News Release

New data presented at ASCO GU confirm survival benefits and favorable safety profile of darolutamide across different subgroups of patients with metastatic hormone-sensitive prostate cancer

- New subgroup analysis from Phase III ARASENS trial shows that darolutamide plus androgen deprivation therapy (ADT) in combination with docetaxel increased overall survival (OS) and improved key clinically relevant endpoints in patients with various types of metastatic disease burden and risk, compared to ADT with docetaxel alone
- Favorable safety profile of darolutamide plus ADT in combination with docetaxel was also reconfirmed
- The results were presented in an oral presentation at the American Society of Clinical Oncology Genitourinary Cancers Symposium (ASCO GU) and simultaneously published in The Journal of Clinical Oncology

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Berlin, February 16, 2023 – New subgroup data from the Phase III ARASENS trial show overall survival (OS) benefits of darolutamide plus androgen deprivation therapy (ADT) in combination with docetaxel in patients with high and low-volume, as well as high and low-risk, metastatic hormone-sensitive prostate cancer (mHSPC), compared to ADT with docetaxel. The overall incidence of adverse events continues to be similar between treatment arms. The full results were presented at an oral presentation during the ASCO GU Congress 2023 and simultaneously published in the Journal of Clinical Oncology.¹

“These latest findings from the ARASENS trial continue to reinforce the strong efficacy and favorable safety profile of darolutamide in mHSPC,” said Maha Hussain, M.D., Genevieve Teuton Professor of Medicine in the Division of Hematology Oncology, Department of Medicine, and the Deputy Director at the Robert H. Lurie Comprehensive Cancer Center of the Northwestern University Feinberg School of Medicine, Chicago, USA. “The growing data from the ARASENS trial continue to demonstrate darolutamide’s value in treating patients with mHSPC. The benefit is especially in those with high-volume
or high-risk disease. They also provide treating physicians with greater insight into the mHSPC patient population that may benefit from this therapy.”

“Despite recent advances, there still remains a need for treatments that extend survival and delay disease progression while maintaining quality of life. This latest subgroup analysis from the ARASENS trial highlights darolutamide’s potential to become a foundational therapy for patients with various types of metastatic disease burden,” said Tara Frenkl, M.D., Senior Vice President and Head of Oncology Development at Bayer. “An important part of our mission at Bayer is to transform prostate cancer care and improve patient outcomes at various stages of the disease. We are working to ensure that as many eligible patients as possible have the opportunity to benefit from darolutamide.”

In the ARASENS trial, patients were randomized 1:1 to receive darolutamide plus ADT in combination with docetaxel versus placebo plus ADT with docetaxel. High-volume disease was defined as visceral metastases and/or ≥4 bone metastases with ≥1 beyond the vertebral column/pelvis, as delineated in the CHAARTED criteria. High-risk disease was defined using the LATITUDE criteria, which includes ≥2 risk factors: a Gleason score of ≥8, ≥3 bone lesions, and the presence of measurable visceral metastasis. Of 1,305 patients in the full analysis set, 1,005 (77%) had high-volume disease, 912 (70%) had high-risk disease, 300 (23%) had low-volume disease, and 393 (30%) had low-risk disease.

The subgroup analysis showed that darolutamide plus ADT in combination with docetaxel prolonged OS in high-volume disease (hazard ratio [HR]=0.69; 95% CI: 0.57-0.82), compared to ADT with docetaxel. A consistent OS benefit was observed in both high-risk (HR=0.71; 95% CI: 0.58-0.86) and low-risk (HR=0.62; 95% CI: 0.42-0.90) disease. In the smaller group of patients with low-volume disease, the results are suggestive of a survival benefit with darolutamide (HR, 0.68; 95% CI, 0.41 to 1.13). Additionally, when compared to the ADT plus docetaxel arm, the darolutamide combination arm showed benefit for key clinically relevant secondary endpoints across all disease volume and disease risk subgroups. Incidences of treatment-related adverse events across subgroups were consistent with the overall ARASENS population.

Only 30% of those diagnosed with mHSPC will survive five years or more after diagnosis.² Most people with mHSPC eventually progress to metastatic castration-resistant prostate cancer (mCRPC), a condition with limited long-term survival.³,⁴
The results of the subgroup analysis build on existing data from the ARASENS trial, as well as the overall population, which show that darolutamide plus ADT in combination with docetaxel significantly reduces the risk of death in patients with mHSPC by 32.5% (HR=0.68; 95% CI 0.57-0.80; P<0.001), compared to ADT with docetaxel. Benefits were also seen across quality of life and patient relevant endpoints including the ability to maintain quality of life with control of disease-related physical symptoms and pain.

Darolutamide plus ADT in combination with docetaxel was recently recommended for EU marketing authorization for the treatment of mHSPC by the European Medicine Agency’s Committee for Medicinal Products for Human Use (CHMP), with a final decision expected in the coming months. The compound is already approved in its second indication, mHSPC, in a number of markets including the U.S. under the brand name Nubeqa™. Filings in other regions are underway or planned. Ongoing reviews are also being conducted under the FDA Oncology Center of Excellence’s (OCE) Project Orbis initiative, which provides a framework for concurrent submission and review of cancer treatments among participating international health authorities.

Darolutamide is being investigated in a broad development program with additional three ongoing or planned large clinical studies, to investigate its potential across prostate cancer patients from the early- to the late-stage of this disease. This includes the ARANOTE Phase III trial evaluating darolutamide plus androgen deprivation therapy (ADT) versus ADT alone for mHSPC.

Darolutamide is developed jointly by Bayer and Orion Corporation, a globally operating Finnish Pharmaceutical company.

**About the ARASENS Trial**

The ARASENS trial is the only randomized, Phase III, multi-center, double-blind, trial which was prospectively designed to compare the use of a second-generation oral androgen receptor inhibitor (ARI), darolutamide, plus ADT in combination with docetaxel to ADT plus docetaxel (a guideline recommended standard-of-care) in metastatic hormone-sensitive prostate cancer (mHSPC). A total of 1,306 newly diagnosed patients were randomized in a 1:1 ratio to receive 600 mg of darolutamide twice a day or matching placebo, plus ADT in combination with docetaxel.
The primary endpoint of this trial was overall survival (OS). Secondary endpoints included time to castration-resistant prostate cancer (CRPC), time to pain progression, time to first symptomatic skeletal event (SSE), time to initiation of subsequent anticancer therapy, all evaluated at 12-week intervals, as well as adverse events (AEs) as a measure of safety and tolerability. Results from this trial were published in the *New England Journal of Medicine*. A plain language summary publication of these data was published in *Future Oncology*. The ARASENS trial demonstrated that darolutamide plus ADT in combination with docetaxel significantly reduced the risk of death by 32.5% compared to ADT with docetaxel alone. Improvements in the secondary endpoints supported the benefit observed in the primary endpoint, overall survival.

**About Metastatic Hormone-Sensitive Prostate Cancer**

Prostate cancer is the second most commonly diagnosed malignancy in men worldwide. In 2020, an estimated 1.4 million men were diagnosed with prostate cancer, and about 375,000 died from the disease worldwide.

At the time of diagnosis, most men have localized prostate cancer, meaning their cancer is confined to the prostate gland and can be treated with curative surgery or radiotherapy. Upon relapse, when the disease will metastasize or spread, or if the disease is newly diagnosed, but has already spread, the disease is hormone-sensitive and androgen deprivation therapy (ADT) is the cornerstone of treatment. Current treatment options for men with metastatic hormone-sensitive prostate cancer (mHSPC) include hormone therapy, such as ADT, androgen receptor pathway inhibitors plus ADT or a combination of the docetaxel chemotherapy and ADT. Despite these treatments, a large proportion of men with mHSPC will eventually progress to metastatic castration-resistant prostate cancer (mCRPC), a condition with high morbidity and limited survival.

**About darolutamide (Nubeqa™)**

Darolutamide is an oral androgen receptor inhibitor (ARi) with a distinct chemical structure that binds to the receptor with high affinity and exhibits strong antagonistic activity, thereby inhibiting the receptor function and the growth of prostate cancer cells. The low potential for blood-brain barrier penetration for darolutamide is supported by preclinical models and neuroimaging data in healthy humans. This is supported by the overall low incidence of central nervous system (CNS)-related adverse events (AEs) compared to placebo as seen in the ARAMIS Phase III trial and the improved verbal learning and memory observed in the darolutamide arm of the Phase II ODENZA trial.
The product is approved under the brand name Nubeqa™ in more than 80 countries around the world, including the U.S., EU, Japan and China, for the treatment of patients with non-metastatic castration-resistant prostate cancer (nmCRPC), who are at high risk of developing metastatic disease. It is also approved for the treatment of patients with metastatic hormone-sensitive prostate cancer (mHSPC) in a number of markets including the U.S. Filings in other regions are underway or planned. The compound is also being investigated in further studies across various stages of prostate cancer, including in the ARANOTE Phase III trial evaluating darolutamide plus androgen deprivation therapy (ADT) versus ADT alone for metastatic hormone-sensitive prostate cancer (mHSPC), as well as the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) led international Phase III co-operative group DASL-HiCaP (ANZUP1801) trial evaluating darolutamide as an adjuvant treatment for localized prostate cancer with very high risk of recurrence. Information about these trials can be found at www.clinicaltrials.gov. In addition, a study to explore the potential of darolutamide in the early setting for patients who have experienced a rise in their prostate specific antigen (PSA) levels following surgery or radiation, is also planned.

About Prostate Cancer at Bayer
Bayer is committed to delivering science for a better life by advancing a portfolio of innovative treatments. The company has the passion and determination to develop new medicines that help improve and extend the lives of people living with cancer. Prostate cancer is the second most commonly diagnosed cancer in men⁸ and a key area of focus for Bayer. The company’s franchise includes two products on the market (Nubeqa™ and Xofigo™) and several compounds in development, including a unique approach of advancing targeted alpha therapies. Bayer is focused on addressing the unique needs of prostate cancer patients, providing treatments that extend their lives throughout the different stages of the disease and allowing them to continue their everyday activities, so that they can live longer, better lives.

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 help people and the planet thrive by supporting efforts to master the major challenges presented by a growing and aging global population. Bayer is committed to driving sustainable development and generating a positive impact with its businesses. At the same time, the Group aims to increase its earning power and create value through innovation and growth. The Bayer brand stands
for trust, reliability and quality throughout the world. In fiscal 2021, the Group employed around 100,000 people and had sales of 44.1 billion euros. R&D expenses before special items amounted to 5.3 billion euros. For more information, go to www.bayer.com.

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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.

References
6. Fizazi, K et al. Quality of life and patient-relevant endpoints with darolutamide in the phase III ARASENS study. European Society for Medical Oncology Congress 2022; September 11, 2022; Paris, France. Abstract 1360MO.