DATA + PERSPECTIVES

Clinical Investigators Explore the Biology Underlying the Role of PARP Inhibition in the Management of Common Cancers

Tuesday, June 23, 2020

7:00 PM – 8:00 PM ET

Faculty

Maha Hussain, MD, FACP, FASCO
Ursula Matulonis, MD
Philip A Philip, MD, PhD, FRCP
Hope S Rugo, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Faculty

Maha Hussain, MD, FACP, FASCO
Genevieve Teuton Professor of Medicine
Division of Hematology/Oncology
Deputy Director
Robert H Lurie Comprehensive Cancer Center
Northwestern University Feinberg School of Medicine
Chicago, Illinois

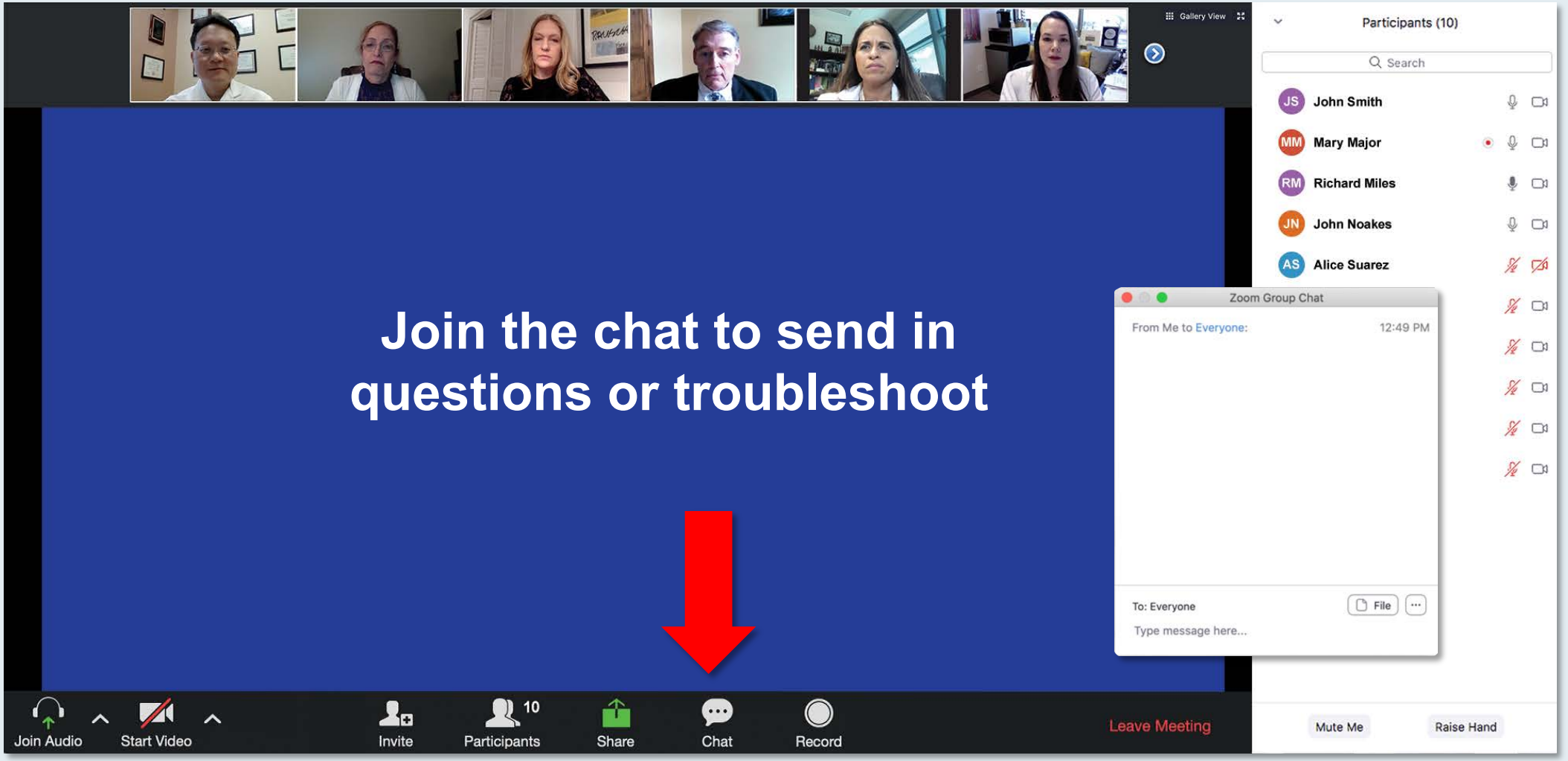
Philip A Philip, MD, PhD, FRCP
Kathryn Cramer Endowed Chair in Cancer Research
Professor of Oncology and Pharmacology
Leader, GI and Neuroendocrine Oncology
Karmanos Cancer Institute
Wayne State University
Detroit, Michigan

Ursula Matulonis, MD
Chief, Division of Gynecologic Oncology
Brock-Wilson Family Chair
Dana-Farber Cancer Institute
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Hope S Rugo, MD
Professor of Medicine
Director, Breast Oncology and Clinical Trials Education
University of California, San Francisco
Helen Diller Family Comprehensive Cancer Center
San Francisco, California

Familiarizing yourself with the Zoom interface

How to participate in the chat



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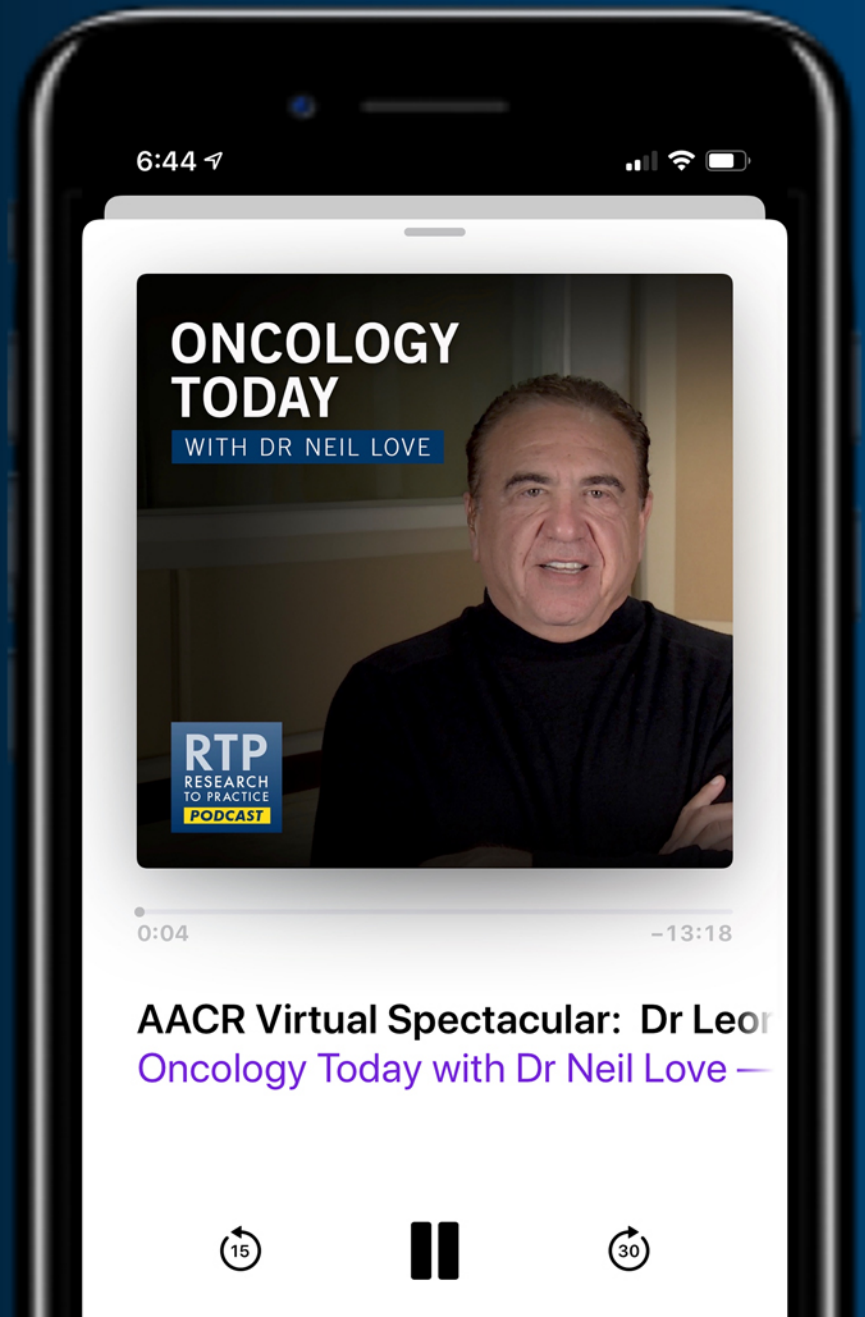

Chronic Lymphocytic Leukemia and Follicular Lymphoma

Join us Wednesday, June 24, for the live webinar
5:00 PM – 6:00 PM ET

Faculty

Jeff Sharman, MD
Willamette Valley Cancer Institute and Research Center
Medical Director of Hematology Research
US Oncology
Eugene, Oregon

Julie M Vose, MD, MBA
Neumann M and Mildred
E Harris Professor
Chief, Division of Hematology/Oncology
Nebraska Medical Center
Omaha, Nebraska

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

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Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Acute Myeloid Leukemia and the General Medical Oncologist: New Agents and Treatment Strategies, Particularly for Older Patients

An Interactive Meet The Professor Series

Thursday, June 25, 2020
12:00 PM – 1:00 PM

Richard M Stone, MD
Chief of Staff
Director, Translational Research Leukemia Division
Dana-Farber Cancer Institute
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

RTP
RESEARCH
TO PRACTICE

Oncology Grand Rounds

New Agents and Strategies in PARP Inhibition in the Management of Common Cancers

Thursday, June 25, 2020

5:00 PM – 6:30 PM ET

Faculty

Emmanuel S Antonarakis, MD
Gretchen Santos Fulgencio, MSN, FNP-BC
Erika Meneely, APRN, BC
Kathleen Moore, MD
Joyce O'Shaughnessy, MD
Michael J Pishvaian, MD, PhD
Deborah Wright, MSN, APRN, CNS

Moderator

Neil Love, MD

Research To Practice®

Clinical Investigator Perspectives on the Current and Future Management of Multiple Myeloma

A Meet The Professor Series

Friday, June 26, 2020
12:00 PM – 1:00 PM

Nikhil C Munshi, MD
Professor of Medicine
Harvard Medical School
Director of Basic and Correlative Science
Associate Director, Jerome Lipper Multiple Myeloma Center
Department of Medical Oncology
Dana-Farber Cancer Institute
Boston, Massachusetts

Co-provided by USF Health RTP RESEARCH TO PRACTICE

DATA + PERSPECTIVES

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RTP RESEARCH TO PRACTICE

About the Enduring Program

- This webinar is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
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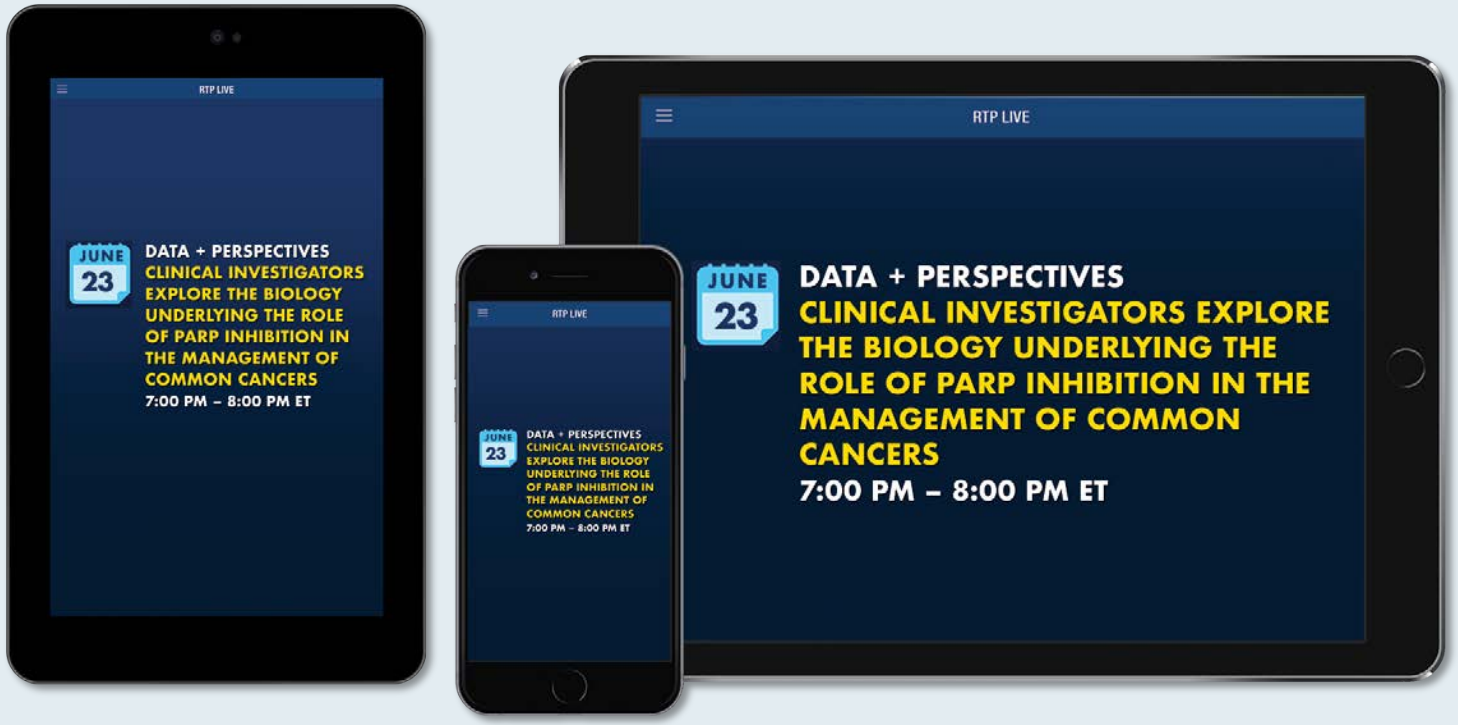


Agenda

Module 1: Overview of PARP Inhibitors: Biologic Rationale and Mechanism of Action

Module 2: Side Effects and Toxicities of PARP Inhibitors

Module 3: PARP Inhibitors for Ovarian Cancer – Dr Matulonis

- Key data sets: SOLO-1, PRIMA, PAOLA-1, VELIA

Module 4: PARP Inhibitors for Breast Cancer – Dr Rugo

- Key data sets: EMBRACA, OlympiAD, BROCADE3

Module 5: PARP Inhibitors for Pancreatic Cancer – Dr Philip

- Key data sets: POLO, RUCAPANC

Module 6: PARP Inhibitors for Prostate Cancer – Dr Hussain

- Key data sets: PROfound, TRITON2, GALAHAD

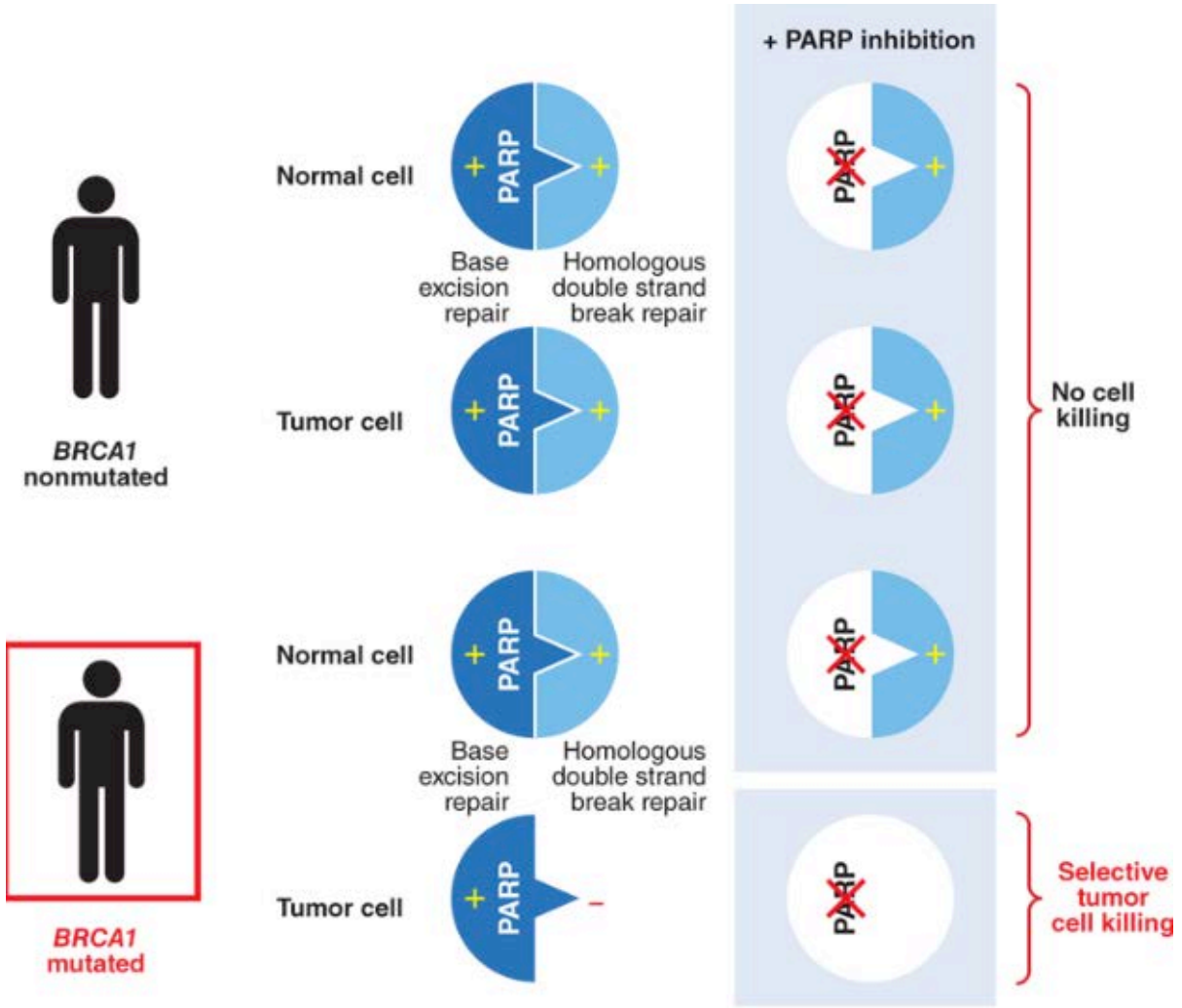
Module 1: Overview of PARP Inhibitors: Biologic Rationale and Mechanism of Action

Genomic assays, PARP sensitivity and biologic rationale for PARP inhibitors

- Germline versus somatic testing
- Role of liquid biopsy
- Mechanism of action, potency of PARP inhibitors; PARP trapping
- Approved PARP inhibitors

PARP inhibitors in DNA repair defect: concept of synthetic lethality

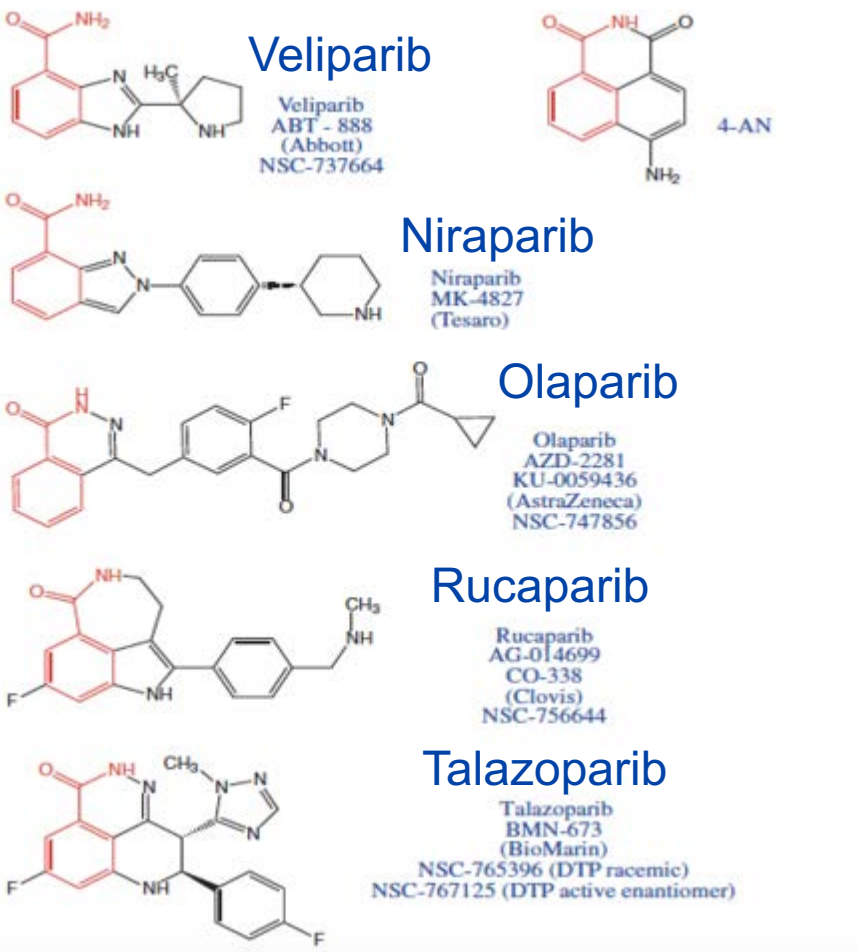
BARBARA ANN Karmanos CANCER INSTITUTE
Wayne State University

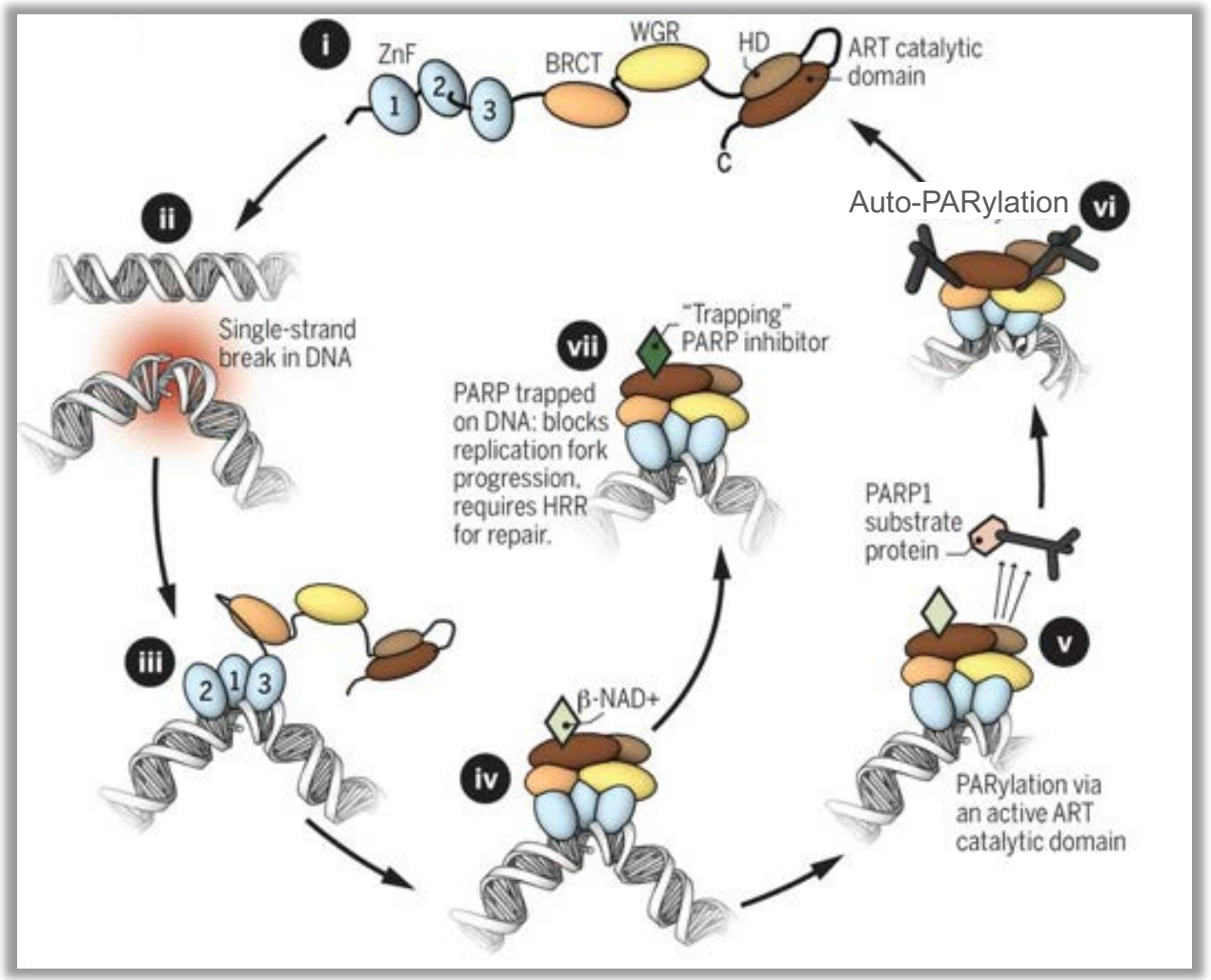


NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

Courtesy of Philip A Philip, MD, PhD, FRCP

PARP Inhibitors and Mechanism of Action





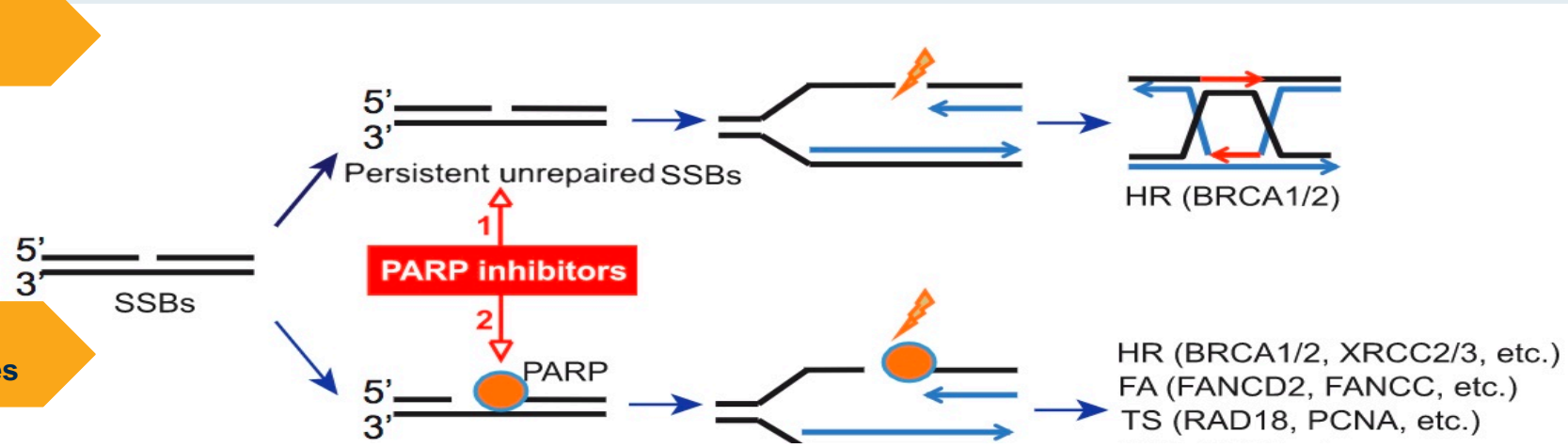
Murai J, Pommier Y. Classification of PARP Inhibitors Based on PARP Trapping and Catalytic Inhibition, and Rationale for Combinations with Topoisomerase I Inhibitors and Alkylating Agents. In: Curtin NJ, Sharma RA, eds. *PARP Inhibitors for Cancer Therapy*. New York: Springer International Publishing;2015:261-274.

Courtesy of Hope Rugo, MD

Dual Mechanisms of Action of PARP Inhibitors

Catalytic inhibition

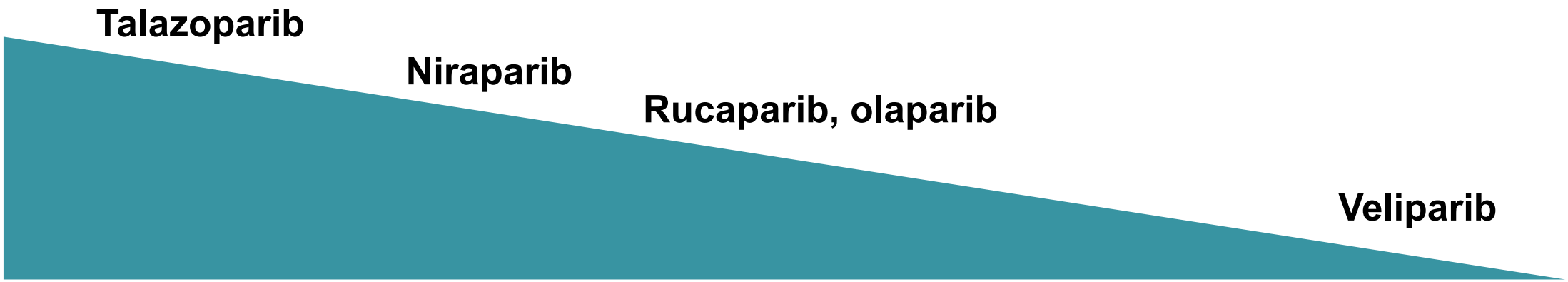
Trapping of PARP-DNA complexes



	Catalytic inhibition IC_{50} in wild-type DT40 cells (nM)	Catalytic inhibition IC_{50} in wild-type DT40 cells (μM)	PARP-trapping potency (relative to olaparib)	Class
Veliparib	30	>50	<0.2	Type 1
Olaparib	6	4.5	1	Type 2
Rucaparib	21	3	1	Type 2
Niraparib	60	2.3	~2	Type 2
Talazoparib	4	0.04	~100	Type 2

Murai J, Pommier Y. Classification of PARP Inhibitors Based on PARP Trapping and Catalytic Inhibition, and Rationale for Combinations with Topoisomerase I Inhibitors and Alkylating Agents. In: Curtin NJ, Sharma RA, eds. *PARP Inhibitors for Cancer Therapy*. New York: Springer International Publishing;2015:261-74.

PARP Targeting Potency: High to Low



Adapted from: Lord CJ, et al. *Science.* 2017;355:1152-1158.

Courtesy of Philip A Philip, MD, PhD, FRCP

FDA-Approved and Late-Stage Investigational PARP Inhibitors

	Olaparib	Niraparib	Rucaparib	Talazoparib	Veliparib
Ovarian	• Front line • Plat-sensitive recurrent • Multiply relapsed	• Front line • Plat-sensitive recurrent • Multiply relapsed	• Plat-sensitive recurrent • Multiply relapsed	—	VELIA Ph3
Breast	• Metastatic	BRAVO Ph3	—	• Metastatic	—
Pancreatic	• Metastatic	—	—	—	—
Prostate	• Metastatic CRPC	Breakthrough therapy (GALAHAD) MAGNITUDE Ph3	• Metastatic CRPC	TALAPRO-2 Ph3	—

Olaparib PI, rev 5/2020; Niraparib PI, rev 4/2020; Rucaparib PI, rev 5/2020; Talazoparib PI, rev 3/2020; Clinicaltrials.gov, Accessed 6/2020

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Module 2: Side Effects and Toxicities of PARP Inhibitors

- Cytopenia
- Gastrointestinal toxicity
- Creatinine elevation
- ALT/AST elevation
- Risk of MDS/AML

Adverse Events: Class Effects and Specific Drug Differences

	Notes	Olaparib	Niraparib	Rucaparib	Talazoparib	Veliparib
Fatigue	50%-70%, mainly Gr1-2	✓	✓	✓	✓	✓
Hematologic AEs						
Anemia	40%-60%	✓	✓	✓	✓	✓ --
Thrombocytopenia	Niraparib dose adjustment, based on platelet counts	✓	✓ ++	✓	✓	✓
Neutropenia	~20%	✓	✓	✓	✓	✓
Gastrointestinal AEs						
Nausea/vomiting	Moderately emetic >30%	✓	✓	✓	✓	✓
Diarrhea	~33%	✓	✓	✓	✓	✓
Laboratory abnormalities						
ALT/AST elevation	5%-10% olaparib, niraparib; 34% rucaparib	✓ --	✓ --	✓ ++	✓ ++	?
Creatinine elevation	10%-12%	✓	✓	✓	**NR**	**NR**

Olaparib PI, rev 5/2020; Niraparib PI, rev 4/2020; Rucaparib PI, rev 5/2020; Talazoparib PI, rev 3/2020; Madariaga A et al. *Int J Gyn Cancer* 2020 April 9;[Online ahead of print]; Litton JK et al. *NEJM* 2018;379:753-63.

NR, not reported

Adverse Events: Class Effects and Specific Drug Differences

	Notes	Olaparib	Niraparib	Rucaparib	Talazoparib	Veliparib
Respiratory disorders						
Dyspnea +/- cough	10%-20%, usually Gr 1-2	✓	✓	✓	✓	NR
Nasopharyngitis	~10%	✓	✓	✓	✓	NR
Nervous system and psychiatric disorders						
Insomnia/headache	10%-25%, usually Gr 1-2	✓	✓	✓	✓	✓
Dermatologic toxicity						
Rash, photosensitivity		<1%	✓	✓++	NR	NR
Cardiovascular toxicity						
Hypertension, tachycardia, palpitation		1%	✓++	NR	NR	NR
Rare AEs						
MDS/AML	~1% of pts	✓	✓	✓	✓	✓

Olaparib PI, rev 5/2020; Niraparib PI, rev 4/2020; Rucaparib PI, rev 5/2020; Talazoparib PI, rev 3/2020; Madariaga A et al. *Int J Gyn Cancer* 2020 April 9;[Online ahead of print]; Litton JK et al. *NEJM* 2018;379:753-63.

NR, not reported

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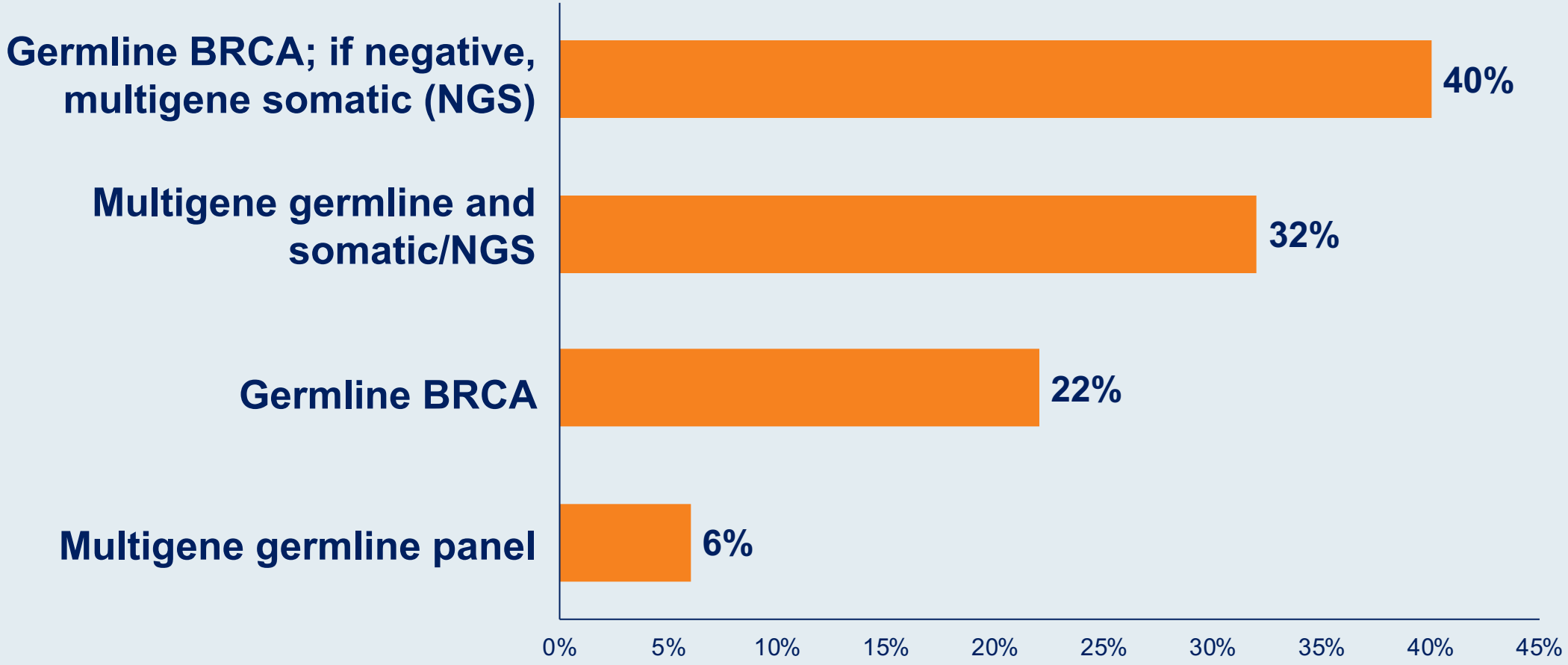
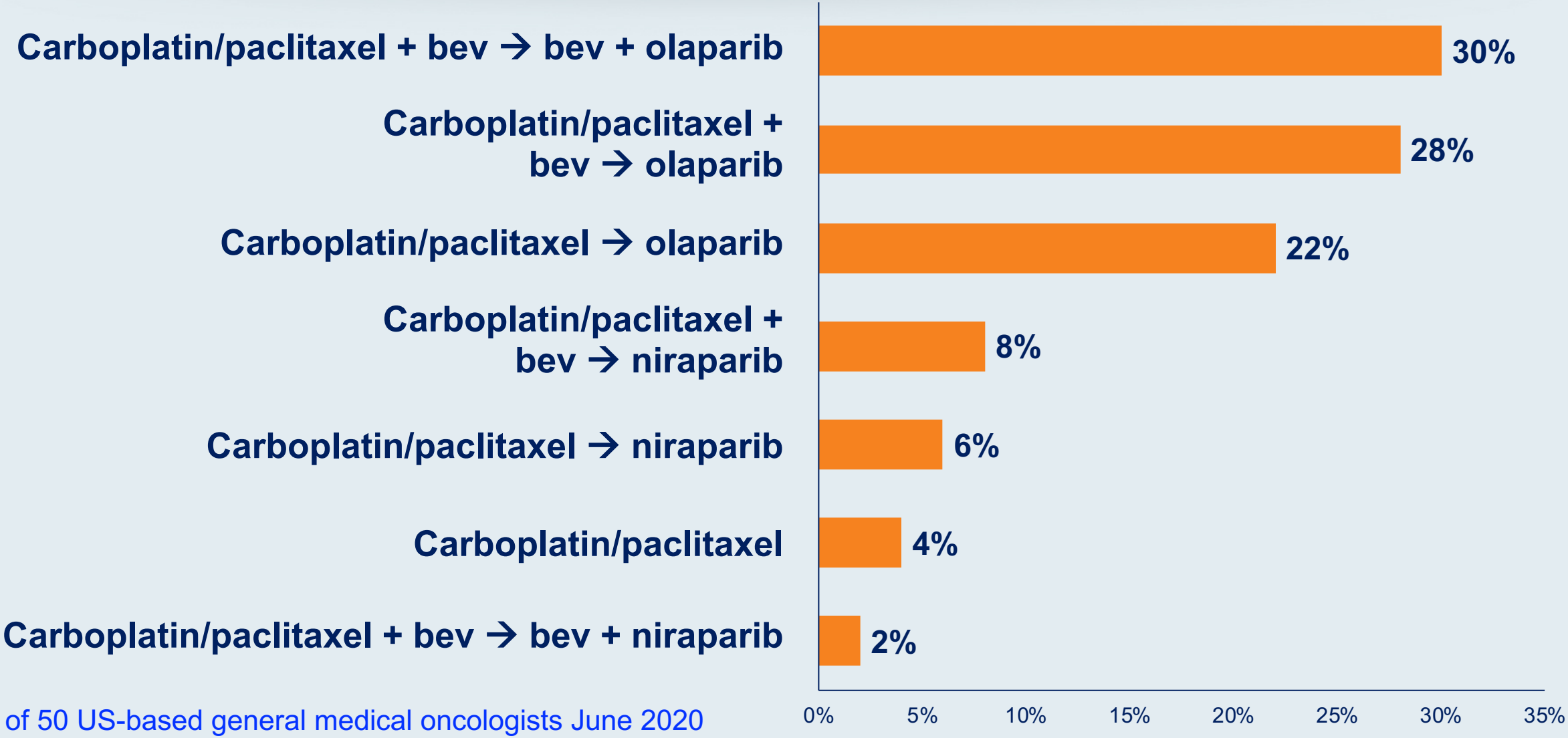
- Genomic profile
- Prior trials in relapse setting: maintenance and monotherapy
- Key recent up-front data sets: SOLO-1, PRIMA, PAOLA-1, VELIA
- Current practice patterns
- Ongoing trials

In general, what is the optimal approach to mutation testing for possible use of a PARP inhibitor for a patient with newly diagnosed ovarian cancer and no family history?



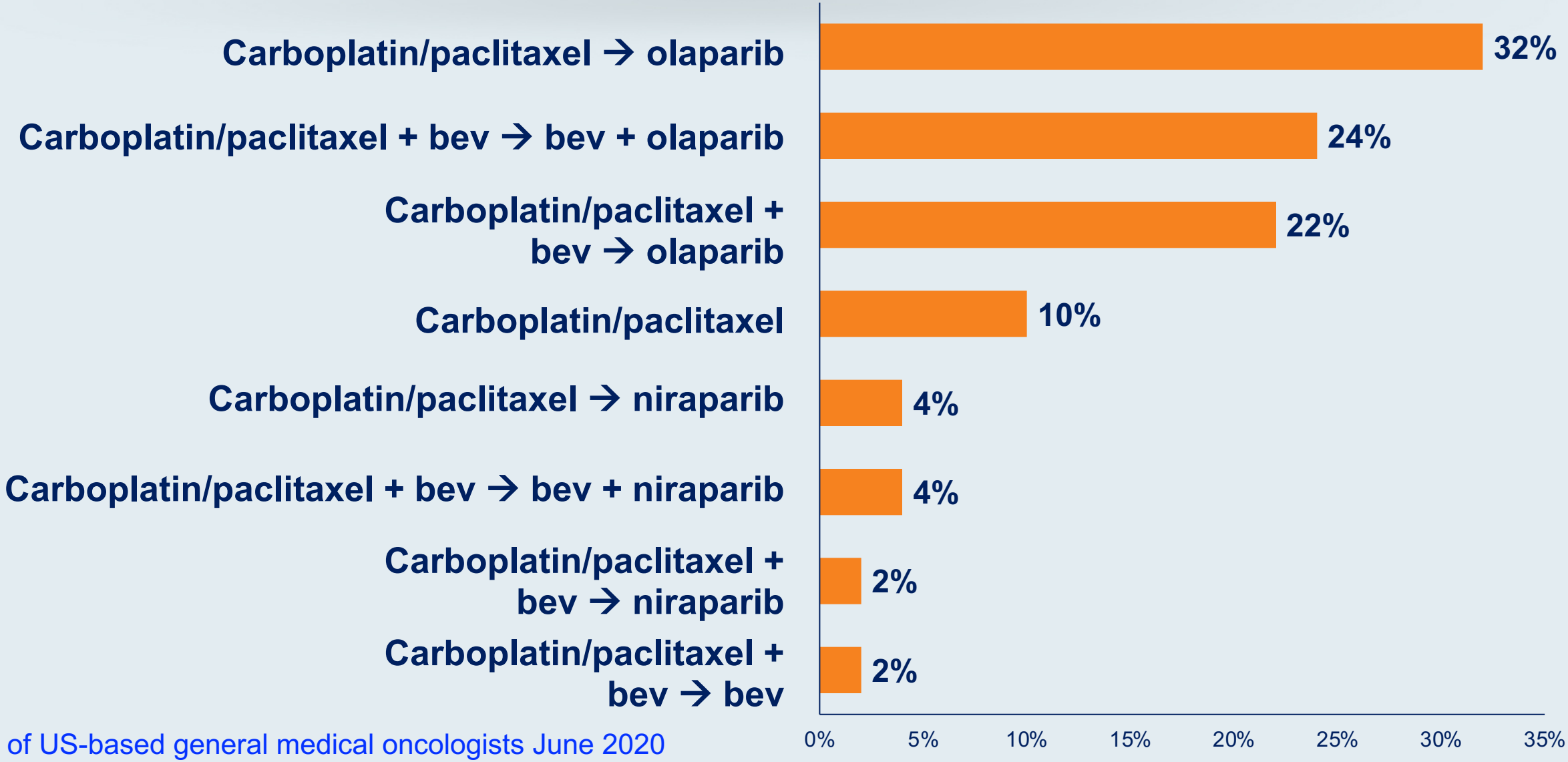
Survey of 50 US-based general medical oncologists June 2020

A 60-year-old woman with Stage IIIC ovarian cancer and a germline BRCA mutation is s/p suboptimal debulking surgery with elevated CA-125. Regulatory and reimbursement issues aside, what would you recommend as postoperative systemic therapy?



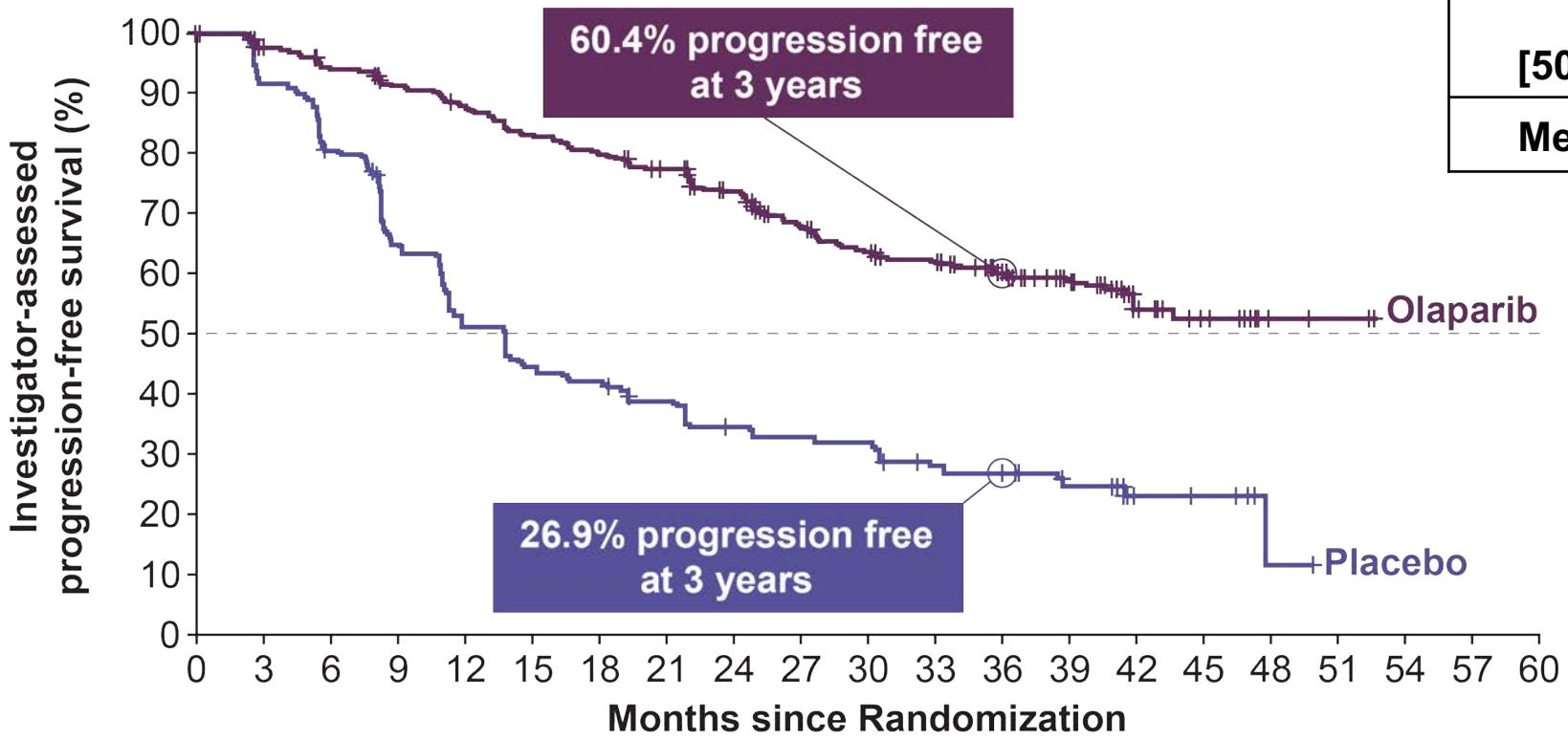
Survey of 50 US-based general medical oncologists June 2020

A 60-year-old woman with Stage IIIC ovarian cancer and a germline BRCA mutation is s/p optimal debulking surgery with a normal CA-125 level. Regulatory and reimbursement issues aside, what would you recommend as postoperative systemic therapy?



Survey of US-based general medical oncologists June 2020

SOLO-1: PFS



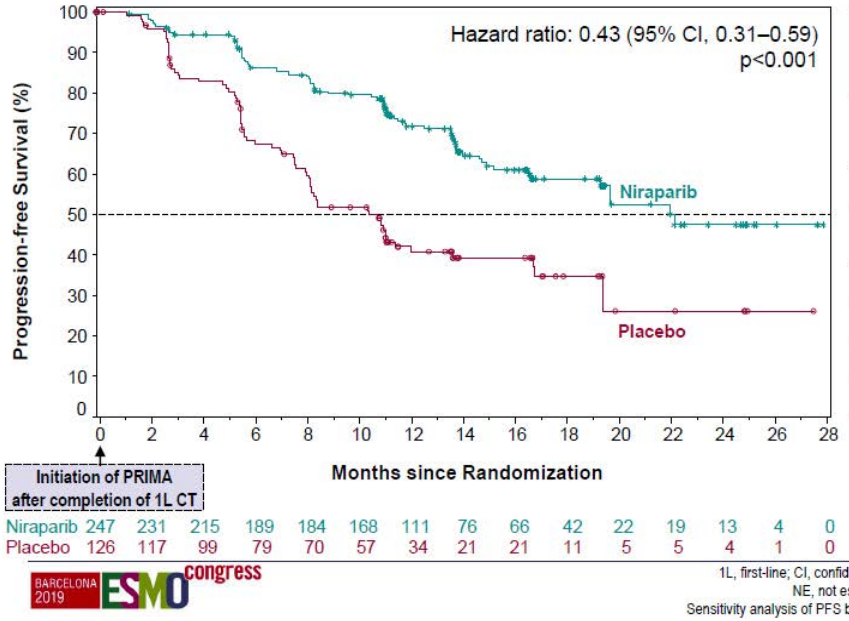
No. at Risk																				
Olaparib	260	240	229	221	212	201	194	184	172	149	138	133	111	88	45	36	4	3	0	0	0
Placebo	131	118	103	82	65	56	53	47	41	39	38	31	28	22	6	5	1	0	0	0	0

	Olaparib (N=260)	Placebo (N=131)
Events (%) [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*<0.0001	

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

PRIMA: Primary endpoints

PRIMA Primary Endpoint, PFS Benefit in the HR-deficient Population

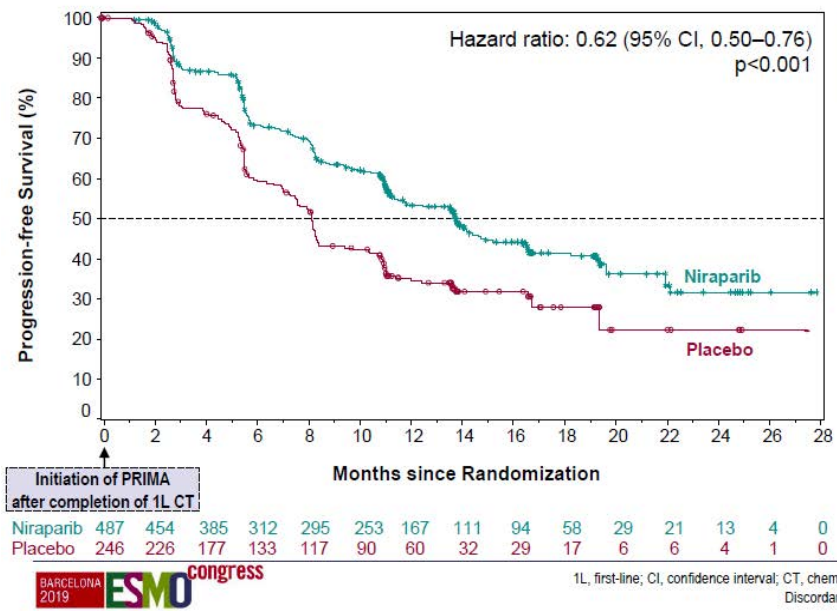


57% reduction in hazard of relapse or death with niraparib

	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 months	86%	68%
12 months	72%	42%
18 months	59%	35%

1L, first-line; CI, confidence interval; CT, chemotherapy; HR, homologous recombination; NE, not estimable; PD, progressive disease; PFS, progression-free survival.
Sensitivity analysis of PFS by the investigator was similar to and supported the BICR analysis.

PRIMA Primary Endpoint, PFS Benefit in the Overall Population



38% reduction in hazard of relapse or death with niraparib

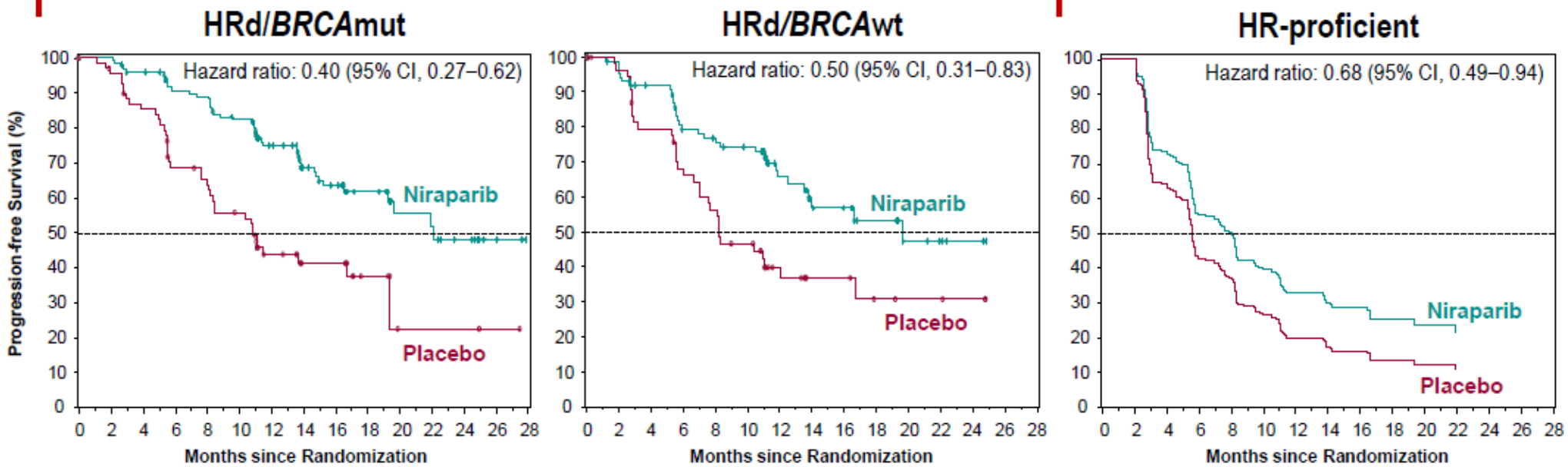
	Niraparib (n=487)	Placebo (n=246)
Median PFS		
months (95% CI)	13.8 (11.5–14.9)	8.2 (7.3–8.5)
Patients without PD or death (%)		
6 months	73%	60%
12 months	53%	35%
18 months	42%	28%

1L, first-line; CI, confidence interval; CT, chemotherapy; PD, progressive disease; PFS, progression-free survival.
Discordance in PFS event between investigator assessment vs BICR ≈12%.

Gonzalez-Martin et al., *N Engl J Med* 2019, ESMO 2019

PRIMA PFS Benefit in Biomarker Subgroups

Homologous Recombination Deficient (HRd)



Subgroup	PFS (niraparib)	PFS (placebo)	HR (95% CI)
HRd/BRCAmut	22.1	10.9	0.40 (0.27-0.62)
HRd/BRCAwt	19.6	8.2	0.50 (0.31-0.83)
HRp	8.1	5.4	0.68 (0.49-0.94)
HR unknown	NR	NR	0.85 (0.51-1.43)

Gonzalez-Martin et al., *N Engl J Med* 2019, ESMO 2019

FDA approves niraparib for first-line maintenance of advanced ovarian cancer

Press Release – April 29, 2020

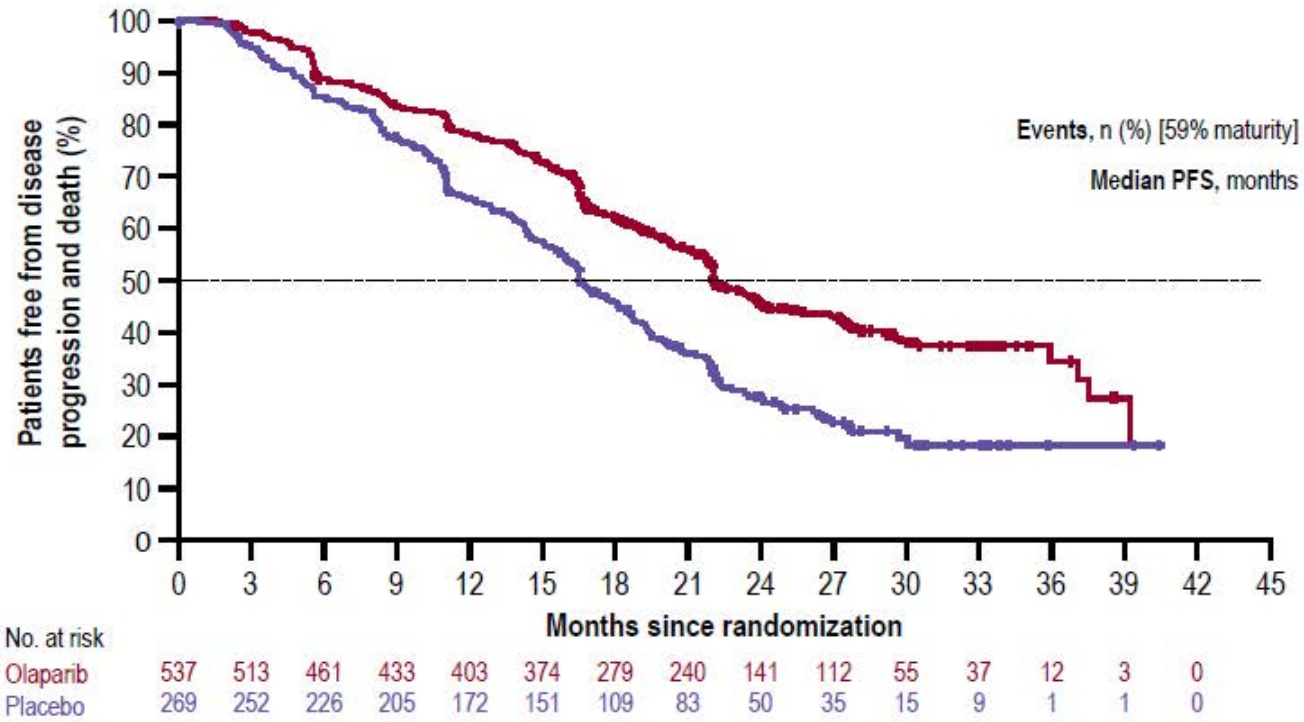
"The Food and Drug Administration approved niraparib for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.

Efficacy was investigated in PRIMA (NCT02655016), a double-blind, placebo-controlled trial that randomized 733 patients to niraparib or matched placebo. Patients were in a complete or partial response to first-line platinum-based chemotherapy."

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

PAOLA-1: PFS in ITT population

PFS by investigator assessment: ITT population



	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)
Events, n (%) [59% maturity]	280 (52)	194 (72)
Median PFS, months	22.1	16.6

HR 0.59 (95% CI 0.49–0.72; *P*<0.0001)

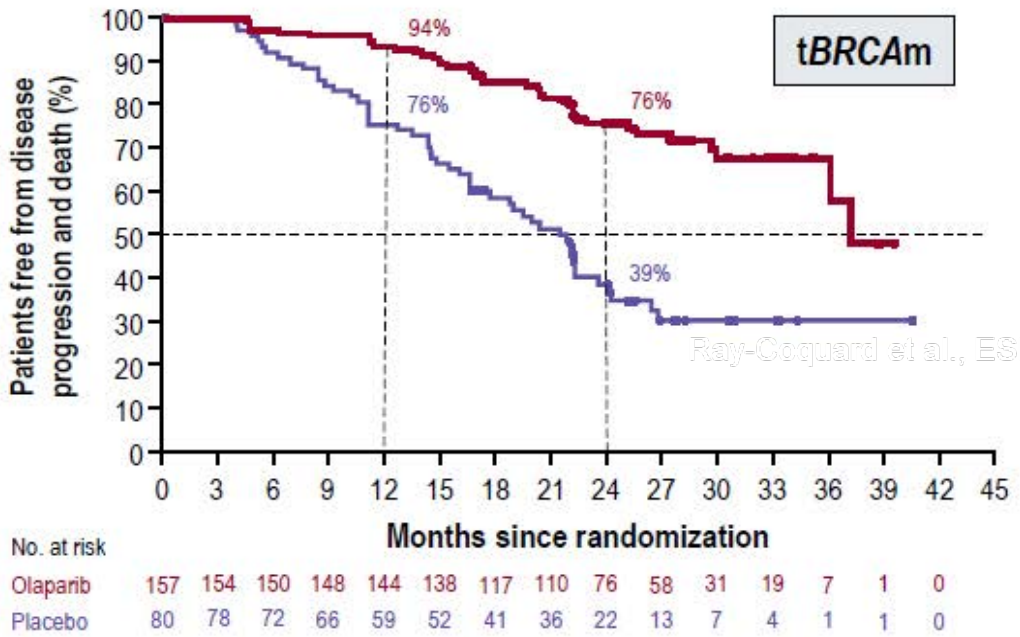
Median time from first cycle of chemotherapy to randomization = 7 months

ITT, intent-to-treat population

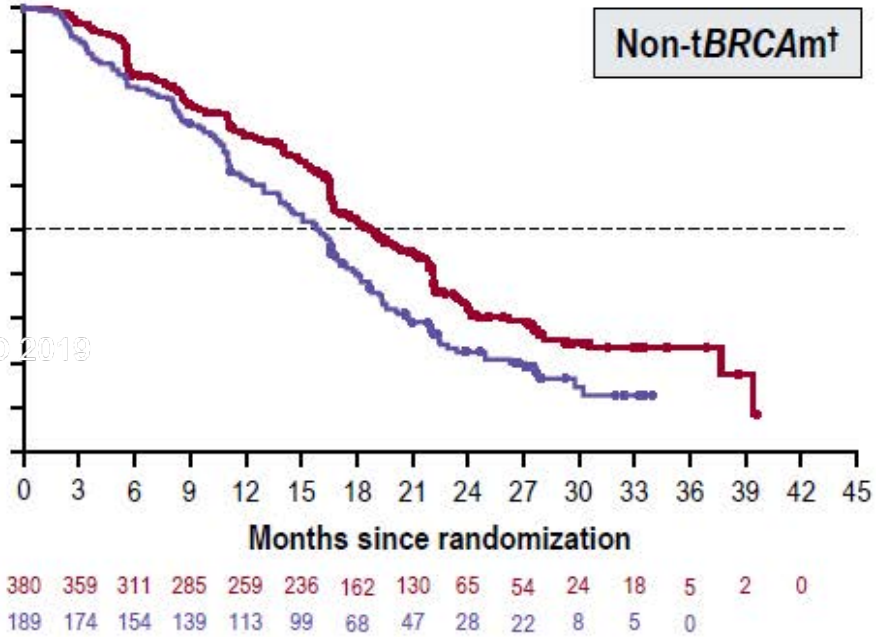
Ray-Coquard et al., ESMO 2019, N Engl J Med 2019; 381:2416-2428

PAOLA-1: PFS by tumor BRCA status

PFS by t*BRCA* mutation status



	Olaparib + bevacizumab (N=157)	Placebo + bevacizumab (N=80)
Events, n (%)	41 (26)	49 (61)
Median PFS, months	37.2*	21.7
	HR 0.31 (95% CI 0.20–0.47)	



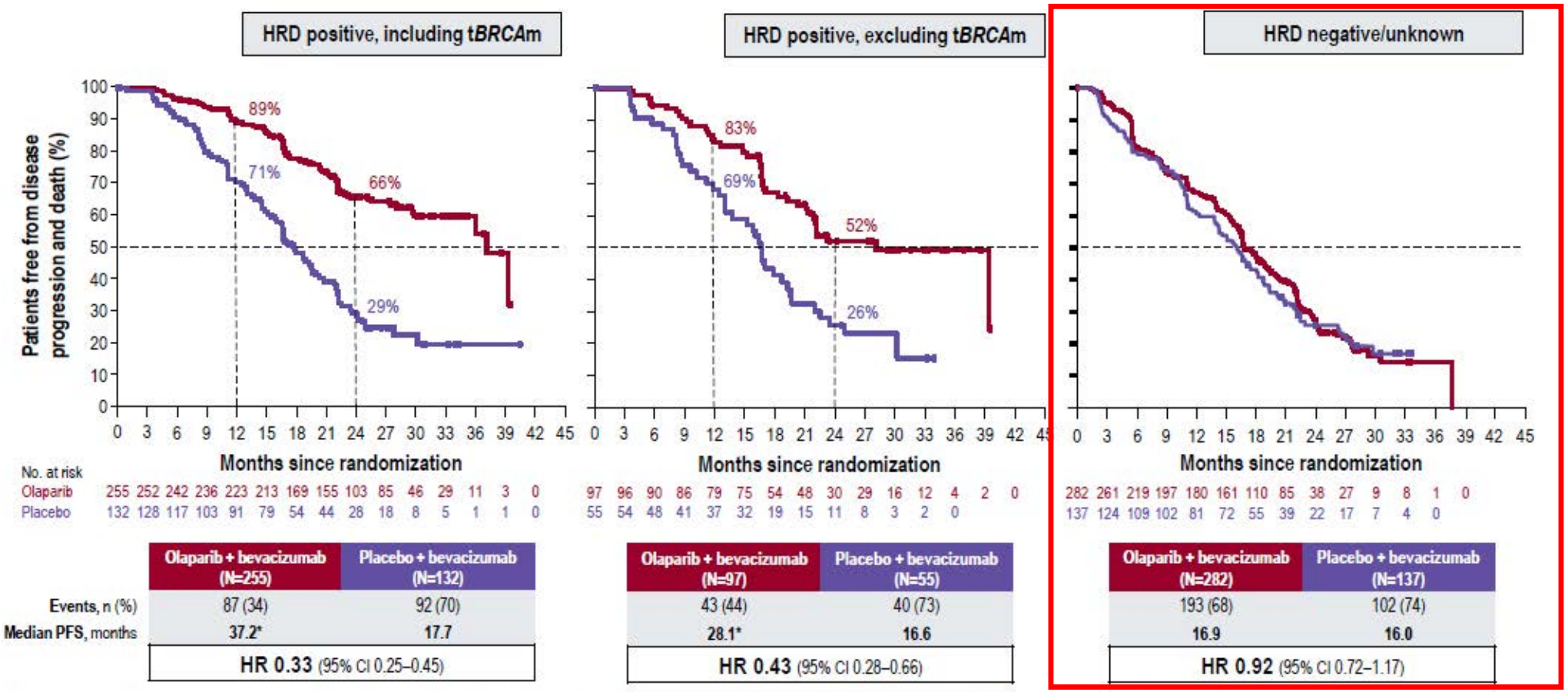
	Olaparib + bevacizumab (N=380)	Placebo + bevacizumab (N=189)
	239 (63)	145 (77)
	18.9	16.0
	HR 0.71 (95% CI 0.58–0.88)	

The percentages of patients progression-free at 12 months and 24 months have been calculated based on Kaplan-Meier estimates. *This median is unstable due to a lack of events – less than 50% maturity; †Includes t*BRCA* unknown

Ray-Coquard et al., ESMO 2019, N Engl J Med 2019; 381:2416-2428

PAOLA-1: PFS by HRD status

PFS by HRD status



	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Events, n (%)	87 (34)	92 (70)
Median PFS, months	37.2*	17.7
	HR 0.33 (95% CI 0.25–0.45)	

	Olaparib + bevacizumab (N=97)	Placebo + bevacizumab (N=55)
Events, n (%)	43 (44)	40 (73)
Median PFS, months	28.1*	16.6
	HR 0.43 (95% CI 0.28–0.66)	

	Olaparib + bevacizumab (N=282)	Placebo + bevacizumab (N=137)
Events, n (%)	193 (68)	102 (74)
Median PFS, months	16.9	16.0
	HR 0.92 (95% CI 0.72–1.17)	

The percentages of patients progression-free at 12 months and 24 months have been calculated based on Kaplan-Meier estimates. HRD positive is an HRD score ≥42. *This median is unstable due to a lack of events – less than 50% maturity

Ray-Coquard et al., ESMO 2019, N Engl J Med 2019; 381:2416-2428

FDA approves olaparib with bevacizumab as maintenance treatment for ovarian, fallopian tube, or primary peritoneal cancers

Press Release – May 28, 2020

"The Food and Drug Administration expanded the indication of olaparib to include its combination with bevacizumab for first-line maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency positive status defined by either a deleterious or suspected deleterious *BRCA* mutation, and/or genomic instability.

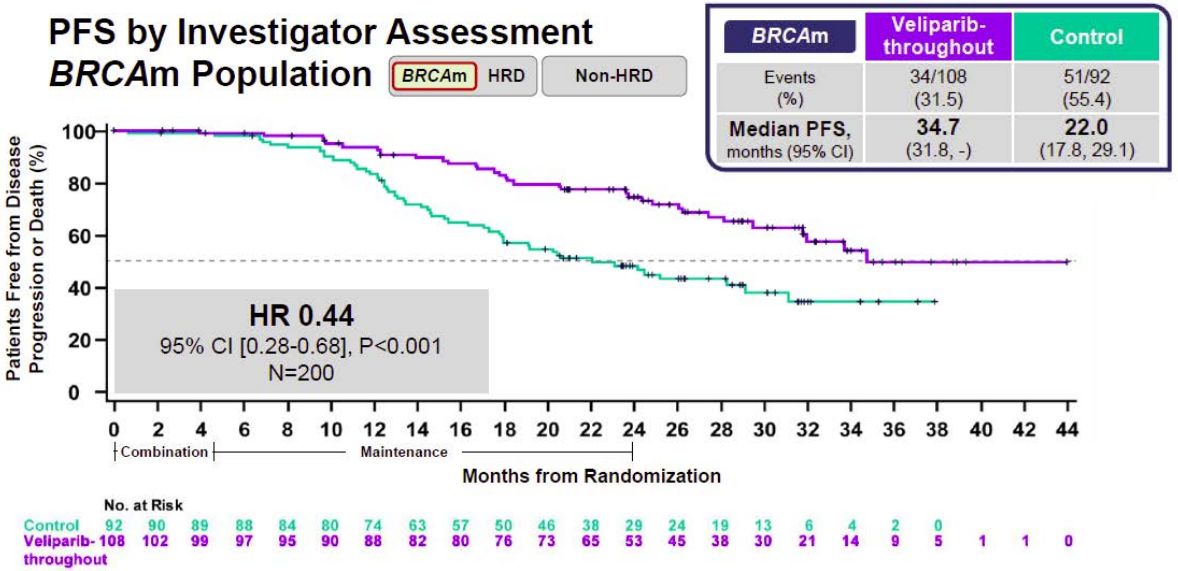
FDA also approved the Myriad myChoice® CDx (Myriad Genetic Laboratories, Inc.) as a companion diagnostic for olaparib.

Efficacy of this new indication was investigated in PAOLA-1 (NCT03737643), a randomized, double-blind, placebo-controlled, multi-center trial comparing olaparib with bevacizumab versus placebo plus bevacizumab in patients with advanced high-grade epithelial ovarian cancer, fallopian tube, or primary peritoneal cancer following first-line platinum-based chemotherapy and bevacizumab."

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

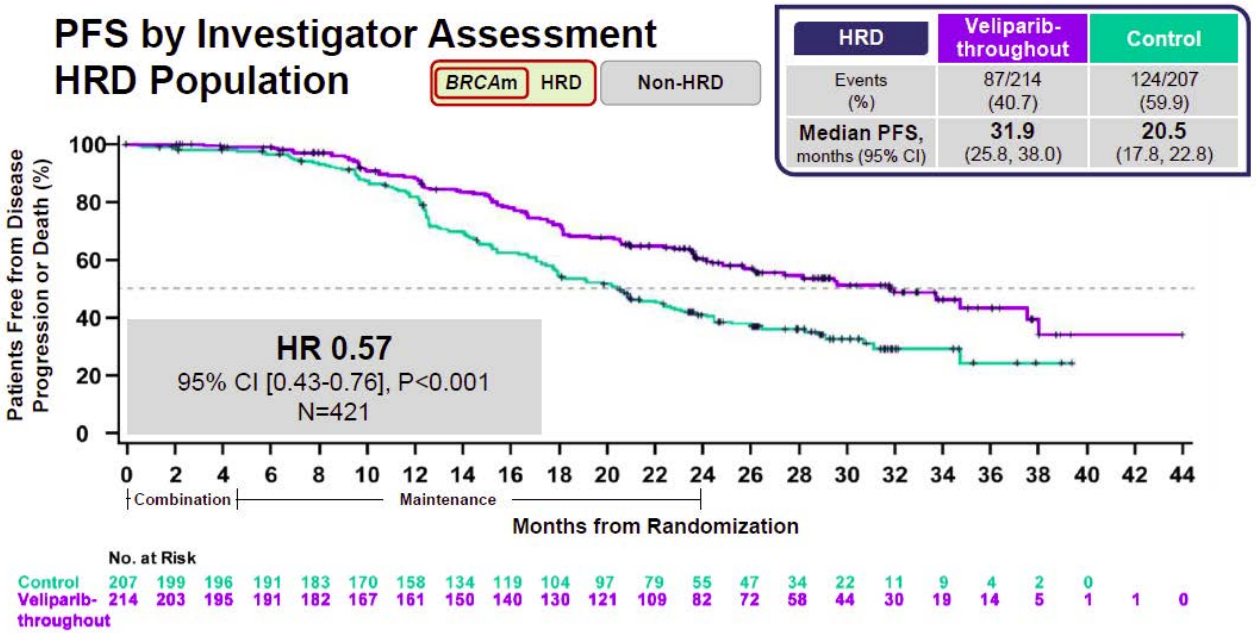
VELIA: PFS primary endpoints

BRCA only



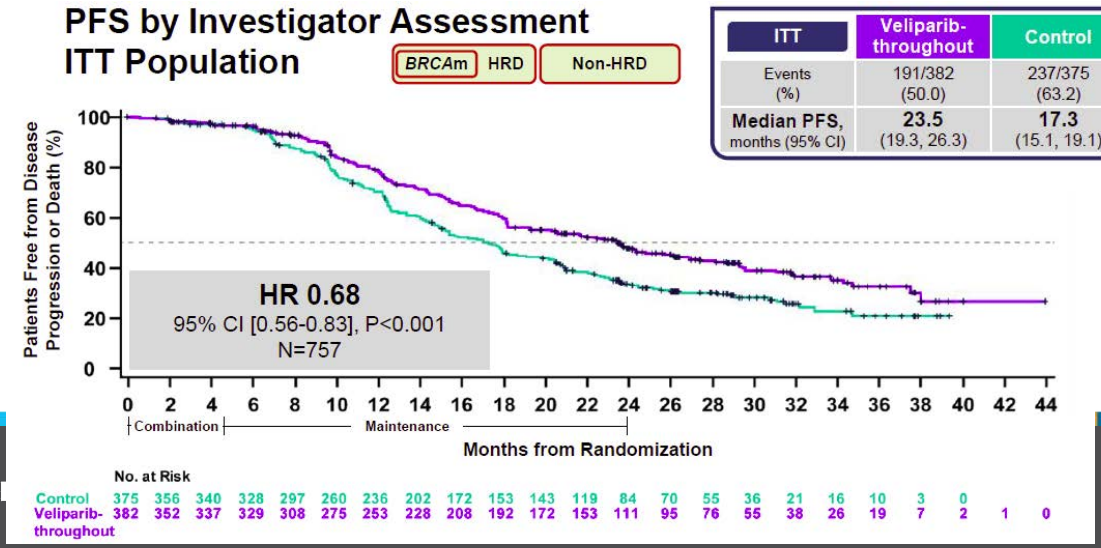
BRCAm	Veliparib-throughout	Control
Events (%)	34/108 (31.5)	51/92 (55.4)
Median PFS, months (95% CI)	34.7 (31.8, -)	22.0 (17.8, 29.1)

BRCA and HRD+



HRD	Veliparib-throughout	Control
Events (%)	87/214 (40.7)	124/207 (59.9)
Median PFS, months (95% CI)	31.9 (25.8, 38.0)	20.5 (17.8, 22.8)

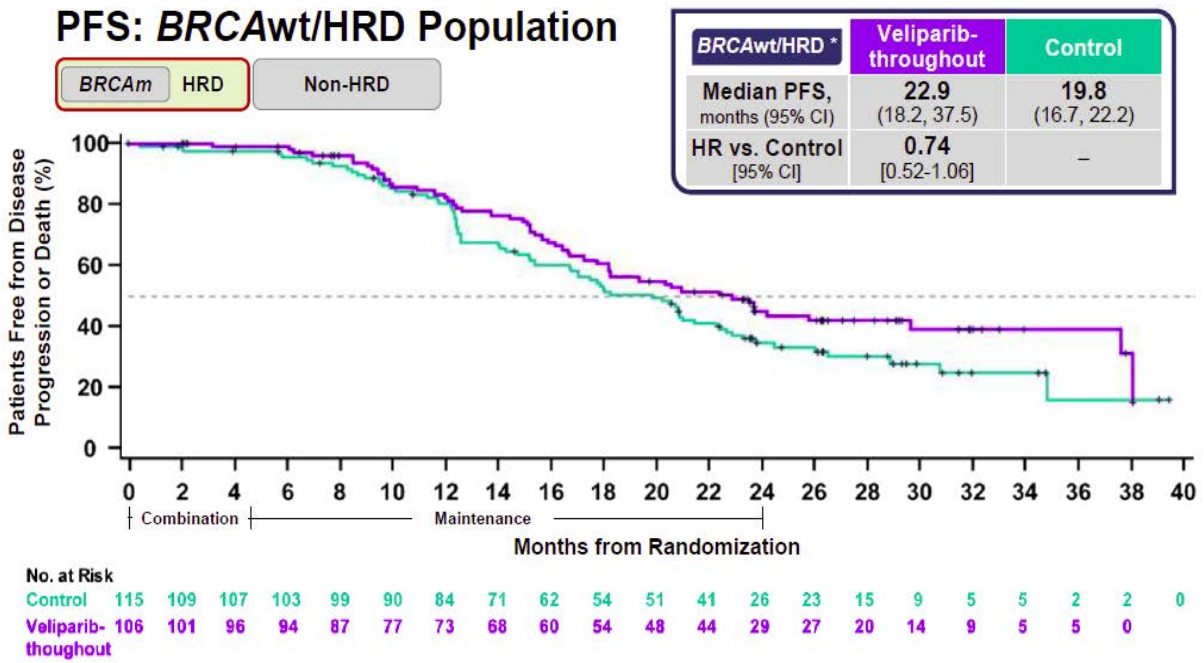
All patients

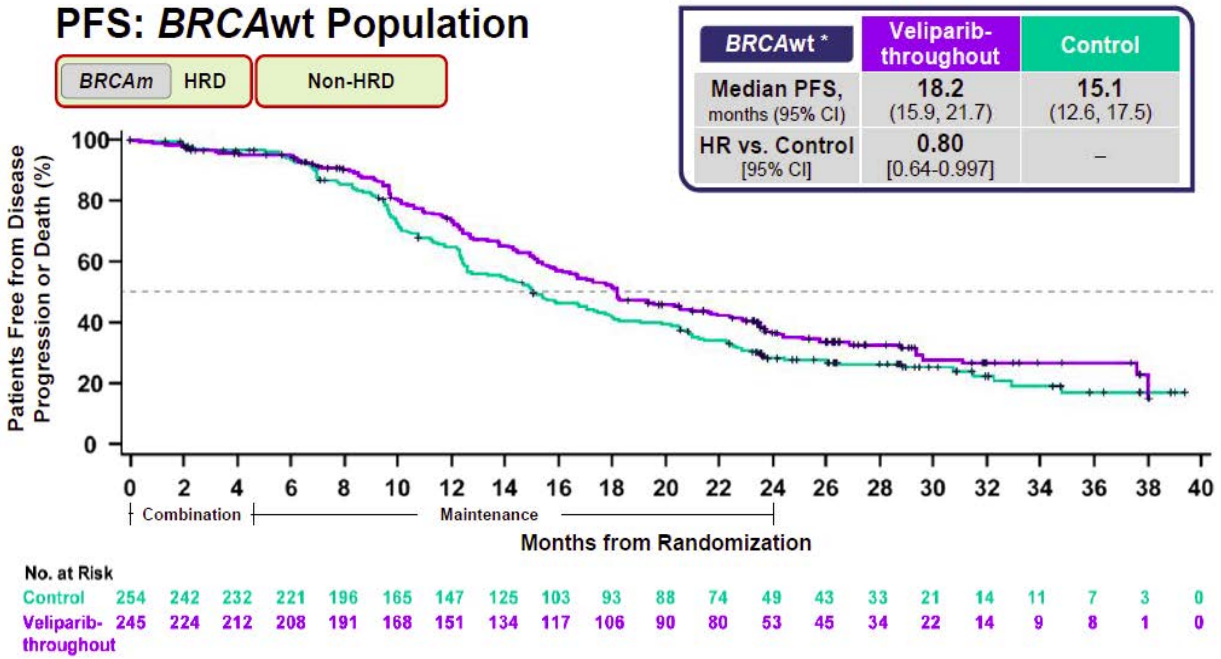


ITT	Veliparib-throughout	Control
Events (%)	191/382 (50.0)	237/375 (63.2)
Median PFS, months (95% CI)	23.5 (19.3, 26.3)	17.3 (15.1, 19.1)

Coleman et al., *N Engl J Med* 2019, ESMO 2019

VELIA: No PFS benefit in non-BRCAmt patients (exploratory)





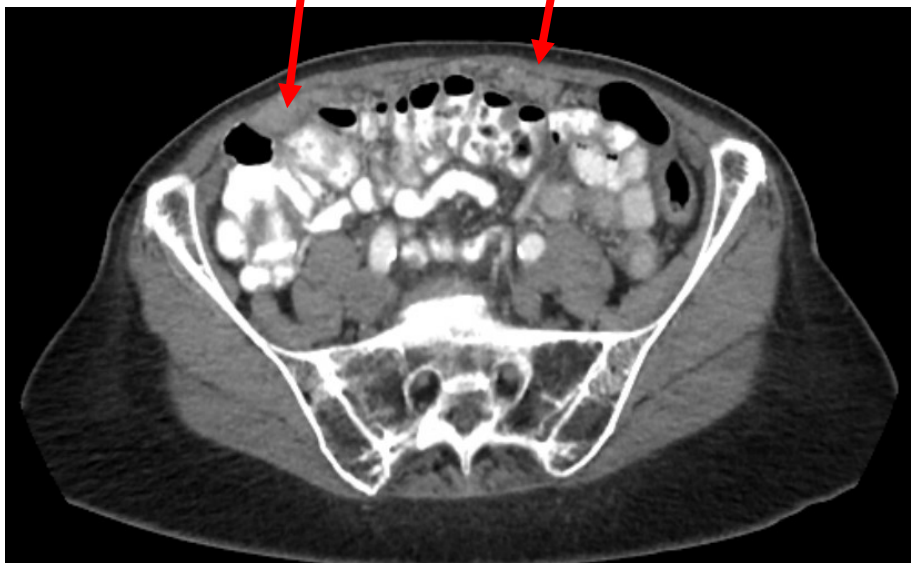
Coleman et al., *N Engl J Med* 2019, ESMO 2019

Dr Matulonis Case Presentation: 85 yo F

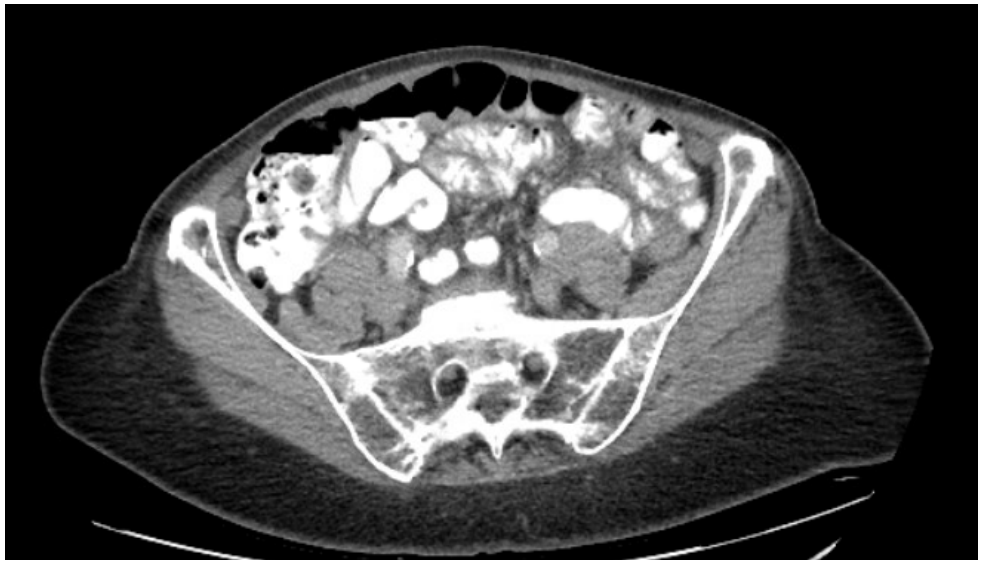
- Self palpated an abdominal mass in 2018
- CT scan showed bilateral ovarian masses, omental caking and peritoneal carcinomatosis.
- Went to laparoscopy in August 2018 and found to have miliary tumor deposits on the right hemidiaphragm, anterior abdominal wall, small and large bowel mesentery, and outside surface of lower colon, omental caking, bilateral ovarian masses; she was deemed not a surgical candidate, and an omental biopsy showed **high grade serous carcinoma**
- Her PMHx included HTN, Afib, small CVA with transient visual loss in the past, hypercholesterolemia, and DJD; Meds include apixaban, atorvastatin, and amlodipine.

Dr Matulonis Case Presentation: 85 yo F (cont)

- Started IV weekly carboplatin AUC 2 and weekly paclitaxel 80 mg/m^2
- CA125 was 112 at start of chemotherapy and dropped to 15 after 9 weeks. Found to have a germline *BRCA1* mutation
- After 9 weeks of chemotherapy, she underwent R0 interval debulking surgery
- ~4 weeks after surgery, she restarted weekly carbo and weekly paclitaxel but completed only 6 weeks of treatment (missed 3 weeks); stopped for fatigue, mild neuropathy. CA125 was 10 at the completion of chemotherapy in Feb 2019



Omental caking
pre-chemotherapy



After 9 weeks of
weekly carbo and weekly paclitaxel

Dr Matulonis Case Presentation: 85 yo F (cont)

- Started Olaparib 300 mg BID in March 2019
- Had some mild nausea (grade 1) and fatigue (grade 1, occ grade 2) during first 2 months of treatment; but this has mostly abated.
- March 2019 Hgb 12.8 g/dl and Hct 38.4%; checked monthly for one year.
- March 2020: Hgb 11.8 g/dl and Hct 34.8%, plts and WBC all WNL
- April 2020: CA125 is stable at 9

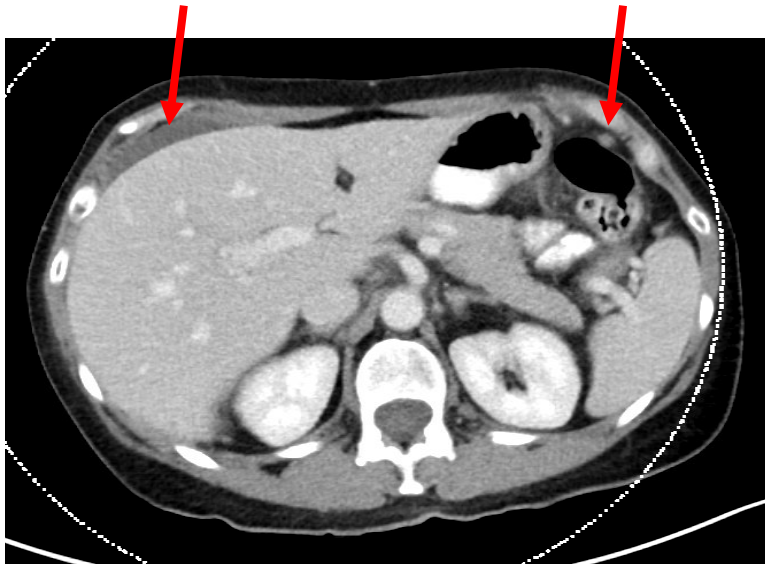
- Plan is for a total of 2 years of olaparib, then stop.
- She is currently NED

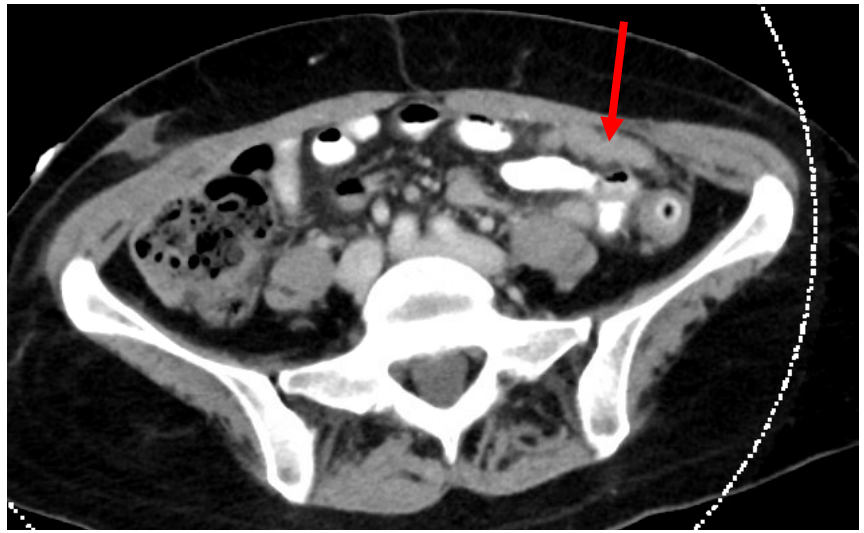
Dr Matulonis Case Presentation: 61 yo F

- Presented with abdominal pain in 2019, and a CT scan showed small volume ascites, peritoneal carcinomatosis, omental caking and a pelvic mass; CA125 was 320
- Went to laparoscopy; deemed not an upfront debulking candidate, and multiple biopsies showed **high grade serous carcinoma**
- Germline and somatic *BRCA* wild-type
- Started IV carboplatin AUC 6 and paclitaxel 175 mg/m^2 in August 2019
- CA125 fell to 24 after 3 cycles of chemotherapy

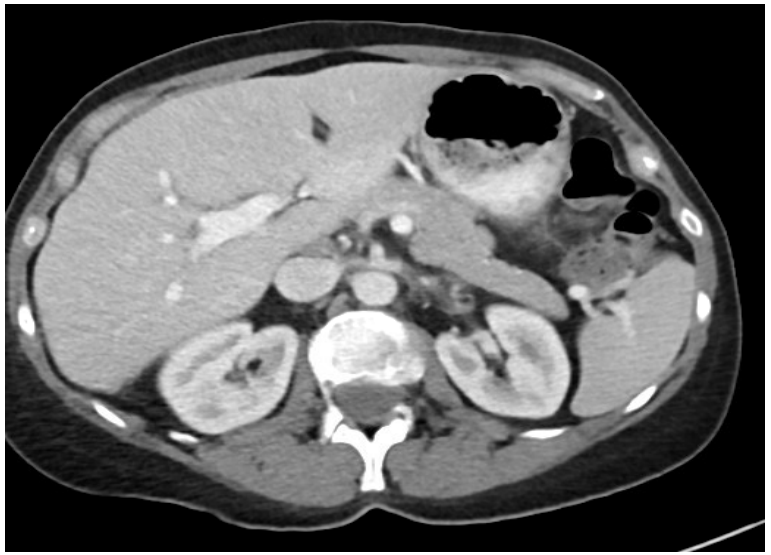
Dr Matulonis Case Presentation: 61 yo F (cont)

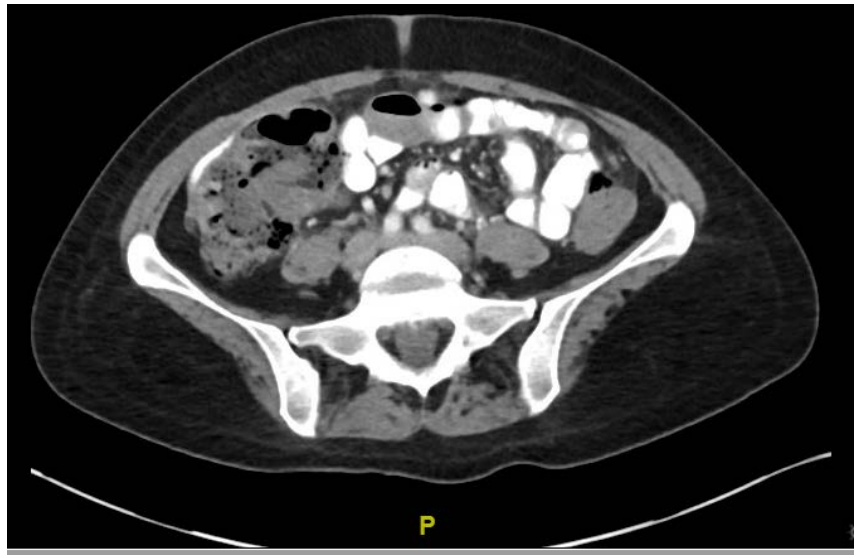
Pre-chemotherapy





After 3 cycles of carboplatin and paclitaxel: near normal CT





Dr Matulonis Case Presentation: 61 yo WF (cont)

- Underwent surgery in October 2019 and had R0 resection
- Completed 3 additional cycles of carboplatin and paclitaxel IV which she completed in late December 2019
- Had tumor HRD testing and was HRD
- Weight 62 kg, so started niraparib 200 mg PO daily in Feb 2020

	Date	ANC	Hgb	Hct	Plts
start niraparib 200 mg/d →	**2/6/20**	**2490**	**13.1**	**38.5**	**264**
	2/13/20	3290	13.7	40.4	239
	2/20/20	3090	13.4	39.9	148
Hold niraparib →	2/27/20	1470	12.9	38.4	118
Restart Niraparib 100 mg/d →	3/5/20	2000	11.8	34.2	157
	3/12/20	3130	12.6	37.8	315
	3/19/20	4100	11.7	35.5	242
	3/26/20	2930	12.9	37.8	206
	4/2/20	3550	12.9	38.2	222
	5/15/20	2680	13	38.3	233

June 2020: Doing well on Niraparib 100 mg per day

Agenda

Module 1: Overview of PARP Inhibitors: Biologic Rationale and Mechanism of Action

Module 2: Side Effects and Toxicities of PARP Inhibitors

Module 3: PARP Inhibitors for Ovarian Cancer – Dr Matulonis

- Key data sets: SOLO-1, PRIMA, PAOLA-1, VELIA

Module 4: PARP Inhibitors for Breast Cancer – Dr Rugo

- Key data sets: EMBRACA, OlympiAD, BROCADE3

Module 5: PARP Inhibitors for Pancreatic Cancer – Dr Philip

- Key data sets: POLO, RUCAPANC

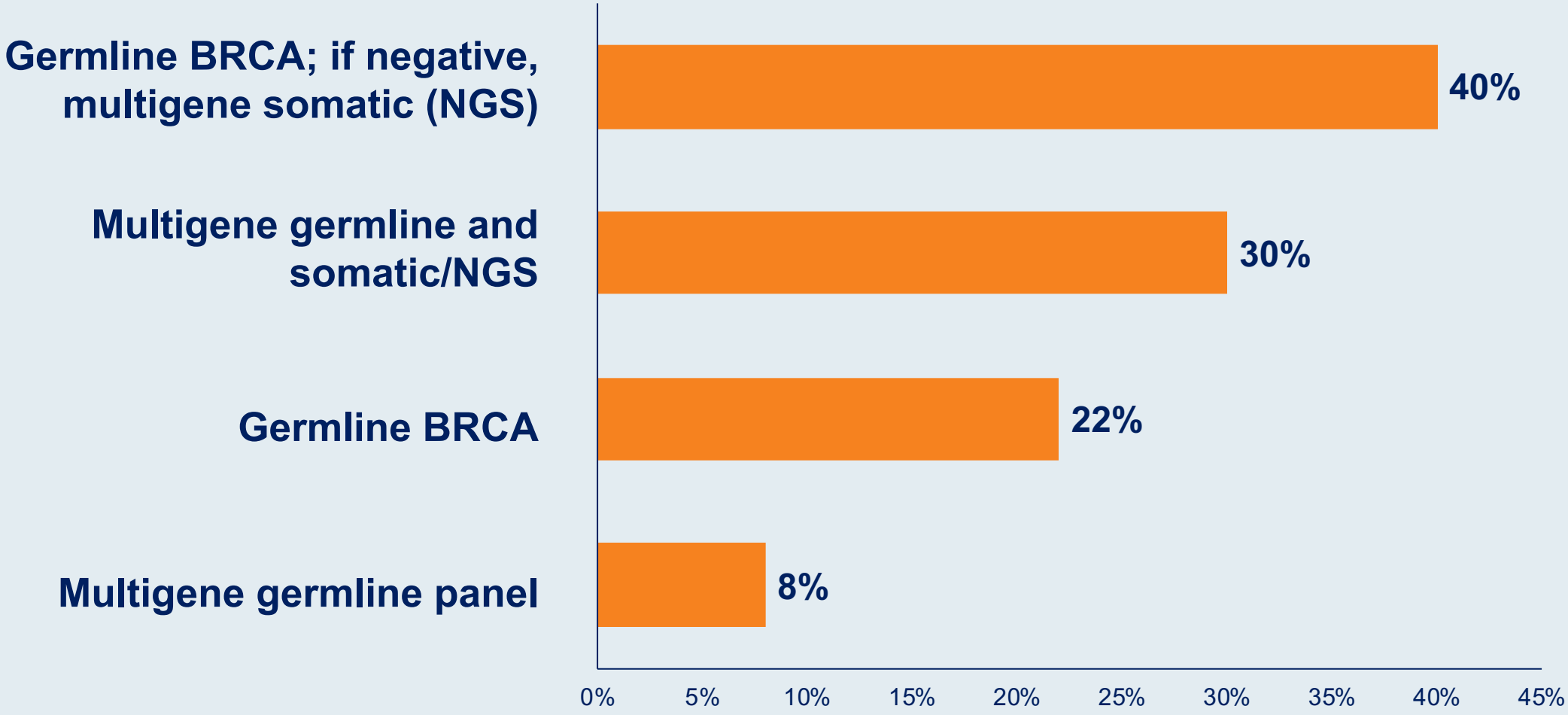
Module 6: PARP Inhibitors for Prostate Cancer – Dr Hussain

- Key data sets: PROfound, TRITON2, GALAHAD

Module 4: PARP Inhibitors for Breast Cancer – Dr Rugo

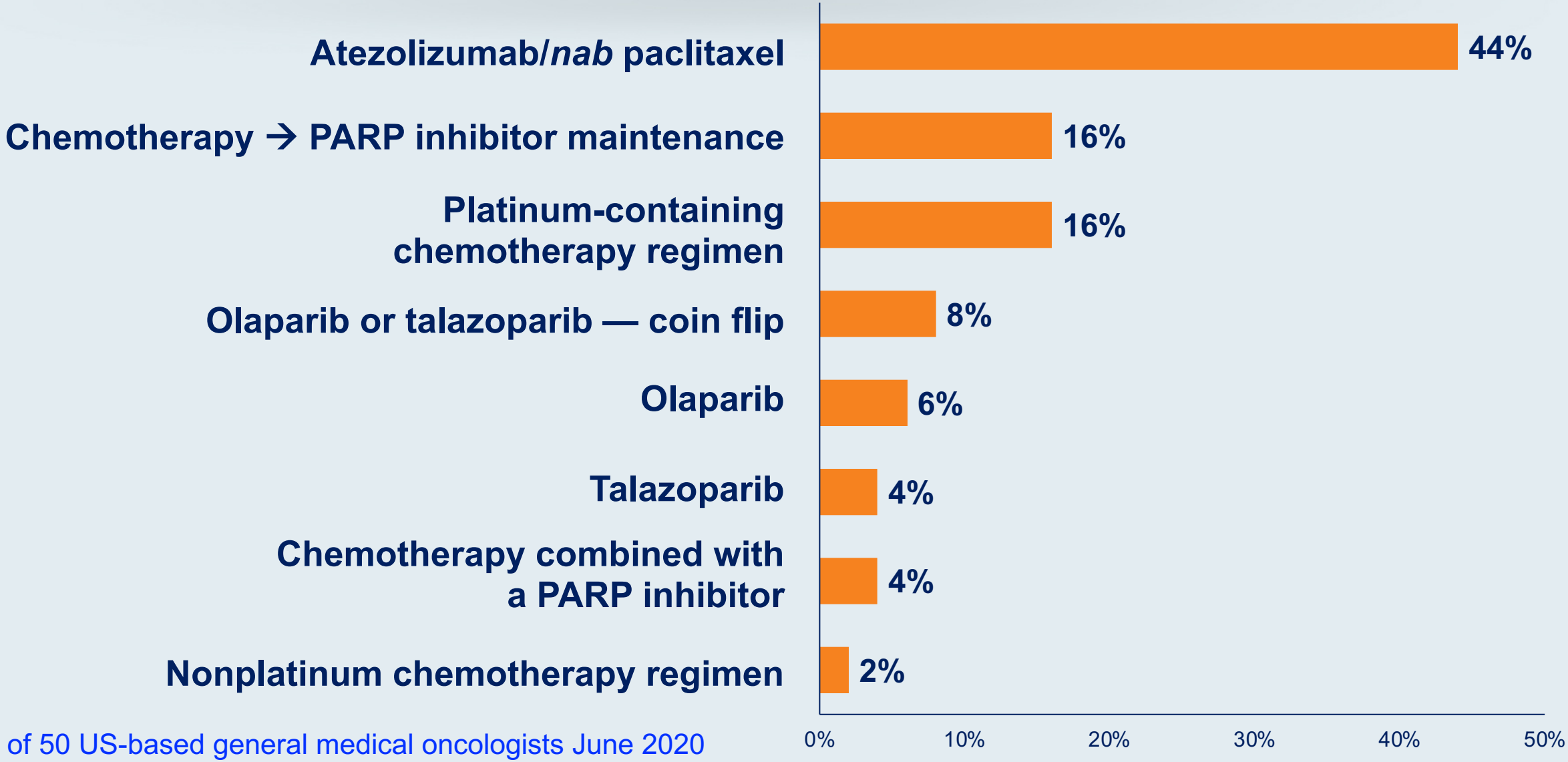
- Genomic profile
- Key recent data sets: EMBRACA, OlympiAD, BROCADE
- Current practice patterns
- Ongoing trials

In general, what is the optimal approach to mutation testing for possible use of a PARP inhibitor for a patient with de novo metastatic triple-negative breast cancer and no family history?



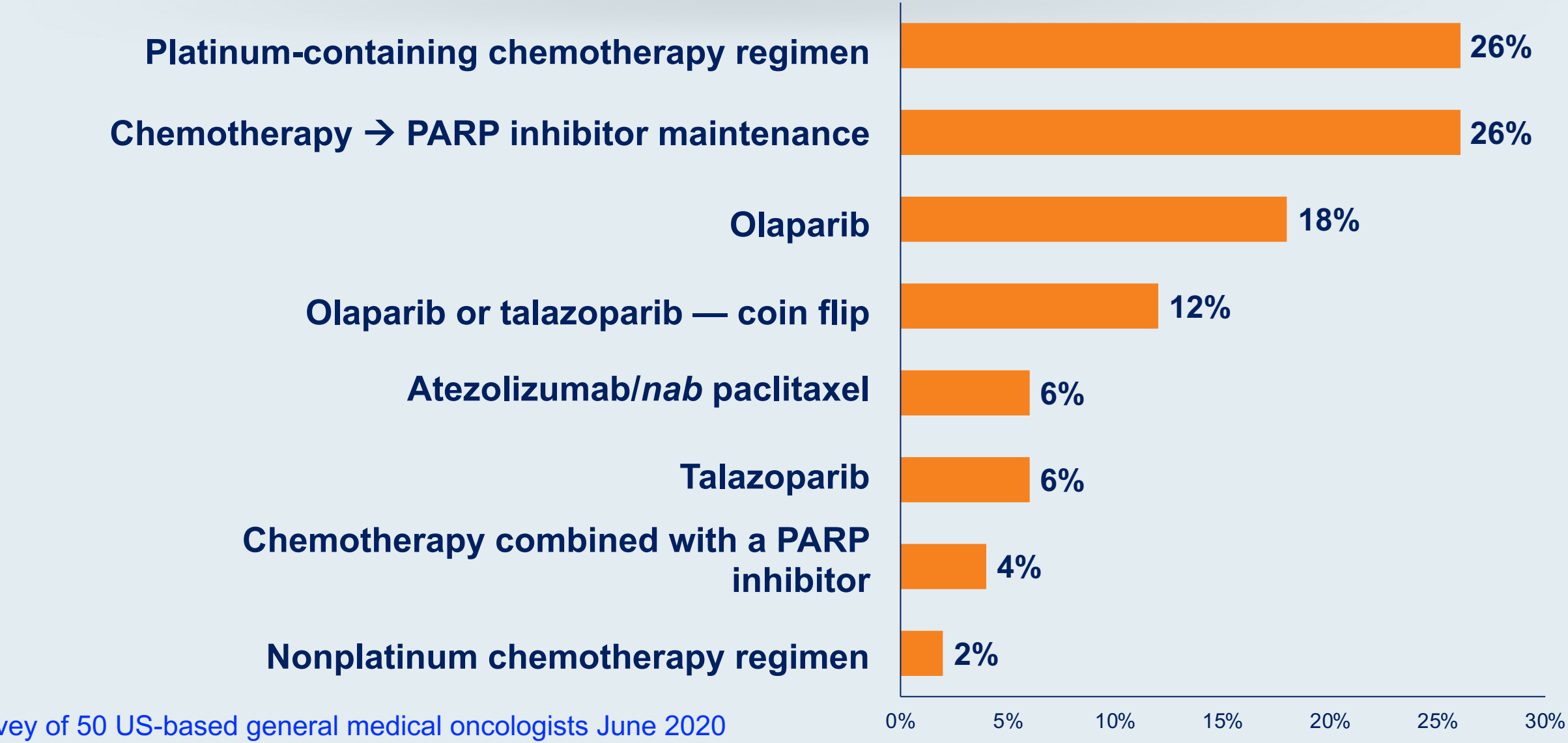
Survey of 50 US-based general medical oncologists June 2020

Reimbursement and regulatory issues aside, what would be your preferred treatment approach for a 60-year-old patient with a germline BRCA mutation and de novo metastatic triple-negative breast cancer that is PD-L1-positive?



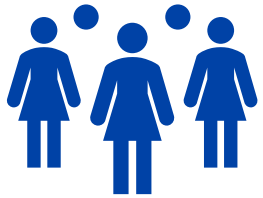
Survey of 50 US-based general medical oncologists June 2020

Reimbursement and regulatory issues aside, what would be your preferred treatment approach for a 60-year-old patient with a germline BRCA mutation and de novo metastatic triple-negative breast cancer that is PD-L1-negative?



Survey of 50 US-based general medical oncologists June 2020

Epidemiology of g*BRCA* Mutations



Female breast cancer

- ~3%–6% of **all breast cancer** patients[1-4]
- 2.7%–4.3% among **MBC** patients[1,2]
- 9.3%–15.4% in **TNBC**[5-7]

Male breast cancer

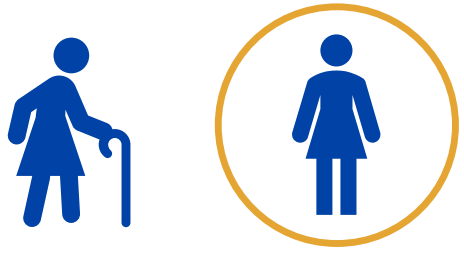
16% of all male breast cancers[8]

Hereditary breast cancer

~25% of hereditary breast cancers[9]

Lifetime risks of breast cancer by age 70

~57% for *BRCA1* mutation carriers; ~49% for *BRCA2* mutation carriers



Younger age at diagnosis

Individuals with g*BRCA* mutations are diagnosed with breast cancer **~20 years younger** than the overall breast cancer population[10]

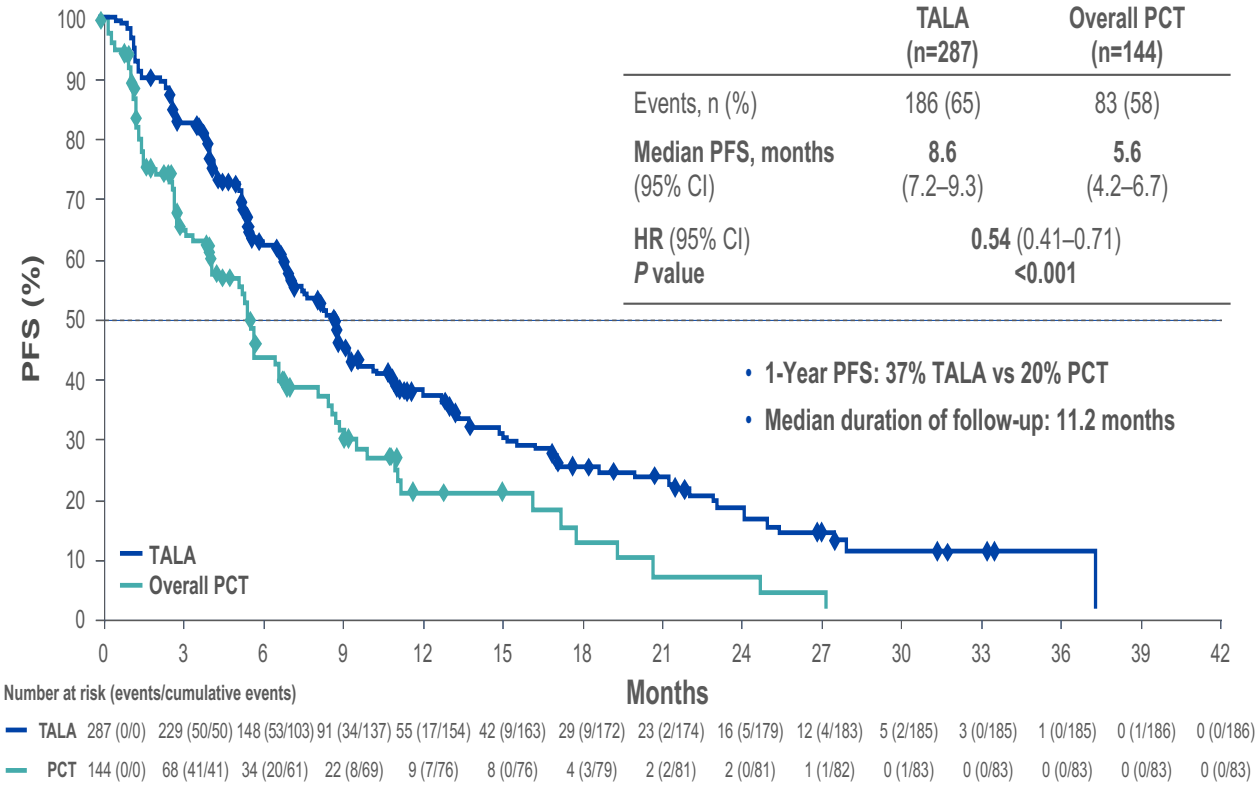
- Women with g*BRCA* mutations are more likely to develop a second breast cancer[11]

BRCA=breast cancer susceptibility gene; MBC=metastatic breast cancer; TNBC=triple-negative breast cancer.

1. Meynard G, et al. Ann Oncol. 2017;28(suppl 5):v74-v108. **2.** Fasching PA, et al. Abstract PD1-02. SABCS 2017. **3.** Tung N, et al. J Clin Oncol. 2016 May 1;34(13):1460-8. **4.** Nelson HD, et al. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer: systematic review to update the U.S. Preventive Services Task Force recommendation. Evidence Synthesis No. 101. Rockville, MD: Agency for Healthcare Research and Quality; 2013. AHRQ Publication No. 12-05164-EF-1. **5.** Wong-Brown MW, et al. Breast Cancer Res Treat. 2015 Feb;150(1):71-80. **6.** Couch FJ, et al. J Clin Oncol. 2015 Feb;33(4):304-11. **7.** Sharma P, et al. Breast Cancer Res Treat. 2014 Jun;145(3):707-14. **8.** Giordano SH. N Engl J Med. 2018 Jun 14;378(24):2311-20. **9.** Arpino G, et al. BMC Cancer. 2016 Nov 29;16(1):924. **10.** Kim R, et al. Poster P5-08-28. SABCS 2016. **11.** Godet I, Gilkes DM. Integr Cancer Sci Ther. 2017 Feb;4(1). doi:10.15761/ICST.1000228.

Progression Free Survival

EMBRACA



	TALA (n=287)	Overall PCT (n=144)
Events, n (%)	186 (65)	83 (58)
Median PFS, months (95% CI)	**8.6** (7.2–9.3)	**5.6** (4.2–6.7)
HR (95% CI)	**0.54** (0.41–0.71)	
***P* value**	**<0.001**	

Number at risk (events/cumulative events)

TALA	287 (0/0)	229 (50/50)	148 (53/103)	91 (34/137)	55 (17/154)	42 (9/163)	29 (9/172)	23 (2/174)	16 (5/179)	12 (4/183)	5 (2/185)	3 (0/185)	1 (0/185)	0 (1/186)	0 (0/186)
PCT	144 (0/0)	68 (41/41)	34 (20/61)	22 (8/69)	9 (7/76)	8 (0/76)	4 (3/79)	2 (2/81)	2 (0/81)	1 (1/82)	0 (1/83)	0 (0/83)	0 (0/83)	0 (0/83)	0 (0/83)

From The New England Journal of Medicine. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline *BRCA* mutation, vol. 379, 753-763. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from the Massachusetts Medical Society.

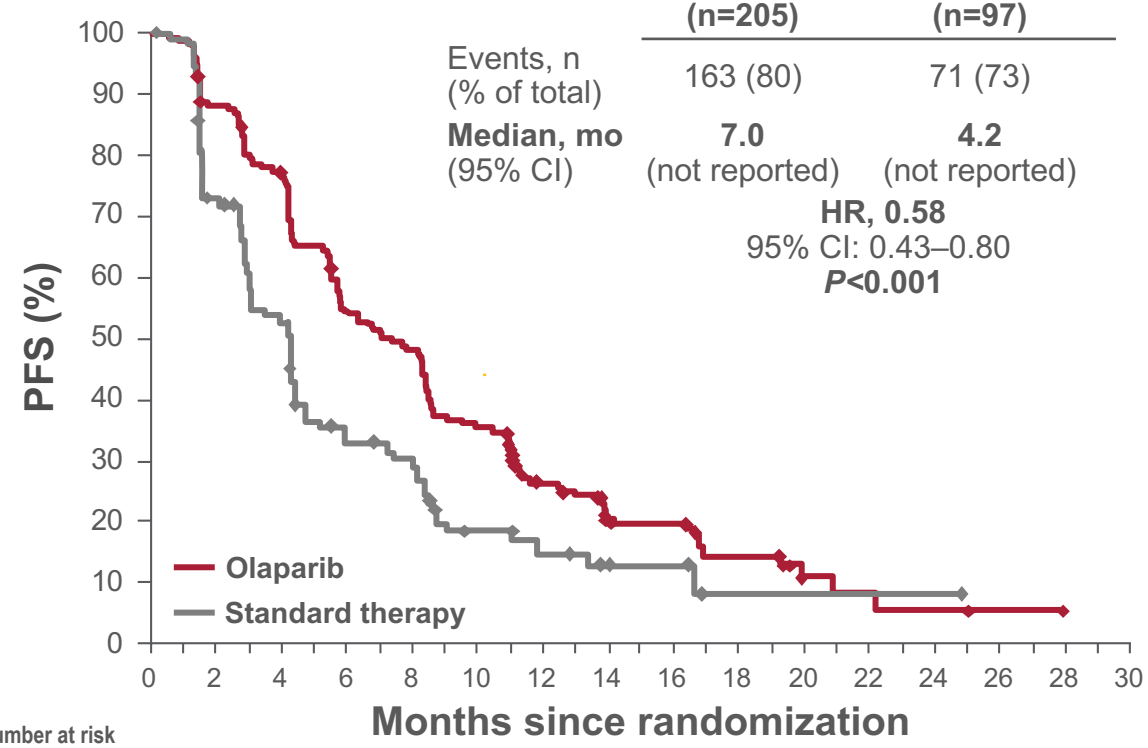
Data cutoff: September 15, 2017.

BRCA=breast cancer susceptibility gene; BICR=blinded independent central review; CI=confidence interval; HR=hazard ratio; PCT=physician's choice of chemotherapy; PFS=progression-free survival; TALA=talazoparib.

Extracted from Litton JK, et al. N Engl J Med. 2018 Aug 23;379(8):753-63. (EMBRACA)

OlympiAD

PFS: ITT Population



	Olaparib (n=205)	Standard therapy (n=97)
Events, n (% of total)	163 (80)	71 (73)
Median, mo (95% CI)	**7.0** (not reported)	**4.2** (not reported)

HR, 0.58
95% CI: 0.43–0.80
***P*<0.001**

Number at risk

Olaparib	205	201	177	159	154	129	107	100	94	73	69	61	40	36	23	21	21	11	11	11	4	3	3	2	2	1	1	1	0
Standard therapy	97	88	63	46	44	29	25	24	21	13	11	11	8	7	4	4	4	1	1	1	1	1	1	1	0	0	0	0	

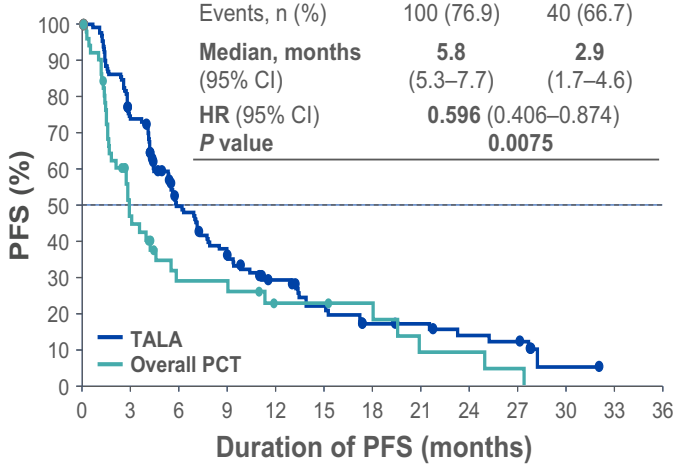
Median duration of follow-up for PFS: 14.5 months (olaparib), 14.1 months (standard therapy)

Robson M et al. N Engl J Med 2017;377:523-33. (OlympiAD)

EMBRACA and OlympiAD: Talazoparib significantly improved PFS in both HR+ and TNBC compared to TPC

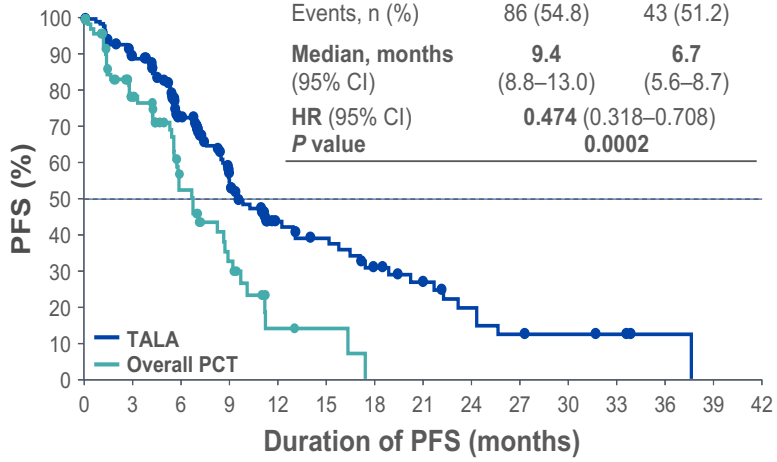
TNBC

	TALA (n=130)	Overall PCT (n=60)
Events, n (%)	100 (76.9)	40 (66.7)
Median, months (95% CI)	**5.8** (5.3–7.7)	**2.9** (1.7–4.6)
HR (95% CI)	**0.596** (0.406–0.874)	
***P* value**	**0.0075**	



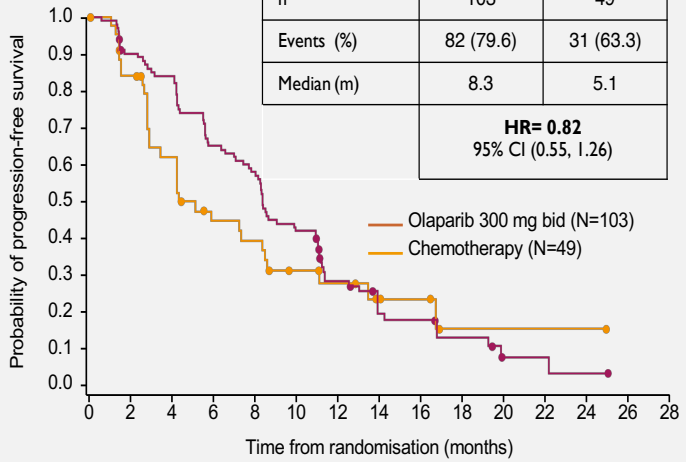
HR+

	TALA (n=157)	Overall PCT (n=84)
Events, n (%)	86 (54.8)	43 (51.2)
Median, months (95% CI)	**9.4** (8.8–13.0)	**6.7** (5.6–8.7)
HR (95% CI)	**0.474** (0.318–0.708)	
***P* value**	**0.0002**	



Patients with HR+ mBC[2]

	Olaparib	TPC
n	103	49
Events (%)	82 (79.6)	31 (63.3)
Median (m)	8.3	5.1
	HR= 0.82 95% CI (0.55, 1.26)	

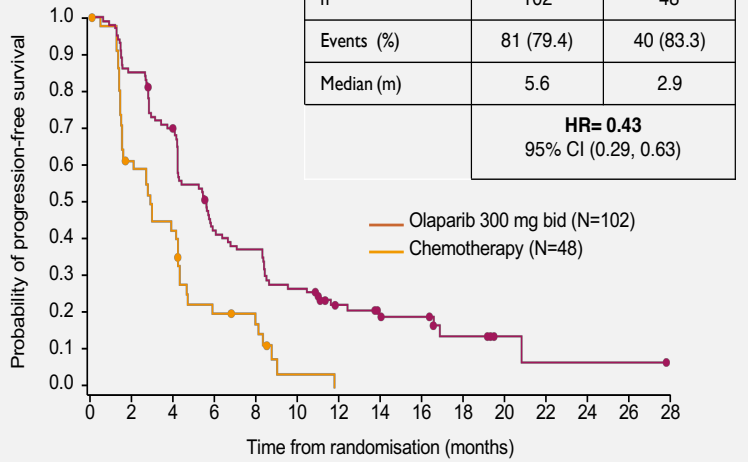


Number of patient's at risk

Olaparib	103	102	91	86	85	75	66	63	58	46	43	39	23	20	13	12	12	6	6	6	2	2	2	1	1	0	0	0	0	0
TPC	49	45	37	27	26	20	17	17	15	11	10	10	8	7	4	4	4	1	1	1	1	1	1	1	0	0	0	0	0	0

Patients with TNBC[2]

	Olaparib	TPC
n	102	48
Events (%)	81 (79.4)	40 (83.3)
Median (m)	5.6	2.9
	HR= 0.43 95% CI (0.29, 0.63)	

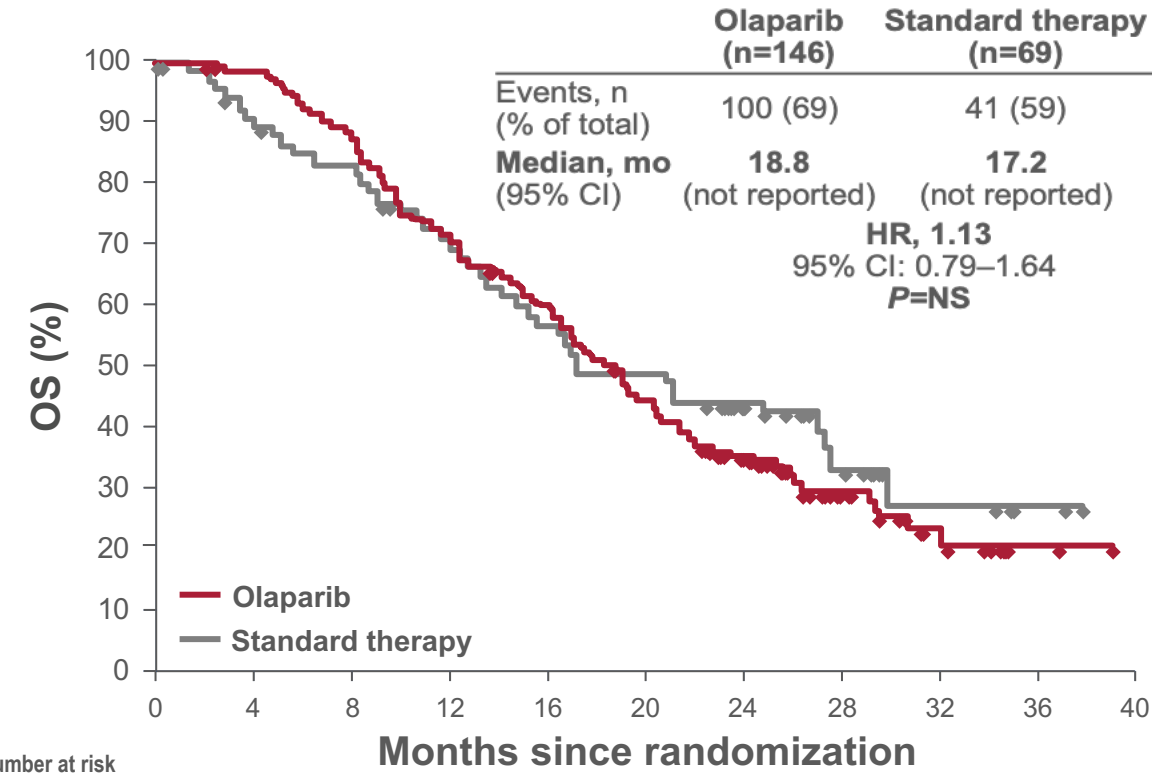


Number of patient's at risk

Olaparib	102	99	86	73	69	54	41	37	36	27	26	22	17	16	10	9	9	5	5	5	2	1	1	1	1	1	1	1	0
TPC	48	43	26	19	18	9	8	7	6	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

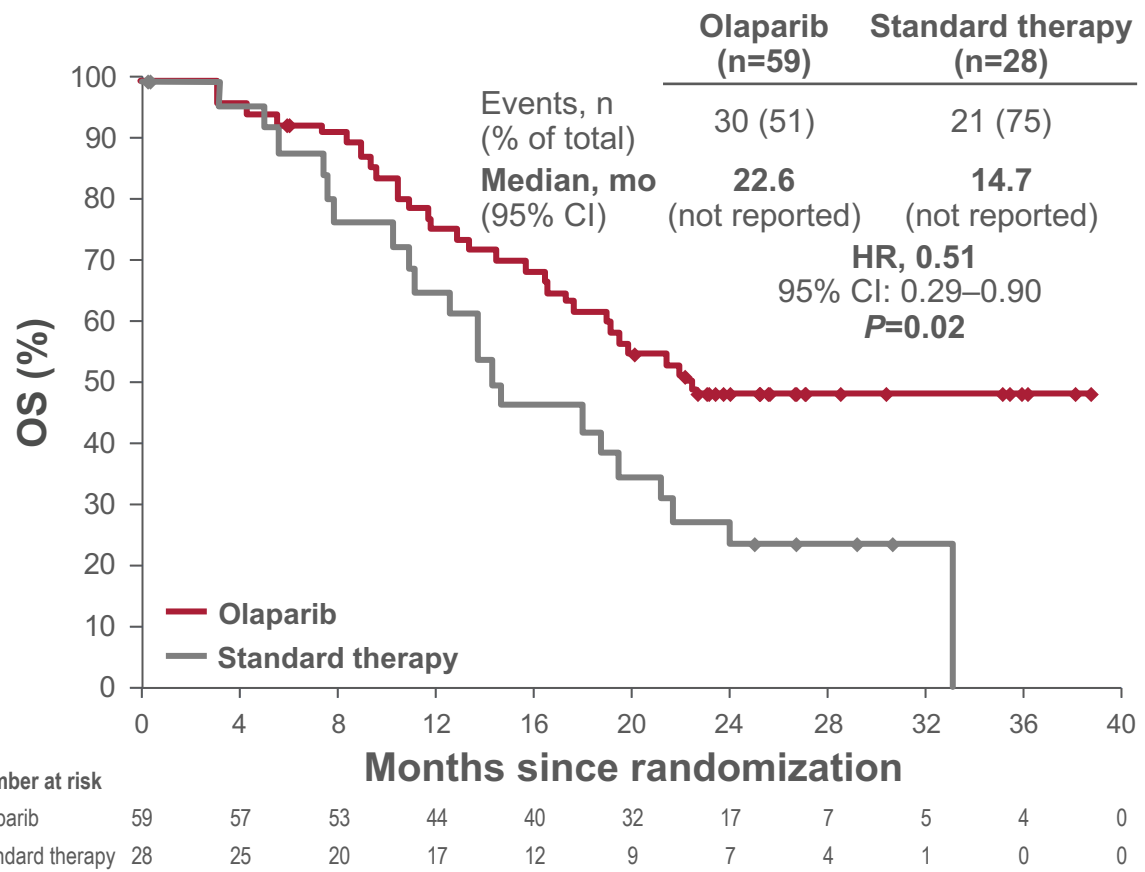
OlympiAD: OS Results

OS: Prior chemotherapy for MBC (2/3L)[2]



Median duration of follow-up for OS*: 25.3 months (olaparib), 26.3 months (standard therapy)

OS: No prior chemotherapy for MBC (1L)[2]



Median duration of follow-up for OS*: 25.3 months (olaparib), 26.3 months (standard therapy)

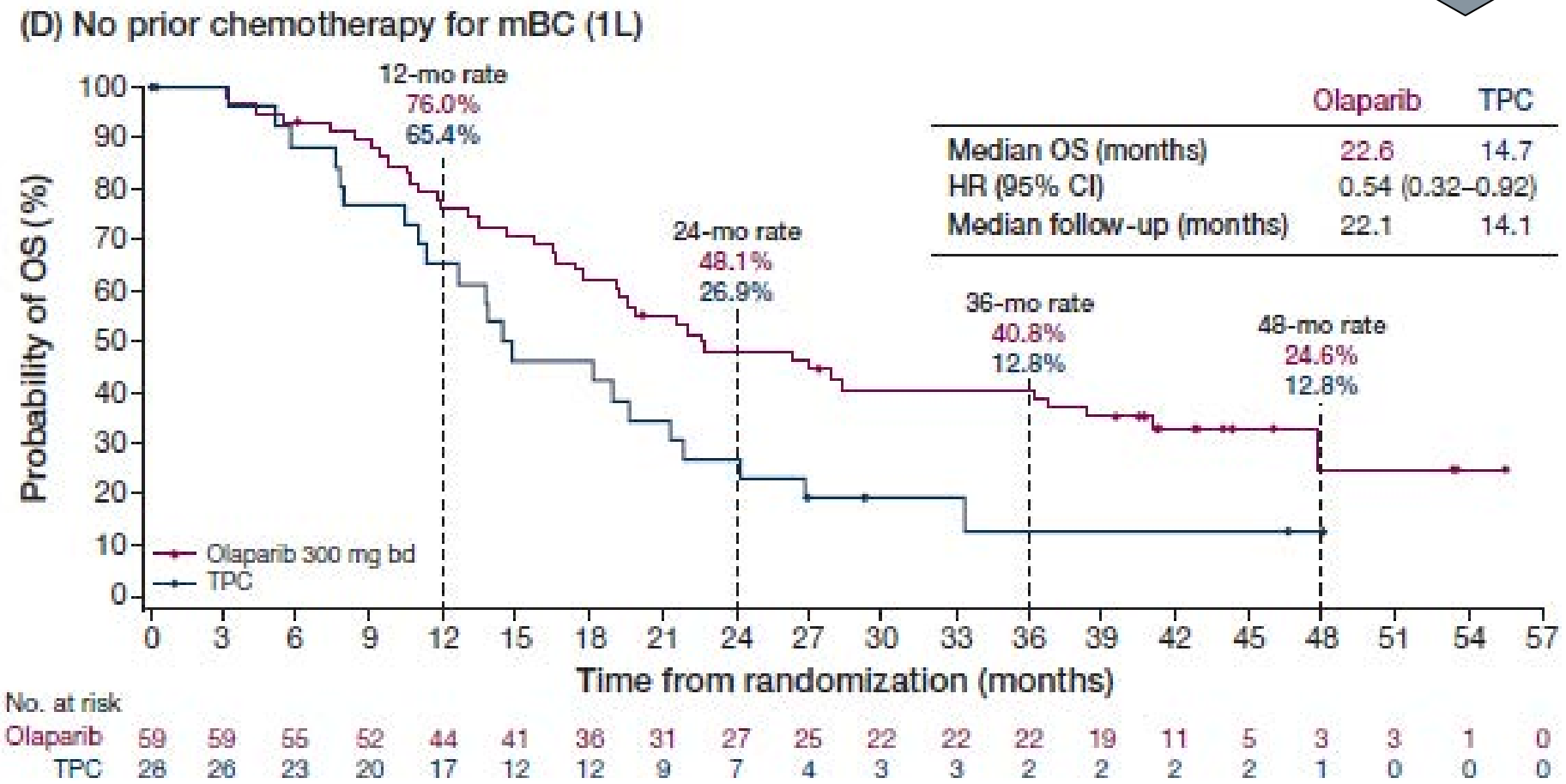
*Final analysis for OS. 1L=first line; 2/3L=second/third line; CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; MBC=metastatic breast cancer; mo=months; NS=not significant; OS=overall survival; PFS=progression-free survival.

1. Extracted from Robson M, et al. N Engl J Med. 2017 Aug 10;377(6):523-33. **2.** Extracted from Robson ME, et al. Ann Oncol. 2019 Apr 1;30(4):558-566.

OlympiAD Extended Follow-Up

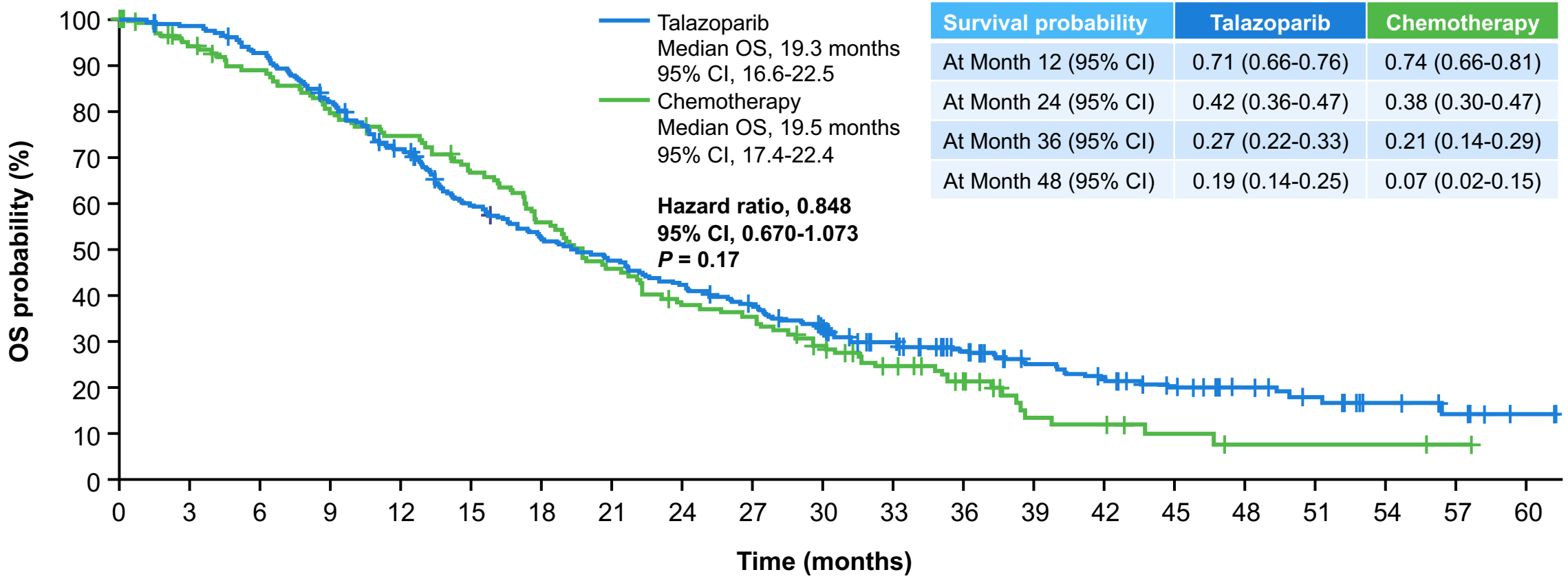
- No statistically significant differences in survival curves in:
  - Overall population and > 1 line of chemotherapy in metastatic setting
  - Tissue receptor subtype
  - Prior exposure to platinums
- No new safety signal –No AML/MDS

- 14 patients still on olaparib
- 8.8% received olaparib >3 years



Robson M, et al. *SABCS 2019*

EMBRACA: Final OS — Results From This Prespecified Analysis Found No Statistically Significant Difference Between The Treatment Groups*



Survival probability	Talazoparib	Chemotherapy
At Month 12 (95% CI)	0.71 (0.66-0.76)	0.74 (0.66-0.81)
At Month 24 (95% CI)	0.42 (0.36-0.47)	0.38 (0.30-0.47)
At Month 36 (95% CI)	0.27 (0.22-0.33)	0.21 (0.14-0.29)
At Month 48 (95% CI)	0.19 (0.14-0.25)	0.07 (0.02-0.15)

Number of patients at risk

Talazoparib	287	280	264	232	199	163	143	128	113	101	85	68	54	41	35	27	20	15	9	6	2
Chemotherapy	144	125	116	105	96	86	71	58	48	44	34	25	18	8	7	4	2	2	2	1	0

*ITT population

Litton et al, AACR 2020

BROCADE 3: Combining PARPi with Chemotherapy in gBRCA-Associated Breast Cancer

Patient Population

- Advanced HER2-negative breast cancer
- Germline *BRCA1* or *BRCA2* mutation
- ≤2 prior lines cytotoxic therapy for metastatic disease
- ≤1 prior lines of platinum; no progression ≤12 months of completing

Stratification Factors

- Hormone Receptor Expression
- Prior Platinum
- CNS Metastasis

2:1 Randomization
N=513

Veliparib + Carboplatin/paclitaxel

Placebo + Carboplatin/paclitaxel

Treat to progression:
If carboplatin and paclitaxel were discontinued prior to progression, dosing of veliparib/placebo increased to 300mg BID continuous, and then 400mg BID if tolerated

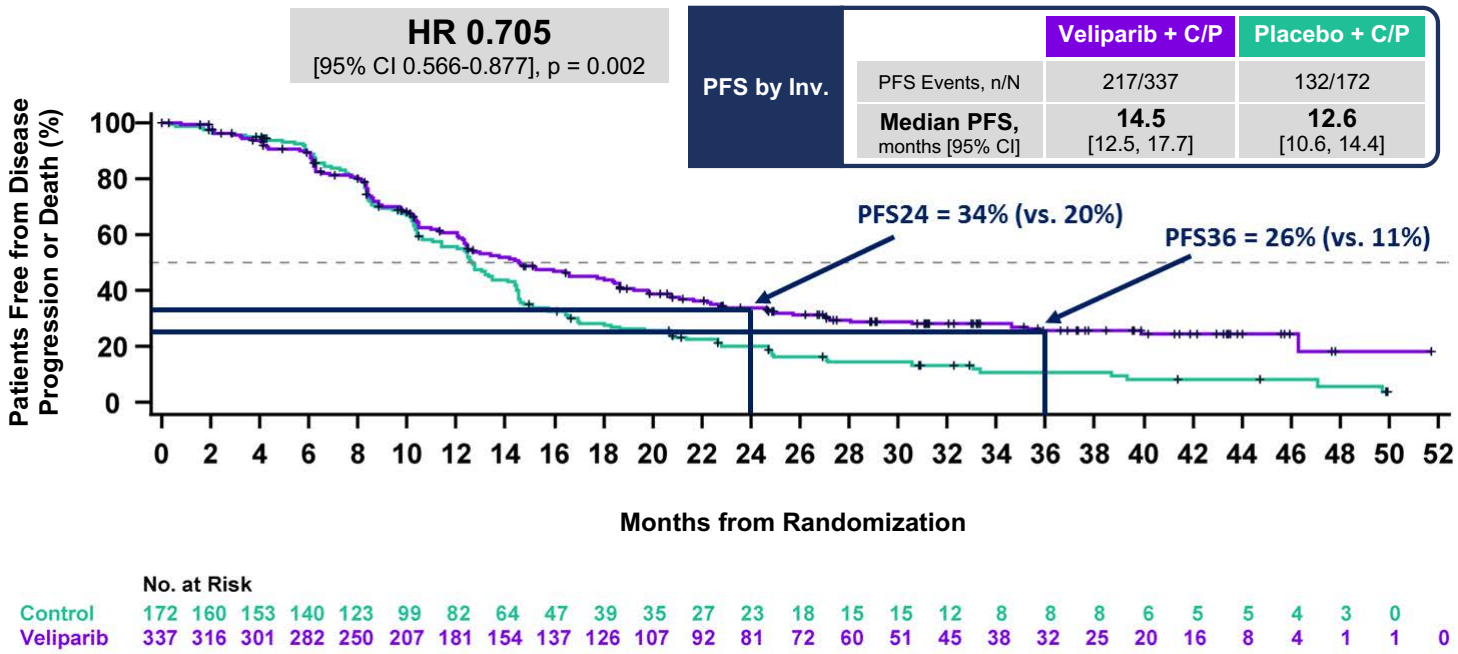
Optional open-label crossover to veliparib

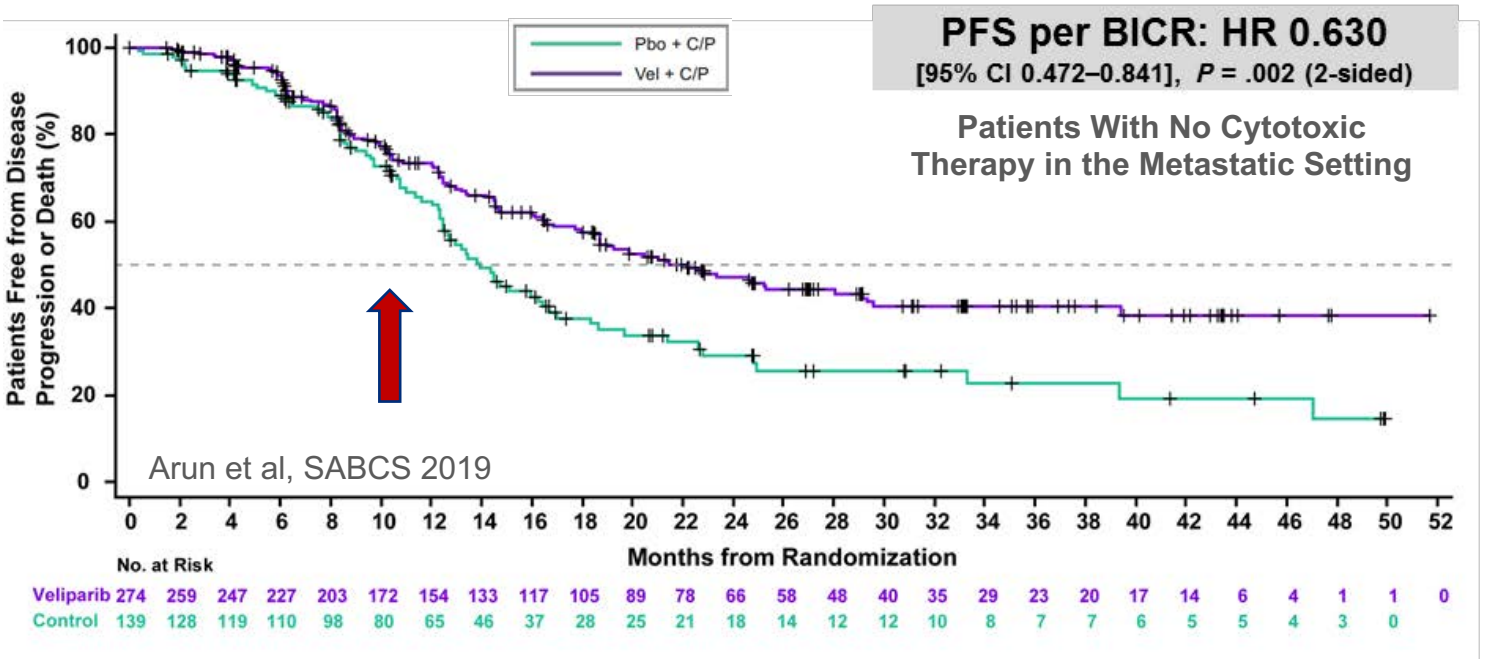
Primary Endpoint:
Investigator-assessed PFS per RECIST 1.1

21-Day Cycles:
- Carboplatin (C): AUC 6 on Day 1
- Paclitaxel (P): 80 mg/m^2 on Days 1, 8, 15
- Veliparib or Placebo: 120mg BID on Days -2 to 5

Dieras et al, ESMO 2019

Primary Endpoint: PFS by Investigator Assessment



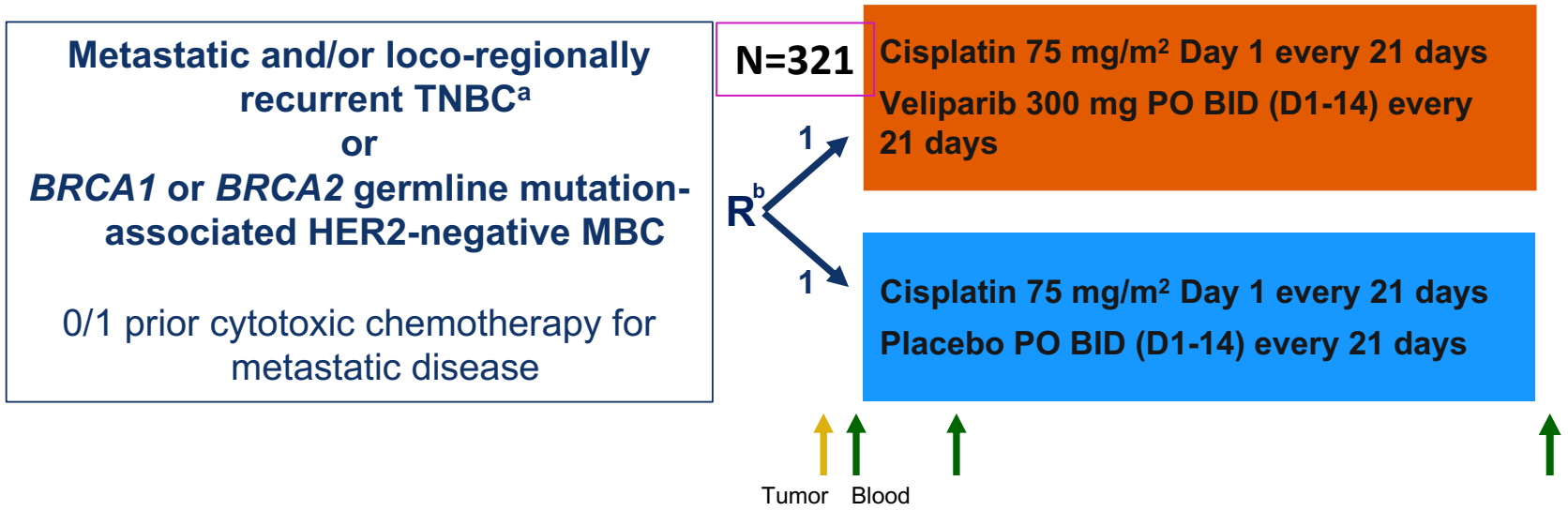


Grade 3+ toxicity

- Thrombocytopenia
  - 40% vs 28%
- No change in neutropenia (80-81%), anemia (40-42%)

- First phase III trial to evaluate the addition of a PARPi to platinum based chemotherapy in patients with MBC and gBRCA mutations
- Maintenance after chemotherapy
  - 42.5% monotherapy with veliparib
  - 32.4% monotherapy with placebo
- 44% cross over with PD from placebo to veliparib

SWOG-S1416: Cisplatin +/- Veliparib in Metastatic TNBC and/or BRCA Associated MBC



Primary end point:

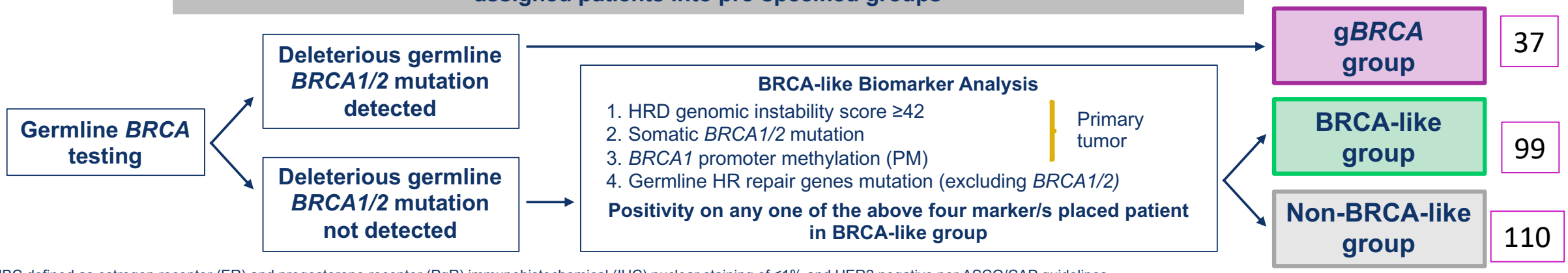
Progression- free survival in three pre-specified groups:

- g*BRCA*
- BRCA-like
- non-BRCA-like

Secondary end points:

- Overall survival
- Objective response rate
- Clinical benefit rate

Post-randomization germline and BRCA-like biomarker testing assigned patients into pre-specified groups



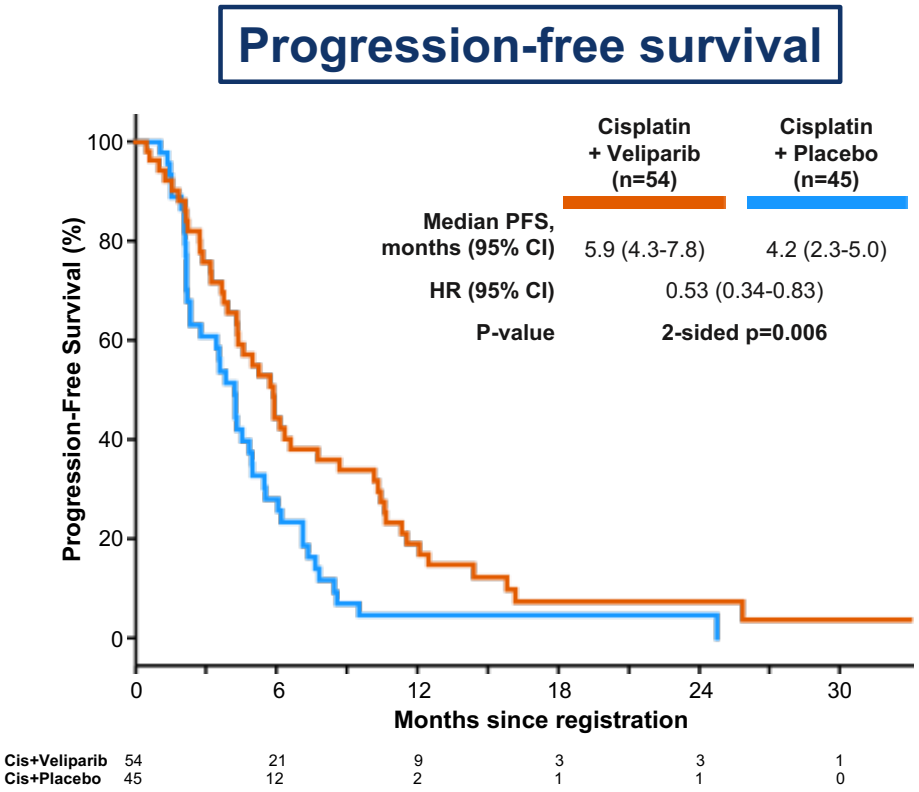
[a]TNBC defined as estrogen receptor (ER) and progesterone receptor (PgR) immunohistochemical (IHC) nuclear staining of ≤1% and HER2 negative per ASCO/CAP guidelines
[b]Randomization stratified by number of prior cytotoxic regimens for metastatic disease (0 vs. 1)

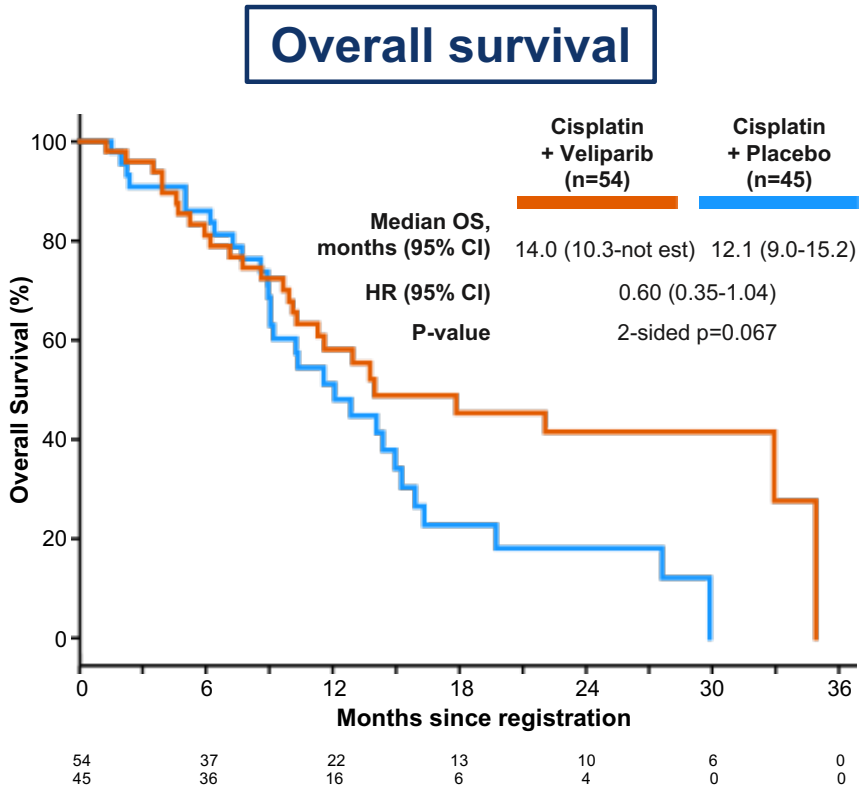
Sharma et al, ASCO 2020

Results: PFS and OS

- gBRCA: no difference in PFS (6.3 mo) or OS (14.4 mo) with veliparib
  - ?small subset?
- Non-BRCA-like: no differences
- BRCA-like:

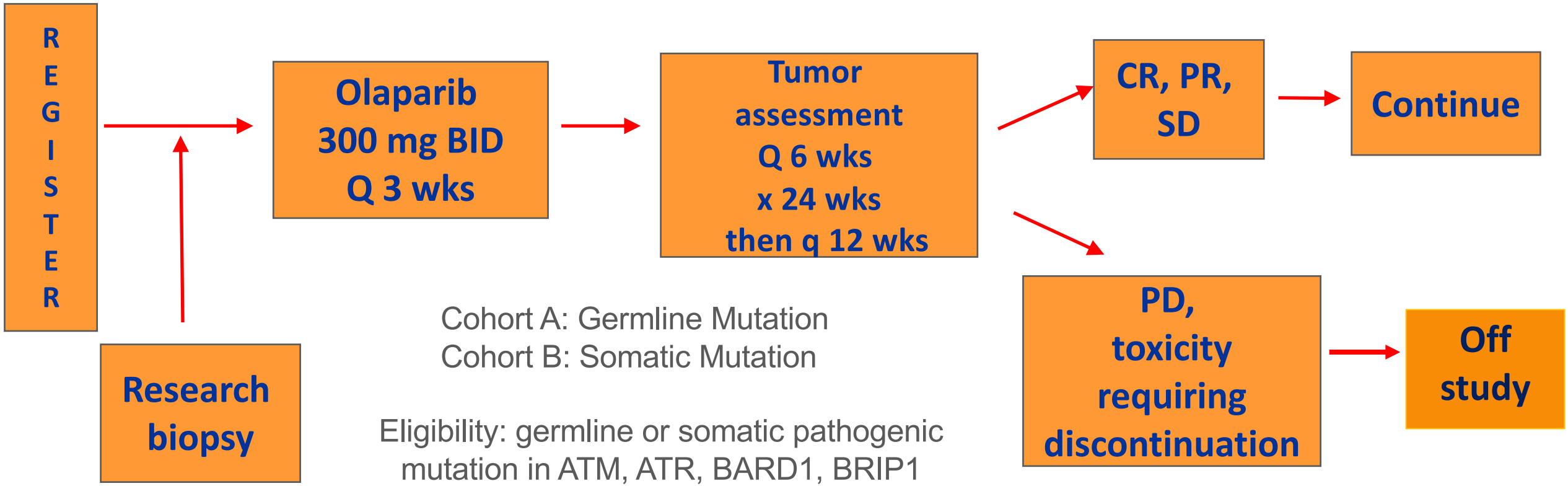
Comments and questions:
- Role of somatic mutations versus HRD?
- Small differences in PFS
- No real maintenance therapy





ORR (n=83): 45% vs 33%

TBCRC 048: Olaparib Expanded



Cohort A: Germline Mutation
Cohort B: Somatic Mutation

Eligibility: germline or somatic pathogenic mutation in ATM, ATR, BARD1, BRIP1 (FANCJ), CHEK2 , FANC genes, MRE11A, NBN, PALB2, RAD50, RAD51C, RAD51D (+ others)*; somatic mutation in BRCA1/2

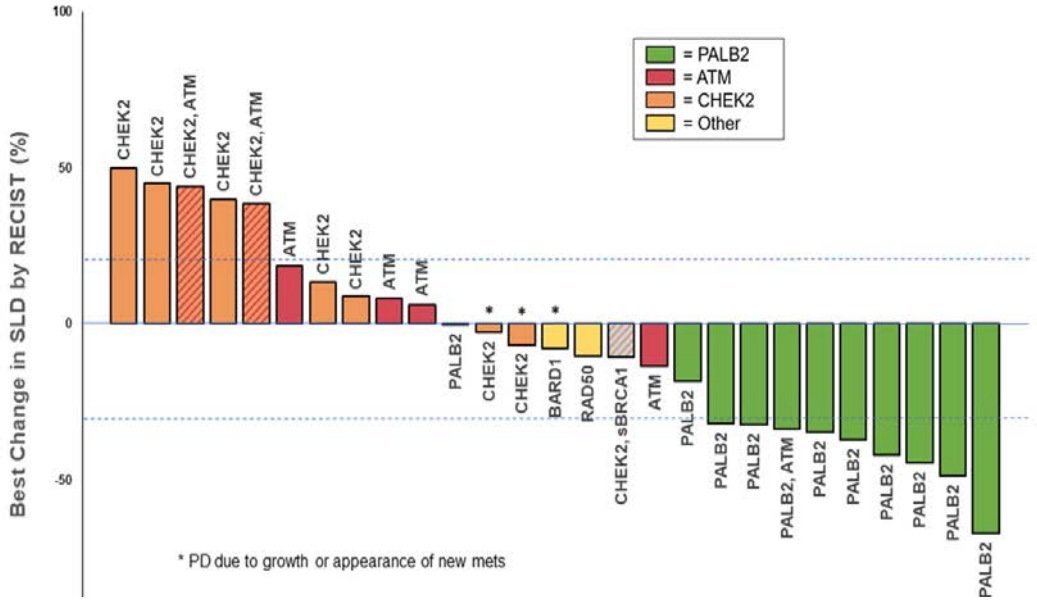
Optional research biopsy

Evidence of activity in prostate cancer and ovarian cancer with HRD

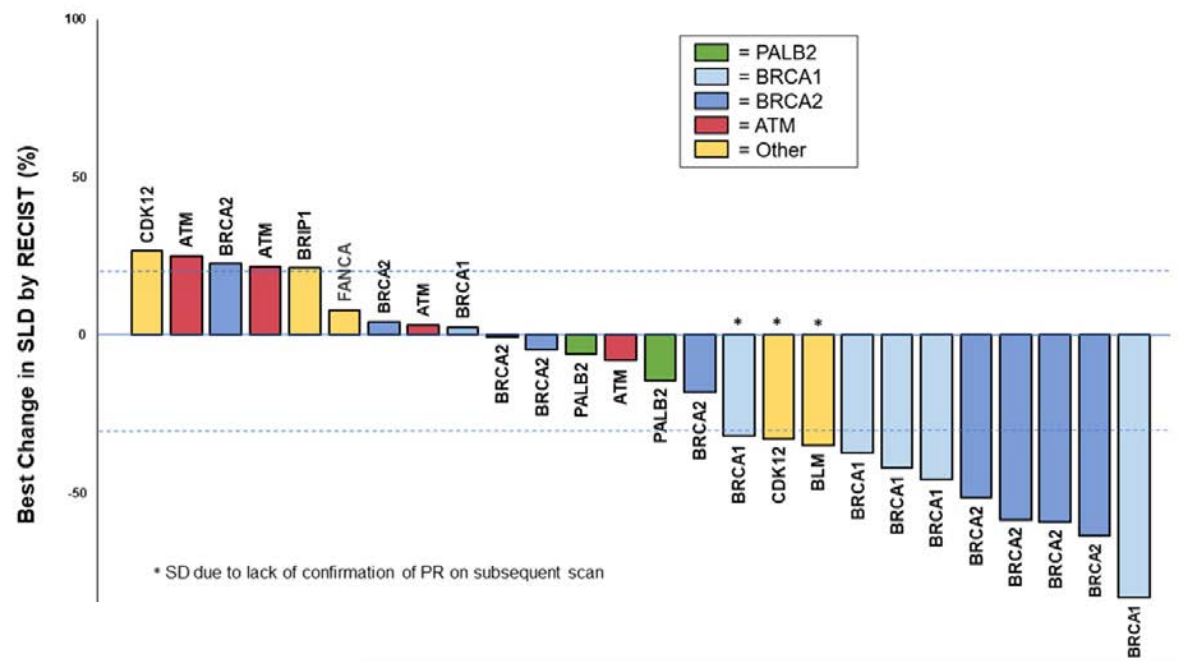
PI: Nadine Tung

ASCO 2020;Abstract 1002

Best Overall Responses: Cohort 1 (Germline)



Best Overall Responses: Cohort 2 (Somatic)



Responses for 5 most common genes (somatic and germline mutations)

PALB2 N=13	*sBRCA1/2* N=17^	*ATM & CHEK2*** N=17
Germline: 9/11 PR (82%) 10/11 had tumor regression; 1 SD > 1 yr **Somatic: 0/2 – both SD*** **(limited assessments)**	**8/16 PR (50%)**	**0/13 germline** **0/4 somatic**

15 patients remain on study

* 1 sPALB2- lost to follow-up after 1st tumor assessment with skin and tumor marker response
^ includes patient from Cohort 1 with sBRCA1 and gCHEK2
** Not included: patient with both gCHEK2 & sBRCA1; patient with gATM and gPALB2

Datacut May 4, 2020

Tung NM et al. ASCO 2020;Abstract 1002.

Dr Rugo Case Presentation: 30 yo F

Age 30, juvenile diabetes

2016: diagnosed with T2N1 grade 2 ER+/PRneg/HER2neg breast cancer

Genetic testing: BRCA1+

Treated on I-SPY 2 phase II clinical trial with NAC including weekly paclitaxel and pembrolizumab followed by AC x 3 (stopped early due to toxicity with neutropenic fevers)

Surgery: bilateral mastectomies with stage III residual disease: T1N2 (7+ nodes)

12/2016 Ovarian suppression and AI

Small focus of disease in chest wall before radiation therapy

6/2017 Palbociclib added post radiation therapy, dose reduced due to cytopenia

11/2018 diagnosed with metastatic disease to bone and liver, spinal cord compression due to pathologic compression fracture at T7

Liver biopsy: ER 90%/PR and HER2 neg

Dr Rugo Case Presentation: 30 yo F (cont)

Fulvestrant

Urgent neurosurgery: decompression T7 etc followed by RT to T7

11/24/2018 – 3/14/2019 Talazoparib 1 mg/d, dose reduced 2/22/2019 due to severe anemia requiring 2U PRBC every other week

CR in liver and PR in bone, resolution of bone pain

3/14/19 – 10/14/2019 olaparib (change due to anemia, N/V)

4/2019 Olaparib dose reduced to 400 mg due to anemia/nausea. Anemia resolved.

8/2019 – 10/14/2019 olaparib increased to 600 mg a day without recurrent anemia but with worsening nausea

10/23/2019 – 12/3/2019 talazoparib 1 mg (change due to mild progression in bone, nausea), tolerated better with nausea but only moderate anemia

Progression in bone and slight progression in liver: found to have PIK3CA mutation

12/23/2019 alpelisib and continued fulvestrant

Dr Rugo Case Presentation: 48 yo F

2013 Age 48

Diagnosed with left breast cancer:

1.2 cm node negative grade 3 ER 80%/PR 10%/HER2 3+

BRCA1+

4/1/14 - 6/14 weekly paclitaxel and trastuzumab x 12

6/24/14 - 12/4/14: **every 3 week trastuzumab, STOPPED d/t EF drop 46% (received 9 months trastuzumab total)**

8/28/14: BSO - atypical cells in fallopian tube

9/16/14 - 12/9/14: letrozole, stopped d/t suicidal ideations, refused additional hormone therapy

Dr Rugo Case Presentation: 48 yo F (cont)

7-8/2017 diagnosed with extensive bone metastases, and destruction of right acetabulum/comminuted fracture of medial acetabular wall

7/31/17 bone biopsy: ER+/PR-/HER2+

8/14/17 total right hip replacement

8/1/17-8/8/19: olaparib 400 mg BID with fulvestrant

(EF 48-50%)

8/2019 progression in bone

Palliative RT to T9, change to anastrozole and palbociclib

On cardiac meds, EF returned to normal

8/2019 – 4/2020 trastuzumab

4/2020 progression in bone, changed to T-DM1 on continued cardiac medications

Stopped trastuzumab, anastrozole and palbociclib

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- Key data sets: POLO, RUCAPANC

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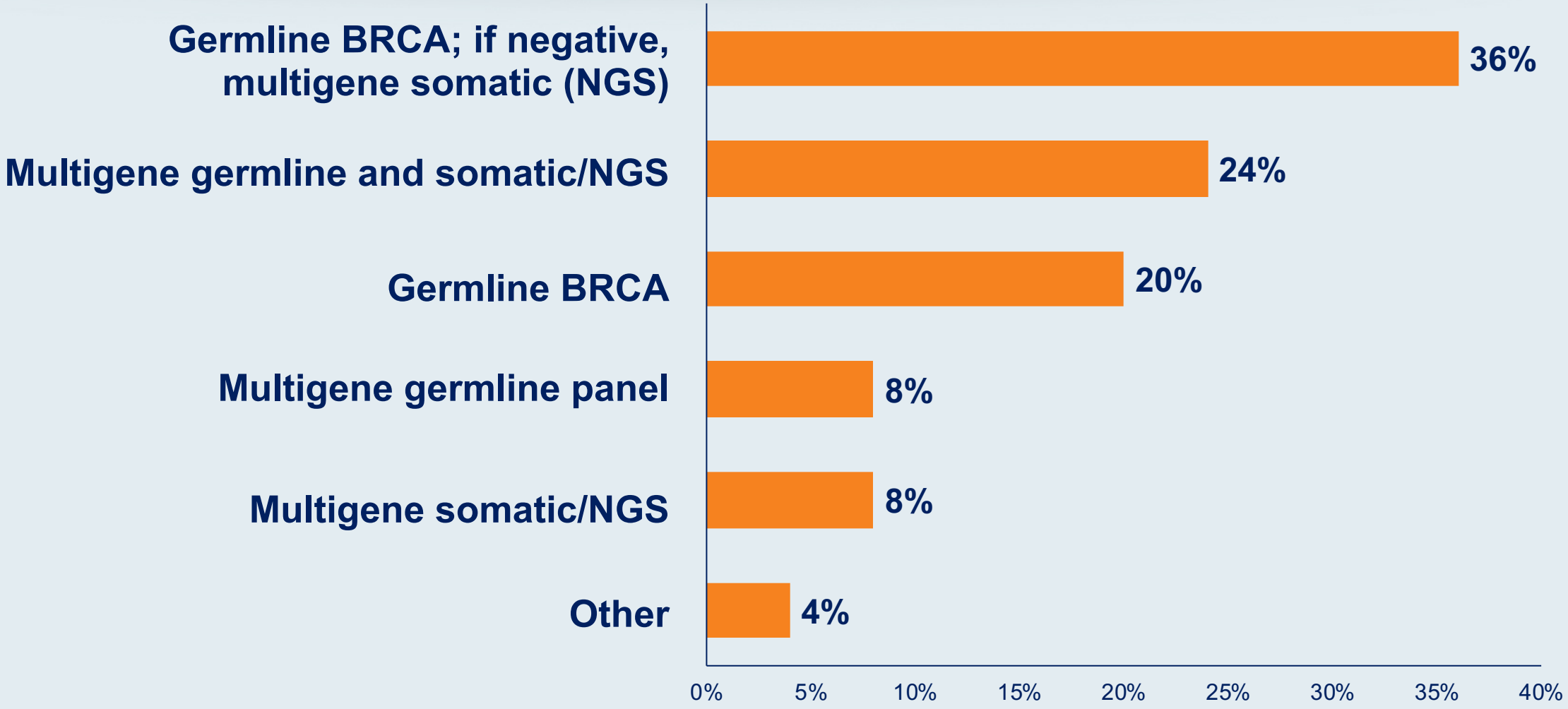
- Key data sets: PROfound, TRITON2, GALAHAD

Module 5: PARP Inhibitors for Pancreatic Cancer – Dr Philip

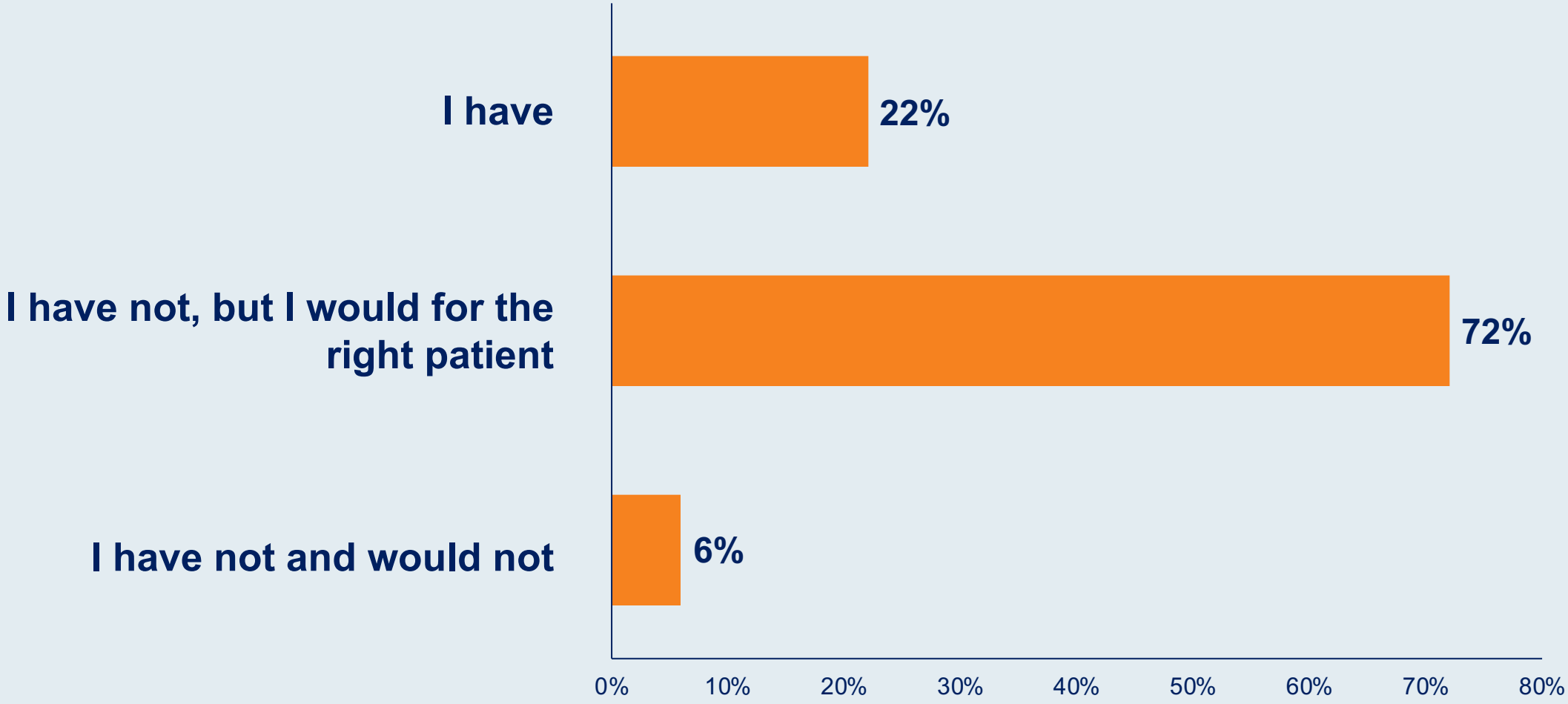
- Genomic profile
- Key recent data sets: POLO, RUCAPANC
- Current practice patterns
- Ongoing trials

In general, what is the optimal approach to mutation testing for possible use of a PARP inhibitor for a patient with metastatic pancreatic cancer and no family history?



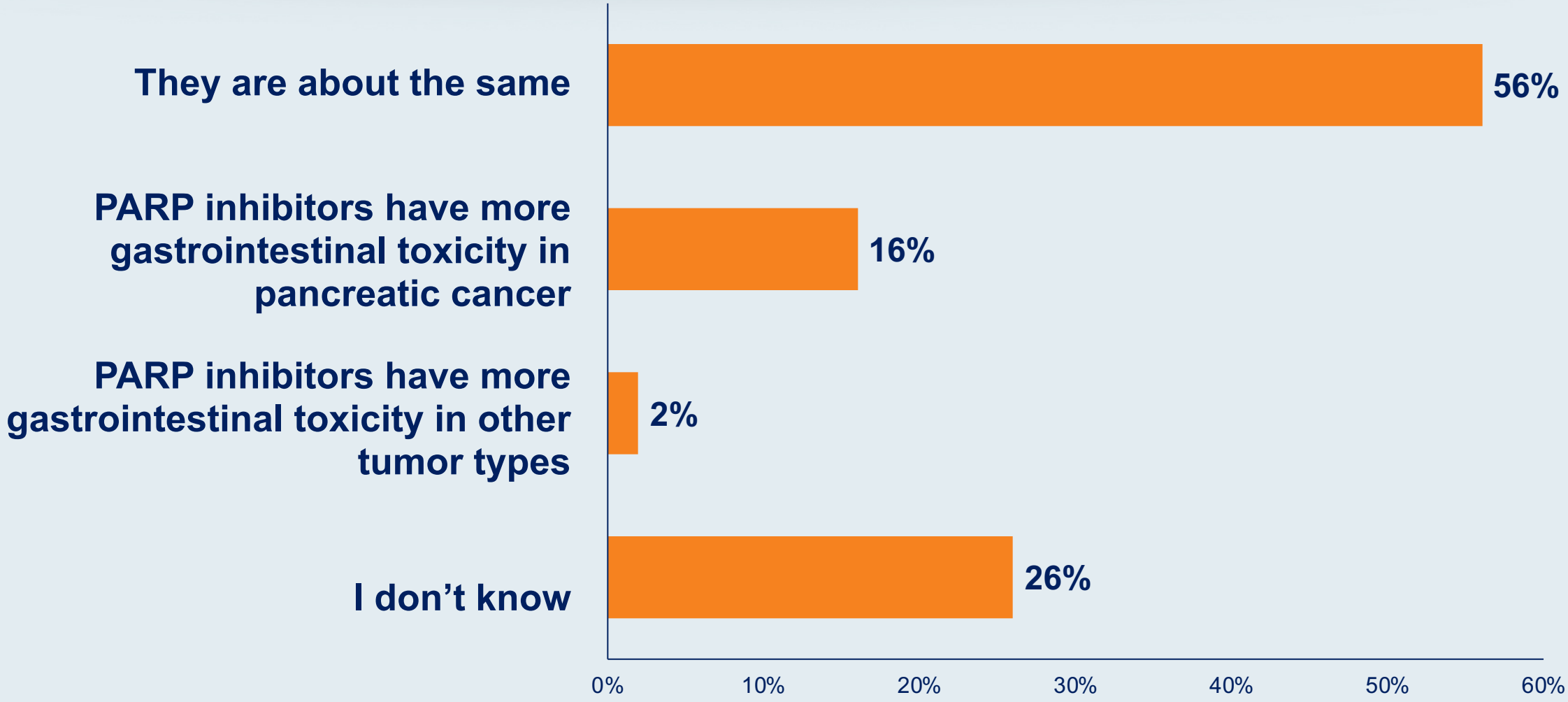
Survey of 50 US-based general medical oncologists June 2020

Have you administered or would you administer PARP inhibitor maintenance to a patient with unresectable locally advanced pancreatic cancer and a germline BRCA mutation?



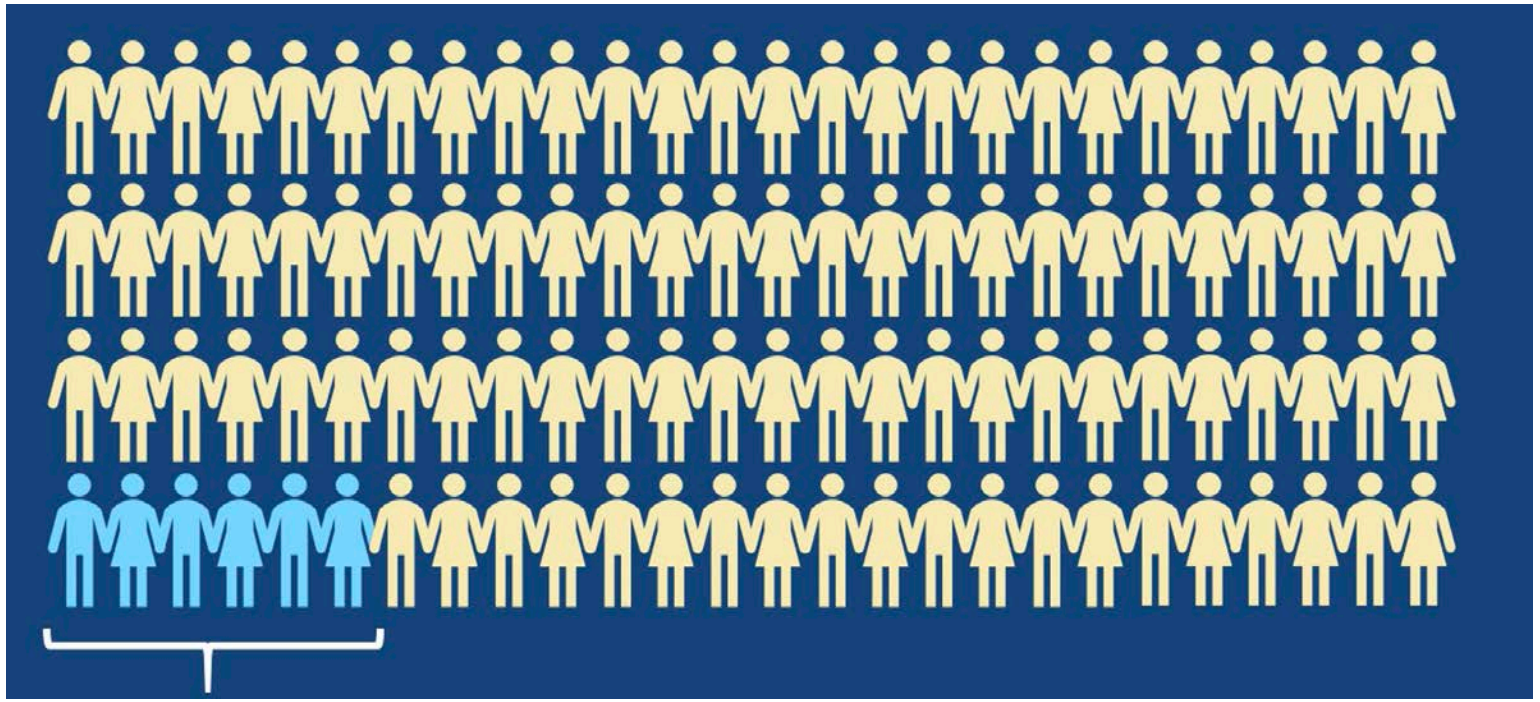
Survey of 50 US-based general medical oncologists June 2020

How would you compare the gastrointestinal toxicity associated with PARP inhibitor use in patients with pancreatic cancer to that in patients with other tumor types?



Survey of 50 US-based general medical oncologists June 2020

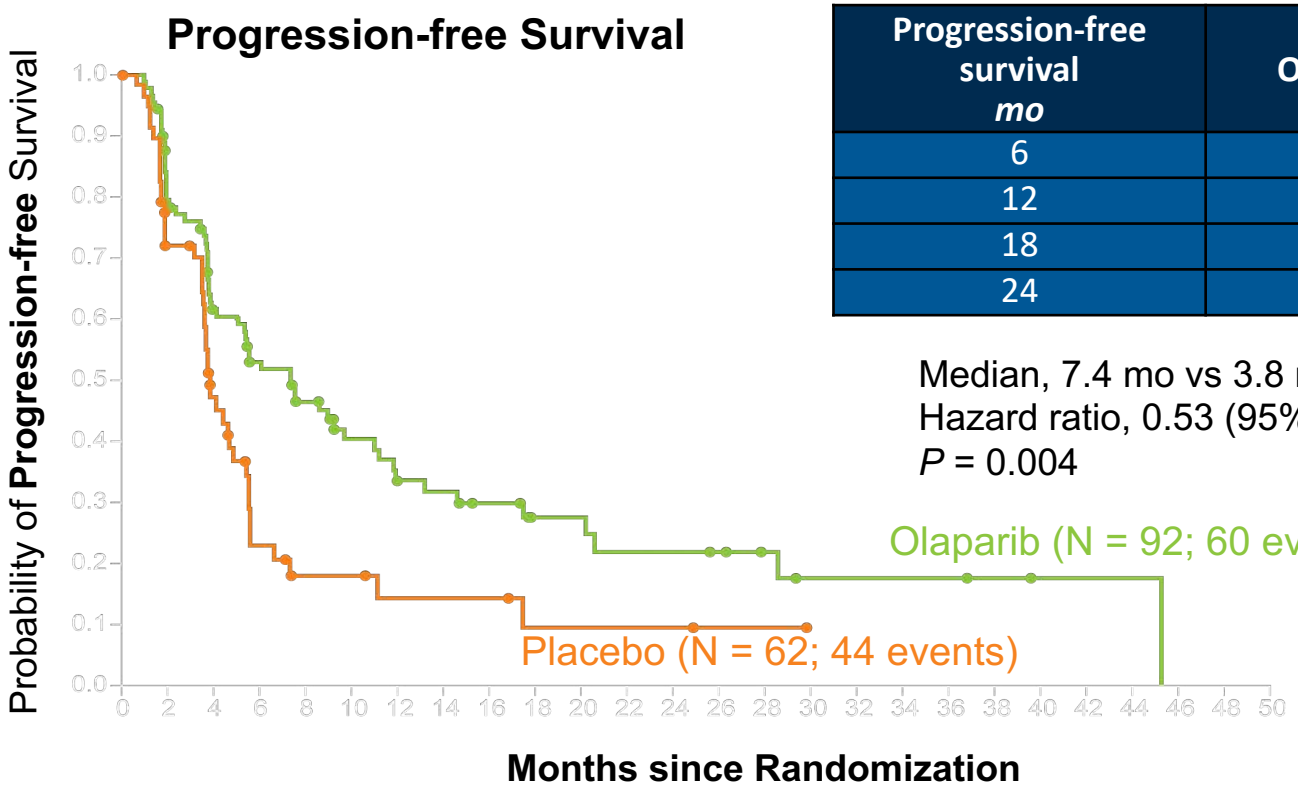
BRCA mutations in pancreatic cancer



4-7% have *BRCA1* or *BRCA2*
Germline mutations

- Significant geographical variations
- Disparities in testing
- Family history is not sufficient to rule out *BRCA* mutation

POLO: A Phase III Trial of Maintenance Olaparib for Metastatic Pancreatic Cancer with BRCA Mutation



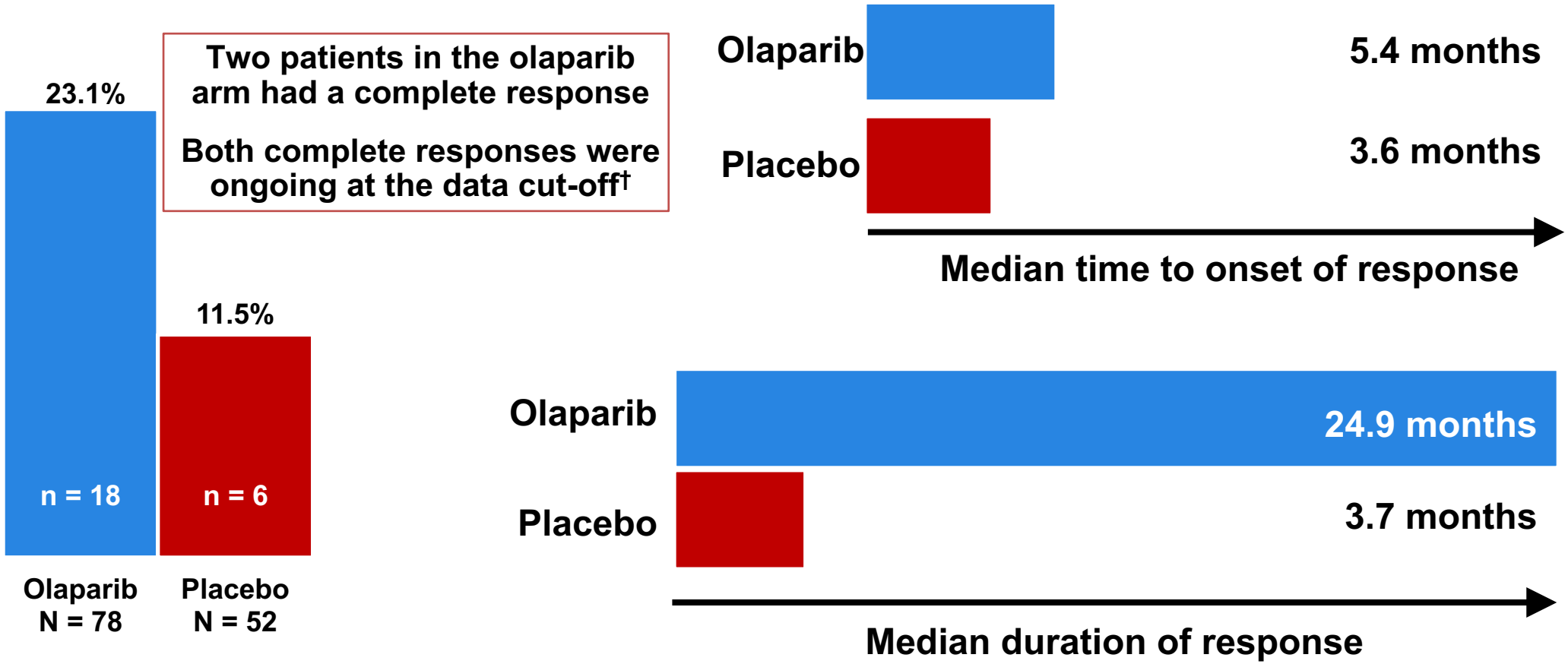
Progression-free survival *mo*	Olaparib group	Placebo group
6	53.0%	23%
12	33.7%	14.5%
18	27.6%	9.6%
24	22.1%	9.6%

Median, 7.4 mo vs 3.8 mo
Hazard ratio, 0.53 (95% CI, 0.35-0.82)
P = 0.004

- An interim analysis of overall survival showed no difference between olaparib and placebo (median 18.9 mo vs 18.1 mo, HR 0.91, *p* 0.68)

Golan T et al. *N Engl J Med* 2019;381(4):317-27.

Objective Response* in Patients With Measurable Disease by Blinded Independent Central Review

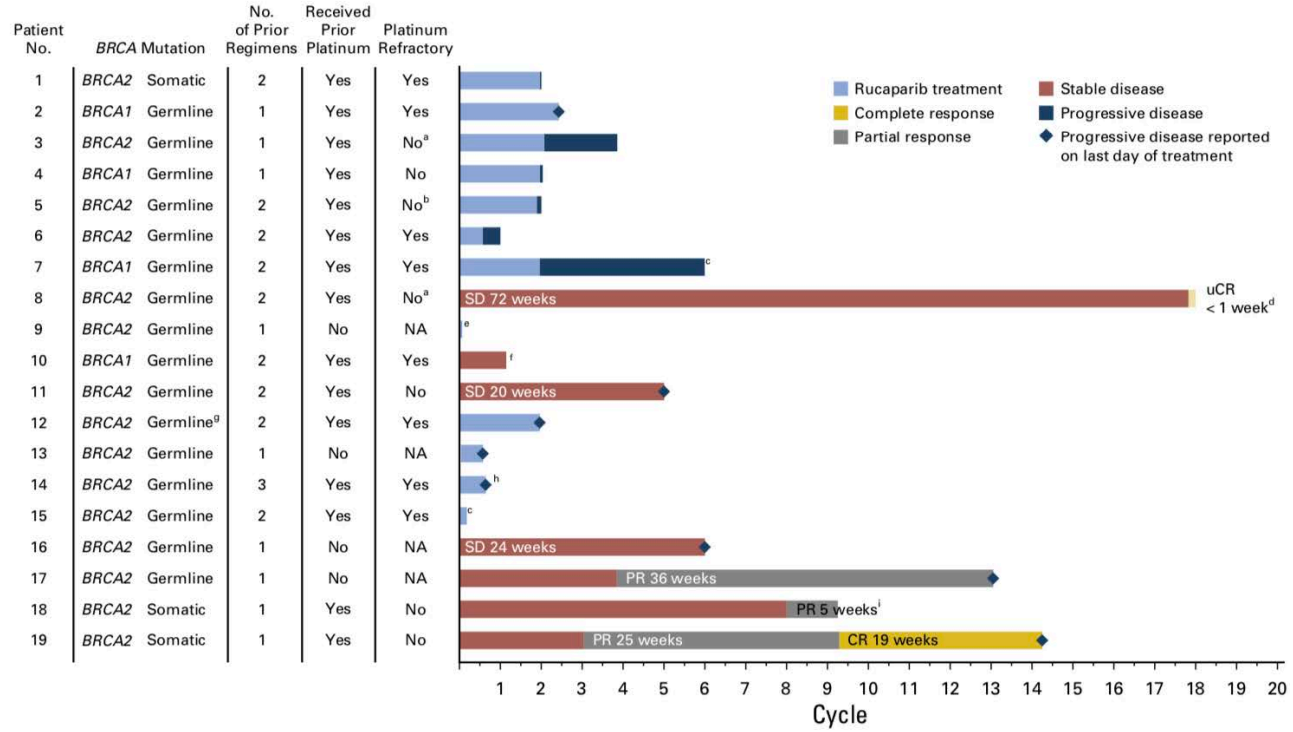


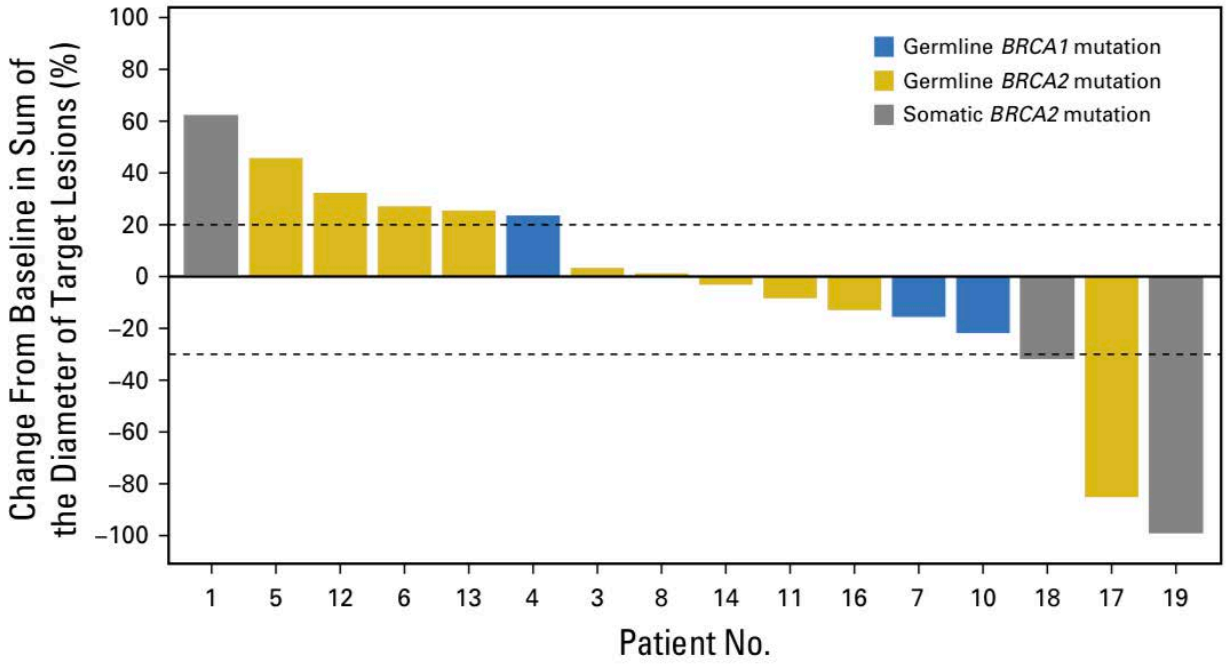
*By modified RECIST v1.1.
†January 15, 2019.

Kindler HL, et al. *J Clin Oncol*. 2019;37(suppl): Abstract LBA4; Golan T, et al. *N Engl J Med*. 2019;381(4):317-327.

RUCAPANC: Rucaparib Monotherapy in Patients With Pancreatic Cancer and a Known Deleterious *BRCA* Mutation

Patient No.	*BRCA* Mutation		No. of Prior Regimens	Received Prior Platinum	Platinum Refractory
1	*BRCA2*	Somatic	2	Yes	Yes
2	*BRCA1*	Germline	1	Yes	Yes
3	*BRCA2*	Germline	1	Yes	No[a]
4	*BRCA1*	Germline	1	Yes	No
5	*BRCA2*	Germline	2	Yes	No[b]
6	*BRCA2*	Germline	2	Yes	Yes
7	*BRCA1*	Germline	2	Yes	Yes
8	*BRCA2*	Germline	2	Yes	No[a]
9	*BRCA2*	Germline	1	No	NA
10	*BRCA1*	Germline	2	Yes	Yes
11	*BRCA2*	Germline	2	Yes	No
12	*BRCA2*	Germline[g]	2	Yes	Yes
13	*BRCA2*	Germline	1	No	NA
14	*BRCA2*	Germline	3	Yes	Yes
15	*BRCA2*	Germline	2	Yes	Yes
16	*BRCA2*	Germline	1	No	NA
17	*BRCA2*	Germline	1	No	NA
18	*BRCA2*	Somatic	1	Yes	No
19	*BRCA2*	Somatic	1	Yes	No





Shroff RT, et al. *JCO Precis Oncol.* 2018;2018.

Dr Philip Case Presentation: 51 yo M

51-year-old software engineer whose father had prostate cancer presented with epigastric abdominal pain. He had weight loss of 5 lbs. CT scan showed a 3 cm mass in the pancreas which was considered resectable. At laparotomy few small liver metastases were seen that were histologically positive for pancreatic adenocarcinoma. CA 19-9 was 150 IU/L. Initial workup showed no abnormalities in liver function and normal CBC. C-reactive protein was within normal range. Patient was seen by supportive care team to optimize pain management and subsequently started on modified FOLFIRINOX. CT scan after 2 months showed significant shrinkage of the pancreatic mass and reduction in CA199 by 80%. He did undergo genetic testing and was found to have *BRCA2* mutation. His father was subsequently tested and indeed he also had the *BRCA2* mutation so did one of the patient's two daughters who were tested. After 5 months of treatment with modified FOLFIRINOX he was switched to olaparib 300 mg per day at which point in time he had side effects from the FOLFIRINOX in the form of fatigue grade 2 and sensory neuropathy grade 2. He stayed on olaparib for 8.5 months before disease progression with increase liver metastases during which he tolerated treatment well except for the continued fatigue. His treatment was switched to 5FU/LCV/Liposomal irinotecan because of the persistent neuropathy.

Dr Philip Case Presentation: 59 yo M

59-year-old pediatric emergency doctor presented with obstructive jaundice, abdominal pain, back pain, and weight loss of 15 pounds and PS of 2. He was also very depressed. CT scan showed a pancreatic head mass of 3 cm, multiple hypodense lesions in the liver, and marked intra- and extrahepatic bile duct dilatation. ERCP failed to place a bile duct stent so he underwent percutaneous external drainage with multiple complications and including cholangitis. Biopsy of the liver lesion showed an adenocarcinoma of the pancreatic-biliary type. His bilirubin dropped from 12 mg/dL to 5 mg/dL and stayed around that level without further dropping. He was started on gemcitabine and cisplatin combination. He had a significant improvement of his symptoms with normalization of the serum bilirubin after several weeks. After six (three-weekly) cycles of gemcitabine and cisplatin he was switched to gemcitabine single agent. Of note CT scan at 9 weeks after starting gemcitabine/cisplatin showed significant partial response. He had somatic *BRCA1* mutation on genomic profiling and later confirmed to have germline *BRCA1* mutation. After 2 months of gemcitabine alone he was started on rucaparib 600 mg BID orally and continued on it for 9 months before progressing in the liver. He underwent a new liver biopsy which showed exactly the same *BRCA2* mutation. He received gemcitabine and cisplatin but progressed after 2 months. He was switched to 5FU/LCV/Nano liposomal irinotecan and had stable disease for approximately six months.

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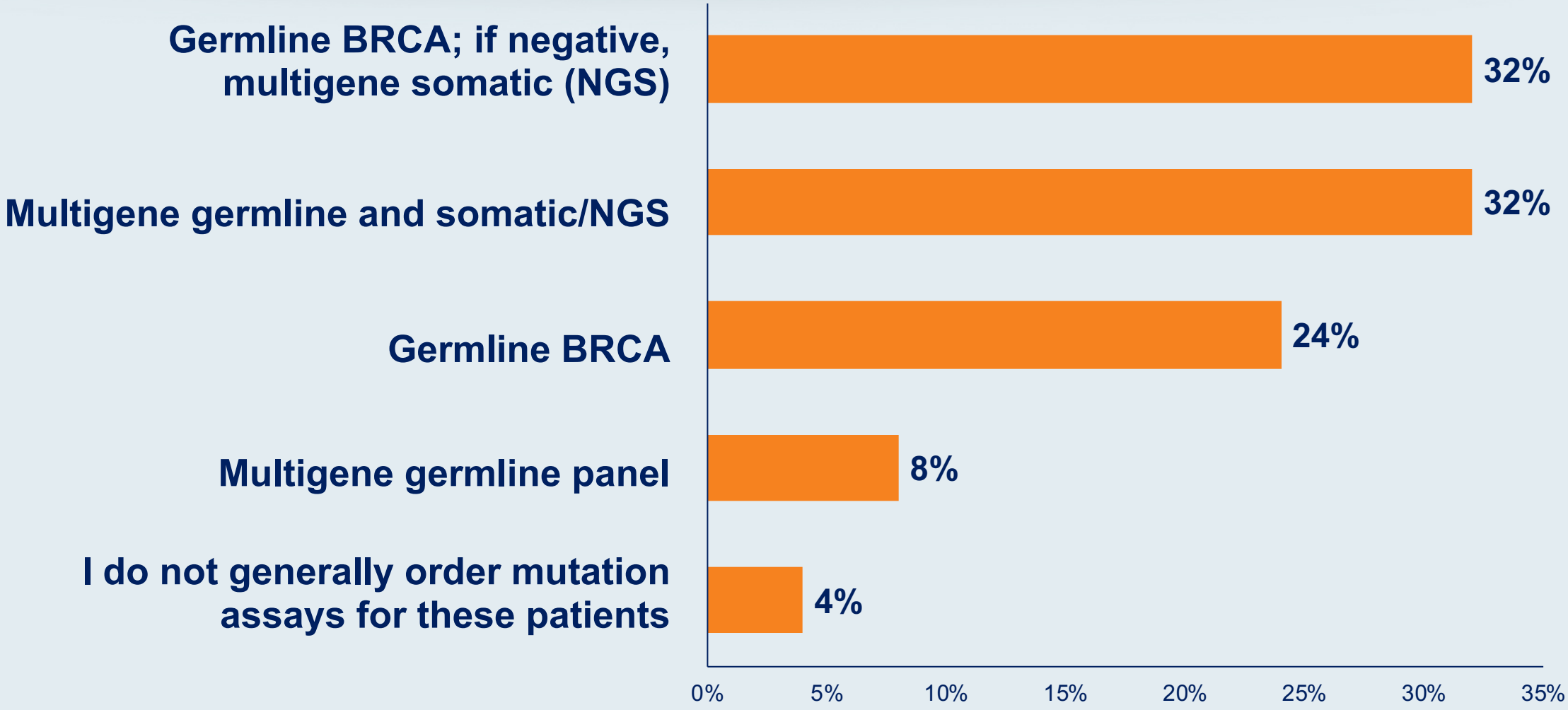
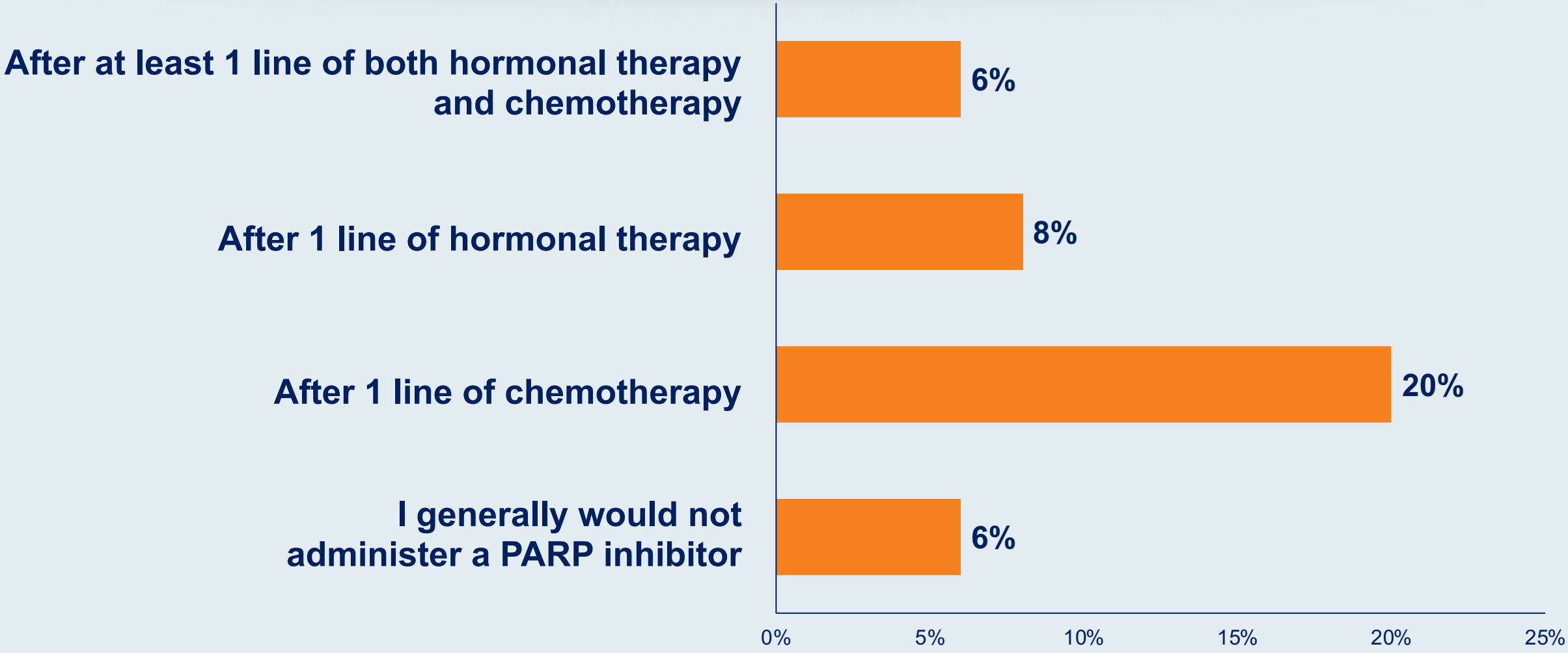


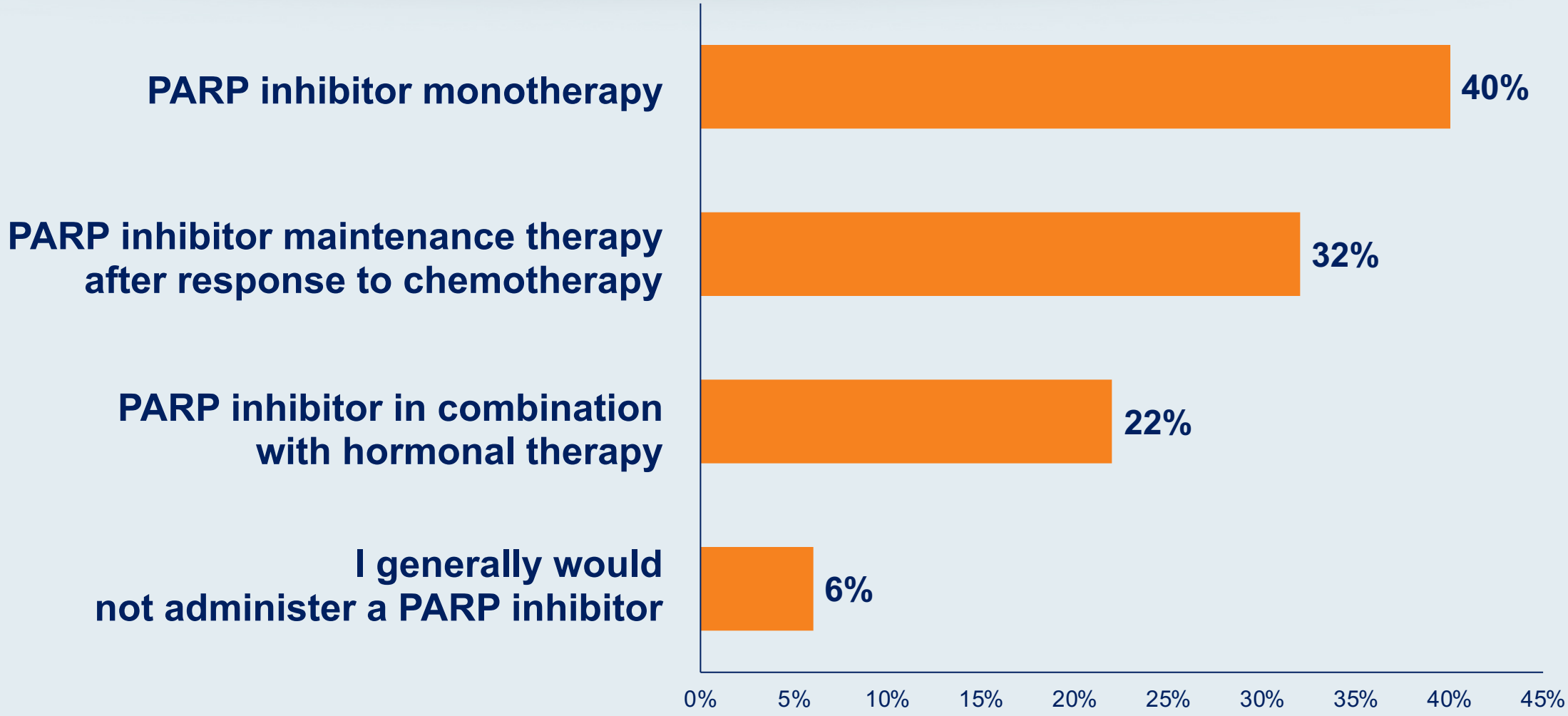
Survey of 50 US-based general medical oncologists June 2020

At what point, if any, do you generally recommend a PARP inhibitor to a patient with metastatic prostate cancer and a germline BRCA mutation?



Survey of 50 US-based general medical oncologists June 2020

For a patient with metastatic prostate cancer and a germline BRCA mutation to whom you would administer a PARP inhibitor at some point, what treatment strategy would you likely use?



Survey of 50 US-based general medical oncologists June 2020

Common BRCAness Genes & Evidence for PARPi Sensitivity

Common BRCAness Genes and Evidence for PARPi sensitivity

Gene	Function in DSD repair	Evidence for PARPi sensitivity	Reference
ATM	protein kinase, DNA damage sensor, involved in repair of DSBs in heterochromatin, V(D)J class switching, meiotic recombination	+++	Mateo J. et al., N. Engl. J. Med. 2015.
ATR	protein kinase, DNA damage sensor, phosporylates CHK1, BRCA1, BLM, FANCD2/FANCI, absence results in deficient HR	++	DeFranco C. et al., Cancer Res. 2016.
BAP1	deubiquitinase required for efficient assembly of BRCA1/RAD51 at site of DSB	++	Goga A. et al., J Clin Oncol. 2016 / Affar E. et al., Proc. Natl. Acad. Sci. USA. 2013.
BRCA1	phosphoprotein that assists in 5` to 3` resection of DSBs, loading of RAD51	+++	Ledermann J. et al., N Engl J Med. 2012 / Mateo J. et al., N. Engl. J. Med. 2015.
BRCA2	phosphoprotein that assists with RAD51 loading	+++	Ledermann J. et al., N Engl J Med. 2012 / Mateo J. et al., N. Engl. J. Med. 2015.
CDK12	regulates expression of BRCA1, FANCI, FANCD2, ATR	++	Ashwoth A. et al., Cancer Res. 2014. / Shapiro G. et al, Cell Rep. 2016.
CHK2	recruits ATM/ATR to cell cycle effectors and DNA repair machinery, phosphorylates BRCA1	+	Fulda S. et al., Oncotarget. 2016
FANCA	member of FA core complex which recruits and activates FANCD2/FANCI that co-localizes with BRCA1	+	McCabe N. et al., Cancer Res. 2006
FANCC	member of FA core complex which recruits and activates FANCD2/FANCI that co-localizes with BRCA1	++	Wells S. et al., Clin Cancer Res. 2015
FANCD2	co-localizes with BRCA1 during process of homologous recombination	+	McCabe N. et al., Cancer Res. 2006 / Villalona-Calero, M., Front Oncol. 2014
FANCF	member of FA core complex which recruits and activates FANCD2/FANCI that co-localizes with BRCA1	+	McCabe N. et al., Cancer Res. 2006
PALB2	promotes BRCA2 function and formation of BRCA complex	+++	Mateo J. et al., N. Engl. J. Med. 2015.
NBS1	localizes to sites of DSBs, complexes with MRE11a/Rad50, activates ATM	+++	McNeish I. et al., Lancet Oncol. 2016
WRN	3` to 5` exonuclease promotes repair of DSBs	+	Helleday, T. et al., Caner Res. 2010
RAD51c	assists with recruitment, stablization, and loading of RAD51	+++	McNeish I. et al., Lancet Oncol. 2016 / Bang Y. et al., Mol Cancer Ther. 2013.
RAD51d	assists with recruitment, stablization of RAD51	+++	McNeish I. et al., Lancet Oncol. 2016
MRE11A	localizes to sites of DSBs, complexes with NBS1/Rad50, activates ATM	++	Li D. et al., Clin Cancer Res. 2014
CHK1	protein kinase, phosporylates BLM, FANCE, FANCD2, RAD51 promoting DSB repair	++	Dent P. et al. Mol Pharmaol. 2012. / Dent P. et al. Cancer Biol Ther. 2013
BLM	RecQ helicase involved in DSB resection	+	Helleday, T. et al., Caner Res. 2010

\+ - cell culture
++ - patient derived xenografts / animal models
+++ - clinical trial

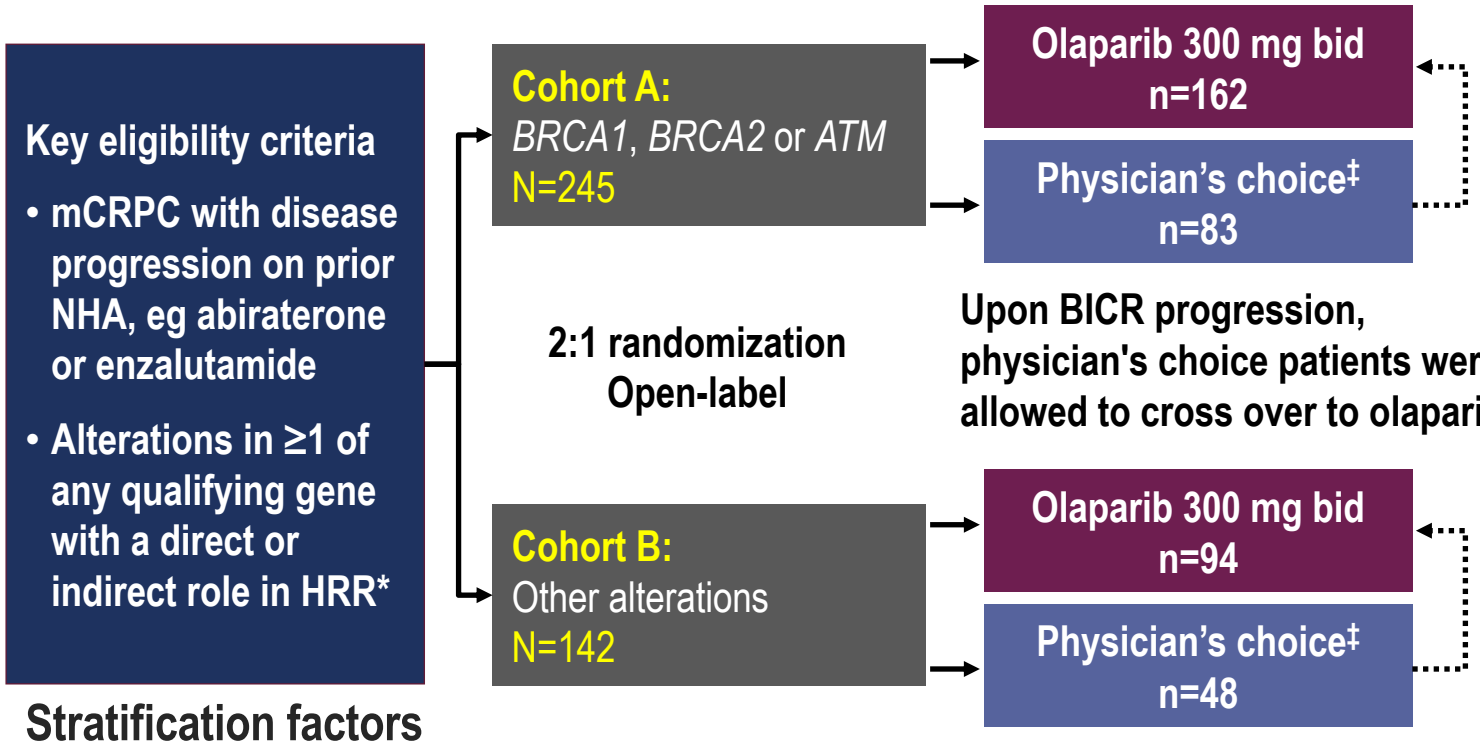
List of genes whose deficiency is associated with homologous repair deficiency. Evidence for PARPi sensitivity based on response to PARPi in presence of deleterious mutation(s) or inhibition of listed gene without associated mutations in BRCA1/2 or other BRCAness genes

PARPi in PCa

- Olaparib
- Rucaparib
- Niraparib
- Talazoparib
- BGB-290 (Pamiparib)

Rimar KJ, et al. *Cancer*. 2017;123(11):1912-1924.

PROfound STUDY DESIGN



Primary Endpoint

Radiographic progression-free survival (rPFS) in Cohort A (RECIST 1.1 & PCWG3 by BICR)

Key Secondary Endpoints

- rPFS in Cohorts A+B
- Confirmed radiographic objective response rate (ORR) in Cohort A
- Time to pain progression (TTPP) in Cohort A
- Overall survival (OS) in Cohort A

***An investigational Clinical Trial Assay, based on a next-generation sequencing test**

Used to prospectively select patients harboring alterations in *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* and/ or *RAD54L* in their tumor tissue

BARCELONA 2019 ESMO congress

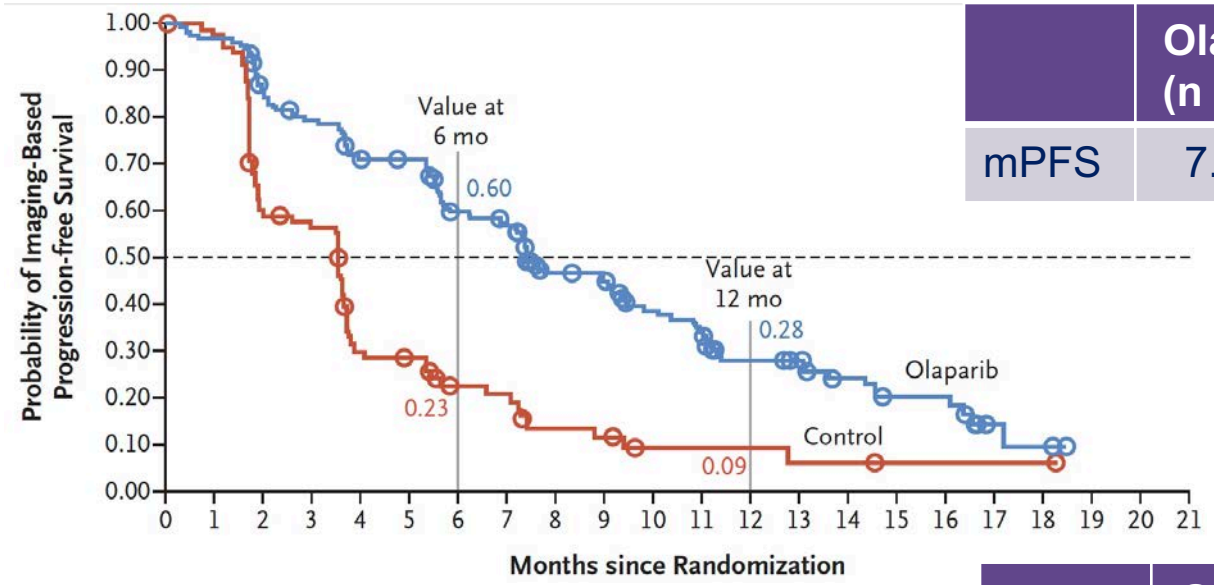
‡Physician's choice of either enzalutamide (160 mg qd) or abiraterone (1000 mg qd + prednisone [5 mg bid])
BICR, blinded independent central review

Hussain M et al. ESMO 2019;Abstract 5059.

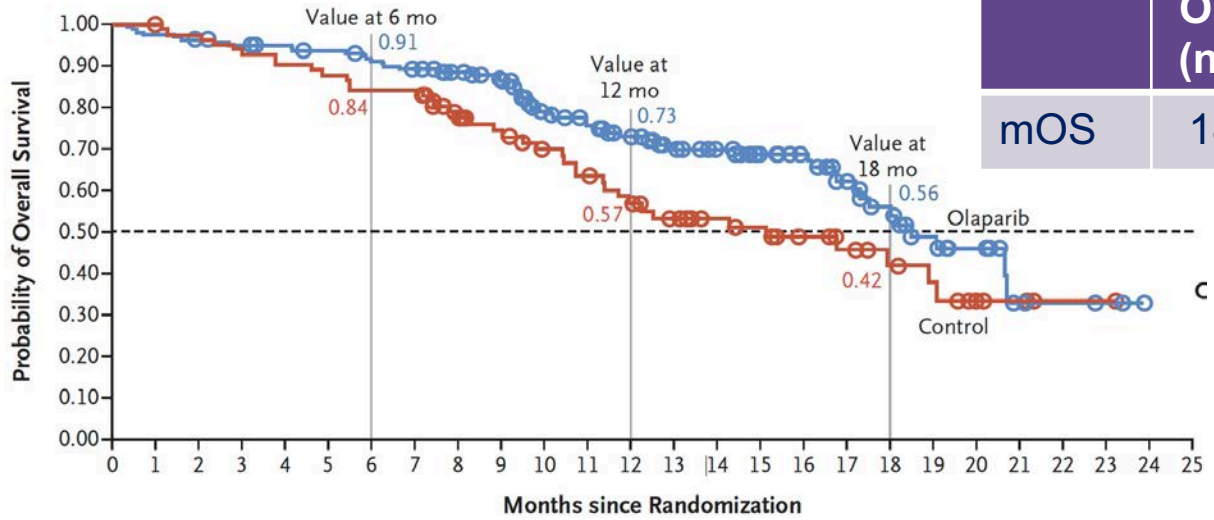
INDIVIDUAL AND CO-OCCURRING GENE ALTERATIONS IN PATIENTS SCREENED IN THE PROfound STUDY

	Gene	Patients with HRR gene alterations (screened)	Proportion of total screened patients successfully tested for HRR gene alterations (n=2792), %	Proportion of total HRR gene alterations in screened population (n=778), %	Patients with HRR gene alterations (randomized)	Proportion of total HRR gene alterations in randomized population (n=387), %
	Any qualifying HRR gene	778	27.9	–	–	–
Cohort A genes	*BRCA2* only	242	8.7	31.1	128	33.1
	ATM only	164	5.9	21.1	86	22.2
	BRCA1 only	27	1.0	3.5	13	3.4
Cohort B genes	*CDK12* only	175	6.3	22.5	89	23.0
	CHEK2 only	34	1.2	4.4	12	3.1
	PPP2R2A only	29	1.0	3.7	10	2.6
	BRIP1 only	12	0.4	1.5	3	0.8
	PALB2 only	9	0.3	1.2	4	1.0
	RAD54L only	8	0.3	1.0	5	1.3
	RAD51B only	7	0.3	0.9	5	1.3
	BARD1 only	5	0.2	0.6	1	0.3
	RAD51D only	4	0.1	0.5	1	0.3
	CHEK1 only	2	0.1	0.3	2	0.5
	FANCL only	1	0.0	0.1	0	0.0
	RAD51C only	0	0.0	0.0	0	0.0
	Co-occurring genes	59	2.1	7.6	28	7.2

PROfound: Imaging-Based PFS and OS in Cohort A



	Olaparib (n = 162)	Control (n = 83)	HR	P-value
mPFS	7.4 mo	3.6 mo	0.34	<0.001

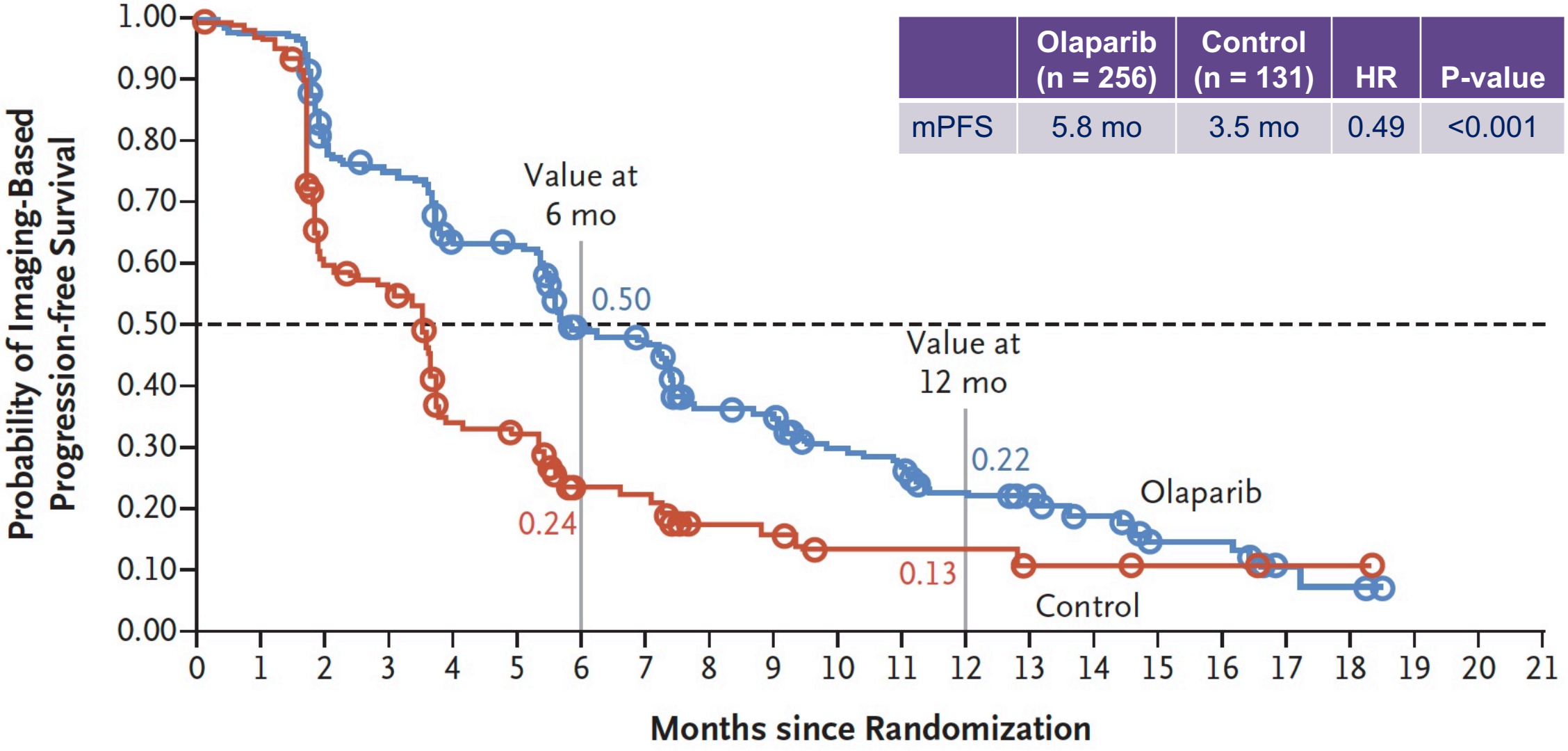


	Olaparib (n = 162)	Control (n = 83)	HR	P-value
mOS	18.5 mo	15.1 mo	0.64	0.02

De Bono J et al. N Engl J Med 2020 May 28;382(22):2091-2101.

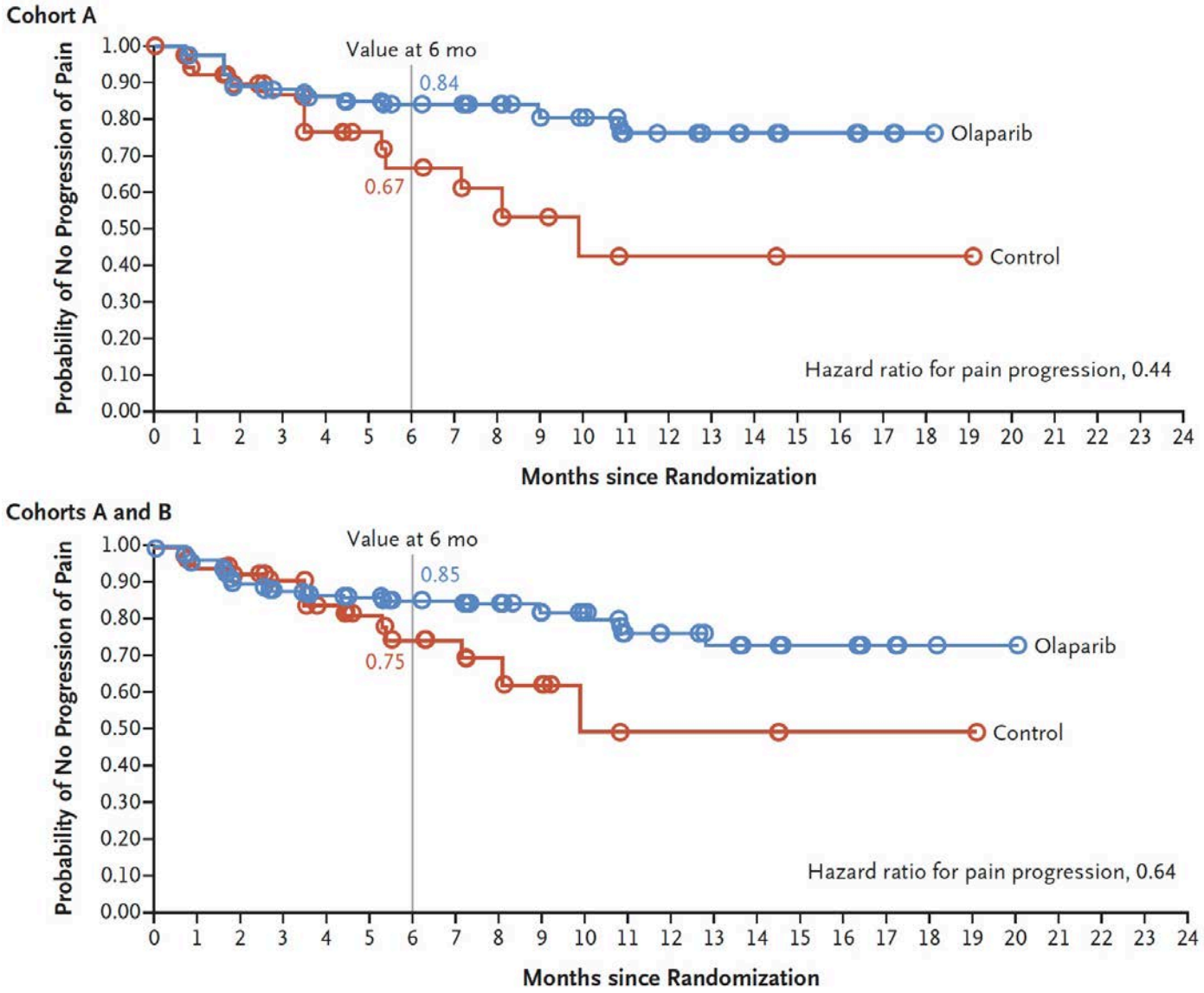
PROfound: Imaging-Based PFS in Cohort A and B

	Olaparib (n = 256)	Control (n = 131)	HR	P-value
mPFS	5.8 mo	3.5 mo	0.49	<0.001



De Bono J et al. N Engl J Med 2020 May 28;382(22):2091-2101.

PROfound: Time to Pain Progression



De Bono J et al. N Engl J Med 2020 May 28;382(22):2091-2101.

FDA approves olaparib for HRR gene-mutated metastatic castration-resistant prostate cancer

Press Release – May 19, 2020

- "The Food and Drug Administration approved olaparib for adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC), who have progressed following prior treatment with enzalutamide or abiraterone.
- Today, the FDA also approved FoundationOne® CDx for selection of patients with mCRPC carrying HRR gene alterations and BRACAnalysis CDx® test for selection of patients with mCRPC carrying germline *BRCA1/2* alterations as companion diagnostic devices for treatment with olaparib.
- Efficacy was investigated in PROfound (NCT02987543), an open-label, multicenter trial randomizing (2:1) 256 patients to olaparib 300 mg twice daily and 131 patients to investigator's choice of enzalutamide or abiraterone acetate. All patients received a GnRH analog or had prior bilateral orchiectomy. Patients were divided into two cohorts based on their HRR gene mutation status. Patients with mutations in either *BRCA1*, *BRCA2*, or *ATM* were randomized in Cohort A (N=245); patients with mutations among 12 other genes involved in the HRR pathway were randomized in Cohort B (N=142); those with co-mutations (Cohort A gene and a Cohort B gene) were assigned to Cohort A."

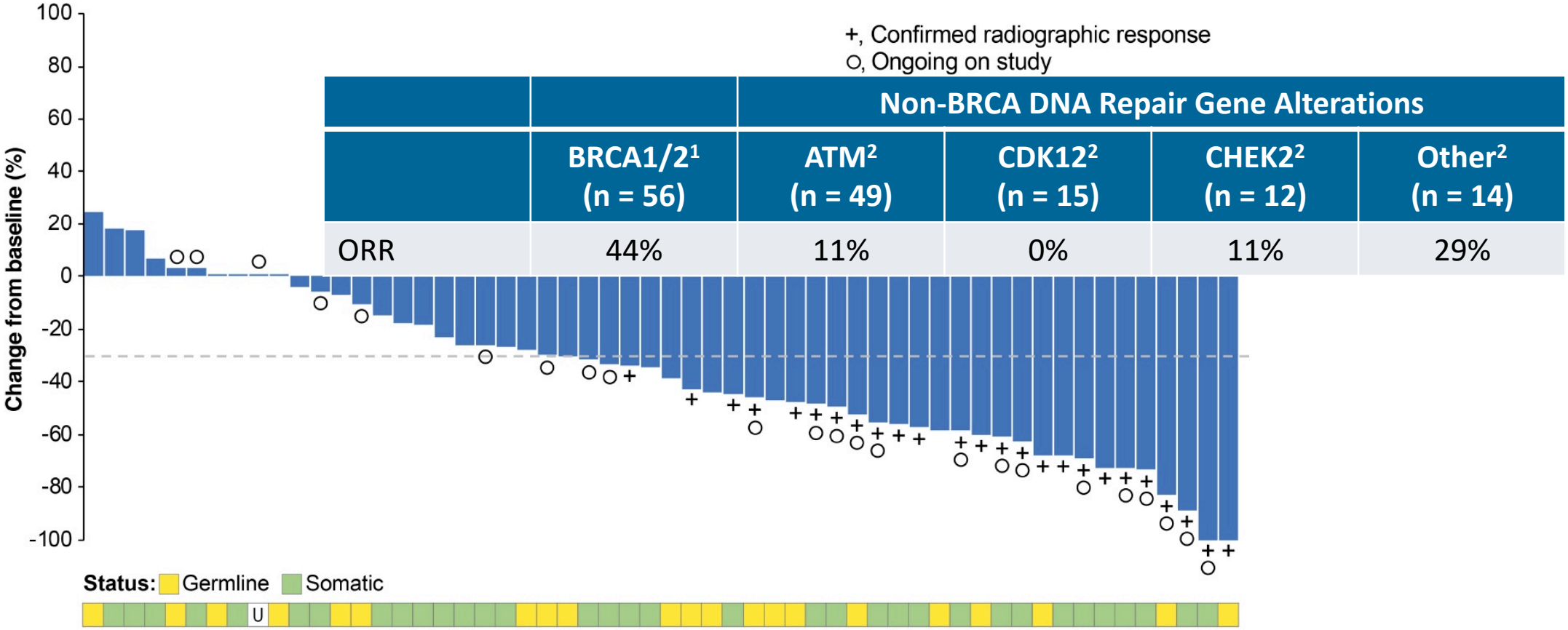
https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-olaparib-hrr-gene-mutated-metastatic-castration-resistant-prostate-cancer

Preliminary Results from the TRITON2 Study of Rucaparib in Patients with DNA Damage Repair (DDR)-Deficient Metastatic Castration-Resistant Prostate Cancer (mCRPC): Updated Analyses

Abida W et al.

ESMO 2019; Abstract 846PD.

TRITON2: Best Change from Baseline in Sum of Target Lesions in Rucaparib-Treated Patients with a BRCA1/2 Alteration (N = 56)[1] and ORR in Patients with Non-BRCA DNA Damage Repair Gene Alterations (N = 78)[2]

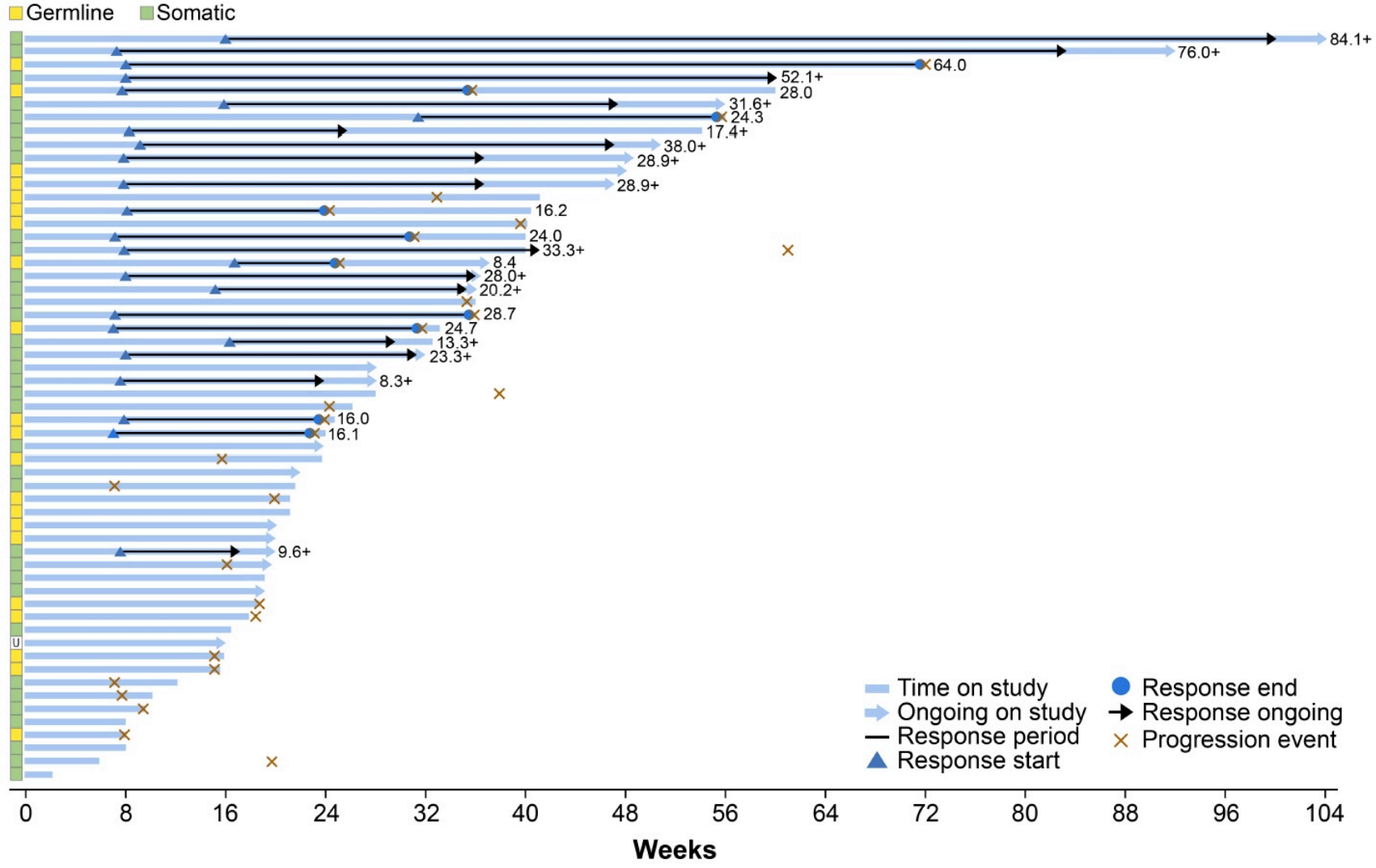


		Non-BRCA DNA Repair Gene Alterations			
	BRCA1/2[1] (n = 56)	ATM[2] (n = 49)	CDK12[2] (n = 15)	CHEK2[2] (n = 12)	Other[2] (n = 14)
ORR	44%	11%	0%	11%	29%

Visit cutoff: 02 Jul 2019. Includes patients with measurable disease at baseline and ≥1 postbaseline scan. Each bar represents a single patient; patients with no change from baseline are shown as 0.5% for visual clarity; the dotted line indicates the threshold for partial response (30% decrease from baseline). Confirmed radiographic responses are per investigator assessment.
U, *BRCA1/2* germline/somatic status unknown.

[1]Abida W et al. ESMO 2019; Abstract 846PD; [2]Abida W et al. Clin Cancer Res 2020;26:2487-96.

TRITON2: Treatment Duration and Duration of Modified Response in Rucaparib-Treated Patients with a BRCA1/2 Alteration and Measurable Disease at Baseline (N = 57)



Abida W et al. ESMO 2019; Abstract 846PD.

FDA grants accelerated approval to rucaparib for BRCA-mutated metastatic castration-resistant prostate cancer

Press Release – May 15, 2020

- "On May 15, 2020, the Food and Drug Administration granted accelerated approval to rucaparib for patients with deleterious *BRCA* mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy.
- Efficacy was investigated in TRITON2 (NCT02952534), an ongoing, multi-center, single arm clinical trial in 115 patients with *BRCA*-mutated (germline and/or somatic) mCRPC who had been treated with androgen receptor-directed therapy and taxane-based chemotherapy. Patients received rucaparib 600 mg orally twice daily and concomitant GnRH analog or had prior bilateral orchiectomy."

https://www.fda.gov/drugs/fda-grants-accelerated-approval-rucaparib-brca-mutated-metastatic-castration-resistant-prostate

GALAHAD: An Ongoing Phase II Trial of Niraparib in Metastatic Castration-Resistant Prostate Cancer and DNA Repair Anomalies

Trial identifier: NCT02854436 **(Open)**

Eligibility (Target N = 301)

- Metastatic castration-resistant prostate cancer
- Biomarker-positive for DRD
- Progressed on or after
  - ≥ 1 line of taxane-based chemo and
  - ≥ 1 line of AR signaling inhibitor
- No prior PARP inhibitor
- No prior platinum-based chemotherapy
- No symptomatic brain mets

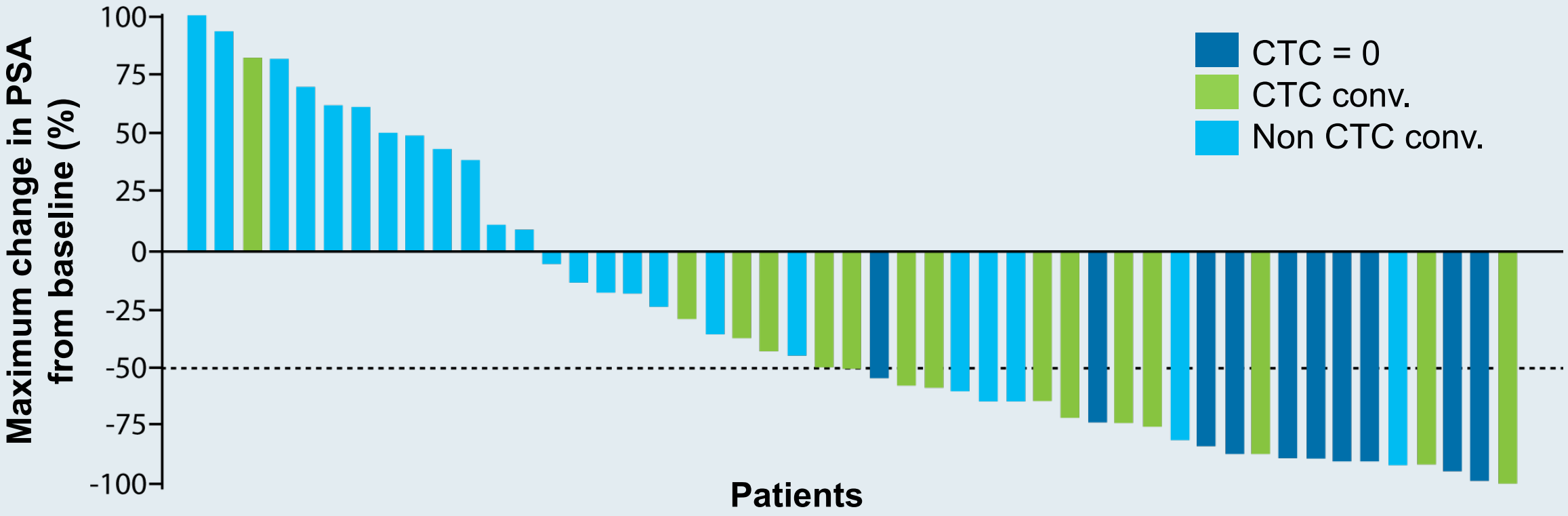
→ **Niraparib 300 mg daily**

Primary endpoint: Objective response rate

www.clinicaltrials.gov. Accessed June 2020.

GALAHAD: Maximum Change in PSA from Baseline in Patients with BRCA Mutation-Positive mCRPC

Waterfall plot of maximum change in PSA from baseline any time on the study. All BRCA patients.



CTC = circulating tumor cells; CTC0 = CTC at baseline; CTC conversion = CTC conversion from unfavorable to favorable

Smith MR et al. Genitourinary Cancers Symposium 2020;Abstract 118.

GALAHAD: Study Outcomes

- CTC at baseline (CTC0) and CTC decrease on treatment (CTC conversion) are early indicators of response associated with longer time on therapy[1]
- Niraparib demonstrates clinical activity in patients with treatment-refractory mCRPC with durable responses particularly in biallelic BRCA mutation carriers[2]

Outcome[2]	All biallelic DRD (n = 81)	
	BRCA (n = 46)	Non-BRCA (n = 35)
Objective response rate	12/29 (41%)	2/22 (9%)
PSA_{50}	23/46 (50%)	1/35 (3%)
CTC conversion*	18/38 (47%)	5/24 (21%)
Composite response rate	29/46 (63%)	6/35 (17%)
Median duration of objective response	5.6 months	Not reported
Median radiographic PFS	8.2 mo	5.3 months
Median OS	12.6 months	14.0 months

*CTC conversion from unfavorable to favorable

[1]Smith MR et al. Genitourinary Cancers Symposium 2020;Abstract 118; [2]Smith MR et al. ESMO 2019;Abstract LBA50.

MAGNITUDE: An Ongoing Phase III Trial of Niraparib + Abiraterone Acetate and Prednisone (AAP) in Metastatic Prostate Cancer

Trial identifier: NCT03748641 **(Open)**

Eligibility (Target N = 1,000)

- Metastatic Prostate Cancer
- Known DRD status
- No prior PARP inhibitor
- No systemic brain mets

Cohort with DRD (n = 400)

R

1:1

- Niraparib AAP
- Placebo + AAP

Cohort without DRD (n = 600)

R

1:1

- Niraparib AAP
- Placebo + AAP

Primary endpoint:

- **rPFS**

Secondary endpoints:

- **OS**
- **Time to symptomatic progression**
- **Time to cytotoxic chemotherapy**

AAP = abiraterone acetate plus prednisone; DRC= DNA repair gene defects; rPFS = radiographic progression-free survival; OS = overall survival

<u>Primary endpoint</u>: Radiographic progression-free survival

www.clinicaltrials.gov. Accessed June 2020; Chi KN et al. ASCO 2020;Abstract TPS5588.

Dr Hussain Case Presentation: 69 yo WM

Patient is a 69-year-old white male

09/2008: diagnosed with GS 4+3 prostate cancer.

12/2008: Radical prostatectomy/bilateral pelvic lymph node dissection. pT3N1 GS 4+4 PCa.

02/27/2009: Bone scan revealed metastatic disease in the sacrum (2.5 x 1.2 cm in diameter).

02/2009: Started ADT (Leuprolide).

03/13/2013: PSA detected 0.1 ng/mL.

09/11/2014: Rising PSA, 04/2015: PSA 2.0 ng/mL. now castration resistant prostate cancer.

05/04/2015 – 06/29/2015: Received 3 Sipuleucel-T infusions and a round of palliative radiotherapy to sacral metastasis on part of IIT of Sipuleucel-T versus Sipuleucel-T plus radiotherapy. Given stable osseous disease on serial restaging scans with slowly rising PSA, patient elected to defer therapy and continue leuprolide only.

08/2017 – 02/2018: Rising PSA and INVITAE testing identified a germline pathogenic mutation in BRCA2.

- 08/2017: PSA 8.4 ng/mL, 02/2018: PSA 23.6 ng/mL

03/2018: Enrolled on BRCAAway trial and randomized to olaparib only (Arm 2). Responded by PSA and imaging.

01/2020: Rising PSA and new bone scan lesion of pelvis. Progression of disease and was taken off treatment.

Dr Hussain Case Presentation: 79 yo WM

Patient is 79 yo white male

- At age 63 he was diagnosed with GS 3+3 prostate cancer 5/2004, s/p brachytherapy.
- 11/2015 had PSA 32, repeat prostate biopsy showed Gleason 5+4 prostate cancer.
- Restaging scans (12/15) focal finding in the left inferior pubic ramus and was started on ADT
- 4/2017: PSA Progression and increased uptake in the left inferior pubic ramus, s/p radiation treatment to osseous pubic ramus.
- 8/2017: Progression in bone, elected clinical trial (NU-16U05), underwent a bone Bx - Germ line: BRCA2 mutation,
- **9/2017** randomized to Arm 3: Olaparib 300 mg po bid + Abiraterone 1000 mg + prednisone 5 mg po bid. Responded by PSA and imaging
- **7/2019** rising PSA and new hip pain, progression by imaging

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 days.