

Beyond PSA Depth: Longitudinal PSA Kinetics Reveals Treatment Modality-Specific Prognostic Windows in Metastatic Prostate Cancer

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Background:

Prostate-specific antigen (PSA) response is routinely used to assess treatment activity in metastatic prostate cancer, but conventional PSA response thresholds may not fully capture the timing and durability of treatment response. We evaluated whether temporal PSA kinetics from serial measurements provide additional information and whether the most informative assessment window differs by therapy.

Methods:

Using data from patients with metastatic hormone-sensitive prostate cancer (mHSPC) enrolled in TITAN (NCT02489318), we performed a 3-month landmark analysis of undetectable PSA (PSA ≤ 0.2 ng/mL) with apalutamide plus androgen deprivation therapy (ADT) or placebo plus ADT. Patients required evaluable PSA at the landmark and ≥ 3 serial PSA measurements within each prespecified 0–3-, 3–6-, and 6–12-month windows. PSA kinetics were quantified as patient-specific slopes (rate of PSA change over time) estimated using linear mixed-effects models. Within each window, k-means clustering of the estimated slopes defined three data-driven PSA kinetics groups. Associations with subsequent radiographic progression-free survival (rPFS) were summarized using hazard ratios (HRs) comparing the most unfavorable versus most favorable groups within each treatment arm. The same framework was applied to independent late-line metastatic castration-resistant prostate cancer (mCRPC) real-world cohorts from ConcertAI (N=781) receiving ¹⁷⁷Lu-PSMA-617 (Pluvicto), ARPI switch (enzalutamide, abiraterone or darolutamide), or chemotherapy (cabazitaxel or docetaxel). Model discrimination was assessed using the concordance index (C-index).

Results:

Among patients who remained free of radiographic progression through the 3-month landmark and had PSA measurements, 263/498 (52.8%) apalutamide-treated and 105/488 (21.5%) placebo-treated patients achieved undetectable PSA. PSA > 0.2 ng/mL was associated with worse rPFS in both the apalutamide arm (HR 2.65, 95% CI 1.83–3.85; $p < 3.13 \times 10^{-7}$) and placebo arm (HR 2.21, 95% CI 1.47–3.31; $p = 1.32 \times 10^{-4}$). Despite clear prognostic separation by PSA depth, substantial heterogeneity in subsequent PSA kinetics remained within depth-defined groups.

In apalutamide-treated patients, HRs comparing the most unfavorable versus most favorable slope-defined dynamic groups were 6.82, 7.81, and 12.88 across the 0–3-, 3–6-, and 6–12-month windows, respectively, with greatest separation at 6–12 months.

In an independent late-line mCRPC real-world cohort, corresponding HRs for Pluvicto were 3.73, 6.36, and 4.39 with the strongest separation at 3–6 months. ARPI switch (HRs 2.81, 2.97, and 3.25) and

chemotherapy (1.94, 2.78, and 2.67) showed relatively consistent separation across windows. Adding PSA kinetics to PSA50 improved discrimination over PSA50 alone, with Δ C-index values of +0.12 for apalutamide, +0.03 for Pluvicto, +0.06 for ARPI switch, and +0.05 for chemotherapy.

Conclusions:

Longitudinal PSA kinetics provides clinically relevant prognostic information beyond “best PSA response,” and reveal relevant differences in response dynamics between therapies. The optimal assessment window appears to be treatment specific, supporting a tailored approach to PSA monitoring in metastatic prostate cancer.

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Conflict of Interest Disclosures:

The authors are all employees and potential shareholders of Johnson & Johnson Innovative Medicine.