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A SPECIAL MEETING REVIEW EDITION

Highlights in Ovarian Cancer From the European Society for Medical Oncology Virtual Congress 2020

A Review of Selected Presentations From the ESMO Virtual Congress 2020

Special Reporting on:

- Patient-Reported Outcomes in Patients Receiving Niraparib in the PRIMA/ENGOT-OV26/GOG-3012 Trial
- Maintenance Olaparib for Patients With Newly Diagnosed, Advanced Ovarian Cancer and a *BRCA* Mutation: 5-Year Follow-Up From SOLO1
- Individualized Starting Dose of Niraparib in Chinese Patients With Platinum-Sensitive Recurrent Ovarian Cancer: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial (NORA)
- Primary Results From IMagyn050/GOG 3015/ENGOT-OV39, a Double-Blind Placebo-Controlled Randomized Phase 3 Trial of Bevacizumab-Containing Therapy +/– Atezolizumab for Newly Diagnosed Stage III/IV Ovarian Cancer
- Efficacy and Safety of Niraparib in Older Patients With Advanced Ovarian Cancer: Results From the PRIMA/ENGOT-OV26/GOG-3012 Trial
- Maintenance Olaparib Plus Bevacizumab in Patients With Newly Diagnosed, Advanced High-Grade Ovarian Carcinoma
- Health-Related Quality of Life in Patients With Newly Diagnosed Stage III or IV Ovarian Cancer Treated With Veliparib + Chemotherapy Followed by Veliparib Maintenance
- INOVATYON Study: Randomized Phase III International Study Comparing Trabectedin/PLD Followed by Platinum at Progression vs Carboplatin/PLD in Patients With Recurrent Ovarian Cancer Progressing Within 6 to 12 Months After Last Platinum Line

PLUS Meeting Abstract Summaries

With Expert Commentary by:

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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, first-line maintenance monotherapy approved for advanced ovarian cancer in complete or partial response to platinum-based chemotherapy, regardless of biomarker status[1-3]

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.

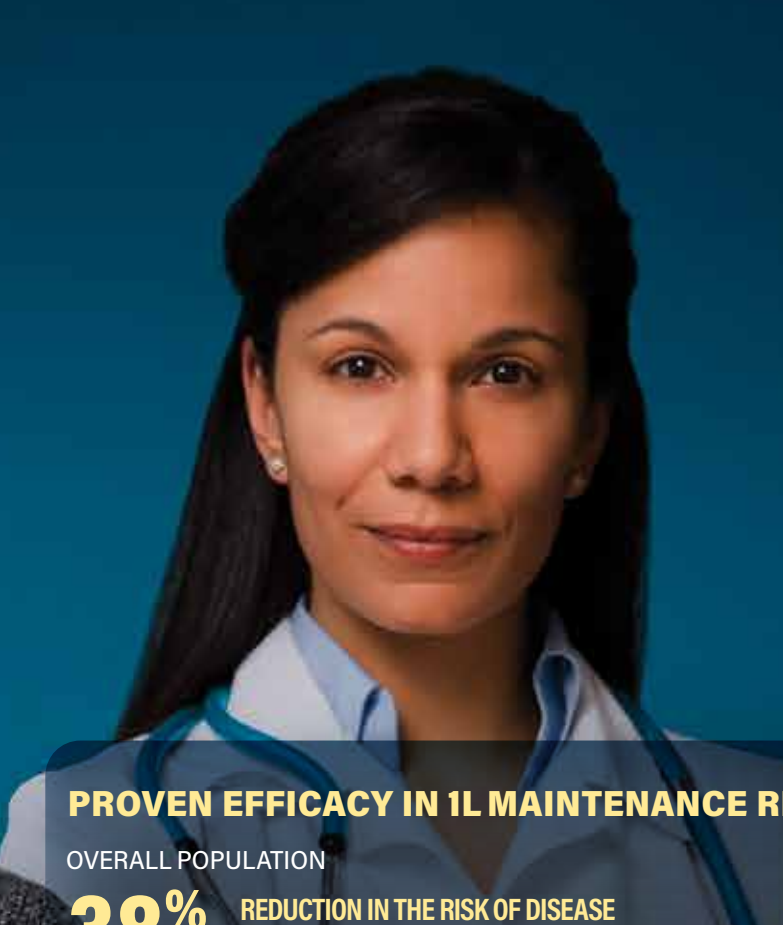
Important Safety Information

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML), including some fatal cases, was reported in 15 patients (0.8%) out of 1785 patients treated with ZEJULA monotherapy in clinical trials. The duration of therapy in patients who developed secondary MDS/cancer therapy-related AML varied from 0.5 months to 4.9 years. These patients had received prior chemotherapy with platinum agents and/or other DNA-damaging agents including radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

Hematologic adverse reactions (thrombocytopenia, anemia and neutropenia) have been reported in patients receiving ZEJULA. 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,

Please see additional Important Safety Information on the adjacent page.



1 DAILY DOSE

Zejula
niraparib
capsules 100 mg

YOU RESPOND WITH ZEJULA[1]

PROVEN EFFICACY IN 1L MAINTENANCE REGARDLESS OF BIOMARKER STATUS[1,4]

OVERALL POPULATION

38% REDUCTION IN THE RISK OF DISEASE 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

57% REDUCTION IN THE RISK OF DISEASE 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: PRIMA, a randomized double-blind, placebo-controlled phase 3 trial, evaluated the safety and efficacy of once-daily ZEJULA versus placebo (2:1) in 733 women with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer following a CR or PR to first-line platinum-based chemotherapy. The primary endpoint was a hierarchical calculation of PFS: first in patients with HRd tumors and then in all patients. PFS was measured from time of randomization to time of disease progression or death. At the time of PFS analysis, limited overall survival data were available with 11% deaths in the overall population.[1,4]

Important Safety Information (continued)

especially coronary insufficiency, cardiac arrhythmias, and hypertension. Manage hypertension with antihypertensive medications and adjustment of the ZEJULA dose, if necessary.

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

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%).

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

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

Visit **ZEJULA.COM/HCP** to explore the PRIMA data

Please see Brief Summary on the following pages.

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 Three 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 three or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either:

- a deleterious or suspected deleterious *BRCA* mutation, or
- genomic instability and who have progressed more than six months after response to the last platinum-based chemotherapy *[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 ZEJULA monotherapy in clinical trials. In 1785 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 (thrombocytopenia, anemia and neutropenia) have been reported in patients treated with 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.

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

In QUADRA, Grade ≥3 thrombocytopenia, anemia and neutropenia were reported, respectively, in 28%, 27%, and 13% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 4%, 2%, and 1% 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 Cardiovascular Effects

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

In PRIMA, Grade 3-4 hypertension occurred in 6% of ZEJULA-treated patients compared to 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 3-4 hypertension occurred in 9% of ZEJULA-treated patients compared to 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 3-4 hypertension occurred in 5% of ZEJULA-treated patients 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 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. Medically manage hypertension with antihypertensive medications and adjustment of the ZEJULA dose, if necessary *[see Dosage and Administration (2.3) and Nonclinical Toxicology (13.2) of full prescribing information]*.

5.4 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)]*.

6 ADVERSE REACTIONS

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

- Myelodysplastic Syndrome/Acute Myeloid Leukemia *[see Warnings and Precautions (5.1)]*
- Bone Marrow Suppression *[see Warnings and Precautions (5.2)]*
- Cardiovascular Effects *[see Warnings and Precautions (5.3)]*

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 to 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 1314 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 (one 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%), 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 Drug Reactions Reported in ≥10% of All Patients Receiving ZEJULA in PRIMA[a]

	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

[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] CTCAE=Common Terminology Criteria for Adverse Events version 4.02

[c] includes neutropenia, neutropenic infection, neutropenic sepsis, febrile neutropenia.

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

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

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

	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 11.0 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 (3.0% 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]

	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

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

	Grades 1-4[b]		Grades 3-4[b]	
	ZEJULA N=169 %	Placebo N=86 %	ZEJULA N=169 %	Placebo N=86 %
Renal and Urinary Disorders				
Acute kidney injury[e]	12	5	1	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]CTCAE=Common Terminology Criteria for Adverse Events version 4.02

[c]includes neutropenia, neutropenic infection, neutropenic sepsis, febrile neutropenia.

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

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

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

	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 ZEJULA monotherapy 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

	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

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

	Grades 1-4[a]		Grades 3-4[a]	
	ZEJULA N=367 %	Placebo N=179 %	ZEJULA N=367 %	Placebo N=179 %
Cardiac Disorders				
Palpitations	10	2	0	0
Gastrointestinal Disorders				
Nausea	74	35	3	1
Constipation	40	20	0.8	2
Vomiting	34	16	2	0.6
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
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

[a]CTCAE=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

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

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

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

alkaline phosphatase increased, weight decreased, depression, epistaxis.

Treatment of Advanced Ovarian Cancer after Three or More Chemotherapies

The safety of ZEJULA monotherapy 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 1-4) 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.

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

	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

[a]CTCAE=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

	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 post-approval 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.

Immune System Disorders: hypersensitivity (including anaphylaxis)

Nervous System Disorders: posterior reversible encephalopathy syndrome (PRES)

Psychiatric Disorders: confusional state/disorientation, hallucination, cognitive impairment

Respiratory, Thoracic, and Mediastinal Disorders: non-infectious pneumonitis

Skin and Subcutaneous Tissue Disorders: photosensitivity

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

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

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

Contraception

Females

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

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]*.

8.5 Geriatric Use

In PRIMA, 39% of patients were aged ≥65 years and 10% were aged ≥75 years. In NOVA, 35% of patients were aged ≥65 years and 8% were aged ≥75 years. No overall differences in safety and effectiveness of ZEJULA were observed between these patients and younger patients but greater sensitivity of some older individuals cannot be ruled out.

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

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

10 OVERDOSAGE

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

17 PATIENT COUNSELING INFORMATION

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

MDS/AML

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

Cardiovascular Effects

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

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 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)]*.

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Research Triangle Park, NC 27709

NRPJRNA200007 August 2020
Produced in USA.

Patient-Reported Outcomes in Patients Receiving Niraparib in the PRIMA/ENGOT-OV26/GOG-3012 Trial

Niraparib is an oral selective inhibitor of poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) 1/2. PARP inhibitors induce apoptosis in cancer cells by interfering with DNA repair mechanisms,[1] and they have shown promising safety and efficacy in patients with homologous recombination–deficient (HRD) ovarian cancer. The double-blind phase 3 PRIMA trial compared niraparib vs placebo in patients with ovarian, primary perineal, or fallopian tube cancer who had developed either a partial response (PR) or a complete response (CR) after first-line treatment with platinum-based chemotherapy.[2] Stratification factors included treatment with neoadjuvant chemotherapy, best response to first-line platinum therapy, and HRD status. Patients were randomly assigned in a 2:1 ratio to receive niraparib or placebo. The dose of niraparib was based on body weight and platelet count. The primary endpoint was progression-free survival (PFS) among patients with HRD-positive tumors and in the overall population. A prespecified interim analysis for overall survival (OS) was conducted at the time of the primary analysis of progression-free survival.

Among the 733 patients who underwent treatment randomization, tumors were HRD-positive in 50.9%.[2] Among the patients in this category, the median PFS was 21.9 months in the niraparib group vs 10.4 months in the placebo group (hazard ratio [HR] for disease progression or death, 0.43; 95% CI, 0.31-0.59; *P*<.001). In the overall population, PFS was 13.8 months vs 8.2 months, respectively (HR, 0.62; 95% CI, 0.50-0.76; *P*<.001). At the 24-month interim analysis, the rate of OS was 84% in the niraparib arm vs 77% in the placebo arm (HR, 0.70; 95% CI, 0.44-1.11).

Patient-reported outcomes were evaluated as a secondary endpoint.[3] These outcomes were collected via 4 instruments: the Functional Assessment of Cancer Therapy–Ovarian Symptom Index (FOSI),[4] the European Quality of Life 5-Dimension 5-Level questionnaire (EQ-5D-5L),[5] the European Organization for Research and

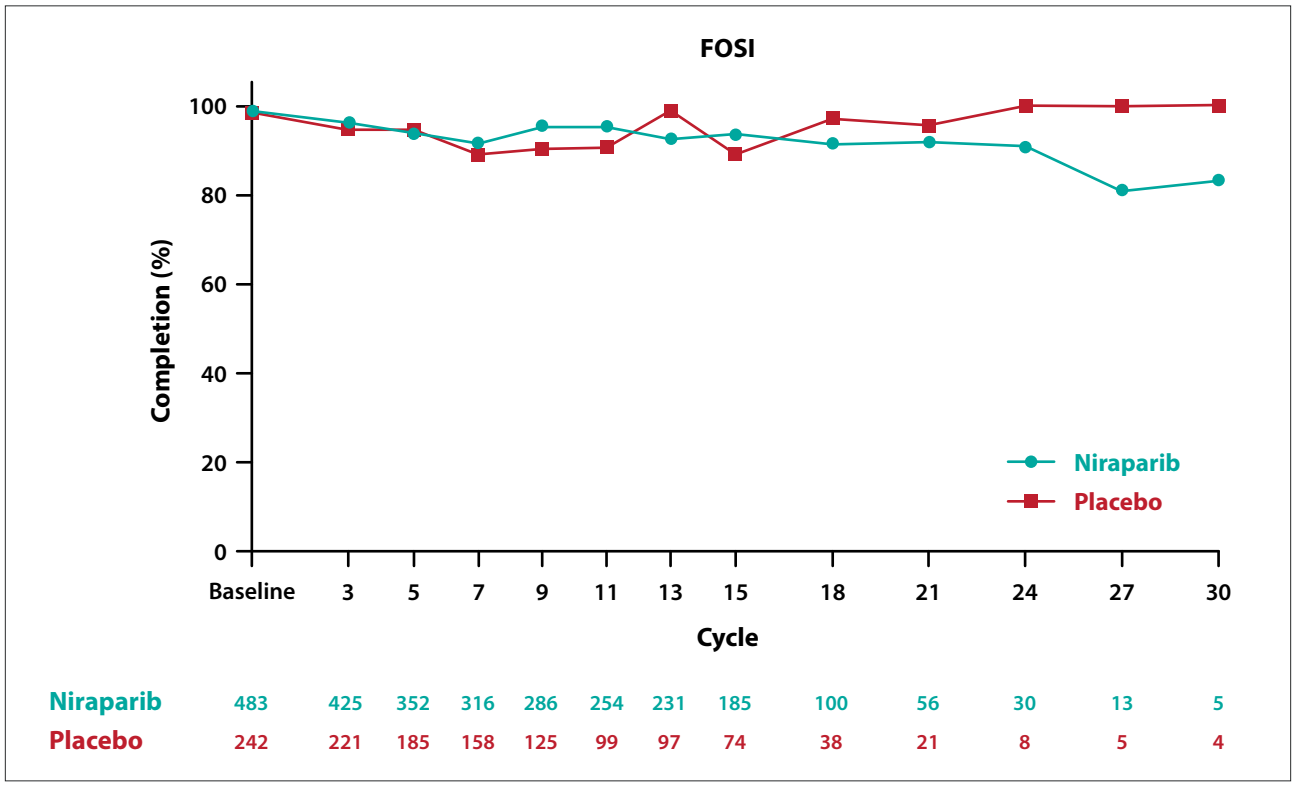

Figure 1. Treatment adherence rates according to the FOSI instrument in the phase 3 PRIMA trial. FOSI, Functional Ovarian Symptom Index. Adapted from Pothuri B et al. ESMO abstract 810MO. *Ann Oncol.* 2020;31(suppl 4):S612-S613.[3]

Treatment of Cancer (EORTC) Quality of Life Questionnaire (EORTC-QLQ-C30),[6] and the EORTC Quality of Life Questionnaire Ovarian Cancer (EORTC-QLQ-OV28) module.[7] The patient-reported outcomes from these questionnaires were obtained at baseline, every 8 weeks through week 56, and then every 12 weeks until study discontinuation. Patients also reported outcomes at the end of treatment and at 4, 8, 12, and 24 weeks after treatment discontinuation. Throughout the study, the rate of patient adherence was high, exceeding 80% across all instruments used to assess patient-reported outcomes (Figure 1).

FOSI is a validated instrument that measures 8 items related to symptoms in response to treatment for ovarian cancer.[4] Patients report on the symptoms they have experienced during the prior 7 days on a 5-point Likert scale ranging from 0 to 4. The Health Utility Index (HUI) is a cumulative score that represents overall outcome across the 8 items. The mean FOSI HUI scores were similar in the patients treated with niraparib or placebo (Figure 2). Results from the FOSI questionnaire showed that the percentages of patients with mild or severe symptoms consisting of lack of energy, nausea, vomiting, and cramping were similar in the 2 treatment arms.

The EORTC QLQ-C30 assesses health-related quality of life with 30 questions.[6] The instrument was developed to provide a common scale for measuring health outcomes from different interventions. The questionnaire addresses several aspects of functioning (physical, role, social, emotional, and cognitive), as well as parameters such as pain, fatigue, finances, appetite, nausea and vomiting, diarrhea, constipation, sleep, and quality of life. Scores from the EORTC QLQ-C30 were similar in the patients treated with niraparib or placebo. No difference between the 2 groups was observed in overall quality of life, physical function, and levels of fatigue and pain.

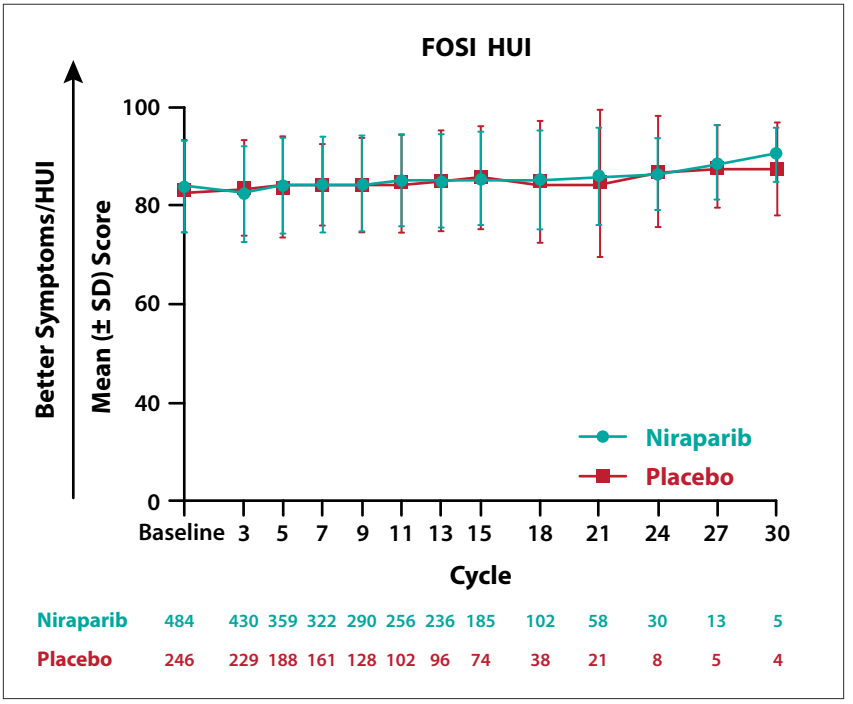

Figure 2. The mean FOSI HUI scores were similar in patients treated with niraparib or placebo in the phase 3 PRIMA trial. FOSI, Functional Ovarian Symptom Index; HUI, Health Utility Index; SD, standard deviation. Adapted from Pothuri B et al. ESMO abstract 810MO. *Ann Oncol.* 2020;31(suppl 4):S612-S613.[3]

The EORTC QLQ-OV28 was developed specifically for patients with ovarian cancer.[7] The results from this instrument also showed similar outcomes in patients treated with niraparib or placebo. No differences were noted in the mean number of abdominal/gastrointestinal symptoms or in other side effects associated with chemotherapy. The HUI based on the EQ-5D-5L questionnaire showed no meaningful difference in changes in health from baseline between the 2 treatment arms. Similarly, EQ-5D-5L scores obtained by means of a visual analogue scale revealed no differences between the niraparib and placebo arms. In conclusion, the results obtained with 4 different instruments used to assess health-related quality of life were similar in patients treated with niraparib or placebo.

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Maintenance Olaparib for Patients With Newly Diagnosed, Advanced Ovarian Cancer and a *BRCA* Mutation: 5-Year Follow-Up From SOLO1

Despite therapeutic advances in the treatment of ovarian cancer, fewer than half of patients with newly diagnosed disease survive for 5 years.[1,2] First-line therapy provides the best opportunity to delay disease progression and prolong survival. The phase 3 SOLO1 trial evaluated maintenance therapy with olaparib among patients with newly diagnosed stage III/IV disease (per criteria from the International Federation of Gynecology and Obstetrics).[3] The trial enrolled patients with high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancer with a germline *BRCA* mutation. Patients had undergone cytoreductive surgery and had developed a PR or CR after receiving platinum-based chemotherapy. The trial randomly assigned 391 patients in a 2:1 ratio to olaparib (300 mg twice daily) or placebo for 2 years or until disease progression. The primary endpoint was investigator-assessed PFS. After a median follow-up of 41 months, the HR for disease progression or death was 0.30 (95% CI, 0.23-0.41; *P*<.001).

A long-term follow-up analysis evaluated efficacy and safety among patients in the SOLO1 trial.[4] The median follow-up was 4.8 years for the olaparib arm and 5.0 years for the placebo arm. The long-term median PFS was 56.0 months in the olaparib arm vs 13.8 months in the placebo arm (HR, 0.33; 95% CI, 0.25-0.43; Figure 3). The median duration of treatment was 24.6 months vs 13.9 months, respectively. Among patients with a CR after chemotherapy, the median recurrence-free survival was not reached with olaparib vs 15.3 months with placebo (HR, 0.37; 95% CI, 0.27-0.52). In the olaparib arm, 52% of the patients remained recurrence-free at 5 years, compared with 22% in the placebo arm. The secondary outcomes were consistent with a PFS benefit from olaparib. In the overall study population, the median PFS2 (time from randomization to second progression) was not reached with olaparib vs 42.1 months with placebo (HR, 0.46; 95% CI, 0.33-0.65). The median time to the second subsequent therapy was not reached vs 40.7 months, respectively (HR, 0.46; 95% CI, 0.34-0.63). Among patients with a CR at baseline (n=189 in the olaparib arm and n=101 in the placebo arm), the median PFS2 was not reached with olaparib vs 52.9

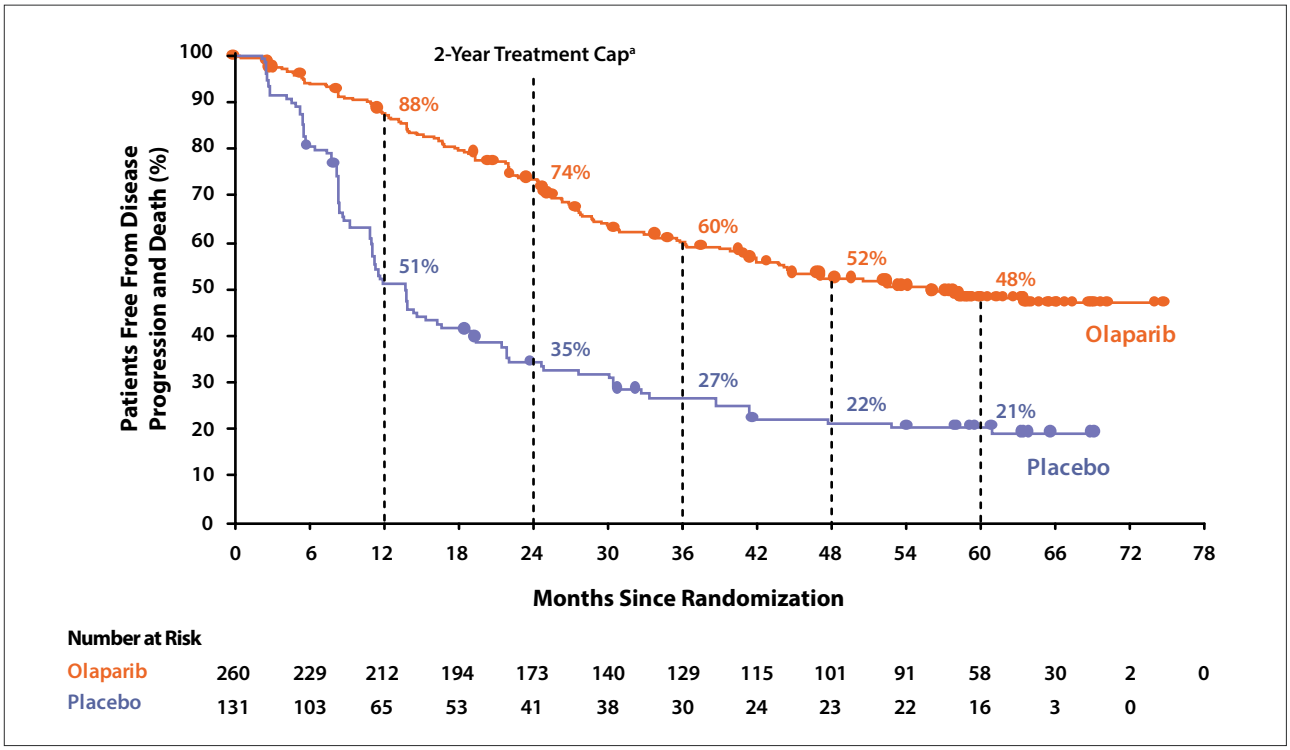

Figure 3. Median progression-free survival in the phase 3 SOLO1 trial of olaparib. [a]Thirteen patients, all in the olaparib arm, continued study treatment past 2 years. Adapted from Banerjee S et al. ESMO abstract 811MO. *Ann Oncol.* 2020;31(suppl 4):S613.[4]

months with placebo (HR, 0.48; 95% CI, 0.32-0.71), and the median time to second subsequent therapy was not reached vs 47.7 months (HR, 0.35; 95% CI, 0.35-0.72).

The safety profile was consistent with previous reports. More than 90% of patients in each arm experienced an adverse event of any grade. Adverse events of grade 3 or higher were reported in 40% of patients in the olaparib arm vs 19% in the placebo arm, with serious adverse events in 21% vs 13%, respectively. An adverse event led to dose interruption in 52% of the patients receiving maintenance therapy with the PARP inhibitor vs 17% of the patients receiving placebo. No additional cases of myelodysplastic syndrome and/or acute myeloid leukemia emerged.

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Individualized Starting Dose of Niraparib in Chinese Patients With Platinum-Sensitive Recurrent Ovarian Cancer: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial (NORA)

The US Food and Drug Administration approved niraparib for platinum-sensitive, recurrent ovarian cancer on the basis of results from the NOVA trial.[1] Patients in the NOVA trial initially received niraparib at 300 mg, with dose reductions allowed for toxicity, per results from a phase 1 dose-escalation study.[2] A subsequent retrospective analysis, however, suggested that an individualized starting dose of niraparib, based on the patient's weight and platelet count, could improve the safety profile while maintaining efficacy.[3] A phase 1 study of niraparib in Chinese patients with recurrent ovarian cancer showed that pharmacokinetics were similar to those observed in White patients.[4]

The double-blind, phase 3 NORA CONSORT trial evaluated the safety and efficacy of niraparib, administered at 2 different starting doses, in Chinese patients with platinum-sensitive recurrent ovarian cancer.[5] Patients were stratified according to germline *BRCA* mutation status, response to the most recent chemotherapy, and time to progression after the penultimate platinum-based regimen. Study participants were then randomly assigned in a 2:1 ratio to receive niraparib (n=177) or placebo (n=88). Patients with a baseline body weight below 77 kg or a platelet count of less than 150,000/μL received niraparib at 200 mg daily, whereas all others received niraparib at 300 mg daily. The primary endpoint was PFS as determined by blinded central review.

At the time of the data analysis, 43% of patients in the niraparib arm and 13% of those in the placebo arm were still receiving treatment. The patients' median age was 54.0 years (range, 35.0-78.0 years). Their median weight was 61.0 kg (range, 39.0-93.0 kg), and their median body mass index was 24.3 (standard deviation, 3.6). High-grade serous ovarian carcinoma was reported in 98.1% of patients. The time to progression following the penultimate platinum therapy was at least

ABSTRACT SUMMARY ICON8: Overall Survival Results in a GCIG Phase III Randomised Controlled Trial of Weekly Dose-Dense Chemotherapy in First-Line Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Carcinoma Treatment

The ICON8 trial investigated first-line treatment with dose-dense, weekly paclitaxel in a predominantly European population of patients with ovarian cancer (Abstract 8050). The trial randomly assigned 1566 patients to 1 of 3 arms. Arm 1 received carboplatin (AUC, 5 mg/mL·min) plus paclitaxel (175 mg/m^2) every 3 weeks for 6 cycles. Arm 2 received carboplatin (AUC, 5 mg/mL·min) every 3 weeks plus paclitaxel (80 mg/m^2) weekly. Arm 3 received carboplatin (AUC, 2 mg/mL·min) weekly plus paclitaxel (80 mg/m^2) weekly. Updated survival data showed no improvement in the median PFS for patients in arm 2 (*P*=.37) or arm 3 (*P*=.48) compared with arm 1. The median PFS was 17.4 months for arm 1, 20.1 months for arm 2, and 20.1 months for arm 3. The median OS also was similar in arm 2 (*P*=.14) and arm 3 (*P*=.27) compared with arm 1.

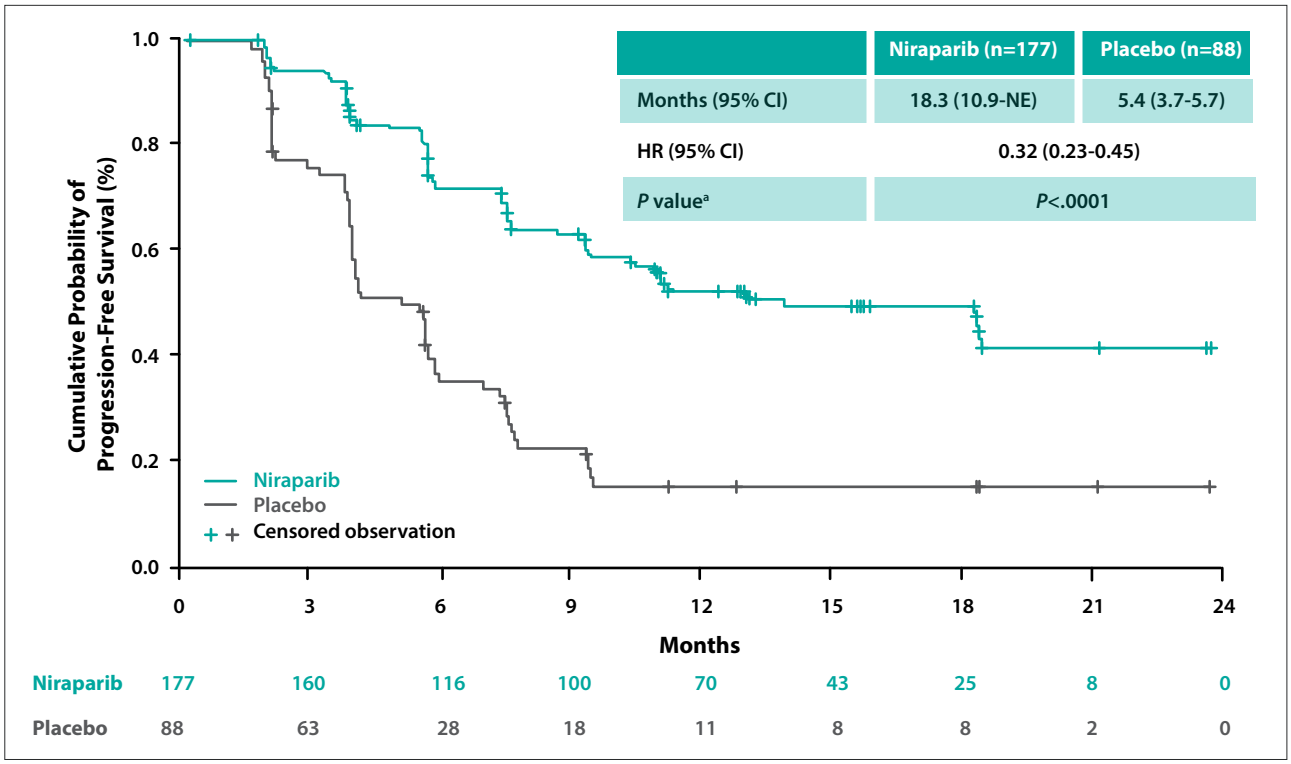

Figure 4. Median progression-free survival in the phase 3 NORA trial, which compared niraparib vs placebo. [a]The *P* value is from a stratified log-rank test. HR, hazard ratio; NE, not estimable. Adapted from Wu X et al. ESMO abstract LBA29. *Ann Oncol.* 2020;31(suppl 4):S1160-S1161.[5]

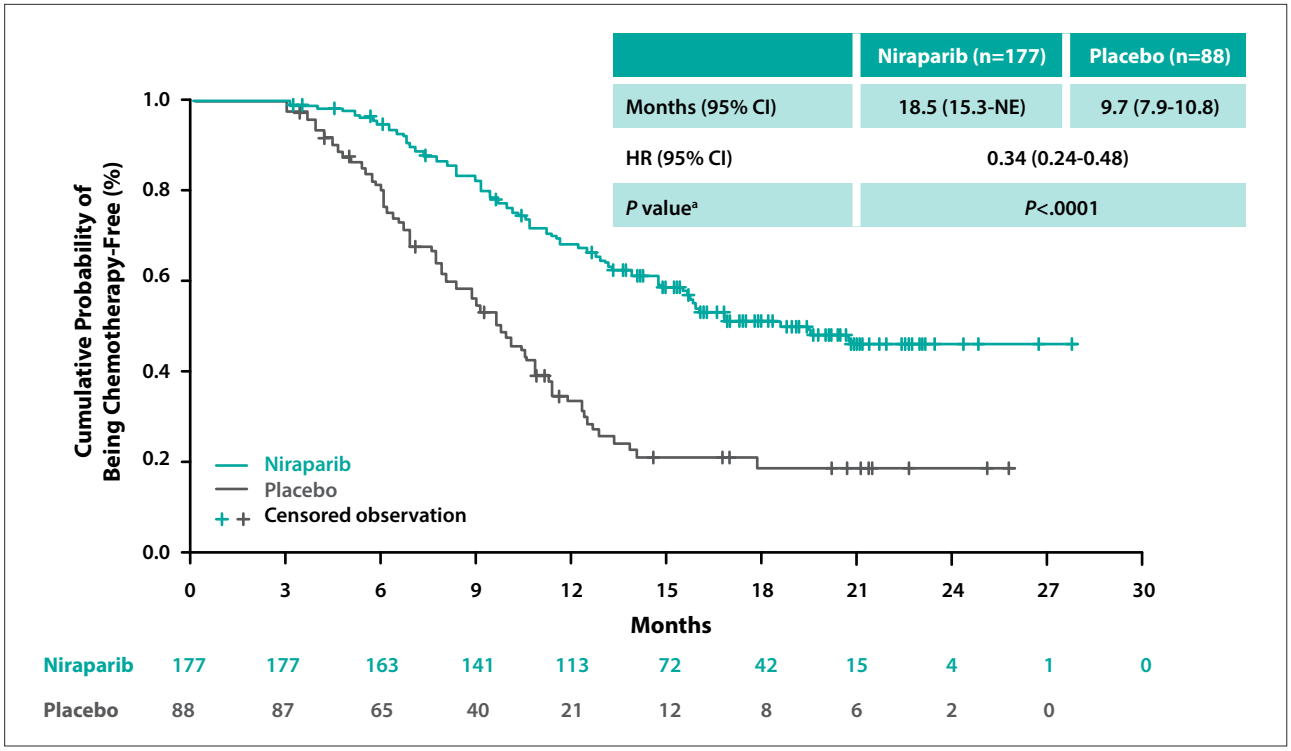

Figure 5. The chemotherapy-free interval in the phase 3 NORA trial, which compared niraparib vs placebo. [a]The *P* value is from a stratified log-rank test. HR, hazard ratio; NE, not estimable. Adapted from Wu X et al. ESMO abstract LBA29. *Ann Oncol.* 2020;31(suppl 4):S1160-S1161.[5]

12 months in 68.3% of patients, and 51.7% of patients had achieved a CR after their most recent platinum-based regimen. Germline *BRCA* mutations were observed in 37.7% of patients.

The NORA study achieved its primary endpoint, demonstrating a median PFS of 18.3 months (95% CI, 10.9 months to not estimable) with niraparib vs 5.4 months (95% CI, 3.7-5.7 months) with placebo (HR, 0.32; *P*<.0001; Figure 4). Nearly all subgroups benefited from niraparib. The median PFS with niraparib was superior in patients with or without a germline *BRCA* mutation (*P*<.0001). The NORA trial also achieved its secondary endpoints of extending the chemotherapy-free interval and the time to first subsequent therapy. The median chemotherapy-free interval was 18.5 months with niraparib vs 9.7 months with placebo (HR, 0.34; 95% CI, 0.24-0.48; *P*<.0001; Figure 5). The time to first subsequent therapy was 16.7 months with niraparib vs 7.7 months with placebo (HR, 0.35; 95% CI, 0.25-0.50; *P*<.0001). OS data were immature and did not show a difference between the 2 arms (*P*=.267).

Grade 3 or higher treatment-emergent adverse events were reported in 50.8% of patients in the niraparib arm vs 19.3% in the placebo arm. Treatment-related adverse events of grade 3 or higher were observed in 44.6% vs 11.4%, respectively. Serious treatment-related, treatment-emergent adverse events were more common in the niraparib arm (13.0% vs 4.5%), as were treatment-related adverse events leading to dose reduction (59.9% vs 13.6%). Discontinuation rates were similar in the 2 arms (4.0% vs 5.7%, respectively). The most common adverse events of any grade in the niraparib arm included white blood cell count decrease (59.3%), neutrophil count decrease (58.8%), and platelet count decrease (54.8%).

ABSTRACT SUMMARY MOONSTONE/GOG-3032: A Phase II, Open-Label, Single-Arm Study to Evaluate the Efficacy and Safety of Niraparib + Dostarlimab in Patients With Platinum-Resistant Ovarian Cancer

The phase 2 MOONSTONE/GOG-3032 trial (Study to Evaluate the Efficacy and Safety of the Combination of Niraparib and Dostarlimab [TSR-042] in Participants With Platinum Resistant Ovarian Cancer) will evaluate the efficacy and safety of niraparib plus dostarlimab, an anti–programmed death 1 antibody, in women with platinum-resistant ovarian cancer (Abstract 883TiP). The single-arm, open-label trial will enroll approximately 150 patients. Niraparib will be administered at 200 mg to patients with a weight below 77 kg or a platelet count below 150,000/μL; the dose will be 300 mg for all others. The first 4 doses of dostarlimab (500 mg) will be administered every 3 weeks, then 3 more doses (1000 mg) will be administered every 6 weeks. The primary endpoint is investigator-assessed ORR in the overall population and in patients with PD-L1–positive tumors. Key secondary endpoints include safety, tolerability, and efficacy.

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Primary Results From IMagyn050/GOG 3015/ENGOT-OV39, a Double-Blind Placebo-Controlled Randomized Phase 3 Trial of Bevacizumab-Containing Therapy +/– Atezolizumab for Newly Diagnosed Stage III/IV Ovarian Cancer

The double-blind, randomized phase 3 IMagyn050 trial evaluated atezolizumab vs placebo, in combination with bevacizumab, carboplatin, and paclitaxel, as first-line therapy in patients with epithelial ovarian, primary peritoneal, or fallopian tube cancer.[1] Enrolled patients had stage III or IV cancer with macroscopic residual disease postoperatively or were candidates for neoadjuvant therapy with planned interval surgery. The patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. All patients received either atezolizumab (1200 mg) or placebo in combination with paclitaxel (175 mg/m^2), carboplatin (area under the curve [AUC], 6 mg/mL·min), and bevacizumab (15 mg/kg) every 3 weeks. After the first 6 cycles, patients continued treatment with bevacizumab and either atezolizumab or placebo for cycles 7 to 22. The primary endpoints were PFS

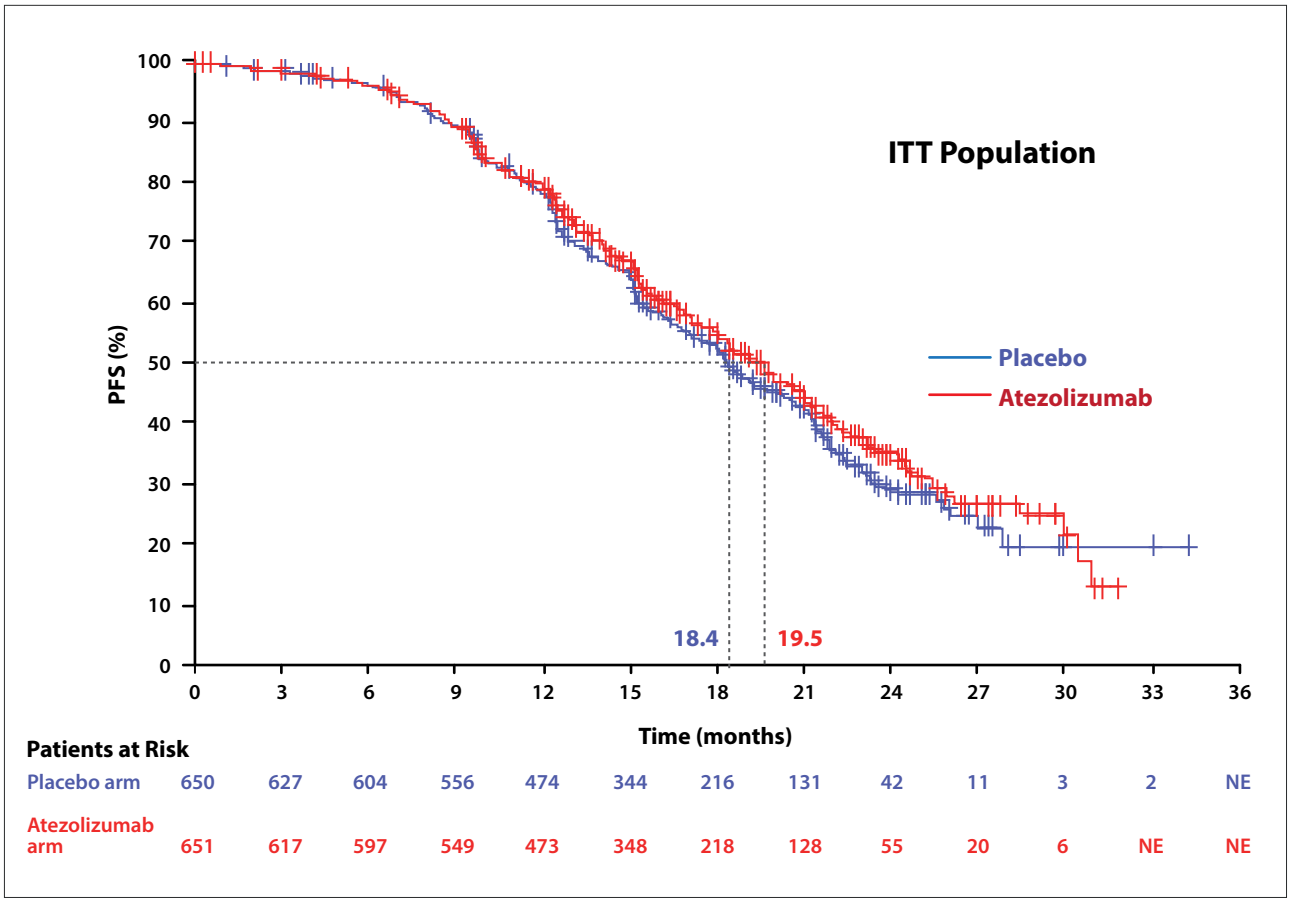

Figure 6. Progression-free survival in the intention-to-treat population of the phase 3 IMagyn050 trial, which evaluated atezolizumab vs placebo, in combination with bevacizumab, carboplatin, and paclitaxel, as first-line therapy. ITT, intention-to-treat; NE, not estimable; PFS, progression-free survival. Adapted from Moore K et al. ESMO abstract LBA31. *Ann Oncol.* 2020;31(suppl 4):S1162-S1163.[1]

based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and OS.

The intention-to-treat population included 650 patients in the atezolizumab arm and 651 in the placebo arm. PD-L1 was detected in at least 1% of immune cells in 60% of patient. The median PFS in the intention-to-treat population was 18.4 months with placebo vs 19.5 months with atezolizumab (HR, 0.92; 95% CI, 0.79-1.07; *P*=.2785; Figure 6).

Among patients with at least 1% PD-L1 expression in the immune cell infiltrate, the median PFS was 18.5 months with placebo vs 20.8 months with atezolizumab (HR, 0.80; 95% CI, 0.65-0.99; *P*=.0376). OS data at the first interim analysis were immature. The median OS in the intention-to-treat population was not evaluable for either arm (HR, 0.96; 95% CI, 0.74-1.26; *P*=.7887). Among patients with at least 1% PD-L1 expression in the immune cells, the median OS was 31.2 months with placebo vs not evaluable with atezolizumab (HR, 0.98; 95% CI, 0.68-1.41; *P*=.9083). Subgroup analysis suggested a potential benefit with atezolizumab in patients who had stage III disease (HR, 0.80; 95% CI, 0.67-0.97). However, subgroups based on age, race, baseline ECOG performance status, treatment approach, and histology did not show a benefit with atezolizumab vs placebo. Treatment with atezolizumab appeared beneficial among patients with at least 5% PD-L1 expression in immune cells in the tumor section (HR, 0.64; 95% CI, 0.43-0.96) and among patients with at least 1% PD-L1 expression in the tumor cells (HR, 0.41; 95% CI, 0.19-0.90).

The safety profile of the novel treatment combination was consistent with prior observations. Serious adverse events were observed in 33% of patients in the placebo arm vs 47% in the atezolizumab arm. Treatment-related serious adverse events were observed in 21% vs 35%, respectively.

Reference

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Efficacy and Safety of Niraparib in Older Patients With Advanced Ovarian Cancer: Results From the PRIMA/ENGOT-OV26/GOG-3012 Trial

The standard-of-care treatment for ovarian cancer is the same for older and younger patients, but older patients may be at greater risk for severe toxicities and treatment discontinuation.[1] The PRIMA trial evaluated the safety and efficacy of niraparib maintenance therapy among patients with ovarian cancer who responded to first-line treatment with a platinum-based regimen. An earlier analysis reported a median PFS of 13.8 months with niraparib vs 8.2 months with placebo (HR, 0.62; 95% CI, 0.50-0.76; *P*<.001) among patients in the intention-to-treat population.[2] A retrospective study examined the effect of age on the safety and efficacy of niraparib in the PRIMA trial.[3] For the evaluation of outcomes, patients were divided into age groups of younger than 65 years vs 65 years or older, and of younger than 75 years vs 75 years or older. Progression was assessed by computed tomography or magnetic resonance imaging every 12 weeks. Patient-related outcomes were assessed by means of questionnaires administered at screening, throughout treatment, and at 4, 8, 12, and 24 weeks after the last dose of niraparib or placebo.

Among 733 enrolled patients, 444 were younger than 65 years and 289 were 65 years or older; 657 patients were younger than 75 years and 76 were 75 years or older. Patients ages 65 years or older and 75 years or older were more likely than younger patients to have a high ECOG performance status score at baseline. Patients age 75 years or older were more likely to have stage IV disease. Homologous recombination proficiency was more common in patients ages 65 years or older and 75

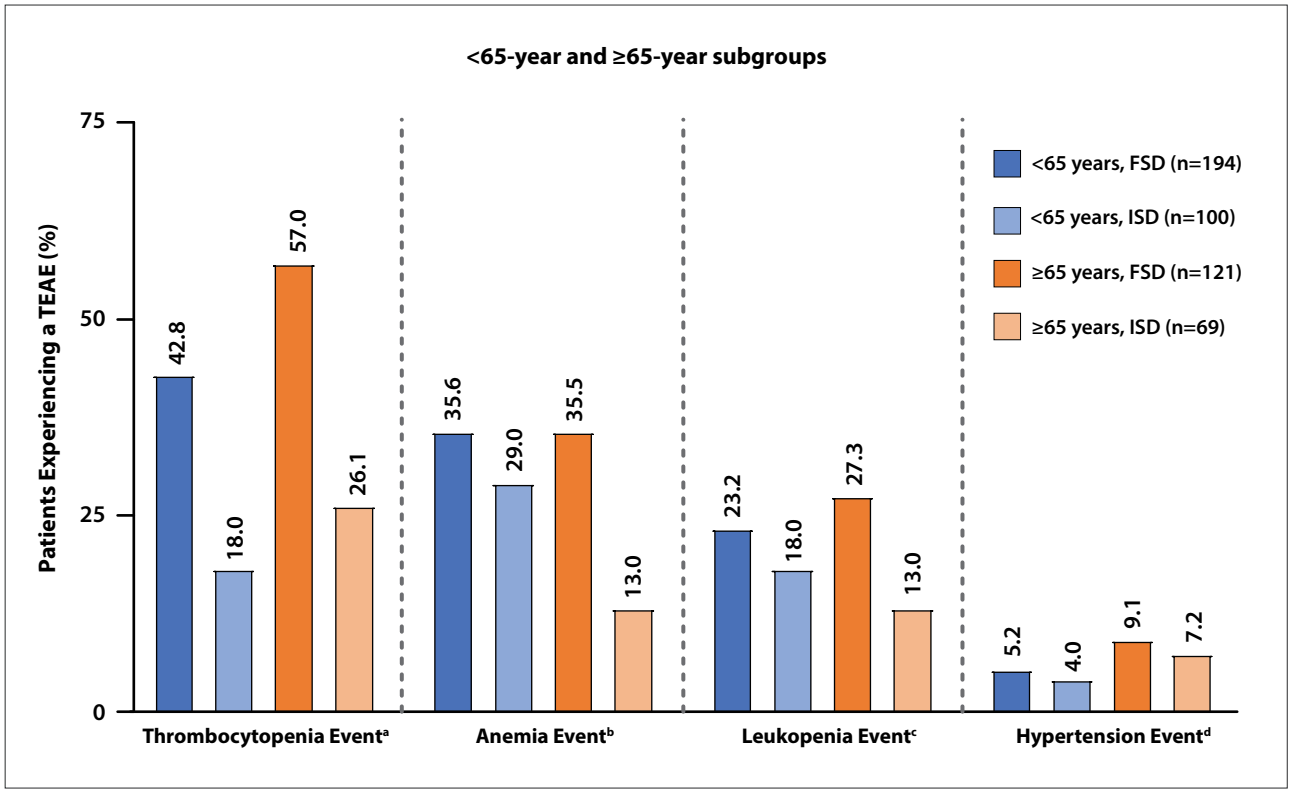

Figure 7. Grade 3 or higher treatment-emergent adverse events according to age (<65 years vs ≥65 years) among patients treated with a fixed starting dose or an individualized starting dose of niraparib in the phase 3 PRIMA/ENGOT-OV26/GOG-3012 trial. [a]Includes thrombocytopenia and platelet count decrease. [b]Includes anemia, hemoglobin decrease, and macrocytic anemia. [c]Includes neutropenia, neutrophil count decrease, leukopenia, white blood cell count decrease, neutropenic sepsis, and febrile neutropenia. [d]Includes hypertension and blood pressure increase. FSD, fixed starting dose; ISD, individualized starting dose; TEAE, treatment-emergent adverse event. Adapted from Valabrega G et al. ESMO abstract 819P. *Ann Oncol.* 2020;31(suppl 4):S619.[3]

years or older. Neoadjuvant chemotherapy was administered at similar rates to all age groups.

Among patients younger than 65 years, the median PFS was 13.9 months with niraparib vs 8.3 months with placebo (HR, 0.61; 95% CI, 0.47-0.81). Among those 65 years or older, the median PFS was 13.7 months vs 8.1 months, respectively (HR, 0.53; 95% CI, 0.39-0.74). Niraparib was also superior to placebo in patients who were younger than 75 years (median PFS, 13.8 vs 8.2 months; HR, 0.62; 95% CI, 0.50-0.77) and in those 75 years or older (median PFS, 13.8 vs 5.6 months; HR, 0.37; 95% CI, 0.17-0.81).

Across all age cohorts, treatment-emergent adverse events were more frequent with niraparib compared with placebo. Rates of treatment-emergent adverse events were generally similar in patients younger than 65 years vs those 65 years or older, as well as in patients younger than 75 years vs those 75 years or older. Among patients treated with niraparib, thrombocytopenia of any grade was reported in 70.5% of those 65 years or older vs 63.6% in younger patients. Grade 3 or higher thrombocytopenia was reported in 45.8% vs 34.4%, respectively. Similarly, thrombocytopenia of any grade was more common among patients 75 years or older than in younger patients (77.8% vs 64.9%), as was thrombocytopenia of grade 3 or higher (53.7% vs 37.0%). Tailoring the dose of niraparib based on patient characteristics reduced the rates of grade 3 or higher thrombocytopenia from 42.8% to 18.0% in patients younger than 65 years and from 57.0% to 26.1% in older patients (Figure 7). Similarly, a personalized dosing regimen was associated with a reduction in the rate of grade 3 or higher thrombocytopenia in patients younger than 75 years (from 46.4% to 19.7%) and in those 75 years or older (from 62.2% to 35.3%). Patient-related outcomes, including FOSI scores and EQ-5D-5L results, were similar across all age cohorts.

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Maintenance Olaparib Plus Bevacizumab in Patients With Newly Diagnosed, Advanced High-Grade Ovarian Carcinoma

Olaparib was investigated as a maintenance therapy in combination with bevacizumab in the phase 3 PAOLA-1/ENGOT-ov25 trial.[1,2] The trial enrolled women with stage III/IV, high-grade serous or endometrioid ovarian, fallopian tube, and/or primary peritoneal cancer. Enrolled patients had responded to first-line therapy with platinum and a taxane, plus at least 2 cycles of bevacizumab. All patients received bevacizumab (15 mg/kg every 3 weeks) for a total of 15 months. In addition, patients were randomly assigned in a 2:1 ratio to receive olaparib tablets (300 mg) or placebo twice daily for 2 years. Stratification factors included presence of the *BRCA* mutation and first-line response. The primary endpoint was investigator-assessed PFS according to RECIST 1.1. In the primary analysis of PAOLA-1, the median PFS was 22.1 months with olaparib plus bevacizumab vs 16.6 months with bevacizumab alone (HR, 0.59; 95% CI, 0.49-0.72; *P*<.001).[2]

The PAOLA-1 trial included a secondary endpoint of PFS2, which was measured from the time of randomization to second progression or death.[1] The prespecified analysis of PFS2 was planned for approximately 53% data maturity or 1 year after the primary analysis. The median follow-up was 35.5 months in the olaparib arm and 36.5 months in the placebo arm. A significant PFS2 benefit was observed with the addition of olaparib to bevacizumab in the intention-to-treat population, with a median PFS2 of 36.5 months in the olaparib arm vs 32.6 months in the placebo arm (HR, 0.78; 95% CI, 0.640.95; *P*=.0125). PARP inhibitors were administered during the first subsequent treatment to 9.1% of patients in the olaparib arm vs 26.8% in the placebo arm. A subgroup analysis showed a superior median PFS2 with olaparib vs placebo among patients with HRD-positive disease. This improvement was observed in an analysis that included patients with the *BRCA* mutation (50.3 vs 35.3 months; HR, 0.56; 95% CI, 0.41-0.77), as well as in an analysis that excluded these patients (50.3 vs 30.1 months; HR, 0.60; 95% CI, 0.38-0.96). The median PFS2 was similar in patients with negative or unknown HRD status (26.3 vs 28.1 months; HR, 0.98; 95% CI, 0.77-1.27). The PFS2 improvement was supported by a significant increase in time to second subsequent therapy in the intention-to-treat population (38.2 vs 31.5 months; HR, 0.78; 95% CI, 0.64-0.95; *P*=.0115). OS data were immature, and did not reveal a survival difference between the olaparib arm and the placebo arm. The median OS was not reached with olaparib vs 45.8 months with placebo (HR, 0.93; 95% CI, 0.74-1.18; *P*=.5631). No new safety signals were observed.

A separate analysis evaluated response rates among the 216 patients

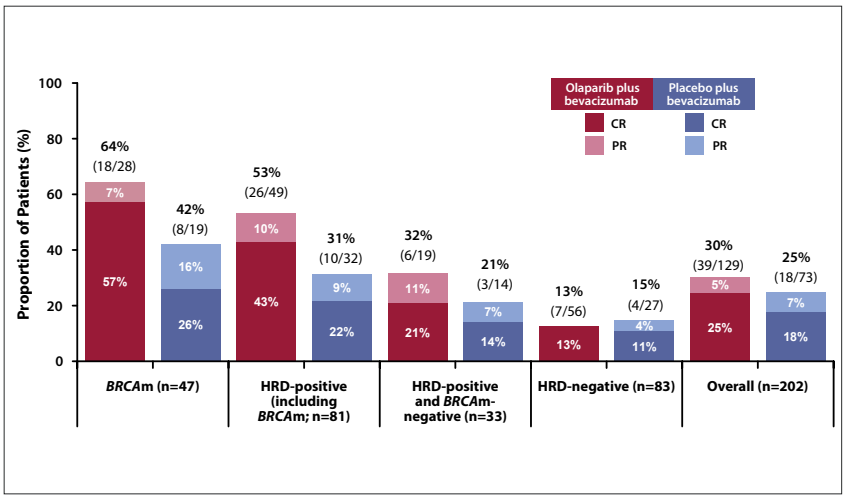

Figure 8. Objective response rates in the phase 3 PAOLA-1 trial of olaparib. *BRCA*m, *BRCA* mutation; CR, complete response; HRD, homologous recombination–deficient; PR, partial response. Adapted from Colombo N et al. ESMO abstract 812MO. *Ann Oncol.* 2020;31(suppl 4):S614.[3]

with evidence of disease according to RECIST and/or CA-125 levels at least twice the upper level of normal at study entry.[3] Baseline characteristics were generally well balanced between the cohorts. Approximately 75% of patients had undergone surgery. The *BRCA* mutation was observed in 21% of patients in the olaparib arm vs 26% of those in the placebo arm; 37% vs 45% of patients, respectively, were HRD-positive. Treatment was discontinued by 78% of patients in the olaparib arm vs 82% in the placebo arm. Reasons included progression (58% vs 71%) and adverse events or symptomatic progression (16% vs 4%).

Among patients with the *BRCA* mutation, the objective response rate (ORR) was 64% (18/28) with olaparib plus bevacizumab vs 42% (8/19) with placebo plus bevacizumab (Figure 8). Among the HRD-positive patients, including those with the *BRCA* mutation, the ORR was 53% (26/49) with olaparib vs 31% (10/32) with placebo. Among HRD-positive patients with *BRCA*-negative tumors, the ORR was 32% (6/19) with olaparib vs 21% (3/14) with placebo. In patients who were HRD-negative, the ORR was 13% (7/56) with olaparib vs 15% (4/27) with placebo.

Patients with evidence of disease or elevated CA-125 levels at study entry comprised 30% of the olaparib arm vs 25% of the control arm. Among patients with elevated CA-125 levels at study entry, ORR was 36% with olaparib plus bevacizumab vs 29% with placebo plus bevacizumab. Similarly, among the entire cohort of patients with evidence of disease and/or elevated CA-125 at baseline, ORR was 35% vs 28%, respectively.

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Health-Related Quality of Life in Patients With Newly Diagnosed Stage III or IV Ovarian Cancer Treated With Veliparib + Chemotherapy Followed by Veliparib Maintenance

Health-related quality of life was evaluated in the phase 3 VELIA trial of veliparib in patients with newly diagnosed, advanced-stage ovarian cancer.[1,2] After stratification according to surgery, residual disease, paclitaxel schedule, disease stage, geographic region, and germline *BRCA* mutation status, 1140 patients were randomly assigned to 1 of 3 arms. Patients in the control arm received placebo and carboplatin (every 3 weeks)/paclitaxel (every 1 or 3 weeks) for 6 cycles, followed by placebo monotherapy. Patients in the veliparib arm received veliparib (150 mg twice daily) and carboplatin/paclitaxel for 6 cycles, followed by placebo monotherapy. Patients in the veliparib maintenance arm were treated with 6 cycles of veliparib, carboplatin, and paclitaxel followed by maintenance veliparib monotherapy (400 mg twice daily) for cycles 7 to 36.

The VELIA trial met its primary endpoint. The median PFS was 34.7 months with veliparib maintenance vs 22.0 months with placebo (HR, 0.44; 95% CI, 0.28-0.68; $P<.001$). Veliparib maintenance improved the median PFS in the intention-to-treat population and in the subgroup of HRD-positive patients ($P<.001$).

The trial investigators assessed health-related quality of life through administration of the National Comprehensive Cancer Network Functional Assessment of Cancer Therapy Ovarian Symptom Index–18 (NFOSI-18) and

the EQ-5D-5L.[2] The rate of on-study adherence was greater than 90%. Baseline demographics were similar among all 3 treatment arms. The NFOSI-18 questionnaire generates information in 4 domains. Scores improved in the domains of disease-related symptoms (Figure 9), side effects, and functional well-being across all 3 arms. Improvements in the veliparib maintenance arm were smaller than those observed in the other 2 arms; however, no meaningful clinical differences were observed between the veliparib maintenance arm and the placebo arm. Emotional well-being scores remained between 0 and 1 for all 3 arms throughout the 35 weeks queried.

Similar outcomes were observed with the EQ-5D-5L questionnaire. Both the health index score and the overall health score improved across all 3 treatment arms. Scores from the veliparib maintenance arm were numerically lower than those in the placebo arm, but the difference was not clinically meaningful. Time to symptom worsening was similar for all 3 treatments, according to the NFOSI-18 questionnaire. Across the 3 treatment arms, time to symptom worsening ranged from 9.8 to 10.2 months for emotional well-being, from 6.5 to 7.7 months for treatment side effects, and from 6.9 to 8.1 months for functional well-being.

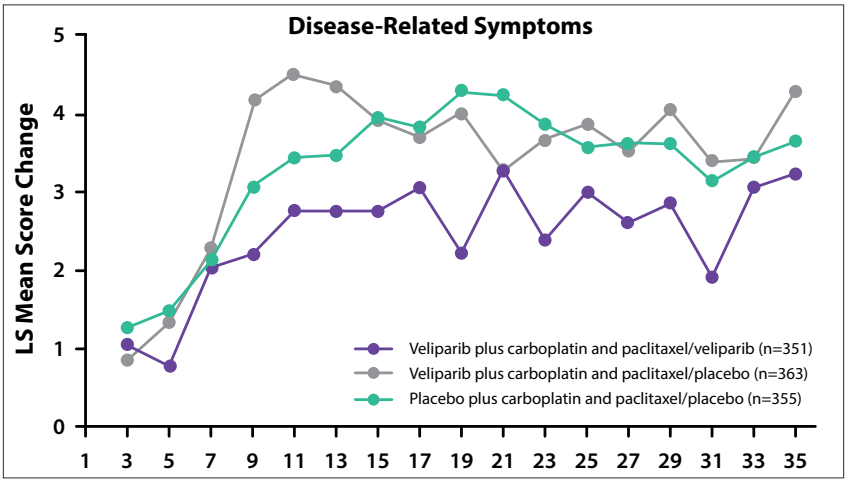

Figure 9. Disease-related symptoms according to treatment group among patients in the phase 3 VELIA trial. LS, least squares. Adapted from Cella D et al. ESMO abstract 809MO. *Ann Oncol.* 2020;31(suppl 4):S612.[2]

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INOVATYON Study: Randomized Phase III International Study Comparing Trabectedin/PLD Followed by Platinum at Progression vs Carboplatin/PLD in Patients With Recurrent Ovarian Cancer Progressing Within 6 to 12 Months After Last Platinum Line

The INOVATYON trial evaluated trabectedin plus pegylated liposomal doxorubicin, followed by platinum rechallenge at disease progression.[1] This phase 3 study recruited patients with relapsed ovarian cancer and an interval of between 6 and 12 months after cessation of first- or second-line platinum therapy. The patients were randomly assigned to receive either trabectedin (1.1 mg/m^2) plus pegylated liposomal doxorubicin (30 mg/m^2) every 3 weeks or carboplatin (AUC, 5 mg/mL·min) plus pegylated liposomal doxorubicin (30 mg/m^2) every 4 weeks. All patients in the trabectedin arm received subsequent platinum challenge at disease progression, whereas patients in the carboplatin arm received subsequent therapy according to the investigator's discretion. The tumors were evaluated according to RECIST at 12 and 24 weeks. The primary endpoint was OS with an HR of 0.75. Secondary endpoints included PFS, safety, and quality of life.

The trial recruited more than 600 patients at 117 European sites. Patient characteristics were well balanced in the 2 arms. Most patients had serous histology (83.2%-86.0%), and 72% of patients had measurable disease at study entry. *BRCA* was mutated in 9.2% to 13.4% of patients and wild-type in 40.1% to 46.7% of patients. (Mutation status was unknown in 44.1% to 46.6% of patients in the 2 arms.) In both arms, 69.7% of patients had received 1 prior line of treatment. Prior anthracycline-based chemotherapy was reported in 9.2% to 9.8% of patients, and the most recent platinum-free interval was 8.3 to 8.4 months.

At least 6 treatment cycles were administered to 68.1% of patients in the carboplatin arm vs 53.4% in the

trabectedin arm. The most common reason for treatment interruption was disease progression (64.0% vs 50.0%, respectively), followed by unacceptable toxicity (15.1% vs 19.3%).

After a median follow-up of 44 months, the trial failed to reach its primary endpoint. The median OS was 21.3 months in the carboplatin arm vs 21.5 months in the trabectedin arm (HR, 1.10; 95% CI, 0.92-1.32; *P*=.284; Figure 10). The median PFS was 9.0 months vs 7.5 months, respectively (HR, 1.26; 95% CI, 1.07-1.49; *P*=.005). Subsequent therapy, reported in 74.0% of patients in the carboplatin arm vs 73.6% of those in the trabectedin arm, consisted of platinum-based therapy in 17.8% vs 63.2%, respectively. PARP inhibitors were administered as maintenance therapy in subsequent treatment lines to 11.5% vs 15.0% of patients, respectively, and were administered to 6.6% vs 0.3% as maintenance after study treatment.

The secondary endpoint of PFS after subsequent therapy was 5.7 months in the carboplatin arm vs 7.4 months in the trabectedin arm (HR, 0.84; 95% CI, 0.70-1.02; *P*=.086). Subgroup analysis suggested a trend in favor of carboplatin in patients who had received 1 prior line of treatment (HR, 1.22; 95% CI, 0.98-1.52). A trend in favor of trabectedin was noted among patients who had received 2 prior lines of treatment (HR, 0.87; 95% CI, 0.63-1.22). Among patients who had received only 1 prior line of treatment, the median PFS was superior with carboplatin vs trabectedin (HR, 1.42; 95% CI, 1.17-1.73; *P*<.001). The median PFS was similar in the 2 arms among patients who had received 2 prior lines of treatment (HR, 1.03; 95% CI, 0.76-1.39; *P*=.863). The median OS showed a trend in favor of carboplatin among patients with 1 prior line of treatment (HR, 1.22; 95% CI, 0.98-1.52; *P*=.073). No difference in OS emerged between the 2 treatment arms among patients who had received 2 prior lines of therapy (HR, 0.87; 95% CI, 0.63-1.22; *P*=.426). Adverse events of grade 3 or higher were reported in 36% of patients in the carboplatin arm vs 69% of those in the trabectedin arm (*P*<.001). Grade 3/4 adverse events that were more common in the trabectedin arm included hematologic toxicities, gastrointestinal toxicities, hepatotoxicity, and asthenia.

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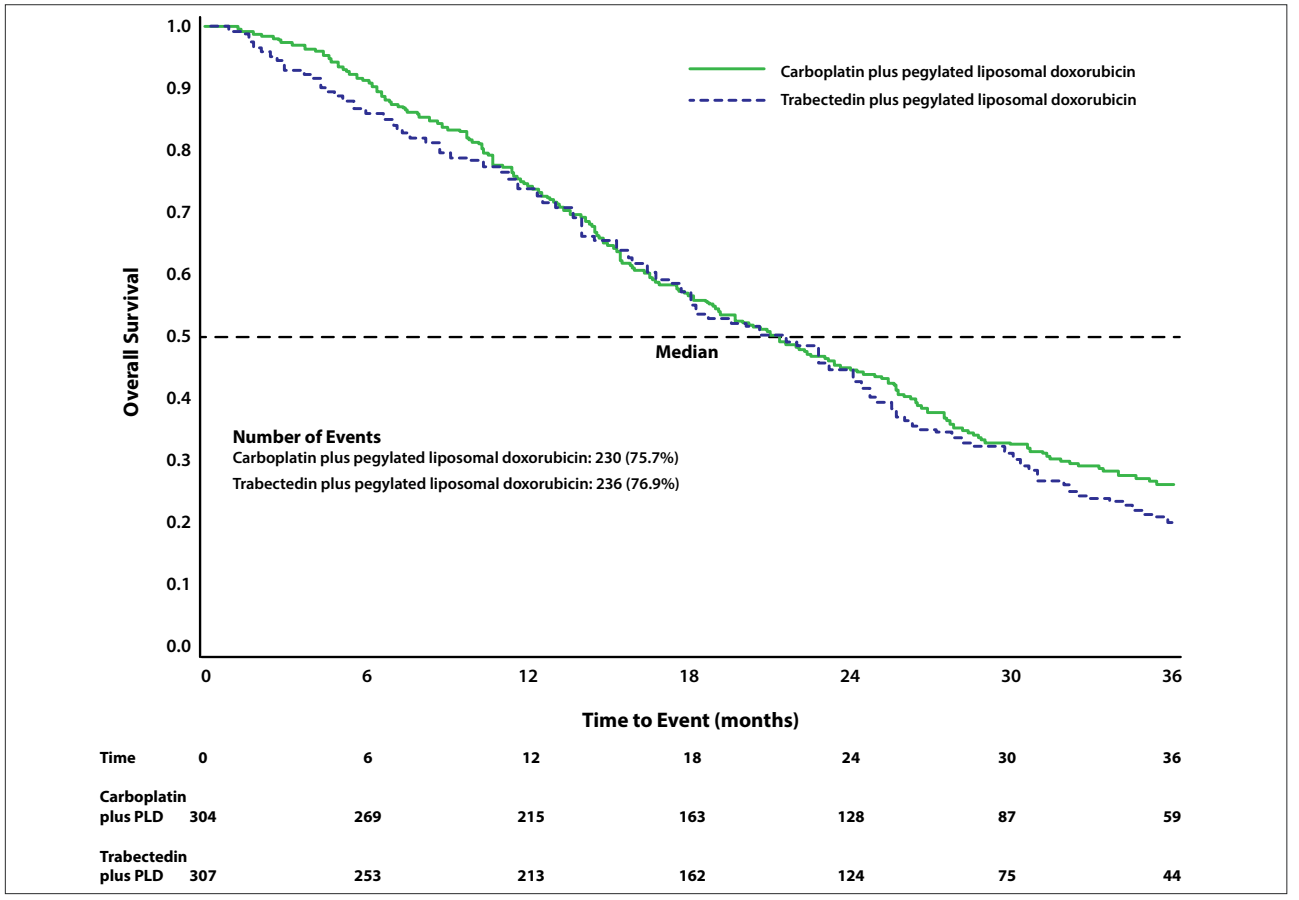

Figure 10. Median overall survival in the phase 3 INOVATYON trial of carboplatin vs trabectedin. PLD, pegylated liposomal doxorubicin. Adapted from Colombo N et al. ESMO abstract LBA30. *Ann Oncol*. 2020;31(suppl 4):S1161.[1]

Highlights in Ovarian Cancer From the European Society for Medical Oncology Virtual Congress 2020: Commentary

Thomas J. Herzog, MD

Several presentations at the European Society for Medical Oncology (ESMO) Virtual Congress 2020 provided important insights into the management of patients with ovarian cancer. Data were presented on the poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors olaparib and niraparib, as well as novel immunotherapy and chemotherapy regimens.

PARP Inhibitors

Olaparib

Dr Susana Banerjee and colleagues provided an updated analysis of the SOLO-1 trial.[1] This trial compared olaparib vs placebo among patients with newly diagnosed ovarian cancer. The patients had stage III/IV disease (per criteria from the International Federation of Gynecology and Obstetrics) with high-grade serous or endometrioid histology and confirmed *BRCA* mutations. They had an Eastern Cooperative Oncology performance status of 0 or 1. Patients had undergone cytoreductive surgery, and they had a complete response or a partial response after receiving platinum-based chemotherapy. The patients were randomly assigned 2:1 to maintenance therapy with olaparib (n=260) or placebo (n=131). Patients were treated for up to 2 years (and some were treated beyond 2 years). The primary endpoint was investigator-assessed progression-free survival (PFS). An initial report was published in 2018.[2] The median PFS was not reached with olaparib vs 13.8 months with the control. In the updated analysis presented at the 2020 ESMO meeting, the final median PFS was 56.0 months with olaparib vs 13.8 months with the control (hazard ratio [HR], 0.33; 95% CI, 0.25-0.43).[1] The median duration of treatment in the olaparib arm was 25 months, which suggests a sustained clinical effect even after treatment cessation. Among the subgroup of patients who had developed a complete response to platinum therapy, the median PFS was not reached in the olaparib arm vs 15.3 months in the placebo arm (HR, 0.37).

The delta in the median PFS between the treatment groups exceeded 42 months. It is rare to see such a large difference between 2 experimental arms in a clinical trial. These results are remarkable because they allow clinicians to consider the significant magnitude of effect observed with use of frontline maintenance PARP inhibitors in patients with a *BRCA* mutation. These data are practice-changing, in that PARP inhibitors continue to be used in new roles that are reinforced with impressive data from each subsequent trial. Several active PARP inhibitors are now approved for the treatment of ovarian cancer. These data contribute to the overall findings that PARP inhibitors are extremely effective in this setting, especially for patients with a *BRCA* mutation, as well as those with homologous recombination deficiency ([HRD]; notably, only *BRCA*-mutated patients were included in the SOLO-1 trial).

Another important finding is that no new safety signals were observed, and the trial did not demonstrate a spike in myelodysplastic syndromes (MDS) or acute myelogenous leukemia (AML). This observation is important because the SOLO-2 trial of platinum-sensitive maintenance therapy showed an increase in MDS/AML.[3] The rate of MDS reached 8% in the long-term analysis of overall survival, which exceeded 12 months and favored the olaparib arm. Fortunately, SOLO-1 did not show a similar increase despite the longer follow-up, which is reassuring in this primary setting.[1] Further surveillance is needed to confirm the safety of long-term treatment, as well as to evaluate the possibility of reaching the elusive goal of curing more women in the frontline setting by adding PARP inhibition maintenance. The possibility of this exciting outcome was raised by the SOLO-1 clinical trial, and thus we eagerly await mature overall survival data.

Niraparib

Dr Bhavana Pothuri and colleagues presented patient-reported outcomes from the PRIMA trial, which evaluated the use of niraparib in patients with newly diagnosed stage III/IV ovarian cancer at high risk for recurrence.[4,5] The trial enrolled patients with a complete response or a partial response after 6 to 9 cycles of first-line platinum-based chemotherapy. The patients were randomly assigned in a 2:1 ratio to maintenance with niraparib or placebo. The primary endpoint was PFS among HRD-positive patients and in the overall intention-to-treat population, as determined by hierarchical testing. Niraparib improved PFS in both subgroups. Among HRD-positive patients, the median PFS was 21.9 months with niraparib vs 10.4 months with placebo (HR for disease progression or death, 0.43; 95% CI, 0.31-0.59; $P<.001$). In the overall population, the PFS was 13.8 months vs 8.2 months, respectively (HR, 0.62; 95% CI, 0.50-0.76; $P<.001$).

This trial administered treatment for 36 months, which raised the question of whether patients would experience any significant detrimental effects that would not be captured by standard

toxicity reporting. To assess patient-reported outcomes, the PRIMA investigators administered questionnaires at baseline, every 8 weeks for the first 56 weeks, and then every 12 weeks. The questionnaires included the Functional Assessment of Cancer Therapy–Ovarian Symptom Index,[6] the European Quality of Life 5-Dimension 5-Level questionnaire,[7] the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire,[8] and the EORTC Quality of Life Questionnaire Ovarian Cancer module.[9]

No statistically significant differences between niraparib and placebo were identified by any of the patient-reported outcome instruments. It appeared that patients in the niraparib arm experienced no detrimental effects, despite receiving active therapy for many years. Another reassuring observation is that the reporting adherence rates were very high, which is unusual in these types of studies. There is typically a tremendous drop-off, especially in the placebo arm and in patients with progressive disease. This finding speaks to a very well-conducted study, in that more than 80% of the patients completed the questionnaires.

Quality of life was comparable between the treatment arms, as were reports of gastrointestinal symptoms. These results are similar to the patient-reported outcomes from the NOVA trial, which evaluated niraparib in platinum-sensitive recurrent ovarian cancer.[10] Niraparib did not have a detrimental impact in the NOVA trial. Most of the toxicities associated with niraparib are laboratory-based, and do not greatly impact the patient's quality of life. For example, a low platelet count—as long as there is no bleeding—will not measurably impact a patient's quality of life. This analysis provides reassuring data for patients who receive PARP inhibitors as maintenance therapy for many years.

A concern related to assessment of patient-reported outcomes is the quality of the tools. The conclusions are only as strong as the available tools. Analysis of the PRIMA trial appeared to provide an accurate assessment.[4] In other studies, however, there have been discrepancies between treatment toxicity profiles and patient-reported outcomes. It appears that some instruments can miss the impact that toxicities have on quality of life. Investigators should continue to explore patient-related outcomes in clinical trials, and more sensitive tools are needed.

Dr Giorgio Valabrega and colleagues reported on the efficacy and safety of niraparib in older patients with advanced ovarian cancer.[11] This analysis is based on data from the PRIMA trial.[5] It should be noted that after a study amendment, approximately one-third of patients in the PRIMA trial received an individualized starting dose based on their body weight and platelet count. Among the 733 patients enrolled in the trial, 444 were younger than 65 years, and 289 were ages 65 years or older. The trial enrolled 76 patients ages 75 years or older, leaving 657 patients younger than 75 years. The efficacy of niraparib was comparable among all age groups. If anything, the benefit of niraparib might have been stronger in older patients. Among patients younger than 65 years, the median PFS was 13.9 months with niraparib vs 8.2 months with placebo (HR, 0.61; 95% CI, 0.47-0.81). Among patients ages 65 years and older, the median PFS was 13.7 months vs 8.1 months, respectively (HR, 0.53; 95% CI, 0.39-0.74). The treatment-emergent adverse events were similar among the age groups. Quality of life did not appear to differ.

Overall, this analysis showed that the efficacy of niraparib was not decreased in older patients. It is clear that niraparib can be used to successfully treat geriatric patients. An encouraging finding is that, with the individualized starting dose of niraparib, rates of thrombocytopenia, anemia, and neutropenia were significantly reduced. Most toxicities were similar between younger and older patients. Thrombocytopenia occurred in 64% of patients younger than 65 and in 78% of those 75 years and older, while grade 3/4 thrombocytopenia occurred in 34% of patients younger than 65 and in 54% of those ages 75 years and older. This analysis supported the use of PARP inhibitors in older patients. Efficacy was not diminished, and toxicity—with the exception of thrombocytopenia—was similar between younger and older patients.

Dr Xiaohua Wu and coworkers presented the phase 3 NORA trial, which evaluated an individualized starting dose of niraparib among 240 Chinese patients with platinum-sensitive recurrent ovarian cancer and either a germline *BRCA* mutation or a high-grade serous histologic subtype.[12] The patients had a complete or partial response to the platinum therapy. This trial was conducted in 32 centers in China; the data were not drawn from a larger trial, as is often the case for data sets focusing on certain demographic features. Previous phase 1 data appeared to show similar pharmacokinetics between White and Chinese patients treated with niraparib.[13] The NORA trial aimed to identify any differences in metabolism, pharmacokinetics, or other issues that could impact efficacy or toxicity.

The individualized starting dose of niraparib was introduced into the PRIMA trial after the enrollment of approximately two-thirds of patients, and this modification prospectively demonstrated the reduction in hematologic toxicity—especially thrombocytopenia—with niraparib.[5] The NORA trial was initiated after the PRIMA trial, and the investigators administered an individualized starting dose to all but 16 patients.

The 256 patients were randomly assigned to niraparib or placebo in a 2:1 ratio. The individualized starting dose of niraparib was based on "weights and plates." The dose was 200 mg/day for patients whose body weight at baseline was less than 77 kg or whose platelet

count was less than 150,000/µL. The dose was 300 mg in all other patients (including the 16 patients treated before the dosing amendment). The primary endpoint was PFS according to blinded independent review. The median PFS was 18.3 months with niraparib vs 5.4 months with placebo (HR, 0.32; 95% CI, 0.23-0.45; *P*<.0001). Rates of grade 3 or higher treatment-emergent adverse events were higher in the niraparib arm, and mostly consisted of neutropenia and platelet-count disturbances or anemia. Data from breast cancer and other malignancies have suggested that some patients exhibit idiosyncratic pharmacokinetics after treatment with PARP inhibitors,[14] but this has not been seen in patients with ovarian cancer. Data from the NORA trial were reassuring, in that the benefits previously seen with niraparib were maintained among Chinese patients.

In terms of toxicity, it appears that the individualized starting dose was equal to the standard dose. There were no new safety signals in the study. The individualized dose appeared to decrease the amount of platelet abnormalities. In the niraparib arm, only 11% of patients developed grade 3 or higher thrombocytopenia. Overall, the results of the NORA study were very encouraging, supporting the applicability of niraparib in the real world while providing insight into the most effective use of PARP inhibitors in these patients.

Immunotherapy

Atezolizumab

Dr Kathleen Moore and colleagues presented results of the randomized phase 3 IMagyn050/GOG 3015/ENGOT-OV39 trial, which compared atezolizumab plus bevacizumab vs bevacizumab alone in patients with newly diagnosed stage III/IV ovarian cancer.[15] Atezolizumab is a programmed death ligand 1 (PD-L1) checkpoint inhibitor that has demonstrated efficacy in other cancers.[16,17] Some data have shown that immuno-oncology agents have some effects in ovarian cancer,[18] even though this disease does not have a high mutational burden. Furthermore, there is reason to believe that the combination of an immuno-oncology agent and a vascular endothelial growth factor blocker might promote T-cell infiltration in the tumor bed. This activity boosts the anti-tumor immune response and decreases the amount of T suppressor cells associated with a hypoxic microenvironment, which is reversed with improved blood flow. There is also some thought that normalizing or "pruning" the vessels will increase drug delivery. This effect might help these agents work together following chemotherapy.

This trial enrolled 1301 patients with newly diagnosed untreated stage III/IV ovarian cancer who underwent either primary cytoreductive surgery with gross residual disease (if stage III) or neoadjuvant chemotherapy and interval surgery.[15] The patients had a performance status of 0 to 2. All patients received treatment with carboplatin and paclitaxel (cycles 1-6) plus bevacizumab (cycles 1-22, except for perioperative cycles). Patients were randomly assigned to receive this treatment with atezolizumab or placebo, for up to 22 cycles. The co–primary endpoints were investigator-assessed PFS and overall survival. The PFS was statistically assessed in the PD-L1 and intention-to-treat populations, simultaneously using a *P* value threshold of <.002. Stratification factors included stage, performance status, adjuvant vs neoadjuvant treatment, and PD-L1 status (immunohistochemistry <1% vs >1%; per the Ventana SP142 assay). The demographic factors were well balanced between the treatment groups.

Unfortunately, there was no significant difference in PFS between the treatment arms. In the intention-to-treat population, the median PFS was 19.5 months with atezolizumab vs 18.4 months without atezolizumab (HR, 0.92; 95% CI, 0.79-1.07; *P*=.2785). Among the PD-L1–positive patients, the median PFS was 20.8 months vs 18.5 months, respectively (HR, 0.80; 95% CI, 0.65-0.99; *P*=.0376, where the threshold for significance was set at *P*<.002). Still, the Kaplan-Meier curves were very close. Data for overall survival were too immature for meaningful assessment. There were no major differences in safety outcomes, and no new safety signals were identified.

There might have been a signal that atezolizumab was beneficial in patients with PD-LI immunohistochemistry staining on tumor-infiltrating immune cells of 5% or higher. It might be necessary to use a cutoff exceeding 10% to identify patients who might benefit. Many of the cutoffs were derived from other cancers, such as lung cancer, and therefore might not be applicable in ovarian cancer; furthermore, the tumor mutational burden for ovarian cancer is relatively low. It remains to be seen whether there could be an advantage in these populations with a higher PD-L1 cut point. Among the group of patients with the highest level of PD-L1 expression (≥5), the unstratified HR was 0.64.

It is unfortunate that this trial did not meet the primary endpoint. There was not even a clinically meaningful trend for PFS improvement in the overall population. It would be of interest to perform an exploratory analysis in the population of patients with PD-L1 expression of 5% or higher. Data for overall survival will also be of interest. In the past, some trials of immunotherapy in ovarian cancer showed modest to very minimal gains in PFS, but then showed a significant improvement in overall survival

Immunotherapy with the checkpoint inhibitor avelumab did not improve outcome in previous studies, such as the frontline JAVELIN 100 trial.[19] The JAVELIN 200 trial of platinum-resistant ovarian cancer was also a negative trial.[20] These trials did not evaluate outcome according to PD-L1 status. The IMagyn050/GOG 3015/ENGOT-OV39 trial highlighted

the importance of incorporating PD-L1 expression. There is no question that immuno-oncology agents are extremely active. However, it appears that ovarian cancers are too "cold" to benefit. Basic science research is needed to explore the possibility of altering these cold tumors into hot tumors to increase the efficacy of immuno-oncology agents. More translational science is needed before hundreds of millions of more dollars are invested into randomized phase 3 trials.

Durvalumab

Dr Yvette Drew presented results of the phase 2 MEDIOLA trial, which evaluated olaparib plus durvalumab and bevacizumab in patients with non-germline, *BRCA*-mutated platinum-sensitive relapsed ovarian cancer.[21] It is thought that PARP inhibition creates more neoantigens that upregulate PD-L1 expression, thereby increasing DNA damage and thus making these agents more effective. Previous data have shown that the combination of vascular endothelial growth factor inhibitors and PARP inhibitors increased PFS in patients with ovarian cancer.[22] The initial cohort analysis of MEDIOLA showed that olaparib plus durvalumab was well tolerated and had good clinical activity. Additional cohorts were added to test the combination of a PARP inhibitor plus an immuno-oncology agent, with or without bevacizumab.

The trial enrolled patients who had received 2 or fewer prior lines of therapy.[21] The patients had not received a PARP inhibitor or an immuno-oncology agent. The patients' median age was similar between the treatment groups. The primary endpoint was the rate of disease control at 24 weeks, with the efficacy target set at 80%. The target was 80%. Secondary endpoints encompassed safety and tolerability. This small study treated just over 30 patients in each arm.

The disease control rate at 24 weeks was 77% with the triplet combination vs 28% with the doublet. The median PFS was 14.7 months vs 5.5 months, respectively. The duration of response was 11.1 months in the triplet arm vs 6.9 months in the doublet arm.

The conclusion of this trial was that the triplet showed promising efficacy in patients without a *BRCA* germline mutation. The high overall response rate seen with the triplet regimen was not driven by genomic instability status, as the overall response rate exceeded 75% in patients with or without genomic instability. There were no new safety signals. The ongoing phase 3 DUO-O trial is evaluating the combination of olaparib, durvalumab, and bevacizumab.[23]

These data are interesting. In my opinion, however, the trial is missing a treatment arm. It would have been informative to understand the contribution effect of each agent by including a durvalumab and bevacizumab cohort. I am skeptical that the use of another checkpoint inhibitor can significantly improve outcomes in an unselected population in the frontline ovarian cancer setting. Data from the upcoming DUO-O study should provide insight into this important question.

Chemotherapy

Paclitaxel

Dr Andrew Clamp presented the final analysis of the ICON8 trial.[24] It was promising to learn about the concept of dose-dense chemotherapy in the frontline setting for ovarian cancer, as studied in the JGOG 3016 trial.[25,26] This trial showed significant gains in PFS and overall survival by changing the administration of paclitaxel from every 3 weeks to every week. The results led to several other trials that evaluated whether an alteration in the dosing schedule—whereby a higher amount of the drug is given over a similar or shorter period—would improve efficacy outcomes. The GOG-262 trial evaluated paclitaxel plus carboplatin given every week or every 3 weeks, with or without bevacizumab.[27] A drawback to the trial design is that patients could choose whether they received bevacizumab. More than 80% of the patients opted to receive this treatment. The primary analysis for the overall patient group showed no differences in outcomes between paclitaxel administered at a dose-dense regimen vs the traditional regimen of once every 3 weeks. A post-hoc analysis of the subgroup of patients who did not receive bevacizumab showed that the dose-dense regimen was superior in this cohort. The post-hoc nature of this analysis, however, means that the results are hypothesis-generating only. The conclusion from the GOG-262 study is that there was no difference between the dose-dense and standard-treatment arms. Overall, the dose-dense paclitaxel regimen was well tolerated, but it was associated with more anemia and sensory neuropathy.

A similar trial, MITO-7, compared carboplatin plus paclitaxel given every 3 weeks in the traditional regimen vs carboplatin at an AUC of 2 and paclitaxel at 60 mg/m^2 given on days 1, 8, and 15.[28] Again, there was no difference in outcome. The HR for PFS was 0.88, which was not statistically significant. The dose-dense arm was associated with slightly increased neuropathy.

The ICON8 trial evaluated 3 regimens: carboplatin at an area under the curve (AUC) of 5 and paclitaxel at 175 mg/m^2 every 3 weeks; fractionated paclitaxel at 80 mg/m^2 every week, with carboplatin every 3 weeks; and fractionated doses of both agents, with carboplatin at an AUC of 2 every week and paclitaxel at 80 mg/m^2 every week.[24] The trial enrolled more than 1500 patients, including those with stage IC through IV disease. Patients had undergone either primary cytoreduction or interval cytoreduction with neoadjuvant chemotherapy. The trial had 2 co–primary endpoints, PFS and overall survival, and the target for the HR was 0.75. Earlier analyses were

published in 2019 and 2020.[29,30]

There was no difference in PFS between the treatment arms. Because the Kaplan-Meier curves were not proportional, a restricted-means analysis was used. Both weekly treatment arms were associated with increased grade 3/4 toxicity, which was mostly neutropenia. Importantly, there was no increase in neurotoxicity, as was seen in other trials of dose-dense therapy. The regimen of carboplatin plus paclitaxel given every 3 weeks should remain the standard of care for frontline treatment in the majority of patients with ovarian cancer. The dose-dense regimen is associated with some increased toxicity, plus extra cost, without any significant improvement in outcome.

Disclosure

Dr Herzog has served on the scientific advisory boards of AstraZeneca, Caris, Clovis, Genentech, GSK, Johnson & Johnson, and Merck.

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