Endometrial Cancer – Highlight Reel

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Uterine Cancer Lead, GOG Partners

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Objectives

• Review key studies from fall meetings
• Discuss ongoing endometrial cancer trials in GOG Partners
• Predict changes in standard of care after first-line studies report
Review of Key Studies
Study 309/K775: Updated efficacy and safety

**Key eligibility criteria**
- Advanced, metastatic, or recurrent endometrial cancer
- Measurable disease by BICR
- One 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 (1: Europe, USA, Canada, Australia, New Zealand, and Israel vs 2: rest of the world)
  - ECOG PS (0 vs 1)
  - Prior history of pelvic radiation (Y vs N)

**Primary endpoints**
- PFS by BICR
- OS

**Secondary endpoints**
- ORR
- HRQoL
- Pharmacokinetics
- Safety

**Key exploratory endpoint**
- Duration of response

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- PFS, OS, and ORR were statistically significant with lenvatinib plus pembrolizumab vs chemotherapy at the primary analysis (Makker 2022, *NEJM)*.
- Median follow-up time: 14.7 months (data cutoff date: 1 March 2022; >16 months of additional follow-up time from the interim analysis for OS).
- PFS and ORR (by BICR per RECIST v1.1) are also presented at this data cutoff; all analyses are descriptive.
Continued OS benefit of lenvatinib plus pembrolizumab vs chemotherapy with follow-up extended by over 16 months

- OS favored lenvatinib plus pembrolizumab despite some pts in the chemotherapy arm receiving subsequent lenvatinib plus pembrolizumab. (In the chemotherapy arm, 10.0% of pts in the pMMR population and 8.7% of pts in the all-comer population).
  - After excluding these pts, the pMMR OS HR was 0.64 (95% CI, 0.54, 0.76); the all-comer OS HR was 0.60 (95% CI, 0.51, 0.71).
Continued PFS\textsuperscript{a} benefit of lenvatinib plus pembrolizumab vs chemotherapy with follow-up extended by over 16 months
Continued tumor responses in pMMR and all-comer pts by BICR per RECIST v1.1

**pMMR ORR**
- **ORR = 32.4%** (95% CI, 27.5–37.6)
  - 5.8% CR (n=20)
  - 26.2% PR (n=92)
  - 12.5% PR (n=44)
- **ORR = 15.1%** (95% CI, 11.5–19.3)
  - 2.6% CR (n=9)

**pMMR DOR**
- Median Duration of Response (Range):
  - Lenvatinib plus pembrolizumab: 9.3 (1.6+, 38.5+)
  - Chemotherapy: 5.7 (0.0+, 37.1+)

**All-comer ORR**
- **ORR = 33.8%** (95% CI, 29.3–38.6)
  - 7.5% CR (n=31)
  - 26.3% PR (n=108)
  - 12.0% PR (n=50)
- **ORR = 14.7%** (95% CI, 11.4–18.4)
  - 2.6% CR (n=11)

**All-comer DOR**
- Median Duration of Response (Range):
  - Lenvatinib plus pembrolizumab: 12.9 (1.6+, 39.5+)
  - Chemotherapy: 5.7 (0.0+, 37.1+)
Conclusions

- At the interim analysis, lenvatinib plus pembrolizumab led to statistically significantly improved PFS (pMMR HR: 0.60; all-comer HR: 0.56), OS (pMMR HR: 0.68; all-comer HR: 0.62), and ORR (pMMR ORR: 30.3% vs 15.1%; all-comer ORR: 31.9% vs 14.7%) compared to chemotherapy (Makker 2022, NEJM).

- At the final prespecified analysis of OS, lenvatinib plus pembrolizumab continued to demonstrate clinically meaningful improvement in OS, PFS, and ORR vs chemotherapy in pts with aEC (pMMR and all-comer populations) who received prior platinum therapy, supporting the robustness of the treatment effect observed at the interim analysis (Makker 2022, NEJM).

- OS KM curves for lenvatinib plus pembrolizumab and chemotherapy arms separated early and remained separated, despite some pts in the chemotherapy arm receiving subsequent lenvatinib plus pembrolizumab.

- No new safety signals were observed, and safety results were consistent with the interim analysis (Makker 2022, NEJM) and with the established safety profile of each agent.

- Results continue to support the use of lenvatinib plus pembrolizumab as a standard therapy in pts with previously treated aEC.
GARNET: Safety and antitumor activity of dostarlimab in dMMR or pMMR endometrial cancer

- GARNET (NCT02715284) is a phase 1, single-arm study of dostarlimab (TSR-042) monotherapy in multiple tumor types
- In part 2B, dostarlimab was dosed at the RTD determined from Part 1 and 2A
  - 500 mg IV Q3W for 4 cycles, then 1000 mg IV Q6W until disease progression

- MMR status was determined by local immunohistochemistry
- Primary endpoint: ORR and DOR

Key inclusion/exclusion criteria for cohorts A1 and A2:
- Patients must have progressed on or after platinum doublet therapy
- Patients must have received ≤2 prior lines of treatment for recurrent or advanced disease
- Patients must have measurable disease at baseline
- Patients must be anti–PD-(L)1 naïve
- Patients could be screened based on local MMR/MSI testing results using IHC, PCR, or NGS performed in a certified local laboratory, but patient eligibility needs to be confirmed by MMR IHC results

Part 1
Dose finding

Part 2A
Fixed-dose safety run-in

Part 2B
Expansion cohorts

A1*: dMMR EC
N=129

A2†: pMMR EC
N=161

E: NSCLC

F: Non-endometrial dMMR/MSI-H basket

G: PROC

*Cohort enrollment includes 3 patients with MMRunk/MSI-H disease; †Cohort enrollment includes 16 patients with MMRunk/MSS disease
Enrollment and Outcomes

Enrolled and dosed (safety population)

- dMMR EC N=126 (100%)
- MMRp EC N=145 (100%)

No measurable disease at baseline or insufficient follow-up

- n=23
- n=3

Measurable disease at baseline and ≥6 months follow-up (efficacy population)

- n=103

Discontinued treatment

- 70 of 126 (56%)
  - Progression, n=49
  - Adverse event, n=14
  - Patient request, n=1
  - Clinical criteria, n=5
  - Other, n=1

- 127 of 145 (88%)
  - Progression, n=89
  - Adverse event, n=14
  - Clinical criteria, n=16
  - Patient request, n=5
  - Other, n=3

Remain on treatment

- n=56 of 126 (44%)
- n=18 of 145 (12%)

Data cut-off date March 1, 2020. dMMR, mismatch mutation repair deficient; EC, endometrial cancer; MMRp, mismatch mutation repair proficient.
Primary Endpoint Analysis

- ORR was 44.7% in patients with dMMR EC, and 13.4% in patients with MMRp EC

<table>
<thead>
<tr>
<th>Variable</th>
<th>dMMR EC, n=103</th>
<th>MMRp EC, n=142</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up time, mo</td>
<td>16.3</td>
<td>11.5</td>
</tr>
<tr>
<td>Objective response rate*, n (%), 95% CI</td>
<td>46 (44.7%, 34.9–54.8)</td>
<td>19 (13.4%, 8.3–20.1)</td>
</tr>
<tr>
<td>Complete response, n (%)</td>
<td>11 (10.7)</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Partial response, n (%)</td>
<td>35 (34.0)</td>
<td>16 (11.3)</td>
</tr>
<tr>
<td>Stable disease, n (%)</td>
<td>13 (12.6)</td>
<td>31 (21.8)</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
<td>39 (37.9)</td>
<td>77 (54.2)</td>
</tr>
<tr>
<td>Not evaluable, n (%)</td>
<td>3 (2.9)</td>
<td>0</td>
</tr>
<tr>
<td>Not done, n (%)</td>
<td>2 (1.9)</td>
<td>15 (10.6)</td>
</tr>
<tr>
<td>Disease control rate†, n (%), 95% CI</td>
<td>59 (57.3%, 47.2–67.0)</td>
<td>50 (35.2%, 27.4–43.7)</td>
</tr>
<tr>
<td>Response ongoing, n (%)</td>
<td>41 (89.1)</td>
<td>12 (63.2)</td>
</tr>
<tr>
<td>Median duration of response, (range) mo</td>
<td>Not reached (2.63–28.09+)</td>
<td>Not reached (1.54+–30.36+)</td>
</tr>
<tr>
<td>Kaplan–Meier estimated probability of remaining in response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>at 6 mo, %</td>
<td>97.8</td>
<td>83.0</td>
</tr>
<tr>
<td>at 12 mo, %</td>
<td>90.6</td>
<td>61.3</td>
</tr>
<tr>
<td>at 18 mo, %</td>
<td>79.2</td>
<td>61.3</td>
</tr>
</tbody>
</table>
Data cut-off date March 1, 2020. CR, complete response; dMMR, mismatch mutation repair deficient; EC, endometrial cancer; MMRp, mismatch mutation repair proficient; PD, progressive disease; PR, partial response; SD, stable disease.

41 of 46 (89.1%) patients remain in response as of the data cutoff.

12 of 19 (63.2%) patients remain in response as of the data cutoff.
Conclusions

• Dostarlimab demonstrated durable antitumor activity in both dMMR and MMRp advanced/recurrent EC

• dMMR status by IHC was associated with a higher response rate

• Dostarlimab demonstrated a notable disease control rate (35.2%; 2.1% CR, 11.3% PR, 21.8% SD) in patients with MMRp EC, was comprised of a higher percentage of patients with Type II EC which is historically associated with a worse prognosis

• No new safety signals were detected, and only 5.5% of patients discontinued dostarlimab due to a TRAE
  
  o Most adverse events were grade 1 or 2
  
  o Safety was consistent between dMMR and MMRp cohorts
Post Hoc Analysis of Objective Response Rate by Mismatch Repair Protein Dimer Loss/Mutation Status in Patients with Mismatch Repair Deficient Endometrial Cancer Treated with Dostarlimab

• MMR deficiency is caused by loss of expression of the MMR proteins MLH1, PMS2, MSH2, and/or MSH6¹
  — These proteins function as heterodimers (MLH1–PMS2 and MSH2–MSH6) to mediate DNA repair

• Loss of expression is caused primarily by 2 mechanisms
  Germline (Lynch syndrome) or somatic mutation of MLH1, PMS2, MSH2, and/or MSH6
  Epigenetic methylation of the MLH1 promoter

• Gene mutation or epigenetic silencing of 1 gene typically leads to loss of expression of the heterodimer (most common dMMR staining pattern) and results in defective MMR and genomic instability¹
  — Other patterns of loss are possible (loss of only 1 protein; loss of 3 proteins; or loss of atypical combinations of 2 proteins, eg, PMS2 and MSH6, etc)
Background

- MLH1 promoter methylation accounts for approximately 75%–80% of cases with MMR deficiency in EC\textsuperscript{1-4}
  - Somatic or germline mutation in an MMR gene is estimated to account for 10-20% of MMR deficiency in EC\textsuperscript{1-4}
- The relationship between mechanism of MMR deficiency and outcomes is not well understood

\[\begin{align*}
\text{Normal} & \quad \text{No mutation or methylation} \\
& \quad \text{Normal transcription and protein production} \\
& \quad \text{Stable MMR heterodimers} \\
& \quad \text{Normal MMR DNA repair} \\
\text{MMR deficiency} & \quad \text{Germline or somatic mutation} \\
& \quad \text{Loss of expression of } \geq 1 \text{ MMR proteins} \\
& \quad \text{Loss of heterodimer (major)} \\
& \quad \text{Loss of expression in atypical patterns (minor)} \\
& \quad \text{Defective MMR and genomic instability} \\
& \quad \text{Loss of } \text{MLH1 also results in loss of } \text{PMS2}
\end{align*}\]

No difference in ORR or DOR by pattern of MMR protein loss

- MMR protein loss is similar to the estimated ratios in the dMMR EC population

<table>
<thead>
<tr>
<th>MMR protein staining pattern (IHC)</th>
<th>Patients, N</th>
<th>Responders, n</th>
<th>ORR, % (95% exact CI)</th>
<th>DOR median (95% CI), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort A1 (dMMR/MSI-H EC)</td>
<td>143</td>
<td>65</td>
<td>45.5 (37.1–54.0)</td>
<td>NR (38.9–NR)</td>
</tr>
<tr>
<td>MLH1–PMS2 dimer loss</td>
<td>94 (66%)</td>
<td>46</td>
<td>48.9 (38.5–59.5)</td>
<td>NR (34.7–NR)</td>
</tr>
<tr>
<td>MSH2–MSH6 dimer loss</td>
<td>16 (11%)</td>
<td>9</td>
<td>56.3 (29.9–80.2)</td>
<td>NR (13.9–NR)</td>
</tr>
<tr>
<td>Othera</td>
<td>33 (23%)</td>
<td>10</td>
<td>30.3 (15.6–48.7)</td>
<td>NR (13.7–NR)</td>
</tr>
</tbody>
</table>


*aOther: any other pattern of loss that is not exclusively MLH1–PMS2 or MSH2–MSH6 dimer loss. This group includes 17 patients with loss of expression of 1 MMR protein, 13 with loss of 3 proteins, 1 with loss of 2 proteins that are not a canonical dimer, and 2 with MMR unknown/MSI-H status.

dMMR, MMR deficient; DOR, duration of response; EC, endometrial cancer; IHC, immunohistochemistry; MMR, mismatch repair; MSI-H, microsatellite instability–high; ORR, objective response rate.
No difference in ORR or DOR in those with MLH1 loss by mutation status

- Most MLH1 loss was not accompanied by mutations, consistent with the estimated rate in the dMMR population\textsuperscript{1-4}

<table>
<thead>
<tr>
<th>Patients, N</th>
<th>Responders, n</th>
<th>ORR, % (95% exact CI)</th>
<th>DOR median (95% CI), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort A1 (dMMR/MSI-H EC)</td>
<td>143</td>
<td>65</td>
<td>45.5 (37.1–54.0)</td>
</tr>
<tr>
<td>Cohort A1 patients with available mutation data</td>
<td>101</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>MLH1 loss by IHC (any pattern)\textsuperscript{a}</td>
<td>78</td>
<td>31</td>
<td>39.7 (28.8–51.5)</td>
</tr>
<tr>
<td>MLH1 loss by IHC (any pattern) and mutation in $MLH1$ or $PMS2$ genes</td>
<td>7 (9%)</td>
<td>3</td>
<td>42.9 (9.9–81.6)</td>
</tr>
<tr>
<td>MLH1 loss by IHC (any pattern) and no mutation in $MLH1$ or $PMS2$ genes</td>
<td>71 (91%)</td>
<td>28</td>
<td>39.4 (28.0–51.7)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}This group includes 66 patients with loss of the MLH1–PMS2 dimer and 12 with another pattern.

Conclusions

• Consistent with the literature, the most common pattern of MMR protein loss was the MLH1–PMS2 heterodimer (66% of patients in the GARNET cohort A1 vs ≈75% in the general EC population)\(^1\)\(^-\)\(^4\)

• Tumors with loss of MLH1 and no mutation identified in *MLH1* or *PMS2* are likely to have MLH1 promoter methylation; however, direct testing of methylation would be the most accurate means to identify these patients
  - There were no noticeable differences observed in ORR by pattern of MMR protein loss or MMR gene methylation/mutation status
  - This data set is the largest to explore the response rate by mechanism leading to MMR deficiency

• These data are hypothesis generating
  - GARNET was not powered to study the effect of MMR protein pattern or mutation status on response to dostarlimab

• The data suggest the route to MMR deficiency does not influence response to dostarlimab (ORR of 39.4% in patients with presumed MLH1 promoter methylation)

Atezolizumab and Bevacizumab in Recurrent Endometrial Cancer: A Phase II, Multi-institutional Trial

**Inclusion criteria:**
- Advanced, recurrent endometrial cancer
- Endometrioid, serous, mixed adenocarcinoma, clear-cell, or carcinosarcoma
- 1-2 prior lines for endometrial cancer
- Measurable disease at time of recurrence
- Prior carboplatin/paclitaxel acceptable
- Archival tissue or tissue biopsy

**Treatment**
- Bevacizumab 15mg/kg IV D1 + Atezolizumab 1200mg D1
  Q 21 day cycle

**Post-treatment blood collection**

**Primary Endpoint:**
Objective response rate (ORR)

**Secondary Endpoints:**
1) PFS
2) OS
3) Safety using CTCAE v4.0
4) ORR by immune related response criteria (irRC)

**Exploratory Endpoint:**
1) Immune subpopulations by CyToF
2) Multiparametric fluorescent imaging by CODEX

NCT03526432
## Results: Overall Adverse events and Clinical Activity

<table>
<thead>
<tr>
<th>Total Number of Subjects</th>
<th>n=57</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse events</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 3 due to atezolizumab</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Grade 3 due to bevacizumab</td>
<td>12 (22%)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
</tr>
<tr>
<td>Dose interruption</td>
<td>45 (79%)</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Discontinued due to toxicity</td>
<td>9 (16%)</td>
</tr>
</tbody>
</table>

### Clinical Activity

- **ORR for all**: 30% (95% CI 18-43)
- **ORR for MMRp**: 33% (95% CI 20-48)
- **Median DOR (months)**: 15 (95% CI 2.9-34)
- **Median PFS (months)**: 7.87 (95% CI 5.5-11.7)
Regimen I  
Whole Pelvis Radiation  
4500 cGy in 25 fractions to the whole pelvis  
(180 cGy/fraction)  
Interstitial or Intracavitary Brachytherapy or external beam boost

Regimen II  
Whole Pelvis Radiation  
4500 cGy in 25 fractions to the whole pelvis  
(180 cGy/fraction)  
Weekly Cisplatin  
40 mg/m²/wk  
Interstitial or Intracavitary Brachytherapy or external beam boost

Institution IMRT Credentialing is required when IMRT is to be used before registering any patient on this trial. A Knowledge Assessment for this study must be completed by the treating radiation oncologist before registering patients on this trial.

For patients with tumors involving the distal vagina and clinically negative groins, the bilateral inguino-femoral lymph node regions should be treated to 4500 cGy.

3-D conformal or IMRT boost is allowed for patients who are not candidates for brachytherapy.
Radiation therapy remains the standard of care for pelvic only/vaginal cuff recurrences.

Low grade endometrioid cancers highly represented (81.5%)

32% of patients treated with radiation therapy recurred
Ongoing Trials
First Line:
I/O
CDK 4/6 inhibition
Nuclear export inhibition
A Phase 3 Randomized, Open-label, Active-comparator Controlled Clinical Study of Pembrolizumab versus Platinum Doublet Chemotherapy in Participants With Mismatch Repair Deficient (dMMR) Advanced or Recurrent Endometrial Carcinoma in the First-line Setting (KEYNOTE-C93/GOG-3064/ENGOT-en15)

Global lead: GOG (PI: Slomovitz co-PI: Backes)

ENGOT PI: S. Pignata
KEYNOTE-177: Robust Activity of Pembrolizumab Monotherapy Compared to SOC in Stage IV MSI-H/dMMR CRC

<table>
<thead>
<tr>
<th>Pembrolizumab</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 153</td>
<td>N = 154</td>
</tr>
<tr>
<td>ORR, n (%)</td>
<td>67 (43.8)</td>
</tr>
<tr>
<td>Difference, estimate (95% CI)</td>
<td>10.7 (-0.2; 21.3)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Best Overall Response, n (%)

- Complete response: 17 (11.1) vs 6 (3.9)
- Partial response: 50 (32.7) vs 45 (29.2)
- Stable disease: 32 (20.9) vs 65 (42.2)
- Disease control rate (CR+PR+SD): 99 (64.7) vs 116 (75.3)
- Progressive disease: 45 (29.4) vs 19 (12.3)
- Not evaluable: 3 (2.0) vs 2 (1.3)
- No assessment: 6 (3.9) vs 17 (11.0)

Median time to response (range), mo

- Pembrolizumab: 2.2 (1.8-18.8)
- Chemotherapy: 2.1 (1.7-24.9)
GOG 3064/ ENGOT–en15/MK KN-C93: 1L dMMR platinum-doublet chemotherapy vs pembro (with formal cross over)

Phase 3, multi-center, randomized, open-label

Key Eligibility Criteria:
- Stage III or IV, persistent/ recurrent, or metastatic EC
- Measurable/non-measurable disease (radiological apparent)
- dMMR/MSI-H
- No previous chemo for first line except as part of chemoradiation
- Prior adjuvant/neoadjuvant chemotherapy allowed, as long as completed > 6 mths before recurrence
- ECOG 0-1

Potential Stratification:
- Previous radiation and/or adj chemotherapy
- Histology – endometrioid vs. non-endometrioid

Standard of Care
Carboplatin+Paclitaxel (Q3W, up to 7 cycles)

Pembro Monotherapy
Q6W (18 Cycles)

1:1
N=350

Dual Primary Endpoints
- PFS (by BICR)
- OS

PD (by BICR)

Pembro Monotherapy
Q6W (18 Cycles)

Investigator choice, outside of study

Second line Treatment

Secondary Endpoints
- ORR (by BICR)
- PFS2
- HRQOL
- Safety

Treatment Phase (up to 2 years of Pembro)
Background on CDK 4/6 Inhibition

• Most endometrial tumors are hormonally driven (type 1 endometrioid adenocarcinoma); estrogen signaling through estrogen receptor acts as an oncogenic signal

• Not all patients can handle more toxic treatments; low grade endometrioid cancer should be treated with endocrine therapy in the 1L, leaving cytotoxic options for later lines

• There is established clinical proof of concept for CDK 4/6i in metastatic endometrial cancer

• Endometrial cancer endocrine sensitivity and frequent cell cycle deregulation suggest that coupling mechanisms of CDKi and estrogen blockade could result in enhanced efficacy
ENGOT-EN3/NSGO-PALEO: Efficacy (ITT population)

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*

* = at 24 weeks

Number at risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Palbociclib + letrozole</th>
<th>Placebo + letrozole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (months)</td>
<td>0  2  5  10  15</td>
<td>0  2  5  10  15</td>
</tr>
<tr>
<td>Palbociclib + letrozole</td>
<td>36  21  14</td>
<td>37  17  10</td>
</tr>
<tr>
<td>Placebo + letrozole</td>
<td>37  17  10</td>
<td>37  17  10</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

Phase 2, two-stage study of letrozole and abemaciclib in estrogen receptor (ER) positive recurrent or metastatic endometrial cancer (EC)

- **Regimen:** Letrozole 2.5mg PO daily and Abemaciclib 150 mg PO BID until progression or toxicity

![Flowchart]

1st Stage:
- Enroll 16 patients

2nd Stage:
- Enroll 19 patients
- Letrozole/Abemaciclib worthy of further study

Overall if:
- $\geq 2$ ORRs
- OR
- $\geq 2$ PFS6
- OR
- $\geq 8$ PFS6

Panagiotis A. Konstantinopoulos et al, SGO 2022
## Objective Response Rate

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>Patients (N=30) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best Overall Response</strong></td>
<td></td>
</tr>
<tr>
<td>Complete Response (CR)</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>9 (30%)</td>
</tr>
<tr>
<td></td>
<td>(1 unconfirmed,</td>
</tr>
<tr>
<td></td>
<td>all PRs in endometrioid</td>
</tr>
<tr>
<td></td>
<td>tumors)</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>13 (43.3%)</td>
</tr>
<tr>
<td>Progressive Disease (PD)</td>
<td>7 (23.3%)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td><strong>ORR, % (95% CI)</strong></td>
<td>30% (14.7-49.4)</td>
</tr>
</tbody>
</table>
Promising Early signal with combined AI and CDK4/6 inhibition in ER+ EC

• Colon-Otero et al ESMO 2020
  – Letrozole 2.5 mg oral +Ribociclib 400 mg oral QD
  – PFS12 weeks 55%
  – PFS24 weeks 35%
  – PFS24 weeks in grade 1-2 EC 45%
  – Median PFS and OS 5.4 and 16

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Subset analysis of PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Patients PFS ≥24 weeks</td>
<td>11/40 (27.5%)</td>
</tr>
<tr>
<td>Ovarian group</td>
<td>4/20 (20.0%)</td>
</tr>
<tr>
<td>Low-grade serous</td>
<td>3/3 (100.0%)*</td>
</tr>
<tr>
<td>High-grade serous</td>
<td>1/17 (5.9%)</td>
</tr>
<tr>
<td>Endometrial group</td>
<td>7/20 (35.0%)</td>
</tr>
<tr>
<td>Grade 1 to 2</td>
<td>5/11 (45.5%)</td>
</tr>
<tr>
<td>High-grade</td>
<td>2/9 (22.2%)</td>
</tr>
</tbody>
</table>
EQ132-303/GOG-3075/ENGOT en-17: A Randomized, Double-Blinded, Placebo-Controlled Phase 3 Study of Lerociclib with Letrozole, versus Placebo in Combination with Letrozole, in Participants with Advanced or Recurrent Grade 1 or Grade 2 Endometrioid Endometrial Carcinoma

Study population:
- Endometrioid EC, Grade 1 or Grade 2
- No prior treatment for metastatic disease
- Naïve to hormone therapy
- Stage III, Stage IV, or recurrent disease
- ECOG PS 0-1

Stratification variables:
- Tumor stage (III vs IV vs recurrent)
- Tumor grade (Grade 1 vs Grade 2)
- Geographic location

Primary endpoint: PFS by BICR
Secondary endpoints: PFS by Investigator, OS, PROs/QoL, safety/tolerability
Exploratory endpoints: ORR, PopPK, exposure-response, financial distress, translational analysis of ctDNA

R 1:1

Letrozole 2.5 mg PO QD and Lerociclib 150 mg PO BID
Letrozole 2.5 mg PO QD and Placebo

PI: Mahdi
ENGOT PI: Ray-Coquard
Prospective double-blind, randomized phase III ENGOT-EN5/GOG-3055/SIENDO study of oral selinexor/placebo as maintenance therapy after first-line chemotherapy for advanced or recurrent endometrial cancer

Ignace Vergote,1 Alejandro Pérez Fidalgo,2 Erika Hamilton,3 Giorgio Valabrega,4 Toon Van Gorp,1 Jalid Sehouli,5 David Cibula,6 Tally Levy,7 Stephen Welch,8 Debra Richardson,9 Eva Maria Guerra Alía,10 Giovanni Scambia,11 Stéphanie Henry,12 Pauline Wimberger,13 David Miller,14 Jerónimo Martínez,15 Bradley Monk,16 Sharon Shacham,17 Mansoor Raza Mirza,17,18 Vicky Makker19

1Catholic University Leuven, Cancer Institute at University Hospitals, Belgium, European Union, 2Hospital Clínico Universitario de Valencia, Spain, 3Sarah Cannon Research Institute USA, 4University of Torino, Candido Cancer Institute, FPO-IRCCS, Italy, 5European Competence Center for Ovarian Cancer, Charité Comprehensive Cancer Center, Charité–Berlin University of Medicine, Germany, 6Charles University and General Faculty Hospital Prague, Czech Republic, 7Wolfson Medical Center, Holon, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Israel, 8London Health Sciences Centre, UK 9University of Oklahoma Medical Center, USA, 10Hospital Universitario Ramón y Cajal, Spain, 11Fondazione Policlinico Universitario A. Gemelli IRCCS, Italy, 12Centre de Maternité Sainte Elisabeth, Namur, Belgium, 13Technische Universität Dresden, University Hospital Carl Gustav Carus, Germany, 14University of Texas Southwestern Medical Center; Harold C. Simmons Comprehensive Cancer Center, USA, 15Hospital Universitario Virgen de la Arrixaca, Spain, 16Biltmore Cancer Center, USA, 17Karyopharm Therapeutics, USA, 18Rigshospitalet, Copenhagen University Hospital, Denmark, 19Memorial Sloan Kettering Cancer Center, USA
Primary Endpoint: PFS in ITT Population

Median PFS

- **Selinexor** (n=174): 5.7 mo (95% CI 3.81-9.20)
- **Placebo** (n=89): 3.8 mo (95% CI 3.68-7.39)

Audited* (by electronic case report form)
- HR = 0.705 (95% CI 0.499-0.996)
- One-sided P value = 0.024

Unaudited* (by interactive response technology)
- HR = 0.76 (95% CI 0.543-1.076)
- One-sided P value = 0.063

*In 7 patients (2.7% of 263), the stratification factor of CR/PR was incorrect and was corrected by the Investigators prior to database lock and unblinding. The statistical analysis was validated by the independent ENGOT statistician and approved by the IDMC.

CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival

Vicky Makker, M.D., ENGOT-ENS/GOG-3055/SIENDO
Preliminary Analysis of a Prespecified Exploratory Subgroup PFS: Patients with p53 wild-type EC

Median PFS

- **Selinexor (n=67)**: 13.7 mo (95% CI 9.20-NR)
- **Placebo (n=36)**: 3.7 mo (95% CI 1.87-12.88)

Audited

- **HR = 0.375 (95% CI 0.210-0.670)**
  - Nominal one-sided P value = 0.0003

Unaudited

- **HR = 0.407 (95% CI 0.229-0.724)**
  - Nominal one-sided P value = 0.0008

CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival
ENGOT-EN20/GOG3083/XPORT-EC-042 Randomized, blinded Phase 3 international study of oral Selinexor once weekly versus placebo for maintenance therapy in patients with p53wt endometrial carcinoma responding to front line

**Primary Objective:** To evaluate the efficacy of selinexor compared to placebo as maintenance therapy in patients with p53wt advanced or recurrent endometrial cancer

**n = 220 PFS (HR 0.7)**

**Key Eligibilities**
- Known p53wt EC by central NGS
- Primary stage IV or recurrent EC
- Received at least 12 weeks of taxane-platinum chemotherapy (1st or 2nd line)

**Stratified by:**
- Primary stage IV vs recurrent
- PR vs CR
- Prior CPI (yes/no)

**Primary Endpoint:**
- PFS assessed by Investigator (BICR as a sensitivity analysis)

**Secondary Endpoint:**
- OS
- Safety

**Randomization (1:1)**

- Selinexor 60mg QW until PD
- Placebo until PD

**PR/CR Per RECIST v1.1**
Second Line: I/O
INCMGA 0012-204/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

Primary Endpoint = ORR
PI: Slomovitz, B

NCT04463771
POD1UM-204: Phase 2, open-label, nonrandomized, umbrella study of retifanlimab alone or combined with other therapies in recurrent advanced/metastatic endometrial cancer*

Patients with advanced or metastatic endometrial cancer with disease progression on or after treatment with ≥1 platinum-containing regimen

**Closed Groups:** *Group C (unselected): completed enrollment (Retifanlimib+Epacadostat), Group E (CPI Naïve, PD-L1+): enrollment closed (Retifanlimib+Epacadostat)*

• Analysis of LAG-3 expression in the The Cancer Genome Atlas dataset showed a wide range of expression among different cancer types. Multiple solid tumors, including endometrial cancer, have considerably high expression of LAG-3 (Panda et al 2020).

• high LAG-3 expression measured by mRNA sequencing correlates significantly with high TMB

• tumor associated LAG-3+ lymphocytes are higher in MMR-deficient tumors compared with intact tumors

• TIM-3 and LAG-3 are frequently co-expressed with PD-1 in TILs

• rationale for PD-1, LAG 3, and TIM-3 combination blockade support exploring the clinical activity of the triplet combination approach in MSI-H/dMMR advanced endometrial cancer with evidence of disease progression on or after prior PD-(L)1 therapy
Predicting the Future
KEYNOTE-B21

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

Key eligibility criteria:
- Newly diagnosed endometrial carcinoma or carcinosarcoma
- High Risk
- No prior therapy including XRT or neo-adjuvant
- Curative intent Hysteroscopy +/- LN sampling/dissemination
- No residual disease

Stage 1
- Pembrolizumab 200 mg IV (Q3W, 5 infusions) + Carboplatin (AUC 6 or 5)
- Placebo IV (Q3W, 6 infusions) + Carboplatin (AUC 6 or 5)
- Pemetrexed 175 mg/m² (Q3W, 4 or 6 cycles)

Stage 2
- Pembrolizumab 400 mg Q6W (6 cycles)
- Placebo Q6W (6 cycles)

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

*High Risk:
- FIGO (2009) Surgical Stage I or II with myometrial invasion of non-endometrioid histology
- FIGO (2009) Surgical Stage III or IVA of any histology

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)

N=990
Closed to accrual
PI: Slomovitz, B, Barber, E
NCT04634877
## Endometrial Cancer: 1st line metastatic recurrent

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Identifier</th>
<th>Design</th>
<th>Status</th>
</tr>
</thead>
</table>
| Front-line, metastatic or recurrence  
PI: Powell  
*ENGOT led                                                                                                                                                                                                 | GOG-3031/RUBY       | 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 | CLOSED TO ACCRUAL |
|                                                                                                                                                                                                                                                                             | NCT03981796         |                                                                                                   |                 |
| Front-line, metastatic or recurrence  
PI: Westin  
Co-PI: Moore  
*GOG led                                                                                                                                                                                                     | GOG-3041/DUO-E      | 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 | CLOSED TO ACCRUAL |
|                                                                                                                                                                                                                                                                             | NCT04269200         |                                                                                                   |                 |
| Front-line, metastatic or recurrent  
PI: Slomovitz, Backes  
*GOG led                                                                                                                                                                                                     | GOG-3064/c93        | A Phase 3 Randomized, Open-label, Active-comparator Controlled Clinical Study of Pembrolizumab Versus Platinum Doublet Chemotherapy in Participants With Mismatch Repair Deficient (dMMR) Advanced or Recurrent Endometrial Carcinoma in the First-line Setting | Recruiting      |
|                                                                                                                                                                                                                                                                             | NCT05173987         |                                                                                                   |                 |
## Endometrial Cancer: 1st line metastatic recurrent

<table>
<thead>
<tr>
<th>Study Description</th>
<th>PI</th>
<th>NCT Number</th>
<th>Study Details</th>
<th>Status</th>
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<tbody>
<tr>
<td>Front-line, metastatic or recurrence</td>
<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>CLOSED</td>
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<tr>
<td>Front-line, metastatic or recurrence</td>
<td>PI: Eskander</td>
<td>NRG-GY-018 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>
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</table>
# Predicting Future in First Line Recurrent-dMMR

<table>
<thead>
<tr>
<th>Scenario #1</th>
<th>Chemo + I/O +/- PARP</th>
<th>LEAP-001</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Either regimen or C93</td>
</tr>
<tr>
<td>Scenario #2</td>
<td>Positive</td>
<td>Negative</td>
<td>Chemo I/O; C93??</td>
</tr>
<tr>
<td>Scenario #3</td>
<td>Negative</td>
<td>Positive</td>
<td>Pembro/Len or C93</td>
</tr>
<tr>
<td>Scenario #4</td>
<td>Negative</td>
<td>Negative</td>
<td>Chemo; EXPORT; CDK4/6</td>
</tr>
</tbody>
</table>

The table above outlines the scenarios and corresponding treatments for predicting future outcomes in first line recurrent-dMMR. Each scenario is characterized by the positivity of Chemo + I/O +/- PARP and LEAP-001, followed by the appropriate treatment recommendation.
## Predicting Future in First Line Recurrent-dMMR

<table>
<thead>
<tr>
<th>Scenario #1</th>
<th>Chemo + I/O +/- PARP</th>
<th>LEAP-001</th>
</tr>
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<tbody>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Scenario #2</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Scenario #3</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Scenario #4</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Scenario #5</td>
<td>Positive or Negative</td>
<td>Positive or Negative</td>
</tr>
</tbody>
</table>
### Predicting Future in First Line Recurrent-pMMR

<table>
<thead>
<tr>
<th>Scenario #1</th>
<th>Chemo + I/O +/- PARP</th>
<th>LEAP-001</th>
<th>Chemo+I/O or Pem/Len</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Chemo+I/O or Pem/Len</td>
</tr>
<tr>
<td>Scenario #2</td>
<td>Positive</td>
<td>Negative</td>
<td>Chemo+I/O</td>
</tr>
<tr>
<td>Scenario #3</td>
<td>Negative</td>
<td>Positive</td>
<td>Pem/Len; EXPORT, CDK4/6</td>
</tr>
<tr>
<td>Scenario #4</td>
<td>Negative</td>
<td>Negative</td>
<td>Chemo; EXPORT, CDK4/6</td>
</tr>
</tbody>
</table>
Predicting Future in First Line Recurrent-pMMR

<table>
<thead>
<tr>
<th>Scenario #</th>
<th>Chemo + I/O +/- PARP</th>
<th>LEAP-001</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>#2</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>#3</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>#4</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>#5</td>
<td>Positive or Negative</td>
<td>Positive or Negative</td>
</tr>
</tbody>
</table>
The Future is Bright