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

#### **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, Agendia Inc, Agios Pharmaceuticals Inc, Amgen Inc, Array BioPharma 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, Guardant Health, Halozyme Inc, 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 and Tolero Pharmaceuticals.

## Faculty



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David M O'Malley, MD Professor Division Director, Gynecologic Oncology Co-Director, Gynecologic Oncology Phase I Program The Ohio State University and the James Cancer Center Columbus, Ohio



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



Krishnansu S Tewari, MD Professor and Division Director Division of Gynecologic Oncology University of California, Irvine Irvine, California

### Dr Birrer — Disclosures

Consulting	AstraZeneca Pharmaceuticals LP, Clovis Oncology,
Agreements	Tesaro, A GSK Company

### Dr Matulonis — Disclosures

Advisory Committee and Consulting Agreement	Novartis
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## Dr O'Malley — Disclosures

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Data and Safety Monitoring Board/Committee	Marker Therapeutics Inc

## Dr Tewari — Disclosures

Advisory Committee	AstraZeneca Pharmaceuticals LP, Clovis Oncology, Eisai Inc, Genentech, a member of the Roche Group, Tesaro, A GSK Company
Contracted Research (institution only)	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Clovis Oncology, Genentech, a member of the Roche Group, Regeneron Pharmaceuticals Inc ,Tesaro, A GSK Company
Data and Safety Monitoring Board/Committee	Iovance Biotherapeutics
Speakers Bureau	AstraZeneca Pharmaceuticals LP, Clovis Oncology, Merck, Roche Laboratories Inc, Tesaro, A GSK Company

## Familiarizing yourself with the Zoom interface How to participate in the chat



#### **SGO 2020 Satellite Virtual Programs**

- Virtual presentations/interviews
- Live/enduring discussions
- Live breakout sessions



#### Agenda

**Module 1 – Dr Birrer:** Checkpoint Inhibitor Therapy for Microsatellite Instability (MSI)-High and Microsatellite-Stable (MSS) Endometrial Cancer

Module 2 – Dr Tewari: Current Indications for and Future Role of Immune Checkpoint Inhibitors in Cervical Cancer

Module 3 – Dr Matulonis: Current and Potential Role of Immune Checkpoint Inhibitor Therapy in Ovarian Cancer Management

**Module 4 – Dr O'Malley:** Novel Targeted Agents and Strategies Under Investigation for Gynecologic Cancers

Module 5: SGO/ASCO 2020 Review

Module 6: COVID-19 and Gynecologic Cancers

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

#### Agenda

**Module 1 – Dr Liu:** Genetic Testing in Ovarian Cancer (OC) and Biologic Basis for the Use of PARP Inhibitors

**Module 2 – Dr Moore:** Integration of PARP Inhibitor Maintenance into the Management of Newly Diagnosed OC

**Module 3 – Dr Lheureux:** *Practical Considerations with the Use of PARP Inhibitors in Advanced OC* 

Module 4 – Dr Coleman: Potential Role of PARP Inhibitors with Chemotherapy; Other Investigational Combination Approaches in Clinical Development for Advanced OC

Module 5: SGO Review 2020

#### 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





LIVE WEBINAR: Thursday, May 21, 2020 5:00 PM – 6:00 PM

## Understanding the Impact of COVID-19 on the Care of Patients with Chronic Lymphocytic Leukemia — A Live CME Webinar

Faculty

Matthew S Davids, MD, MMSc Anthony R Mato, MD, MSCE Jeff Sharman, MD

http://www.researchtopractice.com/Meetings/COVID19/CLL

A link to register for this event will be provided in the CME email you will receive after today's meeting.

MODULE 1: Checkpoint Inhibitor Therapy for Microsatellite Instability (MSI)-High and Microsatellite-Stable (MSS) Endometrial Cancer

#### Endometrial Cancer (EC) – Four molecular subtypes

(Integrated genomic, transcriptomic and proteomic characterization)



GOG 210 Endometrioid (Cosgrove 2018)

Incidence: 49% CNS, 4% POLE mutant, 39% MMR deficient, 8% copy number altered (CNA). Cancer-specific mortality: 5%=CNS ; 2.6% =POLE tumors; 7.6%=MMR deficient tumors; 19% with CNA tumors.

# POLE mutant and MSI-high resemble melanoma in mutation prevalence



Alexandrov et al, Nature 2013

## All Patients with Endometrial Cancer Should be Tested for dMMR!

- PCR Assay for selected PolyA microsatellites
- MLH1/PMS2 and MSH2/MSH6 IHC
- 5% false positive and negative rate



## Checkpoint Inhibitors Have Shown Activity in Endometrial Cancer, Particularly in MSI-H Tumors

	Fader et al <sup>1</sup>	KEYNOTE-028 <sup>2</sup>	NCT01375842 <sup>3</sup>	NCT02501096 <sup>4</sup>	<b>GARNET</b> <sup>5</sup>	Pooled MSI-H <sup>6</sup>
Phase(s)	2	1b	1	1 2 1		—
Population	Previously treated dMMR, recurrent/ persistent EC	Previously treated LA/metastatic PD-L1 positive EC	Recurrent EC	Advanced EC	Previously treated recurrent/advanced MSI-H EC	Previously treated MSI-H/dMMR EC <sup>d</sup>
Patients, n	9	24	15	53	35	14
Treatment	Pembrolizumab	Pembrolizumab	Atezolizumab	Pembrolizumab + lenvatinib	Dostarlimab (TSR-042)	Pembrolizumab
ORR, %	56 <sup>a</sup> (criteria not specified)	13.0 <sup>a,b</sup> (RECIST v1.1)	13 (RECIST v1.1)	39.6ª (irRECIST)	52 <sup>a,c</sup> (irRECIST)	36 <sup>e</sup> (RECIST v1.1 <sup>f</sup> )
DCR, %	89	26.0	13	86.8	64	_
DOR	_	_	_	NE	NRª	Range: 4.2+–17.3+ mo <sup>e</sup>
mPFS	-	1.8 mo	1.4 mo	7.4 mo	_	_
mOS	NR	NR	9.6 mo	—	—	—
Safety summary	No AEs Gr >3	Gr ≥3 TRAEs: 16.7%	Gr ≥3 TRAEs: 47%	Gr ≥3 TRAEs: 70%	Gr ≥3 TRAEs: 11.4%	See PI
Median follow-up	9.1 mo	76.2 wk	Min: 11.2 mo	-	_	—

+ Indicates ongoing response.<sup>a</sup> Primary endpoint. <sup>b</sup> Efficacy analysis included 23 patients. <sup>c</sup> Efficacy analysis included 25 patients. <sup>d</sup> Data pooled across 5 trials; these data led to approval of pembrolizumab for advanced or unresectable MSI-H/dMMR tumors. <sup>e</sup> Major efficacy outcome.

<sup>f</sup> Modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

AE, adverse event; DCR, disease control rate; dMMR, deficient mismatch repair; DOR, duration of response; EC, endometrial cancer; Gr, grade; irRECIST, immune-related RECIST; LA, locally advanced; Min, minimum; mOS, median overall survival; mPFS, median progression-free survival; MSI-H, high microsatellite instability; NR, not reached; ORR, overall response rate; RECIST, Response Evaluation Criteria In Solid Tumors; TRAE. treatment-related adverse event.

1. Fader AN, et al. Presented at SGO Annual Meeting, 2016. Late-Breaking Abstract 3. 2. Ott PA, et al. J Clin Oncol. 2017;35(22):2535-41.

3. Fleming GF, et al. Presented at ASCO Annual Meeting, 2017. Abstract 5585. 4. Makker V, et al. Presented at ASCO Annual Meeting, 2018. Abstract 5596. 5. Oaknin A, et al. Presented at ESMO Annual Meeting, 2018. Abstract 935PD. 6. Pembrolizumab package insert. February 2019.

# Lenvatinib and Pembrolizumab in Patients With Advanced Endometrial Cancer

**Key Eligibility Criteria** 

- Aged ≥18 years
- Pathologically confirmed and metastatic endometrial carcinoma
- ≤2 Prior systemic therapies
- Measurable disease by irRECIST
- ECOG performance status ≤1
- Life expectancy ≥12 weeks



		Not MSI-H	
	Total	or dMMR	MSI-H/dMMR
Response Category	(n = 108)	(n = 94)	(n = 11)
Best overall response, n (%)			
Complete response	11 (10.2)	10 (10.6)	1 (9.1)
Partial response	33 (30.6)	26 (27.7)	6 (54.5)
Stable disease	42 (38.9)	38 (40.4)	3 (27.3)
Progressive disease	14 (13.0)	12 (12.8)	1 (9.1)
Not evaluable	8 (7.4)	8 (8.5)	0
Objective response rate (complete response + partial response), n (%)	44 (40.7)	36 (38.3)	7 (63.6)

Makker V, et al. Presented at ESMO Annual Meeting

# Lenvatinib/Pembro: Challenges



- > 50% HTN, fatigue, diarrhea
- Grade 3 toxicities HTN (34%) and diarrhea (8%)
- HTN develops quickly
- 60% of patients had dose reduction of lenvatinib
- Average dose 14 mg

## Dostarlimab TSR-042

- A humanized monoclonal antibody directed against the negative immunoregulatory human cell surface receptor programmed cell death 1 (PD-1; programmed death-1),
- lgG4
- Dosing 1000 mg every 6 weeks
- Toxicities similar to other immune checkpoint inhibitors

## 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 (n=41)	MSS EC (n=79)	MSI status unknown (n=5)	Total (N=125)
Overall response rate	n (%) (95% Cl)	<b>20 (49%)</b> (32.9, 64.9)	<b>16 (20.%)</b> (12.0, 30.8)	<b>1(20.%)</b> (0.5,71.6)	<b>37 (30%)</b> (218, 38.4)
Complete response	n (%)	2 (49%)	4 (5.1%)	0 (0%)	6 (4.8%)
Partial response	n (%)	181> (43.9%)	12 (15.2%)	1 (20.0%)	31 (248%)
Disease control rated	% (95% CI)	63.4% (46.9, 77.9)	46.8% (355,584)	60.0% (147, 94.7)	52.8% (437, 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.

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

# Lenvatinib/pembrolizumab

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

Cisplatin/doxorubicin

Doxorubicin



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



Survey of general medical and gynecologic oncologists, May 2020

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?





Medical oncologists

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?



Survey of general medical and gynecologic oncologists, May 2020

For a patient with MSI-H 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?

#### 



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

# 400 mg every 6 weeks 0 0 0 0 0 0 0 0 0 0 0 13 200 mg every 3 weeks 0 0 0 0 0 0 0 0 0 0 0 12



# Dr Birrer: Case – MSI-high 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

#### After 12 months of anti-PD-1



#### Before starting anti PD-1







# Dr Birrer: Case – MSS Endometrial Cancer

- 41 year old biopsy proven G3 EMCA → CT scan negative for metastatic disease → proceed with surgery
- Surgery: RTLH/BSO/blSLND → 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



# Dr Birrer: Case – MSS (cont'd)

- 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


MODULE 2: Current Indications for and Future Role of Immune Checkpoint Inhibitors in Cervical Cancer

# Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Cervical Cancer: Results From the Phase II KEYNOTE-158 Study

Hyun Cheol Chung, MD, PhD<sup>1</sup>; Willeke Ros, MSc<sup>2</sup>; Jean-Pierre Delord, MD, PhD<sup>3</sup>; Ruth Perets, MD, PhD<sup>4</sup>; Antoine Italiano, MD, PhD<sup>5</sup>; Ronnie Shapira-Frommer, MD<sup>6</sup>; Lyudmila Manzuk, MD<sup>7</sup>; Sarina A. Piha-Paul, MD<sup>8</sup>; Lei Xu, PhD<sup>9</sup>; Susan Zeigenfuss, RN<sup>9</sup>; Scott K. Pruitt, MD, PhD<sup>9</sup>; and Alexandra Leary, MD, PhD<sup>10</sup>

PD-L1+ Cohort (CPS ≥ 1)		
ENDPOINT	N=77	COMBINED POSITIVE SCORE:
ORR (95% CI)	14.3% (7.4 - 24.1)	<u>PD-L1+ cells (tumor cells, lymphocytes, macropha</u> Total number of tumor cells x 100
Complete response	2.6%	
Partial response	11.7%	
Median duration (mos)	Not reached (4.1 - 18.6+)	
% with duration $\geq$ 6 mos	91%	
Median follow-up (mos)	11.7 (0.6 – 22.7)	

### **US FDA Accelerated Approval of Pembrolizumab** *First Immunotherapy Approved for Cervical Cancer (June 12, 2018)*



Companion Diagnostic PD-L1 IHC 22C3

#### Drugs

Home > Drugs > Drug Approvals and Databases > Approved Drugs

#### Approved Drugs

Hematology/Oncology (Cancer) Approvals & Safety Notifications

 Drug Information Soundcast in Clinical Oncology (D.I.S.C.O.)

Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)

# FDA approves pembrolizumab for advanced cervical cancer with disease progression during or after chemotherapy

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On 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 ≥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.

## BEATcc

### Phase III Randomized Frontline Trial of Atezolizumab (anti-PD-L1)



- Measurable disease by RECIST v1.1
- ECOG-PS: 0-1
- No previous systemic chemotherapy for advanced or recurrent disease
- N=404 pts

#### Primary Endpoints: 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

### Checkpoint Inhibition Key Concepts





#### Abscopal effect of hypofractionated radiotherapy

Endocrinopathies

Hodi FS, et al. J Clin Oncol 2018;36:850-8. Minion LE, Tewari KS. Gynecol Oncol 2018;148:609-21. Wolford JE, Tewari KS. Expert Opin Drug Discov 2018;13:445-57. 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 has received no prior systemic treatment?



Survey of general medical and gynecologic oncologists, May 2020

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 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?



Survey of general medical and gynecologic oncologists, May 2020

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?





# Dr Tewari: Case 1 – Recurrent 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/m<sup>2</sup> 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

# Dr Tewari: Case 1 (cont'd) – Recurrent Cervical Cancer

- 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<sup>®</sup> (3 cans/day)
    - Carboplatin (AUC 6) + Paclitaxel (175 mg/m<sup>2</sup> BSA) + Bevacizumab (15 mg/kg) x 7 cycles
    - Complete clinical response

# Dr Tewari: Case 1 (cont'd) – Recurrent Cervical Cancer

- 2020
  - Presents with left supraclavicular lymphadenopathy and mild hemoptysis
  - PET/CT
    - Supraclavicular node (SUV 12)
    - Bilateral pulmonary metastasis 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

# Dr Tewari: Case 2 – Metastatic Cervical Cancer

- 45 y/o Hispanic married mother of four, housekeeper
- Lives in Orange County, CA
- Lack of access to healthcare (no prior cervical cancer screening)
- Presents with vaginal bleeding and pelvic pain [ECOG PS = 1]
- Physical exam notable for cervical expansion with tumor eroding into the proximal third of the vagina
  - Biopsy confirms adenocarcinoma
- PET/CT demonstrates para-aortic metastases (SUV 8)
- Referred to the University of California, Irvine NCI-Designated Comprehensive Cancer Center
- Management:
  - Screened and enrolled on KEYNOTE-826; still remains on trial and appears to be doing well
  - Randomized to cisplatin (50 mg/m<sup>2</sup> BSA) + paclitaxel (175 mg/m<sup>2</sup> BSA) + bevacizumab (15 mg/kg) plus/minus pembrolizumab 200 mg/placebo q21 days

### MODULE 3: Current and Potential Role of Immune Checkpoint Inhibitor Therapy in Ovarian Cancer Management

#### 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

# Possible ways to improve the effectiveness of immune checkpoint inhibition in ovarian cancer

- Combination with other agents
  - Cytotoxic agents
  - Targeted agents
  - Other immune checkpoint inhibitors
  - Antiangiogenic therapies

### FIRST Trial of Dostarlimab (TSR-042)

#### ClinicalTrials.gov Identifier: NCT03602859



Stratification

· bevacizumab use (investigator choice)

HRR and BRCA status based on ctDNA with tumor sample as back-up

Stage III < 1 cm at PDS versus others</li>

#### Niraparib and Pembrolizumab Resulted in Clinical Activity Across a Broad Study Population



Patient Subgroup	No./Total No. of Patients	ORR, % (90% CI) <sup>a</sup>	
All	11/60	18 (11-29)	
Platinum status			
Resistant	6/29	21 (9-37)	
Refractory	2/16	13 (2-34)	
Not applicable <sup>b</sup>	3/15	20 (6-44)	
Prior lines of therapy <sup>c</sup>			
1-2	7/25	28 (14-46)	
≥3	4/35	11 (4-24)	
Prior bevacizumab use			
Yes	7/37	19 (9-33)	
No	4/23	17 (6-36)	
tBRCA status <sup>d</sup>			
tBRCAmut	2/11	18 (3-47)	
tBRCAwt	9/47	19 (10-31)	
PD-LI Status			
Positive	7/33	21 (10-36)	
Negative	2/21	10 (2-27)	
HRD status <sup>d</sup>			
HRD positive	3/21	14 (4-33)	
HRD negative	6/32	19 (9-34)	

Abbreviations: HRD, homologous recombination deficiency; ORR, objective response rate; PD-L1, programmed death-ligand 1; tBRCA, tumor BRCA; tBRCAmut, tumor BRCA mutation; tBRCAwt, tumor BRCA wild type.

- <sup>a</sup> Includes only confirmed responses using Response Evaluation Criteria in Solid Tumors, version 1.1.
- <sup>b</sup> Includes patients with an interval free of platinum-based chemotherapy of at least 180 days but unable to receive further platinum-based chemotherapy (owing to toxic effects or allergic reaction).
- <sup>c</sup> For pooled analysis, neoadjuvant therapy, adjuvant therapy, and the combination of both were considered to be 1 line of therapy. Small molecules, hormonal agents, and bevacizumab were not counted in the lines of therapy.

<sup>d</sup> Only patients with known biomarker status were included.

Now open....

A Phase 2 Open-Label, Single-Arm Study to Evaluate the Efficacy and Safety of the Combination of Niraparib and Dostarlimab (TSR-042) in Patients With Platinum Resistant Ovarian Cancer (MOONSTONE)

ClinicalTrials.gov Identifier: NCT03955471

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

# 



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



Survey of general medical and gynecologic oncologists, May 2020

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



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Median %

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





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Survey of general medical and gynecologic oncologists, May 2020

#### Dr Mautlonis Case: 74 yo WF

2011: diagnosed with advanced ovarian cancer, high grade serous, received 6 cycles of carbo/paclitaxel IV

2014: recurrence, surgery, and received 3 cycles of IP cisplatin and IV/IP paclitaxel followed by 3 cycles of carboplatin and paclitaxel IV

2016: recurrence and received single agent carboplatin IV

CT after 3 cycles showed PD

2017: went on trial 16-257 (NCT02865811), PLD and pembrolizumab; off study in 2019 because of 2 year mark for pembro (per study, pembro max is 2 years) and continued doxorubicin alone



#### Dr Matulonis Case: 65 yo WF

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

18-303 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



MODULE 4: Novel Targeted Agents and Strategies Under Investigation for Gynecologic Cancers

### Rationale for targeting Tissue Factor

- TF is normally ubiquitously present in the subendothelium
- In tumors TF is co-opted to promote tumor initiated thrombosis and cancer metastasis.



# Mechanism of action of tisotumab vedotin

- Tissue factor (TF) is aberrantly expressed in a broad range of solid tumours, including cervical cancer,<sup>1,2</sup> and TF expression has been associated with higher tumour stage and grade, higher metastatic burden and poor prognosis<sup>2</sup>
- 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<sup>3,4</sup>


## Background - innovaTV 201 Study Design

Tisotumab Vedotin first studied in multiple solid tumors, with specific expansion cohort in Cervical Cancer

- innovaTV 201 is a first-in-human, open-label, single-arm, phase I/IIa dose-escalating (3+3 design) and expansion study of TV in patients with locally advanced or metastatic solid tumors known to express TF
- Patients with clinical benefit (stable disease [SD] or better) at the end of 4 cycles had the option to continue TV for up to 8 additional cycles (12 cycles total) or until disease progression or unacceptable toxicity. After 12 cycles, patients with clinical benefit could continue in an extension study (NCT03245736)



innovaTV 201 Study Design

IV, intravenous; NSCLC, non-small-cell lung cancer; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria In Solid Tumours; SCCHN, squamous cell carcinoma of the head and neck. <sup>a</sup>Subjects were enrolled into cohorts at increasing dose levels of TV in 21-day treatment cycles. <sup>b</sup>The SCCHN cohort was closed by a protocol amendment due to an event of pharyngeal tumour haemorrhage with fatal outcome. The event was deemed to be most likely related to the disease itself. <sup>c</sup>In phase II, ovarian and cervical cohorts were expanded to include more patients based on preliminary efficacy observed in the first 14 patients enrolled. <sup>d</sup>AE severity graded per Common Terminology Criteria for Adverse Events [CTCAE] v4.0. <sup>e</sup>Computed tomography or magnetic resonance imaging was performed at baseline and every 6 weeks during the study for tumour assessments.

Vergote I, Concin N, Dean E, Lassen U, Drew Y, Machiels JP, Nielsen D, Arkenau T, Forster M, Jones R, Slomovitz B, Spicer J, Johnson M, Cornez N, Gennigens C, Fulton B, Basse L, Lisby S, Coleman RL, Hong DS ESMO 2018

## innovaTV 201 – Response Rate



CI=confidence interval; CR=complete response; CT=computed tomography; DCR=disease control rate; ORR=overall response rate; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.

<sup>a</sup>Two patients were withdrawn prior to CT scan, and so are not represented in the graph. <sup>b</sup>PD due to new lesion at same scan. <sup>c</sup>Clinical benefit was defined as the DCR rate, the proportion of patients who achieved a CR, PR, or SD after 12 weeks. <sup>d</sup>Response was as assessed by investigators using standard RECIST 1.1 criteria. <sup>e</sup>One of which is still ongoing. Data cutoff date July 24, 2017.

Vergote I, Concin N, Dean E, Lassen U, Drew Y, Machiels JP, Nielsen D, Arkenau T, Forster M, Jones R, Slomovitz B, Spicer J, Johnson M, Cornez N, Gennigens C, Fulton B, Basse L, Lisby S, Coleman RL, Hong DS ESMO 2018

## innovaTV 201 – Adverse events of special interest

	N=34	
AEOSI Term	Any Grade, n (%)	Grade ≥3, n (%)
Ocular (any) <sup>a</sup>	18 (53%)	1 (3%)
Conjunctivitis	17 (50%)	1 (3%)
Conjunctivitis scar	1 (3%)	0
Conjunctivitis viral	1 (3%)	0
Conjunctival ulceration	0	0
Keratitis	1 (3%)	0
Ulcerative keratitis	2 (6%)	0
Symblepharon	0	0
Neuropathy (any)	12 (35%)	2 (6%)

AESOI = adverse events of special interest.

<sup>a</sup>Most patients who experienced other events than conjunctivitis also experienced conjunctivitis.

Vergote I, Concin N, Dean E, Lassen U, Drew Y, Machiels JP, Nielsen D, Arkenau T, Forster M, Jones R, Slomovitz B, Spicer J, Johnson M, Cornez N, Gennigens C, Fulton B, Basse L, Lisby S, Coleman RL, Hong DS ESMO 2018

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



New dosing schedule

## CheckMate 358 Summary

- The results suggest clinical benefit with both regimens of nivolumab + ipilimumab in patients with R/M cervical cancer
  - While patient subgroups were small, responses were noted regardless of tumor cell PD-L1 expression
  - Across both regimens, efficacy was better in patients without prior systemic therapy versus with prior systemic therapy for R/M disease
- Responses were durable; at median follow-up >10 mo, median duration of response was not reached for either regimen in patients without prior systemic therapy
- The treatment regimens had a manageable safety profile; no new safety signals were detected
- Given the limited treatment options for patients with R/M cervical cancer, these data with nivolumab + ipilimumab are of strong clinical interest and warrant further investigation in this patient population

# Randomized phase II trial of carboplatin-paclitaxel versus carboplatin-paclitaxel-trastuzumab in uterine serous carcinoma that overexpresses HER2/neu: Updated Survival Analysis

- **Primary objective**: To estimate whether the addition of trastuzumab to paclitaxel and carboplatin chemotherapy improves PFS compared to paclitaxel and carboplatin alone
- Eligibility:
  - FIGO stage III-IV USC or recurrent USC
  - HER2/neu+ USC as defined by IHC score of 3+ (ASCO/CAP 2007 criteria) or 2+ with gene amplification confirmed by FISH
  - Patients diagnosed with recurrence were required to have measurable disease, defined as at least one target lesion per RECIST 1.1
  - Patients with recurrent disease may not have received >3 prior chemotherapies for treatment of their EC and a treatment-free interval of >6 months from last C/T was required for patients with recurrent disease
- Design
  - Originally designed to accrue 100 subjects
  - Power calculations for the trial assumed median PFS would be 6 months on the carboplatin/paclitaxel arm and 10.5 months on the carboplatin/paclitaxel/trastuzumab arm, equivalent to a

hazard ratio (HR) of 0.57 with trastuzumab addition

- First subject enrolled in August of 2011, after which (1) the accrual rate was slower than planned, and (2) observed PFS exceeded original expectations
- Because of this, interim futility analysis was performed. Study closed to further accrual in March of 2017 with 61 enrolled subjects.



<u>Amanda N. Fader</u>, Dana M. Roque, Eric Siegel, Natalia Buza, Pei Hui, Osama Abdelghany, Setsuko K. Chambers, Angeles Alvarez Secord, Laura Havrilesky, David M. O'Malley, Floor Backes, Nicole Nevadunsky, Babak Edraki, Dirk Pikaart, William Lowery, Karim S. ElSahwi, Paul Celano, Stefania Bellone, Masoud Azodi, Babak Litkouhi, Elena Ratner, Dan-Arin Silasi, Peter E. Schwartz, and Alessandro D. Santin SGO 2020

#### **OVERALL SURVIVAL**

- Benefit was particularly striking in the stage III-IV pts, with a median OS of 25.4 mos (control) compared with an unreached median OS (experimental; p=0.0406, HR: 0.492, 90%CI 0.249-0.974)
- There was no significant OS benefit observed in the recurrence cohort



## Carboplatin-paclitaxel-trastuzumab - Summary

- First trial of targeted therapy in USC ONLY pts
- Demonstration that HER2 is an important prognostic and actionable target in USC
- NCCN designation of C/T/Trastuzumab as a preferred regimen in HER2+ USC (Level IIA)

Amanda N. Fader, Dana M. Roque, Eric Siegel, Natalia Buza, Pei Hui, Osama Abdelghany, Setsuko K. Chambers, Angeles Alvarez Secord, Laura Havrilesky, David M. O'Malley, Floor Backes, Nicole Nevadunsky, Babak Edraki, Dirk Pikaart, William Lowery, Karim S. ElSahwi, Paul Celano, Stefania Bellone, Masoud Azodi, Babak Litkouhi, Elena Ratner, Dan-Arin Silasi, Peter E. Schwartz, and Alessandro D. Santin SGO 2020 Randomized double-blind placebo controlled trial of primary maintenance vigil immunotherapy (VITAL study) in stage III/IV ovarian cancer: Efficacy assessment in BRCA1/2-wt patients

- Vigil is an autologous tumor cell vaccine constructed from autologous harvested tumor tissue
  - transfected with a DNA plasmid encoding GMCSF
  - transfected with bi-shRNA-furin

## Vigil MOA



Senzer et al. Mol Ther. 2012 Mar;20(3):679-86 | Senzer et al. J Vaccines Vaccine 2013; 4: 209 "The Chinese use two brush strokes to write the word 'crisis.' One brush stroke stands for danger; the other for opportunity. In a crisis, be aware of the danger—but recognize the opportunity."

— John F. Kennedy



https://www.goodreads.com/author/show/3047.John\_F\_Kennedy





#### Dr O'Malley Case 1: A woman in her 20s

- 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 lovance 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

The James



#### Screening







## Cycle 2



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

#### The James



#### Dr O'Malley Case 2: A woman in her 40s

- 2018: Diagnostic laparoscopy biopsy omental
  - Poorly differentiated squamous cell carcinoma consistent with metastatic cervical cancer.
  - Cisplatin and paclitaxel x 4 cycles. CT scan with partial response and resolution of bowel obstruction.
  - 2018: Cisplatin, paclitaxel, and bevacizumab started (avastin added after cycle 5, received 8 cycles total) Mixed response
  - 2019: 12 cycles of Pembro
  - Palliative RT to the pelvis

Tumor testing: Anti-PD-1 Result: High positive for PD-1; Positive for PD-L1 expression (TPS 1-49%); Tumor proportion score (TPS)\*: 5%.





#### innovaTV 205 (GOG 3024) Arm F (TV & pembro)

#### Screening

Cycle 2



- 11% decrease RECIST
- Removed off trial due to recurrent SBO





#### MODULE 5: SGO/ASCO 2020 Review

#### **MODULE 6: COVID-19 and Gynecologic Cancers**

Do you believe that receiving an anti-PD-1/PD-L1 antibody makes a patient more <u>susceptible to contracting COVID-19</u>?



#### 



Medical oncologists

Do you believe that receiving an anti-PD-1/PD-L1 antibody increases a patient's risk of <u>developing complications</u> <u>associated with COVID-19</u>?

## Yes • • • • • • 7 No • • • • • 6

## I don't know



Medical oncologists



Contents lists available at ScienceDirect

#### **Gynecologic Oncology**

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

Clinical Practice Statement

## Anti-cancer therapy and clinical trial considerations for gynecologic oncology patients during the COVID-19 pandemic crisis\*

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e University of Alabama at Birmingham, Birmingham, AL, United States

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<sup>h</sup> University of Oklahoma, Stephenson Cancer Center, Oklahoma City, OK, United States

<sup>i</sup> University of Texas, MD Anderson Cancer Center, Houston, TX, United States

<sup>j</sup> Levine Cancer Center, Atrium Health, Charlotte, NC, United States

Gynecol Oncol 2020;[Online ahead of print].

#### HIGHLIGHTS

- The world wide COVID-19 pandemic has limited cancer care and clinical trials.
- Strategies should be employed to limit contact points with health care facilities.
- All care should consider the risks of cancer care balanced against the risk of COVID-19 infection.

#### **SGO Clinical Practice Statement**

Regardless of geographic location, COVID-19 will impact all practitioners; however, the degree will vary based on COVID-19 burden and available local resources.

Pothuri B et al. Gynecol Oncol 2020;[Online ahead of print].

- COVID-19 infection and early immunotherapy-related pneumonitis have similar presentations. In the case of suspected pneumonitis, test for COVID-19 before starting steroids and collaborate with pulmonary consultants.
- Access to PFTs and bronchoscopy may be limited and decisions may need to be made based on clinical findings and severity of symptoms.

- Consider less-frequent dosing intervals with immune checkpoint inhibitors:
  - Pembrolizumab 400 mg IV q6wk
  - Nivolumab 480 mg IV q4wk
  - Atezolizumab 1,680 mg IV q4wk

- Currently no evidence demonstrates that immunotherapy, in cancer patients, increases COVID-19 susceptibility. Strong overlap exists between immunerelated pneumonitis and COVID-19 infection, including cough, dyspnea, fever and CT findings of ground-glass opacities and interstitial changes.
- Pre-existing lymphopenia is associated with lower immunotherapy response and predicts more severe COVID-19 infections.

- Currently, the WHO and CDC recommend that corticosteroids not be used in treatment of COVID-19 viral pneumonia or ARDS unless indicated for another reason (asthma, COPD, septic shock).
- Pre-existing lymphopenia is associated with lower immunotherapy response and predicts more severe COVID-19 infections.

Pothuri B et al. Gynecol Oncol 2020;[Online ahead of print].

## SGO Clinical Practice Statement: Clinical Trial Considerations

Prioritize Tier 1 studies where there is high potential benefit (ie, trial that offers a drug when alternative treatments are limited) in resource-stratified environments.

Pothuri B et al. Gynecol Oncol 2020;[Online ahead of print].

### Thank you for joining us!

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