Gynecologic Oncology Updates
Beyond Carbo/Taxol

ERIN HICKEY ZACHOLSKI, PHARMD, BCOP
ASSISTANT PROFESSOR, VCU SCHOOL OF PHARMACY

1

Disclosures

I have the following financial disclosures to report over the past 24 months:

- Advisory board, UroGen Pharma
- Speaker - Internal Medical Affairs, Seagen

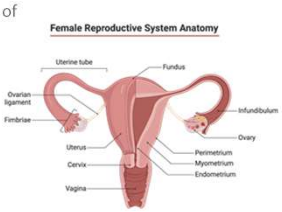
I *will* be discussing off-label indications.

2

Audience response #1

As a pharmacist, I am involved in the care of patients with ovarian, cervical, and/or endometrial cancers:

A. Never
B. Once in a while
C. Most days
D. Every day



Images created with BioRender.

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Objectives

1. Define the historical role of platinum-doublet chemotherapy in the treatment of gynecologic malignancies
2. Identify updates to standard treatment of gynecologic malignancies since 2020
3. Appraise evidence supporting changes to standard treatment of gynecologic malignancies
4. Construct a supportive care plan to prevent and manage toxicity with novel therapies used in gynecologic malignancies

4

Platinum/taxane regimens

- Cell types sensitive to DNA damage (e.g. adenocarcinoma, squamous cell carcinoma)
- Synergy
- Tolerability
  - Carboplatin AUC 5-6 IV + paclitaxel 135-175 mg/m2 IV Q21-28d
  - Cisplatin 75 mg/m2 IV + paclitaxel 135-175 mg/m2 IV Q21d
  - Carboplatin AUC 5-6 IV + docetaxel 60-75mg/m2 IV Q21

Images created with BioRender.
Ozols RF, Bundy BN, Greer BE, et al. JCO. 2003;21(17):3194-3200.
Wiley PA, Jayson GC, Gordon A, et al. JNCI Journal of the National Cancer Institute. 2004;96(22):1682-1691.

5

Platinum/taxane regimens

	Efficacy	Limitations
Platinums ● Carboplatin ● Cisplatin Taxanes ● Paclitaxel ● Docetaxel	Objective response rates: ● Ovarian (primary): 73-76% ● Cervical (1L, recurrent/mx): 62.6% ● Endometrial (1L, recurrent/mx): 52% Overall survival: ● Ovarian (primary): 57.4 mo. ● Cervical (1L, recurrent/mx): 13 mo. ● Endometrial (1L, recurrent/mx): 37 mo.	

Wiley PA, Jayson GC, Gordon A, et al. JNCI Journal of the National Cancer Institute. 2004;96(22):1682-1691.
Kitagawa R, Katsumata N, Shibata T, et al. JCO. 2015;33(19):2129-2135.
Ozols RF, Bundy BN, Greer BE, et al. J Clin Oncol. 2003;21(17):3194-3200.
Wiley PA, Jayson GC, Gordon A, et al. JCO. 2004;96(22):1682-1691.

6

Audience response #2

Which is a limitation of platinum-taxane combinations in the treatment of gynecologic malignancies?

A. Regimens yield response rates <50%
B. Disease commonly recurs after therapy is completed
C. Regimens cause too much toxicity for the outpatient setting
D. Nothing, they are all we'll ever need in Gyn Onc

7

Platinum/taxane regimens

	Efficacy	Limitations
Platinums • Carboplatin • Cisplatin Taxanes • Paclitaxel • Docetaxel	Objective response rates: • Ovarian (primary): 73-76% • Cervical (1L, recurrent/mx): 62.6% • Endometrial (1L, recurrent/mx): 52% Overall survival: • Ovarian (primary): 57.4 mo. • Cervical (1L, recurrent/mx): 17.5 mo. • Endometrial (1L, recurrent/mx): 37 mo.	• High recurrence rates • Genetic and histologic variability in response • Recurrence therapies following primary treatment have low efficacy

Ozols RF, Bundy BN, Greer BE, et al. JCO. Oncol. 2003;21(17):3194-3200.
Miller DS, Filiaci VL, Mannel RS, et al. JCO. 2020;38(13):1341-1352.
Vasey PA, Jayson GC, Gordon A, et al. JNCI Journal of the National Cancer Institute. 2004;96(22):1682-1691.
Kitagawa R, Katsumata N, Shibata T, et al. JCO. 2015;33(19):2129-2135.

8

"Top 2s of the 2020s"

Ovarian	Cervical	Endometrial
1. Changing role of PARP inhibitors 2. Mirvetuximab soravtansine	1. "Quadruplet" therapy 2. Tisotumab vedotin	1. Lenvatinib + pembrolizumab 2. Chemotherapy + pembrolizumab

9

Ovarian Cancer

18th *most common cancer*

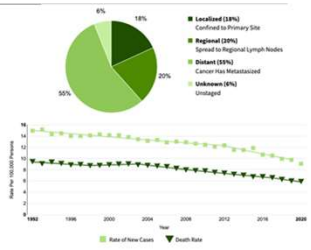
8th *most common cancer (US)*

1st *gyn. cancer mortality*

63 years *median diagnosis*

70% *diagnosed at adv. stage*

50.8% *5-year relative survival*



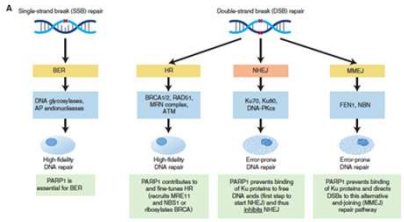
SEER Cancer Stat Facts: Ovarian Cancer. NCI. Bethesda, MD. October 2023.

10

PARP Inhibitors in Ovarian Cancer

PARP - essential repair enzyme:

- SSB repair: BER
- DSB repair: HR (high-fidelity) and NHEJ/MMEJ (error prone)



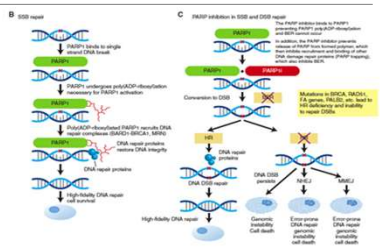
Kinsella, G., Kristeleit, R. Br J Cancer 2016;115, 1157–1173

11

PARP Inhibitors in Ovarian Cancer

PARP inhibitors

- Prevent high-fidelity DNA repair → cell death
- Effect more pronounced in cells with BRCA mutation or HRD



Kinsella, G., Kristeleit, R. Br J Cancer 2016;115, 1157–1173

BRCA: breast cancer; HRD: Homologous recombination deficiency;

12

PARP Inhibitor Indications - Pre-2020

	Maintenance After Primary Treatment	Maintenance After Recurrence	Treatment
Olaparib	2018 (BRCAm)[1]	2017 (all)[2]	2014 (BRCAm)[3]
Rucaparib		2018 (all)[2]	2016 (BRCAm)[4]
Niraparib		2017 (all)[2]	2019 (BRCAm)[5]

1 Patients with germline or somatic (g/s) BRCA1/2 mutation after response to primary chemotherapy
2 Patients after response to recurrence chemotherapy
3 Patients with g BRCA who have received 3+ lines of therapy
4 Patients with g/s BRCA who have received 2+ lines of therapy
5 Patients with recurrent, platinum-sensitive HRD+ disease who have received 3+ lines of therapy

13

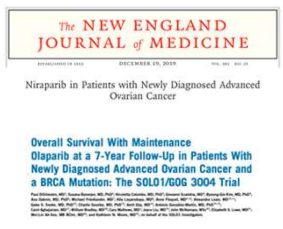
PARP Inhibitor Indications - Post-2020

	Maintenance After Primary Treatment	Maintenance After Recurrence	Treatment
Olaparib	• 2018 (BRCAm) • 2020 (HRD w/ bev.)	2017	2014
Rucaparib		2018	2016
Niraparib	• 2020 (All)	2017	2019

New or sustained FDA approval
FDA approval changed
FDA approval withdrawn

14

In: PARP inhibitors for 1' maintenance


The NEW ENGLAND JOURNAL of MEDICINE

DECEMBER 19, 2019

Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

Overall Survival With Maintenance Olaparib at a 7-Year Follow-Up in Patients With Newly Diagnosed Advanced Ovarian Cancer and a BRCA Mutation: The SOLO1/GOG 3004 Trial


A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (ATHENA–MONO/GOG-3020/ENGOT-ov45)

ORIGINAL ARTICLE

Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer

15

SOLO-1 7-year follow-up

- **Olaparib** maintenance for newly-diagnosed BRCA+ advanced ovarian cancer
- Randomized, double-blind, Phase 3

Population (N=391)

- Newly diagnosed, advanced high grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube
- Upfront or interval surgery
- Complete or partial response to first-line platinum-based chemotherapy (without bevacizumab)
- Somatic/germline BRCA1/2 mutation

1:1

Olaparib 300 mg BID n=130

Placebo n=131

2 years

Endpoints

Primary:
- PFS

Secondary:
- OS
- Time from random assignment to second subsequent therapy or death (TSST)
- Time from random assignment to discontinuation or death (TDT)
- Safety & tolerability

DiSilvestro P, Banerjee S, Colombo N, et al. J Clin Oncol. 2023 Jan 20;41(3):609-617.

BID: twice daily; PFS: progression free survival; OS: overall survival

16

SOLO-1 7-year follow-up

- Median OS
  - Olaparib v. placebo: NR v. 75.2 mo. (HR 0.55 (95% CI, 0.40 to 0.76); P = 0.0004))
  - Olaparib v. placebo: 67% v. 46.5%
  - Not significant, but clinically meaningful:
    - Post-protocol therapy, including PARPi
    - BRCAm → better prognosis
    - Data maturity 38.1%
    - Benefit extends beyond 2 years
- Toxicity
  - Nausea/vomiting, fatigue/asthenia
  - MDS/AML
    - Olaparib v. placebo: 4 (1.5%) v. 1 (0.8%)

DiSilvestro P, Banerjee S, Colombo N, et al. J Clin Oncol. 2023 Jan 20;41(3):609-617.

NR: not reached; HR: hazard ratio; CI: confidence interval; MDS/AML: myelodysplastic syndrome/acute myelogenous leukemia

17

PAOLA-1

- **Olaparib + bevacizumab** maintenance for newly-diagnosed, advanced ovarian cancer
- Randomized, double-blind, Phase 3

Population (N=806)

- Newly diagnosed, advanced high grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube
- Upfront or interval surgery
- Complete or partial response to first-line platinum-based chemotherapy **WITH bevacizumab**
- Central testing to determine BRCA status & HRD

2:1

Olaparib 300mg BID + bevacizumab 15 mg/kg Q3weeks n=537

Placebo + bevacizumab 15 mg/kg Q3weeks n=269

Bev: 15 months
Olaparib/placebo: 2 years

Endpoints

Primary:
- PFS in Overall Pop.

Secondary:
- PFS2
- OS
- Time to subsequent therapy or death
- QoL
- Safety & tolerability

Ray-Coquard I, Pautier P, Pignata S, et al. N Engl J Med. 2019; 381:2416-2428

QoL: quality of life

18

PAOLA-1

- Median PFS (22.9 months):
  - Olaparib v. placebo:
    - All: 22.1 mo. v. 16.6 mo. (HR 0.59; 95% CI, 0.49 to 0.72)
    - BRCAm: 37.2 mo. v. 21.7 mo. (HR 0.31; 95% CI, 0.2 to 0.88)
    - HRD: 37.2 mo. v. 17.7 mo. (HR 0.33; 95% CI, 0.25 to 0.45)
    - HRP or unknown: 16.9 mo. v. 16.0 mo. (HR 1.00; 95% CI, 0.75 to 1.35)
- Toxicity
  - Fatigue, nausea, anemia
  - Hypertension
    - 13% v. 9%
- QoL
  - No difference

Ray-Coquard I, Pautier P, Pignata S, et al. N Engl J Med 2019; 381:2416-2428
Myriad Genetics. Knowing HRD status is essential in determining ovarian cancer treatment options. Accessed Oct 2023 from: https://myriad.com/genetic-tests/mychoice-brca-tumor-test/

HRP: homologous recombination proficient

19

PRIMA

- **Niraparib** maintenance for newly-diagnosed, advanced ovarian cancer
- Randomized, double-blind, Phase 3

Population (N=733)

- Newly diagnosed, advanced high grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube
- Upfront or interval surgery
- Complete or partial response to first-line platinum-based chemotherapy **WITH bevacizumab**
- Central testing to determine BRCA status & HRD

2:1

Niraparib 300mg daily* n=487

Placebo n=246

3 years

Endpoints

Primary:
- PFS in HRD & Overall Pop.

Secondary:
- OS
- PFS2
- Time to subsequent therapy
- PROs
- Safety & tolerability

*Amended to incorporate personalized dosing

González-Martín, Pothuri B, Vergote I, et al. N Engl J Med 2019;381:2391-402

PROs: Patient reported outcomes

20

PRIMA

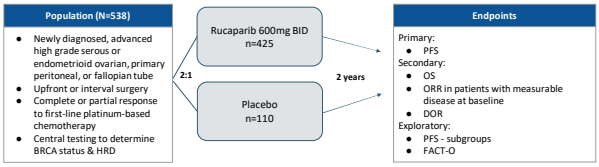
- Median PFS (13.8 months):
  - Niraparib v. placebo:
    - HRD: 21.9 mo. v. 10.4 mo. (HR 0.43; 95% CI, 0.31 to 0.59)
    - All: 13.8 mo. v. 8.2 mo. (HR 0.62; 95% CI, 0.5 to 0.76)
      - HRP or unknown: 8.1 mo. v. 5.4 mo. (HR 0.68; 95% CI, 0.49 to 0.94)
- Toxicity
  - Dose reductions = 70.9%
  - Discontinuation 2/2 AE 12%
  - Myelosuppression, fatigue, nausea

González-Martín, Pothuri B, Vergote I, et al. N Engl J Med 2019;381:2391-402

21

ATHENA-MONO

- **Rucaparib** maintenance for newly-diagnosed, advanced ovarian cancer
- Randomized, double-blind, Phase 3



ORR: objective response rate; DOR: duration of response; FACT-O: Functional Assessment of Cancer

22

ATHENA-MONO

- Median PFS (26.1 months):
  - Rucaparib v. placebo:
    - HRD: 28.7 mo. v. 11.3 mo. (HR 0.47; 95% CI, 0.31 to 0.72)
    - All: 20.2 mo. v. 9.2 mo. (HR 0.52; 95% CI, 0.4 to 0.68)
      - HRP or unknown: 12.1 mo. v. 9.1 mo. (HR 0.65; 95% CI, 0.45 to 0.95)
- Toxicity
  - Dose reductions = 49.4%
  - Discontinuation 2/2 Adverse event (AE) 11.8%
  - Myelosuppression, fatigue, nausea

23

Out: PARP inhibitors for 2' maint. & treatment

AstraZeneca, Merck withdraw Lynparza's late-line ovarian cancer nod amid PARP inhibitor death concerns

By Angus Liu · July 25, 2022 11:04am

SUMMARY: REVISIONS TO FDA APPROVALS FOR PARP INHIBITORS IN THE MANAGEMENT OF OVARIAN CANCER

News > Medscape Medical News

Increased Risk for Death Prompts Withdrawal of Three PARPi Indications for Ovarian Cancer

Sharon Worcester, MA
September 23, 2022

24

PARPi Approval Withdrawals

Recurrent Maintenance Setting

Trial	Design	Initial Results	Updated Results	Outcome
NOVA	• Phase 3 RCT • N=553 ○ 2:1 niraparib or placebo • PSOC with response to platinum-based regimen	Median follow-up 16.9 mo.: • PFS (gBRCA): 21.0 v 5.5 mo. (p<0.001) • PFS (non-gBRCA): 9.3 v 3.9 mo. (p<0.001)	77.9% maturity • OS (gBRCA) = 40.9 v 38.1 mo. (HR 0.85; 95% CI 0.0.61-1.2) • **OS (non-gBRCA) = 31 v. 34.8 mo. (HR 1.06; 95% CI 0.81-1.37**	FDA approval withdrawn for non-gBRCA
ARIEL-3	• Phase 3 RCT • N=564 ○ 2:1 rucaparib or placebo • PSOC with response to platinum-based regimen	• PFS (gBRCA): 16.6 v 5.4 mo. (p<0.0001) • PFS (non-gBRCA): 10.8 v 5.4 mo. (p<0.0001)	70% maturity (pre-planned): • OS (gBRCA) = 45.9 v 47.8 mo. (HR 0.83; 95% CI 0.58-1.19) • **OS (non-BRCA) = 36 v 43.2 mo. (HR 0.995; 95% CI 0.809-1.223)**	FDA approval withdrawn for non-gBRCA

Moore KN, Mirza MR, Matulonis UA. The Poly (ADP-ribose) polymerase inhibitor niraparib: management of toxicities. Gynecol Oncol. 2018;149(1):214-220.
Coleman RL, Oza AM, Lorusso D, et al. Journal of Gynecologic Cancer 2022;32:A220.
Society of Gynecologic Oncology. Summary: Revisions to FDA Approvals for PARP Inhibitors in the Management of Ovarian Cancer. 2022.

RCT: randomized control trial; PSOC: platinum sensitive ovarian cancer

25

PARPi Approval Withdrawals

Single-Agent Treatment Setting

Trial	Design	Initial Results	Updated Results	Outcome
ARIEL-4	• Phase 3 RCT • N=349 ○ 2:1 rucaparib or chemotherapy • Recurrent ovarian cancer, ≥2 lines	PFS: 7.4 v 5.7 mo. (p=0.001)	OS = 19.6 v 27.1 mo. (HR 1.55; 95% CI 1.085-2.214)	FDA approval withdrawn for 2+ lines of therapy
SOLO-3	• Phase 3 RCT • N=266 ○ 2:1 olaparib or chemotherapy • Partially platinum-sensitive or PSOC ≥ 2 lines, BRCAm	• ORR: 72.2% v 51.4% (p=0.002) • PFS (non-gBRCA): 13.4 v 9.2 mo. (p=0.013)	60.9% maturity: • OS (2+) = 34.9 v 32.9 mo. (HR 1.07; 95% CI 0.0.76-1.49) • **OS (3+) = 29.9 v 39.4 mo. (HR 1.33; 95% CI 0.84 to 2.18)**	FDA approval withdrawn for 3+ lines of therapy
QUADRA	• Single-arm • N=463 ○ Niraparib • Recurrent ovarian cancer, ≥3 lines	ORR = 28%	No comparative OS can be obtained due to trial design	FDA approval withdrawn for 3+ lines of therapy

Kristeleit R, Lisyanskaya A, Fedenko A, et al. Lancet Oncology. 2022;23(4):465-476.
Monk BT, Valencia RV, Oliva E, et al. JCO. 2020;38(11):1164-1174.
Moore KN, Secord AA, Geller MA, et al. Lancet Oncology. 2019;20(5):636-648.
Society of Gynecologic Oncology. Summary: Revisions to FDA Approvals for PARP Inhibitors in the Management of Ovarian Cancer. 2022.

26

MDS/AML Risk

- World Health Organization (WHO) Pharmacovigilance Database Systematic review and meta-analysis of PARP inhibitor RCTs
  - 28 RCTs: 43% ovarian cancer
  - Median latency = 17.8 months
  - Incidence across trials = 0.83%
  - OR = 2.63 (95% CI 1.13-6.14)
- Highest rates:
  - Duration > 24 months
  - g/sBRCA mutations

Trial	MDS/AML - PARPi	MDS/AML - Placebo
NOVA	3.8%	1.7%
ARIEL-3	3.7%*	2.1%
SOLO-2	8%	4%

*11.4% of "exceptional responders"
*15.2% of patients with BRCAm treated ≥24 months

Armstrong DK. Gynecologic Oncology. 2022;177:162-163.
Mateo JW, Lord CJ, Banerji U, et al. Lancet Haematology. 2021;8(2):e122-e134.

27

PARPi Pearls

- Dosing
  - Niraparib: 100mg, 200mg, 300mg, tablets
  - Weights and plates
    - Weight < 77kg OR Plt < 150K → 200mg daily
    - Weight > 77kg AND Plt >/=150 K → 300mg daily
  - Olaparib: 100mg & 150mg tablets
  - Rucaparib: 200mg, 250mg, 300mg tablets
- AE Management
  - Top 3:
    - Fatigue
    - Myelosuppression
    - Nausea/vomiting
  - Strategies:
    - Boost patient confidence
    - Liberal dose-reductions and holds
    - Anti-emetic pre-med for some
- Monitoring

	CBC w/ diff	Other
Olaparib	Baseline, monthly	*BMP baseline*
Rucaparib	Baseline, monthly	*BMP baseline*
Niraparib	Baseline, **weekly x 1 month**, monthly	BP/HR weekly x 2 months, then monthly

28

Audience response #3

JR is a 68 yo female with newly-diagnosed Stage III high-grade serous ovarian cancer. She has completed 6 cycles of carboplatin AUC 6 + paclitaxel 175 mg/m2 every 3 weeks.

Genetics: homologous recombination proficient (HRP), g/s BRCA wild-type
Weight: 56kg
CBC (4 weeks post-chemo): ANC 2.0 Plt 212 Hgb 10.0

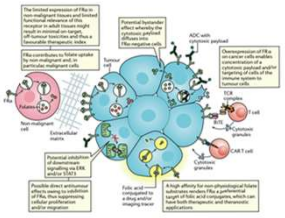
Which is the most appropriate maintenance chemotherapy for her?

A. Niraparib 200mg daily
B. Niraparib 300mg daily
C. Olaparib 300mg BID
D. Olaparib 300mg BID + bevacizumab 15mg/kg IV Q21 days

29

Mirvetuximab (MIRV) soravtansine

- **Folate receptor alpha (FRα)** is a cell-surface transmembrane protein responsible for folate transport into cells
  - Limited to polarized epithelial tissue (ovary, uterus, choroid plexus, kidney, lung)
  - Aberrant FRα overexpression (~80% epithelial OC)
- **FRα** directed antibody and DM-4 conjugate
  - Ab: Humanized anti-FRα monoclonal antibody
  - Linker: cleavable disulfide linker
  - Payload: DM-4 (anti-microtubule maytansine derivative)
  - DAR: 3-4



30

Mirvetuximab soravtansine: Efficacy

- **FDA Accelerated Approval granted November 2022**

Trial Design	Patient Population	Efficacy Results

SORAYA
 	
Multicenter, **single-arm**, phase 3 study
 	
Mirvetuximab soravtansine
	110 adult patients with platinum-resistant ovarian cancer treated with 1-3 prior regimens
	• **High FRα expression (≥ 75% of cells with PS2+ staining intensity)**
	• Prior bevacizumab required
		• Objective response rate (ORR) = 32.4%
		  ○ Complete response = 4.8%
		  ○ Partial response = 27.6%
		  ○ Stable disease = 45.7%
		• Disease Control Rate (DCR) = 51.4%
		• Median DOR = 6.9 months
		• Overall survival 12.1 months

MIRASOL Multicenter, randomized, controlled trial Mirvetuximab soravtansine v. investigator's choice chemotherapy	453 adult patients with platinum-resistant ovarian cancer treated with 1-3 prior regimens • **High FRα expression (≥ 75% of cells with PS2+ staining intensity)** • Prior bevacizumab allowed	• Primary endpoint: ○ **PFS: 5.62 mo. v. 3.98 mo. (p<0.0001)** • OS: 16.46 mo. v. 12.75 mo. (p=0.0046) • ORR: 42.3% v. 25.9%

Matulonis UA, Lorusso D, Oaknin A, et al. Journal of Clinical Oncology. 2023;41(13).
Moore KN, Oza AM, Colombo N, et al. Annals of Oncology. 2021;32(6):757-765.

31

Mirvetuximab soravtansine: Safety

Adverse Effect	Reported Frequencies

Ocular toxicity	• 61% (Severe = 9%; 0.6% leading to discontinuation of MIRV)
	  ○ Blurry vision (41%, Severe = 6%)
	  ○ Corneal problems (36%, Severe = 8%, Grade 4 = 1%)
	  ○ Dry eye (26%, Severe = 2%)
	  ○ Light sensitivity (13%)
	• Most patients had complete or partial resolution of eye symptoms after stopping MIRV

Nausea/vomiting	• 29% of patients (nausea) and 11% of patients (vomiting)
Infusion reactions	• 9% of patients
Neuropathy	• 13% of patients
Other	• Fatigue: 24% • Diarrhea: 22% • Low ANC/platelets/hemoglobin: 13% (Grade 3 = 2%)/9.5%/10.7% • Increased liver enzymes = 30-50% • Pneumonitis = 8-10%

Matulonis UA, Lorusso D, Oaknin A, et al. Journal of Clinical Oncology. 2023;41(13).

32

Mirvetuximab soravtansine: Pearls

- Ocular toxicity

	Day Before Infusion	Days 1-4	Days 5-8	Day 9+
Corticosteroid eye drops (i.e., prednisolone 1%)	1 drop in each eye 6x/day	1 drop in each eye 6x/day	1 drop in each eye 4x/day	Stop
Preservative-free lubricating eye drops	1 drop in each eye 4 times daily and as needed while on treatment with mirvetuximab soravtansine			
Other	• Avoid contact lenses • Obtain eye exam at baseline, every other cycle through cycle 8, and then as clinically indicated			

- Infusion reactions
  - Cycle 1 rate titration: 1mg/min x 30 min → 3 mg/min x 30 min → 5 mg/min
  - Dexamethasone, diphenhydramine, acetaminophen pre-medication
- Nausea/vomiting
  - Moderate emetic risk
- Dosing based on Adjusted Ideal Body Weight
  - AIBW = Ideal body weight (kg) + 0.4 × (actual weight [kg] − ideal body weight [kg])
    - Female ideal body weight (kg) = 0.9 × height (cm) − 92
- Compatible with D5W only

Elahere [package insert]. ImmunoGen, Inc. Waltham, MA. 02451.2022.

33

Cervical Cancer

4th *most common cancer*

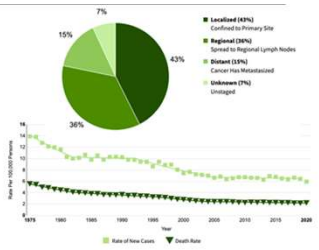
20th *most common cancer (US)*

2nd *gyn. cancer mortality*

50 years *median diagnosis*

79% *diagnosed at early stage*

67.2% *5-year relative survival*



SEER Cancer Stat Facts: Ovarian Cancer. NCI. Bethesda, MD. October 2023.

34

Front-line Therapy for Metastatic/Recurrent Cervical Cancer

- 28-64% of locally-advanced cervical cancer cases will recur
- 15% with metastatic disease at presentation

- *Historical* front-line treatment options:
  - Platinum doublet → OS = 13.3 months
  - Platinum doublet + bevacizumab → OS = 17 months

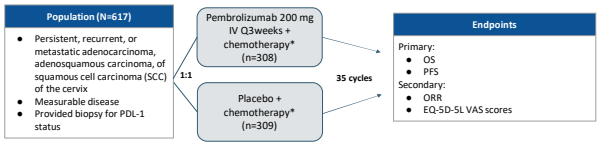
- *Historical* 2+ line treatment options: ORR ~10%
  - Pembrolizumab (PD-L1+) = 14%

Tewari KS, Sill MW, Long HJ, et al. *N Engl J Med.* 2014;370(8):734-743.
Chung HC, Ros W, Delord JP, et al. *J Clin Oncol.* 2019;37(17):1470-1478.

35

KEYNOTE 826

- Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer
- Randomized, double-blind, Phase 3



*Paclitaxel 175 mg/m2 + cisplatin 50 mg/m2 OR carboplatin AUC 5 x 6 cycles +/- bevacizumab 15 mg/kg continued until disease progression or unacceptable toxicity

Colombo N, Dubot C, Lorusso D, et al. *N Engl J Medicine.* 2021;NEJMoa2112435.

36

KEYNOTE 826

- Median PFS
  - Pembrolizumab v. placebo
    - ITT: 10.4 mo. v. 8.2 mo. (HR 0.65; CI 95%, 0.53-0.79)
    - PD-L1 ≥ 1: 10.4 mo. v. 8.2 mo. (HR 0.62; CI 95%, 0.5-0.77)
    - PD-L1 ≥ 10: 10.4 mo. v. 8.2 mo. (HR 0.58; CI 95%, 0.44-0.77)
- Median OS
  - Pembrolizumab v. placebo (24 months):
    - ITT: 50.4% v. 40.4% (HR 0.67; CI 95%, 0.54-0.84)
    - PD-L1 ≥ 1: 53% v. 41.7% (HR 0.64; CI 95%, 0.5-0.81)
    - PD-L1 ≥ 10: 54.4% v. 40.6% (HR 0.61; CI 95%, 0.44-0.84)
- **FDA Approval granted September 2021** - Pembrolizumab in combination with chemotherapy, with or without bevacizumab, for patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥ 1)

- Characteristics

	Pembro	Placebo
Metastatic or recurrent, metastatic	83.4%	78.6%
PD-L1 CPS ≥ 1	88.6%	90%
Bevacizumab	63.6%	62.5%

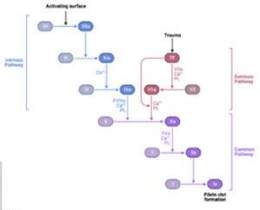
Colombo N, Dubot C, Lorusso D, et al. *N Engl J Medicine* 2021;NEJMoa2112435.

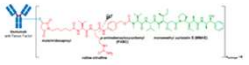
CPS: Combined Prognostic Score

37

Tisotumab vedotin

- **Tissue factor (TF)** is highly prevalent on cervical cancer cells and implicated in disease progression
- TF-directed monoclonal antibody and MMAE conjugate
  - Human anti-TF IgG1 kappa antibody
  - Linker (protease-cleavable valine-citrulline linker
  - MMAE (microtubule-disrupting agent monomethyl auristatin E)





Dong JTW, et al. *Molecules* 2021;26. Image made with Biorender.

38

Tisotumab vedotin: Efficacy

- **FDA Accelerated Approval granted September 2021**

Trial Design	Patient Population	Efficacy Results

innovaTV 204
 	
Single-arm, open-label Phase 2 study
 	
Tisotumab vedotin
	101 adult patients with recurrent or metastatic cervical cancer
	• Disease progression on or after platinum doublet therapy
	• 2 or fewer previous therapies for recurrent/metastatic disease
		• Objective response rate (ORR) = 24%
		  ○ Complete response = 7%
		  ○ Partial response = 17%
		  ○ Stable disease = 49%
		• Ongoing response ≥ 6 months = 62%

innova TV 301
**Planned interim analysis: ESMO 2023*
 	
Multicenter, randomized, open-label Phase 3 trial
 	
Tisotumab vedotin v. investigator's choice chemotherapy
	502 adult patients with recurrent or metastatic cervical cancer
	• Disease progression on or after platinum doublet therapy
	• 2 or fewer previous therapies for recurrent/metastatic disease
		• Primary endpoint:
		  ○ **OS: 11.5 mo. v. 9.5 mo.**
		  ○ **30% risk reduction (HR 0.7; 95% CI 0.54-0.89)**
		• PFS: 4.2 v. 2.9 mo.(HR 0.67; 95%, 0.54-0.82)
		• ORR: 17.8% v. 5.2%

Coleman RL, et al. *Lancet Oncol* 2021; 22: 609–19

Harano K, Gonzalez Martin A, Fujiwara K, et al. *Annals of Oncology*. 2023;34:S1474-5727.

39

Tisotumab vedotin: Safety

Event (innovaTV 204)	Grade 1-2	Grade ≥ 3
Alopecia	38%	0
Epistaxis	30%	0
Nausea	27%	0
Peripheral neuropathy	8%	2%
Arthralgia/myalgia	12%/15%	0
Ocular:		
Conjunctivitis	26%	0
Dry eye	23%	0
Keratitis	11%	0
Rectal hemorrhage	1%	1%
Ulcerative keratitis	0	2%

Coleman RL, et al. Lancet Oncol 2021; 22: 609-19

40

Tisotumab vedotin: Pearls

- Ocular toxicity

Prior to infusion	During infusion	After infusion
Vasoconstrictor eye drop (e.g., brimonidine)	Apply cold packs over both eyes and bridge of nose	Maintain cold packs for 20 minutes after infusion
Corticosteroid eye drop (e.g., dexamethasone)		*Corticosteroid eye drops (e.g., dexamethasone) BID after infusion and TID on Days 2-3*

Continuously while on tisotumab vedotin

- Visual acuity & slit lamp eye exam by eye care provider at baseline, prior to each dose, and as clinically indicated
- Avoid eye irritants and contact lenses
- *Use OTC lubricating eye drops daily as directed and PRN*

- Dosing
  - 2 mg/kg (maximum dose 200mg for patients ≥ 100kg) IV over 30 minutes Q3weeks until disease progression or toxicity

Tivdak [package insert]. ImmunoGen, Inc. Waltham, MA. 02451-2022.

41

Audience response #4

Which of the following reflects the recommended eye care plan for **mirvetuximab soravtansine**?

A. Eye exam including visual acuity and slit lamp exam at baseline, every other cycle for the first 8 cycles, and as clinically indicated
B. Eye exam including visual acuity and slit lamp exam at baseline and prior to each cycle
C. Apply cold packs over both eyes and bridge of nose during mirvetuximab soravtansine infusion
D. Have patient administer corticosteroid eye drops prior to the infusion and on Days 2 & 3 after the infusion

42

Uterine Cancer

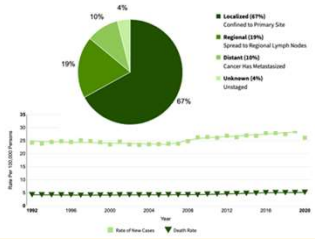
9th *most common cancer (US)*

3rd *gyn. cancer mortality*

63 years *median diagnosis*

86% *diagnosed at early stage*

81% *5-year relative survival*



SEER Cancer Stat Facts: Ovarian Cancer. NCI. Bethesda, MD. October 2023.

43

Front-line Therapy in Advanced Endometrial Cancer

- 29% with regional or distant disease at presentation
- 18% of early-stage endometrial cancer cases will recur
  - Higher for non-endometrioid histologies
- *Historical* front-line treatment options:
  - Platinum doublet → OS = 37 months
- *Historical* 2+ line treatment options: ORR 4-27%
  - ~30% of endometrial cancers have MSI-H/dMMR
    - Usually endometrioid histology
    - PD-1/PD-L1 inhibitors, ORR
      - MSI-H/dMMR = 27%-57%
      - MSS/pMMR = 3-23%

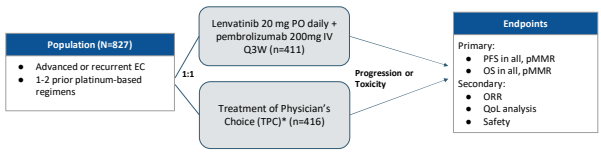
Green AK, Feinberg J, Makker V. *American Society of Clinical Oncology Educational Book.* 2020;(40):238-244.

MSI-H: high microsatellite instability; dMMR: mismatch repair deficient; MMS: microsatellite stable; pMMR: proficient mismatch repair

44

KEYNOTE 775

- Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer
- Randomized, double-blind, Phase 3



*Doxorubicin 60 mg/m2 IV Q3W or paclitaxel 80 mg/m2 D1, 8, 15 Q28D

Makker V, Colombo N, Casado Herraez A, et al. *N Engl J Med.* 2022;386(5):437-448.

45

KEYNOTE 775: Efficacy

- N = 827
  - pMMR = 697
  - Non-endometrioid = 36.7%
  - Race - Black = 17%
- Median PFS
  - Lenvatinib + pembrolizumab v. chemotherapy (TPC)
    - PFS (all) = 7.2 mo. v. 3.8 mo. (HR 0.56; 95% CI, 0.47 to 0.66)
    - PFS (pMMR) = 6.6 mo. v. 3.8 mo. (HR 0.6; 95% CI, 0.5 to 0.72)
- Median OS
  - Lenvatinib + pembrolizumab (LEN-Pem) v. chemotherapy (TPC)
    - OS (all) = 18.3 mo. v. 11.4 mo. (HR 0.62; 95% CI, 0.51 to 0.75)
    - OS (pMMR) = 17.4 mo. v. 12.0 mo. (HR 0.68; 95% CI, 0.56 to 0.84)
- **FDA Accelerated Approval granted September 2019; Regular Approval July 2021**

Makker V, Colombo N, Casado Herraez A, et al. N Engl J Med. 2022;386(5):437-448.

46

KEYNOTE 775: Safety

- Common AEs: hypertension (64%, *37.9%)*, hypothyroidism (57.4%, *1.2%*), diarrhea (54.2%, *1.2%*), nausea/vomiting, decreased appetite, fatigue
- Median duration on treatment = 231 v. 105 days
- LEN+pem:
  - Grade 3+ Treatment emergent adverse effects (TEAE) = 89%
  - Dose-reduction = 67%
    - 45.6% 2+ dose-reductions
  - Interruption = 69.2%
  - Discontinuation = 33%

47

LEN/Pem Pearls

- Monitoring/Management
  - Livenr function test (LFTs) – baseline & Q2weeks x 2 months, then monthly
  - Thyroid stimulating hormone (TSH) – baseline & monthly
  - Urinalysis (UA) – baseline & periodically
  - Blood pressure (BP) – after 1 week, Q2weeks x 2 months, then at least monthly
  - Electrocardiogram (ECG) – high risk patients
- Dosing
  - LEN 20 mg daily v. empirically-reduced starting doses

VEGF TKI	Immune Checkpoint Inhibitor
• Hypertension • Proteinuria • Hypothyroidism • Diarrhea • Nausea/vomiting (≥12 mg mod-high risk) • Mucositis • Hand-foot syndrome	• Immune-related irAEs • Fatigue

Lenvima [package insert]. Woodcliff Lake, NJ: Eisai Inc.; 2021.
Keytruda [package insert]. Whitehouse Station, NJ: Merck; 2021.
Makker V, Taylor MH, Oaknin A, et al. *The Oncologist*. 2021;26(8):e1568-e1668
How JA, Patel S, Fellman B, et al. Gynecologic Oncology. 2021;163(1):54-71.

48

Immunotherapy (IO) + Chemotherapy

- **FDA Approval for dostarlimab granted July 2023**

Trial Design	Patient Population	Efficacy Results
RUBY Multicenter, randomized, placebo-controlled trial Dostarlimab + carboplatin/paclitaxel v. carboplatin/paclitaxel	816 adult patients with advanced (stage III or IV), metastatic, or recurrent endometrial cancer • Carcinosarcoma included • ≥ 6 months since adjuvant chemotherapy • dMMR = 118; pMMR = 376	• Primary endpoints (24-months): ○ **PFS (dMMR) = 61.4% v. 15.7% (HR 0.28; 95% CI, 0.16-0.50)** ○ **PFS (overall pop.) = 36.1% v. 18.1% (HR 0.64; 95% CI, 0.51-0.8)** ○ **OS (overall pop.) = 71.3% v. 56.0% (HR 0.64; 95% CI, 046-0.87)**
NRG-GY018 Multicenter, randomized, placebo-controlled Phase 3 trial Pembrolizumab + carboplatin/paclitaxel v. carboplatin/paclitaxel	816 adult patients with advanced (stage III or IV), metastatic, or recurrent endometrial cancer • Carcinosarcoma excluded • ≥ 12 months since adjuvant chemotherapy • dMMR = 225; pMMR = 591	• Primary endpoint (12-months): ○ **PFS (dMMR) = NR v. 7.3 mo.;74% v. 38% (HR 0.3; 95% CI, 0.19-0.48)** ○ **PFS (pMMR) = 13.1 v. 8.7 mo. (HR 0.54; 95% CI, 0.41-0.71**

Eskander RN, Sill MW, Beffa L, et al. N Engl J Med. 2023;388(23):2159-2170.
Mirza MR, Chase DM, Slomovitz BM, et al. N Engl J Med. 2023;388(23):2145-2158.

49

IO + Chemotherapy: Pearls

- 2 large RCTs meeting primary endpoints
  - Pronounced PFS benefit for dMMR in both trials
  - Benefit for pMMR in GY018
  - OS benefit for all in RUBY
- Remaining questions
  - IO for pMMR, particularly serous histology
  - Duration of IO maintenance therapy
  - Pembrolizumab or dostarlimab

Pembrolizumab	Dostarlimab
Pembrolizumab 200mg IV Q3w x 6 cycles, then 400mg IV Q6w up to 14 cycles	Dostarlimab 500 mg IV Q3w x 6 cycles, then 1000mg IV Q6w up to 3 years

Eskander RN, Sill MW, Beffa L, et al. N Engl J Med. 2023;388(23):2159-2170.
Mirza MR, Chase DM, Slomovitz BM, et al. N Engl J Med. 2023;388(23):2145-2158.

50

Audience response #5

EJ is a 72 yo female with recurrent high-grade serous endometrial cancer previously treated with TAH/BSO+SLD and adjuvant carboplatin and paclitaxel 3 months ago. She is presenting to the oncology clinic for discussion of therapy options.

IHC/genetics: pMMR/MSS

Which is the most appropriate therapy option for her at this time?

A. Paclitaxel 80 mg/m2 D1, 8, 15 every 28 days
B. Lenvatinib 20 mg PO daily + pembrolizumab 200mg IV Q3weeks
C. Pembrolizumab 200mg IV Q3weeks
D. Carboplatin AUC 5 + paclitaxel 135 mg/m2 + pembrolizumab 200mg IV Q3weeks followed by pembrolizumab maintenance

51

"Top 2s of the 2020s"

Ovarian	Cervical	Endometrial
1. Changing role of PARP inhibitors 2. Mirvetuximab soravtansine	1. "Quadruplet" therapy 2. Tisotumab vedotin	1. Lenvatinib + pembrolizumab 2. Chemotherapy + pembrolizumab

52

Gynecologic Oncology Updates

Beyond Carbo/Taxol

ERIN HICKEY ZACHOLSKI, PHARMD, BCOP
ASSISTANT PROFESSOR, VCU SCHOOL OF PHARMACY

53