 complex on B-cells. *Curr Dir Autoimmun*. 2004;7:4–32.

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. *J Clin Oncol.* 2014;32(27):3059-3067.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649-655.