Thank you for joining us. The program will commence momentarily.

Meet The Professors

Clinical Investigators Discuss Existing and Emerging Treatment Strategies for Patients with Ovarian, Cervical and Endometrial Cancer

> Wednesday, August 12, 2020 1:00 PM – 2:00 PM ET

Faculty Stephanie Lheureux, MD, PhD Professor Ignace Vergote



Dr Love and Faculty Encourage You to Ask Questions



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

Familiarizing yourself with the Zoom interface How to answer poll questions



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

This activity is supported by educational grants from AbbVie Inc, AstraZeneca Pharmaceuticals LP, Clovis Oncology, Eisai Inc, Merck, Seattle Genetics and Tesaro, A GSK Company.

Dr Love — Disclosures

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

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

Dr Lheureux — Disclosures

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Contracted Research	AstraZeneca Pharmaceuticals LP, GlaxoSmithKline, Merck, Regeneron Pharmaceuticals Inc, Roche Laboratories Inc

Prof Vergote — Disclosures

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Wednesday, August 12, 2020 5:00 PM – 6:30 PM ET

Recent Advances in Medical Oncology: Hepatocellular Carcinoma and Pancreatic Cancer

Faculty

Tanios Bekaii-Saab, MD Eileen M O'Reilly, MD Philip A Philip, MD, PhD, FRCP Alan P Venook, MD

Moderator

Neil Love, MD

Friday, August 14, 2020 9:00 AM – 10:00 AM ET

Virtual Molecular Tumor Board: Recognition and Management of Targetable Tumor Mutations in Less Common Cancer Types

Faculty Marcia S Brose, MD, PhD

Andrew McKenzie, PhD Milan Radovich, PhD

Monday, August 17, 2020 5:00 PM – 6:00 PM ET

Recent Advances in Medical Oncology: ER-Positive Breast Cancer

Faculty Virginia Kaklamani, MD, DSc Sara M Tolaney, MD, MPH

Moderator Neil Love, MD Tuesday, August 18, 2020 5:00 PM – 6:00 PM ET

Current Questions and Controversies in the Management of Lung Cancer

Faculty Leora Horn, MD, MSc

Wednesday, August 19, 2020 12:00 PM – 1:00 PM ET

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

Faculty Noopur Raje, MD

Moderator Neil Love, MD Thursday, August 20, 2020 5:00 PM – 6:00 PM ET

Clinical Investigator Perspectives on the Current and Future Role of PARP Inhibition in the Management of Ovarian Cancer

Faculty Don S Dizon, MD

Friday, August 21, 2020 12:00 PM – 1:00 PM ET

Optimizing the Selection and Sequencing of Therapy for Patients with Chronic Lymphocytic Leukemia

Faculty Brad S Kahl, MD

Clinical Investigator Perspectives on the Current and Future Role of PARP Inhibition in the Management of Ovarian Cancer A Virtual Meet The Professor Series

Starting August 2020

Participating Faculty

Deborah K Armstrong, MD Don S Dizon, MD Pofessor Jonathan A Ledermann Ursula Matulonis, MD Mansoor Raza Mirza, MD Kathleen Moore, MD Professor Ignace Vergote Shannon N Westin, MD, MPH



Exploring the Role of Immune Checkpoint Inhibitor Therapy and Other Novel Strategies in Gynecologic Cancers A Virtual Meet The Professor Series

Starting August 2020

Participating Faculty

Michael J Birrer, MD, PhD Robert L Coleman, MD David M O'Malley, MD Richard T Penson, MD, MRCP Matthew A Powell, MD Brian M Slomovitz, MD Krishnansu S Tewari, MD



ONCOLOGY TODAY WITH DR NEIL LOVE









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Faculty



Stephanie Lheureux, MD, PhD Clinician Investigator Drug Development Program - Gynecology Division of Medical Oncology and Hematology Gynecology Site Lead Princess Margaret Cancer Centre Assistant Professor University of Toronto Toronto, Canada



Professor Ignace Vergote Chairman Department of Obstetrics and Gynaecology Gynaecological Oncologist Leuven Cancer Institute University Hospital Leuven Leuven, Belgium

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ONCOLOGY TODAY WITH DR NEIL LOVE









Make the Meeting Even More Relevant to You

Download the RTP Live app on your smartphone or tablet to access program information, including slides being presented during the program:

www.ResearchToPractice.com/RTPLiveApp



Data + Perspectives The Current and Future Role of Immune Checkpoint Inhibitors and Other Novel Therapies in the Management of Gynecologic Cancers

Companion Video Series

Access the CME- and MOC-accredited webinar archive proceedings plus a companion lecture series and interview program conducted with Drs Michael J Birrer, Ursula Matulonis and Krishnansu S Tewari

Video Webinar Archive

http://www.ResearchToPractice.com/GynOnc20/NovelTherapies/Video

Video Interview Program

http://www.ResearchToPractice.com/GynOnc20/NovelTherapies/Interviews/Video

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Beyond the Guidelines Perspectives on the Role of PARP Inhibition in the Management of Ovarian Cancer

Companion Video Series

Access the CME- and MOC-accredited webinar archive proceedings plus a companion lecture series and interview program conducted with Drs Robert L Coleman, Stephanie Lheureux, Joyce F Liu and Kathleen Moore

> Video Webinar Archive http://www.ResearchToPractice.com/GynOnc20/PARP/Video

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Co-provided by **USF**Health

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> Moderator Neil Love, MD

Research To Practice® Beyond the Guidelines Perspectives on the Role of PARP Inhibition in the Management of Ovarian Cancer

Monday, May 18, 2020

Moderator Neil Love, MD

Faculty

Robert L Coleman, MD Stephanie Lheureux, MD, PhD Joyce F Liu, MD, MPH Kathleen Moore, MD Data + Perspectives The Current and Future Role of Immune Checkpoint Inhibitors and Other Novel Therapies in the Management of Gynecologic Cancers Wednesday, May 20, 2020

> Moderator Neil Love, MD

Faculty

Michael J Birrer, MD, PhD Ursula Matulonis, MD David M O'Malley, MD Krishnansu S Tewari, MD

Survey Respondents (N = 25)

- 1. Ronald D Alvarez, MD, MBA
- 2. Andrew Berchuck, MD
- 3. Michael J Birrer, MD, PhD
- 4. Susana M Campos, MD, MPH
- 5. Robert L Coleman, MD
- 6. Stephanie L Gaillard, MD, PhD
- 7. Rachel N Grisham, MD
- 8. Thomas Herzog, MD
- 9. Angela Jain, MD
- 10. Beth Karlan, MD
- 11. Professor Jonathan A Ledermann
- 12. Douglas A Levine, MD
- 13. Stephanie Lheureux, MD, PhD

- 14. Joyce F Liu, MD, MPH
- 15. Ursula Matulonis, MD
- 16. Mansoor Raza Mirza, MD
- 17. Bradley J Monk, MD
- 18. Kathleen Moore, MD
- 19. David M O'Malley, MD
- 20. Ana Oaknin, MD, PhD
- 21. Matthew A Powell, MD
- 22. Professor Isabelle Ray-Coquard, MD, PhD
- 23. Krishnansu S Tewari, MD
- 24. Professor Ignace Vergote
- 25. Robert M Wenham, MD




Agenda

Part 1: PARP Inhibitors in Ovarian Cancer

- 58-year-old woman: BRCA1 exon 3 deletion germline mutation; NGS no BRCA mutation
- 53-year-old woman: BRCA germline wild type, LOH score higher than 16 on NGS
- 56-year-old woman: RAD51D germline mutation, on VELIA trial
- 74-year-old woman: Platinum-sensitive recurrence, RAD51C germline mutation with PARP-induced diarrhea, fatigue and cytopenias

Part 2: Immune Checkpoint Inhibitors in Gynecologic Cancers

- 51-year-old woman: MSI-high metastatic endometrial cancer
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• Woman in her 20s: Metastatic cervical cancer, on a trial of tisotumab vedotin

Part 4: COVID-19 and Gynecologic Cancers

 65-year-old woman: Recurrent ovarian cancer responding on a trial of dostarlimab (TSR-042), niraparib and bevacizumab, hospitalized for COVID-19 but recovered

Part 1: PARP Inhibitors in Ovarian Cancer

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In general, which of the following mutation assays do you order for a patient with newly diagnosed ovarian cancer and no family history?



Somatic Testing

HRD Testing







If a patient with ovarian cancer has multiplex testing/next-generation sequencing (NGS) performed on tumor tissue, germline testing is needed only for genetic counseling because germline mutations are detected on NGS.

- a. Agree
- b. Disagree
- c. I don't know

58-year-old woman: BRCA1 exon 3 deletion germline mutation; NGS no BRCA mutation

- 58-year-old woman, newly diagnosed ovarian cancer
- Optimal cytoreductive surgery with multiple bowel resections
- Tumor testing <u>negative</u> for *BRCA* mutation, but germline testing with pathogenic mutation (deletion of *BRCA1* exon 3)
- Completed 6 cycles of adjuvant carboplatin/paclitaxel chemotherapy
- Started on maintenance olaparib

53-year-old woman: BRCA germline wild type, LOH score higher than 16 on NGS

- 53-year-old who presented with abdominal bloating, decreased urination and difficulty with defecation starting 10/2019. She was treated with laxatives which didn't help and presented to her Ob/Gyn where a mass was appreciated on exam.
- TVUS demonstrated a large complex adnexal mass, free fluid
- Ca-125 = 953.6
- She was referred to gynecologic oncology where a CT was ordered.

53-year-old woman: BRCA germline wild type, LOH score higher than 16 on NGS (con't)



Courtesy of Kathleen Moore, MD

53-year-old woman: BRCA germline wild type, LOH score higher than 16 on NGS (con't)

- Pathology
 - High grade serous ovarian cancer
- Comprehensive Genomic Profile:
 - Loss of heterozygosity score > 16%
 - Tumor mutational burden 4mut/Mb, MSS, BRAF D594G, NF1 loss, RB1 loss, TP53 H179R
- Genetics
 - BRCA wt

53-year-old woman: BRCA germline wild type, LOH score higher than 16 on NGS (con't)

- Treated with carboplatin AUC 6 and paclitaxel 175mg/mg² IV every 21 days x 6 cycles
- Ca-125 was 31 post cytoreductive surgery, ended at 9
- Cycle 6 on 4/9/2020, nl Ca125 and neg CT scan = NED
- Now questions regarding maintenance?

NCCN 2020 Guidelines



Courtesy of Kathleen Moore, MD

A 60-year-old woman with Stage IIIC ovarian cancer and a <u>germline BRCA mutation</u> is s/p <u>optimal</u> debulking surgery and platinum-based chemotherapy with a normal CA-125 level. In general, what is your approach to PARP inhibitor maintenance?

- a. Olaparib for 2 years
- b. Olaparib for 3 years
- c. Niraparib for 2 years
- d. Niraparib for 3 years
- e. Other
- f. None

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?

Carboplatin/paclitaxel → olaparib

Carboplatin/paclitaxel + bevacizumab → bevacizumab + olaparib

2

Carboplatin/paclitaxel → niraparib







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

Carboplatin/paclitaxel + bevacizumab → bevacizumab + olaparib

Carboplatin/paclitaxel → olaparib



Medical oncologists

A 60-year-old woman with Stage IIIC ovarian cancer (BRCA wild type, <u>HRD-positive</u>) is s/p <u>optimal</u> debulking surgery with a normal CA-125 level. Regulatory and reimbursement issues aside, what would you recommend as postoperative systemic therapy?

Carboplatin/paclitaxel → niraparib

Carboplatin/paclitaxel + bevacizumab → bevacizumab + olaparib

Carboplatin/paclitaxel \rightarrow olaparib



Carboplatin/paclitaxel + bevacizumab → niraparib







10

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

Carboplatin/paclitaxel + bevacizumab \rightarrow bevacizumab + olaparib

Carboplatin/paclitaxel \rightarrow niraparib



Carboplatin/paclitaxel + bevacizumab → niraparib

Carboplatin/paclitaxel \rightarrow olaparib







Medical oncologists 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?



Carboplatin/paclitaxel + OOOOOO 6 bevacizumab → bevacizumab







A 60-year-old woman with Stage IIIC ovarian cancer (<u>BRCA wild type, HRD-negative</u>) is s/p <u>optimal</u> debulking surgery and platinum-based chemotherapy with a normal CA-125 level. In general, what is your approach to PARP inhibitor maintenance?

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Carboplatin/paclitaxel + bevacizumab → bevacizumab + olaparib

> Carboplatin/paclitaxel → niraparib



Other 3





FDA approves niraparib for first-line maintenance of advanced ovarian cancer Press Release – April 29, 2020

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

Efficacy was investigated in PRIMA (NCT02655016), a double-blind, placebocontrolled 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

FDA approves olaparib plus bevacizumab as maintenance treatment for ovarian, fallopian tube, or primary peritoneal cancers Press Release – May 28, 2020

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

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

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

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

Phase III PAOLA-1/ENGOT-OV25 Study Design



Primary endpoint: Investigator-assessed PFS **Secondary endpoints:** TFST, PFS2, TSST, OS, HRQoL, Safety and tolerability

Ray-Coquard IL et al. ESMO 2019; Abstract 3955.

56-year-old woman: RAD51D germline mutation, on VELIA trial

- gBRCA-wt
- Heavy disease burden with involvement of omentum, diaphragm, and peritoneal lining
- Grossly enlarged pelvic nodes
- Ovarian masses bilaterally
- CA-125: 6713 U/mL
- Enrolled onto VELIA/GOG-3005

56-year-old woman: RAD51D germline mutation, on VELIA trial (con't)

- NACT: Paclitaxel 80 mg/m² + carboplatin AUC6 + placebo/veliparib
 3 cycles of therapy (CA-125: 72 U/mL)
- Imaging prior to surgery
 - Near complete resolution of omental/diaphragm disease, posttreatment peritoneal thickening
 - Nodal disease near normal (largest short axis dimension: 1.2 cm)
 - Ovaries irregular but markedly smaller
- Interval resection accomplished with near complete gross resection
 - Small volume miliary mesenteric disease

56-year-old woman: RAD51D germline mutation, on VELIA trial (con't)

- Completed 6 cycles of chemotherapy plus placebo/veliparib
 - CA-125: 15 U/mL
 - Initiated and completed maintenance phase
 - NED
- Sequencing from interval cytoreduction: Rad51D mutation

Phase III VELIA/GOG-3005 Study Design



Primary endpoint: Progression-free survival (PFS) for veliparib-throughout vs control, including the combination and maintenance phase

Coleman RL et al. ESMO 2019; Abstract 2772.

VELIA/GOG-3005: PFS (ITT)



Coleman RL et al. N Engl J Med 2019;381:2403-15.

VELIA/GOG-3005: PFS in Trial Cohorts



74-year-old woman: Platinum-sensitive recurrence, RAD51C germline mutation with PARP-induced diarrhea, fatigue and cytopenias

- 74yo woman with recurrent platinum-sensitive ovarian cancer
- Germline testing with RAD51C mutation
- Received carboplatin/PLD with complete response
- Started on maintenance olaparib at 300mg BID
 - ~4 weeks after initiation, noted to have increasing fatigue, diarrhea. Platelet count decreased to 99K (from 183K at treatment initiation)
- Drug held, re-initiated with dose reduction to olaparib 250mg BID 2 weeks later after platelet recovery to 165K
 - ~4 weeks at this dose, with increasing intolerable fatigue
- Drug held, re-initiated with dose reduction to olaparib 200mg BID 2 weeks later
- Continues on maintenance olaparib at 200mg BID

Courtesy of Joyce F Liu, MD, MPH

Adverse Events: Class Effects and Specific Drug Differences

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

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

NR, not reported

Adverse Events: Class Effects and Specific Drug Differences

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

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

NR, not reported

Dose Adjustments for Adverse Events

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

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Liver Lesion pre lpi/Nivo



From the practice of Sulfi Ibrahim, MD
Post Ipi/Nivo (non contrast CT scan)



From the practice of Sulfi Ibrahim, MD

51-year-old woman: MSI-high metastatic endometrial cancer

- 51-year-old with G2 EMCA \rightarrow CT scan negative for metastatic disease
- RTLH/BSO/LND → Stage IIIC2 (positive pelvic/paraaortic lymph nodes)
- Adjuvant treatment: carbo/paclitaxel x 6 cycles followed by whole pelvic xRT
- Post treatment scan: NED
- 12-month f/u visit CT scan shows intra-abdominal recurrence
- She was treated with anti-PD-1 single agent

Before starting anti-PD-1



After 12 months of anti-PD-1







Courtesy of Michael J Birrer, MD, PhD

For a patient with <u>MSI-H</u> metastatic endometrial cancer, outside of a clinical trial setting and regulatory and reimbursement issues aside, what is the earliest point at which you would introduce an anti-PD-1/PD-L1 antibody?





In general, what treatment would you recommend for a patient with high microsatellite instability (<u>MSI-H</u>) metastatic endometrial cancer who experienced disease progression on carboplatin/paclitaxel?





For a patient with <u>MSI-H</u> metastatic endometrial cancer and <u>Crohn's</u> disease well controlled with infliximab, regulatory and reimbursement issues aside, what is the earliest point at which you would introduce an anti-PD-1/PD-L1 antibody?





For a patient with <u>MSI-H</u> metastatic endometrial cancer and <u>mild</u> <u>psoriasis not requiring active treatment</u>, regulatory and reimbursement issues aside, what is the earliest point at which you would introduce an anti-PD-1/PD-L1 antibody?





What dose and schedule of pembrolizumab are you currently administering to your patients with metastatic endometrial cancer?





To approximately how many patients with metastatic endometrial cancer have you administered lenvatinib/pembrolizumab?

a.	None
b.	1
C.	2
d.	3
e.	4
f.	5
g.	More than 5

41-year-old woman: MSS metastatic endometrial cancer

- 41-year-old biopsy proven G3 EMCA → CT scan negative for metastatic disease → proceed with surgery
- Surgery: RTLH/BSO/bISLND → Stage IIIC1 (positive pelvic lymph node)
- Adjuvant treatment: carbo/paclitaxel x 6 cycles
- Post treatment scan: NED
- 3 f/u month visit she is in pain, frequent nausea \rightarrow CT scan



Courtesy of Michael J Birrer, MD, PhD

41-year-old woman: MSS metastatic endometrial cancer (con't)

- Biopsy done → metastatic high-grade carcinoma consistent with known uterine primary
- IHC: ER neg
- NGS: amplification of AKT2, FGFR1, CCNE, MSI-S, TMB low
- Started her on Lenvatinib/pembro
- Developed HTN controlled by two anti-HTNs; grade 2 diarrhea—dose reduced to 14 mg lenvatinib
- Re-scan after 4 months



Courtesy of Michael J Birrer, MD, PhD

In general, what treatment would you recommend for a patient with microsatellite-stable (MSS) metastatic endometrial cancer who experienced disease progression on carboplatin/paclitaxel?

Lenvatinib/pembrolizumab

Test for PD-L1 combined positive score (CPS) and administer 01 pembrolizumab if 1% or higher

Cisplatin/doxorubicin

Doxorubicin





Have you observed either of the following side effects in any of your patients with metastatic endometrial cancer who have received lenvatinib/pembrolizumab?

- a. Difficult to control hypertension
- b. Weight loss or anorexia
- c. Both
- d. Neither
- e. I have not used lenvatinib/pembrolizumab

How would you respond to a patient with MSS <u>metastatic</u> <u>endometrial cancer</u> who is about to begin treatment with <u>lenvatinib/pembrolizumab</u> and asks you to estimate the chance that during the first year of treatment she will...



How would you respond to a patient with MSS <u>metastatic</u> <u>endometrial cancer</u> who is about to begin treatment with <u>lenvatinib/pembrolizumab</u> and asks you to estimate the chance that during the first year of treatment she will...



GARNET Study: Best Overall Tumor Response

Dostarlimab demonstrated clinically meaningful response rates regardless of MSI status, with an ORR of 30%, 49% in the MSI-H cohort, and 20% in the MSS cohort

Best Overall Response	MSI-H EC	MSS EC	MSI status	Total
	(n=41)	(n=79)	unknown (n=5)	(N=125)
Overall response rate n (%) (95% Cl)	20 (49%)	1 6 (20.%)	1(20.%)	37 (30%)
	(32.9, 64.9)	(12.0, 30.8)	(0.5,71.6)	(21.8, 38.4)
Complete response n (%)	2 (4.9%)	4 (5.1%)	0 (0%)	6 (4.8%)
Partial response n (%)	181> (43.9%)	12 (15.2%)	1 (20.0%)	31 (24.8%)
Disease control rated %	63.4%	46.8%	60.0%	52.8%
(95% CI)	(46.9, 77.9)	(35.5, 58.4)	(14.7, 94.7)	(43.7, 61.8)
Response ongoing %	85.0%	81.3%	100%	83.8%

•Based on central testing, MSI status could not be determined; 017 confirmed and 1 still on treatment and yet to be confirmed; "11 confirmed and 1 still on treatment and yet to be confirmed; "irCR+irPR+uirPR+irSD.

irCR: immune-related complete response; irPR: immune-related partial response; irSD: immune-related stable dsease; uirPR: unconfirmed immune related partial response. CI: confidence interval.

Data extract date: January 21, 2019.

Oaknin A et al. SGO 2019; Abstract 33.

Courtesy of Michael J Birrer, MD, PhD

GARNET: Dostarlimab in Recurrent or Advanced dMMR Endometrial Cancer



Oaknin A et al. SGO 2020; Abstract LBA9.

GARNET: Dostarlimab in Recurrent or Advanced dMMR Endometrial Cancer



Oaknin A et al. SGO 2020; Abstract LBA9.

36-year-old woman: PD-L1-positive metastatic cervical cancer

- 36 year old Caucasian married mother of two small children, living in rural Georgia
- PMH unremarkable
- Screening sporadic cervical cancer screening 2014-2019
- 2018
 - Post-coital vaginal bleeding (hemoglobin 9.5 mg/dL), dyspareunia, pelvic pain
 - 5 cm friable cervical lesion biopsied: poorly differentiated squamous cell carcinoma (SCCA)
 - PET/CT: FIGO stage IB3 SCCA cervix
 - Management:
 - Cisplatin-based chemoradiation (40 mg/m² BSA weekly with 50.4 Gy IMRT) plus high-dose-rate intracavitary brachytherapy for total dose 85 Gy to Point A
 - Missed 8 radiotherapy sessions due to transportation issues
 - Complete clinical response

Courtesy of Krishnansu S Tewari, MD

36-year-old woman: PD-L1-positive metastatic cervical cancer (con't)

- 2019
 - Presents 14 months following chemoradiation with severe pelvic and right flank pain
 - Cachetic, unable to work as a medical assistant, confined to her apartment [ECOG PS 2]
 - Pelvic examination large, fixed mass with right pelvic side wall extension
 - PET/CT: large necrotic pelvic mass, right hydronephrosis; CT-guided bx confirms pulmonary metastasis of SCCA cervix
 - Serum creatinine = 1.7 mg/dL
 - Travel limited by geography
 - Management:
 - Moore score = 3
 - Percutaneous right nephrostomy and anterograde right ureteral placement
 - Ensure[®] (3 cans/day)
 - Carboplatin (AUC 6) + Paclitaxel (175 mg/m² BSA) + Bevacizumab (15 mg/kg) x 7 cycles
 - Complete clinical response

Courtesy of Krishnansu S Tewari, MD

36-year-old woman: PD-L1-positive metastatic cervical cancer (con't)

- 2020
 - Presents with left supraclavicular lymphadenopathy and mild hemoptysis
 - PET/CT
 - Supraclavicular node (SUV 12)
 - Bilateral pulmonary metastases measuring 2 cm and 4 cm (SUV 6-9)
 - CT-guided bx confirms recurrent disease
 - PD-L1+
 - Combined Positive Score = 16
 - Management:
 - Pembrolizumab 200 mg IV q3 wks (January February 2020)
 - Surveillance PET/CT (March 2020) demonstrates pulmonary metastases enlarged
 - Pembrolizumab 200 mg IV q3 wks (March April 2020)
 - Surveillance PET/CT (May 2020) demonstrates partial response (pseudo-progression)
 - Pembrolizumab 400 mg IV q6 wks (begins May 2020 per COVID-19 US FDA guidance)
 - Hypothyroidism managed with thyroid hormone supplementation

Courtesy of Krishnansu S Tewari, MD

In general, what would be your preferred first-line therapy for a patient with MSS metastatic cervical cancer who has received no prior systemic treatment?





In general, what would be your preferred first-line therapy for a patient with MSS metastatic cervical cancer who experienced relapse 12 months after receiving cisplatin-based chemoradiation therapy for Stage IIIB disease?





In general, what would be your preferred second-line therapy for a patient with MSS metastatic cervical cancer who experienced disease progression on carboplatin/paclitaxel/bevacizumab?







FDA approves pembrolizumab for advanced cervical cancer with disease progression during or after chemotherapy Press Release – June 12, 2018

The Food and Drug Administration approved pembrolizumab for patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS \geq 1) as determined by an FDA-approved test.

Pembrolizumab was investigated in 98 patients with recurrent or metastatic cervical cancer enrolled in a single cohort of KEYNOTE 158 (NCT02628067), a multicenter, non-randomized, open-label, multi-cohort trial. Patients were treated with pembrolizumab intravenously at a dose of 200 mg every 3 weeks until unacceptable toxicity or documented disease progression. Among the 98 patients, approval was based on 77 (79%) patients who had tumors that expressed PD-L1 with a CPS ≥1 and who had received at least one line of chemotherapy for metastatic disease. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx Kit.

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-advanced-cervical-cancer-disease-progression-during-or-after-chemotherapy

Phase II KEYNOTE-158: Pembrolizumab in Previously Treated Advanced Cervical Cancer



Combined Positive Score (CPS) = PD-L1+ cells (tumor cells, lymphocytes, macrophages) / Total number of tumor cells x 100

Chung HC et al. J Clin Oncol 2019;37:1470-78.

BEATcc Phase III Randomized Frontline Trial of Atezolizumab

- Primary Stage IVB, persistent or recurrent carcinoma of the cervix
- Measurable disease by RECIST v1.1
- ECOG-PS: 0-1
- No previous systemic chemotherapy for advanced or recurrent disease

N=404 Cisplatin + paclitaxel + bevacizumab (GOG#240) until disease progression, unacceptable toxicity, death or withdrawal of consent
1:1 Cisplatin + paclitaxel + bevacizumab + atezolizumab until disease progression, unacceptable toxicity, death or withdrawal of consent
Safety run-in cohort: 12 pts after 2 cycles of treatment

Primary Endpoint: Overall survival (OS) Secondary Endpoints:

- PFS
- ORR
- DOR
- Safety
- HR-QOL

Stratification Factors:

- Prior concurrent Cisplatin-RDT
- Histology: SCC vs ADK (including AdenoSquamous)
- Chemotherapy Backbone: Cisplatin vs Carboplatin

ClinicalTrials.gov Identifier: NCT03556839

Do you generally evaluate microsatellite instability status in your patients with advanced ovarian cancer?





Medical oncologists

FDA-Approved Indications for Immunotherapy in Ovarian Cancer

Pembrolizumab: 2017 FDA approval for MSI-high/MMR deficient cancers

- The incidence of germline MMR gene mutations in high grade serous cancers is 1-8%
- MMR deficiency is more common in non-serous ovarian cancer

2020 ASCO ovarian cancer genetics guidelines re MMR testing:

- Women diagnosed with clear cell, endometrioid, or mucinous ovarian cancer should be offered somatic tumor testing for mismatch repair deficiency
- Testing for MMR deficiency may be offered to women diagnosed with other histologic types of epithelial ovarian cancer

Update on Phase III Study of Atezolizumab in Women With Advanced-Stage Ovarian Cancer

Press Release – July 12, 2020

"The Phase III IMagyn050 study showed that the addition of atezolizumab to bevacizumab, paclitaxel and carboplatin did not meet its primary endpoint of progression-free survival (PFS) for the front-line treatment of women with newlydiagnosed advanced-stage ovarian cancer. Topline safety data indicate that safety for atezolizumab in combination with bevacizumab, paclitaxel and carboplatin was consistent with the known safety profile of the combination...

"Data for the overall survival (OS) co-primary endpoint are currently immature and follow-up will continue until the next planned analysis."

Final results from the KEYNOTE-100 trial of pembrolizumab in patients with advanced recurrent ovarian cancer

Matulonis UA et al. ASCO 2020;Abstract 6005.

FIRST Phase 3 Trial of Dostarlimab (TSR-042) in Newly Diagnosed Ovarian Cancer



https://clinicaltrials.gov/ct2/show/NCT03602859

Courtesy of Ursula Matulonis, MD

TOPACIO/KEYNOTE-162: Niraparib and Pembrolizumab in Recurrent Platinum-Resistant Ovarian Cancer



Konstantinopoulos PA, et al. JAMA Oncol. 2019 Jun 13;5(8):1141-9.

Phase II MOONSTONE Study Design

Eligibility

- Completed 1-3 prior lines of therapy for advanced or metastatic ovarian cancer
- Previously treated with platinum-based chemo, taxane and bevacizumab
- Resistant to last administered platinum agent
- No known BRCA 1 or 2 mutation

Primary endpoint: ORR Secondary endpoints: DOR, PFS, OS, DCR


Agenda

Part 1: PARP Inhibitors in Ovarian Cancer

- 58-year-old woman: BRCA1 exon 3 deletion germline mutation; NGS no BRCA mutation
- 53-year-old woman: BRCA germline wild type, LOH score higher than 16 on NGS
- 56-year-old woman: RAD51D germline mutation, on VELIA trial
- 74-year-old woman: Platinum-sensitive recurrence, RAD51C germline mutation with PARP-induced diarrhea, fatigue and cytopenias

Part 2: Immune Checkpoint Inhibitors in Gynecologic Cancers

- 51-year-old woman: MSI-high metastatic endometrial cancer
- 41-year-old woman: MSS metastatic endometrial cancer
- 36-year-old woman: PD-L1-positive metastatic cervical cancer

Part 3: Investigational Agents in Cervical Cancer

• Woman in her 20s: Metastatic cervical cancer, on a trial of tisotumab vedotin

Part 4: COVID-19 and Gynecologic Cancers

 65-year-old woman: Recurrent ovarian cancer responding on a trial of dostarlimab (TSR-042), niraparib and bevacizumab, hospitalized for COVID-19 but recovered

Part 3: Investigational Agents in Cervical Cancer

Woman in her 20s: Metastatic cervical cancer, on a trial of tisotumab vedotin

Would you want to administer tisotumab vedotin to a patient with metastatic cervical cancer who had received all approved treatment options?

a. No

- b. Yes, but only on a clinical trial
- c. Yes, either on or off a clinical trial (eg, compassionate use)
- d. I am not familiar with this agent

Woman in her 20s: Metastatic cervical cancer, on a trial of tisotumab vedotin

- 2016 Diagnosed with stage IIIB cervical cancer
- Received chemoradiation with HDR
- 2018 multiple pulmonary masses biospy confirmed lung recurrence;
- 2018 cisplatin + paclitaxel + Bev x 6 cycles with progression
- New bone lesion treated with RT
- Screen Fail for Iovance C-145-04 TILs trial (due to PFTs)
- 2019: Started on innovaTV 204 GOG 3023 (Genmab)

PD-L1 testing negative; Foundation One with TERT promotor abnormality

Screening

Cycle 2





Cycle 10



- Continues on therapy with persistent lesion
- >16 months
- Approx. 60% regression

Courtesy of David M O'Malley, MD

Tisotumab Vedotin Sees Positive Topline Results in the Phase II innovaTV 204 Trial

Press Release – June 30, 2020

"Positive topline results [were announced] from the single-arm, phase 2 innovaTV 204 trial evaluating tisotumab vedotin administered every 3 weeks for the treatment of patients who have relapsed or progressed on or after prior treatment for recurrent or metastatic cervical cancer...

"Overall, 101 patients were treated with tisotumab vedotin at multiple centers across the US and Europe. Results from the trial demonstrated a 24% confirmed ORR by independent central review (95% CI, 15.9%-33.3%) with a median DOR of 8.3 months. The most common treatment-related adverse events included alopecia, epistaxis, nausea, conjunctivitis, fatigue, and dry eye."

Mechanism of action of tisotumab vedotin

- Tissue factor (TF) is aberrantly expressed in a broad range of solid tumours, including cervical cancer,^{1,2} and TF expression has been associated with higher tumour stage and grade, higher metastatic burden and poor prognosis²
- TF expression in cervical cancer makes TF a novel target for patients with cervical cancer
- ADC targets TF
 - Monoclonal Antibody targets TF
 - Payload: Microtubule disrupting MMAE
- Allowing for direct cytotoxicity and bystander killing, as well as antibody-dependent cellular cytotoxicity^{3,4}



1. Förster Y, et al. *Clin Chim Acta,* 2006. **2.** Cocco E, et al. *BMC Cancer,* 2011. **3.** Breij EC, et al. *Cancer Res,* 2014. **4.** De Goeij BE, et al. *Mol Cancer Ther,* 2015.

innovaTV 201: Best Overall Response to TV



Hong DS et al. Clin Cancer Res 2020;26:1220-8.

innovaTV 201: Time to Response and Duration of Response in Patients with a Confirmed PR to TV



Hong DS et al. Clin Cancer Res 2020;26:1220-8.

innovaTV 201: Treatment-Emergent Adverse Events

	N = 55	
Adverse Events	All Grade	Grade ≥3
Fatigue	51%	9%
Nausea	49%	5%
Neuropathy	55%	11%
Bleeding-related AEs	73%	5%
Ocular AEs	65%	2%
Conjunctivitis	42%	2%
Dry eye	24%	0
Ulcerative keratitis	7%	0
Blepharitis	5%	0
Keratitis	5%	0

Conjunctivitis Before and After Mitigation Measures



Hong DS et al. Clin Cancer Res 2020;26:1220-8.

innovaTV 205 (GOG 3024): Recurrent or Metastatic Cervical Cancer



Courtesy of David M O'Malley, MD

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- 2017: Presented with chronic lower back pain and found to RTP adenopathy and bilateral adnexal masses
- Underwent optimal cytoreductive surgery; stage IIIC HGSC (BRCA wild type)
- Receives 6 cycles of carbo/paclitaxel
- 9 months later recurrence with adenopathy and peritoneal disease on CT, elevated CA125, carbo/PLD
- CA125 starts to rise during cycle 5, and CT shows PD
- March 2019: OPAL: TSR-042, niraparib, and bev (NCT03574779)
- Required DR to 200 of niraparib, PR after 4 cycles
- Developed covid19 in April 2020 (exposed to +family member in same house), hospitalized and now recovering

Courtesy of Ursula Matulonis, MD

Recent Advances in Medical Oncology: Hepatocellular Carcinoma and Pancreatic Cancer

Wednesday, August 12, 2020 5:00 PM – 6:30 PM ET

Faculty

Tanios Bekaii-Saab, MD Eileen M O'Reilly, MD Philip A Philip, MD, PhD, FRCP Alan P Venook, MD

Moderator Neil Love, MD



Thank you for joining us!

CME credit information will be emailed to each participant tomorrow morning.