Emerging Novel Therapies and Clinical Trials, 2\textsuperscript{nd} Line & Beyond

**Floor Backes, MD**  
The Ohio State University,  
Wexner Medical Center and James Cancer Hospital  
Columbus, Ohio, USA

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# NCCN Guidelines Version 1.2024
## Endometrial Carcinoma

### RECURRENT DISEASE

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Second-Line or Subsequent Therapy</th>
</tr>
</thead>
</table>
| - Carboplatin/paclitaxel (category 1 for carcinosarcoma)
- Carboplatin/paclitaxel/pembrolizumab (except for carcinosarcoma) |
- Carboplatin/paclitaxel/dostarlimab-gxly (category 1)
- Carboplatin/paclitaxel/trastuzumab (for HER2-positive uterine serous carcinoma)
- Carboplatin/paclitaxel/trastuzumab (for HER2-positive carcinosarcoma) |
| Other Recommended Regimens |
- Carboplatin/docetaxel |
- Carboplatin/paclitaxel/bevacizumab |

#### Useful in Certain Circumstances

**Biomarker-directed therapy: after prior platinum-based therapy including neoadjuvant and adjuvant**

- MMR-proficient (pMMR) tumors
  - Lenvatinib/pembrolizumab (category 1)
  - TMB-H tumors
  - Pembrolizumab
  - MSI-H/dMMR tumors
  - Pembrolizumab
  - Dostarlimab-gxly

### Other Recommended Regimens

- Cisplatin/doxorubicin
- Cisplatin/doxorubicin/paclitaxel
- Cisplatin
- Carboplatin
- Doxorubicin
- Liposomal doxorubicin
- Paclitaxel
- Albumin-bound paclitaxel
- Topotecan
- Bevacizumab
- Temsirolimus
- Cabozantinib
- Docetaxel (category 2B)
- Ifosfamide (for carcinosarcoma)
- Ifosfamide/paclitaxel (for carcinosarcoma)
- Cisplatin/ifosfamide (for carcinosarcoma)

#### Useful in Certain Circumstances

**Biomarker-directed therapy**

- pMMR tumors
  - Lenvatinib/pembrolizumab (category 1)
  - TMB-H tumors
  - Pembrolizumab
  - MSI-H/dMMR tumors
  - Pembrolizumab
  - Dostarlimab-gxly
  - Avelumab
  - Nivolumab
  - HER2-positive tumors (IHC 3+ or 2+)
  - Fam-trastuzumab deruxtecan-nxki
  - NTRK gene fusion-positive tumors
  - Larotrectinib
  - Entrectinib
Changing Molecular Landscape

PIK3CA 50-60%
CTNNB1 25%
FGFR 12%

25-35%
Mismatch repair deficiency

75-85%
PTEN inactivation

35-40%
ARID1A inactivation

20-30%
ERBB2/KRAS/BRAF/MEK pathway activation

Other factors
- TROP2 (>90%)
- FRα (64%)
- HRD (22%)
- PD-L1
- B7-H4
- CLDN6

Yen, Int J Gynecol Pathol 2021
Novel Agents and combinations for Recurrent Endometrial Cancer

• Immunotherapy
  - IO combinations (FGFR, TIGIT, LAG3,TIM3)

• Antibody Drug Conjugates
  - HER2
  - TROP2
  - FRα

• Targeting cell cycle regulation and DNA repair
  - PI3K inhibitors (eg, alpelisib)
  - CHK1 inhibitor (eg, afuresertib)
  - WEE1 inhibitor (eg, adavosertib, ZN-c312)
  - PARP inhibitor

• Hormonal therapy
  - Anti-estrogen, antiprogesterone, SERM/SERD
  - Combinations: mTOR, PIK3CA inhibitor, CDK4/6 inhibitor
Phase 2 KEYNOTE-158 Trial: Study Design

• Ongoing, international, multicohort, open-label phase 2 study of pembrolizumab in select advanced solid tumors that have progressed on SOC therapy
• Patients with previously treated, MSI-H/dMMR advanced endometrial cancer enrolled in cohorts D and K

Patients
- Age ≥18 years
- Histologically or cytologically confirmed advanced cervical cancer
- Progression on/intolerance to ≥1 line of standard therapy
- ECOG PS 0 or 1
- Tumor sample for biomarker analysis

Primary Endpoint: ORR (RECIST v1.1, ICR)
Secondary Endpoints: DOR, PFS, OS

Efficacy/safety assessed in all pts who received ≥1 dose pembro (all pts as treated)
  - DOR assessed in all pts who had a CR or PR

Phase 1 GARNET Study of Dostarlimab: Endometrial Cancer Cohorts

**GARNET Trial Design**

- **Part 1**: Dose finding
- **Part 2A**: Fixed-dose safety run-in
- **Part 2B**: Expansion cohorts

**A1: dMMR/MSI-H EC**
- N=153

**A2: MMRp/MSS EC**
- N=161

- **E**: NSCLC
- **F**: Non-endometrial dMMR/MSI-H basket
- **G**: PROC

- **Dostarlimab 500 mg Q3W x 4 cycles → dostarlimab 1000 mg Q6W to PD**
- **Until disease progression**

- **Primary endpoints**: ORR and DOR per RECIST V.1.1 (BICR assessment)

- **Key inclusion criteria**:
  - Progression on or after platinum doublet therapy
  - ≤ 2 prior lines of treatment for recurrent/adv disease
  - Measurable disease at baseline
  - Anti-PD-(L)1 naïve
  - Screening via local MMR/MSI testing (IHC, PCR, or NGS) in certified local laboratory; patient cohort assignment was by MMR IHC results
  - 2 scans demonstrating PD on or after latest systemic therapy

- **Cohort A1 – Dostarlimab treatment disposition at DCO: 70.5 (n=108)**
  - Discontinued: 29.4% (n=45) on treatment
  - Efficacy/safety assessed in all patients with measurable disease at baseline and had received ≥6 months dostarlimab (efficacy-evaluable population)

## Single Agent Immunotherapy

<table>
<thead>
<tr>
<th></th>
<th>Keynote-158&lt;sup&gt;1&lt;/sup&gt;</th>
<th>GARNET MSI-H/dMMR</th>
<th>PHAEDRA</th>
<th>GARNET MSS/pMMR</th>
<th>KEYNOTE-028&lt;sup&gt;2&lt;/sup&gt;</th>
<th>NCT01375842&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase / type</strong></td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1b</td>
<td>1a</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>Previously treated MSI-H</td>
<td>Previously treated MSI-H</td>
<td>dMMR</td>
<td>Previously treated MSS</td>
<td>Previously treated PD-L1+ MSS/pMMR</td>
<td>Recurrent EC MSS/pMMR</td>
</tr>
<tr>
<td><strong>Patients, n</strong></td>
<td>90</td>
<td>108</td>
<td>35</td>
<td>156</td>
<td>24</td>
<td>15</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Pembrolizumab</td>
<td>Dostarlimab</td>
<td>Durvalumab</td>
<td>Dostarlimab</td>
<td>Pembrolizumab</td>
<td>Atezolizumab</td>
</tr>
<tr>
<td><strong>Prior lines</strong></td>
<td>0 – &gt;5</td>
<td>1-3</td>
<td>1-3</td>
<td>1-3</td>
<td>1-3</td>
<td>1-3</td>
</tr>
<tr>
<td><strong>ORR, %</strong></td>
<td>48%&lt;sup&gt;*&lt;/sup&gt;</td>
<td>43.5%</td>
<td>47%</td>
<td>14.1%</td>
<td>13%</td>
<td>13</td>
</tr>
<tr>
<td><strong>DCR, %</strong></td>
<td>66%</td>
<td>56%</td>
<td>35%</td>
<td>26%</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td><strong>DOR</strong></td>
<td>NR (3-50+)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>mPFS</strong></td>
<td>13.1 mo</td>
<td>Immature</td>
<td>8.3</td>
<td>1.8 mo</td>
<td>1.7 mo</td>
<td></td>
</tr>
<tr>
<td><strong>mOS</strong></td>
<td>@12-mo : 69%</td>
<td>NR</td>
<td>@12-month: 71%</td>
<td>NR</td>
<td>9.6 mo</td>
<td></td>
</tr>
<tr>
<td><strong>Safety summary (TRAЕ grade ≥3)</strong></td>
<td>12%</td>
<td>13%</td>
<td>3%</td>
<td>19%</td>
<td>16.7%</td>
<td>Any TRAE: 47%</td>
</tr>
</tbody>
</table>

We need better!

**Estimated % probability of PFS**
- **12 mo**: 46.4% (37.8%–54.5%)
- **24 mo**: 40.1% (31.6%–48.4%)

**Median PFS**: 6.0 mo (4.1–)

**Number of patients at risk**
- dMMR/MSI-H EC 143
- 125
- 81
- 65
- 64
- 59
- 55
- 53
- 52
- 46
- 41
- 40
- 33
- 29
- 28
- 24
- 21
- 19
- 16
- 12
- 11
- 8

**Number at risk**
- dMMR: 36
- 23
- 19
- 17
- 10
- pMMR: 35
- 12
- 5
- 1

GARNETT. Oaknin A at al. ASCO 2022

PHAEDRA Trial. Antill, J for ImmunoTher of Cancer 2021
Options for Combinations

PARPis and ICIs
- Neoantigens repertoire expansion
- Upregulation of costimulatory cell-surface receptors
- MHC II expression
- T cells infiltration

anti-VEGF and ICIs
- Vasculature normalization
- Maturation of DC
- Antigen presentation
- T cells infiltration and trafficking
- Downregulation of PD-L1 expression

Vascular normalization
- Anti-VEGF/R
- Increasing of infiltration and activation

Anti-PD1/PDL1
- Increasing of infiltration and activation
- Inhibition

Study 309/KEYNOTE 775 Design

Key eligibility criteria
- Advanced, metastatic, or recurrent endometrial cancer
- Measurable disease by BICR
- 1 Prior platinum-based CT
- ECOG PS 0–1
- Tissue available for MMR testing

Stratification factors
MMR status (pMMR vs dMMR) and further stratification within pMMR by:
- Region (R1: Europe, USA, Canada, Australia, New Zealand, and Israel, vs R2: rest of the world
- ECOG PS (0 vs 1)
- Prior history of pelvic radiation (yes vs no)

Primary endpoints
- PFS by BICR
- Overall survival

Secondary endpoints
- Objective response rate
- HRQoL
- Pharmacokinetics
- Safety

Key exploratory endpoint
- Duration of response

Doxorubicin
60 mg/m² IV Q3W
or
Paclitaxel
80 mg/m² IV QW
(3 weeks on/1 week off)

Lenvatinib
20 mg PO QD
+ Pembrolizumab
200 mg IV Q3W

Treat until progression or unacceptable toxicity

aPatients may have received up to 2 prior platinum-based CT regimens if 1 is given in the neoadjuvant or adjuvant treatment setting.
bMaximum of 35 doses. cMaximum cumulative dose of 500 mg/m².

Makker et al, NEJM 2022
Study 309 / Keynote-775

ORR: 30.3% vs 15.1% in pMMR; 40% vs 12% in dMMR
DOR: 9.2 vs 5.7 months in pMMR; NR (2.1-20.4) vs 4.1 in dMMR

Makker et al, NEJM 2022, Makker JCO 2023

FDA approved for pMMR (July 2021)
EMA approved for pMMR/dMMR (Nov 2021)
### Table 3. Adverse Events of Any Cause with an Incidence of 25% or More among All the Patients in Either Treatment Group, According to Preferred Term.

<table>
<thead>
<tr>
<th>Event</th>
<th>Lenvatinib plus Pembrolizumab (N=406)</th>
<th>Chemotherapy (N=388)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade ≥3*</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>405 (99.8)</td>
<td>361 (88.9)</td>
</tr>
<tr>
<td>Hypertension†</td>
<td>260 (64.0)</td>
<td>154 (37.9)</td>
</tr>
<tr>
<td>Hypothyroidism†‡</td>
<td>233 (57.4)</td>
<td>5 (1.2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>220 (54.2)</td>
<td>31 (7.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>201 (49.5)</td>
<td>14 (3.4)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>182 (44.8)</td>
<td>32 (7.9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>149 (36.7)</td>
<td>11 (2.7)</td>
</tr>
<tr>
<td>Weight decrease</td>
<td>138 (34.0)</td>
<td>42 (10.3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>134 (33.0)</td>
<td>21 (5.2)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>124 (30.5)</td>
<td>7 (1.7)</td>
</tr>
<tr>
<td>Proteinuria†</td>
<td>117 (28.8)</td>
<td>22 (5.4)</td>
</tr>
<tr>
<td>Anemia</td>
<td>106 (26.1)</td>
<td>25 (6.2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>105 (25.9)</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>104 (25.6)</td>
<td>16 (3.9)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>30 (7.4)</td>
<td>7 (1.7)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>22 (5.4)</td>
<td>0</td>
</tr>
</tbody>
</table>
Atezolizumab and Bevacizumab in Recurrent Endometrial Cancer

<table>
<thead>
<tr>
<th>Total Number of Subjects</th>
<th>n=57</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Activity</td>
<td></td>
</tr>
<tr>
<td>ORR for all</td>
<td>30% (95% CI 18-43)</td>
</tr>
<tr>
<td>ORR for MMRp</td>
<td>33% (95% CI 20-48)</td>
</tr>
<tr>
<td>Median DOR (months)</td>
<td>15 (95% CI 2.9-34)</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>7.87 (95% CI 5.5-11.7)</td>
</tr>
</tbody>
</table>

No grade 4 AEs occurred. Dose interruptions, reductions, and discontinuations due to AEs occurred in: 79%, 4%, and 16% of patients.

Fuh, IGCS 2022
Options for Combinations

PARPIs and ICIs
- Neoantigens repertoire expansion
- Upregulation of costimulatory cell-surface receptors
- MCH II expression
- T cells infiltration

anti-VEGF and ICIs
- Vasculature normalization
- Maturation of DC
- Antigen presentation
- T cells infiltration and trafficking
- Downregulation of PD-L1 expression

Diagram showing the interaction between cGAS and STING pathways in the context of SCLC targeting.
DOMEC trial

Phase II; N=50
Durvalumab 1500 mg IV q4w + olaparib 300 mg BID
Primary endpoint PFS 6 months

6-month PFS: 34%; Median PFS 3.4 months; ORR 16%
TRAE grade ≥3 : 16%

Post, Gynecol Oncol 2022
IO after IO

- Arm A: Nivolumab 240 mg IV D1+15 with cabozantinib 40 mg daily (TKI - MET, VEGFR2, RET, AXL) q 28 days
- Arm B: Nivolumab
- Cross-over allowed.
- 94 vs 100% MSS tumors
- ORR 25 vs 11%
- Post-IO: N=20
  - MSI-H: 22%
  - 61% ≥3 prior lines
  - ORR 25%

Lenvatinib/pembrolizumab after IO

- Renal cell cancer
  - 104 patients with prior IO: ORR 62.5%

- Melanoma
  - LEAP-004: PD on or <12 weeks from last CPI
  - ORR 21.4%, OS 14 months

- Endometrial cancer
  - Rose: 8 dMMR patients: Lenvatinib/pembrolizumab: ORR 75%
  - Morton: 11 endometrial patients (8 dMMR, 3 pMMR): ORR 54.5%
    - Variety of single agent and combination therapy
Recurrence dMMR: DUAL Immunotherapy NRG-GY025

**Recurrence dMMR Deficient Endometrial Carcinoma with Measurable or Non-measurable (detectable) Disease**

**STRATIFICATION**
- Prior Radiation
- Prior anti-PD1/PD-L1 therapy
- Measurable disease (yes/no)

**RANDOMIZATION**
- Arm 1
  - Nivolumab Q3W and
  - Low-dose Ipilimumab Q6W (every other cycle x 4) and then nivolumab alone Q4W until disease progression, unacceptable toxicities or CR*
  - See Section 3.1
- Arm 2
  - Nivolumab Q3W x 8 cycles then Q4W until disease progression, unacceptable toxicities or CR*
  - See Section 3.1

*patients with CR will receive maintenance therapy for up to 12 additional months after radiologic evidence of complete response.

*Randomization is 2:1 (Arm 1 vs Arm 2). Twice as many patients will be randomized to Arm 1.

**Activation Date:** 2/7/22
**Accrual:** 16/90

**Li-Chung, Vaccines 2021**
**GOG-3038/POD1UM-204**

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 (PI: Brian Slomovitz, MD)

### Select eligibility criteria

- **Naive to CPI**
  - MSI-H (n=100)
  - dMMR or POLE mutations (n=40)
  - Unselected (n=40)
  - Eligible FGFR1/2/3 mutation or alteration (n=40)
  - MSS, PD-L1+ (n=40)
  - MSI-H (n=40)

- **Prior CPI allowed**
  - Retifanlimab
  - Retifanlimab + epacadostat
  - Retifanlimab + pemigatinib
  - Retifanlimab + epacadostat

- **CPI pretreated**
  - Retifanlimab + INCAGN02385
  - Retifanlimab + INCAGN02390

### Target N=300

<table>
<thead>
<tr>
<th>Primary endpoint: ORR, per RECIST v1.1 and determined by ICR (group A)</th>
<th>Secondary objectives: DoR, DCR, PFS, OS (groups A-B); ORR (groups B-F); safety (all groups)</th>
</tr>
</thead>
</table>
| a Patients eligible to receive retifanlimab monotherapy will first be considered for group A until fully enrolled, unless they do not meet MSI-H criteria. Retifanlimab administered iv on day 1 of each 28-day cycle for up to 26 cycles, if patients continue to derive benefit and do not meet any study treatment discontinuation criteria. b Patients in group A or group B who experience disease progression on retifanlimab monotherapy may be eligible for further treatment with one of the combination regimens in groups D or E. c Closed enrollment groups. d Pemigatinib (FGFR1/2/3 inhibitor) administered orally qd. e INCAGN02385 and INCAGN02390 administered iv q2w. f dMMR, deficient mismatch repair; ICR, independent central review; MSI-H, microsatellite instability-high; MSS, microsatellite stable; POLE, DNA polymerase epsilon.
Antibody Drug Conjugates in Endometrial Cancer

Chau C, Lancet 2019
Targeting HER2

- Prevalence in uterine cancer ~25%
  - 75% of uterine serous carcinoma have TP53 alteration
  - No standard testing (NGS, IHC, FISH)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Payload</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab deruxtecan</td>
<td>Topoisomerase I inhibitor</td>
</tr>
<tr>
<td>(DS-8201a or T-DXd)</td>
<td></td>
</tr>
<tr>
<td>BNT323/DB-1303</td>
<td>Topoisomerase I inhibitor</td>
</tr>
<tr>
<td>Ado-trastuzumab emtansine</td>
<td>Microtubule inhibitor derived from maytansine</td>
</tr>
<tr>
<td>(T-DM1)</td>
<td></td>
</tr>
</tbody>
</table>

Trastuzumab Deruxtecan (TDxd) DESTINY-PanTumor02 Phase II Trial

- N=40 endometrial cancer
- 22% prior Anti-HER2
- 1/3 ≥ 3 prior lines (median 2)
- 10% Black, 25% Asian
- IHC: 3+ 33%, 2+ 43%, 1+ 10%, 0/uk 15%
- ORR 57.5%, DCR 94%

- The most frequent TEAEs of any grade were nausea, vomiting, diarrhea, fatigue.
- Grade 3 or greater was rare (neutropenia, anemia).
- ILD/pneumonitis 10.5% (0.4% grade 3, 1.1% grade 5)
- Alopecia 22%

Meric-Bernstam, F. JCO 2023
Trastuzumab Deruxtecan (TDxd): DESTINY-PanTumor02 Phase II Trial

Meric-Bernstam, F. JCO 2023
STATICE TRIAL: Trastuzumab deruxtecan (DS-8201a or T-DXd)

- HER2 targeting; topoisomerase I inhibitor
- Phase II, N= 34 (22 high, 10 low), Japan
- Carcinosarcoma, HER2 IHC score ≥1+, >1 prior line
- 6.4 mg/kg → 5.4 mg/kg
- Median PFS 6.7 months (95% CI, 5.4 to 8.8)
- Pneumonitis/ILD in 9 (27%)

Nishikawa T, JCO 2023
### BNT323/DB-1303: Phase I/2a

**Phase 1 (Dose Escalation)**
(HER2 IHC 3+, IHC 2+, IHC 1+ or ISH +, or HER2 amplification by NGS, or HER2 mutation by NGS)

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.0</td>
<td>n=3-6</td>
</tr>
<tr>
<td>10.0</td>
<td>n=3-6</td>
</tr>
<tr>
<td>8.0</td>
<td>n=3-6</td>
</tr>
<tr>
<td>7.0</td>
<td>n=3-6</td>
</tr>
<tr>
<td>6.0</td>
<td>n=3-6</td>
</tr>
<tr>
<td>4.4</td>
<td>n=3-6</td>
</tr>
<tr>
<td>2.2</td>
<td>n=1</td>
</tr>
</tbody>
</table>

Additional dose finding cohorts (A total of up to 20 participants)

- **RP2D/MTD**
  - RP2D=8 mg/kg

**Dose extension**
If a dose is confirmed to have a tolerable safety profile by the SMC, the cohort size may be backfilled to a maximum of 15-21 at any dose level ≥4 mg/kg. Up to 57 additional participants (HER2 low BC, HER2+ BC, HER2+low endometrial carcinoma, and HER2 activation mutation NSCLC) will be enrolled.

**Phase 2a (Dose Expansion)**

**Cohort 2a** Trastuzumab-treated HER2+ (IHC3+, IHC2+/ISH positive) gastric or gastroesophageal junction adenocarcinoma (N=30), HER2+ esophageal carcinoma (N=10), and HER2+ CRC (N=15)

**Cohort 2b** Both HER2 overexpression and HER2 low (IHC3+,2+,1+ or ISH positive) endometrial carcinoma, including UC and USC (N=30-60)

**Cohort 2c** HR+/HER2 Low (IHC2+/ISH negative, or IHC1+) BC (N=30-50)

**Cohort 2d** HER2+ (IHC3+, IHC2+/ISH positive) BC (N=20-40)

**Cohort 2e** NSCLC with activating HER2 mutation (N=15-30)

**Cohort 2f** HER2+ or HR+/HER2-low BC with treatment failure of trastuzumab deruxtecan (N=10, HER2+ BC; N=10, HR+/HER2-low BC)

**Objectives**

- **Dose Escalation**
  - Primary: safety and tolerability, MTD or RP2D
  - Secondary: efficacy, PK, and immunogenicity
  - Exploratory: biomarker and ER relationship

- **Dose Expansion**
  - Primary: safety and tolerability, efficacy
  - Secondary: PK, antidrug antibodies, efficacy
  - Exploratory: biomarker, ER relationship, population PK, neutralizing antibody, efficacy

>1 prior line. NCT05150691

Moore, K. ESGO 2023
DB-1303/BNT323

- HER2 targeting; topoisomerase I inhibitor
- N=32
- 59% prior IO
- 38% prior Anti-HER2
- 1/3≥3 prior lines
- 34% Black, 6% Asian
- ORR 10/17 (58.8%) (unconfirmed), DCR 94%

- The most frequent TEAEs of any grade were nausea, fatigue, and vomiting, grade 3 or greater was rare.
- Alopecia 3.1%
## Targeting Folate Receptor (FR)-α

- FRα overexpression in ~64% of endometrial tumors

### Drug Name vs Payload

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Payload</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luveltamab tazivibulin (STRO-002)</td>
<td>Hemiasterlin-derivative Tubulin-inhibitor</td>
</tr>
<tr>
<td>Mirvetuximab Soravtansine</td>
<td>Maytansinoid (DM4) → tubulin targeting</td>
</tr>
<tr>
<td>Farletuzumab ecteribulinm (MORAb-202, FZEC)</td>
<td>Eribulin → microtubule-depolymerizing</td>
</tr>
</tbody>
</table>

Assaraf et al. Drug Resistance Updates (2014); Moore et al. Cancer 2017
STRO-002-GM1: Phase 1 Dose-Expansion Cohort of Luveltamab tazevibulin (luvelta) in Recurrent EC

Key Inclusion and Exclusion Criteria

- Endometrial cancer
  - Excluded: leiomyosarcoma, stromal sarcomas and carcinosarcomas
- ≥1% FolRα expression by central IHC
- Recurrent disease
  - ≥1 platinum-based chemotherapy or 1 immunotherapy-based regimen
  - ≤3 prior regimens
- At least 1 target lesion

17 Patients Enrolled

Luveltamab tazevibulin Dosing Schedule

- Q3W cycles
- 5.2 mg/kg unless prior pelvic XRT, then 4.3 mg/kg X 2 cycles with option to dose escalate to 5.2 mg/kg

Endpoints

- Safety
- PK
- Anti-tumor activity assessed by ORR, DOR and PFS by RECIST v1.1
- CA-125

Most common TEAEs, n (%)

<table>
<thead>
<tr>
<th></th>
<th>Any grade</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>13 (76.5)</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12 (70.6)</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td>Neutropenia†</td>
<td>11 (64.7)</td>
<td>9 (52.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (58.8)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>10 (58.8)</td>
<td>0</td>
</tr>
</tbody>
</table>

DOR, duration of response; IHC, immunohistochemistry; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; XRT, radiotherapy.

ClinicalTrials.gov NCT03748186

Pothuri B. ESMO 2023
Luveltamab tazevibulin Showed Early Evidence Of Anti-tumor Activity in FolRα Expressing EC

Maximum Reduction in Target Lesions*

<table>
<thead>
<tr>
<th>TPS (%)</th>
<th>Overall FolRα ≥1% (n=16)</th>
<th>FolRα ≤25% (n=9)</th>
<th>FolRα &gt;25% (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>5 (15)</td>
<td>1 (11)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>15</td>
<td>6 (25)</td>
<td>4 (44)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>1</td>
<td>30 (8)</td>
<td>4 (57)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>45 (30)</td>
<td>45 (30)</td>
<td></td>
</tr>
<tr>
<td>-30% Partial Response</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Anti-tumor Activity*

<table>
<thead>
<tr>
<th></th>
<th>Overall FolRα ≥1% (n=16)</th>
<th>FolRα ≤25% (n=9)</th>
<th>FolRα &gt;25% (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>3 (19)</td>
<td>1 (11)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>SD&lt;sup&gt;†&lt;/sup&gt;</td>
<td>8 (50)</td>
<td>4 (44)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>PD</td>
<td>5 (31)</td>
<td>4 (44)</td>
<td></td>
</tr>
<tr>
<td>DCR</td>
<td>11 (69)</td>
<td>5 (56)</td>
<td>6 (86)</td>
</tr>
</tbody>
</table>

<sup>†</sup>3 unconfirmed PRs

Data cutoff: 04 August 2023. *n=16 response evaluable patients. DCR, disease control rate; EC, endometrial cancer; PR, partial response; Q3W, every 3 weeks; TPS, tumor proportion score.

Pothuri B. ESMO 2023
**Targeting TROP2**

**TARGET: TROP2**

- **Drug Name**
  - Sacituzumab govitecan (IMMU-132)
    - *approved in TNBC, urothelial*
  - SKB264/MK-2870

- **Payload**
  - SN-38 (irinotecan metabolite) → Topoisomerase I inhibitor
  - Belotecan derivative → Topoisomerase I inhibitor

---

**TROP 2**

- **Overexpression in endometrial cancer is common**
  - Present in 90+% of samples
    - 62% with expression in at least 50% of tumor cells
  - Implicated in intracellular signaling pathways
  - May be a modulator of EpCAM-induced cell signaling
  - Fosters cell migration

---

TROP2 Targeting: IMMU-132/Sacituzumab govitecan-hziy

- ORR 33% in 21 patients with persistent or recurrent endometrial cancer with at least 2+TROP2 by IHC (IMMU-132 study)
- ORR 22% and median PFS 5.7 months in an endometrial cancer cohort (n=28) with progression after prior platinum-based chemotherapy and anti-PD-1/PD-L1-directed therapy (TROPiCS-03 study NCT03964727)
- AE’s: neutropenia (58%), diarrhea (56%), anemia

## ADCs under Development in Endometrial Cancer

<table>
<thead>
<tr>
<th>Monoclonal antibody target</th>
<th>Drug Name</th>
<th>Payload</th>
<th>Ongoing trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>B7-H4</td>
<td>XMT-1660</td>
<td>Auristatin F-Hydroxypropylamide (microtubule inhibitor)</td>
<td>NCT05377996 (Phase I)</td>
</tr>
<tr>
<td>B7-H4</td>
<td>SGN-B7H4V (1 EC)</td>
<td>Monomethyl Auristatin E</td>
<td>NCT05194072 (Phase I)</td>
</tr>
<tr>
<td>B7-H4</td>
<td>AZD8205</td>
<td>Topoisomerase I inhibitor</td>
<td>NCT05123482 (Phase I)</td>
</tr>
<tr>
<td>Folate Receptor α</td>
<td>Farletuzumab ecteribulin (MORAb-202, FZEC) (3 EC)</td>
<td>Eribulin (microtubule inhibitor)</td>
<td>NCT04300556 (Phase I/II)</td>
</tr>
<tr>
<td>Folate Receptor α</td>
<td>Mirvetuximab Soravtansine</td>
<td>Maytansinoid (DM4)→ tubulin targeting</td>
<td>NCT03835819 (Phase II combination with pembro)</td>
</tr>
<tr>
<td>TROP2</td>
<td>Sacituzumab govitecan (IMMU-132)</td>
<td>SN-38 (irinotecan metabolite) → Toiposomerase I inhibitor</td>
<td>NCT04251416 (Phase II) NCT03992131 (combination with rucaparib)</td>
</tr>
<tr>
<td>TROP2</td>
<td>SKB264/MK-2870</td>
<td>Belotecan derivative → Topoisomerase I inhibitor</td>
<td>NCT04152499 (Phase I/II) NCT06132958 (Phase III)</td>
</tr>
</tbody>
</table>
Targeting the Cell Cycle and DNA repair

**Detection of DNA Damage Results in Activation of Checkpoints That Enforce Cell Cycle Arrest**

**TP53**

**NHEJ, BER, HR**

**M**

**G2/M Checkpoint**

**ATR/ATM**

**WEE-1**

**CHK1/2**

**G2**

**G1**

**Spindle Checkpoint**

**G1/S Checkpoint**

**NHEJ, BER, NER**

**S**

**M**, **S**, **G1**, **G2**, **M**

**Cyclin-dependent kinase**

**Cyclin**

**TP53**

**Radiotherapy chemotherapy**

**DNA damage**

**Cancer cells deficient in p53**

**Check point inhibition**

**Mitotic catastrophe and cell death**


BER, base-excision repair; HR, homologous recombination; MMR, mismatch repair; NHEJ, non-homologous end joining; NER, nucleotide-excision repair.
Adavosertib (WEE-1 inhibitor)

- WEE1 kinase, regulator G2/M and S phase checkpoints
- 2-stage Phase II, N=34
- Uterine serous carcinoma
- Adavosertib 300 mg PO D1-5 and D8-12 every 21 days
- ORR 29.4%
- 6-month PFS 47.1%, median PFS 6.1 months
- DOR 9.0 months
- AE: diarrhea, fatigue, nausea, hematologic – 75% of patients required dose hold and 50% reduction, 2 patients discontinued

→ ADAGIO: phase II, N=109 – pending final results
  → ORR 28%, DOR 4.7 months, PFS 2.8 months

Liu, JCO 2021.  Liu, ASCO 2023
Evaluating Azenosertib in Uterine Serous Carcinoma

Key Eligibility: Recurrent or persistent USC; ≥1 prior platinum-based chemotherapy regimen; Prior HER-2 directed therapy for known HER2+; Prior anti-PD(L)1; Measurable disease per RECIST; ECOG PS 0-1

All Comers Enrollment

Cohort 1 (N=30)
Azenosertib 400 mg QD 5:2

Cohort 2 (N=60)
Azenosertib 400 mg QD 5:2

Endpoints (ICR)

ORR
DOR

ClinicalTrials.gov NCT04814108

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1 Except for sites outside the US where aPD1 is not available, or for subjects ineligible for aPD(L)1
2 Response-evaluable subjects

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance score; RECIST, response evaluation criteria in solid tumors; ORR, objective response rate; DOR, Duration of Response
PARP combinations: NRG-GY012

22% of endometrial cancer have mutations in HR pathway (ATM, ATR)

ORR and PFS:
- Cediranib: 24.1% and 3.8 months
- Olaparib: 12.5% and 2.0 months
- Olaparib/cediranib: 31.4% and 5.5 months
- AE >grade 3: 71%, 48%, 80%, respectively

Rimel, Bender, MacKay. Cancer 2023
Other Ongoing Studies

**EAY191-N4**: A Randomized trial of selumetinib (MEKi) and Olaparib or selumetinib alone in patients with recurrent or persistent RAS pathway mutant ovarian and endometrial cancers (ComboMATCH treatment trial) (Westin)
# Hormonal Therapy for Recurrent or Metastatic Endometrial Carcinoma

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
<th>Other Recommended Regimens</th>
<th>Useful in Certain Circumstances</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Megestrol acetate/tamoxifen (alternating)</td>
<td>• Medroxyprogesterone acetate/tamoxifen (alternating)</td>
<td>• ER-positive tumors</td>
</tr>
<tr>
<td>• Everolimus/letrozole</td>
<td>• Progestational agents</td>
<td>‣ Letrozole/ribociclib</td>
</tr>
<tr>
<td></td>
<td>• Medroxyprogesterone acetate</td>
<td>‣ Letrozole/abemaciclib</td>
</tr>
<tr>
<td></td>
<td>• Megestrol acetate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Aromatase inhibitors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Tamoxifen</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Fulvestrant</td>
<td></td>
</tr>
<tr>
<td>Treatment Description</td>
<td>ORR</td>
<td>CBR</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-----</td>
<td>------</td>
</tr>
<tr>
<td>Progesterone single agent</td>
<td>25%</td>
<td>46%</td>
</tr>
<tr>
<td>Progesterone/tamoxifen</td>
<td>19-33%</td>
<td>69%</td>
</tr>
<tr>
<td>SERM/SERD</td>
<td>10%</td>
<td>34%</td>
</tr>
<tr>
<td>Aromatase inhibitor</td>
<td>9-17%</td>
<td>17-44%</td>
</tr>
<tr>
<td>Aromatase and mTOR inhibitor</td>
<td>22-32%</td>
<td>40-78%</td>
</tr>
<tr>
<td>Aromatase and CDK4/6 inhibitor</td>
<td>10-30%</td>
<td>64-73%</td>
</tr>
</tbody>
</table>
Hormonal therapy with mTOR inhibitors: GOG-3007

Everolimus 10 mg daily with letrozole 2.5 mg daily versus Medroxyprogesterone acetate (MPA) 200 mg daily alternating weekly with tamoxifen 20 mg BID

ORR 22% vs 25%

TRAE Grade 3 or > anemia, mucositis, hyperglycemia, fatigue and pneumonitis in the everolimus/letrozole group; versus hypertension and thromboembolic events in the hormonal therapy group

Slomovitz Gynecol Oncol 2022
**VICTORIA**: mTOR Inhibitor, Vistusertib, Combined With Anastrozole in Patients With Hormone Receptor–Positive Recurrent or Metastatic Endometrial Cancer

- **ORR**: 24.5 vs 17.4%

- Most common grade 3/4 AE:
  - V+A arm lymphopenia (20%), hyperglycemia (12%), and fatigue (8%)

Heudel, JAMA Oncol 2022
CDK 4/6 Inhibitors

- Hormonally driven malignancies are known to have actionable therapeutic targets.
- CDK 4/6 inhibitors induce cell-cycle arrest via G1 to S cell cycle checkpoint
- Cyclin D/CDK complex is downstream of estrogen signaling, representing potential synergic antitumor activity when combined with aromatase inhibitor.

Palbociclib
Ribociclib
Abemaciclib
ENGOT-EN3/NSGO-PALEO: letrozole +/- palbociclib, a CDK 4/6 inhibitor

Primary endpoint: PFS

HR=0.56 (95% CI 0.32–0.98) 
p=0.0376
Median: 3.0 vs. 8.3 mo

Secondary endpoint: Disease control rate

<table>
<thead>
<tr>
<th>Disease control rate</th>
<th>Palbociclib + letrozole (n=33)</th>
<th>Placebo + letrozole (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>63.6</td>
<td>37.8</td>
<td></td>
</tr>
</tbody>
</table>

* = at 24 weeks

Letrozole+Abemaciclib

- Phase II, N=30
- Abemaciclib 150 mg PO BID and letrozole 2.5 mg PO daily
- ORR 9/30 (30%) (only in endometrioid)
- Most common ≥ grade 3 TRAE:
  - Neutropenia (20%) and anemia (17%)
- Responses independent of grade, prior hormonal therapy, MMR status, PR
- Possible biomarkers: CTNNB1, KRAS, CDKN2A, TP53

Konstantinopoulos PA, JCO 2023
Letrozole Abemaciclib

9.1 months

Konstantinopoulos PA, JCO 2023
Ongoing Trials

- **NRG GY028**: Phase IB and randomized phase II trial of medroxyprogesterone acetate +/- ipatasertib (AKT inhibitor) in recurrent/metastatic endometrioid endometrial cancer (Onstad Grinsfelder/Westin)

- **GOG-3069**: A Phase 2 Study of Alpelisib (PIK3CA inhibitor) and Fulvestrant for PIK3CA-mutated Estrogen Receptor (ER) Positive Endometroid Endometrial Cancer (Gaillard)
Conclusion

• Subclassification of endometrial cancer is complex
• Molecular profiling, including NGS and IHC, is critical and opens up new opportunities for targeted therapy
• The new landscape will need options for treatment after IO
  – Without progression on IO
  – With progression on IO
• Antibody Drug Conjugates are effective in delivering high potency chemotherapy
  – New toxicity management strategies
• Hormonal therapy and combinations can provide significant clinical benefit