

# *Meet The Professor*

## Management of Ovarian Cancer

### **Mansoor Raza Mirza, MD**

Medical Director, Nordic Society of Gynaecological Oncology

Vice-Chairman, Danish Society of Gynaecologic Oncology

Executive Director, Gynecologic Cancer InterGroup

Chief Oncologist, Department of Oncology

Rigshospitalet, Copenhagen University Hospital

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# Commercial Support

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## Dr Love — Disclosures

**Dr Love** is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, Adaptive Biotechnologies Corporation, Agendia Inc, Agios Pharmaceuticals Inc, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Biodesix Inc, bioTheranostics Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Daiichi Sankyo Inc, Dendreon Pharmaceuticals Inc, Eisai Inc, EMD Serono Inc, Epizyme Inc, Exelixis Inc, Foundation Medicine, Genentech, a member of the Roche Group, Genmab, Genomic Health Inc, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Guardant Health, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Infinity Pharmaceuticals Inc, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Lexicon Pharmaceuticals Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Merrimack Pharmaceuticals Inc, Myriad Genetic Laboratories Inc, Natera Inc, Novartis, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Prometheus Laboratories Inc, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sandoz Inc, a Novartis Division, Sanofi Genzyme, Seagen Inc, Sirtex Medical Ltd, Spectrum Pharmaceuticals Inc, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro, A GSK Company, Teva Oncology, Tokai Pharmaceuticals Inc and Verastem Inc.

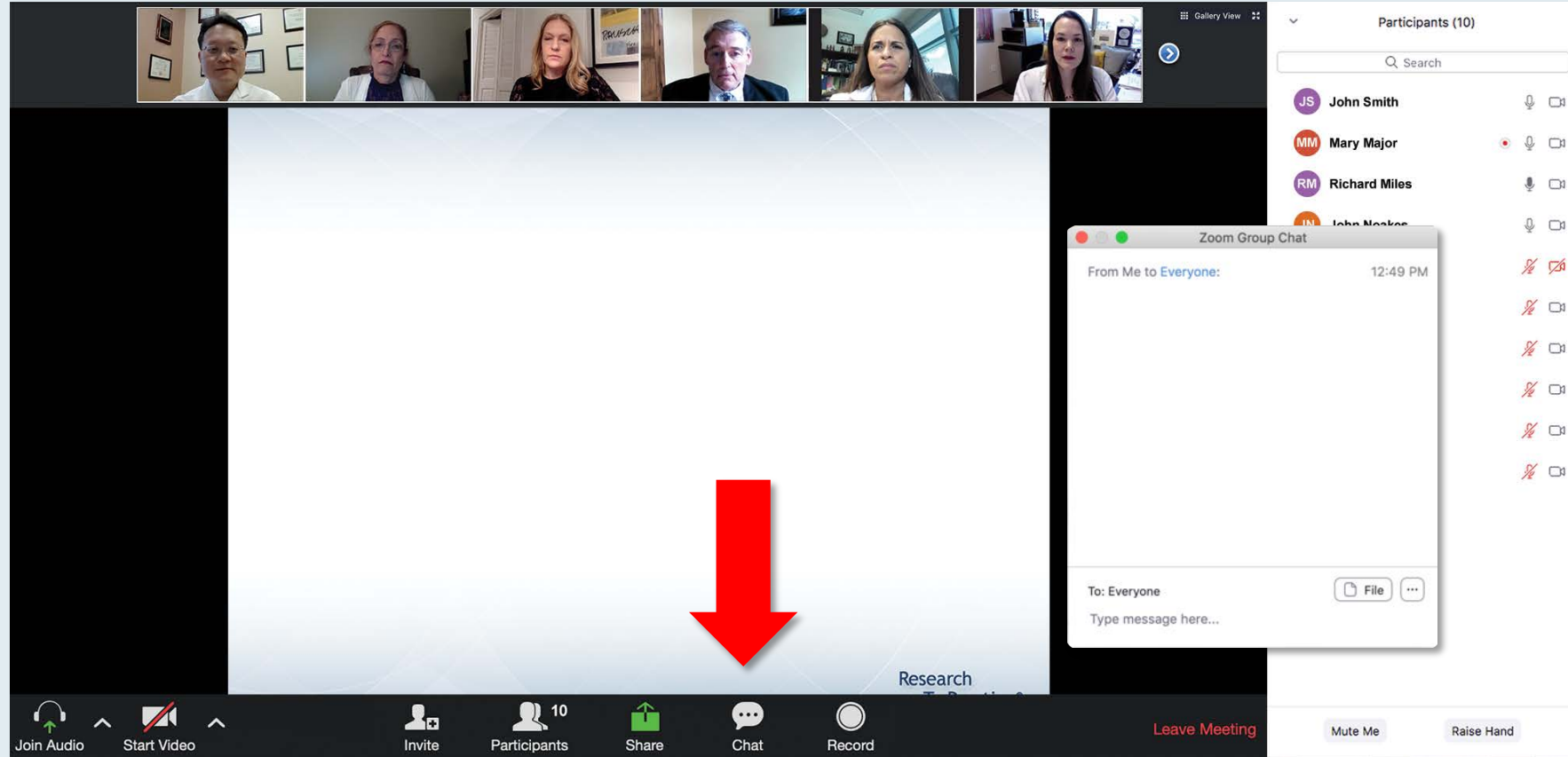
# Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

## Dr Mirza — Disclosures

<b>Advisory Committee</b>	Karyopharm Therapeutics, Sera Prognostics
<b>Global Clinical Lead</b>	ENGOT-OV16/NOVA niraparib, ENGOT-EN6/NSGO-RUBY
<b>Institutional Financial Interests (Study Grants)</b>	AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, Clovis Oncology, Pfizer Inc, Tesaro, A GSK Company, Ultimovacs
<b>Personal Financial Interests</b>	AstraZeneca Pharmaceuticals LP, BIOCAD, Clovis Oncology, Geneos Therapeutics, Genmab, Karyopharm Therapeutics, Merck, Merck Sharp & Dohme Corp, Mersana Therapeutics, Oncology Venture, Pfizer Inc, Roche Laboratories Inc, Seagen Inc, Sera Prognostics, SOTIO LLC, Tesaro, A GSK Company, Zai Lab
<b>Other</b>	Council and Faculty, European Society of Gynaecological Oncology, Chair-Elect, European Network of Gynaecological Oncological Trials Group

# We Encourage Clinicians in Practice to Submit Questions



Feel free to submit questions now before the program begins and throughout the program.

# Familiarizing Yourself with the Zoom Interface

## How to answer poll questions

The screenshot shows a Zoom meeting interface. At the top, there are six video thumbnails of participants. Below them is a slide with a poll question: "What is your usual treatment recommendation for a patient with MM followed by ASCT and maintenance experiences an asymptomatic relapse?". The slide lists ten options, including combinations of Carfilzomib, Pomalidomide, Elotuzumab, Daratumumab, and Ixazomib with or without dexamethasone. A "Quick Poll" window is overlaid on the slide, showing the same options with radio buttons for selection. The Zoom control bar at the bottom includes icons for Join Audio, Start Video, Invite, Participants (10), Share, Chat, Record, and Leave Meeting. On the right side, there is a "Participants (10)" list with names and icons for audio and video status.

Participants (10)

Search

- JS John Smith
- MM Mary Major
- RM Richard Miles
- JN John Noakes
- AS Alice Suarez
- JP Jane Perez
- RS Robert Stiles
- JF Juan Fernandez
- AK Ashok Kumar
- JS Jeremy Smith

What is your usual treatment recommendation for a patient with MM followed by ASCT and maintenance experiences an asymptomatic relapse?

Quick Poll

- Carfilzomib +/- dexamethasone
- Pomalidomide +/- dexamethasone
- Carfilzomib + pomalidomide +/- dexamethasone
- Elotuzumab + lenalidomide +/- dexamethasone
- Elotuzumab + pomalidomide +/- dexamethasone
- Daratumumab + lenalidomide +/- dexamethasone
- Daratumumab + pomalidomide +/- dexamethasone
- Daratumumab + bortezomib +/- dexamethasone
- Ixazomib + Rd
- Other

Submit

Co-provided by USF Health Research To Practice®

Join Audio Start Video Invite Participants 10 Share Chat Record Leave Meeting Mute Me Raise Hand

When a poll question pops up, click your answer choice from the available options.  
Results will be shown after everyone has answered.

## Upcoming Webinars

**Monday, November 9, 2020  
12:00 PM – 1:00 PM ET**

**Meet The Professor:  
Management of Lung Cancer**

**Faculty**

Corey J Langer, MD

**Moderator**

Neil Love, MD

**Friday, November 13, 2020  
12:00 PM – 1:00 PM ET**

**Meet The Professor:  
Immunotherapy and Novel  
Agents in Gynecologic Cancers**

**Faculty**

Krishnansu S Tewari, MD

**Moderator**

Neil Love, MD



***Thank you for joining us!***

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

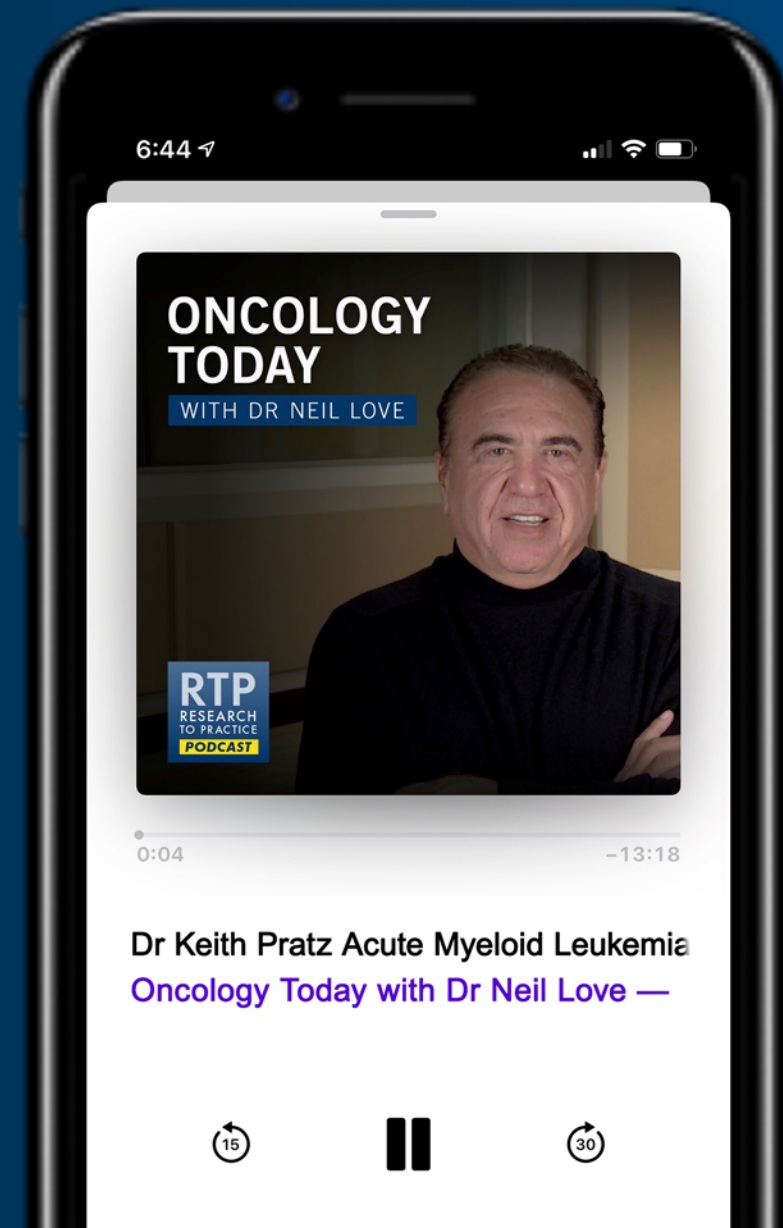
# ONCOLOGY TODAY

## SPECIAL EDITION: ACUTE MYELOID LEUKEMIA WITH FLT3 MUTATIONS

WITH DR NEIL LOVE



DR KEITH PRATZ  
UNIVERSITY OF PENNSYLVANIA



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# Meet The Professor Program Participating Faculty



**Deborah K Armstrong, MD**  
Professor of Oncology  
Professor of Gynecology and Obstetrics  
Skip Viragh Outpatient Cancer Building  
Johns Hopkins Sidney Kimmel  
Comprehensive Cancer Center  
Baltimore, Maryland



**Robert L Coleman, MD**  
Chief Scientific Officer  
US Oncology Research  
Gynecologic Oncology  
McKesson  
The Woodlands, Texas



**Don S Dizon, MD**  
Professor of Medicine, Brown University  
Director, Women's Cancers and Hematology-  
Oncology Outpatient Clinics  
Lifespan Cancer Institute  
Director, Medical Oncology and the Oncology  
Sexual Health Program  
Rhode Island Hospital  
Providence, Rhode Island



**Professor Jonathan A Ledermann**  
Professor of Medical Oncology  
Clinical Director  
University College London Cancer  
Institute  
Director, Cancer Research UK and UCL  
Cancer Trials Centre  
London, United Kingdom



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

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Rigshospitalet, Copenhagen University Hospital  
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**Shannon N Westin, MD, MPH**

Associate Professor  
Director, Early Drug Development  
Department of Gynecologic Oncology and Reproductive Medicine  
The University of Texas  
MD Anderson Cancer Center  
Houston, Texas



**Kathleen Moore, MD**

The Virginia Kerley Cade Endowed Chair in Cancer Development  
Associate Director, Clinical Research  
Director, Oklahoma TSET Phase I Program  
Stephenson Cancer Center  
Associate Professor, Section of Gynecologic Oncology  
Director, Gynecologic Oncology Fellowship  
Department of Obstetrics and Gynecology  
University of Oklahoma Health Sciences Center  
Oklahoma City, Oklahoma



***Project Chair***

**Neil Love, MD**  
Research To Practice  
Miami, Florida

# We Encourage Clinicians in Practice to Submit Questions

The image shows a Zoom meeting interface. At the top, there is a gallery view of six participants. The main area is a white slide with the text: "You may submit questions using the Zoom Chat option below". A large red arrow points downwards from this text. On the right side, there is a "Participants (10)" list with names and initials: John Smith (JS), Mary Major (MM), Richard Miles (RM), John Noakes (JN), and Alice Suarez (AS). Below the list is a "Zoom Group Chat" window showing a message from "Me to Everyone" at 12:49 PM. The bottom toolbar includes icons for "Join Audio", "Start Video", "Invite", "Participants" (10), "Share", "Chat", "Record", "Leave Meeting", "Mute Me", and "Raise Hand".

Feel free to submit questions now before the program begins and throughout the program.



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The screenshot displays a Zoom meeting interface. At the top, there is a gallery view of six participants. The main content area shows a poll question: "What is your usual treatment recommendation for a patient with MM who has been followed by ASCT for 1-5 years who then experiences an asymptomatic relapse?". Below the question is a list of ten treatment options, each with a radio button for selection. A "Quick Poll" dialog box is overlaid on the list, showing the selected option: "Carfilzomib +/- dexamethasone". The bottom of the screen features the Zoom control bar with icons for Join Audio, Start Video, Invite, Participants (10), Share, Chat, Record, and Leave Meeting. On the right side, there is a "Participants (10)" list with search and status icons for each participant.

What is your usual treatment recommendation for a patient with MM who has been followed by ASCT for 1-5 years who then experiences an asymptomatic relapse?

Quick Poll

- Carfilzomib +/- dexamethasone
- Pomalidomide +/- dexamethasone
- Carfilzomib + pomalidomide +/- dexamethasone
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- Elotuzumab + pomalidomide +/- dexamethasone
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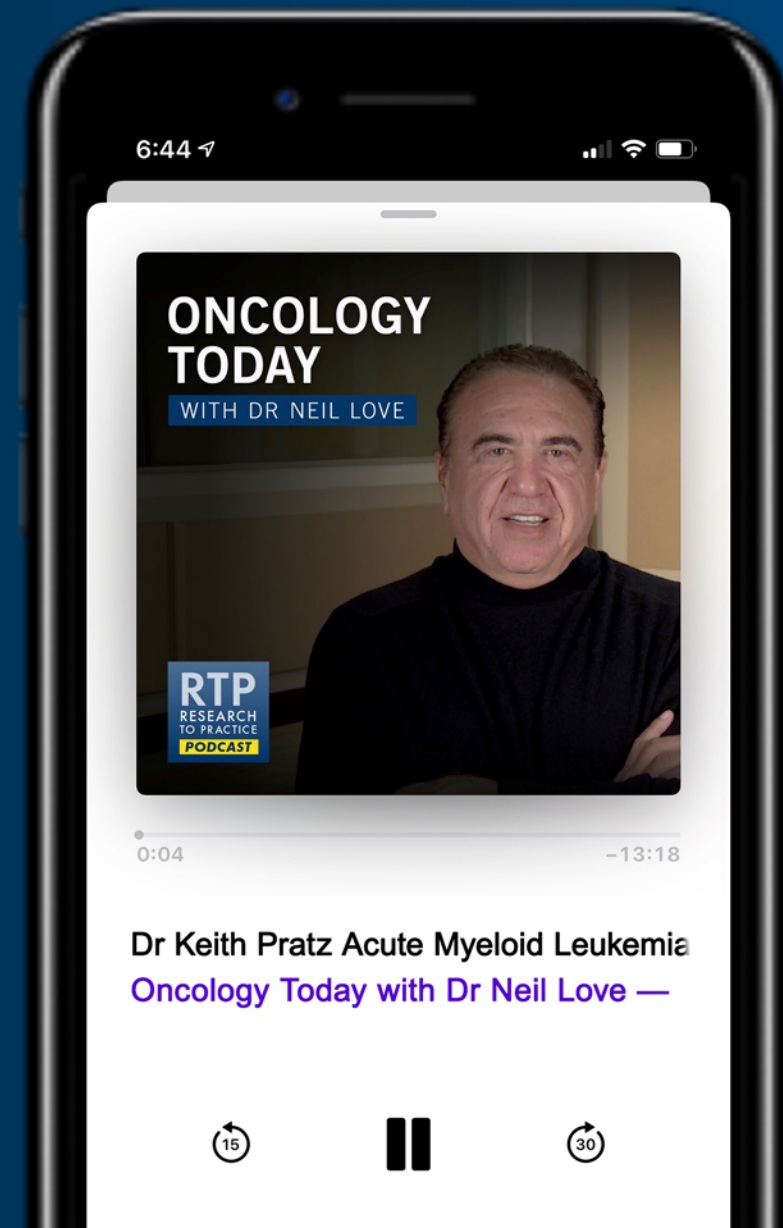
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**Dana M Chase, MD**

Gynecologic Oncologist, Arizona Oncology (US Oncology Network)  
Associate Professor, Creighton University School of Medicine  
Assistant Professor, University of Arizona College of Medicine  
Phoenix, Arizona



**Heidi E Godoy, DO**

Women's Cancer Care Associates  
Albany, New York



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Contents lists available at ScienceDirect

## Gynecologic Oncology

journal homepage: [www.elsevier.com/locate/ygyno](http://www.elsevier.com/locate/ygyno)

Meeting Report

The 2020 SGO Annual Meeting Report

*Gynecol Oncol* 2020;158:12-5

rapid communications

## PARP Inhibitors in the Management of Ovarian Cancer: ASCO Guideline



William P. Tew, MD<sup>1</sup>; Christina Lacchetti, MHSc<sup>2</sup>; Annie Ellis<sup>3,4</sup>; Kathleen Maxian, BSW<sup>5</sup>; Susana Banerjee, PhD<sup>6</sup>; Michael Bookman, MD<sup>7</sup>; Monica Brown Jones, MD<sup>8</sup>; Jung-Min Lee, MD<sup>9</sup>; Stéphanie Lheureux, MD, PhD<sup>10</sup>; Joyce F. Liu, MD<sup>11</sup>; Kathleen N. Moore, MD<sup>12</sup>; Carolyn Muller, MD<sup>13</sup>; Patricia Rodriguez, MD<sup>14</sup>; Christine Walsh, MD<sup>15</sup>; Shannon N. Westin, MD<sup>16</sup>; and Elise C. Kohn, MD<sup>9</sup>

*J Clin Oncol* 2020;[Online ahead of print].

## ASCO Guideline Recommendations

“All patients with newly diagnosed, stage III-IV EOC whose disease is in complete or partial response to first-line, platinum-based chemotherapy with high-grade serous or endometrioid EOC should be offered PARPi maintenance therapy with niraparib.

For patients with germline or somatic pathogenic or likely pathogenic variants in BRCA1 (g/sBRCA1) or BRCA2 (g/sBRCA2) genes should be treated with olaparib.

The addition of olaparib to bevacizumab may be offered to patients with stage III-IV EOC with g/sBRCA1/2 and/or genomic instability and a partial or complete response to chemotherapy plus bevacizumab combination.”

# Meet The Professor with Dr Mirza

## MODULE 1: Cases from Drs Chase and Godoy

- Dr Godoy: An 85-year-old woman with multiple regimen-recurrent ovarian cancer – BRCA1/2 wild type
- Questions and Comments: Niraparib-associated thrombocytopenia and surgical procedures
- Dr Chase: A 76-year-old woman with recurrent ovarian cancer – germline and somatic BRCA2 mutation
- Dr Godoy: An 83-year-old woman with Stage IV serous fallopian tube carcinoma – BRCA1/2 wild type
- Dr Chase: A 72-year-old woman with Stage IVB high-grade serous ovarian cancer (HGSOC) – HR proficient
- Dr Godoy: A 34-year-old woman with Stage IIIC HGSOC – germline BRCA1 mutation
- Questions and Comments: Defining platinum sensitivity

## MODULE 2: Journal Club with Dr Mirza

## MODULE 3: Beyond the Guidelines – Clinical Investigator Approaches to Common Clinical Scenarios

## MODULE 4: Key Recent Papers

# Case Presentation – Dr Godoy: An 85-year-old woman with multiple regimen-recurrent ovarian cancer – BRCA1/2 wild type, longstanding swallowing dysfunction

- 1/2014: S/p TAH-BSO, suboptimal debulking surgery and carboplatin/paclitaxel
- 8/2018 – 1/2020: Multiple recurrences



**Dr Heidi Godoy**



# Questions and Comments: Niraparib-associated thrombocytopenia and surgical procedures



**Dr Heidi Godoy**

# Case Presentation – Dr Chase: A 76-year-old woman with recurrent ovarian cancer – germline and somatic BRCA2 mutation



**Dr Dana Chase**

- 5/2016: Diagnosed with Stage IIIC ovarian cancer → Carboplatin/paclitaxel x 6
- Debulking surgery → Consolidation carboplatin/paclitaxel stopped after 2 weeks due to Grade 3 neuropathy → PD
- 9/2017: Liposomal doxorubicin/bevacizumab stopped after 1 month due to neutropenia
- Genetic testing: BRCA2 mutation
- 2/2018: Olaparib → PD
- 4/2019 – 5/2020: Gemcitabine → PD
  - 4/2020: FoundationOne®: BRCA2, MSS, TMB low

## Question

- For this patient, who had a good response to olaparib previously, would you consider re-treatment with a PARP inhibitor? If so, would you use the same PARPi or a different one?

# Case Presentation – Dr Godoy: An 83-year-old woman with Stage IV serous fallopian tube carcinoma – BRCA1/2 wild type



**Dr Heidi Godoy**

- 6/2014: Diagnosed with Stage IV serous fallopian tube carcinoma
- Carboplatin/paclitaxel x 6 → interval debulking surgery (R0) → carboplatin/paclitaxel x 3
  - Recurrent disease 2.5 years later: Peritoneal nodules, carcinomatosis
- Genetic testing: No actionable mutations; NGS: Unable to obtain due to small amount of tumor
- Carboplatin/paclitaxel x 2, with infusion reaction → carboplatin/docetaxel x 4
- Niraparib 300 mg daily x 4 months → reduced to 100 mg daily due to thrombocytopenia
  - 5/2020: Increased dose to 200 mg daily
- Currently, after approximately 3 years on niraparib: NED

## Questions

- How long would you consider keeping a patient in their 80s on niraparib, who has had a durable response for 3 years? Would you feel comfortable stretching out administration to every 2 months or every 3 months?
- For a patient in their 80s what dose of niraparib do you start with? Do you dose up or down?

# Case Presentation – Dr Chase: A 72-year-old woman with Stage IVB HGSOc – HR proficient



**Dr Dana Chase**

- 8/2019: Diagnosed with Stage IVB HGSOc
- Neoadjuvant carboplatin/paclitaxel x 3 → interval debulking
  - 1/2020: Completion of adjuvant carboplatin/paclitaxel x 3
  - 2/2020 CT: Interval decrease in size of peritoneal implants and liver lesion
- Maintenance niraparib x 6 months → PD
- 3/2020: Presents for transfer of care

## Questions

- How do you treat your patients with HR proficient disease? Do you observe them? Initiate PARPi maintenance therapy? Administer a few more cycles of bevacizumab and then continue bevacizumab maintenance therapy?
- For a patient with a partial response after completion of adjuvant chemotherapy, do you go to maintenance niraparib or administer more chemotherapy in hopes of getting a better response?

# Case Presentation – Dr Godoy: A 34-year-old woman with Stage IIIC HGSOc – germline BRCA1 mutation



**Dr Heidi Godoy**

- 11/2018: Diagnosed with Stage IIIC HGSOc
- S/p TAH-BSO, recto-sigmoid resection with reanastomosis
- Genetic testing: BRCA1 mutation
- Carboplatin/paclitaxel x 6 → Maintenance olaparib x 15 months
- 10/2020
  - CA-125: Increased to 21.2 from 10.2 from 6.6
  - CT: Multiple peritoneal nodules, enlarged mesenteric nodules
- NGS: Pending
- Carboplatin/gemcitabine/bevacizumab

## Questions

- In light of the PAOLA trial data, moving forward would you treat with single-agent PARPi or would you add in bevacizumab as well?
- If she has a CR after carbo/gem/bev x 3, should I give a PARPi alone or PARPi plus bevacizumab?



# Questions and Comments: Defining platinum sensitivity



**Dr Mansoor Raza Mirza**



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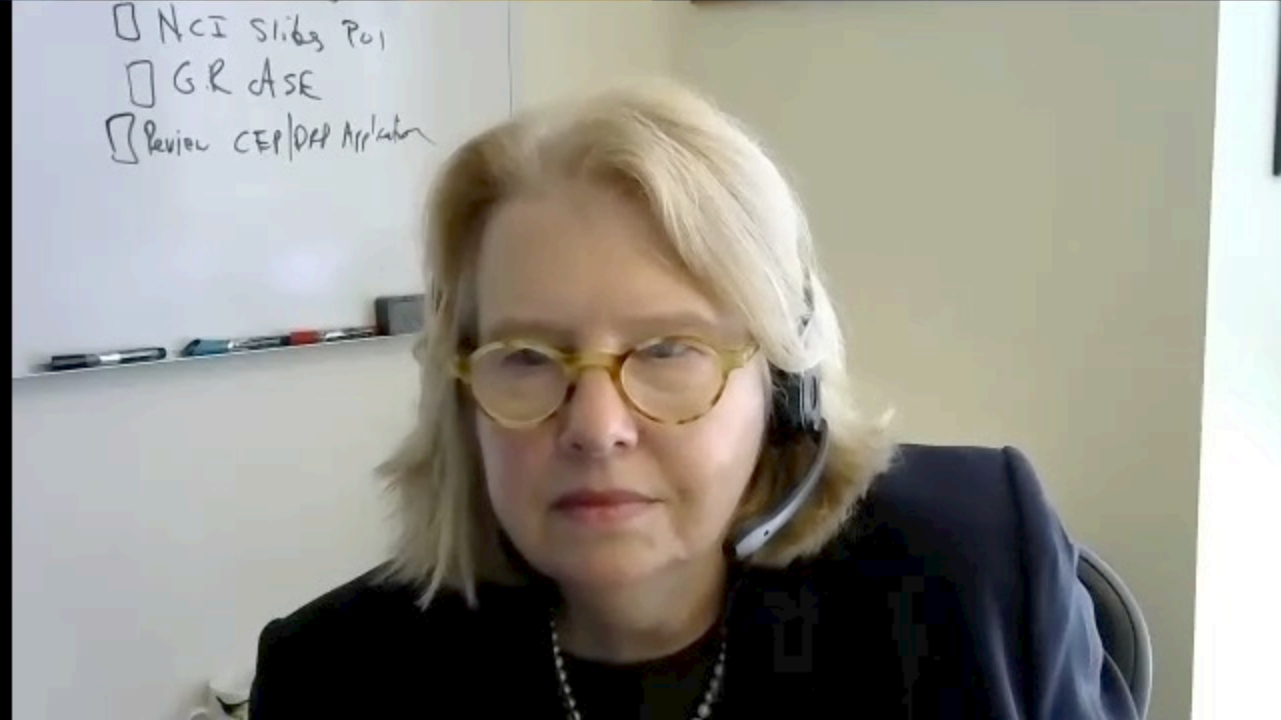
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Journal of Clinical Oncology 2020;[Online ahead of print]

RTP  
RESEARCH  
IN PRACTICE

- NCI Slides P01
- GR ASE
- Review CEP/DP Application



# Meet The Professor with Dr Mirza

## MODULE 1: Cases from Drs Chase and Godoy

## MODULE 2: Journal Club with Dr Mirza

- NSGO-PALEO/ENGOT-EN3 trial: Palbociclib/letrozole for ER-positive advanced/recurrent endometrial cancer (EC)
- PAOLA-1 trial: Maintenance olaparib + bevacizumab for newly diagnosed advanced HGOC
- The DNA repair pathway as a target for novel drugs in gynecologic cancers
- ENGOT-OV16/NOVA trial: Long-term safety of niraparib for recurrent ovarian cancer (OC)
- PRIMA/ENGOT-OV26/GOG-3012 trial: Individualized starting dose of niraparib
- PARP inhibitor activity in BRCA wild-type recurrent OC by HRR mutational gene profile analysis
- Therapeutic options after second-line platinum-based chemotherapy for recurrent OC
- Incorporating PARP inhibitors into the treatment of primary and recurrent OC: A meta-analysis
- Ongoing clinical trials
  - FIRST: First-line platinum +/- dostarlimab → niraparib +/- dostarlimab for OC
  - innovaTV 205: Tisotumab vedotin +/- bevacizumab, pembrolizumab or carboplatin for metastatic cervical cancer (CC)
  - SIENDO: Maintenance selinexor after combination chemotherapy for recurrent or advanced EC
  - KEYNOTE-A18: Pembrolizumab + chemoradiation therapy for high-risk locally advanced CC
  - NSGO-RUBY: Dostarlimab + carboplatin/paclitaxel for recurrent or primary advanced EC

## MODULE 3: Beyond the Guidelines – Clinical Investigator Approaches to Common Clinical Scenarios

## MODULE 4: Key Recent Papers



## A randomised double-blind placebo-controlled phase II trial of palbociclib combined with letrozole in patients with oestrogen receptor-positive advanced/recurrent endometrial cancer

ENGOT-EN3 / NSGO-PALEO

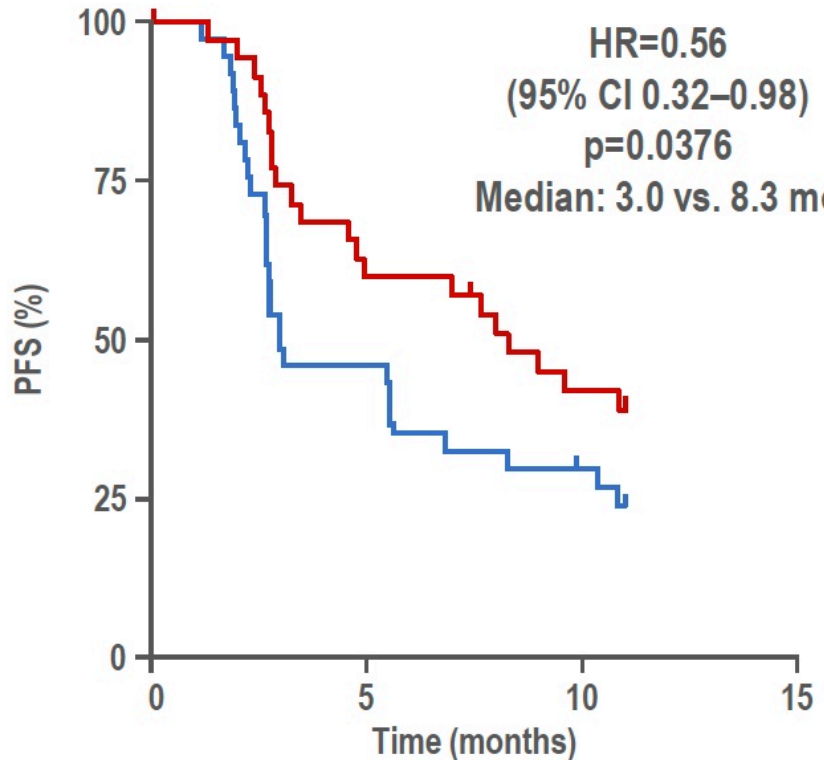
MR Mirza<sup>1</sup>, L Bjørge<sup>2</sup>, F Marmé<sup>3</sup>, R DePont Christensen<sup>4</sup>, M Gil-Martin<sup>5</sup>, A Auranen<sup>6</sup>, B Ataseven<sup>7</sup>, MJ Rubio<sup>8</sup>, V Salutati<sup>9</sup>, B Lund<sup>10</sup>, I Runnebaum<sup>11</sup>, A Redondo<sup>12</sup>, K Lindemann<sup>13</sup>, F Trillsch<sup>14</sup>, MP Barretina Ginesta<sup>15</sup>, H Roed<sup>16</sup>, J Loehndorf<sup>17</sup>, G-B Nyvang<sup>18</sup>, J Sehouli<sup>19</sup>

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# NSGO-PALEO/ENGOT-EN3 Trial: Efficacy (ITT Population)

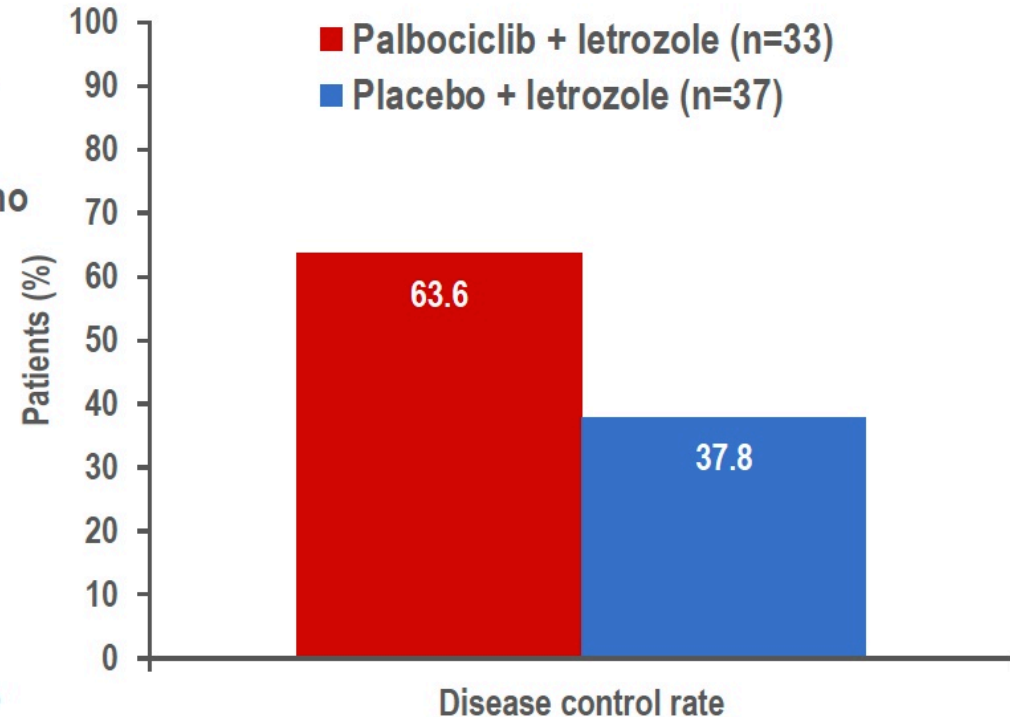
Primary endpoint: PFS



Number at risk	0	5	10
Palbociclib + letrozole	36	21	14
Placebo + letrozole	37	17	10

CI = confidence interval; HR = hazard ratio

Secondary endpoint: Disease control rate\*



\* = at 24 weeks

ENGOT-EN3 / NSGO-PALEO

# **Maintenance Olaparib + Bevacizumab (bev) in Patients (pts) with Newly Diagnosed Advanced High-Grade Ovarian Cancer (HGOC): RECIST and/or CA-125 Objective Response Rate (ORR) in the Phase III PAOLA-1 Trial**

Colombo N et al.

ESMO 2020;Abstract 812MO.

SPECIAL SERIES: ADVANCES IN THE MANAGEMENT OF GYNECOLOGIC CANCERS



# The DNA Repair Pathway as a Target for Novel Drugs in Gynecologic Cancers

Stephanie Lheureux, MD, PhD<sup>1</sup>; Mansoor Mirza, MD<sup>2</sup>; and Robert Coleman, MD<sup>3</sup>

*J Clin Oncol* 2019;37(27):2449-59.

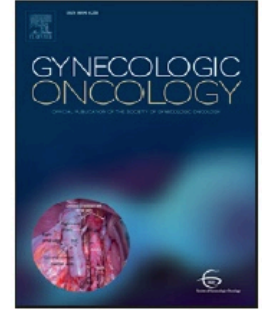




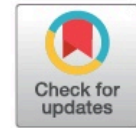
Contents lists available at ScienceDirect

## Gynecologic Oncology

journal homepage: [www.elsevier.com/locate/ygyno](http://www.elsevier.com/locate/ygyno)



### Long-term safety in patients with recurrent ovarian cancer treated with niraparib versus placebo: Results from the phase III ENGOT-OV16/NOVA trial



Mansoor R. Mirza <sup>a,\*</sup>, B. Benigno <sup>b</sup>, A. Dørum <sup>c</sup>, S. Mahner <sup>d</sup>, P. Bessette <sup>e</sup>, I. Bover Barceló <sup>f</sup>, D. Berton-Rigaud <sup>g</sup>, J.A. Ledermann <sup>h</sup>, B.J. Rimel <sup>i</sup>, J. Herrstedt <sup>j,k</sup>, S. Lau <sup>l</sup>, A. du Bois <sup>m</sup>, A. Casado Herráez <sup>n</sup>, E. Kalbacher <sup>o</sup>, J. Buscema <sup>p</sup>, D. Lorusso <sup>q</sup>, I. Vergote <sup>r</sup>, T. Levy <sup>s</sup>, P. Wang <sup>t</sup>, F.A. de Jong <sup>u</sup>, D. Gupta <sup>t</sup>, U.A. Matulonis <sup>v</sup>

# Evaluation of an Individualized Starting-Dose of Niraparib in the PRIMA/ENGOT-OV26/GOG-3012 Study

Mirza MR et al.

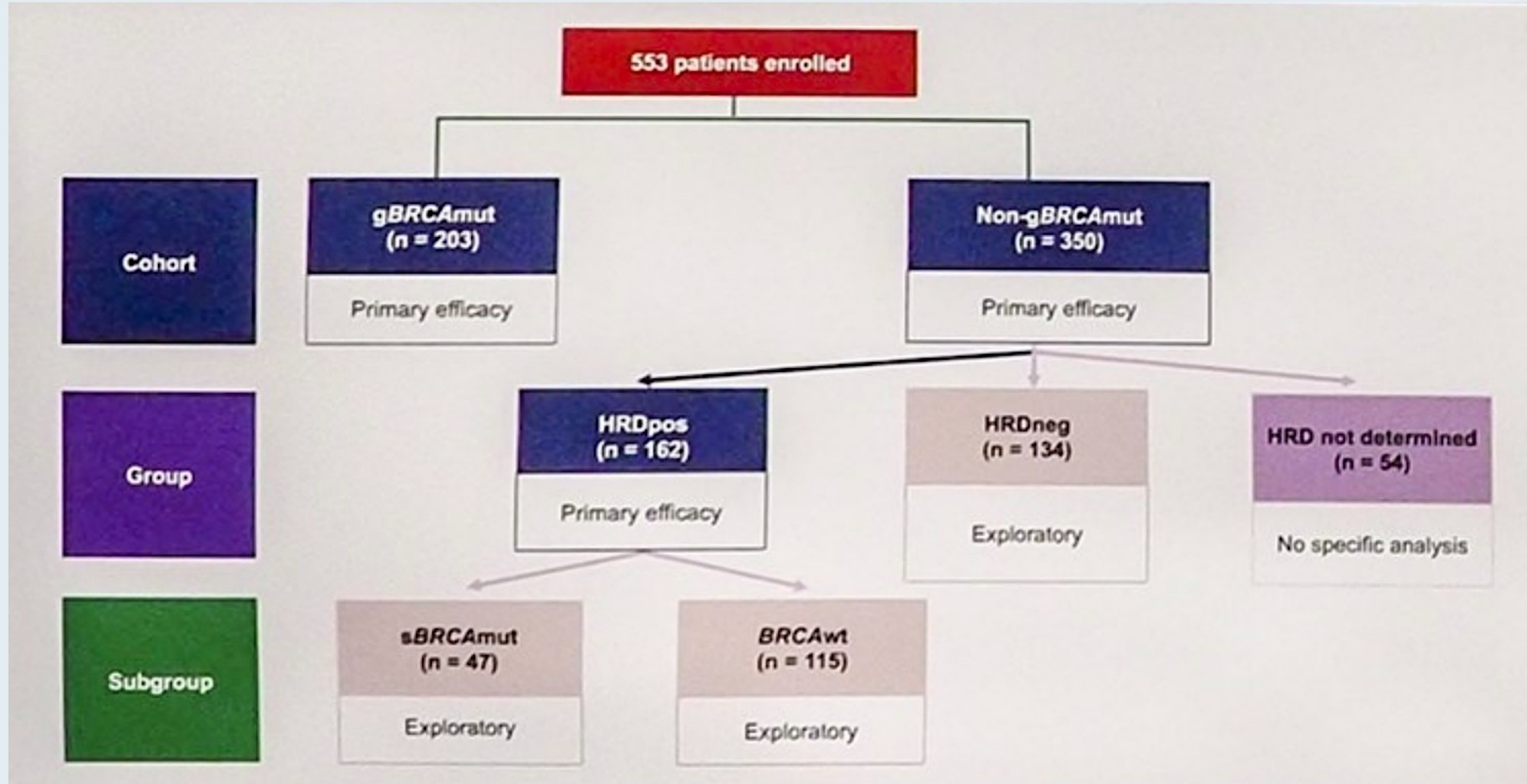
ASCO 2020;Abstract 6050.

# **Elucidation of PARP Inhibitor Activity in BRCAwt Recurrent Ovarian Cancer by HRR Mutational Gene Profile Analysis**

Mirza MR et al.

ASCO 2019;Abstract 5568.

# ENGOT-OV16/NOVA Trial Design





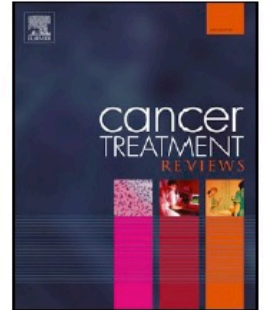


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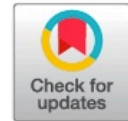
## Cancer Treatment Reviews

journal homepage: [www.elsevier.com/locate/ctrv](http://www.elsevier.com/locate/ctrv)



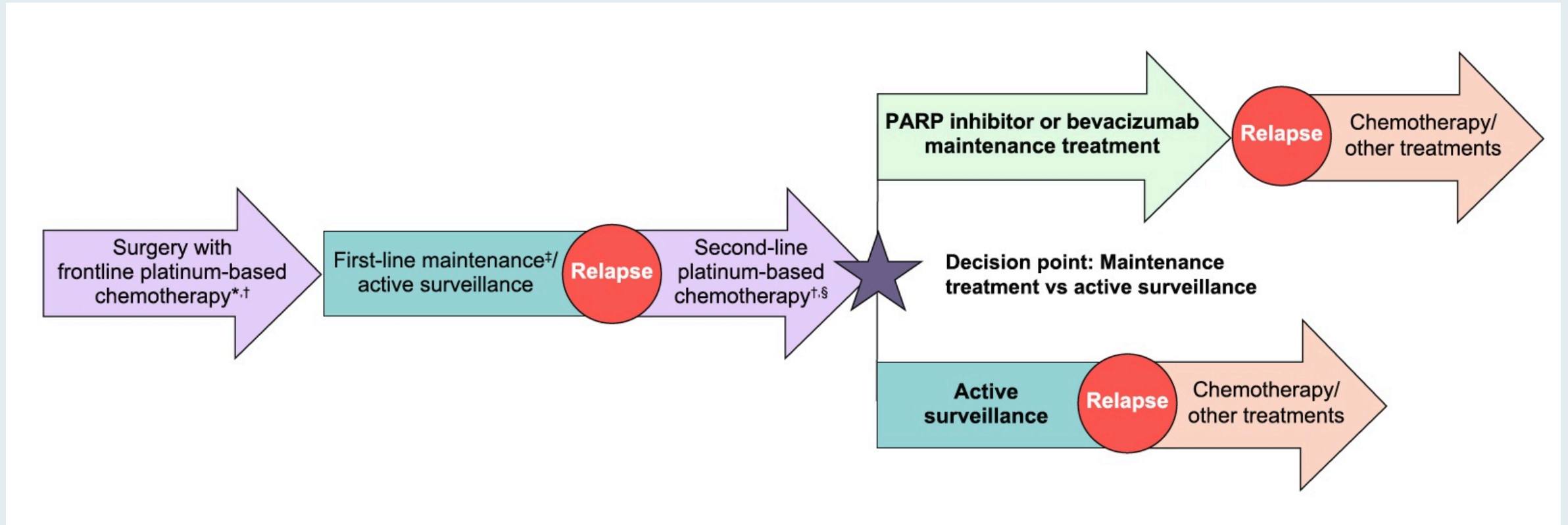
Anti-tumour Treatment

### Therapeutic options following second-line platinum-based chemotherapy in patients with recurrent ovarian cancer: Comparison of active surveillance and maintenance treatment



Isabelle Ray-Coquard<sup>a,\*</sup>, Mansoor Raza Mirza<sup>b</sup>, Sandro Pignata<sup>c</sup>, Axel Walther<sup>d</sup>, Ignacio Romero<sup>e</sup>,  
Andreas du Bois<sup>f</sup>

# Treatment Pathway in Ovarian Cancer, Focusing on the Clinical Decision After a Response to Second-Line Platinum-Based Chemotherapy

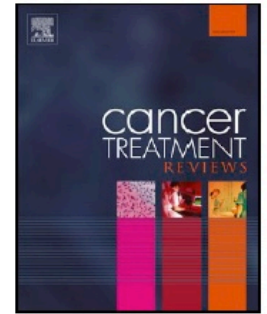




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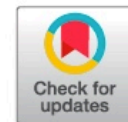
## Cancer Treatment Reviews

journal homepage: [www.elsevier.com/locate/ctrv](http://www.elsevier.com/locate/ctrv)



Systematic or Meta-analysis Studies

### Incorporating Parp-inhibitors in Primary and Recurrent Ovarian Cancer: A Meta-analysis of 12 phase II/III randomized controlled trials



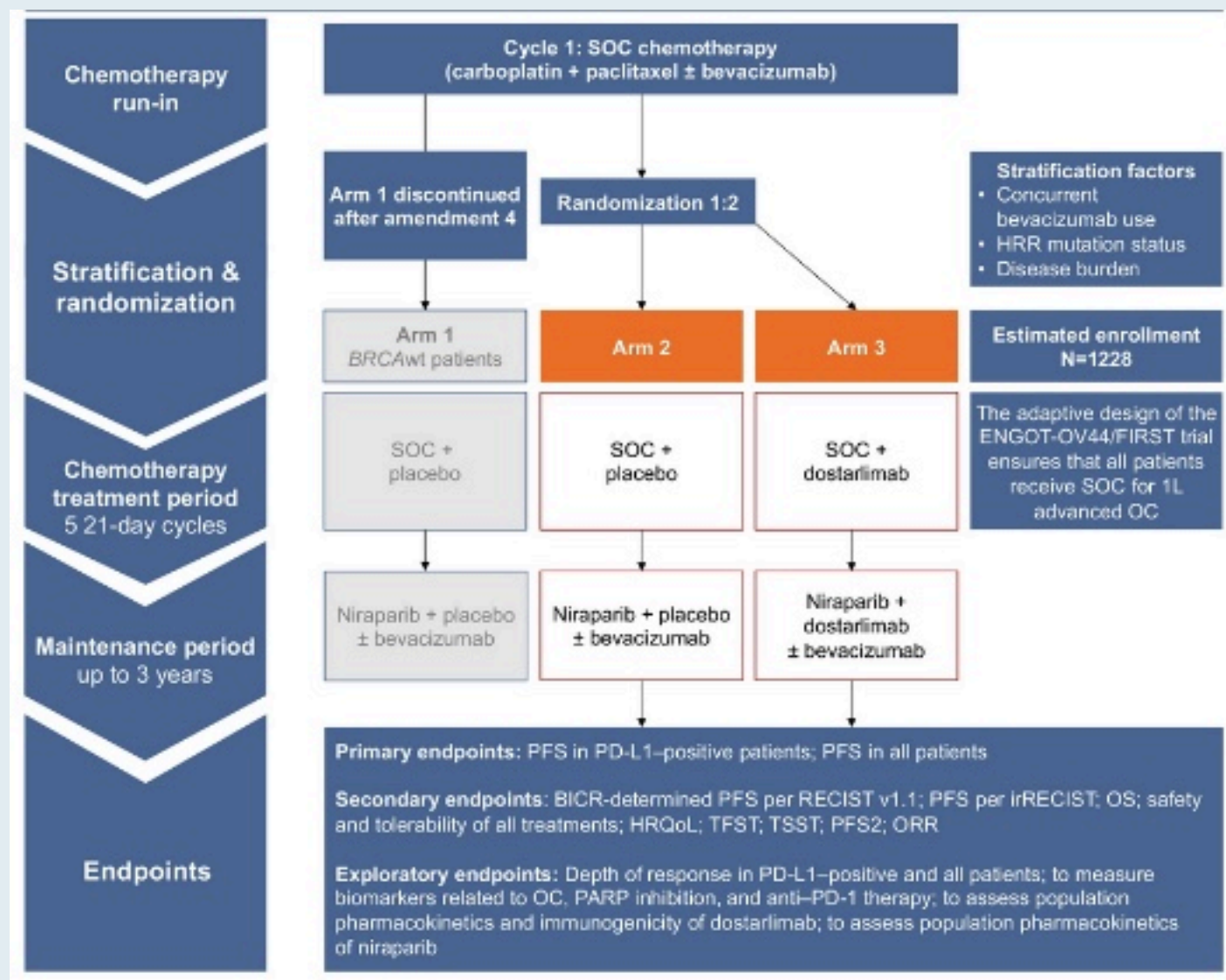
Ilary Ruscito<sup>a,b,c,\*</sup>, Filippo Bellati<sup>a</sup>, Isabelle Ray-Coquard<sup>d</sup>, Mansoor Raza Mirza<sup>e</sup>,  
Andreas du Bois<sup>f</sup>, Maria Luisa Gasparri<sup>g</sup>, Flavia Costanzi<sup>a</sup>, Maria Paola De Marco<sup>a</sup>,  
Marianna Nuti<sup>c</sup>, Donatella Caserta<sup>a</sup>, Sandro Pignata<sup>h</sup>, Oliver Dorigo<sup>i</sup>, Jalid Sehoul<sup>b</sup>,  
Elena Ioana Braicu<sup>b</sup>

**ENGOT-OV44/FIRST Study: A Randomized,  
Double-Blind, Adaptive, Phase III Study of  
Standard of Care (SOC) Platinum-Based Therapy  
± Dostarlimab Followed by Niraparib ±  
Dostarlimab Maintenance as First-Line (1L)  
Treatment of Stage 3 or 4 Ovarian Cancer (OC)**

Hardy-Bessard AC et al.  
ASCO 2020;Abstract TPS6101.



# ENGOT-OV44/FIRST Study Design



**Phase Ib/II Trial of Tisotumab Vedotin (TV)  $\pm$   
Bevacizumab (BEV), Pembrolizumab (PEM), or  
Carboplatin (CBP) in Recurrent or Metastatic Cervical  
Cancer (innovaTV 205/ENGOT-cx8/GOG-3024)**

Vergote I et al.

ASCO 2020;Abstract TPS6095.

# **SIENDO/ENGOT-EN5: A Randomized Phase III Trial of Maintenance with Selinexor/Placebo After Combination Chemotherapy in Patients with Advanced or Recurrent Endometrial Cancer**

Vergote I et al.

ASCO 2020;Abstract TPS6105.

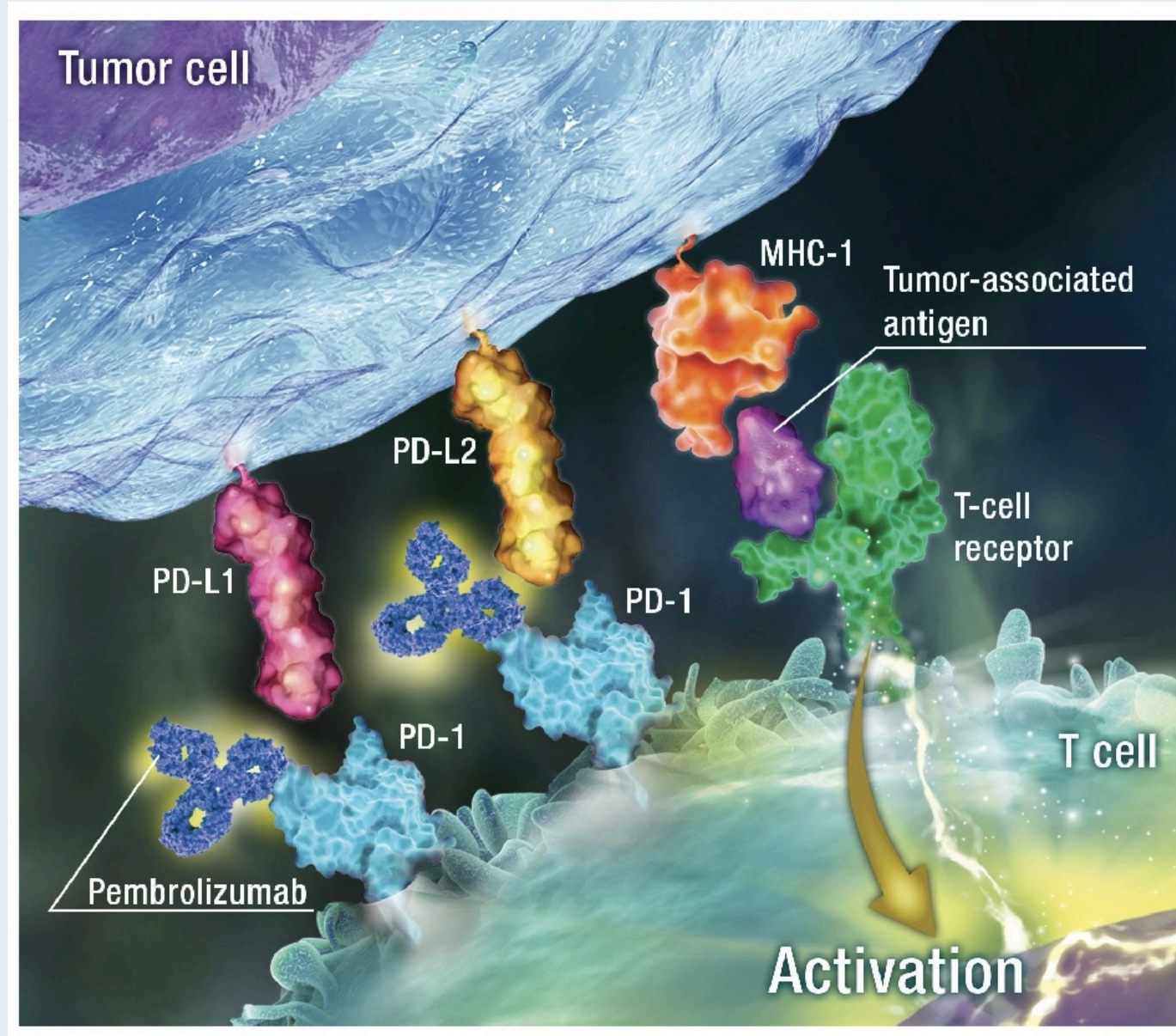
# **ENGOT-cx11/KEYNOTE-A18: A Phase III, Randomized, Double-Blind Study of Pembrolizumab with Chemoradiotherapy in Patients with High-Risk Locally Advanced Cervical Cancer**

Laruso D et al.

ASCO 2020;Abstract TPS6096.



# Pembrolizumab and the PD-1 Pathway



**ENGOT-EN6/NSGO-RUBY: A Phase III, Randomized, Double-Blind, Multicenter Study of Dostarlimab + Carboplatin-Paclitaxel versus Placebo + Carboplatin-Paclitaxel in Recurrent or Primary Advanced Endometrial Cancer (EC)**

Mirza MR et al.

ASCO 2020;Abstract TPS6107.

# Meet The Professor with Dr Mirza

## MODULE 1: Cases from Drs Chase and Godoy









## MODULE 2: Journal Club with Dr Mirza

- NSGO-PALEO/ENGOT-EN3 trial: Palbociclib/letrozole for ER-positive advanced/recurrent endometrial cancer (EC)
- PAOLA-1 trial: Maintenance olaparib + bevacizumab for newly diagnosed advanced HGOC
- The DNA repair pathway as a target for novel drugs in gynecologic cancers
- ENGOT-OV16/NOVA trial: Long-term safety of niraparib for recurrent ovarian cancer (OC)
- PRIMA/ENGOT-OV26/GOG-3012 trial: Individualized starting dose of niraparib
- PARP inhibitor activity in BRCA wild-type recurrent OC by HRR mutational gene profile analysis
- Therapeutic options after second-line platinum-based chemotherapy for recurrent OC
- Incorporating PARP inhibitors into the treatment of primary and recurrent OC: A meta-analysis
- Ongoing clinical trials
  - FIRST: First-line platinum +/- dostarlimab → niraparib +/- dostarlimab for OC
  - innovaTV 205: Tisotumab vedotin +/- bevacizumab, pembrolizumab or carboplatin for metastatic cervical cancer (CC)
  - SIENDO: Maintenance selinexor after combination chemotherapy for recurrent or advanced EC
  - KEYNOTE-A18: Pembrolizumab + chemoradiation therapy for high-risk locally advanced CC
  - NSGO-RUBY: Dostarlimab + carboplatin/paclitaxel for recurrent or primary advanced EC

## MODULE 3: Beyond the Guidelines – Clinical Investigator Approaches to Common Clinical Scenarios

## MODULE 4: Key Recent Papers

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? Do you routinely assess homologous recombination deficiency (HRD) status in your patients with advanced ovarian cancer?

		Optimal approach to mutation testing	Routinely assess HRD status
	DEBORAH K ARMSTRONG, MD	Multigene germline and somatic/NGS	No
	ROBERT L COLEMAN, MD	Multigene germline and somatic/NGS	Yes
	DON S DIZON, MD	Germline BRCA; if negative, multigene somatic (eg, NGS)	Yes
	PROFESSOR JONATHAN A LEDERMANN	Multigene germline and somatic/NGS	No
	URSULA MATULONIS, MD	Multigene germline and somatic/NGS	No
	MANSOOR RAZA MIRZA, MD	Multigene germline and somatic/NGS	No
	KATHLEEN MOORE, MD	Multigene germline and somatic/NGS	Yes
	SHANNON N WESTIN, MD, MPH	Germline BRCA; if negative, multigene somatic (eg, NGS)	Yes

NGS = next-generation sequencing



**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?**



DEBORAH K ARMSTRONG, MD

**Carboplatin/paclitaxel → olaparib**



ROBERT L COLEMAN, MD

**Carboplatin/paclitaxel + bevacizumab → bevacizumab + olaparib**



DON S DIZON, MD

**Carboplatin/paclitaxel → olaparib**



PROFESSOR JONATHAN A  
LEDERMANN

**Carboplatin/paclitaxel → olaparib**



URSULA MATULONIS, MD

**Carboplatin/paclitaxel → olaparib**



MANSOOR RAZA MIRZA, MD

**Carboplatin/paclitaxel → niraparib**



KATHLEEN MOORE, MD

**Carboplatin/paclitaxel + bevacizumab → bevacizumab + olaparib**



SHANNON N WESTIN, MD, MPH

**Carboplatin/paclitaxel → olaparib or niraparib**

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



DEBORAH K ARMSTRONG, MD

**Carboplatin/paclitaxel → olaparib**



ROBERT L COLEMAN, MD

**Carboplatin/paclitaxel + bevacizumab → bevacizumab + niraparib**



DON S DIZON, MD

**Carboplatin/paclitaxel + bevacizumab → bevacizumab + olaparib**



PROFESSOR JONATHAN A LEDERMANN

**Carboplatin/paclitaxel + bevacizumab → bevacizumab + olaparib**



URSULA MATULONIS, MD

**Carboplatin/paclitaxel → olaparib**



MANSOOR RAZA MIRZA, MD

**Carboplatin/paclitaxel + bevacizumab → bevacizumab + olaparib**



KATHLEEN MOORE, MD

**Carboplatin/paclitaxel + bevacizumab → bevacizumab + olaparib**



SHANNON N WESTIN, MD, MPH

**Carboplatin/paclitaxel + bevacizumab → bevacizumab + olaparib**



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



DEBORAH K ARMSTRONG, MD

**Carboplatin/paclitaxel → olaparib**



ROBERT L COLEMAN, MD

**Carboplatin/paclitaxel + bevacizumab → bevacizumab + olaparib**



DON S DIZON, MD

**Carboplatin/paclitaxel + bevacizumab → bevacizumab + olaparib**



PROFESSOR JONATHAN A LEDERMANN

**Carboplatin/paclitaxel + bevacizumab → bevacizumab + olaparib**



URSULA MATULONIS, MD

**Carboplatin/paclitaxel → olaparib**



MANSOOR RAZA MIRZA, MD

**Carboplatin/paclitaxel + bevacizumab → bevacizumab + olaparib**



KATHLEEN MOORE, MD

**Carboplatin/paclitaxel + bevacizumab → bevacizumab + olaparib**



SHANNON N WESTIN, MD, MPH

**Carboplatin/paclitaxel + bevacizumab → bevacizumab + olaparib**

**A 60-year-old woman with Stage IIIC fallopian tube cancer (BRCA wild type, HRD-negative) is s/p optimal debulking surgery. Regulatory and reimbursement issues aside, what would you recommend as postoperative systemic therapy?**

1. Carboplatin/paclitaxel
2. Carboplatin/paclitaxel → olaparib
3. Carboplatin/paclitaxel → niraparib
4. Carboplatin/paclitaxel + bev → olaparib
5. Carboplatin/paclitaxel + bev → niraparib
6. Carboplatin/paclitaxel + bev → bev/olaparib
7. Carboplatin/paclitaxel + bev → bev/niraparib
8. Other

**A 60-year-old woman with Stage IIIC ovarian cancer (BRCA wild type, HRD-negative) 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?**



DEBORAH K ARMSTRONG, MD

**Carboplatin/paclitaxel OR carboplatin/paclitaxel → niraparib**



ROBERT L COLEMAN, MD

**Carboplatin/paclitaxel + bevacizumab → bevacizumab**



DON S DIZON, MD

**Carboplatin/paclitaxel → niraparib**



PROFESSOR JONATHAN A LEDERMANN

**Carboplatin/paclitaxel**



URSULA MATULONIS, MD

**Discuss several options with patient**



MANSOOR RAZA MIRZA, MD

**Carboplatin/paclitaxel → niraparib**



KATHLEEN MOORE, MD









**Carboplatin/paclitaxel + bevacizumab → bevacizumab**



SHANNON N WESTIN, MD, MPH









**Carboplatin/paclitaxel OR carboplatin/paclitaxel → niraparib**

**A 60-year-old woman with Stage IIIC ovarian cancer (BRCA wild type) is s/p suboptimal debulking surgery with an elevated CA-125 level. Regulatory and reimbursement issues aside, what would you recommend as postoperative systemic therapy if her disease was...**

		HRD-positive	HRD-negative
	DEBORAH K ARMSTRONG, MD	Carbo/pac → niraparib	Carbo/pac OR carbo/pac → niraparib
	ROBERT L COLEMAN, MD	Carbo/pac + bev → bev + olaparib	Carbo/pac + bev → bev
	DON S DIZON, MD	Carbo/pac + bev → bev + olaparib	Carbo/pac + bev → niraparib
	PROFESSOR JONATHAN A LEDERMANN	Carbo/pac + bev → bev + olaparib	Carbo/pac + bev → bev
	URSULA MATULONIS, MD	Discuss several options with patient	Discuss several options with patient
	MANSOOR RAZA MIRZA, MD	Carbo/pac + bev → bev + olaparib	Carbo/pac → niraparib
	KATHLEEN MOORE, MD	Carbo/pac + bev → bev + olaparib	Carbo/pac + bev → bev
	SHANNON N WESTIN, MD, MPH	Carbo/pac + bev → bev + olaparib	Carbo/pac + bev → bev

Carbo/pac = carboplatin/paclitaxel; bev = bevacizumab

A 60-year-old woman with Stage IIIC ovarian cancer and a germline BRCA mutation undergoes suboptimal debulking surgery and receives carboplatin/paclitaxel followed by olaparib. For how long would you typically continue the olaparib if the patient is tolerating it well?

 DEBORAH K ARMSTRONG, MD	2 years (depends on disease status at completion of chemotherapy)
 ROBERT L COLEMAN, MD	2 years
 DON S DIZON, MD	Indefinitely
 PROFESSOR JONATHAN A LEDERMANN	2 years
 URSULA MATULONIS, MD	2 years
 MANSOOR RAZA MIRZA, MD	2 years
 KATHLEEN MOORE, MD	2 years
 SHANNON N WESTIN, MD, MPH	2 years

A 60-year-old woman with Stage IIIC ovarian cancer (BRCA wild type, HRD-positive) undergoes suboptimal debulking surgery and receives carboplatin/paclitaxel followed by niraparib. For how long would you typically continue the niraparib if the patient is tolerating it well?









 DEBORAH K ARMSTRONG, MD	3 years
 ROBERT L COLEMAN, MD	3 years
 DON S DIZON, MD	Indefinitely
 PROFESSOR JONATHAN A LEDERMANN	3 years
 URSULA MATULONIS, MD	3 years
 MANSOOR RAZA MIRZA, MD	3 years
 KATHLEEN MOORE, MD	3 years
 SHANNON N WESTIN, MD, MPH	3 years



**Regulatory and reimbursement issues aside, which starting dose of niraparib would you use for a 125-lb patient with advanced ovarian cancer and a platelet count of 200,000 after a response to front-line platinum-based chemotherapy?**

1. 300 mg daily
2. 200 mg daily
3. 100 mg daily
4. Other

**What starting dose of niraparib would you use for a 125-lb patient with advanced ovarian cancer after response to front-line platinum-based chemotherapy with a platelet count of 200,000 for whom you are about to initiate maintenance niraparib?**

	DEBORAH K ARMSTRONG, MD	200 mg daily
	ROBERT L COLEMAN, MD	200 mg daily
	DON S DIZON, MD	300 mg daily
	PROFESSOR JONATHAN A LEDERMANN	200 mg daily
	URSULA MATULONIS, MD	200 mg daily
	MANSOOR RAZA MIRZA, MD	200 mg daily
	KATHLEEN MOORE, MD	200 mg daily
	SHANNON N WESTIN, MD, MPH	200 mg daily

**A woman in her mid-60s with recurrent high-grade serous ovarian cancer begins rucaparib monotherapy (600 mg BID). Within a few weeks her serum creatinine increases from 0.86 mg/dL to 1.6 mg/dL. What would be the optimal management approach?**



DEBORAH K ARMSTRONG, MD

**Continue rucaparib at same dose**



ROBERT L COLEMAN, MD

**Continue rucaparib at the same dose**



DON S DIZON, MD

**Hold rucaparib until creatinine returns to normal, then restart at reduced dose**



PROFESSOR JONATHAN A LEDERMANN

**Hold rucaparib until creatinine returns to normal, then restart at the same dose**



URSULA MATULONIS, MD

**Continue rucaparib at the same dose**



MANSOOR RAZA MIRZA, MD

**Hold rucaparib until creatinine returns to normal, then restart at the same dose**



KATHLEEN MOORE, MD









**Continue rucaparib at the same dose**











SHANNON N WESTIN, MD, MPH

**Continue rucaparib at the same dose**









**In general, what is your approach to antiemetic therapy for a patient with ovarian cancer who is starting treatment on a PARP inhibitor? Does your approach to antiemetic therapy differ according to which PARP inhibitor is administered?**

		<b>Antiemetic approach</b>	<b>Differ by PARPi?</b>
	DEBORAH K ARMSTRONG, MD	<b>Recommend antiemetic if pt has nausea</b>	<b>No</b>
	ROBERT L COLEMAN, MD	<b>Recommend antiemetic if pt has nausea</b>	<b>No</b>
	DON S DIZON, MD	<b>Prophylactic antiemetic prior to PARPi</b>	<b>No</b>
	PROFESSOR JONATHAN A LEDERMANN	<b>Recommend antiemetic if pt has nausea</b>	<b>No</b>
	URSULA MATULONIS, MD	<b>Recommend antiemetic if pt has nausea</b>	<b>Yes (cautious use of ondansetron w/niraparib as niraparib may also cause constipation)</b>
	MANSOOR RAZA MIRZA, MD	<b>Reduce PARPi dose if pt has nausea</b>	<b>No</b>
	KATHLEEN MOORE, MD	<b>Prophylactic antiemetic prior to PARPi for the first 2 months</b>	<b>No</b>
	SHANNON N WESTIN, MD, MPH	<b>Recommend antiemetic if pt has nausea</b>	<b>No</b>

# According to your clinical experience, do PARP inhibitors cause insomnia?

	DEBORAH K ARMSTRONG, MD	No
	ROBERT L COLEMAN, MD	Yes
	DON S DIZON, MD	No
	PROFESSOR JONATHAN A LEDERMANN	Yes
	URSULA MATULONIS, MD	Yes
	MANSOOR RAZA MIRZA, MD	No
	KATHLEEN MOORE, MD	Yes
	SHANNON N WESTIN, MD, MPH	Yes









**A 70-year-old woman with advanced ovarian cancer and a germline BRCA mutation undergoes debulking surgery followed by chemotherapy with carboplatin/paclitaxel and experiences disease relapse 1 year later. Which treatment would you likely recommend?**

 DEBORAH K ARMSTRONG, MD	<b>Carboplatin/PLD → maintenance olaparib</b>
 ROBERT L COLEMAN, MD	<b>Carboplatin/PLD → maintenance rucaparib</b>
 DON S DIZON, MD	<b>Carboplatin/pac → maintenance olaparib</b>
 PROFESSOR JONATHAN A LEDERMANN	<b>Carboplatin/PLD → maintenance olaparib</b>
 URSULA MATULONIS, MD	<b>Carboplatin/PLD → maintenance olaparib</b>
 MANSOOR RAZA MIRZA, MD	<b>Carboplatin/PLD → maintenance niraparib</b>
 KATHLEEN MOORE, MD	<b>Carboplatin/PLD → maintenance olaparib</b>
 SHANNON N WESTIN, MD, MPH	<b>Carboplatin/pac + bevacizumab → maintenance olaparib</b>

PLD = pegylated liposomal doxorubicin











**A 70-year-old woman with advanced ovarian cancer (BRCA wild type, HRD-negative) undergoes debulking surgery followed by chemotherapy with carboplatin/paclitaxel and experiences disease relapse 1 year later. Which treatment would you likely recommend?**

 DEBORAH K ARMSTRONG, MD	<b>Carboplatin/PLD → maintenance rucaparib</b>
 ROBERT L COLEMAN, MD	<b>Carboplatin/PLD + bevacizumab → maintenance bevacizumab</b>
 DON S DIZON, MD	<b>Carboplatin/paclitaxel → maintenance niraparib</b>
 PROFESSOR JONATHAN A LEDERMANN	<b>Carboplatin/PLD → maintenance rucaparib</b>
 URSULA MATULONIS, MD	<b>Carboplatin/PLD → maintenance olaparib or niraparib</b>
 MANSOOR RAZA MIRZA, MD	<b>Carboplatin/PLD → maintenance niraparib</b>
 KATHLEEN MOORE, MD	<b>Carboplatin/PLD + bevacizumab → maintenance bevacizumab</b>
 SHANNON N WESTIN, MD, MPH	<b>Carboplatin/PLD + bevacizumab → maintenance bevacizumab</b>

PARPi = PARP inhibitor

**A 70-year-old woman with advanced ovarian cancer and a germline BRCA mutation undergoes debulking surgery, then receives carboplatin/paclitaxel/bevacizumab followed by maintenance therapy with a PARP inhibitor for 2 years and experiences disease relapse 1 year later. Which treatment would you likely recommend?**

 DEBORAH K ARMSTRONG, MD	<b>Carboplatin/PLD → maintenance rucaparib</b>
 ROBERT L COLEMAN, MD	<b>Carboplatin/PLD → maintenance rucaparib</b>
 DON S DIZON, MD	<b>Carboplatin/paclitaxel → alternate PARPi than previously received</b>
 PROFESSOR JONATHAN A LEDERMANN	<b>Carboplatin/PLD</b>
 URSULA MATULONIS, MD	<b>Carboplatin/PLD → maintenance olaparib considered if platinum sensitive</b>
 MANSOOR RAZA MIRZA, MD	<b>Carboplatin/PLD + bev → maintenance bev</b>
 KATHLEEN MOORE, MD	<b>Carboplatin/PLD → maintenance niraparib</b>
 SHANNON N WESTIN, MD, MPH	<b>Carboplatin/PLD → maintenance olaparib</b>

PARPi = PARP inhibitor

**A 70-year-old woman with advanced ovarian cancer (BRCA wild type, HRD-negative) undergoes debulking surgery, then receives carboplatin/paclitaxel/bevacizumab followed by maintenance therapy with a PARP inhibitor for 2 years and experiences disease relapse 1 year later. Which treatment would you likely recommend?**



DEBORAH K ARMSTRONG, MD

**Gemcitabine/cisplatin → maintenance rucaparib**



ROBERT L COLEMAN, MD

**Carboplatin/PLD + bevacizumab → maintenance bevacizumab**



DON S DIZON, MD

**Carboplatin/paclitaxel**



PROFESSOR JONATHAN A LEDERMANN

**Carboplatin/PLD + bevacizumab → maintenance bevacizumab**



URSULA MATULONIS, MD

**Carboplatin/PLD → maintenance olaparib**



MANSOOR RAZA MIRZA, MD

**Carboplatin/PLD + bev → maintenance bev**



KATHLEEN MOORE, MD

**Carboplatin/PLD + bevacizumab → maintenance bevacizumab**



SHANNON N WESTIN, MD, MPH

**Carboplatin/PLD + bevacizumab → maintenance bevacizumab**

**A 70-year-old woman with advanced ovarian cancer (BRCA wild type, HRD-positive) undergoes debulking surgery, then receives carboplatin/paclitaxel/bevacizumab followed by maintenance therapy with a PARP inhibitor for 2 years and experiences disease relapse 1 year later. Which treatment would you likely recommend?**



DEBORAH K ARMSTRONG, MD

**Carboplatin/PLD**



ROBERT L COLEMAN, MD

**Carboplatin/PLD → maintenance rucaparib**



DON S DIZON, MD

**Carboplatin/paclitaxel → alternate PARPi than previously received**



PROFESSOR JONATHAN A LEDERMANN

**Carboplatin/PLD**



URSULA MATULONIS, MD

**Carboplatin/PLD → maintenance olaparib considered if platinum sensitive**



MANSOOR RAZA MIRZA, MD

**Carboplatin/PLD + bev → maintenance bev**



KATHLEEN MOORE, MD









**Carboplatin/PLD → maintenance olaparib**



SHANNON N WESTIN, MD, MPH

**Carbo/pac → maintenance niraparib *OR* Carbo/PLD → maintenance niraparib**

**Outside of a clinical trial, have you used or would you use a second PARP inhibitor or continue the same PARP inhibitor for a patient with ovarian cancer who experienced disease progression on a PARP inhibitor?**

 <b>DEBORAH K ARMSTRONG, MD</b>	<b>I have</b>
 <b>ROBERT L COLEMAN, MD</b>	<b>I have but would not again</b>
 <b>DON S DIZON, MD</b>	<b>I have</b>
 <b>PROFESSOR JONATHAN A LEDERMANN</b>	<b>I have</b>
 <b>URSULA MATULONIS, MD</b>	<b>I have</b>
 <b>MANSOOR RAZA MIRZA, MD</b>	<b>I have not and would not</b>
 <b>KATHLEEN MOORE, MD</b>	<b>I have</b>
 <b>SHANNON N WESTIN, MD, MPH</b>	<b>I have</b>

# Meet The Professor with Dr Mirza

## MODULE 1: Cases from Drs Chase and Godoy

## MODULE 2: Journal Club with Dr Mirza

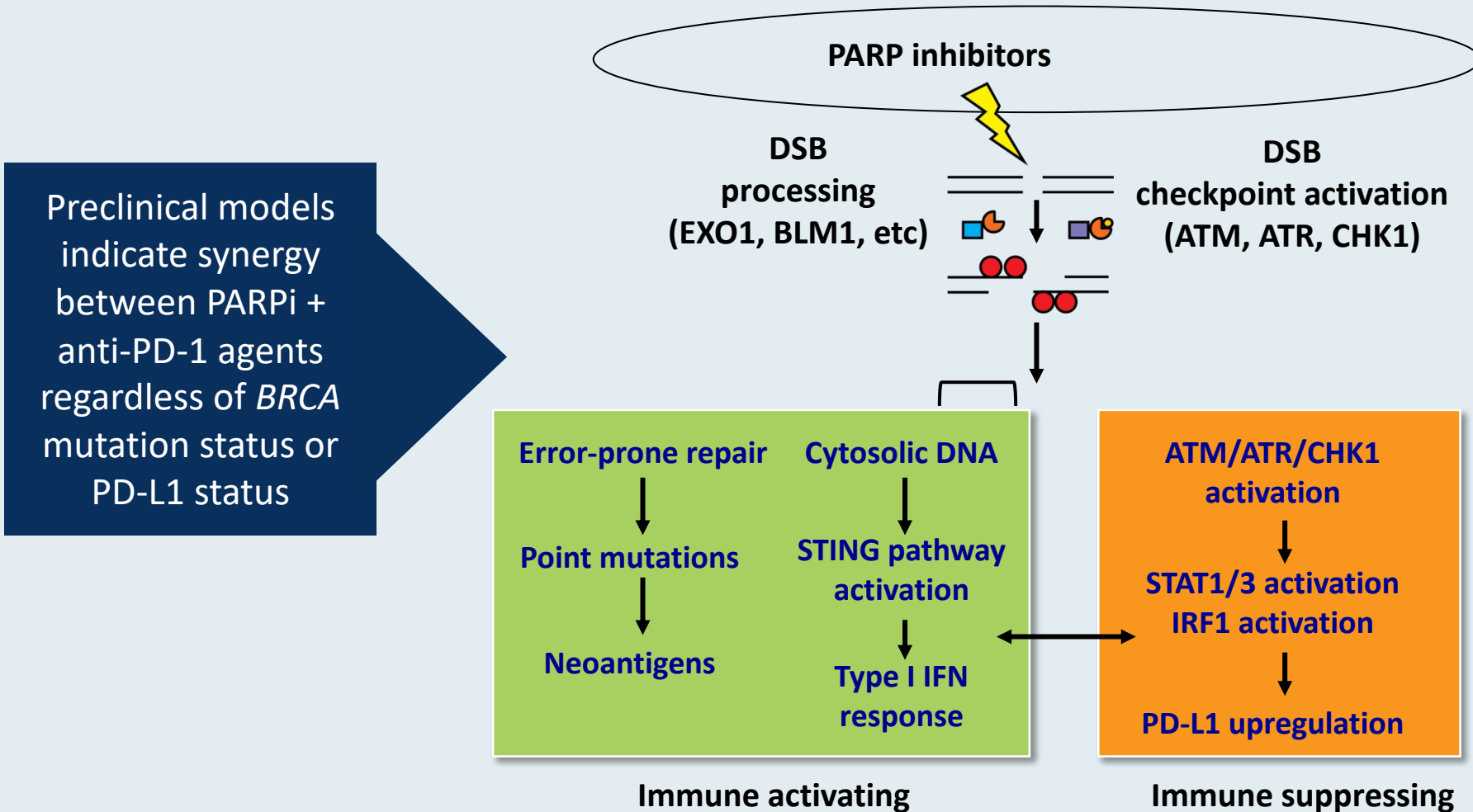
- NSGO-PALEO/ENGOT-EN3 trial: Palbociclib/letrozole for ER-positive advanced/recurrent endometrial cancer (EC)
- PAOLA-1 trial: Maintenance olaparib + bevacizumab for newly diagnosed advanced HGOC
- The DNA repair pathway as a target for novel drugs in gynecologic cancers
- ENGOT-OV16/NOVA trial: Long-term safety of niraparib for recurrent ovarian cancer (OC)
- PRIMA/ENGOT-OV26/GOG-3012 trial: Individualized starting dose of niraparib
- PARP inhibitor activity in BRCA wild-type recurrent OC by HRR mutational gene profile analysis
- Therapeutic options after second-line platinum-based chemotherapy for recurrent OC
- Incorporating PARP inhibitors into the treatment of primary and recurrent OC: A meta-analysis
- Ongoing clinical trials
  - FIRST: First-line platinum +/- dostarlimab → niraparib +/- dostarlimab for OC
  - innovaTV 205: Tisotumab vedotin +/- bevacizumab, pembrolizumab or carboplatin for metastatic cervical cancer (CC)
  - SIENDO: Maintenance selinexor after combination chemotherapy for recurrent or advanced EC
  - KEYNOTE-A18: Pembrolizumab + chemoradiation therapy for high-risk locally advanced CC
  - NSGO-RUBY: Dostarlimab + carboplatin/paclitaxel for recurrent or primary advanced EC

## MODULE 3: Beyond the Guidelines – Clinical Investigator Approaches to Common Clinical Scenarios

## MODULE 4: Key Recent Papers



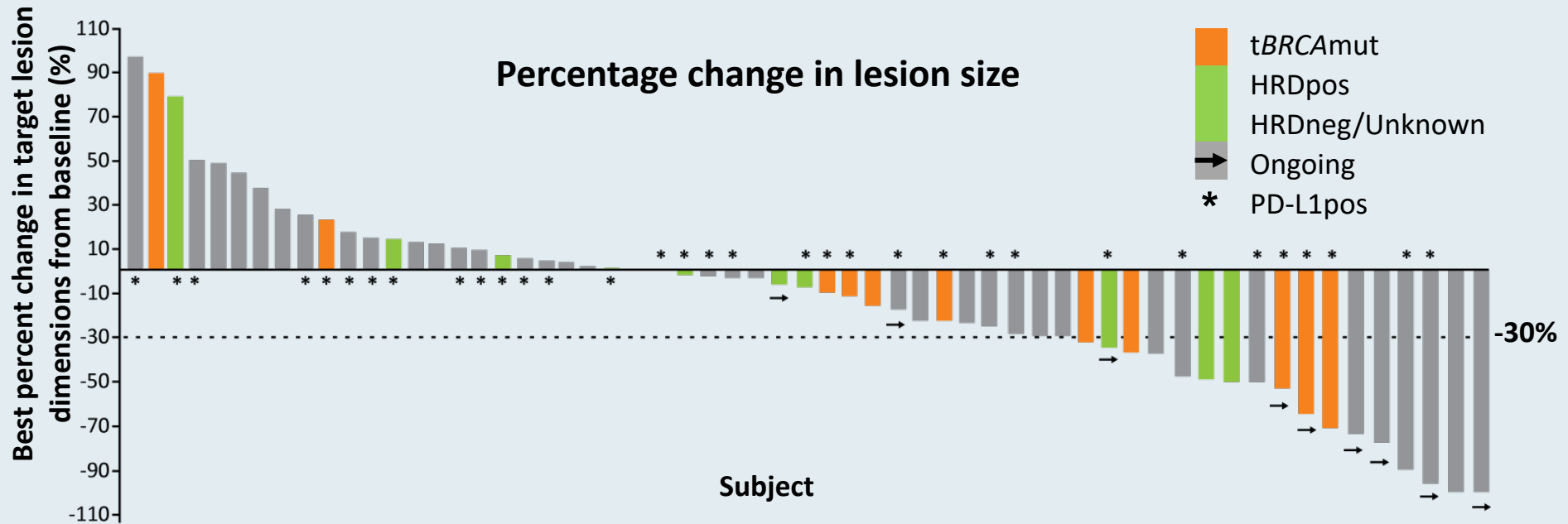
# Biologic Rationale for the Combination of a PARP Inhibitor with an Immune Checkpoint Inhibitor



Preclinical models indicate synergy between PARPi + anti-PD-1 agents regardless of *BRCA* mutation status or PD-L1 status

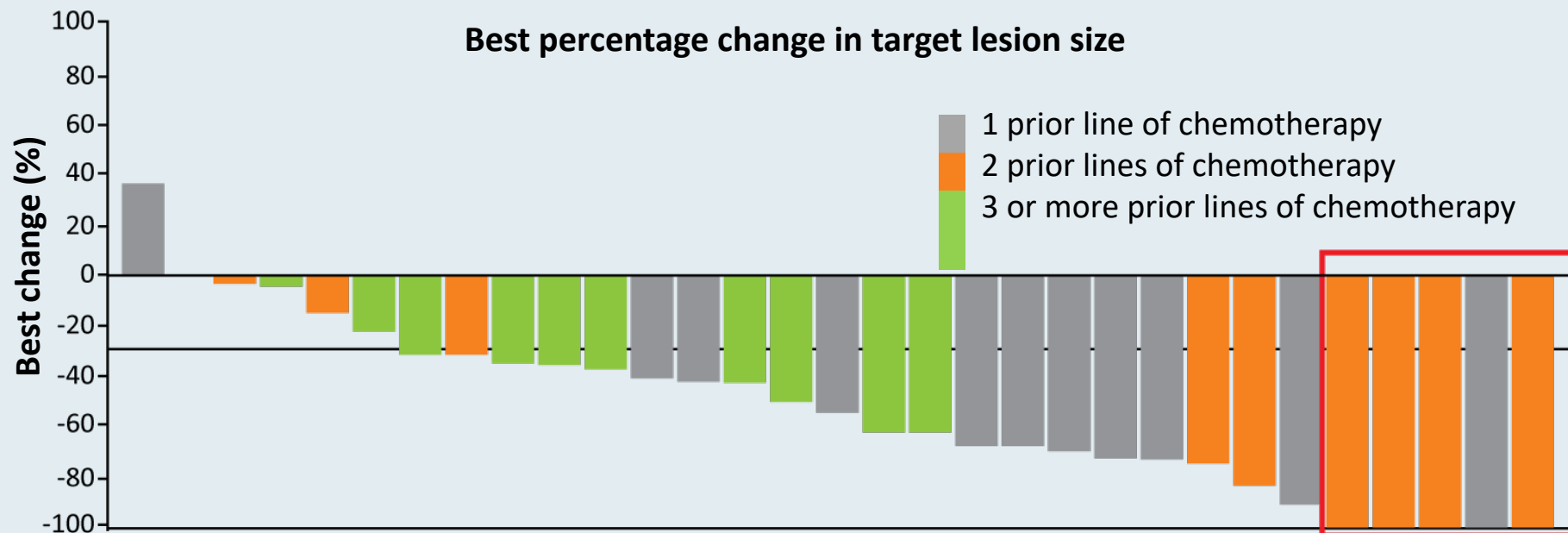
Preclinical data demonstrate synergy with PARPi and anti-PD-1 combinations.

# TOPACIO (KEYNOTE-162): A Phase I/II Study of Niraparib with Pembrolizumab in Recurrent, Platinum-Resistant OC



Response	All patients	tBRCAmut	HRD-pos	tBRCAwt	HRD-neg
ORR	11/47 (23%)	2/8 (25%)	4/16 (25%)	9/37 (24%)	7/26 (27%)
DCR	30/47 (64%)	5/8 (63%)	11/16 (69%)	24/37 (65%)	15/26 (58%)

# MEDIOLA: A Phase I/II Study of Olaparib and Durvalumab in Recurrent, Platinum-Sensitive OC with gBRCA Mutation



	Second line	Third line	Fourth line	All lines
ORR	10/13 (77%)	6/9 (67%)	7/10 (70%)	23/32 (72%)

# OReO/ENGOT Ov-38: A Phase IIIb Trial of Olaparib Maintenance Retreatment in Patients with EOC Previously Treated with a PARP Inhibitor and Responding to Repeat Platinum Chemotherapy

NCT03106987



**Primary endpoint:** Investigator-assessed progression-free survival

## Select Ongoing or Planned Phase III Trials of PARP Inhibitors in Combination Therapy

Trial name (Trial identifier)	N	Setting	Treatment arms
ATHENA (NCT03522246)	1,012	Maintenance therapy after 1L platinum-based chemo	<ul style="list-style-type: none"> <li>• <b>Rucaparib</b> + Nivolumab</li> <li>• <b>Rucaparib</b> + Placebo</li> <li>• Nivolumab + Placebo</li> <li>• Placebo</li> </ul>
DUO-O (NCT03737643)	1,056	Maintenance therapy after 1L platinum-based chemo/Bev ± Durvalumab	<ul style="list-style-type: none"> <li>• Bev</li> <li>• Bev + Durvalumab</li> <li>• Bev + Durvalumab + <b>Olaparib</b></li> </ul>
NRG-GY004 (NCT02446600)	549	Recurrent, platinum-sensitive	<ul style="list-style-type: none"> <li>• Platinum-based chemo</li> <li>• <b>Olaparib</b></li> <li>• <b>Olaparib</b> + Cediranib</li> </ul>
ANITA (NCT03598270)	414	Recurrent, platinum-sensitive	<ul style="list-style-type: none"> <li>• Placebo + Platinum-based chemo → <b>Niraparib</b></li> <li>• ATEZO + Platinum-based chemo → <b>Niraparib</b> + ATEZO</li> </ul>

Bev = bevacizumab; ATEZO = atezolizumab

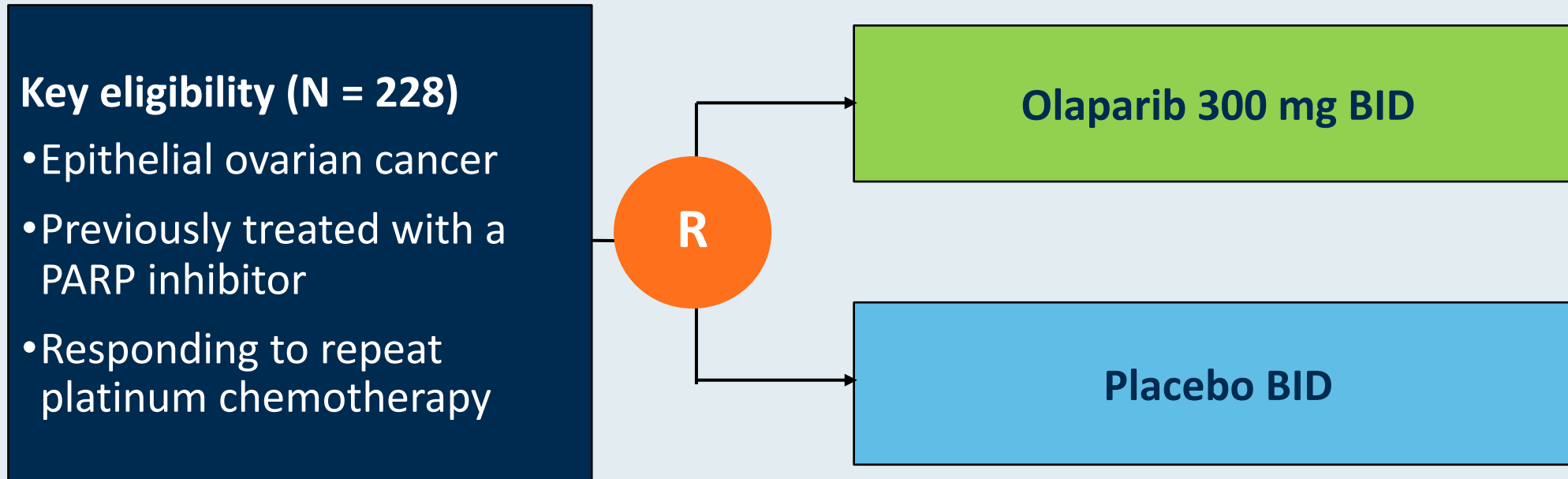
# The Incidence of Myelodysplastic Syndrome in Patients Receiving Poly-ADP Ribose Polymerase Inhibitors for Treatment of Solid Tumors: A Meta-analysis

Nitecki R et al.

ASCO 2020;Abstract 3641.



# OReO/ENGOT Ov-38 Phase III Study Design



**Primary endpoint:** Progression-free survival

# BRCA1/2 Mutations in Ovarian Cancer: Who Should Be Tested?

## NCCN<sup>1</sup>

Genetic counseling and testing should be considered for women with a history of ovarian carcinoma, fallopian tube or primary peritoneal cancer

## SGO<sup>2</sup>

Women diagnosed with epithelial ovarian, tubal and peritoneal cancers should receive genetic counseling and be offered genetic testing even in the absence of family history

## ASCO<sup>3</sup>

Genetic counseling and testing should be considered for women with epithelial ovarian, fallopian tube or primary peritoneal cancer even in the absence of family history

NCCN = National Comprehensive Cancer Network; SGO = Society of Gynecologic Oncology;

ASCO = American Society of Clinical Oncology

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>) for Genetic/Familial High-Risk Assessment: Breast and Ovarian V2.2019.

2. Lancaster JM et al. *Gynecol Oncol* 2015;136(1):3-7.

3. Lu KH et al. *J Clin Oncol* 2014;32(8):833-40.

# Multigene Panel Testing

## Advantages

- More “diagnoses”
- More cost effective
- More time efficient
- Higher mutational detection rate
- Efficient use of single specimen
- Decrease in testing fatigue for patients and providers

## Disadvantages

- Cancer risk and management options often not well defined for low- and moderate-penetrance genes
- High uncertain variant rate
- Longer turnaround time
- Panels may include genes that patients don’t want to test for
- Unexpected findings such as “off-phenotypic-target” gene mutation
- Increased prevalence of VUS

## Current FDA-Approved and Investigational PARP Inhibitors: Differences

PARP inhibitor	IC <sub>50</sub>	PARP trapping potency	PARPi target selectivity (strength of binding)	Half life	Dose
Olaparib	6 nM	1	Potent PARP1 inhibitor, less selective	11.9 hours	400 mg BID
Rucaparib	21 nM	1	Potent PARP1 inhibitor, less selective	18 hours	600 mg BID
Niraparib	60 nM	~2	Selective inhibitor of PARP1 and 2	36 hours	300 mg qd
Veliparib	30 nM	<0.2	Potent PARP1 inhibitor, less selective	5 hours	400 mg BID
Talazoparib	4 nM	~100	Potent PARP1 inhibitor, less selective	50 hours	1 mg qd

# Phase III First-Line Maintenance Trials

Study Design	SOLO-1 (N=451)	PAOLA-1 (N=612)	PRIMA (N=620)	VELIA (N=1140)
Treatment arms vs placebo	Olaparib (n=260)	Bevacizumab ± Olaparib	Niraparib	Veliparib
Patient Population	<i>BRCA</i> mutation	All comers	All comers	<i>All comers</i>
Treatment Duration	24 months	15 months for Bev 24 months for Olaparib	36 months or until PD	24 months

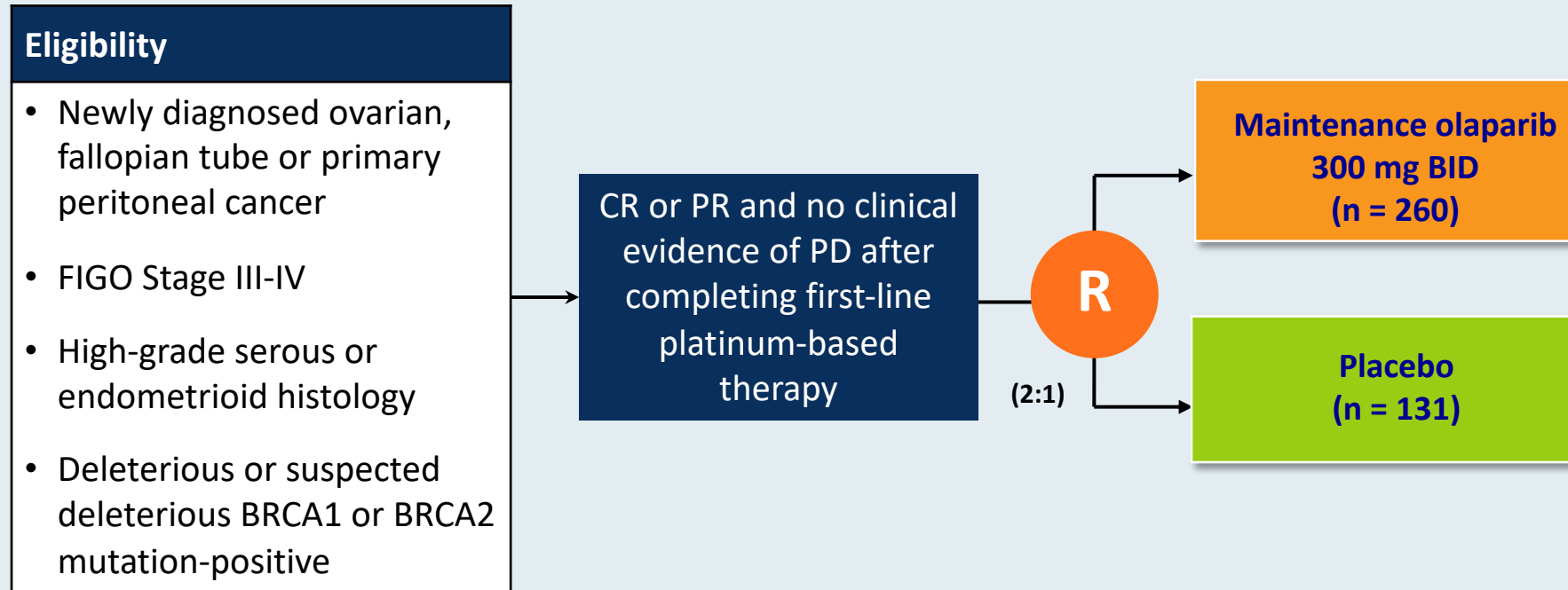
<sup>a</sup>Residual disease based on stage was not reported. <sup>b</sup>Stage III and IV eligible, but requirements for prior surgery not reported (NR) on clinicaltrials.gov

Burger RA, *N Engl J Med* 2011; Norquist B *Clin Cancer Res* 2018; *Bevacizumab* prescribing information; Moore K, *NEJM* 2018; Gonzalez-Martin *NEJM* 2019; Ray-Coquard *NEJM* 2019; Coleman *NEJM* 2019

Courtesy of Shannon N Westin, MD, MPH

# SOLO-1: A Phase III Trial of Maintenance Olaparib in OC with BRCA Mutation

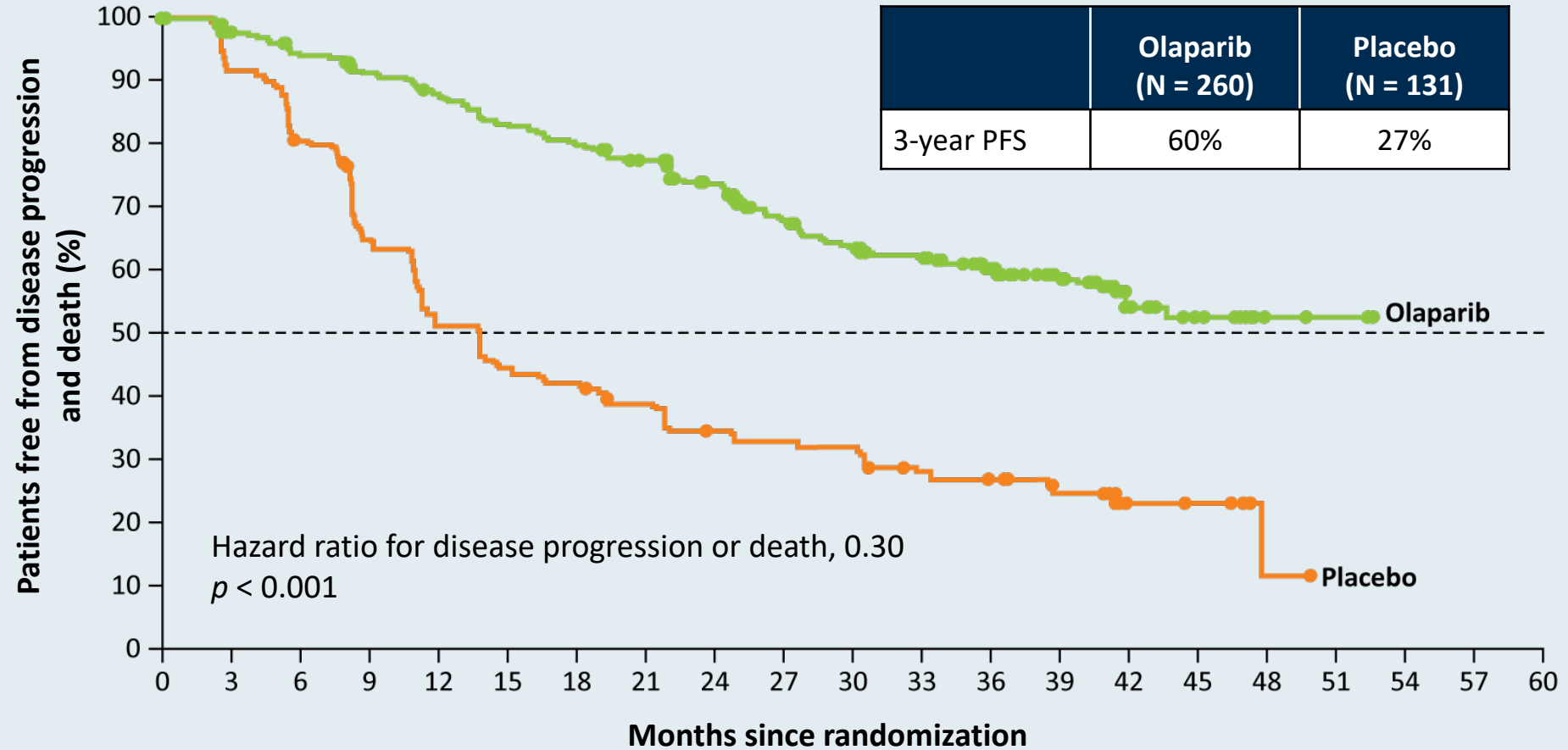
NCT01844986



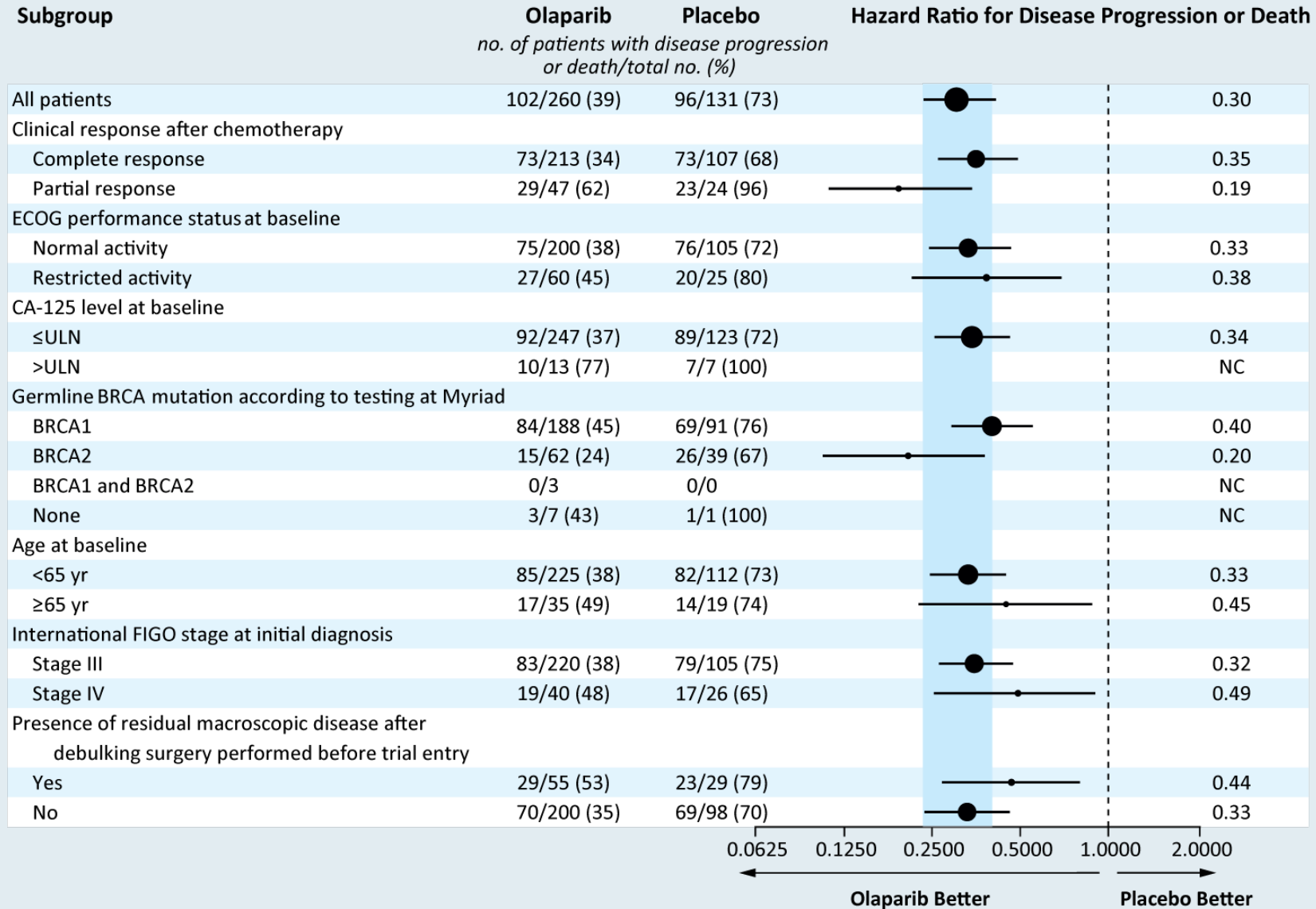
**Primary endpoint:** Investigator-assessed progression-free survival



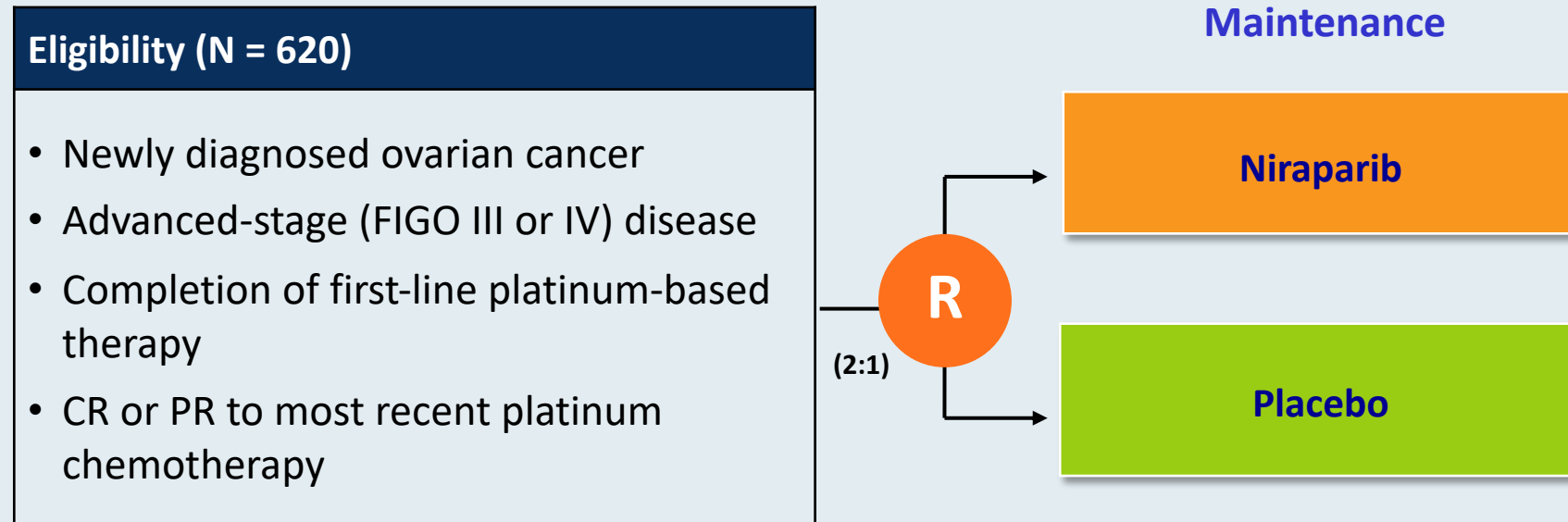
# SOLO-1: Primary Endpoint Progression-Free Survival (Investigator Assessed)



# SOLO-1: PFS Subgroup Analyses

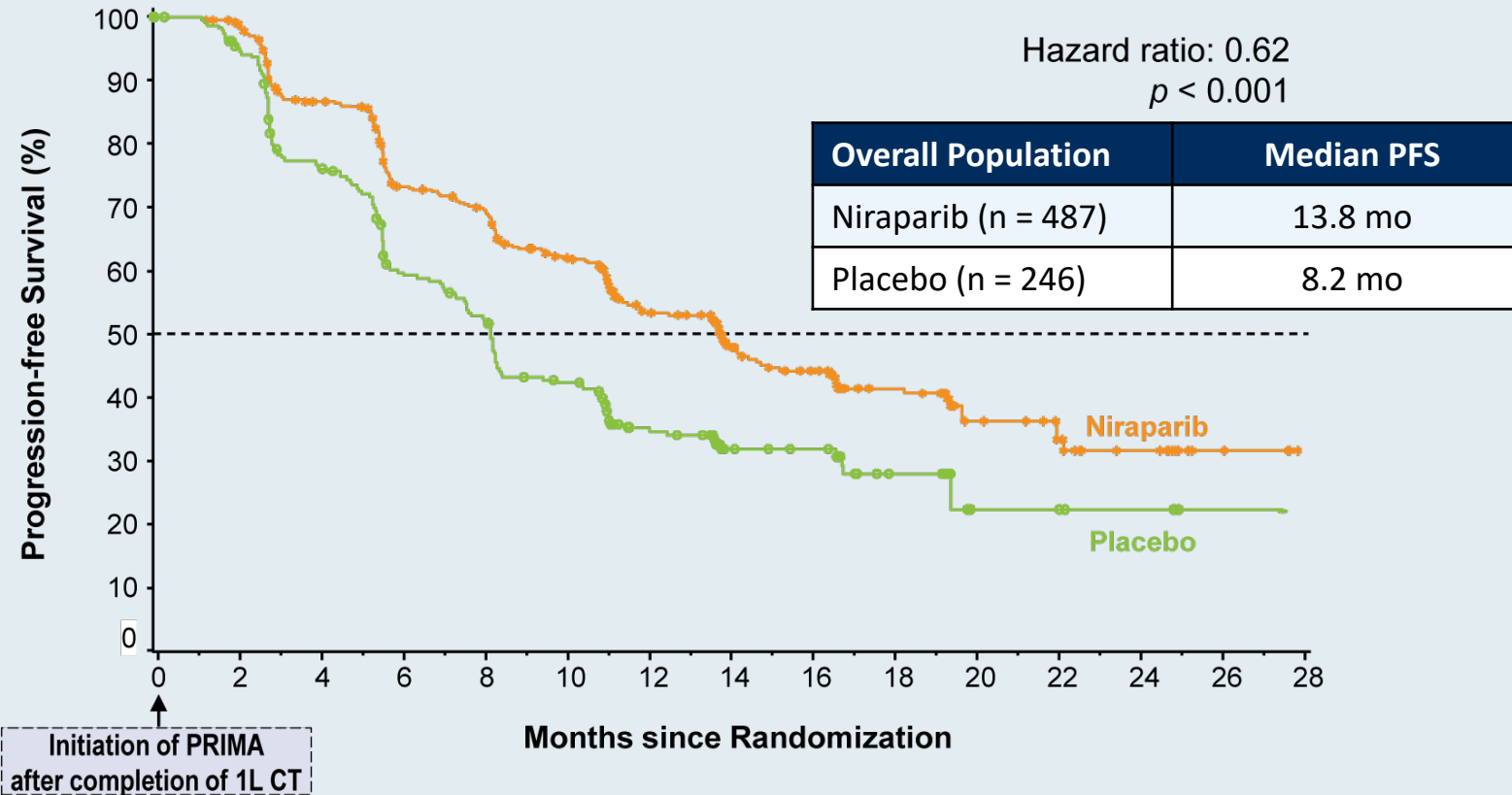


# PRIMA Trial: Maintenance Niraparib for Advanced Ovarian Cancer After Response to Front-Line Platinum-Based Chemotherapy



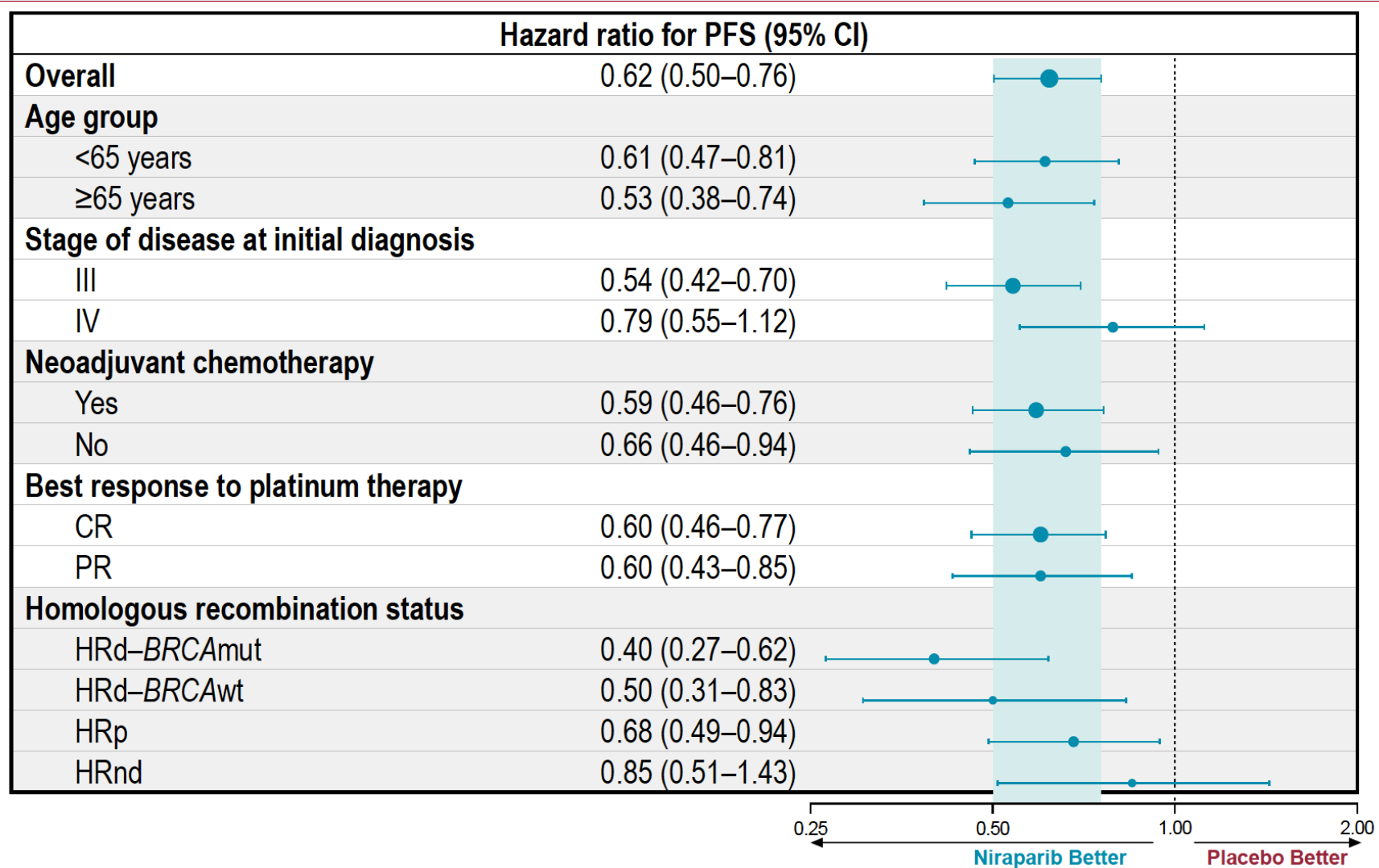
**Primary endpoint: Progression-free survival**

# PRIMA Primary Endpoint: Progression-Free Survival



- Median PFS in the HR-deficient population was 21.9 mo for niraparib and 10.4 mo for placebo (HR 0.43,  $p < 0.001$ ).
- No new safety signals were identified for niraparib.

# PRIMA: Progression-Free Survival Subgroup Analysis



# FDA approves olaparib plus 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.

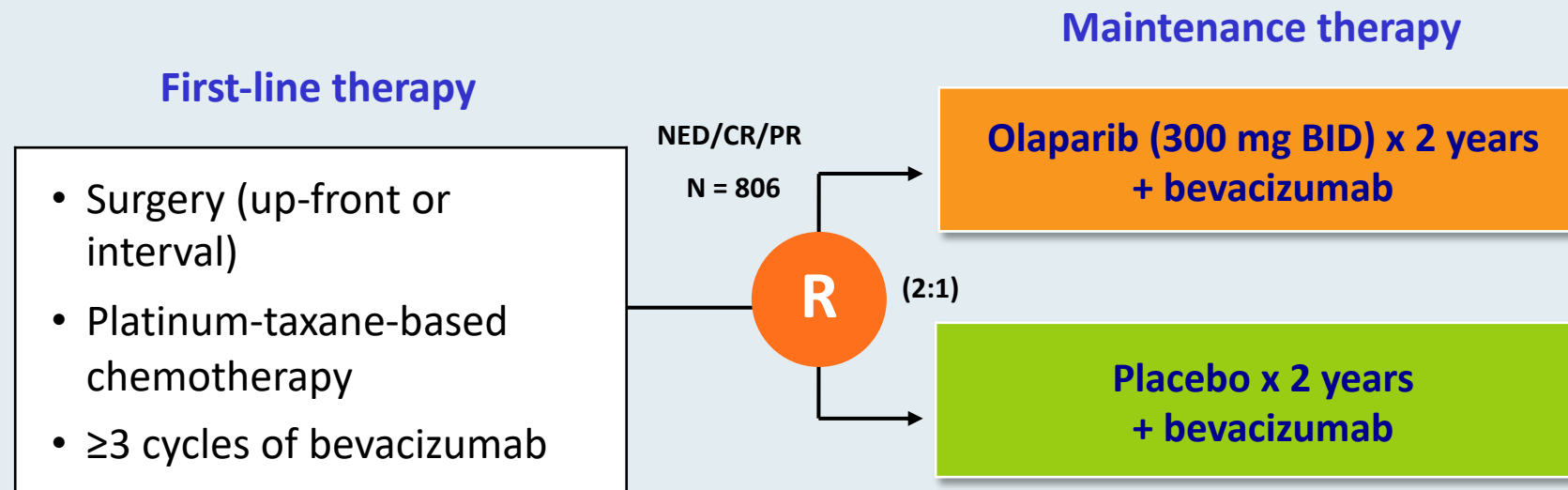
FDA also approved the Myriad myChoice<sup>®</sup> CDx (Myriad Genetic Laboratories, Inc.) as a companion diagnostic for olaparib.

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.”

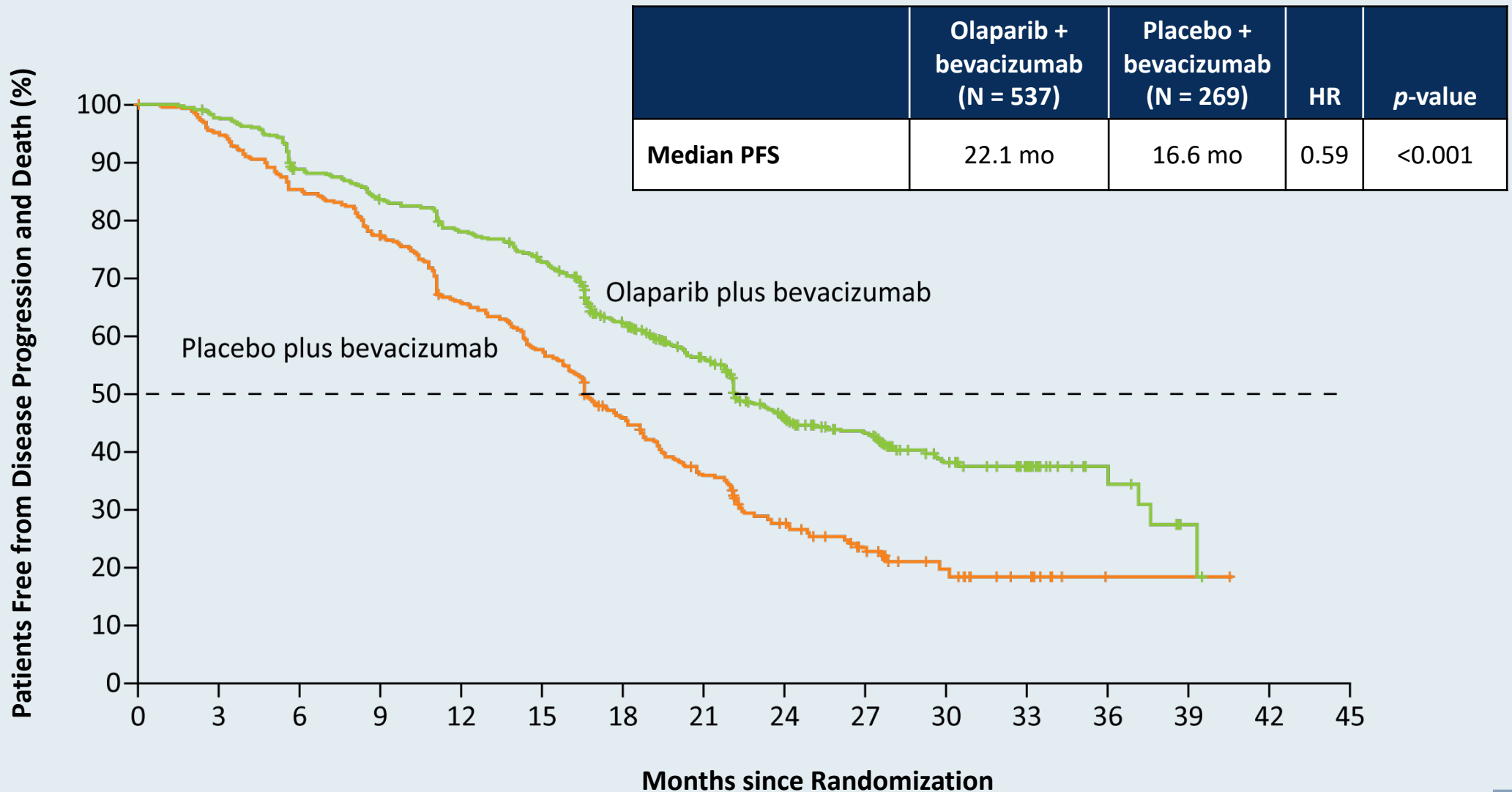


# PAOLA-1 Trial: Maintenance Olaparib with Bevacizumab for Advanced Ovarian Cancer After Response to Front-Line Platinum-Based Chemotherapy and Bevacizumab

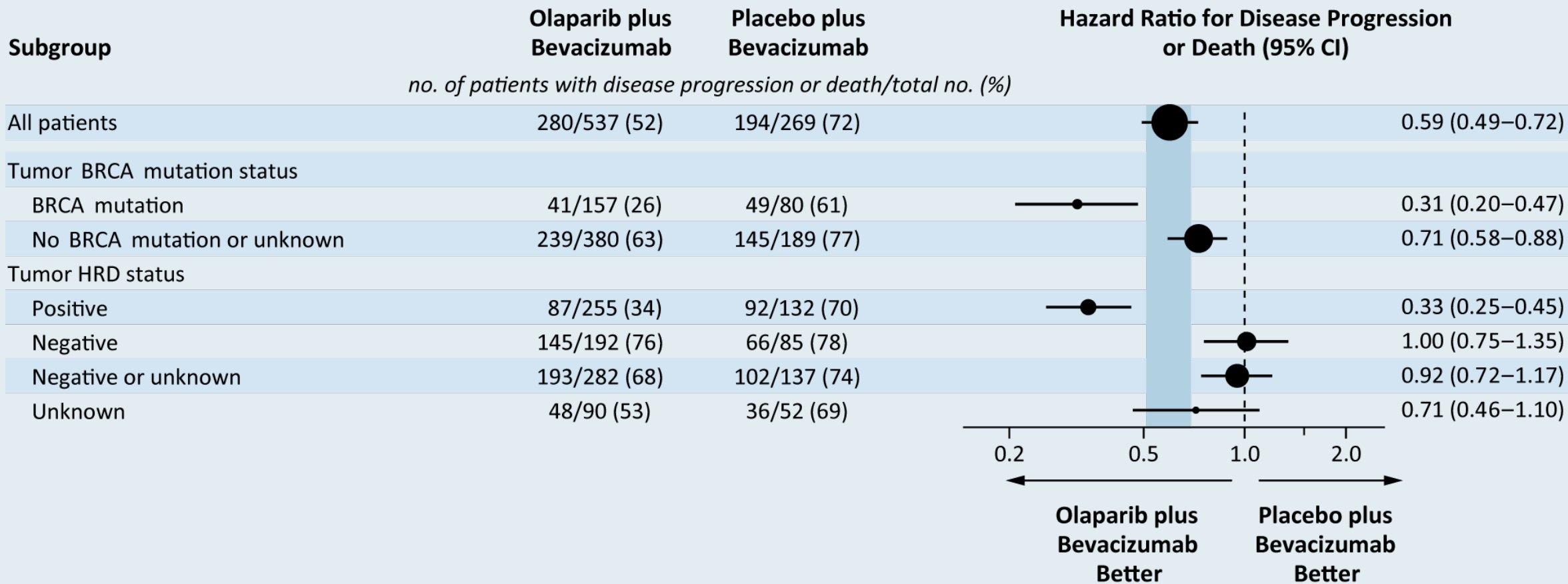
Newly diagnosed FIGO Stage III or IV high-grade serous/endometrioid ovarian, fallopian tube or primary peritoneal cancer



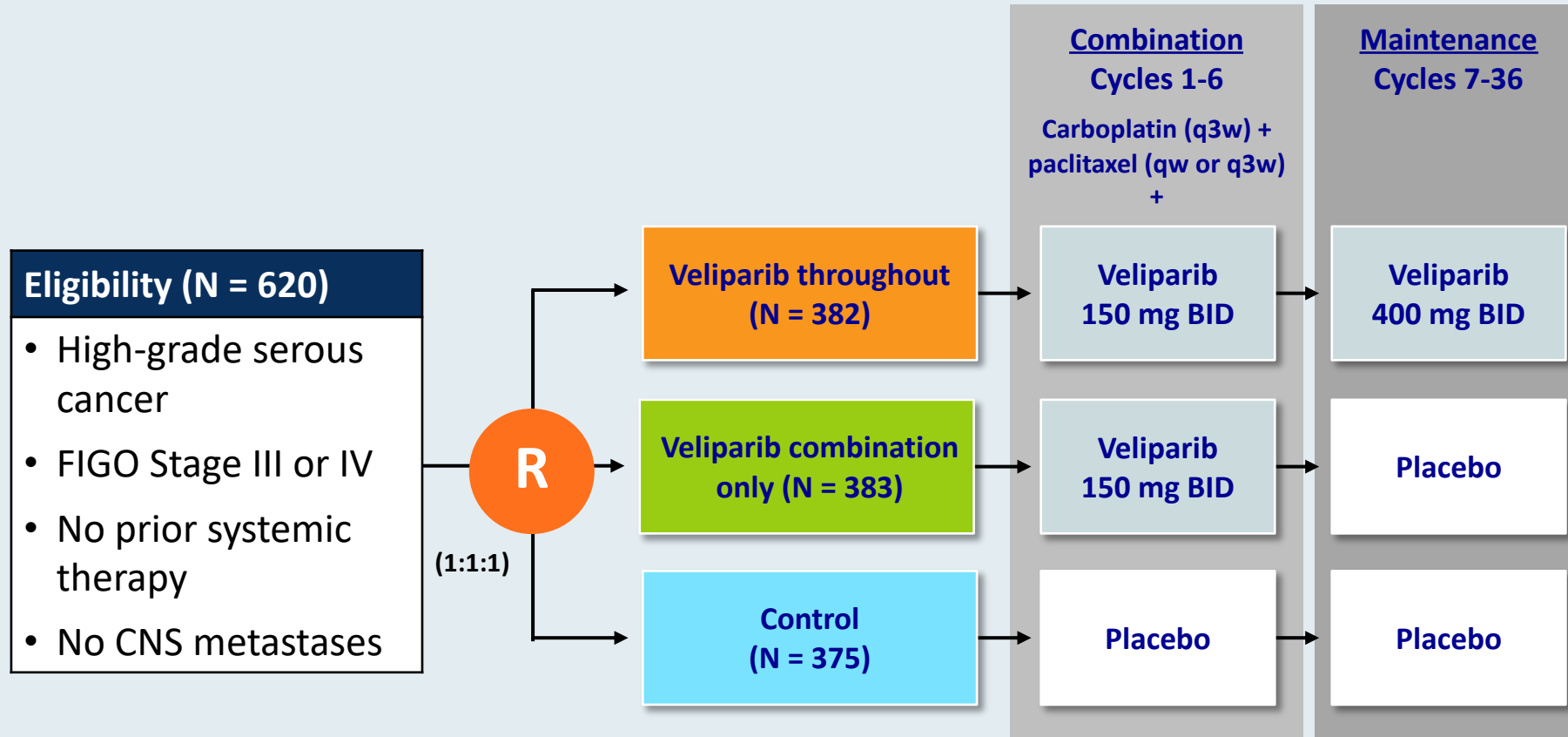
# PAOLA-1: Investigator-Assessed PFS (Primary Endpoint)



# PAOLA-1: Select Subgroup Analysis of PFS

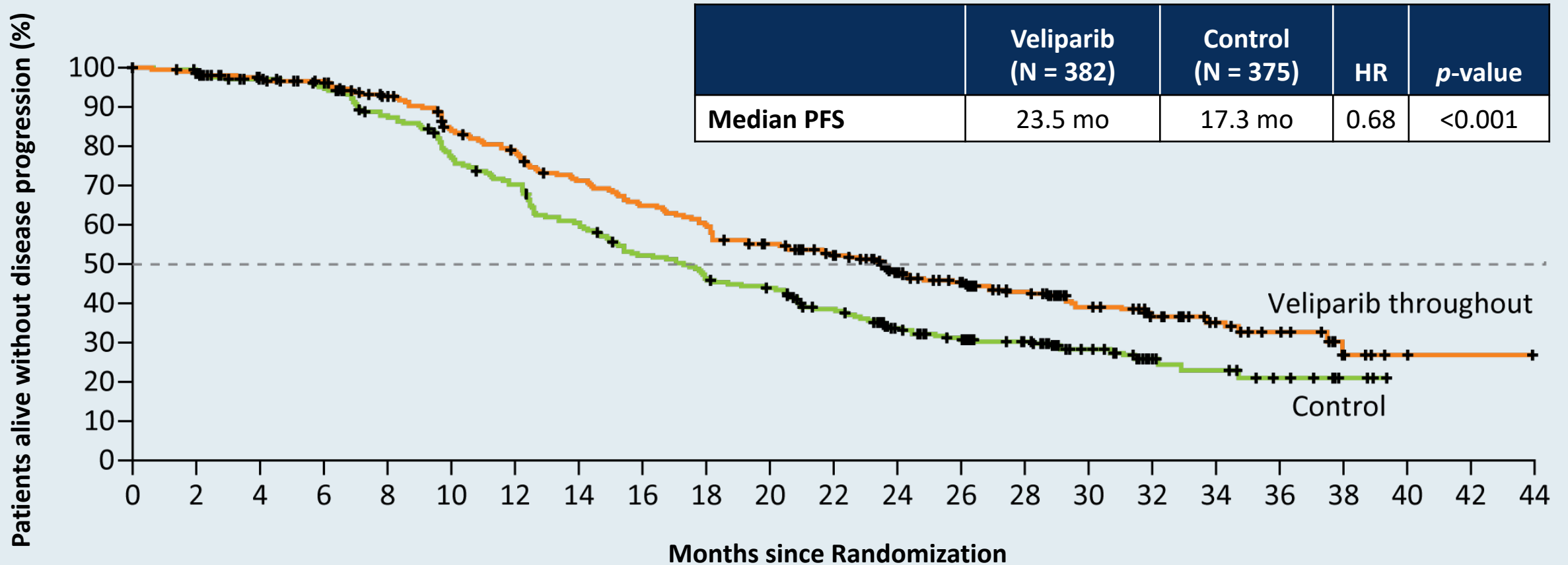


# VELIA/GOG-3005: A Phase III Trial of Veliparib with Front-Line Chemotherapy and as Maintenance Therapy for High-Grade Serous Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancers



**Primary endpoint:** Progression-free survival for “veliparib throughout” versus control

# VELIA/GOG-3005: Investigator-Assessed PFS







# **VELIA/GOG-3005: Integration of Veliparib with Front-Line Chemotherapy and Maintenance in Women with High-Grade Serous Carcinoma of Ovarian, Fallopian Tube, or Primary Peritoneal Origin**

Coleman RL et al.

SGO 2020;Abstract 36.

# Ongoing Phase III Clinical Trials of PARP Inhibitors as Maintenance After First-Line Therapy

Trial name (trial identifier)	N	Eligibility	First-line treatment	Maintenance treatment arms
FIRST (NCT03602859)	960	<ul style="list-style-type: none"> <li>• BRCA mut or wt</li> <li>• Stage III or IV</li> <li>• Surgery or inoperable</li> </ul>	<ul style="list-style-type: none"> <li>• Platinum-based chemo</li> <li>• Platinum-based chemo + TSR-042</li> </ul>	<ul style="list-style-type: none"> <li>• Niraparib + TSR-042</li> <li>• Niraparib + placebo</li> <li>• Placebo + placebo</li> </ul>
ATHENA (NCT03522246)	1,012	<ul style="list-style-type: none"> <li>• BRCA mut or wt</li> <li>• Stage III or IV</li> <li>• Prior surgery</li> </ul>	<ul style="list-style-type: none"> <li>• Platinum-based chemo</li> </ul>	<ul style="list-style-type: none"> <li>• Rucaparib + nivolumab</li> <li>• Rucaparib + placebo</li> <li>• Placebo + nivolumab</li> <li>• Placebo + placebo</li> </ul>

# Adverse Events: Class Effects and Specific Drug Differences

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

NR = not reported

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.

# Adverse Events: Class Effects and Specific Drug Differences

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

NR = not reported

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.

## Dose Adjustments for Adverse Events

Olaparib dose reductions	Dose (tablet)
Starting dose	• 300 mg BID
First dose reduction	• 250 mg BID
Second dose reduction	• 200 mg BID

Niraparib dose reductions	Dose
Starting dose	• 300 mg daily
First dose reduction	• 200 mg daily
Second dose reduction	• 100 mg daily

Rucaparib dose reductions	Dose
Starting dose	• 600 mg twice daily
First dose reduction	• 500 mg twice daily
Second dose reduction	• 400 mg twice daily
Third dose reduction	• 300 mg twice daily

# Determinants of Platinum Sensitivity and Resistance

- Distribution of platinum in the tumor cell
- Cellular metabolism of platinum agents
- Expression levels of epithelial-mesenchymal transition (EMT)-related transcription factors
- PARP1 expression level
- BRCA1/2 mutational status
- Hyperexpression or polymorphism of ERCC1
- Mutational status of homologous recombination (HR) pathway genes



# FDA-Approved PARP Inhibitors as Maintenance Therapy for Recurrent, Platinum-Sensitive Disease

<b>Niraparib</b>	<b>Rucaparib</b>	<b>Olaparib</b>
<p><b>Indications:</b></p> <ul style="list-style-type: none"><li>• Maintenance following response to platinum-based therapy</li><li>• Irrespective of BRCA status</li></ul> <p><b>Pivotal study: ENGOT-OV16/NOVA</b></p> <p><b>Approved: 3/2017</b></p>	<p><b>Indications:</b></p> <ul style="list-style-type: none"><li>• Maintenance following response to platinum-based therapy</li><li>• Irrespective of BRCA status</li></ul> <p><b>Pivotal study: ARIEL3</b></p> <p><b>Approved: 4/2018</b></p>	<p><b>Indications:</b></p> <ul style="list-style-type: none"><li>• Maintenance following response to platinum-based therapy</li><li>• Irrespective of BRCA status</li></ul> <p><b>Pivotal studies: SOLO-2, Study 19</b></p> <p><b>Approved: 8/2017</b></p>

Niraparib FDA insert, revised 3/2017; Rucaparib FDA insert, revised 4/2018; Olaparib FDA insert, revised 1/2018; Pujade-Lauraine E et al. *Lancet* 2017;18(9):1274-84; Mirza MR et al. *N Engl J Med* 2016;375(22):2154-64; Coleman RL et al. *Lancet* 2017;390(10106):1949-61; Ledermann J et al. *N Engl J Med* 2012;366:1382-92.

# Eligibility and Dosing in Pivotal Studies of PARP Inhibitors for Recurrent, Platinum-Sensitive OC

	<b>NOVA<sup>1</sup> (Niraparib)</b>	<b>SOLO-2<sup>2</sup> (Olaparib)</b>	<b>ARIEL3<sup>3</sup> (Rucaparib)</b>
<b>BRCA status</b>	With or without gBRCA mutation	gBRCA mutation (Study 19: +/- gBRCA mutation)	With or without gBRCA mutation
<b>HRD testing</b>	Yes	No	Yes
<b>Tumor assessment schedule</b>	Every 8 wk to C14 → every 12 wk	Every 12 wk until wk 72 → every 24 wk	Every 8 wk to C14 → every 12 wk
<b>Dosing/formulation</b>	300 mg qd	300 mg BID	600 mg BID
<b>No. of prior lines of chemo</b>	2 or more	2 or more	2 or more

<sup>1</sup> Mirza MR et al. *N Engl J Med* 2016;375(22):2154-64; <sup>2</sup> Pujade-Lauraine E et al. *Lancet* 2017;18(9):1274-84; <sup>3</sup> Coleman RL et al. *Lancet* 2017;390(10106):1949-61.

# Efficacy Summary of PARP Inhibitors for Recurrent, Platinum-Sensitive OC

	PARPi	Control	HR
<b>NOVA<sup>1</sup> — Niraparib</b>			
gBRCA mutation	21.0 mo	5.5 mo	0.27
No gBRCA mutation, HRD+	12.9 mo	3.8 mo	0.38
No gBRCA mutation	9.3 mo	3.9 mo	0.45
<b>SOLO-2<sup>2</sup> — Olaparib</b>			
gBRCA mutation	19.1 mo	5.5 mo	0.30
<b>ARIEL3<sup>3-4</sup> — Rucaparib</b>			
ITT (All comers)	10.8 mo	5.4 mo	0.36
g or sBRCA mutation	16.6 mo	5.4 mo	0.23
HRD+	13.6 mo	5.4 mo	0.32
BRCA <sup>WT</sup> /High LOH	13.6 mo	5.4 mo	0.32
BRCA <sup>WT</sup> /Low LOH	6.7 mo	5.4 mo	0.58

<sup>1</sup> Mirza MR et al. *N Engl J Med* 2016;375(22):2154-64; <sup>2</sup> Pujade-Lauraine E et al. *Lancet* 2017;18(9):1274-84; <sup>3</sup> Coleman RL et al. *Lancet* 2017;390(10106):1949-61; <sup>4</sup> Ledermann JA et al. *Lancet Oncol* 2020;21(5):710-722.

# FDA-Approved PARP Inhibitors as Monotherapy for Multiply Relapsed Disease

Olaparib	Rucaparib	Niraparib
<p><b>Indications:</b></p> <ul style="list-style-type: none"><li>• 4th-line therapy and beyond</li><li>• Germline BRCA mutation</li></ul> <p><b>Dosing:</b></p> <ul style="list-style-type: none"><li>• 300 mg BID</li></ul> <p><b>Approved: 12/2014</b></p>	<p><b>Indications:</b></p> <ul style="list-style-type: none"><li>• 3rd-line therapy and beyond</li><li>• Germline <u>and/or</u> somatic BRCA mutation</li></ul> <p><b>Dosing:</b></p> <ul style="list-style-type: none"><li>• 600 mg BID</li></ul> <p><b>Approved: 12/2016</b></p>	<p><b>Indications:</b></p> <ul style="list-style-type: none"><li>• 4th-line therapy and beyond</li><li>• HRD-positive</li></ul> <p><b>Dosing:</b></p> <ul style="list-style-type: none"><li>• Weight- and platelet count-dependent: 200 or 300 mg QD</li></ul> <p><b>Approved: 102/2019</b></p>

# Efficacy Summary of PARP Inhibitors for Multiply Relapsed OC

	Objective Response Rate
<b>QUADRA<sup>1</sup> — Niraparib</b>	
HRD-positive	29/189 (15%)
HRD-negative/unknown	8/230 (3%)
BRCA-mutated	18/63 (29%)
<b>SOLO-3<sup>2</sup> — Olaparib</b>	
gBRCA-mutation	109/151 (72%)
<b>ARIEL2<sup>3-4</sup> — Rucaparib</b>	
g or sBRCA mutation	57/106 (54%)

<sup>1</sup> Moore KN et al. *Lancet Oncol* 2019;20(5):636-648; <sup>2</sup> Penson RT et al. ASCO 2019;Abstract 5506;

<sup>3</sup> Oza AM et al. *Gynecol Oncol* 2017;147:267-75.

# *Meet The Professor*

## Management of Lung Cancer

Monday, November 9, 2020  
12:00 PM – 1:00 PM ET

### Faculty

Corey J Langer, MD

### Moderator

Neil Love, MD

***Thank you for joining us!***

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