Clinical Advances in
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A SPECIAL MEETING REVIEW EDITION

Highlights in Metastatic Prostate Cancer From the European Society for Medical Oncology Congress 2024

A Review of Selected Presentations From the ESMO Congress 2024
September 13-17, 2024 • Barcelona, Spain

Special Reporting on:

- Efficacy and Safety of Darolutamide Plus Androgen-Deprivation Therapy in Patients With Metastatic Hormone-Sensitive Prostate Cancer From the Phase III ARANOTE Trial
- A Randomized, Multicenter, Open-Label, Phase III Trial Comparing Enzalutamide Versus a Combination of Radium-223 and Enzalutamide in Asymptomatic or Mildly Symptomatic Patients With Bone Metastatic Castration-Resistant Prostate Cancer: First Results of EORTC-GUCG 1333/PEACE-3
- Cabozantinib Plus Atezolizumab Versus 2nd Novel Hormonal Therapy in Patients with Metastatic Castration-Resistant Prostate Cancer: Final Overall Survival Results of the Phase III, Randomized, CONTACT-02 Study
- Adding Metformin to Androgen-Deprivation Therapy for Patients With Metastatic Hormone-Sensitive Prostate Cancer: Overall Survival Results From the Multi-Arm, Multi-Stage, Randomized Platform Trial STAMPEDE
- Decipher mRNA Score for Prediction of Survival Benefit From Docetaxel at Start of Androgen-Deprivation Therapy for Advanced Prostate Cancer: An Ancillary Study of the STAMPEDE Docetaxel Trials
- Phenotypic and Genomic Characterization of De Novo Metastatic Prostate Cancer: An Ancillary Study of the PEACE-1 Phase III Trial
- Open-Label, Multicenter, Randomized Trial of Radium-223–Docetaxel Versus Docetaxel–Radium-223 Sequence in Metastatic Castration-Resistant Prostate Cancer With Prospective Biomarker Evaluation (RAPSON Study)
- Nivolumab 3 mg/kg and Ipilimumab 1 mg/kg in Molecularly Selected Patients With Metastatic Castration-Resistant Prostate Cancer

PLUS Meeting Abstract Summaries

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NUBEQA®
(darolutamide) 300 mg tablets

FOR YOUR PATIENTS WITH **mHSPC** OR **nmCRPC**

HELP HIM LIVE FOR WHAT HE LOVES

NUBEQA REDUCED THE RISK OF DEATH BY >30% ACROSS mHSPC and nmCRPC[1-3]

In **mHSPC**, NUBEQA is the only ARI approved in combination with docetaxel in mHSPC. NUBEQA in combination with docetaxel and ADT significantly extended OS beyond docetaxel + ADT; HR: 0.68; 95% CI: 0.57-0.80; *P*<0.0001.[1,2]

ARASENS Study Design: 1305 mHSPC patients on ADT* with docetaxel who received ADT within 12 weeks before study entry were randomized 1:1 and treated with concurrent 600 mg NUBEQA twice daily (n=651) or placebo (n=654) in a multicenter, double-blind, phase III trial. Treatment with NUBEQA or placebo continued until symptomatic progressive disease, change of antineoplastic therapy, or unacceptable toxicity. Concomitant docetaxel was administered at 75 mg/m^2 every 21 days for 6 cycles within 6 weeks of starting NUBEQA or placebo. OS was statistically significant for the NUBEQA arm vs placebo arm; HR: 0.68; 95% CI: 0.57-0.80; *P*<0.0001.[1,2]

In **nmCRPC**, NUBEQA + ADT reduced the risk of death by nearly a third vs ADT alone (OS was a secondary endpoint); HR: 0.69; 95% CI: 0.53-0.88; *P*=0.003. MFS was the primary endpoint.[1,3]

ARAMIS Study Design: 1509 nmCRPC patients on ADT* with a PSA doubling time of ≤10 months were randomized 2:1 to receive concurrent 600 mg NUBEQA twice daily (n=955) or placebo (n=554) in a multicenter, double-blind, phase III trial. Treatment continued until radiographic disease progression as assessed by CT, MRI, ^{99m}Tc bone scan by BICR, unacceptable toxicity, or withdrawal. MFS was statistically significant with a median of 40.4 months vs 18.4 months for placebo; HR: 0.41; 95% CI:0.34-0.50; *P*<0.0001. The final analysis of OS was statistically significant vs placebo; HR: 0.69; 95% CI: 0.53-0.88; *P*=0.003. MFS was the primary endpoint and OS was a key secondary endpoint.[1,3,4]

HAVE A PATIENT IN MIND?
Scan the QR code to request a sample.

CHOOSE NUBEQA 1ST FOR SURVIVAL

INDICATIONS

NUBEQA® (darolutamide) is an androgen receptor inhibitor indicated for the treatment of adult patients with:

- Non-metastatic castration-resistant prostate cancer (nmCRPC)
- Metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel

IMPORTANT SAFETY INFORMATION

Warnings & Precautions

Ischemic Heart Disease – In a study of patients with nmCRPC (ARAMIS), ischemic heart disease occurred in 3.2% of patients receiving NUBEQA versus 2.5% receiving placebo, including Grade 3-4 events in 1.7% vs. 0.4%, respectively. Ischemic events led to death in 0.3% of patients receiving NUBEQA vs. 0.2% receiving placebo. In a study of patients with mHSPC (ARASENS), ischemic heart disease occurred in 3.2% of patients receiving NUBEQA with docetaxel vs. 2% receiving placebo with docetaxel, including Grade 3-4 events in 1.3% vs. 1.1%, respectively. Ischemic events led to death in 0.3% of patients receiving NUBEQA with docetaxel vs. 0% receiving placebo with docetaxel. Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue NUBEQA for Grade 3-4 ischemic heart disease.

Seizure – In ARAMIS, Grade 1-2 seizure occurred in 0.2% of patients receiving NUBEQA vs. 0.2% receiving placebo. Seizure occurred 261 and 456 days after initiation of NUBEQA. In ARASENS, seizure occurred in 0.6% of patients receiving NUBEQA with docetaxel, including one Grade 3 event, vs. 0.2% receiving placebo with docetaxel. Seizure occurred 38 to 340 days after initiation of NUBEQA. It is unknown whether anti-epileptic medications will prevent seizures with NUBEQA. Advise patients of the risk of developing a seizure while receiving NUBEQA and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others. Consider discontinuation of NUBEQA in patients who develop a seizure during treatment.

Embryo-Fetal Toxicity – Safety and efficacy of NUBEQA have not been established in females. NUBEQA can cause fetal harm and loss of pregnancy. Advise males with female partners of reproductive potential to use effective contraception during treatment with NUBEQA and for 1 week after the last dose.

Adverse Reactions

In ARAMIS, serious adverse reactions occurred in 25% of patients receiving NUBEQA vs. 20% of patients receiving placebo. Serious adverse reactions in ≥1% of patients who received NUBEQA included urinary retention, pneumonia, and hematuria. Fatal adverse reactions occurred in 3.9% of patients receiving NUBEQA vs. 3.2% of patients receiving placebo. Fatal adverse reactions in patients who received NUBEQA included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%). The most common adverse reactions (>2% with a ≥2% increase over placebo), including laboratory test abnormalities, were increased AST, decreased neutrophil count, fatigue, increased bilirubin, pain in extremity, and rash. Clinically relevant adverse reactions occurring in ≥2% of patients treated with NUBEQA included ischemic heart disease and heart failure.

In ARASENS, serious adverse reactions occurred in 45% of patients receiving NUBEQA with docetaxel vs. 42% of patients receiving placebo with docetaxel. Serious adverse reactions in ≥2% of patients who received NUBEQA with docetaxel included febrile neutropenia (6%), decreased neutrophil count (2.8%), musculoskeletal pain (2.6%), and pneumonia (2.6%). Fatal adverse reactions occurred in 4% of patients receiving NUBEQA with docetaxel vs. 4% of patients receiving placebo with docetaxel. Fatal adverse reactions in patients who received NUBEQA included COVID-19/COVID-19 pneumonia (0.8%), myocardial infarction (0.3%), and sudden death (0.3%). The most common adverse reactions (≥10% with a ≥2% increase over placebo with docetaxel) were constipation, rash, decreased appetite, hemorrhage, increased weight, and hypertension. The most common laboratory test abnormalities (≥30%) were anemia, hyperglycemia, decreased lymphocyte count, decreased neutrophil count, increased AST, increased ALT, and hypocalcemia. Clinically relevant adverse reactions in <10% of patients who received NUBEQA with docetaxel included fractures, ischemic heart disease, seizures, and drug-induced liver injury.

Drug Interactions

Effect of Other Drugs on NUBEQA – Combined P-gp and strong or moderate CYP3A4 inducers decrease NUBEQA exposure, which may decrease NUBEQA activity. Avoid concomitant use.

Combined P-gp and strong CYP3A4 inhibitors increase NUBEQA exposure, which may increase the risk of NUBEQA adverse reactions. Monitor more frequently and modify NUBEQA dose as needed.

Effects of NUBEQA on Other Drugs – NUBEQA inhibits breast cancer resistance protein (BCRP) transporter. Concomitant use increases exposure (AUC) and maximal concentration of BCRP substrates, which may increase the risk of BCRP substrate-related toxicities. Avoid concomitant use where possible. If used together, monitor more frequently for adverse reactions, and consider dose reduction of the BCRP substrate.

NUBEQA inhibits OATP1B1 and OATP1B3 transporters. Concomitant use may increase plasma concentrations of OATP1B1 or OATP1B3 substrates. Monitor more frequently for adverse reactions and consider dose reduction of these substrates.

Review the Prescribing Information of drugs that are BCRP, OATP1B1, and OATP1B3 substrates when used concomitantly with NUBEQA.

*Concomitant GnRH analog or prior bilateral orchiectmy.

References: 1. NUBEQA (darolutamide) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc.; October 2023. **2.** Smith MR, Hussain M, Saad F, et al; ARASENS Trial Investigators. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. *N Engl J Med.* 2022;386(12):1132-1142. **3.** Fizazi K, Shore N, Tammela T2, et al. Nonmetastatic, castration-resistant prostate cancer and survival with darolutamide. *N Engl J Med.* 2020;383(11):1040-1049. **4.** Fizazi K, Shore N, Tammela TL, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med.* 2019;380(13):1235-1246.

Please see the following page(s) for the brief summary of Prescribing Information.

PP-NUB-US-2879-1 11/23

BAYER

NUBEQA® (darolutamide) tablets, for oral use
Initial U.S. Approval: 2019

BRIEF SUMMARY OF PRESCRIBING INFORMATION
CONSULT PACKAGE INSERT FOR
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NUBEQA is indicated for the treatment of adult patients with:

- non-metastatic castration resistant prostate cancer (nmCRPC)
- metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Ischemic Heart Disease

Ischemic heart disease, including fatal cases, occurred in patients receiving NUBEQA.

In a randomized study of patients with nmCRPC (ARAMIS), ischemic heart disease occurred in 3.2% of patients receiving NUBEQA and 2.5% receiving placebo, including Grade 3-4 events in 1.7% and 0.4%, respectively. Ischemic events led to death in 0.3% of patients receiving NUBEQA and 0.2% receiving placebo.

In a randomized study of patients with mHSPC (ARASENS), ischemic heart disease occurred in 3.2% of patients receiving NUBEQA with docetaxel and 2% receiving placebo with docetaxel, including Grade 3-4 events in 1.3% and 1.1%, respectively. Ischemic events led to death in 0.3% of patients receiving NUBEQA with docetaxel and 0% receiving placebo with docetaxel.

Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue NUBEQA for Grade 3-4 ischemic heart disease.

5.2 Seizure

Seizure occurred in patients receiving NUBEQA.

In ARAMIS, Grade 1-2 seizure occurred in 0.2% of patients receiving NUBEQA and 0.2% receiving placebo. Seizure occurred 261 and 456 days after initiation of NUBEQA.

In ARASENS, seizure occurred in 0.6% of patients receiving NUBEQA with docetaxel, including one Grade 3 event, and 0.2% receiving placebo with docetaxel. Seizure occurred 38 to 340 days after initiation of NUBEQA.

It is unknown whether anti-epileptic medications will prevent seizures with NUBEQA. Advise patients of the risk of developing a seizure while receiving NUBEQA and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others. Consider discontinuation of NUBEQA in patients who develop a seizure during treatment.

5.3 Embryo-Fetal Toxicity

The safety and efficacy of NUBEQA have not been established in females. Based on its mechanism of action, NUBEQA can cause fetal harm and loss of pregnancy when administered to a pregnant female *[see Clinical Pharmacology]*.

Advise males with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA *[see Use in Specific Populations]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Non-Metastatic Castration Resistant Prostate Cancer

The safety of NUBEQA was evaluated in ARAMIS, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, that enrolled patients who had non-metastatic castration-resistant prostate cancer (nmCRPC) *[see Clinical Studies]*. Patients received either NUBEQA at a dose of 600 mg, or a placebo, twice a day. All patients in the ARAMIS study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. Among patients who received NUBEQA, the median duration of exposure was 14.8 months (range: 0 to 44.3 months).

Serious adverse reactions occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions in ≥1% of patients who received NUBEQA included urinary retention, pneumonia and hematuria. Fatal adverse reactions occurred in 3.9% of patients receiving NUBEQA and 3.2% of patients receiving placebo. Fatal adverse reactions in patients who received NUBEQA included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%).

Permanent discontinuation of NUBEQA due to adverse reactions occurred in 9% of patients receiving NUBEQA. The most common adverse reactions requiring permanent discontinuation in patients who received NUBEQA included cardiac failure (0.4%), and death (0.4%).

Dosage interruptions due to adverse reactions occurred in 13% of patients treated with NUBEQA. The most common adverse reactions requiring dosage interruption in patients who received NUBEQA included hypertension (0.6%), diarrhea (0.5%), and pneumonia (0.5%).

Dosage reductions due to adverse reactions occurred in 6% of patients treated with NUBEQA. The most common adverse reactions requiring dosage reduction in patients treated with NUBEQA included fatigue (0.7%), hypertension (0.3%), and nausea (0.3%).

The most common (>2% with a ≥2% increase compared to placebo) adverse reactions, including laboratory test abnormalities, were AST increased, neutrophil count decreased, fatigue, bilirubin increased, pain in extremity, and rash.

Table 1 summarizes the adverse reactions in ARAMIS.

Table 1: Adverse Reactions (>2% with a ≥2% increase compared to placebo) in Patients with Non-Metastatic Castration Resistant Prostate Cancer in ARAMIS

Adverse Reaction	NUBEQA (n=954)		Placebo (n=554)	
	All Grades %	Grades 3 or 4 %	All Grades %	Grade 3 or 4 %
Fatigue[1]	16	0.6	11	1.1
Pain in extremity	6	0	3	0.2
Rash[2]	4	0.1	1.4	0

[1] Includes fatigue and asthenia
[2] Includes rash, eczema, rash maculo-papular, dermatitis, erythema multiforme, rash macular, rash papular, rash pustular, skin exfoliation

Clinically relevant adverse reactions occurring in 2% or more of patients treated with NUBEQA included ischemic heart disease (4%) and heart failure (2.1%).

Table 2 summarizes the laboratory test abnormalities in ARAMIS.

Table 2: Laboratory Test Abnormalities in ARAMIS

Laboratory Abnormality	NUBEQA (N=954)[1]		Placebo (N=554)[1]	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
AST increased	23	0.5	14	0.2
Neutrophil count decreased	20	4	9	0.6
Bilirubin increased	16	0.1	7	0

[1] The denominator used to calculate the rate varied based on the number of patients with a baseline value and at least one post-treatment value.

Metastatic Hormone-Sensitive Prostate Cancer

The safety of NUBEQA, in combination with docetaxel, was evaluated in ARASENS, a randomized (1:1), double-blind, placebo-controlled, multi-center clinical study, that enrolled patients who had mHSPC *[see Clinical Studies]*. Patients were to receive either NUBEQA at a dose of 600 mg, or a placebo, twice a day in combination with docetaxel at a dose of 75 mg/m2 every 21 days for 6 cycles. All patients in the ARASENS study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. Patients with a medical history of seizure were allowed to enter the study. Among patients who received NUBEQA, the median duration of exposure was 41 months (range: 0.1 to 56.5 months) vs. 16.7 months (range 0.3 to 55.8) with placebo. Eighty-eight percent and 86% of patients received the 6 planned cycles of docetaxel, in the NUBEQA with docetaxel arm and placebo with docetaxel arm, respectively.

Serious adverse reactions occurred in 45% of patients receiving NUBEQA with docetaxel and in 42% of patients receiving placebo with docetaxel, respectively. Serious adverse reactions in ≥ 2% of patients who received NUBEQA with docetaxel included febrile neutropenia (6%), neutrophil count decreased (2.8%), musculoskeletal pain (2.6%) and pneumonia (2.6%). Fatal adverse reactions occurred in 4% of patients receiving NUBEQA with docetaxel and 4% of patients receiving placebo with docetaxel. Fatal adverse reactions in patients who received NUBEQA included COVID-19/COVID-19 pneumonia (0.8%), myocardial infarction (0.3%), and sudden death (0.3%).

Permanent discontinuation of NUBEQA due to adverse reactions occurred in 14% of patients treated in the NUBEQA with docetaxel arm. The most common adverse reactions which resulted in permanent discontinuation of NUBEQA were rash (1.1%), musculoskeletal pain (0.9%), and aspartate aminotransferase (AST) increased (0.9%).

Dosage interruptions of NUBEQA due to adverse reactions occurred in 23% of patients treated in the NUBEQA with docetaxel arm. The most common (>2%) adverse reactions requiring dosage interruption of NUBEQA were alanine aminotransferase (ALT) increased (3.2%), AST increased (3.1%) and febrile neutropenia (2.1%).

Dosage reductions of NUBEQA due to adverse reactions occurred in 9% of patients treated in the NUBEQA with docetaxel arm. The most common (>2%) adverse reactions requiring dosage reduction of NUBEQA were ALT increased (2.8%) and AST increased (2.5%).

The most common (>10% with a ≥2% increase over placebo with docetaxel) adverse reactions are constipation, rash, decreased appetite, hemorrhage, weight increased, and hypertension. The most common laboratory test abnormalities (≥30%) are anemia, hyperglycemia, lymphocyte count decreased, neutrophil count decreased, AST increased, ALT increased, and hypocalcemia.

Table 3 summarizes the adverse reactions in ARASENS.

Table 3: Adverse Reactions (≥10% with a ≥2% increase compared to placebo with docetaxel) in ARASENS

Adverse Reaction	NUBEQA with docetaxel (n=652)		Placebo with docetaxel (n=650)	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Constipation	23	0.3	20	0.3
Rash[1]	20	1.8	15	0.2
Decreased Appetite	19	0.2	13	0.6
Hemorrhage[2]	18	1.4	13	1.4
Weight Increased	18	2.1	16	1.2
Hypertension[3]	14	7	10	3.6

[1] Rash includes rash, rash maculo-papular, palmar-plantar erythrodysesthesia syndrome, eczema, dermatitis, skin exfoliation, dermatitis acneiform, drug eruption, rash pruritic, rash erythematous, erythema multiforme, rash macular, dermatitis exfoliative generalized, penile rash, dyshidrotic eczema, rash papular, dermatitis bullous, rash follicular, rash pustular, rash vesicular, toxic skin eruption

[2] Hemorrhage includes hematuria, epistaxis, anal hemorrhage, hemorrhoidal hemorrhage, rectal hemorrhage, upper gastrointestinal hemorrhage, hemoptysis, hemorrhage urinary tract, hemorrhagic stroke, subarachnoid hemorrhage, lower gastrointestinal hemorrhage, cystitis hemorrhagic, gastrointestinal hemorrhage, hemorrhage subcutaneous, intra-abdominal hemorrhage, nail bed bleeding, subdural hemorrhage

[3] Hypertension includes hypertension, blood pressure increased, hypertensive emergency and hypertensive crisis.

Clinically relevant adverse reactions in < 10% of patients who received NUBEQA with docetaxel included fractures (8%), ischemic heart disease (3.2%), seizures (0.6%), and drug-induced liver injury (0.3%).

Table 4 summarizes laboratory test abnormalities in the ARASENS study.

Table 4: Laboratory Test Abnormalities (≥30%) in ARASENS

Laboratory Abnormality	NUBEQA with docetaxel[1] (N=652)		Placebo with docetaxel[1] (N=650)	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Anemia	72	6	71	7
Hyperglycemia	57	7	53	10
Lymphocyte count decreased	52	12	49	13
Neutrophil count decreased	49	33	44	31
AST increased[2]	40	3.6	35	2.3
ALT increased[2]	37	3.7	31	2.9
Hypocalcemia	31	2.8	28	1.9

[1]The denominator used to calculate the rate varied from 470 to 648 based on the number of patients with a baseline value and at least one post-treatment value.

[2]ALT or AST increases to ≥5 x upper limit of normal (ULN) occurred in 5.3% of patients who received NUBEQA with docetaxel. ALT or AST increases to ≥20 x ULN occurred in 0.3% of patients who received NUBEQA with docetaxel. The median time to onset of any grade ALT or AST increases was 2.8 months (range: 0.03 to 46.9).

Clinically relevant laboratory test abnormalities in < 30% of patients who received NUBEQA with docetaxel included blood bilirubin increased (all grades 20%, Grade 3-4 0.5%) compared to placebo with docetaxel (all grades 10%, grades 3-4 0.3%).

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on NUBEQA

Combined P-gp and Strong or Moderate CYP3A4 Inducer

Concomitant use of NUBEQA with a combined P-gp and strong or moderate CYP3A4 inducer decreases darolutamide exposure which may decrease NUBEQA activity *[see Clinical Pharmacology]*. Avoid concomitant use of NUBEQA with combined P-gp and strong or moderate CYP3A4 inducers.

Combined P-gp and Strong CYP3A4 Inhibitors

Concomitant use of NUBEQA with a combined P-gp and strong CYP3A4 inhibitor increases darolutamide exposure *[see Clinical Pharmacology]* which may increase the risk of NUBEQA adverse reactions. Monitor patients more frequently for NUBEQA adverse reactions and modify NUBEQA dosage as needed *[see Dosage and Administration]*.

7.2 Effects of NUBEQA on Other Drugs

Breast Cancer Resistance Protein (BCRP) and Organic Anion Transporting Polypeptides (OATP) 1B1 and 1B3 Substrates

NUBEQA is an inhibitor of BCRP transporter. Concomitant use of NUBEQA increases the AUC and C_{max} of BCRP substrates *[see Clinical Pharmacology]*, which may increase the risk of BCRP substrate-related toxicities.

Avoid concomitant use with drugs that are BCRP substrates where possible. If used together, monitor patients more frequently for adverse reactions, and consider dose reduction of the BCRP substrate drug.

NUBEQA is an inhibitor of OATP1B1 and OATP1B3 transporters. Concomitant use of NUBEQA may increase the plasma concentrations of OATP1B1 or OATP1B3 substrates. Monitor patients more frequently for adverse reactions of these drugs and consider dose reduction while patients are taking NUBEQA *[see Clinical Pharmacology]*.

Review the prescribing information of the BCRP, OATP1B1 and OATP1B3 substrates when used concomitantly with NUBEQA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The safety and efficacy of NUBEQA have not been established in females. Based on its mechanism of action, NUBEQA can cause fetal harm and loss of pregnancy *[see Clinical Pharmacology]*. Animal embryo-fetal developmental toxicology studies were not conducted with darolutamide. There are no human data on the use of NUBEQA in pregnant females.

8.2 Lactation

Risk Summary

The safety and efficacy of NUBEQA have not been established in females. There are no data on the presence of darolutamide or its metabolites in human milk, the effect on the breastfed child, or the effect on milk production.

8.3 Females and Males of Reproductive Potential

Contraception

Males

Based on the mechanism of action, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA *[see Use in Specific Populations]*.

Infertility

Males

Based on animal studies, NUBEQA may impair fertility in males of reproductive potential *[see Nonclinical Toxicology]*.

8.4 Pediatric Use

Safety and effectiveness of NUBEQA in pediatric patients have not been established.

8.5 Geriatric Use

Of the 954 patients who received NUBEQA in ARAMIS, 88% of patients were 65 years and over, and 49% were 75 years and over. Of the 652 patients who received NUBEQA in ARASENS, 63% of patients were 65 years and over, and 16% were 75 years and over. No overall differences in safety or efficacy were observed between these patients and younger patients in both studies.

8.6 Renal Impairment

Patients with severe renal impairment (eGFR 15–29 mL/min/1.73 m^2) who are not receiving hemodialysis have a higher exposure to NUBEQA and reduction of the dose is recommended *[see Dosage and Administration and Clinical Pharmacology]*. No dose reduction is needed for patients with mild or moderate renal impairment (eGFR 30-89 mL/min/1.73 m^2). The effect of end stage renal disease (eGFR ≤15 mL/min/1.73 m^2) on darolutamide pharmacokinetics is unknown.

8.7 Hepatic Impairment

Patients with moderate hepatic impairment (Child-Pugh Class B) have a higher exposure to NUBEQA and reduction of the dose is recommended *[see Dosage and Administration and Clinical Pharmacology]*. No dose reduction is needed for patients with mild hepatic impairment. The effect of severe hepatic impairment (Child-Pugh C) on darolutamide pharmacokinetics is unknown.

10 OVERDOSAGE

There is no known specific antidote for darolutamide overdose. The highest dose of NUBEQA studied clinically was 900 mg twice daily, equivalent to a total daily dose of 1800 mg. No dose limiting toxicities were observed with this dose.

Considering the saturable absorption and the absence of evidence for acute toxicity, an intake of a higher than recommended dose of darolutamide is not expected to lead to systemic toxicity in patients with intact hepatic and renal function *[see Clinical Pharmacology]*.

In the event of intake of a higher than recommended dose in patients with severe renal impairment or moderate hepatic impairment, if there is suspicion of toxicity, interrupt NUBEQA treatment and undertake general supportive measures until clinical toxicity has been diminished or resolved. If there is no suspicion of toxicity, NUBEQA treatment can be continued with the next dose as scheduled.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information)

Ischemic Heart Disease

Inform patients that NUBEQA has been associated with an increased risk of ischemic heart disease. Advise patients to seek immediate medical attention if any symptoms suggestive of an ischemic heart disease event occur *[see Warnings and Precautions]*.

Seizure

Inform patients that NUBEQA has been associated with an increased risk of seizure. Discuss conditions that may predispose to seizures and medications that may lower the seizure threshold. Advise patients of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Inform patients to contact their healthcare provider right away if they have loss of consciousness or seizure *[see Warnings and Precautions]*.

Embryo-Fetal Toxicity

Inform patients that NUBEQA can be harmful to a developing fetus and can cause loss of pregnancy *[see Use in Specific Populations]*.

Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA *[see Warnings and Precautions and Use in Specific Populations]*.

Dosage and Administration

Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with NUBEQA.

Instruct patients to take their dose of two tablets (twice daily). NUBEQA should be taken with food. Each tablet should be swallowed whole.

Inform patients that in the event of a missed daily dose of NUBEQA, to take any missed dose, as soon as they remember prior to the next scheduled dose, and not to take two doses together to make up for a missed dose *[see Dosage and Administration]*.

Infertility

Advise male patients that NUBEQA may impair fertility *[see Use in Specific Populations]*.

Manufactured by: Orion Corporation, Orion Pharma, FI-02101 Espoo, Finland

Manufactured for: Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ 07981 USA

For more information, call Bayer HealthCare Pharmaceuticals Inc. at Bayer at 1-888-842-2937 or go to www.NUBEQA-us.com

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Efficacy and Safety of Darolutamide Plus Androgen-Deprivation Therapy in Patients With Metastatic Hormone-Sensitive Prostate Cancer From the Phase III ARANOTE Trial

In recent years, several phase III trials have been undertaken to assess the optimal combination of androgen-deprivation therapy (ADT), docetaxel, and an androgen receptor pathway inhibitor (ARPI) in patients with metastatic hormone-sensitive prostate cancer (mHSPC). The ARASENS trial demonstrated a significant overall survival (OS) benefit with darolutamide, ADT, and docetaxel vs placebo, ADT, and docetaxel (hazard ratio [HR], 0.68; 95% CI, 0.57-0.80; *P*<.0001).[1]

At ESMO 2024, Fred Saad, MD, presented results from the ARANOTE trial comparing darolutamide plus ADT vs placebo plus ADT, without docetaxel, in patients with mHSPC (Figures 1 and 2).[2] The global, randomized, double-blind, phase III ARANOTE trial enrolled 669 patients with mHSPC who were assigned 2:1 to darolutamide 600 mg twice daily plus ADT (n=446) or placebo plus ADT (n=223). Patients were stratified based on the presence of visceral metastases and use of prior local therapy. The primary endpoint was radiological progression-free survival (rPFS) by central blinded review.

The median age of enrolled patients was 70 years; the trial enrolled patients in Asia (30%), Latin America (29%), and Europe and the rest of the world (41%). Metastases were present in 72% of patients, 71% had high-volume disease, and 12% had visceral metastases.

After a median follow-up of 25 months, darolutamide plus ADT was associated with a significant improvement in rPFS over placebo plus ADT (median rPFS, not reached vs 25.0 months; HR, 0.54; 95% CI, 0.41-0.71; *P*<.0001); 24-month rPFS rates were 70.3% and 52.1%, respectively. The rPFS benefit observed with darolutamide was consistent across key subgroups. Darolutamide plus ADT also showed a benefit over placebo plus ADT in secondary endpoints including time to metastatic castration-resistant prostate cancer (mCRPC; stratified

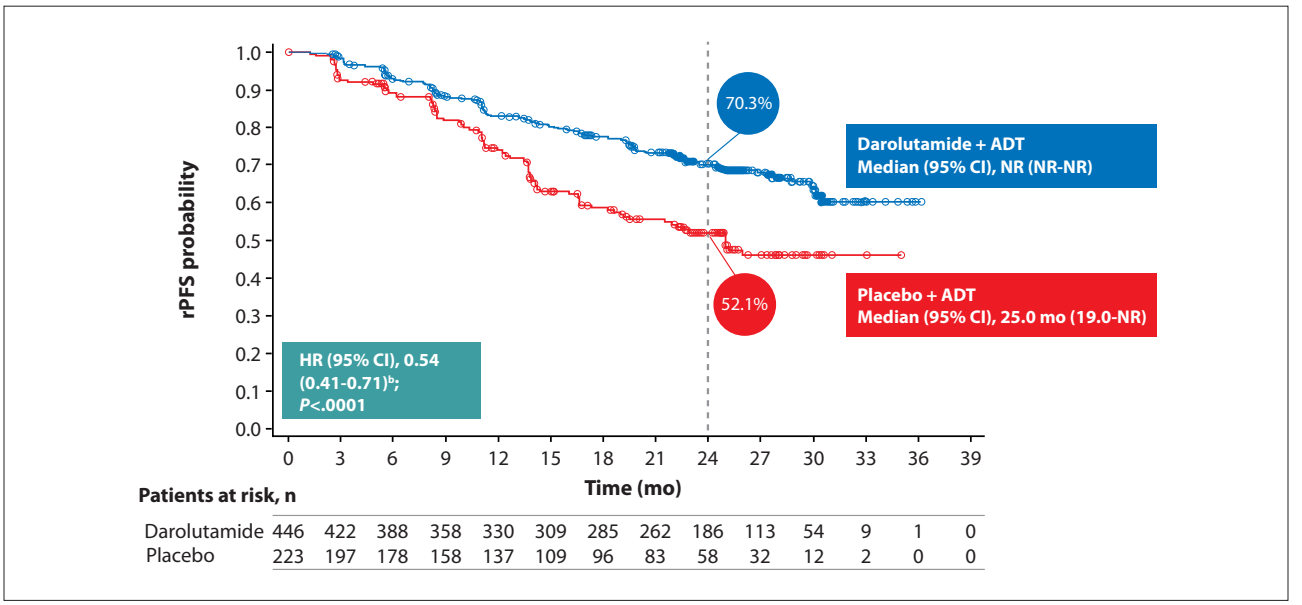

Figure 1. Radiological progression-free survival[a] with darolutamide plus androgen-deprivation therapy in patients with metastatic hormone-sensitive prostate cancer: results from the phase III ARANOTE trial.

ADT, androgen-deprivation therapy; HR, hazard ratio; mo, months; NR, not reached; rPFS, radiological progression-free survival.

[a]Primary analysis occurred after 222 events (darolutamide, 128; placebo, 94) and median follow-up was 25.3 months for the darolutamide group and 25.0 months for the placebo group.

[b]HR and 95% CI were calculated using the Cox model stratified on visceral metastases (Y/N) and prior therapy (Y/N).

Adapted from Saad et al. LBA68: Mini Oral Session. Presented at: ESMO Congress 2024; September 13-17, 2024; Barcelona, Spain.

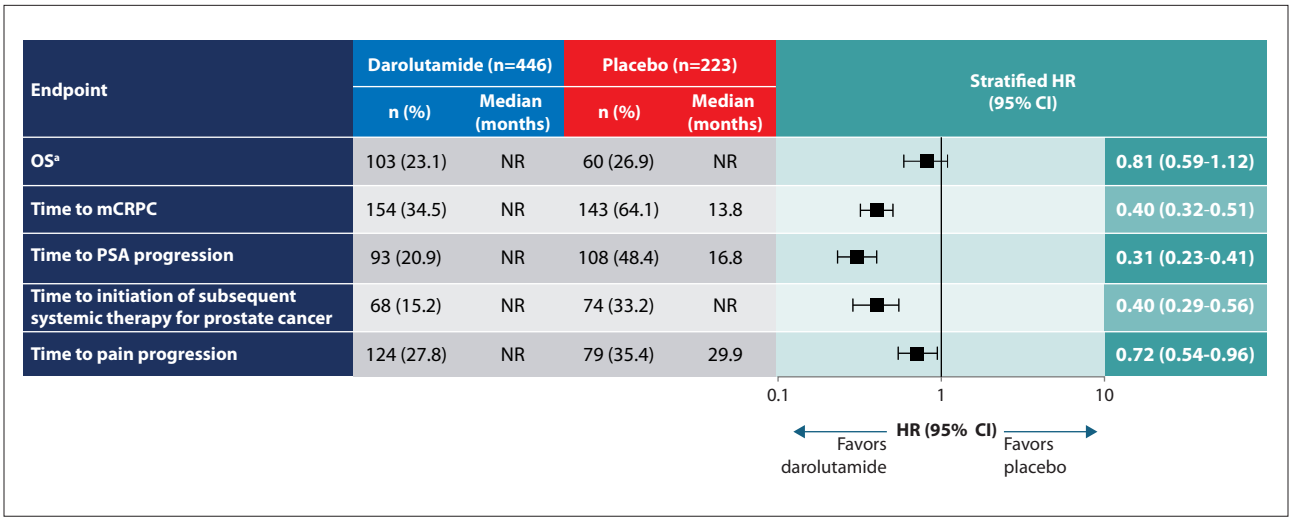

Figure 2. Secondary endpoints with darolutamide plus androgen-deprivation therapy in patients with metastatic hormone-sensitive prostate cancer: results from the phase III ARANOTE trial.

HR, hazard ratio; mCRPC, metastatic castration-resistant prostate cancer; NR, not reached; OS, overall survival; PSA, prostate-specific antigen.

[a]At the time of primary analysis, OS data are immature.

Adapted from Saad et al. LBA68: Mini Oral Session. Presented at: ESMO Congress 2024; September 13-17, 2024; Barcelona, Spain.

HR, 0.40; 95% CI, 0.32-0.51), time to prostate-specific antigen (PSA) progression (stratified HR, 0.31; 95% CI, 0.23-0.41), time to initiation of subsequent therapy (stratified HR, 0.40; 95% CI, 0.29-0.56), and time to pain progression (stratified HR, 0.72; 95% CI, 0.54-0.96). OS data were immature at the time of analysis.

The incidence of grade 3/4 treatment-emergent adverse events (TEAEs) was similar with darolutamide plus ADT and placebo plus ADT (30.8% and 30.3%), as was the rate of grade 5 TEAEs (4.7% and 5.4%). The frequency of TEAEs as assessed by exposure-adjusted incidence rate (EAIR) was similar between arms. The most frequent TEAEs were vasodilation and flushing (EAIR, 5.6 per 100 person-years with darolutamide plus ADT vs 5.0 per 100 person-years with placebo plus ADT), hypertension (5.5 vs 6.7 per 100 person-years), and diabetes mellitus or hyperglycemia (5.3 vs 6.7 per 100 person-years).

Investigators concluded that the addition of darolutamide to ADT was associated with a significant improvement in rPFS, benefits in secondary endpoints, and a favorable safety profile in patients with mHSPC, suggesting that darolutamide plus ADT without docetaxel should be an additional standard of care for these patients.

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Currently, darolutamide is approved in combination therapy with docetaxel and ADT in patients with mHSPC; yet until now there was no support for the use of darolutamide without docetaxel in this setting. The ARANOTE trial demonstrates the superiority of darolutamide and ADT to ADT alone in patients with mHSPC. This is practice-changing and supports the application to the FDA for an additional indication for darolutamide in combination with ADT, in patients with mHSPC.

—Pedro C. Barata, MD, MSc, FACP

A Randomized, Multicenter, Open-Label, Phase III Trial Comparing Enzalutamide Versus a Combination of Radium-223 and Enzalutamide in Asymptomatic or Mildly Symptomatic Patients With Bone Metastatic Castration-Resistant Prostate Cancer: First Results of EORTC-GUCG 1333/PEACE-3

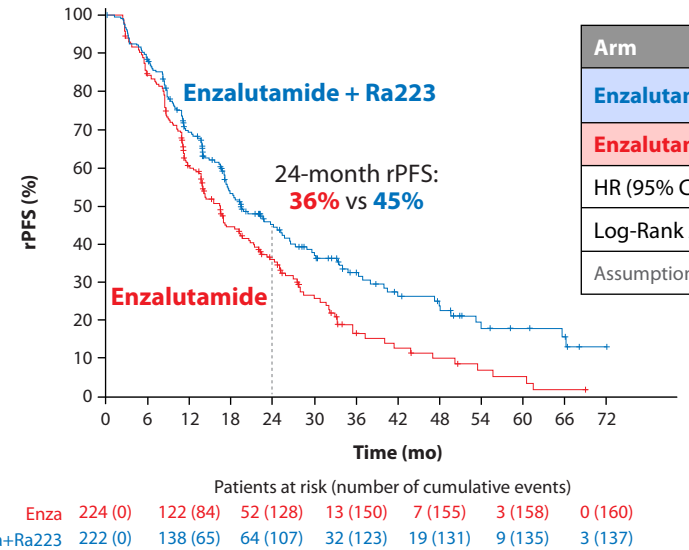
The novel hormonal therapies (NHTs), abiraterone and enzalutamide, are standard first-line treatment options for patients with mCRPC with progression on ADT.[1] Thus far, no first-line combination approach has demonstrated an improvement in rPFS and OS over single-agent therapy.

In the randomized, phase III ALSYMPCA trial, conducted prior to the introduction of NHT, the α-emitter radium-223 demonstrated an OS improvement over placebo in patients with CRPC with bone metastases.[2] In the randomized, phase III ERA-223 trial, the addition of radium-223 to abiraterone and prednisone or prednisolone in patients with CRPC with bone metastases did not improve symptomatic skeletal event (SSE)–free survival or OS and increased the frequency of bone fractures.[3] As a result, this combination was not evaluated further.

At ESMO 2024, Silke Gillessen, MD, presented results from the randomized, open-label, phase III EORTC-GUCG 1333/PEACE-3 trial evaluating the addition of radium-223 to enzalutamide in patients with mCRPC and bone metastases (Figure 3 and Table 1).[4] Enrolled patients had asymptomatic or mildly symptomatic disease with no known visceral metastases. A total of 446 patients were randomly assigned to enzalutamide 160 mg once daily with or without radium-223 55 kBq/kg intravenously (IV) every 4 weeks for 6 cycles. Use of bone-protecting agents was required after the first 119 patients.

The median age of enrolled patients was 70 years; 30% of patients had received prior docetaxel for mHSPC and 2% had received prior abiraterone. The trial met its primary endpoint, demonstrating a significant improvement in rPFS with radium-223 plus enzalutamide vs enzalutamide alone (median rPFS, 19.4 vs 16.4 months; HR, 0.69; *P*=.0009). Median OS was 42.3 months and 35.0 months, respectively (HR, 0.69; 95% CI, 0.52-0.90; *P*=.0031). The difference in OS met prespecified levels of significance and thus the study analysis will continue to a final OS analysis.

Time to next systemic treatment was also significantly improved with radium-223 plus enzalutamide vs enzalutamide alone (HR, 0.57; 95% CI, 0.44-0.75; *P*<.0001). There was



Arm	n/N	Median (95% CI)
Enzalutamide + Ra223	139/222	**19.4** (17.1-25.3) mo
Enzalutamide	160/224	**16.4** (13.8-19.2) mo
HR (95% CI)	**0.69** (0.54-0.87)	
Log-Rank *P*-value	**.0009**	
Assumption of proportional hazard achieved		

Figure 3. Radiological progression-free survival with enzalutamide vs a combination of radium-223 and enzalutamide in asymptomatic or mildly symptomatic patients with bone metastatic castration-resistant prostate cancer: first results of EORTC-GUCG 1333/PEACE-3.

Enza, enzalutamide; HR, hazard ratio; mo, months; Ra223, radium-223; rPFS, radiological progression-free survival.

Adapted from Gillessen et al. LBA1: Proffered Paper Session. Presented at: ESMO Congress 2024; September 13-17, 2024; Barcelona, Spain.

Table 1. Overall Survival With Enzalutamide vs a Combination of Radium-223 and Enzalutamide in Asymptomatic or Mildly Symptomatic Patients With Bone Metastatic Castration-Resistant Prostate Cancer: First Results of EORTC-GUCG 1333/PEACE-3

Arm	n/N	Median OS (95% CI)	HR (95% CI)
Enzalutamide + Ra223	110/222	**42.3** (36.8-49.1) mo	**0.69** (0.52-0.90), Log-Rank *P*-value=.0031
Enzalutamide	129/224	**35.0** (28.8-38.9) mo	

HR, hazard ratio; months; OS, overall survival; Ra223, radium-223.

Preset level of significance for interim analysis was <.0034.

Due to non-proportional hazards plus lack of unequivocal significance for restricted mean survival time sensitivity analysis, study will continue to final overall survival analysis.

Adapted from Gillessen et al. LBA1: Proffered Paper Session. Presented at: ESMO Congress 2024; September 13-17, 2024; Barcelona, Spain.

no significant difference in time to pain progression or time to SSE. The incidence of grade 3 or higher treatment-related AEs (TRAEs) was higher with radium-223 plus enzalutamide vs enzalutamide alone (28% vs 19%). The most common grade 3 or higher TRAEs were hypertension (11.5% vs 12.1%), fatigue (4.1% vs 1.3%), anemia (2.8% vs 0%), and neutropenia (3.2% vs 0%).

Investigators concluded that the PEACE-3 results support use of enzalutamide plus radium-223 plus a bone-protecting agent as a potential first-line treatment option for patients with prostate cancer with bone metastases who have not previously received an ARPI.

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This phase III trial showed superiority of combining radium-223 with enzalutamide vs enzalutamide alone in patients with mCRPC—in terms of progression-free survival, and more importantly, overall survival. This is practice-changing as it redefines the role of radium-223 and reminds us of the role of bone-modifying agents in the contemporary management of mCRPC.

—Pedro C. Barata, MD, MSc, FACP

Cabozantinib Plus Atezolizumab Versus 2nd Novel Hormonal Therapy in Patients with Metastatic Castration-Resistant Prostate Cancer: Final Overall Survival Results of the Phase III, Randomized, CONTACT-02 Study

Currently, patients with mCRPC who develop disease progression on NHT, particularly those with visceral metastases, have limited treatment options and a poor prognosis. Among the options are a second NHT, which is used more frequently in real-world practice, or chemotherapy.[1] There is a need for more effective therapies for these patients. One strategy being evaluated in clinical trials is the combination of the multitargeted tyrosine kinase inhibitor (TKI) cabozantinib and the programmed death-ligand 1 (PD-L1) inhibitor atezolizumab.

At ESMO 2024, Neeraj Agarwal, MD, presented final OS results from the phase III CONTACT-02 trial, which evaluated cabozantinib plus atezolizumab against a second NHT in patients with mCRPC with progression on a first NHT and with measurable extrapelvic soft tissue metastases (Table 2).[2] The combination of cabozantinib and atezolizumab was initially evaluated in the phase 1b COSMIC-021 trial, demonstrating an objective response rate (ORR) of 23% in 132 patients with mCRPC with

Table 2. Cabozantinib Plus Atezolizumab Versus Second Novel Hormonal Therapy in Patients With Metastatic Castration-Resistant Prostate Cancer: Final Overall Survival Results of the Phase III, Randomized, CONTACT-02 Study

Population	Cabo + Azeto		Second NHT		HR (95% CI)
	n	Median (95% CI) OS, mo	n	Median OS (95% CI), mo	
ITT population	289	14.8 (13.4-16.7)	286	15.0 (13.0-18.5)	0.89 (0.72-1.10); *P*=.30
Population with liver metastases	67	12.2 (8.8-13.8)	65	7.1 (5.3-10.4)	0.68 (0.47-1.00); *P*=.051
Population with bone metastases	229	13.8 (11.9-16.3)	217	11.6 (10.5-14.1)	0.79 (0.63-1.00); *P*=.046

Atezo, atezolizumab; Cabo, cabozantinib; HR, hazard ratio; ITT, intention to treat; NHT, novel hormonal therapy; OS, overall survival.

Adapted from Agarwal et al. LBA67: Proffered Paper Session. Presented at: ESMO Congress 2024; September 13-17, 2024; Barcelona, Spain.

progression after enzalutamide, abiraterone, or both, supporting further evaluation of the regimen.[3]

The randomized, phase III CONTACT-02 trial was undertaken to compare the efficacy and safety of cabozantinib plus atezolizumab vs a second NHT in patients with mCRPC with progression on 1 prior NHT and with measurable extrapelvic (visceral or lymph node) soft tissue metastasis.[2] Prior docetaxel for locally advanced or metastatic castration-sensitive prostate cancer (mCSPC) was allowed.

A total of 575 patients were randomly assigned to cabozantinib 40 mg orally each day plus atezolizumab 1200 mg IV every 3 weeks or a second NHT consisting of abiraterone 1000 mg orally daily plus prednisone 5 mg orally twice daily or enzalutamide 160 mg orally daily.

The median age of enrolled patients was 71 years; 59% to 60% had a Gleason score of 8 or greater at diagnosis, and 51% to 52% had metastatic disease at diagnosis. At baseline, visceral metastases were present in 38% to 41% of patients, liver metastases were present in 23%, and bone metastases were present in 76% to 79%. The median duration of first NHT was approximately 12 months.

As presented at the 2024 ASCO Genitourinary Cancers Symposium, the trial met one of its coprimary endpoints, demonstrating a significant improvement in PFS with cabozantinib plus atezolizumab over second NHT (median PFS, 6.3 vs 4.2 months; HR, 0.65; 95% CI, 0.50-0.84; *P*=.0007).[4] The PFS benefit was also observed in the subset of patients with liver metastases (median PFS, 6.2 vs 2.1 months; HR, 0.43; 95% CI, 0.27-0.68) and in patients with bone metastases (median PFS, 6.3 vs 4.1 months; HR, 0.67; 95% CI, 0.50-0.88).

After a median follow-up of 24 months, the second coprimary endpoint of OS showed a nonsignificant trend toward improvement with cabozantinib plus atezolizumab over second NHT (median OS, 14.8 vs 15.0 months; HR, 0.89; 95% CI, 0.72-1.10; *P*=.30). The improvement in OS with cabozantinib plus atezolizumab over second NHT was more notable in patients with liver metastases (median OS, 12.2 vs 7.1 months; HR, 0.68; 95% CI, 0.47-1.00; *P*=.051) and bone metastases (median OS, 13.8 vs 11.6 months; HR, 0.79; 95% CI, 0.63-1.00; *P*=.046).

Investigators noted that the AE profile with cabozantinib plus atezolizumab was consistent with other TKI and checkpoint inhibitor combinations. The most frequent grade 3 or 4 AEs with cabozantinib plus atezoli-

> This trial explores a novel combination strategy of a multikinase inhibitor, cabozantinib, with a PD-L1 inhibitor, atezolizumab, in mCRPC. It is a positive trial for progression-free survival and although we don't see an overall survival advantage, we do see some patient groups that might benefit. This underscores the importance of exploring subsets of patients where a combination strategy might be useful.
>
> —Pedro C. Barata, MD, MSc, FACP

zumab were anemia (8%), hypertension (8%), fatigue (6%), and diarrhea (5%). The most frequent grade 3 or 4 AEs with NHT were anemia (6%), fatigue (2%), and hypertension (2%). TRAEs led to discontinuation in 5% of patients receiving cabozantinib plus atezolizumab and 2% receiving NHT.

Cabozantinib plus atezolizumab was similar to NHT in the median time to clinically meaningful deterioration of quality of life (QOL; HR, 1.19; 95% CI, 0.94-1.51), showed a trend toward improved median time to SSE (HR, 0.73; 95% CI, 0.44-1.20), and was superior to NHT in the median time to initiation of chemotherapy (HR, 0.59; 95% CI, 0.45-0.77).

The investigators concluded that cabozantinib plus atezolizumab could be useful for selected patients with mCRPC with disease progression on an NHT.

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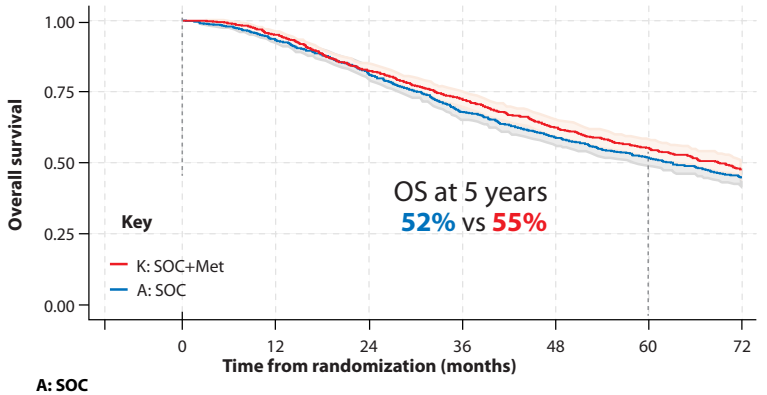
Adding Metformin to Androgen-Deprivation Therapy for Patients With Metastatic Hormone-Sensitive Prostate Cancer: Overall Survival Results From the Multi-Arm, Multi-Stage, Randomized Platform Trial STAMPEDE

Metformin has the potential to be beneficial when added to ADT in patients with advanced prostate cancer, as it could mitigate the metabolic adverse effects of ADT and it has demonstrated anticancer activity in preclinical studies.[1]

At ESMO 2024, Silke Gillessen, MD, presented results from 2 arms of the STAMPEDE trial evaluating the efficacy and safety of adding metformin to standard of care (SOC) in patients with mHSPC (Figure 4).[2] The trial enrolled 1874 patients with mHSPC with an HbA1c less than 6.5% who were not receiving treatment for diabetes. Patients were randomly assigned to SOC (n=938) or SOC plus metformin 850 mg once daily as a starting dose, increasing to a target dose of 850 mg twice daily (n=936). The primary end-



Median Follow-Up: 60 months

HR (95% CI), **0.91** (0.80-1.03); *P*=.142

Kaplan-Meier estimates	Median OS in months (95%CI)
SOC only	**63.1** (57.6-68.7)
SOC+Met	**69.1** (62.7-73.2)

Figure 4. Impact of adding metformin to androgen-deprivation therapy for patients with metastatic hormone-sensitive prostate cancer on overall survival: results from the multi-arm, multi-stage, randomized platform trial STAMPEDE.

HR, hazard ratio; Met, metformin; OS, overall survival; SOC, standard of care.

Adapted from Gillessen et al. LBA70: Mini Oral Session. Presented at: ESMO Congress 2024; September 13-17, 2024; Barcelona, Spain.

There have been efforts to investigate the impact of strict glucose control with an antidiabetic therapy on clinical outcomes of patients with metastatic prostate cancer. In this analysis from the STAMPEDE trial, at least in mHSPC the addition of metformin to systemic therapy did not improve outcomes compared with systemic therapy alone.

—Pedro C. Barata, MD, MSc, FACP

point was OS; secondary endpoints included metabolic effects, toxicity, failure-free survival, PFS, and prostate cancer–specific survival.

The median age of enrolled patients was 69 years; 11% of patients had visceral metastases at baseline. SOC included ADT plus docetaxel (82%), ADT alone (15%), and ADT + ARPI (3%).

After a median follow-up of 60 months, the addition of metformin to SOC was not associated with a significant improvement in OS (median OS, 69.1 vs 63.1 months; HR, 0.91; 95% CI, 0.80-1.03; *P*=.142). The 5-year OS rates were 55% and 52%, respectively. There was some evidence of a benefit with the addition of metformin to SOC in the subgroup of patients with high-volume disease as assessed by OS (HR, 0.79; 95% CI, 0.66-0.93; *P*=.0059) and PFS (HR, 0.76; 95% CI, 0.64-0.89; *P*=.0010). However, the trial was not powered to detect differences in these subsets.

Multiple metabolic parameters improved significantly with the addition of metformin to SOC, including weight, glucose level, HbA1c, total cholesterol, and low-density lipoprotein cholesterol.

Regarding safety, gastrointestinal AEs of any grade occurred in 86% of patients receiving SOC plus metformin vs 67% of patients receiving SOC. Renal or urinary events occurred in 71% and 66% of patients, respectively.

The investigators concluded there was no clear evidence that adding metformin to SOC improves OS in unselected patients with mHSPC, although potential benefit in patients with high-volume disease requires further evaluation. Moreover, the improvement in metabolic parameters could translate to reduced cardiovascular deaths in the future. They added that further research is warranted regarding the potential role of metformin added to an ADT–ARPI doublet backbone.

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Decipher mRNA Score for Prediction of Survival Benefit From Docetaxel at Start of Androgen-Deprivation Therapy for Advanced Prostate Cancer: An Ancillary Study of the STAMPEDE Docetaxel Trials

For men with mHSPC, the standard of care is ADT plus an ARPI such as abiraterone or enzalutamide. The addition of docetaxel to an ARPI and ADT may also be considered.[1] Adding docetaxel to ADT is associated with an improvement in OS but also an increase in AEs and a reduction in QOL.[2,3] Accordingly, it would be useful to be able to identify which patients are most likely to benefit from treatment intensification and which cancers are most likely to be sensitive to docetaxel.

At ESMO 2024, Emily Grist, MBBS, MRCP, PhD, presented results of an analysis of the STAMPEDE trials, which evaluated the prognostic and predictive value of the Decipher 22-gene messenger RNA (mRNA) score (DS) for selecting patients most likely to benefit from the addition of docetaxel to ADT plus ARPI (Figure 5).[4]

The DS was generated based on whole transcription profiling using the Veracyte test on tumor index cores from 895 patients enrolled in the STAMPEDE trial. OS outcomes were assessed in patients dichotomized by DS (≤0.8 vs >0.8) after adjusting for age, World Health Organization performance status, pre-ADT PSA, Gleason score, T stage, N stage, and metastatic volume.

DS was significantly lower among patients with M0N0 disease (adjusted *P*<.001), then showed a similar distribution across M0N1, M1 low-volume,

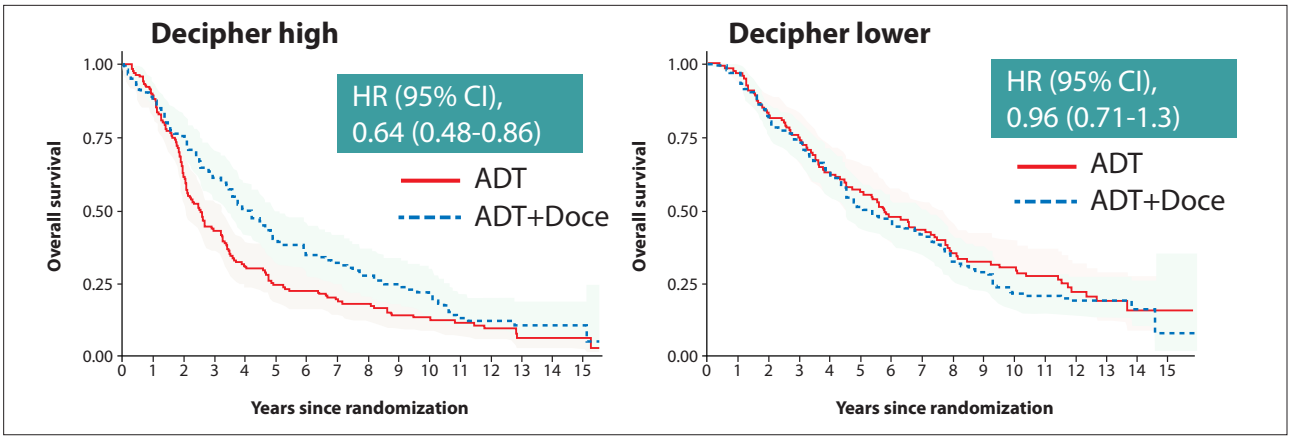

Figure 5. Decipher mRNA score predicts survival benefit from docetaxel at start of androgen-deprivation therapy for advanced prostate cancer: results from an ancillary study of the STAMPEDE docetaxel trials.

ADT, androgen-deprivation therapy; Doce, docetaxel; HR, hazard ratio.

Biomarker treatment interaction effect *P*=.039; no significant interaction effect demonstrated in nonmetastatic disease.

Adapted from Grist et al. 1596O: Proffered Paper Session. Presented at: ESMO Congress 2024; September 13-17, 2024; Barcelona, Spain.

and M1 high-volume disease. DS was prognostic, with each 0.1 increment increasing the risk of death by 11% in M1 disease (HR, 1.11; *P*<.001) and by 9% in M0 disease (HR, 1.10; *P*=.012).

In patients with M1 disease in the docetaxel trial, DS was significantly predictive of an efficacy benefit with docetaxel. The hazard ratio for OS with docetaxel plus ADT vs ADT alone was 0.64 (95% CI, 0.48-0.86) in patients with a high DS vs 0.96 (95% CI, 0.71-1.30) in patients with a low DS. The interaction between DS and OS benefit with docetaxel was statistically significant (*P*=.039). Moreover, the predictive value of DS was consistent whether patients had high-volume or low-volume disease. In contrast, there was no interaction between DS and outcomes in patients with M0 disease.

In the STAMPEDE abiraterone trial, DS was significantly prognostic but there was no statistically or clinically significant biomarker-treatment interaction predicting a benefit with the addition of abiraterone to ADT.

Investigators concluded that the DS can identify patients treated with ADT plus abiraterone with M1 prostate cancer who have a poor prognosis, and it can also identify docetaxel-sensitive tumors. They suggested that the DS provides a rational biomarker for selecting patients to receive ADT plus ARPI plus docetaxel.

This study from STAMPEDE trial highlights the importance of molecular characterization of tumors in mHSPC. In this case, high Decipher 22-gene mRNA score predicted survival benefit from the addition of docetaxel. This is an important effort highlighting the predictive role of tumor gene expression data and leverages further research incorporating molecular characteristics of tumors to improve individualization of treatment intensification for patients diagnosed with mHSPC.

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Phenotypic and Genomic Characterization of De Novo Metastatic Prostate Cancer: An Ancillary Study of the PEACE-1 Phase III Trial

The randomized, open-label, phase III PEACE-1 trial resulted in a paradigm shift in the treatment of first-line mCSPC, demonstrating an OS benefit with the addition of abiraterone to docetaxel and ADT.[1] At ESMO 2024, Cédric Pobel, MD, presented results of an ancillary study of PEACE-1 evaluating prognostic and predictive biomarkers associated with rPFS and OS outcomes, with the aim of detecting aggressive or neuroendocrine-like variants at diagnosis.[2]

The analysis was conducted on paraffin-embedded tumor samples from 595 of the 1173 patients initially randomized in the PEACE-1 trial. The distribution of phenotypic and genomic characteristics was similar to that in the overall trial population.

Immunohistochemistry (IHC) analyses assessed for luminal components, neuroendocrine (NE) features, tumor suppressor proteins, Ki67, and ERG. Approximately 26% of patients had tumors with NE features, which were associated with poor prognosis.

Investigators found that by combining androgen receptor (AR) and NE marker expression, patients could be divided into 5 phenotypes with varying prognosis: AR-high luminal (42.9%), AR-low luminal (27.7%), amphicrine (27.1%), double-negative (0.8%), and NE prostate cancer (1.4%). Among the 5 phenotypes, median OS was longest in patients with AR-high luminal (5.7 years), followed by double-negative (5.5 years), AR-low luminal (4.8 years), amphicrine (4.0 years), and NE prostate cancer (1.1 years).

The genomic analysis found that having alterations in at least 2 of the 3 genes *TP53, PTEN,* and *RB1* predicted poor outcomes, with a median OS of 2.2 years compared with 5.4 years for patients with less than 2 alterations (HR, 2.63; 95% CI, 1.10-6.30; *P*=.03). No biomarkers to predict benefit with abiraterone were found.

ABSTRACT SUMMARY Enzalutamide With or Without Leuprolide in Patients With High-Risk Biochemically Recurrent Prostate Cancer: EMBARK Post Hoc Analysis by Age

Shore and colleagues presented a post hoc analysis of the EMBARK trial that assessed outcomes by age (<70 years vs ≥70 years) among patients with high-risk biochemically recurrent prostate cancer receiving enzalutamide with or without leuprolide or leuprolide alone (Abstract 1638P). Overall, 50.8% of patients were younger than age 70 and 49.2% were age 70 or older. The analysis found improvements in metastasis-free survival with enzalutamide plus leuprolide over leuprolide alone and with enzalutamide monotherapy over leuprolide alone in both the younger and the older cohorts. No significant differences in treatment effect by age group were noted for either treatment comparison. The incidence of serious AEs was higher among older vs younger patients with enzalutamide plus leuprolide (45.0% vs 25.3%), with leuprolide alone (36.2% vs 27.1%), and with enzalutamide monotherapy (43.9% vs 30.4%). However, rates of treatment-related serious AEs were low regardless of age, ranging from 0.6% to 11.7% across arms and age cohorts.

This ancillary study from PEACE-1 explored phenotype groups based on IHC analysis and identified a prognostic role of IHC characteristics in predicting who benefits from treatment intensification with ADT with or without docetaxel, with or without abiraterone acetate plus prednisolone in patients with mCSPC. These findings, if validated, support the incorporation of IHC-based phenotype information from tumors to accurately evaluate response to systemic treatment and prognosis of such patients.

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Open-Label, Multicenter Randomized Trial of Radium-223–Docetaxel Versus Docetaxel–Radium-223 Sequence in Metastatic Castration-Resistant Prostate Cancer With Prospective Biomarker Evaluation (RAPSON Study)

At ESMO 2024, Vincenza Conteduca, MD, PhD, presented results from the RAPSON trial, which evaluated the optimal sequence of radium-223 and docetaxel in patients with symptomatic bone-dominant mCRPC with progression after ADT with or without abiraterone and enzalutamide.[1]

The multicenter, randomized, phase II trial conducted in 70 patients compared radium-223 followed by docetaxel at progression to docetaxel followed by radium-223 at progression. The primary endpoint was the effect of treatment sequence on health-related QOL (HRQOL), which was measured by changes in the Functional Assessment of Cancer Therapy–Prostate (FACT-P) questionnaire and the Brief Pain Inventory–Short Form questionnaire (BPI-SF) for bone pain intensity, from baseline to week 12.

To define meaningful improvements or worsening of symptoms, the upper limit of the minimally important difference range was calculated for each subscale. Patients with an increase of at least a minimally important difference in the FACT-P questionnaire were considered to be responders and patients with a decrease of at least a minimally important difference were considered nonresponders. Secondary endpoints included PFS, OS, safety, and biomarker studies.

In the primary analysis, radium-223 was associated with HRQOL benefits over docetaxel, including less deterioration of HRQOL from baseline to week 12 and a higher likelihood of a response as assessed by pain intensity and its interference with daily activities.

Rates of treatment reductions and discontinuations owing to AEs were reported for the first assigned treatment period. During this time, the rate of treatment reductions owing to toxicity was lower with radium-223 vs docetaxel (1/34 vs 9/36), as was the rate of treatment discontinuations owing to TRAEs (2/23 vs 7/36).

There was no significant difference between starting with radium-223 or docetaxel in median PFS (7.3 vs 9.7

ABSTRACT SUMMARY The STAMPEDE2 ^{177}Lu-PSMA-617 Trial: A Phase III, Randomized, Open-Label Trial in Patients with Metastatic Prostate Cancer Starting ADT

Padden-Modi and colleagues presented the design of the open-label, multicenter, phase III STAMPEDE2 trial, a platform protocol evaluating the addition of 3 different treatments—stereotactic ablative body radiotherapy, ^{177}Lu-PSMA-617, and niraparib-abiraterone acetate plus prednisolone—to SOC in patients with mHSPC (Abstract 1658TiP). The ^{177}Lu-PSMA-617 trial is evaluating the addition of ^{177}Lu-PSMA-617 to SOC earlier in the course of metastatic prostate cancer treatment in patients starting ADT. Patients are randomly assigned to SOC (long-term ADT, androgen receptor signaling inhibitor [ARSI], with or without prostate radiotherapy and with or without docetaxel) with or without ^{177}Lu-PSMA-617 given at 7.4 GBq on days 1 and 8 for three 6-week cycles. A substudy will evaluate responses to ^{177}Lu-PSMA-617 and dose uptake into tumor and normal tissue. All eligible patients will be offered biomarker testing, with the option for a second randomization into the STAMPEDE2 niraparib trial for eligible patients. The coprimary endpoints will be OS and rPFS. The trial aims to enroll 1876 patients.

Appropriate sequencing of different life-prolonging therapies in patients with mCRPC is a clinically important question. This phase II trial tested the sequence radium-223–docetaxel vs docetaxel–radium-223 and its findings support the use of radium-223 prior to chemotherapy in patients with bone-dominant symptomatic mCRPC. This aligns with other studies in this setting that support the use of radium-223 earlier in the setting of mCRPC.

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months; *P*=.074) or in median OS (17.4 months in both arms; *P*=.964).

Investigators concluded that in patients with bone-dominant symptomatic mCRPC, radium-223 followed by docetaxel was associated with improvements in QOL and tolerability compared with docetaxel followed by radium-223. Additional follow-up and studies are needed to further individualize sequential therapy for these patients.

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Nivolumab 3 mg/kg and Ipilimumab 1 mg/kg in Molecularly Selected Patients With Metastatic Castration-Resistant Prostate Cancer

Immune checkpoint inhibitors (ICI) have not demonstrated significant benefit when administered as monotherapy in patients with mCRPC, which has been attributed to a lack of tumor-infiltrating T cells.[1] However, in the CheckMate 650 trial, the combination of the anti-CTLA-4 ipilimumab and the anti-PD-1 nivolumab demonstrated preliminary activity in a cohort of unselected patients with mCRPC, with particular activity noted in several groups of biomarker-selected patients: those with mismatch repair deficiency (MMRd)/microsatellite instability (MSI-H) tumors, those with a high tumor mutational burden (hTMB), and those with DNA damage repair alterations (CDK12 inactivation and *BRCA* mutations).

Based on this preliminary study, the phase II INSPIRE trial was undertaken to further evaluate the efficacy and safety of nivolumab plus ipilimumab in patients with mCRPC with biomarker-selected subtypes. Results were presented at ESMO 2024 by Niven Mehra, MD, PhD.[2]

The efficacy cohort included 65 patients with mCRPC receiving ongoing ADT who had MMRd/MSI-H (n=21), hTMB (n=8), CDK12 inactivation (n=16), and *BRCA* mutations (n=20). The safety cohort included an additional 4 patients who had received prior ICI monotherapy. Patients received nivolumab 3 mg/kg plus ipilimumab 1 mg/kg IV every 3 weeks for up to 4 doses followed by nivolumab 480 mg IV every 4 weeks for up to 1 year.

The primary endpoint was disease control rate (DCR) for at least 6 months. Secondary endpoints included ORR, biochemical response rate, PFS, OS, and grade 3 or higher TRAEs.

Patients were a median of 69 years old (range, 51-82 years); 68% had received prior taxanes and 77% had received a prior ARPI. At baseline, metastases were detectable in the lymph nodes in 68% of patients, in the bone in 83%, in visceral sites in 17%, and in soft tissue in 11%.

The 6-month DCR rate was 38% overall; particular activity was noted in patients with MMRd, with a 6-month DCR rate of 81% and an ORR of 75%. The 6-month DCR rates in patients with hTMB, CDK12 inactivation, and *BRCA* mutations were 25%, 19%, and 15%, respectively, and corresponding ORR rates were 0%, 22%, and 23%, respectively. The median PFS in the MMRd subset was 32.7 months, and the earliest 90% or greater reduction in PSA relative to baseline was 86%.

In the safety cohort, grade 3 or greater TRAEs occurred in 48% of patients, with the most common events including diarrhea (10%), γ-glutamyl transferase increase (10%), lymphocyte count decrease (10%), alanine aminotransferase increase (9%),

ABSTRACT SUMMARY Impact of Concomitant Medications on Safety in Patients With High-Volume mHSPC Receiving Rezvilutamide Plus ADT: A Post Hoc Analysis of the Randomized Phase III CHART Trial

Ye and colleagues presented a post hoc analysis of the randomized, phase III CHART trial that evaluated the impact of concomitant medications on safety outcomes in patients with high-volume mHSPC receiving rezvilutamide plus ADT or bicalutamide plus ADT (Abstract 1649P). The analysis focused on 3 common drugs that could interact with rezvilutamide: antithrombotics, gastric acid disorder–related drugs, and lipid-modifying drugs. Overall, 93.2% of patients in the rezvilutamide plus ADT arm and 92.3% of patients in the bicalutamide plus ADT arm received concomitant medications; distribution of concomitant drugs was comparable between arms. Among patients receiving these 3 types of concomitant antithrombotics, rates of toxicities were comparable or slightly higher with rezvilutamide plus ADT vs bicalutamide plus ADT, which investigators noted could be partially owing to differences in treatment exposure, which were 1.7 to 2.0 times higher in the rezvilutamide arm. Investigators concluded that the results support the safe use of these concomitant medications when clinically indicated.

ABSTRACT SUMMARY Symptomatic Skeletal Events, Health-Related QOL, and Pain in a Phase III Study of ^{177}Lu-PSMA-617 in Taxane-Naive Patients With PSMA-Positive mCRPC: Third Interim Analysis of PSMAfore

The PSMAfore trial demonstrated a significant improvement in rPFS with ^{177}Lu-PSMA-617 over a change in ARPI among taxane-naive patients with prostate-specific membrane antigen (PSMA)–positive mCRPC with progression on a previous ARPI (Morris. *Lancet*. 2024;404:1227.). At ESMO 2024, Fizazi and collegues presented secondary endpoints from the PSMAfore trial, including time to SSE, HRQOL, and pain (Abstract 1599P). Compared with a change in ARPI, ^{177}Lu-PSMA-617 was associated with a significant extension in the median time to SSE or death (7.97 months vs not estimable; HR, 0.41; 95% CI, 0.26-0.63) and a reduction in the rate of pathologic bone fractures (5.6% vs 1.7%). Time to worsening of HRQOL was also significantly better with ^{177}Lu-PSMA-617 vs an ARPI as assessed by the FACT-P (HR, 0.61; 95% CI, 0.50-0.75), the EQ-5D-5L utility score (HR, 0.67; 95% CI, 0.54-0.82), and BPI-SF pain intensity (HR, 0.73; 95% CI, 0.59-0.88).

aspartate aminotransferase increase (9%), and colitis (9%). TRAEs led to discontinuation of ipilimumab and nivolumab in 19% of patients each.

Based on the reported findings, investigators concluded that there is a need for early testing for MMRd in patients with mCRPC to inform treatment with dual ICIs. They also noted the need for additional precision medicine approaches for patients with MMRd, who comprise approximately 5% of the metastatic prostate cancer population.[3]

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Traditionally, immune checkpoint inhibitors have shown limited activity for unselected patients with mCRPC. This phase II trial explored the combination of nivolumab/ipilimumab in molecularly selected patients with mCRPC. While overall the benefit of this regimen was limited, this trial sheds light on certain subgroups of patients, such as those with mismatch-repair deficiency, high-tumor mutational burden, and some HR positives, who might benefit from dual immune checkpoint inhibition.

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