Approval of Erleada for the Treatment of Castration-Resistant Prostate Cancer

Dear All,

On February 14, 2018, FDA approved Erleada (apalutamide) for the treatment of nonmetastatic castration-resistant prostate cancer (NM-CRPC). This is the first FDA-approved treatment for NM-CRPC.

Mechanism of Action: Prostate cancer cells depend on androgens for survival and growth. Erleada is an androgen receptor (AR) inhibitor that binds directly to the ligand-binding domain of the AR. Erleada inhibits AR nuclear translocation, prevents DNA binding, and impedes AR-mediated transcription. Erleada has been shown in mouse xenograft prostate cancer models to decrease tumor cell proliferation and increase tumor cell apoptosis, resulting in a decreased tumor burden.

Regulatory Overview: Janssen Biotech, Inc submitted the new drug application on October 9, 2017. The application was granted a priority review and was approved approximately 4 months later, ahead of its PDUFA goal date of April 10, 2018. A Special Protocol Assessment agreement letter was signed on November 9, 2012, FDA noted that "the magnitude of benefit for your primary endpoint will need to be substantially large in order to provide a positive risk-benefit ratio for this largely asymptomatic population. The approval will also depend on the internal consistency and strength of your overall survival, symptomatic progression and PFS results as well as other clinically meaningful measures… in order to support any benefit demonstrated by your surrogate primary endpoint." On August 11, 2017, FDA also granted Erleada a fast-track designation.
Janssen Biotech was the first participant in FDA's Clinical Data Summary Pilot Program, a program designed to enhance transparency on clinical evidence supporting drug product approvals and FDA's decision-making process. Janssen Biotech submitted a clinical study report, protocol, and statistical analysis plan containing a detailed summary of its clinical trial methods and results. Those reports are now available on FDA's website. The Clinical Study Report is available here.

Analysis of Current Treatment Options: For patients with metastatic prostate cancer that is castration-resistant, there are numerous FDA-approved treatment options available such as abiraterone, enzalutamide, and docetaxel. In contrast, there are no FDA-approved therapies for patients with castration-resistant prostate cancer but no radiographic evidence of metastasis. Management of these patients remains somewhat controversial, with some opting for observation alone, especially for patients who have a prostate-specific antigen doubling time (PSADT) ≥ 10 months. For patients with a PSADT < 10 months, the NCCN guidelines include various secondary hormonal manipulations and therapies as options (although not FDAapproved). Examples include discontinuation of the anti-androgen in patients whose disease progressed on combined androgen blockade to exclude an "anti-androgen withdrawal response," and secondary hormonal therapy. Secondary hormone therapy can be an antiandrogen for patients who initially received medical or survival castration, anti-androgen withdrawal, ketoconazole with or without hydrocortisone, corticosteroid, DES, or other estrogen. These treatment strategies, however, have not demonstrated a survival benefit in randomized clinical trials in patients who have not received docetaxel-based chemotherapy.

Clinical Efficacy: The safety and efficacy of Erleada were evaluated in a multicenter, double-blind, randomized, placebo-controlled trial (SPARTAN) that enrolled 1207 patients with NM-CRPC. A prostate-specific antigen doubling time (PSADT) of 10 months or less was a key eligibility criterion. All patients received concomitant treatment with a gonadotropin-releasing hormone analog or had undergone a bilateral orchiectomy. The study consisted of 3 phases: a screening phase, a double-blind treatment phase, and a long-term follow-up phase. Patients were screened for PSADT during the screening phrase. During the treatment phase, all patients who were not surgically castrated continued treatment with an androgen deprivation therapy to maintain a castrate level of testosterone. Patients were randomized 2:1 to receive either 240 mg of Erleada orally once daily (n = 806) or placebo orally once daily (n = 401) until the occurrence of distant metastases (new bone or soft tissue lesions or enlarged lymph nodes outside the pelvis), unacceptable toxicity, or death due to any cause, as determined via a blinded independent central review (BICR). During the follow-up phase, patients were monitored for disease progression every 4 months. The primary efficacy endpoint was metastasis-free survival (MFS), defined as the time from randomization to the first sign of BICR-confirmed distant metastasis or death due to any cause. Results are presented in Table 1 below.

Table 1. Results of Primary Efficacy Endpoint Analysis

MFS[a]	Erleada-Treated Patients N = 806	Placebo-Treated Patients N = 401
Total events, n (%)	184 (22.8)	194 (48.4)
Median, months	40.51	16.20
MFS difference, months	24.31	
HR (95% CI) *P* value	0.28 (0.23-0.35) < .0001	

[a]Median follow-up time of 18 months

Secondary endpoints were time to metastasis (TTM), progression-free survival (PFS), time to symptomatic progression (TSP), and overall survival (OS). PFS was defined as the time from randomization to either initial detection of BICR-confirmed evidence of distant and/or locoregional progressive radiographic disease or death due to any cause. The distinction between PFS and MFS was that PFS took into account both distant and locoregional disease progression events, whereas MFS considered only evidence of distant metastatic disease. TSP was defined as the period from randomization to the development of a skeletal-related event, initiation of a new systemic anticancer therapy due to pain progression or worsening of disease-related symptoms, or locoregional tumor progression requiring surgery or radiation therapy. All secondary endpoints were assessed via a BICR. The results are described in Table 2 below.

Table 2. Results of Secondary Efficacy Endpoint Analysis

Secondary Endpoint	Erleada-Treated Patients N = 806	Placebo-Treated Patients N = 401
TTM		
Total events, n (%) Median (95% CI), months	175 (21.7) 40.51 (NE-NE)	191 (47.6) 16.59 (14.59-18.46)
HR (95% CI) P value	0.27 (0.22-0.34) < .0001	
PFS		
Total events, n (%) Median (95% CI), months	200 (24.8) 40.51 (NE-NE)	204 (50.9) 14.72 (14.49-8.37)
HR (95% CI) P value	0.29 (0.24-0.36) < .0001	
OS		
Total events, n (%) Median (95% CI), months	62 (7.7) NE (NE-NE)	42 (10.5) 39.03 (39.03-NE)
HR (95% CI) P value	0.70 (0.47-1.04) .07	

Abbreviation: NE, not estimable.

Implication: According to the National Cancer Institute, approximately 161,360 men were diagnosed with prostate cancer in 2017 and 26,730 were expected to die of the disease. It is estimated that approximately 10% to 20% of patients with prostate cancer have castration-resistant prostate cancer (CRPC). Up to 16% of patients with CRPC show no evidence of metastatic disease at the time of the CRPC diagnosis, but 90% of them eventually develop bone metastasis. Richard Pazdur, MD, director of FDA's Oncology Center of Excellence and acting director of the Office of Hematology and Oncology Products in the Center for Drug Evaluation and Research, stated that "this approval is the first to use the endpoint of metastasis-free survival … . In the trial supporting approval, Erleada had a robust effect on this endpoint. This demonstrates the Agency's commitment to using novel endpoints to expedite important therapies to the American public."

Safety: The most common adverse reactions associated with Erleada use (incidence ≥ 10%) were fatigue, hypertension, rash, diarrhea, nausea, weight loss, arthralgia, falls, hot flush, decreased appetite, fracture, and peripheral edema.

Serious Adverse Events and Deaths: The safety analysis of Erleada was performed using data from 1201 patients with NM-CRPC from the SPARTAN trial, 803 of whom were treated with Erleada. Serious adverse events (SAEs) occurred in 25% of patients in the Erleada arm and 23% of patients in the placebo arm. SAEs that occurred in more than 2% of all patients included fracture and hematuria. SAEs that occurred at more than a 0.5% greater frequency in the Erleada arm than in the placebo arm included urinary tract infection, pneumonia, and sepsis. Listed deaths include those that occurred during treatment and up to 28 days after the last dose of the study drug. A total of 62 Erleada-treated patients (8%) and 42 placebo-treated patients (11%) died. According to FDA's review, 8 of these patients were considered to have died as a result of Erleada treatment–related toxicity. These patients died from infection (n = 4), myocardial infarction (n = 3), and cerebral hemorrhage (n = 1).

Advisory Committee: While no advisory committee meeting took place to discuss the approval of Erleada, the MFS efficacy endpoint used to support the approval of Erleada was discussed in 2 Oncologic Drugs Advisory Committee (ODAC) meetings. A non–product-specific ODAC convened on September 14, 2011, to discuss issues relating to trial design, specific populations, and endpoints in the NM-CRPC setting. The committee proposed a trial design to include hormone therapy–

naïve patients with rapid PSADTs who would be randomized to treatment with a new compound in combination with a second-line hormonal therapy. A second, product-specific ODAC convened on February 8, 2012. During this meeting, the committee discussed the value of bone MFS (BMFS) as an established surrogate endpoint, and the members generally agreed that BMFS could be considered an endpoint that demonstrates clinical benefit if the magnitude of the effect is sufficiently large. The approval of Erleada based on an improvement in MFS therefore established a new regulatory precedent for the use of MFS as an endpoint provided that, as per the ODAC discussions, the magnitude of improvement in MFS is large enough to demonstrate a clinically meaningful benefit in the setting of a favorable safety profile.

Postmarketing Requirements: None.

Postmarketing Commitments: The following is required:

- Submit the analyses and datasets with the final report for the SPARTAN clinical trial, titled “A Multicenter, Randomized, Double-blind, Placebo-Controlled, Phase III Study of ARN-509 in Men With Non-Metastatic (M0) Castration-Resistant Prostate Cancer.”

Required Pediatric Assessments: None; the pediatric study requirement was waived because the necessary studies would be impossible or highly impractical, as prostate cancer does not occur in children.

REMS: None.

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Kind regards,
Headwaters Communications,
Regulatory Intelligence Services