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A SPECIAL MEETING REVIEW EDITION

Highlights in Advanced Prostate Cancer From the 2021 American Society of Clinical Oncology Genitourinary Cancers Symposium

A Review of Selected Presentations From the All-Virtual Genitourinary Cancers Symposium • February 11-13, 2021

Special Reporting on:

- ^{177}Lu-PSMA-617 (LuPSMA) Versus Cabazitaxel in Metastatic Castration-Resistant Prostate Cancer Progressing After Docetaxel: Updated Results Including Progression-Free Survival and Patient-Reported Outcomes (TheraP ANZUP 1603)
- Final Results From ACIS, a Randomized, Placebo-Controlled Double-Blind Phase 3 Study of Apalutamide and Abiraterone Acetate Plus Prednisone (AAP) Versus AAP in Patients With Chemo-Naive Metastatic Castration-Resistant Prostate Cancer
- Biomarker Analysis From a Randomized Phase II Study of Olaparib With or Without Cediranib in Men With Metastatic Castration-Resistant Prostate Cancer
- KEYNOTE-365 Cohort B: Pembrolizumab Plus Docetaxel and Prednisone in Abiraterone or Enzalutamide–Pretreated Patients With Metastatic Castration-Resistant Prostate Cancer—New Data After an Additional 1 Year of Follow-Up
- CheckMate 9KD Arm B Final Analysis: Efficacy and Safety of Nivolumab Plus Docetaxel for Chemotherapy-Naive Metastatic Castration-Resistant Prostate Cancer
- Final Analysis Results From TITAN: A Phase III Study of Apalutamide Versus Placebo in Patients With Metastatic Castration-Sensitive Prostate Cancer Receiving Androgen Deprivation Therapy
- PI3K/AKT Pathway Biomarkers Analysis From the Phase III IPATential150 Trial of Ipatasertib Plus Abiraterone in Metastatic Castration-Resistant Prostate Cancer
- Genomic Landscape of Advanced Prostate Cancer in Racial Minority Populations: Real-World Experience in a Safety-Net Hospital Oncology Clinic
- Androgen Deprivation Therapy and Risk of SARS-CoV-2 Infection in Men With Prostate Cancer: A University of California Health System Registry Study

PLUS Meeting Abstract Summaries

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FOR YOUR PATIENTS WITH ADVANCED PROSTATE CANCER

WHY IS PRECISION MEDICINE COMPLICATED IN ADVANCED PROSTATE CANCER?

Precision medicine has traditionally relied on genotypic biomarkers[1,2]; however, the use of genotypic biomarkers in advanced prostate cancer is challenging because of the complexity and heterogeneity of the disease.[3-7]

Phenotypic biomarkers may simplify the use of precision medicine in advanced prostate cancer.[8-13]

Learn more at **www.PhenotypicPrecisionMedicine.com.**

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Advanced Accelerator Applications
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^{177}Lu-PSMA-617 (LuPSMA) Versus Cabazitaxel in Metastatic Castration-Resistant Prostate Cancer Progressing After Docetaxel: Updated Results Including Progression-Free Survival and Patient-Reported Outcomes (TheraP ANZUP 1603)

The radiolabeled small molecule ^{177}Lu-PSMA-617 targets prostate cancer cells that express the prostate-specific membrane antigen (PSMA) on their surface.[1] Once bound to PSMA, the agent delivers beta radiation, allowing for highly specific tumor-cell targeting with the potential to limit effects on normal cells. In early nonrandomized studies of patients with metastatic castration-resistant prostate cancer (mCRPC), ^{177}Lu-PSMA-617 showed initial evidence of clinical activity, as well as a favorable safety profile.[2-5] In a single-arm, phase 2 trial of ^{177}Lu-PSMA-617 in 50 men with mCRPC that had progressed following docetaxel and anti-androgen therapy, 64% of patients achieved a decrease of 50% or more in the prostate-specific antigen (PSA) level.[6,7] Based on these encouraging early clinical data, the randomized phase 2 TheraP trial was conducted to compare the activity and safety of ^{177}Lu-PSMA-617 with cabazitaxel in men for whom cabazitaxel was considered the next appropriate standard treatment. Hofman and colleagues presented updated findings of TheraP at the 2021 American Society of Clinical Oncology Genitourinary Cancers symposium.[8] Results were subsequently published in *The Lancet*.[9]

Key eligibility criteria for enrollment in the TheraP trial included mCRPC that had previously been treated with docetaxel and had progressed (as defined by a rising PSA level and PSA ≥20 ng/mL). Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. All patients underwent gallium-68 [^{68}Ga]Ga-PSMA-11 and 2-fluorine-18 [^{18}F] fluoro-2-deoxy-D-glucose (FDG) positron emission tomography/computed tomography (CT) scans, which were centrally reviewed. All patients had a maximum standardized uptake value exceeding 20 at any site of disease and measurable sites with a maximum standardized uptake value exceeding 10. Patients had no sites of metastatic disease with discordant FDG-positive and PSMA-negative findings.[8,9]

The trial randomly assigned 200 patients in a 1-to-1 ratio to treatment with either ^{177}Lu-PSMA-617 (administered every 6 weeks for up to 6 cycles) or cabazitaxel (20 mg/m^2 every 3 weeks for up to 10 cycles). In the ^{177}Lu-PSMA-617 arm, the starting dose of radioactivity was 8.5 GBq; the dose was decreased by 0.5 GBq per cycle. Planar and single-photon emission CT (SPECT-CT) was performed 24 hours after each administration of

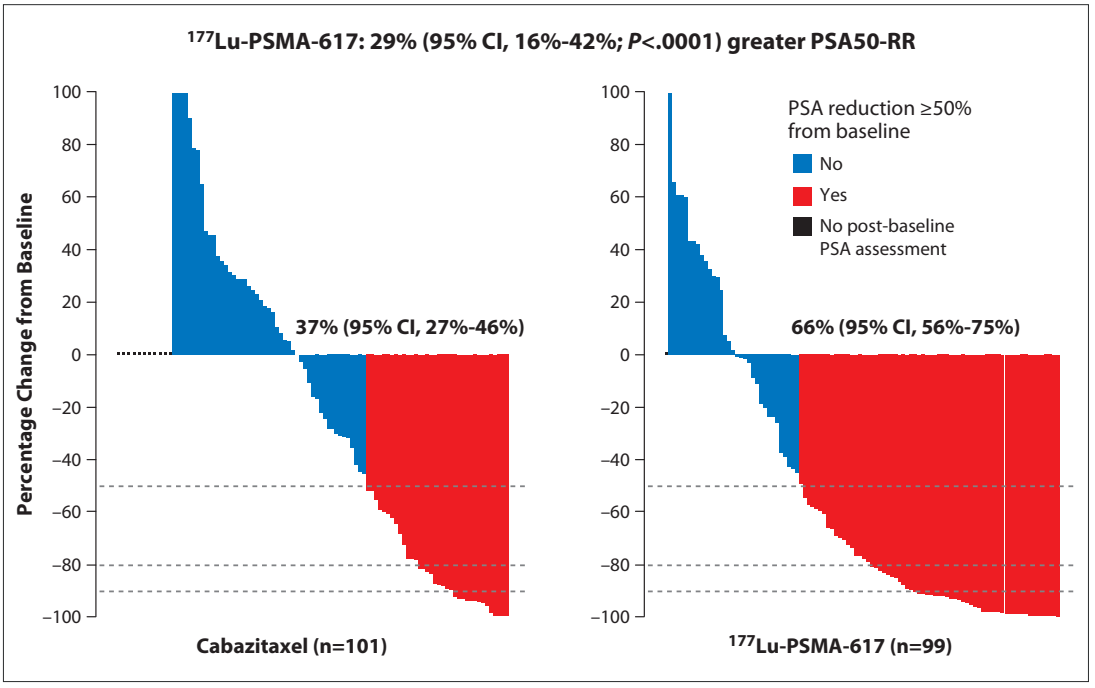

Figure 1. PSA response in the TheraP trial. PSA, prostate-specific antigen; PSA50-RR, 50% PSA response rate. Adapted from Hofman M et al. ASCO GU abstract 6. *J Clin Oncol.* 2021;39(6 suppl).[8]

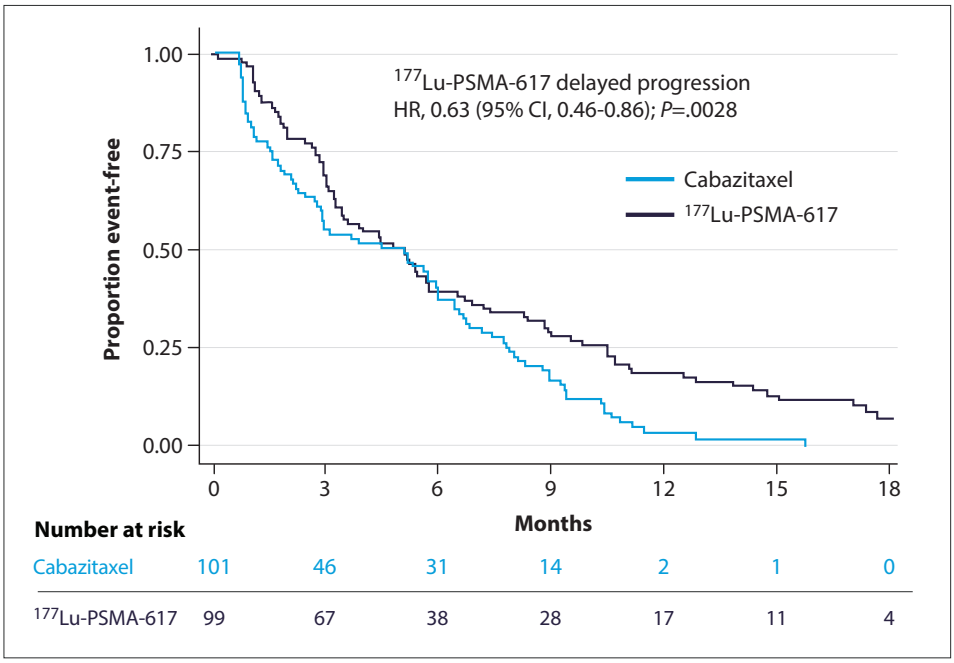

Figure 2. Radiographic or PSA PFS in the TheraP trial. HR; hazard ratio; PSA, prostate-specific antigen. Adapted from Hofman M et al. ASCO GU abstract 6. *J Clin Oncol.* 2021;39(6 suppl).[8]

^{177}Lu-PSMA-617 to evaluate the drug's retention in target and off-target tissues. Treatment was suspended if the SPECT-CT showed no or minimal PSMA uptake after central review (n=7). At the time of randomization, patients were stratified by disease burden (>20 sites vs ≤20 sites), prior treatment with enzalutamide or abiraterone, and study site.[8,9]

The median age of patients was 72 years in both arms. The patients had a significant disease burden, with involvement at more than 20 sites in 77% of the ^{177}Lu-PSMA-617 arm and 79% of the cabazitaxel arm. The median PSA level at baseline was 110 ng/mL and 94 ng/mL, respectively.[8,9]

The primary endpoint of the TheraP trial, the PSA response rate (PSA50-RR), was defined as the proportion of participants with a PSA reduction of 50% or more from baseline. Secondary endpoints included adverse events (AEs), progression-free survival (PFS; radiographic, PSA, and overall), objective response rate (ORR), patient-reported outcomes, and overall survival (OS).[8,9]

The PSA50-RR was 66% (95% CI, 56%-75%) in the ^{177}Lu-PSMA-617 arm vs 37% (95% CI, 27%-46%) in the cabazitaxel arm. This between-group difference of 29% was statistically significant (95% CI, 16%-42%; *P*<.0001). The waterfall plots of PSA50-RR are shown in Figure 1.[8,9]

The median PFS (radiographic and PSA) was 5.1 months in both arms. The effect of the treatments on PFS did not remain consistent over time, with a greater benefit observed for ^{177}Lu-PSMA-617 emerging after 6 months (hazard ratio [HR], 0.63; 95% CI, 0.46-0.86; *P*=.0028; Figure 2). The 12-month PFS rate was 19% (95% CI, 12%-27%) with ^{177}Lu-PSMA-617 and 3% (95% CI, 1%-9%) with cabazitaxel.[8,9]

ORR, another secondary endpoint, was 49% (95% CI, 33%-65%) in the ^{177}Lu-PSMA-617 arm vs 24% (95% CI, 11%-38%) in the cabazitaxel arm. Data for OS remain immature, with 90 deaths reported in all. The planned OS analysis will take place after 170 events have occurred.[8,9]

Overall, 33% of patients in the ^{177}Lu-PSMA-617 arm and 54% of patients in the cabazitaxel arm experienced a grade 3 or 4 AE. Grade 3/4 thrombocytopenia was more common with ^{177}Lu-PSMA-617 compared with cabazitaxel (11% vs 0%). Grade 3/4 neutropenia (with or without fever) was less common (4% vs 13%). Selected grade 1/2 nonhematologic toxicities that were more common with ^{177}Lu-PSMA-617 vs cabazitaxel included dry mouth (60% vs 21%) and dry eye (30% vs 4%). AEs that occurred at a higher rate with cabazitaxel included diarrhea (18% vs 52%), dysgeusia (12% vs 27%), and sensory or motor neuropathy (10% vs 26%). An analysis of patient-reported outcomes found several that were significantly improved with ^{177}Lu-PSMA-617 vs cabazitaxel, including diarrhea (*P*<.001), insomnia (*P*<.05), fatigue (*P*<.05), and social functioning (*P*<.05).[8,9]

^{177}Lu-PSMA-617 is currently under evaluation in the randomized phase 3 VISION trial, in which it is being compared with the best standard of care (or best supportive care) as determined by the treating physician.[10]

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Final Results From ACIS, a Randomized, Placebo-Controlled Double-Blind Phase 3 Study of Apalutamide and Abiraterone Acetate Plus Prednisone (AAP) Versus AAP in Patients With Chemo-Naive Metastatic Castration-Resistant Prostate Cancer

Androgen receptor resistance is a major limitation in the management of patients with mCRPC. Several agents are now available to inhibit the androgen pathway, representing distinct modes of action. The ACIS study, presented by Rathkopf and colleagues, investigated the potential benefit of combining 2 strategies, apalutamide and abiraterone acetate plus prednisone (AAP), for the first-line treatment of mCRPC.[1] Each of these agents engages in androgen annihilation via inhibition of different pathways: apalutamide inhibits the androgen receptor, whereas AAP acts via ligand suppression.[2] In a phase 1 trial, this combination was tolerated

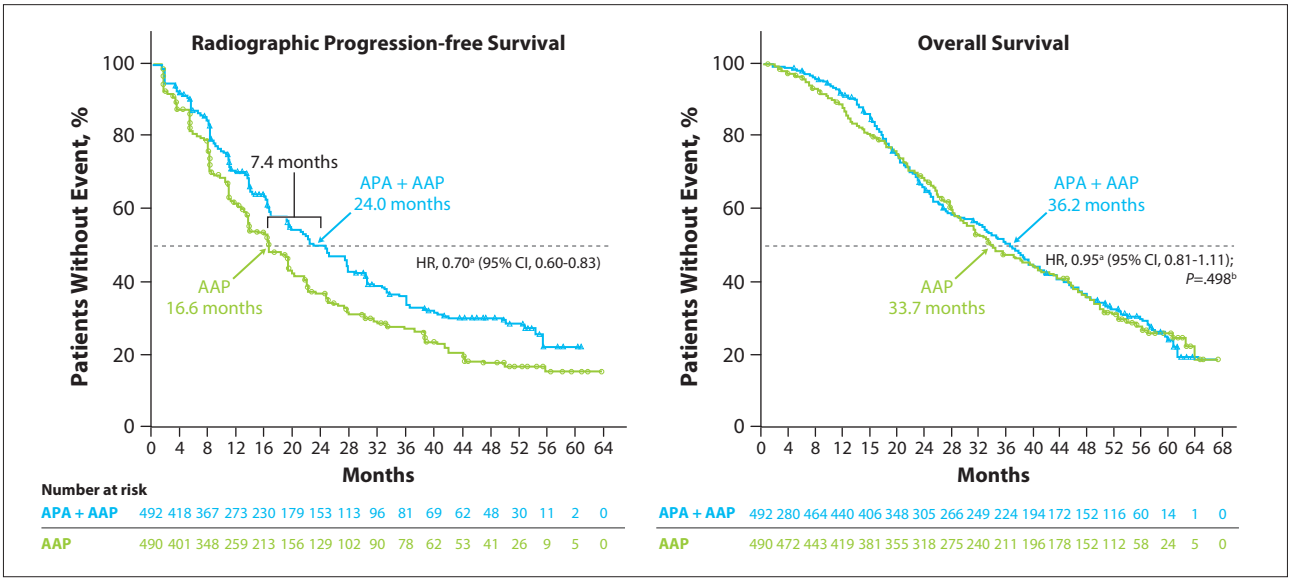

Figure 3. rPFS (left) and OS (right) in patients treated with APA plus AAP vs AAP alone in the ACIS trial. AAP, abiraterone acetate plus prednisone; APA, apalutamide; HR, hazard ratio; OS, overall survival, rPFS, radiographic progression-free survival. [a]Stratified proportional hazards model; [b]Stratified log-rank test. Adapted from Rathkopf DE et al. ASCO GU abstract 9. *J Clin Oncol*. 2021;39(6 suppl).[1]

and showed evidence of antitumor activity in patients with mCRPC, including those with disease progression during treatment with androgen receptor signaling inhibitors.[3]

ACIS was a double-blind, placebo-controlled, randomized phase 3 trial that compared the combination of apalutamide plus AAP vs placebo plus AAP in 982 patients with mCRPC that had progressed during androgen deprivation therapy (ADT). All patients had an ECOG performance status (PS) of 0 or 1, and a pain score (Brief Pain Inventory–Short Form) of 3 or less. Prior treatment with chemotherapy or an androgen signaling inhibitor was not permitted for castration-resistant disease.[1]

A total of 982 patients were randomly assigned in a 1-to-1 ratio to treatment with the combination of apalutamide plus AAP or placebo plus AAP. Treatment was continued until disease progression, withdrawal of consent, or unacceptable toxicity. At the time of randomization, patients were stratified according to the presence or absence of visceral metastases, ECOG PS (0 or 1), and geographic region (North America, Europe/United Kingdom, or rest of the world). The median age in both arms was 71 years. Approximately 53% of patients in both arms had a Gleason score greater than 7 at diagnosis. The median PSA at baseline was 32.3 ng/mL in the apalutamide-plus-AAP arm and 31.2 ng/mL in the AAP arm. The primary site of disease spread in both arms was bone (83.2% in the apalutamide-plus-AAP arm vs 86.9% in the AAP arm), followed by lymph nodes (48.2% vs 47.2%), soft tissue (12.3% vs 13.6%), and visceral tissue (15.2% vs 14.2%).[1]

The primary endpoint, investigator-assessed radiographic PFS (rPFS), was met after a median follow-up of 25.7 months. The median rPFS was 22.6 months with apalutamide plus AAP vs 16.6 months with AAP (HR, 0.69; 95% CI, 0.58-0.83; *P*<.0001). In the final analysis, performed at a longer median follow-up of 54.8 months, the median rPFS was 24.0 months vs 16.6 months, respectively (HR, 0.70; 95% CI, 0.60-0.83; Figure 3).[1]

At the final analysis, OS was similar between the 2 arms (Figure 3). The median OS for apalutamide plus AAP was 36.2 months, compared with 33.7 months for AAP (HR, 0.95; 95% CI, 0.81-1.11); *P*=.498). Other prespecified secondary endpoints were also similar between the 2 groups, including initiation of cytotoxic chemotherapy (HR, 0.94; 95% CI, 0.78-1.13), chronic opioid use (HR, 1.07; 95% CI, 0.87-1.32), and pain progression (HR, 1.12; 95% CI, 0.95-1.33). Two prespecified baseline subgroups were found to have an OS benefit with apalutamide plus AAP vs AAP: the presence of visceral metastasis (HR, 0.76; 95% CI, 0.52-1.10) and older age (≥75 years [HR, 0.75; 95% CI, 0.59-0.96]). A similar number of patients in each arm discontinued study treatment and then went on to treatment with their first subsequent life-prolonging therapy (62.5% in the apalutamide-plus-AAP arm and 64.8% in the AAP arm).[1]

Also measured at the final analysis, 79.5% of patients in the apalutamide-plus-AAP arm and 72.9% of patients in the AAP arm had a confirmed decline of 50% or more in the PSA level (RR, 1.09; 95% CI, 1.02-1.17; *P*=.015). Undetectable PSA (<0.2 ng/mL) at any time during treatment was reported in 24.6% of patients in the apalutamide-plus-AAP arm compared with 19.2% of patients in the AAP arm (RR, 1.28; 95% CI, 1.01-1.62; *P*=.040).[1]

Slightly higher rates of treatment-emergent AEs (TEAEs) were observed in the apalutamide-plus-AAP combination arm compared with the AAP arm, including a higher rate of grade 3 or 4 TEAEs (63.3% vs 56.2%). There was also a higher rate of discontinuations owing to TEAEs in the apalutamide-plus-AAP arm vs the AAP arm (16.9% vs 12.5%). Grade 3/4 hypertension was higher with apalutamide plus AAP (20.6%) compared with AAP (12.5%), as were skin rash (4.5% vs 0.4%), cardiac disorders (9.0% vs 5.7%), and fracture and osteoporosis (4.1% vs 1.4%).[1]

ABSTRACT SUMMARY Severe COVID-19 and Mortality Among Patients With Prostate Cancer Receiving Androgen Deprivation Therapy

Tucker and colleagues used data from the COVID-19 and Cancer Consortium (CCC19) registry to evaluate the potential for ADT to reduce the severity of COVID-19 in patients with prostate cancer (Abstract 39). In a total of 879 patients included for analysis, multivariate regression analysis showed no difference in either the 5-point COVID-19 severity scale or in 30-day mortality between patients who were or were not receiving ADT. Though the subgroup of patients treated with second-generation AR antagonists was small (n=33), they had the lowest mortality rate in the study (12%), as well as the lowest rate of mechanical ventilation. The study authors reported that the overall mortality rate, regardless of ADT, was 15%.

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Biomarker Analysis From a Randomized Phase II Study of Olaparib With or Without Cediranib in Men With Metastatic Castration-Resistant Prostate Cancer

McKay and colleagues presented the results of a study that evaluated combination therapy in mCRPC.[1] This phase 2 trial investigated the potential to combine the vascular endothelial growth factor receptor tyrosine kinase inhibitor cediranib with the poly(ADP-ribose) polymerase inhibitor olaparib. After this combination was found to be superior to olaparib alone in a phase 2 trial in ovarian cancer,[2,3] further work found that cediranib directly inhibits homology-directed DNA repair. Furthermore, it is thought that antiangiogenic agents such as cediranib can induce a hypoxic tumor environment, leading to downregulation of genes involved in homologous recombination.[4] Thus, the potential for this combination to induce a synthetic lethality effect in mCRPC was evaluated.

This open-label phase 2 trial enrolled patients with mCRPC progression who had received at least 1 prior line of therapy for mCRPC. All patients had an ECOG PS of 0 or 1. Ninety patients were randomized in a 1-to-1 ratio to treatment with cediranib plus olaparib or single-agent olaparib; olaparib was administered at a lower dose in the combination arm (200 mg vs 300 mg twice daily). Treatment was continued until radiographic progression, toxicity, or withdrawal. Patients in the olaparib arm were permitted to cross over to cediranib plus olaparib.[1]

At baseline, the median age was 66 years in the cediranib-plus-olaparib arm and 70 years in the olaparib arm. The median PSA levels were 62 and 51 ng/mL, respectively. Measurable disease was reported in 69% of the combination arm and 78% of the olaparib arm (22% of patients in each arm had liver metastases). Overall, 31% of 84 evaluable patients were homologous recombination–deficient (29% in the combination arm and 33% in the olaparib arm). A *BRCA2* mutation was reported in 24.4% of the cediranib-plus-olaparib arm vs 16.3% in the olaparib arm. Overall, 6% of patients had germline alterations.[1]

The primary endpoint, rPFS in the overall population, was 8.47 months in the cediranib-plus-olaparib arm vs 3.97 months in the olaparib arm (HR, 0.625; 95% CI, 0.395-0.990; *P*=.0453). rPFS, according to homologous recombination status, was assessed as a secondary endpoint. The differences did not reach statistical significance. Among homologous recombination–deficient patients, the median rPFS was 10.63 months vs 3.83 months (HR, 0.640; 95% CI, 0.272-1.504; *P*=.3063). Among homologous recombination–proficient patients, the median rPFS was 5.37 vs 4.03 months (HR, 0.814; 95% CI, 0.462-1.436; *P*=.4781). Kaplan–Meier estimates of

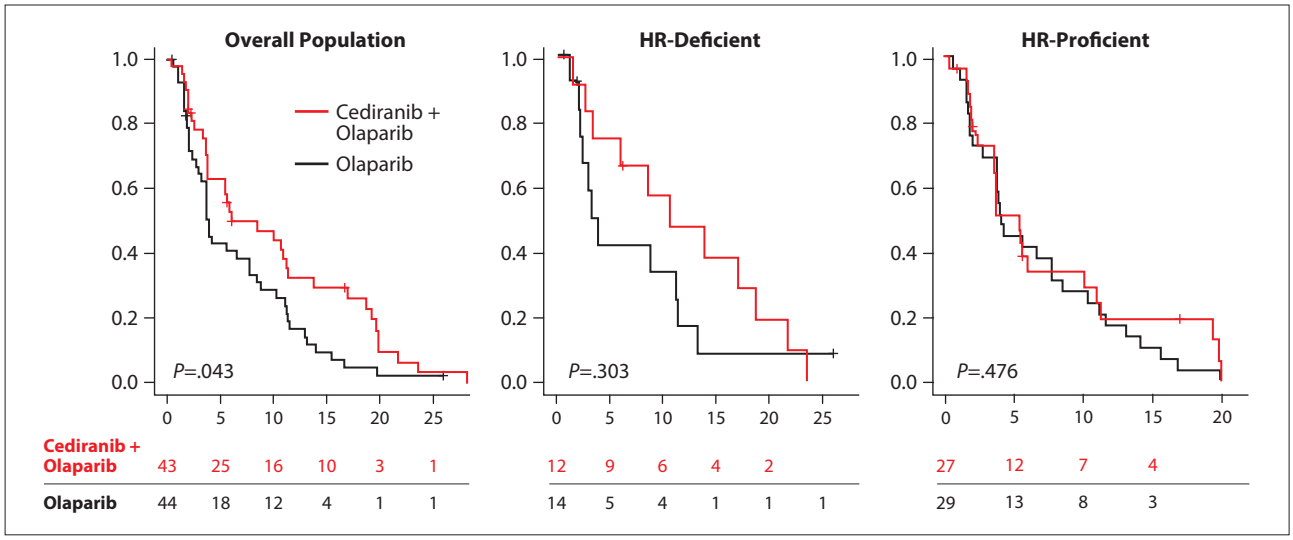

Figure 4. Kaplan–Meier estimates of rPFS among the overall population (left) and patients with HR-deficient (center) and HR-proficient (right) status in a phase 2 trial of cediranib plus olaparib vs olaparib alone in patients with mCRPC. HR, homologous recombination; rPFS, radiographic progression-free survival. Adapted from McKay RR et al. ASCO GU abstract 7. *J Clin Oncol.* 2021;39(6 suppl).[1]

rPFS for the overall population and by homologous recombination status are shown in Figure 4.[1]

OS in the overall population, a secondary endpoint, did not significantly differ between the 2 arms. The median OS was 11.77 months in the cediranib-plus-olaparib arm and 17.37 months in the olaparib-only arm (HR, 1.3; 95% CI, 0.705-2.399; *P*=.4013). Of the 45 patients randomly assigned to the olaparib arm, 13 crossed over upon radiographic disease progression.[1]

The PSA50-RR was 29% in the combination arm vs 18% in the olaparib arm. Among homologous recombination–deficient patients, the PSA50-RR was 17% vs 21%, respectively. Among homologous recombination–proficient patients, the PSA50-RR was 38% vs 17%, respectively. The ORR was 19% in the combination arm and 11% in the olaparib arm. Among homologous recombination–deficient patients, the ORR was 14% vs 20%, respectively. Among the homologous recombination–proficient patients, the ORR was 24% vs 8%, respectively.[1]

Grade 3 or higher AEs were reported in 77% of the cediranib-plus-olaparib arm vs 55% of the olaparib-alone arm. In the combination arm, 84% required a dose reduction and 25% discontinued treatment. These rates were 36% and 16%, respectively, in the olaparib arm. In the combination arm, the most common grade 3 or higher AEs were hypertension, at 26% (vs 2% in the olaparib arm) and fatigue, at 19% (vs 16% in the olaparib arm).[1]

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KEYNOTE-365 Cohort B: Pembrolizumab Plus Docetaxel and Prednisone in Abiraterone or Enzalutamide–Pretreated Patients With Metastatic Castration-Resistant Prostate Cancer—New Data After an Additional 1 Year of Follow-Up

The anti–programmed cell death 1 (PD-1) antibody pembrolizumab showed antitumor activity as monotherapy in patients with heavily pretreated, PD-L1–positive advanced prostate cancer in the KEYNOTE-028.[1] Pembrolizumab was also evaluated in the KEYNOTE-199 study, which enrolled PD-L1–positive and PD-L1–negative patients with mCRPC who had been previously treated with docetaxel and at least one next-generation hormonal agent.[2] KEYNOTE-365 is a 4-cohort phase 1b/2 study to evaluate pembrolizumab in combination with other agents in mCRPC, including olaparib (cohort A), docetaxel plus prednisone (cohort B), enzalutamide (cohort C), and abiraterone plus prednisone (cohort D). Results from cohort B of this study, which evaluated pembrolizumab in combination with docetaxel and prednisone, were previously presented after a median follow-up of 20 months.[3] Here, Appleman and colleagues presented updated data from this cohort, after a median follow-up of 32.4 months (range, 13.9-40.3).[4]

The study enrolled patients who developed disease progression during the 6 months before screening. All patients had received at least 4 weeks of previous treatment with either abiraterone acetate or enzalutamide (not both) in prechemotherapy mCRPC, but therapy failed or was not tolerable. Patients were treated with pembrolizumab and docetaxel in 3-week cycles, and also received prednisone twice daily.[4]

Primary study endpoints included safety, PSA response rate, and ORR as assessed by blinded independent central review according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The secondary endpoints included disease control rate, rPFS (according to Prostate Cancer Working Group [PCWG]-modified RECIST v1.1), and OS.[4]

In all, 104 patients were treated in cohort B of the KEYNOTE-365 study. The median patient age was 68 years (range, 50-86). Almost three-fourths (74.0%) of patients were ages 65 years or older. Patients had an ECOG PS of 0 (53.8%) or 1 (46.2%). Half of patients had measurable disease, and 25.0% had visceral disease of the soft tissue (not brain, bone, or lymph nodes). The majority of patients in this cohort had PD-L1–negative disease (73.1%); the

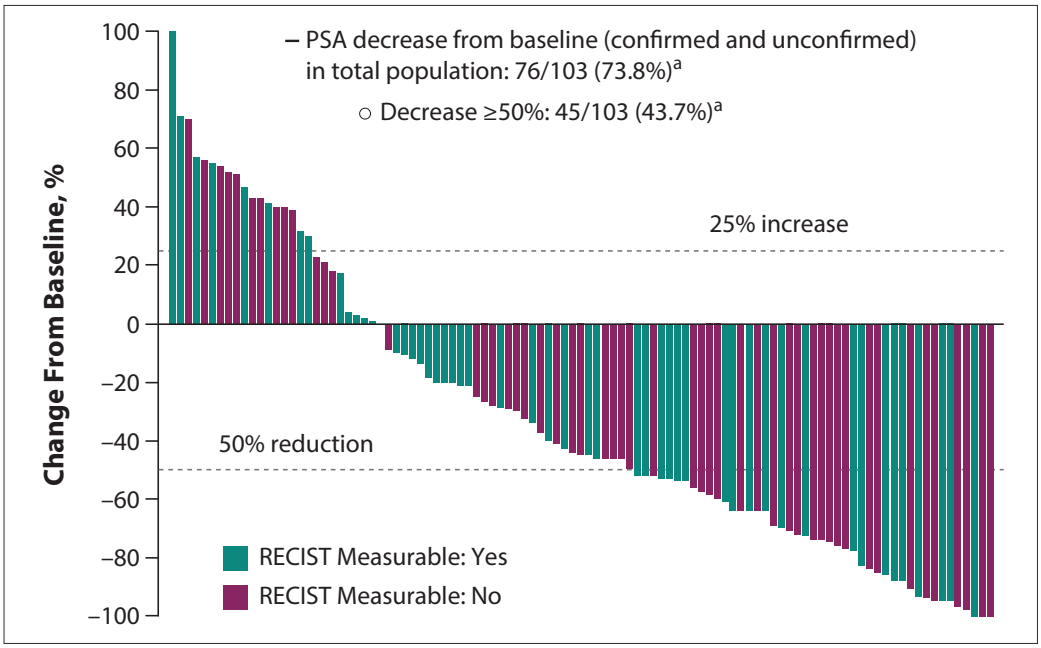

Figure 5. Percentage change from baseline in confirmed and unconfirmed PSA measurements. PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors. [a]Calculation based on patients with nonmissing PSA measurement at baseline; confirmed by subsequent values obtained at least 3 weeks later. Adapted from Appleman L et al. ASCO GU abstract 10. *J Clin Oncol.* 2021;39(6 suppl).[4]

remainder had PD-L1–positive disease (23.1%) or had an unknown PD-L1 status (3.8%).[4]

In total, 34.0% of patients had a confirmed PSA50-RR; this rate was 27.5% among patients with RECIST measurable disease and 40.4% among patients with RECIST nonmeasurable disease. When considering both confirmed and unconfirmed PSA responses, 43.7% had a PSA50-RR (Figure 5).[4]

Among the 52 patients with measurable disease, 23.1% (95% CI, 12.5%-36.8%) achieved an objective response, all of which were partial responses. In the total population of patients with both measurable and nonmeasurable disease, the disease control rate was 76.0% (95% CI, 66.6%-83.8%). A total of 11.5% had a partial response, 25.0% had stable disease of any duration, and 39.4% were defined as having noncomplete response and nonprogressive disease. A total of 42.3% of patients maintained stable disease or noncomplete response and nonprogressive disease for at least 6 months.[4]

The Kaplan–Meier estimate of median rPFS per PCWG3-modified RECIST v1.1 was 8.5 months (95% CI, 8.3-10.1). The 6- and 12-month rPFS rates were 76.9% and 26.2%, respectively. The Kaplan–Meier estimate of median OS was 20.2 months (95% CI, 16.9-24.2). The 12-month OS rate was 75.9%.[4]

The mean duration of therapy was 7.7 months (range, 0.9-23.5). The most frequently occurring TRAEs included diarrhea (41.3%), fatigue (41.3%), alopecia (40.4%), dysgeusia (26.9%), and nausea (26.0%). The most common grade 3 to 5 TRAEs were febrile neutropenia (11.5%), anemia (4.8%), diarrhea (2.9%), fatigue (2.9%), and asthenia (1.9%). Additionally, 32.7% reported an immune-mediated AE or an infusion reaction; of these, 8.7% were grade 3 to 5 in severity. Two patients died of an AE that the investigator considered related to treatment (both due to pneumonitis).[4]

According to the investigators of this study, these data support the further evaluation of this combination. The phase 3 KEYNOTE-921 trial of docetaxel plus prednisone, with or without pembrolizumab, is currently enrolling patients previously treated with a next-generation hormonal agent, but not chemotherapy, for their mCRPC.[5]

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CheckMate 9KD Arm B Final Analysis: Efficacy and Safety of Nivolumab Plus Docetaxel for Chemotherapy-Naive Metastatic Castration-Resistant Prostate Cancer

Nivolumab, another anti–PD-1 antibody, has shown minimal activity in unselected patients with advanced prostate cancer.[1] The CheckMate 9KD trial is a multi-arm, open-label, phase 2 trial to evaluate the efficacy and safety of nivolumab in combination with various agents, including rucaparib (arm A), docetaxel (arm B), or enzalutamide (arm C), in patients with mCRPC. An interim analysis of arm B reported that the combination of nivolumab with docetaxel showed efficacy in comparison to historical data of each agent alone, and had a tolerable safety profile.[2] Here, Fizazi and colleagues presented data from the final analysis of arm B.[3]

To be eligible for enrollment into the CheckMate 9KD trial, patients were required to have mCRPC with an ECOG PS of 0 or 1. Patients were either receiving ongoing ADT with a gonadotropin-releasing hormone analog or had a bilateral orchiectomy. All patients submitted a tumor specimen from within the 5 years before enrollment for homologous recombination deficiency testing before assignment to a treatment arm. Patients were not permitted to have received a prior antibody or a drug targeting T-cell costimulation or an immune checkpoint pathway. A specific requirement for enrollment into arm B was that patients were chemotherapy-naive, eligible for treatment with docetaxel, and had received up to 2 novel antiandrogen therapies (NATs; such as abiraterone or enzalutamide) in the prechemotherapy mCRPC setting. All patients enrolled in arm B were treated with nivolumab and docetaxel on every-3-week cycles, plus prednisone twice daily.[3]

Co–primary endpoints were ORR (investigator-assessed) and PSA50-RR. Secondary endpoints included rPFS, OS, time to response, duration of response, time to PSA progression, and safety. The median duration of follow-up for this analysis was 15.2 months.[3]

Eighty-four patients were treated in arm B. The median patient age was 71 years (range, 53-88). The ECOG PS was 0 (42.9%) or 1 (57.1%). Most patients had a Gleason score greater than 7 (58.3%); the remainder had a Gleason score of 7 or less (39.3%) or had missing Gleason score information (2.4%). The median time since diagnosis was 4.6 years (range, 0.3-47.7), and the median PSA level was 49.5 ng/mL (1.2-1085). A total of 53.6% of patients had measurable disease; 70.2% had no visceral metastases, and 27.4% had visceral metastases. Almost two-thirds (64.3%) of patients had received a NAT, including abiraterone only (20.2%), enzalutamide only (28.6%), abiraterone and enzalutamide (14.3%), and apalutamide only

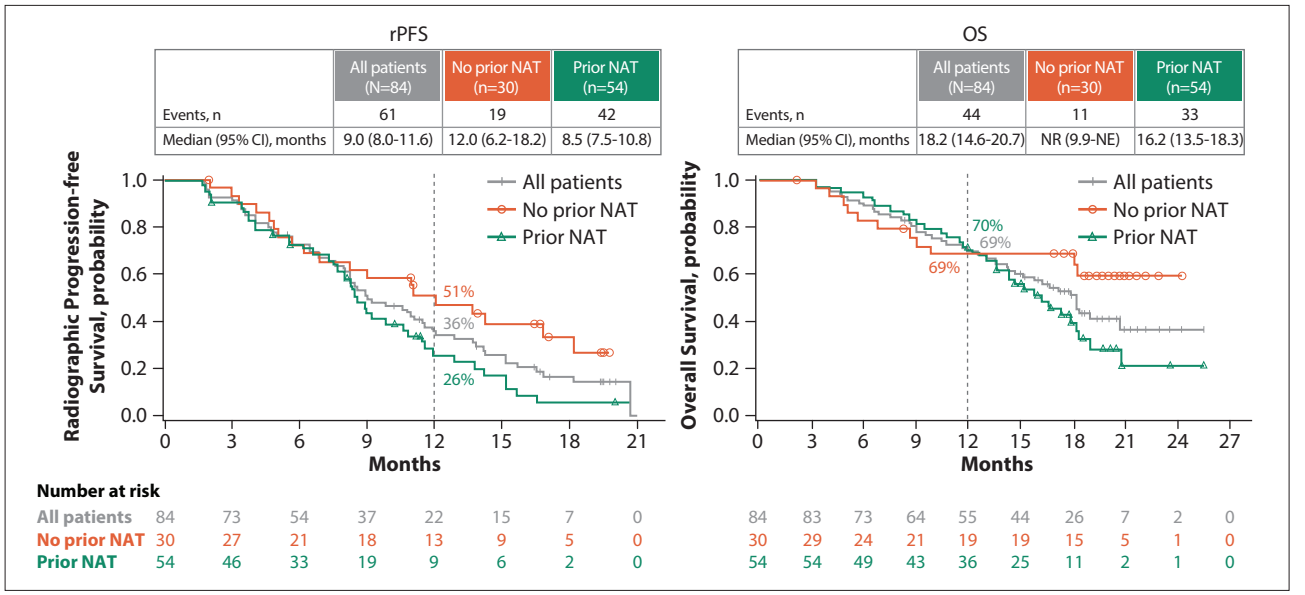

Figure 6. rPFS and OS among patients treated with nivolumab plus docetaxel in the CheckMate 9KD trial. NAT, novel antiandrogen therapy; NE, not estimable; NR, not reached; OS, overall survival; rPFS, radiographic progression-free survival. Adapted from Fizazi K et al. ASCO GU abstract 12. *J Clin Oncol.* 2021;39(6 suppl).[3]

ABSTRACT SUMMARY Evaluating the Role of Stereotactic Body Radiation Therapy With Respect to Androgen Receptor Signaling Inhibitors for Metastatic Prostate Cancer

Brennan and colleagues conducted a retrospective review of patients treated with stereotactic body radiation therapy for oligometastatic prostate cancer either before, during, or after progression on an androgen receptor signaling inhibitor (Abstract 121). The study included 61 patients with 114 lesions in total, who were followed for a median of 15.2 months. The median PFS was not reached in the group with androgen receptor signaling inhibitor–sensitive mCSPC, was 17.3 months in the group with androgen receptor signaling inhibitor–sensitive mCRPC, and was 9.0 months in the group with androgen receptor signaling inhibitor–resistant mCRPC. In this latter group of patients, PFS was markedly better in those individuals who achieved complete ablation of all of their lesions. No acute grade 3 or higher toxicities were reported; grade 3 pelvic bone fractures were reported in 2 patients and 1 patient had grade 4 pneumonitis. The study authors concluded that stereotactic body radiation therapy could perhaps add to the efficacy of androgen receptor signaling inhibition, particularly in patients with androgen receptor signaling inhibitor–resistant mCRPC who received ablative radiation doses to all of their lesions.

(1.2%).[3]

Among the 45 patients with measurable disease, the ORR was 40.0% (95% CI, 25.7%-55.7%). Of these, 1 patient (2.2%) had a complete response and the rest (37.8%) had a partial response. An additional 53.3% of patients had stable disease. Of the 18 patients with an objective response, the median time to response was 2 months (range, 1.6-7.3), and the median duration of response was 7.0 months (95% CI, 6.4-12.4).[3]

Within this group of 45 patients with measurable disease, 31 had received prior NAT and 14 had not received prior NAT. In patients who had received prior NAT, the ORR was 38.7% (95% CI, 21.8%-57.8%), comprised of 35.5% partial responses, and 1 (3.2%) complete response. In patients who had not received prior NAT, the ORR was 42.9% (95% CI, 17.7%-71.1%), all of which were partial responses. The rates of stable disease were 54.8% vs 50.0% in patients who had or had not received prior NAT, respectively.[3]

In 44 patients with a measurable target lesion at baseline and 1 or more on-treatment tumor assessment, 79.5% had a reduction from baseline in the sum of diameters of target lesions. Among these patients, the median change from baseline for all patients was –32.1%. The tumor reductions and PCWG3 responses were observed both in patients who had or had not received a prior NAT.[3]

Among 84 evaluable patients, the co–primary endpoint of PSA50-RR was 46.9% (95% CI, 35.7%-58.3%). The median time to PSA progression was 8.7 months (95% CI, 7.3-10.4). In 53 patients with prior NAT, the PSA50-RR was 39.6% (95% CI, 26.5%-54.0%), vs 60.7% (95% CI, 40.6%-78.5%) in 28 patients with no prior NAT. A reduction from baseline in levels of PSA was observed in 84.0% of patients, with a median change from baseline for all patients of –54.6%. Reductions in PSA were observed in patients who had or had not received a prior NAT.[3]

The median rPFS among all 84 patients was 9.0 months (95% CI, 8.0-11.6), and was slightly prolonged in the 30 patients with no prior NAT (12.0 months; 95% CI, 6.2-18.2) and was similar in the 54 patients with prior NAT (8.5 months; 95% CI, 7.5-10.8). The 12-month rPFS rates were 36%, 51%, and 26% in the overall, no prior NAT, and prior NAT populations, respectively (Figure 6).[3]

The median OS in the group of 84 patients was 18.2 months (95% CI, 14.6-20.7) overall, not reached (95% CI, 9.9 to not estimable) in the 30 patients with no prior NAT, and 16.2 months (95% CI, 13.5-18.3) in the 54 patients with prior NAT. The 12-month OS rates were 69%, 69%, and 70% in the overall, no prior NAT, and prior NAT populations, respectively (Figure 6).[3]

Any-grade TRAEs resulted in the discontinuation of 1 or both study drugs in 29.8% of patients. This was most commonly due to pneumonitis (7.1%), peripheral neuropathy (6.0%), and fatigue (6.0%). Any-grade or grade 3/4 treatment-related select AEs were reported as follows: gastrointestinal (35.7% and 7.1%, respectively), skin-related (26.2% and 3.6%), pulmonary (13.1% and 4.8%), endocrine (8.3% and 0%), hepatic (6.0% and 1.2%), and renal (2.4% and 0%). Three treatment-related deaths were reported: 1 case of pneumonitis related to nivolumab and 2 cases of pneumonitis related to docetaxel.[3]

The study investigators concluded that these data support further investigation of the combination of nivolumab plus docetaxel in patients with mCRPC in the ongoing phase 3 CheckMate 7DX trial.[4]

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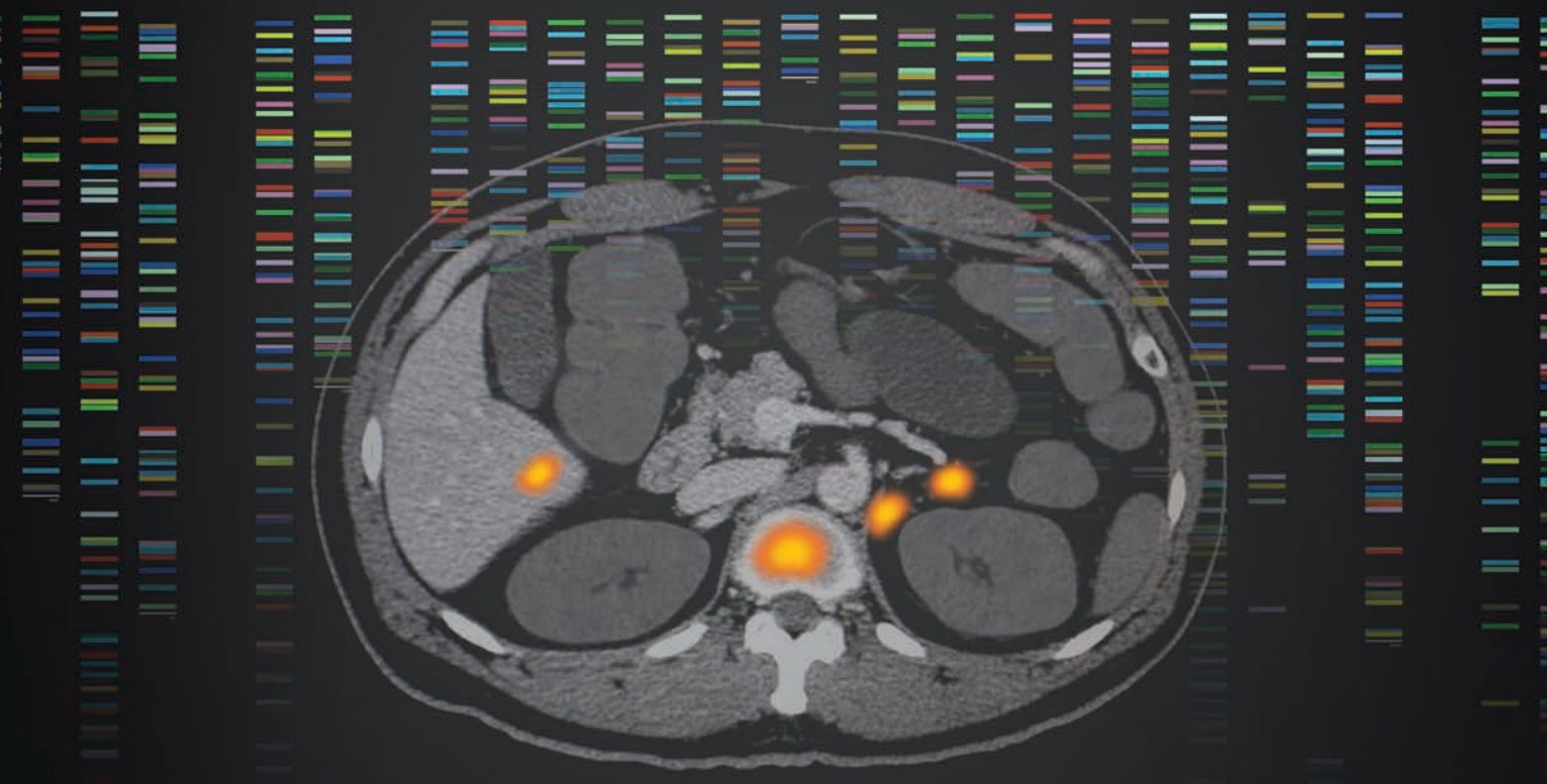

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Final Analysis Results From TITAN: A Phase III Study of Apalutamide Versus Placebo in Patients With Metastatic Castration-Sensitive Prostate Cancer Receiving Androgen Deprivation Therapy

Combining ADT with either docetaxel or abiraterone acetate plus prednisone has been shown to prolong survival in men with metastatic castration-sensitive prostate cancer (mCSPC).[1-3] However, not all patients are candidates for docetaxel. In addition, it is necessary to administer prednisone with abiraterone acetate to prevent an increase in corticotropin, which may lead to mineralocorticoid excess and liver toxicity.[4-6] The antiandrogen agent apalutamide binds to the ligand-binding domain of the androgen receptor, preventing androgen-receptor translocation, DNA binding, and androgen receptor–mediated transcription.[7] It was hypothesized that this direct inhibition of the androgen receptor, when combined with ADT, may provide a more complete block of androgen signaling than ADT alone. Thus, the TITAN study was designed to investigate this combination. The primary analysis of the TITAN study was published in 2019.[8] Chi and colleagues provided the results of the final analysis.[9]

TITAN was a randomized, double-blind, placebo-controlled phase 3 trial that evaluated the efficacy and safety of adding apalutamide to ADT in patients with mCSPC. A broad population of patients with mCSPC (ie, not receiving ADT at the time of disease progression) were enrolled in the study, with the requirement of metastatic disease documented on the basis of at least 1 lesion on bone scanning, with or without visceral or lymph-node involvement. Patients had an ECOG PS of 0 or 1. Prior prostate cancer treatment was limited to docetaxel, ADT for no more than 6 months for mCSPC or for no more than 3 years for localized disease, or localized treatments completed at least 1 year before randomization.[8,9]

A total of 1052 patients were randomly assigned in a 1-to-1 ratio to treatment with either apalutamide plus ADT or placebo plus ADT. The dual primary endpoints of the TITAN study were rPFS and OS, while secondary endpoints (tested by hierarchical order of analysis) were time to cytotoxic chemotherapy, time to pain progression, time to chronic opioid use, and time to a skeletal-related event.[8,9]

At the time of the primary analysis (with a median follow-up of 22.7 months), the median rPFS was not evaluable among patients in the apalutamide-plus-ADT arm, compared with 22.1 months in the placebo-plus-ADT arm (HR, 0.48; 95% CI, 0.39-0.60; *P*<.001). The median OS was not evaluable in either arm, and was significantly prolonged with apalutamide plus ADT (HR, 0.67; 95% CI, 0.51-0.89; *P*=.005).[8]

At the final analysis, after a median follow-up of 44.0 months (Figure 7), the difference in OS remained similar; the median OS was not reached with apalutamide plus ADT vs 52.2 months with placebo plus ADT (HR, 0.65; 95% CI, 0.53-0.79; *P*<.0001).

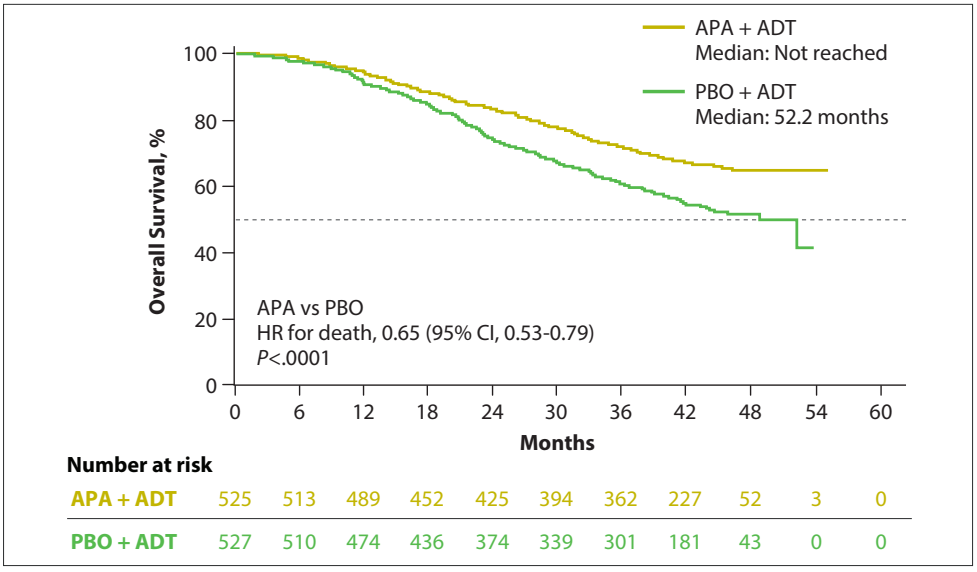

Figure 7. OS at the final analysis of the TITAN trial among patients with mCSPC treated with apalutamide plus ADT vs placebo plus ADT. ADT, androgen-deprivation therapy; APA, apalutamide; OS, overall survival; PBO, placebo. Adapted from Chi KN et al. ASCO GU abstract 11. *J Clin Oncol.* 2021;39(6 suppl).[9]

When the OS analysis was adjusted for the approximately 40% crossover rate in the trial, the reduction in the risk for death was increased to 48% (HR, 0.52; 95% CI, 0.42-0.64; *P*<.0001). The benefit with apalutamide plus ADT on OS was observed across multiple patient subgroups, with the exception of patients with prior docetaxel use and patients with an elevated lactate dehydrogenase level at baseline.[9]

Several other clinically relevant endpoints were evaluated that also favored apalutamide plus ADT over placebo plus ADT. The median second PFS was not reached vs 44.0 months, respectively (HR, 0.62; 95% CI, 0.51-0.75; *P*<.0001). Additionally, the median time to castration resistance was also significantly prolonged (not reached vs 11.4 months; HR, 0.34; 95% CI, 0.29-0.41; *P*<.0001). In general, the health-related quality of life was maintained among patients in both arms.[9]

At the final analysis, the safety profile was consistent with that reported at the primary analysis. Grade 3 or 4 TEAEs were reported in 49.4% of patients in the apalutamide-plus-ADT arm, and 41.7% of patients in the placebo-plus-ADT arm. A TEAE led to death in 20 patients in the apalutamide-plus-ADT arm (3.8%) and 17 patients in the placebo-plus-ADT arm (3.2%). The rates of discontinuation due to any TEAEs were 11.8% vs 5.7%, respectively. The following all-grade AEs of interest were reported: skin rash (29.2% vs 9.3%), fracture (10.3% vs 4.9%), fall (9.4% vs 7.0%), ischemic heart disease (5.9% vs 2.1%), ischemic cerebrovascular disorder (2.5% vs 1.5%), and seizure (0.6% vs 0.4%).[9]

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PI3K/AKT Pathway Biomarkers Analysis From the Phase III IPATential150 Trial of Ipatasertib Plus Abiraterone in Metastatic Castration-Resistant Prostate Cancer

Ipatasertib is an investigational agent currently in evaluation for both prostate and breast cancers.[1,2] Ipatasertib is an oral inhibitor of 3 isoforms of AKT (protein kinase B), administered with the intention to block the PI3 kinase (PI3K)/AKT signaling pathway.[3] This pathway has been demonstrated to be important in prostate cancer carcinogenesis and also potentially in the resistance to antiandrogen therapies, and is potentially connected to the loss of phosphatase and tensin homolog (PTEN).

The phase 3, double-blind, placebo-controlled, randomized IPATential150 trial evaluated the addition of ipatasertib vs placebo to abiraterone acetate and a steroid (either prednisone or prednisolone). Initial results of IPATential150, in 1101 patients with asymptomatic or mildly symptomatic mCRPC who had not received prior treatment for mCRPC, were previously presented by de Bono and colleagues.[4] The co–primary outcomes were investigator-assessed rPFS using PCWG3 criteria among patients with PTEN-loss tumors, as well as rPFS among the entire intention-to-treat (ITT) population.

Prior to randomization within the study, tumor specimens were analyzed for *PTEN* loss using the SP218 immunohistochemistry (IHC) assay. *PTEN* loss was defined as having 50% or more of tumor cells in a field with no specific cytoplasmic *PTEN* staining by IHC. In this initial analysis, median rPFS among patients with *PTEN* loss was significantly longer in the group treated with ipatasertib, abiraterone acetate, and prednisone compared with those receiving placebo, abiraterone acetate, and prednisone (18.5 vs 16.5 months; HR, 0.77; 95% CI, 0.61-0.98; *P*=.0335). In the ITT population, this difference did not reach statistical significance (HR, 0.84; 95% CI, 0.71-0.99; *P*=.0431).[4]

De Bono and colleagues reported the results of an exploratory analysis of the IPATential150 trial to evaluate potential biomarker associations with

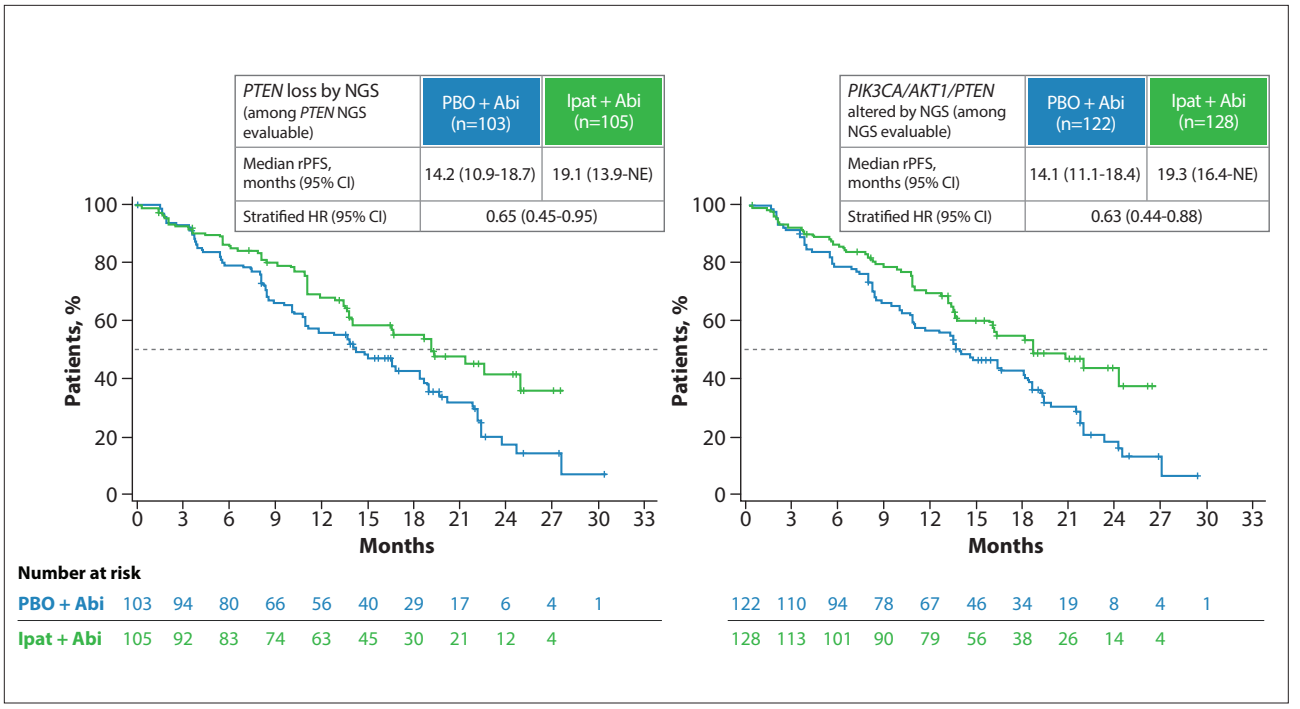

Figure 8. rPFS in patients with PTEN loss (left) or *PIK3CA/AKT1/PTEN* gene alterations (right) by NGS in the IPATential150 trials. Abi, abiraterone; HR, hazard ratio; Ipat, ipatasertib; NGS, next-generation sequencing; PBO, placebo; rPFS, radiographic progression-free survival. Adapted from de Bono J et al. ASCO GU abstract 13. *J Clin Oncol.* 2021;39(6 suppl).[5]

rPFS outcomes.[5] First, this exploratory analysis evaluated the effect of different IHC staining cutoffs on rPFS, and found a consistent benefit in rPFS as the stringency of the definition for *PTEN* loss increased. For example, the hazard ratios for disease progression or death according to the percentage of *PTEN* loss as assessed by IHC were as follows: HR, 0.84 (95% CI, 0.69-1.02) for 10%; HR, 0.82 (95% CI, 0.66-1.02) for 30%; HR, 0.77 (95% CI, 0.61-0.98) for 50%; HR, 0.72 (95% CI, 0.56-0.93) for 70%; and HR, 0.65 (95% CI, 0.39-1.08) for 100%. In contrast, the addition of ipatasertib was not associated with improved rPFS in patients with tumors that showed intact *PTEN* by IHC tumors.[5]

Tumor genomic alterations were profiled by next-generation sequencing (NGS); of 743 patients whose tumor specimens were NGS-evaluable, 518 had specimens evaluable for *PTEN* status by NGS. Of these, 60% were *PTEN* wild-type and 40% showed *PTEN* loss (defined by *PTEN*-inactivating alterations, including homozygous deletion, heterozygous deletion, dominant negative mutations, or biallelic inactivation). Evaluation of *PTEN* status with IHC or NGS demonstrated good concordance, with an overall agreement of 85.5%. Among 208 specimens with *PTEN* loss according to NGS, 91.3% showed *PTEN* loss by IHC; in 247 specimens with *PTEN* loss by IHC, 76.9% showed *PTEN* loss by NGS.[5]

An improvement in the median rPFS with ipatasertib plus abiraterone acetate and prednisone vs placebo plus abiraterone acetate and prednisone was also observed among patients who showed *PTEN* loss according to NGS (19.1 vs 14.2 months; stratified HR, 0.65; 95% CI, 0.45-0.95). An improvement in median rPFS with the addition of ipatasertib vs placebo was also demonstrated in patients who had genomic alterations identified in *PIK3CA*, *AKT1*, or *PTEN* by NGS (19.3 vs 14.1 months; stratified HR, 0.63; 95% CI, 0.44-0.88; Figure 8). Furthermore, patients in the placebo arm who had genomic alterations in the *PIK3CA*, *AKT1*, or *PTEN* genes by NGS showed a trend toward worse prognosis.[5]

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Genomic Landscape of Advanced Prostate Cancer in Racial Minority Populations: Real-World Experience in a Safety-Net Hospital Oncology Clinic

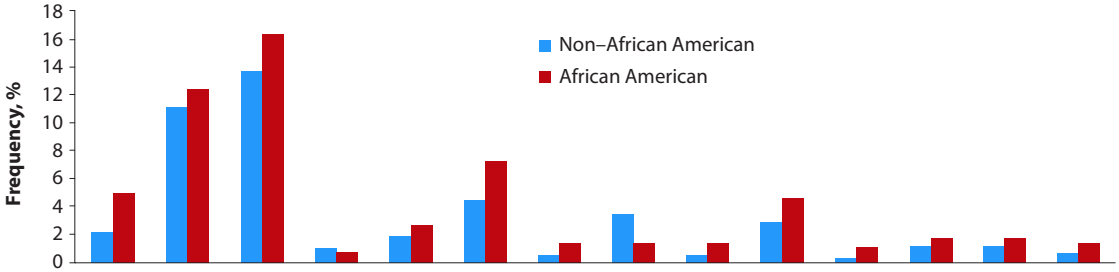
A large health disparity is documented with regard to prostate cancer in Black men.[1-4] These patients have a nearly 1.8-fold higher risk for developing prostate cancer. They are diagnosed at a younger age and at a more advanced stage. They have an increased risk for recurrence after radical prostatectomy, and their rate of mortality is up to 2.5-fold higher compared with men from other racial and ethnic backgrounds. Although some of this disparity may be explained by socioeconomic conditions and environmental factors, genetic differences may also play a role. However, genomic alterations need to be better defined among minority and uninsured populations, which may be underrepresented in routine NGS evaluations.

Khashab and colleagues explored the prevalence and genomic landscape in a retrospective analysis of patients treated at Ben Taub Hospital in Houston in Harris County, Texas.[5] The study investigators noted that this is a community-focused health care system staffed by physicians aligned with the Baylor College of Medicine. At this hospital, just 7% of patients with cancer have commercial insurance. Among the patients with prostate cancer at the hospital, 55% are Black and 35% are Hispanic.[5]

One-hundred patients with prostate cancer (53 of whom were African American) were included in this analysis. All patients had received ADT for locally advanced, biochemically recurrent, or metastatic prostate cancer while being treated at the Ben Taub Hospital. NGS was obtained for all 100 patients using either a 648-gene tissue-based tumor DNA sequencing panel integrated with whole-transcriptome RNA sequencing, or a 105-gene liquid-based circulating tumor DNA (ctDNA) panel. These data were compared with de-identified NGS data from a nationwide cohort of 1765 patients with metastatic prostate cancer, of whom 307 were African American.[5]

Among the 100 patients in the hospital cohort, African American patients had a higher incidence compared with non–African American patients of alterations in several driver genes, including the *TP53* gene (41.5% vs 12.8%), the *SPOP* gene (20.8% vs 10.6%), the androgen receptor gene (*AR*; 18.9% vs 4.3%), and homologous recombination repair genes (22.6% vs 14.9%). Selected homologous recombination repair genes that showed mutations included *BRCA2*, *ATM*, *CDK12*, and *PALB2*. *TMPRSS2* gene fusions were much less common in African American patients with prostate cancer compared with non-African American patients with prostate cancer (18.8% vs 46.9%, respectively).[5]

The higher proportion of *TP53*, *SPOP*, *AR*, and homologous recombination repair gene mutations identified in the hospital cohort were then evaluated in the nationwide cohort. In this larger cohort, these differences were smaller, but still apparent. The *AR* gene was mutated in 20.9% of African American men vs 18.3% of non–African American men. Mutations were reported in the *SPOP* gene in 11.1% vs 7.4%, respectively, and in the homologous recombination repair



	BRCA1	BRCA2	ATM	BARD1	BRIP1	CDK12	CHEK1	CHEK2	FANCL	PALB2	RAD51B	RAD51C	RAD51D	RAD54L
Non–African American (n=1458)	30 (2.1)	162 (11.1)	200 (13.7)	13 (0.9)	26 (1.8)	64 (4.4)	7 (0.5)	49 (3.4)	6 (0.4)	41 (2.8)	4 (0.3)	16 (1.1)	16 (1.1)	9 (0.6)
African American (n=307)	15 (4.9)	38 (12.4)	50 (16.3)	2 (0.7)	8 (2.6)	22 (7.2)	4 (1.3)	4 (1.3)	4 (1.3)	14 (4.6)	3 (1.0)	5 (1.6)	5 (1.6)	4 (1.3)

Figure 9. Frequency of homologous recombination repair gene alterations in African American vs non–African American men with prostate cancer in a nationwide cohort. Adapted from Khashab T et al. ASCO GU abstract 14. *J Clin Oncol.* 2021;39(6 suppl).[5]

genes for 44.0% vs 34.6%. Figure 9 illustrates the pattern of homologous recombination repair gene alteration frequencies among African American and non–African American men in the nationwide cohort. The *TP53* gene did not show the same pattern of incidence in alterations, and was slightly lower among African American men (39.1% vs 44.4%). Again, *TMPRSS2* gene fusions were much less common in African American patients with prostate cancer compared with non-African American patients with prostate cancer (12.1% vs 29.6%, respectively).[5]

The authors of this study concluded that the higher incidence of gene alterations in key oncogenic drivers—in particular, in homologous recombination repair genes—may account in part for the disparities in incidence and outcomes among African American patients with prostate cancer.[5]

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Androgen Deprivation Therapy and Risk of SARS-CoV-2 Infection in Men With Prostate Cancer: A University of California Health System Registry Study

The entry of the SARS-CoV-2 virus is known to be facilitated, in part, by the transmembrane protease TMPRSS2.[1] The gene for *TMPRSS2* is expressed in both lung and prostate tissues.[2] Initial reports suggested that ADT may protect against SARS-CoV-2 infection and potentially attenuate COVID-19 severity.[3,4] However, this finding was contradicted in a subsequent report.[5] Here, Kwon and colleagues examined the relationship between ADT and COVID-19 among men with prostate cancer in the University of California (UC) Health System.[6]

This was a retrospective registry study using the UC Health COVID Research Data Set, comprised of patients identified in a UC-wide centralized database across 5 academic medical centers and 12 affiliated hospitals. The analysis focused on data from men with prostate cancer included in the registry and who had tested either positive or negative for SARS-CoV-2 infection between February 1, 2020 and December 20, 2020.[6]

The investigators identified 5211 men with prostate cancer who underwent SARS-CoV-2 testing. A positive test results was reported for 97 (1.9%) were found to be positive. Among these patients, most were White (73%). Comorbidities included diabetes mellitus (15%), chronic kidney disease (13%), congestive heart failure (7%), obesity (6%), chronic obstructive pulmonary disease (6%), and coronary artery disease (5%).[6]

No association between SARS-CoV-2 infection and ADT was found in the overall population. The rate of infection was 2.3% among the 799 patients on ADT and 1.8% among the 4412 patients not on ADT (odds ratio [OR], 1.30; 95% CI, 0.78-2.19). Furthermore, no association was identified between SARS-CoV-2 infection and ADT within racial or ethnic subgroups, including White patients (OR,

ABSTRACT SUMMARY Association of the Clinical Cell-Cycle Risk Score With Metastasis After Radiation Therapy and Identification of Men With Prostate Cancer Who Can Forgo Combined Androgen Deprivation Therapy

Tward and colleagues examined the ability to identify individuals with localized prostate cancer with such a low risk for metastasis following dose-escalated radiation therapy that there is no benefit to adding ADT (Abstract 195). A combined clinical cell-cycle risk score (CCR) combines the cell cycle progression score (CCP) with the UCSF Cancer of the Prostate Risk Assessment score (CAPRA). The CCR was found to be a significant predictor of metastasis (HR, 2.21; 95% CI, 1.70-2.87; $P=5.6 \times 10^{-9}$). The CCR score continued to be highly predictive for metastasis in bivariate analyses when comparing ADT use vs none (HR, 2.19; 95% CI, 1.68-2.84; $P=1.0 \times 10^{-8}$) or ADT duration as a continuous variable (HR, 2.11; 95% CI, 1.59-2.79; $P=3.0 \times 10^{-7}$). Patients with CCR scores below the identified threshold of 2.112 had less than a 5% risk for 10-year metastasis regardless of ADT use (overall, sufficient ADT, radiation therapy with any duration of ADT, or radiation therapy alone with no ADT) or National Comprehensive Cancer Network risk group (favorable intermediate risk, unfavorable intermediate risk, or high/very high risk).

Table 1. Multivariable Logistic Regression on SARS-CoV-2 Infection in Men With Prostate Cancer in the University of California Health System Registry

Characteristic	Odds Ratio (95% CI)	*P* Value
ADT		
• Received	1.18 (0.70-1.99)	.541
Birth year		
• ≤1955	0.91 (0.57-1.45)	.680
Race		
• White	Reference	
• Black or African-American	1.96 (1.04-3.68)	.037
• Asian, Native Hawaiian/Pacific Islander, or American Indian/ Alaskan native	0.34 (0.08-1.41)	.136
• Other or multiple	2.16 (1.03-4.50)	.041
• Unknown	1.59 (0.83-3.05)	.165
Ethnicity		
• Hispanic/Latinx	1.94 (1.04-3.63)	.038
Comorbidities		
• Diabetes mellitus	1.86 (1.13-3.06)	.015
• Chronic kidney disease	1.08 (0.61-1.92)	.800
• Obesity	1.22 (0.62-2.44)	.569
• Coronary artery disease	1.36 (0.62-3.02)	.444
• Congestive heart failure	0.99 (0.46-2.10)	.974
• Chronic obstructive pulmonary disease	1.60 (0.82-3.15)	.171

Adapted from Kwon D et al. ASCO GU abstract 37. *J Clin Oncol.* 2021;39(6 suppl).[6]

1.38; 95% CI, 0.71-2.56), Black or African American patients (OR, 1.61; 95% CI, 0.48-5.37), or Hispanic/ Latino patients (OR, 0.62; 95% CI, 0.14-2.78).[6]

In a multivariable logistic regression analysis, ADT was not independently associated with SARS-CoV-2 infection (OR, 1.18; 95% CI, 0.70-1.99; *P*=.541). Table 1 shows the results for the multivariable logistic regression performed in this cohort of patients with prostate cancer and SARS-CoV-2 infection. Among 97 men with prostate cancer who were positive for SARS-CoV-2 infection, 1 of 19 (5.3%) who received ADT died, compared with 7 of 78 (9.0%) who did not receive ADT (OR, 0.56; 95% CI, 0.07-4.88; *P*=.60).[6]

Based on these results, the investigators concluded that there was no association between ADT and SARS-CoV-2 infection in a large and diverse population of men with prostate cancer. The investigators noted that although these data did not suggest a benefit of ADT on COVID-19 severity, its effect on mortality was difficult to determine given the few deaths that occurred overall.[6]

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The Role of Androgen Deprivation Therapy on the Clinical Course of COVID-19 Infection in Men With Prostate Cancer

Patel and colleagues conducted a similar analysis on the role of ADT and the clinical course of COVID-19 among men with prostate cancer.[1] They retrospectively analyzed a multi-institutional data set of 465 men with active prostate cancer who had been found to be positive for SARS-CoV-2 infection by polymerase chain reaction between March 1, 2020 and May 31, 2020. The age of patients treated with ADT (n=317) and not treated with ADT (n=148) was 71 and 72 years, respectively.[1]

Medical comorbidities included hypertension in 79% of patients who had received ADT vs 66% of those who had not (*P*=.002), chronic kidney

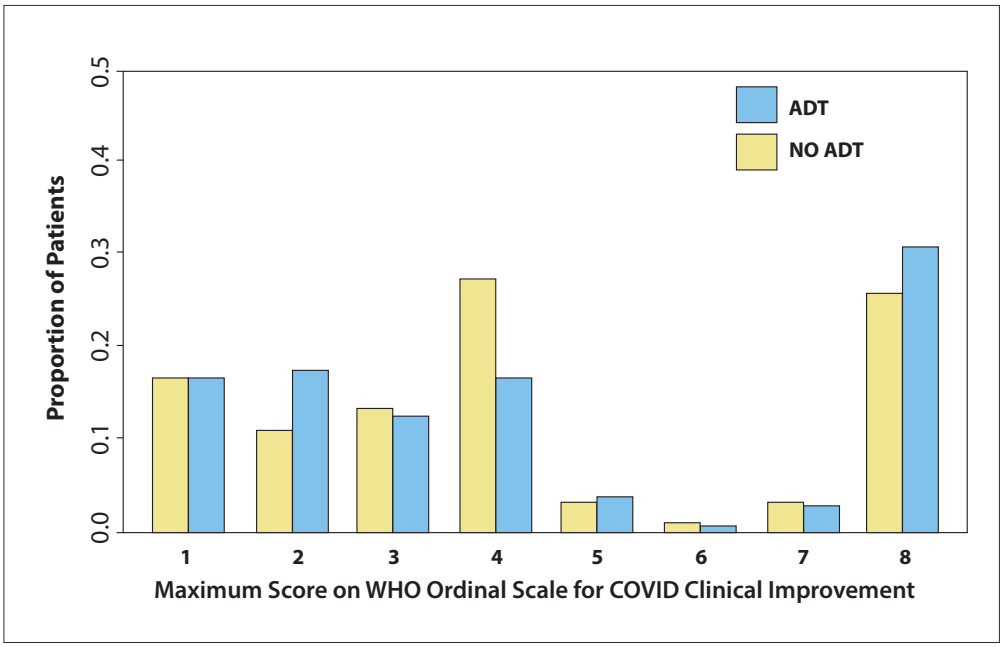

Figure 10. Distribution of clinical severity of COVID-19–related illness among patients with prostate cancer who did or did not receive ADT. ADT, androgen deprivation therapy. Adapted from Patel VG et al. ASCO GU abstract 41. *J Clin Oncol.* 2021;39(6 suppl).[1]

disease in 19% vs 9%, respectively (*P*=.004), cardiac disease in 33% vs 29% (*P*=.417), pulmonary disease in 10% vs 13% (*P*=.321), deep vein thrombosis or pulmonary embolism in 5% vs 9% (*P*=.090), diabetes mellitus in 33% vs 26% (*P*=.124), and obesity in 25% vs 28% (*P*=.009).[1]

The distribution of clinical severity of COVID-19 was similar between the 2 cohorts (Figure 10).[1] The clinical severity of COVID-19 was based on the maximum score on the World Health Organization ordinal scale for COVID-19 clinical improvement, in which 1 indicates ambulatory with no limitations of activities; 2 indicates ambulatory with limitation of activities; 3 indicates hospitalized with no oxygen therapy; 4 indicates hospitalized with oxygen required by mask or nasal prongs; 5 indicates hospitalized with the use of non-invasive ventilation or high-flow oxygen; 6 indicates hospitalized with the use of intubation and mechanical ventilation; 7 indicates hospitalized with the use of ventilation and additional oxygen support (ie, pressors, renal replacement therapy, or extracorporeal membrane oxygenation), and 8 indicates death.[2]

After adjusting for age, body mass index (BMI), and prostate cancer disease state, the OS was similar between the 2 groups (HR, 1.28; 95% CI, 0.79-2.08; *P*=.357). In a subgroup analysis of OS, patients 70 years of age and older had worse survival compared with younger patients (HR, 3.65; 95% CI, 2.22-6.00). In contrast, ADT use, BMI, and prostate cancer clinical disease were not found to be associated with OS.[1]

The study authors also investigated a potential link between ADT use and severe COVID-19–related outcomes. After adjusting for age, BMI, and clinical disease state, the rates of hospitalization (HR, 1.07; 95% CI, 0.61-1.87; *P*=.820), oxygen utilization (HR, 1.29; 95% CI, 0.77-2.17; *P*=.149), and mechanical ventilation (HR, 1.07; 95% CI, 0.51-2.23; *P*=.866) were found to be similar between the 2 groups of patients.[1]

Based on this retrospective analysis, the authors of this study concluded that the use of ADT prior to COVID-19 diagnosis was not protective against severe COVID-19 illness (defined by hospitalization, supplemental oxygen use, or death).[1] The lack of a protective effect may be better defined by a recent preclinical publication, which evaluated the anti-SARS-CoV-2 effect of enzalutamide in prostate cancer and lung cancer cells, human lung organoids, and mice. Enzalutamide was found to inhibit infection with the SARS-CoV-2 virus in prostate cells, but not in lung cancer cells or lung organoids. The investigators additionally concluded that there were no findings to support a protective role of enzalutamide in treating COVID-19 via reduction of *TMPRSS2* expression in lung cells.[3]

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Highlights in Advanced Prostate Cancer From the 2021 Genitourinary Cancers Symposium: Commentary

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The 2021 Genitourinary Cancers Symposium was held virtually in mid-February, a reflection of the continued effect of the COVID-19 pandemic on large meetings and gatherings. This year, several studies presented interesting data that, while perhaps not yet practice-changing, answered some important questions in the field of advanced prostate cancer.

Novel Agents and Combinations

The investigational agent ^{177}Lu-PSMA-617 (LuPSMA) is a radiopharmaceutical that conjugates lutetium-177 to the small molecule ligand PSMA-617, and is designed to bind with high affinity to PSMA, a cell surface enzyme linked to prostate cancer differentiation.[1] Because PSMA is highly expressed on prostate cancer cells, I like to describe this drug to patients as a "smart bomb," whereby the drug can be brought directly to the tumor to release energetic beta particles that destroy cancer cells at the disease site while sparing most normal tissue. ^{177}Lu-PSMA-617 was compared with cabazitaxel in the small, randomized phase 2 TheraP ANZUP 1603 trial, which has now been published in *The Lancet*.[2,3]

In this study, ^{177}Lu-PSMA-617 was shown to be quite active, with a higher degree of PSA response compared to what is considered a standard of care (66% with ^{177}Lu-PSMA-617 vs 36% with cabazitaxel). It also had a beneficial effect on radiographic and PSA progression-free survival. As the Kaplan-Meier curves showed, even though the median was not different (5.1 months in both arms), patients in the ^{177}Lu-PSMA-617 arm achieved more profound and durable responses as reflected by later separation of the curves and the hazard ratio for progression or death (HR, 0.63; 95% CI, 0.46-0.86; *P*=.0028). The other bit of good news shown by this study was that ^{177}Lu-PSMA-617 has a well tolerated safety profile, with less neuropathy and neutropenia (and thus a lower infection risk) than seen with cabazitaxel, though there was a higher rate of thrombocytopenia. PSMA is expressed in lacrimal and salivary glands, and rates of dry mouth and dry eyes were higher with ^{177}Lu-PSMA-617.[2,3]

Ultimately, however, we need to know how this agent will affect long-term radiographic PFS and of course OS, and these are key endpoints of the ongoing phase 3 VISION study, expected to report out soon.[4] In the VISION study, patients will have received at least 1 novel androgen axis drug (eg, enzalutamide or abiraterone) and also were previously treated with 1 to 2 taxane regimens prior to receipt of ^{177}Lu-PSMA-617 plus best supportive/best standard of care or best supportive/best standard of care alone. Given the encouraging results shown in the TheraP ANZUP 1603 trial against cabazitaxel, which is highly effective in this setting, ^{177}Lu-PSMA-617 may prove to have improved OS in VISION, based on data from the phase 3 CARD trial showing cabazitaxel led to better outcomes than a second AR in this setting.[5] The TheraP ANZUP 1603 trial by itself is not practice-changing, but suggests that durable efficacy and quality of life is achievable with ^{177}Lu-PSMA-617, which may provide a promising nonchemotherapy alternative that can result in clinical benefits to many men with mCRPC. A major emerging issue will of course relate to loss of PSMA expression, which can be seen with lineage plasticity and neuroendocrine/small cell transformation, and further targeted approaches are likely needed for these PSMA-negative divergent tumors.

Results of the ACIS trial were also presented. This study was very similar in design to the previously reported Alliance A031201 phase 3 trial of enzalutamide alone compared with enzalutamide, abiraterone, and prednisone for mCRPC.[6] The rationale for both studies was based on the idea that combining 2 androgen pathway antagonists with different mechanisms of action and potentially minimal cross-resistance might show greater efficacy than the one agent alone.

Apalutamide and enzalutamide block the ligand-binding domain of the androgen receptor, while abiraterone reduces androgenic ligands and also reduces AR signaling through this same ligand-binding domain. Remarkably, both studies showed highly similar outcomes, failing to show any difference in OS while delaying rPFS by approximately 5 to 7 months. It was interesting that with longer-term follow-up of ACIS, the difference in rPFS grew to over 7 months, but this rPFS benefit did not translate to an improved OS, perhaps due to the emergence of highly resistant and/or more aggressive tumors following progression. Like PSMA targeting, this can result from a neuroendocrine transformation and/or lineage plasticity and loss of AR dependence, but in this case, it can result from the emergence of AR splice variants, such as AR-V7, which can constitutively signal without ligand. Further, the data showed no benefit in other study outcomes, such as patient-reported outcomes, PSA changes, or clinical progression. This lack of benefit on OS and other outcomes, combined with a higher rate of toxicities and discontinuations, lends no support to the argument to combine the 2 agents together, and these data are not practice-changing. Instead, these agents should remain as sequential therapies, and a focus needs to be made on novel combinations of agents with truly unique mechanisms of action.[7]

A randomized phase 2 trial presented by Dr Rana McKay evaluated the combination of the VEGF receptor inhibitor cediranib with the PARP inhibitor olaparib. The rationale for this combination is preclinical evidence that tumor hypoxia leads to downregulation of DNA repair enzymes, creating the potential for synthetic lethality with agents that further inhibit backup DNA repair mechanisms and agents that cause tumor hypoxia, such as VEGF inhibitors. Thus, olaparib may combine with cediranib to achieve synthetic lethality even in the absence of HR-deficiency.[8] Overall, the rPFS was slightly improved and marginally significant. However, when looking at the rPFS by HR status, it is clear that those patients who are HR-proficient derived no benefit from this combination, and thus the underlying hypothesis of this study is likely disproved. Patients in the HR-deficient category did experience a modest rPFS benefit; however, this may have been driven by an imbalance with a higher incidence of baseline *BRCA2* mutations in this combination group, where *BRCA2*-driven mCRPC is known to result in better outcomes with olaparib already. These results, combined with greater toxicity in the combination arm, suggest that the use of this combination might not be able to broaden to include the mCRPC patient population beyond HR-deficient patients, for whom olaparib is currently approved.[9]

Immunotherapy Combinations

Results from 2 early-stage combination basket studies in PD-1 inhibitor immunotherapy for mCRPC were reported. Cohort B in the KEYNOTE-365 trial evaluated pembrolizumab plus docetaxel and prednisone.[10] Arm B in CheckMate 9KD tested nivolumab plus docetaxel. Outcomes from both trials were generally the same, demonstrating clear evidence for efficacy in PSA, tumor responses, and PFS times in the 8 to 10 month range and survival times in the 18 to 21 month range.[11] These outcomes, however, do not appear to be substantially greater than that of docetaxel alone, although without a contemporary control group, it is challenging to know for sure. In addition, differences in patient populations alone can explain changes in rPFS and OS, based on inclusion of patients with more favorable or unfavorable prognostic characteristics. The inclusion of patients who developed disease progression during prior treatment with AR inhibitors, such as enzalutamide or abiraterone, does suggest that there may be some clinical benefit for this combination of chemoimmunotherapy in some men. However, identifying who such patients are in advance will be critical; such groups may include those with MSI-high mCRPC, CDK12-altered mCRPC, or tumor mutation burden (TMB) high disease. Compared with docetaxel alone, the combination of docetaxel plus pembrolizumab or nivolumab led to higher rates of immune-related toxicities, particularly pneumonitis, as well as potentially life-threatening or fatal toxicities. Both combinations are moving forward to evaluation in ongoing phase 3 studies (CheckMate 7DX and KEYNOTE-921), where we will learn whether overall survival can be impacted by chemoimmunotherapy in this post-ARSI mCRPC setting.[12,13]

Previously published in *The New England Journal of Medicine*, the TITAN study led to the approval of apalutamide in men with metastatic hormone-sensitive disease.[14] Updated data presented here confirmed what we already knew from the initial results; with an additional 22 months of follow-up, the hazard ratio for death changed from 0.67 (95% CI, 0.51-0.89) to 0.65 (95% CI, 0.53-0.79).[15] This is good news for patients, who are living longer than ever before, with a median not reached in patients treated with apalutamide plus ADT. An analysis did show that patients with visceral metastases and prior docetaxel use may receive less benefit, though the numbers in these subgroups were small. There were no new safety signals from this updated report. Interestingly, a cumulative analysis of select side effects revealed that while some toxicities (such as rash) tend to occur early, others, such as falls, hypertension and CV risk, and fractures show a continual risk. This emphasizes the need for ongoing blood pressure and CV risk monitoring, bone-density monitoring and the use of bone health agents, exercise programs, and physical therapy.

Genomic Profiling

Data from the phase 3 IPATential150 trial were previously reported at ESMO 2020, showing that the addition of ipatasertib to abiraterone acetate and prednisone did not lead to a statistically significant improvement in rPFS or OS in the intention-to-treat population.[16] However, patients with *PTEN* loss did show a significant improvement in rPFS, but not in OS. Thus, an exploratory biomarker analysis was performed to try to identify patient groups who would benefit from Akt inhibition.[17] It is interesting that the investigators observed increasing benefit with greater *PTEN* loss, suggesting a dose-related increase in the efficacy of AKT inhibition with increasing activation of the PI3K/Akt pathway. However, the benefit was not large in magnitude, and was limited to rPFS (not OS) and not in direct measures of patient symptoms or benefit. Thus, more data and follow-up are needed before this treatment is considered for clinical use in men with mCRPC.

One of the limitations of genomic profiling in prostate cancer is that many studies are skewed toward having a larger proportion of data from White vs Black men, which disregards the higher incidence of prostate cancer in Black men. Black men face a disproportionately higher prostate cancer mortality and have largely not been included in most prospective clinical trials commensurate with population risk. Dr Tamer Khashab and colleagues conducted an NGS analysis in their hospital system that was much more inclusive of Black men than many previous studies.[18] This group used a multigene sequencing panel of both tissue and liquid specimens from 100 men with prostate cancer (of whom 53 were African American). They reported some interesting findings, namely an enrichment of alterations in the *AR*, *TP53*, *SPOP*, and HR repair genes. When they extended their analysis to a broader nationwide cohort from de-identified NGS data (1765 patients, of whom 307 were African American), the investigators did not observe any major differences between African Americans and non–African Americans in the somatic landscape, however, including within DNA homologous repair genes such as *BRCA2*. They did confirm reduced prevalence of PTEN loss and TMPRSS2-ERG fusions in Black men. It is difficult to understand why they initially observed the higher incidence of gene alterations in their hospital system without having more knowledge about the data, including the hormone sensitivity of the disease, the disease stage, and treatment background, thus emphasizing the importance of large validation studies ideally linked to clinical outcomes.

ADT and COVID-19

TMPRSS2 has been implicated, together with angiotensin-converting enzyme 2 (ACE2), as critical for the SARS-CoV-2 virus port of entry into cells. TMPRSS2 expression in prostate cancer cells is known to be downregulated with ADT. However, it has remained unknown if ADT would have the same effect in lung cancer cells (although a recent report demonstrated that enzalutamide could inhibit SARS-CoV-2 virus infection of prostate cells, but not lung cancer cells or lung organoids).[19] Several studies reported at the ASCO GU meeting explored the hypothesis that ADT might improve COVID-19 outcomes.[20-22] However, it turned out that the data did not support this, with 3 studies reporting there was no difference in the incidence, severity, or mortality of COVID-19 among patients with prostate cancer who were either receiving or not receiving ADT. One dataset did report a slightly reduced death rate with more potent second-generation AR antagonists, but the patient number was small. This hypothesis is under continued evaluation in a prospective Veterans Affairs study to determine if temporary androgen suppression with degarelix will improve clinical outcomes of veterans who are hospitalized within an acute care ward due to COVID-19.[23]

Disclosure

Dr Armstrong has relationships with Astellas Pharma Inc., AstraZeneca, Atheneum, Bayer, Bionest, Bristol Myers Squibb, Cipla, Clarion Healthcare, Clovis Oncology, Core2Ed, Dendreon Valeant Corporation, FirstWord, Global Guidepoint, KeyQuest, Merck Sharpe & Dohme (Merck & Co, USA), Neil Love CME, Pfizer Inc., Ron Schleif Oncology, Schlesinger Associates, and Slingshot Insights. He has received consulting fees/research support from Janssen.

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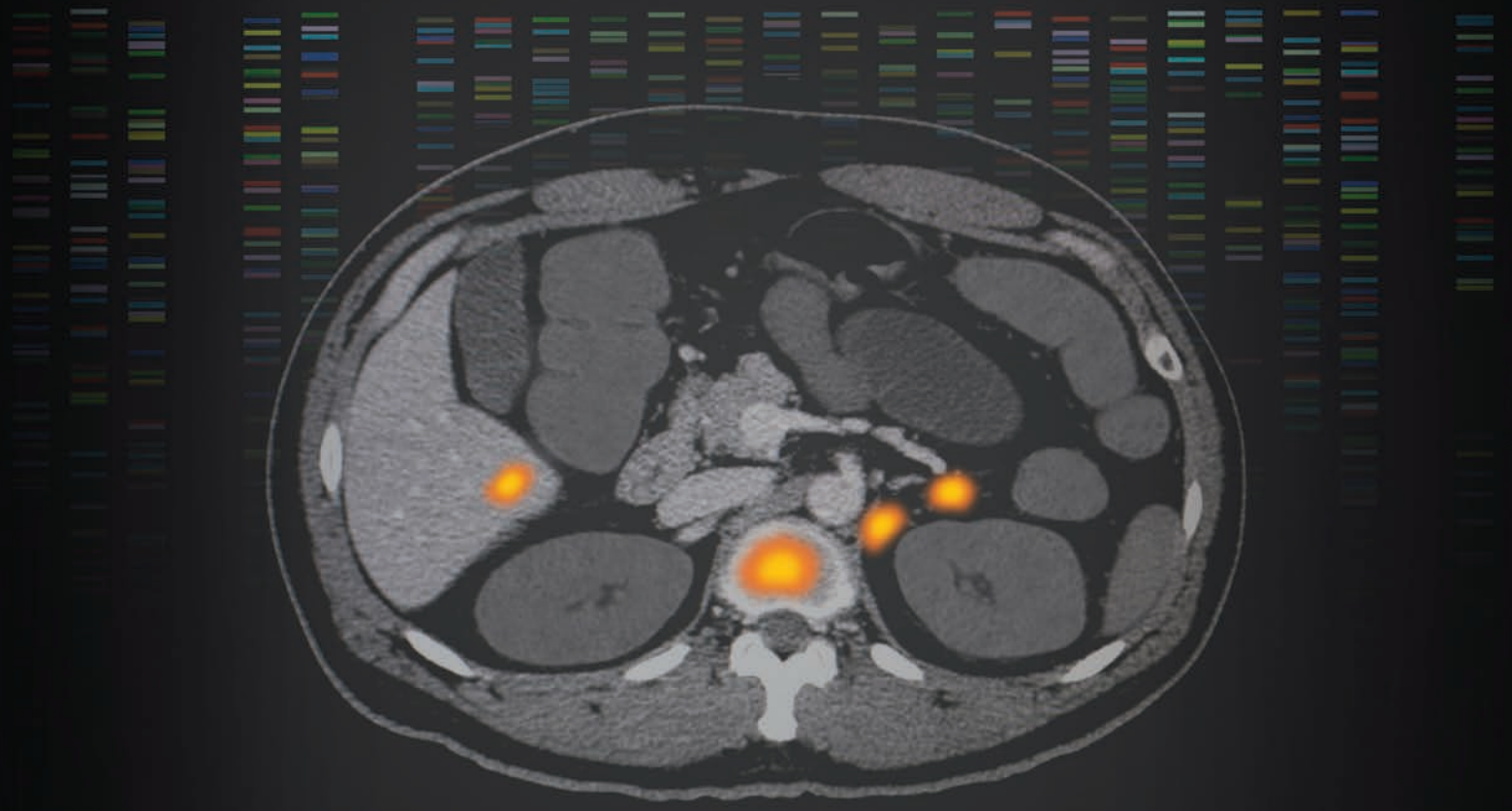

Prostate-specific membrane antigen (PSMA) is overexpressed in **>80%** of men with prostate cancer and can be detected by PSMA PET.[1-3]

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