Gynecologic Oncology: What's Hot Right Now?

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LSU Health NEW ORLEANS | LCMC Health CANCER CENTER

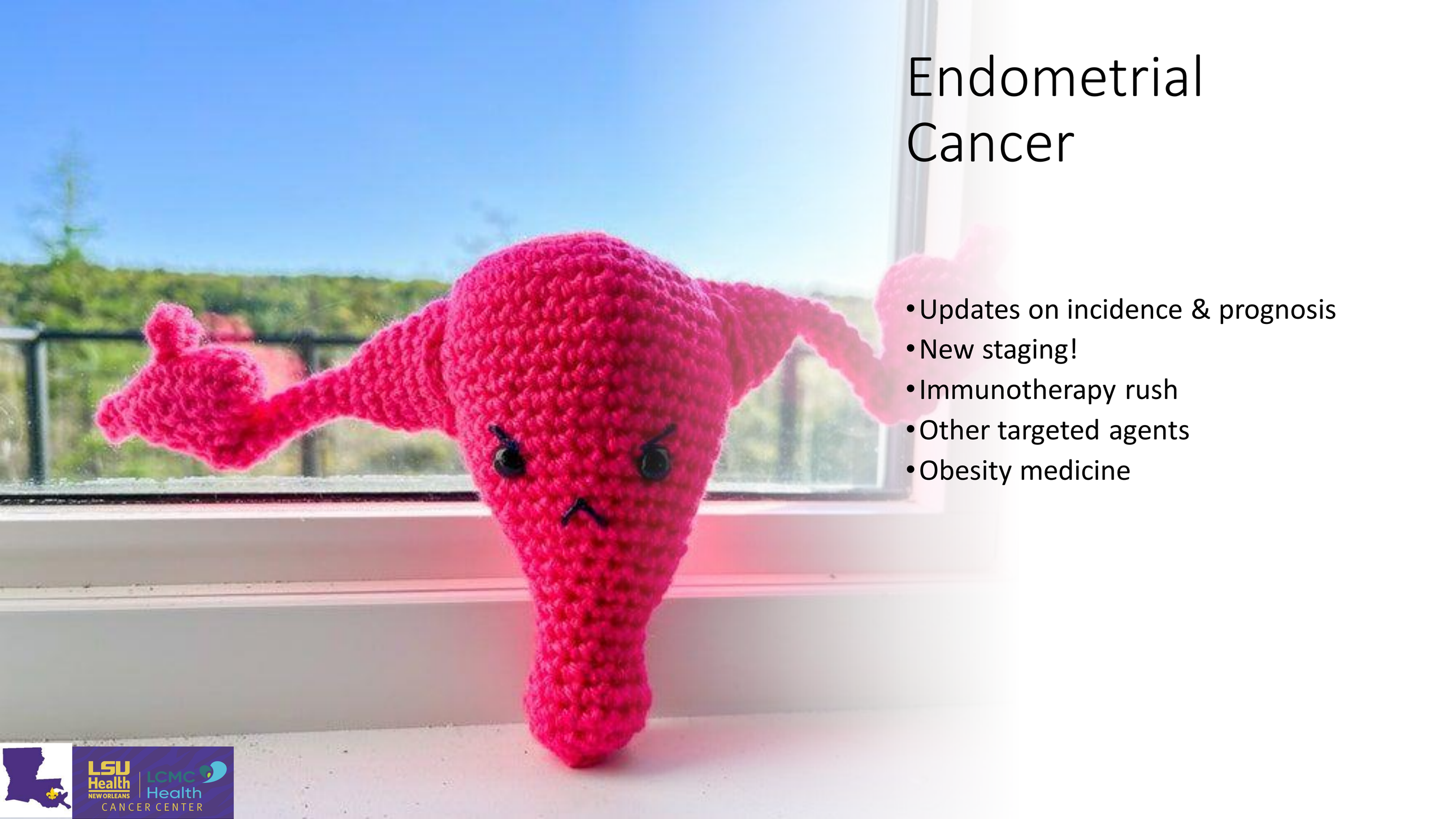
LOUISIANA ONCOLOGY SOCIETY

Disclosures

I am on the Speaker's Bureau for AstraZeneca

Objectives

- Hot new options in:
  - Endometrial cancer
  - Cervical Cancer
  - Ovarian cancer
  - Delivering more equitable care in gynecologic oncology



Endometrial Cancer

- Updates on incidence & prognosis
- New staging!
- Immunotherapy rush
- Other targeted agents
- Obesity medicine

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HEALTH

The New York Times

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Uterine Cancer Is on the Rise, Especially Among Black Women

The cancer eventually will become the third most common type among women, experts say. The mortality rate is highest among Black Americans.

Give this article

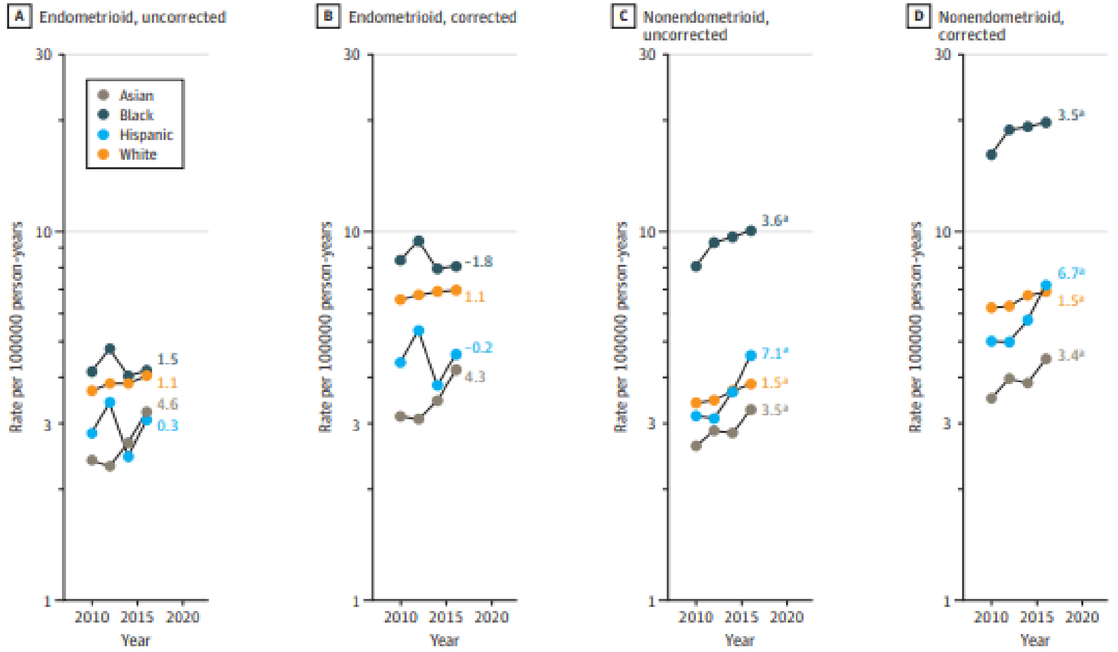
Research

JAMA Oncology | Original Investigation

Racial and Ethnic Differences in Hysterectomy-Corrected Uterine Corpus Cancer Mortality by Stage and Histologic Subtype

Megan A. Clarke, PhD, MHS; Susan S. Devesa, PhD, MHS; Anne Hammer, MD, PhD; Nicolas Wentzensen, MD, PhD, MS

Figure 3. Endometrioid and Nonendometrioid Cancer Incidence-Based Mortality Trends, From Surveillance, Epidemiology, and End Results 18 Database (2010-2017), Uncorrected and Corrected for Hysterectomy Prevalence, by Race and Ethnicity



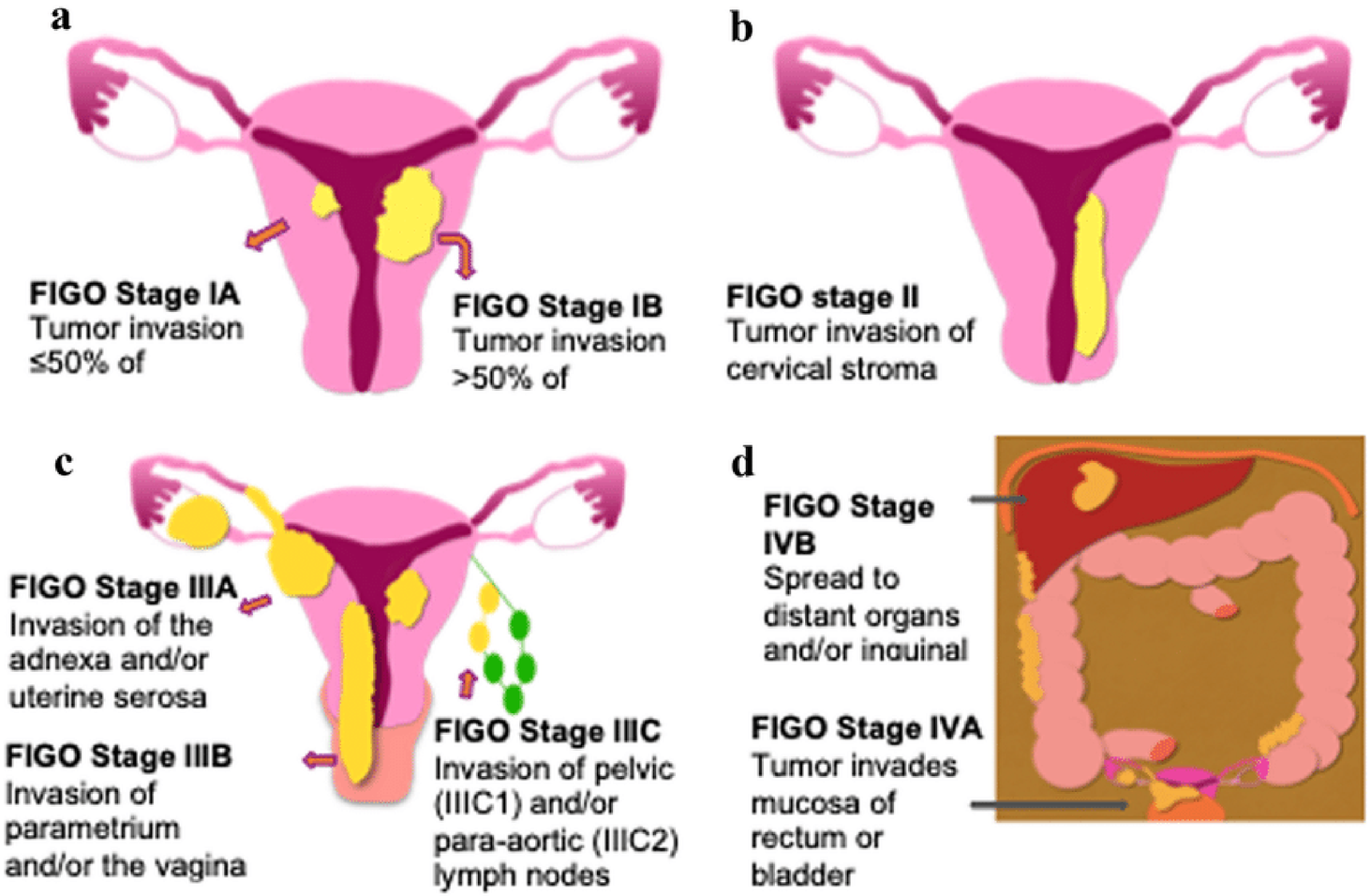
Trends in age-adjusted incidence-based mortality rates of microscopically confirmed endometrioid and nonendometrioid cancers among US women aged 40 years or older. Two-year averages of uncorrected and corrected rates are plotted. All trends are summarized by a single annual percentage change estimate based on annual rates, except for corrected rates of nonendometrioid cancers among Black women, which are summarized by the average annual percentage change (numbers reported at the end of the lines).

[a] Significantly different from 0 at $P < .05$.

Clarke M *JAMA Oncology* 2023; Rabin R *The New York Times* 2022

Setting the stage…

Stage	Description
I	Tumor confined to the uterus
IA	<50% invasion of the myometrium
IB	≥50% invasion of the myometrium
II	Tumor invades the cervical stroma but does not extend beyond the uterus
III	Local or regional spread of tumor
IIIA	Serosal or adnexal invasion
IIIB	Vaginal or parametrial involvement
IIIC	Metastasis to pelvic or paraaortic lymph nodes
IIIC1	Pelvic lymph node involvement
IIIC2	Paraaortic lymph node involvement (with or without pelvic nodes)
IV	Extension to the pelvic wall, lower one-third of the vagina, or hydronephrosis or nonfunctioning kidney
IVA	Invasion of bladder or bowel mucosa
IVB	Distant metastases, including abdominal, or involvement of inguinal lymph nodes



- Surgical staging based on anatomy of disease spread

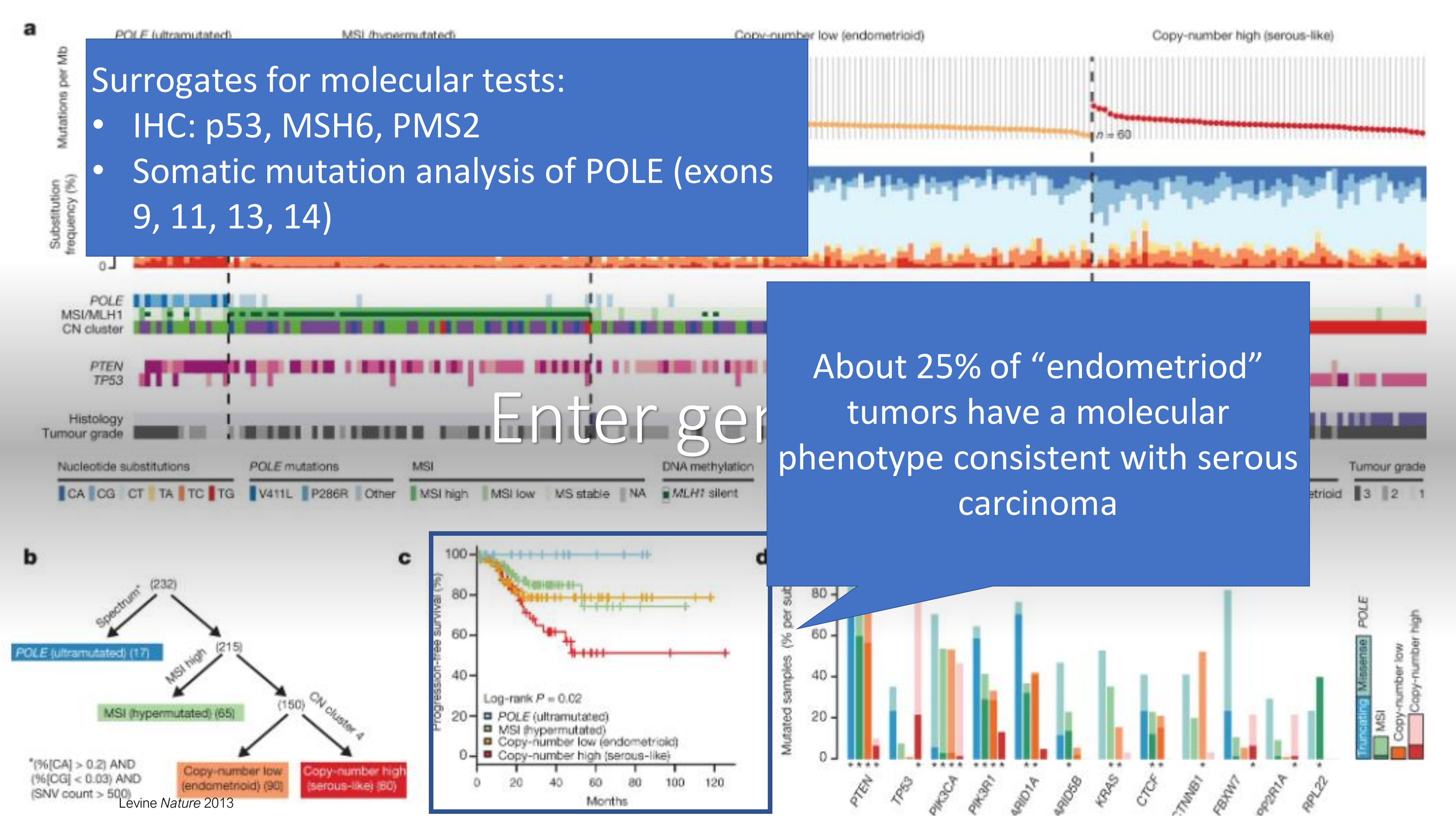
Koskas *Int J Gynaecol Obstet* 2021

Surrogates for molecular tests:

- IHC: p53, MSH6, PMS2
- Somatic mutation analysis of POLE (exons 9, 11, 13, 14)

Enter ger

About 25% of “endometriod” tumors have a molecular phenotype consistent with serous carcinoma



Levine *Nature* 2013

What's new with staging?

STAGE I

Stage I	Confined to the uterine corpus & good prognosis
• IA	Disease limited to the endometrium, OR non-aggressive histotype with invasion of less than half of myometrium with no or focal lymphovascular space involvement (LVSI), OR good prognosis disease
	IA1 Disease limited to an endometrial polyp, OR confined to the endometrium *IA2 Non-aggressive histotype involving less than half of the myometrium with no or focal LVSI* *IA3 Low-grade endometrioid carcinomas limited to the uterus and ovary **
• IB	Non-aggressive histotypes with invasion of half or more of the myometrium, and with no or focal lymphovascular space involvement (LVSI)**
Stage II	**Invasion of cervical stroma without extrauterine extension, OR substantial LVSI, OR aggressive histological types with myometrial invasion**
• IIA	Invasion of the cervical stroma
• IIB	Substantial LVSI **
• IIC	Aggressive histologic types with myometrial involvement, i.e., high-grade histologies***

- Endometrium confined vs <1/2 vs >1/2
- Ovary can be involved for IA3 (low grade)
- LVSI considered
- Histology considered
- Lymph nodes categorized as micro vs macro-metastasis

STAGE III

Stage III	Local and/or regional spread of the tumor
• 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 ** *IIIA2 Involvement of uterine subserosa or spread through the uterine serosa*
• IIIB	Metastasis or direct spread to the vagina, and/or to parametria, or to pelvic peritoneum
	IIIB1 Metastasis or direct spread to the vagina, and/or to parametria *IIIB2 Metastasis to pelvic peritoneum*
• IIIC	Metastasis to pelvic or para-aortic lymph nodes or both ****
	IIIC1 Metastasis to pelvic lymph nodes *IIIC1i Micrometastasis* *IIIC1ii Macrometastasis* *IIIC2 Metastasis to para-aortic lymph nodes, with or without metastasis to pelvic lymph nodes* *IIIC2i Micrometastasis* *IIIC2ii Macrometastasis*

STAGE IV

Stage IV	Spread to the bladder and/or intestinal mucosa and/or distant metastasis
• IVA	Invasion of the bladder, intestinal mucosa, or both
• IVB	Abdominal peritoneal metastasis/intraperitoneal carcinomatosis beyond the pelvis
• IVC	Distant metastasis, including metastasis to the inguinal lymph nodes, lungs, liver, or bone

Immunotherapy & Endometrial cancer

	Keynote-158[1]	GARNET[2]	NCT02912572[3]	PHAEDRA[4]
Treatment	Pembrolizumab	Dostarlimab	Avelumab	Durvalumab
Phase	1/2	1/2	2	2
Cohort	Previously treated dMMR-recurrent or persistent EC	Previously treated dMMR-recurrent EC	Previously treated dMMR- recurrent EC	Previously treated dMMR- recurrent EC
Patients, n	49	103	15	35
ORR, %	57	45	26	43
DCR, %	73	57	53	66
mPFS	26 mo	—	4.4 mo	—
mOS	12-mo OS= 73%	—	NR	—

National Comprehensive Cancer Network®

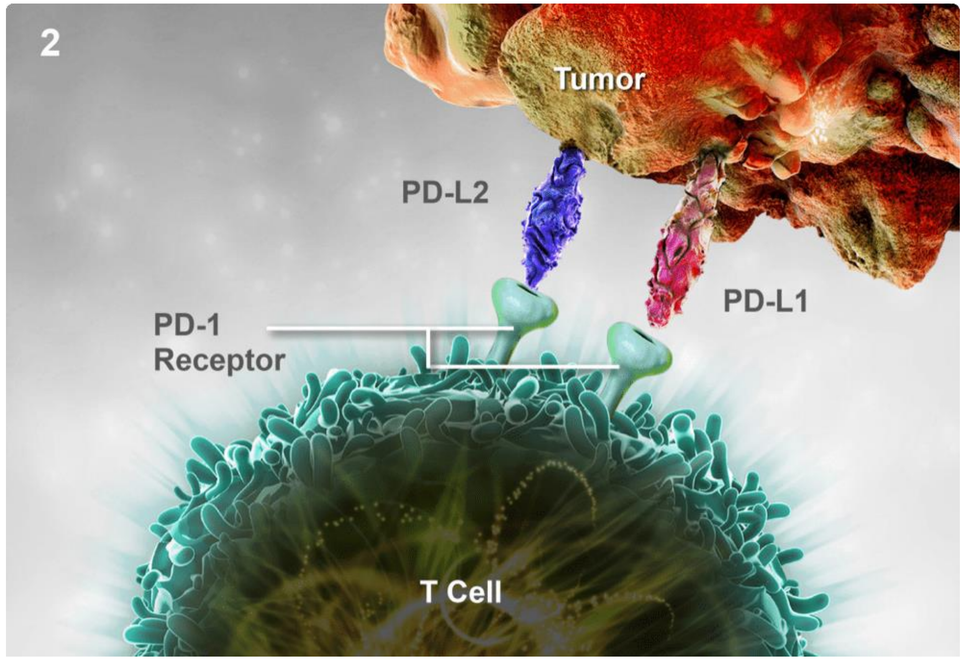
NCCN Guidelines Version 1.2023
Endometrial Carcinoma

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

Recurrent Disease[c,d]

First-Line Therapy[e]	Second-Line or Subsequent Line Therapy
Preferred • Carboplatin/paclitaxel (category 1 for carcinosarcoma)[3] • Carboplatin/paclitaxel/trastuzumab[b] (for recurrent HER2-positive uterine serous carcinoma)[a,4] • Carboplatin/paclitaxel/trastuzumab[b] (category 2B for HER2-positive carcinosarcoma)[a,4] **Other Recommended Regimens** • Carboplatin/docetaxel[f] • Carboplatin/paclitaxel/bevacizumab[g,h,5,6] **Useful in Certain Circumstances (Biomarker directed: after prior systemic therapy)** • Lenvatinib/pembrolizumab (category 1) for mismatch repair proficient (pMMR) tumors[i,j,7] • Pembrolizumab[j] (category 1) for TMB-H[k,8] or MSI-H/dMMR[l] tumors[9]	**Other Recommended Regimens** • Cisplatin/doxorubicin[10] • Cisplatin/doxorubicin/paclitaxel[g,m,10] • Cisplatin • Carboplatin • Doxorubicin • Liposomal doxorubicin • Paclitaxel[11] • Albumin-bound paclitaxel[n] • Topotecan • Bevacizumab[h,o,12] • Temsirolimus[13] • Cabozantinib • Docetaxel[f] (category 2B) • Ifosfamide (for carcinosarcoma) • Ifosfamide/paclitaxel (for carcinosarcoma)[14] • Cisplatin/ifosfamide (for carcinosarcoma) **Useful in Certain Circumstances (Biomarker directed: after prior systemic therapy)** • Lenvatinib/pembrolizumab (category 1) for mismatch repair proficient (pMMR) tumors[j,7] • Pembrolizumab[j] (category 1) for TMB-H[k,8] or MSI-H/dMMR tumors[l,9] • Dostarlimab-gxly for dMMR/MSI-H tumors (category 1)[j,p,15] • Larotrectinib or entrectinib for NTRK gene fusion-positive tumors (category 2B)[g] • Avelumab for dMMR/MSI-H tumors[j] • Nivolumab for dMMR/MSI-H tumors[j,16]



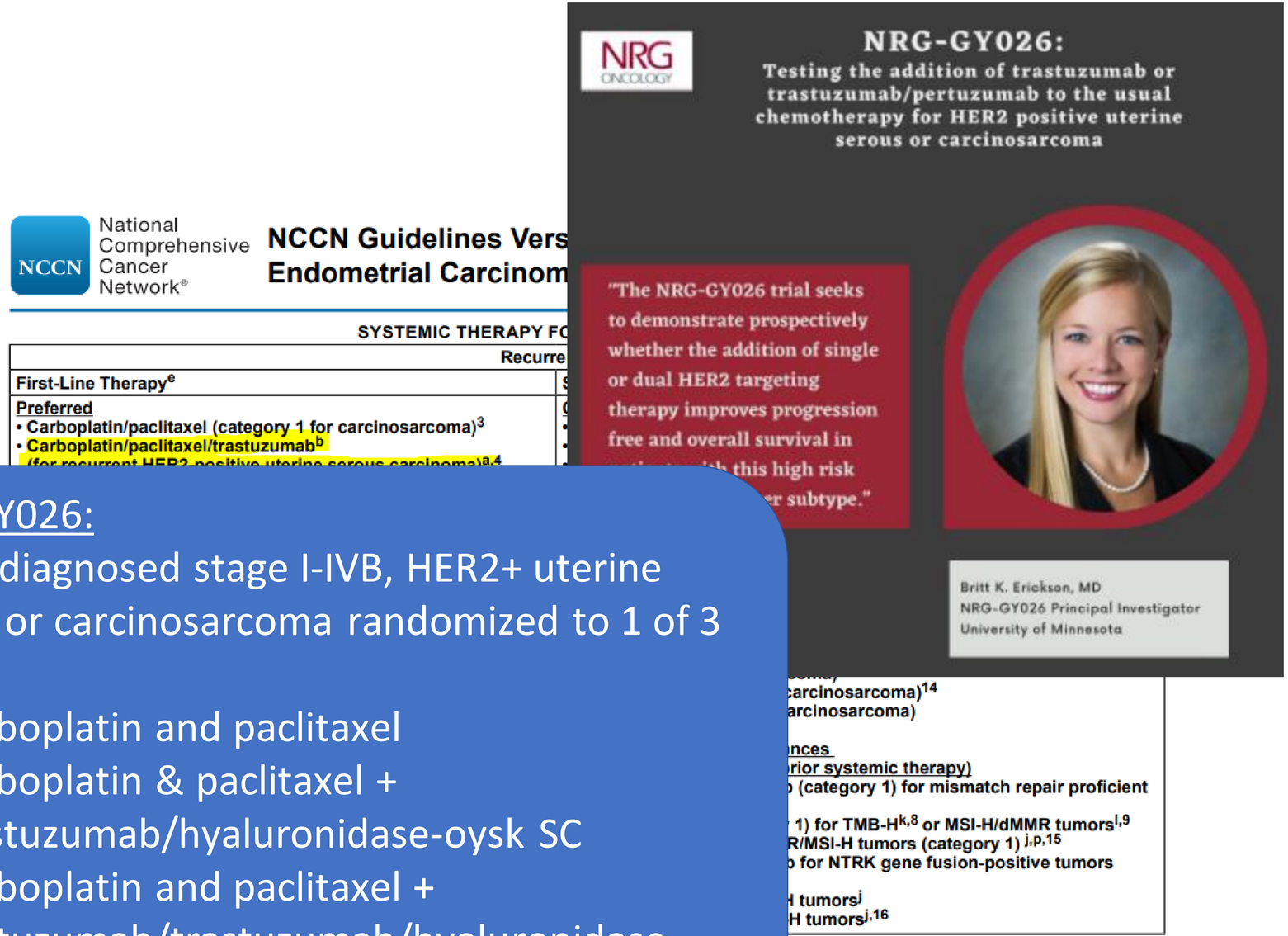
NCCN 1.2023 Endometrial Carcinoma; O'Malley *ESMO* 2019; Konstantinopoulos *JCO* 2019; Makker *NEJM* 2022

Can we bring immunotherapy in earlier and combine with other treatments?

- NRG GY020: Pelvic or vaginal radiation +/- pembrolizumab for dMMR HIR stage I/II endometroid adenocarcinoma
- NRG GY018: Carboplatin and paclitaxel +/- pembrolizumab for stage III-IV or recurrent endometrial cancer

HER2 therapy…. Are you SEROUS?

- Strong Phase II Data supports addition of Herceptin to a carboplatin and paclitaxel backbone for high grade serous cancers.
- Can we build on that?



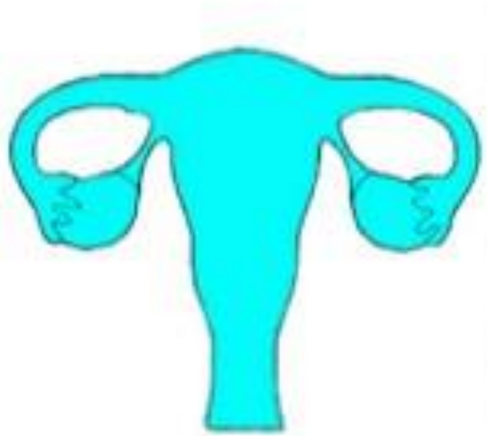
NRG GY026:

Newly diagnosed stage I-IVB, HER2+ uterine serous or carcinosarcoma randomized to 1 of 3 arms:

- Carboplatin and paclitaxel
- Carboplatin & paclitaxel + trastuzumab/hyaluronidase-oysk SC
- Carboplatin and paclitaxel + pertuzumab/trastuzumab/hyaluronidase-zzxf SC

Fader AN *Clin Cancer Res* 2020

Cervical Cancer

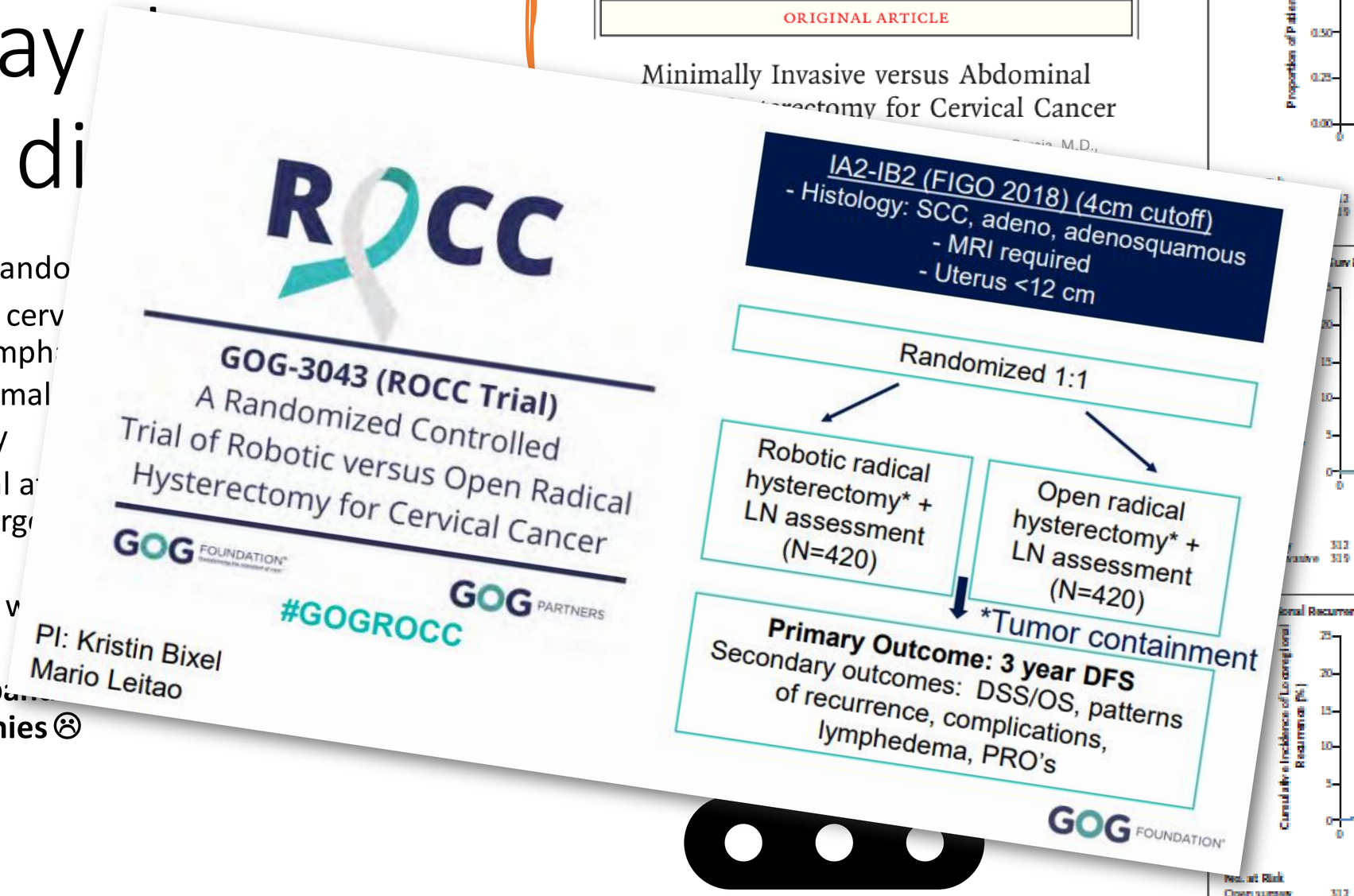


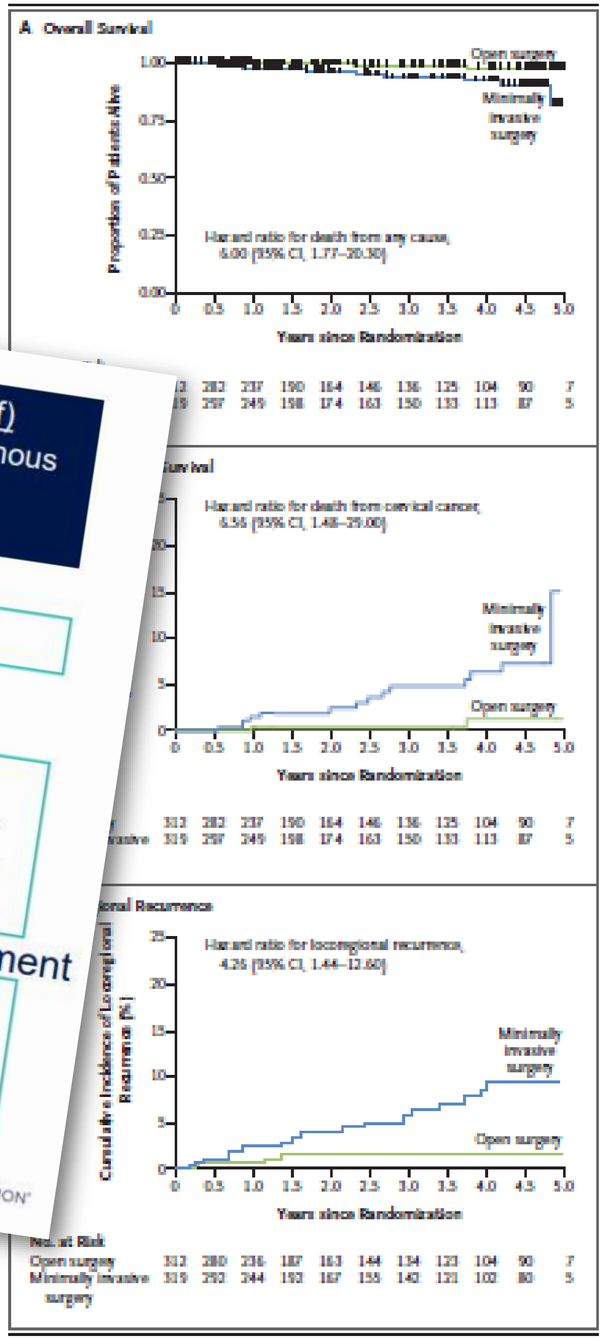
At Your Cervix

- The role of minimally invasive surgery
- Immunotherapy rush!
- Antibody Drug Conjugates

The day robot di

- Multi-institutional rando
- Stage IA1 +LVSI, IB1 cerv hysterectomy nd lymph
  - 319 women minimal
  - 312 open surgery
- Disease free survival a 96.5% with open surg or death was 3.74
- MIS also associated w 99%), HR 6.00
- **Many of us have aba radical hysterectomies ☹**





Ramirez *NEJM* 2018

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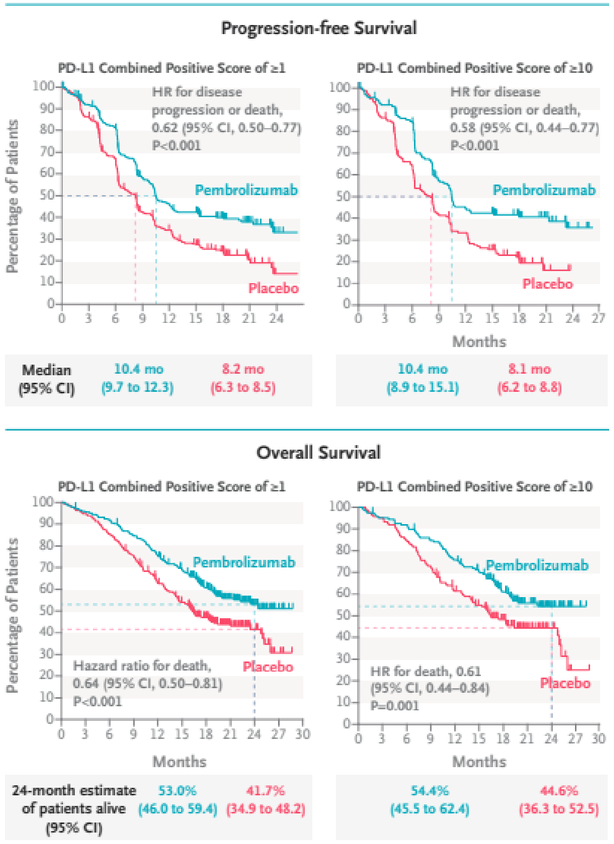

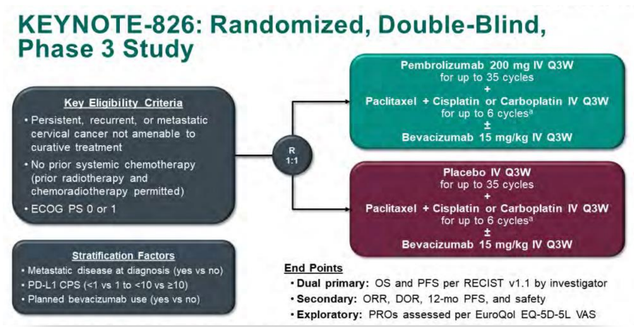

Immunotherapy is KEY ☺

- Pembrolizumab added to platinum based chemotherapy with or without bevacizumab prolonged PFS and OS in patients with persistent, recurrent or metastatic cervical cancer.
- The pembrolizumab arm also had improved QOL/PROs

Colombo *NEJM* 2021; Monk SGO 2022

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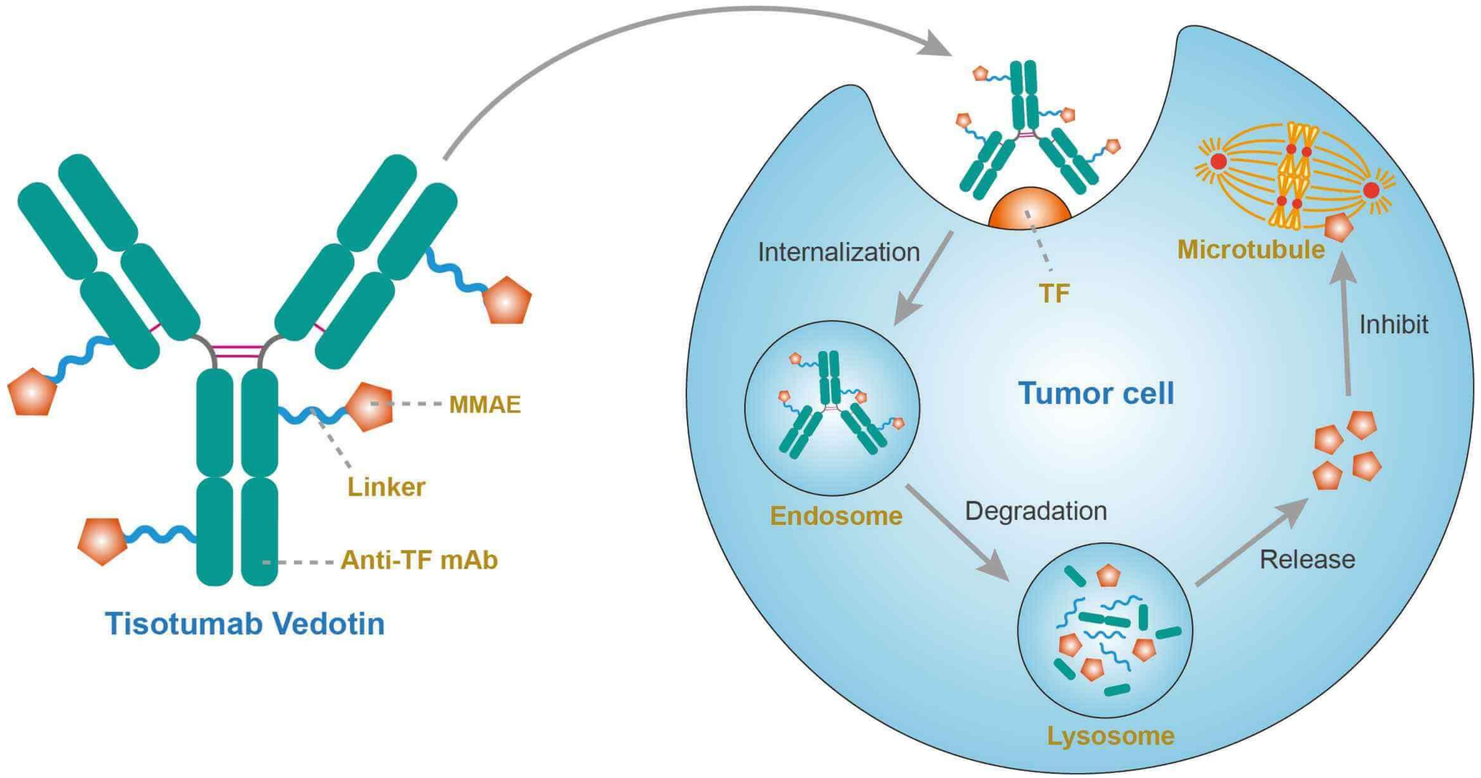
Tisotumab Vedotin

- innovaTV204/GOG-3023/ENGOT-cx6
  - Multicentre open-label single arm phase 2 study of metastatic or recurrent cervical cancer
  - 2.0 mg/kg of tisotumab vedotin IV every 3 weeks
  - Primary endpoint ORR: 24%
    - 7% CR, 17% PR
  - Adverse events: neutropenia, fatigue, ulcerative keratitis, peripheral neuropathy



TV binds TF on cancer cell

Internalization of ADC

Release of MMAE

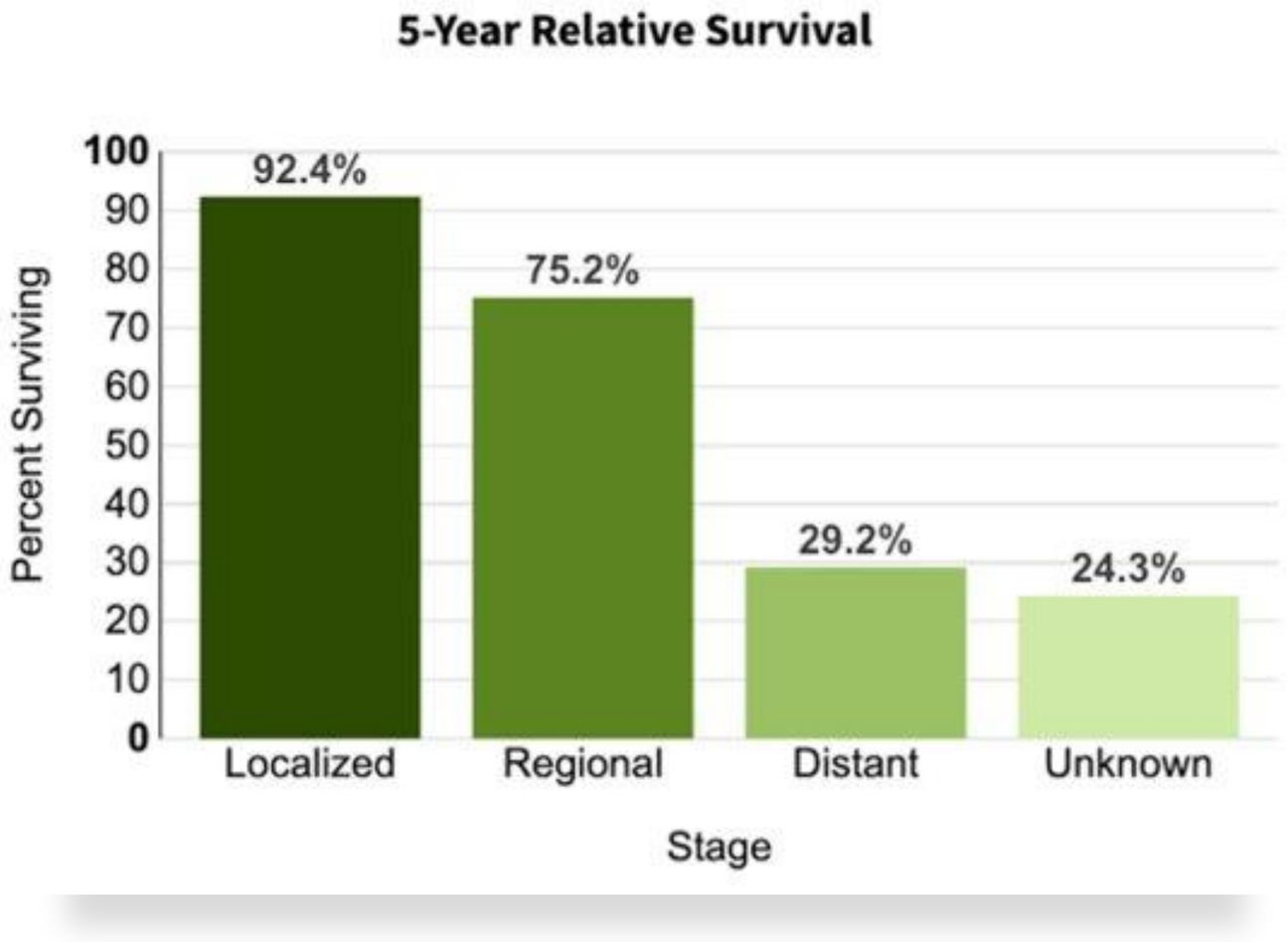
Microtubule disruption

Cancer cell death

Coleman *Lancet Oncol* 2021

Ovarian cancer

- Hyperthermic Intraperitoneal Chemotherapy (HIPEC)
- New approaches to platinum resistant disease
- Parp inhibitors
- Rare tumors (low grade serous)

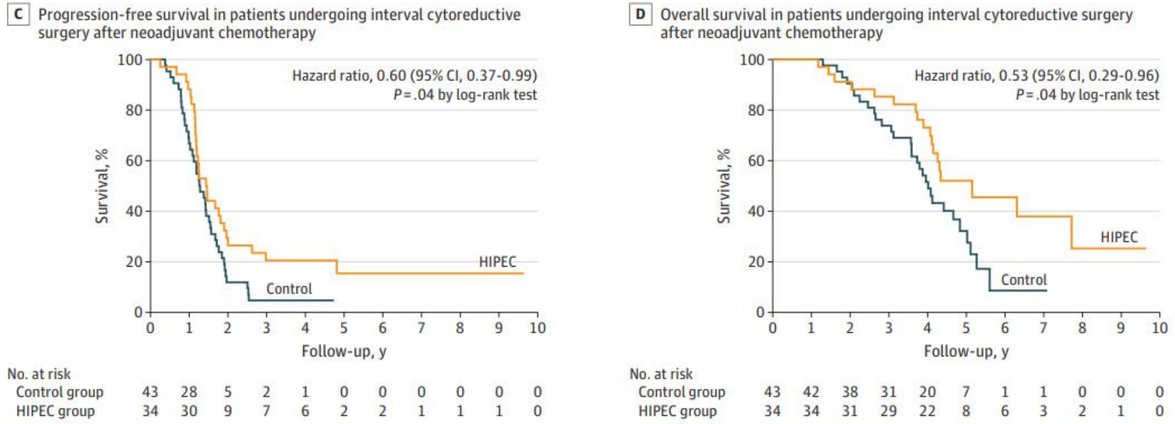


SEER.cancer.gov

Advanced Epithelial Ovarian Cancer has a poor prognosis

- 70% present advanced stage
- >80% have a complete response to primary platinum-based therapy
- However most develop chemoresistance and recurrence
- Survival for advanced stage disease is poor

When they go Low, we go HIPEC!



JAMA Surgery | Original Investigation

Survival After Hyperthermic Intraperitoneal Chemotherapy and Primary or Interval Cytoreductive Surgery in Ovarian Cancer
A Randomized Clinical Trial

Myong Cheol Lim, MD, PhD; Suk-Joon Chang, MD, PhD; Boram Park, PhD; Heon Jong Yoo, MD, PhD; Chong Woo Yoo, MD, PhD; Byung Ho Nam, PhD; Sang-Yoon Park, MD, PhD; for the HIPEC for Ovarian Cancer Collaborators

- The addition of HIPEC To interval cytoreductive surgery resulted in improvement in PFS (15.4 vs 17.4 months) and OS (48.2 vs 61.8 months)
- No improvement at the time of primary cytoreductive surgery.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer

W.J. van Driel, S.N. Koole, K. Sikorska, J.H. Schagen van Leeuwen, H.W.R. Schreuder, R.H.M. Hermans, I.H.J.T. de Hingh, J. van der Velden, H.J. Arts, L.F.A.G. Massuger, A.G.J. Aalbers, V.J. Verwaal, J.M. Kieffer, K.K. Van de Vijver, H. van Tinteren, N.K. Aaronson, and G.S. Sonke

- Median RFS 10.7 vs 14.2 months (primary endpoint)
- Median OS 33.9 vs 45.7 months
- G3-4 events 25% vs 27%
- Study enrolled from 2007 – 2016

(prior European clinical trials of Interval CRS put PFS at about 12 months and OS at about 30 months)

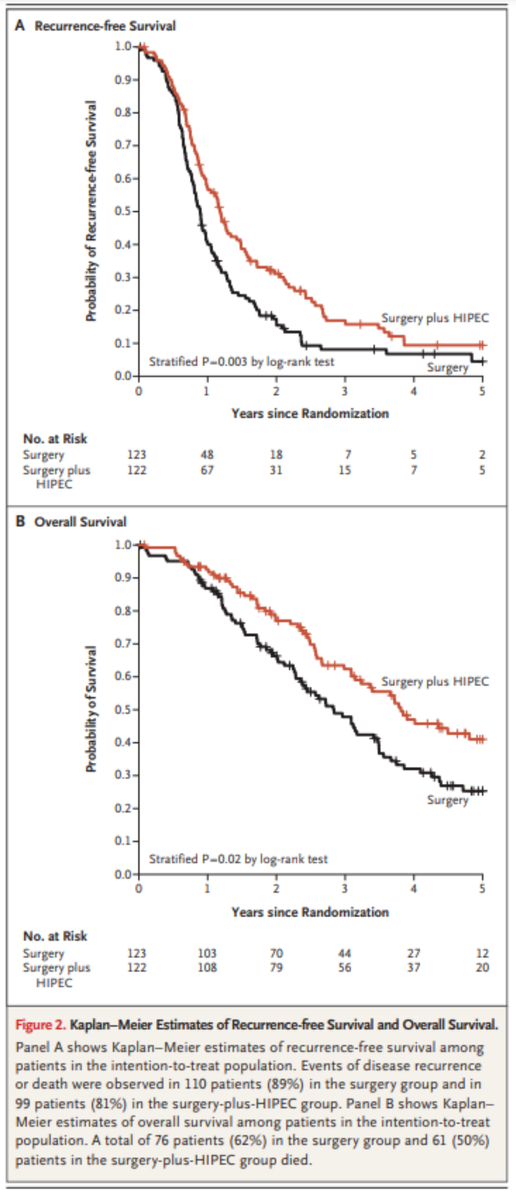


Figure 2. Kaplan–Meier Estimates of Recurrence-free Survival and Overall Survival.
Panel A shows Kaplan–Meier estimates of recurrence-free survival among patients in the intention-to-treat population. Events of disease recurrence or death were observed in 110 patients (89%) in the surgery group and in 99 patients (81%) in the surgery-plus-HIPEC group. Panel B shows Kaplan–Meier estimates of overall survival among patients in the intention-to-treat population. A total of 76 patients (62%) in the surgery group and 61 (50%) patients in the surgery-plus-HIPEC group died.

Armstrong NEJM 2006; Van Driel *NEJM* 2020; Vergoote *NEJM* 2010; Lim *JAMA Surg* 2022

LSU Gynecologic Oncology HIPEC service

- We have now performed over a dozen HIPEC procedures
- Excellent clinical outcomes
- Looking forward to expanding these services

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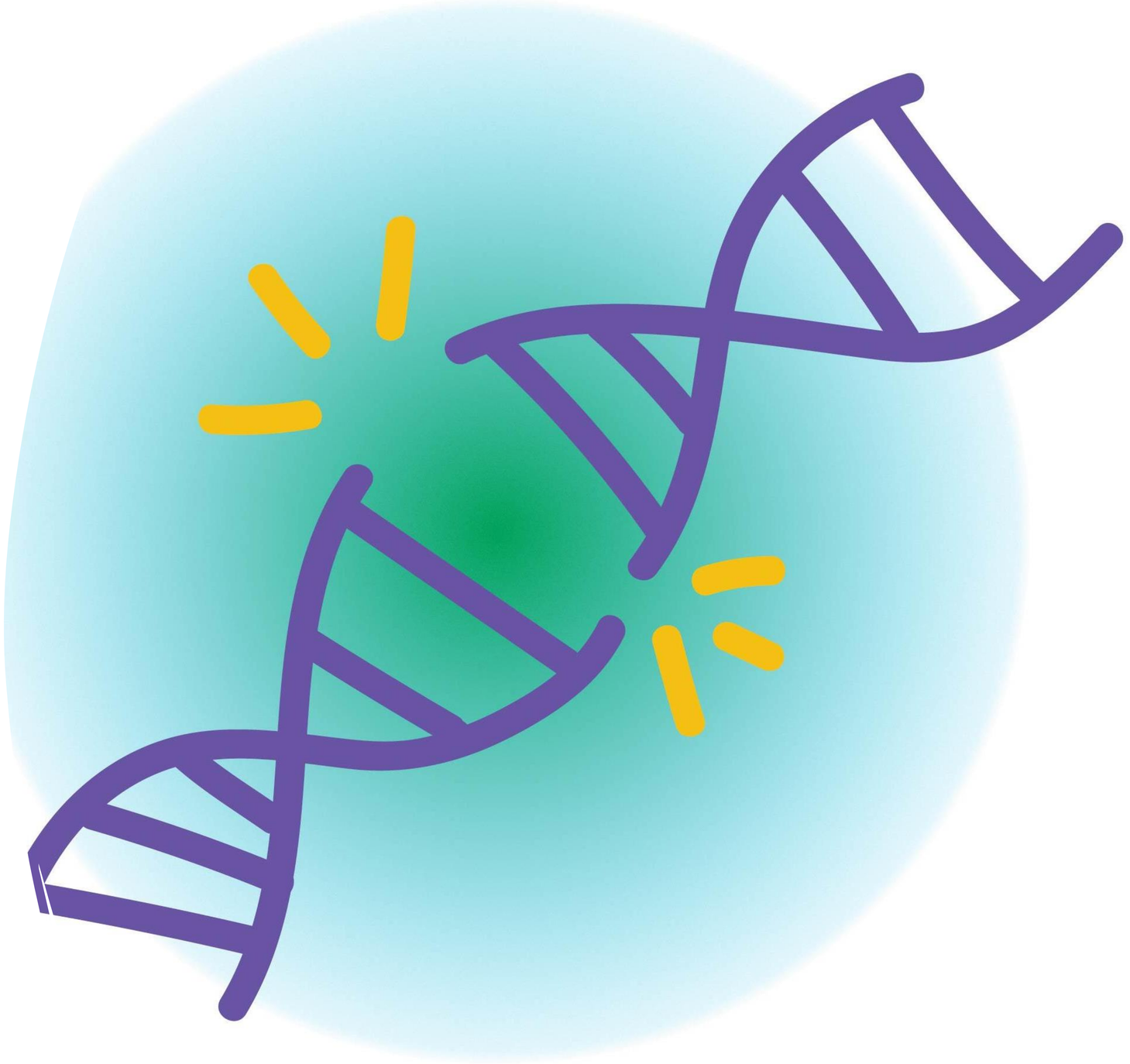
The era of parp inhibitors

- Parp inhibitors have a role as maintenance in the primary and secondary setting
- There are some concerns about use of these agents in the HRD negative population



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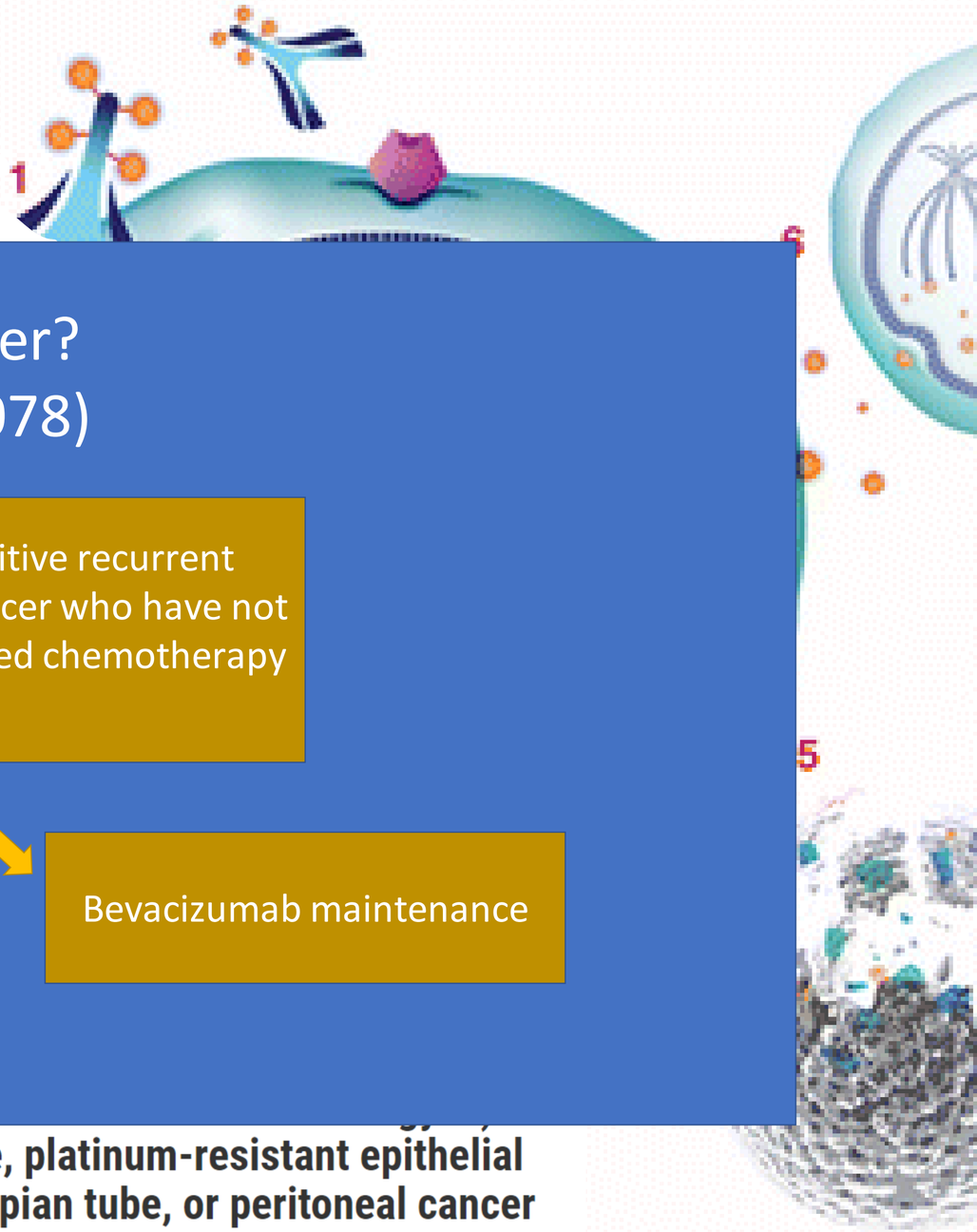
Antibody Drug Conjugate: Mirvetuximab soravtansine -gynx

- VEN
  dia
- SOR
  plat
- Mir
  bas
- 32.
  mo

Can we use it sooner? GLORIOSA (GOG 3078)

Platinum sensitive recurrent FRα positive recurrent platinum sensitive epithelial ovarian cancer who have not progressed on second line platinum based chemotherapy with bevacizumab

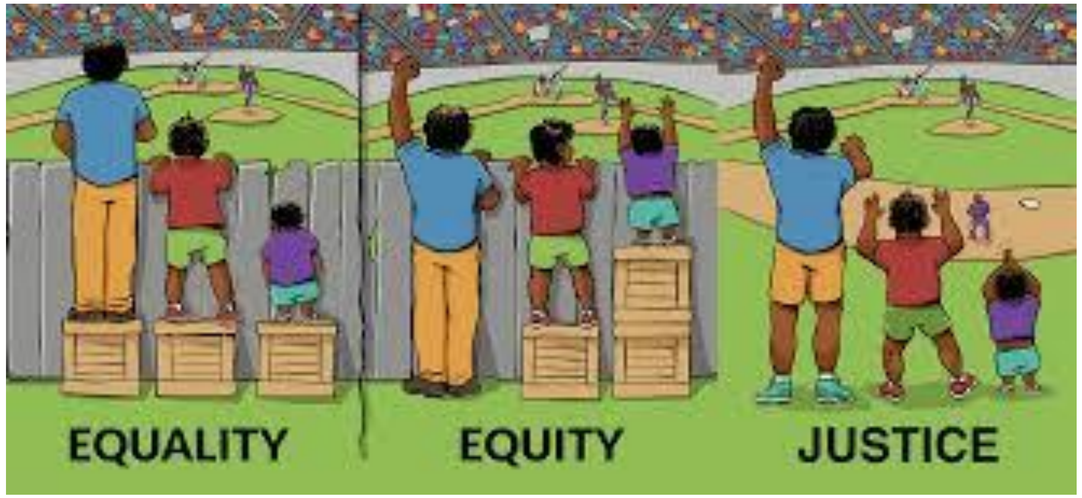
- Bevacizumab + Mirvetuximab soravtansine maintenance
- Bevacizumab maintenance



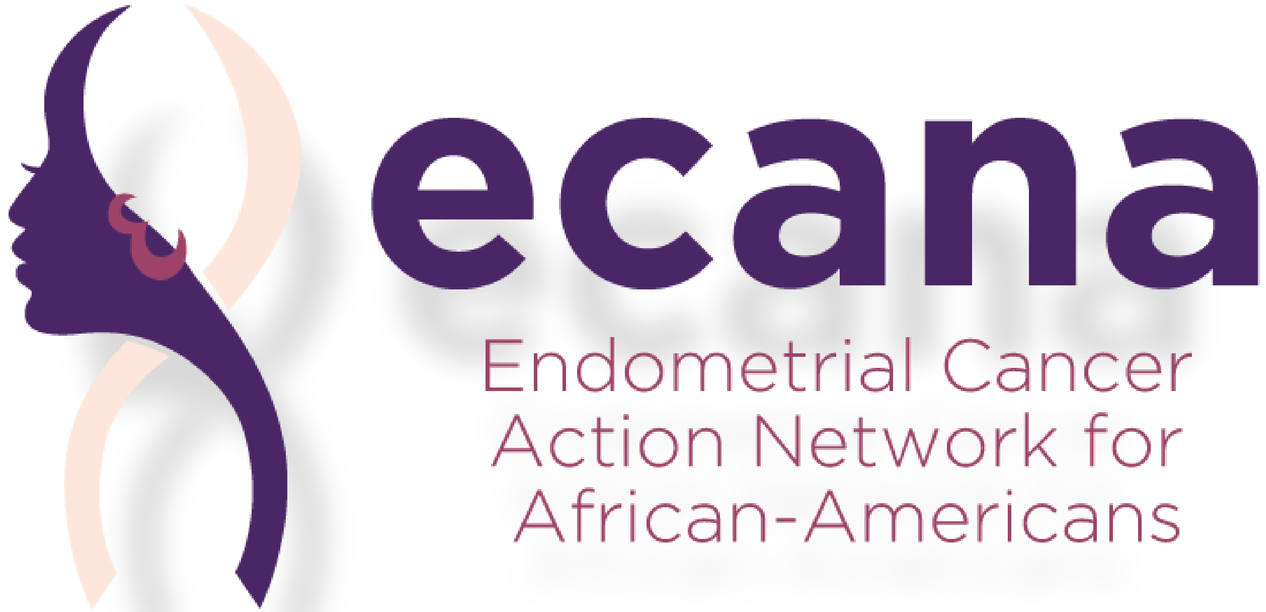
FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or peritoneal cancer

Matulonis *JCO* 2023

To a better future



- We have opened trials and initiatives to tackle inequity and secure justice for the women we care for.



SISTER: Social Interventions for Support During Treatment for Endometrial Cancer and Recurrence

- Prospective, open randomized controlled trial of Black/African-American people with high risk endometrial cancer who require systemic therapy or radiation
- The aim is to identify social support interventions with the primary outcome of completing prescribed treatment
- Arms:
  - Curated written materials
  - Weekly group gatherings (virtual)
  - Individual peer to peer support

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Endometrial Cancer Molecularly Targeted Therapy Consortium:

- Multicenter consortium facilitating the development of real-world data on patterns of genomic testing and use of molecularly targeted therapies in patients with metastatic endometrial cancer.
- Specifically targeting a racially and geographically diverse patient population.

Table 1. Demographic and Disease Characteristics of All the Trial Patients at Baseline.*

Characteristic	Lenvatinib plus Pembrolizumab (N=411)	Chemotherapy (N=416)
Age		
Median (range) — yr	64 (30–82)	65 (35–86)
<65 yr — no. (%)	206 (50.1)	204 (49.0)
Race — no. (%)†		
White	261 (63.5)	246 (59.1)
Black	17 (4.1)	14 (3.4)
Asian	85 (20.7)	92 (22.1)
Geographic region — no. (%)‡		
Region 1	234 (56.9)	240 (57.7)
Region 2	177 (43.1)	176 (42.3)
MMR status — no. (%)		

Secord SGO 2022; Maker *NEJM* 2022

STEEL MAGNOLIAS: Shared TElEheaLth for MultidisciplinAry gyNecOLogIc cAncer Survivorship

- Many patients lack means to transport themselves to the doctor's office in their own vehicle (45%)
- Many patients lack what they would need for a standard telemedicine visit from home (25% lack reliable internet access, 35% lack access to a smart phone, 40% lack access to a personal computer)
- The STEEL MAGNOLIAS program saved time and distance traveled
  - 17.1 miles versus 138.6 miles each way (p=0.001)
  - 27.3 minutes versus 139.2 minutes commute each way (p=0.001)

Jernigan SGO 2020

Thank you!

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