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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)

K. Autio[1], M. Schweizer[2], K.M. Shotts[3], R. Chaudhary[3], M. Brady[4], S. Casanova[4], P. Raciti[5], M.N. Stein[6], C. Baldini[7]

[1] Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, United States of America, [2] Fred Hutchinson Cancer Center, University of Washington, Seattle, United States of America, [3] Department of Oncology Translational Research, Johnson & Johnson Innovative Medicine, Springhouse, United States of America, [4] Department of Oncology Discovery, Johnson & Johnson Innovative Medicine, Springhouse, United States of America, [5] Department of Molecular Pathology, Johnson & Johnson Innovative Medicine, Springhouse, United States of America, [6] Department of Oncology, Columbia University, New York, United States of America[7] Drug Development Department, Institut Gustave Roussy, Villejuif, France

Background

Pasritamig is a first-in-class bispecific T cell engager that binds CD3 and kallikrein 2 (KLK2), a protein highly and specifically expressed in prostate cancer. Pasritamig showed low rates of cytokine release syndrome and promising efficacy in a FIH trial in mCRPC (NCT04898634). Translational analyses were performed to confirm the mechanism of action and support recommended phase 2 dose (RP2D) selection.

Methods

Patients (pts) received pasritamig (N=178) at varying step up doses and escalating target doses of 0.5–2000 mg subcutaneously (SC) weekly (QW) or every 3 wks (Q3W) or 150–900 mg intravenously (IV) Q3W or every 6 wks (Q6W). Archival/fresh and 6–8 wk post treatment biopsies (total N=45) were analyzed for KLK2 expression, immune infiltrate and functionality. Peripheral blood mononuclear cells (PBMCs) from 34 pts were collected 24–72 h after first target dose, frequently during the first 4 cycles, then every 3 mo up to 1 y on treatment; samples were analyzed from pts with/without PSA50 response who were dosed at 800 mg SC vs 300 mg IV Q3W or Q6W. Immunophenotypes associated with activation-induced cell death (AICD) or T-cell exhaustion were analyzed by flow cytometry and machine learning.

Results

Most archival (30/31), fresh baseline (3/4), and post treatment (8/10) tumor biopsies showed high KLK2 expression with evidence of CD8 T cell infiltration in 5 of 7 post treatment samples. Compared with QW or Q3W cohorts, pasritamig dosed at Q6W IV maintained a reprogrammable progenitor CD8 T cell population with lower expression of the apoptotic markers activated caspase-3 and γH2AX in PBMCs (n=186), suggestive of less AICD and less terminal T cell exhaustion and correlating with better clinical efficacy. Among subsets identified by unsupervised analyses, reprogrammable progenitor T cells were positively associated with PSA50 response in the 34 pts tested, regardless of dose.

Conclusions

Biomarker analyses of peripheral and tumor-infiltrating T cells support the proposed mechanism of action of pasritamig and recommended RP2D. Pts with a higher percentage of reprogrammable progenitor T cells were more likely to have a PSA50 response.

Clinical trial identification

ClinicalTrials.gov identifier: NCT04898634.

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