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A SPECIAL MEETING REVIEW EDITION

Highlights in Ovarian Cancer From the 2021 American Society of Clinical Oncology Annual Meeting

A Review of Selected Presentations From the 2021 ASCO Annual Meeting • June 4-8, 2021

Special Reporting on:

- Niraparib Efficacy and Safety in Patients With *BRCA*-Mutated Ovarian Cancer: Results From Three Phase 3 Niraparib Trials
- Mirvetuximab Soravtansine, a Folate Receptor Alpha (FRα)–Targeting Antibody-Drug Conjugate, in Combination With Bevacizumab in Patients With Platinum-Agnostic Ovarian Cancer: Final Analysis
- Real-Life Data of Niraparib Maintenance Treatment in Patients With Recurrent Platinum-Sensitive Ovarian Cancer
- Maintenance Gemogenovatucel-T in Newly Diagnosed Advanced Ovarian Cancer: Efficacy Assessment of Homologous Recombination Proficient Patients in the Phase 2b VITAL Trial
- Safety Assessment of Niraparib Individualized Starting Dose in Patients With Platinum-Sensitive Recurrent Ovarian Cancer: The Randomized, Double-Blind, Placebo-Controlled, Phase III NORA Trial
- EFFORT: Efficacy of Adavosertib in PARP Resistance: a Randomized 2-Arm Noncomparative Phase 2 Study of Adavosertib With or Without Olaparib in Women With PARP-Resistant Ovarian Cancer
- Optimal Treatment Duration of Bevacizumab Combined With Carboplatin and Paclitaxel in Patients With Primary Epithelial Ovarian, Fallopian Tube or Peritoneal Cancer: A Multicenter Open-Label Randomized 2-Arm Phase 3 ENGOT/GCIG Trial of the AGO Study Group, GINECO, and NSGO (AGO-OVAR 17/BOOST, GINECO OV118, ENGOT Ov-15, NCT01462890)
- Efficacy of Niraparib Maintenance Therapy in Chinese Women With Platinum-Sensitive Recurrent Ovarian Cancer With and Without Secondary Cytoreductive Surgery: Results From the NORA Trial
- Efficacy and Safety Results From the NeoPembrOV Study, a Randomized Phase 2 Trial of Neoadjuvant Chemotherapy With or Without Pembrolizumab Followed by Interval Debulking Surgery and Standard Systemic Therapy ± Pembrolizumab for Advanced High-Grade Serous Carcinoma: a GINECO Study

PLUS Meeting Abstract Summaries

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FOR YOUR ADULT PATIENTS WITH PLATINUM-RESPONSIVE ADVANCED OVARIAN CANCER[1]

IF SHE RESPONDS
TO CHEMOTHERAPY

ZEJULA is the only once-daily oral PARP inhibitor maintenance monotherapy approved for all eligible first-line platinum responders with advanced ovarian cancer, regardless of biomarker status[1-4]

Indication

ZEJULA is indicated for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.

Important Safety Information

Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), including some fatal cases, was reported in 15 patients (0.8%) out of 1,785 patients treated with ZEJULA monotherapy in clinical trials. The duration of therapy in patients who developed secondary MDS/cancer therapy-related AML varied from 0.5 months to 4.9 years. These patients had received prior chemotherapy with platinum agents and/or other DNA-damaging agents including radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

Hematologic adverse reactions (thrombocytopenia, anemia, neutropenia, and/or pancytopenia) have been reported in patients receiving ZEJULA. In PRIMA, the overall incidence of Grade ≥3 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 39%, 31%, and 21% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 4%, 2%, and 2% of patients. In patients who were administered a starting dose of ZEJULA based on baseline weight or platelet count, Grade ≥3 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 22%, 23%, and 15% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 3%, and 2% of patients. Do not start ZEJULA until patients have recovered from hematological toxicity caused by prior chemotherapy (≤Grade 1). Monitor complete blood counts weekly for the first month, monthly for the next 11 months, and periodically thereafter. If hematological toxicities do not resolve within 28 days following interruption, discontinue ZEJULA, and refer the patient to a hematologist for further investigations.

Hypertension and hypertensive crisis have been reported in patients receiving ZEJULA. In PRIMA, Grade 3-4 hypertension occurred in 6% of patients receiving ZEJULA vs 1% of patients receiving placebo, with no reported discontinuations. Monitor blood pressure and heart rate at least weekly for the first two months, then monthly for the first year, and periodically thereafter during treatment 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.

Posterior reversible encephalopathy syndrome (PRES) occurred in 0.1% of 2,165 patients treated with ZEJULA in clinical trials and has also been described in postmarketing reports. Monitor all patients for signs and symptoms of PRES, which include seizure, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Diagnosis requires confirmation by brain imaging. If suspected, promptly discontinue ZEJULA and administer appropriate treatment. The safety of reinitiating ZEJULA is unknown.

Embryo-fetal toxicity and lactation: Based on its mechanism of action, ZEJULA can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months after receiving their final dose of ZEJULA. Because of the potential for serious adverse reactions from ZEJULA in breastfed infants, advise lactating women not to breastfeed during treatment with ZEJULA and for 1 month after receiving the final dose.

1 DAILY DOSE

Zejula
niraparib
capsules 100 mg

YOU RESPOND
WITH ZEJULA[1]

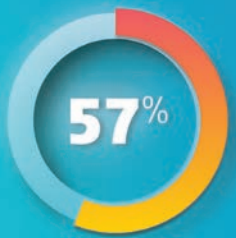
PROVEN EFFICACY IN 1L MAINTENANCE REGARDLESS OF BIOMARKER STATUS[1,2]

OVERALL POPULATION
(N=733)

Reduction in the risk of progression or death

MEDIAN PFS: 13.8 MONTHS WITH ZEJULA VS 8.2 MONTHS WITH PLACEBO (HR, 0.62; 95% CI, 0.50-0.76) *P*<0.0001

HRd POPULATION
(n=373)



Reduction in the risk of progression or death

MEDIAN PFS: 21.9 MONTHS WITH ZEJULA VS 10.4 MONTHS WITH PLACEBO (HR, 0.43; 95% CI, 0.31-0.59) *P*<0.0001

Study Design[1,2]: PRIMA, a randomized, double-blind, placebo-controlled phase 3 trial, evaluated the safety and efficacy of ZEJULA in women (N=733) with newly diagnosed advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer following CR or PR to first-line platinum-based chemotherapy. Patients were randomized 2:1 to receive ZEJULA or placebo once daily. The primary endpoint was PFS in patients who had tumors that were HRd and then in the overall population, as determined on hierarchical testing. PFS was measured from time of randomization to time of disease progression or death. At the time of the PFS analysis, limited overall survival data were available with 11% deaths in the overall population.

Important Safety Information (continued)

Allergic reactions to FD&C Yellow No. 5 (tartrazine): ZEJULA capsules contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

The most common adverse reactions (Grades 1-4) in ≥10% of all patients who received ZEJULA in PRIMA were thrombocytopenia (66%), anemia (64%), nausea (57%), fatigue (51%), neutropenia (42%), constipation (40%), musculoskeletal pain (39%), leukopenia (28%), headache (26%), insomnia (25%), vomiting (22%), dyspnea (22%), decreased appetite (19%), dizziness (19%), cough (18%), hypertension (18%), AST/ALT elevation (14%), and acute kidney injury (12%).

Common lab abnormalities (Grades 1-4) in ≥25% of all patients who received ZEJULA in PRIMA included: decreased hemoglobin (87%), decreased platelets (74%), decreased leukocytes (71%), increased glucose (66%), decreased neutrophils (66%), decreased lymphocytes (51%), increased alkaline phosphatase (46%), increased creatinine (40%), decreased magnesium (36%), increased AST (35%), and increased ALT (29%).

Please see Brief Summary on the following pages.

References: 1. ZEJULA (niraparib). Prescribing Information. GlaxoSmithKline; 2021. **2.** González-Martín A, Pothuri B, Vergote I, et al; PRIMA/ENGOT-OV26/GOG-3012 Investigators. Niraparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med*. 2019;381(25):2391-2402. doi:10.1056/NEJMoa1910962 **3.** Lynparza (olaparib). Prescribing Information. AstraZeneca Pharmaceuticals LP; 2021. **4.** Rubraca (rucaparib). Prescribing Information. Clovis Oncology, Inc; 2020.

1L = first-line; CI = confidence interval; CR = complete response; HR = hazard ratio; HRd = homologous recombination deficient; PFS = progression-free survival; PR = partial response.

Visit **ZEJULAHCP.COM** to explore the PRIMA data

Zejula
niraparib
capsules 100 mg

BRIEF SUMMARY OF PRESCRIBING INFORMATION

ZEJULA (niraparib) capsules, for oral use

The following is a brief summary only; see full prescribing information for complete product information available at www.ZEJULA.com.

1 INDICATIONS AND USAGE

1.1 First-Line Maintenance Treatment of Advanced Ovarian Cancer

ZEJULA is indicated for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.

1.2 Maintenance Treatment of Recurrent Ovarian Cancer

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.

1.3 Treatment of Advanced Ovarian Cancer after 3 or More Chemotherapies

ZEJULA is indicated for the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either:

- a deleterious or suspected deleterious *BRCA* mutation, or
- genomic instability and who have progressed more than 6 months after response to the last platinum-based chemotherapy *[see Clinical Studies (14.3) of full prescribing information].*

Select patients for therapy based on an FDA-approved companion diagnostic for ZEJULA.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia

Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), including cases with fatal outcome, have been reported in patients who received monotherapy with ZEJULA in clinical trials. In 1,785 patients treated with ZEJULA in clinical trials, MDS/AML occurred in 15 patients (0.8%).

The duration of therapy with ZEJULA in patients who developed secondary MDS/cancer therapy-related AML varied from 0.5 months to 4.9 years. All of these patients had received previous chemotherapy with platinum agents and/or other DNA-damaging agents including radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

5.2 Bone Marrow Suppression

Hematologic adverse reactions, including thrombocytopenia, anemia, neutropenia, and/or pancytopenia have been reported in patients treated with ZEJULA *[see Adverse Reactions (6)].*

In PRIMA, the overall incidences of ≥Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 39%, 31%, and 21%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 4%, 2%, and 2%, respectively, of patients. In patients who were administered a starting dose of ZEJULA based on baseline weight or platelet count, ≥Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 22%, 23%, and 15%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 3%, 3%, and 2%, respectively, of patients.

In NOVA, ≥Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 29%, 25%, and 20%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 3%, 1%, and 2%, respectively, of patients.

In QUADRA, ≥Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 28%, 27%, and 13%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 4%, 2%, and 1%, respectively, 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 (2.3) of full prescribing information].*

5.3 Hypertension and Cardiovascular Effects

Hypertension and hypertensive crisis have been reported in patients treated with ZEJULA.

In PRIMA, Grade 3 to 4 hypertension occurred in 6% of patients treated with ZEJULA compared with 1% of placebo-treated patients with a median time from first dose to first onset of 43 days (range: 1 to 531 days) and with a median duration of 12 days (range: 1 to 61 days). There were no discontinuations due to hypertension.

In NOVA, Grade 3 to 4 hypertension occurred in 9% of patients treated with ZEJULA compared with 2% of placebo-treated patients with a median time from first dose to first onset of 77 days (range: 4 to 504 days) and with a median duration of 15 days (range: 1 to 86 days). Discontinuation due to hypertension occurred in <1% of patients.

In QUADRA, Grade 3 to 4 hypertension occurred in 5% of patients treated with ZEJULA with a median time from first dose to first onset of 15 days (range: 1 to 316 days) and with a median duration of 7 days (range: 1 to 118 days). Discontinuation due to hypertension occurred in <0.2% of patients.

Monitor blood pressure and heart rate at least weekly for the first 2 months, then 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 dose of ZEJULA, if necessary *[see Dosage and Administration (2.3) and Nonclinical Toxicology (13.2) of full prescribing information].*

5.4 Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) occurred in 0.1% of 2,165 patients treated with ZEJULA in clinical trials and has also been described in postmarketing reports *[see Adverse Reactions (6.2)].* Signs and symptoms of PRES include seizure, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging.

Monitor all patients treated with ZEJULA for signs and symptoms of PRES. If PRES is suspected, promptly discontinue ZEJULA and administer appropriate treatment. The safety of reinitiating ZEJULA in patients previously experiencing PRES is not known.

5.5 Embryo-Fetal Toxicity

Based on its mechanism of action, ZEJULA can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1) of full prescribing information].* 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 (5.2) and Nonclinical Toxicology (13.1) of full prescribing information].* 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 (8.1, 8.3)].*

5.6 Allergic Reactions to FD&C Yellow No. 5 (Tartrazine)

ZEJULA capsules contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

6 ADVERSE REACTIONS

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

- MDS/AML *[see Warnings and Precautions (5.1)]*
- Bone marrow suppression *[see Warnings and Precautions (5.2)]*
- Hypertension and cardiovascular effects *[see Warnings and Precautions (5.3)]*
- Posterior reversible encephalopathy syndrome *[see Warnings and Precautions (5.4)]*

6.1 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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse reactions of all grades in >10% of 1,314 patients who received ZEJULA in the pooled PRIMA, NOVA, and QUADRA trials were nausea (65%), thrombocytopenia (60%), anemia (56%), fatigue (55%), constipation (39%), musculoskeletal pain (36%), abdominal pain (35%), vomiting (33%), neutropenia (31%), decreased appetite (24%), leukopenia (24%), insomnia (23%), headache (23%), dyspnea (22%), rash (21%), diarrhea (18%), hypertension (17%), cough (16%), dizziness (14%), acute kidney injury (13%), urinary tract infection (12%), and hypomagnesemia (11%).

First-Line Maintenance Treatment of Advanced Ovarian Cancer

The safety of ZEJULA for the treatment of patients with advanced ovarian cancer following first-line treatment with platinum-based chemotherapy was studied in the PRIMA trial, a placebo-controlled, double-blind study in which 728 patients received niraparib or placebo. Among patients who received ZEJULA, the median duration of treatment was 11.1 months (range: 0.03 to 29 months).

All Patients Receiving ZEJULA in PRIMA: Serious adverse reactions occurred in 32% of patients receiving ZEJULA. Serious adverse reactions in >2% of patients were thrombocytopenia (16%), anemia (6%), and small intestinal obstruction (2.9%). Fatal adverse reactions occurred in 0.4% of patients, including intestinal perforation and pleural effusion (1 patient each).

Permanent discontinuation due to adverse reactions occurred in 12% of patients who received ZEJULA. Adverse reactions resulting in permanent discontinuation in >1% of patients who received ZEJULA included thrombocytopenia (3.7%), anemia (1.9%), and nausea and neutropenia (1.2% each). Adverse reactions led to dose reduction or interruption in 80% of patients, most frequently from thrombocytopenia (56%), anemia (33%), and neutropenia (20%).

Table 1 and Table 2 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in all patients treated with ZEJULA in the PRIMA study.

Table 1: Adverse Reactions Reported in ≥10% of All Patients Receiving ZEJULA in PRIMA[a]

Adverse Reaction	Grades 1-4[b]		Grades 3-4[b]	
	ZEJULA (n=484) %	Placebo (n=244) %	ZEJULA (n=484) %	Placebo (n=244) %
Blood and lymphatic system disorders				
Thrombocytopenia	66	5	39	0.4
Anemia	64	18	31	2
Neutropenia[c]	42	8	21	1
Leukopenia[d]	28	9	5	0.4
Gastrointestinal disorders				
Nausea	57	28	1	1
Constipation	40	20	1	0.4
Vomiting	22	12	1	1
General disorders and administration site conditions				
Fatigue	51	41	3	1
Investigations				
AST/ALT elevation	14	7	3	0.8
Metabolism and nutrition disorders				
Decreased appetite	19	8	1	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain	39	38	1	0
Nervous system disorders				
Headache	26	15	0.4	0
Dizziness	19	13	0	0.4
Psychiatric disorders				
Insomnia	25	15	1	0.4
Renal and urinary disorders				
Acute kidney injury[e]	12	5	0.2	0
Respiratory, thoracic and mediastinal disorders				
Dyspnea	22	13	0.4	1
Cough	18	15	0	0.4
Vascular disorders				
Hypertension	18	7	6	1

AST/ALT=Aspartate transaminase/alanine aminotransferase

[a]All adverse reactions in the table consist of grouped preferred terms except for nausea, vomiting, decreased appetite, headache and insomnia, which are single preferred terms.

[b]Common Terminology Criteria for Adverse Events version 4.02.

[c]Includes neutropenia, neutropenic infection, neutropenic sepsis, and febrile neutropenia.

[d]Includes leukopenia, lymphocyte count decreased, lymphopenia, and white blood cell count decreased.

[e]Includes blood creatinine increased, blood urea increased, acute kidney injury, renal failure, and blood creatine increased.

(continued on next page)

Table 2: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZEJULA in PRIMA

Abnormal Laboratory Finding	Grades 1-4		Grades 3-4	
	ZEJULA (n=484) %	Placebo (n=244) %	ZEJULA (n=484) %	Placebo (n=244) %
Decreased hemoglobin	87	66	29	1
Decreased platelets	74	13	37	0
Decreased leukocytes	71	36	9	0
Increased glucose	66	57	3	3
Decreased neutrophils	66	25	23	1
Decreased lymphocytes	51	29	7	3
Increased alkaline phosphatase	46	21	1	0
Increased creatinine	40	23	0	0
Decreased magnesium	36	34	1	0
Increased aspartate aminotransferase	35	17	1	0.4
Increased alanine aminotransferase	29	17	2	1

Patients Receiving ZEJULA with Dose Based on Baseline Weight or Platelet Count in PRIMA: Among patients who received ZEJULA with the dose based on weight and platelet count, the median duration of treatment was 11 months (range: 1 day to 16 months). Serious adverse reactions occurred in 27% of patients receiving ZEJULA. Serious adverse reactions in >2% of patients were anemia (8%) and thrombocytopenia (7%). No fatal adverse reactions occurred.

Permanent discontinuation due to adverse reactions occurred in 14% of patients who received ZEJULA. Adverse reactions resulting in permanent discontinuation in >2% of patients who received ZEJULA included thrombocytopenia and anemia (3% each) and nausea (2.4%). Adverse reactions led to dose reduction or interruption in 72% of patients, most frequently from thrombocytopenia (40%), anemia (23%), and neutropenia (15%).

Table 3 and Table 4 summarize adverse reactions and abnormal laboratory findings in the group of patients who received ZEJULA.

Table 3: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA Based on Baseline Weight or Platelet Count in PRIMA[a]

Adverse Reaction	Grades 1-4[b]		Grades 3-4[b]	
	ZEJULA (n=169) %	Placebo (n=86) %	ZEJULA (n=169) %	Placebo (n=86) %
Blood and lymphatic system disorders				
Thrombocytopenia	54	5	21	1
Anemia	50	28	23	1
Neutropenia[c]	36	8	15	1
Leukopenia[d]	28	11	5	0
Gastrointestinal disorders				
Nausea	53	21	1	0
Constipation	31	15	1	1
Vomiting	17	9	0	1
General disorders and administration site conditions				
Fatigue	48	36	3	0
Metabolism and nutrition disorders				
Decreased appetite	19	5	1	0
Nervous system disorders				
Headache	22	17	1	0
Dizziness	14	13	0	0
Psychiatric disorders				
Insomnia	21	14	0	0
Renal and urinary disorders				
Acute kidney injury[e]	21	14	0	0
Respiratory, thoracic and mediastinal disorders				
Dyspnea	18	10	0	1
Vascular disorders				
Hypertension	17	9	5	2

[a]All adverse reactions in the table consist of grouped preferred terms except for nausea, vomiting, decreased appetite, headache, and insomnia, which are single preferred terms.

[b]Common Terminology Criteria for Adverse Events version 4.02.

[c]Includes neutropenia, neutropenic infection, neutropenic sepsis, and febrile neutropenia.

[d]Includes leukopenia, lymphocyte count decreased, lymphopenia, and white blood cell count decreased.

[e]Includes blood creatinine increased, blood urea increased, acute kidney injury, renal failure, and blood creatine increased.

Table 4: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZEJULA Based on Baseline Weight or Platelet Count in PRIMA

Abnormal Laboratory Finding	Grades 1-4		Grades 3-4	
	ZEJULA (n=169) %	Placebo (n=86) %	ZEJULA (n=169) %	Placebo (n=86) %
Decreased hemoglobin	81	70	21	0
Decreased leukocytes	70	36	6	0
Decreased platelets	63	15	18	0
Increased glucose	63	56	2	1
Decreased neutrophils	60	27	15	0
Decreased lymphocytes	52	30	5	4
Increased alkaline phosphatase	43	17	1	0
Decreased magnesium	44	30	0	0
Increased creatinine	41	22	0	0
Increased aspartate aminotransferase	31	19	1	0
Increased alanine aminotransferase	28	15	2	2

Maintenance Treatment of Recurrent Ovarian Cancer

The safety of monotherapy with ZEJULA 300 mg once daily has been studied in 367 patients with platinum-sensitive recurrent ovarian, fallopian tube, and primary peritoneal cancer in the NOVA trial. Adverse reactions in NOVA 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 NOVA was 15%. The median exposure to ZEJULA in these patients was 250 days.

Table 5 and Table 6 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with ZEJULA in NOVA.

Table 5: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA in NOVA

Adverse Reaction	Grades 1-4[a]		Grades 3-4[a]	
	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[b]	30	6	20	2
Leukopenia	17	8	5	0
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
Mucositis/stomatitis	20	6	0.5	0
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

Table 5: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA in NOVA Cont'd

Adverse Reaction	Grades 1-4[a]		Grades 3-4[a]	
	ZEJULA (n=367) %	Placebo (n=179) %	ZEJULA (n=367) %	Placebo (n=179) %
Musculoskeletal and connective tissue disorders				
Back pain	18	12	0.8	0
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

AST/ALT=Aspartate transaminase/alanine aminotransferase.

[a]Common Terminology Criteria for Adverse Events version 4.02.

[b]Includes preferred terms of neutropenic infection, neutropenic sepsis, and febrile neutropenia.

Table 6: Abnormal Laboratory Findings in ≥25% of Patients Receiving ZEJULA in NOVA

Abnormal Laboratory Finding	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 white blood cell count	66	37	7	0.7
Decrease in absolute neutrophil count	53	25	21	2
Increase in aspartate aminotransferase	36	23	1	0
Increase in alanine aminotransferase	28	15	1	2

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, and epistaxis.

Treatment of Advanced Ovarian Cancer after 3 or More Chemotherapies

The safety of monotherapy with ZEJULA 300 mg once daily has been studied in QUADRA, a single-arm study in 463 patients with recurrent high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who had been treated with 3 or more prior lines of therapy. The median duration of overall study treatment was 3 months (range: 0.03 to 32 months). For the indicated QUADRA population, the median duration was 4 months (range: 0.1 to 30 months).

Fatal adverse reactions occurred in 2% of patients, including cardiac arrest.

Serious adverse reactions occurred in 43% of patients receiving ZEJULA. Serious adverse reactions in >3% of patients were small intestinal obstruction (7%), vomiting (6%), nausea (5%), and abdominal pain (4%).

Permanent discontinuation due to adverse reactions (Grade 1 to 4) occurred in 21% of patients who received ZEJULA.

Adverse reactions led to dose reduction or interruption in 73% of patients receiving ZEJULA. The most common adverse reactions (≥5%) resulting in dose reduction or interruption of ZEJULA were thrombocytopenia (40%), anemia (21%), neutropenia (11%), nausea (13%), vomiting (11%), fatigue (9%), and abdominal pain (5%).

Table 7 and Table 8 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with ZEJULA in QUADRA.

(continued on next page)

Table 7: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA in QUADRA

Adverse Reaction	Grades 1-4[a] (n=463) %	Grades 3-4[a] (n=463) %
Blood and lymphatic system disorders		
Anemia[b]	51	27
Thrombocytopenia[c]	52	28
Neutropenia[d]	20	13
Gastrointestinal disorders		
Nausea	67	10
Vomiting	44	8
Constipation	36	5
Abdominal pain	34	7
Diarrhea	17	0.2
General disorders and administration site conditions		
Fatigue	56	7
Infections and infestations		
Urinary tract infection	15	2
Investigations		
Blood alkaline phosphatase increased	11	2
AST/ALT elevation	11	1
Metabolism and nutrition disorders		
Decreased appetite	27	2
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain	29	3
Nervous system disorders		
Headache	19	0.4
Dizziness	11	0
Psychiatric disorders		
Insomnia	21	1
Renal and urinary disorders		
Acute kidney injury	17	1
Respiratory, thoracic and mediastinal disorders		
Dyspnea	22	3
Cough	13	0
Vascular disorders		
Hypertension	14	5

AST/ALT=Aspartate transaminase/alanine aminotransferase.
[a]Common Terminology Criteria for Adverse Events version 4.02.
[b]Anemia includes events with preferred terms of anemia, hemoglobin decreased, anemia macrocytic, aplastic anemia, and normochromic normocytic anemia.
[c]Thrombocytopenia includes events with preferred terms of thrombocytopenia and platelet count decreased.
[d]Neutropenia includes events with preferred terms of neutropenia, neutrophil count decreased, neutropenic infection, and neutropenic sepsis.

Table 8: Abnormal Laboratory Findings in ≥25% of Patients Receiving ZEJULA in QUADRA

Abnormal Laboratory Finding	Grades 1-4 (n=463) %	Grades 3-4 (n=463) %
Decreased hemoglobin	83	26
Increased glucose	66	5
Decreased platelets	60	28
Decreased lymphocytes	57	18
Decreased leukocytes	53	9
Decreased magnesium	46	1
Increased alkaline phosphatase	40	4
Increased gamma glutamyl transferase	40	8
Increased creatinine	36	0.4
Decreased sodium	34	6
Decreased neutrophils	34	15
Increased aspartate aminotransferase	29	2
Decreased albumin	27	2

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of ZEJULA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: Pancytopenia.

Immune System Disorders: Hypersensitivity (including anaphylaxis).

Nervous System Disorders: Posterior reversible encephalopathy syndrome (PRES).

Psychiatric Disorders: Confusional state/disorientation, hallucination, cognitive impairment (e.g., memory impairment, concentration impairment).

Respiratory, Thoracic, and Mediastinal Disorders: Non-infectious pneumonitis.

Skin and Subcutaneous Tissue Disorders: Photosensitivity.

Vascular Disorders: Hypertensive crisis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, ZEJULA can cause fetal harm when administered to pregnant women *[see Clinical Pharmacology (12.1) of full prescribing information].* 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 (5.2) and Nonclinical Toxicology (13.1) of full prescribing information].* Due to the potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted with niraparib. Apprise pregnant women of the potential risk to a fetus.

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

8.2 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 child or milk production. Because of the potential for serious adverse reactions in a breastfed child, advise a lactating woman not to breastfeed during treatment with ZEJULA and for 1 month after receiving the final dose.

8.3 Females and Males of Reproductive Potential

ZEJULA can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)].*

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating treatment with ZEJULA.

Contraception

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

Infertility

Males: Based on animal studies, ZEJULA may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1) of full prescribing information].*

8.4 Pediatric Use

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

8.5 Geriatric Use

In PRIMA, 39% of patients were aged 65 years or older and 10% were aged 75 years or older. In NOVA, 35% of patients were aged 65 years or older and 8% were aged 75 years or older. 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.

8.6 Renal Impairment

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

8.7 Hepatic Impairment

For patients with moderate hepatic impairment, reduce the starting dosage of niraparib to 200 mg once daily *[see Dosage and Administration (2.4) of full prescribing information].* Niraparib exposure increased in patients with moderate hepatic impairment [total bilirubin ≥1.5 x upper level of normal (ULN) to 3.0 x ULN and any aspartate transaminase (AST) level]. Monitor patients for hematologic toxicity and reduce the dose further, if needed *[see Dosage and Administration (2.3) of full prescribing information].*

For patients with mild hepatic impairment (total bilirubin <1.5 x ULN and any AST level or bilirubin ≤ULN and AST>ULN), no dose adjustment is needed.

The recommended dose of ZEJULA has not been established for patients with severe hepatic impairment (total bilirubin >3.0 x ULN and any AST level) *[see Clinical Pharmacology (12.3) of full prescribing information].*

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Myelodysplastic Syndrome/Acute Myeloid Leukemia

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 MDS or AML, which has been reported in patients treated with ZEJULA *[see Warnings and Precautions (5.1)].*

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 (5.2)].*

Hypertension and Cardiovascular Effects

Advise patients to undergo blood pressure and heart rate monitoring at least weekly for the first 2 months, then monthly for the first year of treatment and periodically thereafter. Advise patients to contact their healthcare provider if blood pressure is elevated *[see Warnings and Precautions (5.3)].*

Posterior Reversible Encephalopathy Syndrome

Inform patients that they are at risk of developing posterior reversible encephalopathy syndrome (PRES) that can present with signs and symptoms including seizure, headaches, altered mental status, or vision changes. Advise patients to contact their healthcare provider if they develop any of these signs or symptoms *[see Warnings and Precautions (5.4)].*

Dosing Instructions

Inform patients on how to take ZEJULA *[see Dosage and Administration (2.2) of full prescribing information].* 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 (5.5) and Use in Specific Populations (8.1)].*

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 (8.3)].*

Lactation

Advise patients not to breastfeed while taking ZEJULA and for 1 month after the last dose *[see Use in Specific Populations (8.2)].*

Allergic Reactions to FD&C Yellow No. 5 (Tartrazine)

Advise patients that ZEJULA capsules contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons or in patients who also have aspirin hypersensitivity *[see Warnings and Precautions (5.6)].*

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Research Triangle Park, NC 27709

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Niraparib Efficacy and Safety in Patients With *BRCA*-Mutated Ovarian Cancer: Results From Three Phase 3 Niraparib Trials

Niraparib is an orally available poly(ADP-ribose) polymerase (PARP) inhibitor.[1,2] Niraparib is approved for the maintenance treatment of adult patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer after first-line or later platinum-based chemotherapy, or after 3 or more prior chemotherapy regimens. The mutated *BRCA* gene is present in up to one-fourth of patients with epithelial ovarian cancers, and the outcomes of patients with *BRCA*-mutated tumors are superior to those of patients with tumors that harbor the wild-type *BRCA* gene.[3,4] A retrospective analysis evaluated the efficacy and safety of niraparib in patients with *BRCA*-mutated ovarian cancer in data drawn from the PRIMA, NOVA, and NORA trials.[5-8] All 3 trials were randomized, double-blind, placebo-controlled phase 3 studies. The PRIMA study evaluated niraparib among patients with advanced ovarian cancer that had responded to first-line platinum-based chemotherapy.[5] The NOVA and NORA trials evaluated niraparib maintenance therapy among patients with recurrent, platinum-sensitive ovarian cancer.[6,7] Subgroup analysis according to *BRCA* mutation status was prespecified for all 3 trials.

Across the 3 trials, 526 patients had *BRCA*-mutated ovarian cancer (Figure 1).[8] The *BRCA1* mutation was the most common, observed in 60.6% to 80.0% of patients across the 3 niraparib and 3 placebo arms. In all 3 trials, progression-free survival (PFS) was superior with niraparib vs placebo in patients who had *BRCA*-mutated disease. In the PRIMA trial, which evaluated niraparib maintenance after first-line therapy, the hazard ratios (HRs) for PFS were 0.40 (95% CI, 0.27-0.62) in patients with any *BRCA* mutation, 0.39 (95% CI, 0.23-0.66) for patients with the *BRCA1* mutation, and 0.35 (95% CI, 0.15-0.84) for patients with the *BRCA2* mutation. In the NOVA trial, which evaluated niraparib maintenance after 2 or more lines of therapy, the HRs for PFS were 0.27 (95% CI, 0.17-0.41) for patients with any germline *BRCA* mutation, 0.39 (95% CI, 0.23-0.66) for patients with the *BRCA1* mutation, and 0.12 (95% CI, 95% CI, 0.05-0.33) for patients with the *BRCA2* mutation. The NORA trial also evaluated niraparib as maintenance therapy in patients who had received at least 2 lines of therapy. The HR for PFS in patients with a germline *BRCA* mutation was 0.22 (95% CI, 0.12-0.39). In the combined population from all 3 niraparib treatment arms, the most common treatment-emergent adverse events (AEs) were thrombocytopenia (54.8%-66.3%), anemia (50.1%-64.3%), and neutropenia (30.2%-58.8%; Figure 2).

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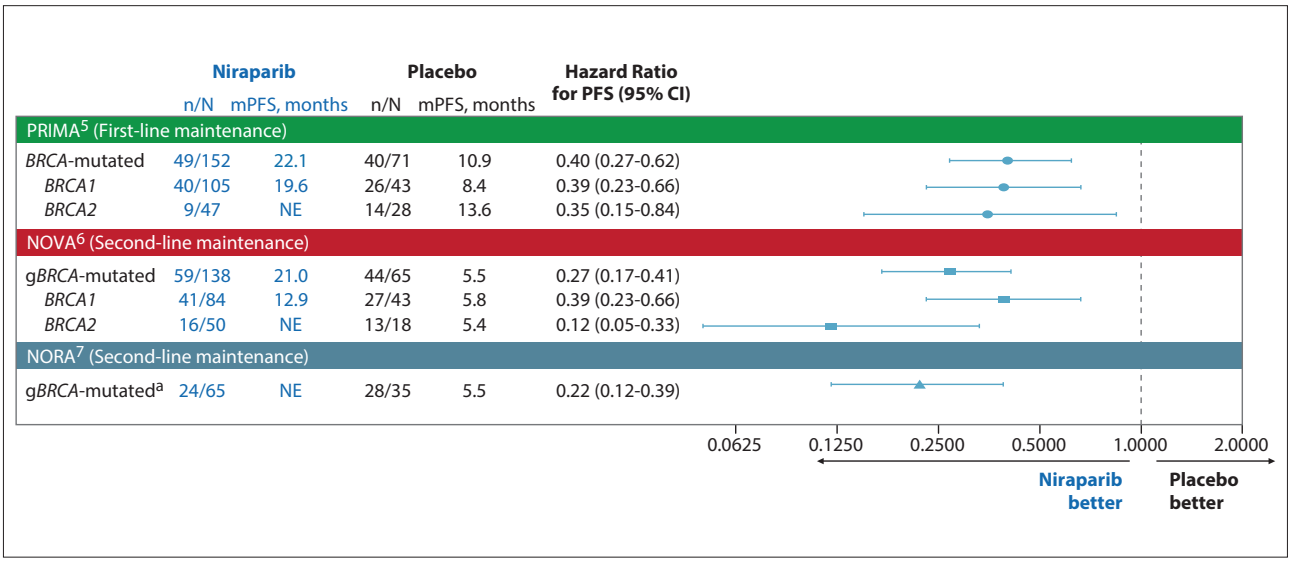

Figure 1. Progression-free survival among patients with *BRCA*-mutated ovarian cancer treated with niraparib in a retrospective analysis. [a]Data for *BRCA1* and *BRCA2* data were not available. g, germline; m, median; NE, not evaluable; PFS, progression-free survival. Adapted from González-Martin A et al. ASCO abstract 5518. *J Clin Oncol.* 2021;39(15 suppl).[8]

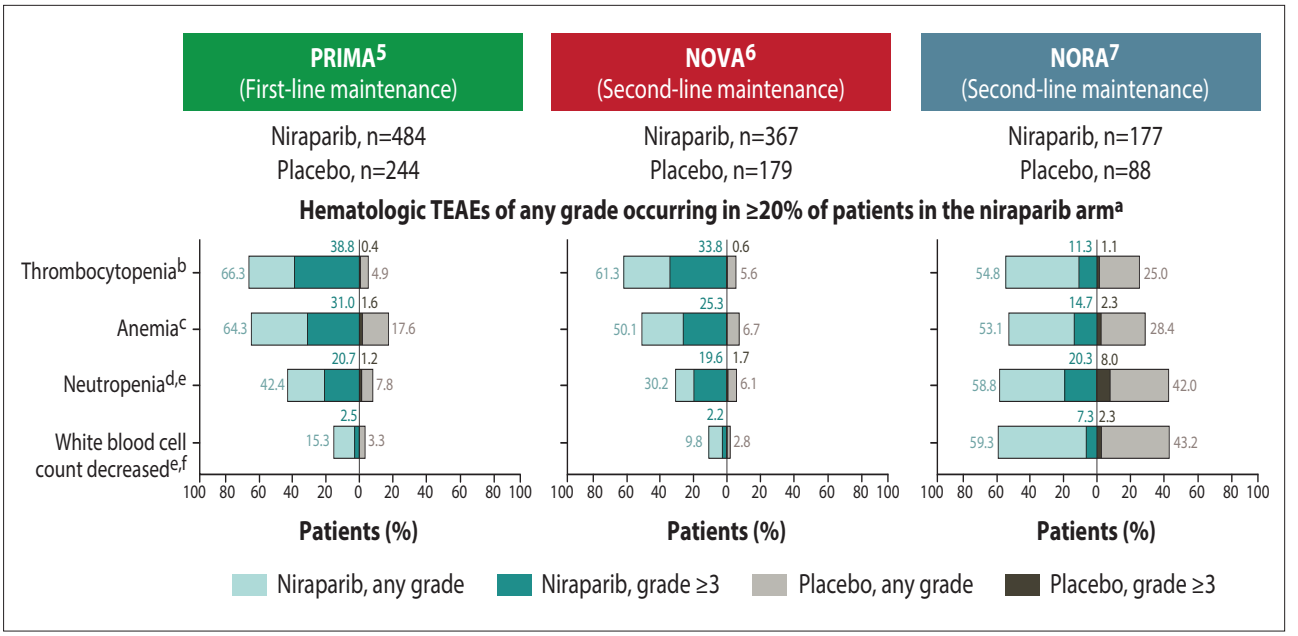

Figure 2. Hematologic TEAEs of any grade among patients with *BRCA*-mutated ovarian cancer treated with niraparib in a retrospective analysis. The investigators included data on file for the PRIMA and NOVA trials. [a]Hematologic TEAEs of any grade occurring in ≥20% of patients in the niraparib arm of PRIMA, NOVA, or NORA. Grade ≥3 TEAEs are also reported for each event. [b]Thrombocytopenia: PRIMA, NOVA, and NORA: thrombocytopenia and platelet count decrease. [c]Anemia: PRIMA, anemia; NOVA, anemia and decreased hemoglobin count; NORA, anemia. [d]Neutropenia: PRIMA, neutropenia, neutrophil count decrease, febrile neutropenia, and neutropenic sepsis; NOVA, neutropenia, neutrophil count decrease, and febrile neutropenia; NORA, neutropenia and neutrophil count decrease. [e]NORA: In the niraparib group, among 105 patients who experienced white blood cell count decrease and 104 patients who experienced neutrophil count decrease, 94 patients had both events reported with overlapping duration, and among 13 patients who experienced grade 3 white blood cell count decrease, 11 patients also had grade 3 neutrophil count decrease reported with overlapping duration. In the placebo group, among the 38 patients who experienced white blood cell count decrease of any grade and 37 patients who experienced neutrophil count decrease, 32 patients reported both events with overlapping duration, and 2 patients who experienced grade 3 white blood cell count decrease also reported grade 3 neutrophil count decrease with overlapping duration. [f]White blood cell decrease: PRIMA and NOVA, white blood cell decrease; NORA, white blood cell decrease and leukopenia. TEAEs, treatment-emergent adverse events. Adapted from González-Martin A et al. ASCO abstract 5518. *J Clin Oncol*. 2021;39(15 suppl).[8]

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Mirvetuximab Soravtansine, a Folate Receptor Alpha (FRα)–Targeting Antibody-Drug Conjugate, in Combination With Bevacizumab in Patients With Platinum-Agnostic Ovarian Cancer: Final Analysis

PARP inhibitor therapy has led to an increase in the population of patients with recurrent ovarian cancer who could benefit from treatment with a platinum-free regimen.[1] Mirvetuximab soravtansine is an antibody-drug conjugate that binds to folate receptor alpha (FRα) and delivers the maytansinoid DM4 into tumor cells.[2] Among patients with platinum-resistant ovarian cancer and high expression of FRα, single-agent

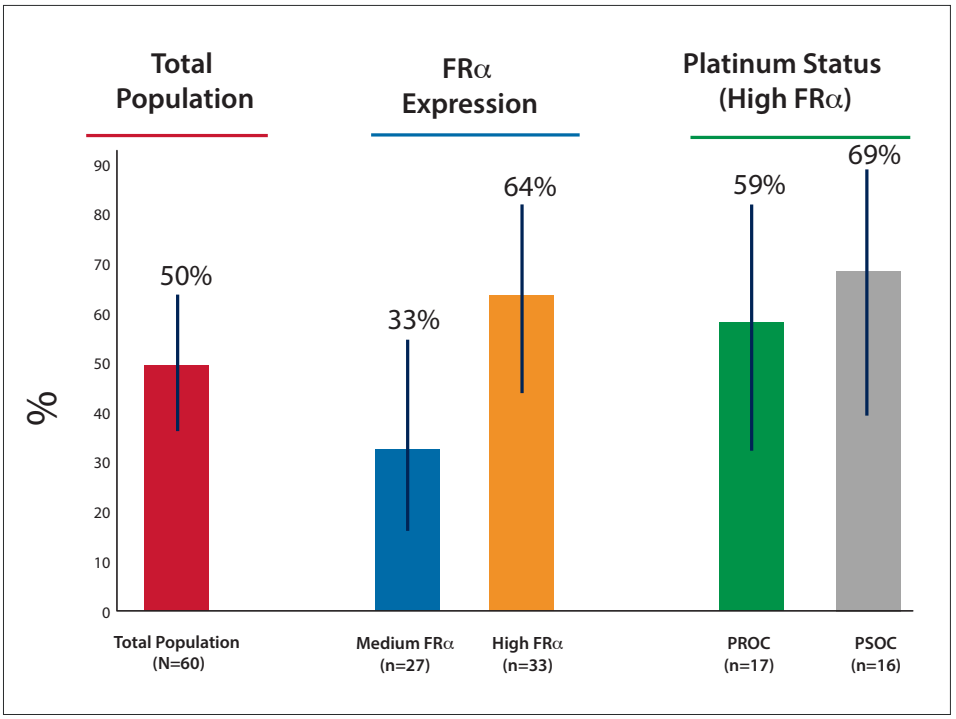

Figure 3. Responses among patients with ovarian cancer who received mirvetuximab soravtansine plus bevacizumab in the phase 1b FORWARD II trial. FRα, folate receptor alpha; PROC, platinum-resistant ovarian cancer; PSOC, platinum-sensitive ovarian cancer. Adapted from O'Malley DM et al. ASCO abstract 5504. *J Clin Oncol.* 2021;39(15 suppl).[7]

mirvetuximab soravtansine has yielded confirmed objective response rates (ORRs) of up to 47%.[3,4] In patients with platinum-resistant ovarian cancer and medium- or high-level expression of FRα, mirvetuximab soravtansine plus bevacizumab yielded confirmed ORRs ranging from 39% to 56%.[5] In an open-label, phase 3 trial of single-agent chemotherapy with or without bevacizumab, the addition of bevacizumab improved median PFS from 3.4 to 6.7 months (HR, 0.48; 95% CI, 0.38-0.60; *P*<.001) and increased the ORR from 12% to 27%.[6]

The combination of mirvetuximab soravtansine plus bevacizumab was evaluated in patients with ovarian cancer as part of the phase 1b FORWARD II trial.[7] Enrolled patients had recurrent ovarian cancer and had received up to 3 prior regimens. They were suitable candidates for treatment with a nonplatinum doublet that included bevacizumab. Patients with platinum-sensitive ovarian cancer had responded to the most recent platinum therapy, and their disease had not progressed within 6 months. Patients with platinum-resistant ovarian cancer had experienced a recurrence within 6 months after receiving their last platinum dose. The tumors of enrolled patients had medium or high expression of FRα according to the percentage of cells staining positive and the intensity of the staining (medium expressors: ≥50% to <75% and ≥2+ intensity; high expressors: ≥75% and ≥2+ intensity).

Mirvetuximab soravtansine (6 mg/kg, adjusted for ideal body weight) and bevacizumab (15 mg/kg) were administered on day 1 of each 3-week cycle. The 60 enrolled patients were a median age of 60 years (range, 44-83). The most common malignancy was epithelial ovarian cancer (68%), followed by fallopian tube cancer (25%) and primary peritoneal cancer (7%). Patients had received a median of 2 prior therapies (range, 1-4). The level of FRα expression was medium in 45% and high in 55% of patients. All patients had received prior treatment with a platinum compound and a taxane; 40% had received prior bevacizumab therapy, and 35% had received prior treatment with a PARP inhibitor. The platinum-free interval was 6 months or less in 53% of patients.

In the overall study population, the confirmed ORR was 50% (Figure 3). The ORR was 33% among those with medium-level expression of FRα and 64% among patients with high-level expression of FRα. The median duration of response was 9.7 months among the overall population (n=30), 8.3 months among 9 patients with medium-level FRα expression, and 11.8 months among 21 patients with high-level FRα expression. Among the patients with platinum-resistant ovarian cancer, the ORR was 59% and the median duration of response was 9.4 months. Among patients with platinum-sensitive ovarian cancer, the ORR was 69% and the median duration of response was 12.7 months. The median PFS was 10.6 months in patients whose tumors showed a high level of FRα expression vs 5.4 months in patients whose tumors showed a medium level of FRα expression. Within the cohort of patients with high-level expression of FRα, the

median PFS was 9.7 months in those with platinum-resistant disease and 13.3 months in those with platinum-sensitive disease. Grade 3/4 AEs observed in at least 5% of patients included hypertension (17%), neutropenia (13%), and increased level of alanine transaminase (5%).

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Real-Life Data of Niraparib Maintenance Treatment in Patients With Recurrent Platinum-Sensitive Ovarian Cancer

In the NOVA study and other clinical trials, niraparib demonstrated a benefit as maintenance therapy in patients with recurrent, platinum-sensitive ovarian cancer.[1] A retrospective, multicenter cohort study evaluated the real-world efficacy and safety of niraparib maintenance therapy in patients with ovarian cancer that had responded to platinum-based chemotherapy.[2] The primary endpoint was the time to first subsequent treatment, measured from the first dose of niraparib. The study included 106 patients with ovarian cancer, of whom 31% had received 3 or more prior lines of therapy, 42% had received prior treatment with bevacizumab, and 3% had received prior treatment with a PARP inhibitor. The median age of the patients was 64 years (range, 38-81),

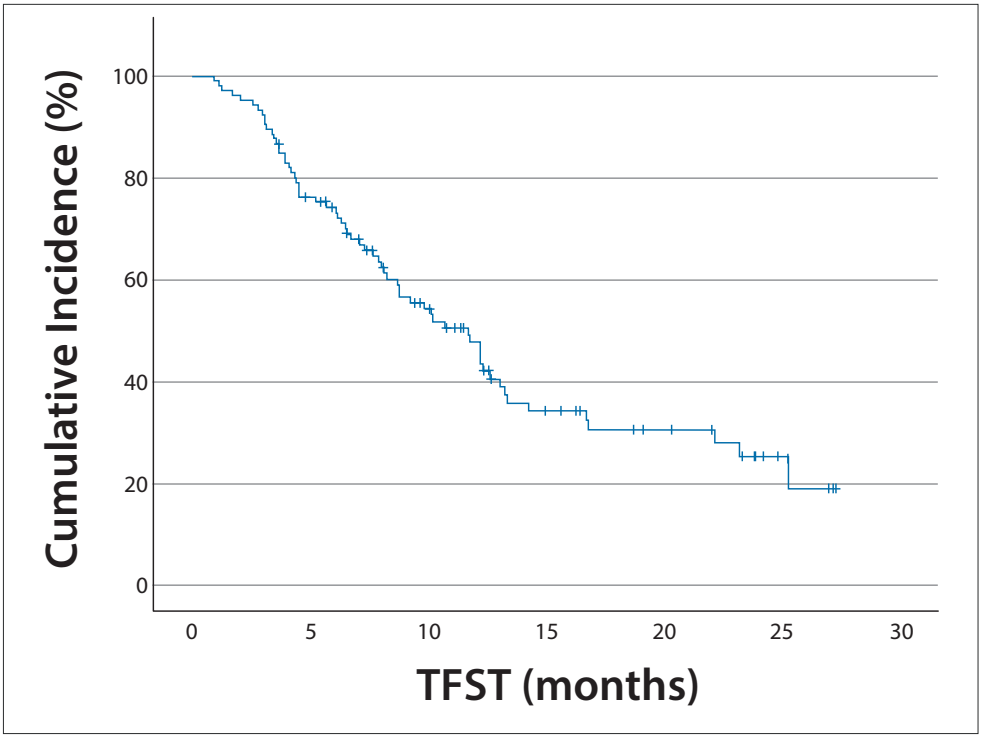

Figure 4. Time from the start of niraparib to first subsequent treatment in a retrospective, multicenter cohort study evaluating the real-world efficacy and safety of niraparib maintenance therapy in patients with ovarian cancer that had responded to platinum-based chemotherapy. TFST, time to first subsequent treatment. Adapted from Vilming B et al. ASCO abstract 5560. *J Clin Oncol*. 2021;39(15 suppl).[2]

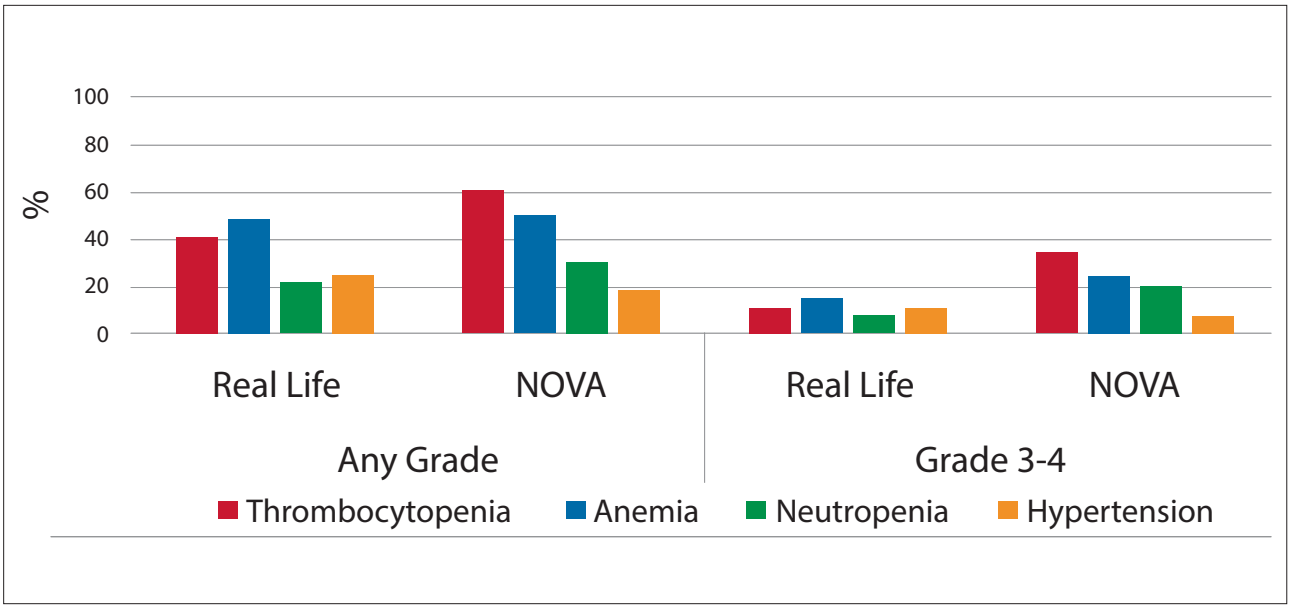

Figure 5. Adverse events among patients treated with niraparib in a real-life, retrospective, multicenter cohort study vs in the phase 3 NOVA trial. Adapted from Vilming B et al. ASCO abstract 5560. *J Clin Oncol.* 2021;39(15 suppl).[2]

and more than 90% had at least one comorbidity. A germline *BRCA* mutation was present in 9% of the patients. According to investigator assessment, outcomes after the most recent chemotherapy before enrollment had included a complete response (CR) in 13%, a partial response (PR) in 75%, and stable disease in 7% (5% of the patients were not evaluable). The cancer antigen 125 (CA-125) level exceeded 35 kU/L in 41% of patients. The daily starting dose of niraparib was 100 mg in 2%, 200 mg in 31%, and 300 mg in 67% of patients.

After a median follow-up of 15.3 months, 67% of the patients had disease progression, 60% had started a new line of treatment, and 24% had died.[2] Niraparib treatment was ongoing in 24% of the patients. The median duration of niraparib treatment was 7.6 months (range, 0.4-27.3). The median time to the first subsequent treatment was 11.7 months (95% CI, 9.2-14.2) for the entire study population (Figure 4) and 10.2 months (95% CI, 7.4-12.9) for patients without a germline *BRCA* mutation. The median time from the last chemotherapy dose to progression was 6.5 months in the patients with elevated CA-125 vs 12 months in those with a normal level (P<.001). The median PFS was 6.9 months for the entire study population vs 6.4 months for patients without a germline *BRCA* mutation.

Grade 3/4 hematologic AEs were observed in 25% of patients, and grade 3/4 nonhematologic AEs were observed in 17% of patients. The proportion of patients experiencing a grade 3/4 AE was lower in the real-world setting than in the NOVA clinical trial (Figure 5). AEs necessitated dose interruption or dose reduction in 38% and 44% of patients, respectively. The proportions of patients who discontinued niraparib therapy because of an AE were similar in the real-world setting (13.2%) and the NOVA trial (14.7%). Fewer dose reductions (P<.001) and fewer dose interruptions (P=.042) occurred among patients who received an individualized dose of niraparib based on weight and platelet count.

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Maintenance Gemogenovatucel-T in Newly Diagnosed Advanced Ovarian Cancer: Efficacy Assessment of Homologous Recombination Proficient Patients in the Phase 2b VITAL Trial

Gemogenovatucel-T is a cellular therapy that is created by genetically modifying a patient's tumor cells via the introduction of a plasmid with 2 genes. One gene interferes with the function of furin; this downregulates the activity of transforming growth factor beta 1 (TGFβ1) and TGFβ2, resulting in an increase in immune activity. The second gene encodes granulocyte-macrophage colony–stimulating factor, which increases the activity of antigen-presenting cells. Gemogenovatucel-T was evaluated in the double-blind, placebo-controlled, phase 2b VITAL trial as first-line maintenance therapy in women with advanced, high-grade ovarian cancer.[1] This double-blind study enrolled patients with stage III/IV, high-grade serous, endometrioid, or clear cell ovarian cancer and a CR after surgery and up to 8 cycles of chemotherapy with carboplatin and paclitaxel. After stratification according to the extent of surgical cytoreduction and neoadjuvant vs adjuvant chemotherapy, 91 patients were randomly assigned to receive between 4 and 12 monthly injections of gemogenovatucel-T at 1×10^7 cells per injection or placebo. The primary endpoint was recurrence-free survival. Of the 91 patients, 47 received gemogenovatucel-T and 44 received placebo.

After a median follow-up of 40 months, the median recurrence-free survival was 11.5 months in the patients who received treatment with the genetically modified autologous tumor cells vs 8.4 months in the placebo arm (HR, 0.69; 90% CI, 0.44-1.07; *P*=.078; Figure 6). The median overall survival (OS) was not reached in the experimental arm vs 16.0 months in the placebo arm (HR, 0.630; *P*=.110). The most common grade 1 to 3 toxicity in both arms was the combined event of general disorders and injection site reactions, which occurred in 63.2% of the gemogenovatucel-T arm vs 59.6% of the placebo arm. Musculoskeletal and connective tissue disorders were reported in 3% vs 15.6%, respectively. Gastrointestinal disorders occurred in 5% vs 2.8%.

A post hoc analysis evaluated outcomes among subgroups of patients classified according to their homologous recombination status.[2] Among patients with homologous recombination proficiency, the median PFS was 10.6 months in the experimental arm (n=25) vs 5.7 months in the placebo arm (n=20; HR, 0.386; *P*=.007). OS was not reached vs 26.9 months (HR,

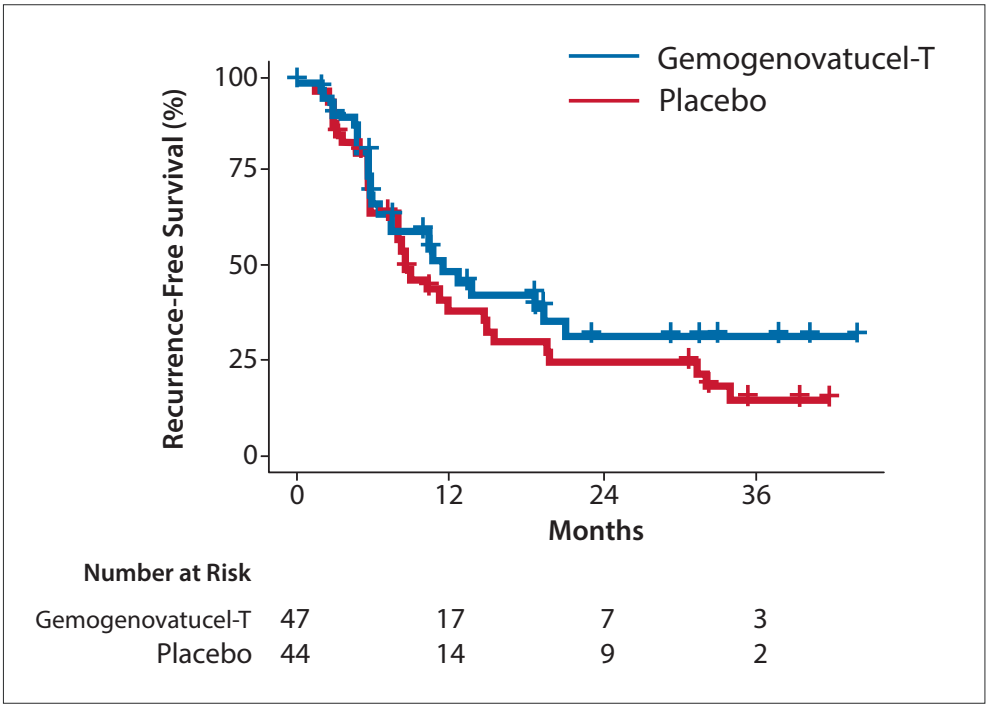

Figure 6. Recurrence-free survival among women with advanced, high-grade ovarian cancer who received gemogenovatucel-T or placebo as first-line maintenance therapy in the phase 2b VITAL. Adapted from Rocconi RP et al. ASCO abstract 5502. *J Clin Oncol*. 2021;39(15 suppl).[2]

0.342; *P*=.019), respectively. The restrictive mean survival time also was significantly better among the patients treated with gemogenovatucel-T, in terms of both recurrence-free survival (20.02 vs 10.77 months; *P*=.017) and OS (38.15 vs 27.81 months; *P*=.008). Among the patients with homologous recombination proficiency, the rate of 2-year OS was 92% in the treatment arm vs 55% in the placebo arm (*P*=.002); the rate of 3-year OS was 70% vs 40% (*P*=.019).

STRING analysis was used to identify a subgroup of patients who were likely to benefit from treatment with gemogenovatucel-T according to their homologous recombination proficiency status and *TP53* mutation status.[3] Among this subset of patients, the median recurrence-free survival was 21.1 months with the treatment vs 5.6 months with the placebo (*P*=.001). OS was not reached vs 26.9 months (*P*=.02).

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Safety Assessment of Niraparib Individualized Starting Dose in Patients With Platinum-Sensitive Recurrent Ovarian Cancer: The Randomized, Double-Blind, Placebo-Controlled, Phase III NORA Trial

The double-blind, multicenter, phase 3 NORA trial evaluated the safety and efficacy of niraparib as maintenance therapy in women with recurrent, platinum-sensitive ovarian cancer.[1,2] Patients who had received 2 or more prior lines of platinum-based chemotherapy were randomly assigned in a 2:1 ratio to receive niraparib or placebo. In the phase 3 NOVA trial, improved safety without any loss of efficacy was observed in patients who received individualized dosing rather than the 300-mg standard dose.[3,4] Namely,

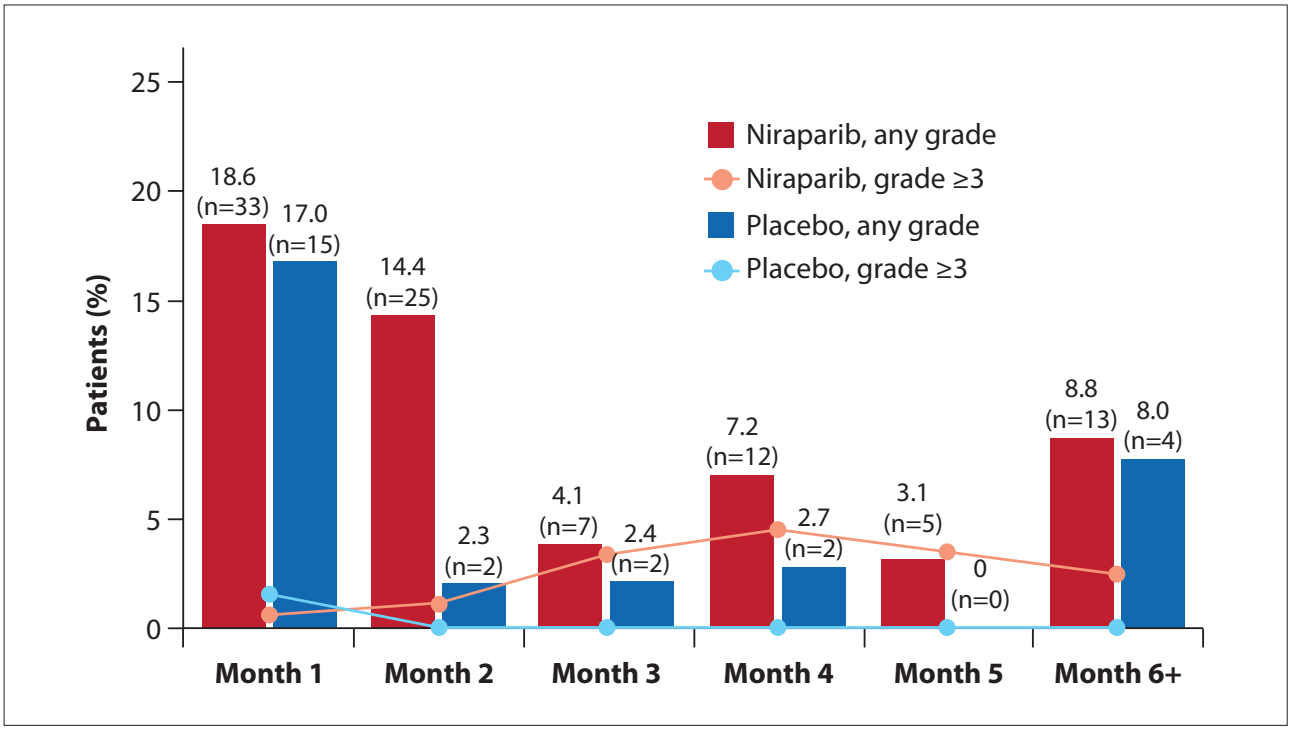

Figure 7. The incidence of treatment-emergent anemia by month of first occurrence in the phase 3 NORA trial, which evaluated the safety and efficacy of niraparib as maintenance therapy in women with recurrent, platinum-sensitive ovarian cancer. The anemia category included anemia and decreased hemoglobulin count. Adapted from Wang J et al. ASCO abstract 5535. *J Clin Oncol*. 2021;39(15 suppl).[2]

patients with a baseline body weight below 77 kg (170 pounds) or a platelet count below 150 × 10^3/μL received an average dose of niraparib of 207 mg daily.[3,4] On the basis of these findings, the NORA trial followed an individualized dosing strategy as well as the standard dosing strategy. Patients with a body weight below 77 kg or a platelet count below 150 × 10^3/μL received niraparib at the lower dose of 200 mg/day. Among the 265 patients, 16 received niraparib at a fixed starting dose of 300 mg daily. The remaining 249 patients received an individualized starting dose of niraparib (n=166) or placebo (n=83). The NORA trial demonstrated a significant prolongation of median PFS with niraparib vs placebo (18.3 vs 5.4 months; *P*<.0001), irrespective of *BRCA* status.

Except for anemia, the incidence of treatment-emergent AEs was highest during the first 6 months after the initiation of treatment (Figure 7).[2] Treatment-emergent AEs of grade 3 or higher were more common in the niraparib arm (50.8% vs 19.3%), as were serious AEs (17.5% vs 11.4%) and treatment-emergent AEs necessitating dose reduction (59.9% vs 13.6%). Treatment-emergent AEs led to discontinuation of therapy in 4% of the niraparib arm vs 5.7% of the placebo arm. In the NOVA trial, in which the experimental treatment consisted of niraparib at 300 mg daily, 14.7% of patients in the niraparib arm discontinued study treatment owing to a treatment-emergent AE.[3,4] In the NORA trial, the most common treatment-emergent AEs reported with niraparib were hematologic and included reductions in counts of white blood cells, neutrophils, and platelets, as well as anemia. Gastrointestinal treatment-emergent AEs of interest included nausea, vomiting, and constipation. Other treatment-emergent AEs of interest included insomnia, heart palpitations, and hypertension.

With most types of AEs, the median time to the first occurrence of a treatment-emergent AE of any grade was shorter in the niraparib group than in the placebo arm, except for anemia, palpitations, and reduced neutrophil count. In the niraparib group, the median times to the first occurrence of anemia, reduced neutrophil count, and reduced platelet count of grade 3 or higher were 87, 28, and 22 days, respectively. Most treatment-emergent AEs were adequately controlled by modifying the dose of niraparib.

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EFFORT: Efficacy of Adavosertib in PARP Resistance: a Randomized 2-Arm Noncomparative Phase 2 Study of Adavosertib With or Without Olaparib in Women With PARP-Resistant Ovarian Cancer

The noncomparative phase 2 EFFORT study evaluated the combination of adavosertib and olaparib in patients with ovarian cancer that had progressed following treatment with a PARP inhibitor.[1] Eligible patients had histologically confirmed recurrent epithelial ovarian, peritoneal, or fallopian tube cancer that had progressed during maintenance treatment with any single-agent PARP inhibitor. The trial enrolled patients treated with an unlimited number of prior therapies. Patients in arm 1 received adavosertib (300 mg daily on days 1-5 and 8-12) in a 21-day cycle. Patients in arm 2 received adavosertib (150 mg twice daily on days 1-3 and 8-10) plus olaparib (200 mg twice daily on every day of the cycle). Tumors were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.[2]

The study enrolled 39 patients into the adavosertib arm and 41 into the adavosertib-plus-olaparib arm. Patient characteristics in the 2 arms were well balanced.[1] Patients had a median age of 60 years (range, 36-76) and had received a median of 4 prior therapies (range, 1-11). More than 90% of patients had high-grade serous carcinoma. The *BRCA* status was negative in 44% and positive in 48%, and 36% had platinum-sensitive disease. The patients had received a median of 1 line of therapy after previous treatment with a PARP inhibitor (range, 0-5). Prior PARP inhibitors included olaparib (51%), niraparib (22.5%), rucaparib (22.5%), and talazoparib (4%). Prior PARP inhibitors had been administered as maintenance therapy in 45% of patients and as treatment in 55% of patients. Prior PARP inhibitor therapy led to a clinical benefit in 86% of patients.

There were 35 evaluable patients

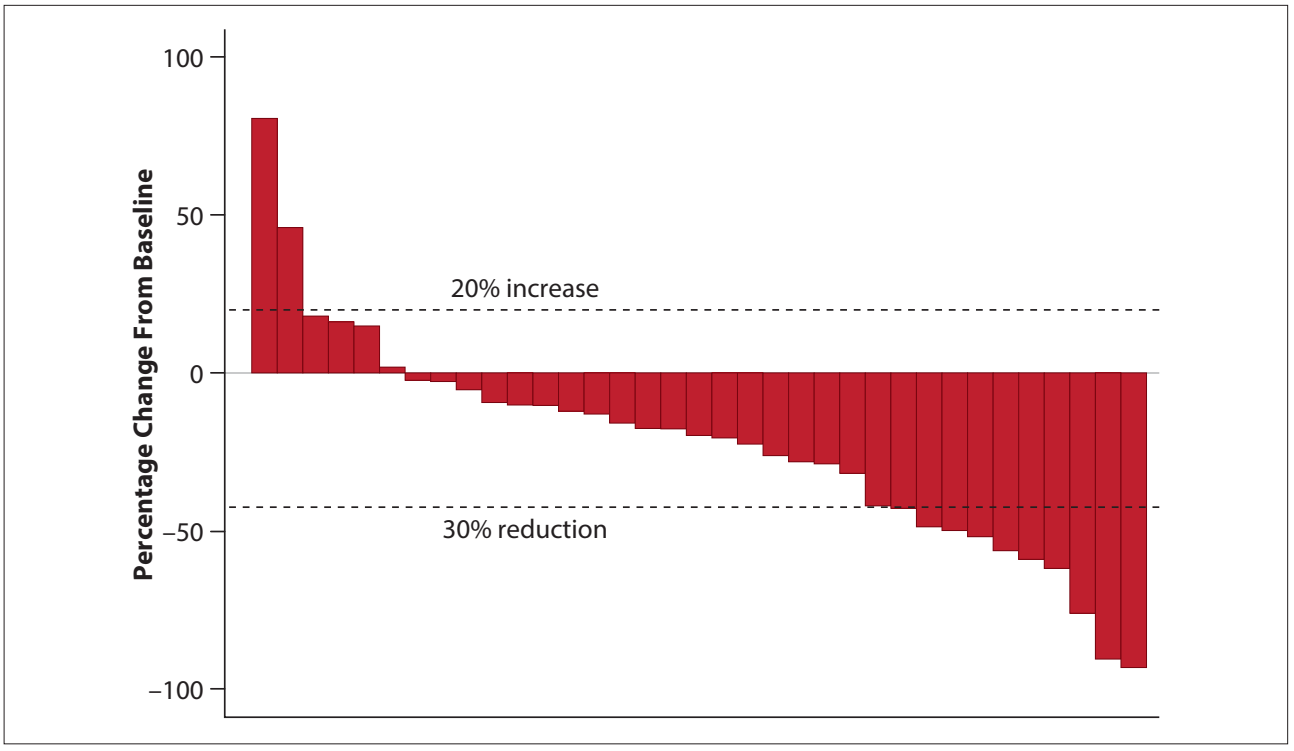

Figure 8. Response to treatment with adavosertib plus olaparib in the phase 2 EFFORT study, which enrolled patients with ovarian cancer that had progressed following treatment with a PARP inhibitor. PARP, poly(ADP-ribose) polymerase. Adapted from Westin SN et al. ASCO abstract 5505. *J Clin Oncol*. 2021;39(15 suppl).[1]

in each treatment arm. The ORR was 23% (95% CI, 12%-38%) with adavosertib monotherapy vs 29% (95% CI, 16%-44%) with adavosertib plus olaparib (Figure 8). The median duration of response was 5.5 months in the adavosertib monotherapy arm vs 6.4 months in the combination arm. The clinical benefit rate was 63% (95% CI, 48%-76%) vs 89% (95% CI, 76%-96%), respectively. The median PFS was 5.5 months (95% CI, 3.9-6.9) vs 6.8 months (95% CI, 4.3-8.3).

Adavosertib alone and in combination with olaparib demonstrated activity in patients with or without a *BRCA* mutation. Among the patients with mutated *BRCA,* the ORR was 20% with adavosertib monotherapy vs 19% with adavosertib plus olaparib. The median duration of response was 5.6 months vs 6.4 months, and the clinical benefit rate was 67% vs 81%. The duration of clinical benefit was 5.6 months in both arms. Among the patients with wild-type *BRCA,* the ORR was 31% with adavosertib monotherapy vs 39% with adavosertib plus olaparib. The median duration of response was 4.1 months vs 8.7 months, and the clinical benefit rate was 69% vs 94%. The duration of clinical benefit was 4.1 months vs 8.4 months.

In the adavosertib monotherapy arm, 97% of patients experienced a treatment-related AE, 5% of patients discontinued study treatment, 54% required a dose reduction, and 72% required a dose interruption. The most common treatment-related AEs were diarrhea (33%), neutropenia (21%), thrombocytopenia (18%), fatigue (18%), and nausea (18%). Grade 4 treatment-related AEs included neutropenia (5%) and thrombocytopenia (8%). In the adavosertib/olaparib combination arm, all patients developed at least 1 treatment-related AE, and 10% of patients discontinued both study drugs. Reductions in the doses of both adavosertib and olaparib were required in 56% of patients, whereas reductions in the dose of only adavosertib or only olaparib were required in 10% and 5% of patients, respectively. Doses of both adavosertib and olaparib were interrupted in 85% of patients. The most common treatment-related AEs in the combination arm included diarrhea (34%), anemia (27%), and thrombocytopenia (27%). Grade 4 treatment-related AEs included thrombocytopenia (10%) and neutropenia (7%).

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Optimal Treatment Duration of Bevacizumab Combined With Carboplatin and Paclitaxel in Patients With Primary Epithelial Ovarian, Fallopian Tube or Peritoneal Cancer: A Multicenter Open-Label Randomized 2-Arm Phase 3 ENGOT/GCIG Trial of the AGO Study Group, GINECO, and NSGO (AGO-OVAR 17/BOOST, GINECO OV118, ENGOT Ov-15, NCT01462890)

As was shown in the GOG-218 study and the ICON7/AGO-OVAR 11 trial, the addition of 12 or 15 months of bevacizumab to standard treatment with carboplatin plus paclitaxel significantly increases PFS.[1,2] In both trials, the improvement in PFS reached a maximum after the last bevacizumab cycle, suggesting that longer treatment with bevacizumab could be beneficial. The phase 3 AGO-OVAR 17/Boost, GINECO OV118, ENGOT Ov-15 trial evaluated whether PFS and other efficacy endpoints could be further improved by continuing bevacizumab treatment for up to 30 months.[3] Enrolled patients had histologically confirmed International Federation of Gynecology and Obstetrics (FIGO) stage IIB to IV epithelial ovarian, fallopian tube, or peritoneal cancer. The patients had undergone primary debulking surgery no more than 8 weeks before the start of treatment and more than 4 weeks before the first dose of bevacizumab. All patients received standard treatment with paclitaxel and carboplatin. Patients were randomly assigned to receive bevacizumab at 15 mg/kg every 3 weeks for 22 cycles (15 months) in the control arm or bevacizumab at the same dose for 44 cycles (30 months)

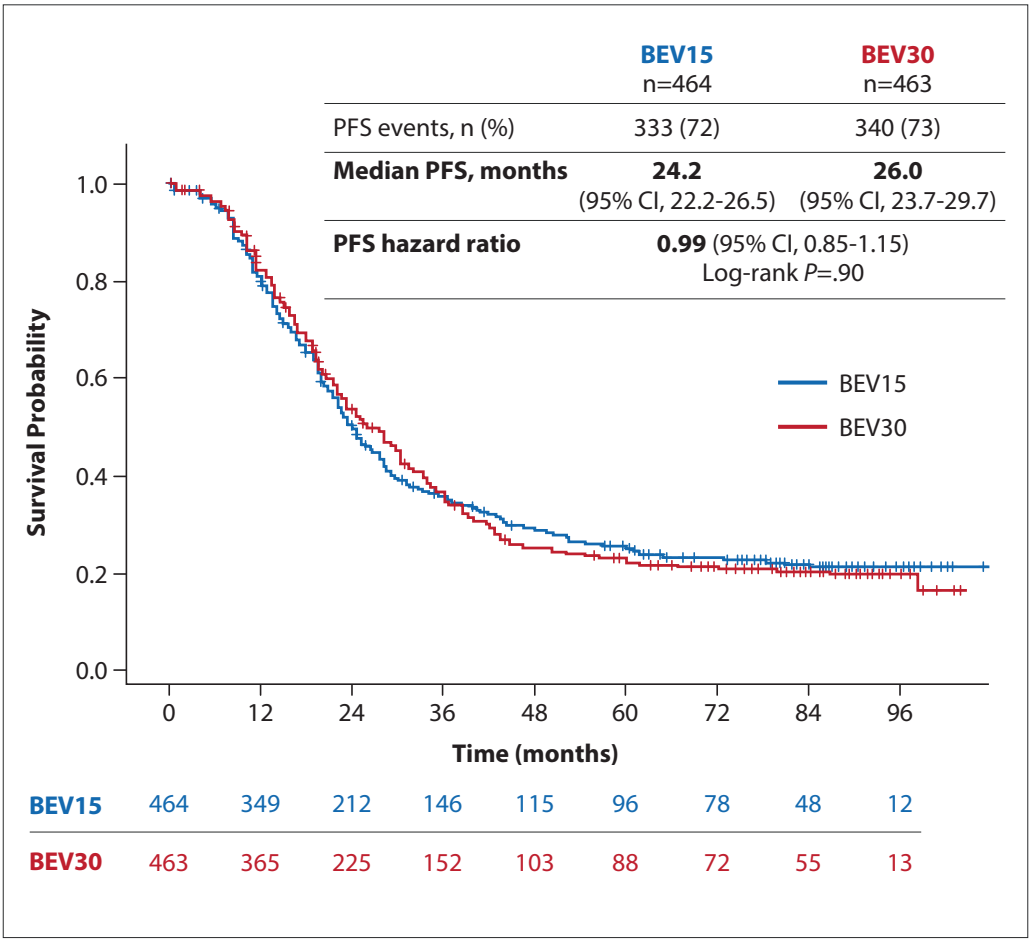

Figure 9. Progression-free survival among patients with epithelial ovarian, fallopian tube, or peritoneal cancer who received 15 or 30 months of bevacizumab after standard treatment with paclitaxel and carboplatin. BEV15, bevacizumab administered for 15 months; BEV30, bevacizumab administered for 30 months; PFS, progression-free survival. Adapted from Pfisterer J et al. ASCO abstract 5501. *J Clin Oncol.* 2021;39(suppl 15).[3]

in the experimental arm. The primary endpoint was PFS according to RECIST 1.1 criteria.[4] The trial was designed to have a power of 80% to detect a PFS HR of 0.66 favoring 30 months of bevacizumab after 697 events. However, a low event rate led the study to close after 673 (97%) of the planned events had been observed.

The trial enrolled 927 patients. The median follow-up was 85 months. The patients' median age was 61 years (range, 21-89). Residual tumor was noted in 58% of patients, and 79% had high-grade serous disease. Most of the patients (84%) had ovarian cancer. Half of the patients had FIGO stage IIB to IIIC disease with no residual tumor, and half had FIGO stage IIB to IIIC disease with residual tumor or FIGO stage IV disease.

Serious AEs were observed in 45% of patients, and grade 3 to 5 AEs occurred in 65%. In a comparison of the 15-month vs the 30-month bevacizumab arm, the most common AEs of special interest included hypertension of grade 3 or higher (20% vs 25%), intestinal perforation or fistula of any grade (5% vs 4%), thromboembolic events of grade 3 or higher (4% vs 3%), and proteinuria of grade 3 or higher (2% vs 4%).

Extending bevacizumab treatment to 30 months did not improve efficacy. The median PFS was 24.2 in the 15-month arm vs 26.0 months in the 30-month arm, (HR, 0.99; 95% CI, 0.85-1.15; *P*=.90; Figure 9). The restricted mean PFS was 39.5 vs 39.3 months (*P*=.92). Among the subgroup of patients with FIGO stage IIB to IIIC disease and no residual tumor, the median PFS was 38.4 vs 38.8 months (HR, 0.93; 95% CI, 0.74-1.18; *P*=.55), and the restricted mean PFS was 51.0 vs 53.2 months (*P*=.53). Among the patients with FIGO stage IIB to IIIC disease and residual tumor or FIGO stage IV disease, the median PFS was 19.3 months with 15 months of therapy vs 18.2 months with 30 months of therapy (HR, 1.06; 95% CI, 0.87-1.29; *P*=.58). The restricted mean PFS was 27.8 vs 25.5 months (*P*=.35). Among the entire population, the median OS was 54.3 months in the 15-month arm vs 60.0 months in the 30-month arm (HR, 1.04; 95% CI, 0.87-1.23; *P*=.68). The restricted mean OS was 60.4 vs 60.8 months (*P*=.87). The standard of care remains 15 months of bevacizumab as a part of first-line treatment in patients with advanced ovarian cancer.

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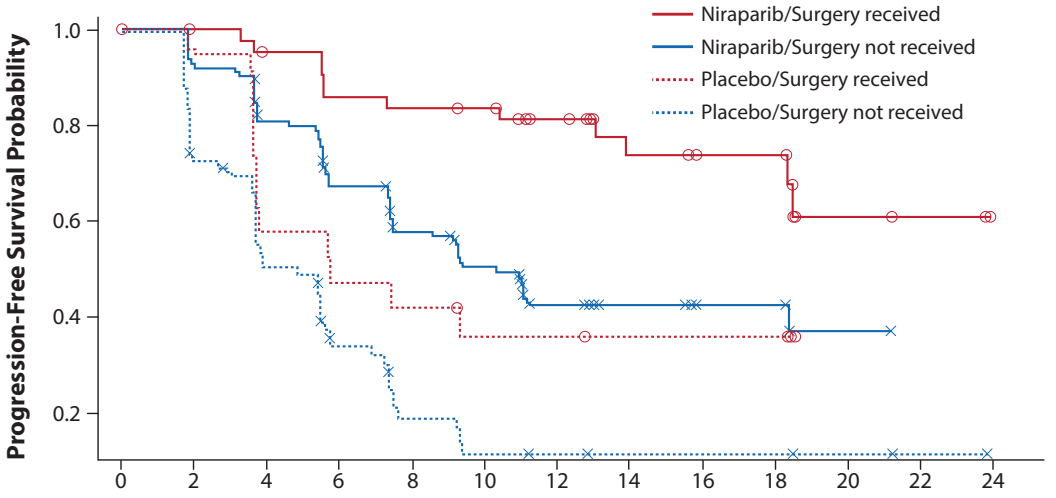
Efficacy of Niraparib Maintenance Therapy in Chinese Women With Platinum-Sensitive Recurrent Ovarian Cancer With and Without Secondary Cytoreductive Surgery: Results From the NORA Trial

Secondary cytoreductive surgery may benefit women with recurrent, platinum-sensitive ovarian cancer, but use of the procedure remains controversial.[1] A retrospective subgroup analysis evaluated the efficacy and safety of niraparib maintenance therapy in Chinese patients enrolled in the NORA trial who underwent secondary cytoreductive surgery.[2,3] The NORA trial enrolled patients with recurrent, platinum-sensitive ovarian cancer whose most recent platinum-based chemotherapy had yielded a PR or CR. Among 265 Chinese women who had recurrent, platinum-sensitive ovarian cancer, 69 underwent secondary cytoreductive surgery and 196 did not. Compared with placebo, niraparib was associated with a reduction in the risk for disease progression or death in patients who underwent secondary cytoreductive surgery (HR, 0.32; 95% CI, 0.13-0.78; *P*=.0102) and in patients who did not undergo secondary cytoreductive surgery (HR, 0.34; 95% CI, 0.23-0.50; *P*<.001). Among the patients who underwent secondary cytoreductive surgery, the median PFS was not reached (95% CI, 18.33 months to not estimable) with niraparib vs 5.75 months (95% CI, 3.68 months to not estimable) with placebo (*P*=.0102; Figure 10). Among patients who did not undergo secondary cytoreductive surgery, the median PFS was 10.28 months (95% CI, 7.49-18.37) with niraparib vs 4.90 months (95% CI, 3.71-5.52) with placebo (*P*<.0001).

Safety outcomes were similar among the patients who did or did not undergo secondary cytoreductive surgery.[3] Among the patients who did undergo secondary cytoreductive



Patients at Risk													
Niraparib/Surgery received	48	44	41	37	36	35	29	20	13	13	6	3	0
Niraparib/Surgery not received	129	117	98	79	65	55	41	23	12	12	2	0	
Placebo/Surgery received	21	18	11	9	8	6	6	5	5	5			
Placebo/Surgery not received	67	47	32	19	10	6	5	3	3	3	2	1	0

Figure 10. Progression-free survival in patients treated with niraparib or placebo according to prior cytoreductive surgery in the phase 3 NORA trial, which enrolled patients with recurrent, platinum-sensitive ovarian cancer. Adapted from Wu L et al. ASCO abstract 5534. *J Clin Oncol.* 2021;39(15 suppl).[3]

surgery, the most common treatment-emergent AEs of any grade with niraparib vs placebo were decreased neutrophil count (52.1% vs 38.1%), anemia (47.9% vs 23.8%), and decreased platelet count (47.9% vs 19.0%). The most common treatment-emergent AEs of at least grade 3 were decreased neutrophil count (22.9% vs 0%), anemia (18.8% vs 0%), and decreased platelet count (14.6% vs 0%). Among the patients who did not undergo secondary cytoreductive surgery, the most common treatment-emergent AEs of any grade with niraparib vs placebo were decreased neutrophil count (61.2% vs 43.3%), anemia (55.8% vs 29.9%), and decreased platelet count (57.4% vs 26.9%). The most common treatment-emergent AEs of at least grade 3 were decreased neutrophil count (19.4% vs 10.4%), anemia (13.2% vs 3.0%), and decreased platelet count (10.1% vs 1.5%).

ABSTRACT SUMMARY Preliminary Results of Anlotinib and Niraparib Dual Therapy Evaluation in Platinum-Resistant Recurrent Ovarian Cancer

The multicenter, single-arm phase 2 ANNIE trial evaluated the efficacy and safety of niraparib plus anlotinib in patients with recurrent ovarian epithelial, fallopian tube, or peritoneal cancer that recurred within 6 months after the most recent platinum-based therapy (Abstract e17532). The 33 enrolled patients were a median age of 56 years and had received a median of 6 prior lines of therapy. The confirmed best ORR was 48.0% (95% CI, 27.0%-69.0%), reflecting 12 PRs among 25 evaluable patients. The median PFS and median duration of response were not reached. Treatment-related AEs of at least grade 3 were observed in 39.4% of patients; the most common events were hand-foot skin reaction (3 patients) and thrombocytopenia, hypertriglyceridemia, and neutropenia (each noted in 2 patients). Trial enrollment is ongoing.

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Efficacy and Safety Results From the NeoPembrOV Study, a Randomized Phase 2 Trial of Neoadjuvant Chemotherapy With or Without Pembrolizumab Followed by Interval Debulking Surgery and Standard Systemic Therapy ± Pembrolizumab for Advanced High-Grade Serous Carcinoma: a GINECO Study

For some patients with advanced ovarian, peritoneal, or tubal cancer, primary debulking surgery may not result in complete tumor resection and is therefore not appropriate. Treatment with neoadjuvant chemotherapy and interval debulking has been proposed as a viable alternative for these patients.[1-3] The multicenter, open-label, noncomparative phase 2 NeoPembrOV study evaluated whether the addition of pembrolizumab to standard neoadjuvant chemotherapy could increase the optimal debulking rate.[4] Patients were randomly assigned in a 1:2 ratio to receive standard neoadjuvant therapy with carboplatin and paclitaxel or the same treatment plus pembrolizumab. After 4 cycles of neoadjuvant therapy, patients underwent interval debulking surgery. Patients then received 5 more cycles of chemotherapy (without or with pembrolizumab), plus optional bevacizumab. Maintenance therapy, which was continued for up to 24 months, consisted of bevacizumab or observation in the standard therapy arm and of pembrolizumab with or without bevacizumab in the experimental arm. The primary endpoint was the rate of complete resection at interval debulking surgery, which was

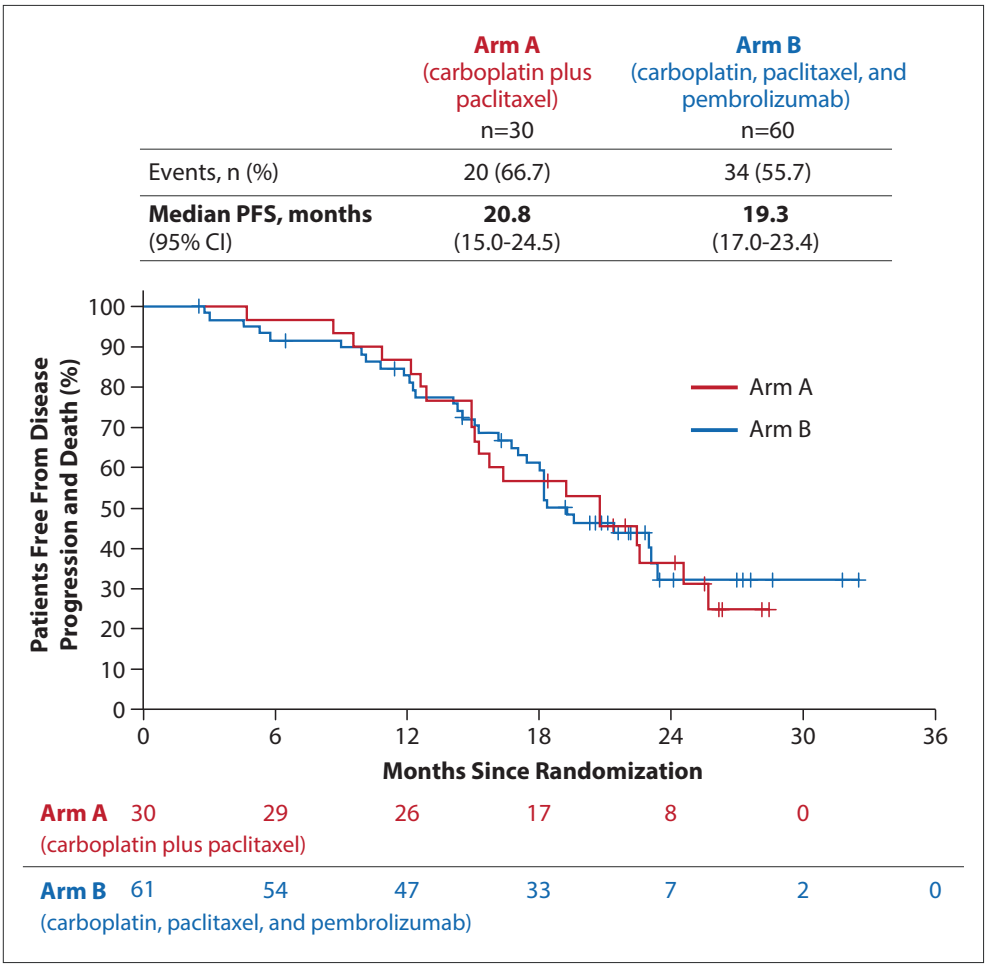

Figure 11. Progression-free survival in the phase 2 NeoPembrOV trial, which evaluated neoadjuvant chemotherapy with or without pembrolizumab followed by interval debulking surgery and standard systemic therapy with or without pembrolizumab in patients with advanced high-grade serous carcinoma. PFS, progression-free survival. Adapted from Ray-Coquard I et al. ASCO abstract 5500. *J Clin Oncol* 2021;39(15 suppl).[4]

evaluated in a blinded, central review by 2 surgical experts.

The study included 30 patients in the standard arm (arm A) and 61 in the experimental arm (arm B). Patient characteristics in the 2 arms were well balanced. In arm A, 10% of patients had mutated *BRCA* and 80% had wild-type *BRCA*. (The *BRCA* status was unknown in 10%.) In arm B, 21% of patients had mutated *BRCA* and 67.2% had wild-type *BRCA*. (The status was unknown in 11%.) Use of bevacizumab was anticipated in 96.6% of patients in arm A vs 88.1% in arm B.

Interval debulking surgery was performed in 96.7% of the patients in arm A vs 95.1% of those in arm B. Cytoreductive surgery achieved complete resection in 72.4% of patients in arm A vs 77.5% of those in arm B, thereby meeting the study's primary endpoint. In arm A vs arm B, after 4 cycles of neoadjuvant chemotherapy, the CR rate was 6.9% vs 3.3%, the PR rate was 55.2% vs 70.0%, and the proportion of patients with stable disease was 37.9% vs 23.3%. In arm A, the best response consisted of a CR in 75.9%, a PR in 10.3%, and stable disease in 13.8%. In arm B, there rates were 75.0%, 16.7%, and 8.3%, respectively. The median PFS was 20.8 months in arm A vs 19.3 months in arm B (Figure 11).

Among the patients who received pembrolizumab plus standard chemotherapy, the most common grade 3/4 AEs during neoadjuvant therapy were neutropenia (13.1%) and anemia).

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Highlights in Ovarian Cancer From the 2021 American Society of Clinical Oncology Annual Meeting: Commentary

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Presentations in ovarian cancer at the 2021 American Society of Clinical Oncology (ASCO) annual meeting provided important information regarding the management of ovarian cancer. New data were presented for treatments such as bevacizumab, checkpoint inhibitors, niraparib and other poly(ADP-ribose) polymerase (PARP) inhibitors, and the antibody-drug conjugate mirvetuximab soravtansine.

Extended Treatment With Bevacizumab

Dr Jacobus Pfisterer presented long-awaited data from a phase 3 trial evaluating the optimal duration of bevacizumab in combination with carboplatin and paclitaxel.[1]

In 2011, two phase 3 trials showed that the use of concomitant and maintenance bevacizumab improved progression-free survival.[2,3] In addition, a subgroup analysis of the ICON7 trial showed that this use of bevacizumab also improved overall survival in a high-risk population.[4] These data led to the use of concomitant and maintenance bevacizumab in patients with ovarian cancer. The duration of bevacizumab reached approximately 15 months in the GOG-218 trial and was 12 months in the ICON7 trial. When the treatment was stopped, the benefits ended. The hypothesis behind the current study was that progression-free survival and overall survival might be prolonged by administration of bevacizumab as maintenance therapy for an extended period (eg, until disease progression or at least double the duration of current treatment).

The trial by Pfisterer and colleagues enrolled patients who had undergone primary debulking surgery.[1] All patients received paclitaxel plus carboplatin. The patients were randomly assigned to receive treatment with bevacizumab for 15 months (the standard-of-care arm) or for 30 months (the experimental arm). Bevacizumab was administered concomitantly with chemotherapy and continued as maintenance therapy for 15 or 30 months. This European trial recruited 927 patients with stage IIB to 4 disease. High-grade serous disease was reported in 79% of patients, and

58% of patients had no residual disease. A stratification factor was stage IIB to IIIC disease with no residual tumor vs stage IIB to IIIC disease with residual tumor or stage IV disease.

Prolonged treatment with bevacizumab did not improve progression-free survival or overall survival. No benefits were seen in the intention-to-treat population or in subgroup analyses of patients with or without residual disease or with stage IIB to III disease or higher. These results were shocking. Previous trials had raised the possibility that bevacizumab could be active for a longer time. For example, in the MITO16 trial, rechallenge with bevacizumab improved outcome in patients who had received initial treatment with bevacizumab followed by chemotherapy and maintenance for progressive disease.[5]

The trial was well-designed, and there were no issues with the enrolled population. Prolonged treatment with bevacizumab did not increase the rate of adverse events. The outcome may be attributable to improvements in surgery compared with 20 years ago. The burden of disease is much lower in these patients, which may decrease the efficacy of bevacizumab. As shown in the ICON7 trial, benefits are seen in high-risk patients.[4] The patients without residual disease had no benefit. The take-home message from this study is that bevacizumab should not be administered beyond 15 months, which is the standard of care.

Checkpoint Inhibitors

Dr Isabelle Laure Ray-Coquard presented results from the phase 2 NeoPembrOV study.[6] This French trial evaluated whether neoadjuvant treatment with chemotherapy in combination with an immune checkpoint inhibitor would be superior to standard-of-care chemotherapy in patients with ovarian cancer. The trial design was innovative. The trial enrolled patients scheduled for neoadjuvant therapy with carboplatin/paclitaxel. The enrollment criteria did not specify any type of biomarker profiles. The patients were randomly assigned to receive pembrolizumab in addition to chemotherapy or chemotherapy alone. After 3 treatment cycles, all patients underwent interval debulking surgery to identify any improvements in pathologic or radiologic response. Unfortunately, the combination of immunotherapy plus chemotherapy did not improve outcome. The study investigators plan to perform a biomarker analysis to see if any subgroups benefitted from the combination regimen.

The trial was initiated before results were available for other major phase 3 trials in this setting. Results are now available for these trials. A trial in patients who were resistant to platinum therapy evaluated treatment with pegylated liposomal doxorubicin alone, pegylated liposomal doxorubicin plus avelumab, or avelumab alone.[7] The addition of avelumab did not improve outcome. A trial in the first-line setting evaluated carboplatin/paclitaxel with or without avelumab.[8] That trial was stopped based on lack of efficacy. A third trial evaluated frontline therapy with carboplatin/paclitaxel plus bevacizumab, with or without atezolizumab.[9] There were no differences between the treatment arms.

Currently, there is no clear goal in how to move forward with immune checkpoint inhibitors in ovarian cancer. It will be necessary to consider how to introduce immune checkpoint inhibitors into the armamentarium. The NeoPembrOV study confirmed other randomized data showing no benefit with the addition of immune checkpoint inhibitors to chemotherapy among the entire population of patients with ovarian cancer.[6-9] Thus far, no studies have shown benefits of immune therapy as a single agent or in combination with chemotherapy or bevacizumab. These agents are not suitable for the entire population, and biomarkers cannot be used to guide treatment at this time. Several recent trials have evaluated the combination of a PARP inhibitor plus immunotherapy with or without bevacizumab, and results are expected shortly.[10-13]

PARP Inhibitors

In the past 5 years, the management of ovarian cancer has completely changed with the introduction of PARP inhibitors. PARP inhibitors are used in multiple lines of therapy, including first-line settings and as maintenance, and they have dramatically improved outcome. In the first-line setting, the longest survival data is from the phase 3 SOLO1 study of maintenance olaparib, which showed that the 5-year survival of patients with the *BRCA* mutation was approximately 50%.[14,15] This long-term finding is incredible, especially because the treatment was given for only 2 years.

Niraparib was first approved by the US Food and Drug Administration for the maintenance of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy, based on results from the NOVA trial.[16] The NOVA trial was the first phase 3 study of a PARP inhibitor in ovarian cancer. The results showed that niraparib was extremely effective as maintenance therapy in patients with platinum-sensitive disease who had responded to chemotherapy. Results were seen among several subgroups of patients: those with *BRCA*-mutated or *BRCA*–wild-type disease, and, among the *BRCA*–wild-type patients, those who were homologous recombination deficiency (HRD)-positive or HRD-negative. In patients with relapsed disease, improvements were seen in both *BRCA*-mutated and *BRCA*–wild-type patients. In the phase 3 PRIMA trial, niraparib administered in the frontline setting improved progression-free survival.[17] Some patients required dose reductions and dose interruptions

owing to hematologic toxicities, primarily thrombocytopenia.

The study investigators of the NOVA trial, including myself, evaluated different aspects of the trial to identify factors that contributed to toxicities and to improve tolerability.[16] We found 2 important factors: the patient's body weight and thrombocyte count at baseline. The standard 300-mg dose of niraparib may be too high for some patients.

A reduced dose of niraparib was tested in 2 recent trials: PRIMA and NORA.[17,18] In both of these trials, the initial protocol designated a fixed dose of 300 mg/daily for all patients. The trials were subsequently amended to follow an individualized starting dose of 200 mg/daily for patients with a baseline body weight below 77 kg and/or a platelet count of less than 150,000/mm^3. The NORA trial was the first phase 3 trial of niraparib in patients with platinum-sensitive recurrent ovarian cancer conducted in Asia.[18] In both trials, niraparib led to dramatic improvements. In addition, adjusting the dose of niraparib according to body weight and thrombocyte count greatly improved the toxicity profile compared with the standard regimen used in the NOVA trial.[16-18]

Dr Antonio González-Martin presented an analysis of data from the PRIMA, NOVA, and NORA trials to assess the efficacy and safety of niraparib in patients with *BRCA* mutations.[19] The analysis showed that niraparib had tremendous efficacy in all 3 trials, whether in the first-line setting in PRIMA or the relapsed setting in NOVA and NORA. The toxicity profile was much better in the NORA and PRIMA trials, which followed the individualized dosing strategy. (Toxicity was especially low in the PRIMA trial.) In the NORA trial, the dose adjustment was made for almost all patients. The NORA trial indirectly showed that efficacy is not affected by dose adjustments. Patients who began treatment at 200 mg instead of 300 mg had similarly high efficacy with a much more controlled toxicity profile.

Dr Xiaohua Wu was the primary investigator of the NORA trial.[18] At the 2021 ASCO meeting, Dr Wu and colleagues presented a retrospective subgroup analysis of the NORA trial that evaluated efficacy according to whether a patient had undergone secondary cytoreductive surgery.[20] No difference in efficacy was found; both subgroups benefitted from treatment. This analysis was important, in that it confirmed that patients should receive maintenance therapy with niraparib regardless of whether they underwent cytoreductive surgery.

Another retrospective analysis of the NORA trial evaluated the safety profile of niraparib according to the individualized starting dose.[21] Most of the patients in this Chinese trial weighed less than 77 kg, and they began treatment at 200 mg. The analysis clearly showed that grade 3/4 toxicity was well controlled with individualized dosing.

Dr Bente Vilming of Norway presented an important real-world study of niraparib, with a focus on patients with *BRCA*–wild-type disease.[22] The investigators aimed to compare the efficacy and toxicity reported in the NOVA trial vs that observed in real-world settings. Results from the NOVA trial showed that the dose of niraparib should be lowered in patients who weigh less. This dosing strategy was already implemented in Norway when the real-world evidence data were collected.

This study showed that the toxicity profile was far better in the real-world setting than in the NOVA trial.[16,22] For most treatments, toxicities are higher in the real world vs in clinical trials. The reverse was seen with niraparib because data from the NOVA trial were used to devise a strategy to manage toxicity in clinical care. This analysis is important because it shows that the dose-reduction strategy is effective.

Treatment After PARP Inhibitors

Dr Shannon Westin presented the results of a phase 2 trial that evaluated adavosertib with or without olaparib in patients who are resistant to PARP inhibitors.[23] There are several different mechanisms of resistance. Adavosertib inhibits the WEE1 kinase. The idea behind the trial was to see if it is possible to make tumors reverse their homologous recombination (HR) reversion back so that they become HR-deficient. A previous trial evaluating an ataxia telangiectasia mutated and Rad3-related (ATR) inhibitor was stopped because a sister trial in breast cancer showed no benefit at the interim analysis.[24]

In the trial presented by Dr Westin, the patients were randomly assigned to treatment with adavosertib alone or in combination with olaparib.[23] All of the patients had received earlier treatment with a PARP inhibitor. The clinical activity in this small randomized phase 2 trial was impressive. The objective response rate was 23% with adavosertib alone and 29% with adavosertib in combination with olaparib. Response is important, but so is tumor shrinkage. The rate of disease control was also impressive. The toxicity profile was well tolerated. Larger phase 3 trials should examine whether it is possible to overcome PARP resistance.

Novel Treatments

Dr David O'Malley presented final results of a phase 1b trial evaluating mirvetuximab soravtansine, an antibody-drug conjugate that targets the folate receptor alpha (FRα), plus bevacizumab in patients with platinum-resistant ovarian cancer.[25] An earlier analysis showed activity in the subgroups of patients with medium or high expression of FRα.[26] The final analysis showed that mirvetuximab soravtansine clearly improved overall response and progression-free survival in these settings.[25] A hypothesis drawn

from these findings is that higher expression of FRα might correspond to better response rates. In the current trial, the patients were not stratified according to level of expression, so confirmation of this hypothesis is needed. An ongoing phase 3 trial is evaluating mirvetuximab soravtansine.[27] If the results are positive, this agent will become a new treatment option for patients in the future.

Disclosure

Dr Mirza has received personal compensation for serving on advisory boards of AstraZeneca, Biocad, GSK, Karyopharm, Merck, Riche, and Zai Lab. He has received personal compensation as an invited speaker for AstraZeneca and GSK. He has received personal compensation from Karyopharm as a member of the Board of Directors and as a holder of stocks/shares. He has received research grants directed to his institution, with no personal financial interests, from Apexigen, AstraZeneca, GSK, and Ultimovacs. He has served as a trial chair for Deciphera, with compensation directed toward his institution and with no personal financial interests.

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