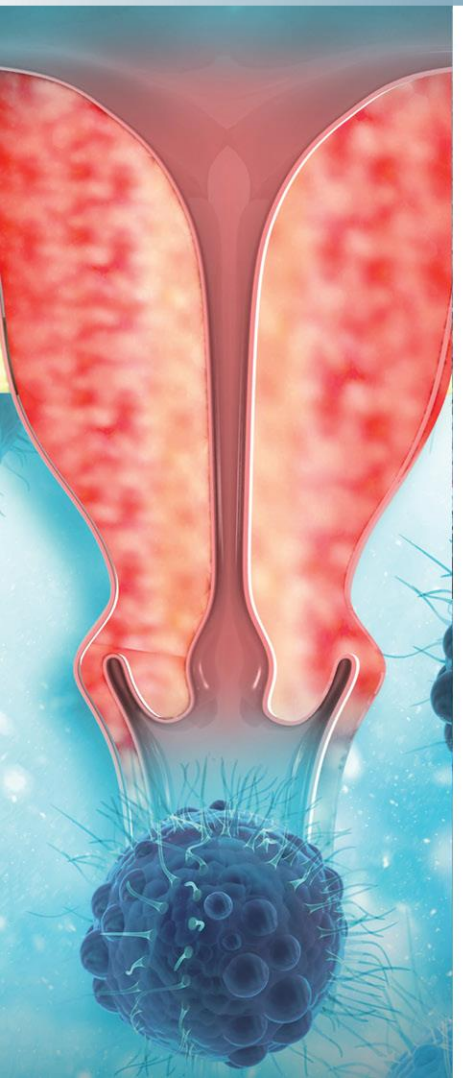
Managing Advanced Gynecologic Cancers

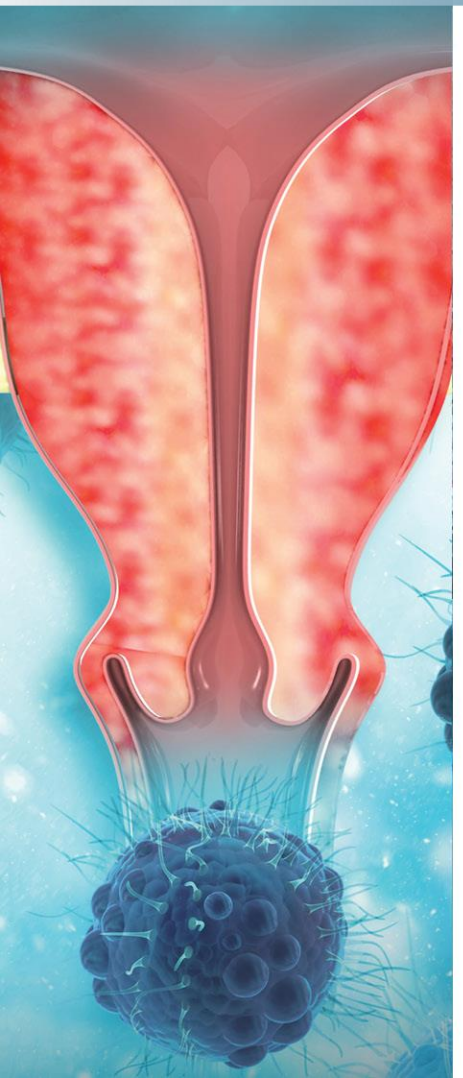
Focus on the Evolving Treatment Landscape

These slides are meant to be used as an accompaniment to the presentation for note taking purposes, they are not intended as a standalone reference.



This educational activity is sponsored by Postgraduate Healthcare Education, LLC and supported by an educational grant from GlaxoSmithKline, LLC.

Faculty

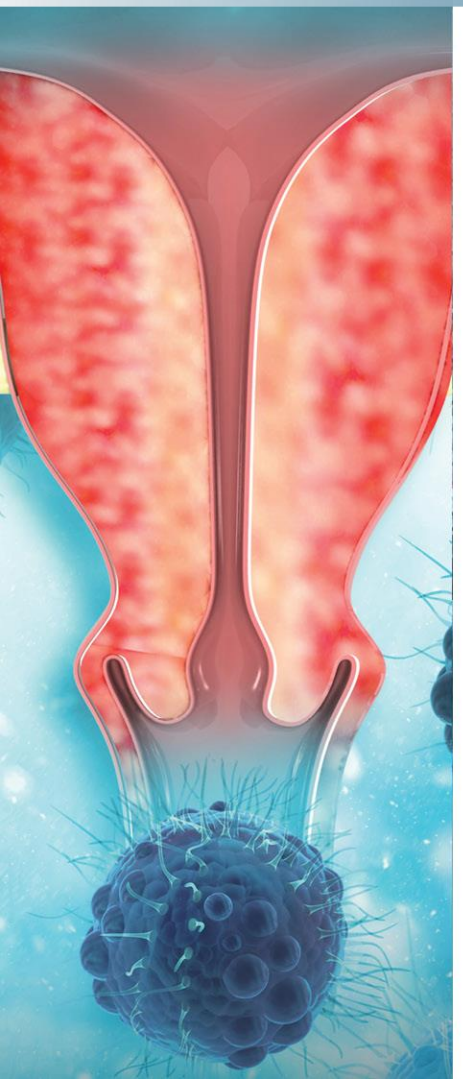


Britny R. Brown, PharmD, BCOP

Clinical Assistant Professor, Pharmacy Practice
University of Rhode Island College of Pharmacy
Kingston, RI

Britny R. Brown is a Clinical Assistant Professor at the University of Rhode Island (URI) with a practice site at Women & Infants Hospital (WIH) where she works as an Oncology Pharmacist. Britny received her PharmD from URI and thereafter completed postgraduate residency training at Hahnemann University Hospital in Philadelphia and Roswell Park Cancer Institute in Buffalo. Britny works within the palliative care clinic in women's oncology at WIH and has research interests in symptom management, health equity, and alternative delivery of oral anticancer therapies. In addition to HOPA, she is an active member of NCODA and is now co-chairing the NCODA committee for intravenous chemotherapy education. She serves as the vice chair of the diversity committee at URI College of Pharmacy, a co-advisor to URI student chapters for Timmy Global Health and SNPhA, and an advisor for the URI NCODA chapter.

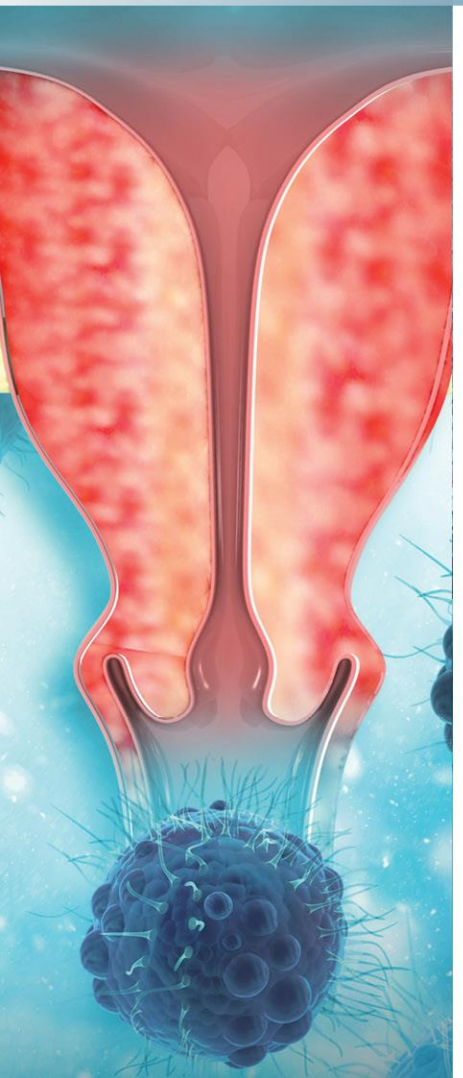
Disclosures



Dr. Brown has disclosed that she has no actual or potential conflicts of interest in relation to this program.

The clinical reviewer, Megan May, PharmD, BCOP has no actual or potential conflicts of interest in relation to this program.

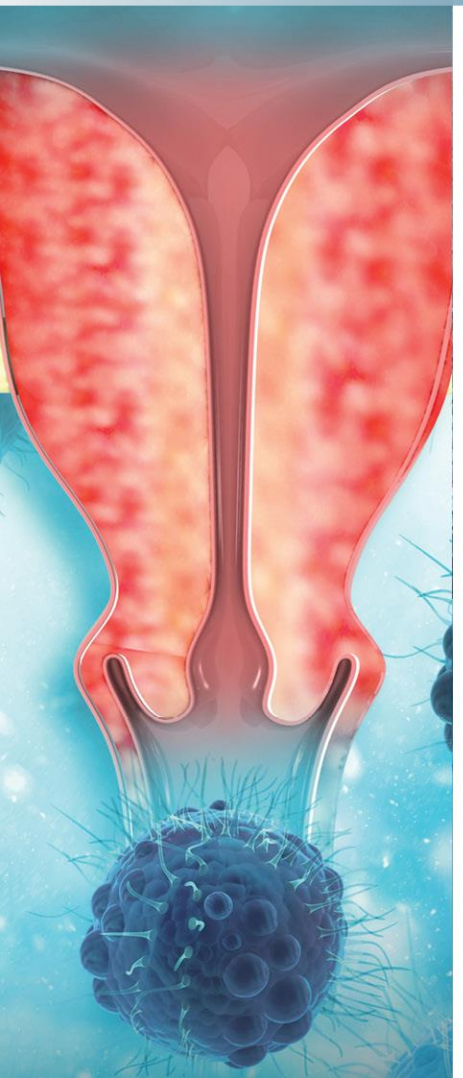
Susanne Batesko, BSN, RN, Robin Soboti, RPh, and Susan R. Grady, MSN, RN, as well as the planners, managers, and other individuals, not previously disclosed, who are in a position to control the content of Postgraduate Healthcare Education (PHE) continuing education activities hereby state that they have no relevant conflicts of interest and no financial relationships or relationships to products or devices during the past 12 months to disclose in relation to this activity. PHE is committed to providing participants with a quality learning experience and to improve clinical outcomes without promoting the financial interests of a proprietary business.



Postgraduate Healthcare Education, LLC is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

UAN: **0430-0000-21-041-H01-P**
Credits: 1.0 hour (0.1 CEU)
Type of Activity: Application

Learning Objectives



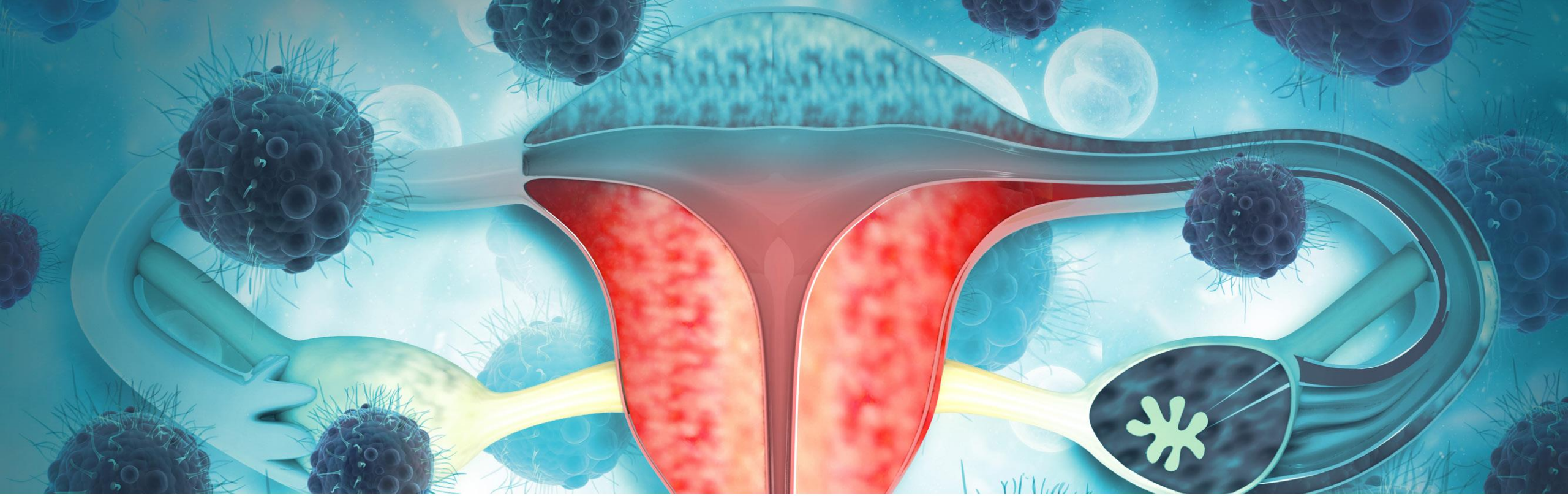
- **Describe** therapeutic options and their mechanisms of action for advanced ovarian and endometrial cancers
- **Appraise** the safety and efficacy of current treatment considerations for advanced ovarian and endometrial cancers
- **Formulate** effective strategies to manage patients' adherence and unique adverse events when utilizing PARP inhibitors, immune checkpoint inhibitors, and TKIs for the management of advanced ovarian and endometrial cancers

Endometrial & Ovarian Cancers

	Endometrial Cancer	Ovarian Cancer
Estimated New Cases 2021 *n (%)*	66,570 (7%)	21,410 (2.3%)
Estimated Deaths 2021 *n (%)*	12,940 (4%)	13,770 (5%)
5-Year Survival	81.2%	48.6%
% Diagnosed at Localized Stage	67%	16%
Presenting Symptoms	Abnormal uterine bleeding	Abdominal fullness, bloating, frequent urination, persistent abdominal pain
Risk Factors	Diabetes, early menarche/late menopause, endometrial hyperplasia, nulliparity, obesity, PCOS, tamoxifen use	BRCA 1/2, low socioeconomic status, nulliparity, older age

BRCA, breast cancer gene; PCOS, polycystic ovary syndrome

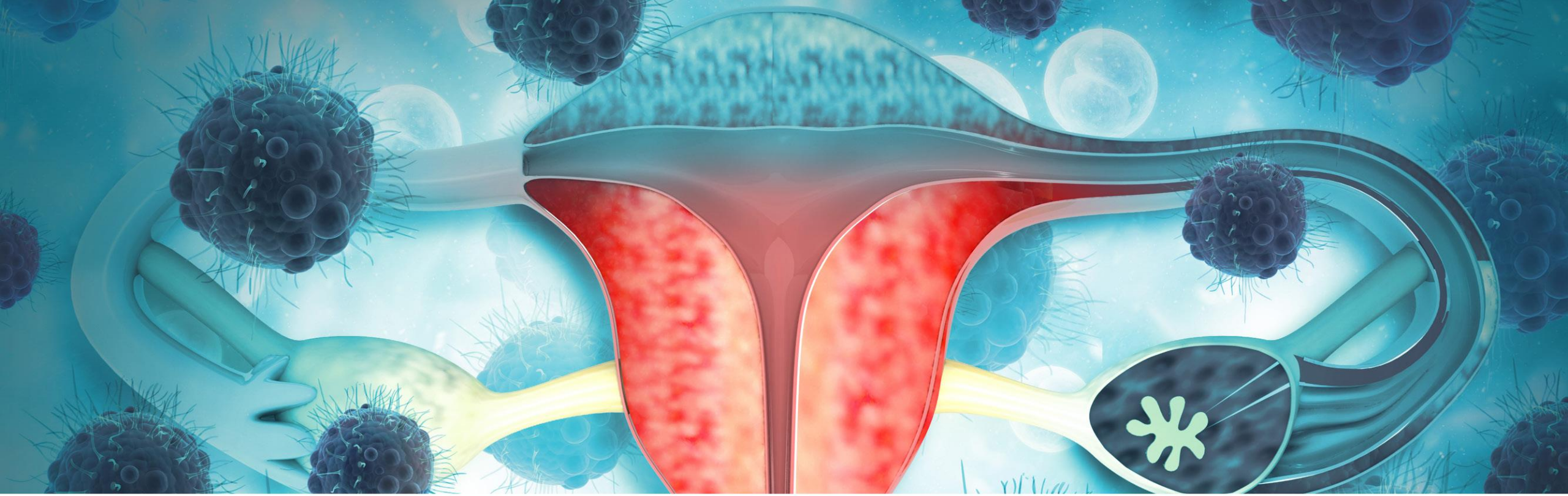
American Cancer Society. *Cancer Facts & Figures 2021*. Atlanta: American Cancer Society, 2021.; Cancer Stat Facts: Ovarian Cancer. https://seer.cancer.gov/statfacts/html/ovary.html; Cancer Stat Facts: Uterine Cancer. https://seer.cancer.gov/statfacts/html/corp.html; Raglan O, et al. *Int J Cancer*. 2019;145(7):1719-1730.; Momenimovahed Z, et al. *Int J Womens Health*. 2019;11:287-299.



Advanced Ovarian & Endometrial Cancer Treatment

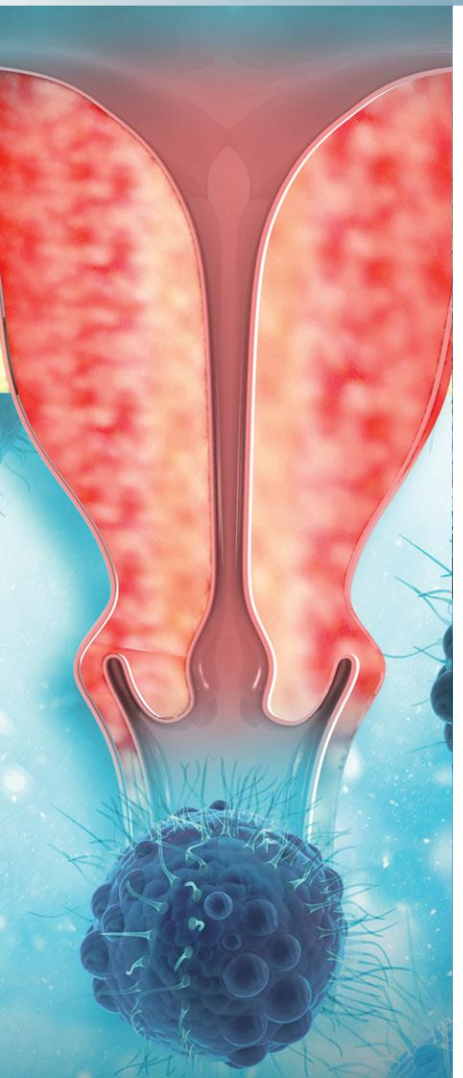
PARP inhibitors ± bevacizumab

Immune checkpoint inhibitors ± TKI



How can we decrease the high rates of relapse after primary treatment in ovarian cancer?

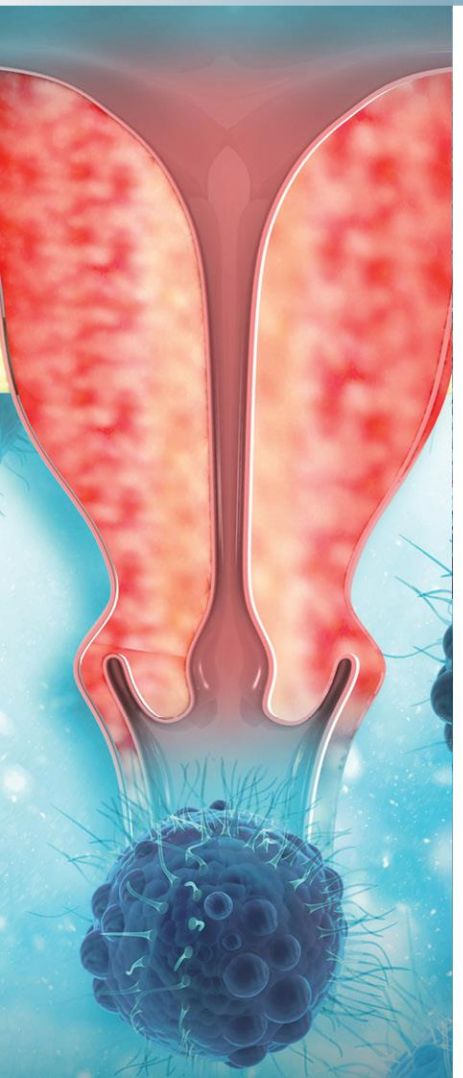
PARP Inhibitors



- Inhibit the enzyme poly(ADP-ribose) polymerase (PARP)
- PARP is recruited to the site of single strand breaks
  - Signals proteins for deoxyribonucleic acid (DNA) repair
- BRCA-proficient cells can repair double strand breaks
  - BRCA-deficient (mutant) cells cannot, leading to apoptosis

Dziadkowiec KN, et al. *Menopause Rev*. 2016;15(4):215-219.

Olaparib: SOLO1



- Advanced (stage III/IV) high-grade serous or endometrioid ovarian cancer
- BRCA mutation
- CR/PR to platinum-based chemo

Olaparib 300 mg PO BID (n=260)

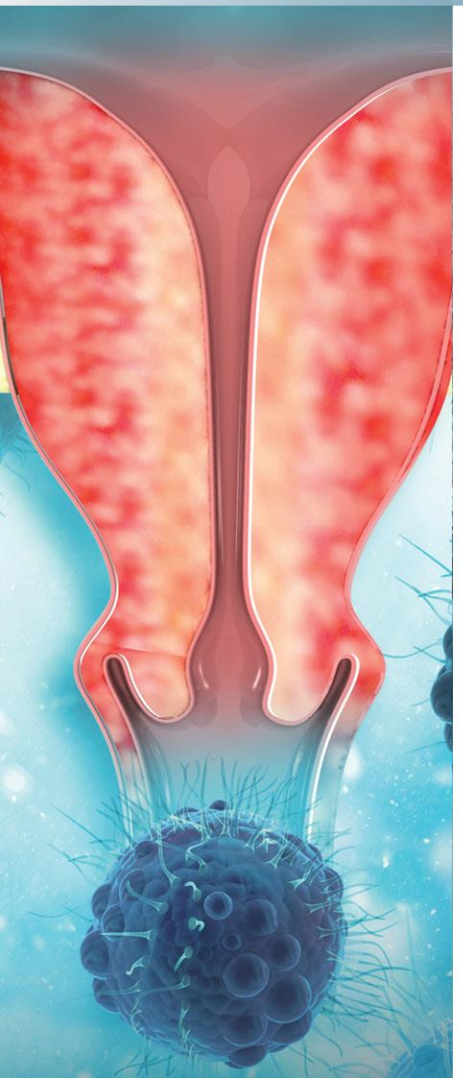
Placebo (n=131)

- International, randomized (2:1), double-blind, phase III trial
- Stratified according to clinical response
- Treatment for up to 2 years

BID, twice daily; CR, complete response; PO, by mouth; PR, partial response

Banerjee S, et al. ESMO Virtual Congress 2020. Abstract 811MO. Presented September 18, 2020.; Moore K, et al. *N Engl J Med*. 2018;379(26):2495-2505.

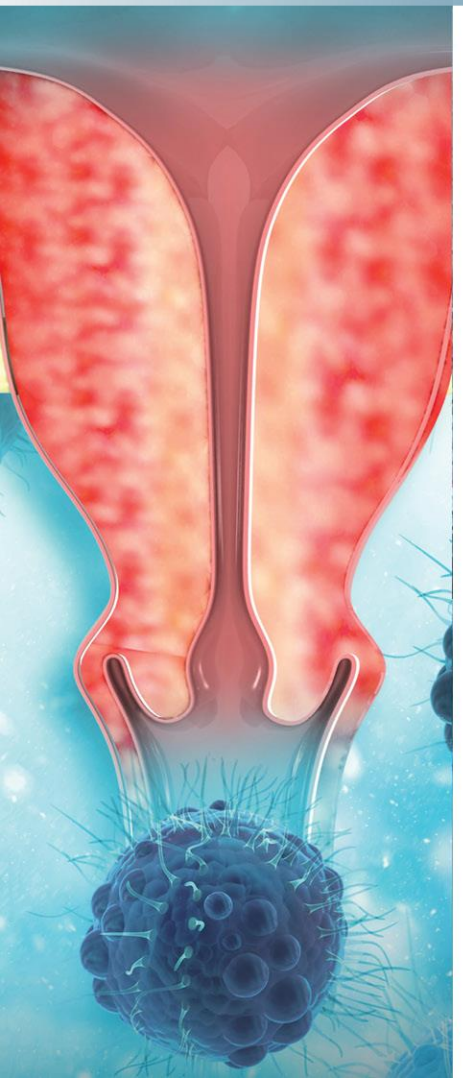
Olaparib: SOLO1



- Primary endpoint
  - Progression-free survival
- Secondary endpoints of interest
  - Overall survival
  - Health-related quality of life
- Median follow-up 41 months

Banerjee S, et al. ESMO Virtual Congress 2020. Abstract 811MO. Presented September 18, 2020.; Moore K, et al. *N Engl J Med*. 2018;379(26):2495-2505.

SOLO1: 5-Year Follow-Up

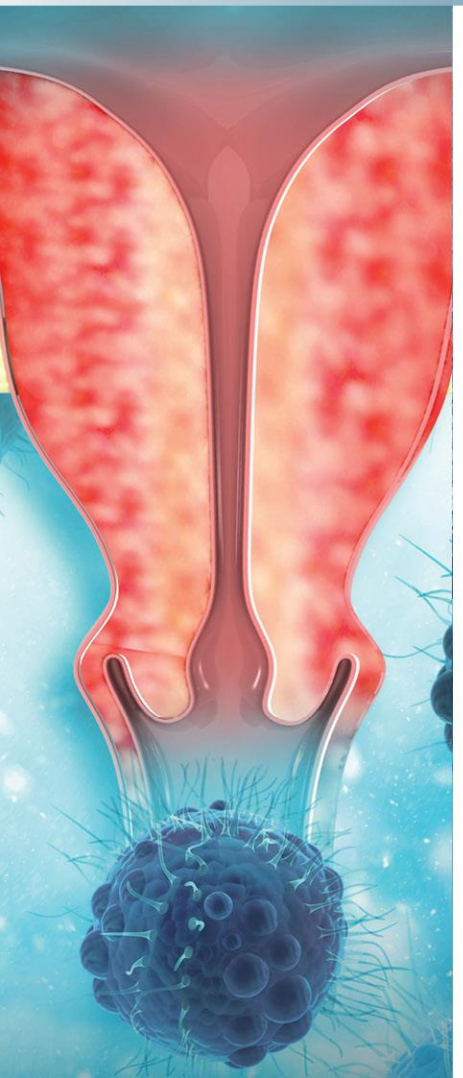


	PFS		RFS	
	Olaparib (n=260)	Placebo (n=131)	Olaparib (n=189)	Placebo (n=101)
Events, n (%)	118 (45)	100 (76)	79 (42)	74 (73)
Median, months	56.0	13.8	NR	15.3
HR (95% CI)	0.33 (0.25–0.43)		0.37 (0.27–0.52)	

NR, not reached; PFS, progression-free survival; RFS, recurrence-free survival

Banerjee S, et al. ESMO Virtual Congress 2020. Abstract 811MO. Presented September 18, 2020.; Moore K, et al. *N Engl J Med*. 2018;379(26):2495-2505.

Olaparib + Bevacizumab: PAOLA-1



- Advanced (stage III/IV) high-grade serous or endometrioid ovarian cancer
- CR/PR to platinum-based chemotherapy
- All patients received bevacizumab 15 mg/kg every 3 weeks for up to 15 months

Olaparib 300 mg PO BID

(n=537)

Placebo

(n=269)

- International, randomized (2:1), double-blind, phase III trial
- Stratified according to clinical response and BRCA status
- Treatment for up to 2 years

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

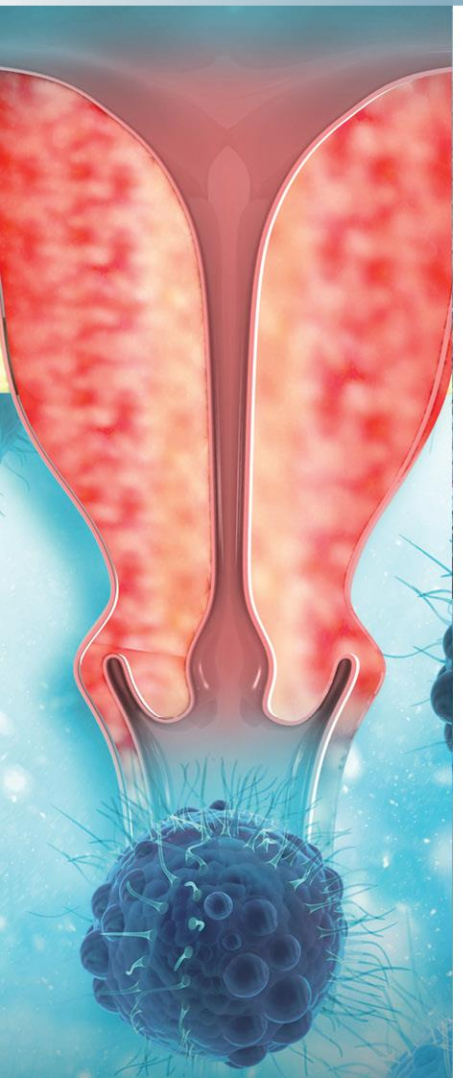
Olaparib + Bevacizumab: PAOLA-1

	PFS		BRCA-mutant		BRCA-WT	
	Olaparib (n=537)	Placebo (n=269)	Olaparib (n=157)	Placebo (n=80)	Olaparib (n=380)	Placebo (n=189)
Events*, n (%)	280 (52)	194 (72)	41 (26)	49 (61)	239 (63)	145 (77)
Median PFS, months	22.1	16.6	37.2	21.7	18.9	16.0
HR* (95% CI)	0.59 (0.49–0.72)		0.31 (0.20–0.47)		0.71 (0.58–0.88)	

WT, wild type
*disease progression or death

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

Olaparib + Bevacizumab: PAOLA-1

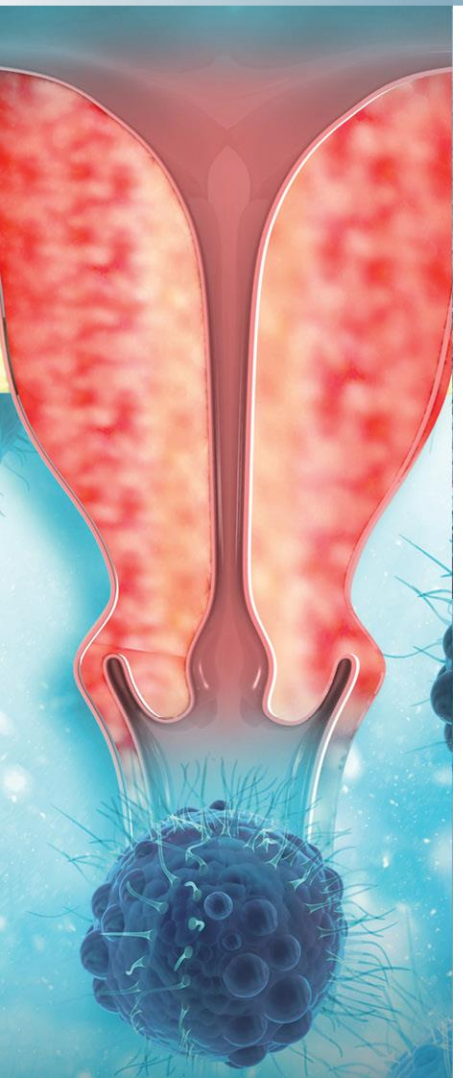


	HRD-positive		HRD-negative	
	Olaparib (n=255)	Placebo (n=132)	Olaparib (n=192)	Placebo (n=85)
Events*, n (%)	87 (34)	92 (70)	145 (76)	66 (78)
Median PFS, months	37.2	17.7	16.6	16.2
HR* (95% CI)	0.33 (0.25–0.45)		1.00 (0.75–1.35)	

HRD, homologous-recombination deficiency
*disease progression or death

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

Niraparib: PRIMA



- Advanced (stage III/IV) high-grade serous or endometrioid ovarian cancer
- CR/PR to platinum-based chemotherapy

Niraparib 300 PO daily (n=487)

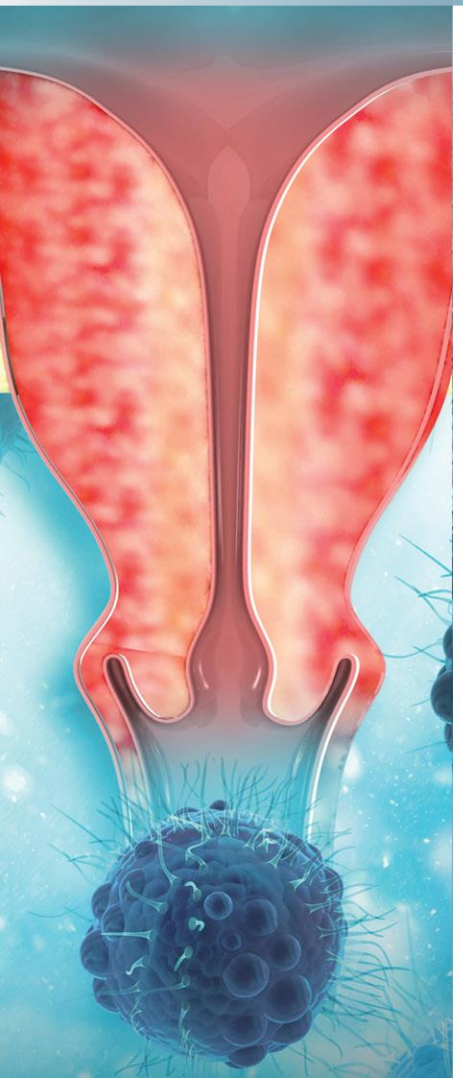
- International, randomized (2:1), double-blind, phase III trial
- Stratified according to clinical response, receipt of neoadjuvant chemotherapy, and HRD tumor status
- Treatment for up to 36 months

Placebo (n=246)

"weights and plates" based dosing began 11/2017: 200 mg daily for patients with baseline weight <77 kg / platelets <150K

González-Martín A, et al. *N Engl J Med*. 2019;381(25):2391-2402.

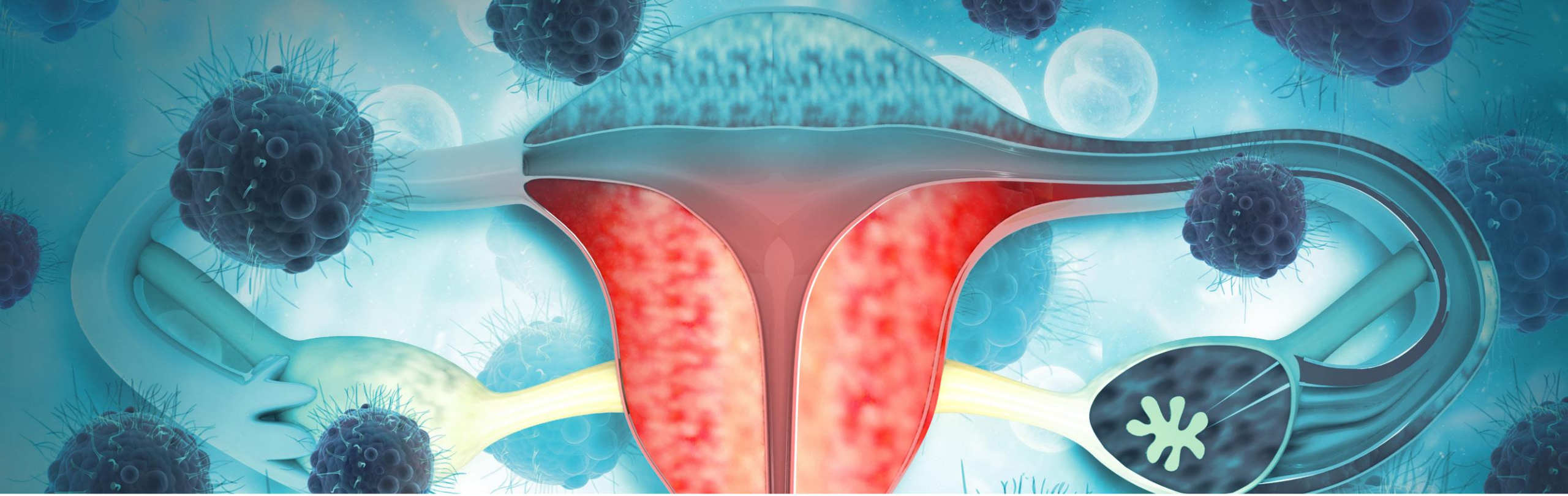
PRIMA: Progression-Free Survival



	Overall Population		HRD-positive (not BRCA-mutant)	
	Niraparib (n=487)	Placebo (n=246)	Niraparib (n=95)	Placebo (n=55)
Disease progression or death, n (%)	232 (47.6)	155 (63.0)	32 (33.7)	33 (60.0)
Median PFS, months	13.8	8.2	21.9	10.4
HR* (95% CI)	0.62 (0.50–0.76)		0.50 (0.31–0.83)	

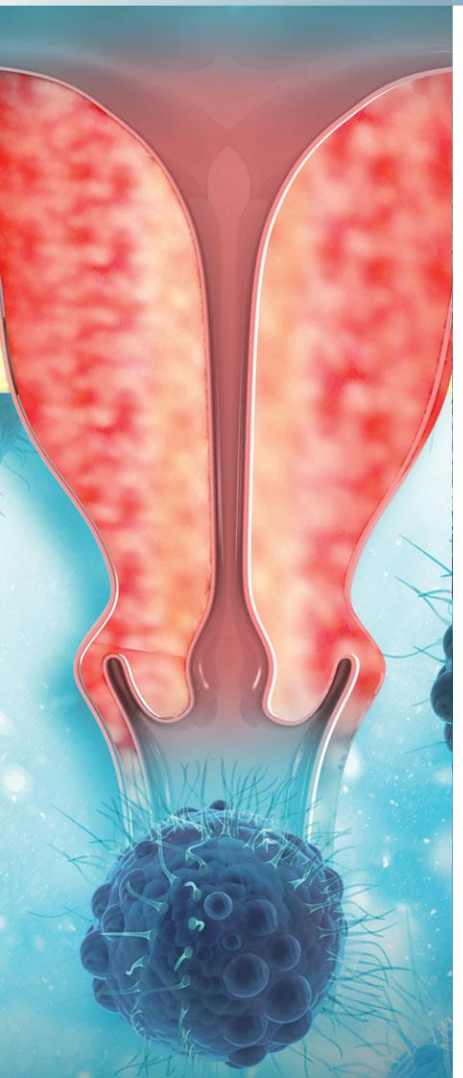
*disease progression or death

González-Martín A, et al. *N Engl J Med*. 2019;381(25):2391-2402.



Relapsed Ovarian Cancer

Niraparib for Relapsed Ovarian Cancer: QUADRA



- **Relapsed,** advanced (stage III/IV) high-grade serous or endometrioid ovarian cancer

- At least 3 prior chemotherapy regimens

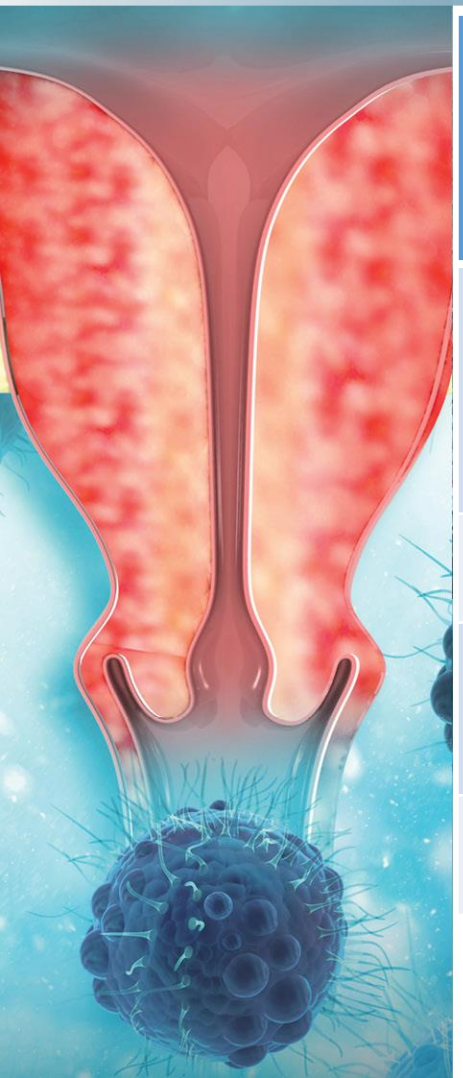
Niraparib 300 mg by mouth once daily

(n=463)

- Multicenter, **open-label, single-arm phase II** trial
- Primary endpoint: overall response rate in patients with HRD-positive tumors sensitive to their last platinum-based therapy

Moore KN, et al. *Lancet Oncol.* 2019;20(5):636-648.

QUADRA: Niraparib Overall Response

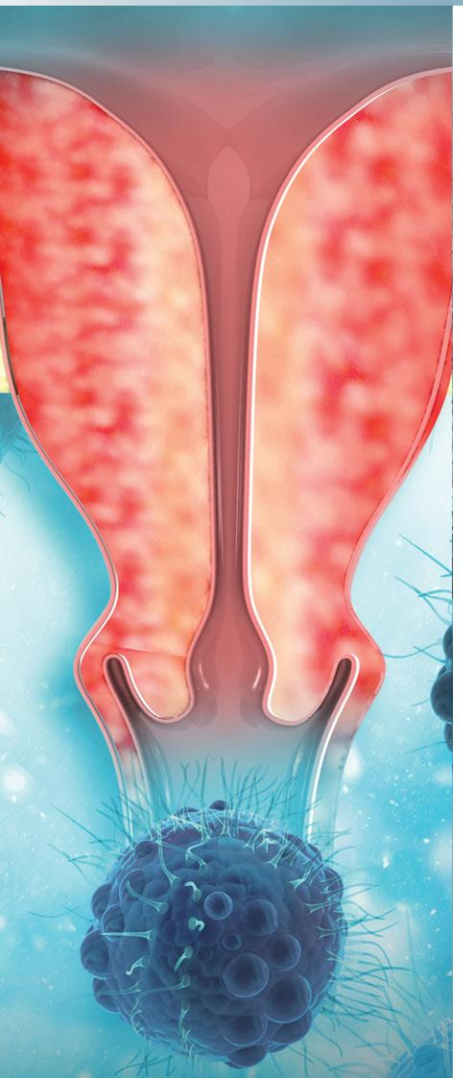


	BRCA-mutant (n=63)	HRD-positive (n=189)	HRD-negative or unknown (n=230)
Platinum-sensitive to most recent treatment	7/18 (39%)	14/53 (26%)	2/52 (4%)
Platinum-r/r	10/37 (27%)	12/120 (10%)	5/169 (3%)
Platinum status unknown	1/8 (13%)	3/16 (19%)	1/9 (11%)
All	18/63 (29%)	29/189 (15%)	8/230 (3%)

r/r, resistant/refractory

Moore KN, et al. *Lancet Oncol.* 2019;20(5):636-648.

Niraparib: AVANOVA2



- **Platinum-sensitive, recurrent** (stage III/IV) high-grade serous or endometrioid ovarian cancer
- ≤ 1 prior non-platinum containing regimen for recurrent disease
- All patients received niraparib 300mg once daily

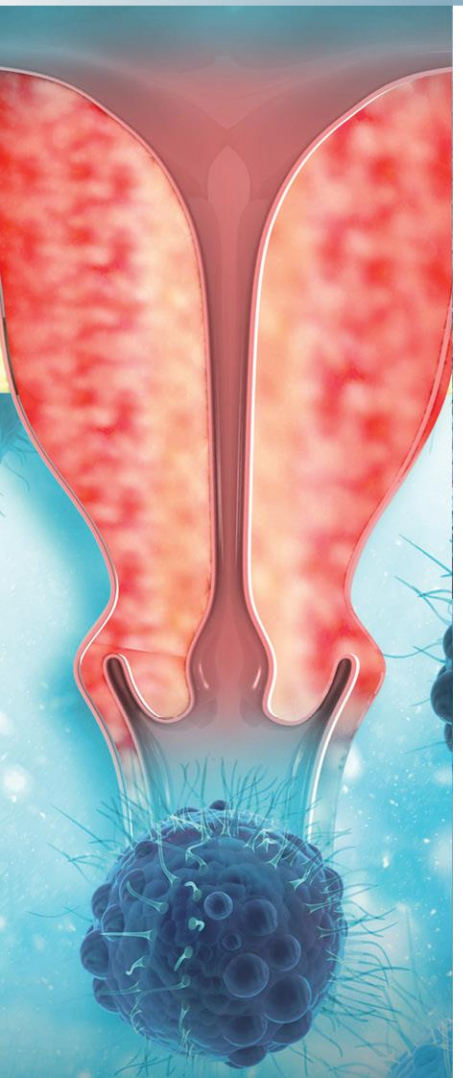
Niraparib + bevacizumab 15 mg/kg every 3 weeks (n=48)

- International, **open-label, randomized, superiority phase II** trial
- Primary endpoint: overall response rate in patients with HRD-positive tumors sensitive to their last platinum-based therapy

Niraparib only (n=49)

Mirza MR, et al. *J Clin Oncol.* 2020;38(suppl 15):6012.; Mirza MR, et al. *Lancet Oncol*. 2019;20(10):1409-1419.

AVANOVA2: Progression-Free Survival

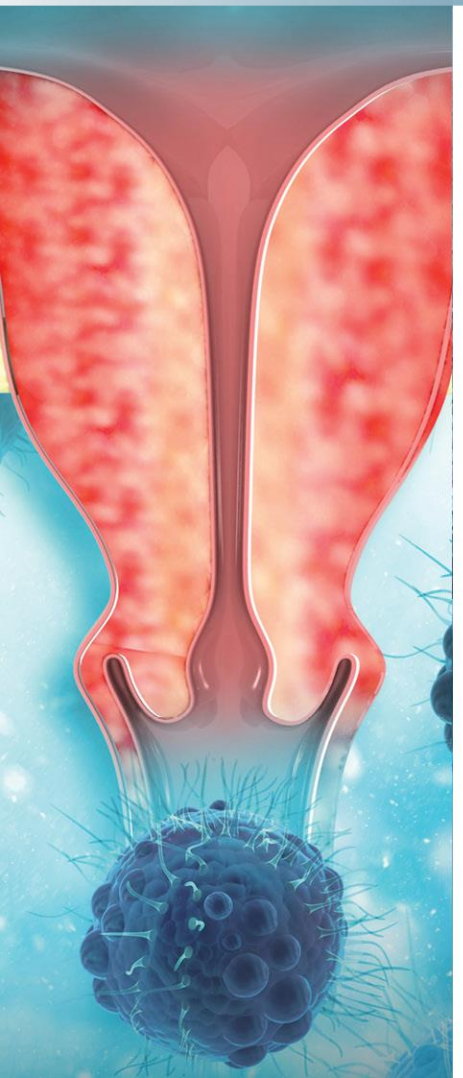


	Niraparib + bevacizumab (n=48)	Niraparib (n=49)
Events*, n (%)	31 (65%)	43 (88%)
Median PFS	12.5 months	5.5 months
HR* (95% CI)	0.34 (0.21–0.55); P<0.0001	
Grade 3/4 AEs, n (%)	31/48 (65%)	22/49 (45%)
Hypertension	22.9%	0%
Neutropenia	8.3%	2.0%

AE, adverse event; *disease progression or death

Mirza MR, *J Clin Oncol.* 2020;38(suppl 15):6012.; Mirza MR, et al. *Lancet Oncol*. 2019;20(10):1409-19.

Rucaparib: ARIEL3



- **Platinum-sensitive, recurrent** (stage III/IV) high-grade serous or endometrioid ovarian cancer
- ≥ 2 prior platinum-containing regimens
- No prior PARP inhibitor

Rucaparib 600 mg PO BID (n=375)

- International, **open-label, randomized, superiority phase II** trial
- Primary endpoint: PFS
- Stratification: HRD classification, response to platinum regimen (CR vs PR)

Placebo PO BID (n=189)

Ledermann JA, et al. *Lancet Oncol*. 2020;21(5):710-722.; Coleman RL, et al. *Lancet*. 2017;390(10106):1949-1961.

Rucaparib: ARIEL3

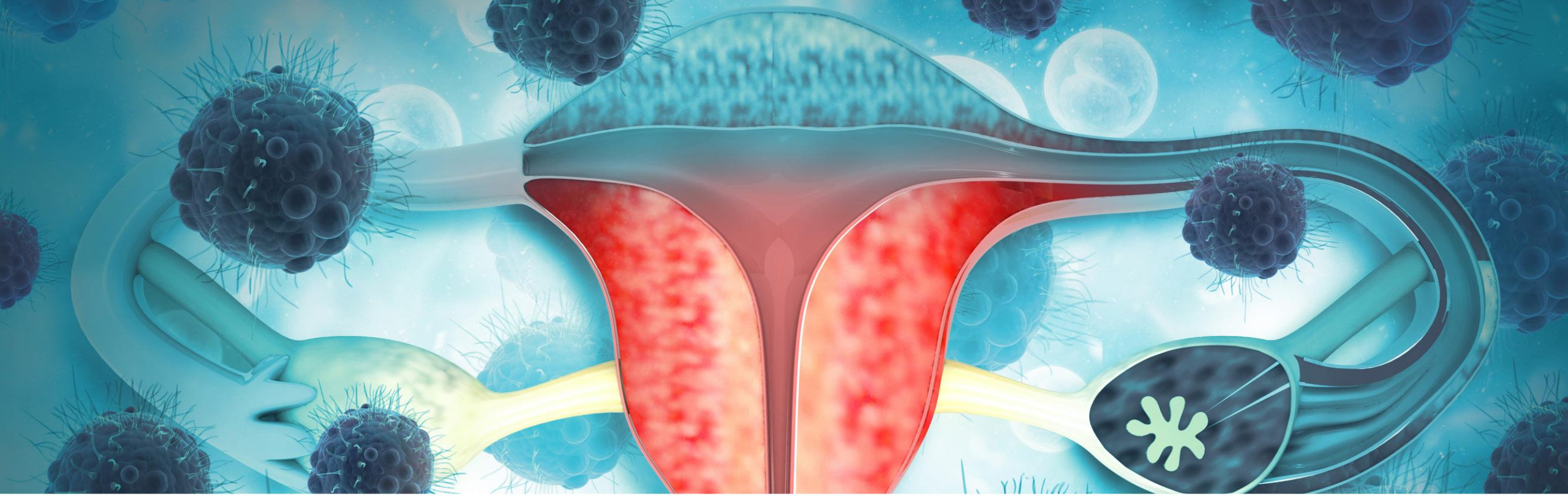
	Rucaparib (n=372)	Placebo (n=189)	HRD-positive Rucaparib (n=236)	HRD-positive Placebo (n=118)
Median PFS, months	10.8	5.4	13.6	5.4
HR (95% CI)	0.36 (0.30–0.45); P<0.0001		0.32 (0.24–0.42); P<0.0001	
Nausea, % (n)	76% (282)	37% (69)		
Fatigue, % (n)	71% (263)	44% (84)		

Ledermann JA, et al. *Lancet Oncol*. 2020;21(5):710-722.; Coleman RL, et al. *Lancet*. 2017;390(10106):1949-1961.

PARP Inhibitors: Current Indications in Ovarian Cancer

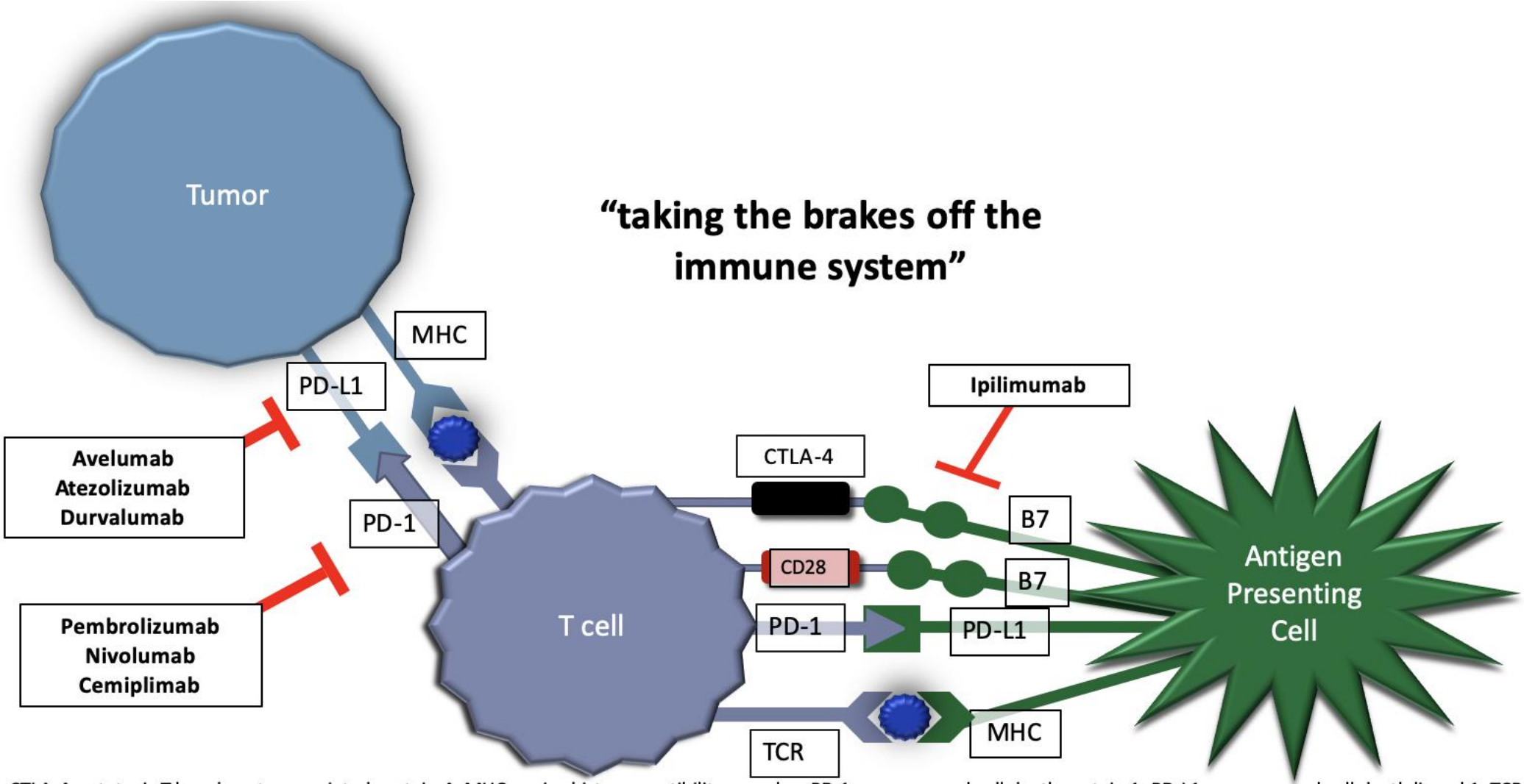
	Olaparib	Rucaparib	Niraparib
First-line maintenance therapy for advanced ovarian cancer after CR/PR to platinum-based treatment	**X** (BRCA-mutant only)		**X** (regardless of BRCA mutation status)
First-line maintenance therapy with bevacizumab after CR/PR to platinum-based treatment	**X** (HRD-positive only)		
Maintenance therapy for recurrent ovarian cancer after CR/PR to platinum-based treatment (regardless of BRCA mutation status)	**X**	**X**	**X**
Other	**Fourth-line and beyond** for advanced ovarian cancer with germline BRCA mutations	**Third-line and beyond** for advanced ovarian cancer with BRCA mutations	**Fourth-line and beyond** for advanced ovarian cancer with HRD-positive disease

Lynparza [package insert]. Wilmington, DE: AstraZeneca; 2021. Rubraca [package insert]. Boulder, CO: Clovis Oncology, Inc.; 2020. Zejula [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2021.



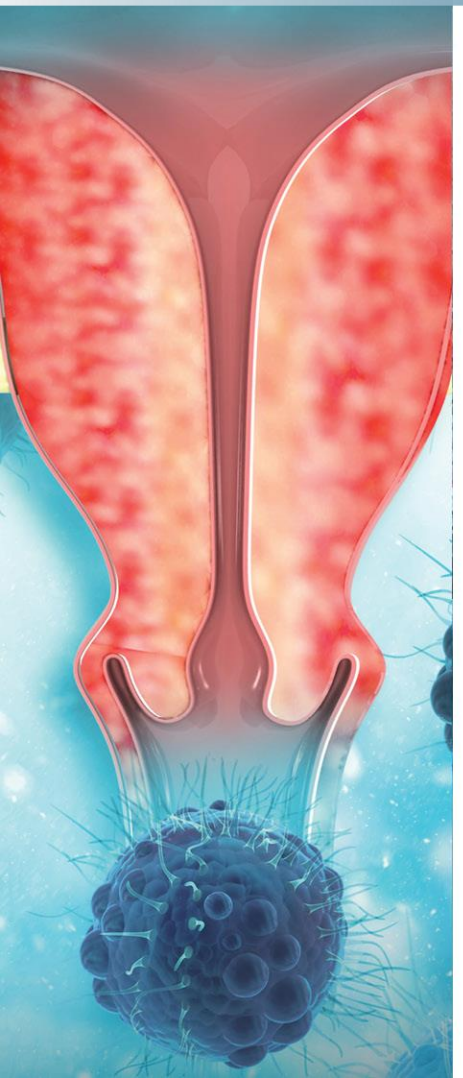
Immune Checkpoint Inhibitors

Mechanism of Action



CTLA-4, cytotoxic T-lymphocyte-associated protein 4; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; TCR, T-cell receptor
Adapted from: Zibelman M et al. J Natl Compr Canc Netw 2014;12:S1-S5.

Role in Gynecologic Malignancies

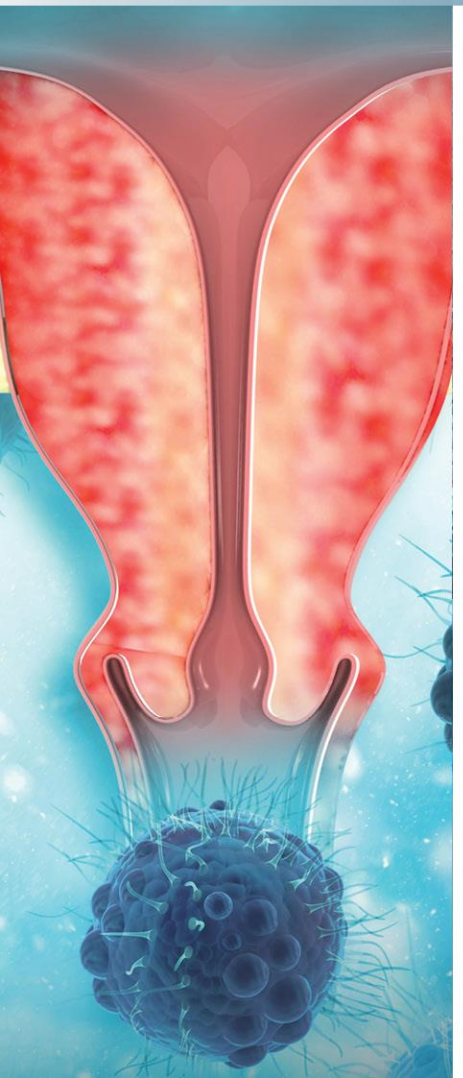


- Ovarian cancer: High PD-L1 expression and DNA damage
- Endometrial cancers: PD-L1 expression 40-80% among endometrioid cancers
  - More variable among serous and clear cell subtypes
  - 30% are MSI-H and 13-30% of recurrent are MSI-H or dMMR
  - Those with high mutational burden (i.e., POLE mutant/hypermutated, MSI-H) express more tumor-specific neoantigens
    - Increased CD3 and CD8 tumor-infiltrating lymphocytes

dMMR, mismatch repair deficient; MSI-H, microsatellite instability high; PD-L1, programmed death-ligand 1; POLE, DNA polymerase epsilon

Palaia I, et al. *Onco Targets Ther*. 2020;13:6109-6129. Green AK, et al. Am Soc Clin Oncol Educ Book. 2020 Mar;40:1-7.

Pembrolizumab: KEYNOTE-158



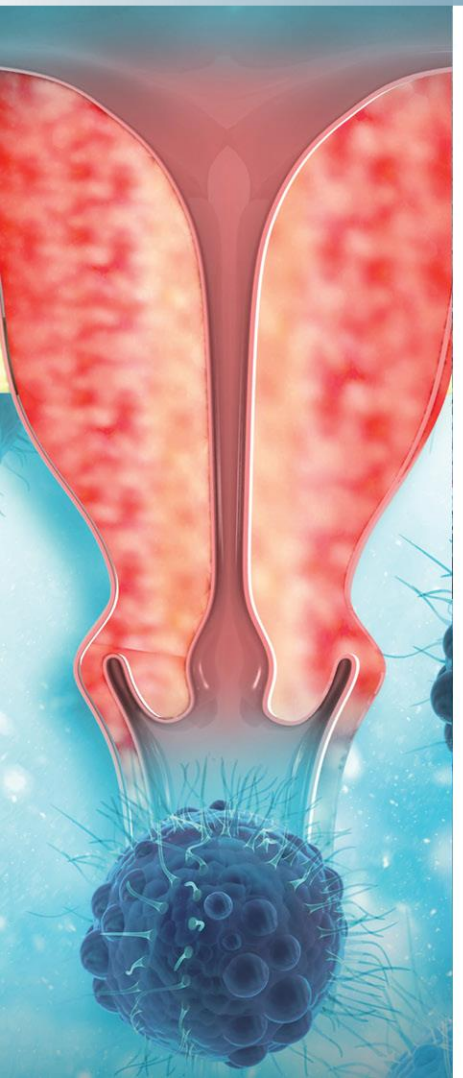
- MSI-H/dMMR advanced non-colorectal cancer
- Progression on prior therapy
- Basket trial

Pembrolizumab 200 mg every 3 weeks x 2 years

- Primary endpoint: objective response
- 27 tumor types represented
- Endometrial cancer: n=49 (21%)

Marabelle A, et al. *J Clin Oncol*. 2020;38(1):1-10.

KEYNOTE-158: Results in Endometrial Cancer



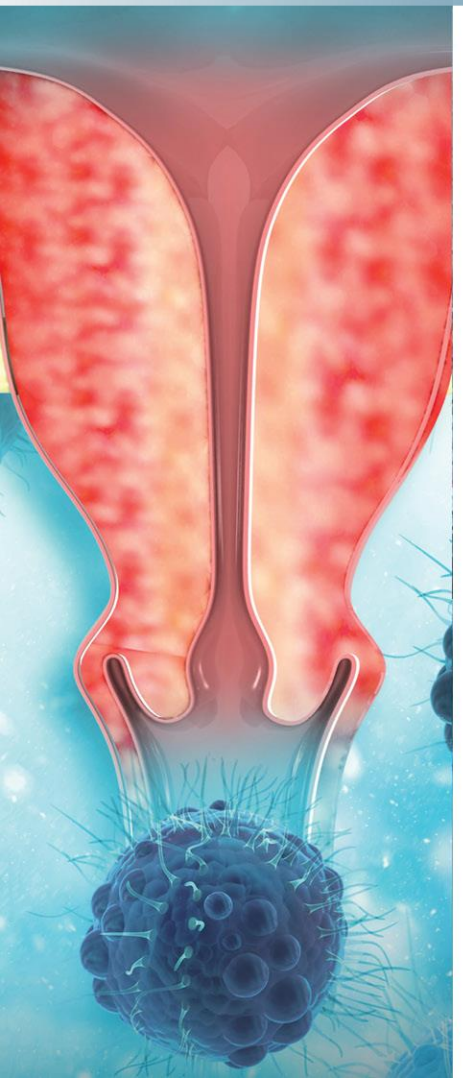
	Endometrial (n=49)	Overall (n=233)
CR, n (%)	[illegible]	[illegible].9%)
PR, n (%)	[illegible]	[illegible].5%)
ORR, % (95% CI)	57.1 (42.2–71.2)	34.3 (28.3–40.8)
Median PFS, months (95% CI)	25.7 (4.9–NR)	4.1 (2.4–4.9)
Median OS, months (95% CI)	NR (27.2–NR)	23.5 (13.5–NR)
Median DOR, months (range)	NR (2.9–27.0+)	NR (2.9–31.3+)

Led to the first site-agnostic FDA approval in oncology

Marabelle A, et al. *J Clin Oncol*. 2020;38(1):1-10.

DOR, duration of response; ORR, objective response rate; OS, overall survival

Pembrolizumab: KEYNOTE-100



- **Advanced, recurrent ovarian cancer**

- Phase II study

Each group received pembrolizumab 200 mg every 3 weeks for up to 2 years

Cohort A:

1 to 3 prior lines of treatment with PFI/TFI for 3 to 12 months

Cohort B:

4-6 prior lines with PFI/TFI ≥ 3 months

PFI, platinum-free interval; TFI, treatment-free interval

Matulonis UA, et al. *Ann Oncol*. 2019;30(7):1080-1087.; Matulonis UA, et al. *J Clin Oncol*. 2020;38(15_suppl):6005.

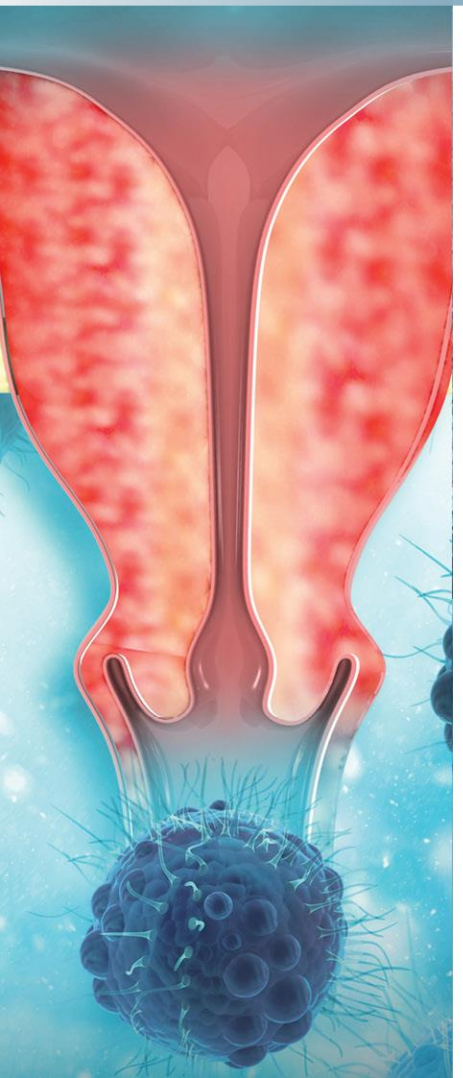
KEYNOTE-100: Results

	Cohort A (n=285)	Cohort B (n=91)
ORR* (95% CI)	8.1% (5.2–11.9)	9.9% (4.6–17.9)
CPS ≥ 1	6.9% (2.8–13.8)	10.2% (3.4–22.2)
CPS ≥ 10	11.6% (3.9–25.1)	18.2% (5.2–40.3)
DOR, months (range)	8.3 (3.9–35.4+)	23.6 (3.3+–32.8+)
DCR (95% CI)	22.1% (17.4–27.4)	22.0% (14.0–31.9)
Median PFS, months	2.1	2.1
Median OS, months (95% CI)	18.7 (17–22.5)	17.6 (13.3–24.4)

*Primary endpoint; CPS, combined positive score; DCR, disease control rate

Matulonis UA, et al. *Ann Oncol*. 2019;30(7):1080-1087.; Matulonis UA, et al. *J Clin Oncol*. 2020;38(15_suppl):6005.

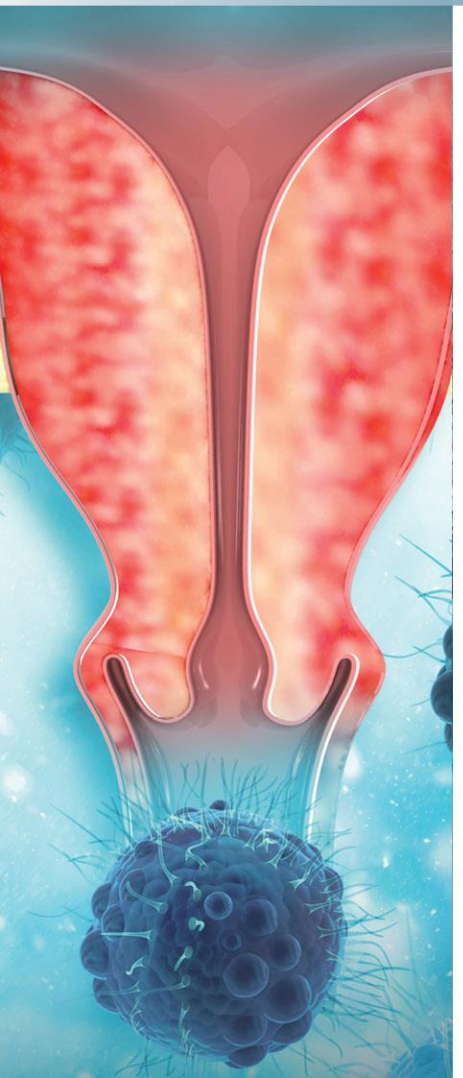
Nivolumab: NCI-MATCH



- Largest precision oncology study to date (>1,100 sites)
- Patients with relapsed/refractory malignancies
- Patients assigned to targeted therapy in parallel phase II studies based on molecular alterations
- Arm Z1D-A: Nivolumab for dMMR non-colorectal tumors

Azad NS, et al. *J Clin Oncol*. 2020;38(3):214-222.

Nivolumab: NCI-MATCH



Screening

- 4,902 patients screened
- 2% had dMMR by immunohistochemistry

Enrollment

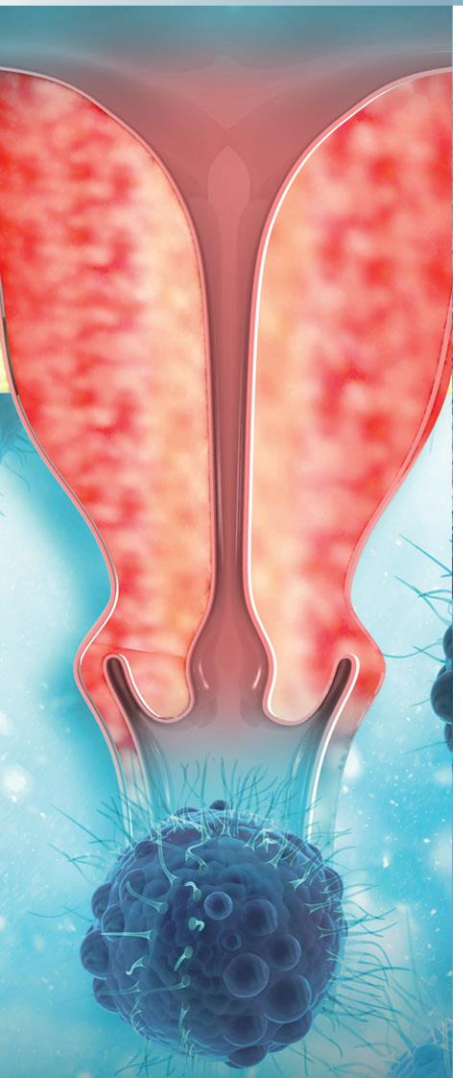
- 42 patients enrolled
- Median of 3 prior therapies
- Endometrioid endometrial adenocarcinoma (n=13)

Treatment

- Nivolumab 3 mg/kg every 2 weeks x 8 doses → 480 mg every 4 weeks
- Primary endpoint: objective response rate

Azad NS, et al. *J Clin Oncol*. 2020;38(3):214-222.

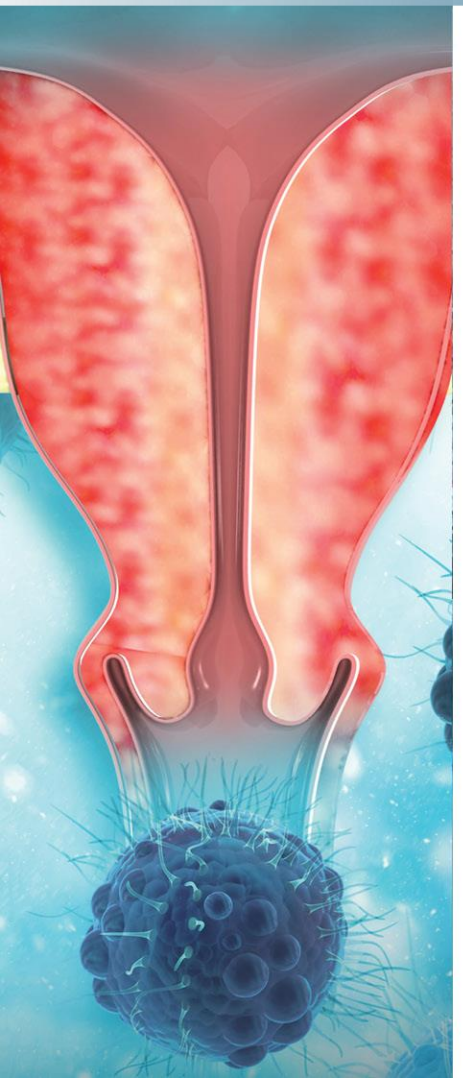
Nivolumab: NCI-MATCH



	Overall Population N=42	Endometrioid endometrial adenocarcinoma N=13
ORR, n (%)	15 (36%)	4 (31%)
CR, n (%)	3 (7%)	2 (15%)
PR, n (%)	13 (29%)	3 (23%)
Stable disease, n (%)	9 (21%)	2 (15%)
Progressive disease, n (%)	12 (23%)	4 (31%)

Azad NS, et al. *J Clin Oncol*. 2020;38(3):214-222.

Pembrolizumab + Lenvatinib: KEYNOTE-146

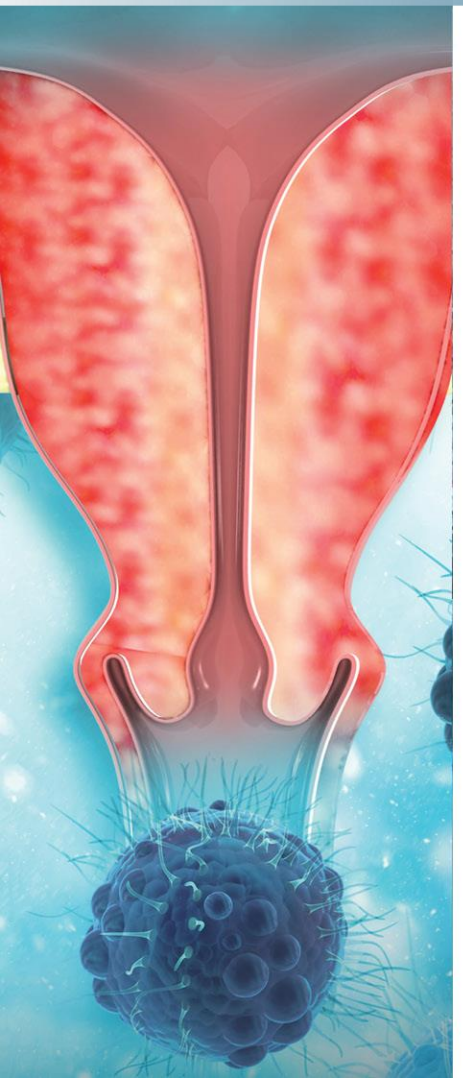


- **Advanced, previously treated endometrial cancer**
- Phase Ib/II study

Pembrolizumab 200 mg/kg every 3weeks for up to 2 years and lenvatinib 20 mg PO daily

Makker V, et al. *J Clin Oncol*. 2020;38(26):2981-2992.

KEYNOTE-146: Lenvatinib

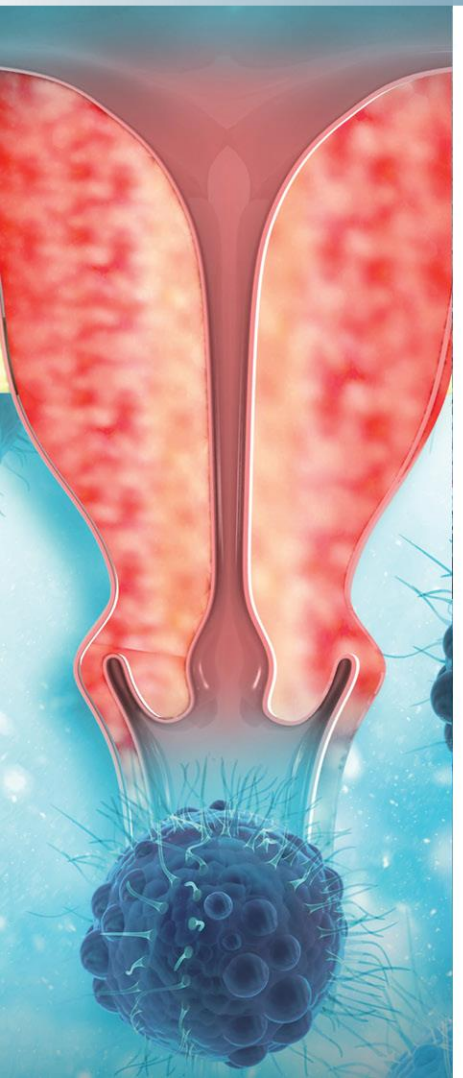


- Multi-tyrosine kinase inhibitor
  - Inhibits VEGF1-3, fTfR1-4, PDGFR alpha, RET, and KIT
- Available in 10 and 4 mg capsules
- Dose reduce for renal impairment
  - CrCl ≤ 30 ml/min: 10 mg once daily
- Severe AEs:
  - Bleeding, diarrhea, hepatotoxicity, hypertension, hypocalcemia, impaired wound healing, ONJ, proteinuria, QTc prolongation, RPLS, thyroid dysfunction, VTE

fTfR, olive flounder transferrin receptor; ONJ, osteonecrosis of the jaw; PDGFR, platelet-derived growth factor; RET, rearranged during transfection; RPLS, reversible posterior leukoencephalopathy syndrome; VEGF, vascular endothelial growth factor; VTE, venous thromboembolism

Lenvima [package insert]. Woodcliff Lake, NJ: Eisai Inc; December 2020.

KEYNOTE-146: Results



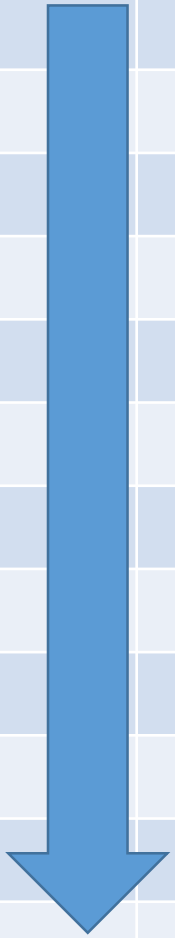
	MSS/pMMR (n=94)	MSI-H/dMMR (n=11)	Total (n=108)
ORR_{24}*	34 (36.2%)	7 (63.6%)	41 (38.0%)
95% CI	26.5–46.7	30.8–89.1	28.8–47.8
DOR (range), months	NE (7.4–NE)	21.2 (7.3–NE)	21.2 (7.6–NE)

*Primary endpoint. ORR_{24}, objective response rate at week 24; MSS, microsatellite stable; pMMR, mismatch repair proficient; NE, not estimable

Makker V, et al. *J Clin Oncol*. 2020;38(26):2981-2992.

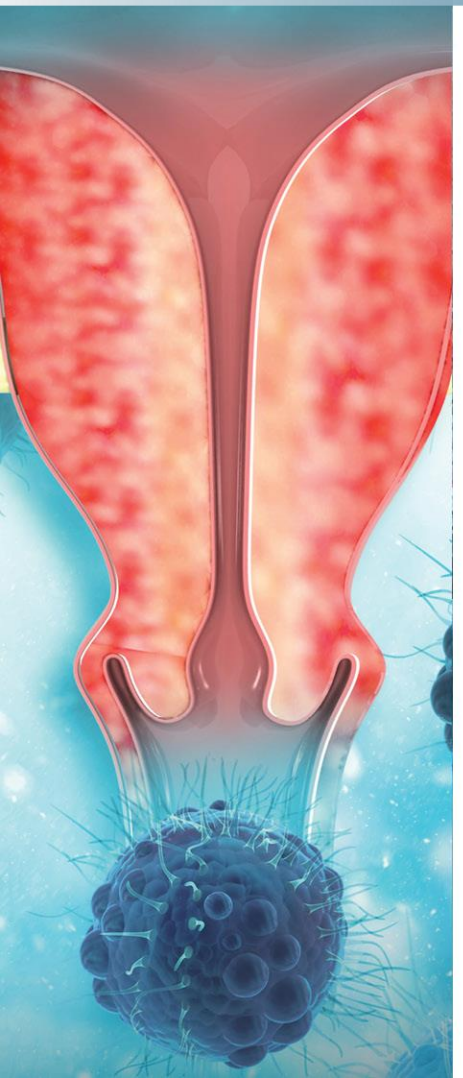
KEYNOTE-146: Toxicity

	Any Grade, n (%)	Grade 3/4, n (%)
Any adverse event	105 (97.2)	75 (69.4)
Hypertension	66 (61.1)	**35 (32.4)**
Diarrhea	57 (52.8)	**7 (6.5)**
Fatigue	56 (51.9)	**9 (8.3)**
Decreased appetite	51 (47.2)	0
Hypothyroidism	48 (44.4)	1 (0.9)
Nausea	43 (39.8)	3 (2.8)
Stomatitis	36 (33.3)	0
Pain/arthralgia	34 (31.5)	2 (1.9)
PPE and severe skin reactions	29 (26.9)	5 (4.6)
Vomiting	29 (26.9)	0
Proteinuria	24 (22.2)	4 (3.7)



Makker V, et al. *J Clin Oncol*. 2020;38(26):2981-2992.

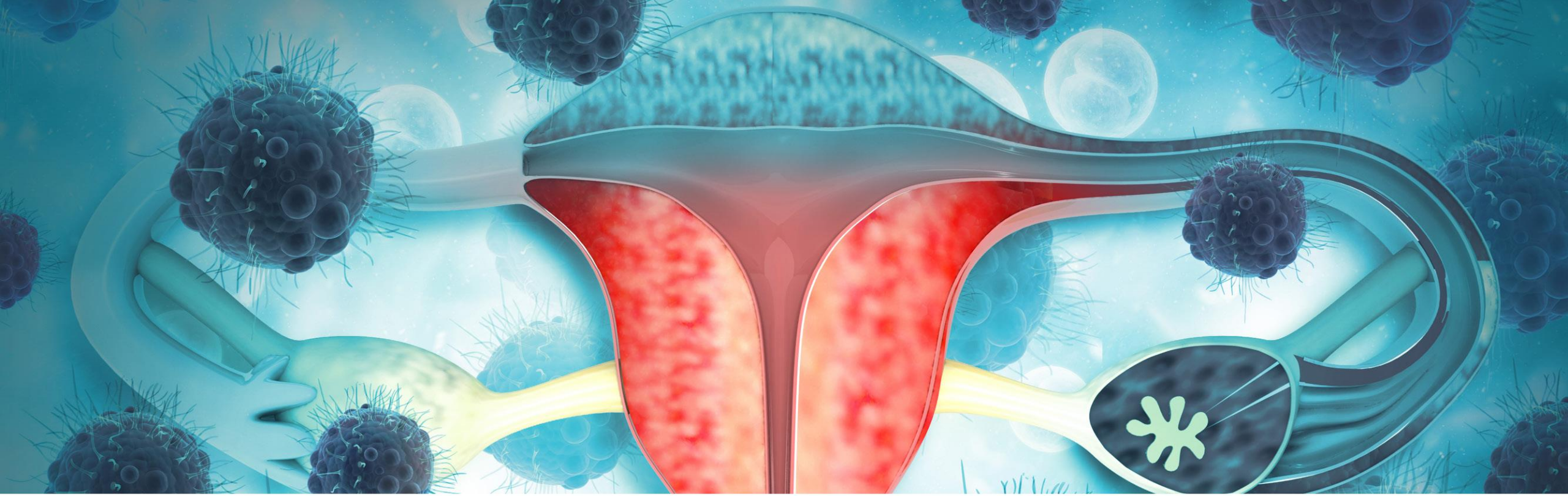
KEYNOTE-775



- Multicenter, randomized, open-label phase 3 study
- Lenvatinib + pembrolizumab versus TPC for advanced endometrial cancer
  - TPC: doxorubicin 60 mg/m^2 every 3 weeks or paclitaxel 80 mg/m^2 weekly (3 weeks on, 1 week off)
- ~790 patients who progressed after 1 prior platinum-based therapy
  - Randomized to lenvatinib + pembrolizumab or TPC
  - Stratification according to dMMR status

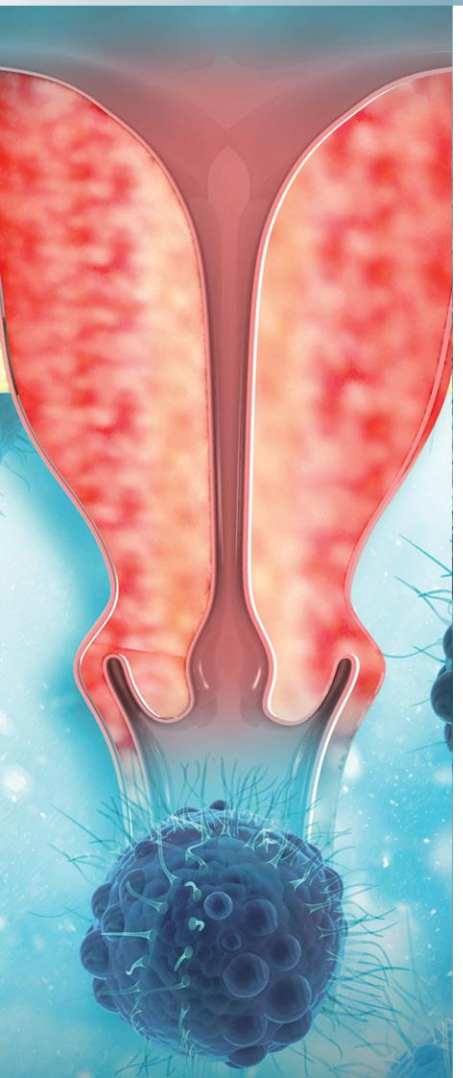
Makker V, et al. *J Clin Oncol* 2019 37:15_suppl, TPS5607-TPS5607

TPC, treatment of physician's choice



Emerging Therapies

Oregovomab



- Mouse monoclonal antibody

Binds CA-125 and forms immune complexes

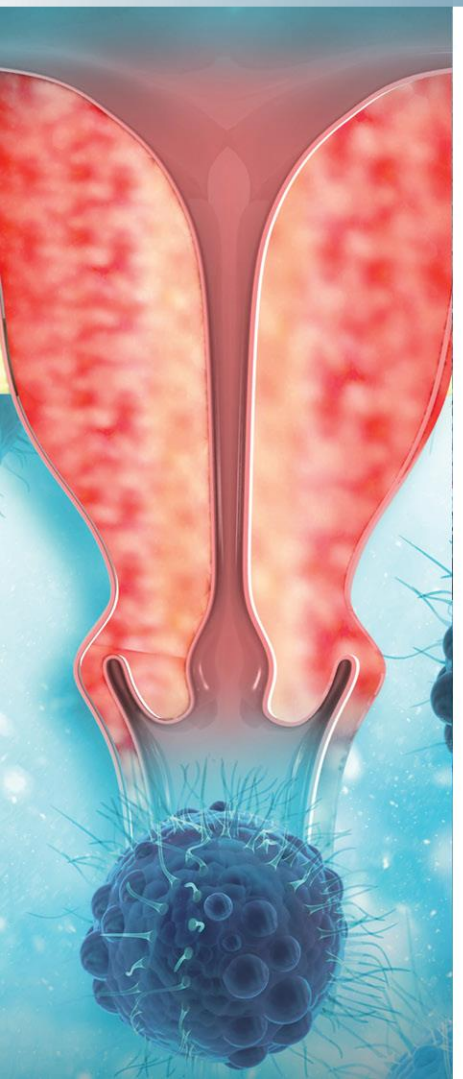
Immune complexes processed and cross-presented by dendritic cells to activate T cells

T cells create anti-CA-125 antibodies

Antibody-dependent cellular toxicity against CA-125 positive cells

Brewer M, et al. *Gynecol Oncol*. 2020;156(3):523-529.

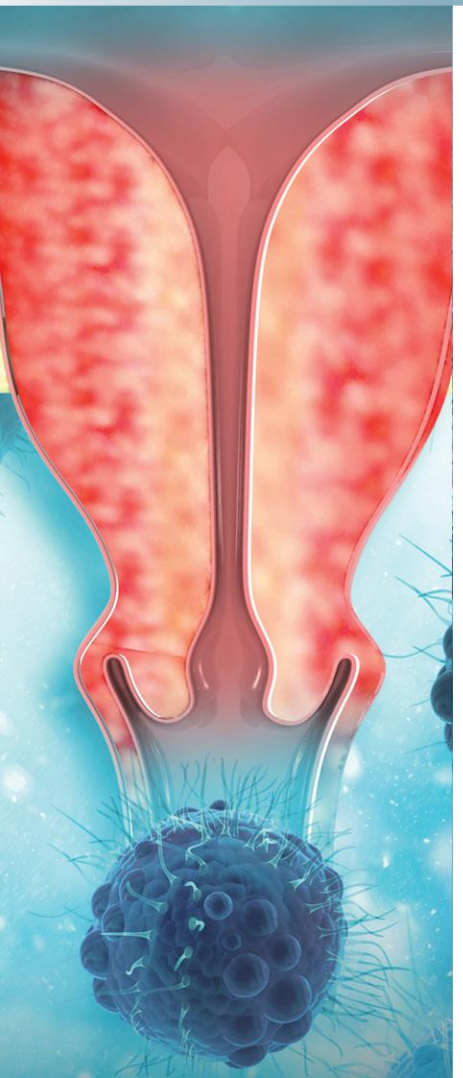
GOG 3035: Oregovomab



- Phase III, double-blind, placebo-controlled trial
- Paclitaxel-carboplatin-oregovomab (CPO) versus paclitaxel-carboplatin-placebo (CP) in advanced ovarian cancer
- Chemotherapy alters the tumor immune microenvironment, potentially making cancer cells more sensitive to immunotherapy

Brewer M, et al. *Gynecol Oncol*. 2020;156(3):523-529.

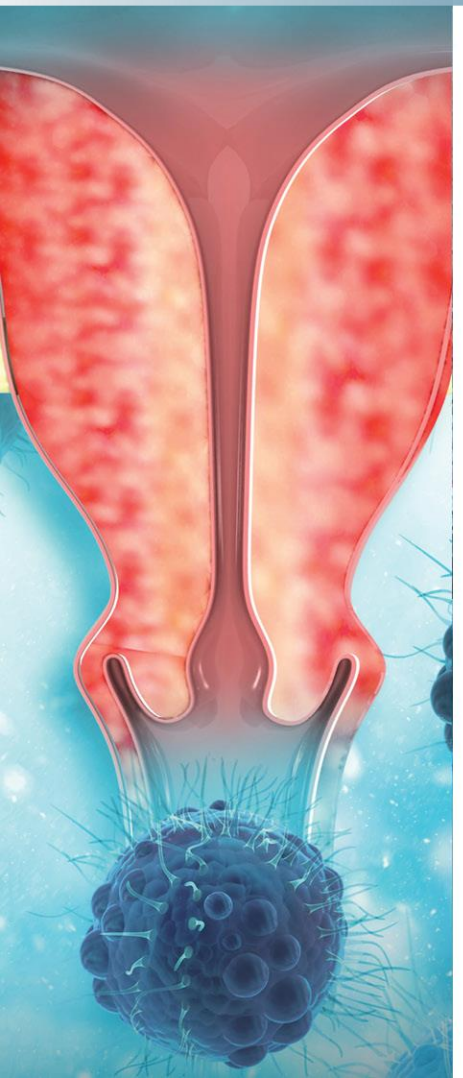
Oregovomab: Phase II Results



	CP (n=50)	CPO (n=47)
Median PFS, months (95% CI)	12.2 (10.4–18.6)	41.8 (21.8–NR)
OS	43.2 (31.8–NE)	NR (45.2–NR)
HR	0.35, CI 0.16-0.74	

Brewer M, et al. *Gynecol Oncol*. 2020;156(3):523-529.

Studies of Interest: Ovarian Cancer

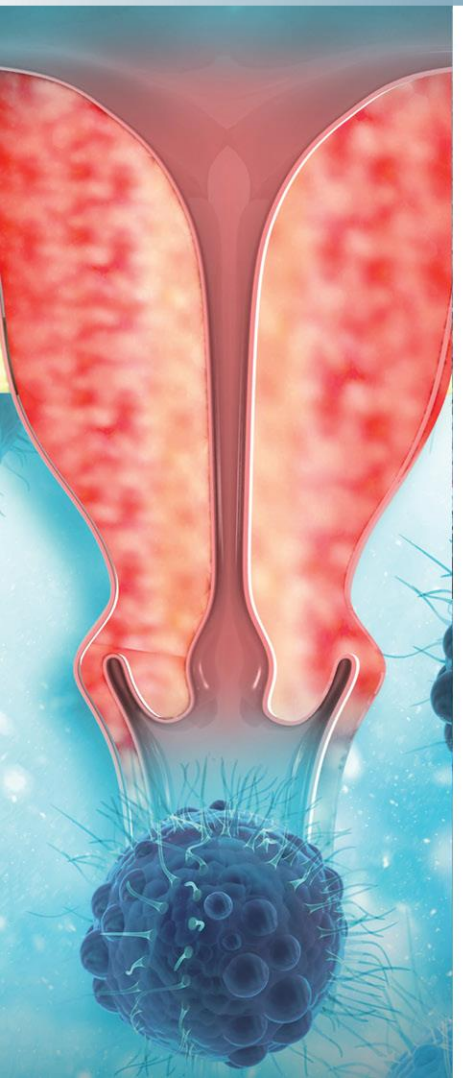


Study Name	Population	Intervention
GOG 3036	Upfront ovarian, BRCA-negative	chemotherapy ± pembrolizumab → maintenance ± olaparib or placebo
Tesaro FIRST	Upfront ovarian	[TSR-042 + niraparib + T/C] vs [T/C]
GY-021	Recurrent ovarian	[olaparib] vs [olaparib + tremelimumab]
GOG-3045	Platinum-resistant ovarian, high FRα positivity	[mirvetuximab soravtansine] vs [paclitaxel, doxorubicin, or topotecan]

Clinicaltrials.gov

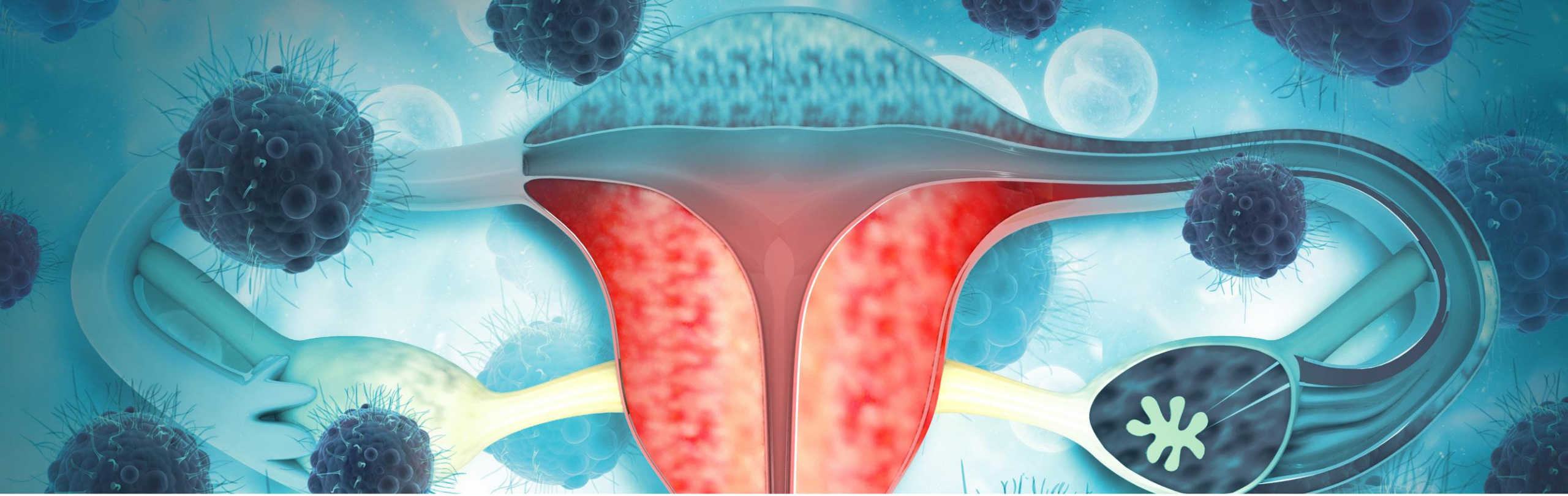
FRα, folate receptor alpha; T/C, paclitaxel and carboplatin

Studies of Interest: Endometrial Cancer



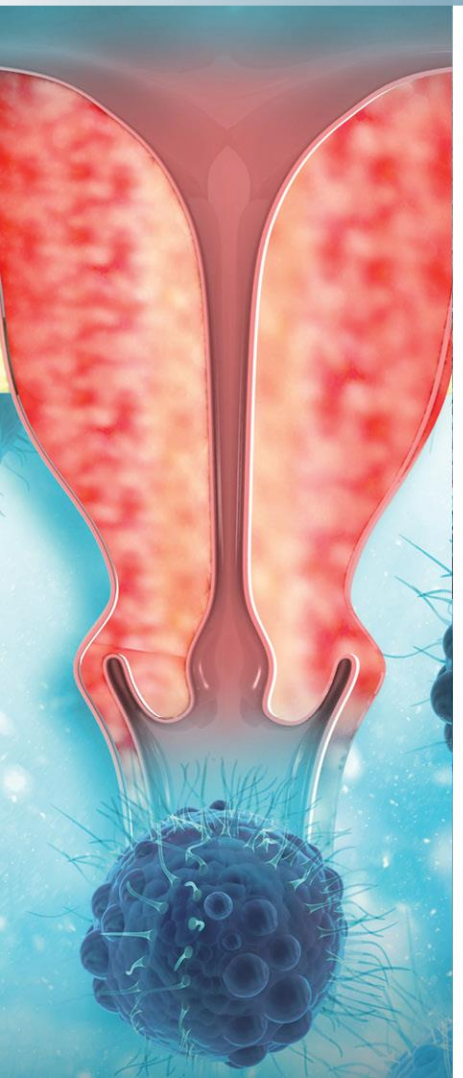
Study Name	Population	Intervention
GOG 3031	Upfront endometrial / first recurrence	[carboplatin + paclitaxel + dostarlimab] vs [carboplatin + paclitaxel + placebo]
NCT03835819	Recurrent or persistent endometrial, FRα positivity	[mirvetuximab soravtansine + pembrolizumab]
SIENDO	Advanced or recurrent endometrial cancer	maintenance with selinexor/placebo after response to combination chemotherapy

Clinicaltrials.gov



Adverse Event Management & Pharmacist Considerations

Immunotherapy-Related Toxicities: *all the itis'*

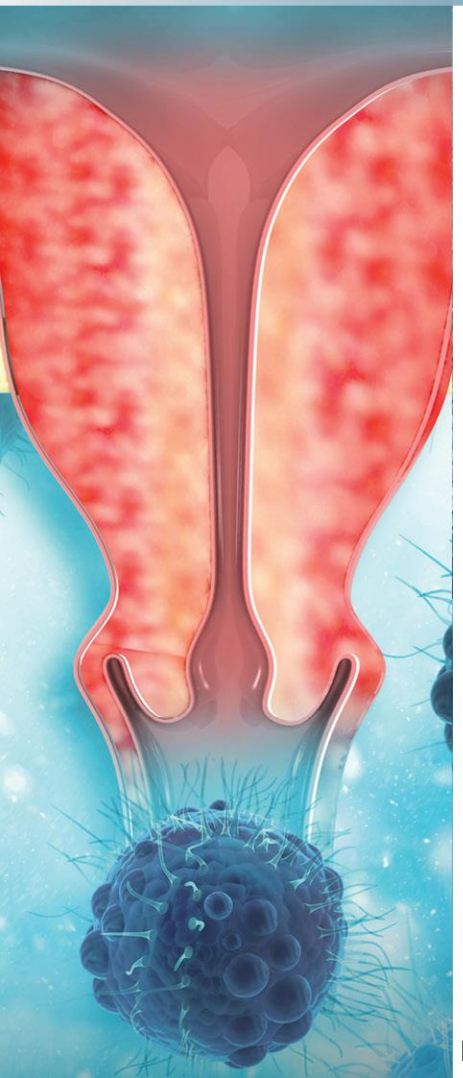


- Cardiovascular: edema
- Colitis/hepatitis
- Endocrine
  - Diabetes mellitus
  - Hypo/hyperthyroidism
  - Adrenal insufficiency
  - Hypophysitis
- Musculoskeletal pain, arthralgias
- Nephritis
- Nervous system: myasthenia gravis, meningoencephalitis
- Ocular
- Pancreatitis
- Pneumonitis
- Pruritis (SJS, TEN)

Brahmer JR, et al. *J Clin Oncol*. 2018;36(17):1714-1768.

SJS, Stevens Johnson Syndrome; TEN, toxic epidermal necrolysis

Counseling Points: Immediately Report



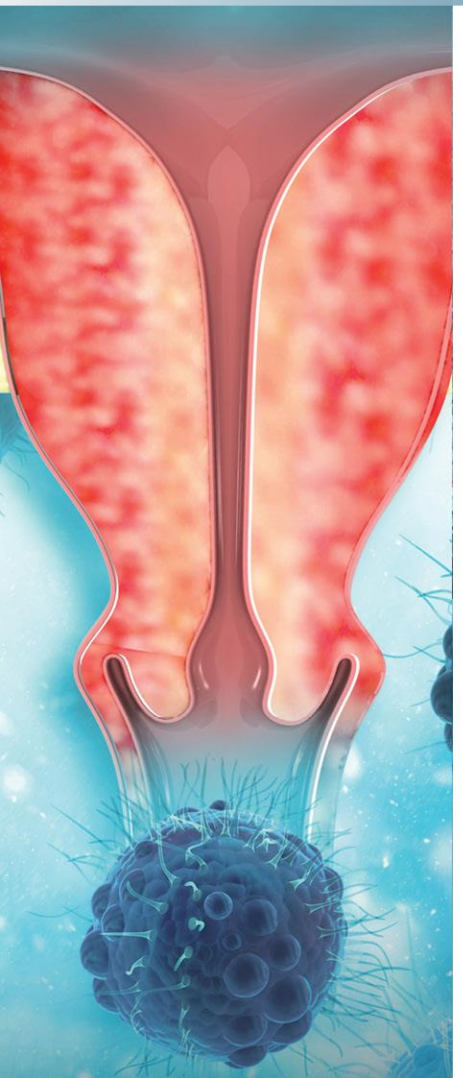
O	
Sk	
He	e, easy loss of
Co	evere ck, tarry,
Ne	or color of
Pr	ath
Pa	
Ne system	ght sensitivity, fever, muscle weakness, neck stiffness, neuropathy

Early intervention can significantly positively impact the course of irAE development

Toxicities can occur ≥ 1 year after treatment

Keytruda [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.;2020; Opdivo [package insert]. Princeton, NJ: Bristol-Myers Squibb;2020.

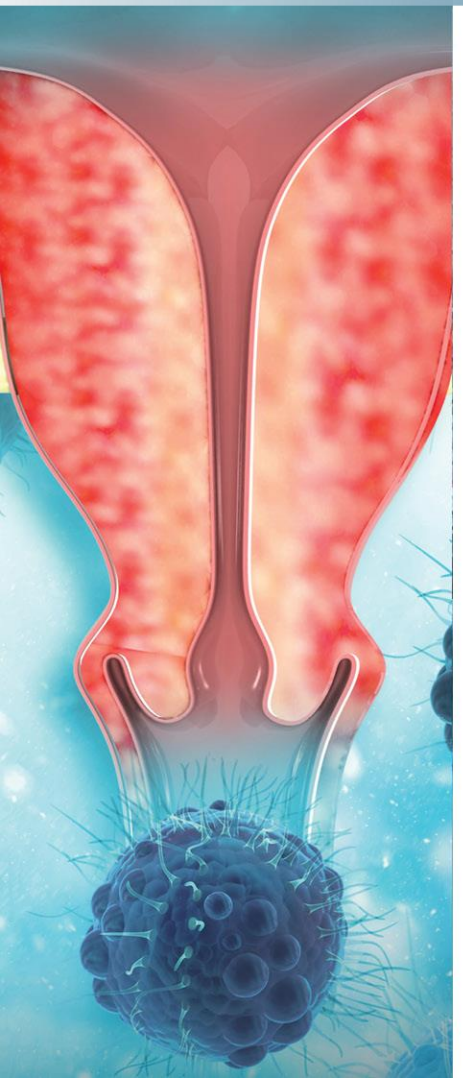
Immunotherapy-Related Toxicities



"There should be a high level of suspicion that any changes are treatment-related."

Brahmer JR, et al. *J Clin Oncol*. 2018;36(17):1714-1768.

Immunotherapy Best Practices



- Steroid initiation:
  - Be conservative with initial dosing when possible
- Taper over at least 4 to 6 weeks
- Can be more aggressive in patients who respond more quickly
- Always provide a schedule to the patient
- Consistent contact to ensure continued response
- Consider supportive medications:
  - Calcium and vitamin D, PCP prophylaxis, PPI

Brahmer JR, et al. *J Clin Oncol*. 2018;36(17):1714-1768.

PCP, pneumocystis pneumonia; PPI, proton-pump inhibitor

PARP Inhibitors

Generic (Brand)	Dosing	How Supplied	CYP450 Interactions	Monitoring	Additional Warnings
Olaparib (Lynparza)	300 mg twice daily ± food Renal dysfunction: 200 mg twice daily	100 mg, 150 mg tablets	CYP3A4 inhibitors, inducers	CBC at baseline and monthly thereafter; renal function	Pneumonitis, secondary malignancy Consider antiemetic prophylaxis
Rucaparib (Rubraca)	600 mg twice daily ± food	200 mg, 250 mg, 300 mg tablets	Inhibits CYP2C19/2C9, 3A4, 1A2; metabolized by CYP2D6	CBC at baseline and monthly thereafter	Secondary malignancy Consider antiemetic prophylaxis
Niraparib (Zejula)	300 mg daily ± food Patients <77 kg or platelets <150K: 200 mg daily (maintenance only)	100 mg capsules	None	CBC with differential weekly x 1 month then monthly	Hypertension Secondary malignancy Consider antiemetic prophylaxis

Lynparza [package insert]. Wilmington, DE: AstraZeneca;2021.; Rubraca [package insert]. Boulder, CO: Clovis Oncology, Inc.;2020.; Zejula [package insert]. Research Triangle Park, NC: GlaxoSmithKline;2021.

CBC, complete blood count

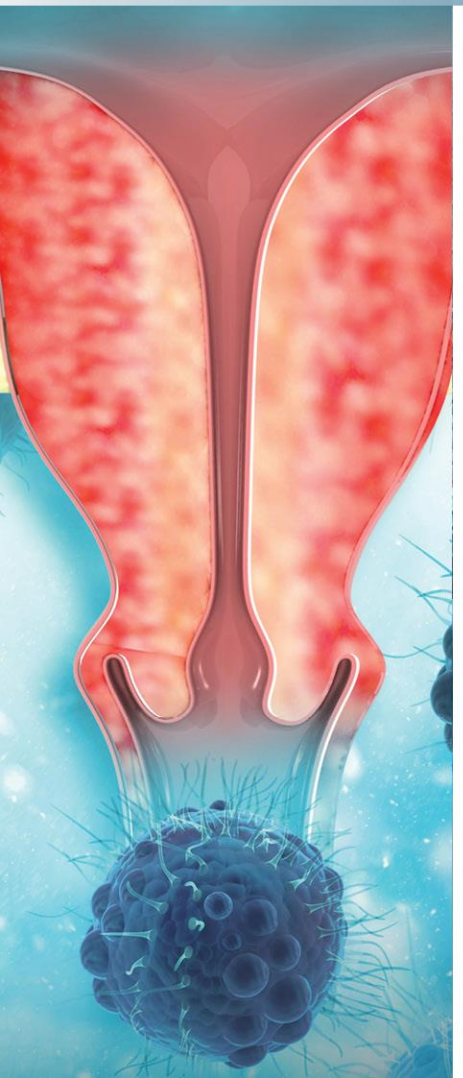
PARP Inhibitors

Side effects, %	Olaparib	Rucaparib	Niraparib
Fatigue/asthenia	66	73	57
Nausea/vomiting	66/43	76/37	74/34
Constipation	22	37	40
Abdominal pain	43	46	33
Anemia (Grade 3/4)	18	21	25
Thrombocytopenia (Grade 3/4)	4	5	29
Neutropenia	9	8	20
Dose reduction/interruption*	40.3%	62%	69%
Treatment discontinuation due to AEs*	3.7%	10%	15%

Hennes ER, et al. *J Oncol Pharm Pract*. 2020;26(3):718-729.

*Taken from a small sampling of trials, avoid cross-comparison.

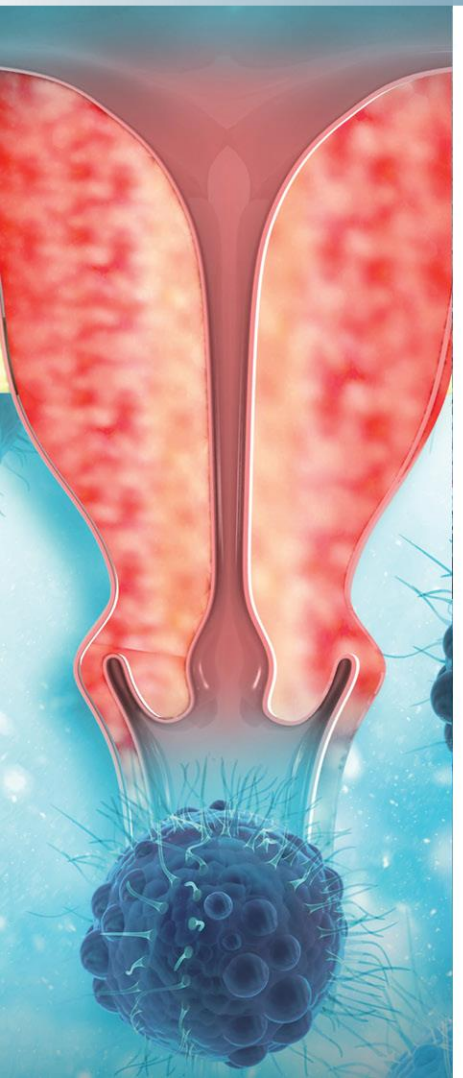
Adherence Strategies: PARP Inhibitors



- PARP inhibitors account for 91% of patient out-of-pocket drug spending
- Addressing financial barriers may help optimize adherence
- Set expectations regarding AEs and management
  - Proactively manage nausea/vomiting
  - Create plans
- PARP inhibitor choice based on patient-specific factors
- Frequent follow-up as needed

Liang MI, et al. *Gynecol Oncol*. 2021;160(3):793-799.; Moore KN, et al. *Oncologist*. 2016;21(8):954-963.

Pembrolizumab + Lenvatinib: Real-World Use



- KEYNOTE-146 addressed patients with ECOG PS 0-1
- Phase II included up to 2 prior lines of systemic therapy
- Adequately-controlled blood pressure
- Adequate bone marrow, cardiac, liver function
- Multi-kinase mechanism of action
  - Many patients may not tolerate full lenvatinib dose
- Patients with baseline organ impairment may need lower starting doses

ECOG PS, Eastern Cooperative Oncology Group performance status

Lenvima [package insert]. Woodcliff Lake, NJ: Eisai Inc;2020.; Makker V, et al. *J Clin Oncol*. 2020;38(26):2981-2992.

Questions & Answers

Thank you!