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Chimeric antigen receptor T-cell therapy targeting a MAGE A4 peptide and HLA-A*02:01 complex for unresectable advanced or recurrent solid cancer: protocol for a multi-institutional phase 1 clinical trial

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a multi-institutional, first-in-human, phase 1 clinical trial to assess the tolerability and toxicity of CAR-T cells targeting MAGE-A4-positive and HLA-A*02:01-positive solid tumours.
⇒ To the best of our knowledge, this is the first clinical study using CAR-T cells that recognise a major histocompatibility complex and peptide complex.
⇒ The requirement of HLA-A*02:01 and MAGE A4 antigen expression limits the number of eligible patients.

ABSTRACT

Introduction Adoptive cell transfer of genetically engineered T cells is a promising treatment for malignancies; however, there are few ideal cancer antigens expressed on the cell surface, and the development of chimeric antigen receptor T cells (CAR-T cells) for solid tumour treatment has been slow. CAR-T cells, which recognise major histocompatibility complex and peptide complexes presented on the cell surface, can be used to target not only cell surface antigens but also intracellular antigens. We have developed a CAR-T-cell product that recognises the complex of HLA-A*02:01 and an epitope of the MAGE-A4 antigen equipped with a novel signalling domain of human GITR (investigational product code: MU-MA402C) based on preclinical studies.

Methods and analysis This is a dose-escalation, multi-institutional, phase 1 study to evaluate the tolerability and safety of MU-MA402C for patients with MAGE A4-positive and HLA-A*02:01-positive unresectable advanced or recurrent solid cancer. Two dose cohorts are planned: cohort 1, MU-MA402C 2×10^8/person; cohort 2, MU-MA402C 2×10^9/person. Prior to CAR-T-cell infusion, cyclophosphamide ( CPA) and fludarabine (FLU) will be administered as preconditioning chemotherapy. Three evaluable subjects per cohort, for a total of 6 subjects (maximum of 12 subjects), will be recruited for this clinical trial. The primary endpoints are safety and tolerability. The severity of each adverse event will be evaluated in accordance with Common Terminology Criteria for Adverse Events V.5.0. The secondary endpoint is efficacy. Antitumour response will be evaluated according to Response Evaluation Criteria in Solid Tumours V.1.1.

Ethics and dissemination This clinical trial will be conducted in accordance with the current version of Good Clinical Practice. The protocol was approved by the Clinical Research Ethics Review Committee of Mie University Hospital (approval number F-2021-017). The trial results will be published in peer-reviewed journals and/or disseminated through international conferences. Trial registration number jRCT2043210077.

INTRODUCTION

Although immune checkpoint inhibitors have improved the treatment outcome for solid tumours, the limitations in their utility are becoming apparent, and the development of new, more effective therapies is desired. Adoptive cell transfer of genetically engineered T cells, including chimeric antigen receptor T cells (CAR-T cells), is a promising treatment for malignancies. Indeed, CD19-specific chimeric antigen receptor T cells (CD19-CAR-T cells) have shown remarkable efficacy against CD19-positive haematological malignancies worldwide.1,2 In contrast, the development of CAR-T cells for solid tumours has not progressed as expected. CAR-T-cell therapy mainly targets cell surface antigens because the CARs consist of a single-chain...
variable fragment (scFv) derived from a monoclonal antibody antigen recognition region. There are few ideal cell surface cancer antigens in solid tumours. Because T-cell receptor engineered T (TCR-T) cells can recognise major histocompatibility complex (MHC) and peptide (pMHC) complexes presented on the cell surface, they can target not only cell surface antigens but also intracellular antigens. However, TCR-T cells have potentially lethal self-reactivity because the engineered TCR α/β chains can mispair with endogenous TCR α/β chains. TCR-like antibodies can exert antitumour effects by recognising pMHC complexes and are not affected by the location in which the antigen is expressed (inside the cell or on the cell surface). CAR-T cells with a pMHC complex recognition region derived from TCR-like antibodies (from TCR-like CAR-T cells) are expected not to have the issue of TCR mispairing. Various TCR-like CAR-T cells have been investigated in preclinical studies, which have reported promising efficacy. Another strong point of TCR-like CAR-T cells is that signalling effects can be added to the T cells by intracellular domain (ICD) optimisation. Whether the tumour microenvironment (TME) influences T-cell therapy for solid tumours remains to be determined. In the TME, the antitumour effect of T cells is weakened by the effects of hypoxia, the tumour stroma, and/or immunosuppressive cells, such as bone marrow-derived mesenchymal stem cells and regulatory T cells. Optimisation of the immunogenic cell death pathway by T cells may provide sufficient antitumour effects even in the TME.

The MAGE A4 antigen is a cancer testis antigen and is expressed intracellularly in various solid tumour tissues, but its expression in normal tissues is limited only to the testis and placenta. MAGE A4 peptide (GVYDGREHTV) is a cytotoxic T lymphocyte (CTL) epitope presented by HLA-A2. In the Department of Personalized Cancer Immunotherapy, Mie University Graduate School of Medicine, a monoclonal antibody that recognises the complex of MAGE A4230-239 peptide and HLA-A*02:01 (MAGE A4230-pMHC) was created, and an scFv with an antigen recognition region derived from the MAGE A4230-pMHC-specific antibody was developed. Glucocorticoid-induced tumour necrosis factor (TNF) receptor (GITR), a member of the TNF receptor superfamily, is known to affect T cell resistance to the immunosuppressive effects of the TME. With the addition of GITR signalling, T cells are expected to overcome the immunosuppression of the TME. In this clinical trial, we will evaluate the tolerability and safety of a CAR-T-cell product equipped with the MAGE A4230-pMHC-specific scFv and GITR ICD (investigational product code: MU-MA402C).

**CAR-T-cell product: MU-MA402C**

MU-MA402C is a novel second-generation CAR-T-cell product containing T cells transduced with a retrovirus vector encoding an scFv specific for the MAGE A4230-pMHC complex, CD3ζ and the GITR ICD (figure 1).

**METHODS AND ANALYSIS**

**Study design**

This is a dose-escalation, uncontrolled, multi-institutional, phase 1 study to evaluate the tolerability and safety of MU-MA402C for patients with MAGE A4+ HLA-A*02:01+ unresectable advanced or recurrent solid cancer.

**Endpoints and assessments**

The primary endpoints are safety and tolerability. The severity of each adverse event (AE) will be evaluated in accordance with Common Terminology Criteria for Adverse Events V5.0. The secondary endpoint is efficacy. The antitumour response will be evaluated according to Response Evaluation Criteria in Solid Tumours (RECIST) V1.1. The kinetics and immune activity after investigational product infusion, effects of the investigational product on immune function and haematological test results, histopathological findings in tumour tissue, if obtained, presence/absence of a specific amplification band, and clonality will also be evaluated as exploratory endpoints.

**Treatment**

The study schedule is shown in figure 2. To produce MU-MA402C, a maximum of 200 mL of peripheral blood will be collected from the subject. Two dose cohorts that will receive MU-MA402C are planned: cohort 1 will receive 2×10^9 cells/person and cohort 2 will receive 2×10^9 cells/person as total viable cells, including CAR-T cells. Prior to MU-MA402C infusion on day 1, fludarabine (FLU) (20 mg/m^2/day for 3 days, days −7 to −5) and cyclophosphamide (CPA) (750 mg/m^2/day for 2 days, days −4 and −3) will be administered as preconditioning chemotherapy. The hospitalisation period will be from the date of FLU initiation to the date of dose-limiting toxicity (DLT) evaluation (day 29).

Preconditioning chemotherapy will be administered prior to MU-MA402C administration with the aim of

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**Figure 1**  Structure of the transgene. The transgene contains the 5′-LTR region, a packaging signal (Ψ), the IgG leader sequence region, the single-chain variable fragment derived from the MAGE A4230-pMHC complex-specific monoclonal antibody, the CL region, the human CD28 transmembrane region (CD28 TM), human CD3ζ, the signalling domain of human GITR (GITR ICD) and the 3′-LTR region, without sequences encoding gag, pol, or env. GITR, glucocorticoid-induced tumour necrosis factor receptor; ICD, intracellular domain; LTR, long terminal repeat; scFv, single-chain variable fragment.
promoting the viability and proliferation of cells in MU-MA402C in vivo. CPA will be administered as daily dose of 750 mg/m² (anhydrous equivalent) for 2 days, which was tolerable in the previous clinical study of TCR-T cell products conducted by Mie University. In clinical trials of genetically modified T-cell therapy, the total dose of FLU, in combination with CPA, ranged from 75 to 125 mg/m². Higher-dose lymphodepletion chemotherapy for solid tumour increases the risk of lethal haematological toxicity. In addition, although many subjects in this trial may have impaired renal function caused by previous platinum-based chemotherapy, which is the standard treatment for oesophageal and head and neck cancer, dose modification of FLU according to renal function in each cohort will not be allowed due to a decision by regulatory authorities. Therefore, the total dose of FLU in this trial will be 60 mg/m².

**Product supply**
MU-MA402C will be transported from the investigational product provider, the Department of Personalized Cancer Immunotherapy, Mie University Graduate School of Medicine, to the investigational sites.

**Patient selection**
There are two registrations of this clinical trial: primary registration for the production of MU-MA402C and secondary registration for MU-MA402C infusion.

**Inclusion criteria**
(Primary registration)
1. Histologically or cytologically confirmed solid cancer.
2. Patients with unresectable advanced or recurrent solid cancer.
3. HLA-A*02:01 positivity.
4. MAGE-A4 expression in tumours by immunohistochemistry.
5. Patients who are incurable after at least one standard systemic therapy regimen for advanced or recurrent disease.
6. Patients with the ability to understand the study content and to give written consent at free will.
7. Patients who are legal adults who can provide informed consent.
8. Life expectancy of at least 16 weeks after consent was obtained.
9. Eastern Cooperative Oncology Group (ECOG) performance status (PS): 0–1.
10. No severe damage to the major organs, and the laboratory result criteria:
   - Neutrophils ≥1500/mm³, lymphocytes ≥500/mm³, haemoglobin ≥80 g/L, platelets ≥100 × 10⁹/L, total bilirubin <1.5 × upper limits of normal (ULN), aspartate aminotransferase <3.0 × ULN, alanine aminotransferase <3.0 ULN, creatinine <1.5 × ULN and creatinine clearance ≥30 mL/min.
11. In cases of gastrointestinal obstruction, nutritional status must be controlled by high-calorie infusions or other means.

(Secondary registration)
1. MU-MA402C can be supplied.
2. Progression after standard systemic therapy for advanced or recurrent disease or intolerance of standard systemic therapy.
3. Patients with the ability to understand the study content and to give written consent at free will.
4. ECOG PS: 0 or 1.
5. No severe damage to the major organs, and the laboratory test criteria mentioned for the primary registration.
6. In cases of gastrointestinal obstruction, nutritional status must be controlled by high-calorie infusions.

**Exclusion criteria**
(Primary registration)
1. Patients with the following complications were excluded from the study: unstable angina, cardiac infarction, heart failure, uncontrolled diabetes or hypertension, uncontrolled active infection, obvious interstitial pneumonia or lung fibrosis by chest X-ray,
and active autoimmune disease requiring steroids or immunosuppressive therapy.
2. Serious hypersensitivity.
3. Tumour cell invasion into the central nervous system (CNS).
4. Multiple active cancers.
5. Positivity for hepatitis B surface antigen or hepatitis B virus-DNA observed in serum, and positivity for anti-hepatitis C virus (HCV) antibody and HCV-RNA observed in serum.
6. Positivity for antibodies against HIV or human T-cell leukaemia virus type 1.
7. Left ventricular ejection fraction (LVEF): <50%.
8. Percutaneous oxygen saturation: <94%.
9. History of serious hypersensitivity reactions to bovine-derived or murine-derived substances.
10. History of hypersensitivity reaction to the drugs used in this study.
11. Current chemotherapy or radiotherapy.
12. Presence of a psychological disorder or drug dependency that may impact consent.
13. Patients refusal to practice adequate birth control.
14. Pregnancy, lactation.
15. Belief that the patient would have difficulty tolerating the therapy protocol or have a significantly increased risk of complications (based on the judgement of the principal investigator (PI) or a subinvestigator).

(Secondary registration)
1. Patients with the complications mentioned above were excluded from the study.
2. Serious hypersensitivity.
3. Patients with uncontrollable thoracic effusion, ascites or pericardial effusion.
4. Tumour cell invasion into the CNS.
5. LVEF: <50% (only applicable for patients who were treated with chemotherapy after primary registration).
6. Percutaneous oxygen saturation: <94%.
7. Treatment for malignancy must be administered within 4 weeks prior to the start of preconditioning.
8. Presence of a psychological disorder or drug dependency that may impact consent.
9. Patient refusal to practice adequate birth control.
10. Pregnancy, lactation.
11. Belief that the patient would have difficulty tolerating the therapy protocol or have a significantly increased risk of complications (based on the judgement of the PI or a subinvestigator).

**Sample size**
This clinical trial plans to investigate the tolerability in two cohorts in a 3+3 design. If DLT is observed, 3 additional subjects will be enrolled in the cohort concerned. In total, the target number of subjects is set at 6 (maximum 12).

**Adverse events**
AEs are defined as all unfavourable or unintended signs, symptoms or illnesses arising in subjects who are infused with the investigational product and administered the medications used in this clinical trial, regardless of their causal relationship to the investigational product or investigational drugs (preconditioning). Information on the AEs occurring in subjects will be collected from the time of blood collection for MU-MA402C manufacture to 1 week after blood collection and from the start of preconditioning chemotherapy to the end of testing at the time of safety evaluation or discontinuation.

**Dose escalation and the recommended dose for this product**
A DLT is defined as any MU-MA402C-related grade 3 or higher AE observed beginning from the administration of MU-MA402C to the time of DLT evaluation. However, any of the treatment-related AEs listed in 1) to 4) shall be defined as DLTs.

1. Cytokine release syndrome (in cases requiring endotracheal intubation or ventilator management or in cases resulting in death).
2. Haematological toxicity (in cases requiring blood transfusion or in cases resulting in death).
3. Febrile neutropenia (grade 4 or higher).
4. Tumour lysis syndrome (grade 4 or higher).

The first three patients will be assigned to cohort 1. If DLT is not observed in three subjects in cohort 1, the cohort will be transitioned into cohort 2. If DLT is observed in one of three subjects in cohort 1, 3 additional subjects will be enrolled in cohort 1. If DLT is observed in two out of three subjects in cohort 1, the clinical trial will be terminated. The same scheme shall be applied to cohort 2. The dose used for the cohort in which DLT occurred in zero of three or one of six patients will be the recommended dose for this product.

**Expression of the MAGE A4 antigen**
Tumour samples obtained from patients will be used. Immunohistochemical staining using an anti-MAGE A4 antibody (clone E710U, Cell Signalling Technology, Massachusetts, USA) will be considered positive when ≥10% of tumour cells show confirmed MAGE A4 expression.

**Cytokine analysis**
Cytokine (TNF-α, IFN-γ, IL-6, IL-2) levels in peripheral blood will be measured before and after administration of MU-MA402C (at secondary registration and on days 1, 2, 3, 4, 8, 15, 22, 29 and 57). ELISA will be used.

**Statistical analysis**
The population analysed and methods of statistical analysis are described below:
- Safety analysis set: all subjects who receive infusion of MU-MA402C.
- Efficacy analysis set: all subjects who receive infusion of MU-MA402C.
- Set for the analysis of haemodynamics, peripheral blood cell phenotype and immune function: all subjects with evaluable data.
The safety of the investigational product will be reviewed on a cohort-by-cohort basis. For efficacy analysis based on RECIST V.1.1, the frequency and percentage of subjects with different outcomes based on overall response will be tabulated by cohort and by cancer type. SAS (V.9.4 or newer) will be used for the safety and efficacy analyses.

Ethics and dissemination
All procedures involving human participants performed in this study will be conducted in accordance with the Declaration of Helsinki. The protocol and the informed consent documents were approved by the Clinical Research Ethics Review Committee of Mie University Hospital in June 2021 (approval number F-2021-017) and then approved by each investigational site’s Institutional Review Board. This clinical trial will be conducted in accordance with the current version of Good Clinical Practice. Written informed consent for participation, for the use of samples collected in the clinical trial and for publication will be obtained from all subjects included in this clinical study. The trial results will be published in peer-reviewed journals and/or disseminated through international conferences.

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Contributors
SO and MI equally contributed to this work. SO, MI and YM contributed to the design of this clinical study and wrote the protocol of the trial. SO, MI, KH, KT, HM, TW, HS and YM contributed to preparing the implementation of the trial. SO, HM and YM contributed to the preparation of MU-MA402C. MI, NK, KY, KT, SKh, HI, ME, KK and SKi contributed to obtaining the approval of the IRB and preparing the implementation at each investigational site. MI, AM, YN and SKa contributed to conducting the clinical trial. TS and SKa contributed to defining the methods for the assessment of MAGE A4 antigen expression in tumours. TY contributed to planning the statistical analyses. All authors contributed to draft revision and approved the final manuscript.

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Competing interests
SO received consulting fees from T Cell Nouveau. MI received honoraria from Chugai, Eisai, MSD, Ono, Daichi-Sankyo and Eli Lilly. NK received consulting fees from Adalit Nortye and Ono, received honoraria from Eli Lilly, Ono, Bristol-Myers Squibb, MSD, Eisai and Bayer, serves on the advisory boards of Chugai and Adalit Nortye, and received research funding from Boehringer Ingelheim, Ono, Bristol-Myers Squibb, Astra Zeneca, Pfizer, Chugai, Rakuten Medical, Bayer and Adalit Nortye. KT received honoraria from Eisai, Janssen, Chugai, Ono, Eli Lilly, Otsuka and Daichi Sankyo. HI received a research grant from Takara Bio Inc. KK received consulting fees from AbbVie, AstraZeneca, Celgene, Chugai, Eisai, Janssen, Novartis and Daichi-Sankyo, honoraria from Takeda, MSD, Kyowa-Kirin, Janssen, Celgene, Ono, Mundipharma-Sumitomo and Bristol-Myers Squibb, and research funding from Chugai, Takeda, Kyowa-Kirin, AbbVie, Novartis, Eisai, Janssen, Celgene, Ono, Novartis and Daichi-Sankyo. SKi received grants and personal fees from Astra Zeneca, grants and personal fees from Pfizer, grants and personal fees from Boehringer Ingelheim, personal fees from Taiho, personal fees from Novartis, grants and personal fees from MSD, personal fees from Sumitomo Pharma, grants and personal fees from Eisai, grants from Astellas, grants from Gilead Sciences, grants and personal fees from Ono, personal fees from Bristol-Myers Squibb, grants and personal fees from REGENERON, personal fees from Rakuten Medical, grants from PACT Pharma, grants from Takara Bio, personal fees from GSK, grants and personal fees from Daichi-Sankyo, grants and personal fees from Chugai, grants from Incyte, personal fees from ImmunIT Research, personal fees from Merck KGaA and personal fees from Takeda. SKa serves on the advisory boards of Otsuka and Nile-Immune Biotech. KH received consulting fees from Pfizer and honoraria from Amgen, Chugai and Novartis. TY received a research grant from Daichi Sankyo. Mie University holds a patent on the MAGE A4-CAR construct. YM and HS are the inventors on the patent.

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Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication
Not applicable.

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