

# Translational Analyses of T-cell Phenotypes and Their Association with Clinical Efficacy in the First-In-Human (FIH) Trial of JNJ-78278343 (Pasritamig) in Metastatic Castration-Resistant Prostate Cancer (mCRPC)

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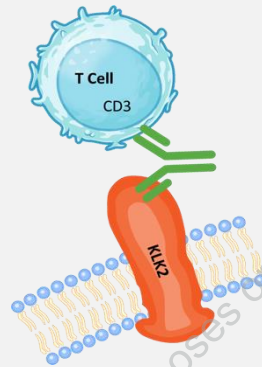
# Disclosures

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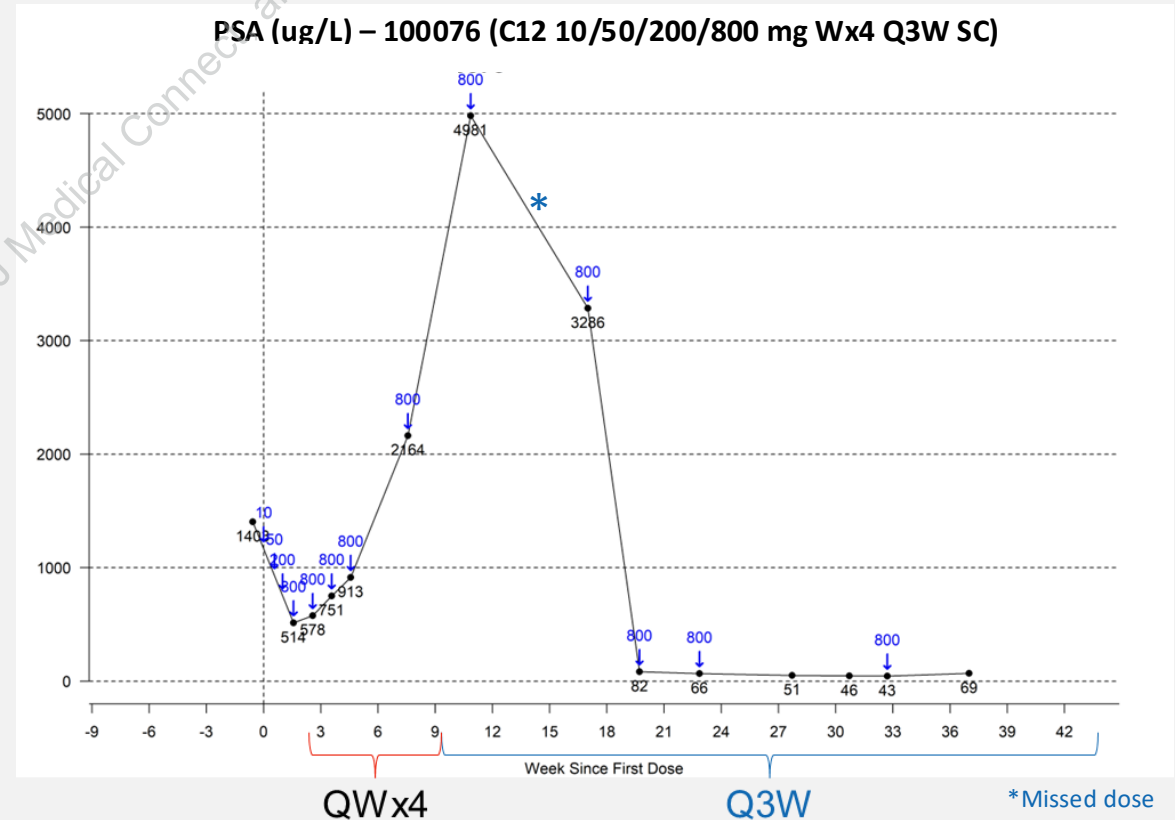


# Weekly dosing of pasritamig was associated with rising PSA values in a subset of patients in contrast to cohorts with less frequent dosing (Q3W)

- KLK2 expression is highly specific to prostate adenocarcinoma
  - Expression is maintained through every stage of the disease<sup>1</sup>
- The FIH trial of pasritamig in mCRPC dose escalation cohorts (21 total) investigated:
  - Step-up dosing to reduce the risk of cytokine release syndrome (CRS)
  - SC and IV dosing; IV dosing was selected to improve exposure to pasritamig and to avoid injection site reactions (ISRs)
  - Exploration of different dose intervals; Q6W dosing optimized drug concentrations for efficacy and mitigates T-cell exhaustion



PSA levels increased during Q1W SC dosing then dropped when the dosing interval was increased to Q3W in a subset of patients



**The RP2D was chosen to be SU1 3.5 mg D1, SU2 18 mg D8, TD 300 mg D15, then 300 mg Q6W - all doses given IV.**

Clinicaltrials.gov identifier for FIH: NCT04898634

CRS=Cytokine release syndrome; D=Day; FIH=First-in-human; ISR=Injection site reaction; IV=Intravenous; KLK2= Kallikrein-related peptidase 2; mCRPC= Metastatic castration-resistant prostate cancer; PSA=Prostate-specific antigen, Q1W=Every week; Q3W = Every 3 weeks Q6W=Every 6 weeks; R2PD= Recommended phase 2 dose; SC=Subcutaneous; SU=Step-up; TD=Target dose.

1. Shen et al. *Clin Can Res*. 2025; doi: 10.1158/1078-0432.CCR-25-0950.



# Why does 300 mg IV given Q6W increase the frequency of PSA50 responders compared to Q3W?

## Hypothesis:

Increasing the dosing interval to Q6W from Q3W may lead to less T-cell terminal exhaustion and activation induced T-cell death (AICD)

## Goal:

Translational research studies were conducted to explore dosing frequency and T-cell exhaustion and AICD pathway markers

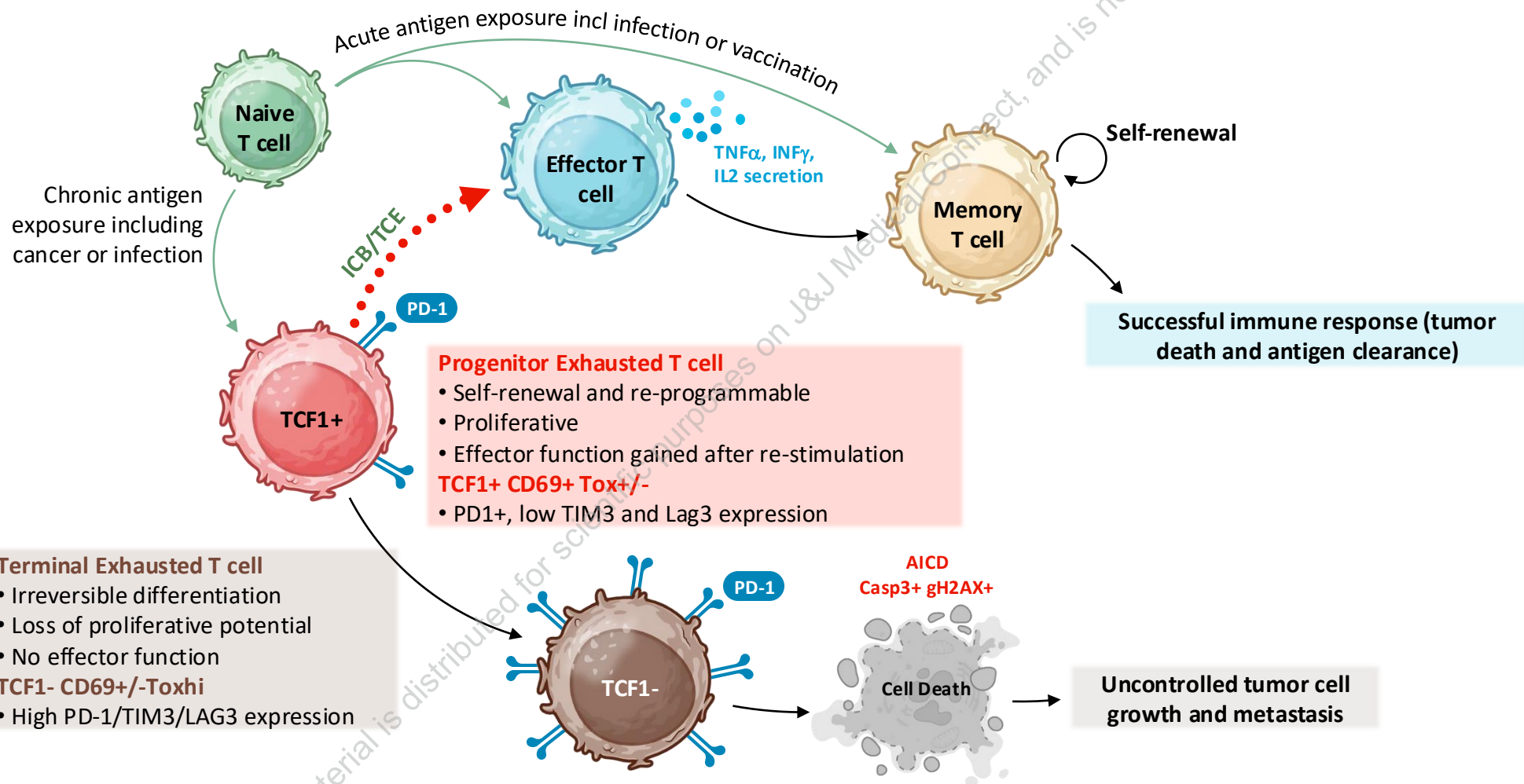
PSA50 Response	300 mg IV Q3W	300 mg IV Q6W
At any time	4/12 (33%)	33/75 (44%)
Confirmed at 3W	2/12 (17%)	26/75 (35%)
Confirmed at 12W	2/12 (17%)	21/63 (33%)

Clinical Cutoff Date: 04-July-2025

AICD=activation-induced T-cell death; IL2=Interleukin 2; INFg=Interferon gamma; IV=Intravenous; PSA=Prostate-specific antigen; Q3W=Every 3 weeks; Q6W=Every 6 weeks; TNFa=Tumor necrosis factor alpha; W=weeks.

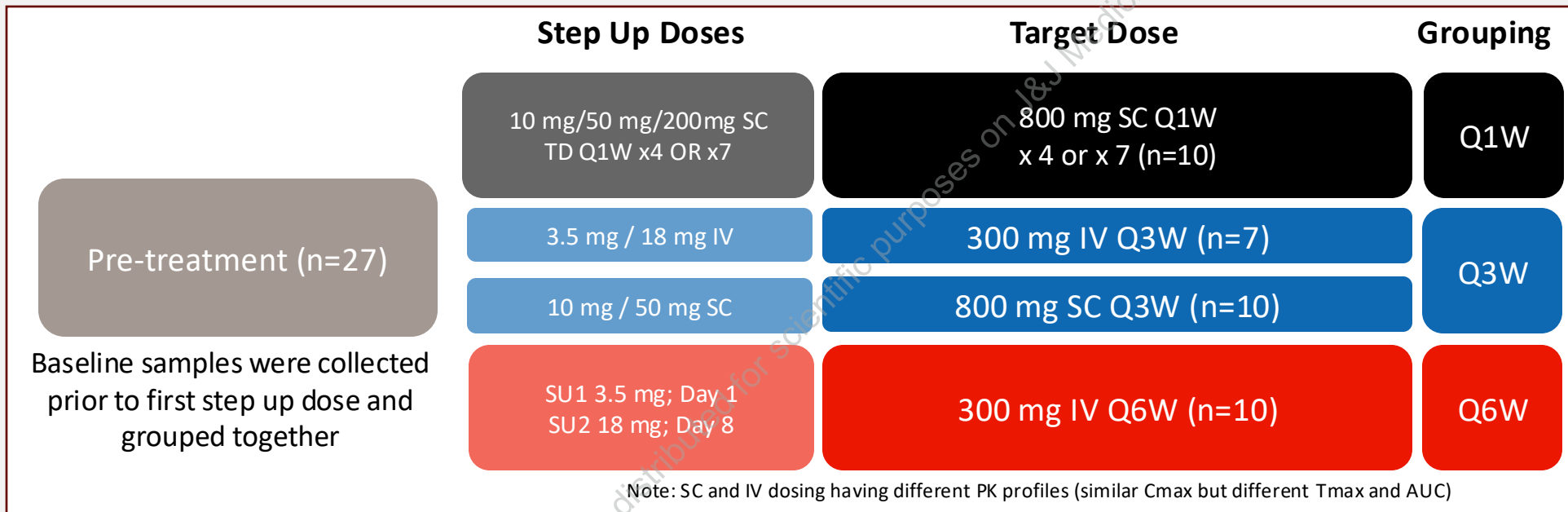


# What is the impact of dosing frequency on T-cell exhaustion?



# PBMCs were analyzed by flow cytometry for immunophenotypes associated with T-cell exhaustion and AICD

- **PBMC Collection:** baseline, pre-dose during the first 4 cycles, then every 3 months up to 1 year
- **Patient Selection:** 27 total patients from 4 dosing cohorts (800 mg SC Q1Wx4 or Q1Wx7 then Q3W; 300 mg IV Q3W vs Q6W), 3 healthy donors for reference
- **Sample Grouping:** pre-treatment; samples grouped if collected during **Q1W**; **Q3W**; or **Q6W** dosing intervals



## T-Cell Flow Cytometry

- T-Cell Exhausted Progenitors (TCF1, CD69, Tox)
- AICD (gH2AX, Casp3)
- T-cell activation, proliferation, and memory/effector subsets

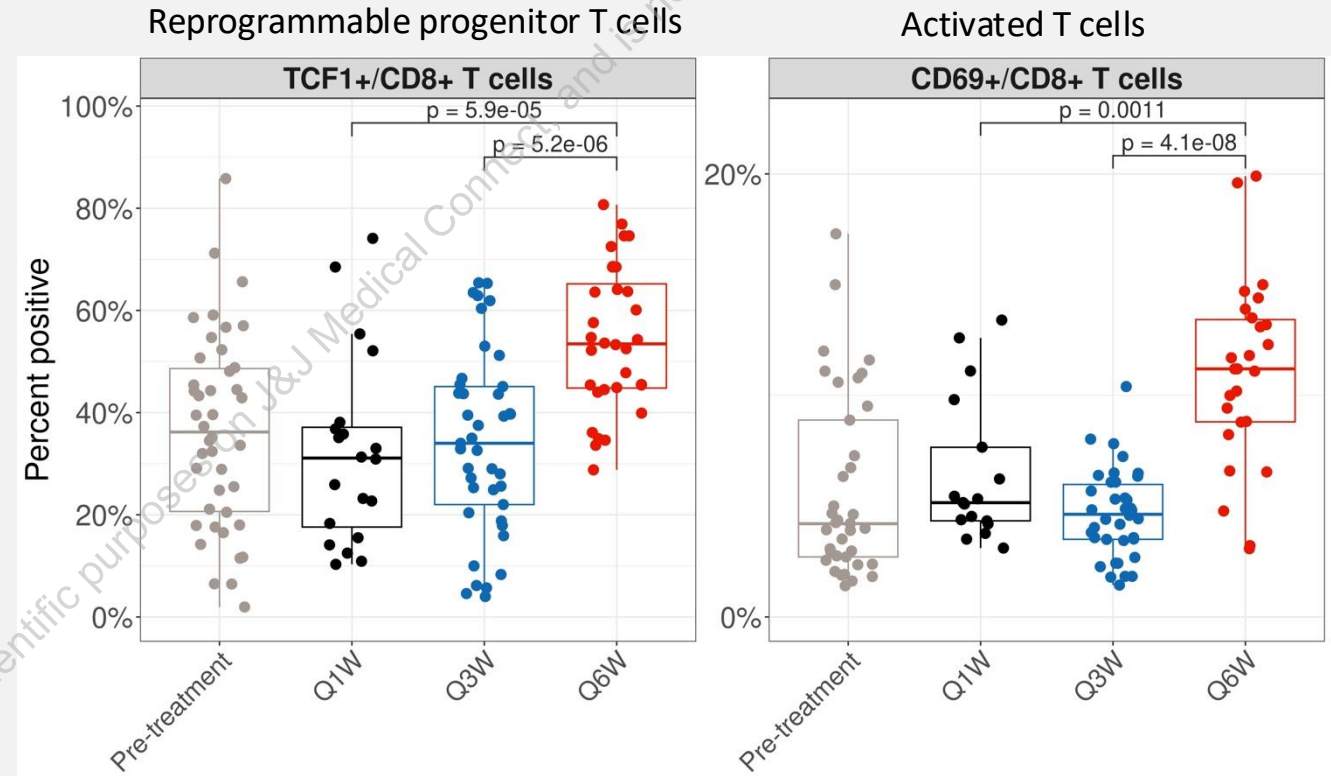
AICD=Activation-induced T-cell death; IV=Intravenous; PK=Pharmacokinetics; PBMC=Peripheral blood mononuclear cell; Q1W=Every week; Q3W=Every 3 weeks; Q6W=Every 6 weeks; SC=Subcutaneous; SU=Step up; TCF1=T cell factor 1; Tox=Thymocyte selection-associated high mobility group box protein.



# Less frequent Q6W dosing drives more productive T cell responses by limiting T-cell exhaustion

## T-Cell Exhaustion

- The expression of TCF1 allows T-cells to remain 'programmable'
- Loss of TCF1 expression leads to terminal exhaustion of T-cells
- CD69 is an early activation marker associated with the ability to migrate from lymphoid tissues into circulation
- Increased activation induced T-cell death (AICD) in Q3W, Q1W (data not shown)



Each group represents samples collected during:

Q1W (800 mg SC doses)

Q3W (300 mg IV & 800 mg SC)

Q6W (300 mg IV)

AICD=Activation-induced T-cell death; CD8=Cluster of Differentiation 8; CD69=Cluster of Differentiation 69; IV=Intravenous; Q1W=Every week; Q3W=Every 3 weeks; Q6W=Every 6 weeks; SC=Subcutaneous; TCF1=T cell factor 1.



# Conclusions

- Biomarker analyses of PBMCs support the proposed mechanism of action of pasritamig and the recommended RP2D (SU1 3.5 mg/SU2 18 mg/300 mg IV Q6W)
  - Increasing the dosing interval from Q1W or Q3W to Q6W mitigates pasritamig induced overactivation of T-cells, T-cell exhaustion and activation induced T-cell death (AICD)
  - Dosing pasritamig Q6W maintains the peripheral pool of a re-programmable, stem-like CD8 T-cell population capable of rapidly differentiating into anti-tumor effector T-cells
  - As reported at ASCO 2025, the Q6W schedule allows for outpatient dosing with a favorable safety profile
- **Key learning:** As the mechanism of action of T-cell engagers is vastly different from currently available modalities, dose optimization should include analyses of immune parameters as well as pharmacokinetics
- Analyses of the association of immune fitness and exhaustion with response or resistance are ongoing
- Pasritamig is now being evaluated in the phase 3 setting (KLK2-comPAS; NCT04898634).

IV=Intravenous; PBMCs=Peripheral blood mononuclear cells; Q1W=Every week; Q3W=Every 3 weeks; Q6W=Every 6 weeks; R2PD=Recommended phase 2 dose.



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