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A Phase 1, First-in-Human, Open-Label, Multicenter, Trial-in-Progress of the Safety, Tolerability, and Preliminary Efficacy of JNJ-87189401 (PSMA-CD28 Bispecific Antibody) Combined with JNJ-78278343 (KLK2-CD3 Bispecific Antibody) for Advanced Prostate Cancer

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Current Status

The study is currently enrolling participants in Part 1 (dose escalation) across 5 sites in USA and France

Registration Information

This study is registered with ClinicalTrials.gov (Identifier: NCT06095089)

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Poster

https://www.congresshub.com/Oncology/ESMO2024/EarlyAssets/Stein

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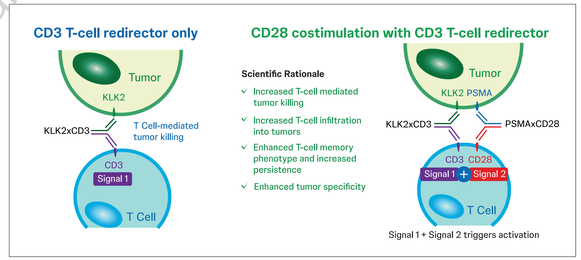
Introduction

- Prostate cancer typically progresses to metastatic castration-resistant prostate cancer (mCRPC) after 2 to 3 years of anti-androgen therapies, with a poor prognosis and mean survival of 16 to 18 months[1,2]
- Despite advances in molecular landscaping and precision medicine, treatments for mCRPC that offer durable responses with acceptable tolerability remain limited[3]
- Bi-specific T-cell engager antibodies (bsAb) are monoclonal antibody-based molecules designed to target epitopes on both T-cells and tumor cells to stimulate T-cell-mediated killing of tumor cells[4,5]
- JNJ-78278343 is a bsAb designed to target both kallikrein 2 (KLK2), a tumor antigen highly enriched in prostatic tissue and prostate cancer, and CD3 on T-cells
- JNJ-87189401 is a bsAb that targets both the prostate-specific membrane antigen (PSMA) on prostate tumor cells and CD28 on T-cells
- Activation of T-cells through the CD3 pathway (signal 1) is significantly enhanced by the activation of CD28, triggering a costimulatory pathway (signal 2) that leads to a more robust T-cell response compared to CD3-mediated activation alone[4]
- Thus, combining JNJ-78278343 (KLK2xCD3) with JNJ-87189401 (PSMAxCD28) is aimed at activating both the CD3 and CD28 pathways, thereby potentiating T-cell activation, increasing T-cell infiltration, T-cell-mediated tumor killing, and promoting a stronger T-cell memory phenotype (**Figure 1**)
- This dual activation is meant to result in a deeper and more durable clinical response compared to JNJ-78278343 monotherapy

Figure 1: Rationale for Combining JNJ-78278343 and JNJ-87189401



CD, cluster of differentiation; KLK2, human kallikrein 2; PSMA, prostate specific membrane antigen.

Objectives

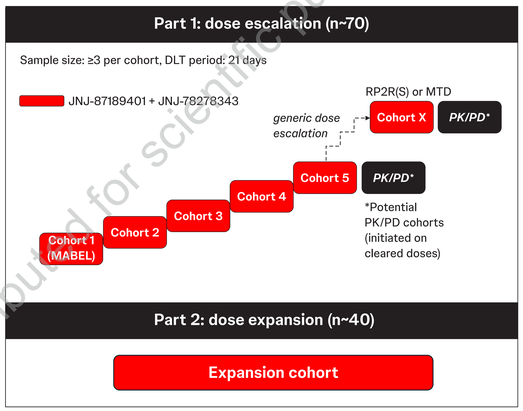
- To determine the recommended phase 2 regimen(s) (RP2R) of JNJ-87189401 in combination with JNJ-78278343 and to evaluate the safety at the RP2R(s) in participants with mCRPC
- Secondary objectives include assessment of preliminary efficacy (objective response rate, duration of response, prostate-specific antigen [PSA] response rate), pharmacokinetics, and immunogenicity

Methods

Study Design

- This is a first-in-human, open-label, multicenter study (NCT06095089) of the safety, tolerability, and preliminary antitumor activity of JNJ-87189401 in combination with JNJ-78278343 in mCRPC
- The ongoing study comprises a dose escalation part (Part 1) and a dose expansion part (Part 2) (**Figure 2**)
- During Part 1, participants will receive a dose of JNJ-78278343 in combination with sequentially escalated doses of JNJ-87189401 to select RP2R(s)
- Participants will receive the combination treatment at the RP2R in Part 2

Figure 2: Schematic Representation of Dosing Regimens



DLT, dose-limiting toxicity; MABEL, minimal anticipated biological effect level; MTD, maximum tolerated dose; PD, pharmacodynamic; PK, pharmacokinetic; RP2R, recommended phase 2 regimen.

Participants

Table 1: Key Inclusion and Exclusion Criteria

Inclusion criteria
• Age ≥18 years
• Histologically confirmed adenocarcinoma of the prostate • Adenocarcinoma with small cell or neuroendocrine features is permitted
• Measurable or evaluable mCRPC per PCWG3 criteria; all participants must have a serum PSA ≥2 ng/mL at screening
• ECOG performance status of 0 or 1
• Prior orchiectomy or medical castration – Participants who have not undergone orchiectomy, must be receiving ongoing androgen deprivation therapy with a GnRH analog (agonist or antagonist), prior to the first dose of study drug and must continue this therapy throughout the treatment phase
Exclusion criteria
• Active autoimmune disease within the 12 months prior to signing consent that requires systemic immunosuppressive medications (eg, chronic corticosteroids, methotrexate, tacrolimus)
• Any of the following within 6 months prior to informed consent - Myocardial infarction - Severe or unstable angina - Clinically significant ventricular arrhythmias - Congestive heart failure (NYHA class II to IV) - Transient ischemic attack - Cerebrovascular accident

ECOG, Eastern Cooperative Oncology Group; GnRH, gonadotropin releasing hormone; mCRPC, metastatic castration-resistant prostate cancer; NYHA, New York Heart Association; PCWG3, Prostate Cancer Working Group 3; PSA, prostate specific antigen.

Study Outcomes

Table 2: Primary Outcomes

Outcome	Description	Time frame
Part 1: number of participants with DLTs	Any toxicity meeting DLT criteria: high grade non-hematologic toxicity or hematologic toxicity	Up to 21 days after first combination dose of study drugs
Part 1 and Part 2: number of participants with AEs by severity	Severity will be graded according to the NCI-CTCAE version 5.0 with the exception of CRS and immune effector cell-associated neurotoxicity syndrome events, which will be graded by ASTCT guidelines	3 years 7 months

AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; DLT, dose-limiting toxicity; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events

Table 3: Secondary Outcomes

Outcome	Description	Time frame
Pharmacokinetics	Serum concentration of JNJ-87189401 and JNJ-78278343	Up to 3 years 7 months
Immunogenicity	Number of participants with antibodies to JNJ-87189401 and JNJ-78278343	
Objective response rate	Proportion of participants who have a confirmed PR or CR according to RECIST version 1.1 without evidence of bone progression according to PCWG3	
PSA response rate	The percentage of participants with a confirmed decline of PSA of ≥50% from baseline	
Duration of response	For participants who achieved response (PR or CR), the time between the date of initial documentation of response (PR or better) to the date of first documented evidence of progressive disease, as defined in the PCWG3, or death due to any cause, whichever occurs first	

CR, complete response; PCWG3, Prostate Cancer Working Group 3; PR, partial response; PSA, prostate specific antigen; RECIST, response evaluation criteria in solid tumors.

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Prostate Cancer