Longitudinal immune profiling in the PrTK05 trial of aglatimagene besadenovec plus valacyclovir with radiation therapy for localized intermediate-risk prostate cancer

Abstract #1172

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Background

Aglatimagene besadenovec (aglatimagene) is a replication-defective adenoviral vector (Ad5) encoding the herpes simplex virus thymidine kinase (HSV-TK) gene. Preclinical and clinical data show that aglatimagene, combined with the prodrug valacyclovir, induces local and systemic anti-tumor activity that is synergistic with radiation therapy.

Aglatimagene besadenovec mechanism of action

01 Intratumoral gene delivery
Aglatimagene is a replication-defective adenoviral vector delivering HSV-TK to tumor cells, minimizing systemic toxicity. It is administered with an oral prodrug for local activation

02 Prodrug activation
HSV-TK converts prodrug into cytotoxic metabolites that are incorporated into DNA in tumor cells undergoing proliferation or repair

03 Radiotherapy synergy
Radiation synergizes with aglatimagene through induction of DNA damage and activation of the tumor microenvironment (TME)

04 Anti-tumor immune priming
Tumor cell death releases antigens and danger signals, while viral particles promote activation of local and recruited immune cells

05 Local and systemic disease control
Tumor-specific T cells maintain local disease control and establish a new state of immunosurveillance

Clinical context: NCT01436968 (PrTK03) clinical trial results

NCT01436968 (PrTK03) is a pivotal placebo-controlled phase 3 trial of aglatimagene + valacyclovir with standard-of-care (SoC) EBRT ± short-course ADT in 745 patients with intermediate- to high-risk localized prostate cancer.

Hazard ratios numerically favored aglatimagene across multiple clinical outcomes compared to placebo in the intention-to-treat cohort

As of March 2026[1], with a median follow-up of 58.0 months (95% CI 56.6, 60.2), in exploratory, descriptive outcomes, the intention-to-treat cohort demonstrated:

- **Improved prostate cancer-specific DFS[1]:** HR=0.61 (95% CI 0.44-0.85; p=0.0031); corresponding to a 39% lower hazard for prostate cancer recurrence or death due to prostate cancer vs placebo + SoC
- **Improved time to biochemical failure[1]:** HR=0.72 (95% CI 0.40-1.31) vs placebo + SoC
- **Improved time to salvage anti-cancer therapy[1]:** HR=0.72 (95% CI 0.39-1.31) vs placebo + SoC
- **Improved time to metastasis[1]:** HR=0.58 (95% CI 0.21-1.59) vs placebo + SoC
- **Fewer patients with new metastatic disease[1]:** 8/496 (1.6%) of participants treated with aglatimagene + SoC versus 7/249 (2.8%) with placebo + SoC

Biomarker Study: NCT07332000 (PrTK05) clinical trial

Intermediate-risk prostate cancer (45 patients)

Open label non-randomized

Active
aglatimagene besadenovec + valacyclovir (3 courses) + EBRT (30 patients)

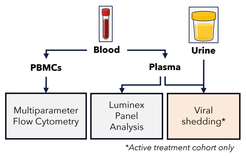
Control
EBRT only (15 patients)

Primary Endpoint
- Viral biodistribution and shedding

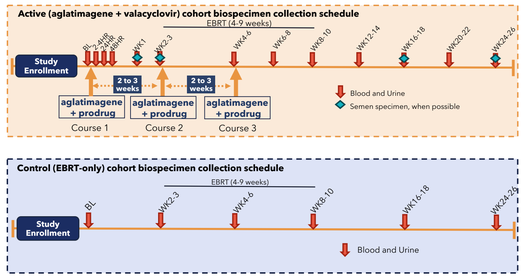
Secondary Endpoints
- Biomarkers of immune activation
- Safety

PrTK05 is an ongoing phase 2, open-label, non-randomized, multicenter biomarker study with an active cohort and an EBRT-only control cohort in intermediate-risk prostate cancer, designed to evaluate biomarker changes, vector biodistribution, and shedding in patients treated with aglatimagene + valacyclovir in addition to SoC EBRT± ADT.

Figure 1. Biospecimen collection schedules for blood and urine in PrTK05. Multiparameter flow cytometry was performed on peripheral blood mononuclear cells (PBMCs) isolated from the longitudinal blood collection timepoints and assessed for changes in immune cell subsets indicative of immune activation. Plasma was also isolated from blood samples for proteomic analysis of soluble analytes via bead-based multiplex immunoassay (Luminex) panels. Viral shedding analysis was performed on plasma and urine samples.

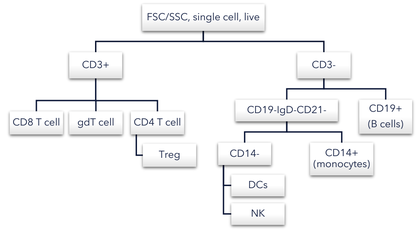


*Active treatment cohort only



Multiparameter flow cytometry gating strategy

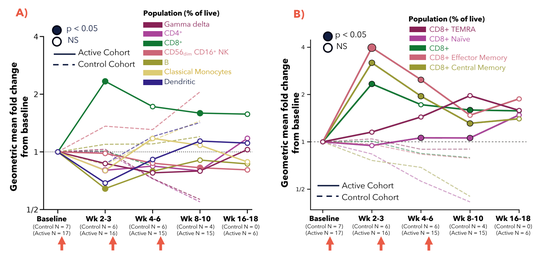
Figure 2. Flow cytometry gating schema. Gating strategy illustrates the general gating strategy used for identification of major PBMC immune cell populations. FSC: Forward Scatter; SSC: Side Scatter. Flow cytometry was used to characterize longitudinal changes in circulating lymphocyte activation, proliferation, and phenotype. CD8 and CD4 compartments were assessed for memory status. All immune populations were further assessed for functional status.



Aglatimagene induces expansion, cytotoxic activation, and remodeling of the peripheral CD8⁺ T cell compartment

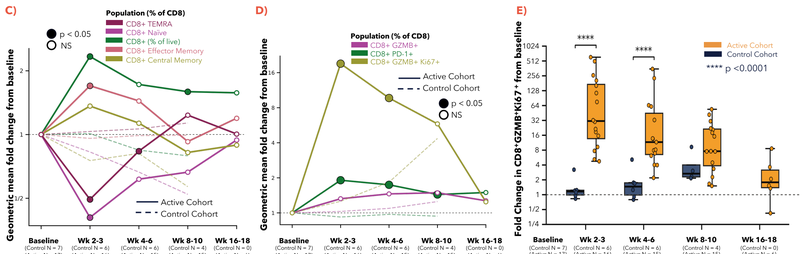
Figure 3. Remodeling of the peripheral CD8⁺ T cell compartment over time.

(A) Aglatimagene-induced early expansion and remodeling of the CD8 compartment. **(B)** Effector- and memory-associated populations remained above baseline at later evaluable visits in the treatment cohort; controlled comparisons were not possible at Week 16-18 because no control cohort samples were available for analysis.
Visits are shown on the x-axis, geometric fold change from baseline is shown on the y-axis. Statistical differences between arms are assessed via ANCOVA, p-values shown are unadjusted.



(C, D) Concurrently, aglatimagene treatment was associated with remodeling within the CD8 compartment (% of CD8) over time, consistent with early cytotoxic activation of T cells and persistence of effector and memory populations. Statistical differences between arms are assessed via ANCOVA, p-values shown are unadjusted.
(E) The proliferating cytotoxic CD8⁺GZMB⁺Ki67⁺ population, shown as % of live, increased approximately 16- to 64-fold from baseline across early post-treatment visits in the treatment cohort. Visit-specific between-cohort differences in fold change from baseline were assessed using Welch t-tests; p-values are nominal and unadjusted.

No comparable changes occurred within samples of patients from the Control cohort, with the exception of late shifts within the CD8 compartment of proliferative effector cells at Week 8-10. Arrows denote aglatimagene injections. Visits are shown on the x-axis, geometric fold change from baseline is shown on the y-axis of line plots in $\log_2$ scale, and fold change from baseline is shown on the y-axis of the boxplot. N=0 indicates no samples were available for analysis.



t-SNE plots demonstrating changes in T cell populations after aglatimagene treatment

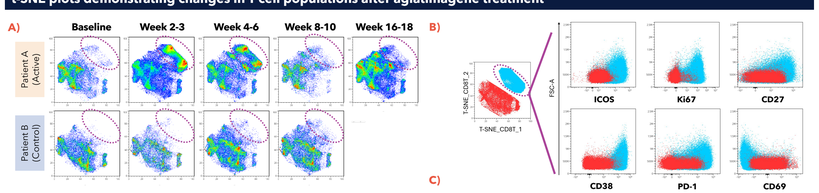


Figure 4. Representative t-SNE profiles identify an expanded CD8⁺ population with an activated, proliferative phenotype after treatment.
(A) t-distributed stochastic neighbor embedding (t-SNE) projections of total CD8 T cells from representative patients in the active and control cohorts at baseline and post-treatment timepoints, showing changes in phenotypic distribution over time. **(B)** Comparison of the upper-right (blue) and lower-left (red) t-SNE populations. Corresponding plots show forward scatter area (FSC-A, y-axis) against the indicated markers (x-axis), retaining the same population colors. The blue population exhibits higher ICOS, Ki-67, CD27, CD38, and PD-1 expression and lower CD69 expression than the red population. **(C)** Summary of the upper-right population's CD38-high, ICOS-high, CD27-high, and CD69-low profile, consistent with activation and retained costimulatory features.

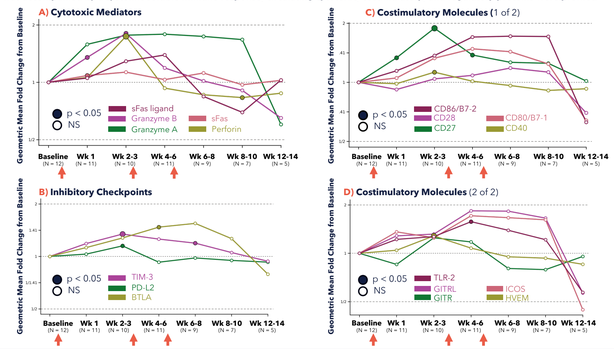
C)

Marker	Functional indicator	Upper-right population
CD38	Activation-associated; may also increase with chronic stimulation	High
ICOS	Inducible co-stimulation after activation	High
CD27	Costimulatory receptor associated with proliferative capacity and less terminal differentiation	High
CD69	Early activation and tissue-retention marker; low expression in this circulating population	Low

Treatment-associated changes in circulating proteins support sustained immune activation with coordinated counter-regulation

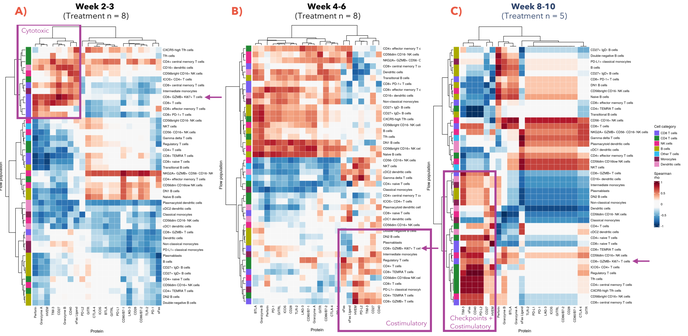
To determine whether cellular remodeling was accompanied by a systemic soluble immune response, circulating cytotoxic, costimulatory, and regulatory proteins were profiled longitudinally.

Figure 5. Aglatimagene treatment induces coordinated changes in circulating immune effector and regulatory proteins. Longitudinal fold changes from baseline are shown for cytotoxic mediators **(A)**, inhibitory checkpoint molecules **(B)**, and costimulatory molecules **(C, D)**, grouped by timepoint. Solid circles indicate significant change from baseline with unadjusted p < 0.05. Values shown are geometric mean fold change from baseline ($\log_2$-scaled axis); arrows indicate treatment injections. Within-patient differences from baseline are tested via paired t-test. Sample sizes at each time point are shown below the x-axis. All samples are from active cohort participants only.



Aglatimagene induces coordinated immune reprogramming

Figure 6. Exploratory cross-platform correlations suggest coordinated immune-response patterns. Spearman correlations compare within-participant changes from baseline in circulating immune populations and soluble proteins at Weeks 2-3 (n=8), 4-6 (n=8), and 8-10 (n=5). Rows and columns were clustered separately using Ward linkage and Euclidean distance. The observed patterns are descriptive and hypothesis-generating; dendrograms are shown for each. Boxes highlight visually coherent correlation patterns associated with changes in CD8⁺GZMB⁺Ki67⁺ compartment.
(A) Change from baseline at Week 2-3.
(B) Change from baseline at Week 4-6.
(C) Change from baseline at Week 8-10.

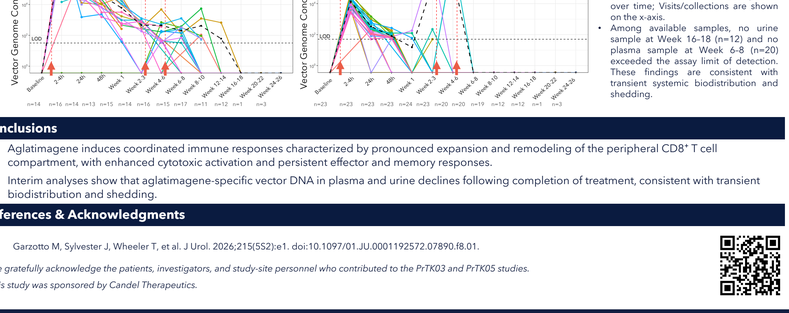


All flow measurements shown are % of parent except for parent populations (see Fig 3A), which are shown as % of live

Aglatimagene vector-DNA biodistribution and shedding signals largely resolve following completion of injection courses



Figure 7. (A) Detection of aglatimagene-specific viral shedding and biodistribution.
- Viral shedding is assessed via quantitative polymerase chain reaction (qPCR) on nucleic acids extracted from biospecimens.
- Junction-spanning primers which amplify a target sequence from inside the engineered insert that is expected to be present as one target copy per vector genome.
- TaqMan probe is labeled with a 5'FAM/3'NFQ-MGB probe and multiplexed with the internal control assay with a 5'Cy5/3'NFQ-MGB-labeled probe.
- The probe and reverse primer have no alignment with human adenoviral sequences.



Aglatimagene-specific vector DNA was transiently detectable in (B) urine and (C) plasma after injection and generally declined over time.
- Biodistribution is shown in Urine (left) and Plasma (right).
- Each line/color depicts vector genome concentration for an individual patient over time; Visits/collections are shown on the x-axis.
- Among available samples, no urine sample at Week 16-18 (n=12) and no plasma sample at Week 6-8 (n=20) exceeded the assay limit of detection. These findings are consistent with transient systemic biodistribution and shedding.

Conclusions

- Aglatimagene induces coordinated immune responses characterized by pronounced expansion and remodeling of the peripheral CD8⁺ T cell compartment, with enhanced cytotoxic activation and persistent effector and memory responses.
- Interim analyses show that aglatimagene-specific vector DNA in plasma and urine declines following completion of treatment, consistent with transient biodistribution and shedding.

References & Acknowledgments

1. Garzotto M, Sylvester J, Wheeler T, et al. J Urol. 2026;215(5S2):e1. doi:10.1097/01.JU.0001192572.07890.f8.01.

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