FDA approves Zejula (niraparib) as the only once-daily PARP inhibitor in first-line monotherapy maintenance treatment for women with platinum-responsive advanced ovarian cancer regardless of biomarker status

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- Zejula is the only oral monotherapy available as first-line maintenance treatment for women regardless of *BRCA* mutational status, addressing a high unmet need in ovarian cancer
- New individualised starting dose based on the patient's baseline weight and/or platelet count approved for first-line maintenance treatment; lower rates of haematological adverse events were observed with the individualised dosing group
- The supplemental New Drug Application was approved under the FDA's Real-Time Oncology Review pilot program

GlaxoSmithKline plc (LSE/NYSE: GSK) today announced the US Food and Drug Administration (FDA) approved the company's supplemental New Drug Application (sNDA) for Zejula (niraparib), an oral, once-daily poly (ADP-ribose) polymerase (PARP) inhibitor, as a monotherapy maintenance treatment for women with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy, regardless of biomarker status. Until now, only 20% of women with ovarian cancer, those with a BRCA mutation (BRCAm), were eligible to be treated with a PARP inhibitor as monotherapy in the first-line maintenance setting.[i]

Dr. Hal Barron, Chief Scientific Officer and President R&D, GSK, said: "Women with advanced ovarian cancer have a five-year survival rate of less than 50%. This expanded indication means that many more women with this devastating disease can receive earlier treatment with Zejula, which can extend the time it takes for their cancer to progress."

Zejula is the only once-daily PARP inhibitor approved in the US as monotherapy for women with advanced ovarian cancer beyond those with *BRCAm* disease in the first-line and recurrent maintenance treatment settings, as well as late-line primary treatment settings.

This new indication is supported by data from the phase III PRIMA study (ENGOT-OV26/GOG-3012), which enrolled patients with newly diagnosed advanced ovarian cancer following a complete or partial response to platinum-based chemotherapy regardless of biomarker status. The PRIMA study enrolled women who had higher risk of disease progression, a population with high unmet needs and limited treatment options.

Dr. Bradley Monk, PRIMA investigator, US Oncology, University of Arizona College of Medicine, Phoenix Creighton University School of Medicine at St. Joseph's Hospital Phoenix, said: "PRIMA was designed for patients with ovarian cancer who have a high unmet need. The positive data observed regardless of biomarker status in this study is extremely encouraging and suggests benefit beyond the *BRCAm* population. This approval is an important step forward in the treatment of ovarian cancer. In my opinion, maintenance treatment with niraparib should be considered an option for appropriate patients who responded to first-line platinum-based chemotherapy versus active surveillance."

The primary endpoint in the PRIMA study was progression-free survival (PFS) analysed sequentially, first in the homologous recombination deficient (HRd) population, then in the overall population. The PRIMA study significantly improved PFS for patients treated with Zejula, regardless of biomarker status. In the HRd population, Zejula resulted in a 57% reduction in the risk of disease progression or death vs. placebo (HR 0.43; 95% CI, 0.31 to 0.59; p<0.0001), and a 38% reduction in the risk of disease progression or death vs. placebo in the overall population (HR 0.62; 95% CI, 0.50 to 0.76; p<0.0001).

Zejula's safety profile, as demonstrated by the PRIMA results, was consistent with clinical trial experience. The most common grade 3 or higher adverse events with Zejula included thrombocytopenia (39%), anaemia (31%) and neutropenia (21%).

At initiation of the PRIMA study, patients received a fixed starting dose of 300 mg of Zejula once-daily. The study was later amended to incorporate an individualised starting dose of either 200 mg or 300 mg of Zejula once-daily based on the patient's baseline weight and/or platelet count. Lower rates of grade 3 and 4 haematologic treatment-emergent adverse events were observed with an individualised starting dose, compared to the overall population, including thrombocytopenia (21% compared to 39%), anaemia (23% compared to 31%) and neutropenia (15% compared to 21%).

The Zejula US prescribing information has been updated to include the individualised starting dose of 200 mg or 300 mg once-daily based on patients' baseline weight and/or platelet count for the first-line maintenance treatment indication. The starting dose for recurrent ovarian cancer and late-line treatment settings is 300 mg once-daily.

"It's so important for patients with ovarian cancer to have treatment options, and this approval is positive news for our community," said Audra Moran, President and CEO, Ovarian Cancer Research Alliance. "PARP inhibitors represent a major advancement in the fight against ovarian cancer, and having a new first-line maintenance option for platinum-responsive advanced ovarian cancer patients — regardless of BRCA mutation status — is especially exciting. We are determined to keep funding research and partnering with scientists who are on the frontline of finding new treatments like

this one to help those impacted by this disease."

PRIMA study results were previously presented at the 2019 European Society for Medical Oncology (ESMO) Congress and published in the New England Journal of Medicine.

Zejula is not approved for use in first-line maintenance treatment outside the US.

About Ovarian Cancer

In the US, ovarian cancer impacts nearly 222,000 women annually,[ii] and it is the fifth most frequent cause of cancer death among women.[iii] Despite high response rates to platinum-based chemotherapy in the front-line setting, approximately 85% of patients will experience disease recurrence.[iv] 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).

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 cell therapy, either alone or in combination.

Indications and Important Safety Information for ZEJULA

Indications

ZEJULA is indicated:

- for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.
- 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 15 patients (0.8%) out of 1785 patients treated with ZEJULA monotherapy in clinical trials. The duration of therapy in patients who developed secondary MDS/cancer therapy-related AML varied from 0.5 months to 4.9 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. The overall incidence of Grade ≥3 thrombocytopenia, anemia and neutropenia were reported, respectively, in 39%, 31%, and 21% of patients receiving ZEJULA in PRIMA; 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 4%, 2%, and 2% of patients in PRIMA; 3%, 1%, and 2% of patients in NOVA; and 4%, 2%, and 1% of patients in QUADRA. In patients who were administered a starting dose of ZEJULA based on baseline weight or platelet count in PRIMA, Grade ≥3 thrombocytopenia, anemia and neutropenia were reported, respectively, in 22%, 23%, and 15% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 3%, and 2% of patients. 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 6% of patients receiving ZEJULA vs 1% of patients receiving placebo in PRIMA, with no reported discontinuations. 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. 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.

First-line Maintenance Advanced Ovarian Cancer

Most common adverse reactions (Grades 1-4) in ≥10% of all patients who received ZEJULA in PRIMA were thrombocytopenia (66%), anemia (64%), nausea (57%), fatigue (51%), neutropenia (42%), constipation (40%), musculoskeletal pain (39%), leukopenia (28%), headache (26%), insomnia (25%), vomiting (22%), dyspnea (22%), decreased appetite (19%), dizziness (19%), cough (18%), hypertension (18%), AST/ALT elevation (14%), and acute kidney injury (12%).

Common lab abnormalities (Grades 1-4) in ≥25% of all patients who received ZEJULA in PRIMA included: decreased hemoglobin (87%), decreased platelets (74%), decreased leukocytes (71%), increased glucose (66%), decreased neutrophils (66%), decreased lymphocytes (51%), increased alkaline phosphatase (46%), increased creatinine (40%), decreased magnesium (36%), increased AST (35%) and increased ALT (29%).

Maintenance Recurrent Ovarian Cancer

Most common adverse reactions (Grades 1-4) in ≥10% of patients who received ZEJULA in NOVA were nausea (74%), thrombocytopenia (61%), fatigue/asthenia (57%), anemia (50%), constipation (40%), vomiting (34%), neutropenia (30%), insomnia (27%), headache (26%), decreased appetite (25%), nasopharyngitis (23%), rash (21%), hypertension (20%), dyspnea (20%), mucositis/stomatitis (20%), dizziness (18%), back pain (18%), dyspepsia (18%), leukopenia (17%), cough (16%), urinary tract infection (13%), anxiety (11%), dry mouth (10%), AST/ALT elevation (10%), dysgeusia (10%), palpitations (10%).

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%).

Treatment of Advanced HRD+ Ovarian Cancer

Most common adverse reactions (Grades 1-4) in ≥10% of patients who received ZEJULA in QUADRA were nausea (67%), fatigue (56%), thrombocytopenia (52%), anemia (51%), vomiting (44%), constipation (36%), abdominal pain (34%), musculoskeletal pain (29%), decreased appetite (27%), dyspnea (22%), insomnia (21%), neutropenia (20%), headache (19%), diarrhea (17%), acute kidney injury (17%), urinary tract infection (15%), hypertension (14%), cough (13%), dizziness (11%), AST/ALT elevation (11%), blood alkaline phosphatase increased (11%).

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

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 "Risk Factors" in the company's Annual Report on Form 20-F for 2019 and any impacts of the COVID-19 pandemic.

[i] Konstantinopoulos PA, Ceccaldi R, Shapiro GI, D'Andrea AD. Homologous Recombination Deficiency: Exploiting the Fundamental Vulnerability of Ovarian Cancer. *Cancer Discov.* 2015; 5(11): 1137-54.

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[iv] Lorusso D, Mancini M, Di Rocco R, Fontanelli R, Raspagliesi F. The role of secondary surgery in recurrent ovarian cancer [published online August 5, 2012]. *Int J Surg Oncol*. 2012. doi:10.1155/2012/613980