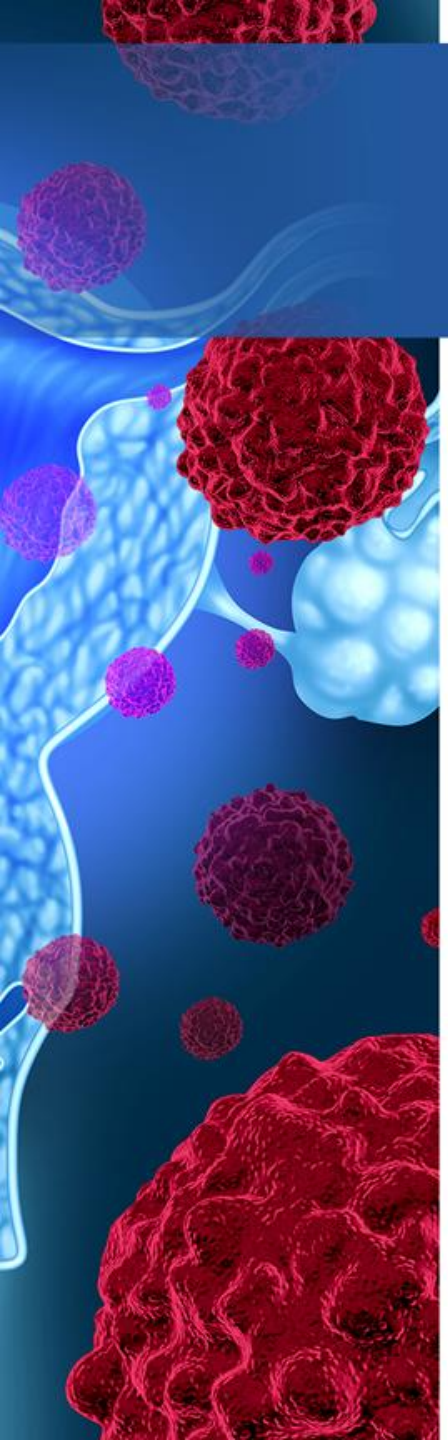
PARP Inhibitors for the Management of Ovarian Cancer:

Implications for Health System Pharmacy Leaders



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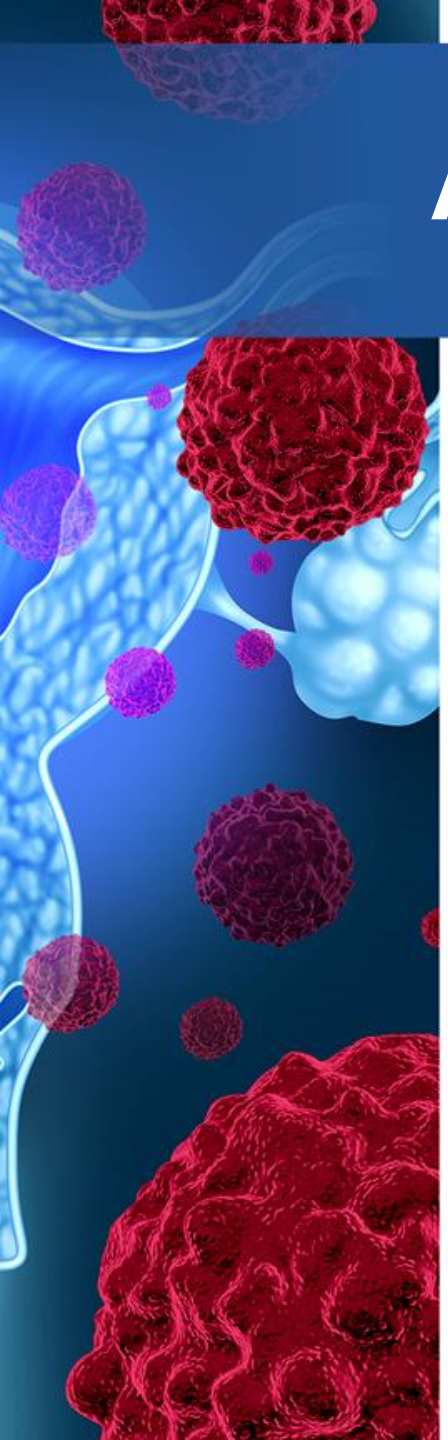

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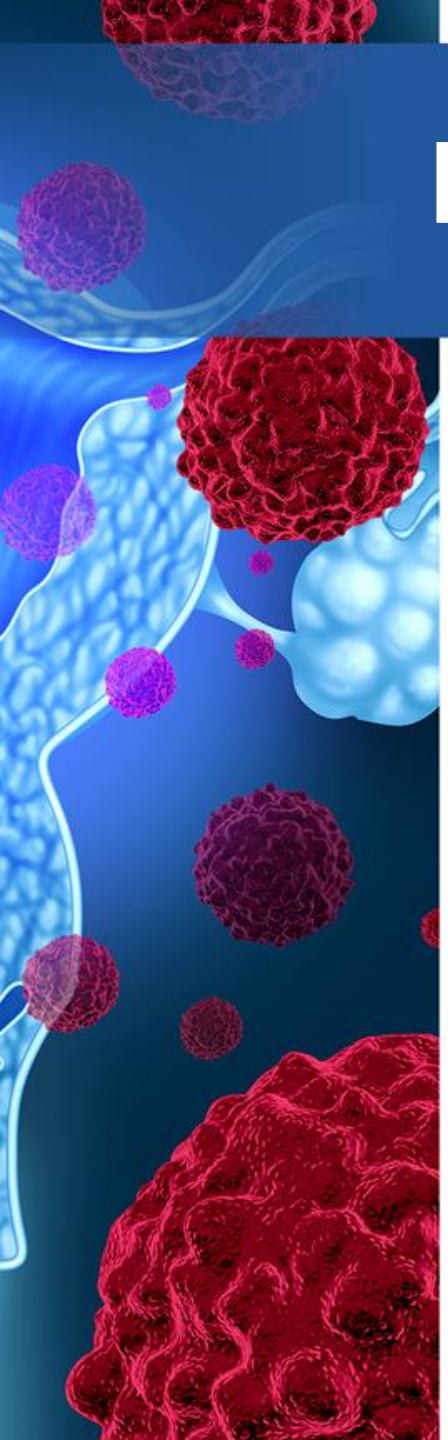

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Associate Professor
Director of Women's Health Integrative Medicine Research Program
McGovern Medical School at UTHealth
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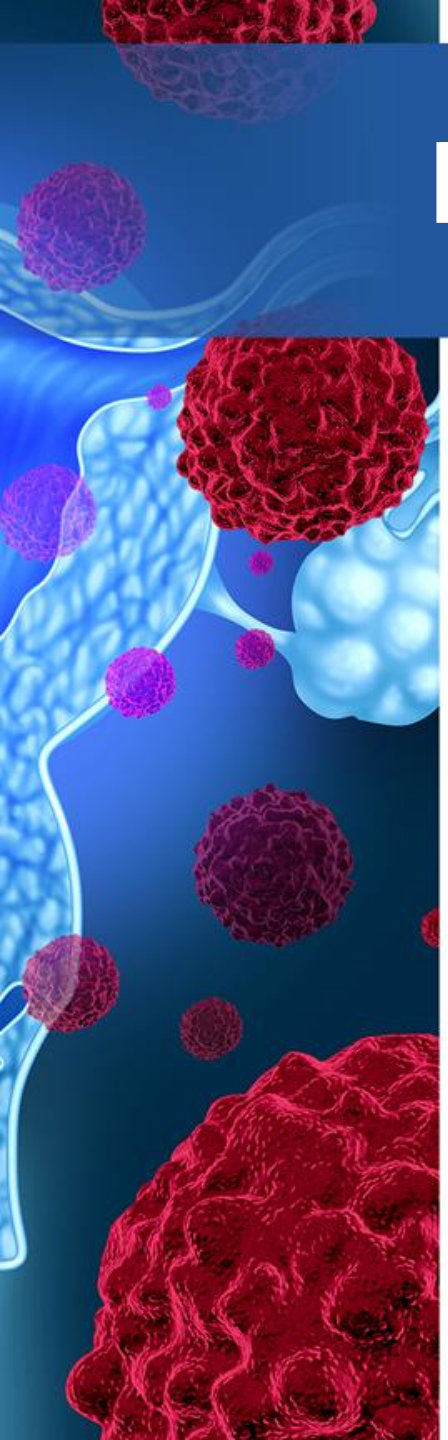

Disclosures

Dr. Smith 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 conflict of interest in relation to this program.

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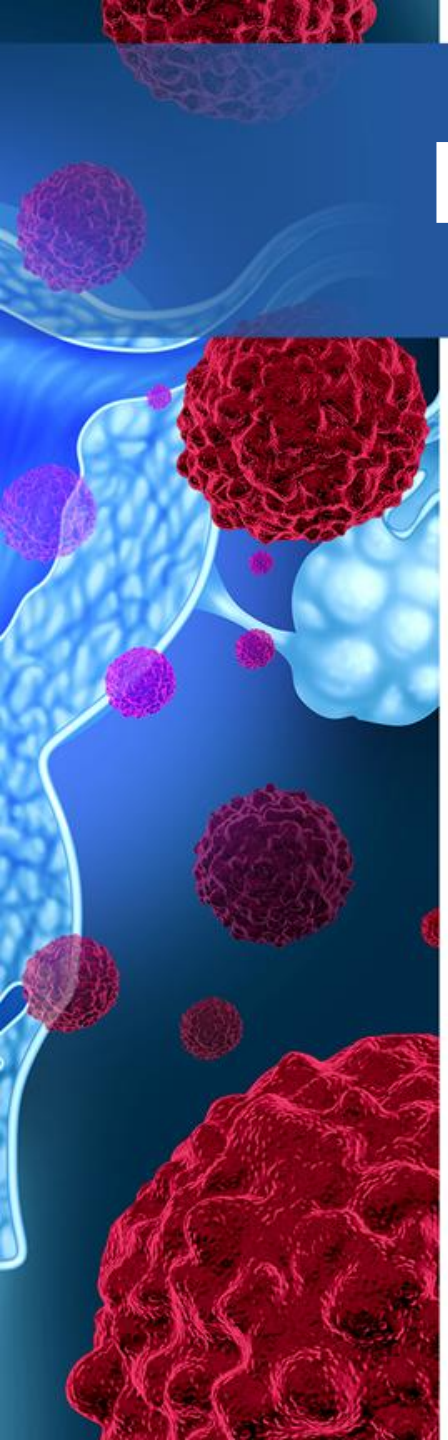


Learning Objectives

- **Review** the evidence-based role of PARP inhibitors in the treatment of ovarian cancer
- **Compare** the similarities and differences in prescribing information, clinically meaningful benefits, and adverse event profiles of each PARP inhibitor approved for use in ovarian cancer
- **Formulate** strategies to effectively incorporate PARP inhibitors into the clinical pathway for patients with ovarian cancer

Ovarian Cancer

- SEER 2019 data
  - Overall mean 5-year survival: 47.6% for all patients diagnosed with ovarian cancer

Extent of disease (portion of patients)	5-year survival rate (%)
Localized/FIGO stage I (15%)	82.4
Regional/FIGO stage II (21%)	76.2
Distant (FIGO stage III/IV) (59%)	***29.2***
Unknown/unstaged (6%)	***24.3***

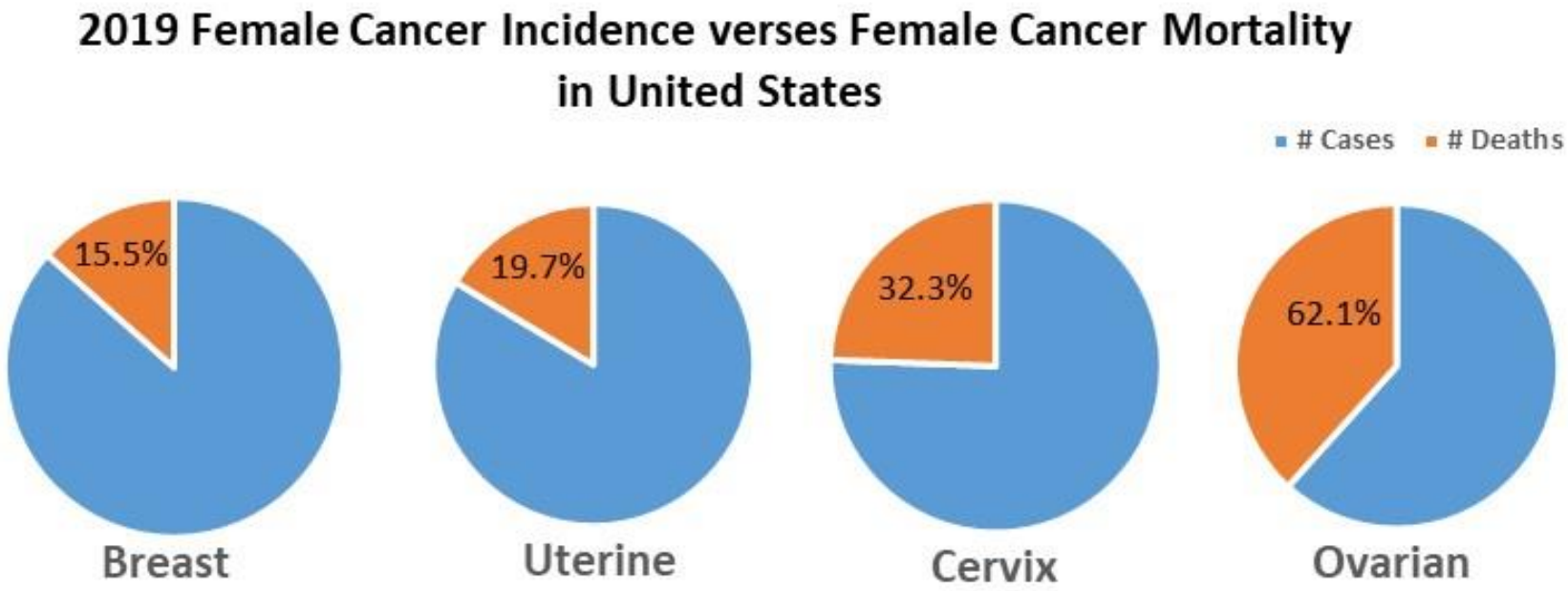
  - Mean age at diagnosis: 63 years
  - Median age at death: 70 years

National Cancer Institute. http://seer.cancer.gov/statfacts/html/ovary.html. Accessed September 6, 2019.

FIGO, International Federation of Gynecology and Obstetrics.

Ovarian Cancer

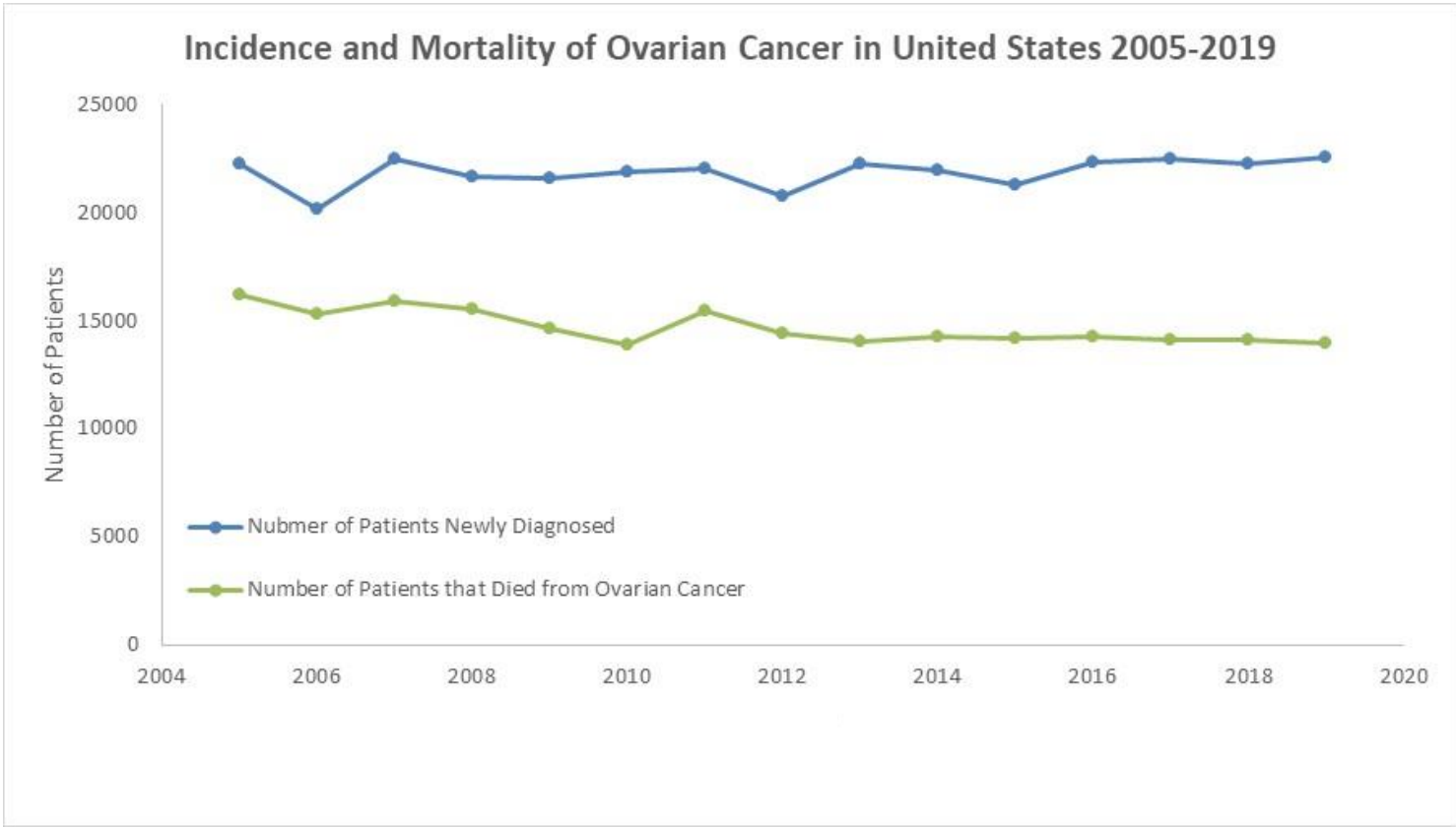
- Ovarian cancer has the highest mortality among all female cancers
  - Often called the "***silent killer***"



American Cancer Society. Cancer Facts & Figures 2019.

Ovarian Cancer

- Minimal improvement over past 7 decades
- Milestones over time:
  - 1990s
    - Integration of taxanes into first-line treatment
    - Topotecan and liposomal doxorubicin approved for recurrent ovarian cancer
  - 2006
    - Landmark intraperitoneal study demonstrated survival advantage
      - Slow on adoption into practice
  - 2012-2013
    - Drug shortages
  - 2014
    - November: bevacizumab approved in recurrent setting with combination regimens
    - December: first PARP inhibitor approved



Ca Cancer J for Clinicians 1995-2019

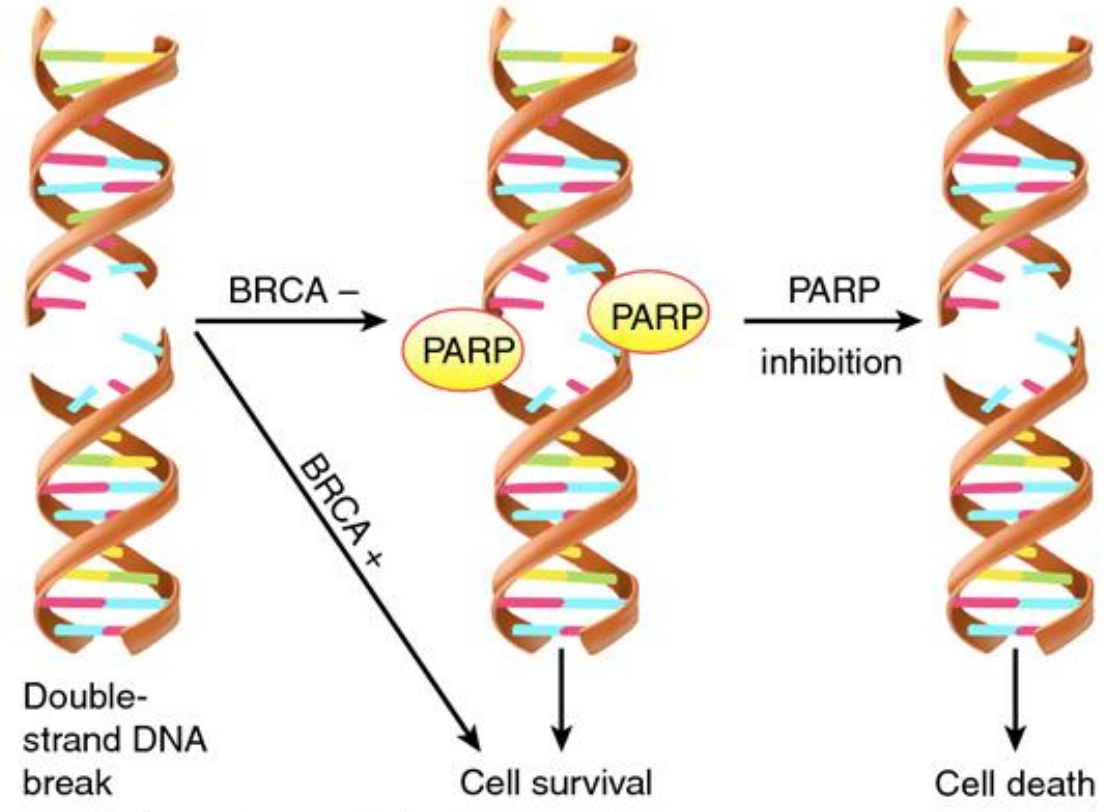
BRCA 1/2 Gene

- Tumor suppressor genes
  - Function is to repair double-stranded DNA breaks via homologous repair
- Approximately 15% of all ovarian cancers have BRCA 1/2 mutations
  - An estimated 44% of women who inherit a harmful *BRCA1* mutation and 17% of women who inherit a harmful *BRCA2* mutation will develop ovarian cancer by the age of 80 years
- Mutations alter the BRCA 1/2 gene such that its protein product is not made or does not function properly and DNA damage may not be repaired properly
    - Germline mutation (inherited, detected in all cells)
    - Somatic (tumor) mutation in *BRCA1/2* allele
  - Compensated by “wild-type” allele: double-stranded break repair function is maintained
  - Loss of heterozygosity (LOH)
    - Occurs if there is loss of the wild-type allele
    - Leads to ineffective homologous repair pathway

Ashworth A. *J Clin Oncol*. 2008;26(22):3785-90.

PARP Inhibitors: Mechanism of Action

- PARP inhibition
- PARP trapping
- Synthetic lethality



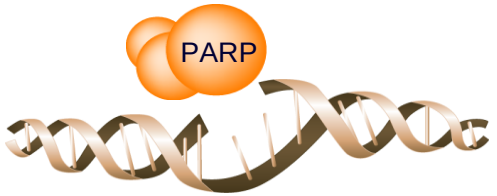
Patel AG, et al. *Proc Natl Acad Sci U S A.* 2011;108(8):3406-11.

What is PARP…. And the Impact of PARP Inhibition

PARP: poly(adenosine diphosphate ribose) polymerase

- 18 proteins play essential parts
  - Repair of DNA single-strand breaks (SSBs) through the base excision repair (BER) pathway
  - Repair of DNA double-strand breaks (DSBs) via inhibition of nonhomologous end-joining repair (NHEJ)

- PARP1—DNA repair enzyme responsible for BER of DNA SSBs



DNA SSBs occur all the time in cells and PARP detects and repairs them

Patel AG, et al. *Proc Natl Acad Sci U S A.* 2011;108(8):3406-11.

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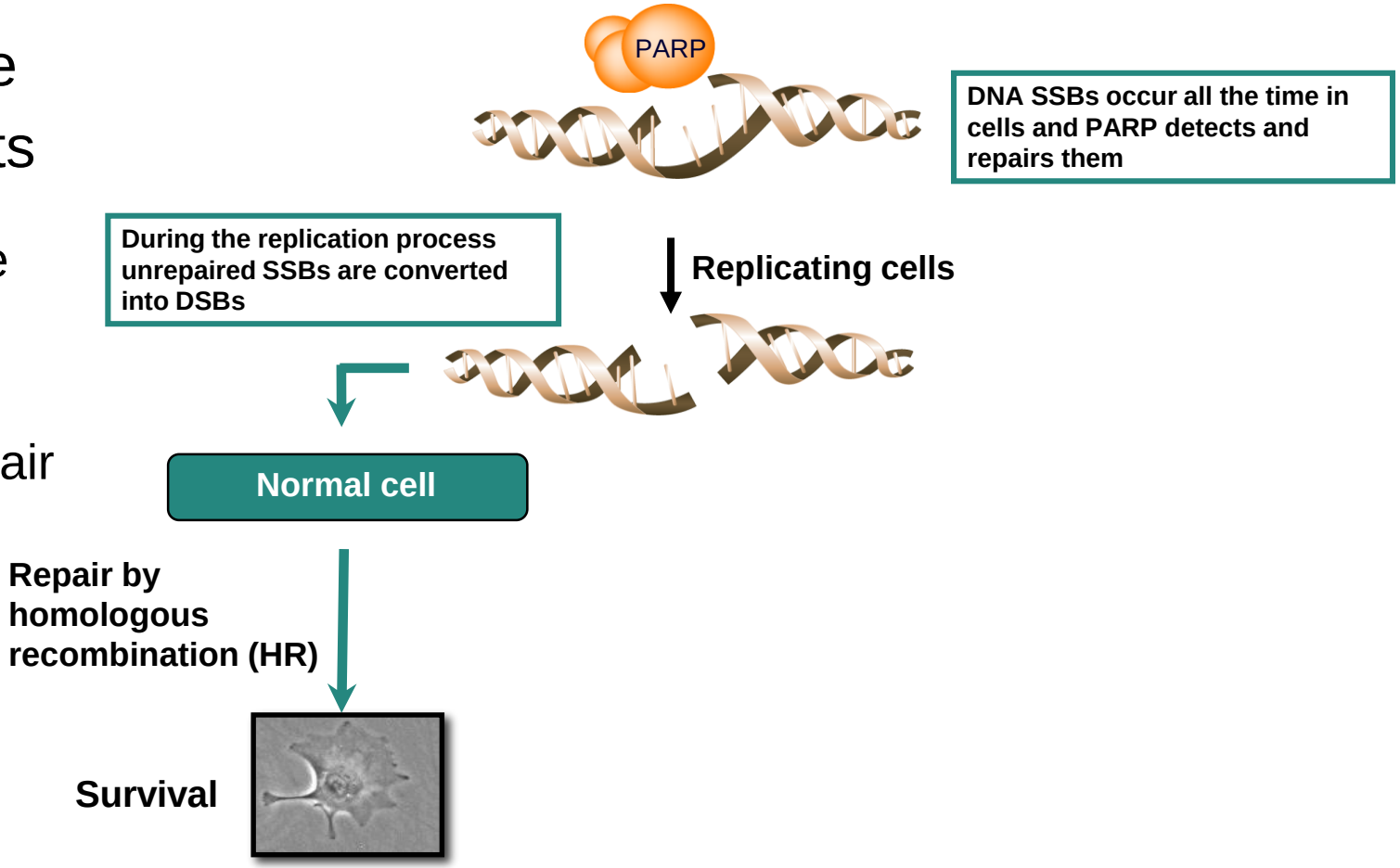

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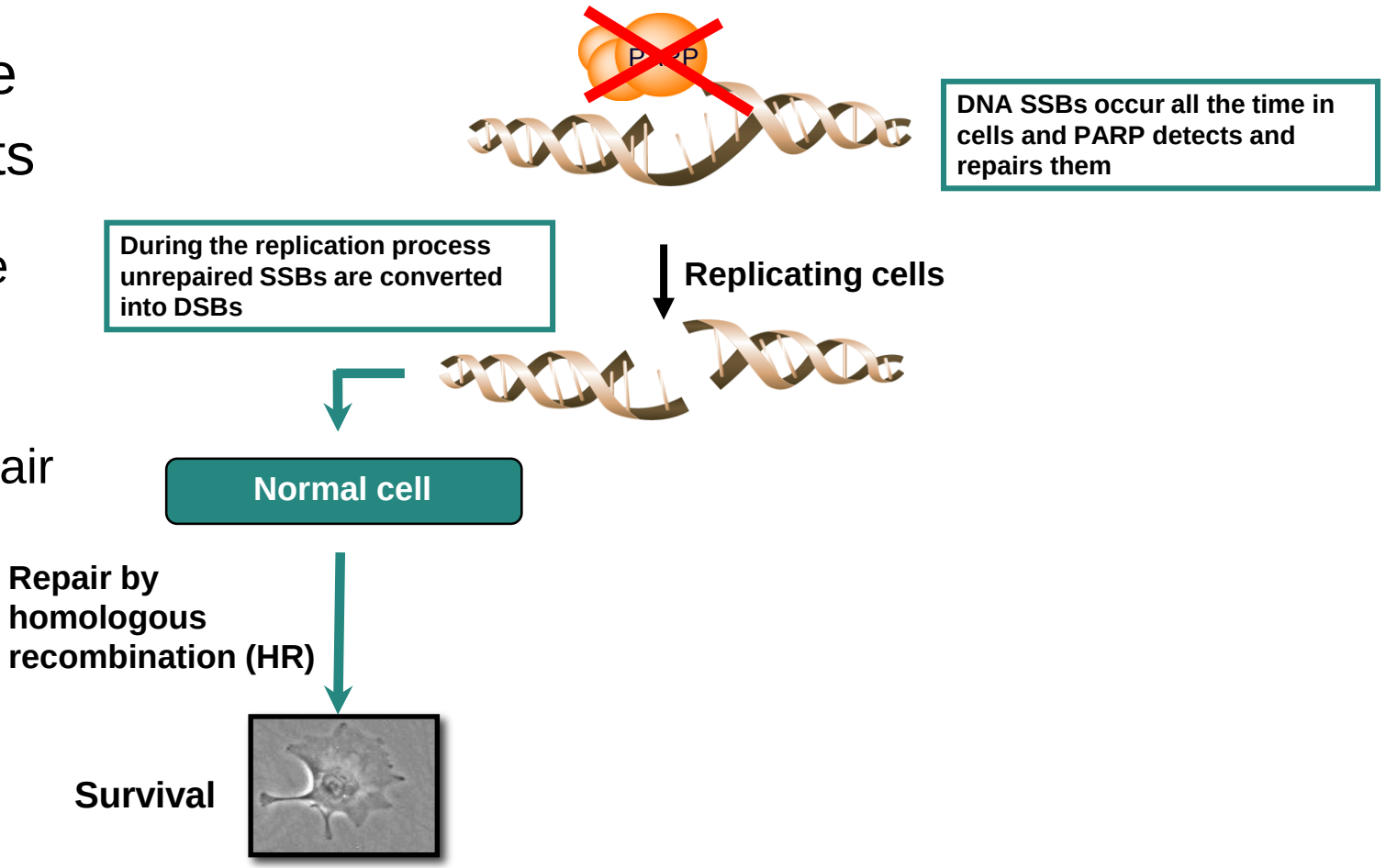

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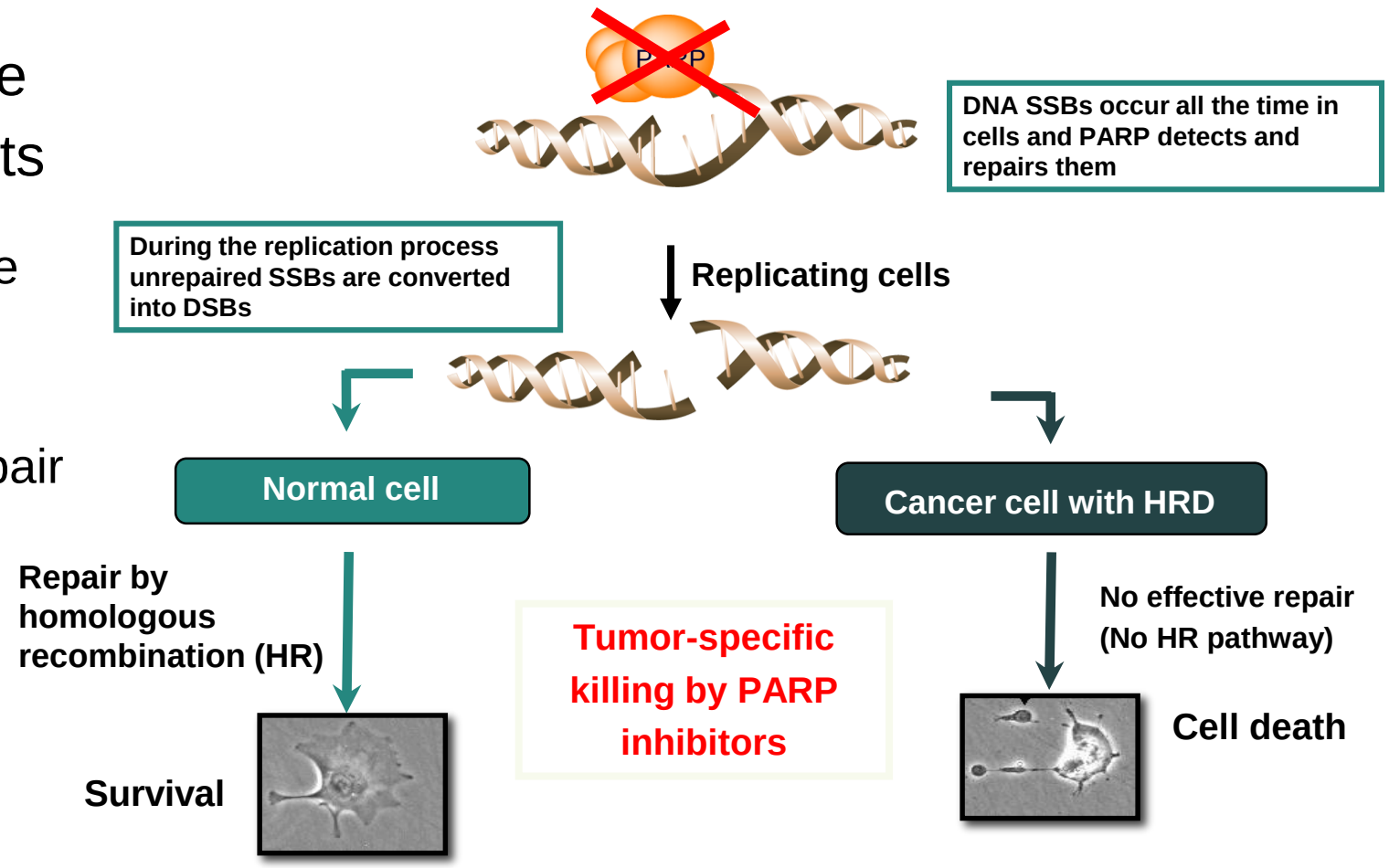


Patel AG, et al. *Proc Natl Acad Sci U S A.* 2011;108(8):3406-11.

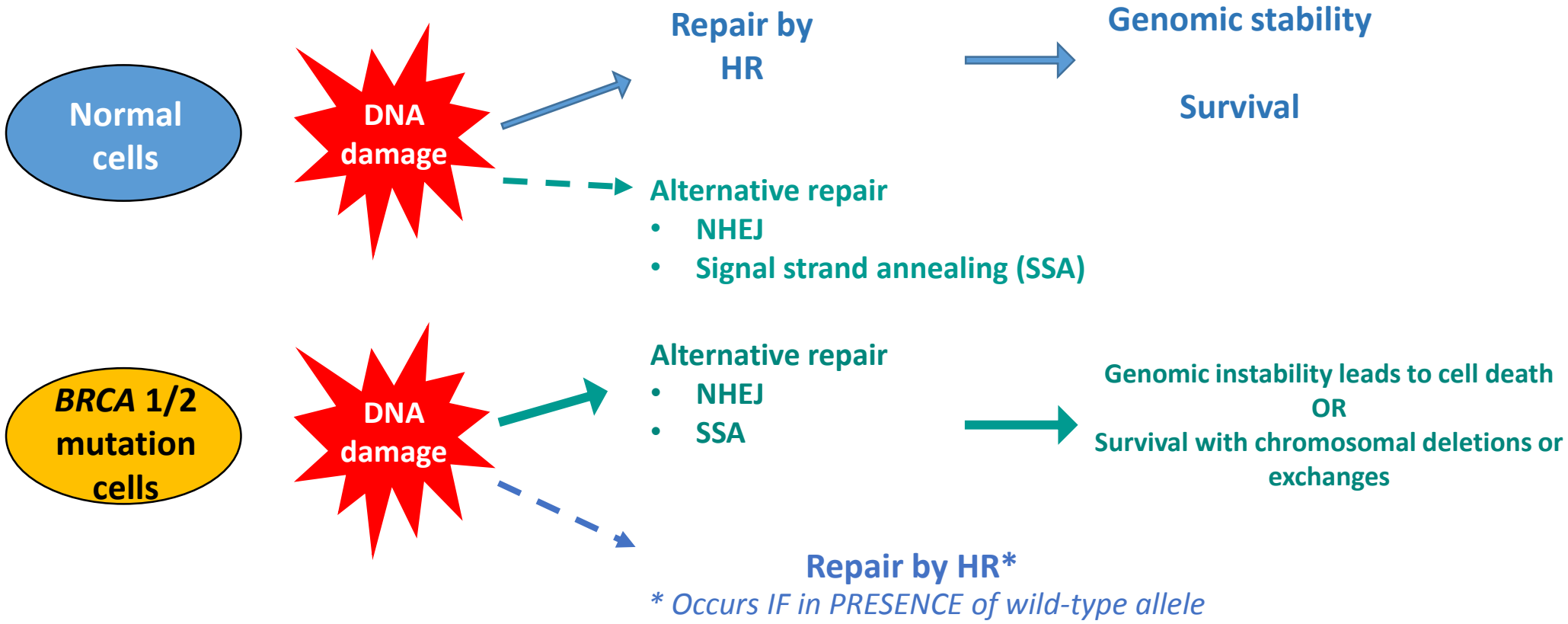
HRD, homologous recombination deficiency.

Synthetic Lethality

- Concept was first described in 1922 by Bridges and colleagues
- Dobzhansky and colleagues labeled the concept “synthetic lethality” in 1946
- What is synthetic lethality?
  - When *2 non-lethal* mutations occurring *individually* have no effect BUT when combined/occurring at the same time will lead to cell death
    - Cancer research application: identify single mutation present in cancer cells but not in normal cells, then inhibit the “partner” gene/enzyme/compensatory mechanism

Bridges CB. *Amer Nat*. 1922;56:51-63.; Dobzhansky T. *Genetics*. 1946;31:269-90.

Capitalizing on the Concept of Synthetic Lethality in Cancer Drug Development



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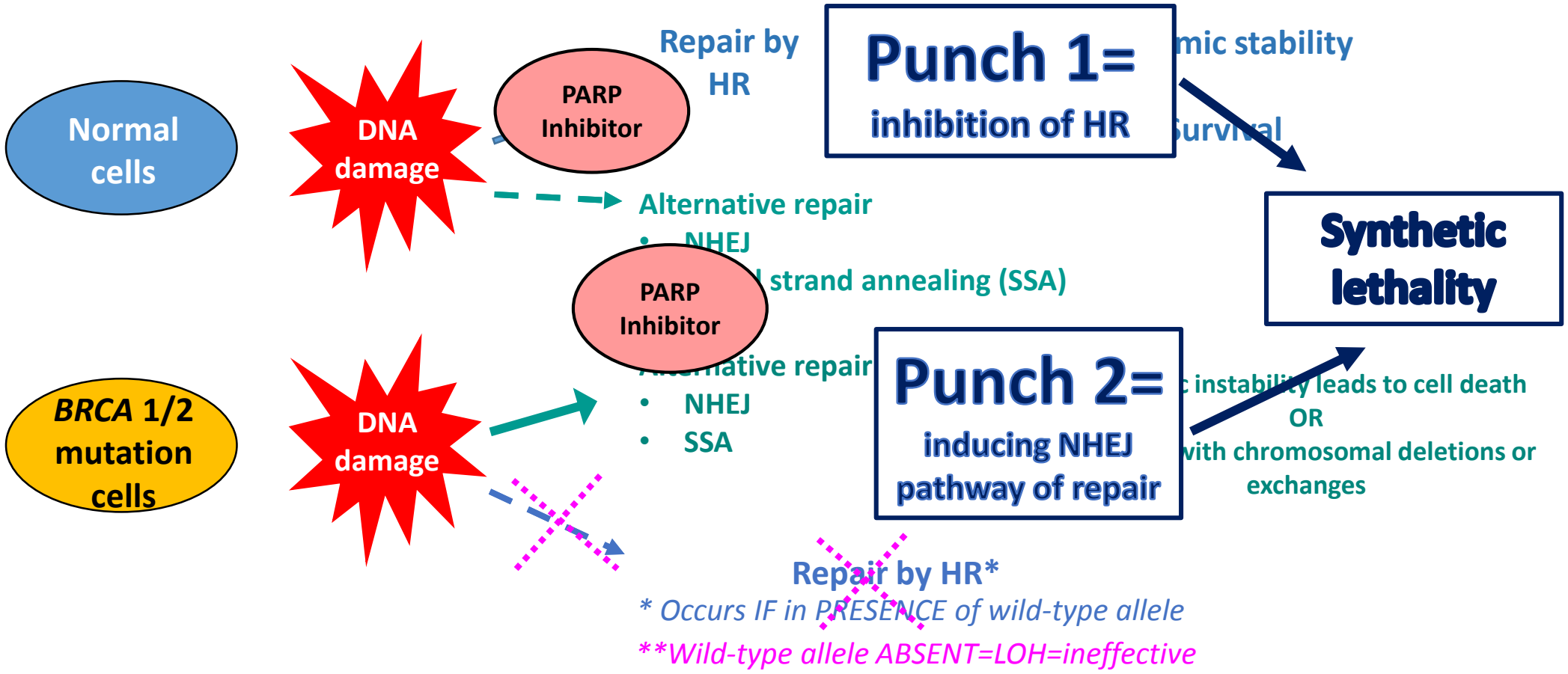
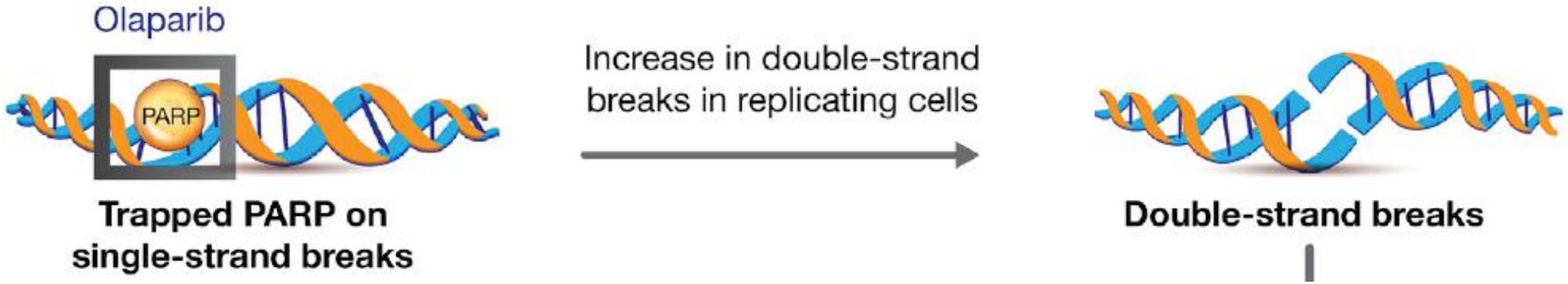
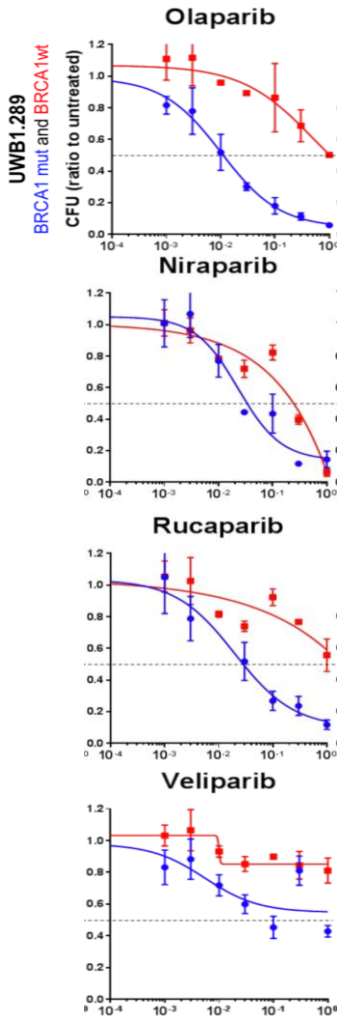


Patel AG, et al. *Proc Natl Acad Sci U S A.* 2011;108(8):3406-11.

PARP Trapping

- Mechanism for some PARP inhibitors
  - Related to catalytic inhibition of PARP1/2
  - Also “trapping” PARP-DNA complexes (chromatin binding)
- Trapping explains the synergism with alkylating agents
- PARP trapping is not universal among all PARP inhibitors





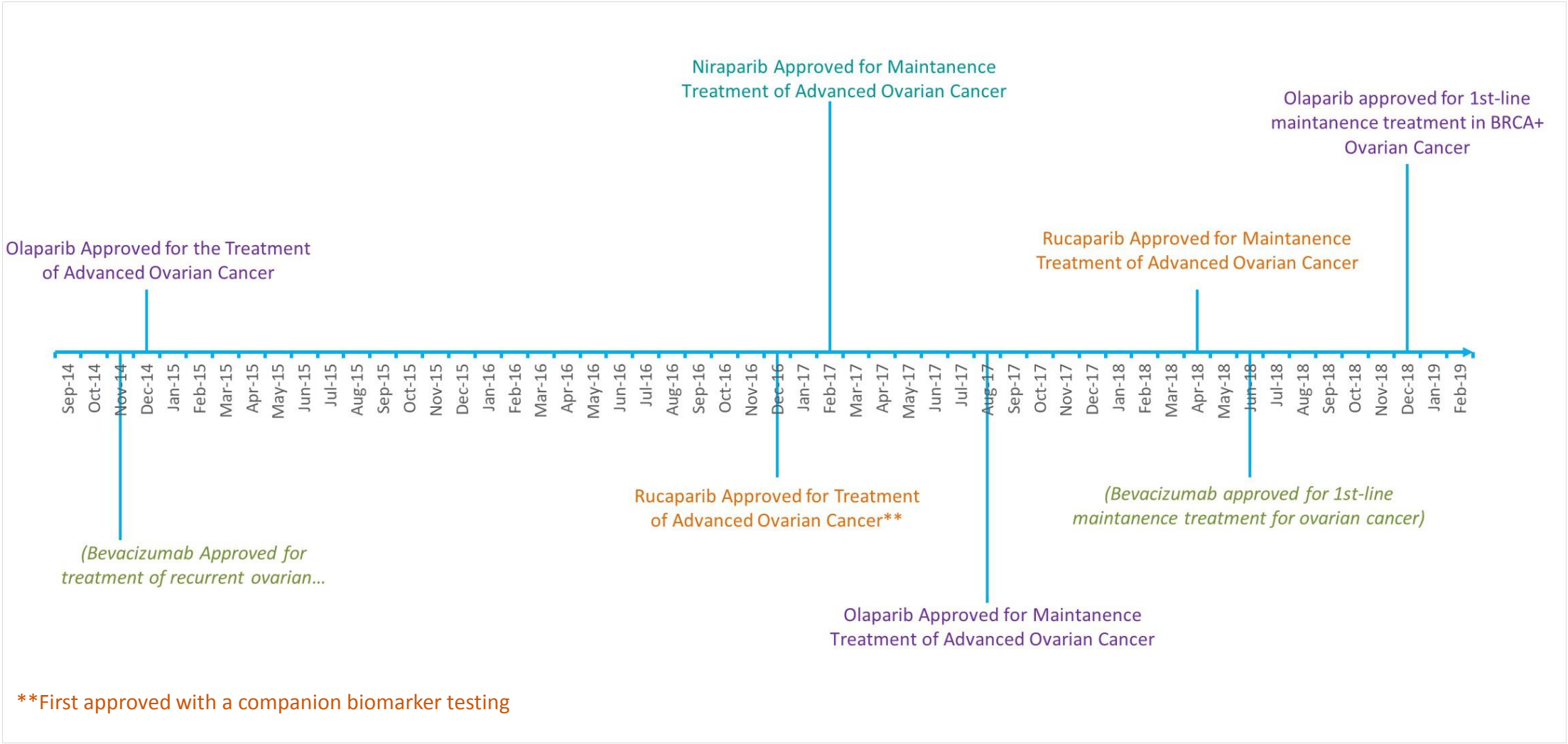
Leo E, et al. *Cancer Res*. 2018;78(13 Suppl):Abstract LB-273.; Murai J, et al. *Cancer Res*. 2012;72(21):5588-99.

ARS Question 1

Which of the following PARP inhibitors is FDA approved for first-line maintenance treatment of ovarian cancer?

1. Rucaparib
2. Niraparib
3. Olaparib
4. Velaparib

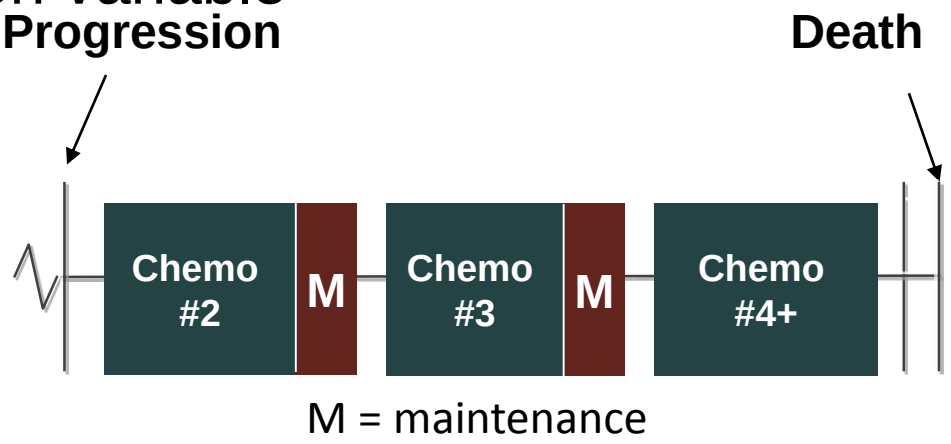
PARP Inhibitors in Ovarian Cancer

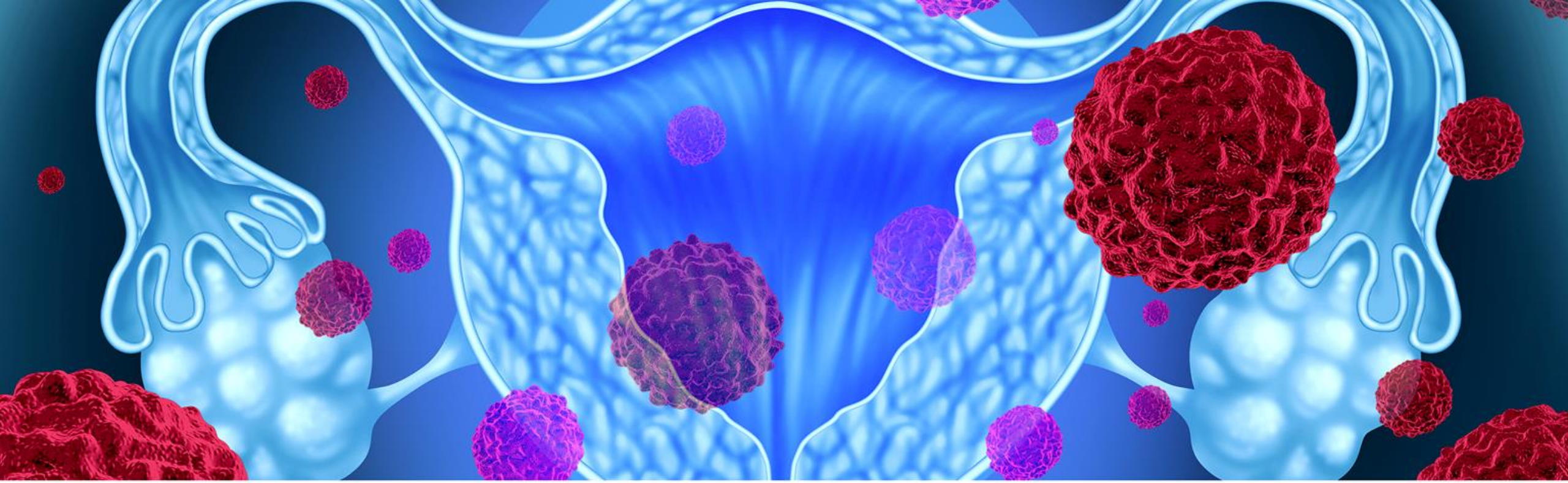


**First approved with a companion biomarker testing

Switch Maintenance

- Measurable disease required at chemotherapy induction
- Treatment is platinum or platinum combination
- Clinical response is needed
- **Partial response (PR) and complete response (CR) are eligibility for randomization**
- Usually a stratification variable





PARP Inhibitors in SECOND-LINE Maintenance

Platinum-Sensitive Relapse - RCTs: Maintenance After Chemotherapy

Status	Study 19[1]	SOLO-2[2]	NOVA[3]	ARIEL3[4]
Drug	Olaparib	Olaparib	Niraparib	Rucaparib
Population	HGSC	gBRCA^{mut}	I: gBRCA^{mut} II: Non-gBRCA HGSC	HGSC or endometrioid
Design	Phase 2	Phase 3	Phase 3	Phase 3
Regimen	Olaparib vs. placebo	Olaparib vs. placebo	Niraparib vs. placebo	Rucaparib vs. placebo
Primary endpoint	PFS	PFS	PFS	PFS
N (randomization)	265 (1:1)	295 (2:1)	553 (2:1)	564 (2:1)

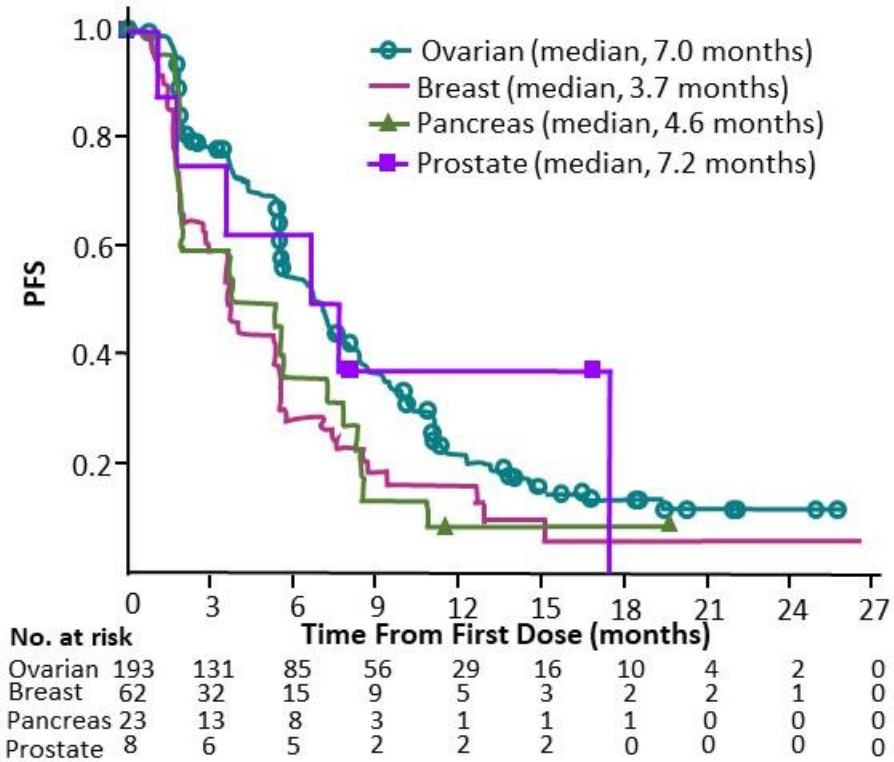
[1]Ledermann J, et al. *N Engl J Med.* 2012;366(15):1382-92.; [2]Pujade-Lauraine E, et al. *Lancet Oncol.* 2017;18(9):1274-84.; [3]Mirza M, et al. *N Engl J Med.* 2016;375(22):2154-64.; [4]Coleman RL, et al. *Lancet Oncol.* 2017;18(1):75-87.

gBRCA, germline BRCA mutation; HGSC, high-grade serous carcinoma; PFS, progression-free survival; RCT, randomized clinical trial.

Olaparib

- Phase II study enrolled 298 patients with germline *BRCA1/2* mutations
  - Included ovarian, breast, pancreatic, and prostate canc
- Olaparib was well-tolerated
  - Common ADRs: fatigue, N/V, anemia
    - ≥ Grade 3: anemia (17%)

	Tumor response (CR/PR/SD), n (%)	Progression/ unevaluable (%)
Ovarian (n=193)	138 (71.5)	55 (28.5)
Breast (n=62)	37 (59.7)	25 (40.3)
Pancreatic (n=23)	13 (56.5)	10 (43.5)
Prostate (n=8)	6 (75)	2 (25)



Kaufman B, et al. *J Clin Oncol*. 2015;33(3):244-50.

ADR, adverse drug reaction; N/V, nausea/vomiting; SD, stable disease.

Olaparib in the Maintenance Setting

- **August 17, 2017**
  - FDA granted approval to olaparib for the maintenance treatment of advanced ovarian cancer patients who are in **CR or PR to platinum-based chemotherapy**
  - In addition, olaparib tablets were introduced and approved for use with both FDA-approved indications
    - Olaparib 150 mg tablets ARE NOT interchangeable with olaparib 50 mg capsules
  - Approval based on data from the SOLO2 and Study 19 trials

SOLO2 (N=295)

- Randomized phase III study of recurrent platinum-sensitive serous ovarian cancer
- Germline *BRCA1/2* mutations
- 300 mg twice daily (tablets)

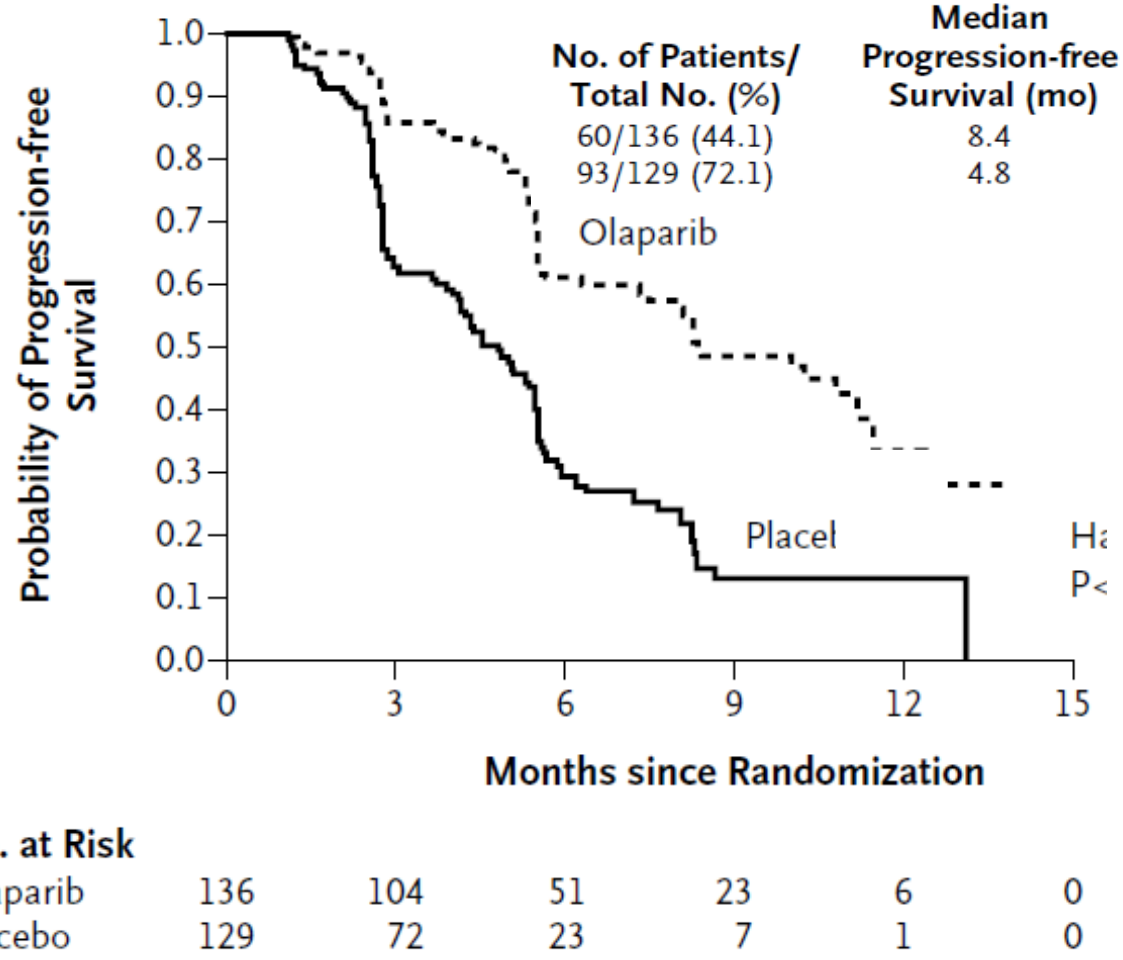
Study 19 (N=265)

- Randomized phase II study of platinum-sensitive, relapsed serous ovarian cancer
- *BRCA*-mut and *BRCA*-wild type
- 400 mg twice daily (capsules)

Gourley C, et al. *J Clin Oncol*. 2017;35(15_suppl):abstract 5533.; Pujade-Lauraine E, et al. *Lancet Oncol.* 2017;18(9):1274-84.;
U.S. Food and Drug Administration. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm572143.htm.

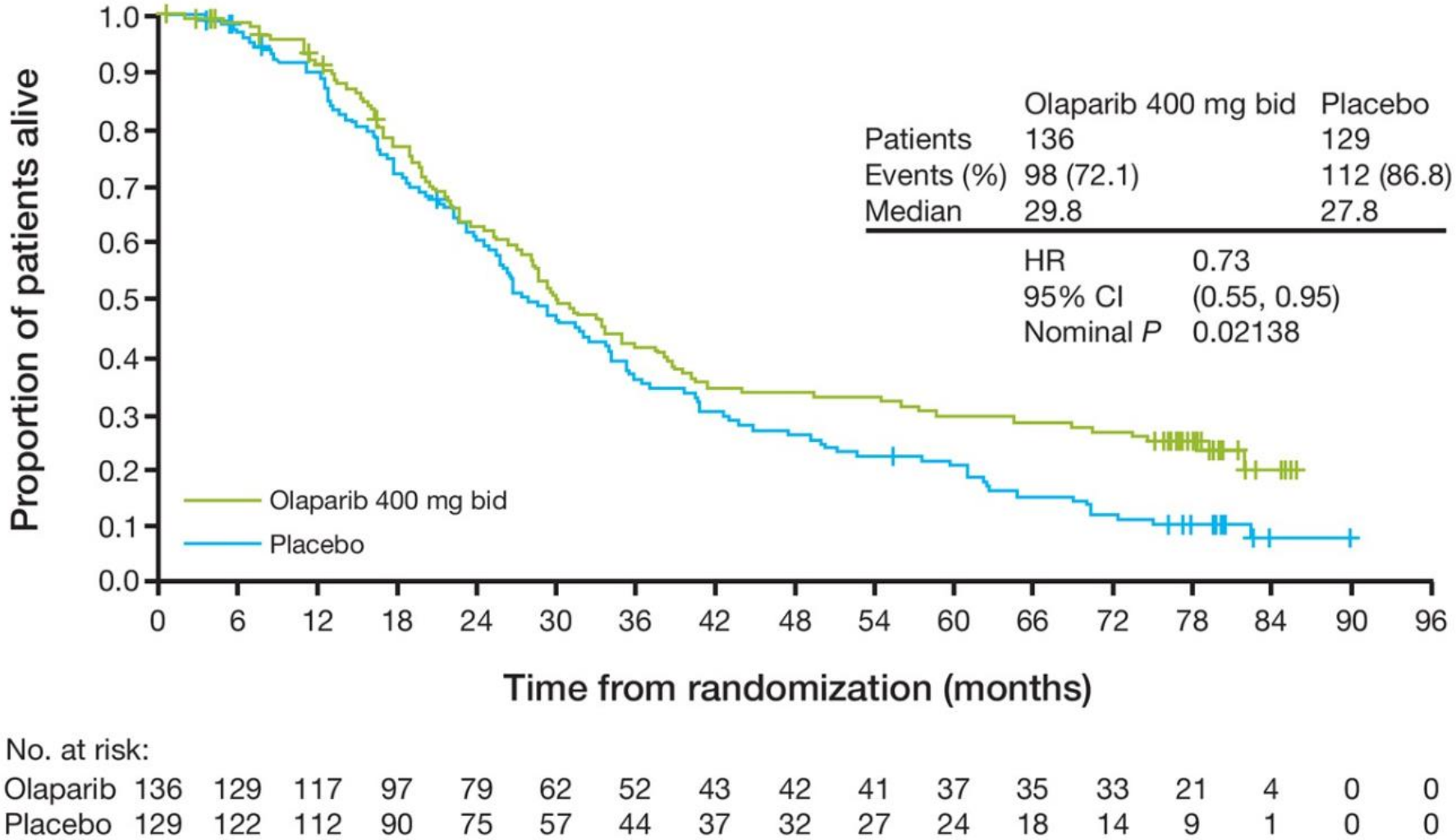
Study 19 – Olaparib Maintenance: PFS

- Progression-free survival
  - 8.4 months with olaparib vs. 4.8 months with placebo
  - HR 0.35 (95% CI: 0.25-0.49)
    $P < 0.001$
- ADRs higher in olaparib group
  - Nausea (68% vs. 35%)
  - Fatigue (49% vs. 38%)
  - Vomiting (32% vs. 14%)
  - Anemia (17% vs. 5%)



Ledermann J, et al. *N Engl J Med.* 2012;366(15):1382-92.

Study 19 – Olaparib Maintenance: Overall Survival



- Overall survival advantage suggested, although criterion for statistical significance was not met because of the alpha spending approach used
- Maintenance therapy with olaparib provides a clinically significant, long-term treatment benefit to ovarian cancer patients, **irrespective** of *BRCA*m status

Gourley C, et al. *J Clin Oncol*. 2017;35(15_suppl):abstract 5533.

SOLO-2/ENGOT-Ov21 – Olaparib Maintenance Therapy

- Multicenter, randomized, double-blind, placebo-controlled phase III trial
- 295 patients with platinum-sensitive, relapsed ovarian cancer with *BRCA1/2* mutation who had received ≥ 2 lines of previous chemotherapy
  - Olaparib 300 mg tablets BID (n=195)
  - Placebo (n=99)
- **Results**
  - PFS = 19.1 months vs. 5.5 months with placebo
  - HR 0.30 (95% CI: 0.22-0.41); $P < 0.0001$
  - ADRs ≥ grade 3
    - Anemia (19%), fatigue/asthenia (4%), neutropenia (5%)
- Olaparib tablet maintenance treatment provided a significant improvement in PFS with no impact on quality of life

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

BID, twice daily.

Rucaparib

- December 19, 2016
  - FDA granted approval to rucaparib as monotherapy treatment for patients with deleterious ***BRCA-mutated*** (***germline and/or somatic*** detected by FDA-approved companion diagnostic) ovarian cancer ***who have been treated with ≥ 2 chemotherapies***
  - Approval based on Study 10 and ARIEL2 trials

  - **A**ssessment of **R**ucaparib **I**n Ovarian Canc**E**r Tria**L** (ARIEL)
    - ARIEL2 (phase II): aimed to identify patients more likely to respond to PARP inhibitor using tumor genetic analysis
    - ARIEL3 (phase III): randomized, double-blind, placebo-controlled study of rucaparib vs. placebo

Jones P, et al. *J Med Chem*. 2015;58(8):3302-14.; U.S. Food and Drug Administration. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm533891.htm.;
U.S. National Library of Medicine. www.clinicaltrials.gov.

ARIEL2 Study – Rucaparib

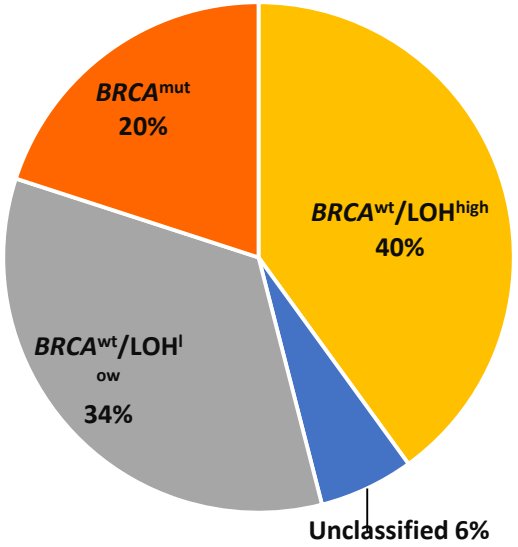
- 204 patients treated with rucaparib
  - Stratified by:
    - *BRCA* mutation (*BCRA*^{mut})
    - *BRCA* wild type/loss of heterozygosity **high** (*BRCA*^{wt}/LOH^{high})
    - *BRCA* wild type/loss of heterozygosity **low** (*BRCA*^{wt}/LOH^{low})
- **Study endpoints**
  - Progression-free survival
  - Overall response rate
    - Response Evaluation Criteria in Solid Tumors (RECIST)
    - RECIST and/or Cancer Antigen 125 (CA-125)
  - Duration of response
  - Safety
  - Pharmacokinetics

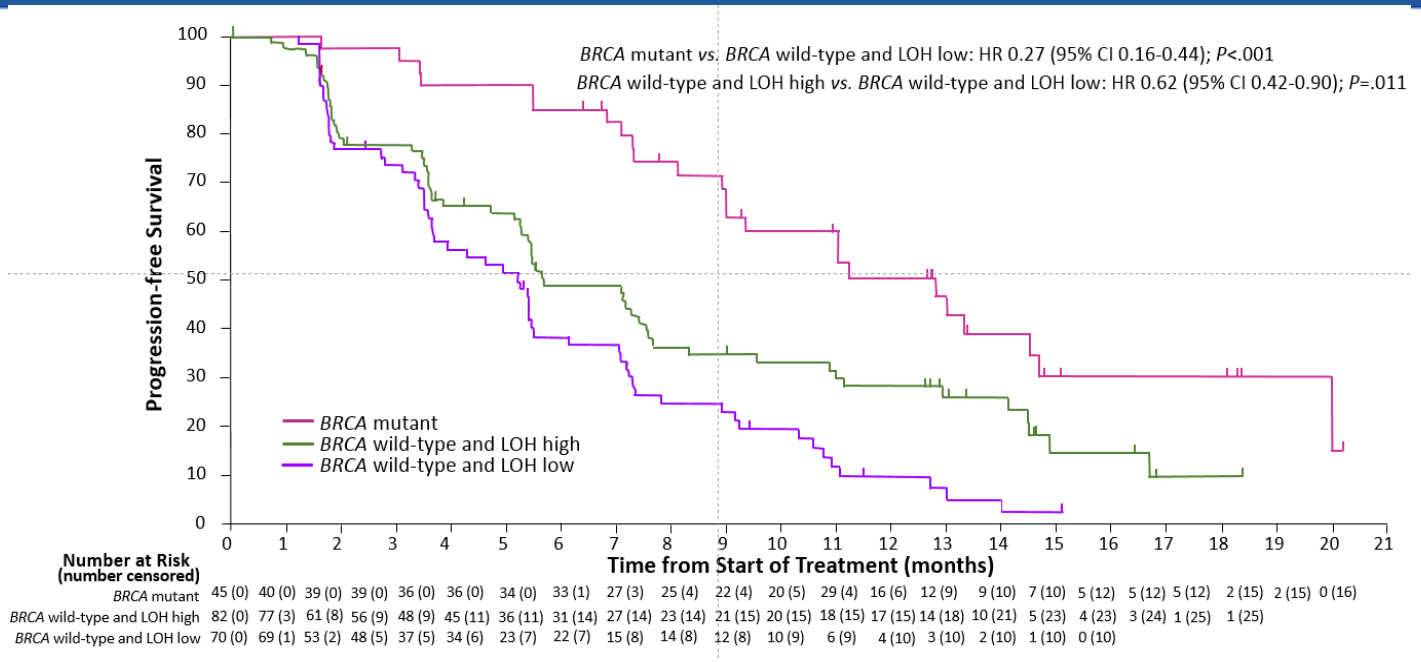
Treatment:
rucaparib 600 mg BID

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

ARIEL2 Study – Rucaparib

Patient Distribution Based on Tumor Molecular Testing (N=204)





HRD subgroup	Median PFS, months (90% CI)	Overall response rate, % (n)	
		RECIST	RECIST + CA-125
BRCA^{mut}	12.8 (9-14.7)	80% (32)	85% (34)
BRCA-like (*BRCA*^{wt}/LOH^{high})	5.7 (5.3-7.6)	29% (24)	44% (36)
Biomarker negative (*BRCA*^{wt}/LOH^{low})	5.2 (3.6-5.5)	10% (7)	20% (14)

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

ARIEL3 Study – Rucaparib

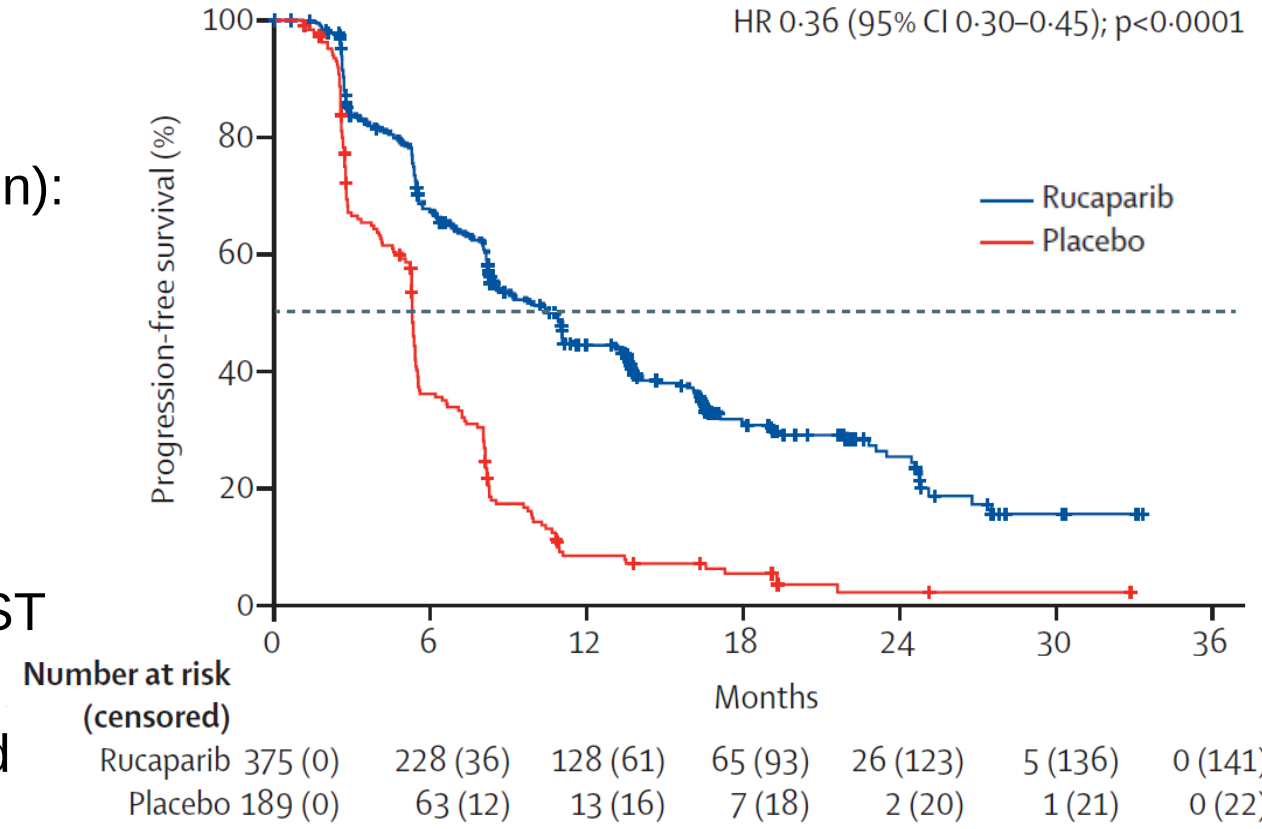
- Multicenter, randomized, double-blind, placebo-controlled trial
- 564 patients with platinum-sensitive, high-grade serous, relapsed ovarian cancer who had ≥ 2 prior platinum-based chemotherapy regimens with CR or PR
  - Randomized 2:1 nested cohorts based on: *BRCA1/2* mutation, HRD deficiencies, or no mutations & platinum-free interval
    - Rucaparib 600 mg BID (n=375)
    - Placebo (n=189)
- Primary outcome was investigator-assessed PFS
  - Independent radiological review was also completed

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

ARIEL3 Study – Rucaparib for Maintenance

- Rucaparib had significant improvement in PFS
  - *BRCA* mutant: 16.6 months (vs. 5.4 months placebo)
  - LOH: 13.6 months (vs. 5.4 months placebo)
  - Intent to treat (included those with no mutation): 10.8 months (vs. 5.4 months placebo)
- Investigator analysis more conservative than independent review
  - Independent review = more favorable PFS
- Adverse effects ≥ grade 3:
  - Anemia (19%), transient elevations in ALT/AST (10%)
- Rucaparib tablet maintenance treatment provided significant improvement in PFS in patients with platinum-sensitive ovarian cancer

Investigator intent-to-treat PFS



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

ALT/AST, alanine aminotransferase/aspartate aminotransferase.

Niraparib

- March 27, 2017
  - Approved by the FDA for ***maintenance treatment*** of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in ***CR or PR to platinum-based chemotherapy***
  - Approval based on the ENGOT-OV16/NOVA phase III study

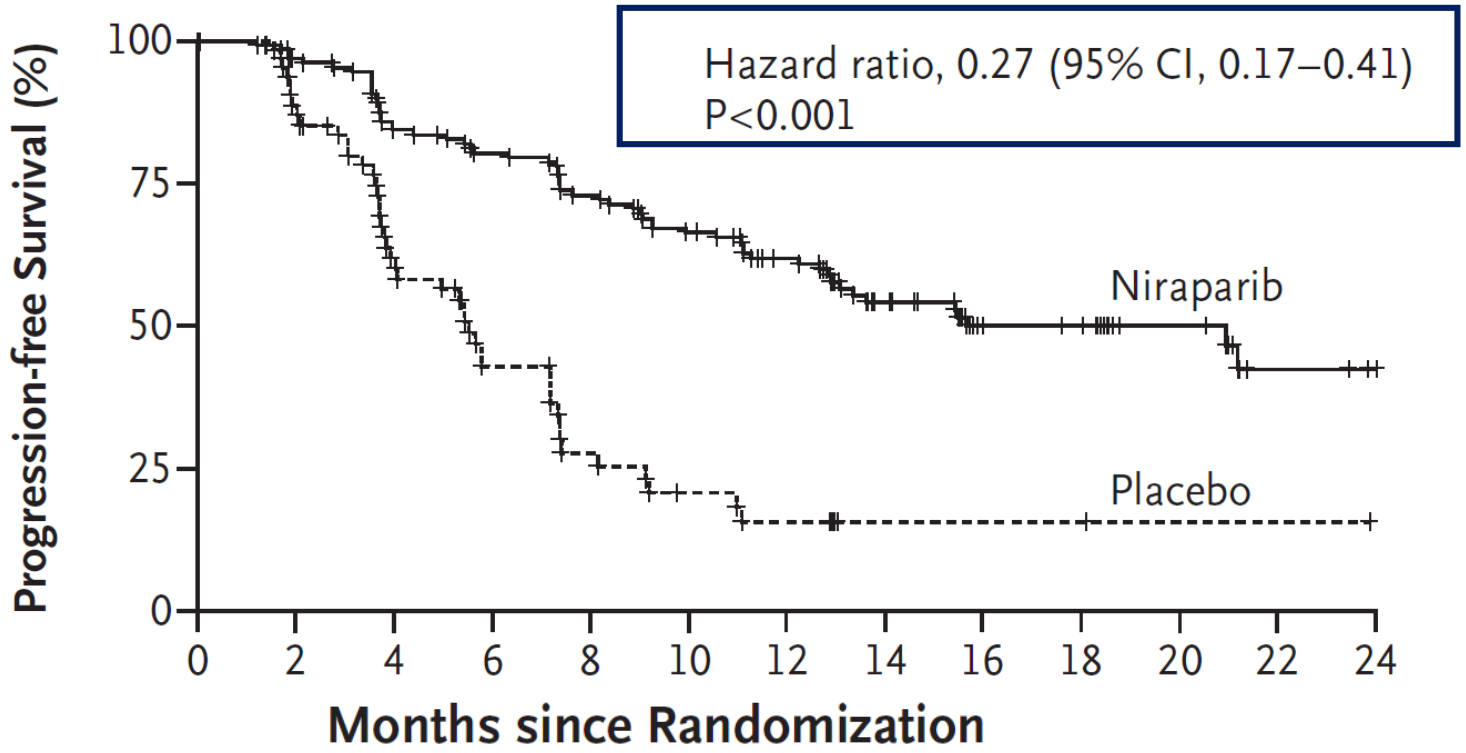
Jones P, et al. *J Med Chem*. 2015;58(8):3302-14.; U.S. Food and Drug Administration. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm548948.htm.

ENGOT-OV16/NOVA Study – Niraparib

- Phase III study
  - Randomized 2:1 maintenance niraparib 300 mg PO once daily **or** placebo
    - Categorized presence or absence of a germline *BRCA* mutation or HRD status
  - 553 patients enrolled
    - 203 with *BRCA* germline mutation
    - 350 without *BRCA* mutation
  - Primary endpoint: PFS
    - Niraparib = longer PFS compared to placebo
      - **g*BRCA* cohort**: 21 months vs. 5.5 months
      - **Non-*BRCA* mutation with HRD status**: 12.9 months vs. 3.8 months
    - Most common ≥ grade 3 adverse effects:
      - Thrombocytopenia (33.8%), anemia (25.3%), neutropenia (19.6%)

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

ENGOT-OV16/NOVA Study – PFS in *gBRCA*



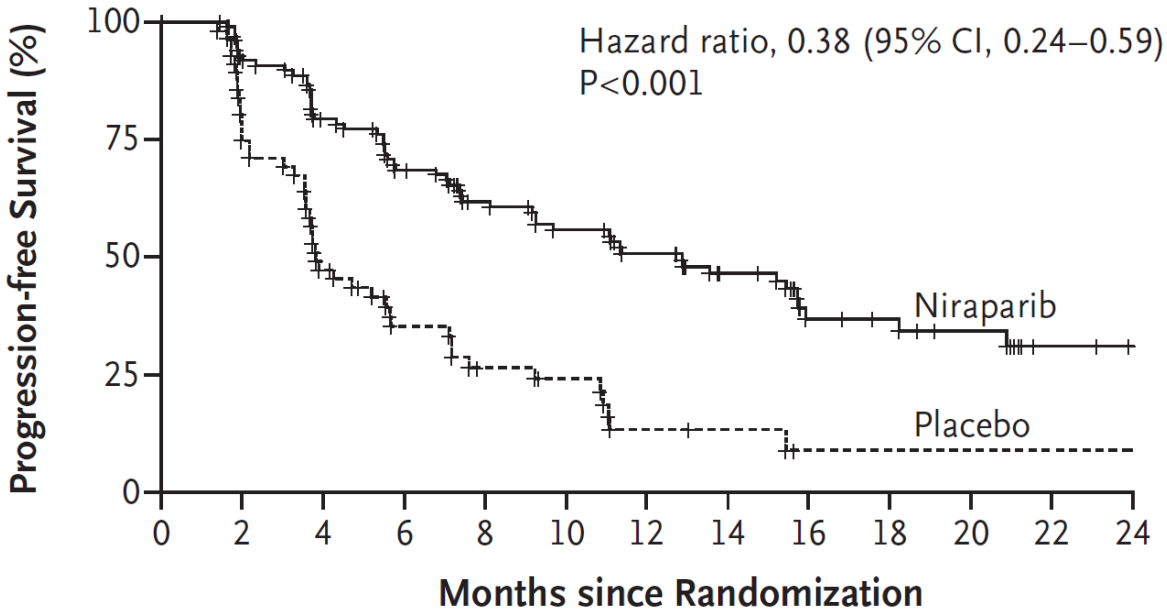
No. at Risk

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

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

ENGOT-OV16/NOVA Study – PFS in non-g*BRCA* With or Without HRD Status

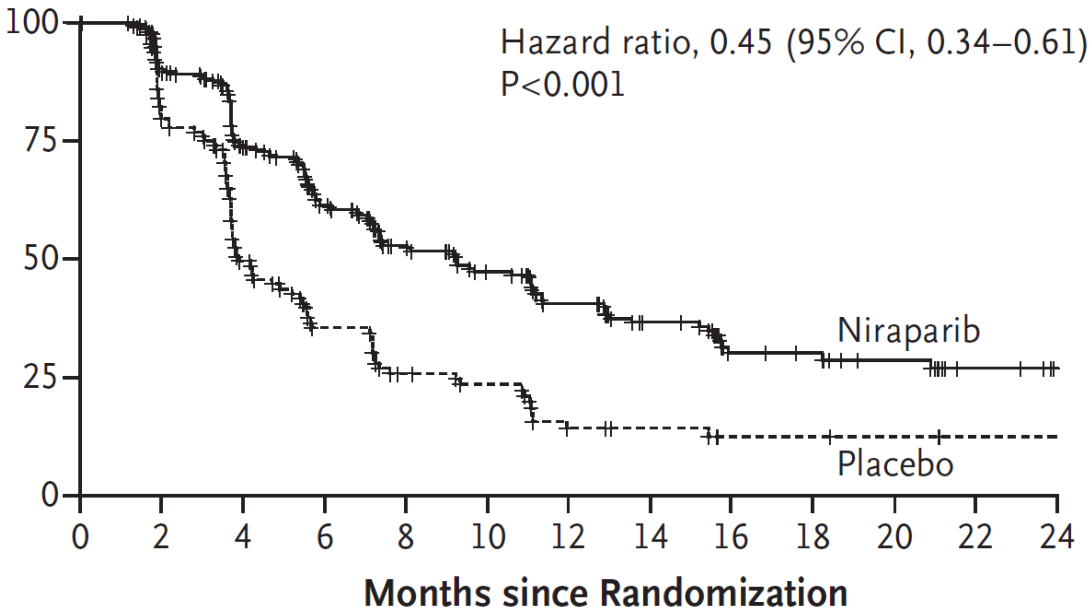
No Germline *BRCA* Mutation with HRD Positivity



No. at Risk

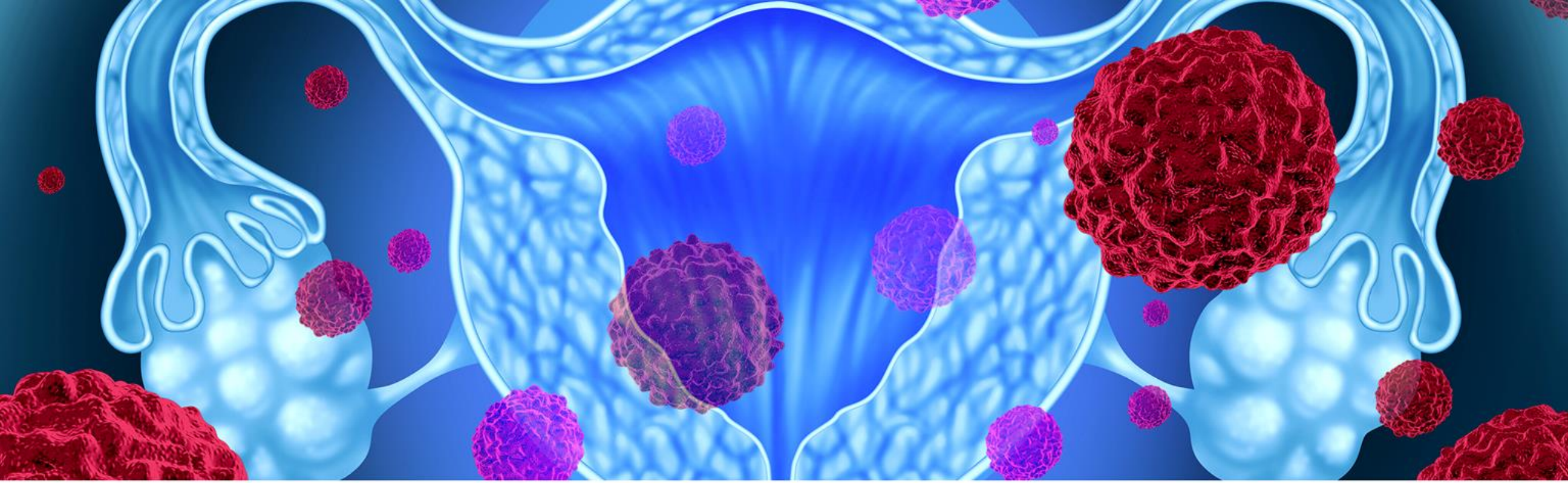
Niraparib	106	90	75	64	52	46	40	29	16	14	11	4	2
Placebo	56	41	26	16	11	9	4	3	1	1	1	1	1

No Germline *BRCA* Mutation



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

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



PARP Inhibitors in FIRST-LINE Maintenance

SOLO1: Maintenance Olaparib

- Newly diagnosed, FIGO stage III–IV, high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancer
- Germline or somatic *BRCA*m
- ECOG performance status 0–1
- Cytoreductive surgery*
- In clinical CR or PR after platinum-based chemotherapy

*Upfront or interval attempt at optimal cytoreductive surgery for stage III disease and either biopsy and/or upfront or interval cytoreductive surgery for stage IV disease.

Olaparib 300 mg bid (N=260)

2:1 randomization

Stratified by response to platinum-based chemotherapy

Placebo (N=131)

- Study treatment continued until disease progression
- Patients with no evidence of disease at 2 years stopped treatment
- Patients with PR at 2 years could continue treatment

2 years' treatment if no evidence of disease

Primary endpoint

- Investigator-assessed PFS (modified RECIST 1.1)

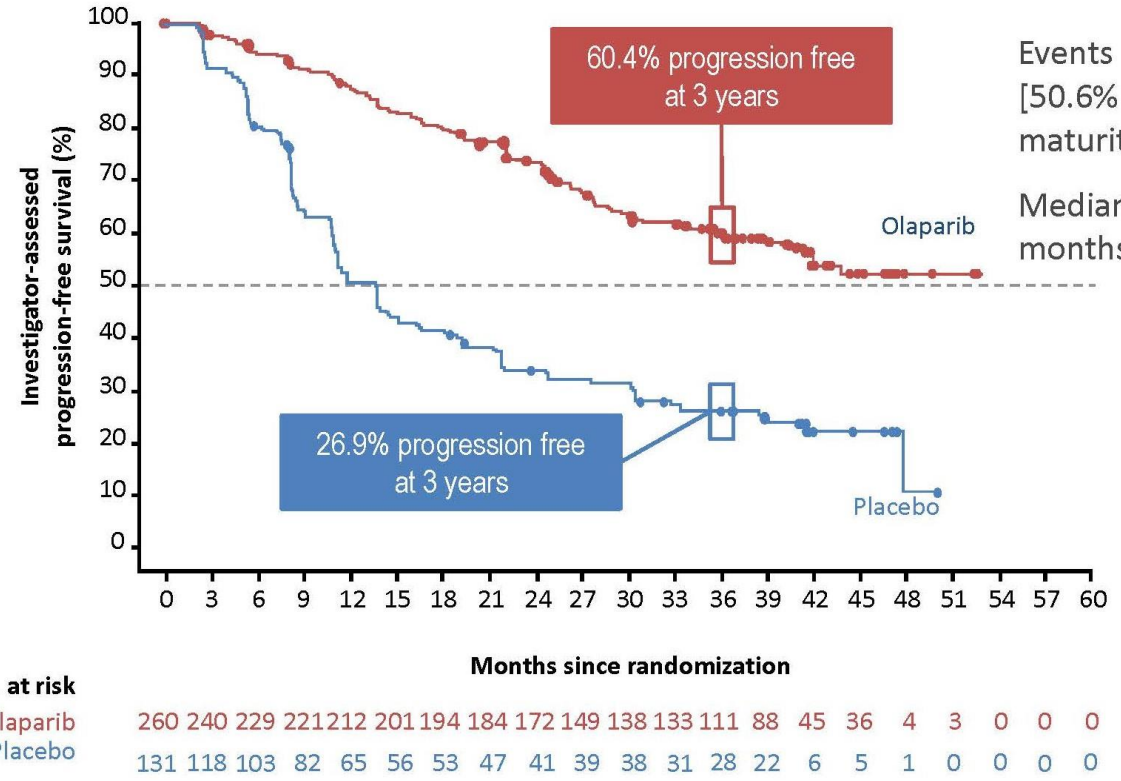
Secondary endpoints

- PFS using BICR
- PFS2
- Overall survival
- Time from randomization to first subsequent therapy or death
- Time from randomization to second subsequent therapy or death
- HRQoL (FACT-O TOI score)

Moore K, et al. *N Engl J Med*. 2018;379(26):2495-505.; Moore KN, et al. Abstract LBA7_PR. European Society for Medical Oncology; October 2018; Munich, Germany.

BICR, blinded independent central review; ECOG, Eastern Cooperative Oncology Group; FACT-O, Functional Assessment of Cancer Therapy – Ovarian Cancer; HRQoL, health-related quality of life; PFS2, time to second progression or death; TOI, Trial Outcome Index.

SOLO1: PFS by Investigator Assessment



	Olaparib (N=260)	Placebo (N=131)
Events (%) [50.6% maturity]	102 (39.2)	96 (73.3)
Median PFS, months	NR	13.8
HR 0.30		
95% CI 0.23, 0.41; *P*<0.0001		

Moore K, et al. *N Engl J Med*. 2018;379(26):2495-505.;
Moore KN, et al. Abstract LBA7_PR. European Society for Medical Oncology; October 2018; Munich, Germany.

NR, not reached.

Summary: FDA-Approved PARP Inhibitors for Ovarian Cancer

	FDA indication(s)	FDA approval date
Olaparib	**Fourth-line** treatment in patients with advanced ovarian cancer with **germline *BRCA1/2* mutations** (as detected by an FDA-approved companion diagnostic test) **Maintenance treatment** in patients with recurrent ovarian, fallopian tube, or primary peritoneal cancer who are in **CR or PR to platinum-based chemotherapy**	December 19, 2014 August 17, 2017
Rucaparib	**Third-line** treatment in patients with advanced ovarian cancer with **germline or somatic *BRCA1/2* mutations** (based on an FDA-approved companion diagnostic test) **Maintenance treatment** in patients with recurrent ovarian, fallopian tube, or primary peritoneal cancer who are in **CR or PR to platinum-based chemotherapy**	December 19, 2016 April 6, 2018
Niraparib	**Maintenance treatment** in patients with recurrent ovarian, fallopian tube, or primary peritoneal cancer who are in **CR or PR to platinum-based chemotherapy**	March 27, 2017

FDA Press Release.

ARS Question 2

Dose-limiting toxicities of the PARP inhibitor class of medications include:

1. Nausea and myelosuppression
2. Nausea and diarrhea
3. Diarrhea and myelosuppression
4. Peripheral neuropathy and nausea

Comparing PARP Inhibitor Pharmacokinetic Profiles

	Olaparib tablet[a,b]	Rucaparib[a]	Niraparib[a]
Time to peak plasma concentration (t_{max})	1-3 hours; food delays t_{max} by 2.5 hours	1.9 hours; high-fat meal delays t_{max} by 2.5 hours	3 hours
Volume of distribution (V_d)	158 ± 136 L	113-262 L	1220 ± 1114 L
Protein binding	82%	70%	83%
Metabolism	CYP3A4	Inhibitor CYP1A2, CYP2D6 (primarily), CYP2C9, CYP1A2, CYP2C19, and CYP3A4	Carboxylesterases/phase II glucuronidation (UGT)
Elimination	Clearance: 7.4 ± 3.9 L/hr; 44% renal elimination, 42% fecal elimination	Clearance: 15.3-79.2 L/hr	Clearance: 16.2 L/hr; 47.5% renal elimination, 38.8% fecal elimination
Half-life	14.9 ± 8.2 hours	17-19 hours	36 hours

[a]No dose adjustments are recommended in hepatic impairment
[b]When CrCl is 31 to 50 mL/min, reduce the dose of olaparib to 200 mg BID. No dose adjustments are recommended in patients with mild renal impairment (CrCl 31-50 mL/min).

Lynparza [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019.;
Rubraca [prescribing information]. Boulder, CO: Clovis Oncology, Inc.; 2018.;
Zejula [prescribing information]. Waltham, MA: Tesaro, Inc.; 2019.

CrCl, creatinine clearance; CYP, cytochrome P450.

Cytochrome P450 Inhibition

Higher drug plasma concentrations = potential increase in activity and toxicities

Drug

↓

CYP reactions

Monooxygenase activity
Peroxygenase activity
Reductase activity
Oxidase activity

↓

Drug metabolite

Cytochrome P450 Inhibition

Higher drug plasma concentrations = potential increase in activity and toxicities

Drug

↓

CYP reactions

Monooxygenase activity
Peroxygenase activity
Reductase activity
Oxidase activity

↓

Drug metabolite

What action do you take?

- When starting new medication that is CYP inhibitor?
  - When patient is on substrate?
  - When patient starts on substrate?
  - When patient stops taking inhibitor?

Common CYP Substrates

- CYP2D6
  - Ondansetron
  - Prochlorperazine
  - Promethazine
  - Fluoxetine
  - Amitriptyline
  - Doxorubicin
  - Haloperidol
  - Risperidone

- CYP1A2
  - Caffeine
  - Conjugated estrogens
  - Lidocaine
  - Theophylline
  - Zolmitriptan
  - Amitriptyline
  - Nicotine

Multidrug And Toxic compound Extrusion (MATE) 1/2 Transporter

- Proximal renal tubule
- MATE proteins facilitate tubular secretion or clearance

Common substrates	Common inhibitors
• Creatinine • Metformin • Corticosteroids • Lamivudine • Platinum agents • PARP inhibitors	• Cimetidine • Pyrimethamine • Fluoroquinolones • Trimethoprim • PARP inhibitors

Ivanyuk A, et al. *Clin Pharmacokinet*. 2017;56(8):825-92.

Multidrug And Toxic compound Extrusion (MATE) 1/2 Transporter

- Proximal renal tubule
- MATE proteins facilitate tubular secretion or clearance

What action do you take?

- When starting new medication that is MATE1/2 inhibitor?
  - When patient is on substrate?
  - When patient starts on substrate?
  - When patient stops taking inhibitor?

Common substrates	Common inhibitors
• Creatinine • Metformin • Corticosteroids • Lamivudine • Platinum agents • PARP inhibitors	• Cimetidine • Pyrimethamine • Fluoroquinolones • Trimethoprim • PARP inhibitors

Ivanyuk A, et al. *Clin Pharmacokinet*. 2017;56(8):825-92.

Adverse Effects & Management of PARP Inhibitors

- **Myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML)**
  - Low incidence among all agents (< 1.5%)
  - Duration of treatment varied: < 1 month to > 2 years
  - All patients had received previous chemotherapy with platinum agents and/or other DNA-damaging agents including radiotherapy
  - All agents with CBC monitoring recommendations
    - Minimum monthly
    - Weekly for first 4 weeks with niraparib

- **Bone marrow suppression**
  - Interrupt PARP inhibitor and monitor blood counts weekly until grade 1 or less
  - If hematological profile recovers, consider restarting drug at a reduced dose
  - If hematological profile has not recovered to grade 1 or less after 4 weeks, refer to hematologist (bone marrow analysis, cytogenics)

CBC, complete blood count.

Lynparza [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019.; Rubraca [prescribing information]. Boulder, CO: Clovis Oncology, Inc.; 2018.; Zejula [prescribing information]. Waltham, MA: Tesaro, Inc.; 2019.; Zhou JX, et al. *Drug Des Devel Ther*. 2017;11:3009-17.

Adverse Effects & Management of PARP Inhibitors

- **Fatigue**
  - Monitor for anemia
  - Patient counseling
    - Self-monitor fatigue levels
    - Encourage physical activity and periods of rest
    - Maintain good nutrition and hydration
    - Maintain good sleep hygiene
  - May consider dose interruption or dose reduction if severe fatigue

- **Nausea and/or vomiting**
  - Considered moderate to high emetic risk by NCCN
  - Prophylactic antiemetics 30 minutes prior to dosing
  - Lifestyle modifications – promote small meals
  - Behavioral modifications – avoid anticipatory nausea

NCCN, National Comprehensive Cancer Network.

Lynparza [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019.; NCCN Cancer-Related Fatigue Guidelines, Version 2.2017.; NCCN Antiemesis Guidelines, Version 2.2017.; Rubraca [prescribing information]. Boulder, CO: Clovis Oncology, Inc.; 2018.; Zejula [prescribing information]. Waltham, MA: Tesaro, Inc.; 2019.

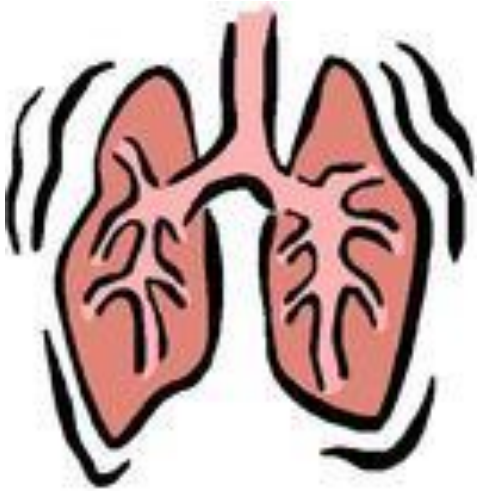
Adverse Effects & Management of PARP Inhibitors

- Other common adverse effects (no specific monitoring recommended)
  - Increase in serum creatinine
  - Dyspnea
  - Arthralgias/myalgias
  - Decreased appetite
  - Diarrhea and/or constipation
  - Dysgeusia
  - Abdominal pain

Lynparza [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019.;
Rubraca [prescribing information]. Boulder, CO: Clovis Oncology, Inc.; 2018.;
Zejula [prescribing information]. Waltham, MA: Tesaro, Inc.; 2019.

Adverse Effects & Management of PARP Inhibitors
Olaparib

- **Pneumonitis**
  - Rare – occurred in < 1% of patients in clinical trials
  - Interrupt treatment and promptly assess for any new or worsening respiratory symptoms such as dyspnea, cough, weight loss, or fever
  - If confirmed, discontinue treatment



Lynparza [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019.

Adverse Effects & Management of PARP Inhibitors *Rucaparib*

- **Transient increased ALT/AST**
  - Close to 75% of all grades, including up to 13% grades 3-4
    - Typically resolves on its own
  - Led to treatment discontinuation in 0.3% of patients (1/377)
  - No routine additional monitoring recommended

- **Increased cholesterol levels**
  - 40% of all grades; 2% of grades 3-4
  - No routine additional monitoring recommended

Rubraca [prescribing information]. Boulder, CO: Clovis Oncology, Inc.; 2018.

Adverse Effects & Management of PARP Inhibitors *Niraparib*

- **Bone marrow suppression**
  - Rates of grade ≥ 3: thrombocytopenia (29%), anemia (25%), and neutropenia (20%)
  - Monitor CBC
    - Month 1 = weekly
    - Months 2 – 12 = monthly
    - After month 12 = periodically
  - Discontinue treatment for CBC that does not resolve within 28 days following interruption

- **Cardiovascular**
  - Hypertension (grade 3-4 in 9% of patients)
    - Monitor blood pressure and heart rate monthly for first year, then periodically thereafter
    - Medically manage hypertension with antihypertensive medications and niraparib dose adjustment, if necessary
  - Palpitations also occurred in 10% of patients
- Mucositis/dry mouth
- Urinary tract infections
- Insomnia

Zejula [prescribing information]. Waltham, MA: Tesaro, Inc.; 2019.

Other Important Counseling Information

- **Pregnancy & lactation**
  - Females who are able to become pregnant should use birth control during treatment and for 6 months after last dose for any PARP inhibitor
  - Do not breast feed during treatment and for 1 month (niraparib/olaparib) or 2 weeks (rucaparib) after last dose

- **Drug interactions**
  - Olaparib
    - Avoid concomitant use of strong or moderate CYP3A inhibitors
      - If necessary to co-administer, dose reduction is recommended
    - Avoid grapefruit, grapefruit juice, and Seville oranges during treatment

Lynparza [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019.; Rubraca [prescribing information]. Boulder, CO: Clovis Oncology, Inc.; 2018.; Zejula [prescribing information]. Waltham, MA: Tesaro, Inc.; 2019.

Summary of PARP Inhibitor ADRs

	Adverse events (grades 1-4)	Adverse events (grades 3-4)	Lab abnormalities (grades 1-4)	Monitoring parameters
Olaparib	**Fatigue/asthenia (66%), nausea (64%),** anemia (34%), diarrhea (31%) nasopharyngitis (26%), URI (26%), myalgia (22%)	Anemia (18%), fatigue/asthenia (8%), vomiting (4%)	Decreased hemoglobin (90%), decreased lymphocytes (56%), increased creatinine (30%), decreased platelets (30%), decreased ANC (25%)	• CBC *(baseline and monthly)*
Rucaparib	**Fatigue/asthenia (77%), nausea (77%),** anemia (44%), dysgeusia (39%), abdominal pain (32%), thrombocytopenia (21%)	Anemia (25%), asthenia/fatigue (11%), thrombocytopenia (5%), nausea (5%), abdominal pain (3%)	Increased creatinine (92%), increased ALT (74%) and AST (73%), decreased hemoglobin (67%), decreased lymphocytes (45%), decreased platelets (39%), decreased ANC (35%)	• CBC *(baseline and monthly)*
Niraparib	**Nausea (74%), *thrombocytopenia (61%)***, fatigue/asthenia (57%), anemia (50%), neutropenia (30%), hypertension (20%), palpitations (10%)	***Thrombocytopenia (29%),*** anemia (25%), neutropenia (20%), hypertension (9%), fatigue/asthenia (8%)	Decreased hemoglobin (85%), decreased platelets (72%), decreased WBC (66%), decreased ANC (53%), increased AST (36%) and ALT (28%)	• CBC *(weekly first month, then monthly)* • Blood pressure and pulse *(monthly for first year)*

Lynparza [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019.; Rubraca [prescribing information]. Boulder, CO: Clovis Oncology, Inc.; 2018.; Zejula [prescribing information]. Waltham, MA: Tesaro, Inc.; 2019.

ANC, absolute neutrophil count; URI, upper respiratory infection; WBC, white blood cell.

Prevention of PARP Inhibitor ADRs

- Prevention
  - Patient education
    - Setting expectations
  - Medication review
    - Drug/drug interactions
  - Prescriptions
    - Antiemetics
  - Supportive care
    - Nutrition
      - Protein intake
      - Hydration
    - Multivitamin with iron

- Monitoring
  - Laboratory
    - CBC
    - Albumin
    - Serum creatinine
      - *CALCULATE* CrCl by Cockcroft-Gualt
    - Liver enzymes (transient)
    - Cholesterol
  - Rare adverse events
    - MDS or AML
    - Pneumonitis

ARS Question 3

TRUE OR FALSE?: **Based on the data, PARP inhibitor maintenance therapy is a cost-effective option for improving PFS in patients with recurrent, platinum-sensitive ovarian cancer.**

1. True
2. False

PARP Inhibitors and Inpatient Use

- Reasons to hold/discontinue PARP inhibitor as an inpatient:
  - Admission related to:
    - Uncontrolled N/V
      - Dehydration
    - Significant hematological toxicity
      - Thrombocytopenia
      - Neutropenic fever
      - Anemia
    - Suspected small bowel obstruction
    - Pulmonary issues/rule out pneumonitis

- Reasons to continue PARP inhibitor as an inpatient*:
  - Admission related to:
    - Uncontrolled pain
    - Psychiatric-related issues
      - Depression/suicidal thoughts

*** When PARP inhibitor therapy needs to be continued, patient home meds should be used.**

Chemotherapy/Biotherapy Request and Approval Process

- **Purpose:**
  - In due diligence for financial stewardship, prior approval will be required for chemotherapy/biotherapy regimens when being given inpatient and/or includes high-cost medications
- **Process for approval:**
  - Chemotherapy order form should be completed with following information:
    - Rationale for administration indicated on the order
      - If as inpatient, justification for reason to be given inpatient (i.e., requires continuous infusion w/ monitoring, risk for tumor lysis, oncologic emergency such as superior vena cava syndrome, prolonged length of stay due to tumor burden)
      - If non-formulary use, justification why alternative approved agents cannot be used
- ***Internal pharmacy approval process:***
  - Business office receives request
  - Request sent to clinical oncology pharmacy specialist/pharmacy designee for review
  - Clinical oncology pharmacy specialist/pharmacy designee will review request/guidelines and make recommendation to Pharmacy Director
  - Pharmacy Director will review request and recommendation from clinical oncology pharmacy specialist/pharmacy designee then render decision
  - Appeals can be made to the Chief Medical Officer (CMO)
  - CMO will contact the Chemotherapy Committee (Sub-committee of Oncology P&T Committee) for review and final decision

Comparing the Costs

Generic	Formulation and strength	Dose	Total required per day	AWP per unit	Total cost for 30-day supply
Olaparib	100-mg and 150-mg tablets	300 mg BID	6 tablets 4 tablets	$140.25	*For 180 tablets:* $25,245 *For 120 tablets:* $16,830
Rucaparib	200-mg and 300-mg tablets	600 mg BID	6 tablets 4 tablets	$159.22	*For 180 tablets:* $28,659.60 *For 120 tablets:* $19,106.40
Niraparib	100-mg capsules	300 mg daily	3 tablets	$276.53	*For 90 tablets:* $24,887.70

AWP, average wholesale price.

Manufacturer Patient-Assistance Programs (PAPs)

- **Not always directly managed by manufacturer**
  - Some free drug programs are referred from the manufacturer to foundations that assess patient's eligibility to receive free drug for the calendar year
- **2 types of PAP programs**
  - Free drug programs
  - Copay assistance programs
- **General eligibility requirements**
  - **Free drug programs:**
    - Cash, uninsured, or under-insured for both private and government insurance patients
  - **Copay assistance programs:**
    - Cash, uninsured, or under-insured private insurance patients only

Manufacturer PAPs: Eligibility Requirements

- U.S. residency
- Proof of income not exceeding threshold
  - Household size and income are considered
  - Expenses are not accounted for
  - Threshold depends on manufacturer
- Assists uninsured or underinsured
- For patients with insurance that does not cover medication
  - At least 2 forms of denial from insurance are necessary to be considered for free drug (prior authorization and appeal denial)

Manufacturer PAPs: Eligibility Requirements

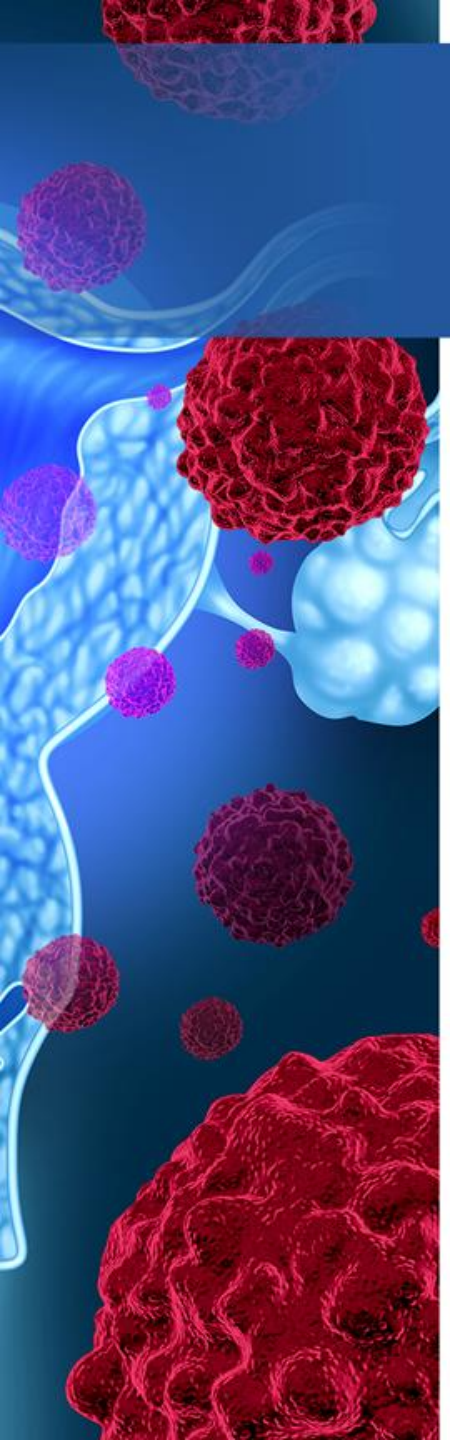
- Following application submission of a complete form, it can take up to 2 weeks for final decision from the manufacturer
  - Average turn-around time is 5 days
  - It can take up to an additional week for patient to receive medication once approved
- If patient is denied for PAP due to income (common denial reason), an appeal can be submitted but denials are rarely overturned
- Administration of medication must be FDA approved
- Patients approved to participate in PAP are approved through the end of the calendar year
  - Renewal applications are required if patient is continuing therapy through the program

Pharmacoeconomic Perspective

- **Cost analysis of PARP maintenance therapy**
  - Decision tree model was constructed to evaluate the costs and effectiveness of olaparib and niraparib compared to placebo
  - Incremental cost-effectiveness ratio (ICER) was computed as measured by dividing the incremental costs by the incremental effectiveness

- **Conclusion**
  - The base case ICERs were around or above $250K/PFS year in this model
  - No formal cost-effectiveness willingness-to-pay (WTP) threshold for health technology assessment exists in the U.S.
    - At a reference WTP of $100K/PFS year, the PARP inhibitors may not be cost-effective options

Zhong L, et al. *J Manag Care Spec Pharm.* 2018;24(12):1219-28.

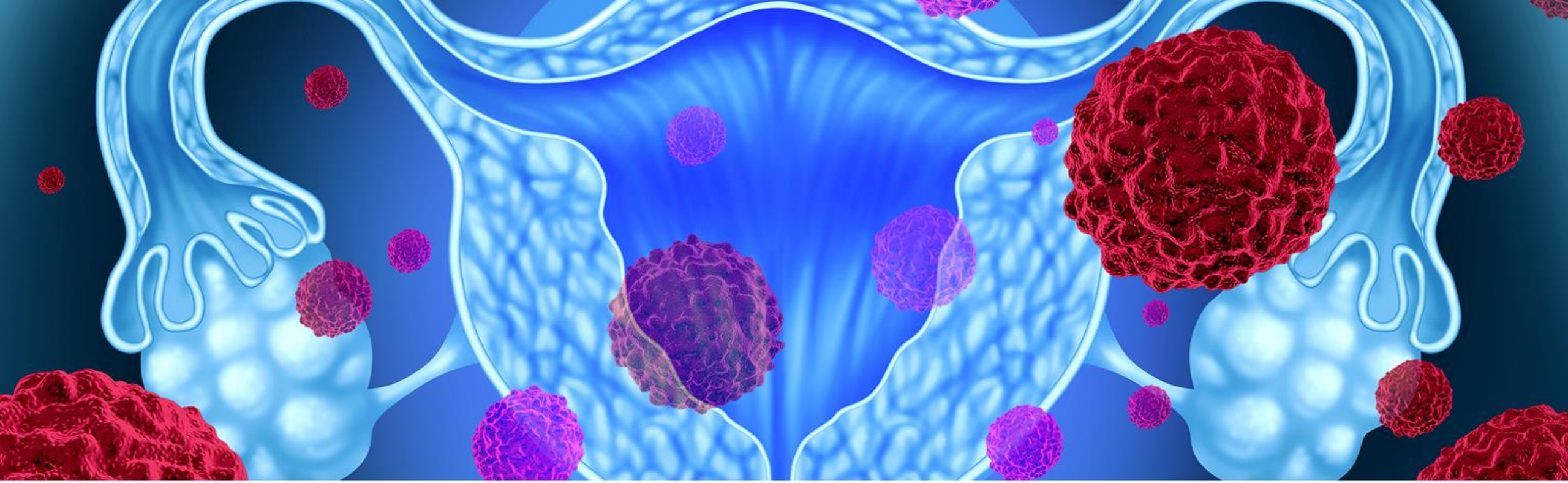


Role of the Oncology Clinical Pharmacy Specialist in Optimizing PARP Inhibitor Therapy

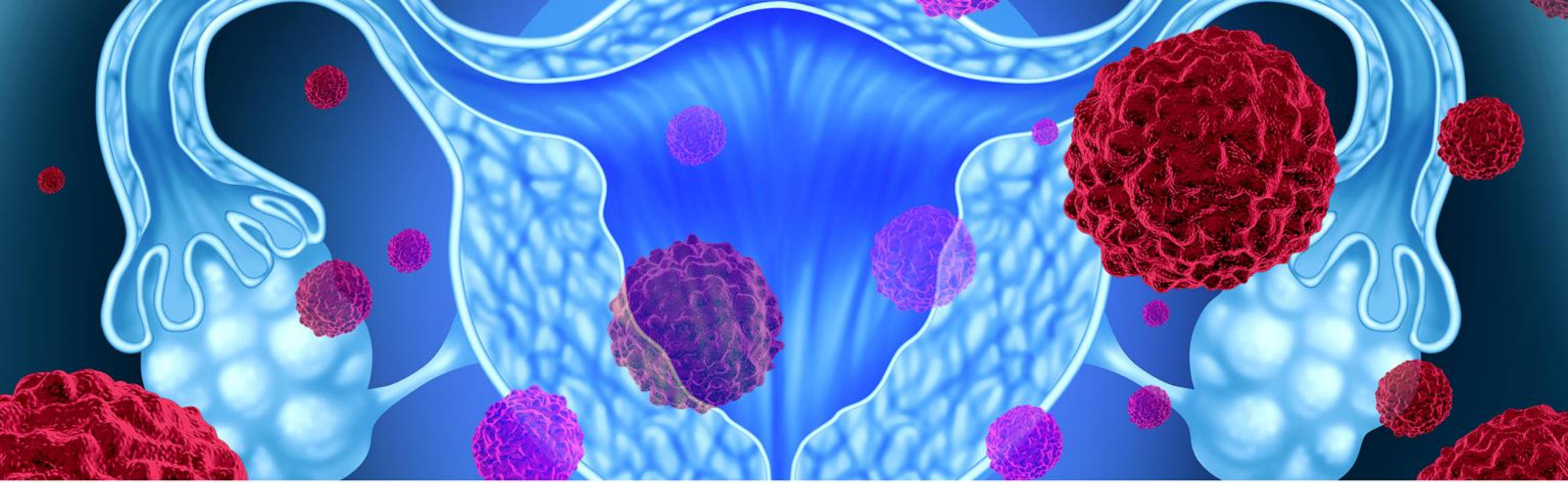
- Selection of appropriate PARP inhibitor
  - Screening for potential drug/drug interactions
  - Assessment of organ function and recommendations of dose adjustments
  - Monitoring weekly labs to detect necessity for dose modifications
  - Chemotherapy teaching/supportive care
    - Prevention of anemia
    - Antiemetics
    - Neutropenic precautions
  - Prior authorization and peer-to-peer appeals

Summary: PARP Inhibitors

- First new class of agents for ovarian cancer in 20 years
- Place in therapy is still evolving
  - Selecting among PARP inhibitors will vary by patient
    - *Utilize support from Oncology Clinical Pharmacy Specialist*
- Available as oral agents, which is a benefit, but associated with considerable toxicity
  - Require close patient monitoring
    - *Provide antiemetics*
    - *Monitor routine labs*
    - *Set realistic patient expectations*
- Oral chemotherapy compliance is a challenge
  - Specialty pharmacy required
- Financial burden/insurance coverage may pose a barrier to use
  - No indication to be continued when inpatient
    - *Utilize chemotherapy approval process for non-formulary/inpatient orders*



Question & Answer



Thank You