Clinical Advances in
HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

August 2021 Volume 19, Issue 8, Supplement 18

A SPECIAL MEETING REVIEW EDITION

Highlights in Advanced Prostate Cancer From the 2021 American Society of Clinical Oncology Annual Meeting

A Review of Selected Presentations From the 2021 ASCO Annual Meeting

• June 4-8, 2021

Special Reporting on:

- Phase 3 Study of ^{177}Lu-PSMA-617 in Patients With Metastatic Castration-Resistant Prostate Cancer (VISION)
- A Phase 3 Trial With a 2×2 Factorial Design of Abiraterone Acetate Plus Prednisone and/or Local Radiotherapy in Men With De Novo Metastatic Castration-Sensitive Prostate Cancer: First Results of PEACE-1
- Decreased Fracture Rate by Mandating Bone-Protecting Agents in the EORTC 1333/PEACE-3 Trial Combining Ra-223 With Enzalutamide Versus Enzalutamide Alone: An Updated Safety Analysis
- Novel Framework for Treatment Response Evaluation in Patients With Metastatic Castration-Resistant Prostate Cancer Using PSMA PET/CT (RECIP): An International Multicenter Study
- Ancestral Characterization of the Genomic Landscape in Prostate Cancer
- PSMA-Targeted Imaging With ^{18}F-DCFPyL-PET/CT in Patients With Biochemically Recurrent Prostate Cancer—A Phase 3 Study (CONDOR): A Subanalysis of Correct Localization Rate and Positive Predictive Value by Standard of Truth
- ODENZA, a Prospective, Randomized, Open-Label, Multicenter, Cross-Over Phase 2 Trial of Preference Between Darolutamide and Enzalutamide in Men With Asymptomatic or Mildly Symptomatic Metastatic Castrate-Resistant Prostate Cancer
- First Results From a Randomized Phase 2 Study of Cabazitaxel vs an Androgen Receptor–Targeted Agent in Patients With Poor-Prognosis Castration-Resistant Prostate Cancer

PLUS Meeting Abstract Summaries

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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]

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Phase 3 Study of ^{177}Lu-PSMA-617 in Patients With Metastatic Castration-Resistant Prostate Cancer (VISION)

Prostate-specific membrane antigen (PSMA) is a membrane-bound enzyme that has restricted expression in normal tissue but is highly expressed in prostate cancer, including metastatic lesions.[1] This feature makes PSMA a suitable target for both positron emission tomography (PET) imaging and radioligand therapy. ^{177}Lu-PSMA-617 is a targeted radioligand therapy that binds with high affinity to PSMA on the cell membrane and delivers a payload of beta particle–emitting lutetium-177 via receptor-mediated endocytosis.

At the plenary session of the 2021 American Society of Clinical Oncology annual meeting, Morris and colleagues presented results of VISION, a phase 3 open-label trial investigating the use of ^{177}Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer (CRPC).[1] The trial enrolled patients who were ineligible for chemotherapy as their next treatment. The patients had a life expectancy of at least 6 months and had previously received at least 1 androgen receptor pathway inhibitor and either 1 or 2 taxane regimens. The patients met the criteria for PSMA-positive cancer according to assessment with ^{68}Gallium-PSMA-PET/computed tomography (CT) scans. Namely, the patients had at least 1 PSMA-positive metastatic lesion as defined by uptake greater than that in the liver and no PSMA-negative metastatic lesions larger than 1 cm in the bone or a solid organ, or larger than 2.5 cm in the lymph nodes.[1]

A total of 831 patients were randomly assigned in a 1:2 ratio to receive standard-of-care treatment alone or in combination with ^{177}Lu-PSMA-617 at a dose of 7.4 GBq (200 mCi) every 6 weeks for 4 cycles.[1] Patients who responded to treatment but who had residual disease were permitted to receive an additional 2 cycles. Standard-of-care treatment was planned before randomization and excluded chemotherapy, radium-223, immunotherapy, and investigational drugs.

The VISION trial was designed with prespecified alternate primary endpoints: radiographic progression-free survival (PFS), as defined by the Prostate Cancer Working Group 3, and overall survival (OS). The trial would be considered positive if either

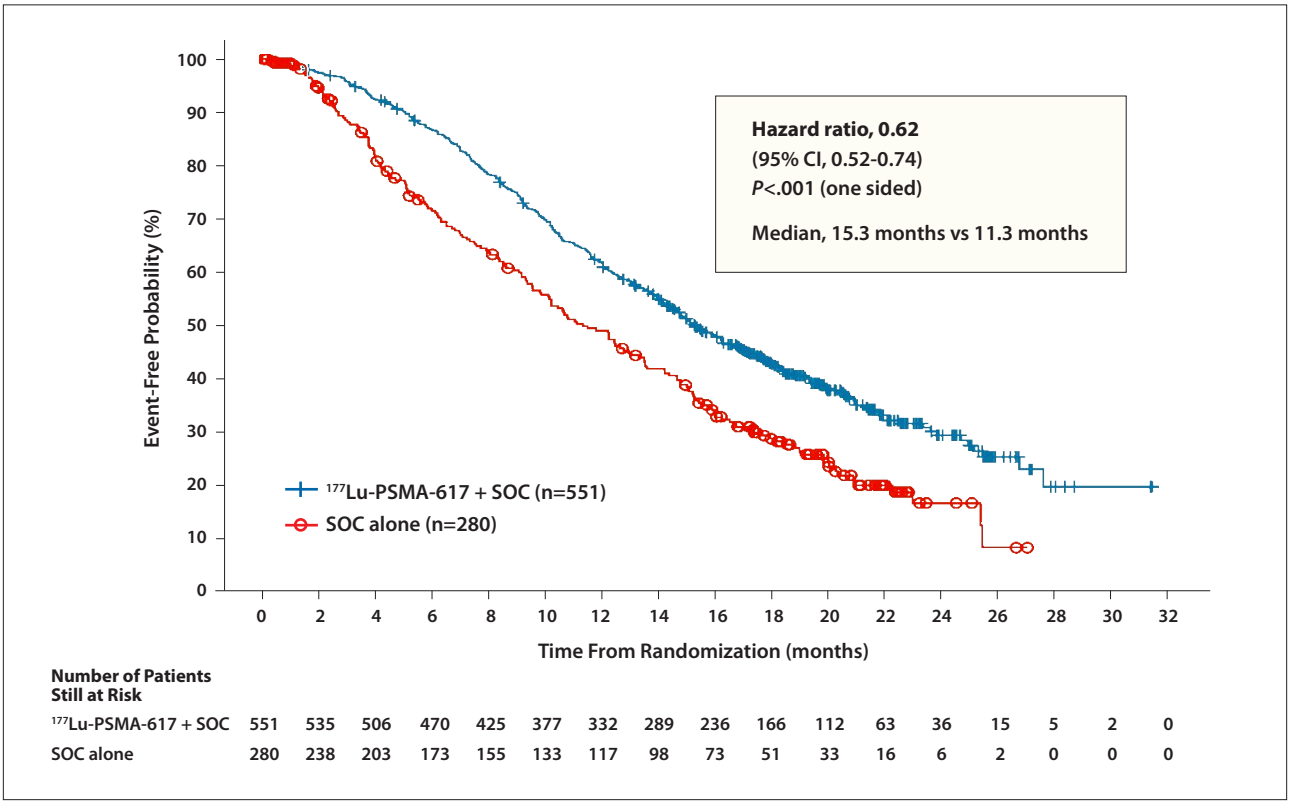

Figure 1. The median overall survival among patients in the phase 3 VISION trial, which evaluated the addition of ^{177}Lu-PSMA-617 to the standard of care in patients with metastatic castration-resistant prostate cancer. SOC, standard of care. Adapted from Morris MJ et al. ASCO abstract LBA4. *J Clin Oncol.* 2021;39(suppl 15).[1]

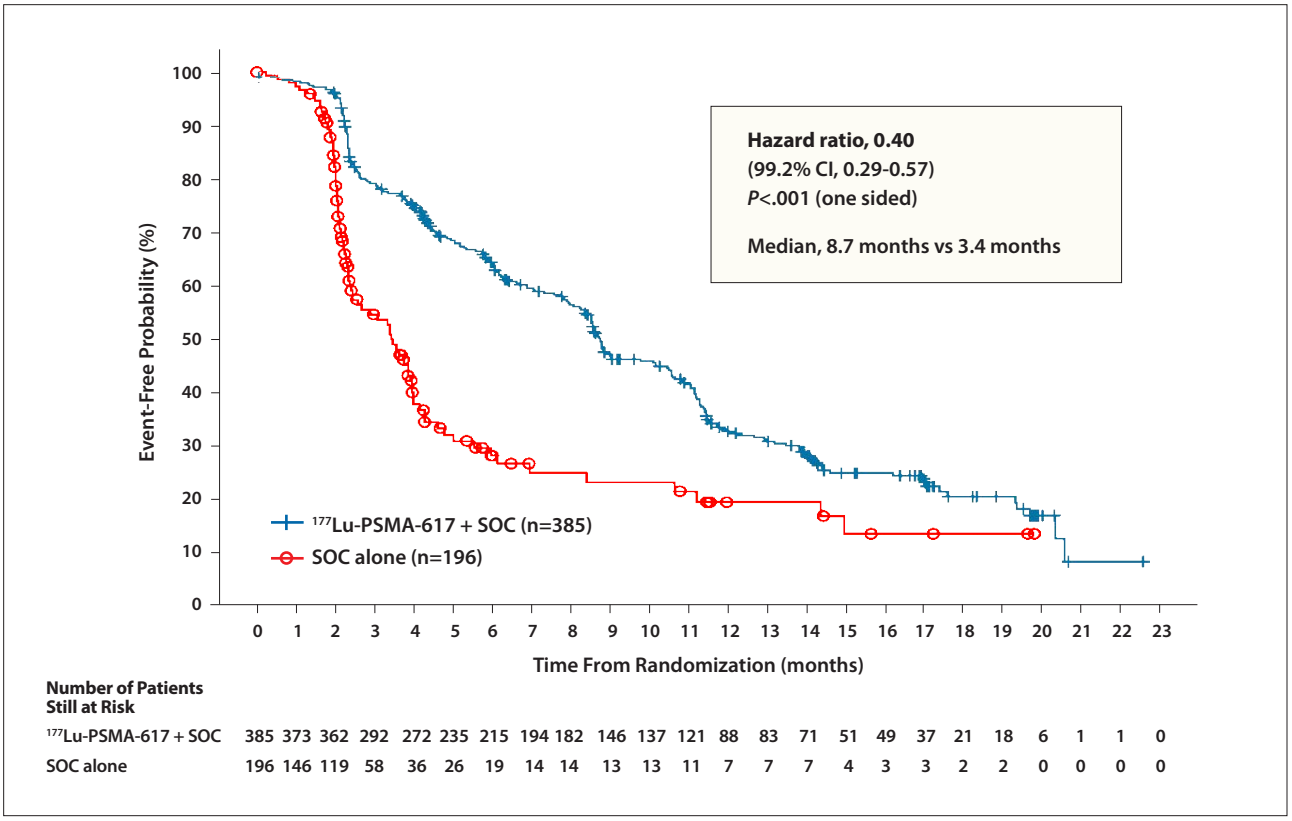

Figure 2. Radiographic progression-free survival among patients in the phase 3 VISION trial, which evaluated the addition of ^{177}Lu-PSMA-617 to the standard of care in patients with metastatic castration-resistant prostate cancer. SOC, standard of care. Adapted from Morris MJ et al. ASCO abstract LBA4. *J Clin Oncol*. 2021;39(suppl 15).[1]

or both of the primary endpoints were statistically significant.

Enrollment began in June 2018.[1] An excessive dropout rate of patients randomly assigned to the control arm was observed prior to the start of the treatment period. The US Food and Drug Administration (FDA) agreed to a strategic remediation plan, commencing in March 2019, that capped accrual at noncompliant trial sites, strengthened collaborations between nuclear medicine physicians and medical oncologists, and reeducated clinicians on the appropriate protocol, conduct, and patient care. As a result, the dropout rate was reduced from 56% to 16% in the control arm. Furthermore, only patients randomly assigned after March 2019 were assessed for the endpoint of radiographic PFS (n=581), to reduce the potential for bias during interpretation of the scans. OS was assessed in all patients randomly assigned to treatment (N=831) because this endpoint was unaffected by such potential for bias.

The patients' baseline characteristics and previous rates of exposure to androgen receptor pathway inhibitors and taxane chemotherapy were well balanced across the treatment arms and the 2 analysis sets (all randomized patients and those in the radiographic PFS subset).[1] Approximately half of the study population (41% to 54%) had received more than 1 of these previous cancer treatments.

Among all the patients randomly assigned to receive treatment, the median OS was 15.3 months with ^{177}Lu-PSMA-617 plus the standard of care (n=551) vs 11.3 months with the standard of care alone (Figure 1). ^{177}Lu-PSMA-617 reduced the risk of death by 38% vs the standard of care alone (n=280; hazard ratio [HR], 0.62; *P*<.001).[1] Similar findings were observed when OS was analyzed in the radiographic PFS analysis set (patients who were enrolled after the implementation of remediations to reduce the dropout rate in the standard-of-care arm). OS was generally consistent across prespecified stratification factor subgroups (eg, use of androgen receptor pathway inhibitors in planned standard of care, use of lactate dehydrogenase).

In the radiographic PFS analysis set, the median radiographic PFS was 8.7 months with ^{177}Lu-PSMA-617 (n=385) vs 3.4 months with the standard of care alone (Figure 2). ^{177}Lu-PSMA-617 reduced the risk by 60% vs the standard of care alone (n=196; HR, 0.40; *P*<.001).[1] The radiographic PFS benefit was maintained throughout the entire population of randomly assigned

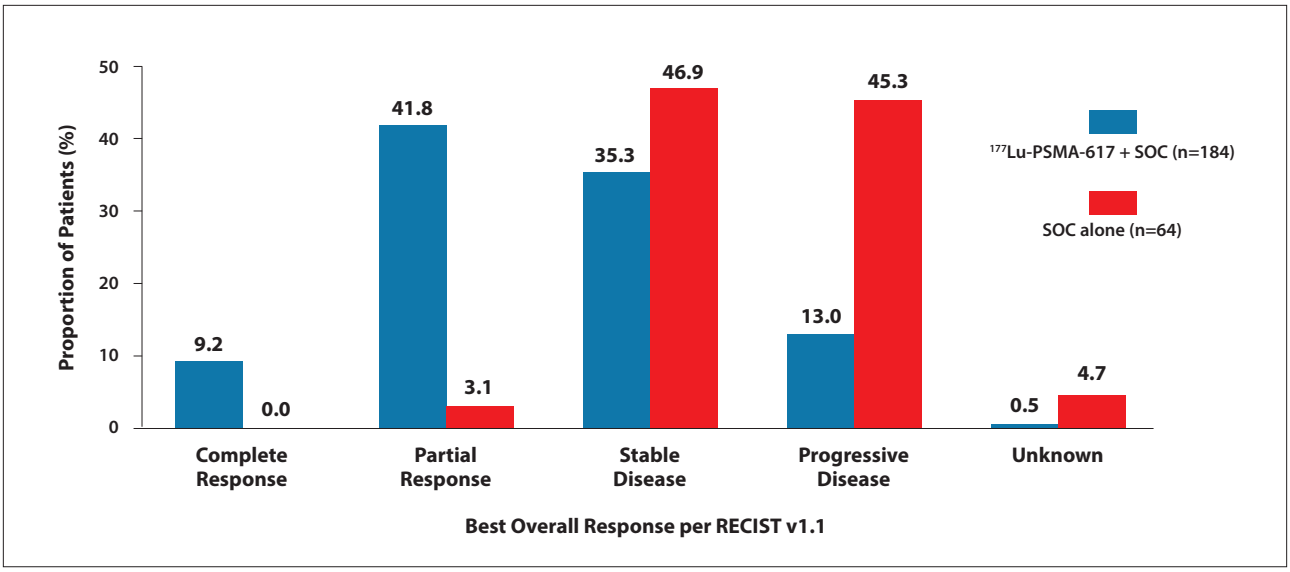

Figure 3. Responses among patients in the phase 3 VISION trial, which evaluated the addition of ^{177}Lu-PSMA-617 to the standard of care in patients with metastatic castration-resistant prostate cancer. RECIST, Response Evaluation Criteria in Solid Tumors; SOC, standard of care. Adapted from Morris MJ et al. ASCO abstract LBA4. *J Clin Oncol*. 2021;39(suppl 15).[1]

patients and was consistent across all stratification subgroups with the exception of 2 racial subgroups—Black/African American and Asian patients—which had low numbers.

Measurable disease was reported in 184 patients in the ^{177}Lu-PSMA-617 arm and 64 patients in the control arm.[1] Response to treatment was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Among patients treated with ^{177}Lu-PSMA-617, the rate of complete response was 9.2% and the rate of partial response was 41.8% (Figure 3). In the control arm, these rates were 0% and 1.3%, respectively. In addition, ^{177}Lu-PSMA-617 improved levels of prostate-specific antigen (PSA). A decrease of at least 50% was reported in 46.0% of the treatment arm vs 7.1% of the control arm. A decrease of at least 80% was reported in 33.0% vs 2.0%, respectively.

The treatment duration was 7.82 months in the ^{177}Lu-PSMA-617 arm vs 2.07 months in the control arm.[1] In the ^{177}Lu-PSMA-617 arm, patients started 5 cycles of the standard-of-care treatment; in the control arm, patients started 2 cycles of treatment. More than 50% of patients received the optional fifth or sixth cycles of ^{177}Lu-PSMA-617. After completing the study, a numerically higher proportion of patients in the standard-of-care arm went on to receive postprotocol taxane chemotherapy (18.0% vs 21.8%), indicating that the OS benefit in favor of ^{177}Lu-PSMA-617 was not related to an imbalance of patients receiving chemotherapy after radioligand therapy. Few patients received postprotocol radiopharmaceutical therapy with radium-223 or an off-study radioligand agent (2.9% in the treatment arm vs 8.2% in the control arm).

The rate of drug-related treatment-emergent adverse events (TEAEs) was higher in the ^{177}Lu-PSMA-617 arm.[1] Any-grade TEAEs were reported in 85.3% of the ^{177}Lu-PSMA-617 arm vs 28.8% of the standard-of-care arm. Grade 3 to 5 TEAEs were reported by 28.4% vs 3.9%, respectively. There were 5 deaths attributed to ^{177}Lu-PSMA-617, resulting in a grade 5 event rate of 0.9% (vs 0% in the standard-of-care arm).

There were no unexpected or concerning safety signals. ^{177}Lu-PSMA-617 was associated with higher rates of any-grade bone marrow suppression (47.4% vs 17.6%), dry mouth (39.3% vs 1.0%), and nausea and vomiting (39.3% vs 17.1%). Grade 3 to 5 bone marrow suppression (23.4% vs 6.8%) occurred at a somewhat higher frequency in the ^{177}Lu-PSMA-617 arm. Similar rates of nausea and vomiting (1.5% vs 0.5%) and renal effects (3.4% vs 2.9%) were observed between the treatment arms.

The study investigators concluded that the addition of ^{177}Lu-PSMA-617 to standard-of-care treatment significantly extended OS and delayed radiographic PFS among patients with metastatic CRPC who had progressed following treatment with androgen receptor pathway inhibitors and chemotherapy. ^{177}Lu-PSMA-617 was safe and well tolerated, with no new safety signals. These findings warrant the adoption of ^{177}Lu-PSMA-617 as a new treatment option in this patient population.

Reference

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A Phase 3 Trial With a 2×2 Factorial Design of Abiraterone Acetate Plus Prednisone and/or Local Radiotherapy in Men With De Novo Metastatic Castration-Sensitive Prostate Cancer: First Results of PEACE-1

The standard of care for patients with metastatic prostate cancer has evolved rapidly since 2013, when clinical trial data began to show that docetaxel and androgen receptor pathway inhibitors (eg, abiraterone acetate, apalutamide, and enzalutamide) improve survival, and radiotherapy of the primary tumor improves outcomes in men with oligometastatic disease.[1-8] The Prostate Cancer Consortium in Europe (PEACE) is an academic program that facilitates phase 3 trials in prostate cancer.[9] The phase 3 PEACE-1 trial was conducted between November 2013 and December 2018 in men with de novo metastatic prostate cancer who were permitted to receive up to 3 months of androgen deprivation therapy. The study used a 2 × 2 factorial design to evaluate abiraterone acetate at 1000 mg/day and external beam radiotherapy administered to the prostate (74 grays in 37 fractions) in combination with the standard of care.[9] The standard-of-care regimen initially consisted of continuous androgen deprivation therapy. The addition of docetaxel was permitted as a component of the standard of care in 2015, and then required from 2017 through the end of the trial.

In the PEACE-1 trial, patients were randomly assigned to receive the standard of care alone (n=296) or in combination with abiraterone acetate plus prednisone at 5 mg twice daily (n=292), radiotherapy (n=293), or abiraterone acetate, prednisone, and radiotherapy (n=292).[9]

Fizazi and colleagues presented data for 1 of the 2 co–primary endpoints, radiographic PFS.[9] This endpoint was defined according to criteria from the Prostate Cancer Working Group 2, with imaging requested at least every 6 months after the patient developed castration resistance. Statistical testing revealed no interaction between abiraterone acetate and radiotherapy, allowing the 2 abiraterone acetate arms to be pooled and limiting the potential for false-positive findings.

There were no meaningful dif-

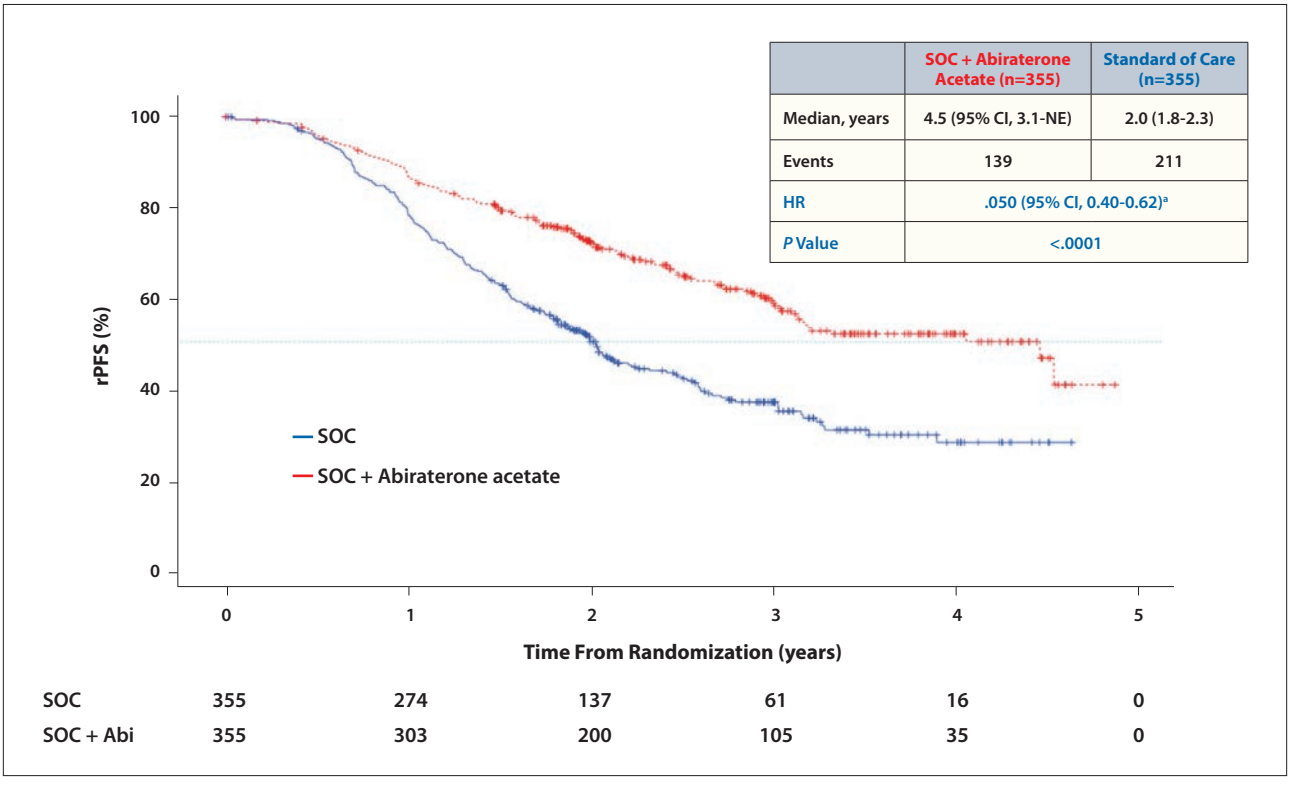

Figure 4. Radiographic progression-free survival among the subset of patients who received docetaxel as a component of the standard-of-care regimen, with or without radiotherapy, in the phase 3 PEACE-1 trial. The trial evaluated the standard of care alone or in combination with abiraterone acetate plus prednisone; radiotherapy; or abiraterone acetate, prednisone, and radiotherapy. [a]Adjusted based on stratification parameters (radiotherapy, performance status, type of castration, and metastatic burden.) Abi, abiraterone acetate; HR, hazard ratio; rPFS, radiographic progression-free survival. Adapted from Fizazi K et al. ASCO abstract 5000. *J Clin Oncol*. 2021;39(suppl 15).[9]

ferences in the baseline characteristics between patients randomly assigned to receive abiraterone acetate in combination with the standard of care (with or without radiotherapy) vs patients randomly assigned to the standard of care (with or without radiotherapy).[9] The median time from diagnosis was 2.3 months, 57% of the trial population had high disease burden, and approximately 60% received docetaxel (median 6 cycles). The median time to discontinuation of abiraterone acetate was 31.4 months.

In the overall population, the median radiographic PFS was 4.5 years in patients treated with abiraterone acetate plus the standard of care vs 2.2 years in those treated with the standard of care alone (HR, 0.54; *P*<.0001).[9] Similar findings were observed in the subset of patients treated with docetaxel. In these patients, the median radiographic PFS was 4.5 years with abiraterone acetate vs 2.0 years with the standard of care alone (HR, 0.50; *P*<.0001; Figure 4). All tested subgroups appeared to benefit from the addition of abiraterone acetate.

CRPC-free survival, a secondary endpoint, was 3.8 years in the abiraterone acetate arm vs 1.5 years in the standard-of-care arm (HR, 0.40; *P*<.0001). Among patients treated with docetaxel, CRPC-free survival was 3.2 years vs 1.4 years, respectively (HR, 0.38; *P*<.0001).[9]

The addition of abiraterone acetate reduced clinical PFS (an exploratory endpoint) by 46% in the overall population and by 50% in the docetaxel population. Clinical PFS was defined as symptomatic progression based on the investigator's judgment, radiographic progression, or death. In the overall population, the median clinical PFS was 4.3 years with abiraterone acetate plus the standard of care vs 2.1 years with the standard of care alone (HR, 0.54; 95% CI, 0.46-0.63; *P*<.0001). In the docetaxel-treated population, these durations were 4.1 years vs 1.9 years, respectively (HR, 0.50; 95% CI, 0.40-0.62; *P*<.0001).

The investigators reported on the high-grade adverse events that occurred during the first 6 months of treatment in the docetaxel analysis set. The concomitant use of abiraterone acetate and docetaxel did not increase the risk for febrile neutropenia (5% with abiraterone acetate vs 5% without abiraterone acetate) or hematologic toxicities related to docetaxel (14% vs 15%). Typical adverse events related to abiraterone acetate, such as hypertension (12% vs 8%), occurred as expected. The adverse events associated with docetaxel, such as gastrointestinal toxicity and fatigue, were less common in the abiraterone acetate arm (each occurring in 2% vs 4%). Concomitant use of prednisone in the abiraterone acetate arm may have impacted these rates.

ABSTRACT SUMMARY First-in-Human Study of TAS3681, an Oral Androgen Receptor (AR) Antagonist With AR and AR Splice Variant Downregulation Activity, in Patients With Metastatic Castration-Resistant Prostate Cancer Refractory to Abiraterone and/or Enzalutamide and Chemotherapy

De Bono and colleagues presented the first-in-human, phase 1 dose-escalation study of TAS3681, an orally available androgen receptor antagonist with demonstrated antitumor activity in androgen receptor splice variant–positive, enzalutamide-resistant models (Abstract 5031). Fifty-six men with metastatic CRPC received 28-day cycles of TAS3681. The main concern was prolongation of the corrected QT interval at higher doses (>400 mg twice daily). Grade 3 or higher adverse events occurred in 38% of patients, and treatment-related adverse events occurred in 20%. The most frequent treatment-related adverse events were fatigue (4%) and diarrhea (4%). In the 300 mg twice daily cohort, the overall tumor response rate was 22%. At the recommended phase 2 dose of 300 mg twice daily, TAS3681 exhibited a manageable safety profile and antitumor activity in heavily pretreated patients with multidrug-resistant metastatic CRPC. The study expansion phase is enrolling patients who developed progressive disease during treatment with abiraterone acetate/enzalutamide with or without taxane therapy.

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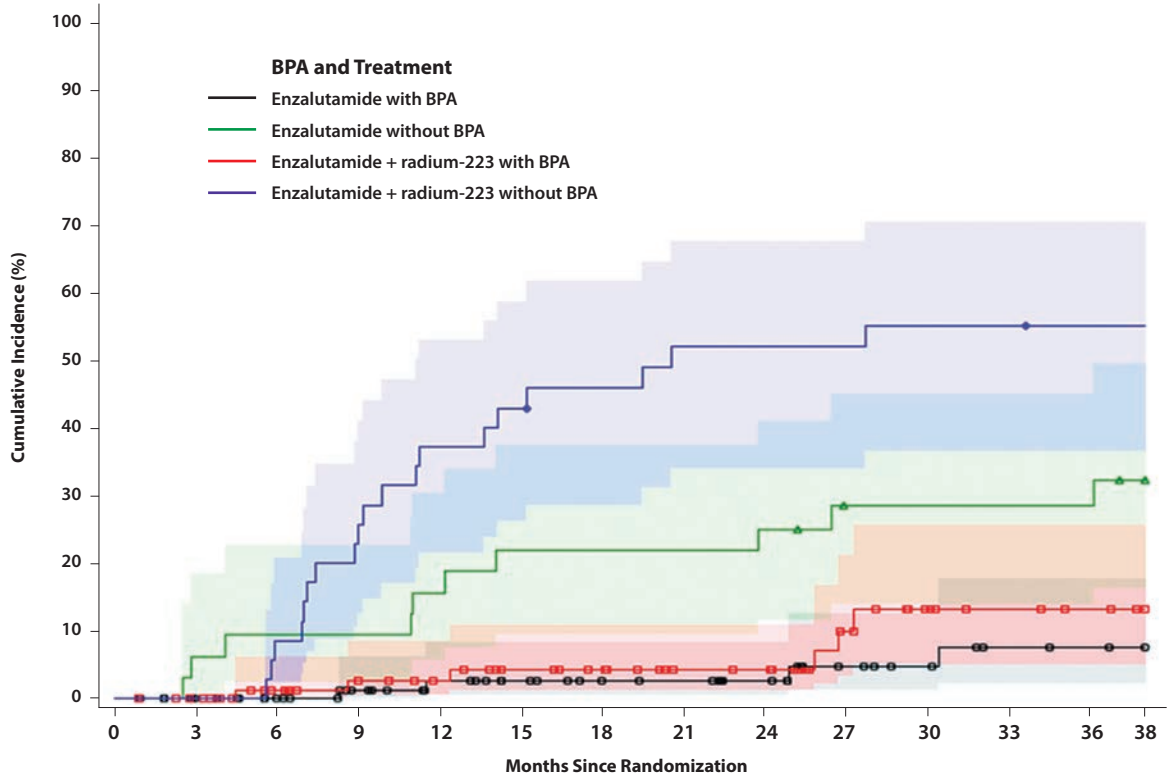
Decreased Fracture Rate by Mandating Bone-Protecting Agents in the EORTC 1333/PEACE-3 Trial Combining Ra-223 With Enzalutamide Versus Enzalutamide Alone: An Updated Safety Analysis

The targeted alpha therapy radium-223 has improved overall survival in patients with metastatic CRPC.[1] It is hypothesized that the combination of this alpha emitter plus a novel androgen receptor pathway inhibitor may improve clinical outcomes. Two large, randomized phase 3 trials, ERA 223 and PEACE-3, are testing this hypothesis.[2,3] In the ERA 223 trial, a higher incidence of fractures and deaths among patients



Patients at Risk

Enzalutamide with BPA	97	89	82	75	67	58	48	46	36	26	21	15	14
Enzalutamide without BPA	32	30	29	29	26	21	21	16	13	8	5	5	5
Enzalutamide +radium-223 with BPA	87	83	74	63	59	51	46	37	36	24	18	15	12
Enzalutamide + radium-223 without BPA	35	35	31	23	18	15	12	9	6	6	4	4	3

Figure 5. The cumulative incidence of fractures according to the treatment arm and the use of bone-protecting agents in the phase 3 PEACE-trial, which evaluated the addition of radium-223 to enzalutamide in patients with bone-predominant metastatic castration-resistance prostate cancer. BPA, bone-protecting agent. Numbers in the circle were noted as small. Adapted from Gillessen S et al. ASCO abstract 5002. *J Clin Oncol.* 2021;39(suppl 15).[2]

treated with abiraterone acetate/prednisone plus radium-223 led an independent data monitoring committee (IDMC) to recommended the unblinding of patients in November 2017. At baseline, 60% of patients were not receiving a bone-protecting agent. A post hoc analysis revealed that bone-protecting agents decreased the rate of fractures in both treatment arms of the trial. As a result, the use of bone-protecting agents for at least 6 weeks prior to entry was made mandatory for patients enrolling into the PEACE-3 trial.

Gillessen and colleagues described the changes that were made to the study design of PEACE-3 following the IDMC recommendation to mandate use of bone-protecting agents.[2] The investigators noted that skeletal complications are common in patients with advanced prostate cancer and result from 2 mechanisms: frailty (osteoporotic) fractures and skeletal-related events. Among men with metastatic CRPC, androgen deprivation therapy induces bone loss. Bone-protecting agents (eg, denosumab, alendronate, and zoledronic acid) mitigate this loss and delay the time to skeletal-related events caused by bone metastases.[3-8] To prevent such skeletal-related events, many guidelines recommend the use of bone-protecting agents in patients with CRPC and bone metastasis.[9-11]

The PEACE-3 trial enrolled men who had bone-predominant metastatic CRPC (≥2 bone metastases).[2] The patients were asymptomatic or mildly symptomatic, they had a good performance status (0 or 1), and they had no known brain or visceral metastases. The patients were randomly assigned to receive enzalutamide at 160 mg/day alone (n=133) or in combination with 6 cycles of radium-223 (55 kBq/kg; n=134). A total of 74 patients in each treatment arm were randomly assigned to treatment after the use of a bone-protecting agent was mandated by the IDMC.

The IDMC mandate increased the proportion of patients receiving bone-protecting agents from 46% to 96%.[2] At the data cutoff of April 2021, 73% of all trial participants were receiving concomitant bone-protecting agents.

As was anticipated, the highest cumulative incidence of fractures was observed among patients who did not receive concomitant bone-protecting agents (Figure 5).[2] The incidence of fractures was highest among the patients treated with enzalutamide plus radium-223, followed by enzalutamide (without radiotherapy). In the absence of bone-protecting agents, the 1-year cumulative incidence of fractures was 37% in the combination arm vs 16% in the enzalutamide-alone arm. In contrast, the lowest cumulative incidence of fractures was observed in patients receiving concomitant bone-protecting agents. The incidence of fractures was lowest with enzalutamide (without radiotherapy), followed by enzalutamide plus radium-223. In the presence of bone-protecting agents, the 1-year cumulative incidence of fractures was 2.7% in the combination arm and 2.7% in the enzalutamide-alone arm. At 18 months, the cumulative incidence was 4.3% and 2.6%, respectively.

The 1-year cumulative incidence of fractures among patients receiving bone-protecting agents was less than 3%, leading the study investigators to conclude that the risk for fractures was controlled in both treatment arms of the PEACE-3 trial.[2] This safety analysis confirmed the importance of providing concomitant bone-protecting agents to prevent skeletal complications when treating patients with CRPC and bone metastases. Accrual to PEACE-3 will continue in order to generate efficacy data.

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Novel Framework for Treatment Response Evaluation in Patients With Metastatic Castration-Resistant Prostate Cancer Using PSMA PET/CT (RECIP): An International Multicenter Study

Compared with conventional imaging, PSMA PET/CT has superior diagnostic accuracy.[1] There is little evidence, however, that this modality has a prognostic role in treatment monitoring. Gafita and colleagues aimed to develop a standardized framework for Response Evaluation Criteria in PSMA imaging (RECIP) in men with metastatic CRPC treated with ^{177}Lu-PSMA-617.[2] Another goal was to devise a composite response classification that combines PSA measurements and PSMA PET/CT responses according to RECIP. This explorative, multicenter, retrospective study enrolled men with metastatic CRPC who received ^{177}Lu-PSMA-617 and then underwent PSMA PET/CT at baseline (baseline PET) and after 2 cycles of treatment (interim PET). Among 287 patients screened retrospectively, 124 met the study criteria, had available OS data, and were included in the present analysis. The median follow-up for survivors was 26.6 months (interquartile range, 23.0-36.3).

Three independent study investigators reviewed pairs of baseline and interim PET scans to identify new lesions.[2] Whole-body tumor lesions were segmented using quantitative PSMA software, and the total PSMA-positive tumor volume was measured. The investigators calculated changes in PSMA-positive tumor volume between the baseline PET and the interim PET. A partial response was defined as a decrease in PSMA-positive tumor volume of 30% or more. Progressive disease was defined as an increase in tumor volume of 20% or more. The appearance of new lesions and changes in PSMA-positive tumor volume were first analyzed separately to identify any associations with OS, and then combined to develop the RECIP.

The median OS was 18.5 months in patients with a partial response (n=52), 15.3 months in those with stable disease (n=27), and 8.5 months

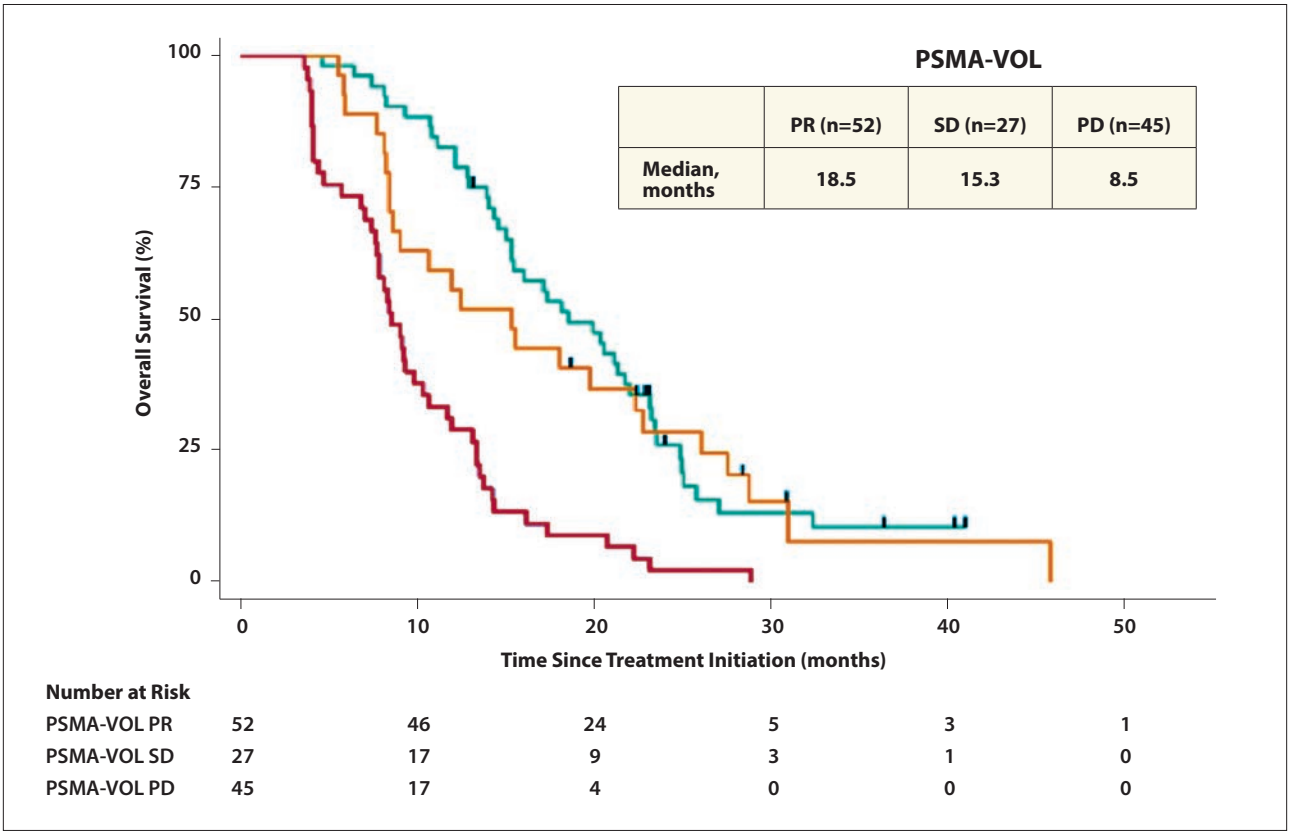

Figure 6. The median overall survival in patients with a partial response, stable disease, or progressive disease as determined by PSMA-positive tumor volume. PD, progressive disease; PR, partial response; PSMA, prostate-specific membrane antigen; SD, stable disease; VOL, volume. Adapted from Gafita A et al. ASCO abstract 5066. *J Clin Oncol.* 2021;39(suppl 15).[2]

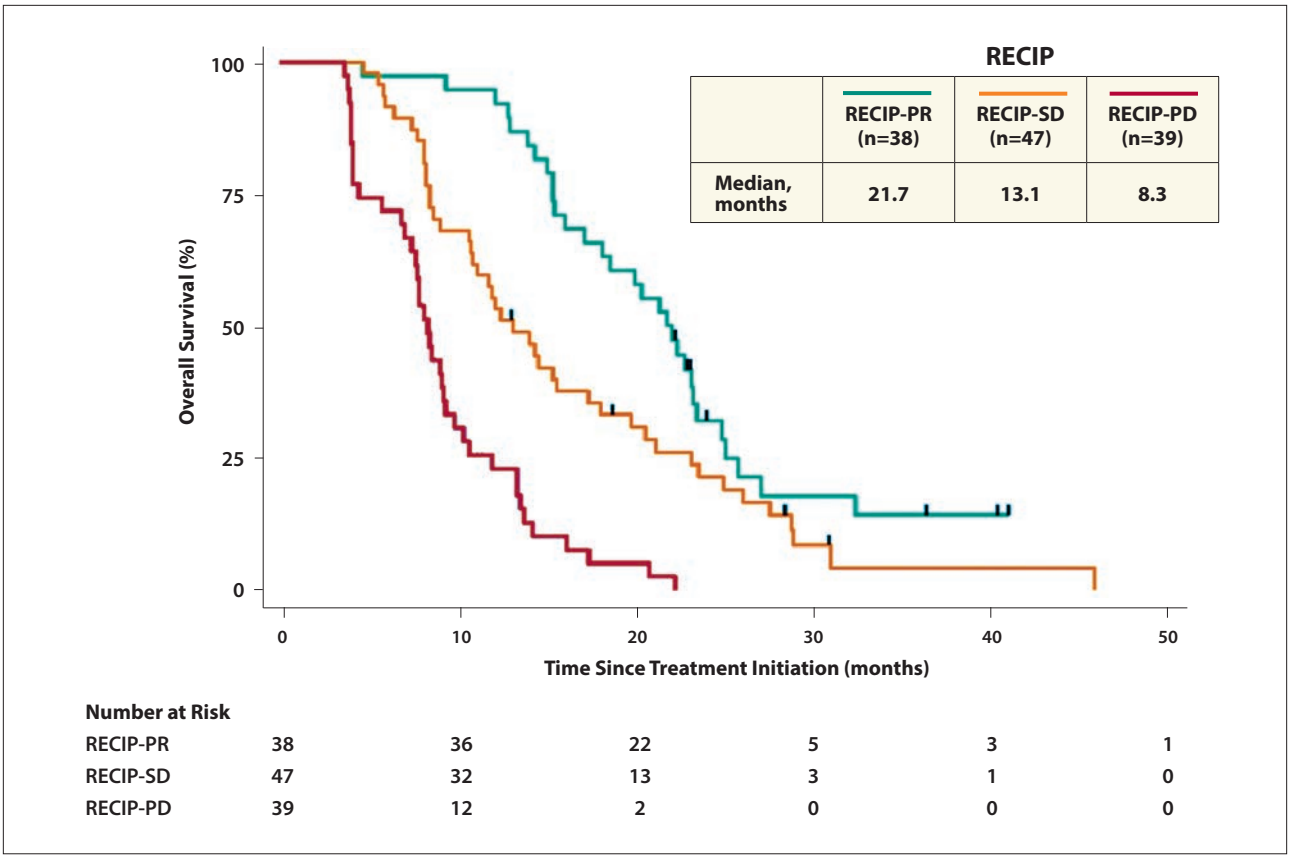

Figure 7. The median overall survival in patients with a partial response, stable disease, or progressive disease as determined by Response Evaluation Criteria in PSMA imaging. PD, progressive disease; PR, partial response; PSMA, prostate-specific membrane antigen; RECIP, Response Evaluation Criteria in PSMA imaging; SD, stable disease. Adapted from Gafita A et al. ASCO abstract 5066. *J Clin Oncol*. 2021;39(suppl 15).[2]

in those with progressive disease (n=45), as determined by PSMA-positive tumor volume (Figure 6).[2] OS was similar between men with a partial response or stable disease. Men with progressive disease had decreased OS. The median OS was 9.2 months in patients with new lesions identified by the interim PET scan (n=72) and 19.9 months in patients without new lesions (n=52).

The RECIP criteria defined a complete response as the absence of any PSMA uptake on the interim PET scan. A partial response on RECIP was defined as a 30% or greater decrease in PSMA-positive tumor volume, in the absence of new lesions.[2] Progressive disease was defined as an increase in PSMA-positive tumor volume of 20% or higher and the appearance of new lesions. Stable disease was defined in several ways: a decline in tumor volume that did not meet the criteria for partial response, a partial response with the appearance of a new lesion, an insufficient increase in tumor volume to qualify for progressive disease, and progressive disease without the appearance of a new lesion.

The RECIP assessment was prognostic for survival among patients treated with ^{177}Lu-PSMA-617.[2] No patients achieved a complete response. OS was superior in men with a partial response as compared with those who had stable disease or progressive disease according to RECIP. The median OS was 21.7 months in patients with a partial response (n=38), 13.1 months in those with stable disease (n=47), and 8.3 months in those with progressive disease (n=39) per RECIP (Figure 7).

The response classification criteria that combined measurements of PSA with RECIP demonstrated superior prognostic accuracy vs PSA responses alone.[2] The C-index of response according to measurement of PSA (0.63) was similar to the RECIP assessment (0.63; *P*=.830) and inferior to the composite response classification of PSA and RECIP (0.66; *P*=.028).[2] Likewise, the C-index of progression by PSA (0.62) was similar to that of RECIP (0.65; *P*=.21) and inferior to that of the composite response classification (0.65; *P*=.044).

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Ancestral Characterization of the Genomic Landscape in Prostate Cancer

There are data to suggest differences in the tumor genomic profile of Black vs White men with advanced prostate cancer.[1] Studies presented at the 2021 ASCO meeting investigated these differences.[1,2] Barata and colleagues performed comprehensive genomic profiling of cell-free DNA using a 73-gene panel in 522 patients (125 African Americans and 427 Caucasians).[1] Multiple pathogenic genomic alterations of interest were enriched among African American patients (Table 1). These findings related to the genomic landscape were supported by probabilistic associations between genomic alterations and race as determined by Bayesian network machine learning.

Use of the G360 74-gene panel in an independent cohort of 261 patients with advanced prostate cancer (106 African Americans and 155 Caucasians) revealed that the *CDK12* mutation was significantly enriched in African American patients (9.4% vs 1.9%; *P*=.006).[1] Identification of molecular drivers of tumor progression that are enriched in different races may enable the development of more tailored systemic therapy.

A presentation by Mahal and colleagues further explored race/genomic ancestry and outcomes in patients with advanced prostate cancer.[2] The investigators noted that men of African ancestry experience the greatest burden of disease, which is likely attributable to the interplay of socioeconomic factors, environmental exposure, and biologic/epigenetic phenomena.[3,4] In addition, precision oncology studies have largely underrepresented men of African ancestry.[5] The investigators performed a large-scale analysis of 11,741 patients who underwent comprehensive genomic profiling as part of routine clinical care. They also analyzed 897 de-identified patients, drawn from a US-based clinical genomic database, to investigate the real-world use of comprehensive genomic profiling, treatment patterns, and clinical trial enrollment.

Table 1. Genetic Alterations Enriched in African American Patients

AR, 58.4% vs 30.7% (*P*=.0000)
BRAF, 23.2% vs 14.5% (*P*=.0233)
BRCA1, 3.2% vs 0.2% (*P*=.0055)
CDK6, 21.6% vs 11.7% (*P*=.0059)
EGFR, 20.8% vs 11.7% (*P*=.0168)
ERBB2, 5.6% vs 0.9% (*P*=.0018)
FGFR1, 16.0% vs 7.5% (*P*=.0055)
FGFR2, 3.2% vs 0.5% (*P*=.0173)
GATA3, 1.6% vs 0% (*P*=.0168)
MET, 16.8% vs 10.1% (*P*=.0390)
MYC, 24.8% vs 10.8% (*P*=.0003)

Adapted from Barata PC et al. ASCO abstract 5058. *J Clin Oncol*. 2021;39(suppl 15).[1]

Among 11,741 patients with advanced prostate cancer and comprehensive genomic profiling, 1422 (12%) had African ancestry as determined by a single nucleotide polymorphism–based approach.[2] The median age of patients of African ancestry was 64 years, compared with 67 years for patients of European ancestry. The proportion of patients younger than 50 years was 4.2% in patients with African ancestry vs 2.5% in patients with European ancestry.

Genes that were significantly depleted in patients of African ancestry were *TP53* (34.7% vs 42.7% in men of European ancestry), *PTEN* (21.2% vs 33.0%), and *TMPRSS22/ERG* (15.0% vs 33.0%).[2] In contrast, genes that were significantly enriched in patients of African ancestry were *SPOP* (11.9% vs 7.3%), *CDK12* (10.0% vs 5.2%), *CCND1* (6.0% vs 3.0%), *KMT2D* (7.1% vs 5.1%), *HGF* (4.1% vs 2.5%), and *MYC* (13.4% vs 10.6%).

ABSTRACT SUMMARY The Efficacy of Enzalutamide Plus Androgen Deprivation Therapy on Bone Oligometastatic Hormone-Sensitive Prostate Cancer: A Post Hoc Analysis of ARCHES

In this post hoc analysis of the phase 3 ARCHES trial, Armstrong and colleagues demonstrated that enzalutamide plus androgen deprivation therapy provided clinical benefit across several commonly used definitions of bone oligometastatic (≤5 metastases) and polymetastatic hormone-sensitive prostate cancer (≥6 metastases), supporting the clinical utility of this treatment irrespective of metastatic disease burden (Abstract 5071). The addition of enzalutamide to androgen-deprivation therapy reduced the risk for radiographic progression across all oligometastatic groups (HRs, 0.16-0.24). Enzalutamide reduced the risk of radiographic progression by 78% among patients with 5 or fewer bone-only metastases. The median radiographic PFS was not reached in the oligometastatic group, regardless of the treatment (median follow-up, 14.4 months). In the polymetastatic group, the median radiographic PFS was not reached with enzalutamide vs 12.4 months with placebo. Patients with oligometastatic disease exhibited a better prognosis than patients with polymetastatic disease after treatment with enzalutamide (HRs vs ≥6 metastases, reference 0.09-0.21) and placebo (HRs vs ≥6 metastases, reference 0.18-0.33).

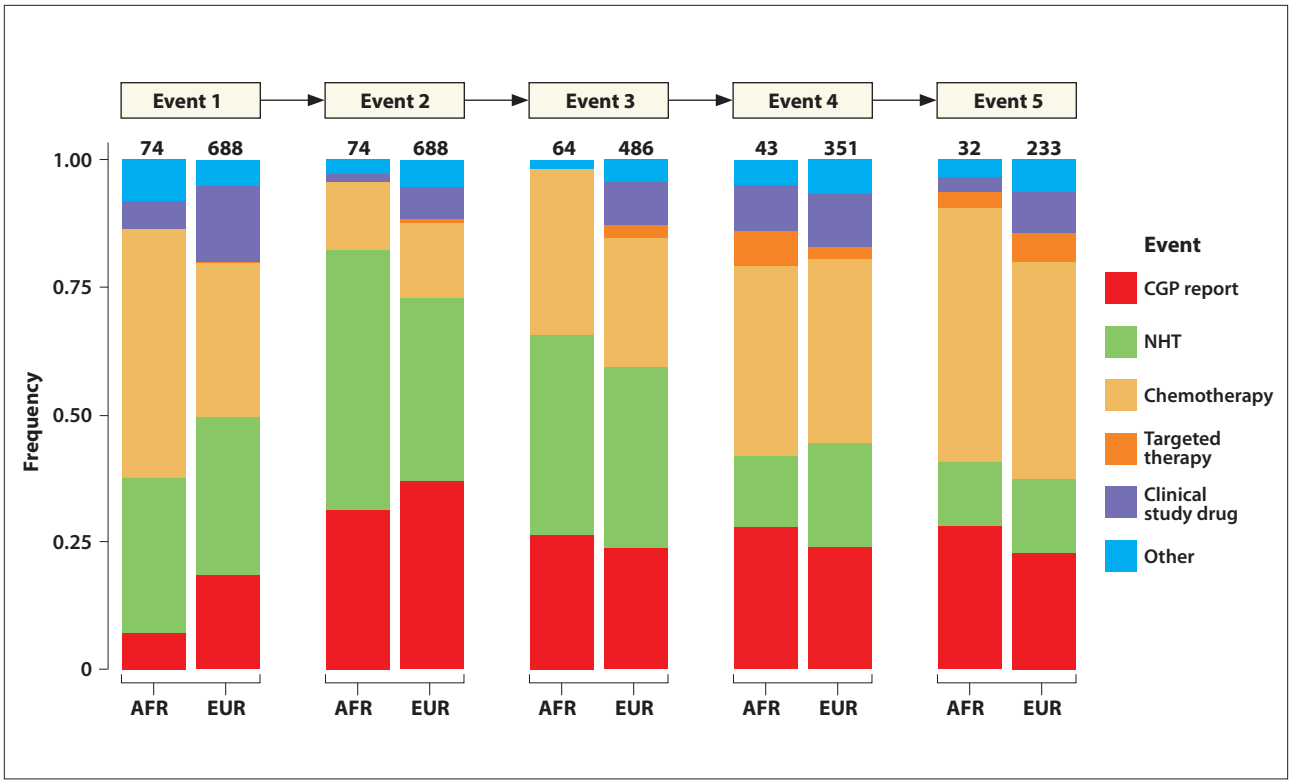

Figure 8. Analysis of a clinical genomic database revealed that patients of African ancestry underwent comprehensive genomic profiling later in their treatment course compared with patients of European ancestry. AFR, African ancestry; CGP, comprehensive genomic profiling; EUR, European ancestry; NHT, neoadjuvant hormonal therapy. Adapted from Sivakumar S et al. ASCO abstract 5003. *J Clin Oncol*. 2021;39(suppl 15).[2]

BRAF was enriched in the African cohort.[2] However, the study detected no other significant differences in the frequency of alterations in actionable genes or in DNA damage response genes.

In an analysis of 897 patients with advanced prostate cancer from the US-based de-identified clinical genomic database, the frequency of CRPC was 85% in men of African ancestry vs 72% in men of European ancestry.[2] Patients of African ancestry had received more prior lines of therapy (2.4 vs 1.8), were more likely to be treated in the community (97% vs 63%), were less often treated at academic centers (<10% vs 37%), and were less likely to enroll in clinical trials and receive clinical study agents (11% vs 30%).

An analysis of the clinical genomic database revealed that patients with African ancestry tended to undergo comprehensive genomic profiling later in their treatment course, after a median of 2 lines of therapy vs 1 line of therapy for patients of European ancestry (Figure 8).[2] This later use of profiling is a critical finding that could explain differences in the observed mutational landscape by ancestry. However, this observation should be interpreted with caution given the relatively small and heterogeneous nature of this set of patients.

Mahal and colleagues concluded that intrinsic biologic differences were unlikely to be a major driver of ancestry-based disparities in outcomes among men diagnosed with advanced prostate cancer. They noted that although it will be necessary to validate these findings, the equitable use of comprehensive genomic profile testing, clinical trial enrollment, and subsequent precision medicine treatment pathways are likely to substantially reduce disparities among patients of different ancestries.

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PSMA-Targeted Imaging With ^{18}F-DCFPyL-PET/CT in Patients With Biochemically Recurrent Prostate Cancer—A Phase 3 Study (CONDOR): A Subanalysis of Correct Localization Rate and Positive Predictive Value by Standard of Truth

The prospective phase 3 CONDOR trial evaluated whether the correct localization rate and positive predictive value of PSMA-targeted ^{18}F-DCFPγL-PET/CT varies with each standard-of-truth criteria, namely, histopathology, correlative imaging, or treatment response. The trial enrolled men with rising PSA levels after definitive therapy and negative or equivocal results on standard-of-care imaging.[1] A single 9 mCi (333 MBq) dose of ^{18}F-DCFPγL was injected intravenously. No dietary or activity restrictions were required before administration. PET/CT imaging was performed 1 to 2 hours later.

Patients with at least 1 lesion detected during ^{18}F-DCFPγL-PET/CT were scheduled for follow-up within 60 days to verify the suspected lesions using a composite standard of truth.[1] The standard-of-truth criteria consisted, in descending order of priority, of histopathology, subsequent correlative imaging findings as determined by 2 central readers, or the PSA response after radiation. The primary endpoint of the CONDOR trial was the correct localization rate, defined as a positive predictive value, plus an additional requirement of anatomic lesion co-localization between ^{18}F-DCFPγL-PET/CT and 1 of the 3 standard-of-truth criteria.[1] Per recommendations from the FDA, the trial would be considered successful if the lower bound of the 95% CI for the correct localization rate exceeded 20% for at least 2 of 3 independent, blinded central reviewers of the ^{18}F-DCFPγL-PET/CT scans.

In total, 208 men with a median PSA of 0.8 ng/mL underwent imaging with ^{18}F-DCFPγL-PET/CT.[1] The CONDOR study met the novel FDA recommended primary endpoint of correct localization rate, as the lower limit of 95% CI greatly exceeded 20% by all 3 central reviewers. Among the 3 reviewers, the correct localization rate ranged from 84.8% to 87.0% (lower bound of 95% CI, 77.8%-80.4%) against the composite standard of truth (n=132). PSMA-targeted ^{18}F-DCFPγL-PET/CT also detected localized metastatic or recurrent lesions with a high positive predictive value, which ranged from 88.7% to 90.7% against the standard of truth.

The correct localization rate (≥1 lesion co-localized) and positive predictive value (≥1 lesion confirmed) of ^{18}F-DCFPγL-PET/CT was maintained through all 3 standard-of-truth criteria.[1] For histopathology (n=31), values ranged from 78.6% to 82.8% for the correct localization rate and from 92.9% to 93.3% for the positive predictive value. Correlative imaging (n=100) ranged from 86.1% to 88.6% and from 87.0% to 89.5%, respectively. The PSA response (n=1) was 100% for both the correct localization rate and the positive predictive value.

Further analyses of the correlative imaging results showed that the correct localization rate remained high across ^{18}F-fluciclovine-PET (86.8%-90.9%; n=71), magnetic resonance imaging (80.0%-86.7%; n=23), and CT (80.0%-100%; n=6). Similarly, the positive predictive value remained high across the imaging modalities: 87.7% to 89.5% for ^{18}F-fluciclovine-PET, 81.3% to 87.5% for magnetic resonance imaging, and 80.0% to 100% for CT.

A change in the intended management after ^{18}F-DCFPγL-PET/CT was reported in 131 of 205 patients (64%). Among these treatment modifications, 103 (79%) were attributable to positive ^{18}F-DCFPγL findings. Management changes included moves from salvage therapy to systemic therapy (n=58), from noncurative systemic therapy to salvage local therapy (n=43), from observation to planned treatment (n=49), and from planned treatment to observation (n=9).

Among the men with biochemically recurrent prostate cancer who had baseline imaging results that were negative or equivocal, PSMA-targeted ^{18}F-DCFPγL-PET/CT detected localized metastatic lesions with a high correct localization rate and positive predictive value, regardless of the criteria. Given the similar performance of correlative imaging and histopathologic standard-of-truth criteria, the investigators noted that such novel standard-of-truth criteria might be used in situations where biopsy is not possible.

Reference

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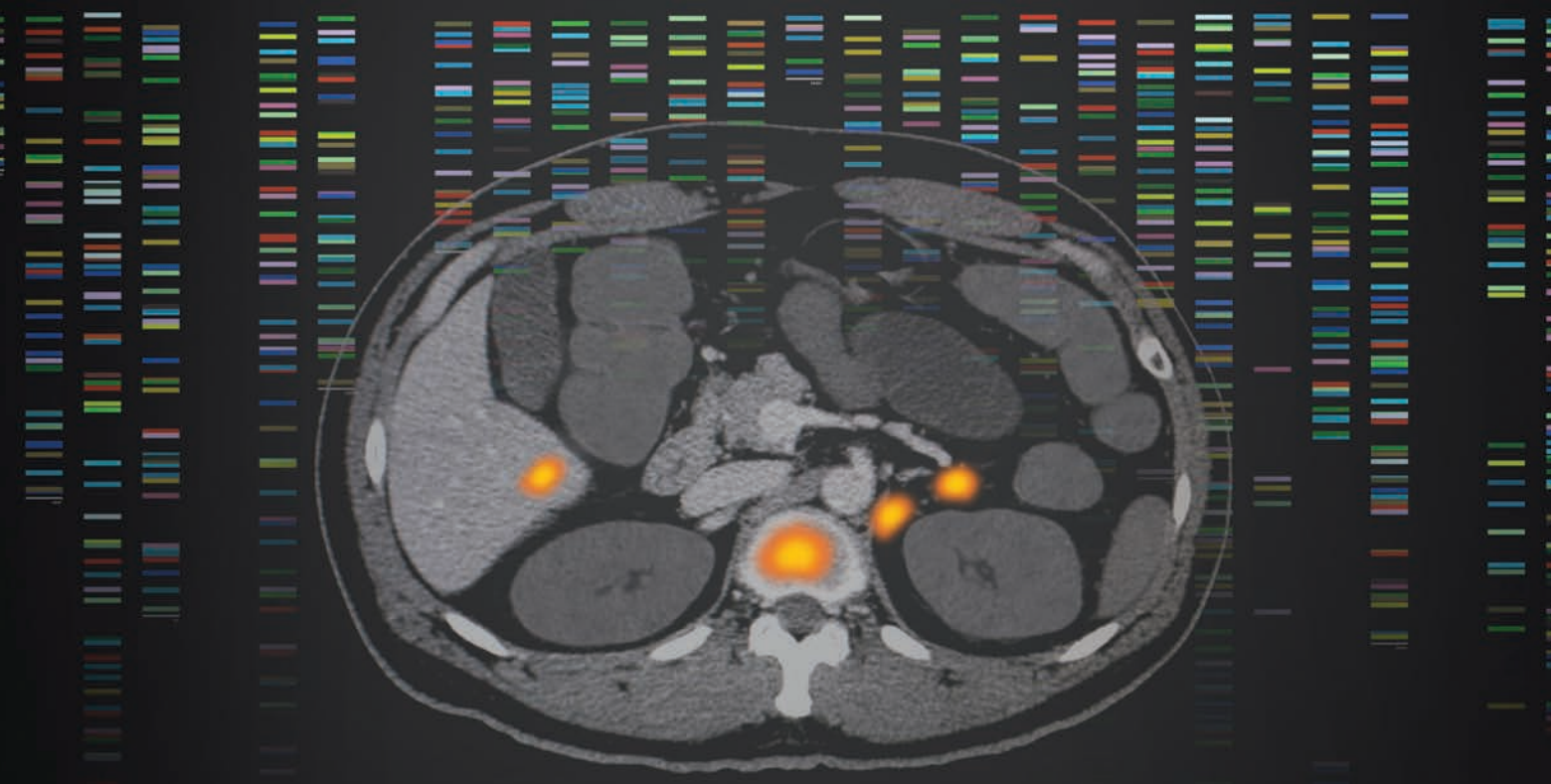

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ODENZA, a Prospective, Randomized, Open-Label, Multicenter, Cross-Over Phase 2 Trial of Preference Between Darolutamide and Enzalutamide in Men With Asymptomatic or Mildly Symptomatic Metastatic Castrate-Resistant Prostate Cancer

ODENZA is a prospective, randomized, open-label, multicenter, cross-over phase 2 trial that compared patient preferences for darolutamide vs enzalutamide.[1] The trial enrolled men with asymptomatic or mildly symptomatic metastatic CRPC. The patients had not received prior androgen receptor inhibitors or docetaxel to treat metastatic CRPC.

The patients were randomly assigned to treatment with 12 weeks of darolutamide at 1200 mg/day or enzalutamide at 160 mg/day. The patients without disease progression then received the alternate treatment. Darolutamide was administered as two 300-mg tablets twice daily, and enzalutamide was administered as four 40-mg tablets once daily.

The primary endpoint was patient preference between the 2 drugs, as assessed by a questionnaire at week 24.[1] The Prescott statistical test was used to determine treatment preferences in patients who met preplanned criteria (eg, exposure to both treatments, no progression at week 12, and completion of the preference questionnaire). *P* values greater than 0.5 indicated no differences in preference.

Colomba and colleagues described key findings from the ODENZA trial.[1] Overall, 250 patients were randomly assigned to treatment. The median age at diagnosis was 72 years, and 49% of trial participants had a Gleason score of at least 8 at baseline. The patient characteristics were well balanced

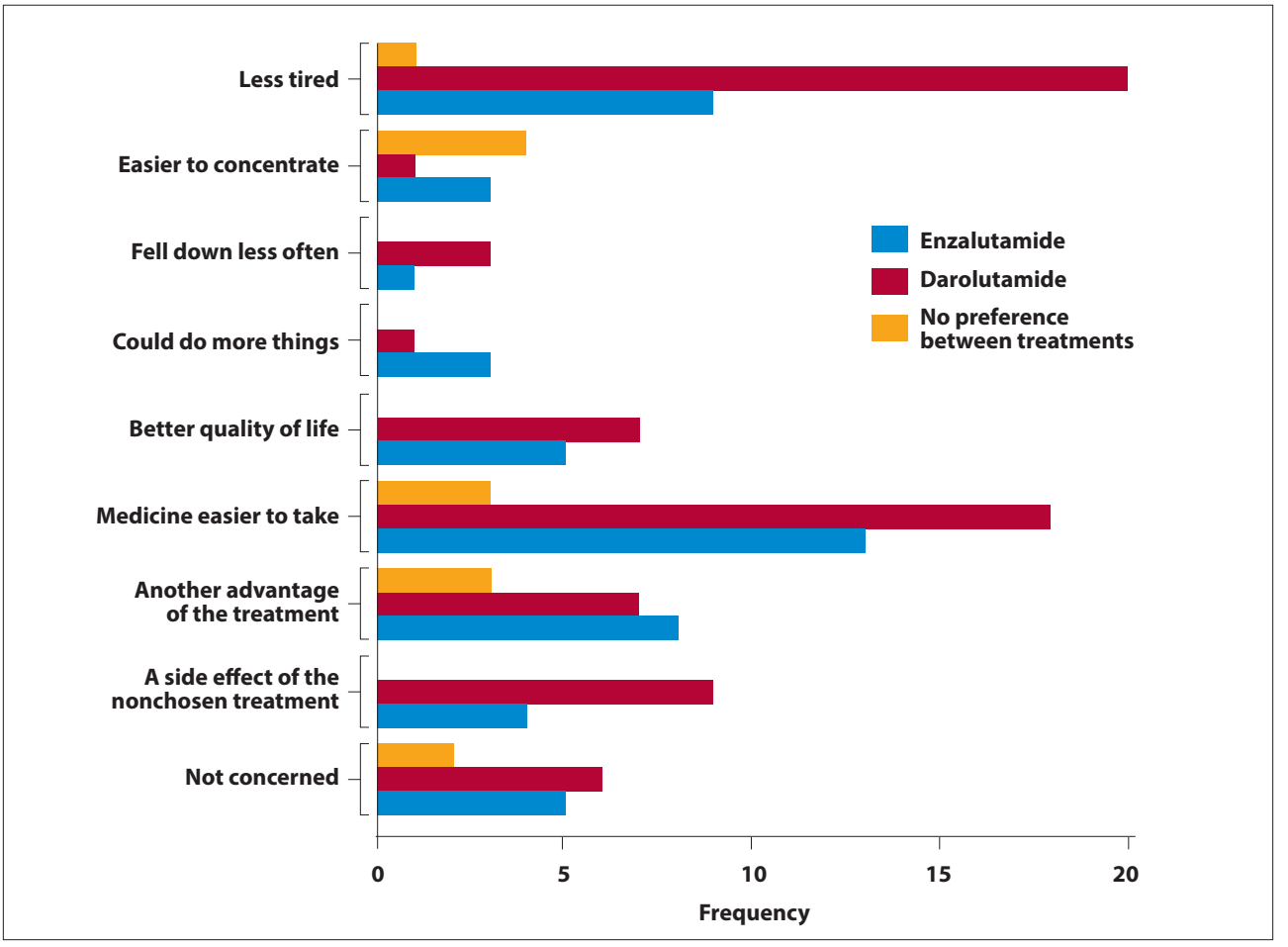

Figure 9. Fatigue was the key factor guiding patient preference for darolutamide vs enzalutamide in the cross-over, phase 2 ODENZA trial. Adapted from Colomba E et al. ASCO abstract 5046. *J Clin Oncol*. 2021;39(suppl 15).[1]

between the treatment arms at baseline. The Eastern Cooperative Oncology Group (ECOG) performance status was 0 in 56% and 1 to 2 in 44%. Prior treatment with taxane chemotherapy was reported in 22%, and 43% had de novo metastases.

A total of 200 patients fulfilled the preplanned criteria for evaluation of the primary endpoint.[1] Overall, 97 patients (48.5%) preferred darolutamide, 80 patients (40%) preferred enzalutamide, and 23 patients (11.5%) expressed no preference. The unilateral *P* value of 0.92 signified that neither treatment was preferred, although numerically more patients preferred darolutamide.

Fatigue was the key factor guiding preference (Figure 9).[1] Fatigue was the most frequently reported all-grade adverse event at week 12, reported in 21% of the darolutamide arm vs 36% of the enzalutamide arm. Other factors influencing patient preference that numerically favored darolutamide included fewer falls, better quality of life, and ease of taking the medication. More patients found it easier to concentrate and to maintain activities during treatment with enzalutamide vs darolutamide. A 50% or higher decline in PSA from baseline was reported in 76.2% of patients after 12 weeks of darolutamide and in 83.9% of patients after 12 weeks of enzalutamide (*P*=.13).[1]

Reference

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First Results From a Randomized Phase 2 Study of Cabazitaxel vs an Androgen Receptor–Targeted Agent in Patients With Poor-Prognosis Castration-Resistant Prostate Cancer

The phase 2 OSTRICH trial compared cabazitaxel vs an androgen receptor targeted therapy in patients who had developed disease progression during prior treatment with docetaxel.[1] The trial enrolled men with metastatic CRPC who had a poor prognosis, which encompassed those with liver metastases, castration-resistant disease that developed within 12 months of starting androgen deprivation therapy, and/or progressive disease that developed within 6 months of starting docetaxel. Previous treatment with

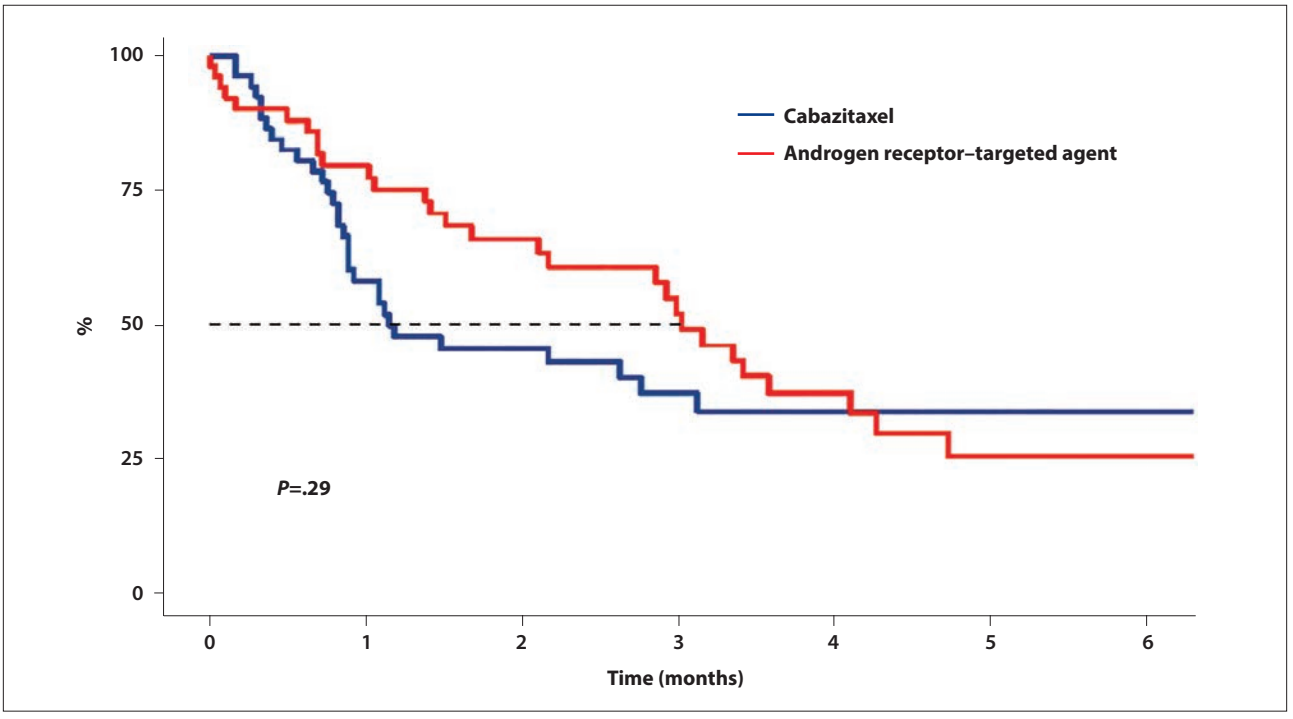

Figure 10. Time to PSA progression in the phase 2 OSTRICH trial, which compared cabazitaxel vs androgen receptor–targeted therapy in patients who had developed disease progression during prior treatment with docetaxel. PSA, prostate-specific antigen. Adapted from van der Zande K et al. ASCO abstract 5059. *J Clin Oncol*. 2021;39(suppl 15).[1]

androgen receptor–targeted agents was permitted, but not between the receipt of docetaxel and trial randomization. For patients randomly assigned to receive androgen receptor–targeted therapy, the choice of treatment with either abiraterone acetate or enzalutamide was made by the investigating physician.

Radiologic evaluations with CT and bone scans were obtained at 6 weeks, 12 weeks, 18 weeks, and 24 weeks, and subsequently every 3 months.[1] The primary endpoint was the clinical benefit rate at 12 weeks in both treatment arms. Clinical benefit was defined as the absence of radiographic or clinical progression. Clinical progression included worsening of cancer-related symptoms resulting in a change of therapy, use of radiotherapy, deterioration of the ECOG performance score by more than 2 points, or death. The primary endpoint was independent of PSA levels.

The trial randomly assigned 53 patients to each treatment arm. The patient characteristics were similar in both arms, except for a higher rate of visceral metastases observed at baseline in the cabazitaxel arm compared with the androgen receptor arm (25% vs 13%). A total of 32% of patients in the cabazitaxel arm and 36% of patients in the androgen receptor arm had received docetaxel to treat metastatic hormone-sensitive disease. Among patients in the cabazitaxel arm, 8% had received abiraterone acetate and 28% had received enzalutamide before joining the study. These rates were 11% and 26%, respectively, among patients in the androgen receptor arm.

The median follow-up was 16.4 months.[1] At week 12, a clinical benefit was achieved by 60% of the cabazitaxel arm (26/43) and 51% of the androgen receptor arm (20/39; *P*=.50). Significantly more patients in the cabazitaxel arm had radiologic stable disease or a response (88% vs 67%; *P*=.046). In contrast, there was no difference between the treatment arms in the proportion of patients achieving clinical stable disease (67% vs 75%; *P*=.49).

The secondary endpoints that favored the androgen receptor arm were a decrease in PSA of 50% or more (23% vs 49%; *P*=.008) and time to clinical progression (4.1 vs 6.1 months; *P*=.012).[1] However, there were no significant differences between the treatment arms in the time to PSA progression (1.2 vs 3.0 months; *P*=.29; Figure 10), radiologic PFS (6.0 vs 5.8 months; *P*=.50), or OS (15.3 vs 13.8 months; *P*=.80). Grade 3 serious adverse events were reported in 28% of the cabazitaxel arm vs 15% of the androgen receptor arm.[1]

Reference

1. van der Zande K, van der Noort V, Busard M, et al. First results from a randomized phase II study of cabazitaxel (CBZ) versus an androgen receptor targeted agent (ARTA) in patients with poor-prognosis castration-resistant prostate cancer (mCRPC) [ASCO abstract 5059]. *J Clin Oncol*. 2021;39(suppl 15).

Highlights in Advanced Prostate Cancer From the 2021 American Society of Clinical Oncology Annual Meeting: Commentary

Andrew J. Armstrong, MD

Several studies presented at the 2021 American Society of Clinical Oncology (ASCO) annual meeting provided important information regarding the management of patients with prostate cancer. New data were presented for treatments such as ^{177}Lu-PSMA-617 for men with metastatic castration-resistant prostate cancer (mCRPC), abiraterone acetate and docetaxel for men with metastatic de novo hormone-sensitive prostate cancer (mHSPC), and enzalutamide in both the mCRPC and mHSPC settings. Studies also provided insights into prostate-specific membrane antigen (PSMA) imaging and the relationship between tumor genotypes and ancestry in men with prostate cancer.

^{177}Lu-PSMA-617

At the plenary session, Dr Michael Morris presented results of the phase 3 VISION trial, which evaluated ^{177}Lu-PSMA-617 in patients with mCRPC.[1] The trial compared ^{177}Lu-PSMA-617 plus the standard of care vs the standard of care alone. The standard-of-care regimen was selected by each investigator, but the treatment could not include chemotherapy, radium-223, immunotherapy, or investigational drugs. (Although I am not a co-author of this presentation, I enrolled patients into the study.)

The alternate primary endpoints consisted of radiographic progression-free survival and overall survival. The study randomly assigned treatment to 831 patients, who were included in the analysis of overall survival. Radiographic progression-free survival was analyzed in 581 patients.

The median overall survival was 15.3 months with ^{177}Lu-PSMA-617 plus the standard of care vs 11.3 months for the standard of care alone (hazard ratio [HR], 0.62; 95% CI, 0.52-0.74; *P*<.001 [one sided]).[1] The median radiographic progression-free survival was 8.7 months vs 3.4 months, respectively (HR, 0.40; 99.2% CI, 0.29-0.57; *P*<.001 [one sided]). The overall response rate was a key secondary endpoint. Patients treated with ^{177}Lu-PSMA-61 achieved a complete response rate of 9.2% and a partial response rate of 41.8%. With

the standard of care, these rates were 0% and 3.1%, respectively. Other secondary endpoints included levels of biomarkers, such as prostate-specific antigen (PSA). In the ^{177}Lu-PSMA-617 arm, confirmed PSA declines of at least 50% were observed in 46% of men, and declines of at least 80% were observed in 33% of men, while among patients in the standard-of-care arm, these decreases were 7.1% and 2%, respectively.

^{177}Lu-PSMA-617 is an exciting, paradigm-shifting treatment. Hopefully, the US Food and Drug Administration (FDA) will approve ^{177}Lu-PSMA-617 in early 2022 for the treatment of men with mCRPC whose disease has progressed despite the use of newer androgen receptor (AR) inhibitors, such as enzalutamide, abiraterone acetate, apalutamide, and darolutamide, and following docetaxel chemotherapy. Many of these patients, however, will choose not to receive docetaxel or are not candidates for docetaxel based on age, frailty, or comorbidities. ^{177}Lu-PSMA-617 represents an important option for such men. The eligibility criteria for the VISION trial required prior treatment with chemotherapy.[1] Ongoing trials are now assessing the activity of ^{177}Lu-PSMA-617 in chemotherapy-naive men,[2,3] but this therapy should become available to patients who develop progressive disease despite treatment with androgen deprivation therapy (ADT) and a potent AR inhibitor, and who cannot receive taxane chemotherapy. ^{177}Lu-PSMA-617 could be an effective, life-prolonging therapy for such patients.

Once ^{177}Lu-PSMA-617 becomes available, administration will be limited to centers of excellence with nuclear medicine or radiation oncology departments that provide expertise in the safe administration and oversight of this radioimmunotherapy. It will be necessary to develop the infrastructure to provide a large number of patients with this effective therapy. Only one other radioimmunotherapy drug is currently approved by the FDA; lutetium ^{177}Lu-DOTATATE is approved for patients with somatostatin-positive gastroenteropancreatic neuroendocrine tumors, a much less common tumor type than metastatic prostate cancer. Therefore, with the approval of ^{177}Lu-PSMA-61, the volume of patients at cancer centers receiving radioimmunotherapy will increase substantially, and such centers should plan to expand their radiation safety rooms and personnel to administer this therapy.

The benefits of ^{177}Lu-PSMA-617 are increased survival, a greater chance of remission, some durable remissions, declines in PSA levels, low toxicity, and high quality of life.[1] A downside to this therapy is that not all patients respond, even among those with a positive PSMA positron emission tomography (PET) scan.

The use of ^{177}Lu-PSMA-617 may require a PSMA PET imaging study as a companion diagnostic. Approximately 10% to 20% of patients lack sufficient PSMA expression and therefore would not be suitable candidates for treatment. There will likely be some debate among regulatory authorities and guideline committees regarding whether patients will need to undergo a PSMA PET scan in order to receive ^{177}Lu-PSMA-617. The test is expensive, and it adds to the labor, costs, and complexities of care. The first FDA approvals of PSMA PET scans arrived in 2020 and 2021, and these modalities are not yet widely available.

Another drawback is that PSMA-negative disease is becoming more common and will emerge even more frequently in the coming years as we potently target PSMA with therapies such as ^{177}Lu-PSMA-617.[4] PSMA-negative disease is frequently associated with more aggressive prostate cancer, such as dedifferentiated tumors that have lost PSMA because of neuroendocrine or small cell differentiation. These tumors do not respond to PSMA-targeting therapy because they lack PSMA expression, and are more likely to be detectable with ^{18}F-fluorodeoxyglucose (^{18}F) PET/computed tomography (CT).[5] Treatment of PSMA-positive disease with a targeted therapy will over time select for tumors with downregulation of this protein, and these tumors may become more aggressive. ^{177}Lu-PSMA-617 is a transformative therapy that improves survival by approximately 4 months, but most patients develop progressive disease within 9 to 12 months.[1] The issue of resistance persists with this treatment.

The toxicity profile of ^{177}Lu-PSMA-617 is very favorable relative to chemotherapy.[1] Toxicities include dry mouth and dry eyes, which are linked to PSMA expression on the lacrimal ducts and the salivary ducts. There is some evidence of bone marrow suppression, such as low platelet counts, but without significant risks of infection or neutropenic fever. Compared with other options in the third-line setting, such as cabazitaxel or radium-223, ^{177}Lu-PSMA-617 is well tolerated.[1,6,7] There are no direct head-to-head comparative trials of ^{177}Lu-PSMA-617 vs radium-223 or cabazitaxel with overall survival as an endpoint. However, one prior randomized phase 2 trial, TheraP, demonstrated improved PSA outcomes and safety with ^{177}Lu-PSMA-617 as compared with cabazitaxel.[8] A criticism of the VISION trial was that the comparator arm—which excluded chemotherapy, immunotherapy, radium-223, and investigational drugs—would not be considered an effective strategy in 2021. In addition, the use of an open-label design led to a high dropout rate for men assigned to the control group. The use of a second AR inhibitor resulted in poor rates of response and progression-free survival because of cross-resistance between the AR inhibitors. Currently, in eligible patients, the true comparator for ^{177}Lu-PSMA-617 in an analysis of survival benefits would be cabazitaxel or radium-223, or olaparib in men with *BRCA2* or *BRCA1* mutations. The overall survival and progression-free survival benefits associated with

cabazitaxel are likely similar to those of ^{177}Lu-PSMA-617.[1,6] However, the toxicity of ^{177}Lu-PSMA-617 is more favorable.[1,6] The decision is not necessarily either/or; a patient can receive treatment with ^{177}Lu-PSMA-617 followed by cabazitaxel and vice versa.

^{177}Lu-PSMA-617 adds a new weapon to the treatment armamentarium for prostate cancer. In ongoing and future trials, this therapy will be moved earlier in the treatment course, into chemotherapy-naive and hormone-sensitive settings.[9,10] This treatment may be even more effective in these patients, who are less likely to have loss of PSMA and who have a lower degree of PSMA heterogeneity.

PSMA Imaging

Dr Andrei Gafita presented results from a study that used a PSMA PET scan index to gauge response to ^{177}Lu-PSMA-617.[11] The idea that follow-up PSMA PET scans might provide insight into survival is intriguing. The development of uniform guidelines for both pre- and post-treatment PSMA PET imaging to risk-stratify patients will be critical to the optimal use of PSMA therapies.

In addition, several studies of PSMA PET imaging, such as the CONDOR trial of ^{18F}-DCFPyL-PET/CT imaging, showed increased sensitivity, specificity, and disease localization, in both the newly diagnosed setting and the relapsed setting, as compared with bone scans, magnetic resonance imaging, and CT.[12-14] The latter modalities are mostly unable to detect metastatic disease. The correct diagnosis and localization of disease allows for selection of the optimal management approach, whether it consists of metastatic-directed therapy, enhanced radiation fields, or local therapy, such as salvage radiation, primary surgery, or radiation. PSMA PET imaging will also likely be used in the castration-resistant setting to select patients for treatment with ^{177}Lu-PSMA-617. Currently, 2 PSMA PET imaging modalities are FDA-approved (piflufolastat F 18 and Ga 68 PSMA-11), but these approvals are presently limited to men with early-stage disease at diagnosis or recurrence, rather than men with mCRPC.

PSMA-targeted therapy may not be appropriate for some patients, such as those with liver metastases, small cell disease, or neuroendocrine disease, as well as those with a disconnect between the amount of disease overall and the amount of PSMA-positive disease. Although PSMA imaging is much better than previous techniques, it still has limitations and may miss important sites of disease owing to lineage plasticity and heterogeneity.

Ancestral Genotyping

Prostate cancer is approximately 2-fold to 3-fold more lethal among African American men compared with men of European ancestry.[15] However, African American men are less likely to be included in clinical trials and genomic sequencing studies, despite having outcomes that are similar, if not better, as compared with white men.[16-19] Several abstracts at the 2021 ASCO meeting examined ancestral genotyping of tumors among patients with prostate cancer to identify any associations with somatic and germline alterations.[20-22] There were key differences related to ancestry in the genotypes of men with prostate cancer, which could have implications for precision medicine and the development of targeted therapies.

Dr Brandon Mahal presented data showing that African American patients were less likely to have the TMPRSS2-ERG fusion protein, PTEN loss, and phosphoinositide 3-kinase mutations as compared with patients of European ancestry.[20] African American men were more likely to have mutations in *SPOP, CDK12,* and *MYC*. There were no differences in the prevalence of actionable alterations, such as microsatellite instability (MSI)-high disease, or mismatch or homologous DNA repair defects, such as *BRCA*2, *BRCA1,* or *ATM* mutations. This finding suggests that testing for the potential benefit of commonly used precision medicine therapies—such as poly(ADP)-ribose polymerase inhibitors for men who are homologous repair–deficient and pembrolizumab for MSI-high men with mCRPC—should not differ by race or ancestry. An abstract evaluating liquid biopsies, such as cell-free DNA, had similar results.[21]

Androgen Receptor Inhibitors

Dr Karim Fizazi presented results from the phase 3 PEACE-1 trial, which is the first randomized trial to evaluate the addition of abiraterone acetate to docetaxel in men with mHSPC.[23] ADT plus docetaxel is a standard-of-care backbone for patients with metastatic, de novo HSPC, but the role of triple therapy with sequential or concurrent chemohormonal therapy plus a potent AR inhibitor is not yet established to improve survival. As shown in the STAMPEDE and CHAARTED trials, the docetaxel/ADT regimen increases overall survival in this setting.[24,25] The increase in survival was maintained regardless of disease volume in the STAMPEDE trial and primarily in high-volume patients in the CHAARTED trial. Preliminary data from the ARCHES,[26] ENZAMET,[27] and TITAN trials[28] suggested that treatment with docetaxel plus ADT followed by a potent AR inhibitor, such as enzalutamide or apalutamide, can confer substantial improvements in progression-free survival beyond those provided by docetaxel and ADT alone.

In the PEACE-1 trial, patients with de novo M1 HSPC were randomly assigned to the standard of care alone, or with the addition of abiraterone acetate plus prednisone, radiotherapy to the primary tumor, or abiraterone plus radiotherapy.[23] When the study was initiated, the standard of care was ADT alone. In October 2015, investigators gained the option of adding docetaxel to the standard of care.

In 2017, accrual was restricted to men receiving ADT plus docetaxel.

The addition of abiraterone acetate improved clinical and radiographic progression-free survival by approximately 50% as compared with ADT plus docetaxel alone, and the use of primary prostate radiation did not impact these outcomes. The question raised by this study is whether clinical practice should change based on the surrogate endpoint of progression-free survival, or whether an improvement in overall survival is needed. The FDA has already approved enzalutamide for the treatment of men with mHSPC based on the ARCHES trial, which showed a benefit in progression-free survival over ADT alone, regardless of disease volume or the presence of synchronous vs metachronous metastases.[26] Therefore, according to the FDA, other regulatory authorities, and many physicians, data for progression-free survival can change clinical practice if the benefits are substantial and the treatment has acceptable risk. A patient's management changes when he develops progressive disease, and therefore delaying this event is important. In the ARCHES trial, the outcome between the treatment groups was so divergent that the investigators believed it would be unethical to continue the study as designed. A crossover component was added to offer patients in the placebo arm the opportunity to receive enzalutamide. Other trials, such as TITAN and ENZAMET, established that potent AR inhibition can further delay clinical or radiographic progression even in the subset of patients who received ADT/docetaxel.[27,28] Overall survival results for this triple therapy remain immature, as they do for ARCHES, ENZAMET, and TITAN.[26-28] Only longer follow-up, and perhaps a formal meta-analysis comparing triple therapy vs ADT/docetaxel for overall survival endpoints, can address this important question. In my opinion, a delay in clinical and radiographic progression is a sufficiently robust endpoint to merit consideration of changing practice. This treatment option can be raised with patients who receive ADT/docetaxel, particularly those with high-volume mHSPC, to allow for informed decision-making. In the PEACE-1 trial, a nearly 2.5-year extension of survival free of progression was seen with ADT/docetaxel and abiraterone as compared with ADT/docetaxel, which is a major improvement.

As was observed in the trials of enzalutamide and apalutamide, results from the PEACE-1 trial suggest that a potent AR inhibitor can further extend the time until radiographic or clinical progression, which is of great importance to patients.[23] The development of progressive disease can be difficult for patients—resulting in emotional trauma and physical pain—and has a major impact on care. The improvement seen by adding abiraterone acetate to ADT plus docetaxel in the PEACE-1 trial is practice-changing for some men. For de novo patients, particularly those with high-volume disease, or men with suboptimal responses to ADT/docetaxel, clinicians should consider ADT plus docetaxel followed by another AR inhibitor—either enzalutamide, abiraterone acetate, or apalutamide—based on data from multiple phase 3 trials.[23,26,27,28] It will be interesting to learn whether the difference in progression-free survival translates into an improvement in overall survival. Follow-up analyses of the phase 3 trials will answer this question.

The PEACE-3 trial evaluated the experimental regimen of enzalutamide plus radium-223 among patients with CRPC.[29] The combination of these agents leads to a high fracture rate. The FDA declined to approve the combination of abiraterone acetate plus radium-223 based on results from the ERA 223 trial, which showed that the fracture rate, including frailty and osteoporosis-type fractures, was 10% to 20% higher among men who received the combination as compared with the hormone therapy alone.[30] Based on these data, the design of the PEACE-3 trial incorporated the mandatory use of antiresorptive therapies, such as denosumab or zoledronic acid.[29] Use of these agents dramatically reduced the risk for fractures. The 18-month risk for fracture dropped from 45% with enzalutamide plus radium-223 and 22% with enzalutamide alone to 4.3% and 2.6%, respectively, with the addition of a bone-protective agent, such as denosumab or zoledronic acid. Therefore, when prescribing radium-223 plus enzalutamide or abiraterone acetate, and even for enzalutamide or abiraterone acetate alone in men with bone metastases, clinicians should strongly consider the regular use of antiresorptive therapy plus calcium and closely monitor the patient's bone health. Patients with bone metastases have a high fracture rate, and potent hormonal therapies control the disease but also increase fragility fracture risk. Patients treated with long-term hormonal therapy, particularly with the more potent agents, have a higher fracture rate because of osteoporosis. Clinicians must be attentive to bone health, and encourage dental clearance, calcium and vitamin D_3 intake, and the use of bone-protective agents.

Dr Kim van der Zande presented results from the randomized phase 2 OSTRICH trial, which compared cabazitaxel vs an AR-targeted agent in patients with poor-prognosis CRPC.[31] In the first-line setting, the standard of care for men with mCRPC is an AR inhibitor.[32] Some patients, however, will not respond to this treatment. These patients are considered to have poor-risk disease, based on factors such as liver metastases or rapid progression to CRPC within 1 year of starting ADT. The idea behind the OSTRICH trial was to determine whether patients with visceral disease, such as liver metastases, would benefit from chemotherapy instead of an AR inhibitor.[31] The trial enrolled patients who had liver metastases, who had progressed to castration-resistant disease within 12 months, or who had developed progressive disease within 6 months

after receiving docetaxel. These patients had not received previous treatment with cabazitaxel. The rates of prior treatment with an AR inhibitor were well balanced between the arms. In the cabazitaxel arm, previous treatment included abiraterone acetate in 8% and enzalutamide in 28%. Among patients in the AR inhibitor arm, previous treatments included abiraterone acetate in 11% and enzalutamide in 26%.

The study identified no significant differences between the treatment groups for the primary endpoint of clinical benefit rate, which consisted of clinical or radiographic progression at 12 weeks.[31] As compared with cabazitaxel, the AR inhibitor led to slight improvements in PSA outcomes and delays in radiographic/clinical progression-free survival. However, there were no differences in any meaningful endpoints between the 2 groups, suggesting that these patients can receive either option. This trial therefore does not change management. The data suggest that even poor-prognosis men with liver metastases and a poor response to prior ADT derive benefit from potent AR blockade and should be offered this approach.

For men with CRPC who have few symptoms, the treatment goal is to maintain the lack of symptoms while administering an effective therapy that delays metastatic progression and improves survival. The phase 2 ODENZA trial was a crossover patient-preference study of 2 potent AR inhibitors: enzalutamide and darolutamide.[33] In the first treatment period of 12 weeks, patients received darolutamide or enzalutamide. In the second treatment period, the patients were switched to the alternate treatment. At the end of the study, the patients were asked which treatment they preferred. The difference in preference was not statistically significant. However, approximately 8% more patients preferred darolutamide, largely based on issues related to fatigue, quality of life, concentration, falling, and muscle fatigue. Darolutamide has a favorable side effect profile as compared with other treatments, with somewhat less fatigue, fewer hot flashes, and decreased impact on muscle, leading to a lower risk for falls and fractures. However, PSA declines were more commonly seen with enzalutamide as compared with darolutamide; PSA decreased by at least 50% in 84% vs 76%, respectively. Longer-term follow-up of efficacy is needed. Clinicians should consider toxicity profiles when selecting treatment, particularly in the nonmetastatic CRPC setting, in which darolutamide is approved.

I presented a subanalysis of the ARCHES study.[34] This important study led to the global approval of enzalutamide in the hormone-sensitive setting.[26] This subanalysis of the trial compared enzalutamide plus ADT vs ADT alone in patients with oligometastatic prostate cancer. These patients have few metastatic sites in the bone, and this analysis addressed the questions of whether the prognosis of such men differed according to a range of oligometastatic definitions, and whether enzalutamide plus ADT improved outcomes in these different groups. The ideal treatment approach is unclear, and there is a wide practice pattern in the clinic, ranging from metastasis-directed therapy, ADT alone, combination approaches, and intensive regimens, such as ADT in combination with docetaxel, abiraterone acetate, enzalutamide, or apalutamide with or without metastasis-directed therapy. Some studies have suggested that PSMA PET/CT–directed radiation could delay progression in these patients and allow them to avoid hormonal therapy for several years.[35] This subanalysis of the ARCHES trial focused on patients who had between 1 and 5 areas of metastases.[34] The analysis found that all of these subgroups had superior progression-free survival, delays in PSA progression, and improved PSA responses when treated with ADT plus enzalutamide as compared with ADT alone. With ADT, worse outcomes corresponded to more metastatic burden within the oligometastatic category of 5 or fewer metastases. However, similar excellent outcomes were seen among the patients who received the more intensive AR inhibitor therapy, suggesting that potent AR inhibitors may overcome the poor prognosis associated with increased metastatic burden, even in men with just a single site of bone metastasis. Updates on overall survival in this study are expected in the coming year. This study did not evaluate whether radiation therapy could improve outcomes even further, which is being presently addressed in the STAMPEDE trial.[24]

Dr Johann de Bono presented a first-in-human study of TAS3681, which is a newer oral AR inhibitor.[36] TAS3681 is thought to have activity against AR splice variants. The objective of this study was to define the appropriate dose and safety profile. The trial enrolled heavily pretreated patients who had already received treatments such as abiraterone acetate, enzalutamide, and chemotherapy. Early data for a range of doses identified declines in PSA and objective responses. At the recommended phase 2 dose, the objective response rate was approximately 33%. The toxicity profile was reasonable; adverse events included nausea, fatigue, diarrhea, and corrected QT prolongation. Among the 56 patients, 15 were able to remain on treatment longer than 6 months.

The study did not provide data regarding any genetic or clinical characteristics shared by the patients who responded. TAS3681 may therefore be an effective therapy for a subset of patients who have progressed during treatment with effective therapies.[28] Further dose expansion and characterization of these patients is ongoing.

Conclusion

Overall, the ASCO 2021 meeting provided practice-changing and practice-

informing studies in several areas. Studies of new PSMA-targeted therapies, PSMA imaging, new AR-targeted therapies, and precision medicine and ancestry provided data that are immediately relevant to patient care.

Disclosure

Dr Armstrong has research relationships with Amgen, Astellas Pharma Inc, AstraZeneca, Bayer, Bristol Myers Squibb/Celgene, Dendreon Valeant Corporation, Forma, Genentech/Roche, Janssen, Merck Sharpe & Dohme (Merck & Co, USA), and Pfizer Inc. He has received consulting fees/research support from Janssen, Clovis, Astellas/Pfizer, Bayer, Dendreon, Merck, AstraZeneca, BMS, and Forma.

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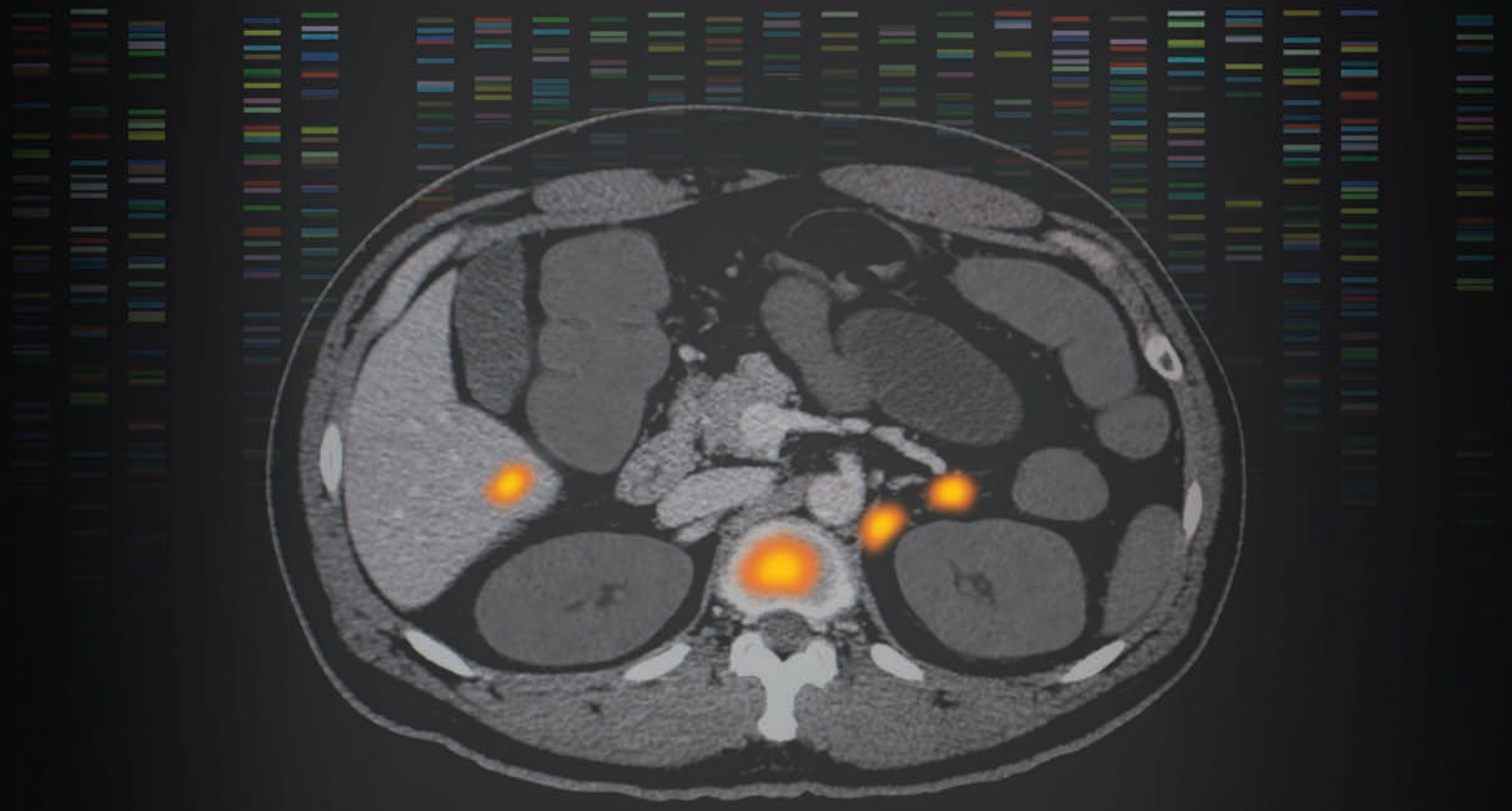
FOR YOUR PATIENTS WITH ADVANCED PROSTATE CANCER

WHY IS PSMA A KEY PHENOTYPIC BIOMARKER IN ADVANCED PROSTATE CANCER?



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

PSMA is a diagnostic and potential therapeutic target, enabling a phenotypic precision medicine approach to treating advanced prostate cancer.[1,4-6]

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

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November 2020 | PSM-1237215