Uterine Cancer, the Knowns and Unknowns – A Heated Discussion on Pivotal Changing Data

Brian Slomovitz, MD, Mount Sinai Medical Center, Miami Beach, Florida, USA
Ritu Salani, MD, MS, UCLA Medical Center, Los Angeles, California, USA
Thomas Herzog, MD, University of Cincinnati, Cincinnati, Ohio, USA
Bhavana Pothuri, MD, NYU Langone, New York City, New York, USA
Advanced/Recurrent Endometrial Cancer

2000’s: Chemotherapy has been standard of care

2010: Carboplatin and paclitaxel became the preferred regimen (GOG209)

PFS ~13 months, OS ~20 months, Response Rate 52% rates

PFS benefit of IO + chemo in dMMR

**GY018**

**RUBY**

**AtTEnd**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + CP</td>
<td>NR (30.6-NR)</td>
<td></td>
</tr>
<tr>
<td>Placebo + CP</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No with events%</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dostarlimab + CP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo + CP</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
First-line Chemotherapy-free Regimens in the dMMR population??

- **KEYNOTE-C93**
  - Pembrolizumab
  - Chemo
  - Primary endpoints: PFS, OS
  - Key secondary endpoints: ORR, DCR, DOR
  - Recruitment ongoing
  - dMMR patient population

- **ENGOT-en13 DOMENICA**
  - Dostarlimab
  - Chemo
  - Primary endpoint: PFS
  - Key secondary endpoints: OS, PROs, ORR, DOR
  - Recruitment ongoing
  - dMMR patient population

- **ENGOT-en9 LEAP-001**
  - Lenvatinib + pembrolizumab
  - Chemo
  - Primary endpoints: PFS, OS
  - Key secondary endpoints: ORR, HRQOL, safety
  - Completed enrollment
  - dMMR and pMMR patient populations
**PFS in pMMR**

**Primary Endpoint: Prespecified**

**GY018**

- HR 0.54, 95%CI 0.41 to 0.71
- Placebo + CT: 70.7, 7.9 (7.6-9.8)
- Dostarlimab + CT: 60.4, 9.9 (9.0-13.3)

**RUBY**

- HR 0.76, 95%CI 0.59 to 0.98
- Placebo + CT: 77, 9.2 (8.5-9.9)
- Atezolizumab + CT: 78, 9.5 (9.0-10.4)

**AtEnd**

- HR 0.92, 95%CI 0.73 to 1.16
- Placebo + CT: 45.5, 8.7 (8.4-10.7)
- Pembro + CT: 30.6, 13.1 (10.5-18.8)

**Secondary Analysis: Not prespecified**

**Number at Risk (Cumulative number censored)**

- D + CP
  - Placebo + CP
  - P + CP
- Pembro + CT
- Placebo + CT
- Maturity

**At risk (events)**

- D + CP
  - Placebo + CP
- P + CP
- Pembro + CT
- Placebo + CT

**Patients at Risk**

- Atezolizumab: 269, 205, 103, 62, 40, 31, 16, 5, 2
- Placebo: 140, 117, 39, 24, 14, 11, 7, 3, 2

**Proportion Alive and Progression-Free**

- 0 6 12 18 24 30 36 42 Months from randomization

**Probability of Progression-free Survival**

- 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 Months from randomization
PFS According to Molecular Subgroup

POLε mut

TP53 mut

HR, 0.55
(95% CI, 0.3–0.99)

HR, 0.31
(95% CI, 0.17–0.56)

dMMR/MSI-H

NSMP

HR, 0.77
(95% CI, 0.55–1.07)
PARPis plus ICIs in advanced Endometrial Cancer
Ongoing phase III randomized trials

**RUBY trial Part 2**
Multicenter Phase 3 study that will evaluate the efficacy and safety of DOSTARLIMAB + carboplatin-paclitaxel followed by DOSTARLIMAB + NIRAPARIB

**DUO-E trial**
Multicenter Phase 3 study that will evaluate the efficacy and safety of DURVALUMAB + carboplatin-paclitaxel followed by DURVALUMAB + OLAPARIB or DURVALUMAB or OLAPARIB
DUO-E: PFS

PFS: ITT (primary endpoint)

<table>
<thead>
<tr>
<th>Group</th>
<th>Events, n (%)</th>
<th>Median PFS (95% CI),* months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>173 (71.8)</td>
<td>9.6 (9.0–9.9)</td>
</tr>
<tr>
<td>Durva</td>
<td>139 (58.4)</td>
<td>10.2 (9.7–14.7)</td>
</tr>
<tr>
<td>Durva+Ola</td>
<td>126 (52.7)</td>
<td>15.1 (12.6–20.7)</td>
</tr>
</tbody>
</table>

HR (95% CI) vs Control†

0.71 (0.57–0.89); P=0.003

HR (95% CI) vs Durva†

0.78 (0.61–0.99)

Overall data maturity 61.0%

PFS: pMMR (80% of population)

<table>
<thead>
<tr>
<th>Group</th>
<th>Events, n (%)</th>
<th>Median PFS (95% CI),* months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>148 (77.1)</td>
<td>9.7 (9.2–10.1)</td>
</tr>
<tr>
<td>Durva</td>
<td>124 (64.6)</td>
<td>9.9 (9.4–12.5)</td>
</tr>
<tr>
<td>Durva+Ola</td>
<td>108 (56.5)</td>
<td>15.0 (12.4–18.0)</td>
</tr>
</tbody>
</table>

HR (95% CI) vs Control†

0.77 (0.60–0.97); P=0.0001

HR (95% CI) vs Durva†

0.76 (0.59–0.99)

Westin S. ESMOA 2023.
Subgroup analysis of PFS: Durva vs Control

By stratification factors and biomarker status

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>Durva n/N (%)</th>
<th>Control n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>0.68 (0.55–0.86)</td>
<td>139/238 (58.4)</td>
<td>173/241 (71.8)</td>
</tr>
<tr>
<td>Disease status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newly diagnosed</td>
<td>0.59 (0.42–0.82)</td>
<td>67/113 (59.3)</td>
<td>81/115 (70.4)</td>
</tr>
<tr>
<td>Recurrent disease</td>
<td>0.79 (0.58–1.07)</td>
<td>72/125 (57.6)</td>
<td>92/126 (73.0)</td>
</tr>
<tr>
<td>MMR status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proficient tumours</td>
<td>0.77 (0.60–0.97)</td>
<td>124/192 (64.6)</td>
<td>148/192 (77.1)</td>
</tr>
<tr>
<td>Deficient tumours</td>
<td>0.42 (0.22–0.80)</td>
<td>15/46 (32.6)</td>
<td>25/49 (51.0)</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>0.98 (0.65–1.49)</td>
<td>44/68 (64.7)</td>
<td>45/68 (66.2)</td>
</tr>
<tr>
<td>Non-Asia</td>
<td>0.59 (0.45–0.76)</td>
<td>95/170 (55.9)</td>
<td>128/173 (74.0)</td>
</tr>
<tr>
<td>HRRm status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRRm</td>
<td>0.57 (0.27–1.13)</td>
<td>12/26 (46.2)</td>
<td>23/32 (71.9)</td>
</tr>
<tr>
<td>Non-HRRm</td>
<td>0.72 (0.54–0.97)</td>
<td>85/138 (61.6)</td>
<td>96/132 (72.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.65 (0.43–0.97)</td>
<td>42/74 (56.8)</td>
<td>54/77 (70.1)</td>
</tr>
<tr>
<td>PD-L1 expression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (TAP score ≥1%)</td>
<td>0.63 (0.48–0.83)</td>
<td>97/170 (57.1)</td>
<td>114/163 (69.9)</td>
</tr>
<tr>
<td>Negative (TAP score &lt;1%)</td>
<td>0.89 (0.59–1.34)</td>
<td>38/61 (62.3)</td>
<td>57/75 (76.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>NC (NC–NC)</td>
<td>4/7 (57.1)</td>
<td>2/3 (66.7)</td>
</tr>
</tbody>
</table>

Stratification factors (disease status, MMR status, and geographic region) are per the randomisation code. PD-L1 status in baseline tumour tissue was determined centrally using Ventana PD-L1 SP263 immunohistochemistry assay. Expression was assessed using a TAP score, calculated based on the proportion of the tumour area populated by tumour cells or immune cells with membranous PD-L1 staining. HRRm status was assessed in baseline tumour tissue using the Foundation One CDx NGS assay and includes a mutation in any of these genes: ATM, BRCAl, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, or RAD54L. HRRm status unknown includes patients recruited in China where HRR testing was not performed and patients with samples that were unavailable for testing.
MAINTENANCE THERAPY

Cancer cells export tumor suppressor proteins (p53) from the nucleus

Restoring function of p53 mediated apoptosis

- Selinexor XPO1 inhibitor
- Navtemadlin: MDM2 inhibitor

PFS ITT

PFS Pre-specified subgroup: P53wt

SIENDO: Long-term PFS, *TP53*

**TP53wt**
- Selinexor (n=77): 27.4 mo (95% CI 13.1-NR)
- Placebo (n=36): 5.2 mo (95% CI 2.0-13.1)
- HR: 0.42 (95% CI 0.25-0.70)
- One-sided nominal P-value = 0.0003

**TP53mut/abn**
- Selinexor (n=79): 4.2 mo (95% CI 3.6-5.6)
- Placebo (n=47): 5.4 mo (95% CI 3.7-7.2)
- HR: 1.34 (95% CI 0.89-2.02)
- One-sided nominal P-value = 0.9202

Pre-specified subgroups
### Ongoing Trials

**ENGOT-EN20/GOG-3083**
- Planned enrollment (N = 220)
  - Patients ≥ 18 years with
    - Known TP53 wt EC by central NGS
    - Primary stage IV disease or first recurrent EC
    - Received ≥ 12 weeks of platinum-based chemotherapy ± immunotherapy

**XPORT-EC-42**
- Study is ongoing and actively enrolling.
  - PR/CR per RECIST v1.1
  - Stratification
    - Primary stage IV vs recurrent
    - PR vs CR

**KRT-232-118/GOG-3089**
- Subjects with TP53wt Advanced or Recurrent Endometrial Cancer Who Have a CR/PR after Chemotherapy

#### ENROLLMENT

#### PART 1 (PHASE 2)
- Navtemadlin 180 mg
  - 7D on / 21D off (n=21)
- Navtemadlin 240 mg
  - 7D on / 21D off (n=71)
- Observational Control
  - 28-day Cycle (n=21)

#### PART 2 (PHASE 3)
- Navtemadlin Phase 3 dose
  - 7D on / 21D off (n=130)
- Placebo (Matching Navtemadlin Phase 3 dose)
  - 7D on / 21D off (n=55)

#### Key endpoints
- Primary endpoint
  - PFS assessed by investigator
- Secondary endpoints
  - CS
  - Safety
  - TP53
  - PFS2
  - PFS assessed by BICR
- QoL (EQ-SD-3L)
- Exploratory endpoints
  - PFS per histology subtypes and per other molecular features
  - CR rate
  - Duration of CR
  - Tumor biomarkers
  - PK exposure parameters and efficacy/safety endpoints

1 Cycle = 28 days
# Single Agent IO in “biomarker” Selected Endometrial Cancer Populations (dMMR)

Response to single agent IO in dMMR or MSI-high endometrial cancer

<table>
<thead>
<tr>
<th>Study &amp; Drug</th>
<th>Patient Population</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keynote 158: Pembrolizumab (N=49)</td>
<td>Advanced stage or metastatic dMMR endometrial cancer</td>
<td>ORR: 57.1%</td>
</tr>
<tr>
<td>PHAEDRA trial: Durvalumab (N=35 dMMR)</td>
<td>Advanced stage or metastatic endometrial cancer</td>
<td>ORR in dMMR: 43%</td>
</tr>
<tr>
<td>GARNET study: Dostarlimab (N=70)</td>
<td>Previously treated, recurrent advanced stage endometrial cancer</td>
<td>ORR in dMMR: 45%</td>
</tr>
<tr>
<td>Ph II Avelumab study (N= 15 dMMR)</td>
<td>Advanced stage or metastatic endometrial cancer</td>
<td>ORR: 26.7%</td>
</tr>
</tbody>
</table>

Antill PSK et al. J Clin Oncol 2019  
Oaknin A et al. SGO virtual meeting 2020  
Konstantinopoulos PA et al. J Clin Oncol 2019
Response to single agent IO in pMMR or MSI-stable endometrial cancer has been modest.

<table>
<thead>
<tr>
<th>Study &amp; Drug</th>
<th>Patient Population</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keynote 28: Pembrolizumab (N=24)</td>
<td>Advanced stage or metastatic PD-L1 + endometrial cancer</td>
<td>ORR: 13%</td>
</tr>
<tr>
<td>PHAEDRA trial: Durvalumab (N=36 pMMR)</td>
<td>Advanced stage or metastatic endometrial cancer</td>
<td>ORR in pMMR: 3%</td>
</tr>
<tr>
<td>GARNET study: Dostarlimab (N=94)</td>
<td>Previously treated, recurrent advanced stage endometrial cancer</td>
<td>ORR in pMMR: 13%</td>
</tr>
<tr>
<td>Ph II Avelumab study (N= 16 pMMR)</td>
<td>Advanced stage or metastatic endometrial cancer</td>
<td>ORR: 6.25%</td>
</tr>
</tbody>
</table>

** = updated data in the pMMR cohort has not been presented

PD-L1 positive endometrial cancer is not approved indication of Pembrolizumab in China, Taiwan, Korea, Singapore, Philippines, and HK.
Combinatorial IO approach: Lenvatinib + Pembrolizumab

Keynote 775 (NCT03517449)

## Checkpoint Combinations in Endometrial Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Publication/Presenation</th>
<th>Treatment</th>
<th>Number of Patients</th>
<th>Median PFS (months)</th>
<th>HR</th>
<th>Median OS (months)</th>
<th>Log-rank P</th>
<th>ORR</th>
<th>DOR (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized Phase 2 Trial Cabozantinib /Nivolumab vs Nivolumab</td>
<td>JITC 2022</td>
<td>Cabozantinib + Nivolumab</td>
<td>36</td>
<td>5.3 (90% CI 3.5-9.2)</td>
<td>0.59 (90% CI 0.35, 0.98)</td>
<td>13.0 months (90%CI 10.2 to 18.4)</td>
<td>0.09</td>
<td>25.0 %</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nivolumab</td>
<td>18</td>
<td>1.9 (90% CI 1.6-3.4)</td>
<td></td>
<td></td>
<td></td>
<td>16.7 %</td>
<td>4</td>
</tr>
<tr>
<td>Prior IO cohort</td>
<td></td>
<td>Cabozantinib + Nivolumab</td>
<td>20</td>
<td>-</td>
<td>-</td>
<td>7.9 months (90%CI 6.1 to not estimable)</td>
<td></td>
<td>25.0%</td>
<td></td>
</tr>
<tr>
<td>Activate Ph 1/2: etililimb (anti-TIGIT) with nivolumab (anti-PD1) in recurrent/advanced solid tumors</td>
<td>ESMO 2023</td>
<td>Nivolumab + etililimb</td>
<td>40 solid tumor</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 em ca</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>30%</td>
<td></td>
</tr>
</tbody>
</table>

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
- Histologically confirmed advanced or metastatic endometrial cancer
- Disease progression on or after treatment with ≥1 platinum-containing regimen
- At least 1 measurable tumor lesion per RECIST v1.1
- Willing to provide tumor tissue sample
- ECOG PS of 0 to 1

Target N=300

Primary endpoint: ORR, per RECIST v1.1 and determined by ICR (group A)1,2
Secondary objectives: DoR, DCR, PFS, OS (groups A-B); ORR (groups B-F); safety (all groups)1,2

NCT04463771

# Wee-1 Inhibitors in Endometrial Cancer

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Phase</th>
<th>Publication/ Presentation</th>
<th>Number of patients</th>
<th>Median Duration of Response</th>
<th>Overall Response Rate</th>
<th>Median Progression-Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>A phase II study of the WEE1 inhibitor adavosertib in recurrent uterine serous carcinoma</td>
<td>II</td>
<td>ASCO 2022</td>
<td>72</td>
<td>9.0 months</td>
<td>29.4%</td>
<td>-</td>
</tr>
<tr>
<td>ADAGIO: A phase IIb international study of the Wee1 inhibitor adavosertib in women with recurrent or persistent uterine serous carcinoma</td>
<td>IIb</td>
<td>JCO 2023</td>
<td>167</td>
<td>-</td>
<td>24.2%</td>
<td>5.3 months</td>
</tr>
<tr>
<td>ZN-c3 Phase 1 Monotherapy Expansion Cohort in Patients with Advanced/Recurrent Uterine Serous Carcinoma</td>
<td>I</td>
<td>AACR 2022</td>
<td>43</td>
<td>-</td>
<td>27.3%</td>
<td>9.9 months</td>
</tr>
</tbody>
</table>

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)ii
Azenosertib 400 mg QD 5:2

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

Endpoints (ICR)

ORR
DOR

ClinicalTrials.gov NCT04814108

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

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

iiResponse-evaluable subjects
ADC’s in Endometrial Cancer

Luveltamab Tazevibulin (STRO-OO2): Early Evidence Of Anti-tumor Activity in FolRα Expressing EC: Phase 1 Dose expansion

Pothuri B, Naumann W, Martin L, et al ESMO 2023

Trastuzumab Deruxtecan: Td-XD Efficacy by HER2 Expression

PFS

NCCN Guidelines 1.2024 9/20/23

Useful in Certain Circumstances (Biomarker-directed therapy)

- pNMR tumors
- Lenvatinib/pembrolizumab (category 1)\(^c\)
- TMB-H tumors\(^n,12\)
  - Pembrolizumab\(^c\)
  - MSI-H/dMMR tumors\(^0\)
  - Pembrolizumab\(^c,15\)
  - Dostarlimab-gxly\(^c,16\)
  - Avelumab\(^c\)
  - Axitinib\(^c,22\)

HER2-positive tumors (IHC 3+ or 2+)
  - Fam-trastuzumab deruxtecan-nxk\(^23\)

NYTTA gene fusion-positive tumors
  - Larotrectinib
  - Entrectinib

F. Meric-Bernstam, V. Makker, A. Oaknin, et al ESMO 2023

Pothuri B, Naumann W, Martin L, et al ESMO 2023
GOG-3095/MK-2870 in Post Platinum and Post Immunotherapy Endometrial Cancer

ClinicalTrials.gov ID NCT06132958

Figure 1  Study Design

Key Eligibility Criteria:
- Histologically-confirmed endometrial carcinoma or carcinosarcoma
- Radiologically-apparent measurable or nonmeasurable disease
- Prior platinum exposure AND prior anti-PD-1/anti-PD-L1 exposure (given separately or in combination) in any setting, including neoadjuvant or adjuvant therapy. Low-dose platinum used for radiosensitization is not included.

1:1 N=710

Arm 1: MK-2870

Arm 2: TPC (doxorubicin or paclitaxel)

Dual Primary Endpoints
- PFS
- OS

Secondary Endpoints
- ORR
- DOR
- QoL
- Safety/Tolerability

Stratification:
- MMR (dMMR vs pMMR)
- TROP2 expression (low vs high)
- Number of prior lines of therapy (≤2 vs 3)
- Disease status at baseline per RECIST 1.1 by BICR (measurable vs nonmeasurable)
Hormonal Therapy

<table>
<thead>
<tr>
<th>Agent</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Megestrol Acetate</td>
<td>24%</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>10%-53%</td>
</tr>
<tr>
<td>MA alternating w/ tamoxifen</td>
<td>27 - 33%</td>
</tr>
<tr>
<td>Anastrazole</td>
<td>9%</td>
</tr>
<tr>
<td>Letrozole</td>
<td>9%</td>
</tr>
<tr>
<td>Leuprolide</td>
<td>~10%</td>
</tr>
</tbody>
</table>

Option for 1st line or ≥2nd line:
- 1st line ORR = 21.6%
- 2nd line ORR = 18.5%
- Median PFS = 2.8mths
- Median OS = 10.2 months
- ↑ORR ER+ (26.5%)/ PgR+ (35.5%) disease
- ↓ORR in ER− (9.2%) or PgR− (12.1%) tumors.
- ↓ORR older age and high grade.

MacKay HJ, 2020 ASCO Educational Book; Ethier et al Gynecologic Oncology 2017; Meenakshi Singh et al. Gynecologic Oncology 2007; Mirza et al. ESMO 2020 ; Slomovitz et al, Gyn Oncol 2022
Summary

• dMMR tumors have unprecedented responses to CPI and should be the standard of care

• pMMR tumors do have improved outcomes with CPI; however, better treatment options remain an unmet need and should be further explored (PARP, non-IO, etc)

• The role of IO after IO needs to be investigated as limited efficacy data to date

• Non-IO treatment options are needed to provide better treatment options; enrollment into clinical trials is crucial