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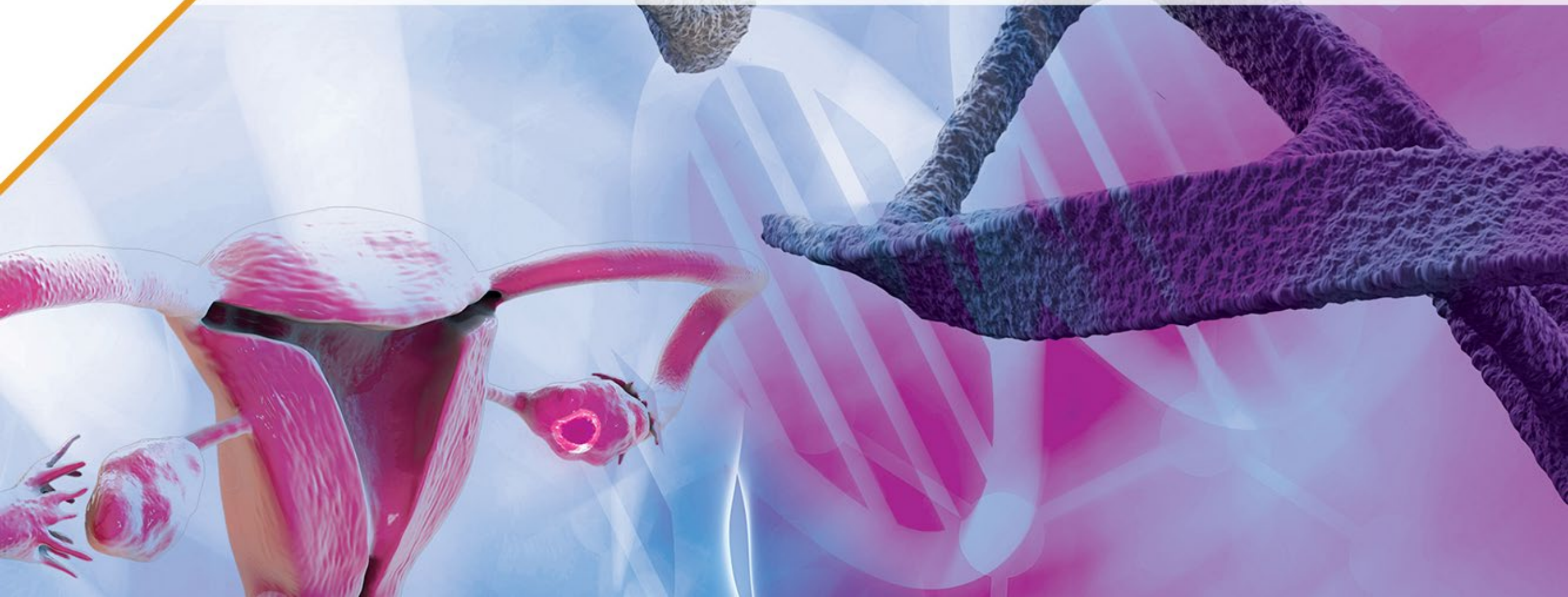
Improving Interprofessional Management and Clinical Outcomes with PARP Inhibitors for Advanced Ovarian Cancer:

PARP Inhibitor-Related Adverse Events and Team-Based Care



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Agenda

- Part 1 Review: PARP Inhibitors as First-Line Maintenance
- How Do Team-Based Management Strategies Mitigate PARP Inhibitor–Related Adverse Events? PARP Inhibitor Adverse Event Profile and Tips and Tricks to Ensuring Adherence
- Shared Decision-Making and Practical Management of Adverse Events for Patients on PARP Inhibitors
- Practical Application Case Illustrations

Learning Objectives

- Develop equitable SDM strategies for patient selection and communication of evidence-based treatment algorithms utilizing disease-specific tools
- Optimize treatment exposure by developing team-based management plans to anticipate, identify, and mitigate adverse events associated with PARP inhibitor therapy for advanced ovarian cancer
- Integrate an interprofessional team-based approach in delivering equitable continuity of care to overcome challenges in treatment delivery and patients' health-related quality of life (HR-QoL)

Part 1 Review: Significant Progress Has Been Made in the First-Line Management of Ovarian Cancer Over the Past Decade

2003

Chemotherapy

No further improvement in survival with chemotherapy alone since the introduction of platinum–taxane chemotherapy[1,2]

2011

Paradigm shift 1:
Bevacizumab

Bevacizumab improved PFS versus chemotherapy alone[3,4]

2018

Paradigm shift 2:
PARP inhibitors for BRCA-mutated ovarian cancer

Olaparib	SOLO-1[5] *NCT01844986*

2019–2022

Paradigm shift 3:
PARP inhibitors beyond BRCA mutation

Olaparib + bevacizumab	PAOLA-1[6] *NCT02477644*
Niraparib	PRIMA[7] *NCT02655016*
Rucaparib[a]	ATHENA-mono[8] *NCT03522246*

Several studies with PARP inhibitor maintenance for newly-diagnosed advanced ovarian cancer[5–8]

[a]Please note: Rucaparib is not licensed for first-line maintenance treatment in patients with newly-diagnosed ovarian cancer.

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1. McGuire WP, et al. *N Engl J Med.* 1996;334:1-6. 2. du Bois A, et al. *J Natl Cancer Inst.* 2003;95(17):1320-1329. 3. Burger RA, et al. *N Engl J Med.* 2011;365(26):2473-2483. 4. Perren TJ, et al. *N Engl J Med.* 2011;365(26):2484-2496. 5. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01844986 (Accessed March 2022). 6. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02477644 (Accessed March 2022). 7. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02655016 (Accessed March 2022). 8. Monk JM, et al. *J Clin Oncol.* 2022;40(34):3952-3964.

BRCA, *BRCA*1 and/or *BRCA*2; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival.

Part 1: Key Considerations

- Most patients with advanced ovarian cancer relapse following first-line multimodality therapy
- Multiple lines of chemotherapy is associated with cumulative toxicity while remission periods decrease
- First-line treatment for advanced ovarian cancer is the optimal setting to achieve a potential cure
- Earlier introduction of PARP inhibitors may benefit significant numbers of patients
- Significant progress has been made in the management of ovarian cancer over the past decade
  - Bevacizumab
  - PARP inhibitors for BRCA-mutated ovarian cancer
  - PARP inhibitors beyond BRCA mutation
- PARP inhibitors as first-line maintenance:
  - SOLO-1: olaparib (BRCAm)
  - PAOLA-1: olaparib + bevacizumab (HRD+)
  - PRIMA: niraparib (all patients)
  - ATHENA-mono: rucaparib (investigational)

HRD, homologous recombination deficiency; PARP, poly(ADP-ribose) polymerase.

How Do Team-Based Management Strategies Mitigate PARP Inhibitor–Related Adverse Events?

PARP Inhibitor Adverse Event Profile and Tips And Tricks To Ensuring Adherence

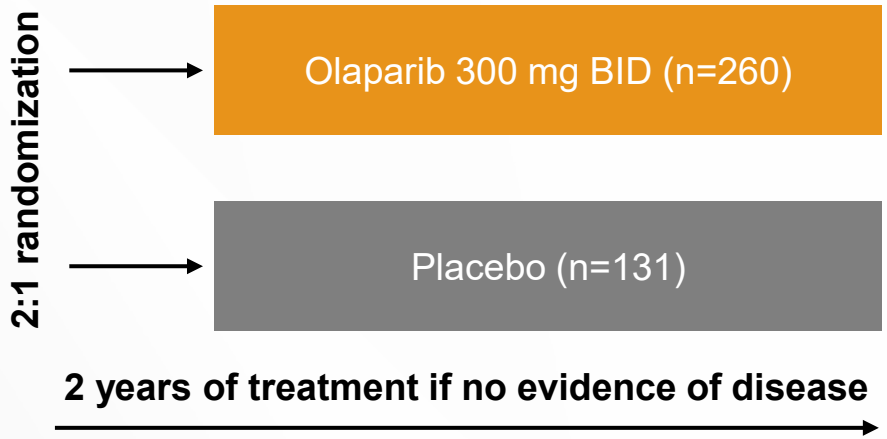
SOLO-1: Maintenance Olaparib for Patients With Newly-Diagnosed BRCAm Advanced Ovarian Cancer

Patient population

- HGSOC or HGEOC
- FIGO Stage III or IV
- Germline or somatic BRCA mutation
- ECOG 0–1
- Cytoreductive surgery
- CR or PR after platinum chemotherapy

Stratification

- Response to platinum chemotherapy



Primary objective

- Investigator-assessed PFS[a]

Secondary efficacy objectives

- PFS by BICR
- Time to second progression or death
- OS
- TFST
- TSST
- HRQoL

Safety and tolerability

[a]Modified Response Evaluation Criteria in Solid Tumors version 1.1

Moore K, et al. *N Engl J Med.* 2018;379:2495-2505.
BICR, blinded independent central review; BID, twice daily; BRCAm, BRCA1- and/or BRCA2-mutated; CR, complete response; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HGEOC, high-grade endometrioid ovarian cancer; HGSOC, high-grade serous ovarian cancer; HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival; PR, partial response; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death.

SOLO-1 Safety Summary: Treatment-Emergent Adverse Events and Exposure

	Olaparib (N=260)	Placebo (N=130)
All-grade TEAEs, n (%)	256 (98.5)	120 (92.3)
Grade ≥3 TEAEs, n (%)	102 (39.2)	24 (18.5)
Serious TEAEs, n (%)	54 (20.8)	16 (12.3)
TEAEs leading to dose interruption, n (%)	135 (51.9)	22 (16.9)
TEAEs leading to dose reduction, n (%)	74 (28.5)	4 (3.1)
TEAEs leading to discontinuation, n (%)	30 (11.5)	3 (2.3)

Moore K, et al. ESMO 2018. Abstract LBA7_PR. DiSilvestro P, et al. *J Clin Oncol*. 2022;41(3):609-617.
TEAE, treatment-emergent adverse event.

SOLO-1: Summary of the First Occurrence of the Most Commonly Reported **Non-Hematologic** Adverse Events*

Non-hematologic AEs	Nausea		Fatigue/asthenia§		Vomiting	
	Olaparib	Placebo	Olaparib	Placebo	Olaparib	Placebo
Patients with events (all grades), n (%)	201 (77)	49 (38)	165 (63)	54 (42)	104 (40)	19 (15)
Median time to first onset, months (range)	0.13 (0.03–21.49)	0.69 (0.03–17.51)	0.72 (0.03–33.91)	1.54 (0.03–20.24)	1.46 (0.03–20.60)	1.94 (0.03–21.91)
Patients with a first event with a resolution date (all grades),† n (%)	194 (75)	47 (36)	126 (48)	44 (34)	101 (39)	19 (15)
Median duration of first event,‡ months	1.41	0.43	3.48	2.30	0.07	0.03

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*The safety analysis set comprised 260 patients in the olaparib group and 130 in the placebo group; †Number (%) of patients with a first event that has a resolution date; ‡AEs with no end date were censored at the end of the safety follow-up or at data cut-off, as applicable; §Grouped-term events.
Moore K, et al. ESMO 2018. Abstract LBA7_PR.
AE, adverse event.

SOLO-1: Summary of the First Occurrence of the Most Commonly Reported **Hematologic** Adverse Events*

Hematologic AEs	Anemia§		Neutropenia§		Thrombocytopenia§	
	Olaparib	Placebo	Olaparib	Placebo	Olaparib	Placebo
Patients with events (all grades), n (%)	101 (39)	13 (10)	60 (23)	15 (12)	29 (11)	5 (4)
Median time to first onset, months (range)	1.94 (0.03–44.52)	1.81 (0.26–24.15)	1.77 (0.26–29.57)	0.49 (0.26–12.02)	2.83 (0.30–25.76)	7.39 (0.26–10.38)
Patients with a first event with a resolution date (all grades),† n (%)	93 (36)	12 (9)	57 (22)	14 (11)	25 (10)	4 (3)
Median duration of first event,‡ months	1.87	1.64	0.76	0.49	0.95	0.49

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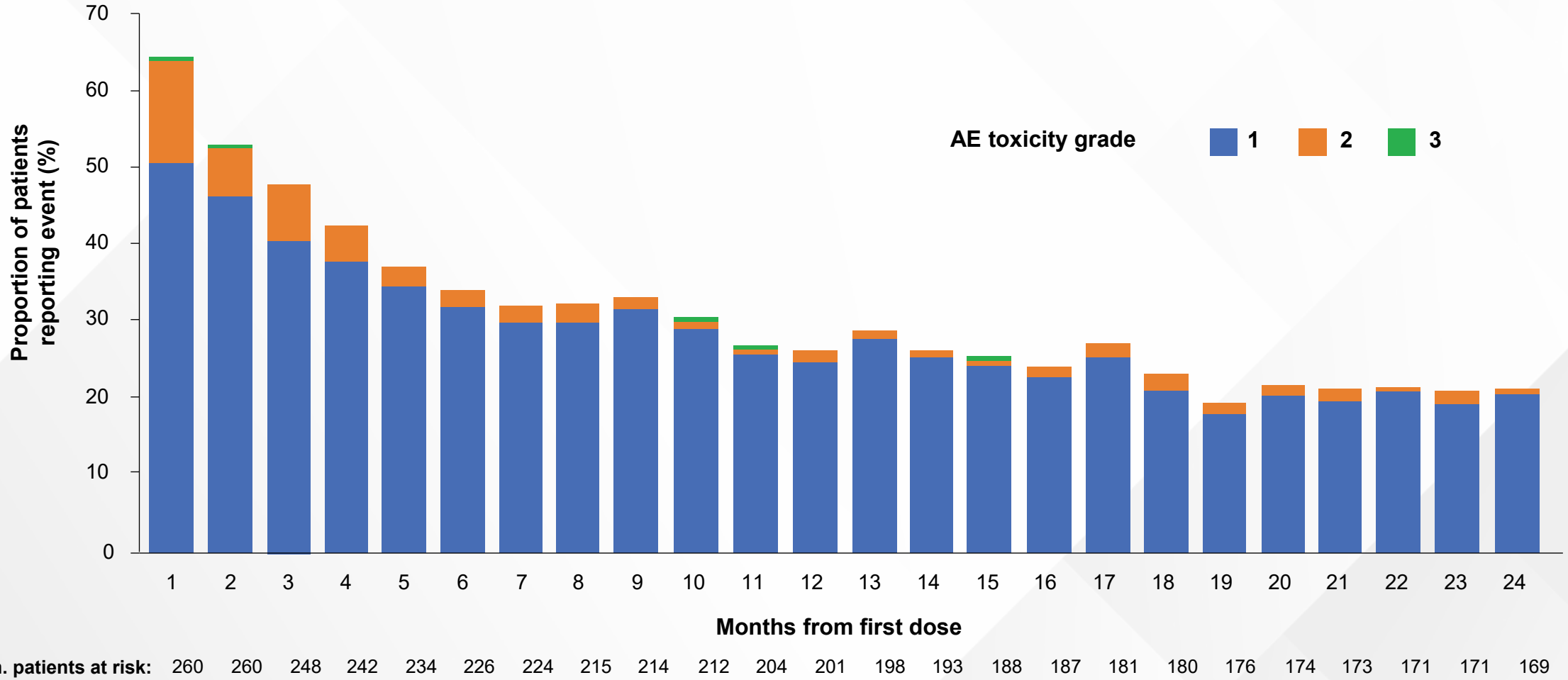
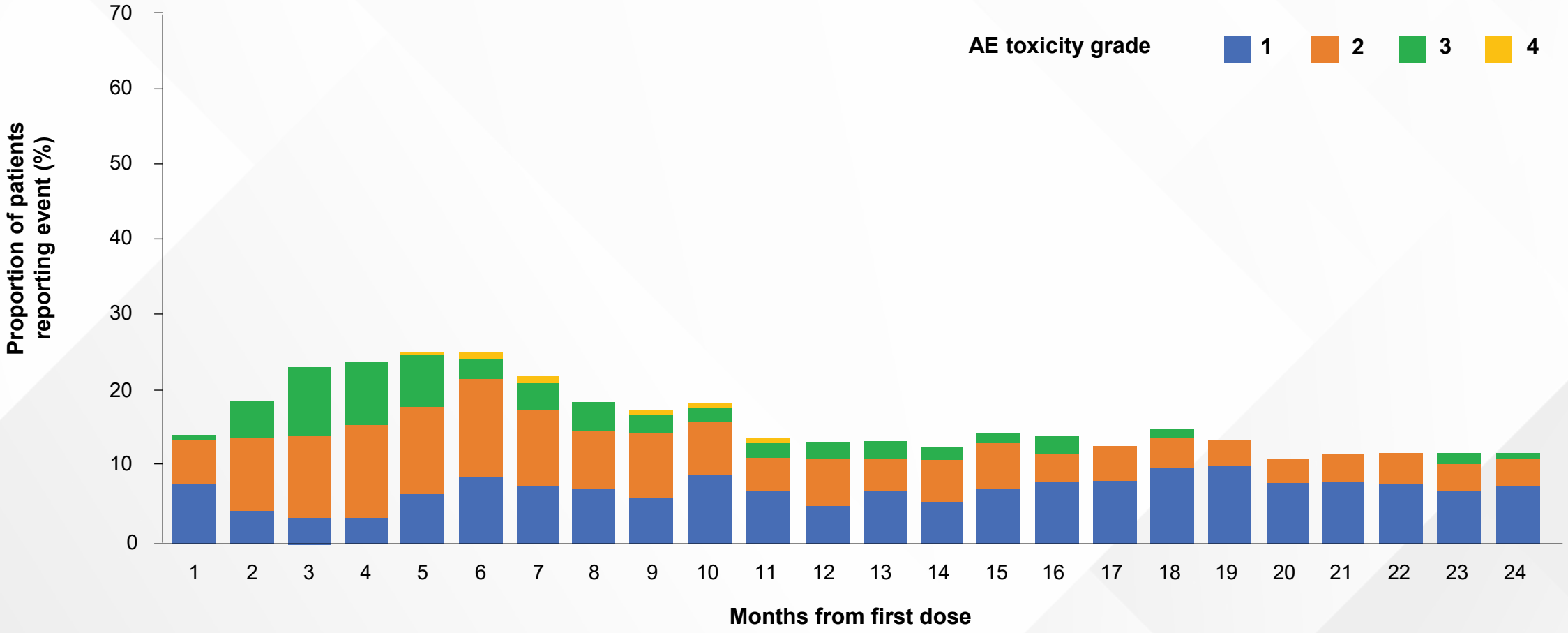
*The safety analysis set comprised 260 patients in the olaparib group and 130 in the placebo group; †Number (%) of patients with a first event that has a resolution date; ‡AEs with no end date were censored at the end of the safety follow-up or at data cut-off, as applicable; §Grouped-term events.
Moore K, et al. ESMO 2018. Abstract LBA7_PR.
AE, adverse event.

SOLO-1: Prevalence By Month and Grade of Nausea in the Olaparib Group



Moore K, et al. ESMO 2018. Abstract LBA7_PR.
AE, adverse event.

SOLO-1: Prevalence By Month and Grade of Anemia in the Olaparib Group



Moore K, et al. ESMO 2018. Abstract LBA7_PR.
AE, adverse event.

SOLO-1: Management and Outcomes for the Most Commonly Reported **Non-Hematologic** Adverse Events*

Non-hematologic AEs	Nausea		Fatigue/asthenia§		Vomiting	
	Olaparib	Placebo	Olaparib	Placebo	Olaparib	Placebo
Patients with events (all grades), n (%)	201 (77)	49 (38)	165 (63)	54 (42)	104 (40)	19 (15)
Management, n (%)†						
Supportive treatment	117 (58)	15 (31)	11 (7)	0	28 (27)	3 (16)
Dose interruption	35 (17)	0	20 (12)	1 (2)	25 (24)	3 (16)
Dose reduction	10 (5)	0	15 (9)	1 (2)	0	0
Discontinuation	6 (3)	1 (2)	6 (4)	1 (2)	2 (2)	0
Outcomes, n (%)†						
Recovered/resolved	183 (91)	46 (94)	103 (62)	41 (76)	100 (96)	19 (100)
Recovered/resolved with sequelae	1 (<1)	0	1 (1)	1 (2)	1 (1)	0
Recovering/resolving	2 (1)	1 (2)	13 (8)	3 (6)	1 (1)	0
Not recovered/resolved	15 (7)	2 (4)	48 (29)	9 (17)	2 (2)	0
Patients with grade ≥3 events, n (%)	2 (1)	0	10 (4)	2 (2)	1 (<1)	1 (1)

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*The safety analysis set comprised 260 patients in the olaparib group and 130 in the placebo group; †Percentages were calculated from the number of patients with that event; §Grouped-term events.

Moore K, et al. ESMO 2018. Abstract LBA7_PR.

AE, adverse event.

SOLO-1: Management and Outcomes for the Most Commonly Reported **Hematologic** Adverse Events*

Hematologic AEs	Anemia§		Neutropenia§		Thrombocytopenia§	
	Olaparib	Placebo	Olaparib	Placebo	Olaparib	Placebo
Patients with events (all grades), n (%)	101 (39)	13 (10)	60 (23)	15 (12)	29 (11)	5 (4)
Management, n (%)†						
Supportive treatment	72 (71)	4 (31)	11 (18)	2 (13)	2 (7)	1 (20)
Dose interruption	58 (57)	1 (8)	30 (50)	5 (33)	6 (21)	0
Dose reduction	44 (44)	1 (8)	10 (17)	1 (7)	4 (14)	0
Discontinuation	6 (6)	0	1 (2)	0	1 (3)	0
Outcomes, n (%)†						
Recovered/resolved	84 (83)	11 (85)	53 (88)	14 (93)	21 (72)	4 (80)
Recovered/resolved with sequelae	2 (2)	0	0	0	2 (7)	0
Recovering/resolving	5 (5)	0	1 (2)	0	0	0
Not recovered/resolved	10 (10)	2 (15)	6 (10)	1 (7)	6 (21)	1 (20)
Patients with grade ≥3 events, n (%)	56 (22)	2 (2)	22 (9)	6 (5)	2 (1)	2 (2)

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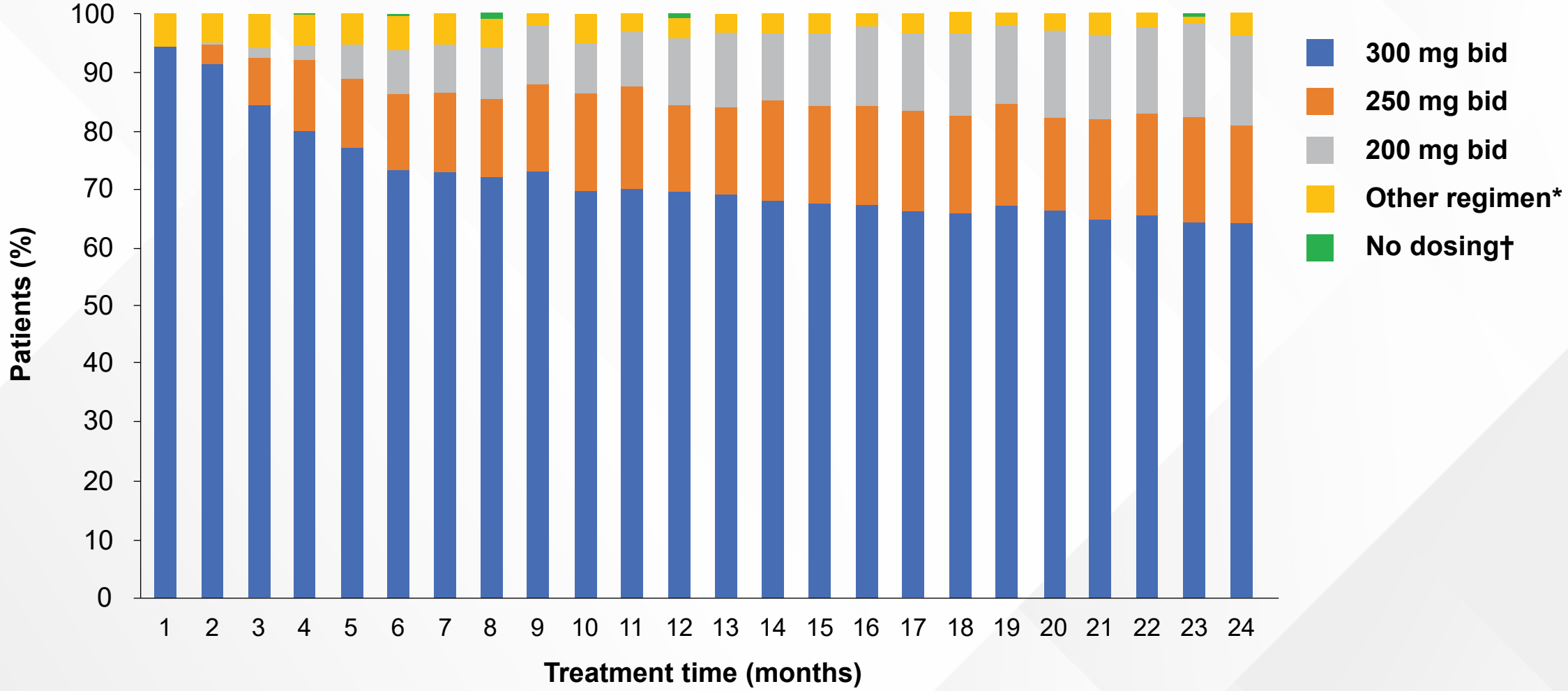
*The safety analysis set comprised 260 patients in the olaparib group and 130 in the placebo group; †Percentages were calculated from the number of patients with that event; ‡§ Grouped-term events.
Moore K, et al. ESMO 2018. Abstract LBA7_PR.
AE, adverse event.

SOLO-1: Olaparib Dose Reductions Over Time



Num. patients at risk:	260	248	242	234	226	224	215	214	212	204	201	198	193	188	187	181	180	176	174	173	172	171	169	162

Number of patients treated at the start of each month. *'Other regimen' includes 150 mg qd, 150 mg bid, 200 mg qd, 250 mg qd, 300 mg qd, and 450 mg bid;
†The category of 'no dosing' was assigned if the patient had dosing interrupted for the entire month window.
Moore K, et al. ESMO 2018. Abstract LBA7_PR.
bid, twice daily.

SOLO-1: Summary of AML Cases*

Event	Patient age, years	BRCAm status	Duration of olaparib therapy, days	Reason for stopping olaparib	Time to AML onset after stopping olaparib, days	Outcome
AML	52	BRCA1m	436	Persistent neutropenia and anemia	173	Fatal
AML	52	BRCA1m	758	Completed 2 years' treatment	49	Fatal
AML	64	BRCA2m	519	URTI with subsequent disease progression	52	Fatal

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*All three patients had previously received six cycles of carboplatin plus paclitaxel.
Moore K, et al. ESMO 2018. Abstract LBA7_PR.
AML, acute myeloid leukemia; URTI, upper respiratory tract infection.

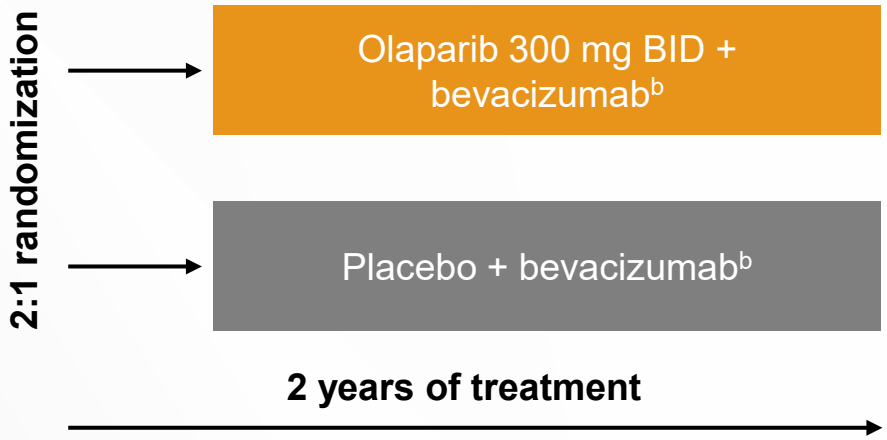
PAOLA-1: Olaparib Plus Bevacizumab as Maintenance Therapy in Patients With Newly-Diagnosed Advanced Ovarian Cancer

Key inclusion criteria

- Newly-diagnosed, FIGO Stage III–IV HGSOC and HGEOC[a]
- PDS or IDS
- ≥2 cycles of bevacizumab[b]
  - Included first-line with platinum-taxane chemo plus bevacizumab
- NED/CR/PR

Stratification

- Tumor BRCA status[c]
- First-line treatment outcome[d]



Primary objective

- Investigator-assessed PFS[a]

Secondary efficacy objectives

- PFS2, OS, TFST, TSST, HRQoL

Safety and tolerability

Exploratory PFS analyses

Higher-risk patients:

- FIGO Stage III patients with PDS and residual disease or who had received NAC
- FIGO Stage IV patients

Lower-risk patients:

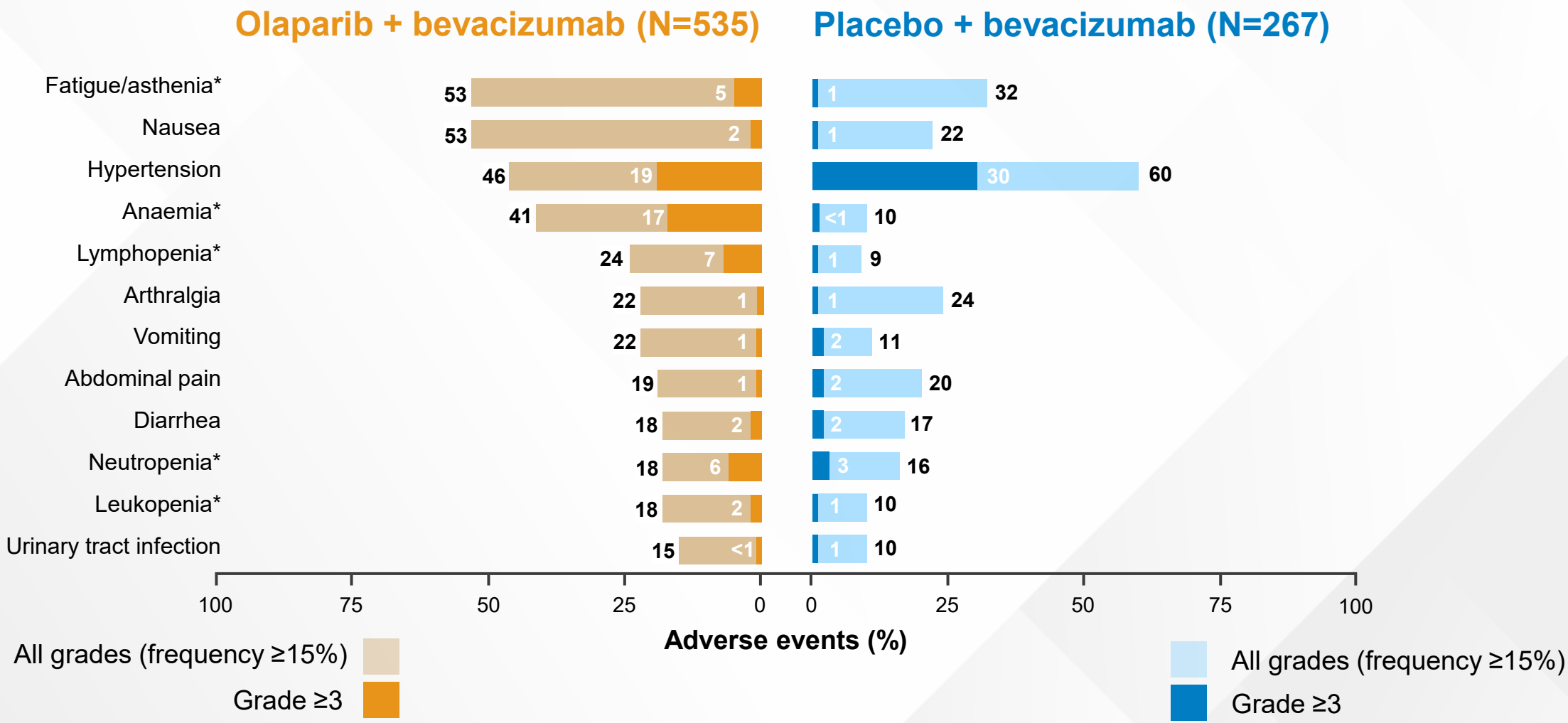
- FIGO Stage III patients with PDS with no residual disease

[a]Includes patients with primary peritoneal and/or fallopian tube cancer; patients with other epithelial non-mucinous ovarian cancer were eligible if they had a germline *BRCA1* and/or *BRCA2* mutation; [b]Bevacizumab 15 mg/kg, every 3 weeks for a total of 15 months, including when administered with chemotherapy; [c]By central labs; [d]According to timing of surgery and NED/CR/PR

Ray-Coquard I, et al. *N Engl J Med.* 2019;381(25):2416-2428. Harter P, et al. *Int J Gynecol Cancer.* 2020;30(suppl 3):A13-A14.

BID, twice daily; BRCA, *BRCA1* and/or *BRCA2*; CR, complete response; FIGO, International Federation of Gynecology and Obstetrics; HGEOC, high-grade endometrioid ovarian cancer; HGSOC, high-grade serous ovarian cancer; HRQoL, health-related quality of life; IDS, interval debulking surgery; NAC, neoadjuvant chemotherapy; NED, no evidence of disease; OS, overall survival; PDS, primary debulking surgery; PFS, progression-free survival; PFS2, time to second progression or death; PR, partial response; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death.

PAOLA-1: Most Common AEs



*Grouped terms. All-grade thrombocytopenia (grouped term) occurred in 8% of patients in the olaparib group and 3% of patients in the placebo group, grade ≥3 thrombocytopenia occurred in 2% of patients in the olaparib group and <1% of patients in the placebo group.

Ray-Coquard I, et al. *N Engl J Med.* 2019;381(25):2416-2428.

AE, adverse event.

PAOLA-1: AEs of Special Interest for Olaparib

	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)
MDS/AML/AA, n (%)	6 (1.1)	1 (0.4)
New primary malignancies, n (%)	7 (1.3)	3 (1.1)
Acute lymphocytic leukaemia	1	0
Breast cancer	2	2
Lung cancer	1	0
Myeloma	1	0
Pancreatic cancer	1	0
Squamous skin cancer	1	0
Thyroid cancer	0	1
Pneumonitis/ILD, n (%)	6 (1.1)	0

Ray-Coquard I, et al. *N Engl J Med.* 2019;381(25):2416-2428.

AA, aplastic anemia; AE, adverse event; AML, acute myeloid leukemia; ILD, interstitial lung disease; MDS, myelodysplastic syndrome.

In Both Trials, the Majority of Patients Receiving Olaparib Were Able to **Maintain** Full Dosing Throughout Treatment

	SOLO-1 (FL BRCA+ OC)[1]		PAOLA-1 (FL OC)[2]	
	Olaparib tablets (n=260) %	**Placebo (n=131) %**	**Olaparib tablets + bevacizumab (n=535) %**	**Placebo + bevacizumab (n=267) %**
Median duration of exposure	25 months	14 months	17.3 months	15.6 months
Dose interruption	51.9%	16.9%	54%	24%
Dose reduction	28.5%	3.1%	41%	7%
Treatment discontinuation	11.5%	2.3%	20%	6%

1. Moore K, et al. *New Engl J Med.* 2018;379:2495-2505.
2. Ray-Coquard I, et al. *N Engl J Med.* 2019;381(25):2416-2428.
FL, full-length; OC, ovarian cancer.

Adverse Events for Olaparib and Olaparib + Bevacizumab

Adverse Events	Olaparib	
Trial	**SOLO-1 (n=260)[1]**	**PAOLA-1 (n=535)[2]**
Dose Reduction	28%	41%
Dose Interruption	52%	54%
Dose Discontinuation (due to TEAE)	12%	20%
Hematologic Toxicity, All Gr/Gr 3/4		
Anemia	39%/22%	41%/17%
Neutropenia	23%/9%	18%/6%
Thrombocytopenia	11%/1%	<15%
Non-Hematologic Toxicity, All Gr/Gr 3/4		
Fatigue	63%/4%	53%/5%
Nausea	77%/1%	53%/2%
Vomiting	40%/<1%	22%/1%
Diarrhea	34%/3%	18/2%
Hypertension		46%/19%

1. Moore K, et al. *New Engl J Med.* 2018;379:2495-2505. 2. Ray-Coquard I, et al. *N Engl J Med.* 2019;381(25):2416-2428.
Gr, Grade; TEAE, treatment-emergent adverse event;.

PRIMA: Maintenance Niraparib for Patients With Newly-Diagnosed Ovarian Cancer, Regardless of BRCAm Status

Key inclusion criteria

- FIGO Stage III–IV HGSOC or HGEOC[a]
- Tissue for HRD testing required at screening (Myriad myChoice®)
- CR or PR (<2 cm[b]) and normalization of CA-125 levels[c,2]

Key exclusion criteria

- Stage III disease with complete cytoreduction after PDS

2:1 randomization

Niraparib

Placebo

Stratification

- CR or PR
- NACT
- HRD-positive or HRD-negative/unknown

Body weight ≥77 kg and platelets ≥150,000/μL started with 300 mg QD

Body weight <77 kg and/or platelets <150,000/μL started with 200 mg QD

35% of patients received a modified starting dose after a protocol change; of these, 72% received 200 mg QD[3]; initial dose for everyone regardless of weight or platelets was 300 mg/day

3 years treatment if no evidence of disease

Primary endpoint

- PFS (BICR)

Secondary endpoints

- OS
- PFS2
- TFST
- PRO
- Safety

Hierarchical PFS testing

- Patients with HRD-positive disease, then ITT population

Patients were treated with niraparib or placebo once daily for 36 months or until disease progression.
[a]Includes patients with primary peritoneal and/or fallopian tube cancer; [b]Based on protocol modification; [c]Normal or >90% decrease in CA-125 with front-line treatment.

1. González-Martín A, et al. *N Engl J Med*. 2019;381(25):2391-2402. 2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02655016. 3. Mirza MR, et al. ASCO Virtual Scientific Program 2020. Abstract 6050.
BICR, blinded independent central review; BRCAm, *BRCA1* and/or *BRCA2* mutation; CA-125, cancer antigen 125; CR, complete response; FIGO, International Federation of Gynecology and Obstetrics; HGEOC, high-grade endometrioid ovarian cancer; HGSOC, high-grade serous ovarian cancer; HRD, homologous recombination deficiency; ITT, intention-to-treat; NACT, neoadjuvant chemotherapy; OS, overall survival; PDS, primary debulking surgery; PFS, progression-free survival; PFS2, time to progression on subsequent therapy; PR, partial response; PRO, patient-reported outcome; QD, once daily; TFST, time to first subsequent therapy.

PRIMA: Adverse Events

- Most common grade ≥3 adverse events in the niraparib group:
  - Anemia (31.0%)
  - Thrombocytopenia (28.7%)
  - Neutropenia (12.8%)
- Myelosuppressive AEs were the main reason for discontinuation but were infrequent (4.3% for thrombocytopenia in the niraparib group)
- One case of myelodysplastic syndrome was identified in a patient in the niraparib group
- Low-grade nausea and fatigue were common in the two groups
- No deaths during treatment with niraparib were reported during the trial
- Safety improved with the implementation of the individualized dosing regimen

Adverse Events	Niraparib (N = 484)		Placebo (N = 244)	
Grade	Any	Grade ≥3	Any	Grade ≥3
Adverse Events	98.8%	70.5%	91.8%	18.9%
TRAE	96.3%	65.3%	68.9%	6.6%
Serious AE (any)	32.2%		13.1%	
Serious TRAE	24.4%		2.5%	
Leading to treatment discontinuation	12.0%		2.5%	
Leading to dose reduction	70.9%		8.2%	
Leading to dose interruption	79.5%		18.0%	
Leading to death	0.4%		0.4%	

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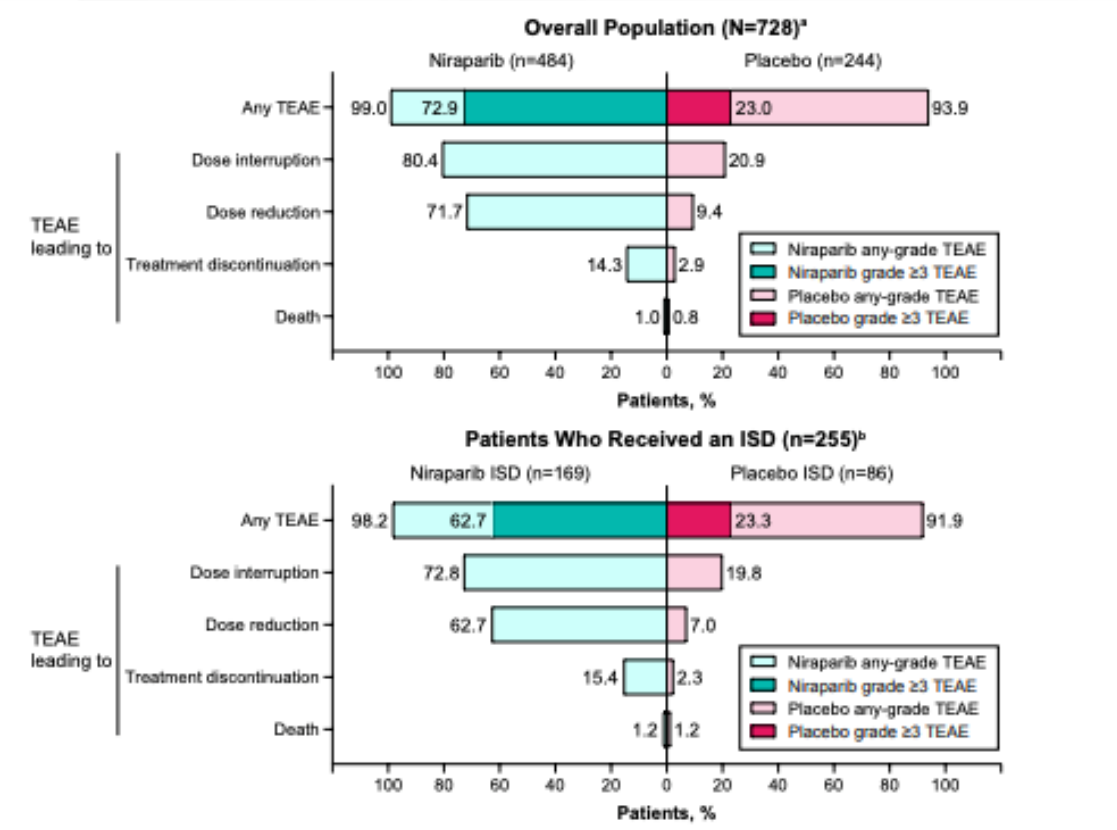
González-Martín A, et al. *N Engl J Med.* 2019;381(25):2391-2402.
AE, adverse event; TRAE; treatment-related adverse event.

PRIMA: Updated TEAEs Overview

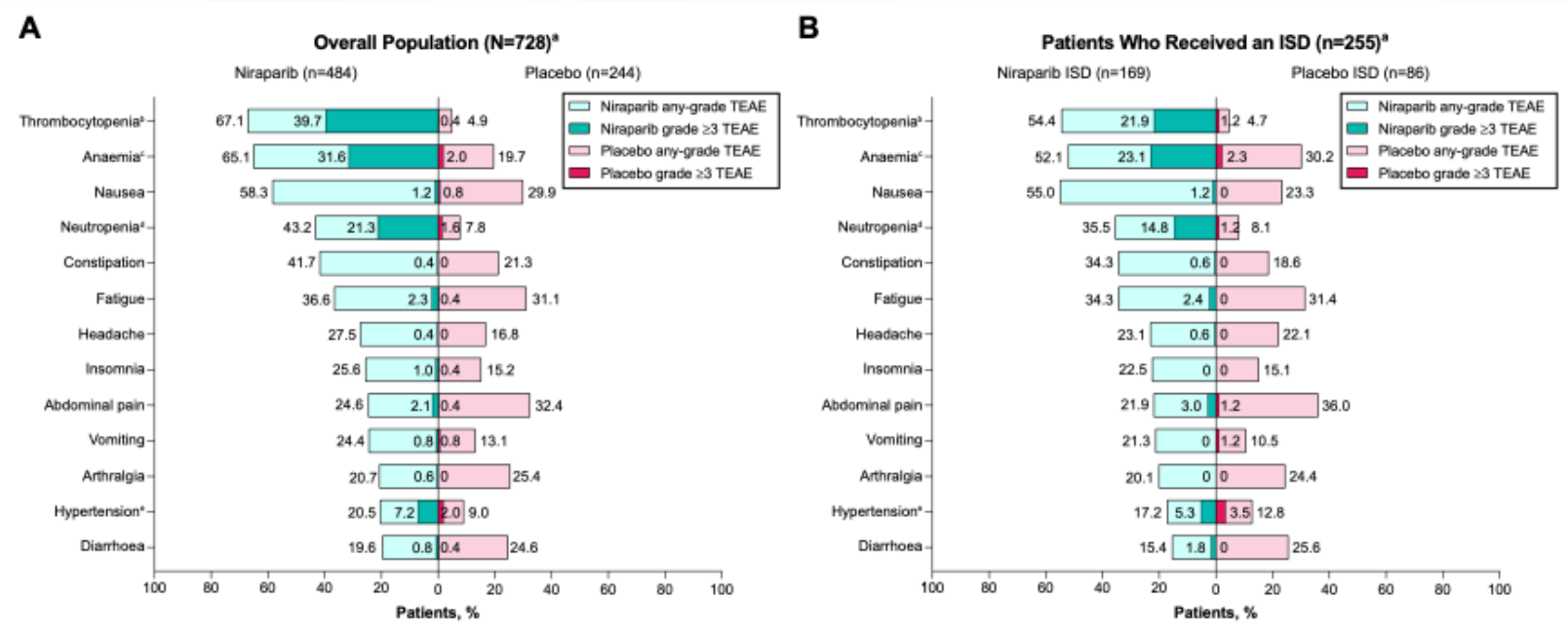


- Long-term niraparib monotherapy was associated with a low rate of discontinuations due to AEs
- TEAEs leading to dose interruptions and reductions were reduced with individualized starting dose (ISD) implementation
- TEAEs leading to death were not treatment-related

[a]Patients who received ≥1 dose of study treatment.
[b]Patients who enrolled after 27 November 2017 and received an ISD based on baseline body weight and platelet count. Patients with baseline body weight <77 kg and/or platelet count <150,000 cells/μL received a starting dose of 200 mg once daily. Patients with baseline body weight ≥77 kg and platelet count ≥150,000 cells/μL received a starting dose of 300 mg once daily.

Nov 17, 2021 cutoff date. Median of 3.5 years of follow-up.
González-Martín A, et al. ESMO 2022. Abstract #530P.
AE, adverse event; ISD, individualized starting dose; TEAE, treatment-emergent adverse event.

PRIMA: Updated TEAEs Reported in ≥20% of Patients



- Most common grade ≥3 TEAEs in the niraparib arm were hematologic:
  - Thrombocytopenia (40%)
  - Anemia (32%)
  - Neutropenia (21%)
- MDS/AML were reported at the same incidence in niraparib (1.2%) and placebo (1.2%) arms
- Patients who received ISD generally had lower incidence of TEAEs
  - Largest reductions seen in any-grade and grade ≥3 events of anemia, thrombocytopenia, and neutropenia

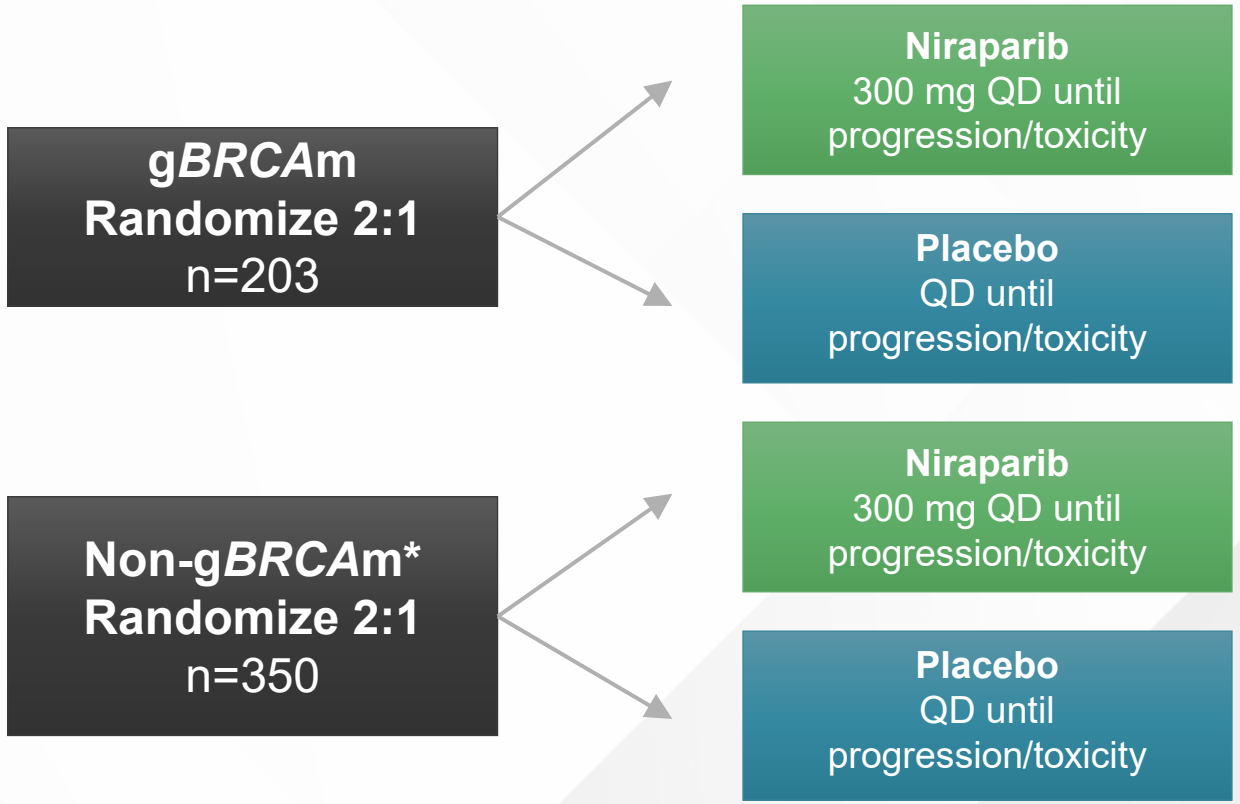
[a]Patients who received ≥1 dose of study treatment.
[b]Includes thrombocytopenia and platelet count decreased.
[c]Includes anemia, hemoglobin decreased, red blood cell decreased, hematocrit decreased, and anemia macrocytic.
[d]Includes neutropenia, neutrophil count decreased, febrile neutropenia, and neutropenic sepsis.
[e]Includes hypertension, blood pressure increased, and blood pressure fluctuation.

Nov 17, 2021 cutoff date. Median of 3.5 years of follow-up.
González-Martín A, et al. ESMO 2022. Abstract #530P.
AML, acute myeloid leukemia; ISD, individualized starting dose; MDS, myelodysplastic syndrome; TEAE, treatment-emergent adverse event.

ENGOT-ov16/NOVA: Study Design

Patients

- PSR high grade serous ovarian* cancer
- ≥2 lines of platinum-based therapy
- Achieved a CR or PR
- No measurable disease <2 cm
- CA-125 in the normal range (or decreased by more than 90% during last regimen and stable for at least 7 days)



Stratification factors:

- TTP on penultimate platinum therapy (6 to <12 months vs ≥12 months)
- Prior bevacizumab treatment
- Best response (complete or partial) during the last platinum regimen

*Includes s*BRCA*m patients.

Mirza MR, et al. *N Engl J Med.* 2016;375(22):2154-2164.

CA-125, cancer antigen 125; CR, complete response; g*BRCA*m, germline *BRCA* mutated; PR, partial response; PSR, platinum-sensitive relapsed; QD, once daily; TTP, time to progression.

ENGOT-ov16/NOVA: Grade ≥3 AEs Occurring in ≥5% of Patients in Niraparib Arm

Events, n (%)	Niraparib (n=367)	Placebo (n=179)
Thrombocytopenia	124 (33.8)	1 (0.6)
Anemia	93 (25.3)	0
Neutropenia	72 (19.6)	3 (1.7)
Fatigue	30 (8.2)	1 (0.6)
Hypertension	30 (8.2)	4 (2.2)

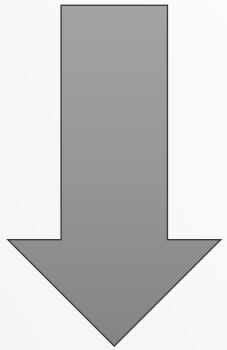
Thrombocytopenia occurs typically in the first month of therapy (median time to onset is 23 days)

Median time to resolution with dose interruption and/or dose reduction is 10 days

Rate of thrombocytopenia after cycle 3 is 2.4%

1. Mirza MR, et al. *N Engl J Med.* 2016;375(22):2154-2164. 2. Zejula. 100mg hard capsules. Summary of Product Characteristics. GlaxoSmithKline; 2021.
AE, adverse event.

ENGOT-ov16/NOVA: Dose Adjustments and Serious AEs



	Niraparib n=367 %	Placebo n=179 %
Dose interruptions	68.9	5
Dose reductions	66.5	14.5
Discontinuations	14.7	2.2

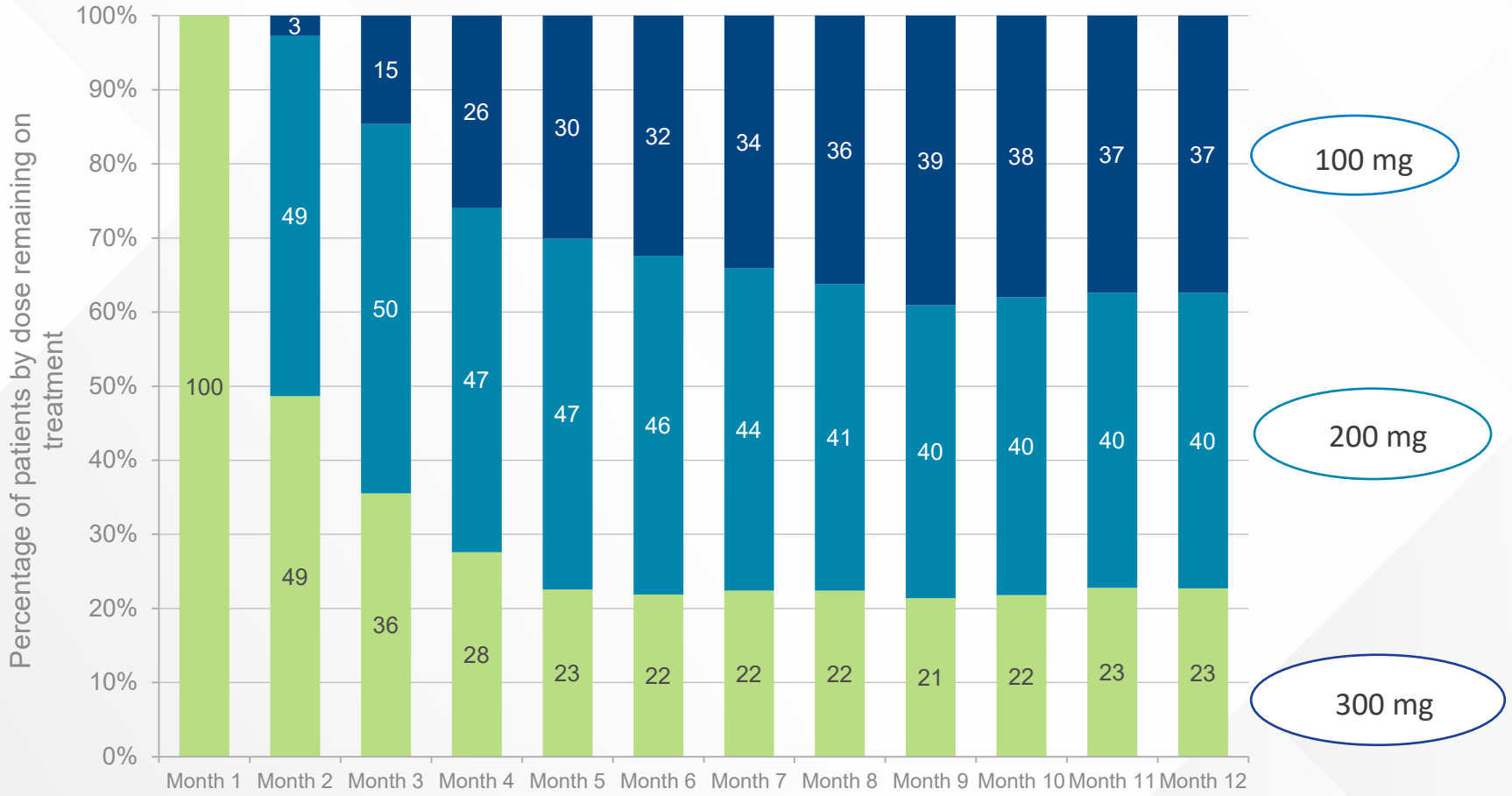
- The rate of patients with ≥1 SAE was 30% (16.9% related to treatment)
- The rate of MDS/AML was 1.4% (5 of 367) in the niraparib arm and 1.1% (2 of 179) in the placebo arm

AXIS Medical Education

AE, adverse event; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; SAE, serious adverse event.

Mirza MR et al. *N Engl J Med.* 2016;375(22):2154-2164.
Center for Drug Evaluation and Research. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208447Orig1s000MultidisciplineR.pdf

ENGOT-ov16/NOVA:
Niraparib Dose Level by Month on Treatment

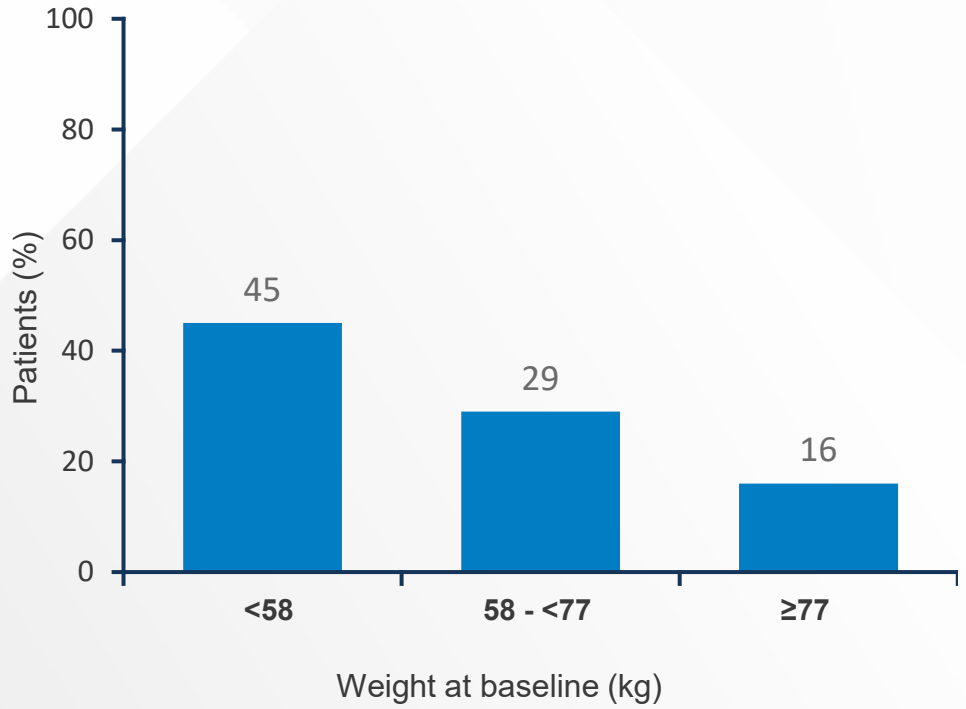


After dose modification, 200 mg was the most commonly administered dose

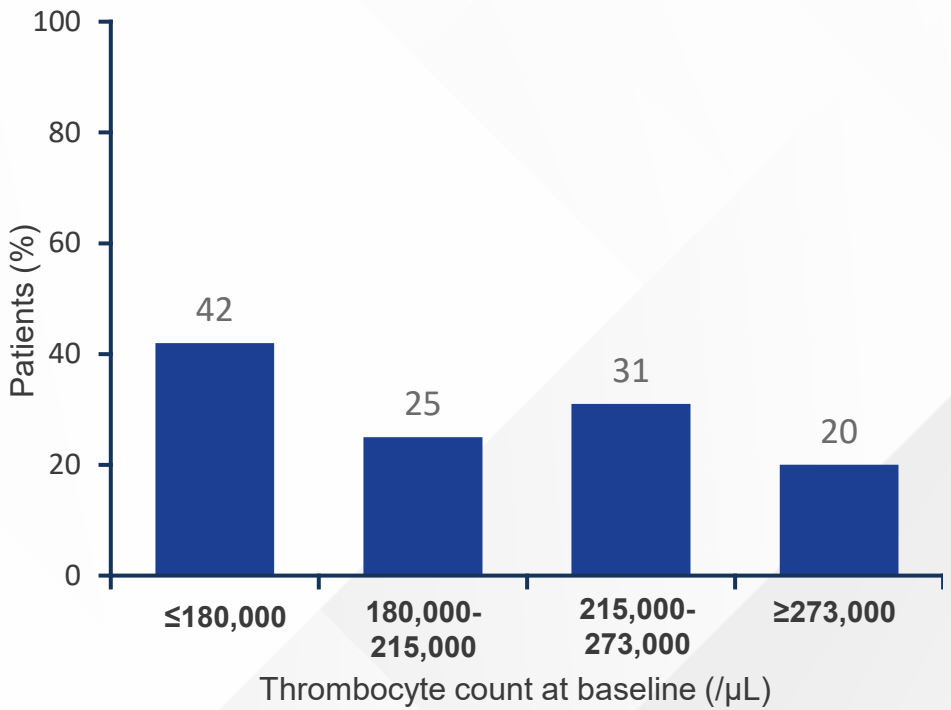
Lord R, et al. SGO 2018. Abstract 20.

ENGOT-ov16/NOVA: Incidence of Grade 3/4 Thrombocytopenia by Baseline Body Weight and Baseline Platelet Count

Grade 3/4 thrombocytopenia events in month 1 by weight



Grade 3/4 thrombocytopenia events in month 1 by baseline platelet count



58 kg = 128 lb; 77 kg = 170 lb

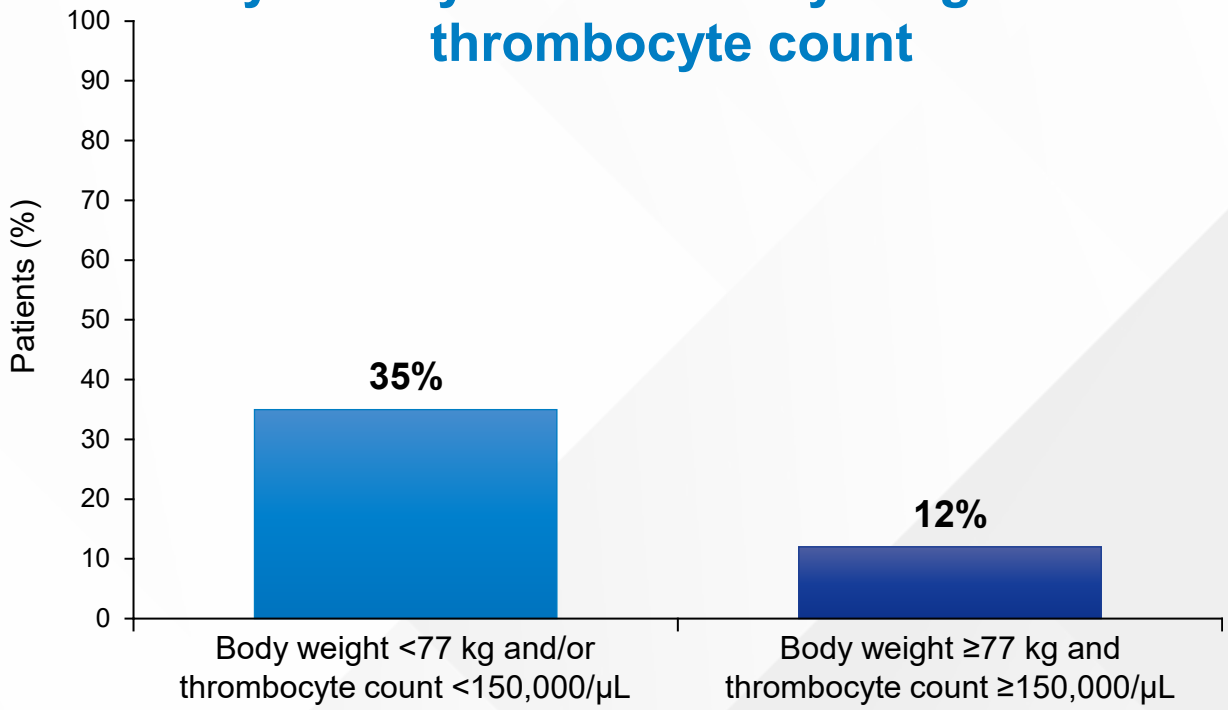
Lord R, et al. SGO 2018. Abstract 20.

ENGOT-ov16/NOVA: The Rapid Adjustment of Dose to Reduce Adverse Reactions (RADAR) Analysis

- Exploratory analysis of the NOVA trial that examined predictive factors for the development of Grade 3/4 thrombocytopenia
- Patients deemed to be most likely to develop thrombocytopenia had:
  - **Baseline body weight <77 kg**

  and/or
  - **Baseline platelet count <150,000/μL**

Grade 3/4 thrombocytopenia during cycle 1 by baseline body weight and thrombocyte count



Berek JS, et al. *Ann Oncol.* 2018;29(8):1784-1792.

Shared Decision-Making and Practical Management of Adverse Events for Patients on PARP Inhibitors

SHARE Decision-Making Model

STEP 1 **Seek** your patient's participation.

STEP 2 **Help** your patient explore & compare treatment options.

STEP 3 **Assess** your patient's values and preferences.

STEP 4 **Reach** a decision with your patient.

STEP 5 **Evaluate** your patient's decision.

AHRQ. The SHARE Approach. https://www.ahrq.gov/health-literacy/professional-training/shared-decision/index.html

Patient Counseling and Dosing Compliance

- Selecting appropriate patients for *PARPi* therapy and setting expectations are key

Select appropriate patients

Basic counseling re: oral regimens

Specific toxicity management

PARPi, poly(ADP-ribose) polymerase inhibitor.

Patient Counseling and Dosing Compliance

- Selecting appropriate patients for *PARPi* therapy and setting expectations are key

Select appropriate patients

Basic counseling re: oral regimens

Specific toxicity management

- Complete or partial response to first-line platinum-based chemotherapy
- Olaparib: select patients for therapy based on an FDA-approved companion diagnostic (*BRCA*m)
- Able to tolerate oral medication
- No significant hepatic (bili >1.5 x ULN) or renal dysfunction

AXIS Medical Education

Lynparza (olaparib). Prescribing Information. AstraZeneca; 2023.
Zejula (niraparib). Prescribing Information. GlaxoSmithKline; 2023.
bili, bilirubin; PARPi, poly(ADP-ribose) polymerase inhibitor; ULN, upper limit of normal.

Patient Counseling and Dosing Compliance

- Selecting appropriate patients for *PARPi* therapy and setting expectations are key

Select appropriate patients

Basic counseling re: oral regimens

Specific toxicity management

Recommended Starting Dose First-line Maintenance Treatment of Advanced Ovarian Cancer	
Niraparib 100 mg capsules 100 mg, 200 mg, or 300 mg tablets	• Patients weighing <77 kg (<170 lbs) OR platelet count <150,000/mcL: 200 mg orally once daily • Patients weighing ≥77 kg (≥170 lbs) AND platelet count ≥150,000/mcL: 300 mg orally once daily • Moderate hepatic impairment: 200 mg once daily
Olaparib 100 mg or 150 mg tablets	• 300 mg taken orally twice daily • Moderate hepatic impairment: 200 mg twice daily

- Instruct patient on:
  - Missed doses (don't repeat)
  - Extra doses (notify provider)
  - No chewing tablets
  - Continue treatment until disease progression or unacceptable toxicity (olaparib: or completion of 2 years of treatment)
- Dosing around meals vs fasting
  - No significant food effects
  - May be taken with or without food
  - Bedtime niraparib administration may be a potential method for managing nausea
- Importance of reviewing other medications being taken
  - Olaparib is metabolized by CYP3A4
    - Use of inhibitors will ↑ olaparib concentrations

AXIS Medical Education

Lynparza (olaparib). Prescribing Information. AstraZeneca; 2023.
Zejula (niraparib). Prescribing Information. GlaxoSmithKline; 2023.
PARPi, poly(ADP-ribose) polymerase inhibitor.

Patient Counseling and Dosing Compliance

- Selecting appropriate patients for *PARPi* therapy and setting expectations are key

Select appropriate patients

Basic counseling re: oral regimens

Specific toxicity management

CYP3A4 inhibitor examples:

Erythromycin
Diltiazem
Fluconazole
Ciprofloxacin

- Instruct patient on:
  - Missed doses (don't repeat)
  - Extra doses (notify provider)
  - No chewing tablets
  - Continue treatment until disease progression or unacceptable toxicity (olaparib: or completion of 2 years of treatment)
- Dosing around meals vs fasting
  - No significant food effects
  - May be taken with or without food
  - Bedtime niraparib administration may be a potential method for managing nausea
- Importance of reviewing other medications being taken
  - Olaparib is metabolized by CYP3A4
    - Use of inhibitors will ↑ olaparib concentrations

AXIS Medical Education

Lynparza (olaparib). Prescribing Information. AstraZeneca; 2023. Zejula (niraparib). Prescribing Information. GlaxoSmithKline; 2023. AstraZeneca; 2018. Zhou SF. *Curr Drug Metab.* 2008;9(4):310-322. Derungs A, et al. *Clin Pharmacokinet.* 2016;55:79-91.
PARPi, poly(ADP-ribose) polymerase inhibitor.

Patient Counseling and Dosing Compliance

- Selecting appropriate patients for *PARPi* therapy and setting expectations are key

Select appropriate patients

Basic counseling re: oral regimens

Specific toxicity management

- **Fatigue**
- **Gastrointestinal**
  - Nausea/emesis
  - Diarrhea
  - Dysgeusia
- **Hematologic**
  - Anemia
  - Neutropenia/Thrombocytopenia
- **AML/MDS**
- To manage adverse reactions, consider interruption of treatment, dose reduction, or dose discontinuation

Lynparza (olaparib). Prescribing Information. AstraZeneca; 2023.
Zejula (niraparib). Prescribing Information. GlaxoSmithKline; 2023.
AML, acute myeloid leukemia; MDS, myelodysplastic syndrome.

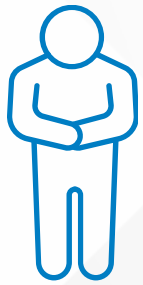
Patient Counseling and Dosing Compliance

Management of fatigue

- **Patient counseling is key**
  - Symptoms are more common at beginning[1]
  - Improve with time[1]
- **Evaluation of fatigue**
  - Assess fatigue like a vital sign[2]
  - Patients encouraged to self report[1,2]
  - Rule out other causes (anemia, insomnia, depression, pain, hypothyroidism)[1,2]
- **Treatment for PARPi related fatigue**
  - Non-pharmacologic
    - > Massage tx, cognitive behavior tx, early involvement of supportive care[2]
    - > Physical exercise[2]
  - Pharmacologic
    - > Methylphenidate[2]
    - > Wisconsin/American ginseng[3]
    - > Dose interruption (for G1/2)[2]
    - > Dose reduction (G3/recurrent) [2]

1. Friedlander M, et al. *Asia Pac J Clin Oncol*. 2016;12(4):323-331. 2. Moore KN, Monk BJ. *Oncologist*. 2016;21(8):954-963.
3. Barton DL, et al. *J Natl Cancer Inst*. 2013;105(16):1230-1238.
G, grade; PARPi, poly(ADP-ribose) polymerase inhibitor.

Patient Counseling and Dosing Compliance



Management of nausea and vomiting

- **Patient counseling is key**
  - Symptoms are more common at beginning[1]
  - Improve with time[1]
  - Niraparib: administration at bedtime is recommended to help minimize nausea
- **Evaluation and treatment of N/V**
  - Rule out other causes[2]
  - Pre-emptive prescriptions for prochlorperazine, lorazepam or metoclopramide, serotonergic antagonist (ondansetron)[2]
  - Avoid aprepitant (CYP3A inhibitor)[2]
  - Dose interruption
  - Dose reduction
- **Evaluation and treatment of dysgeusia / dyspepsia**
  - Dysgeusia → behavioral modification[2]
    - Adjusting the temp of food
    - Good oral hygiene
    - Adjusting flavorings
  - Dyspepsia → start PPIs early[2]

1. Friedlander M, et al. *Asia Pac J Clin Oncol.* 2016;12(4):323-331. 2. Moore KN, Monk BJ. *Oncologist.* 2016;21(8):954-963.
G, grade; PPI, proton pump inhibitor.

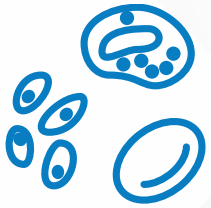
Patient Counseling and Dosing Compliance

Management of hematologic toxicities

- **Labs should be checked monthly x 12**[1]
  - Niraparib: weekly for the first month, monthly for the next 11 months of treatment, and periodically after
  - Olaparib: can reduce lab checks to q 3 months[1]
  - Anemia is main side effect[1]
    - > Does not appear cumulative[2]
- **Evaluation and treatment of anemia**
  - Rule out other causes[1]
  - Mostly managed with dose interruption as long as 28 days (until reduced to G1 or less)[1]
  - Can transfuse w/o interruption or dose modification unless G3/4[1]
  - If anemia is still an issue after 2 dose reductions, consider referral[1]
- **Evaluation and treatment of neutropenia and thrombocytopenia**
  - G1 requires no intervention[1]
  - >G2 requires interruption[1]
    - > Restart at same dose vs. dose mod[1]
  - Persistent significant hematological toxicity warrants referral[1]

1. Friedlander M, et al. *Asia Pac J Clin Oncol*. 2016;12(4):323-331. 2. Moore KN, Monk BJ. *Oncologist*. 2016;21(8):954-963.
G, grade; q, every.

Patient Counseling and Dosing Compliance



Management of AML/MDS

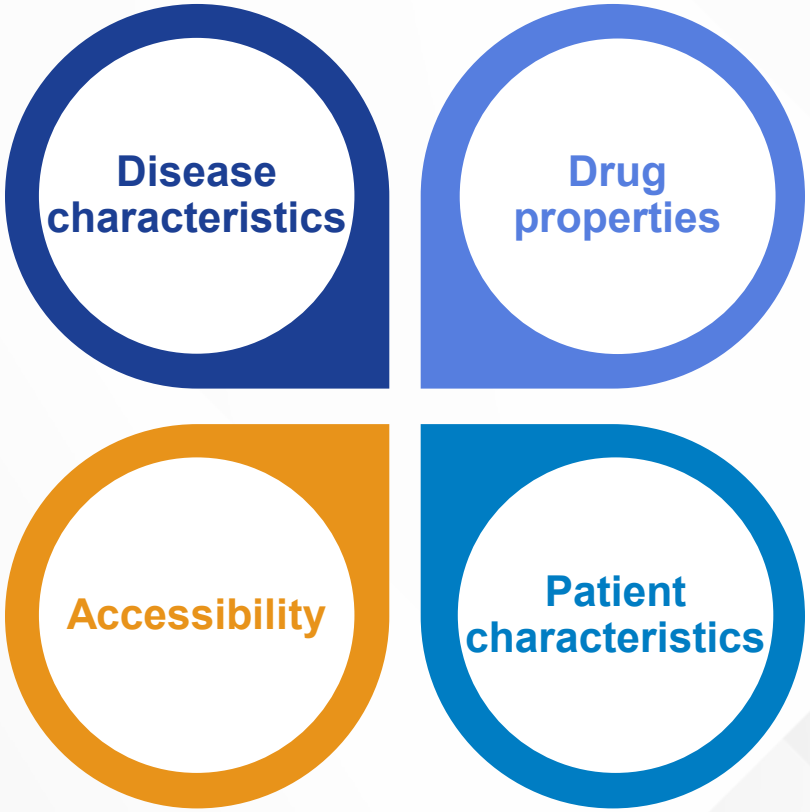
- Patients should be made aware of risk[1]
- Baseline risk is 2.77/1,000 person years for EOC not exposed to PARPi[2]
- AML/MDS (secondary to treatment) have been reported across PARPi studies at 1-2%[3-6]
- Cases related to number of prior regimens, *BRCA* status, and length of PARPi exposure[3]
- Patients with prolonged hematologic toxicity should be referred for hematology consultation +/- bone marrow biopsy[1]
- Currently no screening test to identify patients at highest risk

1. Friedlander M, et al. *Asia Pac J Clin Oncol.* 2016;12(4):323-331. 2. Fulcher N, et al. ASCO 2017. Abstract 5574. 3. Lynparza (olaparib). Prescribing Information. AstraZeneca; 2023. 4. Zejula (niraparib). Prescribing Information. GlaxoSmithKline; 2023. 5. Korach J, et al. *J Clin Oncol.* 2018;36(15_suppl):5548. 6. Zejula. 100mg hard capsules. Summary of Product Characteristics. GlaxoSmithKline; 2021.

AML, acute myeloid leukemia; EOC; epithelial ovarian cancer; MDS, myelodysplastic syndrome; PARPi, poly(ADP-ribose) polymerase inhibitor.

Optimal First-Line Maintenance Therapy Decisions Need to Consider Multiple Factors[1-4]

- Clinical characteristics (symptoms, residual tumor)
- Molecular characteristics (biomarker status)



- Safety and efficacy
- Ease of administration
- Individualized dosing
- Drug interactions

- Genetic *BRCA* and HRD testing
- Approvals and indications
- Reimbursement
- Cost

- Overall treatment plan
- Comorbidities
- Patient preference
- Quality of life/ patient-reported outcomes

1. Buechel M, et al. *Ann Oncol.* 2019;30(5):721-732. 2. Mirza MR, et al. *Ann Oncol.* 2020;31(9):1148-1159.
3. O'Cearbhaill RE. *Oncology (Williston Park).* 2018;32(7):339-343. 4. Havrilesky LJ, et al. *Gynecol Oncol.* 2020;156(3):561-567.

Practical Application Case Illustrations

Patient A's Treatment Journey
*BRCA1*m high-grade serous ovarian cancer

Patient A

42 years old

- BMI: 29 (78 kg)
- Nausea post chemotherapy

Primary debulking surgery

- Complete cytoreduction (residual tumor=0)
- Stage IIIA high-grade serous carcinoma

Genetic testing

*BRCA1*m

IV carboplatin + paclitaxel x 6 cycles

Exam: no evidence of disease

- Imaging: CR
- CA-125 level: <35 U/mL
- Platelet count: 240,000/µL

Additional information for Patient A

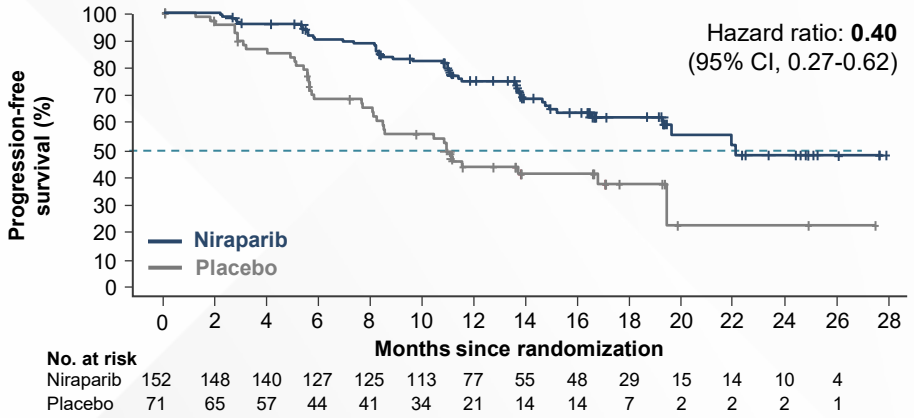
- After learning about her BRCA status, she explored treatment options and asked about PARP inhibitor maintenance
- She prefers a therapy that she can take once a day before bed when she takes her other medication

AXIS Medical Education

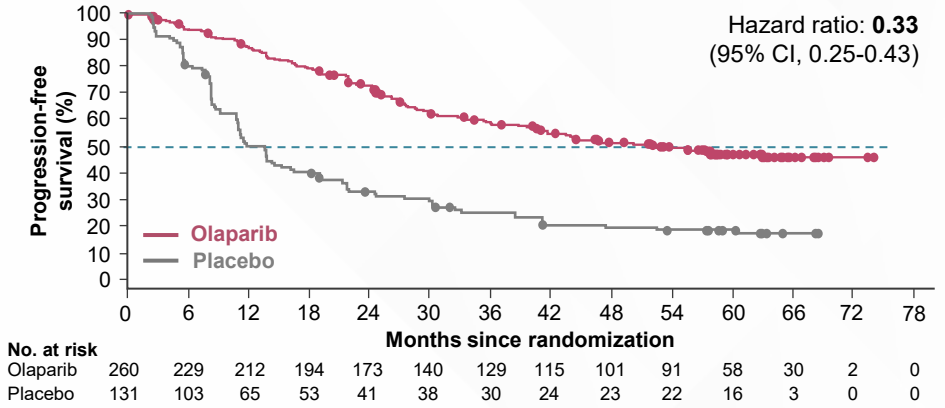
BMI, body mass index; *BRCA1*m, breast cancer gene 1 mutant; CA-125, cancer antigen 125; CR, computed radiography; IV, intravenous; PR, partial response.

Efficacy of PARP Inhibitors and Bevacizumab in *BRCA*m Populations

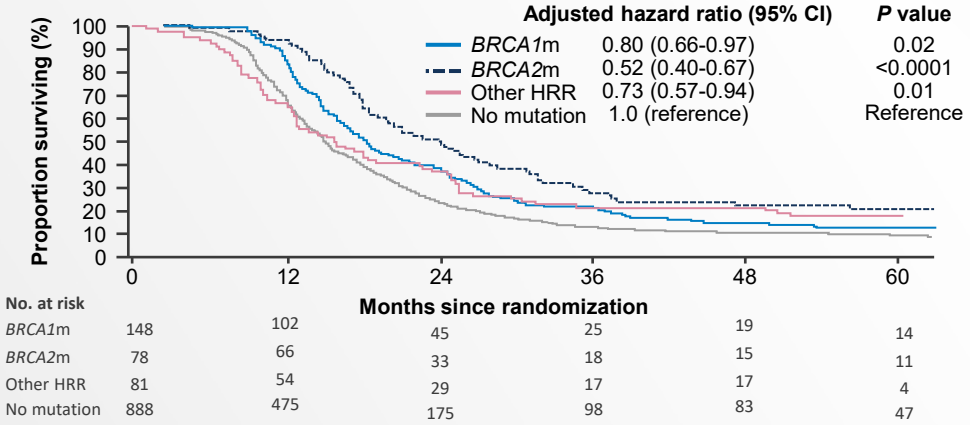
PRIMA: *BRCA*m[1]



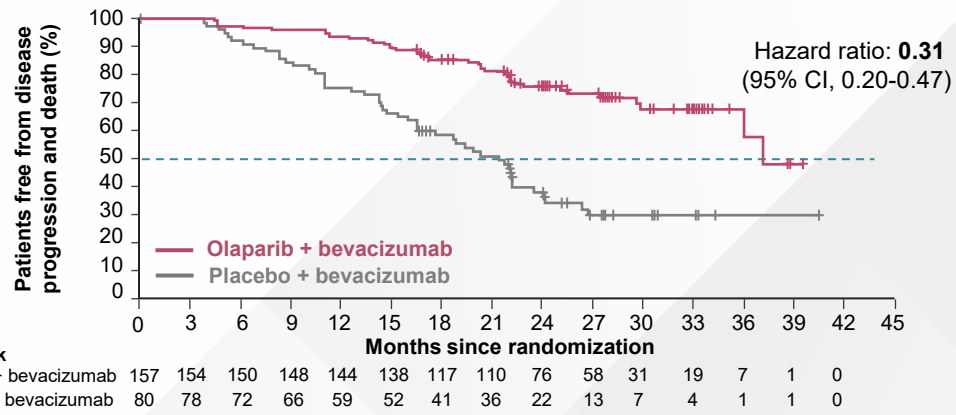
SOLO1: *BRCA*m[2]



GOG-0218: PFS by molecular subgroup[3]



PAOLA-1: *BRCA*m[4]



Head-to-head studies have not been conducted. Cross-trial comparisons are not appropriate.

1. Monk BJ, et al. SGO 2020. Presentation 31. 2. Banerjee S, et al. ESMO Virtual Congress. Abstract 811MO.
3. Norquist BM, et al. *Clin Cancer Res.* 2018;24(4):777-783. 4. Ray-Coquard I, et al. *N Engl J Med.* 2019;381(25):2416-2428.

*BRCA1*m, breast cancer gene 1 mutant; *BRCA2*m, breast cancer gene 2 mutant; *BRCA*m, breast cancer gene mutant; CI, confidence interval; HRR, homologous recombination repair; PARP, poly (ADP-ribose) polymerase; PFS, progression-free survival.

PRIMA: PFS in *BRCA*m Patients Was Comparable Between the FSD and ISD Dose Cohorts (BICR, May 2019)

	FSD		ISD	
	Niraparib	**Placebo**	**Niraparib**	**Placebo**
Median PFS (95% CI)	22.1 (19.3-NE)	11.1 (7.6-19.4)	14.8 (14.8-NE)	10.9 (5.6-NE)
Hazard ratio (95% CI)	0.44 (0.26-0.73)		0.29 (0.13-0.67)	
***P* value**	0.0011		0.0021	
Interaction *P* value	0.7406			

The recommended starting dose of niraparib is 200 mg once daily.
For patients who weigh ≥77 kg and have baseline platelet count ≥150,000/μL, the recommended starting dose of niraparib is 300 mg once daily.[2]

1. Korach J, et al. ESGO 2020. Abstract 571. 2. Zejula. 100mg hard capsules. Summary of Product Characteristics. GlaxoSmithKline; 2021.
BRCAm, breast cancer gene mutant; FSD, fixed starting dose; ISD, individualized starting dose; NE, not estimated; PFS, progression-free survival.

Manageable Safety Profile for PARP Inhibitors ± Bevacizumab in *BRCA*m Populations

	Monotherapy		Combination therapy	
	PRIMA: BRCAm[1]	SOLO1: *BRCA*m[2]	PAOLA-1: *BRCA1*m[3]	PAOLA-1: *BRCA2*m[3]
AEs, n (%)	Niraparib arm (n=152)	Olaparib arm (n=260)	Olaparib + bevacizumab (n=111)	Olaparib + bevacizumab (n=45)
Any grade AEs	150 (99)	256 (98)	111 (100)	45 (100)
Grade ≥3 AEs	98 (65)	103 (40)	36 (32)*	10 (22)*
Dose interruptions due to AEs	114 (75)	136 (52)	67 (60)	26 (58)
Dose reductions due to AEs	103 (68)	75 (29)	48 (43)	19 (42)
Discontinuations due to AEs	14 (9)	30 (12)	22 (20)	8 (18)

Head-to-head studies have not been conducted. Cross-trial comparisons are not appropriate.

AXIS Medical Education

1. Korach J, et al. ESGO 2020. Abstract 571. 2. Banerjee S, et al. ESMO Virtual Congress. Abstract 811MO. 3. Lorusso D, et al. ASCO 2020. Poster 210.
AE, adverse event; *BRCA*m, breast cancer gene mutant; PARP, poly(ADP-ribose) polymerase.

Grade ≥3 Adverse Events With PARP Inhibitor Monotherapy (PRIMA, SOLO1) in *BRCA*m Populations and Combination Therapy (PAOLA-1) in All-Comers Populations

Grade ≥3 AEs, n (%)	PRIMA: BRCAm[1]		SOLO1: BRCAm[2]	PAOLA-1: all-comers[3]
	Niraparib FSD (n=99)	Niraparib ISD (n=53)	Olaparib (n=260)	Olaparib + bevacizumab (n=535)
Thrombocytopenia	49 (50)	10 (19)	2 (1)	9 (2)
Anemia	32 (32)	16 (30)	56 (22)	93 (17)
Neutropenia	18 (18)	7 (13)	22 (9)	32 (6)
Hypertension	9 (9)	1 (2)	-	100 (19)
Lymphopenia	-	-	-	38 (7)
Fatigue or asthenia	-	-	10 (4)	28 (5)
Nausea	-	-	2 (1)	13 (2)
Leukopenia	-	-	-	10 (2)
Abdominal pain	-	-	4 (2)	8 (1)

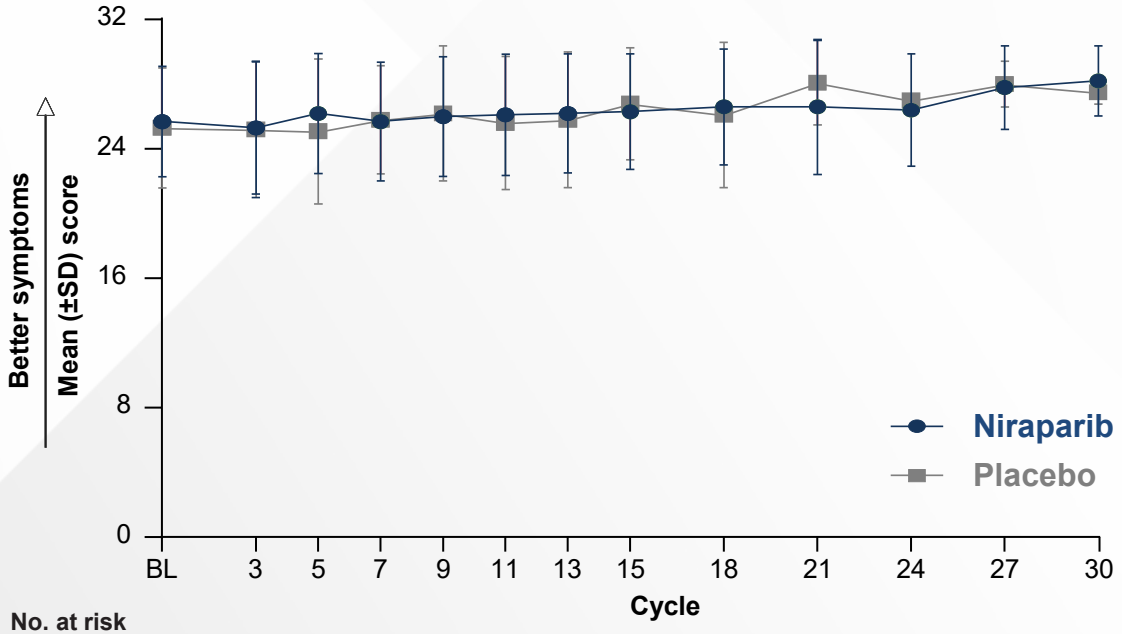
Head-to-head studies have not been conducted. Cross-trial comparisons are not appropriate.

AXIS Medical Education

1. Korach J, et al. ESGO 2020. Abstract 571. 2. Moore K, et al. *N Engl J Med*. 2018;379(26):2495-2505. **3.** Ray-Coquard I et al. *N Engl J Med*. 2019;381(25):2416-2428.
AE, adverse event; *BRCA*m, breast cancer gene mutant; FSD, fixed starting dose; ISD, individualized starting dose; PARP, poly(ADP-ribose) polymerase.

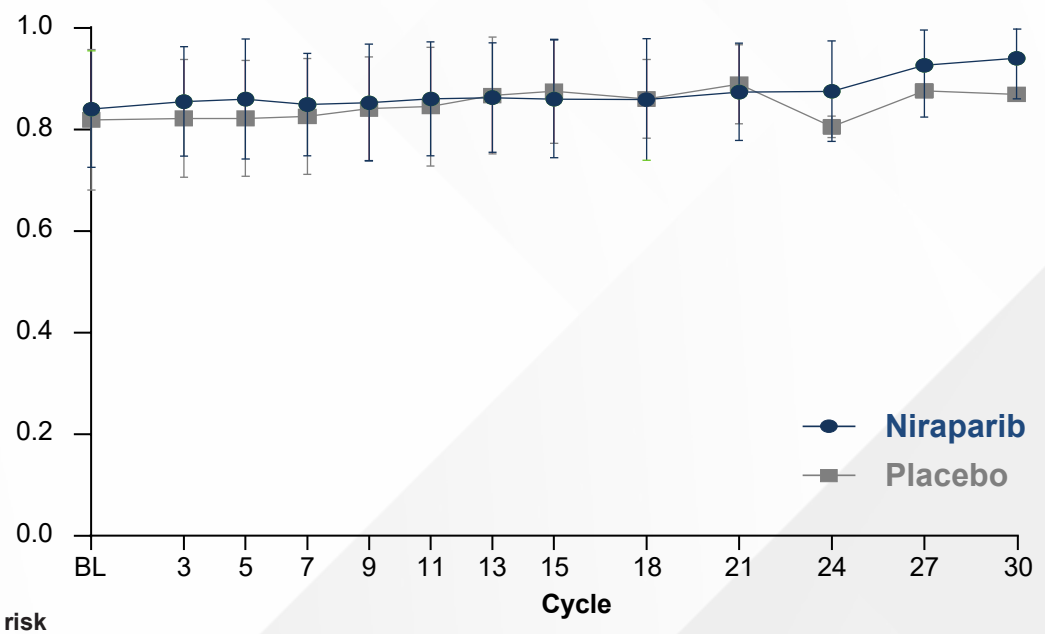
No Meaningful Differences in QOL Were Observed With Niraparib Compared With Placebo in the *BRCA*m Population

PRIMA (*BRCA*m): FOSI



No. at risk													
Niraparib	149	135	124	118	114	110	99	83	48	31	18	10	5
Placebo	70	67	59	55	45	38	36	28	16	7	2	2	2

PRIMA (*BRCA*m): EQ-5D-5L



No. at risk													
Niraparib	147	134	123	118	113	110	101	82	48	30	18	10	5
Placebo	70	67	59	55	47	38	36	28	16	7	2	2	2

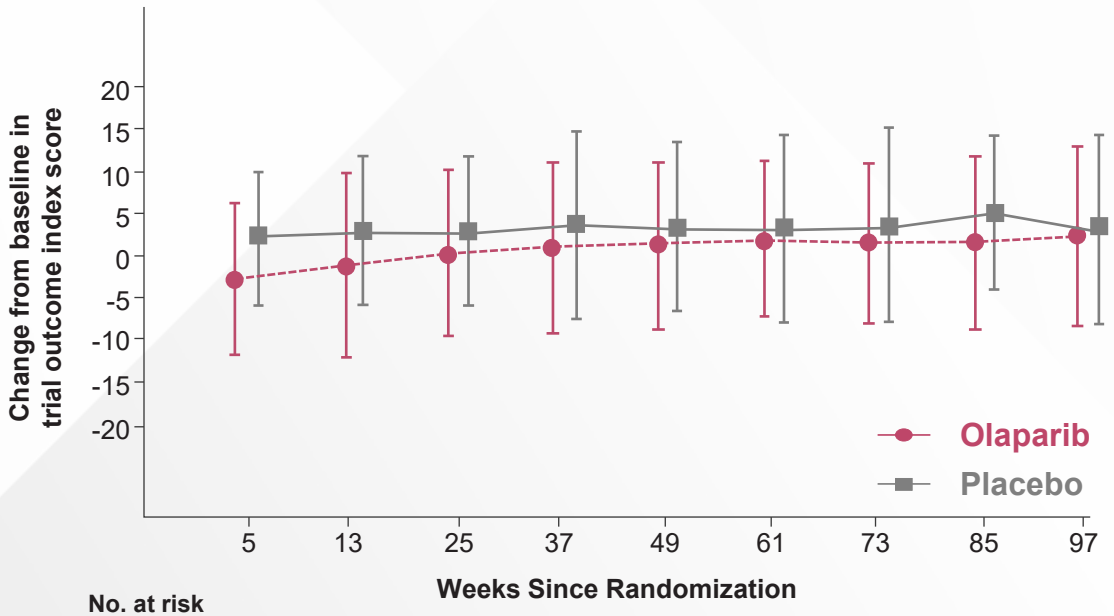
Medical Education

Korach J, et al. ESGO 2020. Abstract 571.

*BRCA*m, breast cancer gene mutant; EQ-5D-5L, European Quality of Life-Dimension 5-Level Scale; FOSI, Functional Assessment of Cancer Therapy Ovarian Symptom Index; QOL, quality of life; SD, standard deviation.

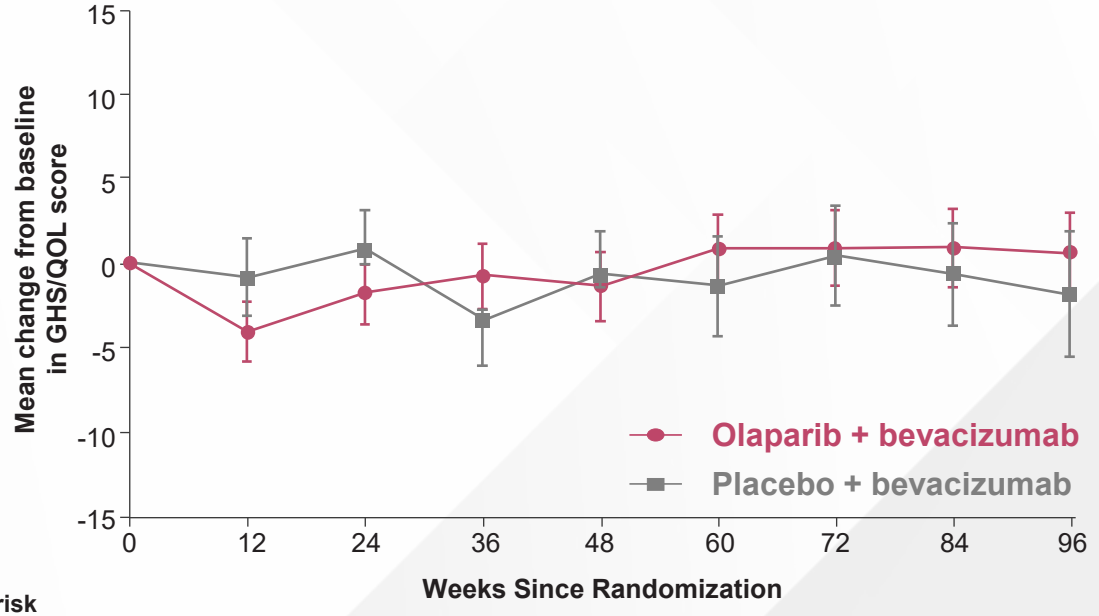
No Meaningful Differences in QOL Were Observed With Olaparib ± Bevacizumab Compared With Placebo in *BRCA*m and All-Comer Populations

SOLO-1 (*BRCA*m): FACT-O[1]



No. at risk									
Olaparib	218	204	191	186	179	163	144	141	137
Placebo	115	114	104	91	75	61	51	49	42

PAOLA-1 (all-comers): EORTC QLQ-C30[2]



No. at risk									
Olaparib + bevacizumab	508	458	432	396	393	352	342	308	252
Placebo + bevacizumab	249	228	207	199	185	171	166	151	123

Head-to-head studies have not been conducted. Cross-trial comparisons are not appropriate.

Moore K, et al. *N Engl J Med*. 2018;379(26):2495-2505. Ray-Coquard I, et al. *N Engl J Med*. 2019;381(25):2416-2428.

*BRCA*m, breast cancer gene mutant; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire; FACT-O, Functional Assessment of Cancer Therapy-Ovarian Cancer; GHS, global health status; QOL, quality of life.

Case Study: Patient A
*BRCA1*m high-grade serous ovarian cancer

42 years old

Diagnosis:
Stage IIIA high-grade serous carcinoma

Genetic testing: *BRCA1*m

What maintenance therapy might be considered for Patient A?

a) Active surveillance
b) VEGF inhibitor monotherapy
c) VEGF inhibitor + PARP inhibitor
d) PARP inhibitor monotherapy
e) Unsure

FDA/EMA agents approved for this patient:
VEGF inhibitor: bevacizumab[1,2]
Combination therapy: bevacizumab + olaparib[3]
PARP inhibitor monotherapies: niraparib and olaparib[3-5]

1. Avastin. Summary of Product Characteristics. Roche; 2021. 2. Avastin. Prescribing Information. Genentech; 2020. 3. Lynparza (olaparib). Prescribing Information. AstraZeneca; 2023. 4. Zejula. 100mg hard capsules. Summary of Product Characteristics. GlaxoSmithKline; 2021. 5. Zejula (niraparib). Prescribing Information. GlaxoSmithKline; 2023.
*BRCA*1m, breast cancer gene 1 mutant; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; PARP, poly (ADP-ribose) polymerase; VEGF, vascular endothelial growth factor.

Patient B's Treatment Journey
*BRCA*wt HRd high-grade serous ovarian cancer

Patient B

49 years old

- Diagnosis: Stage IIIC high-grade serous carcinoma
- BMI: 23 (64 kg)

Neoadjuvant chemotherapy: IV carboplatin + paclitaxel x 3 cycles

Interval debulking surgery

Genetic testing

- Fatigue and nausea (from chemotherapy)
- Incomplete cytoreduction with <2 cm residual mesenteric disease

*BRCA*wt HRd

IV carboplatin and paclitaxel + bevacizumab x 6 cycles

- Imaging: PR
- CA-125 level: 76 U/ml
- Platelet count: 185,000/µL

?

Additional information for Patient B

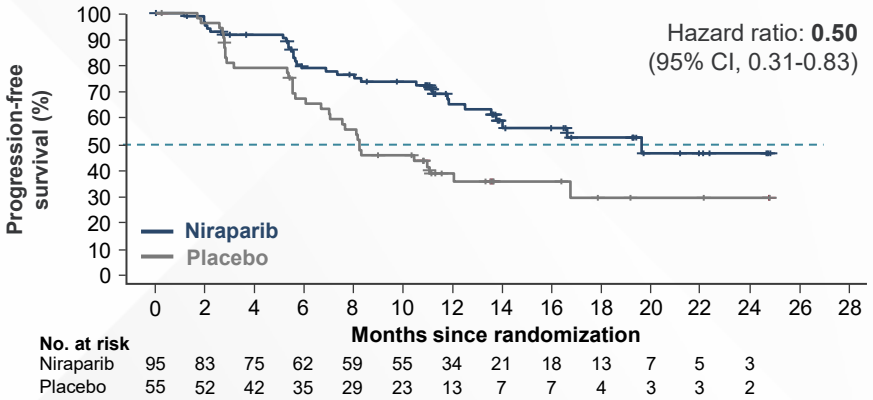
- Patient B wants to avoid additional chemotherapy for as long as possible
- Patient B noted reservations about coming into the hospital and undergoing procedures

AXIS Medical Education

BMI, body mass index; *BRCA*wt, breast cancer gene wild type; CA-125, cancer antigen 125; HRd, homologous recombination deficient; IV, intravenous; partial response.

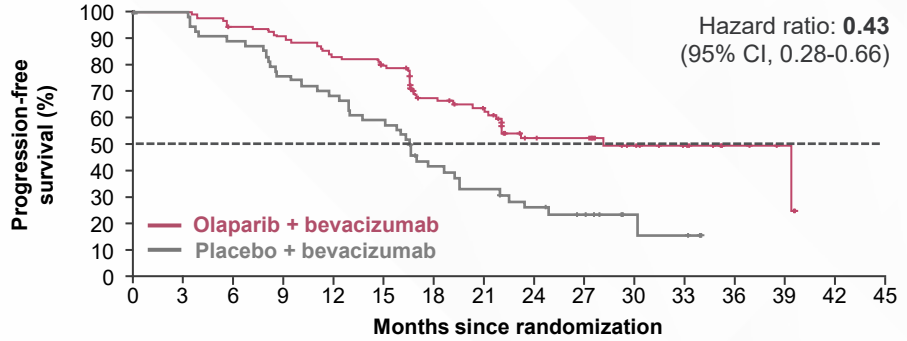
Efficacy of PARP Inhibitors and Bevacizumab in *BRCA*wt and Overall Populations

PRIMA: HRd *BRCA*wt[1]



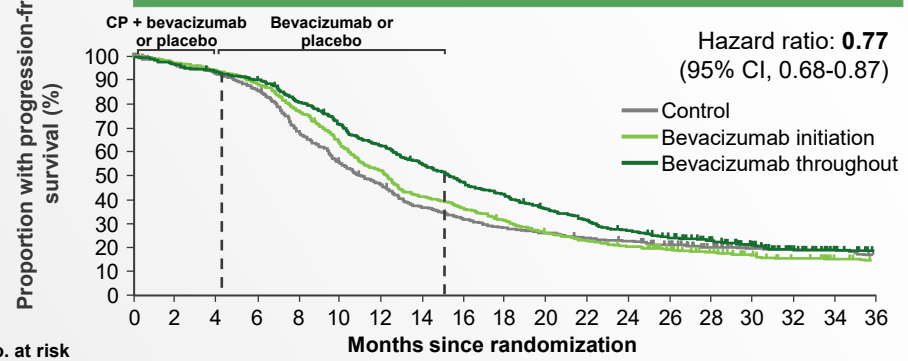
No. at risk													
Niraparib	95	83	75	62	59	55	34	21	18	13	7	5	3
Placebo	55	52	42	35	29	23	13	7	7	4	3	3	2

PAOLA-1: HRd, excluding t*BRCA*m[2]



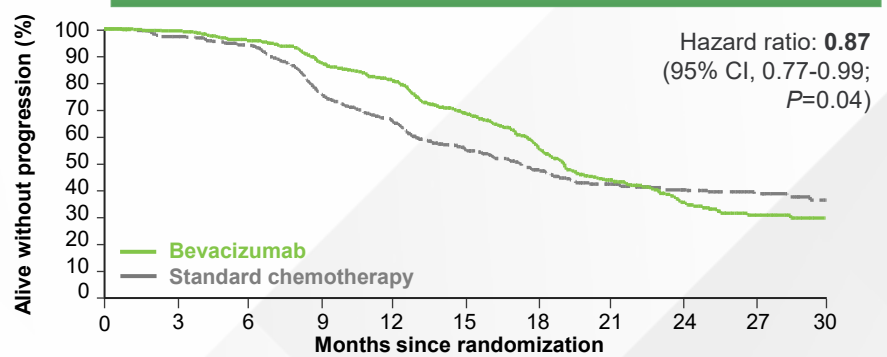
No. at risk															
Olaparib + bevacizumab	97	96	90	86	79	75	54	48	30	29	16	12	4	2	0
Placebo + bevacizumab	55	54	48	41	37	32	19	15	11	8	3	2	0		

GOG-0218: all-comers[3]



No. at risk							
Control	625	535	283	169	133	78	49
Bevacizumab initiation	625	552	319	190	121	67	40
Bevacizumab throughout	623	559	386	256	162	97	56

ICON7: all-comers[4]



No. at risk						
Bevacizumab	764	715	585	263	73	19
Standard chemotherapy	764	693	464	216	91	25

Head-to-head studies have not been conducted. Cross-trial comparisons are not appropriate.

1. Monk BJ, et al. SGO 2020. Presentation 31. 2. Ray-Coquard I, et al. *N Engl J Med.* 2019;381(25):2416-2428.
3. Burger RA, et al. *N Engl J Med.* 2011;365(26):2473-2483. 4. Perren TJ, et al. *N Engl J Med.* 2011;365(26):2484-2496.

*BRCA*wt, breast cancer gene wild type; CI, confidence interval; CP, carboplatin and paclitaxel; HRd, homologous recombination deficient; PARP, poly(ADP-ribose) polymerase; t*BRCA*m, tumor breast cancer gene mutant.

Safety Profile in Niraparib (PRIMA) *BRCA*wt and All-Comer Populations, and in Olaparib + Bevacizumab (PAOLA-1) All-Comer Population

	Monotherapy		Combination therapy
	PRIMA		PAOLA-1: all-comers[3]
AEs, n (%)	Niraparib: all biomarker subgroups (n=484)[1]	Niraparib: BRCAwt (n=307)[2]	Olaparib + bevacizumab* (n=535)
Any grade	478 (99)	304 (99)	531 (99)
Grade ≥3	341 (71)	223 (73)	303 (57)
Dose interruptions due to AEs	385 (80)	249 (81)	291 (54)
Dose reductions due to AEs	343 (71)	222 (72)	220 (41)
Discontinuations due to AEs	58 (12)	39 (13)	109 (20)

Head-to-head studies have not been conducted. Cross-trial comparisons are not appropriate.

AXIS Medical Education

*Patients were treated with bevacizumab during chemotherapy and for maintenance.

1. González Martín A, et al. *N Engl J Med.* 2019;381(25):2391-2402. **2.** Braicu EI, et al. ESGO 2020. Abstract 364. **3.** Ray-Coquard I, et al. *N Engl J Med.* 2019;381(25):2416-2428.

AE, adverse event; *BRCA*wt, breast cancer gene wild type.

Grade ≥3 Adverse Events in Niraparib (PRIMA) *BRCA*wt and All-Comer Populations, and Olaparib + Bevacizumab (PAOLA-1) All-Comer Population

Grade ≥3 AEs, n (%)	PRIMA			PAOLA-1: all-comers[3]
	Niraparib overall (n=484)[1]	Niraparib BRCAwt FSD (n=197)[2]	Niraparib BRCAwt ISD (n=110)[2]	Olaparib + bevacizumab (n=535)
Thrombocytopenia	139 (29)	94 (48)	26 (24)	9 (2)
Anemia	150 (31)	76 (39)	20 (18)	93 (17)
Neutropenia	62 (13)	49 (25)	18 (16)	32 (6)
Hypertension	NR	10 (5)	8 (7)	100 (19)
Fatigue	9 (2)	NR	NR	28 (5)
Headache	2 (0.4)	NR	NR	2 (<1)

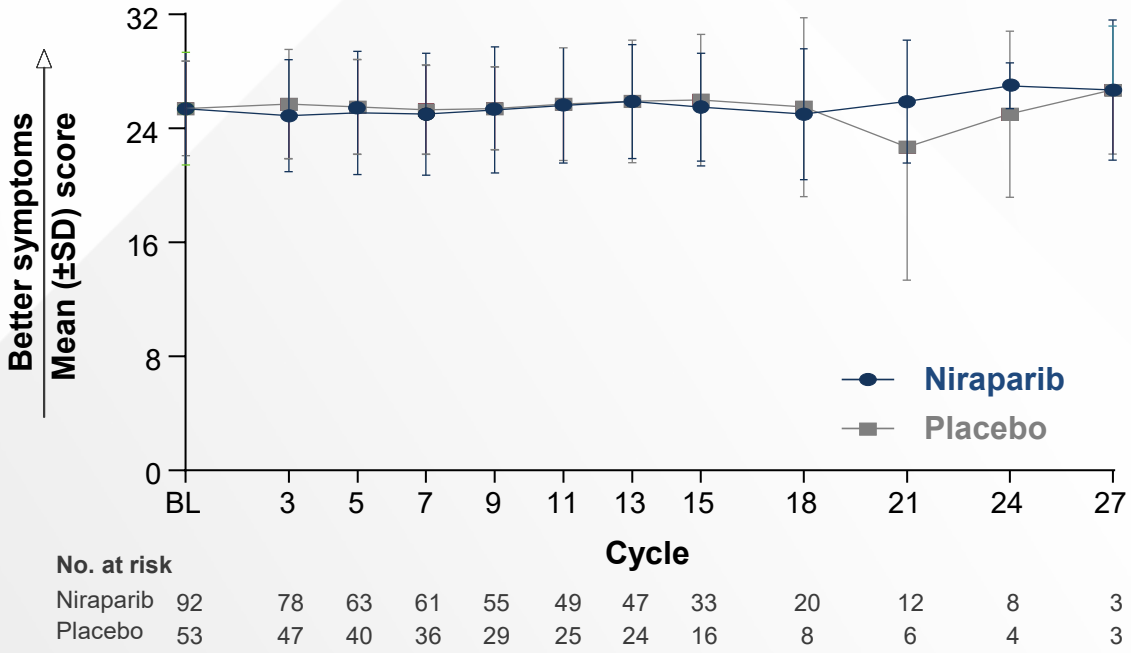
The recommended starting dose of niraparib is 200 mg once daily.
For patients who weigh ≥77 kg and have baseline platelet count ≥150,000/μL, the recommended starting dose of niraparib is 300 mg once daily.[4]

Head-to-head studies have not been conducted. Cross-trial comparisons are not appropriate.

1. González Martín A, et al. *N Engl J Med.* 2019;381(25):2391-2402. 2. Braicu EI, et al. ESGO 2020. Abstract 364. 3. Ray-Coquard I, et al. *N Engl J Med.* 2019;381(25):2416-2428. 4. Zejula. 100mg hard capsules. Summary of Product Characteristics. GlaxoSmithKline; 2021.
AE, adverse event; *BRCA*wt, breast cancer gene wild type; FSD, fixed starting dose; ISD, individualized starting dose; NR, not reported.

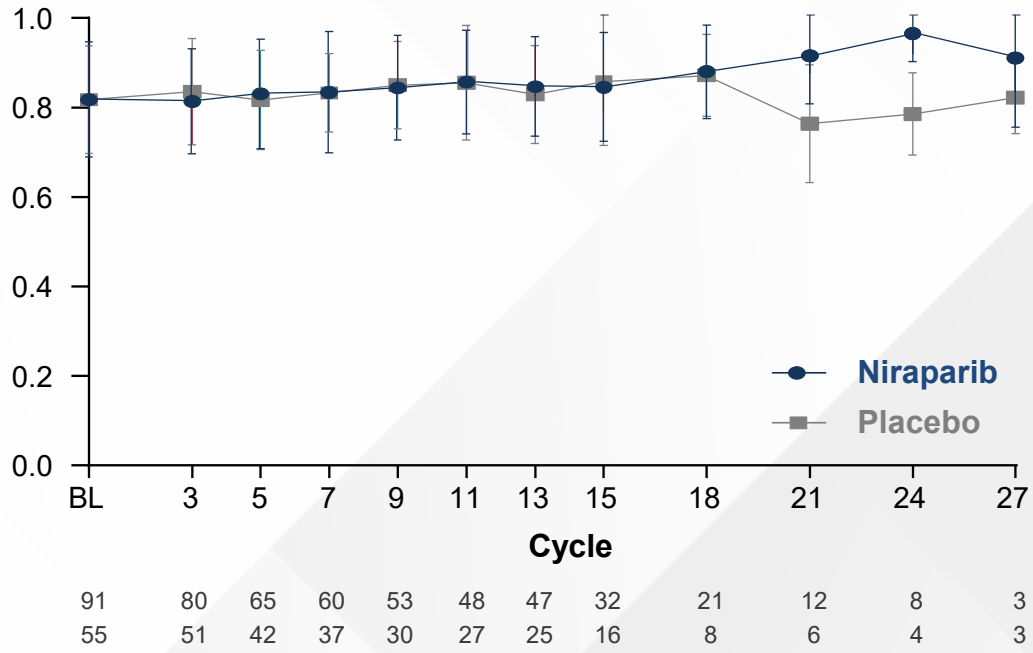
No Meaningful Differences in QOL Were Observed With Niraparib Compared With Placebo in the *BRCA*wt HRd Population

PRIMA (*BRCA*wt HRd): FOSI



No. at risk												
Niraparib	92	78	63	61	55	49	47	33	20	12	8	3
Placebo	53	47	40	36	29	25	24	16	8	6	4	3

PRIMA (*BRCA*wt HRd): EQ-5D-5L



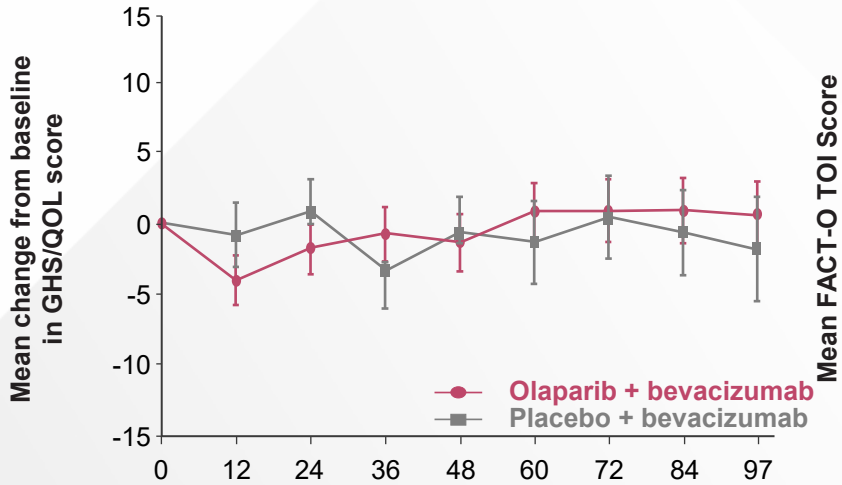
Niraparib	91	80	65	60	53	48	47	32	21	12	8	3
Placebo	55	51	42	37	30	27	25	16	8	6	4	3

Braicu EI, et al. ESGO 2020. Abstract 364.

BL, baseline; *BRCA*wt, breast cancer gene wild type; EQ-5D-5L, EuroQol 5-Dimension 5-Level; FOSI, Functional Assessment of Cancer Therapy Ovarian Symptom Index; HRd, homologous recombination deficient; QOL, quality of life; SD, standard deviation.

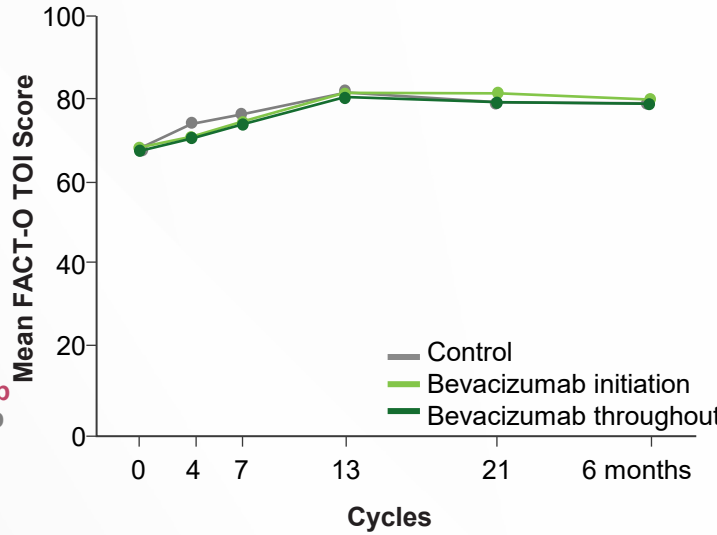
No Meaningful Differences in QOL Were Observed With Bevacizumab ± Olaparib Compared With Placebo in All-Comer Populations

PAOLA-1 (all-comers): EORTC QLQ-C30[1]

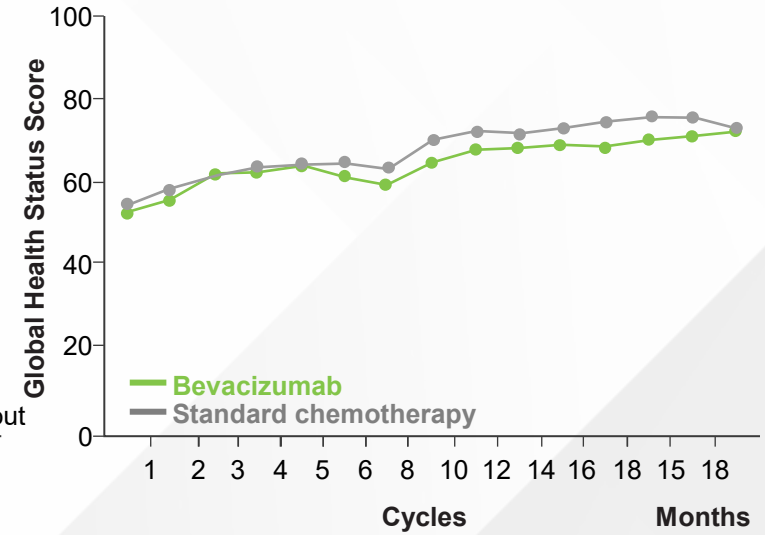


No. at risk									
Olaparib + bevacizumab	508	458	432	396	393	352	342	308	252
Placebo + bevacizumab	249	228	207	199	185	171	166	151	123

GOG-0218 (all-comers): FACT-O TOI[2]



ICON7 (all-comers): EORTC QLQ-C30[3]



Head-to-head studies have not been conducted. Cross-trial comparisons are not appropriate.

1. Ray-Coquard I, et al. *N Engl J Med*. 2019;381(25):2416-2428. 2. Monk BJ, et al. *Gynecol Oncol*. 2013;128(3):573-578. 3. Perren TJ, et al. *N Engl J Med*. 2011;365(26):2484-2496.

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire; FACT-O, Functional Assessment of Cancer Therapy-Ovarian Cancer; GHS, global health status; QOL, quality of life; TOI, Trial Outcome Index.

Case Study: Patient B
*BRCA*wt HRd high-grade serous ovarian cancer

Patient B

49 years old

Diagnosis:
Stage IIIC high-grade serous carcinoma

Genetic testing:
*BRCA*wt HRd

What maintenance therapy might be considered for Patient B?

a) Active surveillance
b) VEGF inhibitor monotherapy
c) VEGF inhibitor + PARP inhibitor
d) PARP inhibitor monotherapy
e) Unsure

FDA/EMA agents approved for this patient:
VEGF inhibitor: bevacizumab[1,2]
Combination therapy: bevacizumab + olaparib[3]
PARP inhibitor monotherapy: niraparib[4,5]

1. Avastin. Summary of Product Characteristics. Roche; 2021. 2. Avastin. Prescribing Information. Genentech; 2020. 3. Lynparza (olaparib). Prescribing Information. AstraZeneca; 2023. 4. Zejula. 100mg hard capsules. Summary of Product Characteristics. GlaxoSmithKline; 2021. 5. Zejula (niraparib). Prescribing Information. GlaxoSmithKline; 2023.
BRCA, breast cancer gene wild type; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; HRd, homologous recombination deficient; PARP, poly(ADP-ribose) polymerase; VEGF, vascular endothelial growth factor.

Patient C's Treatment Journey
HRp high-grade serous ovarian cancer

Patient C

63 years old

- BMI: 30 (82 kg)

Primary debulking surgery

- Stage IIIC high-grade serous carcinoma
- Incomplete cytoreduction with <1 cm residual mesenteric disease

Genetic testing

HRp

IV carboplatin + paclitaxel x 6 cycles

- Imaging: PR
- Improvement of symptoms
- CA-125 level: <35 U/ml
- Platelet count: 170,000/µL

Additional information for Patient C

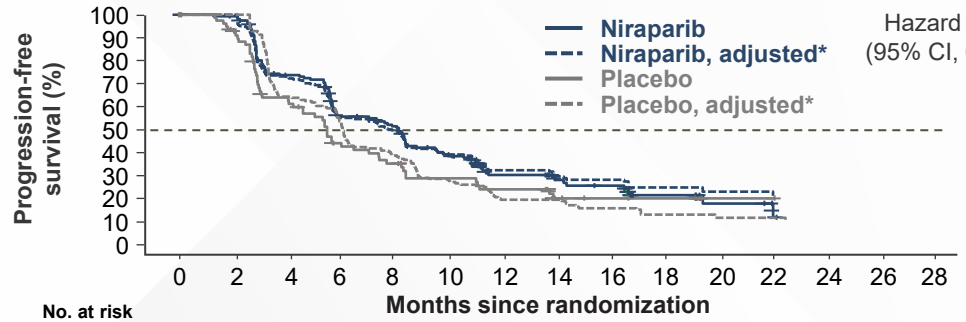
- Patient C wants to continue working and desires minimal disruption to her schedule
- She researches options on the internet and brings printouts of physicians' recommendations for maintenance therapy

AXIS Medical Education

BMI, body mass index; CA-125, cancer antigen 125; HRp, homologous recombination proficient; IV, intravenous; PR, partial response.

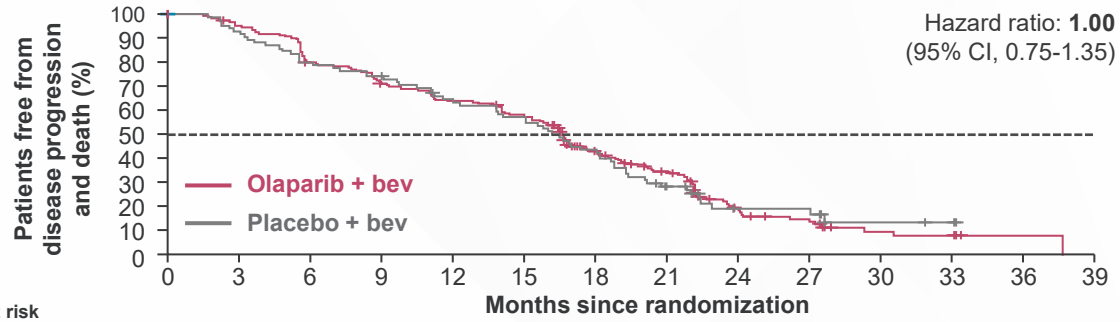
Efficacy of PARP Inhibitors and Bevacizumab in HRp and Overall Populations

PRIMA: HRp[1]



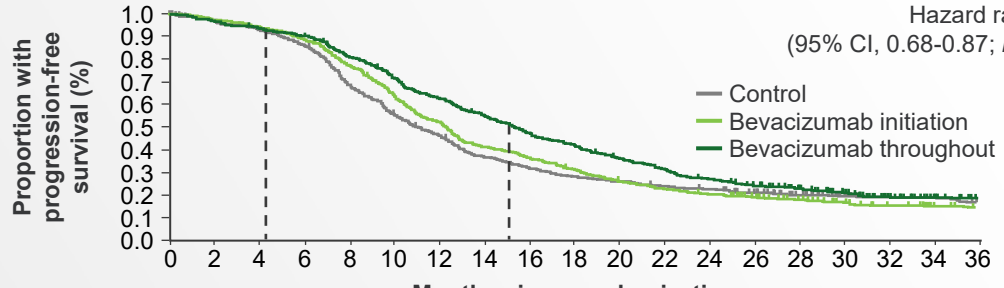
No. at risk												
Niraparib	169	157	113	81	73	53	34	23	20	10	5	1
Placebo	80	70	45	29	24	18	15	8	6	5	1	1

PAOLA-1: HRp[2]



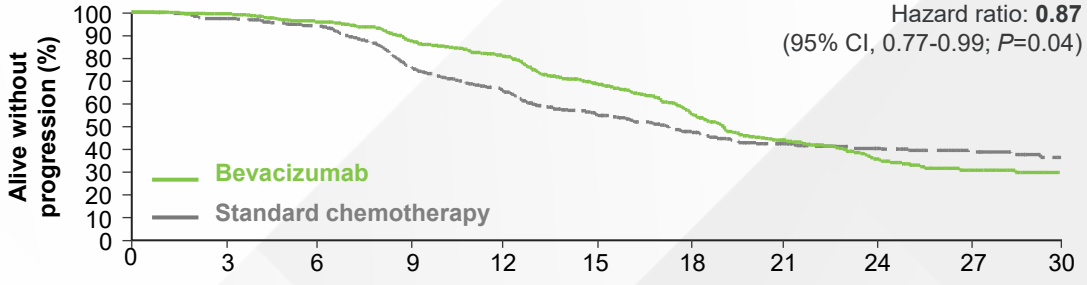
No. at risk														
Olaparib + bevacizumab	192	175	145	128	115	102	67	49	20	13	6	5	1	0
Placebo + bevacizumab	85	79	68	63	52	47	34	20	8	8	3	2	0	

GOG-0218: all-comers[3]



No. at risk							
Control	625	535	283	169	133	78	49
Bevacizumab initiation	625	552	319	190	121	67	40
Bevacizumab throughout	623	559	386	256	162	97	56

ICON7: all-comers[4]



No. at risk						
Bevacizumab	764	715	585	263	73	19
Standard chemotherapy	764	693	464	216	91	25

Head-to-head studies have not been conducted. Cross-trial comparisons are not appropriate.

AXIS Medical Education

*There was no stratification in the HRp subgroup; as a result, in this exploratory analysis, imbalances were observed. To account for these imbalances within the subgroup, statistical adjustments were made to the Kaplan-Meier curve in accordance with accepted statistical methods.

1. Monk BJ, et al. SGO 2020. Presentation 31. 2. Ray-Coquard I, et al. *N Engl J Med.* 2019;381(25):2416-2428. 3. Burger RA, et al. *N Engl J Med.* 2011;365(26):2473-2483. 4. Perren TJ, et al. *N Engl J Med.* 2011;365(26):2484-2496.

CI, confidence interval; HRp, homologous recombination proficient; PARP, poly(ADP-ribose) polymerase.

Grade ≥3 Adverse Events in Niraparib (PRIMA) and Bevacizumab (GOG-0218, ICON7) All-Comer Populations

Grade ≥3 AEs, n (%)	PRIMA: all biomarker subgroups			GOG-0218: all-comers[3]		ICON7: all-comers[4]
	Niraparib overall (n=484)[1]	Niraparib FSD (n=315)[2]	Niraparib ISD (n=169)[2]	Bevacizumab initiation (n=607)	Bevacizumab throughout (n=608)	Bevacizumab (n=745)
Thrombocytopenia	139 (29)	152 (48)	36 (21)	-	-	26 (3)
Anemia	150 (31)	112 (36)	38 (23)	-	-	-
Neutropenia	62 (13)	75 (24)	25 (15)	384 (63)	385 (63)	123 (17)
VTE	-	-	-	-	-	32 (4)
ATE	-	-	-	-	-	20 (3)
Non-CNS bleeding	-	-	-	8 (1)	13 (2)	-
Hypertension	NR	20 (7)	9 (5)	100 (17)	139 (23)	46 (6)
Fatigue	9 (2)	-	-	-	-	-
Headache	2 (0.4)	-	-	-	-	-
Proteinuria	-	-	-	4 (0.7)	10 (2)	4 (1)

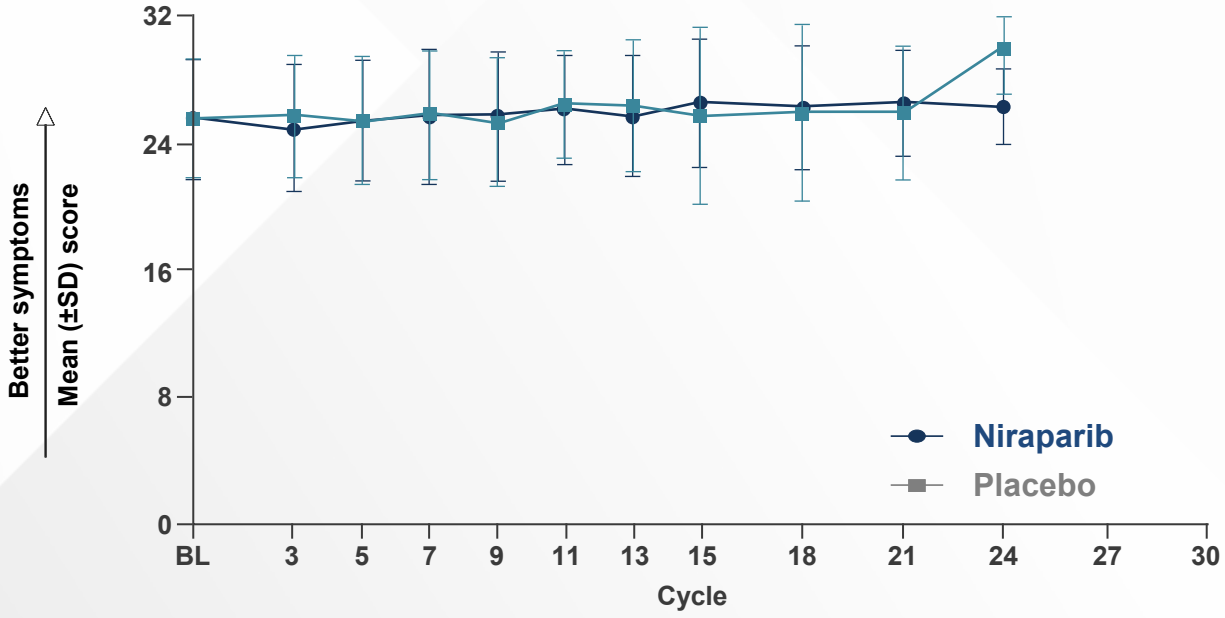
Head-to-head studies have not been conducted. Cross-trial comparisons are not appropriate.

AXIS Medical Education

1. González-Martín A, et al. *N Engl J Med.* 2019;381(25):2391-2402. 2. Mirza MR, et al. ASCO Annual Meeting. Poster 221.
3. Burger RA, et al. *N Engl J Med.* 2011;365(26):2473-2483. 4. Perren TJ, et al. *N Engl J Med.* 2011;365(26):2484-2496.
AE, adverse event; ATE, arterial thromboembolic event; CNS, central nervous system; FSD, fixed starting dose; ISD, individualized starting dose; NR, not reported; VTE, venous thromboembolism.

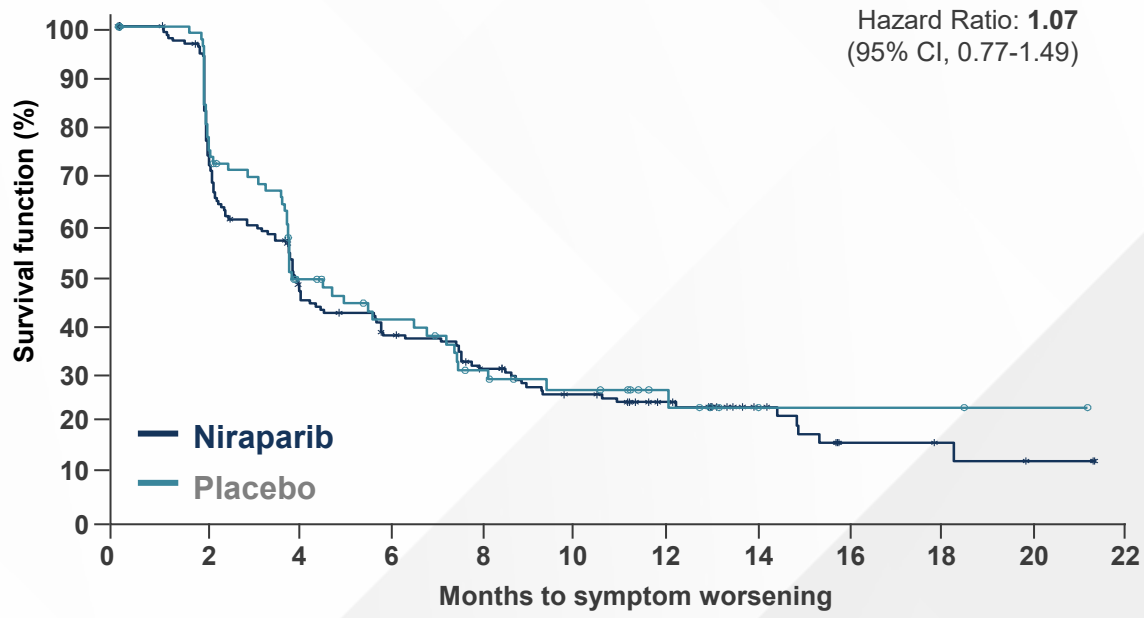
No Meaningful Differences in QOL Were Observed With Niraparib Compared With Placebo in the HRp Population (FOSI)

PRIMA (HRp): FOSI HUI



Niraparib	167	145	113	94	81	64	56	48	23	9	4
Placebo	77	67	52	41	28	21	21	17	9	6	2

PRIMA (HRp): Time to FOSI symptom worsening



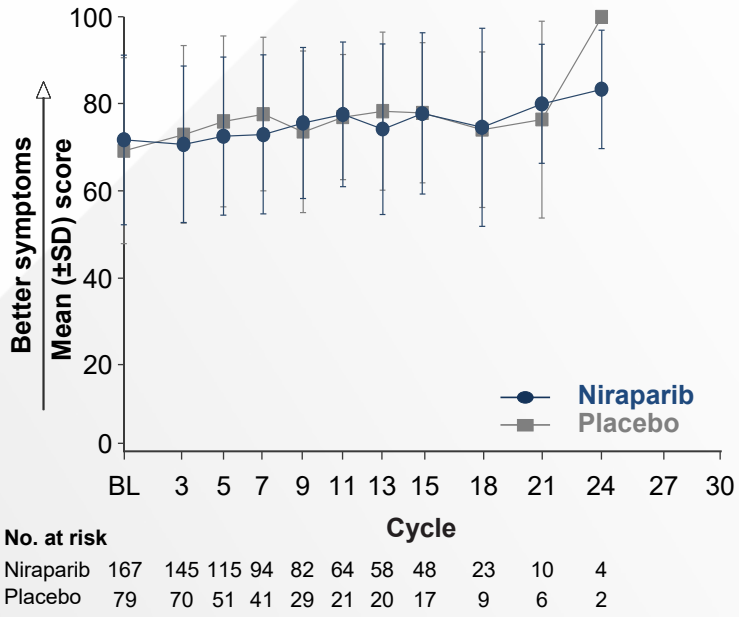
Niraparib	169	116	68	55	42	32	24	13	5	4	2	0
Placebo	80	56	32	24	16	12	7	2	2	2	1	0

Freyer G, et al. IGCS 2020. Presentation 1131.

BL, baseline; CI, confidence interval; FOSI, Functional Assessment of Cancer Therapy Ovarian Symptom Index; HRp, homologous recombination proficient; HUI, health utility index; QOL, quality of life; SD, standard deviation.

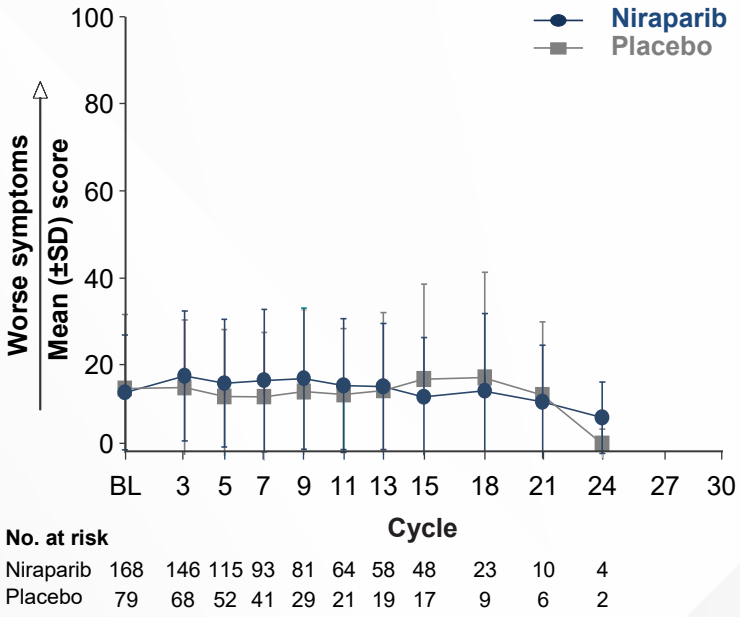
No Meaningful Differences in QOL Were Observed With Niraparib Compared With Placebo in the HRp Population (EORTC-QLQ and EQ-5D-5L)

PRIMA (HRp): EORTC QLQ-C30



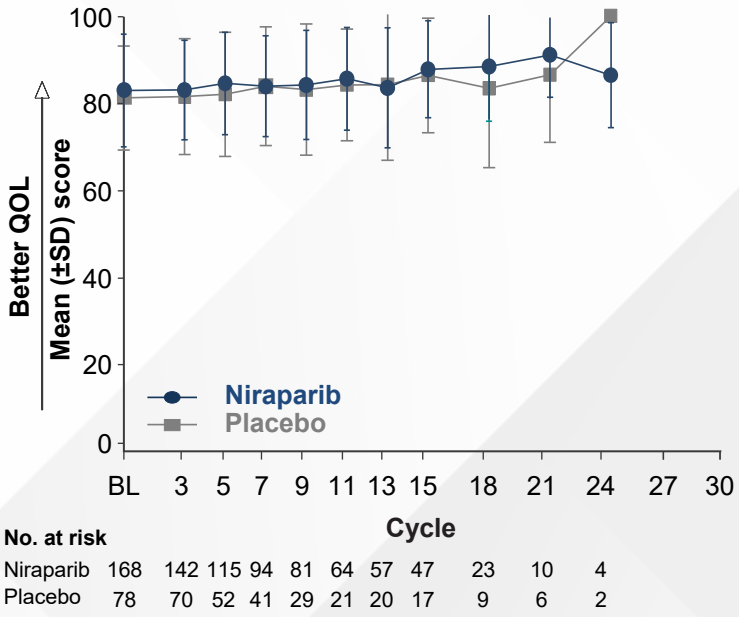
No. at risk											
Niraparib	167	145	115	94	82	64	58	48	23	10	4
Placebo	79	70	51	41	29	21	20	17	9	6	2

PRIMA (HRp): EORTC QLQ-OV28 abdominal/GI symptoms



No. at risk											
Niraparib	168	146	115	93	81	64	58	48	23	10	4
Placebo	79	68	52	41	29	21	19	17	9	6	2

PRIMA (HRp): EQ-5D-5L



No. at risk											
Niraparib	168	142	115	94	81	64	57	47	23	10	4
Placebo	78	70	52	41	29	21	20	17	9	6	2

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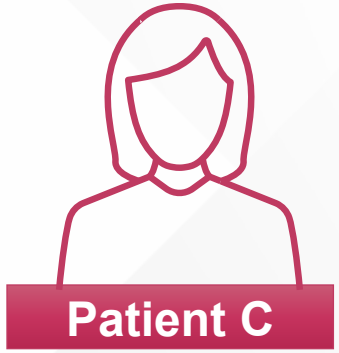
Freyer G, et al. IGCS 2020. Presentation 1131.

BL, baseline; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire; EORTC QLQ-OV28, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Ovarian Cancer Module; EQ-5D-5L, European Quality of Life-Dimension 5-Level Scale; GI, gastrointestinal; HRp, homologous recombination proficient; QOL, quality of life; SD, standard deviation.

Case Study: Patient C
HRp high-grade serous ovarian cancer



Patient C

63 years old

Diagnosis:
Stage IIIC high-grade serous carcinoma

Genetic testing:
HRp

What maintenance therapy might be considered for Patient C?

a) Active surveillance
b) VEGF inhibitor monotherapy
c) VEGF inhibitor + PARP inhibitor
d) PARP inhibitor monotherapy
e) Unsure

FDA/EMA agents approved for this patient:
VEGF inhibitor: bevacizumab[1,2]
Combination therapy: No approvals
PARP inhibitor monotherapy: niraparib[3,4]

1. Avastin. Summary of Product Characteristics. Roche; 2021. 2. Avastin. Prescribing Information. Genentech; 2020. 3. Zejula. 100mg hard capsules. Summary of Product Characteristics. GlaxoSmithKline; 2021. 4. Zejula. Prescribing Information. GlaxoSmithKline; 2023.
EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; HRp, homologous recombination proficient; PARP, poly (ADP-ribose) polymerase; VEGF, vascular endothelial growth factor.

Conclusions

PARPi related AEs are low grade and manageable[1]

Patient counseling and setting expectations is key[1,2]

Prompt management of adverse events, especially non-hematologic issues, will help with patient compliance[2]

Judicious use of dose interruptions over the course of therapy may help avoid dose reductions and maintain dose intensity and efficacy[1,2]

1. Moore KN, Monk BJ. *Oncologist*. 2016;21(8):954-963. 2. Friedlander M, et al. *Asia Pac J Clin Oncol*. 2016;12(4):323-331.
AE, adverse event; PARPi, poly(ADP-ribose) polymerase inhibitor.

Shared Decision-Making Discussion: Improving Patient-Physician Communication

- SDM strategies to improve clinician/patient communication
- Patient education and team-based collaboration/communication to promote timely recognition and optimal management of PARP inhibitor-related AEs
- What aspects of the care/treatment plan should be targeted and how?
- Aligning treatment planning decisions with patient-centric concerns, goals, preferences, values, and ethnic background, and the potential impact this can have on improving patient outcomes and QoL
- Patient selection and communication of evidence-based treatment algorithms

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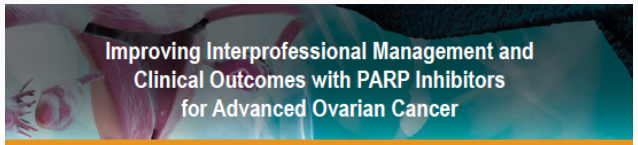
AE, adverse event; PARP, poly(ADP-ribose) polymerase: QoL, quality of life; SDM, shared decision-making.

Guide to Facilitate Shared Decision-Making

Available for Download



What is Shared Decision-Making?

Shared decision-making (SDM) occurs when a healthcare provider and a patient work together to make a healthcare decision that is best for the patient. Optimal decision-making takes into account evidence-based information about available options; the provider's knowledge and experience; and the patient's values, goals, and preferences. Patients and their families/caregivers who are engaged in an SDM process are more likely to arrive at a treatment decision that works best for all those involved.

SHARE Decision Making Model

SEEK	your patient's participation.
HELP	your patient explore & compare treatement options.
ASSESS	your patient's values and preferences.
REACH	a decision with your patient.
EVALUATE	your patient's decision.

Identification of Patients Who Might Benefit From PARP Inhibitor Therapy

- Homologous recombination deficiency (HRD) is present in ~50% of newly-diagnosed, high-grade, epithelial ovarian cancers
  - Approximately 20% of patients with ovarian cancer harbor a BRCA mutation
  - Homologous recombination repair (HRR) gene mutations, altered gene expression, and other causes contribute to genomic instability
- PARP inhibitors trap PARP enzymes on DNA, causing cancer-specific cell death in tumors with HRD
- In the first-line maintenance setting, HRD genomic instability predicts the magnitude of PARP inhibitor benefit

Guideline Recommendations: Tumor Molecular Analyses

- Patients with ovarian cancer should have genetic risk evaluation and germline and somatic testing
- Germline and somatic BRCA1/2 status informs maintenance therapy
- In the absence of a BRCA1/2 mutation, HRD status may provide information on the magnitude of benefit of PARP inhibitor therapy

Setting	Recommendation
Upfront	Choice of somatic testing should, at a minimum, optimize identification of molecular alterations that can inform use of interventions that have demonstrated benefit in this setting, including: **BRCA1/2, LOH, or HRD status in the absence of a germline BRCA mutation**

Selecting Appropriate Patients for PARP Inhibitor Therapy and Setting Expectations Are Key

- Complete or partial response to platinum-based chemotherapy
- Able to tolerate oral medication
- No significant hepatic or renal dysfunction
- PARP inhibitor related adverse events are of low grade and manageable
- Prompt management of adverse events, especially non-hematologic issues will help with patient compliance
- Judicious use of dose interruptions over the course of therapy may help avoid dose reductions and maintain dose intensity and efficacy
- Shared decision-making: Aligning treatment planning decisions with patient centric concerns, goals, preferences, values, ethnical background, and impact on improving patient outcomes and quality of life

FDA-Approved PARP Inhibitor Maintenance for Newly-Diagnosed Advanced Ovarian Cancer

	Olaparib	Olaparib + bevacizumab	Niraparib
Approval	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	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 HRD-positive status defined by either: • a deleterious or suspected deleterious BRCA mutation, and/or • genomic instability	Maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy
Biomarker Testing for Patient Selection	BRCA1m, BRCA2m	HRD+ (BRCA1m, BRCA2m, and/or genomic instability)	Appropriate for all patients regardless of BRCAm status
Dosing/ Administration	300mg taken orally twice daily with or without food	300mg taken orally twice daily with or without food Bevacizumab: 15 mg/kg IV every three weeks	Depending on patient weight and platelet count, 200mg or 300mg taken orally once daily with or without food
Trial	SOLO-1	PAOLA-1	PRIMA
Key Efficacy Data: Median PFS	In BRCAm: NR vs 13.8 months placebo (HR .30)	In HRD+: 37.2 months vs 17.7 months placebo + bevacizumab (HR .33)	In overall population: 13.8 months vs 8.2 months placebo (HR 0.62)
Warnings/ Precautions	MDS/AML Pneumonitis VTE Embryo-fetal toxicity	Pneumonitis VTE Embryo-fetal toxicity	MDS/AML Bone Marrow Suppression Hypertension and cardiovascular effects PRES Embryo-fetal toxicity
Monitoring	Hematologic toxicity/CBC for cytopenia New or worsening respiratory symptoms Signs/symptoms of VTE and PE		CBC Blood pressure Heart rate Signs/symptoms of PRES

AML, acute myeloid leukemia; HR, hazard ratio; HRD, homologous recombination deficiency; IV, intravenous; MDS, myelodysplastic syndrome; NR, not reached; PE, pulmonary embolism; PRES, posterior reversible encephalopathy syndrome; UTI, urinary tract infection; VTE, venous thromboembolism.

Optimal First-Line Maintenance Therapy Decisions Need to Consider Multiple Factors

Disease characteristics	• Clinical characteristics (symptoms, residual tumor) • Molecular characteristics (biomarker status)	
Drug properties	• Safety and efficacy • Ease of administration	• Individual dosing • Drug interactions
Accessibility	• Genetic *BRCA* and HRD testing • Approvals and indications	• Reimbursement • Cost
Patient characteristics	• Overall treatment plan • Comorbidities • Patient preference	• Quality of life/patient-reported outcomes

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