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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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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.

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.

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.[1–4] 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.[5] 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).[6–8] 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.[9–12] 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.[13 14] Optimisation of the immunogenic cell death induced 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,[15–18] but its expression in normal tissues is limited only to the testis and placenta.[19] MAGE $A4_{230\text{-}239}$ peptide (GVYDGREHTV) is a cytotoxic T lymphocyte (CTL) epitope presented by HLA-A2.[20] In the Department of Personalized Cancer Immunotherapy, Mie University Graduate School of Medicine, a monoclonal antibody that recognises the complex of MAGE $A4_{230\text{-}239}$ peptide and HLA-A*02:01 (MAGE $A4_{230}$-pMHC) was created, and an scFv with an antigen recognition region derived from the MAGE $A4_{230}$-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.[21–23] 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 $A4_{230}$-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 $A4_{230}$-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 V.5.0. The secondary endpoint is efficacy. The antitumour response will be evaluated according to Response Evaluation Criteria in Solid Tumours (RECIST) V.1.1.[24] 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^{8} 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

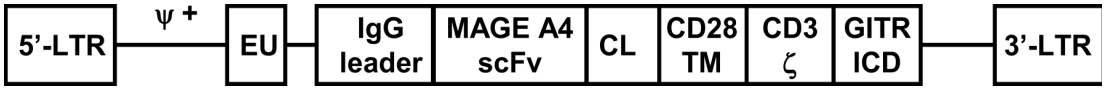
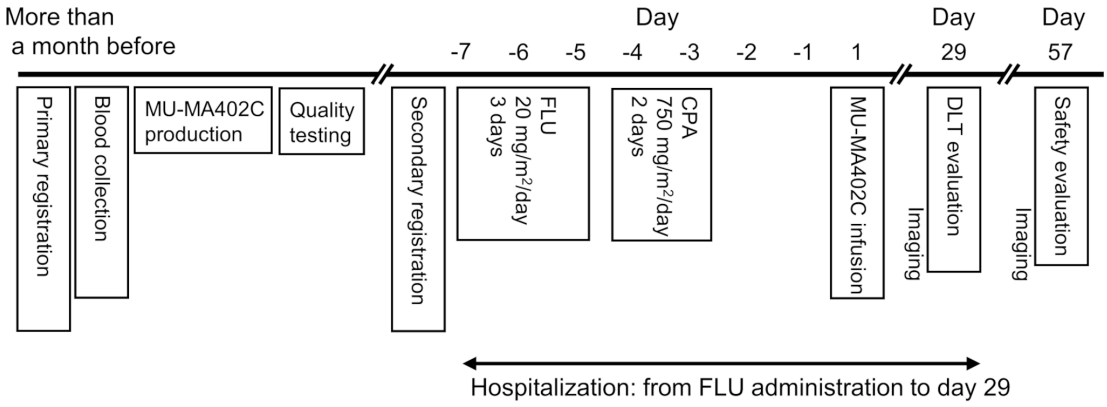


Figure 1 Structure of the transgene. The transgene contains the 5'-LTR region, a packaging signal (Ψ), the IgG leader sequence region, the single-chain variable fragment derived from the MAGE $A4_{230}$-pMHC complex-specific monoclonal antibody, the CL region, the human CD28 transmembrane region (CD28 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.



MU-MA402C infusion: Cohort 1: 2×10^8 cells/body, Cohort 2: 2×10^9 cells/body.

Figure 2 Study schedule. CPA, cyclophosphamide; DLT, dose-limiting toxicity; FLU, fludarabine.

promoting the viability and proliferation of cells in MU-MA402C in vivo. CPA will be administered as daily dose of 750 mg/m^2 (anhydrous equivalent) for 2 days, which was tolerable in the previous clinical study of TCR-T-cell products conducted by Mie University.[25] In clinical trials of genetically modified T-cell therapy, the total dose of FLU, in combination with CPA, ranged from 75 to 125 mg/m^2.[1 4 26 27] Higher-dose lymphodepletion chemotherapy for solid tumour increases the risk of lethal haematological toxicity.[28] 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/m^2.

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 following laboratory result criteria:
    Neutrophils ≥1500/mm^3, lymphocytes ≥500/mm^3, haemoglobin ≥80 g/L, platelets ≥100 × 10^9/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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REFERENCES

1 Neelapu SS, Locke FL, Bartlett NL, *et al*. Axicabtagene Ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med* 2017;377:2531–44.
2 Schuster SJ, Svoboda J, Chong EA, *et al*. Chimeric antigen receptor T cells in refractory B-cell lymphomas. *N Engl J Med* 2017;377:2545–54.
3 Maude SL, Laetsch TW, Buechner J, *et al*. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med* 2018;378:439–48.
4 Schuster SJ, Bishop MR, Tam CS, *et al*. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med* 2019;380:45–56.
5 Bendle GM, Linnemann C, Hooijkaas AI, *et al*. Lethal graft-versus-host disease in mouse models of T cell receptor gene therapy. *Nat Med* 2010;16:565–70.
6 Dao T, Yan S, Veomett N, *et al*. Targeting the intracellular WT1 oncogene product with a therapeutic human antibody. *Sci Transl Med* 2013;5:176ra33.
7 Jain R, Rawat A, Verma B, *et al*. Antitumor activity of a monoclonal antibody targeting major histocompatibility complex class I-Her2 peptide complexes. *J Natl Cancer Inst* 2013;105:202–18.

8 He Q, Liu Z, Liu Z, *et al*. TCR-Like antibodies in cancer immunotherapy. *J Hematol Oncol* 2019;12:99.
9 Akatsuka Y. TCR-Like CAR-T cells targeting MHC-Bound minor histocompatibility antigens. *Front Immunol* 2020;11:257.
10 Poorebrahim M, Mohammadkhani N, Mahmoudi R, *et al*. TCR-Like CARs and TCR-CARs targeting neoepitopes: an emerging potential. *Cancer Gene Ther* 2021;28:581–9.
11 Raskin S, Van Pelt S, Toner K, *et al*. Novel TCR-like CAR-T cells targeting an HLA*0201-restricted SSX2 epitope display strong activity against acute myeloid leukemia. *Mol Ther Methods Clin Dev* 2021;23:296–306.
12 Liu X, Xu Y, Xiong W, *et al*. Development of a TCR-like antibody and chimeric antigen receptor against NY-ESO-1/HLA-A2 for cancer immunotherapy. *J Immunother Cancer* 2022;10:e004035.
13 Zarour HM. Reversing T-cell dysfunction and exhaustion in cancer. *Clin Cancer Res* 2016;22:1856–64.
14 Najafi M, Goradel NH, Farhood B, *et al*. Tumor microenvironment: interactions and therapy. *J Cell Physiol* 2019;234:5700–21.
15 De Plaen E, Arden K, Traversari C, *et al*. Structure, chromosomal localization, and expression of 12 genes of the MAGE family. *Immunogenetics* 1994;40:360–9.
16 De Plaen E, De Backer O, Arnaud D, *et al*. A new family of mouse genes homologous to the human MAGE genes. *Genomics* 1999;55:176–84.
17 Jungbluth AA, Busam KJ, Kolb D, *et al*. Expression of MAGE-antigens in normal tissues and cancer. *Int J Cancer* 2000;85:460–5.
18 Ishihara M, Kageyama S, Miyahara Y, *et al*. MAGE-A4, NY-ESO-1 and SAGE mRNA expression rates and co-expression relationships in solid tumours. *BMC Cancer* 2020;20:606.
19 Haas GG, D'Cruz OJ, De Bault LE. Distribution of human leukocyte antigen-ABC and -D/DR antigens in the unfixed human testis. *Am J Reprod Immunol Microbiol* 1988;18:47–51.
20 Duffour MT, Chaux P, Lurquin C, *et al*. A MAGE-A4 peptide presented by HLA-A2 is recognized by cytolytic T lymphocytes. *Eur J Immunol* 1999;29:3329–37.
21 Nishikawa H, Kato T, Hirayama M, *et al*. Regulatory T cell-resistant CD8+ T cells induced by glucocorticoid-induced tumor necrosis factor receptor signaling. *Cancer Res* 2008;68:5948–54.
22 Imai N, Ikeda H, Tawara I, *et al*. Glucocorticoid-Induced tumor necrosis factor receptor stimulation enhances the multifunctionality of adoptively transferred tumor antigen-specific CD8+ T cells with tumor regression. *Cancer Sci* 2009;100:1317–25.
23 Mitsui J, Nishikawa H, Muraoka D, *et al*. Two distinct mechanisms of augmented antitumor activity by modulation of immunostimulatory/inhibitory signals. *Clin Cancer Res* 2010;16:2781–91.
24 Eisenhauer EA, Therasse P, Bogaerts J, *et al*. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.
25 Ishihara M, Kitano S, Kageyama S, *et al*. NY-ESO-1-specific redirected T cells with endogenous TCR knockdown mediate tumor response and cytokine release syndrome. *J Immunother Cancer* 2022;10:e003811.
26 D'Angelo SP, Melchiori L, Merchant MS, *et al*. Antitumor Activity Associated with Prolonged Persistence of Adoptively Transferred NY-ESO-1 ^{c259}T Cells in Synovial Sarcoma. *Cancer Discov* 2018;8:944–57.
27 Robbins PF, Kassim SH, Tran TLN, *et al*. A pilot trial using lymphocytes genetically engineered with an NY-ESO-1-reactive T-cell receptor: long-term follow-up and correlates with response. *Clin Cancer Res* 2015;21:1019–27.
28 Blumenschein GR, Devarakonda S, Johnson M, *et al*. Phase I clinical trial evaluating the safety and efficacy of ADP-A2M10 SPEAR T cells in patients with MAGE-A10^{+} advanced non-small cell lung cancer. *J Immunother Cancer* 2022;10:e003581.