Meet The Professor
Management of Ovarian Cancer

Thomas J Herzog, MD
Paul and Carolyn Flory Professor
Deputy Director, University of Cincinnati Cancer Center
Vice-Chair, Quality and Safety
Department of Obstetrics and Gynecology
University of Cincinnati Medical Center
Associate Director, GOG Partners
Cincinnati, Ohio

Commercial Support

These activities are supported by an educational grant from GlaxoSmithKline.

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Dr Love — Disclosures

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Dr Herzog — Disclosures

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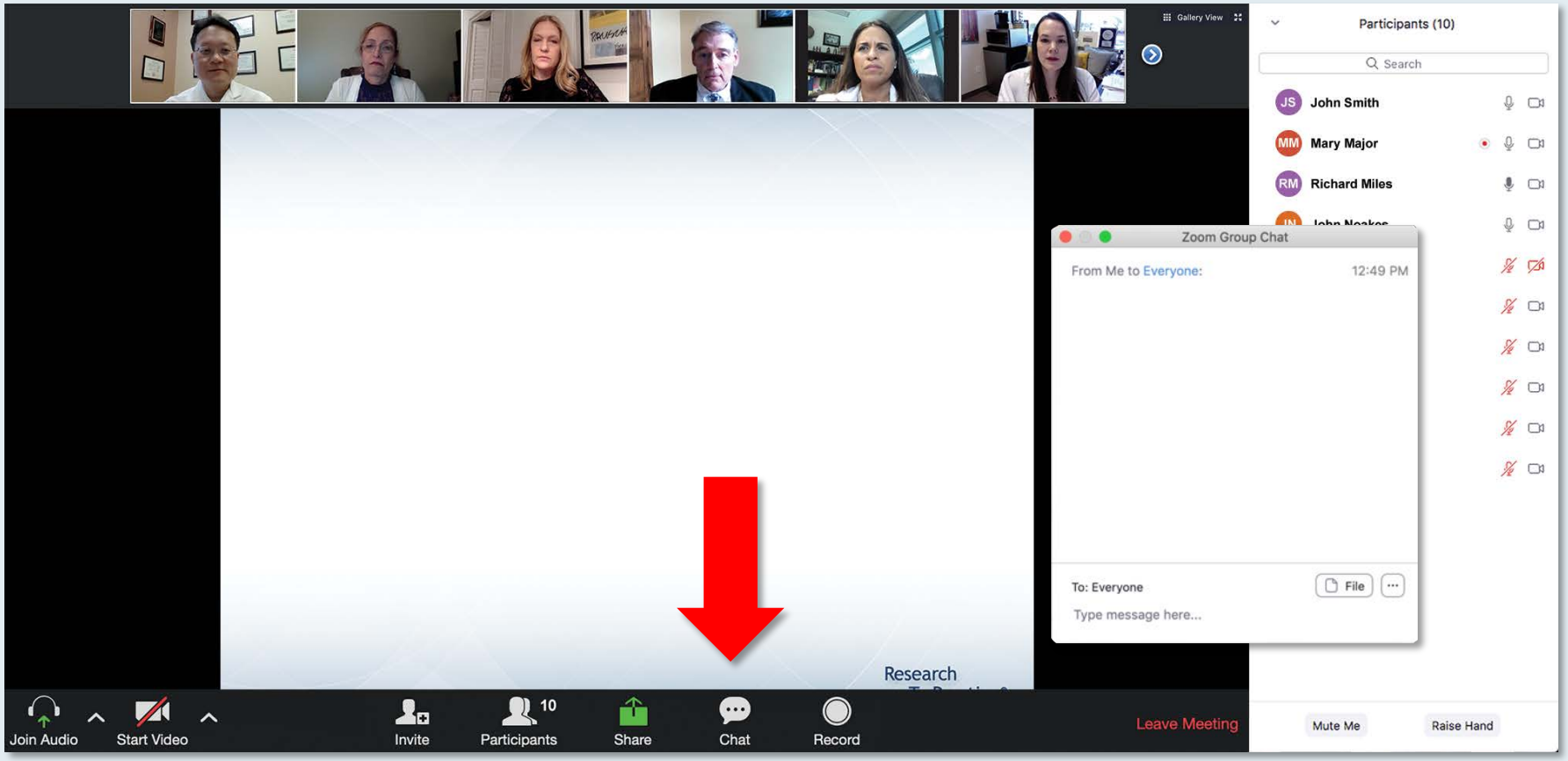
We Encourage Clinicians in Practice to Submit Questions



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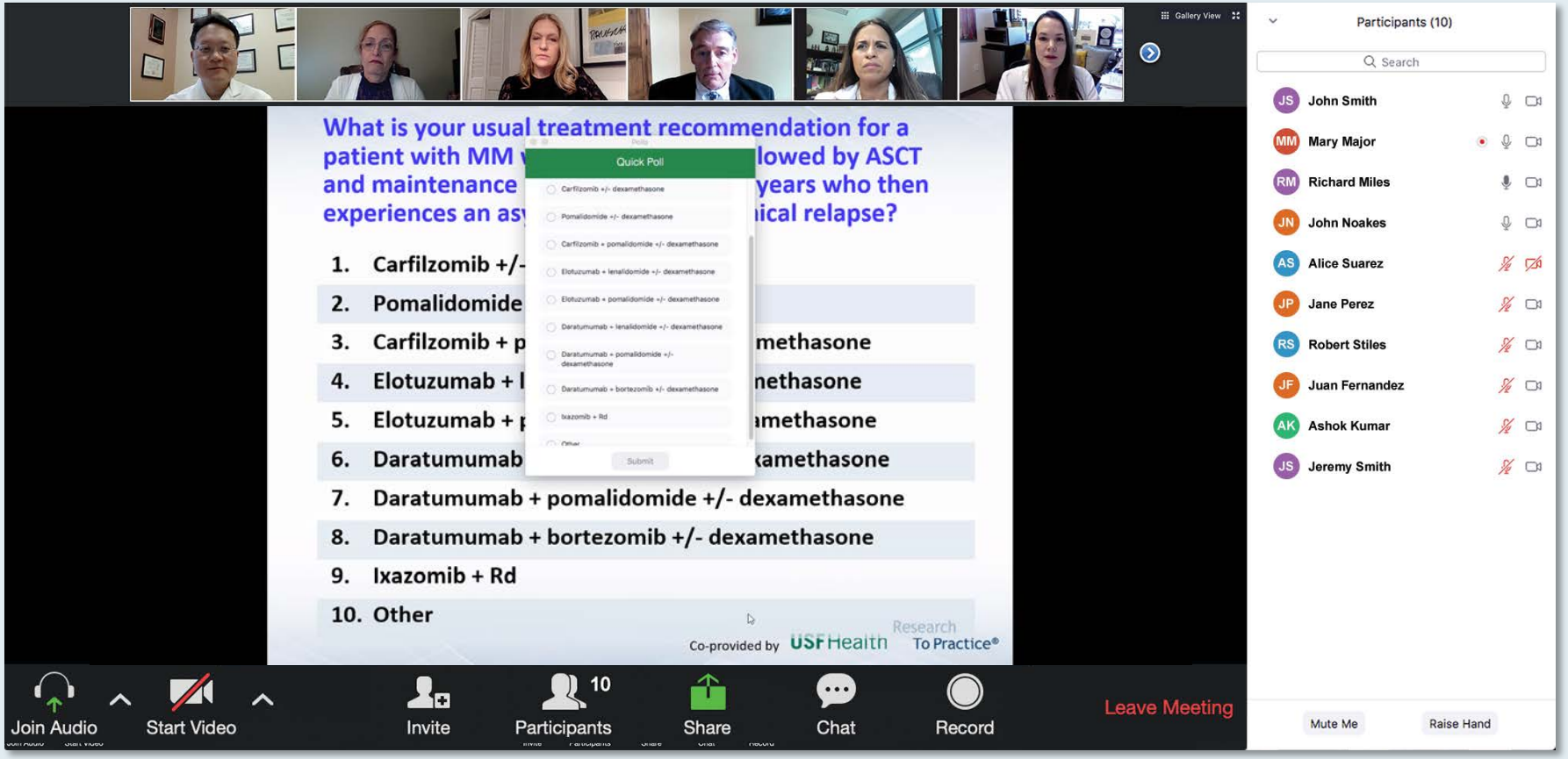

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ONCOLOGY TODAY

WITH DR NEIL LOVE

Current and Future Treatment Strategies for Advanced Ovarian Cancer

DR KATHLEEN MOORE

UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

OKLAHOMA CITY, OKLAHOMA

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Meet The Professor
Management of Multiple Myeloma

Wednesday, March 3, 2021
5:00 PM – 6:00 PM ET

Faculty

Morie A Gertz, MD, MACP

Moderator

Neil Love, MD

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Cases from the Community: Investigators Discuss Emerging Research and Actual Patients with Urothelial Bladder Carcinoma (Part 3 of a 3-Part Series)

Thursday, March 4, 2021
5:00 PM – 6:15 PM ET

Faculty

Arjun Balar, MD
Elisabeth I Heath, MD
Jonathan E Rosenberg, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Cancer Conference Update: What Happened at the 2020 San Antonio Breast Cancer Symposium®

Management of HER2-Positive Breast Cancer

Monday, March 8, 2021
5:00 PM – 6:00 PM ET

Faculty

Mark D Pegram, MD

Moderator

Neil Love, MD

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Data + Perspectives: Investigators Discuss the Effects of Emerging Research on the Care of Patients with Acute Myeloid Leukemia

Wednesday, March 10, 2021
7:00 PM – 8:00 PM ET

Faculty

Alexander Perl, MD
Eunice S Wang, MD

Moderator

Neil Love, MD

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Meet The Professor

Management of Chronic Lymphocytic Leukemia

Thursday, March 11, 2021
5:00 PM – 6:00 PM ET

Faculty

Steven Coutre, MD

Moderator

Neil Love, MD

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Associate Director, GOG Partners
Cincinnati, Ohio

Meet The Professor Program Participating Faculty

Deborah K Armstrong, MD
Professor of Oncology
Professor of Gynecology and Obstetrics
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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

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Director, Women's Cancers and Hematology-
Oncology Outpatient Clinics
Lifespan Cancer Institute
Director, Medical Oncology and the Oncology
Sexual Health Program
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Thomas J Herzog, MD
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University of Cincinnati Medical Center
Associate Director, GOG Partners
Cincinnati, Ohio

Professor Jonathan A Ledermann
Professor of Medical Oncology
UCL Cancer Institute and UCL Hospitals
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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Meet The Professor Program Participating Faculty

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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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

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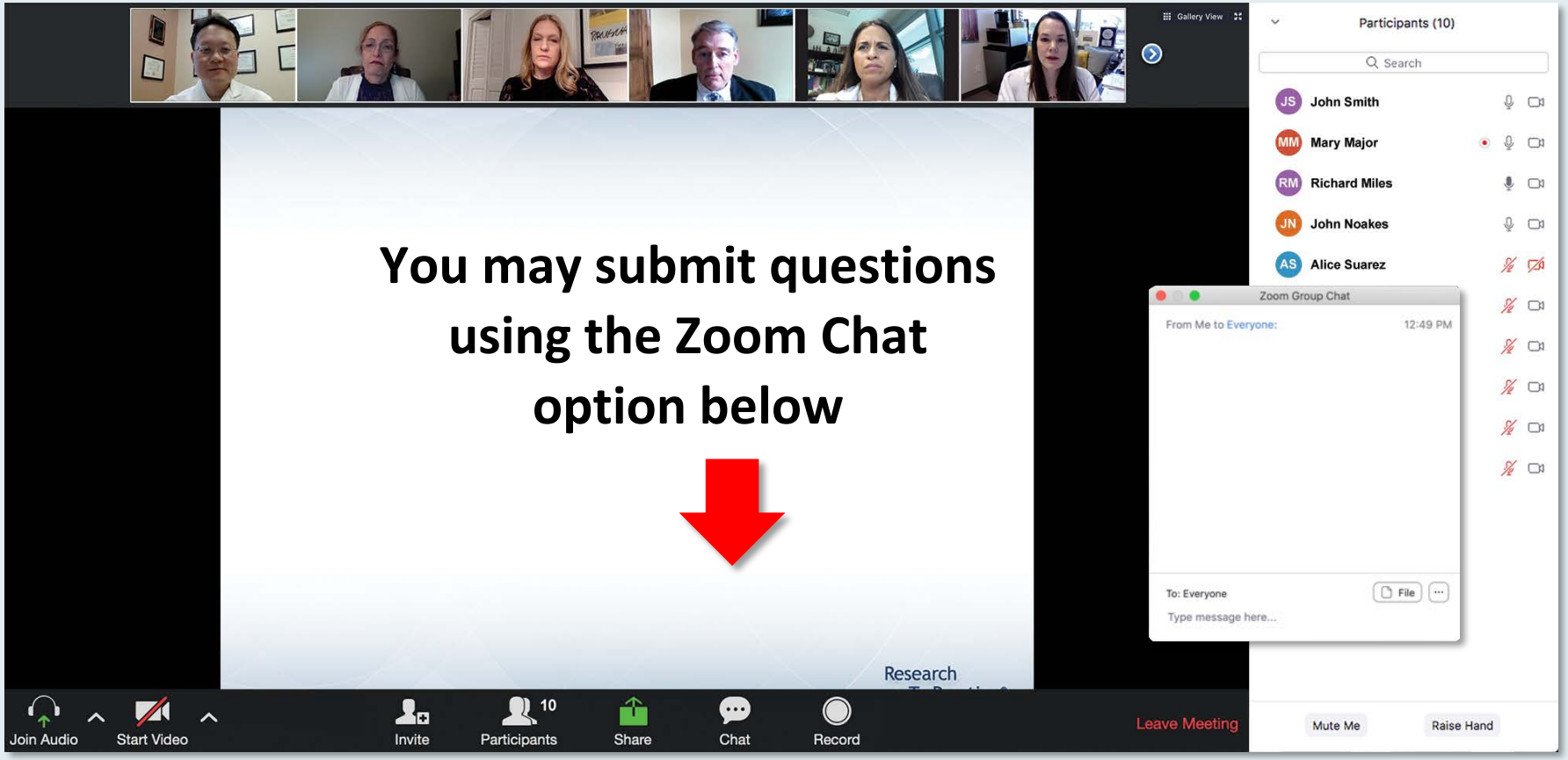
We Encourage Clinicians in Practice to Submit Questions



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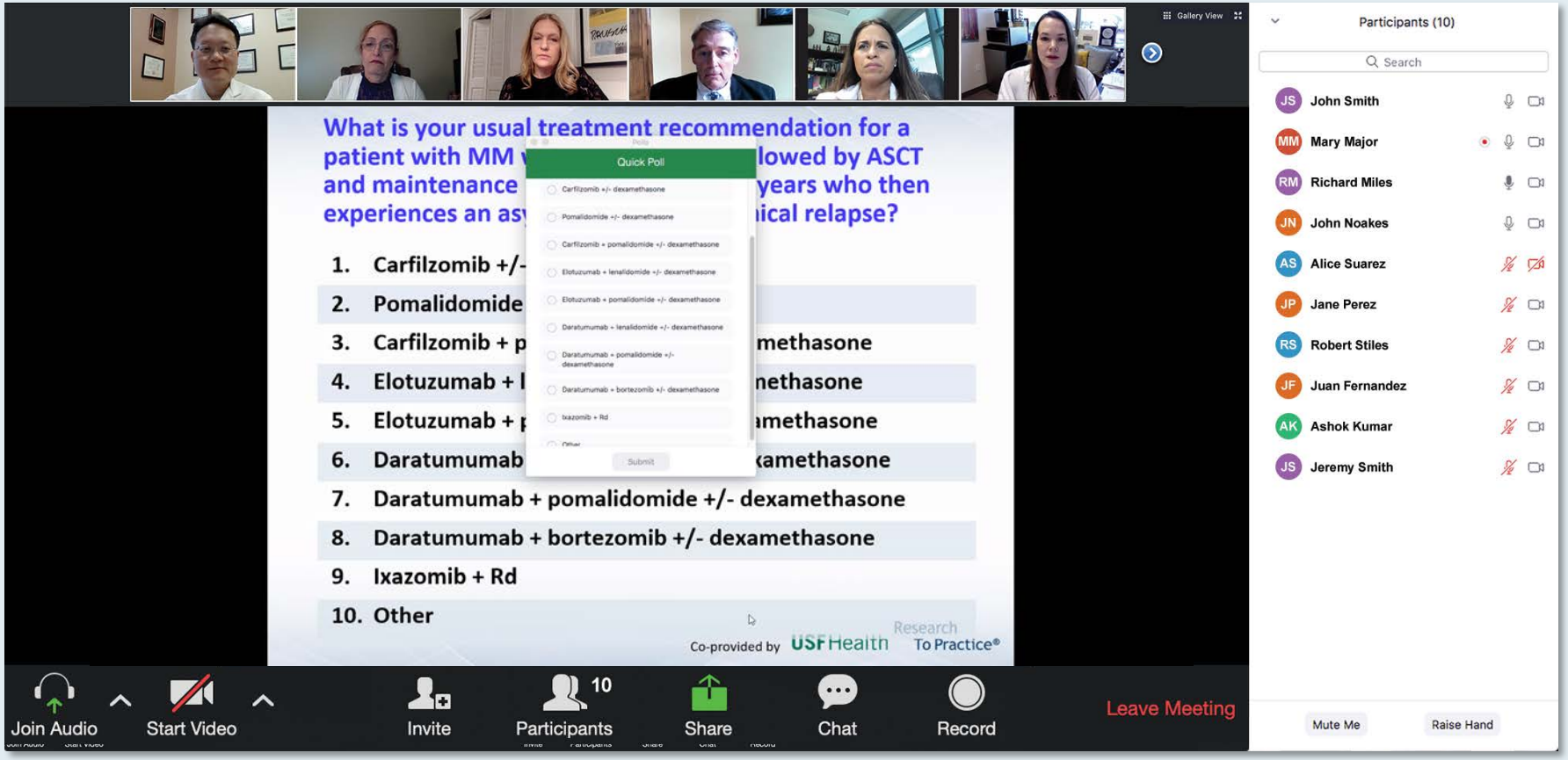

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Shannon N Westin, MD, MPH
Associate Professor
Director, Early Drug Development
Department of Gynecologic Oncology and Reproductive Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Meet The Professor with Dr Herzog

MODULE 1: Cases from Dr Westin

- A 66-year-old woman with Stage IV HGSOC (BRCA-negative, HRD-positive): Parts 1-7
- A 53-year-old woman with Stage IV HGSOC (BRCA-negative, HRD-negative): Parts 1-6

MODULE 2: Journal Club with Dr Herzog

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

MODULE 4: Key Recent Papers

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Case Presentation – Dr Westin: A 66-year-old woman with Stage IV HGSOC (BRCA-negative, HRD-positive) – Part 1

Dr Shannon Westin

- Presents with early satiety and pelvic pain → Imaging: Enlarged left ovary, omental caking, ascites and liver metastases
  - Core biopsy: HGSOC

Questions

- How does the liver metastases change your decision making? Would you still go to surgery with this patient? Would you give neoadjuvant chemotherapy?
- Are you considering laparoscopy? Are you going to do a little peek to try to determine if you can debulk this patient, or have you already made your decision about exactly how you're going to treat this patient from the beginning?
- When you treat this patient, what are you going to utilize? Are you going to use chemotherapy on its own? Are you going to use intraperitoneal chemotherapy? Are you going to add bevacizumab? So, is this a population that you would really want to get that anti-angiogenic activity?

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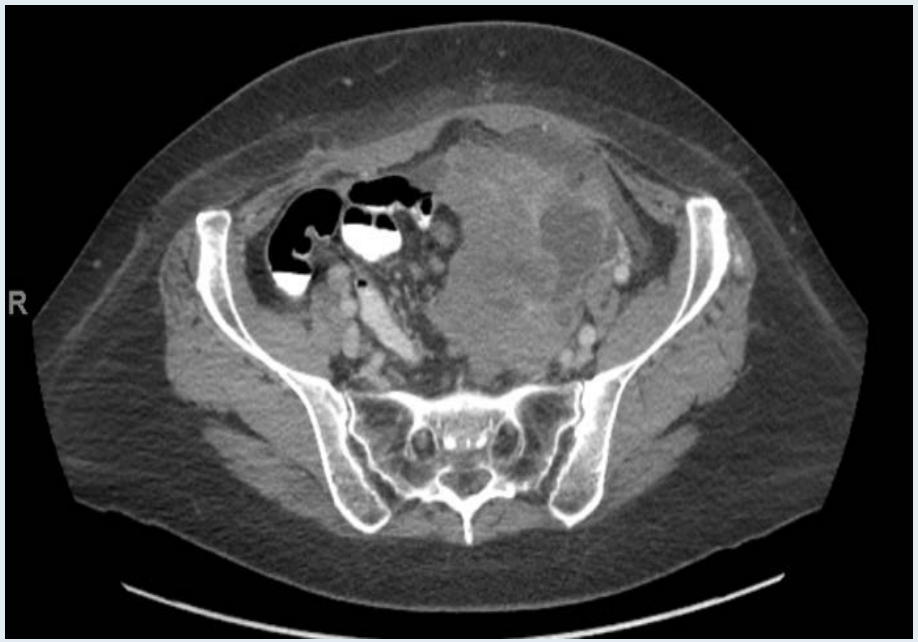
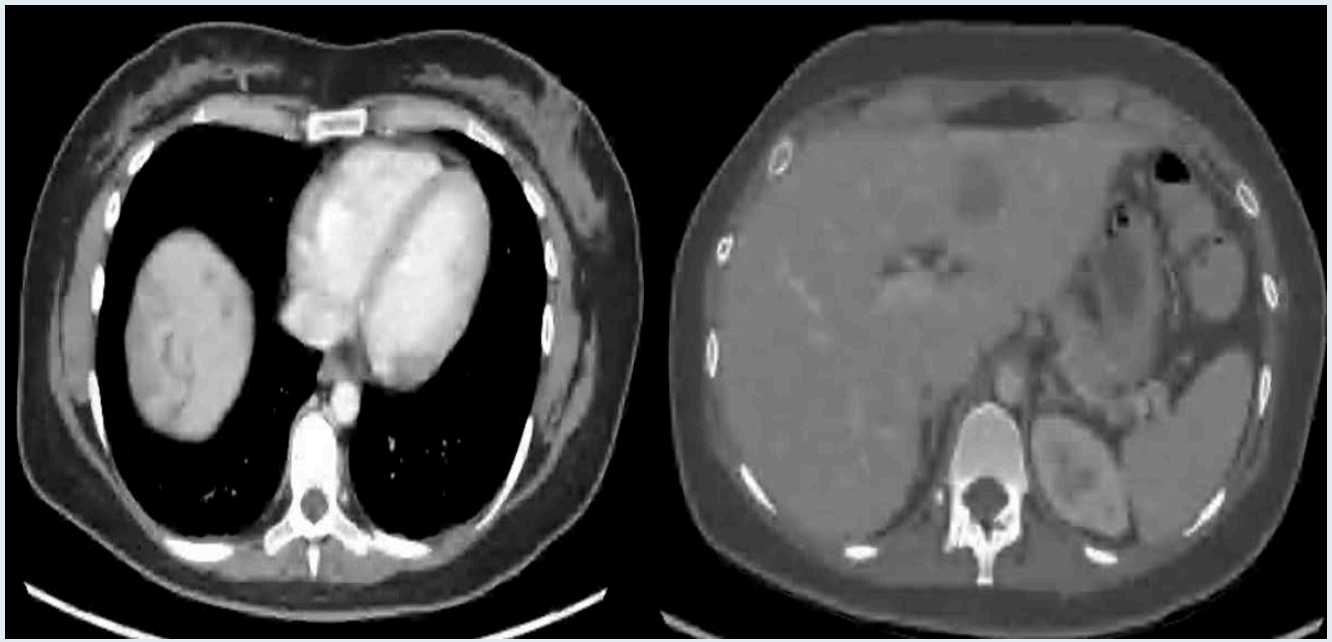
Case Presentation – Dr Westin: A 66-year-old woman with Stage IV HGSOC (BRCA-negative, HRD-positive) – Initial imaging

Dr Shannon Westin





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Case Presentation – Dr Westin: A 66-year-old woman with Stage IV HGSOC (BRCA-negative, HRD-positive) – Part 2

Dr Shannon Westin

- Presents with early satiety and pelvic pain → Imaging: Enlarged left ovary, omental caking, ascites and liver metastases
  - Core biopsy: HGSOC
- ***Neoadjuvant carboplatin/paclitaxel and bevacizumab x 3, with bevacizumab held during cycle 3***

Questions

- ***What's going to make you want to go on with surgery after 3 cycles? What's your goal — Do you want to see complete resolution of disease? Do you want to see shrinkage of disease?***
- ***Are you really just watching that liver tumor? Do you want that to go away? What is going to help you make your decision about whether or not you're going to go to surgery with this patient?***

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Case Presentation – Dr Westin: A 66-year-old woman with Stage IV HGSOC (BRCA-negative, HRD-positive) – Part 3

Dr Shannon Westin

- Presents with early satiety and pelvic pain → Imaging: Enlarged left ovary, omental caking, ascites and liver metastases
  - Core biopsy: HGSOC
- Neoadjuvant carboplatin/paclitaxel and bevacizumab x 3, with bevacizumab held during cycle 3

Comment

- **Determination of resectability; importance of a multidisciplinary surgical team**

Case Presentation – Dr Westin: A 66-year-old woman with Stage IV HGSOC (BRCA-negative, HRD-positive) – Part 4

Dr Shannon Westin

- Presents with early satiety and pelvic pain → Imaging: Enlarged left ovary, omental caking, ascites and liver metastases
  - Core biopsy: HGSOC
- Neoadjuvant carboplatin/paclitaxel and bevacizumab x 3, with bevacizumab held during cycle 3
- ***Testing: Germline and somatic BRCA wildtype → HRD testing: Genomic instability present***

Questions

- ***Are we going to surgery right away? How much more chemotherapy should we give?***
- ***And thinking about our maintenance strategy, am I just continuing the bevacizumab? Am I going to add a PARP inhibitor to bevacizumab? Or, am I going to switch to a PARP inhibitor on its own?***

Case Presentation – Dr Westin: A 66-year-old woman with Stage IV HGSOC (BRCA-negative, HRD-positive) – Part 5

Dr Shannon Westin

- Presents with early satiety and pelvic pain → Imaging: Enlarged left ovary, omental caking, ascites and liver metastases
  - Core biopsy: HGSOC
- Neoadjuvant carboplatin/paclitaxel and bevacizumab x 3, with bevacizumab held during cycle 3
- Testing: Germline and somatic BRCA wildtype → HRD testing: Genomic instability present
- ***Interval tumor reductive surgery to R0***
  - ***Residual HGSOC in ovary, omentum, liver***

Question

- ***What are you going to do with this patient next?***

Case Presentation – Dr Westin: A 66-year-old woman with Stage IV HGSOC (BRCA-negative, HRD-positive) – Part 6

Dr Shannon Westin

- Presents with early satiety and pelvic pain → Imaging: Enlarged left ovary, omental caking, ascites and liver metastases
  - Core biopsy: HGSOC
- Neoadjuvant carboplatin/paclitaxel and bevacizumab x 3, with bevacizumab held during cycle 3
- Testing: Germline and somatic BRCA wildtype → HRD testing: Genomic instability present
- Interval tumor reductive surgery to R0
  - Residual HGSOC in ovary, omentum, liver
- ***Carboplatin/paclitaxel/bevacizumab x 3, with bevacizumab held during cycle 4 → Clinical CR***

Question

- ***What is your maintenance strategy and how are you going to make that decision, in this patient who has a homologous recombination deficient tumor?***

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Case Presentation – Dr Westin: A 66-year-old woman with Stage IV HGSOC (BRCA-negative, HRD-positive) – Part 7

Dr Shannon Westin

- Presents with early satiety and pelvic pain → Imaging: Enlarged left ovary, omental caking, ascites and liver metastases
  - Core biopsy: HGSOC
- Neoadjuvant carboplatin/paclitaxel and bevacizumab x 3, with bevacizumab held during cycle 3
- Testing: Germline and somatic BRCA wildtype → HRD testing: Genomic instability present
- Interval tumor reductive surgery to R0
  - Residual HGSOC in ovary, omentum, liver
- Carboplatin/paclitaxel/bevacizumab x 3, with bevacizumab held during cycle 4 → Clinical CR
- Continue bevacizumab 15 more cycles as maintenance therapy and add olaparib x 2 years

Questions

- ***When you have a patient on these dual therapies, what do you expect for side effects?***
- ***How are you monitoring this patient to make sure you can keep her on full dose of these 2 agents?***

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Case Presentation – Dr Westin: A 53-year-old woman with Stage IV HGSOC (BRCA-negative, HRD-negative) – Part 1

Dr Shannon Westin

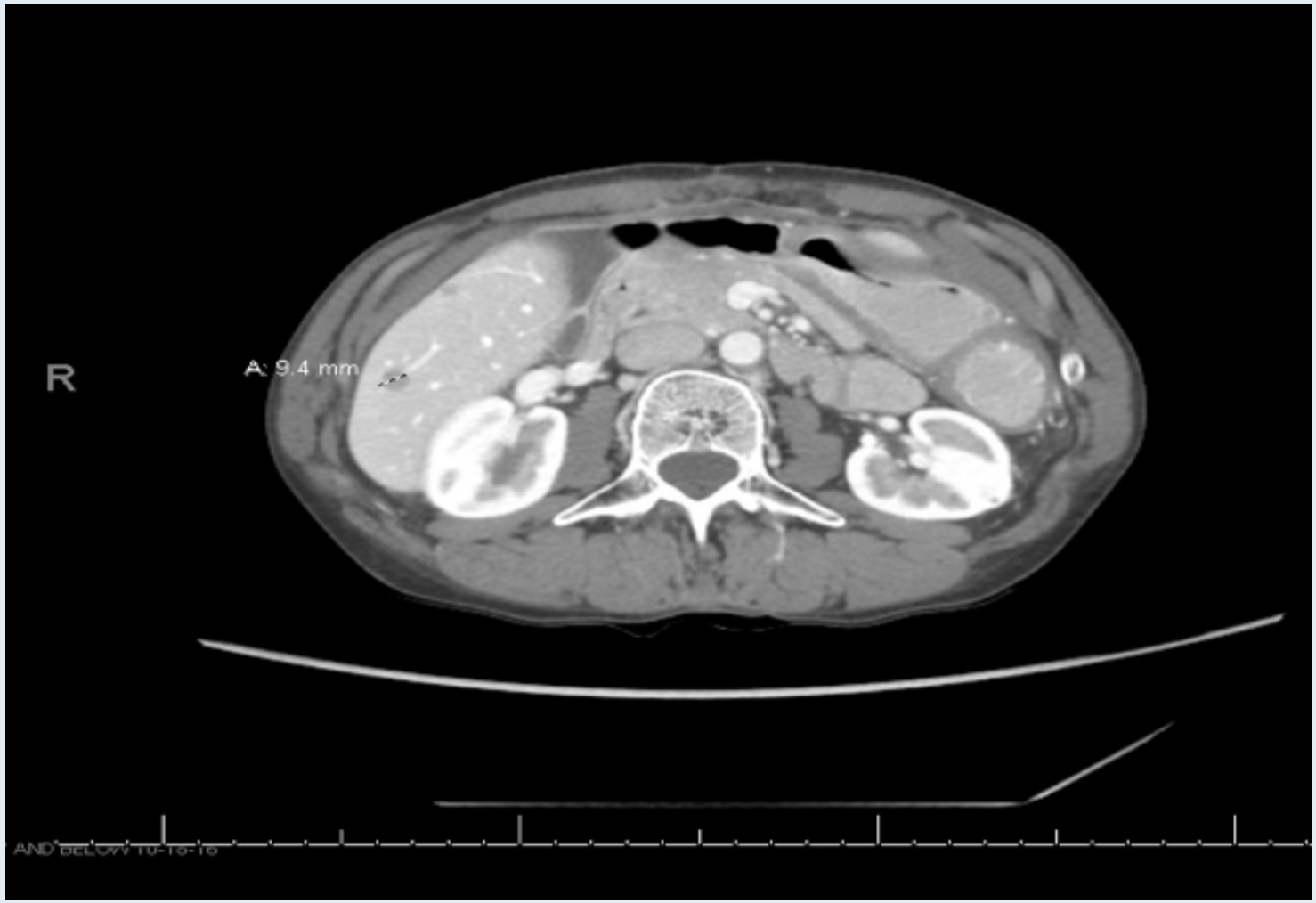
- Presents with abdominal bloating, emesis, and obstructive symptoms
  - Imaging: Peritoneal carcinomatosis and liver metastases
- Testing: Germline and somatic BRCA wildtype → HRD testing: Proficient

Question

- Are we going to surgery with this patient first, or are we giving her neoadjuvant chemotherapy?

Case Presentation – Dr Westin: A 53-year-old woman with Stage IV HGSOC (BRCA-negative, HRD-negative)

Dr Shannon Westin



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Case Presentation – Dr Westin: A 53-year-old woman with Stage IV HGSOC (BRCA-negative, HRD-negative) – Part 2

Dr Shannon Westin

- Presents with abdominal bloating, emesis, and obstructive symptoms
  - Imaging: Peritoneal carcinomatosis and liver metastases
- Testing: Germline and somatic BRCA wildtype → HRD testing: Proficient
- ***Neoadjuvant dose-dense paclitaxel/carboplatin x 3, with disease reduction***
- ***Interval tumor reduction surgery, with miliary-visible disease afterwards***

Questions

- ***Are you going to add bevacizumab to her adjuvant chemotherapy? Are you going to use a PARP inhibitor? Are you going to do active surveillance?***
- ***What are your strategies for this patient and how might you change what you're going to give this patient based on those strategies?***

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Case Presentation – Dr Westin: A 53-year-old woman with Stage IV HGSOC (BRCA-negative, HRD-negative) – Part 3

Dr Shannon Westin

- Presents with abdominal bloating, emesis, and obstructive symptoms
  - Imaging: Peritoneal carcinomatosis and liver metastases
- Testing: Germline and somatic BRCA wildtype → HRD testing: Proficient
- Neoadjuvant dose-dense paclitaxel/carboplatin x 3, with disease reduction
- Interval tumor reduction surgery, with miliary-visible disease afterwards
- ***Adjuvant dose-dense paclitaxel/carboplatin, with clinical CR***
- ***Maintenance niraparib***

Question

- ***How would you approach this patient with BRCA wildtype, HRD proficient disease in terms of PARP maintenance therapy?***

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Case Presentation – Dr Westin: A 53-year-old woman with Stage IV HGSOC (BRCA-negative, HRD-negative) – Part 4

Dr Shannon Westin

- Presents with abdominal bloating, emesis, and obstructive symptoms
  - Imaging: Peritoneal carcinomatosis and liver metastases
- Testing: Germline and somatic BRCA wildtype → HRD testing: Proficient
- Neoadjuvant dose-dense paclitaxel/carboplatin x 3, with disease reduction
- Interval tumor reduction surgery, with miliary-visible disease afterwards
- Adjuvant dose-dense paclitaxel/carboplatin, with clinical CR
- Maintenance niraparib

Questions

- ***How long should maintenance niraparib be continued?***
- ***How will you monitor her labs while she is on treatment? How often are you seeing her in the clinic? How often are you doing an assessment physically? What kind of scans are you doing? Are you going to do scans on this patient? Are you going to use just a CA 125?***
- ***How are you going to counsel your patient on what she's going to expect?***

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Case Presentation – Dr Westin: A 53-year-old woman with Stage IV HGSOC (BRCA-negative, HRD-negative) – Part 5

Dr Shannon Westin

- Presents with abdominal bloating, emesis, and obstructive symptoms
  - Imaging: Peritoneal carcinomatosis and liver metastases
- Testing: Germline and somatic BRCA wildtype → HRD testing: Proficient
- Neoadjuvant dose-dense paclitaxel/carboplatin x 3, with disease reduction
- Interval tumor reduction surgery, with miliary-visible disease afterwards
- Adjuvant dose-dense paclitaxel/carboplatin, with clinical CR
- Maintenance niraparib

Comment

- ***Monitoring of patients receiving maintenance niraparib***

Case Presentation – Dr Westin: A 53-year-old woman with Stage IV HGSOC (BRCA-negative, HRD-negative) – Part 6

Dr Shannon Westin

- Presents with abdominal bloating, emesis, and obstructive symptoms
  - Imaging: Peritoneal carcinomatosis and liver metastases
- Testing: Germline and somatic BRCA wildtype → HRD testing: Proficient
- Neoadjuvant dose-dense paclitaxel/carboplatin x 3, with disease reduction
- Interval tumor reduction surgery, with miliary-visible disease afterwards
- Adjuvant dose-dense paclitaxel/carboplatin, with clinical CR
- Maintenance niraparib

Comment

- Monitoring of patients receiving maintenance niraparib
- ***Dosing strategies with niraparib***

Meet The Professor with Dr Herzog

MODULE 1: Cases from Dr Westin

MODULE 2: Journal Club with Dr Herzog

- Current status of secondary cytoreduction in ovarian cancer
- Maintenance therapy for ovarian cancer: Practice-changing data calls for changing practice
- Selecting new up-front regimens for advanced ovarian cancer with biomarker guidance
- Molecular variations in uterine carcinosarcomas identify therapeutic opportunities
- Clinical trials, adaptability and the COVID-19 pandemic
- COVID-19 pandemic and impact on cancer clinical trials: An academic medical center perspective
- A virtual molecular tumor board to improve efficiency and scalability of delivering precision oncology

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

MODULE 4: Key Recent Papers

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The Current Status of Secondary Cytoreduction in Ovarian Cancer: A Systematic Review

Daniel Margul, MD, PhD, Robert L. Coleman, MD, and Thomas J. Herzog, MD

***Clin Adv Hematol Oncol* 2020;18(6):332-43.**

Oncologist 2019;24(5):576-9.

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Commentary

Ovarian Cancer Maintenance: Practice-Changing Data Calls for Changing Practice

Leslie M. Randall,[a] Michael J. Birrer,[b] Thomas J. Herzog[c]

[a]University of California Irvine Health, Chao Family Comprehensive Cancer Center, Orange, California, USA; [b]O'Neal Comprehensive Cancer Center, Division of Hematology-Oncology, University of Alabama at Birmingham, Birmingham, Alabama, USA; [c]University of Cincinnati Cancer Institute, University of Cincinnati Medical Center, Cincinnati, Ohio, USA

“All eligible patients with ovarian cancer deserve informed counseling regarding the pros and cons of maintenance therapy, and the option of maintenance treatment in these regulatory approved settings.”

Randall LM et al. *Oncologist* 2019;24(5):576-9.

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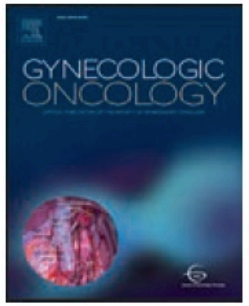
Gynecologic Oncology 159 (2020) 604–606

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno



Clinical Commentary

Selecting new upfront regimens for advanced ovarian cancer with biomarker guidance☆

John K. Chan [a,*], Su-Ying Liang [b], Daniel S. Kapp [c], Joshua E. Chan [c], Thomas J. Herzog [d], Robert L. Coleman [e], Bradley J. Monk [f], Michael T. Richardson [c,g]

Decision #1: Up-front surgery or neoadjuvant chemotherapy?

Chan JK et al. *Gynecol Oncol* 2020;159:604-6.

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Decision #2: Addition of antivascular agent to chemotherapy and maintenance?

Chan JK et al. *Gynecol Oncol* 2020;159:604-6.

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Decision #3: Maintenance PARP inhibitor or in combination?

Chan JK et al. *Gynecol Oncol* 2020;159:604-6.

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Int J Gynecol Cancer 2020;30(4):480-4.

Original research

INTERNATIONAL JOURNAL OF GYNECOLOGICAL CANCER

Molecular variations in uterine carcinosarcomas identify therapeutic opportunities

Erin Crane,[1] Wendel Naumann,[1] David Tait,[1] Robert Higgins,[1] Thomas Herzog,[2] Jubilee Brown[1]

Gynecologic Oncology Reports 35 (2021) 100680

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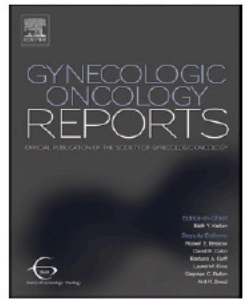
journal homepage: www.elsevier.com/locate/gynor



Short communication

Clinical trials, adaptability and the COVID-19 pandemic

Ramez N. Eskander, Bhavana Pothuri, Leslie Randall, David O'Malley, Brian Slomovitz, Kathleen Moore, Robert Coleman, Thomas Herzog, Bradley J. Monk, Larry Copeland

ORIGINAL RESEARCH

Cancer Medicine Open Access WILEY

COVID-19 pandemic and impact on cancer clinical trials: An academic medical center perspective

Michelle Marcum[1] | Nicky Kurtzweil[1] | Christine Vollmer[1] | Lisa Schmid[1] | Ashley Vollmer[1] | Alison Kastl[1] | Kelly Acker[1] | Shuchi Gulati[1,2] | Punita Grover[1,2] | Thomas J. Herzog[1,3] | Syed A. Ahmad[1,4] | Davendra Sohal[1,2] | Trisha M. Wise-Draper[1,2]

Cancer Med 2020;9(17):6141-6.

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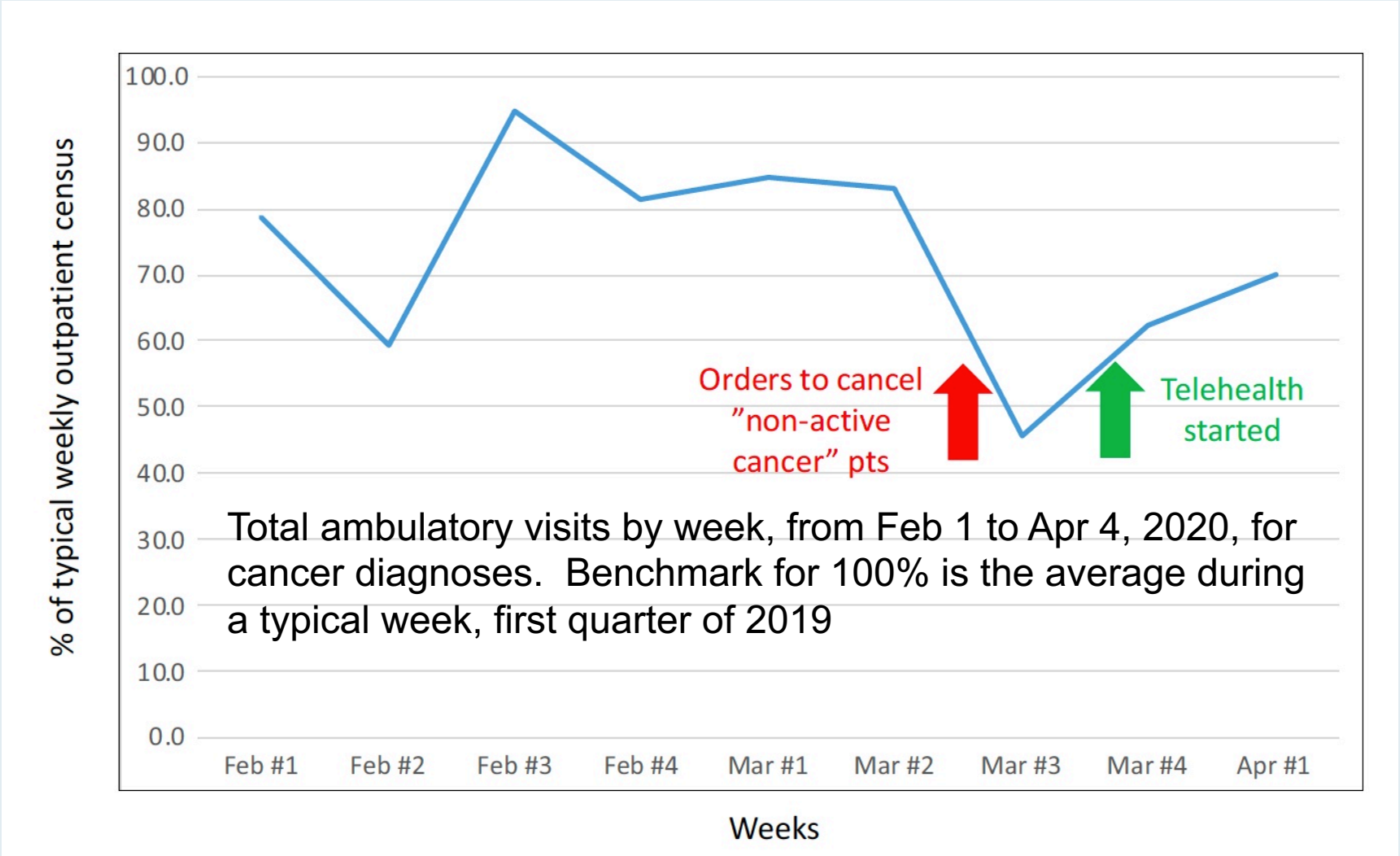
University of Cincinnati Cancer Center Patient-Visit Volume During the COVID-19 Pandemic



Marcum M et al. *Cancer Med* 2020;9(17):6141-6.

JAMIA Open, 2(4), 2019, 505–515
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Research and Applications

Research and Applications

A virtual molecular tumor board to improve efficiency and scalability of delivering precision oncology to physicians and their patients

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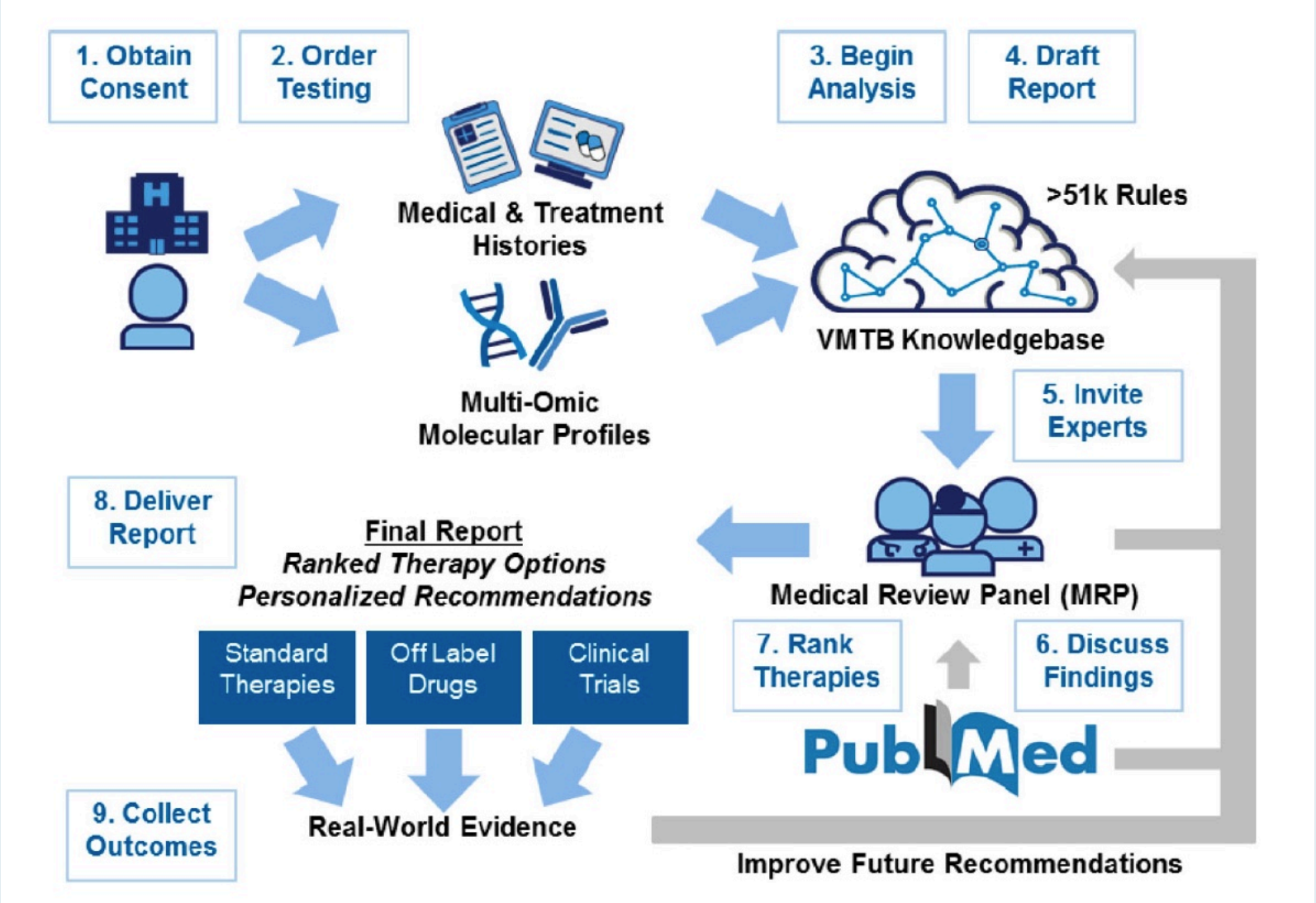
Overview of the Virtual Molecular Tumor Board Workflow



Pishvaian MJ et al. *JAMIA Open* 2019;2(4):505-15.

Meet The Professor with Dr Herzog

MODULE 1: Cases from Dr Westin

MODULE 2: Journal Club with Dr Herzog

- Current status of secondary cytoreduction in ovarian cancer
- Ovarian cancer maintenance: Practice-changing data calls for changing practice
- Selecting new upfront regimens for advanced ovarian cancer with biomarker guidance
- Molecular variations in uterine carcinosarcomas identify therapeutic opportunities
- Clinical trials, adaptability and the COVID-19 pandemic
- COVID-19 pandemic and impact on cancer clinical trials: An academic medical center perspective
- A virtual molecular tumor board to improve efficiency and scalability of delivering precision oncology

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

MODULE 4: Key Recent Papers

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TO PRACTICE

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 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 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 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

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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?

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

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

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

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	Carboplatin/PLD → maintenance rucaparib
 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 niraparib
 SHANNON N WESTIN, MD, MPH	Carboplatin/PLD → maintenance olaparib

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?

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

Meet The Professor with Dr Herzog

MODULE 1: Cases from Dr Westin

MODULE 2: Journal Club with Dr Herzog

- Current status of secondary cytoreduction in ovarian cancer
- Ovarian cancer maintenance: Practice-changing data calls for changing practice
- Selecting new upfront regimens for advanced ovarian cancer with biomarker guidance
- Molecular variations in uterine carcinosarcomas identify therapeutic opportunities
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- COVID-19 pandemic and impact on cancer clinical trials: An academic medical center perspective
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MODULE 3: Beyond the Guidelines – Clinical Investigator Approaches to Common Clinical Scenarios

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

NCCN[1]

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

SGO[2]

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[3]

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®) 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.

ESMO Recommendations on the Clinical Utility of HRD Tests
(Level of agreement = 100% for all statements)

- In the first-line maintenance setting, germline and somatic BRCA mutation testing is routinely recommended to identify HGSC patients who should receive a PARPi.
- In the first-line maintenance setting, it is reasonable to use a validated scar based HRD test to establish the magnitude of benefit conferred by PARPi use in BRCA wild-type HGSC.
- In the first-line maintenance setting, it is reasonable to use a validated scar based HRD test to identify the subgroup of BRCA wild-type patients who are least likely to benefit from PARPi therapy.
- In the platinum-sensitive relapse maintenance setting, it is reasonable to use BRCA mutation testing and validated scar based HRD tests to predict the likely magnitude of PARPi benefit for consideration of risks and benefits of maintenance therapy.

Miller RE et al. Ann Oncol 2020;31(12):1606-22.

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

Lynce F, Isaacs C. *ASCO Educational Book* 2016:72-8.

Current FDA-Approved and Investigational PARP Inhibitors: Differences

PARP inhibitor	IC_{50}	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

Lim JSJ, Tan DSP. *Cancers* 2017;9(8):pii:E109.

Phase III First-Line PARP Maintenance Trials

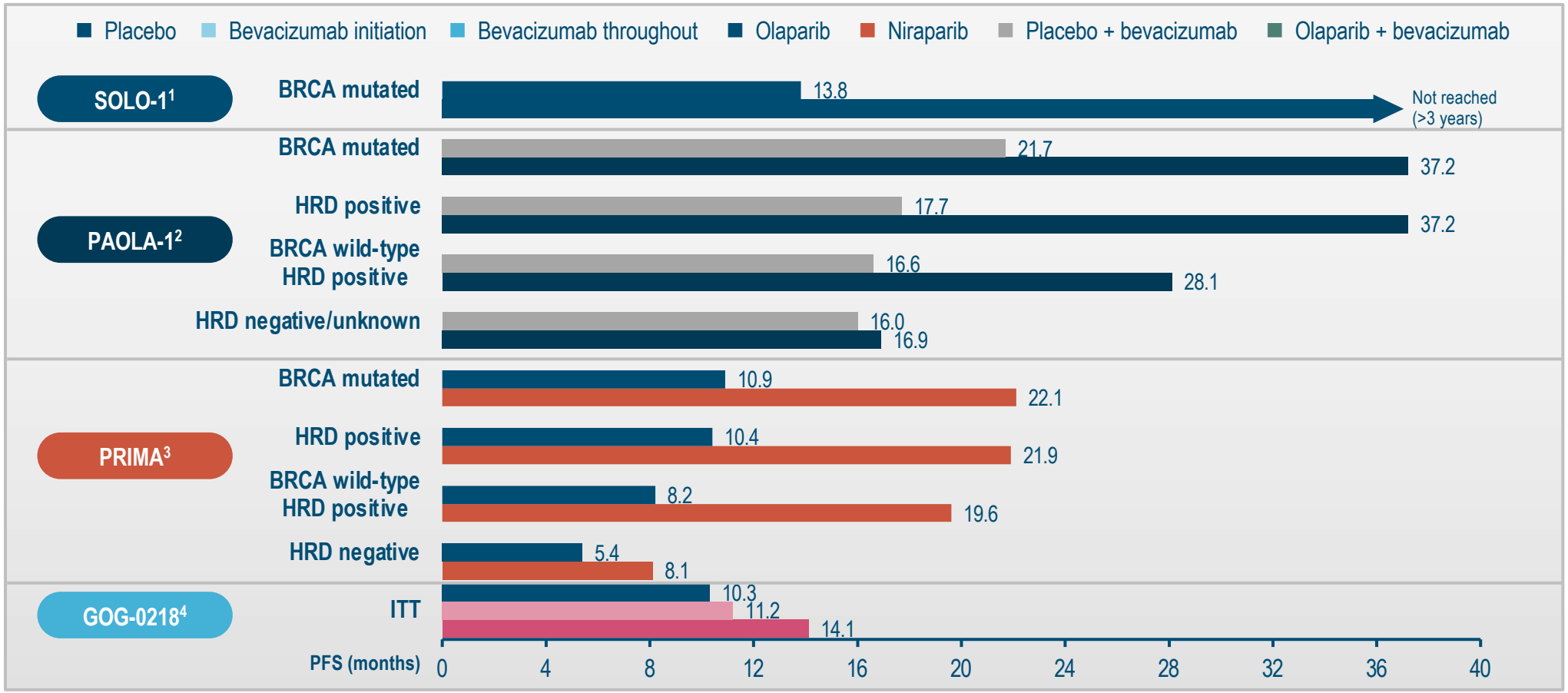
Study Design	SOLO-1 (N=451)	PAOLA-1 (N=612)	PRIMA (N=620)	VELIA (N=1140)
Treatment arms vs placebo	**Olaparib (n=260)**	**Bevacizumab ± Olaparib**	**Niraparib**	**Veliparib**
Patient Population	*BRCA* mutation	All comers	All comers	*All comers*
Treatment Duration	24 months	15 months for Bev 24 months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

[a]Residual disease based on stage was not reported. [b]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

SUMMARY OF APPROVED MAINTENANCE STUDIES IN THE FIRST-LINE



Comparisons across trials should not be made as trials were not head-to-head.

BRCA, breast cancer gene; HRD, homologous recombination deficiency; ITT, intent-to-treat; PFS, progression-free survival

1. Moore K, et al. N Engl J Med 2018;379:2495–2505; 2. Ray-Coquard IL, et al. N Engl J Med 2019; 381:2416–2428; 3. Gonzalez-Martin A, et al. N Engl J Med 2019;381:2391–2402; 4. Burger RA, et al. N Engl J Med 2011;365:2473–2483

Courtesy of Robert L Coleman, MD

FDA Approves Niraparib for First-Line Maintenance Therapy for 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

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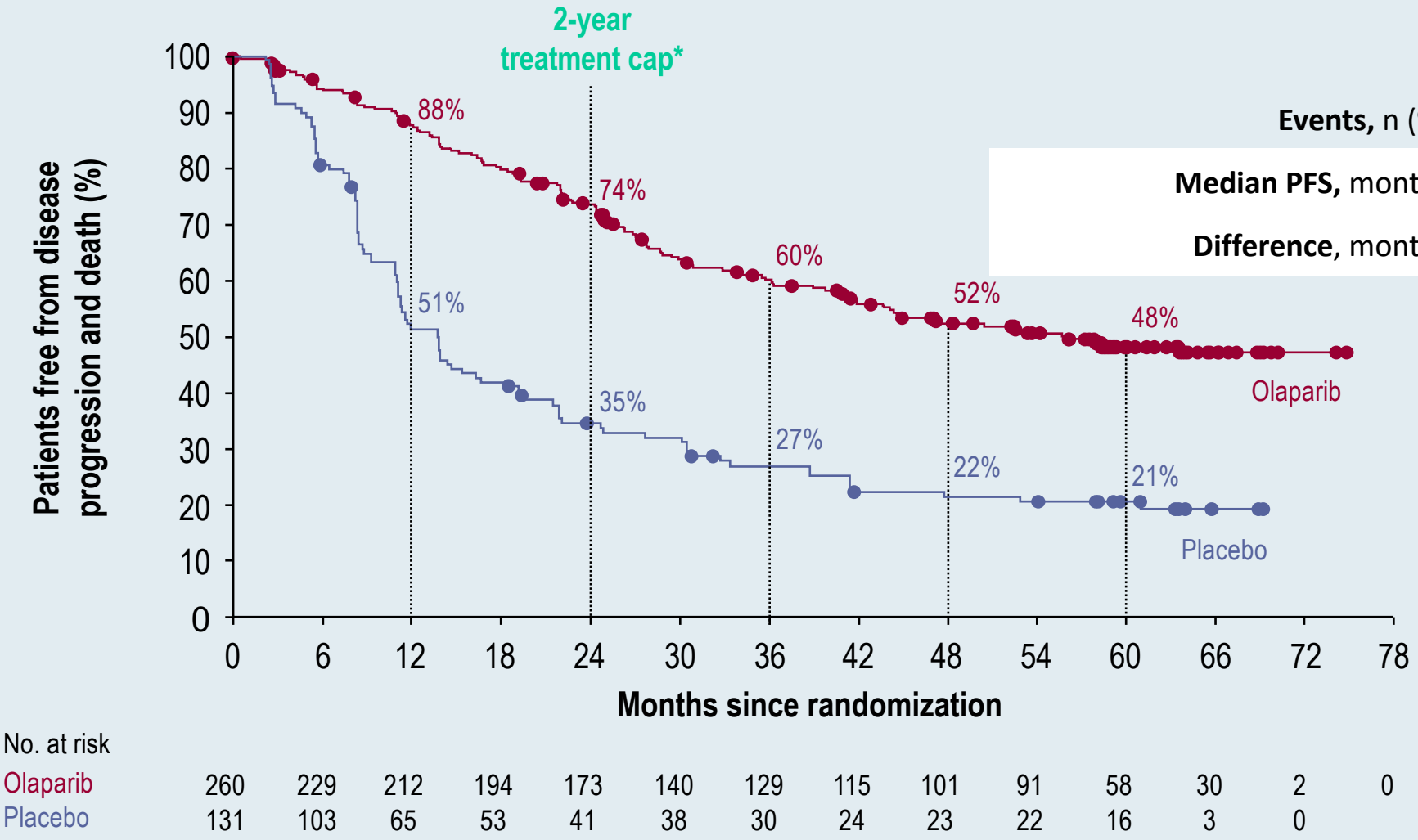
Maintenance Olaparib for Patients (pts) with Newly Diagnosed, Advanced Ovarian Cancer (OC) and a BRCA Mutation (BRCAm): 5-Year (y) Follow-Up (f/u) from SOLO1

Banerjee S et al.

ESMO 2020;Abstract 811MO.

SOLO-1: Updated PFS (60 Months Follow-Up)



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

Median treatment duration:
Olaparib, 24.6 months
Placebo†, 13.9 months

Banerjee S et al. ESMO 2020;Abstract 811MO.

RTP RESEARCH TO PRACTICE

FDA Approves Olaparib with Bevacizumab as Maintenance Therapy for Ovarian, Fallopian Tube or Primary Peritoneal Cancer

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 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

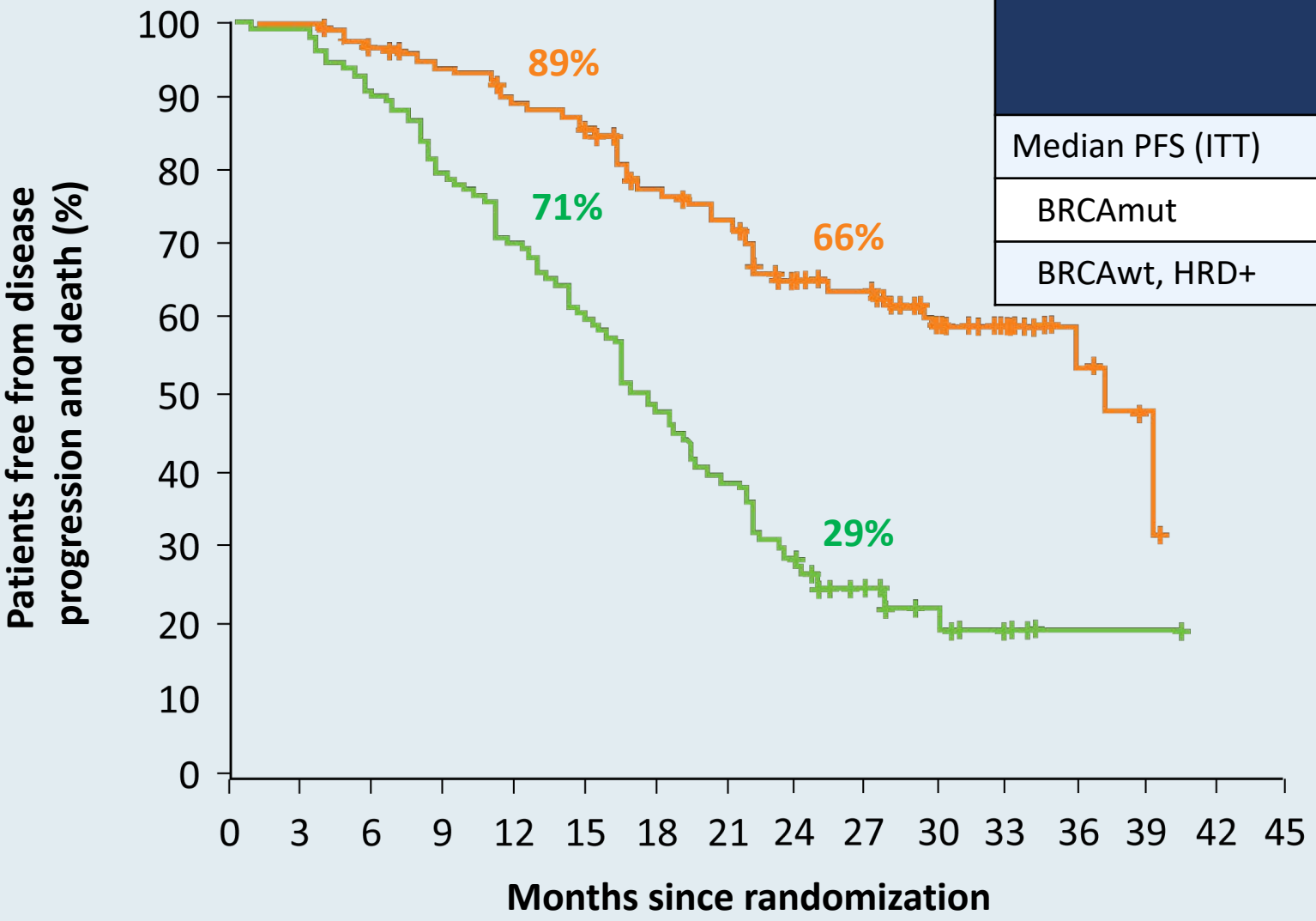
RTP RESEARCH TO PRACTICE

Maintenance Olaparib plus Bevacizumab (bev) in Patients (pts) with Newly Diagnosed Advanced High-Grade Ovarian Carcinoma (HGOC): Final Analysis of Second Progression-Free Survival (PFS2) in the Phase III PAOLA-1/ENGOT-ov25 Trial

Gonzalez Martin A et al.

ESMO 2020;Abstract LBA33

PAOLA-1: Progression-Free Survival (ITT)



	Olaparib + bevacizumab (n = 537)	Placebo + bevacizumab (n = 269)	Hazard ratio
Median PFS (ITT)	22.1 mo	16.6 mo	0.59
BRCAmut	37.2 mo	17.7 mo	0.33
BRCAwt, HRD+	28.1 mo	16.6 mo	0.43

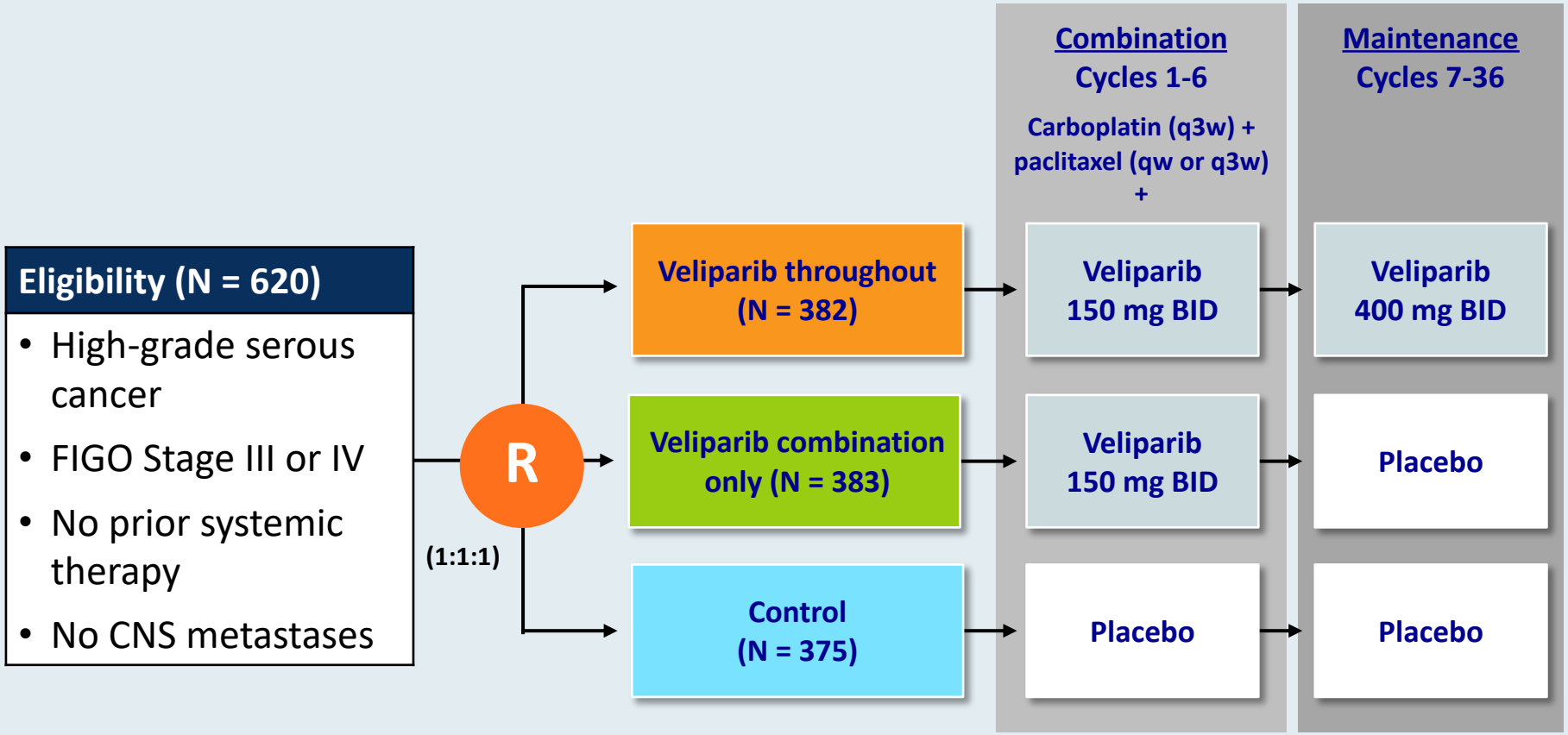
Gonzalez Martin A et al. ESMO 2020;Abstract LBA33.

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.

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 Cancer

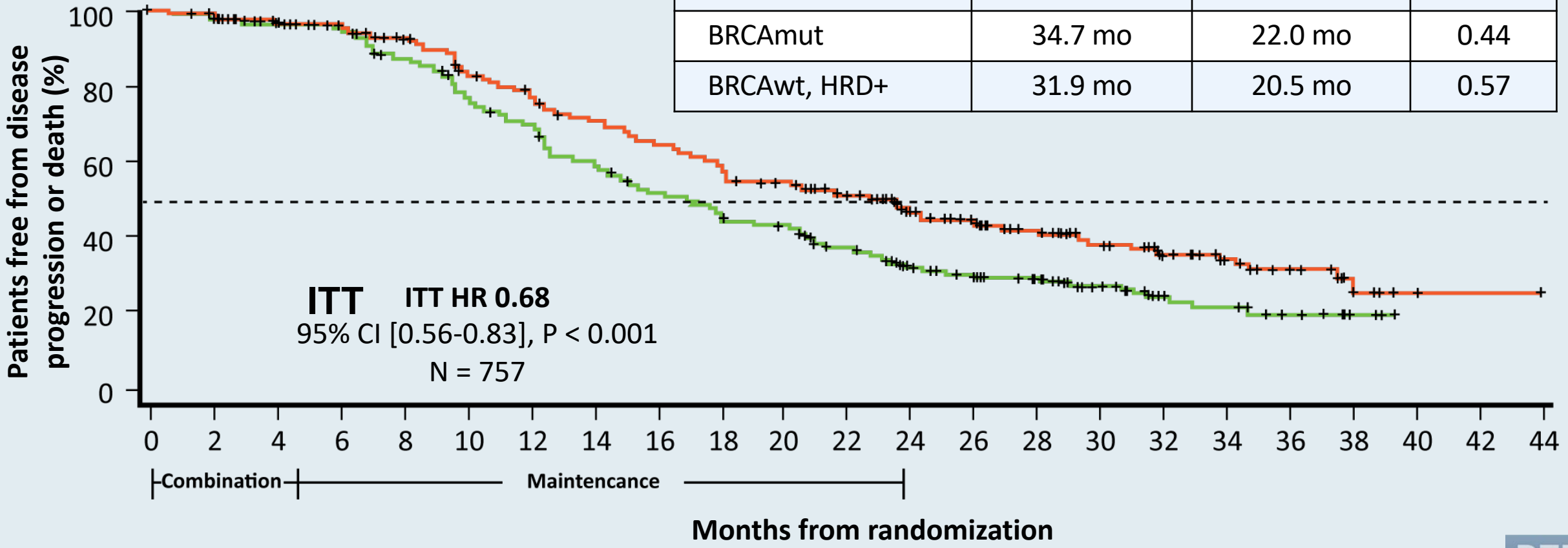


Primary endpoint: Progression-free survival for "veliparib throughout" versus control

Coleman RL et al. SGO 2020;Abstract 36.

VELIA/GOG-3005: Progression-Free Survival (ITT)

	Veliparib-throughout (n = 382)	Control (n = 375)	Hazard ratio
Median PFS (ITT)	23.5 mo	17.3 mo	0.68
BRCAmut	34.7 mo	22.0 mo	0.44
BRCAwt, HRD+	31.9 mo	20.5 mo	0.57



Coleman RL et al. SGO 2020;Abstract 36.

RTP RESEARCH TO PRACTICE

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

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
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	✓	✓	✓	✓	✓

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.

RTP RESEARCH TO PRACTICE

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

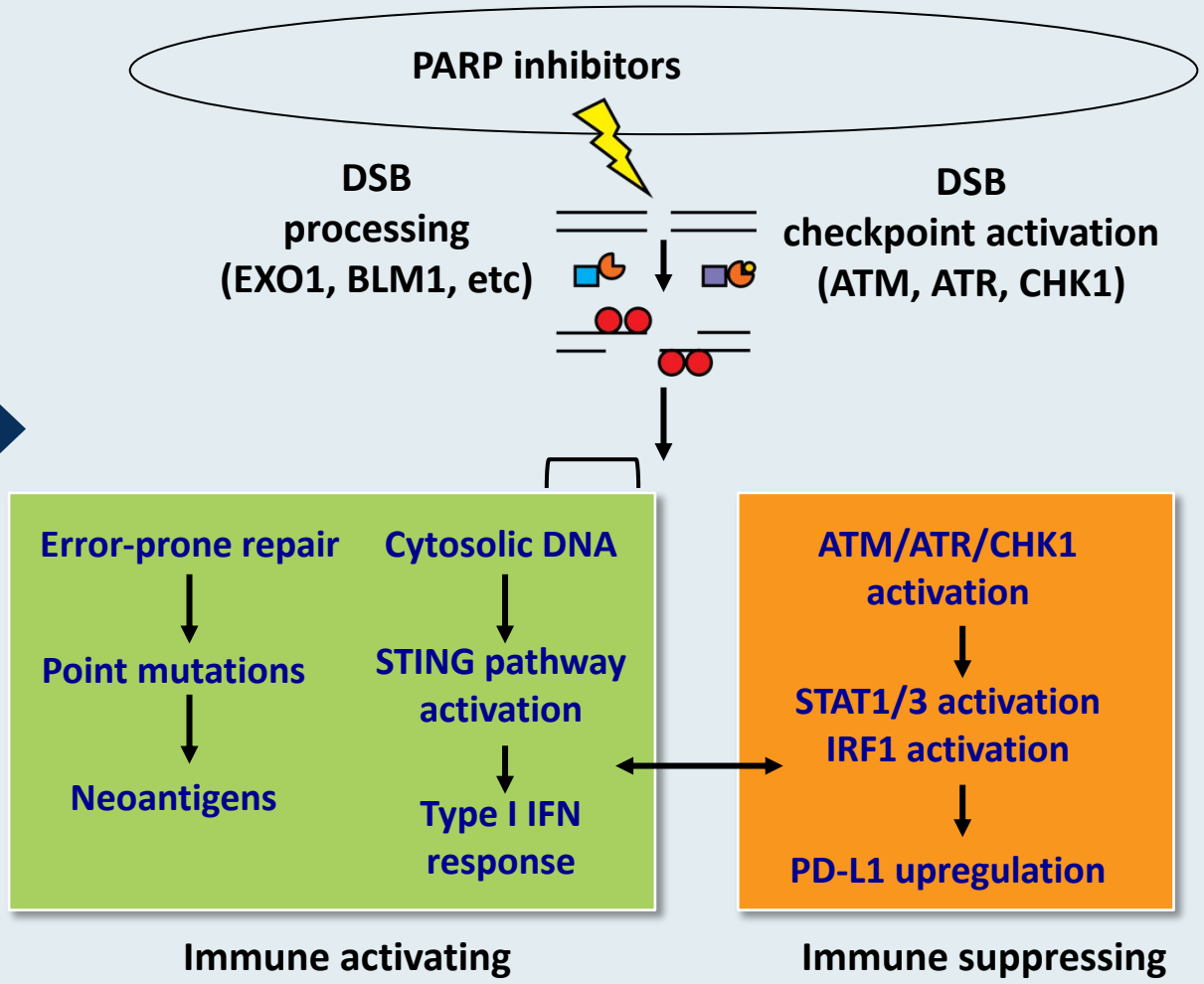
Rucaparib dose reductions	Dose
Starting dose	• 600 mg twice daily
First dose reduction	• 500 mg twice daily
Second dose reduction	• 400 mg twice daily
Third dose reduction	• 300 mg twice daily

Courtesy, Shannon N Westin, MD, MPH

FDA Prescribing Information.

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

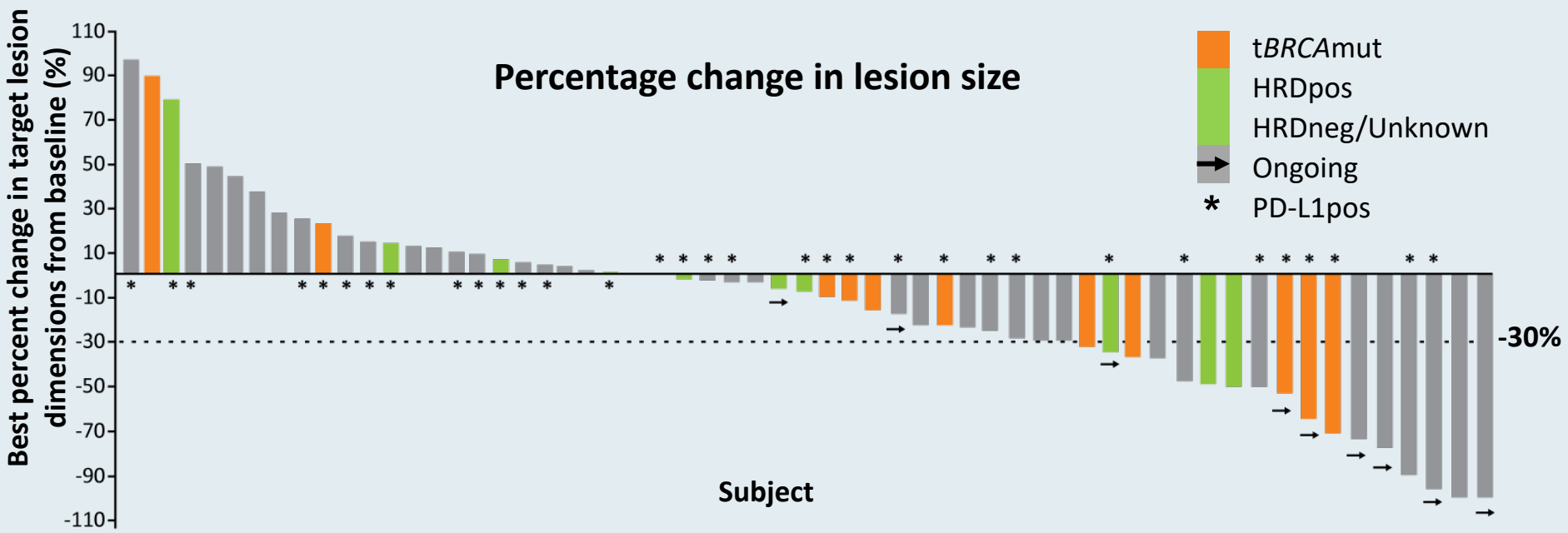
Preclinical models indicate synergy between PARPi + anti-PD-1 agents regardless of *BRCA* mutation status or PD-L1 status



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

Konstantinopoulos P et al. ASCO 2018;Abstract 106.

TOPACIO (KEYNOTE-162): A Phase I/II Study of Niraparib with Pembrolizumab for 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%)

Konstantinopoulos P et al. ASCO 2018;Abstract 106.

Phase II Study of Olaparib (O) plus Durvalumab (D) and Bevacizumab (B) (MEDIOLA): Initial Results in Patients (pts) with Non-Germline BRCA-Mutated (Non-gBRCAm) Platinum Sensitive Relapsed (PSR) Ovarian Cancer (OC)

Drew Y et al.

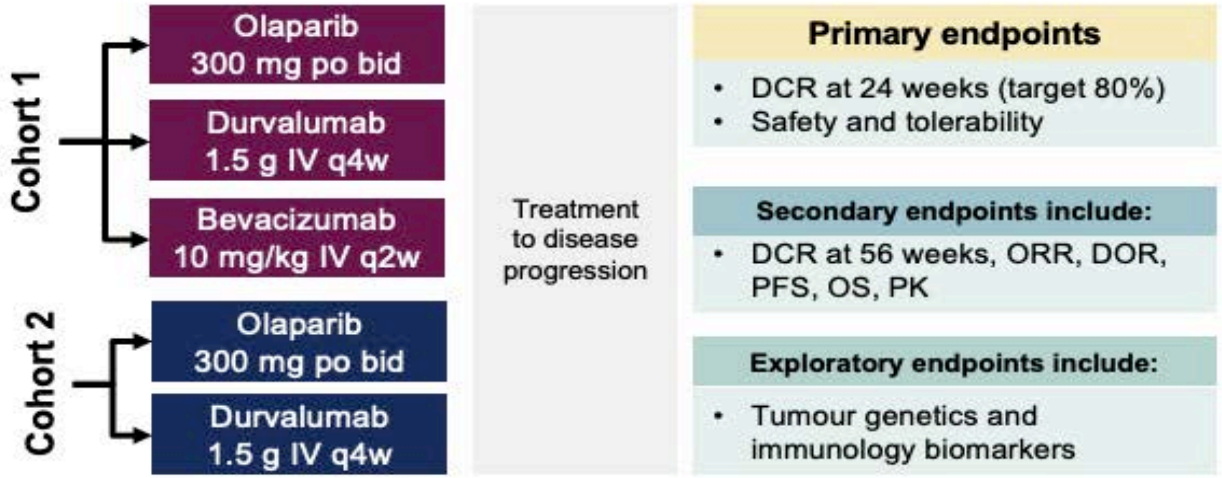
ESMO 2020;Abstract 814MO.

MEDIOLA: gBRCAwt Cohorts

Study Design

Patient population

- gBRCAwt
- PSR ovarian cancer
- ≤2 prior lines of chemotherapy
- PARP inhibitor and IO agent naïve



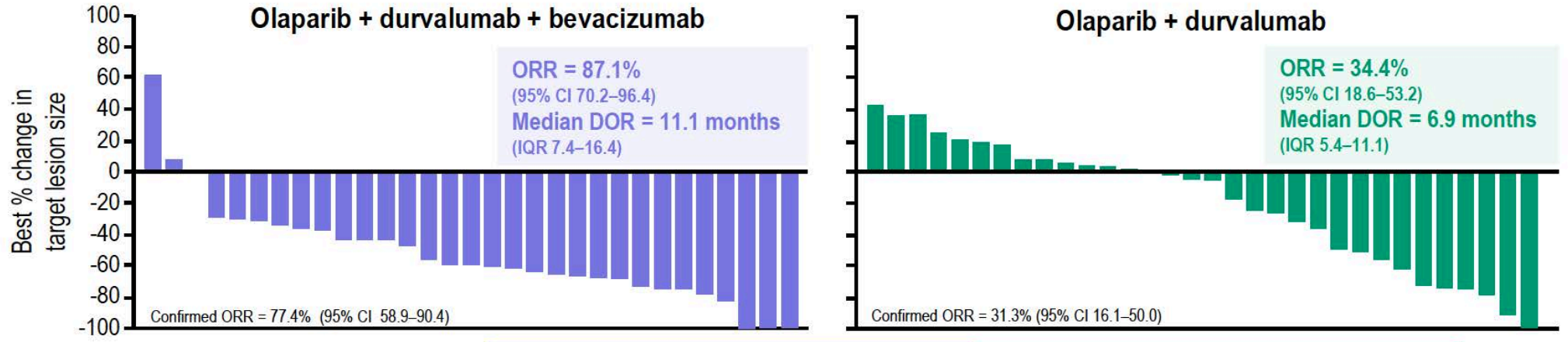
Patient Characteristics

	Olap + durva + bev (N=31)	Olap + durva (N=32)
Median age, years	64.0	68.5
Age group (years), n (%)		
<50	3 (9.7)	4 (12.5)
≥50–<65	14 (45.2)	8 (25.0)
≥65	14 (45.2)	20 (62.5)
Race, n (%)		
White	20 (64.5)	24 (75.0)
Asian	10 (32.3)	3 (9.4)
Other	1 (3.2)	5 (15.6)
Platinum sensitivity, n (%)		
>6–12 months	18 (58.1)	14 (43.8)
>12 months	13 (41.9)	18 (56.3)
Number of prior lines of chemotherapy, n (%)		
1 prior line	20 (64.5)	23 (71.9)
2 prior lines	11 (35.5)	9 (28.1)
Enrolment completed	January 2019	February 2019
Patients on study treatment at DCO, n (%) (13 February 2020)		
Olap; durva; bev	13 (41.9); 13 (41.9); 12 (38.7)	7 (21.9); 6 (18.8); NA

Drew Y et al. ESMO 2020;Abstract 814MO.

MEDIOLA: A Phase II Study of Olaparib and Durvalumab with or without Bevacizumab for Platinum-Sensitive Relapsed OC: No Germline BRCA Mutation Cohort

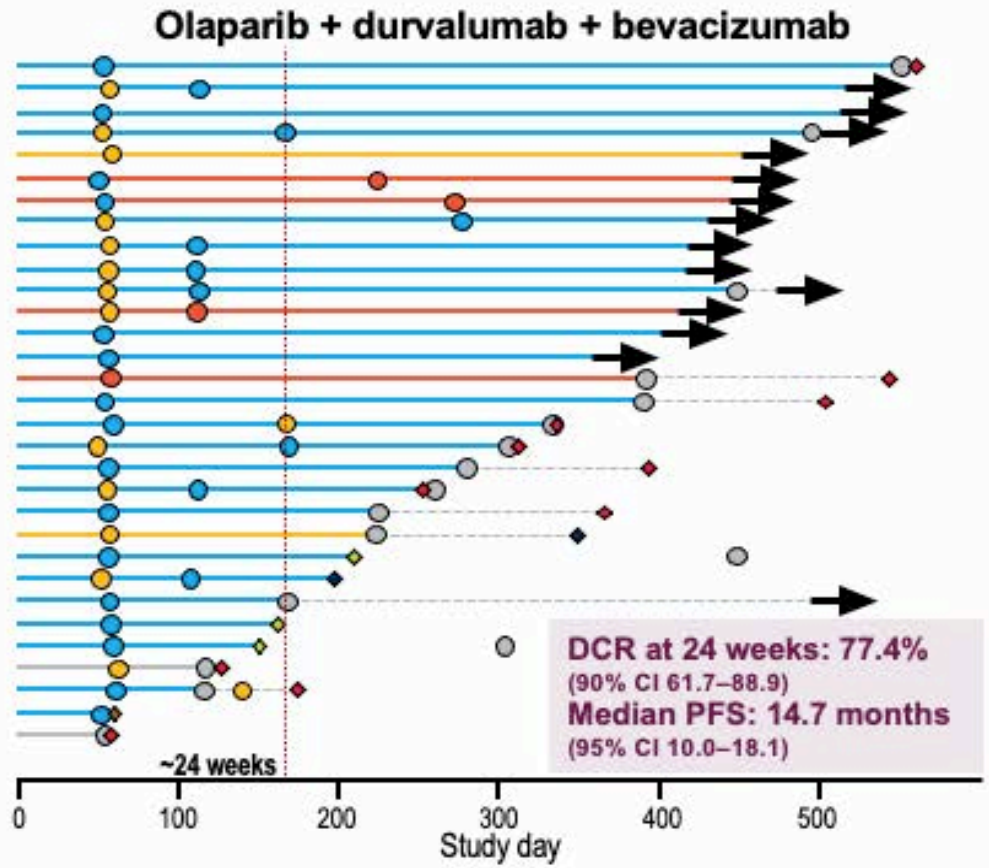
Exploratory analysis suggests ORR with triplet cohort is not dependent on genomic instability status (GIS)

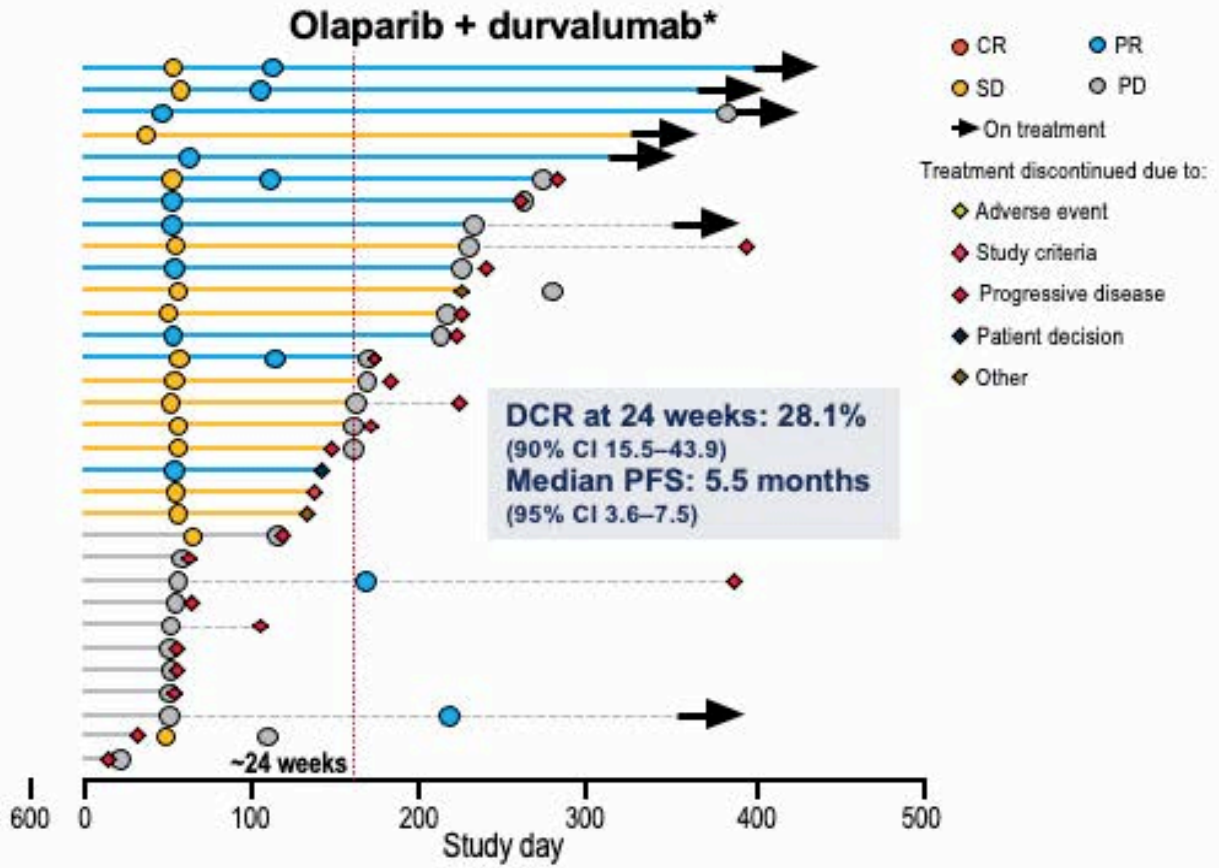


Genomic instability status* subgroup	Olaparib + durvalumab + bevacizumab		Olaparib + durvalumab	
	ORR (95% CI), %	n/N patients	ORR (95% CI), %	n/N patients
GIS-positive	100.0 (69.2–100.0)	10/10	50.0 (18.7–81.3)	5/10
GIS-negative	75.0 (34.9–96.8)	6/8	16.7 (0.4–64.1)	1/6
GIS-unknown	84.6 (54.6–98.1)	11/13	31.3 (11.0–58.7)	5/16

Drew Y et al. ESMO 2020;Abstract 814MO.

MEDIOLA: TTP or Treatment Discontinuation





- **Triplet cohort showed high DCT at 24 weeks and a long median PFS**

Drew Y et al. ESMO 2020;Abstract 814MO.

RTP RESEARCH TO PRACTICE

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	• **Rucaparib** + Nivolumab • **Rucaparib** + Placebo • Nivolumab + Placebo • Placebo
DUO-O (NCT03737643)	1,056	Maintenance therapy after 1L platinum-based chemo/Bev ± Durvalumab	• Bev • Bev + Durvalumab • Bev + Durvalumab + **Olaparib**
NRG-GY004 (NCT02446600)	549	Recurrent, platinum-sensitive	• Platinum-based chemo • **Olaparib** • **Olaparib** + Cediranib
ANITA (NCT03598270)	414	Recurrent, platinum-sensitive	• Placebo + Platinum-based chemo → **Niraparib** • ATEZO + Platinum-based chemo → **Niraparib** + ATEZO

Bev = bevacizumab; ATEZO = atezolizumab

www.clinicaltrials.gov. Accessed December 2018.

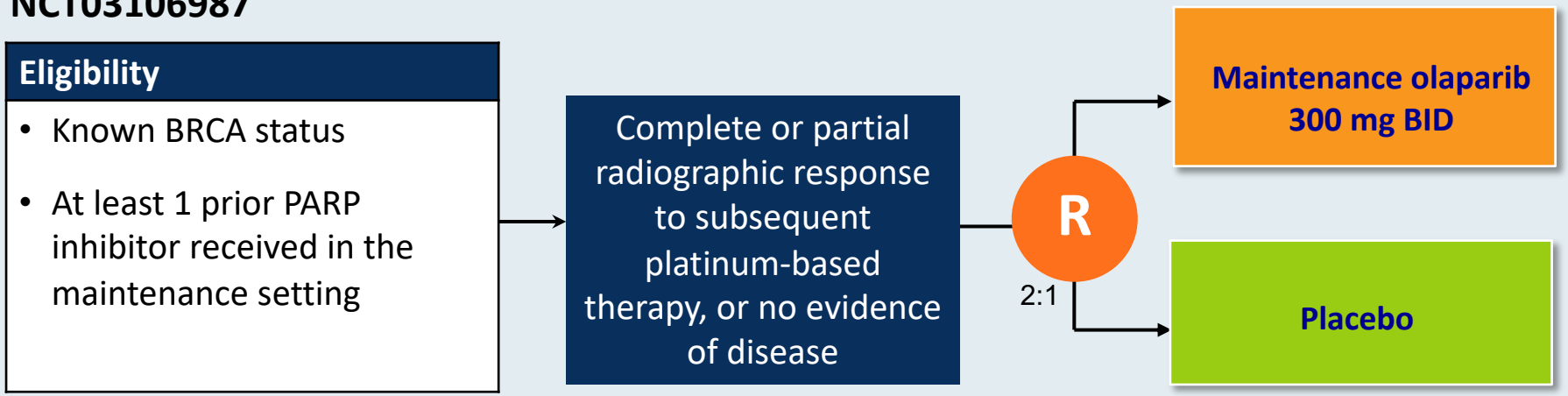
Determinants of Platinum Sensitivity and Resistance

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

Colombo PE et al. *Crit Rev Oncol Hematol* 2014;89(2):207-16.

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

NCT03106987



Primary endpoint: Investigator-assessed progression-free survival

www.clinicaltrials.gov; Accessed August 2020.

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

Niraparib

Indications:
- Maintenance after response to platinum-based therapy
- Irrespective of BRCA status

Pivotal study: ENGOT-OV16/NOVA

Approved: 3/2017

Rucaparib

Indications:
- Maintenance after response to platinum-based therapy
- Irrespective of BRCA status

Pivotal study: ARIEL3

Approved: 4/2018

Olaparib

Indications:
- Maintenance after response to platinum-based therapy
- Irrespective of BRCA status

Pivotal studies: SOLO-2, Study 19

Approved: 8/2017

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

	NOVA[1] (Niraparib)	SOLO-2[2] (Olaparib)	ARIEL3[3] (Rucaparib)
BRCA status	With or without gBRCA mutation	gBRCA mutation (Study 19: +/- gBRCA mutation)	With or without gBRCA mutation
HRD testing	Yes	No	Yes
Tumor assessment schedule	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
Dosing/formulation	300 mg qd	300 mg BID	600 mg BID
No. of prior lines of chemo	2 or more	2 or more	2 or more

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

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

	PARPi	Control	HR
NOVA[1] — Niraparib			
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
SOLO-2[2] — Olaparib			
gBRCA mutation	19.1 mo	5.5 mo	0.30
ARIEL3[3-4] — Rucaparib			
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
$BRCA^{WT}$/High LOH	13.6 mo	5.4 mo	0.32
$BRCA^{WT}$/Low LOH	6.7 mo	5.4 mo	0.58

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

ARIEL4 Trial Evaluating Rucaparib versus Chemotherapy for Relapsed OC with BRCA Mutation Meets Primary Endpoint

Press Release: December 21, 2020

"Today topline data [were announced] from the randomized Phase 3 ARIEL4 study of rucaparib, which met its primary endpoint of improved investigator-assessed progression-free survival (InvPFS) compared to chemotherapy in relapsed ovarian cancer patients with a tumor mutation of BRCA who have received two or more prior lines of chemotherapy.

The ARIEL4 study (NCT02855944) is a Phase 3 multicenter, randomized study evaluating rucaparib versus chemotherapy in platinum-sensitive, partially platinum-sensitive and platinum-resistant patients with relapsed ovarian cancer and a BRCA mutation (inclusive of germline and/or somatic) who have received two or more prior lines of chemotherapy. The primary endpoint of the study is InvPFS, with a step-down analysis from the efficacy population (if significant) to the ITT population."

https://ir.clovisoncology.com/investors-and-news/news-releases/press-release-details/2020/Clovis-Oncologys-Rubraca-rucaparib-Met-the-Primary-Endpoint-of-Significantly-Improving-Progression-Free-Survival-vs.-Chemotherapy-in-the-ARIEL4-Randomized-Phase-3-Treatment-Study-in-Later-line-Ovarian-Cancer-Patients-with-a-BRCA-mutation/default.aspx

FDA-Approved PARP Inhibitors as Monotherapy for Multiple Regimen-Relapsed Disease

Olaparib	Rucaparib	Niraparib
Indications: • 4th-line therapy and beyond • Germline BRCA mutation **Dosing:** • 300 mg BID **Approved: 12/2014**	**Indications:** • 3rd-line therapy and beyond • Germline and/or somatic BRCA mutation **Dosing:** • 600 mg BID **Approved: 12/2016**	**Indications:** • 4th-line therapy and beyond • HRD-positive **Dosing:** • Weight- and platelet count-dependent: 200 or 300 mg QD **Approved: 102/2019**

Olaparib prescribing information, revised 12/2018; Rucaparib prescribing information, revised 4/2018; Niraparib prescribing information, revised 04/2020

Efficacy Summary of PARP Inhibitors for Multiple Regimen-Relapsed OC

	Objective response rate
QUADRA[1] — Niraparib	
HRD-positive	29/189 (15%)
HRD-negative/unknown	8/230 (3%)
BRCA mutation	18/63 (29%)
SOLO-3[2] — Olaparib	
gBRCA mutation	109/151 (72%)
ARIEL2[3-4] — Rucaparib	
gBRCA or sBRCA mutation	57/106 (54%)

[1] Moore KN et al. *Lancet Oncol* 2019;20(5):636-648; [2] Penson RT et al. ASCO 2019;Abstract 5506;
[3] Oza AM et al. *Gynecol Oncol* 2017;147:267-75.

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.

Meet The Professor
Management of Multiple Myeloma

Wednesday, March 3, 2021
5:00 PM – 6:00 PM ET

Faculty

Morie A Gertz, MD, MACP

Moderator

Neil Love, MD

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Thank you for joining us!

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

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