News Release

Intended for U.S. Media Only

U.S. FDA Approves Addition of Overall Survival and Other Secondary Endpoint Data to NUBEQA® (darolutamide) Prescribing Information

- Phase III data showed treatment with NUBEQA resulted in a 31% reduction in risk of death, with a statistically significant improvement in overall survival (OS) compared to placebo (HR=0.69, 95% CI 0.53-0.88; p=0.003), giving men with non-metastatic castration-resistant prostate cancer (nmCRPC) the opportunity to extend their lives[1]
- Time to pain progression, a key secondary endpoint, is meaningful for men living with nmCRPC and an important consideration in treatment decisions[1]
- The final analysis reinforced NUBEQA's safety profile with longer term follow-up[1,2]

WHIPPANY, N.J., January 8, 2021 – Bayer today announced that the U.S. Food and Drug Administration (FDA) approved a supplemental New Drug Application (sNDA) to add overall survival (OS) and other secondary endpoint data from the Phase III ARAMIS trial to the NUBEQA® (darolutamide) Prescribing Information. NUBEQA significantly reduced the risk of death by 31%, offering men with non-metastatic castration-resistant prostate cancer (nmCRPC) extended survival for a greater chance of living longer. Additional data include time to pain progression and time to initiation of cytotoxic chemotherapy. The Prescribing Information was also updated to include additional guidance on drug interactions. The final analysis reinforced NUBEQA's safety profile with an extended follow-up of median 29 months for the overall study population.[1,2]

The updated Prescribing Information follows the presentation of these data at the American Society of Clinical Oncology (ASCO) 2020 Virtual Scientific Program and subsequent September 10 publication in *The New England Journal of Medicine*.

"A key goal of cancer treatment is to ensure that patients can live longer while minimizing side effects," said Scott Z. Fields, M.D., Senior Vice President and Head of Oncology Development at Bayer's Pharmaceutical Division. “NUBEQA has a proven efficacy and safety profile in men with nmCRPC and delayed the effects of disease progression in men

who are otherwise generally asymptomatic. This update also gives physicians added certainty that NUBEQA should be prescribed to appropriate patients at nmCRPC diagnosis to help ensure optimal outcomes for these men."

Data from Primary and Final Analyses of Phase III ARAMIS Trial

Previously published results in 1,509 patients from the Phase III ARAMIS trial demonstrated a highly significant improvement in the primary efficacy endpoint of metastasis-free survival (MFS), with a median of 40.4 months (n=955) with NUBEQA plus androgen deprivation therapy (ADT), compared to 18.4 months (n=554) for placebo plus ADT ($p<0.001$). MFS is defined as the time from randomization to the time of first evidence of blinded independent central review (BICR)-confirmed distant metastasis or death from any cause within 33 weeks after the last evaluable scan, whichever occurred first.[1]

The proven tolerability of NUBEQA was supported by the three adverse reactions occurring more frequently in the NUBEQA arm (≥2% over placebo): fatigue (16% versus 11%), pain in extremity (6% versus 3%) and rash (3% versus 1%). NUBEQA was not studied in women and there is a warning and precaution for embryo-fetal toxicity.[1]

Secondary Endpoint Data from Phase III ARAMIS Trial Now Included in Prescribing Information

In the Phase III ARAMIS trial, men with nmCRPC receiving NUBEQA plus ADT showed a statistically significant improvement in OS compared to placebo plus ADT, with a 31% reduction in risk of death (HR=0.69, 95% CI 0.53-0.88; $p=0.003$). OS was statistically significant despite 31% (n=170) of patients in the ADT arm crossing over to NUBEQA. In total, 55% (n=307) of patients in the ADT arm crossed over to NUBEQA or received another life-prolonging therapy prior to this analysis.[1]

Other secondary endpoints incorporated in the Prescribing Information for NUBEQA also showed statistical significance, including delaying time to pain progression (HR=0.65, 95% CI 0.53-0.79; $p<0.0001$) and time to initiation of cytotoxic chemotherapy (HR=0.58, 95% CI 0.44-0.76; $p<0.0001$).[1]

Time to pain progression was defined as at least a 2-point worsening from baseline of the pain score on Brief Pain Inventory-Short Form or initiation of opioids and reported in 28% of all patients on study.[1]

There was no safety update of the Prescribing Information, reflecting no new safety signals discovered at the final analysis. The Prescribing Information was updated to include additional drug interactions. 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.[1]

About NUBEQA® (darolutamide)[1]

NUBEQA is an androgen receptor inhibitor (ARi) with a distinct chemical structure that competitively inhibits androgen binding, AR nuclear translocation, and AR-mediated transcription.[1] A Phase III study in metastatic hormone-sensitive prostate cancer (ARASENS) is ongoing. Information about this trial can be found at www.clinicaltrials.gov.

On July 30th, 2019, the FDA approved NUBEQA® (darolutamide) based on the ARAMIS trial, a randomized, double-blind, placebo-controlled, multi-center Phase III study, which evaluated the safety and efficacy of oral NUBEQA in patients with nmCRPC who were receiving a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. In the clinical study, 1,509 patients were randomized in a 2:1 ratio to receive 600 mg of NUBEQA orally twice daily or androgen deprivation therapy (ADT) alone. The primary efficacy endpoint was metastasis-free survival (MFS) and secondary endpoints include overall survival (OS), time to pain progression and time to initiation of cytotoxic chemotherapy.

Developed jointly by Bayer and Orion Corporation, a globally operating Finnish pharmaceutical company, NUBEQA is indicated for the treatment of men with nmCRPC.[1] The approvals of NUBEQA in the U.S., European Union (EU), and other global markets have been based on the pivotal Phase III ARAMIS trial data evaluating the efficacy and safety of NUBEQA plus ADT compared to ADT alone.[1] Filings in other regions are underway or planned.

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 ≥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).

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.

For important risk and use information about NUBEQA, please see the accompanying full Prescribing Information.

About Prostate Cancer

Prostate cancer is the second most commonly diagnosed malignancy in men worldwide.[3] In 2020, about 192,000 men in the U.S. were diagnosed with prostate cancer and an estimated 33,000 have died from the disease.[4] Prostate cancer is the fifth leading cause of death from cancer in men.[3] Prostate cancer results from the abnormal proliferation of cells within the prostate gland, which is part of a man's reproductive system.[5] It mainly affects men over the age of 50, and the risk increases with age.[6]

Treatment options range from surgery to radiation treatment to therapy using hormone-receptor antagonists, i.e., substances that stop the formation of testosterone or prevent its effect at the target location.[7] However, in nearly all cases, the cancer eventually becomes resistant to conventional hormone therapy.[8]

Castration-resistant prostate cancer (CRPC) is an advanced form of the disease where the cancer keeps progressing even when the amount of testosterone is reduced to very low levels in the body. The field of treatment options for castration-resistant patients is evolving rapidly for CRPC patients who have prostate cancer that has not spread to other parts of the body with rising prostate-specific antigen (PSA) levels despite a castrate testosterone level, which is called non-metastatic castration-resistant prostate cancer, or nmCRPC.[9,10] About one-third of men with nmCRPC go on to develop metastases within two years.[11] In men with progressive nmCRPC, a short PSA doubling time is correlated with shortened time to first metastasis and death.[10]

About Oncology at Bayer

Bayer is committed to delivering science for a better life by advancing a portfolio of innovative treatments. The oncology franchise at Bayer now expands to six marketed products and several other assets in various stages of clinical development. Together, these products reflect the company's approach to research, which prioritizes targets and pathways with the potential to impact the way that cancer is treated.

About Bayer

Bayer is a global enterprise with core competencies in the life science fields of health care and nutrition. Its products and services are designed to benefit people by supporting efforts to overcome the major challenges presented by a growing and aging global population. At the same time, the Group aims to increase its earning power and create value through innovation and growth. Bayer is committed to the principles of sustainable development, and the Bayer brand stands for trust, reliability and quality throughout the world. In fiscal 2019, the Group employed around 104,000 people and had sales of 43.5 billion euros. Capital expenditures amounted to 2.9 billion euros, R&D expenses to 5.3 billion euros. For more information, go to www.bayer.us.

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Media Contact:
Rose Talarico, Tel. +1 862.404.5302
E-Mail: rose.talarico@bayer.com

Forward-Looking Statements

This release may contain forward-looking statements based on current assumptions and forecasts made by Bayer management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer's public reports which are available on the Bayer website at www.bayer.com. The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

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