Translational analyses of mechanism of action and associations with response or resistance in the first-in-human trial of pasritamig in metastatic castration-resistant prostate cancer

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Key Takeaways

- Pasritamig induces rapid and robust margination to the tumor within 24 hours and T-cell activation by 48 hours after the first target dose in patients with metastatic castration-resistant prostate cancer (mCRPC)
- Soluble kallikrein 2 (sKLK2) and prostate-specific antigen (PSA) levels are highly correlated
- Response to pasritamig was observed in patients across a range of baseline serum sKLK2 and PSA levels
- Ongoing translational analyses on mechanisms of resistance may inform novel therapeutic combinations

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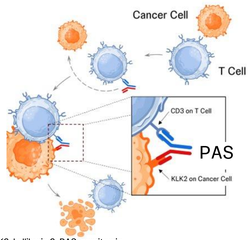
Acknowledgments

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Introduction

- KLK2, also known as hK2, but hereafter referred to as KLK2, is a secreted and membrane-expressed protein that is highly selectively expressed in prostate adenocarcinoma, both on the cell membrane and in soluble forms[1]
  - sKLK2and PSA concentrations in the serum correlate with prostate cancer[2]; understanding if membrane-associated KLK2 correlates with sKLK2 or serum PSA remains an important data gap
- The first-in-human (FIH) trial in mCRPC (NCT04898634) with pasritamig, a first-in-class KLK2 x CD3 T-cell engager (**Figure 1**), showed promising clinical efficacy with every-6-week outpatient dosing and a manageable safety profile[3]
  - In the previously published Global cohort (n=33), the median radiographic progression-free survival (PFS) was ~7.9 months with <10% cytokine release syndrome (all grade 1; fever only)[3]
  - This translational analysis includes additional participants from the Asia-Pacific (APAC) cohort

Figure 1. Pasritamig simultaneously binds KLK2 (encoded by *KLK2*) on prostate cancer cells and CD3 receptor complexes on T cells, leading to T-cell activation and subsequent lysis of cancer cells.



KLK2, kallikrein 2; PAS, pasritamig.

Objective

- To deepen our understanding of the novel mechanism of action of pasritamig and provide hypothesis-generating data for response and resistance mechanisms

Methods

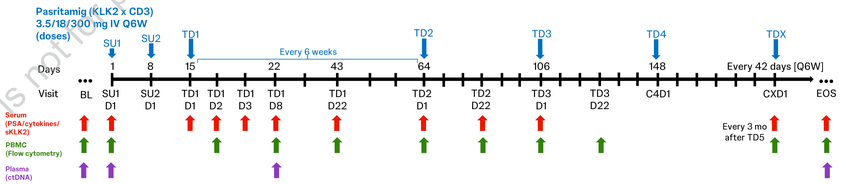
Study design

- Enrolled patients received the recommended phase 2 dose of pasritamig (3.5-mg step-up dose [SU] 1, 18-mg SU2, and 300-mg target dose [TD] intravenously every 6 weeks) (**Figure 2**)
- Plasma, serum, and peripheral blood mononuclear cell samples were collected at baseline (within 30 days before first treatment), while on treatment, and at end of study (occurs at disease progression or end of treatment)
  - Plasma was assessed for circulating tumor DNA (ctDNA) fraction by methylation assay
  - Serum samples were analyzed for PSA, sKLK2, and cytokines
  - Peripheral blood mononuclear cell samples were analyzed using flow cytometry

Figure 2. Study design and sampling.

Key Eligibility Criteria

- Confirmed adenocarcinoma of the prostate, which has spread to other body parts
- Measurable or evaluable disease
- ECOG performance status of 0 or 1
- Prior orchiectomy or medical castration; or must be receiving ongoing ADT with a gonadotropin-releasing hormone analogue
- Toxicity related to prior anticancer therapy must have adequately recovered
- No other serious underlying medical conditions or issues



The 3 dots indicate time points that are within 30 days of treatment. X indicates cycles past cycle 4 up until EOS.
ADT, androgen deprivation therapy; BL, baseline; C, treatment cycle; ctDNA, circulating tumor DNA; D, treatment day; ECOG, Eastern Cooperative Oncology Group; EOS, end of study; IV, intravenously; PBMC, peripheral blood mononuclear cell; PSA, prostate specific antigen; Q6W, every 6 weeks; sKLK2, soluble kallikrein 2; SU, step-up dose; TD, target dose.

Endpoints and assessments

- PSA50 responders were those with a confirmed (2 consecutive measurements 3 weeks apart) decline of ≥50% in PSA
- All analyses were conducted in R, version 4.5.1, within the RStudio environment

Results

Baseline demographics

- In total, 55 patients with mCRPC were enrolled in the Global (ex-APAC) and APAC (Japan and China) cohorts and received pasritamig at the recommended phase 2 dose (**Table**)
  - Sites of metastases consisted of M1b (bone only; n=31), M1a/b (lymph node ± bone; n=12), and M1c (visceral; n=12)

Table. Baseline Demographics and Clinical Characteristics

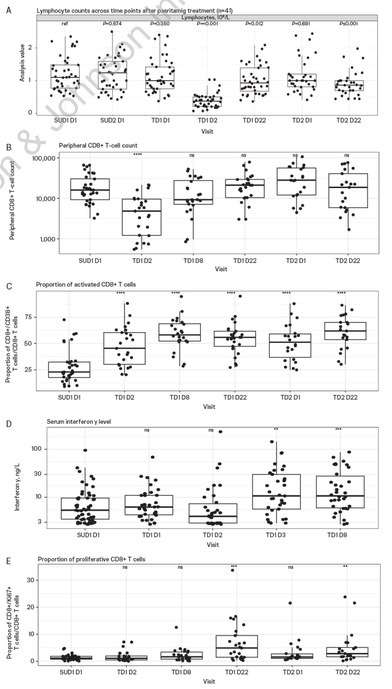
	N=55
Prior LOT	
Taxane	45 (81.8)
ARPI	55 (100.0)
RLT	38 (69.1)
PARP	9 (16.4)
Lines of prior systemic therapy, median (range)	4 (1-8)
Site of metastasis	
M1b (bone only)	31 (56.4)
M1a/b (lymph node ± bone)	12 (21.8)
M1c (visceral)	12 (21.8)
Geographic region	
APAC	22 (40)
Global	33 (60)
Baseline PSA	
Mean (SD)	262.3 (467.9)
Median (range)	85.50 (1.5-2117.6)

Values are the n (%) unless otherwise indicated. Clinical data cut: April 24, 2026. APAC, Asia-Pacific; ARPI, androgen receptor pathway inhibitor; LOT, line of therapy; PARP, poly (ADP-ribose) polymerase inhibitor; PSA, prostate-specific antigen; RLT, radioligand therapy; SD, standard deviation.

Pasritamig monotherapy induces rapid T-cell margination, activation, and cytokine secretion

- Following treatment, peripheral blood lymphocyte and CD8+ T cell counts decreased significantly by 24 hours after TD1 ($P \leq 0.001$), suggesting margination to the tumor (**Figure 3A and 3B**)
- CD8 T-cell activation was observed by 24-48 hours after TD1, with CD8+ T-cell proliferation, assessed by CD38+ expression, T-cell and proinflammatory cytokine (interferon γ) increases (**Figure 3C and 3D**)
- CD8+ T-cell proliferation, assessed by Ki67 expression, increased following treatment (**Figure 3E**)

Figure 3. (**A**) Peripheral blood lymphocyte counts and (**B**) CD8+ T-cell counts decreased significantly by 24 hours after TD1, consistent with margination to the tumor. (**C**) The proportion of CD38+ T cells increased at 24-48 hours after TD1 and were sustained through subsequent dosing cycles. (**D**) The proinflammatory cytokine interferon γ increased following treatment. (**E**) CD8+ T-cell proliferation, assessed by Ki67 expression, increased following treatment.

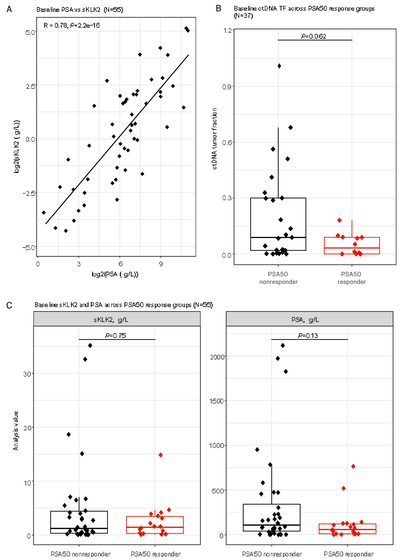


ANOVA and paired Wilcoxon tests were used for statistical analyses. D, treatment day; SU, step-up dose; TD, target dose.

Baseline sKLK2, PSA, and ctDNA and PSA50 response

- Serum sKLK2 and PSA levels were highly correlated (R=0.78) at baseline (**Figure 4A**)
- 34.5% of patients (19/55) had a confirmed PSA50 response
  - Baseline ctDNA tumor fraction was not significantly different between PSA50 response groups (**Figure 4B**)
  - PSA50 response to pasritamig treatment occurred in patients across a range of sKLK2 and PSA levels measured at baseline (**Figure 4C**)

Figure 4. (**A**) Correlation of serum sKLK2 versus PSA at baseline. (**B**) Baseline ctDNA tumor fraction across PSA50 response groups. (**C**) Baseline sKLK2 and PSA across PSA50 response groups.

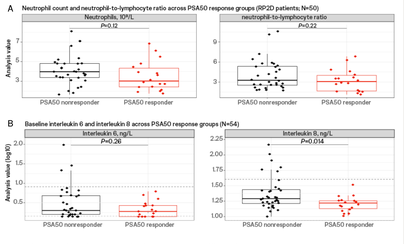


ctDNA, circulating tumor DNA; PSA, prostate specific antigen; PSA50, reduction of at least 50% in PSA; sKLK2, soluble kallikrein 2; TF, tumor fraction.

Baseline neutrophils, IL-6, and IL-8 and PSA50 response

- Patients who were PSA50 responders did not significantly differ in their baseline neutrophil counts or neutrophil-to-lymphocyte ratio (**Figure 5A**) compared with those who did not achieve a PSA50 response
  - Baseline levels of IL-6 were similar in both groups; baseline IL-8 was significantly higher in patients who did not achieve a PSA50 response (P=0.014) (**Figure 5B**)

Figure 5. Measurement of (**A**) neutrophils and (**B**) cytokines by PSA50 response group.

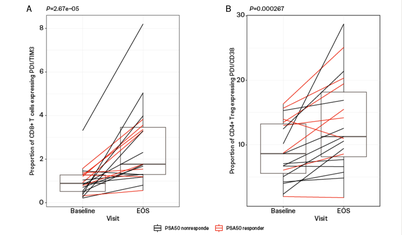


PSA50, reduction of at least 50% in prostate-specific antigen; RP2D, recommended phase 2 dose.

Acquired resistance: preliminary translational analyses

- At progression or end of study, increases in CD8+ T cells expressing PD1/TIM3 and CD4+ regulatory T cells expressing PD1/CD38 were observed in 89% and 84% of patients, respectively (**Figure 6**)

Figure 6. The relative proportions of (**A**) CD8+ T cells expressing PD1/TIM3 and (**B**) CD4+ regulatory T cells (Treg) expressing PD1/CD38 at baseline and end of study for PSA50 responders/nonresponders.



References

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Prostate Cancer

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