Clinical and translational evaluation of ZI-MA4-1, a first-in-class MAGE-A4-targeting TCR-NK cell therapy in advanced solid tumors: design of the ZIMA-101 study

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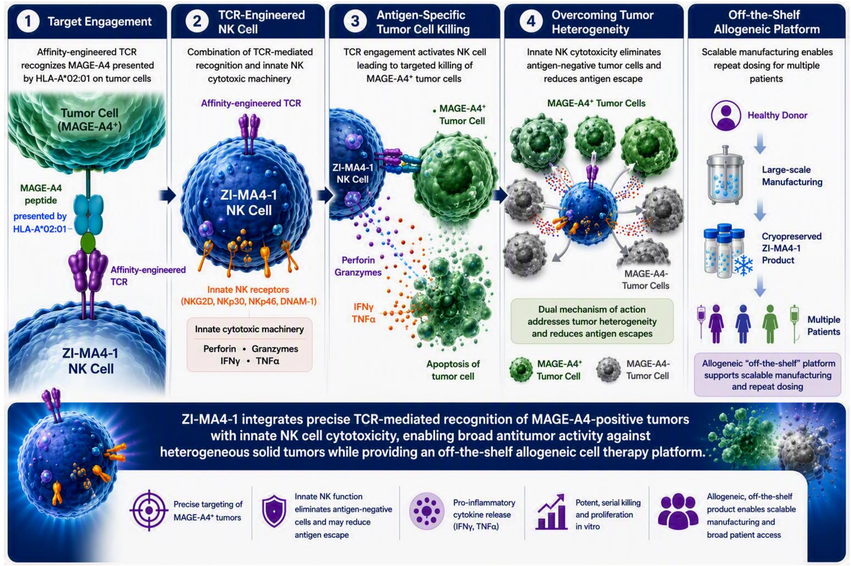
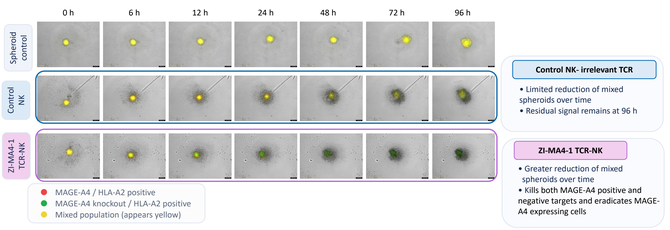
Background

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 tumor-specific engagement and TCR-directed cytotoxicity, while intrinsic NK-cell mechanisms provide complementary, antigen-independent tumor killing, with the potential to address tumor heterogeneity and antigen escape. The allogeneic platform enables scalable manufacturing, with a single batch yielding doses for multiple patients.



ZI-MA4-1 outperforms control NK in *in vitro* tumor spheroid model



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

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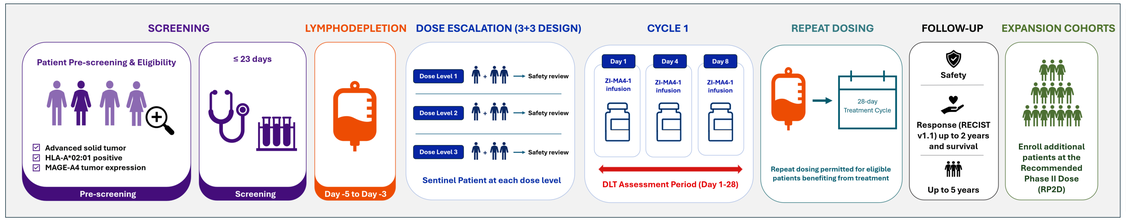
ZIMA-101 trial design



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

Phase 1 cohort

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

Patient population (inclusion criteria)

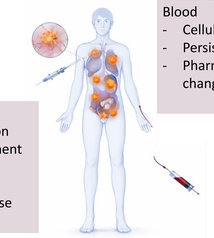
- aged 18 to 75 years
- inoperable locally advanced or metastatic disease
- HLA-A*02:01 and MAGE-A4 positive
- ≥2 lines of prior cancer therapy (≥1 for synovial sarcoma)
- documented objective disease progression while receiving, or within 6 months after the end of the most recent therapy

Exclusion criteria

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

Translational program

The study incorporates an extensive translational program designed to characterize the biological activity of TCR-NK therapy in patients. Correlative analyses will explore relationships between cellular kinetics, tumor microenvironment changes and clinical outcomes.



Blood
- Cellular kinetics
- Persistence
- Pharmacodynamic changes

Biopsies
- Immune cell infiltration
- Tumor microenvironment modulation
- MAGEA4 expression
- Mechanism of response and resistance

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 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

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



Summary

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

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