Preclinical evaluation of JNJ-9401, a prostate-specific membrane antigen (PSMA) × CD28 costimulatory T-cell engager, in combination with CD3-targeted T-cell engagers in prostate cancer

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*At the time of the study.

Key Takeaway

These findings provide preclinical proof of concept and support the clinical development of JNJ-9401 in combination with pasritamig, the first dual tumor antigen (KLK2 and PSMA)–targeting CD3 plus CD28 TCE regimen in prostate cancer

Conclusions

- JNJ-9401 provides tumor-directed CD28 costimulation (signal 2) but demonstrates no independent biologic activity, which is consistent with the requirement for concurrent T-cell activation (signal 1)
- The combination of JNJ-9401 with pasritamig produced synergistic enhancement of T-cell function and antitumor activity in vitro and in vivo
- These findings establish biologic proof of concept for a dual tumor antigen (KLK2 and PSMA)–targeting CD3 plus CD28 TCE strategy in prostate cancer
- The data support continued clinical evaluation of pasritamig plus JNJ-9401 in a first-in-human phase 1 study (NCT06095089)[3] and ongoing phase 3 KLK2-comPAS Part 2 study (NCT07164443)

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Poster

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Disclosures

CGD is an employee of Johnson & Johnson and may own stock or stock options in Johnson & Johnson.

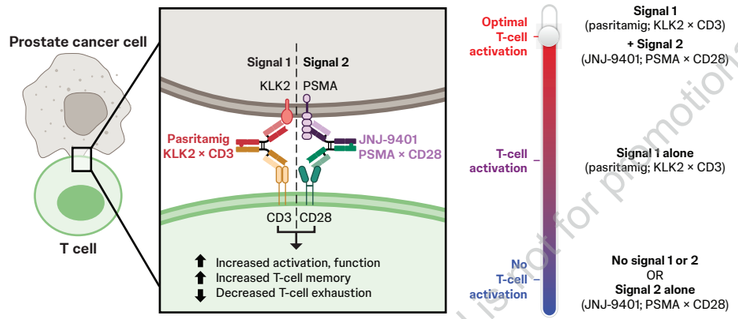
Introduction

- Optimal T-cell activation requires 2 coordinated signals: the T-cell receptor in complex with CD3 bound to antigen loaded onto a major histocompatibility receptor (signal 1) and a costimulatory signal (signal 2), such as the costimulatory receptor CD28 binding to the B7 family ligand CD80/CD86[1,2]
- JNJ-9401, a novel PSMA × CD28 costimulatory T-cell engager (TCE), is an Fc-silent human immunoglobulin G1 (IgG1) antibody designed to deliver tumor-specific costimulatory signal to T cells and increase the depth and durability of responses to active prostate-targeted CD3 TCEs, such as pasritamig (human kallikrein 2 [KLK2] × CD3), as shown in **Figure 1**

Objective

- Here, we present the preclinical activity of JNJ-9401 alone and in combination with pasritamig in prostate cancer models

Figure 1: Synergistic antitumor activity with JNJ-9401 and pasritamig



KLK2, human kallikrein 2; PSMA, prostate-specific membrane antigen.

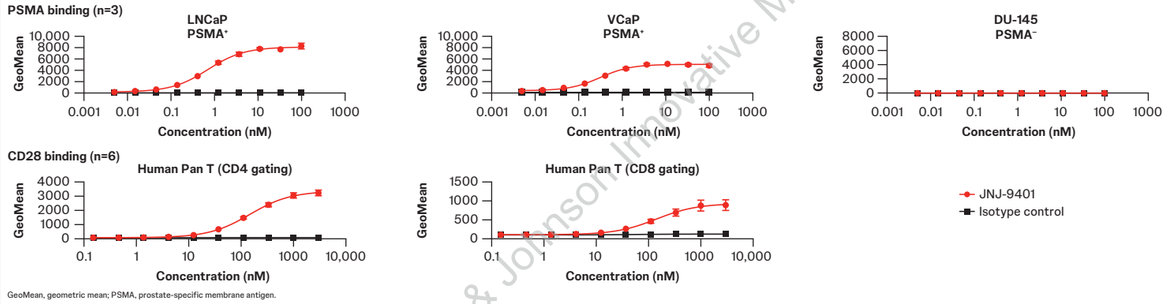
Methods

- JNJ-9401 was evaluated by flow cytometry for cell binding using PSMA-positive cell lines (LNCaP and VCaP) and the PSMA-negative cell line DU-145 (human cell lines were purchased from American Type Culture Collection). Binding to T-cell subsets ($CD4^+$ and $CD8^+$) was also assessed using purified human Pan T cells (Discovery Life Sciences). The ability of JNJ-9401 and pasritamig to mediate T-cell cytotoxicity was examined using fluorescently labeled VCaP cells cocultured with human T cells and monitored via an Incucyte imaging system
- Cytokine secretion was measured in the supernatants of treated cocultures
- The in vivo antitumor activity of JNJ-9401 alone and in combination with pasritamig was assessed in T-cell humanized NSG-immunodeficient mice bearing established VCaP tumors
- The safety profile of JNJ-9401 as a monotherapy was assessed in cynomolgus monkeys in a repeat-dose Good Laboratory Practice–compliant study

Results

- JNJ-9401 selectively bound to PSMA-positive LNCaP and VCaP cells and to isolated $CD4^+$ and $CD8^+$ human T cells (**Figure 2**)

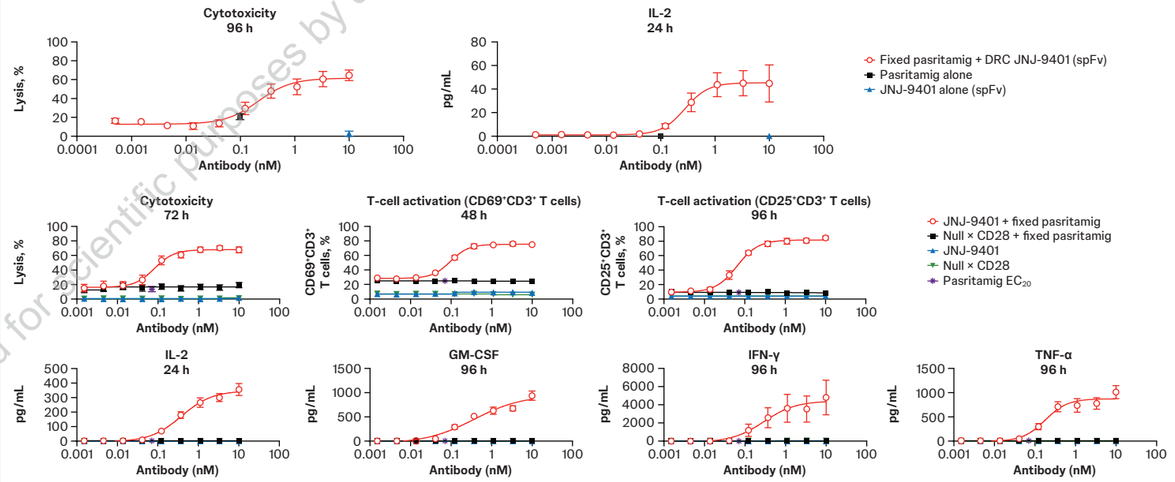
Figure 2: JNJ-9401 binds to PSMA on tumor cells and CD28 on Pan T cells



GeoMean, geometric mean; PSMA, prostate-specific membrane antigen.

- When administered alone, JNJ-9401 did not induce T-cell–dependent cytotoxicity or cytokine secretion in VCaP cells cocultured with human T cells (**Figure 3**)
- When combined with a suboptimal dose of pasritamig, JNJ-9401 substantially enhanced T-cell–mediated VCaP cytotoxicity and T-cell proliferation and induced cytokine secretion compared with pasritamig treatment alone (**Figure 3**)

Figure 3: Effect of JNJ-9401 in combination with a fixed concentration of pasritamig on cytotoxicity, T-cell activation, and cytokine release using PBMCs from healthy donors and VCaP ($PSMA^+$/$KLK2^+$) target cells at a 1:1 E:T ratio

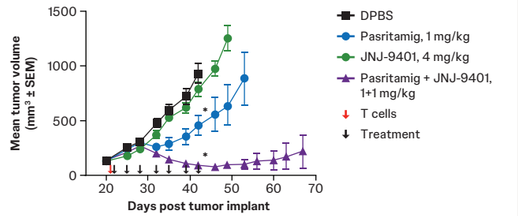


Studies were conducted with human donors' PBMCs (n=5).
The concentration of pasritamig was fixed at the EC_{20} (0.08 nM). Means (± SEM) are graphed.
DRC, dose response curve; EC_{20}, effective concentration 20%; E:T, effector to target; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; KLK2, human kallikrein 2; PBMC, peripheral blood mononuclear cell; PSMA, prostate-specific membrane antigen; SEM, standard error of the mean; spFv, single-chain variable fragment; TNF, tumor necrosis factor.

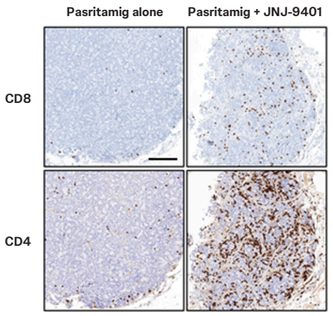
- In vivo, JNJ-9401 in combination with a suboptimal dose of pasritamig demonstrated substantially inhibited tumor growth compared with pasritamig monotherapy, whereas JNJ-9401 monotherapy had no effect on VCaP tumor growth (**Figure 4A**)
- Increased intratumoral $CD4^+$ and $CD8^+$ T cells were observed with JNJ-9401 in combination with pasritamig compared with pasritamig treatment alone (**Figure 4B**)

Figure 4: JNJ-9401 enhances the antitumor activity of pasritamig at a suboptimal dose

A.



B.



DPBS, Dulbecco's phosphate-buffered saline; SEM, standard error of the mean.

- In cynomolgus monkeys, the following were observed:
  - JNJ-9401 was confirmed to not be pharmacologically active as a single agent
  - All doses of JNJ-9401 up to a maximum of 10 mg/kg were tolerated, with no JNJ-9401–related adverse effects
  - No off-target or nonspecific activity was observed for JNJ-9401
  - No JNJ-9401–related cytokine or immunophenotyping changes were observed

References

1. Subudhi SK, et al. *J Immunother Cancer*. 2026;14(2):e013905. **2.** Fontana E, et al. *Lancet Reg Health Eur*. 2026;64:101599. **3.** Graham LS, et al. Presented at: Society for Immunotherapy of Cancer (SITC) Annual Meeting; November 4–8, 2026; Phoenix, AZ, USA. Abstract #1175.

Prostate Cancer

Presented by CG Drake at the Society for Immunotherapy of Cancer (SITC) Annual Meeting; November 4–8, 2026; Phoenix, AZ, USA

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