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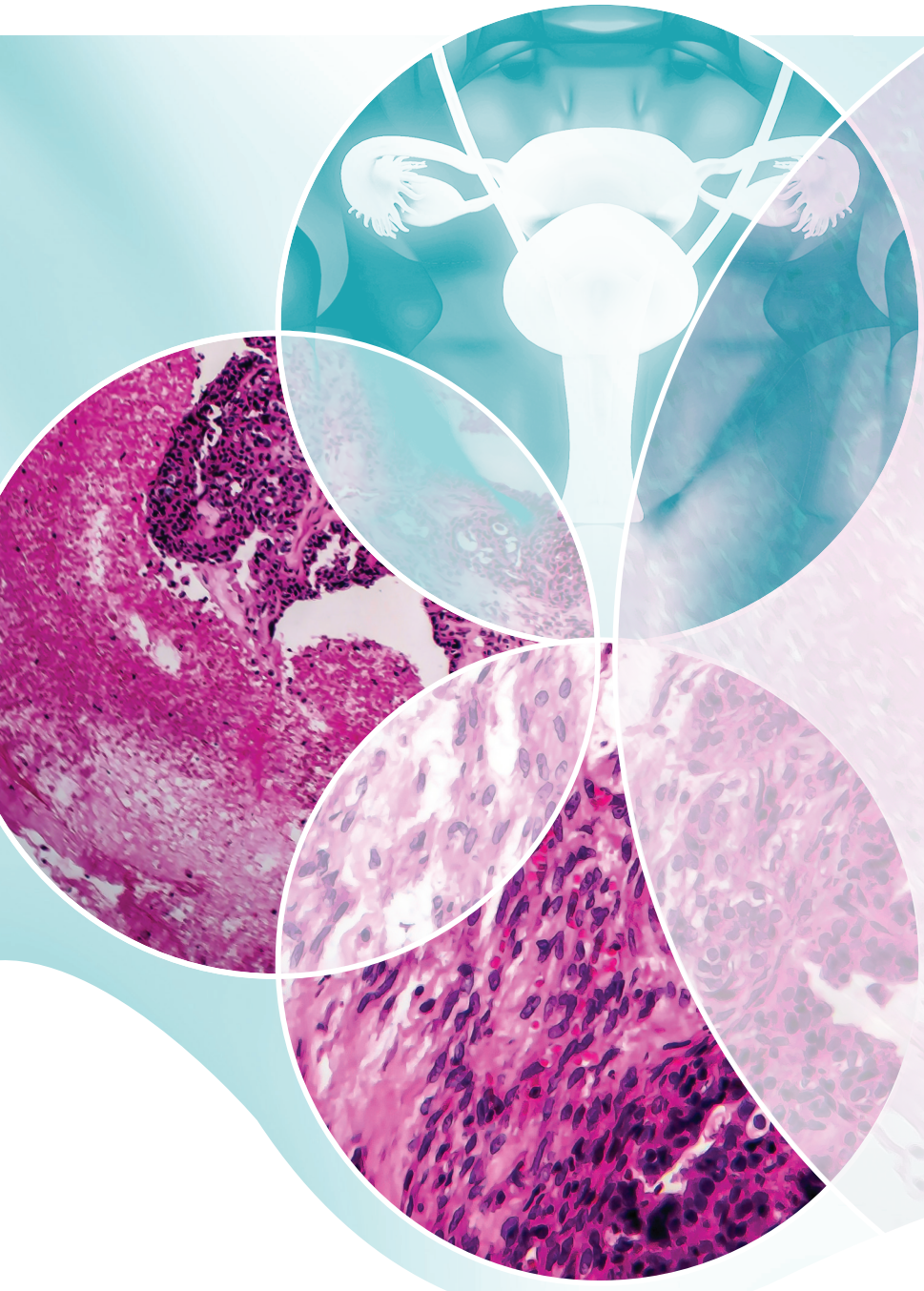
thelynxgroup

OVARIAN CANCER | YEAR IN REVIEW™



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JHOP Journal of Hematology Oncology Pharmacy — The Peer-Reviewed Forum for Oncology Pharmacy Practice — Official Publication of HOPA Hematology/Oncology Pharmacy Association

JONS Journal of Oncology Navigation & Survivorship — The Official Journal of the Academy of Oncology Nurse & Patient Navigators

TON The Oncology Nurse-APNPA — The Official Publication for the Hemonc Nurse & Advanced Practitioner

VBCC Value-Based Cancer Care — Integrating Cost, Quality, Access into Clinical Decision-Making in Oncology

In combination with bevacizumab for the maintenance treatment of

HRD-POSITIVE ADVANCED OVARIAN CANCER*

following complete or partial response to first-line platinum-based chemotherapy[1]

Lynparza®
olaparib
tablets 150 mg

DISCOVER THE POTENTIAL OF 3 YEARS mPFS[1]

Individual results may vary.

Not actual patients. LYNPARZA is not indicated in patients under 18.[1]
*Select patients for this indication based on an FDA-approved companion diagnostic.[1]

INDICATION

LYNPARZA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated:

First-Line Maintenance HRD-Positive Advanced Ovarian Cancer in Combination with Bevacizumab

In combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a deleterious or suspected deleterious *BRCA* mutation, and/or genomic instability. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

There are no contraindications for LYNPARZA.

WARNINGS AND PRECAUTIONS

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML): Occurred in approximately 1.5% of patients exposed to LYNPARZA monotherapy, and the majority of events had a fatal outcome. The median duration of therapy in patients who developed MDS/AML was 2 years (range: <6 months to >10 years). All of these patients had previous chemotherapy with platinum agents and/or other DNA-damaging agents, including radiotherapy.

Do not start LYNPARZA until patients have recovered from hematological toxicity caused by previous chemotherapy (≤Grade 1). Monitor complete blood count for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities, interrupt LYNPARZA and monitor blood count weekly until recovery.

If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. Discontinue LYNPARZA if MDS/AML is confirmed.

Pneumonitis: Occurred in 0.8% of patients exposed to LYNPARZA monotherapy, and some cases were fatal. If patients present with new or worsening respiratory symptoms such as dyspnea, cough, and fever, or a radiological abnormality occurs, interrupt LYNPARZA treatment and initiate prompt investigation. Discontinue LYNPARZA if pneumonitis is confirmed and treat patient appropriately.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings in animals, LYNPARZA can cause fetal harm. A pregnancy test is recommended for females of reproductive potential prior to initiating treatment.

Females

Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months following the last dose.

ADVERSE REACTIONS—First-Line Maintenance Advanced Ovarian Cancer in Combination with Bevacizumab

Most common adverse reactions (Grades 1-4) in ≥10% of patients treated with LYNPARZA/bevacizumab compared to a ≥5% frequency for placebo/bevacizumab in the **first-line maintenance setting** for **PAOLA-1** were: nausea (53%), fatigue (including asthenia) (53%), anemia (41%), lymphopenia (24%), vomiting (22%) and leukopenia (18%). In addition, the most common adverse reactions (≥10%) for patients receiving LYNPARZA/bevacizumab irrespective of the frequency

PAOLA-1

~50% WERE HRD POSITIVE[2]

PRESPECIFIED EXPLORATORY ANALYSIS[1,3]:

Median PFS was 37.2 months with LYNPARZA + bevacizumab (n=255) and 17.7 months with bevacizumab + placebo (n=132); HR=0.33; 95% CI: 0.25–0.45[1]

Data based upon a prespecified exploratory subgroup analysis, which was not controlled for Type 1 error. HRD status was not a stratification factor in PAOLA-1.[3]

STUDY DESIGN[1-3]

PAOLA-1 was a phase 3 trial of women with advanced ovarian cancer that enrolled patients regardless of surgical outcome or *BRCA* mutation status following response to first-line platinum-based chemotherapy with bevacizumab. Patients were randomized 2:1 (N=806) to receive LYNPARZA tablets 300 mg BID in combination with bevacizumab 15 mg/kg (n=537) or placebo BID in combination with bevacizumab 15 mg/kg (n=269).

Bevacizumab was administered every 3 weeks for a total duration of up to 15 months, and LYNPARZA or placebo treatment was administered for up to 24 months or until disease progression or unacceptable toxicity.

The primary endpoint was the investigator-assessed PFS. Prespecified exploratory analyses included PFS in predefined subgroups, including HRD status and *BRCA* mutation status. **PFS within HRD-positive patients served as the basis of the FDA-approved indication.**

There's MORE to learn about LYNPARZA. Explore the data at MoreTo3.com

IMPORTANT SAFETY INFORMATION (Cont'd)

compared with the placebo/bevacizumab arm were: diarrhea (18%), neutropenia (18%), urinary tract infection (15%) and headache (14%).

In addition, venous thromboembolic events occurred more commonly in patients receiving LYNPARZA/bevacizumab (5%) than in those receiving placebo/bevacizumab (1.9%).

Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients for LYNPARZA in combination with bevacizumab in the **first-line maintenance setting** for **PAOLA-1** were: decrease in hemoglobin (79%), decrease in lymphocytes (63%), increase in serum creatinine (61%), decrease in leukocytes (59%), decrease in absolute neutrophil count (35%) and decrease in platelets (35%).

DRUG INTERACTIONS

Anticancer Agents: Clinical studies of LYNPARZA with other myelosuppressive anticancer agents, including DNA-damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

CYP3A Inhibitors: Avoid coadministration of strong or moderate CYP3A inhibitors when using LYNPARZA. If a strong or moderate CYP3A inhibitor must be coadministered, reduce the dose of LYNPARZA. Advise patients to avoid grapefruit, grapefruit juice, Seville oranges, and Seville orange juice during LYNPARZA treatment.

CYP3A Inducers: Avoid coadministration of strong or moderate CYP3A inducers when using LYNPARZA.

USE IN SPECIFIC POPULATIONS

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

Pediatric Use: The safety and efficacy of LYNPARZA have not been established in pediatric patients.

Hepatic Impairment: No adjustment to the starting dose is required in patients with mild or moderate hepatic impairment (Child-Pugh classification A and B). There are no data in patients with severe hepatic impairment (Child-Pugh classification C).

Renal Impairment: No dosage modification is recommended in patients with mild renal impairment (CLcr 51-80 mL/min estimated by Cockcroft-Gault). In patients with moderate renal impairment (CLcr 31-50 mL/min), reduce the dose of LYNPARZA to 200 mg twice daily. There are no data in patients with severe renal impairment or end-stage renal disease (CLcr ≤30 mL/min).

You are encouraged to report negative side effects of AstraZeneca prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

Please see the Brief Summary of Prescribing Information on the following pages.

BID=twice daily; CI=confidence interval; HR=hazard ratio; HRD=homologous recombination deficiency; mPFS=median progression-free survival.

References: 1. LYNPARZA® (olaparib) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2021. **2.** Ray-Coquard I, Pautier P, Pignata S, et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. *N Engl J Med.* 2019;381(25):2416-2428. **3.** Ray-Coquard I, Pautier P, Pignata S, et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. Supplementary Appendix. *N Engl J Med.* 2019;381(25):2416-2428.

MERCK AstraZeneca

LYNPARZA® (olaparib) tablets, for oral use

Initial U.S. Approval: 2014

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

First-Line Maintenance Treatment of *BRCA*-mutated Advanced Ovarian Cancer

Lynparza is indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza *[see Dosage and Administration (2.1) in the full Prescribing Information]*.

First-line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer in Combination with Bevacizumab

Lynparza is indicated in combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either:

- a deleterious or suspected deleterious *BRCA* mutation, and/or
- genomic instability.

Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza *[see Dosage and Administration (2.1) in the full Prescribing Information]*.

Maintenance Treatment of Recurrent Ovarian Cancer

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

Advanced Germline *BRCA*-mutated Ovarian Cancer After 3 or More Lines of Chemotherapy

Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*m) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza *[see Dosage and Administration (2.1) in the full Prescribing Information]*.

DOSAGE AND ADMINISTRATION

Patient Selection

Information on FDA-approved tests for the detection of genetic mutations is available at http://www.fda.gov/companiondiagnostics.

Select patients for treatment with Lynparza based on the presence of deleterious or suspected deleterious HRR gene mutations, including *BRCA* mutations, or genomic instability based on the indication, biomarker, and sample type (Table 1).

Table 1 Biomarker Testing for Patient Selection*

Indication	Biomarker	Sample type		
		Tumor	Blood	Plasma (ctDNA)
First-line maintenance treatment of germline or somatic *BRCA*m advanced ovarian cancer	*BRCA1*m, *BRCA2*m	X	X	
First-line maintenance treatment of HRD-positive advanced ovarian cancer in combination with bevacizumab	*BRCA1*m, *BRCA2*m and/or genomic instability	X		
Maintenance treatment of recurrent ovarian cancer	No requirement for biomarker testing			
Advanced g*BRCA*m ovarian cancer	*gBRCA1*m, *gBRCA2*m		X	

* Where testing fails or tissue sample is unavailable/insufficient, or when germline testing is negative, consider using an alternative test, if available.

Recommended Dosage

The recommended dosage of Lynparza is 300 mg taken orally twice daily, with or without food.

If a patient misses a dose of Lynparza, instruct patient to take their next dose at its scheduled time. Instruct patients to swallow tablets whole. Do not chew, crush, dissolve, or divide tablet.

First-Line Maintenance Treatment of *BRCA*-mutated Advanced Ovarian Cancer

Continue treatment until disease progression, unacceptable toxicity, or completion of 2 years of treatment. Patients with a complete response (no radiological evidence of disease) at 2 years should stop treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating healthcare provider can derive further benefit from continuous treatment, can be treated beyond 2 years.

First-Line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer in Combination with Bevacizumab

Continue Lynparza treatment until disease progression, unacceptable toxicity, or completion of 2 years of treatment. Patients with a complete response (no radiological evidence of disease) at 2 years should stop treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating healthcare provider can derive further benefit from continuous Lynparza treatment, can be treated beyond 2 years.

When used with Lynparza, the recommended dose of bevacizumab is 15 mg/kg every three weeks. Bevacizumab should be given for a total of 15 months including the period given with chemotherapy and given as maintenance. Refer to the Prescribing Information for bevacizumab when used in combination with Lynparza for more information.

Recurrent Ovarian Cancer and Germline *BRCA*m Advanced Ovarian Cancer

Continue treatment until disease progression or unacceptable toxicity for:

- Maintenance treatment of recurrent ovarian cancer
- Advanced germline *BRCA*-mutated ovarian cancer

Dosage Modifications for Adverse Reactions

To manage adverse reactions, consider interruption of treatment or dose reduction. The recommended dose reduction is 250 mg taken twice daily.

If a further dose reduction is required, then reduce to 200 mg taken twice daily.

Dosage Modifications for Concomitant Use with Strong or Moderate CYP3A Inhibitors

Avoid concomitant use of strong or moderate CYP3A inhibitors with Lynparza.

If concomitant use cannot be avoided, reduce Lynparza dosage to:

- 100 mg twice daily when used concomitantly with a strong CYP3A inhibitor.
- 150 mg twice daily when used concomitantly with a moderate CYP3A inhibitor.

After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the Lynparza dose taken prior to initiating the CYP3A inhibitor *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Dosage Modifications for Renal Impairment

Moderate Renal Impairment

In patients with moderate renal impairment (CLcr 31-50 mL/min), reduce the Lynparza dosage to 200 mg orally twice daily *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Myelodysplastic Syndrome/Acute Myeloid Leukemia

Myelodysplastic syndrome (MDS)/Acute Myeloid Leukemia (AML) has occurred in patients treated with Lynparza and some cases were fatal.

In clinical studies enrolling 2901 patients with various cancers who received Lynparza as a single agent *[see Adverse Reactions (6.1) in the full Prescribing Information]*, the cumulative incidence of MDS/AML was approximately 1.5% (43/2901). Of these, 51% (22/43) had a fatal outcome. The median duration of therapy with Lynparza in patients who developed MDS/AML was 2 years (range: < 6 months to > 10 years). All of these patients had received previous chemotherapy with platinum agents and/or other DNA damaging agents including radiotherapy.

Do not start Lynparza until patients have recovered from hematological toxicity caused by previous chemotherapy (≤ Grade 1). Monitor complete blood count for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities, interrupt Lynparza and monitor blood counts weekly until recovery. If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue Lynparza.

Pneumonitis

In clinical studies enrolling 2901 patients with various cancers who received Lynparza as a single agent *[see Adverse Reactions (6.1) in the full Prescribing Information]*, the incidence of pneumonitis, including fatal cases, was 0.8% (24/2901). If patients present with new or worsening respiratory symptoms such as dyspnea, cough and fever, or a radiological abnormality occurs, interrupt Lynparza treatment and promptly assess the source of the symptoms. If pneumonitis is confirmed, discontinue Lynparza treatment and treat the patient appropriately.

Embryo-Fetal Toxicity

Lynparza can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. In an animal reproduction study, administration of olaparib to pregnant rats during the period of organogenesis caused teratogenicity and embryo-fetal toxicity at exposures below those in patients receiving the recommended human dose of 300 mg twice daily. Apprise pregnant women of the potential hazard to a fetus and the potential risk for loss of the pregnancy. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Lynparza. Based on findings from genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of Lynparza *[see Use in Specific Populations (8.1, 8.3) in the full Prescribing Information]*.

ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Myelodysplastic Syndrome/Acute Myeloid Leukemia *[see Warnings and Precautions (5.1) in the full Prescribing Information]*
- Pneumonitis *[see Warnings and Precautions (5.2) in the full Prescribing Information]*

Clinical Trial 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 data described in the WARNINGS AND PRECAUTIONS reflect exposure to Lynparza as a single agent in 2901 patients; 2135 patients with exposure to 300 mg twice daily tablet dose including five controlled, randomized, trials (SOLO-1, SOLO-2, OlympiAD, POLO, and PROfound) and to 400 mg twice daily capsule dose in 766 patients in other trials that were pooled to conduct safety analyses. In these trials, 56% of patients were exposed for 6 months or longer and 28% were exposed for greater than one year in the Lynparza group.

In this pooled safety population, the most common adverse reactions in ≥10% of patients were nausea (60%), fatigue (55%), anemia (36%), vomiting (32%), diarrhea (24%), decreased appetite (22%), headache (16%), dysgeusia (15%), cough (15%), neutropenia (14%), dyspnea (14%), dizziness (12%), dyspepsia (12%), leukopenia (11%), and thrombocytopenia (10%).

First-Line Maintenance Treatment of *BRCA*-mutated Advanced Ovarian Cancer

SOLO-1

The safety of Lynparza for the maintenance treatment of patients with *BRCA*-mutated advanced ovarian cancer following first-line treatment with platinum-based chemotherapy was investigated in SOLO-1 *[see Clinical Studies (14.1) in the full Prescribing Information]*. Patients received Lynparza tablets

300 mg orally twice daily (n=260) or placebo (n=130) until disease progression or unacceptable toxicity. The median duration of study treatment was 25 months for patients who received Lynparza and 14 months for patients who received placebo.

Among patients who received Lynparza, dose interruptions due to an adverse reaction of any grade occurred in 52% and dose reductions due to an adverse reaction occurred in 28%. The most frequent adverse reactions leading to dose interruption or reduction of Lynparza were anemia (23%), nausea (14%), and vomiting (10%). Discontinuation due to adverse reactions occurred in 12% of patients receiving Lynparza. The most frequent adverse reactions that led to discontinuation of Lynparza were fatigue (3.1%), anemia (2.3%), and nausea (2.3%).

Tables 2 and 3 summarize adverse reactions and laboratory abnormalities in SOLO-1.

Table 2 Adverse Reactions* in SOLO-1 (≥10% of Patients Who Received Lynparza)

Adverse Reaction	Lynparza tablets n=260		Placebo n=130	
	All Grades (%)	Grades 3 – 4 (%)	All Grades (%)	Grades 3 – 4 (%)
Gastrointestinal Disorders				
Nausea	77	1	38	0
Abdominal pain†	45	2	35	1
Vomiting	40	0	15	1
Diarrhea‡	37	3	26	0
Constipation	28	0	19	0
Dyspepsia	17	0	12	0
Stomatitis§	11	0	2	0
General Disorders and Administration Site Conditions				
Fatigue¶	67	4	42	2
Blood and Lymphatic System Disorders				
Anemia	38	21	9	2
Neutropenia#	17	6	7	3
Leukopenia♭	13	3	8	0
Thrombocytopenia6	11	1	4	2
Infections and Infestations				
Upper respiratory tract infection/ influenza/nasopharyngitis/bronchitis	28	0	23	0
UTIà	13	1	7	0
Nervous System Disorders				
Dysgeusia	26	0	4	0
Dizziness	20	0	15	1
Metabolism and Nutrition Disorders				
Decreased appetite	20	0	10	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspneaè	15	0	6	0

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.
† Includes abdominal pain, abdominal pain lower, abdominal pain upper, abdominal distension, abdominal discomfort, and abdominal tenderness.
‡ Includes colitis, diarrhea, and gastroenteritis.
§ Includes stomatitis, aphthous ulcer; and mouth ulceration.
¶ Includes asthenia, fatigue, lethargy, and malaise.
# Includes neutropenia, and febrile neutropenia.
Þ Includes leukopenia, and white blood cell count decreased.
6 Includes platelet count decreased, and thrombocytopenia.
à Includes urosepsis, urinary tract infection, urinary tract pain, and pyuria.
è Includes dyspnea, and dyspnea exertional.

In addition, the adverse reactions observed in SOLO-1 that occurred in <10% of patients receiving Lynparza were increased blood creatinine (8%), lymphopenia (6%), hypersensitivity (2%), MDS/AML (1%), dermatitis (1%), and increased mean cell volume (0.4%).

Table 3 Laboratory Abnormalities Reported in ≥25% of Patients in SOLO-1

Laboratory Parameter*	Lynparza tablets n†=260		Placebo n†=130	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in hemoglobin	87	19	63	2
Increase in mean corpuscular volume	87	–	43	–
Decrease in leukocytes	70	7	52	1
Decrease in lymphocytes	67	14	29	5
Decrease in absolute neutrophil count	51	9	38	6
Decrease in platelets	35	1	20	2
Increase in serum creatinine	34	0	18	0

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.
† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

First-line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer in Combination with Bevacizumab

PAOLA-1

The safety of Lynparza in combination with bevacizumab for the maintenance treatment of patients with advanced ovarian cancer following first-line treatment containing platinum-based chemotherapy and bevacizumab was investigated in PAOLA-1 *[see Clinical Studies (14.2) in the full Prescribing Information]*. This study was a placebo-controlled, double-blind study in which 802 patients received either Lynparza 300 mg BID in combination with bevacizumab (n=535) or placebo in combination with bevacizumab (n=267) until disease progression or unacceptable toxicity. The median duration of treatment with Lynparza was 17.3 months and 11 months for bevacizumab post-randomization on the Lynparza/ bevacizumab arm.

Fatal adverse reactions occurred in 1 patient due to concurrent pneumonia and aplastic anemia. Serious adverse reactions occurred in 31% of patients who received Lynparza/bevacizumab. Serious adverse reactions in >5% of patients included hypertension (19%) and anemia (17%).

Dose interruptions due to an adverse reaction of any grade occurred in 54% of patients receiving Lynparza/bevacizumab and dose reductions due to an adverse reaction occurred in 41% of patients who received Lynparza/bevacizumab.

The most frequent adverse reactions leading to dose interruption in the Lynparza/bevacizumab arm were anemia (21%), nausea (7%), vomiting (3%), and fatigue (3%), and the most frequent adverse reactions leading to reduction in the Lynparza/bevacizumab arm were anemia (19%), nausea (7%), and fatigue (4%).

Discontinuation due to adverse reactions occurred in 20% of patients receiving Lynparza/bevacizumab. Specific adverse reactions that most frequently led to discontinuation in patients treated with Lynparza/ bevacizumab were anemia (4%) and nausea (3%).

Tables 4 and 5 summarize adverse reactions and laboratory abnormalities in PAOLA-1, respectively.

Table 4 Adverse Reactions* Occurring in ≥10% of Patients Treated with Lynparza/bevacizumab in PAOLA-1 and at ≥5% Frequency Compared to the Placebo/bevacizumab Arm

Adverse Reactions	Lynparza/bevacizumab n=535		Placebo/bevacizumab n=267	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
General Disorders and Administration Site Conditions				
Fatigue (including asthenia)†	53	5	32	1.5
Gastrointestinal Disorders				
Nausea	53	2.4	22	0.7
Vomiting	22	1.7	11	1.9
Blood and Lymphatic Disorders				
Anemia‡	41	17	10	0.4
Lymphopenia§	24	7	9	1.1
Leukopenia‖	18	1.9	10	1.5

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.
† Includes asthenia, and fatigue.
‡ Includes anemia, anemia macrocytic, erythropenia, haematocrit decreased, haemoglobin decreased, normochromic anemia, normochromic normocytic anemia, normocytic anemia, and red blood cell count decreased. Includes B-lymphocyte count decreased, lymphocyte count decreased, lymphopenia, and T-lymphocyte count decreased.
§ Includes B-lymphocyte count decreased, lymphocyte count decreased, lymphopenia, and T-lymphocyte count decreased.
‖ Includes leukopenia, and white blood cell count decreased.

The most common adverse reactions (≥ 10%) for patients receiving Lynparza/bevacizumab irrespective of the frequency compared with the placebo/bevacizumab arm were nausea (53%), fatigue (including asthenia) (53%), anemia (41%), lymphopenia (24%), vomiting (22%), diarrhea (18%), neutropenia (18%), leukopenia (18%), urinary tract infection (15%), and headache (14%).

The adverse reactions that occurred in <10% of patients receiving Lynparza/bevacizumab were dysgeusia (8%), dyspnea (8%), stomatitis (5%), dyspepsia (4.3%), erythema (3%), dizziness (2.6%), hypersensitivity (1.7%) and MDS/AML (0.7%).

In addition, venous thromboembolic events occurred more commonly in patients receiving Lynparza/ bevacizumab (5%) than in those receiving placebo/bevacizumab (1.9%).

Table 5 Laboratory Abnormalities Reported in ≥25% of Patients in PAOLA-1*

Laboratory Parameter†	Lynparza/bevacizumab n‡=535		Placebo/bevacizumab n‡=267	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in hemoglobin	79	13	55	0.4
Decrease in lymphocytes	63	10	42	3.0
Increase in serum creatinine	61	0.4	36	0.4
Decrease in leukocytes	59	3.4	45	2.2
Decrease in absolute neutrophil count	35	7	30	3.7
Decrease in platelets	35	2.4	28	0.4

* Reported within 30 days of the last dose.
† Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.
‡ This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

Maintenance Treatment of Recurrent Ovarian Cancer

SOLO-2

The safety of Lynparza for the maintenance treatment of patients with platinum sensitive g*BRCA*m ovarian cancer was investigated in SOLO-2 *[see Clinical Studies (14.3) in the full Prescribing Information]*. Patients received Lynparza tablets 300 mg orally twice daily (n=195) or placebo (n=99) until disease progression or unacceptable toxicity. The median duration of study treatment was 19.4 months for patients who received Lynparza and 5.6 months for patients who received placebo.

Among patients who received Lynparza, dose interruptions due to an adverse reaction of any grade occurred in 45% and dose reductions due to an adverse reaction occurred in 27%. The most frequent adverse reactions leading to dose interruption or reduction of Lynparza were anemia (22%), neutropenia (9%), and fatigue/asthenia (8%). Discontinuation due to an adverse reaction occurred in 11% of patients receiving Lynparza.

Tables 6 and 7 summarize adverse reactions and laboratory abnormalities in SOLO-2.

Table 6 Adverse Reactions* in SOLO-2 (≥20% of Patients Who Received Lynparza)

Adverse Reaction	Lynparza tablets n=195		Placebo n=99	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal Disorders				
Nausea	76	3	33	0
Vomiting	37	3	19	1
Diarrhea	33	2	22	0
Stomatitis†	20	1	16	0
General Disorders and Administration Site Conditions				
Fatigue including asthenia	66	4	39	2
Blood and Lymphatic Disorders				
Anemia‡	44	20	9	2
Infections and Infestations				
Nasopharyngitis/URI/sinusitis/ rhinitis/influenza	36	0	29	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia/myalgia	30	0	28	0
Nervous System Disorders				
Dysgeusia	27	0	7	0
Headache	26	1	14	0
Metabolism and Nutrition Disorders				
Decreased appetite	22	0	11	0

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.

† Represents grouped term consisting of abscess oral, aphthous ulcer, gingival abscess, gingival disorder, gingival pain, gingivitis, mouth ulceration, mucosal infection, mucosal inflammation, oral candidiasis, oral discomfort, oral herpes, oral infection, oral mucosal erythema, oral pain, oropharyngeal discomfort, and oropharyngeal pain.

‡ Represents grouped term consisting of anemia, hematocrit decreased, hemoglobin decreased, iron deficiency, mean cell volume increased and red blood cell count decreased.

In addition, the adverse reactions observed in SOLO-2 that occurred in <20% of patients receiving Lynparza were neutropenia (19%), cough (18%), leukopenia (16%), hypomagnesemia (14%), thrombocytopenia (14%), dizziness (13%), dyspepsia (11%), increased creatinine (11%), MDS/AML (8%), edema (8%), rash (6%), and lymphopenia (1%).

Table 7 Laboratory Abnormalities Reported in ≥25% of Patients in SOLO-2

Laboratory Parameter*	Lynparza tablets n†=195		Placebo n†=99	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Increase in mean corpuscular volume‡	89	-	52	-
Decrease in hemoglobin	83	17	69	0
Decrease in leukocytes	69	5	48	1
Decrease in lymphocytes	67	11	37	1
Decrease in absolute neutrophil count	51	7	34	3
Increase in serum creatinine	44	0	29	0
Decrease in platelets	42	2	22	1

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.

† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

‡ Represents the proportion of subjects whose mean corpuscular volume was > upper limit of normal (ULN).

Study 19

The safety of Lynparza as maintenance monotherapy was evaluated in patients with platinum sensitive ovarian cancer who had received 2 or more previous platinum containing regimens in Study 19 *[see Clinical Studies (14.3) in the full Prescribing Information]*. Patients received Lynparza capsules 400 mg orally twice daily (n=136) or placebo (n=128). At the time of final analysis, the median duration of exposure was 8.7 months in patients who received Lynparza and 4.6 months in patients who received placebo.

Adverse reactions led to dose interruptions in 35% of patients receiving Lynparza; dose reductions in 26% and discontinuation in 6% of patients receiving Lynparza.

Tables 8 and 9 summarize adverse reactions and laboratory abnormalities in Study 19.

Table 8 Adverse Reactions* in Study 19 (≥20% of Patients Who Received Lynparza)

Adverse Reaction	Lynparza capsules n=136		Placebo n=128	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal Disorders				
Nausea	71	2	36	0
Vomiting	35	2	14	1
Diarrhea	28	2	25	2
Constipation	22	1	12	0
Dyspepsia	20	0	9	0
General Disorders and Administration Site Conditions				
Fatigue (including asthenia)	63	9	46	3
Blood and Lymphatic Disorders				
Anemia†	23	7	7	1
Infections and Infestations				
Respiratory tract infection	22	2	11	0
Metabolism and Nutrition Disorders				
Decreased appetite	21	0	13	0
Nervous System Disorders				
Headache	21	0	13	1

* Graded according to NCI CTCAE v4.0.

† Represents grouped terms of related terms that reflect the medical concept of the adverse reaction.

In addition, the adverse reactions in Study 19 that occurred in <20% of patients receiving Lynparza were dysgeusia (16%), dizziness (15%), dyspnea (13%), pyrexia (10%), stomatitis (9%), edema (9%), increase in creatinine (7%), neutropenia (5%), thrombocytopenia (4%), leukopenia (2%), MDS/AML (1%) and lymphopenia (1%).

Table 9 Laboratory Abnormalities Reported in ≥25% of Patients in Study 19

Laboratory Parameter*	Lynparza capsules n†=136		Placebo n†=129	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in hemoglobin	82	8	58	1
Increase in mean corpuscular volume‡	82	-	51	-
Decrease in leukocytes	58	4	37	2
Decrease in lymphocytes	52	10	32	3
Decrease in absolute neutrophil count	47	7	40	2
Increase in serum creatinine	45	0	14	0
Decrease in platelets	36	4	18	0

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.

† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

‡ Represents the proportion of subjects whose mean corpuscular volume was > ULN.

Advanced Germline *BRCA*-mutated Ovarian Cancer After 3 or More Lines of Chemotherapy

Pooled Data

The safety of Lynparza was investigated in 223 patients (pooled from 6 studies) with g*BRCA*m advanced ovarian cancer who had received 3 or more prior lines of chemotherapy *[see Clinical Studies (14.4) in the full Prescribing Information]*. Patients received Lynparza capsules 400 mg orally twice daily until disease progression or unacceptable tolerability. The median exposure to Lynparza in these patients was 5.2 months.

There were 8 (4%) patients with adverse reactions leading to death, two were attributed to acute leukemia, and one each was attributed to COPD, cerebrovascular accident, intestinal perforation, pulmonary embolism, sepsis, and suture rupture. Adverse reactions led to dose interruption in 40% of patients, dose reduction in 4%, and discontinuation in 7%.

Tables 10 and 11 summarize the adverse reactions and laboratory abnormalities from the pooled studies.

Table 10 Adverse Reactions Reported in Pooled Data (≥20% of Patients Who Received Lynparza)

Adverse Reaction	Lynparza capsules n=223	
	Grades 1-4 (%)	Grades 3-4 (%)
General Disorders		
Fatigue/asthenia	66	8
Gastrointestinal Disorders		
Nausea	64	3
Vomiting	43	4
Diarrhea	31	1
Dyspepsia	25	0
Decreased appetite	22	1
Blood and Lymphatic Disorders		
Anemia	34	18
Infections and Infestations		
Nasopharyngitis/URI	26	0
Musculoskeletal and Connective Tissue Disorders		
Arthralgia/musculoskeletal pain	21	0
Myalgia	22	0

Table 11 Laboratory Abnormalities Reported in ≥25% of Patients in Pooled Data

Laboratory Parameter*	Lynparza capsules n†=223	
	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in hemoglobin	90	15
Mean corpuscular volume elevation	57	-
Decrease in lymphocytes	56	17
Decrease in platelets	30	3
Increase in creatinine	30	2
Decrease in absolute neutrophil count	25	7

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.

† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

The following adverse reactions and laboratory abnormalities have been identified in ≥10 to <20% of the 223 patients receiving Lynparza and not included in the table: cough (16%), constipation (16%), dysgeusia (16%), headache (15%), peripheral edema (14%), back pain (14%), urinary tract infection (14%), dyspnea (13%), and dizziness (11%).

The following adverse reactions and laboratory abnormalities have been identified in <10% of the 223 patients receiving Lynparza and not included in the table: leukopenia (9%), pyrexia (8%), peripheral neuropathy (5%), hypomagnesemia (5%), rash (5%), stomatitis (4%), MDS/AML (1.8%), and venous thrombosis (including pulmonary embolism) (1%).

Postmarketing Experience

The following adverse reactions have been identified during post approval use of Lynparza. 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 angioedema.

Skin and subcutaneous tissue disorders: Erythema nodosum, rash, dermatitis.

DRUG INTERACTIONS

Use with Anticancer Agents

Clinical studies of Lynparza with other myelosuppressive anticancer agents, including DNA damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

Effect of Other Drugs on Lynparza

Strong and Moderate CYP3A Inhibitors

Coadministration of CYP3A inhibitors can increase olaparib concentrations, which may increase the risk for adverse reactions *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Avoid coadministration of strong or moderate CYP3A inhibitors. If the strong or moderate inhibitor must be coadministered, reduce the dose of Lynparza *[see Dosage and Administration (2.4) in the full Prescribing Information]*.

Strong and Moderate CYP3A Inducers

Concomitant use with a strong or moderate CYP3A inducer decreased olaparib exposure, which may reduce Lynparza efficacy *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Avoid coadministration of strong or moderate CYP3A inducers.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action *[see Clinical Pharmacology (12.1) in the full Prescribing Information]*, Lynparza can cause fetal harm when administered to a pregnant woman. There are no available data on Lynparza use in pregnant women to inform the drug-associated risk. In an animal reproduction study, the administration of olaparib to pregnant rats during the period of organogenesis caused teratogenicity and embryo-fetal toxicity at exposures below those in patients receiving the recommended human dose of 300 mg twice daily *(see Data)*. Apprise pregnant women of the potential hazard to the fetus and the potential risk for loss of the pregnancy.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. The estimated background risk in the U.S. general population of major birth defects is 2-4%; and the risk for spontaneous abortion is approximately 15-20% in clinically recognized pregnancies.

Data

Animal Data

In a fertility and early embryonic development study in female rats, olaparib was administered orally for 14 days before mating through to Day 6 of pregnancy, which resulted in increased post-implantation loss at a dose level of 15 mg/kg/day (with maternal systemic exposures approximately 7% of the human exposure ($AUC_{0\text{-}24h}$) at the recommended dose).

In an embryo-fetal development study, pregnant rats received oral doses of 0.05 and 0.5 mg/kg/day olaparib during the period of organogenesis. A dose of 0.5 mg/kg/day (with maternal systemic exposures approximately 0.18% of human exposure ($AUC_{0\text{-}24h}$) at the recommended dose) caused embryo-fetal toxicities including increased post-implantation loss and major malformations of the eyes (anophthalmia, microphthalmia), vertebrae/ribs (extra rib or ossification center; fused or absent neural arches, ribs, and sternebrae), skull (fused exoccipital), and diaphragm (hernia). Additional abnormalities or variants included incomplete or absent ossification (vertebrae/sternebrae, ribs, limbs) and other findings in the vertebrae/sternebrae, pelvic girdle, lung, thymus, liver, ureter, and umbilical artery. Some findings noted above in the eyes, ribs, and ureter were observed at a dose of 0.05 mg/kg/day olaparib at lower incidence.

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

Pregnancy Testing

Recommend pregnancy testing for females of reproductive potential prior to initiating treatment with Lynparza.

Contraception

Females

Lynparza can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1) in the full Prescribing Information]*. Advise females of reproductive potential to use effective contraception during treatment with Lynparza and for at least 6 months following the last dose.

Pediatric Use

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

Geriatric Use

Of the 2351 patients with advanced solid tumors who received Lynparza tablets 300 mg orally twice daily as monotherapy, 596 (25%) patients were aged ≥65 years, and this included 137 (6%) patients who were aged ≥75 years. Seven (0.3%) patients were aged ≥85 years.

Of the 535 patients with advanced solid tumors who received Lynparza tablets 300 mg orally twice daily in combination with bevacizumab, 204 (38%) patients were aged ≥65 years, and this included 31 (6%) patients who were aged ≥75 years.

No overall differences in the safety or effectiveness of Lynparza were observed between these patients and younger patients.

Renal Impairment

No dosage modification is recommended in patients with mild renal impairment (CLcr 51 to 80 mL/min estimated by Cockcroft-Gault). Reduce Lynparza dosage to 200 mg twice daily in patients with moderate renal impairment (CLcr 31 to 50 mL/min) *[see Dosage and Administration (2.5) in the full Prescribing Information]*. There are no data in patients with severe renal impairment or end-stage disease (CLcr ≤30 mL/min) *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Hepatic Impairment

No adjustment to the starting dose is required in patients with mild or moderate hepatic impairment (Child-Pugh classification A and B). There are no data in patients with severe hepatic impairment (Child-Pugh classification C) *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

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2021 in Review

Colleagues,

In 2021, the COVID-19 pandemic continued to impact the practice of medicine and dissemination of treatment advances presented in scientific forums. Medical societies, such as the American Society of Clinical Oncology and the Society of Gynecologic Oncology, have adopted hybrid formats, including virtual meetings that delivered cutting-edge research in the advancement of oncology care. In addition, several treatment advances continue to be published in peer-reviewed journals. We are publishing the *Year in Review* series to disseminate key information on treatment advances to clinicians in a timely and effective manner.

This edition of *Year in Review* is focused on ovarian cancer, which is associated with high mortality despite significant treatment improvements. Several approved and novel classes of agents continue to be investigated in ovarian cancer to produce better patient outcomes. Here is a quick review of some of the topics discussed in this issue, with a focus on recent advances and potentially practice-changing developments in ovarian cancer.

Treatment options for the management of relapsed ovarian cancer primarily include antiangiogenics, such as bevacizumab, and poly (ADP-ribose) polymerase (PARP) inhibitors (eg, olaparib, niraparib, and rucaparib). Treatment selection is dictated by disease- and patient-related factors, with tumor biology having a key role, particularly genetic alterations resulting in homologous recombination deficiencies (HRDs), such as germline or somatic *BRCA1/2* mutations.

Overall survival analysis of the open-label, nonrandomized, phase 2 LIGHT clinical trial demonstrated that olaparib therapy in patients with platinum-sensitive relapsed ovarian cancer achieved an overall survival benefit across patient cohorts regardless of *BRCA* mutation and HRD status, with the greatest benefit observed in cohorts of patients with *BRCA* mutation–positive disease. Subgroup analysis of the phase 3 ARIEL4 study suggests that heavily pretreated patients with advanced relapsed ovarian carcinoma harboring a *BRCA1/2* mutation derive progression-free survival (PFS) benefit with rucaparib therapy across all platinum sensitivity subgroups. These agents are further being investigated in the first-line setting and as maintenance therapy, which has implications for next lines of therapy since previous exposure to these agents influences options for recurrent disease.

The role of PARP inhibitors as maintenance therapy following response to platinum-based chemotherapy is also being investigated. In patients with newly diagnosed advanced ovarian cancers with *BRCA1/2* mutations, the 5-year follow-up results of the SOLO1 trial indicate that 2 years of maintenance olaparib provided sustained PFS benefit, with no new safety signals. Subgroup analyses of the phase 3 PAOLA-1 trial demonstrated sustained PFS benefit with the addition of maintenance olaparib to bevacizumab compared with placebo in patients with newly diagnosed, HRD-positive, advanced, high-grade ovarian cancer, irrespective of the International Federation of Gynecology and Obstetrics stage and residual disease after upfront surgery. The final analysis of the NOVA trial supports the long-term safe use and PFS benefit beyond first progression of niraparib for maintenance treatment in patients with platinum-sensitive, recurrent ovarian cancer. Pooled analysis data from the PRIMA, NOVA, and NORA trials indicate that patients with *BRCA* mutation–positive ovarian cancer derived a significant PFS benefit from niraparib maintenance treatment, with emergence of no new safety signals. In addition, cost-effectiveness modeling analysis determined that olaparib was more cost-effective compared with niraparib as maintenance therapy for patients with recurrent platinum-sensitive ovarian cancer.

Antiangiogenic strategies are further being optimized, and novel agents, such as the *VEGFR2* tyrosine kinase inhibitor apatinib (rivoceranib) and the multitargeted tyrosine kinase inhibitor anlotinib (AL3818), are being developed. Addressing the issue of optimal duration of bevacizumab treatment, data from a randomized phase 3 trial demonstrated that prolonged treatment with bevacizumab for up to 30 months does not provide survival benefit in patients with advanced ovarian cancer compared with bevacizumab treatment duration of 15 months. Results of the phase 2 APPROVE trial showed significant prolongation of PFS with the addition of apatinib to pegylated liposomal doxorubicin in patients with platinum-resistant or refractory recurrent ovarian cancer. Results of the ovarian cancer cohort of the multicohort phase 1b ACTION trial indicate that anlotinib plus the anti–PD-L1 monoclonal antibody TQB2450 showed encouraging antitumor activity and tolerable toxicity in patients with recurrent advanced ovarian cancer.

Ongoing clinical research efforts are also focused on identifying other pathways and strategies in the pathophysiology of ovarian cancer. These include the GAS6/AXL inhibitor batiraxcept (AVB-500), the *WEE1* inhibitor adavosertib (AZD1775), the cyclin-dependent kinase 4/6 cell-cycle checkpoint inhibitor ribociclib, the antifolate receptor-α monoclonal antibody farletuzumab (MORAb-003), the antifolate receptor-α antibody–drug conjugate mirvetuximab soravtansine (IMGN853), and the immunotherapy with tumor-cell vaccine gemogenovatucel-T, which are all showing encouraging antitumor activities in patients with recurrent ovarian cancer. Results of the phase 2 EFFORT study support the efficacy of adavosertib with and without olaparib in patients with PARP inhibitor–resistant ovarian cancer. Moreover, phase 2b VITAL trial results suggest that immunotherapy with the autologous tumor-cell vaccine gemogenovatucel-T as frontline maintenance therapy in patients with stage III/IV ovarian cancer was well-tolerated and showed a clinical benefit in *BRCA* wild-type and HRD-proficient subgroups.

We are pleased to present the highlights of these topics and more!

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OVARIAN CANCER | YEAR IN REVIEW™

TABLE OF CONTENTS

Continued on next page

OVARIAN CANCER YEAR IN REVIEW™

TABLE OF CONTENTS *(Continued)*

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Phase 3b OPINION Primary Analysis of Olaparib Maintenance Monotherapy for Nongermline *BRCA1/2*-Mutated Platinum-Sensitive Relapsed Ovarian Cancer

Results of the primary analysis of the phase 3b OPINION study supported the use of olaparib maintenance therapy in patients with nongermline *BRCA1/2*-mutated platinum-sensitive relapsed ovarian cancer.

The phase 3b, single-arm, OPINION study (NCT03402841) investigated olaparib maintenance monotherapy in patients with nongermline *BRCA1/2*-mutated (non-g*BRCA*m) platinum-sensitive relapsed ovarian cancer. The results of this study were presented at the 2021 American Society of Clinical Oncology Annual Meeting.

Key eligibility criteria were relapsed high-grade serous or endometrioid ovarian cancer harboring non-g*BRCA*m, ≥2 previous lines of platinum-based chemotherapy, and complete response or partial response to last platinum-based chemotherapy. Eligible patients received maintenance olaparib (300 mg orally, twice a day) until disease progression or unacceptable toxicity. The primary end point was investigator-assessed progression-free survival (PFS). Secondary end points included PFS by homologous recombination deficiency (HRD) and somatic *BRCA* mutation (s*BRCA*m) status, as assessed by central Myriad tumor and germline testing; time to first subsequent treatment; time to treatment discontinuation or death; overall survival; safety; and tolerability. Primary analysis was planned 18 months after the last patient was enrolled; the data cutoff date was October 2, 2020.

A total of 279 patients were enrolled in the study. The mean age of the study population was 64 years; the majority (90.7%) had confirmed non-g*BRCA*m. In the overall study population, the median PFS was 9.2 months; the 12-month PFS rate was 38.5%, and the 18-month PFS rate was 24.3%. The PFS benefit extended to key subgroups evaluated, including those tested by Myriad HRD/*BRCA*m status (HRD-positive including s*BRCA*m: 11.1 months; HRD-positive excluding s*BRCA*m: 9.7 months; s*BRCA*m: 16.4 months). Median time to first subsequent treatment was 13.9 months.

Treatment-emergent adverse events (TEAEs) were consistent with the known safety profile of olaparib. Grade ≥3 TEAEs occurred in 29.0% of patients, and serious TEAEs occurred in 19.7% of patients. TEAEs led to dose interruption in 47.0% of patients, dose reduction in 22.6% of patients, and treatment discontinuation in 7.5% of patients.

Primary analysis results of the OPINION study support the use of olaparib maintenance therapy in patients with non-g*BRCA*m platinum-sensitive relapsed ovarian cancer.

Source: Poveda A, Lheureux S, Colombo N, et al. Olaparib maintenance monotherapy for non-germline *BRCA1/2*-mutated (non-g*BRCA*m) platinum-sensitive relapsed ovarian cancer (PSR OC) patients (pts): phase IIIb OPINION primary analysis. *J Clin Oncol.* 2021;39(suppl_15). Abstract 5545.

Final Overall Survival Results from the LIGHT Study of Olaparib Treatment in Platinum-Sensitive Relapsed Ovarian Cancer by *BRCA* Mutation and Homologous Recombination Deficiency Status

The final overall survival analysis of the phase 2 LIGHT study indicates that olaparib therapy in patients with platinum-sensitive relapsed ovarian cancer provides overall survival benefit across patient cohorts, regardless of *BRCA* mutation and homologous recombination deficiency status, with a safety profile consistent with that previously described.

The open-label, nonrandomized, multicenter, phase 2 LIGHT study (NCT02983799) prospectively evaluated olaparib therapy in patients with platinum-sensitive relapsed ovarian cancer with known *BRCA* mutation (*BRCA*m) and homologous recombination deficiency (HRD) status. The results of the final overall survival (OS) analyses were presented at the 2021 American Society of Clinical Oncology Annual Meeting.

The LIGHT study enrolled patients with platinum-sensitive relapsed ovarian cancer, who had received ≥1 previous lines of platinum-based chemotherapy.

The LIGHT study enrolled patients with platinum-sensitive relapsed ovarian cancer, who had received ≥1 previous lines of platinum-based chemotherapy. Eligible patients were assigned to 1 of 4 cohorts based on their Myriad test results: germline *BRCA*m (cohort 1); somatic *BRCA*m (cohort 2); HRD-positive (non-*BRCA*m; cohort 3); and HRD-negative (cohort 4). All eligible patients received olaparib (starting dose 300 mg twice a day) until disease progression or unacceptable toxicity. OS was a secondary end point, which was analyzed at 12 months after the primary analysis and at 18 months after the last patient was enrolled. The data cutoff date was August 27, 2020.

Of the 271 patients who received olaparib, 270 had measurable disease at baseline and were evaluable for efficacy. At a median follow-up of 26.3 months, 18-month OS rates ranged from 59.6% to 88% (cohort 1: 86%; cohort 2: 88%; cohort 3: 79%; cohort 4: 60%), with the highest OS rates observed in the patients with *BRCA*m regardless of germline or somatic *BRCA*m status. Among patients without a *BRCA*m, higher OS

rates were observed in patients with HRD-positive status. After olaparib discontinuation, the most frequent first subsequent treatment was platinum-based chemotherapy (39%). The median duration of treatment was 7.4 months.

Final safety analyses did not reveal the emergence of any new safety signal compared with the primary analysis or with previous olaparib studies. Serious treatment-emergent adverse events (TEAEs) occurred in 25% of patients; the most frequent serious TEAE was small intestinal obstruction (5.5%). TEAEs leading to treatment discontinuation were reported in 5% of patients. Three adverse events of special interest, which were caused by acute myeloid leukemia (post discontinuation), pneumonitis, and pulmonary fibrosis, were reported in 1 patient each.

The final OS analysis of the LIGHT study indicates that olaparib therapy in patients with platinum-sensitive relapsed ovarian cancer provides OS benefit across patient cohorts, regardless of *BRCA*m or HRD status, with a safety profile consistent with that previously described.

Source: Mathews CA, Simpkins F, Cadoo KA, et al. Olaparib treatment (Tx) in patients (pts) with platinum-sensitive relapsed ovarian cancer (PSR OC) by *BRCA* mutation (*BRCA*m) and homologous recombination deficiency (HRD) status: overall survival (OS) results from the phase II LIGHT study. *J Clin Oncol.* 2021;39(suppl_15). Abstract 5515.

EFFORT Study of Adavosertib with or without Olaparib in Women with PARP-Resistant Ovarian Cancer

Results of the phase 2 EFFORT study support the efficacy of adavosertib, with and without olaparib, in patients with poly (ADP-ribose) polymerase inhibitor–resistant ovarian cancer, with manageable adverse events.

The randomized 2-arm noncomparative phase 2 EFFORT study (NCT03579316) evaluated the efficacy of the *WEE1* inhibitor adavosertib with or without the poly (ADP-ribose) polymerase (PARP) inhibitor olaparib in patients with recurrent PARP inhibitor–resistant ovarian cancer. The results of the study were presented at the 2021 American Society of Clinical Oncology Annual Meeting.

Women with recurrent ovarian, fallopian tube, or primary peritoneal cancer with documented progressive disease on a PARP inhibitor, measurable disease, and adequate end-organ function were enrolled. Eligible patients were randomized to receive adavosertib 300 mg (orally on days 1-5 and 8-12 of a 21-day cycle), or adavosertib (150 mg orally twice a day on days 1-3 and 8-10) plus olaparib (200 mg orally twice a day on days 1-21 of a 21-day cycle). The primary end point was objective response rate (ORR) per RECIST version 1.1; secondary end points included safety, tolerability, duration of response, clinical benefit rate (CBR), progression-free survival (PFS), and efficacy based on *BRCA* status.

A total of 80 patients were enrolled and treated in the study; of these, 39 received adavosertib and 41 received adavosertib/olaparib. The median age of the study population was 60 years; the majority of patients had platinum-resistant disease (64%) and high-grade serous histology (93%). Patients received a median of 4 previous therapies; the majority received previous olaparib treatment and had achieved clinical benefit from previous PARP inhibitor therapy (86%). Nearly half of all patients had *BRCA* mutation–positive disease (48%).

Of the 70 patients evaluable for efficacy, 35 patients were randomized to each arm. ORRs were comparable in both the adavosertib-alone and adavosertib/olaparib combination treatment groups (23% vs 29%, respectively); duration of response was 5.5 months and 6.4 months, respectively. The CBR was 63% in the adavosertib-alone arm, and 89% in the adavosertib/olaparib combination arm. Median PFS was 5.5 months in the adavosertib-alone arm, and 6.8 months in the adavosertib/olaparib combination arm. Although responses were achieved in both treatment groups irrespective of *BRCA* mutation status, responses were lower in the *BRCA* mutation cohorts.

Adavosertib with or without olaparib demonstrates efficacy in patients with PARP inhibitor–resistant ovarian cancer.

Grade 3/4 toxicities were higher in the combination arm compared with the adavosertib-alone arm (76% vs 51%); however, most were manageable with dose modifications. Adavosertib-related grade 3/4 toxicities included neutropenia, thrombocytopenia, and diarrhea; 72% required at least 1 dose interruption, and 51% required dose reduction. Grade 3/4 toxicities in the combination arm included thrombocytopenia, neutropenia, diarrhea, fatigue, and anemia; 88% of patients required at least 1 dose interruption, 71% required dose reduction, and 10% discontinued treatment as a result of toxicity.

These data suggest that adavosertib with or without olaparib demonstrates efficacy in patients with PARP inhibitor–resistant ovarian cancer. Adverse events were manageable with supportive care, dose interruptions, and dose reductions.

Source: Westin SN, Coleman RL, Fellman BM, et al. EFFORT: EFficacy of adavosertib in PARP ResisTance: a randomized two-arm non-comparative phase II study of adavosertib with or without olaparib in women with PARP-resistant ovarian cancer. *J Clin Oncol.* 2021;39(suppl_15). Abstract 5505.

Analysis of the Phase 3 PAOLA-1/ENGOT-ov25 Trial by Disease Stage in Patients with Homologous Recombination Deficiency–Positive Newly Diagnosed Advanced Ovarian Cancer Receiving Bevacizumab with Olaparib/Placebo Maintenance

Results of the PAOLA-1/ENGOT-ov25 study demonstrated sustained progression-free survival benefit with the addition of maintenance olaparib to bevacizumab, compared with placebo and bevacizumab in homologous recombination deficiency-positive patients, irrespective of International Federation of Gynecology and Obstetrics stage and residual disease after up-front surgery.

Analyses of the phase 3 PAOLA-1/ENGOT-ov25 trial (NCT02477644), which evaluated the addition of maintenance olaparib or placebo to bevacizumab in patients with newly diagnosed advanced high-grade ovarian cancer (HGOC), were performed in homologous recombination deficiency (HRD)-positive patients by disease stage; these results were presented at the 2021 American Society of Clinical Oncology Annual Meeting.

The study enrolled patients with newly diagnosed, International Federation of Gynecology and Obstetrics (FIGO) stage III-IV HGOC in response after platinum-based chemotherapy plus bevacizumab. Eligible patients received bevacizumab (15 mg/kg every 3 weeks for 15 months) and either olaparib (300 mg twice a day for 24 months) or placebo. This exploratory analysis evaluated progression-free survival (PFS; data cutoff: March 22, 2019) and second PFS (PFS2; data cutoff: March 22, 2020) in HRD-positive patients (tumor *BRCA1/BRCA2* mutation [t*BRCA*m] or genomic instability score [Myriad myChoice HRD Plus] ≥42) by FIGO stage.

Of the 806 patients randomized in the study, 48% were HRD-positive. In the HRD-positive population, the majority (70%) had stage III disease, and 30% had stage IV disease; of whom 56% and 53% had a t*BRCA*m, respectively. Among patients with HRD-positive stage III disease, 63% had up-front surgery (of whom 30% had residual disease), and 33% had interval surgery (of whom 21% had residual disease). Among patients with HRD-positive stage IV disease, 45% had up-front surgery (of whom 65% had residual disease), and 48% had interval surgery (of whom 33% had residual disease).

Among patients with HRD-positive stage III disease, the olaparib/bevacizumab group (compared with the placebo/bevacizumab group) showed prolonged PFS (median follow-up: 24.8 months; median PFS: 39.3 vs 19.9 months) and PFS2 (median follow-up: 37.2 months; median PFS2: not reached vs 43.0 months). Among patients with HRD-positive stage IV disease, the olaparib/bevacizumab group showed prolonged PFS compared with the placebo/bevacizumab group (median follow-up: 24.0 months; median PFS: 25.1 vs 12.8 months, respectively), as well as PFS2 (median follow-up: 37.0 months; median PFS2: 37.8 vs 27.8 months, respectively). In lower-risk patients with stage III HRD-positive tumors, who benefited from complete resection following up-front surgery, the 2-year and 3-year PFS2 rates were >90% with olaparib/bevacizumab (94.7% and 91.9%, respectively) compared with placebo/bevacizumab (80.6% and 65.7%, respectively). Among higher-risk patients with stage III HRD-positive tumors and residual disease after up-front surgery, or those who received neoadjuvant chemotherapy, or those with HRD-positive stage IV disease, the 2-year PFS2 rate was 73.9%, and the 3-year PFS2 rate was 57.1% with olaparib/bevacizumab compared with placebo/bevacizumab (69.1% and 42.3%, respectively).

In lower-risk patients with stage III HRD-positive tumors, who benefited from complete resection following up-front surgery, the 2-year and 3-year PFS2 rates were >90% with olaparib/bevacizumab.

These results of the PAOLA-1 study demonstrate sustained PFS benefit with the addition of maintenance olaparib to bevacizumab compared with placebo plus bevacizumab in HRD-positive patients, irrespective of FIGO stage and residual disease after up-front surgery.

Source: Pautier P, Harter P, Pisano C, et al. Progression-free survival (PFS) and second PFS (PFS2) by disease stage in patients (pts) with homologous recombination deficiency (HRD)-positive newly diagnosed advanced ovarian cancer receiving bevacizumab (bev) with olaparib/placebo maintenance in the phase III PAOLA-1/ENGOT-ov25 trial. *J Clin Oncol.* 2021;39(suppl_15). Abstract 5514.

Subgroup Analysis of the ARIEL4 Study of the Effect of Platinum Sensitivity on Efficacy of Rucaparib versus Chemotherapy for *BRCA*-Mutated, Advanced, Relapsed Ovarian Carcinoma

Results of the subgroup analysis of the ARIEL4 study suggest that heavily pretreated patients with advanced relapsed ovarian carcinoma harboring a *BRCA1/2* mutation derive progression-free survival benefit from rucaparib treatment across all platinum-sensitivity subgroups.

The confirmatory phase 3 ARIEL4 study (NCT02855944) demonstrated that rucaparib therapy significantly improved progression-free survival (PFS), compared with chemotherapy

in patients with advanced relapsed ovarian carcinoma harboring a *BRCA1/2* (*BRCA*) mutation. Results of the prespecified exploratory analysis, which assessed the effect of platinum sensitivity on efficacy outcomes were reported at the 2021 American Society of Clinical Oncology Annual Meeting.

In the ARIEL4 study, patients with relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who received ≥2 previous chemotherapy regimens, and harbored germline or somatic *BRCA* mutations were enrolled. Eligible patients were randomized 2:1 to oral rucaparib 600 mg twice daily or chemotherapy. Chemotherapy was administered based on platinum sensitivity. Stratification was by progression-free interval (PFI) and platinum status (PFI; ≥1 to <6 months [platinum resistant]; ≥6 to <12 months [partially platinum sensitive]; ≥12 months [fully platinum sensitive]). In the chemotherapy group, patients with platinum-resistant or partially platinum-sensitive disease received weekly paclitaxel 60 to 80 mg/m^2; patients with fully platinum-sensitive disease received investigator's choice of platinum-based chemotherapy (single-agent carboplatin or cisplatin, or platinum doublet). The study design allowed crossover from chemotherapy to rucaparib following radiologic disease progression. Efficacy end points were assessed in patients with a confirmed *BRCA* mutation. The data cutoff date was September 30, 2020.

Patients receiving rucaparib had comparable or higher response rates across all platinum status subgroups compared with those receiving chemotherapy.

Subgroup analysis showed that patients receiving rucaparib had comparable or longer PFS across all platinum status subgroups, compared with those receiving chemotherapy (platinum-resistant: 6.4 vs 5.7 months, hazard ratio, 0.78; partially platinum-sensitive: 8.0 vs 5.5 months, hazard ratio, 0.40; fully platinum-sensitive: 12.9 vs 9.6 months, hazard ratio, 0.69). Similarly, patients receiving rucaparib had comparable or higher response rates across all platinum status subgroups compared with those receiving chemotherapy. In patients with platinum-sensitive disease, rucaparib showed response rates similar to those of platinum-based chemotherapy (63.6% vs 56.5%), with a trend toward a longer duration of response (10.8 months vs 7.6 months).

In the intent-to-treat population, 64% (74/116) of patients in the chemotherapy group crossed over to receive rucaparib, and 66% of the platinum-resistant cohort (39/59), 81% of the partially platinum-sensitive cohort (25/31), and 38% of the fully platinum-sensitive cohort (10/26) crossed over to receive rucaparib.

The safety profile for rucaparib across all platinum status subgroups was consistent with that previously described. In the rucaparib group, the most frequent treatment-emergent adverse events in the platinum-resistant, partially platinum-sensitive, and fully platinum-sensitive subgroups (compared with chemotherapy) were anemia/decreased hemoglobin (47% vs 40%, 63% vs 27%, and 58% vs 20%, respectively) and nausea (52% vs 21%, 51% vs 23%, and 60% vs 68%, respectively).

These results suggest that heavily pretreated patients with advanced relapsed ovarian carcinoma harboring a *BRCA1/2* mutation derive clinical benefit from rucaparib therapy in terms of PFS and response rates across all platinum-sensitivity subgroups.

Source: Oza AM, Lisyanskaya AS, Fedenko AA, et al. Subgroup analysis of rucaparib versus chemotherapy as treatment for *BRCA*-mutated, advanced, relapsed ovarian carcinoma: effect of platinum sensitivity in the randomized, phase 3 study ARIEL4. *J Clin Oncol.* 2021;39(suppl_15). Abstract 5517.

5-Year Follow-Up of the SOLO1/GOG 3004 Trial of Maintenance Olaparib for Patients with Newly Diagnosed Advanced Ovarian Cancer and a *BRCA* Mutation

Five-year follow-up results of the SOLO1 trial indicate that 2 years of maintenance olaparib provides sustained progression-free survival benefit in patients with newly diagnosed advanced ovarian cancer harboring *BRCA1* and/or *BRCA2* mutations, with no emergence of new safety signals.

Primary analysis of the phase 3 SOLO1 trial (NCT01844986; GOG-3004) demonstrated that maintenance olaparib in patients with newly diagnosed advanced ovarian cancer harboring *BRCA1* and/or *BRCA2* mutations (*BRCA*m), who responded to first-line platinum-based chemotherapy provides significant progression-free survival (PFS) benefit compared with placebo. The long-term efficacy and safety data of maintenance olaparib after 5 years of follow-up in the SOLO1 trial were published in the October 26, 2021, issue of *Lancet Oncology*.

The study enrolled patients aged ≥18 years with *BRCA*-mutated, newly diagnosed, advanced, high-grade serous or endometrioid ovarian cancer, who responded to platinum-based chemotherapy, and had an Eastern Cooperative Oncology Group performance status of 0-1. Eligible patients were randomized (2:1) to receive maintenance olaparib (300 mg twice a day) or placebo for up to 2 years. The primary end point was investigator-assessed PFS. The data cutoff for this analysis was March 5, 2020.

Of the total of 391 patients enrolled in the trial, 260 received olaparib and 131 received placebo, with a median

treatment duration of 24.6 months and 13.9 months, respectively. In the intention-to-treat population, median PFS was 56 months in the olaparib cohort (median follow-up of 4.8 years) compared with 14 months in the placebo cohort (median follow-up of 5.0 years).

The safety profile of olaparib was consistent with that previously described. The most frequent grade 3/4 adverse events in the olaparib cohort were anemia (22%) and neutropenia (8%). Serious adverse events occurred in 21% of patients in the olaparib group and 13% in the placebo group. No treatment-related adverse events (that occurred during study treatment or up to 30 days after discontinuation) led to death. The current analysis found no new cases of myelodysplastic syndrome or acute myeloid leukemia.

Long-term safety and efficacy results of the SOLO1 trial demonstrate that 2 years of maintenance olaparib provide sustained PFS benefit. Patients with olaparib-treated, newly diagnosed, advanced ovarian cancer with a *BRCA*m were progression-free past 4.5 years, with the emergence of no new safety signals.

Source: Banerjee S, Moore KN, Colombo N, et al. Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a *BRCA* mutation (SOLO1/GOG 3004): 5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2021;22:1721-1731.

Olaparib Treatment in Patients with Platinum-Sensitive Relapsed Ovarian Cancer by *BRCA* Mutation and Homologous Recombination Deficiency Status: Secondary Safety Results from the Phase 2 LIGHT Study

Secondary efficacy data and subgroup analyses from the LIGHT study indicate that olaparib monotherapy was most effective in *BRCA*-mutated cohorts of patients with platinum-sensitive relapsed ovarian cancer.

The open-label, nonrandomized phase 2 LIGHT (NCT02983799) study evaluated olaparib treatment in patients with platinum-sensitive relapsed ovarian cancer by *BRCA* mutation (*BRCA*m) and homologous recombination deficiency (HRD) status. The results of prespecified secondary efficacy end points and subgroup analyses were reported at the 2021 Society of Gynecologic Oncology Annual Meeting.

The study enrolled patients with platinum-sensitive relapsed ovarian cancer who had received ≥1 previous lines of platinum-based chemotherapy. Eligible patients received olaparib monotherapy (300 mg twice a day) and were assigned to 1 of 4 cohorts based on whether they had a germline *BRCA*m (g*BRCA*m), somatic *BRCA*m (s*BRCA*m), HRD-positive (non-*BRCA*m) tumors, or HRD-negative tumors. Secondary efficacy end points included investigator-assessed progression-free survival (PFS) and CA-125 response. The time to any progression (TTAP) was defined from the date of the first dose of olaparib until the earliest date of RECIST version 1.1 or CA-125 disease progression, or death. The data cutoff was August 27, 2019.

In patients with ≥1 previous lines of chemotherapy, objective response rates of approximately 60% to 70% were achieved in the *BRCA*m cohorts, and approximately 30% in the non-*BRCA*m cohort.

A total of 271 patients received olaparib; of these, 270 patients had measurable disease at baseline and were included in efficacy analyses. Efficacy in 13 patients was analyzed separately, because they could not be assigned to a cohort as a result of failed or missing Myriad test results. In patients with ≥1 previous lines of chemotherapy, objective response rates of approximately 60% to 70% were achieved in the *BRCA*m cohorts, and approximately 30% in the non-*BRCA*m cohort; median PFS was approximately 10 to 11 months in the *BRCA*m cohorts, and 5 to 7 months in the non-*BRCA*m cohort. A high proportion of patients in the *BRCA*m cohorts achieved a CA-125 response and complete response, with a CA-125 complete response rate of 60% to 68%, compared with 29% in the non-*BRCA*m cohort. Median TTAP was approximately 11 months in the *BRCA*m cohorts and 7.2 months in the non-*BRCA*m cohort.

Results of this multicohort study indicate that olaparib monotherapy was most effective in *BRCA*m cohorts of patients with platinum-sensitive relapsed ovarian cancer.

Source: Cadoo K, Simpkins F, Mathews C, et al. Olaparib treatment in patients with platinum-sensitive relapsed ovarian cancer by BRCA mutation and homologous recombination deficiency status: secondary safety results from the phase II LIGHT study. *Gynecol Oncol.* 2021;162(suppl_1):S67-S68.

Progression-Free Survival Benefit from Maintenance Olaparib in Patients with Platinum-Sensitive Relapsed Ovarian Cancer by *BRCA* and Other Homologous Recombination Repair Gene Mutation Status (ORZORA Trial)

Results of the ORZORA trial indicate that patients with platinum-sensitive relapsed ovarian cancer derived progression-free survival benefit from maintenance olaparib, irrespective of somatic or germline *BRCA* mutation status.

The open-label, single-arm, multicenter ORZORA trial (NCT02476968) evaluated the efficacy and safety of maintenance olaparib in patients with platinum-sensitive relapsed ovarian cancer with a *BRCA* mutation (*BRCA*m). The results of this trial were reported at the 2021 Society of Gynecologic Oncology Annual Meeting.

This trial enrolled patients with platinum-sensitive relapsed ovarian cancer harboring a germline *BRCA*m (g*BRCA*m) or somatic (s*BRCA*m), who were in response to their most recent platinum-based chemotherapy after ≥2 lines of treatment. Eligible patients received maintenance olaparib (400 mg twice a day) until disease progression. Co-primary end points were investigator-assessed progression-free survival (PFS) in the *BRCA*m and s*BRCA*m cohorts (conducted at 60% maturity). Secondary end points included time to second progression or death (PFS2), health-related quality of life (HRQOL) as assessed using the Functional Assessment of Cancer Therapy–Ovarian Cancer outcome index, and tolerability. Tumor *BRCA*m status was assessed by central screening using the Myriad myChoice CDx assay; somatic or germline *BRCA*m status was determined by central genomic testing using the Myriad BRACAnalysis CDx assay. An additional exploratory cohort comprised patients with predefined homologous recombination repair gene mutations (*HRR*m) excluding *BRCA*m (determined using the FoundationOne CDx assay). The data cutoff date was April 17, 2020.

At a median follow-up of 22.3 months, median PFS was similar in the *BRCA*m (18.0 months), s*BRCA*m (16.6 months), g*BRCA*m (19.3 months), and *HRR*m cohorts (16.4 months).

Of the 181 patients enrolled, 145 patients had *BRCA*m, 55 patients had s*BRCA*m, 87 patients had g*BRCA*m, and 33 patients had *HRR*m. Patient characteristics were similar between the somatic and germline *BRCA*m cohorts in terms of ≥3 previous lines of chemotherapy (38% vs 48%, respectively); partial response to previous platinum therapy (45% vs 49%, respectively); and the presence of a tumor *BRCA*1 mutation (65% vs 64%, respectively).

At a median follow-up of 22.3 months, median PFS was similar in the *BRCA*m (18.0 months), s*BRCA*m (16.6 months), g*BRCA*m (19.3 months), and *HRR*m cohorts (16.4 months). Median PFS2 was 30.9 months for the *BRCA*m cohort; 24.7 months for the s*BRCA*m cohort; and 32.5 months for the g*BRCA*m cohort. HRQOL was comparable in the *BRCA*m and s*BRCA*m cohorts.

In the safety population (n = 177), the most frequent adverse events (AEs) were nausea (54%), fatigue (43%), anemia (42%), and vomiting (28%). Serious AEs occurred in 25% of patients; grade ≥3 AEs occurred in 35% of patients. Treatment discontinuation as a result of AEs was reported in 5% of patients. Two new primary malignancies were reported, both of which were acute myeloid leukemia; no cases of myelodysplastic syndrome occurred.

Based on these results, patients with platinum-sensitive relapsed ovarian cancer derive PFS benefit from maintenance olaparib, irrespective of somatic or germline *BRCA*m status.

Source: Pignata S, Oza A, Hall G, et al. ORZORA: maintenance olaparib in patients with platinum-sensitive relapsed ovarian cancer: outcomes by somatic and germline *BRCA* and other homologous recombination repair gene mutation status. *Gynecol Oncol.* 2021;162(suppl_1):S29.

ARIEL4 Results of Rucaparib versus Chemotherapy in Patients with Advanced, Relapsed Ovarian Cancer and a Deleterious *BRCA* Mutation

Results of the phase 3, randomized ARIEL4 trial demonstrate that patients with *BRCA*-mutated advanced, relapsed ovarian cancer derive significant progression-free survival benefit from rucaparib therapy compared with standard-of-care chemotherapy, with the emergence of no new safety signals.

The phase 3, randomized, open-label, international, multicenter ARIEL4 (NCT02855944) study compared the efficacy and safety of rucaparib versus standard-of-care chemotherapy in poly (ADP-ribose) polymerase (PARP) inhibitor–naïve patients with relapsed advanced ovarian cancer with deleterious *BRCA* mutations. The results of this study were reported at the 2021 Society of Gynecologic Oncology annual meeting.

The study enrolled patients with high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who had a deleterious *BRCA1/2* mutation and had received ≥2 previous chemotherapy regimens. Eligible patients were randomized (2:1) to rucaparib (600 mg twice daily) or standard-of-care chemotherapy; stratification was based on progression-free interval (≥1 to <6 months [platinum resistant]; ≥6 to <12 months [partially platinum sensitive]; ≥12 months [fully platinum sensitive]). In the chemotherapy arm, platinum-resistant or partially platinum-sensitive disease cohorts received weekly paclitaxel 60 to 80 mg/m^2, and the platinum-sensitive cohort received investigator's choice of platinum-based chemotherapy (single-agent platinum, or platinum doublet). Both deleterious and reversion mutations were assessed. The primary end point was investigator-assessed progression-free survival; secondary end points included objective response rate (ORR) and safe-

ty. Efficacy outcomes were evaluated in the efficacy population (randomized patients with deleterious *BRCA* mutations, excluding *BRCA* reversion mutations) and the intent-to-treat (ITT) population (all randomized patients). The data cutoff date was September 30, 2020.

In the ITT population, 349 patients were randomized to rucaparib (n = 233) or chemotherapy (n = 116). Of these, 179 (51.3%) had platinum-resistant disease, 96 (27.5%) had partially platinum-sensitive disease, and 74 (21.2%) had fully platinum-sensitive disease. A total of 23 (6.6%) patients with *BRCA* reversion mutations, and 1 patient without a *BRCA* mutation were excluded from the efficacy population.

Median PFS was significantly prolonged with rucaparib (vs chemotherapy) in both the efficacy (7.4 vs 5.7 months; hazard ratio [HR], 0.64) and ITT populations (7.4 vs 5.7 months; HR, 0.67). In patients with *BRCA* reversion mutations, rucaparib treatment (n = 13) did not provide PFS benefit (2.9 vs 5.5 months; HR, 2.769) compared with chemotherapy (n = 10). In both populations, ORR was also similar between the rucaparib and chemotherapy arms. Adverse events were consistent with the known safety profiles of rucaparib and chemotherapy.

Results of the ARIEL4 trial demonstrate that patients with *BRCA*-mutated advanced, relapsed ovarian cancer derive significant PFS benefit from rucaparib therapy compared with standard-of-care chemotherapy, with the emergence of no new safety signals. The data also indicate that the presence of a *BRCA* reversion mutation predicts for primary resistance to rucaparib.

Source: Kristeleit R, Lisyanskaya A, Fedenko A, et al. Rucaparib versus chemotherapy in patients with advanced, relapsed ovarian cancer and a deleterious BRCA mutation: efficacy and safety from ARIEL4, a randomized phase III study. *Gynecol Oncol.* 2021;162(suppl_1):S3-S4.

Phase 1 Trial of Ribociclib (LEE-011) with Platinum-Based Chemotherapy in Recurrent Platinum-Sensitive Ovarian Cancer

Preliminary results of a phase 1 study showed favorable safety and tolerability of ribociclib, both concurrently with platinum and taxane chemotherapy and as maintenance therapy, with encouraging antitumor activity in patients with recurrent platinum-sensitive ovarian cancer.

A phase 1, open-label, single-institution, dose-escalation trial assessed the safety and efficacy of the cyclin-dependent kinase (CDK)4/6 cell cycle checkpoint inhibitor, ribociclib (LEE-011), in patients with recurrent platinum-sensitive ovarian cancer. Results of this trial were reported at the 2021 Society of Gynecologic Oncology Annual Meeting.

Patients with a diagnosis of recurrent platinum-sensitive ovarian cancer, who had received at least 1 previous platinum-based chemotherapy regimen, were enrolled in the study. Eligible patients received ribociclib (200 mg, 400 mg, or 600 mg on days 1-4, 8-11, and 15-18); and weekly carboplatin (AUC2) and paclitaxel (60 mg/m^2) on days 1, 8, and 15 of a 28-day cycle for a planned 6 total cycles. Patients with at least a partial response to therapy received maintenance ribociclib 600 mg daily until time of progression. The primary end point was the maximum tolerated dose (MTD) of ribociclib administered concurrently with platinum and taxane chemotherapy. Secondary end points were response rate and progression-free survival (PFS).

Preliminary results of this phase 1 study showed encouraging safety and tolerability of ribociclib, both concurrently with platinum and taxane chemotherapy and as maintenance therapy.

The study enrolled a total of 35 patients. Patients had received a mean of 2.5 previous lines of chemotherapy and 51% had received previous maintenance therapy; of these, 31% had received poly (ADP-ribose) polymerase (PARP) inhibitor therapy, 34.3% had received bevacizumab, and 14.3% had received both. The MTD was established as 400 mg. No dose-limiting toxicities (DLTs) were observed in the 200-mg group; 11 patients (33.3%) in the 400-mg group had DLTs. A higher incidence of grade 3/4 adverse events (AEs) occurred during concurrent therapy (n = 35 events) than during maintenance (n = 9 events). The most frequent AEs included anemia (82.9%), neutropenia (82.9%), fatigue (82.9%), nausea (77.1%), hypertension (62.9%), and thrombocytopenia (40.0%).

In the overall population, response rate was 79.3%, and was similar among patients with and without previous maintenance therapy (82% PARP inhibitor vs 78% without; 83% bevacizumab vs 78% without); and among patients with 1 previous line of chemotherapy versus those with >1 previous line (83% vs 76%). Overall PFS was 11.4 months and was comparable among patients with and without previous maintenance therapy (10.1 vs 14.4 months; *P* = .07).

Preliminary results of this phase 1 study showed encouraging safety and tolerability of ribociclib, both concurrently with platinum and taxane chemotherapy and as maintenance therapy, with encouraging antitumor activity in patients with recurrent platinum-sensitive ovarian cancer.

Source: Coffman L, Orellana T, Normolle D, et al. Phase I trial of ribociclib (LEE-011) with platinum-based chemotherapy in recurrent platinum sensitive ovarian cancer. *Gynecol Oncol.* 2021;162(suppl_1):S69.

Long-Term Safety and Secondary Efficacy End Points in the ENGOT-OV16/NOVA Phase 3 Trial of Niraparib in Recurrent Ovarian Cancer

Final analysis of the NOVA trial supports the long-term progression-free survival benefit and safe use of niraparib beyond first progression for maintenance treatment in patients with platinum-sensitive recurrent ovarian cancer.

The randomized, double-blind, placebo-controlled, phase 3 NOVA (ENGOT-OV16) study demonstrated that maintenance therapy with niraparib significantly prolongs progression-free survival (PFS) in patients with platinum-sensitive recurrent ovarian cancer, regardless of germline *BRCA* mutation (g*BRCA*m) or homologous recombination deficiency biomarker status. Long-term safety and data on secondary efficacy outcomes of the NOVA trial were reported at the 2021 Society of Gynecologic Oncology Annual Meeting.

From year 1 to years 2-3, respectively, the incidence of grade ≥3 thrombocytopenia decreased from 33.8% to 2.8%, anemia decreased from 25.6% to 0.7%, and neutropenia decreased from 19.3% to 2.1%.

The NOVA trial enrolled patients with platinum-sensitive recurrent ovarian cancer. Eligible patients were enrolled into 1 of 2 cohorts by g*BRCA*m status (g*BRCA*m or non-g*BRCA*m). Stratification was by PFS after the penultimate platinum therapy (6 to <12 months vs ≥12 months), best response to the last platinum-based therapy (complete or partial), and previous bevacizumab (yes/no). Eligible patients were randomized (2:1) to receive niraparib (300 mg every day) or placebo. The primary end point was PFS as assessed by blinded independent central review; exploratory secondary end points were second PFS and overall survival (OS). The data cutoff date was October 2020. At data cutoff, 127 deaths occurred in the g*BRCA*m cohort, and 238 deaths occurred in the non-g*BRCA*m cohort.

Long-term safety analysis showed that hematologic treatment-emergent adverse effects decreased after the first year. From year 1 to years 2-3, respectively, the incidence of grade ≥3 thrombocytopenia decreased from 33.8% to 2.8%, anemia decreased from 25.6% to 0.7%, and neutropenia decreased from 19.3% to 2.1%. Secondary malignancies of myelodysplastic syndromes or acute myeloid leukemia occurred in 13 (3.5%) patients receiving niraparib (g*BRCA*m, n = 9; non-g*BRCA*m, n = 4) compared with 3 such malignancies (1.7%) in patients receiving placebo.

A total of 553 patients were randomized in the NOVA study. At a median follow-up of 66 months, prolongation of the second PFS was noted in both the g*BRCA*m cohort (hazard ratio [HR], 0.67) and non-g*BRCA*m cohort (HR, 0.81).

Restricted mean survival time analyses for OS up to 72 months in the niraparib and placebo arms were as follows: 45.9 months with niraparib in the g*BRCA*m cohort (vs 43.2 months with placebo; difference of 2.7 months); and 38.5 months with niraparib in the non-g*BRCA*m cohort (vs 39.1 months with placebo; difference of –0.6 months). However, it is notable that the NOVA study was not powered for OS, and interpretation of OS analysis was confounded by a high rate of crossover and missing data. A total of 46% (30/65) in the g*BRCA*m cohort and 13% (15/116) in the non-g*BRCA*m cohort of the placebo arm went on to receive subsequent poly (ADP-ribose) polymerase–inhibitor therapy (crossover) after disease progression. Survival status data were not obtained for approximately 15% of patients, and postprogression therapy data were not available for 25% of patients.

Final analysis of the NOVA trial supports the long-term safe use of niraparib maintenance treatment and PFS benefit beyond first progression in patients with platinum-sensitive recurrent ovarian cancer.

Source: Matulonis U, Herrstedt J, Oza A, et al. Long-term safety and secondary efficacy endpoints in the ENGOT-OV16/NOVA phase III trial of niraparib in recurrent ovarian cancer. *Gynecol Oncol.* 2021;162(suppl_1):S24-S25.

Phase 2 APPROVE Trial of Apatinib plus Pegylated Liposomal Doxorubicin (PLD) versus PLD for Platinum-Resistant Recurrent Ovarian Cancer

Results of the phase 2 APPROVE trial demonstrated significant prolongation of progression-free survival with the addition of apatinib to PLD in patients with platinum-resistant or refractory recurrent ovarian cancer, with an adverse event profile consistent with that previously described for apatinib and PLD.

The multicenter, randomized, controlled, open-label, phase 2 APPROVE trial evaluated the efficacy and safety of the VEGFR-2 tyrosine kinase inhibitor, apatinib, in combination with pegylated liposomal doxorubicin (PLD) in patients with platinum-resistant or refractory recurrent ovarian cancer. The results of this trial were reported at the 2021 Society of Gynecologic Oncology Annual Meeting.

Between March 22, 2018, and November 16, 2020, the APPROVE trial enrolled patients with histologically confirmed nonmucinous ovarian, primary peritoneal cancer, or fallopian-tube cancer with disease progression during, or within 6 months of discontinuing, any previous line of platinum-based chemotherapy, and with ≥1 measurable and/or nonmeasur-

able lesions. Eligible patients were randomly assigned (1:1) to receive PLD alone (40 mg/m^2 intravenously every 4 weeks, for up to 6 cycles), or in combination with apatinib (250 mg once daily) until disease progression, unacceptable toxicity, or consent withdrawal. Patient stratification was by previous platinum-sensitive relapsed (yes vs no) and platinum-free interval (<3 vs 3-6 months from last platinum therapy to subsequent progression). The primary end point was progression-free survival (PFS) in the intent-to-treat (ITT) population; secondary end points included overall survival (OS), objective response rate (ORR), disease control rate (DCR), and safety.

A total of 152 patients were enrolled in the study; of these, 78 patients received the apatinib/PLD combination, and 74 patients received PLD alone. In the ITT population, at a median follow-up of 8.1 months, median PFS was significantly longer with apatinib/PLD combination therapy compared with PLD alone (5.8 months vs 3.3 months; hazard ratio, 0.41; *P* = .0001). In patients with evaluable disease, the ORR (37.7% vs 9.5%; *P* = .0002) and DCR (82.0% vs 58.7%; *P* = .0050) were also significantly improved. OS data are immature at this time.

The adverse event profiles were consistent with those previously described for both agents. The most frequent adverse events with apatinib therapy were hypertension and hand-foot syndrome.

Based on these results, the investigators concluded that the addition of apatinib to PLD resulted in significant prolongation of PFS in patients with platinum-resistant or refractory recurrent ovarian cancer, with an adverse event profile consistent with that previously described for apatinib and PLD.

Source: Wang T, Li N, Tang J, et al. Apatinib combined with pegylated liposomal doxorubicin (PLD) versus PLD for platinum-resistant recurrent ovarian cancer (APPROVE): a multicenter, randomized, controlled, open-label, phase II trial. *Gynecol Oncol.* 2021;162(suppl_1):S42.

Phase 2 Placebo-Controlled Study to Assess the Efficacy/Safety of Farletuzumab plus Chemotherapy in Women with Low CA-125 Platinum-Sensitive Ovarian Cancer

Results of a placebo-controlled, phase 2 study (MORAb-003-011/ENGOT-ov27) indicate that the addition of farletuzumab to platinum-based chemotherapy was not superior to placebo/chemotherapy in improving progression-free survival or other efficacy parameters in patients with platinum-sensitive recurrent ovarian cancer in first relapse who had low alemtuzumab CA-125 levels.

Based on evidence that low CA-125 levels (≤3 × upper limit of normal [ULN]) might be associated with superior efficacy outcomes, the randomized, double-blind, placebo-controlled, phase 2 study (MORAb-003-011/ENGOT-ov27) compared the efficacy and safety of the antifolate receptor-α monoclonal antibody farletuzumab with placebo in combination with platinum-based chemotherapy, in women with low CA-125 platinum-sensitive ovarian cancer. The results of the trial were reported at the 2021 Society of Gynecologic Oncology Annual Meeting.

The study enrolled women aged ≥18 years; with CA-125 ≤3 × ULN (105 U/mL); and high-grade serous epithelial ovarian cancer; previous treatment with debulking surgery and first-line platinum-based chemotherapy (carboplatin/paclitaxel or carboplatin/pegylated liposomal doxorubicin); in first relapse (platinum-free interval, 6-36 months). During the combination treatment phase, eligible patients were randomized (2:1) to receive 6 cycles with chemotherapy every 3 weeks in combination with either farletuzumab (5 mg/kg weekly) or placebo; tumor assessments were done every 6 weeks. In the maintenance phase, therapy with farletuzumab (5 mg/kg weekly) or placebo was administered until disease progression, and tumor assessments were done every 9 weeks. The study was designed to detect a progression-free survival (PFS) hazard ratio (HR) of 0.667 (33.3% risk reduction) with farletuzumab compared with placebo, and had approximately 85% power and a 1-sided type I error rate of 0.10.

In the intent-to-treat population, no significant difference was noted in median PFS between the farletuzumab/chemotherapy and placebo/chemotherapy treatment groups.

A total of 214 patients were enrolled in the study; of these, 142 patients were randomized to the farletuzumab/chemotherapy group, and 72 patients to the placebo/chemotherapy group. In the intent-to-treat population, no significant difference was noted in median PFS between the farletuzumab/chemotherapy and placebo/chemotherapy treatment groups (11.7 months vs 10.8 months; HR, 0.89). An interim analysis of overall survival showed no significant difference between treatment groups. The overall response rate was also similar between the 2 treatment groups (69.6% vs 73.5%; *P* = .53). No significant between-group differences were observed for any other efficacy parameters.

Safety analysis showed that serious adverse events were generally similar between the 2 treatment groups (30% with farletuzumab vs 24% with placebo plus chemotherapy). However, a higher incidence of interstitial lung disease was reported in the farletuzumab/chemotherapy combination group (7/141 [5%] vs 0/70 [0%]); among the interstitial lung events, 1 was of grade 1 severity; 4 were grade 2; and 2 were grade 3.

Based on these results, the investigators concluded that the addition of farletuzumab to chemotherapy was not superior to placebo/chemotherapy in improving PFS or other efficacy parameters in patients with platinum-sensitive recurrent ovarian cancer in first relapse who also had low CA-125 levels.

Source: Herzog T, Pignata S, Ghamande S, et al. A randomized, double-blind, placebo-controlled, phase II study to assess the efficacy/safety of farletuzumab in combination with carboplatin plus paclitaxel or carboplatin plus pegylated liposomal doxorubicin (PLD) in women with low CA-125 platinum-sensitive ovarian cancer. *Gynecol Oncol.* 2021;162(suppl_1):S38-S39.

Cost-Effectiveness Analysis of Olaparib and Niraparib as Maintenance Therapy for Women with Recurrent Platinum-Sensitive Ovarian Cancer

Olaparib was more cost-effective, compared with niraparib, as maintenance therapy for patients with recurrent platinum-sensitive ovarian cancer, as determined by a model-based analysis.

A model-based analysis evaluated the cost-effectiveness of the poly (ADP-ribose) polymerase (PARP) inhibitors, olaparib and niraparib, as maintenance therapy for patients with platinum-sensitive recurrent ovarian cancer; findings of this analysis were published in *Expert Review of Pharmacoeconomics and Outcomes Research*.

> The analysis showed that, in the base case, olaparib was more cost-effective compared with niraparib or placebo.

The study utilized a decision analysis model to compare the costs and effectiveness of olaparib and niraparib versus placebo for patients with ovarian cancer with or without germline *BRCA* mutations (g*BRCA*m). The 2020 National Health Insurance Administration reimbursement price list was used to estimate resource use and associated costs. Clinical effectiveness was measured in progression-free survival per life-years (PFS-LY) based on results of the clinical trials, SOLO2/ENHOT-Ov21 and ENGOT-OV16/NOVA. The incremental cost-effectiveness ratio (ICER) was estimated from a single-payer perspective.

The analysis showed that, in the base case, olaparib was more cost-effective compared with niraparib or placebo. Compared with placebo, the ICER for olaparib was lower (New Taiwan dollars [NT]$1,804,785 per PFS-LY) than for niraparib (NT$2,340,265 per PFS-LY). The ICER was impacted by PFS and the total resource use cost of the niraparib regimen for patients without g*BRCA*, as assessed by tornado analysis (a type of sensitivity analysis that provides a graphical representation of the degree to which the result is sensitive to the specified independent variables). For both drugs, the ICERs in patients with a g*BRCA* mutation were lower than those in patients without a g*BRCA* mutation. Probabilistic sensitivity analysis estimated that olaparib was more cost-effective than niraparib, based on the willingness-to-pay threshold of NT$2,602,404 per PFS-LY gained.

Based on results of this study, the investigators concluded that olaparib was more cost-effective than niraparib as maintenance therapy for patients with recurrent platinum-sensitive ovarian cancer.

Source: Leung JH, Lang HC, Wang SY, Lo HF, Chan ALF. Cost-effectiveness analysis of olaparib and niraparib as maintenance therapy for women with recurrent platinum-sensitive ovarian cancer. *Expert Rev Pharmacoecon Outcomes Res.* 2021 Aug 6;1-8. doi: 10.1080/14737167.2021.1954506. Online ahead of print.

How to Sequence Treatment in Relapsed Ovarian Cancer

This review outlines treatment sequencing considerations for patients with recurrent ovarian cancer.

In recent years, several treatment options have become available for the management of relapsed ovarian cancer. These therapies include antiangiogenics such as bevacizumab, and poly (ADP-ribose) polymerase (PARP) inhibitors such as olaparib, niraparib, and rucaparib, which now play an integral role in maintenance therapy for recurrent disease, following response to platinum-based chemotherapy. These agents are being investigated further in the first-line setting, which has implications for subsequent lines of therapy, as previous exposure to these agents can influence therapeutic options for recurrent disease. This review, published in the January 2021 issue of *Future Oncology*, outlines treatment sequencing considerations in patients with recurrent ovarian cancer.

Selection of systemic therapy for recurrent ovarian cancer is dictated by several disease-related and patient-related factors. In particular, tumor biology plays a key role in treatment selection, as tumors harboring specific genetic alterations resulting in homologous recombination deficiencies, such as germline or somatic *BRCA1/2* mutations, exhibit specific clinical behaviors and responses to platinum-based chemotherapy and PARP inhibitors.

In potentially platinum-responsive patients with recurrent disease, the following options may be considered, and rechal-

lenge with previously administered agents may be an option for select patients.

- If there has been no previous exposure to biological therapy, platinum-based rechallenge plus bevacizumab is recommended for those with a high disease burden and priority for a symptomatic response. Platinum-based rechallenge followed by a PARP inhibitor is recommended in remaining patients
- If there has been previous exposure to a PARP inhibitor, platinum-based rechallenge plus bevacizumab is recommended
- If there has been previous exposure to bevacizumab, platinum-based rechallenge followed by PARP-inhibitor maintenance therapy may be considered. PARP-inhibitor monotherapy can be considered for heavily pretreated patients.

A major goal in the management of ovarian cancer is delaying the emergence of resistance to platinum-based chemotherapy. A key strategy to delay platinum resistance and improve prognosis of recurrent disease is to alternate treatments with different mechanisms of action. Trabectedin plus pegylated liposomal doxorubicin is currently a nonplatinum combination approved to treat recurrence in patients with platinum-sensitive disease. Identifying additional strategies to delay treatment resistance in ovarian cancer is a key strategy toward improving patient outcomes.

Source: Pignata S, Cecere SC. How to sequence treatment in relapsed ovarian cancer. *Future Oncol.* 2021;17(3s):1-8.

Assessing Comprehensive Care Deficits in US Ovarian Cancer Programs to Inform Quality Improvement Initiatives

Findings of a national survey of US ovarian cancer programs identified several patient care deficits, including a greater need for the integration of palliative care, social work, dietetics, and financial counseling, and the expansion of clinical trials and genetic testing/counseling.

A national survey of US ovarian cancer programs, conducted by the Association of Community Cancer Centers (ACCC), which assessed comprehensive care deficits to inform quality improvement initiatives, was reported at the 2021 American Society of Clinical Oncology Annual Meeting.

The online 20-question survey administered to ACCC and Society of Gynecologic Oncology members (using the Qualtrics platform and distributed via e-mail) was developed by a steering committee comprising gynecologic oncologists, pathologists, genetic counselors, a nurse navigator, and cancer center administrators. The survey sought to collect data about cancer programs, key needs of patients with ovarian cancer, and barriers to, and opportunities for improving, ovarian cancer care.

A total of 26 responses were received; of these, 26% were from the Comprehensive Community Cancer Programs, 22% were from National Cancer Institute-Designated Comprehensive Cancer Programs, 22% were from Academic Comprehensive Cancer Programs, and 13% were from Integrated Network Cancer Programs. The participants indicated that they treated 22 to 190 (median, 50.5) cases of ovarian cancer per year. The majority of the programs (85%) reported a multidisciplinary team for ovarian cancer and are part of a referral network (61%). All programs had ≥1 trials available for ovarian cancer, with an average of 1.5 phase 2 trials and 2 phase 3 clinical trials available. The programs did not routinely integrate palliative care and comprehensive symptom management, which was generally available by consult (81%), with only 15% available at first appointment and 4% integrated at the time of recurrence.

The programs did not routinely integrate palliative care and comprehensive symptom management, which was generally available by consult (81%), with only 15% available at first appointment and 4% integrated at the time of recurrence.

In terms of genetic testing practices aggregated across programs, 79% of patients received germline multipanel testing, 71% received germline *BRCA* alone, 50% received somatic multigene, and 51% received somatic *BRCA* alone. The majority of consultations included genetic counseling (75%), nurse navigation (75%), and social work (50%). Gynecologic oncology programs most frequently ordered genetic evaluations (88%). Genetic testing and counseling was the most frequent choice for a quality improvement project (46%), followed by clinical trial enrollment and availability (23%), multidisciplinary team care (19%), education on best practices (15%), palliative care (15%), and ancillary services (15%).

Based on the findings of a national survey of US ovarian cancer programs, the integration of palliative care, social work, dietetics, financial counseling, and the expansion of clinical trials and genetic testing/counseling were identified as care deficits, whereas multidisciplinary care was typical across a range of cancer programs.

Source: Smeltzer M, Dawkins M, Boehmer L, et al. Assessing comprehensive care deficits in United States (U.S.) ovarian cancer programs to inform quality improvement initiatives. *J Clin Oncol.* 2021;39(suppl_28):256.

Implementation of a Collaborative Model Provides Efficient Oncogenetic Services for Hereditary Breast and Ovarian Cancer

Results of the C-MOnGene study support the adoption of a collaborative oncogenetic model that provides flexible, patient-centered, and efficient genetic counseling and testing for hereditary breast and ovarian cancer and serves as an example for other institutions to incorporate these aspects into their oncology care.

To meet the demand for genetic counseling and testing for hereditary breast and ovarian cancer, an innovative and collaborative oncogenetic service delivery model was developed that sought to optimize efficiency and uptake of existing opportunities. The Collaborative Model in OncoGenetics (C MOnGene) study was designed to gain insights into the context in which the model was developed and implemented, and document the lessons that can be learned to optimize the delivery of oncogenetic services in other settings.

> The adoption of this collaborative oncogenetic model provides flexible, patient-centered, and efficient genetic counseling and testing for hereditary breast and ovarian cancer.

The oncogenetic model was developed and implemented at the Centre Hospitalier Universitaire de Québec-Université Laval, Quebec, Canada. The model emphasized the incorporation of an interdisciplinary oncogenetic team throughout the care trajectory and extended the role of health professionals who are not specialized in genetics. Nurse navigators and clinical oncology nurses trained in oncogenetics worked in collaboration with genetic counselors to identify people likely to benefit from a genetic test, obtained their informed consent, provided genetic counseling, and ordered testing. Genetic group counseling of 15 to 25 people was preferred to individual counseling. The model also prioritized collaboration between institutions, making it possible to better equip primary and secondary healthcare centers of the network.

Adoption of this model for 3 years resulted in double the annual number of patients seen in genetic counseling. This was accompanied by a significant reduction in the average number of days between genetic counseling and disclosure of test results. Group counseling sessions resulted in an improvement in participants' knowledge of breast cancer and genetics. Moreover, the majority of patients indicated that they were satisfied with the genetic counseling and testing initiative.

Based on these results, the investigators concluded that the adoption of this collaborative oncogenetic model provides flexible, patient-centered, and efficient genetic counseling and testing for hereditary breast and ovarian cancer and serves as an example that other institutions can incorporate into their oncology care.

Source: Lapointe J, Dorval M, Chiquette J, et al. A collaborative model to implement flexible, accessible and efficient oncogenetic services for hereditary breast and ovarian cancer: the C-MOnGene study. *Cancers (Basel).* 2021;13:2729.

Intervention of a Health Education Clinical Nursing Pathway Among Patients with Ovarian Carcinoma

Results from a retrospective analysis indicate that health education, using a clinical nursing pathway, results in a more effective understanding of ovarian cancer, reduced psychological burden, improved sleep quality, decreased incidence of complications, improved self-care agency, and improved quality of life among patients with ovarian cancer.

A retrospective study investigated the effect of health education on several parameters, including self-care agency, quality of life, negative emotions, and nursing satisfaction among patients with ovarian carcinoma. Results of this analysis were published in the *American Journal of Translational Research.*

The study identified patients with stage I or II ovarian carcinoma, aged between 30 and 60 years, treated at a hospital in China from January 2019 to January 2020; the clinical data for these patients were analyzed. Patients were classified into 2 groups: a control group that received health education per routine nursing, and an observation group that received the intervention via a specified clinical nursing pathway. Several parameters were analyzed between the 2 groups before and after the intervention, including postoperative complications such as deep vein thrombosis; self-care agency score; quality-of-life score, as evaluated by the Quality-of-Life Questionnaire-30; and health knowledge, as assessed by an ovarian carcinoma knowledge questionnaire. Sleep quality, as evaluated by the Pittsburgh Sleep Quality Index; negative emotions, as assessed by the Hamilton Anxiety Scale and Hamilton Depression Scale; and nursing satisfaction were also assessed.

A total of 61 patients were included in the study; 31 patients were included in the control group and 30 patients in the observation group. Following the health education intervention, patients in the observation group showed significantly higher levels of health knowledge and lower incidence of postoperative complications than those in the control group. The scores of negative emotions and sleep quality were significantly decreased in both groups after intervention compared with

those before intervention (P <.05), and scores in the observation group were significantly lower than those in the control group (P <.05). Similarly, scores of self-care agency and quality of life were significantly higher after intervention than before intervention (P <.05); moreover, patients in the observation group showed higher scores than those in the control group (P <.05). Patients indicated that overall nursing satisfaction was relatively high.

Based on these results, the investigators concluded that health education intervention via a clinical nursing pathway can yield a more effective understanding of ovarian cancer, reduced psychological burden, improved sleep quality, decreased incidence of complications, improved self-care agency, and improved quality of life among patients with ovarian cancer.

Source: Zhao J, Chai G, Yang F, et al. Analysis of the change of clinical nursing pathway in health education among patients with ovarian carcinoma. *Am J Transl Res.* 2021;13:3138-3146.

Immunologic Response to COVID-19 Vaccination in Patients with Ovarian Cancer Receiving PARP Inhibitors

The findings of a prospective study suggest that immunologic response to SARS-CoV-2 vaccination is lower among patients with ovarian cancer who are receiving treatment compared with healthy volunteers, indicating that such patients should maintain precautions against COVID-19 despite vaccination.

A prospective study compared the immunologic response to SARS-CoV-2 vaccination among patients with ovarian cancer who received systemic therapy versus healthy volunteers. The results of the study were published in the October 2021 issue of *Vaccines*.

The study prospectively enrolled both patients with cancer receiving poly (ADP-ribose) polymerase (PARP) inhibitors and healthy volunteers. The kinetics of anti–SARS-CoV-2 neutralizing antibodies after COVID-19 vaccination were assessed. Baseline demographics, comorbidities, and the levels of neutralizing antibodies were compared between the 2 groups.

A total of 36 patients with ovarian cancer who received PARP inhibitor therapy (median age, 64 years) were enrolled in the study; 160 controls (healthy volunteers) were also enrolled with similar characteristics (median age, 63 years). Among the patients with ovarian cancer, 20 received olaparib, 15 received niraparib, and 1 received rucaparib. In terms of vaccination received, 30 of 36 patients received a PARP inhibitor, and 130 of 160 healthy volunteers in the control group received an mRNA vaccine; whereas 6 of 36 patients and 30 of 160 controls received the AZD1222 vaccine; each participant received 2 doses of the assigned vaccine.

No new safety issues were reported in the study population; the most frequent adverse events included pain at the injection site, fever, and fatigue. However, the levels of SARS-CoV-2 neutralizing antibodies were significantly lower in the patients with cancer receiving PARP inhibitor therapy, compared with the matched healthy volunteers, up to day 30 after the second dose. Although no significant difference in neutralizing antibody titers were noted on day 1 between the 2 groups, on day 22, 10 (27.8%) patients receiving a PARP inhibitor had neutralizing antibody titers ≥30%, compared with 119 (74.4%) in the control group (P <.001). The lower neutralizing antibody titers in treated patients with ovarian cancer receiving a PARP inhibitor compared with healthy controls persisted for 1 month after the second vaccination dose (83.6% vs 92.9%, respectively; P <.001). Preclinical evidence suggests that PARP inhibitors affect immune cells by attenuating SARS-CoV-2–induced inflammatory responses and cytokine storms, and reducing lung fibrosis, thus supporting its potential use in the treatment of COVID-19.

No new safety issues were reported in the study population; the most frequent adverse events included pain at the injection site, fever, and fatigue.

These results suggest that immunologic response to SARS-CoV-2 vaccination was lower among patients with cancer receiving PARP inhibitor treatment compared with a healthy population, indicating that such patients should maintain precautions against COVID-19 despite vaccination. The researchers recommend the administration of a third dose after a certain time among patients with ovarian cancer receiving PARP inhibitor therapy, to generate optimal immunity against the SARS-CoV-2 virus.

Source: Liontos M, Terpos E, Markellos C, et al. Immunological response to COVID-19 vaccination in ovarian cancer patients receiving PARP inhibitors. *Vaccines (Basel).* 2021;9:1148.

Impact of the COVID-19 Pandemic on Ovarian Cancer Management: Adjusting to the New Normal

This review outlines the disruptions to delivery of cancer care caused by the COVID pandemic, including delays in diagnosis, surgery, and treatment, as well as the psychological impact. It is crucial that the needs of each patient

and the risk–benefit profile of each therapy are analyzed regularly, so that creative and effective ways can be developed to offer uninterrupted, timely, and safe treatment to patients with ovarian cancer.

The COVID-19 pandemic, caused by SARS-CoV-2, has produced unprecedented disruptions and challenges globally, especially in the oncology community. In particular, the COVID crisis has impacted patients with ovarian cancer in multiple ways, including delays in diagnosis, surgery, and therapy, caused by several factors, including federal guidelines, patient choice, or other circumstances. Specifically, in-person office visits, laboratory tests, imaging studies, treatments, and surgeries have been the most affected by delays, which may have adverse effects on clinical outcomes. Moreover, interruptions in clinical trials have hampered research efforts to discover new therapies for ovarian cancer and may have ramifications for patients for many years to come.

The psychological impact of the pandemic is immense, with treatment delays and disruption of access to cancer care causing high levels of worry, as well as varying levels of anxiety and depression.

The psychological impact of the pandemic is immense, with treatment delays and disruption of access to cancer care causing high levels of worry, as well as varying levels of anxiety and depression, and negatively impacting emotional health and well-being among patients with cancer. Further compounding the issue is the fact that access to psychological support is limited during this time by the same factors impacting oncologic care.

The delivery of cancer care has adapted to overcome these COVID-related challenges, with patients and their oncologists making efforts to balance the fears of COVID-19 with the consequences of delaying cancer care. Alternative strategies are being adopted to limit in-person hospital visits and thereby reduce spread of the disease. Oncology follow-ups are being conducted via telemedicine instead of in-person visits. New standards that are being implemented in clinical practices include the use of masks, temperature checks, and self-assessment questionnaires before entry to the clinic, and social distancing. COVID-19–free hubs have been established, where patients with cancer can receive treatment with less potential exposure to the virus.

Overall, during these pandemic times or during any other disruption, it is important that there are no delays in diagnosis, surgery, or treatment for any patient with cancer, including those with ovarian cancer, and the psychological needs of such patients must be adequately addressed. It is also crucial that the needs of each patient, and the risk–benefit profile of each therapy are analyzed regularly, so that creative and effective ways can be developed to offer uninterrupted, timely, and safe treatment to patients with ovarian cancer.

Source: Jacome LS, Deshmukh SK, Thulasiraman P, Holliday NP, Singh S. Impact of COVID-19 pandemic on ovarian cancer management: adjusting to the new normal. *Cancer Manag Res.* 2021;13:359-366.

Real-World Treatment Patterns of Maintenance Therapy in Platinum-Sensitive Recurrent Ovarian Cancer

Findings of a retrospective study indicate that patients with platinum-sensitive recurrent ovarian cancer were increasingly being administered maintenance therapy after second-line or third-line platinum-based chemotherapy regardless of biomarker status.

A retrospective study evaluated real-world treatment patterns of maintenance therapy with poly (ADP-ribose) polymerase (PARP) inhibitors or bevacizumab in patients with ovarian cancer who had received previous platinum-based chemotherapy. The results were published in the October 2021 issue of *Gynecologic Oncology*.

This study used an electronic health record–derived deidentified (US nationwide Flatiron Health) database to select patients diagnosed with ovarian cancer who had received ≥2 lines of platinum-based chemotherapy. Patients who completed platinum-based chemotherapy on or after March 1, 2017, had ≥2 months of active surveillance or received maintenance therapy with a PARP inhibitor or bevacizumab were analyzed. Data on biomarker status were also obtained.

A total of 2292 eligible patients with ovarian cancer were identified. Of these, 222 patients completed platinum-based chemotherapy and had ≥2 months of active surveillance or received maintenance therapy with a PARP inhibitor or bevacizumab. Biomarker analysis showed that 46 (20%) patients had *BRCA* mutations (*BRCA*m), 132 (59%) had a wild-type *BRCA* (*BRCA*wt) gene, and 47 (21%) were of unknown status. Although the majority of patients with *BRCA*m received a PARP inhibitor (63%), approximately one-third of the eligible patients did not (17% received bevacizumab, and 20% underwent active surveillance). Among the patients with *BRCA*wt, 40% received a PARP inhibitor, 23% received bevacizumab, and 36% underwent active surveillance. Younger patients and those with *BRCA*m received maintenance therapy more frequently. The use of PARP inhibitors increased on average by 1.3% every 3 months ($P = .02$) with no significant change in the use of bevacizumab.

Based on these results, the researchers concluded that maintenance therapy with a PARP inhibitor or bevacizumab was increasingly being administered after second-line or third-line platinum-based chemotherapy, regardless of biomarker status. These results also indicate shifting treatment patterns in a real-world population of patients with recurrent ovarian cancer.

Source: Moss HA, Perhanidis JA, Havrilesky LJ, Secord AA. Real-world treatment patterns of maintenance therapy in platinum-sensitive recurrent ovarian cancer. *Gynecol Oncol.* 2021;163:50-56.

Niraparib Efficacy and Safety in Patients with *BRCA*-Mutated Ovarian Cancer from 3 Phase 3 Trials

Pooled analysis data from the PRIMA, NOVA, and NORA trials suggest that patients with *BRCA*-mutated ovarian cancer derive a significant progression-free survival benefit from niraparib maintenance treatment, with no new safety signals.

Results of pooled analysis of 3 phase 3 trials that evaluated efficacy and safety of the poly (ADP-ribose) polymerase (PARP) inhibitor, niraparib, in patients with ovarian cancer harboring *BRCA* mutations were presented at the 2021 American Society of Clinical Oncology Annual Meeting. Trials considered in the analysis were PRIMA/ENGOT-OV26/GOG-3012 (NCT02655016), ENGOT-OV16/NOVA (NCT01847274), and NORA (NCT03705156).

> Data from the PRIMA, NOVA, and NORA trials indicate that patients with *BRCA*m ovarian cancer derive a significant PFS benefit from niraparib maintenance treatment.

The pooled analysis included patients enrolled in 3 phase 3 trials: PRIMA, NOVA, and NORA. The PRIMA trial enrolled patients with newly diagnosed advanced ovarian, fallopian tube, or primary peritoneal cancer who had stage III or IV high-grade serous or endometrioid tumors and a complete or partial response to their first-line platinum-based chemotherapy. Both the NOVA and NORA trials enrolled patients with platinum-sensitive, advanced ovarian, fallopian tube, or primary peritoneal cancer who had received ≥2 lines of platinum-based chemotherapy. Prespecified subgroup analysis in the PRIMA trial was by tumor *BRCA* mutation status, and by germline *BRCA* mutation status in the NOVA and NORA trials. In all 3 trials, the primary end point was progression-free survival (PFS) by blinded independent central review.

Overall, a total of 526 patients enrolled in the PRIMA, NOVA, and NORA trials had *BRCA* mutations. Of these, 223 patients were enrolled in the PRIMA trial, 203 in the NOVA trial, and 100 in the NORA trial. The majority of *BRCA* mutations were in the *BRCA1* gene (PRIMA: 148 *BRCA1*m, 75 *BRCA2*m; NOVA: 128 *BRCA1*m, 69 *BRCA2*m, and 13 *BRCA1/2*m; NORA: 78 *BRCA1*m, 21 *BRCA2*m, and 1 *BRCA1/2*m).

Patients with ovarian cancer harboring *BRCA* mutations had a significant PFS advantage with niraparib maintenance treatment in the PRIMA trial (*BRCA*m, 22.1 vs 10.9 months; hazard ratio [HR], 0.40), NOVA trial (g*BRCA*m, 21.0 vs 5.5 months; HR, 0.27), and NORA trial (g*BRCA*m, not estimable vs 5.5 months; HR, 0.22), showing a trend that was consistent for both *BRCA1* and *BRCA2* mutations. Across the 3 trials, the most frequent treatment-emergent adverse events were thrombocytopenia, anemia, neutropenia, and hypertension.

Pooled analysis data from the PRIMA, NOVA, and NORA trials indicate that patients with *BRCA*m ovarian cancer derive a significant PFS benefit from niraparib maintenance treatment, with the emergence of no new safety signals.

Source: Martin AG, Matulonis UA, Korach J, et al. Niraparib efficacy and safety in patients with *BRCA* mutated (*BRCA*m) ovarian cancer: results from three phase 3 niraparib trials. *J Clin Oncol.* 2021;39(suppl_15). Abstract 5518.

Anlotinib in Combination with TQB2450 in Patients with Recurrent Ovarian Cancer (ACTION)

Results of the multicohort phase 1b ACTION trial indicated that anlotinib plus TQB2450 shows encouraging antitumor activity and tolerable toxicity in patients with recurrent advanced ovarian cancer.

An open-label, multicohort, multicenter phase 1b trial (ACTION; NCT04236362) evaluated the efficacy and safety of the multitarget tyrosine kinase inhibitor, anlotinib, combined with the PD-L1 monoclonal antibody TQB2450 in patients with advanced gynecologic cancer. The results of the ovarian cancer cohort of the ACTION trial were presented at the 2021 American Society of Clinical Oncology Annual Meeting.

Between February 21, 2020, and January 15, 2021, the study enrolled patients aged 18 to 70 years with platinum-resistant or platinum-refractory epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, as well as an Eastern Cooperative Oncology Group performance status of 0 or 1, and measurable disease according to the Response Evaluation Criteria in Solid Tumors. Eligible patients received anlotinib (12 mg per day orally, days 1-14 of each cycle) and TQB2450

(1200 mg intravenously on day 1 of each cycle) every 3 weeks until disease progression, unacceptable toxicity, or withdrawal of consent. The primary end point was investigator-assessed objective response rate (ORR); secondary end points included progression-free survival (PFS), duration of response (DOR), overall survival (OS), and safety. The data cutoff date was January 15, 2021.

A total of 33 patients received the combination treatment in the ovarian cancer cohort. The median age of the study population was 55 years; the majority had received ≥1 platinum-based chemotherapies, with a median of 3 previous lines of chemotherapy. At median follow-up of 5.1 months, an ORR of 52% was achieved (n = 25 evaluable patients), including 13 partial responses. The median PFS was 6.7 months. The median DOR and the median OS were not reached.

Overall, 54.5% of patients had grade 3 or 4 treatment-related adverse events (TRAEs). The most frequent TRAEs were palmar-plantar erythrodysesthesia syndrome (also known as hand-foot syndrome) (21.2%) and hypertension (18.2%). Immune-related adverse events of grade 1 or 2 severity included hypothyroidism (24.2%) and fatigue (9.1%). No treatment-related deaths were reported.

Based on these results, the investigators concluded that anlotinib plus TQB2450 shows encouraging antitumor efficacy and tolerable toxicity in patients with recurrent advanced ovarian cancer.

Source: Lan C, Zhao J, Yang F, et al. Anlotinib in combination with TQB2450 in patients with recurrent ovarian cancer (ACTION): a multicenter, single-arm, open-label, phase Ib trial. *J Clin Oncol.* 2021;39(suppl_15). Abstract 5557.

Phase 1 Study of GAS6/AXL Inhibitor (AVB-500) in Recurrent, Platinum-Resistant Ovarian Carcinoma

Results of a dose-escalation phase 1 study indicated that AVB-500 is well-tolerated in combination with paclitaxel or pegylated liposomal doxorubicin, with higher antitumor activity seen in combination with paclitaxel, and no previous exposure to bevacizumab.

This phase 1 study (NCT03639246) evaluated the safety, tolerability, and preliminary efficacy of the first-in-class GAS6/AXL inhibitor, AVB-500, in combination with pegylated liposomal doxorubicin (PLD) or paclitaxel and determined the recommended phase 2 dose (RP2D) in patients with platinum-resistant high-grade serous ovarian cancer. The results of this trial were presented at the 2021 American Society of Clinical Oncology Annual Meeting.

The study enrolled patients with recurrent, platinum-resistant, high-grade serous ovarian cancer, Eastern Cooperative Oncology Group performance status 0-1, and 1 to 3 previous lines of therapy. Eligible patients were enrolled in cohorts with escalating doses of AVB-500 (from 10-20 mg/kg every 2 weeks) in combination with weekly paclitaxel (80 mg/m^2 on days 1, 8, and 15 every 28 days) or PLD (40 mg/m^2 on day 1, every 28 days). The study evaluated safety and tolerability, efficacy, RP2D, pharmacokinetics, and pharmacodynamics.

A total of 53 patients were enrolled; of these, 23 patients received paclitaxel plus AVB-500, and 30 patients received PLD plus AVB-500. Grade 3 or 4 treatment-related adverse events were observed in 17% of patients who received paclitaxel and 7% of those who received PLD. No treatment discontinuations caused by adverse events were reported. Adverse events were mostly related to known side-effect profiles of paclitaxel and PLD. The RP2D was identified as 15 mg/kg.

Paclitaxel plus AVB-500 yielded an ORR of 35%, including 2 complete responses; whereas PLD plus AVB-500 yielded an ORR of 11%.

Higher objective response rates (ORRs) were achieved in the paclitaxel-treated subgroup compared with the PLD cohort. Paclitaxel plus AVB-500 yielded an ORR of 35%, including 2 complete responses; whereas PLD plus AVB-500 yielded an ORR of 11%. The ORR was 19% in patients with a platinum-free interval (PFI) of <3 months versus 23% in patients with a PFI of 3 to 6 months. Moreover, the ORR was 11% (2/18) in patients with 1 previous treatment versus 27% (9/33) in patients with 2 to 3 previous lines of therapy. A higher ORR of 33% (9/27) was achieved in patients who had not been exposed to bevacizumab versus 8% (2/24) in those with previous exposure to bevacizumab. Higher efficacy outcomes were achieved in the paclitaxel combination cohort, in which AVB-500 trough levels were above the minimal efficacious concentration (MEC) of 13.8 mg/L, compared with those with trough levels below MEC in terms of ORR (43% [6/14] vs 22% [2/9]), median progression-free survival (3.9 months vs 2.8 months), and median overall survival (17.8 months vs 8.7 months).

Based on these results, the investigators concluded that AVB-500 was well-tolerated in combination with paclitaxel or PLD, with higher response rates seen in combination with paclitaxel, and trough levels >13.8 mg/L, in patients with no previous exposure to bevacizumab.

Source: Fuh KC, Bookman MA, Coleman RL, et al. Phase 1b study of GAS6/AXL inhibitor (AVB-500) in recurrent, platinum-resistant ovarian carcinoma. *J Clin Oncol.* 2021;39(suppl_15). Abstract 5566.

Optimal Treatment Duration of Bevacizumab plus Carboplatin/Paclitaxel in Advanced Ovarian Cancer

Primary results of a randomized phase 3 trial indicate that prolonged treatment with bevacizumab for up to 30 months does not provide survival benefit in patients with advanced ovarian cancer; therefore, bevacizumab treatment duration of 15 months remains the standard of care in this setting.

A multicenter, open-label, randomized, 2-arm phase 3 trial (NCT01462890) evaluated the optimal treatment duration of bevacizumab combined with carboplatin/paclitaxel chemotherapy in patients with advanced ovarian cancer. Primary results of this study were reported at the 2021 American Society of Clinical Oncology Annual Meeting.

The trial enrolled patients with histologically confirmed epithelial ovarian, fallopian tube, or peritoneal cancer, with International Federation of Gynecology and Obstetrics (FIGO) stage IIB-IV, and Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2, who underwent debulking surgery ≤8 weeks before treatment initiation, and >4 weeks before first bevacizumab dose. Eligible patients received 6 cycles of chemotherapy (paclitaxel 175 mg/m^2 plus carboplatin AUC 5, every 3 weeks) plus bevacizumab (15 mg/kg every 3 weeks). Patients were randomized (1:1) to receive bevacizumab for either 15 months (Bev15 arm) or 30 months (Bev30 arm). Stratification was achieved by FIGO stage/residual tumor (stage IIB-IIIC/no residual tumor vs stage IIB-IIIC/residual tumor or stage IV). The primary end point was investigator-assessed progression-free survival (PFS); secondary end points were overall survival, objective response rate, quality of life, safety, and tolerability. The trial was designed with 80.2% (0.82) power to detect a hazard ratio of 0.66, favoring experimental treatment after 697 PFS events.

Although prolonged treatment with bevacizumab for up to 30 months is feasible, it does not provide survival benefit in patients with advanced ovarian cancer.

From November 2011 to August 2013, 927 women were randomized in the study; of these, 464 were assigned to the Bev15 arm, and 463 patients to the Bev30 arm. Baseline characteristics were balanced between arms, and the median age was 61 years. The majority of patients had epithelial ovarian cancer (83%), high-grade serous histology (79%), ECOG PS 0 or 1 (96%), and no residual tumor (58%).

At a median follow-up of 85 months, no significant difference was noted in PFS between the Bev15 and Bev30 arms (median PFS, 24.2 vs 26.0 months). Similarly, no significant differences were seen in subgroup analyses of PFS, when stratified by FIGO IIB-IIIC with or without residual tumor, or FIGO IV. Safety data were consistent with those previously described for bevacizumab, with the emergence of no new safety signals with prolonged treatment.

Primary results of this trial indicate that although prolonged treatment with bevacizumab for up to 30 months is feasible, it does not provide survival benefit in patients with advanced ovarian cancer. Therefore, bevacizumab treatment duration of 15 months remains the standard of care in this setting.

Source: Pfisterer J, Joly F, Kristensen G, et al. Optimal treatment duration of bevacizumab (BEV) combined with carboplatin and paclitaxel in patients (pts) with primary epithelial ovarian (EOC), fallopian tube (FTC) or peritoneal cancer (PPC): a multicenter open-label randomized 2-arm phase 3 ENGOT/GCIG trial of the AGO Study Group, GINECO, and NSGO (AGO-OVAR 17/BOOST, GINECO OV118, ENGOT Ov-15, NCT01462890). *J Clin Oncol.* 2021;39(suppl_15). Abstract 5001.

NeoPembrOV Study of Neoadjuvant Chemotherapy with or without Pembrolizumab Followed by Interval Debulking Surgery and Standard Systemic Therapy with or without Pembrolizumab for Advanced High-Grade Serous Carcinoma

Results of the NeoPembrOV phase 2 trial support the safe addition of pembrolizumab to neoadjuvant chemotherapy in patients deemed nonoptimally resectable. Although the addition of pembrolizumab resulted in an improved complete resection rate, it did not provide a progression-free survival benefit.

The multicenter, open-label, noncomparative, randomized NeoPembrOV phase 2 trial investigated the efficacy and safety of adding pembrolizumab to neoadjuvant carboplatin/paclitaxel chemotherapy after interval debulking surgery (IDS) and standard systemic therapy in patients with initially unresectable high-grade serous carcinoma (HGSC). The results of this study were reported at the 2021 American Society of Clinical Oncology Annual Meeting.

The study enrolled patients with International Federation of Gynecology and Obstetrics (FIGO) stage IIIC or IV ovarian, tubal, or primary peritoneal HGSC, with a ≤8-week interval between diagnosis and enrollment. These patients may have been denied up-front complete debulking surgery, and cytoreduction would have been anticipated with the goal of no residual disease planned at IDS. Eligible patients were randomized (2:1) to receive 4 cycles of pembrolizumab with or without carboplatin/paclitaxel before IDS, followed by postoperative

chemotherapy (2-4 cycles) and optional bevacizumab for 15 months in total, with or without pembrolizumab as maintenance therapy for up to 2 years. Stratification was based on center, FIGO stage, bevacizumab planned after IDS, and disease volume (<5 cm/>5 cm). The primary end point was centrally reviewed complete resection rate (CRR) at IDS; secondary end points were safety, surgical morbidity, overall response rate (ORR), progression-free survival (PFS), and overall survival.

From February 2018 to April 2019, 91 patients were enrolled in the study; of these, 61 patients were in the carboplatin/paclitaxel plus pembrolizumab group, and 30 were in the carboplatin/paclitaxel group. The median age of the study population was 63 years, and the median peritoneal cancer index was 24; the majority had FIGO stage IIIC (82.4%) and either used or anticipated the use of bevacizumab (91%). Eighty (88%) patients received bevacizumab plus carboplatin/paclitaxel, followed by bevacizumab with or without pembrolizumab in maintenance.

> These results support the safe addition of pembrolizumab to neoadjuvant chemotherapy in patients deemed nonoptimally resectable.

In the carboplatin/paclitaxel plus pembrolizumab group (n = 61), 58 (95%) patients had IDS and 78% achieved complete resection. The CRR achieved in the carboplatin/paclitaxel plus pembrolizumab group was 74%; and that in the carboplatin/paclitaxel group was 70%. Higher ORRs were achieved before IDS in the carboplatin/paclitaxel plus pembrolizumab group versus the carboplatin/paclitaxel group (76% vs 61%). No PFS benefit was observed with the addition of pembrolizumab to neoadjuvant chemotherapy.

The incidence of grade ≥3 adverse events (AEs) was similar in the carboplatin/paclitaxel plus pembrolizumab and carboplatin/paclitaxel groups (75.4% vs 66.7%); the more frequent AEs in the carboplatin/paclitaxel plus pembrolizumab group were neutropenia (13.1%), anemia (4.9%), thrombopenia (3.3%), high blood pressure (3.3%), and pulmonary embolism (3.3%). Postoperative complications occurred in 21.3% of patients in the carboplatin/paclitaxel plus pembrolizumab group, compared with 13.3% in the carboplatin/paclitaxel group.

These results support the safe addition of pembrolizumab to neoadjuvant chemotherapy in patients deemed nonoptimally resectable, which resulted in improved CRR, but did not provide PFS benefit.

Source: Ray-Coquard IL, Savoye AM, Mouret-Reynier MA, et al. Efficacy and safety results from neopembrov study, a randomized phase II trial of neoadjuvant chemotherapy (CT) with or without pembrolizumab (P) followed by interval debulking surgery and standard systemic therapy ± P for advanced high-grade serous carcinoma (HGSC): a GINECO study. *J Clin Oncol.* 2021;39(suppl_15). Abstract 5500.

Mirvetuximab Soravtansine plus Bevacizumab in Patients with Recurrent Ovarian Cancer

Results of the phase 1b FORWARD II trial show that the MIRV/bevacizumab combination demonstrates promising antitumor activity with durable responses and favorable tolerability in high FRα recurrent ovarian cancer.

The phase 1b FORWARD II trial (NCT02606305) evaluated the preliminary antitumor activity of the folate receptor alpha (FRα)–targeting antibody–drug conjugate, mirvetuximab soravtansine (MIRV), in combination with bevacizumab in patients with FRα-positive recurrent ovarian cancer. The results of the final analysis of this trial were reported at the 2021 American Society of Clinical Oncology Annual Meeting.

The study enrolled patients with recurrent ovarian cancer who had received up to 3 previous regimens and were diagnosed with FRα-positive disease (medium/high expression; ≥50%/≥75% of cells with PS2+ staining intensity, and for whom a nonplatinum-based doublet would be appropriate). Patients with platinum-resistant ovarian cancer (PROC) were defined as those with recurrence ≤6 months after their last platinum dose; whereas patients with platinum-sensitive ovarian cancer (PSOC) would have responded to the last platinum therapy and did not progress ≤6 months. Eligible patients received MIRV (6 mg/kg) and bevacizumab (15 mg/kg) on day 1 of a 21-day cycle. The objective response rate (ORR), median duration of response (mDOR), and median progression-free survival (mPFS) were assessed.

A total of 60 patients received the MIRV/bevacizumab combination. The median age of the study population was 60 years. All participants had received a median of 2 previous lines of systemic therapy. The majority of patients showed high FRα expression (55%) and had PROC disease (53%). All patients had previous exposure to platinum compounds; 53% had a platinum-free interval (PFI) of ≤6 months, and 33% had a PFI of >6 to ≤12 months.

At a median follow-up of 17.5 months, a confirmed ORR of 47% was achieved in the overall population; mDOR was 9.7 months; and mPFS was 8.3 months. Higher responses were achieved in patients with high FRα expression (n = 33), with an ORR of 64%, mDOR of 11.8 months, and mPFS of 10.6 months. Among patients with PROC and high FRα expression (n = 17), ORR was 59%, mDOR was 9.4 months, and mPFS was 10.1 months. Among patients with PSOC and high FRα expression (n = 16), ORR was 69%, mDOR was 12.9 months, and mPFS was 13.3 months

Most adverse events were low grade, and the most frequent of any-grade treatment-related adverse events (TRAEs) were gastrointestinal and ocular in nature, including diarrhea (62%), blurred vision (60%), fatigue (60%), and nausea (57%). The most frequent grade 3/4 TRAEs were hypertension (17%) and neutropenia (13%); all other grade ≥3 events occurred in ≤10% of patients.

Based on these results, the investigators concluded that the MIRV/bevacizumab combination demonstrates promising antitumor activity with a durable response and favorable tolerability in high FRα recurrent ovarian cancer.

Source: MO'Malley D, Oaknin A, Matulonis UA, et al. Mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), in combination with bevacizumab in patients (pts) with platinum-agnostic ovarian cancer: final analysis. *J Clin Oncol.* 2021;39(suppl_15). Abstract 5504.

Patient Self-Reporting of Tolerability in Phase 2 Trial Comparing Gemcitabine plus Adavosertib or Placebo in Women with Platinum-Resistant Epithelial Ovarian Cancer

Patient-reported outcomes of tolerability with adavosertib indicated greater incidence of fatigue, diarrhea, mucositis, and difficulty swallowing in patients receiving adavosertib and gemcitabine; however, no significant differences were noted in the symptomatic adverse-event profile for gastrointestinal events and anxiety.

A randomized, double-blind, placebo-controlled phase 2 trial (NCT02151292) compared gemcitabine in combination with either the *WEE1* inhibitor, adavosertib, or placebo in women with platinum-resistant epithelial ovarian cancer. Patient-reported outcomes of tolerability were reported at the 2021 American Society of Clinical Oncology Annual Meeting.

Eligible patients received either adavosertib or placebo (days 1-2, 8-9, and 15-16) with gemcitabine (days 1, 8, and 15) in a 28-day cycle. The objectives of the study were to characterize frequency, severity, and/or interference of symptomatic adverse events (AEs; scored 0-4; higher scores indicating worse AEs) in the first 3 months of therapy, as measured by 12-week area under the curve (AUC12w) over time, and incremental AUC12w for adjustment to baseline symptomatic AEs.

The study enrolled 51 patients; of the 47 evaluable patients, 28 patients received adavosertib/gemcitabine, and 19 patients received placebo/gemcitabine. The majority of the study population had an Eastern Cooperative Oncology Group performance status ≤1. Patients in the adavosertib/gemcitabine arm received a median of 5 treatment cycles, and those in the placebo/gemcitabine arm received a median of 2 treatment cycles. More than 90% of patients completed the survey.

Patients who received adavosertib/gemcitabine indicated higher any-grade severity and interference for several AEs; mean AUC12w was significantly higher for fatigue severity and interference, diarrhea frequency, mucositis, and difficulty swallowing severity. No significant between-arm differences were noted in abdominal pain, bloating, nausea, vomiting, or anxiety. The incremental AUC12w was significantly higher in the adavosertib/gemcitabine arm compared with the placebo/gemcitabine arm for difficulty swallowing severity, mucositis severity, and fatigue severity. Compared with placebo, a significantly greater number of 3/4 scores per survey time were observed at cycle 1, day 15 for fatigue severity in the adavosertib/gemcitabine group (55% vs 19%; $P = .044$).

Patients who received adavosertib/gemcitabine indicated higher any-grade severity and interference for several AEs.

Patients' perception of adavosertib-emergent toxicity indicated a higher incidence of fatigue, diarrhea, mucositis, and difficulty swallowing in patients receiving adavosertib and gemcitabine. However, no significant differences were noted in the symptomatic AE profile for nausea, vomiting, abdominal pain, bloating, or anxiety.

Source: Madariaga A, Mitchell SA, Pittman T, et al. Patient self-reporting of tolerability using PRO-CTCAE: a randomized double-blind placebo-controlled phase II trial comparing gemcitabine in combination with adavosertib or placebo in women with platinum resistant epithelial ovarian cancer. *J Clin Oncol.* 2021;39(suppl_15). Abstract 5541.

Maintenance Gemogenovatucel-T Immunotherapy in Newly Diagnosed Advanced Ovarian Cancer

Results of the phase 2b VITAL trial suggest that immunotherapy with the autologous tumor cell vaccine gemogenovatucel-T as frontline maintenance in stage III/IV ovarian cancer is well-tolerated and shows clinical benefit in both *BRCA*-wild type and homologous recombination–proficient subgroups.

The double-blind, placebo-controlled, phase 2b VITAL (NCT02346747) trial demonstrated recurrence-free survival (RFS) benefit with maintenance therapy of the autologous tumor-cell vaccine, gemogenovatucel-T (GEM), following frontline platinum-based chemotherapy in patients with advanced high-grade ovarian cancer. Post-hoc homologous recombina-

tion deficiency (HRD) subgroup analysis and identification of an additional molecular subgroup sensitive to GEM were reported at the 2021 American Society of Clinical Oncology Annual Meeting.

This study enrolled patients with newly diagnosed stage III/IV epithelial ovarian cancer, who achieved a clinical complete response to frontline surgery and platinum-based chemotherapy. Eligible patients received 1×10^7 cells/mL of GEM or placebo intradermally once a month, for up to 12 doses or until disease progression. The primary end point was RFS, assessed by blinded independent central review. HRD status was determined according to the Myriad Genetics myChoice CDx assay (HRD score <42 for proficient). A protein–protein interaction network was constructed using the STRING database and tumor annotated DNA polymorphism data. The per-protocol population included 91 patients.

Of the 62 evaluable patients assessed for HRD status, 45 patients were homologous recombination proficient, and 17 were homologous recombination deficient; 25 of 45 homologous recombination proficient patients received GEM, and 20 received placebo. The 2 groups were mostly well-balanced, except for a higher proportion of patients with Eastern Cooperative Oncology Group performance status of 0 in the placebo group.

GEM, as first-line maintenance therapy in patients with ovarian cancer, was well-tolerated. The incidence of grades 1 to 3 adverse events was similar in the 2 groups; 63.2% in the GEM group and 59.6% in the placebo group. Among all patients, those in the GEM group showed significant benefit in median RFS (11.5 vs 8.4 months; hazard ratio [HR], 0.688; $P = .078$), which did not translate into overall survival (OS) benefit (not reached vs 16.0 months; HR, 0.630; $P = .110$). In the homologous recombination proficient subgroup, from the time of randomization, median RFS was significantly improved with GEM compared with placebo (10.6 vs 5.7 months; HR, 0.386; $P = .007$). The OS in the GEM/homologous recombination proficient group was significantly higher than that in the placebo/homologous recombination proficient group (HR, 0.417; $P = .02$); 2-year OS was 92% in the GEM group, compared with 55% in the placebo group ($P = .002$); and 3-year OS was 70% and 40% ($P = .019$), respectively. STRING analysis of the homologous recombination proficient/*p53*-mutated subgroup demonstrated improvement in RFS and OS.

These results suggest that immunotherapy with the autologous tumor cell vaccine GEM as frontline maintenance in stage III/IV ovarian cancer is well-tolerated and shows clinical benefit in both *BRCA* wild-type and homologous recombination proficient subgroups.

Source: Rocconi RP, Ghamande SA, Barve MA, et al. Maintenance vigil immunotherapy in newly diagnosed advanced ovarian cancer: efficacy assessment of homologous recombination proficient (HRP) patients in the phase IIb VITAL trial. *J Clin Oncol.* 2021;39(suppl_15). Abstract 5502.