Why Is Poly ADP-Ribose Polymerase (PARP) an Excellent Therapeutic Target?

HR[1]

- Uses sister chromatids as template
- G2/M phase
- *High fidelity*, *error free*
- **Dependent on proteins encoded by *BRCA1* and *BRCA2* genes**

Double-strand break (DSB) repair[2]

HR	NHEJ
BRCA1/2, RAD51, MRN complex, ATM	Ku70, Ku80, DNA-PKcs
High-fidelity DNA repair	**Error-prone DNA repair**
PARP1 contributes to and fine-tunes HR (recruits MRE11 and NBS1 or ribosylates BRCA)	PARP1 prevents binding of Ku proteins to free DNA ends (first step to start NHEJ) and thus **inhibits** NHEJ

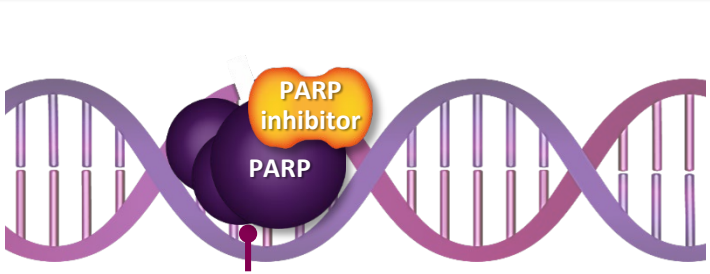
NHEJ[1]

- No template
- DNA trimmed and ligated
- *Low fidelity*, *error prone*
- Can lead to genetic instability
- **Inhibition of PARP pushes NHEJ as repair mechanism**

BRCA1, breast cancer 1; *BRCA2*, breast cancer 2; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; MRN, MRE11-RAD50-NBS1; NHEJ, nonhomologous end-joining.

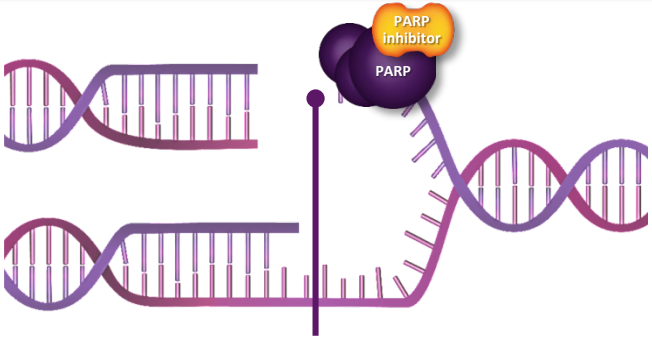
1. Walsh CS. *Gynecol Oncol*. 2015;137:343-350. 2. Konecny GE et al. *Br J Cancer*. 2016;115:1157-1173.

PARPi Exploits the Baseline Vulnerability of Cells With Inherent DNA Repair Deficiency[1]



Trapped PARP on single-strand breaks

Increase in double-strand breaks in replicating cells



Double-strand breaks

HRR-deficient cancer cell

Reliance on error-prone pathways leads to DNA damage accumulation and cell death

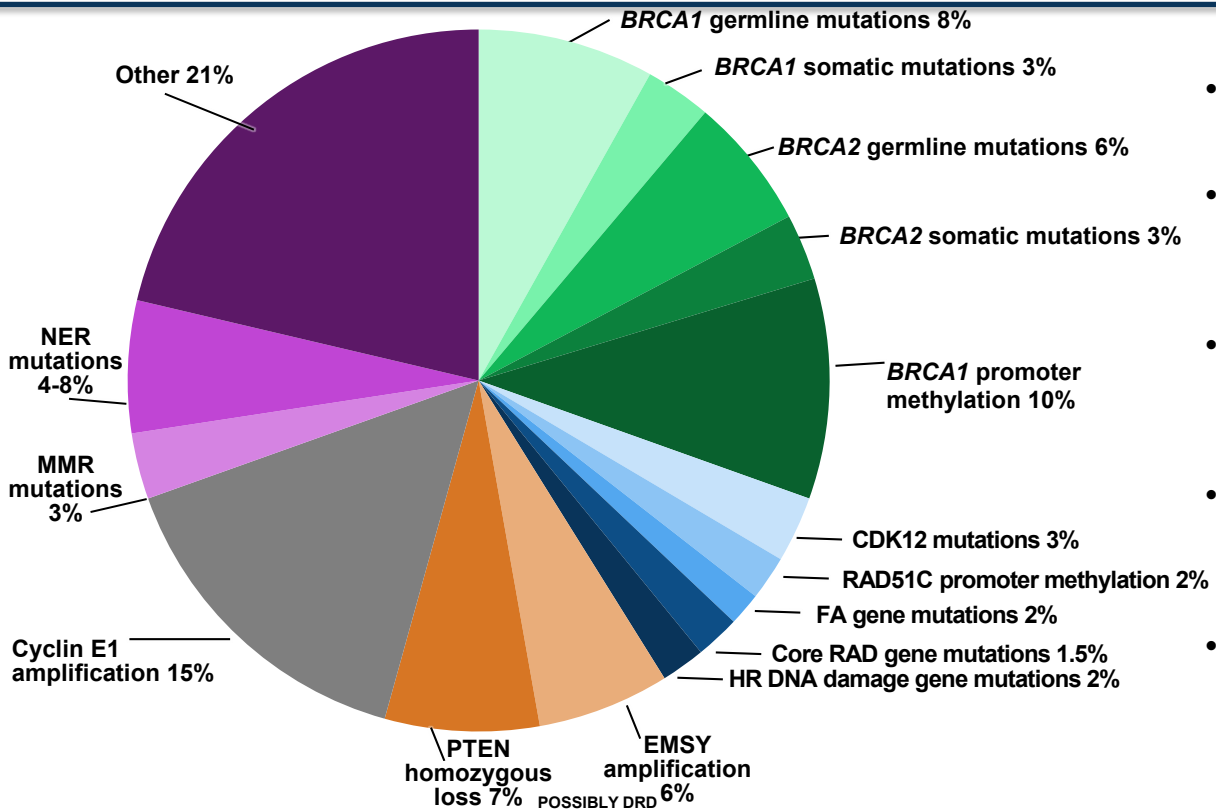
Normal cell

Repair of double-strand breaks via the HRR pathway and cell survival

HRR, homologous recombination repair; PARPi, poly ADP-ribose polymerase inhibitor.

1. O'Connor MJ. *Mol Cell*. 2015;60:547-560.

DNA Repair Deficiency Present in at Least 50% of EOC[1,2]

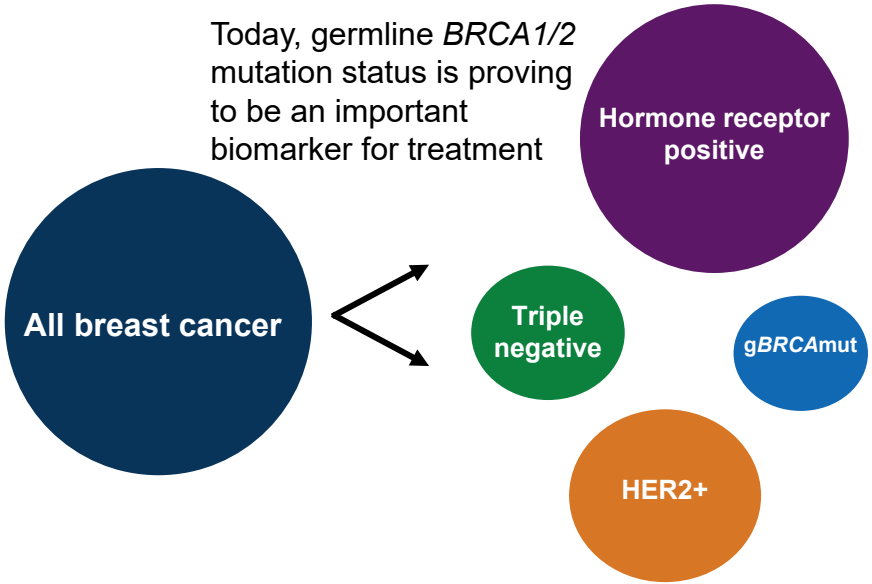


- *BRCA* mutations are known prognostic biomarkers for EOC
- *BRCA* mutations are known predictive biomarkers for DNA damaging therapies such as PARPi
- Knowledge of *BRCA* status informed access to PARPi starting in 2014 for patients with recurrent disease
- Knowledge of *BRCA* status now informs front-line therapy as of January 2019 (SOLO-1)
- Genetic testing is recommended for all women with epithelial ovarian cancer

BRCA1, breast cancer 1; *BRCA2*, breast cancer 2; CDK12, cyclin-dependent kinase 12; HR, homologous recombination; MMR, mismatch repair; NER, nucleotide excision repair; PARPi, poly ADP-ribose polymerase inhibitor ; PTEN, phosphatase and tensin homolog.

1. Konstantinopoulos PA et al. *Cancer Discov*. 2015;5:1137-1154. 2. Rigakos G, Razis E. *Oncologist*. 2012;17:956-962.

g*BRCA* Mutations Present in ~10% of HER2- Breast Cancer[1-4]



- Up to 10% of BC are due to familial mutations in a single gene
  - *BRCA* 1 or 2 is most common
- The evidence that *BRCA* is a prognostic biomarker for BC is mixed
- NCCN guidelines currently recommend that all HER2- advanced BC be tested for *BRCA*
- Before 2018, germline testing did not inform therapeutic decisions; *now it does*

BC, breast cancer; *BRCA1*, breast cancer 1; *BRCA2*, breast cancer 2; g*BRCA*m, germline *BRCA*-mutated; NCCN, National Comprehensive Cancer Center.

1. Figure courtesy of Melinda Telli, MD. 2. Chen S, Parmigiani G. *J Clin Oncol*. 2007;25:1329-1333. 3. NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High Risk Assessment: Breast, Ovarian, and Pancreatic. Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf.
4. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. Version 6.2020. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

Germline *BRCA1/2* Mutation in Pancreatic Cancer[1]

Gene	Syndrome	Pancreatic Cancer Risk, %	Other Associated Cancers[a]
APC	Familial adenomatous polyposis	1-5	Colorectal, upper GI, thyroid, brain
ATM	Ataxia telangiectasia (biallelic)[b]	1-5	Breast, prostate, gastric
BRCA2	Hereditary breast ovarian cancer syndrome	5-10	Breast, ovary, prostate, melanoma
BRCA1	Hereditary breast ovarian cancer syndrome	2	Breast, ovary, prostate, melanoma
CDKN2A	Familial atypical multiple mole melanoma (FAMMM)	10-30	Melanoma
MLH1, MSH2, MSH6, PMS2, EPCAM	Lynch syndrome	5-10	Colorectal, uterine, upper GI, ovary, urinary tract, brain, sebaceous neoplasms
PALB2	–	5-10	Breast, prostate
STK11	Peutz-Jeghers syndrome	10-30	Breast, colorectal, upper GI, lung, reproductive tract
TP53	Li-Fraumeni syndrome	Not defined	Breast, brain, sarcoma, adrenocortical carcinoma

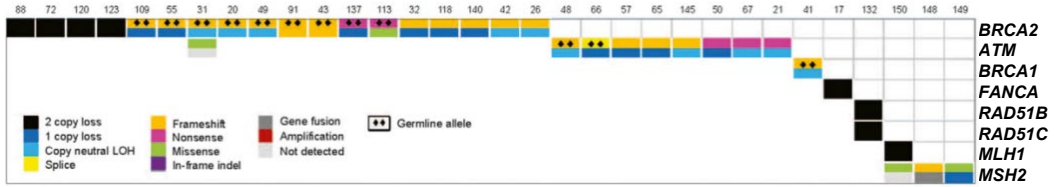
BRCA1, breast cancer 1; *BRCA2*, breast cancer 2; *CDKN2A*, cyclin-dependent kinase inhibitor 2A; *EPCAM*, epithelial cell adhesion molecule; *MLH1*, MutL homolog 1; *MSH2*, MutS homolog 2; *MSH6*, MutS homolog 6; *PALB2*, partner and localizer of BRCA2; *STK11*, serine/threonine kinase 11; *TP53*, tumor protein 53.

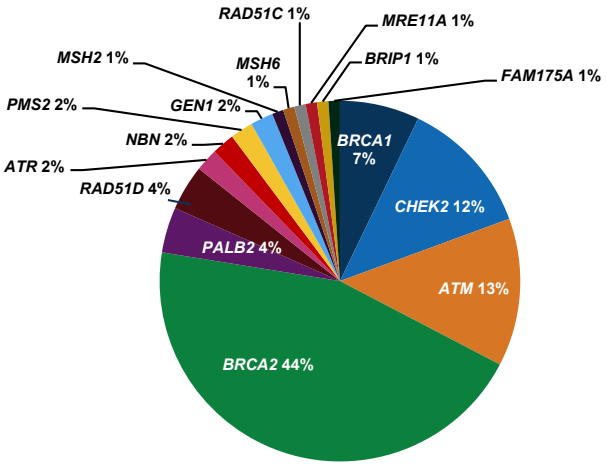
[a] Most commonly associated cancers. [b] Biallelic *ATM* mutation carriers have ataxia telangiectasia, but a single *ATM* mutation is associated with increased risk for pancreatic cancer. 1. Stoffel EM et al. *J Clin Oncol*. 2019;37:153-164.

Germline *BRCA1/2* Mutation in Prostate Cancer[1]

Frequency of Mutations in Advanced Prostate Cancer

- Somatic: 32 of 150 men with CRPC had alterations = 21.3%
  - Many biallelic
- Germline: 82 of 692 men with metastatic PCa (US, UK) = 11.8%
  - *BRCA2* in 37 (5.4%)
  - Not predicted by family history or age at diagnosis

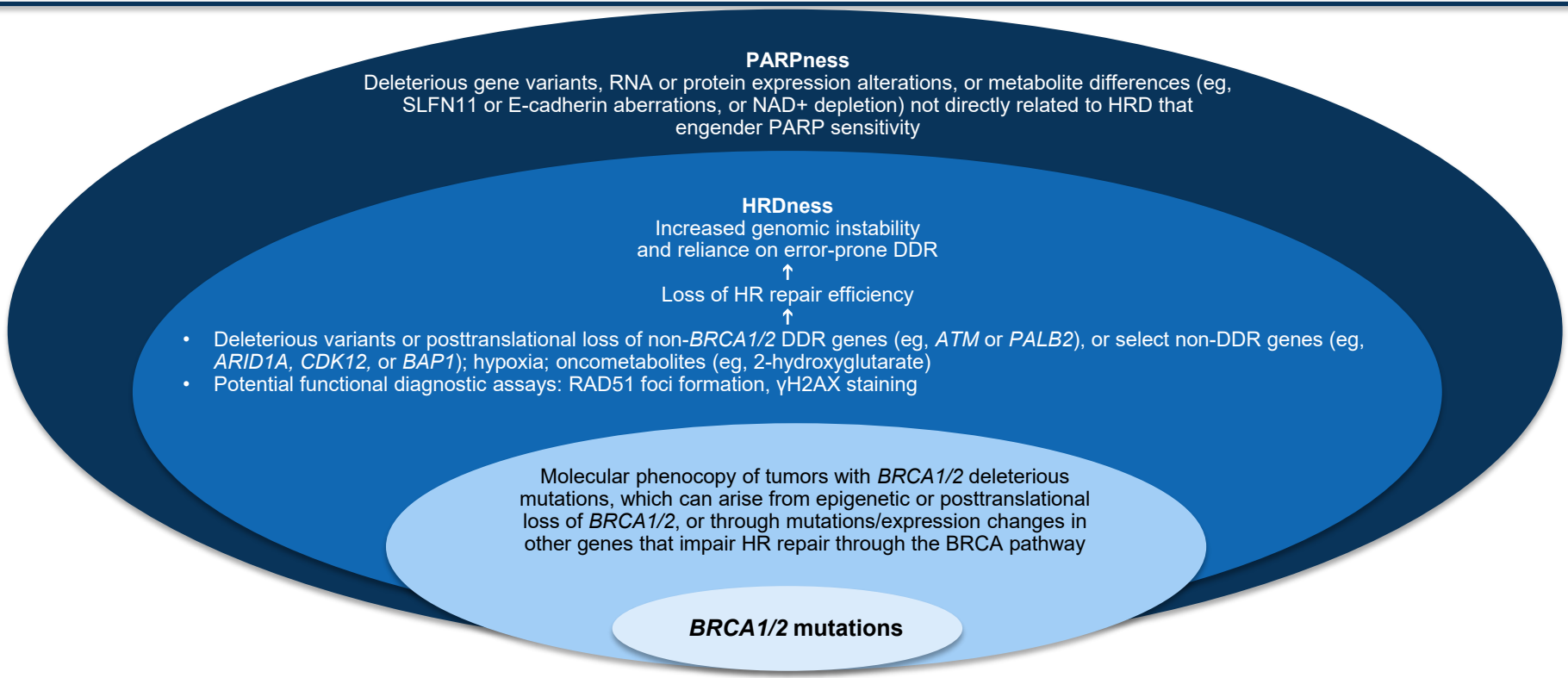




BRCA1, breast cancer 1; *BRCA2*, breast cancer 2; *BRIP1*, BRCA1 interacting protein C-terminal helicase 1; *CHEK2*, checkpoint kinase 2; CRPC, castrate-resistant prostate cancer; *FAM175A*, family with sequence similarity 175 member A; *MSH2*, MutS homolog 2; *MSH6*, MutS homolog 6; *NBN*, nibrin; PCa, prostate cancer.

1. Pezaro C. 2018 American Society of Clinical Oncology Annual Meeting (ASCO 2018).

Categorizing Predictive Biomarkers of Response to PARP Inhibitors[1]



ARID1A, AT-rich interaction domain 1A; *BAP1*, BRCA1 associated protein 1; *BRCA1*, breast cancer 1; *BRCA2*, breast cancer 2; CDK12, cyclin-dependent kinase 12; DDR, DNA damage response; γH2AX, phosphorylated H2A histone family member X; NAD, nicotinamide adenine dinucleotide; *PALB2*, partner and localizer of BRCA2; PARP, poly ADP-ribose polymerase; SLFN11, Schlafen family member 11.

1. Pilie PG et al. *Nat Rev Clin Oncol*. 2019;16:81-104.

Preclinical Features of PARP Inhibitors

PARP Inhibitor	Olaparib Tablets	Niraparib Capsules	Rucaparib Tablets	Talazoparib Capsules	Veliparib Tablets
PARylation IC_{50}, nM[1]					
A549	29	317	19	2	26
UWB1.289 (BRCA1m)	8	89	29	2.5	79
Clonogenic IC_{50}, nM[1] UWB1.289 (BRCA1m)	63 ± 19	98 ± 30	123 ± 54	1.2 ± 0.3	~1,000 (extrapolated)
Clinical doses, mg	300 BID[2]	300 QD[3]	600 BID[4]	1 QD[5]	In combination only[6]
PARP-DNA trapping[7]	+	+	+	++	-

- ***PARylation and clonogenic assays carried out in ovarian cancer and adenocarcinoma cell lines***

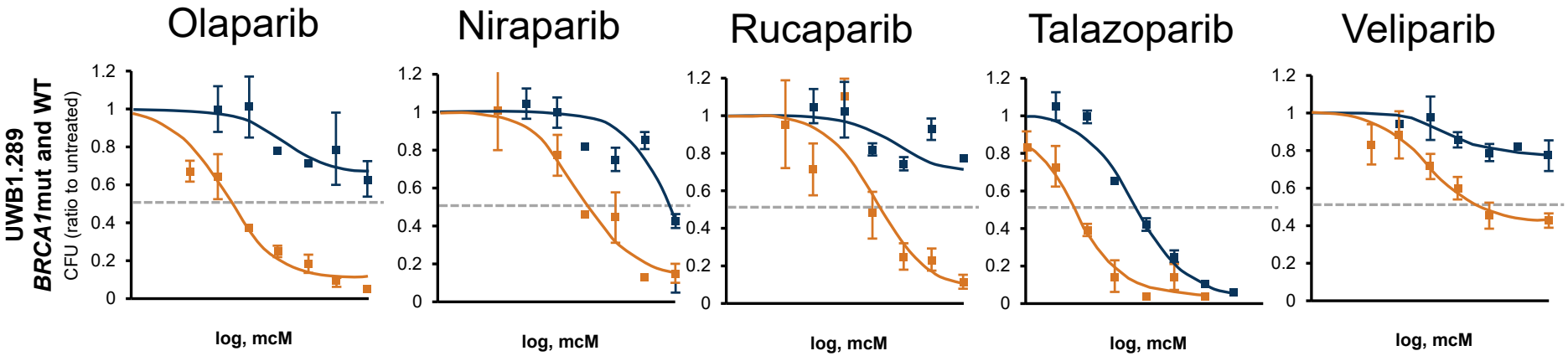
PARP, poly ADP-ribose polymerase.

1. Leo E et al. American Association for Cancer Research Annual Meeting 2018 (AACR 2018). Poster LB-273. 2. Pujade-Lauraine E et al. *Lancet Oncol*. 2017;18:1274-1284. 3. Mirza MR et al. *N Engl J Med*. 2016;375:2154-2164. 4. Coleman RL et al. *Lancet*. 2017;390:1949-1961. 5. Litton J et al. *N Engl J Med*. 2018;379:753-763. 6. Wagner LM. *Onco Targets Ther.* 2015;8:1931-1939. 7. Pilie P et al. *Clin Cancer Res.* 2019;25:3759-3771.

PARP Inhibitors Demonstrate Greater Activity in HRR-Deficient Cancer Cells Compared With Matched Non-HRR–Deficient Cells[1]

Colony formation assay in two isogenic pairs (HRR deficient and non-HRR deficient)

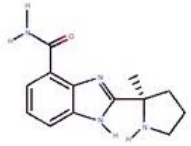
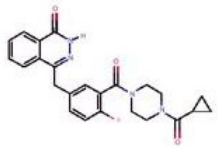
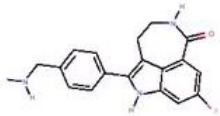
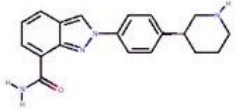
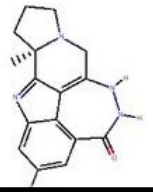
Assay carried out in an ovarian cancer cell line



HRR, homologous recombination repair; PARP, poly ADP-ribose polymerase.

1. Leo E et al. AACR 2018. Poster LB-273.

Toxicity Profile of PARP Inhibitors[1]

	 Veliparib[a]	 Olaparib	 Rucaparib	 Niraparib	 Pamiparib[b]	 Talazoparib
Relative PARP-trapping capacity[c]	-	++	++	++	++	+++
Single-agent dose	400 mg PO BID	300 mg PO BID	600 mg PO BID	300 mg PO QD	60 mg PO BID	1 mg PO QD
Toxicities (most frequent)[d]	Nausea (30%) Fatigue (25%) Lymphopenia (16%)	Nausea (58%-76%) Fatigue (29%-66%) Vomiting (30%-37%) Diarrhea (21%-33%) Dysgeusia (27%) Headache (20%-25%)	Nausea (75%) Fatigue (69%) Vomiting (37%) Diarrhea (32%) Dysgeusia (39%) LFT elevation (34%)	Nausea (74%) Fatigue (59%) LFT elevation (36%) Vomiting (34%) Headache (26%) Insomnia (24%) Hypertension (19%)	Limited early-phase trial data from abstracts only: Nausea (56%) Fatigue (40%)	Nausea (49%) Fatigue (50%) Headache (33%) Vomiting (25%) Alopecia (25%) Diarrhea (22%)
Grade ≥3 hematologic toxicities in ≥5% of study population	NTD	Anemia (16%-19%) Neutropenia (5%-9%)	Anemia (19%) Neutropenia (7%)	Thrombocytopenia (34%) Anemia (25%) Neutropenia (20%)	Limited early-phase trial data from abstracts only: Anemia (10.3%), Neutropenia (8.8%)	Anemia (39%) Neutropenia (21%) Thrombocytopenia (15%)

BID, twice a day; NTD, none to date; PARP, poly ADP-ribose polymerase; QD, once daily.

[a] Mature phase 3 data on single-agent veliparib are not available or being pursued at this time; side effects obtained from phase 2 study. [b] Pamiparib has only been through phase 1 testing to date; phase 3 trials registered as noted. [c] Relative PARP trapping taken from multiple preclinical studies. [d] Most frequent adverse events when given as single agent, followed by occurrence of grade 3 or higher cytopenias when given as single agent.

1. Pilié PG et al. *Clin Cancer Res*. 2019;25:3759-3771.

Role of PARP Inhibitors in Ovarian Cancers

First-Line Maintenance in Patients With Newly Diagnosed Advanced Ovarian Cancer[1]

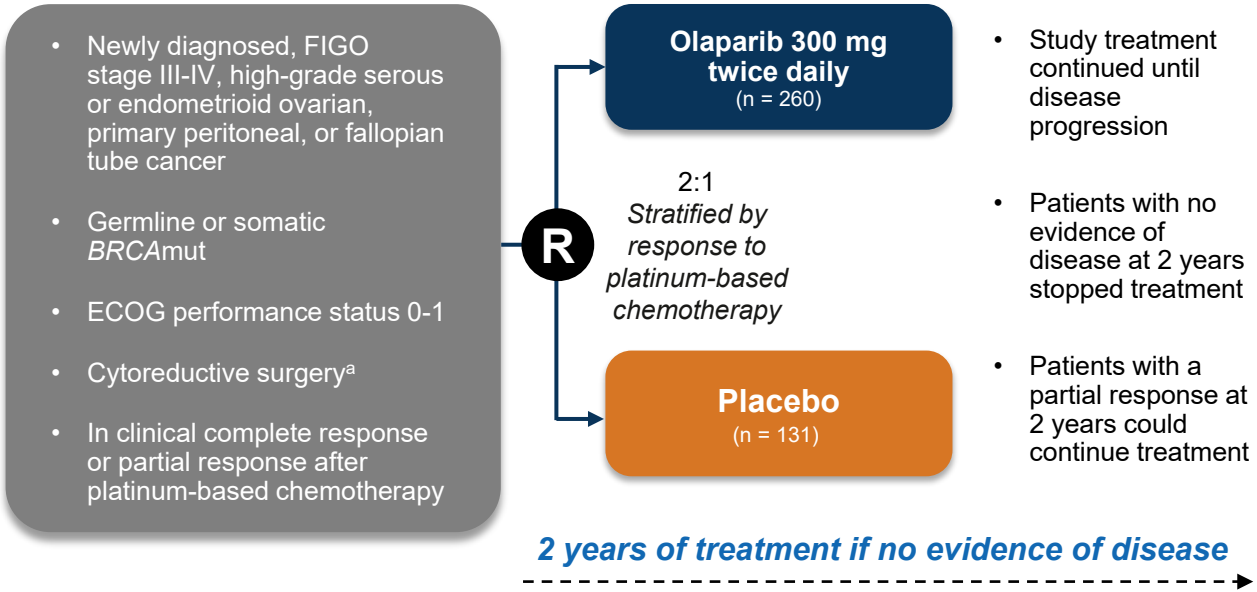
Monotherapy Approaches

SOLO-1[2]
olaparib vs placebo

PRIMA[3]
niraparib vs placebo

1. https://www.clinicaltrials.gov. 2. Moore K et al. *N Engl J Med*. 2018;379:2495-2505. 3. González-Martín A et al. *N Engl J Med*. 2019;381:2391-2402.

SOLO-1: Study Design[1]



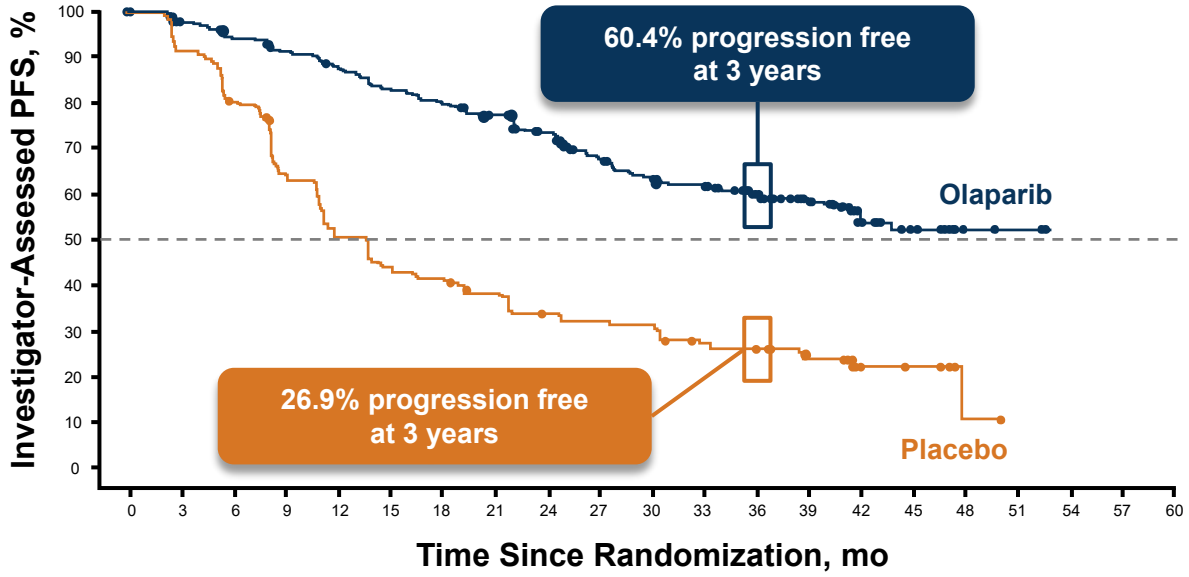
- **Primary endpoint**: investigator-assessed PFS (modified RECIST v1.1)
- **Secondary endpoints**: PFS using BICR, PFS2, overall survival, time from randomization to first subsequent therapy or death, time from randomization to second subsequent therapy or death, HRQOL (FACT-O TOI score)

BICR, blinded independent central review; *BRCA*mut, *BRCA*-mutated; ECOG, Eastern Cooperative Oncology Group; FACT-O TOI, Functional Assessment of Cancer Therapy - Ovarian Trial Outcome Index; FIGO, International Federation of Gynecology and Obstetrics; HRQOL, health-related quality of life; PFS, progression-free survival.

[a] 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.

1. Moore K et al. *N Engl J Med*. 2018;379:2495-2505.

SOLO-1: PFS by Investigator Assessment[1]



No. at Risk																					
Placebo	131	118	103	82	65	56	53	47	41	39	38	31	28	22	6	5	1	0	0	0	0
Olaparib	260	240	229	221	212	201	194	184	172	149	138	133	111	88	45	36	4	3	0	0	0

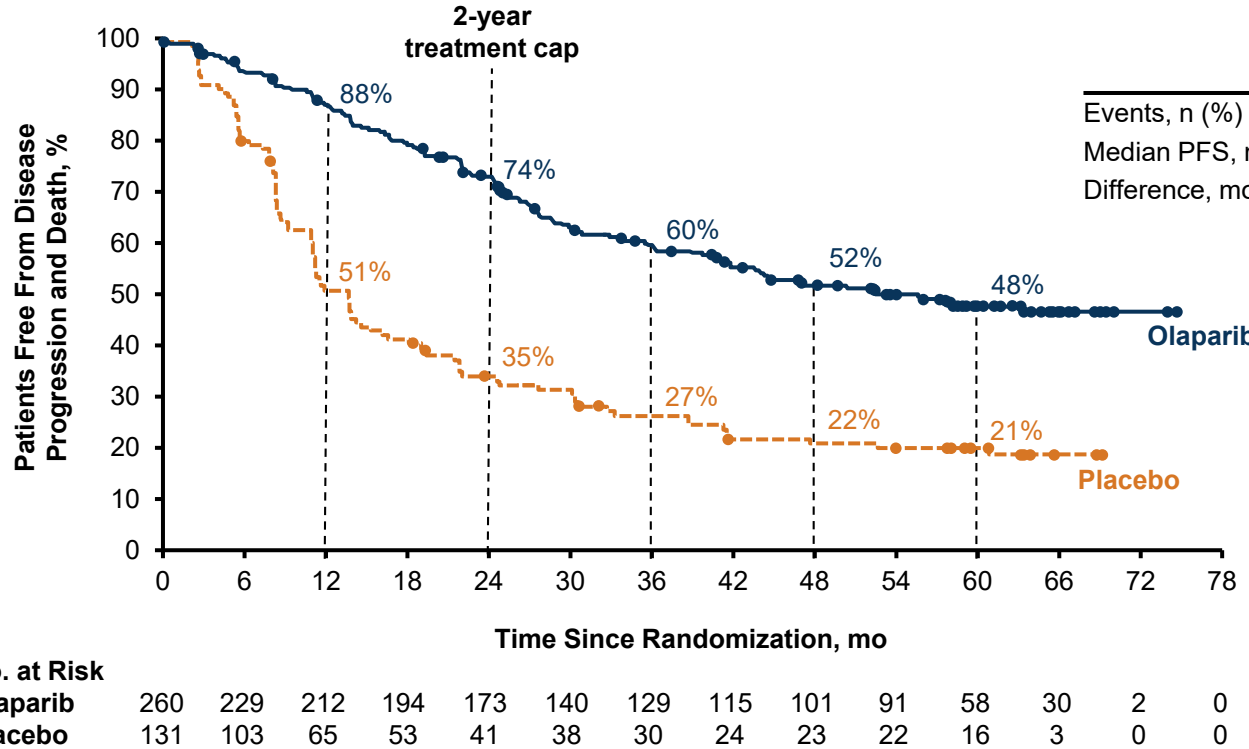
	Olaparib (n = 260)	Placebo (n = 131)
Events, n (%) (50.6% maturity)	102 (39.2)	96 (73.3)
Median PFS, mo	NR	13.8

HR = 0.30 (95% CI, 0.23-0.41; *P* < .0001)

PFS, progression-free survival.

1. Moore K et al. *N Engl J Med*. 2018;379:2495-2505.

PFS Benefit of Maintenance Olaparib Was Sustained Beyond the End of Treatment[1,a]

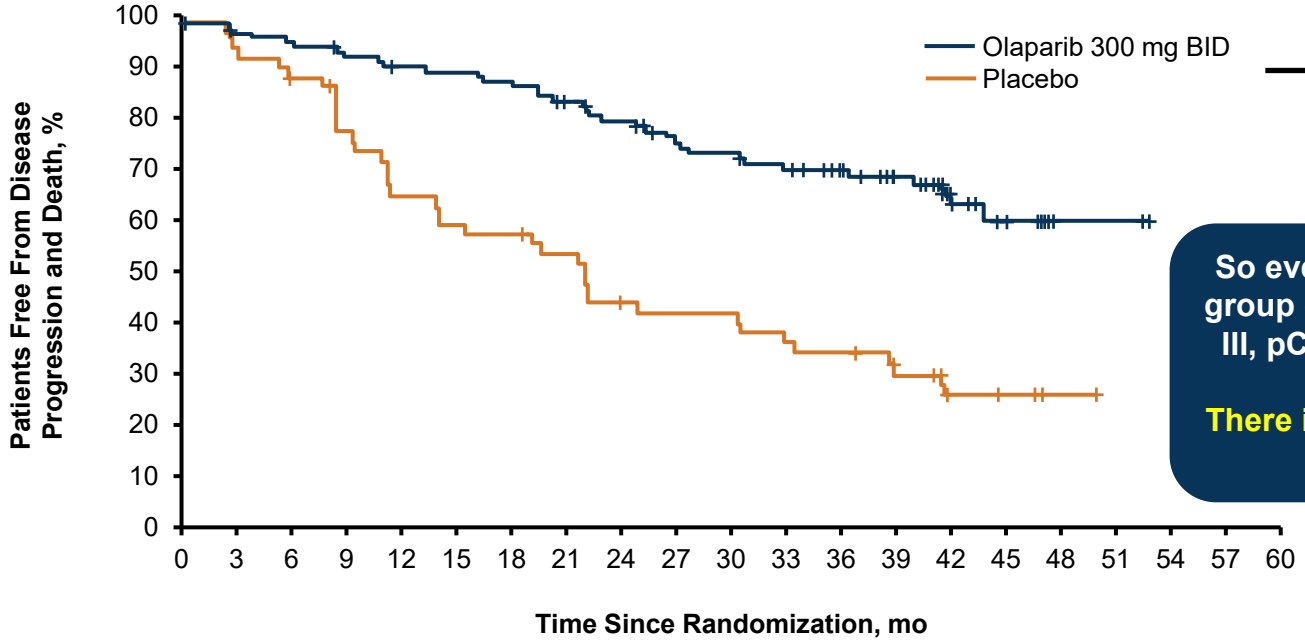


	Olaparib (N = 260)	Placebo (N = 131)
Events, n (%)	118 (45)	100 (76)
Median PFS, mo	56.0	13.8
Difference, mo	42.2	
	HR 0.33 (95% CI, 0.25-0.43)	

Median treatment duration:
Olaparib, 24.6 mo
Placebo[b], 13.9 mo

PFS, progression-free survival.
[a] Investigator assessed by modified RECIST v1.1. DCO: March 5, 2020. [b] N = 130 (safety analysis set).
1. Moore K et al. *N Engl J Med*. 2018;379:2495-2505.

SOLO-1: No Residual Disease After Upfront Surgery for Stage III Disease (44% of Patients)[1]



	Olaparib (N = 114)	Placebo (N = 58)
	NR	21.9

HR = 0.32
(95% CI, 0.20-0.51)

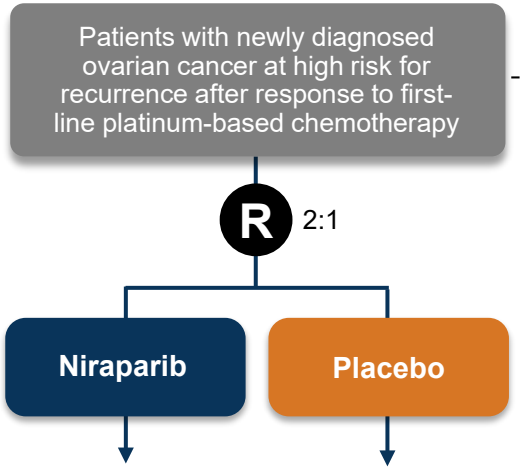
So even in our best prognostic group of patients–BRCA+, stage III, pCRS, NGR–the magnitude of benefit remains
There is no "low-risk" advanced ovarian cancer

No. at Risk																				
Olaparib 300 mg BID	114	105	102	99	96	95	93	87	82	72	70	66	57	48	25	18	3	3	0	0	0
Placebo	58	53	50	43	36	33	32	29	23	22	22	19	18	13	4	3	1	0	0	0	0

NGR, no gross residual disease.

1. Mathews CA et al. ASCO 2019. Abstract 5541.

PRIMA: Study Design[1,2]



Endpoint assessment

- Primary endpoint: PFS by BICR
- Key secondary endpoint: OS
- Secondary endpoints: PFS2, TFST, PROs, and safety

Patients were treated with niraparib or placebo once daily for 36 months or until disease progression

Stratification factors

- Neoadjuvant chemotherapy administered: yes or no
- Best response to first platinum therapy: CR or PR
- Tissue homologous recombination test status: deficient or proficient/not determined

- Body weight ≥77 kg and platelets ≥150,000/mcL started with 300 mg daily
- Body weight <77 kg and/or platelets <150,000/mcL started with 200 mg QD

Hierarchical PFS testing

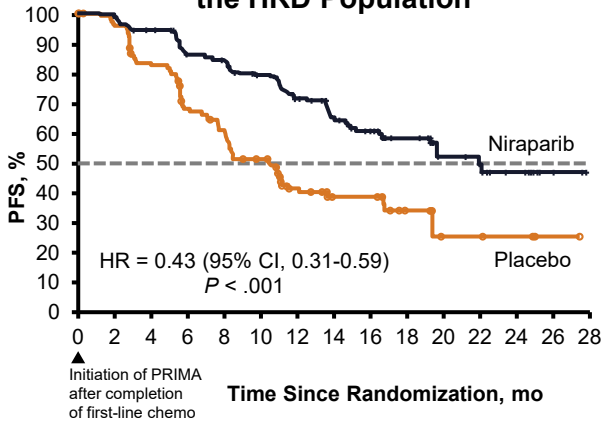
- Patients with homologous recombination deficient tumors, followed by the overall population
- Statistical assumption: a hazard ratio benefit in PFS of
  - *0.5 in homologous recombination–deficient patients*
  - *0.65 in the overall population*
- >90% statistical power and one-sided type I error of .025

BICR, blinded independent central review; CR, complete response; PFS, progression-free survival; PR, partial response; PRO, patient-reported outcome; TFST, time to first subsequent therapy.

1. González-Martín A et al. European Society for Medical Oncology Annual Meeting (ESMO 2019). Abstract LBA1.
2. González-Martín A et al. *N Engl J Med*. 2019;381:2391-2402.

PRIMA: Niraparib in Newly Diagnosed Ovarian Cancer After Response to First-Line Platinum-Based Chemotherapy[1,2]

Primary Endpoint, PFS Benefit in the HRD Population

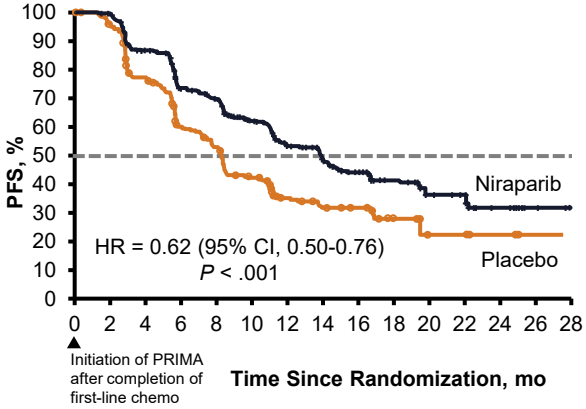


57% reduction in hazard of relapse or death with niraparib

	Niraparib (n = 247)	Placebo (n = 126)
Median PFS		
Months (95% CI)	21.9 (19.3-NE)	10.4 (8.1-12.1)
Patients Without PD or Death, %		
6 mo	86	68
12 mo	72	42
18 mo	59	35

No. at Risk															
Niraparib	277	231	215	189	184	168	111	76	66	42	22	19	13	4	0
Placebo	126	117	99	79	70	57	34	21	21	11	5	5	4	1	0

Primary Endpoint: PFS Benefit in the Overall Population



38% reduction in hazard of relapse or death with niraparib

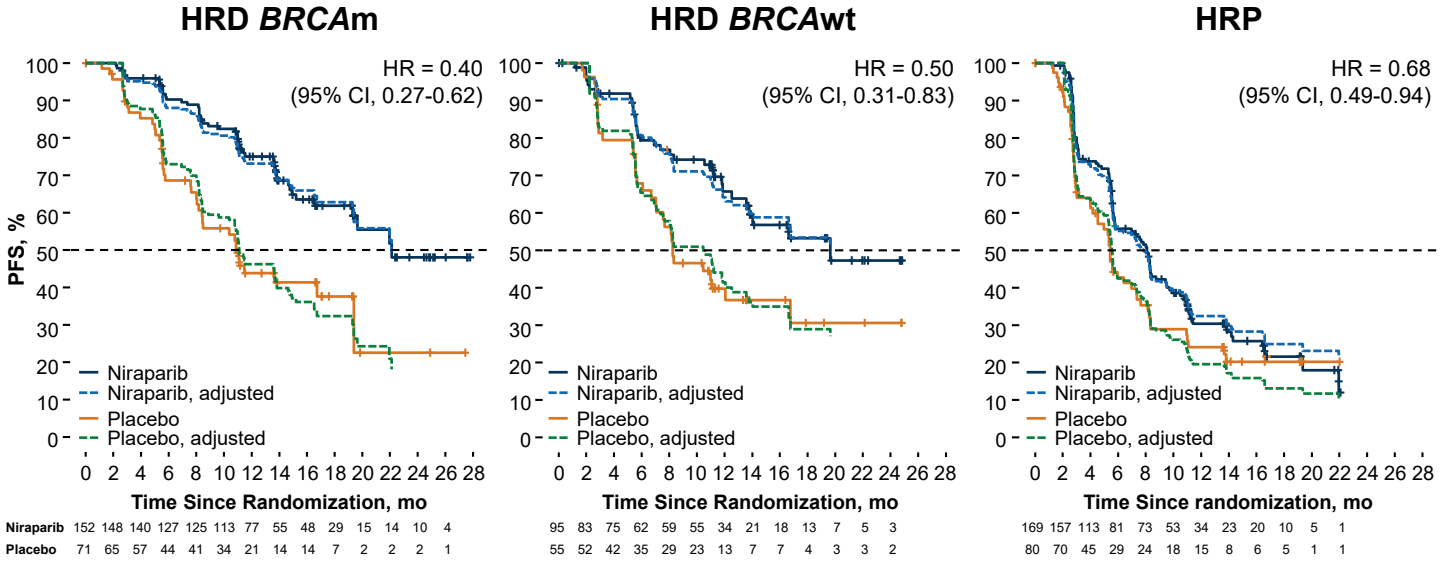
	Niraparib (n = 487)	Placebo (n = 246)
Median PFS		
Months (95% CI)	13.8 (11.5-14.9)	8.2 (7.3-8.5)
Patients Without PD or Death, %		
6 mo	73	60
12 mo	53	35
18 mo	42	28

No. at Risk															
Niraparib	487	454	385	312	295	253	167	111	94	58	29	21	13	4	0
Placebo	246	226	177	133	117	90	60	32	29	17	6	6	4	1	0

PD, progressive disease; PFS, progression-free survival.

1. González-Martín A et al. ESMO 2019. Abstract LBA1. 2. González-Martín A et al. *N Engl J Med*. 2019;381:2391-2402.

PRIMA: PFS Benefit in HRD and HRP Subgroups by BICR[1]



- **Niraparib provided clinical benefit in the HRD (*BRCA*m and *BRCA*wt) and HRP subgroups**
- **All subgroups were analyzed using the adjusted Cox regression method to account for stratification imbalances**

*BRCA*m, *BRCA* mutated; *BRCA*wt, *BRCA* wild type; PFS, progression-free survival.

1. Monk BJ et al. Society of Gynecologic Oncology Annual Meeting (SGO 2020). Abstract 31.

FDA Approvals: Olaparib and Niraparib for Maintenance Treatment[1]

On December 2018, the FDA approved olaparib for the maintenance treatment of patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated (g*BRCA*m or s*BRCA*m) advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR to first-line platinum-based chemotherapy

On April 2020, the FDA approved niraparib for the maintenance treatment of patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR to first-line platinum-based chemotherapy

CR, complete response; g*BRCA*m, germline *BRCA*-mutated; PR, partial response; s*BRCA*m, somatic *BRCA*-mutated.

1. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-niraparib-first-line-maintenance-advanced-ovarian-cancer.

Combination Approaches[1]

PAOLA-1
olaparib + bevacizumab

1. https://www.clinicaltrials.gov.

PAOLA-1/ENGOT-ov25 Trial Design

Patients

- Newly diagnosed, FIGO stage III-IV high-grade serous or endometrioid ovarian, fallopian tube, and/or primary peritoneal cancer[a]

First-line treatment:

- Upfront or interval surgery
- Platinum taxane-based chemotherapy plus ≥2 cycles of bevacizumab[b]

≤9 weeks

NED/CR/PR

Maintenance therapy

2:1 randomization stratified by:
- Tumor *BRCA*m status
- First-line treatment outcome[d]

Olaparib tablets 300 mg BID x 2 y
+ Bevacizumab[c]

Placebo x 2 y
+ Bevacizumab[c]

Primary PFS analysis (DCO 22 March 2019)

	Olaparib + Bev (N = 537)	Placebo + Bev (N = 269)
Median PFS, mo	22.1	16.6

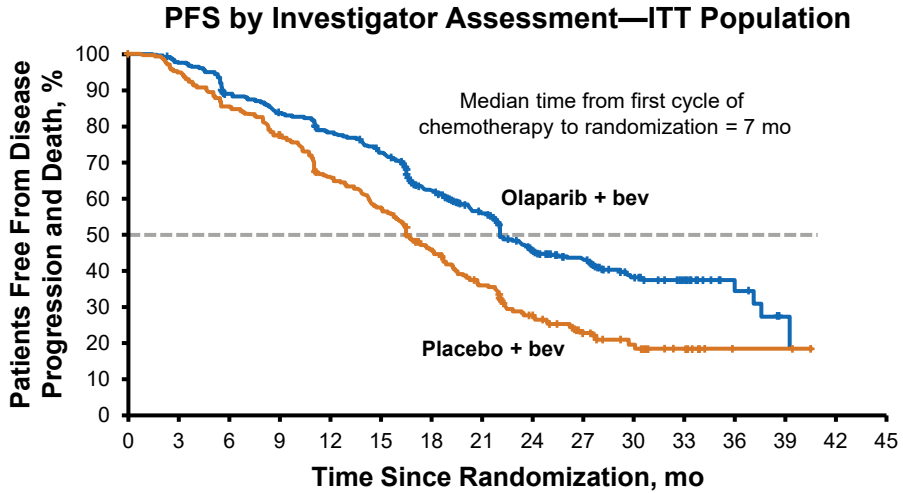
HR = 0.59 (95% CI, 0.49-0.72); *P* < .001

- Primary endpoint: investigator-assessed PFS (modified RECIST v1.1)
- *In the primary analysis, a statistically significant PFS benefit was observed*[1]

BID, twice a day; CR, complete response; FIGO, International Federation of Gynecology and Obstetrics; NED, no evidence of disease; PFS, progression-free survival; PR, partial response.
[a] Patients with other epithelial nonmucinous ovarian cancer were eligible if they had a germline *BRCA1* and/or *BRCA2* mutation. [b] Patients must have received ≥3 cycles of bevacizumab with the last 3 cycles of chemotherapy, apart from patients undergoing interval surgery who were permitted to receive only 2 cycles of bevacizumab with the last 3 cycles of chemotherapy. [c] Bevacizumab 15 mg/kg, every 3 weeks for a total of 15 months, including when administered with chemotherapy. [d] According to timing of surgery and NED/CR/PR.

1. Ray-Coquard I et al. *N Engl J Med.* 2019;381:2416-2428.

PAOLA-1: Olaparib + Bevacizumab as First-Line Maintenance in Ovarian Cancer—PFS[1,2]



	Olaparib + Bev (N = 537)	Placebo + bev (N = 269)
Events, n (%) (59% maturity)	280 (52)	194 (72)
Median PFS, mo	22.1	16.6

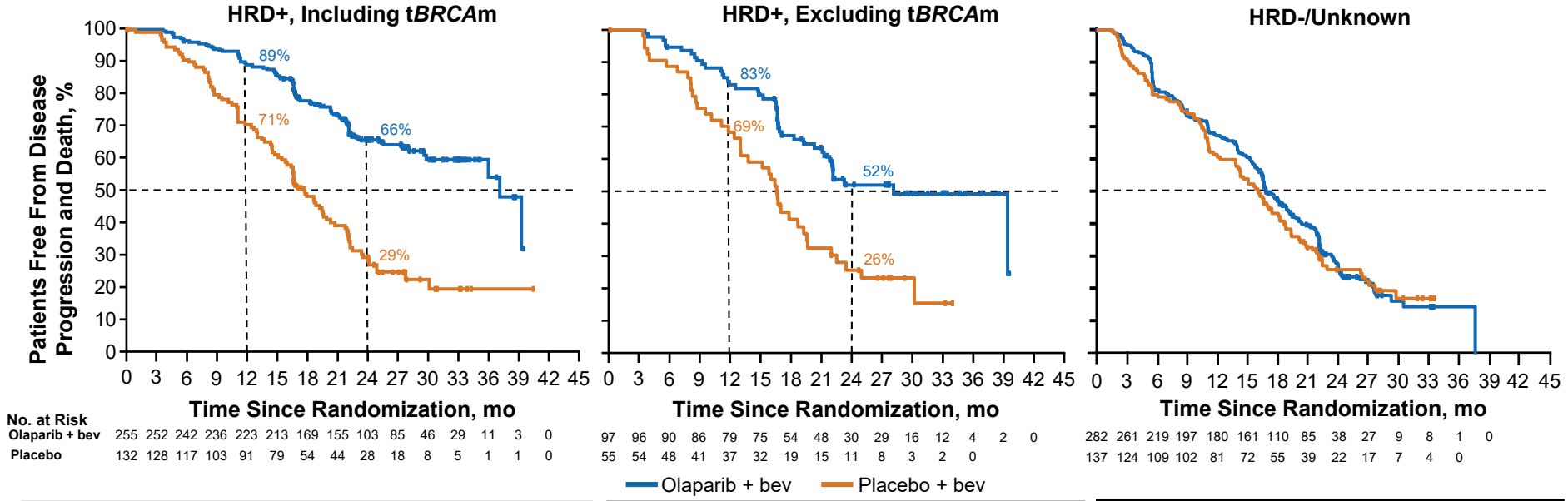
HR = 0.59 (95% CI, 0.49-0.72); P < .0001

- All trial participants were evaluated for HRD using the myChoice HRD test
- Approximately half of the patients in the PAOLA-1 were HRD positive
- Prevalence of HRD in the PAOLA-1 overall study population was consistent with HRD prevalence in the general ovarian cancer population

PFS, progression-free survival.

1. Ray-Coquard I et al. *N Engl J Med*. 2019;381:2416-2428. 2. Ray-Coquard I et al. ESMO 2019. Abstract 3955.

PAOLA-1: Olaparib + Bevacizumab as First-Line Maintenance—PFS by HRD Status[1,2,a]



	Olaparib + Bev (n = 255)	Placebo + Bev (n = 132)
Events, n (%)	87 (34)	92 (70)
Median PFS, mo	37.2[b]	17.7
HR = 0.33 (95% CI, 0.25-0.45)		

	Olaparib + Bev (n = 97)	Placebo + Bev (n = 55)
Events, n (%)	43 (44)	40 (73)
Median PFS, mo	28.1[b]	16.6
HR = 0.43 (95% CI, 0.28-0.66)		

	Olaparib + Bev (n = 282)	Placebo + Bev (n = 137)
Events, n (%)	193 (68)	102 (74)
Median PFS, mo	16.9	16.0
HR = 0.92 (95% CI, 0.72-1.17)		

PFS, progression-free survival; t*BRCA*m, tumor *BRCA*-mutated.

[a] The percentages of patients who were progression free at 12 and 24 mo have been calculated based on Kaplan–Meier estimates. HRD positive is an HRD score ≥42.

[b] This median is unstable because of a lack of events—less than 50% maturity.

1. Ray-Coquard I et al. *N Engl J Med*. 2019;381:2416-2428. 2. Ray-Coquard I et al. ESMO 2019. Abstract 3955.

FDA Approval: Olaparib + Bevacizumab for First-Line Maintenance Treatment[1]

In May 2020, the FDA approved olaparib in combination with bevacizumab for first-line maintenance treatment of patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer in CR or PR to first-line platinum-based chemotherapy and whose cancer is associated with HRD-positive status defined by either a deleterious or suspected deleterious *BRCA*m, and/or genomic instability. Patients will be selected for therapy based on an FDA-approved companion diagnostic test.

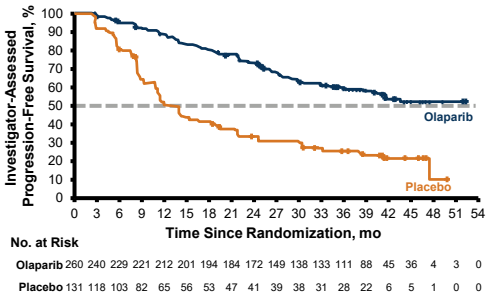
*BRCA*m, *BRCA*-mutated; CR, complete response; PR, partial response.

1. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-olaparib-plus-bevacizumab-maintenance-treatment-ovarian-fallopian-tube-or-primary.

How Do We Interpret PAOLA-1 vs SOLO-1 in *BRCA*-Associated Cancers?

Does an HR of 0.30 for SOLO-1 and 0.33 for PAOLA-1 mean there is no benefit of bev in *BRCA*-associated cancers?

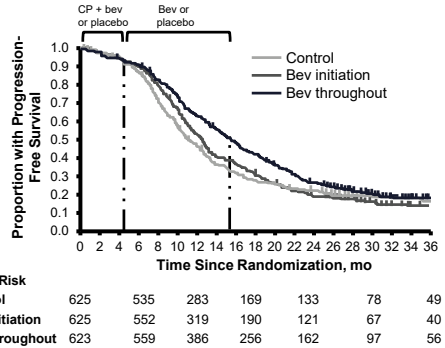
SOLO-1: g*BRCA*m[1]



NR vs 13 mo
HR = 0.30 (95% CI, 0.23-0.41)

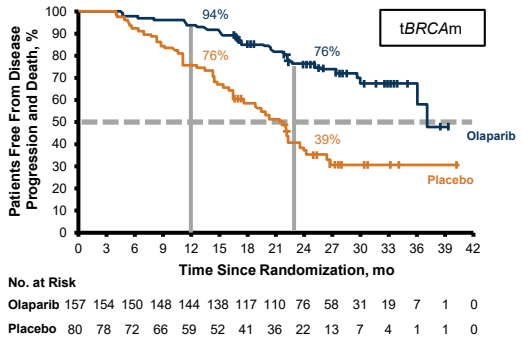
NR vs 14.1 mo
HR = 0.28 (95% CI, 0.2-0.39)

GOG 218[2]



12.0 vs 18.0 mo
HR = 0.645 (95% CI, 0.551-0.756)

PAOLA-1[3]



37.2 vs 17.7 mo
HR = 0.33 (95% CI, 0.25-0.45)

INV REVIEW

BICR REVIEW

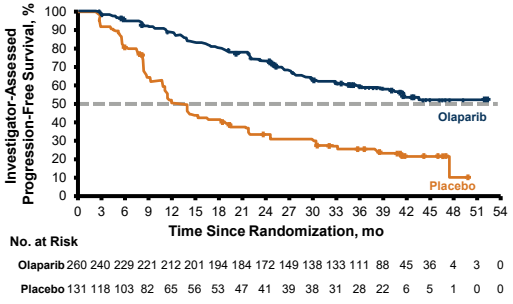
BICR, blinded independent central review; g*BRCA*m, germline *BRCA*-mutated; NR, not reached; t*BRCA*m, tumor *BRCA*-mutated.

1. Moore K et al. *N Engl J Med.* 2018;379:2495-2505. 2. Burger RA et al. *N Engl J Med*. 2011;365:2473-2483.
3. Ray-Coquard I et al. ESMO Congress 2019. Abstract LBA2_PR.

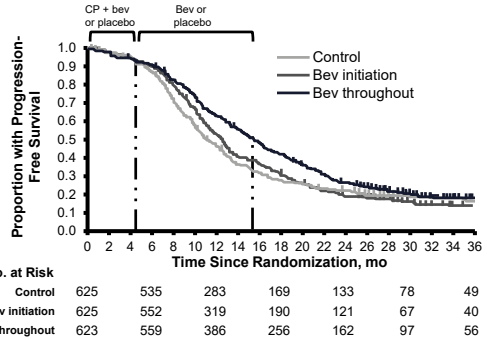
What Is the Best Option for *BRCA*-Associated Cancers?

We cannot say olaparib + bev is the best option for *BRCA*-associated tumors based on PAOLA-1 or this exploratory mathematical exercise. At best we can see the benefit of bev is additive AND—in patients who have already started bev—it allows for continuation during maintenance rather than cessation, which was a point of uncertainty with the original SOLO-1 indication

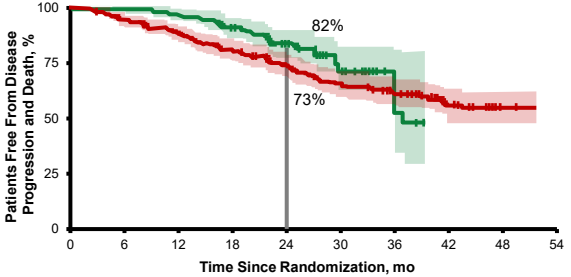
SOLO-1: g*BRCA*m[1]



GOG 218[2]



SOLO-1/PAOLA-1[3]



NR vs 13 mo HR = 0.30 (95% CI, 0.23, 0.41)		HR = 0.71 (95% CI, 0.45-1.09)	INV REVIEW
NR vs 14.1 mo HR = 0.28 (95% CI, 0.2-0.39)	12.0 vs 18.0 mo HR = 0.645 (0.551-0.756)		BICR REVIEW

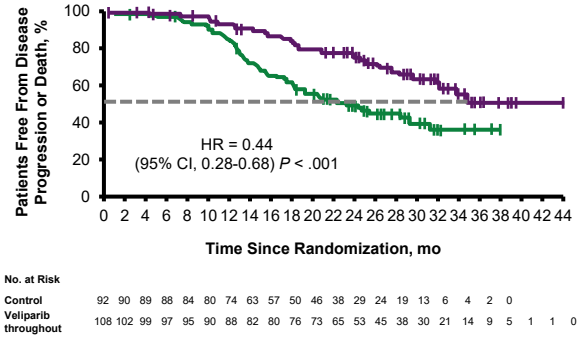
BICR, blinded independent central review; g*BRCA*m, germline *BRCA*-mutated; NR, not reached.

1. Moore K et al. *N Engl J Med.* 2018;379:2495-2505. 2. Burger RA et al. *N Engl J Med*. 2011;365:2473-2483.
3. Vergote IB et al. SGO 2020. Abstract 13205.

What Is the Best Option for HRD+/*BRCA*wt Tumors?

- **Primary endpoint:** PFS

VELIA[1]

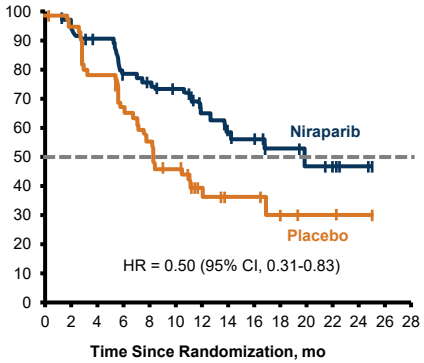


34.7 vs 22 mo
HR = 0.44 (95% CI, 0.28-0.68)

INV REVIEW

- **We really can't answer this question right now**
- **We can say that PARPi monotherapy > placebo**

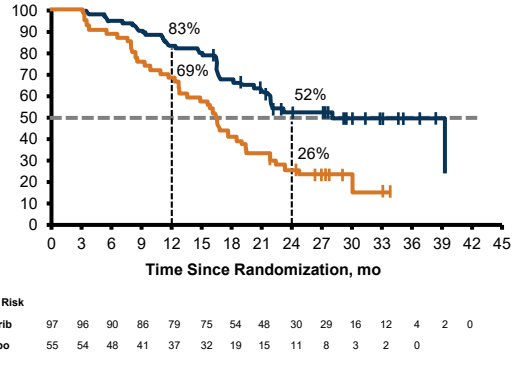
PRIMA[2]



HR = 0.50 (95% CI, 0.31-0.83)

BICR REVIEW

PAOLA-1[3]



28 vs 16.6 mo
HR = 0.43 (95% CI, 0.28-0.66)

INV REVIEW

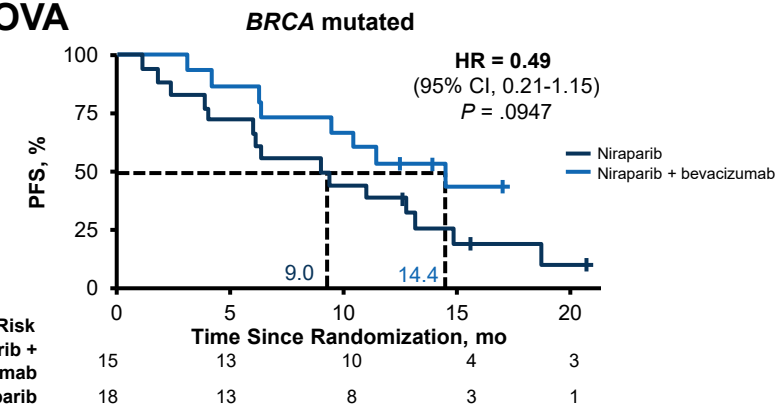
- **We can say that bevacizumab + PARPi > bev**
  But what about bev + PARPi vs PARPi?

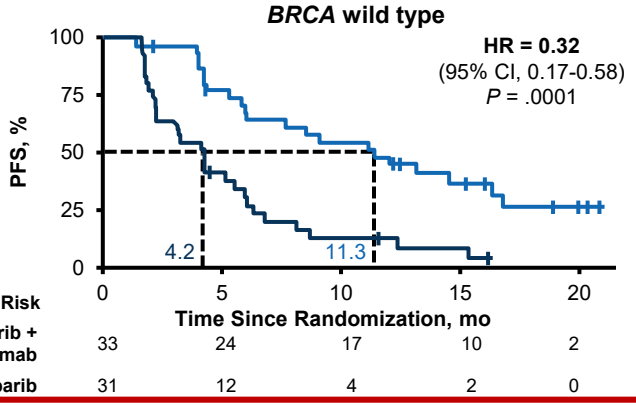
BICR, blinded independent central review; *BRCA*wt, *BRCA* wild type; PARPi, poly ADP-ribose polymerase inhibitor; PFS, progression-free survival.

1. Coleman R et al. *N Engl J Med.* 2019:381:2403-2415. 2. Gonzalez Martin A et al. *N Engl J Med.* 2019:381:2391-2402. 3. Ray-Coquard I et al. *N Engl J Med.* 2019:381:2416-2428.

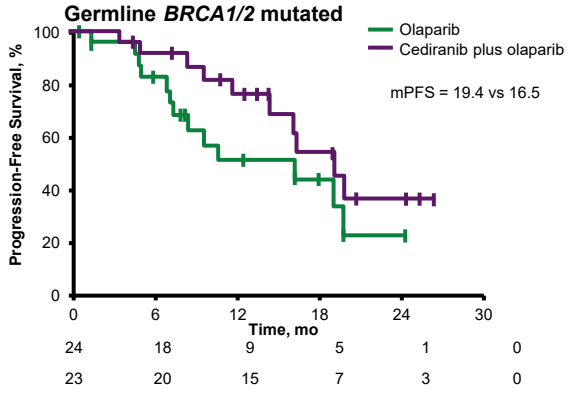
There Are Signals for Combination Antiangiogenics and PARPi in *BRCA*wt

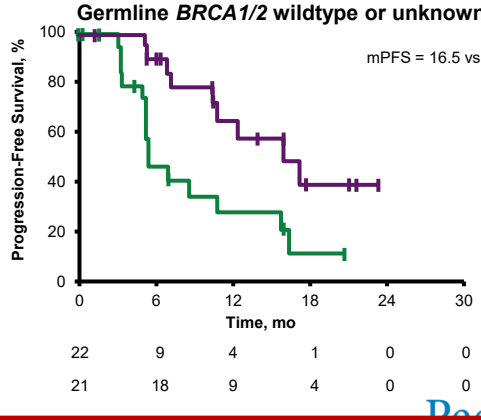
AVANOVA





Liu et al[1]

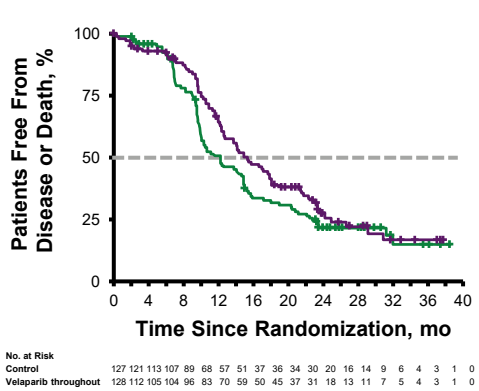
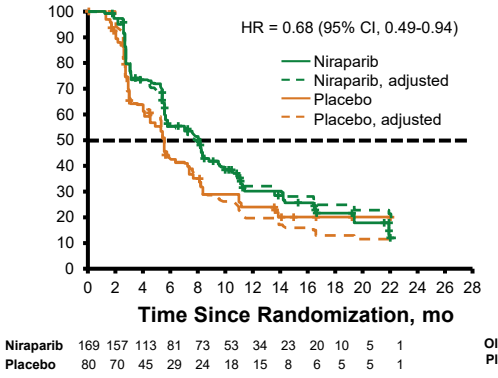
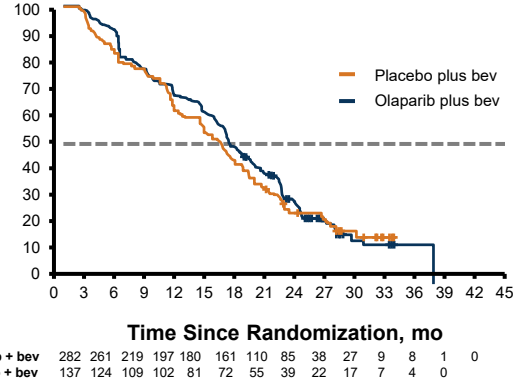




*BRCA*wt, *BRCA* wild type; mPFS, mean progression-free survival; PARPi, poly ADP-ribose polymerase inhibitor 1. Liu JF et al. *Lancet Oncol.* 2014;15:1207-1214.

What Is the Best Option for HRP Tumors?

Primary endpoint: PFS

VELIA[1]	PRIMA[2]	PAOLA-1[3]
		
15.4 vs 12.3 mo **HR = 0.76 (95% CI, 0.55-1.03)**		**16.9 vs 16.0 mo** **HR = 0.92 (95% CI, 0.72-1.17)**
	HR = 0.68 (95% CI, 0.49-0.94)	

INV REVIEW

BICR REVIEW

BICR, blinded independent central review; PFS, progression-free survival.

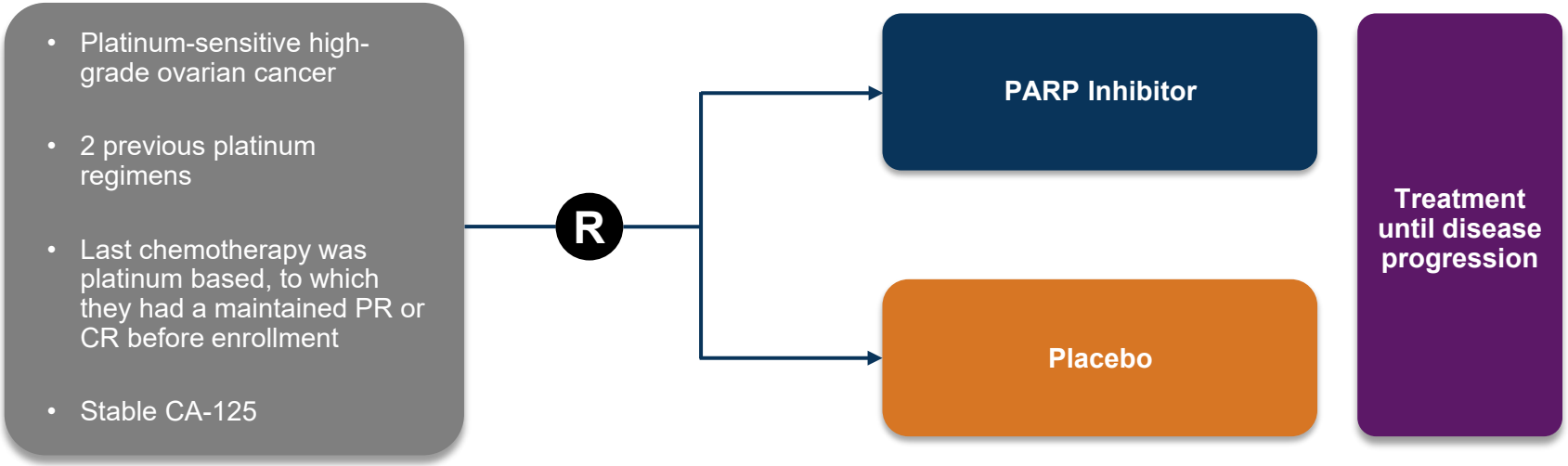
1. Coleman R et al. *N Engl J Med.* 2019:381:2403-2415. 2. Gonzalez Martin A et al. *N Engl J Med.* 2019:381:2391-2402. 3. Ray-Coquard I et al. *N Engl J Med.* 2019:381:2416-2428.

Frontline Ovarian Cancer

- **HRp**
  - Bevacizumab with and to follow chemotherapy
  - Niraparib switch maintenance
  - No maintenance
- **HRD**
  - Niraparib switch maintenance
  - Olaparib + bevacizumab
- ***BRCA*-associated cancers**
  - Olaparib switch maintenance (± bevacizumab)
  - Niraparib switch maintenance

Maintenance Trials in Recurrence Building on the Benefit of Chemotherapy[1-4]

Randomized Trials of PARP Inhibitors in Platinum-Sensitive High-Grade Relapsed Ovarian Cancers



Study 19[1] SOLO-2[2] ----→ Olaparib	NOVA[3] ----→ Niraparib	ARIEL3[4] ----→ Rucaparib

CR, complete response; PARP, poly ADP-ribose polymerase; PR, partial response.

1. Ledermann J et al. *N Engl J Med*. 2012;366:1382-1392. 2. Pujade-Lauraine E et al. *Lancet Oncol*. 2017;18:1274-1284.
3. Mirza MR et al. *N Engl J Med*. 2016;375:2154-2164. 4. Coleman RL et al. *Lancet*. 2017;390:1949-1961.

Pivotal Studies of PARP Inhibitors in Patients With Recurrent Ovarian Cancer After Response to Platinum

	STUDY 19[1] ITT	SOLO-2[2] g*BRCA*m	NOVA[3] g*BRCA*m	NOVA[3] Non-g*BRCA*m	ARIEL3[4] *BRCA*m	ARIEL3[4] ITT
Agent	Olaparib	Olaparib	Niraparib	Niraparib	Rucaparib	Rucaparib
Difference in mPFS, mo	8.4 vs 4.8	19.1 vs 5.5	21.0 vs 5.5	9.3 vs 3.9	16.6 vs 5.4	10.8 vs 5.4
PFS HR (investigator assessed)	0.35 (95% CI, 0.25-0.49; *P* < .001)	0.30 (95% CI, 0.22-0.41; *P* < .0001)	0.27 (95% CI, 0.18-0.40; *P* < .001)	0.53 (95% CI, 0.41-0.68; *P* < .001)	0.23 (95% CI, 0.16-0.34; *P* < .0001)	0.36 (95% CI, 0.30-0.45; *P* < .0001)
PFS HR (BICR)	0.39 (95% CI, 0.27-0.55; *P* < .001)	0.25 (95% CI, 0.18-0.35; *P* < .0001)	0.27 (95% CI, 0.17-0.41; *P* < .001)	0.45 (95% CI, 0.34-0.61; *P* < .001)	0.20 (95% CI, 0.13-0.32; *P* < .0001)	0.35 (95% CI, 0.28-0.45; *P* < .0001)

BICR, blinded independent central review; *BRCA*m, *BRCA*-mutated; g*BRCA*m, germline *BRCA*-mutated; mPFS, mean progression-free survival; PARP, poly ADP-ribose polymerase.

1. Ledermann J et al. *N Engl J Med.* 2012;366:1382-1392. 2. Pujade-Lauraine E et al. *Lancet Oncol.* 2017;18:1274-1284. 3. Mirza MR et al. *N Engl J Med.* 2016;375:2154-2164. 4. Coleman RL et al. *Lancet.* 2017;390:1949-1961.

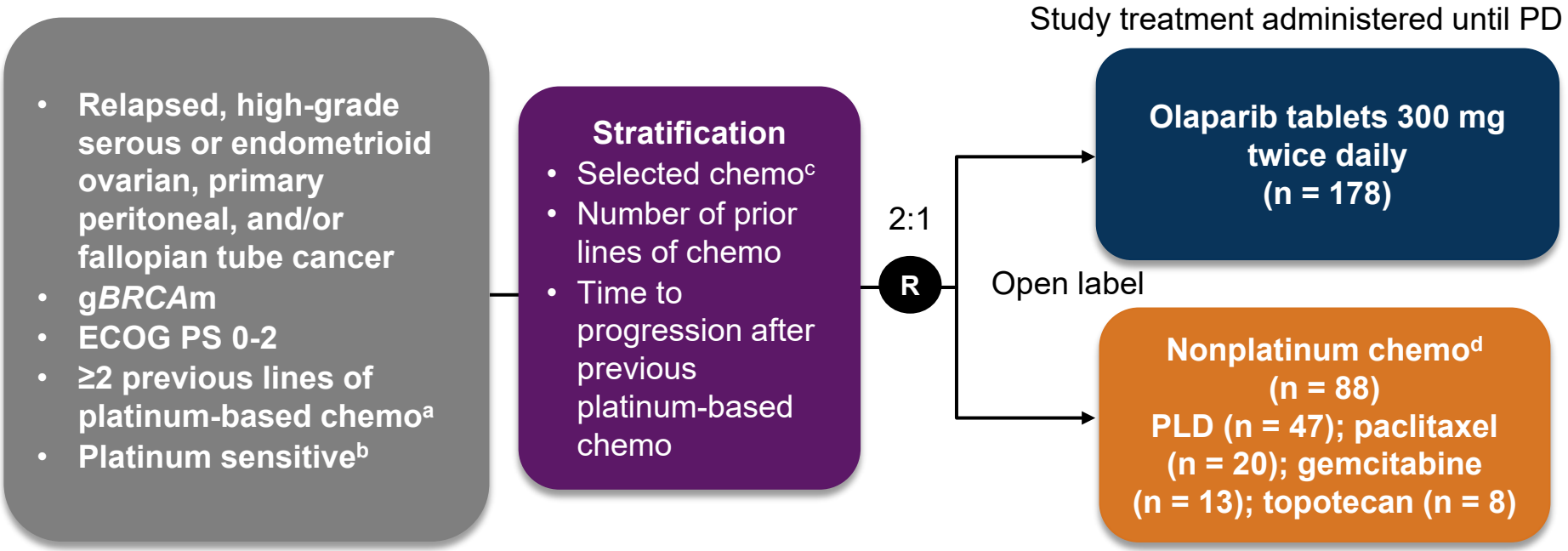
PARP Inhibitors in Recurrent Ovarian Cancer (Treatment Instead of Chemotherapy)

Study	Study 1[1] (N = 137)	ARIEL2/Study 10[2] *BRCA*mut (N = 106)	QUADRA[3] g*BRCA*mut (N = 63)	QUADRA[3] HRD+ (*BRCA*wt)/ (platinum sensitive) (N = 35)
Agent	Olaparib	Rucaparib	Niraparib	Niraparib
ORR	34% (95% CI, 26-42)	54% (95% CI, 44-64)	39% (platinum sensitive) (95% CI, 17-64) 29% (platinum resistant) (95% CI, 11-52) 19% (platinum refractory) (95% CI, 4-46)	20% (95% CI, 8-37)
DOR	7.9 mo (95% CI, 5.6-9.6)	9.2 mo (95% CI, 6.6-11.6)	8.3 (6.5-NR) (entire population)	8.3 (6.5-NR) (entire population)
LOT	≥3	≥2	≥3	≥3

*BRCA*m, *BRCA* mutated; BRCAwt, *BRCA* wild type; g*BRCA*m, germline *BRCA*-mutated; DOR, duration of response; LOT, lines of therapy; ORR, objective response rate; PARP, poly ADP-ribose polymerase.

1. Domchek SM et al. *Gynecol Oncol*. 2016;140:199-203. 2. Oza AM et al. *Gynecol Oncol*. 2017;12:267-275. 3. Moore KN et al. *Lancet Oncol*. 2019;20:636-648.

SOLO-3: Olaparib vs Nonplatinum Chemotherapy in g*BRCA1/2*m Platinum-Sensitive Relapsed Ovarian Cancer[1]

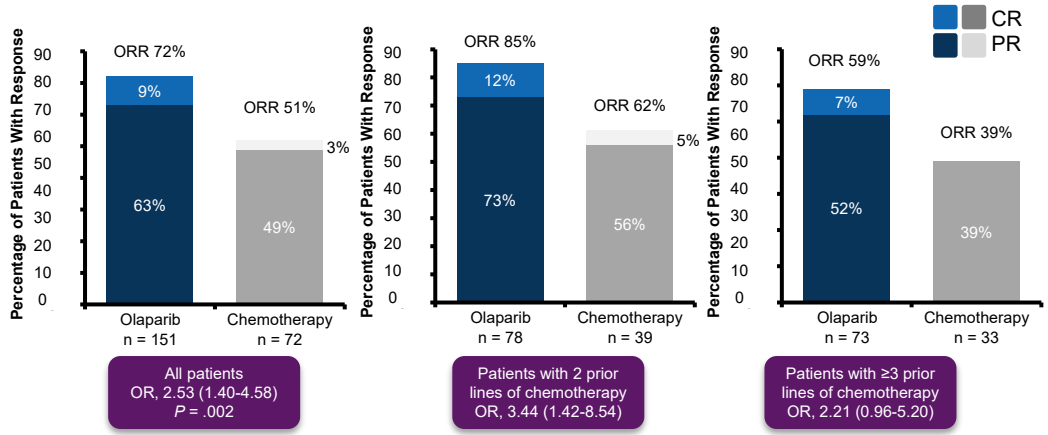


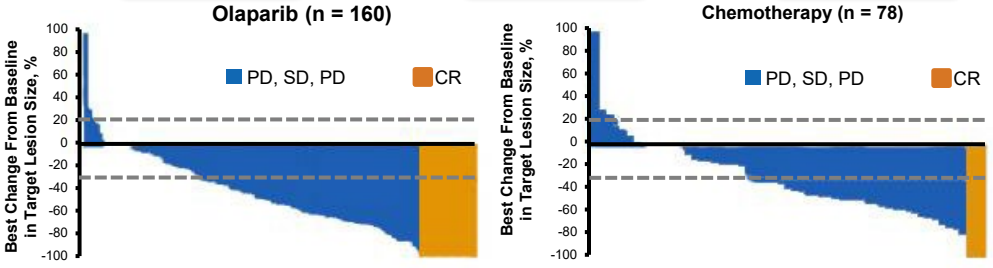
ECOG-PS, Eastern Cooperative Oncology Group performance status; g*BRCA*m, germline *BRCA*-mutated; PD, progressive disease.

[a] Prior treatment with a PARP inhibitor was not permitted. [b] Fully platinum sensitive: progression >12 mo after platinum-based chemo; partially platinum sensitive, progression 6-12 mo after platinum-based chemo. [c] For each patient, the investigator declared their choice of nonplatinum chemo before randomization. [d] PLD, 50 mg/m^2 on d 1 Q4W; paclitaxel, 80 mg/m^2 on d 1, 8, 15, and 22 Q4W; gemcitabine 1,000 mg/m^2 on d 1, 8, and 15 Q4W; topotecan, 4 mg/m^2 on d 1, 8, 15 Q4W.

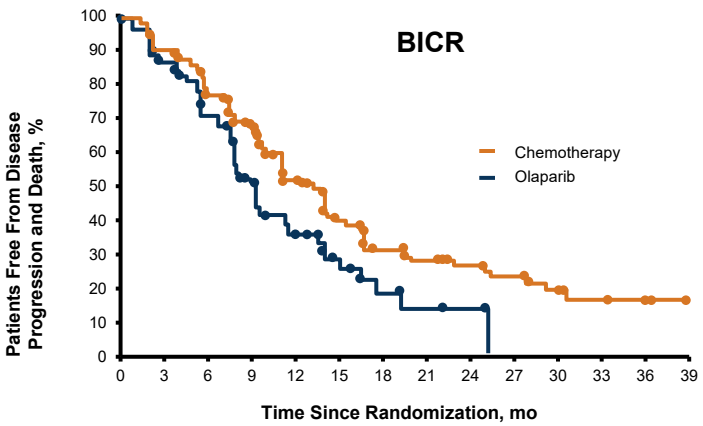
1. Penson RT et al. *J Clin Oncol*. 2020;38:1164-1174.

Efficacy Endpoints for SOLO-3: Primary Endpoint Is ORR[1]





	CR, n	PR, n	SD, n	PD, n	NE, n
Olaparib	21	83	39	6	11
PLD, n = 44	3	23	11	0	7
Paclitaxel, n = 17	0	5	7	2	3
Gemcitabine, n = 10	0	1	4	0	5
Topotecan, n = 7	0	1	1	1	4

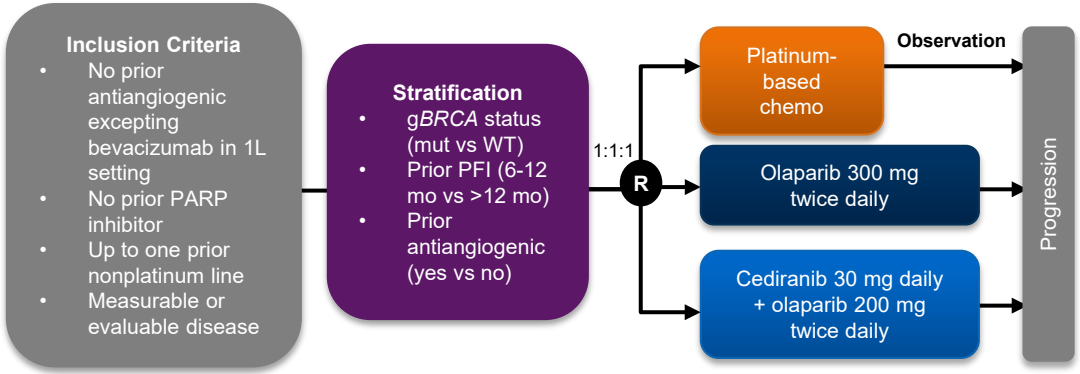


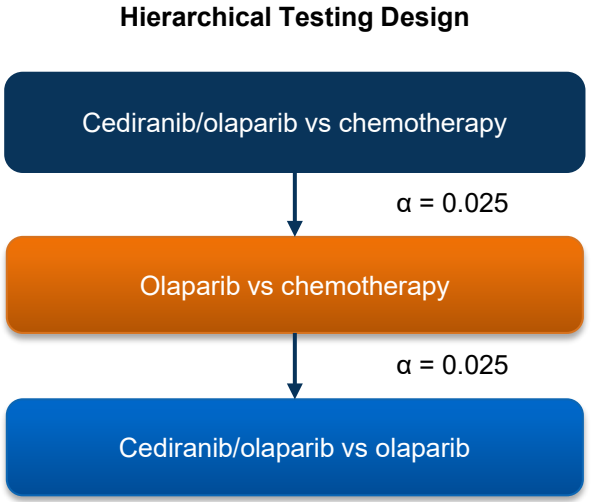
No. at Risk														
Olaparib	178	156	126	108	71	47	30	25	18	14	8	5	2	0
Chemotherapy	88	63	47	31	18	9	5	3	2	0	0	0	0	0

	Olaparib (n = 178)	Chemotherapy (n = 88)
PFS Events, n (%)	110 (62)	49 (56)
Median PFS, mo	13.4	9.2
	P = .013	
	HR = 0.62 (95% CI, 0.43-0.91)	

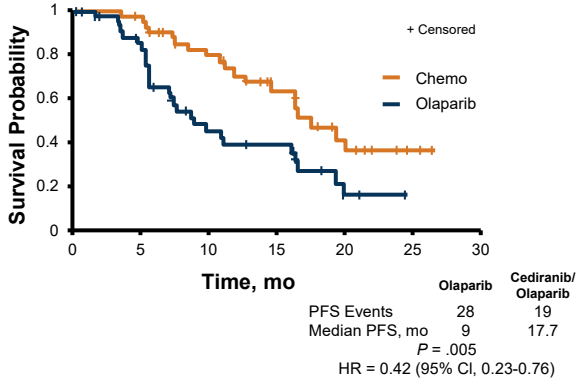
BICR, blinded independent central review; CR, complete response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease. 1. Penson RT et al. ASCO 2019. Abstract 5506.

GY004: A Phase 3 Study Comparing Olaparib or Cediranib + Olaparib to Standard Platinum-Based Chemotherapy in Recurrent Platinum-Sensitive Ovarian Cancer[1]





- **Platinum-sensitive ovarian cancer (PSOC)**
  - Platinum-free interval (PFI) > 6 mo
  - Standard of care: platinum-based doublet ± bevacizumab or ± PARPi maintenence
  - Median PFS 8.4 to 13.8 mo in phase 3 trials
- **Complications of repeated platinum**
  - Increased risk of carboplatin allergy
  - Exacerbation of neuropathy (with paclitaxel)
  - Cumulative hematologic toxicity
- **Cediranib + olaparib with 17.7 mo median PFS in phase 2 trial**
  - Toxicities: fatigue, hypertension, diarrhea



	Olaparib	Cediranib/ Olaparib
PFS Events	28	19
Median PFS, mo	9	17.7

P = .005
HR = 0.42 (95% CI, 0.23-0.76)

gBRCA, germline *BRCA;*PARPi, poly ADP-ribose polymerase inhibitor; PFS, progression-free survival. 1. Liu JF et al. ASCO 2020. Abstract 6003.

2020 ASCO Guidelines for Genetic Testing in Epithelial Ovarian Cancer[1]

Germline testing for *BRCA1*, *BRCA2*, and other ovarian cancer susceptibility genes is recommended for all women with epithelial ovarian cancer, regardless of their clinical features or family history

Somatic tumor testing for both *BRCA1* and *BRCA2* pathogenic or likely pathogenic variants is recommended for women without a germline pathogenic or likely pathogenic *BRCA1/2* variant

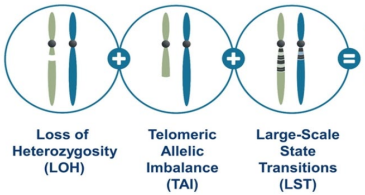
Testing for germline mutations is recommended at the time of disease diagnosis or as soon as possible

BRCA1, breast cancer 1; *BRCA2*, breast cancer 2.

1. Konstantinopoulos PA et al. *J Clin Oncol*. 2020;38:1222-1245.

Tissue Test for Homologous Recombination Deficiency (HRD) and Proficiency (HRP)[1,2]

- Next generation sequencing of DNA from tumor tissue (myChoice Test)
- Provides a score based on algorithmic measurement of 3 tumor factors:
  - Loss of heterozygosity (LOH)
  - Telomeric allelic imbalance (TAI)
  - Large-scale state transitions (LST)

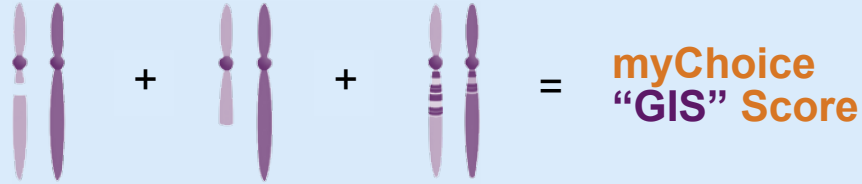


- Homologous recombination status is determined by the following:
  - HR-deficient tumors: tissue test score ≥42 **OR** a *BRCA* mutation
  - HR-proficient tumors: tissue test score <42
  - HR not determined

1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6265286. 2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4308910.

Direct HRD/LOH Assays[1,a]

myChoice
(CDx olaparib, niraparib, veliparib)



Homologous recombination status is determined by Genomic Instability Score:

- **HR-deficient tumors:** tissue GIS ≥42 **OR** a *BRCA*m
- **HR-proficient tumors:** tissue GIS <42
- HR not determined

FoundationOne LOH
(CDx rucaparib)

Loss of heterozygosity (LOH)

Indirect HRD/LOH

Deleterious alteration in HRD genes

- Germline or somatic (eg, *BRCA*m by definition is HRD)

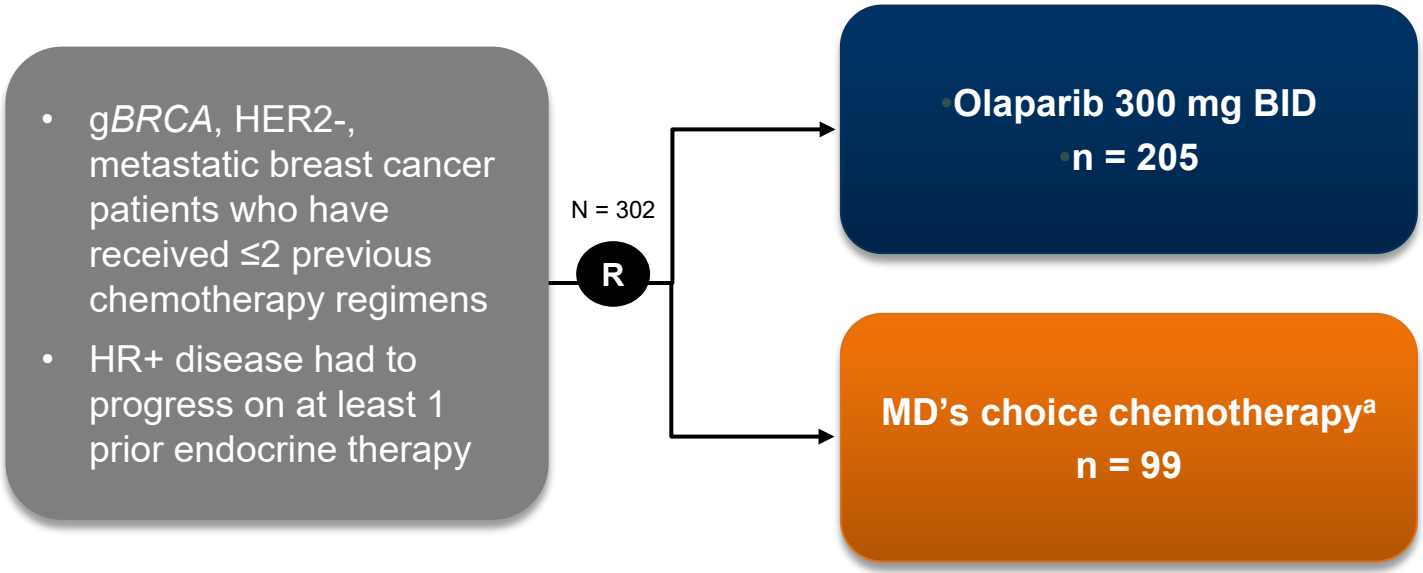
*BRCA*m, *BRCA* mutated; HRD, homologous recombination deficiency.

[a] Tests have not been compared head to head. Paired with development of respective drugs.

1. https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm.

Role of PARP Inhibitors in Breast Cancers

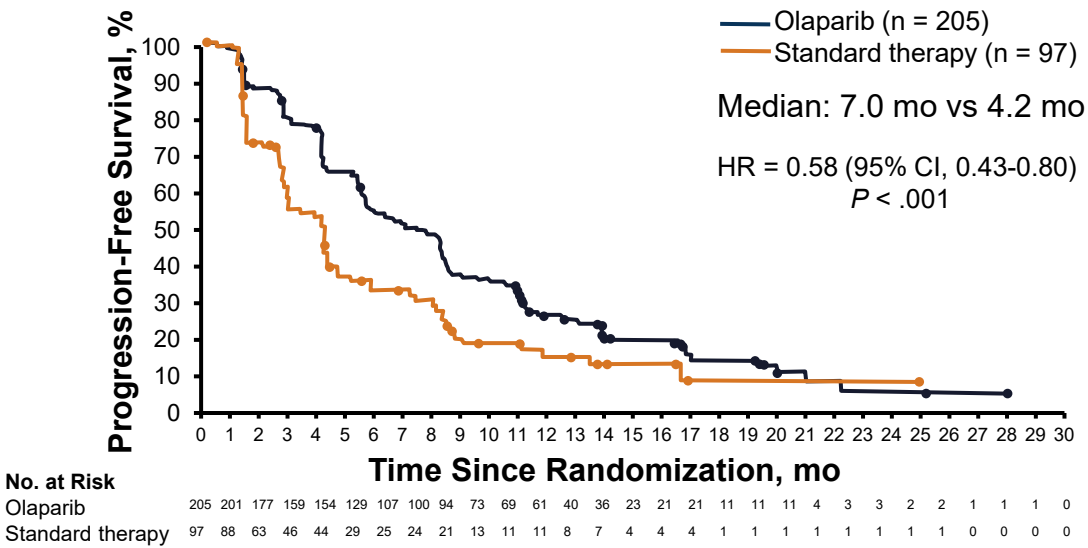
New Indication in Breast Cancer
Olaparib in g*BRCA*m mBC: The OlympiAD Trial[1]



Primary endpoint: PFS (blinded central review)
Secondary endpoints: Safety, OS, time from randomization to second progression after first progression, ORR, and HRQOL scores

g*BRCA*m, germline *BRCA*-mutated; HRQOL, health-related quality of life; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
[a] Capecitabine, eribulin, or vinorelbine.
1. Robson M et al. *N Engl J Med*. 2017;377:523-533.

The Phase 3 OlympiAD Trial: PFS With Olaparib Monotherapy[1]



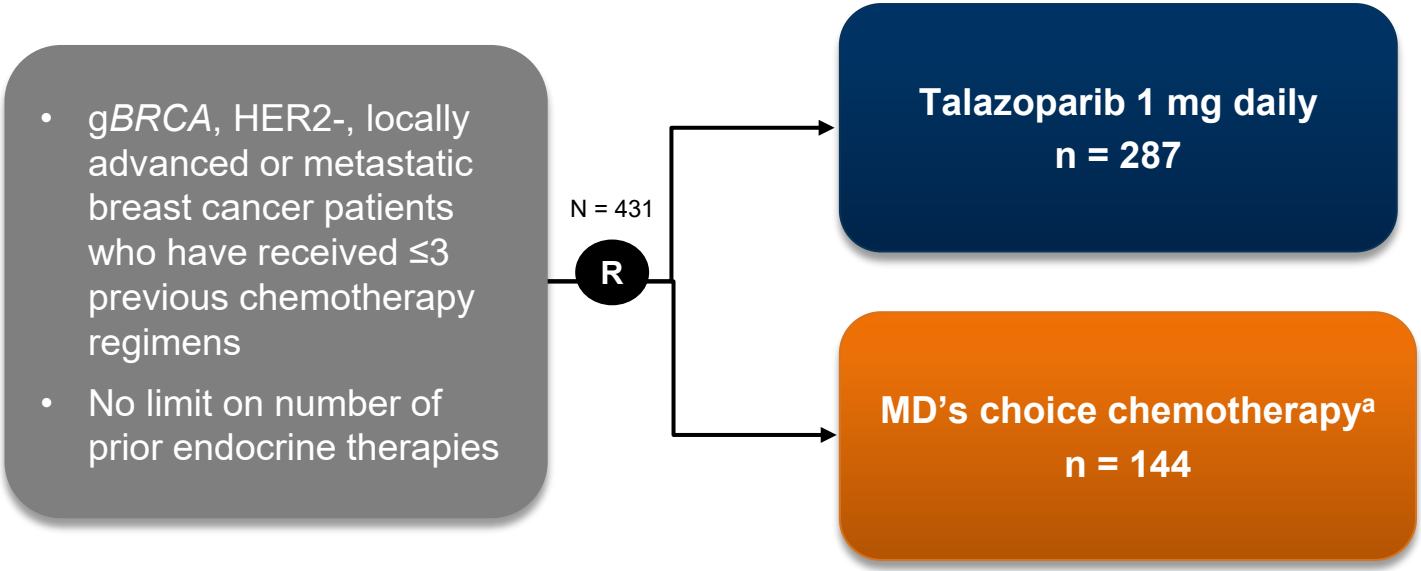
FDA Approval: Olaparib in Breast Cancer (January 12, 2018)

- For the treatment of adult patients with deleterious or suspected deleterious g*BRCA*mut, HER2- metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting
- Patients with HR-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy

g*BRCA*mut, germline *BRCA*-mutated; PFS, progression-free survival.

1. Robson M et al. *N Engl J Med*.2017;377:523-533.

New Indication in Breast Cancer: Talazoparib in g*BRCA*m, mBC or LABC: The EMBRACA Trial[1]



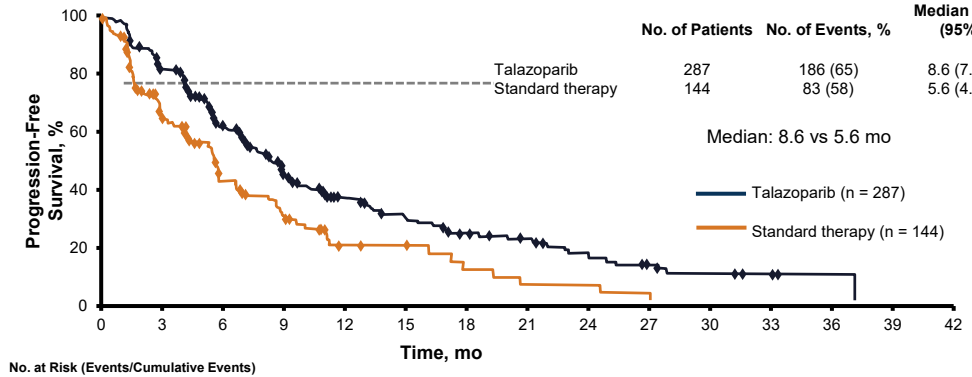
- **Primary endpoint:** PFS (blinded central review)
- **Secondary endpoints:** OS, ORR, CBR24, safety

g*BRCA*m, germline *BRCA*-mutated; LABC, locally advanced breast cancer; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

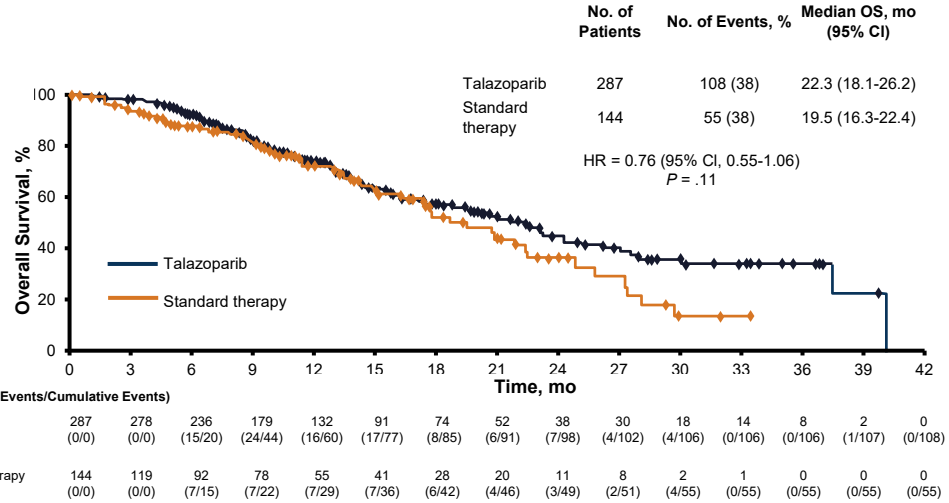
[a] Capecitabine, eribulin, vinorelbine, or gemcitabine.

1. Litton JK et al. *N Engl J Med.* 2018;379:753-763.

The Phase 3 EMBRACA Trial: PFS With Talazoparib Monotherapy[1]



No. of events: 186 (65%) vs 83 (58%)
HR for progression or death, 0.54 (95% CI, 0.41-0.71)
P < .001



OS, overall survival; PFS, progression-free survival.

1. Litton JK et al. *N Engl J Med.* 2018;379:753-763.

Differences in Metabolism and Drug-Drug Interaction

PARP Inhibitor	CYP Enzymes Used for Metabolism	Drug-Drug Interactions	Effect on Cell Transporters
Olaparlb[1]	• CYP3A4 • Reduce dosage if strong or moderate CYP3A inhibitors are coadministered	• Inhibits CYP3A4 • Induces CYP286	• Inhibits MDR1, BCRP, OATP181, OCT1, OCT2, OAT3, MATE1, MATE2-K • Substrate of P-glycoprotein
Talazoparib[2]	• Minimal hepatic metabolism • Mono-oxidation, dehydrogenation, glucuronlde conjugation	• Substrate of P-gp and BCRP transporters	• No interaction with the major hepatic or renal uptake transporters

- Each drug is uniquely metabolized
- Other drugs that patients are taking may influence PARP inhibitor levels
- Drug-drug interactions can occur based on CYP inhibition or induction
- Effect on renal transporter proteins MATE1, MATE2-K, and OCT1/2 can increase serum creatinine

BCRP, breast cancer resistance protein; MATE1, multidrug and toxin extrusion protein 1; MATE2-K, multidrug and toxin extrusion protein 2; MDR1, multidrug resistance mutation; OAT3, organic anion transporter 3; OCT1, organic cation transporter 1; OCT2, organic cation transporter 2; PARP, poly ADP-ribose polymerase.

1. Lynparza (olaparib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208558s001lbl.pdf.
2. Talzenna (talazoparib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211651s000lbl.pdf.

NCCN Genetic Testing Guidelines: Breast Cancer[1]

Personal History of Cancer

- Breast cancer with at least one of the following:
  - Diagnosed at age ≤45 y
  - Diagnosed at age 46-50 y with:
    - Unknown or limited family history
    - A second breast cancer diagnosed at any age
    - ≥1 close blood relative with breast, ovarian, pancreatic, or high-grade (Gleason score ≥7) or intraductal prostate cancer at any age
  - Diagnosed at age ≤60 y with triple-negative breast cancer
  - Bilateral breast cancer, first diagnosed between the ages of 50 and 65 y
  - Diagnosed at any age with:
    - Ashkenazi Jewish ancestry
    - ≥1 close blood relative with breast cancer at age ≤50 y or ovarian, pancreatic, or metastatic or intraductal prostate cancer at any age
    - ≥3 total diagnoses of breast cancer in patient and/or close blood relatives
  - Diagnosed at any age with male breast cancer

NCCN, National Comprehensive Cancer Network.

1. NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High Risk Assessment: Breast, Ovarian, and Pancreatic. Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf.

NCCN Genetic Testing Guidelines: Breast Cancer[1] (Cont'd)

Family History of Cancer

- An affected or unaffected individual with a first- or second-degree blood relative meeting any of the criteria listed in previous slide (except individuals who meet criteria only for systemic therapy decision-making)

- An affected or unaffected individual who otherwise does not meet the criteria in previous slide but has a probability >5% of a *BRCA1/2* pathogenic variant based on prior probability models

BRCA1/2, breast cancer 1/2; NCCN, National Comprehensive Cancer Network.

1. NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High Risk Assessment: Breast, Ovarian, and Pancreatic. Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf.

Role of PARP Inhibitors in Pancreatic Cancers

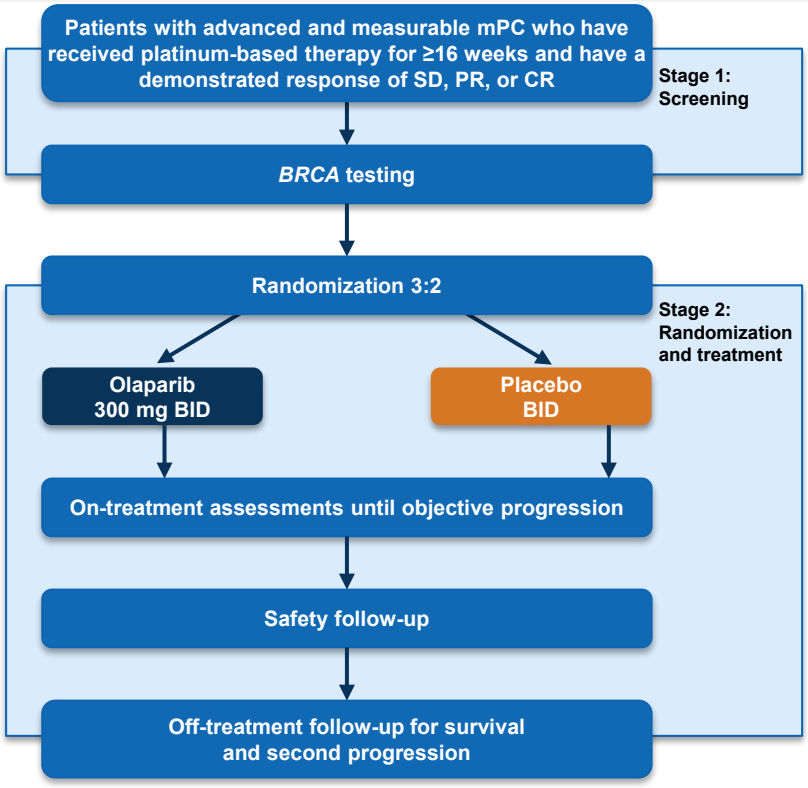
NCCN Genetic Testing Guidelines: Exocrine Pancreatic Cancer[1]

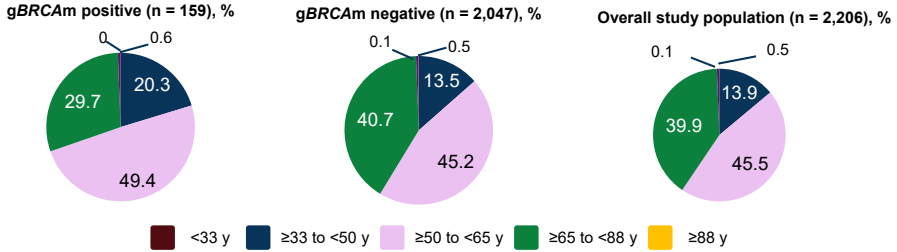
- Recommend genetic counseling and germline testing for:
  - Exocrine pancreatic cancer at any age
  - First-degree relatives of individuals diagnosed with exocrine pancreatic cancer
- ***ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, EPCAM, PALB2, STK11, TP53***
- Consider pancreatic cancer screening beginning at age 50 (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier)

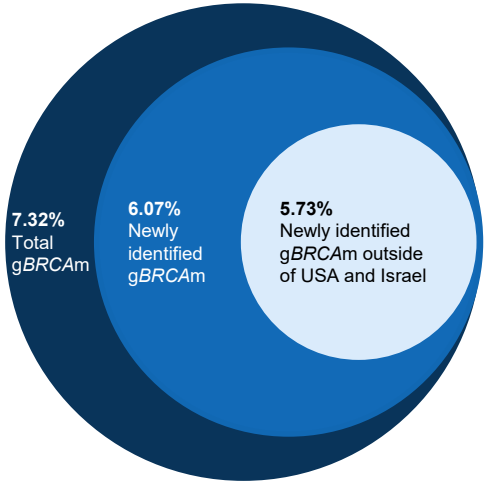
BRCA1, breast cancer 1; *BRCA2*, breast cancer 2; *CDKN2A*, cyclin-dependent kinase inhibitor 2A; *EPCAM*, epithelial cell adhesion molecule; *MLH1*, MutL homolog 1; *MSH2*, MutS homolog 2; *MSH6*, MutS homolog 6; NCCN, National Comprehensive Cancer Network; *PALB2*, partner and localizer of BRCA2; *STK11*, serine/threonine kinase 11; *TP53*, tumor protein 53.

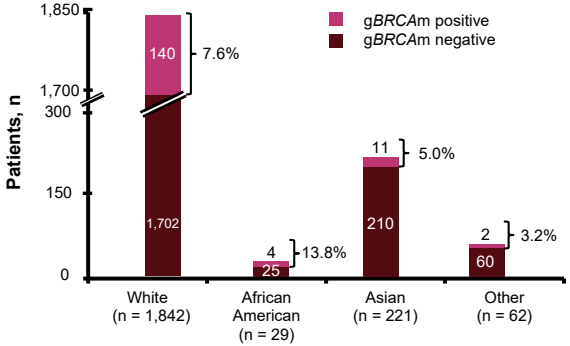
1. NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High Risk Assessment: Breast, Ovarian, and Pancreatic. Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf.

POLO: A Randomized Phase 3 Trial of Olaparib Maintenance Monotherapy in Metastatic Pancreatic Cancer Who Have a Germline *BRCA1/2* Mutation[1,2]





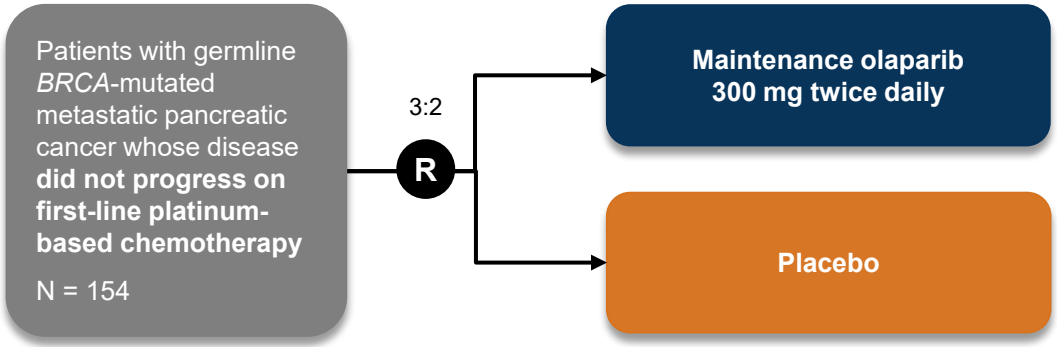




BID, twice a day; *BRCA1/2*, breast cancer 1/2; CR, complete response; g*BRCA*m, germline *BRCA*-mutated; mPC, metastatic pancreatic cancer; PR, partial response; SD, stable disease.

1. Golan T et al. *J Clin Oncol.* 2016;suppl 34:abstr TPS4152. 2. Golan T et al. *J Clin Oncol.* 2018;suppl 36:abstr 4115.

Phase 3 POLO Trial: Olaparib as Frontline Maintenance[1-3]



Efficacy Results (BICR): POLO

	Olaparib (n = 92)	Placebo (n = 62)
PFS		
No. of events (%)[a]	60 (65)	44 (71)
Median, mo	7.4 (4.1-11.0)	3.8 (3.5-4.9)
HR (95% CI)[b]	0.53 (0.35-0.81)	
P	.0035	
Patients with measurable disease, n	78	52
ORR, % (95% CI)	23 (14-34)	12 (4-23)
CR, n (%)	2 (2.6)	0
PR, n (%)	16 (21)	6 (12)
Duration of response		
Median, mo (95% CI)	25 (15-NE)	4 (2-NE)

BICR, blinded independent central review; CR, complete response; NE, not evaluable; ORR, objective response rate; PFS, progression-free survival; PR, partial response.
[a] Number of events: progression, olaparib 55, placebo 44; death before BICR-documented progression, olaparib 5, placebo 0. [b] HR, 95% CI, and *P* calculated from a log-rank test; HR <1 favors olaparib.

1. Golan T et al. *N Engl J Med*. 2019;381:317-327. 2. Kindler H et al. ASCO 2019. Abstract LBA4. 3. Golan T et al. *N Engl J Med*. 2019;381:317-327.

FDA Approval: Olaparib in Pancreatic Cancer (December 30, 2019)[1]

For the maintenance treatment of adult patients with deleterious or suspected deleterious g*BRCA*mut metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen

Select patients for therapy based on an FDA-approved companion diagnostic for olaparib

g*BRCA*mut, germline *BRCA*-mutated.

1. Lynparza (olaparib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208558s001lbl.pdf.

Role of PARP Inhibitors in Prostate Cancers

NCCN Genetic Testing Guidelines: Prostate Cancer[1]

- Metastatic or intraductal prostate cancer at any age
- High-grade (Gleason score ≥7) prostate cancer with:
  - Ashkenazi Jewish ancestry; ***OR***
  - ≥1 close relative with breast cancer at age ≤50 y or ovarian, pancreatic, or metastatic or intraductal prostate cancer at any age; ***OR***
  - ≥2 close relatives with breast or prostate cancer (any grade) at any age
- US/UK multisite study: 5.3% of metastatic prostate cancer patients had *BRCA2* mutation and 0.9% had *BRCA1* mutation[2]

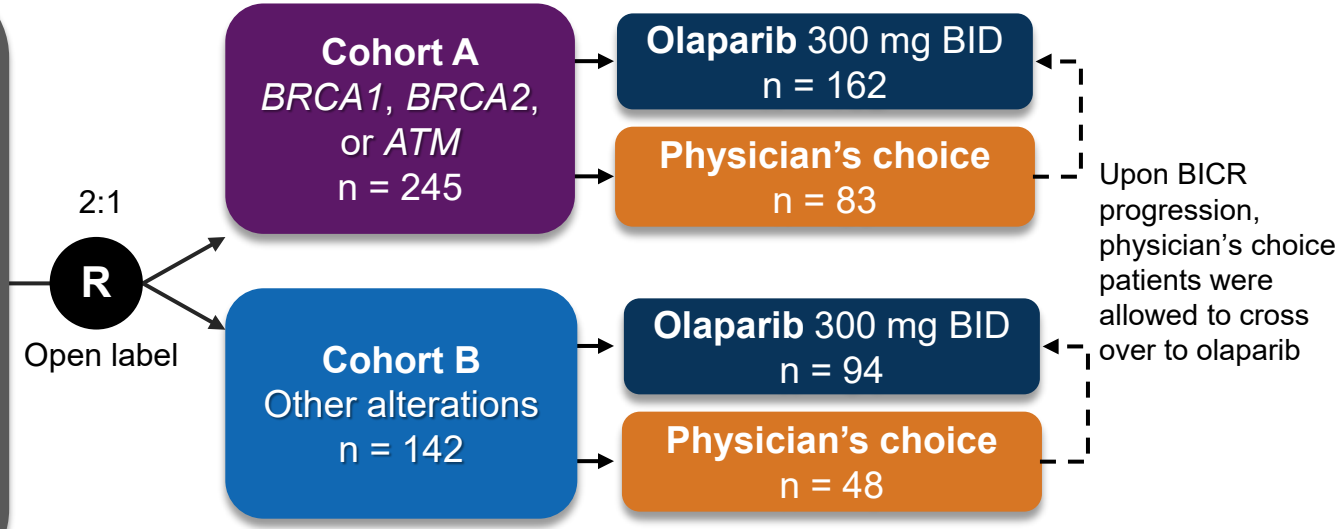
BRCA1, breast cancer 1; *BRCA2*, breast cancer 2; NCCN, National Comprehensive Cancer Network.

1. NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High Risk Assessment: Breast, Ovarian, and Pancreatic. Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf. 2. Pritchard CC et al. *N Engl J Med*. 2016;375:443-453.

PROfound: Study Design[1]

Key Eligibility Criteria
- mCRPC with disease progression on prior NHA (eg, abiraterone or enzalutamide)
- Alterations in ≥1 of any qualifying gene with a direct or indirect role in HRR

Stratification Factors
- Previous taxane
- Measureable disease

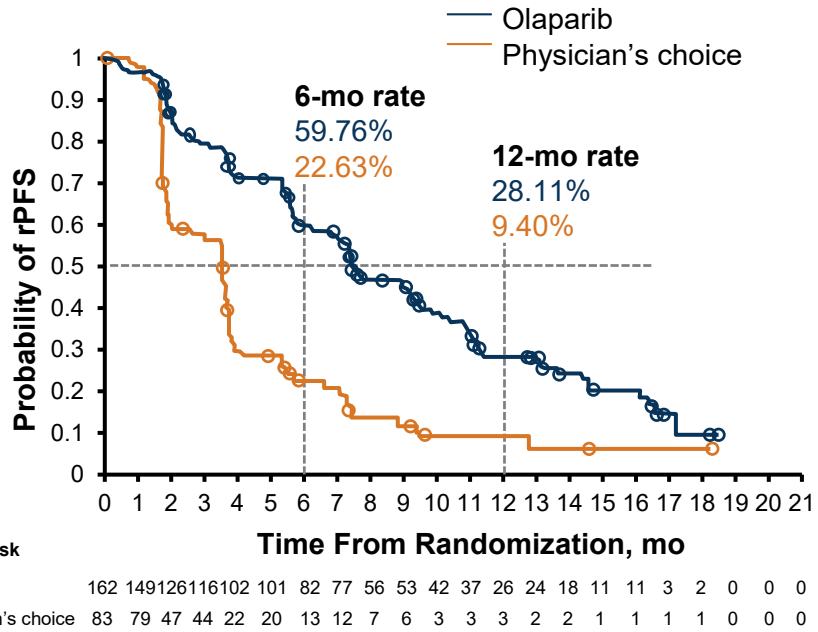


- **Primary endpoint:** rPFS in cohort A (RECIST 1.1 and PCWG3 by BICR)
- **Key secondary endpoints:** rPFS (cohorts A+B); confirmed radiographic ORR in cohort A; time to pain progression in cohort A; OS in cohort A

BICR, blinded independent central review; *BRCA1*, breast cancer 1; *BRCA2*, breast cancer 2; HRR, homologous recombination repair; mCRPC, metastatic castrate-resistant prostate cancer. 1. de Bono J et al. *N Engl J Med*. 2020;382:2091-2102.

PROfound Primary Endpoint: rPFS (Cohort A)[1,2]

rPFS by BICR in Patients With Alterations in *BRCA1*, *BRCA2*, or *ATM* (Cohort A)



	Olaparib (n = 162)	Physician's Choice (n = 83)
Events, %	106 (65.4)	68 (81.9)
Median PFS, mo	7.39	3.55
HR (95% CI)	0.34 (0.25-0.47) *P* < .001	

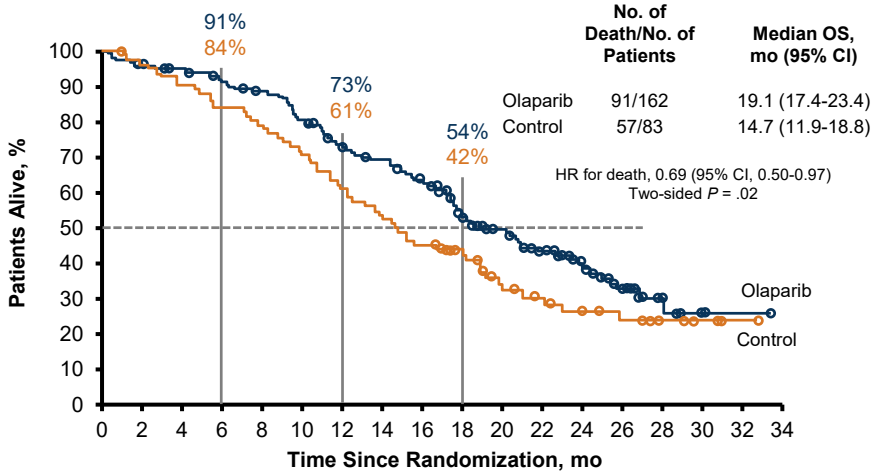
NCT02987543
Prespecified sensitivity analysis based on investigator assessment:
HR = 0.24 (95% CI, 0.17-0.34); *P* < .0001

BRCA1, breast cancer 1; *BRCA2*, breast cancer 2; PFS, progression-free survival; rPFS, radiographic progression-free survival.

1. Hussain M et al. ESMO 2019. Abstract LBA12_PR. 2. de Bono J et al. *N Engl J Med.* 2020;382:2091-2102.

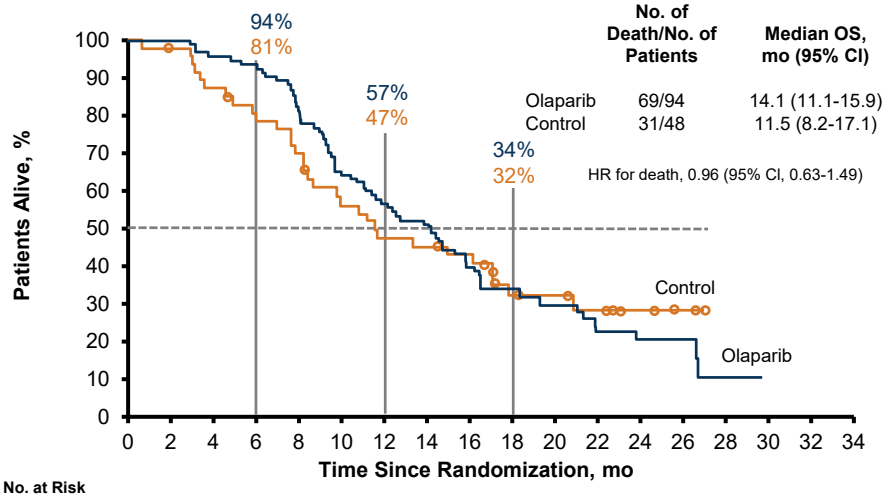
PROfound: OS (Cohorts A and B)[1]

Overall Survival in Cohort A



No. at Risk																		
Olaparib	162	155	150	142	136	124	107	101	91	71	56	44	30	18	6	2	1	0
Control	83	79	74	69	64	58	50	43	37	27	18	15	11	9	6	3	1	0

Overall Survival in Cohort B



No. at Risk																		
Olaparib	94	94	90	86	73	58	50	45	35	25	17	12	9	4	1	0	0	0
Control	48	46	41	37	32	25	21	20	18	10	9	7	4	2	0	0	0	0

OS, overall survival.

1. Hussain M et al. *New Engl J Med*. 2020 Sept 20. [Epub ahead of print].

FDA Approval: Olaparib for mCRPC

In May 2020, based on data from the PROfound study, the FDA approved olaparib for the treatment of patients with pathogenic germline or somatic HRR[a] gene-mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone[1,b]

HRR, homologous recombination repair; mCRPC, metastatic castrate-resistant prostate cancer.

[a] *BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L.* [b] Select patients for therapy based on two FDA-approved companion diagnostic tests: BRACAnalysis CDx and FoundationOne CDx.

1. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-olaparib-hrr-gene-mutated-metastatic-castration-resistant-prostate-cancer.

TRITON2: Phase 2 Study of Rucaparib in mCRPC With HRR Aberrations—Study Design[1]

Screening

Identification of a deleterious somatic or germline alteration in HRR gene[a]

HRR Genes
BRCA1, BARD1, FANCA, RAD51B, BRCA2, BRIP1, NBN, RAD51C, ATM, CDK12, PALB2, RAD51D, CHEK2, RAD51, RAD54L

Key Eligibility Criteria

- mCRPC
- Deleterious somatic or germline alteration in HRR gene
- Progression on AR-directed therapy and 1 prior taxane-based chemotherapy for CRPC
- ECOG-PS 0 or 1
- No prior PARP inhibitor, mitoxantrone, cyclophosphamide, or platinum-based chemotherapy

Treatment (28-d Cycles)

Rucaparib 600 mg BID

- Tumor assessments Q8W for 24 wk, then Q12W
- PSA assessments Q4W

Treatment until radiographic progression or discontinuation for other reason

- **Primary endpoints:** Confirmed ORR per modified RECIST/PCWG3 by central assessment (patients with measurable disease at baseline), confirmed PSA response (≥50% decrease) rate (patients with no measurable disease at baseline)

BARD1, BRCA1-associated RING domain 1; *BRCA1*, breast cancer 1; *BRCA2*, breast cancer 2; *BRIP1*, BRCA1 interacting protein C-terminal helicase 1; *CDK12*, cyclin-dependent kinase 12; *CHEK2*, checkpoint kinase 2; ECOG-PS, Eastern Cooperative Oncology Group performance status; *FANCA*, Fanconi anemia complementation group A; HRR, homologous recombination repair; mCRPC, metastatic castrate-resistant prostate cancer; *NBN*, nibrin; ORR, objective response rate; *PALB2*, partner and localizer of BRCA2; PARP, poly ADP-ribose polymerase; PCWG3, Prostate Cancer Working Group 3; PSA, prostate-specific antigen; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; RECIST, Response Evaluation Criteria in Solid Tumors. [a] Alterations detected by local testing or central testing of blood or tumor samples. Deleterious alterations were defined as protein-truncating mutations, large protein-truncating rearrangements, splice site mutations, deleterious missense mutations, and homozygous deletions.

1. Abida W et al. *Annals Oncol*. 2018:29(Suppl 8):viii271-viii302.

TRITON2: Phase 2 Study of Rucaparib in mCRPC With HRR Aberrations—ORR[1]

Characteristic	By HRR Gene With Alteration				
	BRCA1/2 (n = 57)	*ATM* (n = 21)	*CDK12* (n = 9)	*CHEK2* (n = 5)	Other (n = 13)
ORR, n (%)[a]	25 (43.9)	2 (9.5)	0	0	5 (38.5)
CR, n (%)	3 (5.3)	0	0	0	1 (7.7)[b]
PR, n (%)	22 (38.6)	2 (9.5)	0	0	4 (30.8)[c]
SD, n (%)	26 (45.6)	10 (47.6)	5 (55.6)	3 (60.0)	6 (46.2)
PD, n (%)	5 (8.8)	8 (38.1)	3 (33.3)	2 (40.0)	1 (7.7)
NE, n (%)	1 (1.8)	1 (4.8)	1 (11.1)	0	1 (7.7)
Confirmed PSA response rate (all evaluable patients)	51/98 (52%)	2/57 (3.5%)	1/14 (7.1%)	1/7 (14.3%)	5/14 (35.7%)

- **43.9% confirmed objective responses were reported in 57 patients with *BRCA1/2* mutation**
- **52.0% confirmed PSA response in 98 PSA-evaluable patients with *BRCA1/2* mutation**

BRCA1/2, breast cancer 1/2; *CDK12*, cyclin-dependent kinase 12; *CHEK2*, checkpoint kinase 2; CR, complete response; HRR, homologous recombination repair; mCRPC, metastatic castrate-resistant prostate cancer; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; PSA, prostate-specific antigen; SD, stable disease. [a] Per modified RECIST/PCWG3 criteria. [b] 1 patient had *FANCA* alteration. [c] 2 patients had a *PALB2* alteration; 1 patient each had a *BRIP1* or *RAD51B* alteration. 1. Abida W et al. ESMO 2019. Abstract 846PD.

FDA Approval: Rucaparib for mCRPC

In May 2020, based on data from the TRITON2 study, the FDA granted accelerated approval to rucaparib for the treatment of patients with deleterious *BRCA1/2* (germline and/or somatic)-associated mCRPC who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy[1]

- **The TRITON3 study is underway and recruiting patients with mCRPC and homologous recombination gene deficiency[2]**

BRCA1/2, breast cancer 1/2; mCRPC, metastatic castrate-resistant prostate cancer.

1. https://www.fda.gov/drugs/fda-grants-accelerated-approval-rucaparib-brca-mutated-metastatic-castration-resistant-prostate.
2. https://clinicaltrials.gov/ct2/show/NCT02975934.

Oncology Drug Spend

Drug Spend as a Percentage of PMPY in Commercial Plans[1]

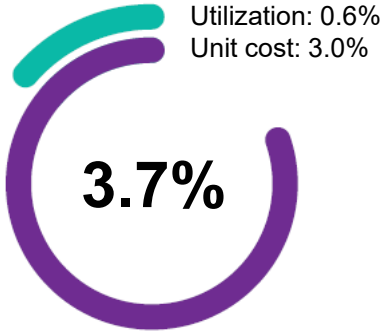
2018 Rank	2017 Rank	Therapeutic Class	PMPY Spend	Trend Components		
				Utilization	Unit Cost	Total
1	1	Inflammatory disease	$189.40	-1.9%	14.8%	12.5%
2	2	Diabetes	$157.39	0.7%	8.9%	9.7%
3	4	Oncology	$72.62	-0.9%	14.2%	13.1%
4	3	Multiple sclerosis	$61.87	-9.6%	4.0%	-6.0%
5	6	Asthma/COPD	$59.31	-0.2%	5.7%	5.5%
6	5	Behavioral health	$58.69	-2.9%	-0.4%	-3.3%
7	7	HIV	$42.61	2.1%	8.9%	11.2%
8	9	Blood disorder	$53.39	1.7%	8.7%	10.5%
9	8	High blood pressure	$31.99	-1.1%	-3.8%	-4.9%
10	11	Seizures	$26.58	-0.7%	7.3%	6.5%
		Other therapeutic classes	$342.77	-3.5%	-3.6%	-6.9%
		Total	**$1,078.63**	**-1.5%**	**3.0%**	**1.5%**

COPD, chronic obstructive pulmonary disease; PMPY, per member per year.

1. MedImpact 2018 Annual Drug Trend Report. Courtesy of Kristi Jhangiani, PharmD, BCPS.

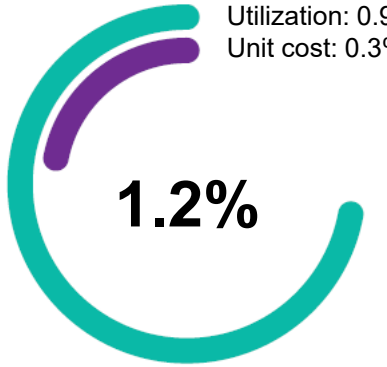
MedImpact 2019 Annual Drug Trend Report[1,a]

Commercial



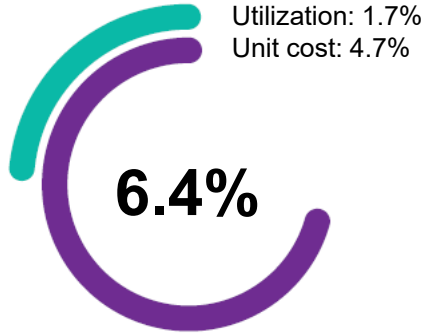
Drug	Utilization	Unit Cost	Total
Traditional	0.6%	0.3%	0.9%
Specialty	5.1%	4.4%	9.5%
Overall	0.6%	3.0%	3.7%

Medicare



Drug	Utilization	Unit Cost	Total
Traditional	0.9%	-1.7%	-0.8%
Specialty	4.0%	1.9%	5.9%
Overall	0.9%	0.3%	1.2%

Medicaid



Drug	Utilization	Unit Cost	Total
Traditional	1.7%	0.5%	2.2%
Specialty	4.5%	7.7%	12.2%
Overall	1.7%	4.7%	6.4%

[a] All cost analyses are compiled net of rebate and measured on a PMPY (per member per year) basis.

1. MedImpact 2019 Annual Drug Trend Report. Courtesy of Kristi Jhangiani, PharmD, BCPS.

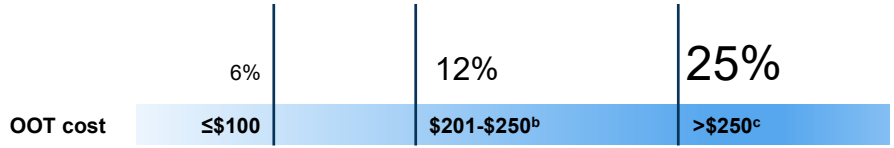
Drivers of Oncology Cost

- New oncology agents are more effective
- Expanding indications are contributing to increase utilization
- Tolerability of new oncology agents is improved
- Products are taken for longer time periods
- Increased cost to patients with larger out-of-pocket amounts, including deductibles, copays, and coinsurance

Nonadherence to Oncology Drugs[1,a]

- Cancer: patients are less likely to start therapy when faced with high out-of-pocket costs
- 1 in 10 patients failed to initiate therapy with a newly prescribed oral cancer agent

Rate of drug abandonment: newly prescribed oral cancer agent



Despite potential benefits, rates of adherence to specialty drugs are suboptimal

- Nonadherence rate for oral cancer drugs is 38%
- Poor adherence to cancer drugs leads to higher direct medical cost

[a] Cost-sharing values depicted above represent values associated with a significant increase in drug abandonment. [b] $P = .04$. [c] $P < .001$ versus ≤$100. Study examined data from a national pharmacy claims database for 10,508 patients with prescription for oral cancer agents between 2007 and 2009. Cost sharing and abandonment of newly initiated oral cancer therapy were examined for 8 oral agents: capecitabine, erlotinib, imatinib, lapatinib, lenalidomide, sorafenib, sunitinib, and temozolomide.

1. Streeter SB et al. *J Oncol Pract*. 2011;7:46s-51s.

Oncology Value Frameworks

AMCP Value Frameworks Position

- AMCP supports the use of frameworks for determining value
- Must be based on sound scientific evidence and economic models
- Combine with formulary reviews
- AMCP Formulary Submissions (Format) is a resource that provides a well-established, evidence-based framework approach to facilitate discussions on therapeutic appropriateness

AMCP, Academy of Managed Care Pharmacy.

Oncology Value Frameworks: Emphasis[1]

	ASCO	NCCN	MSKCC	ICER	ESMO
Application					
Target stakeholder	Patient physician	Patient physician	Physician policymaker	Payer policymaker	Payer policymaker
Conditions addressed	Oncology: solid, blood	Oncology: solid, blood, radiology, surgery	Oncology: solid, blood	All conditions: focus on new drugs or high impact	Oncology: solid, blood, radiology, surgery
Combination therapy evaluation	Yes	Yes	No	Yes	Yes
Clinical trial data					
Breadth of evidence	1 trial, RCT	Published data, panel members' clinical experience, case reports	1 trial, registration trial of first indication (FDA label)	RCT meta-analysis and manufacturer-provided data	1 trial, RCT, comparative outcomes study, meta-analysis
Trial sample size accounted	No	Yes	Yes	Yes	Indirectly, through lower bound of 95% CI
Allows for single-arm trials	Partially	Likely	Yes	Yes	No
Acknowledges trial contamination	No	Likely	No	Yes	Yes
Accounts for patient preference	No	Yes	Yes	No	No
Readout					
Outcomes	Net heath benefit score	Evidence blocks scores	DrugAbacus price	Cost-effectiveness; budget impact	ESMO MCBS
Cost/price	Price (WAC or ASP+) per month or course of therapy	Affordability scale	Abacus price per month or course of therapy	Cost per year	Not specified, left to payers to evaluate

ASCO, American Society of Clinical Oncology; ASP, average sales price; ESMO MCBS, European Society for Medical Oncology Magnitude of Clinical Benefit Scale; ICER, Institute for Clinical and Economic Review; MSKCC, Memorial Sloan Kettering Cancer Center; NCCN, National Comprehensive Cancer Network; RCT, randomized controlled trial; WAC, wholesale acquisition cost. 1. Slomiany M et al. *Am Health Drug Benefits*. 2017;10:253-260.

Oncology Value Frameworks: Outputs[1]

	ASCO	NCCN	MSKCC	ICER	ESMO
Health benefit	Net health benefit	Score (1-5) for each of 5 key measures displayed as evidence blocks	No	Assessment of care value (high/intermediate/low)	A relative ranking of the magnitude of clinically meaningful benefit
Cost readout	Directly reported as regimen cost (WAC or ASP) Advanced disease: drug acquisition cost per month Adjuvant therapy: drug acquisition cost for entire treatment	Reported as relative affordability, considers overall cost of intervention (eg, cost of drug, infusions, supportive care, management)	DrugAbacus value-based price per month or course of therapy; a user-generated value assessment directly compared with reported Medicare payment limit, 106% ASP	Cost per year; cost-effectiveness of drug, with recommendations on what drug price should be to be cost-effective	Not specified; left to payers to evaluate
Drug cost, relative or absolute value	Yes	Yes	Yes	Yes	No
Cost to patient	Yes	No	No	No	No
Cost to healthcare system	No	Total drug and medical costs	Rarity per budget impact	Increment cost-effectiveness ratio and budget impact	No

ASCO, American Society of Clinical Oncology; ASP, average sales price; ESMO, European Society for Medical Oncology; ICER, Institute for Clinical and Economic Review; MSKCC, Memorial Sloan Kettering Cancer Center; NCCN, National Comprehensive Cancer Network; WAC, wholesale acquisition cost.

1. Slomiany M et al. *Am Health Drug Benefits*. 2017;10:253-260.

Summary: Oncology Value Frameworks

- Lack of real-world evidence
- Population heterogeneity adds complexity
- Stakeholders are taking a wait-and-see attitude in many cases
- Need more market uptake to validate
- CVS Caremark is initiating a program that allows clients to exclude any drug launched at a price of greater than $100,000 per QALY from their plan
- ICER has most use in the health plan arena

ICER, Institute for Clinical and Economic Review; QALY, quality-adjusted life-year.

Managed Care Strategies

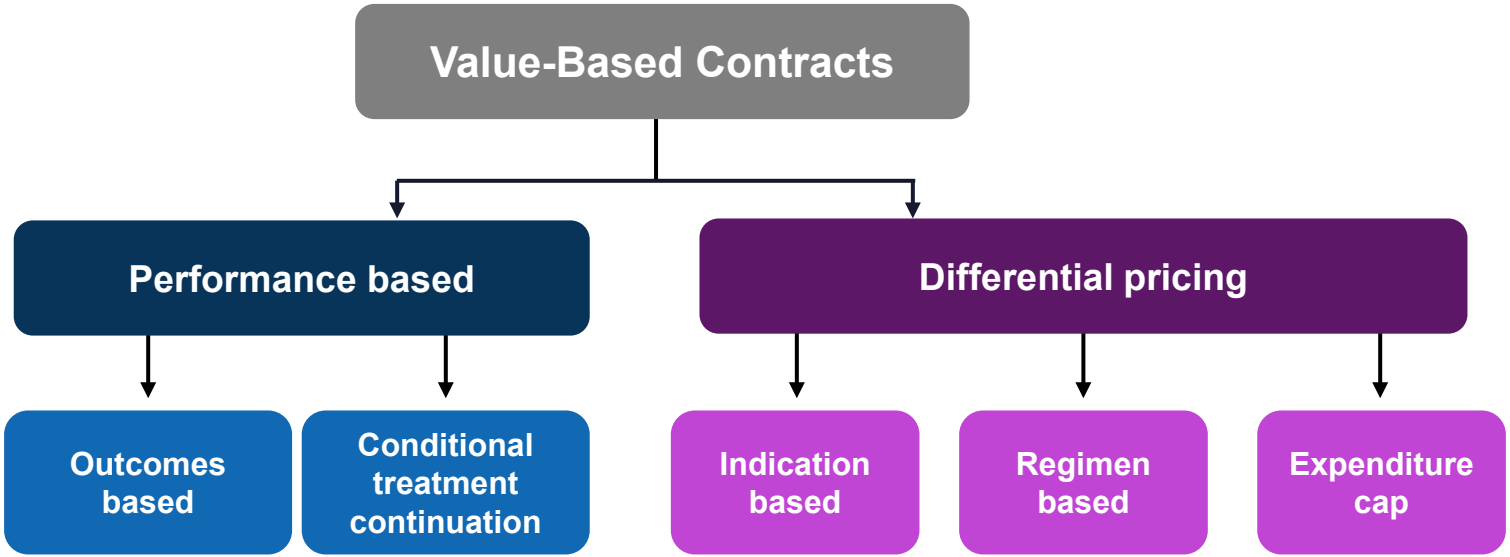
Managed Care Strategies

- Apply management tools to extract value from treatments
- Formulary management includes
  - Prior authorization
  - Step edits
- Negotiating rebates
- Preferred specialty pharmacy networks
- Alternative payment models
- Value-based contracts

Value-Based Contracts

A value-based contract is a written contractual agreement in which the payment terms for medication(s) or other healthcare technologies is tied to agreed-upon clinical circumstances, patient outcomes, or measures.

Value-Based Contracts[1] (Cont'd)



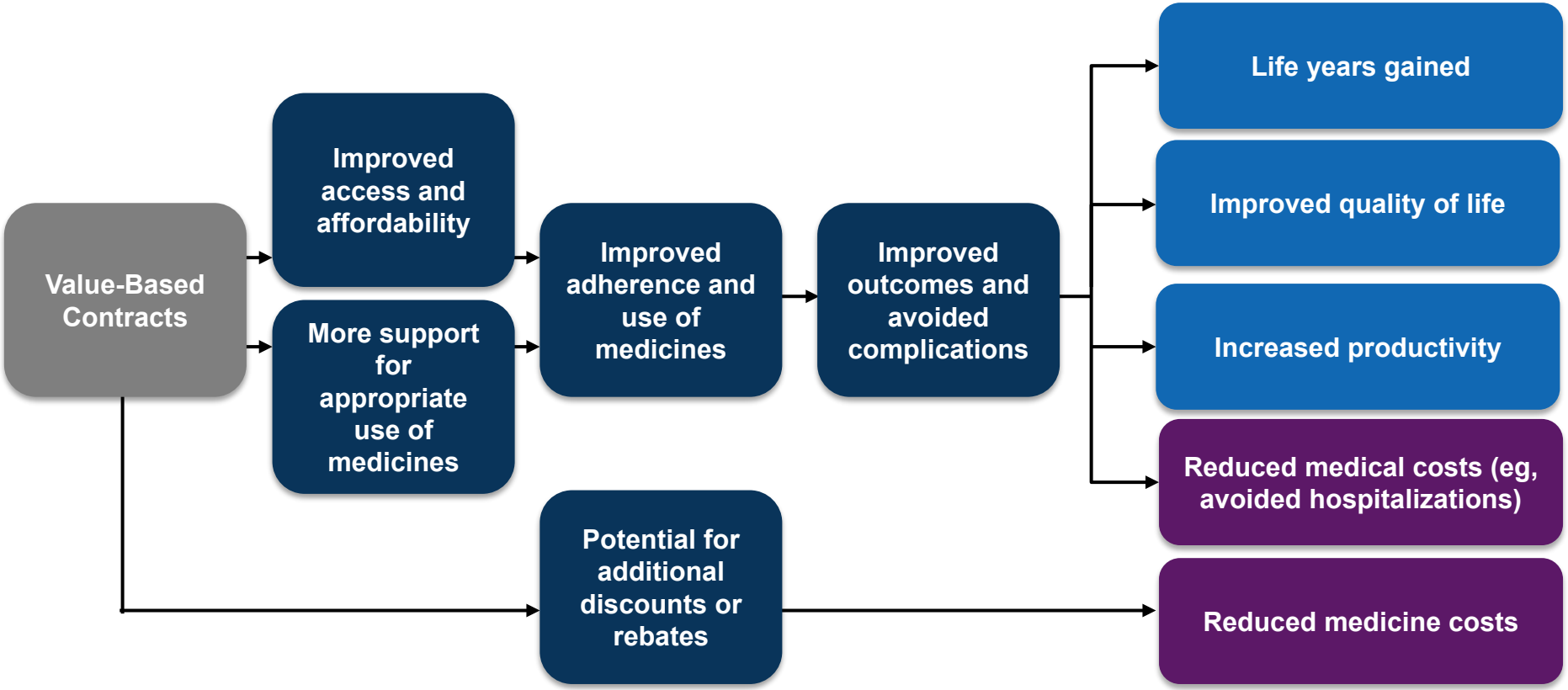
1. Pharmaceutical Research and Manufacturers of America Report: Delivering Results for Patients: The Value of Value-Based Contracts. February 2018.

Value-Based Contracts[1] (Cont'd)

Contract Label	Description
Outcomes-based contract	A contract designed to tie costs or discounts to patient outcomes. This is currently the most common type of publicly disclosed value-based contract.
Conditional treatment continuation	An arrangement in which continuation of coverage of treatment is conditioned on meeting short-term treatment goals, frequently complemented by free trial of the medicine.
Indication-based pricing	A contract is which the net price of a medicine varies for different indications based on an agreement between the contracting entities
Regimen-based pricing	A contract in which the net price of a medicine decreases when a patient must take a second medicine to make the treatment regimen more effective.
Expenditure cap	An agreement which limits medicine cost per patient to a certain negotiated threshold. This has been implemented as a version of indications-based pricing for infused cancer medicines.

1. Pharmaceutical Research and Manufacturers of America Report: Delivering Results for Patients: The Value of Value-Based Contracts. February 2018.

Potential Benefits for Value-Based Contracts[1]



1. Pharmaceutical Research and Manufacturers of America Report: Delivering Results for Patients: The Value of Value-Based Contracts. February 2018.

Payers Solution to Drug Coverage

Alternative Payment Models (APMs)

- Oncology Care Model (OCM)
- Aetna Oncology Medical Home
- CVS Health Transform Oncology Care program
- Precision Medicine Strategy partnered with Tempus
- ASCO's Patient-Centered Oncology Payment (PCOP) model

ASCO, American Society of Clinical Oncology.

Limitations of the Current Strategies to Manage PARP Inhibitors

- Formulary design and utilization management tools
- Assessing value
  - Current value frameworks cannot keep pace with the rapid innovation of PARP inhibitors for new indications
- Lack of real-world evidence
- Inadequate alternative payment models

PARP, poly ADP-ribose polymerase.

Patient Scenario 1: A Woman With Ovarian Cancer

A 46-year old woman with platinum-sensitive, high-grade ovarian cancer, previously received 2 platinum-based regimens, on maintenance therapy with partial response

- Should you consider PARPi for this patient?
  - Olaparib, rucaparib, and niraparib are approved for 1L maintenance in PSOC
- Which PARPi should we use for this patient?

What real-world scenarios will you encounter in managed care setting?

- Cost analysis and value calculations in managed care setting

1L, first line; PARPi, poly ADP-ribose polymerase inhibitor; PSOC, platinum-sensitive ovarian cancer.

Cost Analysis and Value Calculations in the Managed Care Setting[1]

Value Frameworks Within Oncology

- The value-based benchmark prices for a drug are defined as the prices that would achieve incremental cost-effectiveness ratios of $100,000 and $150,000 per QALY gained
- Pricing of PARP inhibitors in 2017 has a potential to align with clinical benefits in recurrent disease, but alignment will be more challenging when used in maintenance settings
- List prices would need to be lowered by 50%-78% for treatment in maintenance setting to facilitate affordability and patient access

Treatment of recurrent OC in patients with *BRCA*mut

Olaparib: $146,200/QALY – P/I

Rucaparib: $294,600/QALY – P/I

Niraparib: Insufficient

Maintenance therapy for recurrent disease in patients who previously responded to platinum-based chemo

Olaparib: $324,100/QALY – C+

Rucaparib: $369,175/QALY – C+

Niraparib: $291,500/ QALY – C+

*BRCA*mut, *BRCA*-mutated; PARP, poly ADP-ribose polymerase; QALY, quality-adjusted life-year.

1. https://icer-review.org/wp-content/uploads/2017/02/MWCEPAC_OVARIAN_FINAL_EVIDENCE_REPORT_10112017.pdf.

Limitations of Using ICER Analysis in Assessing the Value of PARP Inhibitors

- Utility of reports relative to P&T cycle
- ICER reports are not updated regularly
  - ICER report on PARPi was published in 2017 and has not been updated for newer indications or newer PARPi agents
- Requires careful assessment of model inputs as they are not modifiable
  - Population studied in the model does not always match with the distinct population for the payers
- Currently, QALY metrics don't have a practical use in real-world decision-making
- ICER utilizes short-term clinical data to make projections for the budget and cost-effectiveness of the therapy
- Presents value only for the payer perspective

ICER, Institute for Clinical and Economic Review; PARPi, poly ADP-ribose polymerase inhibitor; QALY, quality-adjusted life-year.

Patient Scenario 2: A Man With Prostate Cancer

60-year-old man diagnosed with a metastatic castration-resistant prostate cancer (mCRPC). His germline DNA repair gene testing revealed *BRCA2* mutation.

- Should you consider PARPi for this patient?
  - Both olaparib and rucaparib are FDA approved for mCRPC
- Safety-efficacy of both PARPi

What real-world scenarios will you encounter in managed care setting?

- Barriers for adoption of PARP inhibitors
- Overcoming patient concerns

BRCA2, breast cancer 2; PARPi, poly ADP-ribose polymerase inhibitor.

Strategies to Overcome Barriers for Adoption of PARP inhibitors in Managed Care Settings[1,2]

Adherence programs

- Specialty pharmacist/pharmacist within clinic should talk with the patient at each prescription fill
  - Are patients taking their medication as prescribed?
  - Do they have any follow-up questions or concerns?
  - Are they experiencing any concerning toxicities?

Encourage tumor testing at diagnosis

- Important information for patient

Oral Oncology Split-Fill Program

Waste avoidance through filling 2x per month

Current Fulfillment
- 1 fill/month

✓ Potential for early discontinuation due to intolerance

✓ Remaining drug on hand is wasted

Split-Fill program
- 2 fills/month
- Prorated copay

✓ Increased patient engagement

✓ Reducing waste and realization of accompanying savings

PARP, poly ADP-ribose polymerase;

1. https://www.cancertherapyadvisor.com/home/cancer-topics/general-oncology/oncology-split-fill-program-improves-adherence-cuts-cost-waste-risk.
2. Staskon FC et al. *J Oncol Pract*. 2019;15:e856-e862.

Summary

- Clinical pharmacists or specialty pharmacists can help in further reducing the cost of patient care in the managed care setting by …
  - Starting oral adherence programs
  - Following up with patients
  - Educating patients about the use of PARP inhibitors
  - Confirming biomarker testing
- PARP inhibitors are likely to provide gains in quality-adjusted life years and overall survival over alternative therapies, but are not currently priced in alignment with these benefits
  - Exception: olaparib in recurrent, *BRCA*-mutated ovarian cancer

PARP, poly ADP-ribose polymerase.

Audience Q&A