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GSK Announces U.S. Food and Drug Administration Approval of Additional Indication for Zejula (niraparib) for Late-line Treatment for Women with Recurrent Ovarian Cancer

- Expanded indication allows for treatment of women whose advanced ovarian cancer is associated with homologous recombination deficiency (HRD)
- Zejula is now the only, once-daily PARP inhibitor approved as monotherapy treatment for recurrent ovarian cancer beyond those with a *BRCA* mutation in both the recurrent maintenance and late-line treatment settings

GlaxoSmithKline (LSE/NYSE: GSK) today announced that the company has received approval from the U.S. Food and Drug Administration (FDA) for an expanded indication for Zejula (niraparib), an oral, once-daily poly (ADP-ribose) polymerase (PARP) inhibitor for the treatment of advanced ovarian, fallopian tube, or primary peritoneal cancer patients, 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.

Patient selection is based on an FDA-approved companion diagnostic for Zejula.

This represents the first time a PARP inhibitor has been approved for use in patients beyond those with a *BRCA*-positive (*BRCA*+) mutation as monotherapy in the late-line treatment setting. Now women with late-line, HRD-positive (HRD+) disease are eligible to be treated with a PARP inhibitor.

Axel Hoos, MD, PhD, SVP Oncology R&D, GSK, said: “This new indication reinforces our commitment to providing treatment options for more women impacted by ovarian cancer, especially those with high unmet needs. We look forward to continuing our clinical development program of Zejula and understanding its full potential as a treatment for people living with ovarian cancer.”

This new indication is based on the QUADRA study, a Phase 2, multi-center, open-label, single-arm clinical study representing a real world, difficult-to-treat patient population with high unmet needs. QUADRA is the largest clinical trial of a PARP inhibitor in women who received three or more treatments for advanced ovarian cancer. The trial enrolled a broad patient population including women with *BRCA*+ platinum-sensitive, resistant and refractory disease as well as women with HRD+ platinum-sensitive disease.

PRESS RELEASE

Clinically meaningful and durable benefit was demonstrated in the FDA-indicated patient population with an objective response rate (ORR) of 24% (95% CI, 16–34). A median duration of response (mDOR) of 8.3 months (95% CI, 6.5–not estimable) was observed.

Additional analyses were conducted in various sub populations where efficacy of Zejula was also demonstrated for patients with t*BRCA* and GIS; defined as deleterious or suspected deleterious somatic or germline *BRCA* mutation and genomic instability score (GIS ≥42) as identified with Myriad's myChoice® companion diagnostic test, respectively:

- t*BRCA*+ platinum-sensitive disease, ORR of 39% (95% CI, 17,64);
- t*BRCA*+ platinum-resistant disease, ORR of 29% (95% CI, 11,52);
- t*BRCA*+ platinum-refractory disease, ORR of 19% (95% CI, 4,46); or
- non-*BRCA* mut, GIS-positive, platinum-sensitive disease, ORR of 20% (95% CI, 8,37).

The safety profile was consistent with that seen in the Phase 3 NOVA trial in the recurrent maintenance population. Most common grade ≥3 adverse reactions reported in ≥10% of patients in the QUADRA study included thrombocytopenia (28%), anemia (27%), neutropenia (13%) and nausea (10%).

Dr. Kathleen Moore, Lead Investigator of the QUADRA study; Director, Oklahoma TSET Phase 1 Program; Associate Professor, Section of Gynecologic Oncology, Stephenson Cancer Center, University of Oklahoma, said: "Ovarian cancer has a high rate of recurrence, so there is a real need for therapies for women whose cancer has progressed through multiple lines of treatment and who have few or no options left. It's meaningful to see that Zejula has been approved as a late-line treatment for women including those with and without *BRCA* mutations."

Ovarian cancer affects nearly 222,000 women in the U.S., and approximately 85% of women with advanced ovarian cancer will see the disease return. With each recurrence, the time a woman may spend without her cancer progressing until the next recurrence gets shorter. Currently, there are few effective options available for treatment of platinum-resistant/refractory advanced ovarian cancer or HRD+ ovarian cancer in the late-line setting. Zejula received initial FDA approval in March 2017 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. It is the only oral, once-daily PARP inhibitor.

About QUADRA
QUADRA is a large multi-center, open-label, single-arm, Phase 2 registrational study that evaluated the safety and activity of niraparib in adult patients with relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who were treated with three or more previous chemotherapy regimens. Four hundred and sixty-three patients were enrolled and received oral niraparib at a starting dose of 300 mg once daily. Treatment was continued until disease progression. The primary objective was the proportion of patients achieving an investigator-assessed confirmed overall response in patients with HRD+ tumors, including patients with *BRCA* and without *BRCA* mutations, sensitive to their last platinum-based therapy. Additional objectives of the study were to evaluate the efficacy of niraparib in the broad late-line ovarian cancer population overall, and in subgroups defined by clinical and molecular biomarkers, such as platinum-sensitivity and *BRCA*+ and HRD status.

The Myriad myChoice companion diagnostic test was utilized during this clinical trial and has been approved by the FDA as the companion diagnostic test to determine HRD+ status as either t*BRCA* and/or a genomic instability score (GIS ≥42). GIS is an algorithmic measurement of Loss of Heterozygosity (LOH), Telomeric Allelic Imbalance (TAI), and Large-scale State Transitions (LST).

Information about Myriad myChoice companion diagnostic is available at Myriad.com.

PRESS RELEASE

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. Despite high response rates to platinum-based chemotherapy in the front-line, approximately 85% of patients will experience disease recurrence. Once the disease recurs, its considered incurable with time to each future recurrence getting shorter. Late-line treatment options for women with ovarian cancer are few, with the proportion of patients achieving an overall response typically less than 10% when treated with chemotherapy.

About 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 program by assessing activity across multiple tumor types and by evaluating several potential combinations of niraparib with other therapeutics. The ongoing development program for niraparib includes a Phase 3 trial as monotherapy maintenance treatment in patients with first-line ovarian cancer (PRIMA), data from this study were recently presented at the European Society for Medical Oncology Congress (ESMO), a Phase 3 study as a first-line triplet maintenance treatment in ovarian cancer (FIRST), and a Phase 2 study of niraparib combined with bevacizumab maintenance treatment in advanced ovarian cancer (OVARIO).

Several combination studies are also underway, including trials of niraparib plus pembrolizumab in metastatic, triple-negative breast cancer and advanced, platinum-resistant ovarian cancer (TOPACIO). Janssen Biotech has licensed rights to develop and commercialize niraparib specifically for patients with prostate cancer worldwide, except in Japan.

Important Safety Information

Zejula may cause serious side effects, including:

Bone marrow problems called Myelodysplastic Syndrome (MDS) or a type of blood cancer called Acute Myeloid Leukemia (AML). Some people who have ovarian cancer and who have received previous treatment with chemotherapy or certain other medicines for their cancer have developed MDS or AML during treatment with Zejula. MDS or AML may lead to death.

Symptoms of low blood cell counts (low red blood cells, low white blood cells, and low platelets) are common during treatment with Zejula. They can be a sign of serious bone marrow problems, including MDS or AML. These symptoms may include the following:

- Weakness
- Feeling tired
- Weight loss
- Frequent infections
- Fever
- Shortness of breath
- Blood in urine or stool
- Bruising or bleeding more easily

Uncommonly, fever associated with low white blood cells is observed during treatment with Zejula.

Your doctor will do blood tests to check your blood cell counts before treatment with Zejula. You will be tested weekly for the first month of treatment with Zejula, monthly for the next 11 months of treatment, and from time to time afterward.

PRESS RELEASE

High blood pressure is common during treatment with Zejula, and it can become serious. Your doctor will check your blood pressure and heart rate at least weekly for the first two months, then monthly for the first year, and as needed thereafter during your treatment with Zejula.

Before starting to take Zejula, tell your doctor about all of your medical conditions, including if you:

- Have heart problems
- Have high blood pressure
- Are pregnant or plan to become pregnant. Zejula may harm an unborn baby and may cause loss of pregnancy (miscarriage)
    - If you are able to become pregnant, you should use effective birth control (contraception) during treatment with Zejula and for 6 months after taking the last dose of Zejula
    - If you are able to become pregnant, your doctor may perform a pregnancy test before you start treatment with Zejula
    - You should tell your doctor right away if you become pregnant
- Are breastfeeding or plan to breastfeed
    - Zejula may harm your baby. You should not breastfeed your baby during treatment with Zejula and for 1 month after taking the last dose of Zejula

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

The most common side effects of Zejula include the following:

- Heart not beating regularly
- Nausea
- Constipation
- Vomiting
- Pain in the stomach area
- Mouth sores
- Diarrhea
- Indigestion or heartburn
- Dry mouth
- Tiredness
- Loss of appetite
- Urinary tract infection
- Shortness of breath
- Cough
- Rash
- Changes in liver function or other blood tests
- Pain in your joints, muscles, and back
- Headache
- Dizziness
- Change in the way food tastes
- Trouble sleeping
- Anxiety
- Sore throat
- Changes in the amount or color of your urine

PRESS RELEASE

If you have certain side effects, then your doctor may change your dose of Zejula, temporarily stop, or permanently stop treatment with Zejula.

These are not all the possible side effects of Zejula. For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

For full prescribing information visit www.zejula.com/prescribing-information.

myChoice companion diagnostic is a registered trademark of Myriad.

About GSK Oncology
GSK is focused on maximizing 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 utilizing 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.

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