CLINICAL UPDATE

Brand Name	Zejula®
Generic Name	niraparib
Drug Manufacturer	Glaxosmithkline

Clinical Update

TYPE OF CLINICAL UPDATE

New Dosage Form and Strengths

FDA APPROVAL DATE

April 26, 2023

LAUNCH DATE

June 20, 2023

REVIEW DESIGNATION

Type 3 - New Dosage Form; New Drug Application (NDA): 214876

TYPE OF REVIEW

Standard; Orphan

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

Zejula® is a poly (ADP-ribose) polymerase (PARP) inhibitor 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 deleterious or suspected deleterious germline BRCA-mutated recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Zejula®.

MECHANISMS OF ACTION

Niraparib is an inhibitor of PARP enzymes, including PARP-1 and PARP-2, that play a role in DNA repair. In vitro studies have shown that niraparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage, apoptosis, and cell death. Increased niraparib-induced cytotoxicity was observed in tumor cell lines with or without deficiencies in BRCA1/2. Niraparib decreased tumor growth in mouse xenograft models of human cancer cell lines with deficiencies in BRCA1/2 and in human patient-derived xenograft tumor models with homologous recombination deficiency (HRD) that had either mutated or wild-type BRCA1/2.

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DOSAGE FORM(S) AND STRENGTH(S)

Tablets: 100 mg, 200 mg, 300 mg

DOSE & ADMINISTRATION

First-line maintenance treatment of advanced ovarian cancer:

- For patients weighing <77 kg (< 170 lbs) or with a platelet count < 150,000/mcL, the recommended dosage is 200 mg taken orally once daily.
- For patients weighing ≥77 kg (≥170 lbs) AND a platelet count ≥ 150,000/ mcL, the recommended dosage is 300 mg taken orally once daily.
- Maintenance treatment of recurrent germline BRCA-mutated ovarian cancer: The recommended dosage is 300 mg taken orally once daily.

EFFICACY

First-Line Maintenance Treatment of Advanced Ovarian Cancer

PRIMA was a double-blind, placebo-controlled trial in which patients (N = 733) in complete or partial response to first-line platinum-based chemotherapy were randomized 2:1 to Zejula® or matched placebo. Initially, the patients received a starting dosage of 300 mg once daily regardless of body weight or platelet count. The study was amended to include a starting dose of 200 mg for patients weighing < 77 kg (<170 lbs) OR with a platelet count of <150,000/mcL or 300 mg for patients weighing ≥ 77 Kg (≥ 170 lbs) AND who had a platelet count ≥150,000/mcL.

Patients were randomized post-completion of first-line platinum-based chemotherapy plus surgery. Randomization was stratified by best response during the front-line platinum regimen (complete response vs. partial response), neoadjuvant chemotherapy (NACT) (yes vs. no), and HRD status (positive vs. negative or not determined). HRD status was determined using the FDA-approved Myriad my Choice CDx assay. HRD positive status included either tumor BRCA mutant (tBRCAm) or a genomic instability score (GIS) ≥42.

The major efficacy outcome measure, progression-free survival (PFS), was determined by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. In some cases, criteria other than RECIST, such as clinical signs and symptoms and increasing CA-125, were also applied. Overall survival was an additional efficacy outcome measure. PFS testing was performed hierarchically: first in the homologous recombination (HR)-deficient (HRD positive) population, then in the overall population. The median age of 62 ranged from 32 to 85 years among patients randomized with Zejula® and 33 to 88 years among patients randomized with placebo. Eighty-nine percent of all patients were White. Sixty-nine percent of patients randomized with Zejula® and 71% of patients randomized with placebo had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 at study baseline. Approximately 45% of patients were enrolled in the U.S. or Canada. In the overall population, 65% of patients had stage III disease and 35% had stage IV disease.

Sixty-seven percent of the patients received NACT. Sixty-nine percent of the patients had a complete response to the first-line platinum-based chemotherapy. Approximately 35% (n = 258) of patients received a starting dose of 200 or 300 mg depending on baseline body weight and platelet count. Among those patients, 186 patients received a starting dose of 200 mg.

PRIMA demonstrated a statistically significant improvement in PFS for patients randomized to Zejula® as compared with placebo in the HR-deficient and overall population.

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Maintenance Treatment of Recurrent Germline *BRCA*-mutated Ovarian Cancer

NOVA (NCT01847274) was a double-blind, placebo-controlled trial in which patients (N = 553) with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer were randomized 2:1 to Zejula® 300 mg orally daily or matched placebo within 8 weeks of the last therapy. Treatment was continued until disease progression or unacceptable toxicity. All patients had received at least 2 prior platinum-containing regimens and were in response (complete or partial) to their most recent platinum-based regimen.

Randomization was stratified by time to progression after the penultimate platinum therapy (6 to <12 months and ≥12 months), use of bevacizumab in conjunction with the penultimate or last platinum regimen (yes/no), and best response during the most recent platinum regimen (complete response and partial response). Eligible patients were assigned to 1 of 2 cohorts based on the results of germline *BRCA* testing with Myriad BRAC Analysis CDx. Patients with deleterious or suspected deleterious germline *BRCA* mutations (g*BRCA*mut) were assigned to the germline *BRCA*-mutated (g*BRCA*mut) cohort (n = 203), and those without germline *BRCA* mutations were assigned to the non-g*BRCA*mut cohort (n = 350). The efficacy results are based on the g*BRCA*mut cohort only.

The major efficacy outcome measure, PFS, was determined primarily by central independent assessment per RECIST version 1.1. In some cases, criteria other than RECIST, such as clinical signs and symptoms and increasing CA-125, were also applied. Overall survival (OS) was an additional outcome measure.

For the g*BRCA*mut cohort, the median age of patients was 57 years among patients treated with Zejula® and 58 years among patients treated with placebo. Eighty-eight percent of all patients were White. Sixty-six percent of patients receiving Zejula® and 74% of patients receiving placebo had an ECOG PS of 0 at study baseline. Approximately 40% of patients were enrolled in the U.S. or Canada, and 51% of all patients were in complete response to most recent platinum-based regimen, with 39% on both arms with an interval of 6 to 12 months since the penultimate platinum regimen. Twenty-four percent of those treated with Zejula®and 26% treated with placebo had received prior bevacizumab therapy. Approximately 50% of patients had 3 or more lines of treatment.

The trial demonstrated a statistically significant improvement in PFS for patients randomized to Zejula® as compared with placebo in the g*BRCA*mut cohort.