A Single Arm, Open-Label, Multi-Centre, Phase I/II Study Evaluating the Safety and Clinical Activity of AUTO2, a CAR T Cell Treatment Targeting BCMA and TACI, in Patients with Relapsed or Refractory Multiple Myeloma.

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Phase I: To assess the safety and tolerability of AUTO2 administration and To identify the recommended Phase II dose and maximum tolerated dose (MTD), if an MTD exists, of AUTO2.Phase II: To evaluate the anti-tumour effect of AUTO2 and to assess the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Plasma cell neoplasms
Study type	Interventional

Summary

ID

NL-OMON47144

Source
ToetsingOnline

Brief title
Phase I/II study evaluating AUTO2 in patients with multiple myeloma.

Condition

- Plasma cell neoplasms
- Plasma cell neoplasms

Synonym
Multiple myeloma or cancer of white blood cells

Research involving
Human

Sponsors and support

Primary sponsor: Autolus Limited
Source(s) of monetary or material Support: Autolus Limited

Intervention

Keyword: Chimeric Antigen Receptor (CAR)-T cell, dose-response relationship, Multiple myeloma, safety

Outcome measures

Primary outcome

For Phase I:

1. Incidence of Grade 3 to 5 toxicity occurring within the dose-limiting

toxicity (DLT) period (28 days post AUTO2 infusion).

2. Frequency of dose limiting toxicity (DLT) and the persistence of AUTO2.

For Phase II:

1. Best overall response post-AUTO2 infusion.

2. Frequency and severity of AEs and SAEs.

Secondary outcome

1. Proportion of patients for whom an AUTO2 product can be generated

(feasibility).

2. Determine the clinical benefit (stringent complete response + complete

response + very good partial response + partial response + minor response

[sCR+CR+VGPR+PR+MR]) rate following treatment with AUTO2.

3. To evaluate clinical outcomes including duration of response, time to

disease progression, PFS and OS.

4. Quantitative PCR (qPCR) and/or flow cytometry at a range of time points in

the peripheral blood.

Study description

Background summary

Novel immunotherapies such as CAR T cell therapies hold promise for significant improvement in the overall outcome of MM. Anti-CD19 CAR T cells in clinical development for the treatment of B-lineage malignancies have demonstrated efficacy in clinical trials. Several ongoing clinical studies are utilising CARs targeting BCMA. Early results with this approach have shown encouraging results in the treatment of MM. A restriction of these CARs is that they target BCMA only. Unlike BCMA, CAR AUTO2 expressing APRIL can target 2 antigens expressed on myeloma cells, BCMA and TACI* enabling targeting of tumour cells expressing low antigen. Dual BCMA/TACI targeting may also prevent escape by target antigen down-regulation as observed with CD19 targeting. AUTO2 has also been engineered to be more active with the incorporation of both proliferation CD28 and survival OX40 co-stimulatory signals. Additionally, incorporation of RQR8 safety switch into the CAR adds to the overall safety of AUTO2. This first in human, Phase I/II study will assess the safety and preliminary activity of AUTO2 in patients with relapsed or refractory MM.

Study objective

Phase I: To assess the safety and tolerability of AUTO2 administration and To identify the recommended Phase II dose and maximum tolerated dose (MTD), if an MTD exists, of AUTO2.

Phase II: To evaluate the anti-tumour effect of AUTO2 and to assess the safety and tolerability of AUTO2 administration.

Study design

This is a Phase I/II, open-label, multi-centre study to characterise the safety and clinical activity of APRIL CAR T cells when administered to patients with relapsed or refractory MM. The study will consist of 2 parts, a Phase I /dose escalation followed by a Phase II /expansion. Both parts of the study will involve patients going through the following 5 sequential stages: screening, leukapheresis, pre-conditioning, treatment and follow-up.

Phase I (Dose Escalation): To identify the optimal dose (based on safety, tolerability and antitumour activity) of AUTO2 using an accelerated titration design (Simon et al. 1997). Up to 5 cohorts and a maximum of 42 patients with MM will be treated. Doses from 15 x 10e6 upto 1200 x 10e6 RQR8/APRIL CAR positive T cells will be evaluated.

Phase II (Dose Expansion): To further characterise the safety and assess the efficacy of AUTO2 at the recommended dose identified in Phase I, 30 patients will be treated in the dose expansion phase.

Biomarkers relating to the CAR T cells and tumours will be evaluated in all patients. All patients enrolled in Phase I and II will attend clinic visits for up to 24 months (or less in the event of early discontinuation) post AUTO2 infusion for study-specific assessments including AE assessments, physical examination, and laboratory and immunology tests.

After completion of the 24-month follow-up period or following AUTO2 treatment and early withdrawal from this study, all patients will be followed until death or for up to 15 years from treatment administration under a separate long-term follow-up study protocol.

Intervention

Eligible patients will receive a single dose IV of AUTO2 following pre-conditioning treatment.
Five dose cohorts are planned in Phase I:
- Cohort 1, Dose Level 1: 15 x 10e6 RQR8/APRIL CAR positive T cells
- Cohort 2, Dose Level 2: 75 x 10e6 RQR8/APRIL CAR positive T cells
- Cohort 3, Dose Level 3: 225 x 10e6 RQR8/APRIL CAR positive T cells
- Cohort 4, Dose Level 4: 600 x 10e6 RQR8/APRIL CAR positive T cells
- Cohort 5, Dose Level 5: 900 to 1200 x 10e6 RQR8/APRIL CAR positive T cells

All patients will receive a pre-conditioning regimen using fludarabine 30 mg/m2 IV over 30 minutes immediately followed by cyclophosphamide 300 mg/m2 IV over 30 minutes. Both these drugs will be given on Days -6, -5, and -4 before AUTO2 infusion.

Study burden and risks

There are 5 stages in this study:-
* Screening
* Leukapheresis
* Pre-conditioning chemotherapy
* Treatment with AUTO2
* Follow-up
There are 2 screening visits that last up to 4 hours each. The visit for the

leukapheresis takes all day. For the preconditioning therapy the patient will be hospitalised for 3 days. As of the day of AUTO2 administration the patient will be hospitalised for about 10 days. The Follow-up Visits will take up to 2 hours each. The visits will take longer if scans or bone marrow assessment take place. Bone aspirate and bone biopsies to evaluate the development of the disease will be done up to 7 times.
After informing the patient and signing the informed consent form screening starts with registration of the medical history, the demographic data, the checks of the in-/exclusion criteria, ECOG status, physical examination, vital functions, ECG, cardiac echo or Muga, blood draws and urine tests.
After this the leukapheresis follows. This is the standard procedure to collect T-cells of a patient.
After leukapheresis a 2nd screening visit is done to check that the patient is still eligible. For that reason a part of the assessments is repeated. During this second screening day a bone marrow biopsy will be done as well as further imaging.
The T-cells that are collected during leukapheresis will be manufactured elsewhere to generate AUTO2. This process may take some weeks. After it was confirmed that the production was successful the patient will undergo pre-conditioning chemotherapy. This chemotherapy is not experimental. For this therapy the patient will be hospitalised for 3 days (day -6, day -5, day -4).
Then the infusion with AUTO2 follows on day 0. For this purpose the patient is hospitalised for up to 10 days. During the hospitalisation the patient will be checked on vital functions, blood will be drawn for safety, an ECG will be made, adverse events will be registered and treated where needed, medication will be recorded. Physical examinations will be repeated as appropriate.
After discharge the patient will come weekly for follow-up visits until day 28. During these follow-up visits ECOG assessment, physical examination (as needed), vitals, ECG, adverse events, blood tests and co-medication will be checked.
Thereafter, the patient will come monthly in the first half year every 2 months thereafter. Three more visits will follow in the second year. Two years after the AUTO2 infusion the last follow-up visit takes place.
At the end, the patient will be asked to participate in a 15 year lasting follow-up study.

The risks of the individual procedures are described at E9.

If the treatment is effective it is directly beneficial for (a part of) the patients that take part in this study. If participation does not help for the individual patient, at least the knowledge about MM and the treatment options will grow. This may be of benefit for future MM patients.

Contacts

Public
Autolus Limited

58 Wood Lane Forest House
London W12 7RZ
GB
Scientific
Autolus Limited

58 Wood Lane Forest House
London W12 7RZ
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male or female patients, aged * 18.
2. Willing and able to give written, informed consent for the current study protocol, AUTO2-MM1.
3. Confirmed diagnosis of MM as per IMWG.
4. Measurable disease as defined by any one of the following:
- Serum M-protein * 500 mg/dL;
- Urine M-protein * 200 mg/24 hours;
- Involved serum free light chain level * 10 mg/dL, provided serum free light chain ratio is abnormal.
5. Relapsed or refractory disease after either one of the following:
a. Had at least 3 different prior lines of therapy including proteasome inhibitor (e.g. bortezomib or carfilzomib), immunomodulatory therapy (IMiD; e.g. thalidomide, lenalidomide

or pomalidomide) and alkylator or monoclonal antibody OR
b. Have "double refractory" disease to a proteasome inhibitor and IMiD, defined as progression on or within 60 days of receiving these agents.
6. For females of childbearing potential (defined as less than 2 years after last menstruation or not surgically sterile), a negative serum or urine pregnancy test must be documented at screening, prior to pre-conditioning and confirmed before receiving the first dose of study treatment.
7. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 to 1.
8. Peripheral blood total lymphocyte count > 0.5 x 10e9/L at enrolment and prior to leukapheresis.

Exclusion criteria

1. Women who are pregnant or lactating.
2. Prior treatment with investigational or approved gene therapy or cell therapy products.
3. Clinically significant, uncontrolled heart disease (New York Heart Association Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, sick-sinus syndrome, or electrocardiographic evidence of acute ischaemia or Grade 3 conduction system abnormalities unless the patient has a pacemaker) or a recent (within 6 months) cardiac event.
4. Left Ventricular Ejection fraction < 50 (by ECHO or MUGA) unless the institutional lower limit of normal is lower.
5. Patients with a history or evidence of deep vein thrombosis or pulmonary embolism requiring ongoing therapeutic anticoagulation at the time of pre-conditioning.
6. Patients with any major surgical intervention in the last 3 months, cement augmentation for vertebral collapse is permitted.
7. Significant liver disease: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) * 3 × ULN, or total bilirubin *25 *mol/L (1.5 mg/dL), except in patients with Gilbert*s syndrome or evidence of end stage liver disease (e.g. ascites, hepatic encephalopathy).
8. Chronic renal impairment requiring dialysis, or calculated creatinine clearance & < 30 mL/min.
9. Active infectious bacterial or viral disease (hepatitis B virus, hepatitis C virus, human immunodeficiency virus, human T-lymphotropic virus or syphilis) requiring treatment.
10. Use of rituximab (or rituximab biosimilars) within the last 3 months prior to AUTO2 infusion.
11. Active autoimmune disease requiring immunosuppression.
12. Received any anti-myeloma therapy within the last 7 days prior to pre-conditioning or leukapheresis. G-CSF should stop 10 days prior to leukapheresis.
13. Received any radiotherapy within the last 7 days prior to pre-conditioning or leukapheresis. Localised radiation to a single site, e.g. for bone pain is permitted at any time.
14. Life expectancy < 3 months.
15. Known allergy to albumin, dimethyl sulfoxide, cyclophosphamide or fludarabine.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-08-2018
Enrollment:	27
Type:	Actual

Ethics review

Approved WMO Date:	07-06-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-09-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-03-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-03-2018
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-08-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-09-2018
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
Other	EUCTR2016-003893-42-GB
EudraCT	EUCTR2016-003893-42-NL
CCMO	NL59718.000.17