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Highlights in Advanced Prostate Cancer From the 2019 ASCO Genitourinary Cancers Symposium

A Review of Selected Presentations From the 2019 ASCO Genitourinary
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Special Reporting on:

- ARAMIS: Efficacy and Safety of Darolutamide in Nonmetastatic Castration-Resistant Prostate Cancer
- Clinical Outcomes With Concurrent or Layered Treatment With Radium-223 and Abiraterone Plus Prednisone/Prednisolone: A Retrospective Study of Real-World Experience With Patients With Metastatic Castration-Resistant Prostate Cancer
- Clinical Outcomes of a Dutch Prospective Observational Registry of Metastatic Castration-Resistant Prostate Cancer Patients Treated With Radium-223 (ROTOR Registry)
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PLUS Meeting Abstract Summaries

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ARAMIS: Efficacy and Safety of Darolutamide in Nonmetastatic Castration-Resistant Prostate Cancer

The definition of nonmetastatic castration-resistant prostate cancer (CRPC) refers to a rising level of prostate-specific antigen (PSA), despite ongoing treatment with androgen deprivation therapy (ADT), and no metastases detected by conventional imaging. These patients have a high risk for disease progression and cancer-specific mortality.¹ Just over a decade ago, approximately 1 in 3 patients with nonmetastatic CRPC developed metastatic disease within 2 years of diagnosis.² The next-generation androgen-receptor antagonists enzalutamide and apalutamide have improved the rates of metastasis-free survival.^{3,4} The US Food and Drug Administration (FDA) has approved enzalutamide for CRPC and apalutamide for nonmetastatic CRPC. However, these treatments are associated with adverse events such as fatigue, falls, and fractures.

Darolutamide is a next-generation

androgen receptor inhibitor that is structurally distinct from enzalutamide and apalutamide. Darolutamide has low penetration of the blood-brain barrier, which could potentially result in less central nervous system toxicity and greater tolerability.^{5,6} Additionally, darolutamide has a low potential for drug-drug interaction, with little to no effect on P-glycoprotein or cytochrome P450 enzymes.⁷ In preclinical studies, darolutamide has shown a high affinity to the androgen receptor, with in vivo activity against xenografts.⁸ Two early-phase studies, the ARADES trial (Safety and Tolerability of ODM-201 in Patients With Castrate Resistant Prostate Cancer: Open, Non-Randomised, Uncontrolled, Multicentre, Extension Study) and the ARAFOR trial (A Bioavailability Study of ODM-201 Formulations With a Safety and Tolerability Extension Component in Subjects With Metastatic Chemotherapy-Naive Castration-Resistant Pros-

tate Cancer), evaluated darolutamide in the metastatic CRPC setting.⁹⁻¹¹ In these trials, darolutamide was associated with PSA decreases of 50% or more in 65% to 83% of patients, and an overall response rate (ORR) of 30%. No clear drug-related side effects were reported.

Dr Karim Fizazi presented the results of the double-blind, placebo-controlled phase 3 ARAMIS trial (Androgen Receptor Inhibiting Agent for Metastatic-Free Survival), which evaluated darolutamide in patients with nonmetastatic CRPC.^{12,13} The trial randomly assigned 1509 patients in a 2:1 manner to treatment with darolutamide (two 300-mg tablets twice daily) or placebo. All patients also received ADT. They had a PSA doubling time of 10 months or less. At randomization, patients were stratified according to PSA doubling time (≤ 6 months vs >6 months) and prior treatment with osteoclast-targeted therapy (yes vs no).

The median age at baseline was 74 years in each arm. The median serum PSA was 9.0 months with darolutamide vs 9.7 months with placebo. At baseline, the median PSA doubling time was 4.4 months in the darolutamide arm and 4.7 months in the placebo arm. The use of a bone-sparing agent was reported in 3% of the darolutamide arm and 6% of the placebo arm. In each arm, 76% of patients had received prior treatment with at least 2 hormonal therapies. Baseline events included metastases identified by an independent central efficacy review. A total of 17% of patients in the darolutamide arm and 29% of patients in the placebo arm had involved lymph nodes at baseline according to an independent central review.

The median duration of treatment was 14.8 months in the darolutamide arm and 11.0 months in the placebo

ABSTRACT SUMMARY Overall Survival by Race in Chemotherapy-Naive Metastatic Castration-Resistant Prostate Cancer Patients Treated With Abiraterone Acetate or Enzalutamide

Studies have demonstrated prolonged overall survival among black patients vs white patients with metastatic CRPC after treatment with multiple regimens, including docetaxel and sipuleucel-T. Dr Megan McNamara and colleagues retrospectively compared overall survival outcomes among 787 black patients vs 2123 white patients with metastatic CRPC who were chemotherapy-naive and treated with either abiraterone acetate or enzalutamide (Abstract 212). Data were drawn from the Veterans Health Administration Database. Compared with white patients, black patients at baseline were significantly more likely to have hypertension, type 2 diabetes, and liver damage/abnormality, and significantly less likely to have hyperlipidemia. After a median follow-up of 19 months, overall survival was significantly prolonged in black patients vs white patients in both univariate (HR, 0.887; 95% CI, 0.790-0.996; $P=.0435$) and multivariate (HR, 0.826; 95% CI, 0.732-0.933; $P=.0020$) Cox analyses. The authors concluded that these results demonstrated a need for prospective studies to validate the data, as well as to investigate the mechanism for the disparity in overall survival.

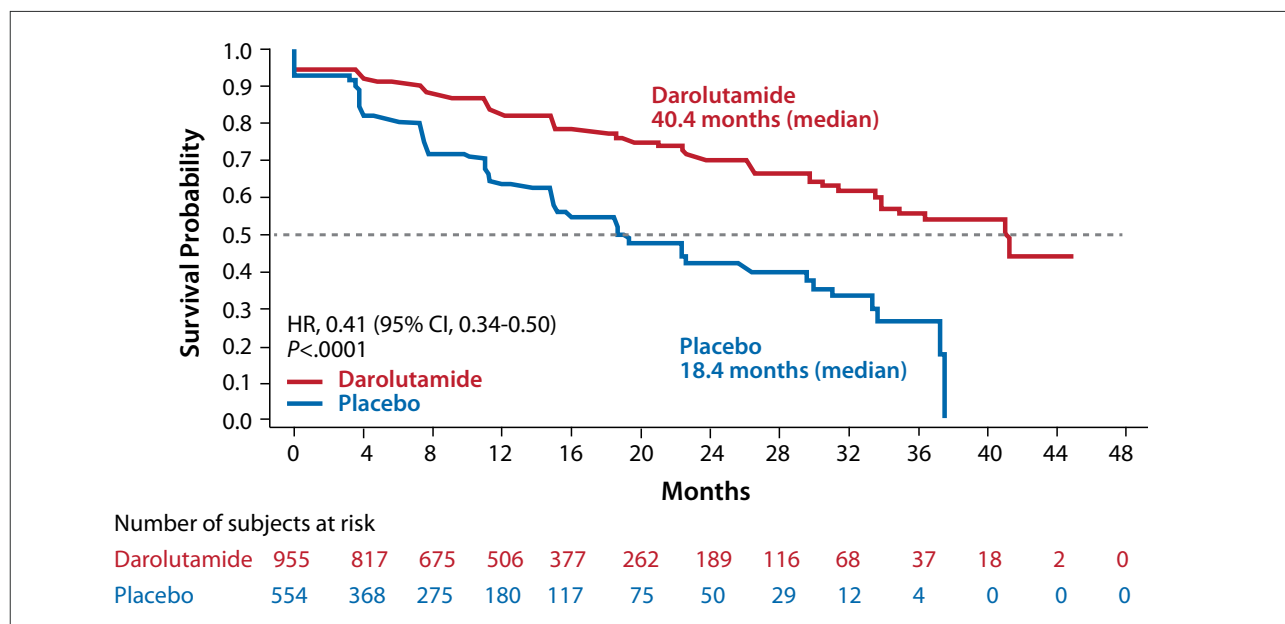


Figure 1. In the ARAMIS trial of men with nonmetastatic CRPC, darolutamide improved the primary endpoint of metastasis-free survival vs placebo. ARAMIS, Androgen Receptor Inhibiting Agent for Metastatic-Free Survival; CRPC, castration-resistant prostate cancer; HR, hazard ratio. Adapted from Fizazi K et al. ASCO GU abstract 140. *J Clin Oncol.* 2019;37(suppl 7S).¹²

arm. At the time of data cut-off, approximately twice as many patients in the darolutamide arm were still receiving treatment (64% vs 36%).

The primary endpoint was metastasis-free survival, which was defined as the time to distant metastases or death from any cause. This endpoint was evaluated through radiologic assessments conducted every 16 weeks. At a median follow-up of 17.9 months, the median metastasis-free survival was 40.4 months with darolutamide vs 18.4 months with placebo (hazard ratio [HR], 0.41; 95% CI, 0.34-0.50; $P < .0001$; Figure 1). This difference equated to a 59% risk reduction of distant metastases or death with darolutamide. The benefit in metastasis-free survival was observed consistently across multiple patient subgroups, including those stratified by age, baseline PSA, baseline PSA doubling time, Gleason score, Eastern Cooperative Oncology Group (ECOG) performance status, and number of prior hormonal therapies.

Darolutamide also improved all secondary endpoints, including overall

survival, time to pain progression, time to cytotoxic chemotherapy, and time to a symptomatic skeletal event. The 3-year estimated overall survival was 83% with darolutamide compared with 73% with placebo. The median overall survival was not reached in either arm (HR, 0.71; 95% CI, 0.50-0.99; $P = .0452$). Darolutamide was associated with a 29% reduction in the risk for death. The median time to pain progression was 40.3 months with darolutamide vs 25.4 months with placebo, a 35% risk reduction (HR, 0.65; 95% CI, 0.53-0.79; $P < .0001$; Figure 2). The median time to initiation of cytotoxic chemotherapy was not reached with darolutamide vs 38.2 months with placebo (HR, 0.43; 95% CI, 0.31-0.60; $P < .0001$). The median time to the first symptomatic skeletal event was not reached in either arm (HR, 0.43; 95% CI, 0.22-0.84; $P = .0113$).

Progression-free survival (PFS), an exploratory endpoint of the study, was also improved with darolutamide vs placebo. The median PFS was 36.8 months with darolutamide vs 14.8

months with placebo (HR, 0.38; 95% CI, 0.32-0.45; $P < .0001$). Treatment with darolutamide was associated with a 62% reduction in the risk for local progression, distant metastases, or death. Assessment of health-related quality-of-life outcomes showed that patient-reported scores tended to favor darolutamide for pain and urinary symptoms.

In the darolutamide arm, 8.9% of patients discontinued treatment owing to a treatment-emergent adverse event, compared with 8.7% in the placebo arm. Fatigue/asthenia was reported in 15.8% vs 11.4%. The incidence of treatment-emergent adverse events of special interest was similar between darolutamide vs placebo. These events included falls (4.2% vs 4.7%), fractures (4.2% vs 3.6%), cognitive disorder (0.4% vs 0.2%), memory impairment (0.5% vs 1.3%), seizures (0.2% vs 0.2%), and hypertension (6.6% vs 5.2%).

The authors of the ARAMIS study concluded that darolutamide could be a novel alternative for the treatment of nonmetastatic CRPC.^{12,13} Treat-

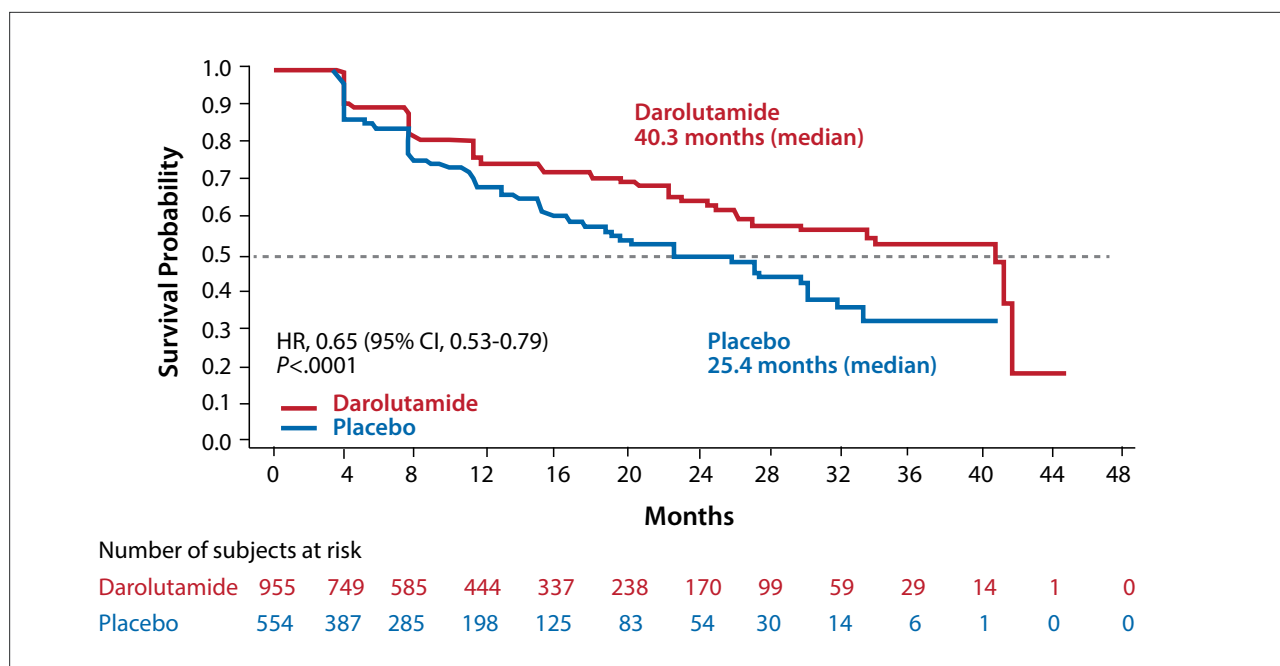


Figure 2. In the ARAMIS trial of men with nonmetastatic CRPC, darolutamide improved the secondary endpoint of time to pain progression vs placebo. ARAMIS, Androgen Receptor Inhibiting Agent for Metastatic-Free Survival; CRPC, castration-resistant prostate cancer; HR, hazard ratio. Adapted from Fizazi K et al. ASCO GU abstract 140. *J Clin Oncol.* 2019;37(suppl 7S).¹²

ment with darolutamide significantly improved the primary endpoint of metastasis-free survival and showed consistent benefit across multiple secondary endpoints, including overall survival. Darolutamide has a favorable safety profile in this class of therapy.

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ABSTRACT SUMMARY ODENZA: A Study of Patient Preference Between ODM-201 (Darolutamide) and Enzalutamide in Men With Metastatic Castrate-Resistant Prostate Cancer

The ongoing ODENZA study (A Study of Patient Preference Between ODM-201 and Enzalutamide in Men With Metastatic Castrate-Resistant Prostate Cancer) is evaluating patient preferences for darolutamide vs enzalutamide in men with asymptomatic or mildly symptomatic metastatic CRPC who have a performance status of 0 or 1 and have not received prior treatment with an androgen receptor-targeted agent or a taxane (Abstract TPS334). ODENZA is a prospective, randomized, open-label, multicenter, cross-over phase 2 trial. Patients will be randomly assigned to the first 12-week treatment period with either darolutamide or enzalutamide, followed immediately by a second 12-week treatment period with the other agent. Patient preferences will be assessed via a questionnaire administered after the second treatment period. Currently, 108 patients have been enrolled into ODENZA since November 2017.

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Clinical Outcomes With Concurrent or Layered Treatment With Radium-223 and Abiraterone Plus Prednisone/Prednisolone: A Retrospective Study of Real-World Experience With Patients With Metastatic Castration-Resistant Prostate Cancer

Radium-223 is an alpha particle-emitting radiotherapeutic agent that is approved for the treatment of patients with CRPC who have symptomatic bone metastases and no known visceral metastatic disease.¹ Radium-223 is a calcium mimetic, which allows it to form complexes with the bone mineral hydroxyapatite at areas of increased bone turnover, such as bone metastases. This accumulation within the bone lesions permits a high linear energy transfer of alpha particles, resulting in a high frequency of double-strand DNA breaks in nearby cells. In this way, radium-223 exerts an antitumor effect on bone metastases while limiting damage to surrounding normal tissue.^{2,3} The phase 3 ALSYMPCA trial (Alpharadin in Symptomatic Prostate Cancer) established the clinical efficacy and safety of radium-223 for the treatment of patients with CRPC and symptomatic bone metastases, demonstrating a significant improvement in overall survival (the primary endpoint of the study). The median overall survival was 14.9 months in the radium-223 arm vs 11.3 months in the placebo arm (HR, 0.7; 95% CI, 0.58-0.83; $P < .001$).⁴

The results of the randomized, placebo-controlled phase 3 ERA 223 study (Radium-223 Dichloride and Abiraterone Acetate Compared to

Placebo and Abiraterone Acetate for Men With Cancer of the Prostate When Medical or Surgical Castration Does Not Work and When the Cancer Has Spread to the Bone, Has Not Been Treated With Chemotherapy and Is Causing No or Only Mild Symptoms) showed that the addition

of radium-223 to abiraterone acetate plus prednisone (or prednisolone) did not improve symptomatic skeletal event-free survival among patients with CRPC and bone metastases compared with abiraterone acetate plus prednisone (or prednisolone) alone.⁵ The median symptomatic

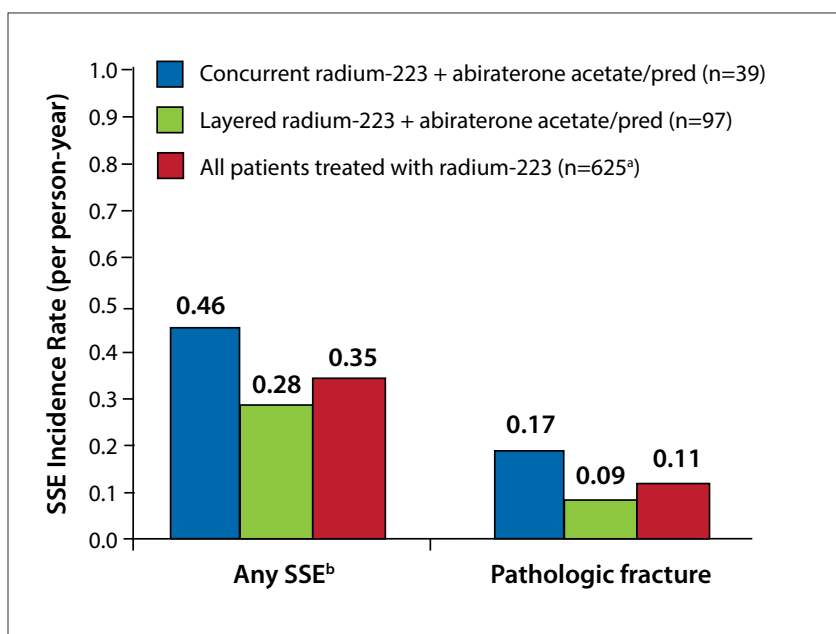


Figure 3. The incidence of SSEs among patients with metastatic CRPC in a retrospective study of concurrent vs layered treatment with radium-223 and abiraterone acetate plus prednisone/prednisolone. ^aTwo patients had no follow-up data and were excluded from the analysis. ^bSSEs included spinal cord compression, pathologic fractures (based on the investigator's assessment), use of external-beam radiation therapy, and surgery to bone. CRPC, castration-resistant prostate cancer; pred, prednisone/prednisolone; SSE, symptomatic skeletal event. Adapted from George DJ et al. ASCO GU abstract 253. *J Clin Oncol*. 2019;37(suppl 7S).⁶

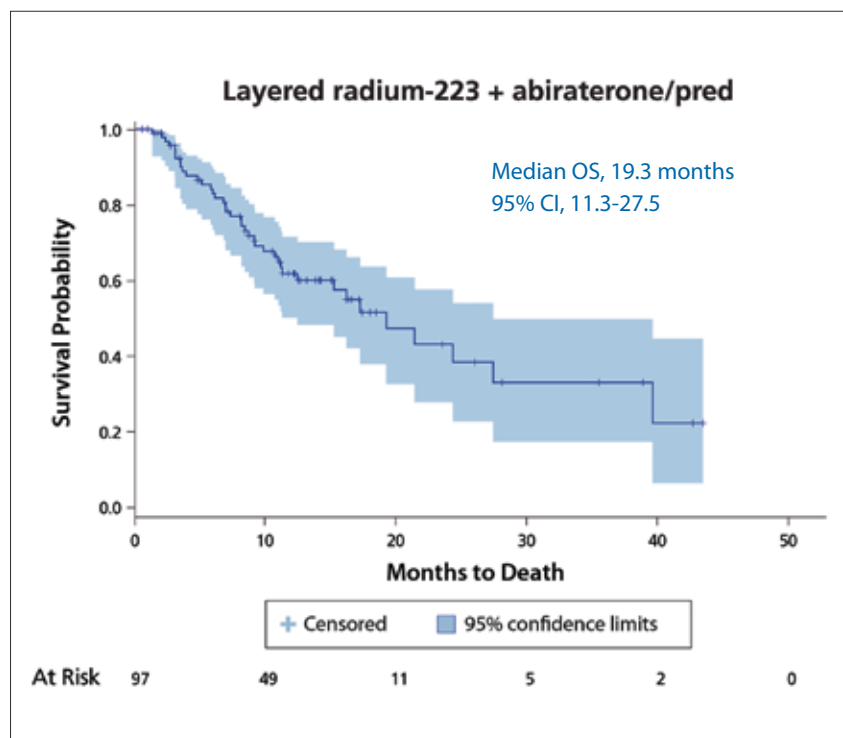


Figure 4. Survival probability among patients with metastatic CRPC who received layered treatment with radium-223 and abiraterone acetate plus prednisone/prednisolone in a retrospective study. CRPC, castration-resistant prostate cancer; OS, overall survival; pred, prednisone/prednisolone. Adapted from George DJ et al. ASCO GU abstract 253. *J Clin Oncol.* 2019;37(suppl 7S).⁶

skeletal event-free survival was 22.3 months with radium-223 vs 26.0 months with placebo (HR, 1.122; 95% CI, 0.917-1.374; $P=.2636$). Fractures of any grade occurred in 29% of the radium-223 arm vs 11% of the placebo arm.

Dr Daniel George and colleagues reported results from a retrospective analysis of patients with metastatic CRPC treated with radium-223 and abiraterone acetate plus prednisone/prednisolone.⁶ The patients were categorized into 2 cohorts according to whether their treatment was concurrent or layered. Concurrent treatment ($n=39$) referred to the initiation of radium-223 within 30 days of the start of treatment with abiraterone acetate

plus prednisone/prednisolone. Layered treatment ($n=97$) referred to the initiation of radium-223 or abiraterone acetate plus prednisone/prednisolone as an add-on therapy at least 30 days after the start of the first therapy. For comparison, the analysis also identified 625 patients with metastatic CRPC who had received radium-223 (either alone or with abiraterone acetate plus prednisone/prednisolone).

At baseline (defined as the start of radium-223 treatment), the median age was 69 years in the concurrent group and 75 years in the layered group. The median time from CRPC diagnosis to baseline was 3 months in the concurrent group and 10 months in the layered group.

The incidence of symptomatic skeletal events was 0.46 per person-years with concurrent treatment vs 0.28 per person-years with layered treatment (Figure 3). As a comparison, the rate of symptomatic skeletal events was 0.35 per person-years among patients treated with radium-223 overall. The incidence of pathologic fractures was 0.17 per person-years with concurrent treatment, 0.09 with layered treatment, and 0.11 with radium-223 overall. The median overall survival (from initiation of radium-223) was 22.1 months with concurrent treatment, 19.3 months with layered treatment (Figure 4), and 15.2 months among all patients treated with radium-223.⁶ The study authors noted that differences in the incidence of symptomatic skeletal events across cohorts could be attributed to the small cohort size, a potential selection bias, or differences in patient populations or disease stage.

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Clinical Outcomes of a Dutch Prospective Observational Registry of Metastatic Castration-Resistant Prostate Cancer Patients Treated With Radium-223 (ROTOR Registry)

In the phase 3 ALSYMPCA trial, radium-223 improved overall survival compared with placebo and was well tolerated in patients with CRPC and symptomatic bone metastases.¹ The ROTOR registry (Registry of Treatment Outcomes of Symptomatic Metastasized Castration Resistant Prostate Cancer Treated With Radium-223) prospectively assessed the efficacy and safety of radium-223 in a nonstudy population. Dr Rebecca Louhanepessy and colleagues presented the results.² The study identified 305 patients with metastatic CRPC from 20 sites throughout the Netherlands from April 2014 to September 2017. The management plans included an intention to initiate treatment with radium-223. A total of 300 patients were evaluable for clinical data, with a median follow-up of 13.2 months. The median patient age was 73.6 years, and 88.0% of patients had an ECOG performance status of 0 or 1. Most patients (82.0%) had more than 6 sites of bone metastases. Other metastases arose within the lymph nodes (27.0%) and visceral organs (0.3%). Prior treatments included abiraterone acetate or enzalutamide in 71.3% of patients, and docetaxel or cabazitaxel in 65.7%.

Patients received a median of 5.0 cycles of radium-223. Outcome data for radium-223 were similar between ROTOR and ALSYMPCA.^{1,2} The median overall survival was 15.2 months in the ROTOR registry vs 14.9 months in the ALSYMPCA trial (Figure 5). The rate of skeletal-related events at 6 months was 19% vs 22%.

PSA responses were uncommon in the ROTOR registry. There was no decline in 80% of patients. The PSA level rose by 30% or more in 5.3%. A 30% or higher decline in the

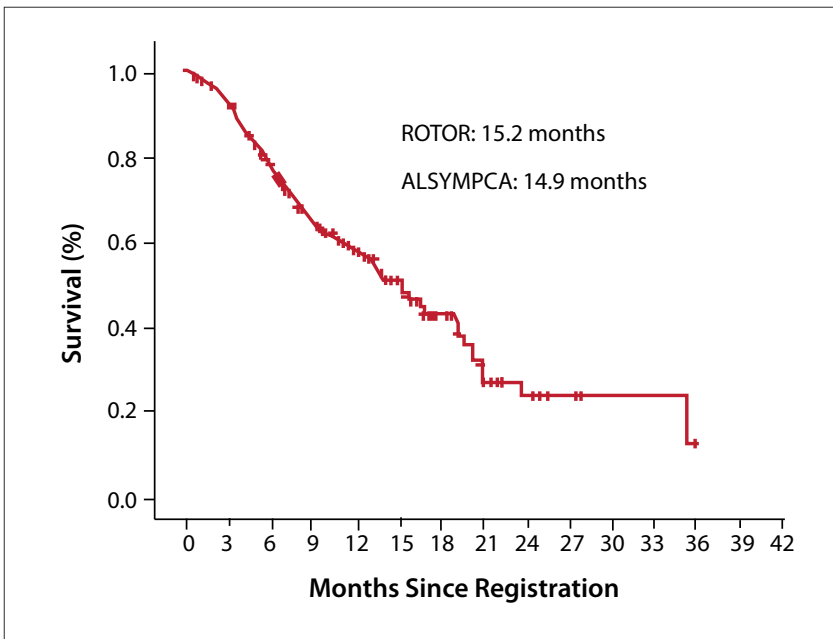


Figure 5. Overall survival in a Dutch prospective observational registry of patients with metastatic CRPC treated with radium-223. ALSYMPCA, Alpharadin in Symptomatic Prostate Cancer; CRPC, castration-resistant prostate cancer; ROTOR, Registry of Treatment Outcomes of Symptomatic Metastasized Castration Resistant Prostate Cancer Treated With Radium-223. Adapted from Louhanepessy RD et al. ASCO GU abstract 323. *J Clin Oncol*. 2019;37(suppl 7S).²

ABSTRACT SUMMARY A Phase III Trial of Docetaxel Vs Docetaxel and Radium-223 in Patients With Metastatic Castration-Resistant Prostate Cancer: DORA

The ongoing DORA study (A Study to Test Radium-223 With Docetaxel in Patients With Prostate Cancer) is an open-label, randomized phase 3 trial that will compare docetaxel plus radium-223 vs docetaxel alone in up to 738 patients with metastatic CRPC (Abstract TPS348). The primary study endpoint is overall survival. Inclusion criteria include at least 2 or more bone lesions; an ECOG performance status of 0 or 1; normal organ function; and progressive disease as evidenced by PSA progression, soft tissue progression, or bone disease progression. Patients will be excluded from enrollment if they received 4 or more systemic anticancer regimens for metastatic CRPC, used anticancer or external beam therapy in the 4 weeks before study enrollment, or used systemic bone-seeking agents in the CRPC setting. Other exclusion criteria include bulky visceral metastases and symptomatic nodal disease. The DORA study began recruiting patients in June 2018.

level of alkaline phosphatase was reported in 40.7% of patients, which was comparable to the rate of 47.0% seen in the ALSYMPCA trial. The time to alkaline phosphatase progression was 6.2 months in the ROTOR registry and 7.4 months in the ALSYMPCA trial.

Grade 3 anemia occurred in

18% of the ROTOR registry vs 11% of patients treated with radium-223 in the ALSYMPCA trial. All-grade fatigue was reported in 59.3% of patients vs 26%, respectively. The ROTOR investigators suggested that these differences might reflect distinctions in patient selection between the 2 studies.

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Initial Results From a Phase 2 Study of Nivolumab Plus Ipilimumab for the Treatment of Metastatic Castration-Resistant Prostate Cancer (CheckMate 650)

The use of immune checkpoint inhibitors induces a T cell–driven immune response in prostate cancer, which seems to be quickly suppressed.¹ In initial clinical studies, the use of anti–programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) antibodies showed little clinical benefit in patients with metastatic CRPC, an effect that has been attributed to the tumor producing an immunologically “cold” microenvironment.^{2,5} Ipilimumab, an immunotherapeutic agent that targets the cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) checkpoint, was associated with modest activity in metastatic CRPC, including a PSA response.⁶⁻⁹ Dr Padmanee Sharma and colleagues reported the initial results of CheckMate 650 (A Phase 2 Trial of Nivolumab Plus Ipilimumab in Men With Metastatic Castration-Resistant Prostate Cancer), a study that evaluated the strategy of combining 2 different immune checkpoint inhibitors—the anti–PD-1 antibody nivolumab and the anti–CTLA-4 antibody ipilimumab—to treat metastatic CRPC.¹⁰

CheckMate 650 was an open-label, multicenter phase 2 trial that enrolled men with metastatic CRPC who were receiving ongoing ADT, had castrate testosterone levels, and had an ECOG performance status of 0 or 1.

Patients were grouped into 2 cohorts. Cohort 1 (n=45) included patients with asymptomatic or minimally symptomatic metastatic CRPC who developed disease progression after treatment with 1 or more second-generation hormonal therapies and had not received chemotherapy in the metastatic CRPC setting. Cohort 2 (n=45) included patients who had progressed after cytotoxic chemotherapy administered in the metastatic CRPC setting. This single-arm study was designed so that all patients in both cohorts initially received nivolumab plus ipilimumab every 3 weeks for the first 4 doses, followed by nivolumab given every 4 weeks. Treatment was continued until unacceptable toxicity or disease progression, but it could continue beyond progression if the patient exhibited clinical benefit.

At baseline, the median patient age was 69 years in cohort 1 and 65 years in cohort 2. The patients' ECOG performance status was 0 in 57.8% of cohort 1 and 55.6% of cohort 2. The performance status was 1 in 42.2% and 44.4%, respectively. The median time to diagnosis was 7.1 months in cohort 1 and 7.5 months in cohort 2. Most patients had at least 4 bone lesions: 66.7% in cohort 1 and 91.1% in cohort 2. In each cohort, 24.4% of patients

had visceral metastases. Approximately two-thirds of patients in each cohort had received prior treatment with abiraterone acetate (62.2% in cohort 1 and 66.7% in cohort 2), and more than half of patients had been treated with enzalutamide (57.8% in cohort 1 and 60.0% in cohort 2).

At the time of the analysis, the median follow-up was 11.9 months in cohort 1 and 13.5 months in cohort 2. All 4 planned combination doses were administered to 33.3% vs 24.4%. In both cohorts, patients received a median of 2.0 maintenance doses of nivolumab monotherapy. The primary reasons for treatment discontinuation were study drug toxicity (51.1% in cohort 1 and 44.4% in cohort 2), followed by disease progression (33.3% vs 44.4%).

There were 2 co–primary endpoints in the CheckMate 650 trial: investigator-assessed ORR per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and radiographic PFS per the Prostate Cancer Working Group 2 criteria.¹⁰ In cohort 1, the confirmed ORR was 25.0% (8 of 32 evaluable patients; 95% CI, 11.5-43.4), of which 6.3% were complete responses and 18.8% were partial responses. In cohort 2, the confirmed ORR was 10.0% (3 of 30 evaluable patients; 95% CI, 2.1-26.5),

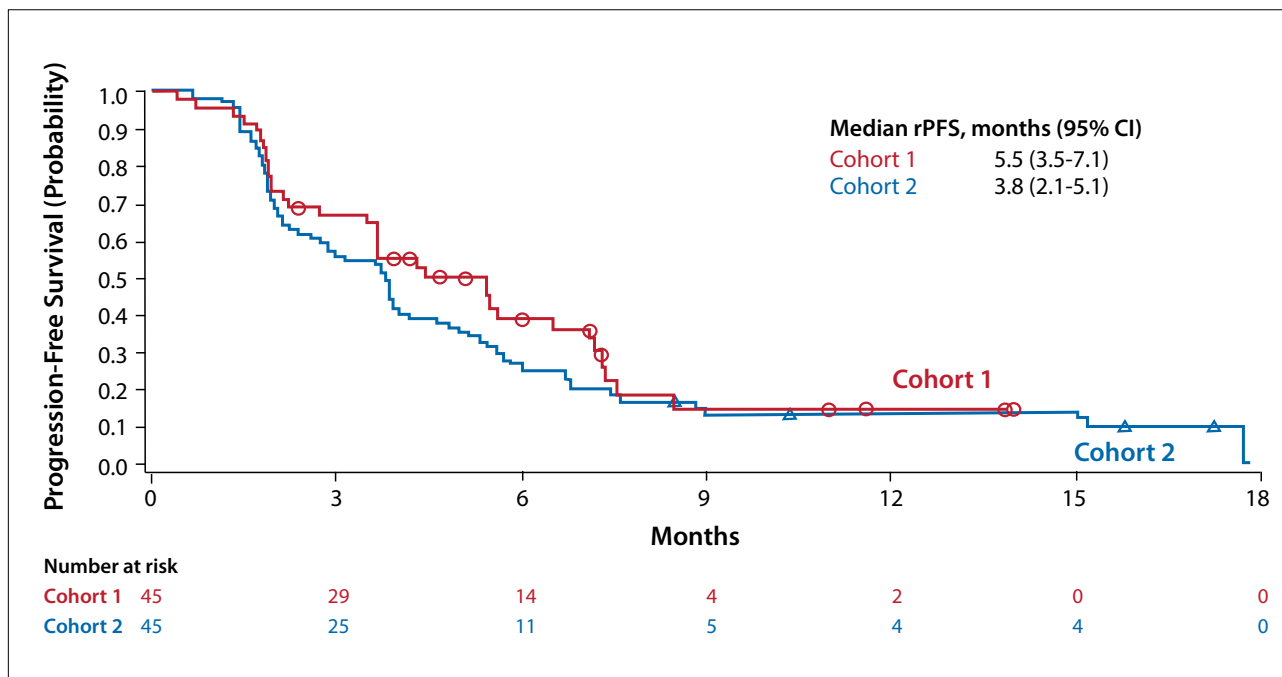


Figure 6. Radiographic PFS per investigator in the phase 2 CheckMate 650 trial, which evaluated nivolumab plus ipilimumab in men with metastatic CRPC. Patients in cohort 1 were asymptomatic or minimally symptomatic, had progressed after ≥ 1 second-generation hormonal therapy, and had not received chemotherapy. Patients in cohort 2 had progressed after cytotoxic chemotherapy. CheckMate 650, A Phase 2 Trial of Nivolumab Plus Ipilimumab in Men With Metastatic Castration-Resistant Prostate Cancer; CRPC, castration-resistant prostate cancer; rPFS, radiographic progression-free survival. Adapted from Sharma P et al. ASCO GU abstract 142. *J Clin Oncol*. 2019;37(suppl 7S).¹⁰

of which 6.7% were complete responses and 3.3% were partial responses. The median time to response was 1.9 months in cohort 1 and 2.1 months in cohort 2. At the time of the analysis, objective responses were ongoing in 5 of the 8 responders in cohort 1 and in all 3 responders in cohort 2. Among the patients in each cohort who achieved a response, a PSA level below 0.2 ng/mL was seen in 4 patients in cohort 1 and 1 patient in cohort 2. In all of these patients, the ongoing response continued at the time of the initial data cut-off. The median investigator-assessed radiographic PFS was 5.5 months in cohort 1 and 3.8 months in cohort 2 (Figure 6). Median overall survival, a secondary endpoint, was 19.0 months vs 15.2 months.

Several biomarkers of immune checkpoint inhibitor response, such as PD-L1 expression, homologous recombination deficiency (HRD),

DNA damage repair mutations, and tumor mutational burden, were assessed in an exploratory manner to identify any relationships with outcomes. In both cohorts, a higher ORR was observed in patients with PD-L1 expression of 1% or higher vs those with expression below 1% (cohort 1, 33.3% vs 19.0%; cohort 2, 40.0% vs 0%). The ORR was higher among patients with tumors that were HRD-positive vs HRD-negative (cohort 1, 50.0% vs 26.3%; cohort 2, 50.0% vs 16.7%) and that were positive for the DNA damage repair mutation vs negative (cohort 1, 33.3% vs 29.4%; cohort 2, 40.0% vs 11.1%). The ORR was also increased among patients with a higher vs lower tumor mutational burden (cohort 1, 50.0% vs 9.1%; cohort 2: 50.0% vs 0%).

The study included an exploratory analysis that combined data from the 2 cohorts. An improvement

in the median radiographic PFS corresponded to several factors. The median radiographic PFS was 5.6 months in patients who were PD-L1 positive ($\geq 1\%$) vs 3.9 months in those who were PD-L1 negative ($<1\%$). Improvements in radiographic PFS were also seen in patients who were HRD-positive vs HRD-negative (7.3 months vs 4.4 months), those with the DNA damage repair mutation vs those without (6.7 months vs 4.1 months), and those with a high vs low tumor mutational burden (7.4 months vs 2.4 months).

A total of 33.3% of patients in cohort 1 and 35.6% of patients in cohort 2 developed a treatment-related adverse event that led to discontinuation of the study drug. In cohort 1, the most common treatment-related adverse events were diarrhea (37.8%), fatigue (33.3%), maculopapular rash (20.0%), and

rash (20.0%). They were diarrhea (53.3%), fatigue (44.4%), decreased appetite (35.6%), nausea (24.4%), and maculopapular rash (22.2%) in cohort 2.

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Phase 3 Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Metastatic Hormone-Sensitive Prostate Cancer: the ARCHES Trial

Despite the advances seen with the use of ADT as the standard of care for patients with metastatic hormone-sensitive prostate cancer, many men progress to metastatic CRPC within 1 to 3 years.^{1,2} The phase 3 ARCHES trial (Androgen Receptor Inhibition With Chemohormonal Therapy in Men With Metastatic Hormone-Sensitive Prostate Cancer) evaluated the safety

and efficacy of enzalutamide when combined with ADT in patients with metastatic hormone-sensitive prostate cancer.³ Specifically, this study assessed the ability of enzalutamide combined with ADT to prolong radiographic PFS—and thereby reduce progression to metastatic CRPC—compared with ADT alone.

Dr Andrew J. Armstrong presented the results.³ The ARCHES

trial randomly assigned patients with metastatic hormone-sensitive prostate cancer and an ECOG performance status of 0 or 1 to treatment with enzalutamide plus ADT or placebo plus ADT. At randomization, 1150 patients were stratified by the volume of disease (low vs high) and previous docetaxel therapy for metastatic hormone-sensitive prostate cancer (none vs 1-5 cycles vs 6 cycles). The primary endpoint was radiographic PFS, defined as the time from randomization to first objective evidence of radiographic progression that was assessed centrally, or death from any cause within 24 weeks of treatment discontinuation. Several key secondary endpoints were planned, including time to PSA progression, time to the use of new antineoplastic therapy, the rate of undetectable PSA, ORR, time to deterioration in urinary symptoms, and overall survival.

At baseline, the median patient age was 70 years in both treatment arms, and approximately three-quarters of patients in each arm had an ECOG performance status of 0 (78% in the enzalutamide-plus-ADT arm and 77%

ABSTRACT SUMMARY A Randomized Trial Comparing Fluorocholine-PET/CT With Conventional Imaging in Primary or Recurrent Prostate Cancer

Fluorocholine (FCH) positron emission tomography (PET)/computed tomography (CT) has shown promising results in early studies in prostate cancer. Choline is a precursor of phosphatidylcholine, a component of cell membranes, and accumulates in prostate magnetic resonance spectroscopy. FCH-PET/CT was compared with conventional imaging in a study presented by Dr Scott Williams, which enrolled patients with a suspected recurrence of prostate cancer or newly diagnosed disease (Abstract 2). Imaging was conducted as a component of first-line or second-line management. In the first-line setting, significantly more high-impact management changes (the primary endpoint) occurred with FCH-PET/CT vs conventional imaging (27.8% vs 11.1%; $P=.032$). However, both imaging strategies were poor at predicting subsequent progressive disease.

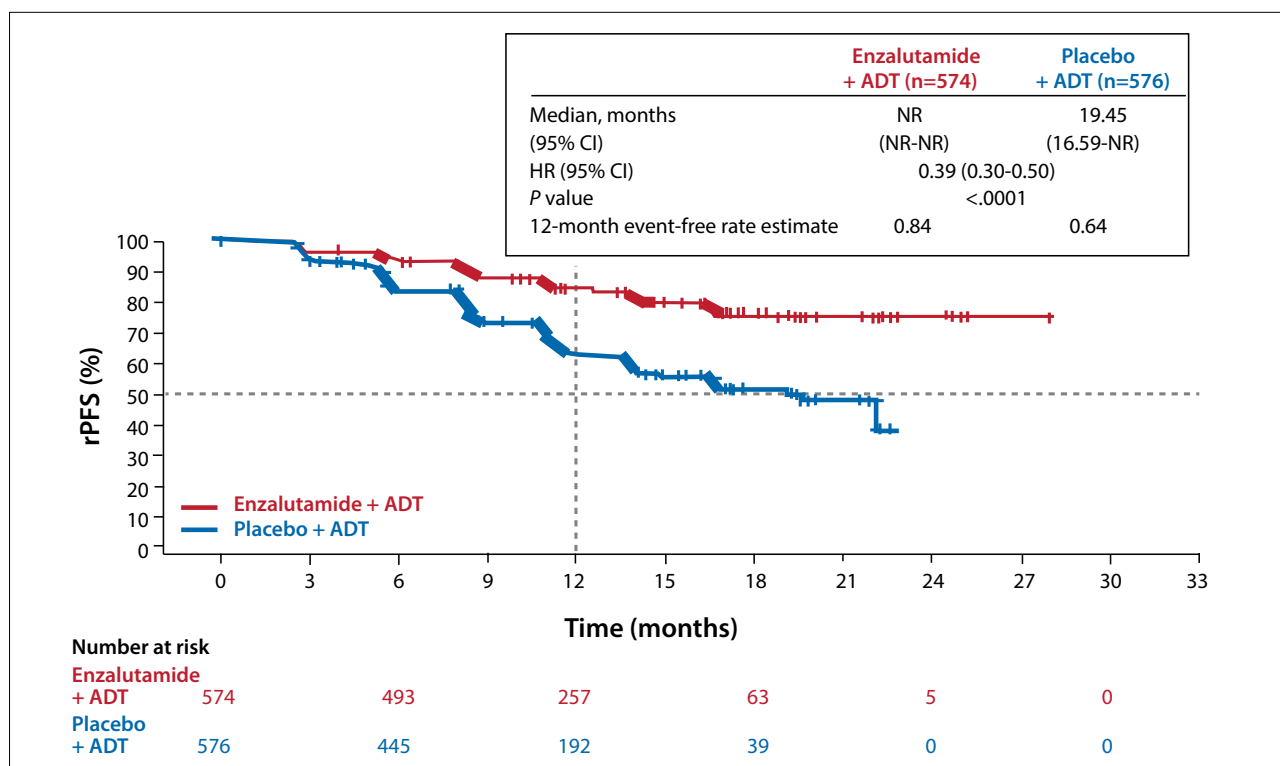


Figure 7. In the phase 3 ARCHES trial of patients with metastatic hormone-sensitive prostate cancer, the addition of enzalutamide to ADT improved radiographic PFS. ADT, androgen-deprivation therapy; ARCHES, Androgen Receptor Inhibition With Chemohormonal Therapy in Men With Metastatic Hormone-Sensitive Prostate Cancer; HR, hazard ratio; NR, not reached; rPFS, radiographic progression-free survival. Adapted from Armstrong AJ et al. ASCO GU abstract 687. *J Clin Oncol.* 2019;37(suppl 7S).³

in the placebo-plus-ADT arm). The median duration of prior ADT in both arms was 1.6 months. The median PSA was 5.4 ng/mL in the enzalutamide arm and 5.1 ng/mL in the placebo arm. The Gleason score was 8 or higher in 67% of the enzalutamide arm and 65% in the placebo arm. High disease volume at baseline was reported in 62% vs 65%. Distant metastases at the time of the initial diagnosis were identified in 70% vs 63%. At baseline, confirmed metastases confined to the bone were found in 47% vs 43%, and metastases confined to the soft tissue were confirmed in 9% vs 8%. In addition, metastases in both the bone and soft tissue were confirmed in 38% vs 42%.

The primary endpoint—radiographic PFS—was not reached in the enzalutamide arm vs 19.45 months in the placebo arm (HR, 0.39; 95% CI, 0.30-0.50; $P<.0001$; Figure 7).³

The estimated 12-month rate of radiographic PFS was 84% in the enzalutamide arm vs 64% in the placebo arm. Enzalutamide improved radiographic PFS in all patient subgroups, including those with a high volume of disease who had previously received docetaxel.

The time to PSA progression was also significantly improved with enzalutamide plus ADT vs placebo plus ADT. The median time to PSA progression was not reached in either arm (HR, 0.19; 95% CI, 0.13-0.26; $P<.0001$). An undetectable PSA level (<0.2 ng/mL) was reported in 68.1% of the enzalutamide arm vs 17.6% of the placebo arm ($P<.0001$). The ORR was 83.1% vs 63.7% ($P<.0001$). The addition of enzalutamide to ADT was associated with a significantly prolonged time to the initiation of a new antineoplastic therapy (HR, 0.28; 95% CI, 0.20-0.40; $P<.0001$).

Enzalutamide did not significantly impact time to deterioration in urinary symptoms (HR, 0.88; 95% CI, 0.72-1.08; $P=.2162$) or quality of life over time. At this interim analysis, the overall survival data were not mature; enzalutamide was associated with a reduction in the risk for death of 19%, a difference that was not statistically significant (HR, 0.81; 95% CI, 0.53-1.25; $P=.3361$).

Slightly more patients in the enzalutamide arm discontinued treatment owing to an adverse event compared with those in the placebo arm (7.2% vs 5.2%). The most common adverse events reported with enzalutamide were hot flashes (27.1% with enzalutamide vs 22.3% with placebo), fatigue (19.6% vs 15.3%), arthralgia (12.2% vs 10.6%), and back pain (7.5% vs 10.8%).

The study was unblinded at the end of the double-blind treatment

period. Based on the improvement in the primary endpoint, eligible patients were offered the opportunity to receive treatment with enzalutamide plus ADT in a prespecified open-label extension study.

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A Multicentric Phase II Randomized Trial of Docetaxel Plus Enzalutamide Versus Docetaxel as First-Line Chemotherapy for Patients With Metastatic Castration-Resistant Prostate Cancer—CHEIRON Study

Dr Orazio Caffo reported results from the CHEIRON study (Chemotherapy Plus Enzalutamide in First Line Therapy for Castration Resistant Prostate Cancer), a multicenter phase 2 trial that randomly assigned patients with progressive metastatic CRPC to treatment with docetaxel plus enzalutamide or docetaxel alone.¹ Patients in both arms additionally received prednisone and ADT. A total of 246 patients were randomly assigned to treatment. They were

stratified according to the presence of pain (yes vs no) and visceral metastases (yes vs no).

The patients' median age was 70 years in the docetaxel-plus-enzalutamide arm and 72 years in the docetaxel arm. Their ECOG performance status was 0 or 1 in 97% of each arm. At baseline, pain was reported by 22% of patients in the docetaxel-plus-enzalutamide arm and 21% in the docetaxel arm. Visceral metastases were present in 22% and 26%, respectively.

The primary endpoint of the CHEIRON study was the rate of patients without disease progression (according to Prostate Cancer Working Group 2 criteria) at 6 months after the first administration of docetaxel.¹ This rate was 89.1% in the docetaxel-plus-enzalutamide arm vs 72.8% in the docetaxel arm (relative risk, 1.22; 95% CI, 1.08-1.38; $P=.002$; Figure 8). Median PFS, a secondary endpoint, was 10.1 months vs 9.1 months (HR, 0.71; 95% CI, 0.54-0.94; $P=.01$). Median overall survival, another secondary endpoint, was 29.6 months with docetaxel plus enzalutamide vs 33.7 months with docetaxel alone (HR, 1.13; 95% CI, 0.75-1.71; $P=.5$). This difference was not significant, and the authors noted that the data were immature.

The most frequent grade 3 or higher adverse events with docetaxel plus enzalutamide were fatigue (12.5% with the combination vs 5.5% with docetaxel alone), neutropenia (10.8% vs 8.7%), and febrile neutropenia (8.3% vs 4.7%).

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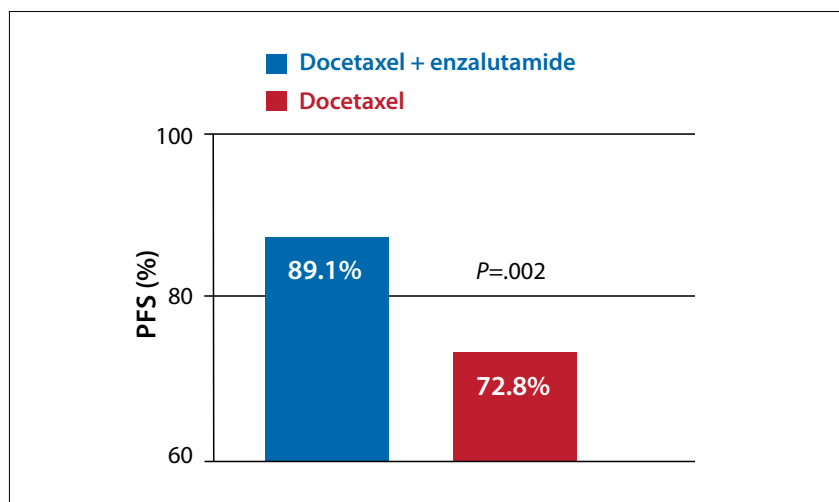


Figure 8. The rates of patients free of progression 6 months after the initiation of docetaxel in the phase 2 CHEIRON trial, which evaluated the addition of enzalutamide to docetaxel as first-line chemotherapy in men with metastatic CRPC. CHEIRON, Chemotherapy Plus Enzalutamide in First Line Therapy for Castration Resistant Prostate Cancer; CRPC, castration-resistant prostate cancer. Adapted from Caffo O et al. ASCO GU abstract 148. *J Clin Oncol*. 2019;37(suppl 7S).¹

Incidence of Hypocalcemia in Patients With Castration-Resistant Prostate Cancer Treated With Denosumab: Data From a Non-Inferiority Phase III Trial Assessing Prevention of Symptomatic Skeletal Events With Denosumab Administered Every 4 Weeks Versus Every 12 Weeks: SAKK 96/12 (REDUSE)

Denosumab, the monoclonal antibody directed against the receptor activator of nuclear factor kappa- β (RANK) ligand, prevents skeletal-related events in patients with prostate cancer. However, the use of denosumab is associated with severe hypocalcemia in up to 5% of patients, and it increases the risk for osteonecrosis of the jaw. One strategy to mitigate these adverse events is to de-escalate the dose and/or frequency of denosumab. The ongoing REDUSE study (Prevention of Symptomatic Skeletal Events With Denosumab Administered Every 4 Weeks Versus Every 12 Weeks—A Non-Inferiority Phase III Trial) aims to determine whether denosumab at 120 mg administered every 12 weeks is

noninferior to denosumab at 120 mg administered every 4 weeks. Patients begin treatment with an induction phase, during which denosumab is administered every 4 weeks for 4 doses.¹ They are then randomly assigned to treatment at every 4 weeks or every 12 weeks.

The study has a planned enrollment of 1380 patients with bone metastases from either metastatic CRPC or breast cancer. In addition to denosumab, all patients will receive mandatory administration of calcium and vitamin D daily. Patients with CRPC have 3 or more bone metastases, an ECOG performance status of 0 to 2, and a corrected serum calcium level between 2 mmol/L and 3

mmol/L. Exclusion criteria include a history of osteonecrosis of the jaw and prior treatment with denosumab or bisphosphonates for bone metastases.

Dr Silke Gillesen and colleagues presented data on hypocalcemia from a preplanned interim evaluation.¹ The data were drawn from 282 patients with metastatic CRPC who had received at least 1 dose of denosumab. During the induction phase, when denosumab was administered every 4 weeks to all patients, the incidence of any-grade hypocalcemia was 28.7%. This event was grade 1 in 19.5%, grade 2 in 6.6%, grade 3 in 2.2%, and grade 4 in 0.4%.

After week 16, during the randomized portion of the study, the rate

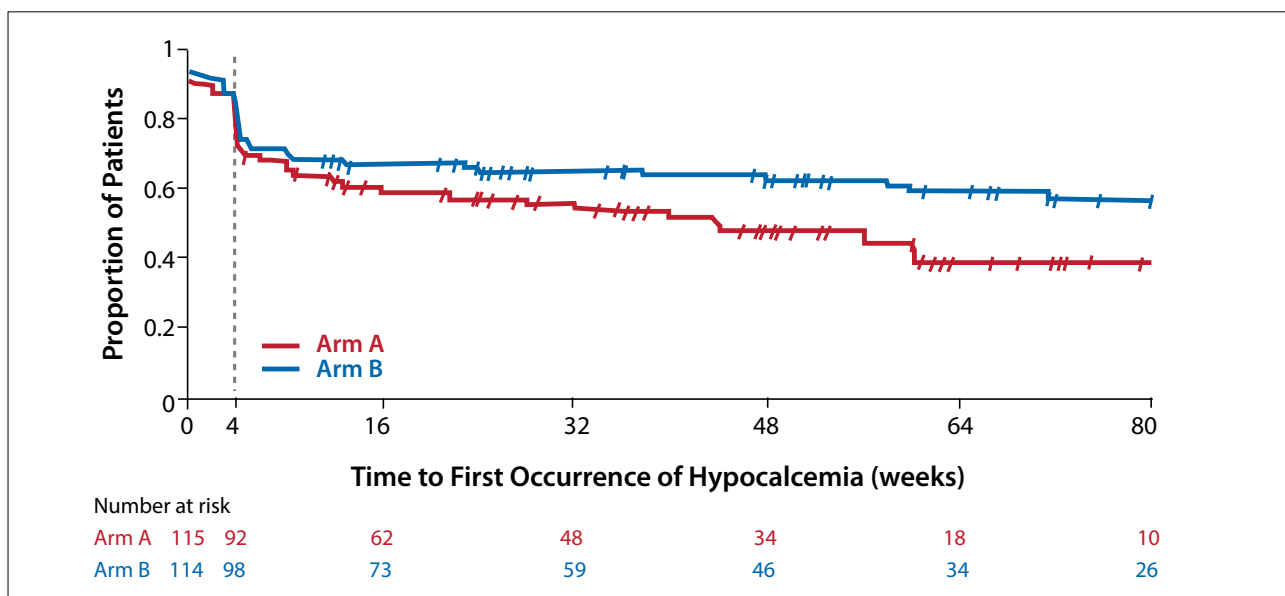


Figure 9. Time to the first occurrence of hypocalcemia in an analysis of data from the REDUSE study, a noninferiority phase 3 trial evaluating the use of denosumab to prevent symptomatic skeletal events in men with CRPC. Patients in arm A received denosumab at 120 mg every 4 weeks. Patients in arm B received denosumab at 120 mg every 12 weeks (after an induction phase). CRPC, castration-resistant prostate cancer; REDUSE, Prevention of Symptomatic Skeletal Events With Denosumab Administered Every 4 Weeks Versus Every 12 Weeks—A Non-Inferiority Phase III Trial. Adapted from Gillesen S et al. ASCO GU abstract 139. *J Clin Oncol.* 2019;37(suppl 7S).¹

of all-grade hypocalcemia was 40.2% in the every-4-weeks arm vs 20.3% in the every-12-weeks arm. In the every-4-weeks arm, hypocalcemia was grade 1 in 29.1%, grade 2 in 10.3%, grade 3 in 0.9%, and grade 4 in 0%. In the every-12-weeks arm, these rates were 15.3%, 3.4%, 0%, and 1.7%, respectively. The time to first occurrence of hypocalcemia in both arms is shown in Figure 9. The overall incidence of hypocalcemia reported in REDUSE, 39.7%, was higher than that previously reported in clinical trials. The rate of all-grade hypocalcemia was 13% in the denosumab arm of a study of patients with metastatic CRPC from 2011.² The authors noted that an independent data monitoring committee recommended continuation of the trial after the interim analysis.

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ABSTRACT SUMMARY Integration of Radium-223 Dichloride (Xofigo) into Clinical Practice for the Treatment of Castration-Resistant Prostate Cancer

A retrospective study by Dr Catherine Doyle and colleagues evaluated radium-223 in a real-world clinical setting (Abstract 312). This evaluation included 114 patients with CRPC and symptomatic bone metastases referred for treatment between 2010 and 2018. Most patients had multiple bone lesions: 38.8% had more than 20 sites, 55.3% had 7 to 20 sites, and 5.8% had 1 to 6 sites. Nearly half of patients (48.1%) had received prior chemotherapy, and 28.0% had received prior sipuleucel-T. The study included 56 patients who completed treatment and 51 who did not. In a multivariate analysis, completion of the radium-223 treatment course was significantly associated with improved overall survival (HR, 0.038; 95% CI, 0.009-0.156; $P < .001$). Other factors that were significantly associated with improved overall survival in a multivariate analysis included baseline PSA less than 30 $\mu\text{g/L}$ ($P = .013$) and an alkaline phosphatase decline of 30% or more after treatment with radium-223 ($P = .003$). The most common adverse events included anemia in 27 patients, diarrhea in 19, and edema in 10.

KEYNOTE-365 Cohort A: Pembrolizumab Plus Olaparib in Docetaxel-Pretreated Patients With Metastatic Castrate-Resistant Prostate Cancer

Pembrolizumab, an anti-PD-1 immune checkpoint inhibitor, is active in certain settings of prostate cancer, including microsatellite-high or mismatch repair-deficient prostate cancer; docetaxel-resistant metastatic CRPC; and heavily pretreated, advanced prostate cancer that is PD-L1-positive.¹⁻³ The KEYNOTE-199 trial (Phase II Trial of Pembrolizumab [MK-3475] in Subjects With Metastatic Castration-Resistant Prostate Cancer [mCRPC]), which evaluated pembrolizumab monotherapy in patients with metastatic CRPC who had received prior docetaxel-based chemotherapy, demonstrated objective

responses even in this heavily pretreated population.² These responses were durable, with a disease control rate lasting 6 months or more in 11%.

The poly(ADP-ribose) polymerase inhibitor olaparib showed promising antitumor activity as a single agent in a phase 2 trial of patients with previously treated metastatic CRPC.⁴ In this trial, responses were seen in 88% of patients with HRD disease and only 6% of those with homologous recombination proficient disease.

Dr Evan Yu reported findings for cohort A of the KEYNOTE-365 trial (Phase Ib/II Trial of Pembrolizumab [MK-3475] Combination Therapies in

Metastatic Castration-Resistant Prostate Cancer [mCRPC]).⁵ This open-label study evaluated pembrolizumab as part of multiple combination regimens in patients with metastatic CRPC. In cohort A, patients received olaparib plus pembrolizumab. Enrolled patients had developed progressive disease within 6 months before the study screening, and they had previously received treatment with docetaxel for metastatic CRPC. Prior treatment for metastatic CRPC could consist of 1 other previous chemotherapy and no more than 2 second-generation hormonal therapies.

Forty-one patients were enrolled

in cohort A. Their median age was 69 years, and 78% were ages 65 years or older. Most patients had an ECOG performance status of 0 (37%) or 1 (54%). A total of 27% of patients were PD-L1-positive (a combined positive score of ≥ 1), and 37% were PD-L1-negative. (Data were missing for the remainder.) At baseline, the median PSA value was 129.1 ng/mL. No visceral disease was reported in 59% of patients, 12% presented with visceral disease in the liver, and 29% had visceral disease outside of the liver. No patients had HRD-positive disease.

The primary endpoints were safety and PSA response rate, defined as a confirmed PSA decrease of 50% or more.⁵ Five patients achieved a confirmed PSA response, equating to a 12% confirmed PSA response rate. Among 28 patients with RECIST measurable disease, 4 patients (14%) showed a confirmed PSA response. Among 13 patients with RECIST nonmeasurable disease, 1 (8%) had a confirmed PSA response. Changes in PSA levels from baseline are shown in Figure 10.

The most frequent treatment-related adverse events were anemia (37%), fatigue (34%), nausea (34%), decreased appetite (29%), asthenia (22%), vomiting (22%), neutropenia (15%), and thrombocytopenia (15%). Anemia was the most frequent grade 3/4 treatment-related adverse event (27%). Several cases of immune-mediated adverse events were reported, including hypothyroidism, colitis, hyperthyroidism, hypophysitis, pneumonitis, and severe skin reaction. All immune-mediated adverse events were grade 1 or 2.

The secondary endpoints included time to PSA progression, ORR, disease control rate, complete response rate, radiographic PFS, and overall survival. Among 28 patients with RECIST measurable disease, the ORR was 7% (all responses were partial). A total of 32% of patients achieved disease control (response or stable disease) lasting

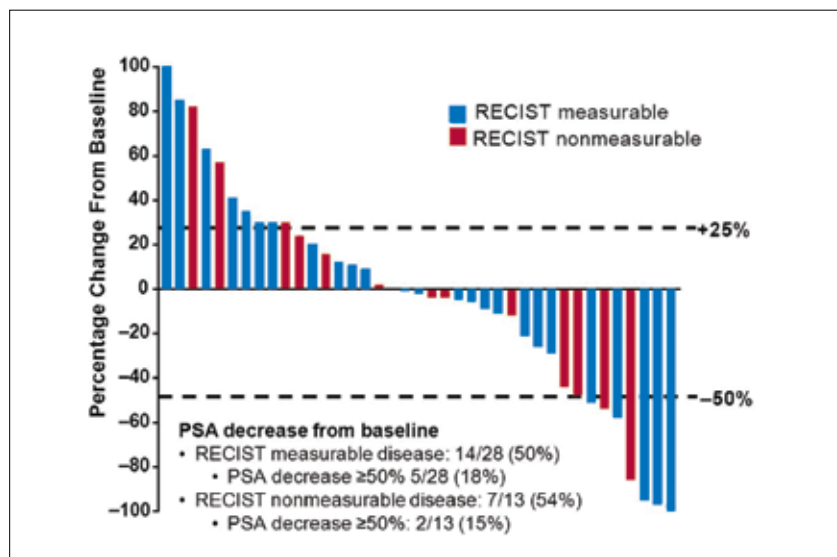


Figure 10. The change in PSA from baseline among patients with metastatic CRPC treated with pembrolizumab plus olaparib in cohort A of the phase 1b/2 KEYNOTE-365 trial. Patients in this cohort had metastatic CRPC previously treated with docetaxel. Data are presented for patients with a baseline and postbaseline assessment of PSA (n=39). Confirmed and unconfirmed PSA decreases from baseline are shown. CRPC, castration-resistant prostate cancer; KEYNOTE-365, Phase 1b/II Trial of Pembrolizumab (MK-3475) Combination Therapies in Metastatic Castration-Resistant Prostate Cancer (mCRPC); PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors. Adapted from Yu EY et al. ASCO GU abstract 145. *J Clin Oncol.* 2019;37(suppl 7S).⁵

6 months or longer. The median radiographic PFS was 4.7 months (95% CI, 4.0-7.7), and the estimated 6-month radiographic PFS rate was 48%. The median overall survival was 13.5 months (95% CI, 7.7 to not reached), and the estimated rate of 6-month overall survival was 73%.

Enrollment to cohort A of the KEYNOTE-365 trial is planned to increase to 100 patients. The currently enrolling, randomized phase 3 trial KEYLYNK-010 (Study of Pembrolizumab [MK-3475] Plus Olaparib Versus Abiraterone Acetate or Enzalutamide in Metastatic Castration-Resistant Prostate Cancer [mCRPC]) will evaluate the combination of olaparib plus pembrolizumab in a molecularly unselected group of patients with metastatic CRPC who had previously received treatment with enzalutamide or abiraterone acetate and had also progressed on chemotherapy.⁶

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Real-World Registry Data From PROCEED: Sipuleucel-T in Elderly Men With Metastatic Castration-Resistant Prostate Cancer

Studies have suggested that elderly patients are likely to exhibit a similar degree of immune cell activation with sipuleucel-T as their younger counterparts.^{1,2} PROCEED (A Registry of Sipuleucel-T Therapy in Men With Advanced Prostate Cancer) is a postmarketing, open-label, multicenter, observational registry for sipuleucel-T.³ The registry collected data on safety and overall survival in men with metastatic CRPC treated with sipuleucel-T in a real-world setting. Between 2011 and 2013, 1976 patients enrolled in PROCEED, and 1902 received at least 1 infusion of sipuleucel-T. The patients had a median follow-up of 46.6 months. The median overall survival was 30.7 months (95% CI, 28.6-32.2).

Dr Andrew Armstrong and colleagues evaluated the clinical experience with sipuleucel-T in patients ages 80 years and older.⁴ In this analysis, patients were divided into 2 groups: those younger than 80 years (n=1528) and those ages 80 years and older (n=374). The median age was 69 years in the first group and 83 years in the second. Among the younger patients, the ECOG performance status was 0 in 70.2% and 1 in 27.1%. Among the older patients, the ECOG performance status was 0 in 51.6% and 1 in 42%. Younger patients were more likely to have higher Gleason scores at diagnosis than were the older patients. Bone metastases were present in 83.3% of the younger group and 86.1% of the older group; 4.6% and 4.5% of patients in each group, respectively, had visceral metastases.

In general, younger and older patients received similar proportions of local and systemic therapies prior to initiating treatment with sipuleucel-T. However, younger patients were less likely to have undergone radical prostatectomy either with or without

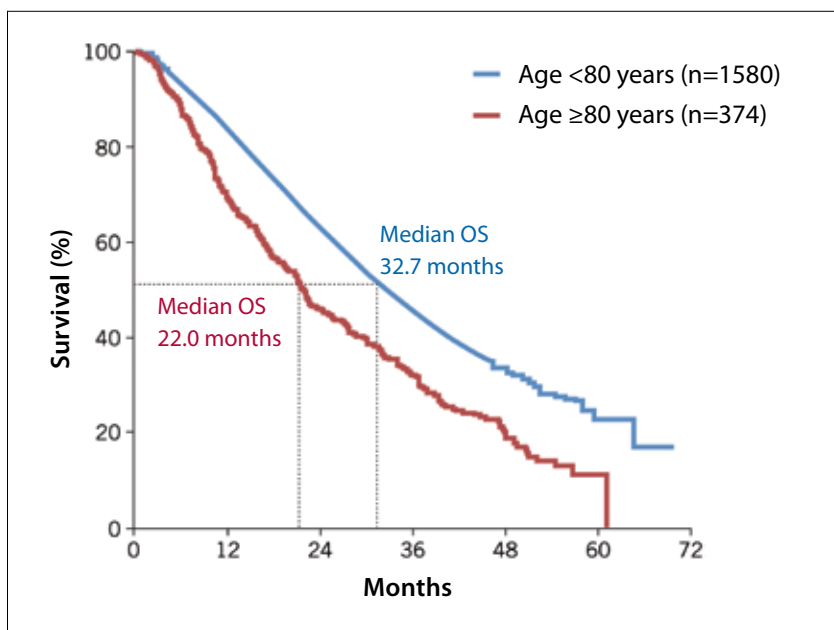


Figure 11. Survival according to age in PROCEED, a real-world registry that evaluated safety and overall survival among patients with mCRPC treated with sipuleucel-T. CRPC, castration-resistant prostate cancer; OS, overall survival; PROCEED, A Registry of Sipuleucel-T Therapy in Men With Advanced Prostate Cancer. Adapted from Armstrong AJ et al. ASCO GU abstract 177. *J Clin Oncol.* 2019;37(suppl 7S).⁴

radiation as a local therapy, and they were more likely to have received radiation alone. After sipuleucel-T, the older group of patients were less likely to have received additional systemic agents.

The median overall survival was 22.0 months among older patients and 32.7 months among younger patients (Figure 11). The median prostate cancer–specific survival was 31.6 months in older patients and 38.5 months in younger patients. For both age groups, prostate cancer was the primary cause of death. Causes of death unrelated to prostate cancer were more common in the older group of patients. The authors noted that the shorter overall survival and prostate cancer–specific survival observed in the elderly population were consistent with the reported literature (regardless of treatment).⁵ The incidence of grade 3 through 5 adverse

events was 9.9% in the younger group vs 10.7% in the older group.

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Highlights in Advanced Prostate Cancer From the 2019 ASCO Genitourinary Cancers Symposium: Commentary

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Several presentations at the 2019 American Society of Clinical Oncology Genitourinary Cancers Symposium described important clinical advances for the management of patients with advanced prostate cancer. New data were presented involving treatments such as darolutamide, radium-223, enzalutamide, abiraterone acetate, and immunotherapies. Below is a summary of these latest findings.

Darolutamide

The ARAMIS study (Androgen Receptor Inhibiting Agent for Metastatic-Free Survival), which was presented by Dr Karim Fizazi, evaluated the efficacy and safety of darolutamide among patients with nonmetastatic castration-resistant prostate cancer (CRPC).¹ This study was a definitive phase 3 analysis of darolutamide, a next-generation androgen receptor antagonist that is specifically designed to avoid passage into the brain through the blood-brain barrier. In these patients with nonmetastatic CRPC (the so-called M0 CRPC setting), darolutamide demonstrated similar efficacy outcomes to those seen in previous phase 3 studies of androgen receptor antagonists, including enzalutamide in the PROSPER trial (Safety and Efficacy Study of Enzalutamide in Patients With Nonmetastatic Castration-Resistant Prostate Cancer) and apalutamide in the SPARTAN trial (A Study of Apalutamide [ARN-509] in Men With Non-Metastatic Castration-Resistant Prostate Cancer).^{2,3} In the ARAMIS trial, the primary endpoint of metastasis-free survival was 40.4 months with darolutamide vs 18.4 months with placebo ($P < .0001$), for

a robust 59% reduction in the risk of distant metastases or death. Darolutamide demonstrated significant benefit in the overall population, as well as in patients at high risk (defined as those with a prostate-specific antigen [PSA] doubling time of ≤ 6 months). Treatment with darolutamide demonstrated a strong trend toward improvement in overall survival (83% vs 73%), although the difference was not statistically significant at the time of the report. Other markers, including time to PSA progression and time to radiographic progression in those with measurable disease, were also improved among patients treated with darolutamide.

What potentially differentiates darolutamide from other agents in the class is the side effect profile. In the ARAMIS study, darolutamide demonstrated relatively less increased fatigue vs placebo (12.1% vs 8.7%) compared with the increases seen with apalutamide vs placebo (30.4% vs 21.1%) in the SPARTAN trial³ or with enzalutamide vs placebo (33% vs 14%) in the PROSPER trial.² There were also no differences in other central nervous system-associated side effects, including falls and dizziness, with darolutamide compared with placebo in ARAMIS, whereas both apalutamide and enzalutamide demonstrated greater rates of each compared with their placebos. There was essentially no difference in the rate of bone fractures with darolutamide vs placebo, at 4.2% vs 3.6%. In contrast, in the phase 3 trial of apalutamide, the rate of fractures was 23.8%.³ With enzalutamide, the rate of falls and nonpathologic fractures was 17%.⁴ The ARAMIS data therefore suggest that darolutamide may have

a different side effect profile than that reported with other androgen receptor antagonists. This observation is important in this group of patients, who are typically older and have more indolent disease (based on their low volume of tumor burden).

Radium-223

My colleagues and I presented a retrospective analysis of the Flatiron Health database to evaluate clinical outcomes with concurrent vs layered treatment with radium-223 and abiraterone acetate plus prednisone/prednisolone.⁴ Layered treatment referred to the initiation of radium-223 or abiraterone acetate plus prednisone/prednisolone as an add-on therapy at least 30 days after the start of the first therapy. An interesting observation was that symptomatic skeletal-related events and fractures were less frequent with layered treatment vs concurrent treatment. Symptomatic skeletal-related events occurred in 36% of the concurrent group vs 23% of the layered group. Pathologic fractures occurred in 18% vs 8%, respectively. Earlier data have shown higher rates of complications, particularly fractures, among patients receiving radium-223 plus abiraterone acetate vs abiraterone acetate alone.⁵ The concomitant use of these agents may result in significant biologic activity, and it should be avoided. The prescribing information for radium-223 contains a new warning against concomitant use with chemotherapy. Our study suggests that the staggered use of radium-223 and abiraterone acetate is reasonable. Nonetheless, fractures remain a significant risk with both of

these treatments, as well as other agents in the class. As a community, physicians should increase documentation of these events and provide more education to patients regarding their risk.

Dr Rebecca Louhanepessy presented an analysis of clinical outcomes of patients with metastatic CRPC treated with radium-223 enrolled in a Dutch prospective observational registry.⁶ The real-world outcomes in this national registry were similar to outcomes in the ALSYMPCA clinical trial (Alpharadin in Symptomatic Prostate Cancer) in terms of overall survival (15.2 months vs 14.9 months) and prevention and delay of symptomatic skeletal-related events (19% vs 22%).⁷ Toxicities, however, were higher in the real-world analysis. Grade 3 anemia occurred in 18.0% of patients (vs 8% in ALSYMPCA). The most common all-grade nonhematologic events were fatigue (59.3% vs 26% in ALSYMPCA), diarrhea (27.7% vs 25%), and nausea (27.0% vs 36%). The increased toxicity suggests that in less-selected patients, radium-223 could be associated with more myelosuppression—in particular, anemia—and gastrointestinal symptoms. For this reason, it is necessary to be proactive in evaluating patients for these risks and monitoring them closely during treatment.

Immunotherapy

Dr Padmanee Sharma presented the initial results of CheckMate 650 (A Phase 2 Trial of Nivolumab Plus Ipilimumab in Men With Metastatic Castration-Resistant Prostate Cancer), a phase 2 study of nivolumab plus ipilimumab for metastatic CRPC.⁸ The study found that nivolumab plus ipilimumab had relatively modest rates of response in this population, with overall response rates of 25.0% in cohort 1 (asymptomatic or minimally symptomatic patients who progressed after receiving ≥ 1 second-generation hormone therapy and who had not received chemotherapy) and 10.0% in cohort 2 (patients who progressed after cytotoxic chemotherapy).

There was a higher incidence of adverse events and less tolerance in this study as compared with clinical trials of immunotherapy in patients with other types of solid tumors, such as melanoma and non-small cell lung cancer.^{9,10} Any-grade treatment-related adverse events occurred in 93.3% of cohort 1 and 95.6% of cohort 2. Grade 3 to 5 events occurred in 42.2% and 53.3%, respectively. This study therefore suggests that the use of current and future immunotherapeutic agents in patients with metastatic CRPC will raise unique concerns regarding tolerability. It will be necessary to be mindful of the doses of these agents (and similar ones) in this population. Future phase 1 safety and tolerability studies of immunotherapies should be considered in patients with metastatic CRPC because of the distinct side effect profiles observed in this population.

Dr Evan Yu provided data for cohort A of the KEYNOTE-365 trial (Phase Ib/II Trial of Pembrolizumab [MK-3475] Combination Therapies in Metastatic Castration-Resistant Prostate Cancer [mCRPC]).¹¹ Patients in this cohort had metastatic CRPC previously treated with docetaxel. They were not selected based on genetic analysis. The treatment consisted of pembrolizumab plus olaparib. This combination was associated with a PSA response rate of 12%, suggesting a possible role for poly(ADP-ribose) polymerase (PARP) inhibitors in unselected patients. It is difficult to treat CRPC after the use of chemotherapy, and yet this trial demonstrated fairly high rates of partial disease response (7%) and stable disease (46%). Although overall response rates were relatively low, these data suggest that there could still be clinical benefit with pembrolizumab plus olaparib in this setting.

Enzalutamide

Dr Andrew J. Armstrong presented results from the phase 3 ARCHES trial (Androgen Receptor Inhibition With Chemohormonal Therapy in Men

With Metastatic Hormone-Sensitive Prostate Cancer), which compared androgen-deprivation therapy with or without enzalutamide in patients with metastatic hormone-sensitive prostate cancer.¹² This definitive phase 3 study clearly demonstrated the activity of enzalutamide in this setting, with a dramatic improvement in progression-free survival. The median progression-free survival was not reached with enzalutamide vs 19.45 months with placebo ($P < .0001$). This study was noteworthy for the high tumor burden seen in the majority of patients (>60%), as well as for enrollment of patients who had previously received docetaxel chemotherapy (18%). The improvement in progression-free survival seen with enzalutamide was maintained in patients who had received previous treatment with docetaxel. The results from this trial may contribute to a new treatment paradigm for high-burden, high-risk patients, who could benefit from both chemotherapy and androgen receptor antagonist therapy.

The multicenter, randomized phase 2 CHEIRON trial (Chemotherapy Plus Enzalutamide in First Line Therapy for Castration Resistant Prostate Cancer) evaluated the addition of enzalutamide to docetaxel as first-line treatment for patients with metastatic CRPC.¹³ The results demonstrated safety and tolerability of docetaxel plus enzalutamide. However, there is some question regarding the validity of the efficacy endpoints. The median progression-free survival was 9.1 months with docetaxel alone vs 10.1 months with docetaxel plus enzalutamide ($P = .01$). This improvement was statistically significant but not clinically significant, with a difference of only a month. There was no significant difference in overall survival. These results suggest that sequential use of these agents is still the best standard of care in this setting.

Denosumab

Dr Silke Gillessen discussed the incidence of hypokalemia among

patients with CRPC treated with denosumab in the REDUSE study (Prevention of Symptomatic Skeletal Events With Denosumab Administered Every 4 Weeks Versus Every 12 Weeks—A Non-Inferiority Phase III Trial).¹⁴ This noninferiority phase 3 trial evaluated the use of denosumab to prevent symptomatic skeletal events. Denosumab was administered at 120 mg every 4 weeks or every 12 weeks (after an induction phase). The analysis showed that the experimental dose of 120 mg every 12 weeks was associated with a lower incidence of hypocalcemia (all grades, 20.3% vs 40.2%). However, this early report did not provide results regarding the prevention of skeletal-related events. Longer follow-up will be needed to conclude whether the alternative regimen of every-3-month dosing is efficacious.

Analyses of Patient Subgroups

An analysis of the real-world registry PROCEED (A Registry of Sipuleucel-T Therapy in Men With Advanced Prostate Cancer) focused on the use of sipuleucel-T in elderly men (≥ 80 years) with CRPC.¹⁵ The analysis found that this patient population tolerates sipuleucel-T well and benefits from treatment. The median overall survival was 32.7 months among younger patients vs 22.0 months among older patients. A serious adverse event occurred in 13.7% vs 16.3%, respectively. This study suggests that age should not be used as a criterion against immunotherapy in CRPC.

My colleagues and I presented an analysis of overall survival according to race among patients with chemotherapy-naïve metastatic CRPC treated with abiraterone acetate or enzalutamide.¹⁶ Data were drawn from a large, retrospective, single-payer system database from the Veterans Health Administration. A third of the patients were African American, and the rest were white. African American patients had higher rates of hypertension, diabetes, and liver abnormalities.

However, when adjusted for prognostic factors, African American patients demonstrated a 20% improvement in overall survival. These data suggest that African American patients, despite having poor prognostic factors and more comorbidities, may derive a greater benefit from treatment with next-generation hormonal agents, such as abiraterone acetate or enzalutamide, in this setting. We therefore need to access these agents for African American patients, when possible, to maximize the survival benefits.

Disclosure

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