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Radiographic Progression Without PSA Progression (R-PD) in Advanced Prostate Cancer Patients

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Key Takeaways

- Patients with radiographic progression without PSA progression (R-PD) are not uncommon in advanced prostate cancer
- Poor prognosis of R-PD patients highlights the importance of monitoring them using imaging and warrants evaluation of new therapeutic approaches for them

Conclusions

- Approximately 10-12% of patients with advanced prostate cancer were R-PD in two randomized phase 3 trials of apalutamide-based regimes, with about equal proportion in each arm
- The addition of apalutamide to ADT prolonged the time to radiographic progression in R-PD patients
- Transcriptomic analysis of primary tumor from a subset of metastatic castration-sensitive patients showed both radiographic- and PSA progression-first patients at equally high risk
- R-PD patients had shorter overall survival compared with patients who had prior or concurrent PSA progression or no progression on the trial
- Our findings underscore the importance of monitoring advanced prostate cancer patients using imaging, independent of PSA dynamics

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Poster

Supplementary material

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Introduction

- Androgen receptor pathway inhibitors (ARPIs) are frequently combined with androgen deprivation therapy (ADT) to treat patients with castration-sensitive (CSPC) or castration-resistant (CRPC) prostate cancer
- In the TITAN and SPARTAN studies, apalutamide (APA) added to continuous androgen deprivation therapy (ADT) improved
  - Radiographic progression-free survival (rPFS), a co-primary endpoint of TITAN[1]
  - Metastasis-free survival, the primary endpoint of SPARTAN[2]
  - Overall survival (OS) and other long-term outcomes, despite crossover from placebo to APA after the studies were unblinded[3,4]
- Radiographic progression in the absence of prior or concurrent prostate-specific antigen (PSA) progression serves as a critical biomarker for identifying patients at risk of poor clinical outcomes[5]

Objective

- To characterize patients who experienced radiographic progression without prior or concurrent PSA progression (R-PD) and to compare them with patients who experienced PSA progression without prior radiographic progression (PSA-PD) while undergoing treatment with ADT or ARPI+ADT

Methods

- A retrospective analysis of two phase 3 trials comparing APA + ADT vs placebo (PBO) + ADT were conducted separately:
  - TITAN (NCT02489318): in 1052 patients with metastatic CSPC (mCSPC)[1]
  - SPARTAN (NCT01946204): in 1027 patients with non-metastatic CRPC (nmCRPC)[2]
- Based on their clinical outcomes in the TITAN and SPARTAN studies, patients were categorized as:
  - **R-PD:** radiographic progression without prior or concurrent PSA progression
  - **PSA-PD:** PSA progression prior or concurrently to radiographic progression
  - **NO-PD:** No PSA progression, radiographic progression, or death
  - **DEATH:** Death before any progression
- Distribution of type of progression, baseline clinical features, and site of radiographic progression in R-PD were assessed
- Time to radiographic progression in R-PD patients and time to PSA progression in PSA-PD patients were compared between treatment groups
- Biomarker analysis:
  - Decipher prostate test by Veracyte was performed on 198 (18.8%) TITAN and 233 (19.3%) SPARTAN primary tumors[6]
  - Gene expression signatures were explored. Classification models were built using Ridge regression to predict the response category
- Overall survival of R-PD, PSA-PD, and NO-PD patients were compared
- Time-to-event end points were analyzed by Kaplan-Meier method
- HR (95% CI) and p values were estimated using Cox proportional hazard models

Results

- TITAN study (N=1052): 130 (12.4%) patients were R-PD, 433 (41.2%) PSA-PD, 469 (44.6%) NO-PD, and 20 (1.9%) DEATH
- SPARTAN study (N=1207): 125 (10.4%) patients were R-PD, 548 (45.4%) PSA-PD, 526 (43.6%) NO-PD, and 8 (0.7%) DEATH

Table 1: Patient disposition by progression outcome

	TITAN (mCSPC)		SPARTAN (nmCRPC)	
	APA+ADT n=525	PBO+ADT n=527	APA+ADT n=806	PBO+ADT n=401
R-PD	64 (12.2%)	66 (12.5%)	95 (11.8%)	30 (7.5%)
PSA-PD	125 (23.8%)	308 (58.4%)	224 (27.8%)	324 (80.8%)
NO-PD	324 (61.7%)	145 (27.5%)	480 (59.6%)	46 (11.5%)
DEATH	12 (2.3%)	8 (1.5%)	7 (0.9%)	1 (0.2%)

APA+ADT, apalutamide + androgen deprivation therapy; DEATH, death before any progression; mCSPC, metastatic castration-sensitive prostate cancer; NO-PD, no PSA progression or radiographic progression or death; nmCRPC, non-metastatic castration-resistant prostate cancer; PBO+ADT, placebo + androgen deprivation therapy; PSA, prostate specific antigen; PSA-PD, PSA progression prior or concurrently to radiographic progression; R-PD, radiographic progression without prior or concurrent PSA progression.

Table 2: Baseline clinical characteristics (Apalutamide ITT population; TITAN and SPARTAN)

Baseline characteristics	TITAN (mCSPC) APA+ADT			
	R-PD (n=64)	PSA-PD (n=125)	NO-PD (n=324)	DEATH (n=12)
PSA (ng/mL), median (range)	87 (0.0; 993.4)	13.09 (0.1; 2256.0)	4.23 (0.0; 2682.0)	25.68 (2.6; 901.7)
ECOG PS score=1	28 (43.8%)	54 (43.2%)	110 (34.0%)	5 (41.7%)
Gleason score at initial diagnosis				
<8	19 (29.7%)	33 (26.4%)	117 (36.1%)	5 (41.7%)
≥8	45 (70.3%)	92 (73.6%)	207 (63.9%)	7 (58.3%)
Extent of disease at study entry				
Bone + only lymph node	22 (34.4%)	50 (40.0%)	88 (27.2%)	3 (25.0%)
Bone + other organ(s) excluding visceral	4 (6.3%)	9 (7.2%)	3 (0.9%)	1 (8.3%)
Bone + visceral and/or other organ(s)	13 (20.3%)	15 (12.0%)	25 (7.7%)	3 (25.0%)
Number of bone lesions at study entry				
>10	28 (43.8%)	80 (64.0%)	93 (28.7%)	6 (50.0%)
>5	35 (54.7%)	98 (78.4%)	145 (44.8%)	8 (66.7%)
High volume	49 (76.6%)	103 (82.4%)	163 (50.3%)	10 (83.3%)
	SPARTAN (nmCRPC) APA+ADT			
	R-PD (n=95)	PSA-PD (n=224)	NO-PD (n=480)	DEATH (n=7)
PSA (ng/mL), median (range)	8.6 (0.8; 75.7)	14.46 (0.3; 294.8)	5.7 (0.1; 111.9)	12.2 (4.7; 109.0)
ECOG PS score=1	29 (30.5%)	50 (22.3%)	102 (21.3%)	2 (28.6%)
Gleason score at initial diagnosis, n	92	216	471	5
<8	52 (56.5%)	114 (52.8%)	273 (58.0%)	4 (80.0%)
≥8	40 (43.5%)	102 (47.2%)	198 (42.0%)	1 (20.0%)

APA+ADT, apalutamide + androgen deprivation therapy; DEATH, death before any progression; ECOG PS, Eastern Cooperative Oncology Group Performance Status; mCSPC, metastatic castration-sensitive prostate cancer; NO-PD, no PSA progression, radiographic progression, or death; nmCRPC, non-metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen; PSA-PD, PSA progression prior or concurrently to radiographic progression; R-PD, radiographic progression without prior or concurrent PSA progression.
Please refer to Supplementary Table 1 for placebo group data.

Table 3: Sites of progression in R-PD patients

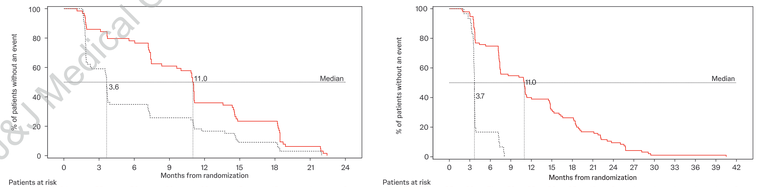
	TITAN (mCSPC)		SPARTAN (nmCRPC)	
	APA+ADT n=525	PBO+ADT n=527	APA+ADT n=806*	PBO+ADT n=401
Bone only	31 (5.9%)	35 (6.6%)	9 (1.1%)	3 (0.7%)
Non-bone	32 (6.1%)	31 (5.9%)	79 (9.8%)	27 (6.7%)
Both	1 (0.2%)	0	0	0

*Missing characterization for 7 (0.9%) R-PD patients in SPARTAN, APA+ADT. APA+ADT, apalutamide + androgen deprivation therapy; mCSPC, metastatic castration-sensitive prostate cancer; nmCRPC, non-metastatic castration-resistant prostate cancer; PBO+ADT, placebo + androgen deprivation therapy; R-PD, radiographic progression without prior or concurrent PSA progression.

Time to radiographic and PSA progression

- Compared with placebo, treatment with APA delayed the time to radiographic progression in R-PD patients (TITAN: HR, 0.51; 95% CI, 0.36–0.73, p=0.0003; SPARTAN: HR, 0.17; 95% CI, 0.1–0.28, p<0.0001) **(Figure 1)**
- Furthermore, treatment with APA delayed the time to PSA progression in PSA-PD patients (TITAN: HR, 0.61; 95% CI, 0.49–0.75; p<0.0001; SPARTAN: HR, 0.22; 95% CI, 0.18–0.27; p<0.0001) (data not shown)

Figure 1: Time to radiographic progression in R-PD patients

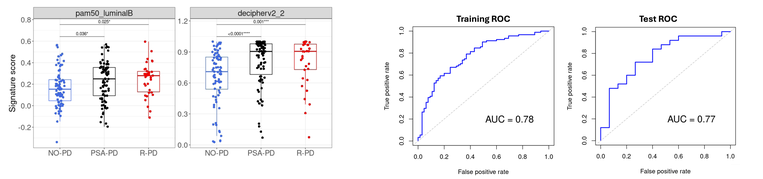


APA+ADT, apalutamide + androgen deprivation therapy; mCSPC, metastatic castration-sensitive prostate cancer; nmCRPC, non-metastatic castration-resistant prostate cancer; PBO+ADT, placebo+ androgen deprivation therapy; R-PD, radiographic progression without prior or concurrent PSA progression.

Biomarker analysis

- Increased luminal B lineage and decipher risk signatures were observed in R-PD and PSA-PD vs NO-PD patients for TITAN (n=196; **Figure 2A**); equivalent signature scores were observed in NO-PD, PSA-PD, and R-PD patients for SPARTAN (n=233; data not shown)
- A transcriptomic classification model achieved moderate discrimination between R-PD or PSA-PD vs NO-PD patients for TITAN, (n=196; **Figure 2B**), while no discrimination of R-PD alone was observed; poor discrimination was observed for SPARTAN (n=233)
- Additional biomarker analysis using genomic and proteomic data is underway

Figure 2: Gene expression signatures and patient classification for TITAN (mCSPC)

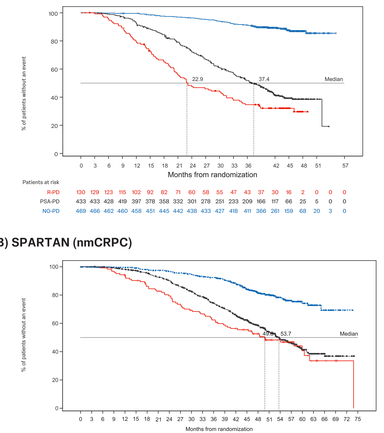


AUC, area under the curve; mCSPC, metastatic castration-sensitive prostate cancer; NO-PD, no PSA progression, radiographic progression, or death; PSA-PD, PSA progression prior or concurrently to radiographic progression; Ref, reference; ROC, receiver operating characteristic; R-PD, radiographic progression without prior or concurrent PSA progression. Note: n=2 patients from the TITAN study with Decipher test results were excluded due to death before any progression. **A.** Left plot shows luminal B and right decipher signature based scores. **B.** p-values in the signature plots were calculated using Wilcox test with multiple comparison correction by Holm method. Left ROC is on training data and right test data.

Overall survival

- R-PD patients had shorter OS compared to PSA-PD patients in both studies (median OS: R-PD vs PSA-PD: 22.9 months vs 37.4 months in the TITAN study; 49.8 months vs 53.7 months in the SPARTAN study) **(Figure 3)**

Figure 3: Overall survival by progression outcome



	TITAN (mCSPC)				SPARTAN (nmCRPC)			
	HR (95% CI)	P-value	Events	Median (95% CI), months	HR (95% CI)	P-value	Events	Median (95% CI), months
R-PD	1.56 (1.22–1.99)	0.0004	66.9% (87/130)	22.9 (20.2–30.9)	1.23 (0.94–1.62)	0.1289	52.8% (66/125)	49.8 (38.6–60.5)
PSA-PD	1.00 (Ref.)	-	56.4% (244/433)	37.4 (33.7–40.3)	1.00 (Ref.)	-	47.1% (258/548)	53.7 (50.3–57.8)
NO-PD	0.14 (0.11–0.19)	<0.0001	11.5% (54/469)	NE (NE–NE)	0.35 (0.27–0.44)	<0.0001	18.3% (96/526)	NE (NE–NE)

CI, confidence interval; HR, hazard ratio; NE, not estimable; mCSPC, metastatic castration-sensitive prostate cancer; nmCRPC, non-metastatic castration-resistant prostate cancer; NO-PD, no PSA progression, radiographic progression, or death; PSA-PD, PSA progression prior or concurrently to radiographic progression; Ref, reference; R-PD, radiographic progression without prior or concurrent PSA progression.

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Prostate Cancer

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Supplementary Table 1: Baseline clinical characteristics (Placebo ITT population; TITAN and SPARTAN)

Baseline characteristics	TITAN (mCSPC)			
	PBO+ADT			
	R-PD (n=66)	PSA-PD (n=308)	NO-PD (n=145)	DEATH (n=8)
PSA (ng/mL), median (range)	9.82 (0.0; 2228.5)	5.13 (0.0; 1882.0)	2.08 (0.0; 802.9)	32.94 (0.3; 1312.5)
ECOG PS score=1	23 (34.8%)	113 (36.7%)	40 (27.6%)	2 (25.0%)
Gleason score at initial diagnosis				
<8	25 (37.9%)	81 (26.3%)	60 (41.4%)	3 (37.5%)
≥8	41 (62.1%)	227 (73.7%)	85 (58.6%)	5 (62.5%)
Extent of disease at study entry				
Bone + only lymph node	21 (31.8%)	101 (32.8%)	43 (29.7%)	1 (12.5%)
Bone + other organ(s) excluding visceral	5 (7.6%)	11 (3.6%)	4 (2.8%)	0
Bone + visceral and/or other organ(s)	16 (24.2%)	42 (13.6%)	11 (7.6%)	3 (37.5%)
Number of bone lesions at study entry				
>10	35 (53.0%)	130 (42.2%)	28 (19.3%)	3 (37.5%)
>5	45 (68.2%)	182 (59.1%)	51 (35.2%)	4 (50.0%)
High volume	55 (83.3%)	206 (66.9%)	69 (47.6%)	5 (62.5%)
	SPARTAN (nmCRPC)			
	PBO+ADT			
	R-PD (n=30)	PSA-PD (n=324)	NO-PD (n=46)	DEATH (n=1)
PSA (ng/mL), median (range)	5.83 (1.1; 112.2)	8.66 (1.2; 291.8)	5.04 (1.5; 54.5)	28.68 (28.7; 28.7)
ECOG PS score=1	6 (20.0%)	76 (23.5%)	6 (13.3%)	1 (100%)
Gleason score at initial diagnosis, n	29	314	43	1
<8	14 (48.3%)	182 (58.0%)	22 (51.2%)	0
≥8	15 (51.7%)	132 (42.0%)	21 (48.8%)	1 (100%)

DEATH, death before any progression; ECOG PS, Eastern Cooperative Oncology Group Performance Status; mCSPC, metastatic castration sensitive prostate cancer; NO-PD, no PSA progression or radiographic progression or death; nmCRPC, non-metastatic castration resistant prostate cancer; PBO+ADT, placebo + androgen deprivation therapy; PSA, prostate specific antigen; PSA-PD, PSA progression prior or concurrently to radiographic progression; R-PD, radiographic progression without prior or concurrent PSA progression.