Emerging Therapies and Clinical Trials

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Objectives

• Discuss current trials by line of therapy
  • First-line adjuvant
  • First-line metastatic or recurrent
  • Second or third line recurrent
• Explore unmet needs and areas of opportunity
“The best way to predict the future is to create it”

Abraham Lincoln
## Endometrial Cancer: Active Trials Adjuvant

| Front-line Adjuvant PI: Slomovitz Co-PI: Barber | GOG-3053/KEYNOTE-B21 NCT04634877 | A Phase 3, Randomized, Double-Blind Study of Pembrolizumab versus Placebo in Combination With Adjuvant Chemotherapy With or Without Radiotherapy for the Treatment of Newly Diagnosed High-Risk Endometrial Cancer After Surgery With Curative Intent | Recruiting |
Key eligibility criteria:
- Newly diagnosed endometrial carcinoma or carcinosarcoma
- High Risk*
- No prior therapy including XRT or neo-adjuvant
- Curative intent TH/BSO +/- LN sampling/dissection
- No residual disease

Pembrolizumab 200 mg IV (Q3W, 6 infusions) +
Carboplatin (AUC 5 or 6)
Paclitaxel 175 mg/m² (Q3W, 4 or 6 cycles)

Placebo IV (Q3W, 6 infusions) +
Carboplatin (AUC 5 or 6)
Paclitaxel 175 mg/m² (Q3W, 4 or 6 cycles)

Stage 1

Stage 2

Pembrolizumab 400 mg Q6W (6 cycles)

Placebo Q6W (6 cycles)

Radiotherapy (+/- Cisplatin) after completion of chemotherapy

Dual Primary Endpoints:
- Disease Free Survival (DFS)
  - Investigator
- Overall Survival (OS)

Secondary Endpoints:
- DFS by blinded independent central review
- DFS/OS by TMB, PD-L1 status
- Safety
- QoL

Stratification factors:
- MMR status (if pMMR then further stratification by:
  - Stage (I/II vs III/IVA)
  - Planned radiation (EBRT vs Chemo-EBRT vs no EBRT)
  - Histology (non-endometrioid vs endometrioid)

* High Risk:
  - FIGO (2009) Surgical Stage I or II with myometrial invasion of non-endometrioid histology
  - or of any histology with known aberrant p53 expression or p53 mutation
  - FIGO (2009) Surgical Stage III or IVA of any histology
<table>
<thead>
<tr>
<th>Study</th>
<th>PI</th>
<th>Study Design</th>
<th>Description</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Front-line, metastatic or recurrence PI: Powell *ENGOT led</td>
<td>GOG-3031/RUBY NCT03981796</td>
<td>A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab (TSR-042) Plus Carboplatin-paclitaxel Versus Placebo Plus Carboplatin-paclitaxel in Patients With Recurrent or Primary Advanced Endometrial Cancer</td>
<td>Recruiting</td>
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<tr>
<td>Front-line, metastatic or recurrence PI: Westin Co-PI: Moore *GOG led</td>
<td>GOG-3041/DUO-E NCT04269200</td>
<td>A Randomised, Multicentre, 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 Endometrial Cancer</td>
<td>Recruiting</td>
<td></td>
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<tr>
<td>Front-line, maintenance PI: Makker *ENGOT led</td>
<td>GOG-3055/SIENDO NCT03555422</td>
<td>A Randomized, Double-Blind, Phase 3 Trial Of Maintenance With Selinexor/ Placebo After Combination Chemotherapy For Patients With Advanced Or Recurrent Endometrial Cancer</td>
<td>Recruiting</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>NCT Number</td>
<td>Description</td>
<td>Status</td>
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<tr>
<td>LEAP-001</td>
<td>NCT04865289</td>
<td>Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) Versus Chemotherapy for Endometrial Carcinoma (ENGOT-en9/MK-7902-001)</td>
<td>Active, not recruiting</td>
<td></td>
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<tr>
<td>Attend</td>
<td>NCT03603184</td>
<td>Phase III Double-blind Randomized Placebo Controlled Trial of Atezolizumab in Combination With Paclitaxel and Carboplatin in Women With Advanced/Recurrent Endometrial Cancer</td>
<td>Active, recruiting</td>
<td></td>
</tr>
<tr>
<td>NRG-GY-018</td>
<td>NCT03914612</td>
<td>Testing the Addition of the Immunotherapy Drug Pembrolizumab to the Usual Chemotherapy Treatment (Paclitaxel and Carboplatin) in Stage III-IV or Recurrent Endometrial Cancer</td>
<td>Recruiting</td>
<td></td>
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</tbody>
</table>
A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab (TSR-042) plus Carboplatin-paclitaxel versus Placebo Plus Carboplatin-paclitaxel in Patients with Recurrent or Primary Advanced Endometrial Cancer (RUBY)  
(4010-03-001 / ENGOT EN-6 / GOG-3031)

**Study Design**

**Population:** Patients with primary Stage III or IV disease or first recurrent endometrial cancer  
**Treatment:** Double-blind PD-1 inhibitor (dostarlimab) or placebo in combo with chemo (6 cycles); monotherapy for up to 3 years  
**Stratification:** MSI Status, Prior pelvic radiotherapy, Disease status  
**N Patients:** 470 patients (235 patients – dostarlimab with chemo; 235 patients – placebo with chemo)  
**N Sites:** Approximately 160 sites in 19 countries  
**Enrollment:** 199 randomized to date  
**Primary Endpoint:** Investigator assessed PFS per RECIST v1.1
Study Design – Part 2

Population: Primary Stage III or IV or First Recurrent Endometrial Cancer

N=270 Randomized 2:1

Dostarlimab 500 mg + Carboplatin AUC 5 + Paclitaxel 175 mg/m² D1 Q3W

Cycle 6

Dostarlimab 1000 mg Q6W + Niraparib ISD QD Q3W For up to 3 yrs

EOT

Placebo + Carboplatin AUC 5 + Paclitaxel 175 mg/m² D1 Q3W

Cycle 6

Placebo Q6W Up to 3 yrs

EOT

Safety and Survival Follow-up

STRATIFICATION
MSI/MMR Status (MSI-H or MSS), Prior External Pelvic Radiotherapy (Yes or No), Disease Status (Primary Stage III or IV, First Recurrent)

PRIMARY ENDPOINT
BICR assessed PFS per RECIST v1.1
GOG-3041/DUO-E: Schema

Key Eligibility Criteria
- Newly diagnosed Stage III/Stage IV or recurrent endometrial cancer
- Naive to first-line systemic anti-cancer treatment
- Prior adjuvant chemotherapy allowed if >= 12 months from last treatment to relapse
- Known MMR status
- Prior radiotherapy allowed
- All histologies except sarcomas

Stratification:
- MMR status
- Recurrent Disease
- Geographic Region

Arm A
N=233
- Q3W² Platinum CTX
- Placebo for Olaparib
- Q4W Placebo for Durvalumab

Arm B
N=233
- Q3W² Platinum CTX
- Placebo for Olaparib
- Q4W Durvalumab 1500 mg (IV)

Arm C
N=233
- Q3W² Platinum CTX
- Olaparib 300mg tablets (bd)
- Q4W Durvalumab 1500 mg (IV)

CTX phase (Cycles 1-6)
Maintenance phase (Cycles 7 and on)

Treatment until Objective Disease Progression
Selinexor Inhibits XPO1 and Induces Cancer Cell Death

Exportin 1 (XPO1) is the major nuclear export protein for:

1. Tumor suppressor proteins (TSPs) – functional inactivation
   (TSPs, e.g. p53, pRb, IκB, p27, p21, FOXOs)
2. eIF4E-bound proto-oncogene mRNAs
   (e.g. c-Myc, Bcl2, Bcl6, BclXL) – enhances translation

Elevated XPO1 expression:
1. Inactivates TSPs by mislocalization
2. Enhances proto-oncoprotein translation
3. Correlates with poor patient prognosis

Selinexor is an oral selective inhibitor of XPO1 that:
1. Reactivates TSPs and blocks proto-oncoprotein translation
2. Blocks DNA damage repair
3. Synergizes with DNA damage inducing therapies
4. Orally active against GCB and non GCB DLBCL in vivo

KCP-330-024-ENGOT-EN5/SIENDO Trial Overview

Eligibility
Patients who completed a single line of at least 12 weeks of taxane-platinum combination therapy including patients who received taxane-platinum combination therapy for:
- Primary Stage IV disease
- First Relapse (i.e., relapse after primary therapy including surgery and/or adjuvant therapy for Stage I-IV disease)

Eligible Patients (N=248) → Randomized 2:1 → Selinexor 80 mg once weekly (60 mg if BMI <20 kg/m²) → Primary Endpoint: PFS from time of randomization until death or PD as determined by Investigator*

Secondary Endpoints: PFS as assessed by BICR, DSS, OS, TFST, PFS2, TSST, DCR, QOL Questionnaires
LEAP-001: 1L phase 3 in endometrial cancer

Key eligibility criteria:
- Stage III, Stage IV or recurrent endometrial carcinoma
- Measurable disease or radiographically apparent disease
- May have received prior chemotherapy only if adjuvant/neoadjuvant therapy and/or administered concurrently with radiation
- ECOG PS 0 or 1

Carboplatin and Paclitaxel
N=360

Lenvatinib and Pembrolizumab
N=360

Dual Primary Endpoints
- PFS
- OS

Secondary Endpoints
- ORR
- Safety (CTCAE)
- PRO (EORTC QLC-C30)
- PK (lenvatinib)

Stratification factors:
- MMR status (pMMR v dMMR), if pMMR:
  - Measurable disease (yes or no)
  - ECOG (0 vs 1)
  - Prior chemotherapy and/or chemoradiation (yes or no)
AtTEnd (ENGOT-en7): atezolizumab + carboplatin/paclitaxel clinical trials

- AtTEnd (ENGOT-en7) is an international (no US patients), multicenter, phase 3, double-blind, randomized, controlled trial of atezolizumab in combination with paclitaxel and carboplatin in women with advanced/recurrent endometrial cancer
- 550 patients with newly diagnosed, advanced stage III/IV, or recurrent endometrial cancer will be accrued during a period of 24 months with a 1:2 randomization ratio into 2 arms:
  - Control group: standard chemotherapy plus placebo IV every 21 days up to 6/8 cycles followed by placebo until progression
  - Experimental group: standard chemotherapy plus 1200 mg atezolizumab IV every 21 days up to 6/8 cycles followed by atezolizumab until progression
- Standard chemotherapy will consist of 175 mg/m² paclitaxel plus AUC5/6 carboplatin. Patients will be stratified by histology, disease stage, microsatellite status, and country of experimental site
- Primary endpoints are OS and PFS. Secondary endpoints include ORR, duration of response, PFS2, quality of life, adverse events, and compliance

Randomized phase II/III study of carboplatin + paclitaxel vs carboplatin + paclitaxel + pembrolizumab in patients with advanced-stage (stage 3 or 4) or recurrent endometrial cancer

Stage III & IV or recurrent endometrial cancer
(Stage 3 or 4A: measurable disease; Stage 4B or recurrent whether there is measurable disease or not)
MMR-proficient vs MMR-deficient

C/T placebo

C/T pembrolizumab + maintenance pembrolizumab x 12 months

Stratification factors: MMR-proficient vs MMR-deficient, performance status, measurable disease status

N=590 pMMR patients
N=185 dMMR patients
## Endometrial Cancer: Active Trials

### 2nd Line

<table>
<thead>
<tr>
<th>Study Description</th>
<th>NCT Number</th>
<th>Details</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>An Umbrella Study of INCMGA00012 Alone and in Combination with Other Therapies in Participants with Advanced or Metastatic Endometrial Cancer Who Have Progressed on or After Platinum-Based Chemotherapy</td>
<td>NCT04463771</td>
<td>Recruiting Selection closed Sites: 23/30 Total: 40 (215) GOG:26</td>
<td></td>
</tr>
<tr>
<td>A Phase II Study of Abemaciclib in Combination with Letrozole in Advanced, Recurrent or Metastatic Endometrioid Endometrial Cancer</td>
<td>NCT04393285</td>
<td>Recruiting Selection closed Sites: 19/25 Total: 5/50</td>
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<tr>
<td>A Phase IB/II Multi-Cohort Study of Targeted Agents With Atezolizumab for Patients With Recurrent or Persistent Endometrial Cancer</td>
<td>NCT04486352</td>
<td>Not yet recruiting</td>
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</tbody>
</table>

**Notes:**
- GOG-3038/POD1UM-204
- AFT-50 EndoMap
- CPI: Platinum-Based Chemotherapy
- PI: Principal Investigator
- Co-PI: Co-Principal Investigator
Phase 2, Open-Label, Non-Randomized, Umbrella Study of Retifanlimab (PD-1 Inhibitor) Alone or With Other Therapies in Patients With Advanced or Metastatic Endometrial Cancer Who Have Progressed on or After Platinum-Based Chemotherapy

**Primary Endpoint**
- Group A: ORR (per RECIST 1.1, by ICR)

**Secondary Endpoints**
- A & B: DOR, DCR, PFS, OS
- C & D: ORR
- All groups: safety and tolerability

**Key Inclusion Criteria**
- Women > 18 years of age (or as applicable per local country requirements)
- Histologically confirmed diagnosis of advanced or metastatic endometrial cancer
- Disease progression on or after treatment with > 1 platinum-containing regimen
- > 1 measurable tumor lesion per RECIST v1.1
- ECOG PS of 0 to 1
- Willingness to provide tumor tissue sample (fresh or archived)

**Key Exclusion Criteria**
- Histologically confirmed diagnosis of sarcoma of the uterus
- Toxicity of prior therapy that has not recovered to < grade 1
- Active autoimmune disease requiring systemic immunosuppression with corticosteroids or immunosuppressive drugs within 14 days before the first dose of study treatment
- Known active hepatitis B or C
- HIV positive, unless viral load undetectable, CD4+ count ≥ 300/μL
- Groups C and D: Limiting immune-related toxicity during prior checkpoint inhibitor therapy

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Retifanlimab administered IV on day 1 of each 28-day cycle for up to 26 cycles.
Epacadostat administered orally BID.
Pemigatinib administered orally QD.

NCT04463771
GOG 3039: Study Schema

Metastatic, persistent or recurrent endometrioid endometrial cancer

Abemaciclib 150mg PO BID
+ Letrozole 2.5mg PO Daily

28-Day Cycle Until Progression or Toxicity
Objectives* (Recently changed)

• Primary: 6 month PFS

• Secondary: response rate, to estimate time to disease progression.
  • To describe toxicities of combination therapy
# AFT-50 Study Overview

<table>
<thead>
<tr>
<th>Study Chair</th>
<th>Brian Slomovitz, MD (Cell: 646-706-2463)</th>
</tr>
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<tbody>
<tr>
<td>Study Type/Phase</td>
<td>Phase IB/II</td>
</tr>
<tr>
<td>Clinical Indication</td>
<td>Endometrial Cancer</td>
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<tr>
<td>Study Drugs</td>
<td>Atezolizumab</td>
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<tr>
<td></td>
<td>Bevacizumab</td>
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<td></td>
<td>Ipatasertib</td>
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<td></td>
<td>Talazoparib</td>
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<tr>
<td>Pharma Partner(s)</td>
<td>Genentech</td>
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<td></td>
<td>Pfizer (one treatment arm)</td>
</tr>
<tr>
<td># Initial Study Subjects</td>
<td>60 (20 per study arm)</td>
</tr>
<tr>
<td># Sites</td>
<td>25</td>
</tr>
<tr>
<td>Estimated Duration</td>
<td>48 Months</td>
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</table>
AFT-50 EndoMap: Study Goals & Obligations - Design

Eligibility criteria:
Recurrent EC
• ≥1 prior chemotherapy (platinum &/or taxane)
• ≤2 prior chemotherapy regimens
• No prior CITs

Primary endpoint:
• ORR

Secondary endpoints:
• 6-month PFS
• DCR
• DoR
• 2-year PFS
• OS
• Safety

Pre-screening & screening registration
→ Radiographic confirmation of recurrence (+ measurable disease)
→ Core biopsy for prospective FoundationOne
→ Sub-protocol assignment

- Biomarker-negative
  - Bevacizumab 10 mg/kg q2w + atezolizumab 1680 mg q4w

- PI3K/AKT signature
  - Ipatasertib 400 mg daily + atezolizumab 1680 mg q4w

- gLOH
  - Talazoparib 1mg PO daily + atezolizumab 1680 mg q4w

https://clinicaltrials.gov/ct2/show/NCT04486352
Areas of Opportunity

• First line adjuvant
  • Biomarker driven (ER, PR, what else)
  • Better identify high risk patients
  • Non-chemotherapy based regimens
  • I/O?

• First-line metastatic or recurrent
  • I/O with or without chemo
  • Hormonal therapy
  • Other biomarker driven therapy
  • Treatment differences MSI v MSS (dMMR v pMMR)
  • Role of radiation combinations?
Areas of Opportunity

• Second line metastatic or recurrent
  • I/O after I/O??
  • Biomarker driven (ER, PR, what else)
  • Future of second line chemo for endometrial cancer
  • Role of re-challenging with platinum therapy
  • Other ideas
Thank you!