U.S. FDA accepts GSK's sNDA application for Zejula (niraparib) for first-line maintenance treatment for women with platinum-responsive advanced ovarian cancer

February 25, 2020

- Submission based on data from the Phase III PRIMA clinical study that demonstrated clinically-meaningful outcomes of niraparib maintenance treatment in the first-line setting regardless of biomarker status
- The application is being reviewed under the FDA's Real-Time Oncology Review pilot program

Issued: London, UK

GlaxoSmithKline plc today announced that the U.S. Food and Drug Administration (FDA) accepted the company's submission of a supplemental New Drug Application (sNDA) seeking approval of Zejula (niraparib) as a maintenance treatment in the first-line setting for women with advanced ovarian cancer who responded to platinum-based chemotherapy regardless of biomarker status. The FDA is reviewing the sNDA under the Real-Time Oncology Review (RTOR) pilot program, which aims to explore a more efficient review process to ensure safe and effective treatments are available to patients as early as possible.

The application is supported by data from the PRIMA study (ENGOT-OV26/GOG-3012), which demonstrated clinically-meaningful outcomes of niraparib treatment in the first-line maintenance setting.[1] Results from the PRIMA study were presented at the 2019 European Society for Medical Oncology Congress and simultaneously published in the New England Journal of Medicine. The PRIMA study enrolled women who responded to first-line treatment with platinum-based chemotherapy, including those at higher risk of disease progression, a population previously under-represented in first-line ovarian cancer studies.

In the U.S., ovarian cancer impacts nearly 222,000 women annually,[2] and approximately 85% of women with advanced ovarian cancer will see their disease return.[3] With each recurrence, the time a woman may spend without her cancer progressing until the next recurrence gets shorter.

Zejula is currently approved in the U.S. as a maintenance treatment for women with recurrent ovarian cancer who are in response to platinum-based chemotherapy regardless of BRCA mutation status. It is also approved as a treatment for women with advanced ovarian cancer, following three or more chemotherapy regimens.

About PRIMA

PRIMA is a double-blind, randomised Phase III study designed to evaluate niraparib versus placebo in women being treated first-line for Stage III or IV ovarian cancer. The study assessed the efficacy of niraparib as maintenance therapy, as measured by progression free survival. Patients in complete or partial response to first-line platinum-based chemotherapy were randomised 2:1 to niraparib or placebo.

About Ovarian Cancer

Approximately 22,000 women are diagnosed each year with ovarian cancer in the U.S. Ovarian cancer is the fifth most frequent cause of cancer death among women.[4] Despite high response rates to platinum-based chemotherapy in the first-line, approximately 85% of patients will experience disease recurrence. Once the disease recurs, it is rarely curable with decreasing time intervals to each subsequent recurrence.

About Zejula (niraparib)

Niraparib is an oral, once-daily PARP inhibitor that is currently being evaluated in multiple pivotal trials. GSK is building a robust niraparib clinical development programme by assessing activity across multiple tumour types and by evaluating several potential combinations of niraparib with other therapeutics. The ongoing development programme for niraparib includes several combination studies, including a Phase III study as a first-line triplet maintenance treatment in ovarian cancer (FIRST). There is also a Phase II study of niraparib combined with bevacizumab maintenance treatment in advanced ovarian cancer (OVARIO); a Phase II study of niraparib plus dostarlimab in patients with platinum resistant ovarian cancer (MOONSTONE); and a separate study with niraparib in combination with pembrolizumab in patients with triple-negative breast cancer or ovarian cancer (TOPACIO).

Important Safety Information for ZEJULA

Indications

ZEJULA is indicated:

- for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

- for the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with three or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either:
    - a deleterious or suspected deleterious BRCA mutation, or
    - genomic instability and who have progressed more than six months after response to the last platinum-based chemotherapy.

Select patients for therapy based on an FDA-approved companion diagnostic for ZEJULA.

Important Safety Information

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML), including some fatal cases, was reported in 14 patients (0.7%) out of 1902 patients treated with ZEJULA in clinical trials. The duration of therapy in patients who developed secondary MDS/cancer therapy-related AML varied from less than 2 months to greater than 4 years. These patients had received prior chemotherapy with platinum agents and/or other DNA-damaging agents including radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

Hematologic adverse reactions (thrombocytopenia, anemia and neutropenia) have been reported in patients receiving ZEJULA. Grade ≥3 thrombocytopenia, anemia and neutropenia were reported, respectively, in 29%, 25%, and 20% of patients receiving ZEJULA in NOVA, and 28%, 27%, and 13% of patients receiving ZEJULA in QUADRA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 1%, and 2% of patients in NOVA, and 4%, 2%, and 1% of patients in QUADRA. Do not start ZEJULA until patients have recovered from hematological toxicity caused by prior chemotherapy (≤ Grade 1). Monitor complete blood counts weekly for the first month, monthly for the next 11 months, and periodically thereafter. If hematological toxicities do not resolve within 28 days following interruption, discontinue ZEJULA, and refer the patient to a hematologist for further investigations.

Hypertension and hypertensive crisis have been reported in patients receiving ZEJULA. Grade 3-4 hypertension occurred in 9% of patients receiving ZEJULA vs 2% of patients receiving placebo in NOVA, with discontinuation occurring in <1% of patients. Grade 3-4 hypertension occurred in 5% of ZEJULA-treated patients in QUADRA, with discontinuation occurring in <0.2% of patients. Monitor blood pressure and heart rate at least weekly for the first two months, then monthly for the first year, and periodically thereafter during treatment with ZEJULA. Closely monitor patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Manage hypertension with antihypertensive medications and adjustment of the ZEJULA dose, if necessary.

Embryo-Fetal Toxicity and Lactation: Based on its mechanism of action, ZEJULA can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months after receiving their final dose of ZEJULA. Because of the potential for serious adverse reactions from ZEJULA in breastfed infants, advise lactating women to not breastfeed during treatment with ZEJULA and for 1 month after receiving the final dose.

The most common adverse reactions in >10% of 830 patients who received ZEJULA in NOVA and QUADRA (n = 830) were nausea (70%), fatigue (58%), thrombocytopenia (56%), anemia (50%), vomiting (40%), constipation (38%), abdominal pain (35%), musculoskeletal pain (34%), decreased appetite (26%), neutropenia (25%), insomnia (23%), headache (22%), dyspnea (21%), diarrhea (18%), hypertension (16%), cough (15%), dizziness (13%), hypomagnesemia (13%), urinary tract infection (13%), acute kidney injury (13%), and white blood cell count decreased (11%).

Common lab abnormalities (Grades 1-4) in ≥25% of patients who received ZEJULA in NOVA included: decrease in hemoglobin (85%), decrease in platelet count (72%), decrease in white blood cell count (66%), decrease in absolute neutrophil count (53%), increase in AST (36%) and increase in ALT (28%).

Common lab abnormalities (Grades 1-4) in ≥25% of patients who received ZEJULA in QUADRA included: decreased hemoglobin (83%), increased glucose (66%), decreased platelets (60%), decreased lymphocytes (57%), decreased leukocytes (53%), decreased magnesium (46%), increased alkaline phosphatase (40%), increased gamma glutamyl transferase (40%), increased creatinine (36%), decreased sodium (34%), decreased neutrophils (34%), increased aspartate aminotransferase (29%), and decreased albumin (27%).

Please see accompanying Prescribing Information

GSK in Oncology

GSK is focused on maximising patient survival through transformational medicines. GSK's pipeline is focused on immuno-oncology, cell therapy, cancer epigenetics and synthetic lethality. Our goal is to achieve a sustainable flow of new treatments based on a diversified portfolio of investigational medicines utilising modalities such as small molecules, antibodies, antibody drug conjugates and cells, either alone or in combination.

About GSK

GSK is a science-led global healthcare company with a special purpose: to help people do more, feel better, live longer. For further information please visit www.gsk.com/about-us.

Cautionary statement regarding forward-looking statements
GSK cautions investors that any forward-looking statements or projections made by GSK, including those made in this announcement, are subject to risks and uncertainties that may cause actual results to differ materially from those projected. Such factors include, but are not limited to, those described under Item 3.D 'Principal risks and uncertainties' in the company's Annual Report on Form 20-F for 2018.

References

[1] González-Martín A, Pothuri B, Vergote I, Christensen R, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. *New England Journal of Medicine*. 2019. doi:10.1056/NEJMoa1910962

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