Sequencing of Treatments for Patients With Ovarian Cancer

Laura Doherty, FNP-BC, AOCNP®

Director of Survivorship Program, Program in Women's Oncology

Katina Robison, MD

Director of Research, Program in Women's Oncology
Co-Director, Women's Intimacy and Sexual Health (WISH) Clinic
Associate Professor of Obstetrics & Gynecology and Medicine
The Warren Alpert Medical School of Brown University

2018 JADPRO Live
THE ANNUAL APSHO MEETING

Learning Objectives

1. Review history of ovarian cancer treatment
2. Evaluate safety and efficacy data for PARP inhibitors
3. Discuss current options for first-line and maintenance therapy
4. Interpret emerging data regarding the combination of PARP inhibitors with immunotherapy or anti-angiogenic agents

Financial Disclosure

Ms. Doherty and Dr. Robison have nothing to disclose.

Ovarian Cancer

Includes ovarian, fallopian tube, and primary peritoneal cancer

#1 cause of gynecologic cancer deaths

5th cause of cancer-related death in women

11th most common cancer in women

22,240 new cases will be diagnosed this year

50% diagnosed are at least 60 years old

Every **24** minutes another woman is diagnosed with ovarian cancer in the U.S.

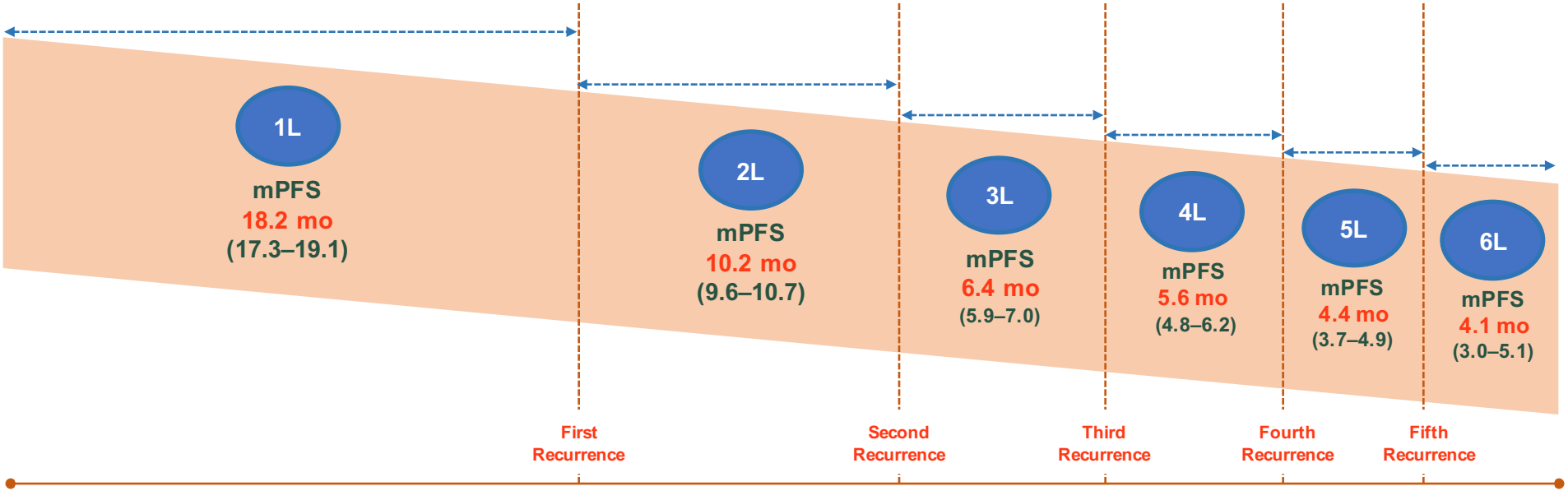
1 in 79 women will develop ovarian cancer in her lifetime

14,070 women will die this year

https://ocrfa.org/

Most Ovarian Cancers Will Recur, Leading to Poor Prognosis and Shorter Treatment Intervals

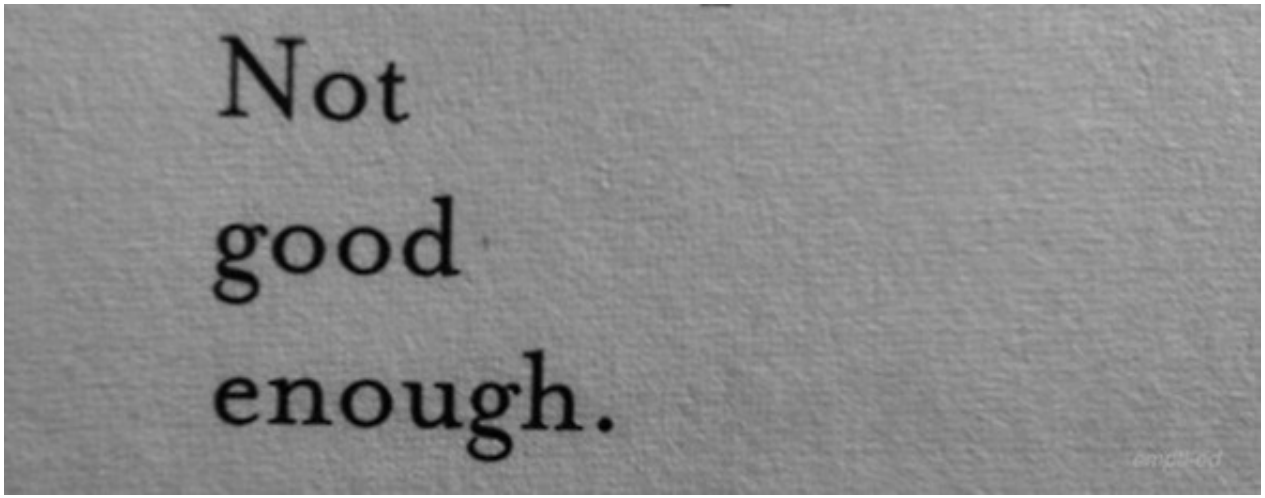
- ~80% of advanced ovarian cancers will recur during or after first-line treatment
- Median PFS decreases after every recurrence



PFS = progression-free survival

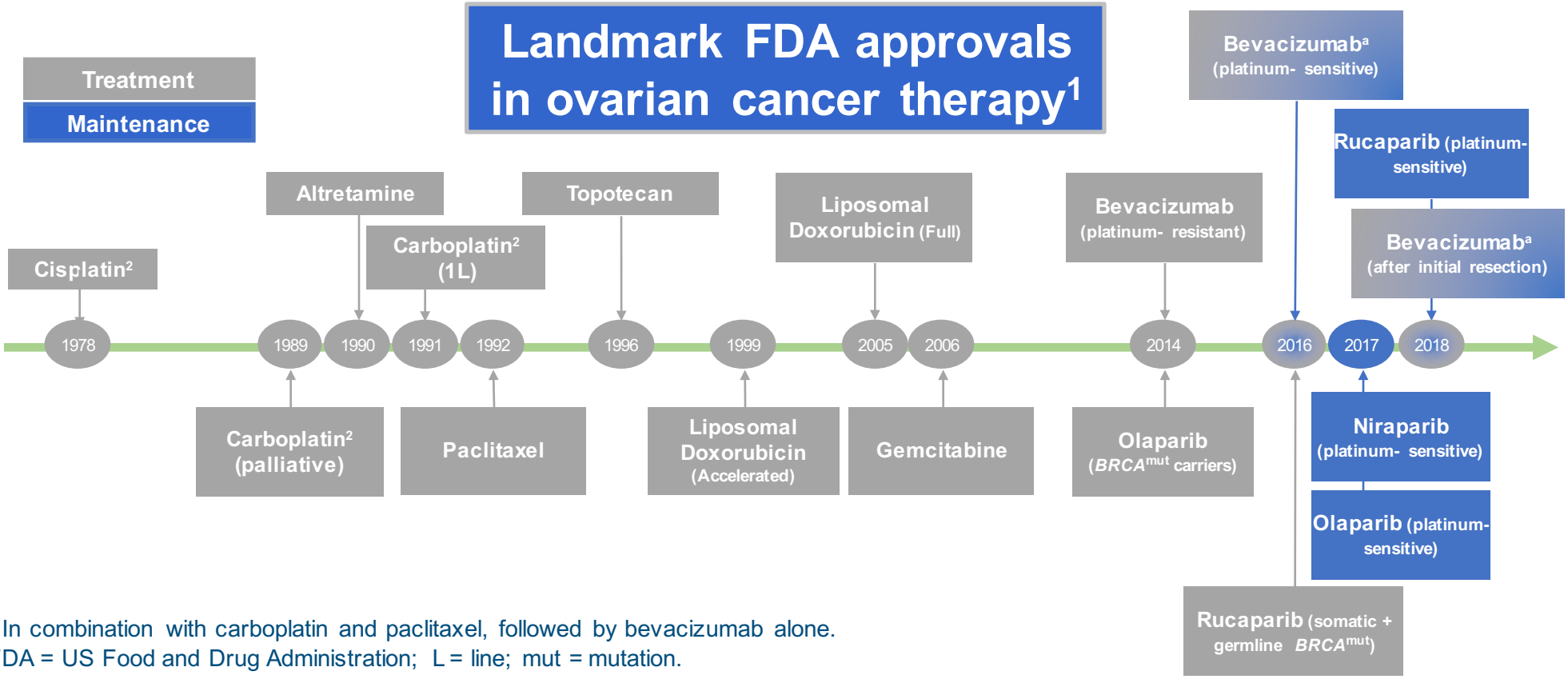
Hanker LC, et al. *Ann Oncol*. 2012;23(10):2605-12.

Less than 30% will be cured.



Frey and Pothuri Gynecologic Oncology Research and Practice (2017) 4:4 DOI 10.1186/s40661-017-0039-8

Landmark FDA approvals in ovarian cancer therapy[1]



[a] In combination with carboplatin and paclitaxel, followed by bevacizumab alone.
FDA = US Food and Drug Administration; L = line; mut = mutation.

1. Drugs@FDA: FDA Approved Drug Products. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed March 29, April 9, and June 13, 2018. **2.** Kelland L. *Nat Rev Cancer*. 2007;7(8):573-84.

Many Therapies Proved Ineffective as Maintenance

	Clinical Benefit	
Strategy	**No**	**Yes**
Prolonged initial therapy[1,2]	✓	
Consolidation therapy with topotecan[3]	✓	
High-dose/shorter interval chemotherapy[4]	✓	
Intraperitoneal[5]	✓	
Interferon-α[6]	✓	
Oregovomab[7]	✓	
Erlotinib[8]	✓	
Tanomastat[9]	✓	
Abagovomab[10]	✓	
Paclitaxel (6 months)[11]	✓	
Paclitaxel (12 months)[12]		✓

1. Lambert HE, et al. *Ann Oncol*. 1997;8(4):327-33. 2. Bertelsen K, et al. *Gynecol Oncol*. 1993;49(1):30-6. 3. De Placido S, et al. *J Clin Oncol*. 2004;22(13):2635-42. 4. Chan JK, et al. *N Engl J Med*. 2016;374(8):738-48. 5. Barakat RR, et al. *J Clin Oncol*. 2002;20(3):694-8. 6. Hall GD, et al. *Br J Cancer*. 2004;91(4):621-6. 7. Berek J, et al. *J Clin Oncol*. 2009;27(3):418-25. 8. Vergote IB, et al. *J Clin Oncol*. 2014;32(4):320-6. 9. Hirte H, et al. *Gynecol Oncol*. 2006;102(2):300-8. 10. Sabbatini P, et al. *J Clin Oncol*. 2013;31(12):1554-61. 11. Conte PF, et al. *J Clin Oncol*. 2007;25(18 suppl):abstr 5505. 12. Markman M, et al. *J Clin Oncol*. 2003;21(13):2460-5.

Additional Taxane Maintenance Did Not Alter OS

- Progression was slightly delayed with additional chemotherapy[1]
- Neither GOG-0178 or GOG-0212 demonstrated an effect of taxane maintenance on overall survival[1,2]

GOG-0212 (NCT00108745)			
Treatment Group	Events	n	mOS, mo
Paclitaxel	206	384	51.3
Paclitaxel poliglumex (CT-2103)	194	387	60.0
Surveillance	200	386	54.8

- Additional taxane therapy increases grades 3 to 4 adverse events, most notably neurotoxicity[2]

mOS = median overall survival; OS = overall survival.

1. Markman M, et al. *J Clin Oncol*. 2003;21(13):2460-5. 2. Copeland LJ, et al. Presented at SGO Annual Meeting, 2017.

Ovarian Cancer

Why the Change?

Genetic Mutations

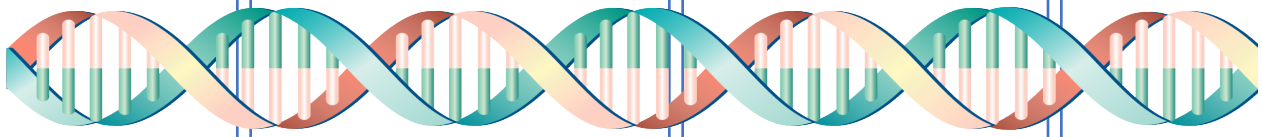
Frequently mutated genes in ovarian cancer (germline and somatic)			
TP53	*CSMD3*	*PTEN*	*EMSY*
BRCA1	*RB1*	*RAD51*	*ATM/ATR*
BRCA2	*NF1*	*CDK12*	*CCNE1*

Genetic Mutations

Frequently mutated genes in ovarian cancer (germline and somatic)			
TP53	*CSMD3*	*PTEN*	*EMSY*
BRCA1	*RB1*	*RAD51*	*ATM/ATR*
BRCA2	*NF1*	*CDK12*	*CCNE1*

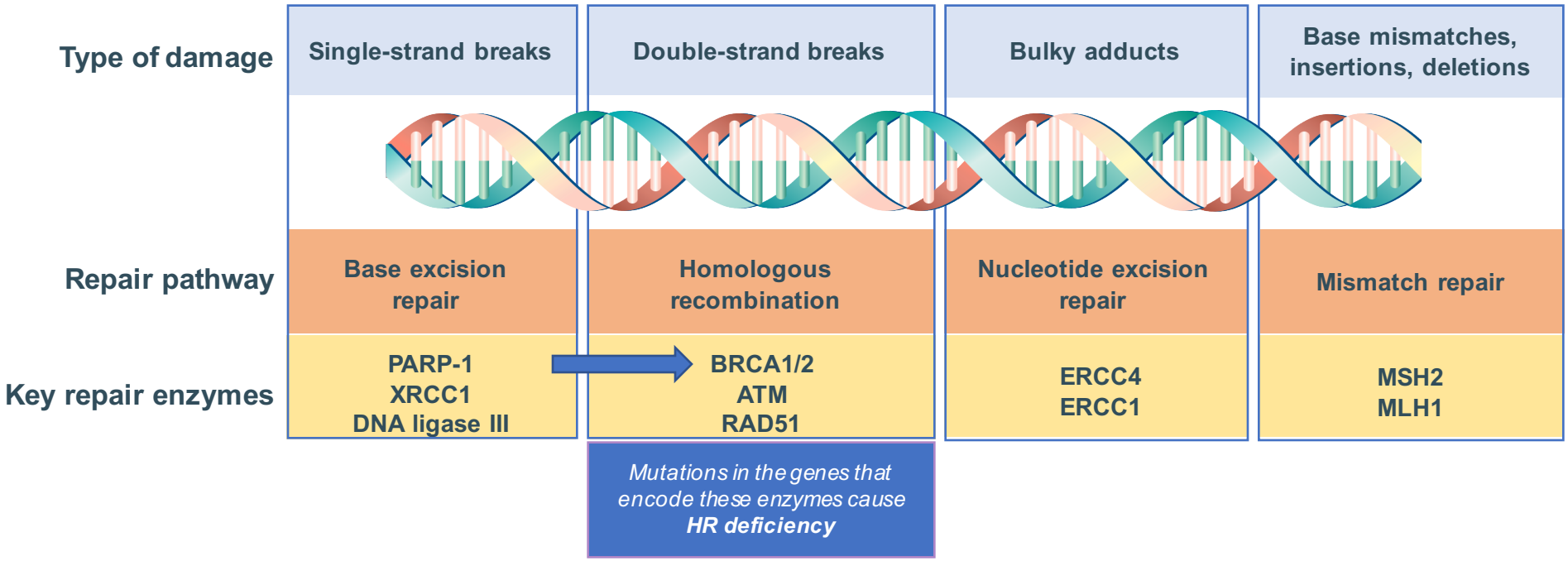
Many abnormal genes in ovarian cancer regulate DNA repair

DNA Repair Involves a Complex Protein Network

Type of damage	Single-strand breaks	Double-strand breaks	Bulky adducts	Base mismatches, insertions, deletions
				
Repair pathway	Base excision repair	Homologous recombination	Nucleotide excision repair	Mismatch repair
Key repair enzymes	PARP-1 XRCC1 DNA ligase III	BRCA1/2 ATM RAD51	ERCC4 ERCC1	MSH2 MLH1

1. Lord CJ, et al. *Nature*. 2012;481(7381):287-94. 2. Hosoya N, et al. *Cancer Sci*. 2014;105(4):370-88.

DNA Repair Involves a Complex Protein Network



1. Lord CJ, et al. *Nature.* 2012;481(7381):287-94. 2. Hosoya N, et al. *Cancer Sci.* 2014;105(4):370-88.

BRCA

- **BR**east **CA**ncer susceptibility gene (BRCA)
  - Code for proteins that are essential for repair of double-strand breaks of DNA through the homologous recombination repair (HRR) pathway

Germline	Somatic	Wild type
Inherited from parent	Spontaneous mutation in tumor tissue	No mutation in BRCA gene
$gBRCA^{mut}$	$sBRCA^{mut}$	$BRCA^{wt}$

$BRCA^{mut}$ refers to both $gBRCA^{mut}$ and $sBRCA^{mut}$

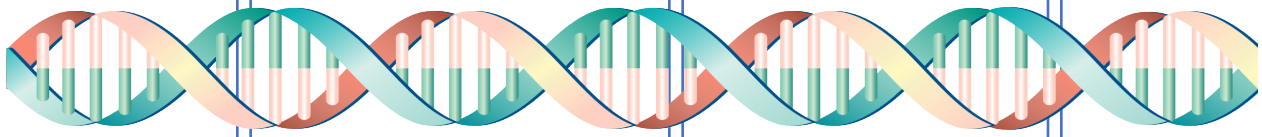
Loss of Heterozygosity (LOH)

- LOH^{low}
- LOH^{high}

Loss of Heterozygosity (LOH)

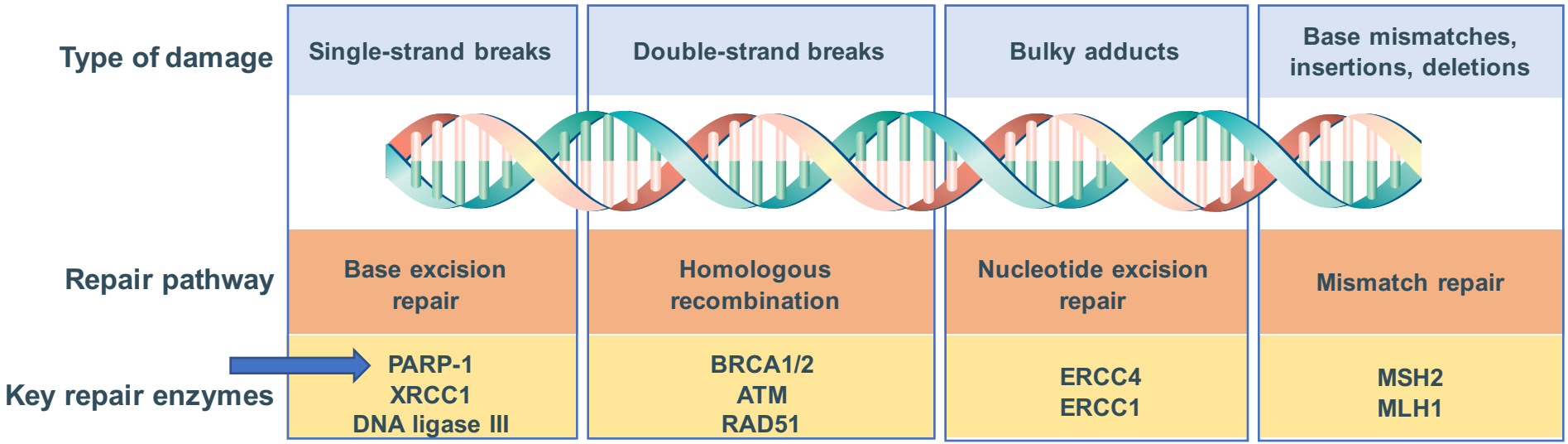
- LOH^{low}
- LOH^{high} → "BRCAness"

DNA Repair Involves a Complex Protein Network

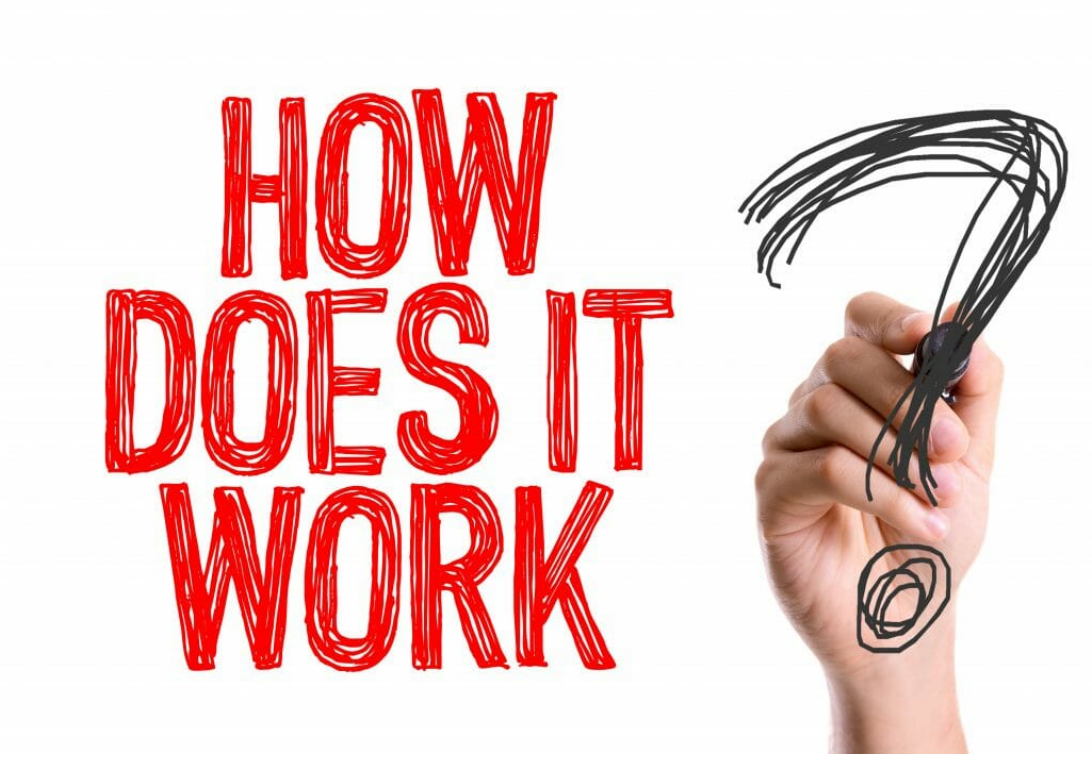
Type of damage	Single-strand breaks	Double-strand breaks	Bulky adducts	Base mismatches, insertions, deletions
				
Repair pathway	Base excision repair	Homologous recombination	Nucleotide excision repair	Mismatch repair
Key repair enzymes	PARP-1 XRCC1 DNA ligase III	BRCA1/2 ATM RAD51	ERCC4 ERCC1	MSH2 MLH1

1. Lord CJ, et al. *Nature*. 2012;481(7381):287-94. 2. Hosoya N, et al. *Cancer Sci*. 2014;105(4):370-88.

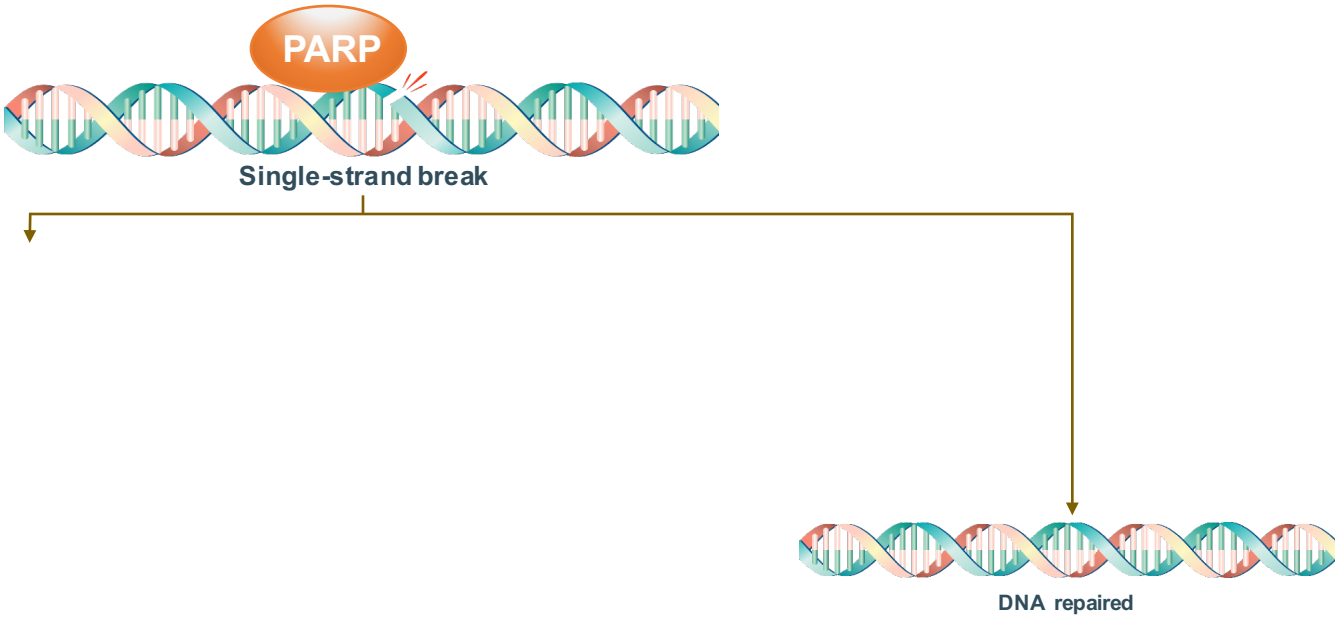
DNA Repair Involves a Complex Protein Network



1. Lord CJ, et al. *Nature*. 2012;481(7381):287-94. 2. Hosoya N, et al. *Cancer Sci*. 2014;105(4):370-88.


HOW
DOES IT
WORK

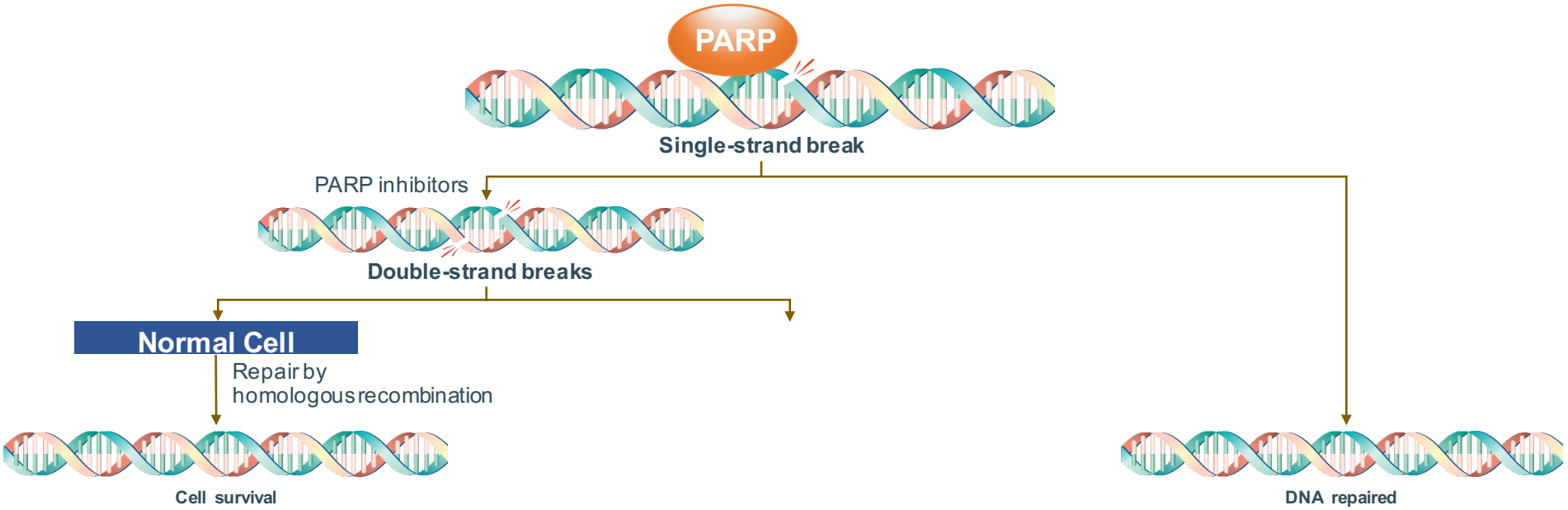
How PARP Inhibitors Work



HRD = homologous recombination deficiency; PARP = poly ADP ribose polymerase.

Sonnenblick A, et al. *Nat Rev Clin Oncol.* 2015;12(1):27-41.

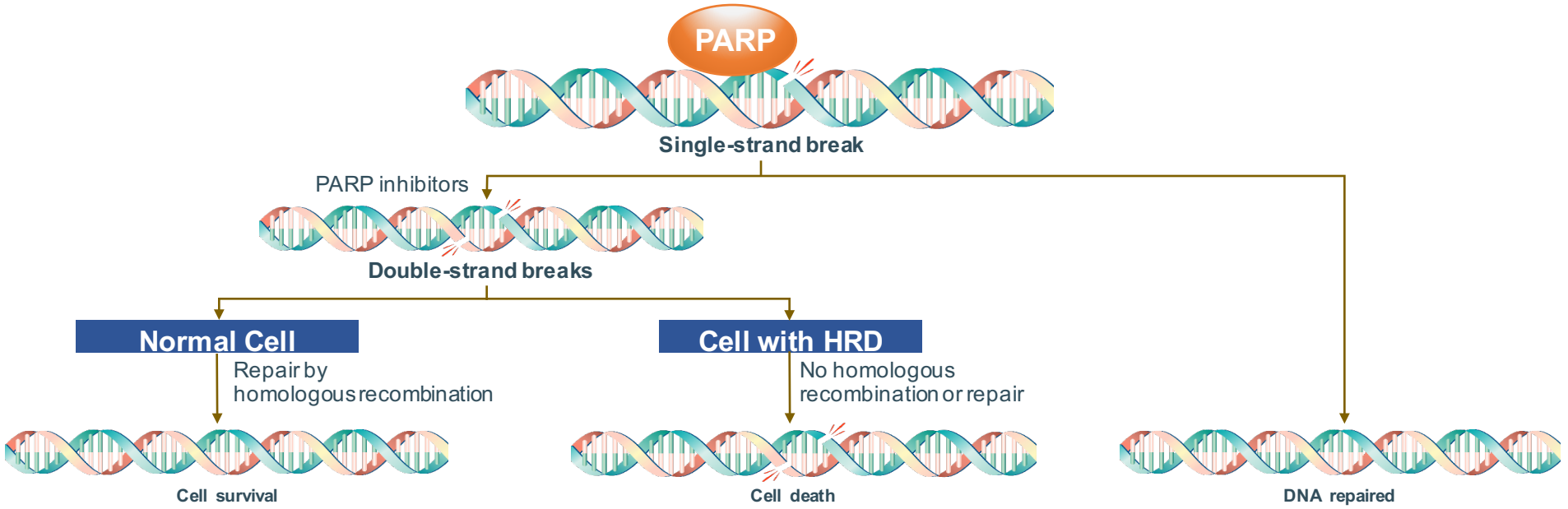
How PARP Inhibitors Work



HRD = homologous recombination deficiency; PARP = poly ADP ribose polymerase.

Sonnenblick A, et al. *Nat Rev Clin Oncol.* 2015;12(1):27-41.

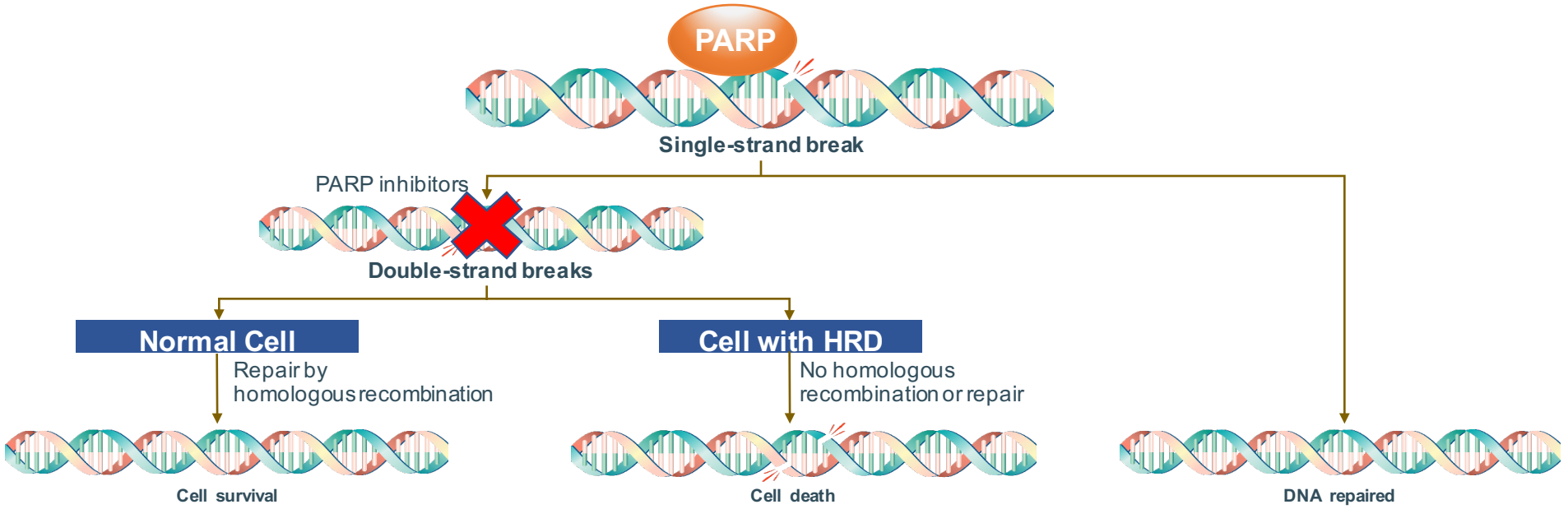
How PARP Inhibitors Work



HRD = homologous recombination deficiency; PARP = poly ADP ribose polymerase.

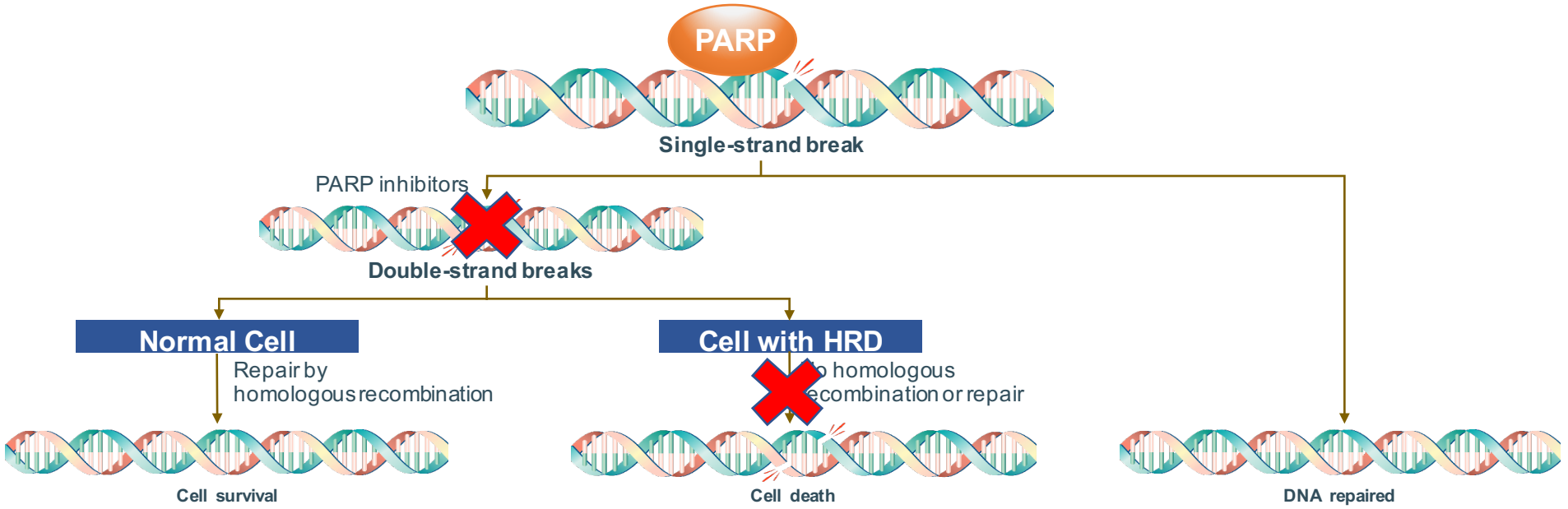
Sonnenblick A, et al. *Nat Rev Clin Oncol.* 2015;12(1):27-41.

How PARP Inhibitors Work



Sonnenblick A, et al. *Nat Rev Clin Oncol.* 2015;12(1):27-41.

How PARP Inhibitors Work



Sonnenblick A, et al. *Nat Rev Clin Oncol.* 2015;12(1):27-41.

Drug	Clinical Trials		s
Olaparib[1,2]	• Study 42	Tre ova bas	eterious germline BRCA-mutated advanced hemotherapy. Select patients for therapy b
	• SOLO-2 • Study 19	Mai peri	lial ovarian, fallopian tube, or primary hemotherapy
Rucaparib[3]	• Study 10 • ARIEL2	Mor ass ther	mutation (germline and/or somatic) with ≥2 chemotherapies. Select patients for r rucaparib
	• ARIEL3	Mai peri	lial ovarian, fallopian tube, or primary hemotherapy
Niraparib[4]	• NOVA	Mai peri	lial ovarian, fallopian tube, or primary hemotherapy

CR = complete response; PR = partial response.

1. Olaparib package insert. AstraZeneca Pharmaceuticals LP; January 2018. 2. FDA. Summary Review for Regulatory Action: Olaparib. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/206162Orig1s000SumR.pdf. Approval date December 19, 2014. Accessed April 10, 2018. 3. Rucaparib package insert. Clovis Oncology, Inc; April 2018. 4. Niraparib package insert. TESARO, Inc; August 2017.

Drug	Clinical Trials	Indications
Olaparib[1,2]	• Study 42	Treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer who have been treated with ≥3 prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for olaparib
	• SOLO-2 • Study 19	Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a CR or PR to platinum-based chemotherapy
Rucaparib[3]	• Study 10 • ARIEL2	Monotherapy for treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with ≥2 chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for rucaparib
	• ARIEL3	Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a CR or PR to platinum-based chemotherapy
Niraparib[4]	• NOVA	Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a CR or PR to platinum-based chemotherapy

1. Olaparib package insert. AstraZeneca Pharmaceuticals LP; January 2018. 2. FDA. Summary Review for Regulatory Action: Olaparib. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/206162Orig1s000SumR.pdf. Approval date December 19, 2014. Accessed April 10, 2018. 3. Rucaparib package insert. Clovis Oncology, Inc; April 2018. 4. Niraparib package insert. TESARO, Inc; August 2017.

Drug	Clinical Trials	Indications
Olaparib[1,2]	• Study 42	Treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer who have been treated with ≥3 prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for olaparib
	• SOLO-2 • Study 19	Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a CR or PR to platinum-based chemotherapy
Rucaparib[3]	• Study 10 • ARIEL2	Monotherapy for treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with ≥2 chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for rucaparib
	• ARIEL3	Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a CR or PR to platinum-based chemotherapy
Niraparib[4]	• NOVA	Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a CR or PR to platinum-based chemotherapy

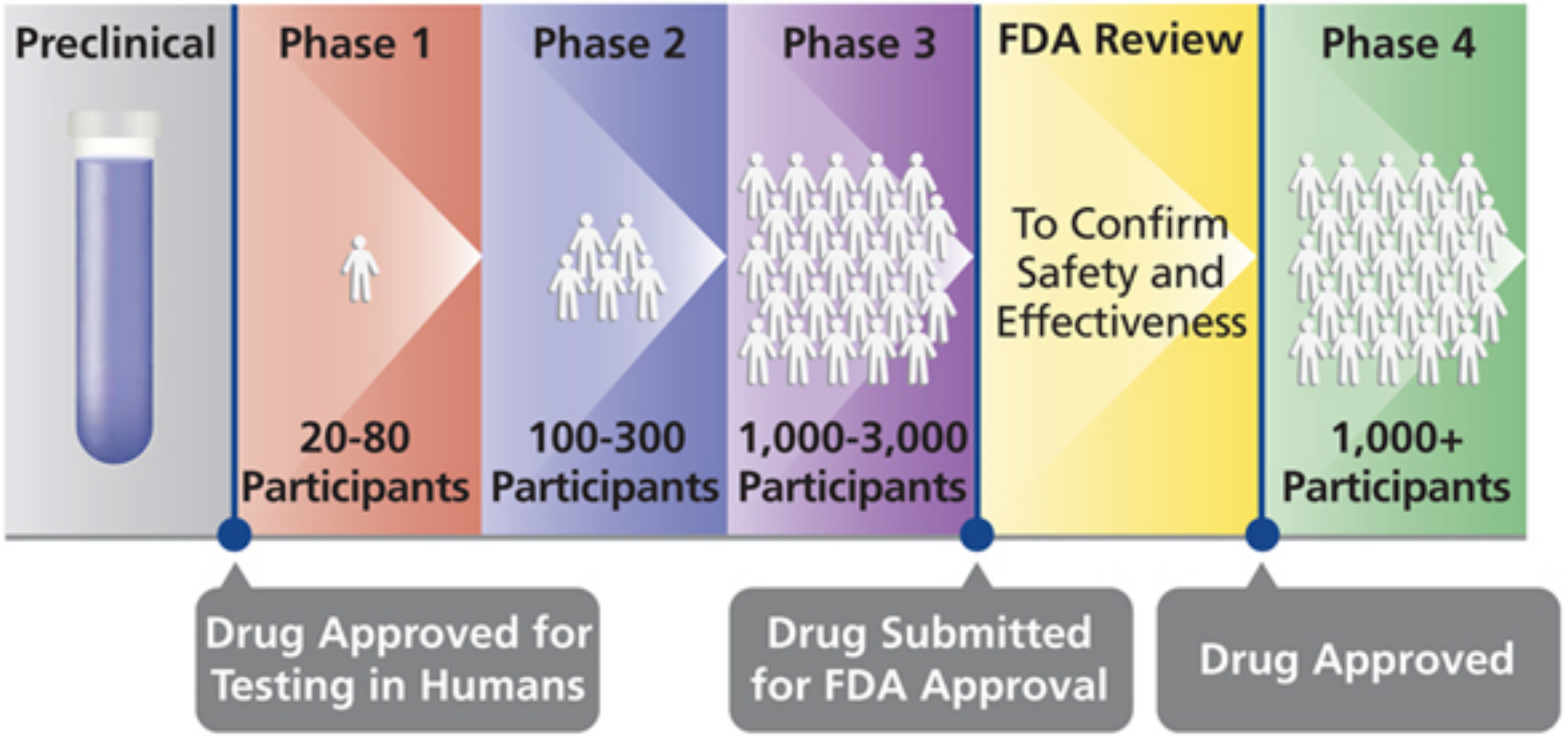
1. Olaparib package insert. AstraZeneca Pharmaceuticals LP; January 2018. 2. FDA. Summary Review for Regulatory Action: Olaparib. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/206162Orig1s000SumR.pdf. Approval date December 19, 2014. Accessed April 10, 2018. 3. Rucaparib package insert. Clovis Oncology, Inc; April 2018. 4. Niraparib package insert. TESARO, Inc; August 2017.

Drug	Clinical Trials	Indications
Olaparib[1,2]	• Study 42	Treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer who have been treated with ≥3 prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for olaparib
	• SOLO-2 • Study 19	Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a CR or PR to platinum-based chemotherapy
Rucaparib[3]	• Study 10 • ARIEL2	Monotherapy for treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with ≥2 chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for rucaparib
	• ARIEL3	Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a CR or PR to platinum-based chemotherapy
Niraparib[4]	• NOVA	Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a CR or PR to platinum-based chemotherapy

1. Olaparib package insert. AstraZeneca Pharmaceuticals LP; January 2018. 2. FDA. Summary Review for Regulatory Action: Olaparib. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/206162Orig1s000SumR.pdf. Approval date December 19, 2014. Accessed April 10, 2018. 3. Rucaparib package insert. Clovis Oncology, Inc; April 2018. 4. Niraparib package insert. TESARO, Inc; August 2017.


Here's the proof...

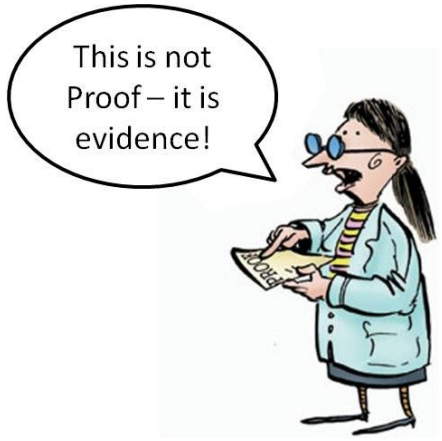
Clinical Trials



TREATMENT

PARPi

Olaparib
Treatment for Patients With Ovarian Cancer, a g*BRCA* Mutation, and ≥3 Prior Lines of Chemotherapy



	Study 42 (NCT01078662)[1,2]
N	137
Design	Phase 2
Patients	Advanced solid tumors with gBRCA1/2 mutation (N=298)
	Recurrent ovarian cancer cohort (n=193): platinum-resistant epithelial ovarian, primary peritoneal, or fallopian tube cancer; ≥3 prior lines of chemotherapy
Treatment	Olaparib 400 mg bid
Results	ORR: 34% mPFS: 6.7 mo
Safety: Most common grade ≥3 AEs	Anemia (20%) Abdominal pain (8%) Fatigue (7%)

[a] Overall study population: N=298; ovarian cancer cohort n=193; safety and PFS analyses: ovarian cancer patients who received ≥3 prior lines of chemotherapy n=154; ORR analysis: ovarian cancer patients with measurable disease who received ≥3 prior lines of chemotherapy n=137.

AE = adverse event; bid = twice daily; g = germline; mPFS = median progression-free survival; ORR = objective response rate.

1. Kaufman B, et al. *J Clin Oncol*. 2015;33(3):244-50. 2. Domchek SM, et al. *Gynecol Oncol*. 2016;140(2):199-203.

	Study 42 (NCT01078662)[1,2]
N	137
Design	Phase 2
Patients	Advanced solid tumors with gBRCA1/2 mutation (N=298)
	Recurrent ovarian cancer cohort (n=193): platinum-resistant epithelial ovarian, primary peritoneal, or fallopian tube cancer; ≥3 prior lines of chemotherapy
Treatment	Olaparib 400 mg bid
Results	ORR: 34% mPFS: 6.7 mo
Safety: Most common grade ≥3 AEs	Anemia (20%) Abdominal pain (8%) Fatigue (7%)

[a] Overall study population: N=298; ovarian cancer cohort n=193; safety and PFS analyses: ovarian cancer patients who received ≥3 prior lines of chemotherapy n=154; ORR analysis: ovarian cancer patients with measurable disease who received ≥3 prior lines of chemotherapy n=137.

AE = adverse event; bid = twice daily; g = germline; mPFS = median progression-free survival; ORR = objective response rate.

1. Kaufman B, et al. *J Clin Oncol*. 2015;33(3):244-50. 2. Domchek SM, et al. *Gynecol Oncol*. 2016;140(2):199-203.

Rucaparib

Treatment for Patients With Ovarian Cancer and a Germline or Somatic *BRCA* Mutation and ≥2 Prior Lines of Chemotherapy

	Study 10 (NCT01482715)[1]	
	Part 1	Part 2
N	56	42
Design	Phase 1 dose escalation	Phase 2 expansion
Patients	Advanced solid tumor, progressed on treatment	Platinum-sensitive, relapsed, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer, with gBRCA1/2 mutation, 2–4 prior regimens
Treatment	Rucaparib 40–840 mg daily or bid (3+3)	Rucaparib 600 mg bid
Results	RP2D: 600 mg bid	ORR: 59.5%
Safety: Most common grade 3 or 4 AEs	NR	Anemia (38.1%) Fatigue/asthenia (26.2%) Neutropenia (16.6%)

NR = not reported; RP2D = recommended phase 2 dose.

Kristeleit R, et al. *Clin Cancer Res*. 2017;23(15):4095-106.

	Study 10 (NCT01482715)[1]	
	Part 1	Part 2
N	56	42
Design	Phase 1 dose escalation	Phase 2 expansion
Patients	Advanced solid tumor, progressed on treatment	Platinum-sensitive, relapsed, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer, with gBRCA1/2 mutation, 2–4 prior regimens
Treatment	Rucaparib 40–840 mg daily or bid (3+3)	Rucaparib 600 mg bid
Results	RP2D: 600 mg bid	ORR: 59.5%
Safety: Most common grade 3 or 4 AEs	NR	Anemia (38.1%) Fatigue/asthenia (26.2%) Neutropenia (16.6%)

NR = not reported; RP2D = recommended phase 2 dose.

Kristeleit R, et al. *Clin Cancer Res*. 2017;23(15):4095-106.

	ARIEL2 (NCT01891344)			
	$BRCA^{mut}$ (all)	$sBRCA^{mut}$*	$BRCA^{wt}$, LOH high	$BRCA^{wt}$, LOH low
N	40	19	82	70
Design	Phase 2			
Patients	Part 1: Platinum-sensitive, high-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal cancer with ≥1 prior line of platinum therapy Part 2 (ongoing): Platinum-sensitive, -resistant, or -refractory; 3–4 prior lines of chemotherapy			
Treatment	Rucaparib 600 mg bid			
Results (Part 1)	mPFS: 12.8 mo	Confirmed ORR: 74%	mPFS: 5.7 mo	mPFS: 5.2 mo
	HR 0.27, P<0.0001 vs LOH low		HR 0.62, P=0.011 vs LOH low	
Safety (Part 1): Most common grade ≥3 AEs	Anemia (22%) Elevated ALT/AST (12%) Fatigue/asthenia (9%)			

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

	ARIEL2 (NCT01891344)			
	BRCA^{mut} (all)	sBRCA^{mut}*	BRCA^{wt}, LOH high	BRCA^{wt}, LOH low
N	40	19	82	70
Design	Phase 2			
Patients	Part 1: Platinum-sensitive, high-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal cancer with ≥1 prior line of platinum therapy Part 2 (ongoing): Platinum-sensitive, -resistant, or -refractory; 3–4 prior lines of chemotherapy			
Treatment	Rucaparib 600 mg bid			
Results (Part 1)	mPFS: 12.8 mo	Confirmed ORR: 74%	mPFS: 5.7 mo	mPFS: 5.2 mo
	HR 0.27, P<0.0001 vs LOH low		HR 0.62, P=0.011 vs LOH low	
Safety (Part 1): Most common grade ≥3 AEs	Anemia (22%) Elevated ALT/AST (12%) Fatigue/asthenia (9%)			

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

Treatment With PARPi

PARPi	Prior lines	Platinum status	gBRCA	sBRCA	BRCAwt
Olaparib	≥ 3 prior lines	Independent of platinum status	Yes	No	No
Rucaparib	≥ 2 prior lines	Independent of platinum status	Yes	Yes	No
Niraparib	Not currently indicated for treatment of ovarian cancer				

MAINTENANCE

Requirements for Long-Term Treatments Apply When Considering Maintenance Therapy

- ✓ Effective
- ✓ Manageable Adverse Effects
- ✓ Convenient

1. Hope JM, et al. *Int J Womens Health*. 2009;1:173-80. 2. Korkmaz T, et al. *Crit Rev Oncol Hematol*. 2016;98:180-8.

FDA-Approved Maintenance

- Anti-angiogenics
  - Bevacizumab: VEGF inhibitor
- PARPi
  - Olaparib
  - Rucaparib
  - Niraparib

VEGF = vascular endothelial growth factor

FRONTLINE MAINTENANCE

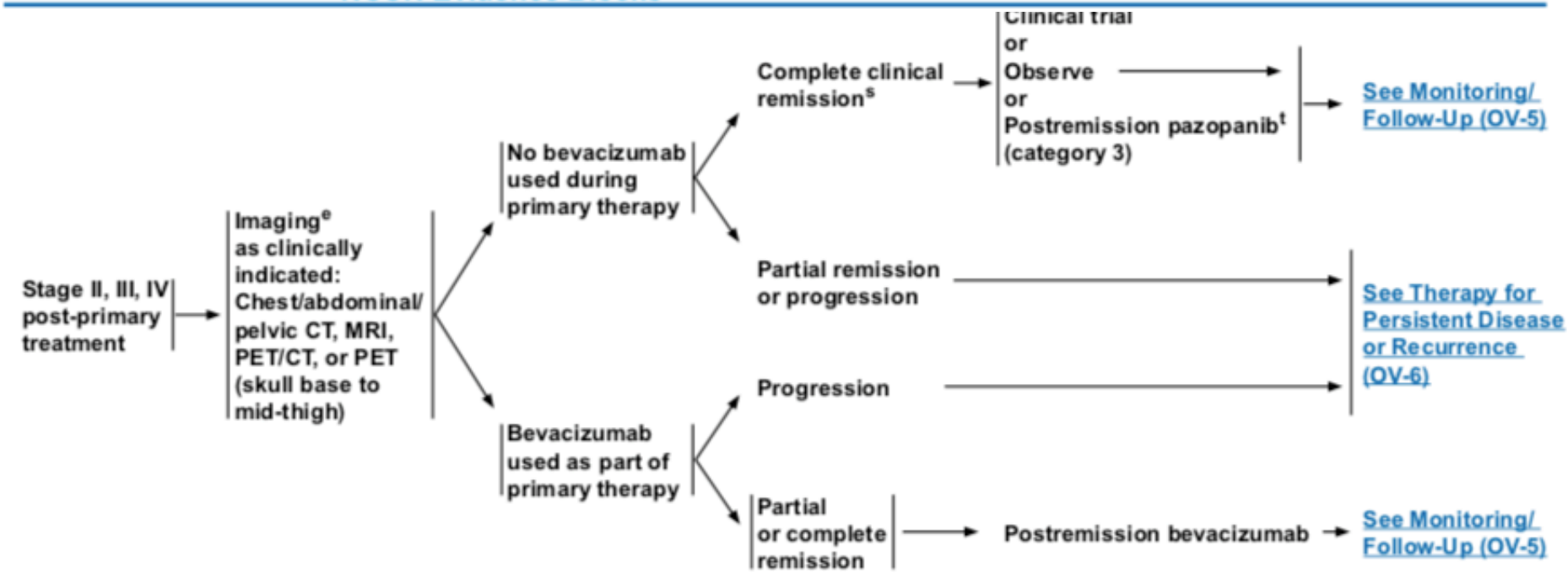
Bevacizumab

NCCN Clinical Practice Guidelines Recommend Maintenance Therapy as an Option for Patients in Response to Platinum-Based Chemotherapy

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2018
Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer
NCCN Evidence Blocks™

NCCN Guidelines Index
Table of Contents
Discussion

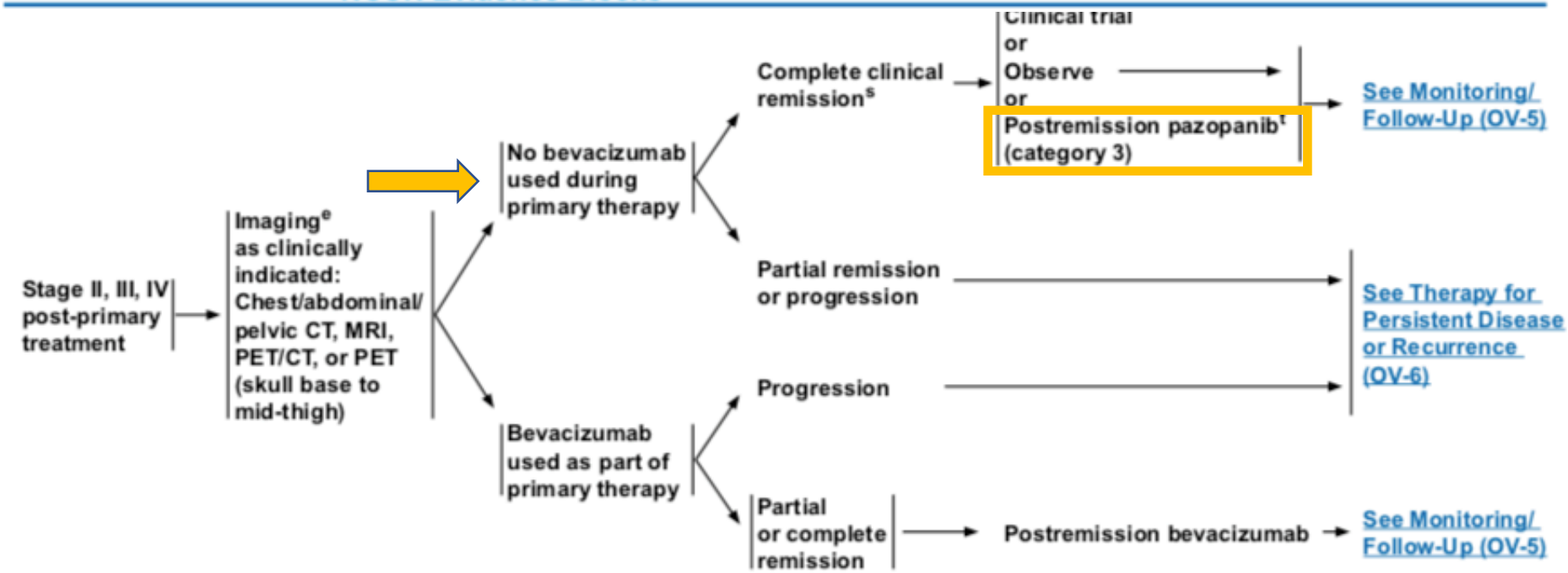


See Evidence Blocks on OV-B (EB-7)

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2018
Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer
NCCN Evidence Blocks™

NCCN Guidelines Index
Table of Contents
Discussion

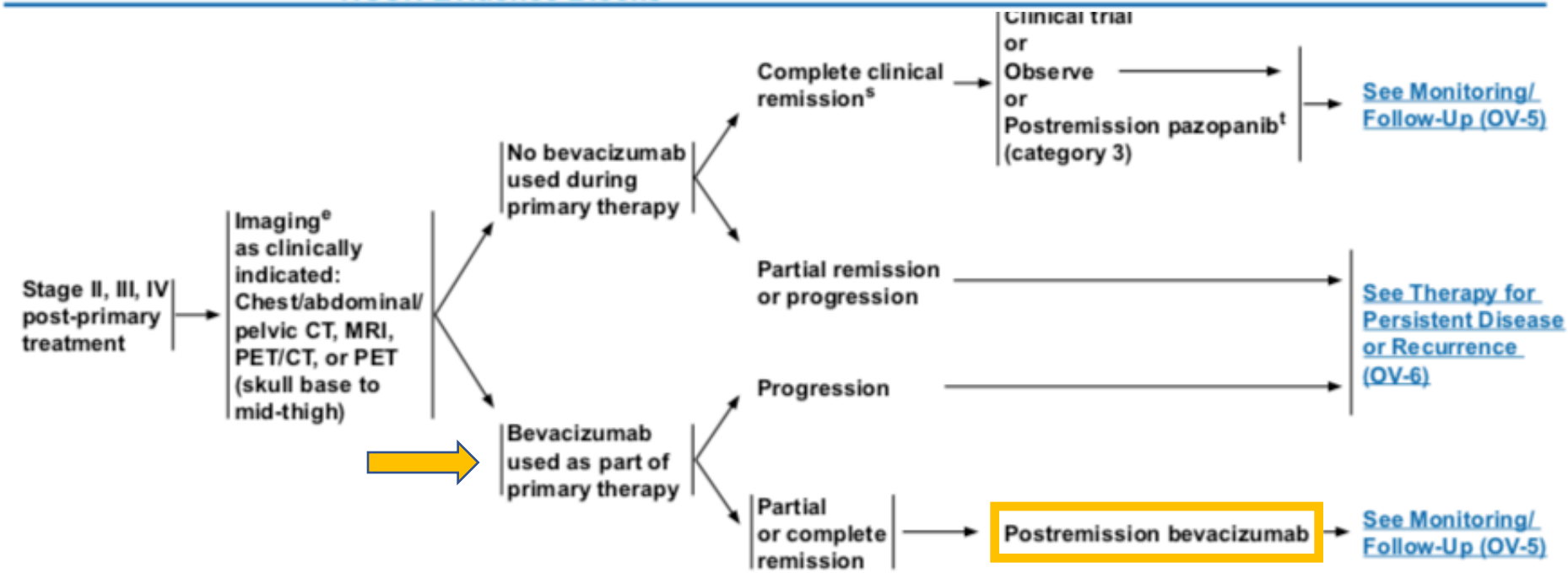


See Evidence Blocks on OV-B (EB-7)

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2018
Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer
NCCN Evidence Blocks™

NCCN Guidelines Index
Table of Contents
Discussion



See Evidence Blocks on OV-B (EB-7)

Anti-Angiogenic Maintenance Therapy in Front-Line Ovarian Cancer Setting

	GOG-0218[4-6] (NCT00262847)		
	CP + Placebo → Placebo (n=625)	**CP + BEV → Placebo (n=625)[a]**	**CP + BEV → BEV (n=623)[a]**
mPFS, mo (95% CI)	10.3 (NR)	11.2 (NR)	14.1 (NR)
HR (95% CI) P value	--	0.908 (0.795–1.040)[b] 0.16	0.717 (0.625–0.824)[b] <0.001
mOS, mo (95% CI)	41.1 (NR)	40.8 (NR)	43.4 (NR)
HR (95% CI) P value	--	1.06 (0.94–1.20)[b] 0.34	0.96 (0.85–1.09)[b] 0.53
Most common serious AEs (%)	Neutropenia (Gr ≥4): 57.7 Pain (Gr ≥2): 41.6 Hypertension (Gr ≥2): 7.2	Neutropenia (Gr ≥4): 63.3 Pain (Gr ≥2): 41.5 Hypertension (Gr ≥2): 16.5	Neutropenia (Gr ≥4): 63.3 Pain (Gr ≥2): 47.0 Hypertension (Gr ≥2): 22.9

1. ClinicalTrials.gov. NCT00866697. Accessed June 27, 2018. 2. du Bois A, et al. *J Clin Oncol*. 2014;32(30):3374-82.
3. Vergote I, et al. Presented at ASCO Annual Meeting, 2018. Abstract 5518. 4. ClincialTrials.gov. NCT00262847. Accessed June 27, 2018. 5. Burger RA, et al. *New Engl J Med*. 2011;365(26):2473-83. 6. Burger RA, et al. Presented at ASCO Annual Meeting, 2018. Abstract 5517.

Anti-Angiogenic Maintenance Therapy in Front-Line Ovarian Cancer Setting

	GOG-0218[4-6] (NCT00262847)		
	CP + Placebo → Placebo (n=625)	**CP + BEV → Placebo (n=625)[a]**	**CP + BEV → BEV (n=623)[a]**
mPFS, mo (95% CI)	10.3 (NR)	11.2 (NR)	14.1 (NR)
HR (95% CI) P value	--	0.908 (0.795–1.040)[b] 0.16	0.717 (0.625–0.824)[b] <0.001
mOS, mo (95% CI)	41.1 (NR)	40.8 (NR)	43.4 (NR)
HR (95% CI) P value	--	1.06 (0.94–1.20)[b] 0.34	0.96 (0.85–1.09)[b] 0.53
Most common serious AEs (%)	Neutropenia (Gr ≥4): 57.7 Pain (Gr ≥2): 41.6 Hypertension (Gr ≥2): 7.2	Neutropenia (Gr ≥4): 63.3 Pain (Gr ≥2): 41.5 Hypertension (Gr ≥2): 16.5	Neutropenia (Gr ≥4): 63.3 Pain (Gr ≥2): 47.0 Hypertension (Gr ≥2): 22.9

1. ClinicalTrials.gov. NCT00866697. Accessed June 27, 2018. 2. du Bois A, et al. *J Clin Oncol*. 2014;32(30):3374-82.
3. Vergote I, et al. Presented at ASCO Annual Meeting, 2018. Abstract 5518. 4. ClincialTrials.gov. NCT00262847. Accessed June 27, 2018. 5. Burger RA, et al. *New Engl J Med*. 2011;365(26):2473-83. 6. Burger RA, et al. Presented at ASCO Annual Meeting, 2018. Abstract 5517.

FRONTLINE MAINTENANCE

Olaparib

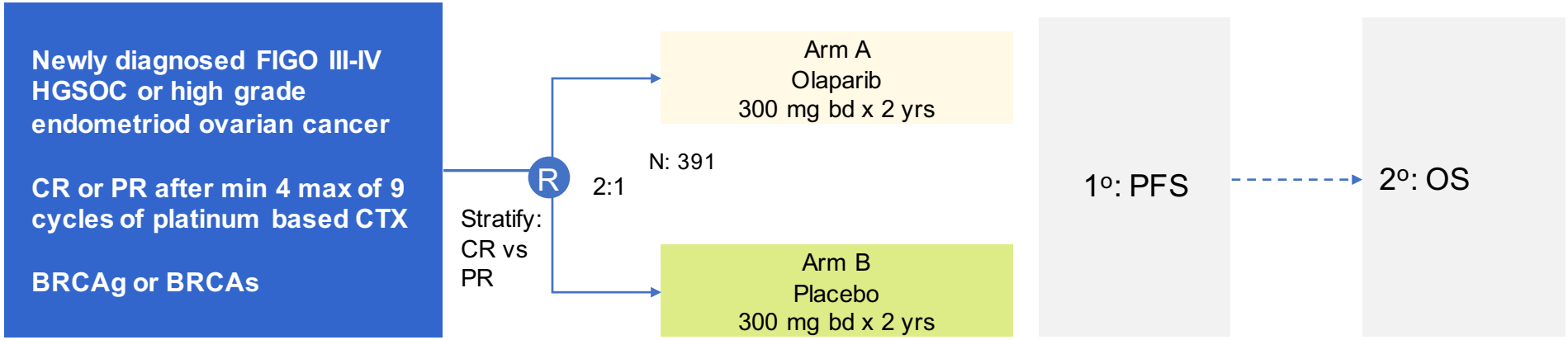
The NEW ENGLAND JOURNAL of MEDICINE

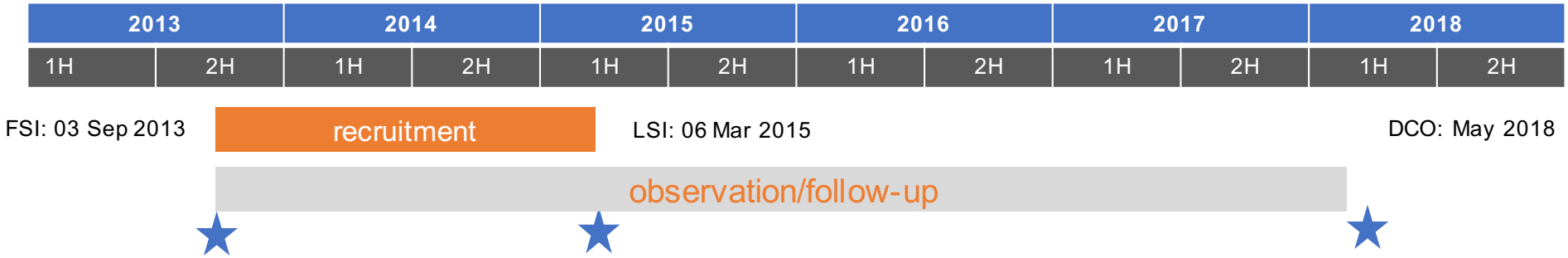
ORIGINAL ARTICLE

Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

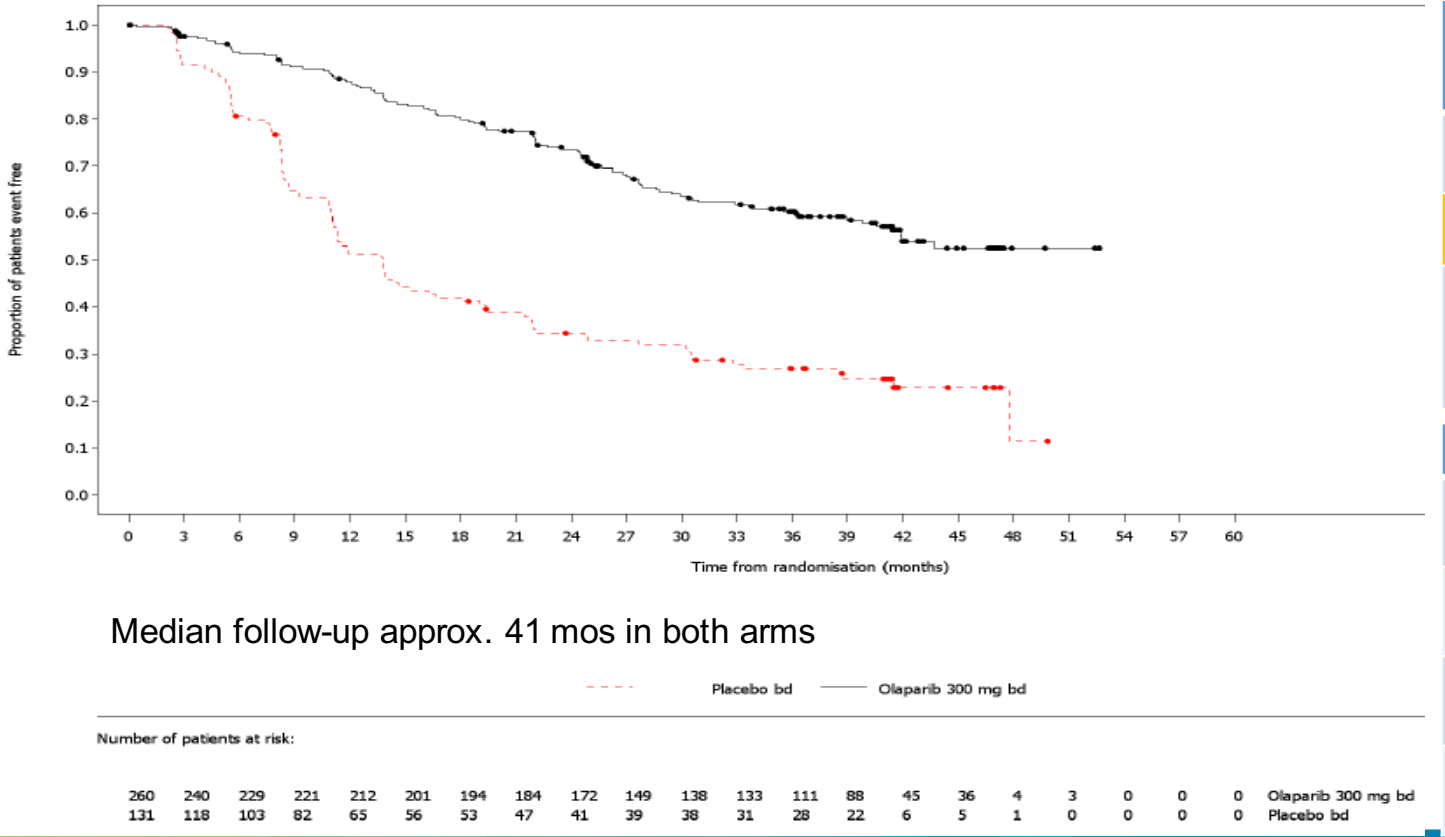
K. Moore, N. Colombo, G. Scambia, B.-G. Kim, A. Oaknin, M. Friedlander, A. Lisyanskaya, A. Floquet, A. Leary, G.S. Sonke, C. Gourley, S. Banerjee, A. Oza, A. González-Martín, C. Aghajanian, W. Bradley, C. Mathews, J. Liu, E.S. Lowe, R. Bloomfield, and P. DiSilvestro

SOLO1: Study Design





Primary Endpoint: PFS; 50.6% Maturity



Median follow-up approx. 41 mos in both arms

	Olaparib 300 mg bd	Placebo
Events	102 (39.2)	96 (73.3)
Median	NR	13.8
	HR = 0.30 95% CI (0.23,0.41) P<0.0001	
Prog free at 12m	87.7%	51.4%
Prog free at 24m	73.6%	34.6%
Prog free at 36m	60.4%	26.9%
Prog free at 48m	52.6%	11.4%

MAINTENANCE RECURRENT

Anti-angiogenic Agents

	OCEANS[1,2,a] (NCT00434642)		GOG-0213[3] (NCT00565851)		ICON6[4,5] (NCT00532194)	
	CG + Placebo (n=242)	CG + BEV (n=242)	CP (n=337)	CP + BEV (n=337)	Chemo + Placebo (n=118)	Chemo + Conc./ Maint. CED (n=164)
mPFS, mo (95% CI)	8.4 (8.3–9.7)	12.4 (11.4–12.7)	10.4 (9.7–11.0)	13.8 (13.0–14.7)	8.7	11.1
HR (95% CI) P Value	0.484 (0.388–0.605) <0.0001		0.628 (0.534–0.739) <0.0001		0.57 (0.45–0.74) <0.00001	
mOS, mo (95% CI)	32.9	33.6	37.3 (32.6–39.7)	42.2 (37.7–46.2)	19.9	27.3
HR (95% CI) P Value	0.952 (0.771–1.176) 0.6479		0.829 (0.683–1.005) 0.056		0.85 (0.66–1.10) 0.21	
Most common serious AEs in experimental arm (%)	Neutropenia (Gr ≥4): 21.1 Hypertension (Gr ≥3): 18.2 Proteinuria (Gr ≥3): 10.9		Hypertension (Gr ≥3): 12 Fatigue (Gr ≥3): 8 Proteinuria (Gr ≥3): 8		Maintenance phase: Diarrhea (Gr ≥3): 12 Fatigue (Gr ≥3): 6 Neutropenia (Gr ≥3): 6	

1. Aghajanian C, et al. *J Clin Oncol*. 2012;30(17):2039-45. **2.** Aghajanian C, et al. *Gynecol Oncol*. 2015;139(1):10-6.
3. Coleman RL, et al. *Lancet Oncol*. 2017;18(6):779-91. **4.** Ledermann JA, et al. Presented at ASCO Annual Meeting, 2017. Abstract 5506. **5.** Ledermann JA, et al. *Lancet*. 2016;387(10023):1066-74.

MAINTENANCE RECURRENT

PARPi

Olaparib

Maintenance Therapy in Patients Recurrent Platinum-Sensitive Ovarian Cancer With or Without a *BRCA* Mutation

2 150 mg tablets
(300 mg per dose)

×

2 times a day, with or without food
(600 mg daily)

Does not represent actual tablet size.

	Study 19 (NCT00753545)[1,2]	
	Olaparib	Placebo
N	136	129
Design	Phase 2	
Patients	Platinum-sensitive, recurrent ovarian or fallopian tube or primary peritoneal cancer with high-grade serous features or a serous component, with or without gBRCA1/2 mutation, ≥2 prior lines of platinum-based chemotherapy, CR or PR in response to last chemotherapy	
Treatment	400 mg bid	Placebo
Results: mPFS and HR (95% CI)	8.4 mo	4.8 mo
	0.35 (0.25–0.49); P<0.001	
Safety: Most common grade 3 or 4 AEs in active treatment group	Fatigue (6.6%) Anemia (5.1%) Nausea (2.2%) Vomiting (2.2%) Diarrhea (2.2%) Back pain (2.2%)	Fatigue (3.1%) Anemia (0.8%) Nausea (0) Vomiting (0.8%) Diarrhea (2.3%) Back pain (0)

1. Ledermann J, et al. *N Engl J Med.* 2012;366(15):1382-92. **2.** Ledermann JA, et al. *Lancet Oncol.* 2016;17(11):1579-89.

	Study 19 (NCT00753545)[1,2]	
	Olaparib	Placebo
N	136	129
Design	Phase 2	
Patients	Platinum-sensitive, recurrent ovarian or fallopian tube or primary peritoneal cancer with high-grade serous features or a serous component, with or without gBRCA1/2 mutation, ≥2 prior lines of platinum-based chemotherapy, CR or PR in response to last chemotherapy	
Treatment	400 mg bid	Placebo
Results: mPFS and HR (95% CI)	8.4 mo	4.8 mo
	0.35 (0.25–0.49); P<0.001	
Safety: Most common grade 3 or 4 A tre	Fatigue (6.6%) Anemia (5.1%) Back pain (2.2%)	Fatigue (3.1%) Anemia (0.8%) Back pain (0)

PFS for those with mutations in BRCA was 11.2 months
No change in overall survival

1. Ledermann J, et al. *N Engl J Med.* 2012;366(15):1382-92. 2. Ledermann JA, et al. *Lancet Oncol.* 2016;17(11):1579-89.

	SOLO-2 (NCT01874353)	
	Olaparib	Placebo
N	195	99
Design	Phase 3	
Patients	Platinum-sensitive, relapsed, high-grade serous ovarian cancer or high-grade endometrioid cancer including primary peritoneal or fallopian tube cancer, gBRCA1/2 mutation, ≥2 prior lines of platinum-based chemotherapy, in response to last chemotherapy	
Treatment	300 mg bid (two 150-mg tablets)	Placebo
Results: mPFS and HR (95% CI)	19.1 mo	5.5 mo
	0.30 (0.22–0.41); P<0.0001	
Safety: Most common grade 3 or 4 AEs in active treatment group	Anemia (19%) Neutropenia (5%) Fatigue/asthenia (4%)	Anemia (2%) Neutropenia (4%) Fatigue/asthenia (2%)

Pujade-Lauraine E, et al. *Lancet Oncol.* 2017;18(9):1274-84.

	SOLO-2 (NCT01874353)	
	Olaparib	Placebo
N	195	99
Design	Phase 3	
Patients	Platinum-sensitive, relapsed, high-grade serous ovarian cancer or high-grade endometrioid cancer including primary peritoneal or fallopian tube cancer, gBRCA1/2 mutation, ≥2 prior lines of platinum-based chemotherapy, in response to last chemotherapy	
Treatment	300 mg bid (two 150-mg tablets)	Placebo
Results: mPFS and HR (95% CI)	19.1 mo	5.5 mo
	0.30 (0.22–0.41); P<0.0001	
Safety: Most common grade 3 or 4 AEs in active treatment group	Anemia (19%) Neutropenia (5%) Fatigue/asthenia (4%)	Anemia (2%) Neutropenia (4%) Fatigue/asthenia (2%)

Pujade-Lauraine E, et al. *Lancet Oncol*. 2017;18(9):1274-84.

Rucaparib

Maintenance Therapy in Patients Recurrent Platinum-Sensitive Ovarian Cancer With or Without a *BRCA* Mutation

	ARIEL3 (NCT01968213)							
	Rucaparib				Placebo			
N	375[a]				189			
Design	Phase 3							
Patients	Platinum-sensitive, high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancer, ≥2 prior lines of platinum chemotherapy							
Treatment	Rucaparib 600 mg bid				Placebo			
Results: mPFS	BRCA^{mut}	HRD	BRCA^{wt} LOH$_{low}$	ITT (all pts)	BRCA^{mut}	HRD	BRCA^{wt} LOH$_{low}$	ITT (all pts)
HR (95% CI) [P value]	16.6 mo	13.6 mo	6.7 mo	10.8 mo	5.4 mo	5.4 mo	5.4 mo	5.4 mo
	0.23 (0.16–0.34) [<0.0001]	0.32 (0.24–0.42) [<0.0001]	0.58 (0.40–0.85) [0.0049]	0.36 (0.30–0.45) [<0.0001]				
Safety: Most common grade ≥3 AEs in active treatment group	Anemia (19%) Elevated ALT/AST (10%) Fatigue/asthenia (7%)				Anemia (1%) Elevated ALT/AST (0) Fatigue/asthenia (3%)			

[a] Safety population n=372. ALT = alanine aminotransferase; AST = aspartate aminotransferase; HRD = homologous recombination deficiency; ITT = intent-to-treat.

Coleman RL, et al. *Lancet.* 2017;390(10106):1949-61.

	ARIEL3 (NCT01968213)							
	Rucaparib				Placebo			
N	375[a]				189			
Design	Phase 3							
Patients	Platinum-sensitive, high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancer, ≥2 prior lines of platinum chemotherapy							
Treatment	Rucaparib 600 mg bid				Placebo			
Results: mPFS	BRCA^{mut}	HRD	BRCA^{wt} LOH$_{low}$	ITT (all pts)	BRCA^{mut}	HRD	BRCA^{wt} LOH$_{low}$	ITT (all pts)
HR (95% CI) [P value]	16.6 mo	13.6 mo	6.7 mo	10.8 mo	5.4 mo	5.4 mo	5.4 mo	5.4 mo
	0.23 (0.16–0.34) [<0.0001]	0.32 (0.24–0.42) [<0.0001]	0.58 (0.40–0.85) [0.0049]	0.36 (0.30–0.45) [<0.0001]				
Safety: Most common grade ≥3 AEs in active treatment group	Anemia (19%) Elevated ALT/AST (10%) Fatigue/asthenia (7%)				Anemia (1%) Elevated ALT/AST (0) Fatigue/asthenia (3%)			

[a] Safety population n=372. ALT = alanine aminotransferase; AST = aspartate aminotransferase; HRD = homologous recombination deficiency; ITT = intent-to-treat.

Coleman RL, et al. *Lancet.* 2017;390(10106):1949-61.

	ARIEL3 (NCT01968213)							
	Rucaparib				Placebo			
N	375[a]				189			
Design	Phase 3							
Patients	Platinum-sensitive, high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancer, ≥2 prior lines of platinum chemotherapy							
Treatment	Rucaparib 600 mg bid				Placebo			
Results: mPFS	$BRCA^{mut}$	HRD	$BRCA^{wt}$ LOH_{low}	ITT (all pts)	$BRCA^{mut}$	HRD	$BRCA^{wt}$ LOH_{low}	ITT (all pts)
HR (95% CI) [P value]	16.6 mo	13.6 mo	6.7 mo	10.8 mo	5.4 mo	5.4 mo	5.4 mo	5.4 mo
	0.23 (0.16–0.34) [<0.0001]	0.32 (0.24–0.42) [<0.0001]	0.58 (0.40–0.85) [0.0049]	0.36 (0.30–0.45) [<0.0001]				
Safety: Most common grade ≥3 AEs in active treatment group	Anemia (19%) Elevated ALT/AST (10%) Fatigue/asthenia (7%)				Anemia (1%) Elevated ALT/AST (0) Fatigue/asthenia (3%)			

[a] Safety population n=372. ALT = alanine aminotransferase; AST = aspartate aminotransferase; HRD = homologous recombination deficiency; ITT = intent-to-treat.

Coleman RL, et al. *Lancet.* 2017;390(10106):1949-61.

	ARIEL3 (NCT01968213)							
	Rucaparib				Placebo			
N	375[a]				189			
Design	Phase 3							
Patients	Platinum-sensitive, high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancer, ≥2 prior lines of platinum chemotherapy							
Treatment	Rucaparib 600 mg bid				Placebo			
Results: mPFS	BRCA^{mut}	HRD	BRCA^{wt} LOH$_{low}$	ITT (all pts)	BRCA^{mut}	HRD	BRCA^{wt} LOH$_{low}$	ITT (all pts)
HR (95% CI) [P value]	16.6 mo	13.6 mo	6.7 mo	10.8 mo	5.4 mo	5.4 mo	5.4 mo	5.4 mo
	0.23 (0.16–0.34) [<0.0001]	0.32 (0.24–0.42) [<0.0001]	0.58 (0.40–0.85) [0.0049]	0.36 (0.30–0.45) [<0.0001]				
Safety: Most common grade ≥3 AEs in active treatment group	Anemia (19%) Elevated ALT/AST (10%) Fatigue/asthenia (7%)				Anemia (1%) Elevated ALT/AST (0) Fatigue/asthenia (3%)			

[a] Safety population n=372. ALT = alanine aminotransferase; AST = aspartate aminotransferase; HRD = homologous recombination deficiency; ITT = intent-to-treat.

Coleman RL, et al. *Lancet.* 2017;390(10106):1949-61.

	ARIEL3 (NCT01968213)							
	Rucaparib				Placebo			
N	375[a]				189			
Design	Phase 3							
Patients	Platinum-sensitive, high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancer, ≥2 prior lines of platinum chemotherapy							
Treatment	Rucaparib 600 mg bid				Placebo			
Results: mPFS	BRCA^{mut}	HRD	BRCA^{wt} LOH$_{low}$	ITT (all pts)	BRCA^{mut}	HRD	BRCA^{wt} LOH$_{low}$	ITT (all pts)
HR (95% CI) [P value]	16.6 mo	13.6 mo	6.7 mo	10.8 mo	5.4 mo	5.4 mo	5.4 mo	5.4 mo
	0.23 (0.16–0.34) [<0.0001]	0.32 (0.24–0.42) [<0.0001]	0.58 (0.40–0.85) [0.0049]	0.36 (0.30–0.45) [<0.0001]				
Safety: Most common grade ≥3 AEs in active treatment group	Anemia (19%) Elevated ALT/AST (10%) Fatigue/asthenia (7%)				Anemia (1%) Elevated ALT/AST (0) Fatigue/asthenia (3%)			

[a] Safety population n=372. ALT = alanine aminotransferase; AST = aspartate aminotransferase; HRD = homologous recombination deficiency; ITT = intent-to-treat.

Coleman RL, et al. *Lancet.* 2017;390(10106):1949-61.

Niraparib

Maintenance Therapy in Patients Recurrent Platinum-Sensitive Ovarian Cancer With or Without a *BRCA* Mutation

	NOVA (NCT01847274)			
	gBRCA^{mut}		Non-gBRCA^{mut}	
N	203		350	
Design	Phase 3			
Patients	Platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer with predominantly high-grade serous features, ≥2 prior lines of platinum therapy, in CR or PR to most recent platinum therapy			
Treatment	Niraparib 300 mg daily	Placebo	Niraparib 300 mg daily	Placebo
Results: mPFS and HR (95% CI)	21.0 mo	5.5 mo	9.3 mo	3.9 mo
	0.27 (0.17–0.41); P<0.001		0.45 (0.34–0.61); P<0.001	
Safety: Most common grade 3 or 4 AEs in patients treated with niraparib	Thrombocytopenia (33.8%) Anemia (25.3%) Neutropenia (19.6%)			

Mirza MR, et al. *N Engl J Med.* 2016;375(22):2154-64.

	NOVA (NCT01847274)			
	gBRCA^{mut}		Non-gBRCA^{mut}	
N	203		350	
Design	Phase 3			
Patients	Platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer with predominantly high-grade serous features, ≥2 prior lines of platinum therapy, in CR or PR to most recent platinum therapy			
Treatment	Niraparib 300 mg daily	Placebo	Niraparib 300 mg daily	Placebo
Results: mPFS and HR (95% CI)	21.0 mo	5.5 mo	9.3 mo	3.9 mo
	0.27 (0.17–0.41); P<0.001		0.45 (0.34–0.61); P<0.001	
Safety: Most common grade 3 or 4 AEs in patients treated with niraparib	Thrombocytopenia (33.8%) Anemia (25.3%) Neutropenia (19.6%)			

Mirza MR, et al. *N Engl J Med.* 2016;375(22):2154-64.

	NOVA (NCT01847274)			
	gBRCA^{mut}		Non-gBRCA^{mut}	
N	203		350	
Design	Phase 3			
Patients	Platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer with predominantly high-grade serous features, ≥2 prior lines of platinum therapy, in CR or PR to most recent platinum therapy			
Treatment	Niraparib 300 mg daily	Placebo	Niraparib 300 mg daily	Placebo
Results: mPFS and HR (95% CI)	21.0 mo	5.5 mo	9.3 mo	3.9 mo
	0.27 (0.17–0.41); P<0.001		0.45 (0.34–0.61); P<0.001	
Safety: Most common grade 3 or 4 AEs in patients treated with niraparib	Thrombocytopenia (33.8%) Anemia (25.3%) Neutropenia (19.6%)			

Mirza MR, et al. *N Engl J Med.* 2016;375(22):2154-64.

	NOVA (NCT01847274) Non-gBRCA^{mut}					
	Non-gBRCA^{mut} HRD-positive		sBRCA^{mut}		HRD-negative	
N	162		47		134	
Treatment	Niraparib 300 mg daily	Placebo	Niraparib 300 mg daily	Placebo	Niraparib 300 mg daily	Placebo
Results: mPFS and HR (95% CI)	12.9 mo	3.8 mo	20.9 mo	11.0 mo	6.9 mo	3.8 mo
	0.38 (0.24–0.59); P<0.001		0.27 (0.08–0.90); P=0.02		0.58 (0.36–0.92); P=0.02	

Mirza MR, et al. *N Engl J Med.* 2016;375(22):2154-64.

	NOVA (NCT01847274) Non-gBRCA^{mut}					
	Non-gBRCA^{mut} HRD-positive		sBRCA^{mut}		HRD-negative	
N	162		47		134	
Treatment	Niraparib 300 mg daily	Placebo	Niraparib 300 mg daily	Placebo	Niraparib 300 mg daily	Placebo
Results: mPFS and HR (95% CI)	12.9 mo	3.8 mo	20.9 mo	11.0 mo	6.9 mo	3.8 mo
	0.38 (0.24–0.59); P<0.001		0.27 (0.08–0.90); P=0.02		0.58 (0.36–0.92); P=0.02	

Mirza MR, et al. *N Engl J Med.* 2016;375(22):2154-64.

Summary of FDA-Approved Maintenance

Agent	Current Label	Registrational Trial Name(s)	Label Dosing and Scheduling
Bevacizumab[1,2]	As combination with CP or CG, followed by monotherapy for ROC in response to platinum	OCEANS (phase 3) GOG-0213 (phase 3)	IV infusion 15 mg/kg q3w
	As combination with CP, followed by monotherapy for stage III/IV OC following initial surgical resection	GOG-0218 (phase 3)	
Olaparib[3]	Recurrence maintenance 2+ lines	Study 19 (phase 2) SOLO-2 (phase 3)	300 mg (two 150-mg tablets) PO bid
Niraparib[4]	Recurrence maintenance 2+ lines	NOVA (phase 3)	300 mg (three 100-mg capsules) PO daily
Rucaparib[5]	Recurrence maintenance 2+ lines	ARIEL 3 (phase 3)	600 mg (two 300-mg tablets) PO bid

1. Bevacizumab package insert. Genentech, Inc; June 2018. **2.** Roche's Bevacizumab Plus Chemotherapy Receives FDA Approval for Platinum-sensitive Recurrent Ovarian Cancer [press release]. Basel, Switzerland: Roche; December 7, 2016. https://www.roche.com/dam/jcr:3050d757-8d1d-48a6-b372-c72dc3715556/en/med-cor-2016-12-07-e.pdf. Accessed April 9, 2018. **3.** Olaparib package insert. AstraZeneca Pharmaceuticals LP; January 2018. **4.** Niraparib package insert. TESARO, Inc; August 2017. **5.** Rucaparib package insert. Clovis Oncology, Inc; April 2018.

IN THE CLINIC

PARPi

Timing

- Bevacizumab is continued q3wk dosing after discontinuation of cytotoxic medication
  - Platelets ≥ 75K
  - ANC ≥ 1000
- PARPi are started after resolution of toxicity
  - Platelets ≥ 75K
  - Hgb ≥ 10
  - WBC ≥ 3000

PARP Inhibitor Pharmacology

	Olaparib	Rucaparib	Niraparib
Dosage forms	Capsules: 50 mg Tablets: 100 or 150 mg	Tablets: 200, 250, or 300 mg	Capsules: 100 mg
Dose	Capsules: 400 mg bid Tablets: 300 mg bid	600 mg bid	300 mg daily
Starting dose modifications	Moderate renal impairment CYP3A inhibitor use	None	None
Metabolized primarily by	CYP3A4/5	CYP2D6	Carboxylesterases
Monitor	CBC at baseline and monthly thereafter	CBC at baseline and monthly thereafter	• CBC weekly for the first month, then monthly for the next 11 months, and then periodically • BP and heart rate monthly during the first year and periodically
Manage adverse reactions through	Dose interruption or dose reduction	Dose interruption or dose reduction	Dose interruption or dose reduction

1. Olaparib package insert. AstraZeneca Pharmaceuticals LP; January 2018. **2.** Rucaparib package insert. Clovis Oncology, Inc; April 2018.
3. Niraparib package insert. TESARO, Inc; August 2017.

Adverse Events

	Olaparib[1,a]		Rucaparib[2]				Niraparib[3]	
	N=223		N=377[b]		N=372[c]		N=367	
	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4
Blood and lymphatic system disorders, %								
Anemia	34	18	44	25	39	21	50	25
Thrombocytopenia	–	–	21	5	29	5	61	29
Neutropenia	–	–	–	–	20	8	30	20

[a] Pooled from 6 studies: patients with g*BRCA*^{mut} ovarian cancer who received 3 or more prior lines of chemotherapy.
[b] Data from Study 10 and ARIEL2. [c] Data from ARIEL3.
[d] Does not include distension. [e] Does not include mucositis. [f] Does not include upper respiratory infection.

1. Olaparib package insert. AstraZeneca Pharmaceuticals LP; January 2018. 2. Rucaparib package insert. Clovis Oncology, Inc; April 2018. 3. Niraparib package insert. TESARO, Inc; August 2017.

	Olaparib[1,a]		Rucaparib[2]				Niraparib[3]	
	N=223		N=377[b]		N=372[c]		N=367	
	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4
Blood and lymphatic system disorders, %								
Anemia	34	18	44	25	39	21	50	25
Thrombocytopenia	–	–	21	5	29	5	61	29
Neutropenia	–	–	–	–	20	8	30	20

[a] Pooled from 6 studies: patients with g*BRCA*^{mut} ovarian cancer who received 3 or more prior lines of chemotherapy.
[b] Data from Study 10 and ARIEL2. [c] Data from ARIEL3.
[d] Does not include distension. [e] Does not include mucositis. [f] Does not include upper respiratory infection.

1. Olaparib package insert. AstraZeneca Pharmaceuticals LP; January 2018. **2.** Rucaparib package insert. Clovis Oncology, Inc; April 2018. **3.** Niraparib package insert. TESARO, Inc; August 2017.

	Olaparib[1,a]		Rucaparib[2]				Niraparib[3]	
	N=223		N=377[b]		N=372[c]		N=367	
	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4
Blood and lymphatic system disorders, %								
Anemia	34	18	44	25	39	21	50	25
Thrombocytopenia	–	–	21	5	29	5	61	29
Neutropenia	–	–	–	–	20	8	30	20

[a] Pooled from 6 studies: patients with g*BRCA*^{mut} ovarian cancer who received 3 or more prior lines of chemotherapy.
[b] Data from Study 10 and ARIEL2. [c] Data from ARIEL3.
[d] Does not include distension. [e] Does not include mucositis. [f] Does not include upper respiratory infection.

1. Olaparib package insert. AstraZeneca Pharmaceuticals LP; January 2018. 2. Rucaparib package insert. Clovis Oncology, Inc; April 2018. 3. Niraparib package insert. TESARO, Inc; August 2017.

	Olaparib[1,a]		Rucaparib[2]				Niraparib[3]	
	N=223		N=377[b]		N=372[c]		N=367	
	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4
Gastrointestinal disorders, %								
Decreased appetite	22	1	39	3	23	1	25	0.3
Nausea	64	3	77	5	76	4	74	3
Vomiting	43	4	46	4	37	4	34	2
Diarrhea	31	1	34	2	32	0.5	20	0.3
Dyspepsia	25	0	–	–	–	–	–	–
Constipation	–	–	40	2	37	2	40	0.8
Abdominal pain/distension	–	–	32[d]	3[d]	46	3	33	2
Mucositis/stomatitis	–	–	–	–	28[e]	1[e]	20	0.5

	Olaparib[1,a]		Rucaparib[2]				Niraparib[3]	
	N=223		N=377[b]		N=372[c]		N=367	
	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4
Gastrointestinal disorders, %								
Decreased appetite	22	1	39	3	23	1	25	0.3
Nausea	64	3	77	5	76	4	74	3
Vomiting	43	4	46	4	37	4	34	2
Diarrhea	31	1	34	2	32	0.5	20	0.3
Dyspepsia	25	0	–	–	–	–	–	–
Constipation	–	–	40	2	37	2	40	0.8
Abdominal pain/distension	–	–	32[d]	3[d]	46	3	33	2
Mucositis/stomatitis	–	–	–	–	28[e]	1[e]	20	0.5

	Olaparib[1,a]		Rucaparib[2]				Niraparib[3]	
	N=223		N=377[b]		N=372[c]		N=367	
	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4
Respiratory, thoracic, and mediastinal disorders %								
Nasopharyngitis/upper respiratory tract infection	26	0	–	–	29	0.3	23[f]	0[f]
Dyspnea	–	–	21	0.5	–	–	20	1
Other disorders, %								
Fatigue/asthenia	66	8	77	11	73	7	57	8
Insomnia	–	–	–	–	–	–	27	0.3
Rash	–	–	–	–	43	1	21	0.5
Hypertension	–	–	–	–	–	–	20	9

[a] Pooled from 6 studies: patients with g*BRCA*^{mut} ovarian cancer who received 3 or more prior lines of chemotherapy. [b] Data from Study 10 and ARIEL2. [c] Data from ARIEL3. [d] Does not include distension. [e] Does not include mucositis. [f] Does not include upper respiratory infection.

1. Olaparib package insert. AstraZeneca Pharmaceuticals LP; January 2018. **2.** Rucaparib package insert. Clovis Oncology, Inc; April 2018. **3.** Niraparib package insert. TESARO, Inc; August 2017.

	Olaparib[1,a]		Rucaparib[2]				Niraparib[3]	
	N=223		N=377[b]		N=372[c]		N=367	
	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4
Respiratory, thoracic, and mediastinal disorders %								
Nasopharyngitis/upper respiratory tract infection	26	0	–	–	29	0.3	23[f]	0[f]
Dyspnea	–	–	21	0.5	–	–	20	1
Other disorders, %								
Fatigue/asthenia	66	8	77	11	73	7	57	8
Insomnia	–	–	–	–	–	–	27	0.3
Rash	–	–	–	–	43	1	21	0.5
Hypertension	–	–	–	–	–	–	20	9

[a] Pooled from 6 studies: patients with g*BRCA*^{mut} ovarian cancer who received 3 or more prior lines of chemotherapy. [b] Data from Study 10 and ARIEL2. [c] Data from ARIEL3. [d] Does not include distension. [e] Does not include mucositis. [f] Does not include upper respiratory infection.

1. Olaparib package insert. AstraZeneca Pharmaceuticals LP; January 2018. **2.** Rucaparib package insert. Clovis Oncology, Inc; April 2018. **3.** Niraparib package insert. TESARO, Inc; August 2017.

	Olaparib[1,a]		Rucaparib[2]				Niraparib[3]	
	N=223		N=377[b]		N=372[c]		N=367	
	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4
Respiratory, thoracic, and mediastinal disorders %								
Nasopharyngitis/upper respiratory tract infection	26	0	–	–	29	0.3	23[f]	0[f]
Dyspnea	–	–	21	0.5	–	–	20	1
Other disorders, %								
Fatigue/asthenia	66	8	77	11	73	7	57	8
Insomnia	–	–	–	–	–	–	27	0.3
Rash	–	–	–	–	43	1	21	0.5
Hypertension	–	–	–	–	–	–	20	9

[a] Pooled from 6 studies: patients with g*BRCA*[mut] ovarian cancer who received 3 or more prior lines of chemotherapy. [b] Data from Study 10 and ARIEL2. [c] Data from ARIEL3. [d] Does not include distension. [e] Does not include mucositis. [f] Does not include upper respiratory infection.

1. Olaparib package insert. AstraZeneca Pharmaceuticals LP; January 2018. **2.** Rucaparib package insert. Clovis Oncology, Inc; April 2018. **3.** Niraparib package insert. TESARO, Inc; August 2017.

	Olaparib[1,a]		Rucaparib[2]				Niraparib[3]	
	N=223		N=377[b]		N=372[c]		N=367	
	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4
Nervous system disorders, %								
Dysgeusia	–	–	39	0.3	40	0	–	–
Headache	–	–	–	–	–	–	26	0.3
Musculoskeletal disorders, %								
Arthralgia/musculoskeletal pain	21	0	–	–	–	–	–	–
Myalgia	22	0	–	–	–	–	–	–

	Olaparib[1,a]		Rucaparib[2]				Niraparib[3]	
	N=223		N=377[b]		N=372[c]		N=367	
	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4
Nervous system disorders, %								
Dysgeusia	–	–	39	0.3	40	0	–	–
Headache	–	–	–	–	–	–	26	0.3
Musculoskeletal disorders, %								
Arthralgia/musculoskeletal pain	21	0	–	–	–-	–	–	–
Myalgia	22	0	–	–	–	–	–	–

	Olaparib[1,a]		Rucaparib[2]				Niraparib[3]	
	N=223		N=377[b]		N=372[c]		N=367	
	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4
Blood and lymphatic system disorders, %								
Anemia	34	18	44	25	39	21	50	25
Thrombocytopenia	–	–	21	5	29	5	61	29
Neutropenia	–	–	–	–	20	8	30	20
Gastrointestinal disorders, %								
Decreased appetite	22	1	39	3	23	1	25	0.3
Nausea	64	3	77	5	76	4	74	3
Vomiting	43	4	46	4	37	4	34	2
Diarrhea	31	1	34	2	32	0.5	20	0.3
Dyspepsia	25	0	–	–	–	–	–	–
Constipation	–	–	40	2	37	2	40	0.8
Abdominal pain/distension			[d]	[d]				2
Mucositis/stoma								0.5
Respiratory,								
Nasopharyngitis/upper respiratory tract infection	26	0	–	–	29	0.3	23[f]	0[f]
Dyspnea	–	–	21	0.5	–	–	20	1
Other disorders, %								
Fatigue/asthenia	66	8	77	11	73	7	57	8
Insomnia	–	–	–	–	–	–	27	0.3
Rash	–	–	–	–	43	1	21	0.5
Hypertension	–	–	–	–	–	–	20	9
ALT/AST elevation	–	–	–	–	38	11	–	–
Nervous system disorders, %								
Dysgeusia	–	–	39	0.3	40	0	–	–
Headache	–	–	–	–	–	–	26	0.3
Musculoskeletal disorders, %								
Arthralgia/musculoskeletal pain	21	0	–	–	–	–	–	–
Myalgia	22	0	–	–	–	–	–	–

Grade 1–4 Occurring in ≥20% of Treated Patients

[a] Pooled from 6 studies: patients with g*BRCA*[mut] ovarian cancer who received 3 or more prior lines of chemotherapy. [b] Data from Study 10 and ARIEL2. [c] Data from ARIEL3.
[d] Does not include distension. [e] Does not include mucositis. [f] Does not include upper respiratory infection.

1. Olaparib package insert. AstraZeneca Pharmaceuticals LP; January 2018. 2. Rucaparib package insert. Clovis Oncology, Inc; April 2018. 3. Niraparib package insert. TESARO, Inc; August 2017.

	Olaparib[1,a]		Rucaparib[2]				Niraparib[3]	
	N=223		N=377[b]		N=372[c]		N=367	
	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4
Hematology, %								
Decrease in hemoglobin	90	15	67	23	88	13	85	25
Decrease in lymphocytes	56	17	45	7	–	–	–	–
Decrease in platelets	–	–	39	6	44	2	72	35
Decrease in absolute neutrophil count	–	–	35	10	–	–	53	21
Decrease in leukocytes	–	–	–	–	44	3	–	–
Decrease in neutrophils	–	–	–	–	38	6	–	–
Decrease in white blood cell count	–	–	–	–	–	–	66	7
Mean corpuscular volume elevation	57	–	–	–	–	–	–	–

[a] Pooled from 6 studies: patients with g*BRCA*^{mut} ovarian cancer who received 3 or more prior lines of chemotherapy.
[b] Data from Study 10 and ARIEL2.
[c] Data from ARIEL3.

1. Olaparib package insert. AstraZeneca Pharmaceuticals LP; January 2018. **2.** Rucaparib package insert. Clovis Oncology, Inc; April 2018.
3. Niraparib package insert. TESARO, Inc; August 2017.

	Olaparib[1,a]		Rucaparib[2]				Niraparib[3]	
	N=223		N=377[b]		N=372[c]		N=367	
	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4
Hematology, %								
Decrease in hemoglobin	90	15	67	23	88	13	85	25
Decrease in lymphocytes	56	17	45	7	–	–	–	–
Decrease in platelets	–	–	39	6	44	2	72	35
Decrease in absolute neutrophil count	–	–	35	10	–	–	53	21
Decrease in leukocytes	–	–	–	–	44	3	–	–
Decrease in neutrophils	–	–	–	–	38	6	–	–
Decrease in white blood cell count	–	–	–	–	–	–	66	7
Mean corpuscular volume elevation	57	–	–	–	–	–	–	–

[a] Pooled from 6 studies: patients with g*BRCA*^{mut} ovarian cancer who received 3 or more prior lines of chemotherapy.
[b] Data from Study 10 and ARIEL2.
[c] Data from ARIEL3.

1. Olaparib package insert. AstraZeneca Pharmaceuticals LP; January 2018. 2. Rucaparib package insert. Clovis Oncology, Inc; April 2018.
3. Niraparib package insert. TESARO, Inc; August 2017.

	Olaparib[1,a]		Rucaparib[2]				Niraparib[3]	
	N=223		N=377[b]		N=372[c]		N=367	
	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4
Hematology, %								
Decrease in hemoglobin	90	15	67	23	88	13	85	25
Decrease in lymphocytes	56	17	45	7	–	–	–	–
Decrease in platelets	–	–	39	6	44	2	72	35
Decrease in absolute neutrophil count	–	–	35	10	–	–	53	21
Decrease in leukocytes	–	–	–	–	44	3	–	–
Decrease in neutrophils	–	–	–	–	38	6	–	–
Decrease in white blood cell count	–	–	–	–	–	–	66	7
Mean corpuscular volume elevation	57	–	–	–	–	–	–	–

[a] Pooled from 6 studies: patients with g*BRCA*^{mut} ovarian cancer who received 3 or more prior lines of chemotherapy.
[b] Data from Study 10 and ARIEL2.
[c] Data from ARIEL3.

1. Olaparib package insert. AstraZeneca Pharmaceuticals LP; January 2018. **2.** Rucaparib package insert. Clovis Oncology, Inc; April 2018.
3. Niraparib package insert. TESARO, Inc; August 2017.

	Olaparib[1,a]		Rucaparib[2]				Niraparib[3]	
	N=223		N=377[b]		N=372[c]		N=367	
	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4
Hematology, %								
Decrease in hemoglobin	90	15	67	23	88	13	85	25
Decrease in lymphocytes	56	17	45	7	–	–	–	–
Decrease in platelets	–	–	39	6	44	2	72	35
Decrease in absolute neutrophil count	–	–	35	10	–	–	53	21
Decrease in leukocytes	–	–	–	–	44	3	–	–
Decrease in neutrophils	–	–	–	–	38	6	–	–
Decrease in white blood cell count	–	–	–	–	–	–	66	7
Mean corpuscular volume elevation	57	–	–	–	–	–	–	–

1. Olaparib package insert. AstraZeneca Pharmaceuticals LP; January 2018. **2.** Rucaparib package insert. Clovis Oncology, Inc; April 2018.
3. Niraparib package insert. TESARO, Inc; August 2017.

	Olaparib[1,a]		Rucaparib[2]				Niraparib[3]	
	N=223		N=377[b]		N=372[c]		N=367	
	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4
Chemistry, %								
Increase in creatinine	–	–	92	1	98	0.3	–	–
Increase in ALT	–	–	74	13	73	7	–	–
Increase in AST	–	–	73	5	61	1	36	1
Increase in cholesterol	–	–	40	2	84	4	–	–
Increase in alkaline phosphatase	–	–	–	–	37	0.3	–	–

	Olaparib[1,a]		Rucaparib[2]				Niraparib[3]	
	N=223		N=377[b]		N=372[c]		N=367	
	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4
Chemistry, %								
Increase in creatinine	–	–	92	1	98	0.3	–	–
Increase in ALT	–	–	74	13	73	7	–	–
Increase in AST	–	–	73	5	61	1	36	1
Increase in cholesterol	–	–	40	2	84	4	–	–
Increase in alkaline phosphatase	–	–	–	–	37	0.3	–	–

	Olaparib[1,a]		Rucaparib[2]				Niraparib[3]	
	N=223		N=377[b]		N=372[c]		N=367	
	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4	Gr 1–4	Gr 3/4
Hematology, %								
Decrease in hemoglobin	90	15	67	23	88	13	85	25
Decrease in lymphocytes	56	17	45	7	–	–	–	–
Decrease in platelets	–	–	39	6	44	2	72	35
Decrease in absolute neutrophil count	–	–	35	10	–	–	53	21
Decrease in l								–
Decrease in n								–
Decrease in white blood cell count	–	–	–	–	–	–	66	7
Mean corpuscular volume elevation	57	–	–	–	–	–	–	–
Chemistry, %								
Increase in creatinine	–	–	92	1	98	0.3	–	–
Increase in ALT	–	–	74	13	73	7	–	–
Increase in AST	–	–	73	5	61	1	36	1
Increase in cholesterol	–	–	40	2	84	4	–	–
Increase in alkaline phosphatase	–	–	–	–	37	0.3	–	–

Grade 1–4 Occurring in ≥35% of Patients

[a] Pooled from 6 studies: patients with g*BRCA*^{mut} ovarian cancer who received 3 or more prior lines of chemotherapy.
[b] Data from Study 10 and ARIEL2.
[c] Data from ARIEL3.

1. Olaparib package insert. AstraZeneca Pharmaceuticals LP; January 2018. **2.** Rucaparib package insert. Clovis Oncology, Inc; April 2018.
3. Niraparib package insert. TESARO, Inc; August 2017.

Myelodysplastic Syndrome and Acute Myeloid Leukemia

	Olaparib[1]	Rucaparib[2]	Niraparib[3]
Rates of MDS/AML in clinical trials	<1.5%	1.1%	1.4%
MDS/AML incidence in clinical trial(s), n / N	21 / 1680	12 / approx. 1100	5 / 367
Monitoring	Monitor for hematologic toxicity at baseline and monthly thereafter	Monitor for hematologic toxicity at baseline and monthly thereafter	Monitor for hematologic toxicity: test CBC weekly for the first month, then monthly for the next 11 months, and then periodically

1. Olaparib package insert. AstraZeneca Pharmaceuticals LP; January 2018. **2.** Rucaparib package insert. Clovis Oncology, Inc; April 2018.
3. Niraparib package insert. TESARO, Inc; August 2017.

MDS/AML Monitoring

- Do not start PARP inhibitors until patients have recovered from hematologic toxicity from prior therapy
- For prolonged hematologic toxicity, interrupt treatment and monitor CBC weekly until recovery
- If no recovery within 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics
- If MDS/AML is confirmed, discontinue PARP inhibitor

General Strategies for Managing Common Adverse Events

Adverse Reaction	Characteristics	Treatments
Diarrhea[1]	• Increase in number of stools per day over baseline • Increase in ostomy output	• Hydration and electrolyte replacement (oral or IV fluids) • Dietary modifications • Antidiarrheal, antibiotic, and/or anticholinergic medication • Complicated diarrhea may require hospital admission; consider somatostatin analog
Nausea and vomiting[2]	• Vomiting results from stimulation of a multistep reflex pathway • Nausea can be acute or delayed	• Oral antiemetic prophylaxis
Cancer-related fatigue[3]	• Distressing and persistent sense of tiredness or exhaustion • Not proportional to recent activity • Interferes with usual functioning	• Management of concurrent symptoms and treatable contributing factors • Nonpharmacologic interventions (eg, physical activity, massage therapy, psychosocial interventions, and energy conservation) • Pharmacologic management

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Palliative Care V.1.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed June 27, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org.
2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis V.3.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed June 27, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org.
3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Cancer-Related Fatigue V.2.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed June 27, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org.

Adverse Reaction	Characteristics	Treatments
Diarrhea[1]	• Increase in number of stools per day over baseline • Increase in ostomy output	• Hydration and electrolyte replacement (oral or IV fluids) • Dietary modifications • Antidiarrheal, antibiotic, and/or anticholinergic medication • Complicated diarrhea may require hospital admission; consider somatostatin analog
Nausea and vomiting[2]	• Vomiting results from stimulation of a multistep reflex pathway • Nausea can be acute or delayed	• Oral antiemetic prophylaxis
Cancer-related fatigue[3]	• Distressing and persistent sense of tiredness or exhaustion • Not proportional to recent activity • Interferes with usual functioning	• Management of concurrent symptoms and treatable contributing factors • Nonpharmacologic interventions (eg, physical activity, massage therapy, psychosocial interventions, and energy conservation) • Pharmacologic management

Adverse Reaction	Characteristics	Treatments
Diarrhea[1]	• Increase in number of stools per day over baseline • Increase in ostomy output	• Hydration and electrolyte replacement (oral or IV fluids) • Dietary modifications • Antidiarrheal, antibiotic, and/or anticholinergic medication • Complicated diarrhea may require hospital admission; consider somatostatin analog
Nausea and vomiting[2]	• Vomiting results from stimulation of a multistep reflex pathway • Nausea can be acute or delayed	• Oral antiemetic prophylaxis
Cancer-related fatigue[3]	• Distressing and persistent sense of tiredness or exhaustion • Not proportional to recent activity • Interferes with usual functioning	• Management of concurrent symptoms and treatable contributing factors • Nonpharmacologic interventions (eg, physical activity, massage therapy, psychosocial interventions, and energy conservation) • Pharmacologic management

Adverse Reaction	Characteristics	Treatments
Diarrhea[1]	• Increase in number of stools per day over baseline • Increase in ostomy output	• Hydration and electrolyte replacement (oral or IV fluids) • Dietary modifications • Antidiarrheal, antibiotic, and/or anticholinergic medication • Complicated diarrhea may require hospital admission; consider somatostatin analog
Nausea and vomiting[2]	• Vomiting results from stimulation of a multistep reflex pathway • Nausea can be acute or delayed	• Oral antiemetic prophylaxis
Cancer-related fatigue[3]	• Distressing and persistent sense of tiredness or exhaustion • Not proportional to recent activity • Interferes with usual functioning	• Management of concurrent symptoms and treatable contributing factors • Nonpharmacologic interventions (eg, physical activity, massage therapy, psychosocial interventions, and energy conservation) • Pharmacologic management

QUALITY OF LIFE

PARP Inhibitors Do Not Appear to Impact QoL

- NOVA analyses of patient-reported outcomes indicated similar outcomes for patients treated with niraparib and placebo
- SOLO-2 HRQoL reported using the TOI of the Functional Assessment of Cancer Therapy–Ovarian and found no difference

HRQoL = health-related quality of life; QoL = quality of life; TOI = Trial Outcome Index.

Pujade-Lauraine E, et al. Presented at SGO 2017 Annual Meeting

No Clinical Effect on QoL With Maintenance Therapy

	Study	Effect on Overall QoL
Extended taxanes	GOG-0178[1]	*Not included*
	GOG-0212[2]	No clinical effect
Anti-angiogenics	OCEANS[3]	*Not included*
	GOG-0213[4]	No clinical effect
	ICON6[5]	No clinical effect
	AGO-OVAR 16	*Not yet presented*
PARP inhibitors	NOVA[6]	No clinical effect
	SOLO-2[7,8]	
	Study 19[9]	
	ARIEL3	

1. Hope JM, et al. *Int J Womens Health.* 2009;1:173-80. 2. Copeland LJ, et al. Presented at SGO Annual Meeting, 2017. 3. Della Pepa C, et al. *Onco Targets Ther.* 2014;7:1025-32. 4. Basen-Engquist K, et al. Presented at ASCO Annual Meeting, 2015. Abstract 9633. 5. Ledermann JA, et al. *Lancet.* 2016;387(10023):1066-74. 6. Oza A, et al. Presented at ESMO Annual Meeting, 2017. Abstract 930O. 7. Pujade-Lauraine E, et al. Presented at SGO Annual Meeting, 2017. 8. Friedlander M, et al. Presented at ASCO Annual Meeting, 2017. Abstract 5507. 9. Ledermann J, et al. *N Engl J Med.* 2012;366(15):1382-92.

CASE STUDY

KM

- 42-year-old woman
  - High school teacher
  - Mother of 2 young children
  - Avid runner
- Stage IV high-grade serous ovarian cancer 3/2016
  - CA-125 7300 at diagnosis
  - Unknown BRCA status

KM (cont.)

- Neoadjuvant carboplatin AUC 6, paclitaxel 175 mg/m^2 x 3 cycles completed 7/2016
- Interval optimal debulking, total laparoscopic hysterectomy, bilateral salpino-oophorectomy, omentectomy 8/2016
- Adjuvant carboplatin/paclitaxel x3 cycles completed 12/2016
- CA-125 = 6 at completion of treatment
- Pt declines genetic evaluation at this time

Would KM be a candidate for maintenance therapy in 2018?

KM (cont.)

- Rising CA-125, CT C/A/P confirms recurrence of pelvic disease 11/2017 (platinum-sensitive)
- Carboplatin/Gemcitabine/Bevacizumab initiated 12/2017
  - Pancytopenia requires G-CSF, multiple transfusions of pRBC and platelets
  - Treatment discontinued following 5th cycle for prolonged thrombocytopenia
  - CA-125 = 10 and CT C/A/P NED 04/2018
  - Pt agrees to genetic evaluation: BRCA 1

KM (cont.)

- What do you think about maintenance for this patient?
  - Bevacizumab
  - PARP
  - None

KM (cont.)

- Initiated bevacizumab maintenance 05/2018
- CA-125 rose to 120 following cycle 1 of single-agent bevacizumab
- Now what?

KM (cont.)

- What PARPs are appropriate in this setting?
- Which toxicities are we most concerned about for KM?

KM (cont.)

- Olaparib 300 mg BID initiated 06/2018
- CA-125 normalized to 8
- Regimen tolerated well with no hematologic toxicities
- Nausea well managed with anti-emetics prn
- Fatigue improved after first month
- KM continues to work full time, care for children, and is able to participate in running and yoga again

Summary of Other Select PARP Inhibitor Trials

Phase 3 Clinical Development Landscape for PARPi

	Olaparib	Rucaparib	Niraparib
Monotherapy in recurrent disease	FDA approved	FDA approved	
	SOLO-3 gBRCA^{mut} NCT02282020	ARIEL4 BRCA^{mut} NCT02855944	
First-line monotherapy			
Maintenance in recurrent disease	FDA approved	FDA approved	FDA approved
	OPINION Non-gBRCA^{mut} NCT03402841		
First-line maintenance	SOLO-1 BRCA^{mut} NCT01844986		PRIMA NCT02655016
Maintenance re-treatment	OReO NCT03106987		

PSOC, platinum-sensitive ovarian cancer.

Olaparib package insert. AstraZeneca Pharmaceuticals LP; January 2018. Rucaparib package insert. Clovis Oncology, Inc; April 2018. Niraparib package insert. TESARO, Inc; August 2017. ClinicalTrials.gov: NCT02282020, NCT03402841, NCT01844986, NCT03106987, NCT02855944, and NCT02655016. Accessed April 10, 2018.

Combination Approaches With PARP Inhibitors Are Moving Into the Clinic

PARP Inhibitor Combinations

- PARPi + DNA damaging agents (chemotherapy)
- PARPi + immunotherapy
- PARPi + anti-angiogenic agents

Why Use Combination Therapy?

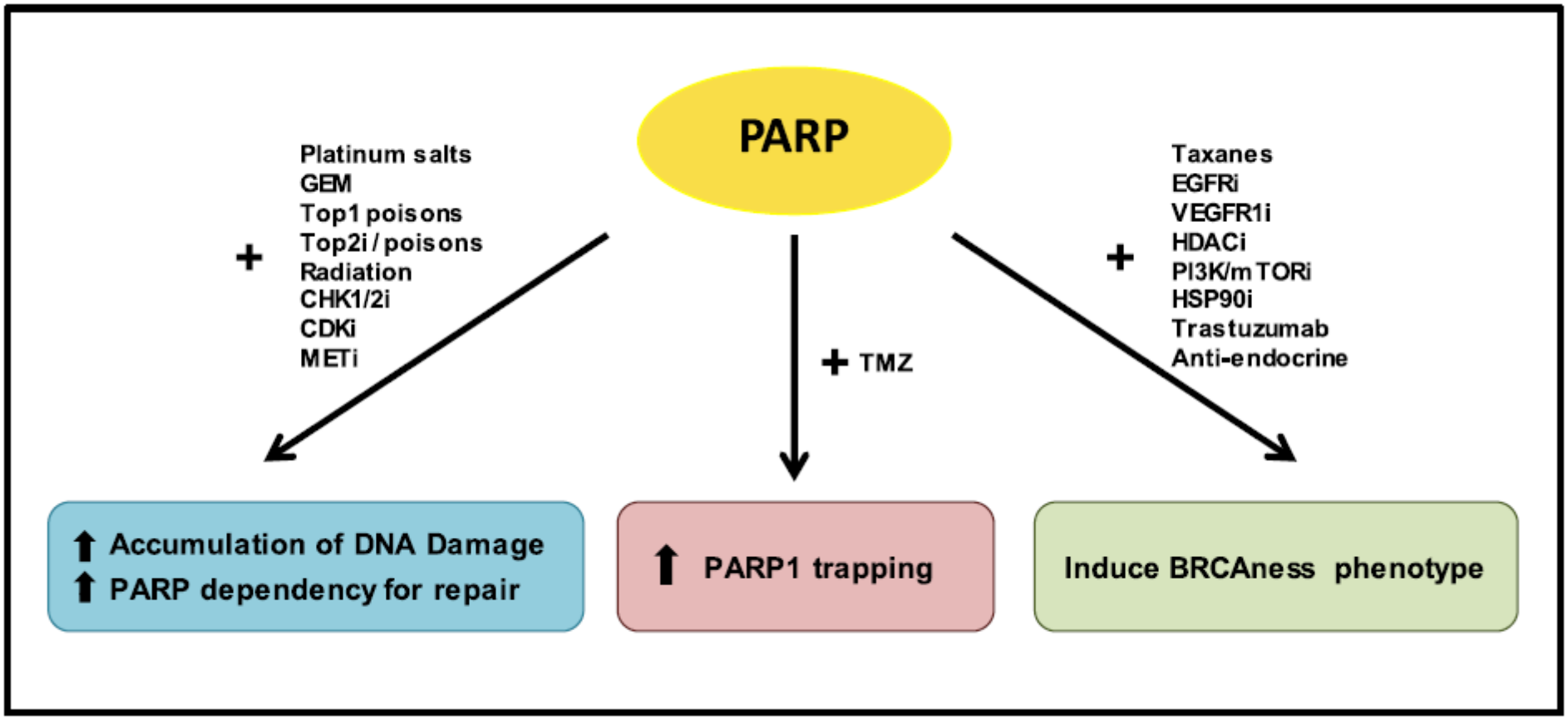
Agent

- Anti-angiogenic agents
- Immunotherapy
- Chemotherapy

Synthetic Mechanism

- Hypoxia may induce *BRCA*-like phenotype
- Mutagenic burden induced by PARP inhibition may improve response to immunotherapy
- Increase DNA damage

Dréan A, et al. *Crit Rev Oncol Hematol*. 2016;108:73-85.


PARP
Platinum salts
GEM
Top1 poisons
Top2i / poisons
Radiation
CHK1/2i
CDKi
METi
+
+ TMZ
Taxanes
EGFRi
VEGFR1i
HDACi
PI3K/mTORi
HSP90i
Trastuzumab
Anti-endocrine
+
Accumulation of DNA Damage
PARP dependency for repair
PARP1 trapping
Induce BRCAness phenotype

	Olaparib	Niraparib	Rucaparib	Veliparib
Anti-angiogenic therapy	PAOLA-1 Ph 3 NDOC (stage III/IV) ICON9 Ph 3 Rec PSOC NRG-GY004 Ph 3 Rec PSOC CONCERTO Ph 2 Rec PROC $BRCA^{wt}$ OCTOVA Ph 2 PROC $BRCA^{mut}$	AVANOVA Ph 1/2 PSOC OVARIO Ph 2 NDOC		
Concurrent chemotherapy	NCT01081951 Ph 2 PSOC ROLANDO Ph 2 PROC		MITO25 Ph2 NDOC (stage III/IV)	NCT02470585 Ph 3 NDOC (stage III/IV) NCT01012817 Ph 1/2 RROC

ClinicalTrials.gov: NCT02477644, NCT03278717, NCT02446600, NCT02889900, NCT03117933, NCT01081951, NCT03161132, NCT02354131, NCT03326193, NCT02657889, NCT02470585, NCT03462212, and NCT01012817. Accessed April 10, 2018.

	Olaparib	Niraparib	Rucaparib	Veliparib
Immunotherapy	PARP-inhibition and CTLA-4 Blockade in BRCA-deficient Ovarian Cancer Ph 1-2 BRCA1/2With Rec OC Olaparib, Durvalumab, and Tremelimumab Ph 1/2 ROC BRCA1 or BRCA2 Mutation (I/II) Durvalumab w/ Olaparib and/or Cediranib Ph 1/2 Rec OC MEDIOLA Ph 1/2 MEDI4736 w/ Olaparib and/or cediranib Rec OC	TOPACIO Ph 2 Rec OC Niraparib with Pembrolizumab FIRST Ph 3 First-line Platinum-Based Therapy With TSR-042 and Niraparib Versus Standard of Care Platinum-Based Therapy OPAL Ph 2 Rec OC niraparib, TSR-042, and bevacizumab TOPACIO Ph 2 Rec OC ANITA Platinum-based Chemotherapy With Atezolizumab and Niraparib Rec OC	ATHENA Maintenance Rucaparib and Nivolumab Following Response to Front-Line Platinum-Based Chemotherapy	

NCT02571725, NCT02953457 NCT02484404, NCT02734004, NCT03598270, NCT02657889

Preliminary Results

Immunotherapy & PARPi

- **TOPACIO/Keynote-162 (NCT02657889)**
  - Phase 1/2 study of niraparib + pembrolizumab in patients with advanced triple-negative breast cancer or recurrent ovarian cancer (ROC)
- At the time of data cutoff, of the 62 patients enrolled with ovarian cancer, 60 were evaluable for an initial response assessment.
- The population had been treated with a median of 2 (range of 1 to 5) prior lines of therapy:
  - 50% had platinum-resistant ovarian cancer
  - 29% were platinum-refractory
  - 63% had received prior bevacizumab
  - 21% were platinum ineligible

https://meetinglibrary.asco.org/record/161618/abstract

TOPACIO/Keynote-162 (NCT02657889)

	ORR	DCR
All	25%	67%
$BRCA^{mut}$	25%	63%
$BRCA^{wt}$	24%	65%

Response rates were not dependent on biomarker status or platinum status.

TOPACIO/Keynote-162 (NCT02657889)

- Median DOR was 9.3 months, with 9 patients remaining on treatment.
- The most common grade ≥ 3 adverse events (AEs) included **anemia** (21%) and **thrombocytopenia** (9%) at a 200-mg starting dose of niraparib.

Platinum Status	ORR
Platinum-resistant	23% (7/30)
Platinum-refractory	24% (4/17)
Platinum ineligible per investigator assessment	31% (4/13)

How Does This Compare?

- For patients with platinum-resistant ovarian cancer, response to chemotherapy is **5-18%,** including the most commonly prescribed regimen in the US, bevacizumab plus pegylated liposomal doxorubicin[1].

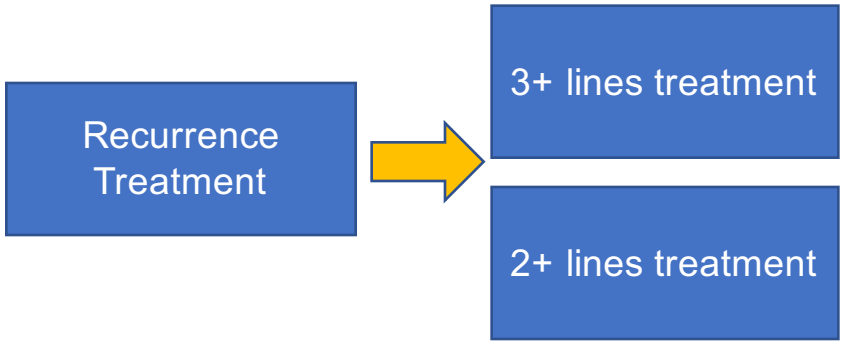
- Platinum refractory patients typically have **even lower** response rates and NCCN treatment guidelines recommend clinical trials for these patients.

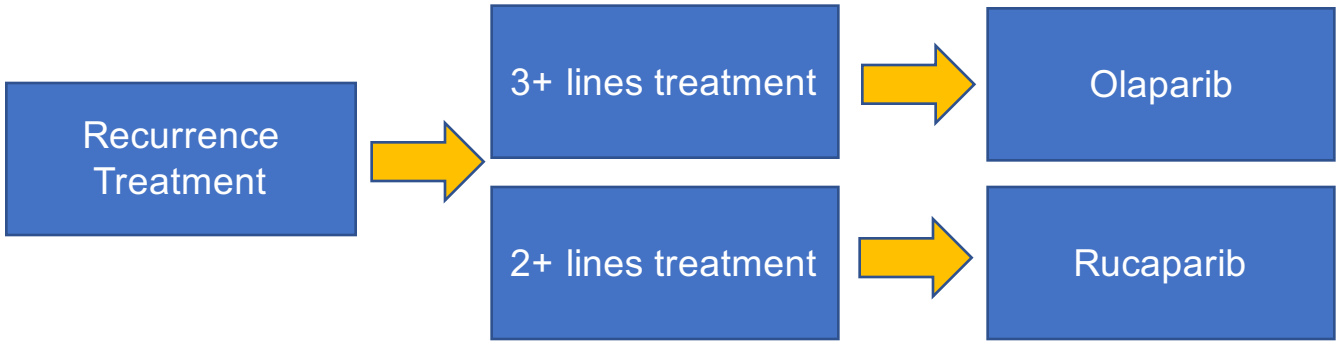
How Does This Compare?

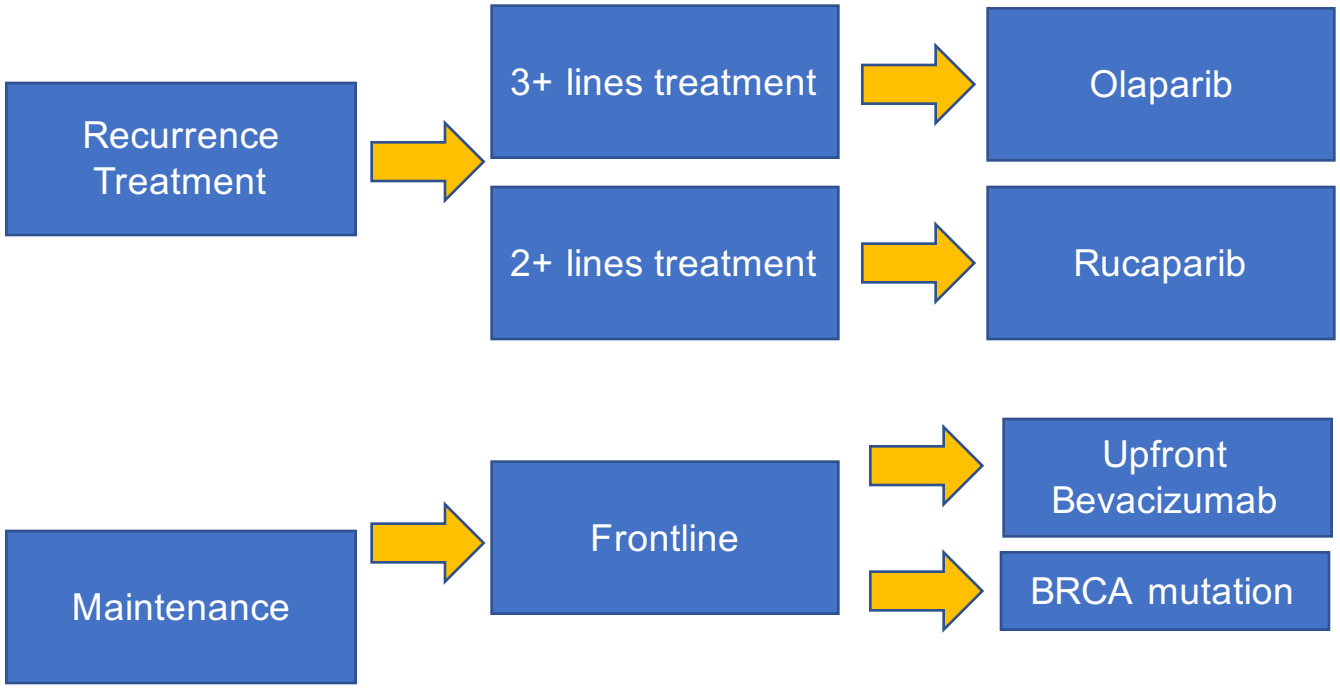
- Historical response to PARP inhibitors is 5-10% in patients without BRCA mutations who have platinum resistant disease and 0-14% in those with BRCA mutations and platinum refractory disease.

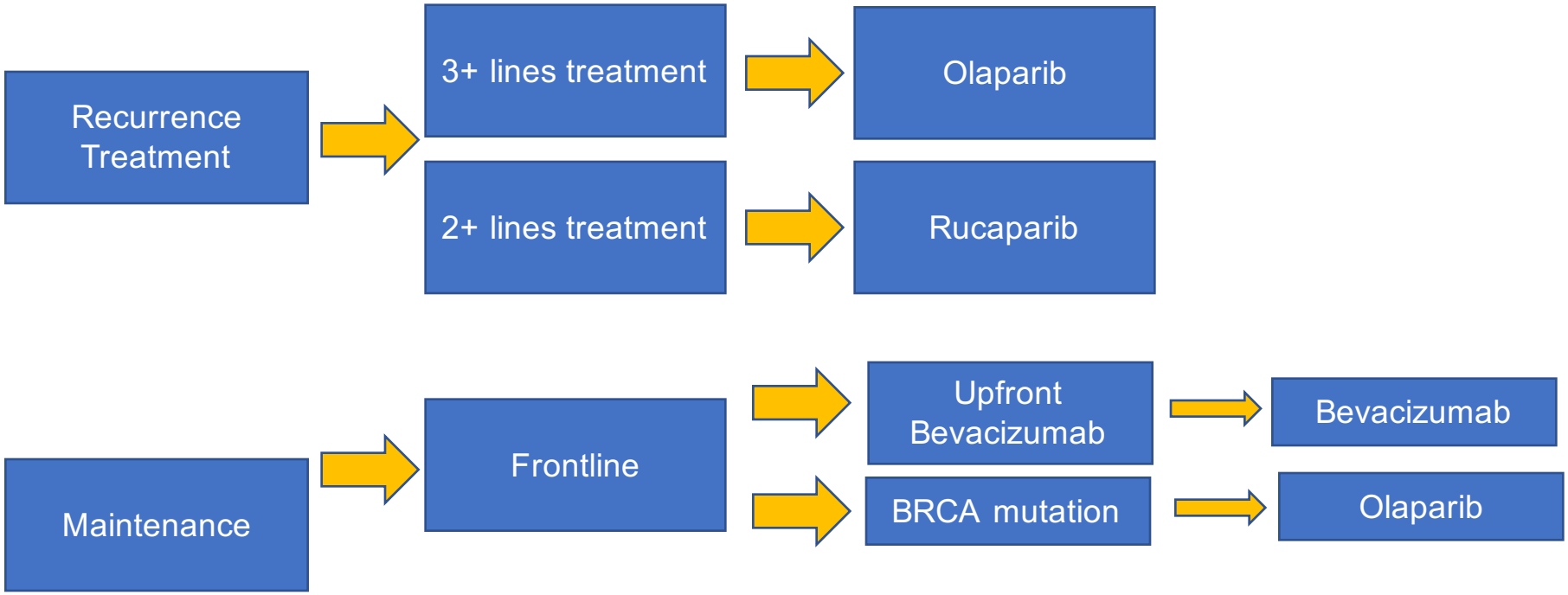
- Response rates of 10-15% have been reported with anti-PD-1 antibodies in this ovarian cancer population.

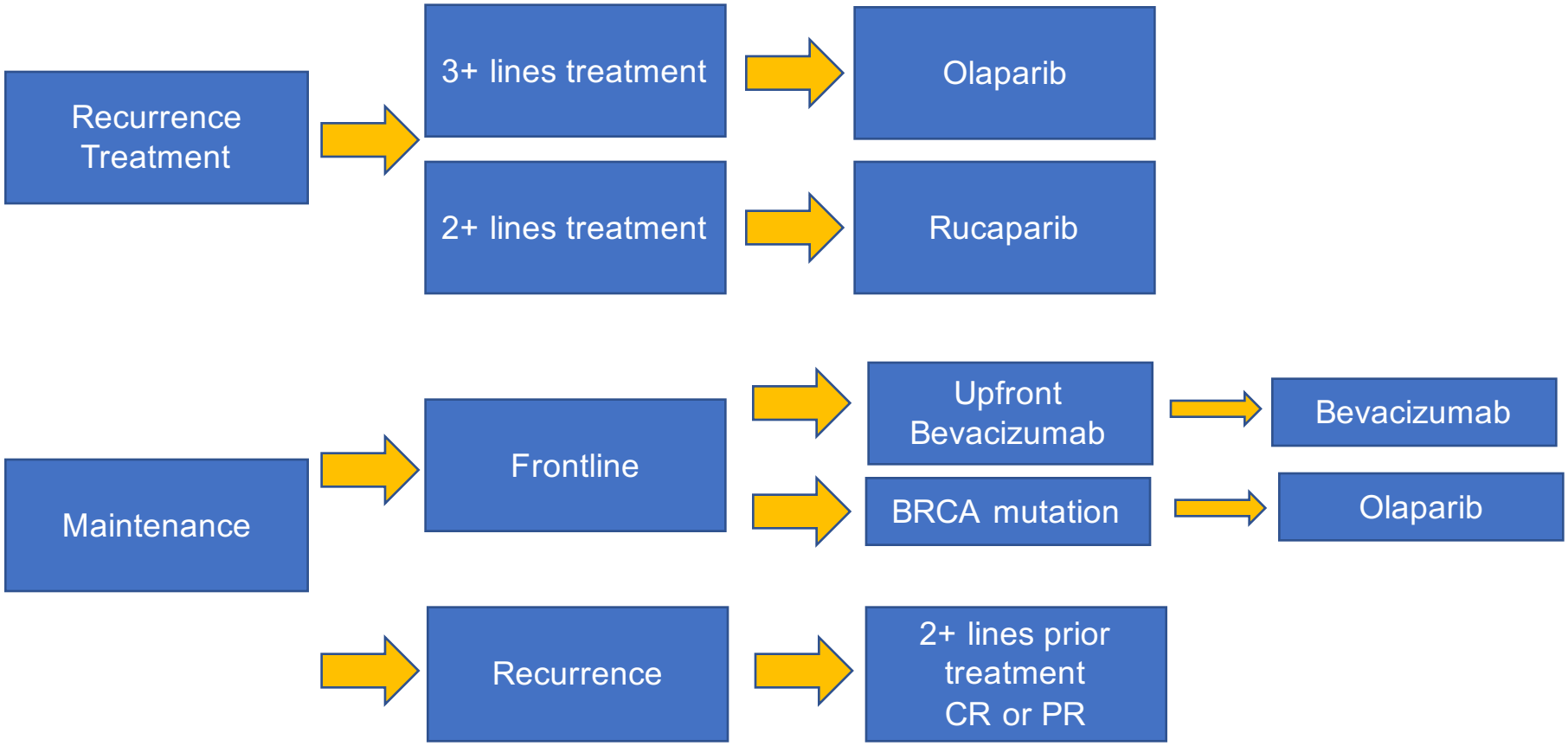
LET'S RECAP...

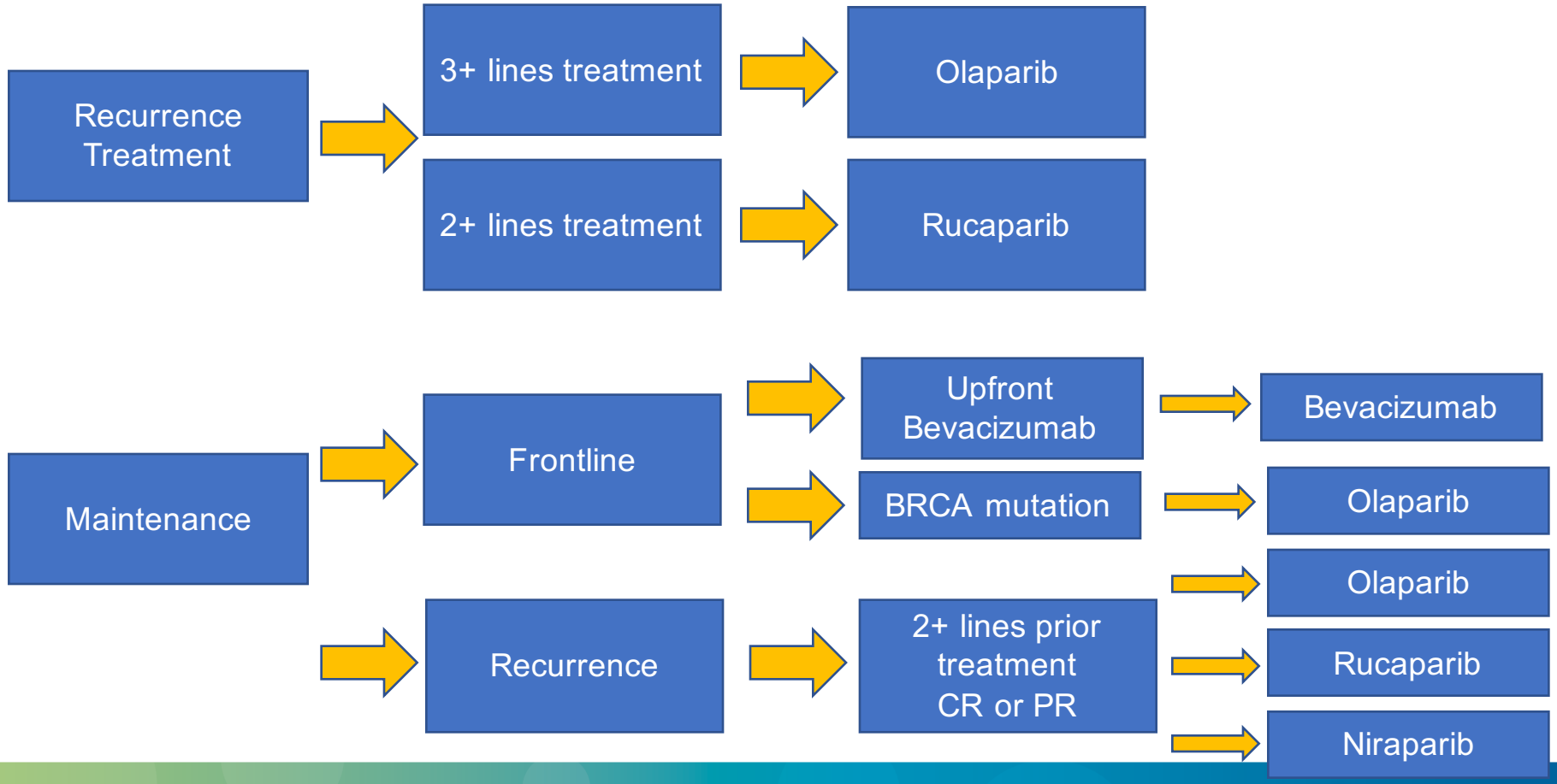

Recurrence Treatment
3+ lines treatment
2+ lines treatment


Recurrence Treatment
3+ lines treatment
2+ lines treatment
Olaparib
Rucaparib


Recurrence Treatment
3+ lines treatment
2+ lines treatment
Olaparib
Rucaparib
Maintenance
Frontline
Upfront Bevacizumab
BRCA mutation


Recurrence Treatment
3+ lines treatment
2+ lines treatment
Olaparib
Rucaparib
Maintenance
Frontline
Upfront Bevacizumab
BRCA mutation
Bevacizumab
Olaparib


Recurrence Treatment
3+ lines treatment
Olaparib
2+ lines treatment
Rucaparib
Maintenance
Frontline
Upfront Bevacizumab
Bevacizumab
BRCA mutation
Olaparib
Recurrence
2+ lines prior treatment CR or PR


Recurrence Treatment
3+ lines treatment
Olaparib
2+ lines treatment
Rucaparib
Maintenance
Frontline
Upfront Bevacizumab
Bevacizumab
BRCA mutation
Olaparib
Recurrence
2+ lines prior treatment CR or PR
Olaparib
Rucaparib
Niraparib

Conclusions

- The treatment landscape for ovarian cancer is rapidly changing.
- Focus on the molecular biology of these tumors and development of targeted treatments to exploit these molecular changes.
- Molecular tumor testing is essential for OC patients to inform treatment decisions.
- Frontline maintenance is now an option with bevacizumab, expect olaparib in near future.
- FDA approved treatment options for maintenance in recurrent setting include bevacizumab, olaparib, rucaparib, and niraparib with improved progression-free survival with no impact on QOL.
- Expect combination targeted therapies for treatment in future.

HOPE

References

- Aghajanian C, et al. *Gynecol Oncol*. 2015;139(1):10-6.
- Aghajanian C, et al. *J Clin Oncol*. 2012;30(17):2039-45.
- Barakat RR, et al. *J Clin Oncol*. 2002;20(3):694-8.
- Basen-Engquist K, et al. Presented at ASCO Annual Meeting, 2015. Abstract 9633.
- Berek J, et al. *J Clin Oncol*. 2009;27(3):418-25.
- Bertelsen K, et al. *Gynecol Oncol*. 1993;49(1):30-6.
- Bevacizumab package insert. Genentech, Inc; June 2018.
- Bouwman P, et al. *Clin Cancer Res*. 2014;20(3):540-7.
- Burger RA, et al. *New Engl J Med*. 2011;365(26):2473-83.
- Burger RA, et al. Presented at ASCO Annual Meeting, 2018. Abstract 5517.

References (cont.)

- Cancer Genome Atlas Research Network. *Nature*. 2011;474(7353):609-15
- Chan JK, et al. *N Engl J Med*. 2016;374(8):738-48.
- ClincialTrials.gov. NCT00262847.
- ClinicalTrials.gov: NCT02282020, NCT03402841, NCT01844986, NCT03106987, NCT02855944, and NCT02655016.
- ClinicalTrials.gov: NCT02282020, NCT03402841, NCT01844986, NCT03106987, NCT02855944, NCT02655016, NCT02477644, NCT03278717, NCT02446600, NCT02889900, NCT03117933, NCT01081951, NCT03161132, NCT02354131, NCT03326193, NCT02657889, NCT02470585, and NCT01012817.

References (cont.)

- ClinicalTrials.gov: NCT02477644, NCT03278717, NCT02446600, NCT02889900, NCT03117933, NCT01081951, NCT03161132, NCT02354131, NCT03326193, NCT02657889, NCT02470585, NCT03462212, and NCT01012817.
- Coleman RL, et al. *Lancet Oncol*. 2017;18(6):779-91.
- Coleman RL, et al. *Lancet*. 2017;390(10106):1949-61.
- Conte PF, et al. *J Clin Oncol*. 2007;25(18 suppl):abstr 5505.
- Copeland LJ, et al. Presented at SGO Annual Meeting, 2017.
- De Placido S, et al. *J Clin Oncol*. 2004;22(13):2635-42.
- Della Pepa C, et al. *Onco Targets Ther*. 2014;7:1025-32.
- Domchek SM, et al. *Gynecol Oncol*. 2016;140(2):199-203.
- Dréan A, et al. *Crit Rev Oncol Hematol*. 2016;108:73-85.

References (cont.)

- Drugs@FDA: FDA Approved Drug Products. https://www.accessdata.fda.gov/scripts/cder/daf/
- du Bois A, et al. *J Clin Oncol.* 2014;32(30):3374-82.
- FDA. Summary Review for Regulatory Action: Olaparib. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/206162Orig1s000SumR.pdf.
- Frey and Pothuri Gynecologic Oncology Research and Practice (2017) 4:4 DOI 10.1186/s40661-017-0039-8
- Friedlander M, et al. Presented at ASCO Annual Meeting, 2017. Abstract 5507.
- Hall GD, et al. *Br J Cancer*. 2004;91(4):621-6.
- Hanker LC, et al. *Ann Oncol*. 2012;23(10):2605-12
- Herzog TJ, et al. *Gynecol Oncol*. 2014;132(1):8-17.
- Herzog TJ, et al. *Gynecol Oncol*. 2017;147(1):3-10.
- Hirte H, et al. *Gynecol Oncol*. 2006;102(2):300-8.

References (cont.)

- Hope JM, et al. *Int J Womens Health*. 2009;1:173-80.
- Hosoya N, et al. *Cancer Sci.* 2014;105(4):370-88.
- https://meetinglibrary.asco.org/record/161618/abstract
- https://ocrfa.org
- https://www.accessdata.fda.gov/scripts/cder/daf/
- Kaufman B, et al. *J Clin Oncol*. 2015;33(3):244-50.
- Kelland L. *Nat Rev Cancer*. 2007;7(8):573-84
- Konstantinopoulos PA, et al. *Cancer Discov*. 2015;5(11):1137-54.
- Korkmaz T, et al. *Crit Rev Oncol Hematol*. 2016;98:180-8.
- Kristeleit R, et al. *Clin Cancer Res*. 2017;23(15):4095-106.
- Lambert HE, et al. *Ann Oncol*. 1997;8(4):327-33.

References (cont.)

- Ledermann J, et al. *Lancet Oncol*. 2014;15(8):852-61.
- Ledermann J, et al. *N Engl J Med*. 2012;366(15):1382-92.
- Ledermann JA, et al. *Lancet Oncol*. 2016;17(11):1579-89.
- Ledermann JA, et al. *Lancet*. 2016;387(10023):1066-74
- Ledermann JA, et al. Presented at ASCO Annual Meeting, 2017. Abstract 5506.
- Lord CJ, et al. *Nature*. 2012;481(7381):287-94.
- Markman M, et al. *J Clin Oncol*. 2003;21(13):2460-5.
- Mirza MR, et al. *N Engl J Med*. 2016;375(22):2154-64
- NCCN Guidelines® Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer (V.2.2018). Available online at NCCN.org.

References (cont.)

- NCT02571725, NCT02953457 NCT02484404, NCT02734004, NCT03598270, NCT02657889
- Niraparib package insert. TESARO, Inc; August 2017.
- Olaparib package insert. AstraZeneca Pharmaceuticals LP; January 2018.
- Oza A, et al. Presented at ESMO Annual Meeting, 2017. Abstract 930O.
- Patch AM, et al. Nature. 2015;521(7553):489-94.
- Pujade-Lauraine E, et al. *Lancet Oncol.* 2017;18(9):1274-84.
- Pujade-Lauraine E, et al. Presented at SGO 2017 Annual Meeting
- Pujade-Lauraine E. Presented at ASCO Annual Meeting, 2002. Abstract 829.
- Pujade-Lauraine E. Recurrent disease. ESMO: Oncology Pro (Educational Portal for Oncologists). http://oncologypro.esmo.org/content/download/58279/1077228/file/Advanced-Ovarian-Cancer-2015-10-Pujade-Lauraine.pdf.

References (cont.)

- Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Palliative Care V.1.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed June 27, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org.
- Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis V.3.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed June 27, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org.
- Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Cancer-Related Fatigue V.2.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed June 27, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
- Roche's Bevacizumab Plus Chemotherapy Receives FDA Approval for Platinum-sensitive Recurrent Ovarian Cancer [press release]. Basel, Switzerland: Roche; December 7, 2016. https://www.roche.com/dam/jcr:3050d757-8d1d-48a6-b372-c72dc3715556/en/med-cor-2016

References (cont.)

- Rucaparib package insert. Clovis Oncology, Inc; April 2018.
- Sabbatini P, et al. *J Clin Oncol*. 2013;31(12):1554-61.
- Sonnenblick A, et al. *Nat Rev Clin Oncol*. 2015;12(1):27-41
- Swisher EM, et al. *Lancet O*ncol. 2017;18(1):75-87.
- Vergote I, et al. Presented at ASCO Annual Meeting, 2018. Abstract 5518.
- Vergote IB, et al. *J Clin Oncol*. 2014;32(4):320-6.

SMARTIE

This has been a SMARTIE presentation.

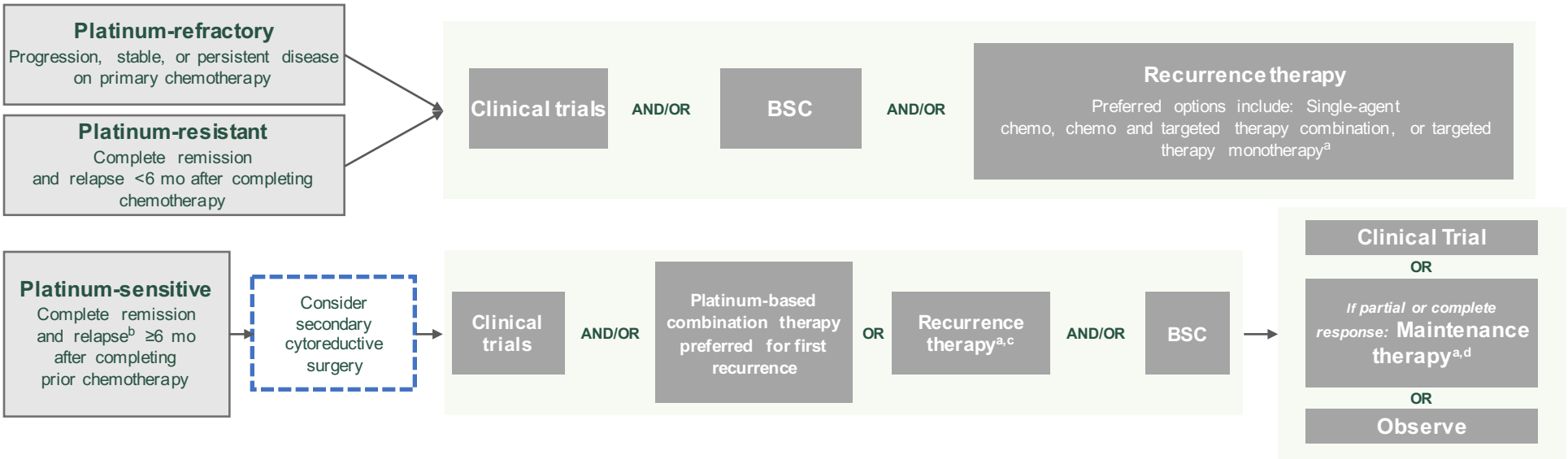
SMARTIE participants, you can now go to smartie2018.com or visit the SMARTIE booth to answer the post-session questions for this presentation.

If you would like more information about this program, please ask a conference staff member or visit the SMARTIE booth.

Anti-Angiogenic Maintenance Therapy Trials in Front-Line Ovarian Cancer Setting

	AGO-OVAR 16[1-3] (NCT00866697)		GOG-0218[4-6] (NCT00262847)		
	PBO (n=468)	**PAZ (n=472)**	**CP + PBO → PBO (n=625)**	**CP + BEV → PBO (n=625)[a]**	**CP + BEV → BEV (n=623)[a]**
mPFS, mo (95% CI)	12.3 (11.8–17.7)	17.9 (15.9–21.8)	10.3 (NR)	11.2 (NR)	14.1 (NR)
HR (95% CI) *P* value	0.77 (0.64–0.91) 0.0021		--	0.908 (0.795–1.040)[b] 0.16	0.717 (0.625–0.824)[b] <0.001
mOS, mo (95% CI)	64.0 (56.0–75.7)	59.1 (53.5–71.6)	41.1 (NR)	40.8 (NR)	43.4 (NR)
HR (95% CI) *P* value	0.960 (0.805–1.145) 0.6431		--	1.06 (0.94–1.20)[b] 0.34	0.96 (0.85–1.09)[b] 0.53
Most Common Serious AEs (%)	Hypertension (Gr 3/4): 5.6 Neutropenia (Gr 3/4): 1.5 Diarrhea (Gr 3/4): 1.1 Abdominal pain (Gr 3/4): 1.1	Hypertension (Gr 3/4): 30.8 Neutropenia (Gr 3/4): 9.9 Liver-related toxicity (Gr 3/4): 9.4	Neutropenia (Gr ≥4): 57.7 Pain (Gr ≥2): 41.6 Hypertension (Gr ≥2): 7.2	Neutropenia (Gr ≥4): 63.3 Pain (Gr ≥2): 41.5 Hypertension (Gr ≥2): 16.5	Neutropenia (Gr ≥4): 63.3 Pain (Gr ≥2): 47.0 Hypertension (Gr ≥2): 22.9

1. ClinicalTrials.gov. NCT00866697. Accessed June 27, 2018. **2.** du Bois A, et al. *J Clin Oncol*. 2014;32(30):3374-82.
3. Vergote I, et al. Presented at ASCO Annual Meeting, 2018. Abstract 5518. **4.** ClincialTrials.gov. NCT00262847. Accessed June 27, 2018. **5.** Burger RA, et al. *New Engl J Med.* 2011;365(26):2473-83. **6.** Burger RA, et al. Presented at ASCO Annual Meeting, 2018. Abstract 5517.



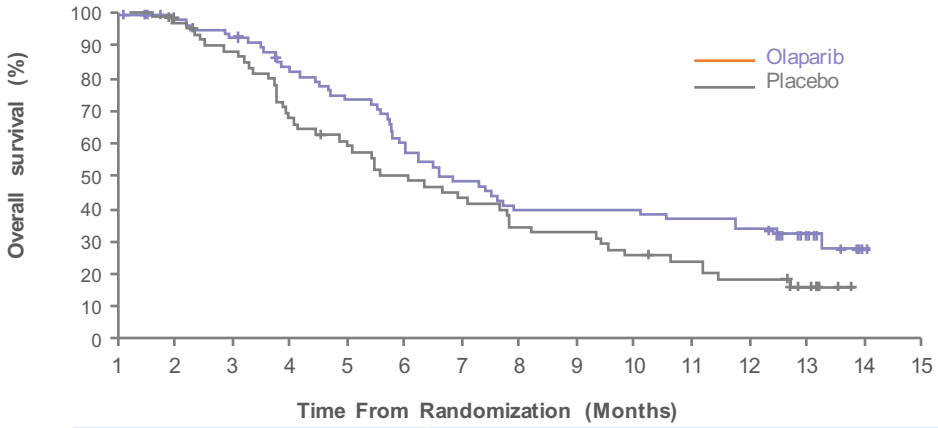
NCCN Guidelines® Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer (V.2.2018). Available online at NCCN.org. Accessed April 9, 2018.

Anti-Angiogenic Maintenance Summary

- Anti-angiogenic agents improve PFS in recurrence treatment, as well as in front-line treatment, of ovarian cancer.[1-5]
- Significant durable effect on OS has not been shown consistently for anti-angiogenic agents.[2,6-9]
- Anti-angiogenic maintenance therapy was associated with increased vascular adverse reactions, bleeding events, and other AEs compared with placebo, and varied by agent used.[2-4,6]

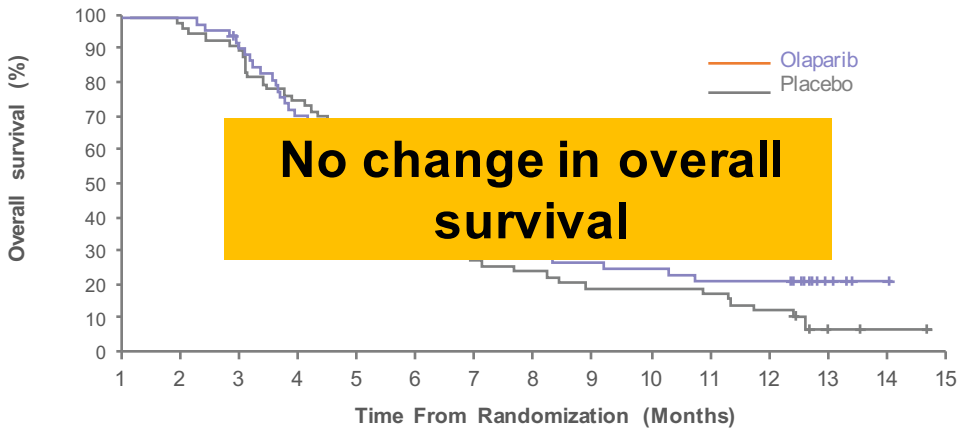
1. Aghajanian C, et al. J Clin Oncol. 2012;30(17):2039-45. 2. Coleman RL, et al. Lancet Oncol. 2017;18(6):779-91. 3. Ledermann JA, et al. Lancet. 2016;387(10023):1066-74. 4. du Bois A, et al. J Clin Oncol. 2014;32(30):3374-82. 5. Burger RA, et al. New Engl J Med. 2011;365(26):2473-83. 6. Aghajanian C, et al. Gynecol Oncol. 2015;139(1):10-6. 7. Ledermann JA, et al. Presented at ASCO Annual Meeting, 2017. Abstract 5506. 8. Burger RA, et al. Presented at ASCO Annual Meeting, 2018. Abstract 5517. 9. Vergote I, et al. Presented at ASCO Annual Meeting, 2018. Abstract 5518.

Patients With *BRCA*^{mut} (n=136)



	BRCA^{mut} (n=136)	
	Olaparib (n=74)	Placebo (n=62)
Events, n (%)	47 (64)	48 (77)
mOS, mo	34.9	30.2
HR (95% CI) Nominal P value	0.62 (0.41–0.94) 0.025	

Patients With *BRCA*$^{wt(b)}$ (n=118)



	BRCA^{wt} (n=118)	
	Olaparib (n=57)	Placebo (n=61)
Events, n (%)	43 (75)	56 (92)
mOS, mo	24.5	26.6
HR (95% CI) Nominal P value	0.83 (0.55–1.24) 0.37	

[a] Study 19 was not designed to show a statistically significant difference in OS.
[b] Wild-type subgroup includes patients with no known *BRCA*^{mut} and those with a *BRCA*^{mut} of unknown significance.
[c] Number of remaining patients in the study for each interval.

CI = confidence interval; HR = hazard ratio; wt = wild-type.

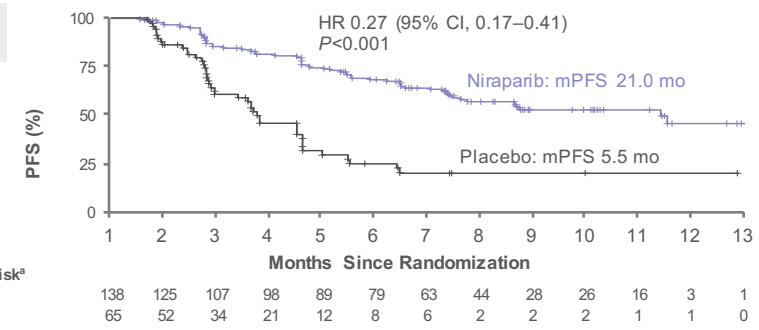
Ledermann JA, et al. *Lancet Oncol*. 2016;17(11):1579-89.

	Study 10 (NCT01482715)[1]	ARIEL2 (NCT01891344)[2]		ARIEL3 (NCT01968213)[3]		
	Part 2	*BRCA*mut	s*BRCA*mut*	*BRCA*mut	HRD	ITT
N	42	40	19	130	236	375
Design	Phase 2 expansion	Phase 2, Part 1		Phase 3		
Patients	Platinum-sensitive, relapsed, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer, with g*BRCA1/2* mutation, 2–4 prior regimens	Platinum-sensitive, high-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal cancer with ≥1 prior lines of platinum therapy		Platinum-sensitive, high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancer, ≥2 prior lines of platinum chemotherapy		
Treatment	Rucaparib 600 mg bid	Rucaparib 600 mg bid		Rucaparib 600 mg bid		
Results	**ORR**: 59.5%	**mPFS:** 12.8 mo	**Confirmed ORR:** 74%	**mPFS:** 16.6 mo	**mPFS:** 13.6 mo	**mPFS:** 10.8 mo
Safety: Most common grade ≥3 AEs	Anemia (38.1%) Fatigue/asthenia (26.2%) Neutropenia (16.6%)	Anemia (22%) Elevated ALT/AST (12%) Fatigue/asthenia (9%)		Anemia (19%) Elevated ALT/AST (10%) Fatigue/asthenia (7%)		

1. Kristeleit R, et al. *Clin Cancer Res*. 2017;23(15):4095-106. **2.** Swisher EM, et al. *Lancet Oncol*. 2017;18(1):75-87. **3.** Rucaparib package insert. Clovis Oncology, Inc; April 2018. **4.** FDA. FDA Approves Rucaparib for Maintenance Treatment of Recurrent Ovarian, Fallopian Tube, or Primary Peritoneal Cancer. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm603997.htm. Last updated April 6, 2018. Accessed April 10, 2018.

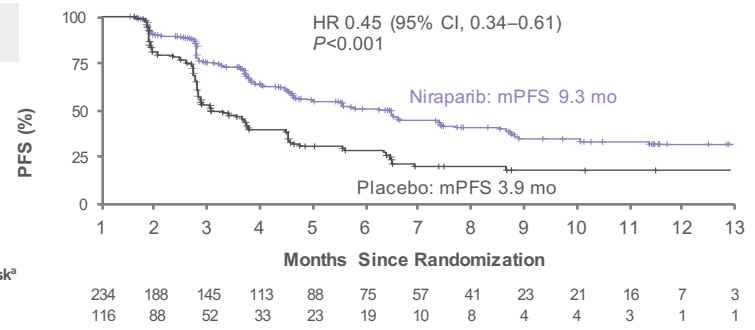
NOVA: PFS Benefit Seen in Pre-Identified Subgroups

Germline *BRCA* Mutation



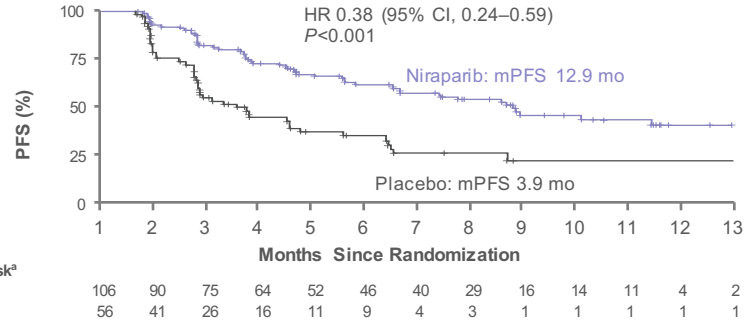
Number at risk[a]													
Niraparib	138	125	107	98	89	79	63	44	28	26	16	3	1
Placebo	65	52	34	21	12	8	6	2	2	2	1	1	0

No Germline *BRCA* Mutation



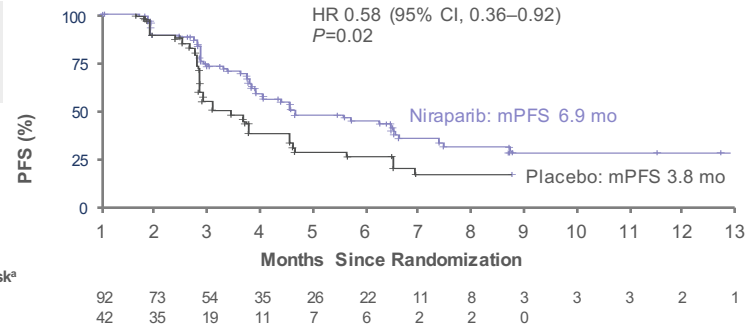
Number at risk[a]													
Niraparib	234	188	145	113	88	75	57	41	23	21	16	7	3
Placebo	116	88	52	33	23	19	10	8	4	4	3	1	1

No Germline *BRCA* Mutation With HRD Positivity



Number at risk[a]													
Niraparib	106	90	75	64	52	46	40	29	16	14	11	4	2
Placebo	56	41	26	16	11	9	4	3	1	1	1	1	1

No Germline *BRCA* Mutation With HRD Negativity



Number at risk[a]													
Niraparib	92	73	54	35	26	22	11	8	3	3	3	2	1
Placebo	42	35	19	11	7	6	2	2	0				

[a] Number of remaining subjects in the study for each interval.

Mirza MR, et al. *N Engl J Med.* 2016;375(22):2154-64.

PARPi Maintenance Therapy Is More Effective Than Observation

Patient Population	Treatment Arm	Range of mPFS Reported in Studies, mo
PSOC[1-3]	Chemo alone	8.4–10.4
	Chemo + anti-angiogenic therapy	11.1–13.8
g*BRCA*^{mut} or *BRCA*^{mut} ovarian cancer in response to platinum[4-7,a]	Placebo	4.3–5.5
	PARPi	11.2–21.0
Non-g*BRCA*^{mut} or *BRCA*^{wt} ovarian cancer in response to platinum[5,7]	Placebo	3.9–5.5
	PARPi	7.4–9.3

This time does not reflect 4–6 mo of induction chemotherapy that precedes maintenance treatment

1. Coleman RL, et al. *Lancet Oncol*. 2017;18(6):779-91. **2.** Ledermann JA, et al. Presented at ASCO Annual Meeting, 2017. Abstract 5506. **3.** Aghajanian C, et al. *J Clin Oncol*. 2012;30(17):2039-45. **4.** Coleman RL, et al. *Lancet*. 2017;390(10106):1949-61. **5.** Ledermann J, et al. *Lancet Oncol*. 2014;15(8):852-61. **6.** Pujade-Lauraine E, et al. *Lancet Oncol*. 2017;18(9):1274-84. **7.** Mirza MR, et al. *N Engl J Med*. 2016;375(22):2154-64.

A Word About Pazopanib

- Phase 3 trial showing PFS 17.9 vs 12.3
- NOT FDA approved
- No increase in OS
- Increased grade 3-4 toxicity
- (see NCCN guidelines)