SPONSOR:

Autolus

PROTOCOL NUMBER:

AUTO3-DB1

STATISTICAL ANALYSIS PLAN

Author:	[redacted]
Version:	**Final 1.0**
Date:	**21-Dec-2023**

1 Cover and signature pages

Sponsor:	Autolus
Protocol Number:	AUTO3-DB1
Study Title:	A Single-arm, Open-label, Multi-centre, Phase I/II Study Evaluating the Safety and Clinical Activity of AUTO3, a CAR T Cell Treatment Targeting CD19 and CD22 with Anti PD-1 Antibody in Patients with Relapsed or Refractory Diffuse Large B Cell Lymphoma
Document Version No	Final 1.0

We, the undersigned, confirm that we have read, understood and agree to the content of this document and hereby authorize its approval.

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	Director		[redacted]

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2 List of Abbreviations and Definition of Terms

AE	Adverse Event
AESI	Adverse Event of special interest
ALT	Alanine Aminotransferase
ATC	Anatomical Therapeutic Chemical
ASCT	Autologous haematopoietic stem cell transplantation
ATIMP	Advanced therapy investigational medicinal product
BM	Bone marrow
BOR	Best overall response
CAR	Chimeric antigen receptor
CD	Cluster of differentiation
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
CR	Complete response
CRF	Case Report Form
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CY	Cyclophosphamide
DLBCL	Diffuse large B cell lymphoma
DNA	Deoxyribonucleic acid
DLT	Dose limiting toxicity
DOR	Duration of response
DSUR	Development safety update report
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FDG	Fluorodeoxyglucose
FISH	Fluorescence In Situ Hybridization

FL	Follicular lymphoma
FLU	Fludarabine
FLU-CY	Fludarabine and Cyclophosphamide
GI	Gastrointestinal
HIV	Human immunodeficiency virus
i.v.	Intravenous(ly)
ICAN	Immune effector cell-associated neurotoxicity syndrome
ICH	International Conference on Harmonisation
IFN	Interferon
Ig	Immunoglobulin
IHC	Immunohistochemistry
IPI	International prognostic index
IVIG	Intravenous immunoglobulin
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NE	Not evaluable
NT	Neurotoxicity
OS	Overall survival
PBMCs	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Progressive Disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PDvs	Protocol deviations
PET	Positron emission tomography
PFS	Progression-free survival
PR	Partial Response
PT	Preferred Term

Q1	25% quartile
Q3	75% quartile
qPCR	Quantitative polymerase chain reaction
QTCF	Heart rate-corrected QT interval (Fridericia's formula)
RCR	Replication competent retrovirus
RP2D	Recommended Phase II dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SCT	Stem cell transplant
SD	Stable Disease
SD	Standard deviation
SEC	Safety Evaluation Committee
SI	International System
SOC	System Organ Class
TNF	Tumour necrosis factor
TEAE	Treatment-emergent adverse event
TFL(s)	Table(s), Figure(s), Listing(s)
WBC	White blood cell
WHODDE	World Health Organization drug dictionary

3 Introduction

The purpose of this document is to describe the statistical methods, data derivations and data summaries to be employed in the analysis of study AUTO3-DB1 for Autolus in AUTO3, a chimeric antigen receptor (CAR) T cell treatment targeting cluster of differentiation (CD) 19 and/or CD22 followed by consolidation with anti-programmed cell death protein 1 (PD-1) antibody in subjects with relapsed or refractory diffuse large B Cell lymphoma (DLBCL).

The preparation of this statistical analysis plan (SAP) has been based on International Conference on Harmonisation (ICH) E3 and E9 Guidelines, in reference to Protocol AUTO3-DB1 Version 10.0 (06-May-2021) and latest available aCRF (14-Dec-2022).

4 Study Objectives

PRIMARY OBJECTIVES

The primary objectives of the study are defined on Phase I and Phase II as follows:

- Primary objectives for Phase I:
  - Escalation:
    - To assess the safety and tolerability of AUTO3 administration with pembrolizumab;
    - To identify the recommended Phase II doses (RP2D) and maximum tolerated dose (MTD), if an MTD exists, of AUTO3.
  - Expansion:
    - To assess the safety and tolerability of AUTO3 administration with pembrolizumab in the outpatient/ambulatory care setting.
- Primary objectives for Phase II:
  - To evaluate the clinical efficacy of AUTO3 at the RP2D(s) with pembrolizumab in Cohort 1;
  - To assess the overall safety and tolerability of AUTO3 with pembrolizumab in Cohort 2 at the RP2D(s).

SECONDARY OBJECTIVES

- To assess the overall safety and tolerability of AUTO3 with pembrolizumab;
- To evaluate the feasibility of generating the advanced therapy investigational medicinal product (ATIMP), AUTO3;
- To evaluate the overall clinical efficacy of AUTO3 with pembrolizumab;
- To determine the expansion and persistence of AUTO3 following adoptive transfer in different lymphoma subtypes;
- Duration of B-cell aplasia.

EXPLORATORY OBJECTIVES

- To determine the time course and magnitude of cytokine release evaluated using an appropriate assay;
- To evaluate the effect of anti-PD-1 antibody on the time course and magnitude of cytokine release using an appropriate assay;
- To assess the duration of depletion of circulating B cells as determined by flow cytometry on the peripheral blood and correlate this with disease response;
- To assess antibody and/or T cell mediated immune responses against AUTO3;
- To characterise the relationship between the CAR T cell phenotype/genomics and persistence *in vivo*;
- Seek any relationship between parameters of activity, level of CD19 or CD22 expression (flow cytometry), tumour programmed cell death ligand 1 (PD-L1) expression, and CAR T cell phenotype;
- Seek any relationship between incidence and severity of cytokine release syndrome (CRS), neurotoxicity (NT) or other toxicity, and tumour burden, level of CD19 or CD22 expression [immunohistochemistry (IHC) or flow cytometry], CAR T cell phenotype, and PD-1 expression;
- To evaluate cerebrospinal fluid (CSF) for potential markers associated with NT.

5 Study Design

5.1 STUDY DESIGN AND POPULATION

The study patient population for this study is DLBCL and large B cell lymphoma subsets, and will include:

- DLBCL, not otherwise specified (NOS), per World Health Organisation classification and DLBCL with MYC and BCL2 and/or BCL6 rearrangements (double/triple hit);
- Transformed DLBCL from follicular lymphoma (FL);
- Transformed DLBCL from other indolent lymphomas (excluding Richter's transformation);
- High-grade B cell lymphoma with MYC expression (excluding Burkitt's lymphoma);
- Primary mediastinal large B cell lymphoma.

In addition, since this is an experimental therapy, the study patient population will be restricted to patients with chemotherapy-refractory disease, or relapse after at least two lines of therapy (including an anti-CD20 monoclonal antibody (unless tumour is CD20-negative) and an anthracycline cycle), or after autologous haematopoietic stem cell transplantation (ASCT) and have PET positive disease (for efficacy assessment).

The study is a single-arm, open-label, multi-center, Phase I/II dose-escalation and expansion study, evaluating the safety and clinical activity of AUTO3 with anti-PD-1 antibody (pembrolizumab) when administered to patients with confirmed diagnosis of relapsed or refractory DLBCL and large B cell lymphoma subsets. The study will consist of 2 parts, a Phase I (dose escalation) followed by a Phase II (dose expansion).

- **Phase I**
    - **Dose escalation:** To identify the optimal dose (based on safety, tolerability, and anti-tumour activity) of AUTO3 using a rolling 6 dose escalation design. Up to 4 cohorts and approximately 30 patients with DLBCL (and its defined subsets) will be enrolled. Each cohort dose may include up to 6 patients, except Cohort 1 which may include up to 12 patients (3 patients without consolidation therapy, and 3-6 patients with consolidation therapy). Doses from 50×10^6 to 900×10^6

CD19/CD22 CAR-positive T cells, administered as a single dose will be evaluated. All patients (except the first three patients in the dose level 1 cohort) will receive limited consolidation or pre-conditioning therapy with pembrolizumab.

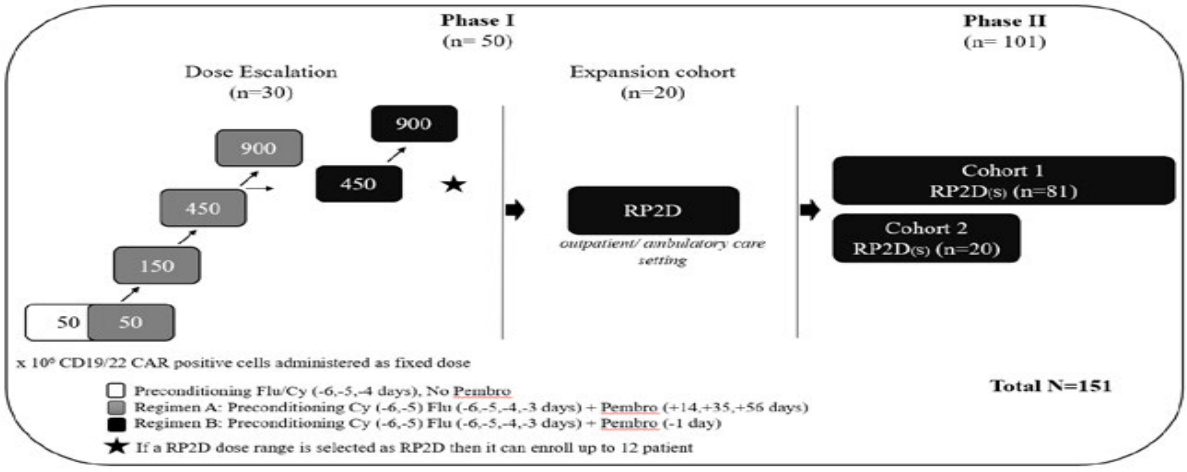
- **Expansion cohort:** To assess the safety and tolerability of AUTO3 at the recommended phase 2 dose(s) (RP2Ds) or dose range and pembrolizumab regimen identified in the dose escalation part. Approximately 20 patients with DLBCL will be treated in an outpatient/ambulatory care setting.

- **Phase II :** To further characterise the safety and assess the efficacy and anti-tumour activity of AUTO3 at the recommended dose(s) or dose range schedule confirmed in Phase I; approximately up to 101 patients will be treated in the dose expansion phase (81 patients with DLBCL subsets and transformed follicular lymphoma in Cohort 1 and, additionally, 20 patients in Cohort 2 with primary mediastinal large B cell lymphoma and those with lymphoma transformed from other indolent histologies).

Approximately up to 171 patients in total are expected to be enrolled (consented) into Phase I and Phase II of the study and approximately 151 patients in total are anticipated to be treated with AUTO3 therapy.

An overview of the study design is presented in Figure 1 below.

Figure 1. Dose Escalation and Dose Expansions Phases



The total study duration is estimated to approximately 7 years from first patient enrolled to the end of study. The end of the study is defined as the last patient last visit (LPLV), expected to be

36 months after the last patient's AUTO3 dose or earlier in the event of patient death or consent withdrawal.

In the event of disease progression prior to the end of the study, patients will continue to be monitored for safety and survival in order to collect Health Authority requested data (e.g. delayed AEs) until the end of the study or until time of early withdrawal or death. The survival follow-up can be conducted via telephone contact if necessary.

At the end of the study or following AUTO3 treatment and early withdrawal from this study, all patients will be followed until death or withdrawal of consent for up to 15 years following their last AUTO3 infusion under a separate long-term follow-up study protocol.

5.2 STUDY TREATMENTS AND ASSESSMENTS

The study will consist of the following six stages:

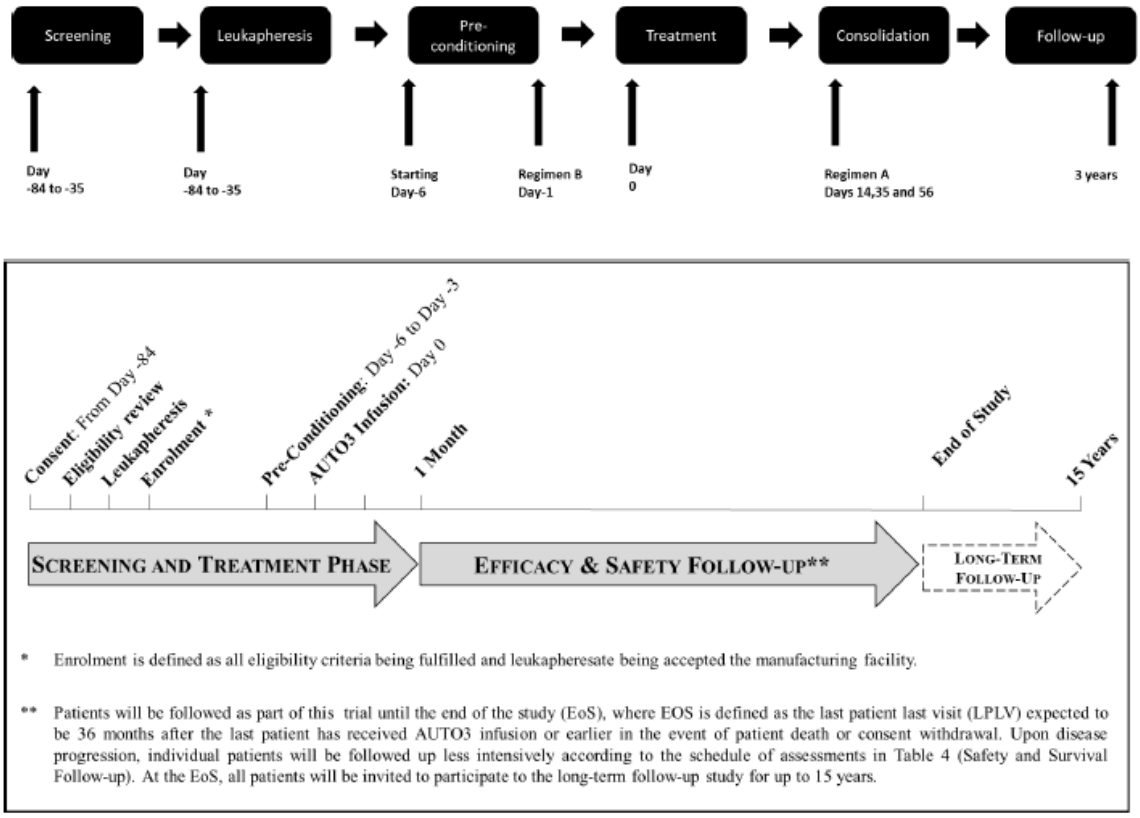
- **Screening**: After providing written informed consent for study participation, all patients will be screened for study eligibility. Eligible patients will proceed to leukapheresis.
- **Leukapheresis**: Eligible patients will undergo leukapheresis to facilitate manufacture of the ATIMP, AUTO3. Once leukaphereses is accepted for manufacturing, the patient will be enrolled on the study.
- **Pre-Conditioning**: If sufficient AUTO3 is successfully manufactured and released, and the patients continue to meet eligibility requirements for the study, they will proceed to receive a standard lymphodepleting pre-conditioning treatment with fludarabine (FLU) for 4 days and cyclophosphamide (CY) for 2 days, to end 3 days before AUTO3 infusion. For Regimen B, pre-conditioning will include in addition to FLU and CY a single dose of pembrolizumab, 200 mg given on Day -1.
- **Treatment**: AUTO3 will be administered intravenously (i.v.) as a single infusion on Day 0. The treatment phase will extend from Day 0 (infusion day) until Day 28 post AUTO3 administration. Patients are expected to be monitored closely (in hospital or ambulatory care as clinically appropriate) for 10 days or longer if clinically necessary for monitoring and management.
- **Consolidation**: Provided any acute toxicities have resolved, anti-PD1 antibody

(pembrolizumab, 200 mg infused over 30 min) will be administered for Regimen A on Days 14, 35 and 56 (±3 days).

- **Follow-up**: The follow-up phase will begin 1 month post AUTO3 infusion and at end of the study; at death or withdrawal of consent, which ever happens first.

An overview of the six study stages is presented in Figure 2.

Figure 2. Overview of the Stages of the Study



From signing of consent until the End of Study visit, information relating to AEs, laboratory abnormalities, disease response and biomarker changes will be collected according to the AE reporting period. The schedule of assessments to be performed during the study is detailed in Appendix A.

Eligible patients will receive a single dose i.v. infusion of AUTO3 following pre-conditioning

treatment. The AUTO3 product contains both transduced (CD19/CD22 CAR-positive) and non-transduced T cells. The dose is expressed as the number of CD19/CD22 CAR-positive T cells. Below dose levels are planned in Phase I:

- Dose Level 1: 50 x 10^6 CD19/CD22 CAR-positive T cells;
- Dose Level 2: 150 x 10^6 CD19/CD22 CAR-positive T cells;
- Dose Level 3: 450 x 10^6 CD19/CD22 CAR-positive T cells;
- Dose Level 4: 900 x 10^6 CD19/CD22 CAR-positive T cells.

The treatment phase will involve infusion of AUTO3 on Day 0. Patients will be monitored for up to 10 days (inpatient or ambulatory care setting), or longer if clinically necessary.

During Phase I the Safety Evaluation Committee (SEC) will meet after the first patient in every cohort completes 14 days, to confirm continuation of enrolment to that cohort and thereafter meet again after the third and or sixth patient in a cohort has completed the dose limiting toxicity (DLT) assessment period. Only after a cohort is declared safe by the SEC can the next higher dose level be opened. Back filling of a cohort (maximum n=6 evaluable patients /cohort) declared safe may be undertaken in parallel to the ongoing enrolment of a higher dose level, to obtain additional biomarker and safety data. All patients will be evaluated for efficacy. A minimum dosing interval of 7 days will be maintained between patients even if they are enrolled to a cohort that is declared safe in the Phase I part of the study.

The planned study cohorts for Phase I are presented in Table 1.

Table 1: Study Treatment Cohorts (phase I/dose escalation)

Dose Levels	Treatment Cohorts	Pre-conditioning (FLU-CY; Days -6, -5, -4, -3)	Total CD19/CD22 CAR-Positive T Cells (Day 0)	Regimen A: Consolidation (pembrolizumab; Days 14, 35, 56)	Regimen B: Pre-conditioning (pembrolizumab; Day -1)
Dose Level 1	Cohort 1	Yes	50 x 10^6	None in first 3 patients, then Yes	
Dose Level 2	Cohort 2A	Yes	150 x 10^6	Yes	
Dose Level 3	Cohort 3A	Yes	450 x 10^6	Yes	
	Cohort 3B	Yes	450 x 10^6		Yes

Dose Levels	Treatment Cohorts	Pre-conditioning (FLU-CY; Days -6, -5, -4, -3)	Total CD19/CD22 CAR-Positive T Cells (Day 0)	Regimen A: Consolidation (pembrolizumab; Days 14, 35, 56)	Regimen B: Pre-conditioning (pembrolizumab; Day -1)
Dose Level 4	Cohort 4A	Yes	900×10^6	Yes	
	Cohort 4B	Yes	900×10^6		Yes
RP2D	RP2D or Dose Range Cohort	Yes	$150 \text{ to } 450 \times 10^6$		Yes
CAR=Chimeric Antigen Receptor; FLU-CY=Fludarabine and Cyclophosphamide; RP2D=recommended Phase II dose.					

A few important aspects considered for the planned dose decision are listed below:

- In dose level 1, the first three patients treated at 50×10^6 CD19/CD22 CAR-positive T cells will not receive consolidation with pembrolizumab.
- Consolidation therapy with pembrolizumab (except dose on Day -1) will be administered only after any CRS has resolved to ≤ Grade 1 or NT has resolved. Based on emerging data, either one or both pembrolizumab dosing regimens will be opened in Dose Level 4 (Cohorts 4A and 4B).
- On occasion, AUTO3 production may fail to generate sufficient cells for the current dose level. In this case, the patient can be treated on study but at a lower dose, however if production fails to generate $\geq 15 \times 10^6$ (approx. 0.2×10^6/kg) CD19/CD22 CAR-positive T cells, near the lowest known active dose of CD19 CAR-positive T cells (1.46×10^5 T cells/kg, approximately total dose of 10×10^6 T cells), then the patient will not be treated on the study. *Only patients treated at planned dose level will be evaluable for dose escalation decision making and primary efficacy analysis (± 20% window)*. Additional patients will be treated to meet the minimum number needed to make the dose escalation decision.
- If emerging data suggest that escalation is appropriate to an intermediate dose, which is a lower than the planned dose, then it can be undertaken with Regimen A or B. Total number of patients of Phase I may also be increased if necessary.
- If emerging safety and efficacy data suggest further dose escalation is warranted, any doses higher than 900×10^6 CD19/CD22 CAR T cells will not be undertaken without a substantial

protocol amendment.

- Note: The dose determination is based solely upon the genetically modified cells (i.e. CD19/CD22 CAR-positive T cells). A patient may be eligible for a planned dose level if the dose is within ±20% of the prescribed CD19/CD22 CAR-positive T cells dose.

Phase I expansion cohort: In this cohort, the safety and tolerability of AUTO3 at the RP2D or dose range will be assessed in an outpatient/ambulatory care setting following declaration of RP2D or dose range in the dose escalation part. Approximately 20 patients will be treated. There will be no inter-patient dosing interval.

Patients enrolled in this cohort will be monitored for at least 10 days in an outpatient/ambulatory care setting, or until all AUTO3-non-haematological related toxicities have returned to Grade ≤1 or baseline, or longer as clinically necessary. During the 10 days following AUTO3 infusion, the patients are monitored at a minimum every 2 to 3 days (in the UK, at least once a day evaluation by a physician or qualified designee). In addition, it is recommended for the patient to have a daily verbal communication with qualified nurse/medical personnel (phone call). Patients will also need adequate caregiver support (in line with institutional outpatient transplant guidelines). Patients enrolled or treated in this cohort can be admitted to the inpatient setting as necessary for the management of AEs or toxicity at any time. Patients can also be admitted based on Investigator discretion should they consider it inappropriate to treat or monitor an already enrolled patient in an outpatient/ambulatory setting. Physicians may also admit patients for social reasons. In all cases the reason for admission should be documented.

Phase II dose expansion: Once the RP2D(s) or dose range is/are determined, the Phase II dose expansion part of the study will open with two cohorts. This part will treat approximately up to 101 patients on the RP2D(s). Cohort 1 will comprise approximately 81 patients on the RP2D with DLBCL subsets and transformed FL, Cohort 2 will comprise approximately 20 patients with PMBCL and DLBCL transformed from other indolent histologies. Patients treated at a dose lower than the RP2D(s) will not be evaluable for primary efficacy endpoint analysis but will be evaluable for secondary efficacy endpoints and safety analysis. Once Phase II starts, patients can be dosed simultaneously at the declared RP2D dose(s) without inter-patient intervals.

5.3 RANDOMISATION AND BLINDING

Randomisation will not be used in this study. As this is an open-label study, blinding procedures are not applicable.

5.4 SAMPLE SIZE JUSTIFICATION

Approximately 171 patients in total are expected to be enrolled (consented) into both the dose escalation and expansion parts of the study, and approximately 151 patients in total are anticipated to be treated with AUTO3 therapy.

- Phase I (Escalation): Up to 30 patients treated (3 to 6 patients per dose cohort, with the exception of dose level cohort 1 one which may include up to 12 patients [up to 6 patients without anti-PD-1 treatment, and 6 patients with anti-PD-1 treatment]), following a rolling 6 design (Skolnik et al. 2008).

An additional 12 patients may be added to RP2D dose /dose range.

- Phase I Expansion Cohort: Approximately 20 patients will be treated in an outpatient/ambulatory care setting.

At the end of Phase I (Escalation), assuming at least 12 patients are treated, the study will terminate if the upper limit of the 2-sided 95% confidence interval in response rate is less than 30%. This is equivalent to observing 0 response in 12 patients. The study will proceed to Phase II if the upper limit of the 2-sided 95% confidence interval in response rate exceeds 30%.

- Phase II: In cohort 1, up to 81 evaluable patients will be analysed, using Simon's 2-stage optimal design. This will include 81 patients with DLBCL (and its defined subsets), and those with transformed FL. Additionally, 20 patients with primary mediastinal large B cell lymphoma and those with lymphoma transformed from other indolent histologies will be enrolled in Cohort 2.

Simon's two-stage design trial will be used (Simon 1989) in the Phase II Cohort 1 only. The null hypothesis that the true response rate is 30% will be tested against a 1-sided alternative. In the first stage, 27 evaluable patients will be accrued. If there are 9 or fewer responses in these 27 patients, the study will be stopped.

Otherwise, 54 additional evaluable patients will be accrued for a total of 81 in Cohort 1. The null hypothesis will be rejected if 31 or more responses are observed in 81 patients. This design yields a type I error rate of 5% and 80% power when the true response rate is 45%.

6 Statistical Considerations

6.1 TERMINATION OF THE STUDY AFTER END OF PHASE I

Important Note – Early Study Termination:

Sponsor informed Cmed team on 03Nov2021 that it was decided not to progress AUTO3 DB1 study into the Phase II part of the study.

Over a period of 4 years (2017-2021), a total of 73 patients were enrolled and 52 patients received AUTO3 in the Phase I part of the study. After reviewing the data and taking into consideration the available treatment landscape in r/r DLBCL, Autolus has decided not to progress AUTO3-DB1 into the Phase II part of study. Therefore, the study will be terminated after the completion of Phase I and not progress to Phase II.

The SAP documents were initially drafted including details for Phase I/Phase II and Interim Analyses for Phase I/Phase II. The study will now focus the analysis only on Sponsor's requirements for end of the study for Phase I only.

6.2 SOFTWARE

The SAS Viya 3.5 (or higher), will be used for all analysis, unless otherwise specified.

6.3 MISSING DATA HANDLING

No other imputation for missing data will be carried out other than to complete partial dates using standard imputation techniques as described below.

For the time to event variables censoring rules will apply as defined in section 8.12, so there should be no missing data.

6.4 PARTIAL DATE IMPUTATION

The following rules should be used when modifying partial or missing dates for reporting purposes such as defining on treatment flags.

A permanent new date variable should be created if there is a requirement to be used in determining flags, sort orders and other derived variables needed for a table, listing or figure. Imputed date variable names will be defined in the derived dataset specifications.

Original (raw) date variables must not be overwritten. Imputed dates will not be displayed in the listings.

Database does not allow adverse events to have any partial dates.

General rules

Prior/Concomitant Medications or Prior Cancer Therapies / Bridging Therapies

Prior/concomitant medications and prior cancer therapies/bridging therapies are considered to have started at the earliest possible date and end at the latest possible date.

In case of partial start dates with missing day:

- Any partial start date in the same month as the AUTO3 infusion would be imputed at the date of the AUTO3 infusion.
- Any partial start date in the month before AUTO3 infusion and in the same month as pre-conditioning treatment would be imputed at the date of earliest pre-conditioning treatment date during that month.
- **Any partial CM start date would be imputed at the first day of the month, regardless of if during the same month as pre-conditioning or AUTO3 infusion.**
- Any partial start date after the month of AUTO3 infusion would be imputed at the first day of the month.
- Any partial start date before the month of first AUTO3 infusion and before the month of first pre-conditioning treatment would be imputed at the last day of the month.

In case of partial start dates with missing day and missing month:

- Any partial start date during the year of AUTO3 infusion would be imputed at the date of the AUTO3 infusion.
- Any partial start date before the year of first AUTO3 infusion and during the year of pre-conditioning treatment would be imputed at the date of earliest pre-conditioning

treatment date during that year.

- **For any concomitant medication or further treatments starting before or during the year of AUTO3 infusion, the start date would be imputed at 01 January of that year.**
- **For any concomitant medication or further treatments starting after the year of first AUTO3 infusion, the start date would be imputed at 01 January of that year.**
- For any concomitant medication or further treatments started before the year of first AUTO3 infusion and before the year of first pre-conditioning treatment, the start date would be imputed as the 31 December of that year.

In case of partial end dates with missing day:

- Partial end dates would be imputed at the last day of the month or at the date of study discontinuation, whichever occurs first.

In case of partial end dates with missing day and month:

- Partial end dates would be imputed at the last day of December (i.e. 31st December) or at the date of study discontinuation, whichever occurs first.

Some examples are given below (YYYY-MM-DD).

In most cases, start dates are imputed as first day of the month or first of January.

Data Type	Start Date	Imputed Start Date	First pre-condition treatment date	Last pre-condition treatment date	First AUTO3 infusion date	End Date	Imputed End Date
Prior/Concomitant Meds/Further treatments	2017-02	2017-02-01	2016-12-11	2016-12-13	2016-12-17	2017-02	2017-02-29
Prior/Concomitant Meds/Further treatments	2017-02	2017-02-01	2017-01-27	2017-01-29	2017-02-03	2017-02	2017-02-29
Prior/Concomitant Meds/Further treatments	2017-02	2017-02-11	2017-02-11	2017-02-13	2017-02-18	2017-02	2017-02-29
Prior/Concomitant Meds/Further treatments	2017-02	2017-02-03	2017-01-27	2017-01-29	2017-02-03	2017-03	2017-03-31

Prior/Concomitant Meds/Further treatments	2017	2017-01-27	2017-01-27	2017-01-29	2017-02-03	2017	2017-03-16 £
Prior/Concomitant Meds/Further treatments	2017-03	2017-03-01	2017-01-27	2017-01-29	2017-02-03	2017-03	2017-03-31
Prior/Concomitant Meds/Further treatments	2017-01	2017-01-27	2017-01-27	2017-01-29	2017-02-03		2017-03-01 *
Prior/Concomitant Meds/Further treatments	2017-01	2017-01-31	2017-02-27	2017-02-29	2017-03-03	2017-01	2017-01-31

£ patient discontinued on 2017-03-16; * patient discontinued on 2017-03-01.

Date of Diagnosis

Partial dates for initial diagnosis will be imputed as the 15th of the month if the month is present, or the 1st of July if only the year is present.

Response Assessment

Partial dates are not expected for response assessment data. However, should partial dates be present on treatment disease assessments:

- First of the month or the date of AUTO3 infusion (whichever is later) if the day part is missing, but month and year parts are present.
- First of January or the date of AUTO3 infusion (whichever is later) if the day and month parts are missing, but year part is present.

Death

Partial dates are not expected for deaths. However, in case of partial date for death, the date would be imputed as:

- The day after the last visit/assessment date when the patient was known alive, if the death date is completely missing, or if the month and year parts are the same as the month and year parts of the last visit/assessment date.
- First of the month if the day part is missing, but month and year parts are present.
- First of January if the day and month parts are missing, but year is present.

6.5 VISIT WINDOWING

Planned assessments will not be re-assigned to any planned visits using statistical programming based on assessment date. All the data will be analysed according to the planned visit as collected in the eCRF.

6.6 BASELINE

Baseline is defined as the last non-missing value/result where assessment date is less than or equal to the date of first pre-conditioning treatment, unless otherwise specified for individual assessments. Baseline will be determined based on all assessments, including additional assessments.

Change from baseline is defined as the difference between the post-baseline assessment value and the baseline value.

6.7 REPORTING GUIDELINES

The following guidelines will be followed:

- **Page Orientation:** Landscape.
- **Post-text TFLs**: will be generated in .rtf using ods rtf within SAS.
- **For final delivery TFLs will be provided in combine files.**
- No in-text outputs are planned.
- **Font**: TFLs will use Courier New font with minimum of 8 point font size.
- **Margins**: Left: 2 cm, Right: 2 cm, Top: 2 cm, Bottom 2 cm on letter paper.
- Columns header will be left aligned.
- **Treatment labels for Phase I** will be the following and displayed in the following order, unless otherwise stated:
    - 50x10^6 (No Pem)
    - 50x10^6 (D14 Pem)
    - 150-450x10^6 (D14 Pem)

- 150-450x10^6 (D-1 Pem) Inpatient
- 150-450x10^6 (D-1 Pem) Outpatient

- All summaries and analyses will be presented by the actual dose, unless otherwise stated.

- **Visit labels**: the visit labels displayed in Table 2 will be used as required.

Table 2: Visit Labels

Study Stage	CRF Visit	Tables, Figures and Listings Label
Screening and Leukapheresis	Screening 1: Day -84 to -35	Screening 1
	Leukapheresis: Day -84 to -35	Leukapheresis
	Screening 2: Day -35 to -6*	Screening 2
Pre-conditioning	Pre-conditioning Day -5	PRE-COND Day -5
	Pre-conditioning Day -4	PRE-COND Day -4
	Pre-conditioning Day -3	PRE-COND Day -3
AUTO 3 Treatment & Anti-PD-1 Consolidation phase#	Day -1 to Day 0**	Day -1 to 0
	Day 1	Day 1
	Day 3	Day 3
	Day 4	Day 4
	Day 5	Day 5
	Day 7	Day 7
	Day 9	Day 9
	Day 10	Day 10
	Day 12	Day 12
	Day 14	Day 14
	Day 16	Day 16
	Day 18	Day 18
	Day 20	Day 20
	Day 28	Day 28
	Day 35	Day 35

Study Stage	CRF Visit	Tables, Figures and Listings Label
	Day 41	Day 41
	Day 56	Day 56
Re-Treatment Pre-conditioning phase	Re-Treatment Pre-conditioning Day -5	Re-TRT PRE-COND Day -5
	Re-Treatment Pre-conditioning Day -4	Re-TRT PRE-COND Day -4
	Re-Treatment Pre-conditioning Day -3	Re-TRT PRE-COND Day -3
Re-Treatment AUTO 3 Treatment & Anti-PD-1 Consolidation phase ***	Re-Treatment Day -1 to Day 0	TRT Day -1 to Day 0
	Re-Treatment Day 1	Re-TRT Day 1
	Re-Treatment: Day 4	Re-TRT: Day 4
	...	...
	Re-Treatment Day 56	Re-TRT Day 56
Follow-up phase Efficacy & Safety Follow-up#	Follow-up: Month 2	FU (M2)
	Follow Up: Month 3	FU (M3)
	Follow Up: Month 4	FU (M4)
	Follow Up: Month 5	FU (M5)
	Follow Up: Month 6	FU (M6)
	Follow Up: Month 9	FU (M9)
	Follow Up: Month 12	FU (M12)
	Follow Up: Month 15	FU (M15)
	Follow Up: Month 18	FU (M18)
	Follow Up: Month 24	FU (M24)
	Efficacy/Safety Month 30	FU (M30)
	Efficacy/Safety Month 36	FU (M36)
	Efficacy/Safety Month 42	FU (M42)
	Efficacy/Safety Month 48	FU (M48)
	Efficacy/Safety - End of Study	End of Study

*Pre-conditioning assessment Day-6 will be covered under Screening 2: Day -35 to -6.

** Pre-conditioning assessment Day-1 will be covered under Day -1 to Day 0.

***Days corresponding to the visits during the Re-Treatment phase are same as the weeks corresponding to the visits during the Treatment phase.

Under 'AUTO 3 Treatment & Anti-PD-1 Consolidation' and 'Follow-up' phases all visits will be reported as per database, depending on which protocol version was followed when the assessment was performed.

Note: Visits from 'Safety and Survival Follow-up' phase are captured as unscheduled visits.

- **Unscheduled visit / repeat assessments /disease assessment visits**: Data obtained at unscheduled or repeat assessments will be included in time to event analyses, baseline determination and anti-tumor effect. All other data from unscheduled or repeat assessment will not be included in summaries but only be presented in data listings, if not otherwise specified.
- Data collected during re-treatment will only be listed, if not otherwise specified.
- **N:** The number of patients in the specified population and cohort.
- **Treatment presentation:** Generally, data will be summarized separately for all data available, unless otherwise specified. The summaries will be presented as follows:
    - 50x10^6 (No Pem)
    - 50x10^6 (D14 Pem)
    - 150-450x10^6 (D14 Pem)
    - 150-450x10^6 (D-1 Pem) Inpatient
    - 150-450x10^6 (D-1 Pem) Outpatient
    - Overall
- **Continuous data** will be summarized using number of patients (n), mean, standard deviation (SD), median, minimum value, maximum value and number of missing data (if there are any). For time to event summaries, median, quartiles (Q1 and Q3) and corresponding 95% confidence interval (CI) for the median and quartiles will be presented.
- **Categorical data** will be summarized using n and percentage based on number of non-missing data.
    - All categories will be presented, even if no patients are counted in a particular category.
    - In case 1 or more patients have missing data for the summary, the number of missing data will be presented as a separate category, labelled accordingly as 'Missing', if not otherwise stated.
    - Counts of zero in any category will be presented without percentage.
    - All summaries percentages will be calculated using the number of patients with an assessment, unless otherwise stated.
    - For AEs, medical history, prior and concomitant medications the counts are based on single counts of patients with multiple events/treatments under same category, while the percentages are calculated using N.

- **Precision of summary statistics:**
    - Integer – Sample size (n, N) and number of missing data (if displayed);
    - One additional decimal place than reported/collected – mean, median, other percentile, confidence interval;
    - Two additional decimal places than reported/collected – standard deviation;
    - Same number of decimal places as reported/collected – minimum, maximum;
    - Percentages – one decimal place.
- **Study day, as per visit schedule is** calculated with reference to first AUTO3 infusion date as Day 0 for consistency with the protocol. **This study day is not used for TFLs.**
- **Study day, for inclusion in CDISC compliant datasets and TFLs will** be calculated with reference to first AUTO3 infusion date as Day 1. It will be included in CDISC compliant datasets only and will be **displayed in TFLs.** This will be calculated as (assessment date – date of first AUTO3 infusion) +1 if it's on or after first date of AUTO3 infusion, or (assessment date – date of first AUTO3 infusion) if it is prior to AUTO3 infusion.
- **DLT period:** 28 days after the infusion of AUTO3 or at least 14 days after the first dose of pembrolizumab, if administration of first pembrolizumab dose is delayed beyond Day 14.
- Data will be presented in listings by cohort. The order will be subject ID, visit, assessment date/time and assessment type/parameters (in order collected on e-CRF, unless otherwise specified). In case of clinical laboratory results, the listings will be presented in order cohort/group, subject ID, parameter, assessment date/time, visit.
- Dates will be presented in format YYYY-MM-DD.
- Version 5.0 of the NCI-CTC grading criteria (CTCAE v5) will be used for relevant tables.
- Latest version of the Medical Dictionary for Regulatory Activities (MedDRA) will be used for relevant tables. The version will be documented in the footnote of the corresponding TFLs.
- Latest version of the WHO-DD/DDE dictionary will be used for prior and concomitant medication coding. The version will be documented in the footnote of the corresponding TFLs.
- File naming: Each TFL output file will be named with a t, l or f to denote the output type and then according to its table numbering.

7 Analysis Sets

7.1 ANALYSIS SETS

Screened set

The screened set will consist of all patients who have signed informed consent and were screened in the study.

Safety set

All patients who received at least 1 dose of AUTO3 therapy will be included in the safety set.

Infused set

All patients who received at least 1 dose of AUTO3 therapy will be included in the infused set. This is the same as the safety set.

Evaluable set

All patients who received at least 1 dose of AUTO3 therapy and had FDG PET scan positive disease prior to pre-conditioning.

7.2 PROTOCOL DEVIATIONS

The full list of types of protocol deviations (PDvs) and their relation to the analysis sets, along with the method of identification of each protocol deviation, are detailed in the protocol deviation criteria form which is separate to this SAP. This will be used as a basis for identifying patients with protocol deviations throughout the study.

Protocol deviations noted during the trial will be tracked throughout the study by Autolus. The PDvs will be read into SAS® prior to reporting.

Prior to database lock, PDvs will be reviewed and agreement of the final analysis populations made.

Important protocol deviations will be summarized by deviation category on the Screened set. A listing of all confirmed reported protocol deviations (with both Important PD = Yes or No) by patient will also be provided along with the deviation category, verbatim term and deviation

date.

8 Methods of Analyses and Presentations

8.1 PATIENT DISPOSITION

The patient disposition summaries will be presented on overall group using the Screened set.

The summary of patient disposition will be showing the number and percentages of patients belonging to the following categories:

- Discontinued before leukapheresis (and reasons)
- Leukapheresed
    - Discontinuation prior AUTO3 infusion (and reasons)
    - AUTO3 infused

Patients in analysis populations will be summarized.

Information on analysis populations, study completion and discontinuation will also be displayed in patient listings.

8.2 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

The following demographic and baseline characteristics will be summarized on the Infused set:

- Age;
- Age group (<65 years, ≥65 years);
- Gender;
- Race;
- Ethnicity;
- Weight;
- ECOG performance at study entry.

Also, the following lymphoma disease characteristics will be summarized, on the Infused set:

- Current lymphoma subtype:
  - Current stage of lymphoma;
  - Current lymphoma subtype;
- Relapsed and/or refractory disease.
- International Prognostic Index (IPI).
- Extranodal disease at baseline.
- Molecular Subtype [Note: This will be available for the patients consented to the study under Protocol amendment 7 (onward)].
- Sum of product of perpendicular (SPD) diameters prior to pre-conditioning.
- Lactate dehydrogenase (LDH) prior to pre-conditioning.

Listings of all demographic and baseline characteristics data will be produced.

8.3 PRIOR LYMPHOMA THERAPIES

Listings of all prior lymphoma therapies and medications along with best response result will be produced. A separate listing with prior lymphoma radiotherapy will be presented. In addition, a listing containing prior stem cell transplant (SCT) details will be also presented.

The following summaries will be presented on the Infused set:

- Lines of therapies (summarized through summary statistics and number and percentages of patients with 1, 2, 3, 4, >=5 lines)
- Number and percentages of patients with prior SCT.

8.4 MEDICAL HISTORY

Medical histories and concomitant diseases will be coded using MedDRA. Summaries of patient medical histories and concomitant diseases will be produced on the Infused set, by system organ class and MedDRA preferred term by cohort and overall.

Listing of medical history will be produced. Also, a separate listing presenting surgical and medical procedures will be provided.

8.5 PRIOR AND CONCOMITANT MEDICATIONS

Medications other than the study treatment (including leukapheresis related medications, pre-conditioning related medications and AUTO3 related medications) will be coded using the WHO-DD/DDE dictionary. Medications will be defined as follows:

- Prior Medication: Any medication whose medication start date is before the first AUTO3 infusion date.
- Concomitant Medication: Any medication whose medication start or end date is either the same as or after the first AUTO3 infusion date.

Any medication with a missing medication end date will be assumed to be concomitant medication. Also, ongoing medications are considered as concomitant medications. A medication can be both a prior and a concomitant medication.

Summaries of prior medications and concomitant medications will be produced by ATC class and preferred term on the Infused set.

Medications defined as both prior and concomitant will appear in both tables.

In addition, a listing of prior and concomitant medications will be presented.

8.6 BRIDGING THERAPIES AND NEW ANTI-CANCER THERAPIES

Bridging therapies (therapies between informed consent up to AUTO3 dosing) and new anti-cancer treatment (anti-cancer medications or new anti-cancer radiotherapy) post AUTO3 infusion will be presented in separate listings.

Bridging therapies will be summarized by ATC class and preferred term on the Infused set.

8.7 IMMUNOGLOBULIN THERAPIES

Intravenous immunoglobulin therapy (IVIG) can also be administered to the patients, if needed.

Immunoglobulin administration details will be presented in a listing.

8.8 LEUKAPHERESIS

A listing of leukapheresis details will be presented. Leukapheresis related medications will be presented and summarized with the prior and concomitant medications.

8.9 LYMPHOMA B-SYMPTOMS

The lymphoma B-symptoms at baseline (Screening) and at post-treatment visits will be listed on the Screened set.

8.10 STUDY TREATMENT

Pre-Conditioning: Fludarabine and Cyclophosphamide

The number and percentage of patients who received at least one dose of the pre-conditioning regimen will be summarized by medication received in the Safety set. Duration of exposure (days) will also be summarized.

A listing of pre-conditioning treatment administration with Fludarabine and Cyclophosphamide will be presented.

Study treatment: AUTO3

Days from leukapheresis to first AUTO3 infusion will be calculated as [(Date of first AUTO3 treatment – Date of last leukapheresis) + 1] and summarized.

For AUTO3 infusion exposure summary statistics will be presented for the following:

- Number of patients treated with AUTO3;
- Number of patients re-treated with AUTO3;
- Number of cells administered to the patient.

Details of AUTO3 infusion administration and treatment exposure, including re-treatment details will be listed.

Consolidation Treatment: Pembrolizumab

A listing of anti-PD-1 consolidation treatment administration with pembrolizumab (Regimen A and Regimen B) will be presented.

8.11 FOLLOW-UP TIMES

Follow-up time will be calculated for each patient using the following formula:

Follow-up time (months) = [(Date of last follow-up visit when patient was known alive (or date of death (if applicable)) – Date of first AUTO3 treatment) + 1]/ 30.4375 days

Time from first AUTO3 treatment to data extraction or LPLV (as applicable) and time from leukapheresis to first AUTO3 treatment will be presented.

Follow-up times will be summarized on the Infused set.

8.12 EFFICACY DATA ENDPOINTS AND ANALYSES

Disease evaluation will be performed to assess disease status at end of DLT period (Day 28), Month 3, Month 6, Month 9, Month 12, and yearly until end of study. Note, the baseline assessment should be performed within 35 days of starting pre-conditioning (approximately 40 days before receiving AUTO3). Patients receiving bridging therapy should have the baseline disease assessment after the bridging therapy is completed and prior to starting pre-conditioning. All post-baseline response assessments will be considered for the analyses (unless otherwise stated).

In Phase I disease response will be assessed by investigators.

All time to event efficacy endpoints defined in section 8.12.2 will be calculated in days and converted to months considering the following conversion: 1 month = 30.4375 days.

Efficacy data will be summarized on the Infused set, unless otherwise specified.

A listing will be provided detailing the disease status, response and progression for each patient at each visit. Disease assessment will be listed. Also, all efficacy endpoints defined as below will be listed.

8.12.1 Primary Efficacy Endpoint and Analyses

8.12.1.1 Anti-tumour effect of AUTO3

Primary efficacy analysis is based on whether a patients achieved an objective response post AUTO3 infusion. An objective response is defined as a complete response (CR) or partial response (PR) post AUTO3 infusion.

The best overall response (BOR) is the first best response (CR>PR>SD>PD>NE)* recorded from

the first post-baseline (post-AUTO3 infusion) assessment until end of study, as assessed by the investigators.

*CR=Complete response, PR=Partial response, SD=Stable disease, PD=Progressive disease, NE=Not evaluable.

Patients who do not have any post-baseline assessments will be classified as having BOR of Not evaluable (NE).

Best overall response post-AUTO3 infusion will be summarized by presenting the number and percentages of patients with each type of best overall response assessed from all assessments post-AUTO3 infusion. The overall response rate will be presented. This is defined as the numbers of responders (CR and PR) out of the number of patients treated with AUTO3.

In summary, the following counts will be presented:

- Number of responders [objective response]: CR+PR.
- Number of patients by each response: CR, PR, SD, PD, NE

The percentage calculation will be based on N.

BOR will be presented on the Evaluable set.

8.12.2 Secondary Efficacy Endpoints and Analyses

8.12.2.1 Duration of response

Duration of response (DOR) is defined as the time from the first observed CR or PR [from the first post-baseline response assessment] until the date of first progressive disease or death due to underlying cancer (primary reason for death=progressive disease), whichever occurs first. Only responders (patients with BOR of CR or PR) will be included in the analysis of duration of response.

Patients with death not due to underling cancer (primary reason for death=AE or Other or Unknown) or who received new anti-cancer therapy other than SCT or discontinued from the study for other reason than PD or who are lost to follow-up or reach the time point of analysis without a known record of progression or death will have the duration of response censored at the date of last adequate disease assessment for response.

Patients who received a new SCT will be censored at the start date of this new date of SCT, if the

patients have not already had disease progression recorded.

Estimates of the survival function for DOR (median [95% CI], Q1 [95% CI] and Q3 [95% CI]) will be obtained using the Kaplan-Meier method. The CI for the median will be calculated using the Brookmeyer and Crowley method. The survival function and associated 95% CI at relevant timepoints will also be presented. The CI will be obtained using the Kaplan-Meier method and a log-log transformation for CI (SAS PROC LIFETEST CONFTYPE=LOGLOG). The final choice of the time points presented in the life table might be updated dependent upon the data at the time of the analysis. DOR will also be presented graphically. DOR will be listed.

8.12.2.2 Progression-Free Survival

The progression-free survival (PFS) is defined as the time from first AUTO3 treatment until the first progression of disease or death from any cause, whichever occurs first.

Patients who reach the time point of analysis without a known record of progression will have the PFS censored at the date of last adequate disease assessment.

Patients who received a new SCT will be censored at the start date of this new SCT.

Patients who received a new anti-cancer therapy or discontinued from the study for other reason than PD and who are lost to follow-up will be censored at the date of last adequate disease assessment.

For patients with no post-baseline disease assessments a censored PFS at day 1 will be considered.

Estimates for the survival function for PFS will be summarized and presented graphically, similarly as the DOR. Also, PFS will be listed.

Swimmer plot of PFS will be presented.

8.12.2.3 Overall Survival

Overall survival (OS) is defined as the time from the date of first AUTO3 treatment up to the date of death, regardless of cause of death.

Patients alive at the time of the analysis will have the OS censored at the date of last assessment when the patient was known alive.

Date of last assessment patient is known alive will be determined based on vital sign, laboratory (hematology and biochemistry), immunoglobulin, lesions (target, non-target, new), blood samples (cytokines, PK, PD, biomarker), adverse events, concomitant medications and ECOG assessments. For patients in the follow-up period, date of last assessment is based also on date of last contact when patient was known alive (e.g. last contact could be telephone contact).

For patients with no post-baseline assessments a censored OS at day 1 will be considered.

Estimates for the survival function for OS will be summarized and presented graphically similarly as the DOR. OS will be listed.

8.12.2.4 Biomarker expression of PD-L1, CD19 and CD22

CD19 and/or CD22 relapse analysis will be covered in PK/PD SAP, outside of this SAP.

8.12.3 Exploratory Efficacy Endpoints and Analyses

8.12.3.1 Time course and magnitude of cytokine release

Individual spaghetti plots for the cytokine levels will be presented over time by treatment groups for each patient for each parameter. Boxplot of peak cytokine level per patient will be also presented per treatment group.

8.12.4 Additional Efficacy and Biomarker Assessments

The following measurements are essential in establishing the clinical efficacy of AUTO3 and associated response on which the primary and secondary efficacy endpoints are based, as described in section 8.12.1 and section 8.12.2.

The following assessments will be listed:

- Immunoglobulin results: IgG, IgA, IgM;
-
- Flow cytometry for B cells as assessed at specific timepoints to characterize the duration of B cell aplasia;
- RCR testing and insertional mutagenesis.

8.12.5 Subgroup Analysis

Not applicable.

8.13 PHARMACODYNAMIC AND PHARMACOKINETIC ENDPOINTS AND ANALYSES

All pharmacokinetics and pharmacodynamic analysis will be performed by Sponsor.

8.14 QUALITY OF LIFE OR PHARMACOECONOMIC ENDPOINTS AND ANALYSES

Not applicable.

8.15 SAFETY DATA ENDPOINTS AND ANALYSES

8.15.1 Adverse Events (AEs)

Adverse events will be coded using the MedDRA coding system. The version of the dictionary will be provided in the adverse events TFLs footnotes.

AUTO3 TEAE is defined as any AE with onset during the post AUTO3 infusion period.

AEs that are considered related to Cyclophosphamide, Fludarabine, pembrolizumab and/or AUTO3 treatment (possibly, probably, or definitely related) will be collected accordingly on the eCRF.

Any AE that is present at baseline but worsens in intensity after the first dose of study treatment should be entered into the eCRF as a different AE record with the differing grade recorded.

The number and percentage of patients will be summarized by System Organ Class (SOC) and Preferred Term (PT) by all grades (1-5) and grade >=3. Patients will be counted only once within each SOC and PT by dose level. SOCs will be sorted by alphabetical order of frequency for each

group, PTs will be sorted by descending order of frequency for each group within each SOC. The following summaries will be presented:

- AUTO3-TEAEs, within 75 days (i.e. occurring on study days 1 through 75) and anytime post infusion
- AUTO3-TEAEs, related to AUTO3 treatment, within 75 days and anytime post infusion
- AUTO3-TEAEs, specific AEs (i.e. Neutropenia or Neutrophil count decreased, Thrombocytopenia or Platelet count decreased, Anemia or Hemoglobin count decreased, Infections (including all SOC Infections and infestations)) within 30 days, within 75 days and anytime post infusion
- CRS
- Neurotoxicity [(Protocol amendments 1-7)]
- Serious AUTO3-TEAEs, within 75 days, and anytime post infusion
- Non-serious AUTO3-TEAEs, within 75 days and anytime post infusion
- Fatal TEAEs (i.e. grade 5 toxicity TEAEs), within 30 days (i.e. occurring on study days 1 through 30) and anytime post infusion

In addition, the number and percentage of patients will be summarized by Preferred Term (PT) by all grades (1-5) and by grade >=3. Patients will be counted only once within each PT by dose level. PTs will be sorted by descending order of frequency for the overall group. The following summaries will be presented within 75 days and any time post infusion:

- AUTO3 TEAEs
- AUTO3-TEAEs, related to AUTO3 treatment
- Serious AUTO3-TEAEs
- Non-serious AUTO3-TEAEs

All summaries will be presented on the Safety set.

All information on AEs will be listed. A separate listing of SAEs will be provided.

8.15.1.1 CRS AEs

The number and percentage of patients with CRS events along with the maximum CRS grade will be summarized.

Time to onset of the first CRS event post AUTO3 infusion, defined as the time from first AUTO3 infusion until the date of first CRS event, will be presented.

Similarly, time to onset for the first Grade 3 or above CRS will be presented.

Duration of CRS events (days), systemic anti-cytokine therapy given, time to first ICU admission (days), duration of ICU stay (days), highest temperature of fever, hypotension that required intervention, hypoxia that required supplemental oxygen, any other symptoms and whether patient dialyzed will be presented.

Listing of CRS information will be provided.

8.15.1.2 ICANS AEs (Protocol amendment 8 onwards)

Listing of ICANS information will be provided.

8.15.1.3 Neurotoxicity AEs (Protocol amendments 1-7)

Similar summaries as the summary for TEAEs by SOC and PT will be presented also for neurotoxicity TEAEs. Data will also be listed.

8.15.2 Clinical Laboratory Evaluations

Laboratory results for all haematology, coagulation and biochemistry (including serum ferritin) parameters will be listed in separate listings.

In addition, infectious disease screen results will be presented in a listing.

A listing containing the pregnancy test results will also be presented.

8.15.3 12-lead Electrocardiogram (ECG)

ECG will be performed during screening and at pre-conditioning phase (Day -6) and will be repeated if clinically indicated. The heart rate, PR, RR, QT intervals, QRS duration, corrected QT intervals and an overall interpretation will be collected.

All ECG assessment measurements will be listed.

8.15.4 Echocardiogram (ECHO) or Multiple Gated Acquisition (MUGA)

ECHO or MUGA will be performed during screening and will be repeated if patient experiences

CRS or if clinically indicated. Generally, for a patient, the same procedure method (ECHO or MUGA) should be used throughout the study to allow for direct comparisons. The ECHO and MUGA will include an evaluation for left ventricular ejection fraction (LVEF).

All LVEF results from ECHO and MUGA assessment results will be listed.

8.15.5 Vital Signs

Temperature, systolic and diastolic blood pressure, pulse/heart rate, respiratory rate and oxygen saturation will be recorded. Blood pressure and pulse/heart rate measurements should be recorded with the patient in a seated position or supine. On Day 1, vital signs will be recorded immediately prior to AUTO3 infusion and every 30 mins (± 10 mins) for 4 hours post AUTO3 infusion, but no less than once a day.

All vital signs measurements will be listed.

8.15.6 Physical and Neurological Examination

A complete physical examination will be conducted at screening including a complete neurological examination. Also, physical and neurological examination will be conducted at subsequent visits during treatment and follow-up phases. Any detected abnormalities will be recorded as medical history (abnormalities noted before AUTO3 infusion) or adverse events (abnormalities noted after AUTO3 infusion) and will be summarized and listed as described in section 8.4 or section 8.15.1, respectively. No separate listing of physical and neurological examination data will be considered.

8.15.7 Eastern Cooperative Oncology Group (ECOG) Performance Status

All ECOG performance assessments will be listed.

8.15.8 Death information

The number and percentage of deaths and the primary reason for death, within 30 days and anytime post infusion will be presented on the Safety set.

All patients who died and their reason for death will also be listed.

8.15.9 Hospitalisation information

Listings of hospitalisation information and health encounters will be provided.

8.15.10 Subsequent therapies

Anti-cancer medications and therapies received post AUTO3 infusion will be listed.

9 Interim Analyses

Given the premature termination of the study, the interim analyses initially planned will not be performed.

10 Development safety update report

A development safety update report (DSUR) will include safety data. DSUR is intended to serve as an annual report to regulatory authorities at the DSUR anniversary of the study. DSUR anniversary is the date of first authorization anywhere in the world. DSUR shells will be created in a separate document.

11 Changes to Planned Analyses

The following are changes to the planned analyses from that stated in the protocol (Version 10.0):

- See section 6.1 – Termination of the study – based on this, the planned Interim analyses and Phase II analyses in the protocol will not be performed.
- Censoring of patients receiving a new anti-cancer treatment will be applied for the analysis of progression-free survival, in addition of the other censoring rules.
- Enrolled set is not being defined or used in the planned analysis.
- Efficacy analysis set is not being defined or used in the planned analysis. Instead,

evaluable set will be used for all the efficacy analyses.

- Decisions following SEC8 meeting (CMED delivery 20200129_SEC9)
  - Declare 150x10^6 to 450x10^6 AUTO3 Regimen B as the recommended Phase 2 doses/range
  - 900x10^6 (Regimen A): Will not open, no longer applicable.
  - 900x10^6 (Regimen B): Will not open, no longer applicable
  - RP2D Cohort: All subjects after SEC9 meeting (planned Cmed delivery SEC10) when RP2D were declared
  - RP2D Outpatient Cohort: To be introduced in the up-coming Protocol Amendment 9

12 Document History

Date	Version	Modified by	Brief details of changes made to template
21Dec2023	1.0	[redacted]	Initial final version of SAP

13 References

[1] Simon R. (1989) Optimal two-stage designs for phase II clinical trials. Control Clin Trials 10(1):1-10.

[2] Skolnik JM, Barrett JS, Jayaraman B, Patel D, Adamson PC. (2008) Shortening the timeline of pediatric phase I trials: the rolling six design. J Clin Oncol 26(2):190-5.

[3] (CTCAE v4)

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

[4] Cheson, BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. (2014). Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol **32**(27):3059-3068.

14 Appendices

14.1 APPENDIX A – Study assessments

Below schedules of assessments can be found in Protocol v10:

- Assessments from Screening to End of Treatment Phase
- Efficacy and Safety Follow-up
- Safety and Survival Follow-up

14.2 APPENDIX B – Lugano Classification (Cheson et.al 2014)

Patients with NHL will be evaluated using response criteria for Non-Hodgkin Lymphoma for Documenting Disease Response.

Response	Site	PET-CT-Based Response	CT-Based Response
Complete		***Complete***	***Complete radiologic response (all of the following)***

	Lymph nodes and extralymphatic sites	Score 1, 2, or 3[a] with or without a residual mass on 5PS[b] It is recognised that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g. with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤1.5 cm in the longest transverse diameter of the lesion (LDi). No extralymphatic sites of disease
	Non-measured lesion	Not applicable	Absent
	Organ enlargement	Not applicable	Regress to normal
	New lesions	None	None
	Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial		***Partial metabolic response***	***Partial remission (all of the following)***

	Lymph nodes and extralymphatic sites	Score 4 or 5b with reduced uptake compared with baseline and residual mass(es) of any size. At interim, these findings suggest responding disease. At end of treatment, these findings indicate residual disease.	≥50% decrease in sum of the product of the perpendicular diameters for multiple lesions (SPD) of up to 6 target measurable nodes and extranodal sites. When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value. When no longer visible, 0 × 0 mm For a node >5 mm × 5 mm, but smaller than normal, use actual measurement for calculation.
	Non-measured lesion	Not applicable	Absent/normal, regressed, but no increase
	Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
	New lesions	None	None
	Bone Marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	Not applicable
No response or		***No metabolic response***	***Stable disease***

stable disease			
	Lymph nodes and extralymphatic sites	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met.
	Non-measured lesion	Not applicable	No increase consistent with progression
	Organ enlargement	Not applicable	No increase consistent with progression
	New lesions	None	None
	Bone marrow	No change from baseline	Not applicable
Progressive disease		***Progressive metabolic disease***	***Progressive disease requires at least 1 of the following:***
	Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	Cross product of the LDi and perpendicular diameter (PPD) progression (as defined below for extranodal lesions).
	Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi >1.5 cm, and increase by ≥50% from PPD nadir, and an increase in LDi or SDi from nadir: 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (e.g. a 15 cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly
	Non-measured	None	New or clear progression of pre-existing non-measured

	lesions		lesions
	New lesions	New FDG-avid foci consistent with lymphoma rather than another aetiology (e.g. infection, inflammation). If uncertain regarding aetiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis. A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, itspresence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
	Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

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

- A score of 3 in many subjects indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g. liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation.
  Non-measured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability, but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g. GI tract, liver, bone marrow), fluorodeoxyglucose uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g. with marrow activation as a result of chemotherapy or myeloid growth factors).
- PET 5PS: 1, no uptake above background; 2, uptake ≤mediastinum; 3, uptake >mediastinum but ≤liver; 4, uptake moderately >liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma

14.3 APPENDIX C – Clinical Laboratory Tests Performed by Local Laboratory

Assessment	Description
Haematology	Haemoglobin, red blood cell count, platelet count, white blood cell (WBC)count with differential (neutrophils, eosinophils, lymphocytes, monocytes, and basophils).
Coagulation	Prothrombin time, international normalised ratio, activated partial thromboplastin time, fibrinogen.
Biochemistry	Sodium, phosphate, potassium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), uric acid, urea, creatinine, creatine phosphokinase (CPK), lactate dehydrogenase, total bilirubin, calcium, albumin. All tests must be performed prior to AUTO3 infusion on Day 0.
Ferritin, C-reactive protein	Ferritin, C-reactive protein.
Pregnancy test	Serum (β-human chorionic gonadotropin) or urine pregnancy testing for females of childbearing potential.
Serology (at screening only)	• HIV antibody. • Hepatitis B core antibody: if positive, further testing (deoxyribonucleic acid [DNA] by PCR) to rule out active disease or chronic carrier. Must be confirmed negative prior to screening. • Hepatitis C virus antibody: if positive for hepatitis C virus, further testing (by ribonucleic acid PCR) should be performed to rule out active infection. • Anti-HTLV-1. • Anti-HTLV-2. • Syphilis Serology. •

DNA = deoxyribonucleic acid; HIV = human immunodeficiency virus; HTLV = human T-cell lymphocyte virus; PCR = polymerase chain reaction.

14.4 Tables, Figures and Listing shells

A separate document was considered to cover the tables, figures and listings shells.

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