
# EMERGING APPROACHES FOR ADVANCED OVARIAN CANCER AND RECURRENT ENDOMETRIAL CANCER

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# DISCLOSURES

I receive a stipend as Editor-in-Chief for *Gynecologic Oncology Reports*

I borrowed and edited (with permission) some slides on Parp inhibitors from my colleague, Dr. Rob Coleman

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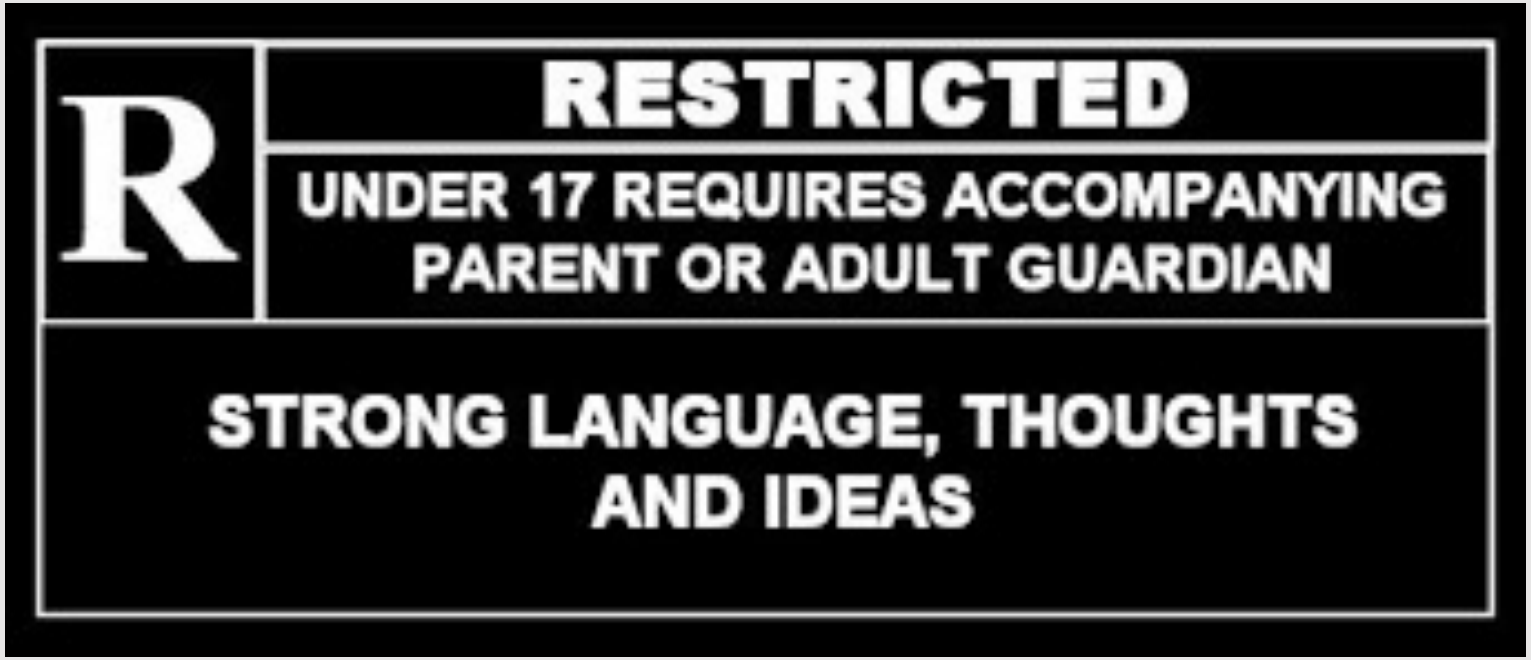

# TALK OVERVIEW

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## Ovarian Cancer

- Incidence
- Etiology
- Upfront treatment
- Approaches to maintenance
- Upcoming agents of interest

## Endometrial Cancer

- Incidence
- Etiologies
- Upfront treatment
- Emerging options for recurrent cancer

# U.S. FEMALE CANCER STATISTICS 2022

| Site | Number | Deaths |
|---|---|---|
| Breast | 287,850 | 43,780 |
| Uterus | 65,950 | 12,550 |
| Ovary | 19,880 | 12,810 |
| Cervix | 14,100 | 4,280 |
| Vulva | 6,330 | 1,560 |

Siegel RL et al. *CA Cancer J Clin*, 72:7-33, 2022

# OVARIAN CANCER

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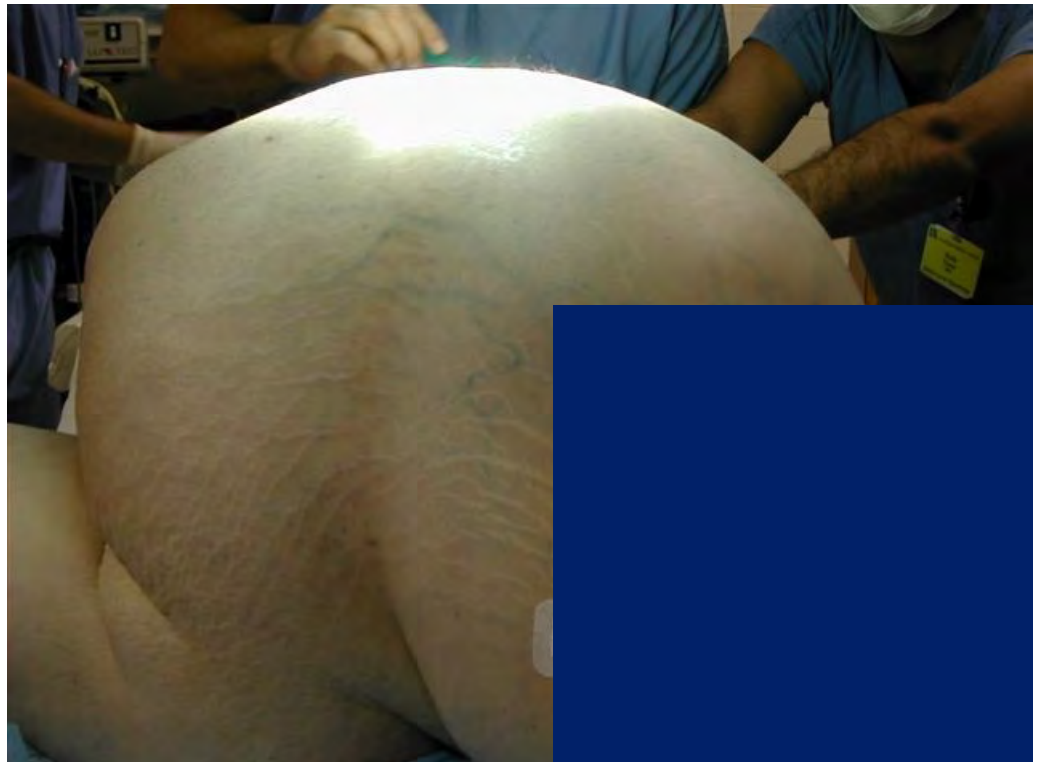
Classic/Hallmark Ovarian cancer symptoms

- Bloating
- Abdominal or pelvic pain
- Difficulty eating or feeling full

Average delay in diagnosis of 6-12 months after onset of symptoms

75% of women are Stage III/IV at diagnosis



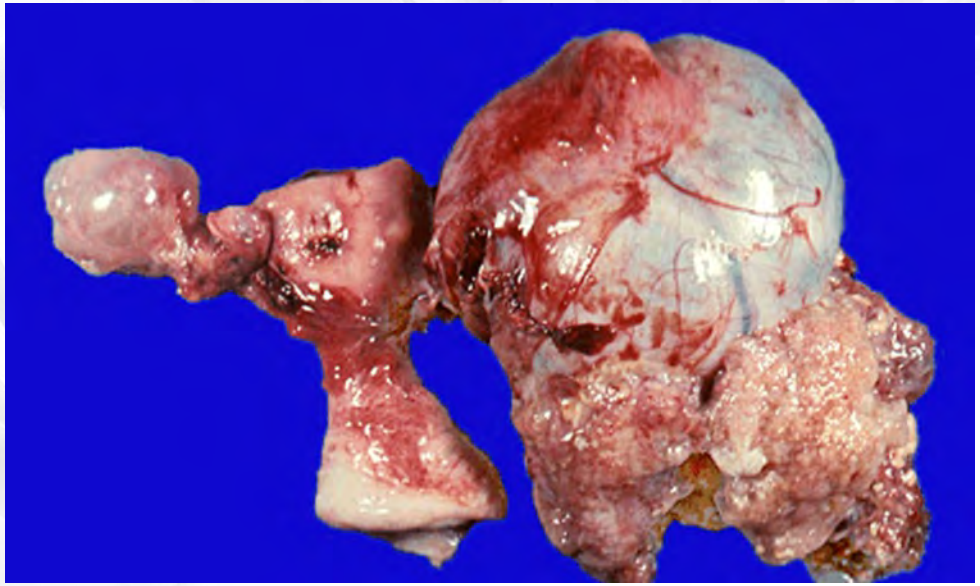
# WHY DO WE CARE?

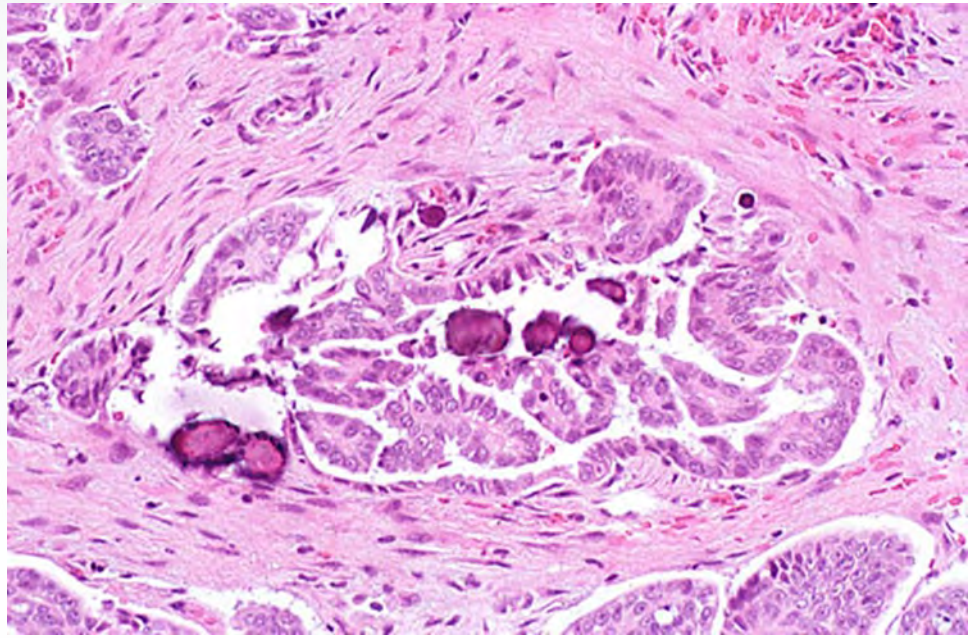
Ovarian cancer is expected to be the 5th leading cause of cancer death in U.S. women in 2022

- 3% of all female cancers but 5% of all deaths

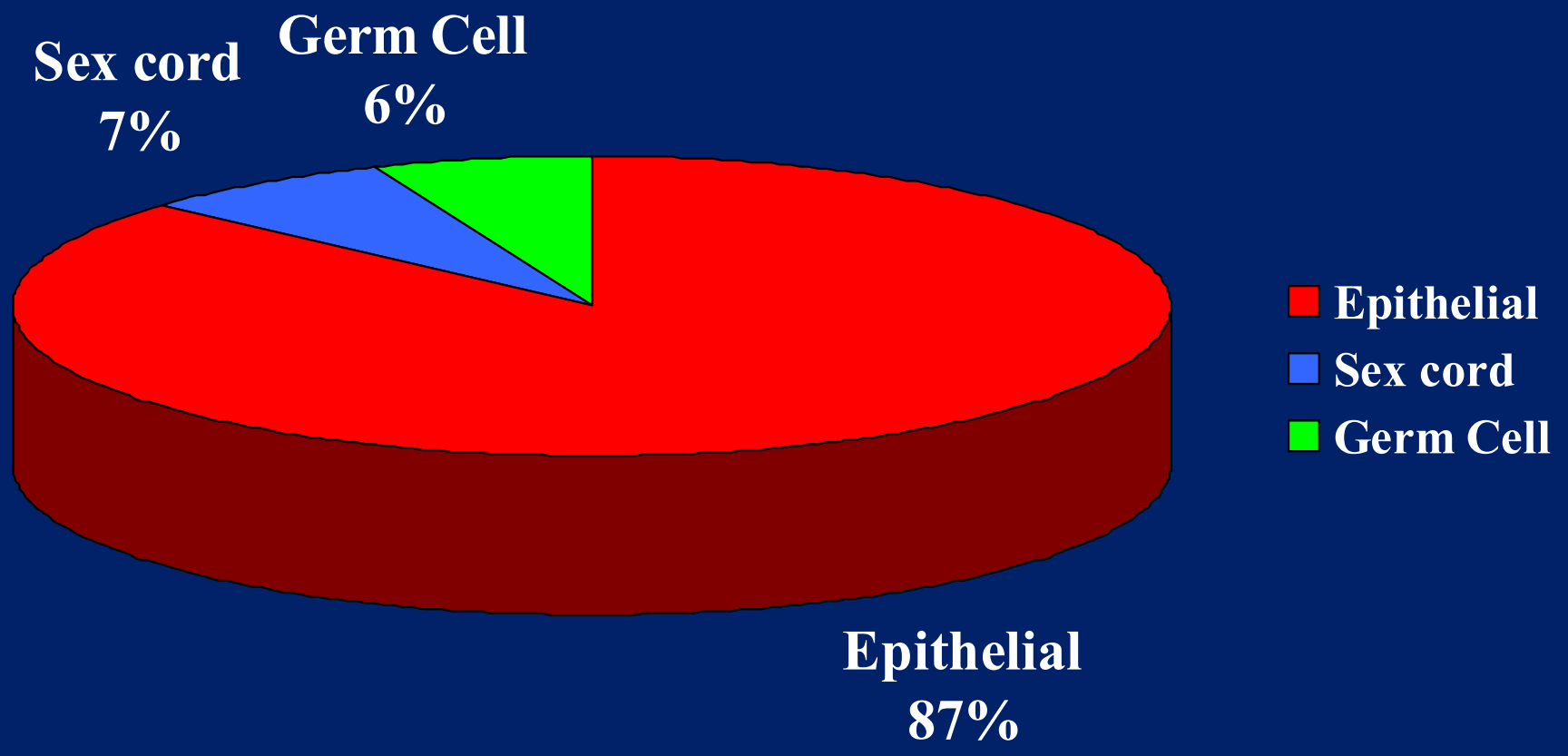
1 out of every 56 women will be diagnosed

Cure rates remain discouraging with surgery and chemotherapy





# TYPES OF OVARIAN CANCER



# HYPOTHESES ON ORIGINS OF EPITHELIAL "OVARIAN" CANCERS

**Ovarian surface epithelium**

- Incessant ovulation
- Gonadotropin stimulation
- Hormonal stimulation
- Inflammation

- **Ovarian Cancer Types**
  - Low grade serous
  - Mucinous
  - Clear cell
  - Endometrioid

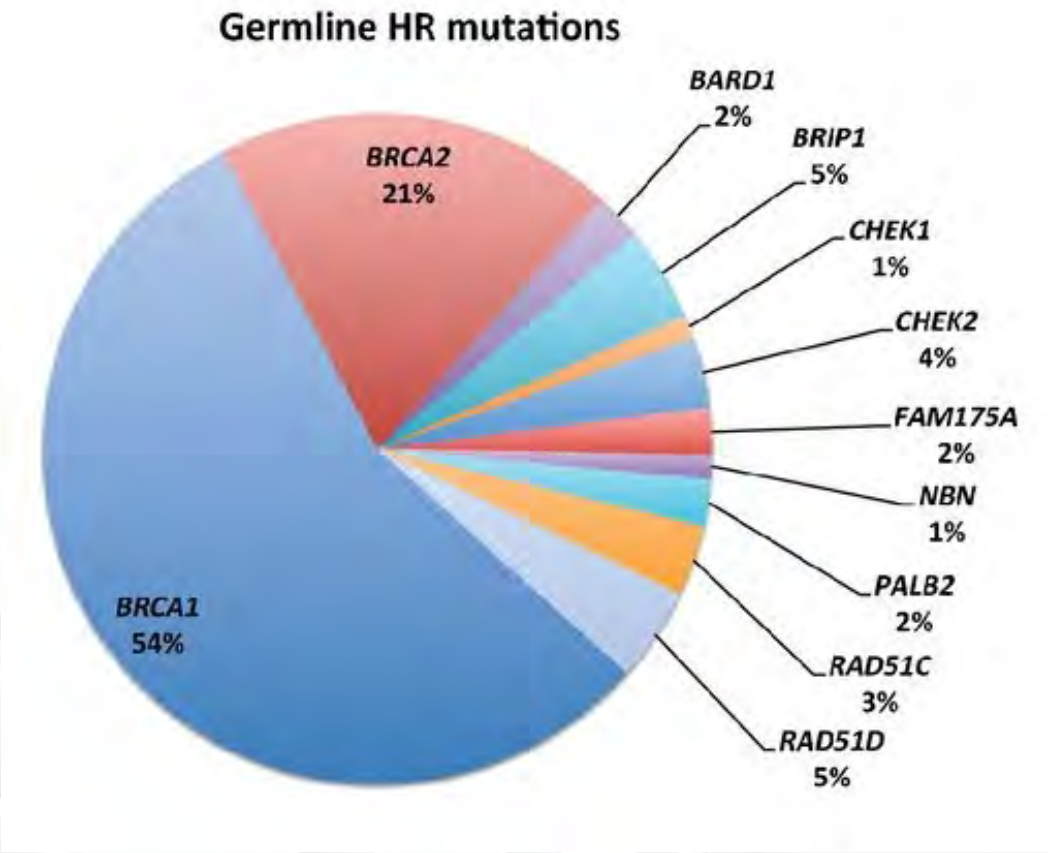
**Tubal inner surface epithelium**

- p53 signatures are very common
- p53 signature ≠ malignancy

- **Ovarian Cancer Types**
  - High Grade Serous
  - Primary Peritoneal
  - Fallopian
  - ?Uterine papillary serous?

**Most high grade "ovarian" cancer isn't really ovarian cancer at all**

# GERMLINE MUTATIONS ACCOUNT FOR ≈ 24% OF OVARIAN CANCERS




- Most ovarian cancer is still sporadic (70-80%)
- BRCA1 and BRCA2 account for majority of germline mutations (75%)
- Lynch syndrome is another main group (NOT HR)
- Other homologous recombination genes

Pennington KP et al. Clin Cancer Res 2014; 20(3): 764-775

# CONVENTIONAL TREATMENT

1. Tumor reductive surgery followed by chemotherapy versus neoadjuvant chemotherapy with an interval debulking
   - Surgical goal to reduce tumor to microscopic or at least to under 1 cm in terms of largest remaining lesions (R0 vs. R1)

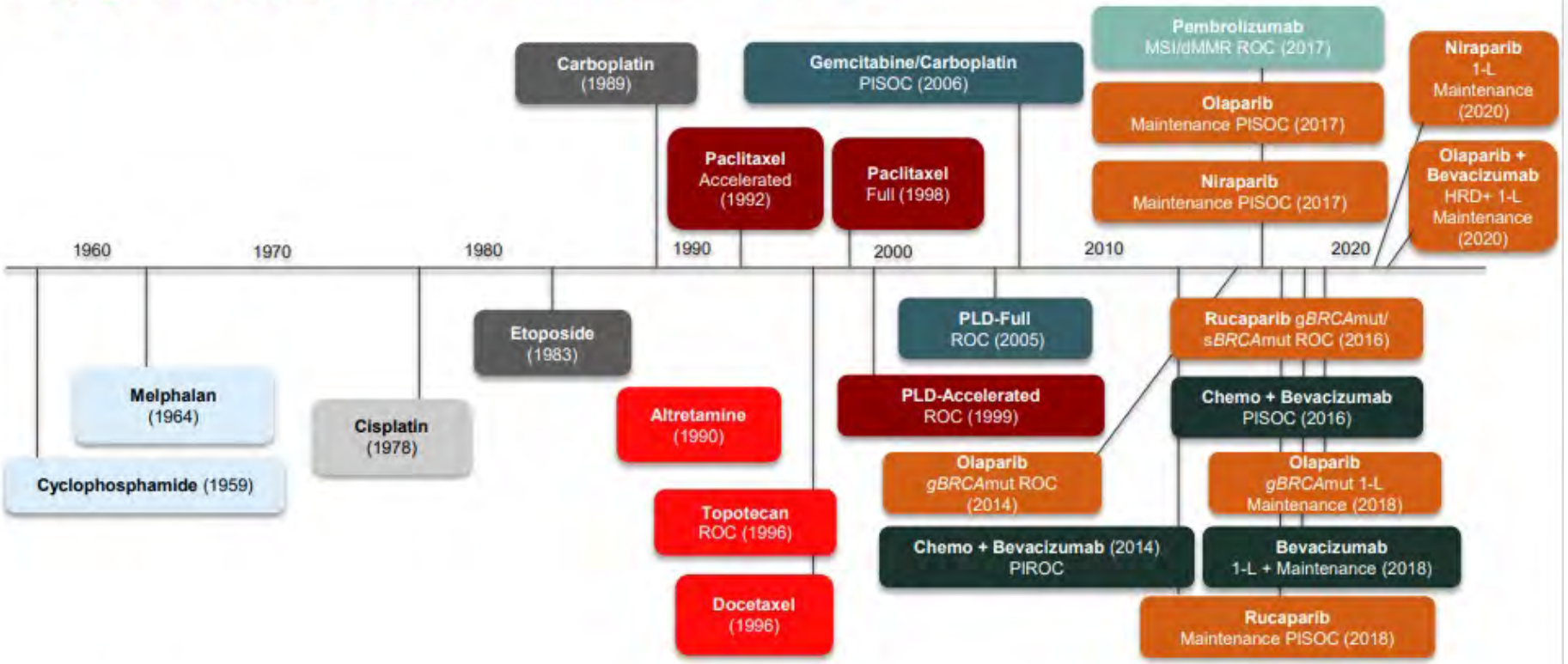
2. Adjuvant Chemotherapy (except in rare Stage I patients)
   - Combination chemotherapy with taxane/platinum agent +/- bevacizumab
   - Intraperitoneal or HIPEC chemotherapy in selected patients

3. Maintenance therapy (PARP and/or bevacizumab) in selected patients (some advocate ALL patients)

4. Clinical trial if available

GOG Highlight Reel

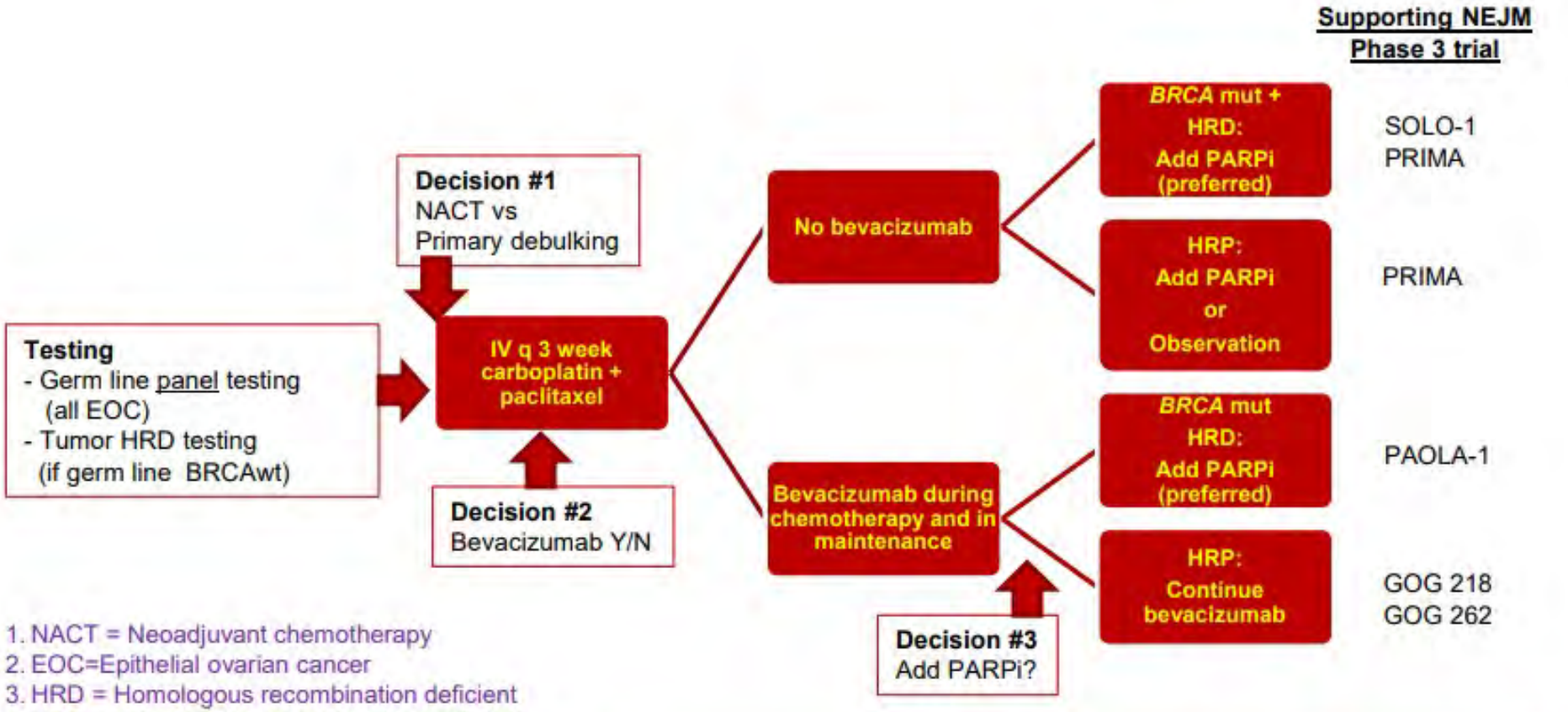
# 12 (Plus Two Pembrolizumab approvals MSI and TMB) Approvals in the Last 6+ Years




GOG FOUNDATION
Transforming the standard of care

The James
The Ohio State University
Wexner Medical Center

# WHAT IS STANDARD SYSTEMIC TREATMENT FOR NEWLY DIAGNOSED ADVANCED EPITHELIAL OVARIAN CANCER?




1. NACT = Neoadjuvant chemotherapy
2. EOC=Epithelial ovarian cancer
3. HRD = Homologous recombination deficient
4. HRP = Homologous recombination proficient
5. PARPi = Poly ADP Ribose inhibitor
6. NEJM = New England Journal of Medicine

Selecting new upfront regimens for advanced ovarian cancer with biomarker guidance. Chan JK, Liang SY, Kapp DS, Chan JE, Herzog TJ, Coleman RL, Monk BJ, Richardson MT. Gynecol Oncol. 2020 Dec;159(3):604-606.

GOG Highlight Reel

**Good judgment comes from experience, which, unfortunately, many times comes from the exercise of bad judgment**

# MAINTENANCE CHEMOTHERAPY

Prior “Successes”

- GOG 178 (paclitaxel)
- GOG 218/ICON 7 (bevacizumab)
- Pazopanib (?, not FDA approved due to lack of OS benefit)

Prior Successes

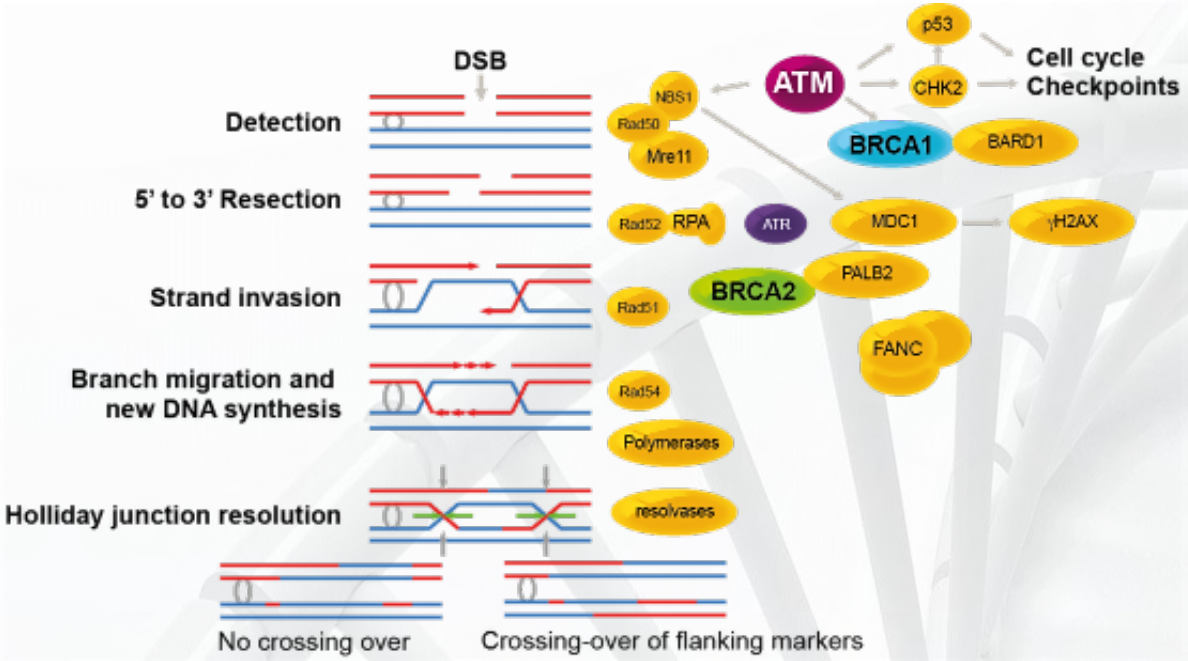
- PARP

Prior Failures

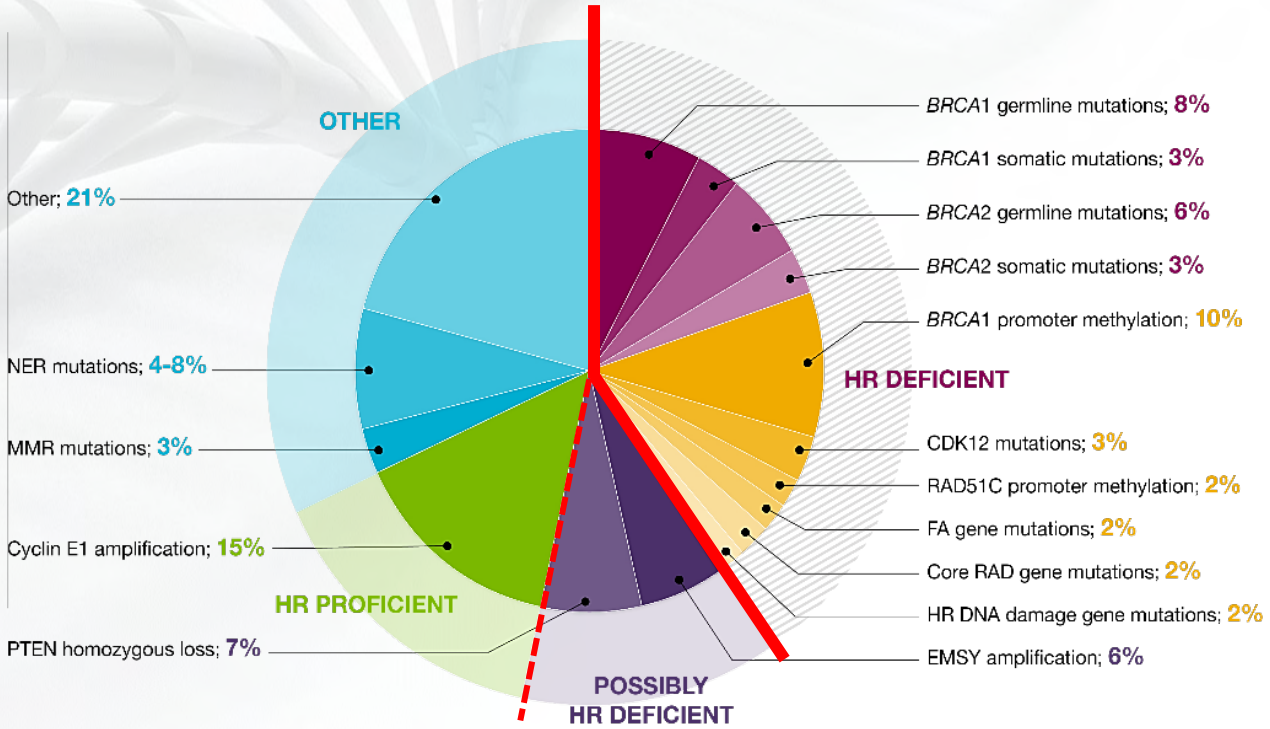
- Oregovomab (monoclonal antibody to Ca-125)

# PARP INHIBITOR TREATMENT IN OVARIAN CANCER: WHY?

Homologous Recombination Repair




Konstantinopoulos PA, et al. *Cancer Discov*. 2015;5:1137-1154.




McCabe N, et al. *Cancer Res*. 2006;66:8109-8115.

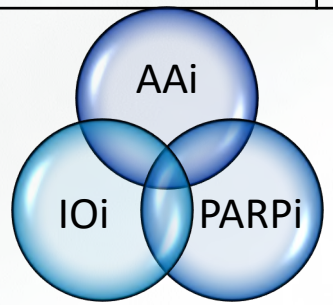
# Primary Maintenance Trials

| | SOLO-1 (N = 391) | PRIMA/ENGOT-OV26 (N = 733) | PRIME (N = 384) | ATHENA-Mono (N = 538) | PAOLA-1/ENGOT-OV25 (N = 806) | VELIA/GOG-3005 (N = 1140) |
|---|---|---|---|---|---|---|
| **Treatment arms** | **Olaparib** vs placebo | **Niraparib** vs placebo | **Niraparib (IBW)** vs placebo | **Rucaparib** vs placebo | **Olaparib** + bevacizumab vs Placebo + bevacizumab | **Veliparib** + CP → **veliparib**<br>**Veliparib** + CP → placebo<br>Placebo + CP → placebo |
| **Randomization** | 2:1 | 2:1 | 2:1 | 4:1 | 2:1 | 1:1:1 |
| **PARP inhibitor duration** | Up to 24 months | Up to 36 months | Up to 36 months | Up to 24 months | Up to 24 months | Up to 24 months |
| **Patient population** | • *BRCA1/2* mutated<br>• No bevacizumab<br>• **CR/PR to CP** | • Stage III, visible residual<br>• Inoperable stage III/Stage IV<br>• **CR/PR to CP** | • Stage III/IV<br>• Cytoreduction<br>• **CR/PR to CP** | • Stage III/IV<br>• Cytoreduction<br>• **CR/PR to CP** | • Stage III/IV<br>• **CR/PR to CP+bevacizumab** | • Stage III/IV<br>• **No Progression to CP** |
| **Stage IV** | 17% | **35%** | 28% | ? | 30% | 22% |
| **PDS/NACT** | 63%/35% | **33%/67%** | 53%/47% | ? | 51%/42% | 68%/27% |
| ***BRCA* mutated** | **100**% | 30% | 32% | ? | 30% | 26% |
| **HRD testing** | N/A | Myriad myChoice® HRD score ≥42 | **BGI Genomics** HRD score | **FoundationOne CDx** HRD LOH > 16% | myChoice® HRD Plus HRD score ≥42 | myChoice® HRD CDx **HRD score ≥33** |
| **Primary endpoint** | **PFS** (investigator assessed) | **PFS (BICR assessed)** HRD and ITT | **PFS (BICR assessed)** ITT population | **PFS** (investigator assessed) | **PFS** (investigator assessed) | **PFS** (investigator assessed) Arm 1 vs 3 (N = 757) *BRCA*-mt, HRD and ITT |

# THE FIRST-LINE OVARIAN CANCER DEVELOPMENT

| First Line Treatment w/ Maintenance | First Line Switch Maintenance |
|---|---|
| JAVELIN100 (avelumab) – NEGATIVE<br><br>ImaGyn50/GOG-3015 (bevacizumab/atezolizumab) – NEGATIVE | ATHENA/GOG-3020<br>Patients completed upfront surgery and platinum/taxane chemotherapy<br><br>Placebo controlled and double blinded (rucaparib +/-nivolumab)<br><br>ATHENA MONO presented at ASCO 2022*<br>HRD: 28.7 vs 11.3 (HR 0.47, p=0.004)<br>HRP: 12.1 vs 9.1 (12 vs. 6)<br><br>ATHENA COMBO not reported |
| FIRST<br>(niraparib/dostarlimab ± bevacizumab) | |
| GOG-3036/ENGOT-ov43<br>(olaparib/pembrolizumab ± bevacizumab) | |
| GOG-3025/ENGOT-ov46<br>(olaparib/durvalumab ± bevacizumab) | |
| FLORA-5/GOG-3035<br>(Oregovomab) | |

AAi: Angiogenesis inhibitor
IOi: PD-1/PD-L1 inhibitor
PARPi: PARP inhibitor



# NEW DRUGS IN CLINICAL TRIALS DEVELOPMENT

GOG 3063 ARTISTRY-7/ALKS 4230-007—Nemvaleukin alpha with Pembro versus investigator choice

GOG 3073/ROSELLA/CORT125134-556 –Phase 3: Relacorilant with Nab-paclitaxel versus investigator choice

GOG 3067-006 MAMMOTH:  ZN-c3 (Wee 1 inhibitor) in combination with niraparib

MORAb-202, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC) linked to Eribulin Mesylate

MIRVETUXIMAB SORAVTANSINE (Folate receptor alpha-targeting ADC with DM4 maytansinoid payload; potent tubulin-targeting agent

# ENDOMETRIAL CANCER

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## ENDOMETRIAL CANCER RISKS

| Factor | Relative Risk |
|---|---|
| Hereditary-Lynch | 6-10 |
| Obesity ≥50 lbs over IBW | 10 |
| Chronic unopposed estrogen | 9.5 |
| Tamoxifen therapy | 7.5 |
| Obesity ≥30 lbs over IBW | 3 |
| Diabetes | 2.8 |
| Nulliparity | 2 |
| Hypertension | 1.5 |

# LYNCH SYNDROME

Mutation in mismatch repair genes

- MLH1, MSH2, MSH6, PMS2 and EPCAM
- Autosomal dominant (1 in 400)

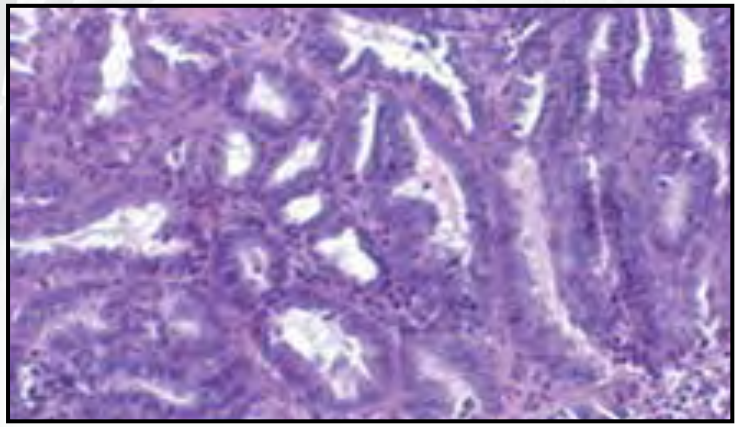
Hallmark cancers

- Colon
- Endometrial
- Ovarian
- Gastric
- Small bowel
- Renal pelvis

# HISTOLOGIC TYPES OF ENDOMETRIAL CANCER

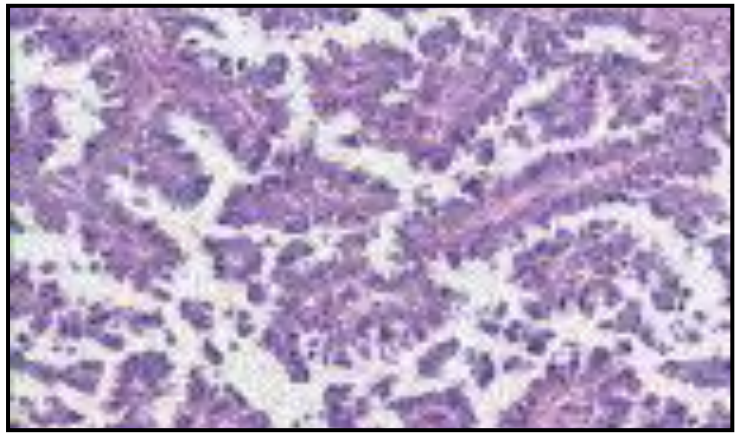
Type I – Endometrioid cell type

- Often occurs in the presence of hyperplasia
- Related to hormones/obesity
- Excellent overall prognosis



Type II – Serous, clear cell, carcinosarcoma, grade III endometrioid

- Often occurs in the presence of a thin endometrium
- Not related to hormones
- More likely to spread



# TYPES OF ENDOMETRIAL CANCER: BEYOND BASIC HISTOLOGY

Analysis of sequencing of endometrial cancers with the TCGA (The Cancer Genome Atlas) have identified 4 molecular subtypes

1. POLE (polymerase epsilon) ultra-mutated
   - Associated with the ***BEST*** clinical prognosis
2. Microsatellite High
   - Associated with intermediate prognosis
3. Copy number high*
   - Associated with the ***WORST*** clinical prognosis
4. Copy number low*
   - Associated with intermediate prognosis

* Copy number can be estimated by p53 expression

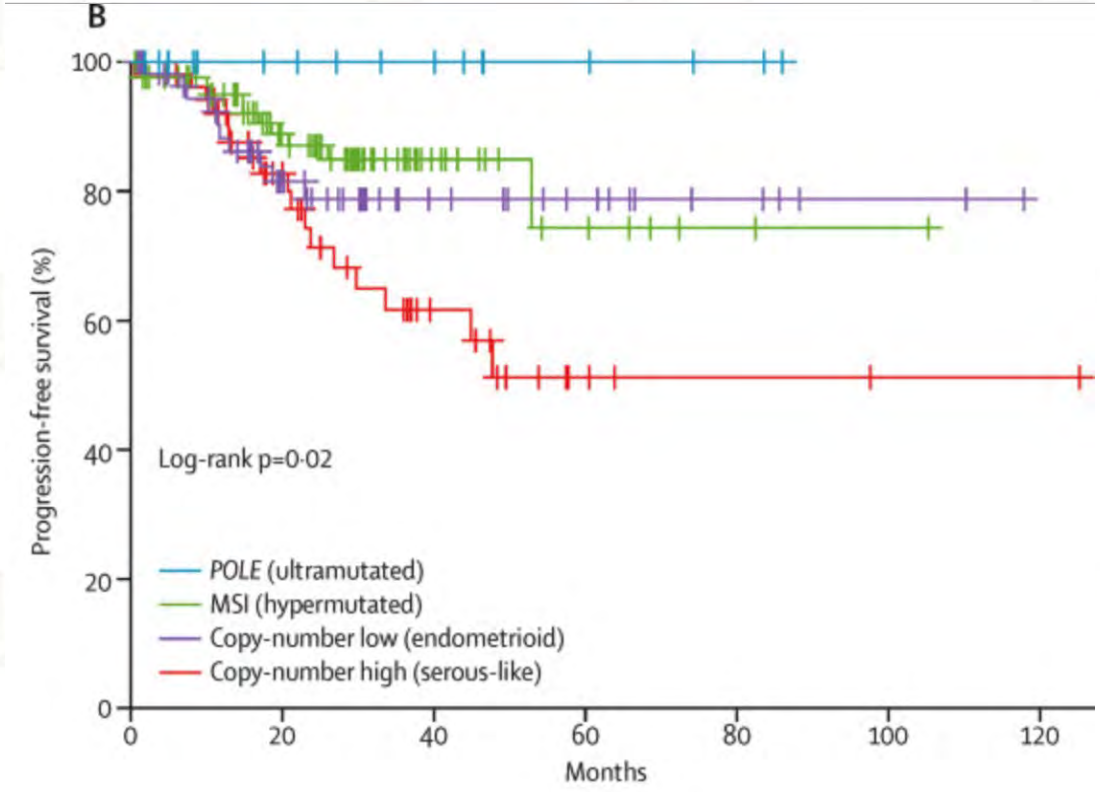
ARTICLE

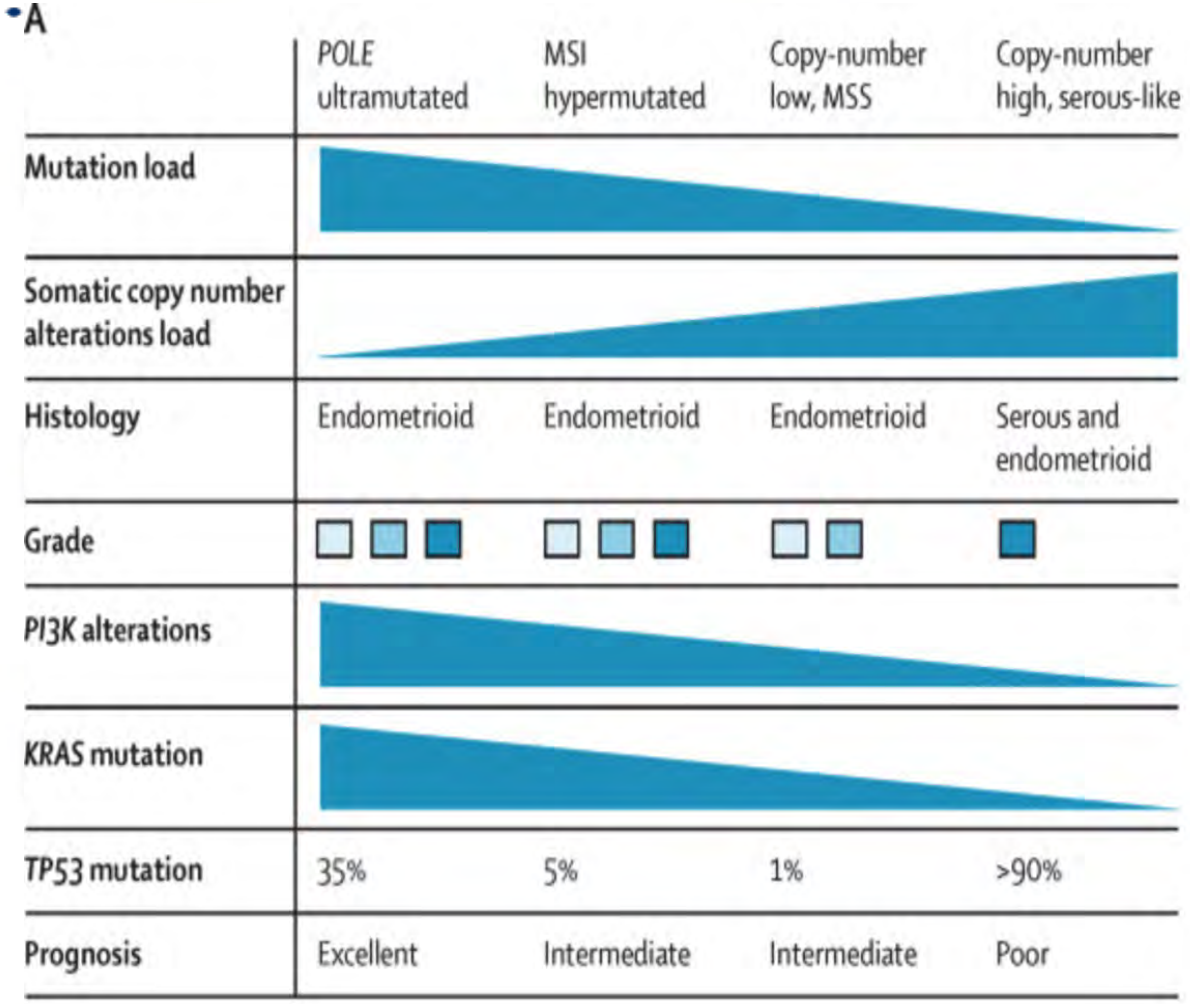
OPEN

doi:10.1038/nature12113

# Integrated genomic characterization of endometrial carcinoma

The Cancer Genome Atlas Research Network*

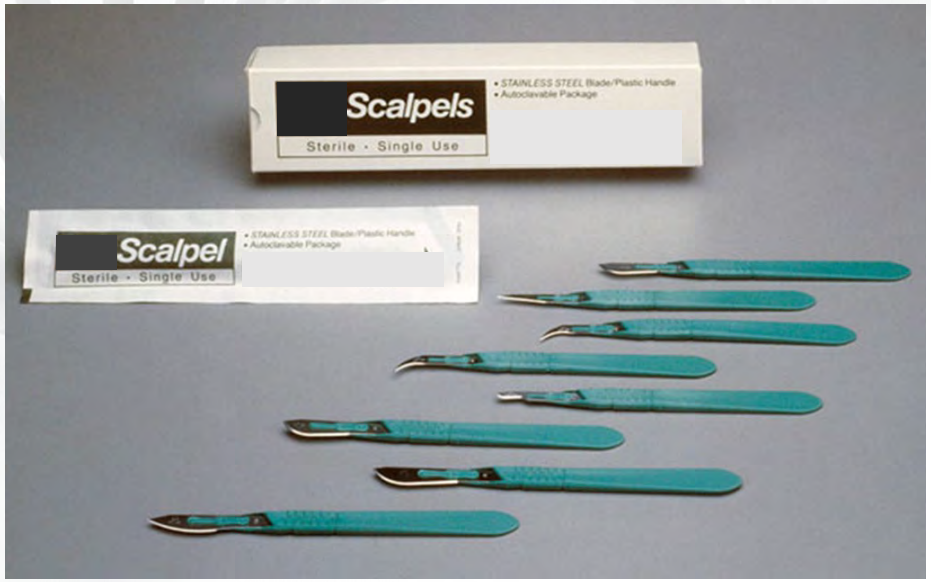



Kandoth C, Schultz N, Cherniack AD, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497(7447):67-73.

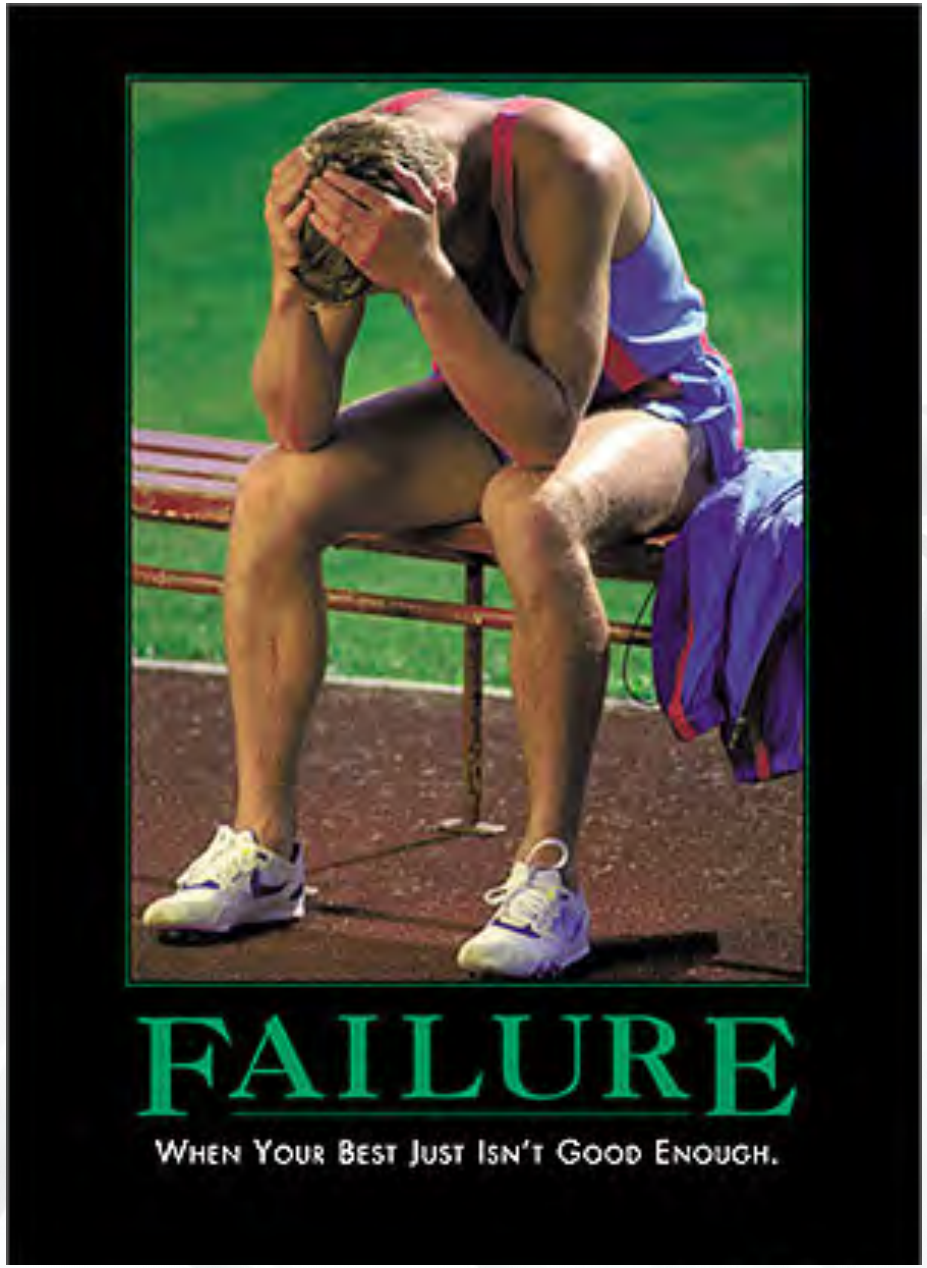
# ENDOMETRIAL CANCER INITIAL TREATMENT OPTIONS

- Surgery
- Radiation
- Chemotherapy*




**Surgery: A chance to cut is a chance to cure**

***Includes standard cytotoxic chemotherapy, hormones, targeted therapy, immunotherapy etc.**




# RECURRENT ENDOMETRIAL CANCER

# TREATMENT OPTIONS FOR RECURRENT ENDOMETRIAL CANCER

## Surgery (Local treatment)

- Isolated site of recurrence

## Radiation (Local treatment)

- Small recurrences that are unresectable (vaginal/nodal)

## Chemotherapy (Systemic treatments)

- Standard cytotoxic chemotherapy
- Hormonal therapy
- Immunotherapy
- Targeted therapies
- Clinical trials

| Recurrent or Metastatic Disease[a,b] | | |
|---|---|---|
| | **Preferred Regimens** | **Other Recommended Regimens** |
| Systemic therapies[a,b] | • Carboplatin/paclitaxel (category 1 for carcinosarcoma)[1]<br>• Carboplatin/paclitaxel/trastuzumab[c] (for stage III/IV or recurrent HER2-positive uterine serous carcinoma)[2] | • Carboplatin/docetaxel[d]<br>• Cisplatin/doxorubicin[3]<br>• Cisplatin/doxorubicin/paclitaxel[e,f,3]<br>• Carboplatin/paclitaxel/bevacizumab[e,g,4]<br>• Cisplatin<br>• Carboplatin<br>• Doxorubicin<br>• Liposomal doxorubicin<br>• Paclitaxel[5]<br>• Albumin-bound paclitaxel[h]<br>• Topotecan<br>• Bevacizumab[g,i,6]<br>• Temsirolimus[7]<br>• Docetaxel[d] (category 2B)<br>• Ifosfamide (for carcinosarcoma)<br>• Ifosfamide/paclitaxel (for carcinosarcoma)[8]<br>• Cisplatin/ifosfamide (for carcinosarcoma) |
| Biomarker-directed systemic therapy for second-line treatment | • Lenvatinib/pembrolizumab (category 1) for non–MSI-high [MSI-H]/non–MMR-deficient [dMMR] tumors[j,9]<br>• Pembrolizumab[k] for TMB-H[10] or MSI-H/dMMR tumors[l,11] | • Nivolumab for dMMR/MSI-H tumors[12]<br>• Dostarlimab-gxly for dMMR/MSI-H tumors[m,13]<br>• Larotrectinib or entrectinib for *NTRK* gene fusion-positive tumors (category 2B)[e]<br>• Avelumab for dMMR/MSI-H tumors<br>• Cabozantinib |

# TUMOR TESTING IN RECURRENT ENDOMETRIAL CANCER

MMR protein testing if not done previously (or microsatellite instability testing)

Hormone receptors

- Estrogen and progesterone

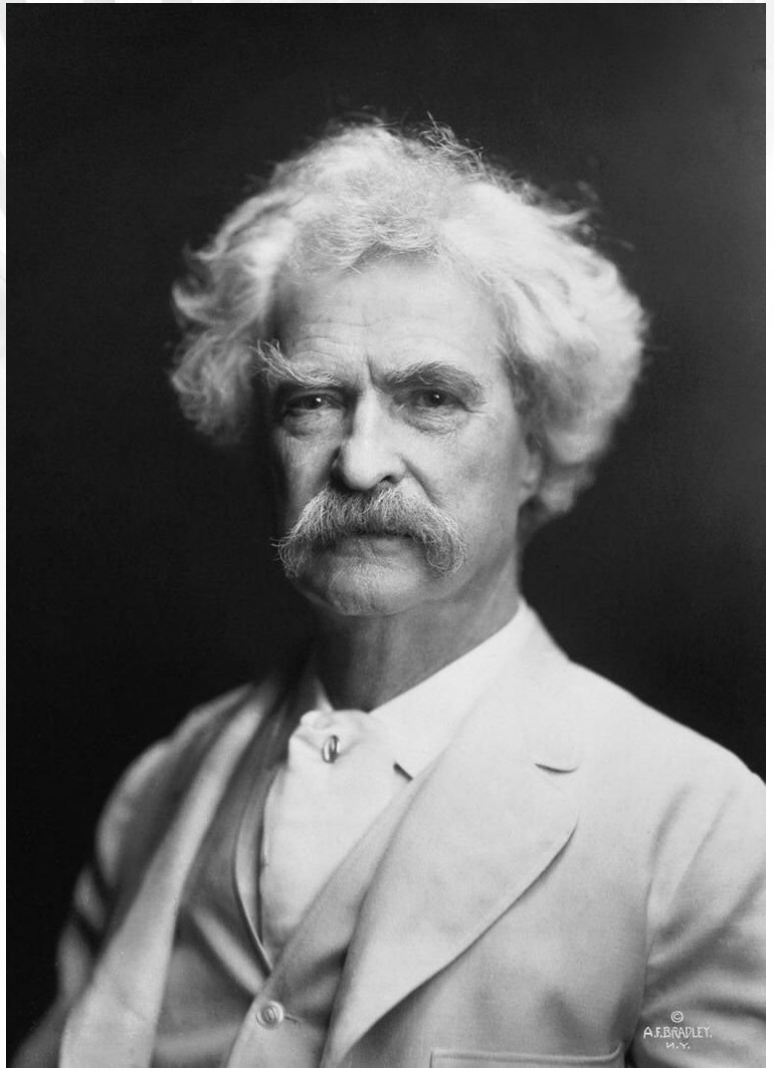
Consider tumor mutational burden (TMB)

Consider NTRK gene fusion

HER-2-neu (serous cancers)

# ATTRIBUTED TO MARK TWAIN

"There are lies, damn lies, and statistics"



# STANDARD CHEMOTHERAPY

Paclitaxel and Carboplatin is standard first line therapy

- Taxane/platinum with bevacizumab
- Taxane/platinum with trastuzumab

- Doxorubicin
- Ifosfamide/paclitaxel

| | | | |
|---|---|---|---|
| Carbo/Paclitaxel | AUC 5-6<br>175 mg/m2 q3W | ORR 40-62% | GOG 209 |
| Q3 week Paclitaxel | 175mg/m2 q3w | ORR 25% among Paclitaxel-naïve patients | GOG 129C<br>(Gyn Onc, 2003)<br>Lincoln, et al. |
| Weekly Paclitaxel | 80mg/m2 q1w | ORR 20.9% among plat-resistant and Paclitaxel-q3w-resistant. | GOG<br>Gyn Onc, 2006<br>Markman, et al. |
| Doxorubicin | 60mg/m2 q3w | *Extrapolated (1st-line data)*<br>ORR ranging 19-37% | |
| Bevicizumab (SA) | Bev 15mg/kg q3w IV | 13.5% ORR, med DOR 6m<br>PFS 4.2m, OS 10.5m | GOG 229-E (JCO, 2011)<br>Phase II trial<br>Aghajanian, et al |
| Doxorubicin HCl (SA) | Doxorubicin HCl<br>50mg/m2 IV q4w | ORR 9.5%<br>Med OS 8.2m | GOG 129H (JCO, 2002)<br>Phase II trial<br>Muggia, et al. |

# TARGETED AND IMMUNOTHERAPY THERAPY OPTIONS IN ENDOMETRIAL CANCER

Bevacizumab

Trastuzumab

MTOR inhibitors

- Temsirolimus
- Everolimus

Immunotherapy

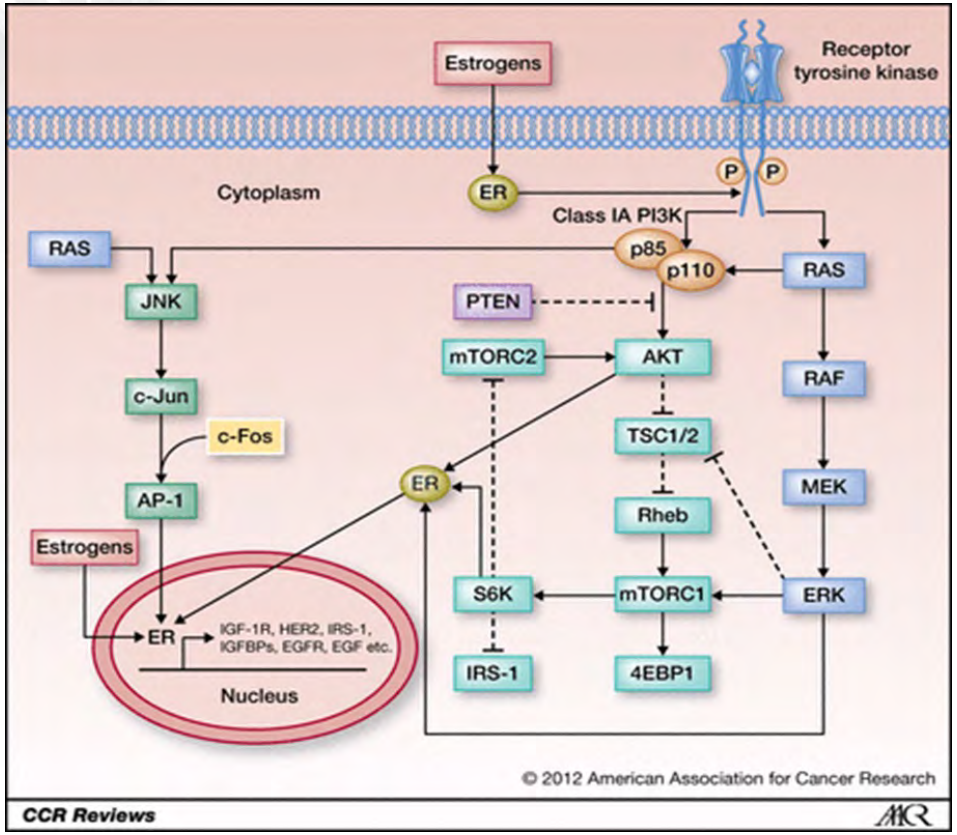
- Pembrolizumab (or dostarlimab, avelumab, nivolumab) for dMMR/MSI-H
- Pembrolizumab with lenvatinib for MMR proficient

Larotrectinib (NTRK gene fusion)

# MTOR INHIBITORS: EVEROLIMUS AND TEMSIROLIMUS

## OFTEN USED IN CONJUNCTION WITH ESTROGEN BLOCKADE AND MOST OFTEN ENDOMETRIOID TUMOR TYPES

| | | | |
|---|---|---|---|
| Temsirolimus (SA) | 25mg IV weekly | -in prior chemo-rx grp…<br>4% PR, 48% SD w/ med dDOR 3.8m<br>Med PFS 3.25m | NCIC CTG<br>JCO, 2011<br>Ivy, et al |
| Temsirolimus + Bevicizumab | Bev 10mg/kg q2 w<br>Temsirolimus 25mg weekly | ORR 25%<br>Med PFS 5.6m<br>Median OS 16.9m | GOG 229-G<br>Gyn Onc, 2013<br>Alvarez, et al |
| Everolimus + Letrozole | Everolimus 10mg + Let 2.5mg po daily | ORR 32%<br>CBR (CR+PR+SD)=40% | (JCO, 2015)<br>Phase II trial<br>Slomovitz, et al |



# EVEROLIMUS AND LETROZOLE IN RECURRENT ENDOMETRIAL CANCER (SLOMOVITZ, 2015)

**Table 2.** Clinical Outcome

| Outcome | No. of Patients | % |
|---|---|---|
| Clinical benefit | | |
| No | 21 | 60.0 |
| Yes | 14 | 40.0 |
| Best response | | |
| Complete response | 9 | 25.7 |
| Partial response | 2 | 5.7 |
| Stable disease | 3 | 8.6 |
| Progressive disease | 21 | 60.0 |
| Reason off study | | |
| Completed treatment | 7 | 20.0 |
| Progressive disease | 28 | 80.0 |
| Progressive disease | | |
| No | 4 | 11.4 |
| Yes | 31 | 88.6 |
| Current status | | |
| Alive with disease | 5 | 14.3 |
| No evidence of disease | 4 | 11.4 |
| Dead | 26 | 74.3 |
| Follow-up, months | | |
| Mean | 18.1 | |
| Standard deviation | 14.5 | |
| Median | 14 | |
| Range | 1.4-46.8 | |

## Overall response rate was 31% but 40% had prolonged stable disease

- Median OS 14 mos
- Median PFS 3 mos

## Side Effects

- Fatigue is most common but often improves
- Stomatitis-66% (mouth sores), should start preventative mouth washes as soon as therapy starts
- Nausea
- Metabolic issues (increased blood sugars and cholesterol that may require treatment)

# GOG-3007:

## NON-COMPARATIVE RANDOMIZED PHASE II TRIAL TO DETERMINE RESPONSE AND PROGRESSION FREE SURVIVAL OF PATIENTS TREATED WITH EVEROLIMUS AND LETROZOLE THERAPY (EL) AND MEDROXYPROGESTERONE ACETATE AND TAMOXIFEN THERAPY (PT)

Table 1.

| Regimen | *N* | RR-Intent-to-treat | RR-NPC | RR or Stable | PFS mos. | Overall Survival mos. | Grade 3/4 TE |
|---|---|---|---|---|---|---|---|
| EL | 37 | 24% | 53% | 78% | 6.4 | 20.0 | 0% |
| PT | 36 | 22% | 43% | 69% | 3.8 | 16.6 | 8.3% |

# PEMBROLIZUMAB

# CURRENTLY APPROVED FOR:

## 1. MMR DEFICIENT TUMORS (MSI HIGH)
## 2. HIGH TUMOR MUTATIONAL BURDEN

VOLUME 35 · NUMBER 22 · AUGUST 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

## Safety and Antitumor Activity of Pembrolizumab in Advanced Programmed Death Ligand 1–Positive Endometrial Cancer: Results From the KEYNOTE-028 Study

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# Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: an interim analysis of a multicentre, open-label, single-arm, phase 2 trial

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## Summary

**Background** Lenvatinib is a multikinase inhibitor of VEGFR1, VEGFR2, and VEGFR3, and other receptor tyrosine

*Lancet Oncol* 2019; 20:711–18

**Dosing**

Lenvatinib 20 mg PO daily (often start lower at 14 or even 10)
Pembrolizumab 300 mg IV q 3 weeks

**Results**

39.6% response rate
Of responders 12/21 responded over 6 months and 7/21 responded over 12 months

**Side Effects**

Hypertension is most common (32%) due to the lenvatinib
Fatigue, Diarrhea
Hypothyroidism (47%) that may require replacement
Immune related side effects (colitis, pneumonitis, pancreatitis etc.)

# HORMONE THERAPY OPTIONS FOR RECURRENT ENDOMETRIAL CANCER

| Hormone Therapy[n] | | |
|---|---|---|
| Preferred Regimens | Other Recommended Regimens | Useful in Certain Circumstances |
| • Medroxyprogesterone acetate/tamoxifen (alternating)<br>• Megestrol acetate/tamoxifen (alternating)<br>• Progestational agents<br>  ▸ Medroxyprogesterone acetate<br>  ▸ Megestrol acetate<br>  ▸ Levonorgestrel intrauterine device (IUD) (for select fertility-sparing cases)<br>• Aromatase inhibitors<br>• Tamoxifen<br>• Fulvestrant | • Everolimus/letrozole (for endometrioid histology) | N/A |

# HORMONE TRIALS SUMMARY

| | | | |
|---|---|---|---|
| Megestrol acetate/ Tamoxifen (Recurrent or advanced) | Tamoxifen 20mg BID x3 weeks then Megestrol acetate 80mg BID x3 weeks alternating | *No prior cytotoxic or hormonal treatment*<br>ORR 27% (38% in gd1, 24% in gd2, 22% in gd3)<br>PFS 2.7m, OS 14m | GOG 153<br>Gyn Onc, 2004<br>Fiorica, et al. |
| Letrozole (Recurrent or advanced) | Letrozole 2.5mg daily continuously | ORR 9.4%, 11/28 SD w/ med duration 6.7m;<br>PFS 3.9m, OS 8.8 | Ma, et al<br>Int J Gyn Cancer, 2004 |
| Anastrazole (Rec or advanced) | Anastrazole 1mg/day orally for at least 28d | 2 PR (9%), 2 SD (9%).<br>PFS 1m, OS 6m | Rose, et al. GOG 168 Gyn Onc 2000 |
| Megestrol acetate alone (recurrent or advanced) | Megestrol acetate 800 mg/d | ORR 24% (11% CR, 13% PR); 22% SD<br>PFS 2.5m, OS 7.6m | Lentz, et al<br>Gyn Onc, 1996<br>GOG 121 |
| Goserelin acetate | IM 3.6mg monthly | ORR 11%<br>PFS 1.9m, OS 7.3m | Asbury, et al.<br>Am. JCO, 2002 |
| Tamoxifen | Tamoxifen 20mg BID | ORR 10%<br>PFS 1.9m, OS 8.8 | GOG 81F<br>Thigpen, et al |

# NEW AGENTS/QUESTIONS ON THE HORIZON

- Up front immunotherapy for early stage but high risk disease
- Maintenance immunotherapy
- Combining PARP inhibitors with immunotherapy for upfront and maintenance
- Abemaciblib with letrozole in advanced/recurrent disease


COMPROMISE
LET'S AGREE TO RESPECT EACH OTHER'S VIEWS,
NO MATTER HOW WRONG YOURS MAY BE.

# QUESTIONS?