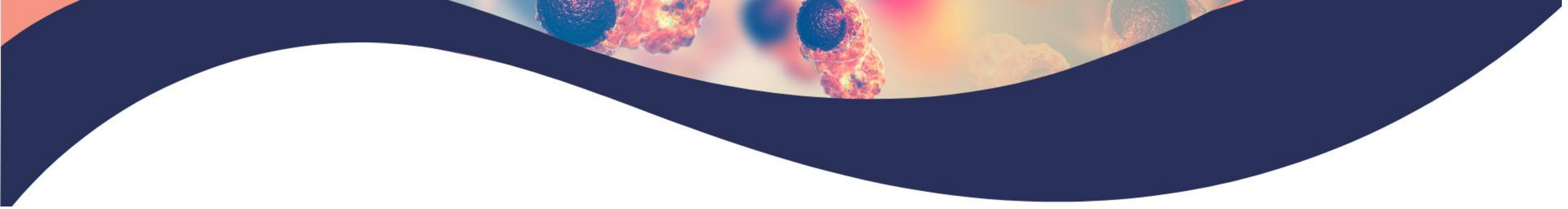

Welcome and Introductions

Matthew Powell, MD
Washington University
St. Louis, Missouri, USA

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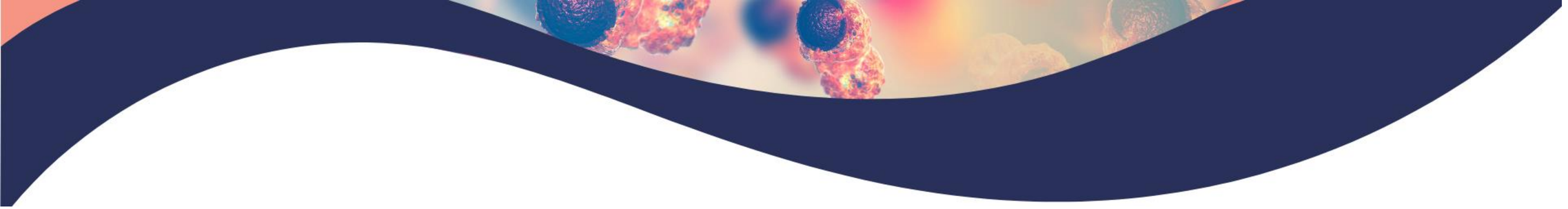

THANK YOU TO OUR SPONSORS FOR TONIGHTS INDUSTRY SUPPORTED SYMPOSIUM

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Our Expert Panel

Matthew Powell, MD
Washington University
St. Louis, Missouri, USA

Amanda Nickles Fader, MD
Johns Hopkins University
Baltimore, Maryland, USA

Floor Backes, MD
The Ohio State University
James Cancer Center
Columbus, Ohio, USA

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NAME	Individual's Role(s) in Activity	Nothing To Disclose	DISCLOSURE <company & role>
Planning Disclosures			
Matthew Powell, MD	**Moderator**		AstraZeneca; Clovis Oncology, Inc.; EISAI INC.; Genentech USA, Inc.; GlaxoSmithKline, LLC.; Merck; Seattle Genetics: Consultant
Speaker Disclosures			
Floor Backes, MD	**Speaker**	X	Agenus; AstraZeneca; EISAI INC.; GSK; Immunogen; Merck: Consultant
Amanda Nickles-Fader, MD	**Speaker**		Verastem, Inc.: Other
Matthew Powell, MD	**Speaker**		AstraZeneca; Clovis Oncology, Inc.; EISAI INC.; Genentech USA, Inc.; GlaxoSmithKline, LLC.; Merck; Seattle Genetics: Consultant
Michelle N Small, MPH	**Staff**	X	
Jill Reese	**Staff**	X	

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Agenda

Topic	Presenter
Welcome and Introduction	**Matthew Powell, MD** Washington University
Front-Line Trials and Current Landscape	**Amanda Nickles Fader, MD** Johns Hopkins University
Emerging Novel Therapies and Clinical Trials, 2nd Line and Beyond	**Floor Backes, MD** The Ohio State University, James Cancer Center
Discussion: And The Science Says . . .	**All Faculty** (Moderator: Mathew Powell, MD)
Audience Q & A	**All Faculty**
Wrap Up & Final Remarks	**Matthew Powell, MD** Washington University

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LEARNING OBJECTIVES

Upon completion of this activity, learners will:

- **Review the current landscape for the treatment of advanced stage or recurrent endometrial cancer based on pivotal clinical trials and insights in 2023.**
- **Discuss biomarker-based strategies to direct chemotherapy, radiation, combined chemoradiation, and biologic-targeted therapies.**
- **Highlight novel therapies and current clinical trials for endometrial cancer.**
- **Decipher how to best treat patients based on debates and discussion from Expert Faculty**

Molecular Testing

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Endometrial Carcinoma

NCCN Guidelines Index
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PRINCIPLES OF MOLECULAR ANALYSIS

- Molecular analysis of endometrial carcinoma has identified four clinically significant molecular subgroups associated with differing clinical prognoses: *POLE* mutations, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), no specific molecular profile (NSMP), and p53 abnormal.[10,11]
- Retrospective analyses indicate that these four molecular subgroups may respond to therapy differently and therefore may require escalation or de-escalation of therapy compared to previous guidelines. Prospective randomized trials are ongoing to determine the role of a molecular profile–guided treatment strategy in the management of high-intermediate-risk and high-risk endometrial carcinomas
- Ancillary studies for *POLE* mutations (hotspot mutations in the exonuclease domain), IHC staining for mismatch repair (MMR) or MSI testing, and p53 IHC are strongly encouraged to complement morphologic assessment regardless of histologic tumor type.[12]
  See Figure 1: Pathology and Genomics in Endometrial Carcinoma (ENDO-A 3 of 4).
- Comprehensive molecular profiling is strongly encouraged via an FDA-approved assay, or a validated test performed in a clinical laboratory improvement amendment (CLIA)-certified laboratory, in the initial evaluation of uterine neoplasms.
- For tumors that are POLE-mutated, MSI-H, or copy number high, clinical trial enrollment is strongly encouraged.
- Molecular testing may be performed on the initial biopsy or D&C material or the final hysterectomy specimen.
- Universal testing of endometrial carcinomas for MMR proteins is recommended.
  - MSI testing is recommended if results are equivocal.
  - MLH1 loss should be further evaluated for promoter methylation to assess for an epigenetic mechanism.
  - Genetic counseling, molecular analysis, and testing for all other MMR abnormalities is recommended.
  - For those who have a strong family history of endometrial and/or colorectal cancer, genetic counseling and testing are recommended regardless of MMR or MLH1 promoter methylation results [see Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer Syndrome) in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal].
- Consider *NTRK* gene fusion testing for metastatic or recurrent endometrial carcinoma.
- Consider tumor mutational burden (TMB) testing through an FDA-approved assay, or a validated test performed in a CLIA-certified laboratory.[13]

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines. Uterine Neoplasms (V1.2024). https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1473

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SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

RECURRENT DISEASE[h,i]

First-Line Therapy for Recurrent Disease[j]	Second-Line or Subsequent Therapy
Preferred • Carboplatin/paclitaxel (category 1 for carcinosarcoma)[k,7] • Carboplatin/paclitaxel/pembrolizumab (except for carcinosarcoma) (category 1)[b,c,d,8] • Carboplatin/paclitaxel/dostarlimab-gxly (category 1)[c,d,e,9] • Carboplatin/paclitaxel/trastuzumab[d,g] (for HER2-positive uterine serous carcinoma)[d,10] • Carboplatin/paclitaxel/trastuzumab[d,g] (for HER2-positive carcinosarcoma)[f,10] **Other Recommended Regimens** • Carboplatin/docetaxel[l] • Carboplatin/paclitaxel/bevacizumab[d,m,11,12] **Useful in Certain Circumstances (Biomarker-directed therapy: after prior platinum-based therapy including neoadjuvant and adjuvant)** • MMR-proficient (pMMR) tumors ▸ Lenvatinib/pembrolizumab (category 1)[c,13] • TMB-H tumors[n] ▸ Pembrolizumab[c,14] • MSI-H/dMMR tumors[o] ▸ Pembrolizumab[c,15] ▸ Dostarlimab-gxly[c,16]	**Other Recommended Regimens** • Cisplatin/doxorubicin[17] • Cisplatin/doxorubicin/paclitaxel[p,14] • Cisplatin • Carboplatin • Doxorubicin • Liposomal doxorubicin • Paclitaxel[14] • Albumin-bound paclitaxel[q] • Topotecan • Bevacizumab[m,r,19] • Temsirolimus[20] • Cabozantinib • Docetaxel (category 2B) • Ifosfamide (for carcinosarcoma) • Ifosfamide/paclitaxel (for carcinosarcoma)[21] • Cisplatin/ifosfamide (for carcinosarcoma) **Useful in Certain Circumstances (Biomarker-directed therapy)** • pMMR tumors ▸ Lenvatinib/pembrolizumab (category 1)[c,13] • TMB-H tumors[n,12] ▸ Pembrolizumab[c] • MSI-H/dMMR tumors[o] ▸ Pembrolizumab[c,15] ▸ Dostarlimab-gxly[c,16] ▸ Avelumab[c] ▸ Nivolumab[c,22] • HER2-positive tumors (IHC 3+ or 2+) ▸ Fam-trastuzumab deruxtecan-nxki[23] • *NTRK* gene fusion-positive tumors ▸ Larotrectinib ▸ Entrectinib

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines. Uterine Neoplasms (V1.2024). https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1473

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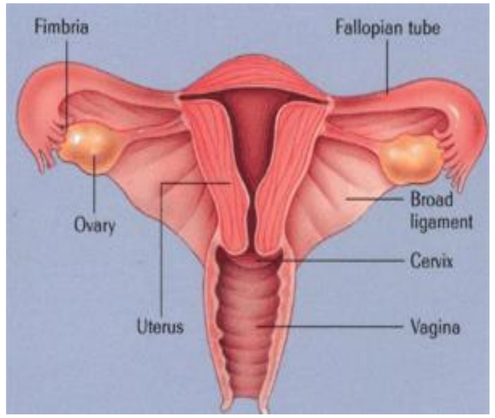
Endometrial Cancer: Annual Incidence and Mortality



Year	Cases	Deaths
1987	35,000	2,900
2024	67,880	13,030

ACS. Key Statistics for Endometrial Cancer. Updated February 14, 2022. https://www.cancer.org/cancer/endometrial-cancer/about/key-statistics.html

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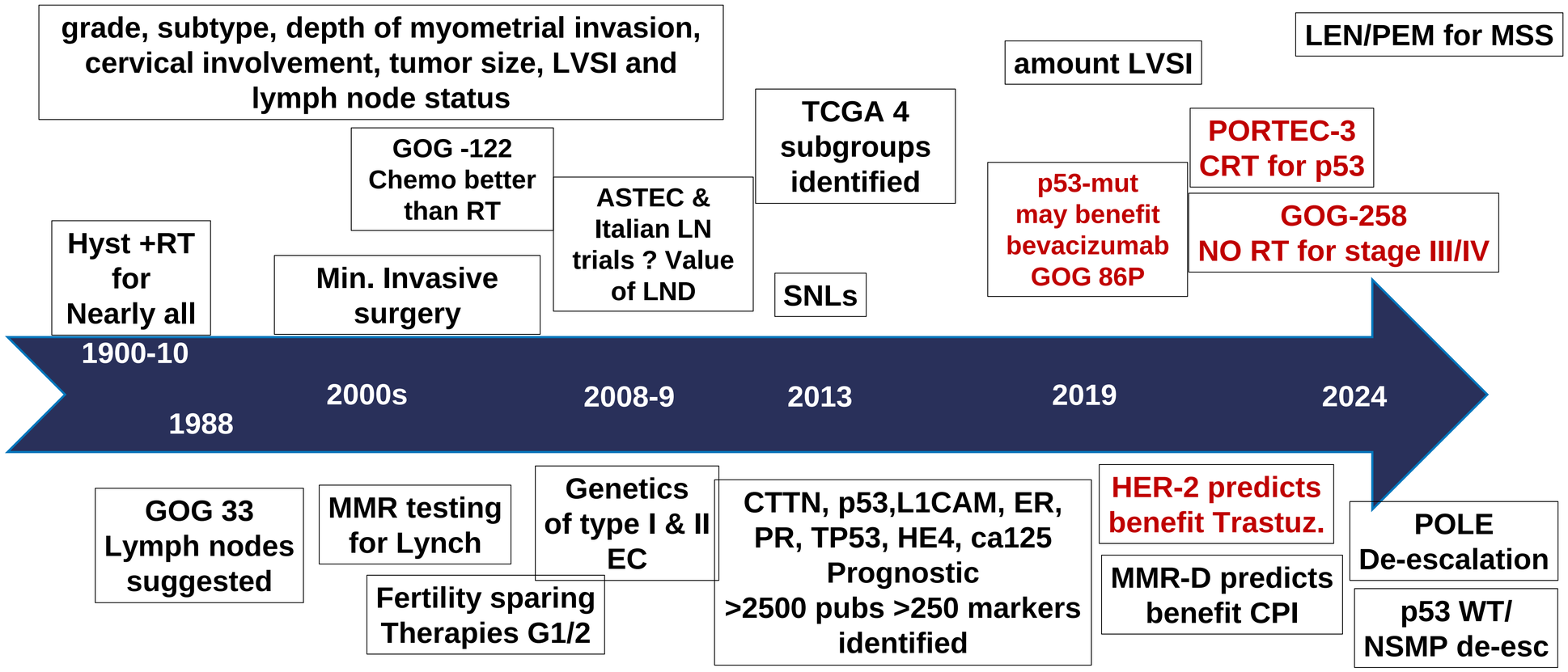
History of management of Endometrial Cancer: Journey from prognostic to predictive markers



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Focused Updates:

Trial	Name	Description	Status
Frontline, metastatic or recurrent PI: Eskander	NRG-GY018	Testing the addition of the immunotherapy drug pembrolizumab to the usual chemotherapy treatment (paclitaxel and carboplatin) in stage III–IV or recurrent EC	**NEJM 3/23, ESMO 10/23**
Frontline, metastatic or recurrent PI: Powell *ENGOT led	GOG-3031/RUBY	A phase III, randomized, double-blind, multicenter study of dostarlimab (TSR-042) + carboplatin-paclitaxel vs placebo + carboplatin-paclitaxel in patients with recurrent or primary aEC	**NEJM 3/23, many updates**
Frontline, metastatic or recurrent PI: Westin Co-PI: Moore *GOG led	GOG-3041/DUO-E	A randomized, multicenter, double-blind, placebo-controlled, phase III study of first-line carboplatin and paclitaxel in combination with durvalumab, followed by maintenance durvalumab with or without olaparib in patients with newly diagnosed advanced or recurrent EC	**ESMO 10/23**

Focused Updates:

Trial	Name	Description	Status
Frontline, metastatic or recurrent PI: Marth	LEAP-001/ ENGOT-en9	A phase III randomized, open-label, study of pembrolizumab (MK-3475) + lenvatinib (E7080/MK-7902) vs chemotherapy for first-line treatment of advanced or recurrent EC	**News release**
Frontline, metastatic or recurrent	AtTEnd	Phase III double-blind, randomized, placebo-controlled trial of atezolizumab in combination with paclitaxel and carboplatin in women with advanced or recurrent EC	**ESMO 10/23**
Frontline, metastatic or recurrent **(dMMR only)**	KEYNOTE-C93/ GOG-3064/ ENGOT-en15	A phase III randomized, open-label, active-comparator controlled clinical study of pembrolizumab vs platinum doublet chemotherapy in participants with mismatch repair-deficient (dMMR) advanced or recurrent EC in the first-line setting	**Recruiting**

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