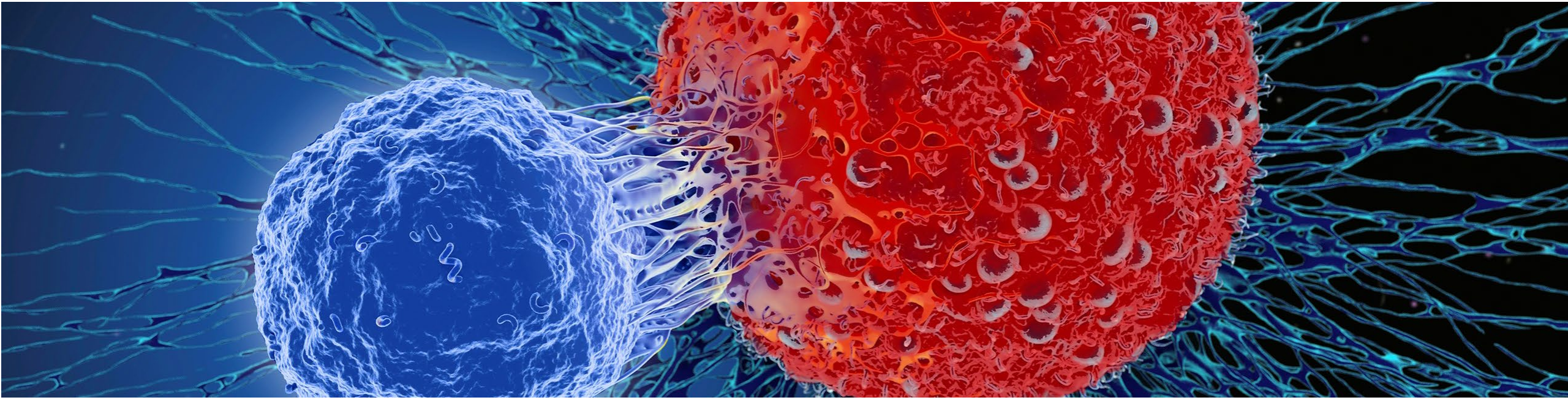
ASGCT 26th Annual Meeting
May 18, 2023



Mechanistic Characterization of Afamitresgene Autoleucel (Afami-cel; Formerly ADP-A2M4)

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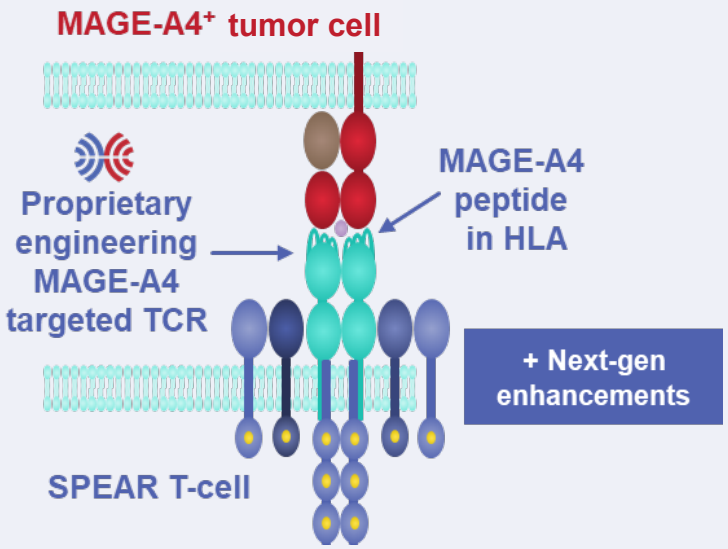
Afami-cel: a genetically modified autologous T-cell immunotherapy product



- T-cells are transduced with a self-inactivating lentiviral vector expressing an enhanced-affinity T-cell receptor specific for human MAGE-A4
- The TCR recognizes an HLA-A*02 restricted MAGE-A4 peptide

MAGE-A4 is a validated target

- A cancer testis antigen
- "Clean" target
- Intracellular protein
- **Only addressable with a T-cell receptor**

MAGE-A4 patient population

- Expression levels ~15%–70%[a] across a broad range of solid tumors
- **Confirmed responses in**
  - Head and neck
  - Gastroesophageal
  - NSCLC-squamous
  - Synovial sarcoma
  - Melanoma
  - Bladder
  - Ovarian
  - MRCLS

Afami-cel

- **Pivotal trial (SPEARHEAD-1, NCT04044768) met the efficacy endpoint** in patients with synovial sarcoma and MRCLS[1]
- In-depth quality control and efficacy testing is performed prior to product release
- The assays presented here are additional analyses for translational insights only
- Variable transduction efficiency values and CD4/CD8 balance is evident across patients in SPEARHEAD-1

[a]MAGE-A4 expression based on Adaptimmune samples and expression cut-off criteria of ≥30% tumor cells at ≥2+ intensity. HLA, human leukocyte antigen; MAGE-A4, melanoma-associated antigen A4; MRCLS, myxoid/round cell liposarcoma; NSCLC, non-small cell lung cancer; SPEAR, specific peptide enhanced affinity receptor; TCR, T-cell receptor. 1. Van Tine B, et al. Presented at: CTOS 2022; Vancouver, Canada.

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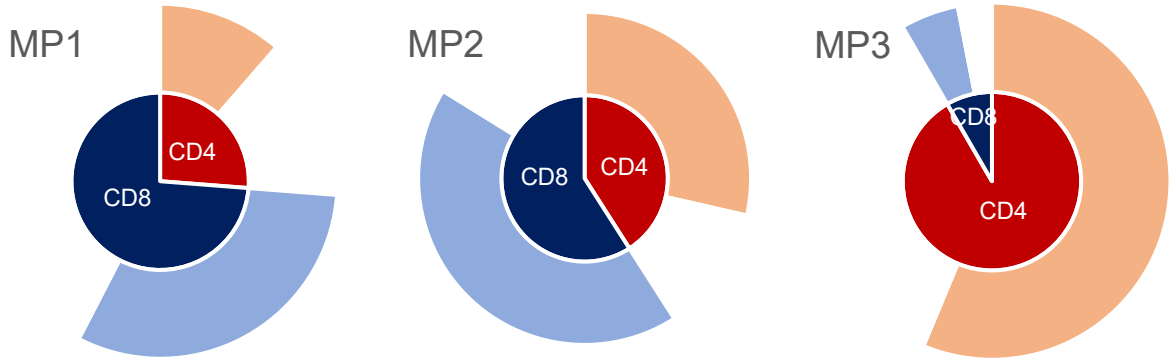
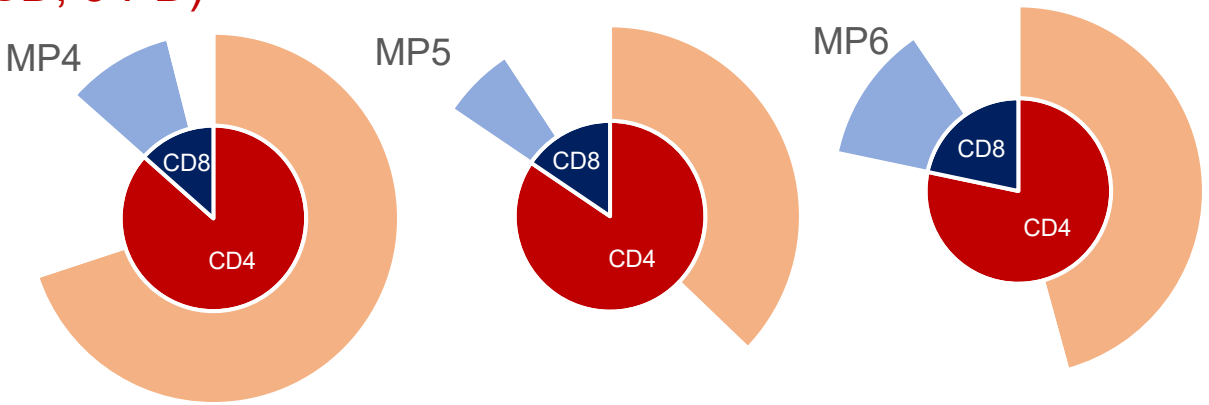
In vitro profiling of afami-cel clinical patient products to translate phenotype to function

Responders[a] (1 CR, 6 PR)

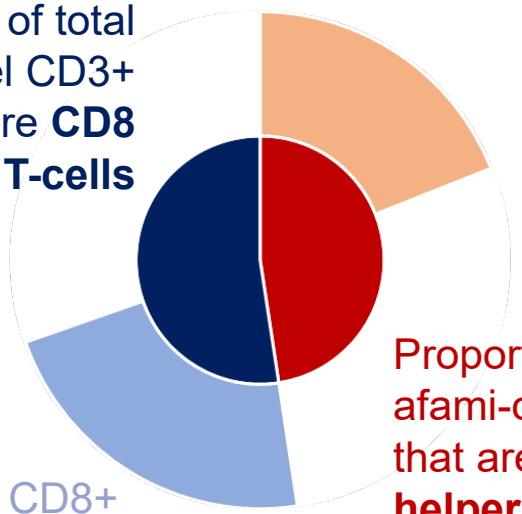


Non-responders[a] (2 SD, 3 PD)



Proportion of CD4+ T-cells that are expressing **transduced MAGE-A4 specific TCR**

Proportion of total afami-cel CD3+ cells that are **CD8 cytotoxic T-cells**



Proportion of total afami-cel CD3+ cells that are **CD4 T helper cells**

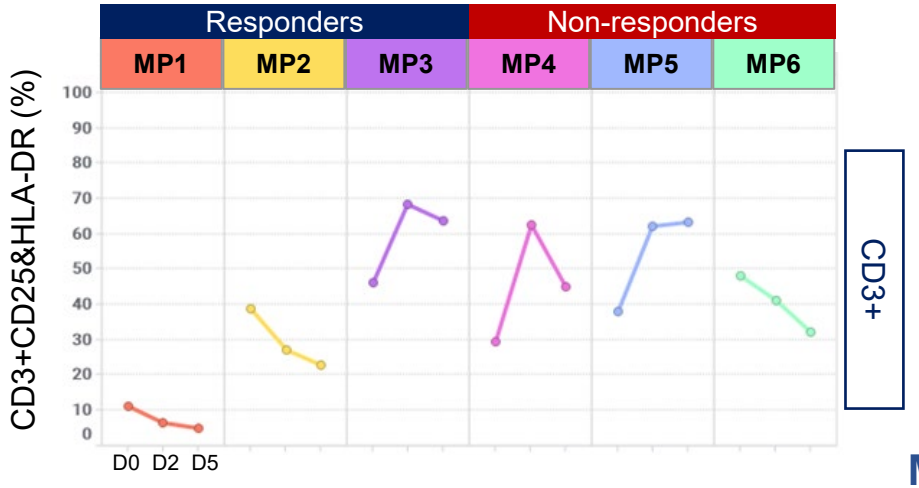
Proportion of CD8+ T-cells that are expressing **transduced MAGE-A4 specific TCR**

[a]RECIST v1.1 by Investigator review, data cut -off August 29, 2022. CR, complete response; MP, manufactured product; PD, progressive disease; PR, partial response; RECIST, response evaluation criteria in solid tumors; SD, stable disease

Increase in activation marker expression upon stimulation relates to cytokine and mitochondrial response

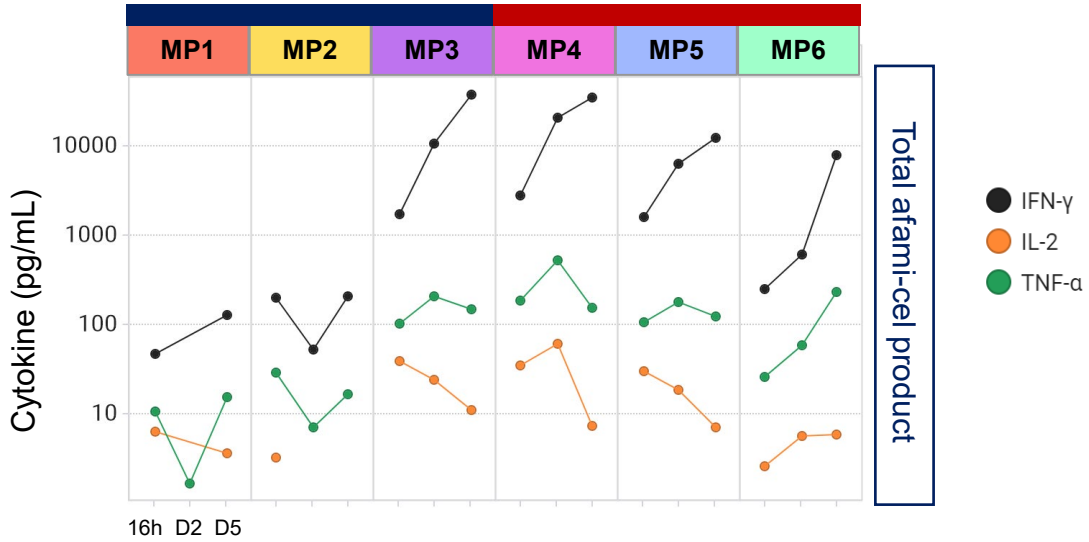
- MP3, MP4, and MP5 show high activation at baseline, high levels of cytokine, and the greatest increase in mitochondrial mass upon stimulation

Activation markers CD25&HLA-DR (%)

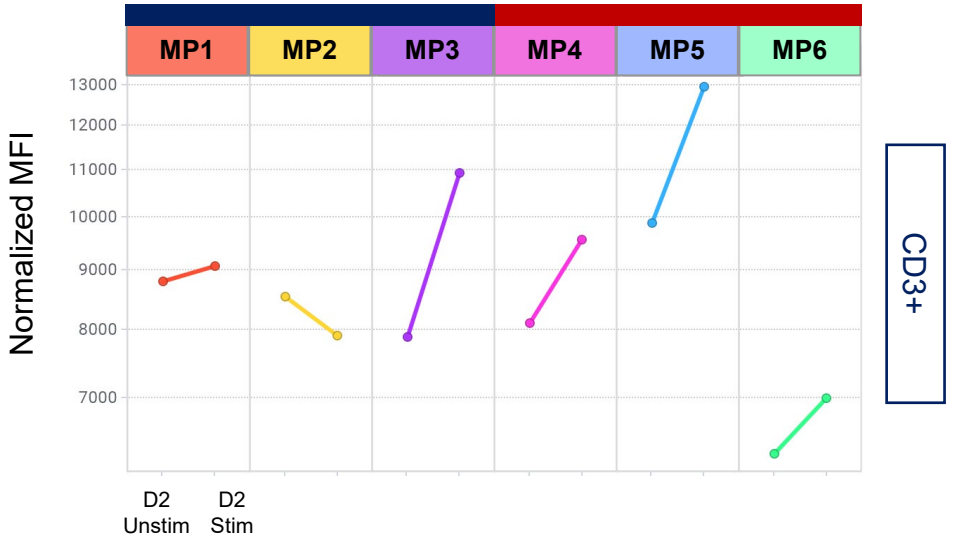


- MP1, MP2, and MP6 have a lower activation state upon stimulation, reflected in less cytokine production and small changes in mitochondrial mass

Cytokines

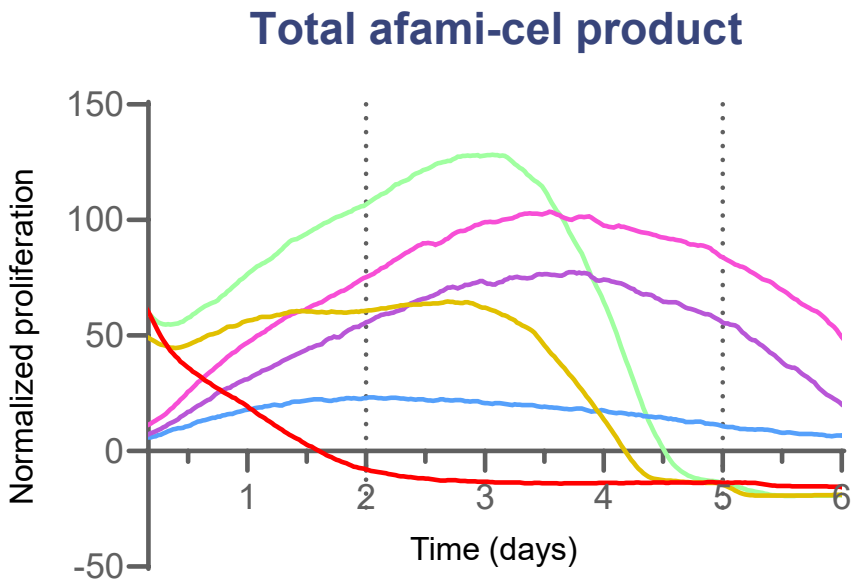


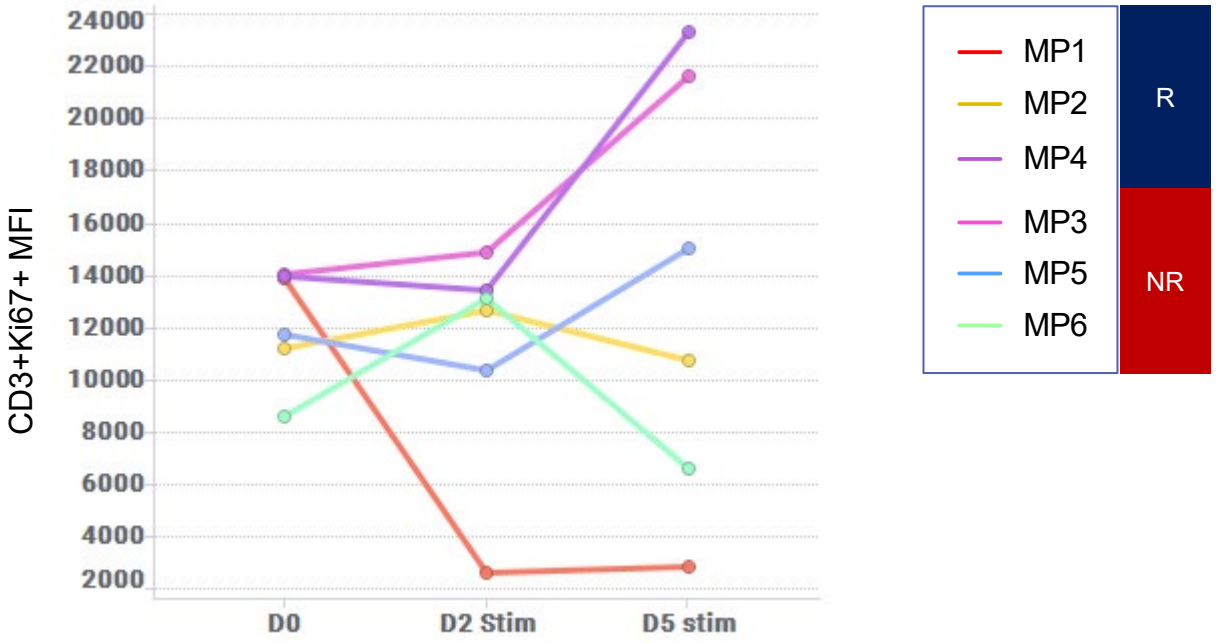
Mitochondrial mass



IFN, interferon; IL, interleukin; MFI, median fluorescence intensity; TNF, tumor necrosis factor

Less sustained proliferation curve relates to transient increase in Ki67 expression

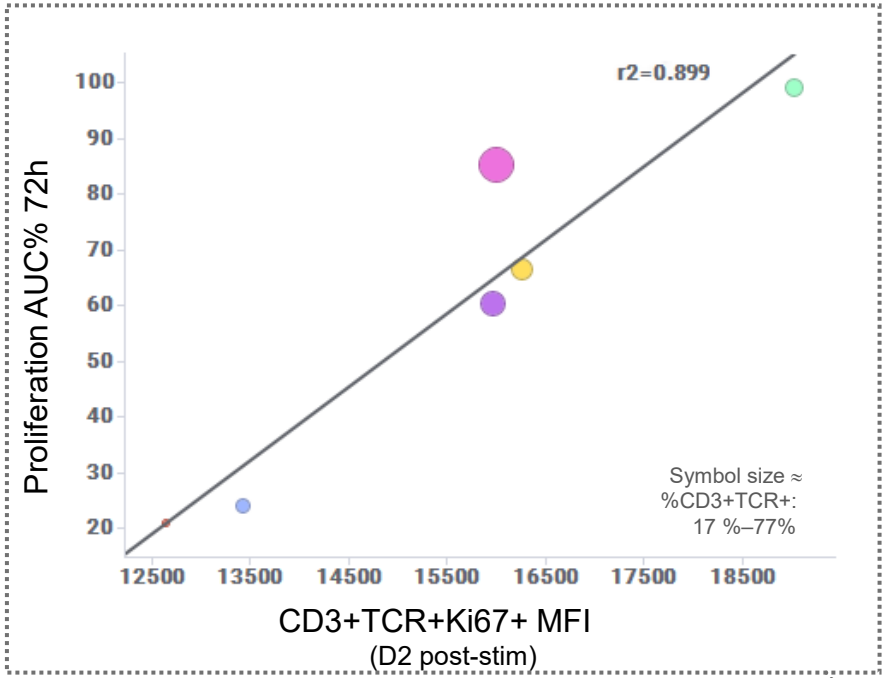


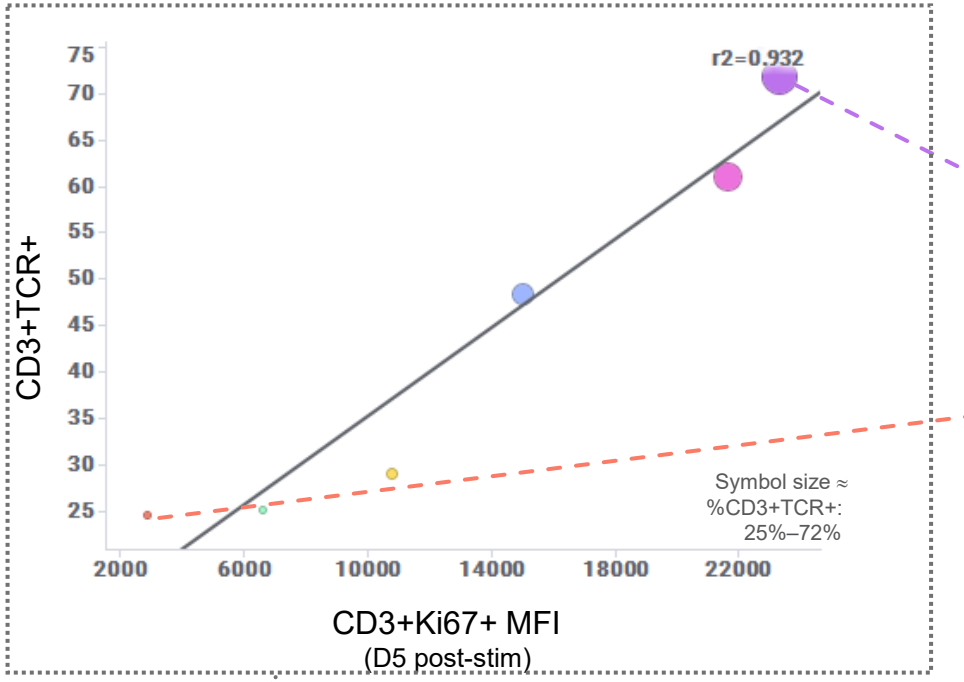


- MP1 does not proliferate well and has low induction of Ki67 expression
- MP2 and MP6 proliferate well initially but stop around Day 4, mirrored with a drop in Ki67 expression by Day 5
- Contribution to proliferation AUC is from height of proliferative response, and how well the response is sustained
- MP3, MP4, and MP5 maintain a sustained proliferative response

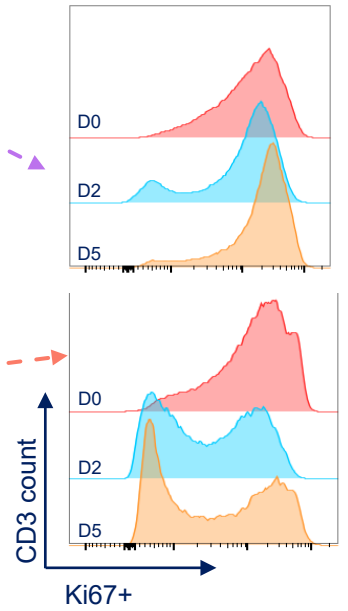
AUC, area under the curve; Ki67, proliferation marker, MFI, median fluorescence intensity; MP, manufactured product; NR, non-responder; R, responder

Greater proliferative response of afami-cel product associates with Ki67 expression and retention of transduced cells on stimulation



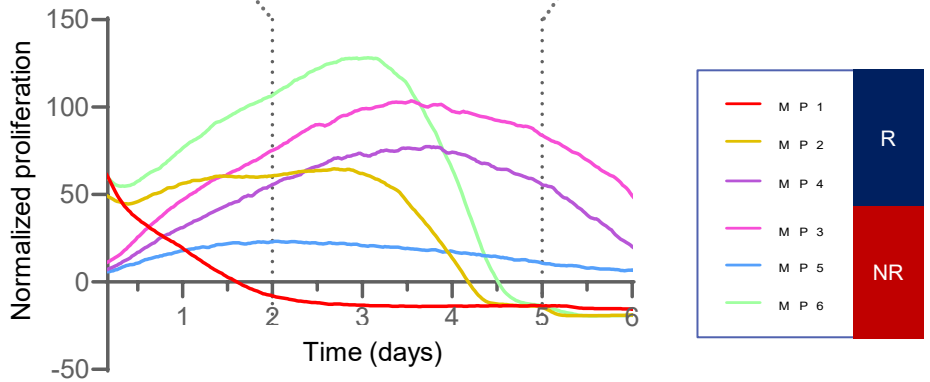


Total CD3+ Ki67 expression



- MP1 loses TCR+ cells by Day 2 and has the lowest AUC for proliferation time course and lowest Ki67 expression
- MP2 and MP6 proliferate well and retain TCR cells at Day 2 but lose their TCR expression by Day 5, resulting in loss of proliferative response

Total afami-cel product



- MP3, MP4, and MP5 retain their TCR over 5 days and proliferate longest
- Although MP5 has low Ki67 expression at Day 2 reflected in a flatter proliferation curve, TCR retention leads to increased Ki67 expression at Day 5 and sustained proliferative response

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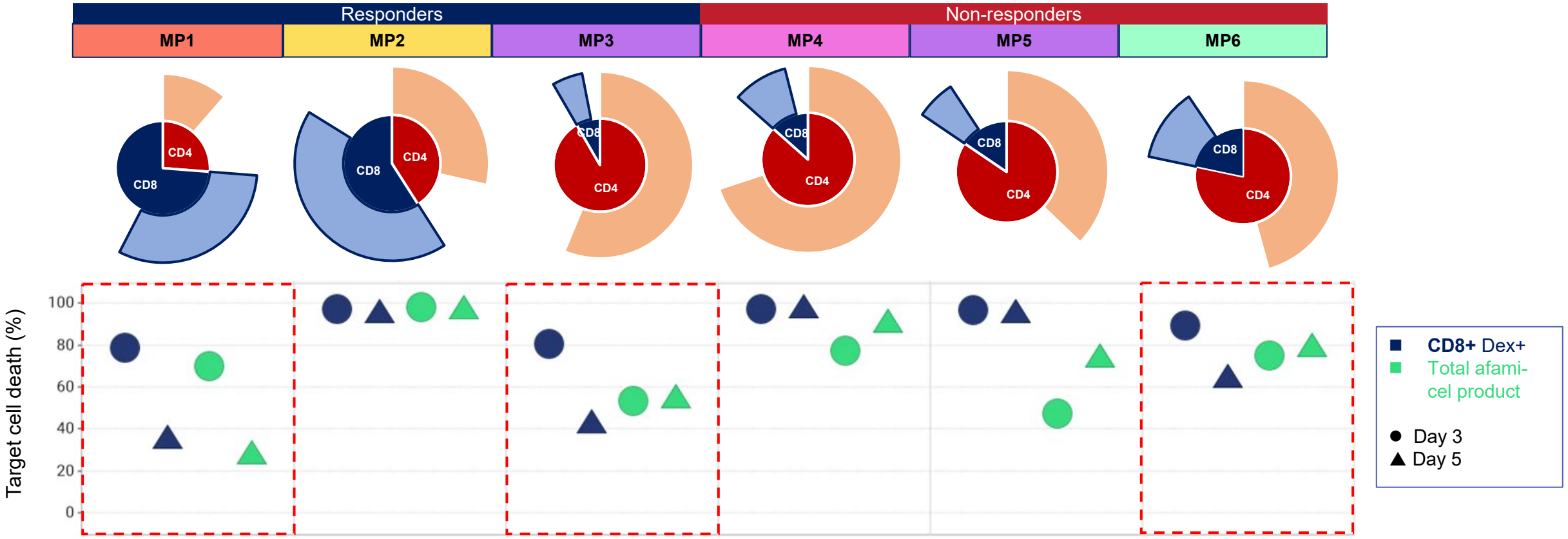
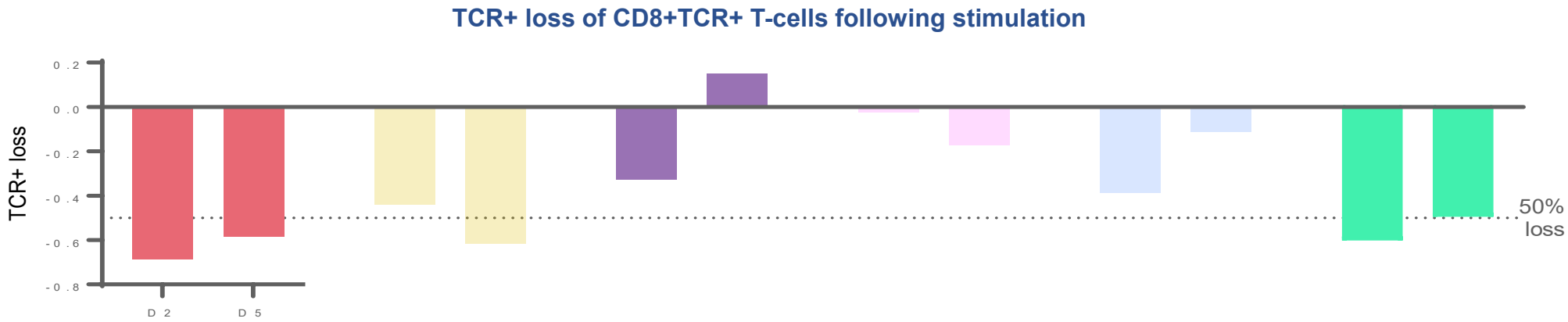
Cytotoxic response of total afami-cel product relates to number of functional CD8+TCR+ T-cells

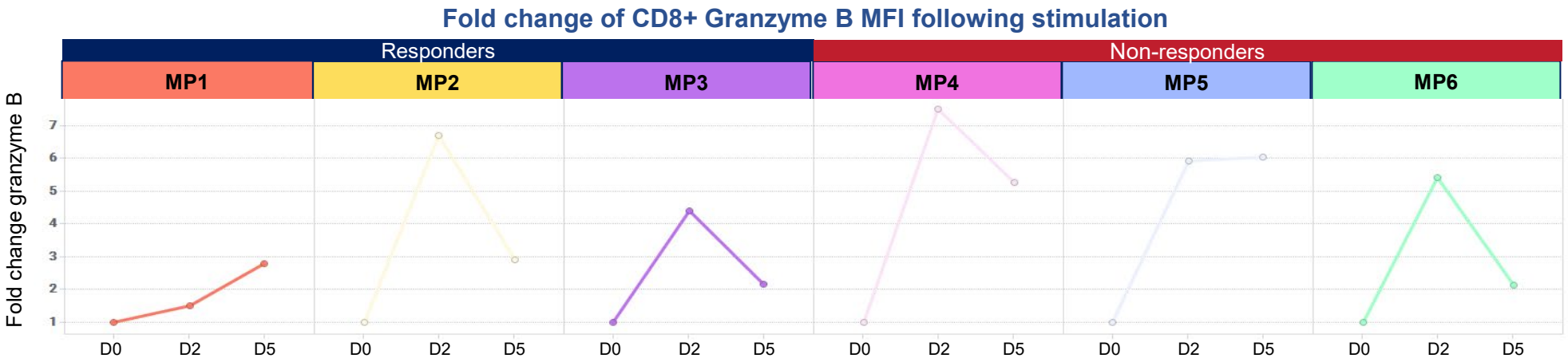


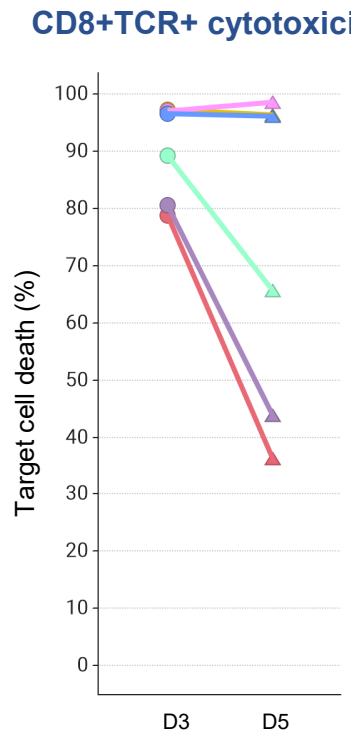
- MP2 performs very well in this assay; CD8+ TCR+ cells alone and the total afami-cel product show 100% killing by Day 3
- MP4 and MP5 show 100% killing for isolated CD8+ TCR+ cells but not for the total afami-cel product, likely due to the lower number of transduced cytotoxic CD8+ T-cells in the MP
- Isolated CD8+TCR+ cells for MP1, MP3, and MP6 do not kill efficiently

Incucyte cytotoxicity assay, nucGFPA375 cell death

Retention of CD8+TCR+ cells following stimulation is linked to cytotoxic response of CD8+TCR+ populations and associated with cytolytic granzyme B release







- MP1 shows over 50% TCR+ loss by Day 2 and is induced to express the lowest levels of granzyme B
- MP6 shows over 50% TCR+ loss by Day 2 and although there is granzyme B expression induced, it is hypothesised that not enough cells are retained and producing these levels of granzyme B to have a 100% cytotoxic response
- MP3 retains TCR+ cells; however, these cells are not induced to express high levels of granzyme B leading to lack of 100% efficient cytotoxic response

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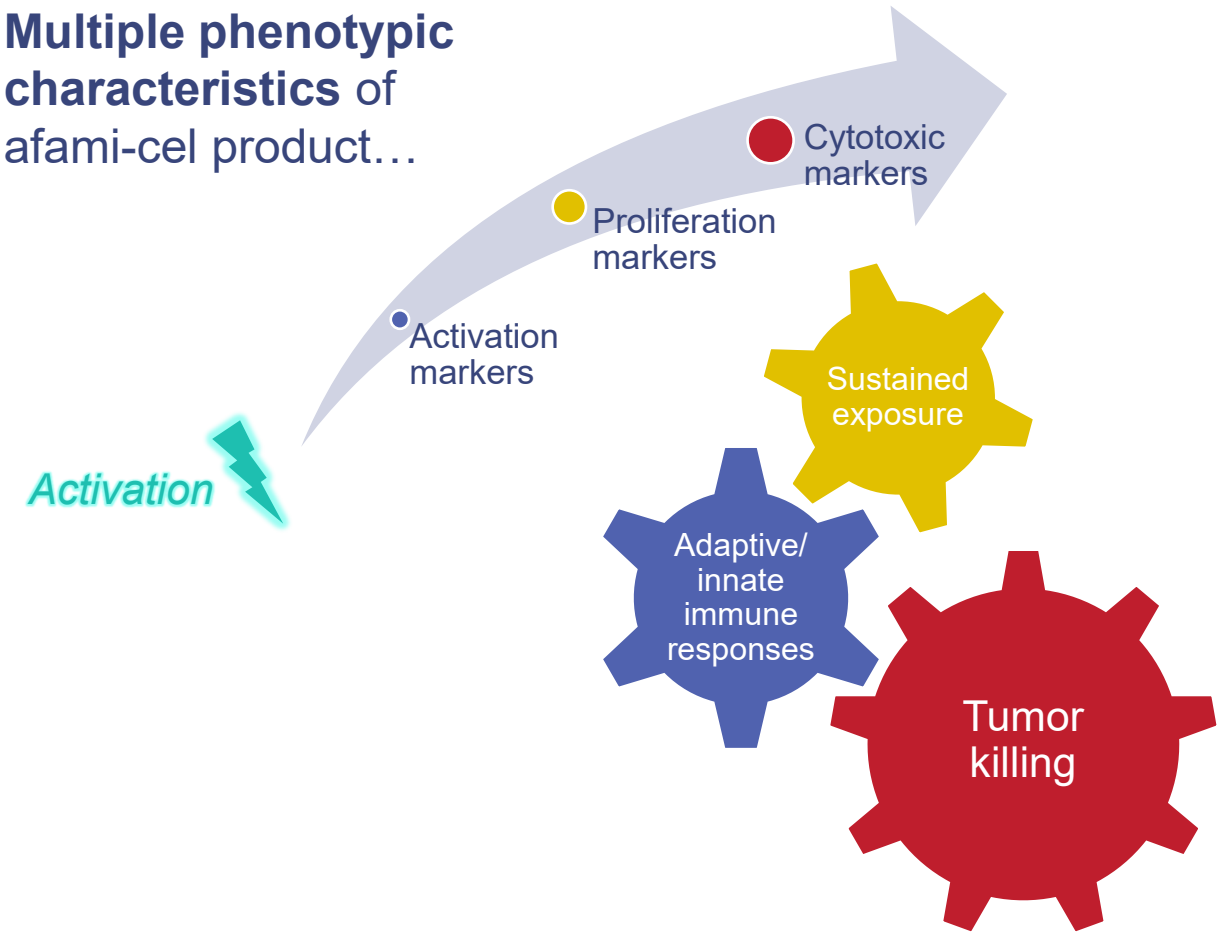
Evidence of afami-cel product anti-tumor mechanism through translation of phenotypic characteristics to functional response

Multiple phenotypic characteristics of afami-cel product…



… are required to support a range of **effector functions:**

- TCR+ T-cells need to be able to expand upon cognate antigen exposure
  - Long-term persistence and formation of memory
- These TCR+ T-cells need to have the capacity to become functionally active
  - Functional cytotoxic response post infusion
- Retain the ability for mobilization of adaptive and innate immune responses (by secreting cytokines/chemokines)
  - Serum cytokine analysis
- These T-cells need fit and healthy mitochondria
  - TCR+ T-cell health post infusion

Ongoing analyses are examining correlative relationships with clinical endpoints

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