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

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The objectives and relevant endpoints of the study are as follows:Primary: To assess the safety and tolerability of ATL001 as amonotherapy and in combination with pembrolizumabSecondary: To evaluate the clinical efficacy of ATL001treatment as a...

Ethical review	Approved WMO
Status	Completed
Health condition type	Respiratory disorders NEC
Study type	Interventional

Summary

ID

NL-OMON50919

Source
ToetsingOnline

Brief title
CHIRON

Condition

- Respiratory disorders NEC

Synonym
Advanced Non-Small Cell Lung Cancer, avenocellular carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Achilles therapeutics UK Limited
Source(s) of monetary or material Support: Achilles Therapeutics UK Limited

Intervention

Keyword: Clonal Neoantigen T cells, Non-Small Cell Lung Cancer, TIL therapy

Outcome measures

Primary outcome

Endpoint: Frequency and severity of adverse events (AEs) and serious adverse events (SAEs) following tissue procurement and administration of lymphodepletion agents, ATL001 and IL-2.

Secondary outcome

Endpoints;

* 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 thepersistence, 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 description

Background summary

The purpose of this study is to understand whether an experimental therapy called ATL001 is safe and beneficial in adult patients with NSCLC. This is the first study of ATL001. Experimental means that the product has not been approved yet by an authority that regulates new medicines and, because of this, it cannot be purchased.

The personalized cell therapy used in this study is called ATL001. It is made by taking a sample from your cancer and identifying a unique set of *targets* found only in the cancer cells and not in your normal healthy cells. The final product, ATL001, consists of immune cells that are extracted from a sample of your cancer, grown in a manufacturing laboratory under specialised conditions, and primed to recognise these cancer cell targets. These cells are then given back to you to help fight the cancer.

Study objective

The objectives and relevant endpoints of the study are as follows:

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

Secondary: To evaluate the clinical efficacy of ATL001 treatment as a monotherapy and in combination with pembrolizumab

Exploratory:
1. To evaluate thepersistence, 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 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 with lymphodepletion and low dose IL-2. Initially it will be given as a monotherapy (i.e. no treatments will be given in combination with or after the infusion until the time of disease progression). In Cohort B, eligible patients will receive 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 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.

Intervention

Eligible patients will receive a single intravenous infusion of ATL001, following 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 1.0 x 107 - 1.0 x 109 CD3+ cells, and a minimum of 20 patients with the target cell dose will be treated in Cohort A. 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, 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.

Study burden and risks

ATL001 may cause side effects.

The following side effects are common:
- Mild to moderate fever, chills, headache
- Mild to moderate hypotension
- ICANS
A condition called immune cell associated neurotoxicity syndrome (ICANS) is commonly reported in patients who received a different form of cell therapy in which a patient*s immune cells are genetically modified before they are given back to the patient. ICANS can cause a variety of symptoms, including confusion, agitation, drowsiness, difficulty in processing information, difficulty in writing and naming objects, nerve function defects, hallucinations, seizures and in severe cases, brain swelling. Patients may need to be moved to an Intensive Care Unit for close monitoring and treatment. The symptoms generally resolve over a period of 2 to 10 days, but some can take weeks to resolve.

The following side effects are rare and can be serious:
- High fever (>38.5ºC)
- Chills
- Mucosal swelling
- Shortness of breath
- CRS
A condition called cytokine release syndrome (CRS) has rarely been reported in patients who received a different form of cell therapy in which a patient*s immune cells are genetically modified before they are given back to the patient. CRS is a serious condition and some patients have needed intensive care. It is considered unlikely that ATL001 treatment will cause severe CRS because it has not been genetically modified.

Side effects associated to DMSO (a component of the ATL001 treatment) are very rare but may include: increase or decrease of blood pressure, seizure or respiratory arrest. The most common reaction is hypertension,

ATL001 can also have side effects that we do not know about at the moment.

Because of these potential risks, the patient will be monitored very carefully for 2 weeks after undergoing lymphodepletion and he/she will need to stay in hospital for this period.

Pembrolizumab can also have side effects. The most important ones are:
- inflammatory disorders of the lungs, skin, gastrointestinal system
- endocrine glands (for example thyroid, adrenal and pituitary glands) disorders
- anaemia

- painful joints
- weakness
- cough
- cytokine release syndrome
- dizziness
- flu-like illness
- infusion related reaction
- Nausea
- Fluid retention

These symptoms can be managed by giving medicines to prevent development of the side effects and if required by temporarily stopping treatment and/or using short courses of corticosteroids.

Other medication that may cause side effects
Fludarabine: The common side effects associated with this drug include poor appetite, nausea and vomiting, fatigue and diarrhoea.

Cyclophosphamide: The common side effects associated with this drug include poor appetite, nausea and vomiting, fatigue and diarrhoea. Less commonly cyclophosphamide can cause bladder irritation.

Both medications target your existing immune cells and temporarily reduce their numbers. The low blood counts may last for 14-21 days, and during this time you may be susceptible to infections, which can be serious and require intravenous antibiotics. Because of this you should not receive any live vaccinations for a 4-month period during the study - one month before and three months after you receive cyclophosphamide and fludarabine. Your study doctor will explain this to you in more detail.

IL-2: IL-2 is a drug that is usually used to treat patients with melanoma skin cancer and kidney cancer at doses 9 or 18 times higher than in this study. In this study, its purpose is to help the ATL001 cells to survive after they are injected into the patients body. The patient will receive IL-2 for 10 days.
The high doses of IL-2 used, over long periods of time, to treat melanoma and kidney cancer are associated with an increased risk of heart problems including heart attack and heart failure. A rare side effect from high doses of IL-2 called *capillary leak syndrome* can cause swelling of arms and legs, low blood pressure, irregular heartbeat, shortness of breath and low levels of protein in the blood. These side effects are not expected with the low dose IL-2 used in this study - the most common side effects reported in other cell therapy studies using low doses of IL-2 are lowered blood pressure, diarrhoea, chills, nausea, vomiting, and rash, which recover quickly after stopping IL-2.

the patient will be monitored in hospital every day while he/she is receiving

IL-2, so if there are any concerns it can be stopped.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

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.
Inclusion Criteria:
1. Patient must be at least 18 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 x10*/L.
c. Absolute Neutrophil Count (ANC) >= 1.5 x10*/L.
d. Platelets >= 100 x10*/L.
e. PT and APTT < 1.5x ULN (unless receiving therapeutic anticoagulation).
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 F for pregnancy testing requirements in Germany. See Section 4.3 for details of acceptable methods of contraception.

In addition to 1-8, the following inclusion criteria must 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 (These patients will not receive ATL001 until their disease has progressed following standard of care therapies, or if they cannot tolerate standard of care therapies - see inclusion number 11).
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 1-8, the following inclusion criteria must be met prior to lymphodepletion for treatment with ATL001:

11. Patients must have locally advanced unresectable or metastatic NSCLC whose disease has progressed or recurred following standard of care or who are

ineligible for, or who cannot tolerate, standard of care therapies, e.g. platinum-based chemotherapy and an immune checkpoint inhibitor.
12. Patients must have measurable disease according to RECIST v1.1 criteria prior to lymphodepletion. (If patients have no measurable disease following standard therapy, lymphodepletion and ATL001 treatment may be delayed until there is evidence of measurable disease).
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, the following inclusion criteria must be met for patients to be eligible for treatment in Cohort B:

14. Prior to treatment with ATL001, the most recent treatment regimen must have included a PD-1/PD-L1 inhibitor and patients should have experienced radiological disease progression on this treatment regimen.
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 urine pregnancy test before each pembrolizumab administration during the treatment period in Cohort B.

Exclusion criteria

Exclusion Criteria:
1. Patients with known CNS metastases at the time of screening.
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 (e.g. EGFR, ALK or ROS-1) at the time of initial screening.
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.
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) 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. refractory disease).
19. Patients with a known 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) for reference safety information for pembrolizumab).
All exclusion criteria except 2, 3, 4, 17 and 18 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 design

Design

Study phase:	2
Study type:	Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	31-01-2022
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous

Ethics review

Approved WMO Date:	26-07-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-12-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-04-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-05-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	06-07-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-001005-85-NL
CCMO	NL77802.000.21