Fred Hutch Cancer Center

# Updates in Gynecologic Oncology:

# Uterine Cancer & Cervical Cancer

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UW Medicine

# Land Acknowledgement

Fred Hutchinson Cancer Center acknowledges the Coast Salish peoples of this land, the land which touches the shared waters of all tribes and bands within the Duwamish, Puyallup, Suquamish, Tulalip and Muckleshoot nations.

# Disclosures

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- I have no other financial disclosures

- I will be discussing the unlabeled use of products

# Objectives

- Describe molecular subtypes of endometrial cancer
- Discuss factors utilized in treatment planning for endometrial cancer cases
- Review treatment options for endometrial and cervical cancer
- Describe approaches that are most applicable for medical oncology practice

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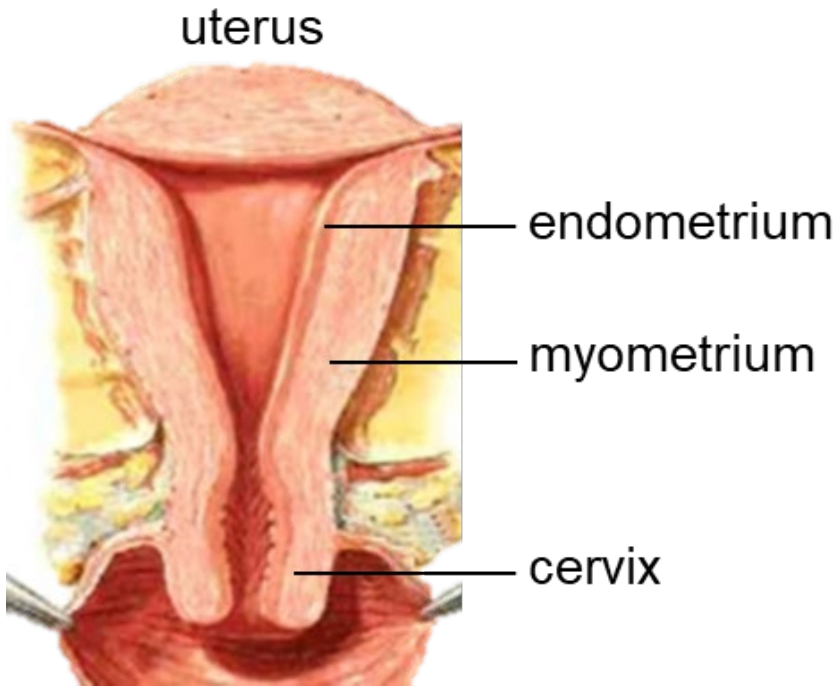
# Uterine Cancer




UW Medicine

# Question 1

Which of the following factors are incorporated into the updated FIGO 2023 staging for endometrial cancer?

A. Histologic subtype

B. Histologic grade

C. Extent of LVSI

D. Anatomic extent of disease

E. All of the above

# Question 1

Which of the following factors are incorporated into the updated FIGO 2023 staging for endometrial cancer?

A. Histologic subtype
B. Histologic grade
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D. Anatomic extent of disease
**E. All of the above**

# Question 2

You are meeting a new patient with stage IIIC2 grade 3 endometrioid endometrial cancer. On imaging, there is residual paraaortic lymphadenopathy. Pathologic and molecular assessment reveals a tumor with MSS, p53 wild-type, Her-2neu 1+ on IHC, no POLE mutation. What treatment would you recommend for her?

A. Carboplatin, paclitaxel, dostarlimab followed by dostarlimab maintenance
B. Carboplatin, paclitaxel, pembrolizumab followed by pembrolizumab maintenance
C. Carboplatin, paclitaxel, trastuzumab followed by trastuzumab maintenance
D. Carboplatin and paclitaxel
E. A or B

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D. Carboplatin and paclitaxel
**E. A or B**


FDA Approvals – primary advanced or recurrent endometrial carcinoma

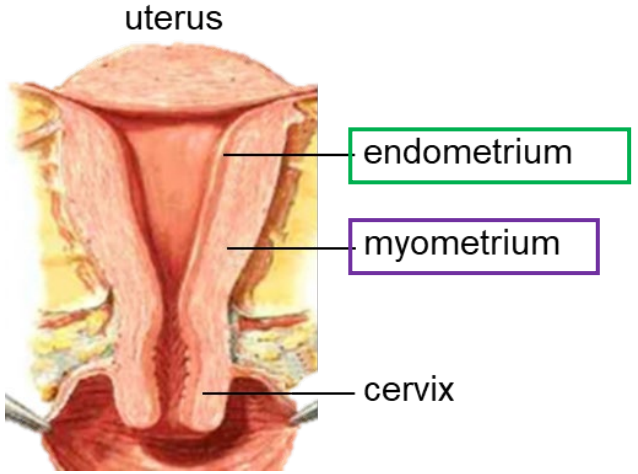
Aug 1, 2024: Dostarlimab-gxly with carboplatin & paclitaxel followed by dostarlimab maintenance (expanded from initial indication for only patients with dMMR/MSI-H tumors)

June 17, 2024: Pembrolizumab with carboplatin & paclitaxel followed by pembrolizaumb maintenance

# Subtypes of Uterine Cancer

## CARCINOMAS

- Endometrioid
  - Grades 1, 2, 3
  - Variants: squamous, mucinous, secretory
- Serous
- Clear Cell
- Carcinosarcoma (MMMT)
- Undifferentiated/dedifferentiated
- Mixed
- Other rare carcinomas (eg mesonephric)




## SARCOMAS

- Endometrial stromal sarcoma (high & low grade)
- Undifferentiated uterine sarcoma
- Adenosarcoma
- Leiomyosarcoma
- Other rare sarcomas (eg PEComa, rhabdomyosarcoma, UTROSCT)

# Epidemiology

- Most common gynecologic cancer in the United States
- Median age at diagnosis 63
- In contrast to other solid tumors, incidence & mortality from uterine cancer in US are **rising**

Incidence

**Female**

| | | |
|---|---|---|
| Breast | 310,720 | 32% |
| Lung & bronchus | 118,270 | 12% |
| Colon & rectum | 71,270 | 7% |
| Uterine corpus | 67,880 | 7% |
| Melanoma of the skin | 41,470 | 4% |
| Non-Hodgkin lymphoma | 36,030 | 4% |
| Pancreas | 31,910 | 3% |
| Thyroid | 31,520 | 3% |
| Kidney & renal pelvis | 29,230 | 3% |
| Leukemia | 26,320 | 3% |
| **All sites** | **972,060** | |

Mortality

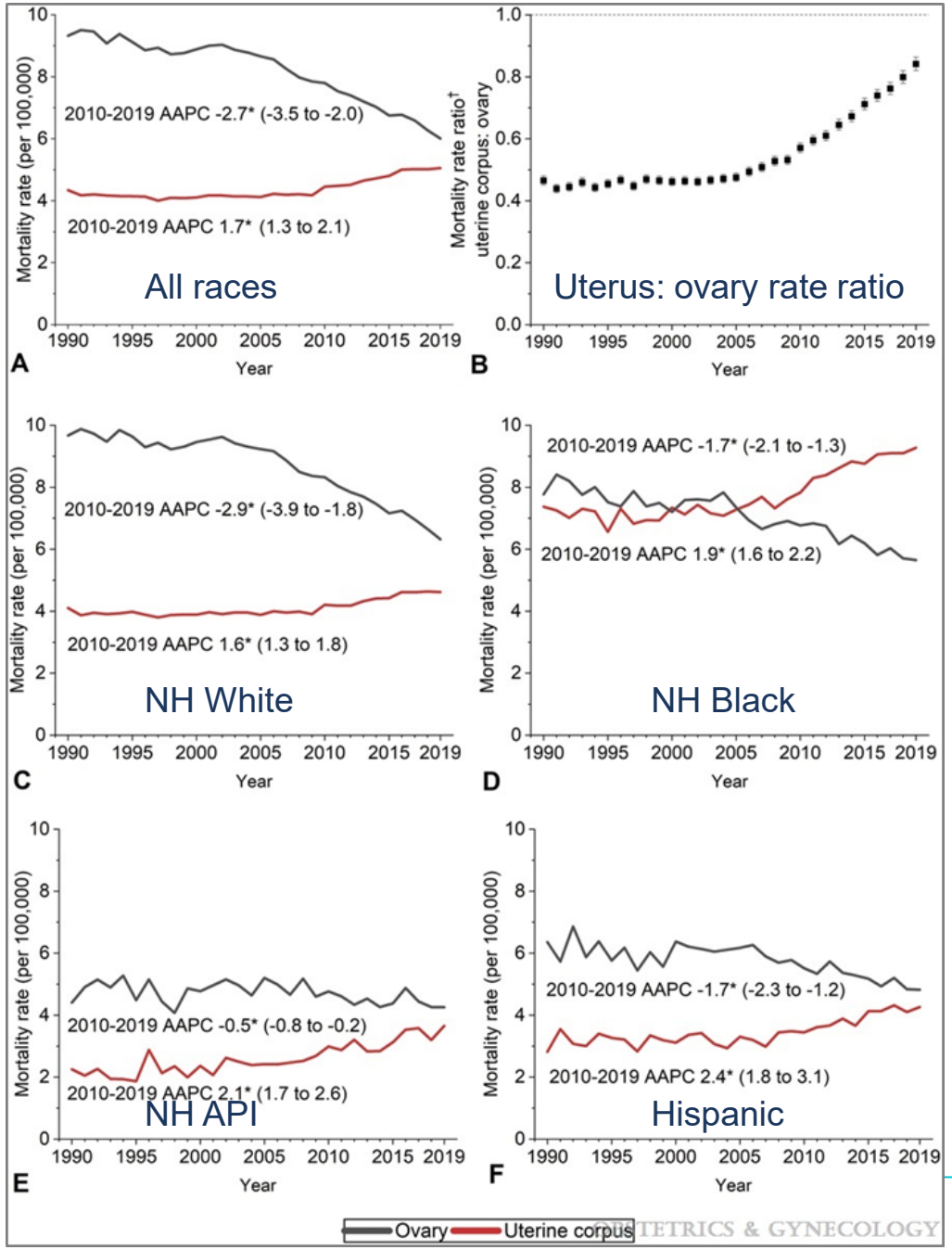
| | | |
|---|---|---|
| Lung & bronchus | ,280 | 21% |
| Breast | 42,250 | 15% |
| Pancreas | 24,480 | 8% |
| Colon & rectum | 24,310 | 8% |
| Uterine corpus | 13,250 | 5% |
| Ovary | 12,740 | 4% |
| Liver & intrahepatic bile duct | 10,720 | 4% |
| Leukemia | 10,030 | 3% |
| Non-Hodgkin lymphoma | 8,360 | 3% |
| Brain & other nervous system | 8,070 | 3% |
| **All sites** | **288,920** | |

ll skin cancers and in situ carcinoma except urinary bladder. Estimates do not include
iffer from the most recent observed data.





ACS Facts & Figures 2023




- In a recent review of SEER data, **the mortality from uterine cancer is now similar to that of ovarian cancer**.

- Causes?
  - Changing disease risk
  - Improved treatment options for patients with ovarian cancer (e.g. PARP inhibitors)
  - Deficit in research investment – in 2018, NCI funding for uterine cancer was 1/7$^{th}$ that for ovarian cancer
  - High disparity for Black women, with twofold higher mortality compared with White women despite similar incidence

Giaquinto AN et al. *Obstet Gynecol* 2022

# ENDOMETRIAL CARCINOMA
# Risk Factors

**Demographic**

- Increasing age
- Black race

**Other risk factors**

- Diabetes
- Lynch syndrome
- Cowden syndrome

**Unopposed/Excess Estrogen**

- Obesity
- Early menarche, late menopause, nulliparity
- Chronic anovulation (eg polycystic ovarian syndrome)
- Hormone replacement therapy
- Ovarian granulosa cell cancers
- Tamoxifen

**Protective Factors**

- Oral contraceptive pills
- Pregnancy
- Physical activity



Lheureux S & Wilson MK. *Exp Opin Investig Drugs* 2014

# Endometrioid endometrial cancers can be further categorized based on molecular profile

An integrated genomic analysis by TCGA network classified endometrioid endometrial cancers into 4 categories

| | |
|---|---|
| **Copy-number low** | • High frequency of mutations in *CTNNB1*, *KRAS*, *SOX17*; frequent *PIK3CA* and *PIK3R1* mutations co-occurring with *PTEN* mutations; elevated levels of progesterone receptor and RAD50 expression<br>• Represents ~49% of endometrioid tumors[a] |
| **MSI hypermutated** | • High mutation rate and few copy number alterations; high rate of *MLH1* promoter methylation; high phospho-AKT; low PTEN expression; frequent *PIK3CA* and *PIK3R1* mutations co-occurring with *PTEN* mutations<br>• Represents ~39% of endometrioid tumors[a,b] |
| **Copy-number high** | • Greatest transcriptional activity; frequent *TP53* mutations; decreased levels of phospho-AKT; mutually exclusive *PIK3CA*, *PIK3R1*, and *PTEN* mutations<br>• Represents ~8% of endometrioid tumors[a]<br>• Worst prognosis |
| ***POLE* ultramutated** | • Ultra-high somatic mutation frequency; MSS; frequent mutations in the exonuclease domain of *POLE*; high ASNS and CCNB1 expression<br>• Represents ~4% of endometrioid tumors[a]<br>• Best prognosis |

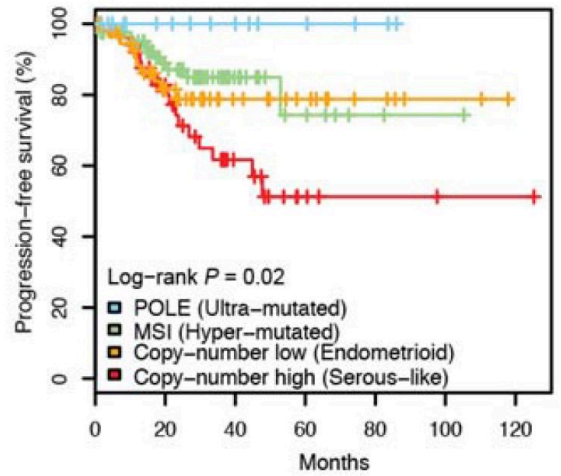


Levine DA et al. *Nature* 2013.; Cosgrove CM et al. *Gynecol Oncol* 2018.

# The Cancer Genome Atlas Project (TCGA)

| | POLE (Ultramutated) | MSI (Hypermutated) | COPY-NUMBER LOW | COPY-NUMBER HIGH (Serous-like) |
|---|---|---|---|---|
| **Copy Number Alterations** | Low | Low | Low | High |
| **MSI/MLH 1 Methylation** | Mixed MSI high, low, stable | MSI High | MSI stable | MSI stable |
| **Mutation Rate** | Very High (232 x 104 Mutations/Mb) | High (18 x 104 Mutations/Mb) | Low (2.09 x 104 Mutations/Mb) | Low (2.3 x 104 Mutations/Mb) |
| **Genomic Profile** | POLE (100%)<br>PTEN (94%)<br>P1K3CA (71%)<br>P1K3R1 (65%)<br>FBXW7 (82%)<br>AR1D1A (76%)<br>KRAS (53%)<br>AR1D5b (47%)<br>PD1/PD-L1 Overexpression | PTEN (88%)<br>RPL22 (32%)<br>KRAS (35%)<br>P1K3CA (54%)<br>P1K3R1 (40%)<br>AR1D1A (37%)<br>PD1/PD-L1 Overexpression | PTEN (77%)<br>CTNNB1 (52%)<br>P1K3CA (53%)<br>P1K3R1 (33%)<br>AR1D1A (42%)<br>FGFR2 (10.9%) | TP53 (92%)<br>PPP2R1A (22%)<br>FBXW7 (22%)<br>P1K3CA (47%)<br>PTEN (11%)<br>FGFR Amplifications & mutations (7%)<br>HER2 amplified 25% |
| **Histology** | Endometrioid | Endometrioid | Endometrioid | Serous, Endometrioid, and Mixed |
| **Grade** | Grades 1-3 | Grades 1-3 | Grades 1-2 | Grade 3 |

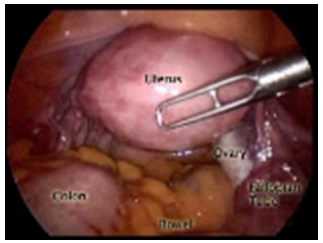
- The POLE, MSI and CNL clusters are composed mostly of endometrioid ECs.
- Serous and 25% of endometrioid ECs are found in the CNH.
- Black women more likely to have CNH ECs
- **All have clinically actionable targets for treatment.**






Kandoth et. al. Nature. 2013;497(7447):67-73;
Walsh et. al., Gyn Oncol, 168 (2023) 48-55

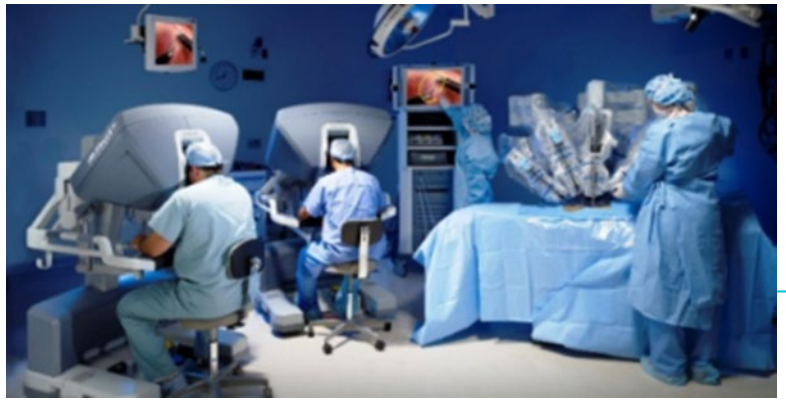
# Endometrial Cancer
# Surgical Staging

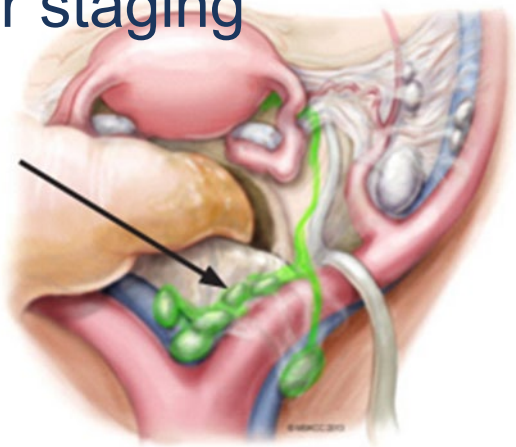



- Total hysterectomy/removal of tubes and ovaries ± pelvic/paraaortic lymphadenectomy
  - More extensive surgery may be beneficial for stage II

- RCT of laparoscopic vs. open surgery showed equivalent recurrence and survival rates

- Sentinel lymph node mapping is preferred option for staging





# 2009 FIGO Staging

| Stage | Anatomic involvement |
|---|---|
| Stage I | Tumor confined to the uterine corpus |
| IA | No or <50% myometrial invasion |
| IB | ≥50% myometrial invasion |
| Stage II | Cervical stromal involvement |
| Stage III | Local and/or regional tumor spread |
| IIIA | Tumor invasion into uterine serosa and/or adnexal involvement |
| IIIB | Vaginal and/or parametrial involvement |
| IIIC | Metastases to lymph nodes |
| IIIC1 | Positive pelvic lymph nodes |
| IIIC2 | Positive para-aortic lymph nodes |
| Stage IV | |
| IVA | Bladder and/or bowel involvement |
| IVB | Distant metastases, including abdominal disease and/or inguinal lymph node involvement |

**Adjuvant Therapy**

- Stage
- Tumor histology
- Tumor grade
- Lymphovascular invasion (present/absent)
- Age



Singh et al Obstetrics and Gynecology International 2013

# 2023 FIGO Staging

| Stage | Description |
|---|---|
| Stage I | Confined to the uterine corpus and ovary[c] |
| IA | Disease limited to the endometrium OR non-aggressive histological type, i.e. low-grade endometroid, with invasion of less than half of myometrium with no or focal lymphovascular space involvement (LVSI) OR good prognosis disease |
| | IA1 Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium |
| | IA2 Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI |
| | IA3 Low-grade endometrioid carcinomas limited to the uterus and ovary[c] |
| IB | Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI[d] |
| IC | Aggressive histological types[e] limited to a polyp or confined to the endometrium |
| Stage II | Invasion of cervical stroma without extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion |
| IIA | Invasion of the cervical stroma of non-aggressive histological types |
| IIB | Substantial LVSI[d] of non-aggressive histological types |
| IIC | Aggressive histological types[e] with any myometrial involvement |
| Stage III | Local and/or regional spread of the tumor of any histological subtype |
| IIIA | Invasion of uterine serosa, adnexa, or both by direct extension or metastasis |
| | IIIA1 Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)[c]<br>IIIA2 Involvement of uterine subserosa or spread through the uterine serosa |
| IIIB | Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum |
| | IIIB1 Metastasis or direct spread to the vagina and/or the parametria<br>IIIB2 Metastasis to the pelvic peritoneum |
| IIIC | Metastasis to the pelvic or para-aortic lymph nodes or both[f] |
| | IIIC1 Metastasis to the pelvic lymph nodes<br>IIIC1i Micrometastasis<br>IIIC1ii Macrometastasis<br>IIIC2 Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes<br>IIIC2i Micrometastasis<br>IIIC2ii Macrometastasis |
| Stage IV | Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis |
| IVA | Invasion of the bladder mucosa and/or the intestinal/bowel mucosa |
| IVB | Abdominal peritoneal metastasis beyond the pelvis |
| IVC | Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone |

## Summary of Major Changes

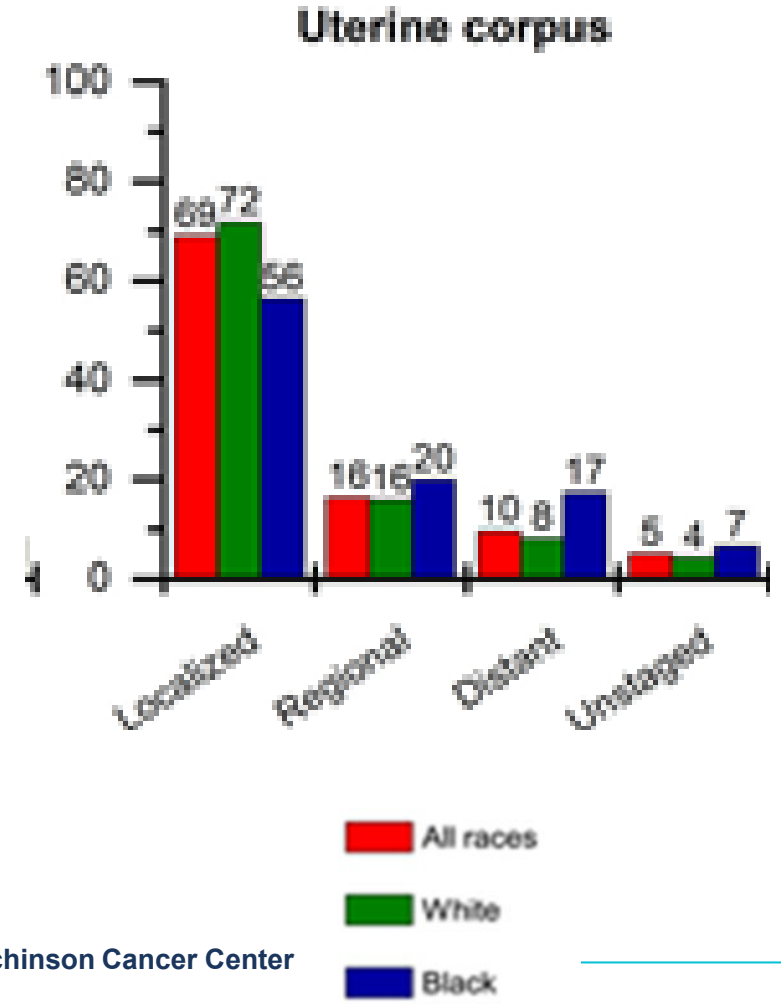
- Introduction of non-anatomical parameters (stages I/II) histologic type/grade, extent of LVI, molecular subgroup
- Subdivision of stage II/IV categories according to location and size of disease
- Creation of a stage for "synchronous" low grade endometrioid tumors of endometrium and ovary

| Stage designation | Molecular findings in patients with early endometrial cancer (Stages I and II after surgical staging) |
|---|---|
| Stage IAm$_{POLEmut}$ | *POLEmut* endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type |
| Stage IICm$_{p53abn}$ | p53abn endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type |



Berek et al Int J Gyncol Obstet 2023

# Postoperative Treatment Relevant Factors




- Anatomic involvement
- Histology & grade
- Extent of lymphovascular invasion
- Lymph node metastases
  - Number of positive lymph nodes
  - ITCs, micro- or macrometastases
- **Molecular profile**
  - MMR/MSI
  - P53 mutation
  - POLE mutation

National Comprehensive Cancer Network®

**CLINICAL FINDINGS (Endometrioid Histology)[a]**

**HISTOLOGIC GRADE/ADJUVANT TREATMENT[g,h,m]**

**Surgically staged: Stage I[e]** →

| FIGO Stage | Histologic Grade | Adjuvant Treatment |
|---|---|---|
| IA | G1, G2 | Observation preferred<br>or<br>Consider vaginal brachytherapy if lymphovascular space invasion (LVSI) and/or age ≥60 y[n] |
| | G3 | Vaginal brachytherapy preferred<br>or<br>Consider observation if no myoinvasion<br>or<br>Consider EBRT if either age ≥70 y or LVSI (category 2B) |
| IB | G1 | Vaginal brachytherapy preferred<br>or<br>Consider observation if age <60 y and no LVSI |
| | G2 | Vaginal brachytherapy preferred<br>or<br>Consider EBRT if ≥60 y and/or LVSI<br>or<br>Consider observation if age <60 y and no LVSI |
| | G3 | RT (EBRT and/or vaginal brachytherapy) ± systemic therapy (category 2B for systemic therapy) |

# Endometrial carcinoma
# ADJUVANT TREATMENT for Stages I/II

- Stage I risk stratified into low risk, low intermediate risk, high intermediate risk and high risk depending on pathologic risk factors: **grade, depth of myometrial invasion, LVSI**
  - GOG 99
  - PORTEC 1 and 2
- Low risk and low intermediate risk require no adjuvant therapy
- High intermediate risk is treated with vaginal brachytherapy (VBT)
- High risk, early-stage disease is treated with some combination of EBRT, VBT and systemic therapy (usually 3-6 cycles of carboplatin / paclitaxel)
  - GOG 249
  - GOG 258
  - PORTEC 1, 2, 3

**GOG 99 High Intermediate Risk**
Risk factors: Grade 2-3, DOI ≥ 66%, LVSI

Age < 50 and 3 RF
Age 50-70 and 2 RF
Age ≥ 70 and 1 RF

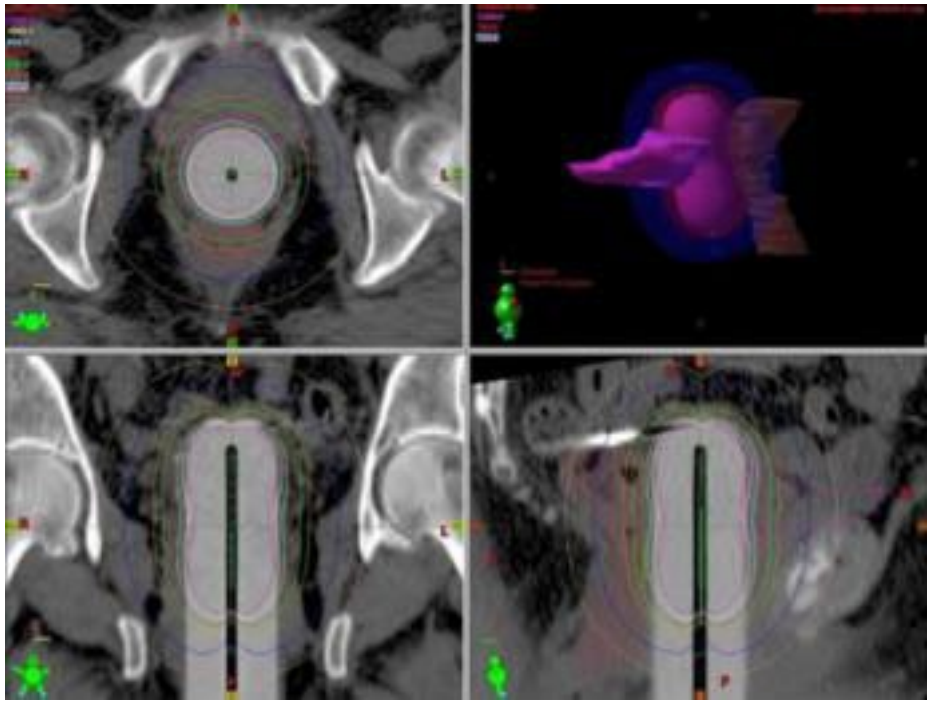
**PORTEC 1, 2 High Intermediate Risk**
Risk factors: Age > 60, Grade 3, DOI >50%

2 of 3 RF must be present

# Postoperative Treatment
# EARLY Stage Disease

- Radiation if pathology suggests increased  risk for recurrence
  - Deep myometrial invasion
  - G2-3 histology
  - LVSI

- Vaginal brachytherapy equivalent to external beam pelvic radiation for prevention of recurrence at vaginal cuff with less toxicity





Nout RA et al. PORTEC-2 *Lancet* 2010.

# Endometrial carcinoma
# ADJUVANT chemotherapy for stages I/II

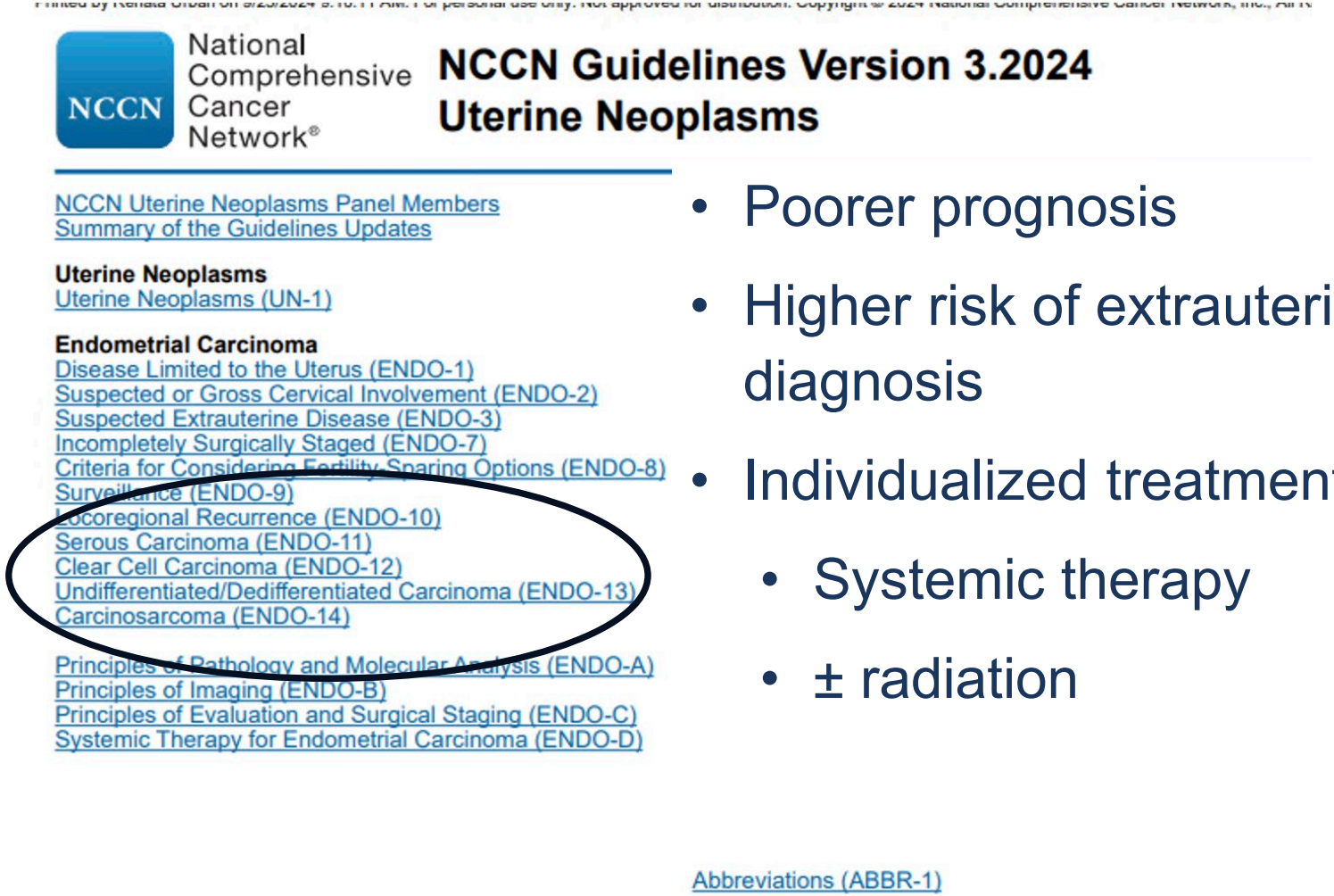
**Major Phase III trials looking at adjuvant chemotherapy that included Stage I/II disease**

| Trial | Inclusion Criteria | Arms | Results |
|---|---|---|---|
| NSGO-EC 9501/EORTC-5591 + MaNGO ILIADE-III | I-III (no RD) and high-risk factors | (1) EBRT<br>(2) EBRT + chemo | Chemo improved PFS but not OS |
| GOG 249 | EEC: I HIR, II<br>S/CC: I-II w neg cytol | (1) EBRT<br>(2) C/T x 3 + VBT | No difference in RFS or OS |
| PORTEC-3 | EEC: IA G3 w LVSI, IB G3, II-III<br>S/CC: all stages | (1) EBRT<br>(2) CisRT + C/T x 4 | Improved RFS, no different in OS in early stages |
| GOG 258 | III-IVA (<2 cm RD)<br>I/II S/CC w pos cytol | (1) C/T x 6<br>(2) CisRT + C/T x 4 | No difference in RFS or OS<br>Fewer vaginal/nodal failures w RT<br>Fewer distant failures with C/Tx6 |
| ENGOT-EN2-DGCG | EEC: I G3, II<br>S/CC: I-II | (1) C/Tx x 6 + VBT<br>(2) VBT | Ongoing |



Hoberg T et al *Eur J Ca* 2010
Randall ME et al *J Clin Oncol* 2019
De Boer SM et al. *Lancet Oncol* 2018
Matei D et al *N Engl J Med* 2019

# High-risk histologic types



National Comprehensive Cancer Network®

**NCCN Guidelines Version 3.2024**
**Uterine Neoplasms**

NCCN Uterine Neoplasms Panel Members
Summary of the Guidelines Updates

**Uterine Neoplasms**
Uterine Neoplasms (UN-1)

**Endometrial Carcinoma**
Disease Limited to the Uterus (ENDO-1)
Suspected or Gross Cervical Involvement (ENDO-2)
Suspected Extrauterine Disease (ENDO-3)
Incompletely Surgically Staged (ENDO-7)
Criteria for Considering Fertility-Sparing Options (ENDO-8)
Surveillance (ENDO-9)
Locoregional Recurrence (ENDO-10)
Serous Carcinoma (ENDO-11)
Clear Cell Carcinoma (ENDO-12)
Undifferentiated/Dedifferentiated Carcinoma (ENDO-13)
Carcinosarcoma (ENDO-14)

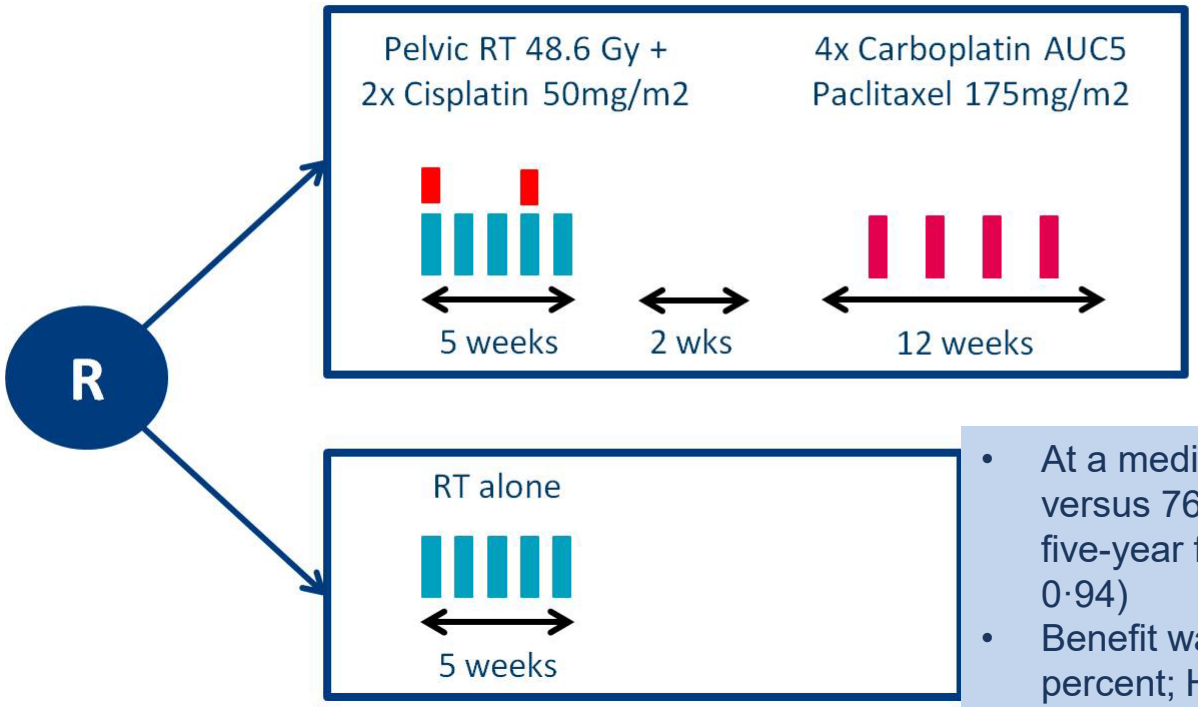
Principles of Pathology and Molecular Analysis (ENDO-A)
Principles of Imaging (ENDO-B)
Principles of Evaluation and Surgical Staging (ENDO-C)
Systemic Therapy for Endometrial Carcinoma (ENDO-D)

Abbreviations (ABBR-1)

- Poorer prognosis
- Higher risk of extrauterine spread at diagnosis
- Individualized treatment paradigms
  - Systemic therapy
  - ± radiation

# Review of PORTEC-3 Trial Design – Radiation/Advanced EC

- **High risk Endometrial Cancer (HREC)**




**High-risk endometrial cancer:**

(1) Stage I, endometrioid grade 3 with deep myometrial invasion or lymph-vascular space invasion (or both)
(2) Stage II or III, endometrioid
(3) Stage I to III with serous or clear cell histology.

- At a median follow-up of 73 months, five-year OS was 81% with chemoradiation versus 76% compared with RT alone (adjusted HR 0·70, 95% CI 0·51-0·97), and five-year failure-free survival was 77 versus 69 percent (HR 0·70, 95% CI 0·52-0·94)
- Benefit was seen particularly in **stage III patients** (five-year OS, 79 versus 69 percent; HR 0.63, 95% CI 0.41-0.99) and in patients with **serous tumors** (five-year OS, 71 versus 53 percent; HR 0.48, 95% CI 0.24-0.96).
- More Grade 3 or higher toxicity with chemoradiation versus RT alone (61% vs 13%)



Presented By Stephanie de Boer at 2017 ASCO Annual Meeting
de Boer SM, et al. Lancet Oncol 2019; 20:1273.
de Boer SM, et al. Lancet Oncol 2016; 17:1114.

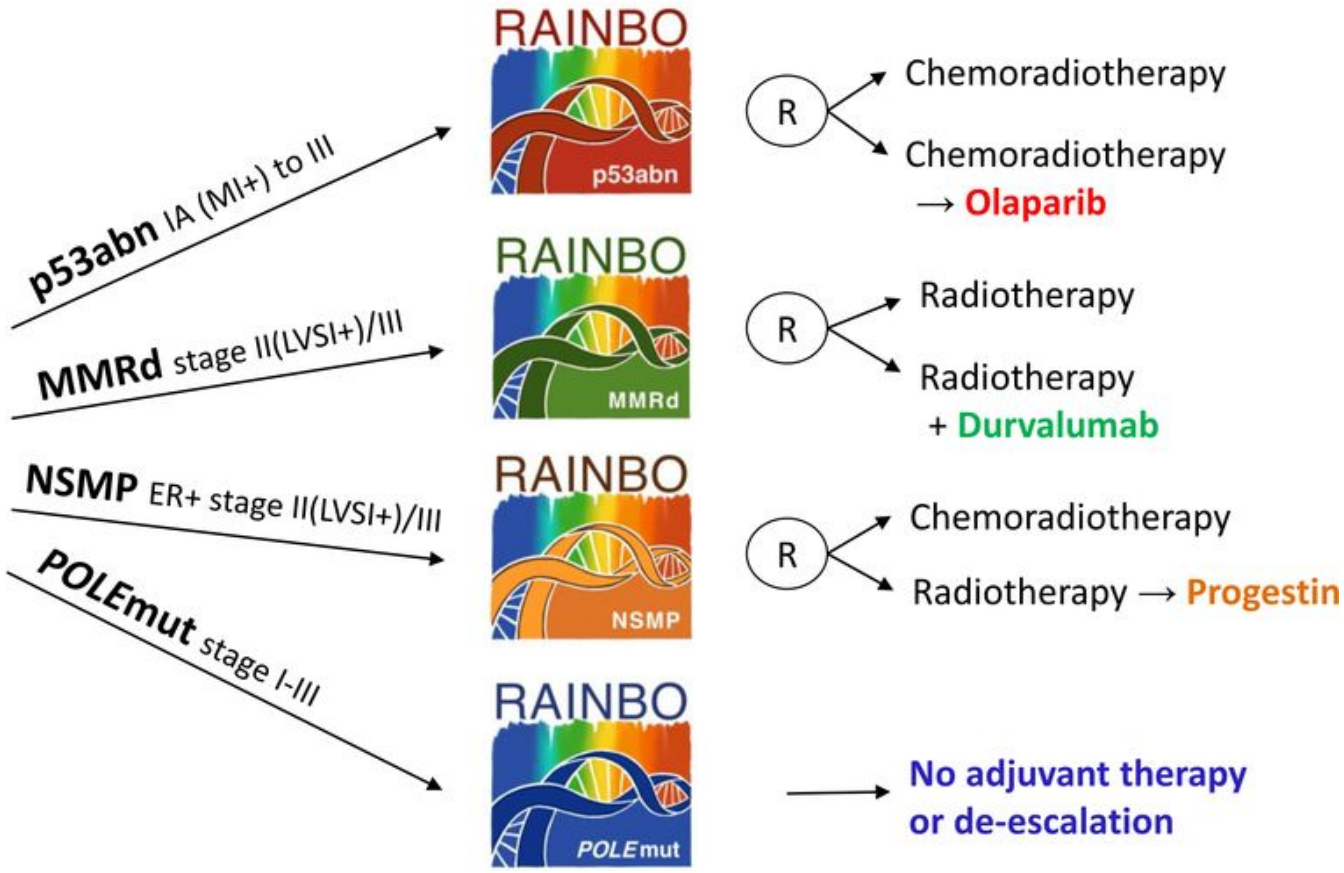
RAINBO

TransPORTEC

Completely resected endometrial cancer

Eligible histotypes:
endometrioid,
serous,
clear cell,
un/dedifferentiated,
mixed and
carcinosarcoma

→ Molecular Classification




# Ongoing PORTEC-4a:

Molecular-integrated risk profile to determine optimal therapy in endometrial cancer



Refining adjuvant treatment in endometrial cancer based on molecular features: the RAINBO clinical trial program
*International Journal of Gynecologic Cancer* Published Online First: 20 December 2022. doi: 10.1136/ijgc-2022-004039

# Endometrial Cancer Treatment – 1st Line

- **GOG 177 – Doxorubicin/Cisplatin (AP) vs Doxorubicin/Cisplatin/Paclitaxel (TAP)**
  - ORR of 57% for TAP vs 34% for AP (PFS 8.3 vs 5.3 months)
  - 1st trial to show a survival benefit for EC
- **GOG 209[1] – TAP vs Carboplatin/Paclitaxel**
  - PFS HR 1.03 (14 months in both arms)
  - OS HR 1.01 (38 vs 32 months)
  - Carboplatin/paclitaxel less toxic – first line treatment
- **GY018 and RUBY – Carboplatin/Paclitaxel + PD-1 Inhibitor**



[1]Fleming et al, J Clin Oncol. 2004; 22: 2159-2166
[2]Miller et. al., J Clin Oncol. 2020; 38: 3841-3850

# Current NCCN Guidelines for Systemic Therapy (March 2024)

- Preferred Regimens:
  - Carboplatin/paclitaxel
  - Carboplatin/paclitaxel/pembrolizumab (for stage III-IV, except for carcinosarcoma)
  - Carboplatin/paclitaxel/dostarlimab-gxly (for stage III-IV)
  - Carboplatin/paclitaxel/trastuzumab (for stage III-IV HER2-positive uterine serous carcinoma or carcinosarcoma)



https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf

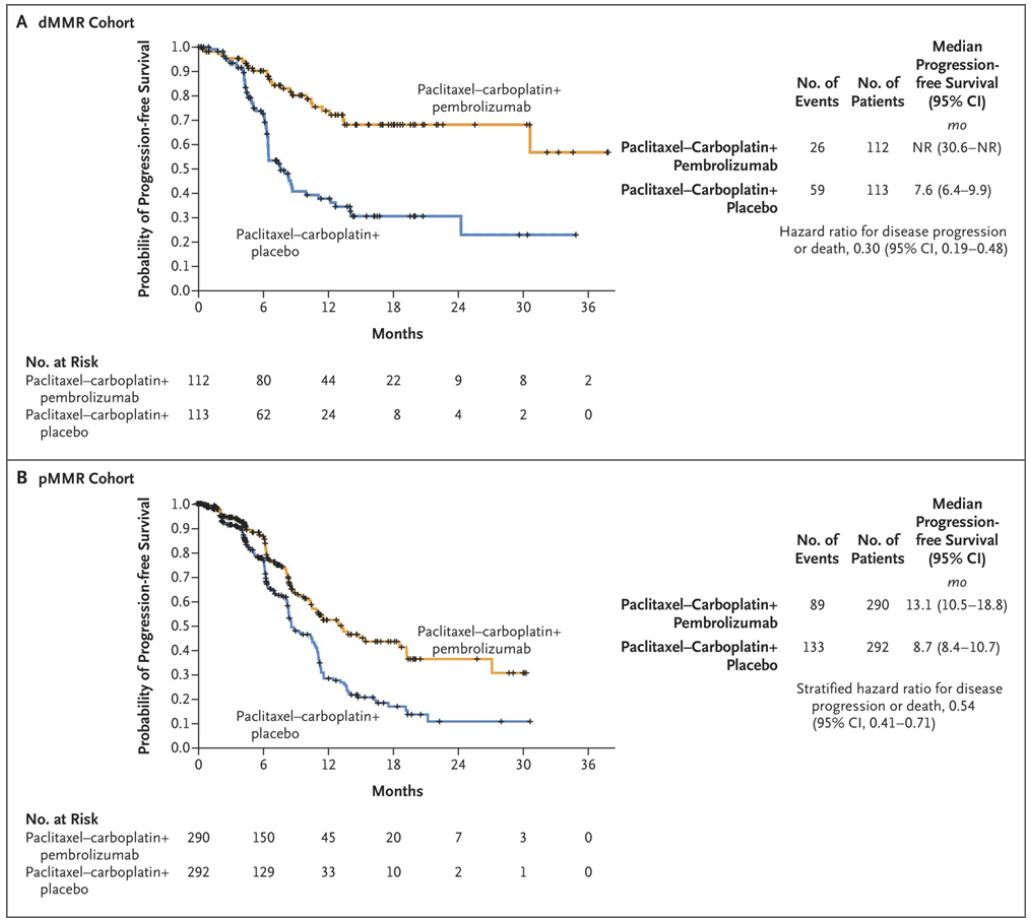
# Immune Checkpoint Blockade + Chemotherapy

- Cytotoxic chemotherapy→→→robust stimulation of the immune system[1]
  - ↑ presentation of tumor-specific antigens
  - ↑ PD-L1 expression on cancer cells
  - ↑ penetration of cytotoxic T-cells into tumor tissue
- **GY018:** – pembrolizumab vs placebo + paclitaxel/carboplatin
- **RUBY:** – dostarlimab vs placebo + paclitaxel/carboplatin
- **AtTEnd:** - atezolizumab vs placebo + paclitaxel/carboplatin
- All enrolled women regardless of MMR status



[1]Green et. al. 2020 ASCO Educational Book

# NRG-GY018 Survival Results




**dMMR Cohort:**

- Median f/u 12 months
- PFS 74% in pembrolizumab group vs 38% in placebo group (HR 0.30, 95% CI 0.19-0.48)
- Median PFS not reached in pembrolizumab group versus 7.6 months in placebo group
- SGO 2024: median OS not reached in either arm (HR 0.55, 95% CI, 0.25-1.19, *P*=.0617)

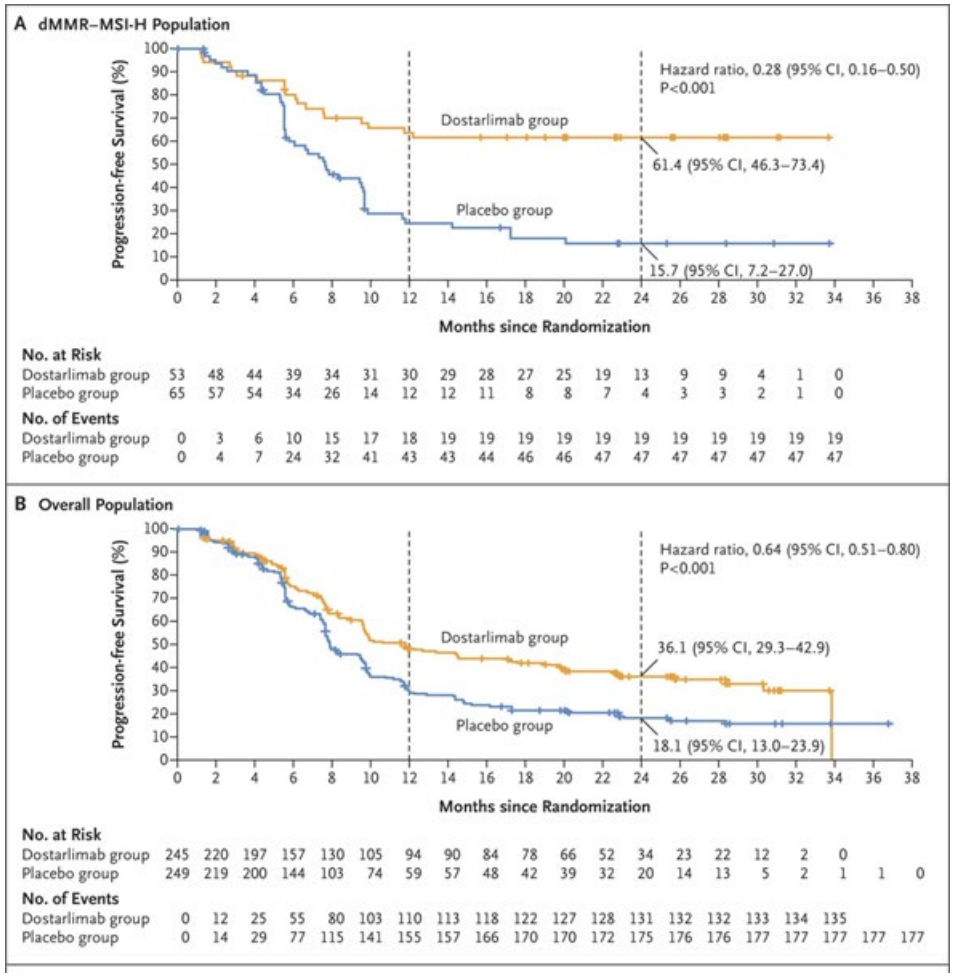
**pMMR Cohort:**

- Median f/u 7.9 months
- Median PFS 13.1 months in pembrolizumab group versus 8.7 months with placebo (HR 0.54, 95% CI, 0.41 to 0.71)
- SGO 2024: median OS was 27.96 months in pembrolizumab are versus 27.37 months in placebo arm (HR 0.79, 95% CI, 0.53-1.17, *P*=.1157)



Eskander R et al. NEJM 2023; 388: 2159-2170.
Eskander R et al. SGO 2024

# RUBY Results




**Overall Population:**

- PFS at 24 months was 36.1% in dostarlimab group and 18.1% in placebo group (HR 0.64, 95% CI, 0.51 to 0.80, *P*<0.001)
- OS at 24 months was 83.3% in dostarlimab group and 58.7% in placebo group (HR 0.30, 95% CI, 0.13 to 0.70)

**dMMR-MSI-H Population:**

- PFS at 24 months was 61.4% in dostarlimab group and 15.7% in placebo group (HR 0.28, 95% CI, 0.16-0.50, *P*<0.001
- OS at 24 months was 71.3% in dostarlimab group and 56% in placebo group (HR 0.64, 95% CI, 0.46-0.87, *P*=0.0021

**pMMR-MSS Population (not pictured):**

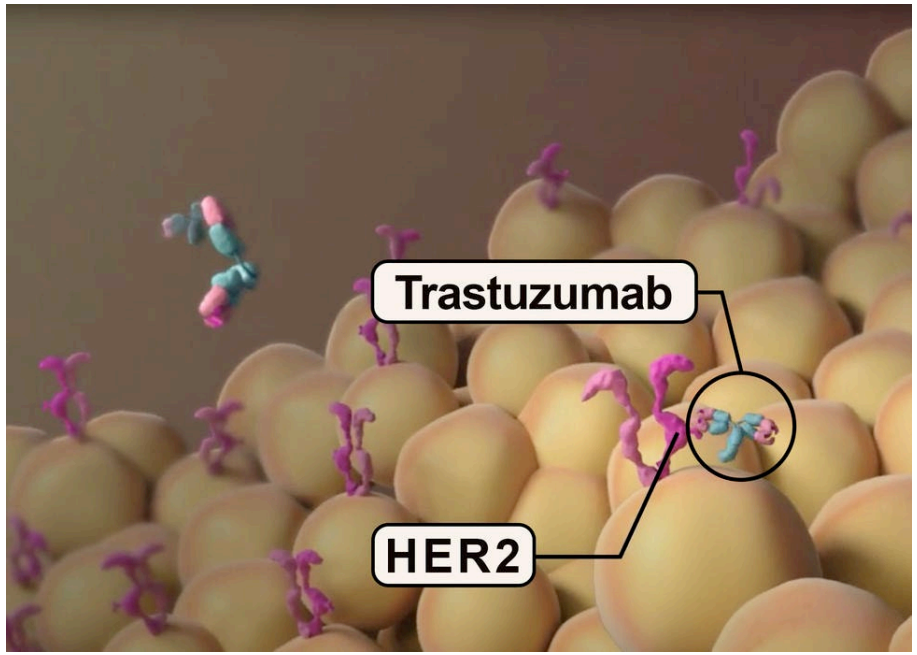
- PFS at 24 months was 28.4% in dostarlimab group and 18.8% in placebo group (HR 0.76, 95% CI, 0.59-0.98)
- OS at 24 months was 67.7% in dostarlimab group and 55.1% in placebo group (HR 0.73, 95% CI, 0.52-1.02)



Mirza MR et al. NEJM 2023; 388: 2145-2158.

# HER2/neu-positive Endometrial Cancers

- 25-30% of serous/carcinosarcomas ECs are HER2/neu-positive
- **NCT01367002**[1] – Randomized Phase 2 Carboplatin/Paclitaxel vs Carboplatin/Paclitaxel/Trastuzumab
- Advanced and recurrent serous endometrial cancer
  - IHC score 2-3+, confirmed by FISH
  - Scoring performed by 2007 guidelines of ASCO/CAP as for breast cancer

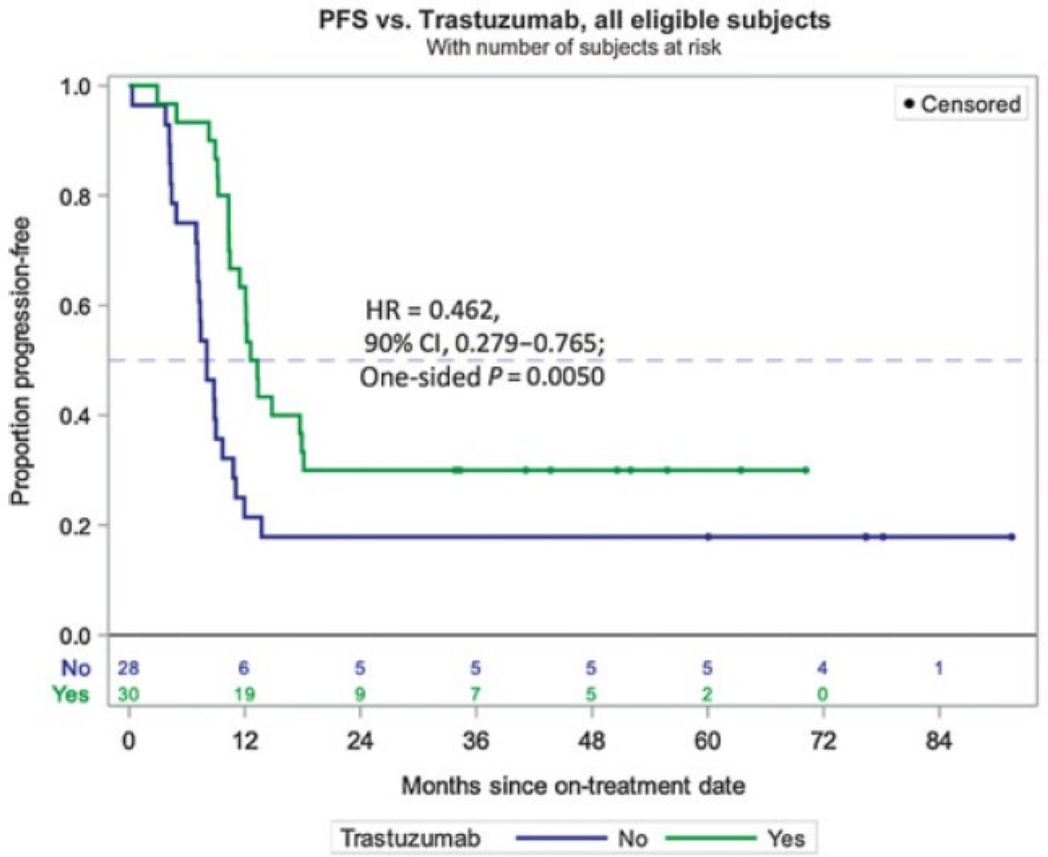





[1]Fader et. al. Clinical Cancer Research, 2020; 26:3928;
Image Courtesy of the National Cancer Institute

# Randomized Phase 2 Carboplatin/Paclitaxel +/- Trastuzumab

- Maintenance trastuzumab until progression or toxicity (n=61)
- PFS in P/C vs P/C/T = 8 vs 12.9 months
- OS = 24.4 vs 29.6
- Stage 3 and 4, primary treatment
  - 41 patients, Median PFS 9.3 vs 17.7 mo
  - OS = 24.4 mo vs not reached
- Recurrent
  - 17 patients, Median PFS 7.0 vs 9.2 mo






Fader et. al. Clinical Cancer Research, 2020; 26:3928

# Role of Radiation for Stage III/IVA EC?

- Pelvic RT incorporation and timing of pelvic RT lacking robust data
- ASTRO Clinical Practice Guidelines
  - Conditionally recommended
    - Chemotherapy (6 cycles) + EBRT
    - ChemoRT + chemotherapy (4 cycles)
- When to add a vaginal cylinder boost?
  - Per ASTRO Guidelines: High risk patients with cervical stromal involvement (Stage II), and/or close or positive vaginal margins
  - Institutional dependent practice based on extensive LVSI or high-ris histology



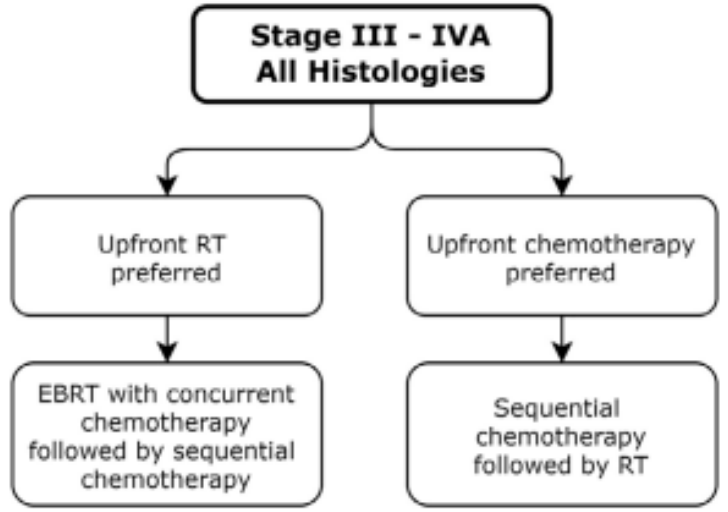



**Figure 3** Stage III to IVA endometroid carcinoma. *Abbreviations:* EBRT = external beam radiation therapy; GOG = Gynecologic Oncology Group; RT = radiation therapy.
Chemotherapy alone is also an option based on GOG 258.[20]



Kitchener, H., & Powell, M. (2010). Radiotherapy for endometrial cancer: A key piece in The jigsaw. *The Lancet*, *375*(9717), 781–782. doi:10.1016/s0140-6736(10)60099-2; Harkenrider MM et al PRO 2022

# Endometrial Cancer

## *Advanced Stage Disease*

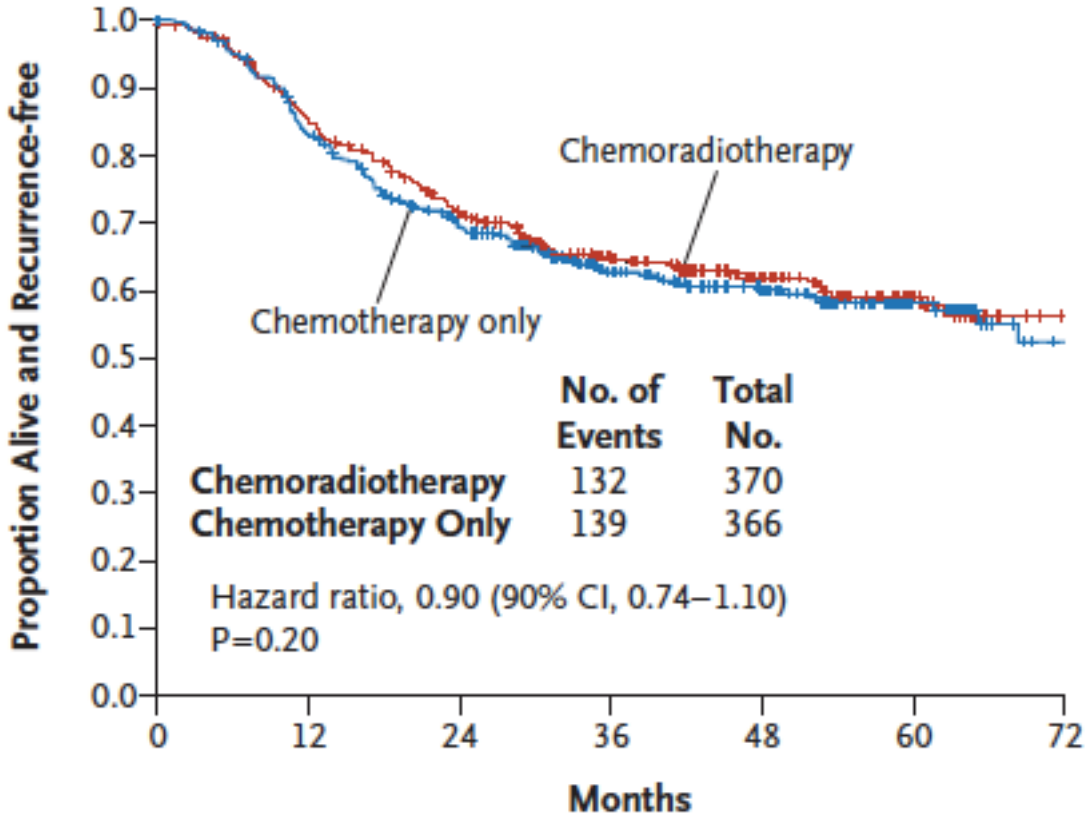
- **GOG 258:** Stage III, IV <2cm residual

[redacted]

[redacted]

<u>5-yr RFS:</u>
Chemo - 58%
ChemoRT - 59%

<u>5-yr OS estimates:</u>
Chemo - 73%
ChemoRT - 70%




ChemoRT arm

↓vaginal recurrence (2% vs 7%)

↑pelvic and PA node recurrence (11% vs 20%)

↑distant recurrence (27% vs 21%)



Matei D et al. New Engl J Med 2019.

# Recurrent Disease

- Local (oligometastatic) – imaging and biopsy, vaginal recurrences most common
  - Radiation therapy (if not seen prior radiation) – PORTEC-1, CR of 87%[1]
  - Surgical resection (including pelvic exenteration)
  - Intra-operative radiation
  - Chemotherapy
  - Multi-modality
- Disseminated disease – palliative chemotherapy
  - OS 14-15 months




[1]Creutzbeg et. al., Gynecol Oncol 2003; 89:201; Image Courtesy of Getty Images

# Targeted Agents for Treatment

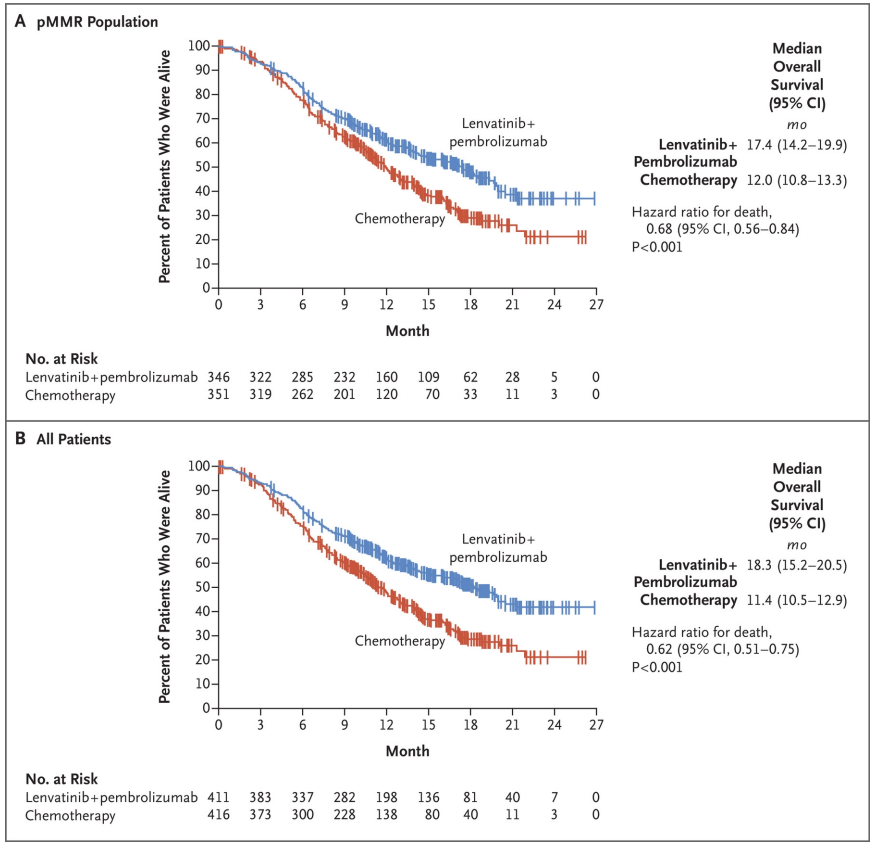
- PD-1/PD-L1 inhibitors (other immunotherapy targets)
- mTOR pathway inhibitors
- HER2/neu inhibitors
- PARP inhibitors
- Anti-angiogenic agents
- Antibody-drug conjugates



# Recurrent Uterine Adenocarcinoma

## *Pembrolizumab & lenvatinib ("len/pem")*

- Options for MSS tumors? Only 16-31% of EC have dMMR
- Lenvatinib: multitargeted tyrosine kinase inhibitor of VEGF-R 1-3, FGF-R 1-4, PDGF-R α, RET& KIT
  - Limited efficacy as second-line treatment for recurrent endometrial carcinoma (OR 14.3%)
- KEYNOTE 146 unselected for MSI or PD-L1 status: 38.0% ORR  for len/pem
  - FDA approval Sept 2019
- KEYNOTE-775
  - Phase III of len/pem vs IC chemo for advanced/ recurrent/metastatic
  - **Longer PFS & OS compared to chemo**






Le DT et al. *N Engl J Med* 2015., Ott PA et al. *J Clin Oncol* 2017., Makker V et al. *J Clin Oncol* 2020. Makker V et al, *N Engl J Med* 2022.

# PI3K/Akt/mTOR Pathway

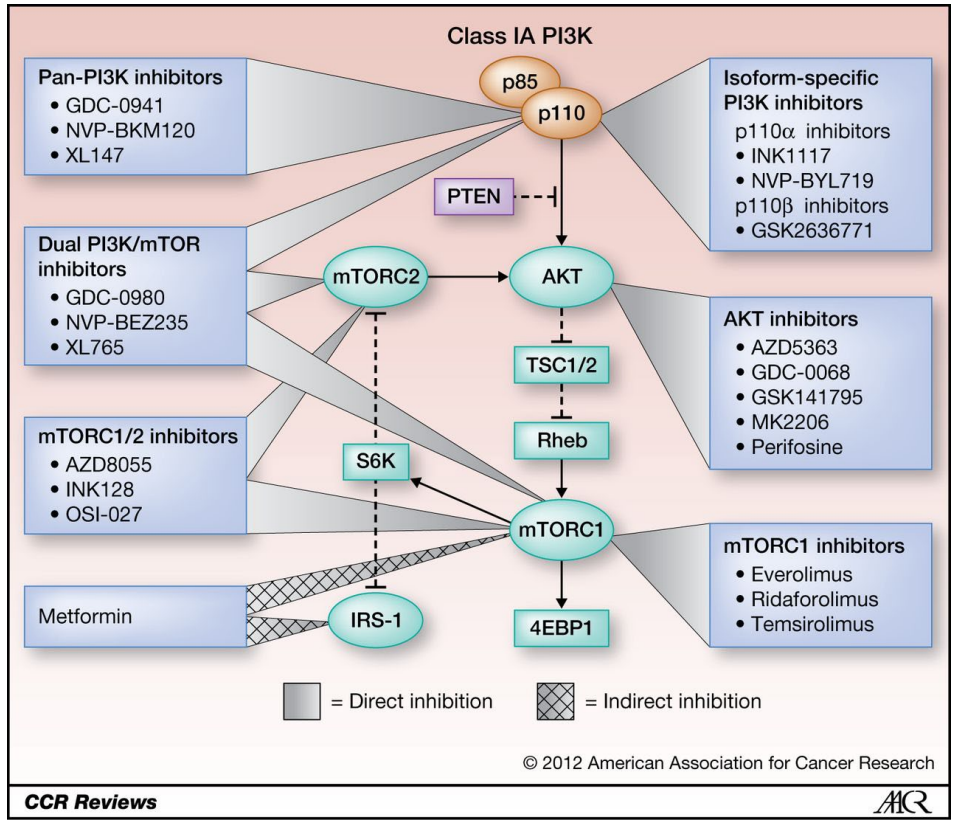
| Somatic Aberration | Potential Clinical Actionability | Endometrioid (Type 1) | Non-endometrioid (Type 2) | POLE | MSI-H | CNL | CNH |
|---|---|---|---|---|---|---|---|
| Mutated PTEN | ▪ PI3K-Akt-mTOR pathway inhibition<br>▪ Synthetic lethality with PARP inhibition<br>▪ CDK4/6 inhibition | 64-80% | 2-3% | 94% | 88% | 77% | 11% |
| Mutated PIK3CA | ▪ PI3K-Akt-mTOR pathway inhibition | 22-39% | 15-35% | 71% | 54% | 53% | 47% |
| Mutated PIK3R1 | ▪ PI3K-Akt-mTOR pathway inhibition | 9-43% | 5-8% | 65% | 40% | 33% | - |



Table Courtesy of Victoria Bae-Jump, MD

# PI3K/Akt/mTOR Pathway Inhibitors

- Single-agent mTORC1 inhibitors – modest activity (<25%)
- No advantage of temsirolimus added to paclitaxel/carboplatin (GOG86P)[1]
  - TSC2 mutations - ↑ PFS
  - Single agent temsirolimus on NCCN guidelines
- Newer generation agents – limited response but others are in development

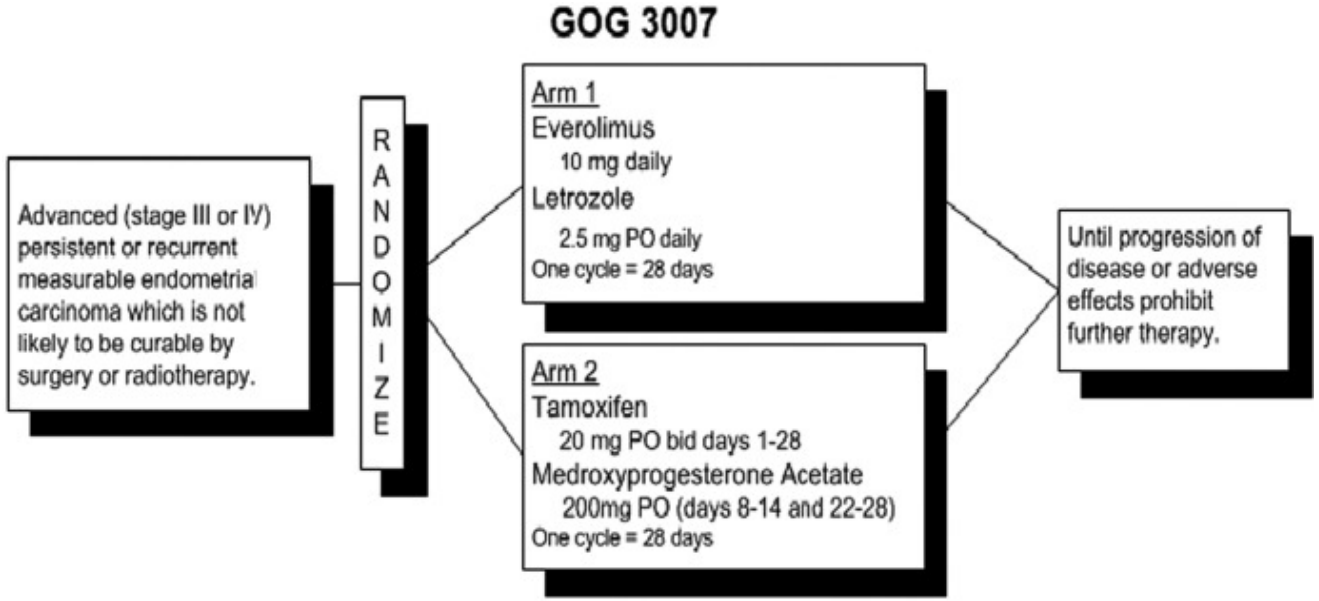





[1]Aghajanian et. al., Gynecol Oncol 2018 150(2):274-281; Slomovitz, B.M., & Coleman, R.L. (2012). The PI3K/AKT/mTOR Pathway as a Therapeutic Target in Endometrial Cancer. *Clinical Cancer Research, 18*, 5856 - 5864.

# GOG 3007 – Phase 2: Letrozole + Everolimus vs Medroxyprogesterone + Tamoxifen

- **22% response rate in the everolimus/letrozole arm**
  - PFS 6 mo, OS 31 mo
  - 28 mo PFS chemo-naïve vs 4 mo prior chemo (25% ORR in chemo-naïve)
  - Serous tumors had limited response
- **25% response rate in the megestrol acetate/tamoxifen arm**
  - PFS 4 mo, OS 17 mo
  - 5 mo PFS chemo-naïve vs 3 mo prior chemo

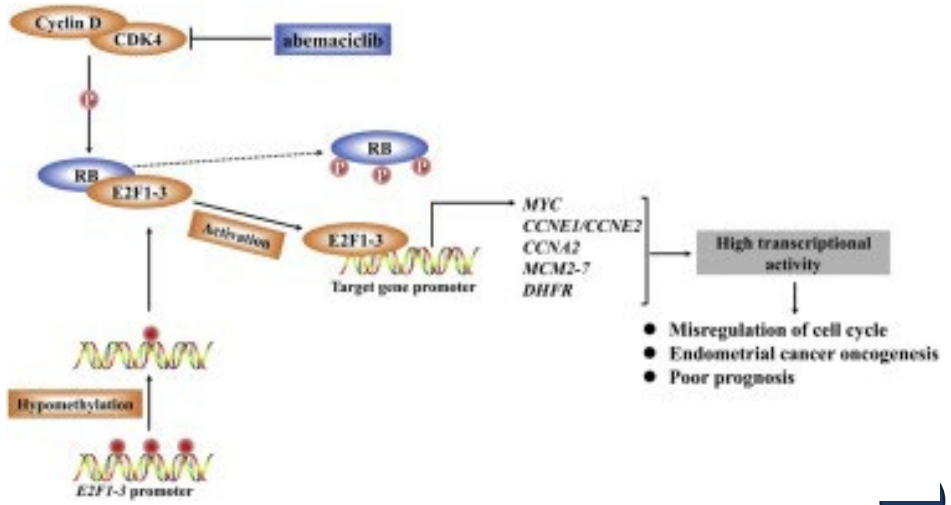





Slomovitz et. al., Gyn Oncology, 164 (2022) 481-491

# Cyclin-dependent Kinase Inhibition

- CDK4/6 inhibition proposed to have synergistic activity with hormonal inhibition
- Phase II two-stage study of letrozole with abemaciclib in ER+ recurrent EC
  - ORR 30%
- Phase II clinical trial of ribociclib & letrozole in ER+ EOC & EC
  - 55% PFS at 12 weeks

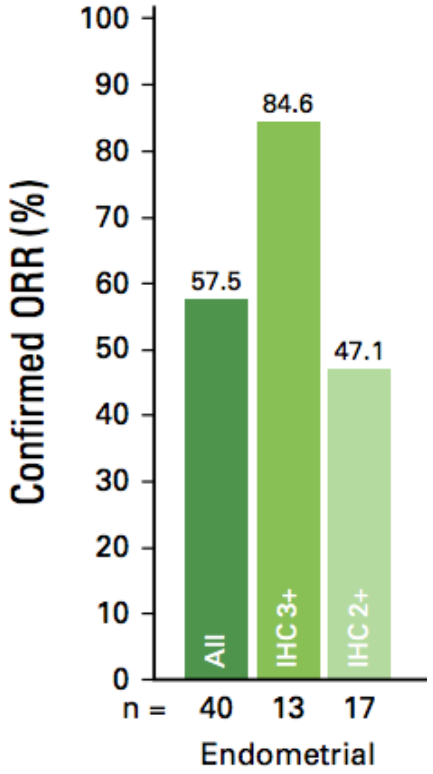


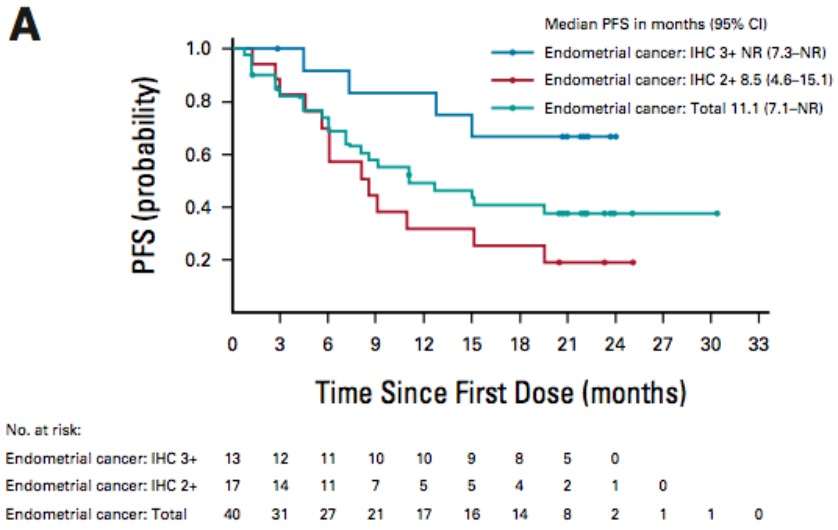


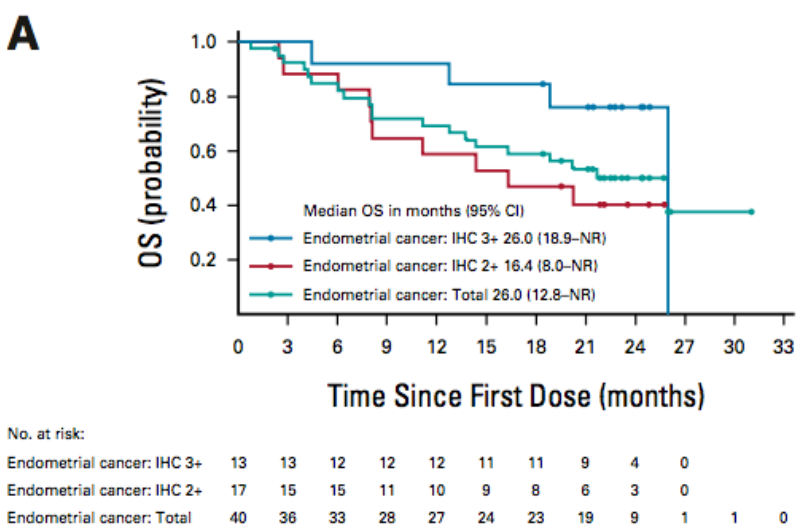

Hu J et al. Biomedicine & Pharmacotherapy. Vol 125, May 2020
Konstatinopoulos PA PMID: 36174113, Colon-Otero G et al, PMID: 33109627

# DESTINY-PanTumor 02 Endometrial CA Cohort

- Open-label phase II study for Her2-expressing locally advanced or metastatic disease after ≥1 systemic treatment or without alternative treatments
- ORR 37.1% in all cohorts




- Listed as an option in NCCN guidelines for recurrent HER2+ (IHC 2+ or 3+) endometrial cancer
- Received accelerated approval by FDA for all patients with previously treated unresectable or metastatic HER-2 positive solid tumors
  - Defined as IHC 3+



Meric-Bernstam F et al. *J Clin Oncol* 2024; 42(1): 47-58.

# PARP Inhibitors and Endometrial Cancer

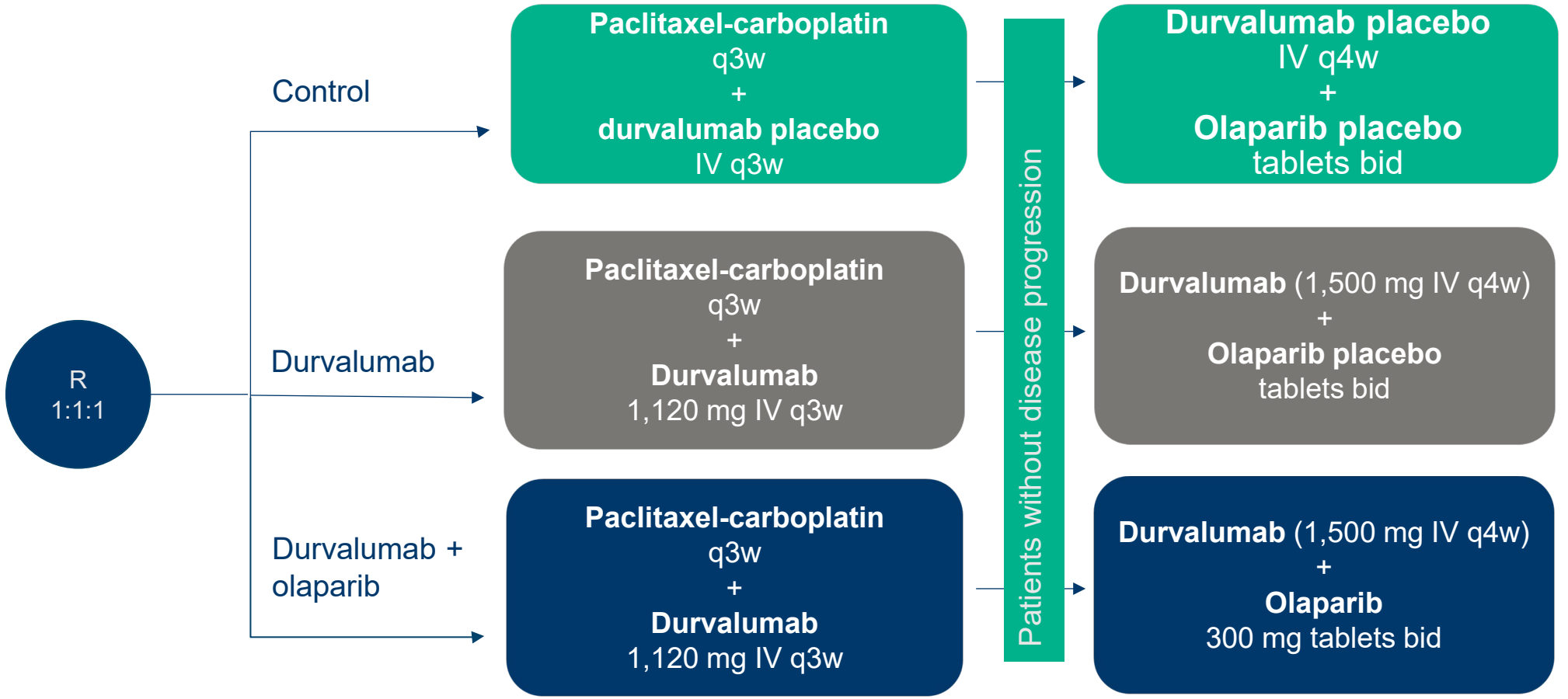
- ARID1A mutations common
- ARID1A deficiency impairs homologous recombination DNA repair – associated with PARP sensitivity
- Rates of homologous recombination deficiency (HRD) in non-endometrioid ECs to range between 15-24%[1,2], no standardized definition

| Trial Name | Phase & Type | EC Patients included | Mutation | Treatment | Primary Outcome |
|---|---|---|---|---|---|
| RAINBO | III | Early and late stage | POLE<br>dMMR<br>TP53 mutant<br>NSMP | TP53 mutant – chemoradiation +/- olaparib | 5-year RFS |
| CAN-STAMP | II-III | Early and late stage | TP53 mutant<br>Serous | Late stage – chemotherapy +/- niraparib | 3-year RFS |



[1]de Jonge et al. Clin Cancer Res. 2019;25(3):1087-97.
[2]Ashley et al. Gynecol Oncol. 2019;152(1):11-9.

# DUO-E Trial *Role of PARP Inhibition*




- All observed outcomes favored chemo + durvulumab and chemo+durvulumab+olaparib vs control
- HR for PFS in pMMR subgroup
  - 0.57 for D+O vs control
  - 0.77 for D vs control

Maintenance therapy continued until disease progression, unacceptable toxicity, or other discontinuation criteria were met



PMID 37864337

# Anti-Angiogenics and Endometrial Cancer

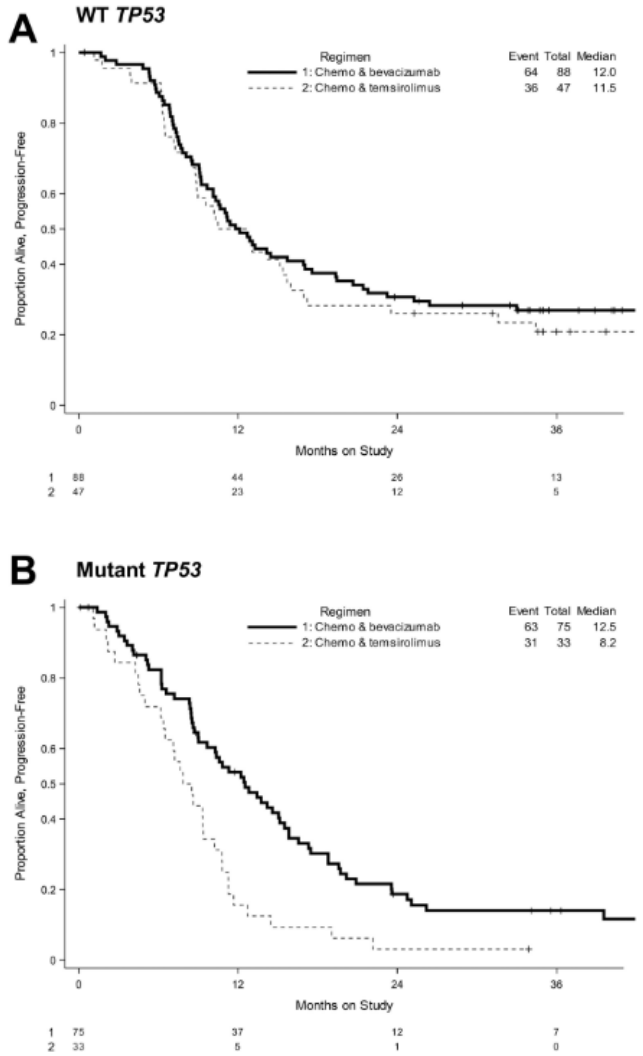
- **Bevacizumab** – 14% response rate, 40% 6-month PFS rate
  - Compares favorably with other second-line cytotoxic regimens
- **GOG86P** – phase II study of frontline paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus, or ixabepilone/carboplatin/bevacizumab in advanced/recurrent EC[1]
  - None better than historical controls
  - CTNNB1 mutations associated with ↑ PFS – activate angiogenesis
- **MITO END-2** - randomized phase II trial of carboplatin-paclitaxel +/- bevacizumab in advanced/recurrent EC[2]
  - No improvement in PFS, no biomarkers



[1]Aghajanian et. al., Gynecol Oncol 2018 150(2):274-281
[2]Lorusso et. al. Gynecol Oncol 2019 155: 406-412

# GOG-86P – TP53 Status

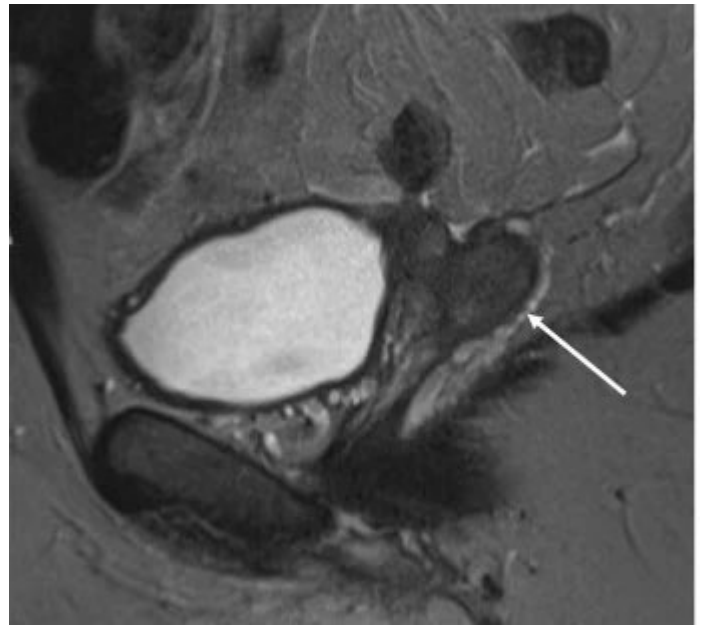
- Mutations in TP53 were associated with improved PFS and OS for patients that received bevacizumab as compared to temsirolimus
  - PFS: HR 0.48, 95% CI 0.31, 0.75
  - OS: HR: 0.61, 95% CI 0.38, 0.98.
- No significant difference in PFS or OS between arms for patients with WT TP53.



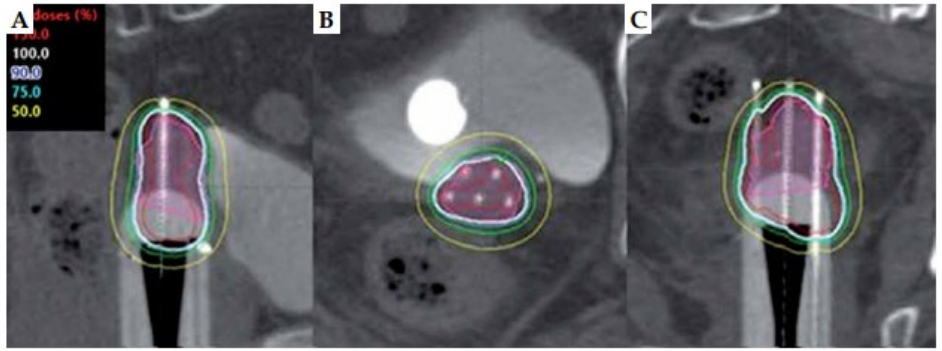



Leslie et. al., Gynecol Oncol. 2021; 161(1): 113–121
Thiel et. al. J Clin Oncol 2023; 40 (28): 3289-3300

# Vaginal Cuff Recurrent Disease



- Early-stage patients managed with observation may have 10-15% risk of recurrence, most often in first 2-3 years
- 60-70% of recurrences are at the vaginal cuff
- If no prior EBRT or vaginal cylinder HDR
  - Recommendation:




Pelvic RT (45-50 Gy)
-Treat LN region
-Shrink primary disease

→

Vaginal brachytherapy using cylinder/multichannel cylinder/interstitial catheters

Steiner, A., Alban, G., Cheng, T. *et al.* Vaginal recurrence of endometrial cancer: MRI characteristics and correlation with patient outcome after salvage radiation therapy. *Abdom Radiol* **45**, 1122–1131 (2020). https://doi.org/10.1007/s00261-020-02453-2; Patel et al, Journal of Contemporary Brachytherapy 2020; Patel P, Deufel C, Haddock M, Petersen I. Preliminary results of modified interstitial MIAMI brachytherapy applicator for treatment of upper and apical vaginal tumors. Journal of Contemporary Brachytherapy. 2020;12(6):562-571. doi:10.5114/jcb.2020.101689.

# Recurrent Disease – Prior Chemotherapy

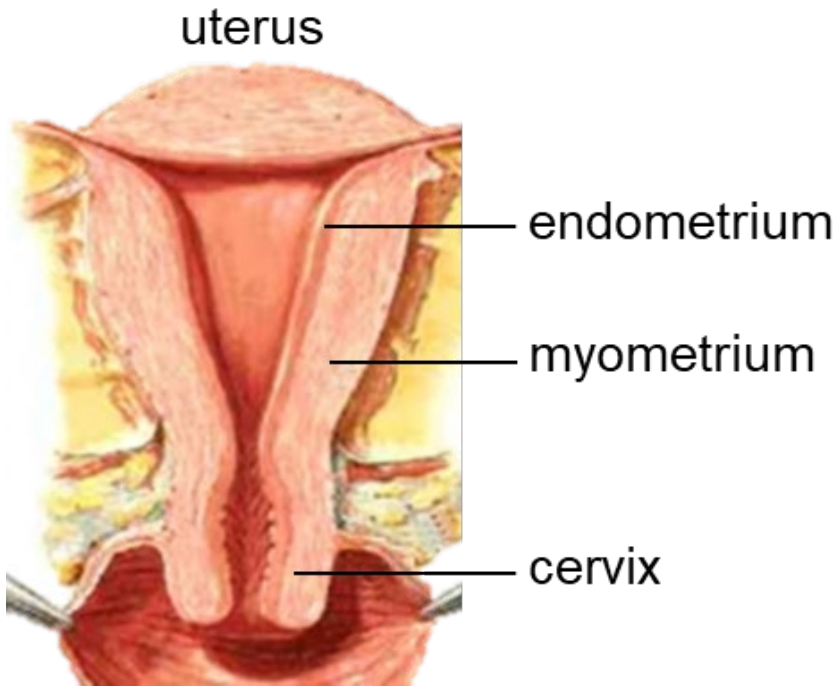
- Platinum-free interval ≥ 6 months – retreat with carboplatin/paclitaxel +/- PD-1 inhibitor
- Platinum-free interval <6 months – 2nd line agents, i.e., Pembrolizumab +/- Lenvatinib
- Relapse on immunotherapy maintenance – stop immunotherapy, resume carboplatin/paclitaxel




Image Courtesy of Getty Images

Fred Hutch
Cancer Center

# Cervical Cancer




UW Medicine

# Question 3

## Which of the following treatment strategies are FDA approved in cervical cancer?

A. Radiation with concurrent cisplatin and pembrolizumab for a patient with IIA squamous cell cervical cancer

B. Radiation with concurrent cisplatin and pembrolizumab for a patient with stage IIIA squamous cell cervical cancer

C. Radiation with concurrent cisplatin for patients with stage IB2-IVA cervical cancer

D. All of the above

E. B and C

F. A and C

# Question 3

## Which of the following treatment strategies are FDA approved in cervical cancer?

A. Radiation with concurrent cisplatin and pembrolizumab for a patient with IIA squamous cell cervical cancer

B. Radiation with concurrent cisplatin and pembrolizumab for a patient with stage IIIA squamous cell cervical cancer

C. Radiation with concurrent cisplatin for patients with stage IB2-IVA cervical cancer

D. All of the above

**E. B and C**

F. A and C

January 12, 2024

FDA approves pembrolizumab with chemoradiotherapy for FIGO 2014 Stage III–IVA cervical cancer

Based on KEYNOTE A-18

# Question 4

Your 55 year-old patient with recurrent squamous cell carcinoma has progressed on pembrolizumab and bevacizumab therapy after completing carboplatin, paclitaxel, bevacizumab and pembrolizumab. IHC of her tumor has shown 1+ expression. Which of the following therapies would be appropriate for her?

A. Cemiplimab
B. Tisotumab-vedotin
C. Pemetrexed
D. Topotecan
E. Trastuzumab-dereuxtecan

# Question 4

Your 55 year-old patient with recurrent squamous cell carcinoma has progressed on pembrolizumab and bevacizumab therapy after completing carboplatin, paclitaxel, bevacizumab and pembrolizumab. IHC of her tumor has shown 1+ expression. Which of the following therapies would be appropriate for her?

A. Cemiplimab

**B. Tisotumab-vedotin**

C. Pemetrexed

D. Topotecan

E. Trastuzumab deruxtecan

**INNOVA TV301/ENGOT-cx12/GOG3057**

Phase III trial of tisotumab-vedotin versus IC chemotherapy in patients with recurrent cervical cancer showed improved overall survival

Global Cancer Facts & Figures, 4th ed.
American Cancer Society

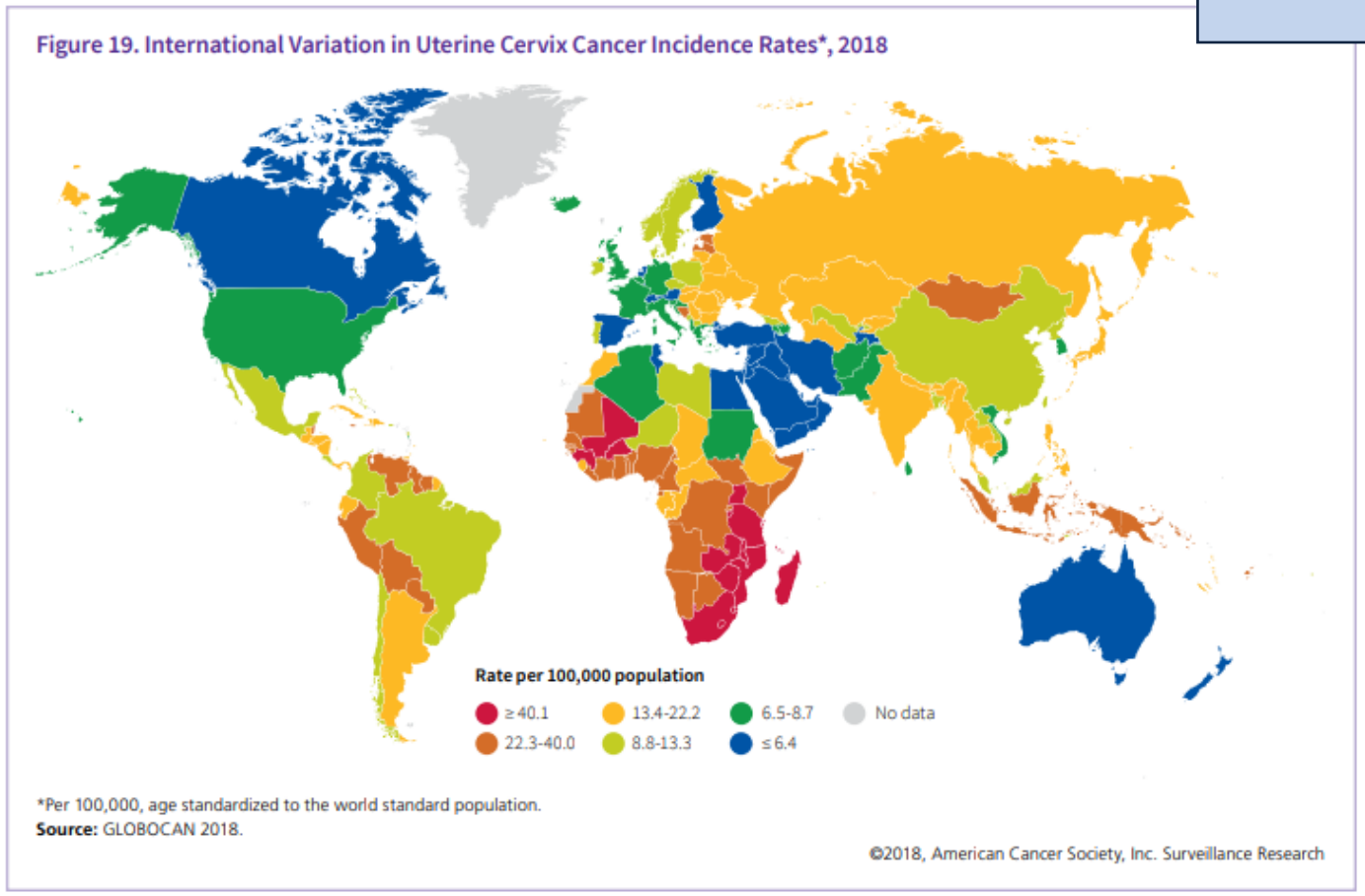
# Cervical cancer epidemiology

**United States**

**14,100** new cases per year (2022)
**4,280** deaths per year (2022)

**Worldwide**

**660,000** new cases per year (2022)
**350,000** deaths per year (2018)




- >85% of all cases of cervical cancer occur in low-resource countries
- Significantly ↓ incidence in developed nations due to implementation of screening with Pap
- Peak incidence 40-60 years

# Epidemiology

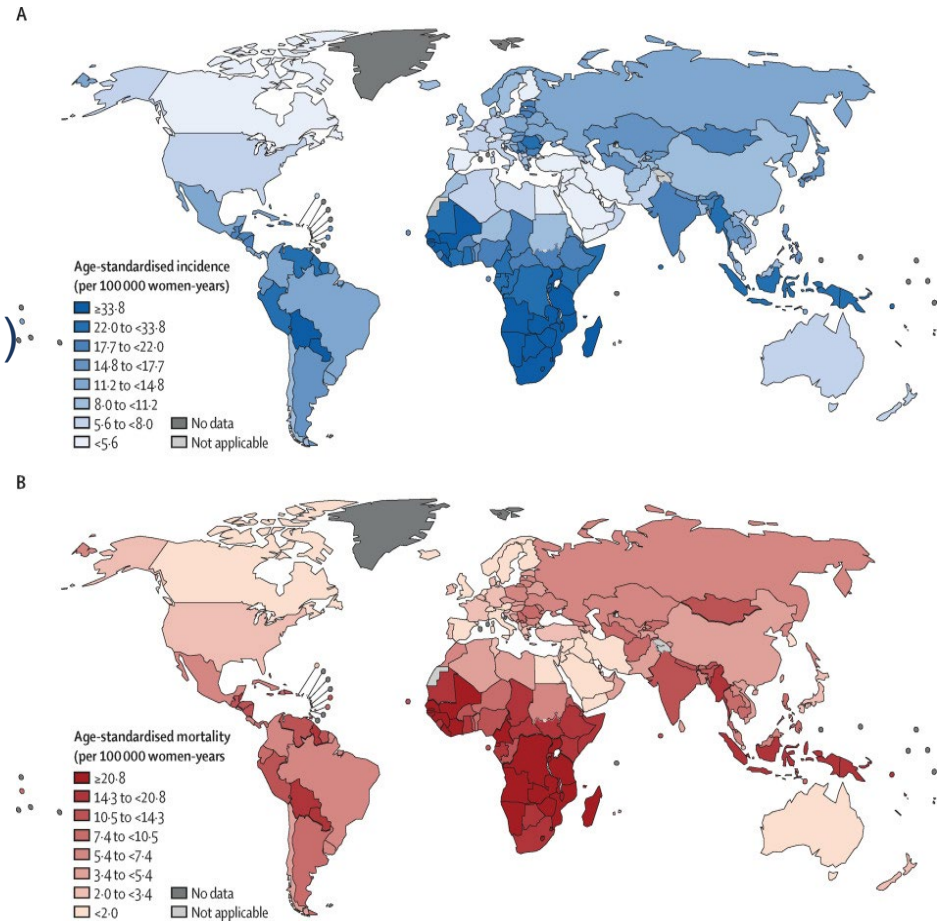
**United States**

**13,820** new cases per year (2024)
**4,360** deaths per year (2024)

**Worldwide**

**660,000** new cases per year (2022)
**350,000** deaths per year (2022)

- >85% of all cases of cervical cancer occur in low-resource countries
- Significantly ↓ incidence in developed nations due to implementation of screening with Pap
- Peak incidence 40-60 years



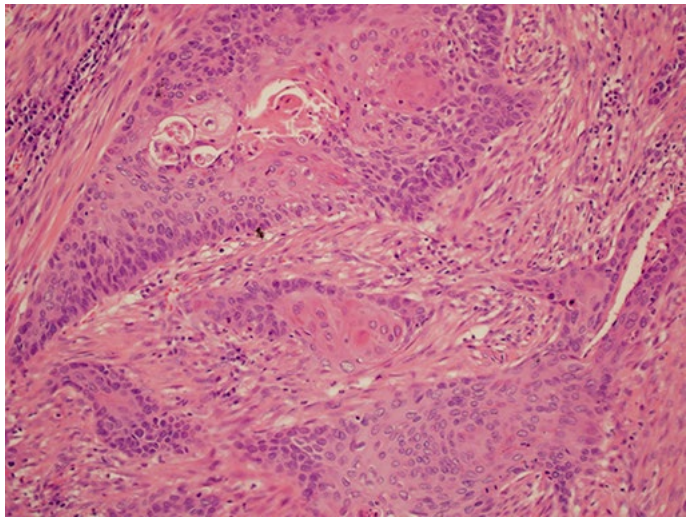



Siegel RL et al. CA Cancer J Clin 2024. Bray F et al. CA Cancer J Clin 2024.; Singh D et al Lancet Global Health 2023.

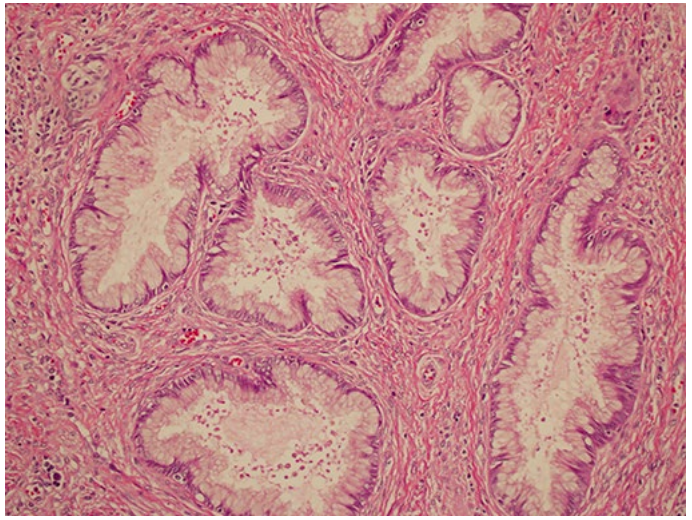
Chi et al. *Principles and Practice of Gynecologic Oncology* 2017

# Cervical cancer
# Histologic types

- Squamous cell carcinoma ~70%
- Adenocarcinoma ~25%
  - Classification based on HPV status, not morphology
  - 10-15% wil be HPV negative
  - HPVneg adenocarcinoma present at more advanced stages, have poorer prognosis
- Adenosquamous
- Glassy cell carcinoma
- Adenoid cystic carcinoma
- Neuroendocrine / small cell carcinoma
- Mixed
- Rhabdomyosarcoma
- Lymphoma



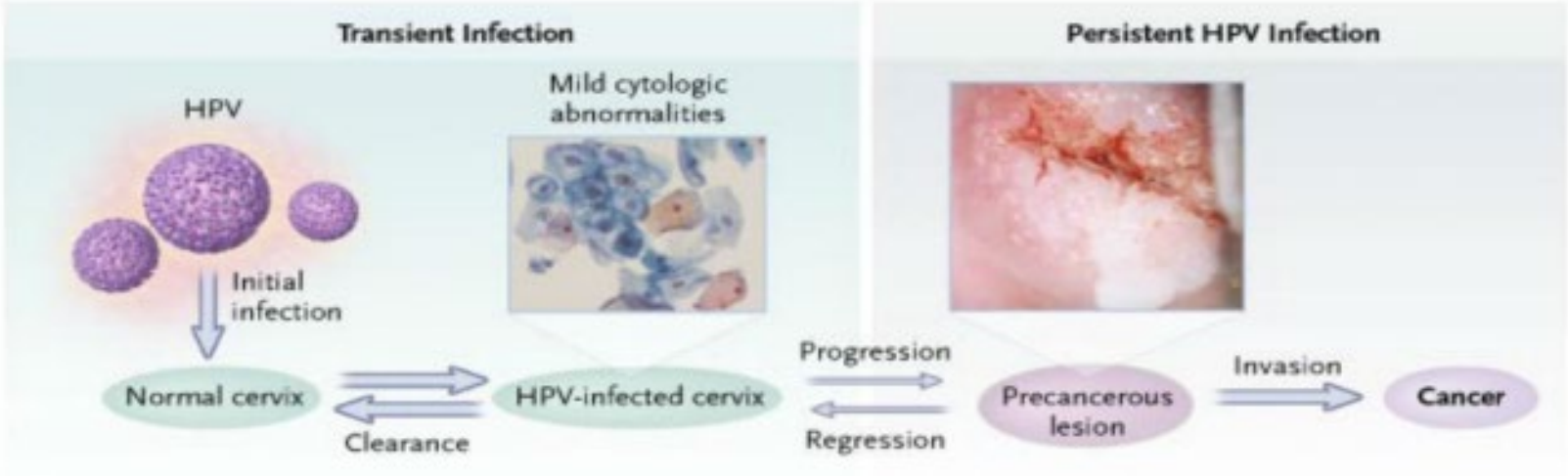
Squamous cell carcinoma



Adenocarcinoma

# Cervical cancer
# Causative role of HPV

- >20 high-risk human papilloma virus (HPV) types associated with anogenital cancers
  - Types 16 & 18:  >70% of cervical cancers
- Persistent infection can ➔ dysplasia
- HPV incorporated into cellular genome
- HPV core proteins E6 and E7 lead to inactivation of p53 and Rb






Wright & Schiffman *N Engl J Med* 2003

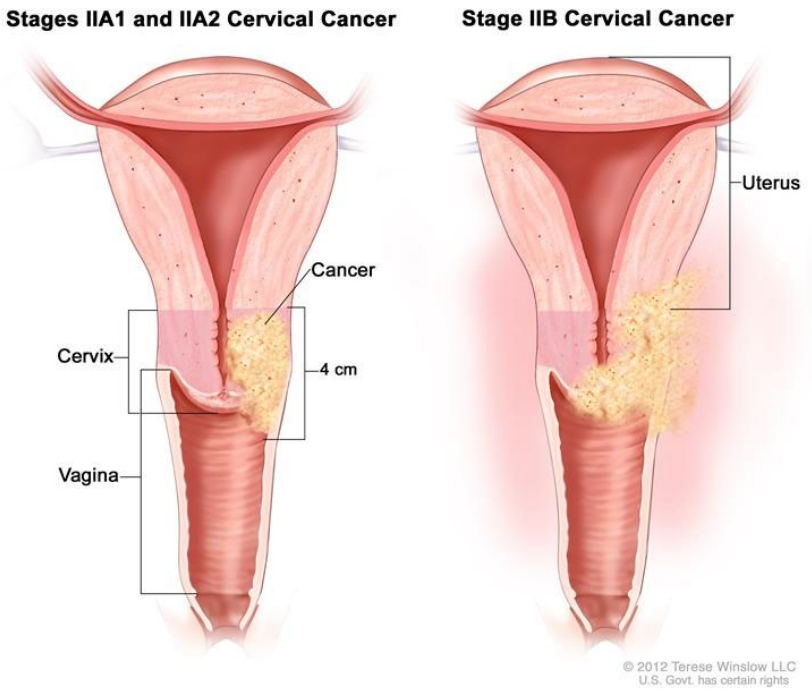
# HPV v. Non-HPV Associated Endocervical Adenocarcinoma

- HPV-associated endocervical adenocarcinoma (83%)
  - HPV types 18,16,45
- HPV-unassociated endocervical adenocarcinoma
  - Gastric type (10%)
  - Clear cell (3%)
  - Endometrioid (1.1%)
  - Mesonephric (0.3%)
  - Miscellaneous and not otherwise specified (2.4%)



Stolnicu S et al *Am J Surg Pathol* 2018, 2019

# Cervical Cancer
# FIGO Staging 2018




| Stage | Definition |
|---|---|
| IA1 | DOI <= 3 mm |
| IA2 | 3 mm > DOI <= 5 mm |
| IB1 | Microscopic > IA2 or visible lesion <= 2 cm |
| IB2 | 2 cm > visible lesion <= 4 cm |
| IB3 | Visible lesion > 4 cm |
| IIA1 | Upper 2/3 vaginal involvement, lesion <= 4 cm |
| IIA2 | Upper 2/3 vaginal involvement, lesion > 4 cm |
| IIB | Parametrial invasion (but not to pelvic side wall) |
| IIIA | Lower 1/3 vaginal involvement |
| IIIB | Pelvic wall and/or hydro / non-functioning kidney |
| IIIC1 | Pelvic node involvement (r and p notations) |
| IIIC2 | Para-aortic node involvement (r and p notations) |
| IVA | Bladder or rectal mucosal involvement |
| IVB | Distant metastases (includes peritoneal spread, supraclavicular, mediastinal, lung, liver, bone) |



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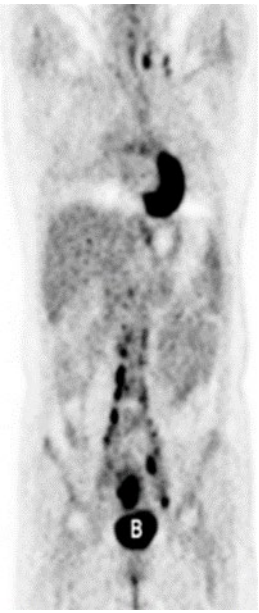
# Modalities of Staging

- Biopsy
- Clinical
  - Physical & pelvic exam
- Procedural/Surgical
  - Exam under anesthesia, cystoscopy, proctoscopy
  - Surgical lymph node assessment (can be done with sentinel lymph node biopsy)

- Radiologic
  - NCCN: “any imaging according to available resources”
  - MRI best for assessment of tumor size, parametrial spread (role of PET/MR?)
  - Meta-analysis has shown PET/CT to have superior sensitivity, specificity in predicting LN involvement
    - In setting of PET/CT showing (+) PLN but negative PALN → false negative rate up to 25% in PALN






NCCN Guidelines: Cervical Cancer, 2024.
Ramirez PT et al. Cancer 2011

# Management

- Diagnosis via biopsy most accurate
- Staging with exam, surgery, imaging

| Spread | Stage | Recommended therapy |
|---|---|---|
| Confined to cervix | IA1 | Hysterectomy, cone biopsy |
| Confined to cervix and upper vagina | IA2-IB2 | Surgery (radiation) |
| Bulky cervix and/or locally advanced disease | IB3-IVA | Radiation + chemotherapy<br>Surgery an option for IB3 – IIA2 |
| Distant spread | IVB | Chemotherapy |

# Indications for Postop Treatment

**Intermediate-Risk Pts**
- ±LVSI
- Tumor size >4 cm
- >50% stromal invasion

Depending on combination of risk factors, **pelvic radiation** shown to ↓ risk of recurrence

**High-Risk Pts**
- Positive lymph nodes
- Parametrial disease
- Positive/close surgical margins

Postop adjuvant treatment with **radiation** and **chemotherapy** indicated to ↓ recurrence and improve overall survival



Peters WA et al. J Clin Oncol 2000; Huang H et al. JAMA Oncol 2021.

# Locally advanced cervical cancer
# Standard of care

| Trial | Intervention | Outcome | Citation |
|---|---|---|---|
| GOG 109 | Adjuvant RT vs. CDDP-based RT | Superiority of Adjuvant ChemoRT | Peters III WA, et al. J Clin Oncol 2000;18:1606-13. |
| GOG 85 | CDDP-based vs. HU-based RT | Superiority of ChemoRT | Whitney CW, et al. J Clin Oncol 1999;17:1339-48. |
| GOG 120 | CDDP-based vs. HU-based RT | Superiority of ChemoRT | Rose PG, et al. N Engl J Med 1999;340:1144-53. |
| GOG 123 | CDDP-based RT vs. RT alone | Superiority of ChemoRT | Keys HM, et al. N Engl J Med 1999;340:1154-61 |
| RTOG 90-01 | CDDP+5FU-based RT vs. RT alone | Superiority of ChemoRT | Morris M, et al. N Engl J Med 1999;340:1137-43. |
| GOG 191 | ChemoRT±Erythropoietin | TERMINATED EARLY | - |
| GOG 219 | ChemoRT±Tirapazimine | TERMINATED EARLY | - |
| AIM2CERV | ChemoRT±Axalimogene Filolisbac | TERMINATED EARLY | - |
| OUTBACK | ChemoRT±consolidation ChemoRx | NEGATIVE (OS) | Mileshkin, LR, et al. Lancet Oncol 2023;24:468-82. |
| CALLA | ChemoRT±anti-PD-L1 Durvalumab | NEGATIVE (PFS) | CALLA: Monk BJ, et al. Lancet Oncol 2023;24:1334-48, LBA#1, NCT03830866. |
| NRG-GY006 | ChemoRT±Triapine | NEGATIVE (OS) | Leath CA, et al. ASCO 2023, Abstract #5502, NCT02466971. |
| KEYNOTE-A18 | ChemoRT±anti-PD-1 Pembrolizmab | PFS significantly improved | Lorusso D, et al. ESMO 2023, LBA#38, NCT04221945. |
| INTERLACE | Induction ChemoRx followed by ChemoRT | OS & PFS significantly improved | McCormack M, et al. ESMO 2023, LBA#8, NCT01566240. |

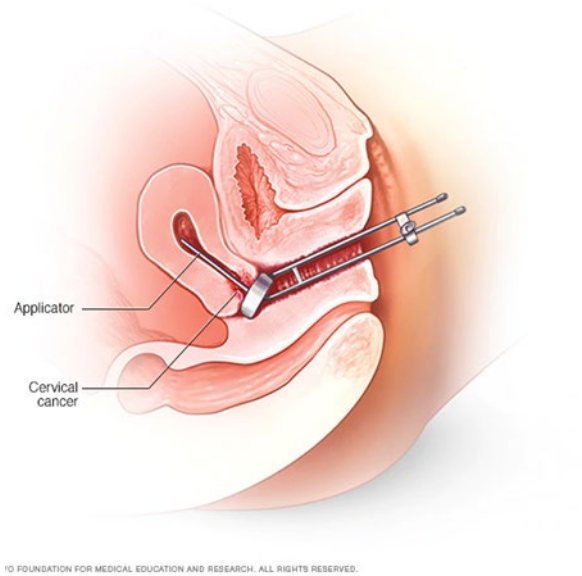
CDDP, cisplatin; HU, hydroxyurea; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression free survival; RT, radiotherapy.

5 RCTs in 1990s showed significant survival benefit with chemotherapy and radiation for stage IB2-IVB diseases



Garcia E et al. J Gynecol Oncol 2023

# Cervical Cancer
## *Locally Advanced Disease*





- Concurrent radiation with chemotherapy, followed by brachytherapy
  - Radiation dose goal: 80–85 Gy
- *Importance of brachytherapy*

  "Brachytherapy is a critical component of definitive therapy for all patients with primary cervical cancer who are not candidates for surgery"
- Recent studies have shown decreased utilization of brachytherapy
  - May be secondary to presumed benefit of IMRT
  - However, lack of brachytherapy incorporation associated with increased recurrence and decreased survival



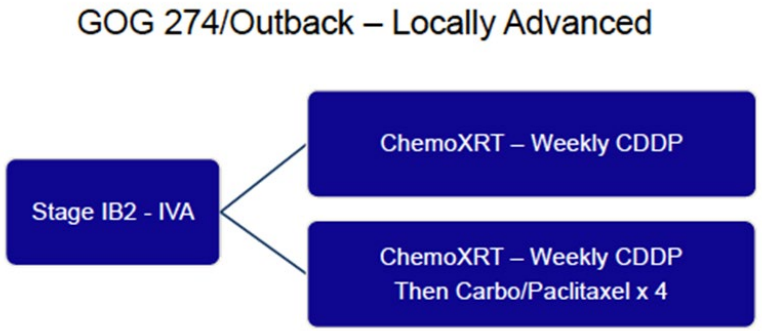
Han K et al. Int J Radiat Oncol Biol Phys 2013.
Mayadev J et al. *Gynecol Oncol* 2018.
Karlsson J et al. *Brachytherapy* 2017.

# Chemotherapy after RT?

## Duenas-Gonzalez

- International Phase III trial in advanced disease
- Arms
  - Weekly Cis/Gem with concurrent EBRT/VBT followed by Cis/Gem q21d x 2 cycles
  - Weekly Cis with concurrent EBRT/VBT
- Results
  - **Significantly improved PFS & OS in Cis/Gem arm**
  - Increased toxicity in Cis/Germ arm
- Issues
  - Toxicities MD (not patient) reported, concern for under-reporting → GOG trial stopped early due to excessive G3/4 toxicities
  - Unclear if benefit due to concurrent or post-radiation chemotherapy

## OUTBACK




- No improvement in DFS or OS



Duenas-Gonzalez et al. *J Clin Oncol* 2011
Mileshkin et al. *J Clin Oncol* 2021

# Chemotherapy before RT?

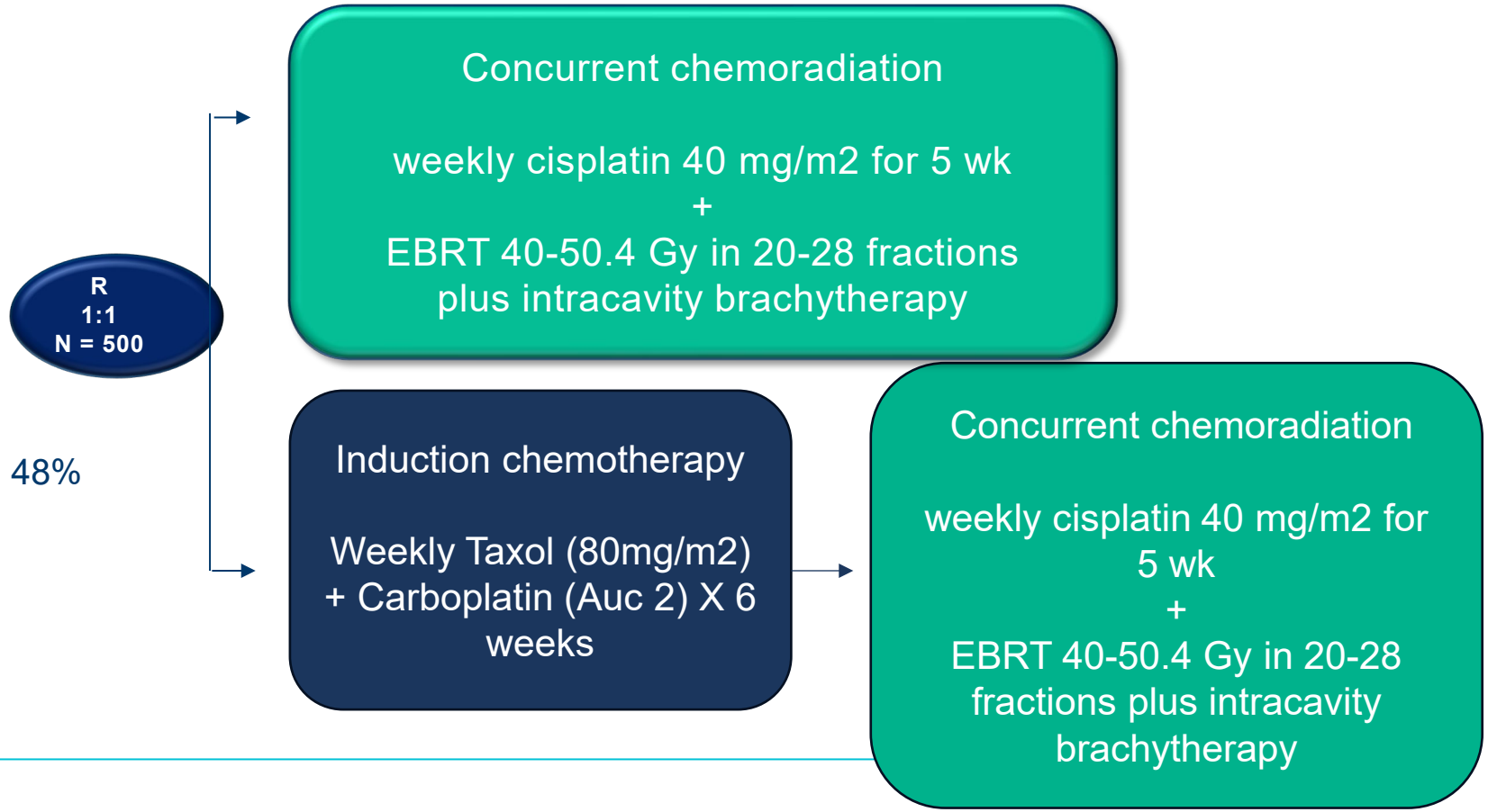
The GCIG INTERLACE Trial

A randomized phase III trial of induction chemotherapy followed by chemoradiation compared with chemoradiation alone in locally advanced cervical cancer

- Newly diagnosed,
- FIGO (2008) stage IB1N+, IB2, II, IIIB, IVA squamous, adeno, adenosquamous
- No prior pelvic RT
- No nodes above aortic bifurcation

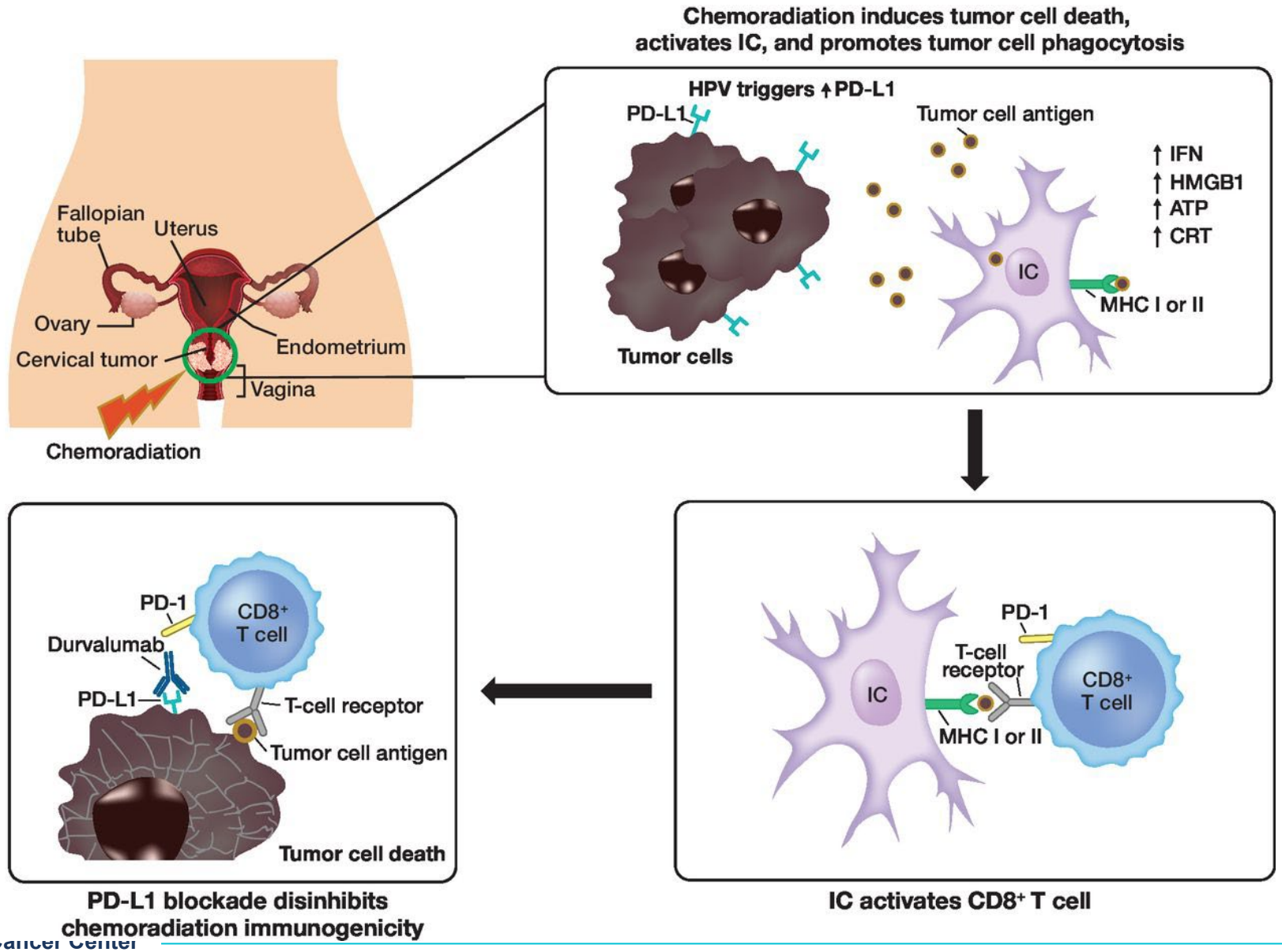
**Results:**

- 77% Stage II, 57% N0
- 82% SCC
- G≥3 adverse events 59% (IC/CRT) vs. 48% (CRT alone)
- **5Y PFS 73% (IC/CRT) vs. 64% (CRT alone) p=0.013**
- **5Y OS 80% (IC/CRT) vs. 72% (CRT alone) p=0.04**






McCormack. ESMO 2023. Abstr LBA8. 5






Mayadev J et al. Int J Gynecol Cancer 2023

# Immunotherapy for LACC

No new safety signals
Comparable discontinuation rate
No meaningful QoL differences

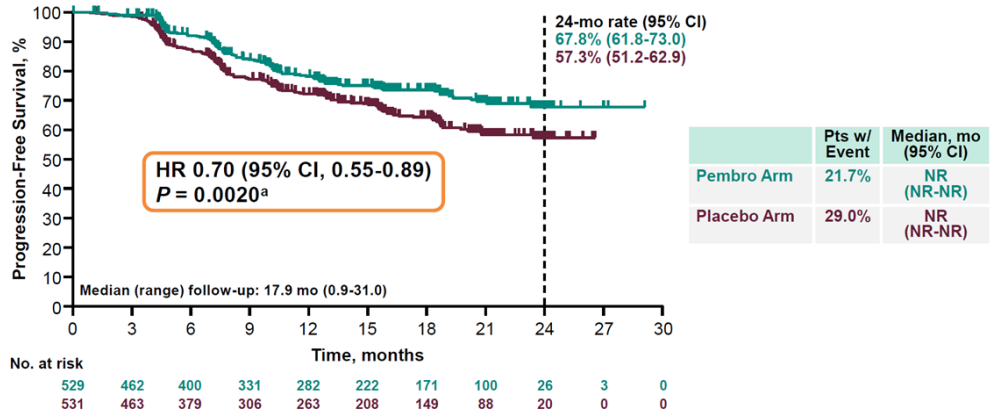
## KEYNOTE A-18

Phase 3 Trial of Pembrolizumab + Chemoradiotherapy for High-Risk Locally Advanced Cervical Cancer

R
1:1
N = 1060

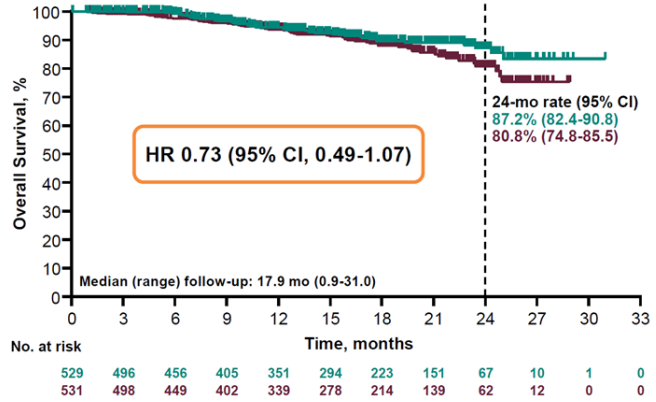
- Cisplatin/Pembrolizumab + EBRT followed by brachytherapy + Maintenance pembrolizumab 400 mg Q6W for 15 cycles
- Cisplatin/Placebo + EBRT followed by brachytherapy + Maintenance placebo Q6W for 15 cycles

PFS




| | Pts w/ Event | Median, mo (95% CI) |
|---|---|---|
| Pembro Arm | 21.7% | NR (NR-NR) |
| Placebo Arm | 29.0% | NR (NR-NR) |

OS

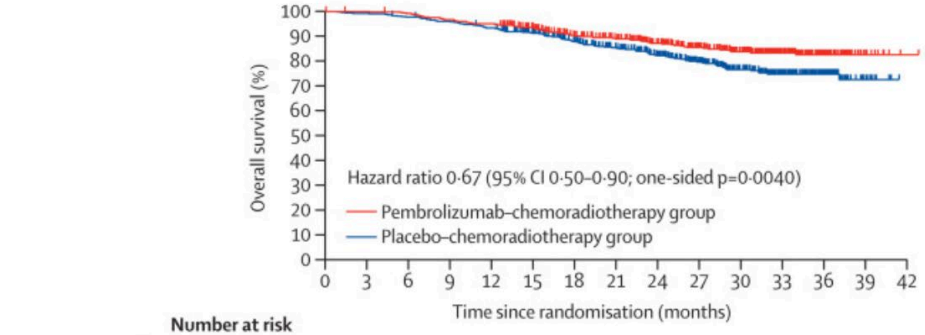



| | Pts w/ Event* | Median, mo (95% CI) |
|---|---|---|
| Pembro Arm | 8.3% | NR (NR-NR) |
| Placebo Arm | 11.1% | NR (NR-NR) |

*42.9% information fraction[a]

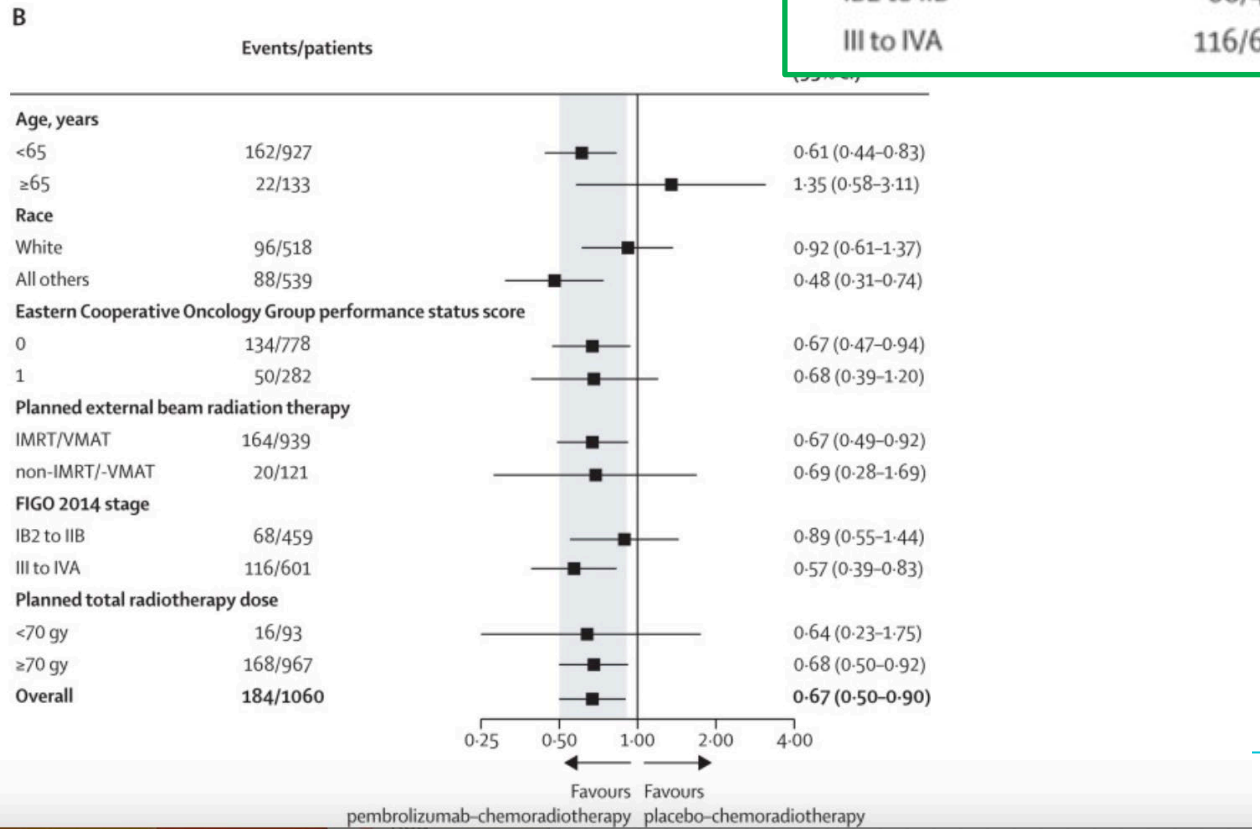


Lancet 2024 Apr 6;403(10434):1341-1350.




| Number at risk (number censored) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab–chemoradiotherapy group | 529 (0) | 527 (2) | 522 (3) | 509 (3) | 500 (3) | 463 (32) | 412 (68) | 374 (100) | 326 (141) | 273 (188) | 210 (246) | 136 (3 | 63 | 11 1 |
| Placebo–chemoradiotherapy group | 531 (0) | 527 (0) | 518 (1) | 508 (2) | 493 (3) | 455 (30) | 405 (64) | 366 (92) | 316 (129) | 259 (177) | 194 (233) | 1 (2 | | |

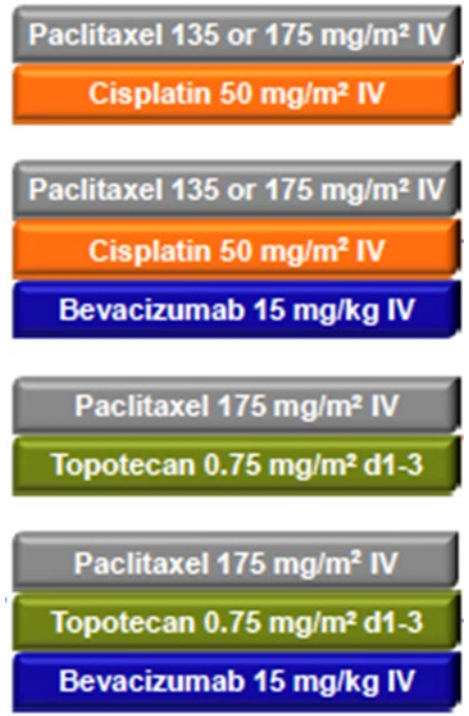
B




# FDA Approval: FIGO 2014 Stage III-IVa 1/12/24

# Metastatic or 1st line recurrent disease

- **GOG 204**
  - Comparison of 4 cisplatin-based doublets for recurrent cervical CA
  - Favored Cis/Taxol
- **GOG 240 →**
  - No difference between chemo arms
  - Arms containing Bev associated with significant improvement in PFS, OS, ORR
- **JCOG 0505**
  - Randomized phase III trial of Cis/Taxol vs Carbo/Taxol
  - Similar OS
  - However, if no prior Cis, OS shorter with Carbo/Taxol
- **KEYNOTE 826**
  - Addition of pembrolizumab to chemo (2/3 received Bev)
  - Improved mPFS (10.4 v 8.2 mo) and 2y OS rates (50 v 40%)

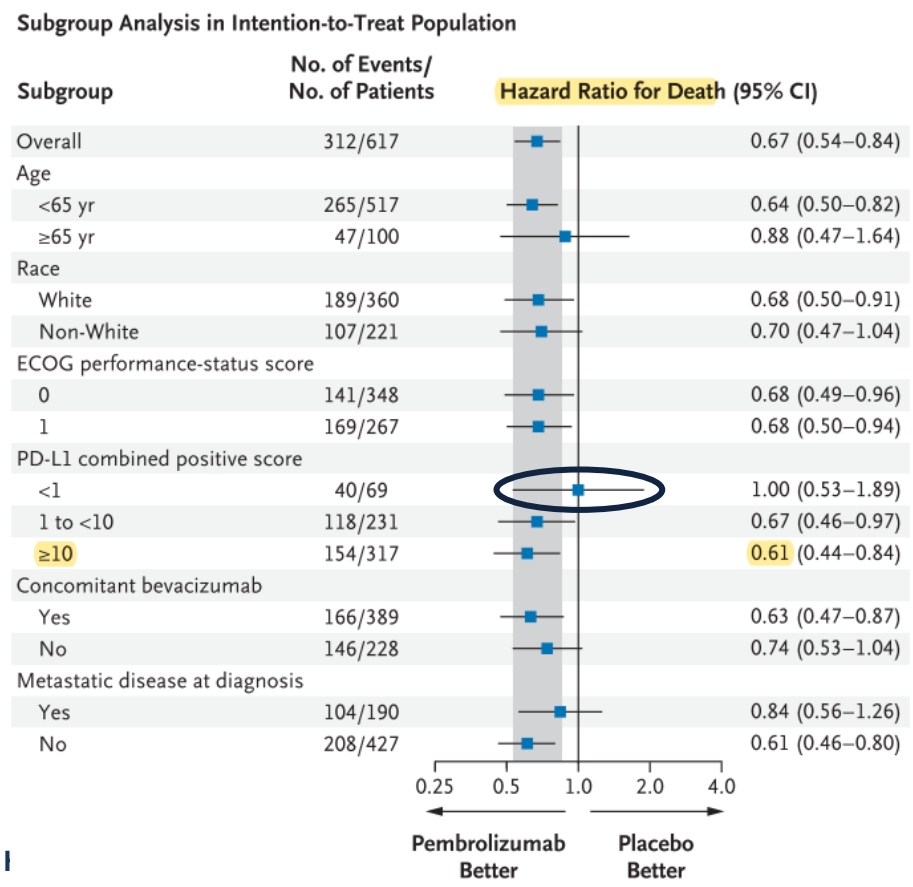


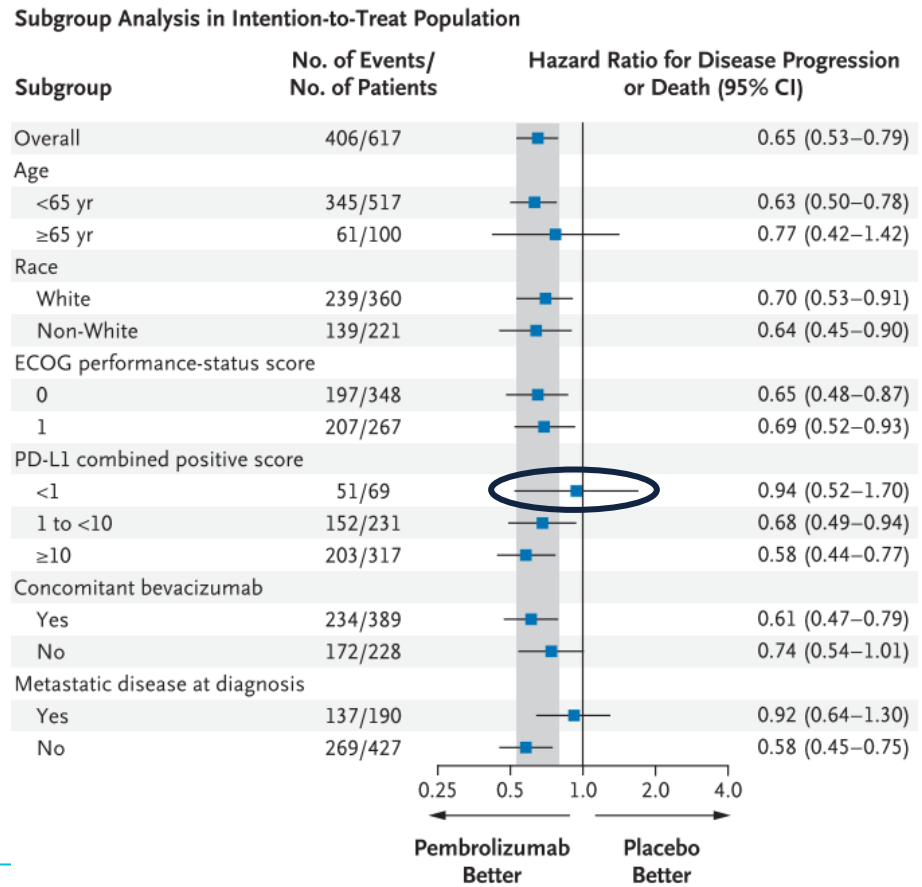

GOG 240



Monk BJ et al. *J Clin Oncol* 2009
Tewari K et al. *N Eng J Med* 2014
Kitagawa R et al *J Clin Oncol* 2015
Colombo N et al *N Eng J Med* 2021

# KEYNOTE




Fred I



Colombo N et al *N Eng J Med* 2021

# Recurrent Cervical Cancer

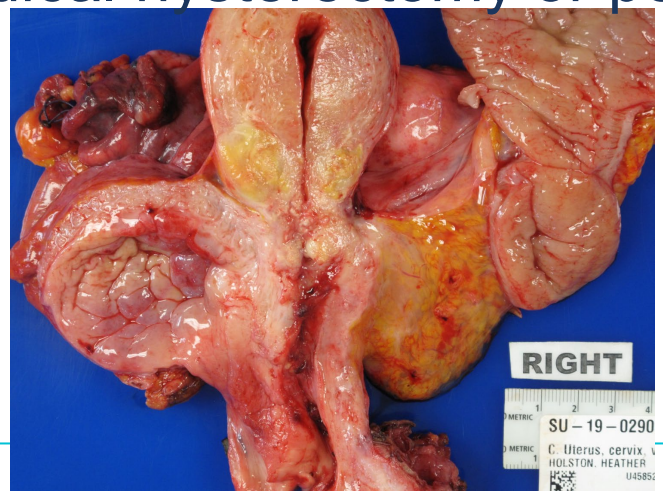
## *Treatment Options*

- Radiation

  Consider if no prior RT or have oligometastatic disease outside of the irradiated field

- Surgery

  Patients with central (i.e. pelvic/vaginal) recurrence are candidates for either radical hysterectomy or pelvic exenteration

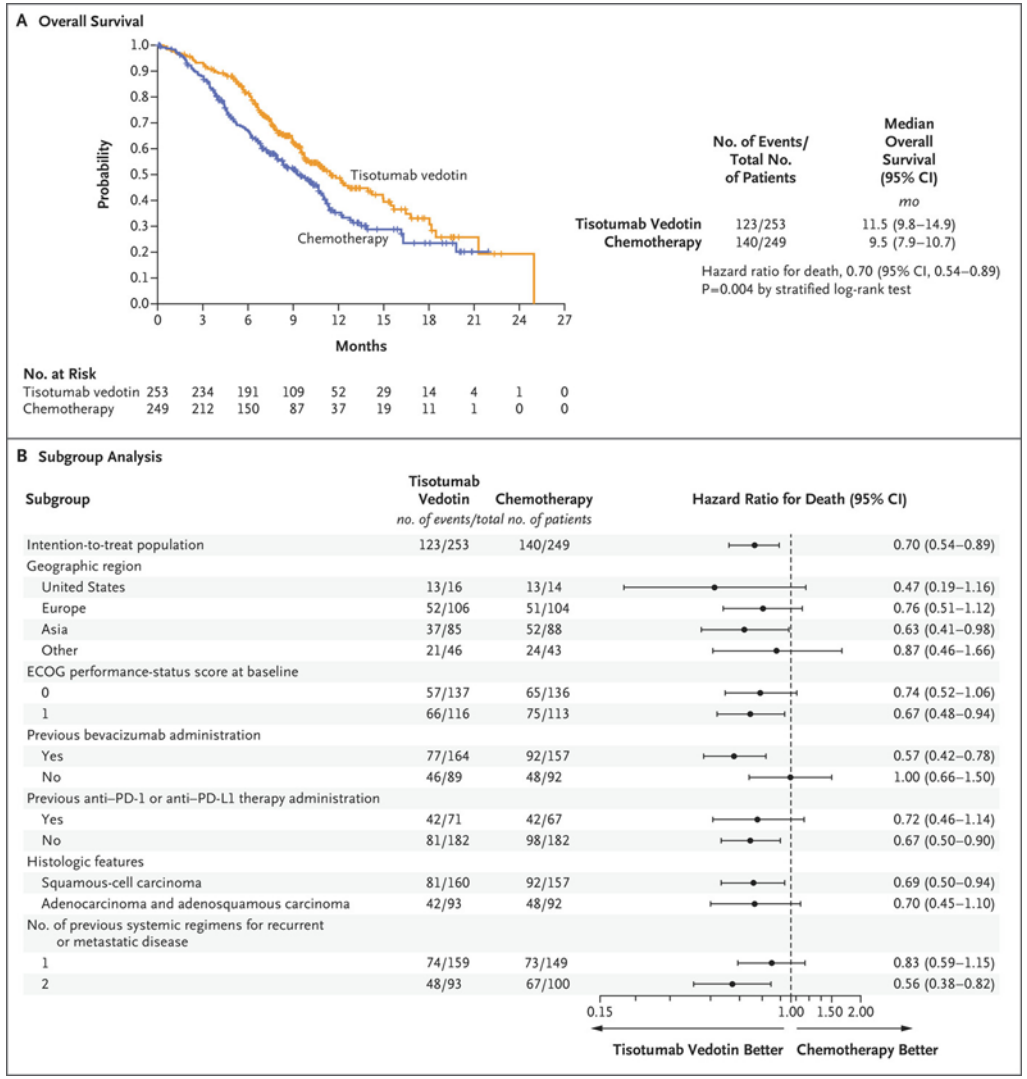





Benn T et al. *Gynecol Oncol* 2011.

# Recurrent Cervical Cancer
# Tisotumab vedotin-tftv

- Tissue factor-directed antibody and microtubule inhibitor drug conjugate
- In single arm, open-label study, RR 24% with 7% CR
- Subsequent phase III trial compared with IC chemotherapy showed **improved PFS and OS**
- Significant ocular toxicity




**Approved by the US FDA for recurrent or metastatic cervical cancer that has progressed on chemotherapy**



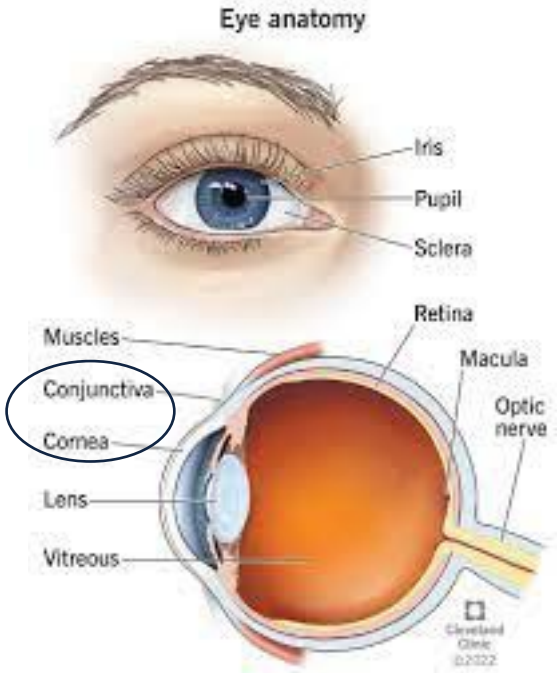
Coleman R et al. *Lancet Oncol* 2021
Vergote I et al. *N Engl J Med* 2024.

# Tisotumab-vedotin ocular toxicities

## By Numbers

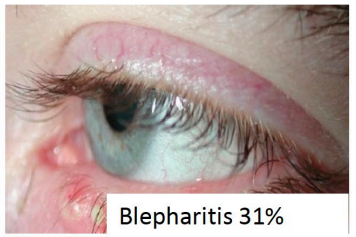
- Any ocular toxicity (60%)
  - Conjunctivitis (26%)
  - Dry eye (23%)
  - Keratitis (11%)
- Grade ≥3 (3.8%)
  - Ulcerative keratitis (2%)
- 1.2 mos (0-6.5 mo) median onset
- 55% complete resolution, 30% partial improvement
- 0.7 mo(0.3-1.6 mo) median time to resolve

## By Pictures





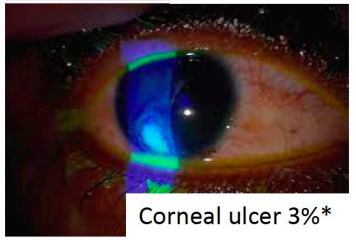
Conjunctivitis 31%


Blepharitis 31%


Symblepharon


Dry eye 25%


Keratitis 11%


Corneal ulcer 3%*



Karpel HC et al. Am Soc Clin Oncol Educ Book 2003.

# Recurrence & no prior IO

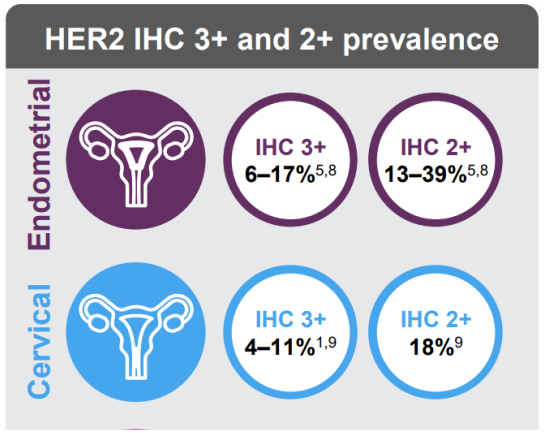
- No prior immunotherapy?
  - Single-agent pembrolizumab
  - Cemiplimab
    - The EMPOWER trial (NCT 03257267) examined whether single-agent cemiplimab, a PD-1-blocking antibody, demonstrated improvement in OS in patients who had disease progression after first-line platinum-containing chemotherapy [32]. Cemiplimab was initially approved to treat skin and lung cancer but has shown potential for clinical efficacy in this patient population. Patients were randomized to receive cemiplimab as 350 mg every 3 weeks or the investigator's choice of single-agent chemotherapy [32]. The median OS was longer in the cohort that received cemiplimab versus chemotherapy (12 vs. 8.5 months) (HR=0.69; 95% CI=0.56–0.84). The survival benefit was seen regardless of histological subtype. This study is the largest randomized study to date in which a meaningful survival benefit was seen in rmCC following progression after failing first-line platinum-containing chemotherapy.No prior
- Her-2neu targeted therapy
  - Approximately 2-6% of cervical cancers have Her-2neu overexpression

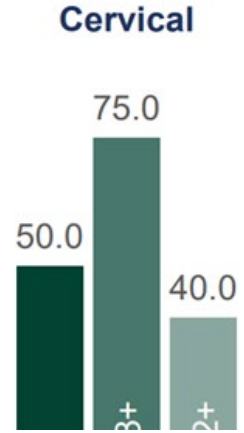


Itkin B et al. PLoS One 2021; Nasioudis D et al. Gynecol Oncol 2024.

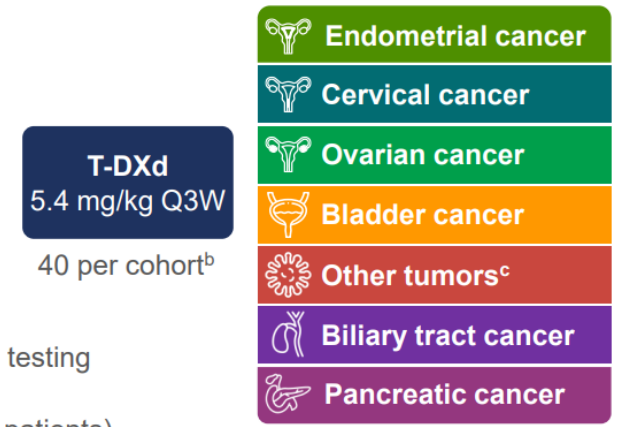
# DESTINY PanTumor02: Trastuzumab Deruxtecan

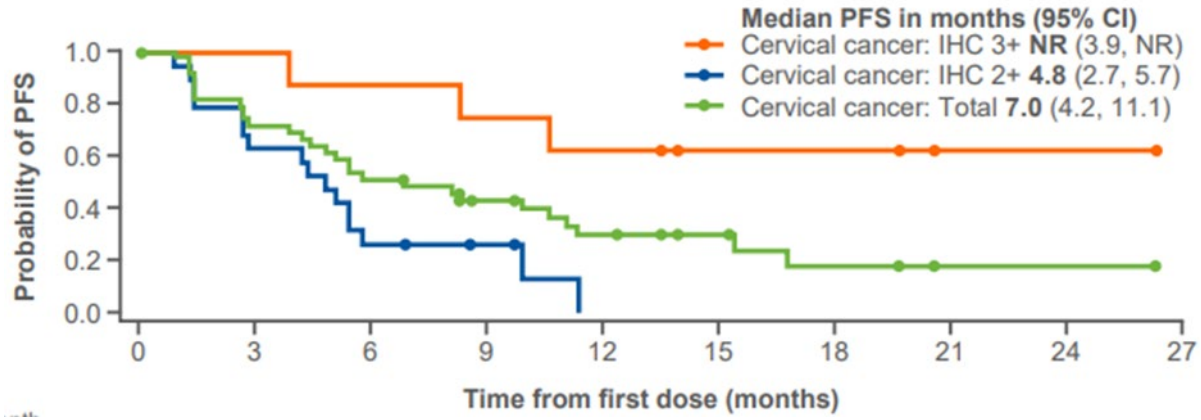
- **Key eligibility criteria**
- Locally advanced, unresectable, or metastatic solid cancers
- ≥1 prior systemic treatment
- HER2 IHC 3+ or 2+ (gastric scoring)
- ECOG PS 0-1




ORR




**T-DXd** is included in the **NCCN Guidelines®** for HER2-positive tumors **IHC 3+ or 2+**
**April 5, 2024: FDA accelerated approval for patients with HER-2 positive (IHC 3+) tumors**



Meric-Bernstam F. JCO 2023. Makker V. SGO 2024.

# Conclusions

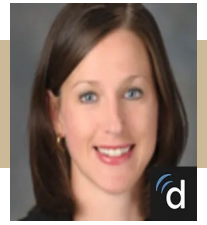
- Gynecologic cancers account for more than **100,000** cancers/year in **US** females
- Treatment often involves multiple interventions, including surgery, chemotherapy and/or radiation
- Involvement of a gynecologic oncologist in patient care has been shown to improve outcomes
  - We provide surgical skills, administer chemotherapy and work closely with our colleagues in Radiation Oncology

# Division of Gynecologic Oncology

## *University of Washington/FHCC*

*Barbara Goff, MD*
*Chair, UW Department of Ob/Gyn*

*Heidi Gray, MD*
*Director, Division of Gynecologic Oncology*



*Nicole Fleming MD*
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*Elizabeth Swisher, MD*

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*Elise Simons, MD*

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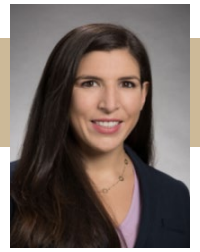
*Renata Urban, MD*

*Jennifer Burzawa, MD*

*Isabal Rodriguez, MD*

*Kalyan Banda, MD*



*Soledad Jorge, MD MPH*

Fred Hutch Cancer Center

# QUESTIONS

*Thank You*

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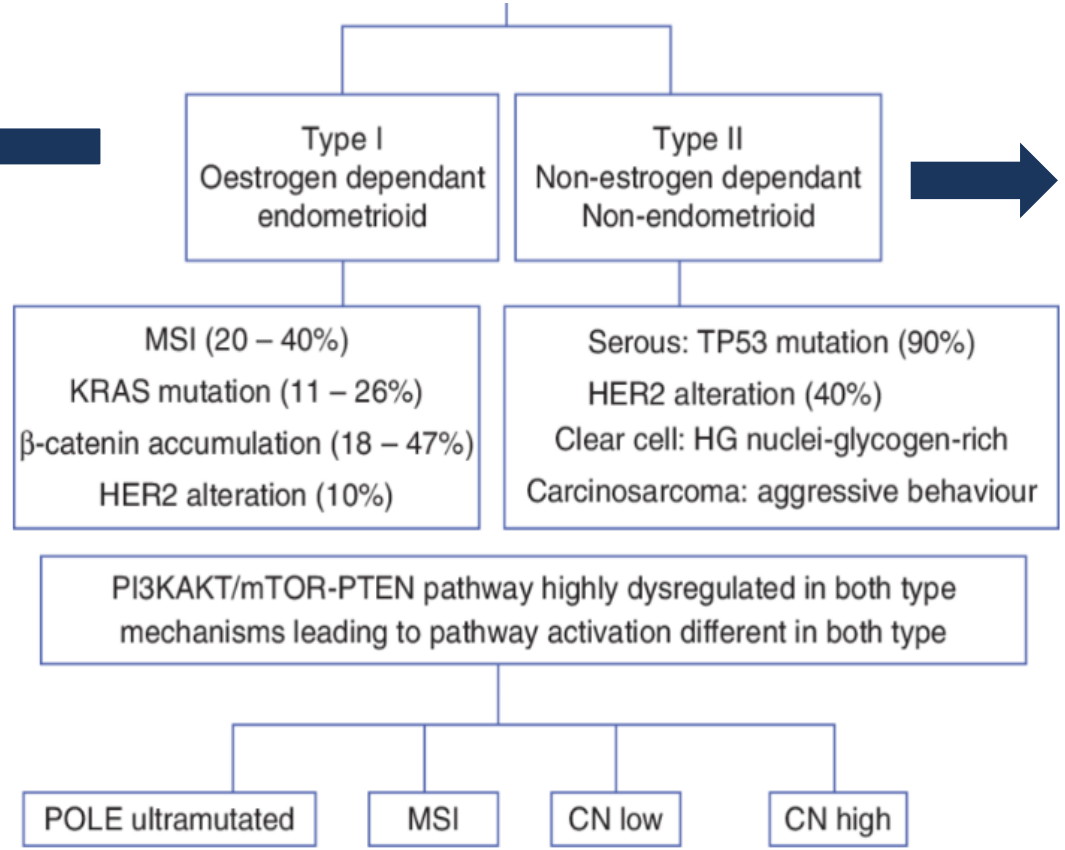
UW Medicine

# Endometrial Adenocarcinoma

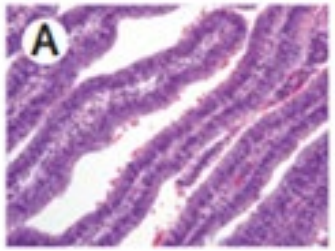
*Clinicopathologic & Molecular Subtypes*

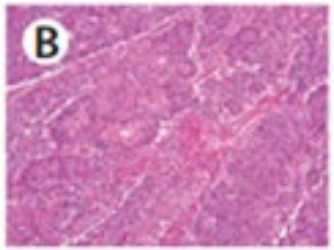
Risk Factors
- Obesity
- HRT
- PCOS
- Unopposed/excess estrogen

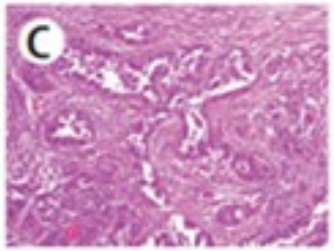


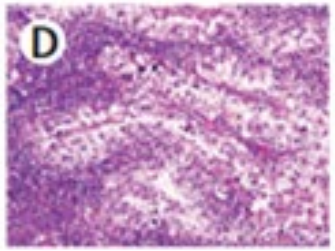

Endometrial cancer is a heterogeneous disease with distinct molecular characteristics. CN: Copy number; HG: High grade; MSI: Microsatellite instability.

Seen with more frequency in Black & older patients










| | | | | |
|---|---|---|---|---|
| **Histological type** | Endometrioid | Endometrioid | Serous | Clear cell |
| **Histological grade** | Low | High | High | High |
| **Metastasis** | Uncommon | Lymph nodes<br>Distant organs | Lymph nodes<br>Peritoneal<br>Distant organs | Lymph nodes<br>Peritoneal –/+ |
| **Prognosis** | Favourable | Poor | Poor* | Poor*† |
| **Molecular markers**[18-21] | | | | |
| ER/PR expression | + | +/– | –/+ | – |
| *PTEN* expression | –/+ | –/+ | + | + |
| DNA MMR loss | –/+ | –/+ | – | –/+ |
| Aberrant P53 | – | –/+ | + | –/+ |
| Ki-67/MIB-1 | Low | High | High | Low or high |



Murali et al. Lancet Oncol 2014.