PRIMA Trial
ENGOT-OV26/ GOG-3012

Zejula® (niraparib) is an oral, once-daily poly (ADP-ribose) polymerase (PARP) 1 and PARP 2 inhibitor that is now approved 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.[i]

PRIMA Study Design[ii,iii]

Randomised, double-blind, placebo-controlled Phase 3 study conducted in 20 countries across 181 sites, designed to assess whether Zejula as a maintenance treatment would increase progression-free survival in the first-line therapy of women with Stage III or IV ovarian cancer who responded to platinum-based chemotherapy.

The primary endpoint was progression-free survival in patients, regardless of biomarker status.

Overall survival was a key secondary endpoint. Other secondary endpoints included the time until the first subsequent therapy, progression-free survival 2, pharmacokinetic analyses, and patient-reported outcomes.

Patients

733
Women with advanced ovarian cancer (Stage III or IV)

2:1
randomized 2:1 to 2 arms. Zejula or placebo

46.9% vs 64.1%
percentage of patients who received neoadjuvant chemotherapy (Zejula vs. placebo)

Zejula

484
Women received Zejula

245
had homologous-recombination deficiency

239
had homologous-recombination proficiency

Placebo

244
women received placebo

125
had homologous-recombination deficiency

119
had homologous-recombination proficiency

Key Findings[ii,iii]

Among patients with newly diagnosed advanced ovarian cancer who had a response to platinum-based chemotherapy, Zejula demonstrated statistically significant improvement in progression-free survival regardless of biomarker status. Among all patients, Zejula resulted in a 38% reduction in the risk of disease progression or death vs. placebo (HR 0.62; 95% CI, 0.50 to 0.76; p<0.001).

In an exploratory analysis, Patient-Reported Outcomes quality of life was consistent between Zejula and placebo.

Zejula (niraparib) Indication and Important Safety Information

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.

References

i ZEJULA U.S. Prescribing Information.

ii Gonzalez-Martin A, Pothuri B, Vergote I, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2019; 381:2391-2402. doi:10.1056/NEJMoa1910962.

iii A Study of Niraparib Maintenance Treatment in Patients With Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy - Full Text View. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02655016. Accessed February 2020.