Poster 590

A first-in-human, phase 1 trial of IMA203 PRAME-directed TCR T-cell therapy with PRAME encoding mRNA-4203 in previously treated, unresectable or metastatic cutaneous melanoma or synovial sarcoma (NCT06946225)

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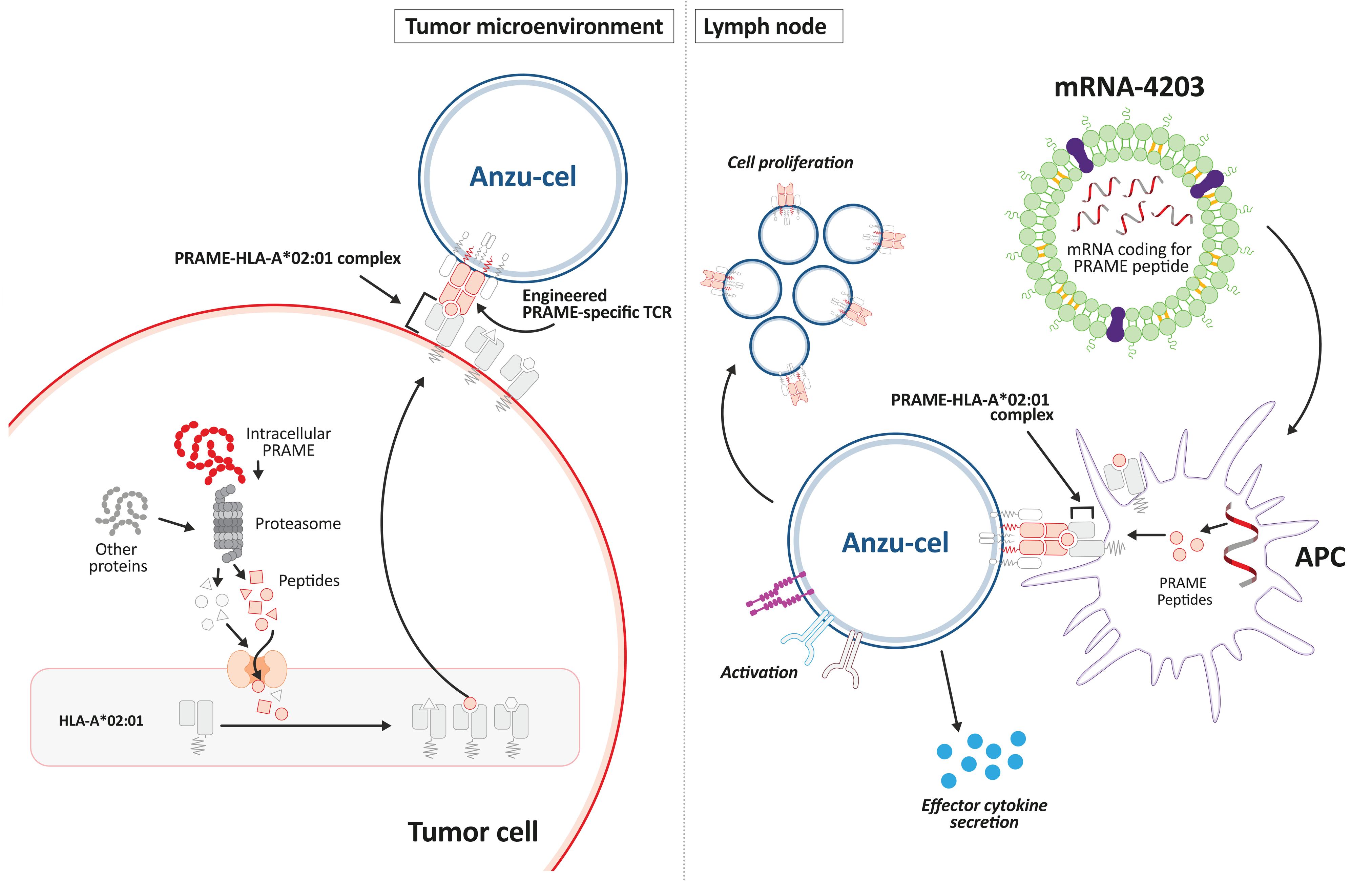
BACKGROUND

- TCR T-cell therapy has demonstrated promising activity in treatment-refractory advanced cutaneous melanoma (CM) and synovial sarcoma (SS); there remain opportunities to improve outcomes by combining immunotherapy modalities[1]
- PRAME is expressed in more than 50 cancer types; 95% of CM and SS cancers express PRAME[2,3]
- **Anzutresgene autoleucel (anzu-cel; formerly IMA203)** is a PRAME-directed TCR T-cell therapy engineered to recognize intracellular PRAME-derived peptides presented by HLA-A*02:01 on the cell surface and initiate a potent and specific antitumor response[1]
- In a phase 1 trial (NCT03686124), anzu-cel exhibited favorable tolerability and encouraging antitumor activity in heavily pretreated patients with advanced melanoma at RP2D[4]
  - Confirmed ORR was 56% (18/32) and median DOR was 12.1 months
  - Median PFS was 6.1 months and OS was 15.9 months
  - Most frequent TEAE at all dose levels and indications (N=74) were lymphodepletion-related cytopenias (99%)
  - CRS was mostly lower grade (84% G1/2; 11% G3; no ≥G4) and ICANS was infrequent (10% G1/2; 4% G3; no ≥G4)
- mRNA-4203 is an LNP-encapsulated mRNA cell therapy enhancer that encodes the PRAME sequence that when translated by APCs, drives activation and proliferation of anzu-cel TCR T cells in the lymph node before encountering the tumor (**Fig. 1**)

Figure 1. Mechanism of action of anzu-cel and mRNA-4203



Following one-time infusion, anzu-cel targets PRAME (presented on tumor cells across >50 cancer types), resulting in immune activation and antitumor response

Anzu-cel antitumor response is boosted by mRNA-4230 administration on Day 15 and later

METHODS

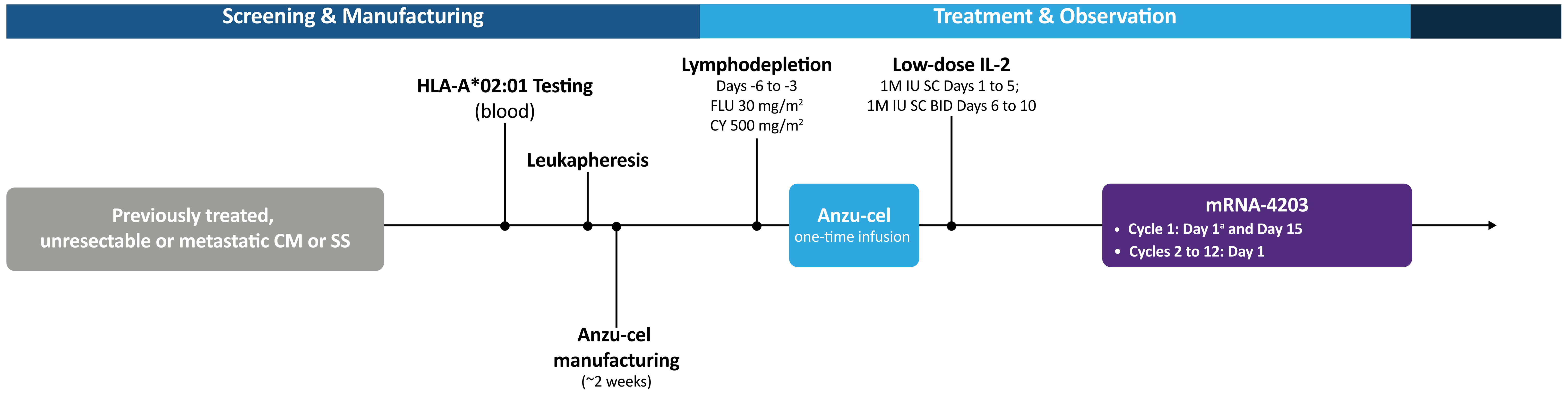
- IMA203-102 is an ongoing open-label, multicenter, first-in-human phase 1a/b trial (NCT06946225) investigating the safety, tolerability, and antitumor activity of anzu-cel in combination with different doses of mRNA-4203 in patients with CM or SS (**Fig 2**)
- Primary endpoints:
  - DLTs of the combination; safety and tolerability
- Secondary endpoints:
  - ORR, DOR, DCR, PFS, PK

Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Unresectable or metastatic CM or SS after ≥1 line of treatment	• Serious autoimmune disease
• HLA-A*02:01 positive	• Active infections and HIV+
• ECOG PS 0-1	• LDH > 2.0 × ULN
• Measurable disease (RECIST 1.1)	• Active brain metastases
• Life expectancy >5 months	• Other malignancies (exceptions apply) within the last 3 years
• Adequate organ function	• Prior ASCT or solid organ transplantation

- Prospective PRAME testing not required

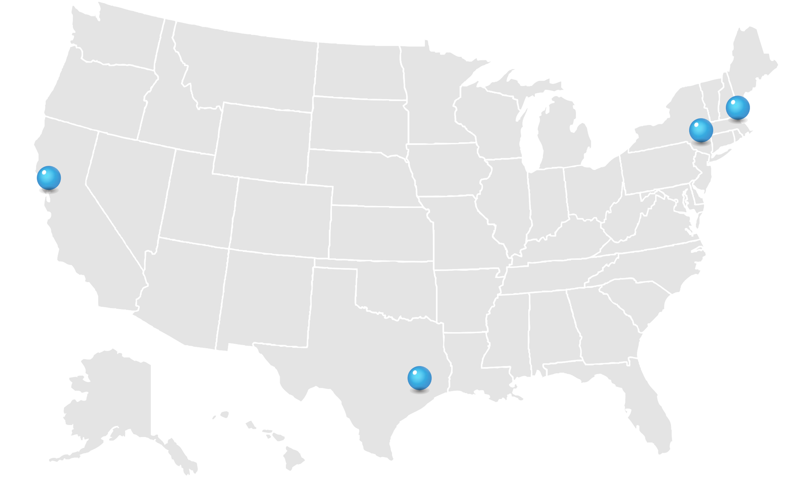
Figure 2. Trial Design



[a] Cycles start on the day of the first mRNA-4203 administration. The first mRNA-4203 administration occurs between 15 to 71 days following anzu-cel infusion (once clinical and laboratory criteria are met).

ENROLLMENT

- The trial is expected to enroll approximately 15 patients across 4 sites in the United States



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ABBREVIATIONS: APC, antigen presenting cell; ASCT, autologous stem cell transplant; BID, twice-daily; CRS, cytokine release syndrome; CY, cyclophosphamide; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FLU, fludarabine; G; grade; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; ICANS, immune effector cell-associated neurotoxicity syndrome; IHC, immunohistochemistry; IL-2, interleukin-2; LDH, lactate dehydrogenase; LNP, lipid nanoparticle; mRNA, messenger ribonucleic acid; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PRAME, preferentially expressed antigen in melanoma; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; SC, subcutaneous; TEAE, treatment-emergent adverse event; TCR, T-cell receptor; ULN, upper limit of normal.

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FPO

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