When treating non-metastatic castration-resistant prostate cancer (nmCRPC),

METASTASIS-FREE SURVIVAL IS JUST THE HALF OF IT

NUBEQA®—focus on both survival* and tolerability.[1-3]

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

Median MFS was 40.4 months for NUBEQA + ADT (95% CI: 34.3-NR) and 18.4 months for ADT alone (95% CI: 15.5-22.3).

NUBEQA + ADT vs ADT alone: HR: 0.41 (95% CI: 0.34-0.50; *P*<0.0001).[1,2]

OS data were not mature at first analysis (57% of the required number of events). At final analysis, OS was statistically significant; median not reached. HR: 0.69 (95% CI: 0.53-0.88); *P*=0.003.[1,3]

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, ^{99m}Tc bone scan by BICR, unacceptable toxicity, or withdrawal.[1,2]

ADT=androgen deprivation therapy; BICR=blinded independent central review; CI=confidence interval; CT=computed tomography; GnRH=gonadotrophin-releasing hormone; HR=hazard ratio; MRI=magnetic resonance imaging; NR=not reached.

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.

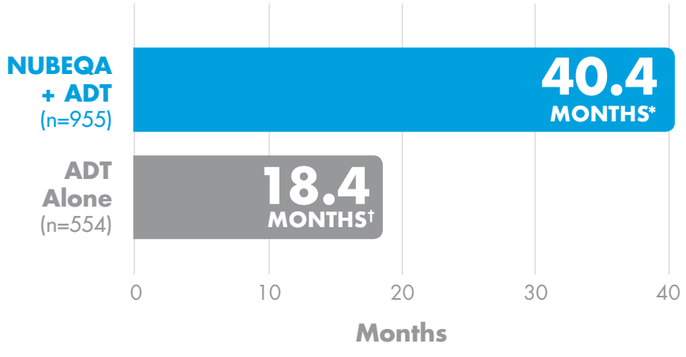
Please see additional Important Safety Information throughout and full Prescribing Information.

NUBEQA®
(darolutamide) 300 mg tablets

40 MONTHS MFS ACHIEVED with NUBEQA® + ADT

Significant increase in median MFS vs ADT alone[1,2]

HR: 0.41; 95% CI: 0.34-0.50; *P*<0.0001



MORE THAN DOUBLE THE MFS of ADT alone

- MFS results were consistent across patient subgroups for[1]:
  - —PSA doubling time (≤6 months or >6 months)
  - —Prior use of bone-targeting agents (yes or no)
- NUBEQA exposure at 600 mg twice daily results in PSA mean reduction of more than 90% from baseline[1]

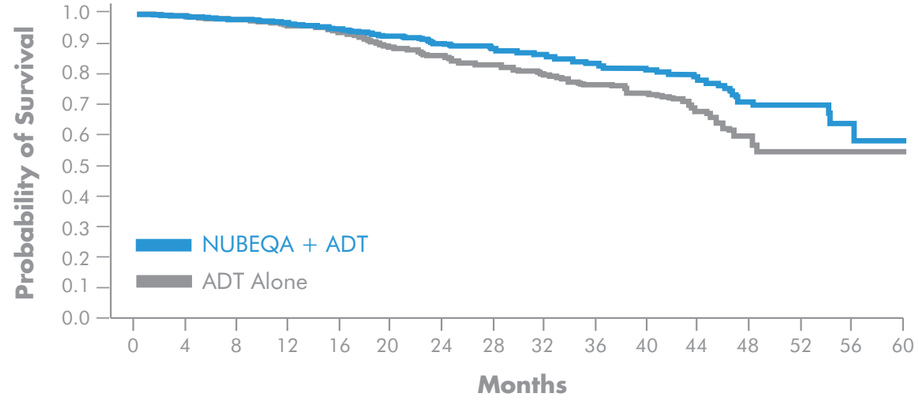
Proven to extend MFS...

*95% CI: 34.3-NR.
†95% CI: 15.5-22.3.

FINAL ANALYSIS of OS secondary endpoint

Now with statistically significant OS[3]

HR: 0.69; 95% CI: 0.53–0.88; *P*=0.003



31% REDUCTION IN RISK OF DEATH

- **Secondary endpoints analysis:** Secondary endpoints were evaluated in a hierarchical order, with a significance level of 0.05 split between the primary analysis and final analysis (planned to occur after 240 deaths from any cause). The OS endpoint was used to determine the alpha spend and significance threshold for each of the secondary endpoints[2]
- Previously, OS data were not mature at first analysis (57% of the required number of events), which prevented other secondary endpoints from being formally evaluated[1]

...now with statistically significant OS

IMPORTANT SAFETY INFORMATION (cont'd)

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.

Please see additional Important Safety Information throughout and full Prescribing Information.

IMPORTANT SAFETY INFORMATION (cont'd)

Adverse Reactions (cont'd)

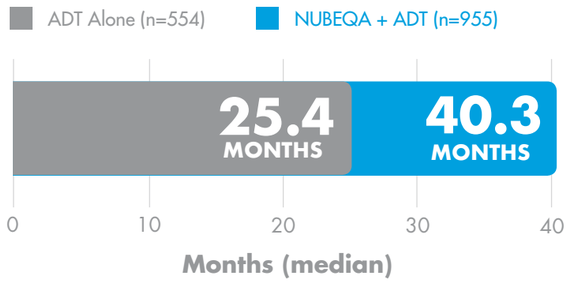
Adverse reactions occurring more frequently in the NUBEQA arm (≥2% over placebo) were fatigue (16% vs. 11%), pain in extremity (6% vs. 3%) and rash (3% vs. 1%).

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

UPDATED SECONDARY ENDPOINTS
on measures of disease progression

Statistically significant delay in time to pain progression[3]



- NUBEQA + ADT delayed time to pain progression by 14.9 months over ADT alone[3]

HR=0.65; 95% CI: 0.53-0.79. *P*<0.001.

- The MFS result was supported by a delay in time to pain progression, defined as at least a 2-point worsening from baseline of the pain score on the Brief Pain Inventory-Short Form or initiation of opioids, in men treated with NUBEQA + ADT as compared to ADT alone. Pain progression was reported in 28% of all men in the first analysis. No additional data for pain progression were collected beyond the first analysis[1,3]

Statistically significant delays in the following secondary endpoints:

Time to first cytotoxic chemotherapy[3]

42% RISK REDUCTION

HR=0.58; 95% CI: 0.44-0.76.
Median: NR for both arms. *P*<0.001.

Time to first symptomatic skeletal event[3]

52% RISK REDUCTION

HR=0.48; 95% CI: 0.29-0.82.
Median: NR for both arms. *P*=0.005.

IMPORTANT SAFETY INFORMATION (cont'd)

Drug Interactions

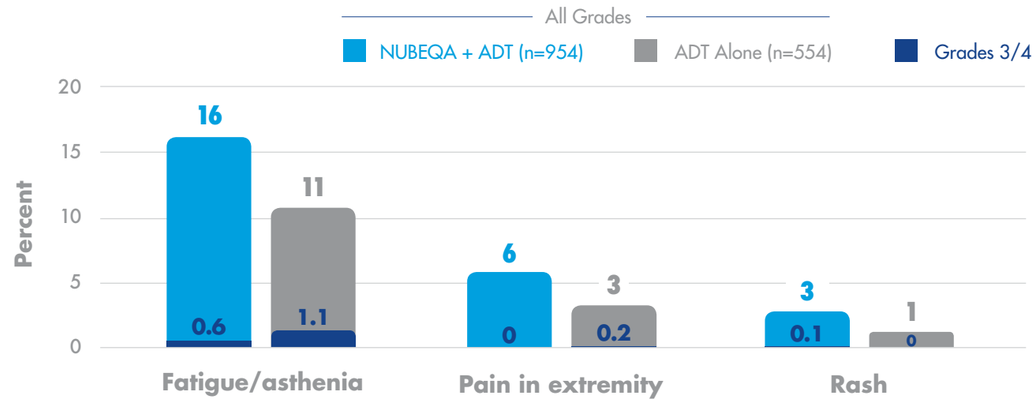
Effect of Other Drugs on NUBEQA – Concomitant use of NUBEQA with a combined P-gp and strong or moderate CYP3A4 inducer decreases darolutamide exposure, which may decrease NUBEQA activity. Avoid concomitant use of NUBEQA with combined P-gp and strong or moderate CYP3A4 inducers.

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.

Please see additional Important Safety Information throughout and full Prescribing Information.

PROVEN TOLERABILITY
in men with nmCRPC

Three adverse reactions occurred more frequently with NUBEQA® + ADT (≥2% over ADT alone)[1,2]



- Overall, serious adverse reactions occurred in 25% of men receiving NUBEQA + ADT and in 20% of men receiving ADT alone[1]
  - Serious adverse reactions in ≥1% of men who received NUBEQA + ADT included urinary retention, pneumonia, and hematuria
- Additionally, clinically significant adverse reactions occurring in ≥2% of men treated with NUBEQA + ADT vs ADT alone included ischemic heart disease (4.0% vs 3.4%) and heart failure (2.1% vs 0.9%)[1]

The only observed adverse reaction in ≥10% of patients receiving NUBEQA was fatigue[1]

IMPORTANT SAFETY INFORMATION (cont'd)

Drug Interactions (cont'd)

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

NUBEQA: FOCUS ON BOTH SURVIVAL* AND TOLERABILITY for men with nmCRPC

In ARAMIS†, NUBEQA® delivered[1-3]

40 MONTHS

More than double the median MFS

with NUBEQA + ADT‡ vs 18 months with ADT alone§

(HR: 0.41; 95% CI: 0.34-0.50; *P*<0.0001)

PROVEN TOLERABILITY

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%)‖

SAME RATE OF PERMANENT DISCONTINUATION

9% of men permanently discontinued due to adverse reactions

whether on NUBEQA + ADT or ADT alone¶

Dose interruptions and reductions due to adverse reactions occurred in 13% and 6%, respectively, of patients treated with NUBEQA + ADT#

NUBEQA: proven to extend MFS, now with statistically significant OS

31% reduction in the risk of death with NUBEQA + ADT compared to ADT alone[3]

***Metastasis-free survival (MFS) was the primary endpoint, and overall survival (OS) was a key secondary endpoint.** OS data were not mature at first analysis (57% of the required number of events). At final analysis, OS was statistically significant; median not reached. HR: 0.69 (95% CI: 0.53-0.88); *P*=0.003.

†A randomized, double-blind, placebo-controlled, multicenter phase III study that evaluated the safety and efficacy of oral NUBEQA in patients with nmCRPC who were receiving a concomitant GnRH analog or had a bilateral orchiectomy.

‡95% CI: 34.3-NR. §95% CI: 15.5-22.3.

‖**All-grade laboratory abnormalities in patients treated with NUBEQA + ADT vs ADT alone were, respectively, decreased neutrophil count (20% vs 9%), increased aspartate aminotransferase (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 most frequent adverse reactions requiring permanent discontinuation in patients treated with NUBEQA + ADT included cardiac failure (0.4%) and death (0.4%).

#In patients treated with NUBEQA + ADT, 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 dose reduction included fatigue (0.7%), hypertension (0.3%), and nausea (0.3%).

INDICATION

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

SELECT SAFETY INFORMATION

Warnings and precautions for embryo-fetal toxicity.

Serious adverse reactions occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving ADT alone.

Decreased neutrophil count, increased AST, and increased bilirubin were reported more frequently in the NUBEQA-treated patients compared to ADT alone.

3.9% of patients receiving NUBEQA and 3.2% of patients receiving ADT alone died from adverse reactions.

Clinically significant adverse reactions occurring in 2% or more of patients treated with NUBEQA included ischemic heart disease and heart failure.

Avoid concomitant use of NUBEQA with combined P-gp and strong or moderate CYP3A4 inducers.

Monitor patients more frequently for NUBEQA adverse reactions and modify dosage as needed when used with a combined P-gp and strong CYP3A4 inhibitor.

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

Please see additional Important Safety Information throughout and full Prescribing Information.

References: 1. NUBEQA (darolutamide) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; July 2019. **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 ND, Tammela T, et al. Overall survival results of the phase III ARAMIS study of darolutamide added to androgen deprivation therapy for non-metastatic castration-resistant prostate cancer. Presented at: 2020 ASCO Annual Meeting; May 29-31, 2020.

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