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A SPECIAL MEETING REVIEW EDITION

Highlights in Advanced Prostate Cancer From the 2022 American Society of Clinical Oncology Genitourinary Cancers Symposium

A Review of Selected Presentations From the ASCO GU Symposium • February 17-19, 2022 • San Francisco, California

Special Reporting on:

- Exposure-Adjusted Safety Analyses of the VISION Phase 3 Trial of ^{177}Lu-PSMA-617 in Patients With Metastatic Castration-Resistant Prostate Cancer
- Overall Survival With Darolutamide Versus Placebo in Combination With Androgen-Deprivation Therapy and Docetaxel for Metastatic Hormone-Sensitive Prostate Cancer in the Phase 3 ARASENS Trial
- Phase 3 MAGNITUDE Study: First Results of Niraparib With Abiraterone Acetate and Prednisone as First-Line Therapy in Patients With Metastatic Castration-Resistant Prostate Cancer With and Without Homologous Recombination Repair Gene Alterations
- PROpel: Phase III Trial of Olaparib and Abiraterone vs Placebo and Abiraterone as First-Line Therapy for Patients With Metastatic Castration-Resistant Prostate Cancer
- Overall Survival in Patients With Metastatic Hormone-Sensitive Prostate Cancer Treated With Enzalutamide Plus Androgen Deprivation Therapy by High or Low Disease Volume and Progression to mHSPC (M0 at Diagnosis) or De Novo mHSPC (M1 at Diagnosis): Post Hoc Analysis of the Phase 3 ARCHES Trial
- An AI-Derived Digital Pathology-Based Biomarker to Predict the Benefit of Androgen Deprivation Therapy in Localized Prostate Cancer With Validation in NRG/RTOG 9408
- Phase 1/2 Study of ARV-110, an Androgen Receptor PROTAC Degrader, in Metastatic Castration-Resistant Prostate Cancer
- A Randomized, Double-Blind, Placebo-Controlled, Phase 3b Study of the Efficacy and Safety of Continuing Enzalutamide in Chemotherapy-Naive, Metastatic Castration-Resistant Prostate Cancer Patients Treated With Docetaxel Plus Prednisolone Who Have Progressed on Enzalutamide: PRESIDE

PLUS Meeting Abstract Summaries

With Expert Commentary by:

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Exposure-Adjusted Safety Analyses of the VISION Phase 3 Trial of ^{177}Lu-PSMA-617 in Patients With Metastatic Castration-Resistant Prostate Cancer

Prostate-specific membrane antigen (PSMA) is highly expressed among patients with metastatic castration-resistant prostate cancer (mCRPC). The radioligand therapy ^{177}Lu-PSMA-617, also known as lutetium (^{177}Lu) vipivotide tetraxetan, is a targeted therapy that delivers beta-particle radiation therapy to cells that express PSMA.[1] The international, open-label phase 3 VISION study is a pivotal trial that evaluated the efficacy and safety of ^{177}Lu-PSMA-617 in men with progressive PSMA-positive mCRPC. The trial enrolled 831 patients who had previously received at least 1 androgen receptor (AR) pathway inhibitor and 1 or 2 taxane regimens. The patients were randomly assigned 2:1 to receive ^{177}Lu-PSMA-617 administered at 7.4 GBq every 6 weeks for 4 to 6 cycles plus protocol-permitted standard of care or standard of care alone.

After a median follow-up of 20.9 months, ^{177}Lu-PSMA-617 was significantly more effective than the standard of care alone.[2] The median radiographic progression-free survival (rPFS) was 8.7 months with ^{177}Lu-PSMA-617 vs 3.4 months with the standard of care (hazard ratio [HR], 0.40; 99.2% CI, 0.29- 0.57; *P*<.001). Overall survival was 15.3 months vs 11.3 months, respectively (HR, 0.62; 95% CI, 0.52-0.74; *P*<.001).

In the primary analysis, the incidence of grade 3 or higher treatment-emergent adverse events (TEAEs) was 52.7% with ^{177}Lu-PSMA-617 vs 38.0% with the standard of care.[2] In the ^{177}Lu-PSMA-617 arm, TEAEs led to dose reductions in 5.7% of patients, dose interruptions in 16.1%, and treatment discontinuations in 11.9%. The investigators noted that the higher rates of toxicity in the ^{177}Lu-PSMA-617 arm should be considered in the context of the longer duration of treatment exposure in that group. In the ^{177}Lu-PSMA-617 arm, the median duration of exposure was 6.9 months for ^{177}Lu-PSMA-617 and 7.6 months for the standard of care. In the control group, the median duration of exposure to the standard of care was 2.1 months. Overall, treatment exposure in the ^{177}Lu-PSMA-617 group was more than 3 times higher than in the standard-of-care group.

Kim N. Chi, MD, presented the results of a post hoc analysis of TEAEs in the VISION trial that adjusted for

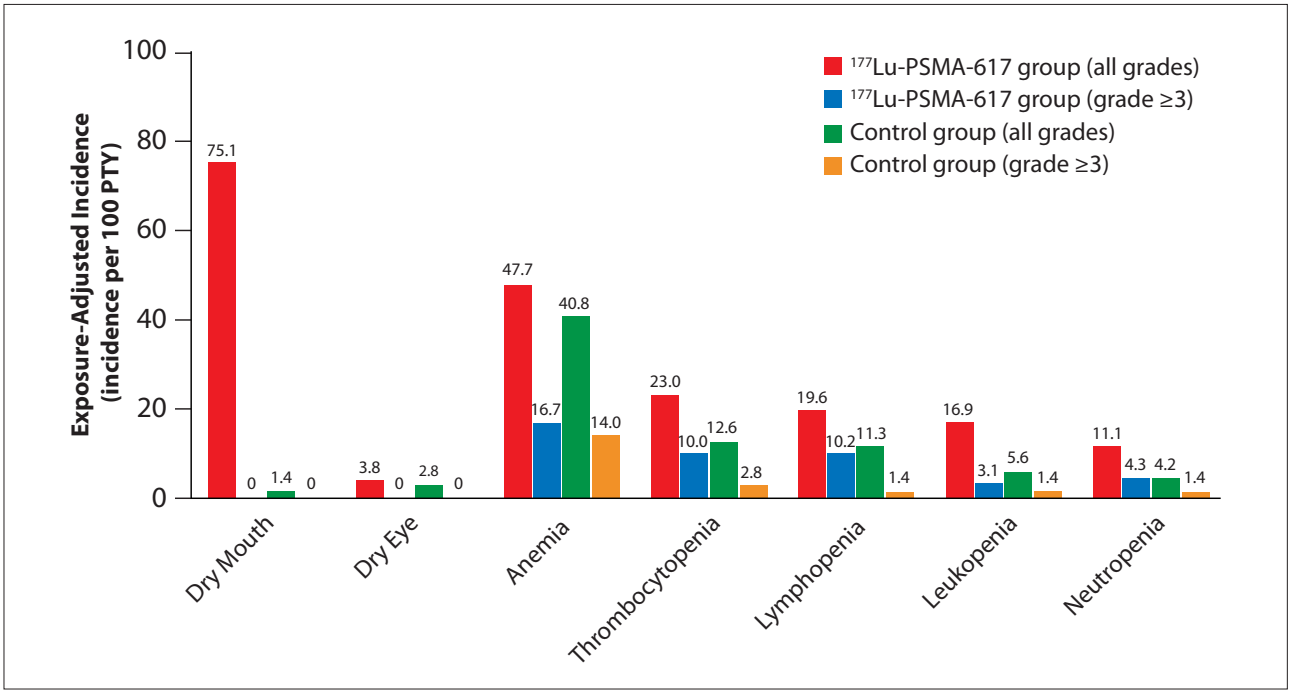

Figure 1. Exposure-adjusted incidences of dry mouth, dry eye, and acute myelosuppression in an analysis of the phase 3 VISION trial of ^{177}Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer. PTY, patient treatment-year. Adapted from Chi KN et al. ASCO GU abstract 85. *J Clin Oncol.* 2022;40(suppl 6).[3]

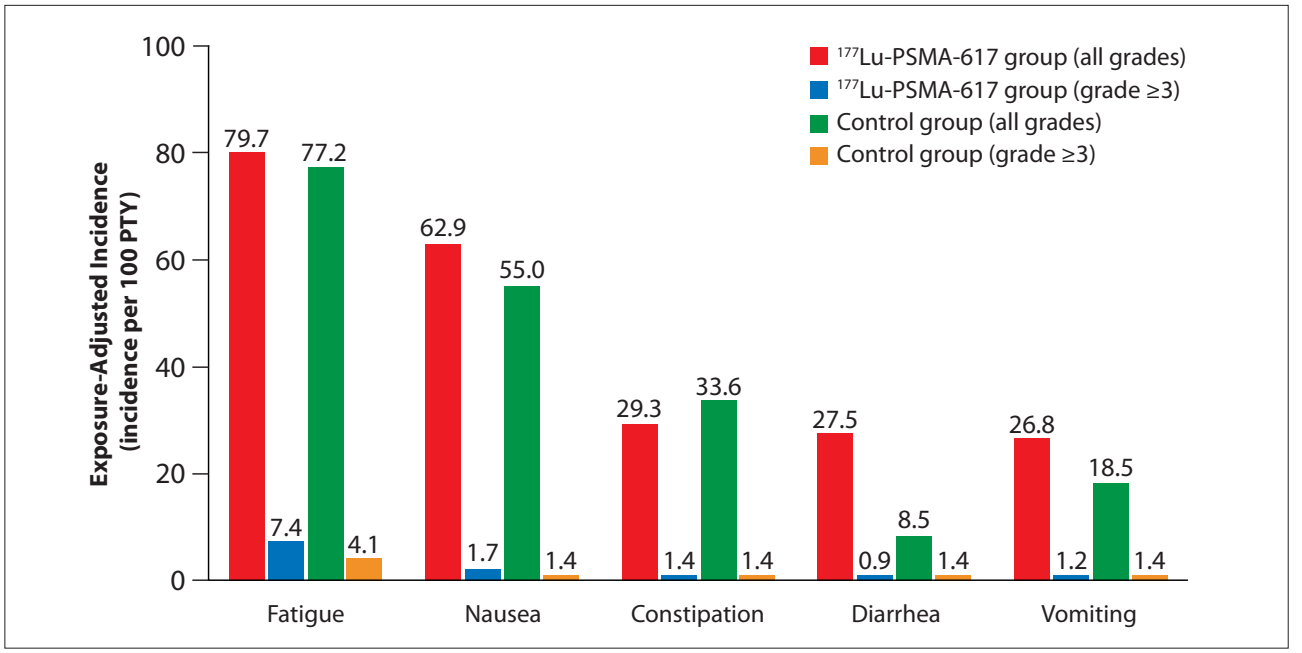

Figure 2. Exposure-adjusted incidences of fatigue and gastrointestinal events in an analysis of the phase 3 VISION trial of ^{177}Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer. PTY, patient treatment-year. Adapted from Chi KN et al. ASCO GU abstract 85. *J Clin Oncol.* 2022;40(suppl 6).[3]

treatment exposure.[3] In the adjusted analysis, the incidence of TEAEs was similar between the arms. Any-grade TEAEs occurred at a rate of 1415.7 per 100 patient treatment-years (PTYs) in the ^{177}Lu-PSMA-617 group vs 1137.0 per 100 PTYs in the standard-of-care group. For grade 3 or higher TEAEs, these rates were 91.1 vs 135.1 per 100 PTYs, respectively.

Three types of TEAEs occurred more frequently among patients in the ^{177}Lu-PSMA-617 arm than in the control arm: dry mouth (75.1 vs 1.4 per 100 PTYs), dry eye (3.8 vs 2.8 per 100 PTYs), and acute myelosuppression events, including anemia (47.7 vs 40.8 per 100 PTYs), thrombocytopenia (23.0 vs 12.6 per 100 PTYs), lymphopenia (19.6 vs 11.3 per 100 PTYs), and leukopenia (16.9 vs 5.6 per 100 PTYs; Figure 1). These TEAEs appeared to be related to treatment with ^{177}Lu-PSMA-617. In contrast, although the unadjusted rates of fatigue and gastrointestinal events were substantially higher in the ^{177}Lu-PSMA-617 arm, these rates were generally similar between the groups after adjusting for treatment duration (Figure 2). The incidence of diarrhea was higher in the ^{177}Lu-PSMA-617 arm than in the standard-of-care arm (27.5 vs 8.5 per 100 PTYs), as was the incidence of vomiting (26.8 vs 18.5 per 100 PTYs). In the unadjusted analysis, musculoskeletal events, renal events, liver events, and dyspnea occurred at a higher frequency in the ^{177}Lu-PSMA-617 group, but these events occurred more frequently in the control group after adjusting for treatment exposure.

The investigators concluded that these findings support the benefit/risk

ABSTRACT SUMMARY A Phase 3 Trial to Compare Treatment With ^{177}Lu-PSMA-617 Plus Standard of Care Versus Standard of Care Alone in Patients With Metastatic Hormone-Sensitive Prostate Cancer

A phase 3 trial in progress is comparing ^{177}Lu-PSMA-617 plus standard of care (a combination of an AR pathway inhibitor and ADT) vs standard of care alone in patients with mHSPC (Abstract TPS210). The trial is enrolling patients with untreated or minimally treated PSMA-positive mHSPC. Stratification factors include disease volume, age, and previous or planned treatment of the primary tumor. The study will randomly assign patients to receive standard of care plus ^{177}Lu-PSMA-617 every 6 weeks for a total of 6 doses, or standard of care alone. Crossover from the control arm to the ^{177}Lu-PSMA-617 arm is allowed upon radiographic progression. The primary endpoint is rPFS. The primary efficacy and safety analyses will be performed after approximately 418 rPFS events per blinded independent central review, to detect an HR of 0.70 with at least 95% power, assuming 2.5% significance on a 1-sided log-ranked test. Nineteen countries are participating in the trial. The first participant was enrolled in June 2021. The estimated study completion date is December 2025.

profile of adding ^{177}Lu-PSMA-617 to standard of care in this patient population. They suggested that differences in treatment exposure between the study groups should be considered when evaluating safety data.

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Overall Survival With Darolutamide Versus Placebo in Combination With Androgen-Deprivation Therapy and Docetaxel for Metastatic Hormone-Sensitive Prostate Cancer in the Phase 3 ARASENS Trial

Darolutamide is a potent inhibitor of the AR pathway that has low penetration of the blood-brain barrier and limited potential for drug-drug interactions. The randomized phase 3 ARAMIS trial evaluated the addition of darolutamide to androgen deprivation therapy (ADT) in patients with nonmetastatic CRPC.[1] The addition of darolutamide improved metastasis-free survival by approximately 2 years, and reduced the risk of death by 31%. The toxicity profile was similar to placebo.[1]

Among patients with metastatic hormone-sensitive prostate cancer (mHSPC), ADT plus darolutamide is a standard of care based on the demonstrated benefit in overall survival.[2] The global, double-blind phase 3 ARASENS trial evaluated the efficacy and safety of adding darolutamide to ADT and docetaxel in patients with mHSPC. The primary analysis of ARASENS was presented by Matthew R. Smith, MD, PhD, and published concurrently in the *New England Journal of Medicine*.[3,4]

The trial enrolled 1306 patients with mHSPC who had an Eastern

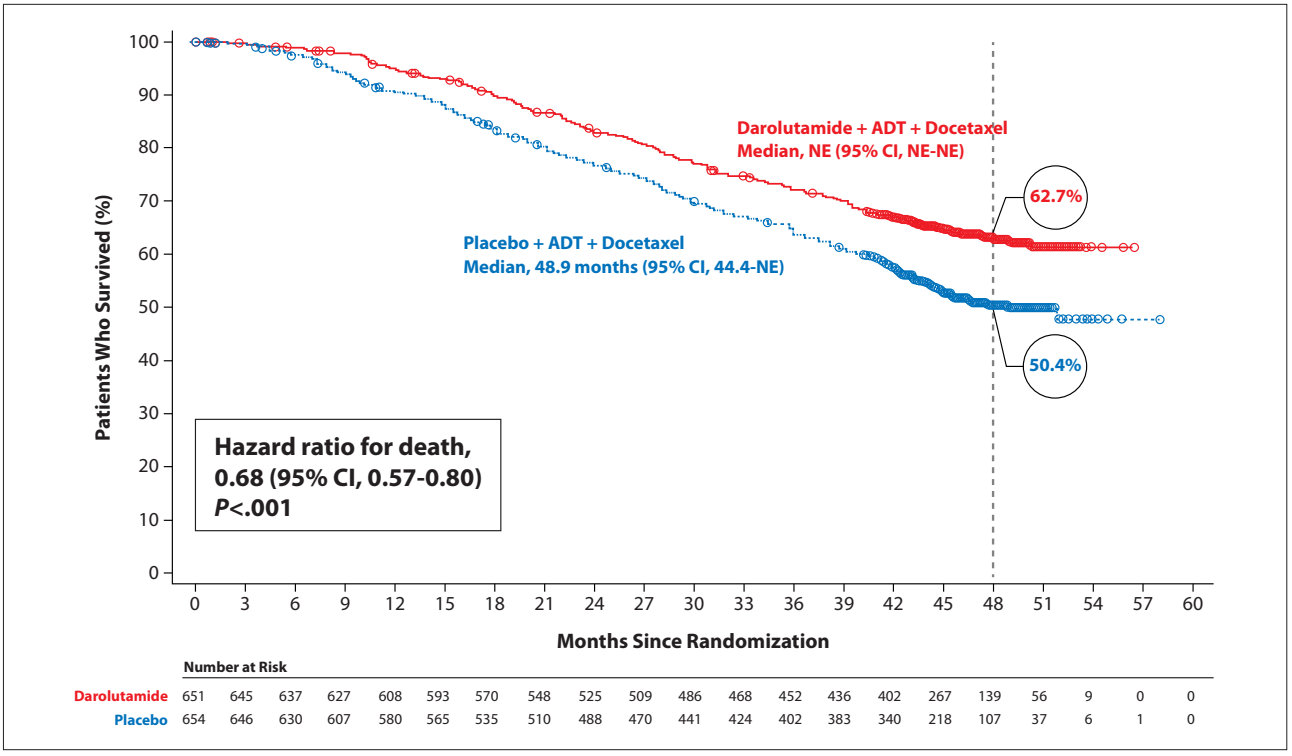

Figure 3. Overall survival in the phase 3 ARASENS trial, which evaluated the addition of darolutamide to ADT and docetaxel in patients with metastatic hormone-sensitive prostate cancer. ADT, androgen deprivation therapy; NE, not estimable. Adapted from Smith MR et al. ASCO GU abstract 13. *J Clin Oncol.* 2022;40(suppl 6).[3]

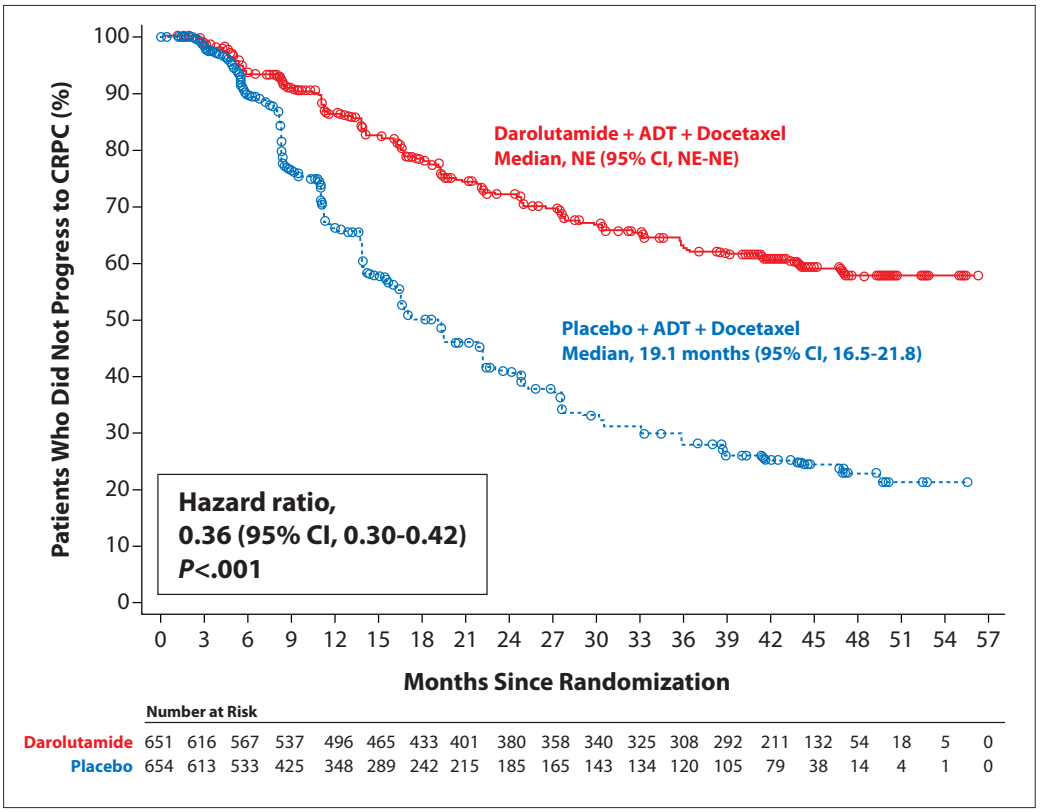

Figure 4. Time to development of castration-resistant prostate cancer in the phase 3 ARASENS trial, which evaluated the addition of darolutamide to ADT and docetaxel in patients with metastatic hormone-sensitive prostate cancer. ADT, androgen deprivation therapy; NE, not estimable. Adapted from Smith MR et al. ASCO GU abstract 13. *J Clin Oncol.* 2022;40(suppl 6).[3]

Cooperative Oncology Group (ECOG) performance status of 0 or 1 and were candidates for ADT and docetaxel. The stratification factors included the extent of disease and the baseline level of alkaline phosphatase. Within 12 weeks of initiating ADT, patients were randomly assigned to treatment with darolutamide at 600 mg twice daily or placebo twice daily. In both groups, docetaxel was started within 6 weeks of randomization and administered for 6 cycles. The baseline characteristics were similar between the arms. The patients' median age was 67 years. At the time of the initial diagnosis, 78% of patients had a Gleason score of 8 or higher, and 86% had metastatic disease.

The trial met its primary endpoint, reporting a significant 32.5% reduction in the risk of death with darolutamide plus ADT and docetaxel compared with placebo plus ADT and docetaxel. The median overall survival was not reached in the darolutamide arm vs 48.9 months in the control arm (HR, 0.68; 95% CI, 0.57-0.80; *P*<.001; Figure 3). At 4 years, the rates of overall survival were 62.7% vs 50.4%. This survival benefit occurred despite substantial use of subsequent life-prolonging therapies in both arms, reported in 56.8% of the darolutamide arm and 75.6% of the placebo arm. In the darolutamide arm, the most common subsequent therapies were abiraterone acetate (35.6%), cabazitaxel (18.1%), enzalutamide (15.2%), and docetaxel (14.6%). The most common subsequent therapies in the placebo arm were abiraterone acetate (46.9%), enzalutamide (27.5%), cabazitaxel (18.0%), and docetaxel (18.0%).

In subgroup analyses, the overall survival benefit with darolutamide was observed across prespecified groups, including those based on extent of disease at study entry, baseline alkaline phosphatase, Gleason score, and whether patients had metastatic disease (HR, 0.71) or recurrent disease (HR, 0.61) at diagnosis. Darolutamide was also associated with improvements in secondary endpoints, including time to CRPC (HR, 0.36; *P*<.001; Figure 4), time to pain progression (HR, 0.79; *P*=.01), time to first symptomatic skeletal event (HR, 0.71; *P*=.02), and time to first subsequent antineoplastic therapy (HR, 0.39; *P*<.001).

Consistent with prior studies, the safety profile of darolutamide was similar to that of placebo, as shown by rates of grade 3 or higher adverse events (AEs; 70.2% vs 67.5%), serious AEs (44.8% vs 42.3%), and AEs leading to discontinuation of treatment (13.5% vs 10.6%). The most frequent grade 3/4 AEs in the darolutamide and placebo arms were neutropenia (33.7% vs 34.2%), febrile neutropenia (7.8% vs 7.4%), hypertension (6.4% vs 3.2%), and anemia (4.8% vs 5.1%). After adjusting for differences in drug exposure, there were no substantial differences between the darolutamide and placebo arms in the rates of key AEs associated with AR pathway inhibitors, including fatigue (12.5 vs 17.8 per 100 patient-years), vasodilation and flushing (7.7 vs 11.7 per 100 patient-years),

and rash (6.2 vs 7.3 per 100 patient-years). Based on the efficacy and safety data, the investigators concluded that darolutamide in combination with ADT and docetaxel should become a new standard of care for the treatment of patients with mHSPC.

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Phase 3 MAGNITUDE Study: First Results of Niraparib With Abiraterone Acetate and Prednisone as First-Line Therapy in Patients With Metastatic Castration-Resistant Prostate Cancer With and Without Homologous Recombination Repair Gene Alterations

Two phase 3 trials presented at the 2022 American Society of Clinical Oncology Genitourinary Cancers Symposium evaluated the combination of a poly(ADP-ribose) polymerase (PARP) inhibitor plus abiraterone as first-line therapy in patients with mCRPC.[1,2] Both trials evaluated the efficacy and safety of this strategy among patients with mCRPC with or without alterations in genes associated with homologous recombination repair (HRR). These types of alterations, which include *BRCA1/2* mutations, are associated with a poor prognosis but confer sensitivity to PARP inhibitors.[3] In a recent phase 2 trial, the PARP inhibitor niraparib demonstrated activity in patients with heavily pretreated HRR gene-altered mCRPC.[4]

Given the demonstrated role of

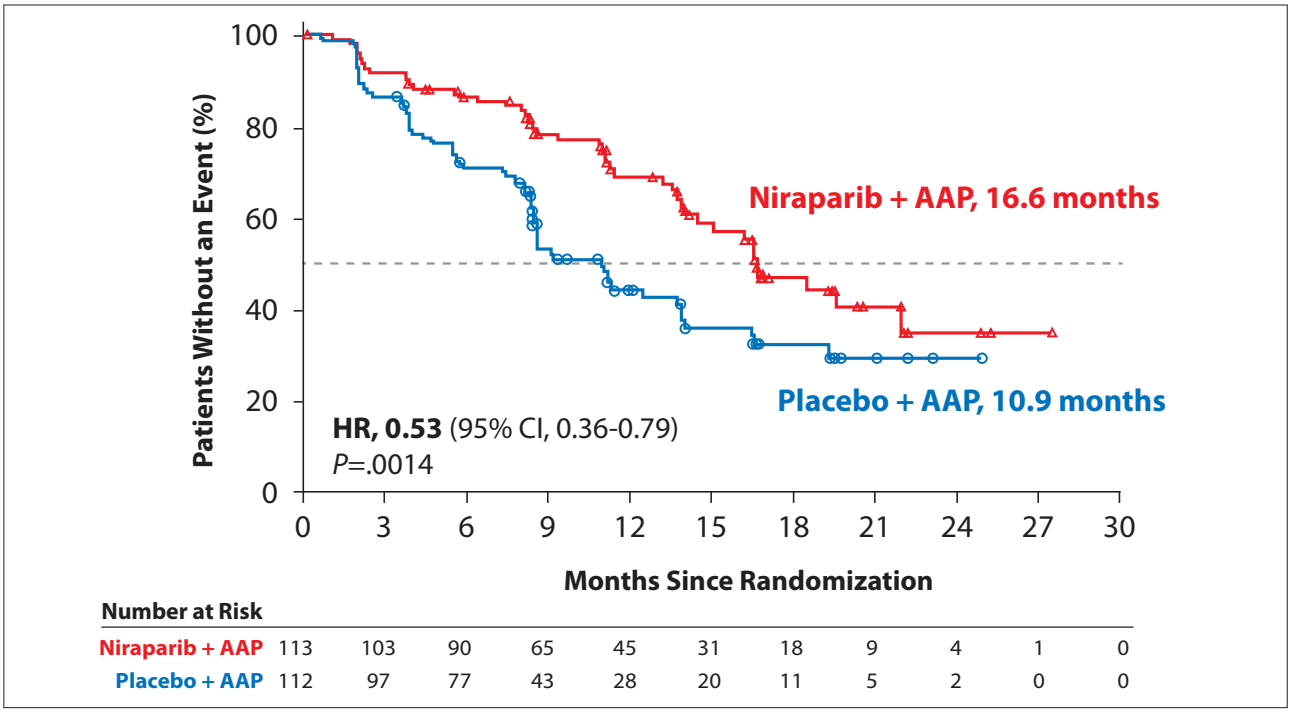

Figure 5. Radiographic progression-free survival, as assessed by central review, in the phase 3 MAGNITUDE study of niraparib plus abiraterone acetate and prednisone as first-line therapy in patients with metastatic castration-resistant prostate cancer. Data are shown for patients with *BRCA1/2* mutations. AAP, abiraterone acetate and prednisone; HR, hazard ratio. Adapted from Chi KN et al. ASCO GU abstract 12. *J Clin Oncol.* 2022;40(suppl 6).[1]

AR signaling in the regulation of DNA repair in prostate cancer and the activity of PARP inhibition in mCRPC with HRR gene alterations, there was a rationale for investigating the combination of PARP inhibition and AR targeting in patients with mCRPC. The phase 3 MAGNITUDE and PROpel trials evaluated this approach in the setting of mCRPC, with niraparib and olaparib, respectively.[1,2]

The MAGNITUDE trial enrolled patients eligible for first-line therapy for mCRPC.[1] Patients could have received up to 4 months of prior abiraterone acetate plus prednisone for mCRPC. Patients were stratified based on prior therapy and underwent prospective biomarker screening for the presence of HRR gene alterations. Based on HRR biomarker status, patients were allocated into biomarker-negative or biomarker-positive cohorts. In the biomarker-positive cohort, patients were stratified based on the presence of *BRCA1/2* mutations vs other HRR gene alterations. Patients in each cohort were randomly assigned to either niraparib at 200 mg daily or placebo, each with abiraterone acetate plus prednisone.

In the HRR biomarker–negative cohort, a prespecified early futility analysis in the first 233 patients showed no benefit with niraparib plus abiraterone acetate and prednisone compared with placebo plus abiraterone acetate and prednisone in a composite endpoint of radiographic or prostate-specific antigen (PSA) progression. There was additional grade 3/4 toxicity in the niraparib arm. Given these findings, the independent data monitoring committee recommended that enrollment in this cohort cease.

In the HRR biomarker–positive cohort, a total of 423 patients were randomly assigned to niraparib plus abiraterone acetate and prednisone (n=212) or placebo plus abiraterone acetate and prednisone (n=211). The patients' median age was 69 years. *BRCA2* mutations were present in 40.6% of patients in the niraparib arm and 41.7% in the control arm. Prior treatment with abiraterone acetate was reported in 23.6% vs 22.7%, respectively. Two parameters were more frequent in the niraparib arm vs the control arm: ECOG performance status of 1 (38.7% vs 30.8%) and visceral metastases (24.1% vs 18.5).

Among patients with *BRCA1/2* mutations, after a median follow-up of 16.7 months, niraparib plus abiraterone acetate and prednisone was associated with a significant improvement in rPFS vs placebo plus abiraterone acetate and prednisone. As assessed by central review, the median rPFS was 16.6 months in the niraparib arm vs 10.9 months in the control arm (HR, 0.53; 95% CI, 0.36-0.79; *P*=.0014; Figure 5). According to investigator review, the median rPFS was 19.3 vs 12.4 months, respectively (HR, 0.50; 95% CI, 0.33-0.75; nominal *P*=.0006). Similar trends were observed in the broader cohort of HRR biomarker–positive patients. After a median follow-up of 18.6 months, the median rPFS by central review was 16.5 months in the niraparib arm vs 13.7 months in the control arm (HR, 0.73; 95% CI, 0.56-0.96; *P*=.0217). Prespecified subgroup analyses showed a consistent effect across categories.

Among patients who were positive for the HRR biomarker, the addition of niraparib to abiraterone acetate plus prednisone was associated with improvements in secondary endpoints, including time to cytotoxic chemotherapy (HR, 0.59; *P*=.0108), time to symptomatic progression (HR, 0.69; *P*=.0444), and time to PSA progression (HR, 0.57; nominal *P*=.0001). The overall response rate was 60% in the niraparib arm vs 28% in the control arm (relative risk, 2.13; nominal *P*<.001). The overall survival data were immature at the time of the analysis; only 27% of deaths had occurred. Health-related quality of life was maintained in both arms, with no clinically meaningful changes observed.

Grade 3/4 TEAEs occurred in 67% of patients in the niraparib arm vs 46.4% of patients in the control arm. The most common AE leading to dose reductions in the niraparib arm was anemia (13.2%), followed by thrombocytopenia (2.8%). Discontinuation of niraparib or placebo occurred in 10.8% of patients in the niraparib

ABSTRACT SUMMARY A Phase 3 Study to Compare ^{177}Lu-PSMA-617 Treatment With a Change in Androgen Receptor Pathway Inhibitor in Taxane-Naive Patients With Metastatic Castration-Resistant Prostate Cancer

PSMAfore is an ongoing, multinational phase 3 trial comparing ^{177}Lu-PSMA-617 against a change in the AR pathway inhibitor in patients with mCRPC who previously received an alternative AR pathway inhibitor, but not a taxane (Abstract TPS211). This trial was prompted by the demonstrated benefit of ^{177}Lu-PSMA-617 in patients previously treated with at least 1 AR pathway inhibitor and 1 or 2 taxanes in the VISION trial (Sartor O et al. *N Engl J Med*. 2021;385[12]:1091-1103). PSMAfore is enrolling patients with PSMA-positive mCRPC who developed disease progression during treatment with a previous AR pathway inhibitor and who have not received a taxane in the CRPC or HSPC setting. Stratification factors include use of previous AR pathway inhibitors (in CRPC vs HSPC) and degree of symptoms. The study will randomly assign patients to receive ^{177}Lu-PSMA-617 administered every 6 weeks for a total of 6 doses or to receive a different AR pathway inhibitor. The primary endpoint is rPFS. Secondary endpoints include overall survival, safety, ORR, time to relevant clinical events, and health-related quality of life. The estimated study completion date is December 2024.

arm vs 4.7% of those in the placebo arm. TEAEs were consistent with the known safety profiles for these agents. Most TEAEs were grade 1/2. The most common grade 3 or higher TEAEs included anemia (29.7% with niraparib vs 7.6% with placebo), hypertension (15.6% vs 14.2%), thrombocytopenia (6.6% vs 2.4%), and neutropenia (6.6% vs 1.4%).

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PROpel: Phase III Trial of Olaparib and Abiraterone vs Placebo and Abiraterone as First-Line Therapy for Patients With Metastatic Castration-Resistant Prostate Cancer

The phase 3 PROpel trial was a global, randomized, double-blind study that evaluated the addition of olaparib to abiraterone acetate plus prednisone or prednisolone in 796 patients with previously untreated mCRPC.[1] In a previous randomized phase 2 study, the combination of olaparib plus abiraterone acetate led to a significant improvement in rPFS vs abiraterone acetate alone, regardless of the patient's HRR mutation status.[2]

The PROpel trial enrolled patients who required first-line treatment for mCRPC. The stratification factors

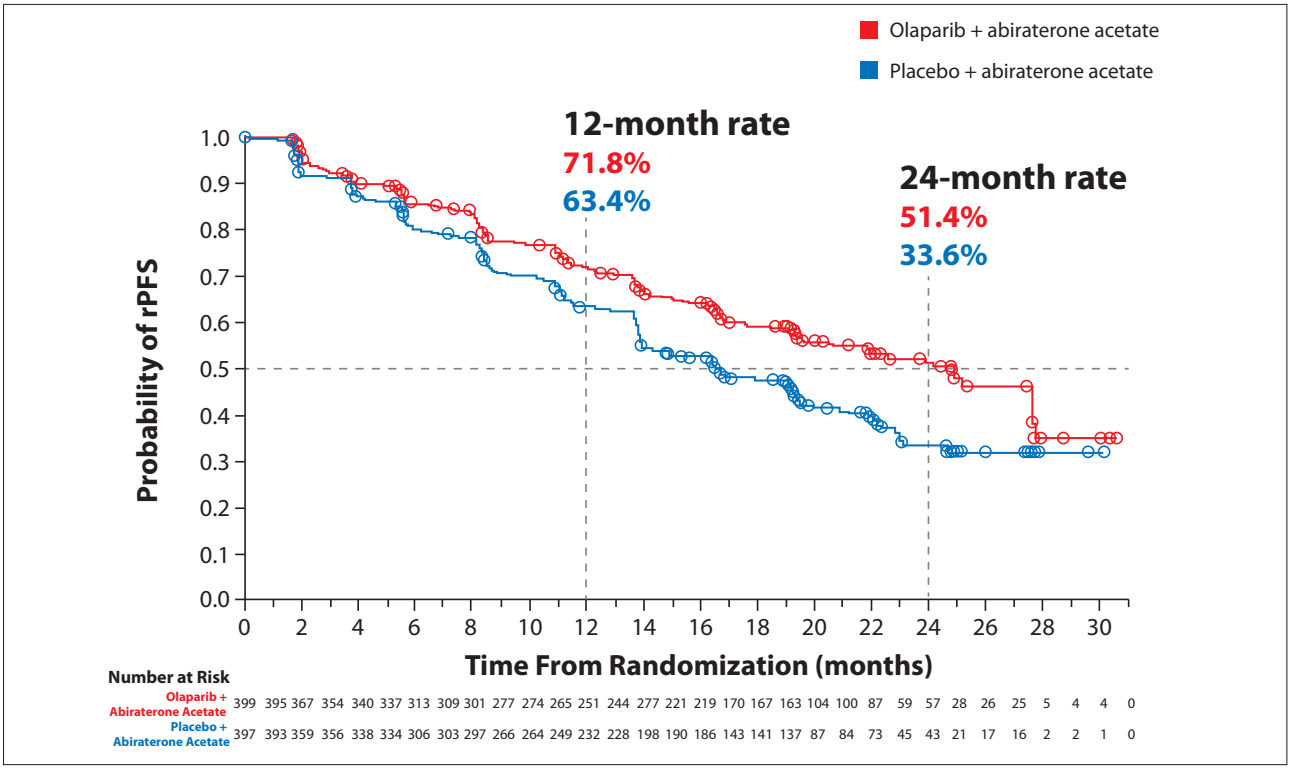

Figure 6. Radiographic progression-free survival according to investigator assessment in the phase 3 PROpel trial, which evaluated the addition of olaparib to abiraterone acetate plus prednisone or prednisolone in patients with previously untreated metastatic castration-resistant prostate cancer. rPFS, radiographic progression-free survival. Adapted from Saad F et al. ASCO GU abstract 11. *J Clin Oncol.* 2022;40(suppl 6).[1]

included the site of distant metastases and prior use of taxanes for mHSPC. The patients were randomly assigned to receive olaparib at 300 mg twice daily or placebo, each administered with abiraterone acetate at 100 mg once daily plus prednisone or prednisolone at 5 mg twice daily. The patient characteristics were well balanced between the arms. The patients' median age was 69 years in the olaparib arm and 70 years in the control arm. HRR mutations were present in 27.8% and 29%, respectively. Use of docetaxel at the mHSPC stage was reported in 22.6% vs 22.4%.

The PROpel trial met its primary endpoint, demonstrating a significant 34% reduction in the risk of investigator-assessed progression or death with olaparib plus abiraterone acetate vs placebo plus abiraterone acetate. The median rPFS was 24.8 months vs 16.6 months, respectively (HR, 0.66; 95% CI, 0.54-0.81; *P*<.0001). At 24 months, rPFS rates were 51.4% vs 33.6% (Figure 6). A blinded central review yielded similar outcomes, with a median rPFS of 27.6 months for the olaparib arm vs 16.4 months for the control arm (HR, 0.61; 95% CI, 0.49-0.74; *P*<.0001).

The benefit with the combination approach was observed across prespecified subgroups. Data for overall survival were not yet mature, with the median overall survival not reached in either arm. Other secondary endpoints favored olaparib vs placebo. The time to first subsequent therapy or death was 25 months vs 19.9 months, respectively (HR, 0.74; 95% CI, 0.61-0.90; *P*=.004). The time to second progression or death was not reached in either arm (HR, 0.69; 95% CI, 0.51-0.94; *P*=.0184). Among the 40% of patients with measurable disease, the objective response rate (ORR) was 58.4% in the olaparib arm vs 48.1% in the control arm (odds ratio, 1.60; 95% CI, 1.02-2.53; *P*=.0409).

More patients discontinued treatment with olaparib vs placebo (13.8% vs 7.8%, respectively). The rate of discontinuation of abiraterone acetate was similar between the arms (8.5% and 8.8%). Grade 3 or higher AEs occurred in 47.2% and 38.4% of patients, respectively. No cases of myelodysplastic syndrome or acute myeloid leukemia were reported. The rates of new primary malignancies and pneumonitis were similar between the arms.

The most common grade 3 or higher AEs were anemia (15.1% in the olaparib arm vs 3.3% in the control arm) and hypertension (3.5% vs 3.3%). Rates of cardiac failure were similar between the arms, at 1.5% and 1.3%, respectively. There was an increased rate of venous thromboembolic events in the olaparib arm compared with the control arm. Pulmonary embolism was the most frequent venous thrombotic event, reported in 6.5% vs 1.8% of patients, respectively. These findings were mostly incidental and did not require discontinuation of treatment. Quality-of-life outcomes were similar between the arms.

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Overall Survival in Patients With Metastatic Hormone-Sensitive Prostate Cancer Treated With Enzalutamide Plus Androgen Deprivation Therapy by High or Low Disease Volume and Progression to mHSPC (M0 at Diagnosis) or De Novo mHSPC (M1 at Diagnosis): Post Hoc Analysis of the Phase 3 ARCHES Trial

In men with mHSPC, the combination of enzalutamide and ADT demonstrated a significant efficacy benefit over placebo plus ADT in the multinational, double-blind phase 3 ARCHES trial.[1] These data led to the 2019 approval of enzalutamide for this indication. The ARCHES trial enrolled 1150 men with mHSPC. Stratification factors included high- or low-volume disease at diagnosis and prior docetaxel use. The patients were randomly assigned to receive enzalutamide at 160 mg/day plus ADT or placebo plus ADT.

In the primary analysis, after a median follow-up of 14.4 months, enzalutamide plus ADT was associated with a 61% reduction in the risk of radiographic progression or death compared with placebo plus ADT (HR, 0.39; 95% CI, 0.30-0.50; *P*<.001). After a median follow-up of 44.6 months, enzalutamide plus ADT was associated with a significant 34% improvement in overall survival vs placebo plus ADT (HR, 0.66; *P*<.0001).[4] The 4-year rates of overall survival were 70.6% vs 57.0%, respectively.

Post hoc analyses were conducted to assess the role of enzalutamide and ADT in different subgroups. In prior

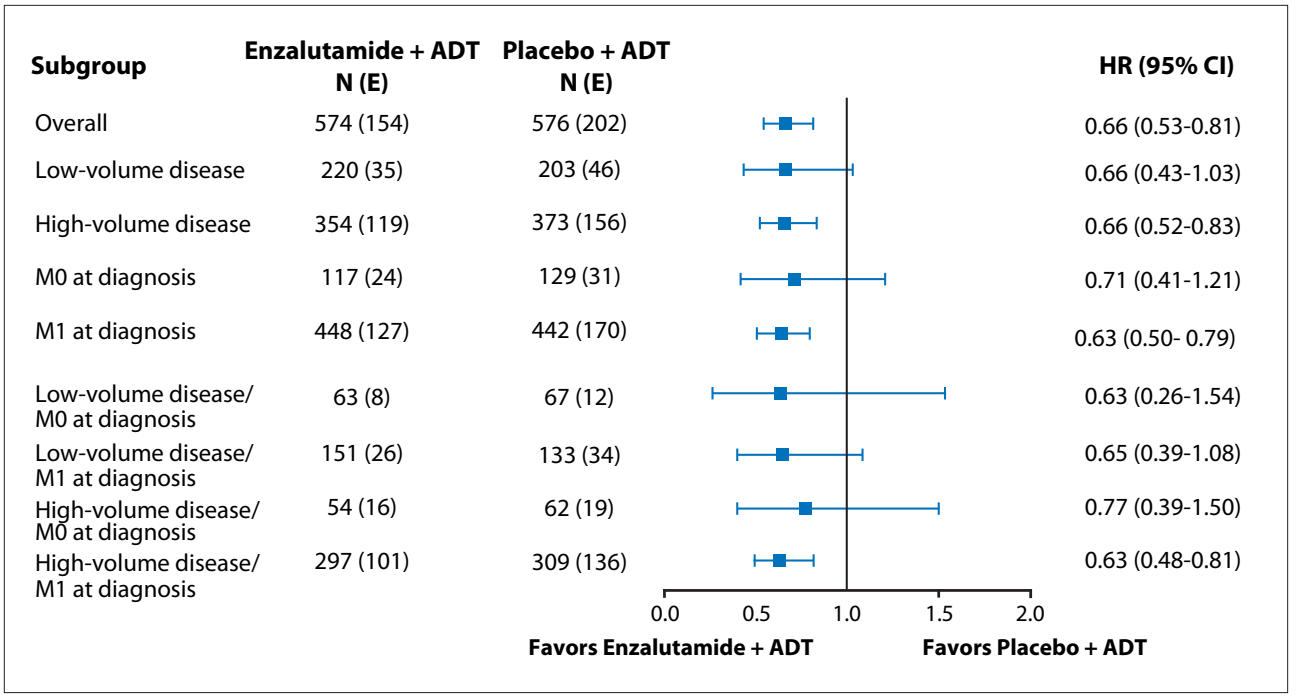

Figure 7. Overall survival according to subgroups in a post hoc analysis of the phase 3 ARCHES trial, which evaluated the addition of enzalutamide to ADT. ADT, androgen deprivation therapy; E, events; HR, hazard ratio; M0, no distant metastases; M1, distant metastases. Adapted from Armstrong AJ et al. ASCO GU abstract 115. *J Clin Oncol.* 2022;40(suppl 6).[6]

post hoc analyses, the rPFS benefit with enzalutamide was maintained whether patients had high-volume or low-volume disease, and whether they were initially diagnosed with localized disease (M0) or had de novo mHSPC at diagnosis (M1).[2,3] High-volume disease was defined as the presence of metastases involving the viscera, or, in the absence of visceral lesions, 4 or more bone lesions, at least 1 of which was a bony structure located beyond the vertebral column and pelvic bone.[5] In the current analysis, investigators assessed whether the overall survival benefit observed with additional follow-up in the overall population would also be observed in patients with high- or low-volume disease and with M0 or M1 disease at diagnosis.[6]

Most patients had high-volume disease at diagnosis: 61.7% of patients in the enzalutamide arm and 64.8% in the control arm. M1 disease at diagnosis was reported in 78% and 76.7%, respectively. Patients with low-volume disease were more likely to have M0 disease at initial diagnosis. The study permitted patients from the control arm to cross over to the enzalutamide arm. The rates of crossover were 43.8% for patients with low-volume disease and 24.4% for those with high-volume disease.

This post hoc analysis was performed after a median follow-up of 44.6 months. The overall survival benefit seen with enzalutamide plus ADT persisted across all patient subgroups and was similar to that reported for the overall population (Figure 7). The HRs ranged from 0.63 to 0.77. In an analysis that adjusted for the impact of crossover, the overall survival benefit with enzalutamide plus ADT was similar across subgroups. The CIs for patients with low-volume disease, and for those with low-volume/M1 disease, no longer exceeded 1.

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An AI-Derived Digital Pathology-Based Biomarker to Predict the Benefit of Androgen Deprivation Therapy in Localized Prostate Cancer With Validation in NRG/RTOG 9408

Currently, there are no validated predictive biomarkers to guide the use or duration of ADT among patients with intermediate- or high-risk localized prostate cancer. Dr Daniel Spratt and colleagues developed and validated the first predictive biomarker for the use of ADT in men with prostate cancer.[1] The investigators hypothesized that artificial intelligence (AI) with deep learning could be used to identify features that are not interpretable by humans.

The multimodal AI biomarker was based on digital histopathology imagery. Dr Spratt noted that tumor grade, primary Gleason scores, and secondary combined scores contributed very little to the model. The training set included approximately 3900 patients enrolled in clinical trials that evaluated radiotherapy with or without hormone therapy (given in various durations). The median follow-up was 13.6 years (interquartile range [IQR], 10.2-17.7). To validate the biomarker, the investigators applied the model to approximately 1700 patients enrolled in the phase 3 NRG/RTOG 9408 study. The median follow-up was 17.6 years (IQR, 15.0-19.7).

Application of the biomarker predicted that 63% of patients would not benefit from the addition of ADT. The multimodal predictive model successfully identified differential benefit with the addition of ADT to radiotherapy (Figure 9). The rate of distant metastasis was significantly lower among patients with the biomarker (HR, 0.33; *P*<.001). At 15 years, patients in the biomarker-positive group experienced a 10% absolute reduction in metastatic disease with the addition of short-term hormone therapy. In biomarker-negative patients, there was no improvement in metastatic disease with the addition of hormone therapy.

Presence of the biomarker also correlated with a consistent differential benefit across other endpoints. Among patients in the biomarker-positive group, the addition of ADT at 15 years was beneficial in terms of prostate cancer–specific mortality (HR, 0.28; 95% CI, 0.15-0.53); *P*<.001), metastasis-free survival (HR, 0.82; 95% CI, 0.68-0.99; *P*=.04), and overall survival (HR, 0.85, 95% CI, 0.70-1.02; *P*=.08). Among patients in the biomarker-negative group, these endpoints were not significantly improved with the addition of ADT.

The investigators concluded that approximately two-thirds of men with intermediate-risk disease could safely avoid ADT, regardless of their prognosis. In these men, the addition of ADT lacked relative and absolute benefit.

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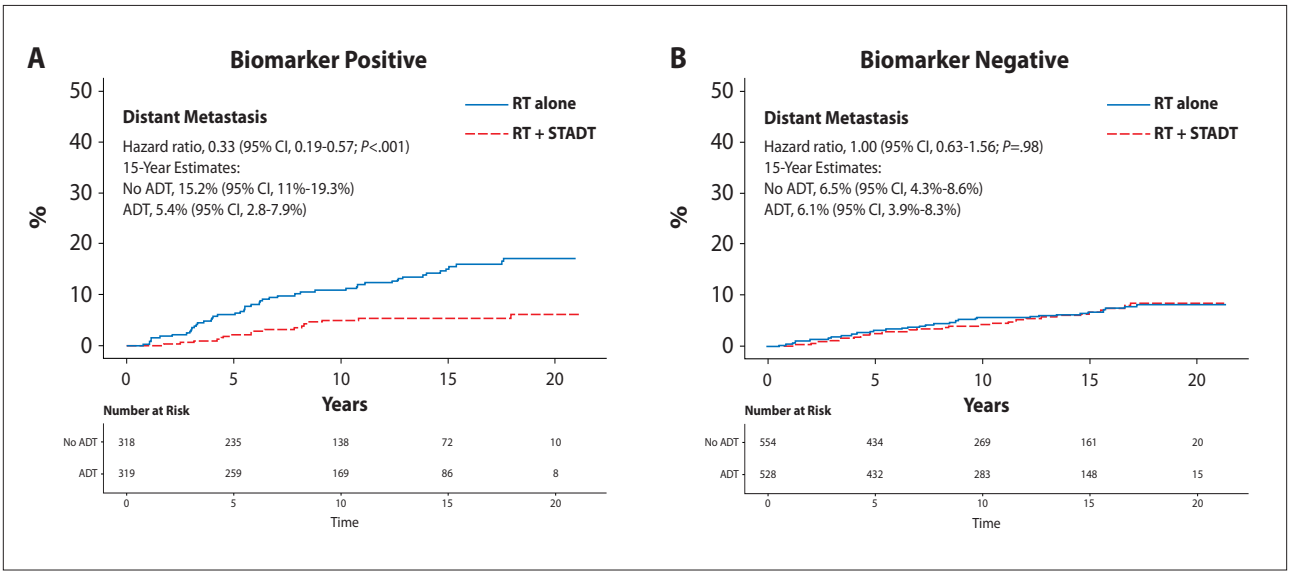

Figure 8. The multimodal AI predictive model identified differential benefit with the addition of androgen deprivation therapy to radiotherapy among patients with the biomarker (A) but not in those without the biomarker (B). AI, artificial intelligence; RT, radiotherapy; STADT, short-term androgen deprivation therapy. Adapted from Spratt DE et al. ASCO GU abstract 223. *J Clin Oncol.* 2022;40(suppl 6).[1]

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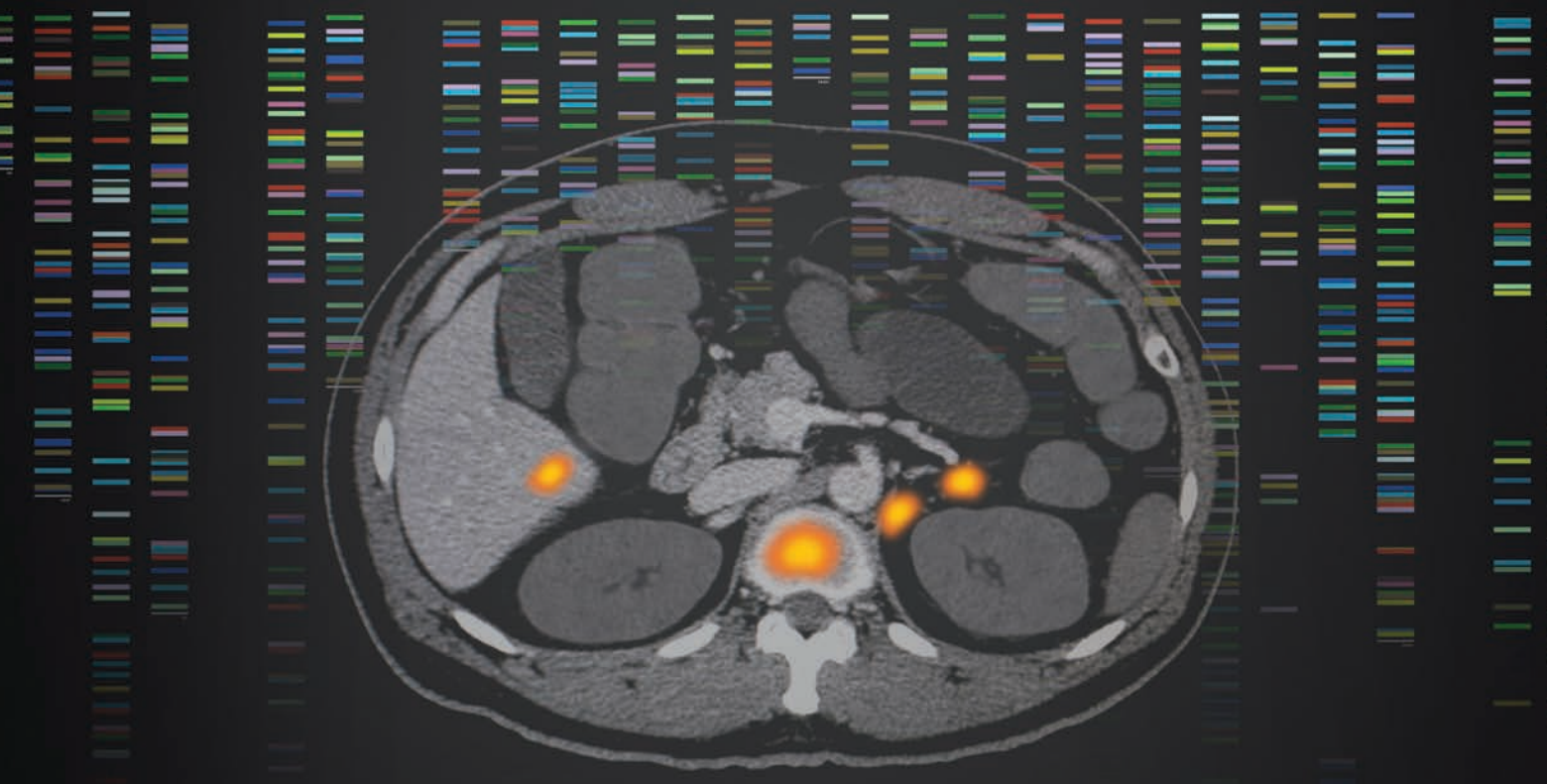

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Phase 1/2 Study of ARV-110, an Androgen Receptor PROTAC Degrader, in Metastatic Castration-Resistant Prostate Cancer

Bavdegalutamide (ARV-110) is a novel oral proteolysis targeting chimera (PROTAC) protein degrader that targets the AR, including wild-type and genetically altered forms. A phase 1/2 study is evaluating ARV-110 in patients with mCRPC. In a prior report of the phase 1 dose-escalation study, ARV-110 demonstrated activity in men with mCRPC who had previously received at least 2 prior therapies, including abiraterone acetate and/or enzalutamide.[1] The trial identified an exposure-activity relationship and revealed enhanced activity among the 5 patients with AR T878X/H875Y-positive tumors, with 40% of these patients showing a best decline of serum PSA by 50% or more (PSA_{50}).

Based on the phase 1 findings, the phase 2 expansion ARDENT trial evaluated ARV-110 in patients with mCRPC and disease progression. Patients had received 1 or 2 prior novel hormonal agents and no more than 1 chemotherapy regimen each for castration-sensitive prostate cancer and CRPC. The patients underwent assessment for biomarkers. They were enrolled into subgroups according to their biomarkers, including T878X/H875Y, wild-type AR or other AR alterations, and AR L702H mutations or AR-V7. A clinically defined, biomarker-agnostic subgroup of patients who had received less previous treatment (up to 1 prior line for CRPC) was also enrolled. Patients received ARV-110 at a starting dose of 420 mg once daily, the recommended phase 2 dose.

A total of 195 patients enrolled in the phase 1 and 2 trials. The median age of these patients was 70 years and 74 years, respectively. Visceral disease was found in 31% and 38%. The median number of prior lines of therapy was 6 (range, 2-14) and 4 (range, 1-11).

The most common treatment-related AEs were nausea (48%), fatigue (36%), vomiting (26%), decreased appetite (25%), and diarrhea (20%). These events were generally grade 1/2. No grade 4 or higher events occurred at the recommended phase 2 dose. Treatment-related AEs led to dose reductions in 8% of patients and discontinuation of therapy in 9%.

To assess antitumor activity, the investigators focused on patients with AR T878X/H875Y mutations. The phase 1 study showed enhanced activity in this subset (n=28). The PSA_{50} response rate was 46%, and the PSA_{30} response rate was 57% (Figure 9). Twelve patients (43%) were treated

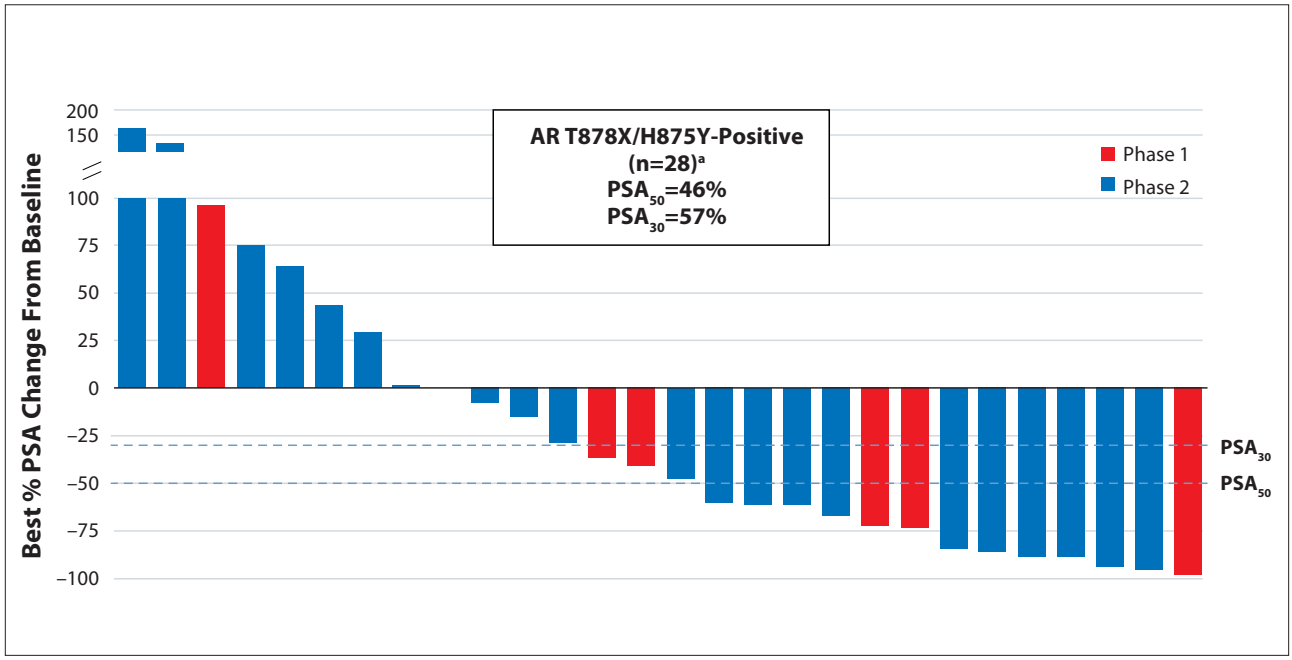

Figure 9. Changes in levels of PSA from baseline in a phase 1/2 trial of ARV-110 in patients with metastatic castration-resistant prostate cancer. Data are shown for patients with an AR T878X/H875Y mutation. [a]Includes biomarker-evaluable patients treated at or above the recommended phase 2 dose (phase 1 and 2) or with exposure above the minimum efficacious threshold in nonclinical xenograft models (phase 1) and with ≥4 weeks of PSA follow-up. AR, androgen receptor; PSA, prostate specific antigen; PSA_{30}, best PSA declines ≥30%; PSA_{50}, best PSA declines ≥50%. Adapted from Gao X et al. ASCO GU abstract 15. *J Clin Oncol.* 2022;40(suppl 17).[1]

with ARV-110 for at least 24 weeks. Among the 7 patients evaluable for response according to the Response Evaluation Criteria in Solid Tumors guidelines, 2 patients had confirmed partial responses and 3 patients were continuing treatment.

Among the broader population of patients, PSA declines of at least 50% were observed across biomarker subgroups, including in patients without AR T878X/H875Y mutations. The investigators noted that the non-AR molecular profiles were similar among the patients with fewer prior treatments and in those in the biomarker subgroups who had received more prior treatments.

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A Randomized, Double-Blind, Placebo-Controlled, Phase 3b Study of the Efficacy and Safety of Continuing Enzalutamide in Chemotherapy-Naive, Metastatic Castration-Resistant Prostate Cancer Patients Treated With Docetaxel Plus Prednisolone Who Have Progressed on Enzalutamide: PRESIDE

Enzalutamide is associated with a significant survival benefit in patients with mCRPC.[1,2] For patients with mCRPC, there may be a benefit to targeting the AR with ADT after disease progression.[3]

Axel Merseburger, MD, PhD, presented results from the randomized, double-blind, placebo-controlled phase 3b PRESIDE study, which evaluated continued therapy with enzalutamide in chemotherapy-naive patients with mCRPC who developed disease progression during treatment with enzalutamide. The study investigators hypothesized that continued treatment with enzalutamide would maintain control of responsive tumor lesions and allow docetaxel to target clonal subpopulations that had adopted pro-survival and proliferation pathways. The trial began with an open-label period in which patients with chemotherapy-naive mCRPC received enzalutamide at 160 mg/day. Patients underwent PSA/imaging evaluation at week 13. Patients with disease progression proceeded to the double-blind period of the trial. These patients were randomly assigned to

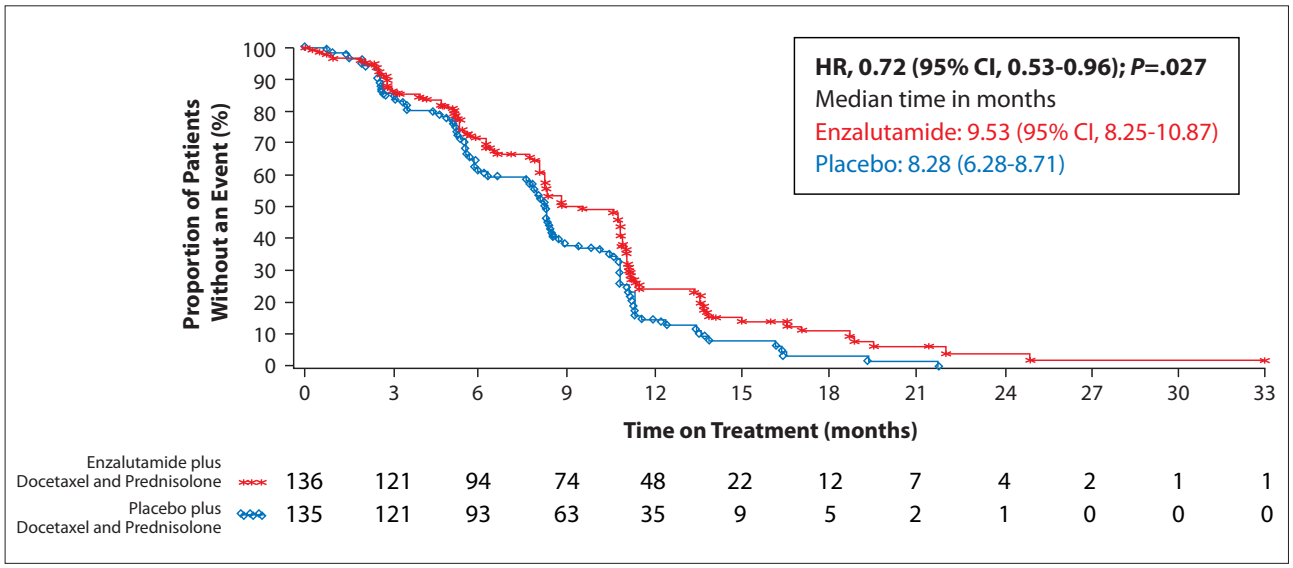

Figure 10. Progression-free survival in the phase 3b PRESIDE trial, which evaluated continued therapy with enzalutamide in chemotherapy-naive patients with metastatic castration-resistant prostate cancer who developed disease progression during treatment with enzalutamide. HR, hazard ratio. Adapted from Merseburger AS et al. ASCO GU abstract 15. *J Clin Oncol.* 2022;40(suppl 6).[4]

continue treatment with enzalutamide at 160 mg/day or to receive placebo, each administered with docetaxel at 75 mg/m^2 every 3 weeks plus prednisolone at 10 mg/day.

The baseline characteristics were similar between the arms. The patients' median age was 71.5 years in the enzalutamide arm and 69.0 years in the control arm. The median serum PSA was 36.9 1 µg/L and 28.1 µg/L, respectively.

The study met its primary endpoint, demonstrating a significant improvement in PFS with enzalutamide plus docetaxel and prednisolone compared with placebo plus docetaxel and prednisolone. The median PFS was 9.53 months vs 8.28 months, respectively (HR, 0.72; *P*=.027; Figure 10). Subgroup analysis showed a consistent benefit across groups in a post hoc analysis. Secondary endpoints were also superior in the enzalutamide arm vs the control arm. The median time to PSA progression was 8.44 months vs 6.24 months, respectively (HR, 0.58; *P*=.002). The mean change in PSA from baseline to week 13 was –37.12% vs 9.11%.The ORR was 31.6% vs 25.9%, but this difference did not reach statistical significance (*P*=.142).

The safety outcomes were as expected. The overall incidence of TEAEs and docetaxel-related TEAEs were comparable between the enzalutamide and placebo arms. However, the rate of serious TEAEs was 49.3% with enzalutamide vs 38.5% with placebo. The most common TEAEs were asthenia (34.6% in the enzalutamide arm vs 25.9% in the control arm), neutropenia (33.8% vs 33.3%), alopecia (32.4% vs 27.4%), fatigue (29.4% vs 20.7%), diarrhea (27.2% vs 32.6%), and anemia (20.6% vs 11.9%). There were 13 deaths (9.6%) in the enzalutamide arm and 7 deaths (5.2%) in the placebo arm.

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Highlights in Advanced Prostate Cancer From the 2022 American Society of Clinical Oncology Genitourinary Cancers Symposium: Commentary

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At the 2022 American Society of Clinical Oncology Genitourinary Cancers Symposium, presentations in advanced prostate cancer provided important new data for the management of these patients. Data were presented for treatments such as androgen receptor (AR) inhibitors in patients with metastatic hormone-sensitive prostate cancer (mHSPC), combinations of poly(ADP-ribose) polymerase (PARP) inhibitors with abiraterone acetate in metastatic castration-resistant prostate cancer (CRPC), ^{177}Lu-PSMA-617 in metastatic CRPC, and novel therapies. Investigators also provided data for an artificial intelligence (AI) pathology predictive biomarker.

AR Inhibitors

The phase 3 ARASENS trial, presented by Dr Matthew Smith, was the highest-impact study presented at the meeting and should quickly improve patient care in the clinic.[1] The trial evaluated whether the addition of darolutamide to androgen-deprivation therapy (ADT) and docetaxel improved overall survival in patients with mHSPC. Most of the patients had de novo disease, meaning they had metastases at diagnosis, rather than disease that relapsed after local therapy (such as a radical prostatectomy or radiation). Men with newly

diagnosed metastatic prostate cancer are likely to have high-volume disease, although the patients in this study were not categorized as such. The patients were stratified based on the pattern of disease spread to the bones or internal organs. In current practice, docetaxel plus ADT is often administered to treat high-volume disease where there is a clear survival benefit, and not commonly in patients with low-volume disease, where the benefits are more limited.

The study met its primary endpoint, reporting significant improvement in overall survival with the triple therapy over ADT/docetaxel in this setting. The median overall survival was not estimable with darolutamide vs 48.9 months with placebo. The hazard ratio (HR) for overall survival was 0.68, which was highly statistically and clinically significant. Treatment with darolutamide significantly improved many of the secondary endpoints that are meaningful to patients, such as delayed castration resistance and pain progression. Improvements were seen regardless of whether the patient had de novo disease or relapsed disease, but only 13% of patients made up this latter group.

Darolutamide is now approved by the US Food and Drug Administration (FDA) to treat nonmetastatic CRPC. Data from the ARASENS trial will likely expand the approval of darolutamide to include patients with mHSPC. The treatment options for these patients include many life-prolonging AR pathway inhibitors, such as enzalutamide, apalutamide, and abiraterone acetate. The ARASENS trial provided the first published data for triple therapy in higher-risk, de novo patients with high disease volume who are considered fit for chemotherapy. This study joins the PEACE-1 trial of abiraterone acetate plus docetaxel triple therapy as 2 positive, dedicated trials in the de novo high-volume setting to demonstrate survival benefits.[1,2]

These data raise the question of whether darolutamide can be administered without chemotherapy. Many patients would prefer to avoid chemotherapy. The ongoing phase 3 ARANOTE trial is evaluating darolutamide plus ADT.[3] In the ARASENS trial, all patients received docetaxel for 6 cycles. Darolutamide was administered concurrently with docetaxel and was well tolerated. Darolutamide is a safe, effective agent that extends survival without many of the side effects typically associated with AR inhibitors, such as cardiovascular disease, fracture, frailty, falls, osteoporosis, cognitive problems, and rash. Darolutamide was associated with higher rates of fatigue and hot flashes. Many oncologists and urologists in the community and academic settings will likely offer darolutamide to these patients, given this treatment's strong efficacy and minimal impact on quality of life.

Dr Axel Merseburger presented results of the randomized PRESIDE study.[4] In this study, patients with metastatic CRPC first received treatment with enzalutamide during an open-label period. Patients who developed early resistance, as indicated by a response followed by rising levels of prostate-specific antigen (PSA), were then randomly assigned to receive docetaxel and prednisolone, with or without enzalutamide. The standard of care is to discontinue enzalutamide upon initiation of docetaxel chemotherapy.

This relatively small study randomly assigned 273 men to treatment and treated 271. The primary endpoint was met, and the study was technically positive. The median progression-free survival (PFS) was 9.53 months in the enzalutamide arm vs 8.28 months in the placebo arm (HR, 0.72; P=.027). However, this small improvement is unlikely to change the clinical practice of using enzalutamide and docetaxel sequentially rather than concurrently. The overall survival data were immature and not reported. Patients should not receive docetaxel solely for PSA progression. Generally, docetaxel should be reserved for patients with radiographic or symptomatic progression, per guidelines from the Prostate Cancer Working

ABSTRACT SUMMARY Phase 1 Results of the ODM-208 First-in-Human Phase 1-2 Trial in Patients With Metastatic Castration-Resistant Prostate Cancer (CYPIDES)

The phase 1/2 CYPIDES trial evaluated ODM-208 in patients with mCRPC (Abstract 18). ODM-208 is a novel complete corticosteroid biosynthesis inhibitor that targets production of androgen and other corticosteroid hormones. The phase 1 study enrolled 44 patients with mCRPC after treatment with at least 1 novel hormonal therapy and 1 taxane. Treatment consisted of oral ODM-208 given twice daily, plus corticosteroid replacement. All patients also continued ADT. The patients were heavily treated; 55% had received abiraterone acetate and enzalutamide. ODM-208 induced undetectable androgen levels. The PSA_{50} response rate was 32% overall, 68% among patients with AR ligand-binding domain (LBD) mutations, and 8% in patients without LBD mutations. Responses exceeding 6 months were observed, particularly in patients with LBD mutations. Regarding safety, 31.8% of patients were hospitalized for symptoms of adrenal insufficiency, which was reversible with transient discontinuation and use of intravenous hydrocortisone and fluids. An ongoing expansion cohort is currently evaluating ODM-208 at 5 mg given twice daily, with modifications to the dosing of dexamethasone and fludrocortisone.

Group 3.[5] There may not be any value to continuing an AR inhibitor, such as enzalutamide, in this setting. In clinical practice, enzalutamide is not stopped for PSA progression, but rather continued until clinical benefit ceases. When a patient develops progression, as evidenced by pain, symptoms, or findings on imaging, we stop enzalutamide and proceed to the next available therapy, such as docetaxel. This study would not encourage me to continue enzalutamide during chemotherapy.

I presented a secondary analysis of the global, randomized phase 3 ARCHES trial, which evaluated ADT with or without enzalutamide in men with mHSPC.[6] Results from the trial were reported in 2019.[7] The trial met its primary endpoint of PFS, which led to the FDA approval of enzalutamide in men with early hormone-sensitive disease. A more recent analysis showed that the improvement in overall survival reached an HR of 0.66.[8] Enzalutamide delayed progression and significantly improved overall survival. This agent is now a standard-of-care therapy in this setting.

The current analysis evaluated overall survival data according to patient characteristics, such as disease volume and whether the patient had de novo disease or had relapsed after local therapy. The analysis showed that overall survival improved irrespective of those categories, with hazard ratios ranging from 0.63 to 0.77. There was no significant heterogeneity according to the subcategories, suggesting that enzalutamide improved survival regardless of whether a patient had low-volume disease vs high-volume disease or relapsed disease vs de novo disease.

The design of the ARCHES trial included a crossover component, in which patients in the placebo group could receive enzalutamide. The recent study also included a sensitivity analysis that adjusted for crossover. The absolute differences in survival were even more striking. For example, the probability of being alive at 4 years was significantly improved with enzalutamide. The improvement was almost 15% in patients with high-volume disease. We are now starting to talk about 5- and 10-year survival for these patients because they are doing so well, which is great news for patients regardless of whether they have de novo or relapsed mHSPC, or low- or high-volume mHSPC. There are clear benefits to the early use of enzalutamide in all of these subsets.

PARP Inhibitors

Dr Fred Saad presented results of the phase 3 PROpel trial, which evaluated the addition of olaparib to abiraterone acetate as first-line therapy for patients with metastatic CRPC.[9] I was a coinvestigator. The study was prompted by several key findings in preclinical studies and a smaller randomized phase 2 study.[10-13] The AR regulates several forms of DNA repair and is the basis for the synergy between radiation and hormone therapy in early disease, where outcomes are improved. Blocking the AR impairs DNA homologous repair, which improves the radiosensitization of tumors. Administering a PARP inhibitor in the setting of a potent AR inhibitor, such as abiraterone acetate, has the same biologic basis as this radiosensitization effect. In this case, however, the PARP inhibitor is causing DNA damage and blocking DNA repair, and this can synergize with potent AR inhibition. A second relevant parallel concept is that AR inhibitors and PARP inhibitors co-regulate the expression of AR-regulated genes.[14] Blocking both may provide a more potent form of hormonal therapy. The PARP inhibitor will work in a new way.

The PROpel study was also fueled by a prior randomized phase 2 trial of abiraterone acetate with or without olaparib in the postdocetaxel metastatic CRPC setting.[15] This phase 2 trial showed that the addition of olaparib to abiraterone acetate improved progression-free survival, irrespective of whether patients had homologous recombination deficiency (HRD) in their tumors or germline DNA. Improvements were seen in patients with or without the *BRCA2* mutation, for example.

The PROpel study enrolled all-comers for the first-line treatment of metastatic CRPC. The patients were randomly assigned to receive abiraterone acetate and prednisone with ongoing ADT or the same regimen plus olaparib administered at standard dosing. The trial met its primary endpoint. The median radiographic PFS per investigator assessment was 24.8 months in the olaparib arm vs 16.6 months in the placebo arm (HR, 0.66; $P<.0001$). According to independent central review, the median radiographic PFS was 27.8 months vs 16.4 months, respectively (HR, 0.61; $P<.0001$). Outcomes were even more significantly improved among the patients who were HRD-positive (HR, 0.50). Treatment with olaparib also improved the secondary endpoints of time to second progression or death (PFS2) and response rate. The toxicity rates were somewhat higher in the olaparib arm. As expected, there were more cases of PARP-related adverse events, such as gastrointestinal toxicity, anemia requiring transfusions, pulmonary emboli, and blood clots. An encouraging finding was that treatment with olaparib did not increase cardiovascular risk or myelodysplasia. Olaparib was not associated with any notable treatment-related mortality or worsening quality of life.

Whether the PROpel study will change clinical practice depends on the FDA's review of the data and the overall perception of the risks and benefits of this treatment in these different patient populations, both overall and in the HRD-positive subsets. The study appeared to show that olaparib substantially delayed disease progression, particularly among men

with HRD. Even in men without HRD, olaparib led to a significant 5- to 6-month improvement in PFS, which might translate into improved survival. The overall survival data remain immature, but a favorable trend was seen in the olaparib arm. It will be important to continue to follow patients for mature survival data, which should be available in the next year, to determine these net benefits.

In contrast to the PROpel study, the phase 3 MAGNITUDE study did not show improvement with the addition of a different PARP inhibitor, niraparib, to abiraterone acetate and prednisone as first-line therapy in unselected patients with metastatic CRPC.[16] The trial enrolled an all-comer patient population that was stratified according to the presence of HRD. The patients received first-line therapy with abiraterone acetate with or without niraparib. This component of the trial was closed early owing to futility. The addition of niraparib did not show any benefits. The HR for survival was close to 1. Benefits were found, however, in patients with HRD, particularly those with *BRCA2* mutations. In these HRD–positive patients, niraparib improved PFS by approximately 3 to 5 months (HR, 0.73). An even greater improvement of approximately 5 to 7 months was reported in men with *BRCA1/2* mutations (HR, 0.53).

The designs of these trials were similar, but there were some small differences in the patient populations. For example, the MAGNITUDE trial permitted enrollment of men who had received prior AR inhibitors, and approximately 5% of the population had received this treatment. In the MAGNITUDE trial, approximately a quarter of the patients had already received abiraterone acetate for up to 4 months before enrollment, but this was not part of the PROPEL eligibility criteria or patient population. Prior use of abiraterone acetate could have selected for a more aggressive patient population in MAGNITUDE, for example, if these patients were having suboptimal responses at study entry. There were some slight imbalances in the patient characteristics, such as the pattern of spread and visceral metastases.

The outcomes of these trials differed greatly. In the PROpel study, the addition of olaparib benefited all patients, including those who were HRD-positive.[9] In the MAGNITUDE study, the addition of niraparib was beneficial only in patients with *BRCA1/2* mutations and did not seem to extend to non-*BRCA1/2* HRD-positive patients.[16]

In both studies, the PARP inhibitors led to adverse events, such as anemia and gastrointestinal toxicity. The net risks and benefits tend to favor olaparib, at least with these early data. In both trials, the data for overall survival were immature, and follow-up analyses are awaited.

It is not known why the outcomes of these trials differed. It may be that there are differences in the properties of these drugs—or in the trial designs and enrolled patient populations—that led to differing outcomes. Olaparib might be a more effective PARP inhibitor, or toxicities might have prevented the optimal dosing of niraparib. Anemia and thrombocytopenia were much more common with niraparib than olaparib, and these toxicities could have led to differences in dose intensity and PARP inhibition. Ultimately, physicians will face a decision on the use of a PARP inhibitor plus abiraterone acetate combination. The decision will be based on several characteristics, such as HRD status, projected outcomes with AR inhibitor therapy alone,[17] and the risks/comorbidities of individual patients.

^{177}Lu-PSMA-617

Dr Kim Chi presented an exposure-adjusted safety analysis of the phase 3 VISION trial.[18] I was a coauthor of this presentation. The VISION trial previously reported very positive results, including dramatic responses and improved survival, for ^{177}Lu-PSMA-617 in men with metastatic CRPC who had received prior treatment with docetaxel and an AR inhibitor.[19] The patients had tested positive for prostate-specific membrane antigen (PSMA) per positron emission tomography/computed tomography (PET/CT) scans. Based on the results of the VISION trial, the FDA is expected to approve ^{177}Lu-PSMA-617 in this setting. The secondary analysis by Dr Chi evaluated the safety per cycle, adjusted for the length of exposure to treatment. In the VISION trial, treatment exposure was more than 3 times longer in patients receiving ^{177}Lu-PSMA-617 vs supportive care. Adjusting for the exposure time may help define comparable levels of toxicity between the treatments.

Some of the adverse events related to ^{177}Lu-PSMA-617, such as dry mouth, dry eyes, gastrointestinal toxicities, bone marrow suppression, reduced platelet counts, and anemia, occurred at a notably higher rate vs the control group, even after adjustment for exposure time. Side effects such as dyspnea, elevated liver enzymes, kidney injury, and pain syndromes, when adjusted for the time variable, were equal across the treatment groups. These issues are probably more closely related to disease progression than toxicity. The results of this analysis can help providers and patients understand the risks and benefits of this new treatment.

Dr James Buteau presented an analysis of the phase 2 TheraP study that evaluated outcome according to PET scans measuring PSMA and ^{18}F-fluorodeoxyglucose (FDG).[20] The TheraP trial randomly assigned men with metastatic CRPC to treatment with ^{177}Lu-PSMA-617 or cabazitaxel.[21] Unlike the VISION trial, the TheraP trial had an active comparator against cabazitaxel chemotherapy, whereas in the VISION trial, the comparator

was a second or third AR pathway inhibitor. The study was conducted in Australia, and the PSMA criteria used for enrollment differed from that typically followed in the United States. The patients were assessed according to their maximum standardized uptake value (SUV), where intense uptake of 20 or higher on a gallium-68 PET/CT scan was associated with greater benefit from PSMA targeted therapy but not cabazitaxel. Patients with FDG-positive disease were excluded from enrollment. The patients underwent 2 PET scans, one with FDG and one with PSMA. Patients with a negative PSMA and positive FDG, who are known to derive less benefit from PSMA-directed therapy, were excluded from the study. For example, patients with neuroendocrine small-cell prostate cancer typically lack PSMA, and they have high FDG uptake.[22] These patients would not be expected to benefit from ^{177}Lu-PSMA-617, and so they were excluded from the study.

This analysis evaluated whether PSMA and FDG PET characteristics could be used to predict a greater benefit with ^{177}Lu-PSMA-617. The investigators found that the higher the PSMA uptake, the greater the benefit. This outcome makes sense because ^{177}Lu-PSMA-617 targets PSMA. Patients with a brighter PSMA PET scan have a greater chance of responding to PSMA-directed radioligand therapy. The study showed that those patients with a PSMA SUV_{mean} of 10 or higher had a 91% probability of a PSA response. Among patients with an SUV_{mean} of less than 10, the probability of response was 50%. The same levels were not predictive for cabazitaxel. In the ^{177}Lu-PSMA-617 arm, PFS was also higher among those patients with an SUV_{mean} of 10 or more.

The patients' FDG uptake was not predictive of outcome because the study excluded patients who had this discordance, and thus it could not truly assess PSMA-directed therapies for these patients. However, FDG uptake was adversely prognostic for both treatments. In both treatment arms, patients with intense uptake of FDG did poorly. These patients probably need a combination treatment, such as cabazitaxel plus carboplatin, or they might benefit from enrollment in a clinical trial. High FDG uptake was an adverse prognostic feature. For patients with high FDG uptake, more aggressive therapy might be an option.

Novel Agents

Dr Xin Gao and colleagues presented updated results from a phase 1/2 trial of ARV-110, which is an androgen-receptor degrader.[23] There is strong interest in finding new strategies to manage prostate cancer that has become resistant to standard AR inhibitors, such as abiraterone acetate and enzalutamide. An innovative approach would be to develop a novel compound that can degrade the full-length androgen receptor. The phase 1 component of this trial began with dose escalation. The phase 2 study is now evaluating dose expansion. The presentation by Dr Gao and colleagues identified some of the limitations of degrading full-length AR using the ligand-binding domain.[23] This approach does not appear to benefit most patients with metastatic CRPC that is resistant to standard AR therapies, in which the ligand-binding domain is frequently mutated, deleted, or spliced out. The response rates were low in the overall population. The response rates according to PSA criteria were less than 15% in patients with AR-V7, those who were heavily pretreated, and those with wild-type AR. The study identified a small subset of 5% to 10% of patients with specific AR point mutations in the ligand-binding domain (LBD), such as T878 or H875Y mutations. The response rate was much higher among these patients, reaching 46% using PSA criteria. The data are still immature, so the durability is unknown. PFS data were not available for this small subset. There were some responses according to the Response Evaluation Criteria in Solid Tumors, some of which lasted beyond 6 months. Future studies will examine ARV-110 in this patient subgroup.

This study showed that it is necessary to focus on other mechanisms of resistance besides the full-length AR. The AR splice variants are important, as are genomic alterations in AR that disrupt AR LBD degradation. With lineage plasticity, the tumor ignores the AR. AR gain and other mutations can confer resistance to AR degradation. This study has provided important insights that can be used to develop other novel combination therapies that may benefit patients.

Dr Karim Fizazi presented phase 1 results from the CYPIDES study, which is evaluating the efficacy and safety of ODM-208.[24] This adrenolytic agent targets the enzyme CYP11A1. ODM-208 blocks one of the highest-up molecules and enzymes in the androgen-synthesis pathway from cholesterol all the way to androgen. ODM-208 works at a higher mechanism than abiraterone acetate. This drug is associated with some risks. Blocking CYP11A1 blocks all androgens, as well as glucocorticoids and mineralocorticoids. Patients in this study preemptively received glucocorticoids and mineralocorticoid replacement because the investigators knew that ODM-208 would block all adrenal function. The goal was to enroll patients who had received unsuccessful treatment with abiraterone acetate or enzalutamide, who represent an unmet need. The investigators reduced testosterone as intended, so the pharmacodynamic effect of the agent was observed. The investigators also found reductions in glucocorticoids and mineralocorticoids. Many patients developed symptoms of adrenal insufficiency.

Approximately 32% of patients had a good PSA response, a higher rate than that reported with the AR degrader ARV-110.[23] Among patients with a mutation in the ligand-binding domain, 68% had a good PSA response. In many of these patients, particularly those with AR-activating, ligand binding–domain mutations, responses lasted beyond 6 months.

A limitation to this treatment was adrenal insufficiency, which resulted in hypotension, electrolyte disturbances, fatigue, and abdominal pain. The side effect profile was not acceptable. This study is ongoing, and the investigators are trying to optimize the dose and safety. They are exploring combinations with adrenal-supporting agents. They are treating adrenal insufficiency more proactively, and they reduced the dose of ODM-208. Overall, the efficacy of ODM-208 in this trial was intriguing, suggesting that there may be some patients who could benefit from this approach.

An AI Biomarker

Dr Daniel Spratt presented the results of a study that evaluated a biomarker derived from artificial intelligence and based on digital pathology.[25] I was also involved in this study, which drew data from many US cooperative group trials. This study was impactful for several reasons. The study used a machine-learning artificial intelligence algorithm to read pathology slides. The algorithm distills important, clinically useful information that would not be discernible to a pathologist. A computer program reads the slide and detects patterns associated with an outcome of interest, such as metastasis-free survival. The biomarker was validated based on large data sets drawn from prospective, randomized clinical trials conducted throughout the US cooperative group system. The biomarker was evaluated in the context of intermediate-risk prostate cancer.

The goal of the study was to determine whether all of these patients require hormonal therapy or if a biomarker could identify patients who might achieve good outcomes without this treatment. Many men with intermediate-risk prostate cancer can probably do well without hormonal therapy. They have high cure rates with intensity-modulated radiation therapy at modern dose and fraction schedules. There are certain patients at intermediate to unfavorable risk who probably do need hormonal therapy. Some patients at favorable, intermediate risk might not need hormonal therapy. There are some molecularly defined subsets of patients with favorable intermediate-risk disease who have poor outcomes, as well as some patients with unfavorable intermediate-risk disease who do well on a genetic level without hormonal therapy.

The AI biomarker successfully used pathologic features to predict whether a patient needed hormonal therapy in this early-stage radiation setting based on significant predictive associations with metastasis-free survival and prostate cancer–specific mortality. This study suggested that testing for this biomarker could allow approximately 60% of patients to safely avoid ADT during treatment with radiation therapy and still maintain excellent long-term outcomes.

Patients who tested negative for the biomarker did not benefit from the addition of ADT, whereas patients who tested positive for the biomarker had an HR of 0.33 for the ability of ADT to prevent metastasis. All of the other endpoints were strikingly positive, including prostate cancer–specific mortality, distant metastases, and metastasis-free survival.

This study has identified the first validated predictive biomarker of intermediate-risk prostate cancer.[25] The biomarker can be used to spare men 6 months of ADT, with the associated side effects. Once the data are published and commercialized, many patients will be interested in this AI approach. The success of this study speaks to the way AI can be applied to help develop and validate a pathologic biomarker that can be clinically useful. Many AI algorithms are being applied to radiology, pathology, and other areas to identify characteristics that are too complex for the human eye to appreciate.

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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NOTES

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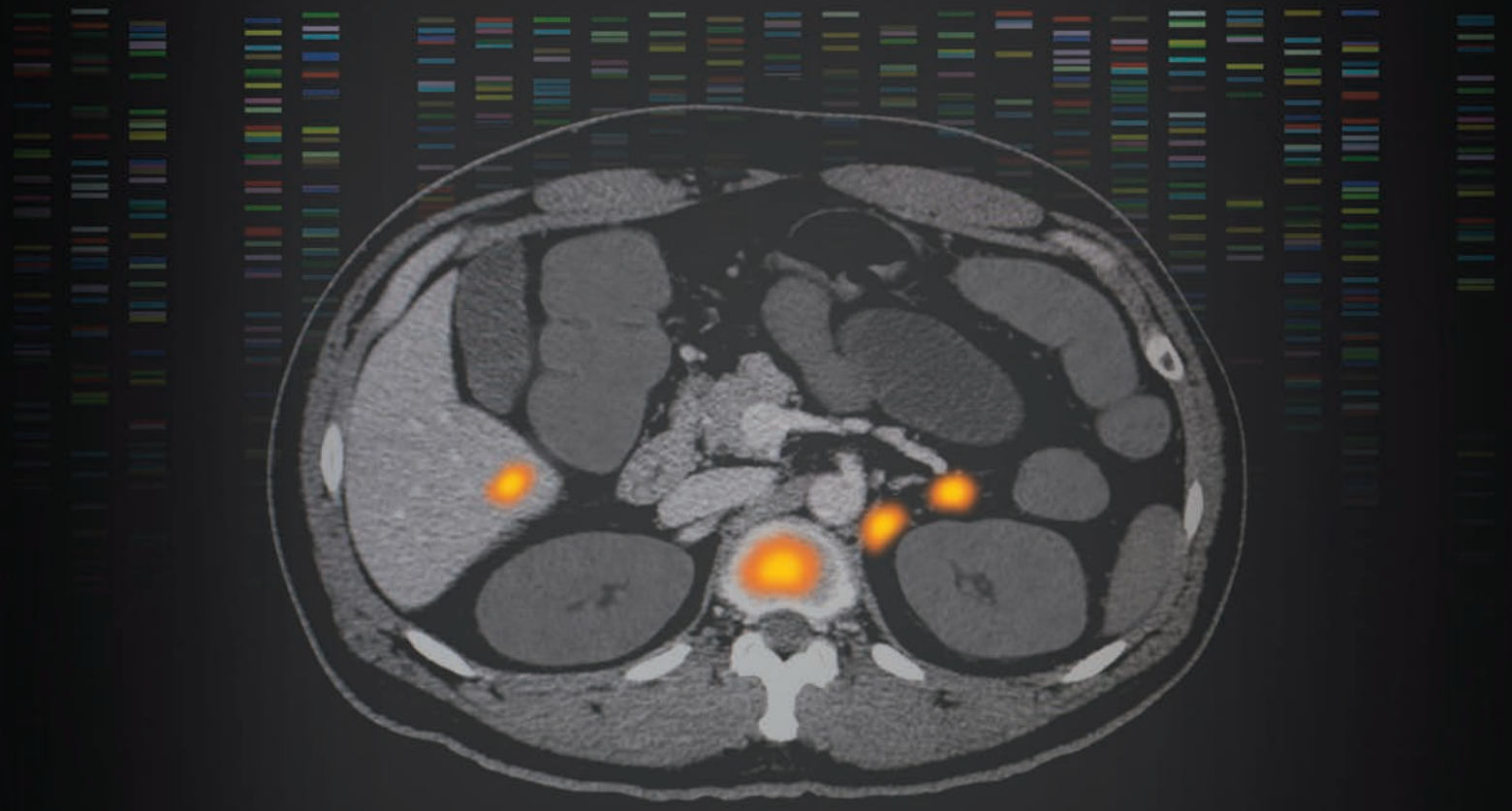
WHY IS PSMA A KEY PHENOTYPIC BIOMARKER IN ADVANCED PROSTATE CANCER?



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