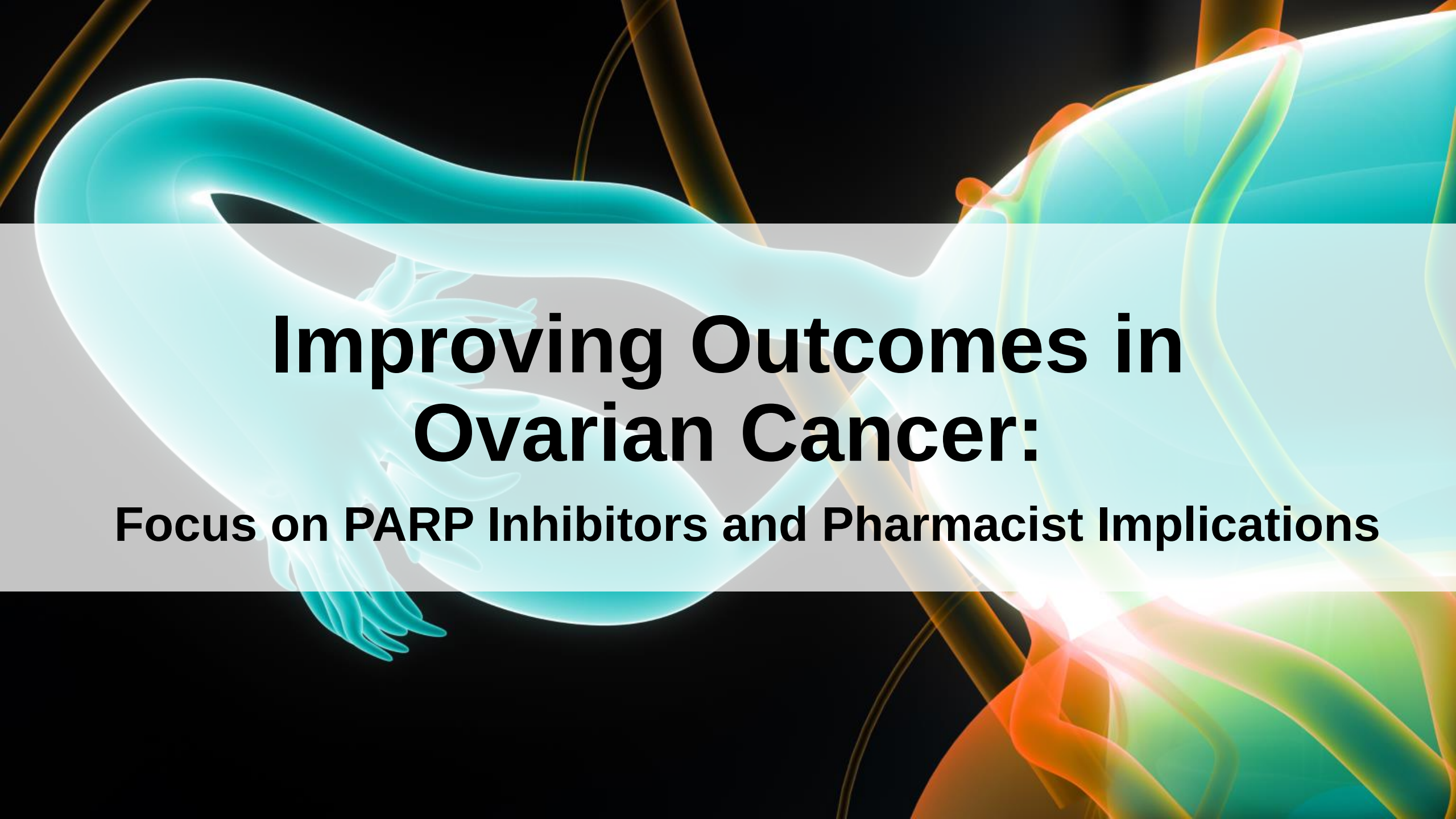
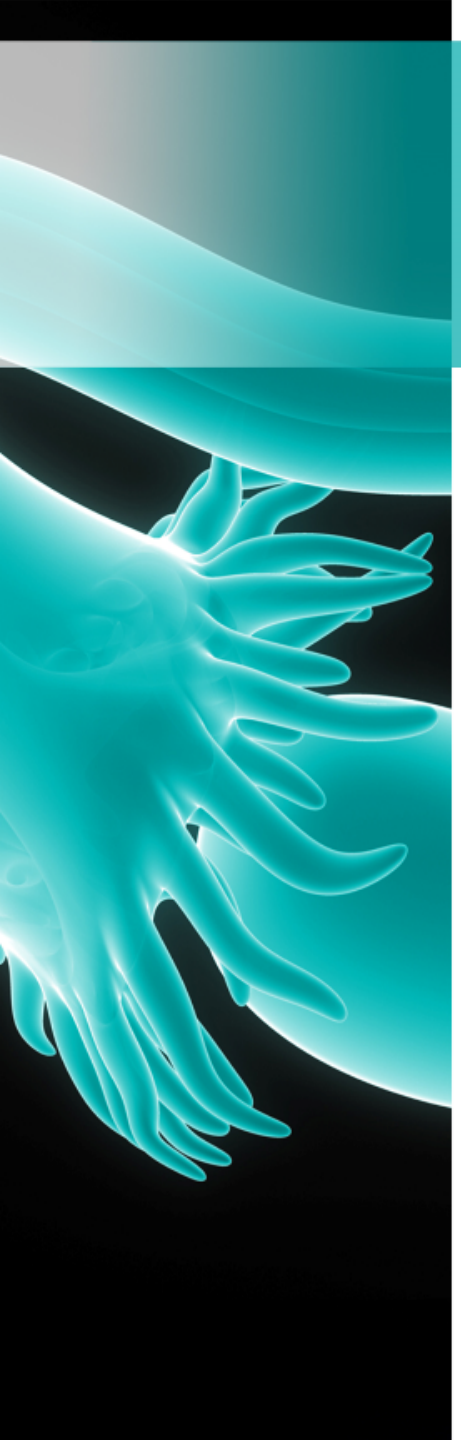


Improving Outcomes in Ovarian Cancer:

Focus on PARP Inhibitors and Pharmacist Implications



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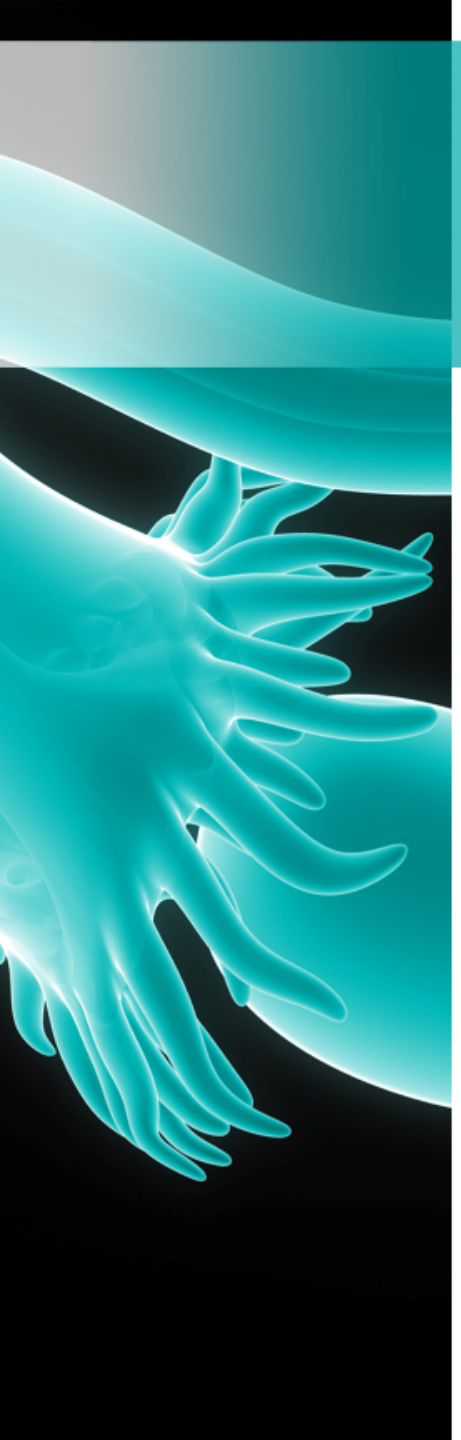
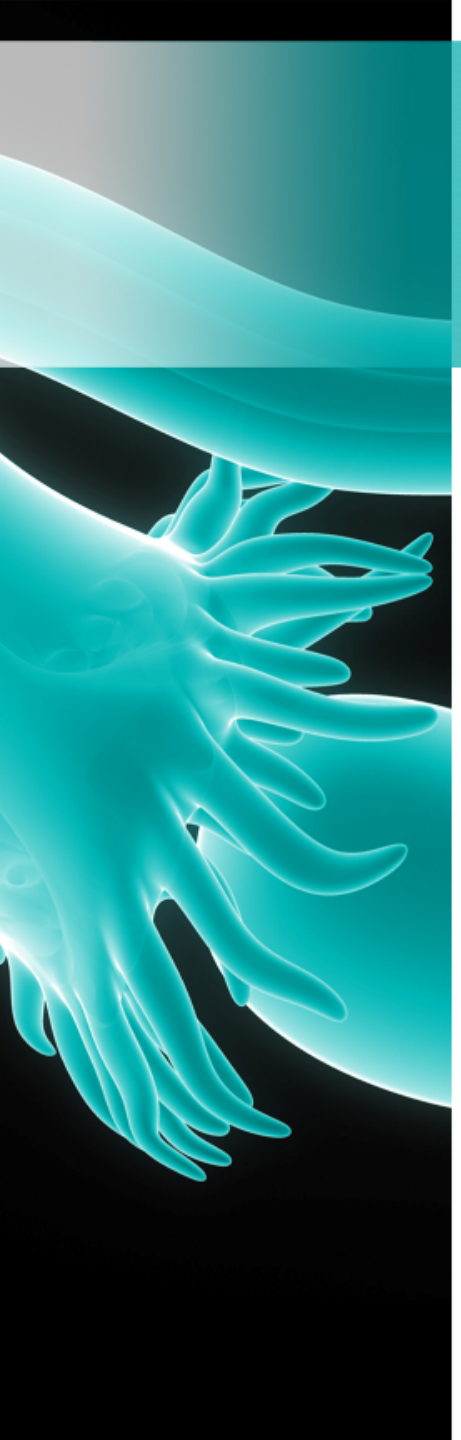


Faculty

Amy Ly Indorf, PharmD, BCOP

Clinical Oncology Pharmacist
UW Medicine
Seattle Cancer Care Alliance
Seattle, WA

Dr. Indorf is a clinical oncology pharmacist at the University of Washington/Seattle Cancer Care Alliance. Her professional responsibilities include working in a variety of multidisciplinary solid-tumor clinics at the Seattle Cancer Care Alliance and University of Washington, primarily in breast and gynecologic oncology. She serves as a clinical instructor at the University of Washington School of Pharmacy. She received her PharmD degree from the University of Washington School of Pharmacy in Seattle, WA, and completed her oncology specialty residency at the University of Washington/Seattle Cancer Care Alliance.



Disclosures

Dr. Indorf has no relevant affiliations or financial relationships with a commercial interest to disclose.

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

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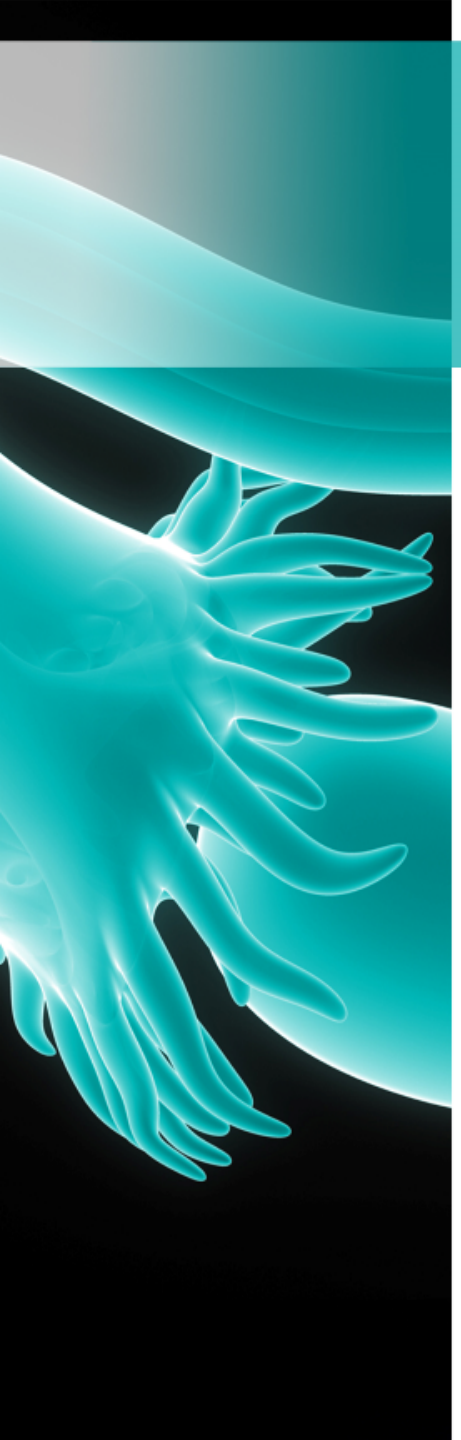

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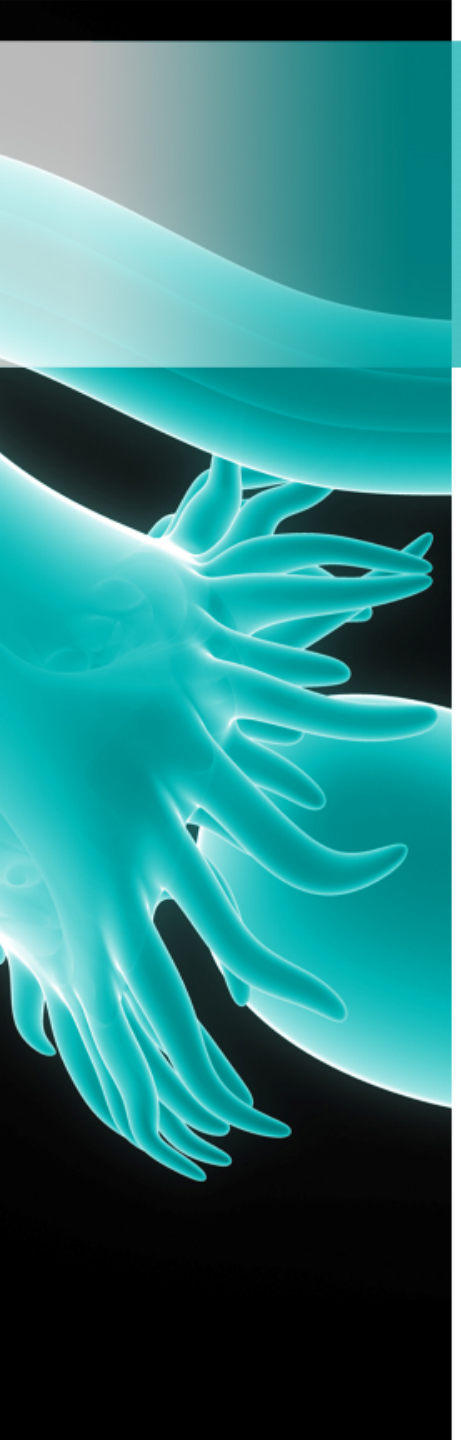
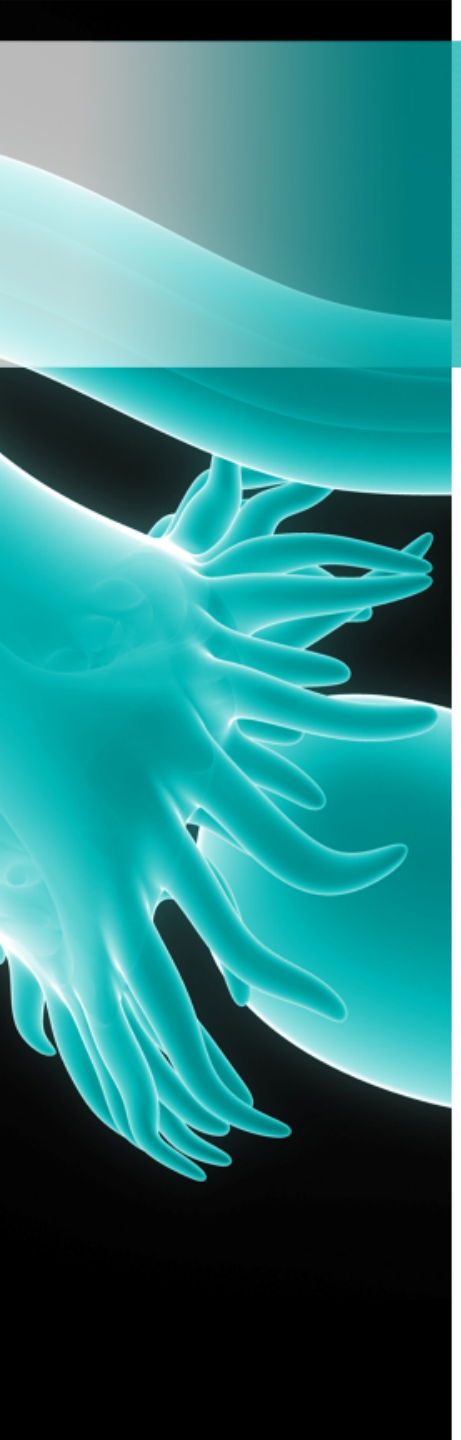
Type of Activity: Application



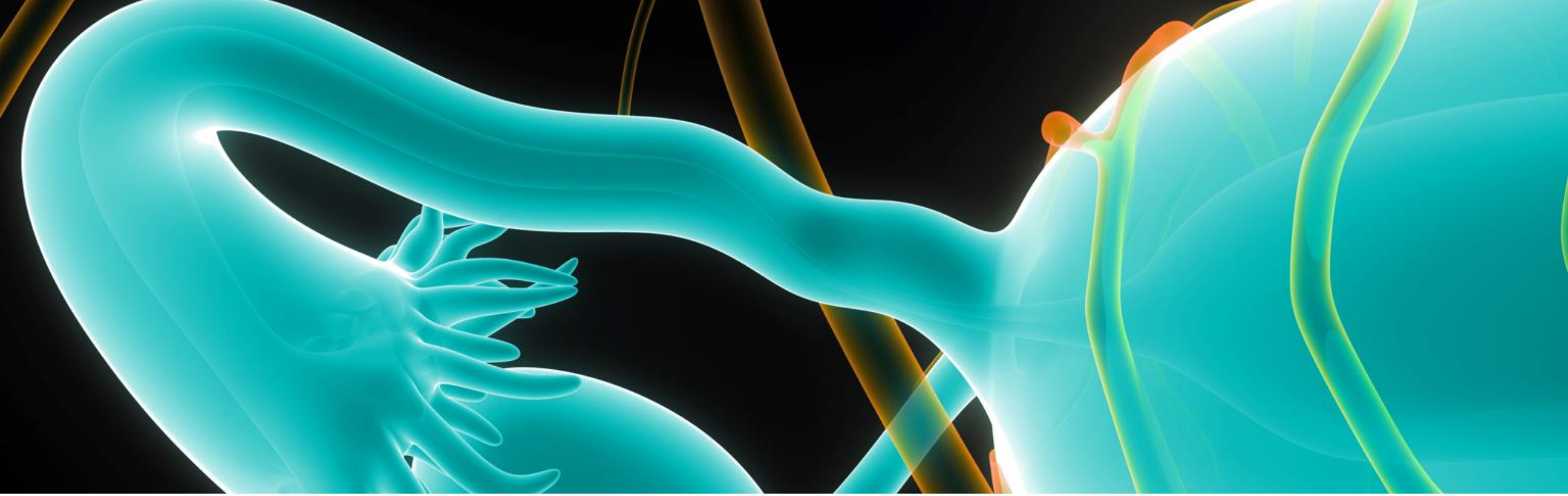
Learning Objectives

- **Discuss** the safety and efficacy of PARP inhibitors in ovarian cancer
- **Compare** and **contrast** available PARP inhibitors in the personalized treatment of patients with ovarian cancer
- **Demonstrate** effective strategies to optimize oral pharmacotherapy for patients with ovarian cancer including adherence and adverse event management



Outline

- Ovarian Cancer Overview
- Mechanism of Action of PARP Inhibitors
- PARP Inhibitor Trials
  - Upfront Maintenance
  - Recurrent Maintenance
  - Treatment
  - Combination therapy
- Adverse Effects and Management
- Real-World Data

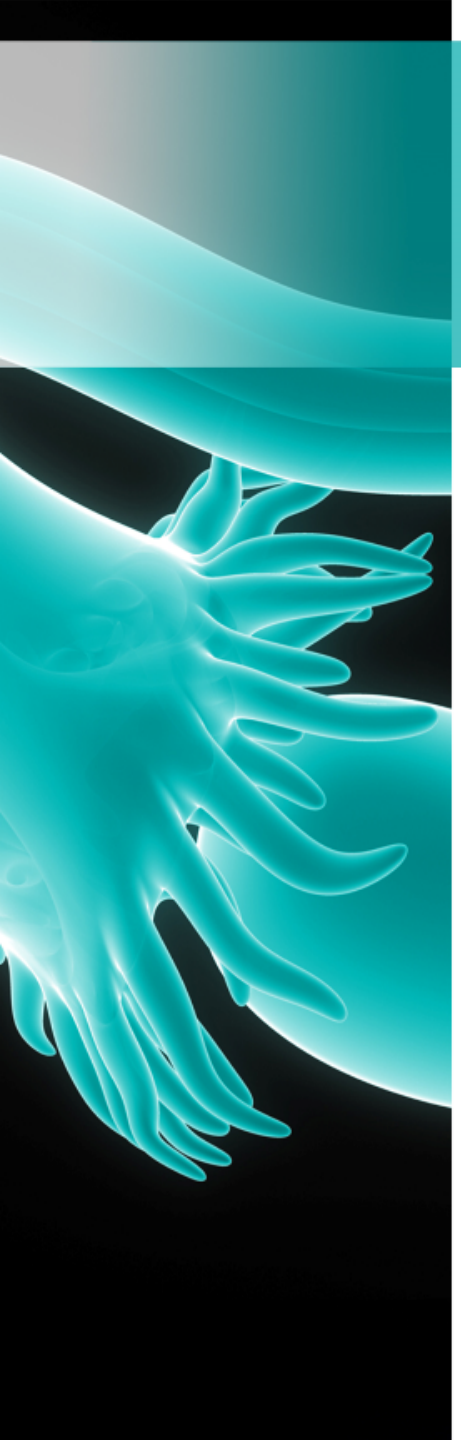


Overview of Ovarian Cancer

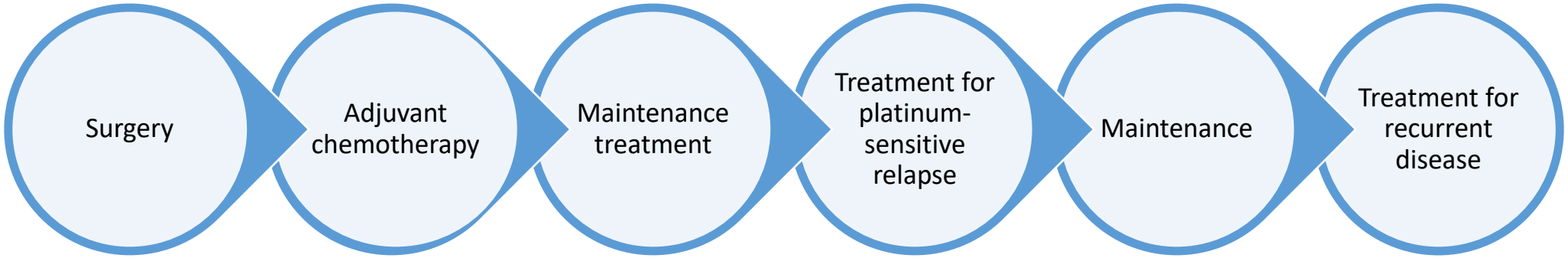
Ovarian Cancer Overview

- Ovarian cancer is the leading cause of death from gynecologic cancer
  - 5-year survival is about 47.6%
  - Median age at diagnosis is 63 years old
  - > 70% of patients present with advanced disease
- Fallopian tube and primary peritoneal cancer are managed in a similar way to ovarian cancer

National Cancer Institute. https://seer.cancer.gov/statfacts/html/ovary.html. Accessed 8 Apr 2020.;
National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/ovarian_blocks.pdf. Published March 11, 2020.



Treatment Course



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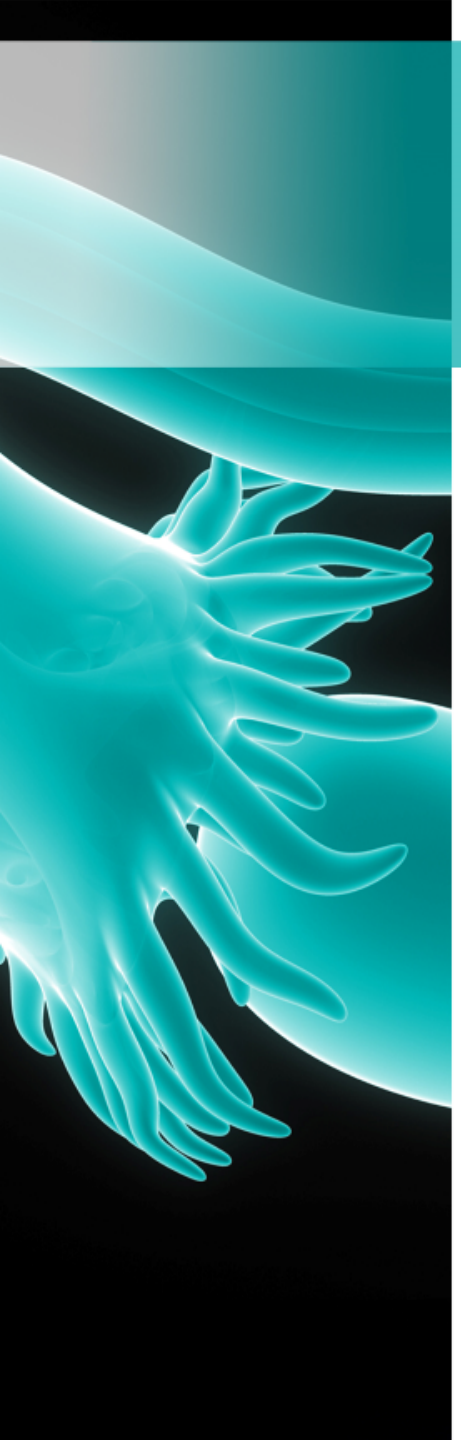


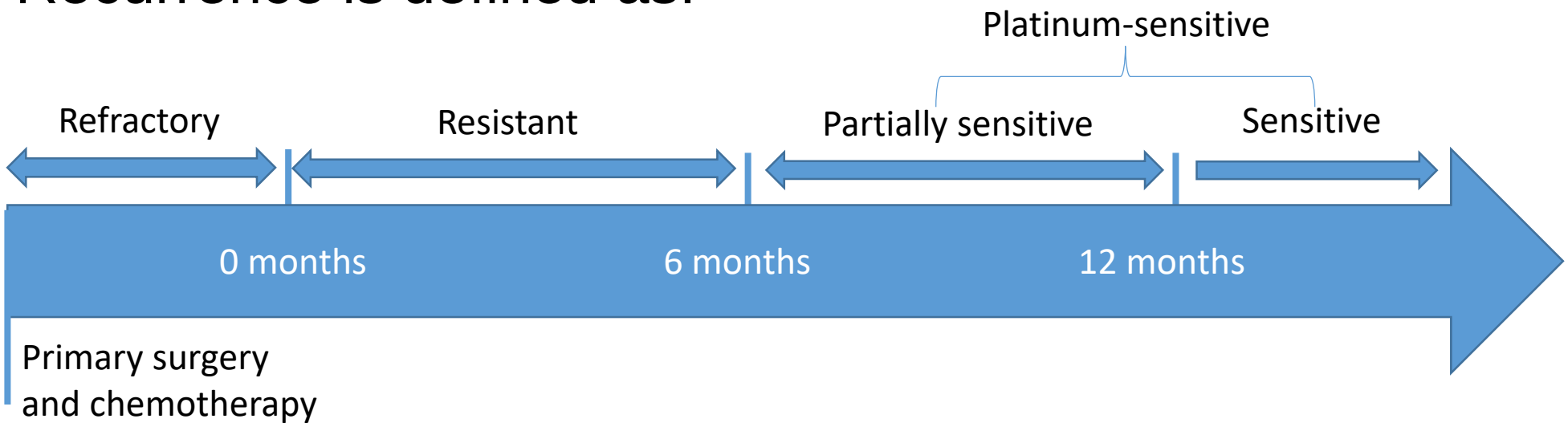
Chemotherapy Treatments

- First-line: carboplatin + paclitaxel +/- bevacizumab
- Platinum-based chemotherapy is the first-line treatment
  - Given adjuvantly or neoadjuvantly
- Regimens for platinum-sensitive recurrence:
  - Carboplatin + paclitaxel +/- bevacizumab
  - Carboplatin + liposomal doxorubicin +/- bevacizumab
  - Carboplatin + gemcitabine +/- bevacizumab

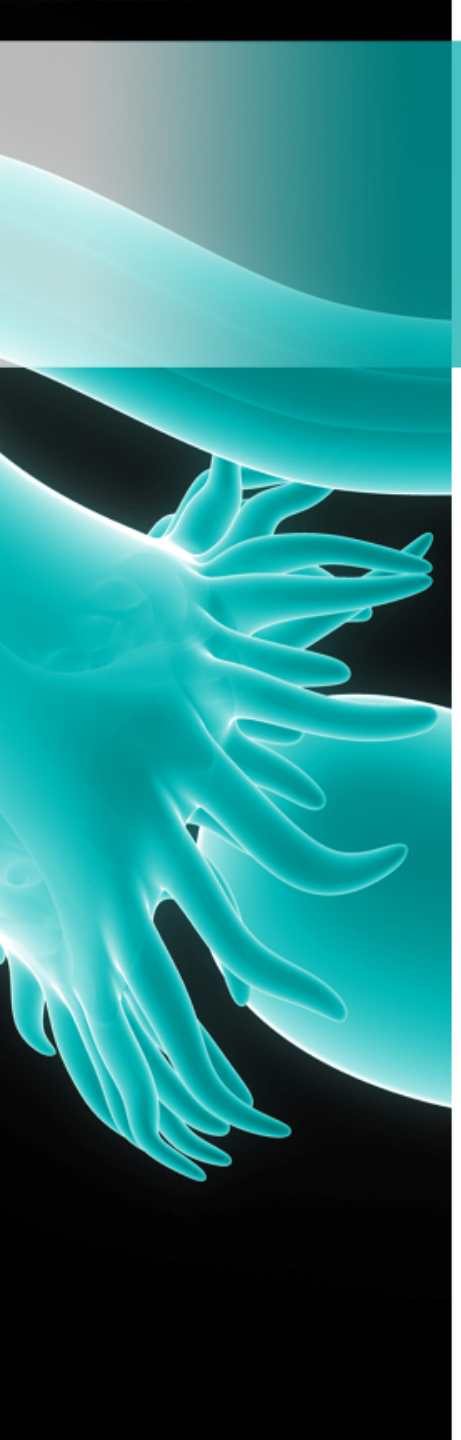
National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/ovarian_blocks.pdf. Published March 11, 2020.

Defining Platinum Sensitivity

- Recurrence is defined as:



National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/ovarian_blocks.pdf. Published March 11, 2020.

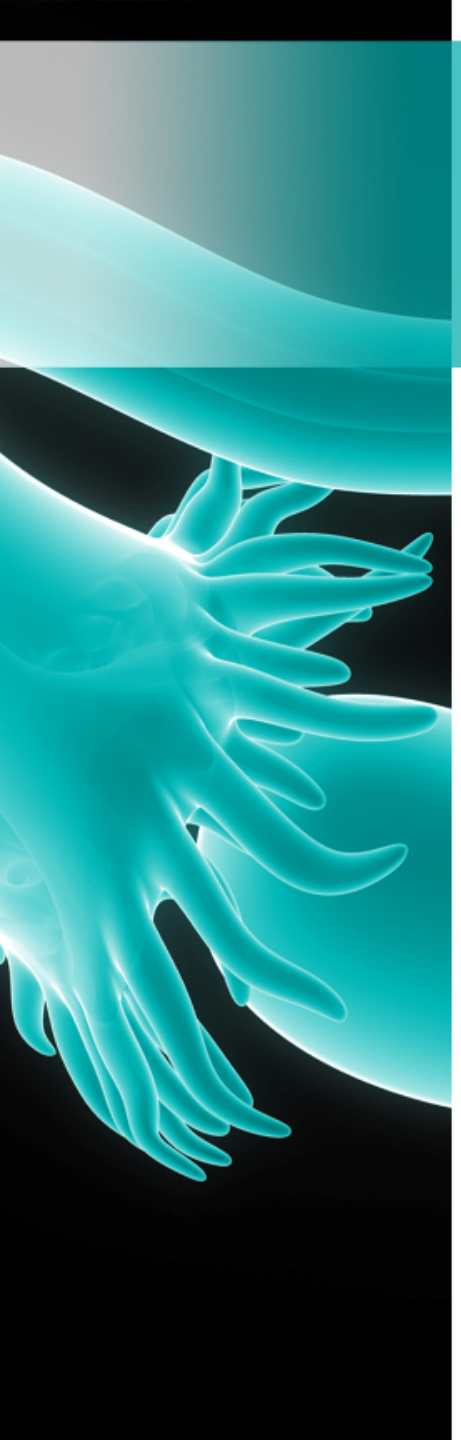


Common Side Effects of Chemotherapy

	Common side effects
Carboplatin	Bone marrow suppression, electrolyte abnormalities, nausea/vomiting
Paclitaxel	Peripheral neuropathy, alopecia, bone marrow suppression
Liposomal doxorubicin	Mucositis, hand-foot syndrome, bone marrow suppression
Gemcitabine	Peripheral edema, rash, bone marrow suppression

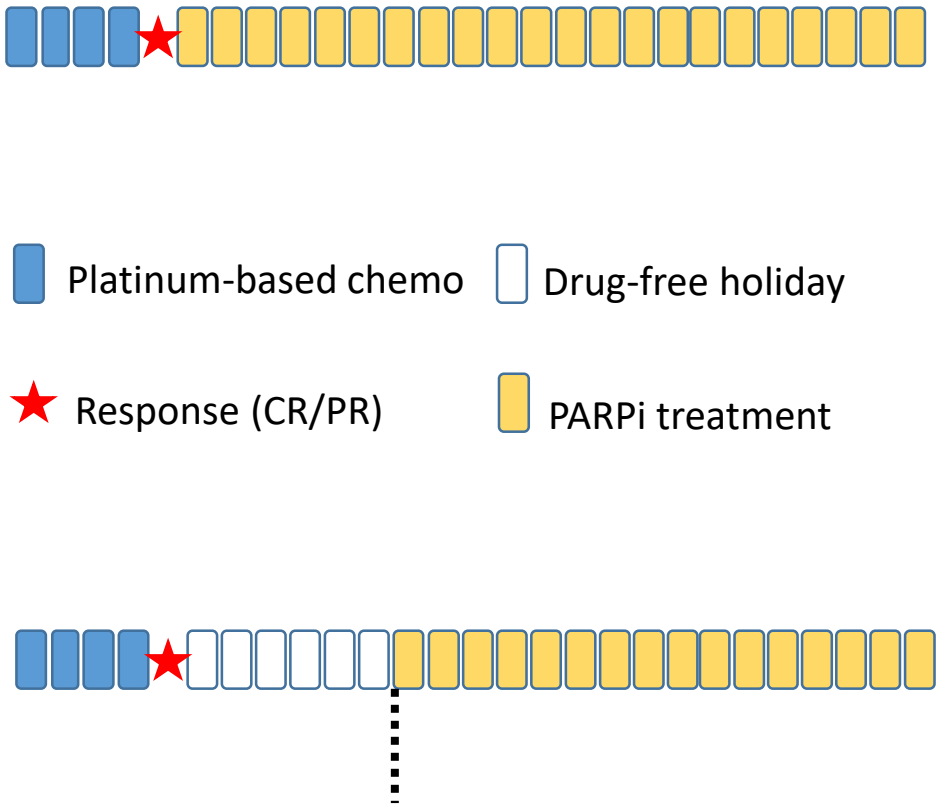
It is important to understand what treatments and side effects patients have previously experienced to address their concerns during chemotherapy education and adverse effect management.

Aghajanian C, et al. *J Clin Oncol*. 2012;30(17):2039-45.;
Ozols RF, et al. *J Clin Oncol*. 2003;21(17):3194-200.;
Pujaide-Lauraine E, et al. *J Clin Oncol*. 2010;28(20):3323-9.



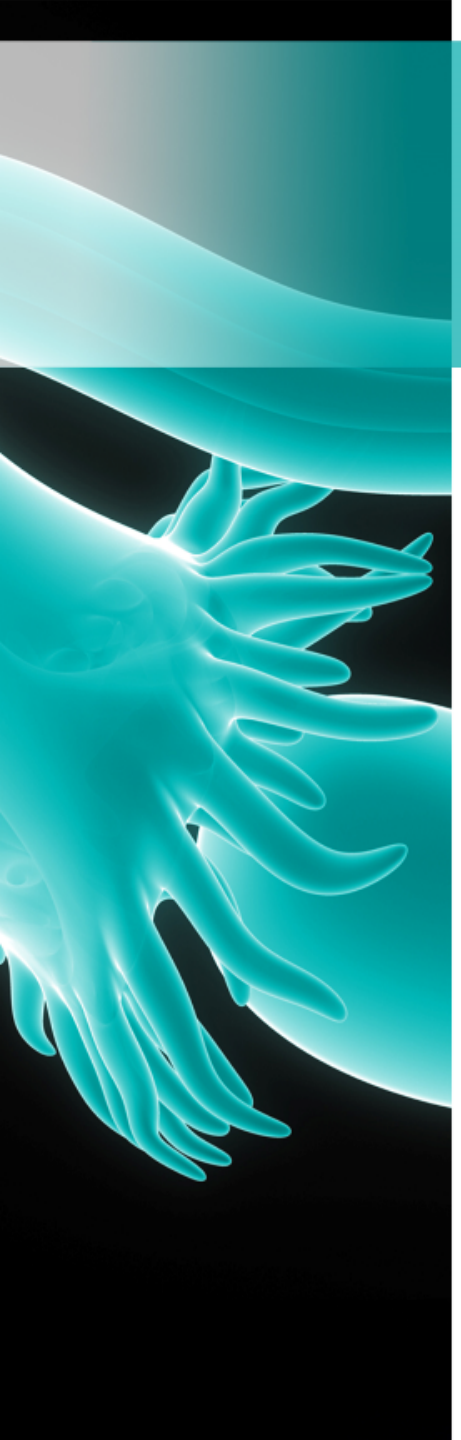
Ovarian Cancer Treatment

- Maintenance:
  - Extend response to treatment
  - Delay next line of chemotherapy
  - Longer duration of good-quality life
  - Delay onset of symptoms of progression
  - Acceptable subjective toxicity profile
- Treatment:
  - After disease relapse or progression
  - Not given immediately after response to platinum-based chemotherapy



Coleman RL, et al. *European Oncology & Haematology*. 2019;15(1):29-40.;
Friedlander M, et al. *Lancet Oncol*. 2018;19(8):1126-34.;
Graybill WS, et al. *Gynecol Oncol*. 2017;146(1):11-5.

CR, complete response;
PARPi, PARP inhibitor;
PR, partial response.

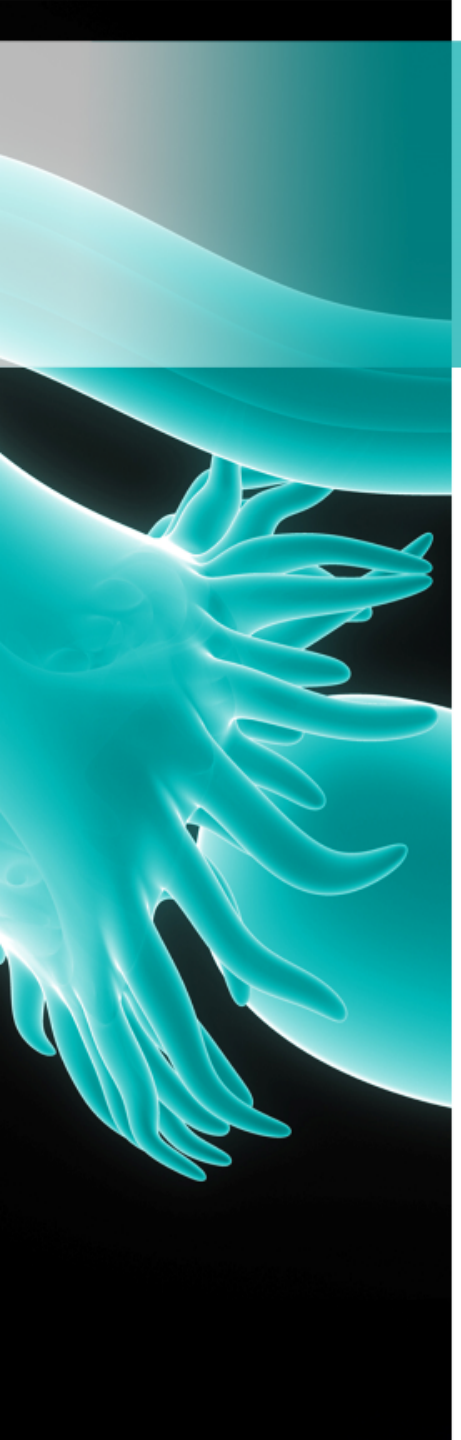


Genetic Risk Factors

- Family history
  - ≥ 2 first-degree relatives with ovarian cancer
- BRCA1- and BRCA2-mutation positive
  - Mutations in tumor suppressor genes
- Lynch syndrome
- Earlier age at onset of ovarian cancer

- Genetic risk evaluation is recommended for all ovarian cancer patients

National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/ovarian_blocks.pdf. Published March 11, 2020.; Roett MA, et al. *Am Fam Phys*. 2009;80(6):609-16.

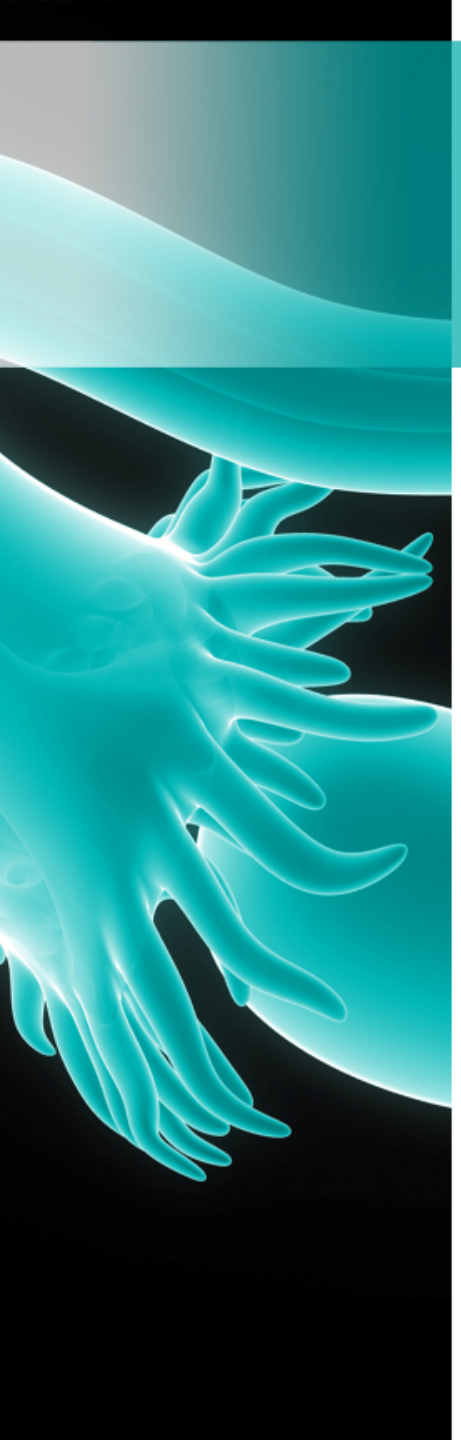


Genetic Risk Factors: BRCA Mutation

- What is the BRCA gene?
  - Breast cancer susceptibility genes (BRCA) 1 and 2
  - BRCA-mutated genes (*BRCAm)* increase the risk of developing cancer due to the inability to repair DNA

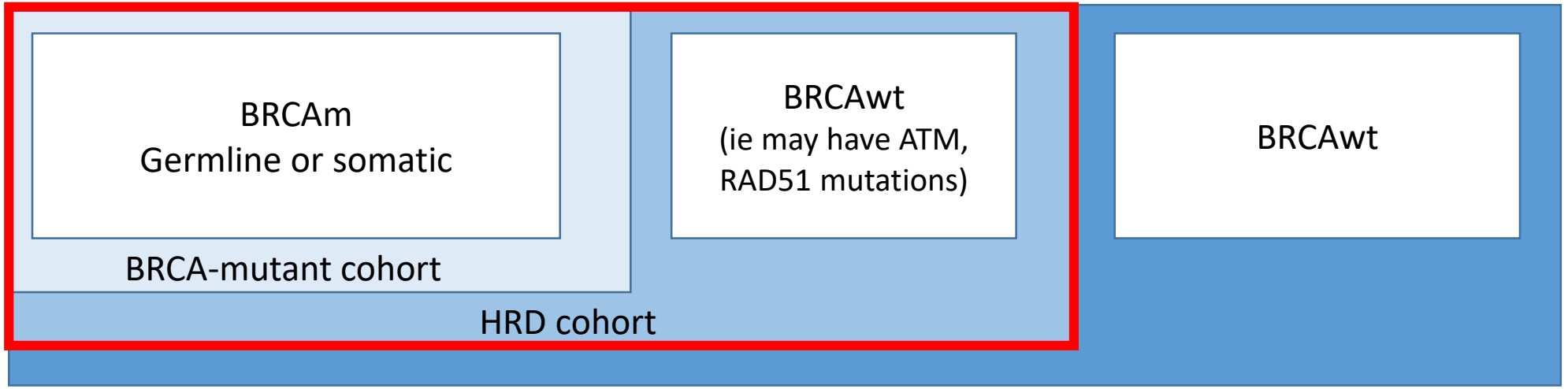
- These genes are involved in homologous recombination repair of damaged DNA

National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/ovarian_blocks.pdf. Published March 11, 2020.

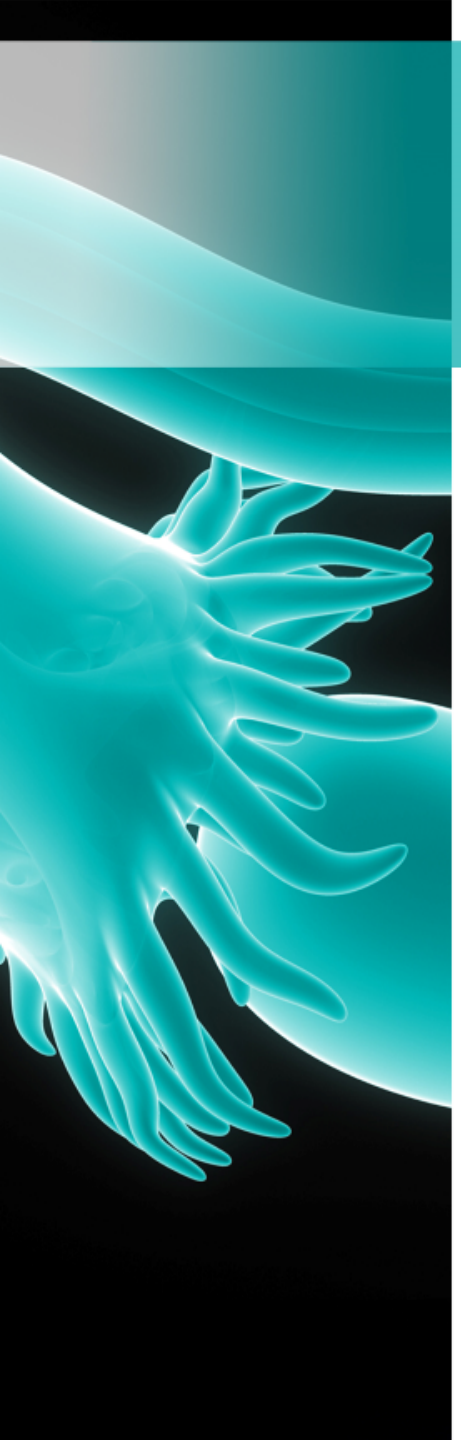


Homologous Repair Deficiency (HRD)

- 50% of high-grade serous ovarian carcinomas are HRD
  - Defect in 1 or more genes involved in homologous repair
  - Includes germline and somatic BRCA mutations
  - Includes mutations of *ATM*, *CHEK2*, *RAD51*, and *MRE11A* genes
- HRD is the phenotype evaluated by various diagnostic



Ledermann JA, et al. *Eur J Cancer.* 2016;60:49-58.



Companion Diagnostics

BRACAnalysis (Myriad Genetics)	Foundation Focus CDxBRCA (Foundation Medicine)	myChoice HRD (Myriad Genetics)
SOLO-2 Olaparib	ARIEL 2 & 3 Rucaparib	NOVA Niraparib
Identify germline BRCA1/2 mutation	Calculate % LOH to identify HRD subgroups	Identify HRD populations

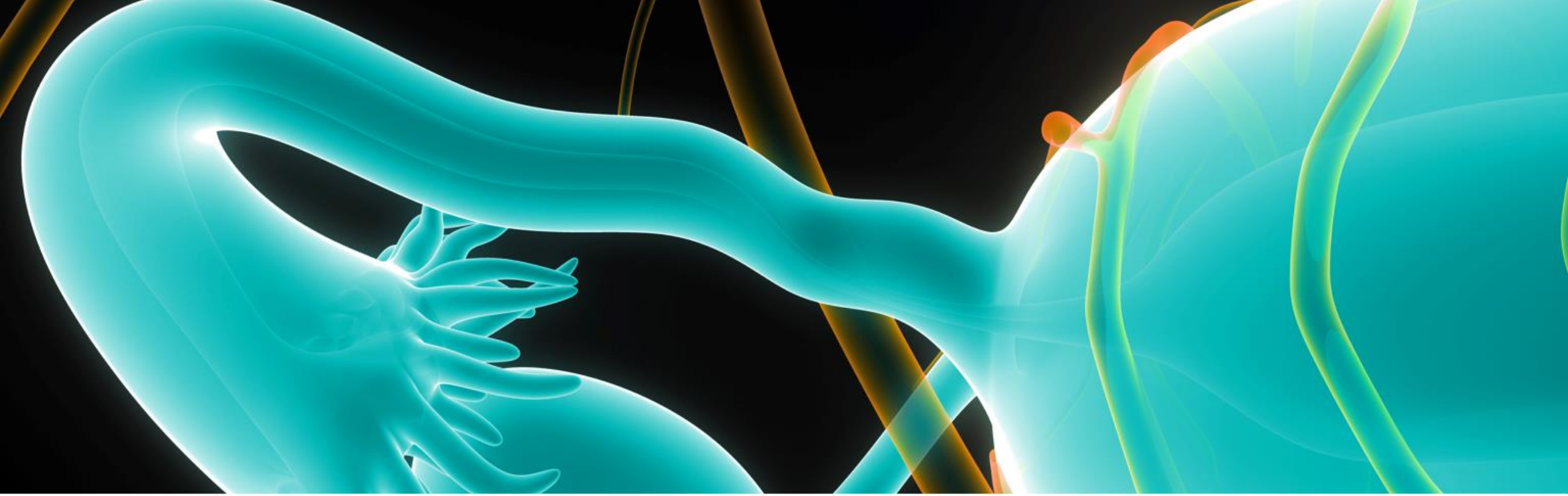
No standard test across trials for all 3 PARPi

Mirza MR, et al. *N Engl J Med*. 2016;375(22):2154-64.;
Pujade-Lauraine E, et al. *Lancet Oncol*. 2017;18(9):1274-84.;
Swisher EM, et al. *Lancet Oncol*. 2017;18(1):75-87.

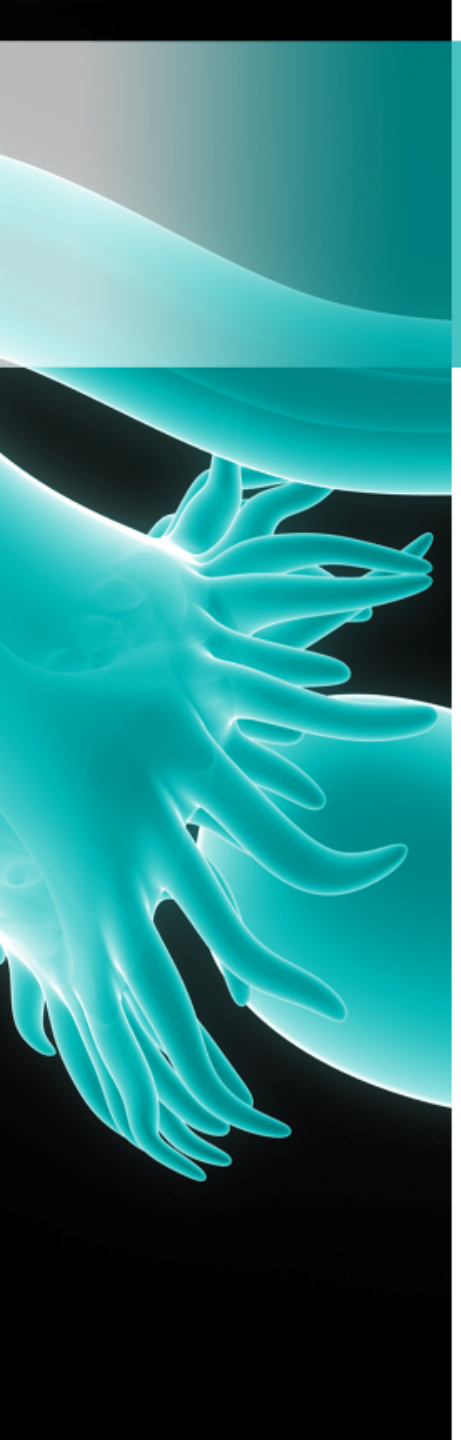
LOH, loss of heterozygosity.

Summary: Ovarian Cancer Overview

- Maintenance therapy is given after response to platinum-based chemotherapy to extend response to therapy and delay progression
- Treatment is after relapse of disease and may not immediately follow platinum-based chemotherapy
- HRD is a phenotype that signal defects in DNA repair

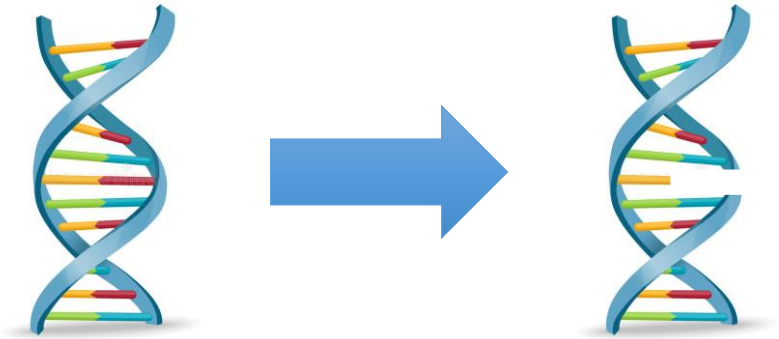


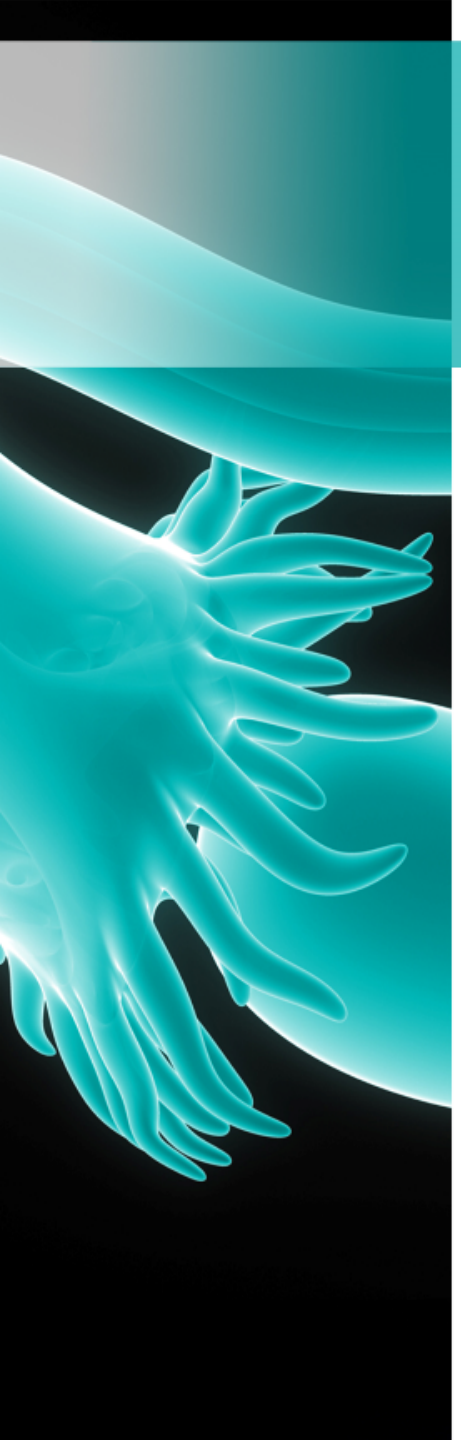
PARP Inhibitors
Mechanism of Action



PARP Inhibitors: Mechanism of Action

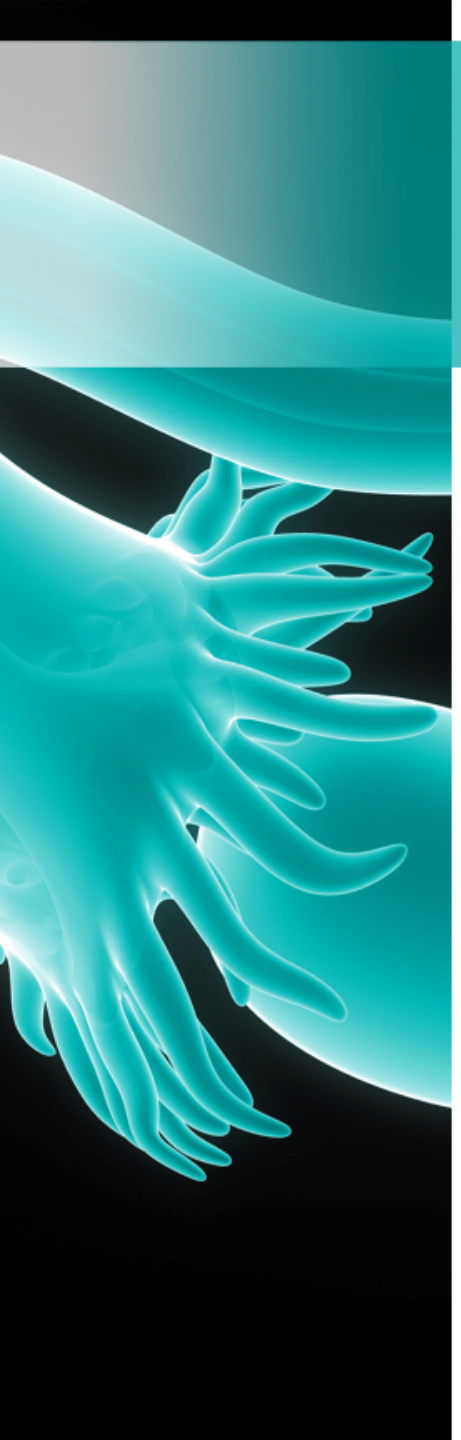
- DNA undergoes single-strand breaks





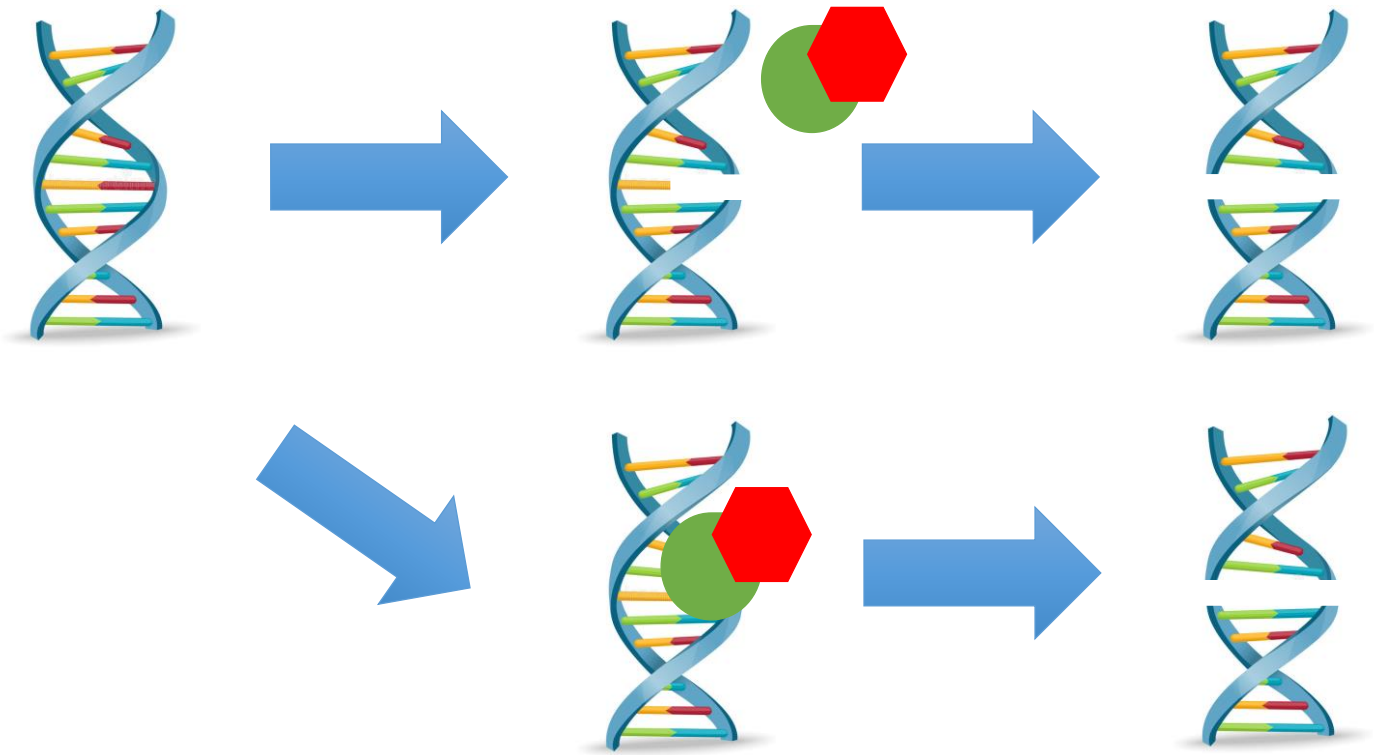
PARP Inhibitors: Mechanism of Action

- Poly-ADP ribose polymerase (PARP) identifies the single-strand break and recruits repair proteins



PARP Inhibitors: Mechanism of Action

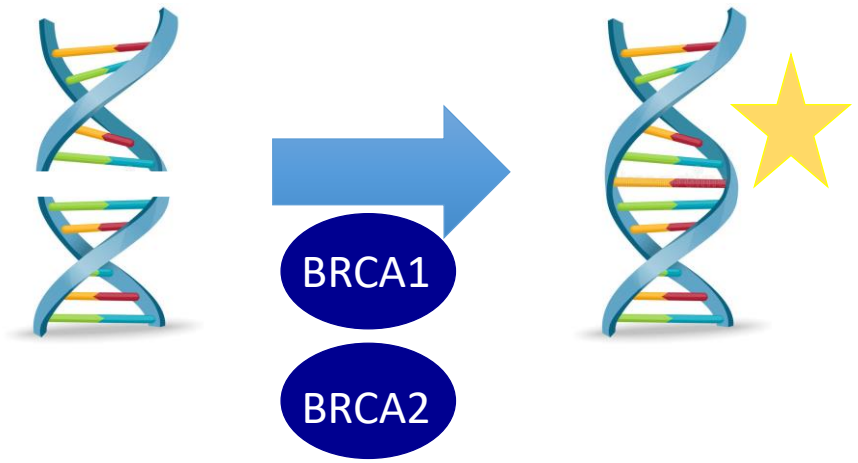
- PARP inhibitors (PARPi) bind PARP and prevent binding at the single-strand break leading to formation of double-strand breaks



PARPi can also trap PARP at the single-strand break and prevent DNA repair machinery from proceeding

PARP Inhibitors: Mechanism of Action

- Double-strand breaks undergo repair by homologous recombination (HR) or non-homologous end joining (NHEJ)



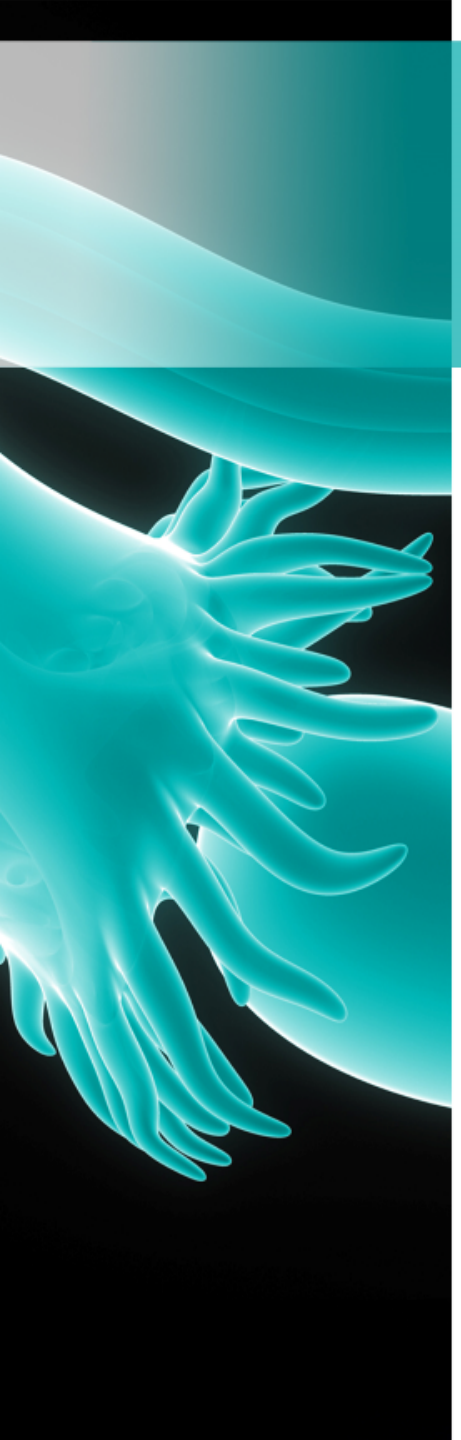
PARP

PARPi

BRCA mutated or HRD

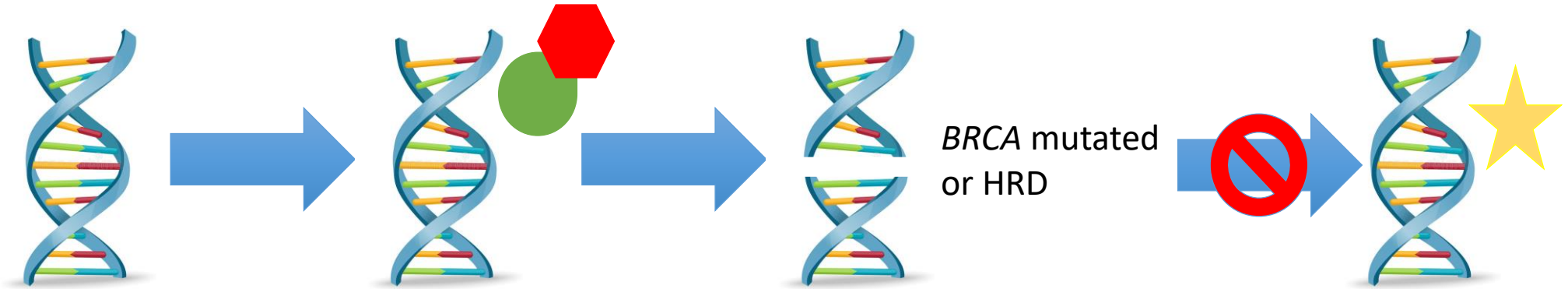
NHEJ is a low-fidelity process

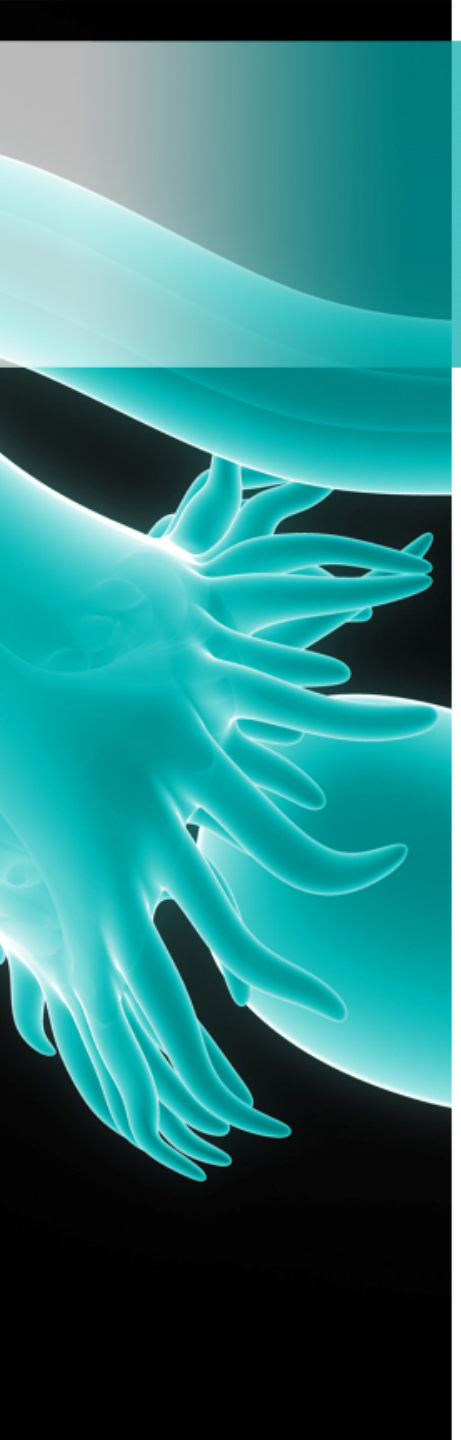
Cell death



PARP Inhibitors: Mechanism of Action

- Synthetic lethality
  - *BRCA mutations* or HR deficiency (HRD) plus PARPi means the double-strand breaks must undergo repair by NHEJ

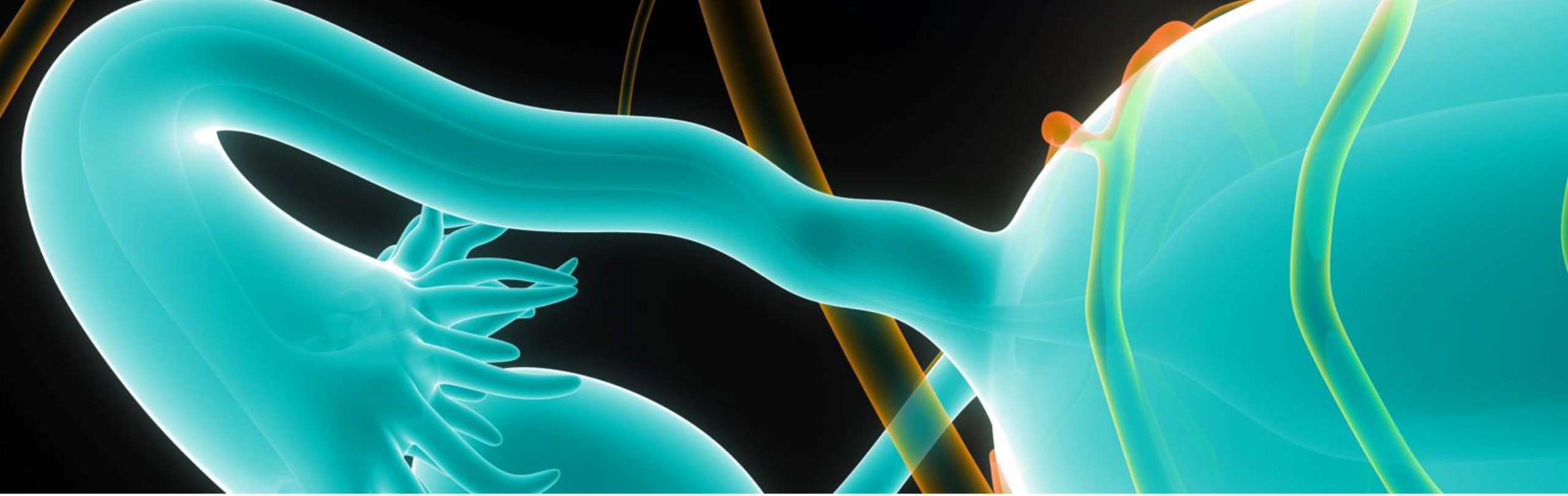




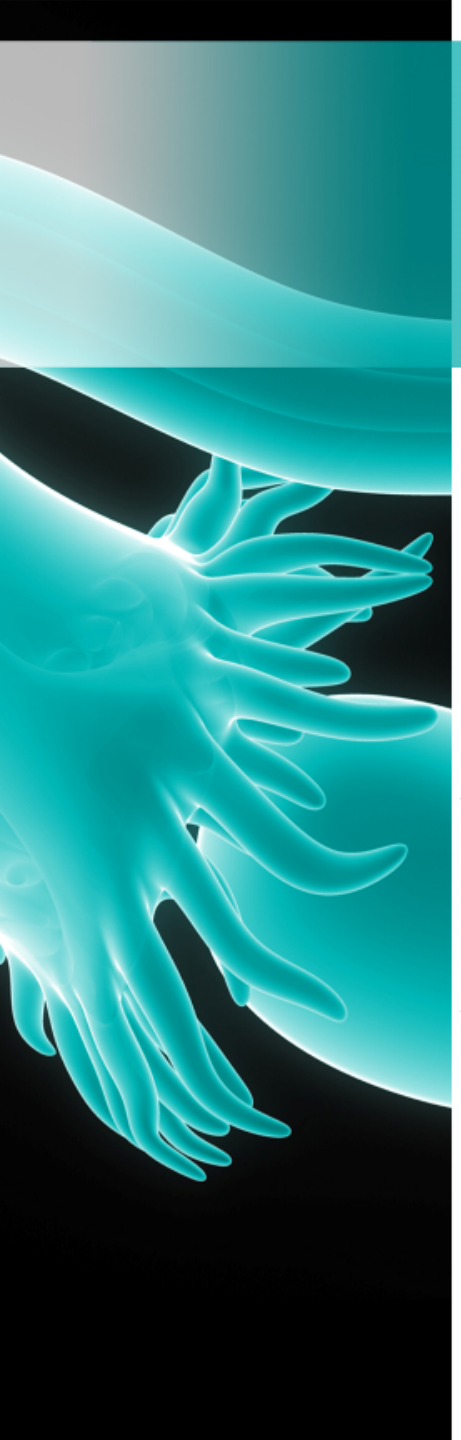
ARS Question #1

Which statement best describes “synthetic lethality” with PARPi?

A. PARPi induces the formation of double-strand DNA breaks, which persist in patients with HRD
B. PARPi inhibits PARP and prevents its binding to single-strand DNA breaks and traps PARP on the site of single-strand DNA breaks
C. PARPi blocks repair of single-strand DNA breaks, and HRD decreases the ability to fix double-strand DNA breaks, which leads to cell death
D. PARPi decreases DNA synthesis in BRCA-mutated cells, which leads to cell death



PARP Inhibitors
Trials in Ovarian Cancer



PARP Inhibitors in Ovarian Cancer

2014

- Olaparib (capsules) treatment after 3+ lines of therapy, *BRCAm*

2016

- Rucaparib treatment after 2+ lines of therapy

2017

- Niraparib recurrent maintenance
- Olaparib tablets approved, capsules phased out

2018

- Rucaparib recurrent maintenance
- Olaparib recurrent maintenance

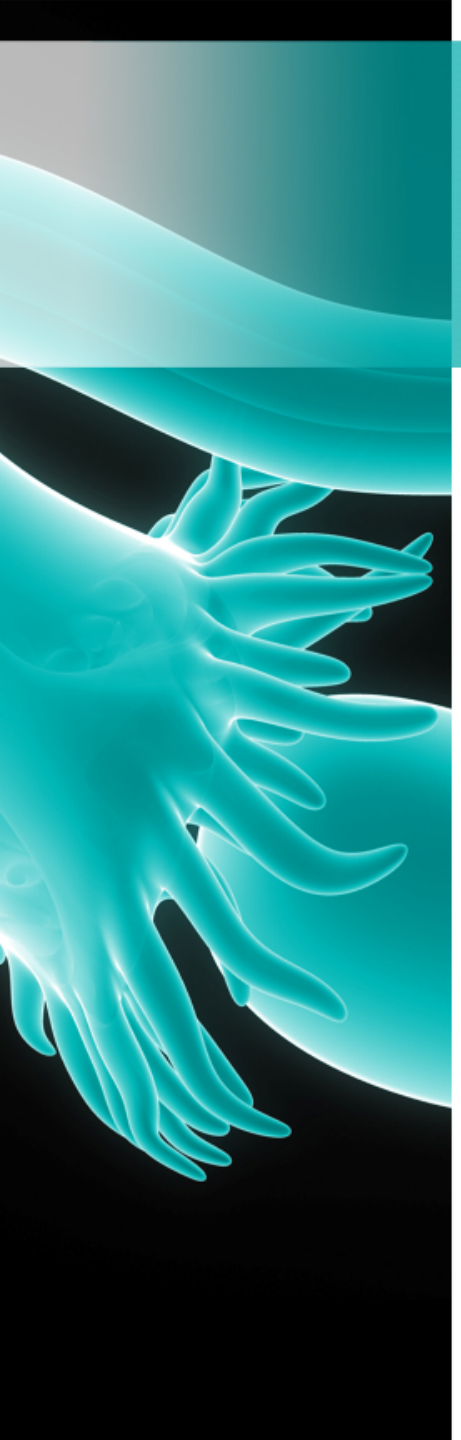
2019

- Olaparib first-line maintenance, *BRCAm*
- Niraparib treatment after 3+ lines of therapy, HRD

2020

- Niraparib first-line maintenance
- Olaparib + bevacizumab first-line maintenance

BRCAm, BRCA mutated.



PARP Inhibitor Trials in Ovarian Cancer

Upfront maintenance

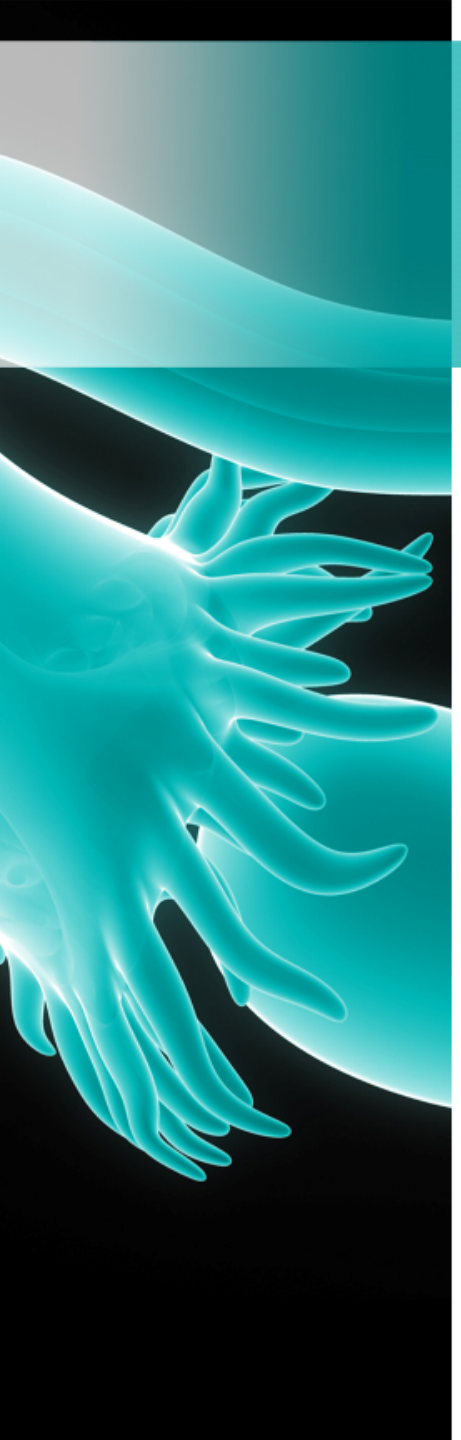
- SOLO-1
  Olaparib
- PRIMA
  Niraparib
- PAOLA
  Olaparib + bevacizumab
- VELIA
  Veliparib + chemo

Recurrent maintenance

- SOLO-2, Study 19
  Olaparib
- ARIEL3
  Rucaparib
- NOVA
  Niraparib
- AVANOVA
  Niraparib + bevacizumab

Treatment

- Study 42, SOLO-3
  Olaparib
- Study 10
  Rucaparib
- QUADRA
  Niraparib
- TOPACIO-KEYNOTE-162
  Niraparib + pembrolizumab



PARP Inhibitor Trials in Ovarian Cancer

Upfront maintenance

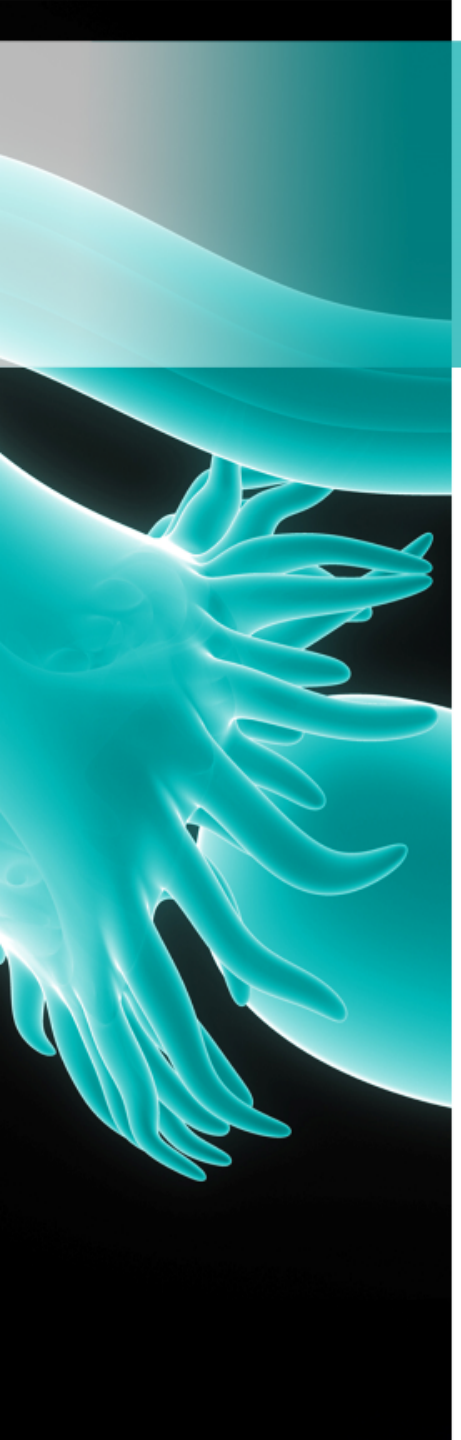
- SOLO-1
  Olaparib
- PRIMA
  Niraparib
- PAOLA
  Olaparib + bevacizumab
- VELIA
  Veliparib + chemo

Recurrent maintenance

- SOLO-2 Study 19
  Olaparib
- ARIEL3
  Rucaparib
- NOVA
  Niraparib
- AVANOVA
  Niraparib + bevacizumab

Treatment

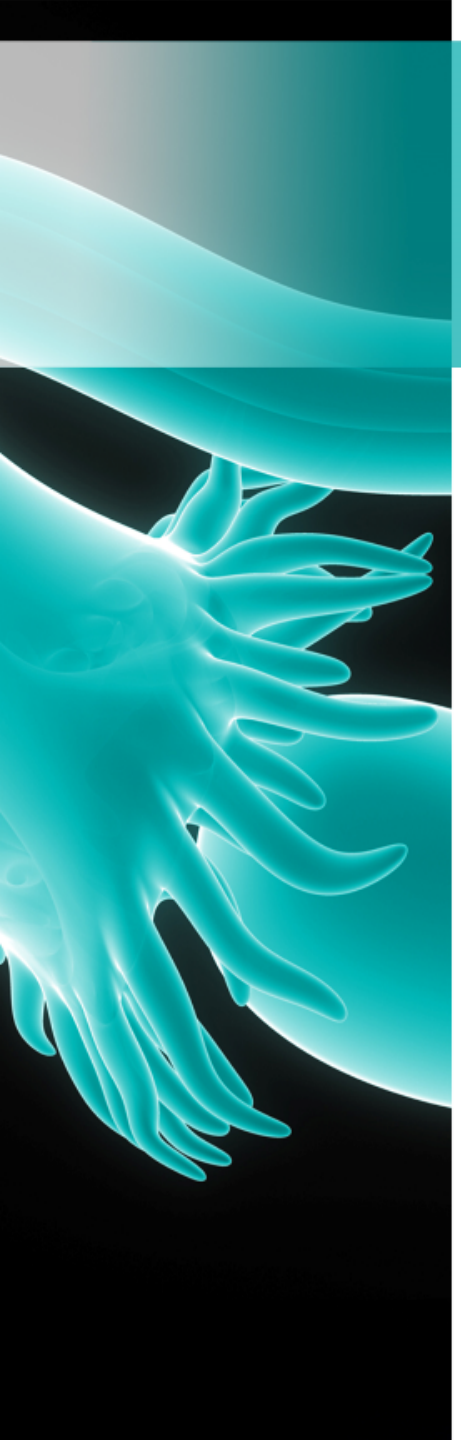
- Study 42 SOLO-3
  Olaparib
- Study 10
  Rucaparib
- QUADRA
  Niraparib
- TOPACIO-KEYNOTE-162
  Niraparib + pembrolizumab



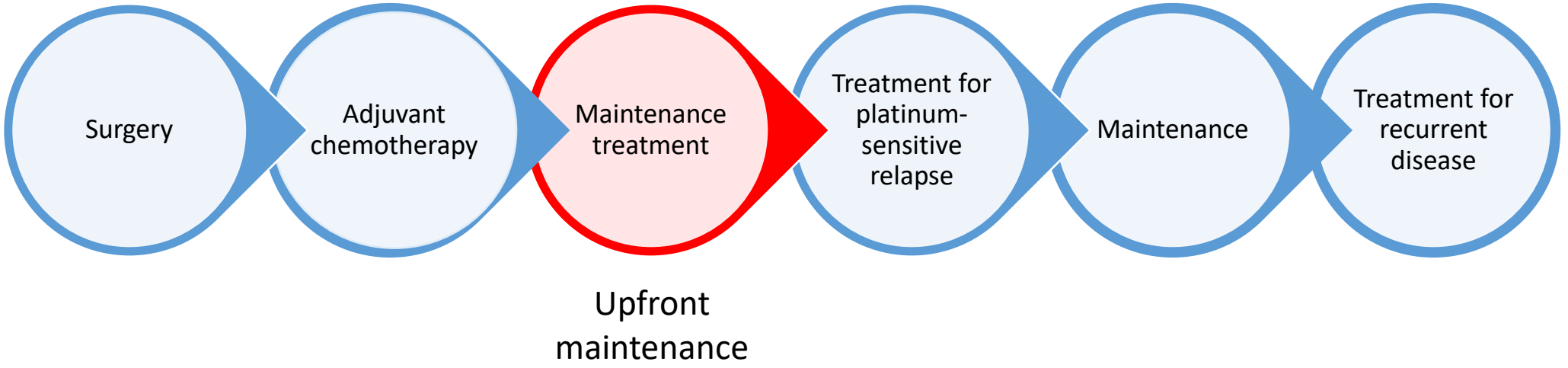
PARP Inhibitor Trial Endpoints

- Progression-free survival (PFS)
- General consensus to support PFS as the primary endpoint in recurrent ovarian cancer trials
- Supported secondary endpoints include time to second subsequent therapy and patient-reported outcomes

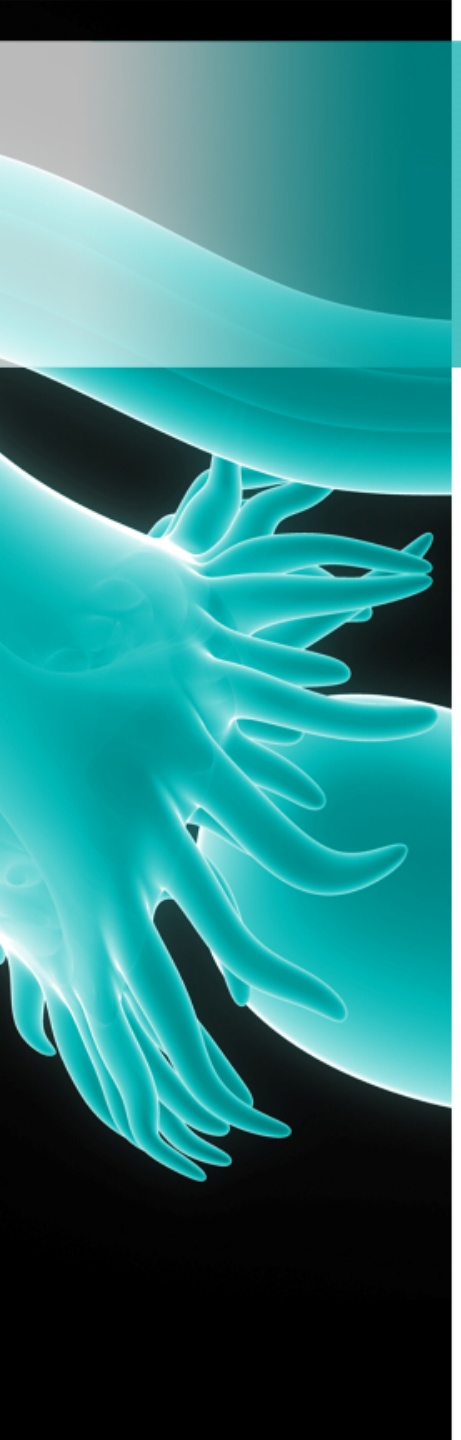
Friedlander M, et al. *Lancet Oncol*. 2018;19(8):1126-34.



Treatment Course



Lafargue CJ, et al. *Lancet Oncol*. 2019;20(1):e15-28.



PARP Inhibitor Trials in Ovarian Cancer

Upfront maintenance

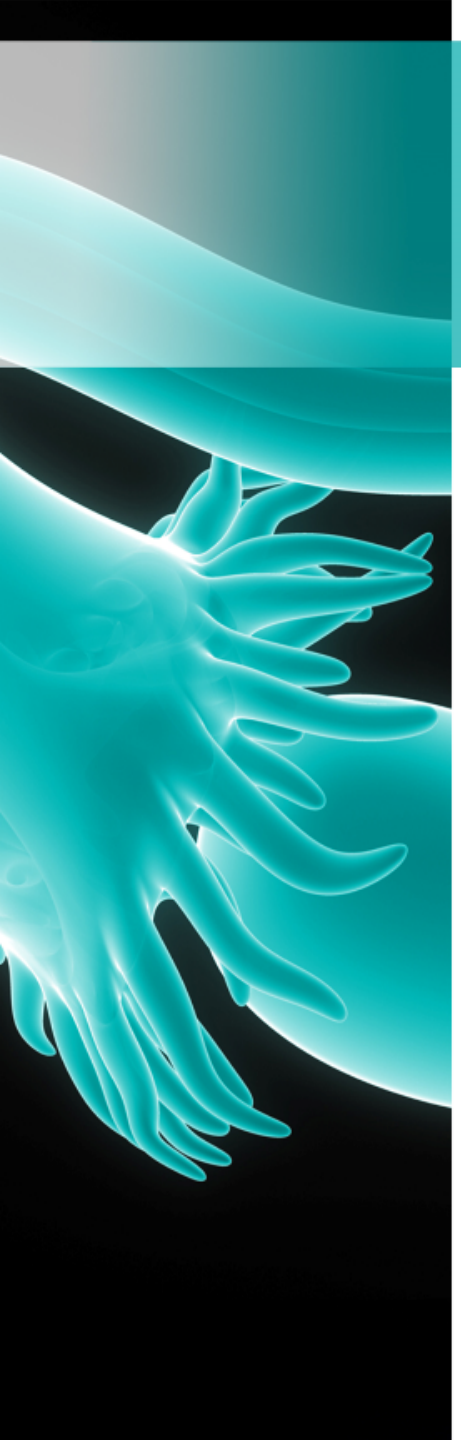
- SOLO-1 Olaparib
- PRIMA Niraparib

Recurrent maintenance

- SOLO-2, Study 19 Olaparib
- ARIEL3 Rucaparib
- NOVA Niraparib

Treatment

- Study 42, SOLO-3 Olaparib
- Study 10 Rucaparib
- QUADRA Niraparib



PARP Inhibitors: Upfront Maintenance

SOLO-1

Olaparib

- Randomized, double-blind, phase III
- Olaparib 300 mg BID vs. placebo
- Maintenance treatment first-line platinum-based chemo
- BRCA1 or BRCA2 mutated

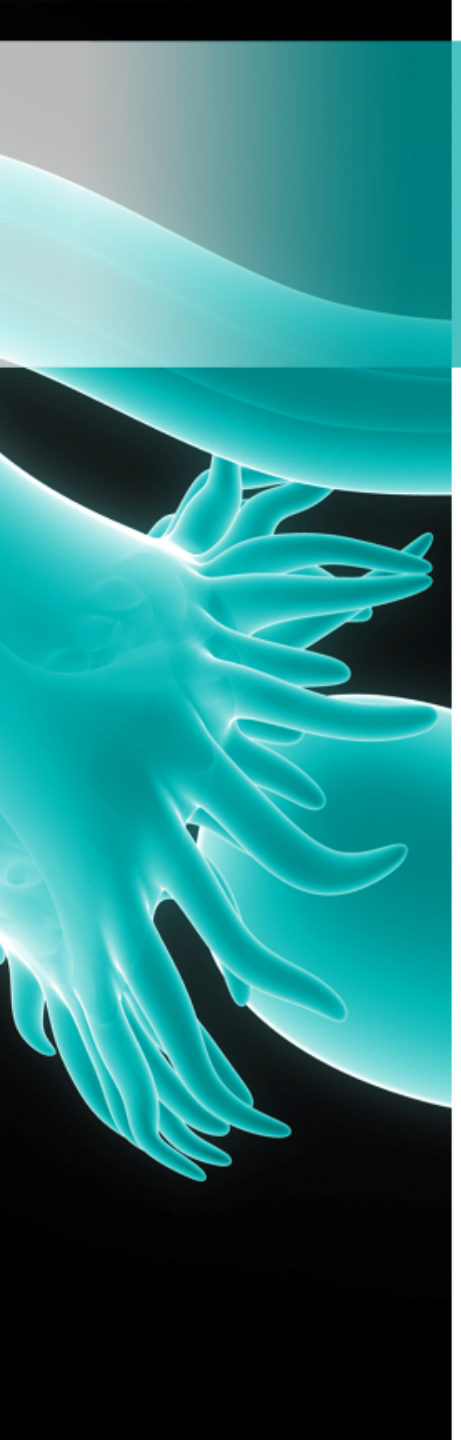
PRIMA

Niraparib

- Randomized, double-blind, phase III
- Niraparib 300 mg QD vs. placebo
- Maintenance treatment first-line platinum-based chemo
- Regardless of HRD

Gonzalez-Martin A, et al. *N Engl J Med*. 2019;381(25):2391-402.; Moore K, et al. *N Engl J Med*. 2018;379(26):2495-505.

BID, twice a day; QD, once daily.



PARP Inhibitors: Upfront Maintenance

SOLO-1	PRIMA
Olaparib	Niraparib
Randomized, double-blind, phase III	Randomized, double-blind, phase III
Olaparib 300 mg BID vs. placebo	Niraparib 300 mg QD vs. placebo
Maintenance treatment first-line platinum-based chemo	Maintenance treatment first-line platinum-based chemo
BRCA1 or BRCA2 mutated	Regardless of HRD

Gonzalez-Martin A, et al. *N Engl J Med*. 2019;381(25):2391-402.; Moore K, et al. *N Engl J Med*. 2018;379(26):2495-505.

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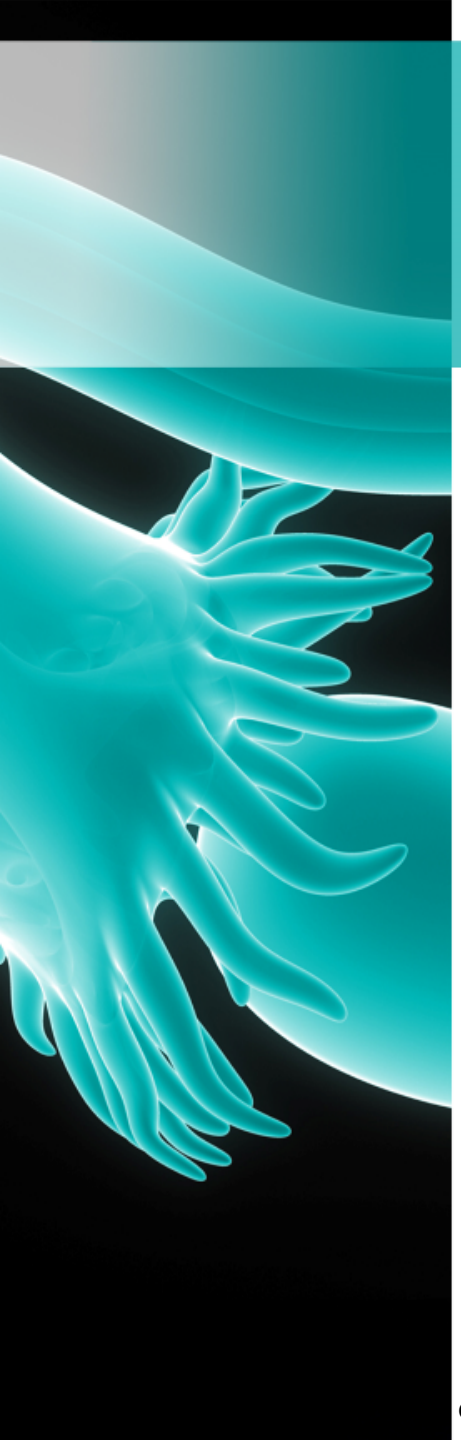


PARP Inhibitors: Upfront Maintenance

SOLO-1

Olaparib

- PFS: 49.9 vs. 13.8 months favoring olaparib
  HR: 0.3, p<0.001

PRIMA

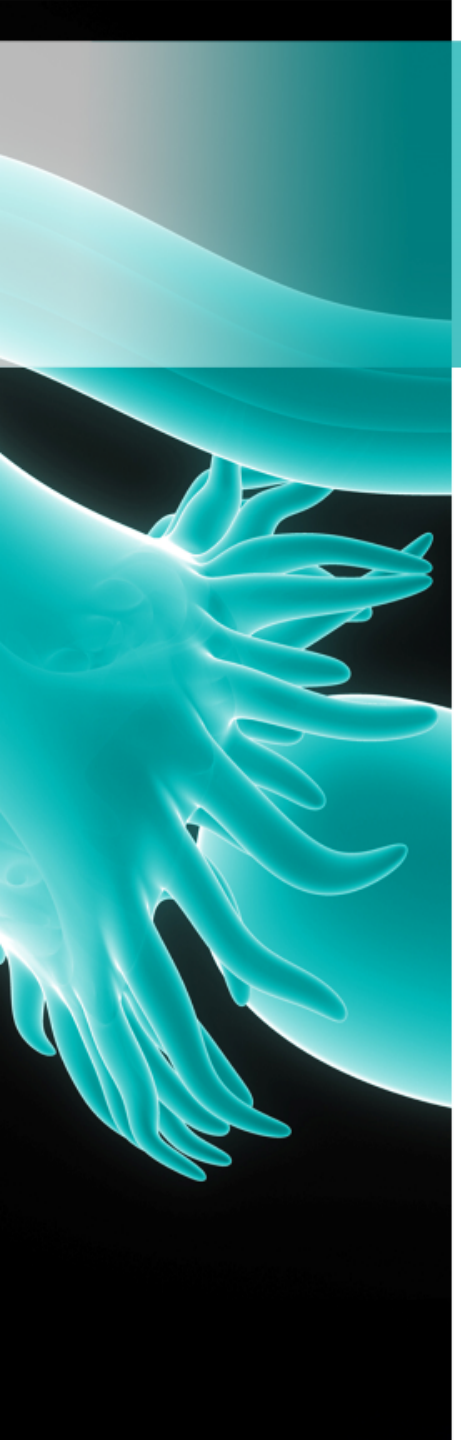
Niraparib

- PFS: 13.8 vs. 8.2 months favoring niraparib

HRD	HRD, BRCAm	HRD, BRCAwt	Non-HRD
PFS: 21.9 vs. 10.4 m HR: 0.43, p<0.001	PFS: 22.1 vs. 10.9 m HR: 0.4	PFS: 19.6 vs. 8.2 m HR: 0.5	PFS: 8.1 vs. 5.4 m HR: 0.68

Gonzalez-Martin A, et al. *N Engl J Med*. 2019;381(25):2391-402.; Moore K, et al. *N Engl J Med*. 2018;379(26):2495-505.

BRCAwt, BRCA wild-type; HR, hazard ratio.

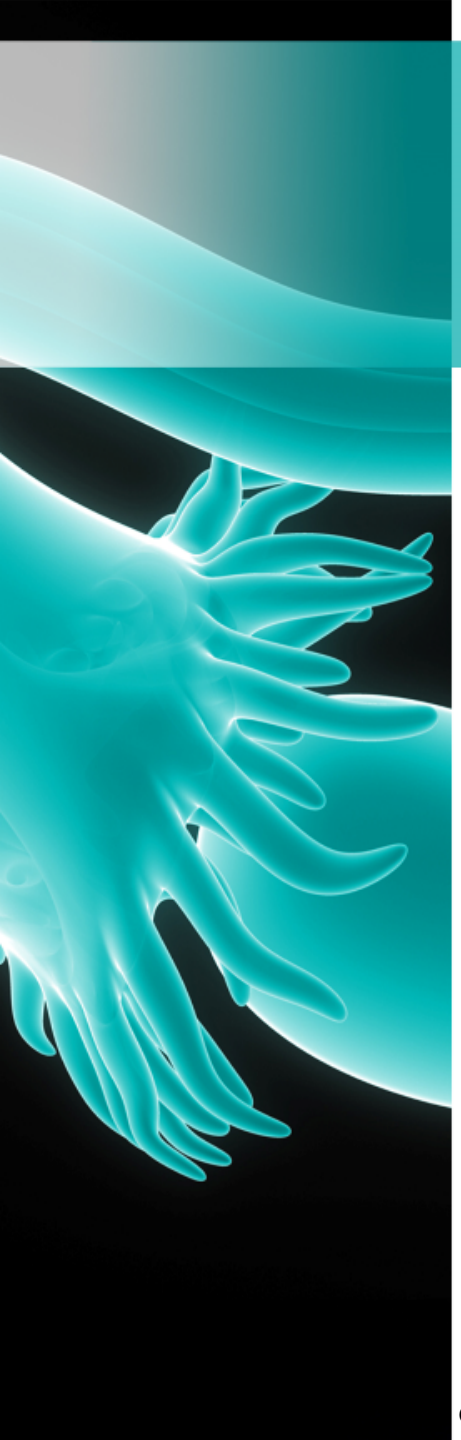


PARP Inhibitors: Upfront Maintenance

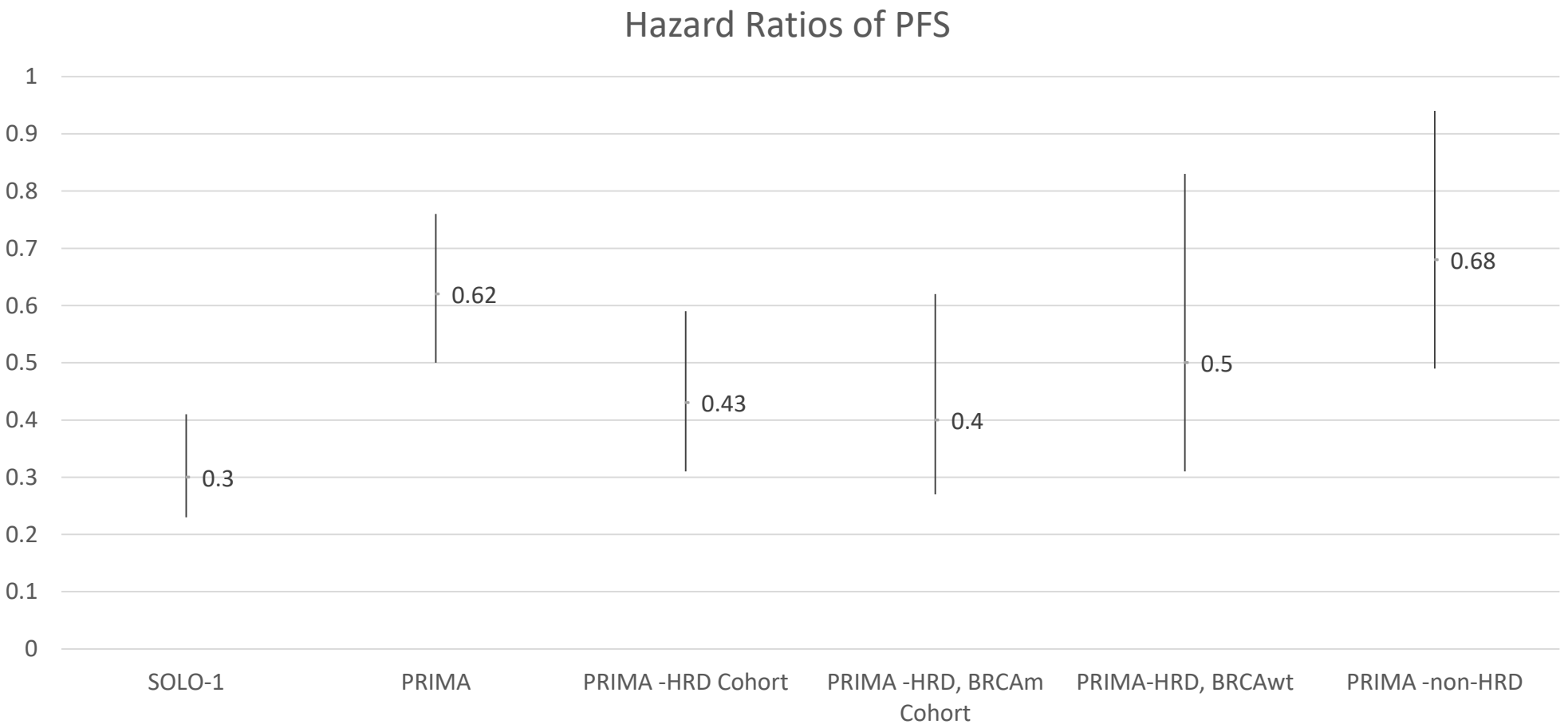
- SOLO-1
  - Partial response after platinum-based chemotherapy (18%)
  - Patients did not receive neoadjuvant therapy
  - Received olaparib for 24 months

- PRIMA - subgroups
  - Patients who received neoadjuvant therapy (66.7%)
    - PFS: 13.9 vs. 8.2 months; HR: 0.59; 95% CI: 0.46-0.76
  - Partial response after platinum-based chemotherapy (30.8%)
    - PFS: 16.4 vs. 9.5 months; HR: 0.6; 95% CI: 0.46-0.77
  - Received niraparib for 36 months

Gonzalez-Martin A, et al. *N Engl J Med*. 2019;381(25):2391-402.; Moore K, et al. *N Engl J Med*. 2018;379(26):2495-505.



PARP Inhibitors: Upfront Maintenance



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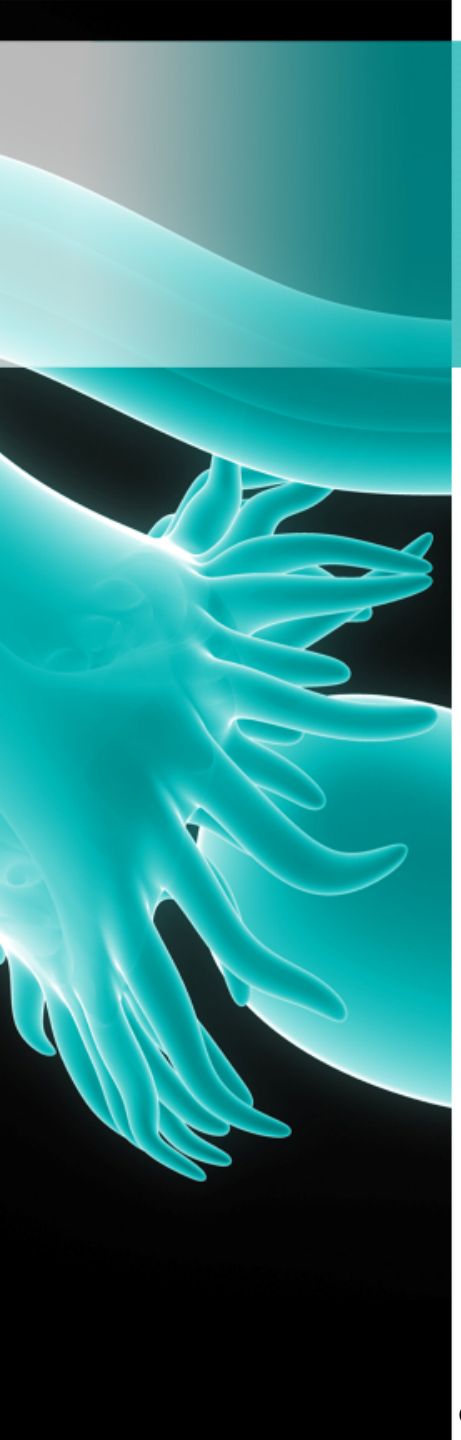
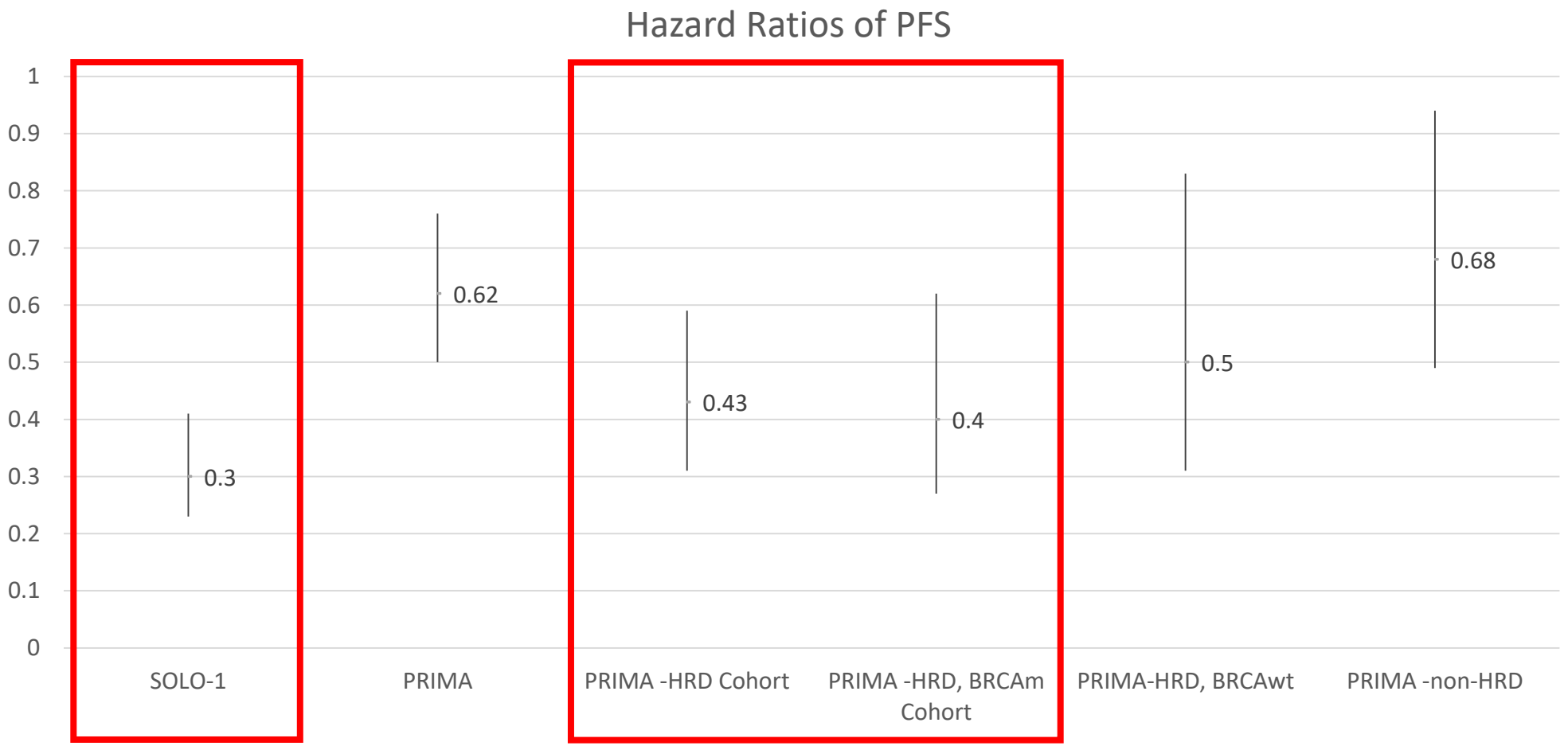
PARP Inhibitors: Upfront Maintenance





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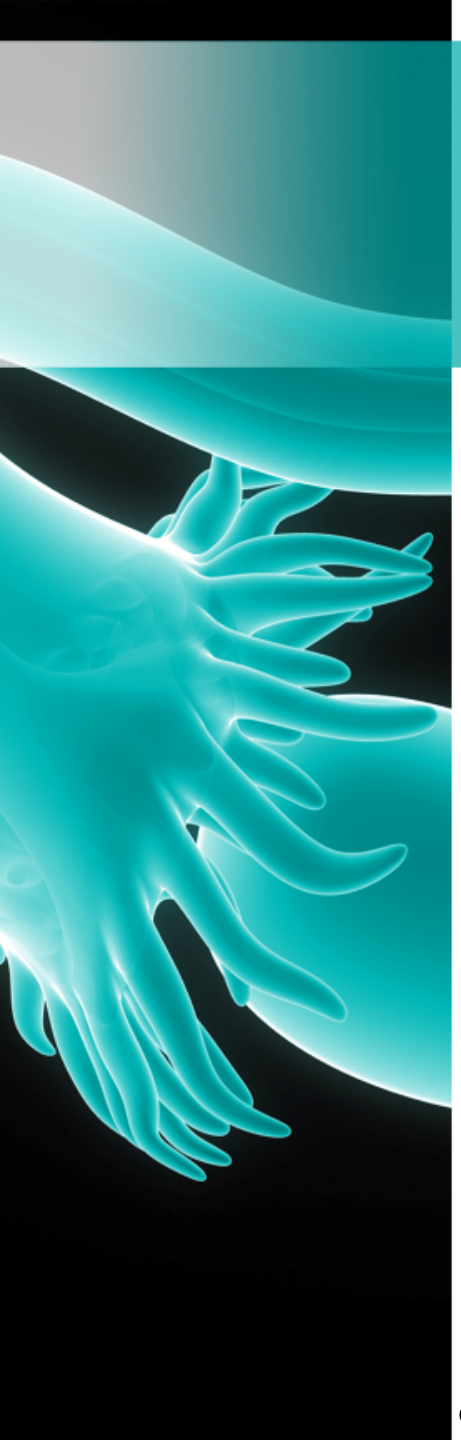
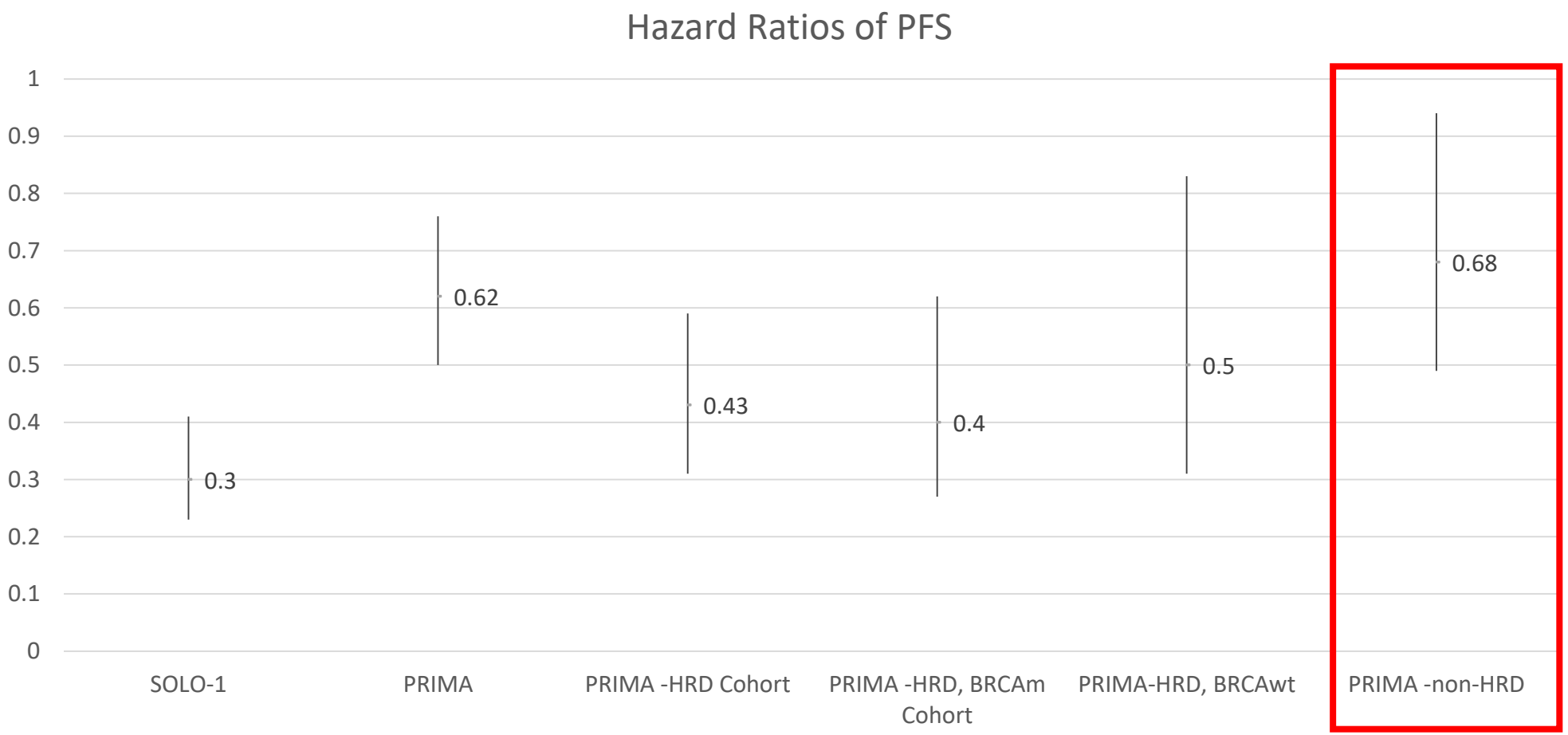
PARP Inhibitors: Upfront Maintenance

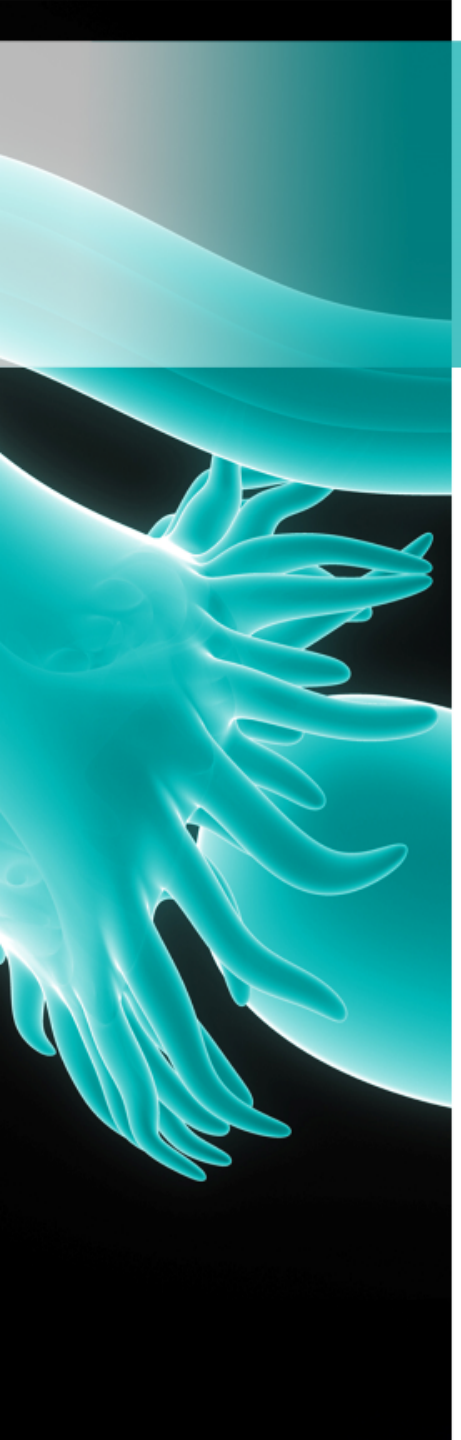




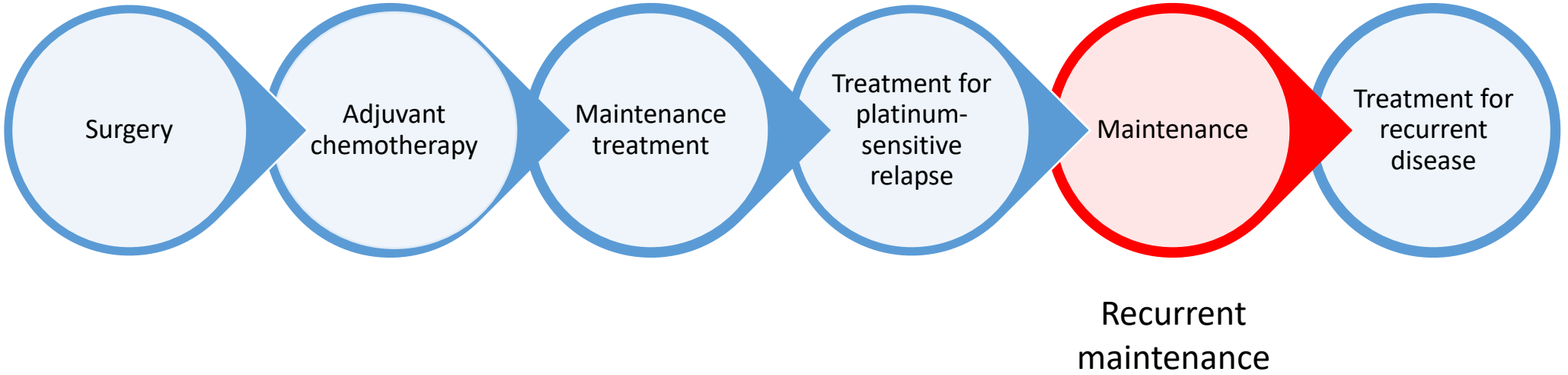
Gonzalez-Martin A, et al. *N Engl J Med*. 2019;381(25):2391-402.; Moore K, et al. *N Engl J Med*. 2018;379(26):2495-505.

Summary: Upfront Maintenance

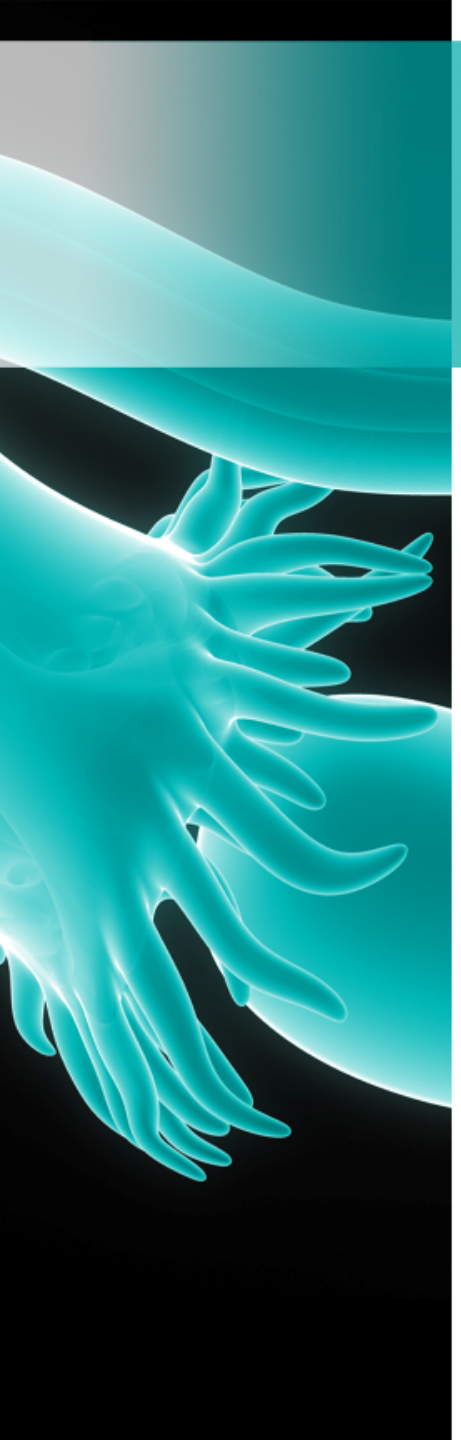
- Use of PARPi in the upfront maintenance setting decreases risk for progression by 60-70% in patients who are HRD
- For non-HRD patients, there was a benefit for patients on niraparib and decreased risk for progression by ~30%
- Both olaparib and niraparib are approved in this setting
- Olaparib monotherapy is only approved for BRCA mutated patients



Treatment Course



Lafargue CJ, et al. *Lancet Oncol*. 2019;20(1):e15-28.



PARP Inhibitor Trials in Ovarian Cancer

Upfront maintenance

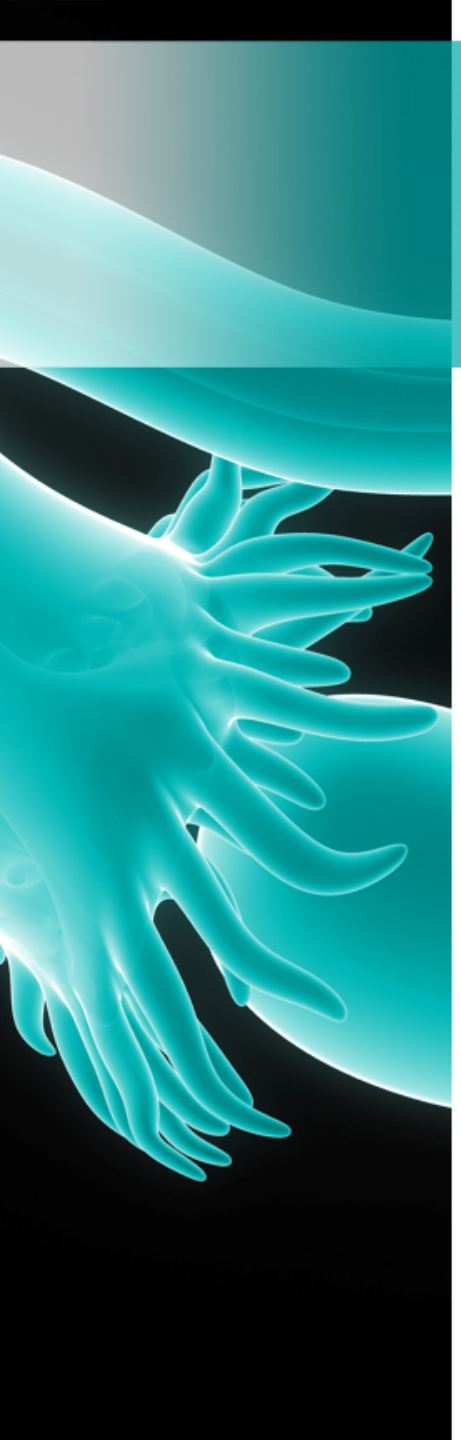
- SOLO-1
  Olaparib
- PRIMA
  Niraparib

Recurrent maintenance

- SOLO-2, Study 19
  Olaparib
- ARIEL3
  Rucaparib
- NOVA
  Niraparib

Treatment

- Study 42, SOLO-3
  Olaparib
- Study 10
  Rucaparib
- QUADRA
  Niraparib



PARP Inhibitors: Recurrent Maintenance

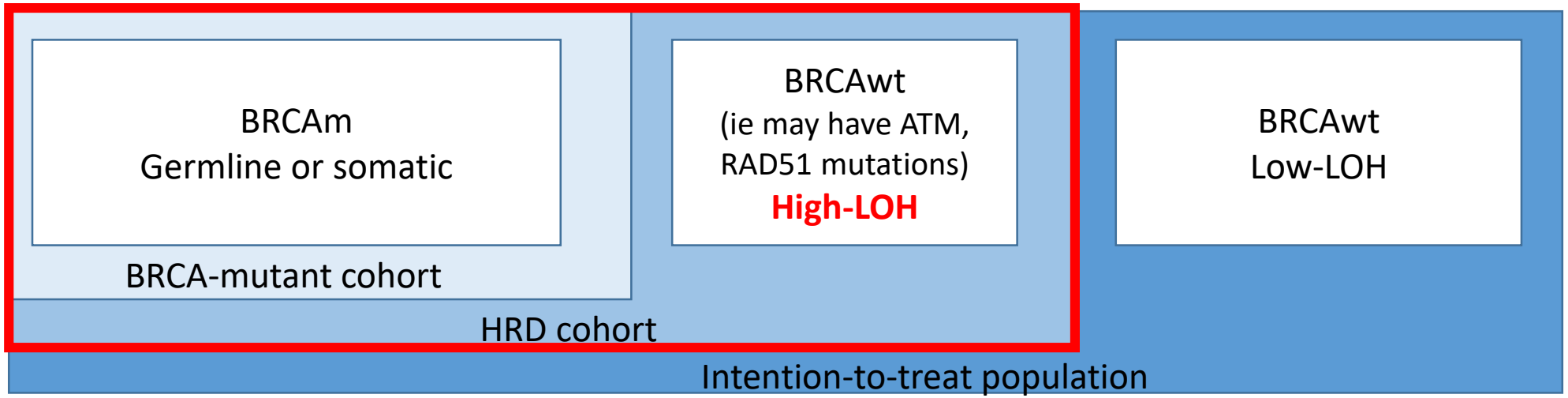
SOLO-2	ARIEL3	NOVA
Olaparib	Rucaparib	Niraparib
Randomized, double blind phase III		
Olaparib 300 mg BID vs. placebo	Rucaparib 600 mg BID vs. placebo	Niraparib 300 mg QD vs. placebo
Maintenance treatment of platinum-sensitive recurrent ovarian cancer after response to platinum-based chemo		
BRCA1 or BRCA2 mutated	Regardless of HRD	Regardless of HRD

Coleman RL, et al. *Lancet*. 2017;390(10106):1949-61.;
Mirza MR, et al. *N Engl J Med*. 2016;375(22):2154-64.;
Pujade-Lauraine E, et al. *Lancet Oncol*. 2017;18(9):1274-84.

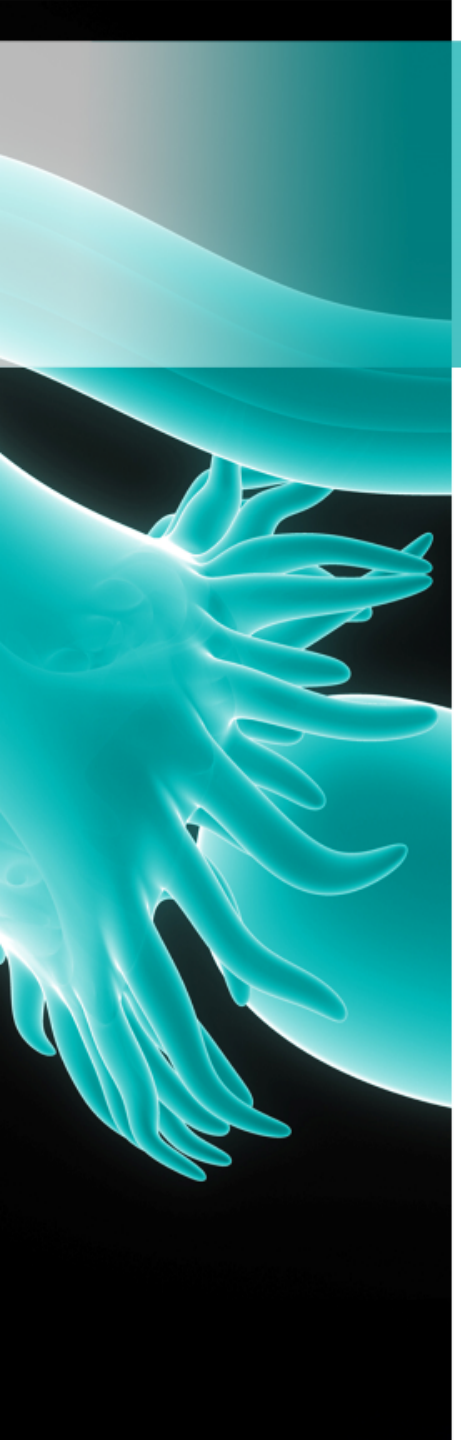
PARP Inhibitors: Recurrent Maintenance

- ARIEL3 trial used loss of heterozygosity (LOH) to identify HRD subgroups

- LOH > 16% considered LOH-high
  - Phenotypically resemble HRD population



Swisher EM, et al. *Lancet Oncol*. 2017;18(1):75-87.



PARP Inhibitors: Recurrent Maintenance

SOLO-2

- Olaparib
- PFS: 19.1 vs. 5.5 months favoring olaparib (HR: 0.3)

ARIEL3

- Rucaparib
- PFS: 10.8 vs. 5.4 m (HR: 0.36)
- *BRCAm* – PFS: 16.6 vs. 5.4 m (HR: 0.23)
- HRD: 13.6 vs. 5.4 m (HR: 0.32)
- PFS benefit in all arms

NOVA

- Niraparib
- *BRCAm* – PFS: 21 vs. 5.5 m (HR: 0.27)
- HRD, non-*BRCAm* – PFS: 12.9 vs. 3.8 m (HR: 0.38)
- Non-*BRCAm* – PFS: 9.3 vs. 3.9 m (HR: 0.45)
- PFS benefit in all arms

Response to PARPi is driven by HRD tumors

Coleman RL, et al. *Lancet*. 2017;390(10106):1949-61.;
Mirza MR, et al. *N Engl J Med*. 2016;375(22):2154-64.;
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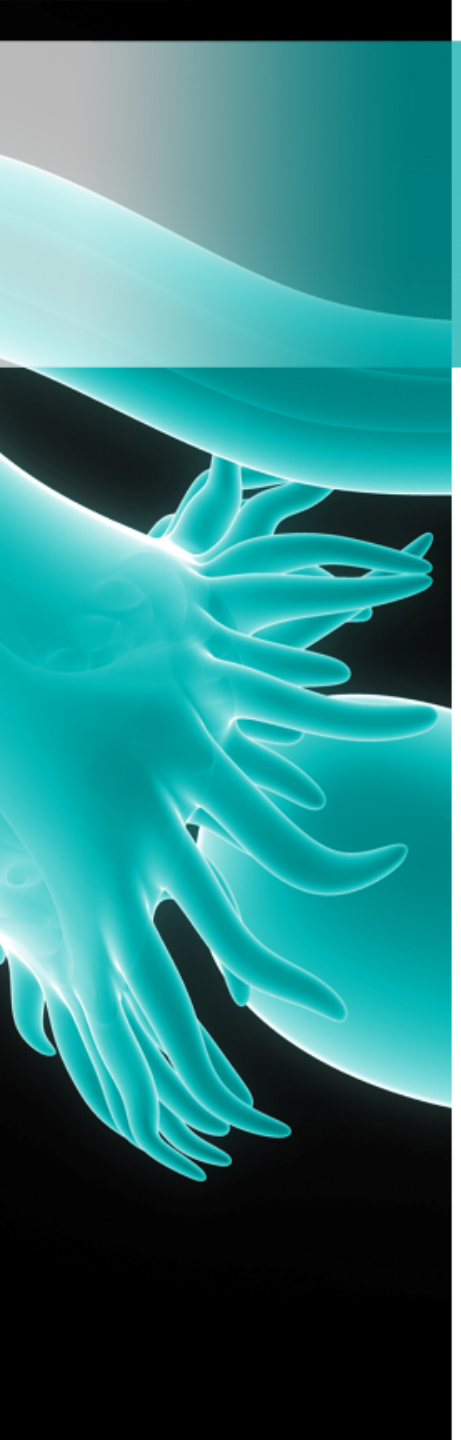
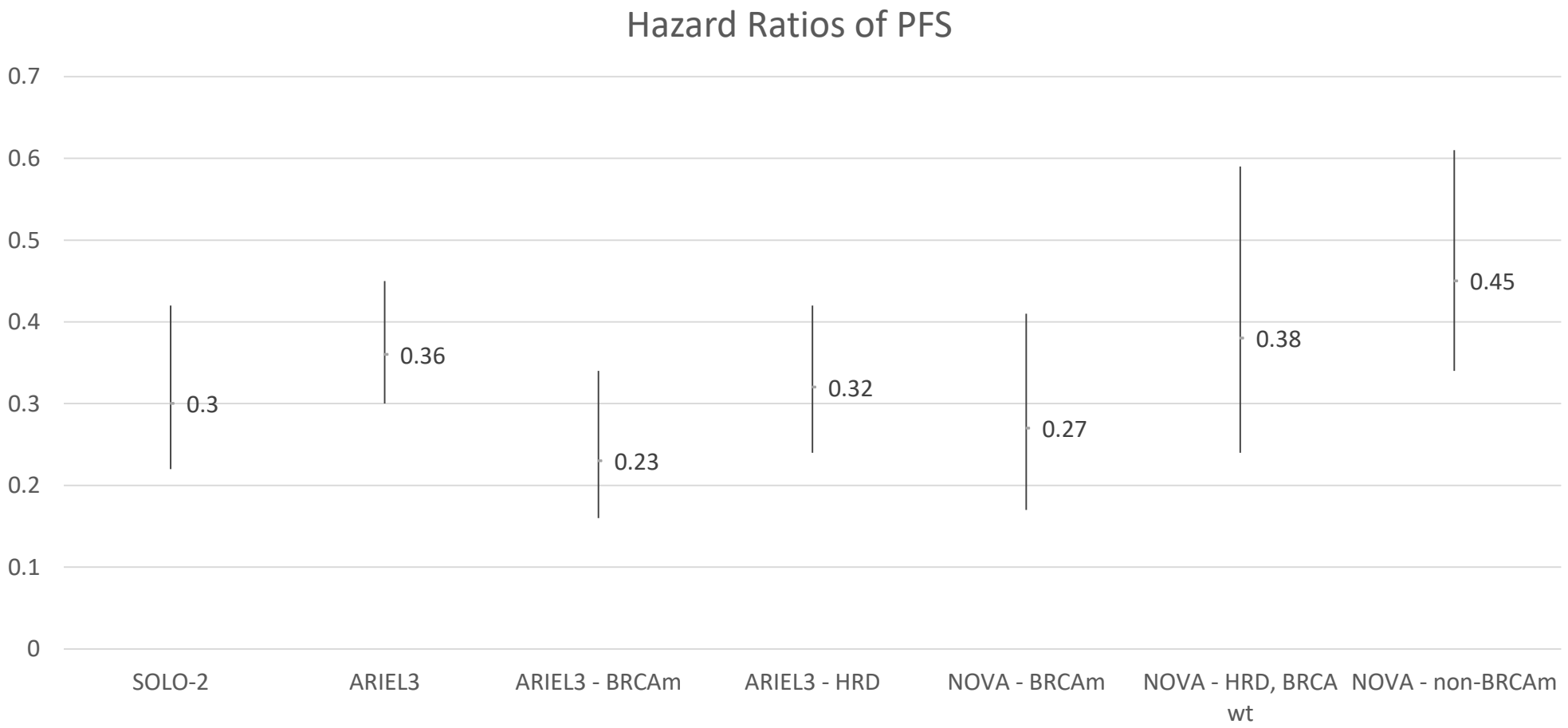


PARP Inhibitors: Recurrent Maintenance



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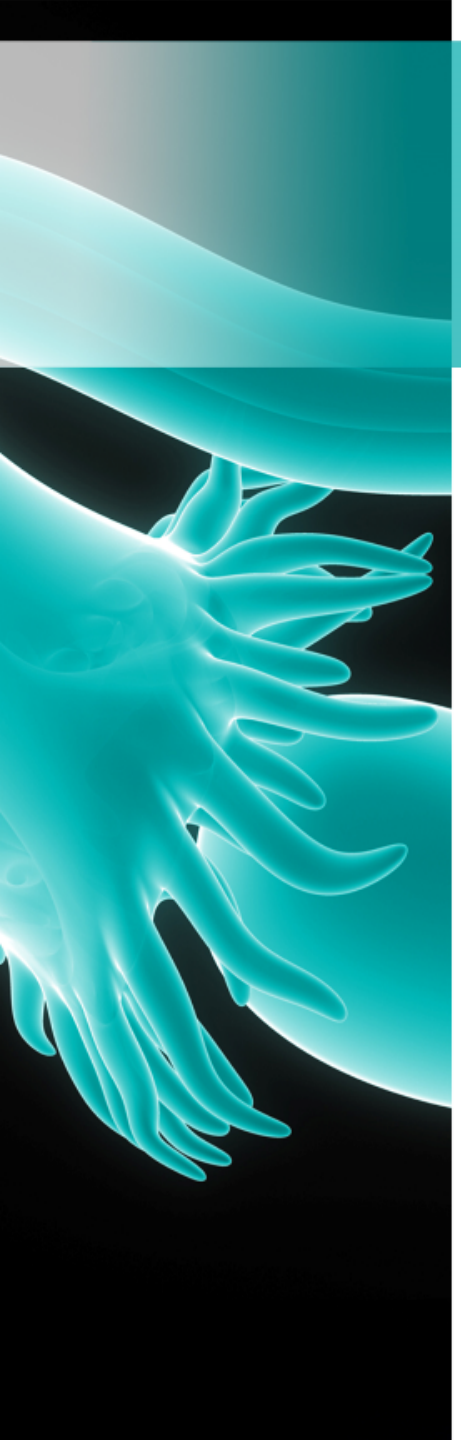
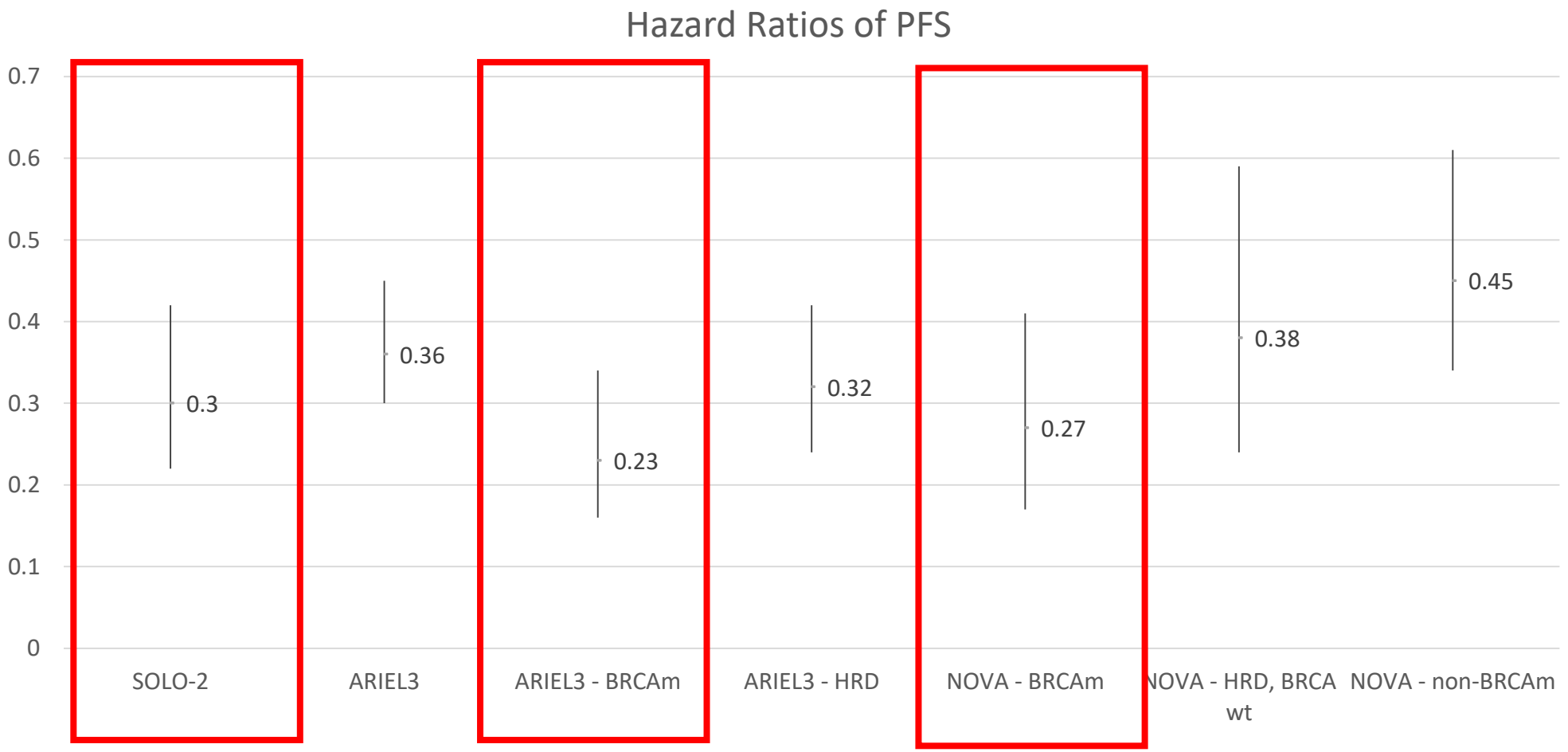
PARP Inhibitors: Recurrent Maintenance





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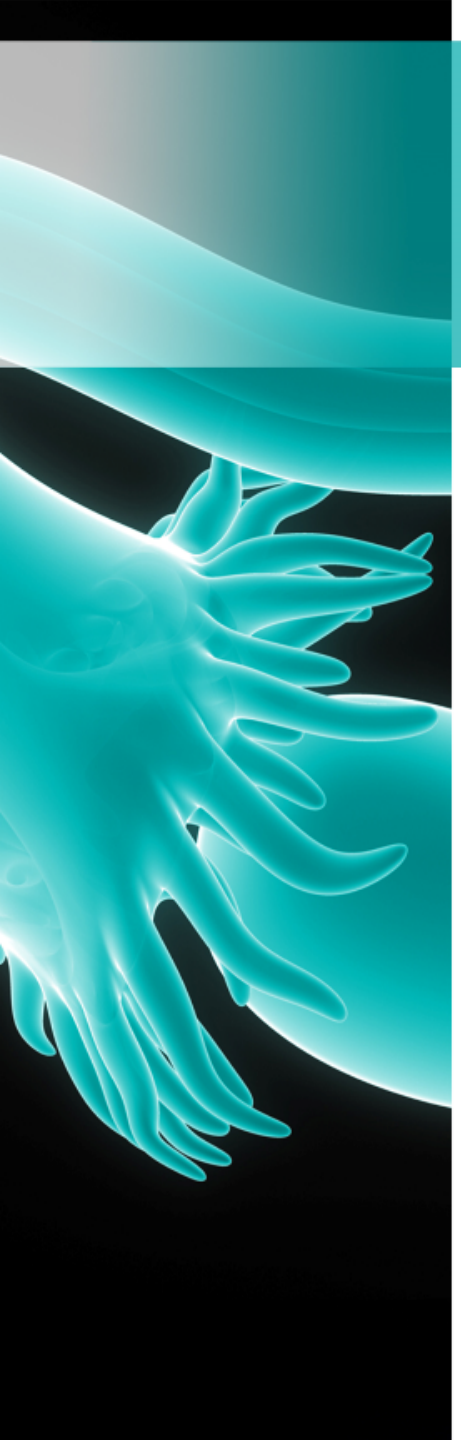


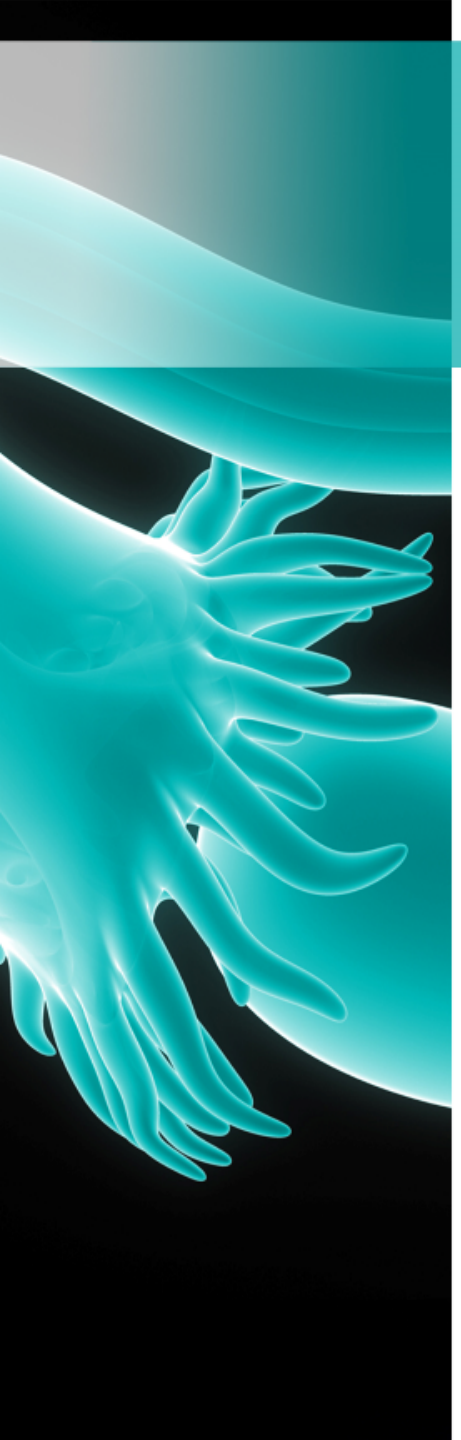
PARP Inhibitors: Recurrent Maintenance

- Study 19 looked at olaparib 400 mg *capsules* BID in recurrent maintenance setting
  - Randomized, phase II trial
  - Long-term survival follow-up data

N=265	Olaparib (n=136)	Placebo (n=129)	Hazard ratio
PFS	8.4 months	4.8 months	0.35 [95% CI: 0.25-0.49], p<0.001
OS	29.8 months	27.8 months	0.73 [95% CI: 0.55-0.95], p=0.02 (NS)
OS – *BRCAm*	34.9 months	30.2 months	0.62 [95% CI: 0.42-0.93], p=0.02
OS – *BRCAwt*	24.5 months	26.6 months	0.82 [95% CI: 0.57-1.25], p=0.4

Friedlander M, et al. *Br J Cancer*. 2018;119(9):1075-85.; Ledermann J, et al. *N Engl J Med*. 2012;366(15):1382-92.

OS, overall survival. NS, not significant



PARP Inhibitors: Recurrent Maintenance

- Study 19 secondary endpoints

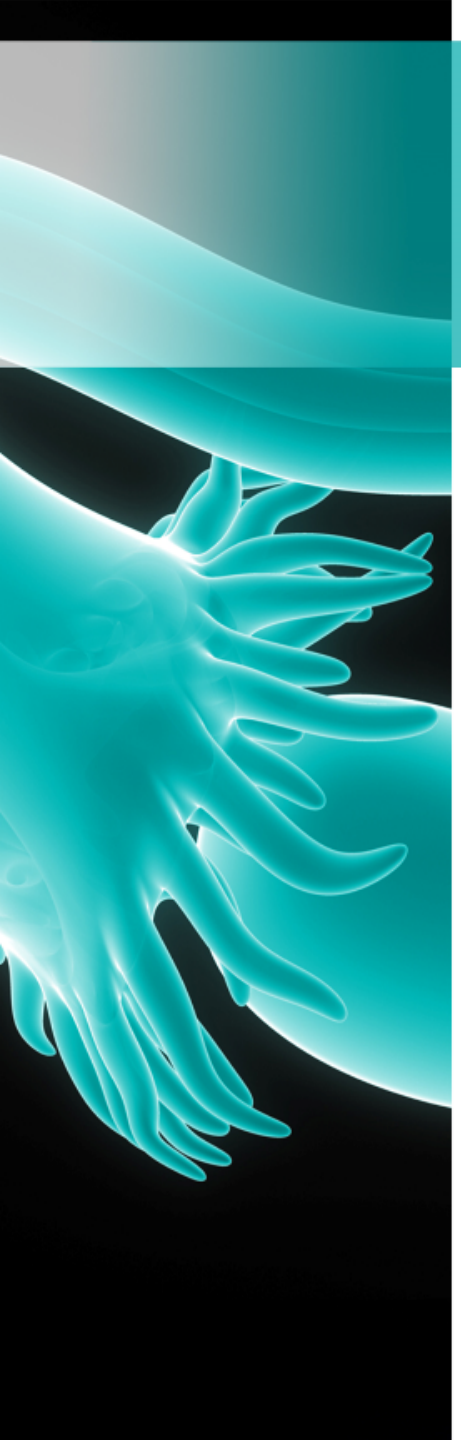
N=265	Olaparib (n=136)	Placebo (n=129)	Hazard ratio
TFST	13.3 months	6.7 months	0.39 [95% CI: 0.3-0.52], p<0.00001
TFST, BRCAm	15.6 months	6.2 months	0.33 [95% CI: 0.22-0.49], p<0.00001
TSST	19.1 months	14.8 months	0.53 [95% CI: 0.4-0.69], p<0.00001
TSST, BRCAm	21.4 months	15.3 months	0.43 [95% CI: 0.29-0.64], p<0.00003

Friedlander M, et al. *Br J Cancer*. 2018;119(9):1075-85.; Ledermann J, et al. *N Engl J Med*. 2012;366(15):1382-92.

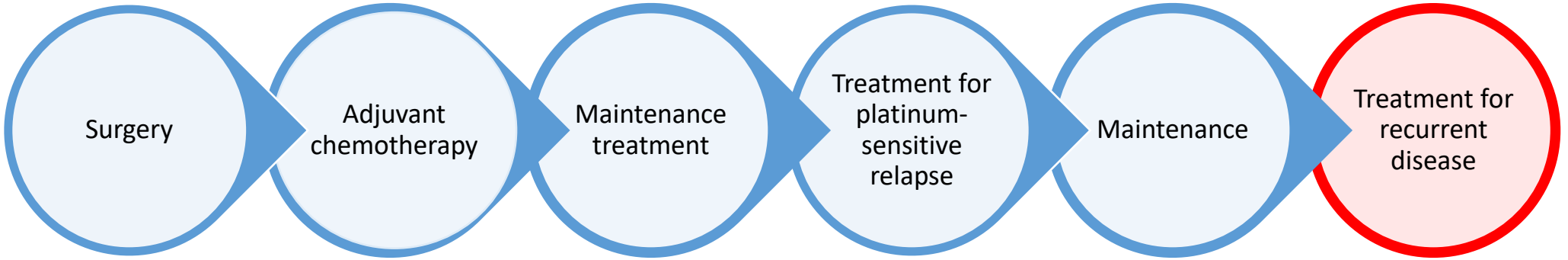
TFST, time to first subsequent therapy;
TSST, time to second subsequent therapy.

Summary: Recurrent Maintenance

- Use of PARPi in the recurrent maintenance setting decreases risk for progression by 60-70% in patients who are HRD
- For non-HRD patients, there was a benefit for patients on niraparib and rucaparib
- All three agents are approved in this setting regardless of HRD.



Treatment Course



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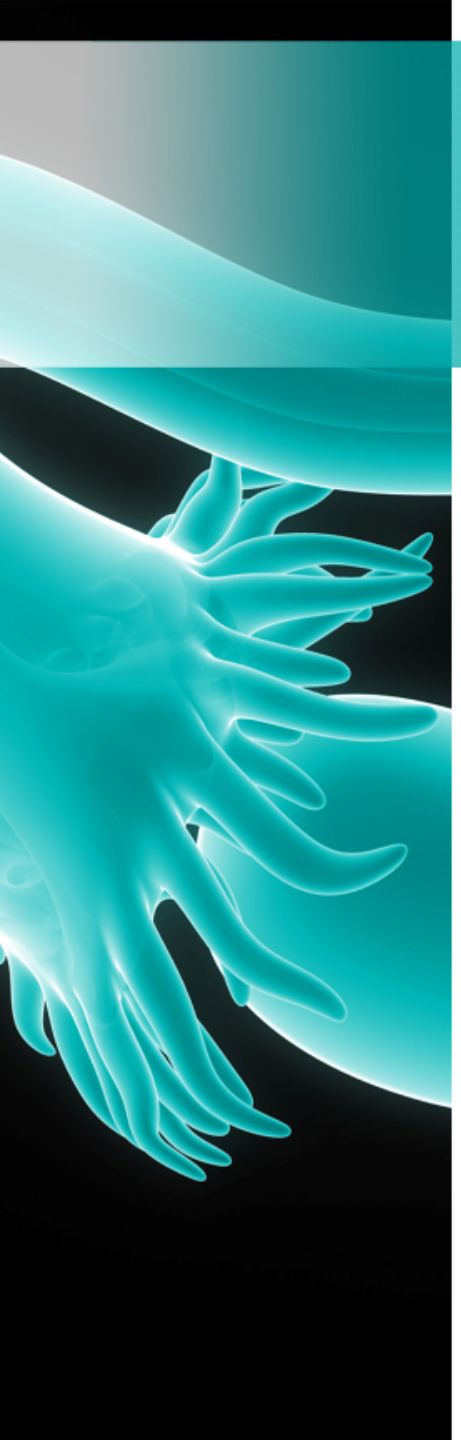

PARP Inhibitor Trials in Ovarian Cancer

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- SOLO-1 Olaparib
- PRIMA Niraparib

Recurrent maintenance

- SOLO-2, Study 19 Olaparib
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Treatment

- Study 42, SOLO-3 Olaparib
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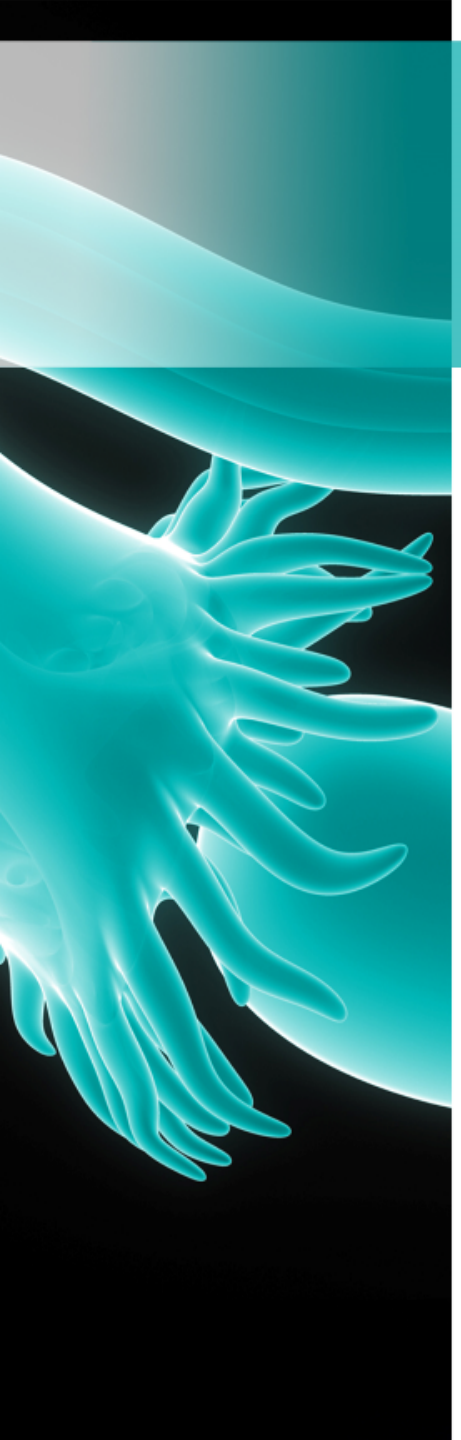
- QUADRA Niraparib



PARP Inhibitors: Treatment

Study 42

- Olaparib
- Single-arm, phase II
- Olaparib 300 mg BID vs. placebo
- Platinum-resistant ovarian cancer; breast and prostate cancer
- BRCA1 or BRCA2 mutated

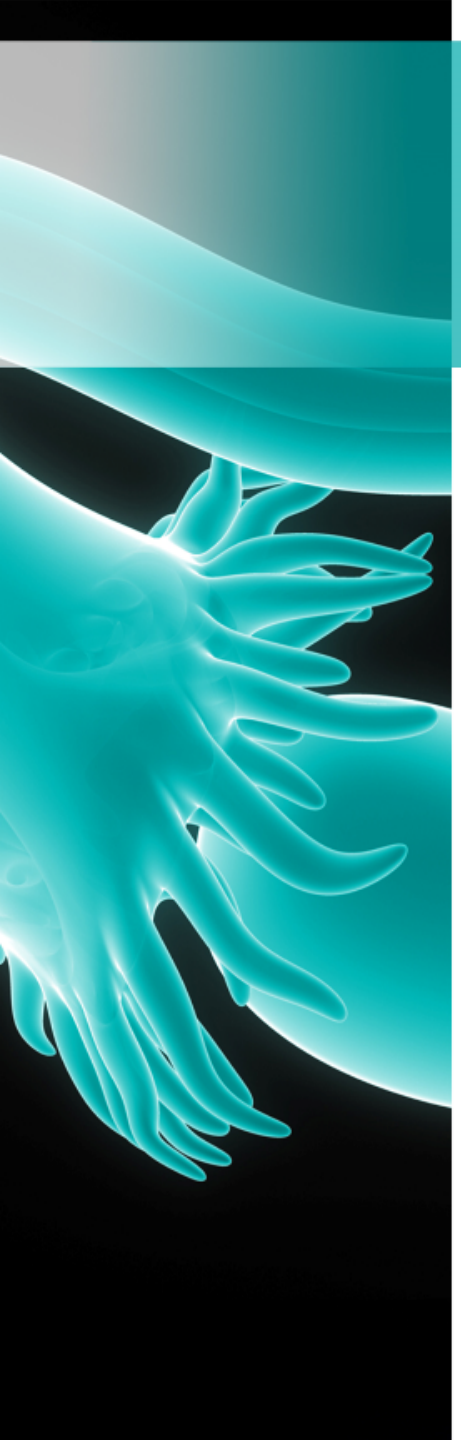
Study 10

- Rucaparib
- Single arm, dose finding, phase I-II
- Rucaparib 600 mg BID vs. placebo
- Platinum-sensitive ovarian cancer after 2-4 lines of therapy
- BRCA1 or BRCA2 mutated
  Phase 2A expansion

QUADRA

- Niraparib
- Single-arm, phase II
- Niraparib 300 mg QD vs. placebo
- Relapsed ovarian cancer after 3+ chemo regimens
- Regardless of HRD

Kaufman B, et al. *J Clin Oncol*. 2015;33(3):244-50.;
Kristeleit R, et al. *Clin Cancer Res*. 2017;23(15):4095-106.;
Moore KN, et al. *Lancet Oncol*. 2019;20(5):636-48.



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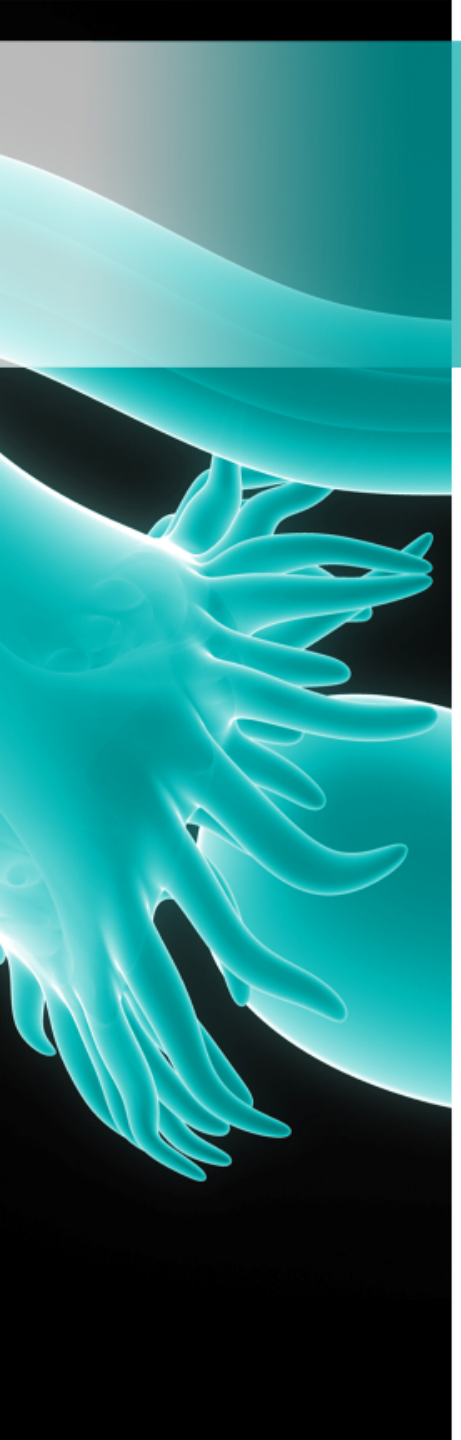

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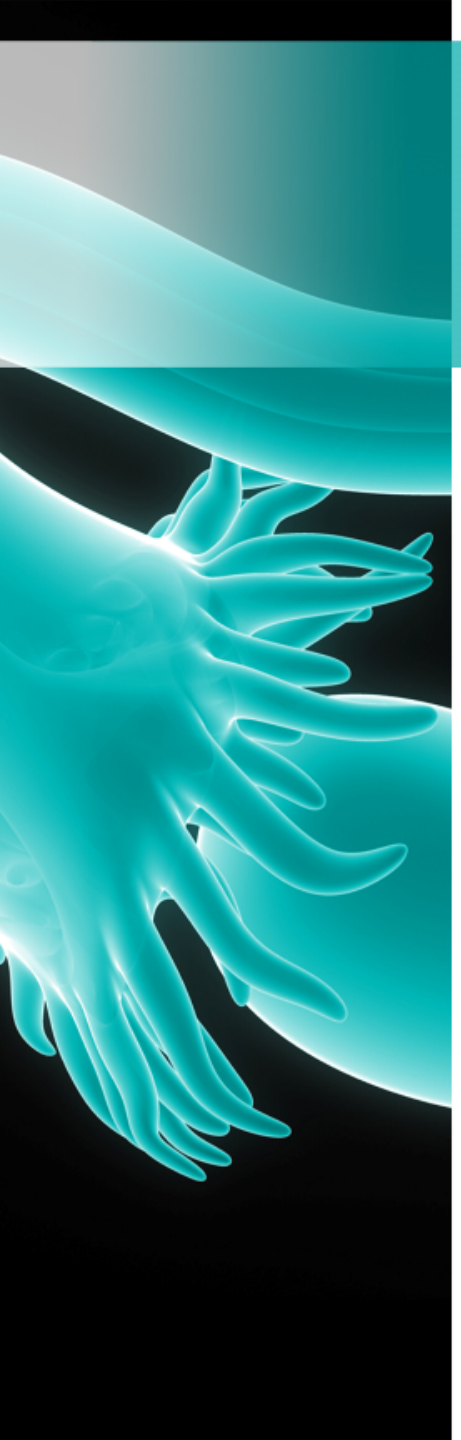


PARP Inhibitors: Treatment

Study 42

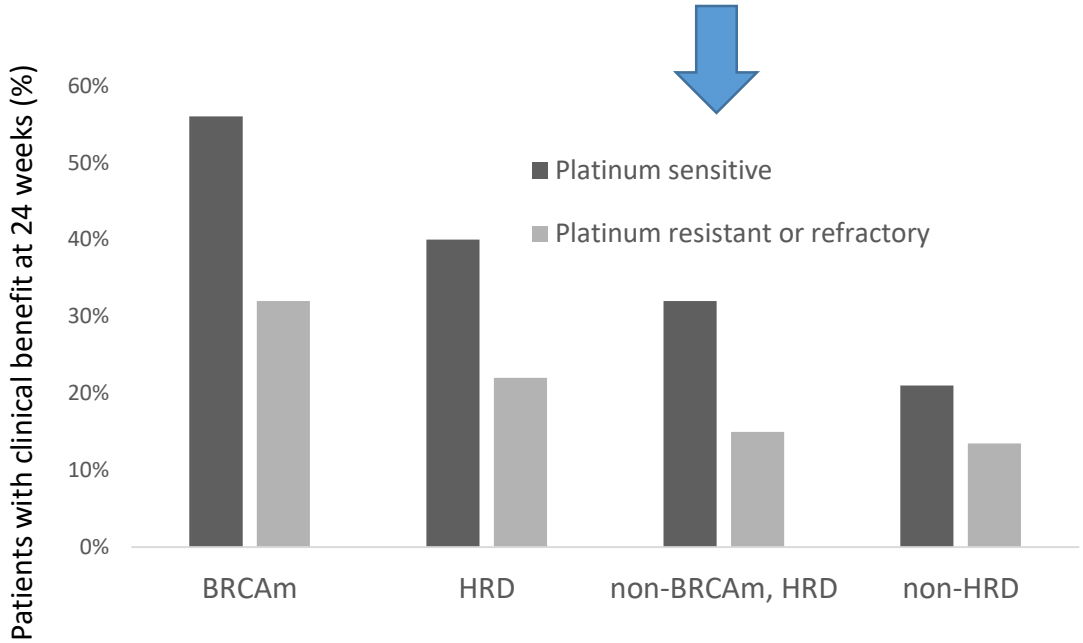
- Olaparib
- Tumor response rate: 31.1%

Study 10

- Rucaparib
- ORR: 59.5%

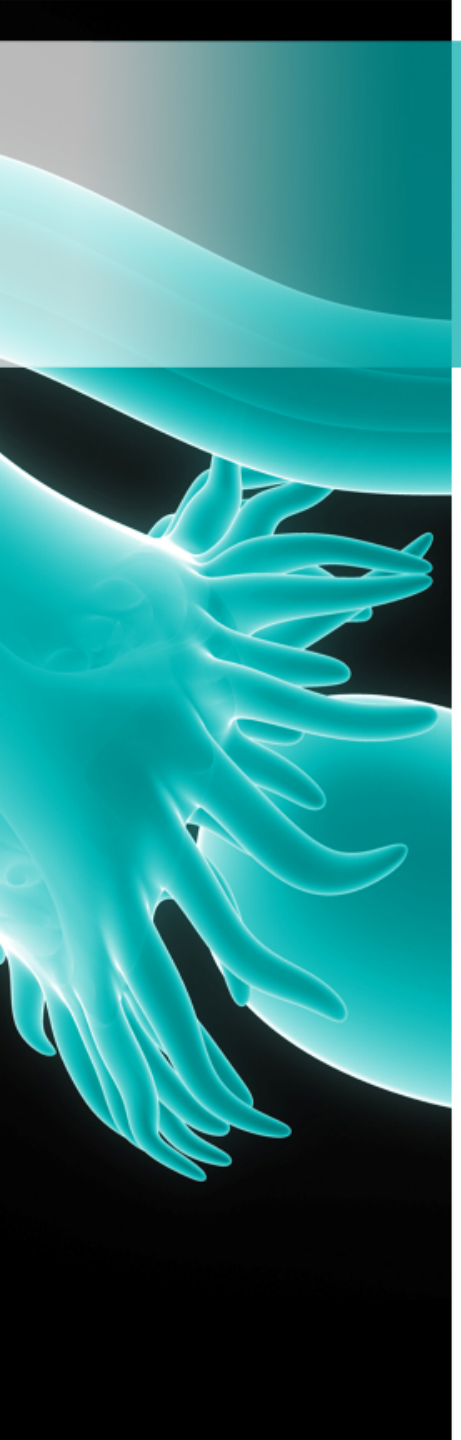
QUADRA

- Niraparib
- ORR: 34% in *BRCAm* patients



Kaufman B, et al. *J Clin Oncol*. 2015;33(3):244-50.;
Kristeleit R, et al. *Clin Cancer Res*. 2017;23(15):4095-106.;
Moore KN, et al. *Lancet Oncol*. 2019;20(5):636-48.

ORR, overall response rate.



PARP Inhibitors: Treatment

- SOLO3 looked at olaparib vs. physician's choice, single-agent non-platinum chemotherapy
  - Randomized, open-label, phase III
  - *BRCAm*, platinum-sensitive relapsed ovarian cancer after 2 prior lines of platinum-based chemotherapy
  - Liposomal doxorubicin, paclitaxel, topotecan, gemcitabine

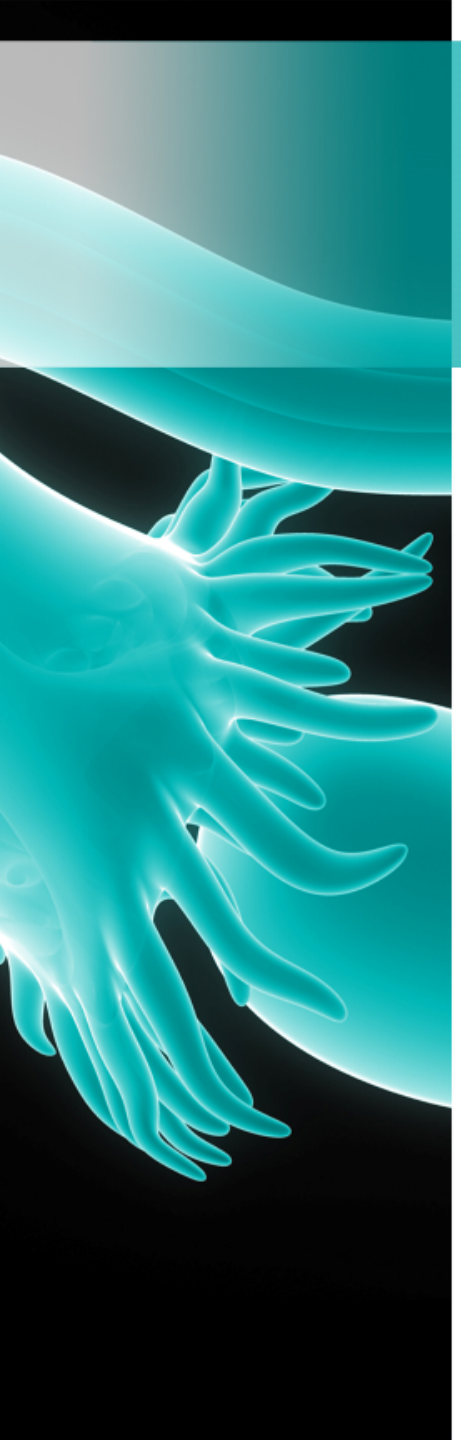
N=266	Olaparib (n=178)	Chemotherapy (n=88)	OR/HR
ORR	72.2%	51.4%	OR: 2.53 [95% CI: 1.4-4.58], p<0.002
PFS	13.4 months	9.2 months	HR: 0.62 [95% CI: 0.43-0.91], p=0.013

Friedlander M, et al. *Br J Cancer*. 2018;119(9):1075-85.; Ledermann J, et al. *N Engl J Med*. 2012;366(15):1382-92.

OR, odds ratio; ORR, objective response rate.

Summary: Treatment

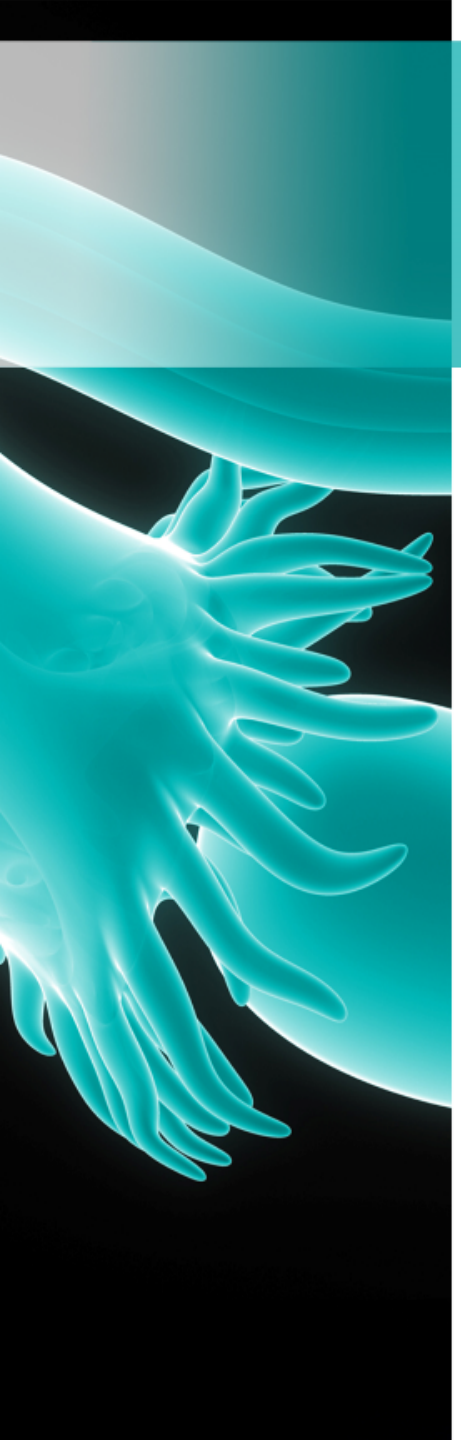
- All three PARPi are approved in this setting
- Benefit is driven by HRD patients and patients who are platinum-sensitive



Combination Therapy with PARP Inhibitors

- PARPi + bevacizumab maintenance
- PARPi + chemo followed by maintenance PARPi
- PARPi + immunotherapy

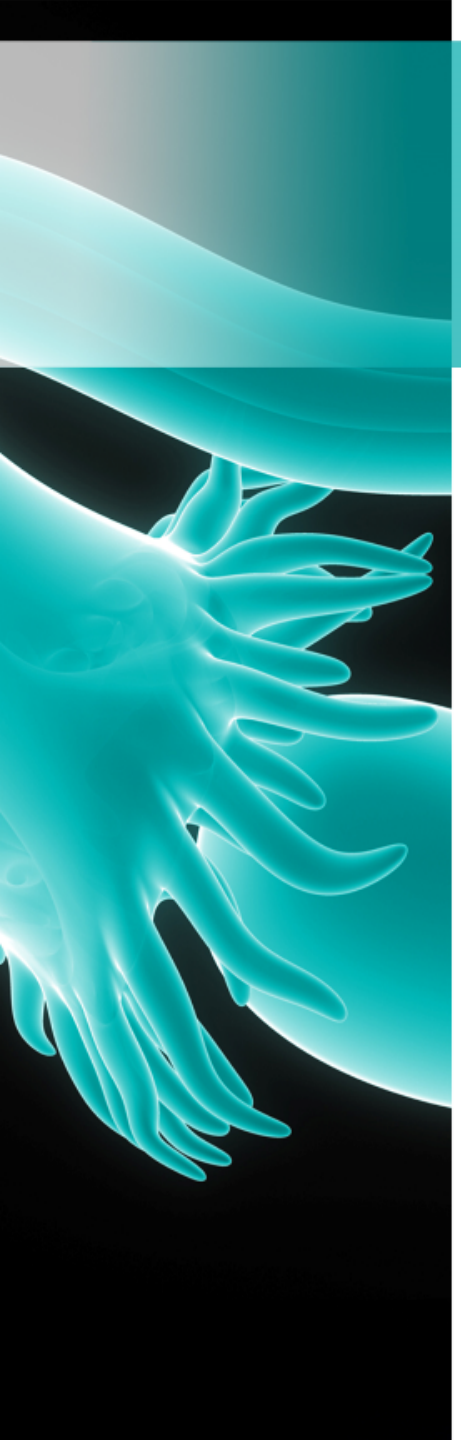
Coleman RL, et al. *N Engl J Med*. 2019;381(25):2403-15.;
Mirza MR, et al. *Lancet Oncol*. 2019;20(10):1409-19.;
Ray-Coquard I, et al. *N Engl J Med*. 2019;381(25):2416-28.



PARP Inhibitor + Bevacizumab

	PAOLA-1	AVANOVA
	Olaparib	Niraparib
	Randomized, double-blind phase III	Randomized, open-label phase II
	Olaparib 300 mg BID vs. placebo, with bevacizumab 15 mg/kg Q3 weeks for 15 months	Niraparib 300 mg QD +/- bevacizumab 15 mg/kg Q3 weeks until progression
	After first-line platinum-based chemo with bevacizumab	For recurrent, platinum-sensitive ovarian cancer; allowed prior PARPi or bevacizumab
	Regardless of HRD	Regardless of HRD

Mirza MR, et al. *Lancet Oncol*. 2019;20(10):1409-19.; Ray-Coquard I, et al. *N Engl J Med*. 2019;381(25):2416-28.



PARP Inhibitor + Bevacizumab

PAOLA-1

Olaparib

- PFS: 22.1 vs. 16.6 months favoring combination therapy
- PFS (*BRCAm*): 37.2 vs. 17.7 months favoring combination therapy
- PFS (HRD, *BRCAwt*): 28.1 vs. 16.6 months favoring combination therapy
- PFS (non-HRD): 16.9 vs. 16 months (NS)

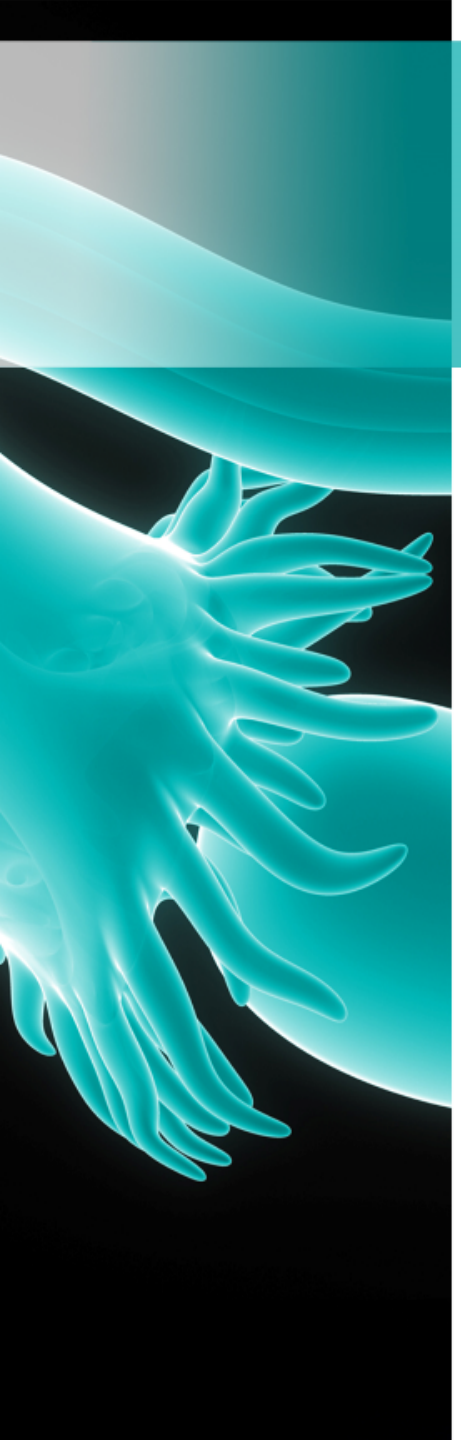
AVANOVA

Niraparib

- PFS: 11.9 vs. 5.5 months favoring combination therapy
- PFS (*BRCAm*): 14.4 vs. 9 months (NS)
- PFS (HRD): 11.9 vs. 6.1 months favoring combination therapy
- PFS (non-HRD): 11.3 vs. 4.2 months favoring combination therapy

Mirza MR, et al. *Lancet Oncol*. 2019;20(10):1409-19.; Ray-Coquard I, et al. *N Engl J Med*. 2019;381(25):2416-28.

NS, not significant.

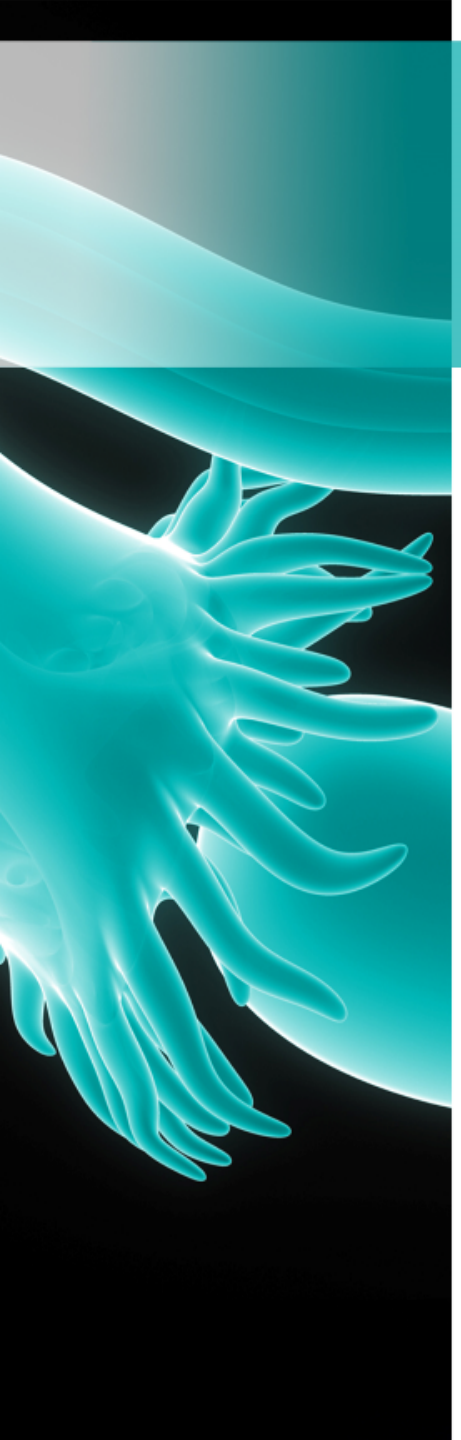


PARP Inhibitor + Bevacizumab

Adverse effects

- PAOLA-1 vs. SOLO1 trial
  - More hypertension with the addition of bevacizumab to olaparib
- AVANOVA
  - More hypertension and proteinuria in the bevacizumab-plus-niraparib arm

Mirza MR, et al. *Lancet Oncol*. 2019;20(10):1409-19.; Ray-Coquard I, et al. *N Engl J Med*. 2019;381(25):2416-28.



PARP Inhibitor + Chemotherapy

VELIA trial

Previously untreated stage III-IV high-grade serous ovarian carcinoma

Chemotherapy:
carboplatin AUC6 +
paclitaxel 175 mg/m^2
Q3 weeks
or 80 mg/m^2 weekly

N=1140

Randomized, phase III

→ Control arm: Chemo Q21 days + placebo followed by placebo maintenance

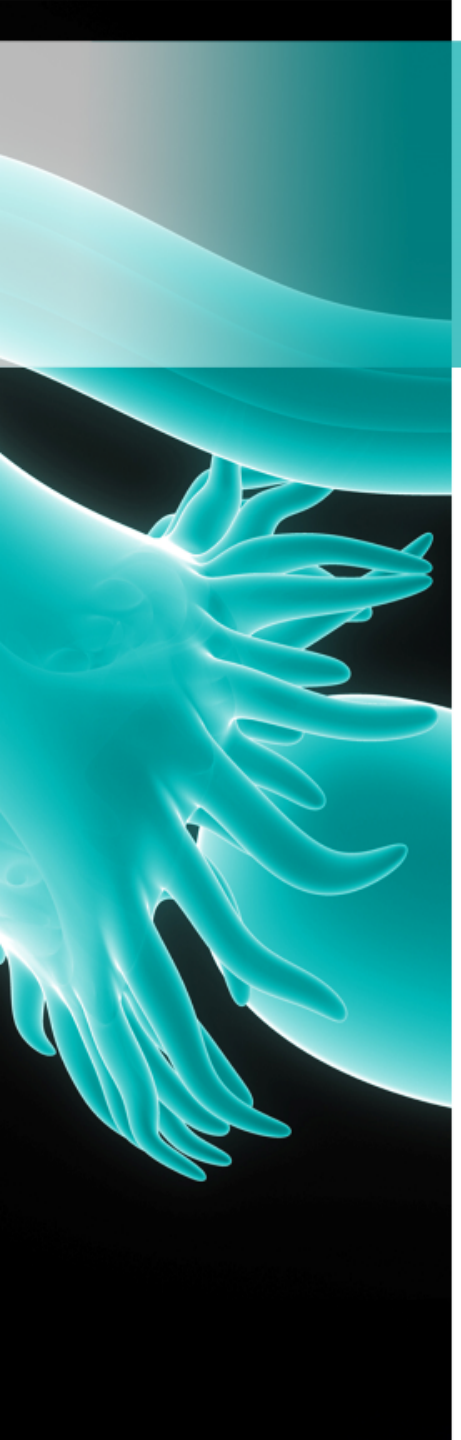
→ Chemo Q21 days + veliparib 150 mg BID followed by placebo maintenance

→ Veliparib-throughout arm:
Chemo Q21 days + veliparib 150 mg BID followed by veliparib 300 mg BID maintenance increasing to 400 mg BID if tolerated

Primary endpoint: PFS

Coleman RL, et al. *N Engl J Med*. 2019;381(25):2403-15.

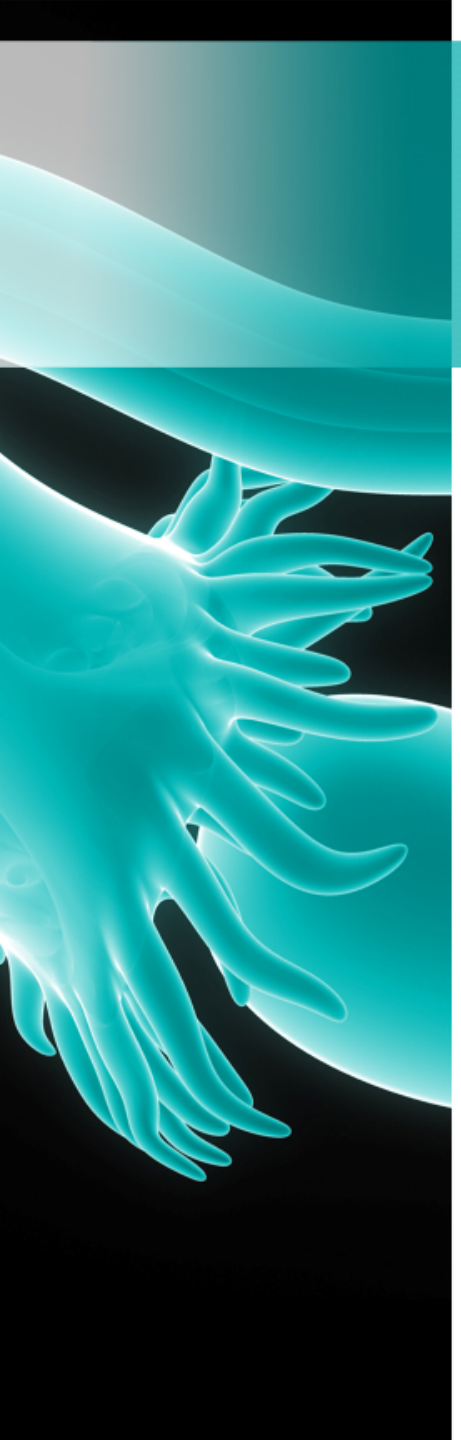
AUC, area under the curve.



PARP Inhibitor + Chemotherapy

- PFS: 23.5 months vs. 17.3 months in veliparib-throughout arm compared to control
  - BRCAm cohort: 34.7 vs. 22 months favoring veliparib-throughout arm
  - HRD cohort: 31.9 vs. 20.5 months favoring veliparib-throughout arm
- Higher incidence of nausea (80%) and thrombocytopenia in the combination phase of veliparib-throughout arm
  - Lower dose intensity in the maintenance phase of veliparib-throughout arm

Coleman RL, et al. *N Engl J Med*. 2019;381(25):2403-15.



PARP Inhibitor + Immunotherapy

TOPACIO-KEYNOTE-162

Advanced or metastatic TNBC or ovarian cancer

Regardless of BRCA mutation status

N=60

Primary endpoint: ORR

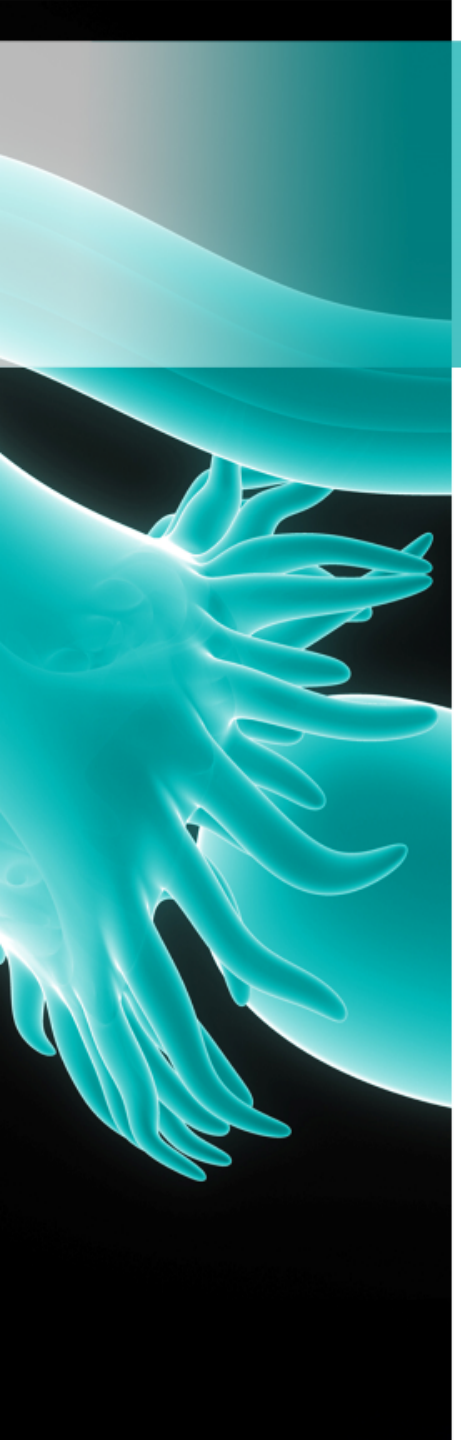
Open-label, single-arm, phase I/II

→ Phase I: Dose-finding arm

→ Phase II:
Niraparib 200 mg QD +
pembrolizumab 200 mg Q3 weeks

Konstantinopoulos PA, et al. *JAMA Oncol*. 2019;5(8):1141-9.

TNBC, triple-negative breast cancer.



PARP Inhibitor + Immunotherapy

- Objective response rate: 18%
- Single-agent PARPi ORR: 0%-5% for patients who were *BRCAwt* or platinum-refractory
- Single-agent PD-1/PD-L1 inhibitors ORR: 4%-10% in platinum-resistant ovarian cancer

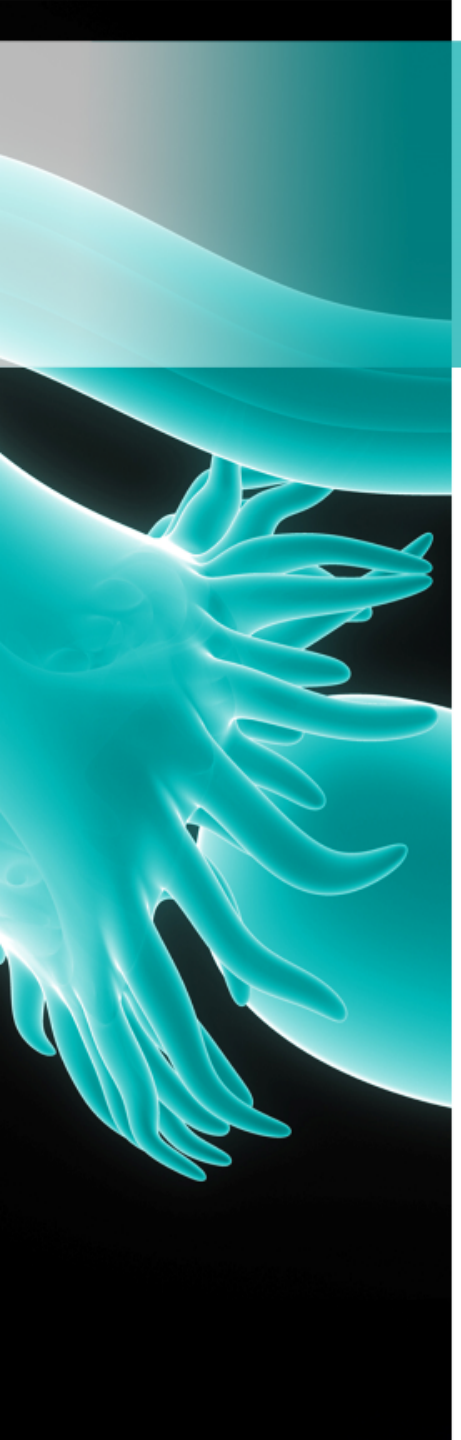
Konstantinopoulos PA, et al. *JAMA Oncol*. 2019;5(8):1141-9.

PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

Summary: Combination Therapy

- PARPi + bevacizumab
  - Difficult to compare – no olaparib maintenance alone arm in PAOLA-1
  - Olaparib + bevacizumab approved in HRD patients
- PARP inhibitor + chemo followed by maintenance PARPi
  - Awaiting FDA approval of veliparib
  - Difficult to compare – no veliparib maintenance alone arm
- PARP inhibitor + immunotherapy
  - More data needed to confirm efficacy and place in therapy
- Consideration for total cost of treatment

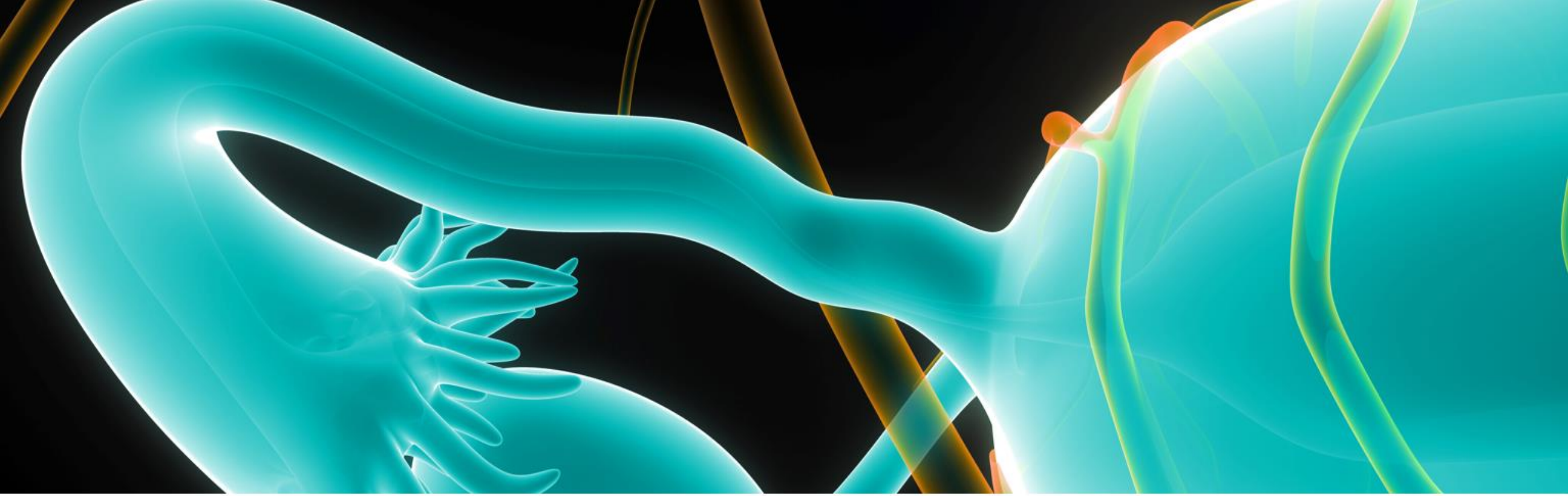
FDA, United States Food and Drug Administration.



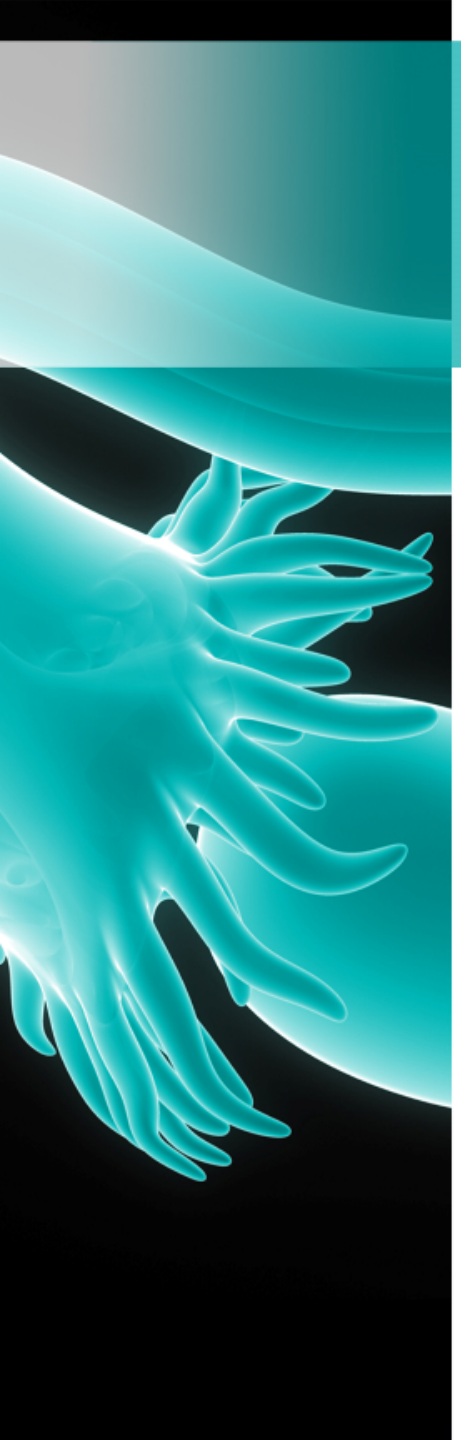
ARS Question #2

SB is 67-year-old woman with ovarian cancer. She was treated with 3 cycles of neoadjuvant carboplatin and paclitaxel followed by optimal debulking surgery. Genetic risk evaluation reveals that she is not *BRCAm* but is HRD. Which PARP inhibitor (or inhibitors) is FDA approved for use in the upfront maintenance setting?

A. Olaparib monotherapy
B. Niraparib and olaparib plus bevacizumab
C. Olaparib monotherapy and niraparib
D. Olaparib monotherapy, niraparib, and rucaparib



PARP Inhibitors in Detail

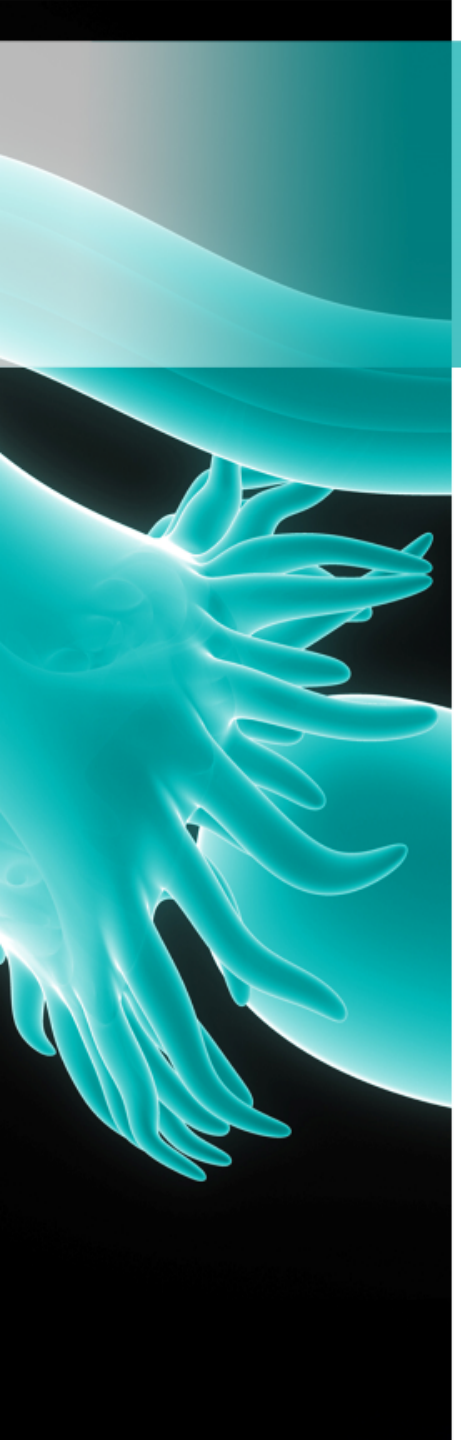


Olaparib

	Olaparib
Target	Pan-PARP inhibitor
Dose	300 mg BID
Dose adjustments	CrCl 31-50 mL/min: 200 mg BID
Class ADR	Nausea, diarrhea, fatigue, bone marrow suppression, secondary malignancy
Unique ADR	Asymptomatic elevation of serum creatinine, hypomagnesemia, pneumonitis
DDIs	Substrate of CYP3A4 (avoid grapefruit juice, Seville oranges, pomegranate) Inhibits MATE1 and MATE2-K
PK	Mean half-life = 14.9 +/- 8.2 hours
Notes	Tablets and capsules are not interchangeable (capsules are phased out)

Antolin AA, et al. *Sci Rep*. 2020;10(1):2585.;
Lynparza [package insert].; 2019.

CrCl, creatinine clearance; CYP, cytochrome P450; DDIs, drug-drug interactions; PK, pharmacokinetics.

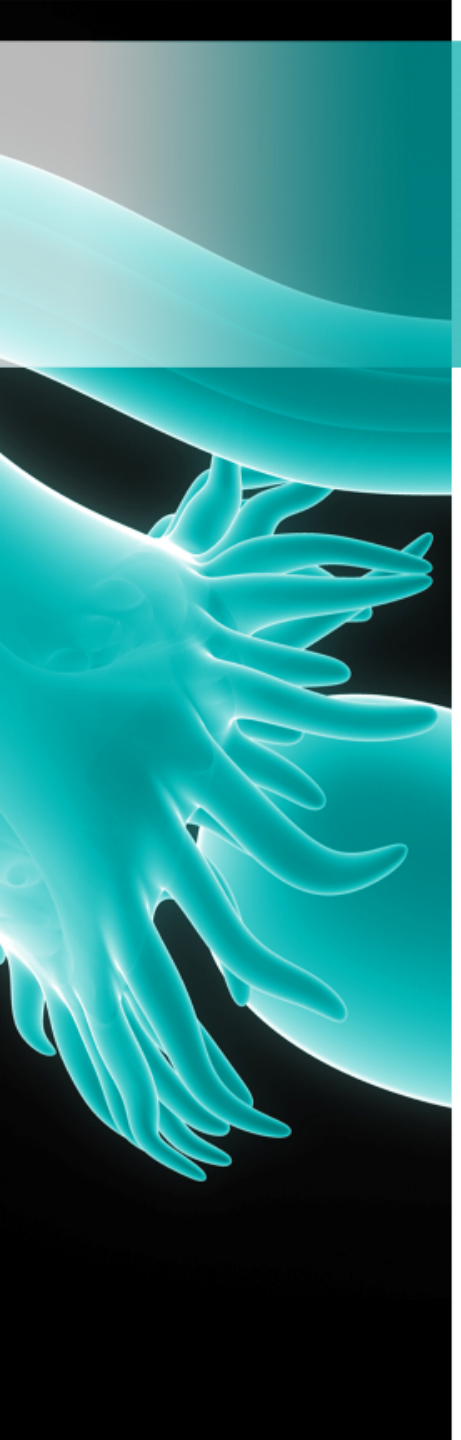


Rucaparib

	Rucaparib
Target	Pan-PARP inhibitor
Dose	600 mg BID
Class ADR	Nausea, diarrhea, fatigue, bone marrow suppression, secondary malignancy
Unique ADR	Transaminitis, asymptomatic increase in serum creatinine, GERD, dysgeusia, hypomagnesemia, rash
DDI	Substrate of CYP2D6 Inhibits CYP2C9 (caution with warfarin) Inhibits MATE1 and MATE2-K
PK	Mean half-life = 17-19 hours

Rubraca [package insert].; 2018.

GERD, gastroesophageal reflux disease.

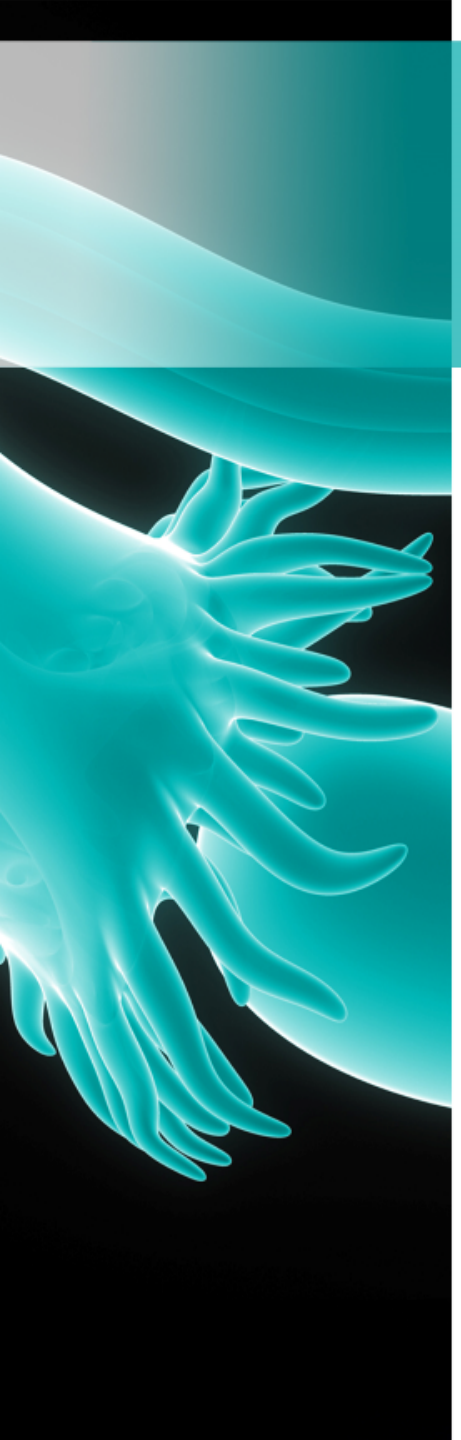


Niraparib

	Niraparib
Target	PARP 1 and 2
Dose	300 mg daily
Dose adjustment	If < 77 kg or platelets < 150,000/µL: 200 mg daily May titrate up if tolerated
Class ADR	Nausea, diarrhea, bone marrow suppression, secondary malignancy
Unique ADR	Insomnia, hypertension
PK	Mean half-life = 36 hours
Notes	• Similar efficacy despite up-front dose reduction to 200 mg daily • Weekly CBC for the first month of therapy

Berek JS, et al. *Ann Oncol*. 2018;29(8):1784-92.; Zejula [package insert].; 2020.

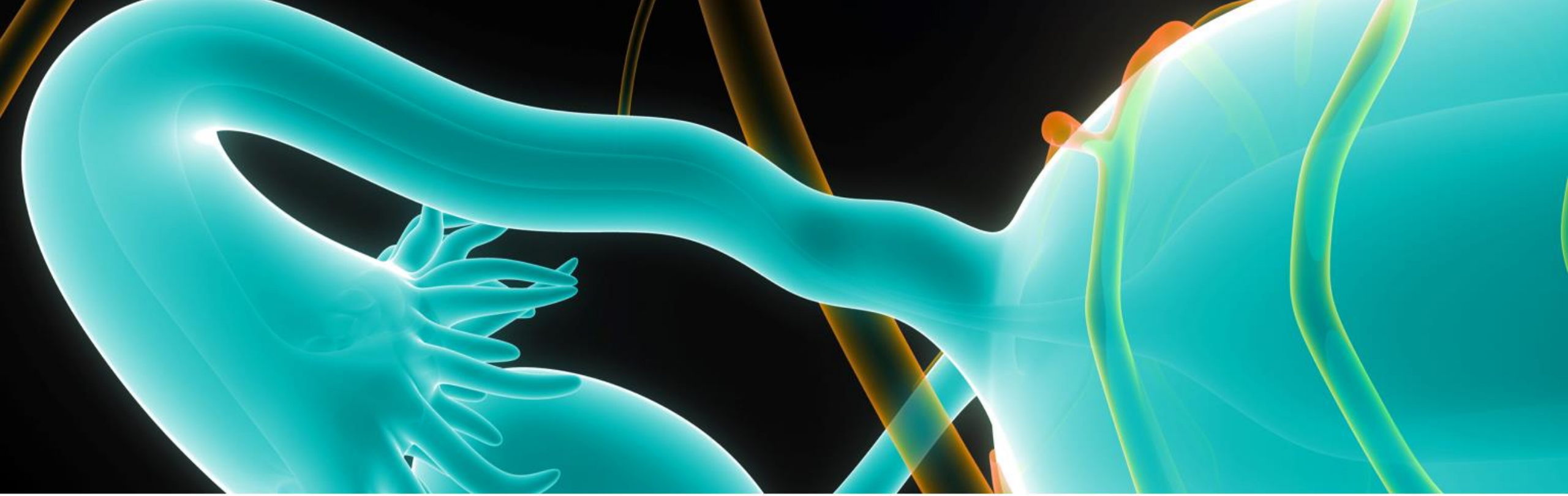
CBC, complete blood count



Adverse Effects: PARP Inhibitor Dose Levels

	Dose levels	Tablet strength	Tablet/capsule sizes
Olaparib	Starting dose: 300 mg BID Dose level -1: 250 mg BID Dose level -2: 200 mg BID	150 mg tablets 100 mg tablets	14 mm
Rucaparib	Starting dose: 600 mg BID Dose level -1: 500 mg BID Dose level -2: 400 mg BID Dose level -3: 300 mg BID	300 mg tablets 250 mg tablets 200 mg tablets	16 mm 15 mm 11 mm
Niraparib	Starting dose: 300 mg QD Dose level -1: 200 mg QD Dose level -2: 100 mg QD	100 mg capsules	22 mm

Lynparza [package insert].; 2019.;
Rubraca [package insert].; 2018.;
Zejula [package insert].; 2020.

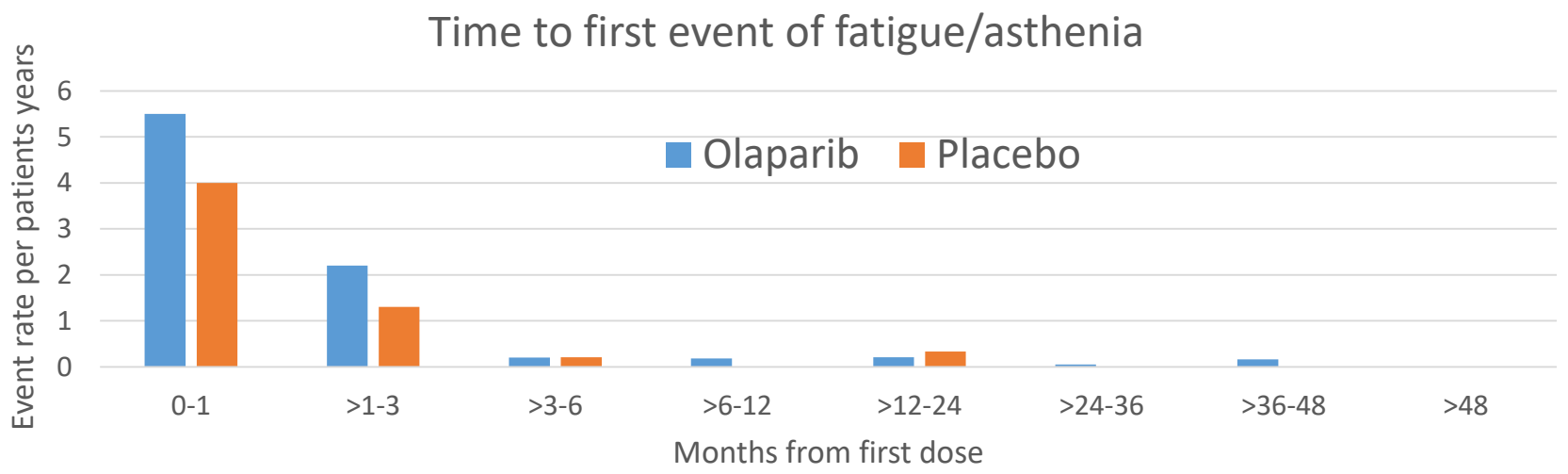


PARP Inhibitors
Class-Wide Adverse Effects

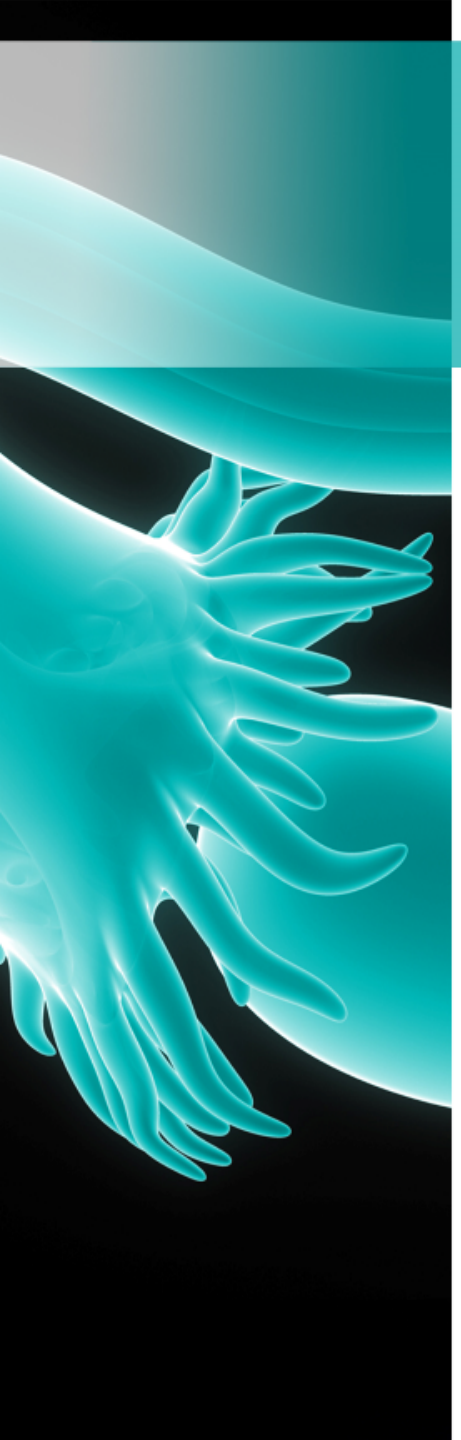
Adverse Effects: Fatigue

	Olaparib	Rucaparib	Niraparib
Grade ≥ 3	4%	7%	8%

Similar across all 3 PARPi



Coleman RL, et al. *Lancet*. 2017;390(10106):1949-61.; Friedlander M, et al. *Br J Cancer*. 2018;119(9):1075-85.; Mirza MR, et al. *N Engl J Med*. 2016;375(22):2154-64.; Pujade-Lauraine E, et al. *Lancet Oncol*. 2017;18(9):1274-84.



Adverse Effects: Fatigue

	Olaparib	Rucaparib	Niraparib
Grade ≥ 3	4%	7%	8%

Similar across all 3 PARPi

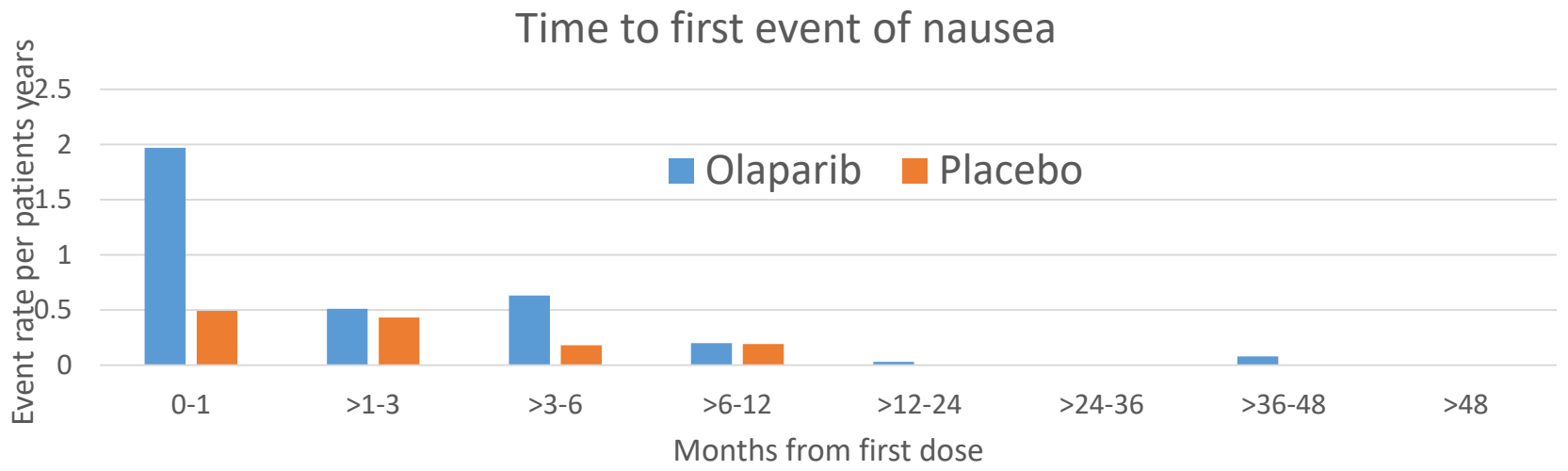
- Non-pharmacologic management of fatigue includes:
  - Exercise
  - Cognitive behavioral therapy
  - Massage therapy

Coleman RL, et al. *Lancet*. 2017;390(10106):1949-61.; Friedlander M, et al. *Br J Cancer*. 2018;119(9):1075-85.; LaFargue CJ, et al. *Lancet Oncol*. 2019;20(1):e15-28. Mirza MR, et al. *N Engl J Med*. 2016;375(22):2154-64.; Pujade-Lauraine E, et al. *Lancet Oncol*. 2017;18(9):1274-84.

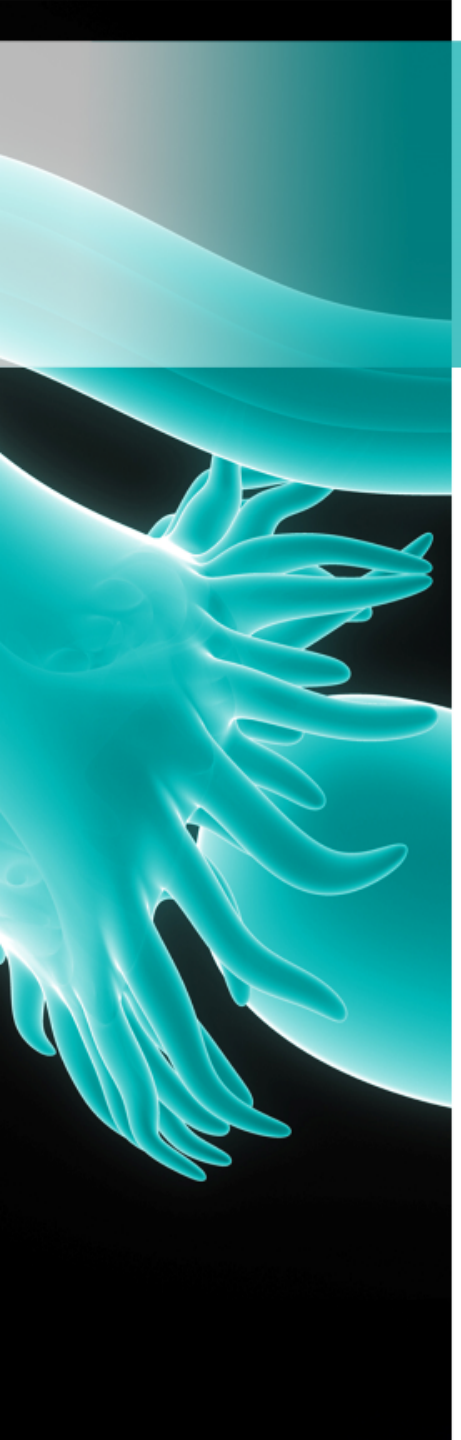
Adverse Effects: Nausea

	Olaparib	Rucaparib	Niraparib
All grades	76%	75%	74%
Grade ≥ 3	3%	4%	3%

Similar across all 3 PARPi
PARPi are moderately emetogenic



Coleman RL, et al. *Lancet*. 2017;390(10106):1949-61.; Friedlander M, et al. *Br J Cancer*. 2018;119(9):1075-85.; Mirza MR, et al. *N Engl J Med*. 2016;375(22):2154-64.; Pujade-Lauraine E, et al. *Lancet Oncol*. 2017;18(9):1274-84.



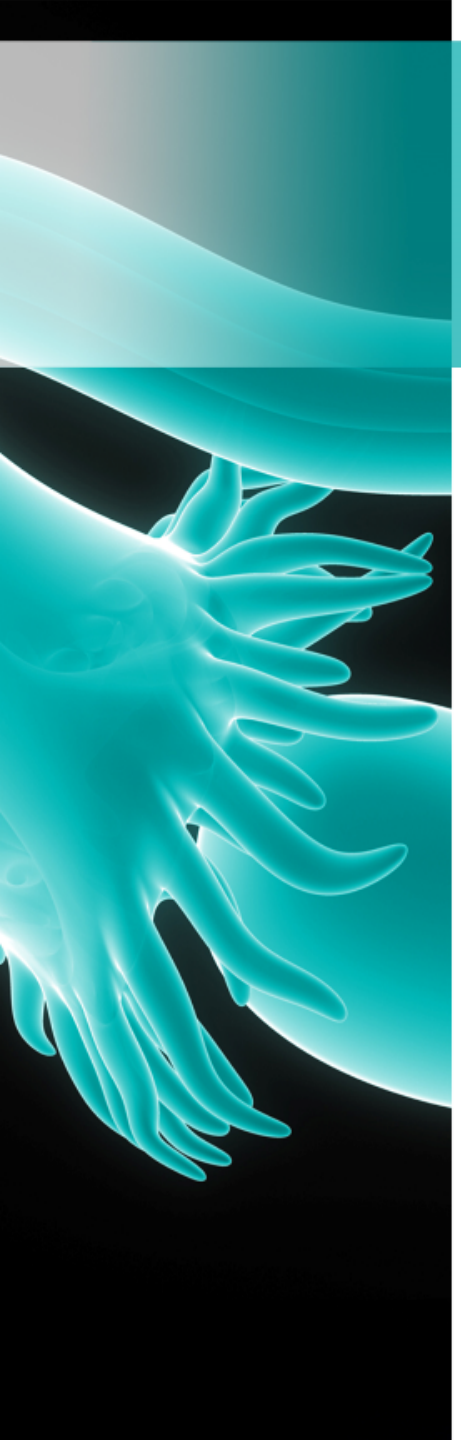
Adverse Effects: Nausea

	Olaparib	Rucaparib	Niraparib
All grades	76%	75%	74%
Grade ≥ 3	3%	4%	3%

Similar across all 3 PARPi
PARPi are moderately emetogenic

- Moderately emetogenic
  - Ondansetron 4-8 mg with each olaparib dose (8-16 mg/day)
  - May add prochlorperazine as needed

Coleman RL, et al. *Lancet*. 2017;390(10106):1949-61.; Friedlander M, et al. *Br J Cancer*. 2018;119(9):1075-85.; LaFargue CJ, et al. *Lancet Oncol*. 2019;20(1):e15-28.
Mirza MR, et al. *N Engl J Med*. 2016;375(22):2154-64.; Pujade-Lauraine E, et al. *Lancet Oncol*. 2017;18(9):1274-84.
https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf. Published February 19, 2020.; U.S. Dept of Health and Human Services.



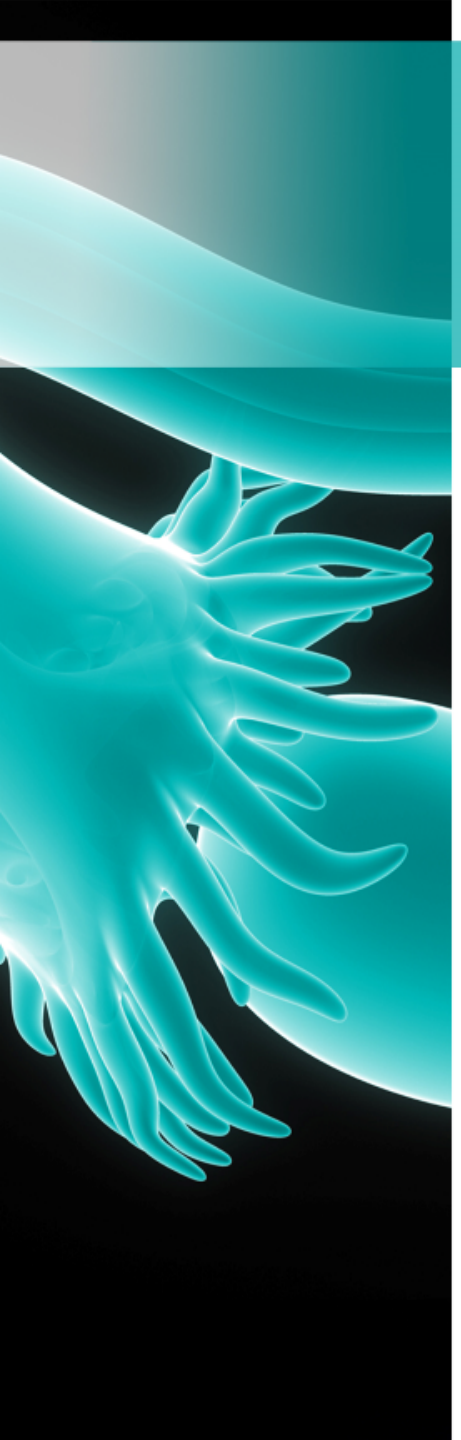
Adverse Effects: Diarrhea

	Olaparib	Rucaparib	Niraparib
All grades	33%	32%	20%
Grade ≥ 3	1%	1%	< 1%

Similar across all 3 PARPi

- Counsel patients to report increases of 4-6 stools per day over baseline (Grade 2) or diarrhea limiting ADLs

Coleman RL, et al. *Lancet*. 2017;390(10106):1949-61.; Friedlander M, et al. *Br J Cancer*. 2018;119(9):1075-85.; LaFargue CJ, et al. *Lancet Oncol*. 2019;20(1):e15-28.
Mirza MR, et al. *N Engl J Med*. 2016;375(22):2154-64.; Pujade-Lauraine E, et al. *Lancet Oncol*. 2017;18(9):1274-84.
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf. Published November 27, 2017



Compared to Chemotherapy

- Less cyclical
- Lower emetogenic risk, but nausea may be more constant

Aghajanian C, et al. *J Clin Oncol*. 2012;30(17):2039-45.;
Ozols RF, et al. *J Clin Oncol*. 2003;21(17):3194-200.;
Pujaide-Lauraine E, et al. *J Clin Oncol*. 2010;28(20):3323-9.

Summary: Non-hematologic Toxicities

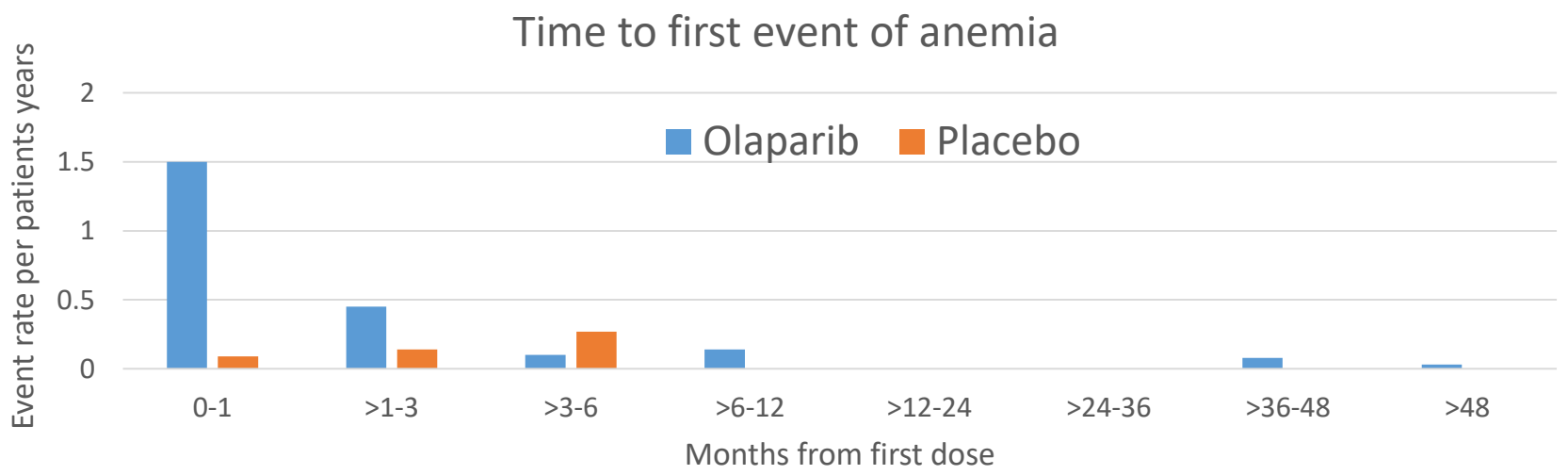
- Management of side effects within the first 4-8 weeks is crucial
  - Can be managed symptomatically without dose reduction

- Class wide adverse effects:
  - Fatigue
  - Nausea
  - Diarrhea

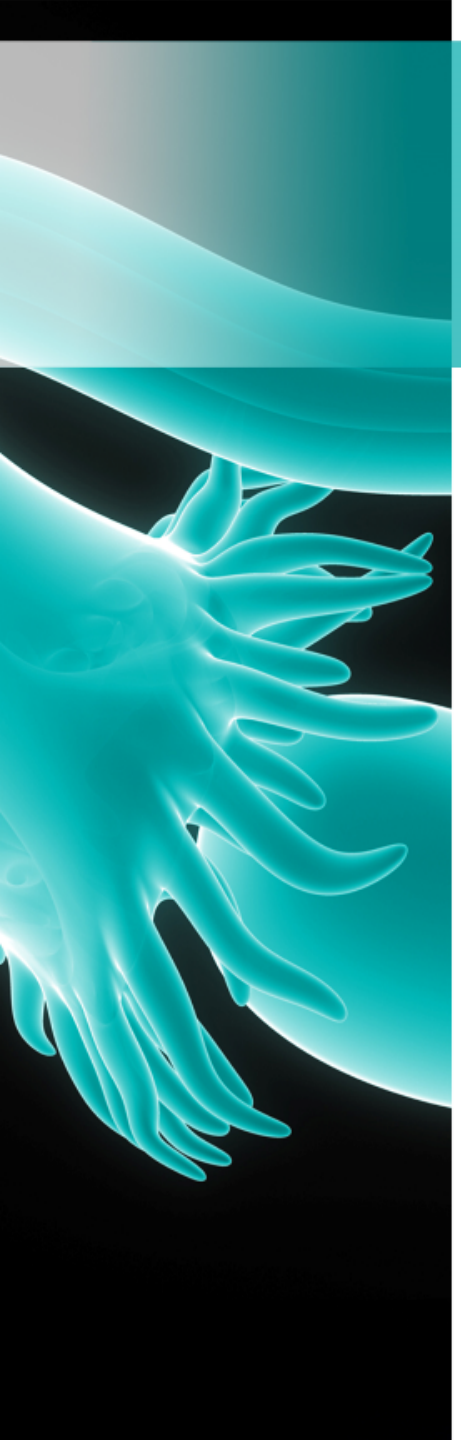
Adverse Effects: Anemia

	Olaparib	Rucaparib	Niraparib
Grade ≥ 3	20%	19%	25%

Similar across all 3 PARPi



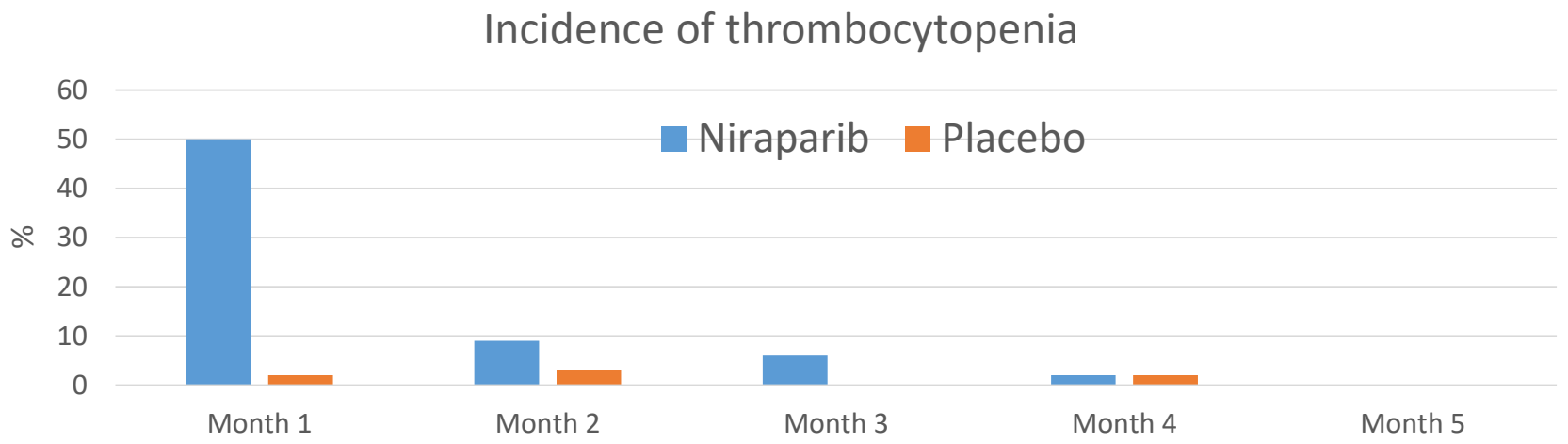
Coleman RL, et al. *Lancet*. 2017;390(10106):1949-61.; Friedlander M, et al. *Br J Cancer*. 2018;119(9):1075-85.; Mirza MR, et al. *N Engl J Med*. 2016; 375(22):2154-64.; Pujade-Lauraine E, et al. *Lancet Oncol*. 2017;18(9):1274-84.



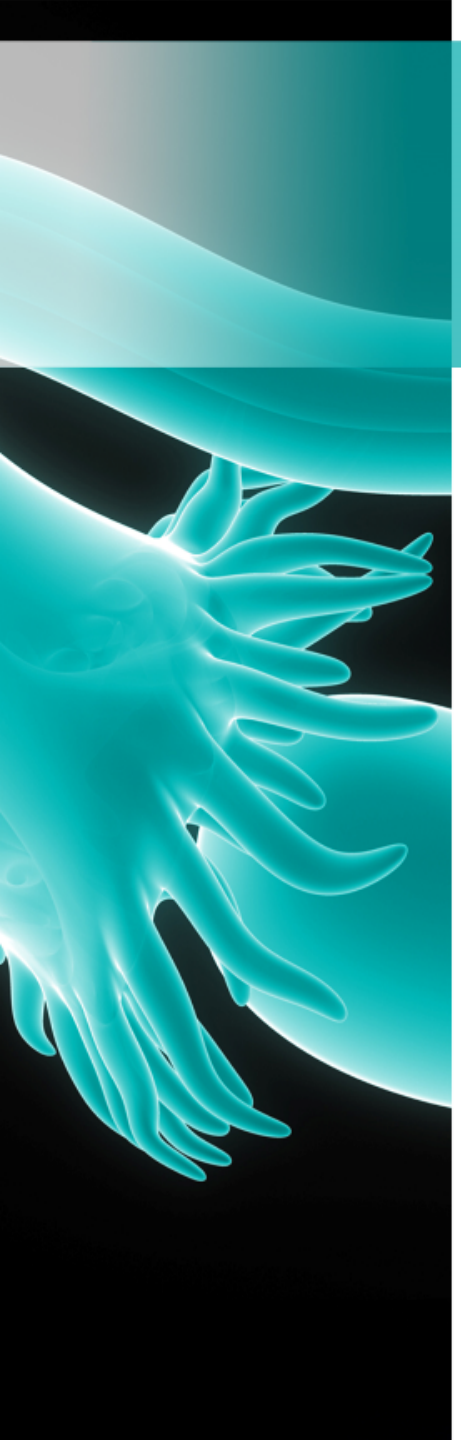
Adverse Effects: Thrombocytopenia

	Olaparib	Rucaparib	Niraparib
Grade ≥ 3	0%	5%	34%

Niraparib has a higher incidence of thrombocytopenia than other PARPi



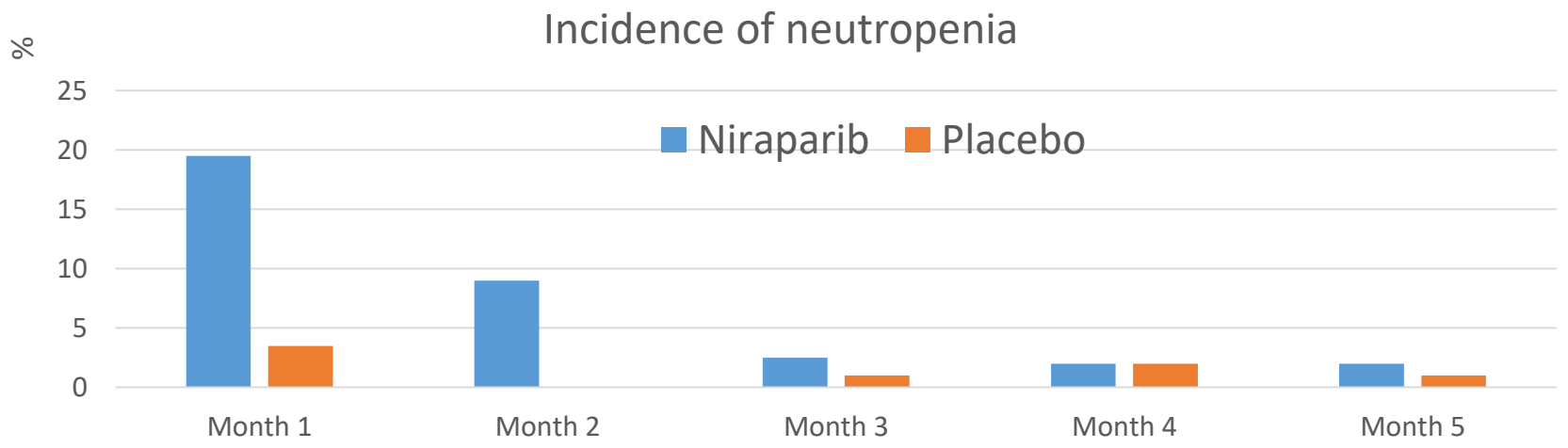
Coleman RL, et al. *Lancet*. 2017;390(10106):1949-61.; Friedlander M, et al. *Br J Cancer*. 2018;119(9):1075-85.; Mirza MR, et al. *N Engl J Med*. 2016; 375(22):2154-64.; Pujade-Lauraine E, et al. *Lancet Oncol*. 2017;18(9):1274-84.



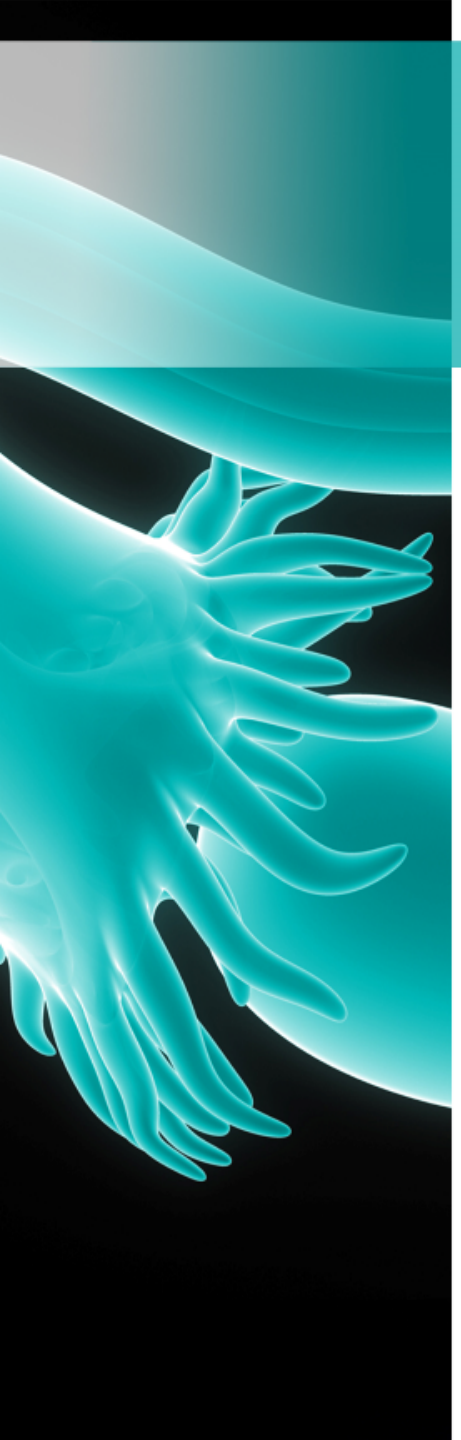
Adverse Effects: Neutropenia

	Olaparib	Rucaparib	Niraparib
Grade ≥ 3	5%	7%	20%

Niraparib has a higher incidence of neutropenia than other PARPi



Coleman RL, et al. *Lancet*. 2017;390(10106):1949-61.; Friedlander M, et al. *Br J Cancer*. 2018;119(9):1075-85.; Mirza MR, et al. *N Engl J Med*. 2016; 375(22):2154-64.; Pujade-Lauraine E, et al. *Lancet Oncol*. 2017;18(9):1274-84.

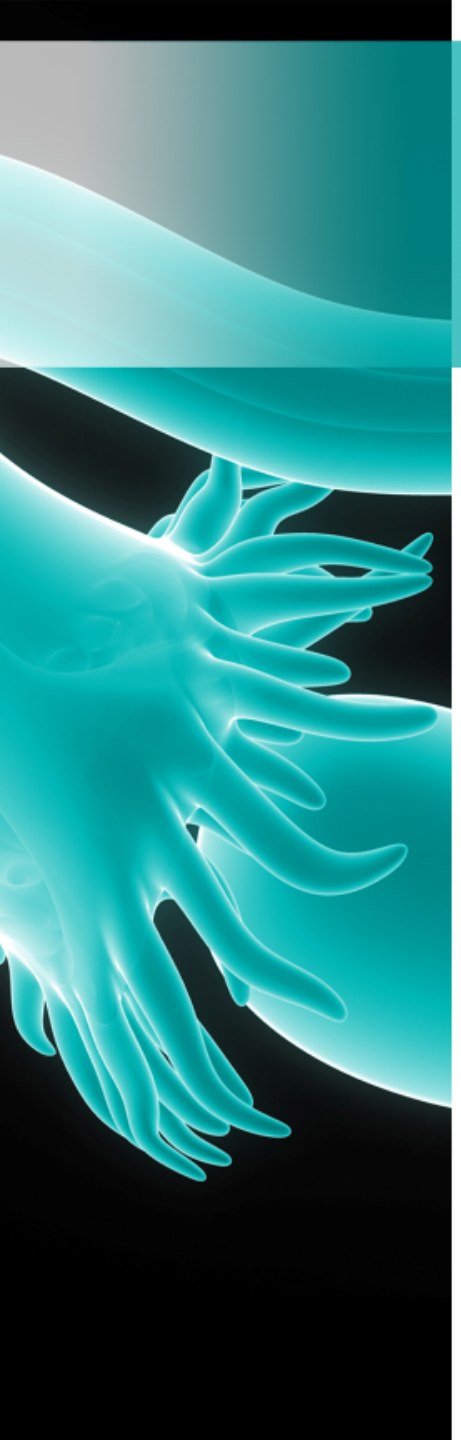


Adverse Effects: Hematologic Toxicity Management

	Grade 1	Grade 2	Grade 3-4
Anemia	Monitor and continue	Consider hold and resume at lower dose when Grade 1	Consider transfusion; Hold and resume at reduced dose when Grade 1
Neutropenia	Monitor and continue	Consider hold and resume at lower dose when Grade 1	Hold and resume at reduced dose when Grade 1
Thrombocytopenia	Monitor and continue	Hold and resume at lower dose when Grade 1	Hold and resume at lower dose when Grade 1
Thrombocytopenia (niraparib)	**Monitor weekly with niraparib** Plt < 100,000: hold, resume at same or reduced dose Plt < 75,000: hold, resume at reduced dose		

Discontinue if toxicity not recovered by 28 days, consider heme consult

LaFargue CJ, et al. *Lancet Oncol*. 2019;20(1):e15-28.



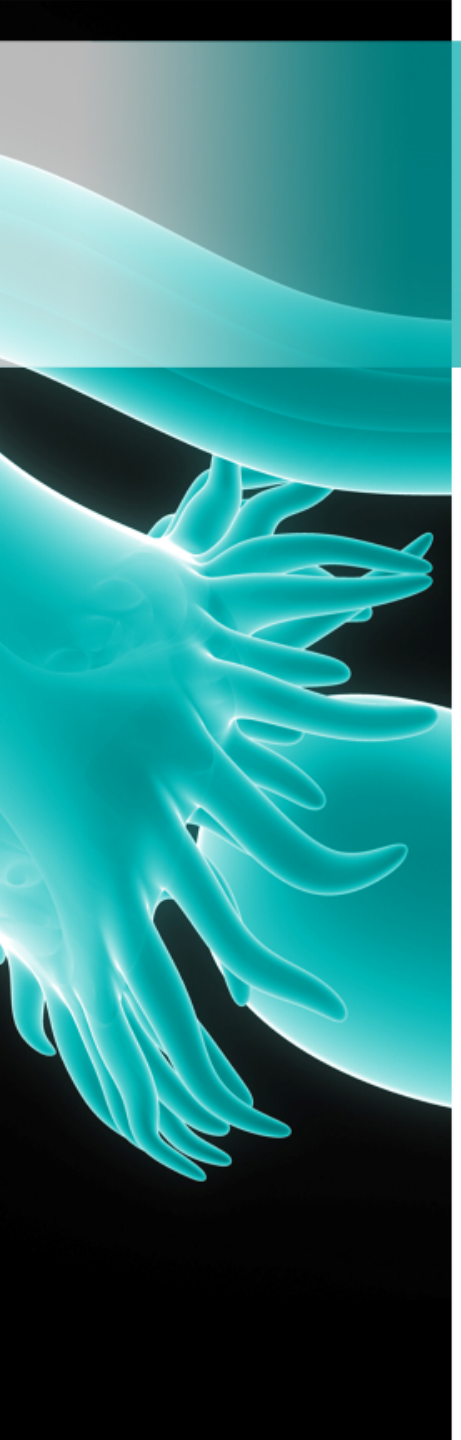
Adverse Effects: Secondary Malignancy

	Incidence of MDS/AML
Olaparib	
SOLO-2	2%
SOLO-1	1%
Rucaparib	
ARIEL 2	0%
ARIEL 3	1%
Niraparib	
NOVA	1.3%
QUADRA	< 1%
PRIMA	0.3%

AML, acute myeloid leukemia;
CBC, complete blood count;
MDS, myelodysplastic syndrome.

- Long-term monitoring: consider CBC monthly throughout therapy

Coleman RL, et al. *Lancet*. 2017;390(10106):1949-61.;
Gonzalez-Martin A, et al. *N Engl J Med*. 2019;381(25):2391-402.;
Mirza MR, et al. *N Engl J Med*. 2016;375(22):2154-64.;
Moore K, et al. *N Engl J Med*. 2018;379(26):2495-505.;
Moore KN, et al. *Lancet Oncol*. 2019;20(5):636-48.;
Pujade-Lauraine E, et al. *Lancet Oncol*. 2017;18(9):1274-84.;
Swisher EM, et al. *Lancet Oncol*. 2017;18(1):75-87.



Compared to Chemotherapy

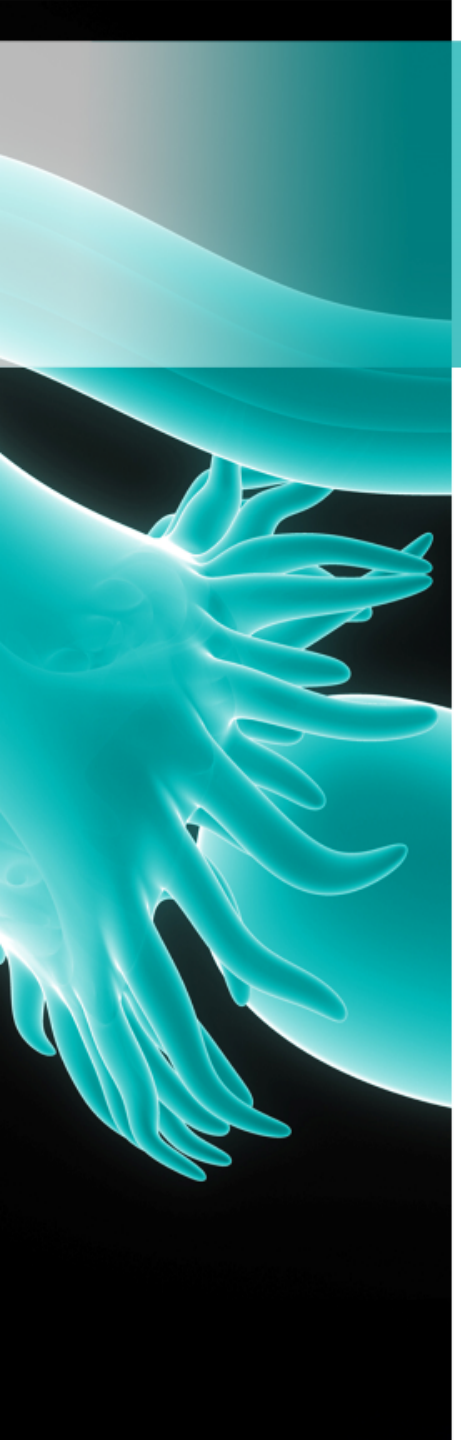
- Less cyclical
- May be as profound as with chemotherapy
- No recommendation for use of growth factors

Aghajanian C, et al. *J Clin Oncol*. 2012;30(17):2039-45.;
Ozols RF, et al. *J Clin Oncol*. 2003;21(17):3194-200.;
Pujaide-Lauraine E, et al. *J Clin Oncol*. 2010;28(20):3323-9.

Summary: Hematologic Toxicities

- CBC at least monthly
- Weekly CBC for the first-month of niraparib
- Discontinue if toxicity not recovered by 28 days and consider hematology consult

CBC, complete blood count

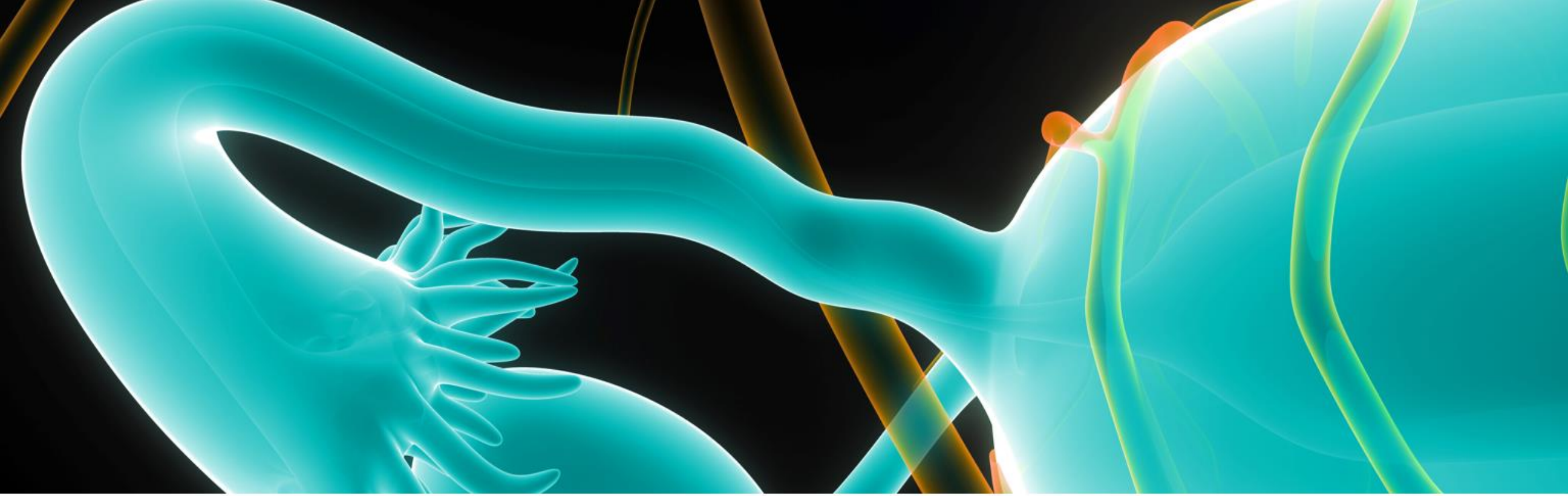


ARS Question #3

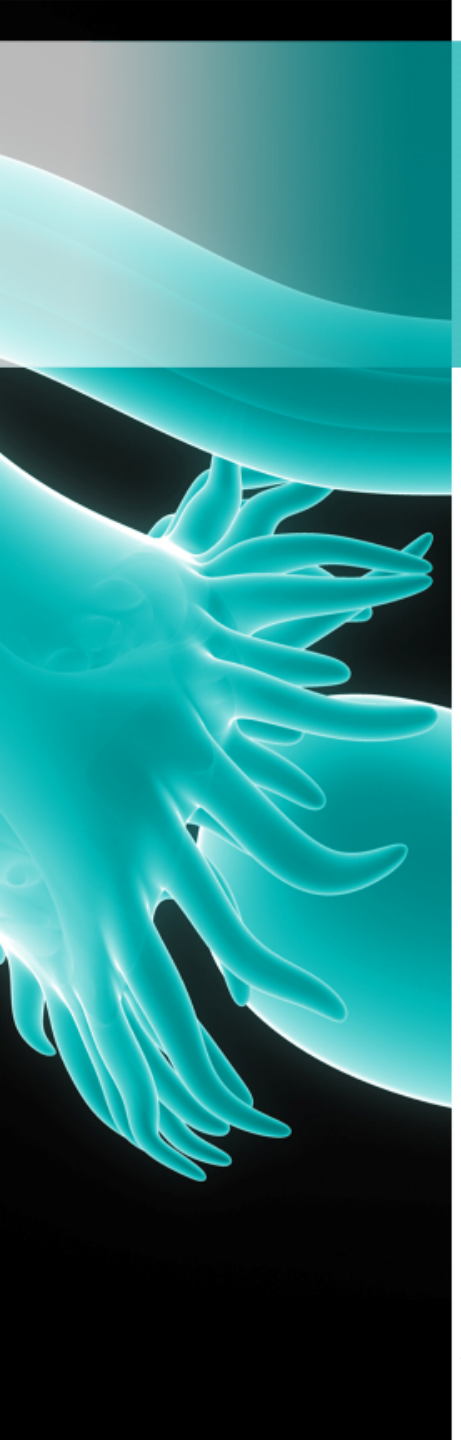
SB is 67-year-old woman with ovarian cancer. She was treated with 3 cycles of neoadjuvant carboplatin and paclitaxel followed by optimal debulking surgery and will be starting olaparib maintenance.

Which of the following is a recommended initial antiemetic regimen for olaparib?

A. Ondansetron 4-8 mg with each olaparib dose (8-16 mg/day)
B. Palonosetron 0.25 mg and dexamethasone 8 mg on Day 1
C. Prochlorperazine 5-10 mg every 6 hours as needed
D. Prochlorperazine 5-10 mg with each olaparib dose (10-20 mg/day)

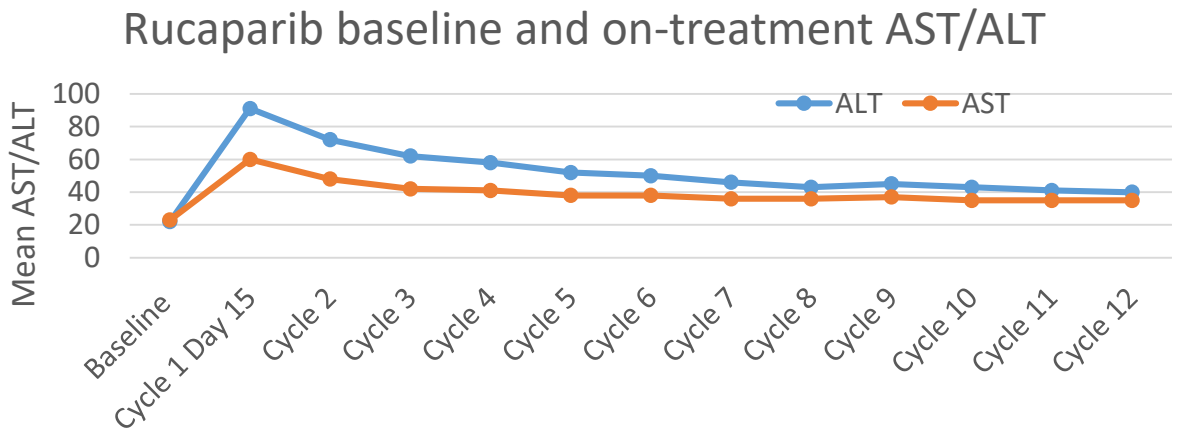


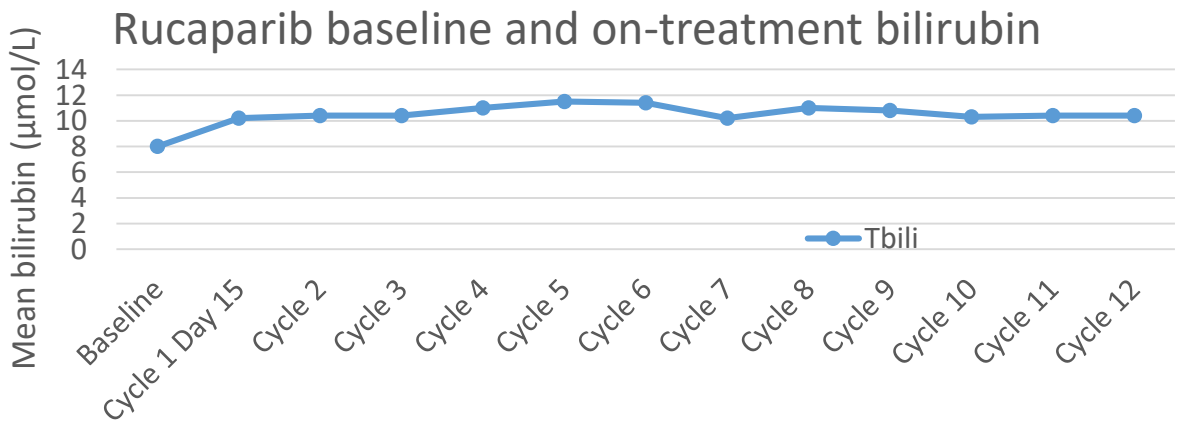
PARP Inhibitors
Unique Adverse Effects



Unique Adverse Effects

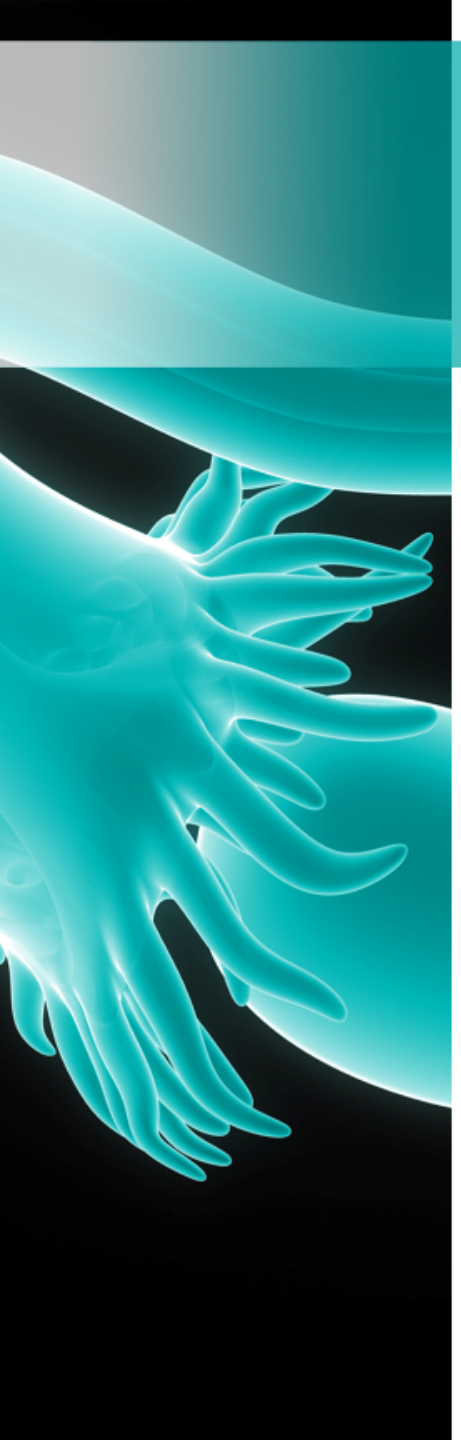
- Rucaparib
  - Transaminitis (34%)
  - Self-resolving
  - May increase monitoring frequency





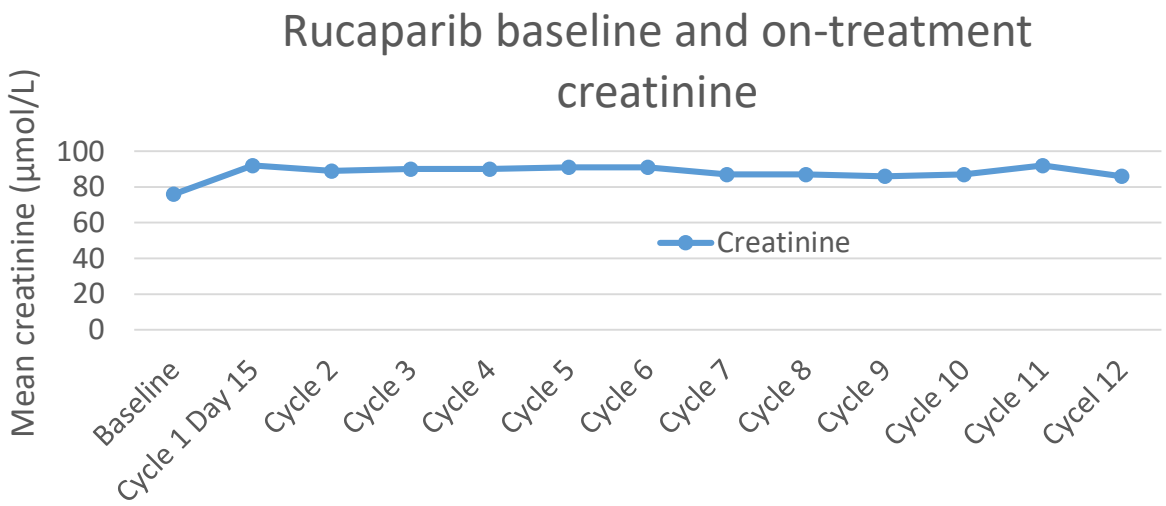
AST, aspartate transaminase;
ALT, alanine transaminase;
Tbili, total bilirubin.

Oza AM, et al. *Gynecol Oncol*. 2017;147(2):267-75.



Unique Adverse Effects

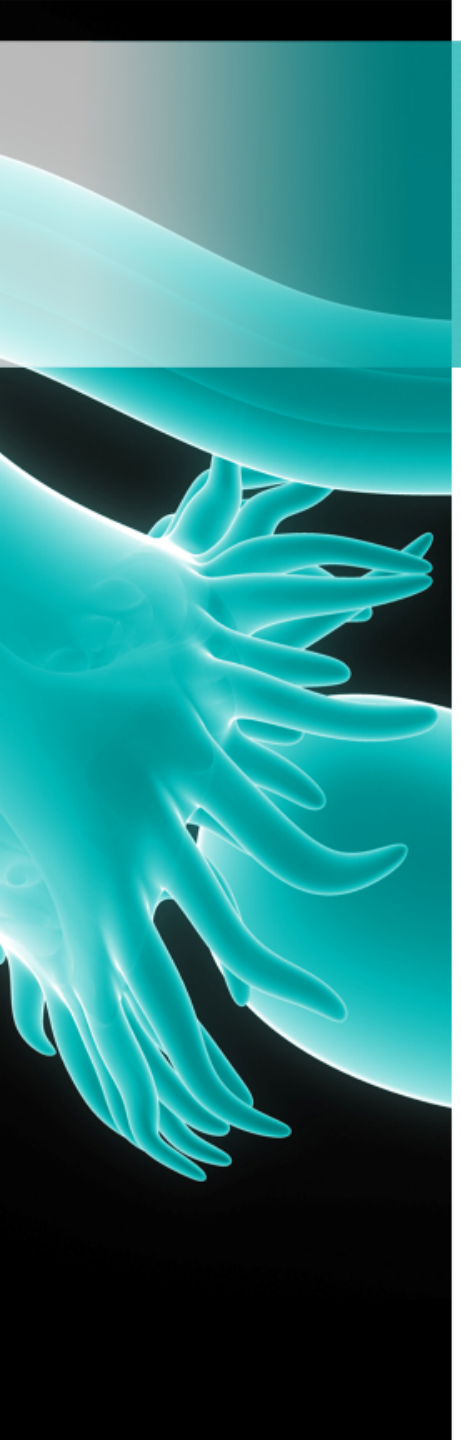
- Olaparib and rucaparib
  - Increased SCr
  - 11% with olaparib
  - 15% with rucaparib



- Due to inhibition of OAT/MATE transporters
- May use cystatin C to estimate GFR

Mirza MR, et al. *N Engl J Med*. 2016;375(25):2154-64.;
Oza AM, et al. *Gynecol Oncol*. 2017;147(2):267-75.
Pujade-Lauraine E, et al. *Lancet Oncol*. 2017;18(9):1274-84.

SCr, serum creatinine.



Unique Adverse Effects

Olaparib	Rucaparib	Niraparib
• Pneumonitis (< 1%)	• Hypercholesterolemia (40%-84%) • Photosensitivity • Dyspepsia • Dysgeusia	• Insomnia (24%) • Hypertension (8%)

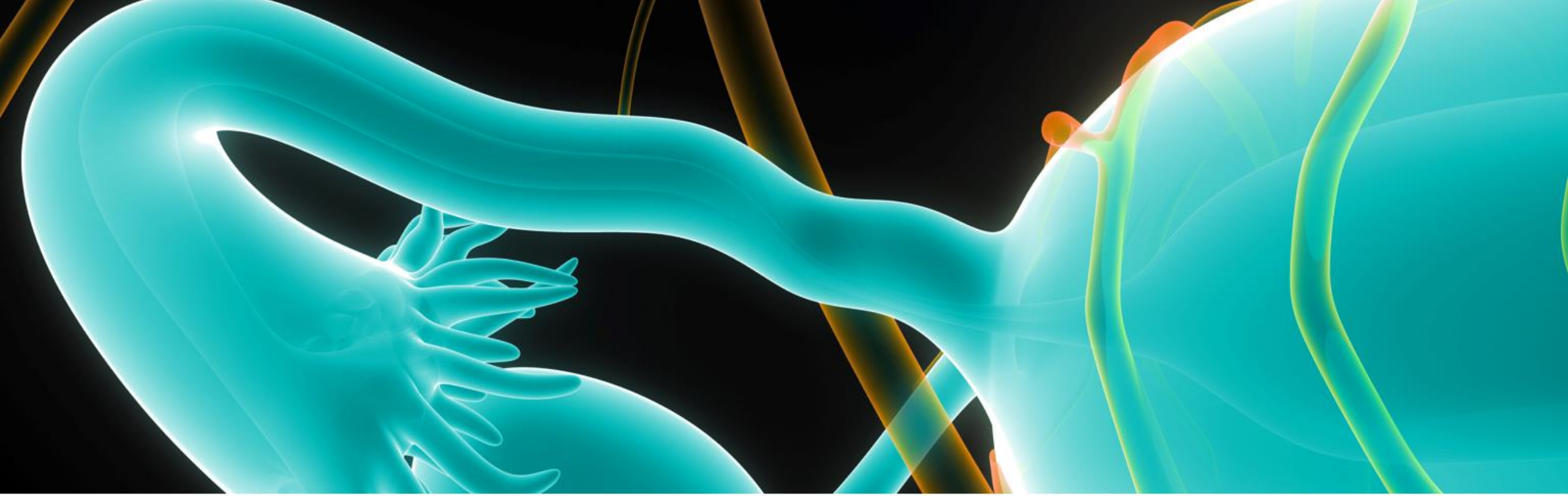
LaFargue CJ, et al. *Lancet Oncol*. 2019;20(1):e15-28.

Summary: Unique Adverse Effects

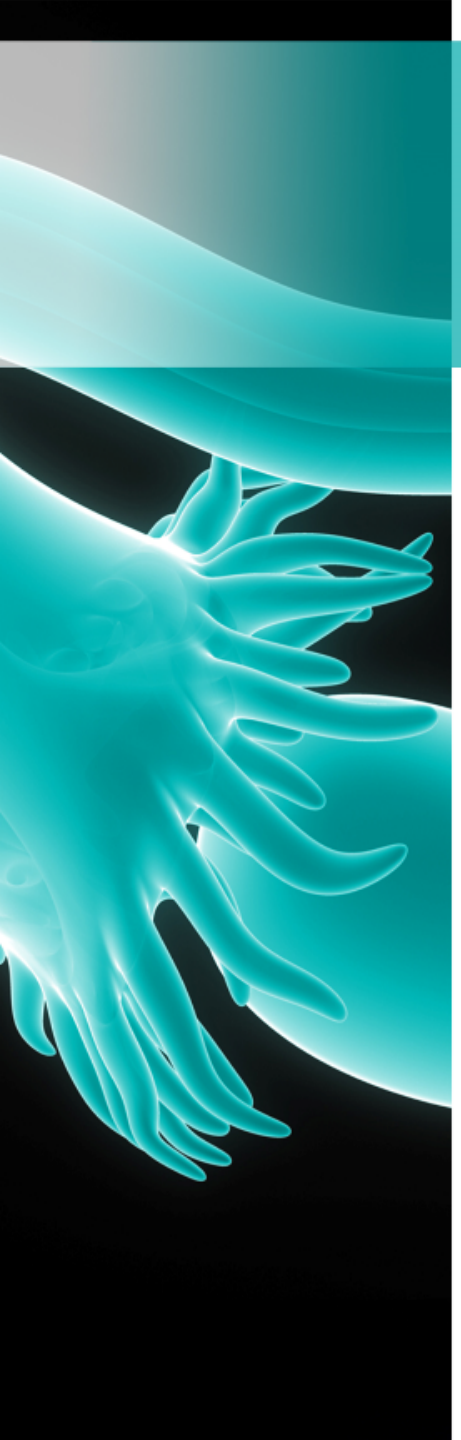
- Niraparib
  - Monitor blood pressure monthly
  - Take dose in the morning
- Rucaparib
  - Use sunscreen and good sun-protection practices (hats, long sleeves)
  - Consider PPI for dyspepsia, as well as non-pharmacologic interventions
  - Consider good oral hygiene and dietary changes for dysgeusia
  - Consider use of statins for hypercholesterolemia
- Olaparib
  - Hold for new or worsening respiratory symptoms and rule out pneumonitis
- Olaparib and rucaparib – asymptomatic increase in serum creatinine

LaFargue CJ, et al. *Lancet Oncol*. 2019;20(1):e15-28.

GFR, glomerular filtration rate; PPI, proton pump inhibitor.



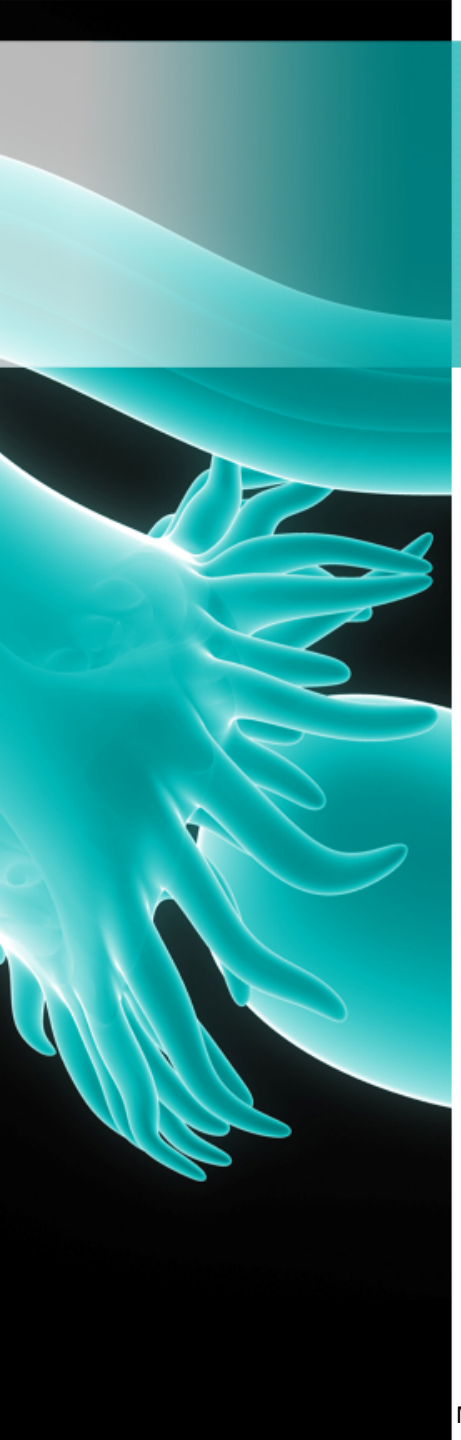
PARP Inhibitors Quality of Life and Real-World Data



Olaparib: TWiST Analysis

- TWiST: time without significant symptoms or toxicity
- TWiST analysis from study of olaparib maintenance in recurrent, platinum-sensitive ovarian cancer (SOLO-2)
  - Used the FACT-O questionnaire
- PFS benefit of olaparib maintenance in recurrent, platinum-sensitive disease achieved without sacrificing quality of life
  - Mean duration of TWiST was 15 months with olaparib vs. 7.7 months with placebo ($p<0.0001$)

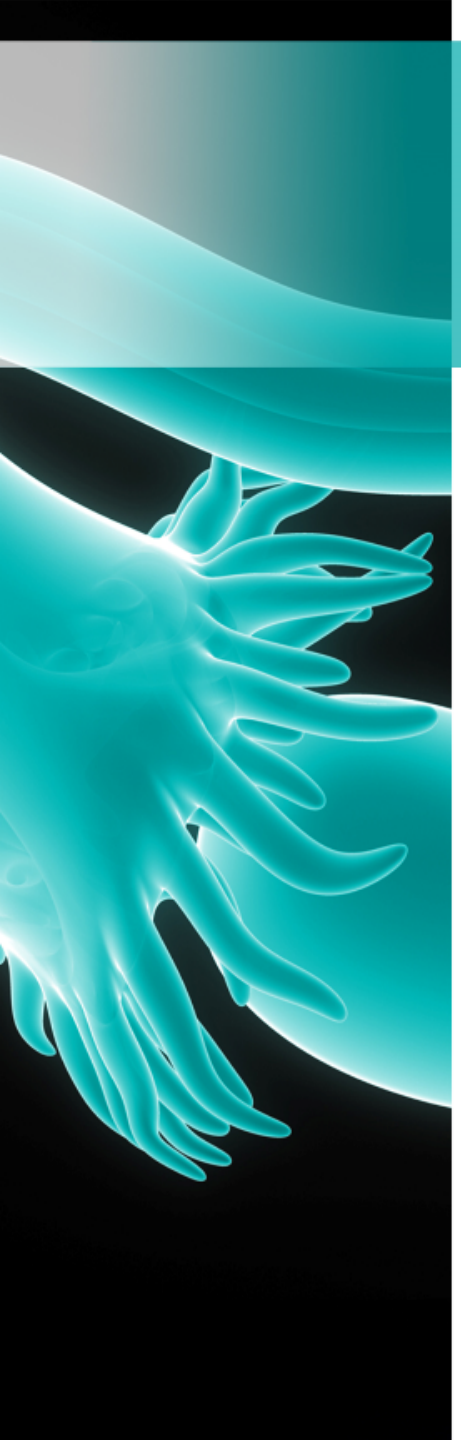
Friedlander M, et al. *Lancet Oncol*. 2018;19(8):1126-34.



Niraparib: TWiST Analysis

- TWiST analysis from study of niraparib maintenance in recurrent, platinum-sensitive ovarian cancer (NOVA)
  - Data gathered from adverse event monitoring, lab tests, physical exams, vital signs
- PFS benefit of niraparib reinforced by analysis showing 2- to 4-fold greater mean TWiST than patients receiving placebo

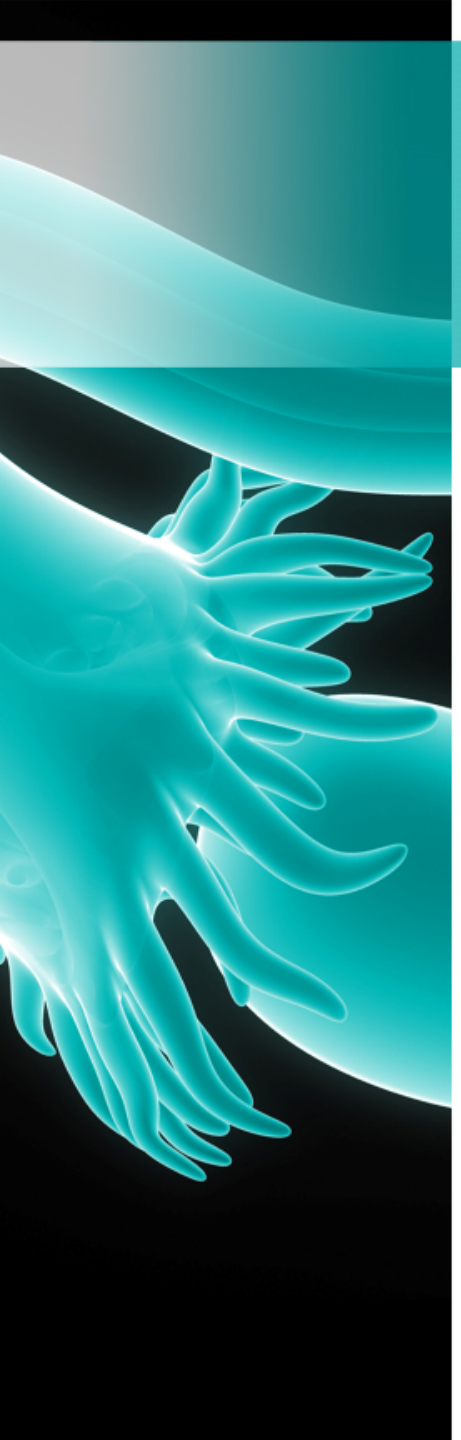
Matulonis UA, et al. *J Clin Oncol*. 2019;37(34):3183-91.



Real-World Analyses of Olaparib Use

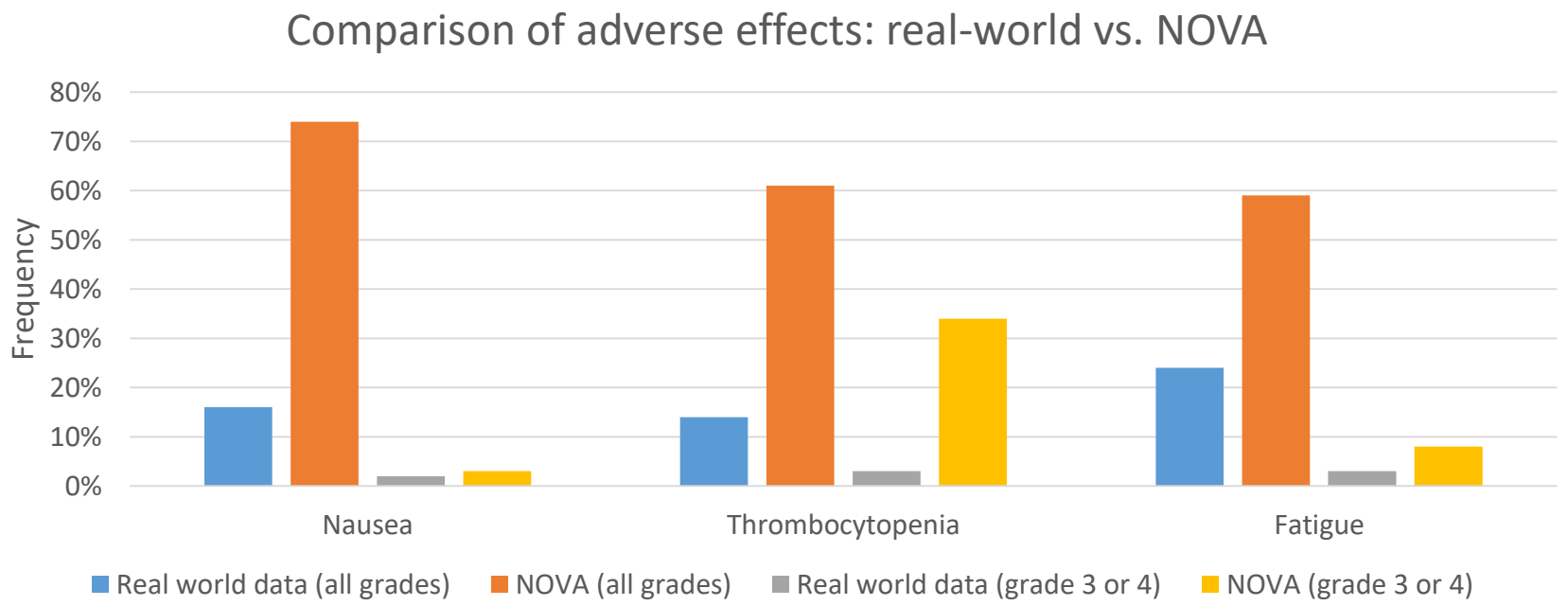
- Data on real-world use from Sweden, China, Korea, Italy
- Well tolerated with most common adverse effects consistent with major trials
  - Common: nausea, fatigue
  - Most frequent grade 3-4 adverse effect: anemia
- Efficacy outcomes consistent with major trials

Cao Y, et al. *Cancer Reports*. 2019;2:e1180.; Cecere SC, et al. *Gynecol Oncol*. 2020;156(1):38-44.;
Eriksson I, et al. *Targeted Oncology*. 2018;13(6):725-33.; Paik ES, et al. *Ann Oncol*. 2018;29(Suppl 9):ix84.

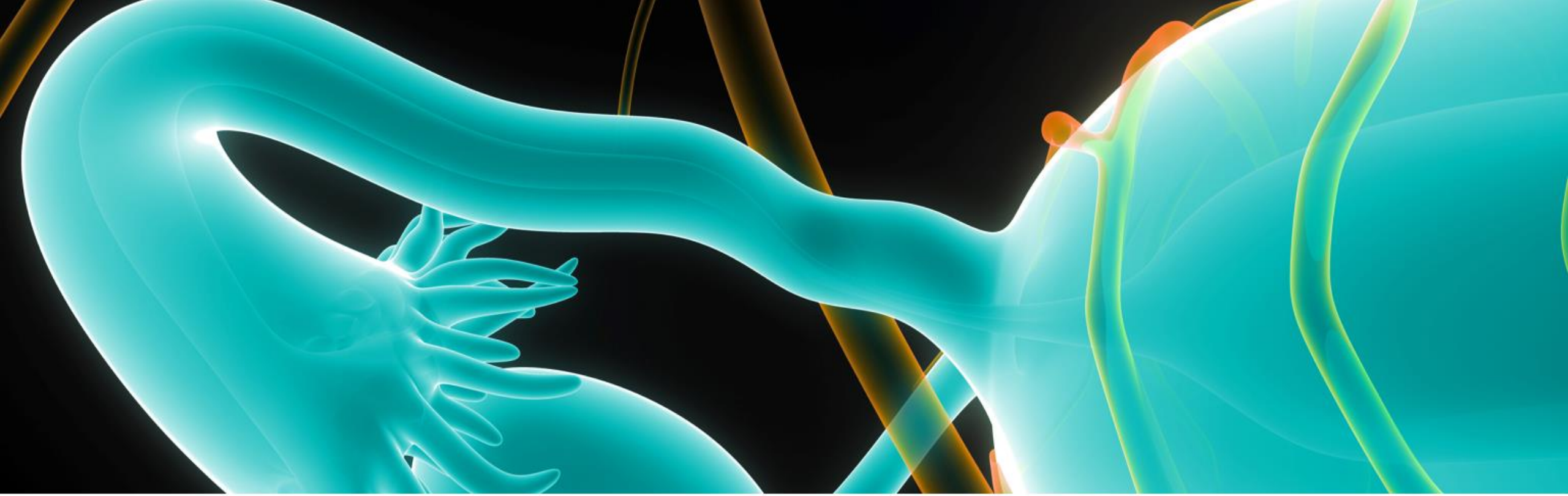


Real-World Analyses of Niraparib Use

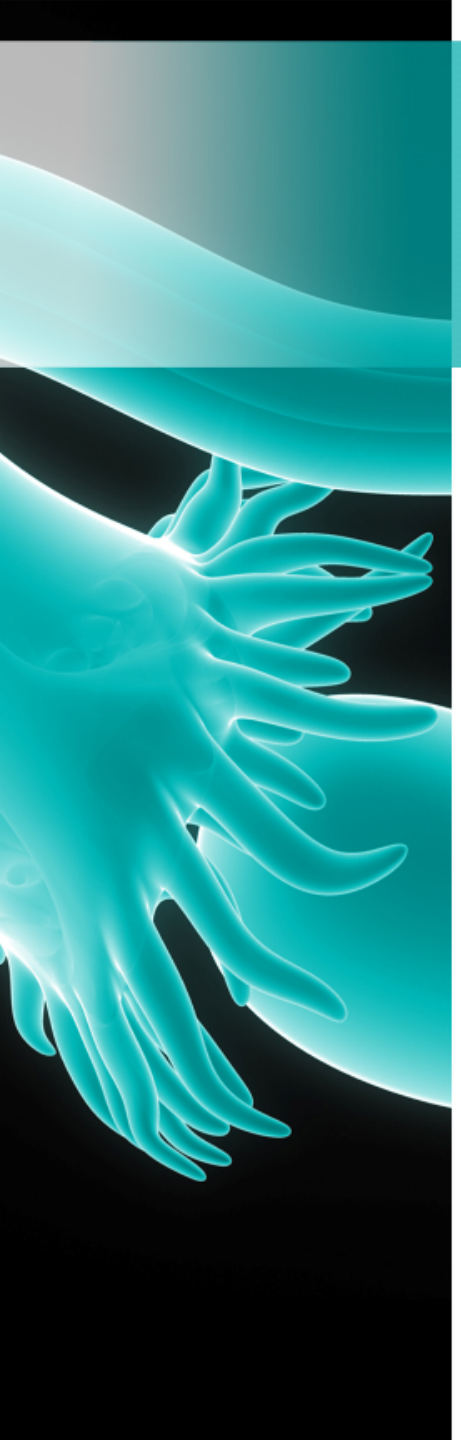
- Adverse events when initiating patients on 200 mg/day
  - Patients < 77 kg or baseline platelets < 150,000/µL
  - Based on median dose intensity in the NOVA trial



Gallagher J, et al. *Ann Oncol*. 2018;29:(suppl_8):vIII332-58.; Gallagher JR, et al. *Future Oncol*. 2019;15(36):4197-206.



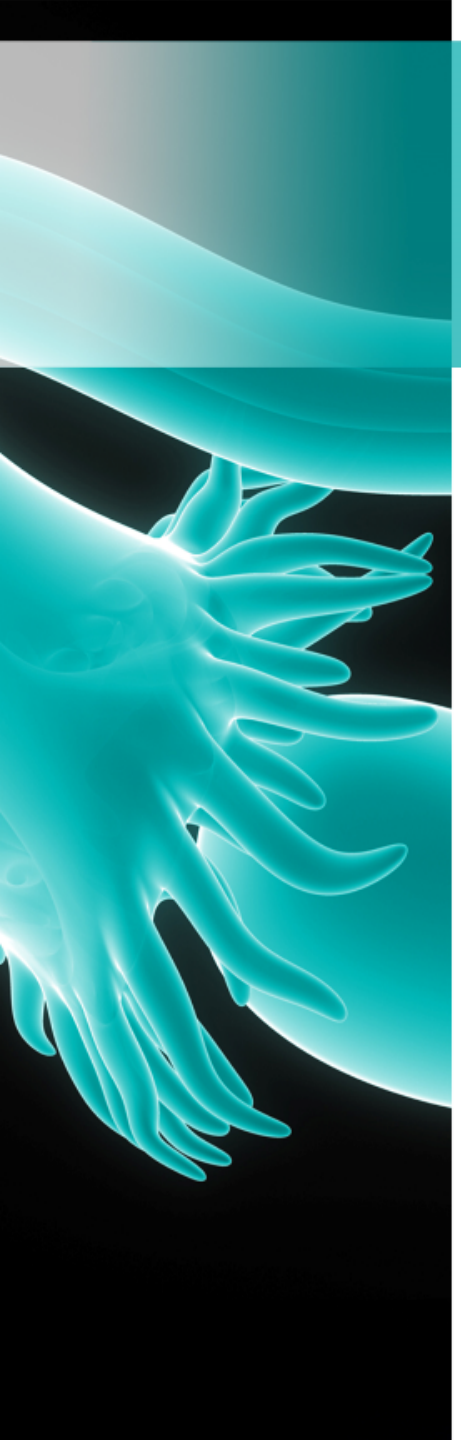
PARP Inhibitors
Implications for a Pharmacist



Real-World Considerations for PARP Inhibitor Use

- ASCO QOPI (Quality Oncology Practice Initiative)
  - Increasing numbers of patients are receiving oral chemotherapy at home
  - Shift in responsibility of management from provider to patient
  - Assessment of adherence is critical
    - Barriers to adherence: adverse effects, financial toxicity

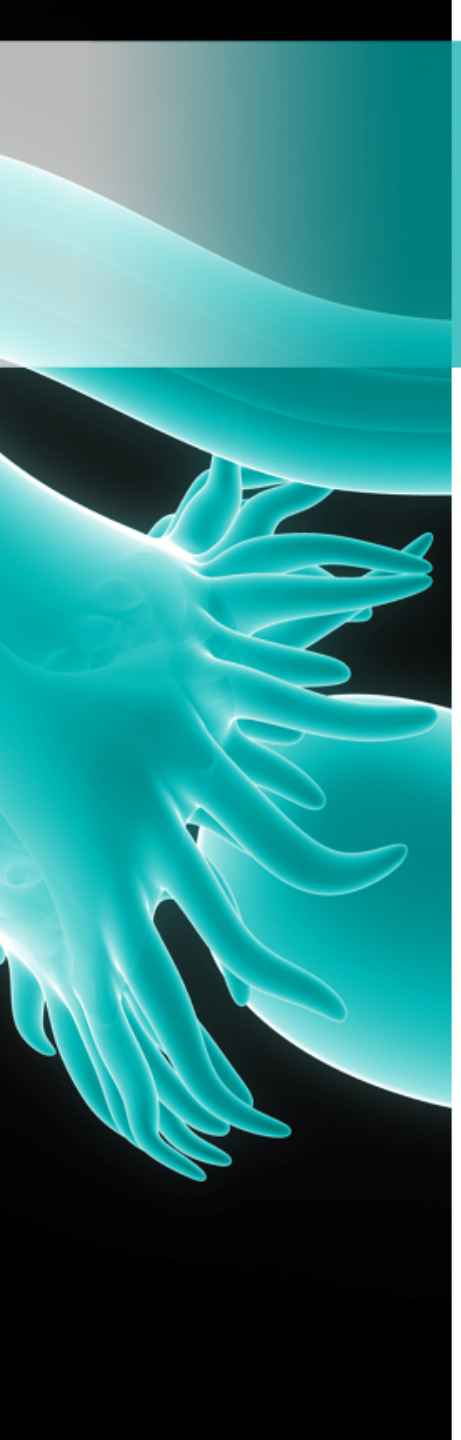
Mulkeron P, et al. *J Oncol Pract*. 2016;12(10):e912-23.



Real-World Considerations for PARP Inhibitor Use

- HOPA (Hematology/Oncology Pharmacist Association)
  - Best practice recommendation for management of oral oncolytics
  - Ensuring safe prescribing
  - Ensuring safe monitoring
  - Providing patient education
  - Collaborating with specialty pharmacies

Mackler E, et al. *J Oncol Pract*. 2019;15(4):e346-55.



Adherence Strategies

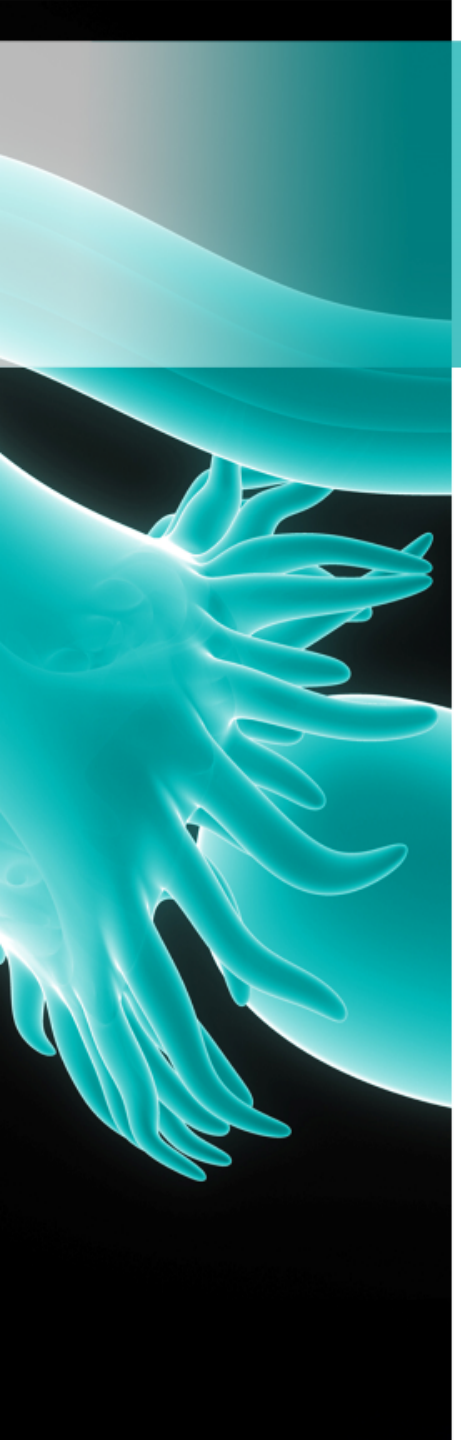
For pharmacists

- Perform medication education
- Ensure patient has antiemetics
- Assess financial barriers
- Assess symptoms routinely
- Communicate dose changes and tablet sizes
- Evaluate prescription refill rates

For patients

- Use alarms
- Use pill diaries
- Use pill organizers
- Have written concrete guidance for when to call their provider

Mackler E, et al. *J Oncol Pract*. 2019;15(4):e346-55.



ARS Question #4

SB is a 67-year-old woman with ovarian cancer. She was treated with 3 cycles of neoadjuvant carboplatin and paclitaxel followed by optimal debulking surgery and will be starting olaparib maintenance.

Which of the following counseling points should be covered in her patient education visit?

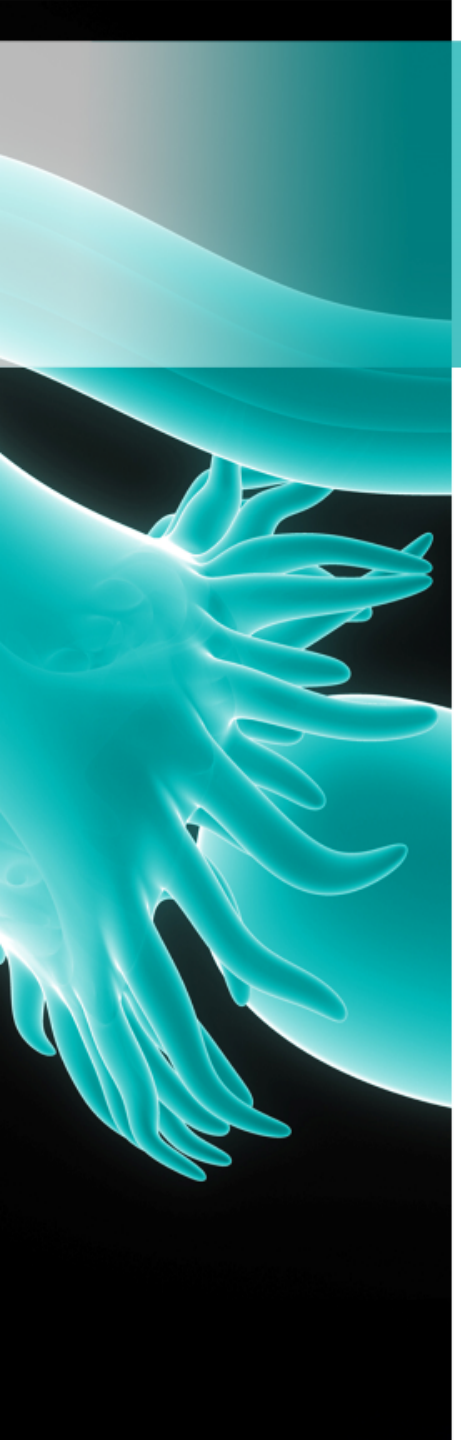
A. Most side effects occur in the first 2 months

B. Nausea can be managed with an antiemetic and can improve within the first 2 months

C. Fatigue is a common side effect and quality of life is important for maintenance therapy; report changes in activity level

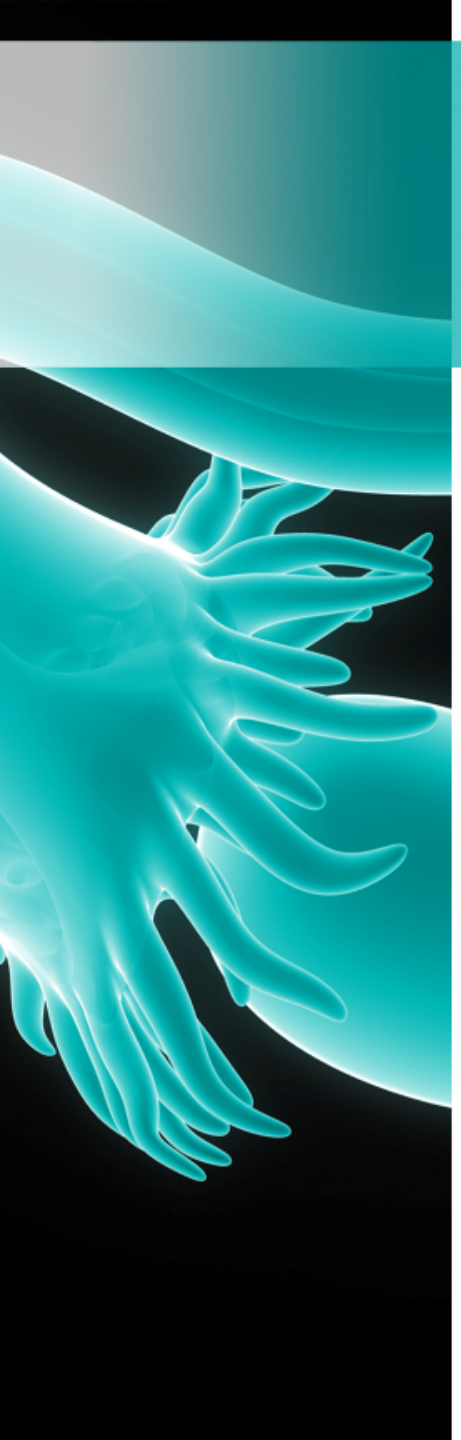
D. Adherence to lab monitoring schedule for hematologic toxicity is essential to ensure the safety of the drug

E. All of the above



Drug Acquisition Considerations

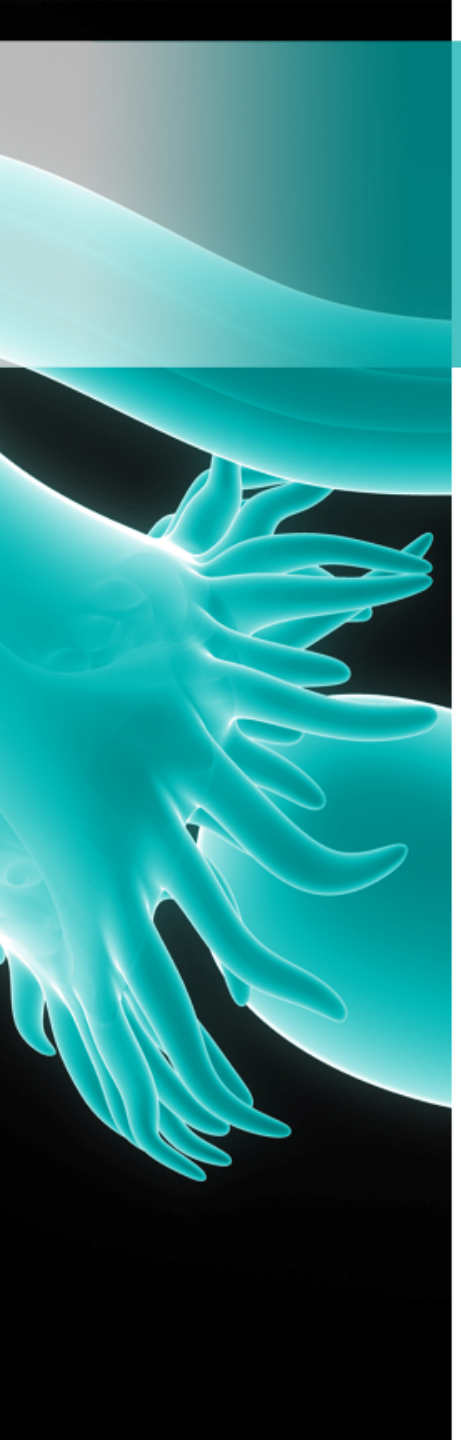
- Distribution through specialty pharmacies
  - Implications for dose reductions
- Patient assistance available
- Manufacturer drug programs



Drug Acquisition Considerations

	Olaparib	Rucaparib	Niraparib
Cost: 30-day supply	~$17,000/120 tablets	~$20,000/120 tablets	~$26,000/90 capsules

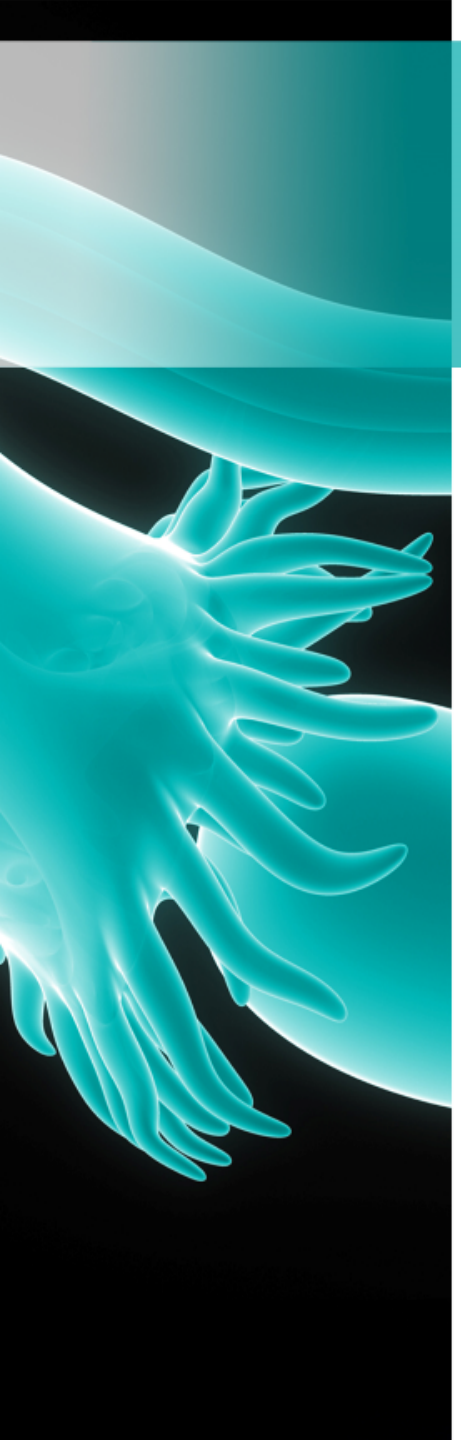
10%-20% copay is approximately $2100-$4200



Summary

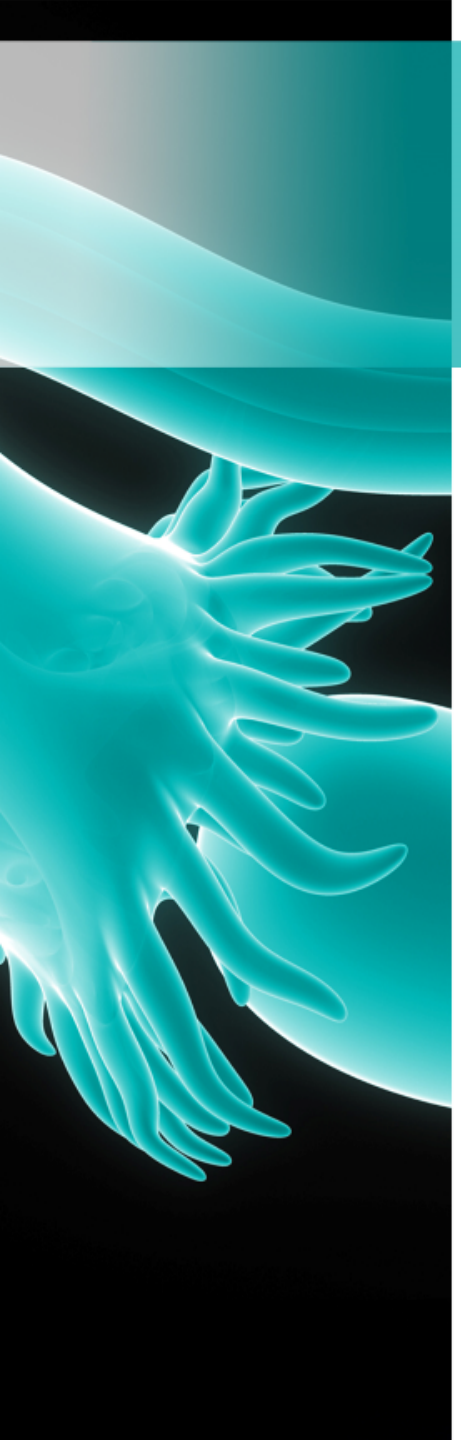
FDA approval of PARPi in ovarian cancer

	Upfront maintenance	Recurrent maintenance	Treatment
Olaparib	X *BRCAm*	X	X
Olaparib + bevacizumab	X HRD		
Rucaparib		X	X
Niraparib	X	X	X



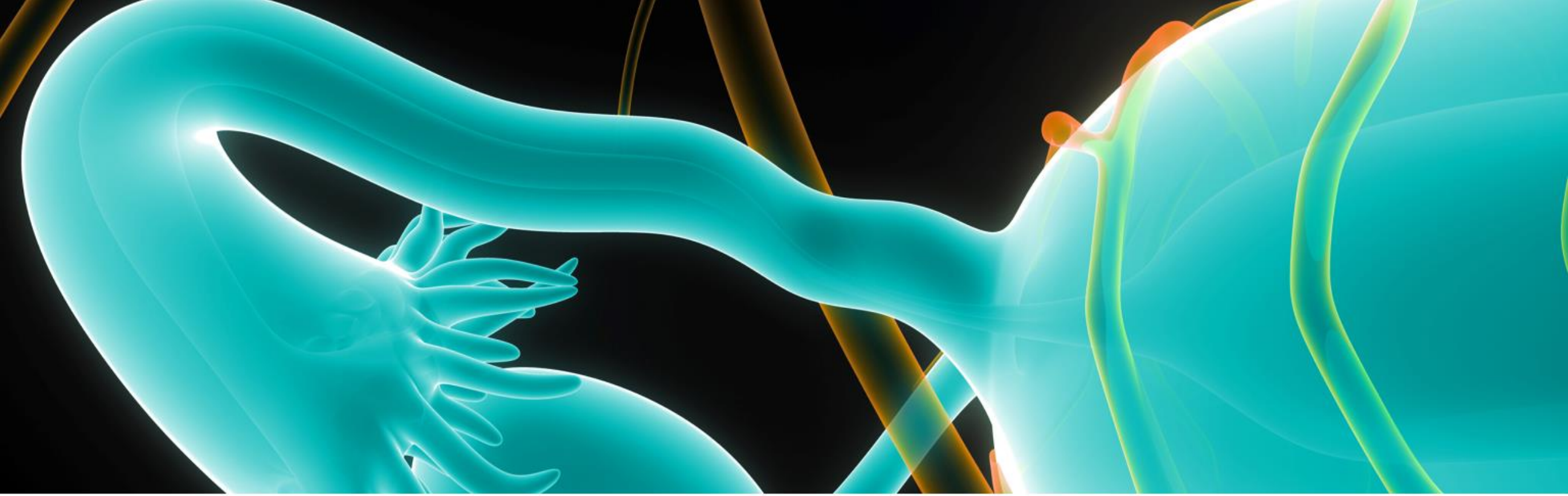
Summary

- Most common adverse effects are nausea, fatigue, diarrhea, and bone marrow suppression
  - More thrombocytopenia, neutropenia, and insomnia with niraparib
- Most side effects occur within the first 4-8 weeks and can be managed symptomatically

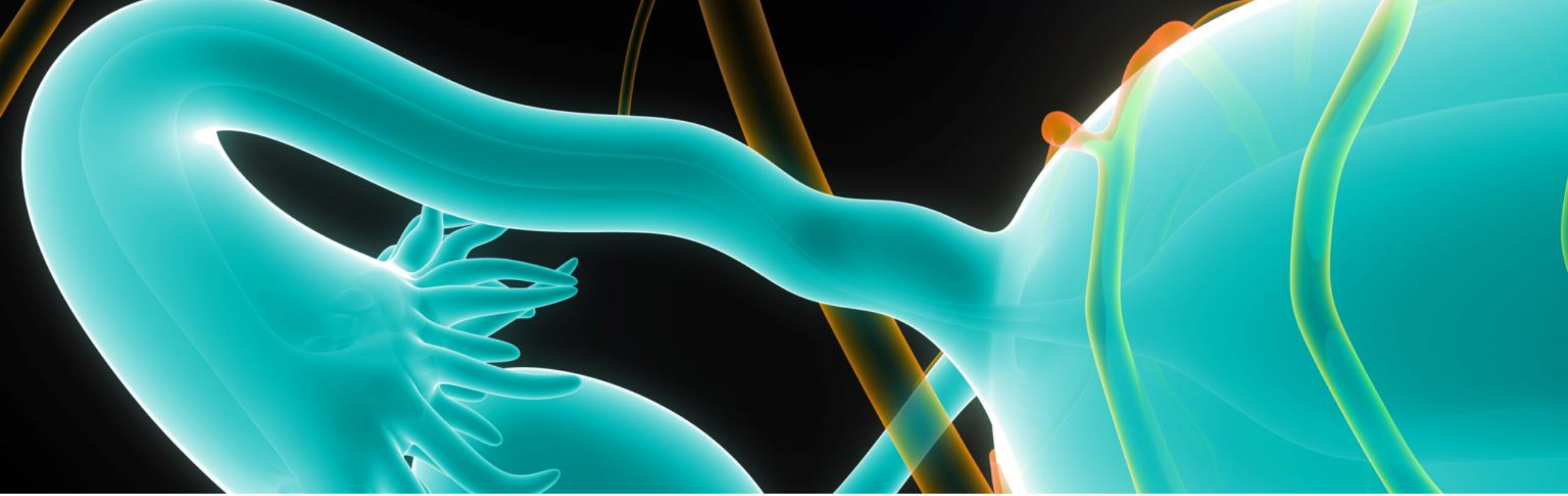


Future Directions/Outstanding Questions

- PARPi combination therapy
  - FIRST trial with chemo + anti-PD-1 + niraparib
  - OVARIO phase III trial with niraparib + bevacizumab
  - ATHENA trial with rucaparib + nivolumab
  - ENGOT-OV46/AGO/DUO-O trial with durvalumab + bevacizumab + chemo + olaparib
  - ENGOT-OV43/BGOG chemo + pembrolizumab + olaparib
- Re-trialing PARPi after patient progression



Question & Answer



Thank you!