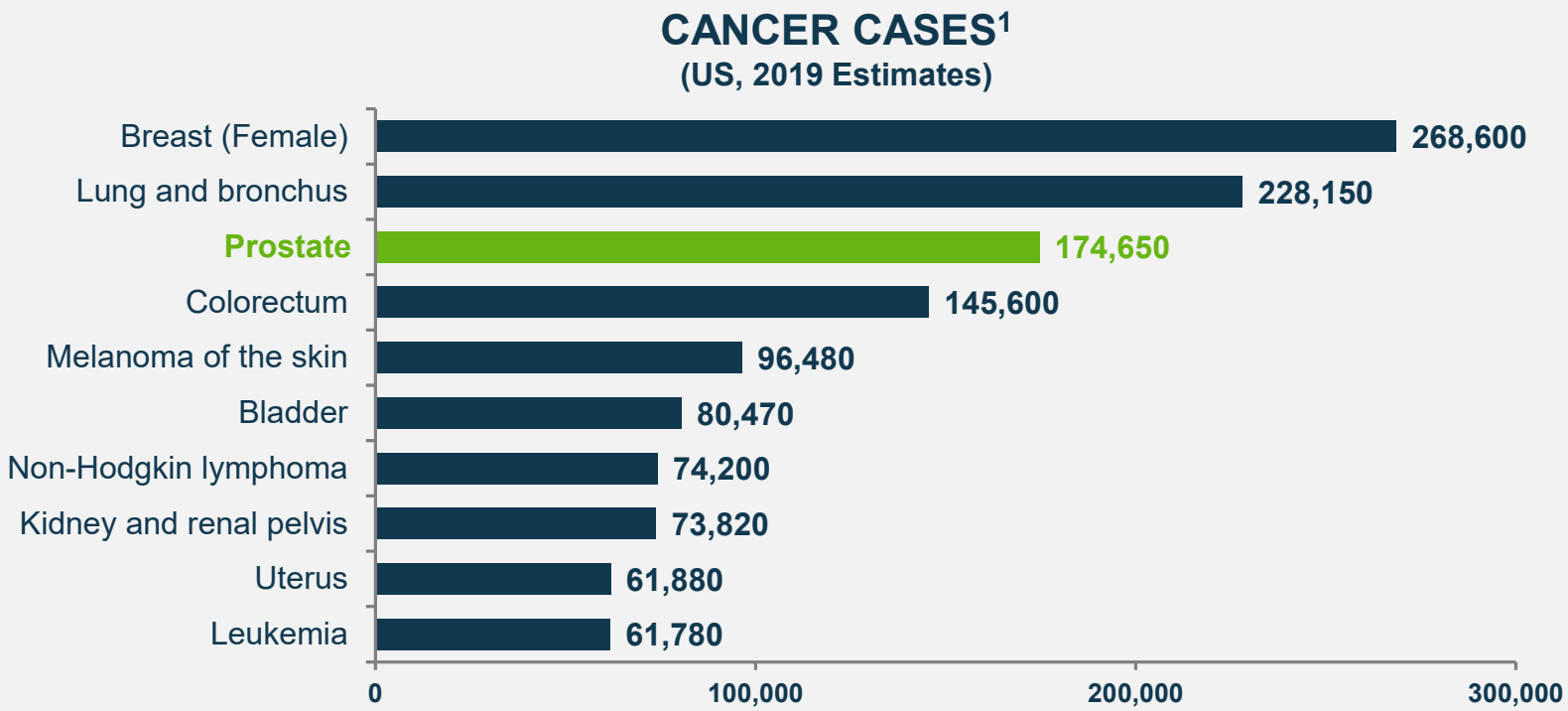
Prostate Cancer and Non-Metastatic Castration-Resistant Prostate Cancer

Landscape Overview

Prostate Cancer Is One of the Most Commonly Occurring Cancers Among Men in the United States

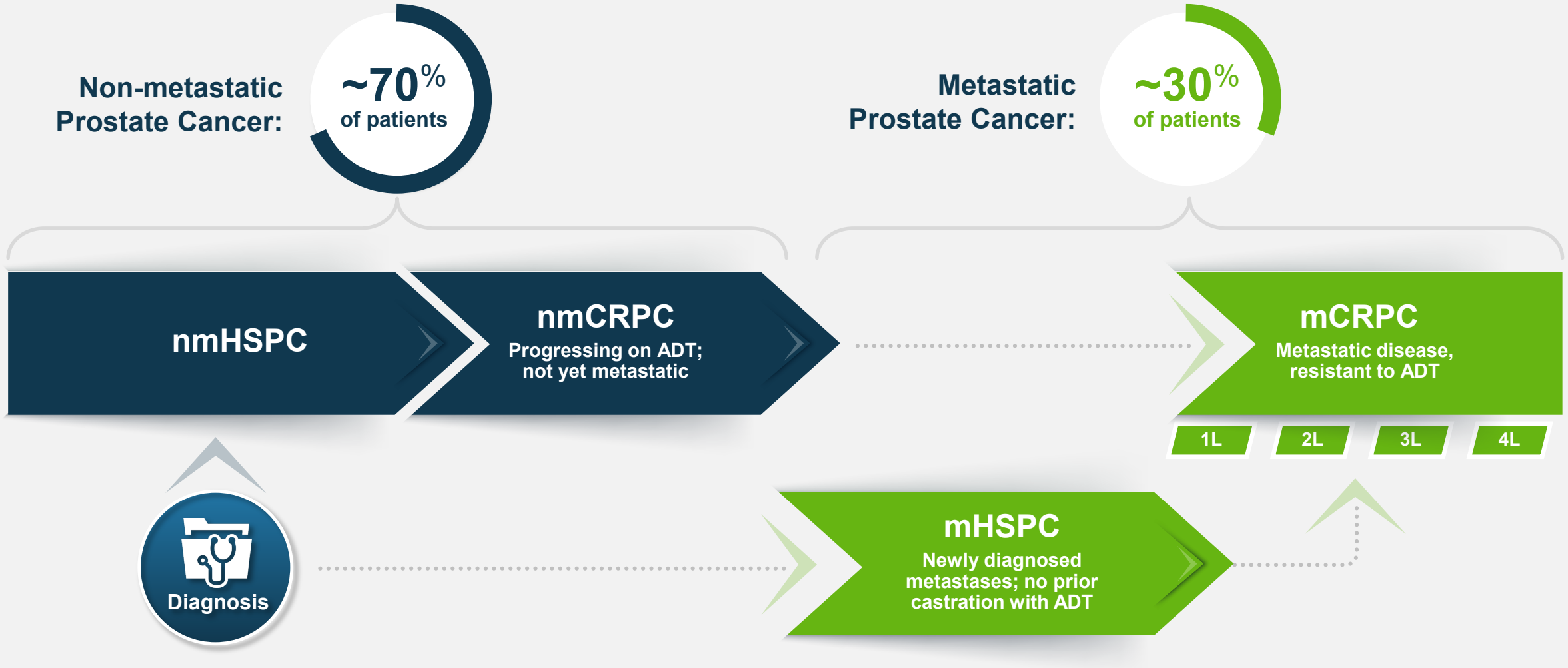


Prostate cancer is a leading cause of cancer-related mortality in men[2]

~31,620 prostate cancer-related deaths are projected for the US in 2019[1]

References: 1. SEER. Prostate cancer. http://seer.cancer.gov/statfacts/html/prost.html. Accessed July 11, 2019. **2.** Siegel RL et al. *CA Cancer J Clin*. 2017;67(1):7–30.

Diagnosis Can Occur at Different Stages of the Disease and Progress Through Different Pathways[1,2]



ADT=androgen deprivation therapy; mCRPC=metastatic castration-resistant prostate cancer; nmCRPC=non-metastatic castration-resistant prostate cancer; mHSPC=metastatic hormone-sensitive prostate cancer; nmHSPC=non-metastatic hormone-sensitive prostate cancer.

References: 1. National Cancer Institute. https://www.ncbi.nim.nih.gov/books/NBK66036. Accessed July 3, 2019. **2.** National Comprehensive Cancer Network website. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed July 3, 2019.

NUBEQA® (darolutamide)

A new androgen receptor inhibitor for the treatment of non-metastatic castration-resistant prostate cancer

NUBEQA® (darolutamide) 300 mg tablets

Please see the Important Safety Information (slides 12-13) and full Prescribing Information for NUBEQA available at this presentation.

NUBEQA® (darolutamide): Approved by the FDA on 7/30/2019[1]

- **NUBEQA® (darolutamide):** an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer[2]
- NUBEQA will be distributed through an **extensive specialty pharmacy network**
- NUBEQA is available in bottles of **120 tablets each**, with a per-tablet dose of 300 mg. The NDC is 50419-395-01[2]

ADT=androgen deprivation therapy; CI=confidence interval; FDA=US Food and Drug Administration; NDC=national drug code; NR=not reached.

References: 1. Bayer website. https://www.bayer.us/en/newsroom/press-releases/article/?id=123336. Accessed July 31, 2019. **2.** NUBEQA [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; July 2019.

Please see the Important Safety Information (slides 12-13) and full Prescribing Information for NUBEQA available at this presentation.

NUBEQA® (darolutamide) 300 mg tablets

NUBEQA® (darolutamide) Indication and Important Safety Information

INDICATION

NUBEQA® (darolutamide) tablets 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 ≥ 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 (≥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 ≥ 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).

NUBEQA® (darolutamide) 300 mg tablets

For additional important risk and use information, please see the full Prescribing Information for NUBEQA available at this presentation.

NUBEQA® (darolutamide) Important Safety Information (cont'd)

Drug Interactions:

Effect of Other Drugs on NUBEQA – Concomitant use of NUBEQA with a combined P-gp and strong or moderate CYP3A4 inducer decreases darolutamide exposure, which may decrease NUBEQA activity. Avoid concomitant use of NUBEQA with combined P-gp and strong or moderate CYP3A4 inducers.

Concomitant use of NUBEQA with a combined P-gp and strong CYP3A4 inhibitor increases darolutamide exposure, which may increase the risk of NUBEQA adverse reactions. Monitor patients more frequently for NUBEQA adverse reactions and modify NUBEQA dosage as needed.

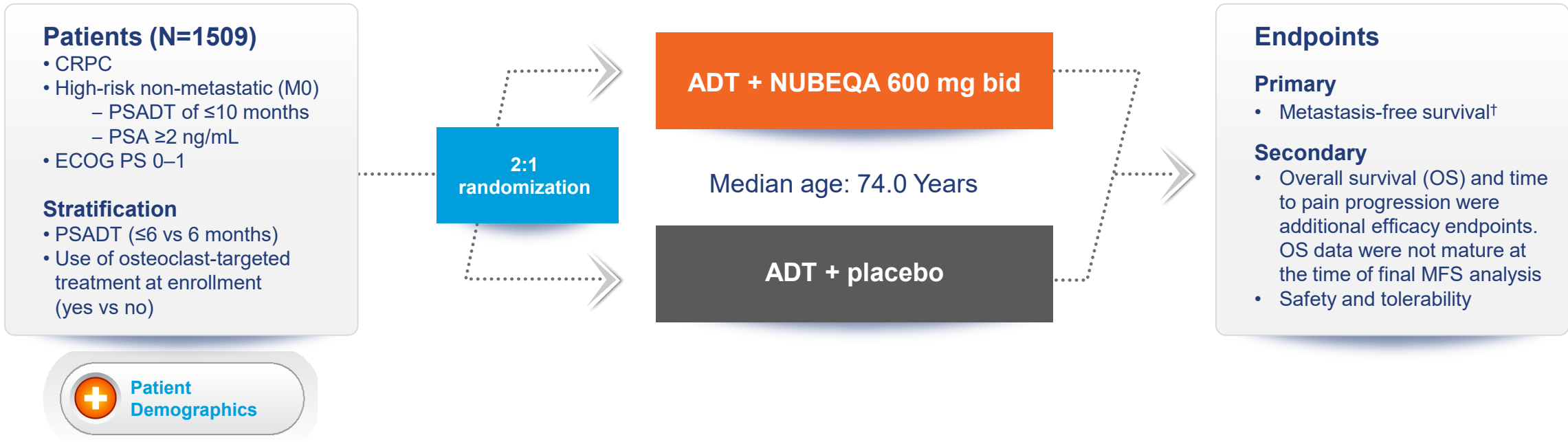
Effects of NUBEQA on Other Drugs – NUBEQA is an inhibitor of breast cancer resistance protein (BCRP) transporter. Concomitant use of NUBEQA increases the exposure (AUC) and maximal concentration of BCRP substrates, which may increase the risk of BCRP substrate-related toxicities. Avoid concomitant use 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. Consult the approved product labeling of the BCRP substrate when used concomitantly with NUBEQA.

NUBEQA® (darolutamide) 300 mg tablets

For additional important risk and use information, please see the full Prescribing Information for NUBEQA available at this presentation.

ARAMIS Phase 3 Trial[1,2]

ARAMIS (Androgen Receptor inhibiting Agent for Metastatic-free Survival, NCT02200614) is a global,* randomized, double-blind, placebo-controlled phase 3 trial investigating the safety and efficacy of NUBEQA® (darolutamide) in men with nmCRPC at high risk for metastasis



ADT=androgen deprivation therapy; bid=twice a day; CRPC=castration-resistant prostate cancer; CT=computed tomography; ECOG PS=Eastern Cooperative Oncology Group Performance Status; MRI=magnetic resonance imaging; nmCRPC=non-metastatic castration-resistant prostate cancer; OS=overall survival; PSA=prostate-specific antigen; PSADT=prostate-specific antigen doubling time; SSE=symptomatic skeletal event.

*400 centers in North and South America, Europe, Africa, the Middle East, and Asia-Pacific regions.
†In the phase 3 ARAMIS trial with NUBEQA, radiographic evidence of metastasis is by CT/MRI and bone scan. Pelvic lymph nodes <2 cm in the short axis below the aortic bifurcation are not considered evidence of metastasis.

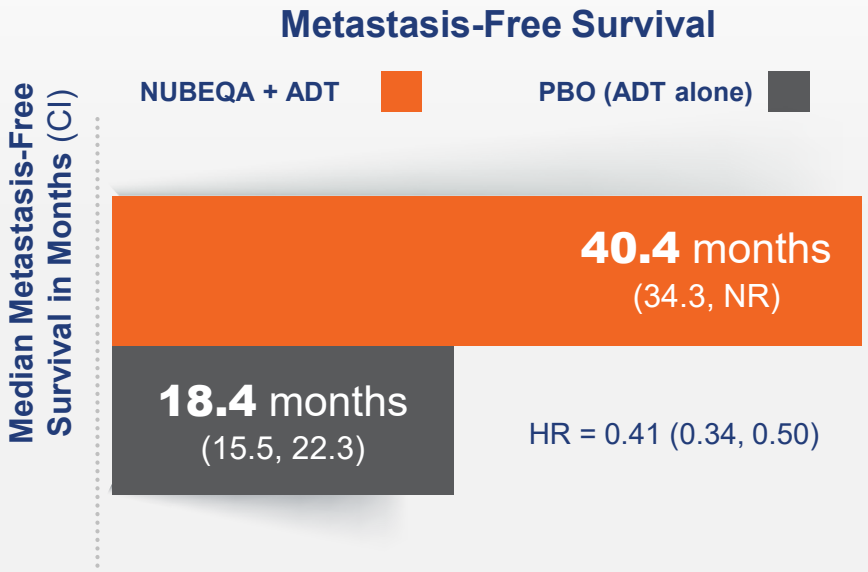
References: 1. ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT02200614. Accessed July 3, 2019. **2.** Fizazi K et al. *N Engl J Med*. 2019;380(13):1235-1246.

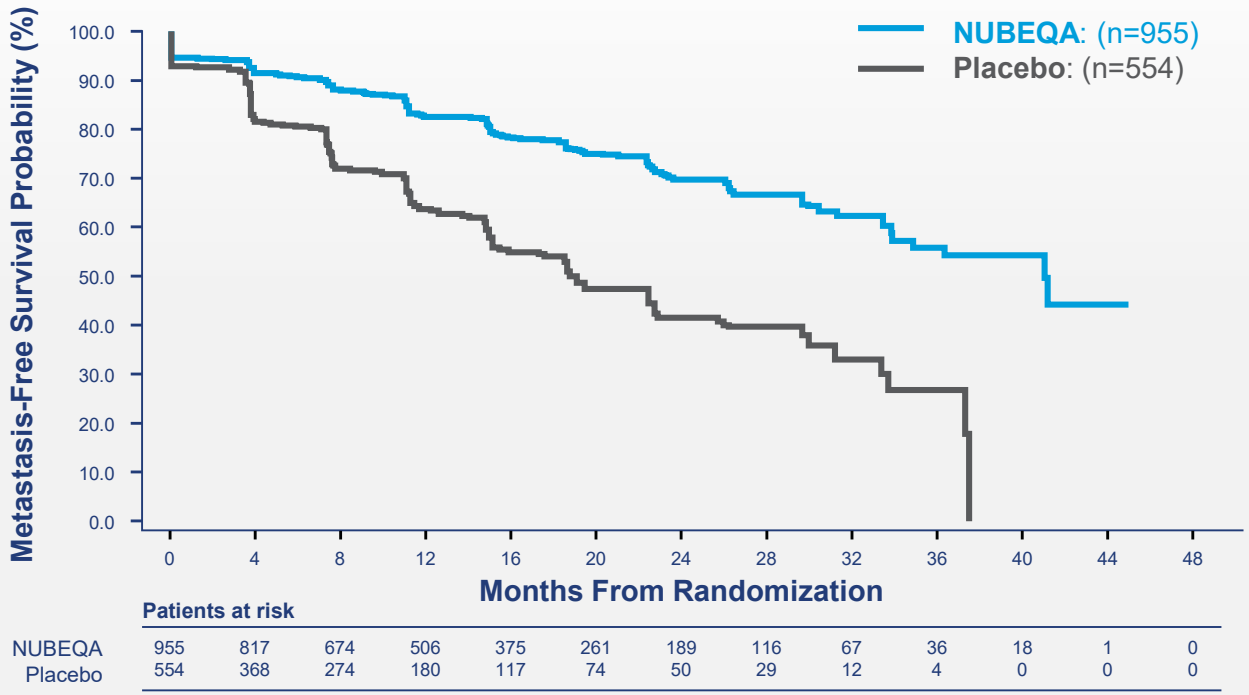
Please see the Important Safety Information (slides 12-13) and full Prescribing Information for NUBEQA available at this presentation.

NUBEQA® (darolutamide) 300 mg tablets

NUBEQA® (darolutamide) Demonstrated Statistically Significant Metastasis-Free Survival Compared to Placebo

Primary Endpoint





ADT=androgen deprivation therapy; CI=confidence interval; HR=hazard ratio; NR=not reached; PBO=placebo.

Reference: NUBEQA [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; July 2019.

Please see the Important Safety Information (slides 12-13) and full Prescribing Information for NUBEQA available at this presentation.

MECHANISM OF ACTION

DOSING

NUBEQA® (darolutamide) 300 mg tablets

NUBEQA® (darolutamide) Safety Data

Data on Adverse Events of Any Grade From the *New England Journal of Medicine* Publication of the ARAMIS Trial

Adverse Events*	NUBEQA (n=954)		Placebo (n=554)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	Number of patients (percent)			
Any adverse events	794 (83.2)	236 (24.7)	426 (76.9)	108 (19.5)
Serious adverse events	237 (24.8)	151 (15.8)	111 (20.0)	70 (12.6)
Grade 5 adverse events	37 (3.9)	—	18 (3.2)	—
Adverse event leading to discontinuation of the trial regimen	85 (8.9)	32 (3.4)	48 (8.7)	24 (4.3)
Adverse events that occurred in ≥5% of patients in either group				
Fatigue	115 (12.1)	4 (0.4)	48 (8.7)	5 (0.9)
Back pain	84 (8.8)	4 (0.4)	50 (9.0)	1 (0.2)
Arthralgia	77 (8.1)	3 (0.3)	51 (9.2)	2 (0.4)
Diarrhea	66 (6.9)	0	31 (5.6)	1 (0.2)
Hypertension	63 (6.6)	30 (3.1)	29 (5.2)	12 (2.2)
Constipation	60 (6.3)	0	34 (6.1)	0
Pain in an extremity	55 (5.8)	0	18 (3.2)	1 (0.2)
Anemia	53 (5.6)	8 (0.8)	25 (4.5)	2 (0.4)
Hot flush	50 (5.2)	0	23 (4.2)	0
Nausea	48 (5.0)	2 (0.2)	32 (5.8)	0
Urinary tract infection	47 (4.9)	6 (0.6)	28 (5.1)	3 (0.5)
Urinary retention	33 (3.5)	15 (1.6)	36 (6.5)	11 (2.0)

Adverse Events*	NUBEQA (n=954)		Placebo (n=554)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	Number of patients (percent)			
Adverse events of interest				
Fatigue or asthenic conditions†	151 (15.8)	6 (0.6)	63 (11.4)	6 (1.1)
Bone fracture‡	40 (4.2)	9 (0.9)	20 (3.6)	5 (0.9)
Falls, including accident§	40 (4.2)	8 (0.8)	26 (4.7)	4 (0.7)
Seizure, any event	2 (0.2)	0	1 (0.2)	0
Rash¶	28 (2.9)	1 (0.1)	5 (0.9)	0
Weight decrease, any event	34 (3.6)	0	12 (2.2)	0
Dizziness, including vertigo	43 (4.5)	2 (0.2)	22 (4.0)	1 (0.2)
Cognitive disorder	4 (0.4)	0	1 (0.2)	0
Memory impairment	5 (0.5)	0	7 (1.3)	0
Change in mental status	0	0	1 (0.2)	0
Hypothyroidism	2 (0.2)	0	0	0
Cerebral ischemia‖	13 (1.4)	7 (0.7)	8 (1.4)	4 (0.7)
Coronary-artery disorder**	31 (3.2)	16 (1.7)	14 (2.5)	2 (0.4)
Heart failure††	18 (1.9)	5 (0.5)	5 (0.9)	0

* Exposure-adjusted incidences of adverse events in the NUBEQA group and the placebo group were as follows: fatigue or asthenic conditions (11.3 patients per 100 years of exposure and 11.1 patients per 100 years of exposure, respectively), back pain (6.3 and 8.8), arthralgia (5.8 and 9.0), diarrhea (4.9 and 5.5), hypertension (4.7 and 5.1), constipation (4.5 and 6.0), pain in extremity (4.1 and 3.2), anemia (4.0 and 4.4), hot flush (3.7 and 4.1), nausea (3.6 and 5.6), weight loss (2.5 and 2.1), falls (2.7 and 4.1), bone fracture (3.0 and 3.5), memory impairment (0.4 and 1.2), cognitive disorder (0.3 and 0.2), and seizure (0.2 and 0.2); *Exposure-adjusted incidences of adverse events in the NUBEQA group and the placebo group were as follows: fatigue or asthenic conditions (11.3 patients per 100 years of exposure and 11.1 patients per 100 years of exposure, respectively), back pain (6.3 and 8.8), arthralgia (5.8 and 9.0), diarrhea (4.9 and 5.5), hypertension (4.7 and 5.1), constipation (4.5 and 6.0), pain in extremity (4.1 and 3.2), anemia (4.0 and 4.4), hot flush (3.7 and 4.1), nausea (3.6 and 5.6), weight loss (2.5 and 2.1), falls (2.7 and 4.1), bone fracture (3.0 and 3.5), memory impairment (0.4 and 1.2), cognitive disorder (0.3 and 0.2), and seizure (0.2 and 0.2).

†This category combines the following Medical Dictionary for Regulatory Activities, version 20.0 (MedDRA) terms: Asthenic conditions, disturbances in consciousness, decreased strength and energy, malaise, lethargy, asthenia, and fatigue.

‡This category combines the following MedDRA terms: Any fractures and dislocations, limb fractures and dislocations, skull fractures, facial bone fractures and dislocations, spinal fractures and dislocations, and thoracic cage fractures and dislocations.

§All events that had been recorded under the MedDRA term "accident" were determined to have been accidental falls and are included in this category.

¶This category combines the following MedDRA terms: Dermatitis, erythema, rash, macular rash, maculopapular rash, papular rash, and pustular rash.

‖This category combines the following MedDRA terms: Cerebral infarction, cerebral ischemia, cerebrovascular accident, ischemic stroke, and transient ischemic attack. Grade 5 events occurred in one patient receiving NUBEQA and three patients receiving placebo.

**This MedDRA High Level Group Term includes coronary-artery disorders not elsewhere classified, coronary-artery arteriosclerosis, coronary artery disease, coronary-artery occlusion, and coronary-artery stenosis. Grade 5 events occurred in three patients receiving NUBEQA and one patient receiving placebo.

††This MedDRA High Level Group Term includes heart failure not elsewhere classified, cardiac failure, acute cardiac failure, chronic cardiac failure, congestive cardiac failure, and cardiogenic shock. Grade 5 events occurred in four patients receiving NUBEQA and three patients receiving placebo.

Reference: Fizazi K et al. *N Engl J Med*. 2019;380(13):1235-1246.

NUBEQA® (darolutamide) 300 mg tablets

Please see the Important Safety Information (slides 12-13) and full Prescribing Information for NUBEQA available at this presentation.

NUBEQA® (darolutamide) Prescribing Information Safety Outcomes: Adverse Reactions[1]

Adverse Reaction	NUBEQA (n=954)[2,*]		Placebo (n=554)	
	All Grades %	Grades ≥3 %	All Grades %	Grades ≥3 %
Fatigue[†]	16	0.6	11	1.1
Pain in extremity	6	0	3	0.2
Rash	3	0.1	1	0

In the ARAMIS trial, both arms showed a 9% discontinuation rate due to adverse reactions. The most frequent adverse reactions requiring discontinuation in patients who received NUBEQA included cardiac failure (0.4%), and death (0.4%). 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)

*In the ARAMIS clinical trial, 1 patient in the NUBEQA group did not start treatment.
[†]Includes fatigue and asthenia.

References: 1. NUBEQA [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; July 2019. **2.** Fizazi K et al. *N Engl J Med*. 2019;380(13):1235-1246.

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NUBEQA® (darolutamide) Drug-Drug Interactions[1,2]

Effect of NUBEQA on Other Drugs

Drug Class	Drug Interactions
BCRP Substrates	• NUBEQA is an inhibitor of BCRP transporter. Concomitant use of NUBEQA increases the AUC and C_{max} of BCRP substrates, which may increase the risk of BCRP substrate-related toxicities – Examples: Rosuvastatin and sulfasalazine • 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. Consult the approved product labeling of the BCRP substrate when used concomitantly with NUBEQA

Effect of Other Drugs on NUBEQA

Drug Class	Drug Interactions
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 – Examples: Bosentan, carbamazepine, efavirenz, enzalutamide, etravirine, mitotane, modafinil, phenytoin, rifampin, St. John's wort • 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, which may increase the risk of NUBEQA adverse reactions – Examples: Clarithromycin and itraconazole • Monitor patients more frequently for NUBEQA adverse reactions and modify NUBEQA dosage as needed

BCRP=breast cancer resistance protein; CYP=cytochrome P-450 system; P-gp=P-glycoprotein.

References: 1. NUBEQA (darolutamide) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; July 2019. **2.** US Food and Drug Administration website. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#classSub. Accessed July 29, 2019.

NUBEQA® (darolutamide) 300 mg tablets

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Assisting Patients With Access to NUBEQA® (darolutamide)

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Support From DUDE Access Services™

DUDE™
ACCESS SERVICES
Darolutamide User Drug Experience

For more information,
visit **NUBEQAhcp.com**

- Administers NUBEQA Free Trial Program*
- NUBEQA $0 Co-pay Program for commercially insured patients†
- Identify and refer appropriate patients to independent cost assistance foundations or the Bayer US Patient Assistance Foundation
- Perform benefits verification to identify patient's insurance coverage and out-of-pocket expenses
- Assistance with prior authorizations and appeals, as well as provision of payer policy information
- Identify and triage prescription to specialty pharmacy covered by patient's health plan

*The NUBEQA Free Trial Program provides 2 months' 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, please call DUDE Access Services at 1-833-337-DUDE (1-833-337-3833) or visit NUBEQAhcp.com to download the Patient Service Request Form with full terms and conditions.
†Restrictions may apply. For full terms and conditions, please call DUDE Access Services at 1-833-337-DUDE (1-833-337-3833) or visit NUBEQAhcp.com to download the Patient Service Request Form with full terms and conditions. Patients who are enrolled in any type of government insurance or reimbursement programs are not eligible. As a condition precedent of the co-payment support provided under this program, eg, co-pay refunds, participating patients and pharmacies are obligated to inform insurance companies and third-party payers of any benefits they receive and the value of this program, as required by contract or otherwise. Void where prohibited by law, taxed, or restricted. Eligibility and participation are subject to review and may be modified or discontinued at any time.

NUBEQA® (darolutamide) 300 mg tablets

Please see the Important Safety Information (slides 12-13) and full Prescribing Information for NUBEQA available at this presentation.

NUBEQA Free Trial Program

Overview, Terms, and Eligibility

Program

- Offers **2 months of free drug** to all eligible patients
- Begins at **launch** and runs **through year-end, 2020**

Eligible Patients

- **All new patients are eligible** for participation in the FTP (regardless of insurance coverage)
- Patients **already taking** NUBEQA® (darolutamide) are **not eligible** for the FTP

Program Logistics

- **Centrally managed by enrollment to DUDE Access Services™**
- **Single specialty pharmacy** (Theracom) outside of the closed specialty pharmacy distribution network will dispense all FTP-related drug

Program Profile

- **2 months of free drug**
- Offers physicians and patients the opportunity to **try NUBEQA for free to assess safety and PSA response**

FTP=free trial program; PSA=prostate-specific antigen.

NUBEQA® (darolutamide) 300 mg tablets

Please see the Important Safety Information (slides 12-13) and full Prescribing Information for NUBEQA available at this presentation.

Bayer Is Committed to Patients With Prostate Cancer

NUBEQA® (darolutamide) 300 mg tablets

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

Xofigo® radium Ra 223 dichloride INJECTION

Xofigo® (radium Ra 223 dichloride) is indicated for the treatment of patients with castration-resistant prostate cancer (CRPC), symptomatic bone metastases and no known visceral metastatic disease.

Please see the Important Safety Information (slides 12-13) and full Prescribing Information for NUBEQA available at this presentation. Please see the Important Safety Information (slides 24-26) and full Prescribing Information for Xofigo® available at this presentation.

NUBEQA® (darolutamide) 300 mg tablets

Xofigo® (radium Ra 223 dichloride) Injection
Important Safety Information

INDICATION

Xofigo is indicated for the treatment of patients with castration-resistant prostate cancer (CRPC), symptomatic bone metastases and no known visceral metastatic disease.

IMPORTANT SAFETY INFORMATION

Contraindications: Xofigo® is contraindicated in women who are or may become pregnant. Xofigo can cause fetal harm when administered to a pregnant woman

Warnings and Precautions:

- **Bone Marrow Suppression:** In the phase 3 ALSYMPCA trial, 2% of patients in the Xofigo arm experienced bone marrow failure or ongoing pancytopenia, compared to no patients treated with placebo. There were two deaths due to bone marrow failure. For 7 of 13 patients treated with Xofigo bone marrow failure was ongoing at the time of death. Among the 13 patients who experienced bone marrow failure, 54% required blood transfusions. Four percent (4%) of patients in the Xofigo arm and 2% in the placebo arm permanently discontinued therapy due to bone marrow suppression. In the randomized trial, deaths related to vascular hemorrhage in association with myelosuppression were observed in 1% of Xofigo-treated patients compared to 0.3% of patients treated with placebo. The incidence of infection-related deaths (2%), serious infections (10%), and febrile neutropenia (<1%) was similar for patients treated with Xofigo and placebo. Myelosuppression–notably thrombocytopenia, neutropenia, pancytopenia, and leukopenia–has been reported in patients treated with Xofigo.

  Monitor patients with evidence of compromised bone marrow reserve closely and provide supportive care measures when clinically indicated. Discontinue Xofigo in patients who experience life-threatening complications despite supportive care for bone marrow failure

For additional important risk and use information, please see the full Prescribing Information for Xofigo® available at this presentation.

Xofigo®
radium Ra 223 dichloride
SOLUTION FOR INJECTION

Xofigo® (radium Ra 223 dichloride) Injection Important Safety Information (cont'd)

Warnings and Precautions: (cont'd)

- **Hematological Evaluation:** Monitor blood counts at baseline and prior to every dose of Xofigo. Prior to first administering Xofigo, the absolute neutrophil count (ANC) should be ≥1.5 × 10^9/L, the platelet count ≥100 × 10^9/L, and hemoglobin ≥10 g/dL. Prior to subsequent administrations, the ANC should be ≥1 × 10^9/L and the platelet count ≥50 × 10^9/L. Discontinue Xofigo if hematologic values do not recover within 6 to 8 weeks after the last administration despite receiving supportive care
- **Concomitant Use With Chemotherapy:** Safety and efficacy of concomitant chemotherapy with Xofigo have not been established. Outside of a clinical trial, concomitant use of Xofigo in patients on chemotherapy is not recommended due to the potential for additive myelosuppression. If chemotherapy, other systemic radioisotopes, or hemibody external radiotherapy are administered during the treatment period, Xofigo should be discontinued
- **Increased Fractures and Mortality in Combination With Abiraterone Plus Prednisone/Prednisolone:** Xofigo is not recommended for use in combination with abiraterone acetate plus prednisone/prednisolone outside of clinical trials. At the primary analysis of the phase 3 ERA-223 study that evaluated concurrent initiation of Xofigo in combination with abiraterone acetate plus prednisone/prednisolone in 806 asymptomatic or mildly symptomatic mCRPC patients, an increased incidence of fractures (28.6% vs 11.4%) and deaths (38.5% vs 35.5%) have been observed in patients who received Xofigo in combination with abiraterone acetate plus prednisone/prednisolone compared to patients who received placebo in combination with abiraterone acetate plus prednisone/prednisolone. Safety and efficacy with the combination of Xofigo and agents other than gonadotropin-releasing hormone analogues have not been established

Administration and Radiation Protection: Xofigo should be received, used, and administered only by authorized persons in designated clinical settings. The administration of Xofigo is associated with potential risks to other persons from radiation or contamination from spills of bodily fluids such as urine, feces, or vomit. Therefore, radiation protection precautions must be taken in accordance with national and local regulations

For additional important risk and use information, please see the full Prescribing Information for Xofigo® available at this presentation.

Xofigo®
radium Ra 223 dichloride
SOLUTION FOR INJECTION

Xofigo® (radium Ra 223 dichloride) Injection Important Safety Information (cont'd)

Fluid Status: Dehydration occurred in 3% of patients on Xofigo and 1% of patients on placebo. Xofigo increases adverse reactions such as diarrhea, nausea, and vomiting, which may result in dehydration. Monitor patients' oral intake and fluid status carefully and promptly treat patients who display signs or symptoms of dehydration or hypovolemia

Injection Site Reactions: Erythema, pain, and edema at the injection site were reported in 1% of patients on Xofigo

Secondary Malignant Neoplasms: Xofigo contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure may be associated with an increased risk of cancer and hereditary defects. Due to its mechanism of action and neoplastic changes, including osteosarcomas, in rats following administration of radium-223 dichloride, Xofigo may increase the risk of osteosarcoma or other secondary malignant neoplasms. However, the overall incidence of new malignancies in the randomized trial was lower on the Xofigo arm compared to placebo (<1% vs 2%; respectively), but the expected latency period for the development of secondary malignancies exceeds the duration of follow-up for patients on the trial

Subsequent Treatment With Cytotoxic Chemotherapy: In the randomized clinical trial, 16% of patients in the Xofigo group and 18% of patients in the placebo group received cytotoxic chemotherapy after completion of study treatments. Adequate safety monitoring and laboratory testing was not performed to assess how patients treated with Xofigo will tolerate subsequent cytotoxic chemotherapy

Adverse Reactions: The most common adverse reactions (≥10%) in the Xofigo arm vs the placebo arm, respectively, were nausea (36% vs 35%), diarrhea (25% vs 15%), vomiting (19% vs 14%), and peripheral edema (13% vs 10%). Grade 3 and 4 adverse events were reported in 57% of Xofigo-treated patients and 63% of placebo-treated patients. The most common hematologic laboratory abnormalities in the Xofigo arm (≥10%) vs the placebo arm, respectively, were anemia (93% vs 88%), lymphocytopenia (72% vs 53%), leukopenia (35% vs 10%), thrombocytopenia (31% vs 22%), and neutropenia (18% vs 5%)

For additional important risk and use information, please see the full Prescribing Information for Xofigo® available at this presentation.

Xofigo®
radium Ra 223 dichloride
SOLUTION FOR INJECTION

Thank You

MAC-DAR-US-0054-1 07/19

NUBEQA®
(darolutamide) 300 mg tablets

Appendix

NUBEQA®
(darolutamide) 300 mg tablets

ARAMIS Patient Demographics

The following patient demographics and disease characteristics were balanced between treatment arms:

- **The median age was 74 years** (range 48-95) and 9% of patients were 85 years of age or older, with a **racial distribution of 79% white, 13% Asian,** and **3% black**
- **73% had a Gleason score ≥7** at diagnosis and the median **PSADT was 4.5 months**
- **42%** of patients in both treatment arms had **prior surgery or radiotherapy** to the prostate and **73%** of patients received **prior treatment with an antiandrogen** (bicalutamide or flutamide)
- **11%** of patients had **enlarged pelvic lymph nodes** less than 2 cm at study entry and **6%** of patients were **retrospectively identified** by BICR as having metastases at baseline
- All patients had an **ECOG PS score of 0 or 1** at study entry

BICR=blinded independent central review; ECOG PS=Eastern Cooperative Oncology Group Performance Status; PSADT=prostate-specific antigen doubling time.

Reference: NUBEQA [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; July 2019.

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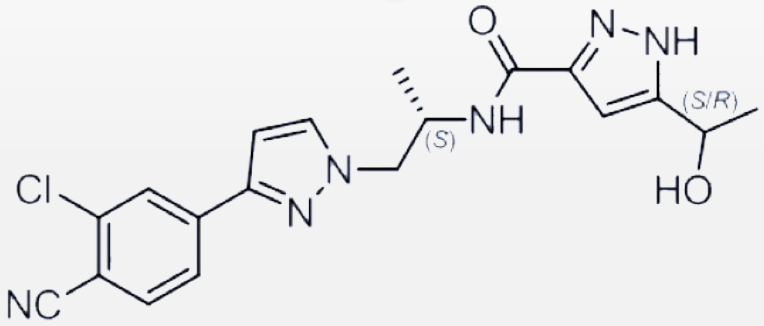
Please see the Important Safety Information (slides 12-13) and full Prescribing Information for NUBEQA available at this presentation.

NUBEQA® (darolutamide) Mechanism of Action

- NUBEQA is an AR inhibitor
- NUBEQA competitively inhibits androgen binding, AR nuclear translocation, and AR-mediated transcription
- A major metabolite, keto-darolutamide, exhibited similar in vitro activity to NUBEQA. In addition, NUBEQA functioned as a PR antagonist in vitro (approximately 1% activity compared to AR)
- NUBEQA decreased prostate cancer cell proliferation in vitro and tumor volume in mouse xenograft models of prostate cancer

NUBEQA Structural Formula



The chemical name of NUBEQA is N-{(2S)-1-[3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl]propan-2-yl}-5-(1-hydroxyethyl)-1H-pyrazole-3-carboxamide, with a molecular weight of 398.85 and a molecular formula of $C_{19}H_{19}Cl\ N_6O_2$.

AR=androgen receptor; PR=progesterone receptor.

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NUBEQA® (darolutamide) Dosing Information

Recommended Dosage

- The recommended dose of NUBEQA is 600 mg (two 300-mg film-coated tablets) taken orally, twice daily, equivalent to a total daily dose of 1200 mg. Swallow tablets whole with food
- Patients receiving NUBEQA should also receive a GnRH analog concurrently or should have had a bilateral orchiectomy
- Advise patients 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

Dosage Modification

- If a patient experiences a greater than or equal to Grade 3 toxicity or an intolerable adverse reaction, withhold dosing or reduce to 300 mg twice daily until symptoms improve. Then the treatment may be resumed at a dose of 600 mg twice daily
- Dose reduction below 300 mg twice daily is not recommended
- Patients with severe renal impairment
  - For patients with severe renal impairment (eGFR 15–29 mL/min/1.73 m^2) not receiving hemodialysis, the recommended dose of NUBEQA is 300 mg twice daily
- Patients with moderate hepatic impairment
  - For patients with moderate hepatic impairment (Child-Pugh Class B), the recommended dose of NUBEQA is 300 mg twice daily

How Supplied

- NUBEQA (darolutamide) 300 mg film-coated tablets are white to off-white, oval shaped, marked with “300” on one side, and “BAYER” on the other side. NUBEQA 300 mg tablets are available in bottles of 120 tablets
- NDC 50419-395-01

eGFR=estimated glomerular filtration rate; GnRH=gonadotropin-releasing hormone; NDC=national drug code.

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