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A SPECIAL MEETING REVIEW EDITION

Highlights in Ovarian Cancer From the 2017 American Society of Clinical Oncology Annual Meeting

A Review of Selected Presentations From the 2017 American Society of Clinical Oncology Annual Meeting • June 1-5, 2017 • Chicago, Illinois

Special Reporting on:

- Long-Term Benefit of Niraparib Treatment of Recurrent Ovarian Cancer
- Overall Survival Results of ICON6: A Trial of Chemotherapy and Cediranib in Relapsed Ovarian Cancer
- Efficacy of Niraparib on Progression-Free Survival in Patients With Recurrent Ovarian Cancer With Partial Response to the Last Platinum-Based Chemotherapy
- Relationship of Health-Related Quality of Life and Patient-Centered Outcomes With the Clinical Outcomes With Olaparib Maintenance Following Chemotherapy in Patients With Germline *BRCA*-Mutated Platinum-Sensitive Relapsed Serous Ovarian Cancer: SOLO2 Phase III Trial
- The Successful Phase 3 Niraparib ENGOT-OV16/NOVA Trial Included a Substantial Number of Patients With Platinum Resistant Ovarian Cancer
- Randomized Controlled Phase III Study Evaluating the Impact of Secondary Cytoreductive Surgery in Recurrent Ovarian Cancer: AGO DESKTOP III/ENGOT OV20

PLUS Meeting Abstract Summaries

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Long-Term Benefit of Niraparib Treatment of Recurrent Ovarian Cancer

In most women with advanced ovarian cancer, the disease will recur after first-line treatment. Niraparib is a poly(ADP-ribose) polymerase (PARP) inhibitor approved by the US Food and Drug Administration (FDA) as maintenance therapy for patients with recurrent epithelial ovarian, fallopian tube, or peritoneal cancer who are in a complete response (CR) or partial response (PR) after receiving platinum-based therapy.[1] The European Network of Gynaecological Oncological Trial Groups (ENGOT)-OV16/NOVA trial (A Maintenance Study With Niraparib Versus Placebo in Patients With Platinum Sensitive Ovarian Cancer) compared niraparib vs placebo as maintenance treatment in patients with recurrent, platinum-sensitive ovarian cancer.[2] Enrolled patients had received at least 4 prior cycles of a platinum agent. The multicenter, double-blind phase 3 study randomly assigned patients 2:1 to receive once-daily niraparib (300 mg) or placebo. Patients were assigned to cohorts based on their *BRCA* mutation status. The median age ranged from 57 years to 63 years across cohorts. Approximately one-third of patients had 3 or more sites of metastatic disease. Disease assessment, which included imaging, was performed at baseline, every 8 weeks through cycle 14, and then every 12 weeks until treatment was discontinued. Disease progression was evaluated by independent central radiologic review that incorporated Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 or clinical signs and symptoms.

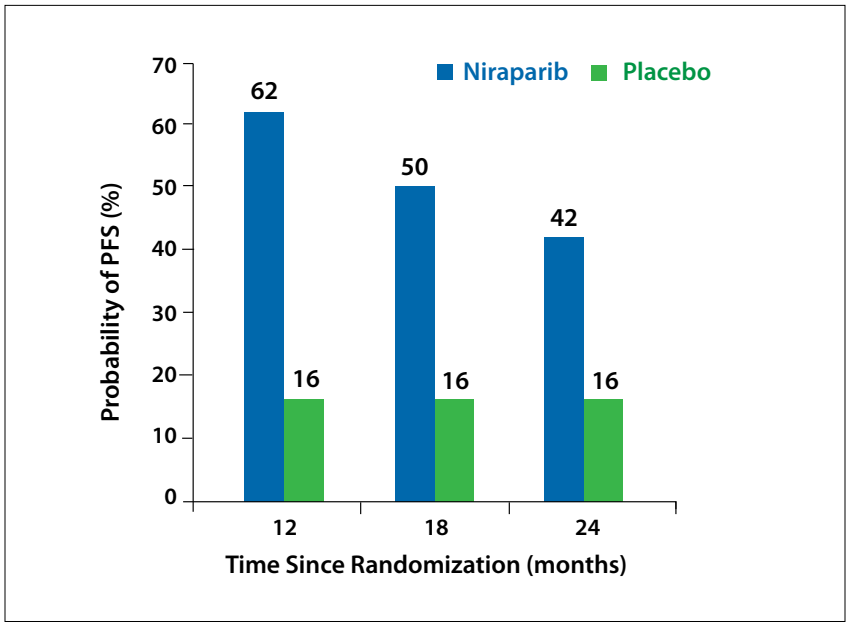

Figure 1. Probability of PFS among patients with the germline *BRCA* mutation in the NOVA trial. NOVA, A Maintenance Study With Niraparib Versus Placebo in Patients With Platinum Sensitive Ovarian Cancer; PFS, progression-free survival. Adapted from Matulonis UA et al. ASCO abstract 5534. *J Clin Oncol.* 2017;35(15 suppl).[3]

Among the 203 patients with a germline *BRCA* mutation, niraparib maintenance yielded a median progression-free survival (PFS) of 21.0 months vs 5.5 months with placebo (hazard ratio [HR], 0.27; 95% CI, 0.17-0.41; *P*<.0001). Among the 350 patients without the germline *BRCA* mutation, PFS was 9.3 months with niraparib vs 3.9 months with placebo (HR, 0.45; 95% CI, 0.34-0.61; *P*<.001). Niraparib also prolonged PFS in the subgroup of patients who lacked the germline *BRCA* mutation but had tumors with homologous recombination deficiency (12.9 months vs 3.8 months; HR, 0.38; 95% CI, 0.24-0.59; *P*<.001). The most common grade 3/4 adverse events (AEs) associated with niraparib were thrombocytopenia (33.8%), anemia (25.3%), and neutropenia (19.6%).

Dr Ursula Matulonis and colleagues analyzed data from the NOVA trial to determine the long-term efficacy of niraparib and its impact on subsequent therapy.[3] The product-limit/Kaplan-Meier method was used to estimate the PFS probability at 12, 18, and 24 months after randomization. The impact of niraparib on subsequent therapy was determined by subtracting the patient's first PFS (PFS1) from the second PFS (PFS2).

Niraparib was associated with a superior estimated PFS probability at 12, 18, and 24 months, regardless of the patient's *BRCA* mutation status. Among patients with the germline *BRCA* mutation, PFS probabilities were 62% for niraparib vs 16% for placebo at 12 months, 50% vs 16%

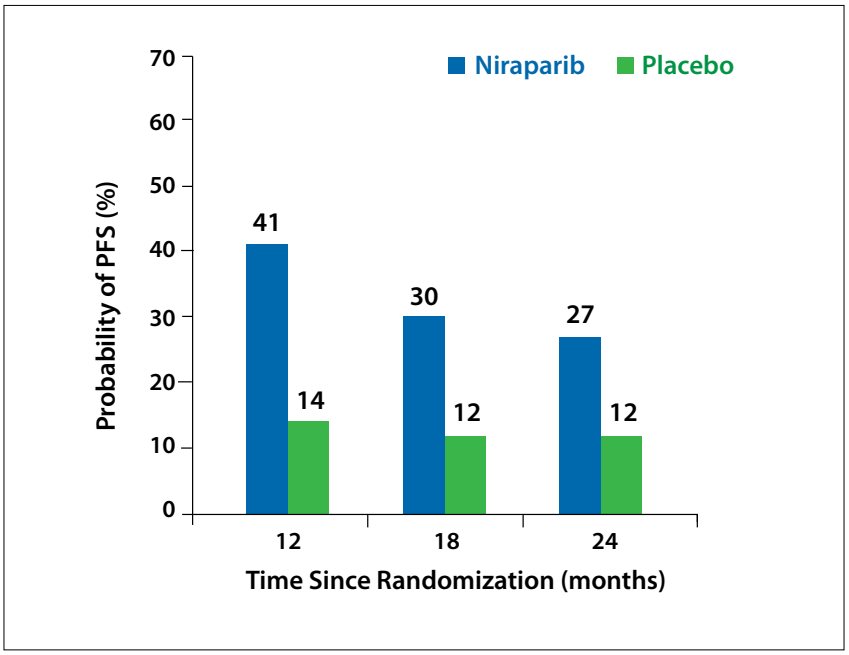

Figure 2. Probability of PFS among patients without the germline *BRCA* mutation in the NOVA trial. NOVA, A Maintenance Study With Niraparib Versus Placebo in Patients With Platinum Sensitive Ovarian Cancer; PFS, progression-free survival. Adapted from Matulonis UA et al. ASCO abstract 5534. *J Clin Oncol.* 2017;35(15 suppl).[3]

at 18 months, and 42% vs 16% at 24 months (Figure 1). In patients without the germline *BRCA* mutation, PFS probabilities were 41% for niraparib vs 14% for placebo at 12 months, 30% vs 12% at 18 months, and 27% vs 12% at 24 months (Figure 2).

Among patients in the combined cohorts, PFS2 minus PFS1 was similar in the niraparib and placebo arms (HR, 1.02; Figure 3). This finding suggests that patients who had received treatment with niraparib were not resistant to subsequent therapy.

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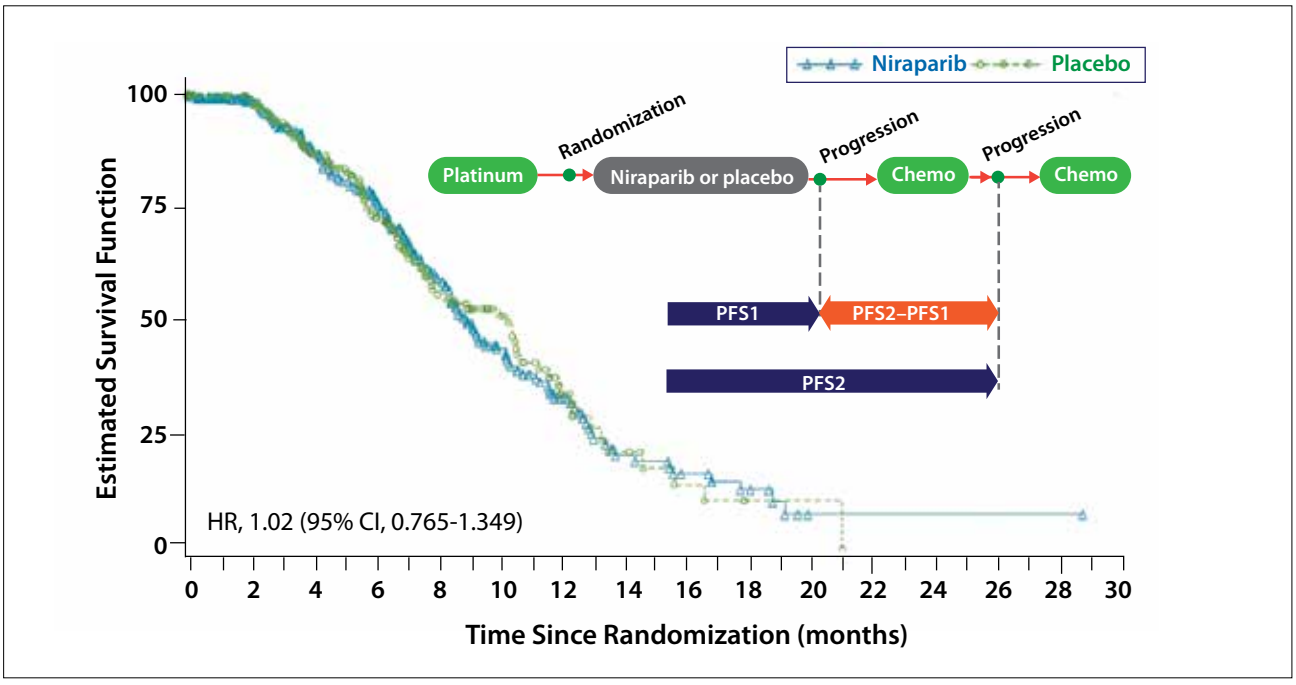

Figure 3. Estimated survival among all patients in the NOVA trial. Chemo, chemotherapy; HR, hazard ratio; NOVA, A Maintenance Study With Niraparib Versus Placebo in Patients With Platinum Sensitive Ovarian Cancer; PFS, progression-free survival. Adapted from Matulonis UA et al. ASCO abstract 5534. *J Clin Oncol.* 2017;35(15 suppl).[3]

Overall Survival Results of ICON6: A Trial of Chemotherapy and Cediranib in Relapsed Ovarian Cancer

In patients with relapsed ovarian cancer, the duration of response shortens with each successive line of therapy. Maintenance therapy has been proposed as a potential means to increase the intervals between treatments. Cediranib is a potent oral inhibitor of the vascular endothelial growth factor receptors (VEGFRs) 1 to 3 and c-Kit, with up to 5000-fold selectivity for VEGFR2.[1] Cediranib has been shown to inhibit growth of established lung, colorectal, prostate, breast, and ovarian xenografts.[2] It demonstrated single-agent activity in a phase 2 trial of patients with recurrent epithelial ovarian cancer, peritoneal cancer, or fallopian tube cancer.[3]

Dr Joshua Ledermann presented overall survival (OS) results from the ICON6 trial (A Randomised, Placebo-Controlled, Trial of Concurrent Cediranib [AZD2171] [With Platinum-Based Chemotherapy] and Concurrent and Maintenance Cediranib in Women With Platinum-Sensitive Relapsed Ovarian Cancer), which evaluated the safety and efficacy of cediranib in combination with platinum-based chemotherapy and as maintenance therapy in patients with a first relapse of platinum-sensitive ovarian cancer.[4,5] Patients were enrolled at 63 centers in Australia, Canada, New Zealand, Spain, and the United Kingdom. Enrolled patients had epithelial ovarian, fallopian tube, or serous primary peritoneal cancer that had relapsed more than 6 months after first-line chemotherapy. Patients were required to have measurable or nonmeasurable relapsed disease confirmed by computed tomography or magnetic resonance imaging. Patients had a clinical need for chemotherapy and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Prior maintenance with a biological therapy, such as bevacizumab, was allowed. Patients who had received prior chemotherapy maintenance were excluded.

There were 3 treatment arms. Patients in arm A received chemotherapy plus placebo followed by placebo maintenance. Patients in arm B received chemotherapy plus cediranib (20 mg daily) followed by placebo maintenance. Patients in arm C received chemotherapy plus cediranib (20 mg daily) followed by cediranib maintenance (20 mg daily). Patients received up to 6 cycles of platinum-based chemotherapy followed by the maintenance phase. Patients were randomly assigned 2:3:3 into arms A, B, or C, respectively.

The original trial design included 3 stages. During the safety stage, a projected 33 patients would receive cediranib (30 mg daily). The initial efficacy stage would evaluate the addition of cediranib (20 mg daily) to chemotherapy, with a planned enrollment of 600 patients. The second efficacy stage had a planned enrollment of 2000 patients throughout the 3 arms. In 2011, however, the study was redesigned based on pivotal trials of cediranib that yielded negative results in nonovarian tumor types.[6,7] The primary endpoint was altered to PFS, targeting an HR of 0.65 for the comparison between arm A and arm C. The expected enrollment was 440 patients.

The trial enrolled 118 patients into arm A, 174 into arm B, and 164 into arm C. Patients had a median age of 62 years (range, 30-86 years), and approximately 60% had an ECOG performance status of 0. For approximately two-thirds of patients, more than 12 months had elapsed since they last received chemotherapy. Nearly 90% of patients had received prior paclitaxel, and 5% of patients had received prior bevacizumab. The trial demonstrated a superior PFS in patients treated with cediranib, yielding

ABSTRACT SUMMARY LION: Lymphadenectomy in Ovarian Neoplasms—a Prospective Randomized AGO Study Group Led Gynecologic Cancer Intergroup Trial

The phase 3 LION trial (Lymphadenectomy in Ovarian Neoplasms) investigated the impact of systemic pelvic and paraaortic lymphadenectomy in patients with advanced ovarian cancer and macroscopic complete resection (Abstract 5500). Enrolled patients had FIGO stage IIB or IV disease, a macroscopic complete resection, no bulky nodes, and no contraindication to lymphadenectomy. Patients in the control arm did not undergo lymphadenectomy. Patients had a median age of 60 years (range, 21-83 years), and 78% of patients had stage III/IV disease. In the lymphadenectomy arm, the median number of resected pelvic lymph nodes was 35 (range, 26-43), and the median number of resected paraaortic lymph nodes was 22 (range, 16-33). Subclinical retroperitoneal lymph node metastases were detected and removed in 56% of patients. Median OS was 65.5 months for patients who underwent systemic pelvic and paraaortic lymphadenectomy vs 69.2 months for patients in the control arm (HR, 1.057; 95% CI, 0.833-1.341).

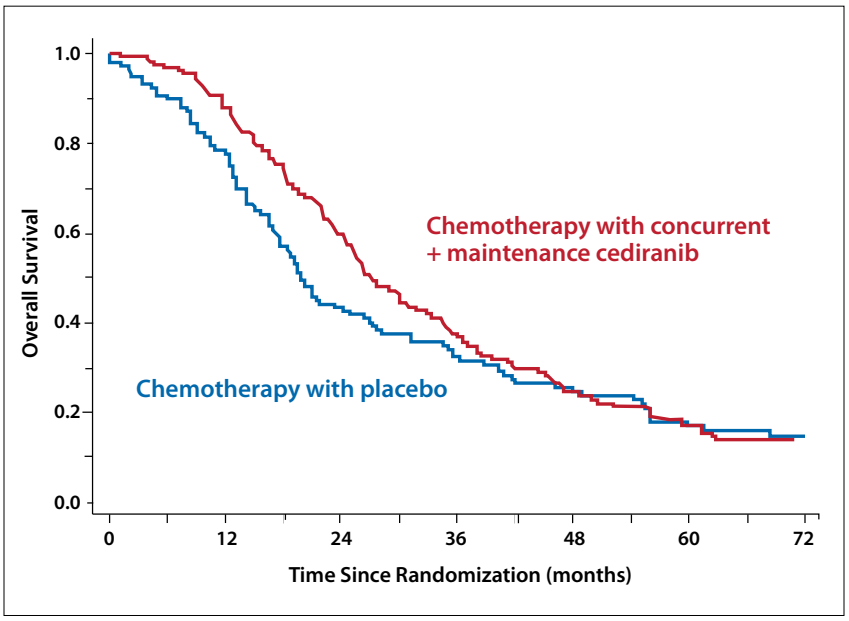

Figure 4 Overall survival in the ICON6 trial. ICON6, A Randomised, Placebo-Controlled, Trial of Concurrent Cediranib (AZD2171) (With Platinum-Based Chemotherapy) and Concurrent and Maintenance Cediranib in Women With Platinum-Sensitive Relapsed Ovarian Cancer. Adapted from Ledermann JA et al. ASCO abstract 5506. *J Clin Oncol.* 2017;35(15 suppl).[5]

ABSTRACT SUMMARY Pembrolizumab in Patients With PD-L1–Positive Advanced Ovarian Cancer: Updated Analysis of KEYNOTE-028

The phase 1b KEYNOTE-28 trial evaluated the safety and efficacy of pembrolizumab in patients with advanced, recurrent, ovarian cancer positive for programmed death ligand 1 (Abstract 5513). The 26 enrolled patients had a median age of 57.5 years (range, 44-75 years), and 73% of patients had received 3 or more prior lines of therapy for advanced disease. Patients received pembrolizumab (10 mg/kg) every 2 weeks for a maximum of 24 months. One patient experienced a grade 3 treatment-related AE of increased transaminase levels. However, no study treatment discontinuations occurred owing to treatment-related AEs. No patients died. The most common treatment-related AEs of grade 2 or higher were arthralgia (19.2%), nausea (15.4%), and pruritus (15.4%). One patient had a CR and 2 had a PR, yielding an ORR of 11.5% (95% CI, 2.4%-30.2%). Tumor size reduction was maintained in the 3 patients who demonstrated a response, and 4 additional patients experienced a reduction in tumor size. Pembrolizumab will be further investigated in the phase 2 KEYNOTE-100 trial in patients with advanced, recurrent ovarian cancer.

a median PFS of 11.1 months for arm C vs 8.7 months for arm A (HR, 0.57; 95% CI, 0.45-0.74; *P*=.00001).

Median OS was 19.9 months in arm A vs 27.3 months in arm C (HR, 0.85; 95% CI, 0.66-1.10; *P*=.21; Figure 4). Nonproportionality was evidenced by a *P* value of .0029. The restricted mean survival time was 29.4 months for arm A vs 34.2 months for arm C, reflecting a difference of 4.8 months (95% CI, -0.1 to 9.8 months) throughout 6 years. In the 2 arms, 81% of patients received a third line of treatment. The median time to the next line of treatment was 10.7 months in arm A vs 13.2 months in arm C. Fifty-eight percent of patients received a fourth line of treatment, and 34% received 5 or more lines of treatment.

Toxicity was generally higher in arm C. Throughout the study, rates of treatment discontinuation owing to toxicity were 12% in arm A vs 39% in arm C. During the chemotherapy phase, these rates were 7% in arm A vs 27% in arm C. During the maintenance phase, 5% of patients in arm A vs 20% of those in arm C discontinued therapy owing to toxicity. The most common AEs during the chemotherapy and maintenance phases were fatigue, diarrhea, hypertension, hypothyroidism, and voice changes.

The ICON9 trial (Randomised Trial of Cediranib and Olaparib Maintenance in Patients With Relapsed Platinum Sensitive Ovarian Cancer) will evaluate cediranib plus olaparib maintenance following platinum-based chemotherapy for first-line treatment of platinum-sensitive, relapsed, high-grade ovarian cancer in patients with wild-type or mutated *BRCA*.

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Efficacy of Niraparib on Progression-Free Survival in Patients With Recurrent Ovarian Cancer With Partial Response to the Last Platinum-Based Chemotherapy

The phase 3 ENGOT-OV16/NOVA trial demonstrated a significant improvement in PFS with niraparib vs placebo in patients with recurrent ovarian cancer (N=553) who had achieved a CR or PR with platinum-based chemotherapy prior to trial enrollment.[1] The European Society for Medical Oncology guidelines recommend maintenance therapy for patients who have any type of response to platinum-based chemotherapy.[2] The National Comprehensive Cancer Network recommends consideration of niraparib maintenance therapy for patients who achieve a CR or PR in response to platinum-based treatment.[3]

Dr Mansoor Mirza presented results of a post hoc analysis of efficacy, safety, and patient-reported outcomes from the subset of patients in the ENGOT-OV16/NOVA trial who had achieved a PR after their last platinum-based chemotherapy (n=272).[4] Among patients with the germline *BRCA* mutation, a PR after the most recent platinum-based chemotherapy was reported in 67 of 138 patients in the niraparib arm and 32 of 65 patients in the placebo arm. These rates were similar among patients with wild-type *BRCA*, at 117 of 234 patients in the niraparib arm and 56 of 116 patients in the placebo arm.

This analysis aimed to identify any characteristics associated with a CR or PR within the cohorts of patients with vs without a germline *BRCA* mutation. Median age and duration of last platinum-based chemotherapy did not differ. Patients with a CR had a better ECOG performance status at baseline. Patients who achieved a PR were more likely than those with a CR to have had a PR to their penultimate platinum-based chemotherapy. Compared with patients who had achieved a CR, those with a PR had received more lines of platinum-based therapy and other types of chemotherapy prior to randomization.

A comparison of the PFS HRs showed no difference between the overall population in the ENGOT-OV16/NOVA trial and patients who achieved a PR to their most recent platinum-based chemotherapy. Specifically, among patients with a germline *BRCA* mutation, PFS HRs were 0.24 (95% CI, 0.131-0.441) in those who had achieved a PR to their most recent platinum-based chemotherapy vs 0.27 (95% CI, 0.173-0.410) in the overall study population (Figure 5). Among patients with the wild-type *BRCA* mutation, PFS HRs were 0.35 (95% CI, 0.230-0.532) in patients who had achieved a PR with their most recent

ABSTRACT SUMMARY Phase II Randomized Trial of Neoadjuvant Chemotherapy With or Without Bevacizumab in Advanced Epithelial Ovarian Cancer (GEICO 1205/NOVA TRIAL)

The multicenter, randomized phase 2 GEICO 1205/NOVA study (Neoadjuvant Therapy in Advanced Ovarian Cancer With Avastin) randomly assigned 68 patients with newly diagnosed, high-grade serous or endometrioid epithelial ovarian cancer to receive neoadjuvant carboplatin and paclitaxel with or without bevacizumab before interval debulking surgery (Abstract 5508). The 68 evaluable patients had a median age of 60 years, and 33.8% had stage IV disease. The rate of complete macroscopic resection was similar for both arms (6% each; *P*=.247). The rate of surgical feasibility was higher in patients treated with bevacizumab (89% vs 67.%; *P*=.029). The 2 arms demonstrated similar optimal surgery rates, and similar numbers of patients were considered unresectable at the time of interval debulking surgery. The median PFS was 20.1 months in the control arm vs 20.4 months in the bevacizumab arm (HR, 1.14; 95% CI, 0.656-1.994; *P*=.664). One patient in the bevacizumab arm died of postoperative sepsis. Eight patients in the bevacizumab arm developed AEs of special interest, which included proteinuria, hypertension, fistula, surgical dehiscence, thrombosis, and bleeding. However, rates of serious AEs were lower in the bevacizumab arm (69.7% vs 42.9%; *P*=.026).

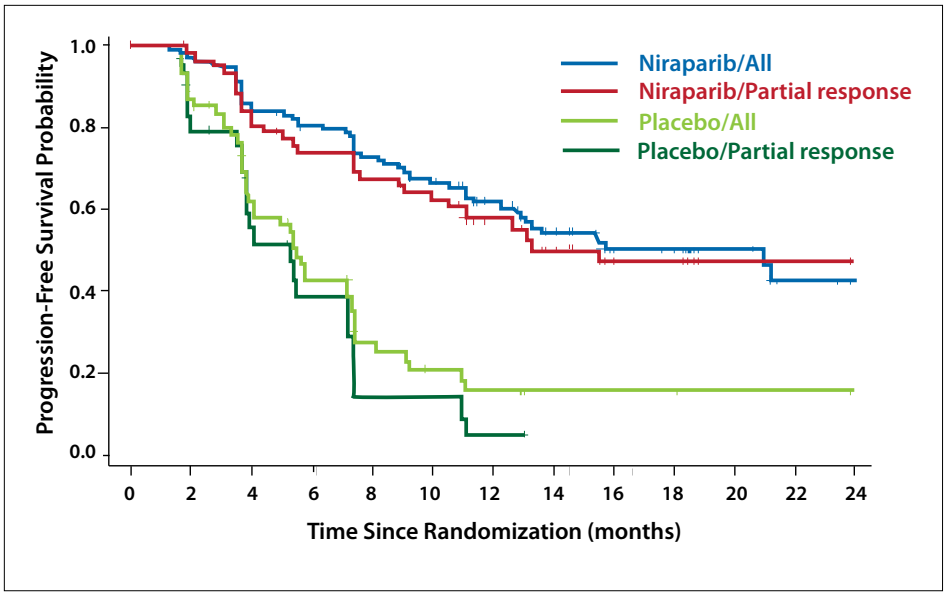

Figure 5. Progression-free survival among patients with a germline *BRCA* mutation in the NOVA trial of niraparib. This subanalysis focused on patients who had achieved a partial response to their most recent platinum-based chemotherapy. NOVA, A Maintenance Study With Niraparib Versus Placebo in Patients With Platinum Sensitive Ovarian Cancer. Adapted from Mirza MR et al. ASCO abstract 5517. *J Clin Oncol*. 2017;35(15 suppl).[4]

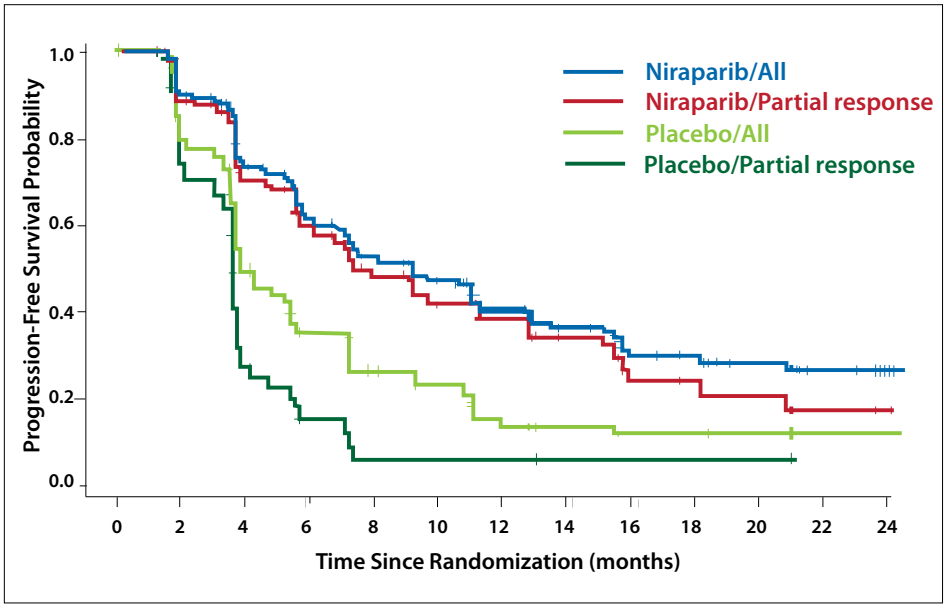

Figure 6. Progression-free survival among patients with wild-type *BRCA* in the NOVA trial of niraparib. This subanalysis focused on patients who had achieved a partial response to their most recent platinum-based chemotherapy. NOVA, A Maintenance Study With Niraparib Versus Placebo in Patients With Platinum Sensitive Ovarian Cancer. Adapted from Mirza MR et al. ASCO abstract 5517. *J Clin Oncol*. 2017;35(15 suppl).[4]

platinum-based chemotherapy vs 0.45 (95% CI, 0.338-0.607) in the overall study population (Figure 6).

Among patients with a PR, quality of life did not differ for those treated with niraparib vs placebo. Niraparib yielded a similar safety profile in patients with a PR compared with the overall study population. Among patients treated with niraparib, the incidence of grade 3 or higher AEs was similar for patients who had achieved a PR and for the overall study population. Among the niraparib-treated patients who had achieved a PR with their most recent platinum-based chemotherapy, the most common grade 3/4 AEs were thrombocytopenia (25.6%), anemia (26.1%), neutropenia (10.0%), hypertension (9.4%), and fatigue (2.8%).

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Relationship of Health-Related Quality of Life and Patient-Centered Outcomes With the Clinical Outcomes With Olaparib Maintenance Following Chemotherapy in Patients With Germline *BRCA*-Mutated Platinum-Sensitive Relapsed Serous Ovarian Cancer: SOLO2 Phase III Trial

Dr Michael Friedlander presented findings from an evaluation of patient-centered outcomes and health-related quality of life in patients from the SOLO2 trial (Studies of Olaparib in Ovarian Cancer 2)/ENGOT-OV21.[1] Based on the consensus statement from the fifth Ovarian Cancer Consensus Conference, PFS is the preferred endpoint for clinical trials in ovarian cancer when the expected median OS of the study population exceeds 12 months. However, because OS is heavily dependent on subsequent therapy in this patient population, PFS must be supported by additional endpoints, including predefined patient-reported outcomes, time to second subsequent therapy, and time until definitive deterioration of quality of life. Because PFS alone does not reflect the patients' health-related quality of life during treatment, several points should be considered when designing patient-reported outcomes in the context of maintenance therapy. The vast majority of patients who complete chemotherapy and respond to treatment are relatively well and not experiencing side effects. Treatment should therefore have a limited impact on quality of life. Any delay in disease progression should be accompanied by preservation of the patient's quality of life.

The phase 3 SOLO2 study evaluated olaparib among patients with relapsed serous ovarian cancer that was sensitive to platinum therapy. Patients had a germline *BRCA1/2* mutation, had received 2 or more prior lines of platinum-based therapy, and had achieved a CR or PR with their most recent therapy.[2] Patients were randomly assigned 2:1 to receive maintenance treatment with olaparib (300 mg) twice daily or placebo. The primary endpoint was PFS. The study's main hypothesis was that maintenance therapy with olaparib would not negatively impact health-related quality of life compared with placebo, and that patients would experience quality-of-life benefits.

SOLO2 showed a significant difference in PFS for olaparib vs placebo (19.1 vs 5.5 months; HR, 0.30; 95% CI, 0.22-0.41; *P*<.0001). The study also reached its secondary efficacy endpoints, showing that olaparib extended the median time to first subsequent treatment (27.9 vs 7.1 months; HR, 0.28; 95% CI, 0.21-0.38; *P*<.0001) and the median time to second subsequent treatment (not reached vs 18.2 months; HR, 0.37; 95% CI, 0.27-0.53; *P*<.0001).

An AE of any grade was reported in 98.5% of patients in the olaparib arm vs 94.9% of patients in the placebo arm. The most common AEs of any grade in the olaparib arm were nausea, fatigue/asthenia, vomiting, and diarrhea. AEs of grade 3 or higher were more frequent in the olaparib arm vs the placebo arm (36.9% vs 18.2%), as were AEs leading to a dose reduction (25.1% vs 3.0%) or discontinuation (10.8% vs 2.0%). One patient in the olaparib arm died.

The main health-related quality-of-life endpoint was change from baseline in the Trial Outcome Index (TOI), which is based on the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) questionnaire. The FACT-O questionnaire combines questions about ovarian cancer symptoms with indicators of functional and physical well-being. FACT-O and EQ-5D-5L questionnaires were administered at several points, with

ABSTRACT SUMMARY A Randomized Phase II Evaluation of Weekly Gemcitabine Plus Pazopanib Versus Weekly Gemcitabine Alone in the Treatment of Persistent or Recurrent Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Carcinoma

An open-label, multisite, randomized phase 2 trial evaluated gemcitabine (1000 mg/m^2) administered on days 1 and 8 of each 3-week cycle with or without daily pazopanib (800 mg) in patients with ovarian cancer who had received up to 3 prior lines of chemotherapy (Abstract 5532). The study randomly assigned 73 patients to the control arm and 75 to the pazopanib arm. Patients had a median age of 63 years (range, 30-82 years), two-thirds had serous histology, and three-fourths had received 2 or 3 prior lines of therapy. Approximately 60% of patients in each arm had platinum-resistant disease. The most common grade 3/4 AE in the pazopanib arm was neutropenia (occurring in 35% of patients vs 21% in the gemcitabine-only arm). The mean number of treatment cycles was 4.56 in the gemcitabine-only arm and 4.9 in the gemcitabine-plus-pazopanib arm.

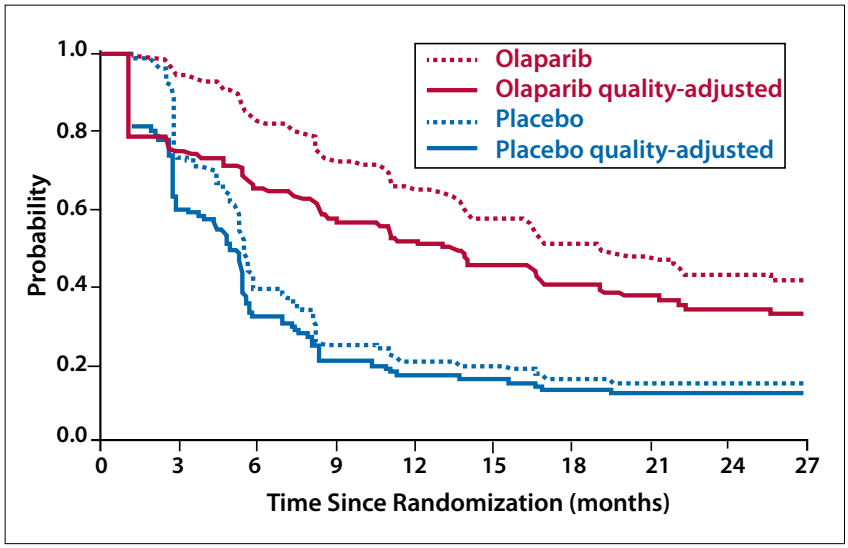

Figure 7. Quality-adjusted progression-free survival in the SOLO2 study. SOLO2, Studies of Olaparib in Ovarian Cancer 2. Adapted from Friedlander M et al. ASCO abstract 5507. *J Clin Oncol*. 2017;35(15 suppl).[1]

ABSTRACT SUMMARY Bevacizumab, Eribulin, and Oxaliplatin in Patients With Platinum-Resistant Ovarian Carcinomas: a Phase II Study With Biomarker Analysis

A phase 2 study with a 2-stage design investigated eribulin, bevacizumab, and oxaliplatin in patients with platinum-resistant and -refractory ovarian cancer (Abstract 5550). Treatment was administered on days 1, 8, and 15 in 4-week cycles. The 34 patients had a median age of 59 years (range, 35-76 years), 91% had FIGO stage III/IV disease, and 62% had received 4 or more prior lines of chemotherapy. After observation of 3 responses in the first stage, the study proceeded to the second stage. Two patients (6%) had a CR, 8 (24%) had a PR, and 16 (47%) had stable disease. Median PFS was 4 months (range, 1 to 27+ months). Four patients (11%) experienced grade 3/4 hematologic AEs. Median PFS was 3.0 ±1.9 months in patients with high p53 levels and 6.0 ±0.8 months in patients with low p53 levels. Median PFS was 2.0 ±1.6 months in patients with high interleukin 6 levels and 7.0 ±1.0 months in patients with low levels.

and without RECIST assessment. The questionnaires were administered at baseline and on day 29 of treatment. They were then administered with RECIST assessment every 12 weeks until disease progression. After disease progression, the questionnaires were administered when the patient visited the office to discontinue study treatment, 30 days after the final dose, and then every 12 weeks until data cutoff. Adherence was generally high during study treatment and ranged from more than 90% in both arms at baseline to approximately 80% at week 73. Adherence dropped to a low of approximately 60% for olaparib patients and 40% for placebo patients at 24 weeks after the end of treatment.

Analysis of the FACT-O TOI showed no significant detrimental effect for olaparib vs placebo throughout 12 months. At the start of maintenance therapy, patients were relatively well, with a TOI of 75 out of a maximum of 100.

The combined benefit of PFS plus quality of life was evaluated by the quality-adjusted PFS, which was defined by combining the mean PFS time found by the area under the curve with an estimation of the average results from the EQ-5D-5L questionnaire until the time of disease progression. This analysis demonstrated a clear benefit for olaparib treatment over placebo, with a quality-adjusted PFS of 13.96 months with olaparib vs 7.28 months with placebo (difference, 6.7 months; $P<.0001$; Figure 7). Patient-centered benefits were further assessed by means of the time without symptoms of disease or toxicity (TWiST), which considered AEs and represented the duration of the patient's good quality of life. To determine TWiST, patients were evaluated for the presence of significant symptoms during the interval after randomization and before protocol-defined disease progression or censoring for disease progression. For olaparib, specific toxicities included nausea, vomiting, and fatigue of grade 2 or higher, based on findings from earlier studies. The net result yielded a TWiST of 13.50 months with olaparib vs 7.21 months with placebo ($P<.0001$). Olaparib therefore elicited a significant improvement in PFS over placebo, and patients treated with olaparib experienced a longer period of time without cancer-related symptoms or treatment toxicity.

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The Successful Phase 3 Niraparib ENGOT-OV16/NOVA Trial Included a Substantial Number of Patients With Platinum Resistant Ovarian Cancer

Dr José Del Campo and colleagues evaluated platinum sensitivity and outcomes in patients with recurrent ovarian cancer assigned to the placebo arm of the phase 3 ENGOT-OV16/NOVA trial.[1,2] Patients were divided into cohorts based on their *BRCA1/2* mutation status. Within each cohort, patients were randomly assigned 2:1 to receive niraparib (300 mg once daily) or placebo. Randomization occurred up to 8 weeks after patients received their last dose of their most recent platinum-based chemotherapy. PFS was measured from the time of randomization to death or earliest disease progression as assessed by an independent review committee. Sensitivity to the most recent platinum-based treatment prior to randomization was determined for patients in the placebo arm. Platinum resistance was defined as a duration of response to the most recent platinum-based treatment that lasted less than 6 months. The analysis was restricted to patients in the placebo arm because inclusion of patients receiving active treatment would have confounded the ability to determine the duration of response to platinum alone.

The study also compared characteristics of patients in the placebo arm who experienced disease progression within 6 months of their last platinum-based therapy vs patients whose disease progressed at 6 months or later. Outcomes from these patient populations were compared because patients with a shorter time to progression would be considered platinum-resistant and would likely not be candidates for platinum-based therapy.

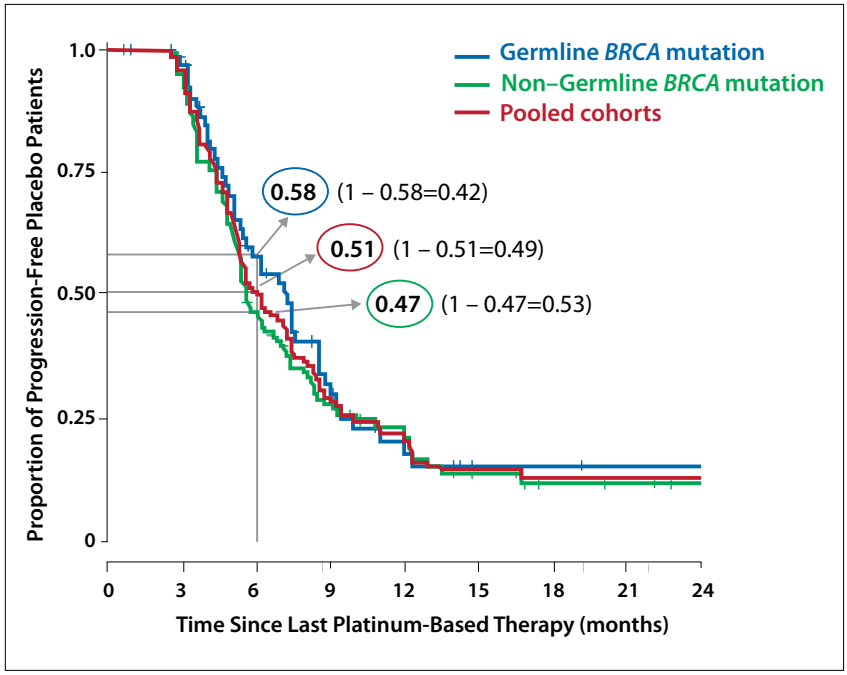

Figure 8. Patients in the placebo group who developed progressive disease within 6 months after treatment with their last platinum-based chemotherapy regimen in the NOVA trial. NOVA, A Maintenance Study With Niraparib Versus Placebo in Patients With Platinum Sensitive Ovarian Cancer. Adapted from Del Campo JM et al. ASCO abstract 5560. *J Clin Oncol*. 2017;35(15 suppl).[2]

Among the 181 patients who were randomly assigned to placebo, 65 had the germline *BRCA1/2* mutation and 116 had the wild-type germline *BRCA1/2* mutation. An estimated 42% of patients with the germline *BRCA1/2* mutation and an estimated 53% of patients without the mutation developed progressive disease within 6 months after treatment with their last platinum-based chemotherapy regimen (Figure 8). An estimated 82% of placebo-treated patients with the germline *BRCA1/2* mutation and 78% without the mutation had progressive disease within 12 months after their last platinum-based chemotherapy regimen. Among all patients in the placebo arm, an estimated 49% progressed within 6 months, and an estimated 79% progressed within 12 months after their last platinum-based chemotherapy. In the cohort of patients without the germline *BRCA1/2* mutation, patients who experienced disease progression within 6 months of their last platinum-based chemotherapy were more likely to have had a PR after both the penultimate and the last platinum-based therapy compared with patients who experienced disease progression at 6 months or later (39.7% vs 14.6% for the penultimate platinum-based regimen; 65.5% vs 22.9% for the last platinum-based regimen).

Patients who experienced disease progression within 6 months after their last platinum-based regimen had

ABSTRACT SUMMARY Overall Survival and Updated Progression-Free Survival Results From a Randomized Phase 2 Trial Comparing the Combination of Olaparib and Cediranib Against Olaparib Alone in Recurrent Platinum-Sensitive Ovarian Cancer

An open-label phase 2 study investigated cediranib plus olaparib in women with recurrent, platinum-sensitive, high-grade serous or *BRCA*-related ovarian cancer (Liu JF et al. *Lancet Oncol.* 2014;15[11]:1207-1214; Abstract 5535). Ninety patients were randomly assigned to receive olaparib monotherapy or olaparib plus cediranib. Germline *BRCA1/2* mutations were identified in 24 of 46 patients in the olaparib monotherapy arm and 23 of 44 patients in the combination arm. In each arm, 13% of patients had received prior antiangiogenic therapy. Updated median PFS was 8.2 months for olaparib monotherapy vs 16.5 months for olaparib plus cediranib (HR, 0.50; 95% CI, 0.20-0.83; *P*=.007). Median OS was 33.3 months for olaparib only vs 44.2 months for the combination (HR, 0.64; 95% CI, 0.36-1.11; *P*=.11). Among patients with the germline *BRCA1/2* mutation, PFS and OS were similar for both treatment groups. In patients without a known germline *BRCA1/2* mutation, the updated median PFS was 5.7 months with olaparib monotherapy vs 23.7 months with olaparib plus cediranib (HR, 0.32; *P*=.002). The updated median OS was 23.0 months with olaparib vs 37.8 months with the combination (HR, 0.48; *P*=.074).

ABSTRACT SUMMARY Clinically Significant Long-Term Maintenance Treatment With Olaparib in Patients With Platinum-Sensitive Relapsed Serous Ovarian Cancer

In Study 19, olaparib maintenance significantly improved PFS vs placebo in patients with platinum-sensitive, relapsed serous ovarian cancer (HR, 0.35; 95% CI, 0.25-0.49; Ledermann J et al. *Lancet Oncol.* 2014;15[8]:852-861). The greatest benefit was observed in patients with a *BRCA*1/2 mutation. An interim OS analysis also suggested a benefit for treatment with olaparib (Ledermann J et al. *Lancet Oncol.* 2014;17[11]:1579-1589). Results from the protocol-specified final OS analysis also suggested an OS benefit with olaparib vs placebo; however, the results failed to achieve statistical significance (Abstract 5533). After a median follow-up of 78.0 months, OS data for the full analysis set were 79% mature. Median OS was 29.8 months in patients treated with olaparib (400 mg twice daily) vs 27.8 months with placebo (HR, 0.73; 95% CI, 0.55-0.95; nominal *P*=.02138). More than 10% of patients continued to have a good response after receiving maintenance olaparib for more than 6 years.

received more prior lines of platinum-based therapy, as well as more lines of any chemotherapy, compared with patients whose remission lasted 6 months or longer. Among patients with the germline *BRCA1/2* mutation, 46% of those who progressed within 6 months and 39% of those who had progressed at 6 months or later had received 3 or more lines of platinum-based therapy, and 63% vs 45%, respectively, had received 3 or more lines of any type of chemotherapy. Among patients without the germline *BRCA1/2* mutation, 29% of those who progressed within 6 months and 15% of those who progressed at 6 months or later had received 3 or more lines of platinum-based therapy, and 43% vs 19%, respectively, had received at least 3 lines of any chemotherapy. There was no significance difference in quality-of-life scores based on time to progression.

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Randomized Controlled Phase III Study Evaluating the Impact of Secondary Cytoreductive Surgery in Recurrent Ovarian Cancer: AGO DESKTOP III/ENGOT OV20

The DESKTOP I study aimed to develop a predictive score that would identify patients likely to have a complete resection during secondary cytoreductive surgery. Positive prognostic factors included a good performance status, complete resection during first-line therapy, and ascites less than 500 mL.[1] The prospective, multicenter DESKTOP II trial validated the AGO score by demonstrating that it could predict complete resection in more than two-thirds of patients with 95% probability.[2]

Dr Andreas Du Bois presented interim results from the randomized, controlled phase 3 DESKTOP III study (ENGOT-OV20).[3] Patients experiencing their first relapse of platinum-sensitive ovarian cancer and who had a positive AGO score were enrolled at 80 centers in 12 countries. The study randomly assigned 408 patients to receive treatment with either platinum-based chemotherapy or cytoreductive surgery (aiming toward complete resection) followed by chemotherapy. Chemotherapy regimens were based on the institutional standards.

The interim results were based on data from 407 patients with a median age of approximately 61 years. Approximately 91% had received prior therapy consisting of platinum plus a taxane. The platinum-free interval was greater than 12 months in approximately 75% of patients, and the median platinum-free interval was approximately 20 months.

Rates of nonadherence were 3.9% in the chemotherapy arm and 5.9% in the surgery arm. After randomization, approximately 90% of patients received platinum-containing chemotherapy. Bevacizumab was administered to 22.2% of the patients who did not receive secondary cytoreductive surgery and to 18.6% of the patients who did. The macroscopic complete resection rate was 72.5%. Pooled data yielded a 2-year OS rate of 83% in the entire study population, which was higher than the anticipated rate of 55% to 66%.

Per the trial design, an interim analysis took place after 122 OS events. The analysis did not show a significant difference (which had been set to an alpha of 0.0052 for a 2-sided test). Review of the blinded data led the monitoring committee to recommend that follow-up should continue until the mature analysis, which will occur in approximately 2 years, after 244 events.

The median PFS was 19.6 months in the group of patients who received secondary cytoreductive surgery vs 14.0 months in the patients who did not (P<.001). A planned analysis of PFS by surgical outcome showed that patients who achieved a complete resection with secondary cytoreductive surgery experienced a median PFS of 21.1 months, and those who received chemotherapy alone had a median PFS of 14.0 months (P<.0001). Patients who had residual disease after surgery had a median PFS of 13.7 months. The prespecified endpoint of time to first subsequent therapy also favored the surgery arm (21.0 months vs 13.9 months; P<.001). Mortality at 6 months was 2.46% in patients treated with chemotherapy alone and 0.49% in patients treated with secondary cytoreductive surgery. Rates of grade 3/4 AEs were similar in both treatment arms, with the exception of grade 3/4 leukopenia/neutropenia, which occurred in 5% of patients who received chemotherapy vs 1% of patients who received secondary cytoreductive surgery

ABSTRACT SUMMARY INNOVATE: A Phase II Study of TTFields (200 kHz) Concomitant With Weekly Paclitaxel for Recurrent Ovarian Cancer—Updated Safety and Efficacy Results

Tumor-treating fields are low-intensity fields of alternating current delivered continuously by a battery-operated, noninvasive device consisting of transducer arrays (Abstract 5580). The INNOVATE trial (Safety, Feasibility and Effect of TTFields [200 kHz] Concomitant With Weekly Paclitaxel in Recurrent Ovarian Carcinoma) investigated the combination of tumor-treating fields and weekly paclitaxel in 31 patients with recurrent, platinum-resistant ovarian cancer. Patients had a median age of 60 years (range, 45-77 years), and 77% had serous histology. Patients had received a median 4.1 prior chemotherapy regimens (range, 1-11). The mean number of treatment cycles was 5.5 for paclitaxel and 4.2 for tumor-treating fields. Median PFS was 8.9 months, and 6-month PFS was 57%. A PR was reported in 25% of patients, and 46.4% had stable disease. The median duration of clinical benefit was 6.9 months. Median OS was not reached. Ten patients (32%) experienced serious AEs, with none related to tumor-treating fields. Mild-to-moderate skin irritation was reported in most patients, and 2 patients (6.4%) developed severe skin irritation.

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Highlights in Ovarian Cancer From the 2017 American Society of Clinical Oncology Annual Meeting: Commentary

Ursula A. Matulonis, MD

Several presentations at the 2017 American Society of Clinical Oncology meeting that focused on ovarian cancer have the potential to impact practice. Updates were presented for trials of poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors and antiangiogenic therapies, along with newer agents. Analyses of the NOVA trial (A Maintenance Study With Niraparib Versus Placebo in Patients With Platinum Sensitive Ovarian Cancer) provided insight into the use of niraparib as maintenance therapy. Trial data were presented for cediranib, olaparib, pembrolizumab, and bevacizumab. Other studies evaluated the benefit of surgery. Novel modalities under investigation include quisinostat and tumor-treating fields (TTFields). Results from the long-anticipated LION study (Lymphadenectomy in Ovarian Neoplasms), which tested the benefit of lymphadenectomy during ovarian cancer surgery, were also presented.

Niraparib

The previously published and presented NOVA trial evaluated the PARP inhibitor niraparib as maintenance therapy after response to platinum-based chemotherapy for patients with platinum-sensitive recurrent ovarian cancer.[1] The trial enrolled 553 patients, who were randomly assigned 2:1 to receive niraparib or placebo. Patients had received platinum-based chemotherapy, and they were assigned to treatment after their blood counts normalized. The original study showed that niraparib was associated with a significantly longer median duration of progression-free survival (PFS) than placebo. PFS was 21.0 months with niraparib vs 5.5 months with placebo in patients with the *BRCA* mutation, and 12.9 months vs 3.8 months, respectively, among patients without the *BRCA* mutation whose tumors were positive for homologous recombination deficiency (HRD).

I was first author on a poster that assessed the long-term benefit of niraparib in patients with recurrent ovarian cancer.[2] This study evaluated PFS at 12, 18, and 24 months, looking specifically at outcome according to *BRCA* mutation status. At all of these time points, and regardless of which *BRCA* group the patient was in, the percentages of patients who were disease-free were always higher in the patients receiving niraparib vs placebo. The study also analyzed outcome according to HRD status among patients without the germline *BRCA* mutation. The HRD test identifies the level of DNA repair within the tumor. A tumor that is HRD-positive has underlying DNA repair problems that might make it more amenable to treatment with a PARP inhibitor. In a tumor that is HRD-negative, the DNA repair mechanism is likely intact. However, regardless of the HRD status, our analysis showed a benefit for niraparib vs placebo in both HRD-positive and HRD-negative populations at all time points.

Another important component of the analysis involved PFS1 and PFS2. PFS1 is measured from the date that the patient was randomly assigned to treatment to the date of first documented progression. PFS2 is the date of treatment randomization to the date when progression occurs during treatment with the next anticancer therapy. In other words, the patient receives the study treatment, eventually has cancer progression, enters into a second treatment—perhaps chemotherapy—and spends some time on it, and then develops disease progression again. There has been concern that treatment with a PARP inhibitor might confer resistance to the next subsequent therapy. Our analysis showed, however, that the difference between PFS2 and PFS1 was identical for the patients on niraparib and placebo, suggesting that treatment with niraparib had no negative effect on the patient's response to the next treatment.

Dr Mansoor Mirza analyzed data from the NOVA trial to evaluate the efficacy of niraparib on PFS in patients who had a partial response to their previous platinum-based chemotherapy.[3] When patients were enrolled into the NOVA trial, the investigators indicated whether their response to previous platinum-based chemotherapy was complete or partial. A partial response to platinum-based chemotherapy suggests that the tumor was more platinum-resistant, and there was a concern that these patients might not benefit from a PARP inhibitor. Approximately 50% of the patients in the NOVA trial entered the study with a partial response to their previous platinum-

based chemotherapy. In addition, the number of lines of prior treatment prior to entry into the NOVA study was higher in the patients who had a partial response compared with those who had a complete response. The analysis by Dr Mirza showed that treatment with niraparib had significant benefit in patients with a partial response to previous platinum chemotherapy in both the *BRCA*-mutated group and the non-*BRCA* mutated group. This analysis therefore dispels the thought that patients with a prior partial response may derive less benefit from a PARP inhibitor.

Dr José del Campo presented another analysis of the NOVA trial that examined the level of platinum resistance of the study population.[4] Among patients who were treated with placebo, approximately 50% were found to have platinum-resistant cancer following their previous platinum-based chemotherapy. The same percentage was assumed for the niraparib arm. Although these patients had high-grade serous cancers and were responding to platinum therapy, many developed tumor progression within 6 months. The analysis from Dr del Campo suggested that niraparib has effects on both platinum-sensitive and platinum-resistant cancer.

Cediranib

Dr Jonathan Ledermann presented follow-up analysis of ICON6 (A Randomised, Placebo-Controlled, Trial of Concurrent Cediranib [AZD2171] [With Platinum-Based Chemotherapy] and Concurrent and Maintenance Cediranib in Women With Platinum-Sensitive Relapsed Ovarian Cancer), a randomized, placebo-controlled phase 3 trial of cediranib, an oral antiandrogenic drug that blocks the vascular endothelial growth factor (VEGF) receptors 1, 2, and 3.[5-7] This trial randomly assigned patients with platinum-sensitive recurrent ovarian cancer into 3 treatment arms. Arm A was platinum-based chemotherapy, such as carboplatin and paclitaxel, carboplatin and gemcitabine, or single-agent platinum therapy. After chemotherapy, patients in arm A were treated with placebo. Arm B was platinum-based chemotherapy plus cediranib followed by placebo maintenance. Arm C consisted of platinum-based chemotherapy plus cediranib, followed by cediranib as maintenance. Patients were randomly assigned to treatment in a 2:3:3 manner.

This trial design has been through several iterations, and the original primary endpoint was overall survival. The design was revised in 2011 when the development of cediranib was discontinued by the manufacturer. The primary endpoint was changed to PFS, and the enrollment goal was reduced, thus underpowering the overall survival analysis.

Previously published data showed an improvement in PFS between arm A (chemotherapy only) vs arm C (chemotherapy plus cediranib with cediranib maintenance).[5,6] PFS was 8.7 months in arm A vs 11.1 months in arm C, a highly significant difference. The analysis presented at the 2017 ASCO meeting by Dr Ledermann evaluated overall survival.[7] The median overall survival was 19.9 months for arm A, 26.6 for arm B, and 27.3 months for arm C. The difference between arm A and arm C was not statistically significant, but the trend toward improved survival in arm C led Dr Ledermann to state that these data suggested a promising future for cediranib. An important caveat is that cediranib has toxicities, and adverse events include hypertension, diarrhea, and hand-foot syndrome. Earlier data showed higher discontinuation rates owing to toxicities in arm C as compared with arm A.[5]

Dr Joyce Liu provided updated results of the randomized phase 2 trial of olaparib plus cediranib vs olaparib alone as primary therapy for patients with platinum-sensitive recurrent ovarian cancer.[8,9] This trial, sponsored by the National Cancer Institute, randomly assigned approximately 90 patients to olaparib capsules, 400 mg twice daily, or a combination of cediranib plus olaparib. The study was not blinded, and patients were followed for disease progression after treatment.

The current ASCO presentation provided updated data on PFS and a more mature analysis of overall survival.[9] The benefit of olaparib plus cediranib was noted mostly in non-germline *BRCA* mutation carriers or those with an unknown status, and these updated data demonstrated consistent prolongation of PFS with the combination, which had been shown previously.[8] The new analysis showed a nonsignificant trend toward improvement in overall survival. A phase 3 study is currently testing this combination against both platinum-based chemotherapy and single-agent olaparib in patients with platinum-sensitive recurrent ovarian cancer.[10]

Olaparib

Dr Michael Friedlander evaluated health-related quality of life and patient-centered outcomes in the SOLO2 trial (Studies of Olaparib in Ovarian Cancer 2).[11] Data from SOLO2 were previously presented at the 2017 Society of Gynecologic Oncology meeting.[12] The SOLO2 trial evaluated the PARP inhibitor olaparib as maintenance therapy following platinum response in patients with cancers that had underlying deleterious *BRCA1* or *BRCA2* mutations. After completion of platinum-based chemotherapy, patients received maintenance with olaparib or placebo. The primary endpoint was PFS. As in the NOVA trial, enrollment criteria included a prior response to chemotherapy.

Quality of life was measured using the treatment outcome index (TOI), which comes from the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) questionnaire. Questions focus on cancer symptoms as well as overall functional and physical well-being. In the analysis by Dr Friedlander, the adherence rate for

completion of the questionnaires was high, at approximately 90%.[11] The study found no differences in quality of life between the patients receiving olaparib vs placebo. Olaparib did not impact the overall TOI score throughout the follow-up of 12 months. The analysis also measured the time without symptoms of disease or toxicity (TWiST). Olaparib was administered for a longer duration than placebo, and the TWiST score was higher in the olaparib arm.

A study from Dr Charlie Gourley provided updated data for Study 19, one of the original randomized PARP inhibitor studies.[13,14] The study evaluated olaparib as maintenance therapy in patients with a high-grade tumor that was responding to platinum therapy administered for treatment of platinum-sensitive recurrence. Nearly 11% of patients receiving olaparib in this study continued to have a good response after more than 6 years of olaparib. The analysis showed that patients with platinum-sensitive recurrent disease can be treated with chemotherapy followed by maintenance with a PARP inhibitor, and remain disease-free for many years.

Pembrolizumab

Dr Andrea Varga presented data for patients with ovarian cancer enrolled in the KEYNOTE-028 trial (Study of Pembrolizumab [MK-3475] in Participants With Advanced Solid Tumors).[15] The KEYNOTE trials are evaluating pembrolizumab in multiple different tumor types.[16-18] This phase 1b trial KEYNOTE-28 provided data for 26 patients with PD-L1–positive ovarian cancer. Almost 40% of the patients had received 5 or more lines of therapy.

The overall response rate was 11.5%.[15] The complete response rate was 3.8%, and the partial response rate was 7.7%. Approximately 60% of patients developed progressive disease, and 27% of patients had stable disease. The median PFS was only 1.9 months, but the responses were durable. The safety profile was reasonable and consistent with that seen in other trials of single-agent pembrolizumab. The phase 2 KEYNOTE-100 trial of pembrolizumab in women with advanced ovarian cancer was recently completed.[19] Results are forthcoming.

Bevacizumab

Dr Florence Joly presented results from the randomized ANTHALYA trial (Neoadjuvant Therapy for Ovarian Cancer).[20] This French study evaluated bevacizumab in the neoadjuvant setting. Currently, ovarian cancer patients are treated in 1 of 2 ways. They can have upfront cytoreductive surgery and then proceed to chemotherapy. The other option, for patients deemed inoperable upfront, is to administer chemotherapy for 3 cycles, perform interval cytoreductive surgery after the tumor size decreases, and then administer additional platinum and taxane chemotherapy. Although bevacizumab is approved in the upfront setting in several European countries, currently it is not approved in this setting in the United States. Another reason for its cautious use upfront is that as an antiangiogenic agent, bevacizumab can introduce surgical complications by preventing wounds from healing, and, potentially, inducing bowel perforations.

The ANTHALYA trial added bevacizumab to carboplatinum- and paclitaxel-based chemotherapy. The response rates did not differ substantially. At cycle 8, the objective response rates were 45.9% without bevacizumab vs 46.6% with bevacizumab. By cycle 26, the objective response was 18.9% in both arms. The use of bevacizumab did not add to the toxicities.

Dr Yolanda Garcia Garcia presented results from a randomized phase 2 study evaluating neoadjuvant chemotherapy with or without bevacizumab.[21] Patients in this study were initially considered unresectable, and therefore required treatment with neoadjuvant chemotherapy. Patients received 4 cycles of neoadjuvant treatment. The first arm received carboplatin and paclitaxel, and the second arm received carboplatin, paclitaxel, and bevacizumab in cycles 1, 2, and 3. Bevacizumab was not administered during cycle 4, just before surgery. Among all patients, surgery was followed by an additional 3 cycles of carboplatin and paclitaxel plus bevacizumab for 15 months. Interestingly, the study found no difference in the primary endpoint of complete macroscopic response rate. The addition of bevacizumab improved surgical feasibility at interval surgery, but not the rate of optimal cytoreduction or PFS.

Surgical Approaches

Gynecologic oncology surgeons perform upfront surgery in patients with newly diagnosed ovarian cancer to remove or debulk the entire tumor. Surgery may consist of a systematic pelvic and para-aortic lymphadenectomy, which removes retroperitoneal lymph nodes. Lymphadenectomy involves removal of areas of microscopic disease, which might ultimately benefit the patient according to retrospective data.[22] Although this approach is performed by many surgeons, there is no evidence that it is beneficial. The lymphadenectomy can lead to toxicities, namely, increased operative time and bleeding complications. When multiple lymph nodes are removed, some patients develop lower-extremity lymphedema. In addition, lymphoceles can develop after surgery.

The LION trial, from the European Network of Gynaecological Oncological Trial (ENGOT) group, evaluated the benefit of lymphadenectomy in patients with newly diagnosed ovarian cancer.[23] Most patients had confirmed or suspected stage III to IV disease. The study included some patients with earlier-stage disease because it is not always possible to assess the stage preoperatively. Most patients had high-grade serous cancer. The primary endpoint was overall

survival, which is a critical aspect of this study. Secondary endpoints were PFS, quality of life, and the number of resected lymph nodes. The study randomly assigned 640 patients to undergo systematic pelvic and paraaortic lymphadenectomy or to no lymphadenectomy, with standard-of-care treatment afterward.

Among the patients who underwent lymphadenectomy, asymptomatic or symptomatic lymphoceles occurred in 7.5% of patients who underwent a lymphadenectomy compared with nearly 0% among patients who did not undergo lymph node removal.[23] The need for secondary surgeries to address complications was twice as high in the lymphadenectomy group. Overall survival was 65.5 months in the patients who underwent lymph node dissection vs 69.2 months in the patients who did not. This difference was not statistically significant. Survival is not improved by nodal removal during upfront surgery, so this is a really important quality-of-life improvement for patients who undergo primary upfront surgery. PFS was 25.5 months following nodal removal, which was the same for patients who did not undergo a lymphadenectomy. The lack of improvement in overall survival and PFS is an important finding and will change how surgery is performed in newly diagnosed patients.

Dr Andreas Du Bois presented results from the DESKTOP III trial (Descriptive Evaluation of Preoperative Selection Kriteria for Operability in Recurrent Ovarian Cancer III).[24] This randomized phase 3 study evaluated the use of secondary cytoreductive surgery in patients with recurrent ovarian cancer and is addressing the question of whether patients with recurrent cancer should undergo surgery. Most of the studies that have addressed this question are retrospective and nonrandomized. The primary endpoint of this study is overall survival, and other secondary endpoints include PFS, resection rate, and treatment burden.

Earlier DESKTOP studies developed the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) score to predict complete cytoreduction in recurrent ovarian cancer.[25,26] The score can be positive or negative. A positive score encompasses patients with a good performance status, complete resection during the first line of therapy, and ascites less than 500 mL. A positive score predicts a 95% probability of complete resection in more than 2 of 3 patients.

The DESKTOP III trial enrolled patients with ovarian cancer in first relapse.[24] Patients had platinum-sensitive recurrent ovarian cancer and a positive AGO score. The trial enrolled 408 patients from 80 centers throughout 12 countries. The treatment arms consisted of cytoreductive surgery or no surgery. Treatment with platinum-based chemotherapy was strongly recommended for all patients, either after surgery or, in the control arm, after study enrollment. Most patients received platinum-based chemotherapy: 91% in the no-surgery arm and 89% in the surgery arm. Bevacizumab was added to the regimen in 22% of the no-surgery arm and 19% of the surgery arm. Among patients who underwent surgery, the macroscopic complete resection rate was 72%. PFS was 19.6 months for the surgery arm vs 14.0 months for the no-surgery arm, a statistically significant difference. The benefit of surgery was seen exclusively in patients with a complete resection of their tumor. Overall survival data were not yet available and are eagerly awaited.

Novel Agents

The histone deacetylase (HDAC) inhibitor quisinostat was evaluated in a phase 2 trial performed mostly in Russia.[27] Preclinically, HDAC inhibitors have been shown to overcome platinum resistance and may have synergy with platinum-based chemotherapy. This study used quisinostat in combination with carboplatinum and paclitaxel chemotherapy. The complete response rate was 3.2%, and the partial response rate was 48%. These data are interesting, but require follow-up in a randomized study.

The phase 2 INNOVATE study (Safety, Feasibility and Effect of TTFields [200 kHz] Concomitant With Weekly Paclitaxel in Recurrent Ovarian Carcinoma) examined TTFields administered concomitantly with weekly paclitaxel in patients with recurrent ovarian cancer.[28] TTFields are low-intensity electric fields that are delivered to the regions of the cancer through transducer arrays. Patients in this trial wore a device along the outside of the abdomen. All patients were platinum-resistant, and the median platinum-free interval was 4 months. The poster does not indicate whether the patients were resistant to paclitaxel. The median PFS was 8.9 months, and 25% of patients who had evaluable tumors had a partial response. The patient population was highly selected, and this modality will need to be assessed in a randomized trial.

Dr Linda Duska presented data from a randomized trial of pazopanib, an oral VEGF receptor inhibitor, in 148 patients with recurrent ovarian cancer.[29] Patients could have platinum-sensitive or platinum-resistant disease. All patients received gemcitabine in the typical dosing of 1000 mg/m^2 on days 1 and 8 on an every-3-weeks cycle. They were randomly assigned to receive this regimen alone or with pazopanib at a dose of 800 mg/daily on days 1 through 21.

The PFS data will be available in December 2017. Dr Duska presented the toxicity data in this ASCO poster.[29] Grade 3/4 fatigue occurred in 10.7% of the pazopanib combination arm vs 1.4% of the single-agent arm. Grade 3/4 hypertension was reported in 15% on the pazopanib combination arm vs 1.4% of the single-agent arm. An important finding that raises some concerns about this regimen is the rate of grade 3/4 perforations observed in the pazopanib arm. There were three grade 4 gastrointestinal perforations

in the combination arm vs none in the gemcitabine-alone arm. It does not appear that any patients developed grade 5 toxicity. It will be interesting to see the PFS data.

Eribulin is approved by the US Food and Drug Administration for breast cancer. Dr Masashi Takano conducted a phase 2 trial combining eribulin with bevacizumab and oxaliplatin in patients with platinum-resistant ovarian cancer.[30] The regimen was unusual, and it tested a low dose of bevacizumab: 2 mg/kg weekly. (The typical dose is 5 mg/kg weekly.) The dose of eribulin was 1 mg/m^2 weekly. The regimen also included oxaliplatin, which is not typically used in traditional ovarian cancer. The complete response rate was 6%, and the partial response rate was 23%. The median PFS was approximately 4 months. The toxicities were manageable. A larger randomized trial would be needed to confirm these findings.

Disclosure

Dr Matulonis is a paid advisory board member of 2X Oncology. She is the US principal investigator of the NOVA study and Study 19. She has received travel expenses from AstraZeneca.

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Zejula™
niraparib
capsules

BRIEF SUMMARY OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZEJULA safely and effectively. See full prescribing information for ZEJULA available at www.ZEJULA.com.

ZEJULA™ (niraparib) capsules

INDICATIONS AND USAGE

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.

DOSAGE AND ADMINISTRATION

Recommended Dosage

The recommended dose of ZEJULA as monotherapy is 300 mg (three 100 mg capsules) taken orally once daily.

Instruct patients to take their dose of ZEJULA at approximately the same time each day. Each capsule should be swallowed whole. ZEJULA may be taken with or without food. Bedtime administration may be a potential method for managing nausea.

Patients should start treatment with ZEJULA no later than 8 weeks after their most recent platinum-containing regimen.

ZEJULA treatment should be continued until disease progression or unacceptable toxicity.

In the case of a missed dose of ZEJULA, instruct patients to take their next dose at its regularly scheduled time. If a patient vomits or misses a dose of ZEJULA, an additional dose should not be taken.

Dose Adjustments for Adverse Reactions

To manage adverse reactions, consider interruption of treatment, dose reduction, or dose discontinuation. The recommended dose modifications for adverse reactions are listed in Tables 1, 2 and 3.

Table 1: Recommended dose modifications for adverse reactions

Dose level	Dose
Starting dose	300 mg/day (three 100 mg capsules)
First dose reduction	200 mg/day (two 100 mg capsules)
Second dose reduction	100 mg/day* (one 100 mg capsule)

*If further dose reduction below 100 mg/day is required, discontinue ZEJULA.

Table 2: Dose modifications for non-hematologic adverse reactions

Non-hematologic CTCAE* ≥ Grade 3 adverse reaction where prophylaxis is not considered feasible or adverse reaction persists despite treatment	• Withhold ZEJULA for a maximum of 28 days or until resolution of adverse reaction. • Resume ZEJULA at a reduced dose per Table 1. Up to 2 dose reductions are permitted.
CTCAE ≥ Grade 3 treatment-related adverse reaction lasting more than 28 days while patient is administered ZEJULA 100 mg/day	Discontinue medication.

*CTCAE=Common Terminology Criteria for Adverse Events

Table 3: Dose modifications for hematologic adverse reactions

Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment and periodically after this time *[see Warnings and Precautions]*.

Platelet count <100,000/µL	First occurrence: • Withhold ZEJULA for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/µL. • Resume ZEJULA at same or reduced dose per Table 1. • If platelet count is <75,000/µL, resume at a reduced dose.
	Second occurrence: • Withhold ZEJULA for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/µL. • Resume ZEJULA at a reduced dose per Table 1. • Discontinue ZEJULA if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg once daily.*
Neutrophil <1,000/µL or Hemoglobin <8 g/dL	• Withhold ZEJULA for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥1,500/µL or hemoglobin returns to ≥9 g/dL. • Resume ZEJULA at a reduced dose per Table 1. • Discontinue ZEJULA if neutrophils and/or hemoglobin have not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg once daily.*
Hematologic adverse reaction requiring transfusion	• For patients with platelet count ≤10,000/µL, platelet transfusion should be considered. If there are other risk factors such as co-administration of anticoagulation or antiplatelet drugs, consider interrupting these drugs and/or transfusion at a higher platelet count. • Resume ZEJULA at a reduced dose.

*If myelodysplastic syndrome or acute myeloid leukemia (MDS/AML) is confirmed, discontinue ZEJULA *[see Warnings and Precautions]*.

DOSAGE FORMS AND STRENGTHS

100 mg capsule having a white body with "100 mg" printed in black ink, and a purple cap with "Niraparib" printed in white ink.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Myelodysplastic Syndrome/Acute Myeloid Leukemia

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML), including cases with fatal outcome, have been reported in patients who received ZEJULA. In Trial 1 (NOVA), MDS/AML occurred in 5 out of 367 (1.4%) of patients who received ZEJULA and in 2 out of 179 (1.1%) patients who received placebo. Overall, MDS/AML has been reported in 7 out of 751 (0.9%) patients treated with ZEJULA in clinical studies.

The duration of ZEJULA treatment in patients prior to developing MDS/AML varied from <1 month to 2 years. All patients had received previous chemotherapy with platinum and some had also received other DNA damaging agents and radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

Bone Marrow Suppression

Hematologic adverse reactions (thrombocytopenia, anemia and neutropenia) have been reported in patients treated with ZEJULA. Grade ≥3 thrombocytopenia, anemia and neutropenia were reported, respectively, in 29%, 25%, and 20% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 1%, and 2% of patients.

Do not start ZEJULA until patients have recovered from hematological toxicity caused by previous chemotherapy (≤ Grade 1). Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment, and periodically after this time. If hematological toxicities do not resolve within 28 days following interruption, discontinue ZEJULA, and refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics *[see Dosage and Administration]*.

Cardiovascular Effects

Hypertension and hypertensive crisis have been reported in patients treated with ZEJULA. Grade 3-4 hypertension occurred in 9% of ZEJULA treated patients compared to 2% of placebo treated patients in Trial 1. Discontinuation due to hypertension occurred in <1% of patients.

Monitor blood pressure and heart rate 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. Medically manage hypertension with antihypertensive medications and adjustment of the ZEJULA dose, if necessary *[see Dosage and Administration]*.

Embryo-Fetal Toxicity

Based on its mechanism of action, ZEJULA can cause fetal harm when administered to a pregnant woman. ZEJULA has the potential to cause teratogenicity and/or embryo-fetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients (e.g., bone marrow) *[see Warnings and Precautions]*. Due to the potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted with niraparib.

Apprise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months after the last dose of ZEJULA *[see Use in Specific Populations]*.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Myelodysplastic Syndrome/Acute Myeloid Leukemia *[see Warnings and Precautions]*
- Bone Marrow Suppression *[see Warnings and Precautions]*
- Cardiovascular Effects *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of ZEJULA monotherapy 300 mg once daily has been studied in 367 patients with platinum-sensitive recurrent ovarian, fallopian tube, and primary peritoneal cancer in Trial 1 (NOVA). Adverse reactions in Trial 1 led to dose reduction or interruption in 69% of patients, most frequently from thrombocytopenia (41%) and anemia (20%). The permanent discontinuation rate due to adverse reactions in Trial 1 was 15%. The median exposure to ZEJULA in these patients was 250 days.

Table 4 and Table 5 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with ZEJULA.

Table 4 Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA

	Grades 1-4*		Grades 3-4*	
	ZEJULA N=367 %	Placebo N=179 %	ZEJULA N=367 %	Placebo N=179 %
Blood and lymphatic system disorders				
Thrombocytopenia	61	5	29	0.6
Anemia	50	7	25	0
Neutropenia	30	6	20	2
Leukopenia	17	8	5	0

(continued)

Table 4 Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA (continued)

	Grades 1-4*		Grades 3-4*	
	ZEJULA N=367 %	Placebo N=179 %	ZEJULA N=367 %	Placebo N=179 %
Cardiac Disorders				
Palpitations	10	2	0	0
Gastrointestinal Disorders				
Nausea	74	35	3	1
Constipation	40	20	0.8	2
Vomiting	34	16	2	0.6
Abdominal pain/ distention	33	39	2	2
Mucositis/stomatitis	20	6	0.5	0
Diarrhea	20	21	0.3	1
Dyspepsia	18	12	0	0
Dry mouth	10	4	0.3	0
General disorders and Administration Site Conditions				
Fatigue/Asthenia	57	41	8	0.6
Metabolism and Nutrition Disorders				
Decreased appetite	25	15	0.3	0.6
Infections and Infestations				
Urinary tract infection	13	8	0.8	1
Investigations				
AST/ ALT elevation	10	5	4	2
Musculoskeletal and Connective Tissue Disorders				
Myalgia	19	20	0.8	0.6
Back pain	18	12	0.8	0
Arthralgia	13	15	0.3	0.6
Nervous system Disorders				
Headache	26	11	0.3	0
Dizziness	18	8	0	0
Dysgeusia	10	4	0	0
Psychiatric Disorders				
Insomnia	27	8	0.3	0
Anxiety	11	7	0.3	0.6
Respiratory, Thoracic, and Mediastinal Disorders				
Nasopharyngitis	23	14	0	0
Dyspnea	20	8	1	1
Cough	16	5	0	0
Skin and Subcutaneous Tissue Disorders				
Rash	21	9	0.5	0
Vascular disorders				
Hypertension	20	5	9	2

*CTCAE=Common Terminology Criteria for Adverse Events version 4.02

Table 5 Abnormal Laboratory Findings in ≥25% of Patients Receiving ZEJULA

	Grades 1-4		Grades 3-4	
	ZEJULA N=367 (%)	Placebo N= 179 (%)	ZEJULA N= 367 (%)	Placebo N= 179 (%)
Decrease in hemoglobin	85	56	25	0.5
Decrease in platelet count	72	21	35	0.5
Decrease in WBC count	66	37	7	0.7
Decrease in absolute neutrophil count	53	25	21	2
Increase in AST	36	23	1	0
Increase in ALT	28	15	1	2

N=number of patients; WBC=white blood cells; ALT=Alanine aminotransferase; AST=Aspartate aminotransferase

The following adverse reactions and laboratory abnormalities have been identified in ≥1 to <10% of the 367 patients receiving ZEJULA in the NOVA trial and not included in the table: tachycardia, peripheral edema, hypokalemia, bronchitis, conjunctivitis, gamma-glutamyl transferase increased, blood creatinine increased, blood alkaline phosphatase increased, weight decreased, depression, epistaxis.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on its mechanism of action, ZEJULA can cause fetal harm when administered to pregnant women. There are no data regarding the use of ZEJULA in pregnant women to inform the drug-associated risk. ZEJULA has the potential to cause teratogenicity and/or embryo-fetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients (e.g., bone marrow) *[see Warnings and Precautions]*. Due to the potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted with niraparib. Apprise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Lactation

Risk Summary

No data are available regarding the presence of niraparib or its metabolites in human milk, or on its effects on the breastfed infant or milk production. Because of the potential for serious adverse reactions in breastfed infants from ZEJULA, advise a lactating woman not to breastfeed during treatment with ZEJULA and for 1 month after receiving the final dose.

Females and Males of Reproductive Potential

Pregnancy Testing

ZEJULA can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations]*.

A pregnancy test is recommended for females of reproductive potential prior to initiating ZEJULA treatment.

Contraception

Females

ZEJULA can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations]*.

Advise females of reproductive potential to use effective contraception treatment with ZEJULA and for at least for 6 months following the last dose.

Infertility

Males

Based on animal studies, ZEJULA may impair fertility in males of reproductive potential.

Pediatric Use

Safety and effectiveness of ZEJULA have not been established in pediatric patients.

Geriatric Use

In Trial 1 (NOVA), 35% of patients were aged ≥65 years and 8% were aged ≥75 years. No overall differences in safety and effectiveness of ZEJULA were observed between these patients and younger patients but greater sensitivity of some older individuals cannot be ruled out.

Renal Impairment

No dose adjustment is necessary for patients with mild (CLcr:60 to 89 mL/min) to moderate (CLcr:30 to 59 mL/min) renal impairment. The degree of renal impairment was determined by creatinine clearance as estimated by the Cockcroft-Gault equation. The safety of ZEJULA in patients with severe renal impairment or end stage renal disease undergoing hemodialysis is unknown.

Hepatic Impairment

No dose adjustment is needed in patients with mild hepatic impairment according to the National Cancer Institute – Organ Dysfunction Working Group (NCI-ODWG) criteria. The safety of ZEJULA in patients with moderate to severe hepatic impairment is unknown.

OVERDOSAGE

There is no specific treatment in the event of ZEJULA overdose, and symptoms of overdose are not established. In the event of an overdose, healthcare practitioners should follow general supportive measures and should treat symptomatically.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling.

MDS/AML

Advise patients to contact their healthcare provider if they experience weakness, feeling tired, fever, weight loss, frequent infections, bruising, bleeding easily, breathlessness, blood in urine or stool, and/or laboratory findings of low blood cell counts, or a need for blood transfusions. This may be a sign of hematological toxicity or myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) which has been reported in patients treated with ZEJULA *[see Warnings and Precautions]*.

Bone Marrow Suppression

Advise patients that periodic monitoring of their blood counts is required. Advise patients to contact their healthcare provider for new onset of bleeding, fever, or symptoms of infection *[see Warnings and Precautions]*.

Cardiovascular Effects

Advise patients to undergo monthly blood pressure and heart rate monitoring for the first year of treatment and then periodically thereafter and to contact their healthcare provider if blood pressure is elevated *[see Warnings and Precautions]*.

Dosing Instructions

Inform patients on how to take ZEJULA *[see Dosage and Administration]*. ZEJULA should be taken once daily. Instruct patients that if they miss a dose of ZEJULA, not to take an extra dose to make up for the one that they missed. They should take their next dose at the regularly scheduled time. Each capsule should be swallowed whole. ZEJULA may be taken with or without food. Bedtime administration may be a potential method for managing nausea.

Embryo-Fetal Toxicity

Advise females to inform their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy *[see Warnings and Precautions and Use in Specific Populations]*.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with ZEJULA and for at least 6 months after receiving the last dose *[see Use in Specific Populations]*.

Lactation

Advise patients not to breastfeed while taking ZEJULA and for 1 month after the last dose *[see Use in Specific Populations]*.

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Rev. 1: 03/2017

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Indication and Important Safety Information for ZEJULA

Indication

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.

Important Safety Information

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML), including some fatal cases, was reported in 1.4% of patients receiving ZEJULA vs 1.1% of patients receiving placebo in Trial 1 (NOVA), and 0.9% of patients treated with ZEJULA in all clinical studies. The duration of ZEJULA treatment in patients prior to developing MDS/AML varied from <1 month to 2 years. All patients had received prior chemotherapy with platinum and some had also received other DNA damaging agents and 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 in 29%, 25%, and 20% of patients receiving ZEJULA, respectively. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, in 3%, 1%, and 2% of patients, respectively. 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 of treatment, 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 Trial 1, with discontinuation occurring in <1% of patients. Monitor blood pressure and heart rate 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.

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. 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.

In clinical studies, the most common adverse reactions (Grades 1-4) in ≥10% of patients included: thrombocytopenia (61%), anemia (50%), neutropenia (30%), leukopenia (17%), palpitations (10%), nausea (74%), constipation (40%), vomiting (34%), abdominal pain/distention (33%), mucositis/stomatitis (20%), diarrhea (20%), dyspepsia (18%), dry mouth (10%), fatigue/asthenia (57%), decreased appetite (25%), urinary tract infection (13%), aspartate aminotransferase (AST)/alanine aminotransferase (ALT) elevation (10%), myalgia (19%), back pain (18%), arthralgia (13%), headache (26%), dizziness (18%), dysgeusia (10%), insomnia (27%), anxiety (11%), nasopharyngitis (23%), dyspnea (20%), cough (16%), rash (21%) and hypertension (20%).

Common lab abnormalities (Grades 1-4) in ≥25% of patients 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%).

Please see Brief Summary of Prescribing Information for ZEJULA on the following pages.
The full Prescribing Information is available at ZEJULA.com.

Reference: 1. ZEJULA [package insert]. Waltham, MA: TESARO, Inc; 2017.

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