MYE Symphony: A First-in-Human Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Preliminary Efficacy of the in vivo mRNA CAR therapy, MT-302, targeting TROP2 in Adults with Advanced Epithelial Tumors

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Abstract

Background

This is the first clinical trial of an *in vivo* chimeric antigen receptor (CAR) therapy. The *in vivo* approach, with repeat dosing and no conditioning, has the potential to overcome many of the challenges of *ex vivo* CAR therapies. MT-302, as an mRNA-lipid nanoparticle (LNP) formulation for intravenous delivery, allows for dose and schedule optimization. The mRNA encodes for a receptor consisting of a TROP2-targeted scFv, as well as the transmembrane domain and cytoplasmic tail of CD89. Upon MT-302 dosing the LNP is taken up by numerous cell types, but a functional CAR can only be expressed on the surface of cells that also express the Fc receptor common gamma chain, predominately myeloid cells (**Figure 1**). *In vivo* delivered MT-302 resulted in TROP2 CAR expression and anti-tumor efficacy in an HCC-1954 breast cancer xenograft model (Argueta, AACR 2024, #1321) (**Figure 2**). In a syngeneic model, *in vivo* delivered surrogate CD89-based CAR treatment inhibited tumor growth with demonstrated intra-tumoral accumulation of activated CD8+ T cells and reduced tumor associated Tregs (Prod'homme, AACR 2023, LB027) (**Figure 3**). Thus, this first-in-class *in vivo* CAR-M (myeloid) therapy will be tested to treat TROP2 expressing cancers with the goal of infiltrating the tumor microenvironment and initiating a broad anti-tumor immune response.

Methods

MYE Symphony is a multicenter first-in-human study of MT-302 in participants with advanced epithelial cancers enriched for high TROP2 expression (**Table 1**). MT-302 is given every 14 days. The dose escalation employs a Bayesian Optimal Interval design with backfill for further dose evaluation. Primary endpoints are to assess safety and define the MTD and RP2D. Secondary endpoints include defining the PK and rates of ICANs and CRS. Exploratory endpoints include efficacy measures (e.g. ORR and DOR) and treatment induced immunologic impact (e.g. peripheral CAR expression, cytokine release, and T-cell receptor clonality, as well as changes in the tumor immune environment and TROP2 expression). NCT05969041.

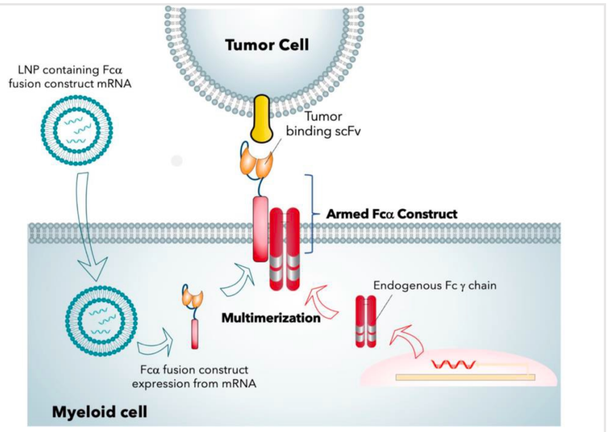

Figure 1. CAR Design Impacts Selective Expression. The FcαRI (CD89) underpins myeloid specificity of CAR expression. Co-expression of FcRγ chain, found only in myeloid cell lineages, forms full FcαRI (CD89) construct. Without the FcRγ chain in non-myeloid cells, the construct cannot trigger cell activation.

Background

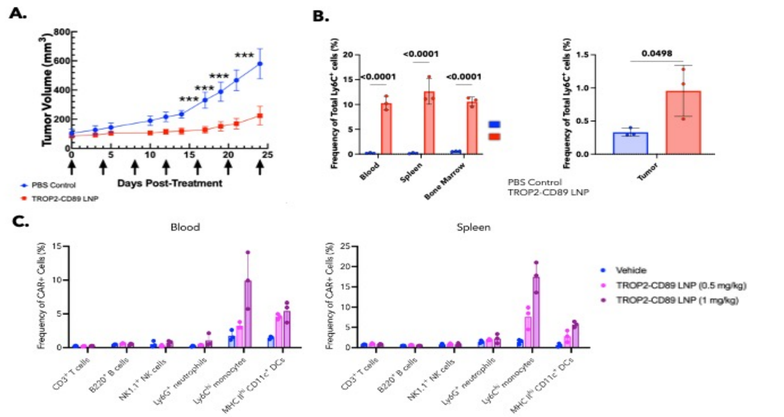

Figure 2. Specific expression and anti-tumor efficacy of TROP2 CAR in HCC-1954 breast cancer xenograft model. **(A)** Anti-tumor efficacy of TROP2 CAR was examined using TROP2+ HCC-1954 cells in NSG micel (n=5/group). Mice were injected i.v. Q4D with either TROP2 CAR LNP (2 mg/kg) or PBS when tumor volume was >50 mm³. Statistical significance was established using multiple Mann-Whitney tests followed by false-discovery rate. **(B)** Detection of CAR expression in Ly6C+ cells in blood, spleen, bone marrow and tumor following i.v. injection of TROP2 CAR LNP. **(C)** CAR expression was detected in blood and spleen, 6 hours following i.v. injections of TROP2 CAR LNP (1 mg/kg) in C57Bl/6 mice.

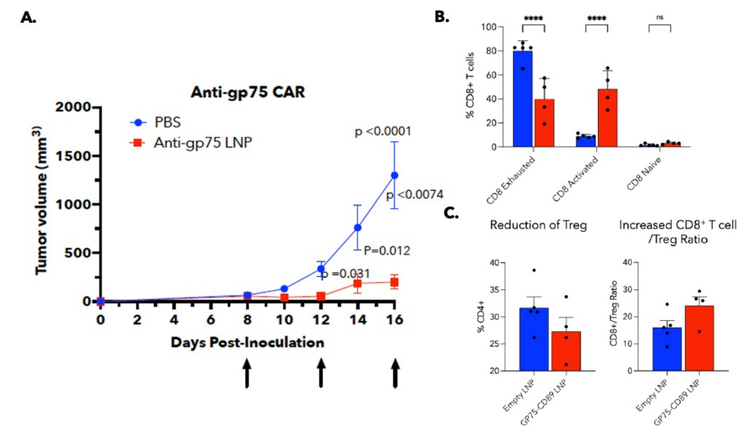

Figure 3. Anti-tumor efficacy in the B16 syngeneic model. (A) 0.2 x 106 B16/F10-OVA cells were implanted s.c. in C57Bl/6 Females (6-8 week-old). n=5/group. Mice were injected i.v. Q4D with either anti-gp75 LNP or PBS (Vehicle) when tumor volume was >50 mm³. **(B)** Treatment with anti-gp75 LNP (2 mg/kg) significantly reduced the percentage of PD1hi TOX+ exhausted CD8+ T cells and, conversely, significantly increased the frequency of activated CD8+ T cells. Empty LNP were used as controls. **(C)** Significant reduction of the frequency of CD4+ FoxP3+ CD25+ regulatory T cells (Treg) and increased the CD8+/Treg ratio.

Cancer Type	TROP2 Expression	5-year Survival
Cervical	86%	17%
Colorectal	70%	15%
Esophageal carcinoma	75%	5.7%
Gastric adenocarcinoma	70%	6.0%
HR+/HER2- breast	85%	24%
Non-small cell lung	75%	7.0%
Ovarian epithelial	90%	31%
Pancreatic ductal adenocarcinoma	70%	3.1%
Triple-negative breast	85%	12%
Urothelial	83%	7.7%

5- year survival data based on SEER Cancer Stats, Distant 5-Year Relative Survival Rates; Source Documents : TROP-2 expression data Dum 2022, Sakach 2022

Table 1. Incidence of TROP2 Tumors and 5-year Survival Rates. TROP2 is a 33 kDa transmembrane glycoprotein that is upregulated in most human solid epithelial cancer types. TROP2 overexpression in cancer cells is linked to enhanced cell migration, proliferation, and anchorage-independent growth, leading to increased tumor size (Goldenberg 2015). Consequently, high TROP2 expression correlates with poor prognosis (Fong 2008).

References: **Dum** D, Taherpour N, Menz A, Höflmayer D, Völkel C, Hinsch A, et al. Trophoblast Cell Surface Antigen 2 Expression in Human Tumors: A Tissue Microarray Study on 18,563 Tumors. Pathobiology. 2022;89(4):245-258.; **Fong** D, Moser P, Krammel C, Gostner J, Margreiter R, Mitterer M, et al. High expression of TROP-2 correlates with poor prognosis in pancreatic cancer. Br J Cancer. 2008;99(8):1290-1295. doi: 10.1038/sj.bjc.6604677.; **Goldenberg** D, Cardillo T, Govindan S, Rossi E, Sharkey R. TROP-2 is a novel target for solid cancer therapy with sacituzumab govitecan (IMMU-132), an antibody-drug conjugate (ADC)*. Oncotarget. 2015;6(26):22496-22512. doi: 10.18632/oncotarget.4318.; **Sakach** E, Sacks R, Kalinsky K. Trop-2 as a Therapeutic Target in Breast Cancer. Cancers (Basel). 2022 Nov 30;14(23):5936. doi: 10.3390/cancers14235936. PMID: 36497418; PMCID: PMC9735829.

Study Information

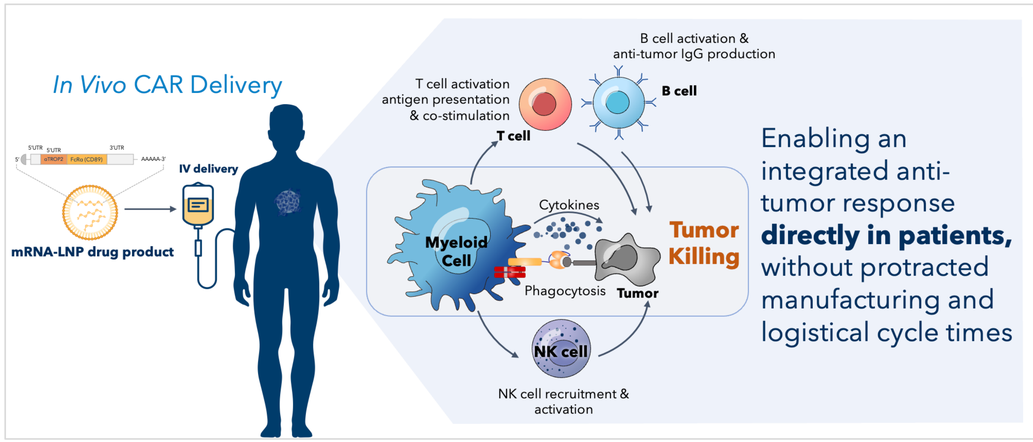

Figure 4. MT-302 Programs Immune Cells In Vivo Using mRNA. Myeloid Therapeutics, Inc is a biotechnology company looking to leverage the large numbers of immune cells, specifically myeloid cells, in solid tumors, with the aim of reprogramming them to become capable of killing cancer cells directly and indirectly through their ability to stimulate adaptive immune responses. This is achieved through the in vivo delivery of innate immune cell chimeric antigen receptors (CARs) delivered as messenger ribonucleic acid (mRNA) constructs encapsulated in lipid nanoparticles (LNP). MT-302 is one promising candidate being developed to arm myeloid cells to recognize and kill cancer cells that express the tumor-associated calcium signal transducer 2 (TROP2) protein. Through this approach, myeloid cells are specifically armed in vivo to target TROP2, becoming activated, resulting in tumor cell killing and elicitation of a broad anti-tumor adaptive immunity.

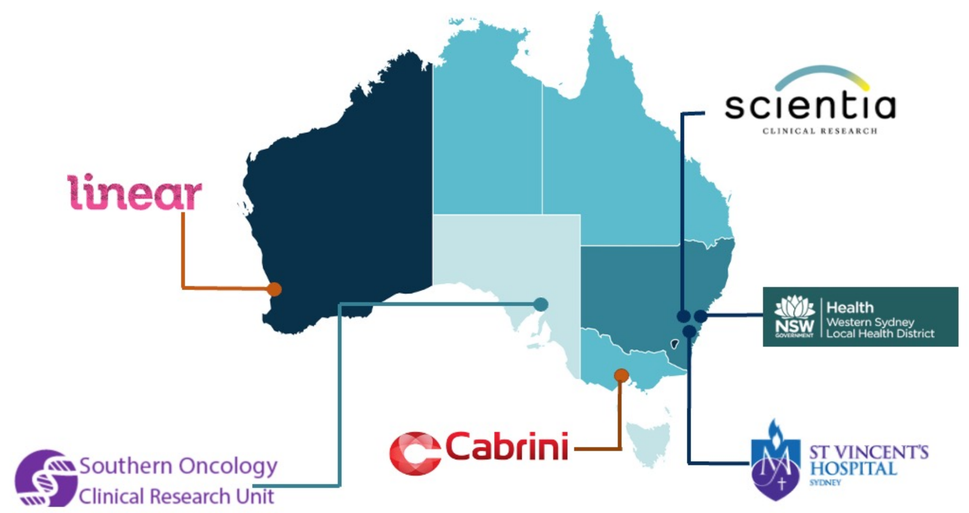

Figure 5. MYE Symphony Sites Actively Enrolling Patients. Currently, 6 sites are enrolling patients in MYE Symphony across Australia. MT-302 is given every 14 days. The dose escalation employs a Bayesian Optimal Interval design with backfill for further dose evaluation. A Safety Review Committee (SRC) provides oversight for this study. The primary responsibility of the SRC is to safeguard study participants by reviewing and assessing the clinical safety data being collected during the conduct of the study.

Inclusion

- Adults age ≥ 18 inclusive at the time the Informed Consent Form (ICF) is signed.
- Histologically proven, metastatic or advanced epithelial cancer including the following cancer types:
  - Urothelial
  - Cervical
  - Ovarian epithelial
  - Triple-negative breast
  - HR+/HER2- breast
  - Pancreatic ductal adenocarcinoma
  - Gastric adenocarcinoma
  - Esophageal carcinoma
  - Non-small cell lung
  - Colorectal
- Progressive disease at baseline, refractory or relapsed to standard of care or who have declined standard therapy.
- Measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria v 1.1.
- Eastern Cooperative Oncology Group (ECOG) performance status grade of 0 or 1.
- Adequate organ function as defined by laboratory values at Screening.

Exclusion

- Known active CNS metastasis and/or carcinomatous meningitis.
- Active autoimmune disease not related to prior therapy for primary malignancy that has required systemic therapy in the last 1 year.
- Prior grade > 3 immune-related AEs such as pneumonitis, colitis, hepatitis, nephritis
- Active systemic bacterial, fungal, or viral infection within 7 days
- Active infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV).
- History of symptomatic congestive heart failure (New York Heart Association classes II-IV) or serious active arrhythmias or other clinically significant cardiac disease within 12 months of enrollment.

Figure 6. Key Eligibility Criteria. More detailed eligibility criteria can be found on clinicaltrials.gov (NCT05969041). Primary endpoints are to assess safety and define the MTD and RP2D. Secondary endpoints include defining the PK and rates of ICANs and CRS. Exploratory endpoints include efficacy measures (e.g. ORR and DOR) and treatment induced immunologic impact (e.g. peripheral CAR expression, cytokine release, and T-cell receptor clonality, as well as changes in the tumor immune environment and TROP2 expression).

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