Abstract #313

Characterization of PRAME-specific CD4–CD8+ and CD4+CD8+ T-cell Populations Following IMA203CD8 T-cell Therapy and Their Associated Helper and Cytotoxic Functions

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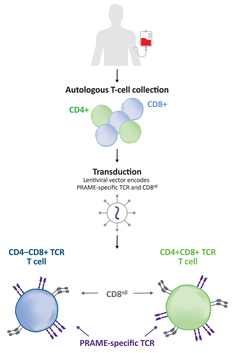
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BACKGROUND

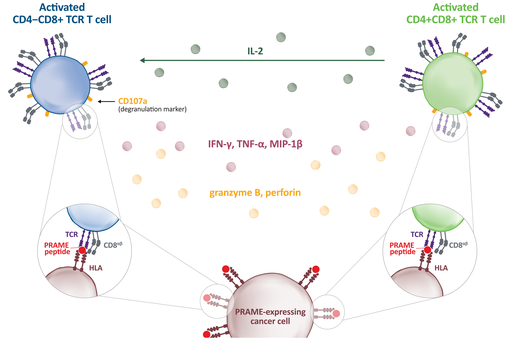
- IMA203CD8 is an autologous PRAME-directed TCR T-cell therapy engineered to recognize an intracellular PRAME-derived peptide presented by HLA-A*02:01 (**Figure 1**)[1]
- Coexpression of a CD8$^{\alpha\beta}$ coreceptor with the TCR grants PRAME-specific recognition and antitumor immune activity to both engineered CD4–CD8+ and CD4+CD8+ TCR T-cell populations[1]
- By harnessing CD4+CD8+ TCR T cells, IMA203CD8 has the potential to increase the total number of engineered T cells capable of targeting PRAME-expressing tumors while leveraging the distinct but complementary functions of both CD4–CD8+ and CD4+CD8+ TCR T cells to support effective antitumor immunity
- Here, we investigated the functional characteristics of the two engineered populations and the contribution of CD4+CD8+ TCR T cells to the postinfusion behavior of IMA203CD8

Figure 1. IMA203CD8 mechanism of action

A. CD4–CD8+ and CD4+CD8+ TCR T cells are generated by lentiviral transduction of autologous CD8+ and CD4+ T cells with a PRAME-specific TCR and CD8$^{\alpha\beta}$ coreceptor



B. Coordinated action of CD4–CD8+ and CD4+CD8+ TCR T cells may help support antitumor activity
- IL-2 from CD4+CD8+ TCR T cells supports expansion, activation, and persistence of CD4–CD8+ TCR T cells
- Both T-cell populations exhibit effector functions, including cytokine/chemokine production (IFN-γ, TNF-α, MIP-1β) and cytotoxicity (granzyme B, perforin)



METHODS

- IMA203-101 (NCT03686124) is an ongoing phase 1/2 study evaluating IMA203CD8 in patients with solid tumors expressing PRAME (**Figure 2**)
- Postinfusion (≤3 months) PBMCs isolated from these patients were evaluated using flow cytometry–based assays (for evaluation of surface marker expression on T cells) and qPCR (for pharmacokinetic analyses)
- Additionally, the final cell product after manufacturing was analyzed using intracellular cytokine staining to assess effector molecule expression upon PRAME stimulation
- The correlation of total infused CD4–CD8+ and CD4+CD8+ TCR T cells with IMA203CD8 activation, expansion, and persistence was investigated

Figure 2. Study design of the IMA203CD8 cohort in IMA203-101

KEY OBJECTIVES

Primary
- Tolerability
- Determination of RP2D

Secondary
- Efficacy
- Pharmacokinetics

KEY ELIGIBILITY CRITERIA
- Advanced or metastatic solid tumors
- Age ≥18 years
- ECOG PS 0-1
- HLA-A*02:01 positive
- PRAME positive
- No available SOC treatment options
- Measurable disease (RECIST 1.1)
- Adequate organ function

PATIENT JOURNEY

Screening/Manufacturing | Treatment/Observation | Follow-up

HLA-A*02:01 testing (blood)
PRAME testing: Biopsy or archived tissue. *No longer required for indications with high PRAME prevalence, including ovarian and uterine cancer*
Leukapheresis
IMA203CD8 manufacturing (~2 weeks)
Lymphodepletion: Fludarabine 30 mg/m²; Cyclophosphamide 500 mg/m²; Days −6 to −3
IMA203CD8 *one-time infusion*
± Low-dose IL-2[a,b]: 1×10⁶ IU SUBQ QD for 3 d, then 1×10⁶ IU SUBQ BID for 5 d

DOSE ESCALATION SCHEME[c]

DL3 (n=1)	DL4a (n=6)	DL4c (n=2)	DL5 (n=5)	DL6 (n=8)	DL7 (n=5)
~0.36-0.86×10⁹ total TCR T cells	~0.87-1.44×10⁹ total TCR T cells	~1.45-2.16×10⁹ total TCR T cells	~2.17-3.6×10⁹ total TCR T cells	~3.6-7.2×10⁹ total TCR T cells	~7.2-10×10⁹ total TCR T cells

Enrichment at relevant DLs: ~1.4-10 billion total TCR T cells

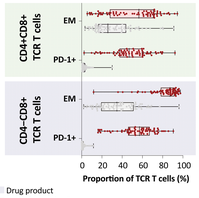
[a] Levels ≥DL4c were evaluated with or without IL-2, starting without IL-2. If tolerable, IL-2 was added at the same dose level or escalated to the next dose level without IL-2.
[b] Outpatient IL-2 administration was performed at investigator's discretion. [c] Based on initial safety data observed with anzutresegene autoleucel (anzu-cel, IMA203), IMA203CD8 dose escalation was initiated at DL3. Total TCR T cells were calculated from defined number of TCR T cells/m² BSA per dose level multiplied by 1.8 m² BSA.

RESULTS

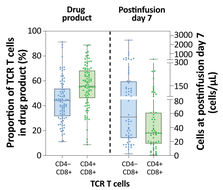
- Ex vivo analysis of patient PBMCs without additional stimulation showed:
  - PRAME peptide engagement and activation of engineered T cells shortly after infusion, as evidenced by PD-1 expression and effector induction (**Figure 3A**)
  - Distinct expansion capacity and differentiation trajectories upon PRAME engagement of CD4–CD8+ and CD4+CD8+ TCR T cells, with CD4+CD8+ expanding less and retaining the expression of costimulatory markers and central memory phenotype (**Figure 3B-C**)
- Upon ex vivo stimulation of PRAME, engineered CD4+CD8+ TCR T cells were the main source of IL-2, but also expressed CD107a, a degranulation marker which indicates cytotoxic potential (**Figure 4**)
  - Altogether, CD4+CD8+ TCR T cells appeared to retain their native helper-like functionality in addition to cytotoxic potential
- Total infused engineered CD4+CD8+ TCR T cells correlated with activation of engineered CD4–CD8+ TCR T cells and cumulative expansion and exposure of IMA203CD8 T cells in patients who did not receive low-dose IL-2 following IMA203CD8 infusion (**Figure 5**)

Figure 3. Engineered CD4–CD8+ and CD4+CD8+ TCR T cells showed early activation but distinct postinfusion behavior

A. Early activation was observed in both TCR T-cell subsets



B. Higher expansion capacity of CD4–CD8+ TCR T cells was observed after infusion



C. CD4–CD8+ and CD4+CD8+ TCR T cells have distinct differentiated states after activation

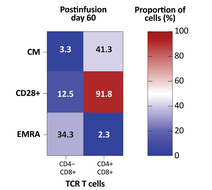
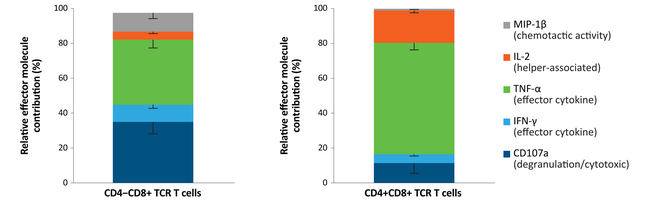
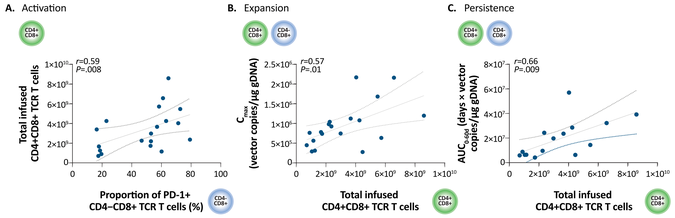


Figure 4. CD4+CD8+ TCR T cells showed helper-associated features while retaining cytotoxic potential following PRAME engagement[a,b,c]



[a] Nine patients were included in this analysis. [b] Graphs depict median with interquartile range. [c] Bars show representative data in patients with ovarian cancer, but patients with melanoma show a similar pattern of effector molecule production upon encountering PRAME. A similar profile of effector molecule production was seen after infusion.

Figure 5. Total number of infused CD4+CD8+ TCR T cells was associated with activation, expansion, and persistence of IMA203CD8 T cells postinfusion[a]



T-cell populations are visualized using green and blue circles for CD4–CD8+ and CD4+CD8+ TCR T cells, respectively. Solid lines indicate the linear regression fit; dotted lines indicate the 95% CI.
[a] In patients who did not receive IL-2 after infusion.

CONCLUSIONS

- Our results show that in patients with PRAME-positive solid tumors who received IMA203CD8, both engineered CD4–CD8+ and CD4+CD8+ TCR T cells are activated but retain distinct characteristics
- While displaying cytotoxic potential, CD4+CD8+ TCR T cells also retain their native CD4 helper-associated features
- Higher infused CD4+CD8+ TCR T-cell numbers were positively associated with subsequent activation, expansion, and persistence of IMA203CD8 T cells
- Thus, coengineering CD4–CD8+ and CD4+CD8+ T-cell populations with a PRAME-specific TCR and CD8$^{\alpha\beta}$ coreceptor may provide complementary helper and cytotoxic functions, enabling coordinated antitumor responses of IMA203CD8

ABBREVIATIONS: AUC, area under the curve; BID, twice daily; BSA, body surface area; CD, cluster of differentiation; C_{max}, maximum concentration; DL, dose level; ECOG PS, Eastern Cooperative Oncology Group performance status; EM, effector memory; EMRA, effector memory cells re-expressing CD45RA; gDNA, genomic deoxyribonucleic acid; HLA, human leukocyte antigen; IFN-γ, interferon gamma; IL-2, interleukin 2; IU, international unit; MIP-1β, macrophage inflammatory protein 1 beta; PBMC, peripheral blood mononuclear cell; PD-1, programmed cell death protein 1; PRAME, preferentially expressed antigen in melanoma; QD, daily; qPCR, quantitative polymerase chain reaction; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; SOC, standard of care; SUBQ, subcutaneous; TCR, T-cell receptor; TNF-α, tumor necrosis factor alpha.

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REFERENCES:
1. Busse A, et al. *Immuno-Oncol Technol*. 2025;28(suppl):101162.

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