Welcome and Introductions

Matthew Powell, MD
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St. Louis, Missouri, USA
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NEW TERM *An “ineligible company” is any entity whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

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

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

NCCN Guidelines Version 1.2024
Endometrial Carcinoma

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.\(^\text{1,11}\)
- 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.\(^\text{12}\)
  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.\(^\text{13}\)
# Systemic Therapy for Endometrial Carcinoma

## Recurrent Disease

### First-Line Therapy for Recurrent Disease

**Preferred**
- Carboplatin/paclitaxel (category 1 for carcinosarcoma)<sup>h,7</sup>
- Carboplatin/paclitaxel/pembrolizumab (except for carcinosarcoma) (category 1)<sup>i</sup>
- Carboplatin/paclitaxel/dostarilimab-gxly (category 1)<sup>c,d,e,9</sup>
- Carboplatin/paclitaxel/trastuzumab<sup>p,9</sup>
  - (for HER2-positive uterine serous carcinoma)<sup>h,10</sup>
- Carboplatin/paclitaxel/trastuzumab<sup>p,9</sup>
  - (for HER2-positive carcinosarcoma)<sup>h,10</sup>

**Other Recommended Regimens**
- Carboplatin/docetaxel<sup>e</sup>
- Carboplatin/paclitaxel/bevacizumab<sup>d,m,11,12</sup>

**Useful in Certain Circumstances**
(Biomarker-directed therapy: after prior platinum-based therapy including neoadjuvant and adjuvant)
- MMR-proficient (pMMR) tumors
  - Lenvatinib/pembrolizumab (category 1)<sup>c,13</sup>
- TMB-H tumors<sup>n</sup>
  - Pembrolizumab<sup>6,14</sup>
- MSI-H/dMMR tumors<sup>o</sup>
  - Pembrolizumab<sup>12</sup>
- Dostarilimab-gxly<sup>c,16</sup>

### Second-Line or Subsequent Therapy

**Other Recommended Regimens**
- Cisplatin/doxorubicin<sup>17</sup>
- Cisplatin/doxorubicin/paclitaxel<sup>p,14</sup>
- Carboplatin
- Doxorubicin
- Liposomal doxorubicin
- Paclitaxel<sup>14</sup>
- Albumin-bound paclitaxel<sup>1</sup>
- Topotecan
- Bevacizumab<sup>18,19</sup>
- Temsiroliimus<sup>20</sup>
- Cabozantinib
- Docetaxel (category 2B)
- Ifosfamide (for carcinosarcoma)
- Ifosfamide/paclitaxel (for carcinosarcoma)<sup>21</sup>
- Carboplatin/ifosfamide (for carcinosarcoma)

**Useful in Certain Circumstances**
(Biomarker-directed therapy)
- pMMR tumors
  - Lenvatinib/pembrolizumab (category 1)<sup>c,13</sup>
- TMB-H tumors<sup>n,12</sup>
- Pembrolizumab<sup>c</sup>
- MSI-H/dMMR tumors<sup>0</sup>
  - Pembrolizumab<sup>15</sup>
  - Dostarilimab-gxly<sup>f,16</sup>
- Avelumab<sup>c</sup>
  - Nivolumab<sup>c,22</sup>
- HER2-positive tumors (IHC 3+ or 2+):
  - Fam-trastuzumab deruxtecan-nxk<sup>23</sup>
- NTRK gene fusion-positive tumors
- Larotrectinib
- Entrectinib
## Endometrial Cancer: Annual Incidence and Mortality

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
<th>Deaths</th>
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<tr>
<td>1987</td>
<td>35,000</td>
<td>2,900</td>
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<tr>
<td>2024</td>
<td>67,880</td>
<td>13,030</td>
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History of management of Endometrial Cancer: Journey from prognostic to predictive markers

1900-10

- Hyst + RT for Nearly all
- GOG -122 Chemo better than RT
- GOG 33 Lymph nodes suggested
- MMR testing for Lynch

2000s

- Min. Invasive surgery
- ASTEC & Italian LN trials ? Value of LND
- TCGA 4 subgroups identified
- SNLs

2008-9

- Genetics of type I & II EC
- CTTN, p53, L1CAM, ER, PR, TP53, HE4, ca125
- Prognostic >2500 pubs >250 markers identified

2013

- HER-2 predicts benefit Trastuz.

2019

- POLE De-escalation
- p53 WT/NSMP de-esc
- MMR-D predicts benefit CPI
- LEN/PEM for MSS
- GOG-258 NO RT for stage III/IV

2024

- p53-mut may benefit bevacizumab GOG 86P
- CRT for p53
- CTTN, p53, L1CAM, ER, PR, TP53, HE4, ca125
- Prognostic >2500 pubs >250 markers identified
- MIN. Invasive surgery
## Focused Updates:

<table>
<thead>
<tr>
<th>Trial</th>
<th>Name</th>
<th>Description</th>
<th>Status</th>
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<tbody>
<tr>
<td>Frontline, metastatic or recurrent PI: Eskander</td>
<td>NRG-GY018</td>
<td>Testing the addition of the immunotherapy drug pembrolizumab to the usual chemotherapy treatment (paclitaxel and carboplatin) in stage III–IV or recurrent EC</td>
<td>NEJM 3/23, ESMO 10/23</td>
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<tr>
<td>Frontline, metastatic or recurrent PI: Powell *ENGOT led</td>
<td>GOG-3031/RUBY</td>
<td>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</td>
<td>NEJM 3/23, many updates</td>
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<tr>
<td>Frontline, metastatic or recurrent PI: Westin Co-PI: Moore *GOG led</td>
<td>GOG-3041/DUO-E</td>
<td>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</td>
<td>ESMO 10/23</td>
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<th>Status</th>
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<tbody>
<tr>
<td>Frontline, metastatic or recurrent PI: Marth</td>
<td>LEAP-001/ ENGOT-en9</td>
<td>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</td>
<td>News release</td>
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<tr>
<td>Frontline, metastatic or recurrent</td>
<td>AtTEnd</td>
<td>Phase III double-blind, randomized, placebo-controlled trial of atezolizumab in combination with paclitaxel and carboplatin in women with advanced or recurrent EC</td>
<td>ESMO 10/23</td>
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<tr>
<td>Frontline, metastatic or recurrent (dMMR only)</td>
<td>KEYNOTE-C93/ GOG-3064/ ENGOT-en15</td>
<td>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</td>
<td>Recruiting</td>
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