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First-in-human Phase I study of ZI-MA4-1, a first-in-class MAGE-A4–targeting TCR-NK cell therapy in advanced solid tumours (ZIMA-101)

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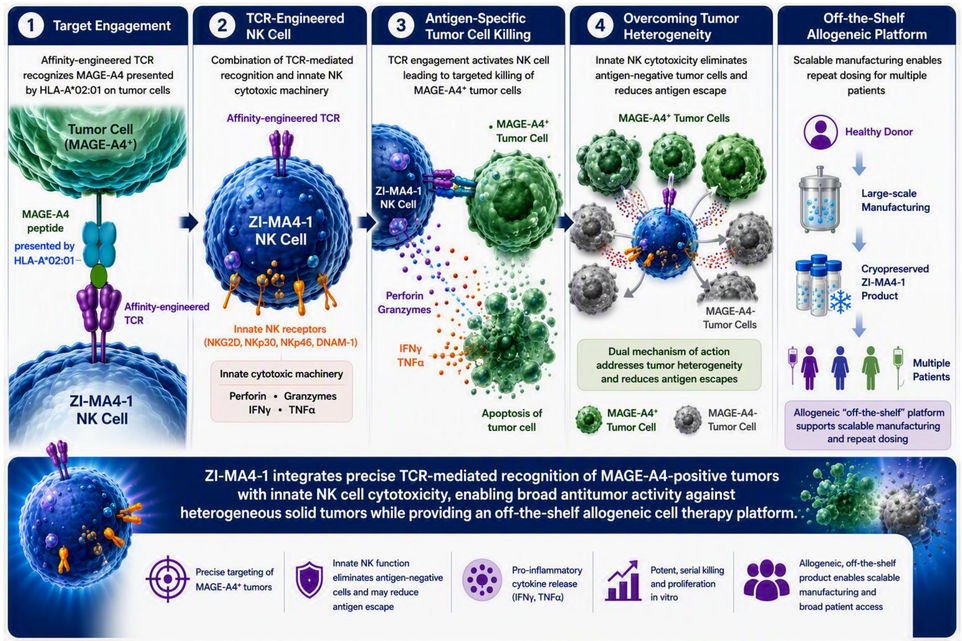
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Background and Study Rationale

ZI-MA4-1 is an allogeneic TCR-engineered NK cell therapy targeting MAGE-A4, combining antigen-specific targeting with the innate cytotoxicity of NK cells. An affinity-engineered TCR recognizing the MAGE-A4:HLA-A*02:01 complex enables tumour-specific engagement and TCR-directed cytotoxicity, while intrinsic NK-cell mechanisms provide complementary, antigen-independent tumour killing, with the potential to address tumour heterogeneity and antigen escape. The allogeneic platform enables scalable manufacturing, with a single batch yielding doses for multiple patients.

The rationale for this FIH study is to translate the demonstrated potency, selectivity, and favourable non-clinical safety profile of ZI-MA4-1 into a clinical setting. The study design, including a dose-escalation approach and rigorous safety monitoring, was informed by the ZI-MA4-1 non-clinical data, clinical experience with TCR-based and NK-cell therapies, and the study's translational objectives.

Mode of Action



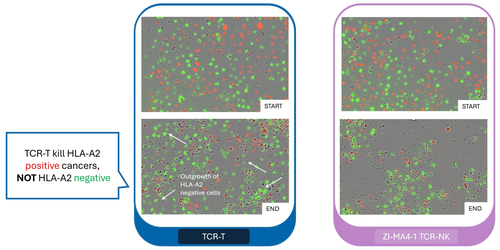
Summary

ZIMA-101 represents the first clinical evaluation of a MAGE-A4-targeting TCR-NK cell therapy in patients with advanced solid tumours. The integrated translational programme, including paired baseline and on-treatment tumour biopsies and longitudinal immune monitoring, is designed to provide insights into the cellular kinetics, biological activity and effects within the tumour microenvironment of this first-in-class TCR-NK platform.

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Preclinical Findings

ZI-MA4-1 outperforms clinical MAGE-A4 TCR-T in *in vitro* heterogenous tumour model

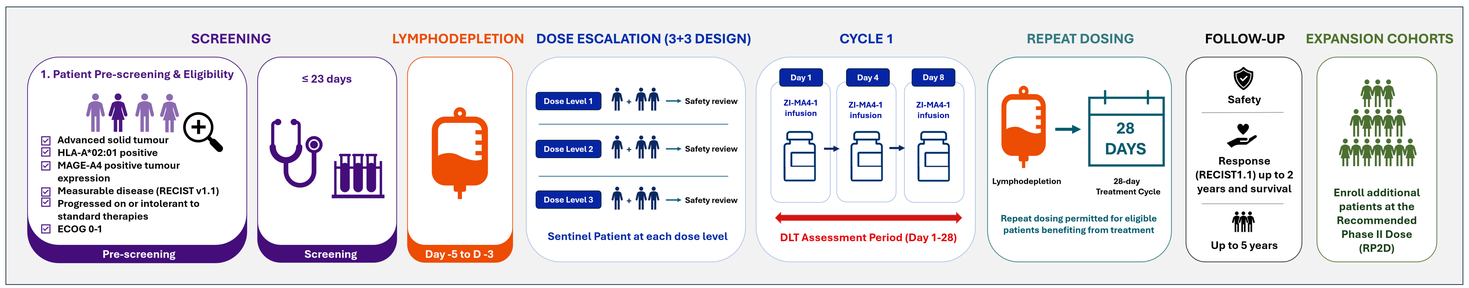


The non-clinical data package for ZI-MA4-1 demonstrated a strong mechanistic rationale, potent anti-tumour activity, and a safe non-clinical profile consistent with other receptor-engineered NK cell therapies, providing a sound scientific basis for clinical evaluation.

Left figure: ZI-MA4-1 demonstrates killing of heterogenous tumor cells
ZI-MA4-1 shows killing of both MAGE-A4 peptide:HLA positive and negative target cells compared to TCR-T cells killing MAGE-A4 peptide:HLA presenting targets only. Images display cell death induced by co-cultures of ZI-MA4-1 or benchmark clinical control TCR-T cells with tumour cell mix of MAGE-A4pos HLA-A2pos (A-431-A2) and MAGE-A4pos HLA-A2neg (A-431) at 24h timepoint (bottom images).

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ZIMA-101 trial design



Phase 1 cohort

- Ovarian cancer
- Head and Neck cancer
- Synovial Sarcoma
- Squamous Non-Small-Cell Lung Cancer

Patient population (inclusion criteria)

- aged 18 to 75 years
- inoperable locally advanced or metastatic disease
- HLA-A*02:01 tissue marker
- MAGE-A4 protein expression
- ≥2 lines of prior cancer therapy (≥1 for synovial sarcoma)
- documented objective disease progression while receiving, or within 6 months after the end of the most recent therapy

Exclusion criteria

- any prior cellular or gene therapy
- any prior MAGE-A4 targeted therapy or active malignancy besides the tumour under study within 3 years of screening
- documented history of autoimmune disease
- disease requiring immunosuppressive therapy or corticosteroid therapy

Dose Levels	
DL1	5×10^8 transduced cells/dose
DL2	1.5×10^9 transduced cells/dose
DL3	3.0×10^9 transduced cells/dose

Recruitment and Site Locations

- Dose Level 1 enrolment ongoing
- First patient completed the first treatment cycle
- Independent safety review recommended enrolment of two additional patients at Dose Level 1
- Patient screening and recruitment ongoing at both UK sites
  - The Christie, Manchester, UK
  - The Royal Marsden, London, UK



Study Objectives

Primary Endpoint	▪ Safety and tolerability of ZI-MA4-1
Secondary Endpoint	▪ Determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) of ZI-MA4-1 ▪ Long term safety ▪ Identify the minimum biologically active dose ▪ Evaluate the efficacy of ZI-MA4-1 ▪ Evaluate the persistence of ZI-MA4-1 in the blood
Exploratory Endpoint	▪ Investigate the Mode of Action

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Clinical Trial Number: NCT07613723

Disclaimer: This trial is actively enrolling/in progress. In accordance with conference submission guidelines, no preliminary safety or efficacy data are presented.

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