Updates in Gynecologic Cancer Treatment: Latest and Greatest

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WE ARE MAKING PROGRESS!

- Most talks on cancer talk about how bad things are…this is not that talk!
- We have made substantial progress in the treatment of cancers
  - Tripled the overall survival in ovarian cancers in last 15 years
  - Increased survival of pancreatic caner by 11% in the last decade
  - “Molecularized” the treatment of several cancers
    - Endometrial Cancer
    - Cervical Cancer

CNN health Life, But Better Fitness Food Sleep Mindfulness Relationships

Cancer death rates fall steadily in the US, with more survivors than ever

By Carma Hassan, CNN
Published 6:47 PM EDT, Wed September 21, 2022

CNN health Life, But Better Fitness Food Sleep Mindfulness Relationships

US breast cancer rate drops 43% in three decades, but racial disparities remain, American Cancer Society report finds

By Jacqueline Howard, CNN
Published 8:46 AM EDT, Fri October 7, 2022

healthline Health Conditions Discover Plan Connect

The Number of Cancer Survivors in the U.S. is at a Record High: How We Got Here

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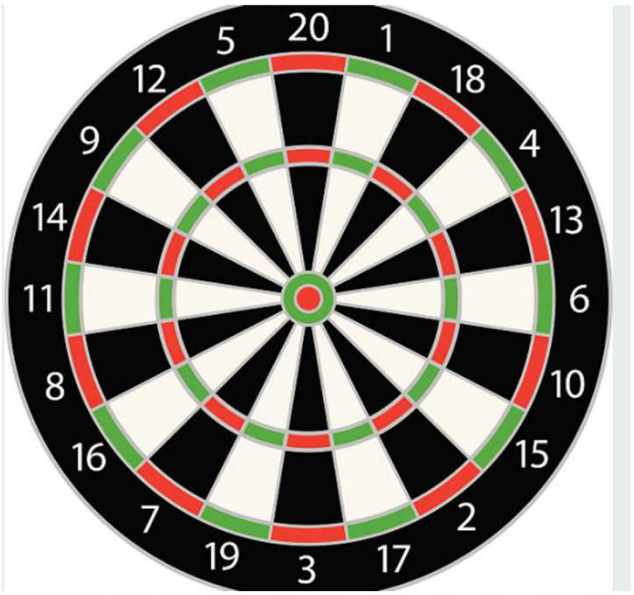
The State of Treatment Until Now…

- Cancers were largely treated in a non-specific way utilizing broad chemotherapy drugs
  - Cytotoxic drugs
  - Anti-metabolites
  - Anti-tumor antibiotics
- These techniques in essence, utilized the “general” mechanisms of carcinogenesis to fight disease and could, in essence, be used in any cancer
- Very non-specific way of treating patients
  - Side effects
  - True efficacy



How do we hit the bulls-eye?

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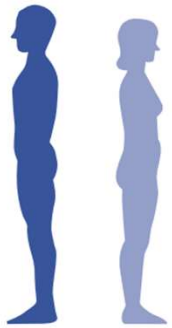
Figure 3. Leading Sites of New Cancer Cases and Deaths – 2022 Estimates

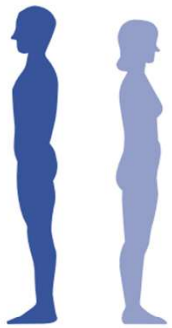
Estimated New Cases

Male			Female		
Prostate	268,490	27%	Breast	287,850	31%
Lung & bronchus	117,910	12%	Lung & bronchus	118,830	13%
Colon & rectum	80,690	8%	Colon & rectum	70,340	8%
Urinary bladder	61,700	6%	Uterine corpus	65,950	7%
Melanoma of the skin	57,180	6%	Melanoma of the skin	42,600	5%
Kidney & renal pelvis	50,290	5%	Non-Hodgkin lymphoma	36,350	4%
Non-Hodgkin lymphoma	44,120	4%	Thyroid	31,940	3%
Oral cavity & pharynx	38,700	4%	Pancreas	29,240	3%
Leukemia	35,810	4%	Kidney & renal pelvis	28,710	3%
Pancreas	32,970	3%	Leukemia	24,840	3%
All sites	**983,160**		**All sites**	**934,870**	



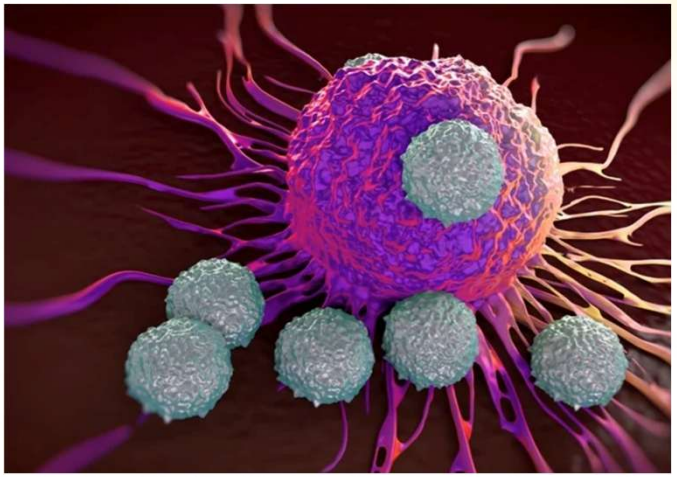
Estimated Deaths

Male			Female		
Lung & bronchus	68,820	21%	Lung & bronchus	61,360	21%
Prostate	34,500	11%	Breast	43,250	15%
Colon & rectum	28,400	9%	Colon & rectum	24,180	8%
Pancreas	25,970	8%	Pancreas	23,860	8%
Liver & intrahepatic bile duct	20,420	6%	Ovary	12,810	4%
Leukemia	14,020	4%	Uterine corpus	12,550	4%
Esophagus	13,250	4%	Liver & intrahepatic bile duct	10,100	4%
Urinary bladder	12,120	4%	Leukemia	9,980	3%
Non-Hodgkin lymphoma	11,700	4%	Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,710	3%	Brain & other nervous system	7,570	3%
All sites	**322,090**		**All sites**	**287,270**	

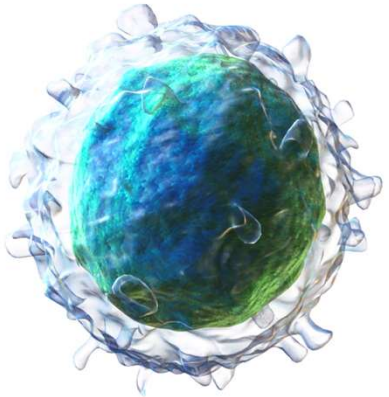


Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

Immune Systems



- Harnessing the host immune system to fight cancer has been postulated for >100 years
- In a matter by which immune cells fight off infection, scientists have theorized that the same could be done using T cells and other parts of the immune system
- Must have a brief review of how immune cells work…
- T- Cells
  - Workhouse of the immune system
  - T cells are a part of the immune system that **focuses on specific foreign particles**. Rather than generically attack any antigens, T cells circulate until they encounter their specific antigen. As such, T cells play a critical part in immunity to foreign substances.
- B cells produce antibody molecules that can latch on and destroy invading viruses or bacteria.



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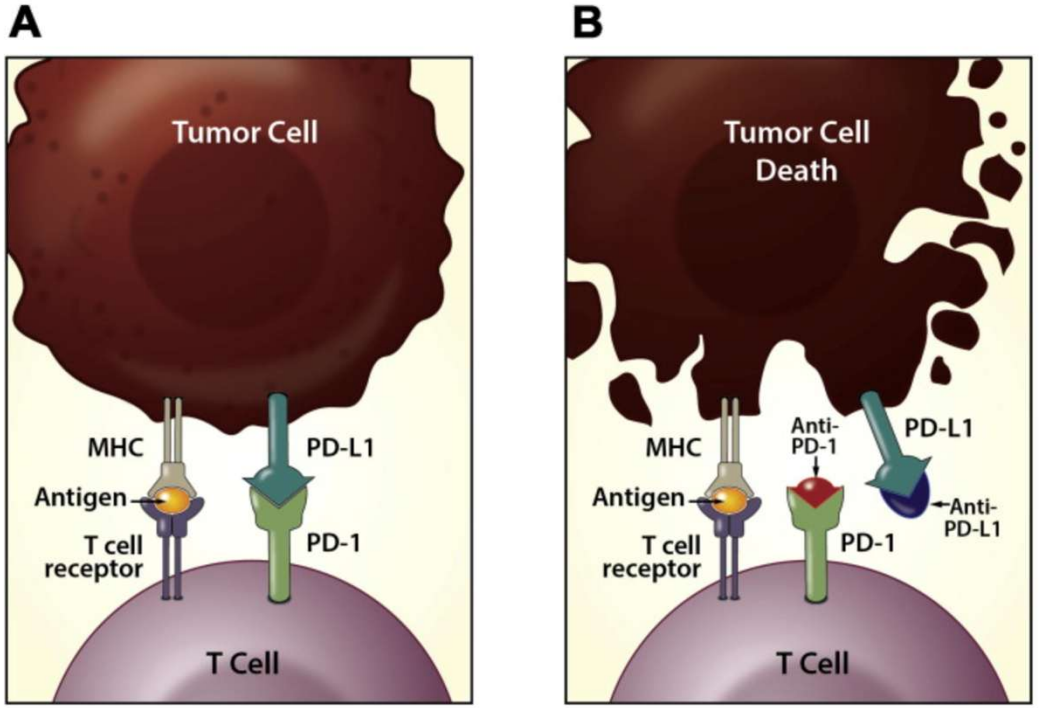
How T cells Work and How Cancer Evades Them.....

- Two key receptors on both cancer cells and T cells have been identified in the hos-tumor cell interaction
  - Programmed death ligand 1 (PDL-1)
  - Programed death protein 1
- How do we harness the interaction between these two to fight cancer?
- Immune cells will naturally try to fight cancer since they fight “non-self” proteins
- Tumor cells are smart ..they bind to PD-1 receptors on T cells and inactive them causing the tumor cell to “evade” the immune system



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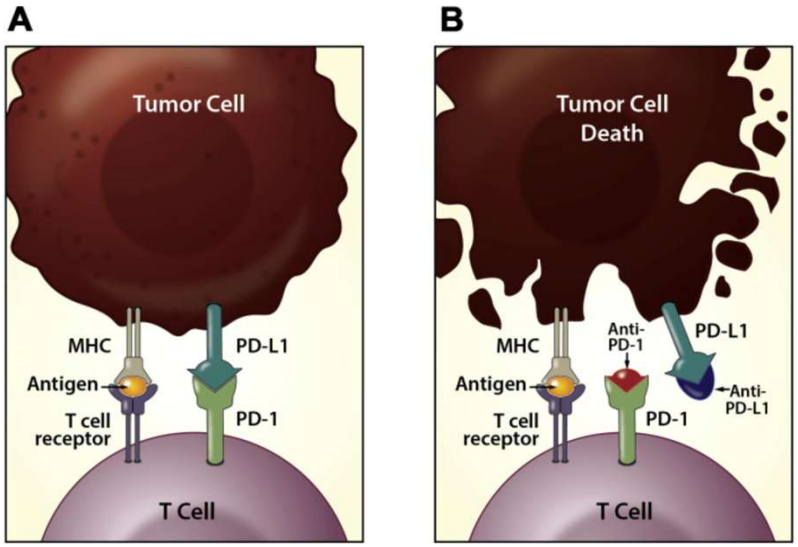
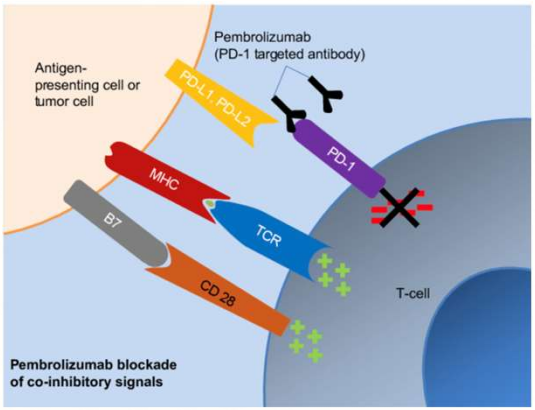
PDL-1 inhibitors….the new breakthrough..

- As the immune system was further studied the idea of blocking the interaction between tumor cells and host immune cells was explored
- The development of PDL-inhibitors/blockers inhibit the interaction and inactivation of T cells
- This allows the host immune system to attack tumor cells and kill them
- The main issue- not all tumor cells express PDL-1
- Pembrolizumab one of the first drugs to block the PDL-1/PD1 interaction
  - By doing this it allows T cell to activate cytokines and other mechanisms by which to kill of tumor cells
- Other drugs such as nivolumab





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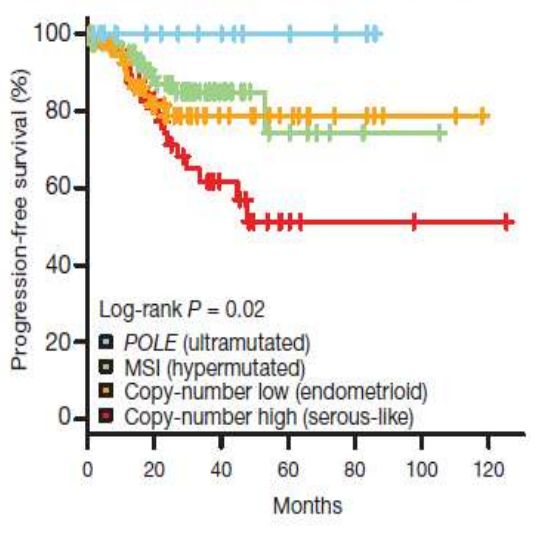
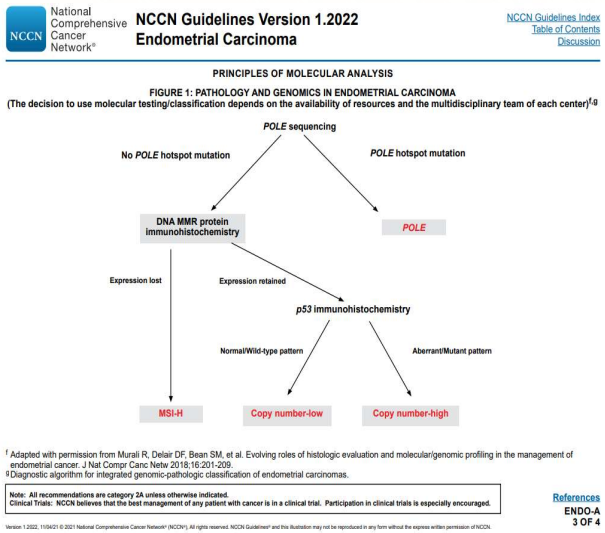
Endometrial/Uterine Cancer

- Cancer of the lining of the uterus
- Most common of the gynecologic cancers
- Incidence is increasing!
  - 20 years ago there were about 42,000 new cases of endometrial cancer
  - In 2023 there were 66,000 new cases!
- Why is this happening?
  - Increasing rates of obesity
  - Toxins in various foods/products

Clinical and Molecular Implications for Endometrial Cancer





National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Endometrial Carcinoma

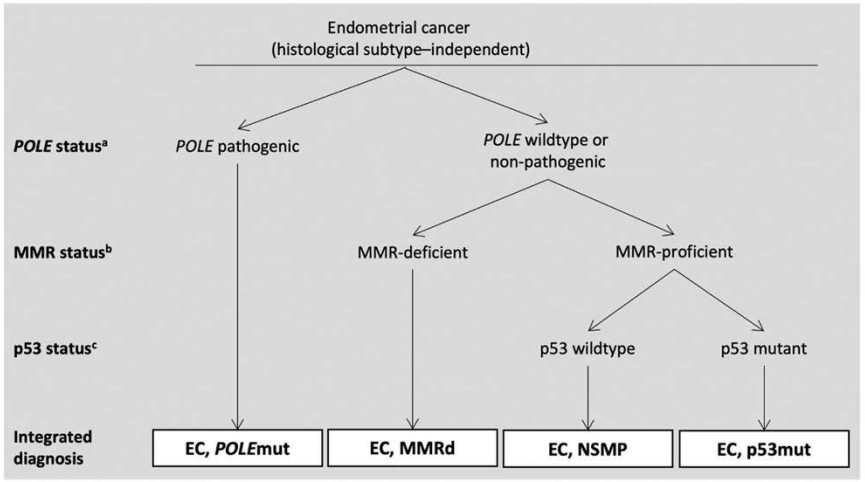
NCCN Guidelines Index
Table of Contents
Discussion

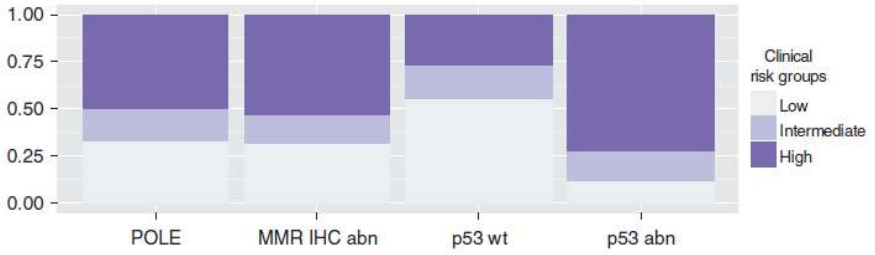
All staging in guideline is based on updated FIGO staging. (ST-1)

CLINICAL FINDINGS (Endometrioid Histology)[g]	HISTOLOGIC GRADE/ADJUVANT TREATMENT[g,h,m]		
	FIGO Stage	Histologic Grade	Adjuvant Treatment
Surgically staged: Stage I[e] →	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)

Improving Outcomes in Endometrial Cancer Patients

- A molecular revolution has taken place in gynecologic cancer
- Endometrial cancer has been completely rethought at the molecular level
  - NO longer just about stage/grade
  - What does the molecular signature of this tumor show





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Improving Outcomes in Endometrial Cancer Patients

- How do we stay ahead in cancer therapy and how do we offer the most cutting edge care for our patients
- Endometrial cancer is one of the few cancers whose incidence is increasing in the US with now >60,000 cases/year
- What can we offer our patients that is different and may be actionable to maximize survival

Cancer: Volume 123, Issue 5

Pages: **711-893**

March 1, 2017

Original Article

Confirmation of ProMisE: A Simple, Genomics-Based Clinical Classifier for Endometrial Cancer

Aline Talhouk, PhD[1]; Melissa K. McConechy, PhD[2]; Samuel Leung, MSc[3]; Winnie Yang, BSc[1]; Amy Lum, BSc[1]; Janine Senz, BSc[1]; Niki Boyd, PhD[1]; Judith Pike, MD[4]; Michael Anglesio, PhD[1]; Janice S. Kwon, MD, MSc[4]; Anthony N. Karnezis, MD, PhD[1]; David G. Huntsman, MD[1]; C. Blake Gilks, MD[5]; and Jessica N. McAlpine, MD[4]

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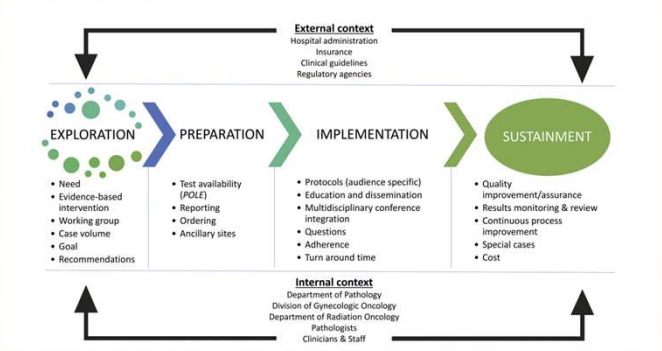
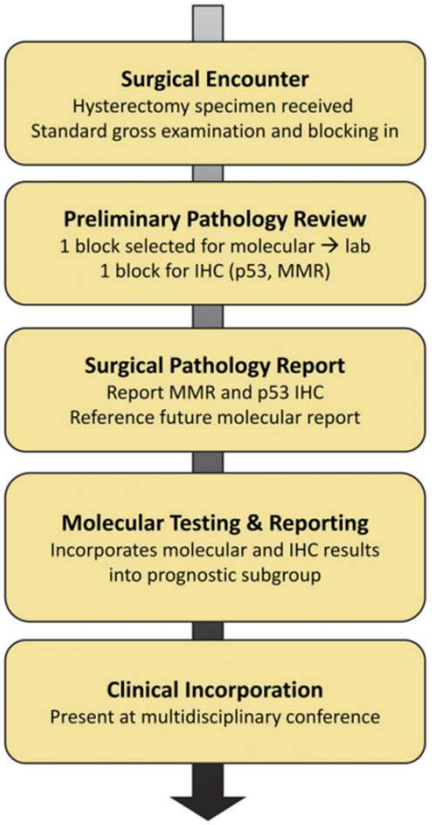
Improving Outcomes in Endometrial Cancer Patients





International Journal of Gynecological Pathology
00:1–15, Lippincott Williams & Wilkins, Baltimore

Original Article

Prospective Clinical Prognostication of Endometrial Carcinomas Based on Next-generation Sequencing and Immunohistochemistry—Real-world Implementation and Results at a Tertiary Care Center

Kurtis D. Davies, Ph.D., Lynelle P. Smith, M.D., Amy Guimaraes-Young, M.D., Ph.D., Bradley R. Corr, M.D., Christine M. Fisher, M.D., M.P.H., Saketh R. Guntupalli, M.D., Amber A. Berning, M.D., Miriam D. Post, M.D., Devon Pino, M.D., Dara L. Aisner, M.D., Ph.D., and Rebecca J. Wolsky, M.D.

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International Journal of Gynecological Pathology
43:335–348, Lippincott Williams & Wilkins, Baltimore

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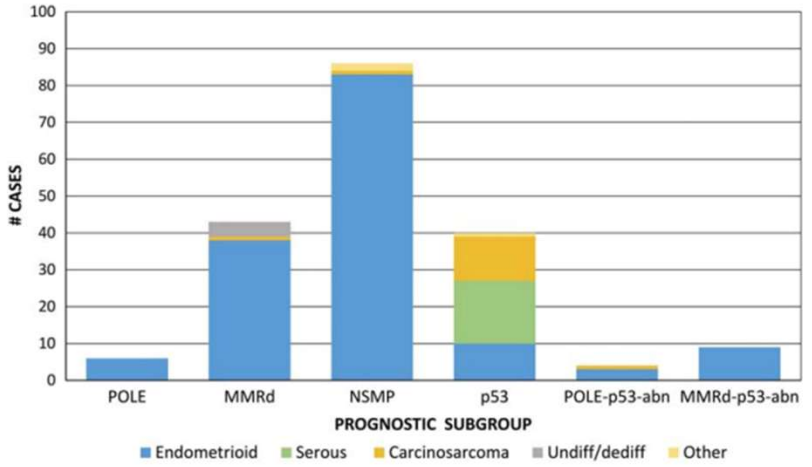
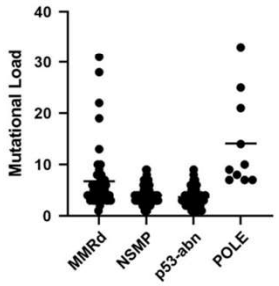
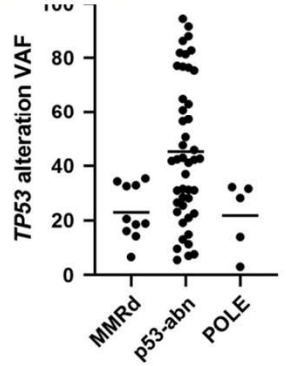


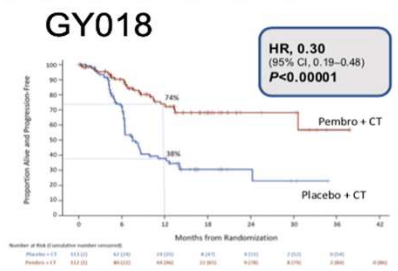
FIG. 3. Prognostic subgroup composition by histotype. MMRd indicates mismatch repair deficient; NSMP, no specific molecular profile; Undiff/dediff, undifferentiated/dedifferentiated carcinoma.

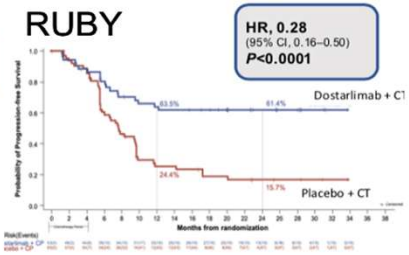
- Results showed that our patients largely mirror findings in other cohorts including the original PRoMIsE cohort
- Our patients are mainly copy number low/low tumor mutational burden (endometrioid phenotype)
  - A sizable percentage were “endometrioid” with *mutP*53 suggesting a need for more aggressive treatment
  - A small number were ”high intermediate risk” but *POLE* hypermutated suggesting possible de-escalation





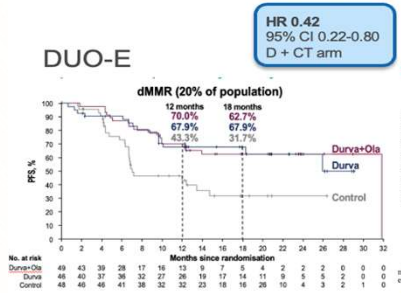
NRG-GY018[1]	RUBY Part 1[2]	RUBY Part 2[3]	DUO-E[4]	AtTEnd[5]
dMMR (mPFS, mo)	**dMMR (24-mo PFS)**	**dMMR (mPFS, mo)**	**dMMR (mPFS, mo)**	**dMMR (mPFS, mo)**
Pembro + CT (n=112): **NR (95% CI, 30.6-NR)** Placebo + CT (n=113): **7.6 (95% CI, 6.4-9.9)** **HR=0.30** **(95% CI, 0.19-0.48); *P*<0.001**	Dostar + CP (n=53): **61.4% (95% CI, 46.3-73.4)** Placebo + CP (n=65): **15.7% (95% CI, 7.2-27.0)** **HR=0.28** **(95% CI, 0.16-0.50); *P*<0.001**	Dostar + CP + Nira (n=50): **NE (95% CI, 11.8-NE)** Placebo + CP (n=25): **7.9 (95% CI, 5.4-NE)** **HR=0.48** **(95% CI, 0.24-0.96); *P*=0.0174**	Durva + Ola (n=48): **31.8 (95% CI, 12.4-NR)** Durva (n=46): **NR (95% CI, NR-NR)** Control (n=49): **7.0 (95% CI, 6.7-14.8)** **HR (combo vs control) = 0.41** **(95% CI, 0.21-0.75)**	Atezo + CP (n=81): **NE (95% CI, 12.3-NE)** Placebo + CP (n=44): **6.9 (95% CI, 6.2-9.0)** **HR=0.36** **(95% CI, 0.23-0.57); *P*=0.0005**

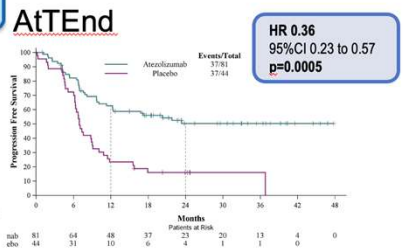




	No with events%	Median
Pembro + CT	23.2	NR (30.6-NR)
Placebo + CT	52.2	7.6 (6.4-9.9)

	No with events%	Median
Dorsta + CT	35.8	NR (11.8-NR)
Placebo + CT	72.3	7.7 (5.6-9.7)





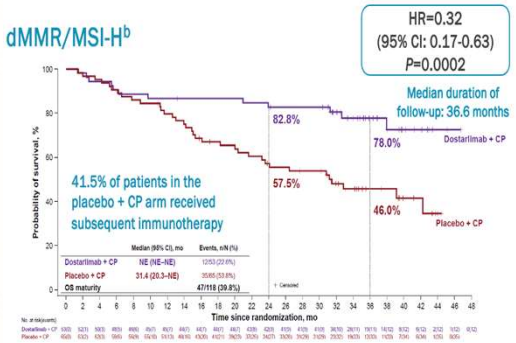
	No with events %	Median
Durva + CT	32.6	NR (NR-NR)
Durva + O + CT	37.5	31.8 (12.4-NR)
Placebo + CT	51	7.0 (6.7-14.8)

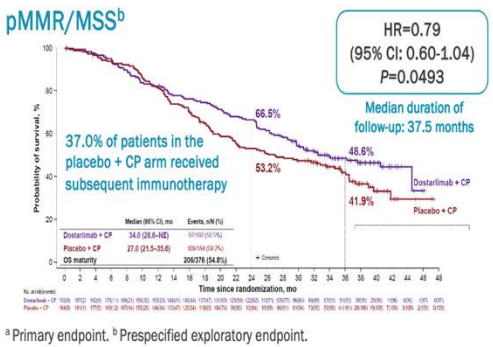
	No with events%	Median
Atezo + CT	45.7	NR (12.3-NR)
Placebo + CT	84.1	6.9 (6.2-9.0)

Eskander RN, et al. *N Engl J Med 2023*; Mirza MR, et al. *N Engl J Med*. 2023; Westin SN, et al. *J Clin Oncol* 2024. Colombo N, et al. ESMO 2023. Abstract LBA40. Annals Oncol

Overall Survival Results: Benefit of IO + Chemotherapy in Endometrial Cancer

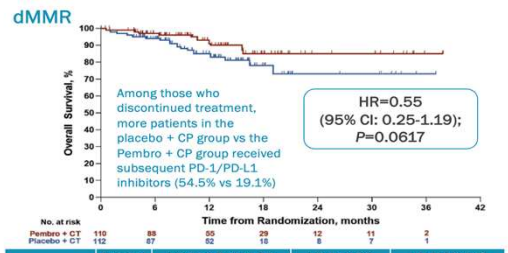
The RUBY Trial





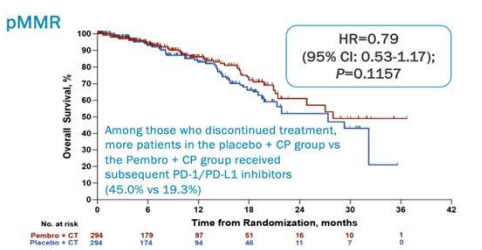
[a] Primary endpoint. [b] Prespecified exploratory endpoint.

The GY018 Trial



	Events, n/N	Median Follow-Up Duration[a] (range), mo	Median OS (95% CI), mo	HR (95% CI)[b] *P* value[c]
Pembro + CP	10/110	13.3 (0.6-39.4)	NR (NR-NR)	0.55 (0.25-1.19)
Placebo + CP	17/112	13.7 (1.0-38.0)	NR (NR-NR)	*P*=0.0617

▪ Data immature at IA (18% information fraction)



	Events, n/N	Median Follow-Up Duration[a] (range), mo	Median OS (95% CI), mo	HR (95% CI)[b] *P* value[c]
Pembro + CP	45/294	8.8 (0.1-37.0)	27.96 (21.42-NR)	0.79 (0.53-1.17)
Placebo + CP	54/294	8.4 (0.1-37.2)	27.37 (19.52-NR)	*P*=0.1157

▪ Data immature at IA (27.2% information fraction)

Powell M. et al. SGO 2024; Eskander R. et al. SGO 2024

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FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for unresectable or metastatic HER2-positive solid tumors

On April 5, 2024, the Food and Drug Administration granted accelerated approval to fam-trastuzumab deruxtecan-nxki (Enhertu, Daiichi Sankyo, Inc.) for adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.

Conclusions

Evolution of Molecularly Directed Therapy in Endometrial Cancer Beyond Mismatch Repair/Immunotherapy

TP53

- Predictor of response to anti angiogenic therapy…
- **GOG-86P:**
  PFS HR 0.48 vs 0.87 in mutant TP53 vs. TP53wt
- Inhibition of nuclear export of wild type TP53
  - **Selinexor median PFS in TP53wt of 13.7 mo vs 3.7 months with placebo (HR 0.41; 95% CI 0.42-0.71)**

Anti-HER2

Evolution of anti-HER2 treatments…

Fader et al. 2018:
Trastuzumab + C/P **PFS HR 0.44; OS HR** 0.58

- **DESTINY-Pan Tumor02**:
  ORR 57.5%; Median DOR: NR
- **Nishikawa et al. 2023: ORR** 54.5% & 70%
- **NRG GY026…**

DNA Damage Repair

- Potential opportunity in the mutant TP53 population
- **ADAGIO:** Adavosertib single agent
  Medial prior LOT = 3
  BICR ORR 26%
  Median PFS 2.8mo
- **PARPi**
  - **(UTOLA) – Joly F et al. ESMO 2023**
  - **DUO-E- Westin et al. ESMO 2023**
  - **Corr et al. SGO 2024 (Rucaparib maintenance)**

Hormonal Therapies

Possible role in the copy number low TP53wt population

PALEO Study: Letrozole vs Palbocilcib + letrozole
HR 0.56
Median PFS 8.3 vs 3 mo

- **Letrozole + Abemaciclib: ORR 30%**

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We are making progress……

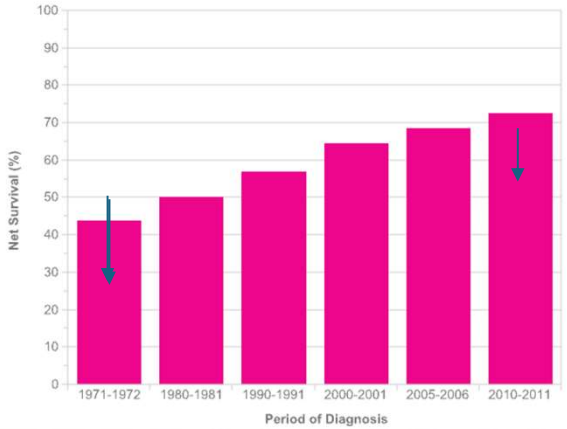
Original Research

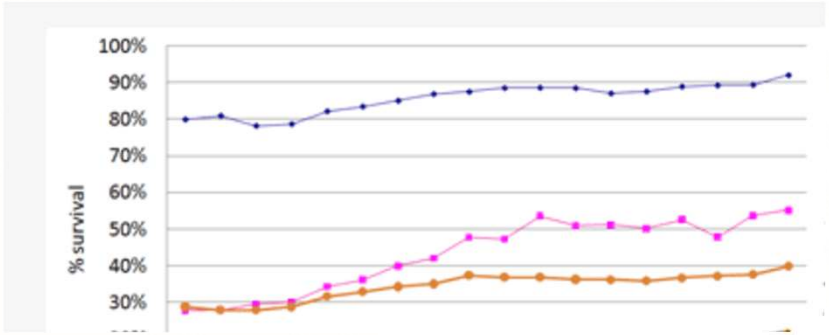
Characteristics of Long-Term Survivors of Epithelial Ovarian Cancer

Rosemary D. Cress, DrPH, Yingjia S. Chen, MPH, Cyllene R. Morris, PhD, Megan Petersen, MD, and Gary S. Leiserowitz, MD

DISCUSSION

This study provided a unique opportunity to examine the characteristics of women who are long-term survivors of epithelial ovarian cancer, commonly thought to be a highly fatal disease. There has been limited information about women surviving greater than 10 years, many of whom are cured. Using cancer registry data not only allowed us to collect long-term survival data beyond 10 years (most studies are limited to 5 years of survival[3–5]), but the cohort was far larger than seen in other studies.[6] Most surprising was that nearly one third of patients with ovarian cancer were long-term survivors, which is very important for counseling about prognosis.





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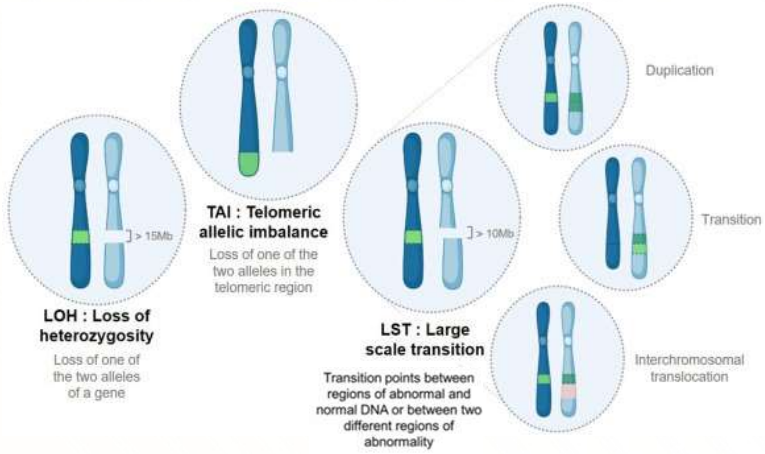
Genomic Testing – sBRCA, HRD

- Tumor DNA - from formalin-fixed paraffin embedded block
- Somatic *BRCA1* and *BRCA2* variants (sequencing and large rearrangements)
- HRD assays
  - Loss of heterozygosity (LOH)
  - Genomic Instability Score (GIS): sum of 3 tissue biomarkers
- Ovarian Cancer Classification - Implications for Therapy
  - Germline BRCA mutation
  - Somatic BRCA mutation
  - HRD+
  - HRD negative (proficient)

BRCA sequencing
HRD assays



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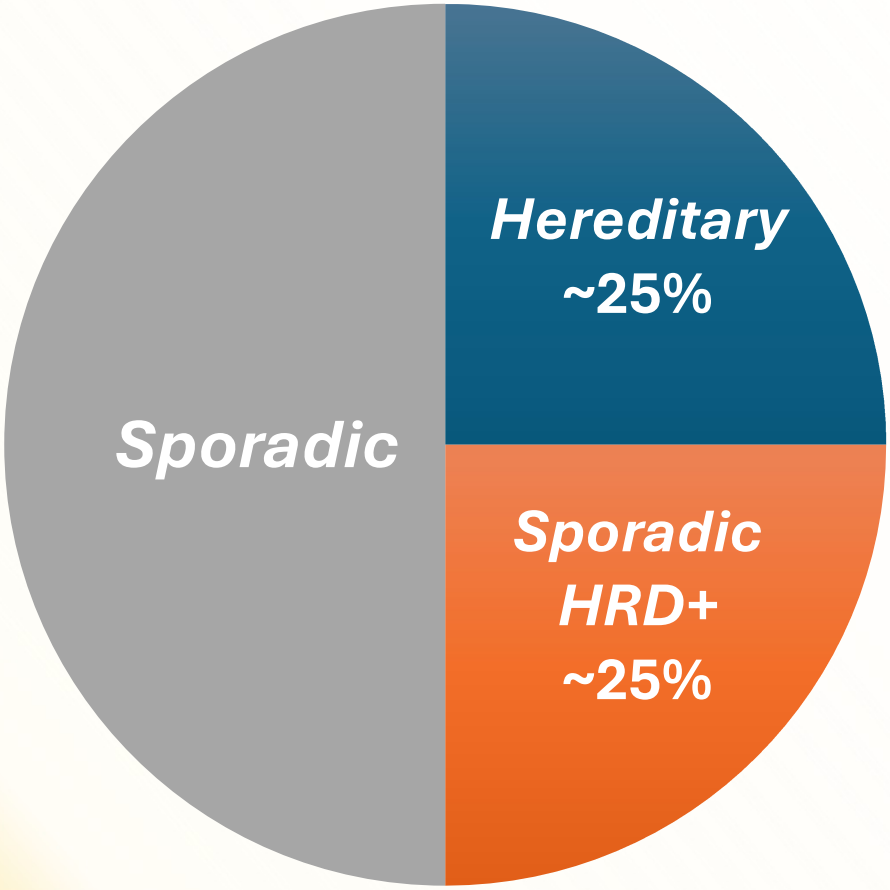
Ovarian Cancer – Hereditary and Somatic HRD+



Somatic *BRCA1* or *BRCA2* inactivation
3% *BRCA1* or *BRCA2* somatic mutation
11% Epigenetic *BRCA1* silencing

Other Homologous Recombination Deficiency (HRD)
Amplification of *EMSY*
Deletion/Mutation of *PTEN*
Methylation of *RAD51C*
Somatic mutation of other HR genes

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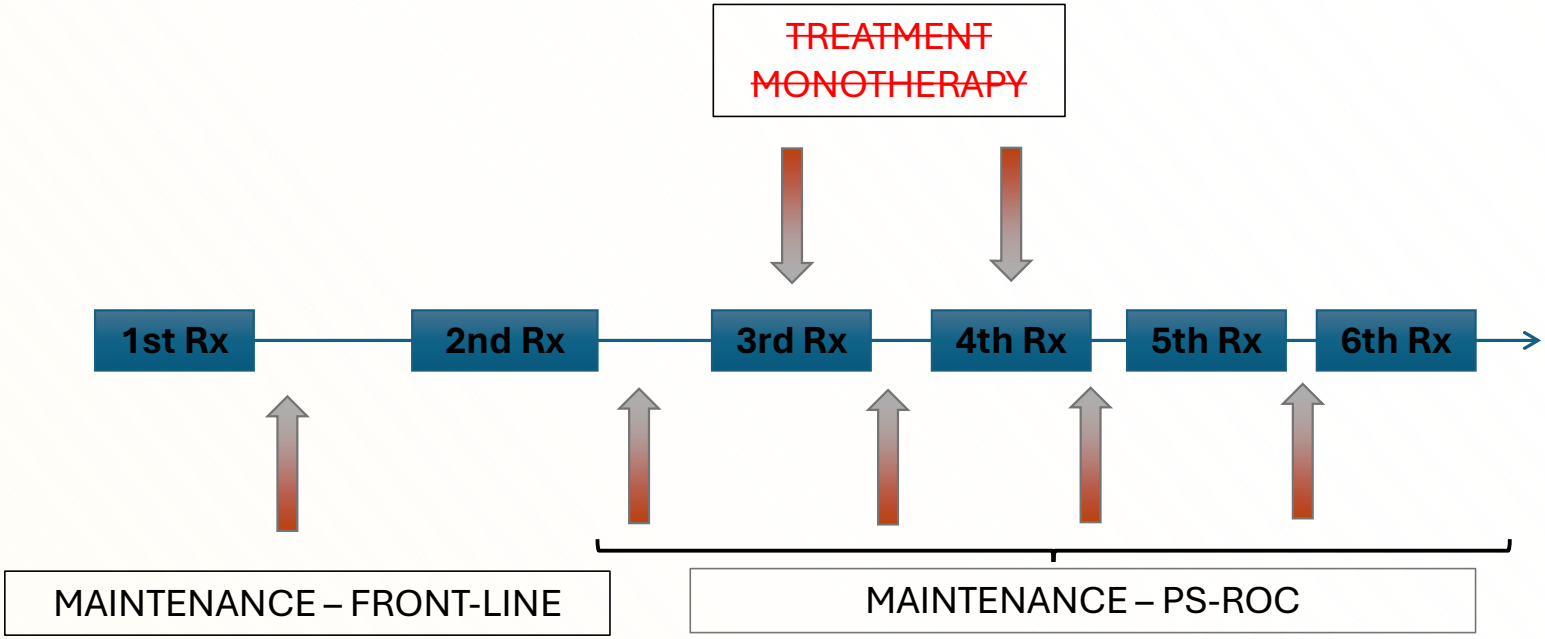
Current Landscape of US FDA Approvals for PARPi Use in Ovarian Cancer



MAINTENANCE – FRONT-LINE
Olaparib (g/sBRCA+)
Niraparib
Olaparib/bevacizumab (BRCA/HRD+)

MAINTENANCE – PS-ROC
Niraparib – gBRCA+
Olaparib – g/sBRCA+
Rucaparib – tBRCA+

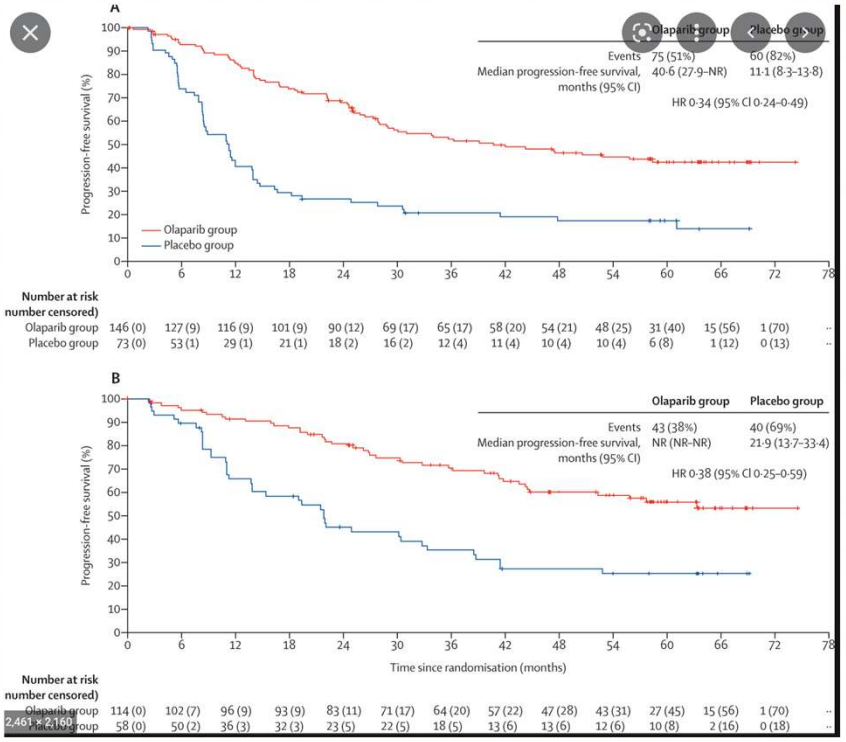
Current US Indications for PARPi Maintenance

	Maintenance after primary chemotherapy		
g*BRCA*	Olaparib	Olaparib/bevacizumab	Niraparib
s*BRCA*			
HRD+			
HRp			

	Maintenance after chemotherapy for platinum-sensitive recurrence		
g*BRCA*	niraparib	olaparib	
s*BRCA*	rucaparib		
HRD+			
HRp			

New Updates on BRCA positive Ovarian Cancer…

- Two weeks ago at the European Society of Medical Oncology meeting in Paris…
- Update on the SOLO 1 trial on survival in BRCA+ ovarian cancer patients treated with Olaparib (PARP inhibitor)
- At 7 years follow-up
  - Median OS was not reached with olaparib compared with 75.2 months with placebo (hazard ratio [HR] 0.55; 95% confidence interval [CI] 0.40–0.76).
- In essence at 7 years, so many patients who received Olaparib are alive that they study has not met its median survival!



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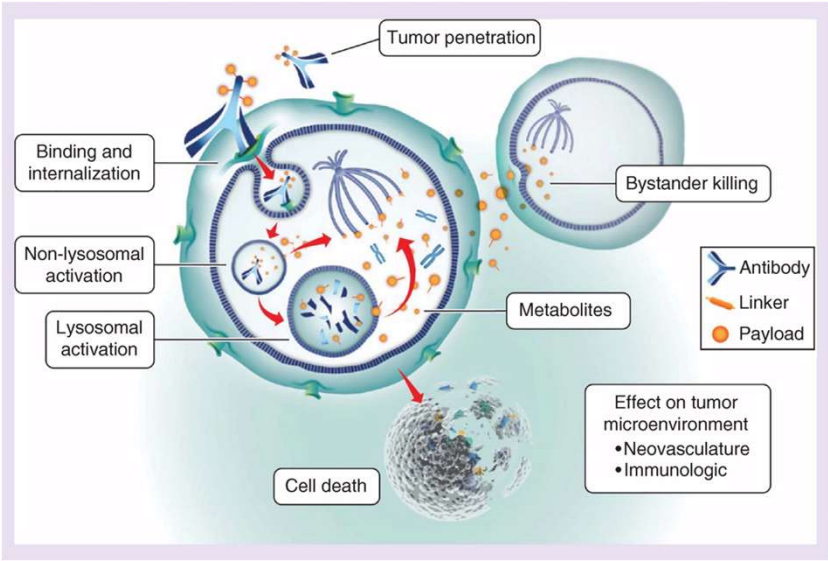
Folate Receptor Antibodies

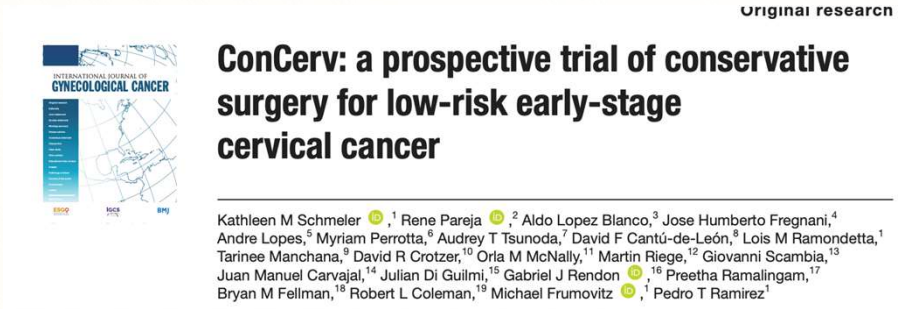
- Expression of folate receptor alpha is another new and novel avenue in the treatment of ovarian cancer
- Specific ovarian cancers express folate receptor alpha which is involed in tumorigenesis and metastasis
- Antibodies have been developed to block these and ultimately cause cell death

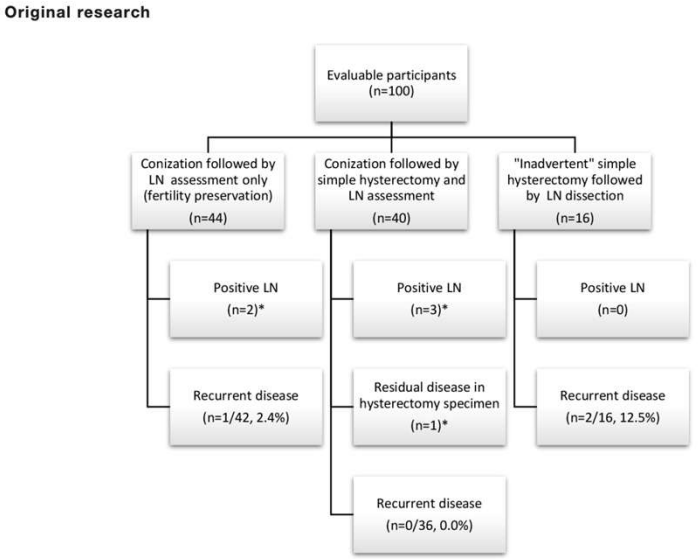


SORAYA Study with mirvetuximab

- A single arm study of platinum resistant patients
- Patients had to be folate receptor “high”
- 106 patients were enrolled and most had received bevacizumab or a PARP inhibitor prior
- The main outcome was a ”response rate”
- Results
  - 33% of patients had a response with 5 patients having a complete response
  - Median duration of response was 6 months
  - Generally well tolerated
    - Ocular toxicities

ConCERV Trial Early State Cervical Cancer





- Stage 1A2 to IB1
- Squamous or Adenocarcinoma
- No LVSI on biopsy and <2cm
- MRI/PET/CT no metastatic disease
- Patients underwent
  - Conization followed by LN dissection
  - Conization then simple hysterectomy and LN dissection
  - Inadvertent hysterectomy with LN dissection

The 2-year recurrence-free survival probability was 0.95 (95% CI 0.88 to .98, P<.05)

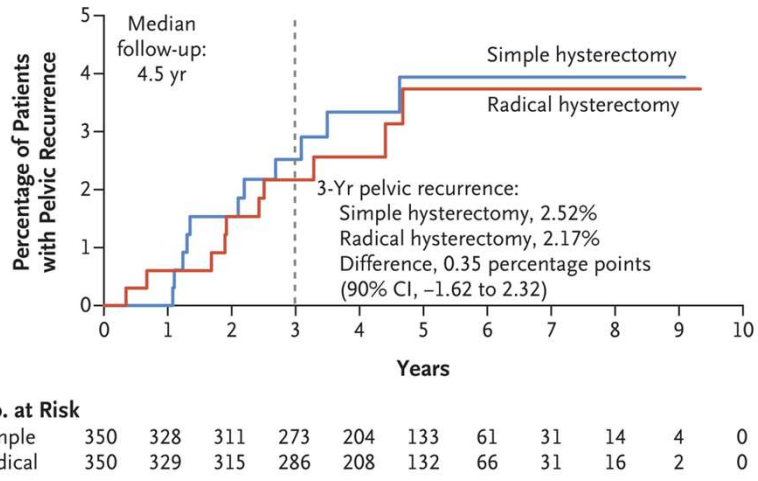
SHAPE Trial for Early Stage Cervical Cancer

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Simple versus Radical Hysterectomy in Women with Low-Risk Cervical Cancer

Marie Plante, M.D., Janice S. Kwon, M.D., Sarah Ferguson, M.D., Vanessa Samouëlian, M.D., Gwenael Ferron, M.D., Amandine Maulard, M.D., Cor de Kroon, M.D., Willemien Van Driel, M.D., John Tidy, M.D., Karin Williamson, M.D., Sven Mahner, M.D., Stefan Kommoss, M.D., Frederic Goffin, M.D., Karl Tamussino, M.D., Brynhildur Eyjólfsdóttir, M.D., Jae-Weon Kim, M.D., Noreen Gleeson, M.D., Lori Brotto, Ph.D., Dongsheng Tu, Ph.D., and Lois E. Shepherd, M.D., for the CX.5 SHAPE investigators*

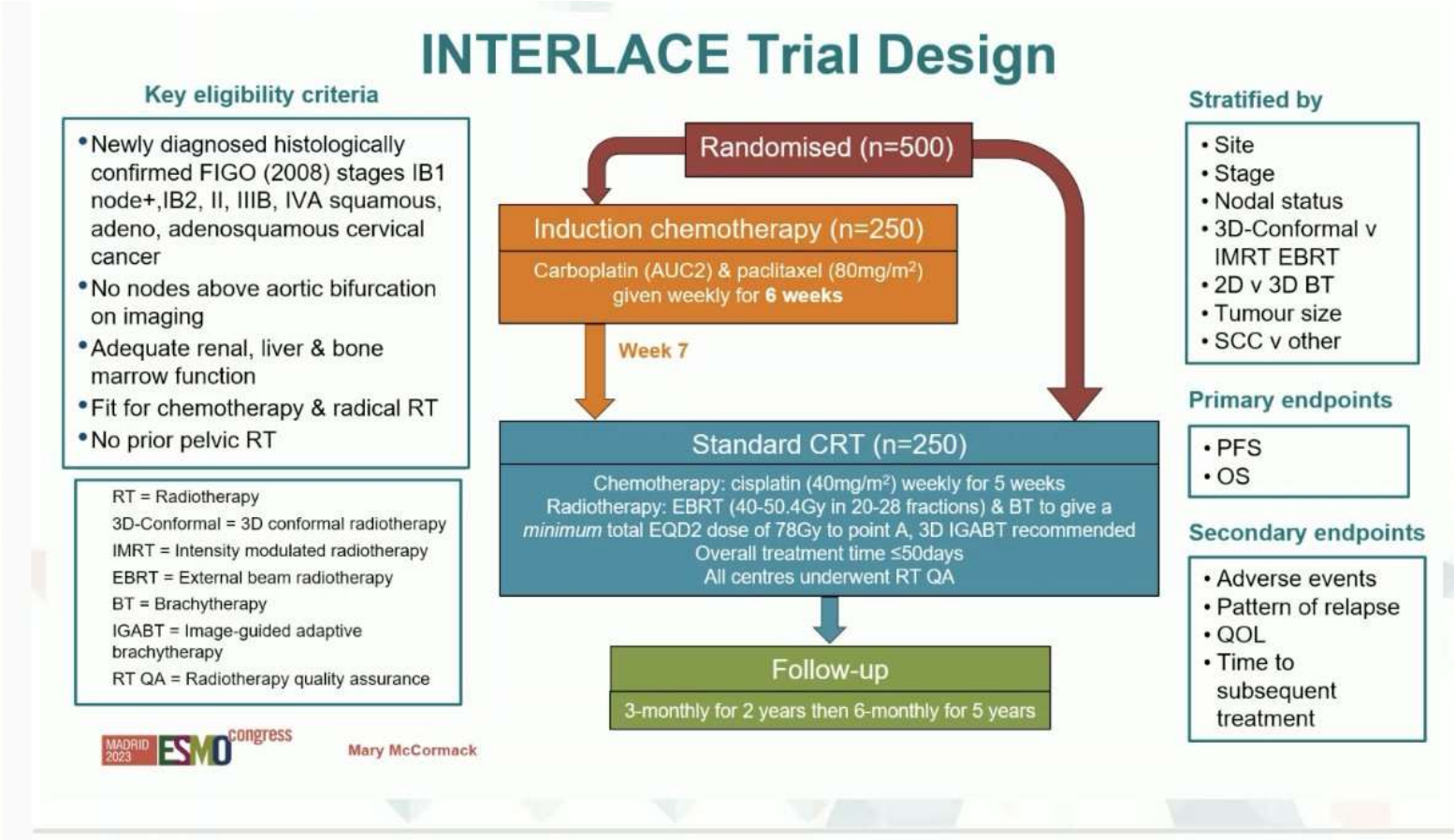


In early-stage, low-risk cervical cancer, pelvic recurrence rate at 3 years with simple hysterectomy was not inferior to radical hysterectomy.

Fewer urological surgical complications and better quality of life and sexual health measures were seen following simple hysterectomy.

At 3 years, the pelvic recurrence rate for simple hysterectomy was 2.52% compared with 2.17% for radical hysterectomy

Where Are We with Upfront Treatment?



INTERLACE Trial Results

- 5-year PFS: 72% (NACT + CTRT) vs 64% (CTRT alone)
- 5-year OS: 80% (NACT + CTRT) vs 72% (CTRT alone)
- Distant metastasis: 7% (NACT + CTRT) vs 12% (CTRT alone)
- Grade 3–4 toxicity: 59% (NACT + CTRT) vs 48% (CTRT alone)

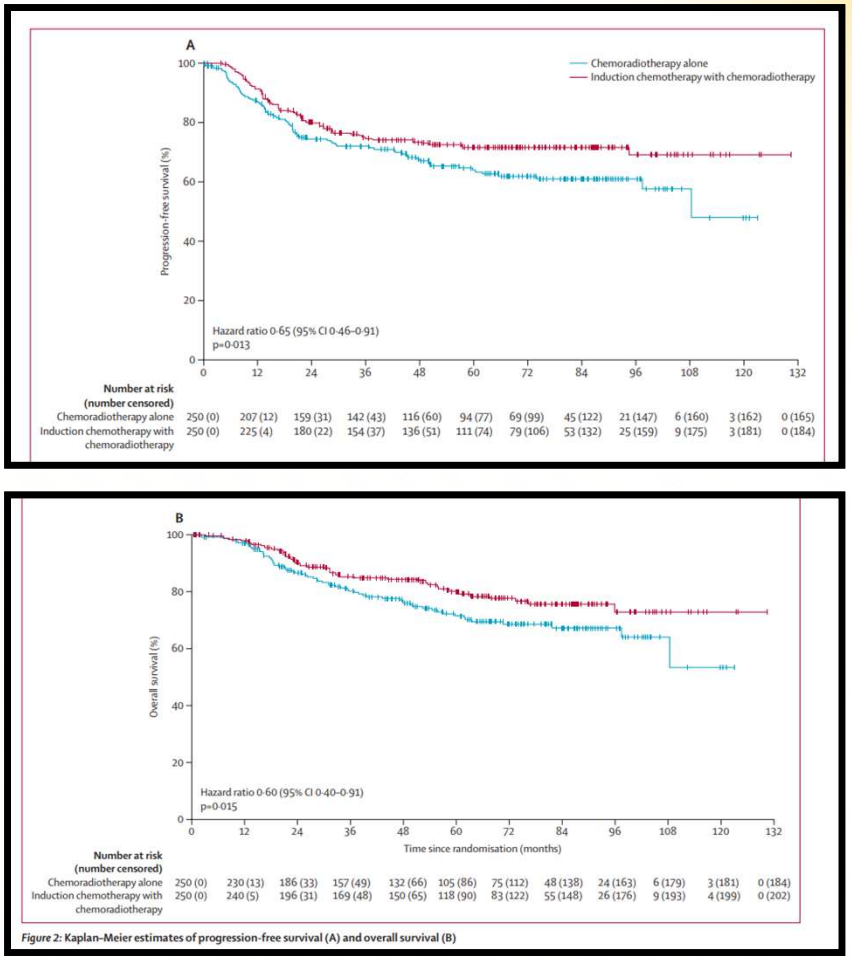


Figure 2: Kaplan-Meier estimates of progression-free survival (A) and overall survival (B)

KEYNOTE-A18: Study Design

Phase 3 study of pembrolizumab + concurrent CCRT vs placebo + CCRT in high-risk LACC

KEY ELIGIBILITY CRITERIA

- FIGO 2014 stage IB2-IIB (node-positive disease) or stage III-IVA (either node-positive or node-negative disease)
- RECIST 1.1 measurable or non-measurable disease
- Treatment naive

R
1:1
N=1060

Cisplatin *(40 mg/m^2 QW for 5 cycles[a])* **+ ERBT followed by brachytherapy + pembrolizumab** *(200 mg Q3W for 5 cycles)*

Mtx pembro *(400 mg Q6W for 15 cycles)*

Cisplatin *(40 mg/m^2 QW for 5 cycles)* **+ ERBT followed by brachytherapy**

Mtx placebo *(Q3W for 5 cycles)*

PRIMARY ENDPOINTS

- PFS (per RECIST v1.1)
- OS

SECONDARY ENDPOINTS

- 24-month PFS, ORR, Patient-reported outcomes, safety

Trial Design:
Global phase 3, randomized, double-blind, multicenter

Stratification:

- EBRT type (IMRT or VMAT vs non-IMRT or non-VMAT)
- Stage at screening (IB2-IIB vs III-IVA)
- Total radiotherapy dose (<70 Gy vs ≥70 Gy [EQ2D])

[a]A 6th cycle was allowed per investigator discretion.
EBRT, external beam radiotherapy; EQ2D, equivalent dose in 2-Gy; FIGO, International Federation of Gynecology and Obstetrics; Gy, grays; IMRT, intensity-modulated radiotherapy; LACC, locally advanced cervical cancer; Mtx, methotrexate; ORR, overall response rate; OS, overall survival; pembro, pembrolizumab; PFS, progression-free survival; QW, weekly; Q3W, every 3 weeks; Q6W, every 6 weeks; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors; VMAT, volumetric-modulated arc therapy.

1. NCT04221945. Updated July 30, 2024. Accessed October 1, 2024. https://www.clinicaltrials.gov/study/NCT04221945. **2.** Lorusso et al. ESMO 2023. Abstract LBA38.

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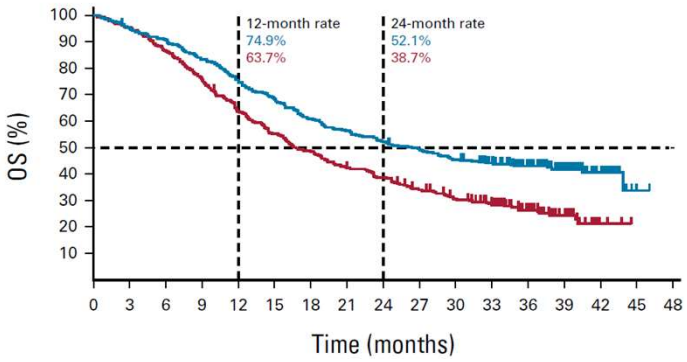
KEYNOTE-826: Results

Phase 3 study of pembro + chemo vs chemo in persistent, recurrent, or metastatic cervical cancer

Efficacy: Pembro + chemo ± bev showed enduring survival benefits at final analysis

OS: All-Comer Population



Efficacy	All-Comer	
	Pembro + chemo (n=308)	Chemo (n=309)
Median PFS, mo (95% CI)	10.4 (9.1-12.2)	8.2 (6.4-8.4)
ORR, % (95% CI)	66.2 (60.7-71.5)	51.5 (45.7-57.2)
Median DOR, mo (range)	18 (1.3+-40.9+)	10.4 (1.5+-40.7+)

Safety: Safety findings for pembro + chemo in this trial were consistent with the established safety

Drug-related AEs, n (%)	Pembro + chemo (n=308)	Chemo (n=309)
AEs, %	99.3	99.4
Grade ≥3, %	82.4	75.4
AEs leading to death, n (%)	16 (5.2)	15 (4.9)
Death related to Tx, n (%)	2 (0.7)	4 (1.3)
Potential IRAEs, %	34.5	16.5
Grade ≥3, %	12.1	2.9

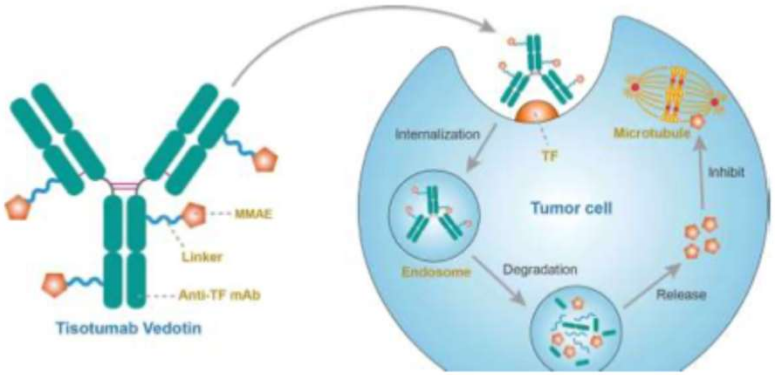
[a]Prior HER2 therapy was permitted.

AE, adverse event; CI, confidence interval; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; T-DXd, trastuzumab deruxtecan; ORR, overall response rate; OS, overall survival; PFS, progression free survival; Q3W, every 3 weeks.

1. NCT03635567. Updated June 25, 2024. Accessed October 4, 2024. https://www.clinicaltrials.gov/study/ NCT03635567. **2.** Monk BJ et al. *J Clin Oncol*. 2023;41(36):5505-5511.

Evolution

- On September 20, 2021, tisotumab vedotin-tftv, an antibody drug conjugate or ADC, was granted accelerated approval for the treatment of adults with recurrent or metastatic cervical cancer who have had disease progression on or after chemotherapy
- A CR or PR was seen in 24% of patients with CR in 7%



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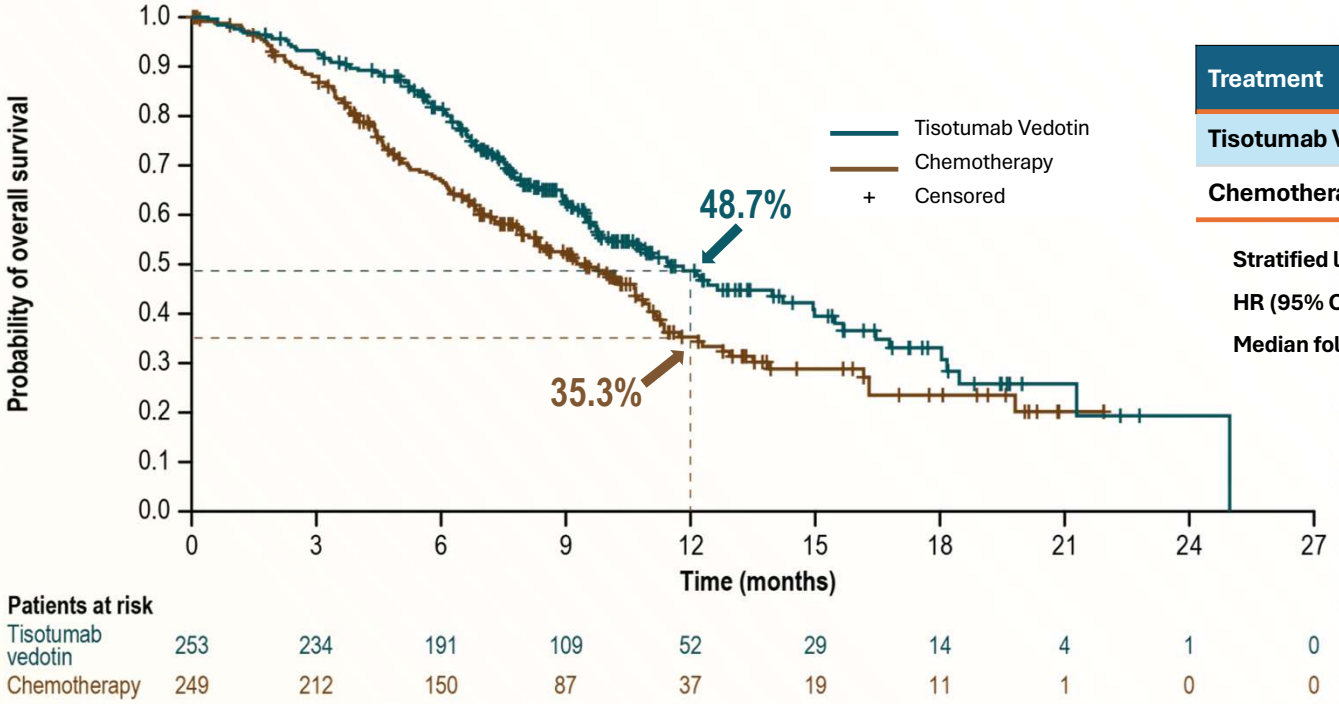
OS (Primary Endpoint)

- The study met overall survival statistical significance at the planned interim analysis
- The tisotumab vedotin arm showed a 30% reduction in risk of death versus chemotherapy



Treatment	Events/Total	Median (95% CI)
Tisotumab Vedotin	123/253	11.5 (9.8, 14.9)
Chemotherapy	140/249	9.5 (7.9, 10.7)

Stratified log-rank *P* value[a]: 0.0038

HR (95% CI): 0.70 (0.54, 0.89)

Median follow-up time (95% CI): 10.8 months (10.3, 11.6)

[a]The threshold for statistical significance is 0.0226 (2-sided), based on the actual number of OS events at interim analysis.
CI, confidence interval; HR, hazard ratio; OS, overall survival.
Vergote IB. ESMO 2023: Oral presentation LB9.

SYSTEMIC THERAPY FOR CERVICAL CANCER[a]

Squamous Cell Carcinoma, Adenocarcinoma, or Adenosquamous Carcinoma

Chemoradiation	Recurrent or Metastatic Disease	
	First-line Therapy[b,c]	Second-line or Subsequent Therapy[g]
Preferred Regimens • Cisplatin • Carboplatin if patient is cisplatin intolerant	**Preferred Regimens** • Pembrolizumab + cisplatin/paclitaxel ± bevacizumab for PD-L1–positive tumors (category 1)[d,e,f,1] • Pembrolizumab + carboplatin/paclitaxel ± bevacizumab for PD-L1–positive tumors (category 1)[d,e,f,1] • Cisplatin/paclitaxel/bevacizumab[d,2] (category 1) • Carboplatin/paclitaxel/bevacizumab[d] **Other Recommended Regimens** • Cisplatin/paclitaxel (category 1)[3,4] • Carboplatin/paclitaxel[5,6] (category 1 for patients who have received prior cisplatin therapy) • Topotecan/paclitaxel/bevacizumab[d,2,7] (category 1) • Topotecan/paclitaxel[7] • Cisplatin/topotecan[7] • Cisplatin[4] • Carboplatin[8,9]	**Preferred Regimens** • Pembrolizumab for TMB-H tumors[e,h] or PD-L1–positive or MSI-H/dMMR tumors[e,f,10] • Tisotumab vedotin-tftv[11] **Other Recommended Regimens** • Bevacizumab[d] • Paclitaxel[9,12] • Albumin-bound paclitaxel • Docetaxel • Fluorouracil • Gemcitabine • Pemetrexed • Topotecan • Vinorelbine • Irinotecan (category 2B) **Useful in Certain Circumstances** • Nivolumab for PD-L1–positive tumors[e,f,13] • Selpercatinib for RET gene fusion-positive tumors • Larotrectinib or entrectinib for *NTRK* gene fusion-positive tumors (category 2B)

[a] Cisplatin, carboplatin, docetaxel, and paclitaxel may cause drug reactions (See NCCN Guidelines for Ovarian Cancer--Management of Drug Reactions [OV-D]).
[b] Cost and toxicity should be carefully considered when selecting an appropriate regimen for treatment.
[c] If not used previously, these agents can be used as second-line or subsequent therapy as clinically appropriate.
[d] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

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Conclusions

- We have made substantial progress in the treatment of all gynecologic malignancies and continue to improve outcomes
- Overall survival for ovarian cancer has tripled in the last 20 years!
- Endometrial/Uterine cancer has now been molecularized and we know far more about how it progresses.
- We have 2 new agents in the treatment of cervical cancer approved in the last 2 years

Acknowledgements

1. University of Colorado Ob/Gyn
2. University of Colorado Cancer Center
3. UCHealth University of Colorado Hospital
4. Freda Iriegbe
5. Patrice Hauptman
6. CGCA
7. All of our wonderful sponsors!