

**A SPECIAL MEETING REVIEW EDITION**

## Highlights in Prostate Cancer From the 2021 European Society for Medical Oncology Congress and the 2021 American Urological Association Meeting

A Review of Selected Presentations From the 2021 ESMO Congress and the 2021 AUA Meeting

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**Special Reporting on:**

- Objective Computerized Cognitive Assessment in Men With Metastatic Castrate-Resistant Prostate Cancer Randomly Receiving Darolutamide or Enzalutamide in the ODENZA Trial
- Darolutamide Maintenance in Metastatic Castration-Resistant Prostate Cancer Previously Treated With Novel Hormonal Agents and Nonprogressive Disease After Subsequent Treatment With a Taxane: A Randomized, Double-Blind, Placebo-Controlled Phase II Trial (SAKK 08/16)
- Cabozantinib in Combination With Atezolizumab in Patients With Metastatic Castration-Resistant Prostate Cancer: Results of Expanded Cohort 6 of the COSMIC-021 Study
- Impact of Darolutamide on Local Symptoms in Patients With Nonmetastatic Castration-Resistant Prostate Cancer
- Abiraterone Acetate Plus Prednisolone With or Without Enzalutamide Added to Androgen Deprivation Therapy (ADT) Compared to ADT Alone for Men With High-Risk Nonmetastatic Prostate Cancer: Combined Analysis From Two Comparisons in the STAMPEDE Platform Protocol
- Time Course Profile of Adverse Events of Interest and Serious Adverse Events With Darolutamide in the ARAMIS Trial
- Biomarker Analysis of Men With Enzalutamide-Resistant Metastatic Castration-Resistant Prostate Cancer Treated With Pembrolizumab + Enzalutamide in KEYNOTE-199
- Health-Related Quality of Life, Pain, and Safety Outcomes in the Phase III VISION Study of <sup>177</sup>Lu-PSMA-617 in Patients With Metastatic Castration-Resistant Prostate Cancer
- Final Overall Survival Analysis From ARCHES: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Enzalutamide Plus Androgen Deprivation Therapy in Men With Metastatic Hormone-Sensitive Prostate Cancer

**PLUS Meeting Abstract Summaries**

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# POWERFUL EFFICACY, PROVEN TOLERABILITY.

Extend patient survival with  
**NUBEQA (darolutamide)**  
in non-metastatic castration  
resistant prostate cancer

## Focus on both Survival AND Tolerability with NUBEQA

### INDICATION

NUBEQA® (darolutamide) is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer.

### IMPORTANT SAFETY INFORMATION

**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

Serious adverse reactions occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions in  $\geq 1$  % of patients who received NUBEQA were urinary retention, pneumonia, and hematuria. Overall, 3.9% of patients receiving NUBEQA and 3.2% of patients receiving placebo died from adverse reactions, which included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%) for NUBEQA.

Adverse reactions occurring more frequently in the NUBEQA arm ( $\geq 2$ % over placebo) were fatigue (16% vs 11%), pain in extremity (6% vs 3%) and rash (3% vs 1%).

Clinically significant adverse reactions occurring in  $\geq 2$ % of patients treated with NUBEQA included ischemic heart disease (4.0% vs 3.4% on placebo) and heart failure (2.1% vs 0.9% on placebo).

#### 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.

Please see the following pages for brief summary of full Prescribing Information.



## MEN LIVED 2X LONGER WITHOUT CANCER SPREADING

with NUBEQA + ADT\* vs ADT alone†  
(40 months vs 18 months, respectively)  
(HR: 0.41; 95% CI: 0.34-0.50; P<0.0001)  
\*95% CI: 34.3-NE. †95% CI: 15.5-22.3.

## PRESCRIBE WITH CONFIDENCE ~19 out of 20 patients started on and stayed on full dose

Low rates of dose reduction (6%) and interruptions (13%)§ with no increase in permanent discontinuation due to adverse reactions when NUBEQA was added to ADT (9% vs. 9% with ADT alone)‡

## REDUCED RISK OF DEATH BY NEARLY A THIRD

31% reduction in the risk of death with NUBEQA + ADT vs ADT alone  
(HR: 0.69; 95% CI: 0.53-0.88; P=0.003)  
Medians not estimable.

## MOST NUBEQA PATIENTS DID NOT REPORT ANY FATIGUE (84%)

Three adverse reactions occurred more frequently with NUBEQA + ADT (≥2% over ADT alone): fatigue (16% vs 11%), pain in extremity (6% vs 3%), and rash (3% vs 1%)||

### Metastasis-free survival (MFS) was the primary endpoint, and overall survival (OS) was a key secondary endpoint.

The efficacy and safety of NUBEQA were assessed in a randomized, double-blind, placebo-controlled, international, multicenter, phase III study (ARAMIS) in nmCRPC patients with a prostate-specific antigen doubling time of ≤10 months. 1509 patients were randomized 2:1 to receive either 600 mg NUBEQA twice daily (n=955) or matching placebo (n=554). All patients received concurrent ADT (treatment with GnRH analog or previous bilateral orchiectomy). The primary endpoint was MFS, defined as the time from randomization to the time of first evidence of BICR-confirmed distant metastasis or death from any cause within 33 weeks after the last evaluable scan, whichever occurred first. Treatment continued until radiographic disease progression, as assessed by CT, MRI, <sup>99m</sup>Tc bone scan by BICR, unacceptable toxicity, or withdrawal. The final analysis of OS and time to initiation of cytotoxic chemotherapy was event-driven and conducted after 254 OS events had occurred and 14 months after MFS analysis.<sup>1,2</sup>

§In patients treated with NUBEQA + ADT, the most frequent adverse reactions requiring dose reduction included fatigue (0.7%), hypertension (0.3%), and nausea (0.3%); the most frequent adverse reactions requiring dose interruption included hypertension (0.6%), diarrhea (0.5%), and pneumonia (0.5%).

‡The most frequent adverse reactions requiring permanent discontinuation in patients treated with NUBEQA + ADT included cardiac failure (0.4%) and death (0.4%).

**||All-grade laboratory abnormalities in patients treated with NUBEQA + ADT vs ADT alone were, respectively, decreased neutrophil count (20% vs 9%), increased AST (23% vs 14%), and increased bilirubin (16% vs 7%). Grade 3-4 for same lab abnormalities were, respectively, 4% vs 0.6%, 0.5% vs 0.2%, and 0.1% vs 0%.**

†The NUBEQA Free Trial Program provides 1 month's supply of NUBEQA at no cost to patients who meet the program eligibility requirements and agree to the terms and conditions. For full terms and conditions and to enroll patients, please call Access Services by Bayer at 1-800-288-8374 or visit NUBEQAhcp.com.

PSA=prostate-specific antigen; ADT=androgen deprivation therapy; HR=hazard ratio; CI=confidence interval; NE=not estimable; GnRH=gonadotropin-releasing hormone; BICR=blinded independent central review; CT=computed tomography; MRI=magnetic resonance imaging; AST=aspartate aminotransferase.



**NUBEQA**<sup>®</sup>  
(darolutamide) 300 mg tablets

Start new NUBEQA patients with a 1-month free trial<sup>¶</sup>

Visit [NUBEQAhcp.com](http://NUBEQAhcp.com)

**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 patients with non-metastatic castration resistant prostate cancer (nmCRPC).

**4 CONTRAINDICATIONS**

None.

**5 WARNINGS AND PRECAUTIONS**

**5.1 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* (12.1)].

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* (8.1, 8.3)].

**6 ADVERSE REACTIONS**

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.

ARAMIS, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had non-metastatic castration-resistant prostate cancer (nmCRPC). In this study, 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. The median duration of exposure was 14.8 months (range: 0 to 44.3 months) in patients who received NUBEQA.

Overall, serious adverse reactions occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions in  $\geq 1\%$  of patients who received NUBEQA included urinary retention, pneumonia and hematuria. Overall 3.9% of patients receiving NUBEQA and 3.2% of patients receiving placebo died from adverse reactions, which included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%) for NUBEQA.

Permanent discontinuation due to adverse reactions occurred in 9% of patients receiving NUBEQA or placebo. The most frequent 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 frequent 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 frequent adverse reactions requiring dosage reduction in patients treated with NUBEQA included fatigue (0.7%), hypertension (0.3%), and nausea (0.3%).

Table 1 shows adverse reactions in ARAMIS reported in the NUBEQA arm with a  $\geq 2\%$  absolute increase in frequency compared to placebo. Table 2 shows laboratory test abnormalities related to NUBEQA treatment and reported more frequently in NUBEQA-treated patients compared to placebo-treated patients in the ARAMIS study.

**Table 1: Adverse Reactions in ARAMIS**

Adverse Reaction <sup>2</sup>	NUBEQA (n=954)		Placebo (n=554)	
	All Grades %	Grades $\geq 3$ %	All Grades %	Grade $\geq 3$ %
Fatigue <sup>1</sup>	16	0.6	11	1.1
Pain in extremity	6	0	3	0.2
Rash	3	0.1	1	0

<sup>1</sup> Includes fatigue and asthenia

<sup>2</sup> Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Additionally, clinically significant adverse reactions occurring in 2% or more of patients treated with NUBEQA included ischemic heart disease (4.0% versus 3.4% on placebo) and heart failure (2.1% versus 0.9% on placebo).

**Table 2: Laboratory Test Abnormalities in ARAMIS**

Laboratory Abnormality	NUBEQA (N=954) <sup>1</sup>		Placebo (N=554) <sup>1</sup>	
	All Grades <sup>2</sup> %	Grade 3-4 <sup>2</sup> %	All Grades <sup>2</sup> %	Grade 3-4 <sup>2</sup> %
Neutrophil count decreased	20	4	9	0.6
AST increased	23	0.5	14	0.2
Bilirubin increased	16	0.1	7	0

<sup>1</sup> 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.

<sup>2</sup> Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

**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* (12.3)]. 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* (12.3)] 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* (2.2)].

**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<sub>max</sub> of BCRP substrates [see *Clinical Pharmacology* (12.3)], 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.

**References:** **1.** NUBEQA (darolutamide) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc.; January 2021. **2.** Fizazi K, Shore N, Tammela TL, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med.* 2019;380(13):1235-1246. **3.** Fizazi K, Shore N, Tammela TL, et al. Nonmetastatic, castration-resistant prostate cancer and survival with darolutamide. *N Engl J Med.* 2020;383(11):1040-1049.

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* (12.3)].

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* (12.1)]. 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* (8.1)].

#### *Infertility*

##### Males

Based on animal studies, NUBEQA may impair fertility in males of reproductive potential [see *Nonclinical Toxicology* (13.1)].

### 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. No overall differences in safety or efficacy were observed between these patients and younger patients.

### 8.6 Renal Impairment

Patients with severe renal impairment (eGFR 15–29 mL/min/1.73 m<sup>2</sup>) who are not receiving hemodialysis have a higher exposure to NUBEQA and reduction of the dose is recommended [see *Dosage and Administration* (2.3) and *Clinical Pharmacology* (12.3)]. No dose reduction is needed for patients with mild or moderate renal impairment (eGFR 30-89 mL/min/1.73 m<sup>2</sup>). The effect of end stage renal disease (eGFR ≤15 mL/min/1.73 m<sup>2</sup>) 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* (2.4) and *Clinical Pharmacology* (12.3)]. 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* (12.3)].

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.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies to evaluate the carcinogenic potential of darolutamide have not been conducted.

Darolutamide was clastogenic in an *in vitro* chromosome aberration assay in human peripheral blood lymphocytes. Darolutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in the *in vivo* combined bone marrow micronucleus assay and the Comet assay in the liver and duodenum of the rat.

Fertility studies in animals have not been conducted with darolutamide. In repeat-dose toxicity studies in male rats (up to 26 weeks) and dogs (up to 39 weeks), tubular dilatation of testes, hypospermia, and atrophy of seminal vesicles, testes, prostate gland and epididymides were observed at doses ≥ 100 mg/kg/day in rats (0.6 times the human exposure based on AUC) and ≥ 50 mg/kg/day in dogs (approximately 1 times the human exposure based on AUC).

## 17 PATIENT COUNSELING INFORMATION

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

#### 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* (2.1)].

#### 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* (8.1)].

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* (5.1) and *Use in Specific Populations* (8.1, 8.3)].

#### Infertility

Advise male patients that NUBEQA may impair fertility [see *Use in Specific Populations* (8.3)].

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

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## Objective Computerized Cognitive Assessment in Men With Metastatic Castrate-Resistant Prostate Cancer Randomly Receiving Darolutamide or Enzalutamide in the ODENZA Trial

The second-generation androgen receptor inhibitor enzalutamide has been associated with cognitive changes and adverse events related to the central nervous system, such as fatigue.<sup>1</sup> Penetration of the blood-brain barrier is lower with darolutamide than enzalutamide, which may reduce the risk of fatigue and cognitive impairment.<sup>2</sup> The phase 2 ODENZA trial was an open-label, multicenter, prospective, randomized, crossover study that compared patient preferences for darolutamide vs enzalutamide.<sup>3,4</sup> The trial randomly assigned 250 patients with asymptomatic or mildly symptomatic metastatic castration-resistant prostate cancer (mCRPC) to treatment with

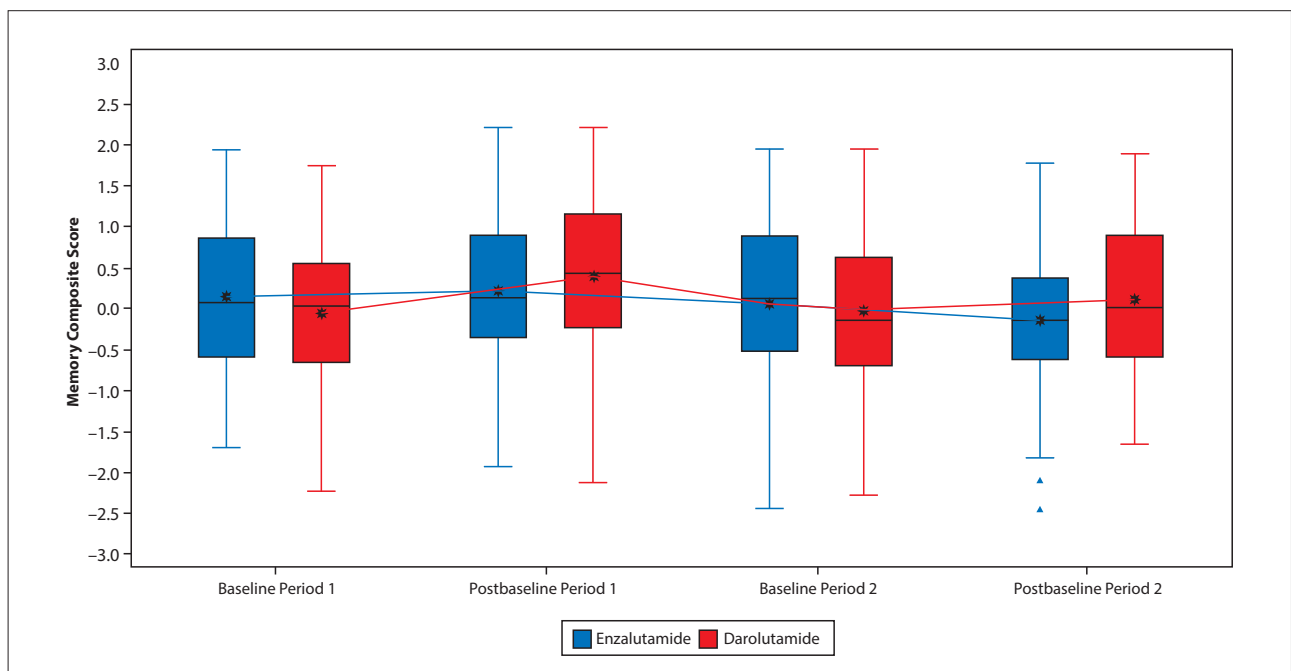
darolutamide (1200 mg/day for 12 weeks) followed by enzalutamide (160 mg/day for 12 weeks) or the opposite sequence. Darolutamide is a structurally distinct androgen receptor antagonist approved by the US Food and Drug Administration (FDA) for treatment of nonmetastatic castration-resistant prostate cancer (nmCRPC).

As reported at the 2021 American Society of Clinical Oncology annual meeting, 48.5% of patients preferred darolutamide, 40.0% preferred enzalutamide, and 11.5% had no preference.<sup>3</sup> This difference did not reach statistical significance. Decreased fatigue was reported as the most common factor influencing patient preference.

A key secondary endpoint of the

ODENZA trial was assessment of cognitive function with computerized cognitive tests. At the 2021 European Society for Medical Oncology (ESMO) congress, Emeline Colomba, MD, presented an analysis of the ODENZA trial that focused on differences in cognitive changes with enzalutamide vs darolutamide.<sup>4</sup> The patients completed cognitive tests measuring psychomotor function, visual attention, working memory, executive function, verbal learning, and verbal memory prospectively at baseline and during each 12-week treatment period.

Data were available for 193 patients. Performance on verbal learning, assessed using the International Shopping List Test, was significantly



**Figure 1.** CogState memory composite score according to assessment period and visit among the modified intention-to-treat population in the randomized, crossover phase 2 trial ODENZA trial. The trial compared patient preferences for darolutamide vs enzalutamide in men with asymptomatic or mildly symptomatic mCRPC. The box indicates the IQR (first and third) and median. The asterisk indicates the mean. The whiskers indicate the minimum/maximum. The outlier is  $>1.5$  (IQR). A higher score indicates better performance. The score from assessment period 1 postbaseline is equivalent to the score from assessment period 2 baseline for the individual tests. IQR, interquartile range; mCRPC, metastatic castration-resistant prostate cancer. Adapted from Colomba E et al. ESMO abstract 603P. *Ann Oncol.* 2021;32(suppl 5).<sup>4</sup>

better with darolutamide vs enzalutamide in both treatment periods, reaching clinically meaningful differences in the second period (effect size, 0.62;  $P=.0001$ ) and overall (effect size, 0.54;  $P<.0001$ ). Performance on the International Shopping List Test–Delayed Recall, which measured verbal memory, was also significantly better with darolutamide vs enzalutamide, although the effect sizes were less pronounced, at 0.4 ( $P=.01$ ) for the second period and 0.29 ( $P=.0075$ ) overall.

The investigators noted that the

improvements with darolutamide vs enzalutamide on episodic memory impacted both the learning of new information and the recall of that information following a short delay. Composite memory scores also showed a moderate benefit in episodic memory with darolutamide vs enzalutamide (Figure 1). Tests measuring executive function showed nonsignificant trends toward a benefit with darolutamide.

## References

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cognitive function. *Prostate Cancer Prostatic Dis.* 2020;23(2):207-219.

2. Crawford ED, Stanton W, Mandair D. Darolutamide: an evidenced-based review of its efficacy and safety in the treatment of prostate cancer. *Cancer Manag Res.* 2020;12:5667-5676.

3. Colomba E, Jonas SF, Eymard JC, et al. ODENZA: a French prospective, randomized, open-label, multicenter, cross-over phase II trial of preference between darolutamide and enzalutamide in men with asymptomatic or mildly symptomatic metastatic castrate-resistant prostate cancer (CRPC) [ASCO abstract 5046]. *J Clin Oncol.* 2021;39(15 suppl).

4. Colomba E, Jonas SF, Eymard JC, et al. Objective computerized cognitive assessment in men with metastatic castrate-resistant prostate cancer randomly receiving darolutamide or enzalutamide in the ODENZA trial [ESMO abstract 603P]. *Ann Oncol.* 2021;32(suppl 5).

## Darolutamide Maintenance in Metastatic Castration-Resistant Prostate Cancer Previously Treated With Novel Hormonal Agents and Nonprogressive Disease After Subsequent Treatment With a Taxane: A Randomized, Double-Blind, Placebo-Controlled Phase II Trial (SAKK 08/16)

The FDA approval of darolutamide for patients with nmCRPC was based on the results of the randomized, double-blind phase 3 ARAMIS trial. The trial compared darolutamide plus androgen deprivation therapy (ADT) vs placebo plus ADT in men with nmCRPC with a prostate-specific antigen (PSA) doubling time of 10 months or less. Patients were assigned 2:1 to treatment with darolutamide at 600 mg twice daily ( $n=955$ ) or placebo ( $n=554$ ), along with ADT.<sup>1</sup> In the primary analysis, the median metastasis-free survival was 40.4 months in the darolutamide arm vs 18.4 months in the placebo arm (hazard ratio [HR] for metastasis or death in the darolutamide group, 0.41; 95% CI, 0.34-0.50;  $P<.001$ ).<sup>1</sup> Given the benefit of darolutamide among patients with nmCRPC, trials are underway evaluating the potential role of this treatment in other prostate cancer settings.

At the 2021 ESMO congress, Richard Cathomas, MD, presented

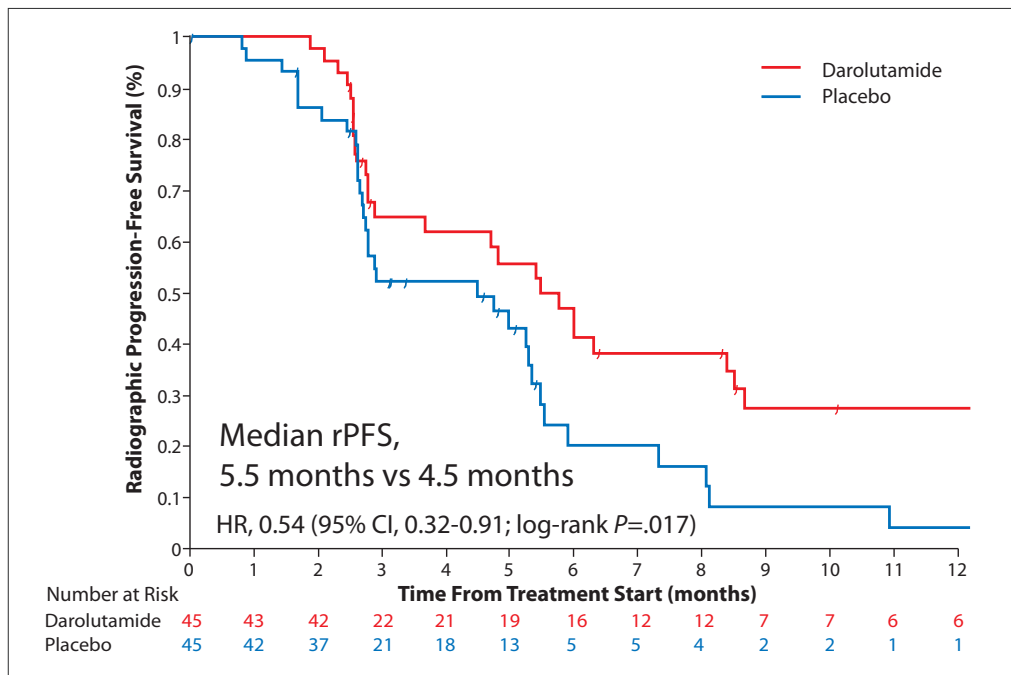
the results of SAKK 08/16, an international, double-blind, placebo-controlled, proof-of-concept phase 2 trial that evaluated darolutamide as maintenance therapy among patients with mCRPC previously treated with a novel hormonal agent.<sup>2</sup> The trial enrolled 92 patients with mCRPC who had received enzalutamide and/or abiraterone acetate for at least 8 weeks before receiving a taxane. The patients had nonprogressive disease after treatment with docetaxel (at a cumulative dose of  $\geq 300$  mg/m<sup>2</sup>) or cabazitaxel (at a dose of  $\geq 80$  mg/m<sup>2</sup>) and were continuing to receive ADT.

Patients were randomly assigned to receive darolutamide at 600 mg twice daily or placebo twice daily, each with best supportive care. Stratification factors included country of residence, performance status, sites of metastases, prior treatment, and planned start of maintenance treatment after the last taxane dose ( $<35$  days vs  $\geq 35$  days). The start of maintenance was planned for 2 to 8 weeks after the last

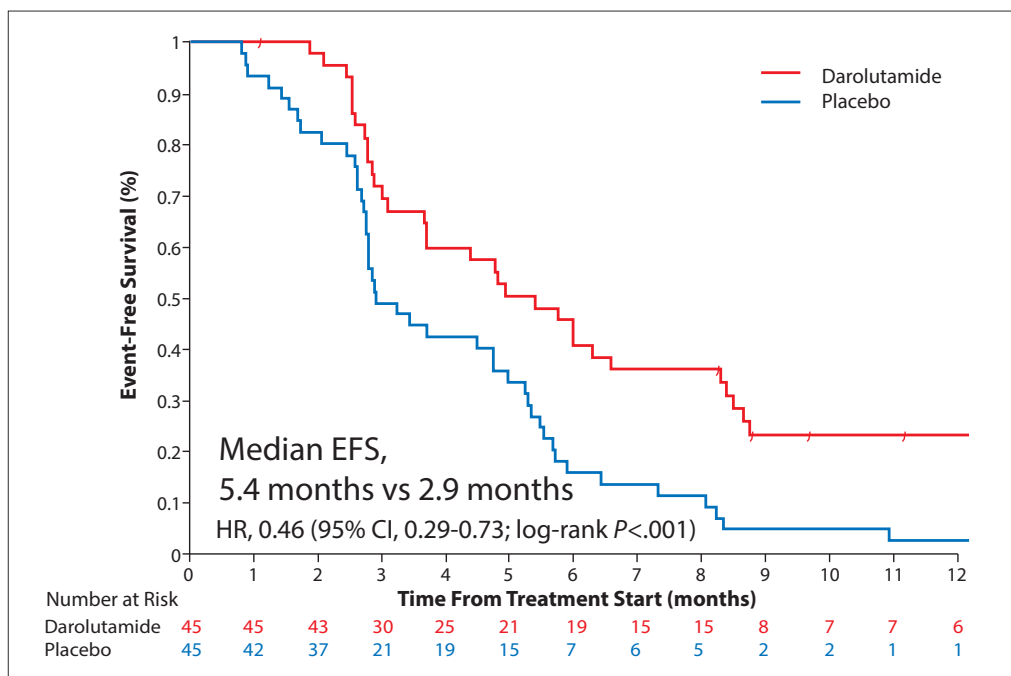
taxane dose. The primary endpoint was radiographic progression-free survival (rPFS) at 12 weeks after initiation of treatment. The baseline characteristics for the 90 evaluable patients were well balanced between the arms. The patients' median age was 71 years. Prior novel hormonal agents included abiraterone acetate in 60%, enzalutamide in 31%, and both in 9%; 26% of patients had a response to their novel hormonal agent.

The trial met its primary endpoint. At week 12, rPFS was 64.7% (95% CI, 47.6%-77.5%) with darolutamide vs 52.2% with placebo (95% CI, 36.1%-66.1%).<sup>2</sup> The median rPFS was 5.5 months vs 4.5 months, respectively (HR, 0.54; 95% CI, 0.32-0.91; log-rank  $P=.017$ ; Figure 2). Dr Cathomas noted that the improvement was statistically significant but clinically modest. The median event-free survival was 5.4 months with darolutamide vs 2.9 months with placebo (HR, 0.46; 95% CI, 0.29-0.73; log-rank  $P<.001$ ; Figure 3). The median overall survival

**Figure 2.** Radiographic progression-free survival in the SAKK 08/16 study, a double-blind, placebo-controlled, proof-of-concept phase 2 trial that evaluated darolutamide as maintenance therapy in patients with mCRPC previously treated with a novel hormonal agent. HR, hazard ratio; mCRPC, metastatic castration-resistant prostate cancer; rPFS, radiographic progression-free survival. Adapted from Cathomas R et al. ESMO abstract LBA26. *Ann Oncol.* 2021;32(suppl 5).<sup>2</sup>



**Figure 3.** Event-free survival in the SAKK 08/16 study, a double-blind, placebo-controlled, proof-of-concept phase 2 trial that evaluated darolutamide as maintenance therapy in patients with mCRPC previously treated with a novel hormonal agent. EFS, event-free survival; HR, hazard ratio; mCRPC, metastatic castration-resistant prostate cancer. Adapted from Cathomas R et al. ESMO abstract LBA26. *Ann Oncol.* 2021;32(suppl 5).<sup>2</sup>



(OS) was 24.0 months vs 21.3 months, respectively, a difference that did not reach statistical significance ( $P=.18$ ).

PSA response rates were higher with darolutamide vs placebo. A PSA response of 30% was reported in 31% of the darolutamide arm vs 9% of the placebo arm. A PSA response of 50%

was reported in 22% vs 4%, respectively. A PSA response of 90% was seen in 2% vs 0%. The median duration of a 50% decrease in PSA was 7.7 months with darolutamide vs 2.8 months with placebo.

Subgroup analyses suggested that the benefit of darolutamide may vary

based on the patient's response to the previous new hormonal agent.<sup>2</sup> The 29 patients with a complete or partial response to a previous novel hormonal agent appeared to have a greater rPFS and OS benefit with darolutamide vs placebo. This benefit was not observed among the 61 patients in whom the



prior novel hormonal agent led to stable or progressive disease.

Treatment with maintenance darolutamide appeared to be well tolerated. Grades 1, 2, and 3 treatment-related adverse events (TRAEs) were reported in 26%, 13%, and 2%, of patients, respectively. Rates in the placebo arm were 22%, 15%, and 2%, respectively. Fatigue was reported in 11% of the darolutamide arm vs 20% of the placebo arm. The most common TRAE reported with darolutamide

was bone pain and arthralgia, which occurred in 13% of patients (vs 2% in the placebo arm).

In summary, this proof-of-concept study met its primary endpoint, demonstrating an improvement in rPFS with maintenance darolutamide. Darolutamide had a favorable toxicity profile. Dr Cathomas noted that findings from the subgroup analysis—which identified an association between a patient's response to a prior new hormonal agent and benefit from

maintenance darolutamide—may help inform the design of a phase 3 trial.

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## Cabozantinib in Combination With Atezolizumab in Patients With Metastatic Castration-Resistant Prostate Cancer: Results of Expanded Cohort 6 of the COSMIC-021 Study

**C**abozantinib is a multitargeted tyrosine kinase inhibitor (TKI) that is approved by the FDA for use in certain patients with advanced renal cell carcinoma, hepatocellular carcinoma, and locally advanced or metastatic differentiated thyroid cancer.<sup>1</sup> Biomarker analyses and preclinical studies have suggested that cabozantinib activates the immune system,<sup>2,3</sup> providing a rationale for combination with immune checkpoint inhibitors.

The phase 1b COSMIC-021 study is evaluating cabozantinib in combination with atezolizumab, an antibody that binds to programmed death ligand 1 (PD-L1), in patients with various solid tumors.<sup>4</sup> Cohort 6 focuses on patients with mCRPC who developed radiographic progression after enzalutamide and/or abiraterone acetate. The patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, and they had not received prior chemotherapy, except for docetaxel for metastatic castration-sensitive prostate cancer. Patients received cabozantinib orally at 40 mg/day plus atezolizumab intravenously at 1200 mg every 3 weeks.

The primary endpoint of the COSMIC-021 study was investigator-

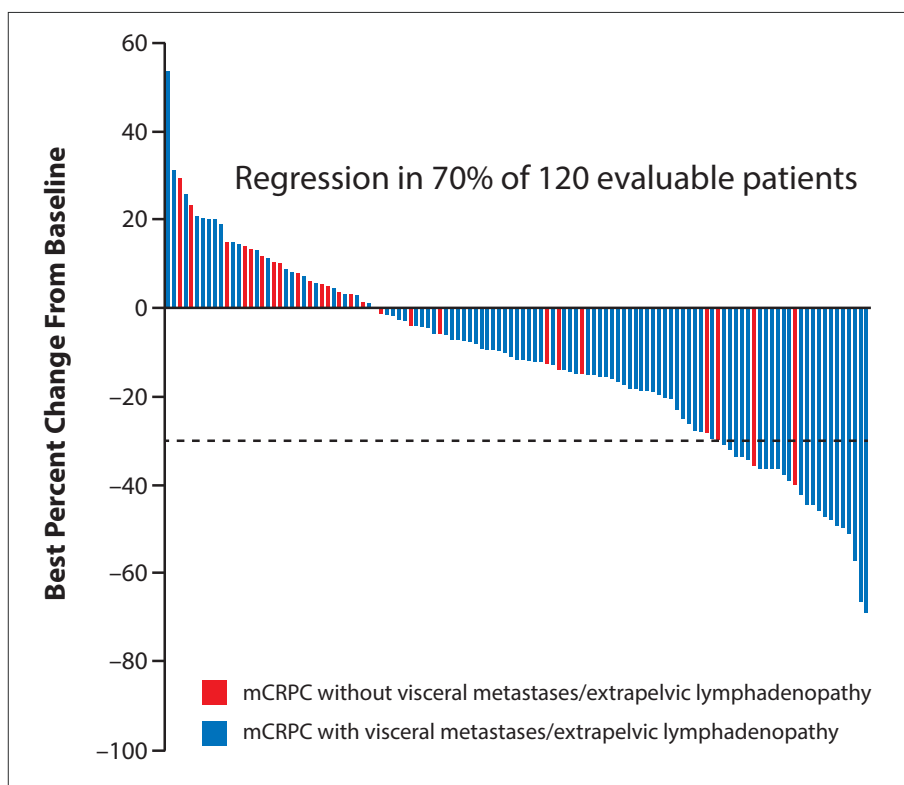
assessed objective response rate (ORR) per the Response Evaluation Criteria in Solid Tumors v1.1. Secondary and exploratory endpoints included safety, progression-free survival (PFS), OS, and biomarker analysis. The subset of patients with visceral metastases or extrapelvic lymphadenopathy was noted as a key subgroup.

In an early analysis of this cohort, presented in 2020, cabozantinib in combination with atezolizumab demonstrated encouraging activity and a manageable toxicity profile, including in patients with visceral metastases and/or extrapelvic lymphadenopathy.<sup>4</sup> At the 2021 ESMO congress, Neeraj Agarwal, MD, reported updated findings for 132 enrolled patients, with a median follow-up of 15.2 months.<sup>5</sup> The patients' median age was 70 years (range, 49-90). The Gleason score at diagnosis was 8 or higher in 63%, 41% had undergone a prior prostatectomy, and 25% had received docetaxel for metastatic castration-sensitive prostate cancer. Visceral metastases were present in 32% of patients, and extrapelvic lymphadenopathy was reported in 60%. Metastatic sites included the lymph nodes (80%), bone (54%), lungs (19%), and liver (13%).

Treatment with cabozantinib plus atezolizumab led to an investigator-assessed ORR of 23% (including complete responses in 2%) and stable disease in 61%, for a disease control rate of 84%.<sup>5</sup> Among the 101 patients with visceral metastases or extrapelvic lymphadenopathy, the investigator-assessed ORR was 27%, which included a complete response rate of 2%. Stable disease was reported in 61%. The disease control rate was therefore 88%. The regimen therefore appears to be active in this subgroup of patients with a poor prognosis. The median duration of response was 6.9 months in patients with and without visceral metastases or extrapelvic lymphadenopathy. The median time to response was 1.7 months in both sets of patients.

The blinded independent review committee reported ORR rates of 15% to 18%.<sup>5</sup> PD-L1 status was known for 75 patients and did not correspond to response. The median PFS was 5.5 months per investigator assessment and 5.7 months per assessment by the independent review committee. The median OS was 18.4 months. Reductions in PSA were observed in 47% of evaluable patients (55 of 118); the PSA

**Figure 4.** Best change from baseline in the sum of target lesions per a blinded independent review committee among patients with mCRPC in the phase 1b COSMIC-021 study, which evaluated cabozantinib in combination with atezolizumab in patients with solid tumors. mCRPC, metastatic castration-resistant prostate cancer. Adapted from Agarwal N et al. ESMO abstract LBA24. *Ann Oncol.* 2021;32(suppl 5).<sup>5</sup>



reduction was 50% or higher in 23% of patients. Similar rates of PSA reductions were reported for patients with visceral metastases and/or extrapelvic lymphadenopathy. Analyses of best change from baseline in the sum of the target lesions showed regression in 77% of 128 evaluable patients according to investigator review and in 70% of 120 evaluable patients according to independent review (Figure 4).

The median duration of treatment was 5.7 months (range, 0.4-27 months). Adverse events (AEs) led to dose reductions in 43% of patients and dose delays in 43%. Disease progression was the most common reason for discontinuation of study treatment, and reported in 45% of patients. Discontinuations owing to TRAEs were attributed to cabozantinib and/or atezolizumab in 21% of patients, cabozantinib in 18%, atezolizumab in 14%, and both in 10%.

Dr Agarwal noted that the safety profile was manageable and consistent with prior reports.<sup>5</sup> The most common

TRAEs of any grade included diarrhea (55%), fatigue (43%), nausea (42%), decreased appetite (34%), dysgeusia (27%), palmar-plantar erythrodysesthesia (25%), vomiting (23%), weight loss (23%), and aspartate aminotransferase elevation (20%). The most common grade 3/4 TRAEs included pulmonary embolism (8.3%), diarrhea (6.8%), fatigue (6.8%), and hypertension (6.8%). Grade 4 TRAEs were infrequent, occurring in 3% of patients. The single grade 5 event was dehydration in a 90-year-old patient. Potential immune-related AEs were reported in 66% of patients; these events were grade 3/4 in 20%. Corticosteroids were needed to treat AEs in 17% of patients.

The study investigators concluded that cabozantinib plus atezolizumab showed encouraging activity in patients with mCRPC, including in the subgroup of patients with visceral disease or distant lymph node metastasis. The phase 3 CONTACT-02 trial is evaluating cabozantinib plus atezolizumab vs

a second novel hormonal therapy in patients with mCRPC with visceral or extrapelvic lymph node metastasis after 1 prior novel hormonal therapy.<sup>6</sup>

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## Impact of Darolutamide on Local Symptoms in Patients With Nonmetastatic Castration-Resistant Prostate Cancer

In the phase 3 ARAMIS trial, the addition of darolutamide to ADT improved median metastasis-free survival.<sup>1</sup> At the 2021 meeting of the American Urological Association (AUA), Neal Shore, MD, presented an analysis of the ARAMIS trial that evaluated the relationships between PSA response and the following factors: urinary and bowel AEs, time to deterioration in quality of life, and prostate cancer–related invasive procedures with darolutamide vs placebo.<sup>2</sup> A prior prostatectomy was reported in 25.0% of the darolutamide arm and 24.2% of the placebo arm. Prior radiotherapy was reported in 18.5% vs 16.1% of patients, respectively.

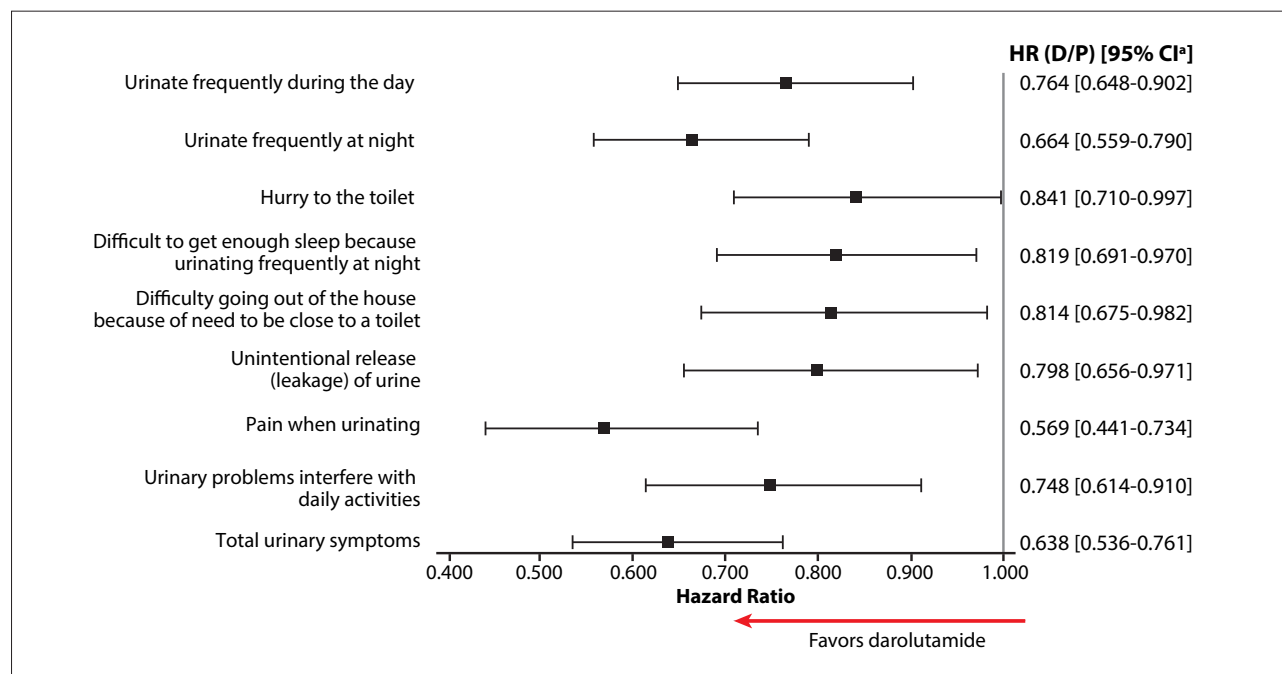
There were minimal differences with darolutamide vs placebo in the incidences of urinary tract infections

(5.3% vs 5.6%), abnormally frequent urination (4.4% vs 3.2%), and hematuria (4.5% vs 5.4%).<sup>2</sup> Rates were lower with darolutamide vs placebo for urinary retention (3.8% vs 7.4%) and dysuria (2.6% vs 5.2%). In the darolutamide arm, greater PSA responses appeared to be associated with lower rates of urinary retention and dysuria. These events were each reported in 5.1% of patients with a PSA response below 50%. Among patients with a PSA response between 50% to 90%, urinary retention occurred in 4.2% and dysuria occurred in 3.2%. Among those with a PSA response higher than 90%, they were reported in 2.2% and 0.5%, respectively.

Darolutamide was also associated with a significant delay vs placebo in the time to deterioration of quality

of life, defined as the first occurrence of a minimally important difference in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Prostate Cancer (EORTC QLQ-PR25) subscales of urinary symptoms (25.8 vs 14.8 months; HR, 0.64; 95% CI, 0.54-0.76;  $P < .01$ ; Figure 5) and bowel symptoms (18.4 vs 11.5 months; HR, 0.78; 95% CI, 0.66-0.92;  $P < .01$ ). The time to first occurrence of a 3-point or higher decline from baseline in the Functional Assessment of Cancer Therapy–Prostate, Prostate Cancer Subscale (FACT-P PCS) was also extended with darolutamide vs placebo (11.1 vs 7.9 months; HR, 0.80; 95% CI, 0.70-0.91;  $P = .0005$ ).

The need for locally invasive procedures differed between the treatment



**Figure 5.** Urinary symptoms reported by patients in an analysis of the phase 3 ARAMIS trial, which compared darolutamide plus ADT vs ADT alone in men with nmCRPC. Patients completed the EORTC QLQ-PR25. ADT, androgen deprivation therapy; EORTC QLQ-PR25, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Prostate Cancer; D, darolutamide; HR, hazard ratio; nmCRPC, nonmetastatic castration-resistant prostate cancer; P, placebo. \*Nominal 95% CIs are provided uncontrolled for multiple inferential analyses. Adapted from Shore N et al. AUA abstract PD34-10. *J Urol.* 2021;206(suppl 3).<sup>2</sup>

arms. An invasive procedure related to prostate cancer was required by 4.7% of the darolutamide arm vs 9.6% of the placebo arm. The time to first procedure was significantly delayed with darolutamide vs placebo (HR, 0.416; 95% CI, 0.279-0.620;  $P < .001$ ).

In summary, this analysis of local symptoms reported in the ARAMIS trial showed that darolutamide reduced local urinary and bowel symptoms, improved quality of life, and decreased requirements for locally invasive procedures among men with nmCRPC.

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## Abiraterone Acetate Plus Prednisolone With or Without Enzalutamide Added to Androgen Deprivation Therapy (ADT) Compared to ADT Alone for Men With High-Risk Nonmetastatic Prostate Cancer: Combined Analysis From Two Comparisons in the STAMPEDE Platform Protocol

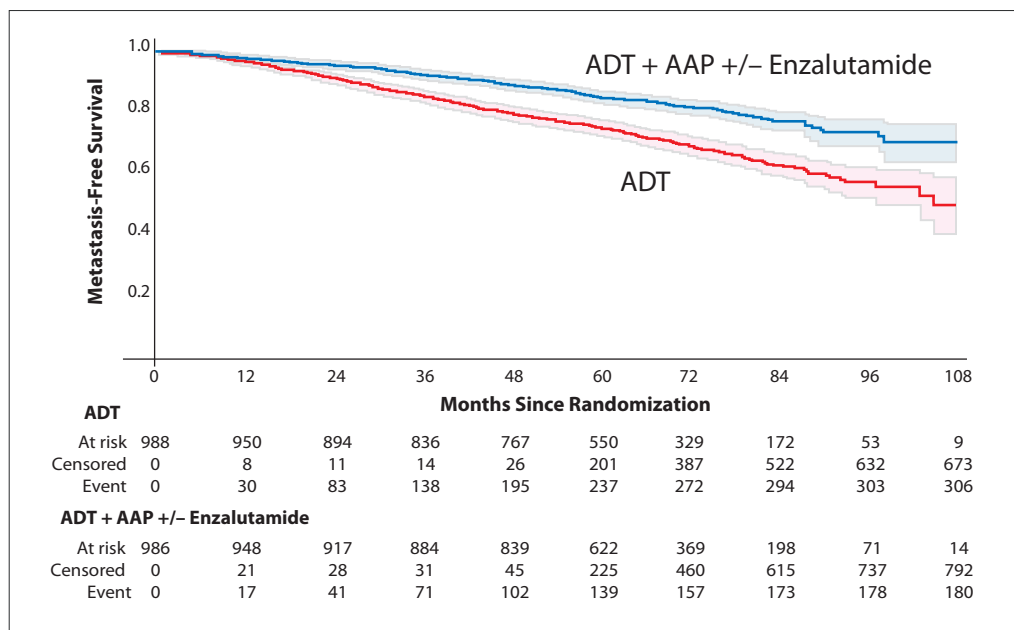
**A**mong patients with high-risk nonmetastatic prostate cancer, the current standard treatment of 3 years of ADT plus local radiotherapy is associated with high rates of post-treatment failure.<sup>1</sup> The randomized, open-label phase 2/3 STAMPEDE trial evaluated various approaches to the treatment of men with hormone-naïve prostate cancer. Although docetaxel has demonstrated a significant OS benefit in patients with M1 prostate cancer, it provided

no significant improvement in OS or metastasis-free survival in patients with M0 prostate cancer in the STAMPEDE trial or the GETUG-12 trial.<sup>2,3</sup> Similarly, the addition of abiraterone acetate, enzalutamide, or apalutamide to ADT improved outcomes among patients with M1 prostate cancer in the STAMPEDE study and other trials.<sup>4-8</sup> However, initial analyses indicated that there was no clear benefit seen with the addition of abiraterone acetate and prednisolone/prednisone

(AAP) to ADT in patients with M0 prostate cancer.

At the 2021 ESMO congress, Gerhardt Attard, MD, PhD, presented an analysis from the STAMPEDE trial that evaluated the benefit of adding AAP, with or without enzalutamide, to ADT in patients with high-risk M0 prostate cancer.<sup>9</sup> For newly diagnosed patients, high risk was defined as the presence of node-positive disease or at least 2 of the following criteria: stage T3 or T4, PSA of 40 ng/mL or

**Figure 6.** Metastasis-free survival in an analysis of the STAMPEDE trial, which evaluated the benefit of adding AAP, with or without enzalutamide, to ADT in patients with high-risk M0 prostate cancer. AAP, abiraterone acetate and prednisolone/prednisone; ADT, androgen deprivation therapy. Adapted from Attard et al. ESMO abstract LBA4 PR. *Ann Oncol.* 2021;32(suppl 5).<sup>9</sup>



higher, or a Gleason score of 8 to 10. Patients who relapsed after prior radical prostatectomy or radiation therapy were eligible for enrollment if they had node-positive disease, a PSA of 4 ng/mL or higher that was rising at a doubling time of less than 6 months, or a PSA of 20 ng/mL or higher. Patients received the standard of care plus 2 years of AAP with or without enzalutamide. Local radiotherapy was planned when appropriate.

The trial enrolled 1974 patients. Their median age was 68 years, their median PSA was 34 ng/mL, and 39% had N1 disease.<sup>9</sup> Only 3% of patients were experiencing relapsed disease after their prior treatment. Local radiotherapy was planned for 99% of newly diagnosed patients with N0 disease, 71% with N1 disease, and 7% of previously treated patients.

After a median follow-up of 72 months, the addition of AAP (with or without enzalutamide) to ADT was associated with a significant improvement in metastasis-free survival (HR, 0.53;  $P=2.9 \times 10^{-11}$ ; Figure 6) and OS (HR, 0.60;  $P=9.3 \times 10^{-7}$ ).<sup>9</sup> The 6-year

metastasis-free survival rate improved from 69% to 82% with the addition of AAP-based therapy, and the 6-year OS rate improved from 77% to 86%. Improvements were also reported for prostate cancer-specific survival (HR, 0.49;  $P=1.3 \times 10^{-6}$ ) and PFS (HR, 0.44;  $P=5.2 \times 10^{-15}$ ). Subgroup analyses showed no differences in the benefit of AAP according to baseline factors. A prespecified subgroup analysis by randomization period showed no difference in treatment effect with AAP alone vs AAP with enzalutamide.

The addition of enzalutamide to AAP was associated with increased toxicity, including higher rates of grade 3 erectile dysfunction, hypertension, fatigue, and grade 3/4 transaminitis. The investigators concluded that AAP-based therapy should be considered a new standard of care for patients with high-risk M0 prostate cancer who are initiating treatment with ADT.

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## Time Course Profile of Adverse Events of Interest and Serious Adverse Events With Darolutamide in the ARAMIS Trial

**T**reatment-related toxicity is a significant concern for patients with nmCRPC, who are often asymptomatic. These patients may be treated with long-term androgen receptor inhibitor therapy, which can lead to significant toxicities that affect quality of life, including fatigue, falls, fractures, hypertension, mental impairment, and rash.<sup>1,2</sup> In the pivotal phase 3 ARAMIS trial, darolutamide was associated with a low incidence of AEs, with rates similar to placebo.<sup>3,4</sup> The only AE occurring in more than 10% of patients receiving darolutamide was fatigue, reported in 13.2%

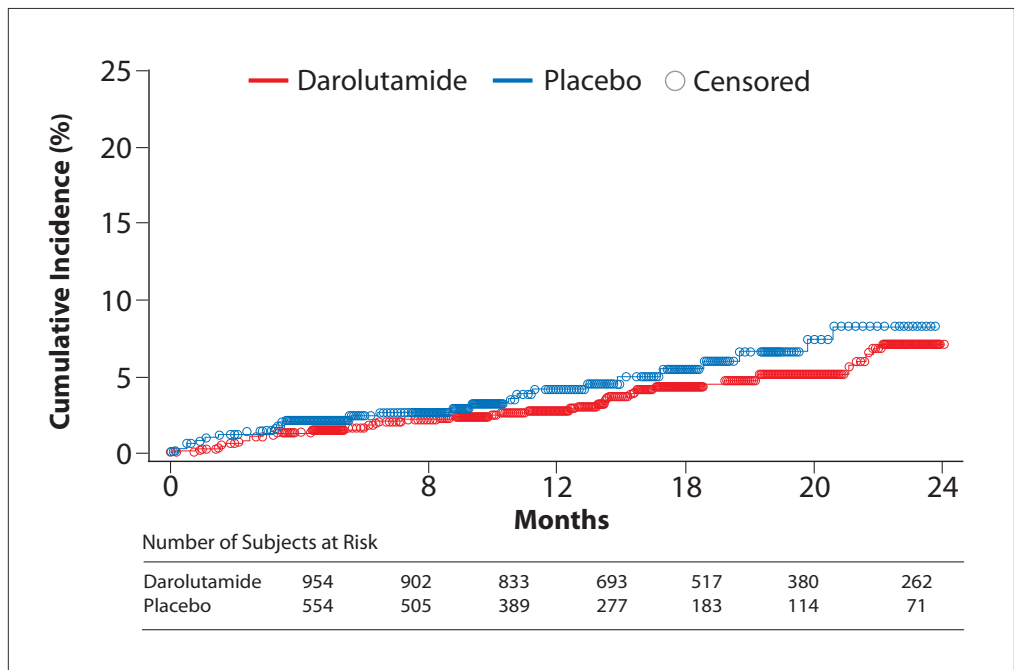
of patients vs 8.3% for placebo.

To gain further understanding regarding the timing of AEs associated with darolutamide, Christian Gratzke, MD, and colleagues conducted an analysis of the ARAMIS trial that focused on the time intervals in which AEs arose.<sup>5</sup> Throughout the first 24 months of the double-blind treatment period, fatigue was the only AE with an incidence that was more than 2% higher with darolutamide than placebo (12.6% vs 8.3%). Darolutamide and placebo were associated with similar rates of other AEs, including hypertension (7.3% vs 6.3%), falls (4.8% vs

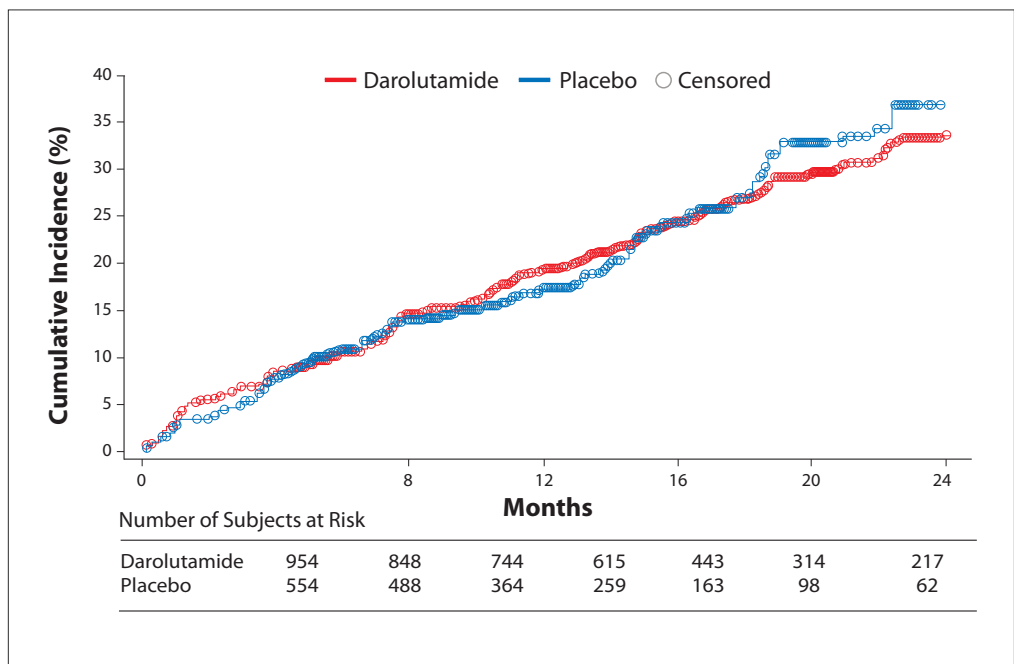
4.7%), fractures (4.6% vs 3.4%), rash (2.9% vs 1.1%), and mental impairment (1.8% in each arm).

Fatigue tended to develop early during treatment in both arms. Cases of fatigue occurred during the first month of treatment in 5.9% of patients in the darolutamide arm vs 4.0% of those in the placebo arm. Conversely, falls and fractures most often occurred after the first month of treatment in both arms (Figure 7). Development of new-onset hypertension did not correspond to a specific time interval. Rash most often occurred during the first 4 months of treatment and was usually grade 1 or 2.

**Figure 7.** The cumulative incidence of falls in the ARAMIS trial of darolutamide plus ADT vs ADT alone in men with nmCRPC. Data are shown for the preferred terms “fall” and “accidents.” Falls most often occurred after the first month of treatment. ADT, androgen deprivation therapy; nmCRPC, nonmetastatic castration-resistant prostate cancer. Adapted from Gratzke C et al. ESMO abstract 630P. *Ann Oncol.* 2021;32(suppl 5).<sup>5</sup>



**Figure 8.** Grade 3/4 adverse events in the ARAMIS trial, which compared darolutamide plus ADT vs ADT alone in men with nmCRPC. Falls most often occurred after the first month of treatment. ADT, androgen deprivation therapy; nmCRPC, nonmetastatic castration-resistant prostate cancer. Adapted from Gratzke C et al. ESMO abstract 630P. *Ann Oncol.* 2021;32(suppl 5).<sup>5</sup>



The rates of initial onset and cumulative incidence of grade 3/4 toxicities were similar between the arms (Figure 8). Investigators concluded that the analysis confirmed the safety profile of darolutamide, showing a similar time of onset and cumulative incidence as placebo for most AEs.

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## Biomarker Analysis of Men With Enzalutamide-Resistant Metastatic Castration-Resistant Prostate Cancer Treated With Pembrolizumab + Enzalutamide in KEYNOTE-199

**K**EYNOTE-199 was a 5-cohort open-label phase 2 trial that evaluated the antitumor activity and safety of pembrolizumab in patients with mCRPC.<sup>1</sup> Cohorts 1 through 3 focused on patients previously treated with chemotherapy, whereas cohorts 4 and 5 enrolled chemotherapy-naïve patients who developed progressive disease after an initial response to enzalutamide. Patients in cohort 4 (n=81) had measurable disease. Patients in cohort 5 (n=45) had bone-predominant disease. Patients in cohorts 4 and 5 received pembrolizumab at 200 mg every 3 weeks, plus continuation of enzalutamide, for up to 2 years or until progression,

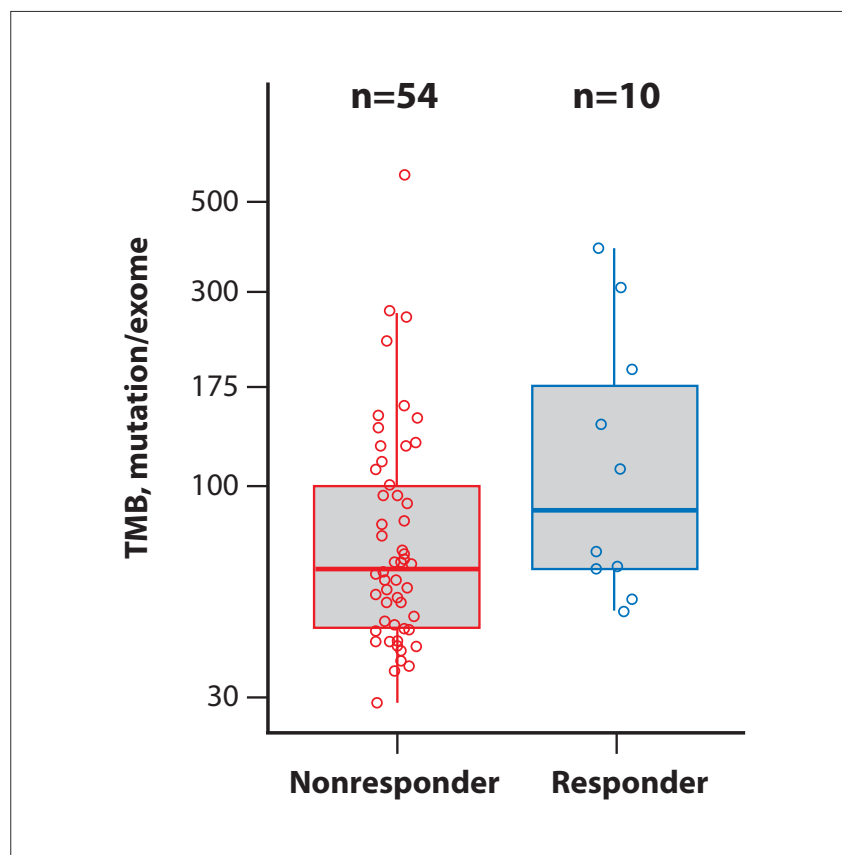
toxicity, or withdrawal. Key endpoints included ORR, duration of response, time to PSA progression, rPFS, OS, and safety.<sup>2</sup>

Results from cohorts 4 and 5 were previously reported. Pembrolizumab demonstrated an ORR of 12% in cohort 4, with a median duration of response of 6 months.<sup>2</sup> The disease control rate in cohorts 4 and 5 was 51%, and the PSA response rate was 14%.<sup>2</sup>

At the 2021 ESMO congress, Julie Graff, MD, presented results from a biomarker analysis of cohorts 4 and 5 from the KEYNOTE-199.<sup>3</sup> Assessments included tumor mutational burden as measured by whole exome

sequencing (n=64), the PD-L1 combined positive score by immunohistochemistry (n=124), and an 18-gene T-cell-inflamed gene expression profile (n=51). Researchers investigated associations between these biomarkers and clinical outcomes, including ORR in cohort 4 only and disease control rate ( $\geq 6$  months), PSA response, PFS, PSA progression, and OS in cohorts 4 and 5.

The analyses identified potential trends toward a positive association between responses to pembrolizumab and tumor mutational burden (Figure 9), with potential correlations noted for ORR, disease control rate, disease control rate of at least 6 months, and



**Figure 9.** A biomarker analysis of men with enzalutamide-resistant mCRPC treated with pembrolizumab plus enzalutamide in the KEYNOTE-199 trial showed a positive association between responses to pembrolizumab and tumor mutational burden. mCRPC, metastatic castration-resistant prostate cancer; TMB, tumor mutational burden. Adapted from Graff JN et al. ESMO abstract 61MO. *Ann Oncol.* 2021;32(suppl 5).<sup>3</sup>

PSA response, as well as time-to-event outcomes (PFS, PSA progression, and OS).<sup>3</sup> No associations were noted for the PD-L1 combined positive score or T-cell-inflamed gene expression profile. Dr Graff noted that this study was an exploratory analysis with small

sample sizes, and therefore results should be interpreted with caution.

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## Health-Related Quality of Life, Pain, and Safety Outcomes in the Phase III VISION Study of <sup>177</sup>Lu-PSMA-617 in Patients With Metastatic Castration-Resistant Prostate Cancer

**L**utetium-177 (<sup>177</sup>Lu)-PSMA-617 is a radioligand therapy that delivers beta-particle radiation in a targeted manner to cells that express the prostate-specific membrane antigen (PSMA) and to the microenvironment. The international, open-label phase 3 VISION trial evaluated the addition of <sup>177</sup>Lu-PSMA-617 to standard of care in men with PSMA-positive, previously treated mCRPC.<sup>1</sup> The patients had received previous treatment with at least 1 androgen receptor pathway inhibitor and 1 or 2

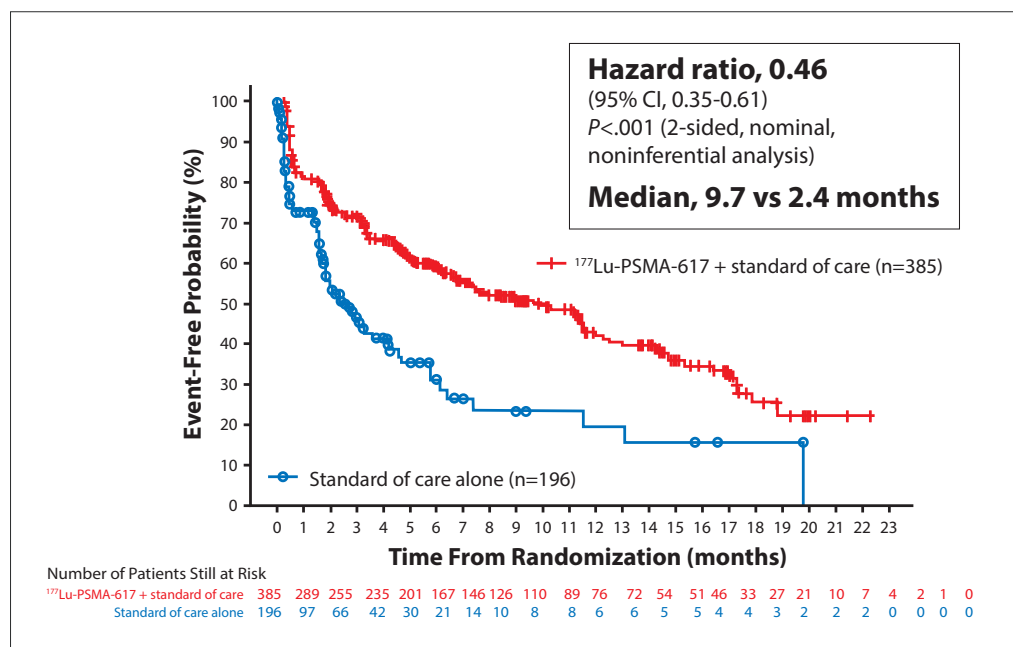
taxane regimens. Protocol-permitted standard of care, as selected by the investigator, was planned before randomization and excluded chemotherapy, immunotherapy, radium-223, and investigational drugs. An ECOG performance status of 0 to 2 was required for enrollment, as was adequate organ and bone marrow function. Patients were randomly assigned 2:1 to <sup>177</sup>Lu-PSMA-617 plus standard of care or standard of care alone.

The study met the primary endpoints of rPFS and OS. The addition

of <sup>177</sup>Lu-PSMA-617 to the standard of care significantly improved the median rPFS (8.7 vs 3.4 months; HR, 0.40; 99.2% CI, 0.29-0.57;  $P < .001$ ) and the median OS (15.3 vs 11.3 months; HR, 0.62; 95% CI, 0.52-0.74;  $P < .001$ ).<sup>1</sup>

At the 2021 ESMO congress, Karim Fizazi, MD, PhD, presented additional secondary outcomes from the VISION trial, including health-related quality of life, pain, and safety.<sup>2</sup> Health-related quality of life was assessed with the FACT-P questionnaire. Pain was assessed using the Brief

**Figure 10.** Time to worsening of health-related quality of life among patients in the rPFS analysis set of the VISION trial, which evaluated the addition of <sup>177</sup>Lu-PSMA-617 to standard of care in men with PSMA-positive, previously treated metastatic castration-resistant prostate cancer. PSMA, prostate-specific membrane antigen; rPFS, radiographic progression-free survival. Adapted from Fizazi K et al. ESMO abstract 576MO. *Ann Oncol*. 2021;32(suppl 5).<sup>2</sup>





Pain Inventory–Short Form.

The analyses revealed significant improvements with  $^{177}\text{Lu}$ -PSMA-617 plus standard of care vs standard of care alone in the median time to worsening of health-related quality of life (9.7 vs 2.4 months; HR, 0.46; 95% CI, 0.35-0.61;  $P < .001$ ; Figure 10) and the median time to worsening of pain (14.3 vs 2.9 months; HR, 0.45; 95% CI, 0.33-0.60;  $P < .001$ ).<sup>2</sup> The median time to first symptomatic skeletal event was also significantly longer with  $^{177}\text{Lu}$ -PSMA-617 plus standard of care vs standard of care alone (11.5 vs 6.8

months; HR, 0.50; 95% CI, 0.40-0.62;  $P < .001$ ).

The most common treatment-emergent AE was fatigue, reported in 49.1% of patients in the  $^{177}\text{Lu}$ -PSMA-617 arm vs 29.3% in the control arm. Grade 3 or higher bone marrow suppression occurred in 23.4% vs 6.8% of patients, respectively. The most common hematologic AE was anemia, which was reported in 31.8% and 13.2% of patients, respectively. The incidence of dry mouth was 39.3% in the  $^{177}\text{Lu}$ -PSMA-617 arm and 1.0% in the control arm. Nausea

and vomiting occurred in 39.3% and 17.1% of patients, respectively, and renal events occurred in 8.7% and 5.9% of patients.

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## Final Overall Survival Analysis From ARCHES: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Enzalutamide Plus Androgen Deprivation Therapy in Men With Metastatic Hormone-Sensitive Prostate Cancer

For men with metastatic hormone-sensitive prostate cancer (also known as castration-sensitive prostate cancer), recommended therapeutic options include ADT with either an androgen pathway inhibitor (eg, abiraterone acetate, apalutamide, or enzalutamide) or docetaxel.<sup>1</sup> For patients who have de novo low-volume disease, external beam radiation therapy to the primary tumor is also recommended.

The FDA approved the combination of enzalutamide plus ADT for patients with metastatic hormone-sensitive prostate cancer based on results of the phase 3 ARCHES trial. This study demonstrated a significant improvement in outcomes with the addition of enzalutamide to ADT.<sup>2</sup> The ARCHES trial enrolled 1150 men with metastatic hormone-sensitive prostate cancer with an ECOG performance status of 0 to 1. Upon enrollment, the patients' current duration of ADT in the metastatic setting was 3 months or less; the duration could reach 6 months in patients who had

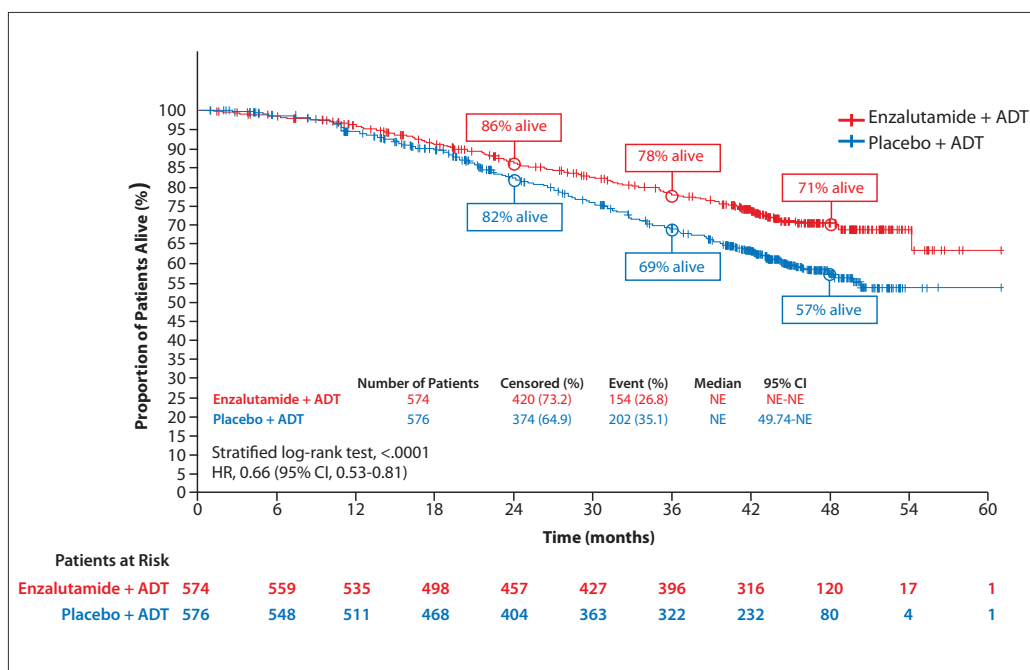
received prior docetaxel. The patients were stratified based on the volume of disease and the duration of any prior docetaxel therapy. They were randomly assigned to receive enzalutamide at 160 mg/day plus ADT (n=574) or placebo plus ADT (n=576). Discontinuation criteria included radiographic progression, unacceptable toxicity, or initiation of a new or investigational therapy for prostate cancer.

In the primary analysis, the addition of enzalutamide to ADT was associated with a significant improvement in the primary endpoint of rPFS (HR, 0.39;  $P < .001$ ), along with reductions in the risk of PSA progression, initiation of new therapy, first symptomatic skeletal event, castration resistance, and pain progression.<sup>2</sup> The patients' baseline quality of life was high and maintained over time. The addition of enzalutamide was well tolerated. Grade 3 or higher AEs occurred in 24.3% of the enzalutamide arm vs 25.6% of the placebo arm. Based on the demonstrated benefit of enzalutamide, the trial was unblinded to allow patients

in the placebo arm to cross over to receive enzalutamide plus ADT as part of an ongoing open-label extension trial. Overall, 184 patients in the placebo arm (31.9%) gave consent to cross over, and 180 patients (31.3%) received treatment with enzalutamide plus ADT. The median time to cross-over was 21.5 months.

At the time of the primary analysis of the ARCHES trial, the OS data were immature. At the 2021 ESMO congress, Andrew Armstrong, MD, MSc, presented updated results from ARCHES, including the final prespecified analyses of OS, time to subsequent therapy, and safety data.<sup>3</sup> The baseline characteristics were well balanced between the 2 arms. The patients' median age was 70 years, and 77% had an ECOG performance status of 0.<sup>2</sup> Patients in the placebo crossover group tended to have more favorable characteristics. Their rate of high-volume disease was 50%, vs 64.8% in the overall placebo arm and 61.7% in the enzalutamide arm. Distant metastases at diagnosis were

**Figure 11.** Overall survival in the final analysis of the randomized phase 3 ARCHES trial, which compared enzalutamide plus ADT vs ADT alone in men with metastatic hormone-sensitive prostate cancer. ADT, androgen deprivation therapy; HR, hazard ratio; NE, not evaluable. Adapted from Armstrong AJ et al. ESMO abstract LBA25. *Ann Oncol.* 2021;32(suppl 5).<sup>3</sup>



reported in 58.3% of the crossover arm, 63.4% of the placebo arm, and 70.0% of the enzalutamide arm.

After a median follow-up of 44.6 months, the addition of enzalutamide to ADT was associated with a significant improvement in OS (HR, 0.66; 95% CI, 0.53-0.81;  $P<.0001$ ; Figure 11).<sup>3</sup> The median OS was not reached in either arm. The rates of 4-year OS were 71% with enzalutamide plus ADT vs 57% with ADT alone. Subgroup analyses showed a consistent benefit with enzalutamide based on age, geographic region, ECOG performance status, Gleason score, disease localization, baseline PSA, and disease volume. There was no significant difference in OS between the treatment arms among the 18% of patients who had received prior docetaxel or the 11% of patients with visceral metastases.

The time to next antineoplastic therapy was not reached with enzalutamide vs 40.54 months with placebo (HR, 0.38; 95% CI, 0.31-0.48). Subsequent therapies included docetaxel, enzalutamide, and abiraterone acetate. Including the crossover group, 70% of patients in the placebo arm received

some type of life-extending therapy after the study treatment and 42% received enzalutamide plus ADT.

Safety findings were consistent with previous reports. Rates of some TRAEs were higher in the enzalutamide arm. However, the investigators noted that this increase should be considered in the context of the substantially longer treatment duration in the enzalutamide arm of 40.2 months, compared with 13.8 months in the placebo arm and 23.9 months in the crossover arm. Key TRAEs included musculoskeletal events (39.0% with enzalutamide plus ADT vs 29.8% with placebo plus ADT), fatigue (32.2% vs 20.6%), hypertension (14.3% vs 6.8%), fractures (13.5% vs 5.4%), falls (10.1% vs 3.3%), cognitive/memory impairment (6.6% vs 2.6%), and hepatic disorder (5.9% vs 6.1%). The only grade 3/4 event reported in 5% or more of patients receiving enzalutamide plus ADT was hypertension (5.1%). Dr Armstrong noted that cardiovascular risks remained low, but the incidence was slightly increased at this later follow-up. Ischemic heart disease was reported in 4.5% of patients receiving

enzalutamide plus ADT vs 1.9% of patients receiving placebo plus ADT. Other cardiovascular events occurred in 4.4% vs 1.7%, respectively.

In summary, this extended analysis confirmed the benefit of adding enzalutamide to ADT in men with metastatic hormone-sensitive prostate cancer, showing a long-term survival benefit that was maintained across many subgroups, and a delay in the need for subsequent therapies. Dr Armstrong concluded that additional follow-up was needed to assess the benefit of enzalutamide in men treated with docetaxel and in those with visceral metastases.

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## Highlights in Prostate Cancer From the 2021 European Society for Medical Oncology Congress and the 2021 American Urological Association Meeting: Commentary

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Several studies presented at the 2021 European Society for Medical Oncology (ESMO) congress and the 2021 American Urological Association (AUA) meeting provided important insights into the management of patients with prostate cancer. Studies provided new data for darolutamide, abiraterone acetate, cabozantinib plus atezolizumab, enzalutamide plus androgen deprivation therapy (ADT), <sup>177</sup>Lu-PSMA-617, and pembrolizumab combinations.

### Darolutamide

At the ESMO meeting, Dr Emeline Colomba and colleagues presented an

analysis of the phase 2 ODENZA trial that focused on objective computerized cognitive assessment.<sup>1</sup> Darolutamide and enzalutamide are androgen receptor (AR) antagonists that are approved by the US Food and Drug Administration (FDA) for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC). The ODENZA trial compared patient preferences for darolutamide or enzalutamide in the setting of metastatic castration-resistant prostate cancer (mCRPC).<sup>2</sup> The analysis by Dr Colomba evaluated the potential differential impact of darolutamide vs enzalutamide on cognitive function, the rationale being

that darolutamide has very minimal penetration of the central nervous system (CNS). In murine studies, the CNS concentrations are approximately 3% of plasma concentrations.<sup>3</sup> Patients enrolled in the ODENZA trial took defined cognitive tests every 12 weeks. As expected, there was a meaningful reduction in cognitive impairment with darolutamide as compared with enzalutamide. The improvement was especially apparent in episodic memory recall, for both the acquisition of new information and the recall of information after a brief delay.

At the ESMO meeting, Dr Richard Cathomas and colleagues presented results from a double-blind, placebo-controlled phase 2 trial that evaluated darolutamide maintenance in men with mCRPC.<sup>4</sup> The trial enrolled patients who had received a taxane, discontinued it, and had nonprogressive disease. The patients had also received another AR targeting agent prior to study entry. The patients were randomly assigned to darolutamide or placebo to evaluate disease progression. At least some of the agents that target the AR are known to be less effective as second-line therapy compared with first-line therapy. For example, in the mCRPC setting, enzalutamide leads to prostate-specific antigen (PSA) responses rates of approximately 30% to 35% when administered after abiraterone acetate vs close to 90% when given as first-line

### ABSTRACT SUMMARY Masitinib Plus Docetaxel as First-Line Treatment of Metastatic Castrate-Refractory Prostate Cancer: Results From Study AB12003

Masitinib is a TKI that targets mast cells and macrophage activity. The randomized, double-blind, placebo-controlled phase 3 AB12003 trial is evaluating masitinib (6.0 mg/kg/day) plus docetaxel as first-line therapy in patients with chemotherapy-naïve mCRPC. The trial enrolled 714 patients who developed progressive disease during prior treatment with abiraterone acetate or who had an indication to start docetaxel. Michel Pavic, MD, PhD, presented results at the 2021 AUA meeting (Abstract LBA02-11). There was a significant PFS benefit with masitinib plus docetaxel vs docetaxel plus placebo in the prespecified target subgroup of patients with baseline alkaline phosphatase levels of 250 IU/mL or lower (n=450). The median PFS was 6.3 months with masitinib plus docetaxel vs 5.4 months with docetaxel plus placebo (HR, 0.79; 95% CI, 0.64-0.97; *P*=.0087). OS was not significantly different between the arms. There were no significant PFS or OS differences in the overall population. Severe AEs were reported in 79.2% of the masitinib arm vs 73.1% of the control arm.

treatment.<sup>5</sup> When abiraterone acetate is administered after enzalutamide, the PSA response rates are less than 10%. The study by Dr Cathomas showed a modest impact of darolutamide on delaying progression,<sup>4</sup> which was not surprising. It is yet to be determined whether this difference will translate into a meaningful clinical benefit. It is uncertain whether this regimen will advance to a phase 3 study.

At the AUA meeting, Dr Neal Shore and colleagues presented a study evaluating the impact of darolutamide on local symptoms in patients with nmCRPC.<sup>6</sup> As expected, darolutamide reduced local symptoms, especially in patients who had a PSA response to treatment. Urinary retention was reported in 3.8% of the darolutamide arm vs 7.4% of the placebo arm. Dysuria occurred in 2.6% vs 5.2%, respectively. This finding supports the efficacy of darolutamide in the nmCRPC setting.

At the ESMO meeting, Dr Christian Gratzke and coworkers presented an analysis of the time course profile of adverse events among men enrolled in the randomized, double-blind,

placebo-controlled phase 3 ARAMIS trial of darolutamide in nmCRPC.<sup>7</sup> The results of the ARAMIS trial led to the FDA approval of darolutamide in these patients.<sup>8</sup> As previously published, the ARAMIS study showed a marked improvement in metastasis-free survival with the addition of darolutamide to ADT.<sup>8</sup> Remarkably, only 3 adverse events—fatigue, rash, and lower extremity pain—were at least 2% more frequent with darolutamide vs placebo. The analysis by Dr Gratzke focused on adverse events that are common with other AR inhibitors, as well as events related to darolutamide.<sup>7</sup> The study found no difference in the rates of falls and fractures, hypertension, or mental impairment for darolutamide vs placebo. The mental impairment reported with other AR inhibitors may be related to CNS penetration, which is expected to be minimal with darolutamide based on preclinical in vivo studies.<sup>3</sup> There was a small difference over time in the incidence of fatigue and rash in the darolutamide arm vs the placebo. The greatest difference in incidence was for fatigue. At 24 months during the double-blind

treatment period, fatigue occurred in 12.6% of the darolutamide arm vs 8.3% of the placebo arm. This analysis adds to the data showing that darolutamide has an outstanding adverse event and safety profile. Darolutamide may be a particularly good choice for patients who are at risk for falls and fractures, as well as those who might experience fatigue after treatment with ADT or other AR inhibitors.

### Abiraterone Acetate

Dr Gerhardt Attard and colleagues presented a combined analysis from 2 comparisons in the STAMPEDE trial at the ESMO meeting.<sup>9</sup> STAMPEDE is the largest controlled trial of patients with castration-sensitive prostate cancer. The study was initiated in 2005,<sup>10</sup> and it has made important contributions to the management of metastatic castration-sensitive prostate cancer and nonmetastatic high-risk castration-sensitive prostate cancer. The analysis by Dr Attard evaluated the role of abiraterone acetate plus prednisolone added to ADT in men with high-risk nonmetastatic prostate cancer or metastatic castration-sensitive prostate cancer.<sup>9</sup> The initial results, which were published in 2017, demonstrated a clear, unequivocal benefit for the addition of abiraterone acetate and prednisolone to ADT, but the improvement was largely restricted to patients with metastatic (M1) disease.<sup>11</sup> The current analysis had longer follow-up, plus more endpoints for statistical power. Importantly, the investigators made a prospective change in the protocol to allow for metastasis-free survival to be the primary endpoint for the nonmetastatic patients. This change was based on results from the ICECaP study, which demonstrated that metastasis-free survival is a good surrogate for overall survival in nonmetastatic patients.<sup>12</sup> Radiation was administered to most of the nonmetastatic patients as part of their initial management. The duration of abiraterone acetate and prednisolone when added to ADT

#### ABSTRACT SUMMARY Pembrolizumab Plus Olaparib in Patients With Docetaxel-Pretreated Metastatic Castration-Resistant Prostate Cancer: Updated Results From KEYNOTE-365 Cohort A With a Minimum of 11 Months of Follow-Up for All Patients

Cohort A of the phase 1/2 KEYNOTE-365 trial is evaluating pembrolizumab plus olaparib in molecularly unselected patients with mCRPC who received previous treatment with docetaxel and developed progressive disease within 6 months of screening. After a median follow-up of 3 months in 84 treated patients, pembrolizumab plus olaparib was associated with a PSA response rate of 9% and an ORR of 8%. The disease control rates were 21% in patients with measurable disease and 24% in those with unmeasurable disease (Yu EY et al. 2020 ASCO GU abstract 100. *J Clin Oncol.* 2020;38[6 suppl]). At the 2021 AUA meeting, Luke Nordquist, MD, presented an update after a median follow-up of 19.3 months (Abstract M24-14). In the 104 enrolled patients, 102 received treatment. The confirmed PSA response rate among 102 evaluable patients was 14.7%. Among the 58 patients with measurable disease, the confirmed ORR was 6.9%. The median rPFS was 5.2 months, and median OS was 14.4 months. The most frequent TRAEs were anemia (41.2%), nausea (41.2%), decreased appetite (30.4%), and fatigue (30.4%).

was 2 years, along with 3 years of ADT.

The analysis showed a significant improvement in metastasis-free survival when abiraterone acetate and prednisolone were added to ADT as compared with ADT alone.<sup>9</sup> There was also a marked improvement in overall survival. Given the magnitude of the effect, these results are practice-changing. There were 2 groups of patients treated with abiraterone acetate. The first group received abiraterone acetate plus prednisolone alone. This treatment was subsequently changed to include the addition of enzalutamide. The addition of enzalutamide to the abiraterone acetate arm did not have a meaningful impact on efficacy, but it did add toxicity. Similarly, the addition of enzalutamide to abiraterone acetate does not improve overall survival in the mCRPC setting.

The study population had very high-risk disease; patients typically had 2 of the following features: stage T3 or T4 disease, lymph-node positive disease, and a high Gleason score. The results, therefore, do not necessarily apply to all high-risk patients. It is important to be mindful of the inclusion criteria of this study when adding abiraterone acetate to ADT in patients with nonmetastatic castration-sensitive prostate cancer.

### Cabozantinib Plus Atezolizumab

The phase 1b COSMIC-021 study is evaluating the tyrosine kinase inhibitor cabozantinib plus the checkpoint inhibitor atezolizumab in patients with several types of solid tumors, including CRPC, renal cell carcinoma, and advanced urothelial carcinoma.<sup>13</sup> At the ESMO meeting, Dr Neeraj Agarwal and colleagues presented the results of expanded cohort 6, which enrolled 132 patients with mCRPC, including those with visceral metastases and/or extrapelvic lymphadenopathy.<sup>14</sup> Cabozantinib had previously been studied as a single agent in prostate cancer, but it did not improve outcomes.<sup>15</sup>

The combination of cabozantinib plus atezolizumab led to a reasonably high objective response rate of approximately 25% (as assessed by the investigators).<sup>14</sup> This benefit, along with the biochemical response rate, has led to the development and initiation of a phase 3 study.<sup>16</sup> If results of the phase 3 study are positive, mCRPC may gain another combination regimen that consists of 2 agents that are not used as monotherapies in this setting.

### Enzalutamide Plus ADT

At the ESMO meeting, Dr Andrew Armstrong and colleagues presented results from a final overall survival analysis of the randomized, double-blind, placebo-controlled phase 3 ARCHES trial, which evaluated the addition of enzalutamide to ADT in men with metastatic hormone-sensitive prostate cancer.<sup>17</sup> There are now 4 different therapies—docetaxel, abiraterone acetate plus prednisone, enzalutamide, and apalutamide—that improve overall survival in patients with metastatic castration-sensitive prostate cancer.<sup>18-21</sup> In the large phase 3 ENZAMET trial, enzalutamide improved overall survival in metastatic castration-sensitive prostate cancer.<sup>19</sup> Overall survival was the primary endpoint in the ENZAMET trial.<sup>19</sup> Interestingly, in the ARCHES trial, radiographic progression-free survival was the primary endpoint, and overall survival was a secondary endpoint.<sup>18</sup>

The final analysis of overall survival in the ARCHES trial showed an improvement with the addition of enzalutamide to ADT, with a hazard ratio that was similar to those for other drugs approved in this setting.<sup>17</sup> These agents all have a hazard ratio for overall survival of approximately 0.6 to 0.7.<sup>18-21</sup> In general, efficacy is similar for docetaxel, abiraterone acetate, enzalutamide, and apalutamide in patients with metastatic castration-sensitive prostate cancer. These agents do have different side effect profiles, contraindications, and drug-drug interactions.

In the United States, docetaxel is largely used in patients with high-volume disease, and abiraterone acetate is used in patients with high-risk disease (which is similar, but not identical, to high-volume disease). In contrast, enzalutamide and apalutamide have improved overall survival irrespective of tumor burden. This analysis of the ARCHES trial lends further support to the role of enzalutamide as a potential option to improve overall survival for patients with metastatic castration-sensitive prostate cancer.<sup>17</sup>

### <sup>177</sup>Lu-PSMA-617

At the ESMO meeting, Dr Karim Fizazi and coworkers presented an analysis of health-related quality of life, pain, and safety in the phase 3 VISION study, which evaluated the effect of <sup>177</sup>Lu-PSMA-617 on overall survival among patients with mCRPC who had received at least 1 androgen-receptor signaling inhibitor and docetaxel-based chemotherapy.<sup>22</sup> The results for the primary endpoints of overall survival and radiographic progression-free survival were previously published.<sup>23</sup> The trial compared the addition of <sup>177</sup>Lu-PSMA-617 to the protocol-permitted standard of care vs the standard of care alone. The standard of care excluded chemotherapy, immunotherapy, radium-223, and investigational drugs because of safety issues associated with combining these agents with <sup>177</sup>Lu-PSMA-617. Therefore, the control arm did not reflect the best available therapy.

The VISION study had key secondary endpoints related to safety and tolerability.<sup>22</sup> These endpoints included time to first skeletal-related event, health-related quality of life, and pain as measured by the FACT-P Brief Pain Inventory Short Form and EQ-5D-5L instruments. The analysis showed that patients in the prostate-specific membrane antigen (PSMA)-based radionuclide therapy arm had a significant improvement in these quality-of-life endpoints. <sup>177</sup>Lu-PSMA-617 delayed

the onset of the first symptomatic skeletal event and improved quality of life. This study adds to the data suggesting that  $^{177}\text{Lu}$ -PSMA-617 cannot only improve quantity of life, but also quality of life. This study will provide further support for the use of  $^{177}\text{Lu}$ -PSMA-617 after it is approved by the FDA, which is expected in the first half of 2022.

Dr Shahneen Sandhu and colleagues presented results from an interim analysis of the phase 1b PRINCE study, which evaluated  $^{177}\text{Lu}$ -PSMA-617 in combination with pembrolizumab in mCRPC, at the ESMO meeting.<sup>24</sup> The idea behind this study is that lutetium can serve as an immunomodulator by resulting in the immunogenic cell death of targeted cells, in this case prostate cancer cells. By inducing cell death,  $^{177}\text{Lu}$ -PSMA-617 can trigger the release of novel tumor antigens that are detectable to infiltrating T cells and thereby prime these infiltrating T cells to respond to an immunotherapy, such as the checkpoint inhibitor pembrolizumab. Utilization of pembrolizumab may therefore be particularly effective in this population. In addition, there is a clinical need for an agent that can be added to PSMA-based radionuclide therapy, which is administered for a

finite period of no more than 6 cycles. Typically, after a patient receives 6 cycles of therapy, he will develop disease progression after a relatively short duration. The addition of a drug like pembrolizumab, which could be continued beyond this time-frame, could in principle influence long-term outcomes by prolonging the duration of response.

This interim analysis did not detect any unexpected side effects of the combination.<sup>24</sup> There were some immune-related side effects, which are consistent with pembrolizumab, but not at a high frequency. The side effects of  $^{177}\text{Lu}$ -PSMA-617 were also similar to those observed in prior studies. These adverse events typically include fatigue, dry mouth, and gastrointestinal toxicities, such as nausea and vomiting, which are mostly grades 1 and 2. The PSA response rate was high, at more than 70%. In the phase 3 VISION study of  $^{177}\text{Lu}$ -PSMA-617 alone, the PSA response rate was 66%. It is therefore difficult to know whether the addition of pembrolizumab improved the impact of  $^{177}\text{Lu}$ -PSMA-617 on PSA. In addition, the follow-up was too short to assess the long-term impact of treatment. However, based on the strong rationale

behind the combination and the lack of unexpected safety signals, this treatment will likely advance to phase 2 or phase 3 studies.

### Pembrolizumab Combinations

At the AUA meeting, Dr Luke Nordquist and colleagues presented updated results from patients in cohort A of the KEYNOTE-365 study.<sup>25</sup> This study evaluated pembrolizumab in combination with several different agents in patients with mCRPC. The investigators presented the results of cohort A, which included patients previously treated with docetaxel who received pembrolizumab plus olaparib.<sup>26</sup> The analysis included patients with a minimum of 11 months of follow-up. Pembrolizumab was administered every 3 weeks. The primary endpoints were PSA response and objective response. The confirmed PSA response was very low, at 14.7%. The objective response rate in patients who had measurable disease was only 6.9%. Importantly, these patients were not selected based on next-generation sequencing, so they were not necessarily expected to respond to olaparib monotherapy, which is known to be effective for tumors with *BRCA2*, *BRCA1*, or *PALB2* mutations.<sup>27</sup> The results of this trial are disappointing. The combination of pembrolizumab and olaparib did not enhance response in this unselected population. Better patient selection would be needed for continued research of this regimen.

At the ESMO meeting, Dr Julie Graff and colleagues presented a biomarker analysis of cohorts 4 and 5 of the KEYNOTE-199 trial.<sup>28</sup> The analysis focused on men with enzalutamide-resistant mCRPC who received pembrolizumab plus enzalutamide. These patients had not yet received chemotherapy for mCRPC. They had an initial response to enzalutamide, but then developed progressive disease. They were receiving maintenance therapy with enzalutamide. Pembrolizumab was subsequently added to treatment.

#### ABSTRACT SUMMARY PRINCE: Interim Analysis of the Phase 1b Study of $^{177}\text{Lu}$ -PSMA-617 in Combination With Pembrolizumab for Metastatic Castration-Resistant Prostate Cancer

The phase 1b PRINCE trial is evaluating the safety and efficacy of  $^{177}\text{Lu}$ -PSMA-617 plus pembrolizumab in patients with mCRPC who have high expression of PSMA. At the 2021 ESMO congress, Shahneen Sandhu, MD, presented results for 37 patients (Abstract 5770). The median follow-up was 38 weeks. The median age of enrolled patients was 72 years; 73% had received prior docetaxel and 100% had received a prior androgen receptor-targeted agent. The combination was associated with a 50% PSA response rate of 73%. Partial responses were observed in 7 of 9 patients with measurable disease (78%). At 24 weeks, the rPFS rate was 64% and the PSA-PFS rate was 68%. The most common TRAEs included xerostomia (76%), fatigue (43%), nausea (24%), and rash (22%). Key hematologic TRAEs included grade 1/2 thrombocytopenia (14%) and grade 2/3 anemia (8%). Grade 3 immune-related events were reported in 10 patients (27%), and 4 patients (11%) discontinued treatment owing to toxicity.

There had been some early signals that the addition of enzalutamide to pembrolizumab would result in relatively high and deep PSA responses beyond those expected with pembrolizumab monotherapy.<sup>29</sup> In this study, the patients were not selected based on programmed death ligand 1 (PD-L1) status or tumor mutational burden. The goal was to determine if there were any biomarkers that could predict for outcome. The investigators evaluated tumor mutational burden, PD-L1 expression via immunohistochemistry, and an 18-gene, T cell-inflamed gene expression profile. The analysis found very little association between these factors and outcome. The only factor that was predictive of outcome was tumor mutational burden, which showed a modest prediction for disease control rate, but not for PSA response rate. There is much to learn about the combination of enzalutamide and pembrolizumab. The early signal that this combination might be effective may not persist as more patients are studied.

### Disclosure

Dr Rettig is a consultant for Amgen, Clovis, and Ambrx. He is a speaker for Janssen and Bayer. He has received research support from Novartis, Janssen, Exini, and Merck.

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