

A SPECIAL MEETING REVIEW EDITION

Highlights in Ovarian Cancer From the 2017 Society of Gynecologic Oncology Annual Meeting on Women's Cancer

A Review of Selected Presentations From the 2017 Society of Gynecologic Oncology Annual Meeting on Women's Cancer
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Special Reporting on:

- ENGOT-OV16/NOVA: Results of Secondary Efficacy Endpoints of Niraparib Maintenance Therapy in Ovarian Cancer
- Treatment With Olaparib Monotherapy in the Maintenance Setting Significantly Improves Progression-Free Survival in Patients With Platinum-Sensitive Relapsed Ovarian Cancer: Results From the Phase III SOLO2 Study
- Rucaparib in Patients With Relapsed, Primary Platinum-Sensitive High-Grade Ovarian Carcinoma With Germline or Somatic *BRCA* Mutations: Integrated Summary of Efficacy and Safety From the Phase II Study ARIEL2
- A Phase II, Randomized, Double-Blind, Placebo-Controlled Study of Chemo-Immunotherapy Combination Using Motolimod With Pegylated Liposomal Doxorubicin in Recurrent or Persistent Ovarian Cancer: a Gynecologic Oncology Group Partners Study
- A Phase III Trial of Maintenance Therapy in Women With Advanced Ovarian/Fallopian Tube/Peritoneal Cancer After a Complete Clinical Response to First-Line Therapy: an NRG Oncology Study
- Comparison of Clinical Outcomes in Women With Advanced Ovarian Cancer Undergoing Neoadjuvant Chemotherapy Who Receive Three Vs Greater Than Three Cycles of Chemotherapy After Interval Cytoreductive Surgery

PLUS Meeting Abstract Summaries

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ENGOT-OV16/NOVA: Results of Secondary Efficacy Endpoints of Niraparib Maintenance Therapy in Ovarian Cancer

Niraparib is an oral inhibitor of poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) 1/2 that improved progression-free survival (PFS) when used as maintenance therapy in the phase 3 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).¹ The trial enrolled patients with recurrent, high-grade serous ovarian cancer who had achieved a response to their most recent platinum-based chemotherapy. The 533 patients had received at least 4 prior cycles of a platinum agent. Patients in cohort 1 were carriers of the germline *BRCA* mutation. Patients

in cohort 2 lacked the germline *BRCA* mutation and could have tumors that were positive or negative for homologous recombination deficiency (HRD). Within each cohort, patients were randomly assigned 2:1 to treatment with once-daily niraparib (300 mg) or placebo. Among the patients in cohort 1, 138 received niraparib and 65 received placebo. In cohort 2, 234 received niraparib and 116 received placebo. The median patient age was 57 years in cohort 1 and 62 years in cohort 2. In both cohorts, approximately two-thirds of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0. The primary tumor site was the ovary in more than 80% of patients. Median follow-up was 16.9 months.

The study's primary endpoint was PFS.

Among patients with a germline *BRCA* mutation, median PFS was 21.0 months with niraparib vs 5.5 months with placebo (hazard ratio [HR], 0.27; 95% CI, 0.17-0.41; $P < .001$). In patients without the germline *BRCA* mutation, PFS was 9.3 months vs 3.9 months, respectively (HR, 0.45; 95% CI, 0.34-0.61; $P < .001$). Niraparib also improved PFS among the subgroup of patients without the germline *BRCA* mutation who had tumors with HRD (12.9 months vs 3.8 months; HR, 0.38; 95% CI, 0.24-0.59; $P < .001$).

The secondary endpoints of the NOVA trial included time to first subsequent therapy (TFST), the chemotherapy-free interval, time to second subsequent therapy (TSST),

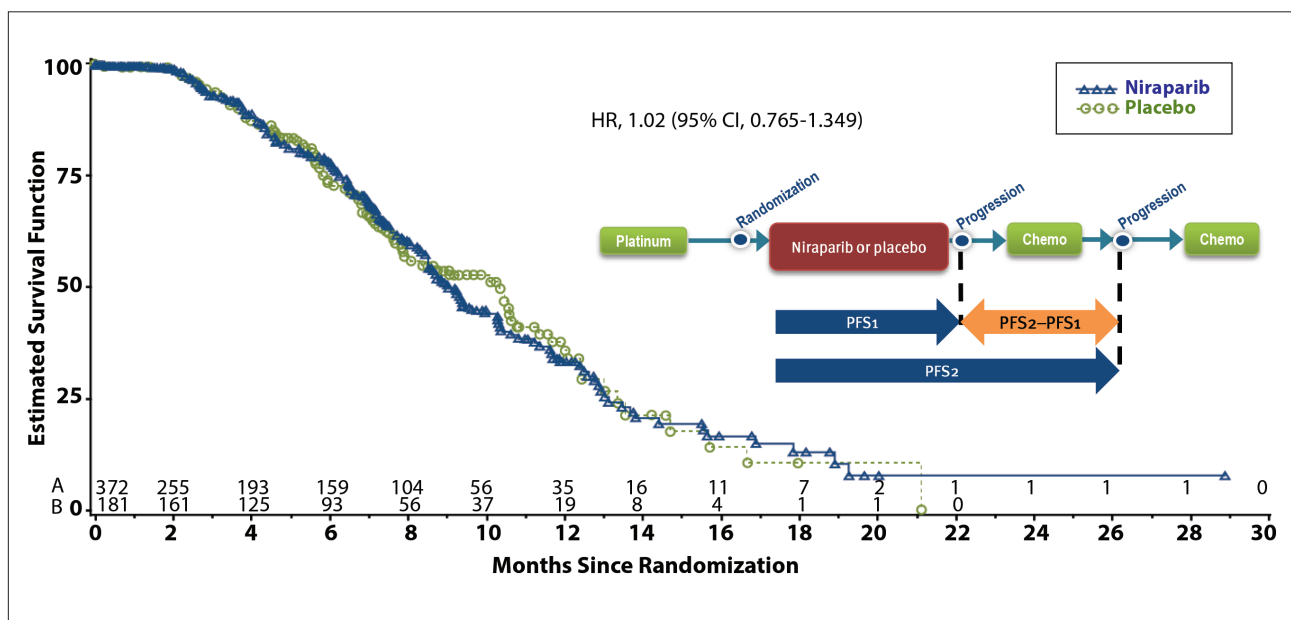


Figure 1. In the phase 3 ENGOT-OV16/NOVA trial, the use of niraparib did not impact the efficacy of next-line therapy. The numbers along the bottom indicate the patients at risk in the niraparib arm (A) and the placebo arm (B). Chemo, chemotherapy; ENGOT, European Network for Gynaecological Oncological Trial; HR, hazard ratio; NOVA, A Maintenance Study With Niraparib Versus Placebo in Patients With Platinum Sensitive Ovarian Cancer; PFS, progression-free survival. Adapted from Mahner S et al. Seminal session 1 presentation. 2017 Society of Gynecologic Oncology Annual Meeting on Women's Cancer.²

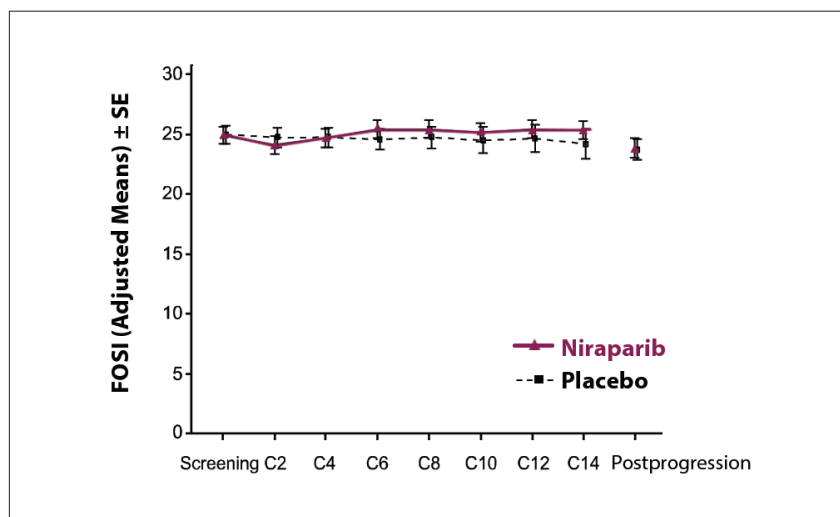


Figure 2. Patient-reported outcome in the phase 3 ENGOT-OV16/NOVA trial of niraparib. The FOSI score is shown for patients with the germline *BRCA* mutation. C, cycle; ENGOT, European Network for Gynaecological Oncological Trial; FOSI, Functional Assessment of Cancer Therapy–Ovarian Symptom Index; NOVA, A Maintenance Study With Niraparib Versus Placebo in Patients With Platinum Sensitive Ovarian Cancer; SE, standard error. Adapted from Mahner S et al. Seminal session 1 presentation. 2017 Society of Gynecologic Oncology Annual Meeting on Women’s Cancer.²

second PFS (PFS2), and overall survival (OS). Dr Sven Mahner presented available data.²

Niraparib significantly improved the chemotherapy-free interval and TFST in both cohorts. The chemotherapy-free interval was 22.8 months with niraparib vs 9.4 months with placebo (HR, 0.26; $P < .0001$) in cohort 1 and 12.7 months vs 8.5 months in cohort 2 (HR, 0.50; $P < .0001$). In the subset of cohort 1 patients with HRD-positive tumors, the chemotherapy-free interval was 18.2 months with niraparib vs 7.7 months with placebo (HR, 0.31; $P < .0001$). TFST was 21.0 months with niraparib vs 8.4 months with placebo (HR, 0.31; $P < .0001$)

for cohort 1 and 11.8 months vs 7.2 months (HR, 0.55; $P < .0001$) for cohort 2. In the subset of cohort 2 patients with HRD-positive tumors, TFST was 15.9 months with niraparib vs 6.0 months with placebo (HR, 0.36; $P < .0001$). Based on immature data, niraparib demonstrated a superior PFS2 in cohort 1 (HR, 0.48) and cohort 2 (HR, 0.69), a superior TSST in cohort 1 (HR, 0.48) and cohort 2 (HR, 0.74), and a superior OS in the entire study group (HR, 0.73).

An exploratory analysis of PFS1 and PFS2 suggested that maintenance treatment with niraparib did not have a meaningful impact on the efficacy of subsequent therapies (Figure 1).^{2,3}

This analysis, however, was conducted on an immature data set.

The most common grade 3/4 adverse events (AEs) associated with niraparib were thrombocytopenia (33.8%), anemia (25.3%), neutropenia (19.6%), fatigue (8.2%), and hypertension (8.2%). Most of these events occurred during treatment cycles 1 and 2. The most common treatment-related reasons for discontinuation were any-grade thrombocytopenia and fatigue, each of which led 3.3% of patients to stop treatment. Myelodysplastic syndrome/acute myeloid leukemia occurred in 1.4% of patients treated with niraparib vs 1.1% of placebo patients. No grade 3 or 4 bleeding events and no grade 5 AEs were observed; however, 1 patient had grade 3 petechiae and hematoma concurrent with pancytopenia. Adherence rates exceeded 75% and were similar for both treatment groups.

Patient-reported outcomes were collected during the screening visit, at every other cycle through cycle 14, and after progression. Throughout the study, patient-reported outcomes were similar for patients receiving niraparib or placebo (Figure 2).

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Treatment With Olaparib Monotherapy in the Maintenance Setting Significantly Improves Progression-Free Survival in Patients With Platinum-Sensitive Relapsed Ovarian Cancer: Results From the Phase III SOLO2 Study

The oral PARP inhibitor olaparib has demonstrated activity in patients with ovarian cancer. In a phase 2 trial, maintenance monotherapy with olaparib significantly prolonged PFS compared with placebo in patients with platinum-sensitive recurrent serous ovarian cancer.¹ The improvement in PFS was highest in patients with a *BRCA1/2* mutation.² Dr Eric Pujade-Lauraine presented results from the placebo-controlled phase 3 SOLO2 (Studies of Olaparib in Ovarian Cancer 2)/ENGOT-OV21 trial, which evaluated olaparib in patients with

platinum-sensitive, relapsed ovarian cancer and the *BRCA1/2* mutation.³ Patients were required to have received at least 2 lines of prior platinum therapy and to have experienced a complete response (CR) or partial response (PR) after their most recent treatment. Patients were randomly assigned 2:1 to receive olaparib (300 mg twice daily) or placebo. The primary endpoint was PFS by blinded central review. Key secondary endpoints included TFST, PFS2, TSST, OS, safety, and health-related quality of life.

The study randomly assigned 196 patients to olaparib and 99 to placebo.

Patients had a median age of 56 years (range, 29-83 years). The primary tumor types were ovarian (82.7% in the olaparib arm vs 86.9% in the placebo arm) and fallopian tube/primary peritoneal (15.8% vs 13.1%). Previous lines of therapy numbered 2 (56.1% vs 62.6%), 3 (30.6% vs 20.2%), or at least 4 (12.8% vs 17.2%). Approximately 40% of patients had experienced a platinum-free interval of 6 to 12 months, and approximately 46% had achieved a CR with their most recent therapy. Median follow-up was 22.1 months for patients in the olaparib arm and 22.2 months for the placebo arm. Based on investigator assessment, median PFS was 19.1 months with olaparib vs 5.5 months with placebo (HR, 0.30; 95% CI, 0.22-0.41; $P < .0001$; Figure 3). A sensitivity analysis using a blinded independent review supported the improvement in PFS, with an HR of 0.25. Median PFS2 was not reached with olaparib vs 18.4 months with placebo (HR, 0.50; 95% CI, 0.34-0.72; $P = .0002$). Median TFST was 27.9 months with olaparib vs 7.1 months with placebo (HR, 0.28; 95% CI, 0.21-0.38; $P < .0001$). Median TSST was not reached with olaparib vs 18.2 months with placebo (HR, 0.37; 95% CI, 0.26-0.53; $P < .0001$).

An AE of any grade occurred in 98.5% of the olaparib arm vs 94.9% of the placebo arm. AEs of grade 3 or higher occurred in 36.9% vs 18.2%. AEs led to a dose reduction in 25.1% vs 3.0%. AEs leading to discontinuation of study treatment occurred in 10.8% vs 2.0% of patients. One patient in the olaparib arm died. The most common hematologic AEs of grade 3 or higher were anemia (reported in 19.5% of the olaparib arm vs 2.0% of the placebo

ABSTRACT SUMMARY *BRCA1* and *RAD51C* Promoter Hypermethylation Confer Sensitivity to the PARP Inhibitor Rucaparib in Patients With Relapsed, Platinum-Sensitive Ovarian Carcinoma in ARIEL2 Part 1

An analysis of patients from the ARIEL2 trial evaluated whether rucaparib is more effective in patients with *BRCA1* or *RAD51C* promoter hypermethylation (Abstract 7). This analysis categorized patients with recurrent, platinum-sensitive, high-grade ovarian cancer as *BRCA* mutant, wild-type *BRCA* with high loss of heterozygosity (LOH high), or wild-type *BRCA* with low LOH (LOH low). Treatment with rucaparib was initiated at 600 mg twice daily in continuous 28-day cycles. As of January 18, 2016, 192 patients were classified: 40 as *BRCA* mutant, 82 as LOH high, and 70 as LOH low. PFS was 12.8 months in the *BRCA* mutant subgroup, 5.7 months in the LOH-high subgroup, and 5.2 months in the LOH-low subgroup. The improvement seen in the *BRCA* mutant subgroup was significant when compared with the other subgroups (vs the LOH-low subgroup: HR, 0.27; $P < .0001$; vs the LOH-high subgroup: HR, 0.62; $P = .011$). The presence of *BRCA1* and *RAD51C* mutations were mutually exclusive ($P = .015$). Median PFS was 7.4 months in patients with methylated *BRCA1* and 9.5 months in patients with methylated *RAD51C*. Methylation of *BRCA1* and *RAD51C* in ovarian carcinomas was associated with high LOH and sensitivity to rucaparib, whereas loss of *BRCA1* methylation was commonly observed after exposure to platinum therapy, even in platinum-sensitive patients. Routine sequencing of high-grade ovarian cancer would identify 10% to 15% of patients with somatic mutations and 20% of those with germline mutations associated with a likely response to PARP inhibition.

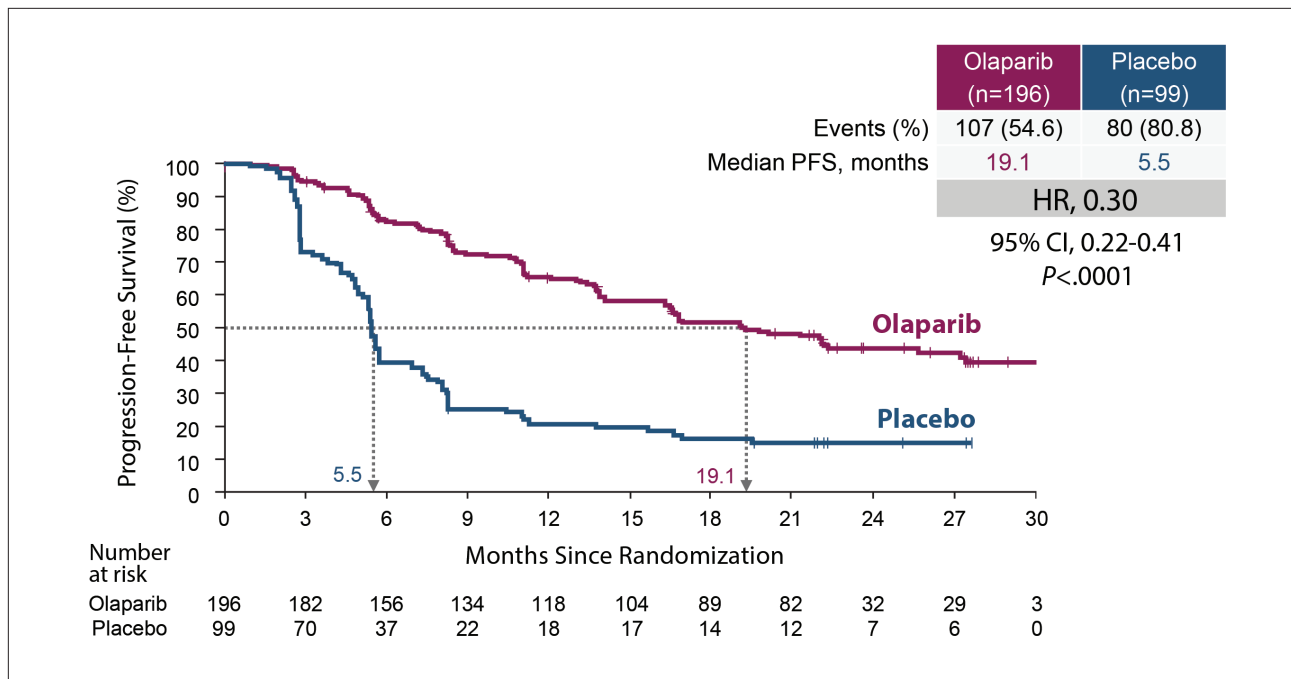


Figure 3. Progression-free survival according to investigator assessment in the phase 3 SOLO2/ENGOT-OV21 trial of olaparib monotherapy in the maintenance setting. ENGOT, European Network for Gynaecological Oncological Trial; HR, hazard ratio; PFS, progression-free survival; SOLO2, Olaparib Treatment in *BRCA* Mutated Ovarian Cancer Patients After Complete or Partial Response to Platinum Chemotherapy. Adapted from Pujade-Lauraine E et al. Abstract LBA2. 2017 Society of Gynecologic Oncology Annual Meeting on Women’s Cancer.³

arm), neutropenia (5.1% vs 4.0%), and thrombocytopenia (1.0% in both arms). Myelodysplastic syndrome/acute myeloid leukemia was observed in 2.1% vs 4.0% of patients. The most common nonhematologic AEs of any grade were nausea (75.9% vs 33.3%), fatigue/asthenia (65.6% vs 39.3%), vomiting (37.4% vs 19.2%), and diarrhea (32.8% vs 20.2%). Most nonhematologic toxicity was observed during the first weeks of treatment. The most common grade 3 or higher nonhe-

matologic AEs were fatigue/asthenia (4.1% vs 2.0%), vomiting (2.6% vs 1.0%), abdominal pain (2.6% vs 3.0%), nausea (2.6% vs 0.0%), diarrhea (1.0% vs 0.0%), and constipation (0.0% vs 3.0%). Health-related quality of life was similar in both arms.

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Rucaparib in Patients With Relapsed, Primary Platinum-Sensitive High-Grade Ovarian Carcinoma With Germline or Somatic *BRCA* Mutations: Integrated Summary of Efficacy and Safety From the Phase II Study ARIEL2

PARP inhibitors are synthetically lethal to tumor cells with *BRCA* mutations.¹ The PARP inhibitor rucaparib is approved in the United States as monotherapy for treatment of patients with deleterious germline or somatic *BRCA* mutations associated with advanced ovarian cancer who have been treated with 2 or more chemotherapies.² Dr Gottfried Konecny presented an integrated summary of efficacy and safety data from the phase 2 ARIEL2 trial (Assessment of Rucaparib in Ovarian Cancer).³ The objectives of the study were to assess the objective

response rate (ORR) and PFS in ovarian cancer patients from ARIEL2 with germline or somatic *BRCA* mutations and to determine whether platinum sensitivity and the number of prior lines of chemotherapy impacted ORR and PFS.

Eligible patients had a diagnosis of ovarian, primary peritoneal, or fallopian tube cancer, measurable disease based on Response Evaluation Criteria In Solid Tumors (RECIST), and an ECOG performance status of 0 or 1. All patients received initial treatment with oral rucaparib (600 mg twice

daily). Treatment continued until disease progression or discontinuation for other reasons. Responses were investigator-assessed based on RECIST 1.1.⁴ ARIEL2 enrolled 493 patients with germline or somatic *BRCA* mutations or wild-type *BRCA*. There were 2 parts to ARIEL2. Part 1 enrolled patients with at least 1 prior platinum-based therapy, who had received platinum as their most recent treatment, and who had platinum-sensitive disease (n=206). Patients recruited to part 2 had received 3 to 4 prior chemotherapies and had disease that was sensitive, resistant, or refractory to platinum therapy (n=287). Dr Konecny's presentation included data from patients with germline or somatic *BRCA* mutations, including 41 patients from part 1 and 93 patients from part 2.

The 134 patients had a median age of 60 years (range, 33-82 years), and 50.7% had an ECOG performance status of 0. Most patients (82.1%) had epithelial ovarian cancer. Other types included fallopian tube cancer (9.0%) and primary peritoneal cancer (7.5%). The *BRCA* mutation was germline in 58.2% of patients, somatic in 17.2%, and of uncertain origin in 24.6%. The *BRCA1* mutation was reported in 64.2% of patients, and 35.8% had *BRCA2*.

Among the 57 patients with platinum-sensitive disease, the ORR was 70%. The ORR was 83% in the 18 patients who had received 1 prior line of therapy, 86% in the 14 patients with 2 prior lines of therapy, and 52% in patients with 3 or more prior lines of therapy. Among patients with platinum-sensitive disease who had received 1 intervening nonplatinum-

ABSTRACT SUMMARY A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Niraparib Maintenance Treatment in Patients With Advanced Ovarian Cancer Following Response on Frontline Platinum-Based Chemotherapy

In the phase 3 ENGOT-OV16/NOVA trial, niraparib demonstrated a significant improvement in median PFS compared with placebo in patients with recurrent platinum-sensitive ovarian cancer (Mirza MR et al. *N Engl J Med*. 2016;375[22]:2154-2164). Median PFS was prolonged with niraparib regardless of the patient's *BRCA* mutation or HRD status, which could reflect the failure of the genetic test to properly identify the niraparib-responsive population. Trial NCT02655016 is a multicenter, double-blind, randomized, placebo-controlled phase 3 study originally designed to evaluate maintenance therapy with niraparib vs placebo in patients with stage III/IV ovarian cancer with HRD-positive tumors and a CR or PR following first-line treatment with platinum-based chemotherapy. In light of the ENGOT-OV16/NOVA trial results, the original protocol of the current study was amended to allow enrollment of ovarian cancer patients regardless of HRD status (Abstract 203). This ongoing study plans to recruit 330 patients with ovarian cancer (high-grade serous or endometrioid, or high-grade predominantly serous or endometrioid), fallopian tube cancer, or primary peritoneal cancer. Patients will be randomly assigned 2:1 to receive daily niraparib (300 mg) or placebo in 28-day cycles until disease progression or death. The primary objective is PFS based on independent review. Secondary objectives are OS, patient-reported outcomes, time to CA-125 progression, PFS2, TFST, safety, and tolerability. HRD testing will be performed with next-generation sequencing.

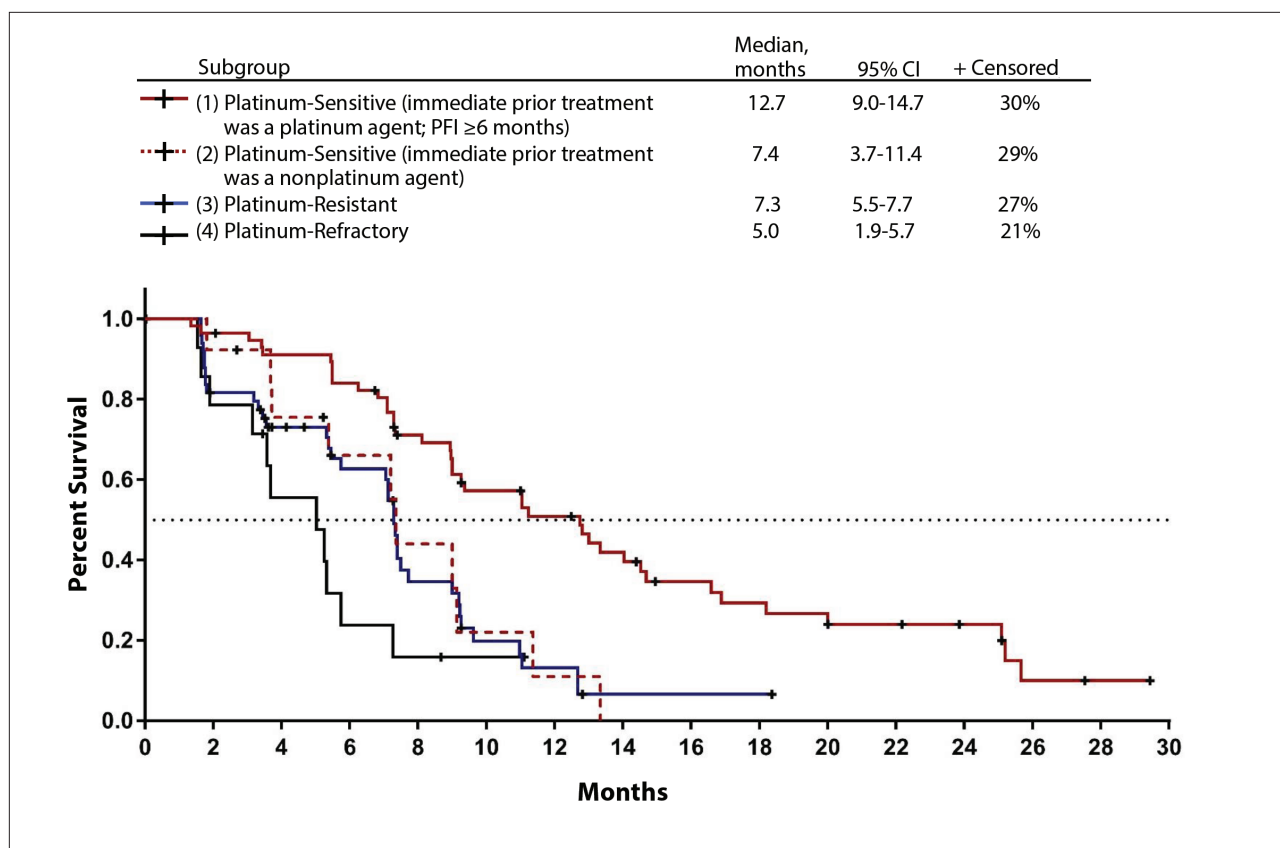


Figure 4. Progression-free survival according to platinum sensitivity in the phase 2 ARIEL2 trial of rucaparib. All patients had a *BRCA* mutation. ARIEL, Assessment of Rucaparib in Ovarian Cancer Trial; PFI, progression-free interval. Adapted from Konecny GE et al. Abstract 1. 2017 Society of Gynecologic Oncology Annual Meeting on Women's Cancer.³

based regimen, the ORR was 43%. Among the 49 patients with platinum-resistant disease, who had all received at least 3 prior lines of therapy, the ORR was 25%. No responses were reported in the 14 patients with platinum-refractory disease. The disease control rate in the 57 patients with platinum-sensitive disease was 81%. In patients who had received 1, 2, or 3 or more prior lines of therapy, the disease control rates were 94%, 86%, and 68%, respectively. In patients with platinum-sensitive disease who had received 1 intervening nonplatinum-based therapy, the ORR was 57%. The disease control rate was 39% in patients with platinum-resistant disease and 29% in those with platinum-refractory disease.

Platinum sensitivity generally showed a positive correlation with PFS.

Median PFS was 12.7 months among the subgroup of patients with platinum-sensitive disease, whose immediate prior treatment was platinum-based, and who had a platinum-free interval of at least 6 months (Figure 4). In patients with platinum-sensitive disease whose immediate prior treatment did not contain platinum, median PFS was 7.4 months. In patients with platinum-resistant disease, median PFS was 7.3 months, and in those with platinum-refractory disease, median PFS was 5.0 months.

Median PFS also showed a positive correlation with the platinum-free interval. Patients with a platinum-free interval of at least 18 months had the longest median PFS, 25.1 months. Median PFS was 16.9 months in patients with a platinum-free interval of at least 12 months, and 12.7

months when the platinum-free interval was at least 6 months. Patients with platinum-sensitive disease whose immediate prior treatment was not platinum-based had a median PFS of 7.4 months. As observed in patients with platinum-sensitive disease, median PFS was similar for patients with the germline vs somatic *BRCA* mutation (12.8 vs 12.7 months) and for patients with the mutation in *BRCA1* vs *BRCA2* (12.8 vs 11.2 months).

In patients with an initial germline mutation in *BRCA1/2*, secondary somatic mutations may restore the *BRCA1/2* protein by correcting the reading frame.⁵ These secondary mutations have been observed in approximately 20% to 30% of patients who have platinum-resistant disease. Among the 55 patients from ARIEL2 with available tissue or DNA samples,

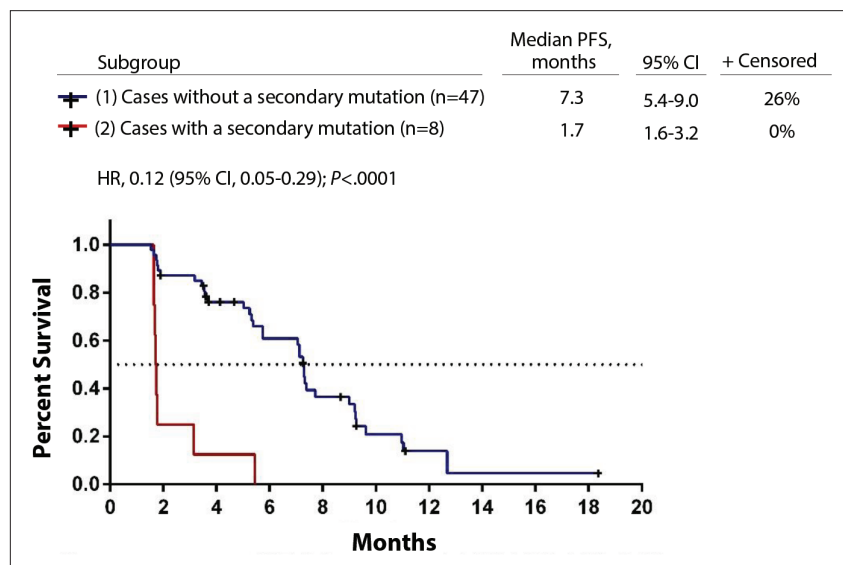


Figure 5. The effect of secondary *BRCA* mutations on progression-free survival in the phase 2 ARIEL2 trial of rucaparib. Secondary somatic mutations were reported in 8 of 55 patients with disease that was resistant or refractory to platinum therapy. ARIEL, Assessment of Rucaparib in Ovarian Cancer Trial; HR, hazard ratio; PFS, progression-free survival. Adapted from Konecny GE et al. Abstract 1. 2017 Society of Gynecologic Oncology Annual Meeting on Women's Cancer.³

ABSTRACT SUMMARY A SEER-Medicare Analysis of the Impact of Metformin on Overall Survival in Ovarian Cancer Patients

A retrospective cohort study was conducted to determine the impact of metformin on survival in patients with ovarian cancer (Abstract 310). The study examined records of all patients with a diagnosis of first epithelial ovarian cancer from 2007 to 2011 in the combined Surveillance, Epidemiology, and End Results (SEER)/Medicare database. Among 2291 patients, 189 had received treatment with metformin. Patients had a median age of 73 years, 51.5% of cases were serous, 64.9% had stage III or later disease at diagnosis, and 74.1% had undergone primary surgery. Based on bivariate analysis, metformin use was associated with higher disease stage, non-white race, higher Charlson index score, and diagnosis of diabetes. Median OS was similar in patients who did or did not receive metformin (35 vs 38 months; HR, 0.96). Median OS was also similar in a matched sample analysis (30 months in metformin users vs 32 months in metformin nonusers). Survival was not impacted by the metformin dose or duration. However, an exploratory regression analysis in patients with at least 30 months of follow-up suggested that metformin might provide a protective effect (HR, 0.37).

secondary reversion mutations were observed in 15%, including 1 patient who had 8 secondary reversion mutations. Median PFS was 7.3 months in patients without secondary mutations

vs 1.7 months in those with them (Figure 5).

The most common treatment-emergent AEs of any grade reported were nausea (78%), asthenia/fatigue

(78%), vomiting (49%), and anemia (48%). The most common grade 3/4 AEs were anemia (29%), transaminase increase (10%), and asthenia/fatigue (10%). One patient died from intestinal obstruction, and 1 died from generalized edema and general health deterioration. The median duration of treatment was 7.6 months (range, 0.1-32.7 months). Treatment-emergent AEs led to dose reductions in 49% of patients and included anemia (25%), fatigue (11%), and thrombocytopenia (10%). Treatment-emergent AEs led to discontinuation in 13% of patients. Reductions in the levels of hemoglobin, platelets, and absolute neutrophil counts were rarely severe and generally remained stable after the initial decrease. Similarly, changes in laboratory parameters were common but rarely severe. An ongoing phase 3 trial is comparing rucaparib vs chemotherapy in patients with *BRCA*-mutated, high-grade ovarian, fallopian tube, or primary peritoneal cancer.⁶

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A Phase II, Randomized, Double-Blind, Placebo-Controlled Study of Chemo-Immunotherapy Combination Using Motolimod With Pegylated Liposomal Doxorubicin in Recurrent or Persistent Ovarian Cancer: a Gynecologic Oncology Group Partners Study

Motolimod is a highly selective, small-molecule agonist of Toll-like receptor 8 (*TLR8*) administered by subcutaneous injection. Activation of *TLR8* stimulates the innate immune response, which involves monocytes, myeloid dendritic cells, and natural killer cells, and helps to coordinate development of an adaptive immune response. The most common AEs associated with motolimod are injection site reactions and transient, mild flu-like symptoms. Pegylated liposomal doxorubicin induces immunogenic cell death, a process that involves secretion of high-mobility group box 1 protein from dying cells and the appearance of tumor-infiltrating lymphocytes within the tumor.¹

The combination of motolimod plus pegylated doxorubicin was previously evaluated in healthy human volunteers and cancer patients, in primates, and in a mouse model reconstituted with human CD34-positive cells to provide a humanized immune system.^{2,3} The mice with the humanized immune system were injected with OVCAR5 cells, a high-grade serous ovarian cancer cell line. The combination of motolimod plus pegylated liposomal doxorubicin induced a significant decrease in tumor volume vs controls ($P=.01$). The combination was also more effective than either agent alone, and tumor-infiltrating lymphocytes were observed in the tumor microenvironment. In first-in-human testing of motolimod, the most common toxicities were injection site reaction (reported in 85%), chills (58%), pyrexia (46%),

fatigue (40%), and nausea (33%).³ Cytokine-release syndrome occurred in 3%, and grade 3 hypotension occurred in 3%.³

The combination of motolimod plus either pegylated liposomal doxorubicin or paclitaxel was evaluated in a phase 1b expansion study of patients with recurrent or persistent ovarian cancer.² The study yielded CRs in 15% of patients, and 53% of patients had a PR or stable disease. The most common AEs of grade 3 or higher were neutropenia (23.1%), anemia (15.4%), and fever, chills, leukopenia, vomiting, and arthralgia, each occurring in 7.7% of patients.

Dr Bradley Monk presented the results of trial 3003 from the Gynecologic Oncology Group (GOG), a double-blind, randomized, placebo-controlled phase 2 study that evaluated pegylated liposomal doxorubicin plus placebo or motolimod in patients with recurrent, platinum-resistant ovarian cancer.^{4,5} Treatment consisted of 4-week cycles given until disease progression, with pegylated liposomal doxorubicin administered at 40 mg/m² on day 1 and motolimod given at 3.0 mg/m² on days 3, 10, and 17 for the first 4 cycles, then only on day 3 of subsequent cycles. Key eligibility requirements included recurrent or

ABSTRACT SUMMARY Weekly Paclitaxel for Recurrent Ovarian Cancer: Does Weekly Administration During Primary Therapy Impact Efficacy and Toxicity at Recurrence?

A retrospective study was conducted to compare the efficacy and toxicity of paclitaxel administered every week vs every 3 weeks in patients with recurrent epithelial ovarian cancer (Abstract 331). Patients were treated at 4 academic institutions between 2002 and 2015. Among the 98 patients, 92% had advanced-stage disease at diagnosis. Among the patients who underwent primary cytoreductive surgery (79%), 41% had no gross residual disease. Six percent of patients had diabetes mellitus, and 2% had preexisting neuropathy from their diabetes. Primary paclitaxel therapy was administered every week in 20.4% of patients and every 3 weeks in 79.6%. Bevacizumab was a component of primary therapy in 27.2%. At the time of treatment for recurrence, grade 1/2 preexisting peripheral neuropathy induced by chemotherapy was noted in 27.1% of patients. The overall rate of chemotherapy-induced peripheral neuropathy during weekly treatment for recurrence was 44.8%. Grade 1 occurred in 32.3% of patients, grade 2 in 10.4%, and grade 3 or higher in 2.1%. Rates of chemotherapy-induced peripheral neuropathy were similar between the treatment groups ($P=.30$). Patients who received paclitaxel every week vs every 3 weeks had similar rates of response ($P=.14$). Median PFS was also similar ($P=.43$). Use of weekly paclitaxel was associated with a trend toward an improved rate of clinical benefit (36.1% vs 60%; $P=.055$).

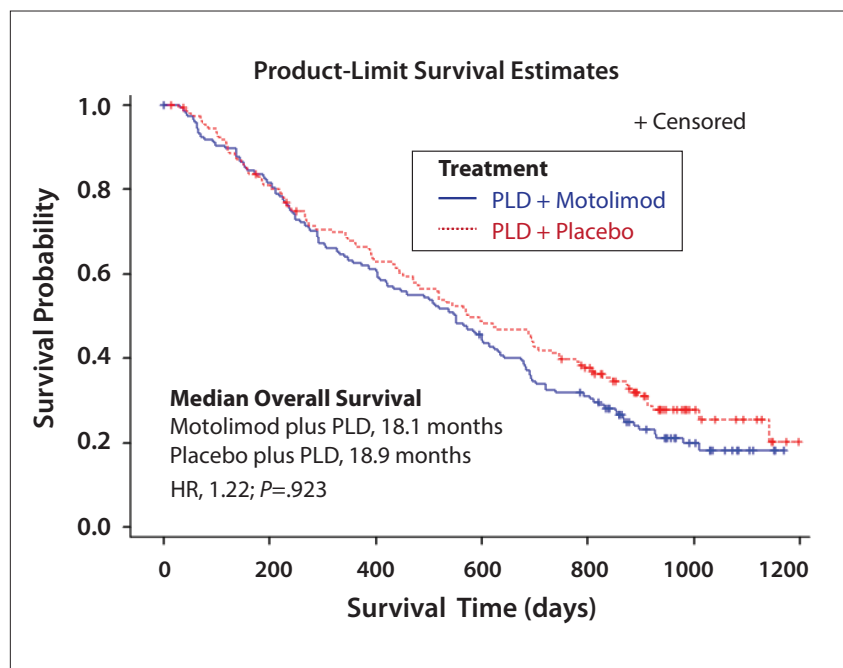


Figure 6. Overall survival among the intent-to-treat population in a phase 2 trial combining motolimod with PLD. HR, hazard ratio; PLD, pegylated liposomal doxorubicin. Adapted from Monk BJ et al. Abstract LB4. 2017 Society of Gynecologic Oncology Annual Meeting on Women's Cancer.⁵

ABSTRACT SUMMARY Neoadjuvant Chemotherapy and Cycle Number: a National Multicenter Study

Among patients with an initial diagnosis of advanced-stage ovarian cancer, approximately 90% respond to primary chemotherapy, yet 75% will eventually relapse. Use of neoadjuvant chemotherapy before interval surgical debulking has been associated with reduced rates of postoperative AEs compared with primary debulking, without reducing efficacy (Vergote I et al. *N Engl J Med.* 2010;363[10]: 943-953). A retrospective, multicenter cohort study investigated the effects of treatment with 0 to 3 vs 4 or more cycles of neoadjuvant chemotherapy in patients with stage IIIC/IV high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer (Abstract 347). The patients' median age was 63 years, and they had received a mean of 3.1 cycles of neoadjuvant chemotherapy and a mean of 3.5 cycles of adjuvant chemotherapy. The median OS was superior among patients who had received 3 or fewer cycles of neoadjuvant chemotherapy ($n=263$) compared with patients who had received 4 or more cycles ($n=139$; $P=.045$), possibly owing to a greater prevalence of poor prognostic factors among patients who received more cycles of treatment. A multivariate analysis showed that factors associated with survival included the number of neoadjuvant chemotherapy cycles ($P=.011$) and the extent of residual disease after surgery ($P<.001$). The number of consolidation cycles did not affect OS ($P=.59$).

persistent epithelial ovarian, fallopian tube, or primary peritoneal cancer, with measurable disease based on RECIST 1.1⁶; and prior treatment with 1 platinum-based chemotherapy, with or without an additional cytotoxic agent. Patients with refractory disease and those with prior anthracycline exposure were excluded. Stratification factors included treatment-free interval and GOG performance status. The trial had 2 primary endpoints: OS and PFS as assessed by immune-related RECIST.

The trial enrolled 297 patients between October 2012 and April 2014. Baseline characteristics were well-balanced between the 2 arms. Patients had a median age of 62.7 years (range, 29.7-91.1 years), and 94% were white. The primary tumor origin was the ovary (in 79.1%), peritoneum (in 12.5%), or fallopian tube (in 8.4%). The predominant histology was serous adenocarcinoma (82.8%), followed by unspecified adenocarcinoma (7.1%), endometrioid adenocarcinoma (1.7%), clear cell carcinoma (1.7%), undifferentiated carcinoma (1.3%), and transitional cell carcinoma (0.7%). Most patients had received 1 (50.5%) or 2 (46.5%) primary regimens, and 51.2% of patients had experienced a platinum-free interval of 6 months or less.

Based on intent-to-treat analysis, the addition of motolimod to pegylated liposomal doxorubicin did not improve the median OS compared with placebo (18.1 months vs 18.9 months; HR, 1.22; $P=.923$; Figure 6). The median PFS was also similar for pegylated liposomal doxorubicin given with motolimod or placebo (4.8 months vs 5.2 months; HR, 1.21; $P=.943$).

The secondary endpoint of response rate was assessed with immune-related RECIST. Among patients in the motolimod arm, the CR rate was 3.4%, and the PR rate was 17.6%. The rate of stable disease was 36.5%. These rates were 2.7%, 18.8%, and 39.6%

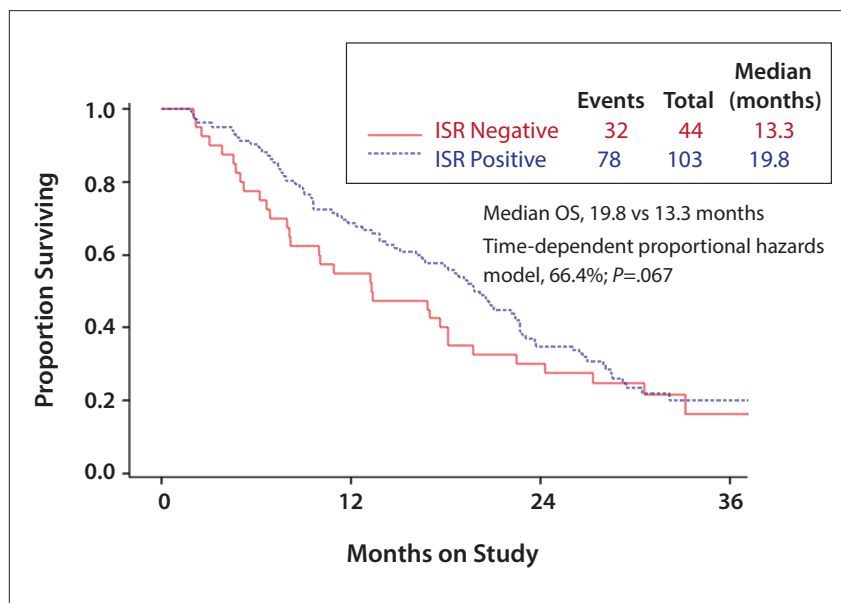


Figure 7. Overall survival according to injection-site reaction among patients treated with motolimod plus PLD in a phase 2 trial. Among the patients treated with PLD plus motolimod, 73.5% (n=108) developed an ISR. In most patients (n=103), the ISR developed within the landmark period of 56 days. ISR, injection-site reaction; OS, overall survival; PLD, pegylated liposomal doxorubicin. Adapted from Monk BJ et al. Abstract LB4. 2017 Society of Gynecologic Oncology Annual Meeting on Women's Cancer.⁵

in the placebo arm. Response rates based on RECIST 1.1 were similar. A prespecified subgroup analysis showed that 73.5% of patients treated with motolimod developed an injection-site reaction, and these patients showed a trend toward improved median OS compared with patients without an injection-site reaction (19.8 months vs 13.3 months; $P=.067$; Figure 7).

Dose reductions or discontinuations occurred in 50.3% of the motolimod arm vs 30.6% of the placebo arm. Dose reductions or discontinuations of pegylated liposomal doxorubicin occurred in 28.6% vs 23.1% of patients. Nearly all patients

in the study experienced at least 1 treatment-emergent AE. One or more treatment-emergent AEs of grade 3 or higher occurred in 63.9% of the motolimod arm and 61.9% of the placebo arm. In both arms, 40.8% of patients experienced at least 1 serious treatment-emergent AE. A treatment-emergent AE led to treatment discontinuation in 7.5% of the motolimod arm vs 1.4% of the placebo arm. Deaths were reported in 4.8% of the motolimod arm vs 4.1% of the placebo arm. In the motolimod arm, the most common treatment-emergent AEs of any grade were fatigue (87.8%), injection site

reaction (73.5%), and chills (63.3%). Flu-like symptoms were observed in 30.6% of patients in the motolimod arm, and cytokine-release syndrome was reported in 16.3%.

No significant association was detected between the PFS (as assessed by immune-related RECIST) and the type, density, or location of tumor-infiltrating lymphocytes, *TLR8* polymorphisms, mutations in *BRCA1/2* or other DNA repair genes, or auto-antibody biomarkers. Survival was superior in patients with higher levels of interferon- γ , tumor necrosis factor α , or interleukin-12p, and in patients with lower levels of interleukin-10.

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A Phase III Trial of Maintenance Therapy in Women With Advanced Ovarian/Fallopian Tube/Peritoneal Cancer After a Complete Clinical Response to First-Line Therapy: an NRG Oncology Study

Although standard first-line therapy achieves satisfactory response rates in patients with advanced ovarian cancer, rates of recurrence are high, even among patients with a clinical CR.¹ Maintenance therapy has been investigated as a means to reduce the risk of recurrence and extend survival. A phase 3 trial evaluated maintenance paclitaxel administered for 12 months vs 3 months in patients with advanced ovarian cancer who had achieved a CR with platinum-based and paclitaxel-based chemotherapy.² The trial was discontinued after an interim analysis demonstrated a significant prolongation of PFS for patients who received 12 months of maintenance therapy ($P=.0035$). However, subsequent analysis demonstrated that OS

was similar for both arms ($P=.34$), despite updated results that continued to showed superior PFS ($P=.006$).³

Dr Larry Copeland presented data from an analysis of the randomized phase 3 GOG-212 trial, which evaluated maintenance therapy with paclitaxel or CT-2103 (paclitaxel poliglumex) vs surveillance in patients with stage III/IV cancer of the ovary, fallopian tube, or peritoneum who attained a clinical CR after first-line therapy with platinum and taxane therapy.⁴ Patients were randomly assigned 1:1:1 to undergo surveillance, maintenance with paclitaxel (135 mg/m² every 28 days for 12 cycles), or maintenance with CT-2103 (135 mg/m² every 28 days for 12 cycles). The study opened in March 2005 and closed in January 2014. The primary

endpoints were OS, quality of life, and patient-reported neurotoxicity. The trial accrued 1157 patients. As of May 19, 2016, patients had a median follow-up of 71 months. A third scheduled interim analysis indicated that neither taxane maintenance regimen was likely to demonstrate a superior OS compared with surveillance.

Baseline patient characteristics were generally well-balanced among the 3 arms. The ovary was the primary tumor site in approximately 86% of patients, followed by the peritoneum in approximately 11%. Eighty-five percent of patients had stage III disease, 84% to 87% had serous histology, and most tumors were of high grade.

Median OS was 54.8 months with surveillance, 51.3 months with paclitaxel, and 60.0 months with CT-2103 (Figure 8). In comparison with surveillance, treatment with paclitaxel yielded an HR of 1.104, and treatment with CT-2103 yielded an HR of 0.979. Median PFS with surveillance was 13.4 months vs 18.9 months with paclitaxel (HR, 0.783) and 16.3 months with CT-2103 (HR, 0.847). AEs of interest included grade 3/4 neurotoxicity (occurring in 1.9% of the surveillance arm, 39.3% of the paclitaxel arm, and 50.7% of the CT-2103 arm) and grade 2 alopecia (occurring in 13.9%, 44.9%, and 24.5%). Quality of life was slightly lower in the taxane arms compared with the surveillance arm, but the differences did not exceed the threshold considered to be relevant. Both paclitaxel and CT-2103 were associated with a clinically meaningful increase in neuropathy compared with surveillance.

Two exploratory analyses were

ABSTRACT SUMMARY Impact of Adjuvant Chemotherapy in Patients With FIGO Stage I Ovarian Clear Cell Cancer in the Platinum Era: a Surveillance, Epidemiology, and End Results Cohort Study, 2000-2013

A study was conducted to determine whether adjuvant chemotherapy impacts survival in patients with stage I ovarian clear cell carcinoma according to criteria from the International Federation of Gynecology and Obstetrics (Abstract 415). Data from patients with stage I ovarian clear cell carcinoma who received treatment from 2000 to 2013 were gathered from the SEER database. The analysis identified 2332 patients. They had a median age of 55 years (range, 18-91 years), and 68% had received treatment with adjuvant chemotherapy. The use of adjuvant chemotherapy was associated with cancer of stage IC (odds ratio [OR], 1.775; $P<.001$) and more recent diagnosis (OR, 1.044; $P=.001$). The 5-year OS rate was significantly higher in patients with stage IA/IB disease compared with patients who had stage IC disease (87% vs 82%; $P=.023$). However, 5-year OS rates were similar in patients who received adjuvant chemotherapy (85%) vs those who did not (83%; $P=.434$). Multivariate analysis showed that OS was associated with patient age (HR, 1.059; $P=.003$) and substage IC (HR, 1.344; $P=.009$). Use of adjuvant chemotherapy did not impact OS ($P=.871$).

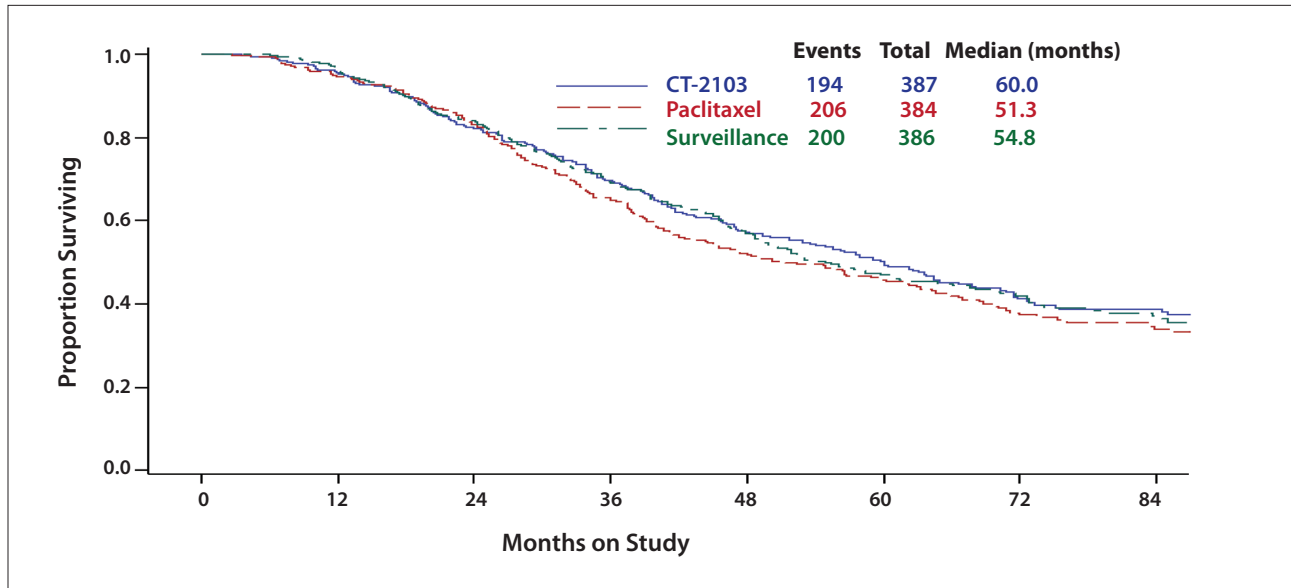


Figure 8. Overall survival in a phase 3 trial of maintenance therapy after a complete response to first-line therapy. CT-2103, paclitaxel poliglumex. Adapted from Copeland LJ et al. Abstract LBA2. 2017 Society of Gynecologic Oncology Annual Meeting on Women's Cancer.⁴

ABSTRACT SUMMARY Neoadjuvant Chemotherapy for Advanced Ovarian, Fallopian Tube and Peritoneal Cancer: an Ancillary Study of GOG-262

An analysis of patients from the GOG-262 trial evaluated demographic and clinicopathologic characteristics and outcomes in patients with advanced ovarian, fallopian tube, or peritoneal cancer (Abstract 133). GOG-262 randomly assigned 692 patients to treatment with paclitaxel given every week or every 3 weeks. Among these patients, 13% received neoadjuvant chemotherapy (paclitaxel given week or every 3 weeks). Among the 88 patients treated with neoadjuvant chemotherapy, 78% underwent cytoreductive surgery. Their median age was 63 years, and most patients had stage III (60%) or IV (39%) disease. The median OS was 41.9 months, and median PFS was 14.9 months. Based on multivariate analysis, patients treated with neoadjuvant therapy rather than primary surgery were more likely to have primary peritoneal cancer ($P=.009$). A nonsignificant trend suggested that patients with stage IV disease were more likely to have received neoadjuvant treatment ($P=.079$). After adjusting for known prognostic factors, median OS was not different for patients who underwent neoadjuvant chemotherapy vs primary surgery.

conducted. Median OS was 70.0 months in patients who achieved complete gross resection during their primary surgery compared with 43.6 months in patients with residual disease. However, in the patients with no residual disease after surgery, all

3 maintenance treatments yielded similar OS values, ranging from 61.6 months to 72.6 months. A second exploratory analysis investigated whether maintenance chemotherapy induced chemoresistance. In patients with gross residual disease,

maintenance therapy with either paclitaxel or CT-2103 yielded a median OS of 39.9 months vs 48.7 months with surveillance, but the difference was not significant.

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Comparison of Clinical Outcomes in Women With Advanced Ovarian Cancer Undergoing Neoadjuvant Chemotherapy Who Receive Three Vs Greater Than Three Cycles of Chemotherapy After Interval Cytoreductive Surgery

For decades, the standard-of-care treatment for advanced-stage ovarian cancer has consisted of primary cytoreductive surgery followed by adjuvant chemotherapy. Recently, neoadjuvant chemotherapy followed by interval cytoreductive surgery, with subsequent completion of chemotherapy, has been shown to be noninferior to the surgery-first approach.^{1,2} This strategy may result in lower perioperative morbidity and is being implemented increasingly in the United States.^{3,4} After primary cytoreductive surgery, most patients receive 6 cycles of adjuvant chemotherapy, based on

the finding that treatment beyond 6 cycles increased toxicity without an improvement in outcomes.^{5,6} However, in the neoadjuvant setting, most ovarian cancer patients receive 3 cycles of preoperative chemotherapy followed by interval surgery and from 3 to 6 cycles of postoperative chemotherapy, leading to a higher median number of chemotherapy cycles for patients treated with the neoadjuvant approach.

A study was conducted to compare clinical outcomes in patients with stage IIIC/IV ovarian cancer treated with neoadjuvant chemotherapy and interval cytoreductive surgery followed by 3 vs more than 3 cycles of postop-

erative chemotherapy.⁷ A retrospective chart review evaluated data from several institutions. Enrolled patients had been treated for stage IIIC/IV ovarian, fallopian tube, or primary peritoneal cancer with neoadjuvant, platinum-based chemotherapy followed by interval cytoreductive surgery and postoperative chemotherapy. The study included 40 patients who had received 3 cycles of postoperative chemotherapy and 47 patients who had received more than 3 cycles of postoperative chemotherapy. Median follow-up was 23.4 months and 31.1 months, respectively. Patients had a median age of approximately 65 years. No gross residual disease after cytoreduction was reported in 70.0% of patients treated with 3 cycles of postoperative chemotherapy vs 61.7% of patients treated with more than 3 cycles. Serous histology was noted in 70.0% vs 76.7% of patients, respectively, and grade 3 tumor status was observed in 80.0% vs 89.4% of patients. In the group of patients who had received more than 3 cycles of postoperative chemotherapy cycles, the median number of cycles was 5 (range, 4-7).

Median PFS was similar for both groups of patients ($P=.91$; Figure 9). However, median 3-year OS was significantly improved in patients who had received 3 or more postoperative chemotherapy cycles (82.4% vs 59.4%; $P=.03$; Figure 10).

Levels of CA-125 normalized more quickly among the patients who received 3 cycles of postoperative chemotherapy ($P=.04$). However, the study excluded patients whose CA-125 levels remained persistently

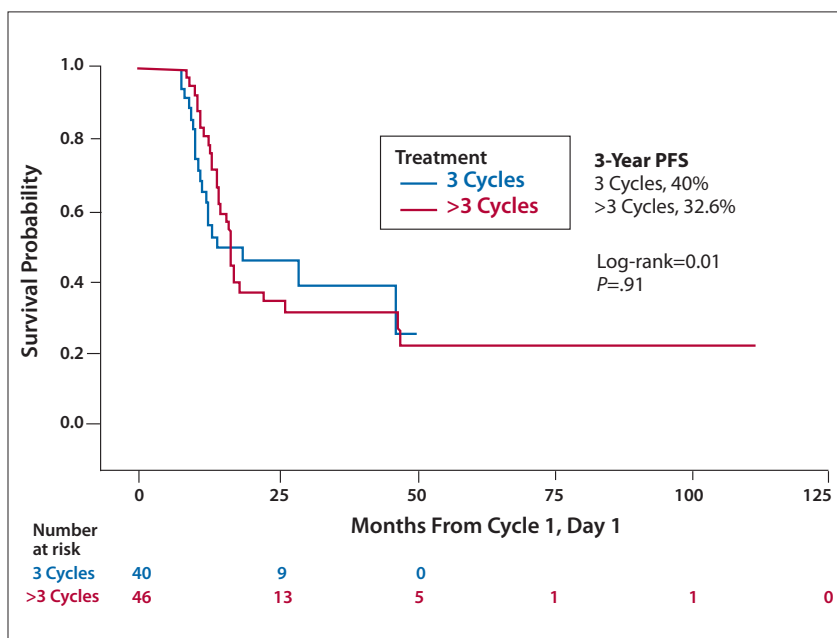


Figure 9. Progression-free survival in a study comparing the number of neoadjuvant chemotherapy cycles (3 vs >3) after interval cytoreductive surgery. PFS, progression-free survival. Adapted from Kim JS et al. Abstract 141. 2017 Society of Gynecologic Oncology Annual Meeting on Women's Cancer.⁷

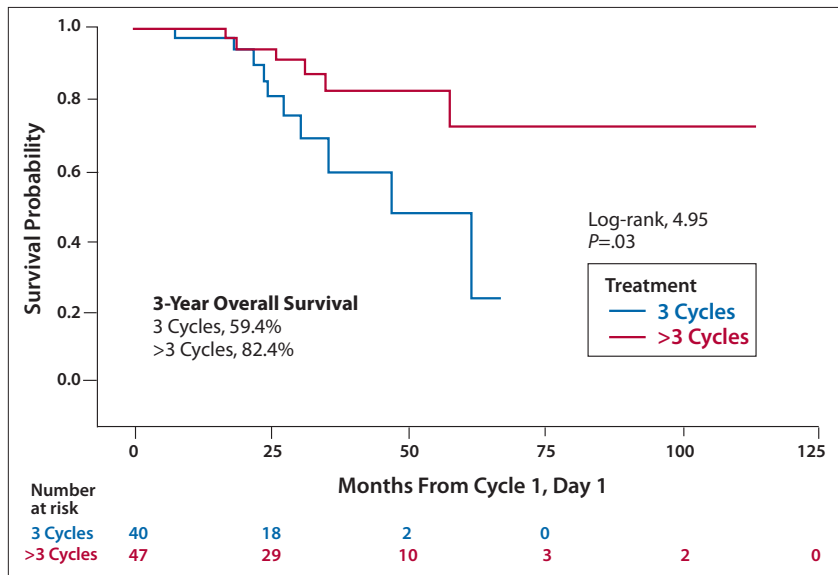


Figure 10. Overall survival in a study comparing the number of neoadjuvant chemotherapy cycles (3 vs >3) after interval cytoreductive surgery. Adapted from Kim JS et al. Abstract 141. 2017 Society of Gynecologic Oncology Annual Meeting on Women's Cancer.⁷

ABSTRACT SUMMARY IV and IV/IP Chemotherapy as Adjuvant Treatment in Patients With Ovarian Cancer Leads to Similar Rates of Progression Free, and Overall Survival After Neoadjuvant Chemotherapy

A study compared outcomes following neoadjuvant chemotherapy and surgical debulking in patients who received intravenous (IV) or intravenous plus intraperitoneal (IV/IP) adjuvant therapy (Abstract 333). The study included 89 ovarian cancer patients in the IV cohort and 18 in the IV/IP cohort. Demographic and clinicopathologic characteristics were similar for the 2 cohorts, with the following exceptions: Patients in the IV group had received a mean of 3.4 cycles of adjuvant treatment, and those in the IV/IP group had received a mean of 5.2 cycles ($P=.005$). Also, the frequency of comorbid conditions was higher in the IV group (74.2% vs 50%). The most common primary disease site was the ovary (62.9%-72.2%), followed by the fallopian tube (22.2%-23.5%) and the peritoneum (5.5%-10.1%). Optimal debulking with no gross residual disease was achieved with the primary debulking surgery in 57.3% of the IV group vs 83% of the IV/IP group. Residual disease of 1 cm or less was achieved in 36.0% vs 16.7%. Rates of recurrent or progressive disease were 85.5% in the IP patients vs 77.8% in the IV/IP patients ($P=.66$). Median PFS was 9.5 months vs 10 months ($P=.52$), and median OS was 23.1 months vs 29.3 months ($P=.58$).

elevated after 3 postoperative cycles of chemotherapy. No significant increase in toxicity was observed in patients who received more than 3 cycles of postoperative chemotherapy. Among the patients who received 3 vs greater than 3 cycles of postoperative chemotherapy, the most common AEs of at least grade 2 were neutropenia (27.5% vs 19.1%), neuropathy (12.5% vs 25.5%), anemia (10.0% vs 17.0%), and fatigue (15.0% vs 17.0%).

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Highlights in Ovarian Cancer From the 2017 Society of Gynecologic Oncology Annual Meeting on Women's Cancer: Commentary

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Presentations at the 2017 Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer provided important information on ovarian cancer. New data from clinical trials on niraparib, olaparib, rucaparib, chem-immunotherapy, and taxanes were presented. Several retrospective analyses evaluated the role of neoadjuvant chemotherapy.

Niraparib

Dr Sven Mahner presented an analysis of secondary efficacy endpoints for niraparib maintenance in ovarian cancer from 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).¹ In the NOVA trial, maintenance therapy with niraparib significantly improved progression-free survival (PFS) among patients with platinum-sensitive, recurrent ovarian cancer.² Improvement was seen in patients with and without germline *BRCA* mutations and regardless of the homologous recombination deficiency (HRD) status. The background to the current analysis was the concern that a new treatment paradigm might negatively alter the outcomes from subsequent treatments.

When results from the NOVA trial were presented and published in late 2016, concern was raised that exposure to poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors might reduce the response to subsequent therapies.^{2,3}

Several components were included in the evaluation of primary and secondary endpoints. The study included a measurement more common in Europe than the United States: time to first and second subsequent treatments. This measures the time from when the patient entered the trial to the time she received her next chemotherapy regimen and then the regimen thereafter. The study also measured 2 types of PFS: the first interval, starting at randomization (PFS1); and the second interval, measured from randomization to the second progression (PFS2). There were subtle differences among these data points. In ovarian cancer, meaningful improvements in PFS from several different treatments can be cobbled together to demonstrate an improvement in overall survival.

The secondary endpoint analysis was somewhat immature, with data for PFS2 demonstrating less than 50% of events and less than 40% of events for time to subsequent treatment. (For the survival analysis, less than 20% of events were mature.) Nonetheless, the analysis found a consistent treatment

effect for both of the main cohorts: patients with or without the germline *BRCA* mutation. For PFS2, the hazard ratio (HR) was 0.48 for patients with the mutation vs 0.69 for patients without the mutation. The HRs for time to second subsequent treatment were 0.48 vs 0.74, respectively. This analysis therefore appeared to show a similar magnitude of effect as the primary analysis from NOVA.²

There was a significant improvement in the chemotherapy-free interval, which is important to patients. These data are robust. Among patients with the germline *BRCA* mutation, the median chemotherapy-free interval was 22.8 months with niraparib vs 9.4 months with placebo (HR, 0.26; $P < .0001$), which again is similar to the treatment effect seen in the primary analysis in the germline mutated cohort. Among patients without the germline mutation, the interval was 12.7 months with niraparib vs 8.6 months with placebo (HR, 0.50; $P < .001$).

The most important discovery of this analysis was that niraparib had no impact on the efficacy of next-line therapy. When PFS1 was subtracted from PFS2, which measures time to next progression, survival was similar. Niraparib significantly improved the primary and secondary endpoints following a partial or complete response

to platinum, regardless of the patient's *BRCA* mutation status or HRD status. The analysis suggests that there is a prolonged clinical effect, and no diminution in subsequent response to DNA-damaging agents. This positive finding confirms the efficacy of niraparib in this setting for patients with recurrent, high-grade ovarian cancer who have responded to platinum, irrespective of their *BRCA* mutation status. Again, these data raised no concern regarding a decreased response to subsequent therapy, which is important.

A poster presented by Dr Antonio González Martín described an open and enrolling, randomized, double-blind phase 3 trial of niraparib maintenance in patients with advanced ovarian cancer who responded to frontline platinum-based chemotherapy.⁴ Importantly, this study will stratify patients according to the presence or absence of HRD. Other stratification factors include whether the patient was treated with neoadjuvant chemotherapy and whether she achieved a complete response or partial response to frontline therapy. This exciting trial should help inform our understanding of where to best position PARP inhibitors based on the magnitude of effect and how patients respond over the long-term with regard to overall survival and other outcomes. It will also be best to monitor late treatment effects in the frontline setting.

Olaparib

Dr Eric Pujade-Lauraine presented results from the phase 3 SOLO2 study (Studies of Olaparib in Ovarian Cancer 2) of olaparib monotherapy in the maintenance setting for patients with platinum-sensitive recurrent ovarian cancer.⁵ This study aimed to confirm findings from the phase 2 Study 19, published in 2012, which showed that olaparib maintenance significantly improved PFS in these patients.⁶ The approval of olaparib was based on several studies throughout the world.⁷

Study 19 was an important European study. The SOLO2 trial focused on patients with the *BRCA1* or *BRCA2* mutation, and it used the tablet formulation of olaparib. The switch from the capsule formulation used in Study 19 is important because clinicians were anxious to learn what kind of efficacy and toxicity would be associated with the tablet formulation.

Patients in the SOLO2 trial had received at least 2 previous lines of platinum therapy, and they had achieved a complete response or partial response to their most recent platinum therapy. Patients were randomly assigned 2:1 to treatment with olaparib 300 mg twice daily or placebo. They were treated until objective disease progression.

The primary endpoint was investigator-assessed PFS. The study also included a blinded, independent central review of PFS with sensitivity analysis. Secondary endpoints included time to first subsequent treatment or death, time to second progression (PFS2), time to second subsequent treatment or death, overall survival, safety, and health-related quality-of-life parameters.

The demographic characteristics were fairly well-balanced. Importantly, in both groups, approximately 40% of patients had a platinum-free interval of 6 to 12 months, and approximately 60% had an interval of more than 12 months.

The primary outcome was impressive, with a median PFS of 19 months in the olaparib group and 5.5 months in the placebo group (HR, 0.30). The sensitivity analysis, which incorporated a blinded independent review of PFS, also showed improvement with olaparib, with an HR of 0.25.

The analysis of secondary endpoints showed that olaparib significantly improved the time to first subsequent treatment (28 months vs 7 months). PFS2 and time to second treatment were not reached for the olaparib arm. In the placebo group,

both endpoints were approximately 18 months. Follow-up has already extended beyond the 30-month mark at this point, so these data indicate strong efficacy.

The change from capsules to tablets did not appear to raise any new safety signals. Adverse events of grade 3 or higher occurred in 37% of the olaparib arm and 18% of the placebo arm. Dose reductions occurred in 25% of the olaparib arm and 3% of the placebo arm. Adverse events led to treatment discontinuation in 11% of the olaparib arm vs 2% of the placebo arm. Olaparib is therefore associated with somewhat more toxicity but much more efficacy than placebo.

In terms of the most common nonhematologic adverse events, nausea was still an issue for patients treated with olaparib; it was reported in 76% of patients. Approximately 33% of patients in the placebo arm reported nausea. Fatigue occurred in 66% of the olaparib arm and almost 40% of the placebo arm. Vomiting was also more common among the patients receiving olaparib, at 37%, vs 19% with placebo. Diarrhea was also increased, at approximately 33% vs 20%, respectively. Small differences were seen for the other nonhematologic events.

There were few nonhematologic adverse events of grade 3 or higher, and the differences between olaparib and placebo were minimal for fatigue (4.1% vs 2%), vomiting (2.6% vs 1%), abdominal pain (2.6% vs 2.0%), and nausea (2.6% vs 0%).

Anemia of all grades was reported among 44% of the olaparib arm vs 7% of the placebo arm. Grade 3 or higher anemia occurred in 20% vs 2% of patients. Grade 3 or higher neutropenia was only 5% vs 4%. All-grade neutropenia occurred in 20% vs 6%. Rates of all-grade thrombocytopenia were 14% vs 3%.

Liver toxicity was a concern as a class effect. There were no reports of grade 3 or higher liver toxicity in either arm. Rates of elevated alanine

aminotransferase (ALT) were barely higher with niraparib, at 5.1% vs 4%. Therefore, there were no important signals regarding the impact of olaparib on liver function. The patient-reported outcomes showed no differences between the treatment arms.

The data from this trial are encouraging, as they showed a significant benefit in favor of olaparib for PFS, as well as the secondary endpoints. The nonhematologic toxicity was mainly low-grade, and there was no detrimental impact on quality of life. With the exception of anemia, the frequency of grade 3 and higher hematologic toxicity was very low. The tablet formulation will be studied moving forward, and these results support this change.

Rucaparib

The phase 2 ARIEL2 trial (Assessment of Rucaparib in Ovarian Cancer), presented by Dr Gottfried Konecny, evaluated rucaparib in patients with platinum-sensitive, relapsed, high-grade ovarian cancer with germline or somatic *BRCA* mutations.⁸ ARIEL2 examined a novel PARP inhibitor and builds upon the concept of synthetic lethality for patients treated with PARP inhibitors who are deficient in homologous recombination, resulting in cell death. Synthetic lethality is the simultaneous perturbation of 2 genes that results in cellular death. This therapeutic principle leverages preexisting *BRCA* mutations or HRD presence when PARP inhibition is employed. The presentation provided integrated summary data based upon 2 parts of ARIEL2. Part 1 enrolled patients who had received 1 or more previous platinum-based therapies, had received a platinum agent as their last treatment, and were platinum-sensitive. Part 2 enrolled patients who had received 3 or 4 previous chemotherapies and were platinum-sensitive, platinum-resistant, or platinum-refractory. The presentation by Dr Konecny provided data for

41 patients from part 1 and 93 patients from part 2.

In this analysis, 58% of the patients had a germline mutation, 17% had a somatic mutation, and the origin was unknown in the remainder. Among patients with the *BRCA* mutation, 64% had *BRCA1* and 36% had *BRCA2*. Among all patients, 53% were platinum-sensitive and 37% were platinum-resistant.

The efficacy data were reassuring and congruent with previous studies. There were fairly good response rates. For platinum-sensitive patients, the overall response rate was 70%, which is remarkable for any compound, let alone a single agent. The overall response rates were 83% among patients who had received 1 prior line of therapy and 86% among those with 2 prior lines. The overall response rate dropped to 52% among patients who had received 3 or more prior lines of therapy. The take-home message from the trial is that increasing prior lines of therapy corresponded with a decrease in response rate.

Among the platinum-sensitive patients who had received non-platinum-based therapy as their previous treatment, the response rate was 43%. Patients who were resistant to platinum therapy—who had received at least 3 prior lines—had a response rate of 25%. No significant responses were seen among the 14 patients with platinum-refractory disease.

These results are reflected in the rates of PFS. The highest median PFS, 12.7 months, was seen among platinum-sensitive patients with a progression-free interval of at least 6 months and who had received a platinum therapy as their last treatment. Among platinum-sensitive patients whose last treatment was not a platinum agent—who therefore probably did not respond as well to platinum—the mean PFS was 7.4 months. Median PFS was 7.3 months among platinum-resistant patients and 5.0 months among platinum-refractory

patients. There was a significant drop in PFS from patients who were highly platinum-sensitive to those who were platinum-resistant and platinum-refractory.

An important observation in this study is that secondary somatic mutations can restore *BRCA* function. This theme was raised in several of the scientific sessions at the 2017 SGO meeting, and it is an important concept with potential clinical relevance. There are multiple mechanisms of resistance for PARP inhibitors, but among these, secondary reversion mutations that can restore *BRCA* function are prominent. This concept must be better understood to develop strategies that can best predict responses to PARP inhibition.

The analysis of adverse events showed no new safety signals. The most common all-grade events were nausea (reported in 78%), asthenia and fatigue (78%), vomiting (49%), anemia (48%), and dysgeusia (40%). The rates dropped below 40% for all other events. The most common grade 3/4 adverse events were anemia (29%), asthenia and fatigue (10%), and increase in ALT/aspartate transaminase (10%). All other grade 3/4 events occurred in less than 10% of patients. Thrombocytopenia has been seen with other PARP inhibitors. In this study, all-grade thrombocytopenia occurred in 25% of patients, and grade 3/4 thrombocytopenia occurred in only 7%.

Dr Elizabeth Swisher presented an analysis that evaluated *BRCA1* and *RAD51C* promoter hypermethylation, which increases sensitivity to rucaparib, among patients from part 1 of the ARIEL2 trial.⁹ As mentioned, these patients were platinum-sensitive and had received at least 1 prior line of platinum chemotherapy. They had measurable disease, and, importantly, investigators were able to access their screening biopsies and archival tissue. Patients were randomly assigned to treatment with placebo

or rucaparib. They were divided into 3 groups. The first was patients with a *BRCA* mutation. The second was patients who were *BRCA* wild-type, but had demonstrated HRD. These patients had a loss of heterozygosity that was expressed as high. In the third group, patients had wild-type *BRCA* and a low expression of loss of heterozygosity, indicating that they were HRD-negative.

It was interesting to see a high response rate exceeding 50% among patients who were *BRCA1*-methylated. In ovarian cancer, the *BRCA1* and *RAD51C* genes are associated with high loss of heterozygosity. These genes therefore act as surrogates for HRD and, consequently, suggest likely sensitivity to rucaparib. The patient samples commonly showed loss of *BRCA1* methylation after exposure to platinum chemotherapy, even among the patients in part 1, who were platinum-sensitive. This finding can help predict which patients will respond to treatment. When using methylation as a predictor of PARP sensitivity, a recent biopsy is needed because the original tissue may not have been methylated, and methylation can occur later. Tumor sequencing may be important when choosing these therapies.

Chemoimmunotherapy

Dr Brad Monk presented results from a randomized, double-blind, placebo-controlled phase 2 trial that evaluated a chemoimmunotherapy combination consisting of motolimod, a highly selective agonist of the Toll-like receptor 8 (*TLR8*) gene, and pegylated liposomal doxorubicin in recurrent or persistent ovarian cancer.¹⁰ This study was from the Gynecologic Oncology Group (GOG).

Despite a strong preclinical rationale, the study found no difference when motolimod was added to pegylated liposomal doxorubicin. One interesting observation was drawn

from a prespecified subgroup analysis of injection site reaction. The median overall survival was 19.8 months among patients with a reaction vs 13.3 months among those without. This finding is hypothesis-generating. However, a troubling aspect is that it was not possible to gain insight into whether injection site reaction was a surrogate for a more intact immune system. Injection site reaction did not correspond with the immune score. The significance of the injection site reaction is therefore unknown, and more work will be required before this modality can be considered further in the clinical arena.

Although this study did not provide positive data, the idea of combining immunotherapy with targeted agents, as well as traditional chemotherapies, is fascinating. We will certainly see more data emerge in this area in the future.

Taxanes

Dr Larry Copeland provided data for the phase 3 GOG-212 study.¹¹ This study builds upon data from GOG-178, which showed improved PFS among patients who received prolonged monthly paclitaxel treatment.¹² The study was prompted by the high rate of recurrence among advanced-stage patients (60% to 70%). The goal was to eradicate disease earlier to increase cure rates or overall survival. The study enrolled patients with stage 3/4 disease. Patients had received at least 5 cycles of chemotherapy and had achieved a complete clinical response. Patients were required to have a good performance status with no significant neuropathy, and were randomly assigned to 1 of 3 arms: surveillance; paclitaxel given every month at 135 mg/m² for a year; or a novel taxane, CT-2103, administered at the same dosage as paclitaxel.

This large trial had a superiority design and enrolled 1157 patients. It spanned nearly a decade, as it was

activated in 2005 and closed in 2014. The median duration of follow-up was 71 months.

The study was closed when a log-rank statistic for each taxane regimen dropped below the interval specified in the study design, indicating that it was unlikely that either maintenance regimen had a superior overall survival compared with surveillance. Compared with the surveillance arm, the novel taxane extended median survival by 5.2 months, and paclitaxel did so by 3.5 months, but these differences were not statistically significant. The HRs were .98 and 1.1, respectively. The taxanes slightly improved PFS, as might be expected with maintenance therapy. Interestingly, for PFS, the novel taxane did less well than paclitaxel. The improvement over surveillance was 3 months for CT-2103 and 5.5 months for paclitaxel. Again, these differences were not statistically significant. The HRs were .84 and .78.

Adverse events were more common among the patients treated with taxanes. Allergic reactions, alopecia, fatigue, nausea, constipation, and sensory neuropathy were significantly more common. The differences in quality of life were thought to be of minimal clinical importance. There was no substantial difference in patient-reported scores from the Functional Assessment of Cancer Therapy-Ovarian questionnaire. The taxanes, particularly CT-2103, were associated with significantly more neuropathy. In the case of CT-2103, the effect was thought to be clinically meaningful.

Kaplan-Meier analysis showed that the experimental taxane was better than paclitaxel, but the difference was not statistically significant. An exploratory analysis evaluated whether maintenance chemotherapy was more effective in patients who were cytoreduced to no gross residual disease at their primary surgery. As expected, these patients had better survival overall than those with residual disease.

Another exploratory analysis assessed whether maintenance chemotherapy induced resistance to chemotherapy. Among patients with residual disease, the surveillance arm improved overall survival by 8.8 months over the taxane arms. This difference did not reach statistical significance.

This important study showed no significant improvement in overall survival for the treatment arms. The hope was that maintenance therapy would eliminate resistant clones and improve overall survival, which is the most important potential outcome for a maintenance trial in the frontline setting. The slight improvement in PFS is difficult to interpret because the endpoint was confounded by the administration of an active therapy vs placebo. Treatment was associated with increased adverse events, particularly neuropathy.

The results of this trial will likely curtail interest in trials of taxane maintenance in this setting. There may be renewed interest in the use of targeted agents and drugs that have a novel mechanism of action compared with the patient's original treatment.

A retrospective chart review presented by Dr Camille Gunderson was prompted by concern that the use of paclitaxel on a weekly basis would lead to a decreased response when using weekly paclitaxel again at recurrence.¹³ There is some thought that paclitaxel may have different, more antiangiogenic properties when administered weekly as compared with when it is given up-front as a bolus every 3 weeks.

The use of weekly paclitaxel did not appear to attenuate any efficacy associated with the subsequent use for recurrence. These data are reassuring, even with a relatively small number of patients (N=98). The analysis provides strong evidence to alleviate the concern about using paclitaxel on a weekly basis before using it again at recurrence.

Neoadjuvant Chemotherapy

An analysis by Dr Josephine Kim compared clinical outcomes in women with advanced cancer according to the number of cycles of neoadjuvant chemotherapy (3 vs >3) received after interval cytoreductive surgery.¹⁴ When chemotherapy is given before aggressive cytoreduction, there is less gross disease and a higher rate of no residual disease (R0). An interesting question, however, is why these outcomes do not translate into a survival advantage. Among the theories is that we may be selecting for resistant clones by not performing initial up-front cytoreduction. Another theory is that we are not administering enough chemotherapy on the back end to eradicate what disease remains following the interval cytoreduction. In the frontline setting, approximately 6 cycles of chemotherapy are administered. With neoadjuvant treatment, often only 3 cycles are given. Dr Kim examined whether more cycles would improve outcome.

The analysis found that overall survival was higher among patients treated with more than 3 cycles vs 3 cycles (82% vs 59%; $P=.03$). Surprisingly, PFS was not improved (32.6% vs 40%; $P=.91$). It is common to see an improvement in PFS that does not translate into an improvement in overall survival, but the reverse observation is more rare. This outcome is difficult to interpret.

A study from Canada also examined the optimal number of cycles of neoadjuvant chemotherapy.¹⁵ This analysis by Dr Alon Altman included patients with stage 3C or 4, high-grade, serous ovarian cancer who underwent neoadjuvant chemotherapy. The study focused on 2 aspects: the number of cycles before the interval cytoreduction and the number of cycles given adjuvantly after cytoreduction. The study found worse outcomes among patients treated with 4 or more cycles

of neoadjuvant cytoreduction compared with those who received between 0 and 3. The worse outcome was not completely unexpected because patients requiring more cycles prior to interval cytoreduction are likely those with a larger initial tumor volume. This study also evaluated the benefit of subsequent therapy, and it found no association between the number of cycles and overall survival. Data from the studies by Dr Kim and Dr Altman are somewhat conflicting, and more research is necessary to examine the optimal number of cycles after interval surgery.

Dr John Chan analyzed ancillary data to evaluate the role of neoadjuvant chemotherapy in the GOG-262 study.¹⁶ Among the 692 patients in the study, only 13% underwent neoadjuvant chemotherapy. The analysis showed an unadjusted overall survival of 48 months without neoadjuvant therapy vs 42 months with neoadjuvant therapy. This difference lost significance after adjusting for known prognostic factors, for an HR of 1.08.

The analysis found that patients who received neoadjuvant therapy were older, more likely to have stage 4 disease than stage 2/3 disease, and more likely to have primary peritoneal cancer than ovarian or fallopian tube cancer.

Dr Anton Oseledchik examined a database from the Surveillance, Epidemiology, and End Results registry spanning approximately 13 years to evaluate the impact of adjuvant chemotherapy in patients with stage 1 clear cell cancer of the ovary (based on criteria from the International Federation of Gynecology and Obstetrics) in the platinum era.¹⁷ The study found that these patients did not appear to benefit from adjuvant chemotherapy. New biomarkers are needed in this histologic type.

It should be noted, however, that

this study was not randomized, and these large, administrative databases do not provide sufficient details about why chemotherapy was administered to some patients but not others. The results should be interpreted cautiously. Thus, there may be patients with stage I clear cell disease who would benefit. Certainly, patients with high-grade tumors, including high-risk histologies, should receive chemotherapy until better evidence is developed to refute this practice.

Disclosure

Dr Herzog is a member of the advisory boards of AstraZeneca, Clovis, Johnson & Johnson, Roche, and Tesaro.

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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.

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.

Non-hematologic CTCAE* ≥ Grade 3 adverse reaction where prophylaxis is not considered feasible or adverse reaction persists despite treatment	<ul style="list-style-type: none"> 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

Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment and periodically after this time [see <i>Warnings and Precautions</i>].	
Platelet count <100,000/μL	First occurrence: <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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.

	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)				

	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

	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. Advise 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 (CL_{Cr}:60 to 89 mL/min) to moderate (CL_{Cr}: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*].

Manufactured for: TESARO, Inc. 1000 Winter St., Waltham, MA 02451

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PP-ZEJ-US-0087 03/17



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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 (\leq 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 $\geq 10\%$ 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 $\geq 25\%$ 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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