Meet The Professor
Management of Ovarian Cancer

Professor Jonathan A Ledermann
Professor of Medical Oncology
UCL Cancer Institute and UCL Hospitals
London, United Kingdom

Commercial Support

These activities are supported by an educational grant from GlaxoSmithKline.

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Dr Love — Disclosures

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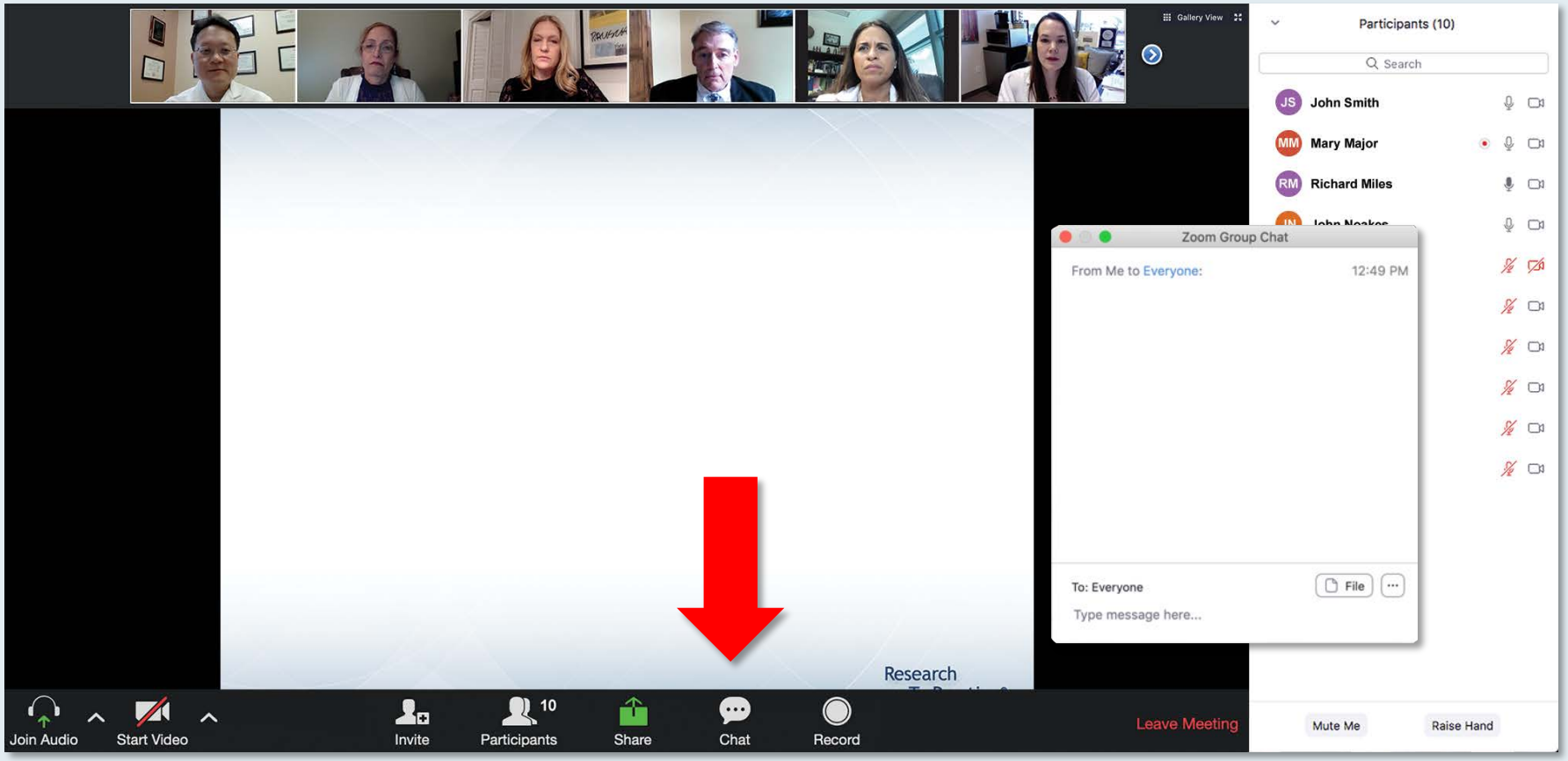

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Familiarizing Yourself with the Zoom Interface

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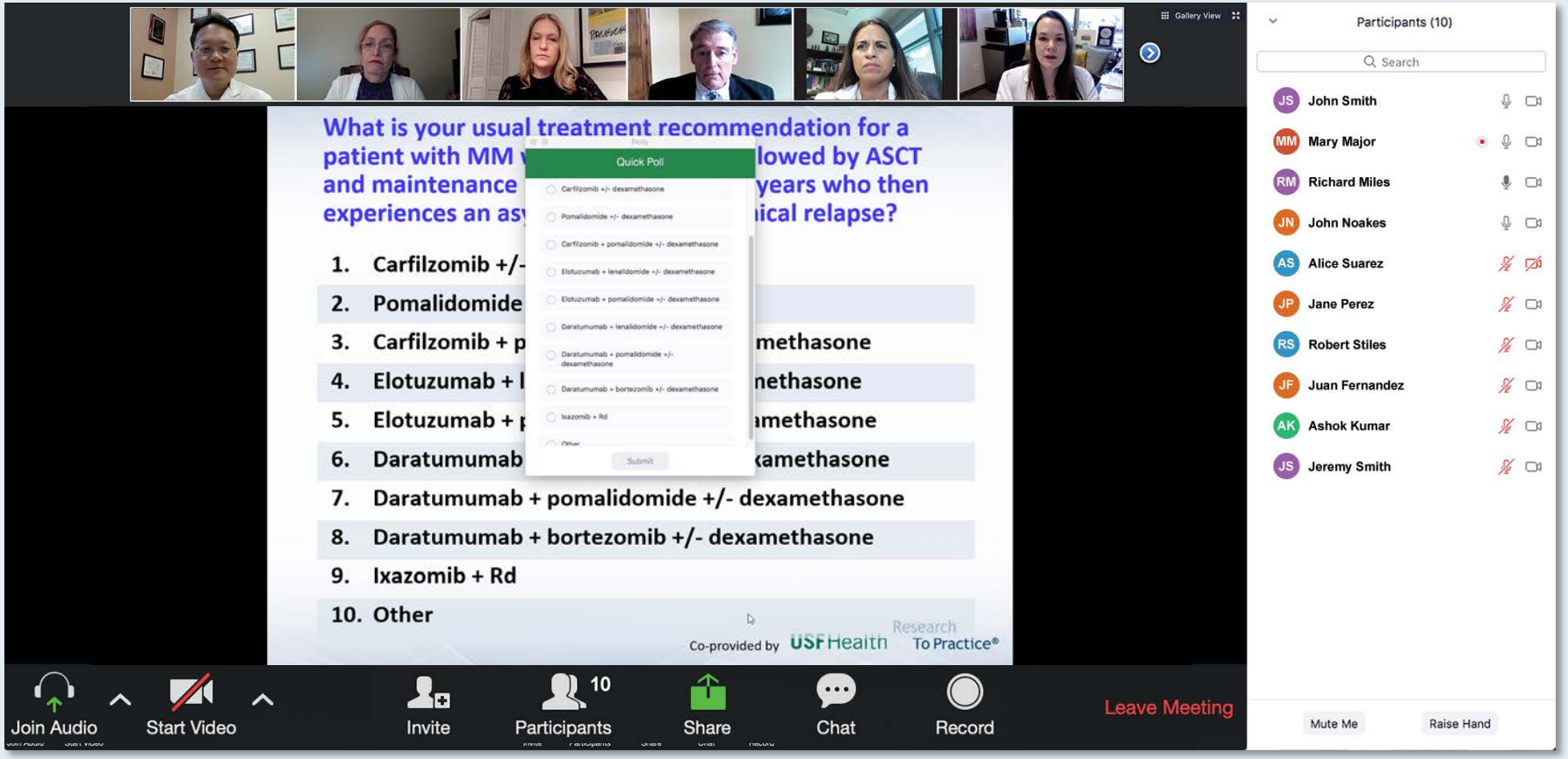

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CME and MOC credit information will be emailed to each participant within 5 business days.

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ONCOLOGY TODAY

WITH DR NEIL LOVE

THE EVOLVING ROLE OF PARP INHIBITION IN THE MANAGEMENT OF OVARIAN CANCER

DR SHANNON WESTIN

MD ANDERSON CANCER CENTER

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

Management of HER2-Positive Breast Cancer

Monday, January 25, 2021
5:00 PM – 6:00 PM ET

Faculty

Erika Hamilton, MD

Moderator

Neil Love, MD

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Year in Review — Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology:

Targeted Therapy for Lung Cancer

Tuesday, January 26, 2021
5:00 PM – 6:00 PM ET

Faculty

Joel W Neal, MD, PhD
Paul K Paik, MD

Moderator

Neil Love, MD

RTP Year in Review 2020

Cases from the Community: Investigators Discuss Emerging Research and Actual Patients with Hepatocellular Carcinoma (Part 1 of a 3-Part Series)

Wednesday, January 27, 2021
5:00 PM – 6:30 PM ET

Faculty

Richard S Finn, MD
Tim Greten, MD
James J Harding, MD
Ahmed Omar Kaseb, MD, CMQ

Moderator

Neil Love, MD

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Multiple Myeloma

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Rafael Fonseca, MD
Jonathan L Kaufman, MD

Moderator

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The patient in the previous scenario receives carboplatin/paclitaxel → olaparib. How long would you typically continue the olaparib if the patient is tolerating it well?
1 year
2 years
Indefinitely
Other


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?
11%
33%
4%
11%
4%
4%

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London, United Kingdom

Meet The Professor Program Participating Faculty

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Director, Medical Oncology and the Oncology Sexual Health Program
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Dana-Farber Cancer Institute
Professor of Medicine
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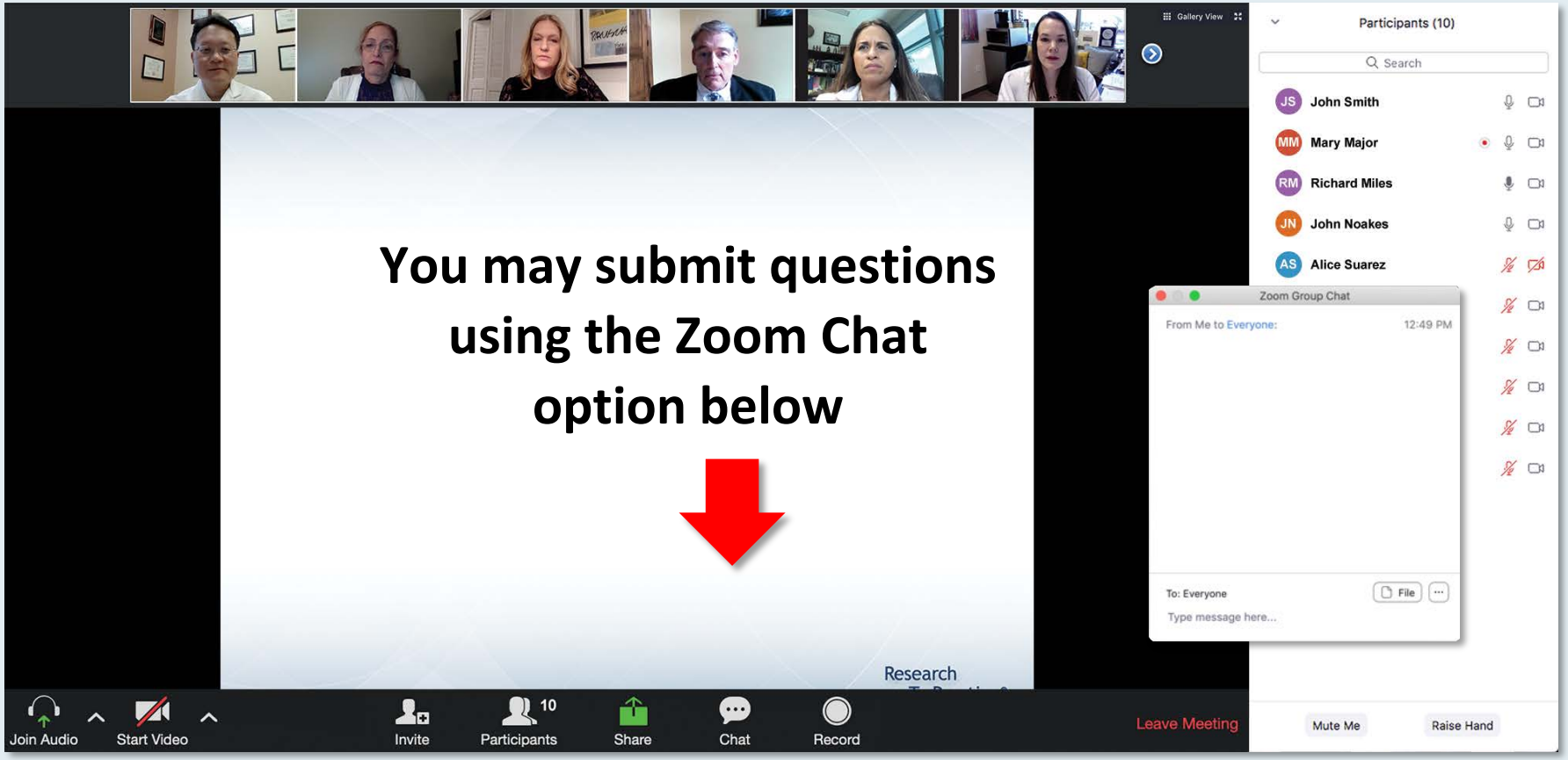

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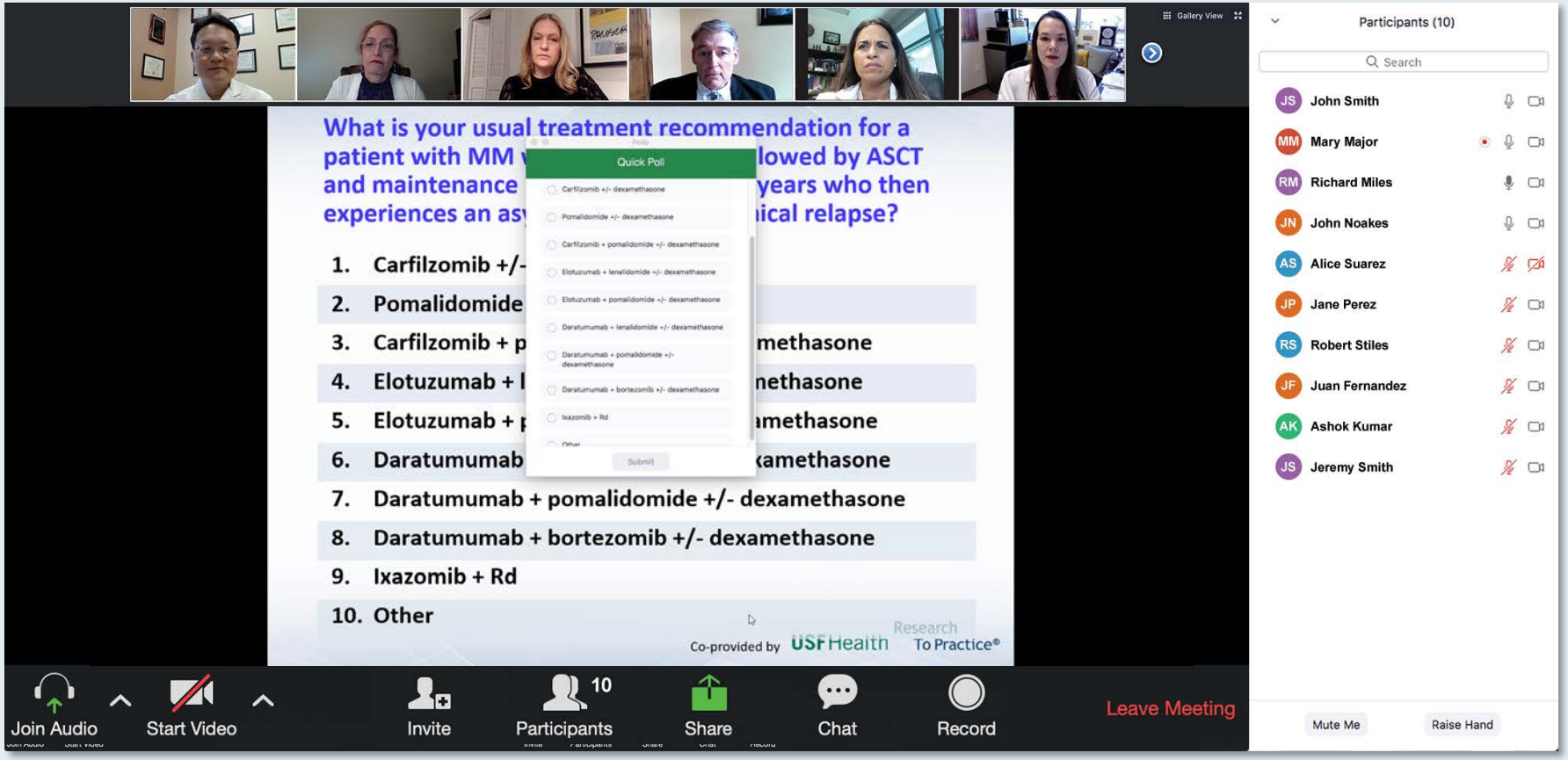

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Meet The Professor with Prof Ledermann

MODULE 1: Cases from Drs Bachow and Chen

- Dr Chen: A 42-year-old woman with Stage IIIA high-grade serous fallopian tube carcinoma – BRCA1 mutation
  - Part 1
  - Part 2
- Dr Chen: A 72-year-old woman with Stage IIIC ovarian cancer (OC) – germline BRCA wild type
  - Part 1
  - Part 2
- Dr Bachow: A 66-year-old woman with high-grade Stage IIIC papillary serous OC – Intermediate tumor mutation burden, BRCA2 VUS
- Dr Bachow: A 49-year-old woman with recurrent platinum-resistant OC
- Dr Bachow: A 41-year-old woman with early-stage endometrioid OC – ER-positive, BRCA wild type

MODULE 2: Journal Club with Prof Ledermann

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

MODULE 4: Key Recent Papers

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Case Presentation – Dr Chen: A 42-year-old woman with Stage IIIA high-grade serous fallopian tube carcinoma – germline BRCA1 mutation, Part 1

Dr Gigi Chen

- Postpartum right fallopian tube mass (CA125: 110) → debulking surgery (R0)
- Diagnosed with Stage IIIA high-grade serous carcinoma with paraaortic LN involvement
- Genetic testing: Germline BRCA1 mutation, maternal grandmother with breast and colon cancer
- Carboplatin/paclitaxel x 6 → Maintenance olaparib
  - Discussed bevacizumab in addition to olaparib but childcare demands preclude frequent office visits

Questions

- What would be the best adjuvant chemotherapy for this young, very healthy woman? Is there a role for IV/IP chemotherapy versus IV chemotherapy?
- What is the role of maintenance therapy for her, and what would be the best maintenance therapy in light of her BRCA1 positivity?

Case Presentation – Dr Chen: A 42-year-old woman with Stage IIIA high-grade serous fallopian tube carcinoma – BRCA1 mutation, Part 2

Dr Gigi Chen

- Postpartum right fallopian tube mass (CA125: 110) → debulking surgery (R0)
- Diagnosed with Stage IIIA high-grade serous carcinoma with paraaortic LN involvement
- Genetic testing: BRCA1 mutation, maternal grandmother with breast and colon cancer
- Carboplatin/paclitaxel x 6 → Maintenance olaparib
  - Discussed bevacizumab in addition to olaparib but childcare demands preclude frequent office visits
  - ***Olaparib dose reduced from 300 mg BID to 200 mg BID due to GI side effects, hypertension***

Questions

- ***Does the dose reduction of olaparib compromise its efficacy?***

Case Presentation – Dr Chen: A 72-year-old woman with Stage IIIC ovarian cancer – Germline BRCA wild type – Part 1

Dr Gigi Chen

- Presents with painful abdominal mass → EGD/colonoscopy: Negative
- PET/CT: Peritoneal carcinomatosis, CA125: 116
- Debulking surgery: Stage IIIC ovarian cancer, germline BRCA wildtype
- NGS: LOH <16%. MSS, TMB 1, BRIPI rearrangement intron 2 and BRAF deletion intron 3-intron 4, MDM2, MYC amplification, RAD21 amplification and TP53
- Carboplatin/paclitaxel x 6
  - Currently discussing maintenance therapy options

Questions

- Since she is gBRCA wildtype with LOH <16% and has an excellent performance status, what would be the best treatment at this point?
- Would you offer maintenance therapy, and if so, what would be best – Maintenance bevacizumab versus a PARP inhibitor versus observation?

Case Presentation – Dr Chen: A 72-year-old woman with Stage IIIC ovarian cancer – Germline BRCA wild type – Part 2

Dr Gigi Chen

- Presents with painful abdominal mass → EGD/colonoscopy: Negative
- PET/CT: Peritoneal carcinomatosis, CA125: 116
- Debulking surgery: Stage IIIC ovarian cancer, germline BRCA wildtype
- NGS: LOH <16%. MSS, TMB 1, BRIPI rearrangement intron 2 and BRAF deletion intron 3-intron 4, MDM2, MYC amplification, RAD21 amplification and TP53
- Carboplatin/paclitaxel x 6
  - Currently discussing maintenance therapy options

Comments

- ***Niraparib dosing***

Case Presentation – Dr Bachow: A 66-year-old woman with high-grade Stage IIIC papillary serous ovarian cancer – Intermediate TMB, BRCA2 VUS

Dr Spencer Bachow

- PMH of node-positive breast IDC 20 years ago s/p lumpectomy, RT and adjuvant chemotherapy and hormonal therapy
- 11/2019: TAH-SPO, lymphadenectomy and washings and diagnosed with high-grade Stage IIIC papillary serous ovarian cancer
- TMB: Intermediate, BRCA2 VUS; Ejection fraction: 35-40%
- Carboplatin/paclitaxel/bevacizumab x 6 → PET/CT: Negative → Maintenance niraparib

Questions

- In patients with serous ovarian carcinomas, when do you use the combination of olaparib and bevacizumab as maintenance therapy? Would you only use it in patients that have a germline BRCA mutation or HRD-positive patients?
- Is anybody using bevacizumab with carboplatin and paclitaxel for the chemotherapy and then in the maintenance setting withholding bevacizumab and using the PARP inhibitor alone, especially in patients that are BRCA negative and HRD negative?

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Case Presentation – Dr Bachow: A 49-year-old woman with recurrent, platinum-resistant ovarian cancer

Dr Spencer Bachow

- 2018: S/p cytoreductive exploratory laparotomy with hysterectomy and BSO → carboplatin/paclitaxel x 6 for Stage IIC clear cell ovarian cancer
- Genetic testing: Negative; positive family history of breast and ovarian cancer
- 10/2018: CA125 rising, PET/CT: Focal bowel wall thickening
  - Paracentesis of ascites: Clear cell ovarian cancer
- Liposomal doxorubicin/bevacizumab x 6 → Maintenance bevacizumab
- CA125 rising, PET/CT: Relapse → EBRT to site of relapse
- Declined clinical trial, not a candidate for ICI + PARPi
- Gemcitabine x 6 → PET/CT: NED → Maintenance niraparib
  - After 1 month, CA125 rising, paracentesis of new-onset ascites: Clear cell carcinoma
- Pembrolizumab + niraparib 200 mg qd

Questions

- In what clinical scenarios can you make an argument for giving a checkpoint inhibitor to a patient with advanced platinum-resistant ovarian cancer? Is it really just the patients that have a clear cell histology? Is anybody giving pembrolizumab off label with a PARP inhibitor?
- What dose of niraparib would you use — 200 mg or 300 mg?

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Case Presentation – Dr Bachow: A 41-year-old woman with early-stage endometrioid ovarian cancer – ER-positive, BRCA wild type

Dr Spencer Bachow

- 6/2020: s/p TAH-SPO and diagnosed with grade 2 endometrioid ovarian cancer, with no evidence of metastatic disease
  - ER-positive, BRCA wildtype, HRD-negative, MSH3 VUS
- Carboplatin/paclitaxel switched to carboplatin/docetaxel x 6 due to hypersensitivity reactions
- Second-look surgery: No residual disease
- Plans to begin niraparib

Questions

- In patients with early-stage endometrioid ovarian carcinomas, can maintenance therapy with anti-estrogen therapy (eg, aromatase inhibitor) be considered in lieu of a PARP inhibitor?
- What is the risk of developing MDS/AML associated with PARP inhibitor treatment?
- What do you do with a patient who has a microsatellite instability mutation variant of unknown significance, such as MSH3, PMS2?

Meet The Professor with Prof Ledermann

MODULE 1: Cases from Drs Bachow and Chen

MODULE 2: Journal Club with Prof Ledermann

- Role of PARP inhibitors beyond ovarian cancer with BRCA mutation: Definition of HRD
- Concordance between CA-125 and disease progression in the SOLO-2 trial
- Can survival outcomes be predicted? Secondary endpoints in first-line maintenance olaparib trials
  - SOLO-1 and PAOLA-1
- Patient experiences with genetic testing in ovarian cancer
- ICON8: Neoadjuvant carboplatin/paclitaxel regimens for ovarian cancer
- SOLO-2: Final survival analysis, patterns of progression, subsequent therapy and risk of MDS/AML
- Meta-analysis of MDS/AML in patients treated with PARP inhibitors
- Accuracy of physician estimates for survival time for women with recurrent ovarian cancer
- Perceptions, expectations and experiences of patients with gynecologic cancer

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

MODULE 4: Key Recent Papers

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REVIEW

CURRENT OPINION

Role of Poly (ADP-Ribose) Polymerase inhibitors beyond BReast CAncer Gene-mutated ovarian tumours: definition of homologous recombination deficiency?

Charlie Gourley[a], *Rowan E. Miller*[b,c], *Robert L. Hollis*[a], *and Jonathan A. Ledermann*[b,d]

***Curr Opin Oncol* 2020;32(5):442-50.**

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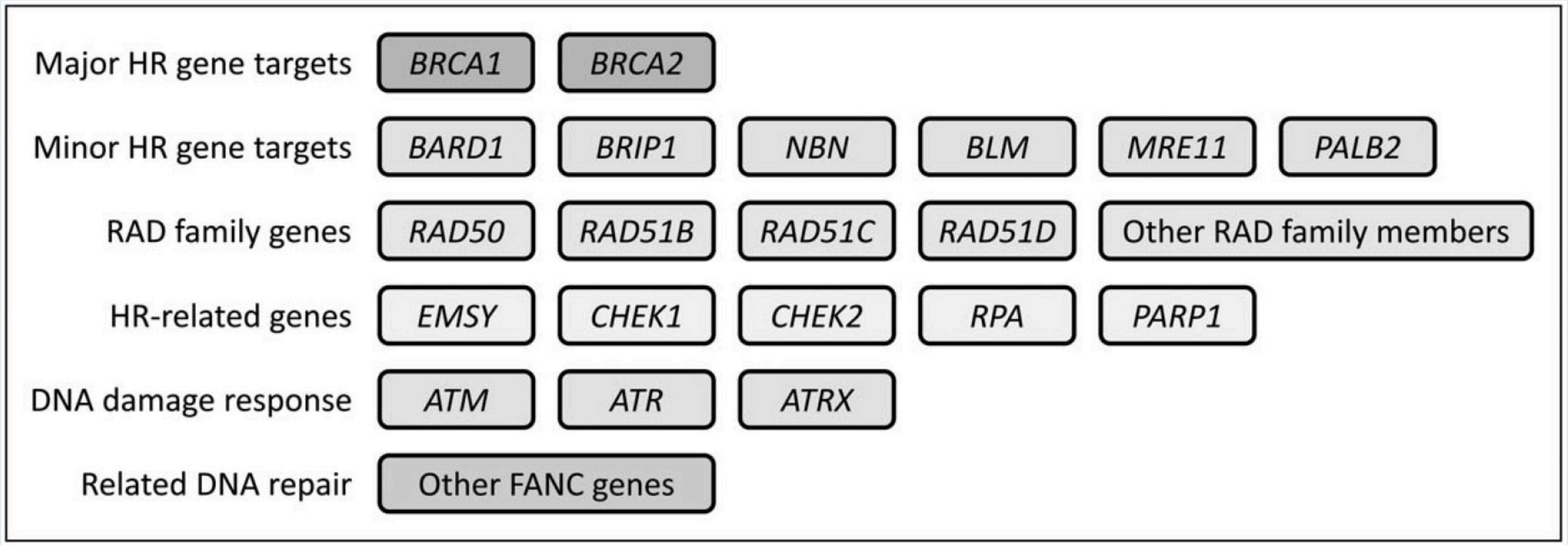
Targets of Genomic Disruption Related to Homologous Recombination Deficiency



Gourley C et al. *Curr Opin Oncol* 2020;32(5):442-50.

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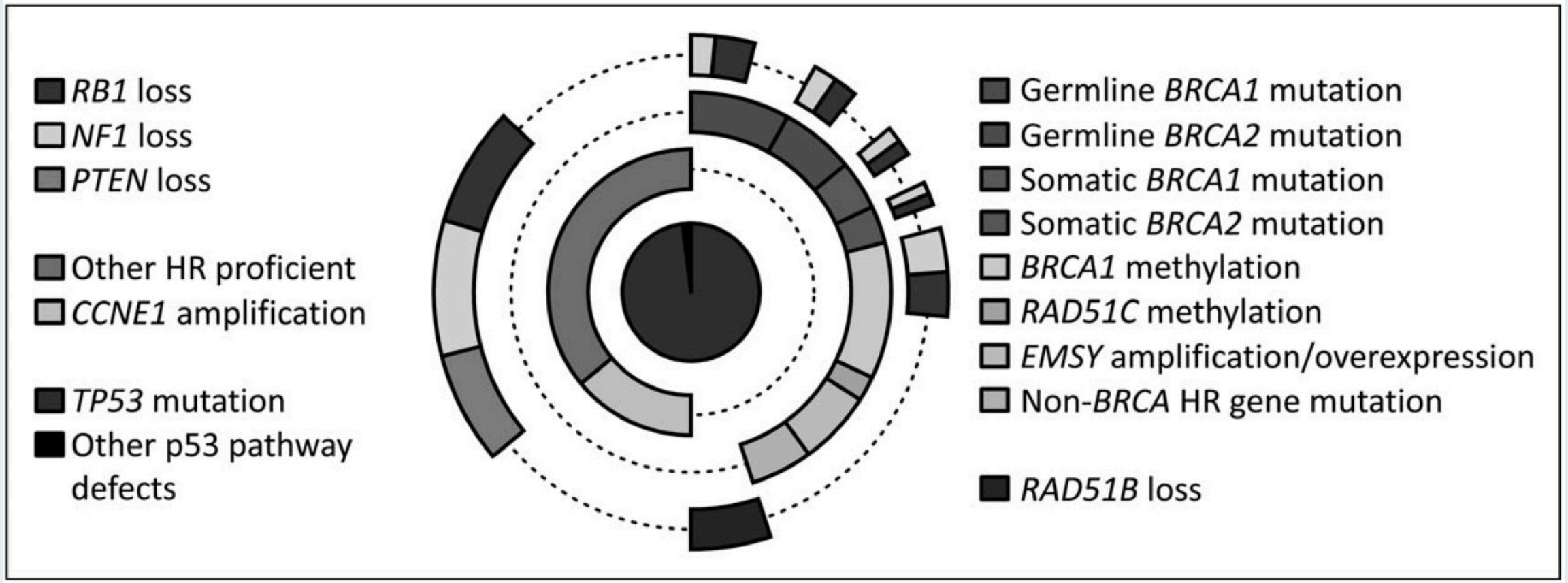
Onion Plot Showing Molecular Subgroups of HGSOC



Gourley C et al. *Curr Opin Oncol* 2020;32(5):442-50.

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European Journal of Cancer 139 (2020) 59–67

ELSEVIER

journal homepage: www.ejcancer.com

Original Research

Concordance between CA-125 and RECIST progression in patients with germline *BRCA*-mutated platinum-sensitive relapsed ovarian cancer treated in the SOLO2 trial with olaparib as maintenance therapy after response to chemotherapy☆

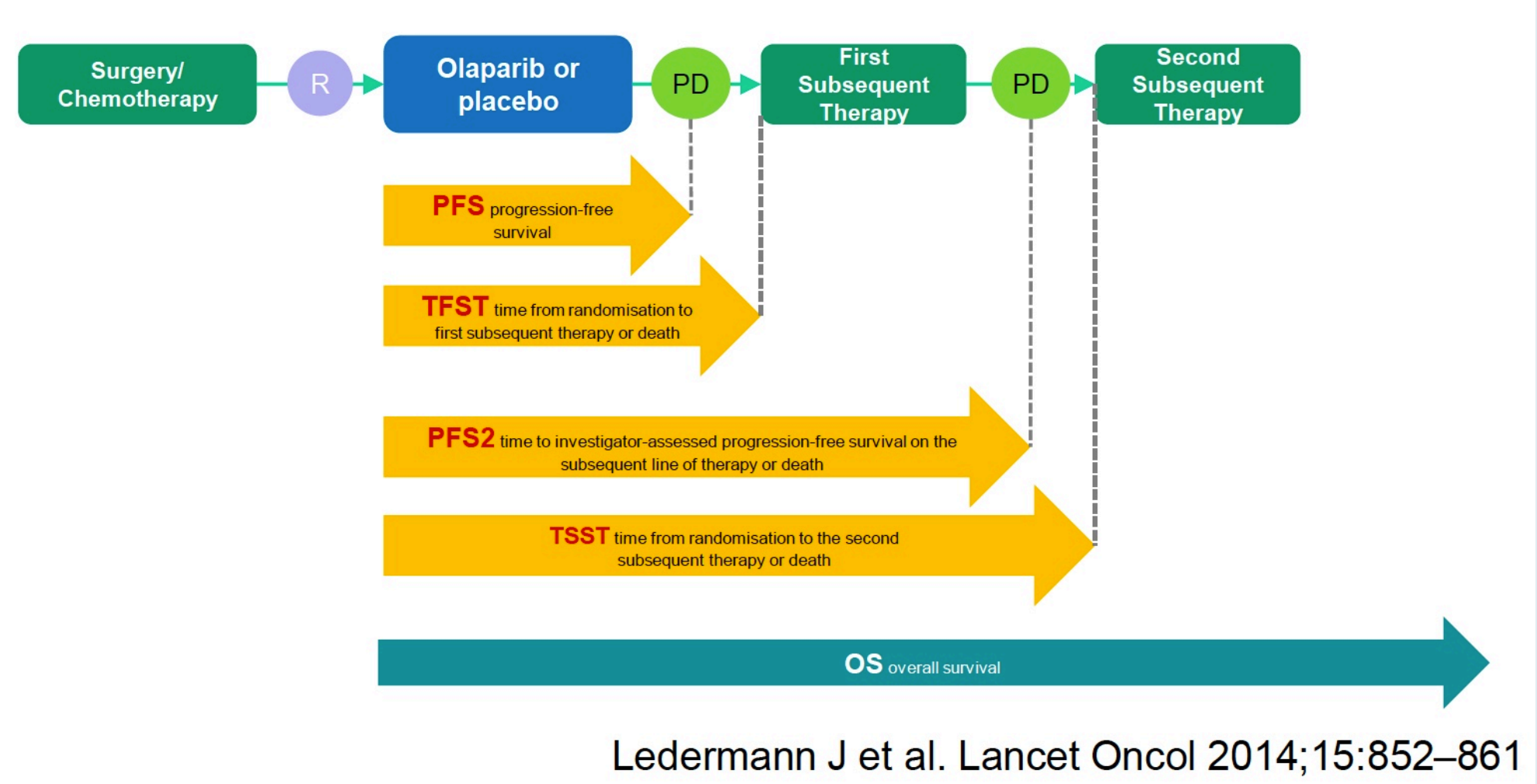
Angelina Tjokrowidjaja [a,b,*], Chee K. Lee [a,b], Michael Friedlander [c], Val Gebski [a], Laurence Gladieff [d], Jonathan Ledermann [e], Richard Penson [f], Amit Oza [g], Jacob Korach [h], Tomasz Huzarski [i], Luis Manso [j], Carmela Pisano [k], Rebecca Asher [a], Sarah J. Lord [a,l], Se Ik Kim [m], Jung-Yun Lee [n], Nicoletta Colombo [o,p], Tjoung-Won Park-Simon [q], Keiichi Fujiwara [r], Gabe Sonke [s], Ignace Vergote [t,u], Jae-Weon Kim [m], Eric Pujade-Lauraine [v,w]

Can Survival Outcomes Be Predicted: Prolonged Follow Up and Secondary Endpoints in First-Line Olaparib Maintenance Trials in Ovarian Cancer

Ledermann JA et al.

ESMO 2020;Discussant.

Secondary Endpoints After Progression-Free Survival
A Surrogate for Overall Survival

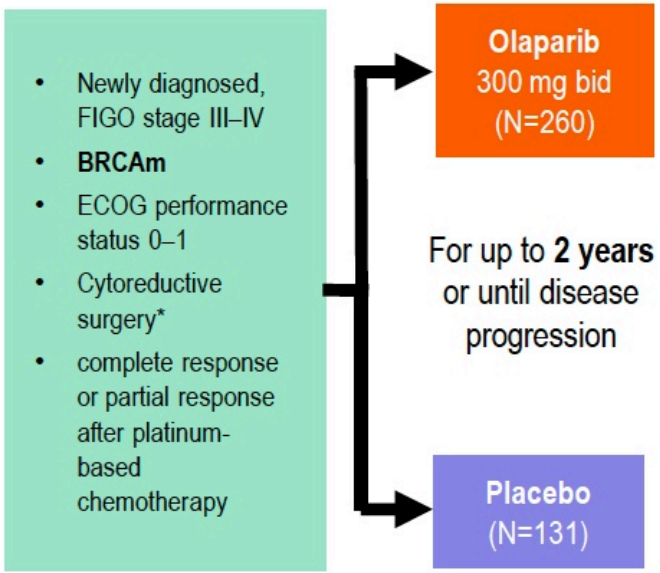


Ledermann J et al. Lancet Oncol 2014;15:852–861

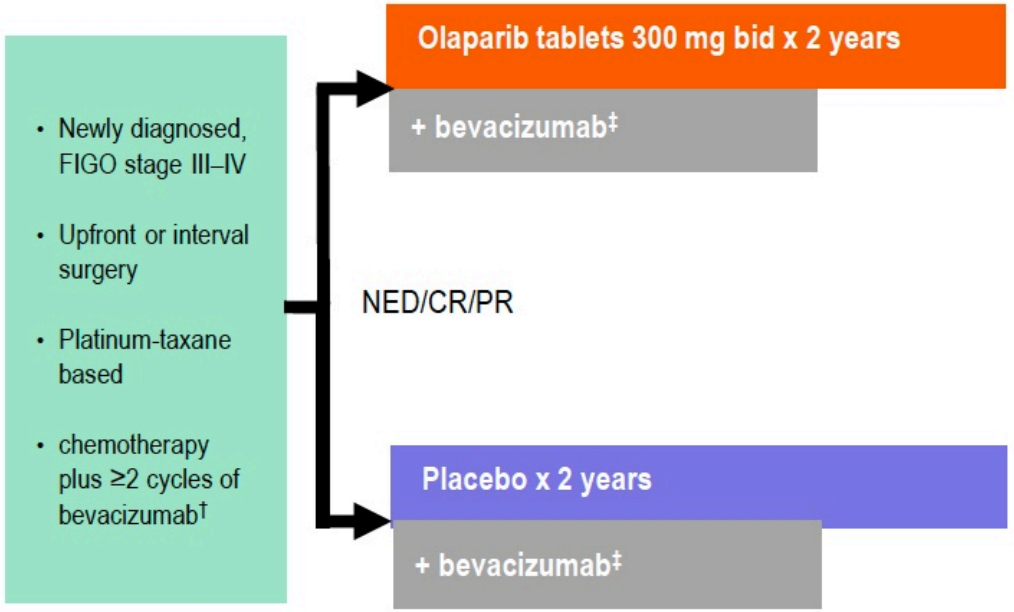
Lederman JA. ESMO 2020;Discussant.

First-Line Olaparib Maintenance Trials in Newly Diagnosed Ovarian Cancer

SOLO1 Trial



PAOLA-1/ENGOT-ov25 trial



Primary endpoint

- PFS (investigator-assessed)

Secondary endpoints included

- PFS2, TSST
- Safety
- OS

Moore K, et al. *N Engl J Med.* 2018;379:2495-2505
Ray-Coquard I *et al. N Engl J Med* 2019;381:2416–28

Lederman JA. ESMO 2020;Discussant.

VIRTUAL 2020 ESMO congress

Secondary Event Analysis in SOLO1

Looking to the future…… not quite overall survival

	PFS		PFS2		TSST	
	Olaparib (n=260)	Placebo (n=131)	Olaparib (n=189)	Placebo (n=131)	Olaparib (n=260)	Placebo (n=131)
Events, n (%)	118 (45)	100 (76)	80 (31)	61 (47)	95 (37)	77 (59)
Event free at 5 years, %	48	21	64	41	62	36
Median, months	56.0	13.8	NR	42.1	NR	40.7
	HR 0.33 (95% CI 0.25–0.43)		HR 0.46 (95% CI 0.33–0.65)		HR 0.46 (95% CI 0.34–0.63)	

PFS2 takes account of second line treatment and cross-over to a PARP inhibitor

- At 5 years, 64% patients who were treated with first line olaparib remain event-free
- 41% patients initially on control arm remain event-free

Lederman JA. ESMO 2020;Discussant.

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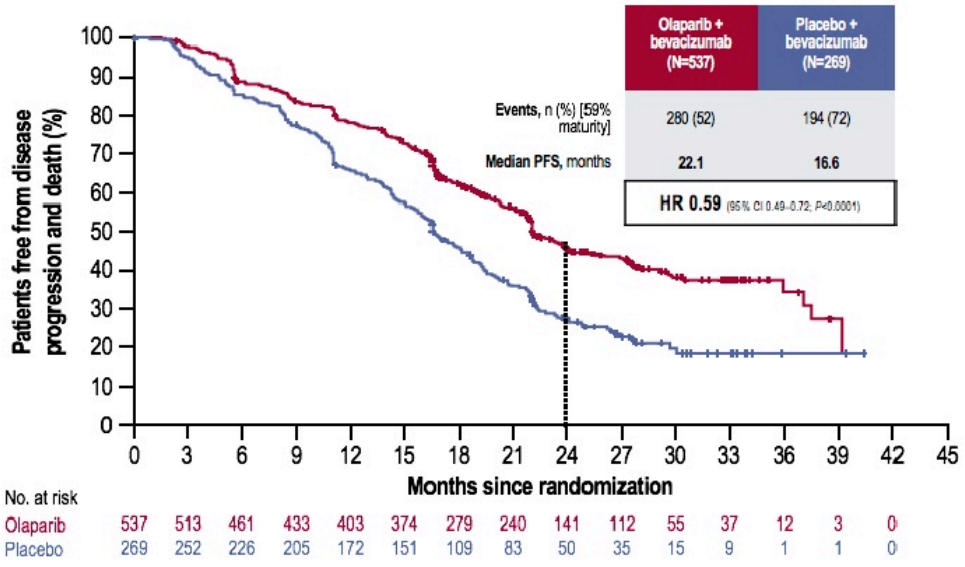
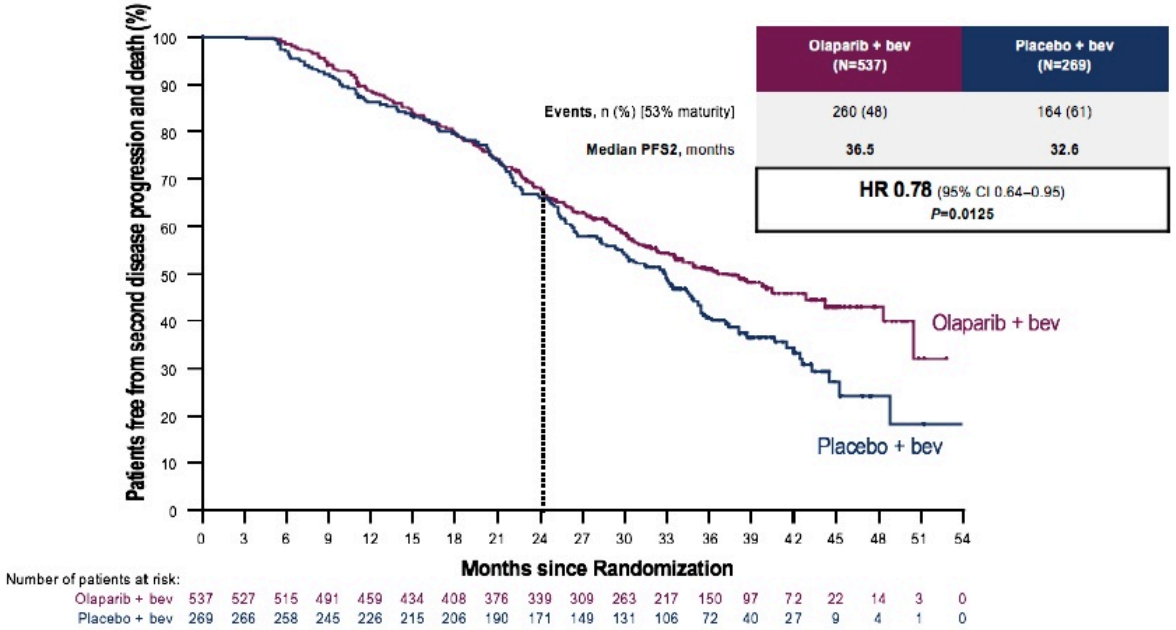
PAOLA-1 Progression-Free Survival events - Intent to Treat Analysis

PFS



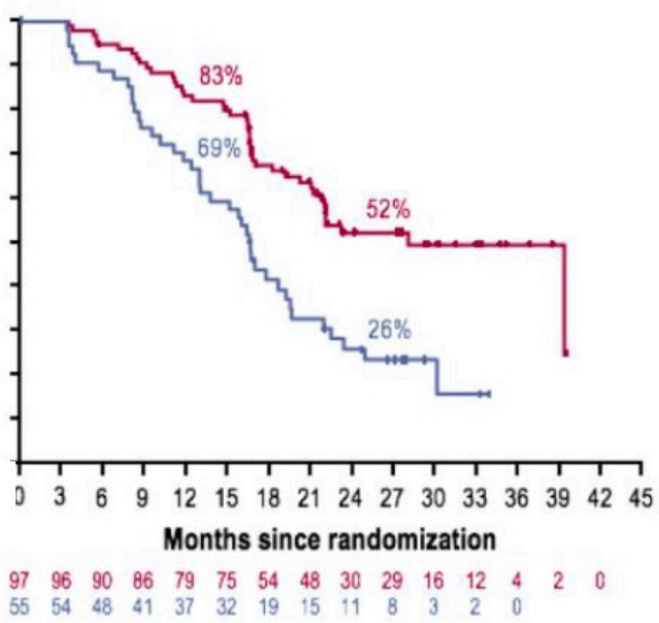
PFS2



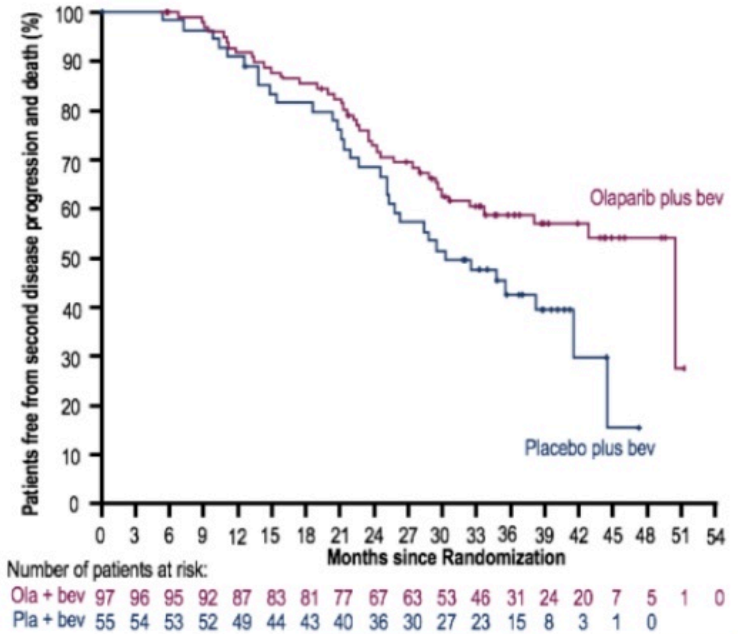
Lederman JA. ESMO 2020;Discussant.

PAOLA 1- Progression-Free Survival Events

PFS and PFS2 in the BRCA^{wt} HRD+ve subgroup



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



	Olaparib + bev (n=97)	Placebo + bev (n=55)
Events, n (%)	41 (42)	33 (60)
Median PFS2, months	50.3†	30.1
HR 0.60 (95% CI 0.38–0.96)		

Med months	Olaparib + bev (N=97)	Placebo + bev (N=55)
mPFS (mths)	28.1	16.6
mPFS2 (mths)	50.3	30.1

Lederman JA. ESMO 2020;Discussant.

PFS2- Secondary Events in PAOLA-1

- PFS2 confirms the benefit of olaparib + bevacizumab versus placebo/bevacizumab alone in mBRCA tumours
- mBRCA and BRCA$^{wt/}$HRD+ve have similar PFS2 outcomes with some 'catch up' in second-line treatment
  - 27% placebo group crossed over to PARP inhibitor at recurrence
  - med PFS2 still less than first-line olaparib/bevacizumab
- ITT median PFS2 is similar in both arms; results are driven by mBRCA and BRCA$^{wt/}$HRD+ve patients

Lederman JA. ESMO 2020;Discussant.

VIRTUAL 2020 ESMO congress

Do these results predict the future?

SOLO 1 has median FU 5 years with a mature control arm event rate of 76%

In the olaparib arm only a small percentage increase in events in last 2 years from 39% to 45%

Are there subgroups with different outcomes?

- CR v PR patients?
- BRCA1 v BRCA2?

Appears hopeful that a significant number of patients may be cured

PAOLA-1 Follow up is less mature; both arms show similar median PFS2 outcome

Improvements very much driven by mBRCA and HRD groups where PFS2 benefit persists

PFS2 in both trials demonstrates that first-line olaparib maintenance leads to prolonged clinical benefit

Lederman JA. ESMO 2020;Discussant.

RTP RESEARCH TO PRACTICE

Original research

INTERNATIONAL JOURNAL OF GYNECOLOGICAL CANCER

Mainstreamed genetic testing in ovarian cancer: patient experience of the testing process

Laura McLeavy ,[1] Belinda Rahman,[1] Rebecca Kristeleit,[2] Jonathan Ledermann,[2] Michelle Lockley,[2,3] Mary McCormack,[2] Tim Mould,[2] Lucy Side,[4] Anne Lanceley[1]

Int J Gynecol Cancer 2020;30(2):221-6.

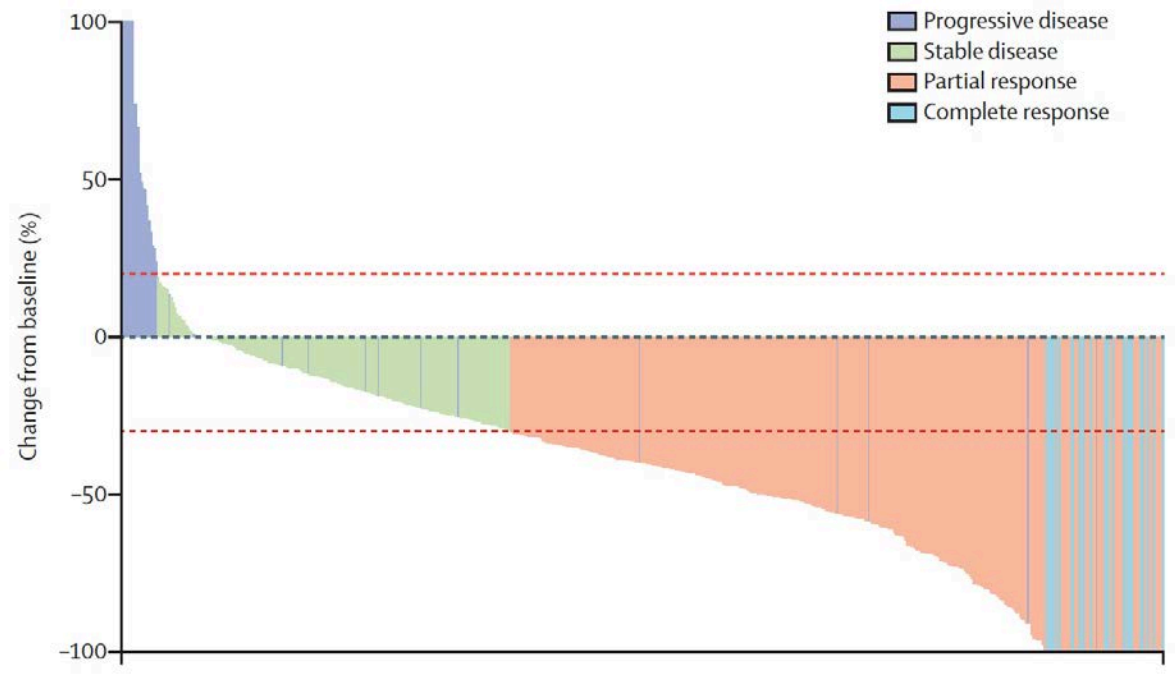
Objective responses to first-line neoadjuvant carboplatin–paclitaxel regimens for ovarian, fallopian tube, or primary peritoneal carcinoma (ICON8): post-hoc exploratory analysis of a randomised, phase 3 trial

Robert D Morgan, Iain A McNeish, Adrian D Cook, Elizabeth C James, Rosemary Lord, Graham Dark, Rosalind M Glasspool, Jonathan Krell, Christine Parkinson, Christopher J Poole, Marcia Hall, Dolores Gallardo-Rincón, Michelle Lockley, Sharadah Essapen, Jeff Summers, Anjana Anand, Abel Zachariah, Sarah Williams, Rachel Jones, Kate Scatchard, Axel Walther, Jae-Weon Kim, Sudha Sundar, Gordon C Jayson, Jonathan A Ledermann, Andrew R Clamp

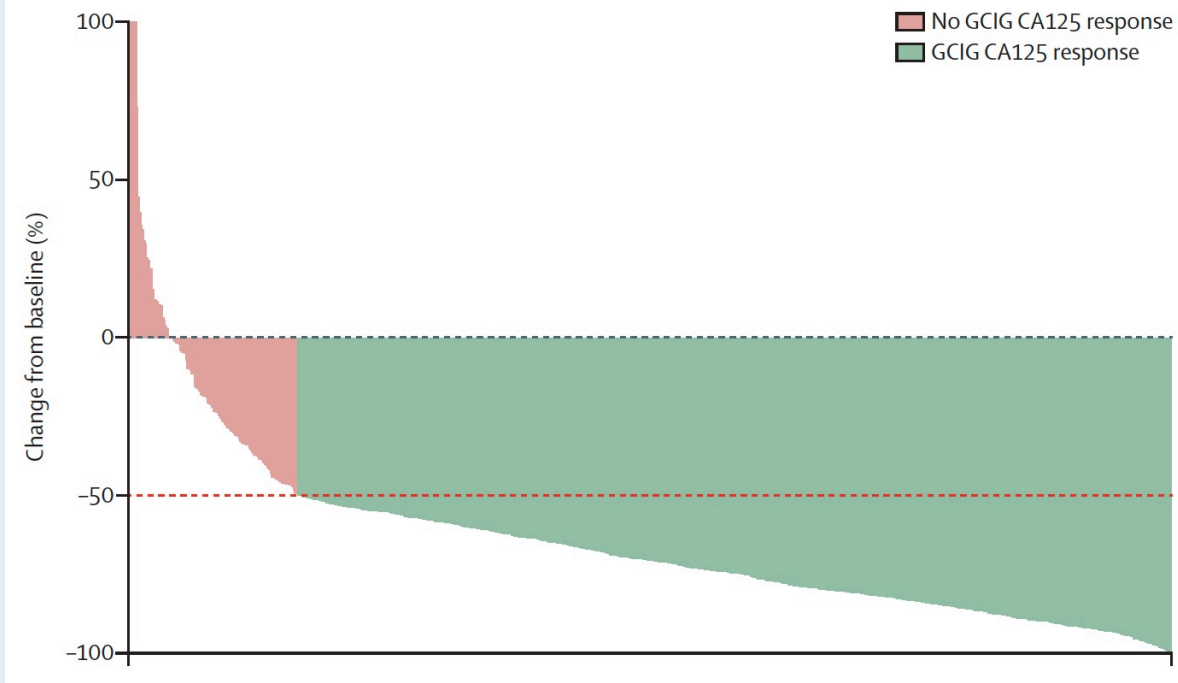
***Lancet Oncol* 2020;[Online ahead of print].**

ICON8: Waterfall Plots

Percentage Change in RECIST Marker Lesions and GCIG CA125 Level



Percentage Change in RECIST Marker Lesions from Baseline, Capped at 100%



Morgan RD et al. *Lancet Oncol* 2020:S1470-2045(20)30591-X.

RTP RESEARCH TO PRACTICE

Final Overall Survival (OS) Results from SOLO2/ENGOT-ov21: A Phase III Trial Assessing Maintenance Olaparib in Patients (pts) with Platinum-Sensitive, Relapsed Ovarian Cancer and a BRCA Mutation

Poveda A et al.

ASCO 2020;Abstract 6002.

Final overall survival results from SOLO2/ENGOT-ov21: a Phase III trial assessing maintenance olaparib in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA mutation

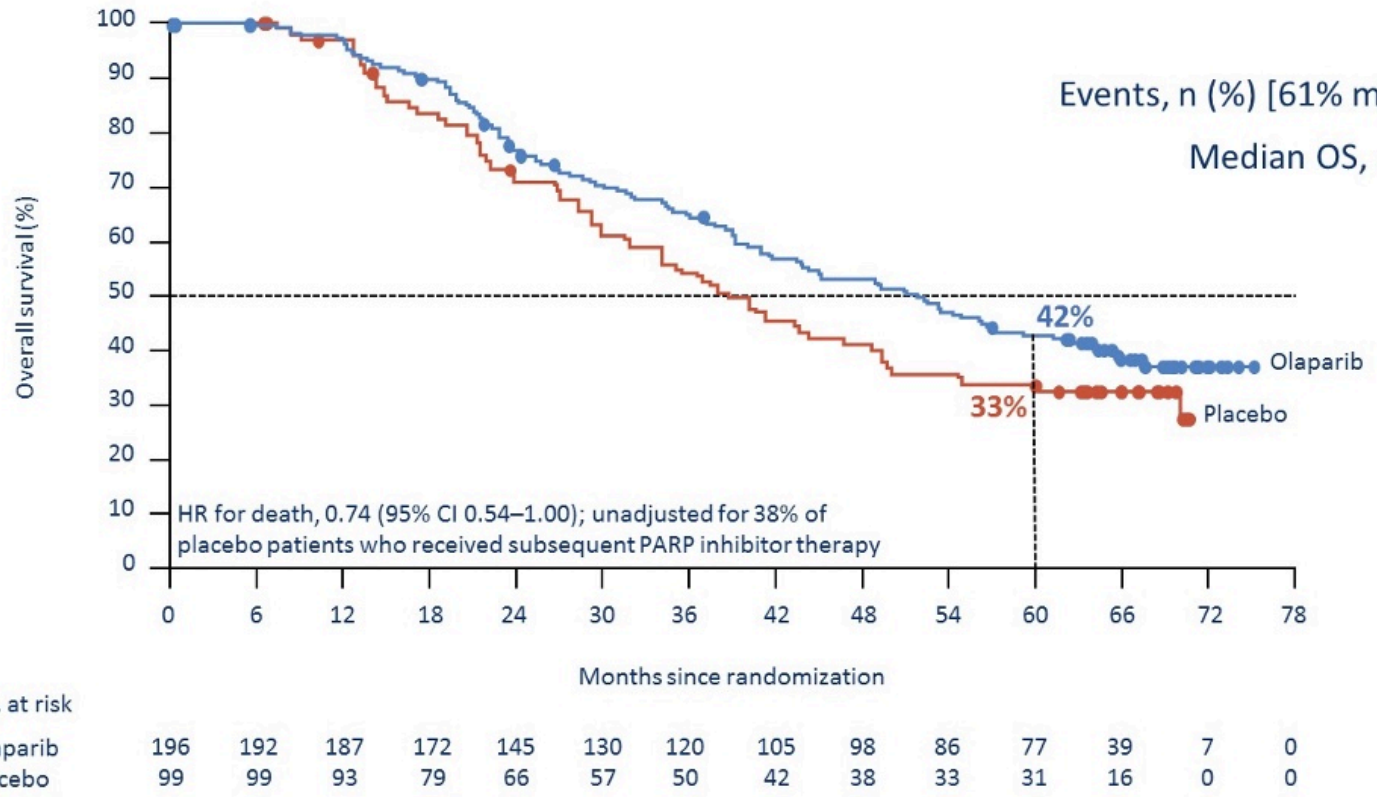
Andrés Poveda,[1] Anne Floquet,[2] Jonathan Ledermann,[3] Rebecca Asher,[4] Richard Penson,[5] Amit Oza,[6] Jacob Korach,[7] Tomasz Huzarski,[8] Sandro Pignata,[9] Michael Friedlander,[10] Alessandra Baldoni,[11] Tjoung-Won Park-Simon,[12] Gabe Sonke,[13] Alla Lisyanskaya,[14] Jae-Hoon Kim,[15] Elias Abdo Filho,[16] Ignace Vergote,[17] Phil Rowe,[18] Eric Pujade-Lauraine[19]

[1]Initia Oncology, Hospital Quirónsalud, Valencia and GEICO, Spain; [2]Institut Bergonié, Comprehensive Cancer Centre, Bordeaux and GINECO, France; [3]UCL Cancer Institute, University College London, London and NCRI, UK; [4]University of Sydney, Camperdown, Sydney, Australia; [5]Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA; [6]Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada; [7]Sheba Medical Center, Tel Aviv University, Tel Hashomer and ISGO, Israel; [8]Department of Genetics and Pathology, Pomeranian Medical University and Read-Gene SA, Grzepnica, Szczecin, Poland; [9]Istituto Nazionale Tumori 'Fondazione G Pascale', IRCCS, Napoli and MITO, Italy; [10]University of New South Wales Clinical School, Prince of Wales Hospital, Randwick, Australia; [11]Istituto Oncologico Veneto, IOV-IRCCS, Padova and MANGO, Italy; [12]Department of Gynaecology and Obstetrics, Hannover Medical School, Hannover and AGO, Germany; [13]The Netherlands Cancer Institute, Amsterdam and DGOG, The Netherlands; [14]St Petersburg City Clinical Oncology Dispensary, St Petersburg, Russia; [15]Yonsei University College of Medicine, Seoul, South Korea; [16]Instituto do Câncer do Estado São Paulo-Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil; [17]University Hospital Leuven, Leuven Cancer Institute, Leuven and BGOG, Belgium; [18]AstraZeneca, Cambridge, UK; [19]Université Paris Descartes, AP-HP, Paris, France

ClinicalTrials.gov identifier: NCT01874353. This study was sponsored by AstraZeneca and is part of an alliance between AstraZeneca and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA

SOLO-2: Final Analysis of OS

Median OS improved by 12.9 months with maintenance olaparib over placebo, despite 38% of placebo patients receiving subsequent PARP inhibitor therapy



	Olaparib (N=196)	Placebo (N=99)
Events, n (%) [61% maturity]	116 (59)	65 (66)
Median OS, months	51.7	38.8
HR 0.74		
95% CI 0.54–1.00; *P*=0.0537		

38% of placebo patients and 10% of olaparib patients received subsequent PARP inhibitor therapy*

OS analysis per eCRF in the full analysis set†
HR 0.70 (95% CI 0.52–0.96)

OS analysis in the Myriad gBRCAm subgroup†
HR 0.71 (95% CI 0.52–0.97)

*According to medical review of PARP inhibitor use; †Not adjusted for multiplicity
CI, confidence interval

Poveda A et al. ASCO 2020;Abstract 6002.

SOLO-2: AEs of Special Interest – Primary and Final Analyses

	Olaparib (N=195)		Placebo (N=99)	
	Primary	Final	Primary	Final
Mean total treatment duration (SD), months	17.4 (9.8)	**29.1 (24.7)**	9.0 (8.1)	**13.1 (18.6)**
MDS/AML, n (%)	4 (2)	**16 (8)**	4 (4)	**4 (4)**
During the safety follow-up period (TEAE)		**7 (4)**		**0**
After the safety follow-up period (non-TEAE)		**9 (5)**		**4 (4)**
Pneumonitis, n (%)	3 (2)	**3 (2)**	0	**0**

MDS/AML

- **Actively solicited throughout study treatment and follow-up**
- **Incidences should be interpreted in the context of their late onset‡ and the longer OS observed with olaparib vs placebo**
- **Association with the number of prior platinum regimens, olaparib treatment and other potential risk factors is being explored**

In patients with newly diagnosed ovarian cancer and a BRCAm, at median follow-up of 65 months, MDS/AML occurred in 1% of olaparib patients and no placebo patients[1]

*Includes AEs that occurred outside safety follow-up period (during treatment and up to 30 days after discontinuation); †New primary malignancies (excluding hematologic malignancies) occurred in one olaparib patient (1%) and one placebo patient (1%) in the primary analysis, and in eight olaparib patients (4%) and two placebo patients (2%) in the final analysis; ‡After the safety follow-up period
AML, acute myeloid leukemia; MDS, myelodysplastic syndrome

1. AstraZeneca data on file for the SOLO1 trial (NCT01844986)

Poveda A et al. ASCO 2020;Abstract 6002.

Patterns of Progression and Subsequent Management of Patients with BRCA1/2 Mutated Platinum-Sensitive Recurrent Epithelial Ovarian Cancer (EOC) Progressing on Olaparib Versus Placebo: The SOLO2/ENGOT Ov-21 Trial (NCT01874353)

Frenel JS et al.

ASCO 2020;Abstract 6070.

SOLO-2: Patterns of Progression and Subsequent Management

MAJOR FINDINGS

- Patterns of disease progression and subsequent chemotherapy were similar in patients receiving O or P in the SOLO-2 trial.
- Instead of switching to chemotherapy, continuing O at the time of RECIST progression was an option for 35% of the patients.

Frenel JS et al. ASCO 2020;Abstract 6070.

Myelodysplastic syndrome and acute myeloid leukaemia in patients treated with PARP inhibitors: a safety meta-analysis of randomised controlled trials and a retrospective study of the WHO pharmacovigilance database

Pierre-Marie Morice, Alexandra Leary, Charles Dolladille, Basile Chrétien, Laurent Poulain, Antonio González-Martín, Kathleen Moore, Eileen Mary O'Reilly, Isabelle Ray-Coquard, Joachim Alexandre

PARP inhibitors—understanding the risk of myelodysplastic syndrome and acute myeloid leukaemia

Lancet Haematol **2020;[Epub ahead of print].**

Incidence of MDS and AML Across PARP Inhibitor Groups

- PARP inhibitor groups: 0.73% (95% CI 0.50-1.07; I^2 = 0%, χ^2 p = 0.87; 21 events out of 4,533 patients)
- Placebo groups: 0.47% (0.26-0.85; I^2 = 0%, χ^2 p = 1.00; 3 events out of 2,774 patients)

Morice PM et al. *Lancet Haematol* 2020;[Epub ahead of print].

How Long Have We Got? The Accuracy of Physicians' Estimates and Scenarios for Survival Time in 898 Women with Recurrent Ovarian Cancer (ROC)

Roncolato F et al.

ASCO 2019;Abstract 6002.

Original article

INTERNATIONAL JOURNAL OF GYNECOLOGICAL CANCER

Perceptions, expectations, and experiences of gynecological cancer patients: a pan-European ESGO-ENGAGe survey

Esra Urkmez,[1,2] Elif Andac-Jones ,[3] David Cibula,[4] Denis Querleu,[5] Michael J Halaska,[6] Daniel Driak,[6] Jalid Sehouli,[7] Jacek P Grabowski,[7] Gulhan Inci,[7] Kamil Zalewski,[8,9] Lucas Minig ,[10] Cristina Zorrero,[11] Muzaffer Sancı,[12] Murat Alan,[12] Jonathan A Ledermann,[13] Christina Fotopoulou,[14] Murat Gultekin[15]

Int J Gynecol Cancer 2019;29(9):1425-30.

Meet The Professor with Prof Ledermann

MODULE 1: Cases from Drs Bachow and Chen

MODULE 2: Journal Club with Prof Ledermann

- Role of PARP inhibitors beyond ovarian cancer with BRCA mutation: Definition of HRD
- Concordance between CA-125 and disease progression in the SOLO-2 trial
- Can survival outcomes be predicted? Secondary endpoints in first-line maintenance olaparib trials
  - SOLO-1 and PAOLA-1
- Patient experiences with genetic testing in ovarian cancer
- ICON8: Neoadjuvant carboplatin/paclitaxel regimens for ovarian cancer
- SOLO-2: Final survival analysis, patterns of progression, subsequent therapy and risk of MDS/AML
- Meta-analysis of MDS/AML in patients treated with PARP inhibitors
- Accuracy of physician estimates for survival time for women with recurrent ovarian cancer
- Perceptions, expectations and experiences of patients with gynecologic cancer

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

MODULE 4: Key Recent Papers

RTP RESEARCH 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

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 Prof Ledermann

MODULE 1: Cases from Drs Bachow and Chen

MODULE 2: Journal Club with Prof Ledermann

- Role of PARP inhibitors beyond ovarian cancer with BRCA mutation: Definition of HRD
- Concordance between CA-125 and disease progression in the SOLO-2 trial
- Can survival outcomes be predicted? Secondary endpoints in first-line maintenance olaparib trials
  - SOLO-1 and PAOLA-1
- Patient experiences with genetic testing in ovarian cancer
- ICON8: Neoadjuvant carboplatin/paclitaxel regimens for ovarian cancer
- SOLO-2: Final survival analysis, patterns of progression, subsequent therapy and risk of MDS/AML
- Meta-analysis of MDS/AML in patients treated with PARP inhibitors
- Accuracy of physician estimates for survival time for women with recurrent ovarian cancer
- Perceptions, expectations and experiences of patients with gynecologic cancer

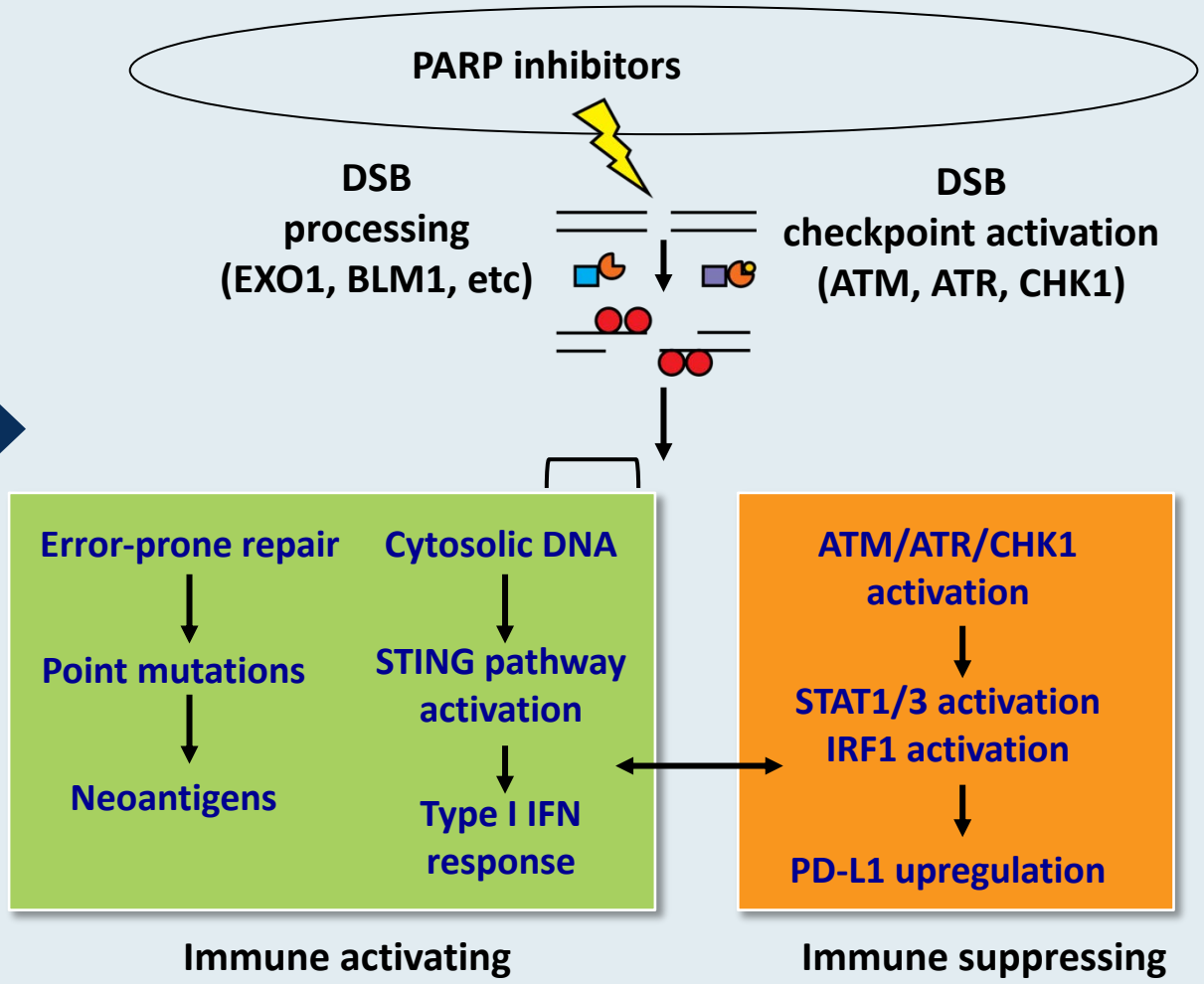
MODULE 3: Beyond the Guidelines – Clinical Investigator Approaches to Common Clinical Scenarios

MODULE 4: Key Recent Papers

RTP RESEARCH TO PRACTICE

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

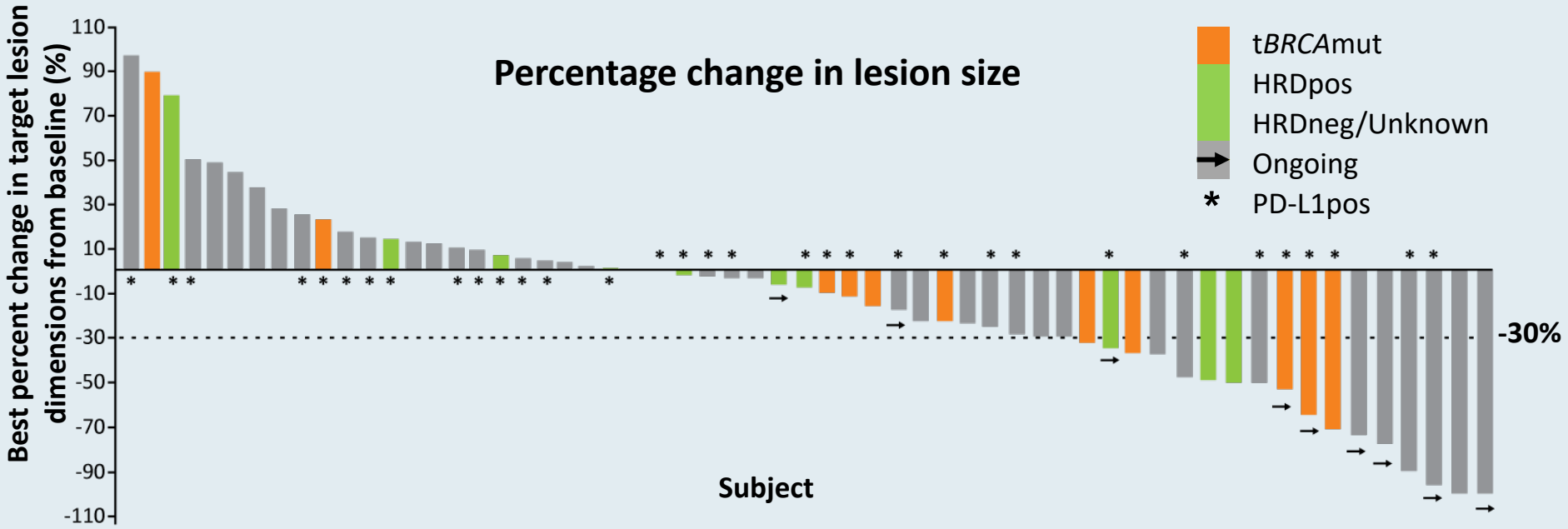
Preclinical models indicate synergy between PARPi + anti-PD-1 agents regardless of *BRCA* mutation status or PD-L1 status



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 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%)

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.

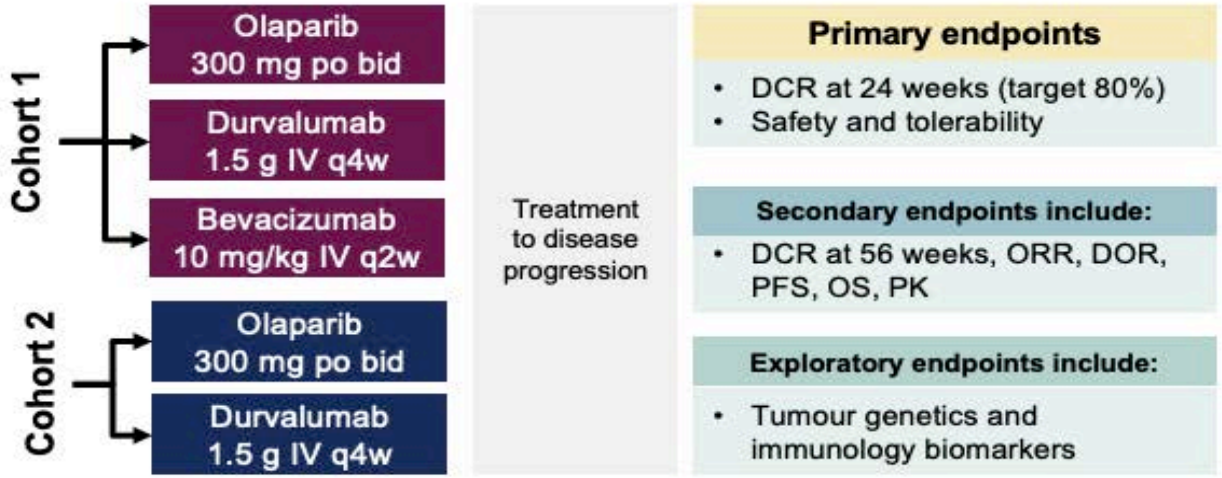
ESMO 2020;Abstract 814MO.

MEDIOLA: gBRCAwt Cohorts

Study Design

Patient population

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



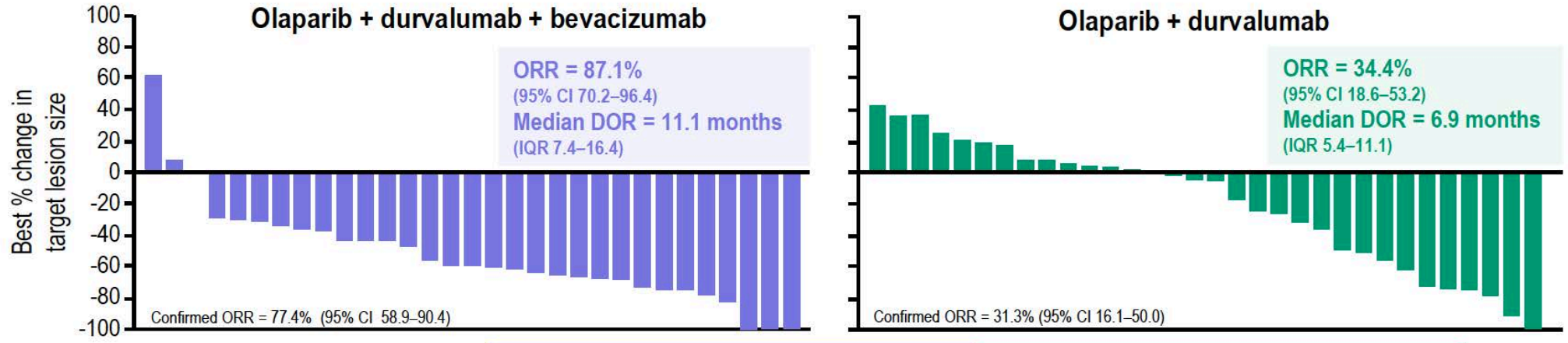
Patient Characteristics

	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

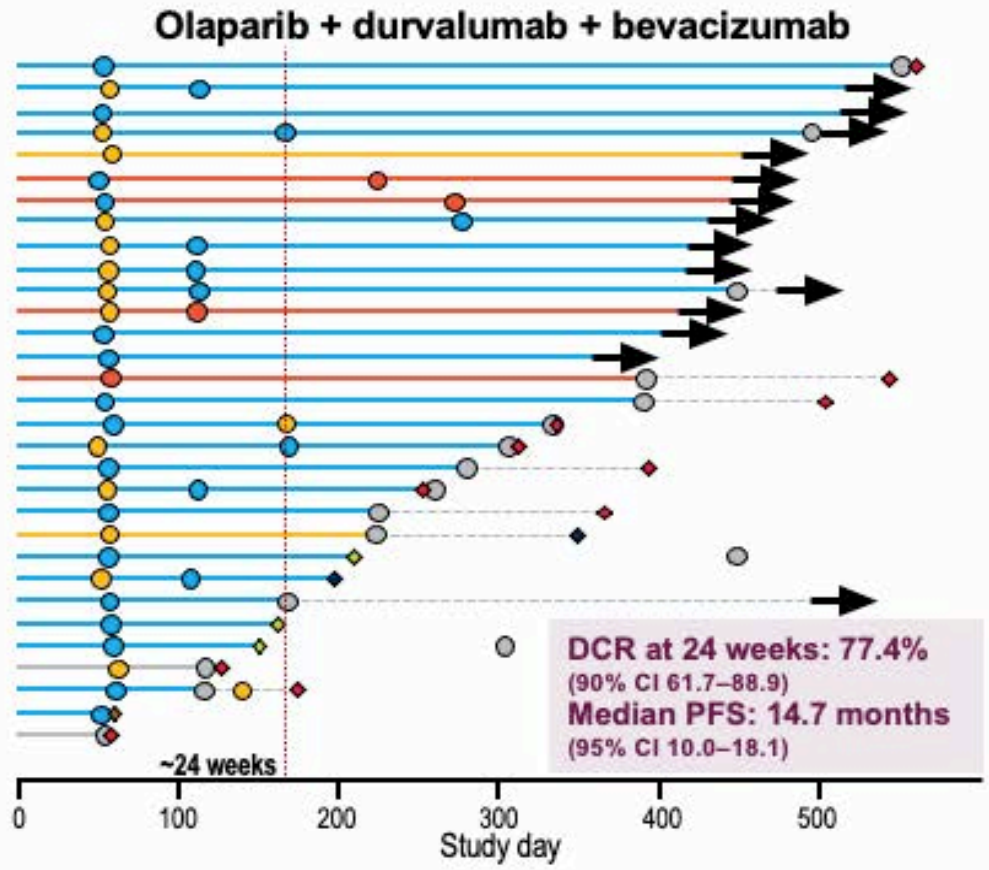
Exploratory analysis suggests ORR with triplet cohort is not dependent on genomic instability status (GIS)

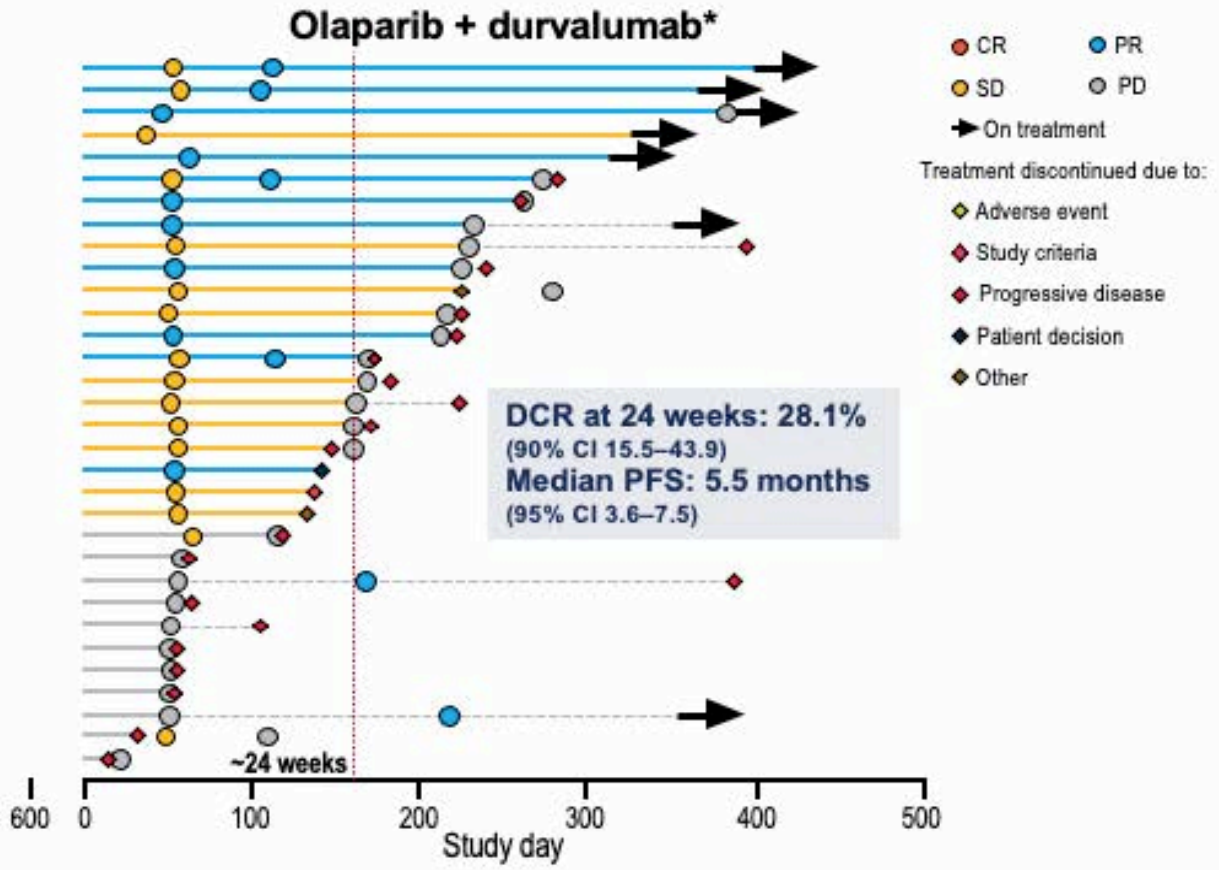


Genomic instability status* subgroup	Olaparib + durvalumab + bevacizumab		Olaparib + durvalumab	
	ORR (95% CI), %	n/N patients	ORR (95% CI), %	n/N patients
GIS-positive	100.0 (69.2–100.0)	10/10	50.0 (18.7–81.3)	5/10
GIS-negative	75.0 (34.9–96.8)	6/8	16.7 (0.4–64.1)	1/6
GIS-unknown	84.6 (54.6–98.1)	11/13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

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.

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.

RTP RESEARCH TO PRACTICE

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	*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

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.

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.

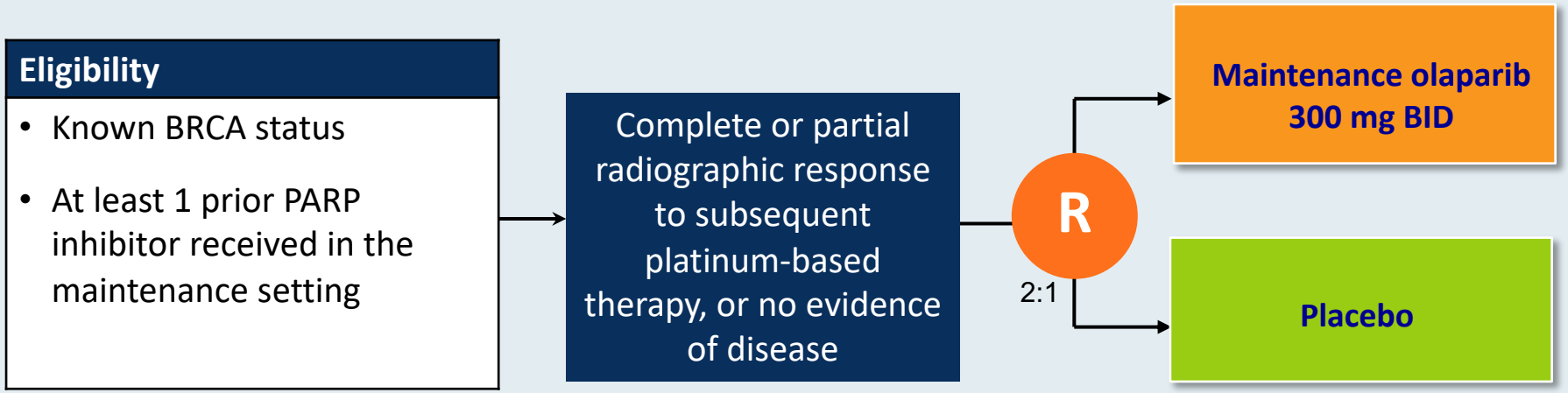
Determinants of Platinum Sensitivity and Resistance

- 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

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

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

www.clinicaltrials.gov; Accessed August 2020.

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

Niraparib

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

Pivotal study: ENGOT-OV16/NOVA

Approved: 3/2017

Rucaparib

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

Pivotal study: ARIEL3

Approved: 4/2018

Olaparib

Indications:
- Maintenance following 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.

FDA-Approved PARP Inhibitors as Monotherapy for Multiply 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 Multiply Relapsed OC

	Objective Response Rate
QUADRA[1] — Niraparib	
HRD-positive	29/189 (15%)
HRD-negative/unknown	8/230 (3%)
BRCA-mutated	18/63 (29%)
SOLO-3[2] — Olaparib	
gBRCA-mutation	109/151 (72%)
ARIEL2[3-4] — Rucaparib	
g 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.

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

Management of HER2-Positive Breast Cancer

Monday, January 25, 2021
5:00 PM – 6:00 PM ET

Faculty

Erika Hamilton, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us!

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

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