CLINICAL STUDY PROTOCOL

An Open-Label, Multi-Centre Phase I/IIa Study Evaluating the Safety and Clinical Activity of Neoantigen Reactive T cells in Patients with Advanced Non-Small Cell Lung Cancer **(CHIRON)**

Investigational Medicinal Product: ATL001

Protocol Number: ATX-NS-001

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PHASE I/IIa

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Sponsor: ACHILLES THERAPEUTICS UK LIMITED

KEY TRIAL CONTACTS

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PROTOCOL SYNOPSIS

Title	An Open-Label, Multi-Centre Phase I/IIa Study Evaluating the Safety and Clinical Activity of Neoantigen Reactive T cells in Patients with Advanced Non-Small Cell Lung Cancer
Protocol Number	ATX-NS-001
Sponsor	Achilles Therapeutics UK Limited
Development Phase	I/IIa
Investigational Product	ATL001, Autologous clonal neoantigen reactive T cells
Indication	Treatment of patients with locally advanced unresectable or metastatic NSCLC, who have received ≥ 1 prior line of standard therapy
Objective(s) and endpoints	The objectives and relevant endpoints of the study are as follows:

Objectives	Endpoints
Primary: To assess the safety and tolerability of ATL001 as a monotherapy and in combination with pembrolizumab	Frequency and severity of adverse events (AEs) and serious adverse events (SAEs) following tissue procurement and administration of lymphodepletion agents, ATL001 (monotherapy or in combination with pembrolizumab) and IL-2.
Secondary: To evaluate the clinical efficacy of ATL001 treatment as a monotherapy and in combination with pembrolizumab	• Percentage change from baseline in tumour size at 6 weeks, 12 weeks and best change from baseline. • Overall Response Rate (ORR) (based on RECIST v1.1 and imRECIST). • Time to response (based on RECIST v1.1 and imRECIST). • Duration of response (based on RECIST v1.1 and imRECIST). • Disease Control Rate (CR + PR + durable SD) (based on RECIST v1.1). • Progression free survival (PFS) (based on RECIST v1.1 and imRECIST). • Overall survival (OS).
Exploratory:	

1. To evaluate the persistence, phenotype and functionality of cNeT and to explore possible relationships with clinical outcomes	Measures of numbers, phenotype and functionality of immune cells in starting materials, product intermediates and ATL001 product. Measures of the persistence, phenotype and functionality of infused T cells in the peripheral blood.
2. To evaluate potential biomarkers of clinical activity and factors affecting response	Changes from baseline in bespoke clonal and subclonal mutation/neoantigen specific circulating tumour DNA (ctDNA) panels. Potential factors affecting response to be explored include but are not limited to: patient factors e.g. previous therapies; tumour biology factors e.g. total tumour mutation burden at baseline, tumour T cell infiltrate, major histocompatibility complex (MHC) expression and loss of heterozygosity (LOH-HLA), tumour expression of PD-L1 and other immune checkpoint proteins, Lung Immune Prognostic Score and primary vs acquired resistance to a PD-1/PD-L1 inhibitor; product factors e.g. cNeT dose; cNeT engraftment.
3. To evaluate the manufacturing rate and factors that may affect the quality of ATL001	Number of products made from procured samples. Reasons for not manufacturing products. Potential factors affecting ATL001 quality include but are not limited to: patient factors e.g. previous therapies; procurement sample quality; tumour biology factors e.g. PD-L1 expression and TIL phenotype.
4. To evaluate the utility of a bespoke plasma ctDNA assay	Changes from baseline in bespoke clonal and subclonal mutation/neoantigen specific ctDNA panels and relationship with clinical outcomes.

Study Design

This is a first-in-human, open-label multi-centre phase I/IIa study to characterise the safety and clinical activity of ATL001 (as a monotherapy and in combination with pembrolizumab) administered intravenously in up to 50 adults with non-small cell lung cancer (NSCLC).

In Cohort A, ATL001 will be given as a single dose monotherapy with non-myeloablative chemotherapy and low dose IL-2.

In Cohort B, ATL001 will be given as a single dose monotherapy with non-myeloablative chemotherapy and low dose IL-2 in combination with one dose of pembrolizumab between days -13 and -7 before receiving ATL001. Pembrolizumab will then re-start 3 weeks after receiving ATL001 (provided any immune-related adverse events have resolved at that time). Patients will then continue pembrolizumab, if tolerated, for up to 12 months, up to 6 months

	following a complete response (CR) or until RECIST v1.1 confirmed disease progression, whichever is sooner. See Section 2 for full details. In Cohort C, ATL001 will be given as a single dose monotherapy with non-myeloablative chemotherapy followed by high dose IL-2 (up to 6 doses of intravenous IL-2). The study will be considered to have proceeded from Phase I to Phase II following an Independent Data Safety Monitoring Committee (IDSMC) review of the first six patients on this study, provided that the IDSMC agrees that the study can proceed without modification.
Number of Patients	Approximately 50 patients will be enrolled for treatment. Cohort A (monotherapy): A minimum of 20 evaluable patients. Cohort B (combination with pembrolizumab): Up to approximately 20 evaluable patients. Cohort C (monotherapy with higher dose IL-2): Up to approximately 20 evaluable patients. Additional patients may be enrolled if considered appropriate to further explore clinical activity in a subgroup of patients. An interim analysis is planned in this study, after which the protocol may be amended to increase the sample size by approximately 100 patients to further explore clinical activity.
Study Duration	Each patient who receives ATL001 will be followed up for 24 months, to withdrawal of consent or death, following the infusion of ATL001. Patients will continue to be followed up for a minimum of 5 years, as part of a separate Long Term Follow Up Protocol, or, if the separate protocol is not available at the study site, within this protocol. Once the final patient has completed or withdrawn from this study, this protocol will close. If the sample size is increased, the protocol will be amended, and timelines revised.
Study Population	To be eligible to participate in this study, eligibility criteria will apply at two timepoints: at study entry prior to procurement of tumour and blood for manufacture of ATL001, and then prior to lymphodepletion for treatment with ATL001. **Inclusion Criteria:** 1. Patient must be between 18 and 75 years old at the screening visit. 2. Patient must have given written informed consent to participate in the study. 3. Patients must have histologically confirmed diagnosis of non-small cell lung cancer that is considered to be smoking-related. 4. Patient is considered medically fit enough to undergo all study procedures and interventions: procedures to procure blood and tumour

tissue, including a general anaesthetic if required, and to receive fludarabine, cyclophosphamide and IL-2 at protocol doses and schedules.

5. Patient is considered, in the opinion of the Investigator, capable of adhering to the protocol.
6. Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1.
7. Adequate organ function indicated by the following laboratory parameters:
    a. Haemoglobin ≥ 10.0 g/dL.
    b. White Blood Cell Count (WBC) ≥ 3.0 x10⁹/L.
    c. Absolute Neutrophil Count (ANC) ≥ 1.5 x10⁹/L (without support of filgrastim (G-CSF)).
    d. Platelets ≥ 100 x10⁹/L.
    e. INR/PT and APTR/APTT < 1.5x ULN, unless receiving therapeutic anticoagulation. Investigator discretion is required to ensure surgery is safe or that anticoagulants can be safely stopped.
    f. AST or ALT ≤ 2.5x ULN.
    g. Bilirubin < 1.5x ULN (< 3x ULN in Gilbert's Syndrome).
    h. Creatinine clearance/estimated glomerular filtration rate (GFR) ≥ 50 mL/min.
8. Female patients who are of childbearing potential must agree to use a highly effective method of contraception during the study and for at least 12 months after the ATL001 infusion. Non-sterilised male participants who intend to be sexually active with a female partner of childbearing potential must use an acceptable method of contraception from the time of screening, throughout the duration of the study and for at least 6 months after the ATL001 infusion. Refer to Appendix G for pregnancy testing requirements in Germany. See Section 4.3 for details of acceptable methods of contraception.

In addition to a re-evaluation of criteria 1-8, the following inclusion criteria must also be met prior to tissue procurement:

9. To be eligible to enter this study for **procurement**, the patient must fall into one of the following groups:
    a. Patients with advanced stage (III-IV) NSCLC who have accessible sites of disease suitable for collection of adequate tissue for ATL001 manufacture prior to starting standard treatment.
    b. Patients with advanced stage (III-IV) NSCLC who have received or are receiving standard treatments and have

accessible sites of residual disease suitable for collection of adequate tissue for ATL001 manufacture.

c. Other patients with advanced stage disease for whom no other alternative approved treatments are available, may be considered on a case-by-case basis and should be discussed with the Sponsor prior to enrolment.

10. Anticipated life expectancy ≥ 6 months at the time of tissue procurement.

In addition to a re-evaluation of criteria 1-8, the following inclusion criteria must also be met prior to lymphodepletion for treatment with ATL001:

11. Patients must have locally advanced unresectable or metastatic NSCLC and:

    a. Whose disease has progressed or recurred following standard of care. This includes patients who have received a component of standard of care therapy as part of a previous clinical trial in first line treatment; or

    b. Who are ineligible for, or who cannot tolerate, standard of care therapies. Patients who stop treatment due to immunotherapy toxicities do not need to progress in order to receive treatment with ATL001.

12. Patients must have measurable disease according to RECIST v1.1 criteria prior to lymphodepletion.

13. Patient is considered, in the opinion of the Investigator, well enough (i.e. ECOG Performance Status 0-1) to receive ATL001 treatment (This will be checked prior to lymphodepletion and again prior to receiving ATL001).

In addition to 1-13, except inclusion 11a, the following inclusion criteria must be met for patients to be eligible for treatment in Cohort B:

14. Prior to treatment with ATL001, the treatment regimen must have included a PD-1/PD-L1 inhibitor and patients should have experienced:

    a. Radiological disease progression; or

    b. Stable disease following at least 4 doses of a PD-1/PD-L1 inhibitor.

15. In addition to the need for highly effective contraception as outlined in Inclusion Criterion 8 above, female patients in Cohort B of childbearing potential must agree to use effective contraception during treatment with pembrolizumab and for at least 4 months after the last dose of pembrolizumab. Patients must also agree to provide a serum or urine pregnancy test before each pembrolizumab administration during the treatment period in Cohort B.

Exclusion Criteria:

1. Patients with known central nervous system (CNS) metastases that are untreated or symptomatic or progressing. Lesions should be clinically and radiologically stable for 2 months after treatment, as determined by MRI or CT evaluation, in line with accepted standard of care procedures, and should not require steroids.
2. Patients with hepatitis B or C, human immunodeficiency virus infection (HIV1/2), syphilis or HTLVI/II infection (see Section 6.1.1).
3. Patients who have never smoked (defined as having smoked < 100 cigarettes in their lifetime, per WHO criteria).
4. Patients for whom there is documented evidence of an actionable tumour driver oncogene mutation (EGFR, ALK or ROS-1) at the time of initial screening. Patients who have progressed on standard targeted therapies, or for whom no approved targeted treatments are available, are not excluded.
5. Patients with active, known, or suspected autoimmune disease requiring immunosuppressive treatments.
6. Patients requiring regular treatment with steroids at a dose higher than prednisolone 10 mg/day (or equivalent).
7. Patients with superior vena cava syndrome.
8. Patients with a current or recent history, as determined by the Investigator, of clinically significant, progressive, and/or uncontrolled renal, hepatic, haematological, endocrine, pulmonary, cardiac, gastroenterological or neurological disease. Additionally, the following criteria apply:
    a. Patients with a Left Ventricular Ejection Fraction (LVEF) < 45%.
    b. Patients with a history of coronary revascularization.
    c. Patients with clinically significant atrial and/or ventricular arrhythmias including but not limited to: atrial fibrillation, ventricular tachycardia, 2° or 3° heart block.
    d. Patients with a forced expiratory volume in one second (FEV1) of less than or equal to 60% of their predicted normal.
9. Patients with a history of immune mediated central nervous system toxicity that was caused by, or suspected to be caused by, immunotherapy.
10. Patients with a history of ≥ Grade 2 diarrhoea/colitis caused by previous immunotherapy within 6 months of screening. Patients that have been asymptomatic for at least 6 months or have had a normal colonoscopy post-immunotherapy (with uninflamed mucosa by visual

assessment following discontinuation of immune suppression other than permitted modified release steroids) are not excluded.

11. Patients who are pregnant or breastfeeding.
12. Patients who have undergone major surgery in the previous 3 weeks.
13. Patients with an active concurrent cancer or a history of cancer within the past 3 years (except for in situ carcinomas, early prostate cancer with normal Prostate-Specific Antigen (PSA) or non-melanomatous skin cancers).
14. Patients with a history of organ transplantation.
15. Patients who have previously received any investigational cell or gene therapies.
16. Patients with contraindications for cyclophosphamide, fludarabine and IL-2 at per protocol doses (see Investigator's Brochure for details).
17. Patients who have received any cytotoxic chemotherapy or anti-angiogenesis agent within the 3 weeks prior to tissue and blood procurement.
18. Patients with evidence of disease progression at the first scan after commencing standard first line therapy (i.e. primary refractory disease), unless responsive to subsequent lines of therapy. Patients who are refractory to pembrolizumab monotherapy are not excluded.
19. Patients with a confirmed history of allergic reactions to amphotericin b, penicillin and/or streptomycin.

In addition, the following exclusion criteria will apply for eligibility for Cohort B:

20. Patients with any contraindications for pembrolizumab (Refer to the latest available prescribing information (e.g. SmPC/Package Insert) for reference safety information for pembrolizumab).

All exclusion criteria, except 2, 3, 4 and 17, will apply again to all patients prior to lymphodepletion for treatment with ATL001.

In addition, the following criteria will apply:

21. Patients who have received a live vaccination within the 28 days prior to lymphodepletion.
22. Patients with an active infection requiring antibiotics.
23. Patients who have received any cytotoxic chemotherapy within the 3 weeks prior to lymphodepletion.

Study Product Dose, Dosing Regimen and Administration	Eligible patients will receive an intravenous infusion of ATL001, following non-myeloablative pre-conditioning treatment. The infusion should be administered as soon as possible after thawing and within 30 minutes. The active cell dose range to be administered will be 5-1000 x 10^7 $CD3^+$ cells, and a

	minimum of 20 patients with the target cell dose will be treated within each cohort. In the event that a product is manufactured for a patient but does not meet the IMP product release specifications for total $CD45^+$ or $CD3^+$ cells and/or autologous cell based impurities and/or potency, the treating Investigator may make a request for the product to be released for use by an individual patient under his/her direct responsibility following suitable assessment of the potential benefits and risks for the patient. In such cases, the patients will be treated and followed up within this protocol, according to the scheduled visits and assessments.
Pre-conditioning Treatment	Patients will receive a non-myeloablative lymphodepletion regimen of fludarabine 25 mg/m^2 i.v on each of Days -5 to -1 and cyclophosphamide 60 mg/kg i.v. on Days -5 and -4 prior to cell infusion. These can be administered according to local standard operating procedures (SOPs). For safety purposes, at least the first 3 patients will receive fludarabine 25 mg/m^2 i.v on each of Days -5 to -1 and cyclophosphamide 30 mg/kg i.v. on Days -5 and -4 prior to cell infusion.
Pre-infusion Medication	Patients will be pre-medicated with a standard regimen to prevent infusion reactions (e.g. chlorphenamine and paracetamol/acetaminophen) according to local SOPs prior to the infusion of ATL001. This prophylactic regimen should not contain corticosteroids. Patients in Cohort B will receive a dose of pembrolizumab 200 mg i.v. between days -13 and -7 prior to the infusion of ATL001.
Post-infusion	Patients in Cohort A will receive 10 doses of IL-2 1M IU/m^2 s.c. daily from days 0-9 of the study, starting between 3 and 12 hours post-infusion. Patients in Cohort B will receive IL-2 as per Cohort A with the addition of pembrolizumab starting 3 weeks post infusion and continue, if tolerated, for up to 12 months, up to 6 months following a CR or until RECIST v1.1 confirmed disease progression, whichever is sooner. See Section 2 for more details. Patients in Cohort C will receive IL-2 at a dose of 600,000 IU/kg, administered by intravenous infusion at a frequency of 8-12 hourly, starting between 3 and 24 hours post-infusion, and continued for up to a maximum of six doses as tolerated.
Safety Evaluation	Safety will be assessed by regular assessments of infusion reactions, adverse events, physical examinations, ECOG performance status, laboratory tests, vital signs, electrocardiograms, and concomitant medication usage. The severity of AEs will be assessed using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Cytokine Release Syndrome (CRS) and Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS) will be assessed using American Society for Transplantation and Cellular Therapy (ASTCT) criteria. For patients in Cohort B, AEs related to pembrolizumab will be assessed against NCI CTCAE Version 4.0, as per the SmPC/Package Insert.

	An Independent Data Safety Monitoring Committee (IDSMC) will be formed to monitor patient safety during the study. Details of IDSMC reviews and study stopping criteria are described in Section 7.8.
Efficacy Evaluation	Efficacy will be assessed by MRI/CT scans every 6 weeks to week 24 and then every 12 weeks. Efficacy will be evaluated per RECIST v1.1 criteria. Immune modified response criteria (imRECIST) will also be evaluated.
Exploratory Evaluations	Biomarker evaluation will include the following: • Engraftment, expansion, reactivity and persistence of ATL001 as determined by T cell receptor (TCR) repertoire, enzyme-linked immunospot (ELISPOT) and flow cytometry in peripheral blood. • Changes from baseline in ctDNA in blood. Manufacturing rate will be assessed: • The number of products released out of the number of patients undergoing tissue procurement will be reported. • The reasons for not manufacturing products will be reported. Factors affecting the quality of the final product will be explored including tumour characteristics, sample quality and prior therapies.
Special Study Procedures	**Tumour tissue procurement for manufacture of ATL001 (Section 6.1.1):** A surgical procedure will be necessary to acquire at least 1.5 g (1.5 cm^3) tumour tissue for assessment, T cell extraction and manufacturing of ATL001. The surgical procedures for tumour tissue procurement should be clinically relevant procedures which do not cause undue risk to patients, as determined by the Investigator, taking into consideration the risk/benefit for the patient. **Blood procurement for manufacture of ATL001 (Section 6.1.2):** A blood sample (target volume 140 mL) will be required from all patients as part of the ATL001 manufacturing procedure. Samples for infectious disease monitoring, germline DNA sequencing and human leukocyte antigen (HLA) typing will also be required as part of this process. **Additional Blood Samples:** Prior to, and following ATL001 infusion, serial blood samples will be required for monitoring of response by ctDNA, and monitoring the expansion, persistence and functionality of ATL001 cells. At week 6 an additional 150 mL blood will be required to perform an extended panel of immunological assays to aid the interpretation of the RECIST response at that time-point, unless the clinical condition of the patient precludes it (see Section 8.4). **Archival Primary Tumour Sample:** For patients with metastatic disease, access to the archived primary tumour sample may be requested for analysis of the tumour microenvironment.

	Optional tumour biopsies to assess tumour microenvironment: If a patient has a tumour that can be safely accessed, optional pre- and post-treatment tumour biopsies will be requested to assess changes in the tumour microenvironment at one or more of the following times: • Between procurement and treatment with ATL001. • Following treatment with ATL001. • At the time of disease progression. **Optional samples to be acquired from standard of care procedures:** If a patient undergoes any standard of care procedures that involve the collection of biological material deemed relevant to ATL001 treatment, at any time during the period that they are enrolled in the study, a sample may be requested for research purposes if one can be provided at no additional risk to the patient.
Statistical Considerations and Analysis	Since this is a first-in-human study, there will be no formal hypothesis testing and as such, the study has not been formally powered. The sample size has been selected to provide adequate information about the safety and efficacy of ATL001, whilst also exposing minimal numbers of patients to experimental therapy and procedures prior to an initial signal of efficacy. In Cohort A, a minimum of 20 patients will receive ATL001, at the target cell dose, following standard of care therapies. It is expected that most patients will have received a PD-1/PD-L1 inhibitor as part of this standard therapy unless patients have contraindications to these agents. The expectation is that ATL001 could achieve a response in at least 30% of patients, based on a response rate of 35% in studies of first generation TIL in patients with metastatic melanoma that has recurred following treatment with PD-1 inhibitors, and based on a response rate of 20% in studies of standard second line agents in NSCLC. Based on a sample size of 20 evaluable patients treated at the active dose (5-1000 x 10^7 $CD3^+$ cells), if the true ORR were 30%, there would be approximately a 90% probability of observing 4 or more responders out of 20 patients. Conversely, if the true response rate were only 10% there would be a 13% probability of observing 4 or more responses by chance. In Cohort B, up to 20 patients will receive at least one dose of pembrolizumab between days -13 and -7 before receiving ATL001 and will then re-start treatment with pembrolizumab 3 weeks after receiving ATL001 (provided there are no ongoing immune-related adverse events at that time). Patients will then continue pembrolizumab, if tolerated, for up to 12 months, up to 6 months following a CR or until RECIST v1.1 confirmed disease progression, whichever is sooner. The sample size of 20 patients has been selected to establish the safety, tolerability, and clinical activity of ATL001 followed by pembrolizumab, in the context of the overall safety and efficacy profile of ATL001 from Cohort A. The totality of the safety and tolerability data from the

study will contribute to decisions regarding the continuation of the combination to the next stage of development.

In Cohort C, up to 20 patients will receive ATL001 followed by higher dose IL-2 (600,000 IU/kg) administered by intravenous infusion, after standard of care therapies. IL-2 will be given 8-12 hourly and continued for up to a maximum of six doses as tolerated. The sample size of 20 patients has been selected to establish the safety, tolerability, and clinical activity of ATL001 followed by higher doses of IL-2, in the context of the overall safety and efficacy profile of ATL001 from Cohort A.

Decisions about study conduct will be made taking into consideration the totality of the safety and efficacy data for the cohort. In addition to ORR, the magnitude of tumour regression, the disease control rate and the durability of response and PFS times will also be considered.

Analysis plans are described in detail in Section 9.

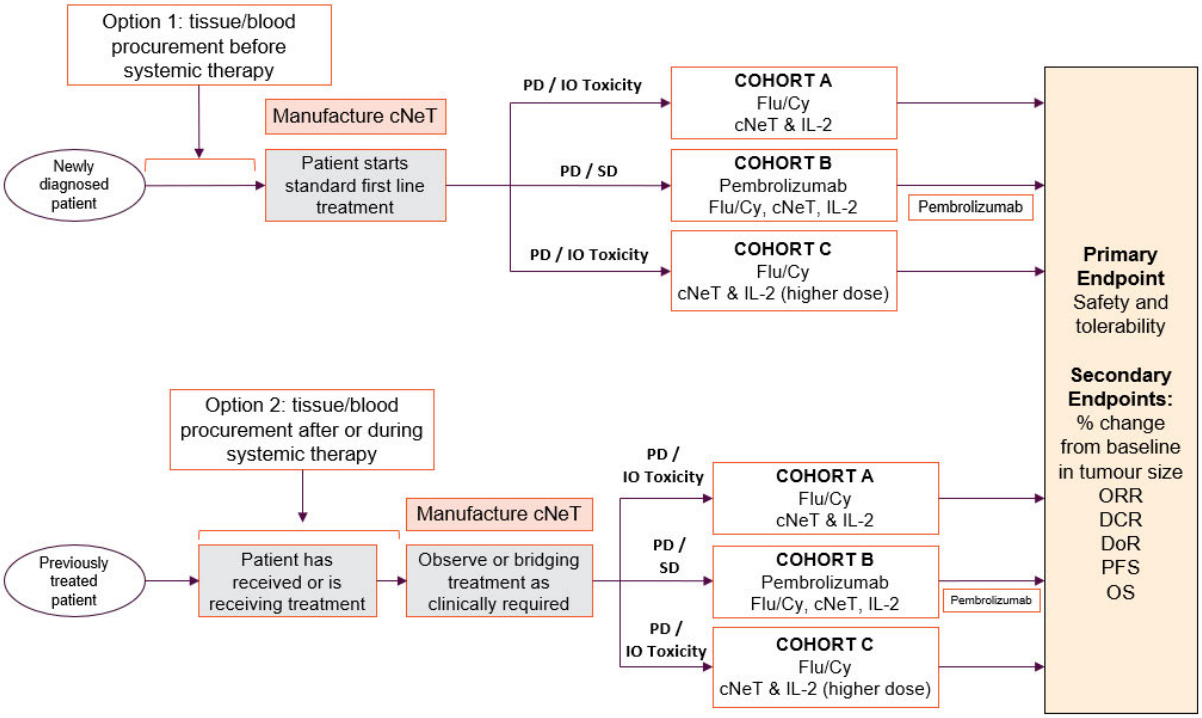
Unless otherwise stated, data from Cohorts A, B and C (if performed) will be presented separately.

The data will be summarised using descriptive statistics. Continuous variables will be summarised using the number of observations, mean, standard deviation, coefficient of variation, median, and range as appropriate. Categorical values will be summarised using the number of observations and percentages as appropriate. Time-to-event endpoints will be estimated using Kaplan-Meier methodology.

The Surgical Population will include all patients who undergo tissue procurement. The safety of the tumour and blood procurement procedures, the manufacturing rate, and the factors affecting product quality will be reported for this population and presented separately.

Data from all patients treated with ATL001 (the Treated Population) will be used for safety analyses. Exposure to fludarabine, cyclophosphamide, ATL001 and IL-2, along with reasons for discontinuation of any study drug will also be tabulated. Associations of administered cell dose with safety and efficacy outcome measures may be explored. All RECIST and imRECIST-based endpoints will be evaluated in the evaluable for response (EFR) population. Overall survival will be evaluated in the Treated Population (TP).

STUDY FLOW CHART



PATIENT SCHEMA

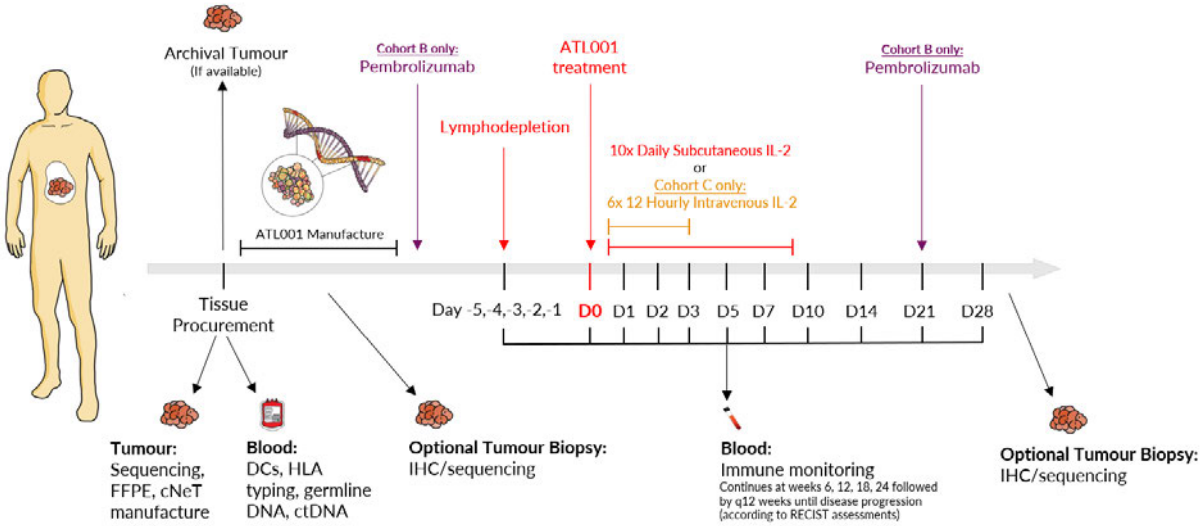


TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACT	Adoptive cell therapy
ADME	Absorption, distribution, metabolism and excretion
ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANC	Absolute neutrophil count
APTR	Activated partial thromboplastin ratio
APTT	Activated partial thromboplastin time
AST	Aspartate transaminase
ASTCT	American Society for Transplantation and Cellular Therapy
ATIMP	Advanced therapy investigational medicinal product
BOR	Best Overall Response
BP	Blood pressure
BUN	Blood Urea Nitrogen
CAR	Chimeric antigen receptor
CD3	Cluster of differentiation 3
CD45	Lymphocyte common antigen
CFR	Code of Federal Regulations
CHMP	Committee for Human Medicinal Products
CLL	Chronic lymphocytic leukaemia
CMV	Cytomegalovirus
CNS	Central nervous system
cNeT	Clonal neoantigen reactive T cell
CPI	Checkpoint inhibitor
CR	Complete Response
CRF	Case Report Form
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSP	Clinical Study Protocol
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
ctDNA	Circulating tumour DNA
Cy	Cyclophosphamide
DCO	Data cut-off
DCR	Disease Control Rate
DMSO	Dimethyl sulphoxide
DNA	Deoxyribonucleic acid
DoR	Duration of Response
EBMT	European Society for Blood and Marrow Transplantation
EBUS	Endobronchial Ultrasound
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EFR	Evaluable for Response
EGFR	Epidermal growth factor receptor
ELISPOT	Enzyme-linked immunospot
EMA	European Medicines Agency

Abbreviation	Definition
EU	European Union
FAS	Full Analysis Set
FDA	U.S. Food and Drug Administration
FEV1	Forced expiratory volume in one second
FFPE	Formalin Fixed Paraffin Embedded
Flu	Fludarabine
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GFR	Glomerular filtration rate
Hb	Haemoglobin
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HR	Hazard ratio
i.v.	Intravenous
ICANS	Immune effector Cell-Associated Neurotoxicity Syndrome
ICE	Immune effector Cell-associated Encephalopathy
ICF	Informed Consent Form
ICH	International Committee on Harmonisation
ICP	Intracranial pressure
IDM	Infectious disease marker
IDSMC	Independent Data Safety Monitoring Committee
IEC	Independent Ethics Committee
IFN	Interferon
IL	Interleukin
imBOR	imRECIST-based Best Overall Response
imDOR	imRECIST-based Duration of Response
imORR	imRECIST-based Overall Response Rate
IMP	Investigational Medicinal Product
imPFS	imRECIST-based Progression Free Survival
imRECIST	Immune modified Response evaluation criteria in Solid Tumours
imTTR	imRECIST-based Time to Response
INR	International normalised ratio
IRB	Institutional Review Board
IU	International units
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
JACIE	Joint Accreditation Committee of ISCT and EBMT
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LOH-HLA	Loss of heterozygosity of HLA
LP	Lumbar Puncture
LVEF	Left Ventricular Ejection Fraction
MCS	Microscopy, Culture and Sensitivity
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major histocompatibility complex
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NMA	Non-myeloablative
NSCLC	Non-small cell lung cancer
NTL	Non-target lesion
ORR	Overall Response Rate

Abbreviation	Definition
OS	Overall Survival
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase Chain Reaction
PD	Progressive disease
PD-1	Programmed cell death receptor-1
PD-L1	Programmed cell death ligand-1
PFS	Progression free survival
PFT	Pulmonary function test
PPEFR	Per Protocol Evaluable for Response
PR	Partial Response
PS	Performance Status
PSA	Prostate-Specific Antigen
PT	Prothrombin time
QC	Quality control
RECIST v1.1	Response Evaluation Criteria In Solid Tumours v1.1
RNA	Ribonucleic acid
RSI	Reference safety information
s.c.	Subcutaneous
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Stable disease
SEER	Surveillance, Epidemiology, and End Results
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
SP	Surgical Population
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBI	Total body irradiation
TBNK	T cell, B cell and NK cell phenotyping
TCR	T cell receptor
TFT	Thyroid function test
TIL	Tumour infiltrating lymphocyte
TMB	Tumour mutational burden
TNF	Tumour necrosis factor
TP	Treated Population
TPS	Tumour proportion score
TS	Tumour size
TTR	Time to Response
UK	United Kingdom
US	United States
ULN	Upper limit of normal
WBC	White blood cell count

1 INTRODUCTION

1.1 Background: Standard Systemic Treatments for Advanced NSCLC

Lung cancer is the most common cause of cancer-related death worldwide with over 1.6 million deaths per year. In the UK, the age standardised incidence rate of lung cancer is 72 per 100,000, with mortality estimated at 56 per 100,000 [Cancer Research UK, 2017]. The majority (75%) of patients present with inoperable large invasive tumours and/or with distant metastatic spread (Stages IIIB, IIIC and IV) at diagnosis [National Cancer Intelligence Network, 2016] and for these patients the aim is to achieve and maintain disease control to extend life. In the US, there were 228,150 estimated new cases of lung cancer in 2019, accounting for ~13% of all new cancer cases, and an estimated 142,700 deaths, accounting for 25% of all cancer deaths. The majority (79%) of patients presented with local or distant metastatic spread (Stages III and IV) at diagnosis [SEER, 2019]. For patients with advanced disease, the therapeutic aim is to achieve and maintain disease control to extend life.

Non-small cell lung cancer (NSCLC) accounts for 80% of all cases [Howlader et al, 2015], and the majority of these are adenocarcinomas. Overall the 5-year survival for operable NSCLC is approximately 50% but in patients with Stage IIIB, IIIC and IV this percentage falls to 25%, 12% and 5% respectively [Detterbeck et al, 2017].

Systemic treatment options for patients with advanced NSCLC include cytotoxic chemotherapy, targeted therapies for cancers with specific mutations, and immunotherapy with checkpoint inhibitors.

Figure 1 summarises the management of advanced NSCLC without a targetable driver mutation.

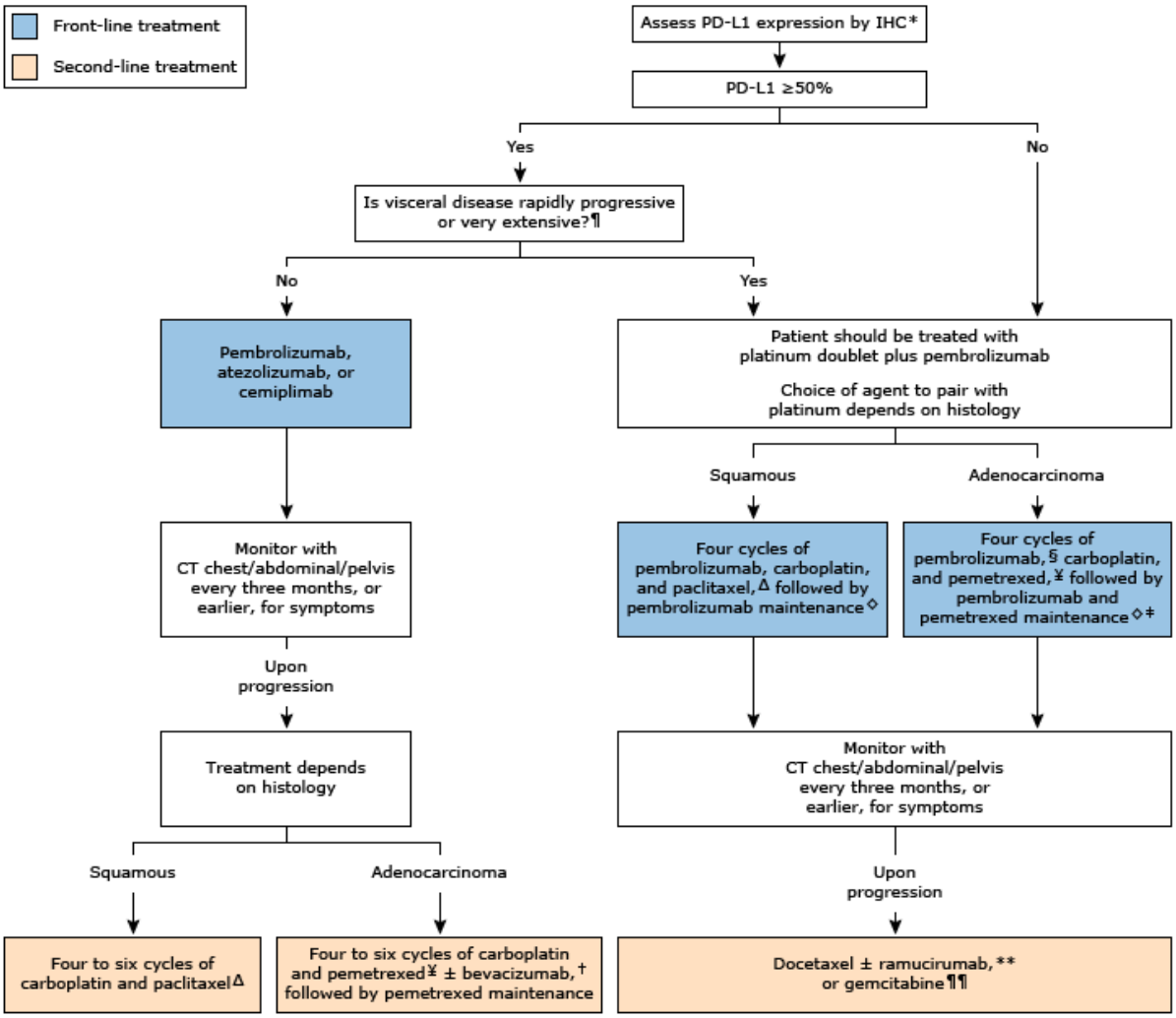


Figure 1: Management of Advanced NSCLC Without a Targetable Driver Mutation
Source: UpToDate, 2022

1.1.1 First Line Treatments

In the absence of a driver mutation, combination, platinum-based chemotherapy regimens have historically been the standard of care for most patients with newly diagnosed stage IIIB/IV or relapsed NSCLC.

Randomised trials suggest that cisplatin-based regimens are slightly more effective than carboplatin-based combinations or non-platinum regimens. Pemetrexed-cisplatin has shown superior outcomes compared to gemcitabine-cisplatin in patients with non-squamous histology, and vice versa for squamous cancers [Scagliotti et al, 2008]. First line platinum doublet chemotherapy regimens generally gave an overall response rate (ORR) of 25-35%, median time to progression of 5-6 months and median overall survival (OS) of 10-12 months [Schiller et al, 2002]. The PARAMOUNT study [Paz-Ares et al, 2012] demonstrated that pemetrexed continuation maintenance therapy reduced the risk of disease progression and death vs placebo in 939 patients with advanced non-squamous NSCLC.

A minority of NSCLC patients have detectable driver molecular aberrations in signalling pathways that can be targeted by monoclonal antibodies or tyrosine kinase inhibitors. Approximately 15% of in the US have an EGFR mutation and may be treated with erlotinib, gefitinib, afatinib or osimertinib; 4% have rearrangements in ALK or ROS-1 which are sensitive to agents such as alectinib, ceritinib, brigatinib, and 1-2% have a BRAF V600E mutation which is responsive to BRAF and MEK inhibition.

Clinical trials have demonstrated comparable or superior clinical outcomes for patients with driver mutations when treated with targeted agents, with fewer severe adverse events than chemotherapy, and targeted agents are the standard of care for these patients.

Checkpoint Inhibitors are drugs that enhance the ability of tumour infiltrating lymphocytes (TILs) to recognise and kill tumour cells. Activated cytotoxic T cells express the Programmed Cell Death Receptor 1 (PD-1), which recognises a ligand (PD-L1) that is expressed on a proportion of tumour cells and antigen presenting cells. When PD-1 binds to PD-L1, T cell anti-tumour activity is suppressed. Checkpoint inhibitors (CPIs) prevent this interaction by either binding PD-1 (e.g. nivolumab and pembrolizumab) or PD-L1 (e.g. atezolizumab, durvalumab) and in doing so they enhance the ability of TILs to recognise and kill tumour cells.

Pembrolizumab is authorised as monotherapy for the first line treatment of patients with metastatic NSCLC with high PD-L1 expression (TPS ≥ 50%) and no detectable mutation in EGFR or ALK. This group comprises approximately 25% of Stage IV patients. The recommendation was based on the KEYNOTE-024 study of pembrolizumab vs platinum-based therapy in 305 patients, with a primary endpoint of progression free survival (PFS) [Reck et al, 2016]. The median PFS on pembrolizumab was 10.3 months vs 6.0 months on chemotherapy (HR 0.5; P=<0.001) and median OS 30.0 months and 14.2 months respectively [Brahmer et al, 2017]. Pembrolizumab improved the ORR from 27.8% to 44.8% and the proportion of patients alive at 6 months was 80.2% on pembrolizumab vs 72.4% on chemotherapy. There were fewer Grade 3-5 adverse events on the pembrolizumab arm (26.6% vs 53.3%).

In recent years, the addition of checkpoint inhibitors to first line chemotherapy has been shown to improve patient outcomes. In the Phase III study of pembrolizumab plus standard platinum-based chemotherapy compared to chemotherapy alone (KEYNOTE 189) in patients with non-squamous NSCLC, the addition of pembrolizumab significantly improved the response rate (47.6% vs. 18.9%), PFS (8.8m vs 4.9m) and proportion of patients alive at 12 months (69.2% vs. 49.4%) [Gandhi et al, 2018]. Similarly in patients with squamous NSCLC, the addition of pembrolizumab to standard carboplatin plus paclitaxel/nab-paclitaxel in the Phase III KEYNOTE 407 study demonstrated statistically significant improvements in response rate (57.9% vs. 38.4%), PFS (6.4m vs. 4.8m) and OS (15.9m vs 11.3m) [Paz-Ares et al, 2018]. The benefits were statistically significant in all patients regardless of PD-L1 status but for some endpoints they were most marked in patients with high PD-L1 TPS score > 50%). The safety profile of the combinations was similar to the safety profiles of the chemotherapy regimens alone. The combination regimens were approved in the US and EU in 2018.

Similar results were reported with combinations of platinum-based chemotherapy regimens with the PD-L1 inhibitor atezolizumab in squamous and non-squamous NSCLC, which also received US and EU approvals in this indication [Jotte et al, 2018; Socinski et al, 2018].

1.1.2 Second and Later Line Treatments

CPIs in the second line treatment setting generally give an ORR of 20%, and PFS of 3.5-4 months but clear advantages over the previous standard of care, single agent docetaxel have been in demonstrated including improvements in OS and severe adverse events. Nivolumab was associated with 12.2 month median OS compared to 9.4 months on docetaxel (HR 0.73, p=0.002) in patients with non-squamous metastatic NSCLC [Borghaei et al, 2015] and 9.2 months median OS compared to 6.0 months on docetaxel (HR 0.59, p=0.0002) in patients with squamous metastatic NSCLC [Brahmer et al, 2015] while pembrolizumab demonstrated a median OS improvement of 10.4 months compared to 8.5 months on docetaxel (HR 0.71, p =0.0008) in patients with metastatic NSCLC (any histology) whose tumours expressed PD-L1 (TPS ≥ 1%) [Herbst et al, 2016]. Atezolizumab, has also demonstrated an OS

improvement compared to docetaxel in patients with metastatic NSCLC, independent of PD-L1 expression (13.8 months vs 9.6 months; HR 0.74, p=0.0004) [Rittmeyer et al, 2017].

The improvements in clinical outcomes with PD-1/PD-L1 inhibitors are significant and some patients experience long term benefit. However, notwithstanding these encouraging statistics, 45-50% of patients with metastatic NSCLC do not achieve an optimal response with the chemotherapy plus PD-1 /PD-L1 antibody combinations, and 60-70% patients experience disease progression, or die, within 12 months of starting treatment.

Existing approved 2nd line chemotherapy options include docetaxel +/- ramucirumab, docetaxel + nintendinib (not in the US), pemetrexed or gemcitabine.

1.2 Rationale for Targeting Tumour Neoantigens with Immunotherapies

Immune evasion is a hallmark of cancer, and the success of the checkpoint inhibitors demonstrates the benefit of enhancing the power of intra-tumoural T cells to attack cancers; some patients experience long-term survival benefits. It has not yet been possible to accurately predict which patients may benefit most from treatment with checkpoint inhibitors. Resistance to PD-1/PD-L1 inhibitors may be primary or acquired, and several mechanisms may contribute to both phenotypes. Primary resistance may be a result of intrinsically low antigenicity, low T cell infiltration or a failure of the T cell recognition machinery. Acquired resistance may evolve through adaptive loss of antigenicity (e.g. through loss of tumour neoantigen expression or defective surface presentation through loss of MHC) and/or recognition machinery, and/or modulation of the tumour microenvironment through treatment.

There are, however, multiple reports of positive prognostic significance of the degree of lymphocyte infiltration in lung cancer patients [Kinoshita et al, 2016; Feng et al, 2016; Zeng et al, 2016] and it is increasingly recognised that the proportion of intra-tumoural $CD8^+$ T cells recognising tumour neoantigens is an important predictor of outcome to checkpoint inhibitors [Rizvi et al, 2015].

Tumour-specific neoantigens arise from mutations that accumulate in tumours over time and have been demonstrated to elicit T cell responses within the patient. Tumours with the highest mutational burden present more tumour neoantigens to the host and appear to be more susceptible to immunotherapy [Rizvi et al, 2015; McGranahan et al, 2016]. These neoantigens are thought to be the major contributors to the clinically relevant responses that have been documented following treatment with immune-therapeutic approaches, either checkpoint inhibitors or adoptive T cell therapies in patients with melanoma [Lee & Margolin, 2012]. More recently, Iovance Biotherapeutics, Inc. have also been able to demonstrate the efficacy of targeting tumour neoantigens in patients with advanced melanoma who have limited treatment options after progression on immune checkpoint inhibitors. A total of 153 patients were treated with lifileucel following non-myeloablative lymphodepletion with an ORR of 31.4%. Of the patients that demonstrated a response, 41.7% of those responses were maintained for ≥18 months [Chesney et al, 2022a].

Antigens expressed by tumours may be tumour-specific or tumour-associated. Tumour-specific neoantigens are unique to the tumour as they arise from tumour-specific mutations, while tumour-associated antigens may be preferentially expressed by tumours but are shared by normal tissues. As cancers are collections of cells which have been exposed to multiple tumour initiating events, they include numerous sub-clones of the original tumour initiating cells. Each of these sub-clones has a different set of mutations but recent data suggest that the mutations arising from the earliest transforming mutagenic events (known as truncal or clonal mutations) are retained in all the sub-clones, and are tumour-specific, despite the acquisition of more mutations during the natural history of the tumour [Jamal-Hanjani et al, 2017]. NSCLC patients whose tumours contain large numbers of these original truncal mutations appear to have a survival benefit over those whose tumours are heavily branched [McGranahan et al, 2016], suggesting that T cell responses are more effective in these cases.

A therapeutic approach of expanding specific clonal neoantigen reactive T cells (cNeT) and treating patients with their own cell therapy product is expected to effectively increase the proportion of cNeT in tumours. As these active T cells are able to recognise the clonal neoantigens that are present in all the tumour cells, this may bring long term benefits to patients with NSCLC, either as a stand-alone treatment or in combination with checkpoint inhibitors.

1.3 Adoptive Cell Therapy

1.3.1 ACT using Autologous Tumour Infiltrating Lymphocytes

TILs have been isolated successfully from multiple solid tumours and expanded *ex vivo* for clinical trials since the first report in 1986 [Rosenberg, Speiss & Lafrenier, 1986] but clinical success to date has been largely limited to the treatment of malignant melanoma. In this setting *ex vivo* expanded TILs have achieved clinically meaningful results (ORRs of 30-50%, CR rates of 20%) and patients who achieve CR have demonstrated long term disease free survival for many years [Itzhaki et al, 2011; Hinrichs & Rosenberg, 2014; Besser et al, 2013; Dudley et al, 2013; Goff et al, 2016; Andersen et al, 2016; Ellebaek et al, 2012]. Most of these studies were initiated some years ago, before the widespread use of PD-1 inhibitors and may not all be considered clinically relevant based on current clinical practice. However, Sarnaik et al, 2019 recently presented data on the safety and efficacy of cryopreserved autologous TIL therapy (LN-144, lifileucel) in 66 advanced metastatic melanoma patients who progressed on multiple prior line of therapy including anti-PD-1 [Sarnaik et al, 2019]. In this heavily pre-treated and PD-1 resistant group, the response rate was 38% with 3% CR and 80% disease control rate (DCR). Durable responses were observed, and some responses were observed in patients with PD-1 negative tumours, suggesting that TIL-ACT may be an effective option for patients with PD-1 resistant cancers or cancers with lower immunogenicity.

Refer to Section 1.4.2 for additional information.

1.3.2 ACT using Genetically Modified T cells

Genetic engineering advances have facilitated the development of ACT by T cells that can recognise specific tumour antigens. One approach is to transduce specific T cell receptors into T cells [Morgan et al, 2006]. The most successful approach, however, has been the development of chimeric antigen receptor (CAR) T-cell therapy, whereby T cells are isolated from a patient's blood and undergo *ex vivo* expansion followed by genetic engineering to express CAR molecules and are then re-infused. In a CAR, the ligand-binding domain is derived from the single chain variable fragment of a monoclonal antibody which recognises a specific tumour antigen in a non-HLA restricted context. In 2017, the FDA approved two CD19-targeted CAR T-cells, tisagenlecleucel and axicabtagene ciloleucel, based on unprecedented efficacy in refractory B cell haematological malignancies. In one trial of 101 patients with refractory B-cell lymphoma, 82% patients achieved an objective response, and 54% had a complete response [Neelapu et al, 2017]; in another trial of 75 patients with relapsed or refractory B-cell acute lymphoblastic leukaemia, an ORR of 81% was seen [Maude et al, 2018] and an 89% ORR was observed in a smaller study of 18 patients with relapsed and refractory multiple myeloma [Berdeja et al, 2017].

To date, CAR-T cell therapy has not produced efficacy in trials in patients with solid tumours. Potential hypotheses for this differential efficacy include poor trafficking of blood derived lymphocytes into the tumour, or the suppressive tumour microenvironment. Safety has been a concern with both TCR-transduced T cells and CAR-T cells because their targets are generally shared tumour-associated antigens rather than tumour-specific neoantigens which has resulted in unacceptable or life threatening autoimmune reactions in some patients [Johnson et al, 2009; Parkhurst et al, 2011]. Some encouraging results have been observed with receptor-engineered T-cells directed against the tumour-germline antigen, NY-ESO-1 which is expressed in the majority of synovial sarcomas, and 25% of melanomas.

In a phase I study of 38 patients selected for the appropriate HLA subtype, objective response rates of 55-61% were observed, including some complete and durable responses, and there was no evidence of autoimmunity [Robbins et al, 2015].

1.3.3 Differential Toxicity Profile of TILs and CAR-T cells

As described above, CAR-T cell therapies have been associated with some severe toxicities related to *in vivo* T cell proliferation and activation, whereas similar toxicities have not generally been reported for TIL therapies. The contrasting tolerability profiles of TIL therapies and CAR-T cell therapies suggests that ACT can be well tolerated as long as the cell therapy recognizes tumour-specific antigens only. Furthermore, conventional tumour infiltrating T cells are populations of naturally occurring central memory T cells which have been subject to *in vivo* immune selection for self-tolerance. This selection is largely driven by their avidity for self-antigens; the high avidity clones are selected out during T cell development. In contrast, CAR-T cells carry artificial high avidity T cell receptors which may react against normal tissue that expresses low levels of tumour-associated antigens.

In addition, use of cells expressing the native T cell receptor reduces the risk of severe cytokine-associated toxicities that have been documented with CAR-T therapies where the chimeric TCR has a supra-physiological affinity for the cognate antigen and inherent co-stimulation within the CAR construct. CAR-T cells are capable of far more rapid proliferation than TILs, and both CD4 and CD8 T cells are equally triggered by the tumour antigen, with proinflammatory CD4 cells potentially releasing pathological levels of inflammatory cytokines. In contrast, expanded, naturally occurring TILs remain constrained by their need to be triggered by tumour peptides presented by the HLA molecules expressed on the surface of the tumour cells; the majority of which are MHC class I restricted and can only initiate CD8 T cell activation and triggering, whilst a smaller number of CD4 TILs can respond to MHC class II restricted peptides presented by intra-tumoural antigen presenting cells and releasing physiological levels of cytokines to support CD8 TIL expansion and formation of effector memory populations.

1.4 ATL001: A Novel Personalised Immunotherapy for NSCLC

ATL001 is a T cell advanced therapy investigational medicinal product (ATIMP) derived from autologous tumour-infiltrating lymphocytes enriched for neoantigen specificity following co-culture with antigen presenting cells that present predicted immunogenic clonal neoantigen epitopes expressed within the patient's tumour.

By sequencing a patient's tumour, comparing it to the germline DNA of the patient and applying bioinformatics algorithms, it is possible to identify tumour-specific mutations. As downregulation of HLA genes may result in reduced antigen presentation [Tran et al, 2016] and has been observed in 40% of NSCLC [McGranahan et al, 2017], this is also assessed, to identify the clonal neoantigens that are most likely to be presented to the immune system. The corresponding peptide neoantigens are manufactured and cultured with antigen presenting cells, which can process them for presentation to T cells. Using these clonal neoantigens to specifically activate and expand clones of tumour infiltrating lymphocytes enhances the ability of TILs to recognise such neoantigens and to target the cells that express them.

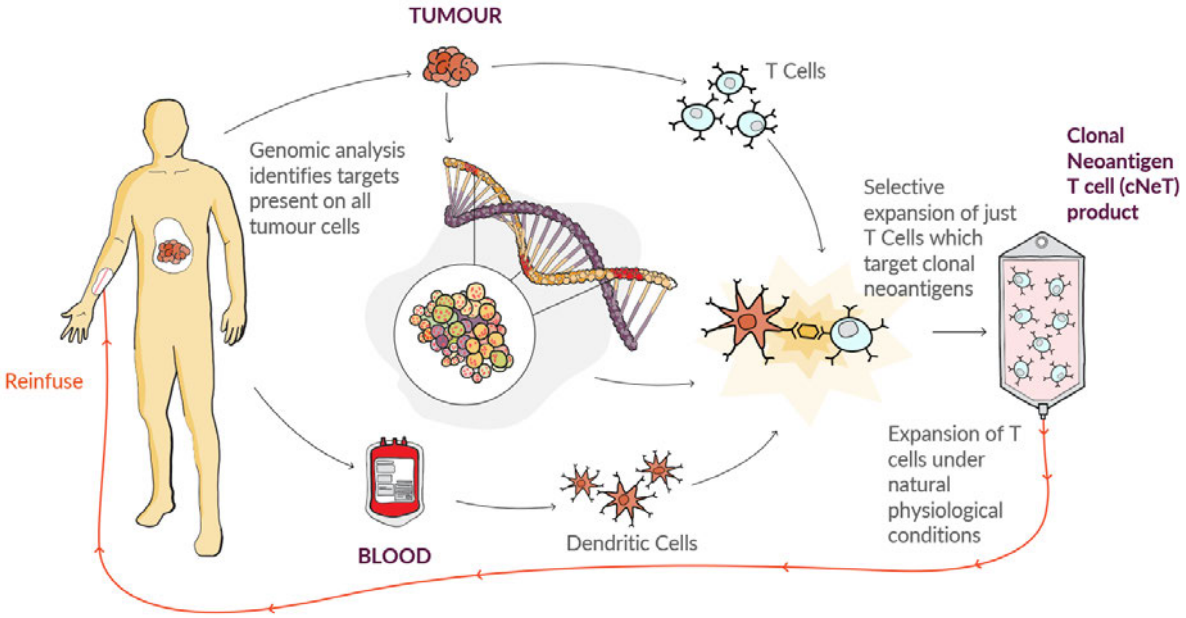


Figure 2: Outline Principle of cNeT Therapy and Manufacturing Process for ATL001

1.4.1 Pre-clinical Experience

Clinical Pharmacology

Animal models in immune compromised mice are not considered relevant for evaluating pharmacological activity of cNeT. Whilst murine models of T cell biology are well established, they have very limited use as pre-clinical correlates of cNeT; not least because there is no relevant murine model of NSCLC. A human primary NSCLC model in immunodeficient mice can be generated but this is an unreliable model of the clinical setting since the *in vivo* tracking of cNeT is dependent upon ligation of human adhesion molecules on the cNeT to their cognate ligands which are not present in a murine model.

Experiments using primary human lung cancer tissue are considered to be the most relevant pre-clinical data. The Sponsor has generated $CD4^+$ and $CD8^+$ cNeT from primary NSCLC and demonstrated that cNeT retained specificity for the predicted neoantigens when re-challenged, determined by secretion of effector cytokines, IFN-γ and TNF-α, in functional potency assays.

The Sponsor has successfully generated pilot-scale cNeT products from NSCLC patient tumour material in 10 out of 12 proof-of-concept manufacturing runs. In all cNeT products, the number of reactivities against neoantigen peptide pools was between 2 and 20 with both $CD4^+$ and $CD8^+$ T cell responses detected. Further details are provided in the Investigator's Brochure.

Pharmacokinetics and Toxicology

In accordance with the EMA Guideline on Human Cell Based Medicinal Products (EMEA/CHMP/410869/2006) and FDA Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products conventional absorption, distribution, metabolism and excretion (ADME) studies are not considered relevant for ATL001. Similarly, acute toxicology, chronic toxicology, genotoxicity, carcinogenicity, reproductive and developmental toxicity, safety pharmacology and immunotoxicity studies are not planned (http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html). Animal models are not considered relevant for the toxicology evaluation of human cells in this context as there are clear challenges to using the human cells in rodent models.

1.4.2 Clinical Experience

This is a first-in-human study so there is little clinical information for ATL001 to date. Refer to the Investigator's Brochure for the latest available clinical information on patients treated with ATL001.

Clinical data have been published from over 1000 patients treated with TIL adoptive cell therapy (ACT), mostly in patients with malignant melanoma [Merhavi-Shoham et al, 2017]. ACT with TILs produced in this manner appears to be well tolerated, adverse effects reported in the literature being limited to transient pancytopenia related to the lymphodepletion regimens employed, febrile neutropenia and/or sepsis as a consequence, and effects related to IL-2 treatment.

Table 1 and Table 2 summarise the clinical activity and safety data observed with TIL therapy in recently published Phase 2 clinical trials in patients with NSCLC and melanoma.

Recent reports have demonstrated that TIL therapy can deliver a significant reduction in tumour burden in late stage cancer patients suffering from a diverse set of epithelial tumours as well as melanoma, including a 44% response rate, with 2 CRs in 27 patients with advanced recurrent cervical cancer [Jazaeri et al, 2019], and case histories of durable remissions in patients with metastatic cholangiocarcinoma [Tran et al, 2014] and chemotherapy resistant metastatic triple-negative breast cancer [Zacharakis et al, 2018]. The case reported by Tran et al, showed a durable PR lasting over 35 months, in a patient with metastatic cholangiocarcinoma following the infusion of a neoantigen-specific $CD4^+$ T cell product that was 95% reactive against a single neoantigen (ERBB2IP) identified by whole-exome sequencing. In another study, a TIL product containing polyclonal $CD8^+$ T cells directed against a neoantigen (KRAS G12D) was able to lead to an objective regression of seven lung metastases in a metastatic colorectal cancer patient [Tran et al, 2014; Tran et al, 2016].

In the case reported by Zacharakis et al, 2018, the adoptive transfer of autologous TILs that were reactive to multiple tumour-specific mutant proteins led to a durable CR in a patient with metastatic chemo-refractory hormone receptor positive breast cancer, that was still ongoing after 22 months [Zacharakis et al, 2018].

A response rate of 28% was reported in 18 patients with human papilloma virus-related cervical cancer using HPV-targeted T cells [Stevanovic et al, 2019], two of whom achieved ongoing durable CRs for over 4 years at the time of reporting.

There have been limited studies of TIL therapies in NSCLC but its responsiveness to PD-1/PD-L1 inhibitors and its high mutation burden suggest that it would be a good candidate for this approach. In 1996, a first clinical study using TIL therapy in NSCLC was published [Ratto et al, 1996]. TIL cultures were successfully expanded from 113 out of 118 Stage II and III lung cancer patients, who were treated with TIL either in a monotherapy setting (stage II) or in combination with standard radio- and/or chemotherapy. The TILs were infused without any preconditioning regimen, but despite this limitation, a statistically significant improvement in OS compared to control was shown in stage III patients in the TIL plus IL-2 plus radiotherapy treatment cohort. This study was the initial proof that TIL therapy can successfully by applied to late stage lung cancer patients.

In 2018, Creelan et al demonstrated that they were able to isolate and expand TIL from metastatic tumour tissue from 13 out of 14 heavily pre-treated NSCLC patients who were enrolled in a phase I clinical trial [Creelan et al, 2018]. The patients were treated with nivolumab for 8 weeks, and 9 patients with progressive disease at this time received a lymphodepleting regimen (cyclophosphamide/fludarabine) and were infused with a median of 81×10^9 expanded TIL. Patients then received 6 doses of IL-2 and nivolumab maintenance treatment. The Grade 3 adverse events were primarily related to the lymphodepletion regimen: lymphopenia (90%), leukopenia (80%), neutropenia (60%) and thrombocytopenia (60%). One patient developed Grade 3 pulmonary edema and one patient with pre-existing carotid stenosis died of a cerebrovascular accident, which was

considered unrelated to the TIL treatment. In this initially nivolumab-resistant population, 7 out of 9 patients showed a reduction in tumour size post baseline, with 3 PRs and 1 pathological CR.

In a recent update of the study, Creelan et al, 2021, demonstrated that the end point of safety was met according to the pre-specified safety criteria defined as a dose-limiting toxicity rate of 17% or less. The rate of severe toxicity was 12.5% and out of the 13 evaluable patients, 11 patients had a reduction in tumour burden with 3 demonstrating CR, 2 of them were ongoing 1.5 years later [Creelan et al, 2021].

At present, Iovance Biotherapeutics, Inc. are investigating the potential for adoptive cell therapy in patients with metastatic NSCLC (IOV-LUN-202 (NCT04614103)) using 2 doses of cyclophosphamide at 60mg/kg and 5 doses of fludarabine at 25mg/m^2 in combination with up to 6 doses of IL-2 (600,000 IU/kg). In a preliminary analysis, an ORR of 26.1% (n=6, one CR and five PRs) were observed, with a DCR of 82.6%. Treatment emergent adverse events were consistent with the underlying disease and known adverse event profiles of non-myeloablative lymphodepletion and IL-2 [Chesney et al, 2022b].

In 2021, Nissani et al demonstrated that non-myeloablative lymphodepletion at a cumulative dose of 120 mg/kg cyclophosphamide and 125 mg/m^2 fludarabine was efficient in achieving deep lymphopenia and neutropenia in patients with metastatic melanoma. The most common adverse event was acute G 3-4 neutropenic fever affecting 91% of patients, with subsequent resolution by day 7 [Nissani et al, 2021].

Historically, >50% response rate with a substantial number of durable and CR in metastatic melanoma patients have been demonstrated using ACT [Dudley et al, 2002; Dudley et al, 2005]. This high response rate has been subsequently confirmed in two independent second trials. These phase II studies by Besser et al at the Sheba Medical Center, Israel, and at MD Anderson, US, showed similar results (ORR of about 50% in pretreated stage IV melanoma patients) [Besser et al, 2010].

Another publication from the National Cancer Institute (NCI) showed an ORR of 58% in patients treated with young TIL and an ORR of 48% in patients treated with young TIL with increased lymphodepletion [Dudley et al, 2010].

Based on these results, Rohaan et al, 2022, initiated a randomized controlled phase III study comparing TIL treatment to ipilimumab as the new standard for pretreated stage IV melanoma patients following the same treatment modality, consisting of non-myeloablative chemotherapy, infusion of TIL and intravenous high dose bolus IL-2 treatment. The results in a total of 168 patients showed a median PFS of 7.2 months in the TIL group and 3.1 months in the ipilimumab group (hazard ratio for progression or death, 0.50; 95% CI, 0.35 to 0.72; P<0.001); 49% (95% CI, 38 to 60) and 21% (95% CI, 13 to 32) of the patients, respectively, had an objective response. Median OS was 25.8 months (95% CI, 18.2 to not reached) in the TIL group and 18.9 months (95% CI, 13.8 to 32.6) in the ipilimumab group. Treatment-related adverse events (G3 or higher) in the TIL group, were mainly chemotherapy-related myelosuppression [Rohaan et al, 2022].

These reports demonstrated that it is feasible to isolate TIL from metastatic epithelial cancers, including NSCLC, and expand them *ex vivo* for adoptive T cell treatment within a clinical trial setting, with some encouraging signals of clinical activity in heavily pre-treated and PD-1 resistant patients. The tumour antigens recognised by TILs are a mixture of tumour-associated antigens (molecules which are expressed preferentially by tumour cells but are not exclusive to the tumour cells and are present at lower densities on normal cells) and tumour-specific antigens (neoantigens) which are peptides derived from unique proteins created by the tumour-specific mutations. Although the non-myeloablative (NMA) and high dose IL-2 treatments have been demonstrated to be well manageable, common toxicities are expected and may or will occur, and in particular transient bone marrow suppression requiring granulocyte-colony stimulating factor (G-CSF) for neutropenia, red cell

and platelet support with an increased chance of infections from NMA chemotherapy, and high fever, rash, low blood pressure, decreased urinary output and oedema from high dose IL-2.

However, these expected and manageable possible toxicities justify and balance the fact that these patients may have a high chance of durable objective responses.

Table 1: Summary of Safety Information, Conditioning Cumulative Dose, IL-2 and Response Rate Across TIL Trials

Study	Phase	Indication	N=	Conditioning (max cumulative dose)	IL-2 dose (max cumulative units)	ORR %	CR %	Grade 3+ AEs (most frequent)
IOV-COM-202 (Iovance Biotherapeutics, Inc.)	2	NSCLC	28	8400mg Cy / 225mg Flu	252M	21	4	Thrombocytopenia (67.9%) Anaemia (50%)
IOV LUN-202 (Iovance Biotherapeutics, Inc.)	2	NSCLC	23	8400mg Cy / 225mg Flu	252M	26	4	Not reported
IOV-COM-202 (Iovance Biotherapeutics, Inc.)	2	NSCLC + CPI	17	8400mg Cy / 225mg Flu	252M	47	N/A	Not reported
Moffitt (Creelan et al, 2021)	1	NSCLC + CPI	13	8400mg Cy / 225mg Flu	123M (decrescendo)	31	15	Lymphocyte count decreased (100%) White blood cell count decreased (100%) Anaemia (81%)
C-144-01 (Iovance Biotherapeutics, Inc.)	2	Metastatic melanoma	153	8400mg Cy / 225mg Flu	252M	31.4	5	Thrombocytopenia (76.9%) Anaemia (50%) Febrile neutropenia (41.7%)

Cumulative doses based on 70kg/170cm height with a calculated Body Surface Area (BSA) of 1.82m. Cumulative dose 8400 Cy/225 Flu is equivalent to literature doses of 60mg/kg/day Cyclophosphamide for 2 days and 25mg/m^2/day Fludarabine for 5 days.

Table 2: Clinical Activity and Safety Data with TIL Therapies in Phase 2 Clinical Trials

Treatment	Phase/ Design	N=	ORR (%)	CR (%)	DoR	Grade 3+ AEs	Reference
TIL	Phase 2 Single arm	93	56	22	Ongoing at 3-7 years if CR	Not reported	Rosenberg, et al., 2011
CD8 enriched young TIL	Phase 2 NMA/IL-2 without TBI	33	58	9	Not reported	50% Neutropenia	Dudley, et al., 2010
	NMA/IL-2 with TBI	23	48	9	Not reported		
TIL	Phase 2 NMA/IL-2 without TBI	51	46	24	mOS 38 months	50% Neutropenia	Goff, et al., 2016
	NMA/IL-2 with TBI	50	62	24	mOS 36 months	70% Neutropenia 26% Thrombotic microangiopathy	
TIL	Phase 2 Uveal melanoma Single arm	20	35	5	Not reported	100% Thrombocytopenia 67% Anaemia 29% Infection	Chandran, et al., 2017
TIL + Ipilimumab	Phase 2 Single arm	13	39	1	mPFS 7.3 months (6-30 months)	Hypothyroidism (3) Hepatitis (2) Uveitis (1) Colitis (1) (Ipilimumab related)	Mullinax, et al., 2018
TIL	Phase 2 Single arm	74	42	11	mOS 17.3 months	Fatigue (13%) Hyperbilirubinemia (11%) Febrile neutropenia (8%)	Forget, et al., 2018

Treatment	Phase/ Design	N=	ORR (%)	CR (%)	DoR	Grade 3+ AEs	Reference
						Capillary leak syndrome (4%)	
TIL	3rd line and later – all PD-1 resistant	66	38	3	Not reported	Thrombocytopenia (80%) Anemia (55%) Febrile neutropenia (53%) Neutropenia (38%) Hypophosphatemia (33%) Lymphopenia (29%)	Sarnaik, et al., 2019

2 TRIAL DESIGN

This is a first-in-human, open-label, multi-centre, phase I/IIa study to characterise the safety and clinical activity of autologous clonal neoantigen reactive T cells (cNeT) administered intravenously in adults with non-small cell lung cancer (NSCLC).

Following consent and screening, eligible patients will initially enter the study for procurement of tissue and blood to manufacture ATL001. Tissue may be procured either before or after receiving standard systemic therapies for advanced NSCLC. If patients have received prior systemic therapy, they must have no therapy induced toxicities at the time of tissue procurement. Procedure-related AEs and all SAEs from the time of the procurement to 28 days following procurement, or the start of anti-cancer therapy if sooner, will be collected.

The surgical procedures for tumour tissue procurement should be clinically relevant procedures which do not cause undue risk to patients, as determined by the Investigator, taking into consideration the risk/benefit for the patient.

While ATL001 is being manufactured, patients can receive further standard of care therapy for NSCLC. Any therapies not deemed standard should be discussed with the Sponsor before initiation. Patients must have received a PD-1/PD-L1 inhibitor before receiving ATL001 unless contraindicated.

When ATL001 is ready for infusion, patients will undergo additional screening procedures and if they remain eligible, they will undergo 5 days of lymphodepletion therapy followed by administration of ATL001, followed by administration of IL-2. For Cohorts A and B, patients will receive 10 daily subcutaneous doses of IL-2, while those in Cohort C will receive up to 6 doses of intravenous IL-2 every 8-12 hours.

ATL001 will be given as a monotherapy in Cohort A and Cohort C, i.e. no anti-cancer treatments will be given after treatment, until the time of confirmed disease progression.

Once ATL001 monotherapy has been shown to be safe and tolerable in Cohort A, following a planned IDSMC safety review when a minimum of 6 patients have been treated and followed up for 28 days,

there will be an option to open Cohort B in which ATL001 will be given in combination with pembrolizumab. Additionally, provided that the IDSMC agrees that the study can proceed without modification, the study will be considered to have proceeded from Phase I to Phase II following this IDSMC review. Once the IDSMC have approved continuation to Cohort B, the timing of opening Cohort B will be decided by the Sponsor.

Eligible patients for Cohort B must have experienced radiological disease progression after treatment with a PD-1/PD-L1 inhibitor or stable disease following 4 doses of PD-1/PD-L1 inhibitor, prior to receiving ATL001, and who are enrolled at a centre where Cohort B is open at the time of re-screening for ATL001 infusion. Patients should not have experienced any toxicity that would prevent them from receiving pembrolizumab.

Patients will be informed about all treatment cohorts and those who may be eligible will be asked if they will consider receiving ATL001 either as a monotherapy in treatment Cohort A and Cohort C, or in combination with pembrolizumab in treatment Cohort B, dependent upon which of the cohorts are open at the centre at the time of treatment.

In Cohort A, eligible patients will receive non-myeloablative chemotherapy consisting of cyclophosphamide (60 mg/kg/day i.v. x 2 days) and fludarabine (25 mg/m^2/day i.v. x 5 days) lymphodepletion, followed by 10 doses of IL-2 1M IU/m^2 s.c. daily from days 0-9 of the study, starting between 3 and 12 hours following ATL001 dosing.

Patients in Cohort B will receive a single dose of pembrolizumab 200 mg i.v. between day -13 and -7, aiming to give it as close to day -5 (the first day of lymphodepletion) as practical, prior to receiving non-myeloablative chemotherapy consisting of cyclophosphamide (60 mg/kg/day i.v. x 2 days) and fludarabine (25 mg/m^2/day i.v. x 5 days) lymphodepletion followed by 10 doses of IL-2 1M IU/m^2 s.c. daily from days 0-9 of the study, starting between 3 and 12 hours following ATL001 dosing. Following ATL001 dosing, patients will receive one dose of pembrolizumab 200 mg i.v. 3 weeks provided that any treatment related adverse events have resolved and that patients have no contraindications to restarting pembrolizumab. Patients will then commence pembrolizumab at a dose of 400 mg i.v. every 6 weeks, starting from week 6 post ATL001 infusion, and will continue treatment, if tolerated, for up to 12 months, or up to 6 months following a complete response (CR) or until RECIST v1.1 confirmed disease progression, whichever is sooner.

Patients in Cohort C will receive non-myeloablative chemotherapy consisting of cyclophosphamide (60 mg/kg/day i.v. x 2 days) and fludarabine (25 mg/m^2/day i.v. x 5 days) lymphodepletion), followed by 600,000 IU/kg IL-2 by intravenous infusion which will begin between 3 and 24 hours after ATL001 dosing. IL-2 at a frequency of 8-12 hourly and continued for up to a maximum of six doses as tolerated. IL-2 dosing will be interrupted if patient experiences Grade 3 or 4 toxicity related to IL-2 (with the exception of reversible Grade 3 toxicities attributable to IL-2 such as diarrhoea, nausea, vomiting, hypotension, rash/skin changes, anorexia, mucositis, dysphagia, or constitutional symptoms and laboratory changes). Management of IL-2 toxicity is detailed in Appendix F. If toxicities can be reversed within 24 hours by supportive measures, then additional doses may continue. If greater than two doses of IL-2 are skipped, IL-2 administration will be ceased. In addition, dosing may be held or stopped at the discretion of the treating Investigator.

For safety purposes, regardless of cohort, at least the first 3 patients will receive fludarabine 25 mg/m^2 i.v on each of Days -5 to -1 and cyclophosphamide 30 mg/kg i.v. on Days -5 and -4 prior to cell infusion.

Patients will be followed up for a period of 24 months post ATL001 infusion, at which time they will have completed their participation in the study. Patients who experience disease progression before this time should still be followed up for survival and adverse events of special interest. Each patient who received ATL001 will continue to be followed up for a minimum of 5 years, as part of a separate Long

Term Follow Up Protocol, or, if the separate protocol is not available at the study site, within this protocol.

2.1 Rationale for Study Design, Treatment Groups and Cell Dose

Tobacco-associated non-small cell lung cancer is a tumour characterised by high neoantigen burden and has been shown to be responsive to immunological therapies which increase T cell infiltration into tumour tissue. As such, it is a tumour that is likely to benefit from a cNeT therapy. Tumour tissue can be obtained via planned surgery from accessible sites with limited risk to patients and the Sponsor has demonstrated that TILs can be obtained from NSCLC tumours and expanded ex vivo upon recognition of tumour-specific clonal neoantigens. The prediction of clonal neoantigens from metastatic tumours may be enhanced by sequencing the primary tumour, so a sample of the archived primary tissue will be requested for patients with metastatic disease, where available.

While ATL001 is being manufactured, patients can receive further standard of care therapy for NSCLC. Any therapies not deemed standard should be discussed with the Sponsor before initiation. Patients must have received a PD-1/PD-L1 inhibitor before receiving ATL001 unless contraindicated.

In treatment Cohort A, patients will receive ATL001 as a monotherapy following standard of care therapies. It is expected that all patients will have received a platinum-based chemotherapy regimen and a PD-1/PD-L1 inhibitor as part of their standard therapy unless patients have contraindications to these agents.

The option to open treatment Cohort B (combination with pembrolizumab) will allow an assessment of the potential therapeutic interaction of cNeTs and an immune checkpoint inhibitor. Since cNeTs express the effector cytokine IFN-γ, which is known to promote upregulation of PD-L1 in tumour cells, the concurrent use of pembrolizumab, an inhibitor of PD-1 interaction, may enhance the clinical anti-tumour activity of cNeTs.

In treatment Cohort C, patients will receive ATL001 as a monotherapy as per Cohort A. Cohort C differs from Cohort A in that a higher dose of IL-2 is administered following ATL001 infusion. The Cohort C IL-2 dose regimen is closer in range to traditional IL-2 dosing in stage IV melanoma and has been used in other TIL clinical trials for the treatment of NSCLC [Iovance Biotherapeutics, Inc., 2021; Iovance Biotherapeutics, Inc., 2023]. These doses of IL-2 may enhance clinical anti-tumour activity by promoting *in vivo* proliferation and survival of the infused cells.

Since this is a single arm, first-in-human study, there will be no formal hypothesis testing and as such, the study has not been formally powered. The cohort size has been selected based on historical response data for checkpoint inhibitors in patients with NSCLC, to provide adequate information about the safety and efficacy of ATL001, whilst exposing minimal numbers of patients to experimental therapy and procedures prior to an initial signal of efficacy.

As the ATL001 product is patient specific, the cell dose will fall within a range. The lowest active cell dose to be infused is 5 x 10^7 $CD3^+$ cells. The maximum active dose is 1000 x 10^7 $CD3^+$ cells. This range has been selected based on prior reports of TIL-based adoptive cell therapy. A dose of cells may be comprised of one or more bags. Due to the manufacturing processes, it is unlikely that more than 1000 x 10^7 $CD3^+$ cells reactive to clonal neoantigens will be generated. However, should additional cells be generated, an additional dose may be prepared and stored for infusion at a future time point if clinically indicated.

A variety of T cell dose regimens have been utilised in previous studies of adoptive cell therapy but, to date, there is no convincing evidence that the likelihood of efficacy correlates with administered cell dose, nor is increasing administered cell dose clearly associated with increased risk of toxicity. Early TIL trials used T cell doses exceeding 10^{11} cells with no apparent toxicity, but the cells were over

expanded *in vitro*, with concomitant induction of senescence, down regulation of CD27 [Dudley et al, 2005] and increased expression of CD57. Subsequent and current trials of conventional TIL therapies have generally investigated cell doses of 10^{10} cells with minimal *ex vivo* expansion, retention of CD27 and CD28 expression and retention of proliferative capacity as determined by telomere length [Robbins et al, 2004]. In contrast with overall cell dose, the retention of proliferative capacity correlates with *in vivo* persistence of TIL therapy and with positive clinical outcome in the treatment of melanoma [Zhou et al, 2005].

The lack of correlation between administered dose and efficacy from previous studies supports the concept of a "threshold" dose; i.e. that which provides an immunological network of cells capable of sustaining *in vivo* proliferation. The data to support this hypothesis are from various clinical trials of adoptive T cell immunotherapy of viral infections where doses of 10^4-10^6 T cells reactive to viral neoantigens have been shown to be efficacious [Peggs et al, 2003; Peggs et al, 2011] and lead to substantial expansion *in vivo* and sustained immunity, in contrast to the transient immunity associated with infusion of doses of 10^{11} *ex vivo* expanded anti-viral T cells [Riddell et al, 1992].

Given the lack of previous correlation between cell dose and efficacy or toxicity we plan to administer an active dose of TILs generated for each patient product within the target range of 5-1000 x 10^7 $CD3^+$ cells. The lower end of the active dose range is set at 5 x 10^7 $CD3^+$ cells to maximise the chance of observing clinical activity, if a cell dose-efficacy relationship exists. However, there is no data to suggest that this cell dose is the minimally clinically active dose.

In the event that a product is manufactured for a patient but is considered to be "out of specification" because it does not meet the minimum cell doses and/or it contains higher than permitted autologous cell based impurities and/or it has not met the required potency, the Investigator may still consider it to be in the best interest of the patient to receive the product, based on a lack of alternative treatment and clinical trial options. In such cases, per applicable regulatory guidelines, the treating Investigator may make an exceptional request for the product to be released for use following a risk assessment.

In up to 20 such cases, patients may receive an "out of specification" product within this study protocol, as long as all of the protocol requirements are met except product related attributes. All instances of patients receiving an "out of specification" product will be recorded. The safety and efficacy data from patients receiving an "out of specification" product will be presented separately to the data from patients receiving the intended cell dose range. Thus, the collection of data within this protocol from up to 20 patients treated with "out of specification" products will allow flexibility to explore and understand possible dose-safety and dose-efficacy relationships, to inform the target dosing range for future studies.

The supply of an ATL001 product that is considered "out of specification" with data to be captured in this protocol will be upon request from the treating Investigator, taking into account the alternative options for the subject and the consequences of not receiving the product. Refer to Appendix G for restrictions related to the use of "out of specification" products in Germany.

2.2 Assessment of Benefit and Risk

2.2.1 Unmet Medical Need

Patients are most often diagnosed with NSCLC when the disease is advanced, invasive, inoperable and/ or metastatic. Patients who receive initial treatment with platinum-based chemotherapy, can expect to experience disease progression within 5-6 months of starting treatment. Of the patients fit enough to receive a second line therapy with a checkpoint inhibitor, 50% experience disease progression within 3-4 months. The improvements in clinical outcomes with checkpoint inhibitors are significant and some patients experience long term benefit, but once patients have experienced disease progression following checkpoint inhibitor therapy and chemotherapy, there is currently no standard treatment for their

condition. Advanced NSCLC remains incurable in most cases, with a 5-year survival of 4.7% in Stage IV disease (https://seer.cancer.gov/statfacts/html/lungb.html).

2.2.2 Potential Benefit

ATL001 is a novel, personalised treatment that is expected to target a patient's tumour-specific clonal neoantigens and may have the potential for long term clinical benefit in NSCLC as the target is present in every tumour cell. This concept is supported by the following observations: (1) First generation TILs have demonstrated clinically important responses in patients with metastatic melanoma; (2) resident TIL infiltrates are associated with improved outcomes in NSCLC; (3) High TMB and high numbers of clonal mutations are associated with improved outcomes when treated with immunotherapies in NSCLC [McGranahan et al, 2016].

2.2.3 Assessment and Management of Risk

The principal anticipated safety risks anticipated for ATL001 therapy are associated with the procurement procedure, the infusion of cells and the administration of auxiliary medications (fludarabine, cyclophosphamide and IL-2).

Monitoring and management plans for all potential safety risks are described in Section 7.

Procurement Procedure Risks

The protocol eligibility criteria require that the patient is considered medically fit enough to undergo procedures to procure blood and tumour tissue, including a general anaesthetic if required.

The surgical procedures for tumour tissue procurement should be clinically relevant procedures which do not cause undue risk to patients, as determined by the Investigator, taking into consideration the risk/benefit for the patient.

The precise risks of surgical procurement procedures will vary according to the specific surgical procedure required to procure at least 1.5 g (1.5 cm^3) of tissue and/or the anaesthetic. Anticipated surgery-related events could include infection, bleeding and pain. Procedure-related AEs and all SAEs from the time of the procurement to 28 days following procurement, or the start of anti-cancer therapy if sooner, will be collected.

The requirement to provide 140 mL blood to make the ATL001 product should not pose a significant risk to patients in itself. UK national transfusion guidelines recommend that a maximum of 15% of total blood volume (i.e. 750 mL for men and 565 mL for women) can be safely donated without risk of hypovolaemia [Joint UK Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee National Transfusion Guidelines; https://www.transfusionguidelines.org]. However, minimum pre-donation haemoglobin concentration requirements for blood donors are 125 g/L for females and 135 g/L for males, whereas patients with NSCLC may have lower haemoglobin levels. National guidelines for transfusion may vary. The prior donation of 140 mL of blood may modestly increase the likelihood of requiring a blood transfusion if there is any significant bleeding during the procedure.

ATL001 Infusion Risks

There may be a risk of an infusion reaction (e.g. fever, chills, headache). This risk will be reduced by the administration of standard prophylactic regimens (e.g. chlorphenamine and paracetamol/acetaminophen) before the infusion is given according to local SOPs. The use of corticosteroids for prophylaxis is prohibited.

Very rarely, adverse reactions associated with the cryoprotectant agent 10% dimethyl sulphoxide (DMSO) have been reported, most commonly hypertension. Blood pressure (BP) and other vital signs will be monitored at the start and end of the infusion, and frequently post infusion.

Cytokine release syndrome (CRS) and associated toxicities, including neurological toxicity, is considered a potential risk because of *in vivo* T cell proliferation and activation, although this is not anticipated to be as great with a TIL product as for patients receiving a CAR-T cell therapy due to the limited potential for on-target off-tumour toxicities, and physiological rather than supraphysiological stimulation of the T cell through its native receptor rather than the CAR (as described in Section 1). CRS usually occurs within one week of CAR-T cell therapy. In this study, patients should remain in the hospital facility for the time required by clinical consideration. A suggested management plan for CRS, based on European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) guidelines, is provided in Section 7.6.4.

Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS) is considered a potential risk as it is the second most common adverse event reported with CAR-T cell therapies and has been observed with other immunotherapies. It may occur at the same time as CRS or after CRS has resolved, and manifests as a variety of symptoms, including delirium, somnolescence, seizures, cognitive defects, ataxia, nerve palsies, dysphasia, encephalopathy, hallucinations and in severe cases, rapid onset of cerebral oedema. Symptoms generally resolve over a period of 2 to 9 days, with management. A suggested monitoring and management plan for ICANS, based on EBMT and JACIE guidelines, is provided in Section 7.6.5.

It is noted that many patients receiving ATL001 infusion will have received prior checkpoint inhibitors and may have experienced immune-related adverse events related to these agents. For those with a history of primary or secondary hypoadrenalism who are receiving physiological glucocorticoid replacement for adrenal insufficiency, and for those with adrenal insufficiency who do not usually require maintenance, it is important to recognise the need for increased doses, or initiation of dosing of glucocorticoids to cover the "stress" period associated with the study intervention. Institutions may have their own standard approaches which should be followed, but general considerations include doubling of daily doses, switching to short-acting, more rapidly absorbed preparations for patients receiving long-acting preparations, and consideration of switching from oral to parenteral routes of administration in patients who are unable to take oral medications or with significant gastro-intestinal symptoms (vomiting/severe diarrhoea). It is also important that patients remain aware of the potential need for increased dosing should they become unwell following discharge from hospital.

The risk of administering a product that does not meet the IMP product release specifications for $CD45^+$ or $CD3^+$ cell dose, and/or includes increased levels of autologous cell based impurities and/or has not met the required potency, is that the product may be less likely to expand *in vivo* and lead to sustained immune response than an active product containing $\geq 5 \times 10^7$ $CD3^+$ cells reactive to clonal neoantigens. To maximise the chances of observing a sustained response, an active dose range of 5-1000 x 10^7 $CD3^+$ cells has been set, although it is acknowledged that this range has not been evaluated clinically and there is no data to suggest that this is a minimal clinically active dose. However, if no other treatment or clinical trial options are considered to be beneficial and if the Investigator considers it to be in the best interest of the patient, administration of ATL001 that did not meet the set release criteria may be considered preferable to no treatment. In this case, the protocol makes provision for such patients to receive the product and be followed up within this protocol, per applicable regulatory guidelines, in order to ensure adequate safety monitoring, and to enable the collection of all safety and efficacy data from such patients. These data are pertinent to the study objectives and will contribute to the overall understanding of the safety profile and the association between cell dose and clinical endpoints.

Risks of Auxiliary Medications

The fludarabine and cyclophosphamide lymphodepletion regimen is expected to cause transient pancytopenia for up to 14 days, during which time patients will be susceptible to infections. Other common side effects associated with fludarabine and cyclophosphamide include poor appetite, nausea and vomiting, fatigue and diarrhoea. Cyclophosphamide is also known to cause bladder irritation and fluid retention.

IL-2 is known to cause hypotension, diarrhoea, chills, nausea, vomiting, and rash. A very rare side effect is 'capillary leak syndrome' which can cause limb oedema, hypotension, arrhythmias, dyspnoea and hypoalbuminaemia. The daily doses of IL-2 that will be used in Cohorts A and B of this study are significantly lower than the doses used in the past to treat melanoma and renal cancer so it is considered unlikely that capillary leak syndrome will occur, as it has not generally been reported in previously published TIL studies using lower doses of IL-2. As additional precautions, in particular for patients in Cohort C, patients will need to be hospitalised for close monitoring during the IL-2 administration period.

Patients with a history of ≥ Grade 2 diarrhoea/colitis caused by previous immunotherapy, within 6 months of screening, will not be eligible for any Cohort. However, patients that have been asymptomatic for at least 6 months or have had a normal colonoscopy post-immunotherapy (with uninflamed mucosa by visual assessment) are not excluded. Additionally, any patient with a history of neurological toxicity related to, or suspected to be related to, immunotherapy will also be excluded.

These auxiliary medicines are discussed further in Section 5.2.

Each of the first 3 patients enrolled in the study (from each treatment cohort) will be observed for 14 days following ATL001 infusion before the next patient can undergo lymphodepletion. This observation period is considered sufficient to identify symptoms of immediate cytokine release syndrome and enable dose adjustment, if appropriate, for future patients. Following reviews of safety data from the initial patients, the observation period between patient administrations may be reduced (see Section 7.2 for the review procedure and decision criteria).

Risks of Pembrolizumab (Cohort B Patients Only)

Immune-related adverse reactions are common with pembrolizumab and most are reversible but some severe and fatal cases have occurred. Some events have occurred after completion of treatment. Immune related events include pneumonitis, colitis, endocrinopathies, hepatitis, nephritis, skin reactions, uveitis, arthritis, myositis, myocarditis, pancreatitis, Guillain-Barré syndrome, myasthenic syndrome, haemolytic anaemia, sarcoidosis, encephalitis and myelitis.

Patients who receive pembrolizumab in Cohort B will have previously received a PD-1/PD-L1 inhibitor as part of standard of care treatments and will not be eligible for Cohort B if they have any contraindications for treatment, i.e. if they have experienced previously any recurrent Grade 3 immune-related adverse events or any Grade 4 immune related adverse events attributed to a PD-1/PD-L1 inhibitor.

Refer to the latest available prescribing information (e.g. Summary of Product Characteristics (SmPC)/Package Insert) for further reference safety information for pembrolizumab.

Potential Long-Term Risks

Concerns about risks of tumorigenicity have been raised for genetically modified ACTs. Given that TILs undergo relatively modest expansion, and that $CD3^+$ T-cells are diploid, differentiated cells with a finite proliferation potential, a very low risk of tumorigenicity is foreseen. Even in the setting of genetically modified T cell therapies, it has been demonstrated that mature T-cells exhibit resistance to oncogenic transformation [Newrzela et al, 2008]. In clinical trials involving gene transfer into mature

T cells, leukaemia was never observed, despite follow-up assessments of more than 10 years. On this basis, neither *in vitro* nor *in vivo* evaluations of tumourigenic potential are planned as the risk is considered low. This approach is consistent with the development of sipuleucel-T (EPAR, EMA/440011/2013; STN, BL 125197) and Zalmoxis (EPAR, EMA/CHMP/589978/2016). The safety follow-up period of 2 years is considered appropriate to monitor this risk in patients with advanced NSCLC in whom the 5-year survival is currently less than 20%.

2.3 Overall Benefit-Risk and Ethical Assessment

Advanced inoperable NSCLC remains an incurable disease for the vast majority of patients and there is a need for effective therapies to elicit deep and durable responses and to extend life without the cost of long-term tolerability burden. ATL001 represents a novel approach to NSCLC therapy and may address this unmet need in patients with advanced disease. It is considered appropriate to investigate ATL001 in patients with advanced or relapsed NSCLC following standard therapeutic interventions.

3 OBJECTIVES AND OUTCOME MEASURES

3.1 Objectives

3.1.1 Primary Objective

To assess the safety and tolerability of ATL001 as a monotherapy and in combination with pembrolizumab.

3.1.2 Secondary Objective

To evaluate the clinical efficacy of ATL001 (using RECIST v1.1 and imRECIST) as a monotherapy and in combination with pembrolizumab.

3.1.3 Exploratory Objectives

1. To evaluate the persistence, phenotype and functionality of cNeT and to explore possible relationships with clinical outcomes.
2. To evaluate potential biomarkers of clinical activity and factors affecting response.
3. To evaluate the manufacturing rate and factors that may affect the quality of ATL001.
4. To evaluate the utility of a bespoke plasma ctDNA assay.

3.2 Outcome Measures/Endpoints

3.2.1 Primary Endpoint

Frequency and severity of adverse events (AEs) and serious adverse events (SAEs) following tissue procurement and administration of lymphodepletion agents, ATL001 (monotherapy or in combination with pembrolizumab) and IL-2.

3.2.2 Secondary Endpoints

1. Percentage change from baseline in tumour size at 6 weeks and 12 weeks.
2. Best percentage change from baseline in tumour size.
3. Overall Response Rate (ORR).
4. Time to response (TTR).

5. Duration of response (DoR).
6. Disease Control Rate (CR + PR + durable SD).
7. Progression free survival (PFS).
8. Overall survival (OS).

3.2.3 Exploratory Endpoints

1. Measures of numbers, phenotype and functionality of immune cells in starting materials, product intermediates, and ATL001 product.
2. Measures of persistence, phenotype, functionality of infused T cells in the peripheral blood.
3. Changes from baseline in bespoke clonal and subclonal mutation specific ctDNA panels.
4. Number of products made from procured samples.
5. Reasons for not manufacturing products.
6. Potential factors affecting product quality to be explored, include but are not limited to: patient factors e.g. previous therapies; procurement sample quality; tumour biology factors e.g. PD-L1 expression and TIL phenotype.
7. Potential factors affecting clinical response to be explored include but are not limited to: patient factors e.g. previous therapies; tumour biology factors e.g. total tumour mutation burden at baseline, tumour T cell infiltrate, MHC expression and LOH-HLA, tumour expression of PD-L1 and other immune checkpoint proteins, Lung immune prognostic score and primary vs acquired resistance to a PD-1/PD-L1 inhibitor; product factors e.g. cNeT dose; and cNeT engraftment.

4 PARTICIPANT ELIGIBILITY CRITERIA

4.1 Inclusion Criteria

To be eligible to participate in this study, eligibility criteria will apply at two timepoints: at study entry prior to procurement of tumour and blood for manufacture of ATL001, and then prior to lymphodepletion for treatment with ATL001. Participation in this clinical study should not preclude patients from receiving approved therapies that are considered likely to be beneficial for their condition.

Inclusion Criteria:

1. Patient must be between 18 and 75 years old at the screening visit.
2. Patient must have given written informed consent to participate in the study.
3. Patient must have histologically confirmed diagnosis of non-small cell lung cancer, which is considered to be smoking-related.
4. Patient is considered medically fit enough to undergo all study procedures and interventions: procedures to procure blood and tumour tissue, including a general anaesthetic if required, and to receive fludarabine, cyclophosphamide and IL-2 at protocol doses and schedules.
5. Patient is considered, in the opinion of the Investigator, capable of adhering to the protocol.
6. ECOG Performance Status 0-1.
7. Adequate organ function, indicated by the following laboratory parameters:

a. Haemoglobin ≥ 10.0 g/dL.

b. White Blood Cell Count (WBC) ≥ 3.0 x10^9/L.

c. Absolute Neutrophil Count (ANC) ≥ 1.5 x10^9/L (without support of filgrastim (G-CSF)).

d. Platelets ≥ 100 x10^9/L.

e. INR/PT and APTR/APTT < 1.5x ULN, unless receiving therapeutic anticoagulation. Investigator discretion is required to ensure surgery is safe or that anticoagulants can be safely stopped.

f. AST or ALT ≤ 2.5x ULN.

g. Bilirubin < 1.5x ULN (or < 3 x ULN in Gilbert's Syndrome).

h. Creatinine clearance/estimated GFR ≥ 50 mL/min.

8. Female patients who are of childbearing potential must agree to use a highly effective method of contraception during the study and for at least 12 months after the ATL001 infusion. Non-sterilised male participants who intend to be sexually active with a female partner of childbearing potential must use an acceptable method of contraception from the time of screening, throughout the duration of the study and for at least 6 months after the ATL001 infusion. Refer to Appendix G for pregnancy testing requirements in Germany. See Section 4.3 for details of acceptable methods of contraception.

In addition to a re-evaluation of criteria 1-8, the following inclusion criteria must also be met prior to tissue procurement:

9. To be eligible to enter this study for **procurement**, a patient must fall into one of the following groups:

   a. Patients with advanced stage (III-IV) NSCLC who have accessible sites of disease suitable for collection of adequate tissue for ATL001 manufacture prior to starting standard treatment.

   b. Patients with advanced stage (III-IV) NSCLC who have received or are receiving standard treatments and have accessible sites of residual disease suitable for collection of adequate tissue for ATL001 manufacture.

   c. Other patients with advanced stage disease for whom no other alternative approved treatments are available, may be considered on a case-by-case basis and should be discussed with the Sponsor prior to enrolment.

10. Anticipated life expectancy ≥ 6 months at the time of tissue procurement.

In addition to a re-evaluation of criteria 1-8, the following inclusion criteria must also be met prior to lymphodepletion for treatment with ATL001:

11. Patient must have locally advanced unresectable or metastatic NSCLC and:

    a. Whose disease has progressed or recurred following standard of care. This includes patients who have received a component of standard of care therapy as part of a previous clinical trial in first line treatment; or

b. Who are ineligible for, or who cannot tolerate, standard of care therapies. Patients who stop treatment due to immunotherapy toxicities do not need to progress in order to receive treatment with ATL001.

12. Patients must have measurable disease according to RECIST v1.1 criteria prior to lymphodepletion.

13. Patient is considered, in the opinion of the Investigator, well enough (i.e. ECOG Performance Status 0-1) to receive ATL001 treatment (This will be checked prior to lymphodepletion and again prior to receiving ATL001).

In addition to 1-13, except inclusion 11a, the following inclusion criteria must be met for patients to be eligible for treatment in Cohort B:

14. Prior to treatment with ATL001, the treatment regimen must have included a PD-1/PD-L1 inhibitor and patients should have experienced:

    a. Radiological disease progression; or

    b. Stable disease following at least 4 doses of a PD-1/PD-L1 inhibitor.

15. In addition to the need for highly effective contraception as outlined in Inclusion Criterion 8 above, female patients in Cohort B of childbearing potential must agree to use effective contraception during treatment with pembrolizumab and for at least 4 months after the last dose of pembrolizumab. Patients must also agree to provide a serum or urine pregnancy test before each pembrolizumab administration during the treatment period in Cohort B.

4.2 Exclusion Criteria

Exclusion Criteria:

1. Patients with known central nervous system (CNS) metastases that are untreated or symptomatic or progressing. Lesions should be clinically and radiologically stable for 2 months after treatment, as determined by MRI or CT evaluation, in line with accepted standard of care procedures, and should not require steroids.

2. Patients with hepatitis B or C, human immunodeficiency virus infection (HIV1/2), syphilis or HTLVI/II infection (see Section 6.1.1).

3. Patients who have never smoked (defined as having smoked < 100 cigarettes in their lifetime, per WHO criteria).

4. Patients for whom there is documented evidence of an actionable tumour driver oncogene mutation (EGFR, ALK or ROS-1) at the time of initial screening. Patients who have progressed on standard targeted therapies, or for whom no approved targeted treatments are available, are not excluded.

5. Patients with active, known, or suspected autoimmune disease requiring immunosuppressive treatments.

6. Patients requiring regular treatment with steroids at a dose higher than prednisolone 10 mg/day (or equivalent).

7. Patients with superior vena cava syndrome.

8. Patients with a current or recent history, as determined by the Investigator, of clinically significant, progressive, and/or uncontrolled renal, hepatic, haematological, endocrine,

pulmonary, cardiac, gastroenterological or neurological disease. Additionally, the following criteria apply:

a. Patients with a Left Ventricular Ejection Fraction (LVEF) < 45%.

b. Patients with a history of coronary revascularization.

c. Patients with clinically significant atrial and/or ventricular arrhythmias including but not limited to: atrial fibrillation, ventricular tachycardia, 2° or 3° heart block.

d. Patients with a forced expiratory volume in one second (FEV1) of less than or equal to 60% of their predicted normal.

9. Patients with a history of immune mediated central nervous system toxicity that was caused by, or suspected to be caused by, immunotherapy.

10. Patients with a history of ≥ Grade 2 diarrhoea/colitis caused by previous immunotherapy within 6 months of screening. Patients that have been asymptomatic for at least 6 months or have had a normal colonoscopy post-immunotherapy (with uninflamed mucosa by visual assessment following discontinuation of immune suppression other than permitted modified release steroids) are not excluded.

11. Patients who are pregnant or breastfeeding.

12. Patients who have undergone major surgery in the previous 3 weeks.

13. Patients with an active concurrent cancer or a history of cancer within the past 3 years (except for in situ carcinomas, early prostate cancer with normal PSA or non-melanomatous skin cancers).

14. Patients with a history of organ transplantation.

15. Patients who have previously received any investigational cell or gene therapies.

16. Patients with contraindications for cyclophosphamide, fludarabine and IL-2 at per protocol doses (see Investigator's Brochure for details).

17. Patients who have received any cytotoxic chemotherapy or anti-angiogenesis agent within the 3 weeks prior to tissue and blood procurement.

18. Patients with evidence of disease progression at the first scan after commencing standard first line therapy (i.e. primary refractory disease), unless responsive to subsequent lines of therapy. Patients who are refractory to pembrolizumab monotherapy are not excluded.

19. Patients with a confirmed history of allergic reactions to amphotericin b, penicillin and/or streptomycin.

In addition, the following exclusion criteria will apply for eligibility for Cohort B:

20. Patients with any contraindications for pembrolizumab (Refer to the latest available prescribing information (e.g. SmPC/Package Insert) for reference safety information for pembrolizumab).

All exclusion criteria, except 2, 3, 4 and 17, will apply again prior to lymphodepletion for treatment with ATL001.

In addition, the following criteria will apply:

21. Patients who have received a live vaccination within the 28 days prior to lymphodepletion.

22. Patients with an active infection requiring antibiotics.
23. Patients who have received any cytotoxic chemotherapy within the 3 weeks prior to lymphodepletion.

4.3 Restrictions, Contraception Requirements and Prohibited Medications during the Study

Patients should not receive any live vaccinations for at least 3 months following lymphodepletion.

Patients requiring blood product support at any time in the future should receive irradiated blood products.

Patients should not receive steroids at a dose higher than prednisolone 10 mg/day (or equivalent) or other immunosuppressive agents post infusion during the study, unless necessary to manage toxicity (see Section 7). For participants in Cohort B receiving pembrolizumab, this remains the case during treatment and until 4 months after the last dose of pembrolizumab.

No new anti-cancer agents should be given post infusion prior to documented disease progression.

A list of prohibited and allowed concomitant medicines is provided in Appendix C.

The contraception requirements for the study comply with the latest available prescribing information (e.g. SmPC/Package Insert) for cyclophosphamide and fludarabine. Female patients of childbearing potential must agree to use adequate contraception during the study and for at least 12 months after administration of ATL001. Non-sterilised male participants who intend to be sexually active with a female partner of childbearing potential must use an acceptable method of contraception from the time of screening, throughout the duration of the study and for at least 6 months after the ATL001 infusion. Refer to Appendix G for pregnancy testing requirements in Germany. For participants in Cohort B receiving pembrolizumab, this remains the case during treatment and until 4 months after the last dose of pembrolizumab.

The definition of a woman of childbearing potential is a woman who is between menarche and post-menopausal (no menses for 12 months without an alternative medical cause) unless permanently sterile due to hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

Acceptable Highly Effective Methods of Contraception for women of childbearing potential include:

a. Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation.
b. Progestogen-only hormonal contraception associated with inhibition of ovulation.
c. Intrauterine device (IUD).
d. Intrauterine hormone-releasing system (IUS).
e. Bilateral tubal occlusion.
f. Vasectomised partner (provided that partner is the sole sexual partner of the patient and that the vasectomised partner has received medical assessment of the surgical success).
g. Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments, i.e. from enrolment until 12 months post administration of ATL001 for women of childbearing potential and until 6 months post administration of ATL001 for patients with female partners of childbearing potential). Periodic abstinence is not acceptable. The reliability of sexual abstinence needs to be evaluated in relation to the preferred and usual lifestyle of the subject.

Acceptable Methods of Contraception for non-sterilised male participants who intend to be sexually active with a female partner of childbearing potential include:

a. Condom.

b. Vasectomy/orchiectomy.

Contraception used by men or women should be consistent with local regulations regarding the use of contraceptive methods for patients participating in clinical trials.

4.4 Criteria for Participant Discontinuation

Patients may be discontinued from study treatment and/or assessments at any time, at the discretion of the Investigator(s).

4.4.1 Discontinuation from Study Treatment

As ATL001 is given as an intravenous infusion, the only reason to discontinue it is for a severe infusion reaction requiring i.v. corticosteroid or in case of voluntary discontinuation/withdrawal by the patient. See Section 7 for guidelines on management of infusion reactions.

Specific reasons for discontinuing a patient from other components of protocol interventions (lymphodepletion agents or IL-2) may include:

a. Severe infusion reaction requiring i.v. corticosteroid.

b. Grade 3 or worse autoimmunity, cytokine release syndrome, capillary leak syndrome, that does not resolve to Grade 2 or below within 2 days.

c. Grade 2 or worse neurological toxicity that does not resolve to Grade 1 or baseline within 2 days.

d. The omission of more than 2 doses of IL-2 due to an adverse event related to IL-2.

e. Protocol non-compliance (e.g. patient refuses to remain in hospital facility for required time).

f. Voluntary discontinuation/withdrawal by the patient.

Patients who are found to be pregnant prior to lymphodepletion (i.e. at re-screening) or on planned day of administration of ATL001 (i.e. Day 0) (refer to Appendix G) should discontinue all study treatments.

Cohort B patients should discontinue treatment with pembrolizumab when they experience disease progression. If a patient in Cohort B becomes pregnant, they should discontinue treatment with pembrolizumab within this study (refer to Appendix G).

Adverse events leading to discontinuation should be followed up until resolution.

Patients who have discontinued treatment should wherever possible remain in the study and continue with follow up assessments for disease progression and survival.

4.4.2 Discontinuation from Study

All patients who meet the eligibility criteria and receive study treatment are expected to remain “on-study” for 24 months following ATL001 treatment, to enable the evaluation of the longer-term safety and efficacy.

Specific reasons for discontinuing a patient from the study prior to 24 months may include:

a. Inability to make ATL001.

b. Patient does not meet pre-lymphodepletion eligibility criteria.

c. Investigator decision.

d. Voluntary discontinuation/withdrawal by the patient.

e. Adverse event.

f. Lost to follow up.

g. Death.

h. Study termination.

A withdrawal/completion visit should be completed for all patients who discontinue from the study. See Section 6.4.10 for the requirements.

5 INVESTIGATIONAL AND AUXILIARY MEDICINAL PRODUCTS

5.1 Investigational Medicinal Products

5.1.1 ATL001

5.1.1.1 Composition

The active moiety is clonal neoantigen reactive T cells (cNeT) formulated in a cryopreservation media. The final ATL001 is a cryopreserved cell therapy product.

5.1.1.2 Manufacturing Summary

The tumour and blood samples procured from the patient are shipped to the Sponsor's manufacturing site for further processing. Tumour infiltrating lymphocytes (TILs) are isolated from the tumour tissue. The tumour is sequenced to identify the clonal neoantigen peptides which are subsequently manufactured. The blood sample is used to manufacture antigen presenting cells which can process and present the neoantigens to the TILs. In this way, clonal neoantigen reactive T cells are specifically isolated and expanded. The cNeT are harvested and formulated to form ATL001.

5.1.1.3 Shipping and Storage

The Sponsor will ensure that the cell therapy product ATL001 is appropriately shipped from the manufacturing facility to the study site. ATL001 cryopreserved products are shipped at -135°C or below in a qualified dry shipper by a courier company experienced in handling such materials.

Each ATL001 shipment will be temperature monitored across shipment and storage and accompanied by the appropriate documentation. Temperature monitoring logs and associated data are required to be collected for verification of events and personnel handling related to ATL001.

On receipt of ATL001 by the study site, the product should be stored at -135°C or below in a monitored vapour phase liquid nitrogen dewar or in a monitored and compliant cell therapy storage facility until the patient is ready for product administration. All medications must be stored in a safe and locked site with no access for unauthorised personnel.

Clinical trial ATL001 supplies will be provided as a single dose in cryopreserved bags.

All cryopreserved bags will have a label in an integrated sealed pocket with appropriate information for use in the clinical trial. The bags will be covered with a protective secondary outer bag in accordance with relevant competent regulatory authority requirements.

Lymphodepletion should not commence until ATL001 is available.

Thawing and Infusion

No manipulation of the product is required at the clinical site prior to administration, apart from thawing. The cryopreserved cells should be thawed rapidly in a water bath at 37°C or alternative suitable thawing device for cell therapies (see Procurement and Cell Handling Manual) for immediate administration. Patients may be premedicated according to local SOPs (e.g. with paracetamol/acetaminophen (max 1 g) and chlorphenamine).

ATL001 Cell Administration: Autologous cNeT as a single dose will be given. ATL001 will be administered by intravenous infusion within 30 minutes through either a peripheral or an existing central line. Do not filter with a leukoreduction filter. An infusion set with a standard blood filter (pore size no smaller than 170 microns) may be used, per institutional SOPs. To ensure all the product is infused, the bag may be flushed with a volume of sterile saline solution at the end of the infusion or as per institutional SOPs permit. See Investigator's Brochure for detailed administration instructions.

In addition to any protocol specific patient monitoring requirements, monitoring will follow the hospital standards for administration of blood products and an Investigator or Sub-Investigator should be available throughout the entire infusion. Patients should receive supportive care for acute or chronic toxicity or other supportive care if needed at the discretion of their physician, however prohibited medications and/or treatments will not be allowed except in the case of a medical emergency. Please see Section 4.3 for restricted medications and Section 7 for safety management guidelines.

ATL001 will not be supplied by the Investigator to other Investigators not listed on the FDA Form 1572 or equivalent, nor allow use of additional investigational products as instructed in this protocol. Due to the autologous nature of this product, the Investigator will dispense ATL001 only from the designated study site and administer only to the patient for whom it was manufactured.

Further details will be provided in the Procurement and Cell Handling Manual.

Dose Adjustments

No dose modifications are permitted for ATL001. Delays to dosing are not recommended however any delays should be communicated to the Sponsor medical monitor by the Investigator.

5.1.1.4 Destruction of ATL001 and Administration Components

After the administration of ATL001 has been completed, the empty infusion bag and used clinical supplies will be destroyed as clinical waste. If ATL001 is unused for any reason, the Sponsor should be notified to agree whether the product may be destroyed as clinical waste or may be returned to the Sponsor and used for research, quality control (QC) or training purposes.

5.1.1.5 Accountability

It is mandatory for the Investigator at the study site to maintain appropriate records of the disposition of ATL001, including dates, quantity, and use by patients throughout the study to ensure full traceability is maintained. Records will be kept on product accountability and inventory forms. Product administration process will be documented on the administration record. The empty cryopreservation bag and disposables will be discarded in a biohazard container, witnessed and recorded by the research staff.

In the case that ATL001 has been delivered to the site but cannot be administered, the site must notify the Sponsor to agree further steps for either the destruction or return of the ATL001 to Sponsor.

Accountability of the investigational product will be verified by the study monitor during on-site monitoring visits.

In the event, for any reason, the Sponsor instructs the study to be terminated, suspended, discontinued, or completed, the Investigator may return the unused supplies to the Sponsor. Final study agent accountability forms, which complete the accountability of the entire study, must be provided to Sponsor.

5.1.2 Pembrolizumab (Cohort B Only)

Pembrolizumab is a monoclonal antibody that targets and inhibits the immune checkpoint, PD-1. Activated cytotoxic T cells express PD-1, which recognises a ligand (PD-L1) that is expressed on a proportion of tumour cells and antigen presenting cells. When PD-1 binds to PD-L1, T cell anti-tumour activity is suppressed. Pembrolizumab prevents this interaction by binding PD-1 and in doing so it enhances the ability of TILs to recognise and kill tumour cells.

Since cNeTs express the effector cytokine IFN-γ, which is known to promote upregulation of PD-L1 in tumour cells, the concurrent use of pembrolizumab, an inhibitor of PD-1 interaction, may enhance the clinical anti-tumour activity of cNeTs.

Pembrolizumab is authorised for the treatment of patients with advanced NSCLC at doses of either 200 mg i.v. every 3 weeks or 400 mg i.v. every 6 weeks.

Please consult the latest available version of the SmPC, package leaflet and/or other healthcare intended materials before taking any action relating to this agent. Please refer to the SmPC/Package Insert for pembrolizumab for reference safety information.

Patients who enrol in treatment Cohort B will receive a single dose of pembrolizumab 200 mg i.v. between days -13 and -7 prior to lymphodepletion dose. Following ATL001 infusion, 200 mg i.v. dose of pembrolizumab will be given on Day 21. Patients will then commence pembrolizumab 400 mg i.v. every 6 weeks from week 6, for up to 12 months, or up to 6 months following a CR or until RECIST v1.1 confirmed disease progression, whichever is sooner. Prior to pembrolizumab treatment administration, ECOG performance status and vital signs should be performed on the day of administration but physical examination (if applicable with the addition of a serum or urine pregnancy test prior to each pembrolizumab administration for female participants of childbearing potential) may be performed at the most recent clinic visit (if not on the same day, prior to administration) if ≤3 days prior to administration (refer to Appendix G for additional pregnancy testing requirements in Germany).

Further details will be provided in the Pharmacy Manual.

5.2 Auxiliary Medicinal Products

5.2.1 Lymphodepletion Agents: Fludarabine and Cyclophosphamide

All current ACT trials employ some form of lymphodepletion, which is required to eliminate regulatory T cells and endogenous lymphocytes that compete with the transferred cells for homeostatic cytokines, effectively providing the infused T cells with the optimum environment to expand and re-populate the tumour micro-environment. Current trials most commonly use a combination of cyclophosphamide and fludarabine. The more intensive regimens cause 10-14 days of cytopenia but facilitate greater anti-tumour activity.

Fludarabine is a purine analogue antineoplastic agent which inhibits ribonucleotide reductase, DNA polymerase α/δ and ε, DNA primase and DNA ligase thereby inhibiting DNA synthesis. Furthermore, partial inhibition of RNA polymerase II and consequent reduction in protein synthesis occur. All of these contribute to inhibition of cell growth. Its effect is particularly marked in haematopoietic cells

especially lymphocytes and it is indicated for the treatment of chronic lymphocytic leukaemia (CLL). For this reason, fludarabine is also commonly used as a lymphodepleting agent for ACT trials.

The safety information for fludarabine refers to the recommended dose used for CLL, which is 25 mg/m^2 body surface area given daily for 5 consecutive days per 28-day cycle for up to 6 cycles.

In ACT studies, fludarabine is generally given at doses of 25-30mg/m^2 for 3-5 days. The lymphodepletion dose of fludarabine to be used for this study is 25 mg/m^2 body surface area for five doses in total.

Refer to the latest available prescribing information (e.g. SmPC/Package Insert) for fludarabine safety information. Further safety information is available in the Investigator's Brochure.

Cyclophosphamide is an alkylating agent which has been demonstrated to have a cytostatic effect in many tumour types. Cyclophosphamide also has an immunosuppressive effect due largely to an inhibitory effect on B-cells, CD4$^+$ T-cells and to a lesser extent CD8$^+$ T-cells. It is approved for the treatment of a number of haematological and solid tumours at a range of doses. It is also used as a preparation for bone marrow transplantation when it is either given for 2 days at 60 mg/kg or 4 days at 50 mg/kg.

Doses of cyclophosphamide vary between ACT studies, ranging from 20-60 mg/kg for 2-3 days. The dose of cyclophosphamide to be used in this study is 60 mg/kg for two days. For safety purposes, at least the first 3 patients will receive fludarabine 25 mg/m^2 i.v on each of Days -5 to -1 and cyclophosphamide 30 mg/kg i.v. on Days -5 and -4 prior to cell infusion. If tolerated, the subsequent non-myeloablative lymphodepleting chemotherapy regimen will be fludarabine 25mg/m^2 i.v. on each of Days -5 to -1 and cyclophosphamide 60mg/kg on Days -5 and -4 prior to cell infusion with appropriate supportive care.

Refer to the latest available prescribing information (e.g. SmPC/Package Insert) for cyclophosphamide safety information. Further safety information is available in the Investigator's Brochure.

5.2.2 IL-2

Interleukin-2 (IL-2) has essential roles in key functions of the immune system via direct effects on T cells. It promotes the differentiation of immature T cells to effector and memory T cells and has a role in the development of T cell immunologic memory. It is approved for the treatment of some solid tumours, notably melanoma and renal cell carcinoma. In the context of adoptive cell therapy, IL-2 is used to augment the clinical efficacy of TIL therapies by supporting *in vivo* proliferation and persistence of the infused cells. The high intravenous doses used in the early TIL studies enhanced clinical effectiveness but were also associated with significant toxicities. In more recent studies, lower i.v. doses resulted in a more gradual accumulation of toxicities, allowing for early adjustment of symptomatic and supportive care. In most cases this allowed 90% of the intended dose to be received. The Herlev group reported a small pilot study in which 6 melanoma patients received a low-dose subcutaneous IL-2 regimen consisting of 2M IU/day for 14 days [Ellebaek et al, 2012]. Two of the patients achieved complete, long-lasting response, suggesting that low-dose IL-2 was effective, and it was also well tolerated; all planned injections were given without dose reduction. The most common adverse events were fever, chills, nausea and fatigue, none of these exceeding CTCAE Grade 2. Since then a number of studies have employed variable schedules of 'low dose' IL-2, with doses ranging from 0.5M IU/m^2/day to 2M IU/kg/day, administered for between 5 and 14 days.

More recent literature by Rohaan et al, 2022, reported the outcome of TIL therapy vs ipilimumab in patients with advanced melanoma. This phase 3, multicentre, open-label trial studied a total of 168 patents where 84 patients were allocated to the TIL group. These patients received lymphodepleting chemotherapy (cyclophosphamide at a dose of 60mg/kg for 2 days and fludarabine at a dose of 25mg/m^2

for 5 days) with high-dose IL-2 at 600,000 IU/kg every 8 hours for a maximum of 15 doses. It was noted that 49% of patients in the TIL group had an objective response compared to 21% in the ipilimumab group. Please also refer to Table 1 which summarises the range of maximum cumulative IL-2 doses in recent ACT trials and their corresponding clinical response and safety data.

Based on a review of the available literature and experience with cell therapies, the chosen regimens of IL-2 will include:

For Cohorts A and B, IL-2 will be administered at a dose of 1M IU/m^2 s.c. for 10 days, starting 3-12 hours after the completion of the ATL001 infusion, as long as systolic BP ≥ 90 mmHg, pulse ≤ 100 bpm and there is no infection requiring antibiotics.

For Cohort C, IL-2 will be administered at a dose of 600,000 IU/kg i.v. (based on total body weight) for up to a maximum of six doses, as tolerated, starting 3-24 hours after the completion of the ATL001 infusion at a frequency of 8-12 hourly, as long as systolic BP ≥ 90 mmHg, pulse ≤ 100 bpm and there is no infection requiring antibiotics. IL-2 dosing will be interrupted if patient experiences Grade 3 or 4 toxicity related to IL-2 (with the exception of reversible Grade 3 toxicities attributable to IL-2, such as diarrhoea, nausea, vomiting, hypotension, rash/skin changes, anorexia, mucositis, dysphagia, or constitutional symptoms and laboratory changes).

Refer to the latest available prescribing information (e.g. SmPC/Package Insert) for IL-2 safety information. Further safety information is available in the Investigator's Brochure.

5.3 Prior and Concomitant Medications

All anti-cancer medications received by the patient will be recorded. All prescription, non-prescription, or over-the-counter medication given to, or taken by, the patient at entry and during the study must be clearly documented on the appropriate eCRF.

Information on COVID-19 vaccination is provided in Appendix C.

6 STUDY PLAN AND PROCEDURES

6.1 Tumour and Blood Procurement for Manufacture of ATL001

6.1.1 Tumour Procurement for Manufacture of ATL001

For patients with advanced stage (III-IV) disease who have accessible sites of disease suitable for surgical removal, attempts should be made to obtain at least 1.5 g (1.5 cm^3) of tumour tissue for assessment, sequencing and manufacturing of ATL001. A sample of the archival tumour may be requested for analysis of the tumour microenvironment.

The surgical procedures for tumour tissue procurement should be clinically relevant procedures which do not cause undue risk to patients, as determined by the Investigator, taking into consideration the risk/benefit for the patient.

Access to the archival FFPE sample of primary tumour may be requested at any time during the study.

When practical and safe to do so, surgery should be undertaken before the commencement of standard first line therapy. Alternatively, patients may be enrolled following initial therapy and surgery may be scheduled at a time that is clinically safe (i.e. after recovery from any chemotherapy-induced toxicity) and convenient, in which case the patient must meet the additional eligibility criteria prior to the procurement procedure.

Patients should be considered to have 6 months life expectancy at the time of surgery to accommodate manufacturing time and a 12 week follow up period after therapy.

Additional haematological and biochemical safety evaluations, ECGs, radiological investigations and urinalysis may be routinely required for surgical procedures at the study site and, if so, the site should follow its usual pre-operative practice. These additional evaluations should not be considered as a requirement for this study protocol.

Infectious disease screening within 30 days of surgery (IDM1) and a repeat screen on the day of surgery (IDM2) is required at any time that tumour tissue is procured. This screen will include the following tests: Anti-HIV 1 & 2, HBs Ag, Anti-HBc, Anti-HCV-Ab, Syphilis (*Treponema pallidum*) IgG/IgM and Anti-HTLV 1 & 2. Additional tests per local requirements, if required, should also be performed. Patients should have clearance for IDM1 within 30 days of the procurement of tumour tissue to allow material to be accepted into the manufacturing facility.

Full instructions for tissue collection, labelling and transportation to the manufacturing facility is provided in the Procurement and Cell Handling Manual.

6.1.2 Blood Procurement for Manufacture of ATL001

The following blood samples will be collected:

- A blood sample (target volume 140 mL whole blood) for ATL001 manufacture.
- A blood sample for germline DNA which is needed for the identification of tumour-specific clonal mutations (~10 mL).
- A blood sample for ctDNA monitoring (~30 mL).
- A blood sample for HLA testing (~4 mL).

Patients will consent separately for germline DNA sequencing as part of the overall study consent process.

In general, the 140 mL whole blood should be collected on the same day of tissue procurement unless otherwise agreed with the Sponsor. Tissues and blood procurement may be collected at different timepoints where same day collection is not clinically appropriate.

UK and EU Only: For patients where tissue will be stored for potential future treatment on relapse, the 140 mL blood sample for the manufacturing process, germline DNA, HLA and ctDNA blood samples will not be collected until the time of relapse when product manufacture is to be initiated. Where tissue has been previously stored and blood samples (140 mL whole blood, germline, ctDNA and HLA typing) are to be collected at the time of relapse, IDM1 clearance is required within 30 days of blood sample collection.

6.1.3 Situations Requiring Recollection of Blood

In the case that a blood sample does not yield enough antigen presenting cells to make ATL001 or for other reasons which are clinically relevant, additional blood sample(s) may be requested.

If additional blood is requested, the following procedures must be performed:

- Additional IDM1 (within 30 days of recollection) and IDM2 (day of recollection).

  Note: Additional IDM1 is not required if less than 30 days have elapsed since the last IDM screen.

- Procedure-related AEs and all SAEs from the time of the recollection to 28 days following recollection, or the start of anti-cancer therapy if sooner, will be collected.

All cases should be discussed with the Sponsor prior to any activities for recollection.

6.2 Lymphodepletion and Administration of ATL001 and IL-2

Prior to receiving the ATL001 infusion, all patients will undergo non-myeloablative lymphodepleting chemotherapy. For safety purposes, at least the first 3 patients will receive fludarabine 25 mg/m^2 i.v on each of Days -5 to -1 and cyclophosphamide 30 mg/kg i.v. on Days -5 and -4 prior to cell infusion with appropriate supportive care. These can be administered according to local SOPs.

If tolerated, the non-myeloablative lymphodepleting chemotherapy regimen will be increased up to fludarabine 25mg/m^2 i.v. on each of Days -5 to -1 and cyclophosphamide 60mg/kg on Days -5 and -4 prior to cell infusion with appropriate supportive care.

Patients allocated to Cohort B will receive a single dose of pembrolizumab 200 mg i.v on day -7. There is a window of 7 days prior to this to administer the pembrolizumab if more convenient for the patient.

The ATL001 infusion is planned for day 0. A window of 5 days is considered acceptable to account for the case whereby a patient is not deemed clinically well enough to receive the cell infusion on the planned day. If any further delay is required, each case should be discussed with the Sponsor. Following a more prolonged delay, it is likely that a second course of lymphodepletion will be required.

On the day of ATL001 infusion (Day 0), patients should be pre-medicated with a standard regimen to prevent infusion reactions (e.g. chlorphenamine and paracetamol/acetaminophen) according to local SOPs prior to the infusion of ATL001. This prophylactic regimen should not include corticosteroids.

The infusion should be administered as soon as possible and within 30 minutes after thawing. The infusion should be administered via a giving set with the tap fully open i.e. rate controlled by gravity, and as per local SOPs. A saline flush should be used to ensure that all the contents of the bag and giving set are infused where possible and as permitted in local SOPs. Patients in Cohorts A and B will receive 10 doses of IL-2 1M IU/m^2 s.c. daily from days 0-9 of the study, starting between 3 and 12 hours post infusion. Patients in Cohort C will receive up to 6 doses of 600,000 IU/kg i.v. at a frequency of 8-12 hourly, starting between 3 and 24 hours post infusion.

6.2.1 Possibility to Re-administer ATL001

In a case where an additional ATL001 dose can be manufactured for a patient, this will be stored. If the Investigator considers it is clinically appropriate for a patient to receive an additional infusion of ATL001 within the study protocol at the time of disease progression, this must be discussed with the Sponsor. In order to proceed, the following must be met:

- The first infusion must have been adequately tolerated with no reports of infusion related serious adverse events or CTCAE Grade 4 adverse events.
- Patient must have undergone at least one RECIST assessment following the initial ATL001 administration which shows a clinical response or durable (> 12 weeks) stable disease.
- Patient must be re-screened and confirmed eligible per protocol with the following exceptions:
    - Inclusion criteria 9 and 10 are not applicable.
    - Exclusion criteria 2, 3, 4, 17 and 18 are not applicable.
- The study must still be open to recruitment.
- The product must be within its storage stability period.

A repeat tumour biopsy (e.g. Endobronchial Ultrasound (EBUS)) will be requested, if safely accessible, to assess any changes in the neoantigen profile or tumour microenvironment.

A further course of lymphodepletion may not be required in this case. Safety and efficacy data following a second administration will not contribute to the main study analysis and will be reported separately.

6.3 Schedule of Assessments

6.3.1 Schedule of Assessments for Cohorts A and C

	Screening	**Procurement**	**Procurement Follow Up**	**Pre-Lymphodepletion Re-Screening**	**Lymphodepletion**			**ATL001 Treatment & IL-2 Administration Period**			**Follow up**			**Withdrawal / Completion**	**Survival Follow up[a]**	**CSP section**
Visit No.	1	2	3	4	5	6	7	8	9	10 – 19	20 – 22	23 – 26	27 – 32	33		
Visit Schedule	Up to 30 D to D7 before procurement	Procurement	D28 after procurement (± 7 D)	D -28 to D -7	D -5	D-4	D-3 (Visit 7 Day 1) D-2 (Visit 7 Day 2) D-1 (Visit 7 Day 3)	D -1 [b]	D0 [c] (+5 D)	D 1 – D10 [d]	D14, D21 (±3 D) and D28 (±7 D)	W6, W12, W18 and W24 (±7 D)	W36, W48, W60, W72, W84, W96 (±14 D)	W104 / withdrawal (±14 D) [f]	Every 12 weeks (±14 days) until W364 [g]	
Informed Consent	X			X												6.4.1, 6.4.2 6.4.4, 11.1
Inclusion / Exclusion Criteria	X			X	X[v]			X								4.1, 4.2
Enrolment	X			X												6.4.1
Demography	X															8.1.10
Medical History	X			X												6.4.2, 6.4.4, 9.4.3
NSCLC History	X			X												6.4.2, 6.4.4
NSCLC risk factors	X															8.1.9
ECOG PS	X		X	X				X			X	X	X	X		6.4, 8.1.1
Anti-cancer Therapies	X			X											X	6.4.2, 6.4.4
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X		6.4
Physical Examination	X		X	X				X		X	X	X				6.4, 8.1.2
Vital Signs	X			X	X	X	X	X	X	X						6.4, 8.1.3

	Screening	**Procurement**	**Procurement Follow Up**	**Pre-Lymphodepletion Re-Screening**	**Lymphodepletion**			**ATL001 Treatment & IL-2 Administration Period**			**Follow up**			**Withdrawal / Completion**	**Survival Follow up [a]**	**CSP section**
Visit No.	1	2	3	4	5	6	7	8	9	10 – 19	20 – 22	23 – 26	27 – 32	33		
Visit Schedule	Up to 30 D to D7 before procurement	Procurement	D28 after procurement (± 7 D)	D -28 to D -7	D -5	D-4	D-3 (Visit 7 Day 1) D-2 (Visit 7 Day 2) D-1 (Visit 7 Day 3)	D -1 [b]	D0 [c] (+5 D)	D 1 – D10 [d]	D14, D21 (±3 D) and D28 (±7 D)	W6, W12, W18 and W24 (±7 D)	W36, W48, W60, W72, W84, W96 (±14 D)	W104 / withdrawal (±14 D) [f]	Every 12 weeks (±14 days) until W364 [g]	
Body Weight	X			X				X		X		X	X	X		6.4, 8.1.6
Height	X															6.4.2
Pulse Oximetry [h]								X	X	X						6.4.5, 8.1.4
12-Lead ECG				X				X	X[i]							6.4.4, 6.4.5, 8.1.5
Echocardiogram	X[j]			X[k]												6.4.2, 6.4.4
MRI/CT Tumour burden evaluation				X								W6, W12, W18, W24 and then every 12 W, until confirmed radiological disease progression				6.4, 6.4.12, 8.3
Colonoscopy	X[l]															6.4.2
Pulmonary Function Tests	X[m]			X[n]												6.4.2, 6.4.4
Adverse Events [o]		X	X[o]	X	X	X	X	X	X	X	X	X[o]	X[o]	X[o]	X[o]	6.4, 8.2
CRS Grading								X		X	X					6.4, 8.2.4
ICANS Grading								X		X	X	W6, W12[p]				6.4, 8.2.4
Blood Sampling for:																
Infectious Disease Marker Screening	X	X														6.1.1, 6.4.2, 6.4.3.1
Haematology	X		X	X	X	X	X	X	X	X[q]	X	X	X	X		6.4, 8.1.8
HLA Typing		X														6.1.2, 6.4.3.2
Coagulation Screen	X[r]			X				X		D1, D2, D3, D5, D7, D10[r]						6.4, 8.1.8

	Screening	**Procurement**	**Procurement Follow Up**	**Pre-Lymphodepletion Re-Screening**	**Lymphodepletion**			**ATL001 Treatment & IL-2 Administration Period**			**Follow up**			**Withdrawal / Completion**	**Survival Follow up [a]**	**CSP section**
Visit No.	1	2	3	4	5	6	7	8	9	10 – 19	20 – 22	23 – 26	27 – 32	33		
Visit Schedule	Up to 30 D to D7 before procurement	Procurement	D28 after procurement (± 7 D)	D -28 to D -7	D -5	D-4	D-3 (Visit 7 Day 1) D-2 (Visit 7 Day 2) D-1 (Visit 7 Day 3)	D -1 [b]	D0 [c] (+5 D)	D 1 – D10 [d]	D14, D21 (±3 D) and D28 (±7 D)	W6, W12, W18 and W24 (±7 D)	W36, W48, W60, W72, W84, W96 (±14 D)	W104 / withdrawal (±14 D) [f]	Every 12 weeks (±14 days) until W364 [g]	
Clinical Chemistry	X			X	X	X	X	X	X	X[q]	X	X	X	X		6.4, 8.1.8
Thyroid Function Test				X								W12, W24	W48, W72	X		6.4, 8.1.8
CRP				X				X		D1, D2, D3, D5, D7, D10	X	X				6.4, 8.1.8
Immunomonitoring (PBMC and TBNK) [e]				X						D3, D7, D10	X	X	X	X		6.4, 8.4
Immunomonitoring (Cytokines)[e]				X				X		D1, D2, D3, D5, D7, D10	X	X	X	X		6.4, 8.4
Immunological assay												W6 only				6.4.8, 8.4
TCR RNA				X						D7, D10	X	X	X	X		6.4, 8.4
ctDNA		X		X				X		D7 only	X	X	X	X		6.4. 8.4
Germline DNA		X														6.1.2, 6.4.3.2
Pregnancy Test (Females) [s,t]	X			X					X[s,t]			X[s,t]	X[s,t]			6.4, 8.1.7
Tissue Procurement		X														6.1.1, 6.1.3, 6.4.3
Archival tissue (if available)	X															6.1.1, 6.4.3.1, 8.1.11
Blood for Manufacturing		X														6.1.2, 6.1.3, 6.4.3
Infusion Reaction Prophylaxis									X							6.2, 6.4.5.2

	Screening	**Procurement**	**Procurement Follow Up**	**Pre-Lymphodepletion Re-Screening**	**Lymphodepletion**			**ATL001 Treatment & IL-2 Administration Period**			**Follow up**			**Withdrawal / Completion**	**Survival Follow up[a]**	**CSP section**
Visit No.	1	2	3	4	5	6	7	8	9	10 – 19	20 – 22	23 – 26	27 – 32	33		
Visit Schedule	Up to 30 D to D7 before procurement	Procurement	D28 after procurement (± 7 D)	D -28 to D -7	D -5	D-4	D-3 (Visit 7 Day 1) D-2 (Visit 7 Day 2) D-1 (Visit 7 Day 3)	D -1 [b]	D0 [c] (+5 D)	D 1 – D10 [d]	D14, D21 (±3 D) and D28 (±7 D)	W6, W12, W18 and W24 (±7 D)	W36, W48, W60, W72, W84, W96 (±14 D)	W104 / withdrawal (±14 D)[f]	Every 12 weeks (±14 days) until W364 [g]	
ATL001 Infusion									X[d]							5.1.1, 6.2, 6.4.5.2
Lymphodepletion (Flu)					X	X	X									6.2, 6.4.4.2
Lymphodepletion (Cy)					X	X										6.2, 6.4.4.2
IL-2 Administration									X[u]							6.2, 6.4.5.2, 6.4.6
Optional Tumour Biopsy				X								W6 or W12, and at disease progression[v]				6.4.4.1, 6.4.8, 8.5.2
Survival Status															X	6.4.8, 6.4.9

D = Day(s); W = Week(s)

a. After confirmed disease progression, the patient would move to Survival Follow Up visits. These visits could be conducted by telephone if deemed clinically appropriate by the Investigator.
b. Assessments at the Baseline Pre-treatment Evaluations Visit can be performed any time following the final dose of lymphodepletion and prior to cell infusion.
c. Eligibility to be checked pre-lymphodepletion.
d. Dosing must take place at least 24 hours after the last dose of fludarabine.
e. For Immunomonitoring (PBMC and TBNK), Immunomonitoring (Cytokines), TCR RNA and ctDNA samples collected between Day 0 and Day 10, the following windows apply: Day 3 ± 1 day window; Day 5 and Day 7 ± 1 day window (if + 1 day visit window is used for Day 3 visit, then Day 5 visit will have + 1 day visit window; if + 1 day visit window is used for Day 5 visit, then Day 7 visit will have + 1 day visit window); Day 10 ± 1 day window.
f. If withdrawal is after ATL001 treatment and prior to week 104, the assessments should follow the previous visit, except undertaking RECIST scans if already performed. If withdrawal is prior to ATL001 infusion, then the assessments required at procurement follow up visit should be completed.
g. Patients may have Survival Follow Up visits until W104, or until W364, until such time as the Long Term Follow Up study is available at study site.
h. Pulse Oximetry: Continuous monitoring during infusion with pre- and post-infusion measurements recorded and with vital signs.
i. 12 lead ECG within 30 minutes following end of infusion, and as clinically indicated.
j. Echocardiogram within 60 days prior to screening.
k. Echocardiogram within 60 days prior to start of lymphodepletion.
l. Colonoscopy is only required for patients who have had a documented Grade 2 or greater diarrhoea or colitis due to previous immunotherapy within 6 months of screening.

m. Pulmonary function test (spirometry) to include FEV1 within 90 days prior to screening.
n. Pulmonary function test (spirometry) to include FEV1 within 90 days prior to start of lymphodepletion.
o. Adverse Events: Following tissue procurement, collect AEs related to procurement procedure and all SAEs only for up to 28 days or until start of standard therapy for lung cancer; After Week 36 or during Survival Follow Up visits, collect AEs of special interest only.
p. If any abnormalities are detectable at Week 12, ICANs assessments should be repeated at Week 24.
q. Haematology and clinical chemistry to be conducted daily post cell infusion until values return to normal or baseline, or as clinically indicated.
r. Coagulation screen: At screening visits: INR/PT and APTR/APTT only. At visits Day-1 to day 10, screen includes Fibrinogen and D Dimer.
s. Minimum requirements for protocol. National health authority requirements should be followed if additional testing is mandated.
t. Refer to Appendix G for pregnancy testing requirements in Germany.
u. IL-2 administration: Days 0-9 (Cohorts A and B); Days 0-3 (Cohort C). The first dose of IL-2 should be administered 3-12 hours post completion of ATL001 infusion in Cohorts A and B, and 3-24 hours post completion of ATL001 infusion in Cohort C.
v. If a biopsy cannot be collected at Week 6 or Week 12, a tumour biopsy may be provided at a different timepoint. This will be agreed following a discussion with the Sponsor.

6.3.2 Schedule of Assessments for Cohort B

	Screening	**Procurement**	**Procurement Follow up**	**Pre-Lymphodepletion Re-Screening**	**Pembrolizumab Administration**	**Lymphodepletion**			**ATL001 Treatment & IL-2 Administration Period**			**Follow Up &Pembrolizumab Administration**										**Withdrawal / Completion**	**Survival Follow up [a-g]**	**CSP section**
Visit No.	1	2	3	4	P	5	6	7	8	9	10 – 19	20	21	22	23 -26	P	27	P	28	P	29-32	33		
Visit Schedule	Up to 30 D to D7 before procurement	Procurement	D28 ± 7 D after procurement	D -28 to D -7	D -13 to D -7	D-5	D-4	D-3 (Visit 7 Day 1) D-2 (Visit 7 Day 2) D-1 (Visit 7 Day 3)	D -1 [b]	D0 [c] (+5 D)	D 1 – D10 [e]	D14 (±3 D)	D21 (±3 D)	D28 (±7 D)	W6, W12, W18 and W24 (±7 D)	W30 (±3 D)	W36 (±14 D)	W42 (±3 D)	W48 (±14 D)	W54 (±3 D)	W60, W72, W84, W96 (±14 D)	W104 / withdrawal (±14 D) [f]	Every 12 weeks (±14 days) until W364 [d]	
Informed Consent	X			X																				6.4.1, 6.4.2 6.4.4, 11.1
Inclusion / Exclusion Criteria	X			X		X[d]			X															4.1, 4.2
Enrolment	X			X																				6.4.1
Demography	X																							8.1.10
Medical History	X			X																				6.4.2, 6.4.4, 9.4.3
NSCLC History	X			X																				6.4.2, 6.4.4
NSCLC Risk Factors	X																							8.1.9
ECOG PS	X		X	X	X				X			X	X	X	X	X	X	X	X	X	X	X		6.4, 8.1.1
Anti-cancer Therapies	X			X																			X	6.4.2, 6.4.4
Concomitant Medications	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X		6.4
Physical Examination	X		X	X					X		X	X	X	X	X	X	X	X	X	X				6.4, 8.1.2
Vital Signs	X			X	X	X	X	X	X	X	X		X		X	X	X	X	X	X				6.4, 8.1.3
Body Weight	X			X					X		X				X	X	X	X	X	X	X			6.4, 8.1.6
Height	X																							6.4.2

	Screening	**Procurement**	**Procurement Follow up**	**Pre-Lymphodepletion Re-Screening**	**Pembrolizumab Administration**	**Lymphodepletion**			**ATL001 Treatment & IL-2 Administration Period**			**Follow Up &Pembrolizumab Administration**										**Withdrawal / Completion**	**Survival Follow up [a,g]**	**CSP section**
Visit No.	1	2	3	4	P	5	6	7	8	9	10 – 19	20	21	22	23 -26	P	27	P	28	P	29-32	33		
Visit Schedule	Up to 30 D to D7 before procurement	Procurement	D28 ± 7 D after procurement	D -28 to D -7	D -13 to D -7	D-5	D-4	D-3 (Visit 7 Day 1) D-2 (Visit 7 Day 2) D-1 (Visit 7 Day 3)	D -1 [b]	D0 [c] (+5 D)	D 1 – D10 [e]	D14 (±3 D)	D21 (±3 D)	D28 (±7 D)	W6, W12, W18 and W24 (±7 D)	W30 (±3 D)	W36 (±14 D)	W42 (±3 D)	W48 (±14 D)	W54 (±3 D)	W60, W72, W84, W96 (±14 D)	W104 / withdrawal (±14 D) [f]	Every 12 weeks (±14 days) until W364 [d]	
Pulse Oximetry [h]									X	X[h]	X													6.4.5, 8.1.4
12-Lead ECG				X	X				X	X[i]														6.4.4, 6.4.5, 8.1.5
Echocardiogram	X[j]			X[k]																				6.4.2
MRI/CT Tumour burden evaluation				X											W6, W12, W18, W24 and then every 12 W, until confirmed radiological disease progression									6.4, 6.4.12, 8.3
Colonoscopy	X[l]																							
Pulmonary Function Tests	X[m]			X[n]																				6.4.2
Adverse Events [o]		X	X[o]	X	X	X	X	X	X	X	X	X	X	X	X[o]	X	X[o]	X	X[o]	X	X[o]	X	X[o]	6.4, 8.2
CRS Grading									X		X	X	X	X										6.4, 7.7.4, 8.2.4
ICANS Grading									X		X	X	X	X	W6, W12[p]									6.4, 7.7.5, 8.2.4
Blood Sampling for:																								
Infectious Disease Marker Screening	X	X																						6.1.1, 6.4.2, 6.4.3.1
Haematology	X		X	X		X	X	X	X	X	X[q]	X	X	X	X		X		X		X	X		6.4, 8.1.8
HLA Typing		X																						6.1.2, 6.4.3.2

	Screening	**Procurement**	**Procurement Follow up**	**Pre-Lymphodepletion Re-Screening**	**Pembrolizumab Administration**	**Lymphodepletion**			**ATL001 Treatment & IL-2 Administration Period**			**Follow Up &Pembrolizumab Administration**											**Withdrawal / Completion**	**Survival Follow up** [a,g]	**CSP section**
Visit No.	1	2	3	4	P	5	6	7	8	9	10 – 19	20	21	22	23 -26	P	27	P	28	P	29-32	33			
Visit Schedule	Up to 30 D to D7 before procurement	Procurement	D28 ± 7 D after procurement	D -28 to D -7	D -13 to D -7	D-5	D-4	D-3 (Visit 7 Day 1) D-2 (Visit 7 Day 2) D-1 (Visit 7 Day 3)	D -1 [b]	D0 [c] (+5 D)	D 1 – D10 [e]	D14 (±3 D)	D21 (±3 D)	D28 (±7 D)	W6, W12, W18 and W24 (±7 D)	W30 (±3 D)	W36 (±14 D)	W42 (±3 D)	W48 (±14 D)	W54 (±3 D)	W60, W72, W84, W96 (±14 D)	W104 / withdrawal (±14 D) [f]	Every 12 weeks (±14 days) until W364 [d]	
Coagulation Screen	X[r]			X					X		D1, D2, D3, D5, D7, D10[r]														6.4, 8.1.8
Clinical Chemistry	X			X		X	X	X	X		X[q]	X	X	X	X		X		X		X	X			6.4, 8.1.8
Thyroid Function Test				X											W12, W24				X		W72 only	X			6.4, 8.1.8
CRP				X					X		D1, D2, D3, D5, D7, D10	X	X	X	X										6.4, 8.1.8
Immunomonitoring (PBMC and TBNK)				X							D3, D7, D10	X	X	X	X		X		X		X	X			6.4, 8.4
Immunomonitoring (Cytokines)				X					X		D1, D2, D3, D5, D7, D10	X	X	X	X		X		X		X	X			6.4, 8.4
Immunological assay															W6 only										6.4.8, 8.4
TCR RNA				X							D7, D10	X	X	X	X		X		X		X	X			6.4, 8.4
ctDNA		X		X					X		D7 only	X	X	X	X		X		X		X	X			6.4. 8.4
Germline DNA		X																							6.1.2, 6.4.3.2
Pregnancy Test (Females) [s,t]	X			X	X					X[t]			X		X	X	X	X	X	X					6.4, 8.1.7
Tissue Procurement		X																							6.1.1, 6.1.3, 6.4.3
Archival tissue (if available)	X																								6.1.1, 6.4.3.1, 8.1.11

	Screening	**Procurement**	**Procurement Follow up**	**Pre-Lymphodepletion Re-Screening**	**Pembrolizumab Administration**	**Lymphodepletion**			**ATL001 Treatment & IL-2 Administration Period**			**Follow Up &Pembrolizumab Administration**										**Withdrawal / Completion**	**Survival Follow up [a,g]**	**CSP section**
Visit No.	1	2	3	4	P	5	6	7	8	9	10 – 19	20	21	22	23 -26	P	27	P	28	P	29-32	33		
Visit Schedule	Up to 30 D to D7 before procurement	Procurement	D28 ± 7 D after procurement	D -28 to D -7	D -13 to D -7	D-5	D-4	D-3 (Visit 7 Day 1) D-2 (Visit 7 Day 2) D-1 (Visit 7 Day 3)	D -1 [b]	D0 [c] (+5 D)	D 1 – D10 [e]	D14 (±3 D)	D21 (±3 D)	D28 (±7 D)	W6, W12, W18 and W24 (±7 D)	W30 (±3 D)	W36 (±14 D)	W42 (±3 D)	W48 (±14 D)	W54 (±3 D)	W60, W72, W84, W96 (±14 D)	W104 / withdrawal (±14 D) [f]	Every 12 weeks (±14 days) until W364 [d]	
Blood for Manufacturing		X																						6.1.2, 6.1.3, 6.4.3
Infusion Reaction Prophylaxis										X														6.2, 6.4.5.2
ATL001 Infusion										X[c]														5.1.1, 6.2, 6.4.5.2
Administration of Pembrolizumab					X								X		X	X	X	X	X	X				6.4.13
Lymphodepletion (Flu)						X	X	X																6.2, 6.4.4.2
Lymphodepletion (Cy)						X	X																	6.2, 6.4.4.2
IL-2 Administration										X[u]														6.2, 6.4.5.2, 6.4.6
Optional Tumour Biopsy				X											W6 or W12, and at disease progression[v]									6.4.4.1, 6.4.8, 8.5.2
Survival Status																							X	6.4.8, 6.4.9

D = Day(s); W = Week(s); P = Standalone pembrolizumab dosing visit

a. After confirmed disease progression, the patient would move to Survival Follow Up visits. These visits could be conducted by telephone if deemed clinically appropriate by the Investigator.
b. Assessments at the Baseline Pre-treatment Evaluations Visit can be performed any time following the final dose of lymphodepletion and prior to cell infusion.
c. Dosing must take place at least 24 hours after the last dose of fludarabine.
d. Eligibility to be checked pre-lymphodepletion.

e. For Immunomonitoring (PBMC and TBNK), Immunomonitoring (Cytokines), TCR RNA and ctDNA samples collected between Day 0 and Day 10, the following windows apply: Day 3 ± 1 day window; Day 5 and Day 7 ± 1 day window (if +1 day visit window is used for Day 3 visit, then Day 5 visit will have +1 day visit window; if +1 day visit window is used for Day 5 visit, then Day 7 visit will have +1 day visit window); Day 10 ± 1 day window.
f. If withdrawal is after ATL001 treatment and prior to week 104, the assessments should follow the previous visit, except undertaking RECIST scans if already performed. If withdrawal is prior to ATL001 infusion, then the assessments required at procurement follow up visit should be completed.
g. Patients may have Survival Follow Up visits until W104, or until W364, until such time as the Long Term Follow Up study is available at study site.
h. Pulse Oximetry: Continuous monitoring during infusion with pre- and post-infusion measurements recorded and with vital signs.
i. 12 lead ECG within 30 minutes following end of infusion, and as clinically indicated.
j. Echocardiogram within 60 days prior to screening.
k. Echocardiogram within 60 days prior to lymphodepletion.
l. Colonoscopy is only required for patients who have had a documented Grade 2 or greater diarrhoea or colitis due to previous immunotherapy within 6 months of screening.
m. Pulmonary function test (spirometry) to include FEV1 within 90 days prior to screening.
n. Pulmonary function test (spirometry) to include FEV1 within 90 days prior to start of lymphodepletion.
o. Adverse Events: Following tissue procurement, collect AEs related to procurement procedure and all SAEs only for up to 28 days or until start of standard therapy for lung cancer; After Week 36 or during Survival Follow Up visits, collect AEs of special interest only.
p. If any abnormalities are detectable at Week 12, ICANs assessments should be repeated at Week 24.
q. Haematology and clinical chemistry to be conducted daily post cell infusion until values return to normal or baseline, or as clinically indicated.
r. Coagulation screen: At screening visits: INR/PT and APTR/APTT only. At visits Day-1 to day 10, screen includes Fibrinogen and D Dimer.
s. Minimum requirements for protocol. National health authority requirements should be followed if additional testing is mandated.
t. Refer to Appendix G for pregnancy testing requirements in Germany.
u. IL-2 administration: Days 0-9. The first dose of IL-2 should be administered 3-12 hours post completion of ATL001 infusion.
v. If a biopsy cannot be collected at Week 6 or Week 12, a tumour biopsy may be provided at a different timepoint. This will be agreed following a discussion with the Sponsor.

6.4 Study Procedures by Visit

The same visits and procedures would be followed by all patients regardless of whether they receive a target dose range product or an "out-of-specification" product.

6.4.1 Consent and Enrolment Procedure

A 2-part consent and enrolment procedure will apply for this study.

Patients will consent for the whole study but will initially be enrolled only for the donation of materials required for the manufacturing of ATL001. Following the successful manufacture of ATL001, patients will provide additional consent for treatment with ATL001 prior to confirmation of patient eligibility and enrolment for treatment. Patients will be informed that the follow up period in this protocol is 2 years after treatment with ATL001, but that the total follow up period is 7 years after treatment with ATL001, and that after 2 years the follow up visits will be scheduled according to a separate Long Term Follow Up Protocol.

At the time of the Screening Visit, patients who may be eligible for the study, will be informed about all treatment cohorts and will be asked to consider receiving ATL001 either as a monotherapy in treatment Cohort A and Cohort C or in combination with pembrolizumab in treatment Cohort B, dependent upon which of the cohorts are open at the time of treatment. In centres where Cohort B and/or Cohort C are open, eligible patients will be asked, at the time of the Pre-Lymphodepletion Re-screening Visit, to confirm that they agree to receiving treatment within Cohort B or Cohort C.

Patients will undergo all the procedures pertaining to the Screening Visit and Tissue/Blood Procurement Visit. Germline DNA sequencing is required as part of the manufacturing procedure as it is needed to identify the tumour-specific clonal mutations. Patients will separately consent for germline DNA sequencing as part of the overall study consent process.

6.4.2 Screening Visit (30 Days to 7 Days before Tissue Procurement)

Procedures and assessments at this visit will be:

a. Informed consent.

b. Inclusion/exclusion criteria.

c. Demographics (see Section 9.4.2).

d. Relevant medical/surgical history (see Section 9.4.3).

e. Prior therapies.

f. NSCLC history (stage, subtype, molecular profile, treatment history).

g. NSCLC risk factors (see Section 8.1.11).

h. Physical examination.

i. ECOG Performance status.

j. Vital signs – BP, pulse rate, respiratory rate, and body temperature (oral or otic).

k. Pulmonary function tests (spirometry). This is a baseline measurement and should contribute to the assessment of exclusion criterion 8. The results of any routine spirometry tests carried out within the previous 90 days will be acceptable.

l. Body weight and height.

m. Echocardiogram within 60 days prior to screening. This is a baseline measurement and should contribute to assessment of exclusion criterion 8.

n. Colonoscopy for patients who have had a documented Grade 2, or greater diarrhoea or colitis due to previous immunotherapy within six months of screening. Patients that have been asymptomatic for at least 6 months or have had a normal colonoscopy post-immunotherapy (with uninflamed mucosa by visual assessment) are not excluded. See Exclusion Criterion 10.

o. Serum or urine pregnancy Test (for women of childbearing potential).

p. Concomitant medications.

q. Blood samples for:

- IDM1: Including serology for Anti-HIV 1 & 2, HBs Ag, Anti-HBc, Anti-HCV-Ab, Syphilis (*Treponema pallidum*) IgG/IgM and Anti-HTLV 1 & 2. Additional tests per local requirements, if required, should also be performed. If performed, any positive test results must be reported to the Sponsor.
- Haematology.
- Coagulation screen (INR/PT and APTR/APTT only).
- Clinical chemistry.

If it is not possible to perform all screening assessments 7 days prior to procurement, Sponsor approval may be granted to perform procedures within 7 days of procurement under exceptional circumstances.

6.4.2.1 Rescreening of Patients

Patients may be rescreened under conditions such as the following:

a. Marginally failed laboratory screening criteria for haemoglobin, neutrophil count, liver or kidney function tests.

b. Transient or erroneous out of range safety laboratory values.

c. Mild illness (e.g., a self-limiting viral illness) at the time of testing.

If the repeat values for the laboratory screening criteria meet the pre-defined limits as outlined in the list of inclusion criteria and after the patient makes a complete recovery from the illness, the patient may be enrolled.

6.4.3 Tissue and Blood Procurement for ATL001 Manufacture

6.4.3.1 Tumour Tissue Procurement

Upon enrolment, a surgical procedure for tumour sample collection will be scheduled to enable manufacture ATL001. The surgical procedures for tumour tissue procurement should be clinically relevant procedures which do not cause undue risk to patients, as determined by the Investigator, taking into consideration the risk/benefit for the patient.

Access to the archival FFPE block of primary tumour may be requested for analysis of the tumour microenvironment, if available.

Patients should have clearance of the first infectious disease marker screening sample (IDM1) within 30 days of the procurement of tumour tissue to allow material to be accepted into the manufacturing facility, and then a second infectious disease marker screening (IDM2) sample should be taken on the day of tumour tissue procurement.

See Section 6.1.1 for full details of the procurement procedure.

Further instructions for tissue collection, labelling and transportation to the manufacturing facility are provided in the Procurement and Cell Handling Manual.

6.4.3.2 Blood Sampling

The following blood samples will be collected:

a. A blood sample (target volume 140 mL whole blood) for ATL001 manufacture.

b. A blood sample for germline DNA (~10 mL).

c. A blood sample for ctDNA monitoring (~30 mL).

d. A blood sample for HLA testing (~4 mL).

See Section 6.1.2 for full details of the procurement procedure.

Further instructions for tissue collection, labelling and transportation to the manufacturing facility are provided in the Procurement and Cell Handling Manual.

Refer to Section 6.1.3 if additional blood is required.

6.4.3.3 Procurement Follow-up (Day 28 ± 7 days after tumour procurement)

Procedures and assessments at this visit will be:

a. Adverse events (see Section 8.2).

b. Concomitant medications.

c. Physical examination.

d. ECOG performance status.

e. Haematology.

6.4.4 Pre-Lymphodepletion Re-screening (Day -28 to Day -7)

6.4.4.1 Pre-Lymphodepletion Evaluations

a. Informed consent, and assignment to Cohort A, Cohort B or Cohort C (if eligible).

b. Physical Examination.

c. Medical History.

d. Prior therapies.

e. NSCLC history (stage, subtype, molecular profile, treatment history).

f. ECOG performance status.

g. Check eligibility criteria – patients must meet all criteria.

h. Body Weight.

i. Vital signs.

j. Echocardiogram within 60 days prior to lymphodepletion.

k. Pulmonary function test (spirometry) to include FEV1 within 90 days prior to lymphodepletion.

l. Concomitant medications.

m. 12-lead ECG.

n. Blood draws for:

- Haematology.
- Coagulation screen (INR/PT and APTR/APTT only).
- Clinical chemistry.
- Thyroid Function Test.
- CRP.
- ctDNA (~10 mL).
- Baseline samples for immunomonitoring – PBMC, TBNK and plasma cytokines (as close to Day -6 as possible) (~30 mL and up to ~3 mL samples).
- Baseline sample for TCR RNA (as close to Day -6 as possible) (~3 mL).

o. Adverse Events.

p. Serum or urine pregnancy test (for women of childbearing potential).

q. MRI/CT tumour burden assessment must be after last cycle of previous systemic anti-cancer therapy and be within 3 weeks prior to lymphodepletion.

r. Optional tumour biopsy [may be taken at any time between visit 3 and visit 5 if more convenient].

See Section 6.4.14 for Cohort B pembrolizumab treatment administration.

6.4.4.2 Lymphodepletion (Study Days -5 to -1)

Prior to receiving the ATL001 infusion, all patients will undergo non-myeloablative lymphodepleting chemotherapy administered according to local SOPs. For safety purposes, at least the first 3 patients will receive fludarabine 25 mg/m^2 i.v on each of Days -5 to -1 and cyclophosphamide 30 mg/kg i.v. on Days -5 and -4 prior to cell infusion with appropriate supportive care.

If tolerated, the non-myeloablative lymphodepleting chemotherapy regimen will be increased up to fludarabine 25mg/m^2 i.v. on each of Days -5 to -1 and cyclophosphamide 60mg/kg on Days -5 and -4 prior to cell infusion with appropriate supportive care.

Lymphodepletion is contra-indicated in patients with active infections requiring antibiotics, so exclusion 21 should be re-checked prior to commencing lymphodepletion on Day -5, and this will be documented.

Patients will be admitted to the hospital facility for close monitoring on Day -5 (the first day of lymphodepletion).

Patients in Cohort B will receive one dose of pembrolizumab 200mg i.v. on day -7. There is an option to give this up to 7 days before day -6 if more convenient (i.e. any time from day -13 to day -7). Patients who enrol in treatment Cohort B will undergo the same assessments as those patients in Cohort A with the addition of a baseline ECG and vital signs prior to first pembrolizumab dose, and vital signs and physical examination assessments at each subsequent pembrolizumab treatment visit. For assessments prior to pembrolizumab, vital signs should be performed on the day of administration but physical examination (and urine tests, if applicable) may be performed at most recent clinic visit (if not on the same day, prior to administration) if ≤3 days prior to administration. A serum or urine pregnancy test will be required prior to each pembrolizumab administration for female participants of childbearing potential.

On each day of lymphodepletion, the following assessments should be conducted:

a. Blood draws for:
    - Haematology.
    - Clinical chemistry.
b. Adverse events.
c. Concomitant medications.

6.4.5 Pre-Treatment Evaluation and ATL001 Infusion (Study Days -1 to 0 [+5 Days])

6.4.5.1 Baseline Pre-treatment Evaluations (Day -1)

Assessments at the Baseline Pre-treatment Evaluations visit can be performed any time following the final dose of lymphodepletion and prior to cell infusion. Prior to infusion, patients should be considered, in the opinion of the Investigator, well enough (i.e. ECOG Performance Status 0-1) to receive the infusion otherwise a delay should be considered (Section 6.2).

a. Check Inclusion criteria 13 (Patient is well enough to receive ATL001).
b. Adverse Events.
c. Baseline CRS and ICANS Grading.
d. Physical Examination.
e. ECOG Performance Status.
f. Concomitant medications.
g. Body Weight.
h. Vital signs.
i. 12-lead ECG.
j. Pulse oximetry.
k. Blood draws for:
    - Haematology.
    - Coagulation screen (INR/PT and APTR/APTT, fibrinogen and D-Dimer).
    - Clinical chemistry.
    - CRP.

- Immunomonitoring – plasma cytokines only (e.g. IL-6, TNFα, IL-17, INF-γ, IL-1b, IL-2, IL-8, IL-15, IL-10) (~3 mL).
- ctDNA (~10 mL).

6.4.5.2 ATL001 Infusion (Study Day 0 [+5 Days])

Patients should be pre-medicated with a standard regimen to prevent infusion reactions (e.g. chlorphenamine and paracetamol/acetaminophen) according to local SOPs prior to the infusion of ATL001. This prophylactic regimen should not contain corticosteroids. A single dose of ATL001 cell dispersion will be infused within 30 minutes of thawing on Day 0, at least 24 hours after the last dose of fludarabine.

The following should be monitored on Day 0:

a. Pulse oximetry – baseline measure (as close to the start of infusion as possible) and continuous throughout the infusion and for as long as clinically indicated. The readings at the beginning and end of the infusion should be recorded in the eCRF. Post infusion measures at 30 minutes (± 5 minutes), 1 hour (± 10 minutes), 2 hours (± 15 minutes) and 4 hours (± 15 minutes) from the start of infusion, and as clinically indicated.

b. Vital signs – baseline measure (as close to the start of the infusion as possible) and post infusion measures at 30 minutes (± 5 minutes), 1 hour (± 10 minutes), 2 hours (± 15 minutes) and 4 hours (± 15 minutes) from the start of infusion, and as clinically indicated.

c. 12 lead ECG (within 30 minutes following end of infusion, and as clinically indicated).

d. Blood draws for:
   - Haematology.
   - Clinical chemistry.

e. Adverse events.

f. Concomitant medications.

Refer to Appendix G for additional testing requirements in Germany.

Patients should receive a single dose of IL-2 1M IU/m^2 s.c. at 3-12 hours post completion of infusion (Cohort A and Cohort B) or single dose of IL-2 600,000 IU/kg i.v. 3-24 hours post completion of infusion (Cohort C), as long as systolic BP ≥ 90 mmHg and pulse ≤ 100 bpm or pre-infusion levels. The injection can be delayed if needed to allow recovery to these levels. Time of injection should be recorded.

6.4.6 Post Infusion Monitoring (Study Days 1 – 10)

In Cohort A and Cohort B, patients will receive 9 further doses of IL-2 1M IU/m^2 s.c. daily from days 1-9 of the study, as long as clinically stable and there is no evidence of severe infection, capillary leak syndrome or adverse events ≥ Grade 2 that are attributed to IL-2.

Patients in Cohort A and Cohort B should remain in the hospital facility for the time required by clinical consideration, or until any signs/symptoms of treatment-related adverse events have resolved to Grade 1 or baseline levels, whichever is longer.

In Cohort C, patients will receive up to 5 further doses of IL-2 600,000 IU/kg i.v. 8-12 hourly as long as clinically stable and there is no evidence of severe infection, capillary leak syndrome or adverse events ≥ Grade 3 that are attributed to IL-2.

Patients in Cohort C must remain in the hospital facility for the duration of IL-2 administration or until any signs/symptoms of treatment-related adverse events have resolved to Grade 1 or baseline levels, whichever is longer.

Assessments (every day will be a study visit day)

a. Adverse events (daily).
b. CRS and ICANS Grading.
c. Physical examination (daily).
d. Concomitant medications (daily).
e. Vital signs and pulse oximetry (every day until day 10, and as clinically indicated).
f. Body Weight (daily as an early indicator of fluid retention).
g. Blood draws for:
    - Haematology (to be conducted daily post cell infusion until values return to normal or baseline, or as clinically indicated).
    - Coagulation screen (INR/PT and APTR/APTT, fibrinogen and D-Dimer) (Days 1, 2, 3, 5, 7, and 10 post infusion and as clinically indicated.
    - Clinical chemistry evaluations (except TFTs) (to be conducted daily post cell infusion until values return to normal or baseline, or as clinically indicated).
    - CRP (Days 1, 2, 3, 5, 7 and 10 post infusion and as clinically indicated).
    - Immunomonitoring – Plasma cytokines (Days 1, 2, 3, 5, 7, and 10 post infusion, and repeated on day 12 if hospitalisation is prolonged due to CRS or ICANS for event assessment).
    - Immunomonitoring – PBMC and TBNK (~30 mL, Days 3, 7 and 10 post-infusion).
    - ctDNA (~10 mL day 7).
    - TCR RNA (~3 mL, Days 7 and 10 post-infusion).

See Section 6.3 for Immunomonitoring (PBMC and TBNK), Immunomonitoring (Cytokines), TCR RNA and ctDNA sample collection windows.

6.4.7 Early Follow-Up Period (Days 14 – 28)

Following discharge, all patients will attend clinic visits on days 14 (±3 days), 21 (±3 days), 28 (±7 days), post ATL001 infusion. The following study-specific assessments will be performed at each visit for all patients.

a. Adverse Events.
b. CRS and ICANS Grading.
c. Concomitant medications.

d. Physical examination (Cohort A and C: anytime during the day; Cohort B: prior to pembrolizumab treatment administration).

e. ECOG Performance Status (Cohort B: prior to pembrolizumab treatment administration).

f. Blood draws for:

- Haematology (not coagulation unless clinically indicated).
- Clinical chemistry safety evaluations (including CRP but not TFTs unless clinically indicated).
- Immunomonitoring – PBMC, TBNK and plasma cytokines (Plasma cytokines may additionally be performed on days 17 and 24 if hospitalisation is prolonged due to CRS or ICANS for event assessment).
- TCR RNA.
- ctDNA (~10 mL).

Patients in treatment Cohort B will receive pembrolizumab on day 21 at a dose of 200 mg i.v.. If patients have any toxicity that would prevent them from receiving pembrolizumab at the day 21 visit, the treatment should be delayed until they have resolved to Grade 1 or baseline. Refer to the latest available prescribing information (e.g. SmPC/Package Insert) and to local and national treatment guidelines for further reference safety information for pembrolizumab.

6.4.8 Intermediate Follow-Up Period (Week 6 – Week 24)

Patients will attend clinic visits every 6 weeks (weeks 6, 12, 18 and 24, all ±7 days) for the first 6 months post ATL001 infusion. The following study-specific assessments will be performed at each visit prior to, and at the visit of, confirmed disease progression.

a. Adverse Events.

b. ICANS Grading until Week 12 (and at Week 24 if not Grade 0 at Week 12).

c. Concomitant medications.

d. Physical examinations (Cohort B only: Prior to pembrolizumab treatment administration may be performed at most recent clinic visit if ≤ 3 days prior to administration).

e. ECOG Performance status (Cohort B only: Prior to pembrolizumab treatment administration).

f. Body Weight.

g. Vital signs (Cohort B only: Prior to pembrolizumab treatment administration).

h. Blood draws for:

- Haematology (not coagulation unless clinically indicated).
- Clinical chemistry safety evaluations including CRP (TFTs on weeks 12 and 24 only unless more frequent assessment is clinically indicated).
- Immunomonitoring – PBMC, TBNK and plasma cytokines (~33 mL each visit – see Section 8.4).

- Immunomonitoring – for extended immunological assays, one 150 mL sample at week 6 only (unless the patient's clinical condition precludes this sample) – see Section 8.4).
- TCR RNA (Week 6, 12, 18 and 24).
- ctDNA (~10 mL at all timepoints but ~30 mL at week 12).

i. MRI/CT tumour burden evaluations (Week 6, 12, 18 and 24 and then every 12 weeks until the time of confirmed radiological disease progression – see Section 6.4.13).

j. Optional Tumour Biopsies: post treatment tumour biopsies will be requested (at week 6 or week 12 and/or at disease progression in patients whose tumour is safely accessible for biopsy. These samples will be used to assess the immune status of the tumour after ATL001 treatment and to explore changes related to efficacy/resistance to treatment). If a biopsy cannot be collected at week 6 or week 12, a tumour biopsy may be provided at a different timepoint. This will be agreed following a discussion with Sponsor.

For patients of childbearing potential:

All Cohorts: Additional urine or serum pregnancy testing is required if the patient is being treated in Germany. This testing is required every 6 weeks for 12 months following ATL001 dose, study completion or withdrawal from study (refer to Appendix G).

Cohort B: Urine or serum pregnancy testing is required prior to each pembrolizumab administration (i.e. every 6 weeks). For Cohort B patients being treated at sites in Germany, if pembrolizumab doses are delayed, omitted, or discontinued for any reason then the frequency of pregnancy testing should be adjusted accordingly but must satisfy the 6-weekly requirement seen in Cohort A (refer to Appendix G).

Patients in treatment Cohort B will attend for additional visits to receive pembrolizumab at dose of 400 mg i.v. every 6 weeks, if tolerated, for up to 12 months, up to 6 months following a CR or until RECIST v1.1 confirmed disease progression, whichever is sooner.

If a patient has disease progression during this study period, refer to Section 6.4.10.

6.4.9 Long Term Follow-Up Period (Week 36 – Week 104)

Patients will attend clinic visits every 12 weeks (weeks 36, 48, 60, 72, 84, 96 and 104) (all ±14 days), post ATL001 infusion. The following limited study-specific assessments will be performed at each visit prior to, and at the visit of, confirmed disease progression.

a. Adverse Events of Special Interest (see Section 8.2.4).

b. Concomitant medications.

c. Physical examinations (Cohort B only: Prior to pembrolizumab treatment administration may be performed at most recent clinic visit if ≤ 3 days prior to administration).

d. ECOG Performance status (Cohort B only: Prior to pembrolizumab treatment administration).

e. Body Weight.

f. Vital signs (Cohort B only: Prior to pembrolizumab treatment administration).

g. Blood draws for:
    - Haematology (not coagulation unless clinically indicated).
    - Clinical chemistry safety evaluations, except CRP (TFTs on weeks 48, 72 and 104 only, unless more frequent assessment is clinically indicated).
    - Immunomonitoring – PBMC, TBNK and plasma cytokines.
    - TCR RNA.
    - ctDNA (~10 mL).

h. MRI/CT tumour burden evaluations (until the time of confirmed radiological disease progression – see Section 6.4.13).

Patients in treatment Cohort B will attend for additional visits to receive pembrolizumab at dose of 400 mg i.v. every 6 weeks, if tolerated, for up to 12 months, up to 6 months following a CR or until RECIST v1.1 confirmed disease progression, whichever is sooner.

If the patient has disease progression during this study period, refer to Section 6.4.10.

For patients of childbearing potential:

All Cohorts: Additional urine or serum pregnancy testing is required if the patient is being treated in Germany. This testing is required every 6 weeks for 12 months following ATL001 dose, study completion or withdrawal from study (refer to Appendix G).

Cohort B: Urine or serum pregnancy testing is required prior to each pembrolizumab administration (i.e. every 6 weeks). For Cohort B patients being treated at sites in Germany, if pembrolizumab doses are delayed, omitted, or discontinued for any reason then the frequency of pregnancy testing should be adjusted accordingly but must satisfy the 6-weekly requirement seen in Cohort A (refer to Appendix G).

6.4.10 Survival Follow-up Visits

If the patient has confirmed disease progression prior to Week 104, patients will move into Survival Follow-Up. These study visits will be scheduled every 12 weeks (± 14 days) until Week 104 (or Week 364, until such time as the Long Term Follow Up study is available at study site), and assessments will consist only of assessments listed below. These visits could be conducted by phone if deemed clinically appropriate by the Investigator.

a. Anti-cancer treatments.

b. Survival Status.

c. Adverse Events of Special Interest (see Section 8.2.4).

6.4.11 Withdrawal/Completion Visit

After week 104 (2 years ±14 days) following ATL001 infusion, no further follow up visits will be performed in this protocol, and the patient will have completed the study. Patients will continue to be followed up for a further 5 years in a separate Long Term Follow Up Protocol. The assessments will be the same as described in Section 6.4.10 with a reduced frequency.

Patients who complete the study or who withdraw from the study for any reason prior to the week 104 visit will be asked to complete a Withdrawal/Completion Visit.

For patients who withdraw from the study within 28 days of procurement, the withdrawal/completion visit should be completed at Visit 3. If patients are withdrawn after Visit 3 and before lymphodepletion, no further follow up investigations are required provided that the Visit 3 assessments were performed after procurement and any ongoing procurement-related adverse events have resolved. For patients who withdraw from the study after commencing lymphodepletion but before receiving ATL001, the withdrawal/completion visit will require information about toxicities related to study treatments, which should be followed up until resolution.

For patients who withdraw from the study after receiving ATL001, the withdrawal/completion visit assessments will be completed (except MRI/CT scan if performed at the preceding visit).

Patients who have received ATL001 and who withdraw from the study prior to the week 104 visit will be asked consent to the collection of survival status information and adverse events of special interest at 3-monthly periods until week 104 (or Week 364, until such time as the Long Term Follow Up study is available at study site) after dosing. After this period, patients will be asked to consent to the collection of survival status as part of the separate Long Term Follow Up Protocol. Overall, each patient will continue to be followed up for a minimum period of 5 years, as part of the separate Long Term Follow Up Protocol.

If the Long Term Follow Up protocol is not yet available at the study site, patients will continue to be followed up in the original study protocol until such time as the Long Term Follow Up is available at study site.

6.4.12 Unscheduled Visit

At the Investigators' discretion, an Unscheduled Visit may be completed at any time during the study, if deemed necessary for the patients' safety and wellbeing. Unscheduled visits may also be completed in the cases of re-collection of blood or re-administration of ATL001 or the collection of excess biological material from standard of care procedures.

6.4.13 Efficacy Monitoring

6.4.13.1 Assessment Modalities

Anti-tumour activity will be assessed at scheduled timepoints by CT scans of chest, abdomen and pelvis, and other locations if indicated. If CT scanning is not acceptable, MRI may be an alternative. The same modality should be used per patient throughout the study to assess lesion responses.

Access to the scan most recently preceding procurement and any CT scans conducted as part of standard clinical practice to assess the patient's response to the most recent therapy, may be required to retrospectively evaluate response to the immediately preceding therapy, in order to aid the assessment and interpretation of clinical activity.

6.4.13.2 imRECIST Considerations

In this study protocol, both RECIST 1.1 and imRECIST tumour responses will be recorded.

ATL001 may induce an inflammatory reaction within tumours due to the infiltration and activation of T cells, and as a result, the phenomenon of pseudo-progression may be observed at the initial scan, as has been documented when treatment is initiated with checkpoint inhibitors. The immune modified RECIST (imRECIST) guidelines [Hodi et al, 2018] have been developed to take this into account and there are some important considerations to be aware of which have implications for the conduct of the study.

According to RECIST v1.1 criteria [Eisenhauer et al, 2009] an observation of disease progression (PD) at the first scan should be recorded as a best response of PD whereas imRECIST criteria recognise responses that are observed following an initial radiological PD, provided that a minimum time-period of at least 4 weeks has elapsed following the initial PD and the subsequent scan.

Secondly, unlike RECIST v1.1, the imRECIST criteria do not consider non-target lesions in the definition of disease progression and the appearance of new lesions per se is also not considered to be evidence of disease progression, unless the dimension of the new lesion when added to the target lesions would result in an increase in tumour burden ≥ 20% relative to the nadir.

The implications for efficacy monitoring are:

1. All patients should have at least two post-baseline scans, regardless of whether a RECIST v1.1 progression or imRECIST progression was observed at the first post-baseline scan.
2. Investigators should use imRECIST criteria in determining whether disease progression has been detected and whether further radiological imaging is required in the study.
    a. As per imRECIST guidelines, all imRECIST progression events should be confirmed by scanning at two consecutive timepoints at least 28 days apart.

Further details are provided in Section 15, Appendix B and the study Statistical Analysis Plan (SAP).

6.4.14 Cohort B: Pembrolizumab Treatment Administration

6.4.14.1 Day -13 to Day -7

A single dose of pembrolizumab 200 mg i.v. between Day -13 and Day -7 will be administered prior to lymphodepletion dose.

6.4.14.2 Day 21

A dose of pembrolizumab 200 mg i.v. will be administered on Day 21 (+3 days). If patients have any toxicity that would prevent them from receiving pembrolizumab at the Day 21 visit, the treatment should be delayed until toxicity resolved to Grade 1 or baseline. Refer to the latest available prescribing information (e.g. SmPC/Package Insert) and to local and national treatment guidelines for further reference safety information for pembrolizumab.

6.4.14.3 Week 6 and then Every 6 Weeks (Up to 12 months)

Patients in treatment Cohort B will attend for additional visits to receive pembrolizumab at dose of 400 mg i.v. at Week 6 (± 3 days) and then every 6 weeks (± 3 days), if tolerated, for up to 12 months, up to 6 months following a CR or until RECIST v1.1 confirmed disease progression, whichever is sooner.

Refer to the latest available prescribing information (e.g. SmPC/Package Insert) and to local and national treatment guidelines for further reference safety information for pembrolizumab.

7 SAFETY MONITORING AND MANAGEMENT GUIDELINES

7.1 Anticipated Safety Risks

The principal anticipated safety risks, as summarised in Section 2.2, are associated with the procurement procedures, transient pancytopenia due to the lymphodepletion regimen, adverse events related to the administration of IL-2, and to the cell infusion itself, including infusion

reactions, cytokine release syndrome (CRS) and Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS). CRS is considered a potential risk because of *in vivo* T cell proliferation and activation, although this is not anticipated to be as great with a TIL product as for patients receiving a CAR-T cell therapy. CRS is a result of excessive IL-6 production from activated T cells, and treatment with the anti-IL-6 receptor antibody, tocilizumab, has been shown to be an effective strategy in patients receiving CAR-T therapies for other cancers and will need to be available on site. Due to shortages of tocilizumab caused by the COVID-19 pandemic, siltuximab (anti-IL-6 antibody) may be used in first line treatment of CRS, rather than in second line (See Table 4).

7.2 General Precautions

Patients will be admitted to hospital for close monitoring on Day -5 and should remain in the hospital facility for the time required by clinical consideration, or until any signs/symptoms of treatment-related adverse events have resolved to Grade 1 or baseline levels, whichever is longer. Patients in Cohort C must remain in the hospital facility for the duration of IL-2 administration or until any signs/symptoms of treatment-related adverse events have resolved to Grade 1 or baseline levels, whichever is longer.

Following discharge from hospital patients should be advised to remain within close distance of the Investigational Site or an alternative local cell therapy treatment centre for 4 weeks in case any new adverse events arise between scheduled visits. Patients should be advised not to drive for 8 weeks following the cell infusion.

ATL001 is being studied in two clinical trials for solid tumours which are recruiting concurrently (one is this study and the second is a study in patients with recurrent or metastatic melanoma, ATX-ME-001). Safety of the IMP will be evaluated in all patients to whom the IMP has been administered. The first 3 patients to receive ATL001 (across both ATX-NS-001 and ATX-ME-001) had been observed for 14 days following ATL001 infusion before the next patient underwent lymphodepletion. This is considered sufficient to identify symptoms of immediate cytokine release syndrome or severe infusion reactions.

Providing none of the following events are observed in any of the first three patients to receive ATL001 across both studies, the observation period between patient administrations (inter- and intra-study) may be reduced to 7 days:

- Severe infusion reaction requiring i.v. corticosteroid.
- Grade 3 or worse autoimmunity, cytokine release syndrome or capillary leak syndrome, that does not resolve to Grade 2 or below within 2 days.
- Grade 2 or worse neurological toxicity that does not resolve to Grade 1 or baseline within 2 days.
- The omission of more than 2 doses of IL-2 due to an adverse event related to IL-2.
- Any other clinically significant adverse event considered to be related to ATL001 infusion.

The IDSMC will review all safety data from the first 6 patients to whom ATL001 is administered across both studies and if ≤1 of these events have been observed in 6 patients, the requirement for an observation period between patient administrations will be discontinued. This decision will be documented in the IDSMC meeting minutes.

7.3 Adverse Events Related to Tissue Procurement Procedures

Patients should be managed according to local standard surgical and anaesthetic guidelines. Procedure-related AEs and all SAEs will be collected for 28 days post tumour tissue procurement or until the patient starts systemic therapy for lung cancer, whichever is sooner.

7.4 Management of Adverse Events Related to Lymphodepletion Regimen

The fludarabine and cyclophosphamide lymphodepletion regimen is expected to cause transient pancytopenia for approximately 14 days, during which time patients will be susceptible to infections. Other common side effects associated with fludarabine and cyclophosphamide include poor appetite, nausea, vomiting, fatigue and diarrhoea. Cyclophosphamide at high doses can cause bladder irritation and fluid retention.

Patients should receive prophylactic treatment with cotrimoxazole, acyclovir and fluconazole if required according to local SOPs following fludarabine and cyclophosphamide, for the prevention of infections in neutropenic patients. Cytomegalovirus (CMV)/Epstein-Barr virus (EBV) polymerase chain reaction (PCR) assays may be assessed if clinically indicated following lymphodepletion.

Urinalysis may be assessed as clinically indicated from the start of lymphodepletion throughout the duration of the study at the discretion of the Investigator.

Patients may receive supportive care with growth factors and irradiated blood products as required to treat neutropenia and anaemia. The use of filgrastim (G-CSF) is permitted from Day 1 as per Investigator discretion and local SOPs.

Patients requiring blood product support at any time in the future after receiving fludarabine should receive irradiated blood products.

Patients should not receive any live vaccinations for at least 3 months following lymphodepletion, per fludarabine Summary of Product Characteristics (SmPC).

Please consult the latest available version of the SmPC, package leaflet and/or other healthcare intended materials before taking any action relating to fludarabine and cyclophosphamide.

7.5 Management of Adverse Events Related to IL-2

IL-2 is known to cause hypotension, diarrhoea, chills, nausea, vomiting, and rash. A very rare side effect is ‘capillary leak syndrome’ which can cause limb oedema, hypotension, arrhythmias, dyspnoea and hypoalbuminaemia. The daily doses of IL-2 in Cohorts A and B are 18 times lower than the doses used to treat melanoma and renal cancer, so it is considered unlikely that capillary leak syndrome will occur. In Cohort C, IL-2 dosing will be 600,000 IU/kg and administered by intravenous infusion at a frequency of 8-12 hourly for up to a maximum of six doses as tolerated. Toxicities are more likely at higher doses over shorter periods of time. If toxicities can be reversed within 24 hours by supportive measures, then additional doses may continue. If greater than two doses of IL-2 are skipped, IL-2 administration will be ceased. In addition, dosing may be held or stopped at the discretion of the treating Investigator.

Vital signs, pulse oximetry, weight and adverse events will be monitored daily while patients are receiving IL-2 so that adverse reactions can be detected early and dose modifications may be made accordingly. IL-2 dosing will be interrupted if patient experiences Grade 3 or 4 toxicity related to IL-2 (with the exception of reversible Grade 3 toxicities attributable to IL-2, such as diarrhoea, nausea, vomiting, hypotension, rash/skin changes, anorexia, mucositis, dysphagia, or constitutional symptoms and laboratory changes). Management of IL-2 toxicity is detailed in Appendix F.

Please consult the latest available version of the SmPC, package leaflet and/or other healthcare intended materials before taking any action relating to IL-2.

7.6 Management of Adverse Events Related to Pembrolizumab (Cohort B Patients Only)

Pembrolizumab may cause autoimmune-related pathologies including endocrinopathies, pneumonitis, colitis, nephritis, hepatitis and skin reactions.

Based on the severity of the adverse reaction, pembrolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid taper should be initiated and continued over at least 1 month. Pembrolizumab may be restarted within 12 weeks after last dose if the adverse reaction recovers to Grade ≤ 1 and corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day.

For guidance on treatment/dose modifications necessitated by immune-related AEs involving pembrolizumab, refer to Table 2 extracted from the SmPC/Package Insert for pembrolizumab.

Please consult the latest available version of the SmPC, package leaflet and/or other healthcare intended materials before taking any action relating to this agent. Please also refer to local, regional and national guidelines for the management of pembrolizumab toxicity and to the SmPC/Package Insert for pembrolizumab for reference safety information.

Table 3: Recommended Treatment/Dose Modifications for Pembrolizumab (Adapted from SmPC and Package Insert)

Immune-related adverse reactions	Severity	Treatment modification
Pneumonitis	Grade 2	Withhold until adverse reactions

		recover to Grades 0-1*
	Grades 3 or 4, or recurrent Grade 2	Permanently discontinue
Colitis	Grade 2 or Grade 3	Withhold until adverse reactions recover to Grades 0-1*
	Grade 4 or recurrent Grade 3	Permanently discontinue
Nephritis	Grade 2 with increased blood creatinine	Withhold until adverse reactions recover to Grades 0-1*
	Grade ≥ 3 with increased blood creatinine	Permanently discontinue
Endocrinopathies	Grade 2 adrenal insufficiency and hypophysitis	Withhold treatment until controlled by hormone replacement
	Grades 3 or 4 adrenal insufficiency or symptomatic hypophysitis Type 1 diabetes associated with Grade ≥ 3 hyperglycaemia (glucose > 250 mg/dL or > 13.9 mmol/L) or associated with ketoacidosis Hyperthyroidism Grade ≥ 3	Withhold until adverse reactions recover to Grades 0-1* For patients with Grade 3 or Grade 4 endocrinopathies that improved to Grade 2 or lower and are controlled with hormone replacement, if indicated, continuation of pembrolizumab may be considered after corticosteroid taper, if needed. Otherwise treatment should be discontinued.
	Hypothyroidism Grade 3 and 4	Withhold until clinically stable or permanently discontinue depending on severity
Hepatitis	Grade 2 with AST or ALT > 3 to 5 times ULN or total bilirubin > 1.5 to 3 times ULN	Withhold until adverse reactions recover to Grades 0-1*
	Grade ≥ 3 with AST or ALT > 5 times ULN or total bilirubin > 3 times ULN	Permanently discontinue
	In case of liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥ 50% and lasts ≥ 1 week	Permanently discontinue
Skin reactions	Grade 3 or suspected SJS or TEN	Withhold until adverse reactions recover to Grades 0-1*
	Grade 4 or confirmed SJS or TEN	Permanently discontinue
Other immune-related adverse reactions	Based on severity and type of reaction (Grade 2 or Grade 3) Grades 2, 3 or 4 myocarditis Grades 3 or 4 encephalitis Grades 3 or 4 Guillain-Barré Syndrome Grade 4 or recurrent Grade 3	Withhold until adverse reactions recover to Grades 0-1* Permanently discontinue
Infusion-related reactions	Grades 1 or 2 Grades 3 or 4	Interrupt or slow the rate of infusion Permanently discontinue

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v.4).

** If treatment-related toxicity does not resolve to Grades 0-1 within 12 weeks after last dose of pembrolizumab, or if corticosteroid dosing cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks, pembrolizumab should be permanently discontinued.*

ALT, alanine aminotransferase; AST, aspartate aminotransferase; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; ULN, upper limit of normal.

7.7 Management of Adverse Events Related to ATL001 Infusion

7.7.1 Infusion Reactions

There may be a risk of an infusion reaction (e.g. fever, chills, headache). This risk will be reduced by the administration of a standard prophylactic regimen (e.g. chlorphenamine and paracetamol/acetaminophen) according to local SOPs before the infusion is given. However, prophylactic corticosteroids must be avoided.

If a patient develops an infusion reaction during the infusion, the following procedures should be followed:

- **Mild to moderate reactions** (e.g. low-grade fever (< 38.5°C); hypotension (< 30 mmHg decrease from baseline))
    - Slow down the infusion rate.
    - Consider giving PRN antipyretic/antihistamine medication.
    - Avoid corticosteroids where possible.
- **Moderate to severe reactions** (e.g. fever > 38.5°C; chills; mucosal swelling; shortness of breath; hypotension (> 30 mmHg from baseline))
    - Stop the infusion and treat the symptoms with antihistamine/antipyretic medication and supportive care.
    - Consider need for i.v. hydrocortisone.
    - If cytokine release syndrome is suspected, tocilizumab or siltuximab therapy may be beneficial. See Section 7.7.4.

In the event of an infusion reaction which does not require corticosteroid treatment, the infusion may be restarted once the symptoms have resolved and completed, provided this is not more than 30 minutes from thawing and the symptoms/signs do not recur. The Sponsor (or representative) should be contacted to inform them of any patient that does not receive the full infusion and the remaining infusate should be retained at 2-8°C pending instructions from the Sponsor.

In the event of an infusion reaction severe enough to require i.v. corticosteroid, the infusion should be permanently discontinued, and the Sponsor should be informed.

7.7.2 DMSO Toxicities

These are very rare but may include: raised or lowered blood pressure, seizure or respiratory arrest. The most common reaction is hypertension, in which case giving anti-hypertensive medication and diuretics is recommended.

7.7.3 Autoimmune Related Toxicity

It is considered unlikely that ATL001 infusion will trigger autoimmune related toxicity as there is no genetic modification of the T-cell receptor, the product is derived from TILs that have undergone selection for self-tolerance, and clonal neoantigens are tumour-specific rather than tumour-associated antigens so cross reaction with naturally occurring proteins should not occur. However, as this is a first-in-human study, patients will undergo monitoring for development of autoimmune conditions. Patients in Cohort B may be at greater risk of developing autoimmune related toxicity than patients in Cohort A and Cohort C, as a result of more prolonged exposure to the immune checkpoint inhibitor pembrolizumab, which is associated with this adverse effect.

In addition to sequential measurements of thyroid function for two years, neurological toxicity and autoimmune conditions are defined as Adverse Events of Special Interest for ATL001, to ensure they will be monitored, and their relatedness to ATL001 will be considered, throughout the study and the long term follow up period.

7.7.4 Cytokine Release Syndrome

Cytokine release syndrome (CRS) and associated toxicities is considered a potential risk because of *in vivo* T cell proliferation and activation. Cytokine release syndrome may develop within minutes or hours following a CAR-T cell infusion but can have a later onset during the first 2 weeks.

Patients should be monitored for symptoms/signs of cytokine release syndrome during the first 10 days after the infusion (and for longer if any evidence of CRS on day 10).

Appendix D provides an example CRS Monitoring Chart which can be used by investigational sites for these assessments.

Patients should be treated according to the severity grade as initially recommended by Lee et al, 2014 and updated in the American Society for Transplantation and Cellular Therapies (ASTCT) Consensus Grading which recognised **fever, hypotension and hypoxia** as the principal determinants of CRS severity [Lee et al, 2019]. Patients who develop fever or other symptoms/signs of CRS during this period must remain in hospital until symptoms have resolved. For the purposes of recording events of CRS, the ASTCT Consensus Grading System (see Table 4) should be used rather than the common terminology criteria for adverse events (CTCAE) system.

Table 4: ASTCT Consensus Grading of CRS (Taken from Lee et al, 2019)

ASTCT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[*]	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or[†]		
Hypoxia	None	Requiring low-flow nasal cannula[‡] or blow-by	Requiring high-flow nasal cannula[‡], facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.
[*] Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
[†] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.
[‡] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Multiple treatment algorithms for CRS have been developed since the approvals of CAR-T cell therapies [reviewed by Riegler et al, 2019], with a common goal of preventing irreversible organ damage without compromising clinical activity. All recommend the early use of the IL-6 receptor inhibitor, tocilizumab in patients with Grade 2 CRS that is not responding to conservative management and in patients who are developing severe CRS (Grade 3 or 4). High dose

corticosteroids are recommended in severe and life-threatening conditions. The best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) for the management of CRS aligned to the ASTCT Grading System 2019 [Yakoub-Agha, 2020] are presented here as a suggested management plan, although it is expected that sites will also follow their local SOPs.

Table 5: Suggested CRS Treatment Algorithm (Adapted from Lee et al, 2019 and Yakoub-Agha, 2020)

CRS Grade	Treatment
Grade 1 Fever ≥ 38°C without hypotension or hypoxia	**Corticosteroids should be avoided** Investigate potential sources of infection, then commence supportive care according to institutional standards including analgesics, antipyretics, and broad-spectrum antibiotics. If no improvement after 3 days, consider tocilizumab 8mg/kg/i.v.
Grade 2 Fever ≥ 38°C Hypotension not requiring vasopressors Hypoxia requiring low flow nasal cannula or blow-by	**Corticosteroids should be avoided unless condition deteriorates** Alert the ICU and Sponsor Medical Monitor. Investigate potential sources of infection, then commence supportive care (as above) including fluid substitution for hypotension and low-flow oxygen. Use tocilizumab 8mg/kg/i.v. early if symptoms do not improve soon or worsen and repeat if required*. If condition deteriorates consider adding i.v. dexamethasone 10mg q.d.s. for 1 to 3 days. [Corticosteroids should be tapered as soon as possible, as clinical condition permits].
Grade 3 Fever ≥ 38°C WITH Hypotension requiring a vasopressor with or without vasopressin AND/OR Hypoxia requiring high flow nasal cannula, face mask, nonrebreather mask, venturi mask	Intensive care. Single vasopressor with or without vasopressin. High flow oxygen. Tocilizumab 8mg/kg/i.v. (repeated as necessary*) and dexamethasone 10mg i.v. q.d.s. for 1 to 3 days. [Corticosteroids should be tapered as soon as possible, as clinical condition permits]. If condition deteriorates consider increasing i.v. dexamethasone to 20mg q.d.s. for 1 to 3 days.
Grade 4 Fever ≥ 38°C	Intensive care.

CRS Grade	Treatment
WITH Hypotension requiring multiple vasopressors (excluding vasopressin) AND/OR Hypoxia requiring positive pressure	Positive Pressure Oxygen e.g. CPAP, BiPAP, intubation and mechanical ventilation. Tocilizumab 8mg/kg/i.v. (repeated as necessary*) and dexamethasone 20mg i.v. q.d.s. for 3 days, tapering over 7 days. If condition deteriorates consider changing dexamethasone to methylprednisolone 1000mg/day for 3 days, then 250mg b.d. for 2 days, then 125mg b.d. for 2 days and then 60mg b.d. for 2 days.

**The initial dose of tocilizumab given should be 8 mg/kg administered over 60 minutes as an i.v. infusion. If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, up to 3 additional doses may be administered. The interval between consecutive doses should be at least 8 hours. Doses exceeding 800 mg per infusion are not recommended in CRS patients. Siltuximab 11mg/kg for 1 day may be considered as a second line option if unresponsive to tocilizumab.*

Adapted from: Lee et al, 2019 and Yakoub-Agha, 2020.

**https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125276s114lbl.pdf*

7.7.5 Immune Effector Cell-Associated Neurotoxicity Syndrome

Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS) is defined by ASTCT as 'a disorder characterized by a pathologic process involving the central nervous system (CNS) following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema.' It may occur at the same time as CRS or after CRS has resolved and symptoms generally resolve over a period of 2 to 9 days with management.

The earliest manifestations of ICANS are tremor, dysgraphia, mild difficulty with expressive speech (especially in naming objects), impaired attention, apraxia and mild lethargy, so it is important that patients are closely monitored for these symptoms during the early period of hospitalisation. The Immune effector Cell-associated Encephalopathy (ICE) score is recommended for these assessments (see Table 5). ICANS assessments should be documented at baseline (pre-infusion) and should be assessed at least once daily from the day of cell infusion, and at each visit until week 12 as part of the general assessment of the patient's neurological condition. If any abnormalities are detectable at week 12, the assessments should be repeated at week 24. From the first sign of any neurological or behavioural disturbance, these assessments should be performed at least twice a day. These assessments, along with the level of consciousness and signs of seizure, motor weakness or raised intracranial pressure give the overall ICANS Grade (see Table 6). Appendix E provides an example Neurotoxicity Monitoring Chart which can be used by investigational sites for these assessments.

Table 6: ICE Score (Adapted from Lee et al, 2019)

Domain	Score
Orientation: To year, month, city, hospital	4
Naming: Ability to name 3 objects	3
Following commands: Ability to follow simple	1

Writing: Ability to write a standard sentence	1
Attention: Ability to count back from 100 by 10	1

Table 7: ASTCT Consensus Grading of ICANS (Taken from Lee et al, 2019)

ASTCT ICANS Consensus Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging§	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.
N/A indicates not applicable.
* A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.
† Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).
‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.
§ Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Patients should be managed according to the overall severity grade of ICANS, as defined in the ASTCT Consensus Grading System [Lee et al, 2019] (see Table 6). For the purposes of recording events of ICANS, the ASTCT Grading System should be used rather than the CTCAE system.

The best practice recommendations of the EBMT and JACIE for the management of ICANS aligned to the ASTCT Grading System [Yakoub-Agha, 2020] are presented here as a suggested management plan, although it is expected that sites will also follow their local SOPs.

As a further precaution, prophylactic treatment with the non-sedating anti-seizure medication levetiracetam (Keppra) at a dose of 500 mg b.d. should be commenced at the earliest sign of neurological or behavioural abnormality, even if the ICANS Grade at the time is normal. This recommendation will be reviewed by the IDSMC at scheduled safety reviews.

Table 8: Suggested ICANS Treatment Algorithm (Adapted from Lee et al, 2019 and Yakoub-Agha, 2020)

ICANS Grade	Treatment
Commence Levetiracetam seizure prophylaxis 500 mg b.d. at the earliest sign of neurological or behavioural disturbance even if ICANS assessment is normal	
Grade 1 ICE Score 7-9, decreased level of consciousness but spontaneously awakes	**Alert neurologist and ICU** Alert Sponsor Medical Monitor. Close monitoring and supportive care. ICANS Grade assessment at least twice daily. Avoid medications that cause CNS depression. Daily EEG and Fundoscopy. MRI scan or CT if not available. Lumbar Puncture (LP) as clinically indicated.

ICANS Grade	Treatment
	Commence Levetiracetam seizure prophylaxis 500 mg b.d. if not already started. Consider low doses of haloperidol (0.5mg i.v. every 6 hrs) or lorazepam (0.25-0.5mg i.v. every 8 hrs) to manage agitation.
Grade 2 ICE Score 3-6, decreased level of consciousness but awakes to voice	**Alert neurologist and move to ICU** Close monitoring including EEG, Fundoscopy, MRI and then LP if no suggestion of raised intracranial pressure (ICP). Commence Levetiracetam seizure prophylaxis 500 mg b.d. if not already started. Commence i.v. dexamethasone 10mg q.d.s. for 1 to 3 days. [Corticosteroids should be tapered as soon as possible when symptoms resolve to Grade 1, as clinical condition permits]. *Tocilizumab not indicated unless concurrent CRS.*
Grade 3 ICE Score 0-2, very decreased level of consciousness and only awakes to tactile stimulus Any seizures Evidence of focal or local cerebral oedema	Intensive care. Manage seizures with benzodiazepine and levetiracetam (Keppra). Commence dexamethasone 10mg i.v. q.d.s. or 20mg i.v. b.d. for 1 to 3 days. [Corticosteroids should be tapered as soon as possible when symptoms resolve to Grade 1, as clinical condition permits]. *Tocilizumab not indicated unless concurrent CRS.* If Grade 3 ICANS persists, consider repeating neuroimaging every 2 to 3 days.
Grade 4 ICE Score impossible Unrousable or only awakens to vigorous repetitive stimulation Life threatening prolonged or repetitive seizures Deep focal motor weakness Generalised cerebral oedema Papilloedema, Cushing's triad or Cranial nerve VI palsy	Intensive care. Methylprednisolone 1000mg/day for 3 days, then 250mg b.d. for 2 days, then 125mg b.d. for 2 days and then 60mg b.d. for 2 days. Consider alternatives e.g high dose cyclophosphamide, Siltuximab, Anakinra (IL-1R antagonist)

ICANS Grade	Treatment
Decorticate or Decerebrate posturing	

7.8 Study Safety Stopping Criteria and Procedures

An Independent Data Safety Monitoring Committee will be formed to monitor patient safety during the study (see Section 9.5 for description and meeting schedule).

An initial formal review of safety by the IDSMC will take place after the first 6 evaluable patients have received ATL001 treatment in all studies of ATL001 running concurrently and all these patients have been followed up for a minimum of 28 days. For the purpose of the IDSMC review, an evaluable patient is a patient who has received lymphodepletion and ATL001. All safety data from any patients treated in the study during this period will be considered in the review.

A second IDSMC safety review will take place when 6 evaluable patients have received ATL001 treatment within this study and followed up for a minimum of 28 days. This safety review will determine whether enrolment into Cohort B can commence at centres. These two reviews may be combined depending on recruitment timings. The IDSMC will be informed about other study related activities as deemed relevant to the ongoing oversight of patient safety including the initiation of additional cohorts or procedures.

An IDSMC safety review of the first 6 patients treated in each treatment Cohort will also be scheduled. Reviews of safety will take place when the first 3 patients have been treated and followed up for a minimum of 28 days in each additional treatment Cohort, with similar reductions in observation period(s) if there are no unexpected toxicities associated with these Cohorts.

At any of these 6-patient safety reviews, if 2 or more patients out of 6 exhibit any of the following toxicities, within 28 days after receiving ATL001, enrolment may be paused if these are considered to be a result of study interventions. The IDSMC will be asked to review eligibility criteria, doses of all study treatments and all available safety data, and to make recommendations as to the further conduct of the study:

- Grade 3 or worse non-haematological toxicity that does not resolve to Grade 2 or less within 7 days.
- Grade 2 or worse neurological toxicity that does not resolve to Grade 1 or baseline within 7 days.
- Grade 4 haematological toxicity (excluding lymphopenia) that does not resolve to Grade 1 or baseline within 28 days.

The committee will also be convened in the event of any patient developing a serious infusion reaction or Grade ≥ 3 CRS. In addition, any death within 30 days of ATL001 infusion (other than as a result of the underlying disease for which the patient is being treated) and any Grade 4 ICANS event will trigger a study pause and IDSMC review.

Following the change in lymphodepletion regimen associated with Protocol Version 9.0 (Master), the IDSMC will be informed of the data from at least the first 3 patients treated across all cohorts who have received the new lymphodepletion regimen.

An additional IDSMC safety review may take place when 20 patients in this study have been treated and followed up for a minimum of 14 days post-infusion. This will be scheduled if 6 or more patients experience the above toxicities as a result of study treatments.

The IDSMC will make recommendations for continuation, modification, suspension or discontinuation of the study conduct in accordance with their review of all data available to them, taking into consideration the clinical significance of the events and the likelihood of relatedness to ATL001 or other study medications. If the decision is to suspend enrolment it may be restarted, after appropriate preventative or management guidelines have been established, in a protocol amendment.

Patients may also be discontinued from study treatment and/or assessments at any time, at the discretion of the Investigator(s). Specific reasons for discontinuing a patient are summarised in Section 4.

Patients who have discontinued treatment should wherever possible remain in the study and continue with follow up assessments for disease progression and survival.

The study may be terminated at any time and for any reason at the discretion of the Sponsor relating to observed safety or clinical efficacy parameters.

8 MEASUREMENT OF STUDY VARIABLES

8.1 Screening and On Study Measurements

8.1.1 Performance Status

Performance Status (PS) will be assessed according to the ECOG Performance Status Scale (See Appendix A).

8.1.2 Physical Examination

The physical examination should include medical assessments according to clinical relevance. Findings considered as clinically significant changes since the physical examination at Screening will be recorded as adverse events.

8.1.3 Vital Signs

Vital signs (BP [systolic and diastolic], pulse rate, respiratory rate, and body temperature [oral or otic]) will be recorded with the patient resting in the supine position for at least at 10 minutes.

8.1.4 Pulse Oximetry

Pulse oximetry to measure the oxygen level (oxygen saturation) of the blood. Continuous monitoring during ATL001 infusion with pre- and post-infusion measurements recorded.

8.1.5 Electrocardiogram

12-lead electrocardiogram (ECG) recordings will be made at the time points designated. The Investigator should review all ECG recordings and record as normal or abnormal. Clinically significant abnormalities should be recorded as adverse events.

8.1.6 Echocardiogram

At screening, an echocardiogram will be performed for all patients, unless results are available from within 60 days prior to the screening visit. At re-screening, an echocardiogram will be performed for all patients unless results from scans within 60 days prior to start of lymphodepletion are available.

8.1.7 Colonoscopy

Colonoscopy is only required for patients who have had a documented Grade 2 or greater diarrhoea or colitis due to previous immunotherapy within 6 months of screening.

8.1.8 Body Weight

Body weight will be determined at the scheduled timepoints.

8.1.9 Pregnancy Test (Female Patients)

For female participants of childbearing potential, serum or urine pregnancy tests are required. In Cohort B, additional serum or urine pregnancy test prior to each pembrolizumab administration for female participants of childbearing potential is required. Refer to Appendix G for pregnancy testing requirements in Germany.

8.1.10 Safety Laboratory Measurements

See Table 8 for clinical laboratory safety assessments to be performed.

Clinically significant derangements should be reported as adverse events per Section 8.2, and tests repeated as appropriate.

Table 9: Clinical Laboratory Safety Assessments

Laboratory Assessments	Parameters
Haematology	Haemoglobin (Hb) White cell count and differential (neutrophils/lymphocytes/monocytes/eosinophils/basophils) Platelet count
Chemistry	Alanine transaminase (ALT/SGPT), OR Aspartate transaminase (AST/SGOT) Albumin Alkaline phosphatase (ALP) Bicarbonate Bilirubin Chloride Lactate dehydrogenase (LDH) Total Protein Urea or Blood Urea Nitrogen (BUN) Uric acid Calcium Creatinine Creatinine kinase

	Magnesium Phosphate Potassium Sodium Estimated GFR (by Cockcroft-Gault equation*) Glucose (non-fasting)
Thyroid Function Tests	Thyroid Function Tests (baseline and selected timepoints in Cohort A and Cohort C, and every 12 weeks for patients in Cohort B; these are to include T4 and TSH ± T3) – see Schedule of Assessments, withdrawal/completion and as clinically indicated
Coagulation	International normalised ratio (INR) or Prothrombin time (PT) Activated partial thromboplastin ratio (APTR) or Activated partial thromboplastin time (APTT) D-Dimer Fibrinogen
Urinalysis	Reagent strip (dipstick) analysis if clinically indicated for: Glucose, Protein, pH, Ketones, Blood, Nitrites, Leucocytes To be sent for Microscopy, Culture and Sensitivity (MCS) if indicated
Other	CRP (C-reactive protein) Pregnancy test (serum or urine) Infection screening (anti-HIV 1&2, HBs Ag, Anti-HBc, Anti-HCV-Ab, syphilis (*treponema pallidum*) IgG/IgM, and Anti-HTLV 1&2)

**The Cockcroft-Gault equation may be used to estimate GFR:*
Creatinine clearance = (((140 – age in years) x (weight in kg)) x 1.23) / (serum creatinine in micromole/L).
For women, multiply the result of the calculation by 0.85.

8.1.11 NSCLC Risk Factors

NSCLC risk factors, including but not limited to smoking history, family history, exposure to radon, and exposure to asbestos, will be assessed at a screening visit.

8.1.12 Demographics

Demographic data, including but not limited to age, gender, weight, height, race and ethnicity, will be collected at baseline.

8.1.13 Archival Tumour Tissue (if available)

Archival FFPE block or slides of primary tumour may be requested for analysis of the tumour microenvironment, if available anytime from screening to study withdrawal.

8.2 Adverse Events

8.2.1 Definitions per ICH E2A

Table 10: Adverse Event Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.
Adverse Drug Reaction (ADR)	All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The criteria 'responses to a medicinal product' applies if there are facts (evidence) or arguments to suggest a causal relationship.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death. • Is life-threatening. • Requires inpatient hospitalisation or prolongation of existing hospitalisation. • Results in persistent or significant disability/incapacity. • Is a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above outcomes. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator or Achilles Therapeutics (or representative), believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information: • In the case of a product with a marketing authorisation, this could be in the Summary of Product Characteristics (SmPC)/Package Insert for that product, so long as it is being used within its license. If it is being used off label an assessment of the SmPC/Package Insert suitability will need to be undertaken. • In the case of any other investigational medicinal product, the Reference Safety Information (RSI) for assessment of expectedness of serious adverse reactions is located in the section of the Investigator's Brochure relating to the product in question.

8.2.2 Reporting and Recording of Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether related to the medicinal (investigational) product or not. For patients in the US, adverse events will be reported as specified in 21 CFR 312.32.

The protocol requirements for reporting of AEs and SAEs are as follows:

- Procedure-related AEs and all SAEs (including non-procedure-related) from the time of the procurement to 28 days following procurement, or the start of anti-cancer therapy if sooner, will be collected.
- Cohort A and Cohort C: All AEs and SAEs from Pre-Lymphodepletion Re-Screening Visit until Week 36 or until confirmed disease progression (whichever is sooner), and then only AESIs until Week 104 (or Week 364, until such time as the Long Term Follow Up study is available at study site).
- Cohort B: All AEs and SAEs from Pre-Lymphodepletion Re-Screening Visit until 4 months after the last dose of pembrolizumab (but with a minimum reporting period of up to Week 36) or until confirmed disease progression (whichever is sooner), and then only AESIs until Week 104 (or Week 364, until such time as the Long Term Follow Up study is available at study site).

Signs or symptoms of the condition/disease for which the investigational product is being studied should be recorded as AEs only if their nature changes or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the Investigator from the patients' history or from screening to IMP administration.

The patient will be given an opportunity to report AEs spontaneously at each study visit. A general prompt will also be given to detect AEs, e.g. 'Did you notice anything unusual about your health since your last visit?'.

When recording an AE, the Investigator should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The eCRF and source documents should be consistent. Any discrepancies between the patient's own words on his/her own records (e.g. diary card) and the corresponding medical terminology should be clarified in the source documentation. Details for completion of the AE eCRF (including judgment of relationship to study drug) are described in the eCRF Completion Guidelines.

AEs should be followed until it resolved, has a stable sequela, the Investigator determines that it is no longer clinically significant, or the patient is lost to follow up. If an AE is still ongoing at the end of the study for any patient, follow up should be provided in the separate Long Term Follow Up study. If no follow up is provided, the Investigator must provide a justification.

8.2.3 Reporting and Recording of Serious Adverse Events

Once it is determined that a patient experienced an AE, the seriousness of the AE must be determined. An SAE is any untoward medical occurrence that at any dose:

a. Results in Death.

b. Is life-threatening.

c. Results in significant or persistent disability/incapacity.

d. Is a congenital anomaly/birth defect.

e. Requires inpatient hospitalisation or prolongation of existing hospitalisation.

Admission to hospital for reasons not associated with the occurrence of an AE (e.g. pre-planned surgery or elective surgery for a pre-existing condition that has not worsened or manifested in an unusual or uncharacteristic manner) do not qualify for reporting. Additionally, SAEs deemed to be caused exclusively by disease progression do not qualify for reporting.

If a pre-existing condition has worsened or manifested in an unusual or uncharacteristic manner, this should be reflected in a change of AE grade if necessary and the possible seriousness of the event would need to be determined.

All Investigators will be thoroughly instructed and trained on all relevant aspects of the Investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarised in the instructions for SAE reporting included in the Investigator Site File. This information will be updated as needed.

If an SAE is reported, the Sponsor or its representative must be informed within 24 hours of knowledge of this information by the site. The Investigator must forward to the Sponsor (or its representative) a duly completed SAE Report Form, even if the data are incomplete, or if it is obvious that more data will be needed to draw any conclusions. It is important for the Investigator, when completing the SAE report form, to include the assessment as to the causal relationship between the SAE and the ATIMP administration. This insight from the Investigator is very important for the Sponsor to consider in assessing the safety of the ATIMP and in determining whether the SAE requires reporting to the regulatory authorities in an expedited manner.

Additional information (e.g. autopsy or laboratory reports) received by the Investigator must be provided within 24 hours of the Investigator's awareness. For this, an AE page in the CRF as well as the SAE form must be completed for each SAE. Information not available at the time of the initial report must be documented on a follow-up SAE form. The Investigator is specifically requested to collect and report to the Sponsor (or its representative) any SAEs (even if the Investigator is certain that they are in no way associated with the ATIMP), up to 90 days from the end of the study for each patient, and to also inform participating patients of the need to inform the Investigator of any SAE within this period. Serious AEs that the Investigator thinks may be associated with the ATIMP must be reported to the Sponsor (or its representative) regardless of the time between the event and the end of the study.

An SAE should be followed until it has resolved, has stable sequelae, the Investigator determines that it is no longer clinically significant, or until the end of the study. Information on SAEs obtained after clinical database lock will be captured. In addition, an Investigator may be requested by the Sponsor (or its representative) to obtain specific information in an expedited manner.

The grading scale used to assess the severity of AEs will be the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. CRS and ICANS will be assessed using American Society for Transplantation and Cellular Therapy (ASTCT) criteria (see Section 7.7.4 and Section 7.7.5). For patients in Cohort B, AEs related to pembrolizumab will be assessed against NCI CTCAE Version 4.0, as per the SmPC/Package Insert, and treatment modified accordingly (see Section 7.6).

8.2.4 Adverse Events of Special Interest

An AE of special interest is any AE that the Sponsor, or a regulatory authority, has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of study medication. The following events are considered AEs of special interest and must be informed to the Sponsor (or its representative) using the same process as for SAEs:

a. Grade 3 and higher cytokine release syndrome (CRS).

b. Second documented malignancies.

c. Grade 2 and higher neurological adverse events.

d. Autoimmune conditions.

An AE of special interest should be followed until it has resolved, has stable sequelae, the Investigator determines that it is no longer clinically significant, or until the end of the study. In addition, an Investigator may be requested by the Sponsor (or its representative) to obtain specific information in an expedited manner.

8.2.5 Pregnancy Reporting

Should a patient become pregnant after ATL001 administration, the Sponsor (or its representative) should be informed immediately.

The Investigator must inform the patient of information currently known about potential risks and about available treatment alternatives.

The pregnancy will be documented on the Pregnancy Initial Report Form provided to the Investigator. The progression of the pregnancy and the eventual birth (if applicable) must be followed up using the Pregnancy Follow-up Report Form in which the Investigator must report on the health of the mother and of the child. The health of the child must be followed for 1 year after birth for any significant medical issues and until stabilisation of any post-natal conditions. In certain circumstances, the Sponsor (or its representative) may request that follow up is continued for a longer period.

In cases where the partner of a male patient enrolled in a clinical study becomes pregnant, the Sponsor (or its representative) will ask the Investigator or designee to contact the patient and his partner to request consent via a Pregnant Partner Pregnancy Consent Form. If the partner consents to provide additional information, this will be collected on the Pregnancy Initial Report Form and Pregnancy Follow-up Report Form.

A pregnancy becomes an SAE in the following circumstances: miscarriage, abortion, or anomaly/birth defect of the child. Those SAEs must be additionally reported using the SAE/AESI Report Form in accordance with Section 8.2.3.

8.2.6 Expedited Safety Reporting

The Sponsor (or its representative) will notify Investigators of all reportable SAEs. This notification will be in the form of an expedited safety report. Upon receiving such notices, the Investigator must review and retain the notice with other study-related documentation.

The Sponsor (or its representative) will ensure that SAEs are reported to the Ethics Committees and regulatory authority(ies) according to local requirements.

Suspected Unexpected Serious Adverse Reactions and other significant safety issues reported from ATX-NS-001 shall be reported to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited safety reports and/or in aggregate reports), by the Sponsor (or its representative).

8.3 Clinical Efficacy Measurements

Anti-tumour activity will be assessed at scheduled timepoints by CT scans of chest, abdomen and pelvis, and other locations if indicated. If CT scanning is not acceptable, MRI may be an alternative. The same modality should be used per patient throughout the study to assess lesion response. MRI scans may be used for scheduled brain imaging in patients with stable brain metastases at baseline, and if clinically indicated.

Efficacy assessments will be recorded by the Investigator and confirmed by an Independent Central Reviewer.

Efficacy will be evaluated by MRI/CT scans every 6 weeks to week 24 and then every 12 weeks according to RECIST v1.1 and Immune modified RECIST (imRECIST) criteria as described in Section 9.

See Appendix B for a summary of the differences between RECIST v1.1 and imRECIST assessment criteria.

8.4 Immunomonitoring Measurements

Immune-monitoring samples for cellular assays (30 mL samples in heparin tubes for peripheral blood mononuclear cells (PBMC) and basic T cell, B cell and NK cell phenotyping (TBNK)) will be taken at baseline (pre-lymphodepletion) and on days 3, 7, 10, 14, 21 and 28, weeks 6, 12, 18, 24 and every 12 weeks thereafter until the visit of confirmed disease progression. Samples should be handled and transported as specified in the site laboratory manual.

Persistence, phenotype and functionality of T cells will be assessed by multiple assays including but not limited to multi-parametric flow cytometry, cytokine assessment, T cell receptor repertoire diversity, ELISPOT and intracellular cytokine staining.

Additional immunomonitoring samples are: up to 3 mL samples for plasma cytokines, which will be taken at baseline (pre-lymphodepletion) and on days -1, 1, 2, 3, 5, 7, 10, 14, 21 and 28, then weeks 6, 12, 18, 24 and every 12 weeks thereafter until the visit of confirmed disease progression, and 3 mL samples for TCR-RNA sequencing which will be taken baseline (pre-lymphodepletion) and on days 7, 10, 14, 21 and 28, then weeks 6, 12, 18, 24 and every 12 weeks thereafter until the visit of confirmed disease progression.

At the week 6 visit, an extra 150 mL blood sample is required for extended immunological assays, as long as the patient's clinical condition does not preclude it. This will facilitate the evaluation of T cell reactivities using professional antigen presenting cells. The extra blood is needed to generate enough antigen presenting cells to determine if cNeT therapy promotes spreading of T cell responses to neoantigenic epitopes different from those in the original product (epitope spreading) and will facilitate single cell analysis of cNeTs circulating in the blood of patients post therapeutic intervention.

8.5 Exploratory Measurements

8.5.1 Circulating Tumour DNA (ctDNA)

Plasma samples (derived from 10 mL of blood) for ctDNA assessment will be monitored at time of tumour procurement, pre-lymphodepletion, pre-infusion and on Days 7, 14, 21, 28, weeks 6, 12, 18, 24 and every 12 weeks thereafter until disease progression. These samples are all 10 mL samples except on the procurement visit and the week 12 visit when they will be 30 mL samples. The extra 20 mL volume at both timepoints is needed to profile how the patient tumour heterogeneity changes in response to ATL001 treatment.

A bespoke ctDNA assay will be created based on the specific truncal (clonal) and branched (subclonal) mutations/predicted neoantigens detected in the patient's tumour at baseline. These samples will be analysed retrospectively to assess the potential value of the assay as a biomarker of response.

8.5.2 Optional Tumour Biopsies

If a patient has a tumour that can be safely accessed, optional pre- and post-treatment tumour biopsies will be requested to assess changes in the tumour microenvironment at one or more of the following times:

- Between procurement and treatment with ATL001.
- Following treatment with ATL001.
- At the time of disease progression.

8.5.3 Optional Samples to be Acquired from Standard of Care Procedures

If a patient undergoes any standard of care procedures that involve the collection of biological material deemed relevant to ATL001 treatment, at any time during the period that they are enrolled in the study, a sample may be requested for research purposes if one can be provided at no additional risk to the patient.

9 STATISTICAL METHODS

9.1 Sample Size Calculation

Since this is a first-in-human study, there will be no formal hypothesis testing and as such, the study has not been formally powered. The sample size has been selected to provide adequate information about the safety and efficacy of ATL001, whilst also exposing minimal numbers of patients to experimental therapy and procedures prior to an initial signal of efficacy.

In treatment Cohort A, a minimum of 20 patients will receive ATL001 following standard of care therapies with an active cell dose of 5-1000 x 10^7 $CD3^+$ cells. It is expected that most patients will have received a PD-1/PD-L1 inhibitor as part of their standard therapy unless patients have contraindications to these agents.

The expectation is that ATL001 could achieve a response in at least 30% of patients, based on a response rate of 35% in studies of first generation TIL in patients with metastatic melanoma that has recurred following treatment with PD-1 inhibitors, and based on a response rate of 20% in studies of standard second line agents in NSCLC.

Based on a sample size of 20 evaluable patients treated with a product with an active cell dose range of 5-1000 x 10^7 $CD3^+$ cells, if the true ORR were 30%, there would be approximately a 90%

probability of observing 4 or more responders out of 20 patients. Conversely, if the true response rate were only 10% there would be a 13% probability of observing 4 or more responses by chance.

The collection of data within this protocol from up to 20 patients treated with "out of specification" products will allow flexibility to explore and understand possible dose-efficacy relationships and to inform the target dosing range for future studies.

In treatment Cohort B, up to 20 patients will be offered ATL001 followed by pembrolizumab. The sample size of 20 patients has been selected in order to establish the safety, tolerability and clinical activity of ATL001 followed by pembrolizumab, in the context of the overall safety and efficacy profile of ATL001 from treatment Cohort A.

In Cohort C, up to 20 patients will receive ATL001 followed by higher dose IL-2 (600,000 IU/kg) administered by intravenous infusion, after standard of care therapies. The sample size of 20 patients has been selected to establish the safety, tolerability, and clinical activity of ATL001 followed by higher doses of IL-2, in the context of the overall safety and efficacy profile of ATL001 from Cohort A.

The Sponsor will also have the ability to stratify patient data across Cohort A, Cohort B and Cohort C according to disease status at dosing.

The totality of the safety and tolerability data from the study will contribute to decisions regarding the continuation of the combination to the next stage of development. Unless otherwise stated, data from treatment Cohorts A, B and C (if B and/or C performed) will be presented separately. The data from any patients receiving an "out of specification" product will be presented separately to data from patients receiving the target cell dose.

One or more interim analyses may be performed in this study (see Section 9.6). Following one of these analyses, and dependent on the emerging data, the protocol may be amended to increase the sample size or an expansion cohort. The sample size will be decided following interactions with regulatory authorities.

9.2 Analysis Populations

9.2.1 All Patients

Population Disposition, screen failures and reasons for screen failures, will be reported for this population.

9.2.2 Surgical Population

The Surgical Population (SP) will include all patients in whom tumour procurement procedures were performed, regardless of whether the patient later went on to receive ATL001 treatment. The SP will be used only to evaluate the safety of the tumour procurement procedure. The safety of the tumour procurement procedure will be presented separately to the safety of the ATL001 treatment.

9.2.3 Full Analysis Set (FAS)

The Full Analysis Set (FAS) is based on the intention-to-treat principle and is defined as all patients who initiated lymphodepletion treatment, regardless of whether they subsequently received treatment with ATL001 or IL-2.

The FAS data will used to understand the tolerability of lymphodepletion and evaluate the likely attrition rates prior to receiving ATL001. Note, the FAS will not be the primary analysis set used

for the evaluation of safety and tolerability, since it is possible that not all patients in the FAS may have received the investigational product (ATL001).

9.2.4 Treated Patient Population

The Treated Patient population (TP) is a subset of the FAS and is defined as all patients who received treatment with ATL001, regardless of whether they completed the planned infusion and/or pembrolizumab and/or subsequent IL-2 injections. The TP population will be the primary analysis population used to evaluate the safety and tolerability of ATL001. The TP population will also be used to assess the secondary endpoint, Overall Survival.

9.2.5 Evaluable for Response (EFR) Population

The evaluable for response (EFR) population is defined as the subset of the TP population with the intended disease and indication, and measurable disease at baseline.

The EFR population will be the primary analysis population used to assess all RECIST and imRECIST-based efficacy endpoints (ORR, imORR, DOR, imDOR, TTR, imTTR, DCR, PFS and imPFS). Since measurable disease is an entry criterion for the study, the EFR should be identical to the TP, unless there are any patients who did not meet this entry criterion.

9.2.6 Per Protocol Evaluable for Response (PPEFR) Population

The PPEFR population is defined as the subset of the EFR without a major deviation. In addition to the absence of measurable disease, major deviations that would lead to the exclusion of a patient from the PPEFR population include:

a. Patients who did not have the intended disease or indication.

b. Patients with baseline radiological scan performed before the start of protocol specified interval prior to study enrolment.

c. Patients who did not receive the intended doses of fludarabine, cyclophosphamide or IL-2.

d. Patients whose ATL001 infusion is not completed within 30 minutes of thawing.

e. Patients who did not have at least two post-baseline radiological assessments, for reasons other than death.

f. Patients whose baseline radiological scan did not cover all protocol-specified anatomical areas (i.e. chest, abdomen, pelvis) and were determined to have lesions at the next scan in one of these areas.

In addition to the above criteria, if there are any patients whose product contained an active dose of 5-1000 x 10^7 $CD3^+$ cells, but who received less than 5 x 10^7 $CD3^+$ cells for any reason, their data, for the purpose of the PPEFR outputs, will be presented alongside data for the patients that received "out of specification" products. The cell dose received will be estimated based on the residual volume and total cell content of the bag.

The PPEFR will be used to assess the sensitivity of efficacy analyses based on the EFR to major deviations.

9.3 Study Endpoints

9.3.1 Safety and Tolerability

Safety and tolerability will be assessed based on adverse events, safety assessments (including vital signs, ECG, clinical laboratory tests) and physical examination.

9.3.2 Efficacy Endpoints

9.3.2.1 Tumour Size

The percentage change from baseline in tumour size (TS) is a secondary endpoint and will be evaluated at three time points:

1. The percentage change from baseline at week 6 ($\%\Delta TS_{Wk6}$).
2. The percentage change from baseline at week 12 ($\%\Delta TS_{Wk12}$).
3. The best percentage change from baseline in TS ($\%\Delta TS_{best}$), at any time point.

$\%\Delta TS_{Wk6}$ and $\%\Delta TS_{Wk12}$ will be defined as follows:

- Baseline TS: defined as the sum of longest diameters of target lesions at baseline.
- Week X TS: defined as the sum of longest diameters of target lesions at Week X (where X is either 6 or 12).

$\%\Delta TS_{WkX}$ = 100 x (Week X TS – Baseline TS)/Baseline TS

Patients who do not have Week X TS will be handled as follows:

1. Patients who die by any cause other than an accident before Week X (+ 7 days) TS measurement without radiographic evidence of progression, an increase from baseline of 20% will be imputed.
2. Patients with missing data at Week X (+ 7 days) due to prior radiological disease progression will be included in the analysis and will be assigned a percentage change from baseline of 20%, or the value that was observed at the time of disease progression (whichever is larger).

Note: Allowing for the protocol-permitted visit window of 7 days, any data collected up to week X + 7 days will be considered evaluable when calculating $\%\Delta TS_{WkX}$.

The best percentage change from baseline in TS ($\%\Delta TS_{best}$), at any time point will be defined as follows:

- Baseline TS: defined as the sum of longest diameters of target lesions at baseline.
- Best TS: defined as the smallest sum of longest diameters of target lesions at observed at any time point following the start of study treatment up to disease progression (regardless of whether it was a scheduled assessment).

$\%\Delta TS_{best}$ = 100 x (Best TS – Baseline TS)/Baseline TS

Patients in the Evaluable for Response (EFR) set without any evaluable post-baseline target lesion data will be excluded from the waterfall plot of $\%\Delta TS_{best}$, except if the patient is known to have died (other than an accident), or if non-target lesion or new lesion data is available prior to Week 12 (+7 days) which is indicative of disease progression. In such cases, the patient will have an increase from baseline of 20% imputed.

9.3.2.2 Objective Response Rate

The RECIST ORR is defined as the number (%) of patients with confirmed Best Overall Response (BOR) of CR or PR. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Any responses with an onset date after the start of a subsequent anti-cancer treatment will not be counted as responses in the ORR. Further details of the derivation of the BOR, and the criteria for response are provided in Appendix B and will be further expanded in the study Statistical Analysis Plan.

The imRECIST ORR (imORR) is defined as the number (%) of patients with confirmed imRECIST Best Overall Response (imBOR) of CR or PR. The key difference between the ORR and imORR is that the imORR may include responses observed following an initial disease progression (PD), provided that minimum time-period has elapsed following the initial PD and the subsequent response (PR and CR). Furthermore, the imRECIST criteria does not necessarily consider the appearance of new lesions as evidence of progression, unless the dimension of the new lesion when added to the target lesions would result in an increase in tumour burden □ 20% relative to the nadir. Similarly, non-target lesion (NTL) evaluations do not contribute to the evaluation of the imORR, other than to preclude an imBOR of CR if the NTLs have not completely disappeared. A summary of the differences between RECIST v1.1 and the imRECIST criteria is provided in Appendix B and details on the derivation of imBOR and imORR will be further expanded in the study Statistical Analysis Plan.

9.3.2.3 Time to Response

Time to Response (TTR) is defined as the time (days) from the start of treatment with ATL001 to the onset of response (partial response (PR) or complete response (CR)) in the subset of patients who were categorized as confirmed responders for ORR.

The imTTR, is defined as the time (days) from the start of treatment with ATL001 to the onset of response (PR or CR) in the subset of patients who were categorized as confirmed responders for imORR.

9.3.2.4 Duration of Response

The duration of response (DoR) is defined as the time from the date of first documented response until the date of documented disease progression or death in the absence of disease progression, in the subset of patients classified as responders for ORR (based on RECIST v1.1). The end of response should coincide with the date of disease progression or death from any cause used for the PFS endpoint. DoR will be calculated programmatically.

The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR. For example, if the patient was first noted to have a PR at week 6, and the target and non-target lesions were assessed on different dates at this visit, then the later of the two assessment dates would be used as the start date of the response.

If a patient does not progress following a response, then their DoR will use the PFS censoring date.

Duration of response will not be defined for those patients who do not have a documented response.

The immune-modified duration of response (imDOR) will be calculated analogously, i.e. it is defined as the time from the date of first documented response until the date of documented disease progression or death in the absence of disease progression, in the subset of patients classified as responders for imORR (based on imRECIST). The end of response should coincide with the date of disease progression or death from any cause used for the imPFS endpoint.

The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR. For example, if the patient was first noted to have a PR at week 6, and the target and non-target lesions were assessed on different dates at this visit, then the later of the two assessment dates would be used as the start date of the response.

If a patient does not progress following a response, then their imDoR will use the imPFS censoring date. The imDOR will not be defined for those patients who do not have a documented imRECIST response.

9.3.2.5 Progression Free Survival

Progression free survival (PFS) is a secondary endpoint in the study.

The RECIST PFS is defined as the time from starting treatment until the date of objective disease progression or death (by any cause in the absence of disease progression) regardless of whether the patient completes the scheduled study treatment or receives another antitumour therapy prior to disease progression. Patients who have not experienced disease progression or died at the time of the data cut-off will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment. However, if a patient progresses or dies following missed RECIST assessments, with an interval of > 12 weeks + 14 days from the previous assessment (to accommodate the 7 day window surrounding the preceding and subsequent assessments), the patient will be censored at the time of the latest evaluable RECIST v1.1 assessment.

The PFS time will always be derived based on the scan/assessment dates rather than visit dates and the following rules will be applied:

- Date of disease progression will be determined based on the **earliest** of the dates of the component that triggered the disease progression, i.e. if both the target lesions and the non-target lesions indicate disease progression but were scanned on different days, the earlier of the 2 dates would be applied.
- When censoring a patient for PFS the patient will be censored at the **latest** of the dates contributing to a particular overall visit assessment.

Immune-modified RECIST PFS (imPFS) will be defined in accordance with the imRECIST criteria. The key differences between the imRECIST criteria and RECIST v1.1, with respect to the determination of progression, are below:

1. Non-target lesions will not be taken into account when determining when a patient has had an imPFS event.
2. New lesions will only be taken into account if the new lesion is measurable, and the longest diameter of the new lesion, when added to the sum of longest diameters of target lesions at the same visit results in an increase in tumour burden relative to the nadir x 20%.
3. An imRECIST PD will not be considered an imPFS event if a subsequent scan (4 weeks later) shows an imSD/PR or CR.

To aid interpretation of the study results, the proportions of patients alive and progression-free at 6, 12 and 18 months will be presented for both PFS and imPFS.

Both PFS and imPFS will be derived programmatically. Further details will be provided in the SAP.

9.3.2.6 Disease Control Rate

Disease control rate (DCR) is defined as the proportion of patients with a confirmed response of PR or CR (confirmed at least two consecutive assessments at least 28 days apart), or with a BOR of stable disease (SD) or better sustained for at least 12 weeks (-7 days to allow for the visit window) after starting treatment based on the RECIST v1.1 definitions of PR, CR and SD.

9.3.2.7 Overall Survival

Overall survival is defined as the time from starting treatment until death due to any cause. Any patient not known to have died at the time of the data cut-off will be censored based on the last recorded date on which the patient was known to be alive. OS will be assessed based on the Treated Patient population (TP) (see Section 9.2.4).

Note: Survival calls may be made following the date of data cut-off (DCO) for the analysis, and if patients are confirmed to be alive or if the death date is after the DCO these patients will be censored at the date of DCO.

9.3.3 Exploratory Endpoints

The exploratory objectives will be assessed by a number of assays in the starting material, product intermediates and final ATL001 product. These may include but not limited to:

- Tumour Mutational Burden and the Tumour Immune Checkpoint Landscape (whole exome sequencing, effector/regulatory T cell balance, PD-L1 expression and MHC Class I and II expression).
- cNeT phenotype, functionality and persistence (Multi-parametric Flow cytometry, Cytokine assessment, T cell receptor repertoire diversity from RNA analysis, Neoantigen reactivity by ELISPOT and intracellular cytokine staining, and ctDNA).
- The manufacturing rate will be defined as the number of products made from the number of patients undergoing tumour and blood procurement.
- Reasons for not manufacturing a product may include sample not acceptable, patient death before product manufactured, patient withdrew consent, failure of in-process control, QC release failure.
- Factors affecting the manufacturing rate and product quality will be explored including clinical, tumour and sample characteristics.

9.4 Methods of Statistical Analysis

All statistical analyses will be performed by, or under the direct auspices of, Achilles Therapeutics UK Limited.

Unless stated otherwise, data from treatment Cohorts A, B and C will be presented separately. The data from any patients receiving an “out of specification” product will be presented separately from treatment Cohorts A, B and C.

The data cut-off for primary analysis for each treatment Cohort will be a minimum of 12 weeks after the last patient is recruited in the Cohort of Interest. Following the primary analysis, the study will continue for further evaluation of the longer-term efficacy endpoints such as DoR, PFS and OS. End of study is defined as the last visit of the last patient undergoing the study.

9.4.1 Assessment of Safety and Tolerability

9.4.1.1 Safety and Tolerability of the Procurement Procedures and Lymphodepletion

The safety and tolerability of the procurement procedures (tumour and blood) will be assessed in the Surgical Population (SP). All SAEs, collected from the date of the procurement procedure, until 28 days after the tissue procurement procedure (or commencement of systemic anti-cancer therapy, if sooner), will be listed. Additionally, all AEs considered related to the procurement procedures, with an onset date and time following the start of the first procurement procedure until 28 days after the tissue procurement procedure (or commencement of first line therapy, if sooner), will be summarised in order of descending frequency (i.e. most frequent event will be shown first).

In the unlikely event that any patients commence lymphodepletion, but do not commence study treatment (ATL001) as planned, a listing of adverse event data from the subset of the FAS, who are not also in the TP population, will also be provided.

9.4.1.2 Safety and Tolerability of the Study Treatment

The safety and tolerability of the study treatment will be assessed using the TP population.

All AE data will be listed along with information regarding onset time (study day), duration, severity, and relationship to study treatment. Adverse events will be tabulated and summarised according to the current version of the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class and preferred term. Serious AEs will be tabulated and listed separately with CRS and ICANS Grades listed. Full details will be provided in the study SAP.

All clinical laboratory data (clinical chemistry, haematology data), and vital signs data will be listed and, where appropriate, summarised. In addition, all data measured on a continuous scale (except pulse oximetry, respiration rate and pulse) will be displayed graphically as described below:

- Profile plots over time, including reference lines at the lower limit of normal (LLN) and upper limit of normal (ULN).
- Profile plots of the change from baseline over time, including a horizontal reference line at zero.

Furthermore, to understand the feasibility of intended treatment regimen, the proportion of patients receiving the completing the full treatment regimen will be presented, taking as a denominator the number of patients in the TP population. Patients will be considered to have completed the full treatment regimen if they received:

- For patients treated prior to Protocol Version 9.0 (Master), a non-myeloablative lymphodepletion regimen of fludarabine 30 mg/m^2 i.v. and cyclophosphamide 300 mg/m^2 i.v. on each of Days -6, -5, and -4 prior to cell infusion. For patients treated from Protocol Version 9.0 (Master) onwards, a non-myeloablative chemotherapy regimen of fludarabine 25mg/m^2 i.v. on each of Days -5 to -1 and cyclophosphamide 30mg/kg on Days -5 and -4 prior to cell infusion, or a non-myeloablative chemotherapy regimen of fludarabine 25mg/m^2 i.v. on each of Days -5 to -1 and cyclophosphamide 60mg/kg on Days -5 and -4 prior to cell infusion.
- A complete ATL001 infusion.
- In Cohorts A and B: 10 doses of IL-2 1M IU/m^2 s.c. daily from days 0-9 of the study, starting between 3 and 12 hours post-infusion.

- In Cohort C: 6 doses of IL-2 600,000 IU/kg i.v. every 8-12 hours, starting between 3 and 24 hours post-infusion.

Further details will be provided in the study SAP.

9.4.2 Demographics and Baseline Characteristics

Patient disposition, including but not limited to, the date of informed consent, date of first dose and reasons for discontinuation from study treatment will be listed and summarised.

Baseline demographic data, which may include but is not limited to the following will be listed and summarised using appropriate descriptive statistics, based on the SP and the TP:

Table 11: Descriptive Statistics for Baseline Demographic Data

Demographic Data	Baseline Characteristics
Age Gender Weight Height Race Ethnicity	Disease stage at study entry ECOG PS (0 or 1) Presence of Driver Mutations (e.g. EGFR/ALK/ROS-1) Smoking history (current/ex; light/heavy) PD-L1 Tumour Proportion Score Lung Cancer Immune Prognostic Score at diagnosis (if known) Number of prior lines of therapy before tissue procurement Number of prior lines of therapy before ATL001 infusion Origin of tumour starting material (e.g. primary/metastasis/lymph node)

9.4.3 Medical History and Prior and Concomitant Medications

Relevant medical history and prior treatment for NSCLC will be listed.

All medications received following the start of treatment (including those that were ongoing prior to first dose) will be listed.

9.4.4 Efficacy Data

All RECIST and imRECIST-based data will be listed, and the BoR, ORR and DCR will be summarised (n and %). For those patients with a BOR of PD, the summary will include sub-categories to distinguish between PD as defined by the RECIST criteria, and early deaths that have been assigned to the PD category. A listing of early deaths will also be provided.

Dependent on the number of responders, DoR (based on both RECIST and imRECIST) may also be summarised using Kaplan-Meier (KM) statistics. PFS and imPFS will be listed and will be summarised based on KM estimates. To aid interpretation, the proportion of patients' progression-free at 6, 12 and 18 months will also be presented. PFS and imPFS will be displayed graphically using Kaplan-Meier curves, if there are sufficient PFS events.

The percentage change from baseline in tumour size at week 6 ($\%\Delta TS_{Wk6}$), week 12 ($\%\Delta TS_{Wk12}$) and the best percentage change from baseline in tumour size ($\%\Delta TS_{best}$), will be presented graphically using waterfall plots. The waterfall plots will present each patient's %ΔTS as a separate bar with the bars ordered from the largest increase to the largest decrease. Reference lines at the +20% and –30% change in tumour size levels will be added to the plots, which correspond with the definitions of disease progression and PR, respectively. Data imputation rules, to account for missing data are provided in Section 9.3.2.1.

Each patient's percentage change from baseline in tumour size, over time, will also be displayed graphically using patient profile plots (spider plots).

The primary analysis of all RECIST and imRECIST-based will be performed using the EFR set. In order to assess the sensitivity of the primary endpoint to major deviations, a sensitivity analysis will also be performed using the PP set.

Overall survival data will be listed and summarized using the TP based on KM descriptive statistics. To aid interpretation, the proportion of patients' event-free at 6, 12 and 18 months will also be presented. OS will be displayed graphically using Kaplan-Meier curves, if there are sufficient OS events.

9.4.5 Exploratory Endpoint Data

Not all Exploratory Endpoint data will be presented in the Clinical Study Report. A separate Translational Research Report will be produced. Full details will be provided in the Translational Science Statistical Analysis Plan.

Data to be presented in the CSR will be listed, summarised and displayed graphically according to the nature of the data.

9.5 Independent Data Safety Monitoring Committee Reviews

An Independent Data Safety Monitoring Committee will be formed to monitor patient safety during the study. The IDSMC will also oversee the ATX-ME-001 clinical study of ATL001 in patients with recurrent or metastatic melanoma, and potentially additional future clinical studies in other cancers. The members include an independent statistician and three independent physicians, one of whom is an expert in lung cancer, one is an expert in melanoma and one is an expert in adoptive cell therapies. The members of the IDSMC serve in an individual capacity and provide their expertise, including recommendations regarding the continuation, modification, or termination of the studies in the clinical programme. The IDSMC will review cumulative study data to evaluate safety, study conduct, scientific validity and data integrity of the studies. Pertinent data from all ongoing clinical studies will be shared with the IDSMC.

An initial formal review of safety by the IDSMC will take place after the first 6 evaluable patients across ATX-NS-001 and ATX-ME-001 have all been treated and followed up for a minimum of 28 days post infusion. All safety data recorded during this period will be reviewed.

A subsequent IDSMC safety review will take place when 6 evaluable patients in ATX-NS-001 have all been treated and followed up for a minimum of 28 days. This safety review will determine whether enrolment into Cohort B can commence at centres. The IDSMC will be informed about other study related activities as deemed relevant to the ongoing oversight of patient safety including the initiation of additional cohorts or procedures.

Provided that the IDSMC agrees that the study can proceed without modification, the study will be considered to have proceeded from Phase I to Phase II following this IDSMC review. These two reviews may be combined depending on recruitment timings.

Similarly, an IDSMC safety review will be triggered when 6 evaluable patients have received ATL001 within the ATX-ME-001 study protocol and followed up for a minimum of 28 days. All safety data from patients treated in ATX-NS-001 will be considered in the review.

An additional IDSMC safety review will take place when 20 patients in this study have all been treated and followed up for a minimum of 28 days post infusion.

An IDSMC safety review of the first 6 patients treated in each treatment Cohort will also be scheduled when the 6th patient has been followed up for a minimum of 28 days post-infusion.

Additional safety reviews may be performed at other times as deemed appropriate by the Sponsor or IDSMC.

An evaluable patient for the IDSMC safety review will be defined as a patient who has received lymphodepletion and ATL001 infusion, at the target dose.

The committee will meet at regular intervals commensurate with the recruitment rate during the recruitment period to review progress and safety.

The committee will also be convened in the event of any patient developing a serious infusion reaction or Grade ≥ 3 CRS. In addition, any death within 30 days of ATL001 infusion (other than as a result of the underlying disease for which the patient is being treated) and any Grade 4 ICANS event will trigger a study pause and IDSMC review.

The committee will meet at least twice a year during the 2 year follow up phase after completion of recruitment. Further details will be provided in an IDSMC charter.

9.6 Interim Analyses

The following interim analyses of efficacy may be performed:

1. Optional interim analyses when approximately 10 evaluable patients have been followed up for 6 and 12 weeks.
2. An interim analysis of each treatment cohort separately when all patients in a cohort have been followed up for 12 weeks.
3. A final analysis when all patients have either died or have been followed up for 2 years.

Additional interim analyses may be performed at other times during the study. Based on the emerging data, Cohort A may be terminated for futility following an internal data review or interim analysis if it is felt that sufficient data have already been generated to address the study objectives for ATL001 as a monotherapy. No cohort will be terminated early as a result of a positive efficacy signal.

Since the study is open label, there are no blinding issues associated with performing interim analyses. Similarly, since the study is not formally powered and there are no planned hypothesis tests, no multiplicity adjustments are required to be accounted for in the interim analyses.

10 ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) guidelines and applicable regulatory requirements.

10.2 Independent Ethics Committee (IEC) / Institutional Review Board (IRB) Review & Reports

The final study protocol and the final version of the Written Informed Consent Form(s) will be approved or given a favourable opinion in writing by the IEC or IRB as appropriate. The Investigator will provide the Sponsor with a copy of the communication from the IRB or IEC to the Investigator indicating approval of the protocol and consent form, referring to the study by date, title, protocol number and the documents reviewed.

The Investigator must receive written approval from the Sponsor before he or she can enrol any patient into the study.

All changes to the protocol and consent form must be reviewed and approved prior to implementation, except where necessary to eliminate apparent immediate hazards to human subjects. The Principal Investigator is responsible for informing the IEC or IRB of any amendment to the protocol in accordance with local requirements. In addition, the IEC or IRB must approve all advertising used to recruit patient for the study.

Under no circumstances will the investigation be extended beyond the limitations defined in this protocol or any subsequent amendments.

The protocol must be re-approved by the IEC or IRB annually, as local regulations require. The Investigator must report to the IRB or IEC, at least annually, on the progress of the investigation. Continuing IRB/IEC review should be documented by a letter from the IRB. Notification to the IRB/IEC by the Investigator within 3 months after completion, termination, or discontinuation of the study at the specific site must be documented or in an appropriate timeframe as required by the relevant IRB or ethics committee.

10.3 Peer Review

The final study protocol and the final version of the Written Informed Consent Form(s) will undergo a process of Peer Review by a representation of the study Investigators and any other internal research or scientific committee per institution standards.

10.4 Regulatory Compliance

The final study protocol must be approved or given a favourable opinion in writing by the national regulatory authority prior to initiation of the study.

10.5 Notification of Serious Breaches to GCP and/or the Protocol

The Sponsor will notify the Regulatory Authorities in writing of any serious breaches without undue delay and in accordance with local regulatory requirements.

A “serious breach” is a breach which is likely to effect to a significant degree:

a. The safety or physical or mental integrity of the subjects of the trial; or

b. The scientific value of the trial.

11 STUDY MANAGEMENT

11.1 Patient Information and Consent

The Principal Investigator at the centre will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time (at least 24 hours) to consider the information provided.

The consent form that is used must comply with the requirements of ICH E6 and local regulatory authorities, be the current version, and must be approved by both the reviewing IRB/IEC and by the Sponsor prior to use. The patient's signed and dated informed consent(s) must be obtained before conducting any procedure specifically for the study.

The original, signed copy of the informed consent must be maintained in the institution's records, and is subject to inspection by a Sponsor representative.

A copy of the written Informed Consent Form must be given to the patient. If modifications are made according to local requirements, the new version has to be approved by the Sponsor.

11.2 Data Protection and Patient Confidentiality

The written Informed Consent Form (ICF) will explain that study data will be stored in a database, maintaining confidentiality in accordance with national data protection legislation. All data will be pseudonymised and patients will be identified by a Sponsor-assigned patient number/study code. The Written Informed Consent Form will also explain that for data verification purposes, authorised representatives of the Sponsor, a regulatory authority, an IEC or IRB may require direct access to parts of the hospital or practice records relevant to the study, including patients' medical history.

All collected patient data will be treated confidentially. As required for autologous cellular products, 100% traceability and identification have to be maintained from the procurement of materials required for manufacturing through product manufacture to the administration and disposal of ATL001. Each autologous product will be identified with a combination of four patient identifiers to ensure absolute identification. The four pseudo-anonymised identifiers used in this study will be the patient's unique study number, initials, gender and date of birth.

In compliance with ICH, E6 guidelines regarding the monitoring of clinical studies, and in fulfilment of the Investigator's obligation to the Sponsor, it is required that the Investigator must permit the study monitor or competent regulatory authority representative direct access to review that portion of the patient's medical record that is directly related to the study. This includes all study relevant documentation (including signed inform consent, medical histories to verify eligibility, laboratory test results to verify transcription accuracy, treatment and diagnostic reports, admission/discharge summaries for hospital admissions occurring while the patient is on study and autopsy reports for deaths occurring during or in temporal proximity to the study).

It is the Investigator's responsibility to obtain patient signatures on any locally required confidentiality documents. As part of the required content of informed consent, the patient must be informed that his/her records will be reviewed by Sponsor, the study monitor, or a representative of the relevant competent regulatory authority. Should access to the medical record require a separate waiver or authorization, it is the Investigator's responsibility to obtain such permission from the patient in writing before the patient is entered into the study.

All information provided to the Investigator by Sponsor, including nonclinical data, protocols, eCRFs, and verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting this study, and no disclosure shall be made except in accordance with any right of publication granted to the Investigator.

11.3 Case Report Form Completion

Case Report Form (CRF) completion will be via an electronic data capture (EDC) and will be reviewed for completeness and accuracy by the Sponsor or designee. The eCRFs per patient will be created by designee for use by the Investigator or site coordinator during data collection. Once the eCRF screens are programmed and tested, the site will be given access to the application and will be responsible for entering all applicable patient data directly into the database. The Sponsor designee will review all patient data for completeness and accuracy. Only the Investigator may sign eCRFs. If no other issues or questions arise from the final data revisions, the data will be locked by the Sponsor to preserve the "clean and complete" status of the eCRF data until the final locking of the database. All forms must be entered into the electronic data capture system in a timely manner. Data will be entered into the eCRF as information becomes available on a visit-by-visit basis. The Study Completion Information page of the eCRF must be signed by the Principal Investigator.

All eCRF corrections are to be made by an Investigator or other designated study site personnel. The Principal Investigator or Sub-Investigator must authorize changes to the recorded safety and efficacy data.

11.4 Monitoring and Data Verification

The monitoring of this study will be performed in accordance with the principles of Good Clinical Practice (GCP) as laid out in the International Conference on Harmonisation (ICH) document "Good Clinical Practice: Consolidated Guideline".

Study monitors or clinical staff designated by the Sponsor will visit the study site periodically to monitor compliance with the protocol, applicable regulatory regulations/requirements, and to ensure the maintenance of adequate and accurate clinical records. Monitoring functions will be performed in compliance with recognised Good Clinical Practices (GCP). The Investigator agrees to allow these study monitors, and other authorised Sponsor personnel, access to the clinical supplies, the investigational agent dispensing and storage area, patient medical records, laboratory data, and other source documentation of the study patients.

Source data verification will be conducted in the review of all CRFs. During this detailed review by the study monitor, the decision will be made as to their acceptability. Missing or incorrect or further clarification of data will be handled by data Clarification or Query Forms. Data queries will be generated either automatically, by programmed edit checks, or manually by the Sponsor designee. Data queries are then presented to study site staff (coordinators and/or Investigators) for resolution. Data clarifications or query forms are to be completed by the site staff in a timely manner. At the conclusion of the study, the completed CRFs and data queries will be reviewed and approved by the Investigator's signature, in the appropriate space of the CRF.

The dates of monitoring visits will be recorded on the monitoring sign-in log kept at the site. Sponsor expects that, during monitoring visits, the study coordinator, study personnel and Investigator will be available, the source documentation will be available, and a suitable environment will be provided for review of study-related documents. The Investigator agrees to assist Sponsor personnel in their duties, if requested.

11.5 Data Management

Data will be entered onto the clinical study database and validated. Any missing, impossible or inconsistent recordings in the eCRFs will be referred back to the Investigator and be documented for each individual patient before clean file status is declared. Source data should be made available to the monitor for review.

All entries to the study database will be available in an audit trail.

The study monitor will check data at the monitoring visits to the investigational site. The Investigator, together with delegates and the study monitor, will ensure that the data in the eCRFs are accurate and complete.

11.6 Management and Archiving of Study Documents

It is the responsibility of the Investigator and study staff to maintain a comprehensive and centralised filing system of all study-related documentation that is suitable for inspection at any time by the study monitor and the relevant competent regulatory authority. Elements must include, but are not limited to:

- All essential regulatory documents as required by ICH E6, Good Clinical Practices.
- Patient files containing the signed informed consent(s) and supporting source documentation (e.g. laboratory reports, progress notes, medical histories, physical and diagnostic findings, diagnoses and dates of treatment prior to and during this study) that support data entered on the eCRFs.
- Pharmacy or Investigator files, containing the investigational agent accountability records or dispensation logs and all study agent-related correspondence.

These documents should be updated as needed during the course of the study. In addition to the documents required prior to the study, other documentation may be required during the course of the study. A copy of the completed eCRFs for each patient will be provided to the site at the end of the study and must be stored with the site's study files.

The Sponsor will retain all documentation pertaining to this study.

The FDA requires that the Investigator must retain study files for a period of at least 5 years after study completion or 2 years following the date that a marketing application is approved for the indication in which the study agent is being investigated (whichever is later).

The hospital in which ATL001 is used will be required to establish and maintain a system for patient and product traceability containing sufficient detail to enable traceability between the donated tissues and cells used for manufacture and receipt by the patient of the final product.

The Investigator/institution where ATL001 is used, should keep their parts of the traceability records for a minimum of 30 years, or longer if required by the terms of the clinical trial authorisation or by the agreement with the Sponsor.

If no marketing application or license is to be filed, or if the application or license is not approved for such an indication, the files must be stored until 2 years after the Sponsor notifies the FDA and the Investigator that the indication has been discontinued.

If the Investigator for any reason desires to dispose of the study files/records, they may be transferred to another institution, another Investigator, or to Sponsor upon written agreement between the Investigator and Sponsor.

11.7 Audits and Inspections

Authorised representatives of the Sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the centre to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, GCP guidelines of the ICH and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection at his or her centre.

11.8 Training of Staff

Before the first patient is entered into the study, a Sponsor representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures including collection of samples and EDC system used.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

11.9 Amendments to the Protocol

Through the course of the study amendments to the protocol may be required as identified by the Sponsor and/or study site.

Amendments to the protocol will originate from the Sponsor and will be provided to the Investigator for submission to his/her IRB or IEC for their review and approval prior to implementation. It should be noted that when an amendment to a protocol substantially alters the study design or increases potential risk to the study patient, the informed consent should be revised and re-submitted to the IRB or IEC for approval, and, if applicable, the patient's consent to continue participation should be obtained. Local requirements must be followed.

The Sponsor will distribute amendments and new versions of the protocol to the Principal Investigator who in turn is responsible for the distribution of these documents to his or her IEC or IRB, and to the staff at his or her centre. The distribution of these documents to the regulatory authority will be handled according to local practice by the Sponsor.

11.10 Study Agreements

The Principal Investigator at the centre must comply with all the terms, conditions, and obligations of the study agreement for this study. In the event of any inconsistency between this protocol and the study agreement, this protocol shall prevail.

11.11 Financial Disclosure

All Investigators are required to declare in writing any conflict of interest with their ability to perform the functions of an Investigator in an independent manner. This includes any financial interest that are either held by the Investigator or his/her Sub-Investigators themselves, their spouse or dependent children, and any other relationships with employees of the Sponsor that could affect the Investigator's objectivity.

In accordance with US 21 CFR, Part 54.4, Investigators are required to provide information on financial interest and arrangements during the course of the study and for one year after the completion of the study.

11.12 Study Timetable and Termination

The timelines for the study will be as per the study agreement with the study site. The start of the study is defined as the first patient signing informed consent. The end of the study is defined as the last visit of the last patient undergoing the study.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. The Sponsor may also terminate the entire study prematurely based on business decisions, efficacy, safety, or other reasons.

11.13 Sample Management

Biological samples will be used up, disposed of after analyses or retained for further use for a maximum of 15 years following the patient's last visit in the study.

Biological samples remaining after planned analyses will be retained will be retained for future and optional research for a maximum of 15 years following the last patient's last visit in the study.

A full chain of custody will be maintained for all samples throughout their lifecycle.

The Principal Investigator at each centre will maintain a full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal.

The sample receiver will maintain a full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

Samples will be stored by Achilles Therapeutics UK Limited in a biobank and provided for research purposes in order to further understand the disease and therapy.

This biomaterial may be shared with Achilles Therapeutics UK Limited authorised representatives. Samples shipped to external vendors for analysis will be returned to the Sponsor upon completion of analysis, where available. These return shipments may be planned in batches.

Biomaterial ownership will be transferred to Achilles Therapeutics UK Limited.

12 USE OF INFORMATION AND PUBLICATION POLICY

The information provided in support of or generated as a result of this study is confidential. Any use or reproduction thereof, including but not limited to publications or presentations by the Investigator or his/her associates, must be submitted to the Sponsor for review and the opportunity to make comments prior to publication or presentation in any form. All publications must acknowledge the Sponsorship.

All information not previously published concerning information such as patent applications, formulas, manufacturing processes, basic scientific data, and formulation information supplied by the Sponsor to the Investigator is considered confidential and shall remain the sole property of the Sponsor. The Investigator agrees to use this information only to accomplish this study and will not use it for other purposes without the Sponsor's written consent.

13 EMERGENCY PROCEDURES

13.1 Medical Emergency Contact Procedure

In the case of a medical emergency, contact personnel shown below.

[redacted] [redacted]

13.2 Overdose

It is not possible for a patient to receive an overdose of ATL001 due to the fixed volume in a Product Infusion Bag.

Investigators should be advised that any patient who receives a higher dose than that intended of any other component of study medication should be monitored closely, managed with appropriate supportive care and followed up expectantly.

Such overdoses should be recorded as AEs/SAEs as follows:

- An overdose with associated AEs/SAEs is recorded as the AE diagnosis/symptoms on the relevant AE/SAE modules in the CRF and on the overdose CRF module.
- An overdose with no associated symptoms is only reported on the overdose CRF module.

If an overdose occurs in the course of the study, then Investigators or other site personnel must inform Achilles Therapeutics (or its representative) immediately, or **no later than 24 hours** of when he or she becomes aware of it.

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15 APPENDICES

15.1 Appendix A: ECOG Performance Status Score

Developed by the Eastern Cooperative Oncology Group

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Source: Oken et al, 1982 *Am J Clin Oncol* 5(6):649-655

15.2 Appendix B: Summary of Differences Between RECIST v1.1 and imRECIST

Table 1. Comparison of imRECIST With RECIST v1.1 and irRC

Criterion	RECIST v1.1	irRC[6]	imRECIST*
Tumor burden	Unidimensional Up to five target lesions/two per organ	Bidimensional per WHO Up to 10 target lesions/ five per organ	Unidimensional, with other target lesion criteria (number, measurability) per RECIST v1.1
New lesions	Always represent PD	New lesions do not categorically define PD Measurable new lesions incorporated into the total tumor burden Nonmeasurable new lesions preclude CR	
Nontarget lesions	Can contribute to defining CR or PD (unequivocal progression)	Nontarget progression does not define PD Can only contribute to defining CR (complete disappearance required)	
PD	≥ 20% increase in the SLD (RECIST) and ≥ 5 mm increase compared with nadir, unequivocal progression in nontarget lesions, and/or appearance of new lesions	Determined only on the basis of measurable disease	
		Negated by subsequent non-PD assessment ≥ 4 weeks from the date first documented (lack of confirmation)	
		≥ 25% increase in the SLD compared with baseline/ nadir	≥ 20% increase in SLD (RECIST) compared with baseline/nadir
	Confirmation of PD not required	Best response may occur before confirmed PD	Best response may occur after any number of PD assessments

Abbreviations: CR, complete response; imRECIST, immune-modified RECIST; irRC, immune-related response criteria; PD, progressive disease; RECIST, Response Evaluation Criteria In Solid Tumors; SLD, sum of longest diameters.
*imRECIST follows RECIST v1.1 conventions unless otherwise stated.

Source: Hodi et al, 2018 *J Clin Oncol* 36(9):850-858

15.3 Appendix C: Prohibited and Concomitant Medications

Prohibited Medications:

- Prior to procurement:
  - **Regular, ongoing** immunosuppressive treatments for active autoimmune disease – including but not limited to: azathioprine, abatacept, adalimumab, anakinra, basiliximab, certolizumab, cyclosporin, daclizumab, etanercept, golimumab, infliximab, ixekizumab, leflunomide, methotrexate, mycophenolate, natalizumab, rituximab, sarilumab, secukinumab, tacrolimus, tocilizumab, tofacitinib, ustekinumab, vedolizumab.
  - **Regular, ongoing** treatment with steroids at a dose higher than prednisolone 10 mg/day (or equivalent – i.e. prednisone 5 mg, triamcinolone 8 mg, dexamethasone 1.6 mg, betamethasone 1.2 mg, methylprednisolone 8 mg, hydrocortisone 40 mg). Patients receiving modified-release, oral preparations of steroids with low systemic availability (e.g. beclomethasone dipropionate, budesonide) should be discussed with the Sponsor.
  - Any investigational cell or gene therapies.
  - Any cytotoxic chemotherapy or anti-angiogenesis agent (e.g. bevacizumab) within the 3 weeks prior to procurement.
- Between re-screening and Lymphodepletion:
  - **Regular, ongoing** immunosuppressive treatments for active autoimmune disease.
  - **Regular, ongoing** treatment with steroids at a dose higher than prednisolone 10 mg/day or equivalent.
  - Any live vaccination within the 28 days prior to lymphodepletion.
  - Any cytotoxic chemotherapy agent within the 3 weeks prior to lymphodepletion.
  - Any investigational cell or gene therapies.
- From Lymphodepletion through follow up period:
  - Non-Steroidal Anti-Inflammatory agents (e.g. ibuprofen), aspirin or any other drug with an anti-platelet effect should not be used from lymphodepletion until recovery of normal platelet counts.
  - G-CSF is not recommended as a routine prophylaxis in all patients following lymphodepletion as it can stimulate myeloid derived suppressor cells (however, its use is at the discretion of the Investigator dependent on the clinical situation and it should be used to manage cytopenia).
  - Corticosteroids as anti-emesis prophylaxis or infusion reaction prophylaxis.

- Any immunosuppressive treatments, unless needed to treat emerging toxicity (e.g. tocilizumab or siltuximab for CRS).
- Treatment with steroids at a dose higher than prednisolone 10 mg/day (or equivalent), unless needed to treat emerging toxicity.
- Any investigational cell or gene therapies.
- Any live vaccination within 3 months of last dose fludarabine.
- Non-irradiated blood products.

Permitted Concomitant Medications:

- Procurement:
  - Any standard pre-medication agents and anaesthetic agents.
- Lymphodepletion:
  - Fludarabine and cyclophosphamide per protocol.
  - Any anti-emetic prophylaxis (per local SOPs) except corticosteroids.
  - Anti-infective prophylaxis, per local SOPs (e.g. cotrimoxazole, acyclovir, fluconazole).
  - G-CSF to manage prolonged neutropenia, per local SOPs.
- Prior to ATL001 infusion or during follow up period:
  - Chlorphenamine and paracetamol/acetaminophen to prevent infusion reactions, per local SOPs.
  - Tocilizumab or siltuximab to treat cytokine release syndrome, per protocol guidelines.
  - IL-2 (aldesleukin) per protocol.
- COVID-19 vaccination:
  - Currently authorised COVID-19 vaccines do not use mechanisms or vectors that would classify them as “live vaccinations”. As such, Exclusion Criterion 21 does not apply to the use of these vaccines in study participants; nor does the SmPC/Package Insert guidance for live vaccination following fludarabine or pembrolizumab administration (i.e. avoidance of live vaccination for 3 and 4 months, respectively).
  - There is a risk that immunosuppressed individuals may have a suboptimal immunological response to COVID-19 vaccines. As such, COVID-19 vaccine doses should ideally be given to trial participants at least two weeks pre-lymphodepletion and two weeks post-ATL001 infusion (or as per local SOPs, if already in place).

15.4 Appendix D: CRS Monitoring Chart

Date	**Baseline**															
Time																
Temperature ≥ 38°C																
Hypotension																
Hypoxia																
CRS grade																

Date																	
Time																	
Temperature ≥ 38°C																	
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Hypoxia																	
CRS grade																	

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CRS grade																	

Date																	
Time																	
Temperature ≥ 38°C																	
Hypotension																	
Hypoxia																	
CRS grade																	

15.5 Appendix E: Neurotoxicity Monitoring Charts

Date	**Baseline**									
Time										
Year (1p)										
Month (1p)										
City (1p)										
Hospital (1p)										
Follow commands (1p)										
Naming three nearby objects (max 3p)										
Writing a standard sentence (1p)										
Count backwards from 100 in tens (1p)										
ICE Score										
Depression level of consciousness										
Seizures										
Motor findings										
Elevated ICP/cerebral oedema										
ICANS Grade										

Date	**Time**	**Short sentence**
Baseline		

15.6 Appendix F: Expected IL-2 Toxicities and Their Management

Expected toxicity	Expected Grade	Supportive Measures	Stop Treatment*
Chills/rigors	3	IV Pethidine 25-50 mg, IV q1h, prn	No
Fever	3	Paracetamol 500 mg, po, q4h; Indomethicin 50-75 mg, po, q8h	No
Pruritis	3	Chlorpheniramine 10mg IV q6h, prn or 4mg po q6h, prn; Hydroxyzine HCL 10-20 mg po q6h, prn; Diphenhydramine HCL 25-50 mg, po, q4h, prn	No
Nausea/ Vomiting/ Anorexia	3	Ondansetron 10 mg, IV, q8h, prn; Prochlorperazine 25 mg q4h p.r., prn or 10 mg IV q6h prn; or as per local standard	No
Diarrhoea	3	Loperamide 2 mg, po, q3h, prn; codeine sulphate 30-60 mg, po, q4h, prn	If uncontrolled after 24 hours despite all supportive measures
Malaise	3 or 4	Bedrest	If other toxicities occur simultaneously
Hyperbilirubinaemia	3 or 4	Observation	If other toxicities occur simultaneously
Anaemia	3 or 4	Transfusion with PRBCs	If uncontrolled despite all supportive measures
Thrombocytopaenia	3 or 4	Transfusion with platelets	If uncontrolled despite all supportive measures
Neutropaenia	4	Observation	No
Oedema/Weight gain	3	Diuretics prn	No
Hypotension	3	Fluid resuscitation; Vasopressor support	If uncontrolled despite all supportive measures
Dyspnea	3 or 4	Oxygen or ventilatory support	If requires ventilatory support
Oliguria	3 or 4	Fluid boluses	If uncontrolled despite all supportive measures
Increased creatinine	3 or 4	Observation	Yes (grade 4)
Renal failure	3 or 4	Dialysis	Yes
Pleural effusion	3	Consider thoracentesis	If uncontrolled despite all supportive measures
Confusion/somnolence	3	Observation	Yes
Arrhythmia	3	Correction of fluid and electrolyte imbalances; chemical conversion or electrical conversion therapy	If uncontrolled despite all supportive measures
Elevated Troponin levels/myocardial infarction	3 or 4	Observation/standard supportive care	Yes
Elevated transaminases	3 or 4	Observation	For grade 4 without liver metastases
Electrolyte imbalances	3 or 4	Electrolyte replacement	If uncontrolled despite all supportive measures

*Unless the toxicity is reversed within 24 hours.

15.7 Appendix G: Country Specific Requirements - Germany

The following additional restrictions apply in Germany:

- The administration of any “out of specification” products in Germany is not permitted.

The following additional requirements apply to sites in Germany participating in the study:

- Patients must undergo pregnancy testing from Day 0 (day of infusion +/– 1 day) and then at every 6 week visit for 12 months or until either completion of the study or withdrawal of the study, whichever is sooner. Refer to the Schedule of Assessments (Section 6.3) for details of pregnancy testing requirements for participating sites in Germany.
- Cohort B patients require a higher frequency of pregnancy testing whilst receiving pembrolizumab. Urine or serum pregnancy testing is required prior to each pembrolizumab administration (i.e. every 6 weeks) for female participants of childbearing potential. For Cohort B patients being treated at sites in Germany, if pembrolizumab doses are delayed, omitted, or discontinued for any reason then the frequency of pregnancy testing should be adjusted accordingly but must satisfy the 6-weekly requirement described above.