Fred Hutch Cancer Center

Updates in Gynecologic Oncology:

Uterine Cancer & Cervical Cancer

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Professor, Division Chief
Division of Gynecologic Oncology
October 2025

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

- Advisory board participant in last 24 months: GSK, Merck, AstraZeneca, Immunogen/Abbvie, Tempus
- 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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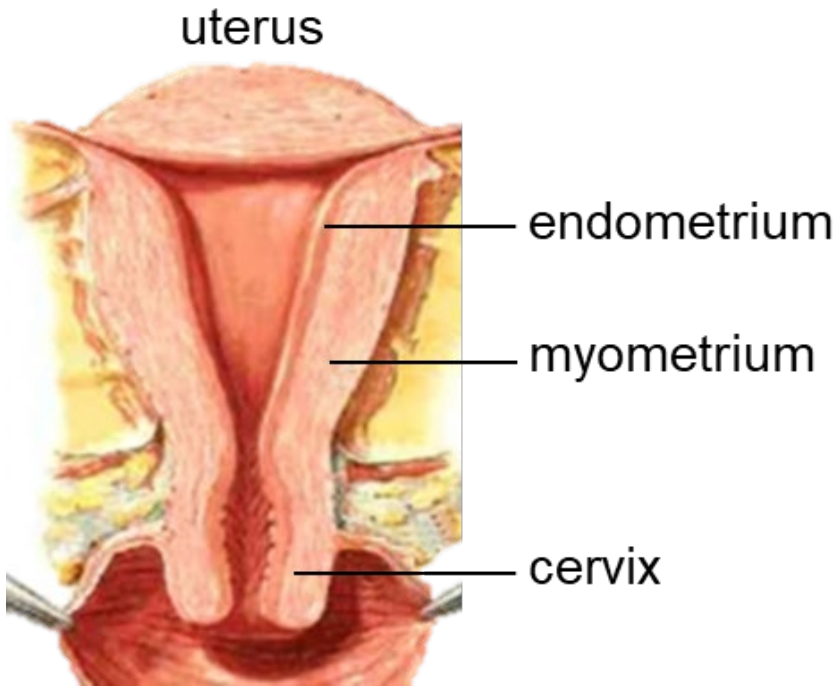
Uterine Cancer



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
C. Extent of LVSI
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

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 MSI, p53 wild-type, Her-2neu 1+ on IHC, no POLE mutation. What treatment would you recommend for her?

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

FDA Approvals – primary advanced or recurrent endometrial carcinoma

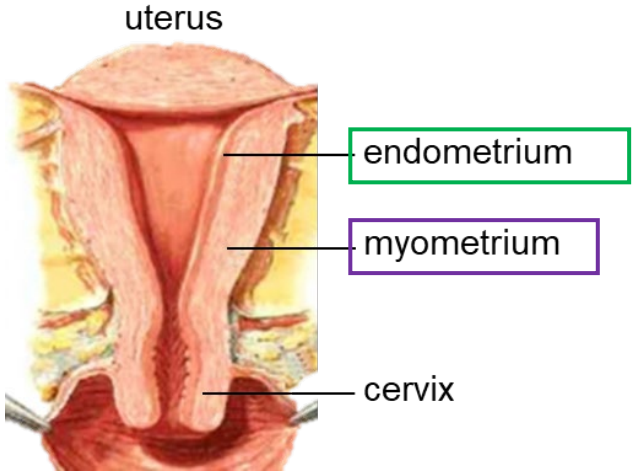
Aug 1, 2024: Dostarlimab-gxly with carboplatin & paclitaxel followed by dostarlimab maintenance (expanded from initial indication for only patients with dMMR/MSI-H tumors)

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)

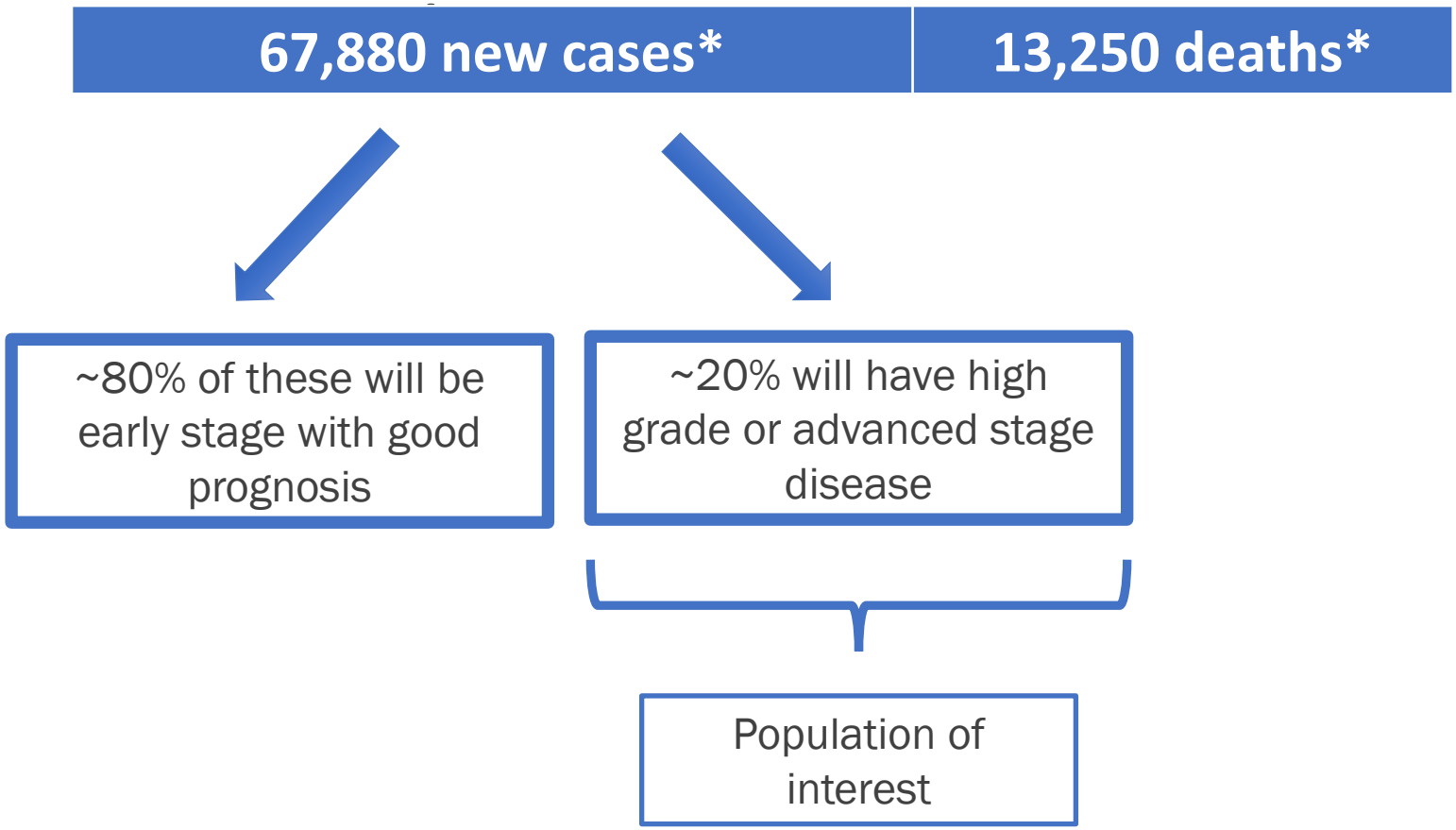


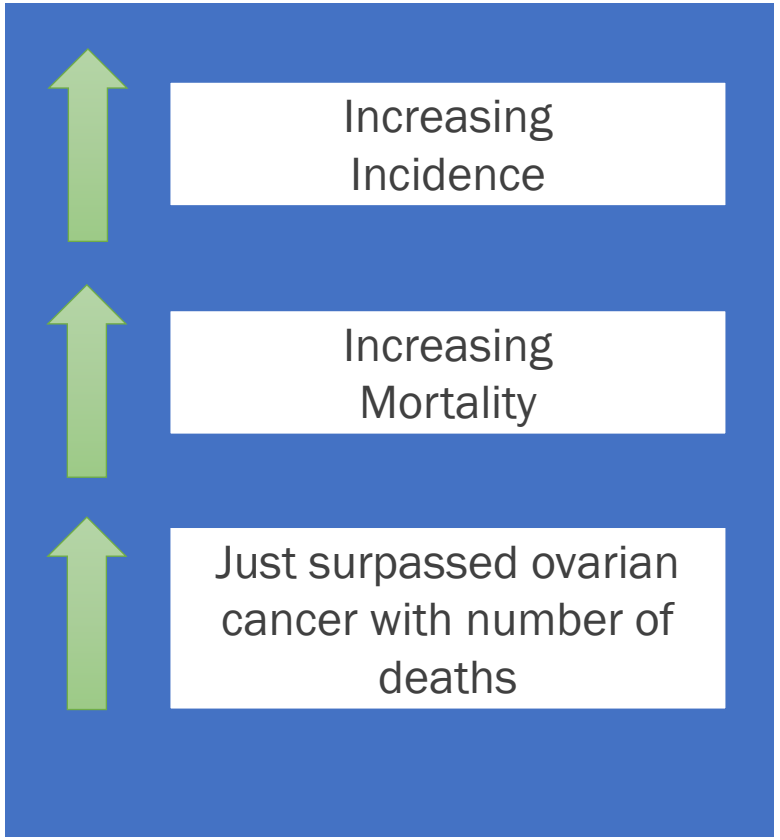
SARCOMAS

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

Endometrial Cancer 2025

- ***Only gynecologic cancer with rising incidence and mortality***
- Corrected for hysterectomy rates, uterine cancer is the **2nd most common cancer**

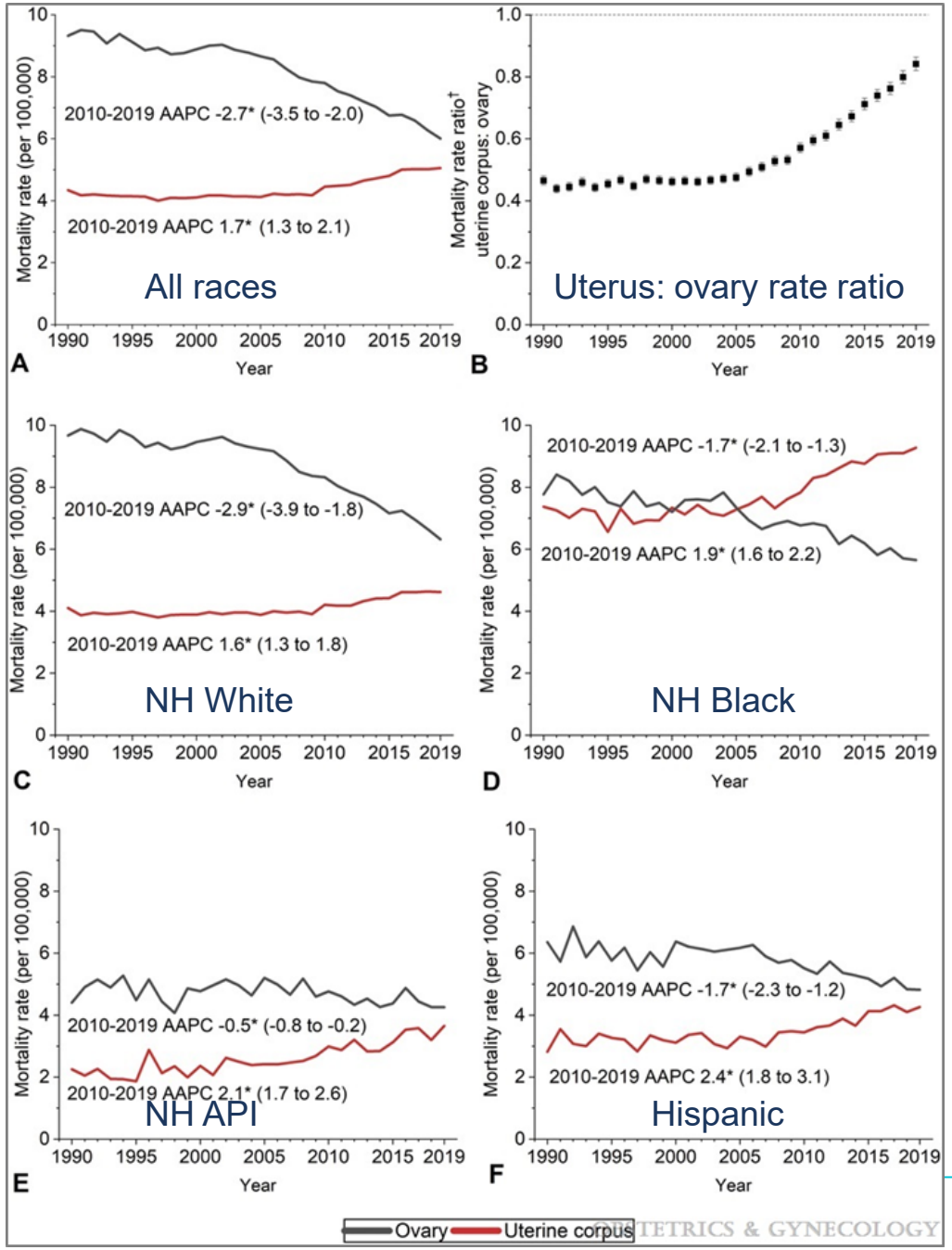




Siegel et al. Cancer Statistics 2024
Cancer Facts & Figures 2024. American Cancer Society. Available at https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2023/2023-cancer-facts-and-figures.pdf. Accessed January 10, 2024.

5-year relative survival by stage at diagnosis, Uterine corpus, 2013-2019

Data source: Surveillance, Epidemiology, and End Results 22 registries, National Cancer Institute, 2023
Survival is adjusted for normal life expectancy and based on cases diagnosed 2013-2019 and followed through 2020.



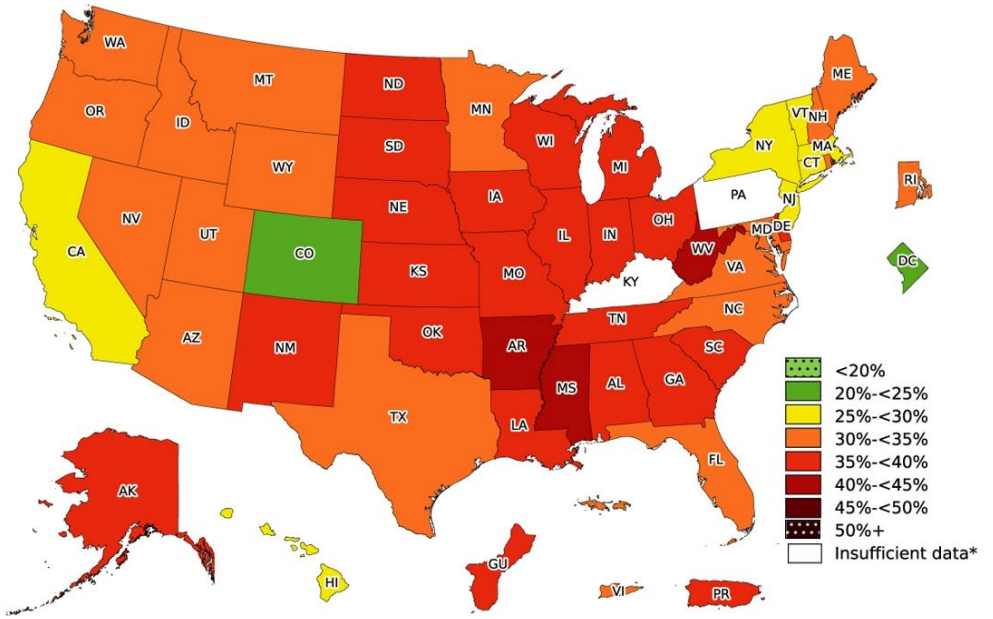
- In a recent review of SEER data, **the mortality from uterine cancer is now similar to that of ovarian cancer**.

- 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 1/7th 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

Why has this not improved?

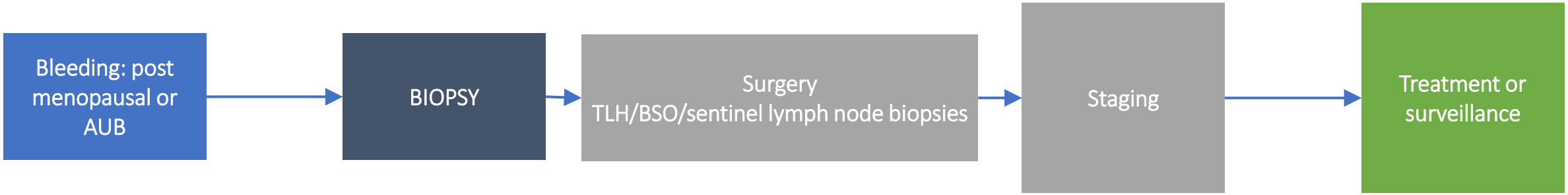
- Obesity
- Increasing rates of high risk histologies (serous, carcinosarcoma etc)
  - Link between endocrine-disrupting chemicals and hormone related cancers
    - PFAS, Phenols (BPA) PFDE, PFNA
    - Hair straighteners, hair dyes, cosmetics, plastic bottles, lavender and tea tree oils etc.
- Poor access to early uterine cancer care.



https://www.cdc.gov/obesity/data-and-statistics/adult-obesity-prevalence-maps.html

Cathey, A.L., Nguyen, V.K., Colacino, J.A. *et al.* Exploratory profiles of phenols, parabens, and per- and poly-fluoroalkyl substances among NHANES study participants in association with previous cancer diagnoses. *J Expo Sci Environ Epidemiol* **33**, 687–698 (2023). https://doi.org/10.1038/s41370-023-00601-6

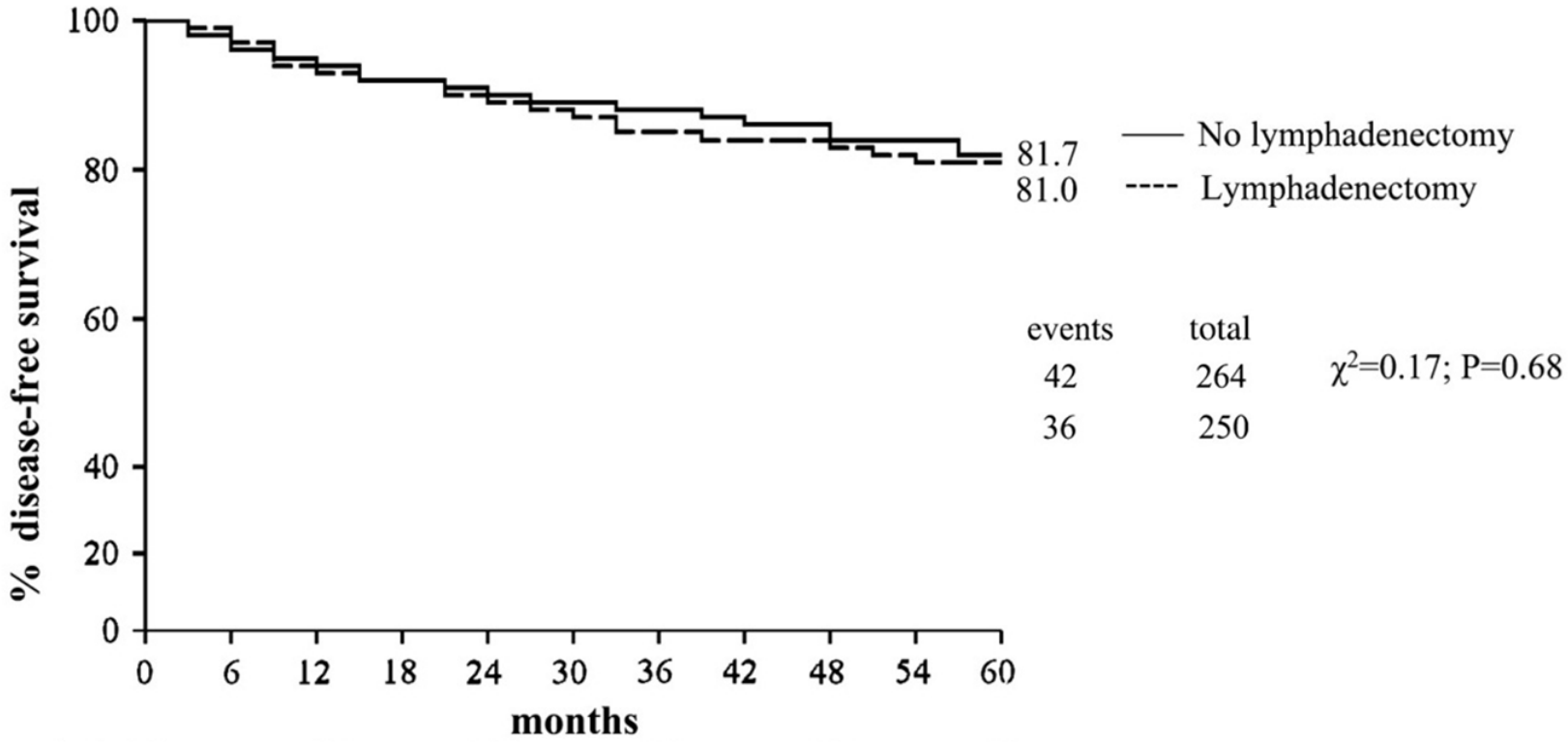
The Typical Course of Endometrial Cancer



Why sentinel nodes?

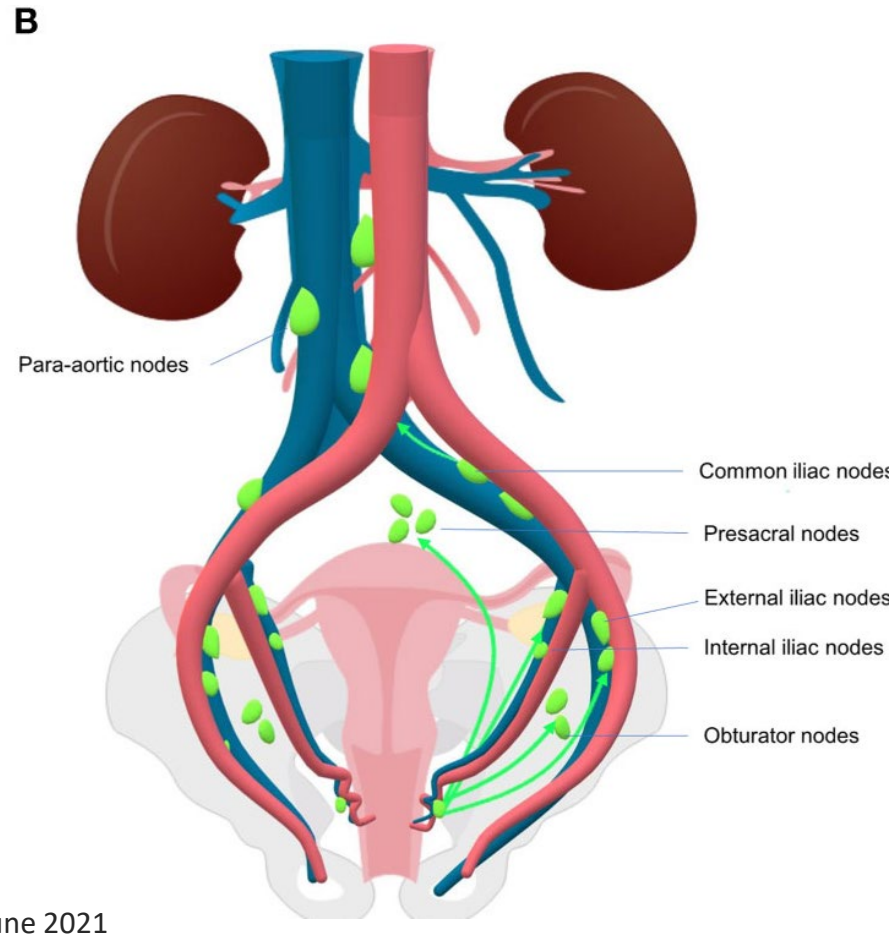
*

Does Lymphadenectomy increase survival?



Panici P B et al. JNCI J Natl Cancer Inst 2008;100:1707-1716

Sentinel nodes: less morbidity and same prognostication



- Holloway et al. Gynecol Oncol. 2016 May;141(2):206-210
  - Retrospective comparison of SLN vs. standard LND n=781, (SLN=119)
  - More lymph node mets seen in mapped nodes (30.3% vs. 14.7%)
  - No data on recurrence or survival
- Rossi et al (FIRES Trial) Lancet Oncol. 2017 Mar;18(3):384-392
  - Prospective cohort study of clinical stage I, all histologies and grades
  - 293 (86%) patients had successful mapping of at least one sentinel lymph node. 41 (12%) patients had positive nodes, 36 of whom had at least one mapped sentinel node.
  - Nodal metastases were identified in the sentinel lymph nodes of 35 (97%) of these 36 patients, yielding a **sensitivity to detect node-positive disease of 97·2% (95% CI 85·0-100), and a negative predictive value of 99·6% (97·9-100)**

Front. Oncol., 28 June 2021
Sec. Gynecological Oncology
Volume 11 - 2021 | https://doi.org/10.3389/fonc.2021.701758

PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

Figure 1: Common cervical injection sites for mapping uterine cancer[a]

Figure 2: Most common location of SLNs (blue, arrow) following a cervical injection[a]

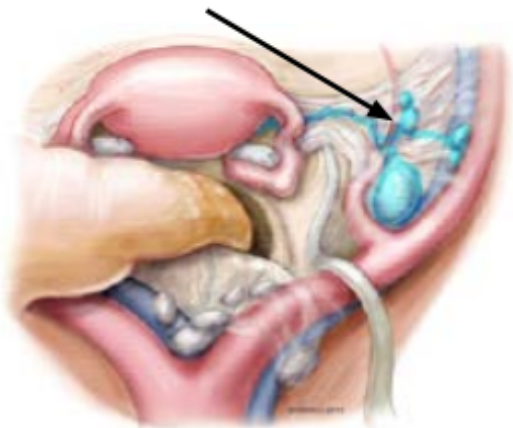
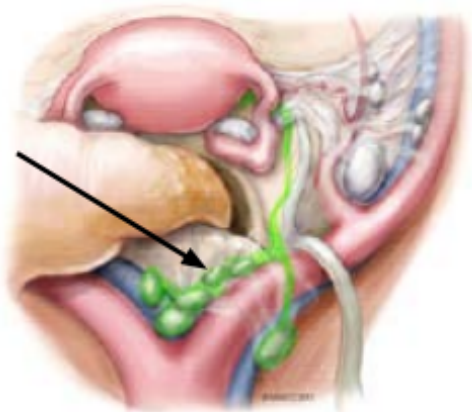


Figure 3: Less common location of SLNs (green, arrow) usually seen when lymphatic trunks are not crossing over the umbilical ligament but following the mesoureter cephalad to common iliac and presacral region[a]



Confined to the uterus: Stage 1

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NCCN Guidelines Version 3.2025
Endometrial Carcinoma

Why are we using 2009 staging?

All staging in guideline is based on 2009 FIGO staging. (ST-1)

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 or Consider vaginal brachytherapy if lymphovascular space invasion (LVSI) and/or age ≥60 y[n]
	G3	Vaginal brachytherapy preferred or Consider observation if no myoinvasion or Consider EBRT if either age ≥70 y or LVSI (category 2B)
IB	G1	Vaginal brachytherapy preferred or Consider observation if age <60 y and no LVSI
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	G3	RT (EBRT and/or vaginal brachytherapy) ± systemic therapy (category 2B for systemic therapy)

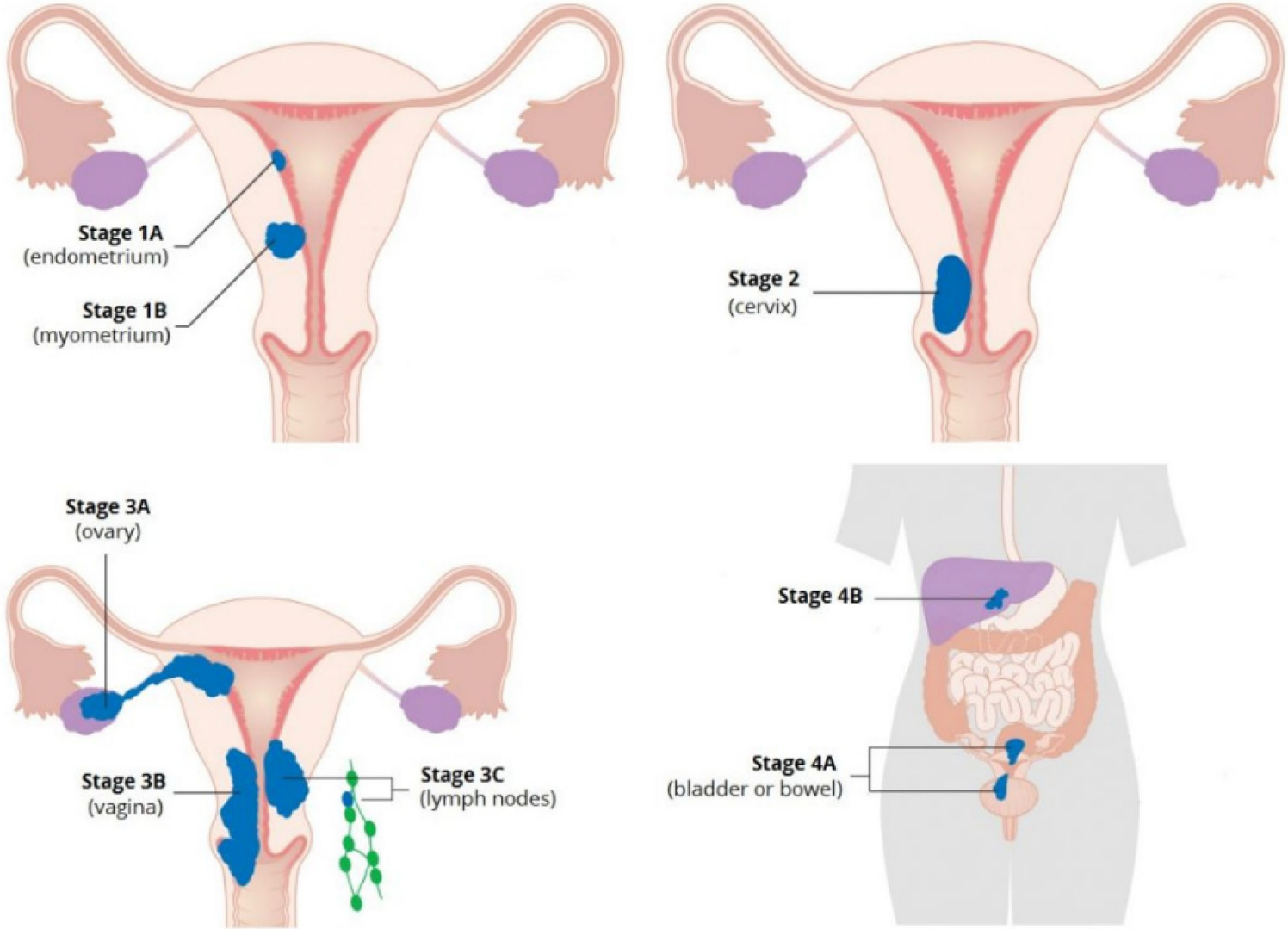
Why do we stage?

TO PROGNOSTICATE

TO PLAN FOR TREATMENT

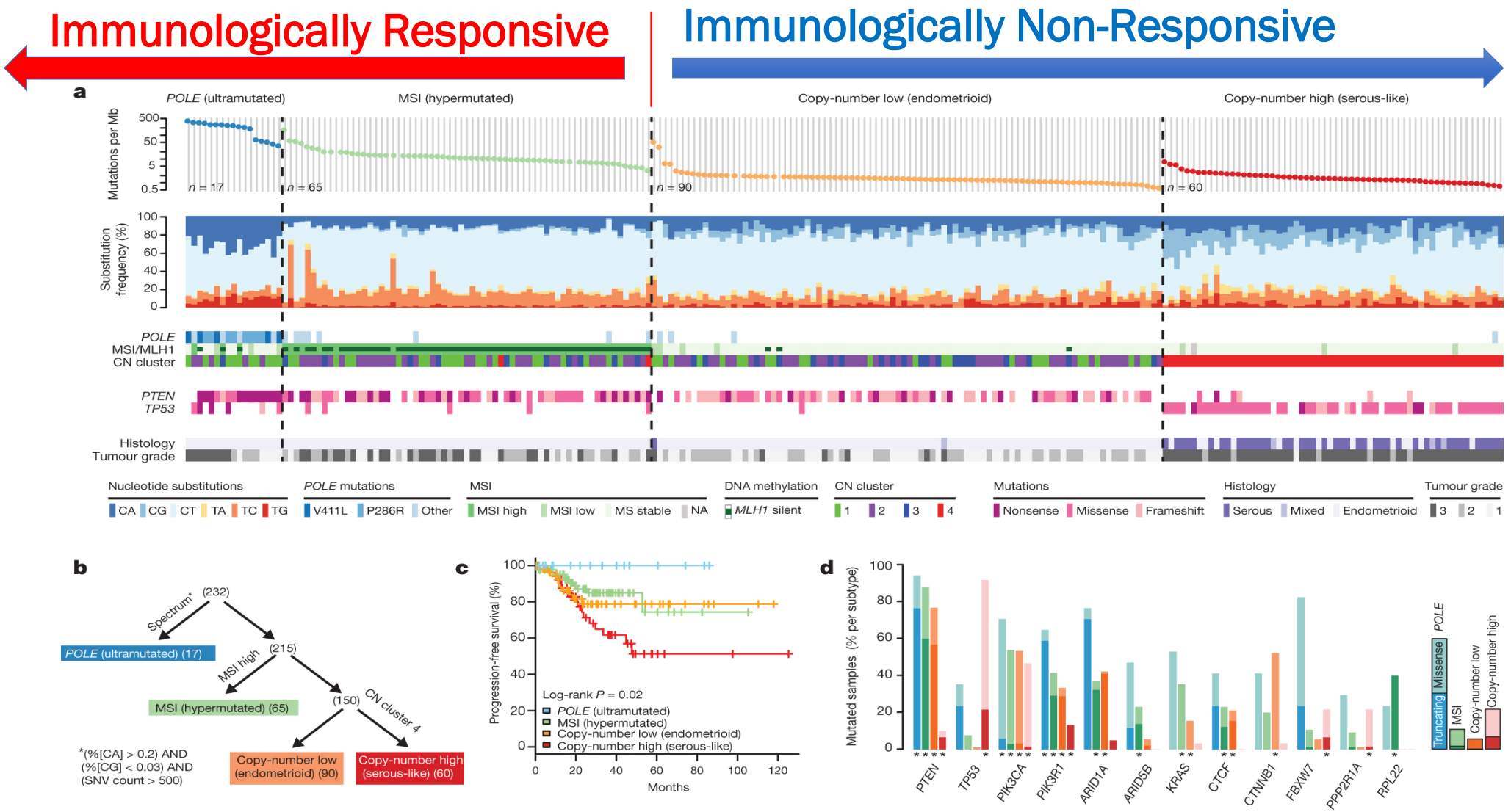
TO PORTION INTO CLINICAL TRIALS

FIGO 2009



Kasius, J. C., et al (2021). Risk Stratification of Endometrial Cancer Patients: FIGO Stage, Biomarkers and Molecular Classification. *Cancers*, *13*(22), 5848. https://doi.org/10.3390/cancers1322584

Disease Homogeneity to Molecular Granularity



G Getz *et al. Nature* **497**, 67-73 (2013) doi:10.1038/nature12113

Endometrial Cancer: Molecular Subtypes

POLE ultramutated	• Ultra-high somatic mutation frequency; MSS; frequent mutations in the exonuclease domain of *POLE*; high ASNS and CCNB1 expression • Represents ~4% of endometrioid tumors* • Best prognosis
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 • Represents ~39% of endometrioid tumors*†
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 • Represents ~49% of endometrioid tumors*
Copy-number high‡	• Greatest transcriptional activity; frequent *TP53* mutations; decreased levels of phospho-AKT; mutually exclusive *PIK3CA*, *PIK3R1,* and *PTEN* mutations • Represents ~9% of endometrioid tumors* • Worst prognosis

G Getz *et al. Nature* **497**, 67-73 (2013) doi:10.1038/nature12113


FIGO 2023:
Because you need more complexity to go with your daily grind
shutterstock.com · 1532204195

FIGO 2023 staging of cancer of the endometrium (part 1)

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

FIGO 2023 Staging: Cancer of the endometrium (part 2)

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

FIGO 2023 Staging: Cancer of the endometrium (part 3)

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] 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 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 IIIC1i Micrometastasis IIIC1ii Macrometastasis IIIC2 Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes IIIC2i Micrometastasis IIIC2ii Macrometastasis

FIGO 2023 Staging: Cancer of the endometrium (part 4)

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

What to choose for uterine confined disease?

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Endometrial Carcinoma

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All staging in guideline is based on 2009 FIGO staging. (ST-1)

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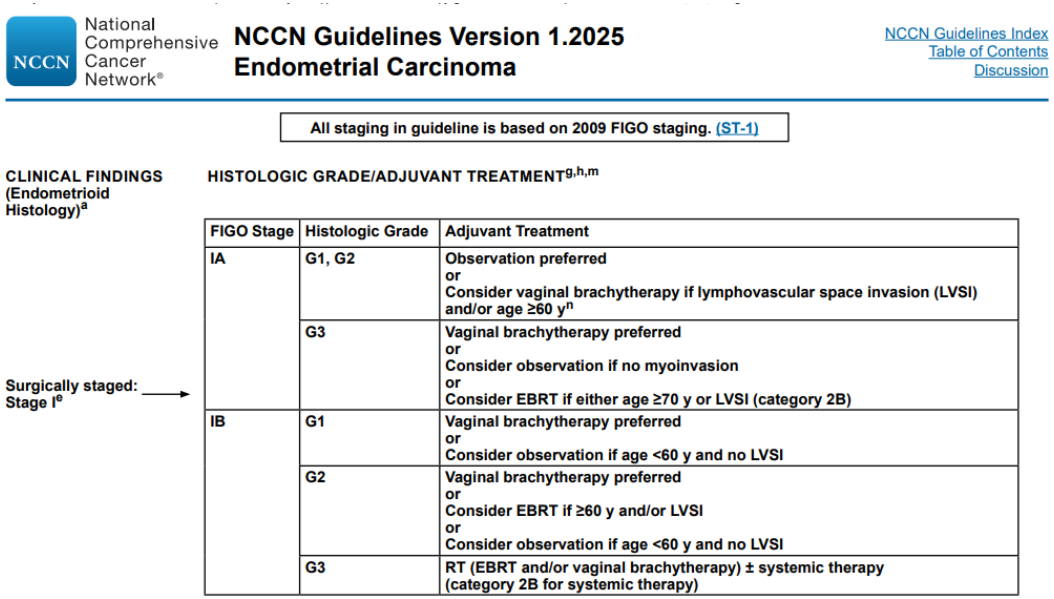
Stage I (FIGO 2009)

- Previously used GOG 33 (1987) data to prognosticate
- GOG 99 and PORTEC 1 and PORTEC 2 to predict
- Stage IA or IB (less than 50% invasion or more than 50%)



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5 trials have examined radiation therapy in early stage endometrial cancer

- Norwegian study
- PORTEC 1
- PORTEC 2
- GOG 99
- ASTEC/CGC/EN.5

- All show no benefit in overall survival to radiation therapy. (*some were not powered to do so)

- Local control only.

High inter

High intermediate risk (HIR) factors:
G2-3 tumor, Lymph vascular space invasion, outer 1/3 myometrial invasion:

1) >70 yrs old with only 1 other risk factor,
2) >50 yrs old with 2 risk factors;
3) any age with 3 risk factors.

- GOG 99
  - A phase III tr
    therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study." (Keys HM et al. Gynec Oncol. 2004 Mar;92(3):744-51.) Median F/U 5.7 years
    - Outcome: 2-year recurrence rate: 3% vs 12% (SS). 2-year isolated Locoregional recurrence 2% vs 7%. 4-year OS 92% vs 86% (NS). **In HIR subgroup (34%): 2-yr recurrence, 6% vs 26%.**
- PORTEC 1
  - Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma." Creutzberg CL et al. Lancet. 2000 Apr 22;355(9213):1404-11 Median F/U 4.3 years
    - Outcome: **Locoregional failure: 4% vs 14% (SS);** 73% of recurrences in vagina. Distant mets same (7%). OS same (80% vs 84%, NS) with ~50% deaths due to other causes

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GRADE/ADJUVANT TREATMENT[g,h,m]

	Histologic Grade	Adjuvant Treatment
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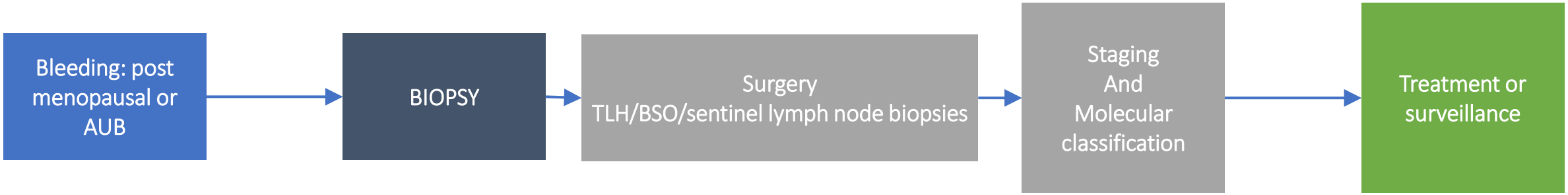
With staging goals in mind, we need an answer to each question

What is the prognosis of this stage?

What is the treatment recommended for this stage?

What clinical trial gives evidence for the above answer?

The (new) Typical Course of Endometrial Cancer



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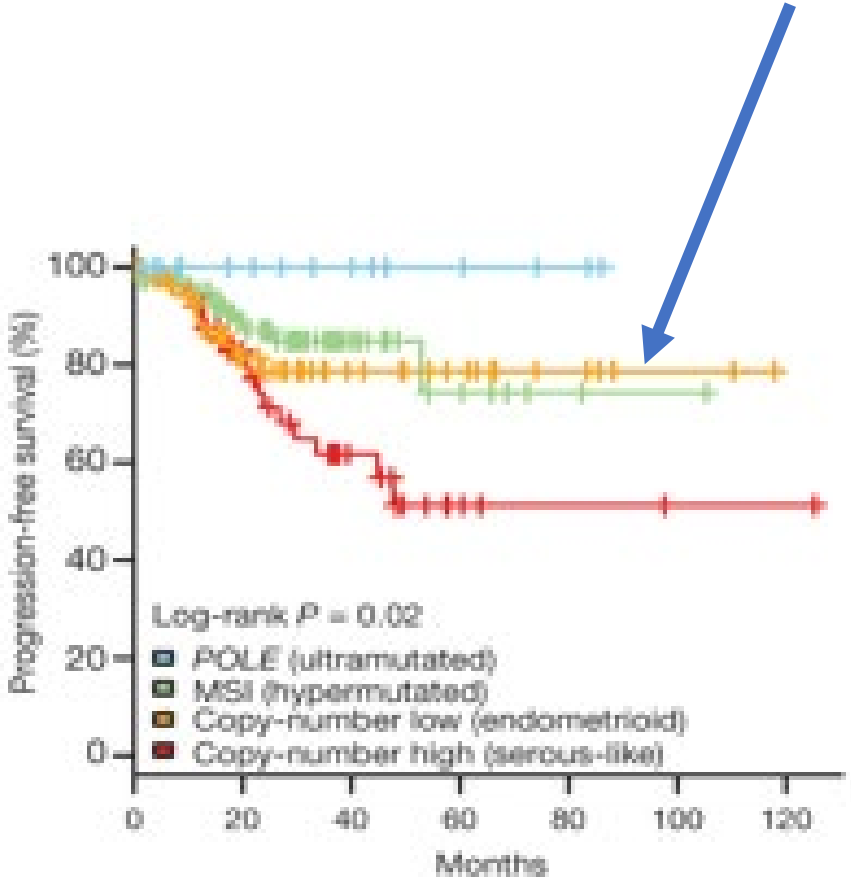
Stage IA1 :FIGO 2023

- Limited to endometrial polyp OR
- Confined to endometrium of a non-aggressive histology (grade 1 or 2 endometrioid) p



Stage IA1: FIGO 2023

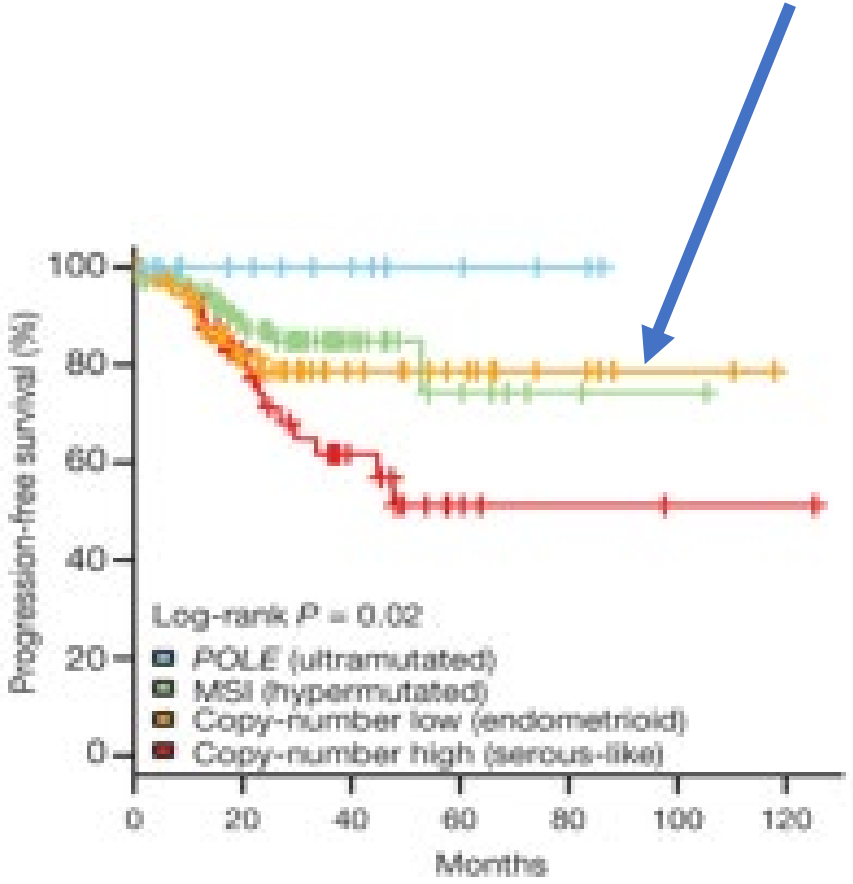
- What is the prognosis of this stage?
- What is the treatment recommended for this stage?
- What clinical trial gives evidence for the above answers?

- Excellent. Risk of recurrence between 1-5%
- Nothing (Observation)
- None- only retrospective case series

Ouyang et al IJGC 2018, Assem et al Human Path 2021

Stage IA2: FIGO 2023

- Grade 1 or Grade 2 endometrioid histology
- Up to 50% myometrial invasion
- NO or “focal” LSVI



Stage IA2: FIGO 2023

- What is the prognosis of this stage?
- What is the treatment recommended for this stage?
- What clinical trial gives evidence for the above answers?

- Very good. Recurrence rate 8.9%
- Nothing. Observation
- None. Retrospective studies only

Yarandi, F., Shirali, E., Akhavan, S. *et al.* The impact of lymphovascular space invasion on survival in early stage low-grade endometrioid endometrial cancer. *Eur J Med Res* **28**, 118 (2023). https://doi.org/10.1186/s40001-023-01084-9

Stage IA3

- Grade 1 or Grade 2
- Low grade endometrioid ovarian involvement (unilateral, low grade limited to the ovary without capsule invasion/rupture pT1a)
- Up to 50% myometrial invasion
- “absence of substantial or extensive LVSI” (*Rimel interpretation =NO or “focal” LVSI*)
- No other mets

Stage IA3

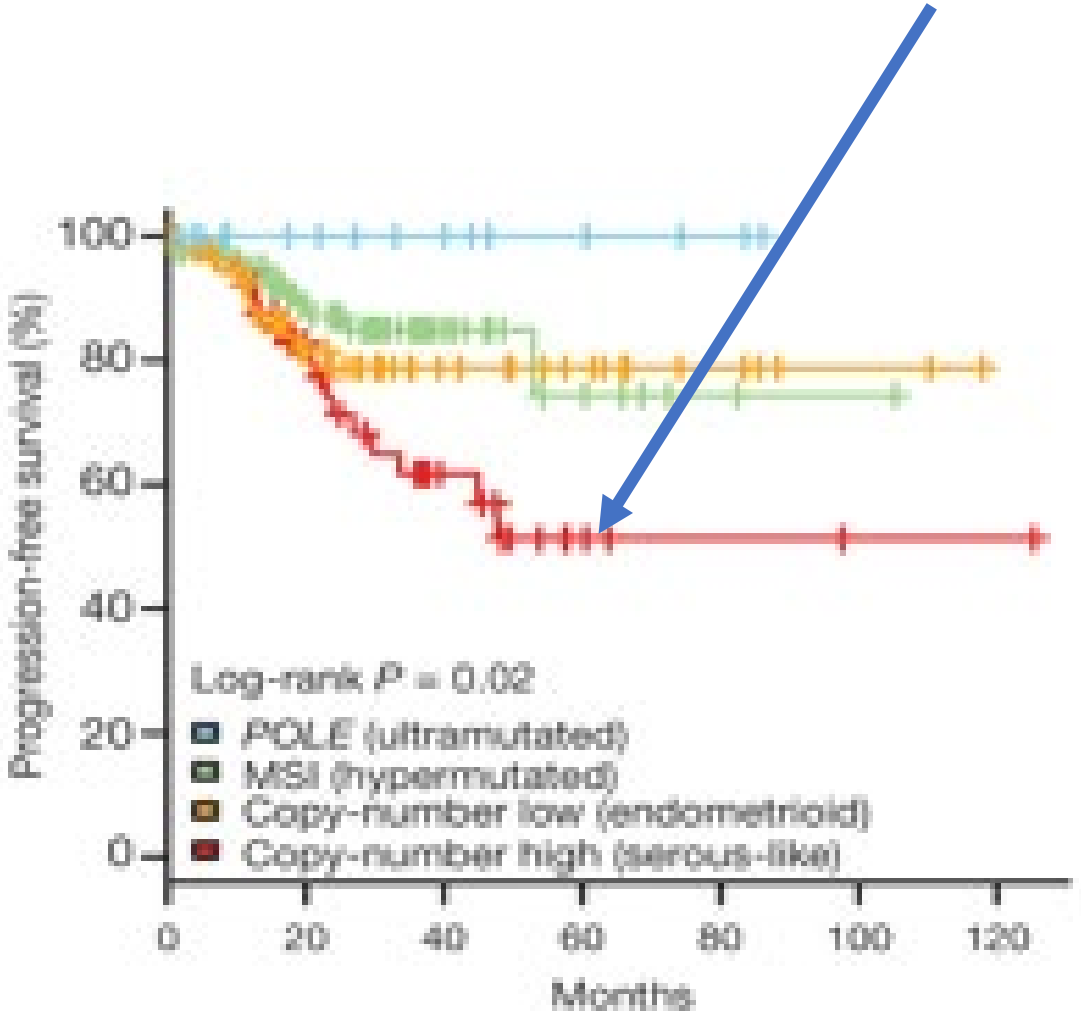
- What is the prognosis of this stage?
- What is the treatment recommended for this stage?
- What clinical trial gives evidence for the above answers?

- Controversial? This was stage IIIA in 2009 - A study in Italy analyzing 46 SEOC patients found that age affects patient prognosis, the 5-year survival rate for patients under 50 years old was 94.1%, while for those over 50 years old, it was 53.7% (64).
- NCCN says consider chemotherapy
- Included in GOG 209, and B21 – all got carbo/taxol

Caldarella A, Crocetti E, Taddei GL, Paci E. Coexisting endometrial and ovarian carcinomas: a retrospective clinicopathological study. Pathol Res Pract (2008) 204:643–8. doi: 10.1016/j.prp.2008.02.001

Stage IC

- Aggressive tumor types (grade 3, serous, clear cell, mesonephric de-differentiated etc)
- Limited to a polyp or confined to endometrium only
- No myometrial invasion



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- Local control only.
- NO MOLECULAR classification.
- Who does radiation really help?

What to choose?

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Surgically staged: Stage I[e] →

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

Current NCCN Guidelines for Systemic Therapy (March 2025)

- 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)

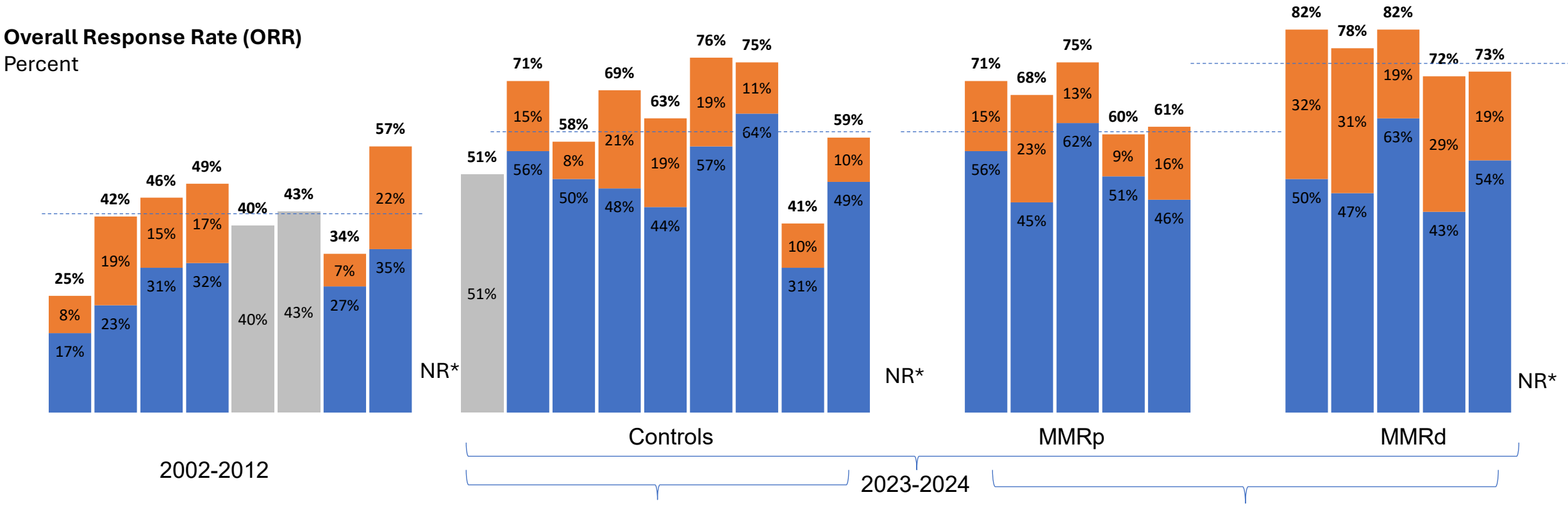
https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf

Endometrial Cancer: Molecular Subtypes

POLE ultramutated	• Ultra-high somatic mutation frequency; MSS; frequent mutations in the exonuclease domain of *POLE*; high ASNS and CCNB1 expression • Represents ~4% of endometrioid tumors* • Best prognosis	→ Clear IO Efficacy
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 • Represents ~39% of endometrioid tumors*†	→ Clear IO Efficacy
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 • Represents ~49% of endometrioid tumors*	→ ? Role for IO Hormonal Txt ? Novel targets
Copy-number high‡	• Greatest transcriptional activity; frequent *TP53* mutations; decreased levels of phospho-AKT; mutually exclusive *PIK3CA*, *PIK3R1,* and *PTEN* mutations • Represents ~9% of endometrioid tumors* • Worst prognosis	→ ? Role for IO ? Anti-Her2 ? Other ADCs ? VEGF targets

G Getz *et al. Nature* **497**, 67-73 (2013) doi:10.1038/nature12113

Evolution of Outcomes in first line measurable metastatic/recurrent Endometrial Cancer: ORR



Treatment with:

- doxorubicin
- doxorubicin + cisplatin
- doxorubicin + cisplatin circadian
- doxorubicin + paclitaxel
- doxorubicin + cisplatin + paclitaxel*

Control arms of Paclitaxel + Carboplatin for:

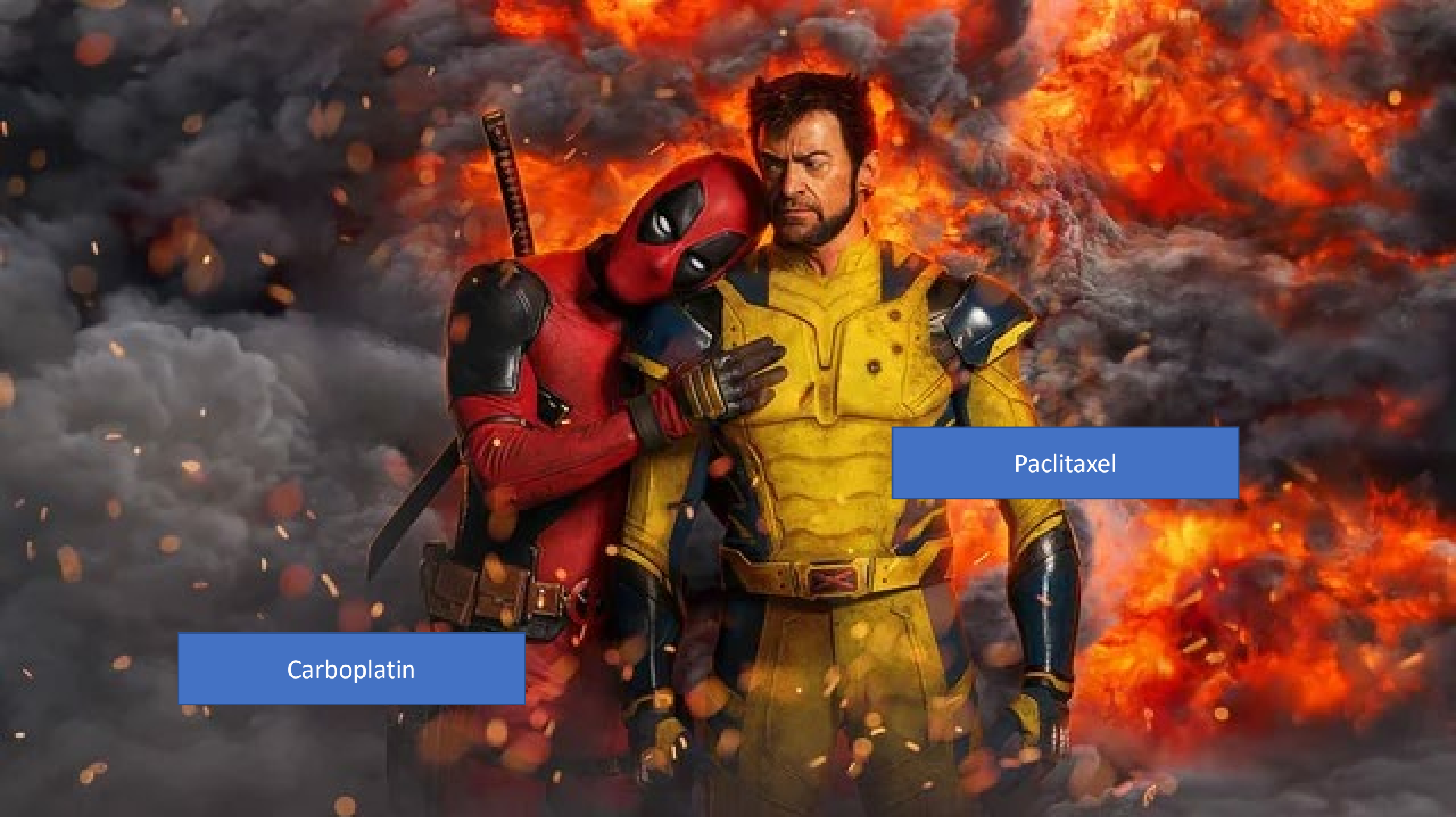
- GY018
- Ruby
- ATTEND
- DUO-E
- Ruby2*

Placlitaxel + Carbopatin + :

- pembrolizumab
- dostarlimab
- atezolizumab
- durvalumab
- durvalumab+olaparib
- dostarlimab + niraparib*

Slide credit K. Moore MD

Thigpen et al. J Clin Oncol 2004, Gallion et al. J Clin Oncol 2003, Fleming et al. J Clin Oncol 2004, Fleming et al. J Clin Oncol 2004 11(22), Miller et al. J Clin Oncol 2020; Aghajanian et al. Gynecol Oncol 2018, Eskander ESMO 2023; Eskander et al. NEJM 2023; Eskander et al. SGO 2024, Mirza et al. NEJM 2023; Powell et al. SGO 2024, Colombo et al. ESMO 2023, Westin et al. ESMO 2023


Paclitaxel
Carboplatin

GY018

Placebo
Carboplatin AUC 5
Paclitaxel 175 mg/m²
Q3W for 6 -10 cycles

→ Placebo IV Q6W

up to 14 additional cycles

Pembrolizumab 200 mg IV
Carboplatin AUC 5
Paclitaxel 175 mg/m²
Q3W for 6 -10 cycles

→ Pembrolizumab 400 mg IV Q6W

up to 14 additional cycles

Both Q3 weeks and same chemo backbone

Both Q6 weeks in maintenance

= 21 months
<2 years

RUBY

Placebo
Carboplatin AUC 5
Paclitaxel 175 mg/m²
Q3W for 6 cycles

→ Placebo IV Q6W

up to 26 additional cycles

Dostarlimab IV 500 mg
Carboplatin AUC 5
Paclitaxel 175 mg/m²
Q3W for 6 cycles

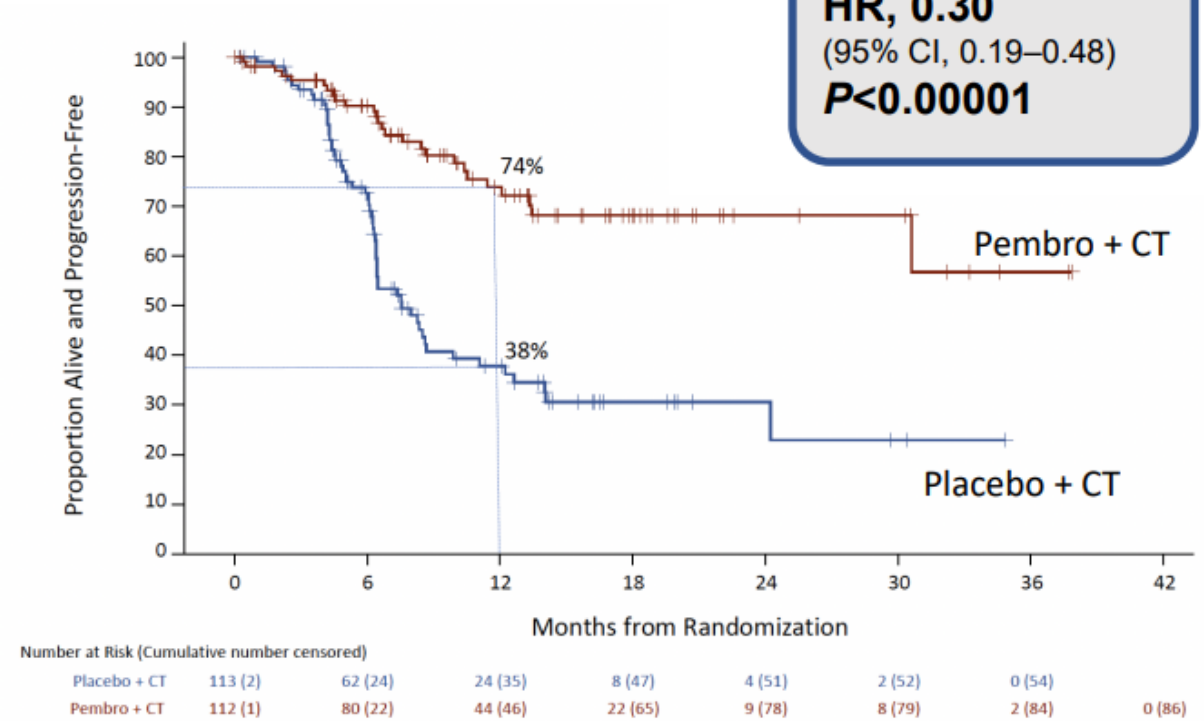
→ Dostarlimab 1000 mg IV Q6W

up to 26 additional cycles

3 years

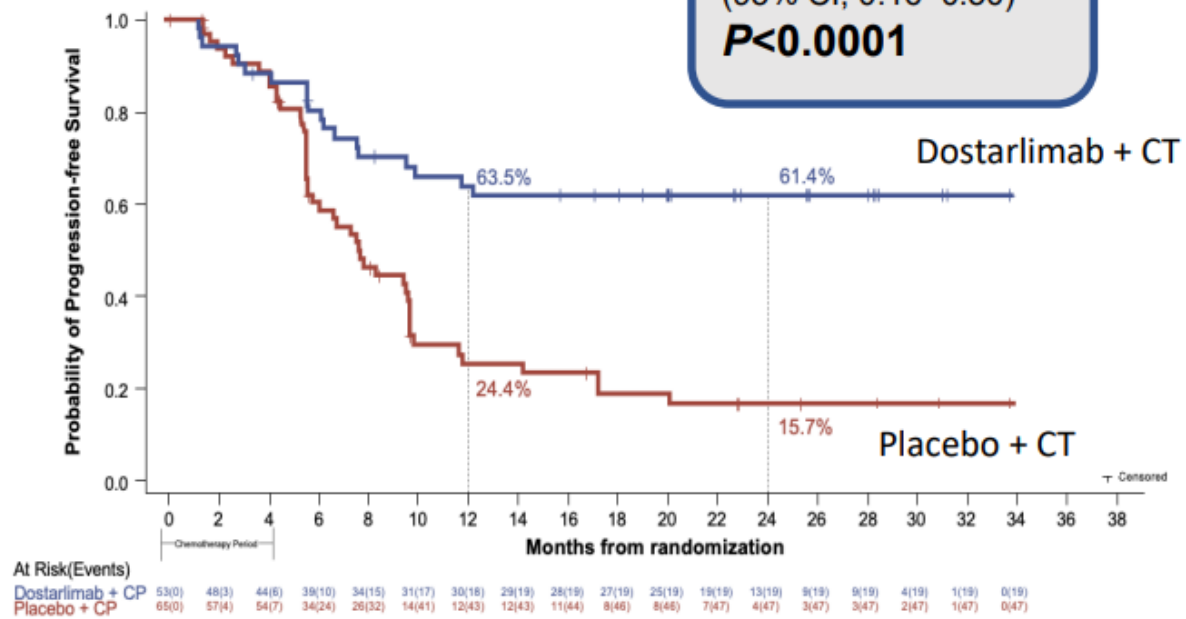
GY018 dMMR/MSI-H RUBY

HR, 0.30
(95% CI, 0.19–0.48)
***P*<0.00001**



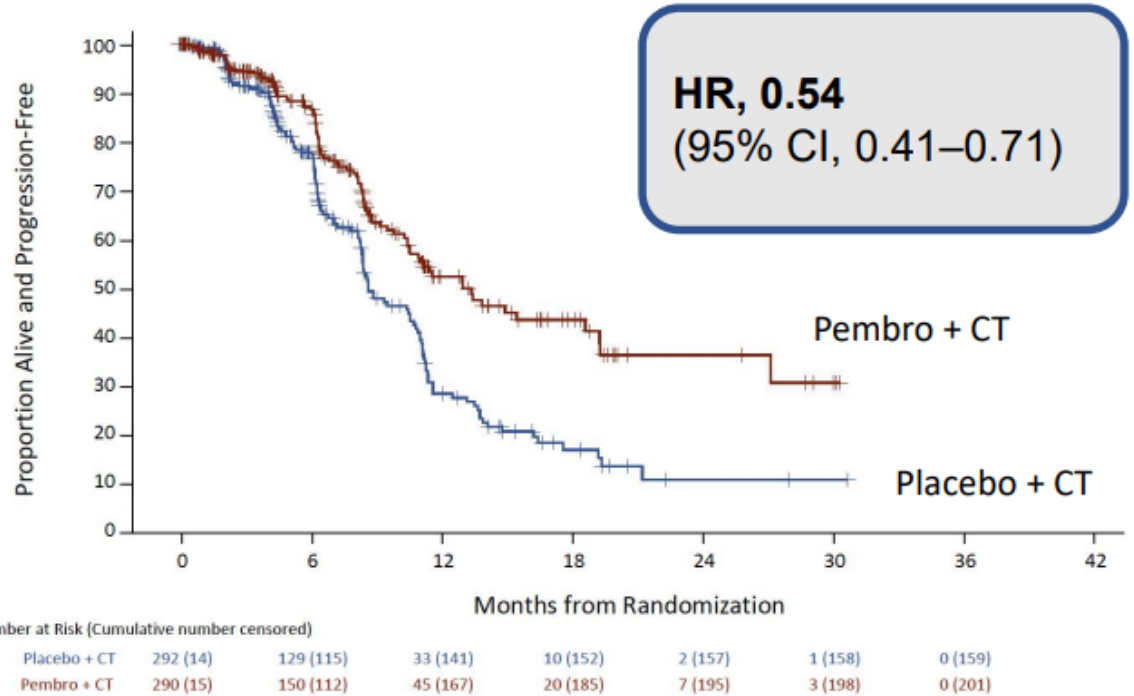
	No. with events, %	Median (95% CI), mo
Pembro + CT	23.2	NR (30.6–NR)
Placebo + CT	52.2	7.6 (6.4–9.9)
PFS maturity	37.7	

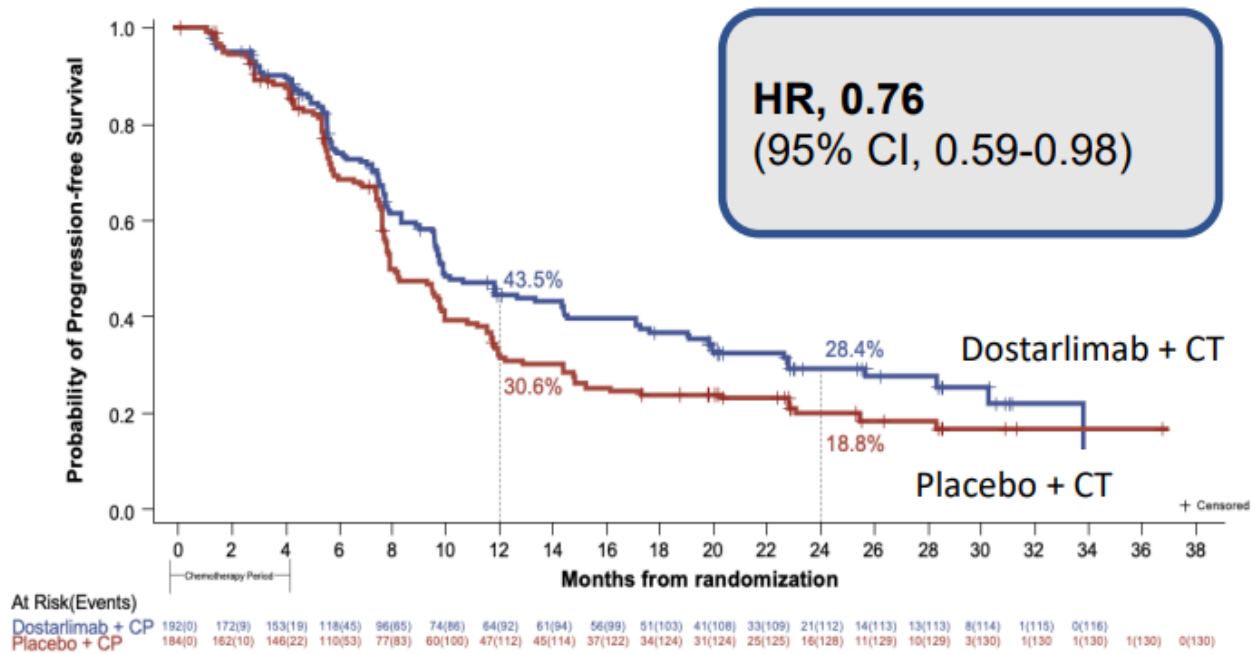
HR, 0.28
(95% CI, 0.16–0.50)
***P*<0.0001**



	No. with events, %	Median (95%CI), mo
Dostarlimab + CP	35.8	NR (11.8–NR)
Placebo + CP	72.3	7.7 (5.6–9.7)
PFS maturity	55.9	

GY018 MMRp/MSS RUBY





	No. with event, %	Median (95% CI), mo
Pembro + CT	30.6	13.1 (10.5–18.8)
Placebo + CT	45.5	8.7 (8.4–10.7)
PFS Maturity	38.1	

	No. with event, %	Median (95%CI), mo
Dostarlimab + CP	60.4	9.9 (9.0–13.3)
Placebo + CP	70.7	7.9 (7.6–9.8)
PFS maturity	65.4	

SGO ANNUAL MEETING ON WOMEN'S CANCER TAMPA, FL • 2023 PATIENTS • PURPOSE • PROGRESS

Overall survival in patients with primary advanced or recurrent endometrial cancer treated with dostarlimab plus chemotherapy in Part 1 of the ENGOT-EN6-NSGO/GOG-3031/RUBY trial

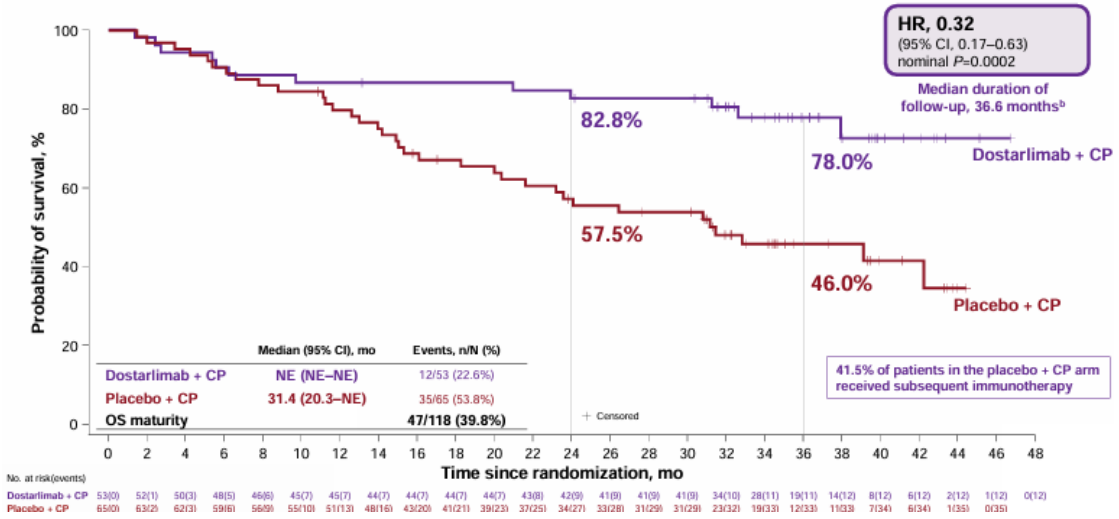
Matthew A. Powell,[1] Annika Auranen,[2] Lyndsay Willmott,[3] Lucy Gilbert,[4] Destin Black,[5] David Cibula,[6] Sudarshan Sharma,[7] Giorgio Valabrega,[8] Lisa M. Landrum,[9] Lars C. Hanker,[10] Ashley Stuckey,[11] Ingrid Boere,[12] Michael A. Gold,[13] Mark S. Shahin,[14] Bhavana Pothuri,[15] Brian Slomovitz,[16] Matt Grimshaw,[17] Shadi Stevens,[17] Robert L. Coleman,[18] Mansoor Raza Mirza[19]

[1]National Cancer Institute–sponsored NRG Oncology, Washington University School of Medicine, St Louis, MO, USA; [2]Tays Cancer Centre and FICAN Mid, Tampere University and Tampere University Hospital, Tampere, Finland; [3]Arizona Cancer Care, Phoenix, AZ, USA; [4]Division of Gynecologic Oncology, McGill University Health Centre, Montreal, QC, Canada; [5]Department of Obstetrics and Gynecology, LSU Health Shreveport, and Willis-Knighton Physician Network, Shreveport, LA, USA; [6]Department of Gynaecology, Obstetrics and Neonatology, General University Hospital in Prague, First Faculty of Medicine, Charles University, Prague, Czech Republic; [7]Department of Obstetrics/Gynecology, AMITA Adventist Hinsdale Hospital, Hinsdale, IL, USA; [8]University of Torino, AO Ordine Mauriziano, Torino, Italy; [9]Indiana University Health and Simon Cancer Center, Indianapolis, IN, USA; [10]Department of Gynecology and Obstetrics, University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck, Germany; [11]Women and Infants Hospital, Providence, RI, USA; [12]Department of Medical Oncology, Erasmus MC Cancer Centre, Rotterdam, The Netherlands; [13]Oklahoma Cancer Specialists and Research Institute, Tulsa, OK, USA; [14]Hanjani Institute for Gynecologic Oncology, Abington Hospital–Jefferson Health, Asplundh Cancer Pavilion, Sidney Kimmel Medical College of Thomas Jefferson University, Willow Grove, PA, USA; [15]Laura & Isaac Perlmutter Cancer Center, NYU Langone Health, New York, NY, USA; [16]Department of Gynecologic Oncology, Mount Sinai Medical Center, and Department of Obstetrics and Gynecology, Florida International University, Miami Beach, FL, USA; [17]GSK, London, UK; [18]Sarah Cannon Research Institute, Nashville, TN, USA; [19]Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, and Nordic Society of Gynaecologic Oncology–Clinical Trial Unit, Copenhagen, Denmark

THE POWER OF SHARED PURPOSE:
Transforming Gynecologic Cancer Care

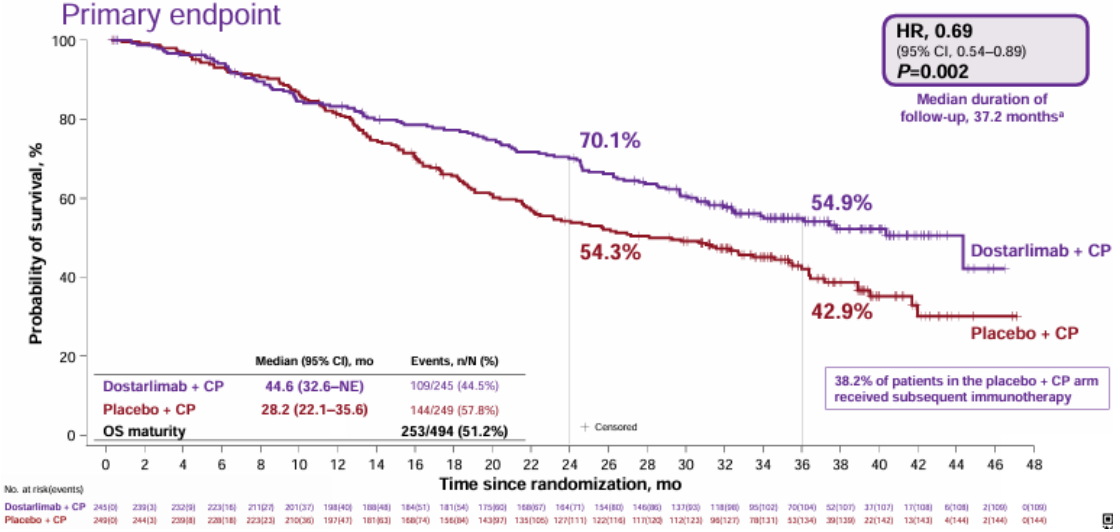
SGO ANNUAL MEETING ON WOMEN'S CANCER
San Diego, CA • 2024

Substantial OS Benefit in dMMR/MSI-H Population[a]

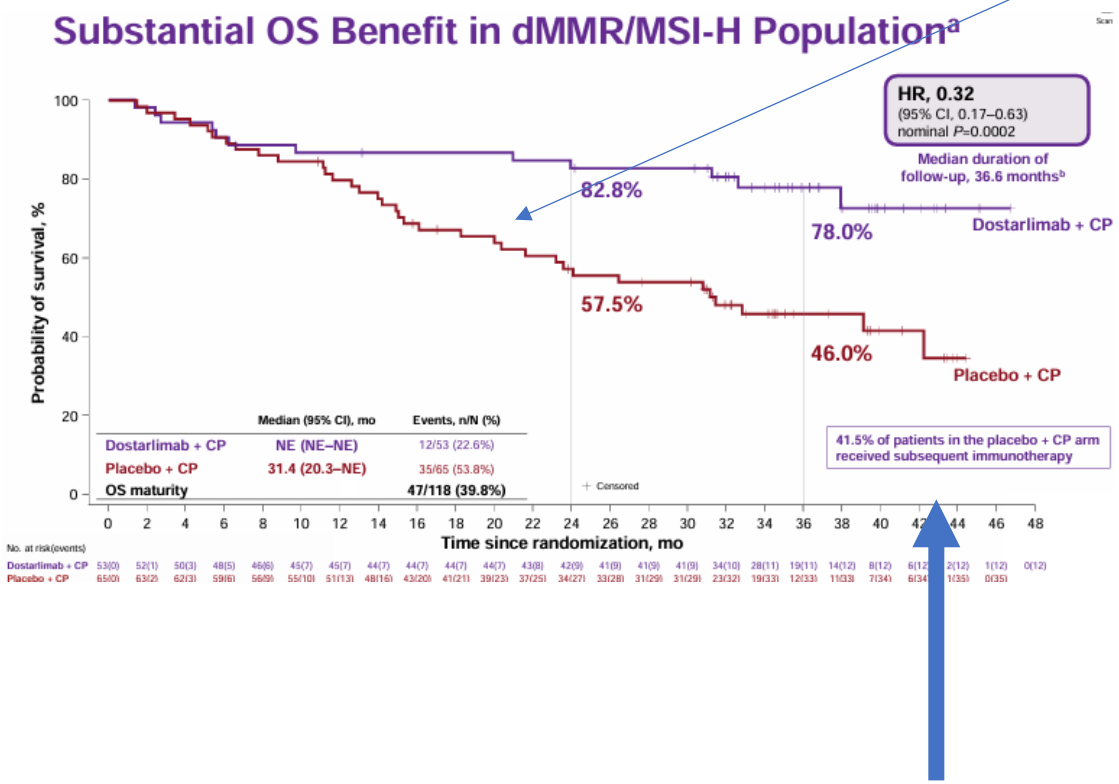


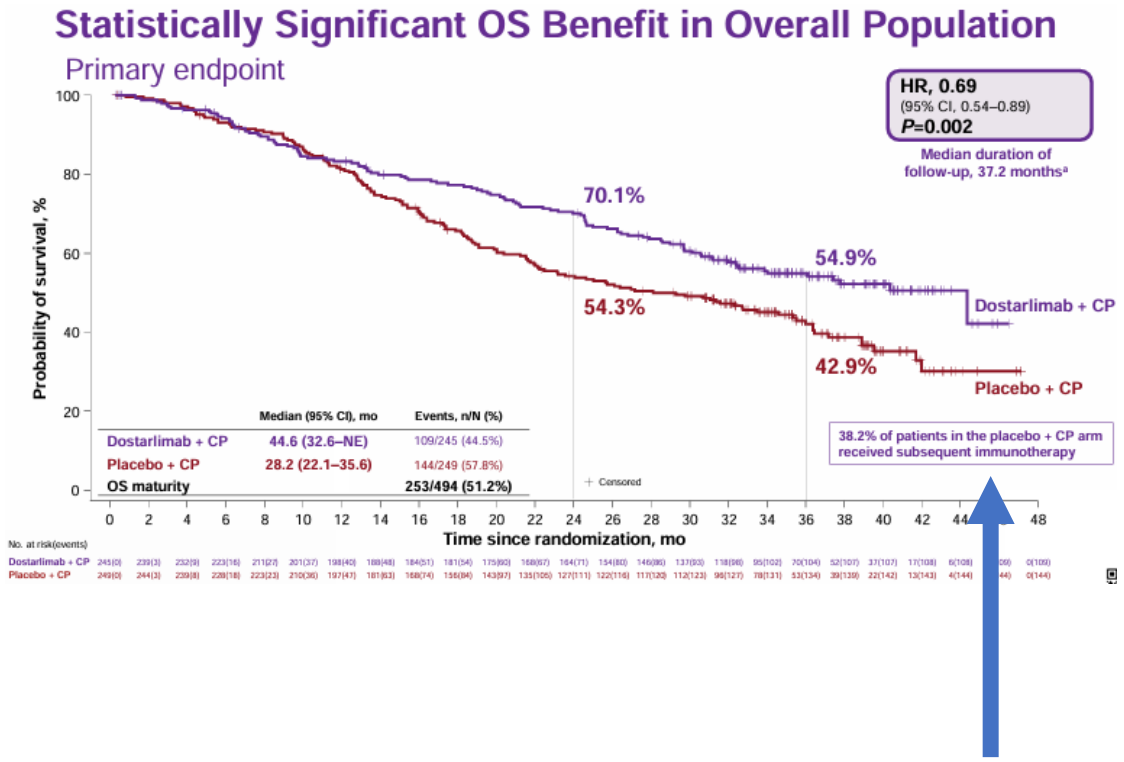
Statistically Significant OS Benefit in Overall Population

Primary endpoint



EVEN MORE IMPRESSIVE!





ENGOT-EN11/GOG-3053/KEYNOTE-B21: A Phase 3 Study of Pembrolizumab or Placebo in Combination With Adjuvant Chemotherapy With or Without Radiotherapy in Patients With Newly Diagnosed, High-Risk Endometrial Cancer

Toon Van Gorp,[1] Lukáš Rob,[2] Weiguo Lv,[3] Floor Backes,[4] Fırat Ortaç,[5] Kosei Hasegawa,[6] Sakari Hietanen,[7] Antonella Savarese,[8] Annouschka Laenen,[9] Yong Man Kim,[10] Lubomir Bodnar,[11] Maria-Pilar Barretina-Ginesta,[12] Lucy Gilbert,[13] Bhavana Pothuri,[14] Xiaojun Chen,[15] Jasmine Lichfield,[16] Wei Wang,[17] Robert Orlowski,[18] Alain Lortholary,[19] Brian Slomovitz[20]

[1]University Hospital Leuven, Leuven Cancer Institute, Leuven, Belgium; and BGOG; [2]3rd Faculty Medicine Charles University and Faculty Hospital Kralovske Vinohrady, Prague, Czech Republic; and CEEGOG; [3]Zhejiang University, Hangzhou, Zhejiang, China; [4]Ohio State University and James Cancer Hospital, Columbus, OH, USA; and GOG; [5]Ankara University School of Medicine, Ankara, Turkey; and TRSGO; [6]Saitama Medical University, Hidaka, Saitama Prefecture, Japan; [7]Turku University Hospital and University of Turku, Turku, Finland; TYKS Cancer Centre, FICAN West, Organization of EU Cancer Institutes, Finland; and NSGO-CTU; [8]IRCCS - Istituto Nazionale Tumori Regina Elena, Rome, Italy; and MITO; [9]Leuven Biostatistics and Statistical Bioinformatics Center, KU Leuven, Leuven, Belgium; and BGOG; [10]Asan Medical Center, University of Ulsan, Seoul, Republic of Korea; [11]Mazovia Regional Hospital, Siedlce Oncology Center, Siedlce, Poland; and ENGOT groups – PGOG; [12]Catalan Institute of Oncology and Girona Biomedical Research Institute, Medical School University of Girona, Girona, Spain; and GEICO; [13]McGill University Health Centre; Research-Institute, McGill University Health Centre; and Gerald Bronfman Department of Oncology, McGill University, Montreal, Quebec, Canada; [14]Obstetrics and Gynecology and Medicine, Gynecologic Oncology, Perlmutter Cancer Center, NYU Langone Health, New York, New York, USA; and GOG; [15]Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China; and SGOG; [16]MSD, UK; [17]MSD, China; [18]Merck & Co., Inc., Rahway, NJ, USA; [19]Centre Catherine de Sienne, Hôpital Privé du Confluent, Nantes, France; and GINECO; [20]Mount Sinai Medical Center, Miami Beach, FL, USA; and GOG Foundation

ENGOT-EN11/GOG-3053/KEYNOTE-B21 Study Design

Key Eligibility Criteria

- Newly diagnosed EC or carcinosarcoma
- Curative surgery with no residual disease
- At high risk for recurrence:
  - FIGO (2009) surgical stage I/II, non-endometrioid with myometrial invasion ← Now stage IIC, FIGO2023
  - FIGO (2009) surgical stage I/II of any histology with known aberrant p53 expression or *TP53* mutation with myometrial invasion
  - FIGO (2009) surgical stage III/IVA of any histology
- No prior radiation or systemic therapy (including neoadjuvant) for EC

R 1:1
N=1095

	Stage 1	Stage 2
	Carboplatin (AUC 5 or 6) + paclitaxel 175 mg/m^2 (Q3W, 4 or 6 cycles)[a]	± radiotherapy ± cisplatin[b]
	Pembrolizumab 200 mg Q3W (6 cycles)	Pembrolizumab 400 mg Q6W (6 cycles)
	Carboplatin (AUC 5 or 6) + paclitaxel 175 mg/m^2 (Q3W, 4 or 6 cycles)[a]	± radiotherapy ± cisplatin[b]
	Placebo Q3W (6 cycles)	Placebo Q6W (6 cycles)

Stratification Factors

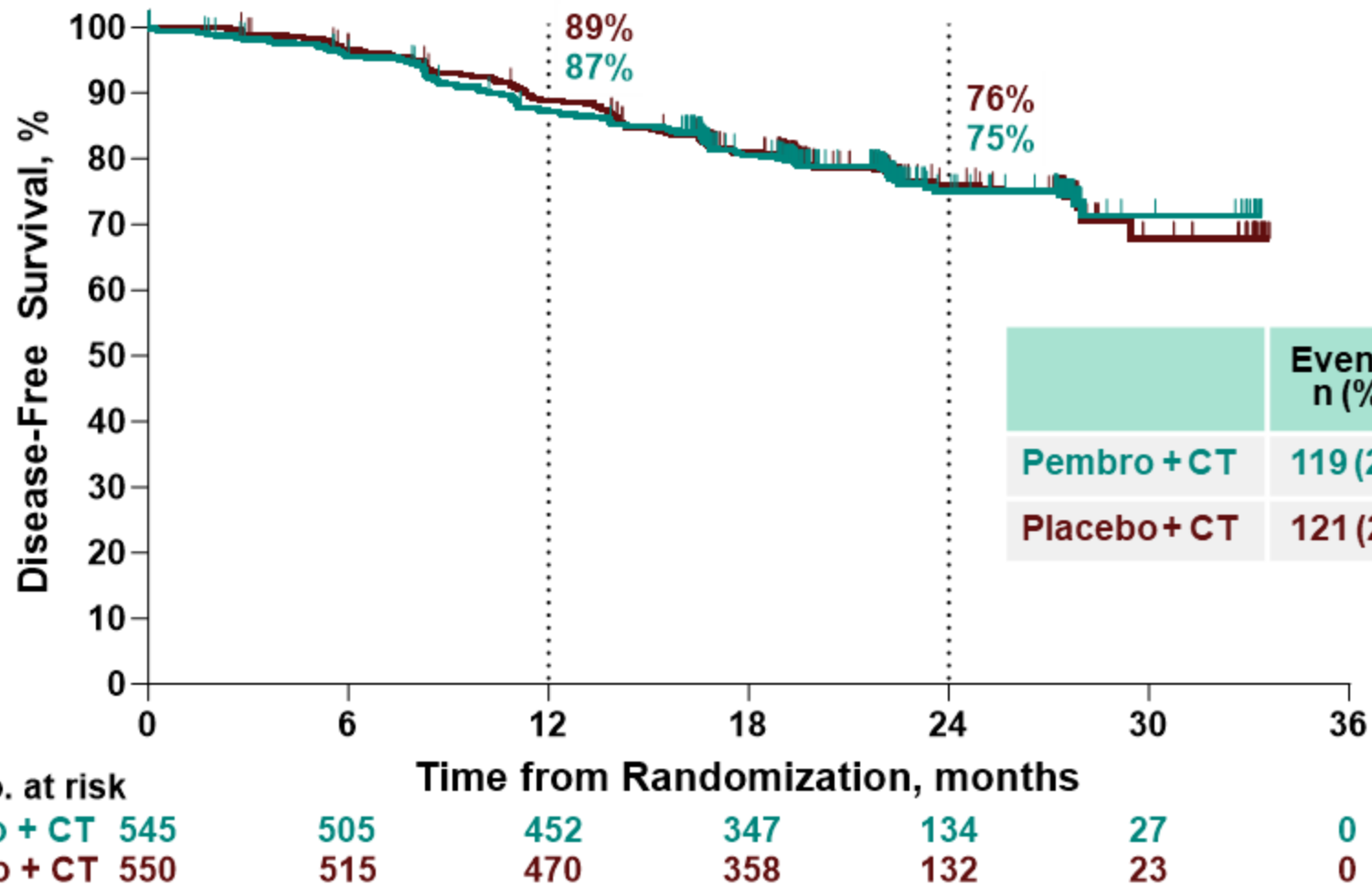
- **MMR status (pMMR vs dMMR)**, and within pMMR stratum:
  - Planned radiation (chemo-EBRT vs EBRT vs no EBRT)
  - Histology (endometrioid vs non-endometrioid)
  - FIGO (2009) surgical stage (I/II vs III/IVA)

Dual primary endpoints

- DFS as assessed radiographically by the investigator or by histopathologic confirmation
- OS

[a]Chemotherapy was administered for 4 cycles in patients planned to receive chemoradiotherapy and 6 cycles for all other patients, including those planned for radiotherapy without radiosensitizing cisplatin. [b]Radiotherapy was optional at the discretion of the investigator, and cisplatin may have been given with EBRT as radiosensitizer; radiotherapy was started within 6 weeks after completion of carboplatin and paclitaxel (radiation may have been initiated during Stage 1 or Stage 2 depending on the number of cycles of chemotherapy that were administered).

DFS[a] Similar Between Treatment Groups: ITT Population (Primary Endpoint)



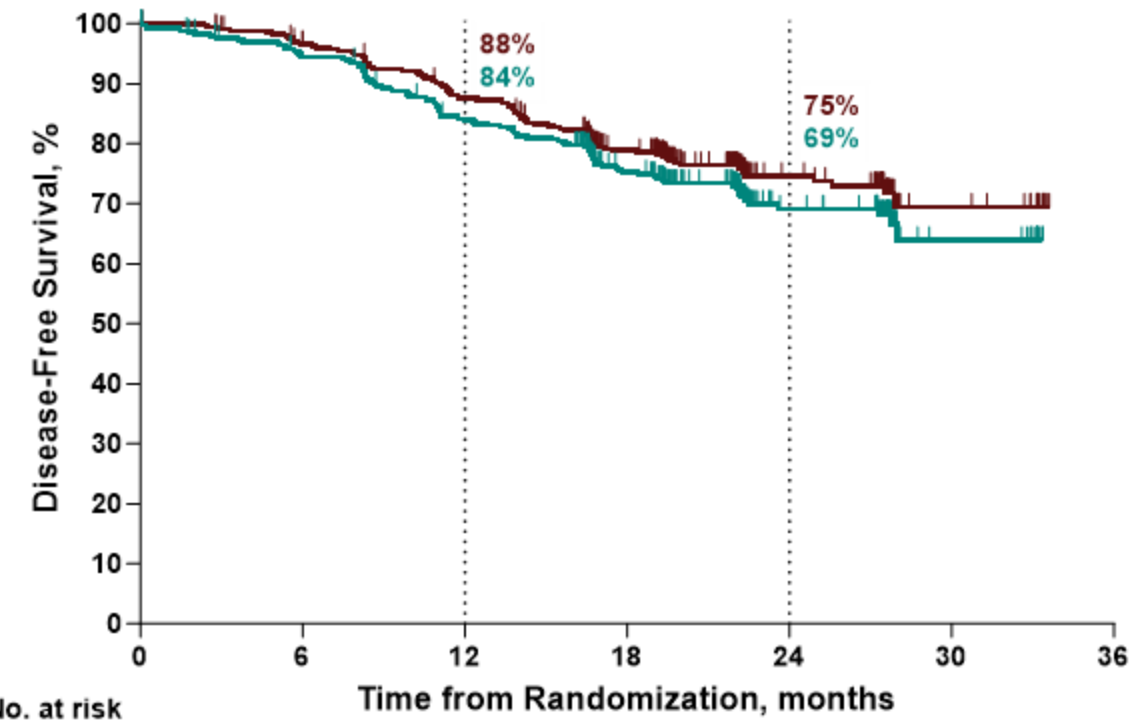
	Events, n (%)	Median (95% CI), mo	HR (95% CI)	*P* value
Pembro + CT	119 (22)	NR (NR–NR)	1.02 (0.79–1.32)	0.570
Placebo + CT	121 (22)	NR (NR–NR)		

[a]DFS was defined as the time from randomization to local or distant recurrence of EC (assessed radiographically by the investigator or by histopathologic confirmation) or death from any cause.
Data cutoff date: March 4, 2024.

Pembrolizumab Plus Chemotherapy Improved DFS[a] in dMMR Subgroup

pMMR Subgroup

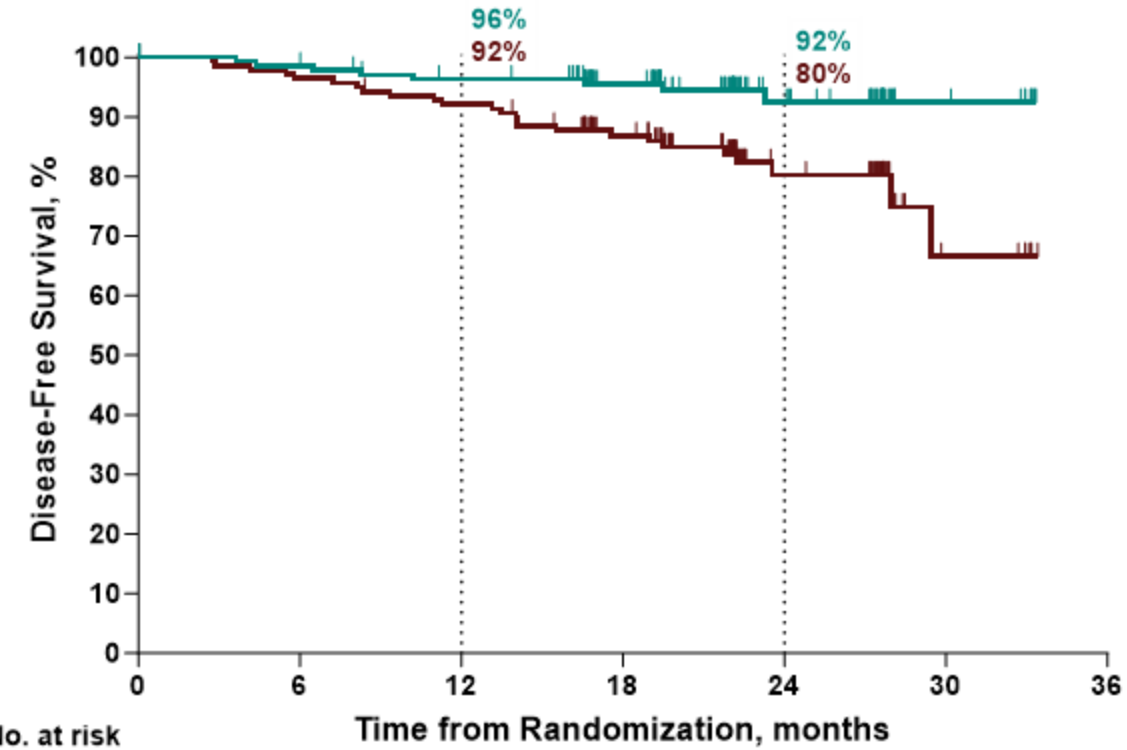
	Events, n (%)	Median (95% CI), mo	HR (95% CI)
Pembro + CT	111 (27)	NR (NR–NR)	1.20 (0.91–1.57)
Placebo + CT	96 (23)	NR (NR–NR)	



No. at risk							
Pembro + CT	404	369	323	244	88	17	0
Placebo + CT	410	381	343	259	94	16	0

dMMR Subgroup

	Events, n (%)	Median (95% CI), mo	HR (95% CI)
Pembro + CT	8 (6)	NR (NR–NR)	0.31 (0.14–0.69)
Placebo + CT	25 (18)	NR (29.5–NR)	



No. at risk							
Pembro + CT	141	136	129	103	46	10	0
Placebo + CT	140	134	127	99	38	7	0

[a]DFS was defined as the time from randomization to local or distant recurrence of EC (assessed radiographically by the investigator or by histopathologic confirmation) or death from any cause.
Data cutoff date: March 4, 2024.

Van Gorp T, et al ENGOT-en11/GOG-3053/KEYNOTE-B21: Ann Oncol. 2024 Nov;35(11):968-980

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

DESTINY-PanTumor02: T-DXd for HER2-expressing solid tumors

A Phase 2, open-label, multicenter study (NCT04482309)

Key eligibility criteria

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)*
  - Cervical cohort was expanded to include five IHC 1+ patients†
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1

T-DXd 5.4 mg/kg Q3W

n≈40 per cohort‡

Primary endpoint

- Confirmed ORR (investigator)

Secondary endpoints

- DOR, DCR, PFS, OS
- Safety

Exploratory analyses

- Subgroup analyses by HER2 status§
- Subgroup analyses by biomarkers§

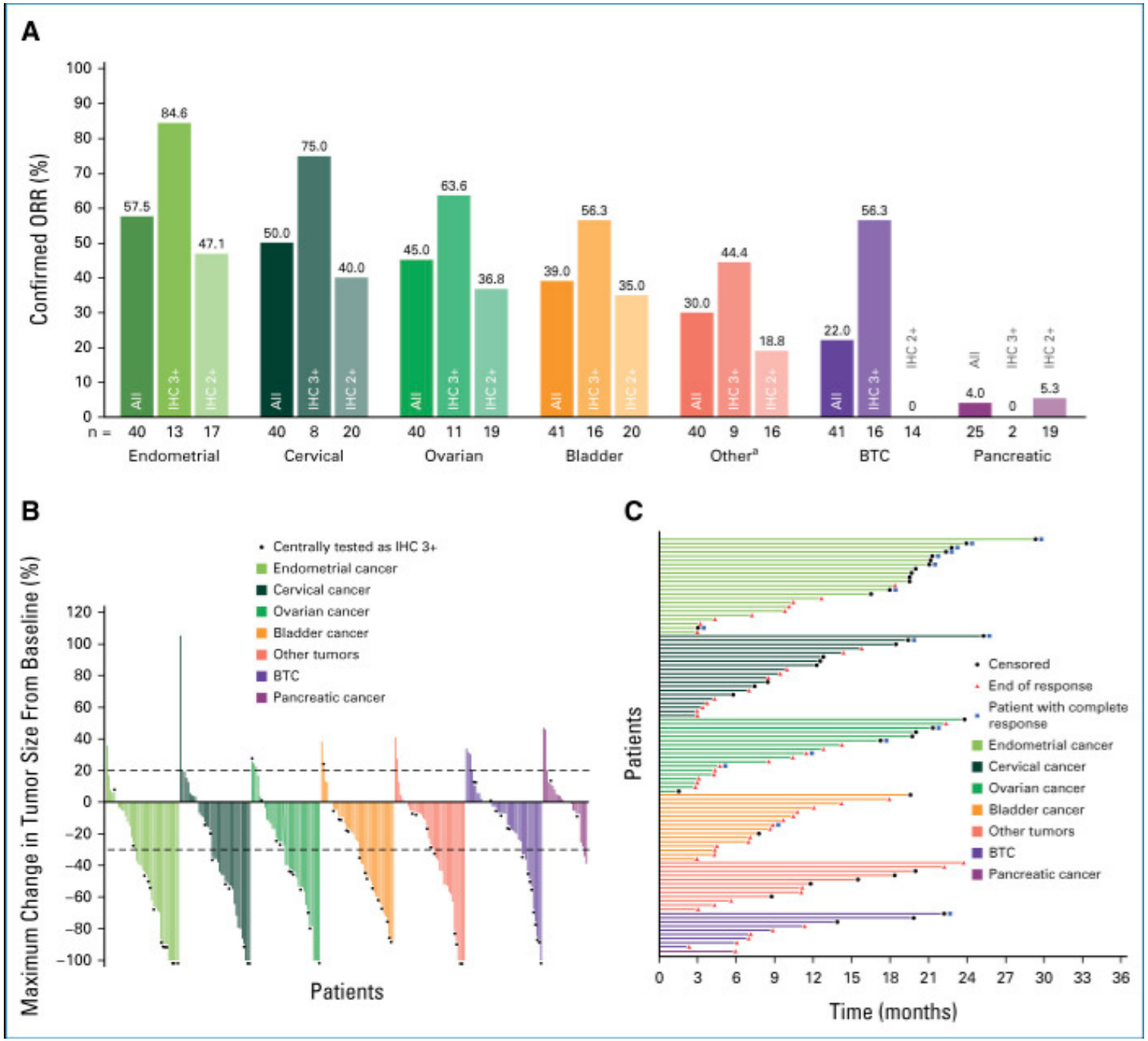
Primary analysis DCO

- June 8, 2023

- Endometrial
- Cervical
- Ovarian
- Bladder
- Other tumors¶
- Biliary tract
- Pancreatic

*Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer scoring[1]); patients were eligible for either test. All patients were centrally tested; †if ≥3 objective responses were observed in the first 15 patients in any of the tumor-specific cohorts (with IHC 3+ or 2+ confirmed by central testing), confirmed on repeat scan 4 weeks or later after first response documented, subsequent patients with IHC 1+ were also eligible for recruitment, up to a maximum of 10 patients with IHC 1+ per cohort; ‡planned recruitment; cohorts with no objective responses in the first 15 patients were to be closed; §subgroup analyses were based on central HER2 testing ¶patients with tumors that express HER2 (IHC 3+ or 2+), excluding tumors in the tumor-specific cohorts, and breast cancer, non-small cell lung cancer, gastric cancer, and colorectal cancer. 2L, second line; ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; DCO, data cutoff; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization.

1. Hofmann M, et al. *Histopathology*. 2008;52:797–805



Highest response rates seen IHC 3+

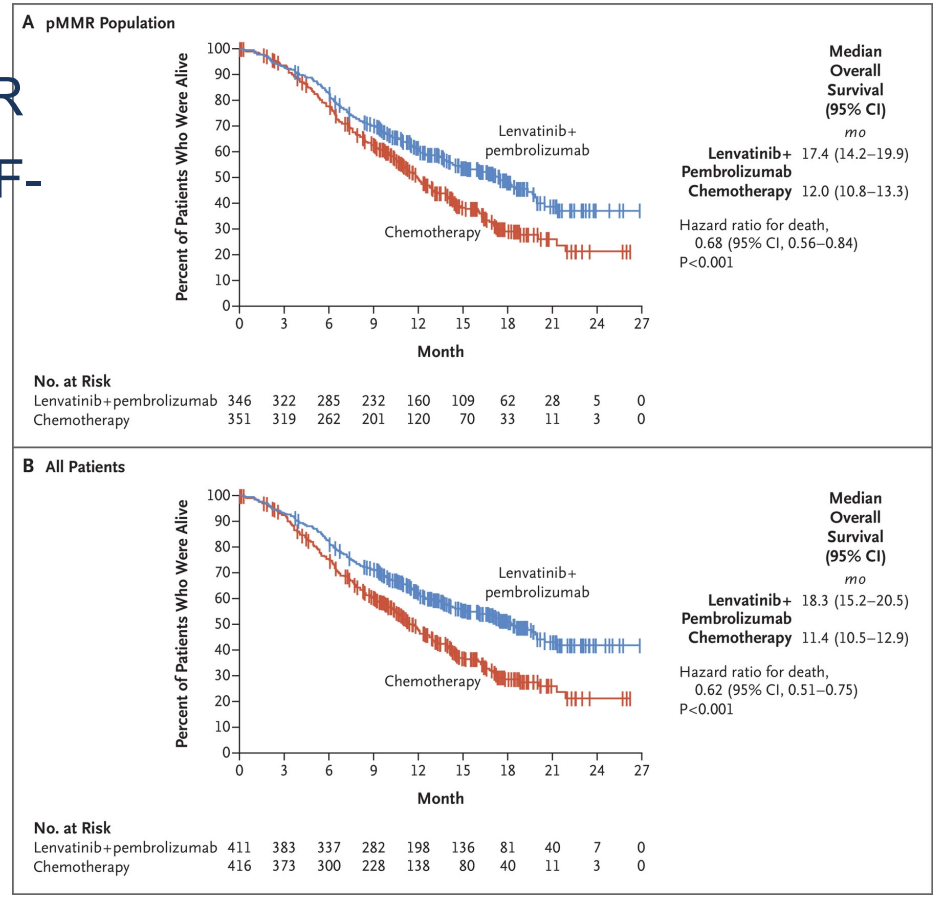
Durable responses of >12 months in all gyn histologies

Meric-Bernstam F, et al. Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial. J Clin Oncol. 2024 Jan 1;42(1):47-58

Recurrent Endometrial cancer (endometrioid and serous)

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.

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
DUO-E	III	III/IV	POLE dMMR TP53 mutant NSMP	C/T alone C/T + durvalumab C/T + Olaparib and Durvalumab	PFS Then OS
NRG GY012	II (platform)	recurrent	All welcome	Cediranib Olaparib Cediranib+olaparib	PFS

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

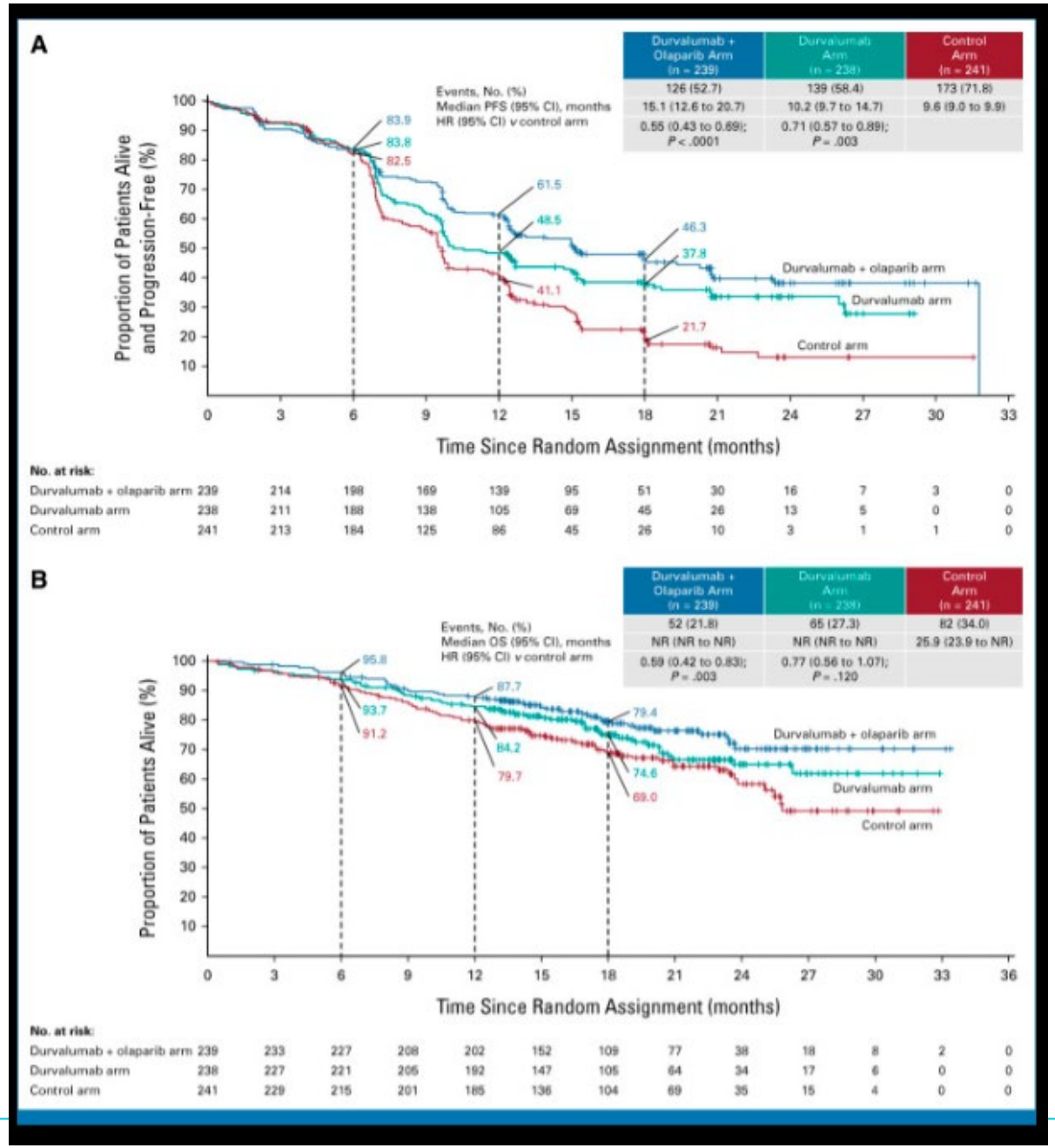
DUO-E

Stage III/IV endometrial cancer

Carbo/paclitaxel alone (control)

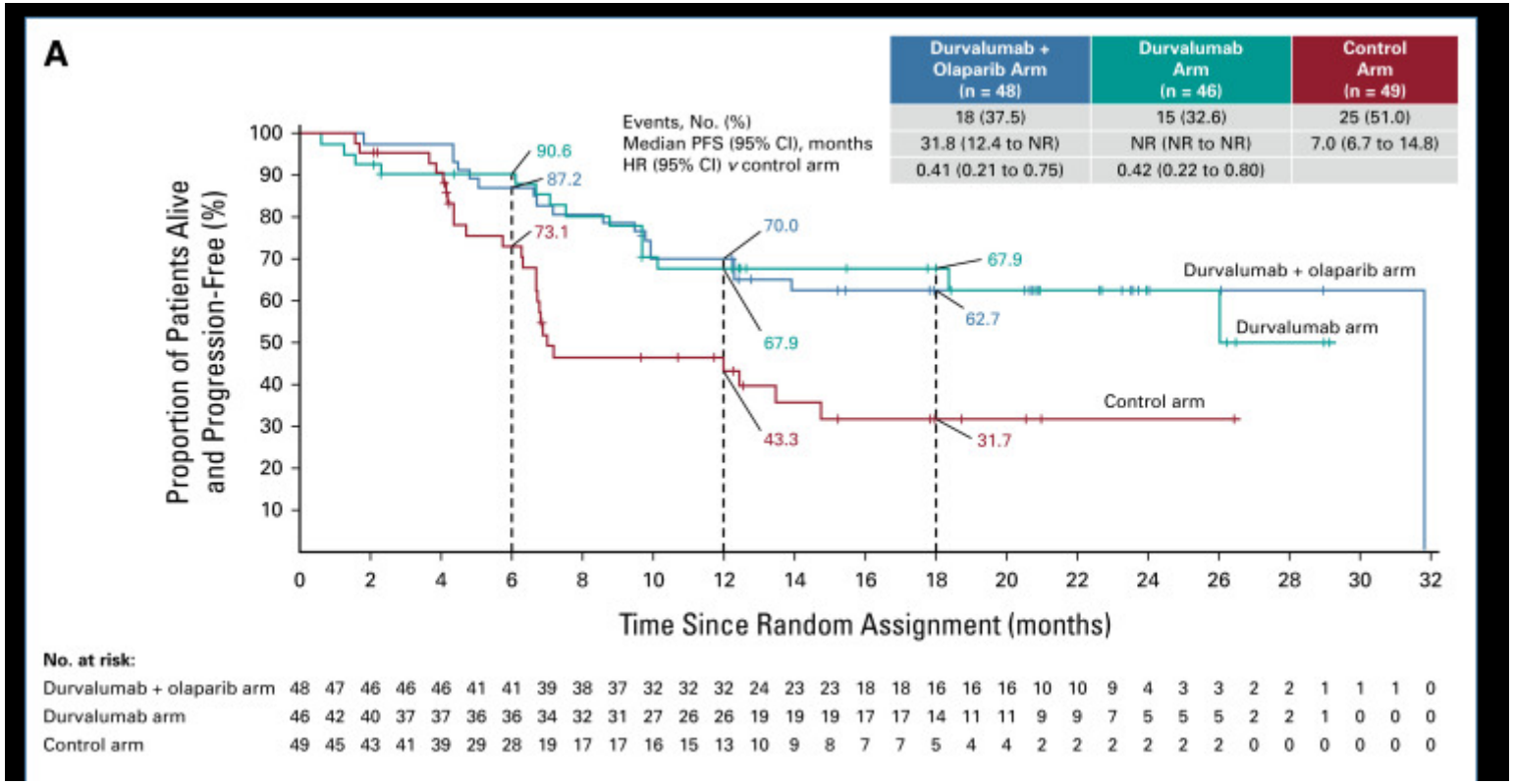
C/T +Durvalumab

CT + Olaparib +Durvalumab

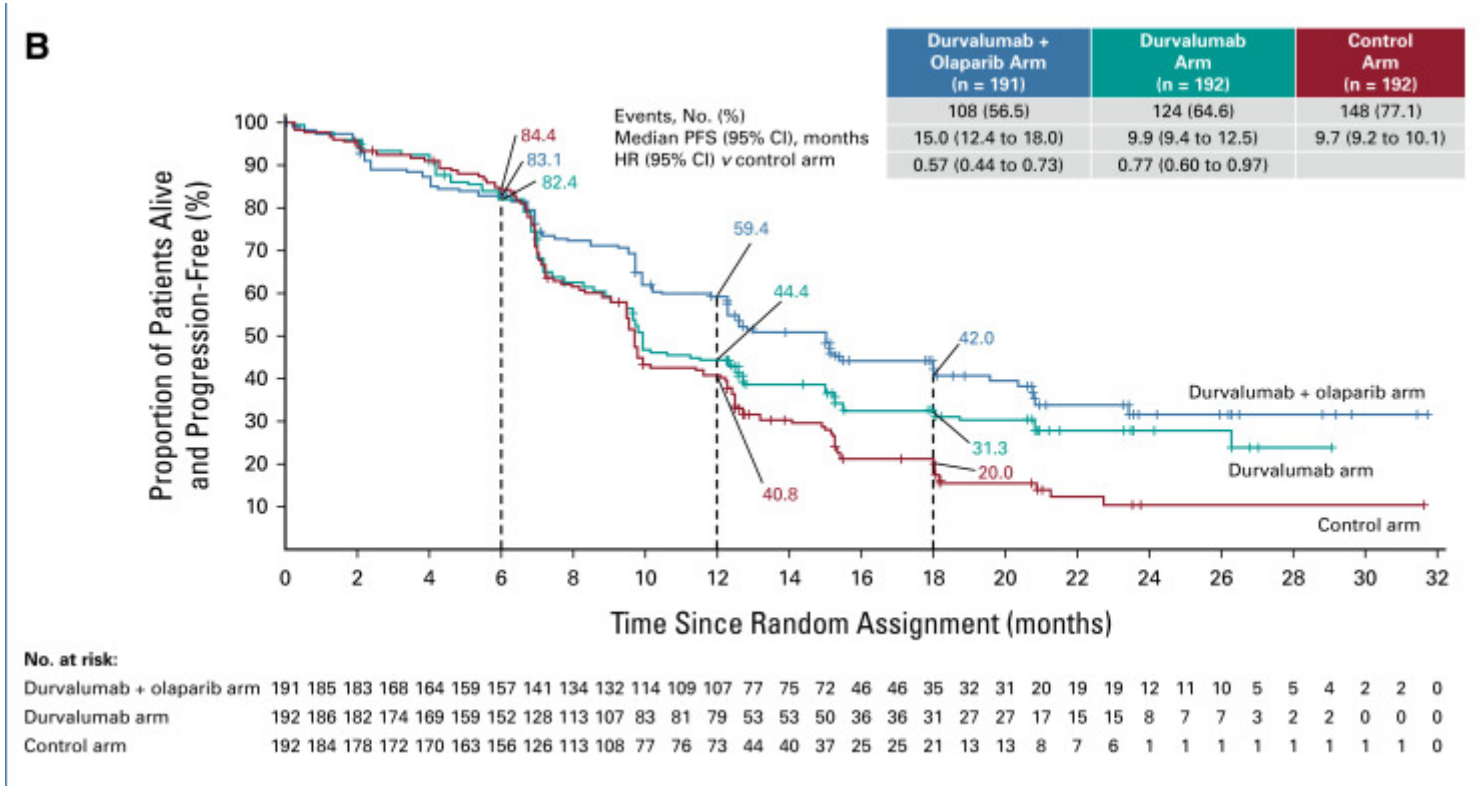


Westin SN, et al The Phase III DUO-E Trial. J Clin Oncol. 2024 Jan 20;42(3):283-299. doi: 10.1200/JCO.23.02132. Epub 2023 Oct 21.

PFS of dMMR (exploratory analysis)

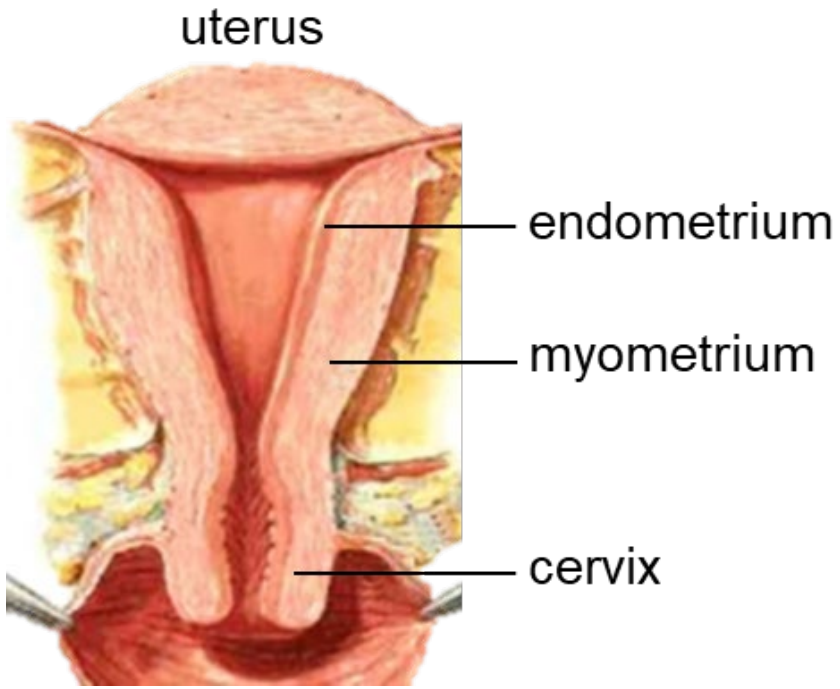


PFS pMMR


B
Durvalumab + Olaparib Arm (n = 191)
Durvalumab Arm (n = 192)
Control Arm (n = 192)
Events, No. (%)
108 (56.5)
124 (64.6)
148 (77.1)
Median PFS (95% CI), months
15.0 (12.4 to 18.0)
9.9 (9.4 to 12.5)
9.7 (9.2 to 10.1)
HR (95% CI) v control arm
0.57 (0.44 to 0.73)
0.77 (0.60 to 0.97)
Proportion of Patients Alive and Progression-Free (%)
100
90
80
70
60
50
40
30
20
10
84.4
83.1
82.4
59.4
44.4
42.0
31.3
20.0
40.8
Durvalumab + olaparib arm
Durvalumab arm
Control arm
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32
Time Since Random Assignment (months)
No. at risk:
Durvalumab + olaparib arm 191 185 183 168 164 159 157 141 134 132 114 109 107 77 75 72 46 46 35 32 31 20 19 19 12 11 10 5 5 4 2 2 0
Durvalumab arm 192 186 182 174 169 159 152 128 113 107 83 81 79 53 53 50 36 36 31 27 27 17 15 15 8 7 7 3 2 2 0 0 0
Control arm 192 184 178 172 170 163 156 126 113 108 77 76 73 44 40 37 25 25 21 13 13 8 7 6 1 1 1 1 1 1 1 1 0

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

Epidemiology

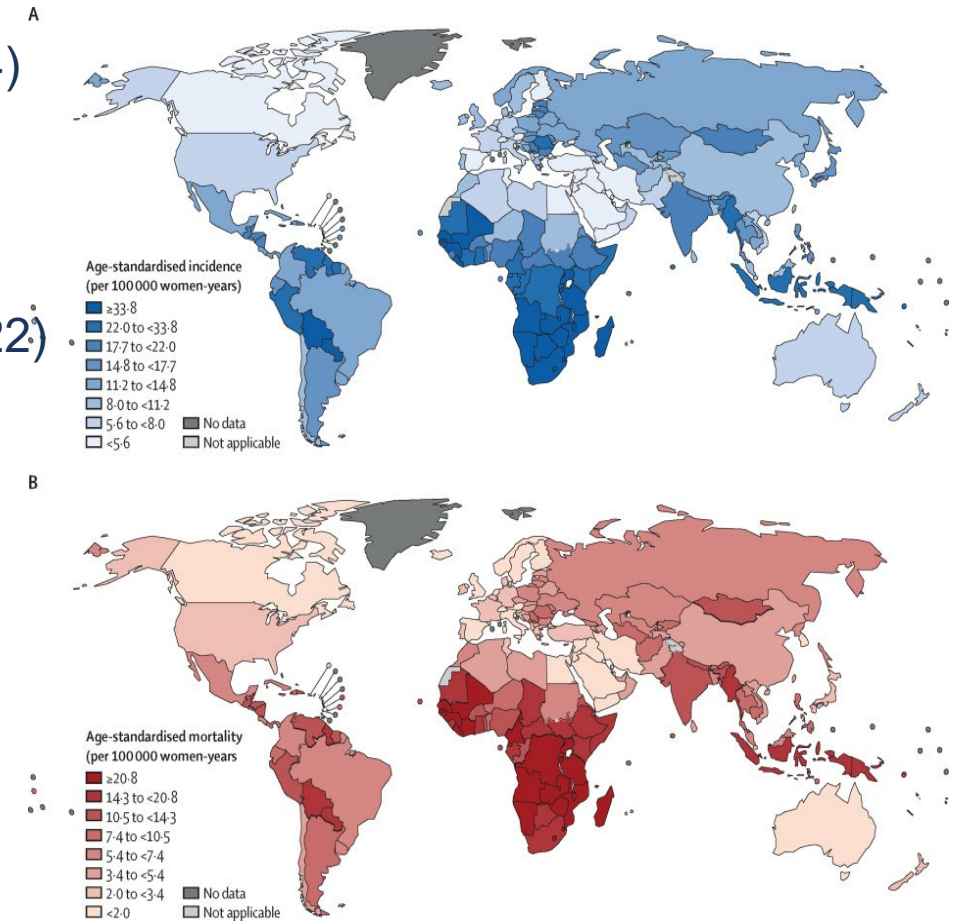
United States

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)

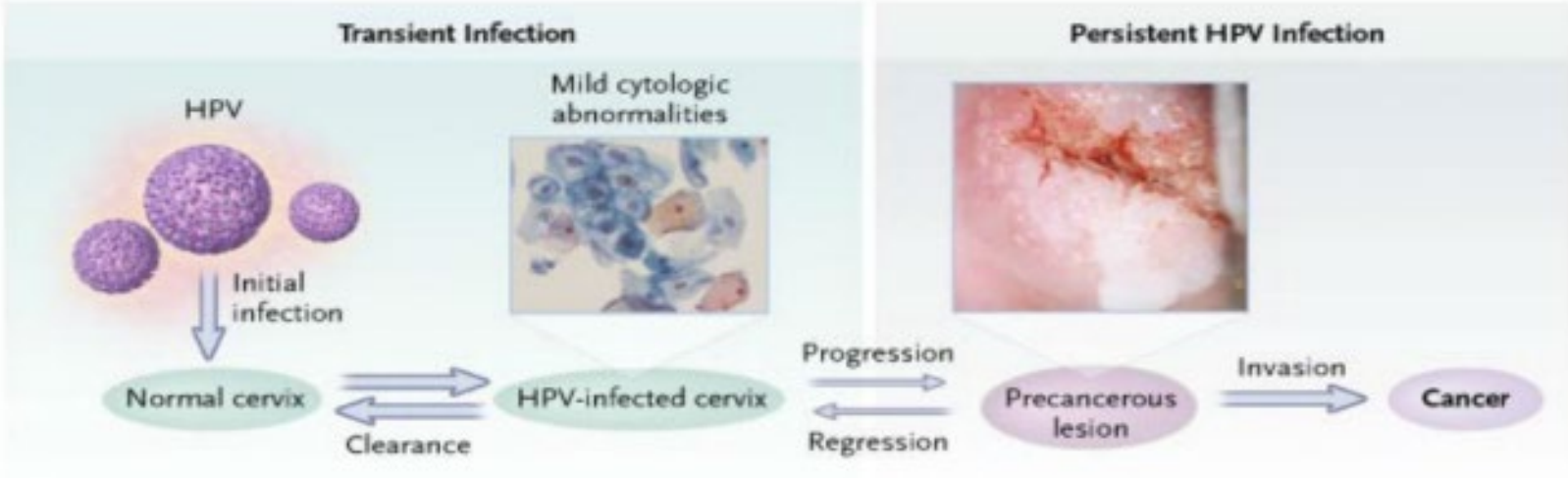
- >85% of all cases of cervical cancer occur in low-resource countries
- Significantly ↓ incidence in developed nations due to implementation of screening with Pap
- Peak incidence 40-60 years



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.

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

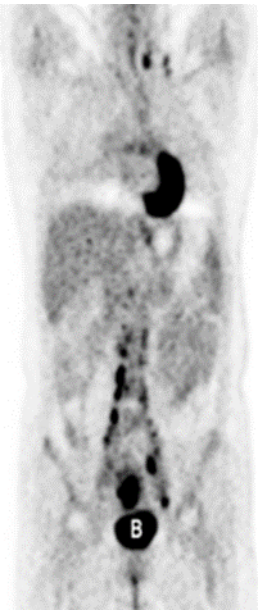
- HPV-associated endocervical adenocarcinoma (83%)
  - HPV types 18,16,45
- HPV-unassociated endocervical adenocarcinoma
  - Gastric type (10%)
  - Clear cell (3%)
  - Endometrioid (1.1%)
  - Mesonephric (0.3%)
  - Miscellaneous and not otherwise specified (2.4%)

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

Modalities of Staging

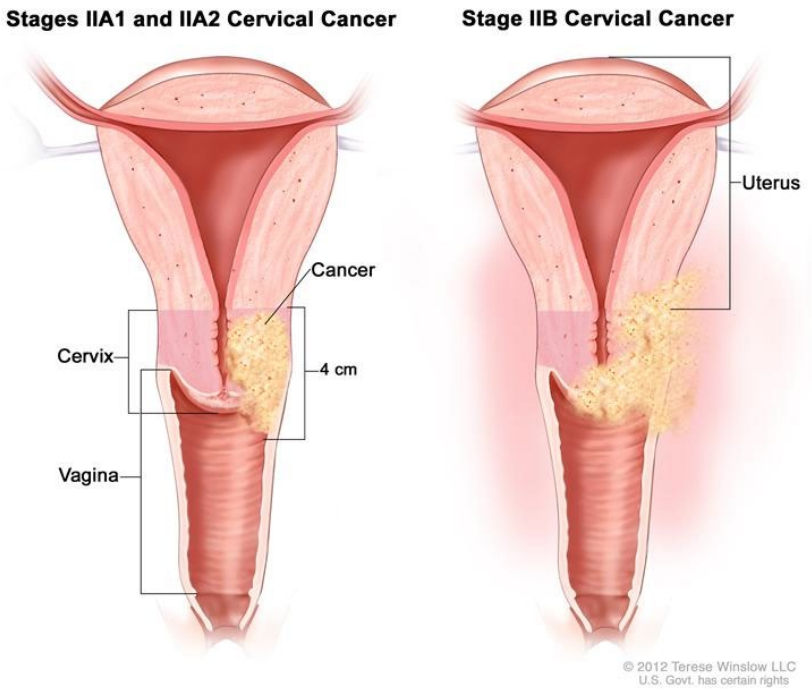
- Biopsy
- Clinical
  - Physical & pelvic exam
- Procedural/Surgical
  - Exam under anesthesia, cystoscopy, proctoscopy
  - Surgical lymph node assessment (can be done with sentinel lymph node biopsy)

- 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

Cervical Cancer
FIGO Staging 2018



Stage	Definition
IA1	
IA2	
IB1	
IB2	
IB3	Vi
IIA1	
IIA2	
IIB	
IIIA	
IIIB	
IIIC1	
IIIC2	
IVA	Bl
IVB	

Simple vs. Radical hysterectomy and sentinel vs. full lymphadenectomy

Chemoradiotherapy with cisplatin with stage IIIC can also give pembrolizumab

Platinum/taxane/bevacizumab (with pembrolizumab for CPS>1)

***

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

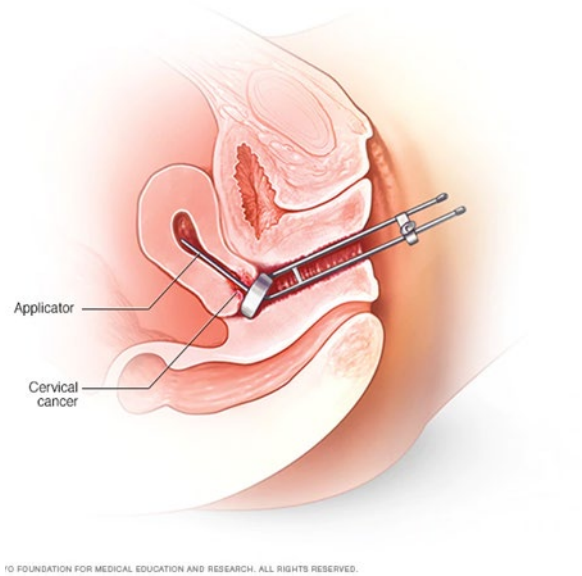
Trial	Intervention	Outcome	Citation
GOG 109	Adjuvant RT vs. CDDP-based RT	Superiority of Adjuvant ChemoRT	Peters III WA, et al. J Clin Oncol 2000;18:1606-13.
GOG 85	CDDP-based vs. HU-based RT	Superiority of ChemoRT	Whitney CW, et al. J Clin Oncol 1999;17:1339-48.
GOG 120	CDDP-based vs. HU-based RT	Superiority 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

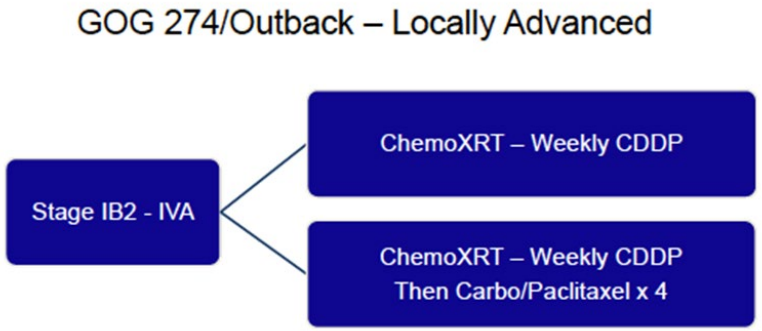
Han K et al. Int J Radiat Oncol Biol Phys 2013.
Mayadev J et al. *Gynecol Oncol* 2018.
Karlsson J et al. *Brachytherapy* 2017.

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?

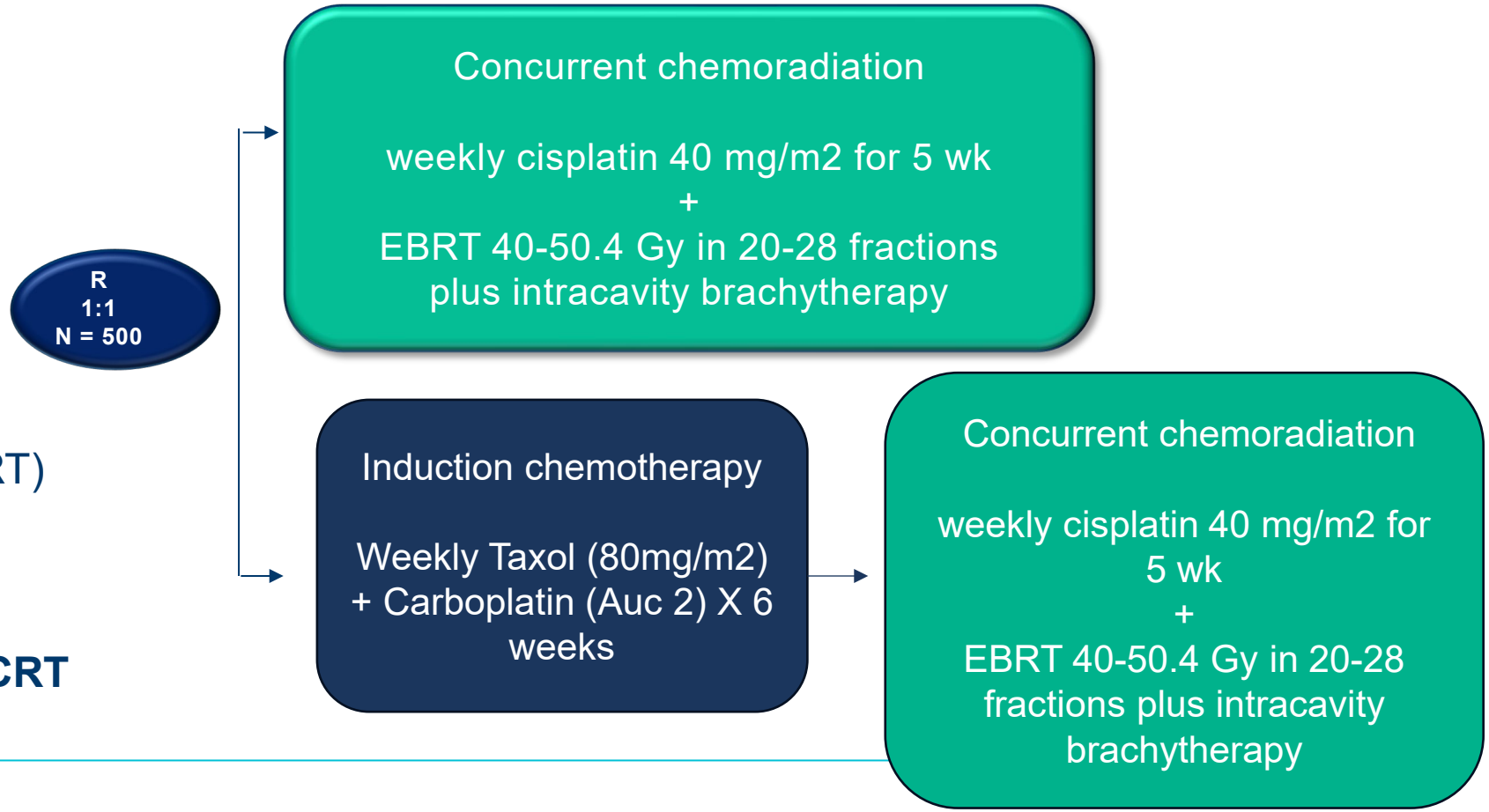
The GCIG INTERLACE Trial

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

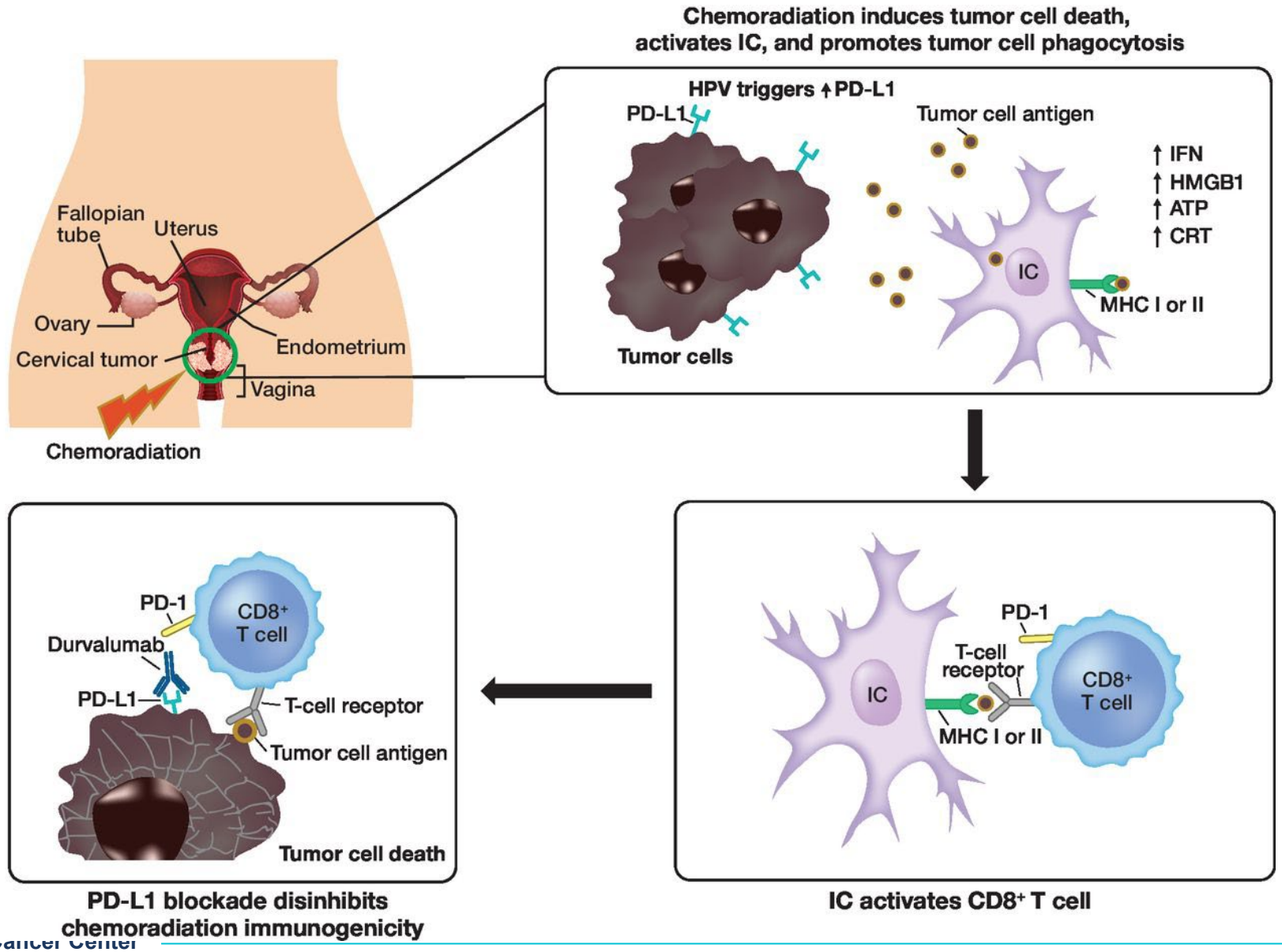
- Newly diagnosed,
- FIGO (2008) stage IB1N+, IB2, II, IIIB, IVA squamous, adeno, adenosquamous
- No prior pelvic RT
- No nodes above aortic bifurcation

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

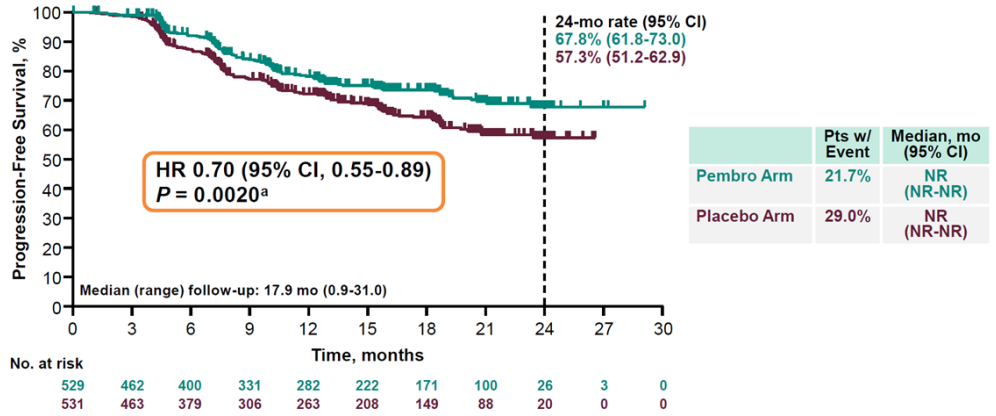
KEYNOTE A-18

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

R
1:1
N = 1060

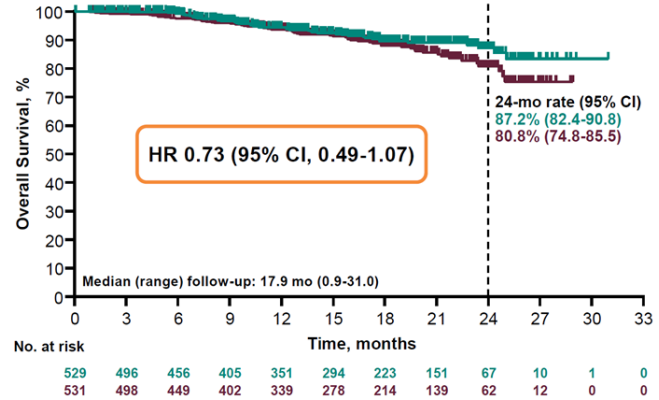
- Cisplatin/Pembrolizumab + EBRT followed by brachytherapy + Maintenance pembrolizumab 400 mg Q6W for 15 cycles
- Cisplatin/Placebo + EBRT followed by brachytherapy + Maintenance placebo Q6W for 15 cycles

PFS



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

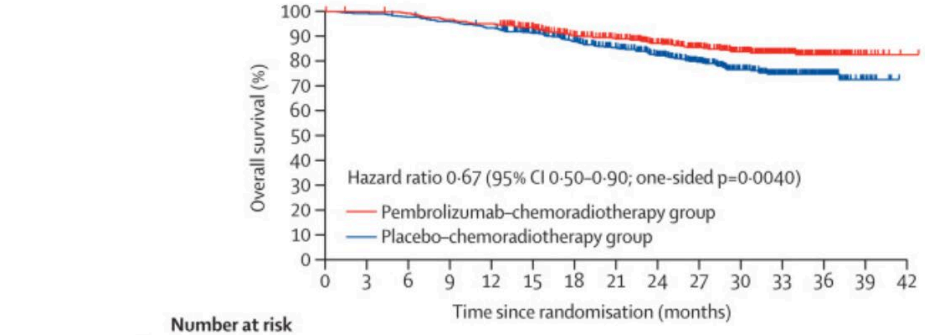
OS



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

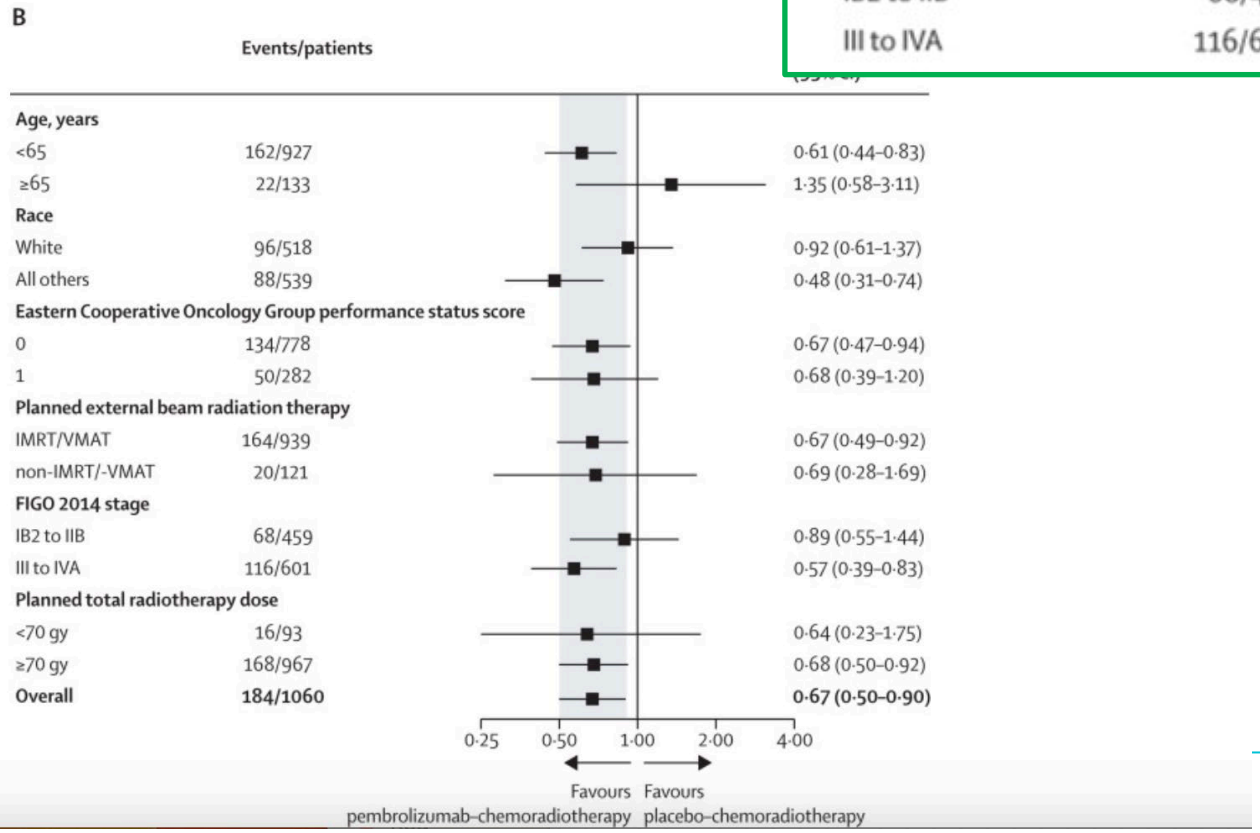
*42.9% information fraction[a]

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		

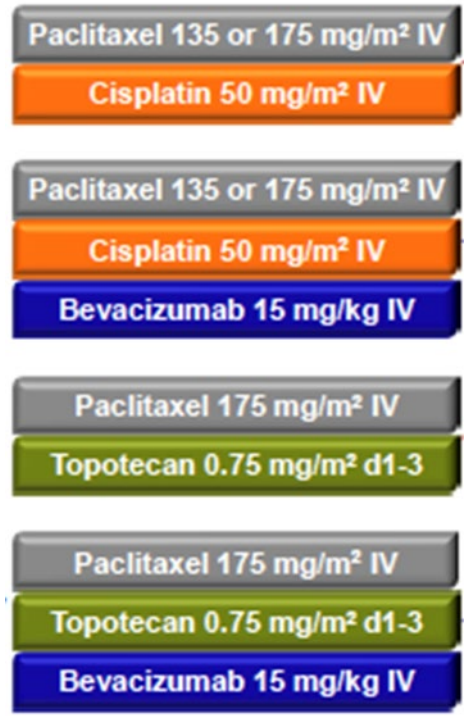
B



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

Metastatic or 1st line recurrent disease

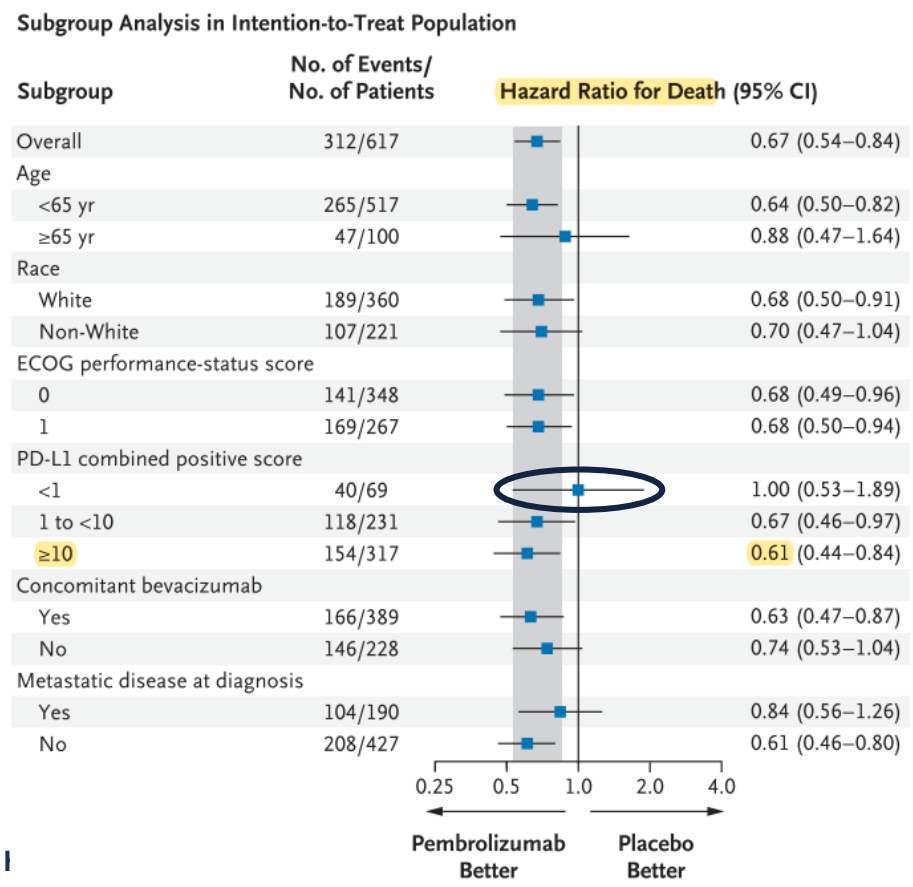
- **GOG 204**
  - Comparison of 4 cisplatin-based doublets for recurrent cervical CA
  - Favored Cis/Taxol
- **GOG 240 →**
  - No difference between chemo arms
  - Arms containing Bev associated with significant improvement in PFS, OS, ORR
- **JCOG 0505**
  - Randomized phase III trial of Cis/Taxol vs 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%)

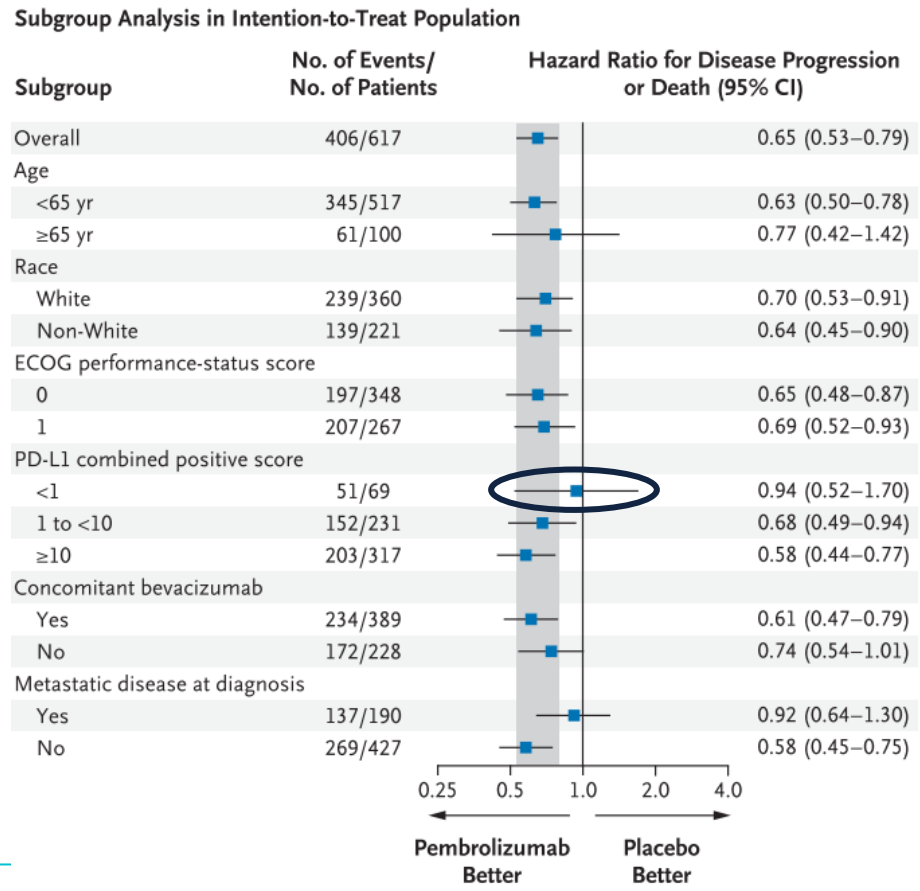


GOG 240

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

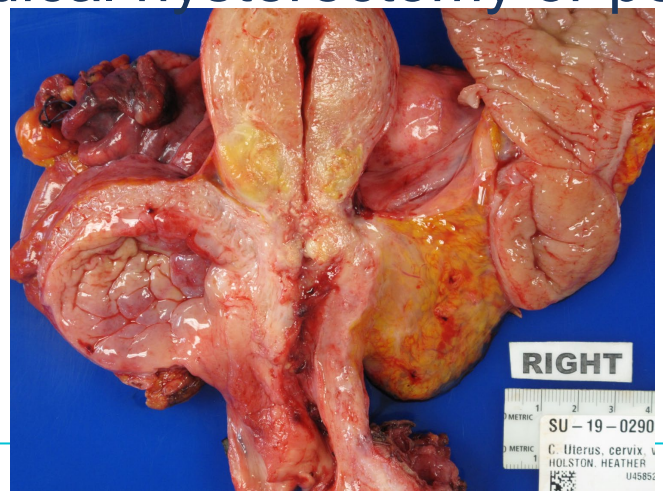
Treatment Options

- Radiation

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

- Surgery

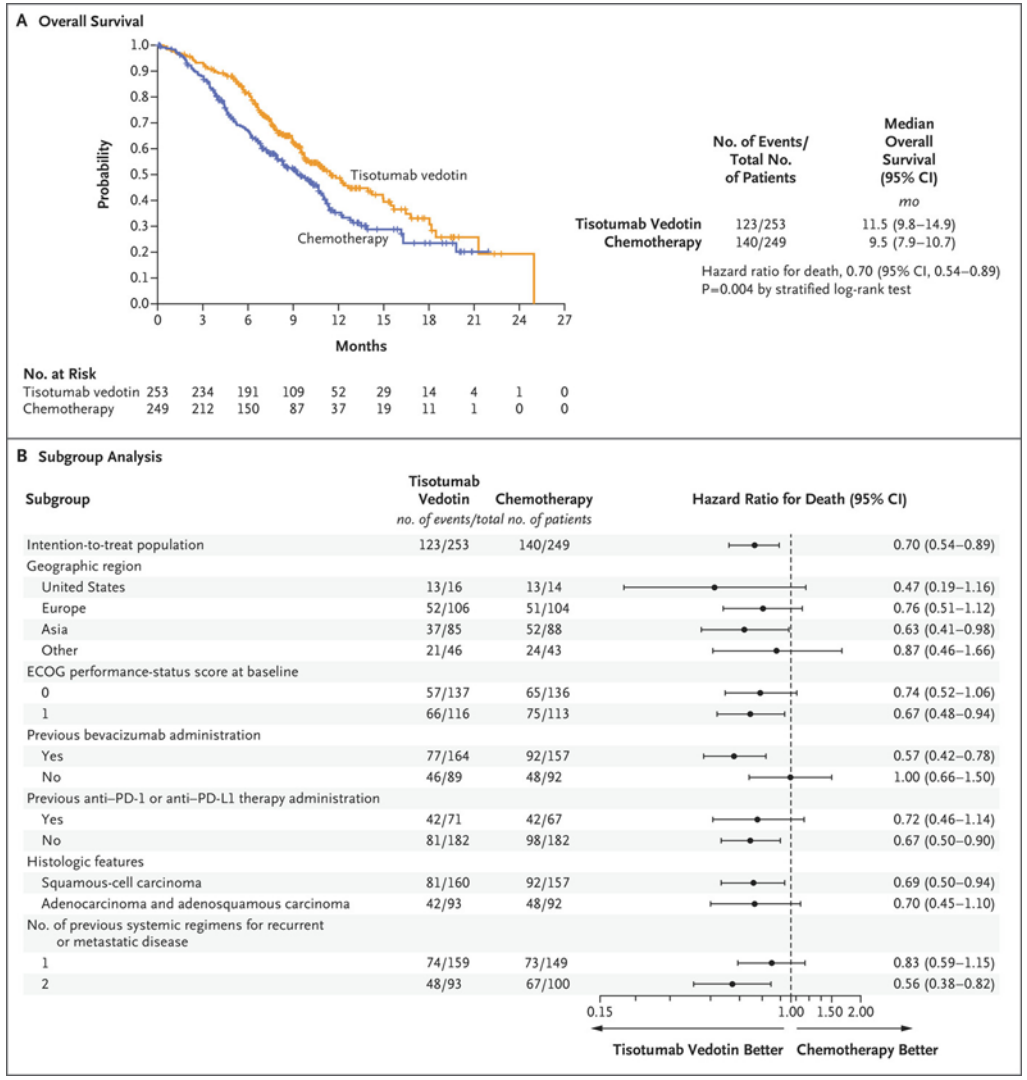
  Patients with central (i.e. pelvic/vaginal) recurrence are candidates for either radical hysterectomy or pelvic exenteration



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

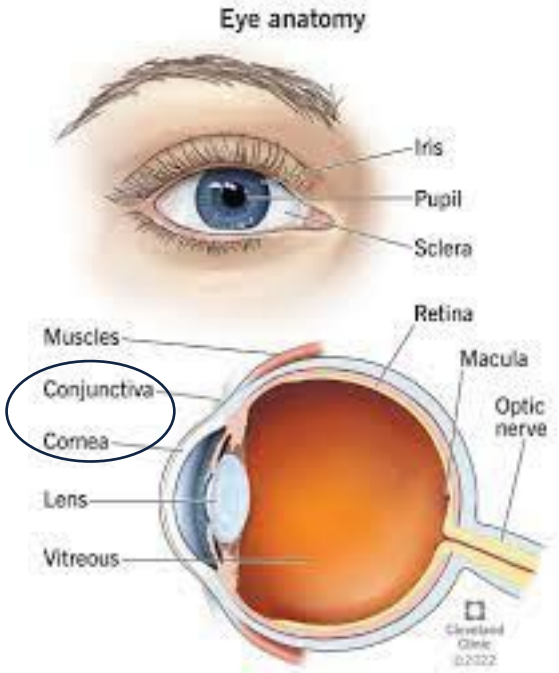
Coleman R et al. *Lancet Oncol* 2021

Tisotumab-vedotin ocular toxicities

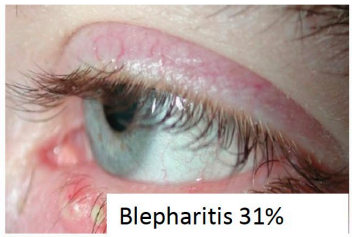
By Numbers

- 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



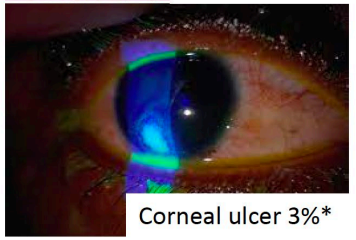

Conjunctivitis 31%


Blepharitis 31%


Symblepharon


Dry eye 25%

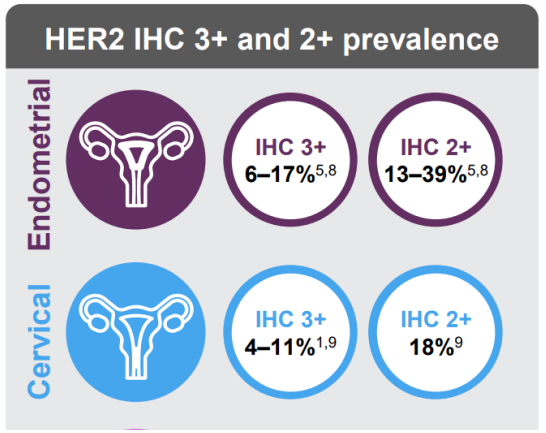

Keratitis 11%

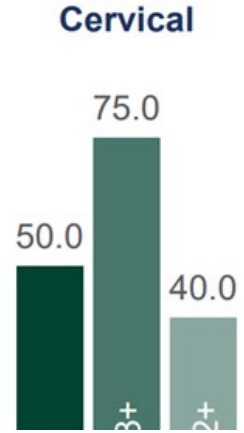

Corneal ulcer 3%*

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

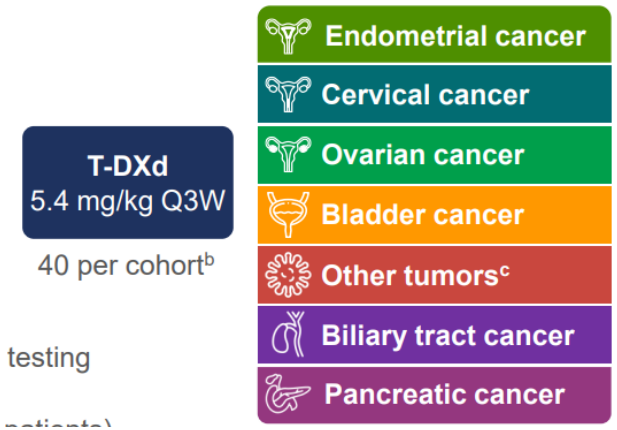
DESTINY PanTumor02: Trastuzumab Deruxtecan

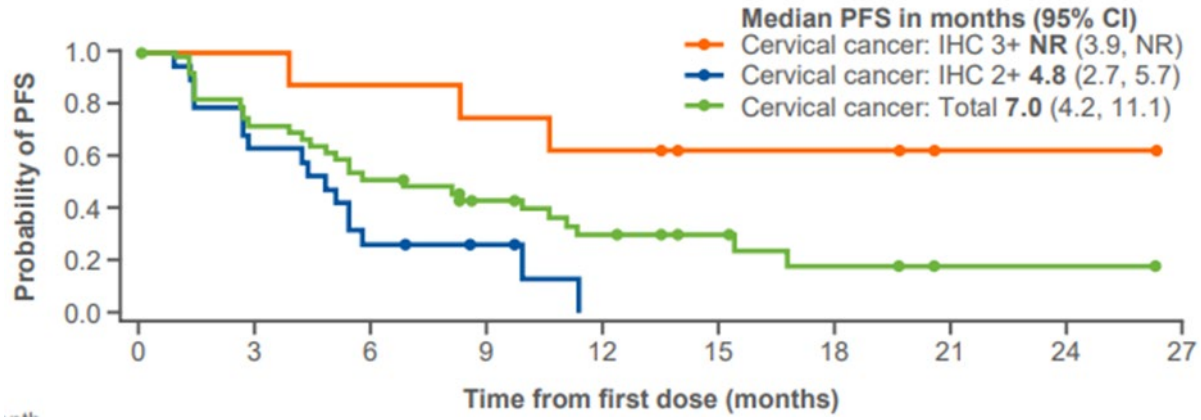
- **Key eligibility criteria**
- Locally advanced, unresectable, or metastatic solid cancers
- ≥1 prior systemic treatment
- HER2 IHC 3+ or 2+ (gastric scoring)
- ECOG PS 0-1





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 Gyn ME gic Oncology

University of ington/FHCC

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

Heidi Gray, MD

Elizabeth Swisher, MD

Kemi Doll, MD, MSCR

Elise Simons, MD

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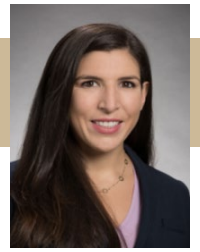

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QUESTIONS

Thank You

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