Endometrial Cancer – Highlight Reel

Brian M. Slomovitz, MD, MS, FACOG
Professor, Florida International University
Director, Gynecologic Oncology, Mount Sinai Medical Center
Member, Board of Directors, GOG Foundation
Uterine Cancer Lead, GOG Partners

Friday, June 9, 2022
Objectives

• Diversity
• Selinexor
• CDK 4/6
• HER2 ADC (even for HER-low tumors)
• mTOR ADC
• First-line I/O in dMMR patient
New FDA Guidance on “Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials Guidance for Industry”, April 13 2022

- Diverse groups need to be a part of the study to evaluate whether the study drug is effective and safe for everyone who will be administered study drug, or what side effects might emerge in one ethnic group or another
- Sponsors must present effectiveness and safety data by gender, age, and ethnic group (eg, race, ethnicity, ancestry) and must identify any modifications of dose or dose interval needed for a specific subgroup, as applicable
- Sponsors should discuss their strategy to enroll a diverse study population at any time throughout the medical product’s development
- A Diversity Plan is required for clinical studies intended to support a marketing submission for a stand alone BLA

https://www.fda.gov/media/157635/download
Real World Data from Endometrial Cancer Molecularly Targeted Consortium: Portrait of Advanced/Recurrent Endometrial Cancer

- MSI and dMMR more common in white patients ($p<0.001$)
- Based on all patients who had NGS testing by Foundation One and CARIS
- Testing status unknown for 4.3% of white (29) and 1.8% of black (4) patients

<table>
<thead>
<tr>
<th></th>
<th>White (N=668), n (%)</th>
<th>Black (N=226), n (%)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NGS or IHC tumor testing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>527 (78.9)</td>
<td>175 (77.4)</td>
<td>0.23</td>
</tr>
<tr>
<td>No</td>
<td>112 (16.8)</td>
<td>47 (20.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Mutations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI3K</td>
<td>228 (34.1)</td>
<td>51 (22.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PTEN</td>
<td>200 (29.9)</td>
<td>27 (11.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TP53</td>
<td>178 (26.6)</td>
<td>94 (41.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Beta-catenin</td>
<td>56 (8.4)</td>
<td>9 (4)</td>
<td>0.02</td>
</tr>
<tr>
<td>AKT</td>
<td>13 (1.9)</td>
<td>8 (3.5)</td>
<td>0.15</td>
</tr>
<tr>
<td>mTOR</td>
<td>8 (1.2)</td>
<td>2 (0.9)</td>
<td>1.00</td>
</tr>
<tr>
<td>ESR</td>
<td>11 (1.6)</td>
<td>3 (1.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>POLE</td>
<td>5 (0.7)</td>
<td>1 (0.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>TSC2</td>
<td>5 (0.7)</td>
<td>1 (0.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>ERBB2 Amplification/overexpression</td>
<td>29 (4.3)</td>
<td>12 (5.3)</td>
<td>0.56</td>
</tr>
<tr>
<td>ERBB3 Amplification/overexpression</td>
<td>19 (2.8)</td>
<td>4 (1.8)</td>
<td>0.42</td>
</tr>
<tr>
<td>TMB status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>47 (7)</td>
<td>7 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>69 (10.3)</td>
<td>15 (6.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Low</td>
<td>134 (20.1)</td>
<td>67 (29.6)</td>
<td></td>
</tr>
</tbody>
</table>

Secord et al, SGO, 2022
Black and Hispanic patient representation in NCCN-recommended systemic therapy regimens for endometrial cancer

Amita Kulkarni MD, Helen Daifotis MD, Alexander Melamed MD, MPH, Joseph Dottino MD, Jason Wright MD, Fady Khoury Collado MD, June Hou MD, Caryn St Clair MD, Allison Gockley MD

Columbia University Irving Medical Center, New York, NY
Patient representation in NCCN endometrial cancer guidelines compared to the CDC’s US Cancer Statistics Database, by race

<table>
<thead>
<tr>
<th>Race</th>
<th>Trial Enrollment</th>
<th>National Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>2.1</td>
<td>3.2</td>
</tr>
<tr>
<td>Black</td>
<td>7.4</td>
<td>9.9</td>
</tr>
<tr>
<td>White</td>
<td>86.7</td>
<td>85.4</td>
</tr>
<tr>
<td>Other</td>
<td>3.8</td>
<td>1.5</td>
</tr>
</tbody>
</table>

p < 0.001
Patient representation in NCCN endometrial cancer guidelines compared to the CDC’s US Cancer Statistics Database, by ethnicity

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Trial Enrollment</th>
<th>National Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic</td>
<td>3</td>
<td>7.6</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>90.7</td>
<td>92.4</td>
</tr>
</tbody>
</table>

p < 0.001
Conclusion

• Racial ethnic minority patients were commonly under-represented in cited NCCN studies when compared to national rates of endometrial cancer among these groups

• Continuing to improve minority recruitment as well as transparency with reporting on race and ethnicity in therapeutic trials will help to ensure generalizability of treatment guidelines
Future Direction: Diversity

• Identifying solutions
• Working within our communities to overcome barriers to research
• Ensuring that all trials have equal representation
• Takes a team!
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, Candiolo 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
Exportin 1 (XPO1) is the major nuclear export protein for:
- Tumor suppressor proteins (TSPs, e.g., p53, IκB, and FOXO)

Inhibition of XPO1 results in:
- Tumor by reactivating multiple TSPs by preventing nuclear export
- Reduction of oncoprotein levels

Selinexor is an oral selective XPO1 inhibitor
**140 events needed to provide 80% power to detect a hazard ratio of 0.6 (median 4.5 months for placebo and 7.5 months for selinexor) with a one-sided alpha of 0.025 and 2:1 randomization ratio favoring selinexor.**

BMI, body mass index; DCR, disease control rate; DSS, disease-specific survival; QW, once weekly; CR, complete response; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival on subsequent therapy; PR, partial response; PROs, patient-reported outcomes; R, randomized; TFST, time to first subsequent therapy; TSST, time to second subsequent treatment

---

**GOG-3055/ENGOT-EN5/SIENDO**

**Stage IV or first relapse of endometrial cancer**
- endometrioid, serous, undifferentiated, or carcinosarcoma (NCT03555422)

---

Stage IV or first relapse of endometrial cancer
- Taxane-carboplatin*
- Prior surgery, radiotherapy, or hormonal therapy allowed

*Chemo for at least 12 weeks

---

**Primary endpoint:**
- PFS**
  - (Investigator assessed)

**Secondary endpoints:**
- OS
- PFS per BICR
- PROs
- TFST
- TSST
- PFS2
- DSS
- DCR

**Pre-defined exploratory endpoints:**
- Histological subtype
- Molecular subclassification (including p53, MMR, and POLE)

---

**RECIST**
- PR/CR on first-line chemo
- Stratification
  - Primary stage IV vs recurrent
  - PR vs CR

**Arm A**
- Selinexor 80mg QW
  - If BMI<20: 60 mg QW
  - Until PD
  - N=174

**Arm B**
- Placebo
  - Until PD
  - N=89
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
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
Preliminary Analysis of a Prespecified Exploratory Subgroup PFS: Patients with p53 Mutant/Aberrant EC

Median PFS

- **Selinexor** (n=74): 3.7 mo (95% CI 3.32-5.55)
- **Placebo** (n=40): 5.6 mo (95% CI 3.71-7.49)

Audited

- HR = 1.306 (95% CI 0.795-2.145)
- Nominal one-sided P value = 0.8530

Unaudited

- HR = 1.345 (95% CI 0.819-2.208)
- Nominal one-sided P value = 0.8785

CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival
SIENDO: Summary and Conclusions

• Once-weekly oral selinexor may prolong progression-free survival compared to placebo in patients with advanced or recurrent endometrial cancer; the audited ITT population had a 30% decrease of risk for progression and/or death compared to placebo.

• Pre-specified exploratory subgroup analyses identified p53 wild-type as a potential predictor of efficacy of selinexor, with 10-month PFS improvement over placebo; no benefit for selinexor was seen in patients with p53 mutant/aberrant tumors.

• In this small, exploratory subgroup analysis, potential benefit may be observed for selinexor over placebo in the patients with p53 wild-type including MSS and Copy-Number Low endometrial cancer.

• Further investigation is warranted for selinexor as a maintenance treatment for patients with p53 wt endometrial cancer.
Future Direction: Selinexor

• Evaluate OS in Siendo
• Better understand role of p53 WT and mutant to predict response
• Siendo 2?
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.
Inclusion criteria:
- Measurable/evaluable endometrial cancer
- Primary stage 4 or relapsed disease
- ≥1 prior systemic therapy
- ER+ (≥10%) endometrioid adenocarcinoma
- ECOG PS 0/1
- No prior endocrine therapy except MPA and megestrol acetate
- No prior CDK inhibitor

Stratification:
- No. of prior lines (primary advanced disease vs 1st relapse vs ≥2 relapses)
- Measurable vs evaluable disease per RECIST
- Prior use of MPA/megestrol acetate

1:1 randomization
- Placebo 125 mg days 1–21
- Letrozole 2.5 mg days 1–28
- Palbociclib 125 mg days 1–21
- Letrozole 2.5 mg days 1–28
Repeated every 28 days until progression

Primary endpoint: Investigator-assessed PFS (target HR 0.625, 80% power, 15% 1-sided α)

Secondary endpoints:
- PFS in subgroups
- Objective response rate, disease control rate, PFS2, overall survival
- PROs
- Safety and tolerability

CDK, cyclin-dependent kinase; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HR, hazard ratio; MPA, medroxyprogesterone acetate; PFS, progression-free survival; PROs, patient-reported outcomes; PS, performance status

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*

Disease control rate

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

* = at 24 weeks

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

**H0:** true ORR $\leq$ 5% AND PFS6 $\leq$ 10% whereas improvement to a 20% ORR or 30% PFS6 rate

---

**ER+ Recurrent Endometrial Cancer**

1st Stage

- Enroll 16 patients

2nd Stage

- Enroll 19 patients

Overall if:

- $\geq$ 2 ORRs
- $\geq$ 2 PFS6

Letrozole/Abemaciclib worthy of further study

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

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>Patients (N=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
</tr>
<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, all PRs in endometrioid 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>
Trastuzumab deruxtecan (T-DXd) vs treatment of physician’s choice in patients with HER2-low unresectable and/or metastatic breast cancer: Results of DESTINY-Breast04, a randomized, phase 3 study

Shanu Modi  Memorial Sloan Kettering Cancer Center, Memorial Hospital, New York, NY, USA

June 5, 2022

*Additional authors:* William Jacot, Toshinari Yamashita, Joo Hyuk Sohn, Maria Vidal, Eriko Tokunaga, Junji Tsurutani, Naoto Ueno, Yee Soo Chae, Keun Seok Lee, Naoki Niikura, Yeon Hee Park, Xiaojia Wang, Binghe Xu, Dhiraj Gambhire, Lotus Yung, Gerold Meinhardt, Yibin Wang, Nadia Harbeck, David Cameron

*On behalf of the DESTINY-Breast04 investigators*
HER2-low mBC: Unmet Clinical Need

**Current Standard of Care**

**HER2-negative**
- **IHC 0**
- **IHC 1+**
- **IHC 2+/ISH−**

**HER2-low**

- **HR+a**
- **HR−b**

**Endocrine therapy (ET)**
- ET combinations
- PARP inhibitors (gBRCA+)

**Checkpoint inhibitors (PD-L1+)**
- PARP inhibitors (gBRCA+)
- Sacituzumab govitecan

**Chemotherapy**

- HER2-low mBC is defined by IHC scores of 1+ or 2+/ISH−
  - This is a heterogeneous population with a high prevalence of HR coexpression and without a distinct biology

- HER2-low mBC is treated as HER2− mBC, with limited options for later lines of therapy
  - Current HER2-targeted therapies are not effective for patients with tumors that express lower levels of HER2

- Therapeutic options for patients with HR+/HER2− mBC after CDK4/6i progression have limited efficacy
  - Real-world studies suggest a PFS of <4 months after progressive disease with CDK4/6i

- Limited benefit exists for patients who progress after multiple lines of chemotherapy
  - In a pooled analysis of patients with HER2− mBC, eribulin and capecitabine provide minimal benefit, with a mPFS of ∼4 months and mOS of ∼15 months

**CDK4/6i,** cyclin-dependent kinase 4/6 inhibitors; gBRCA+, germline breast cancer gene positive; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; mOS, median overall survival; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed death ligand 1; mPFS, median progression-free survival; T-DXd, trastuzumab deruxtecan.

T-DXd MOA, Bystander Effect, and Rationale for Targeting HER2-low mBC

Internalization of T-DXd leads to release of the DXd payload and subsequent cell death in the target tumor cell and neighboring tumor cells through the bystander effect\(^1,2\).

- Results from a phase 1b study have reported efficacy of T-DXd in heavily pretreated patients (\(N = 54\)) with HER2-low mBC, with a mPFS of 11.1 months and an ORR of 37.0\(^%\).\(^3\)

HER2, human epidermal growth factor receptor 2; MOA, mechanism of action; mBC, metastatic breast cancer; mPFS, median progression-free survival; ORR, objective response rate; T-DXd, trastuzumab deruxtecan.

DESTINY-Breast04: First Randomized Phase 3 Study of T-DXd for HER2-low mBC

An open-label, multicenter study (NCT03734029)

Patients
- HER2-low (IHC 1+ vs IHC 2+/ISH−), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

Stratification factors
- Centrally assessed HER2 status (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

T-DXd
- 5.4 mg/kg Q3W (n = 373)
- HR+ = 480
- HR− = 60

TPC
- Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel (n = 184)

Primary endpoint
- PFS by BICR (HR+)

Key secondary endpoints
- PFS by BICR (all patients)
- OS (HR+ and all patients)

ASCO/CAP, American Society of Clinical Oncology/Collage of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician’s choice.

*If patients had HR+ mBC, prior endocrine therapy was required. *Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint. *TPC was administered accordingly to the label. *Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only (I/U) Assay system.
PFS in HR+ and All Patients

Hormone receptor–positive

Hazard ratio: 0.51
95% CI, 0.40-0.64
P < 0.0001

Δ 4.7 mo
T-DXd
mPFS: 10.1 mo

TPC
mPFS: 5.4 mo

All patients

Hazard ratio: 0.50
95% CI, 0.40-0.63
P < 0.0001

Δ 4.8 mo
T-DXd
mPFS: 9.9 mo

TPC
mPFS: 5.1 mo

PFS by blinded independent central review.
HR, hormone receptor; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician’s choice.
OS in HR+ and All Patients

**Hormone receptor–positive**

Hazard ratio: 0.64
95% CI, 0.48-0.86
*P = 0.0028*

**All patients**

Hazard ratio: 0.64
95% CI, 0.49-0.84
*P = 0.0010*

HR, hormone receptor; mOS, median overall survival; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician’s choice.
The mTOR Pathway Integrates Environmental Signals to Regulate Cellular Growth and Homeostasis

• The mTOR signaling pathway coordinates cell growth and metabolism with environmental cues such as growth factors and nutrients.

• mTOR activation ultimately regulates cell growth through the phosphorylation of p70S6 kinase 1 (S6K1) and eIF4E binding protein (4EBP) and cell proliferation.

4EBP, eIF4E binding protein; Akt, protein kinase B; eIF4E, eukaryotic translation initiation factor 4E; ERK, extracellular signal-regulated kinases; MEK, mitogen-activated protein kinase kinase; mTOR, mechanistic target of rapamycin; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; Raf, rapidly accelerated fibrosarcoma protein; Raptor, regulatory-associated protein of mTOR; Ras, rat sarcoma virus homolog; Rheb, Ras homolog enriched in brain; S6K, p70S6 kinase; TSC1/2, tuberous sclerosis complex subunit 1/2.

## GOG 3007: Results

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>Objective Response</th>
<th>Objective Response - NPC</th>
<th>CBR</th>
<th>CBR-NPC</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everolimus/Letrozole</td>
<td>37</td>
<td>22%, (95%CI, 11% to 37%)</td>
<td>53%</td>
<td>78%</td>
<td>87%</td>
<td>6 mos (95% CI, 4-18)</td>
<td>31 mos (95% CI 14-40)</td>
</tr>
<tr>
<td>MPA/Tamoxifen</td>
<td>37</td>
<td>25%, (95%CI, 14% to 41%)</td>
<td>43%</td>
<td>69%</td>
<td>86%</td>
<td>4 mos (95% CI, 3-6)</td>
<td>17 Mos (95% CI 9-289)</td>
</tr>
</tbody>
</table>

**Median follow-up: 37 mos**

CBR, clinical benefit response; MPA, medroxyprogesterone acetate; NPC, no prior chemotherapy; OS, overall survival; PFS, progression-free survival

# GOG 3007: Outcomes in Patients Who Did Not Receive Prior Chemotherapy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>RR</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everolimus/letrozole</td>
<td>47%</td>
<td>28 months</td>
</tr>
<tr>
<td>Tamoxifen/MPA</td>
<td>43%</td>
<td>6.1 months</td>
</tr>
<tr>
<td>Carboplatin/paclitaxel (GOG 209)</td>
<td>51%</td>
<td>14 months</td>
</tr>
</tbody>
</table>

MPA, medroxyprogesterone acetate; PFS, progression-free survival; RR, response rate

Slomovitz BM et al. *Gynecol Oncol*. March 2022
**nab-Sirolimus Mechanism of Action**

- **mTOR pathway activation is prevalent in PEComas**
  - mTOR pathway controls cell proliferation, division, and numerous metabolic pathways
  - Mutations of mTOR inhibitory genes (e.g., PTEN, TSC1, and TSC2) can lead to their inactivation, which triggers mTORC1 formation and uncontrolled cell division
  - mTOR inhibitors bind to mTORC1 and halt cancer cell proliferation and division

- **mTOR inhibitors such as sirolimus have shown clinical benefit in malignant PEComa**
  - However, currently available mTOR inhibitors are limited by poor solubility, low bioavailability, and incomplete target inhibition
  - Nanoparticle albumin-bound (nab) technology enhances bioavailability and tumor targeting of chemotherapeutic agents (e.g., paclitaxel, sirolimus)

- **nab technology complexes sirolimus to human albumin, leveraging natural albumin-based transport mechanisms to enhance intra-tumoral drug accumulation**

- **nab platform improves drug bioavailability, tumor targeting, and efficacy**

---

Akt, protein kinase B; ERK, extracellular signal-regulated kinases; mTOR, mechanistic target of rapamycin; mTORC1, mTOR complex 1; nab, nanoparticle albumin-bound; PEComa, perivascular epithelioid cell tumor; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; Raptor, regulatory-associated protein of mTOR; Ras, rat sarcoma virus homolog; Rheb, Ras homolog enriched in brain; TSC1/2, tuberous sclerosis complex subunit 1/2.

**nab-sirolimus Combines Sirolimus with nab Technology**

- *nab* technology is a proprietary method of binding therapies to albumin
  - achieves better tumor targeting and uptake than solvent-based treatment in preclinical models\(^1\)\(^2\)\(^3\)\(^4\)
  - may translate to better efficacy and safety in clinical studies\(^2\)\(^3\)\(^4\)
- *nab*-sirolimus adapts the *nab* process for sirolimus to enhance anti-tumor activity compared with currently approved mTOR inhibitors and is currently FDA approved for adult patients with advanced malignant PEComa\(^1\)

---

**Significantly Higher Tissue Drug Accumulation with nab-Sirolimus\(^1\)**

**Stronger Inhibition of Tumor Growth and Longer Survival in Animals with nab-Sirolimus\(^1\)**

<table>
<thead>
<tr>
<th>Tumor Tissue Sirolimus or Everolimus AUC (ng*hr/g)</th>
<th>Treatment Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>nab-Sirolimus IV</td>
<td>0</td>
</tr>
<tr>
<td>Sirolimus PO</td>
<td>15 mg/kg/wk</td>
</tr>
<tr>
<td>Everolimus PO</td>
<td>0</td>
</tr>
</tbody>
</table>

**Total Weekly dose:** 15 mg/kg/wk

\(1\)\(^2\)\(^3\)\(^4\)

---

**ANOVA, analysis of variance; IV, intravenous; nab, nanoparticle albumin-bound; NSCLC, non-small cell lung cancer; PEComa, perivascular epithelioid cell tumor; PO, by mouth; qd, once daily; wk, week.**

AMPECT: Best Response, Duration of Response by Independent Review

<table>
<thead>
<tr>
<th>Confirmed Overall Response Rate</th>
<th>N = 31*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed Overall Response Rate</td>
<td>39% (12/13, 95% CI: 22, 58)</td>
</tr>
<tr>
<td>CR</td>
<td>7% (2/31)</td>
</tr>
<tr>
<td>PR</td>
<td>32% (10/31)</td>
</tr>
<tr>
<td>SD</td>
<td>52%</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>10%</td>
</tr>
<tr>
<td>Disease Control Rate (CR, PR, SD ≥12 weeks)</td>
<td>71%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median DOR (n=12 responders)†</th>
<th>Not Reached</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range: min–max, months</td>
<td>5.6–55.5+</td>
</tr>
<tr>
<td>DOR rate at 6 months</td>
<td>92%</td>
</tr>
<tr>
<td>DOR rate at 12 months</td>
<td>75%</td>
</tr>
<tr>
<td>DOR rate at 24 months</td>
<td>66%</td>
</tr>
<tr>
<td>DOR rate at 36 months</td>
<td>66%</td>
</tr>
</tbody>
</table>

Total may exceed 100% due to rounding.

- 2 patients converted from a PR to CR after 11 months and 34 months of treatment, respectively
- Median DOR has not been reached; 50% of patients had a DOR of 36.1+ months (range, 5.6–55.5+ months)

*3/34 treated patients were not evaluable: 2 patients confirmed as “not PEComa” (misdiagnosis), 1 pt had no tissue for central confirmation of PEComa. †DOR median and rates are based on KM estimates; “+” indicates ongoing value.

CI, confidence interval; CR, complete response; DOR, duration of response; KM, Kaplan-Meier; max, maximum; min, minimum; PEComa, perivascular epithelioid cell tumor; PR, partial response; SD, stable disease.

Future Direction: Biomarker directed

- CDK 4/6
- Her 2
- mTOR
RESULTS  A total of 12 patients have completed treatment with dostarlimab and have undergone at least 6 months of follow-up. All 12 patients (100%; 95% confidence interval, 74 to 100) had a clinical complete response, with no evidence of tumor on magnetic resonance imaging, $^{18}$F-fluorodeoxyglucose–positron-emission tomography, endoscopic evaluation, digital rectal examination, or biopsy. At the time of this report, no patients had received chemoradiotherapy or undergone surgery, and no cases of progression or recurrence had been reported during follow-up (range, 6 to 25 months). No adverse events of grade 3 or higher have been reported.
Dostarlimab in Advanced/Recurrent Mismatch Repair Deficient/Microsatellite Instability–High or Proficient/Stable Endometrial Cancer: the GARNET study

Ana Oaknin, 1 Bhavana Pothuri, 2 Lucy Gilbert, 3 Renaud Sabatier, 4 Sharad Ghamande, 5 Adriano Gravina, 6 Emiliano Calvo, 7 Susana Banerjee, 8 Rowan E. Miller, 9 Joanna Pikiel, 10 Mansoor R. Mirza, 11 Tao Duan, 12 Sybil Zildjian, 13 Eleftherios Zografos, 14 Jennifer Veneris, 13 Anna V. Tinker 15

1Gynaecologic Cancer Programme, Vall d’Hebron Institute of Oncology (VHI), Hospital Universitari Vall d’Hebron, Vall d’Hebron Barcelona Hospital Campus, Barcelona, Spain; 2Gynecologic Oncology Group (GOG) and Department of Obstetrics/Gynecology, Laura & Isaac Perlmutter Cancer Center, NYU Langone Health, New York, NY, USA; 3Division of Gynecologic Oncology, McGill University Health Centre, Montreal, Quebec, Canada; 4Department of Medical Oncology, Institut Paoli Calmettes, Aix-Marseille University, Marseille, France; 5Department of Obstetrics & Gynecology, Georgia Cancer Center, Augusta University, Augusta, GA, USA; 6Clinical Trials Unit, Istituto Nazionale Tumori Fondazione G. Pascale, Naples, Italy; 7START Madrid—CICO, Centro Integral Oncologico Clara Campo, Madrid, Spain; 8Gynaecology Unit, The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, UK; 9University College London, St. Bartholomew’s Hospitals London, London, UK; 10Department of Chemotherapy, Regional Center of Oncology, Gdansk, Poland; 11Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Denmark, Nordic Society of Gynaecologic Oncology—Clinical Trial Unit, Copenhagen, Denmark; 12GlaxoSmithKline, Pennington, NJ, USA; 13GlaxoSmithKline, Waltham, MA, USA; 14GlaxoSmithKline, London, UK; 15Department of Medicine, British Columbia Cancer, Vancouver Centre, University of British Columbia, Vancouver, British Columbia, Canada
## Primary Endpoint Analysis

<table>
<thead>
<tr>
<th></th>
<th>dMMR/MSI-H EC</th>
<th>MMRp/MSS EC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=143</td>
<td>N=156</td>
</tr>
<tr>
<td><strong>Median follow-up time, months</strong></td>
<td>27.6</td>
<td>33.0</td>
</tr>
<tr>
<td><strong>ORR, % (95% CI; n/N)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response, n (%)</td>
<td>45.5% (37.1–54.0; 65/143)</td>
<td>15.4% (10.1–22.0; 24/156)</td>
</tr>
<tr>
<td>Partial response, n (%)</td>
<td>23 (16.1)</td>
<td>4 (2.6)</td>
</tr>
<tr>
<td>Stable disease, n (%)</td>
<td>42 (29.4)</td>
<td>20 (12.8)</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
<td>21 (14.7)</td>
<td>29 (18.6)</td>
</tr>
<tr>
<td>Not evaluable, n (%)</td>
<td>51 (35.7)</td>
<td>88 (56.4)</td>
</tr>
<tr>
<td></td>
<td>6 (4.2)</td>
<td>15 (9.6)</td>
</tr>
<tr>
<td><strong>Median time from cycle 1 day 1 to best overall response, mo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>2.79</td>
<td>2.81</td>
</tr>
<tr>
<td>Partial response</td>
<td>2.69</td>
<td>2.79</td>
</tr>
<tr>
<td><strong>Disease control rate, % (95% CI; n/N)</strong></td>
<td>60.1% (51.6–68.2; 86/143)</td>
<td>34.0% (26.6–42.0; 53/156)</td>
</tr>
<tr>
<td><strong>Response ongoing, n (%)</strong></td>
<td>54 (83.1)</td>
<td>9 (37.5)</td>
</tr>
<tr>
<td><strong>Median duration of response (range), months</strong></td>
<td>NR (1.18+ to 47.21+)</td>
<td>19.4 (2.8 to 47.18+)</td>
</tr>
<tr>
<td><strong>Probability of maintaining response, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>96.8</td>
<td>82.6</td>
</tr>
<tr>
<td>12 months</td>
<td>93.3</td>
<td>60.3</td>
</tr>
<tr>
<td>24 months</td>
<td>83.7</td>
<td>44.2</td>
</tr>
</tbody>
</table>

dMMR, mismatch repair deficient; EC, endometrial cancer; MMRp, mismatch repair proficient; MSI-H, microsatellite instability–high; MSS, microsatellite stable; NR, not reached; ORR, objective response rate.
Probability of Progression-Free Survival: dMMR/MSI-H

- 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 (4.1–18.0 mo)

- Number of patients at risk:
  dMMR/MSI-H EC 143 125 81 65 64 59 55 53 52 46 41 40 35 33 26 24 21 19 16 12 11 8 6 4 2 0 0

dMMR, mismatch repair deficient; EC, endometrial cancer; MSI-H, microsatellite instability–high; PFS, progression-free survival.
Probability of Overall Survival: dMMR/MSI-H

Estimated % probability of OS
12 mo 24 mo
73.3% (65.2%–79.8%) 60.5% (51.5%–68.4%)

Median OS NR (27.1–NR)

Number of patients at risk
dMMR/MSI-H EC 153 132 112 95 84 70 60 52 38 32 22 13 5 0 0

dMMR, mismatch repair deficient; EC, endometrial cancer; MSI-H, microsatellite instability–high; NR, not reached; OS, overall survival.
KEYNOTE-177: Robust Activity of Pembro Monotx Compared to SOC in Stage IV MSI-H/dMMR CRC

### Key Points
- **Patients**
  - MSI-H or dMMR mCRC
  - No prior therapy
  - Measurable disease per RECIST v1.1
  - ECOG PS 0 or 1

### Study Design
- Open label, N = 385.
- Curative resection permitted on study.
- Response assessment: every 9 weeks per RECIST v1.1.
- Primary endpoints: PFS, ORR.
- Secondary endpoint: ORR.

### Key Outcomes
- **ORR, n (%)**
  - Pembrolizumab: 67 (43.8%)
  - Chemotherapy: 51 (33.1%)
- **Difference, estimate (95% CI)**
  - 10.7 (-0.2 to 21.3)
- **P-value**
  - 0.0273

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

### Median Time to Response
- **Pembrolizumab**
  - 2.2 (1.8-18.8) mo
- **Chemotherapy**
  - 2.1 (1.7-24.9) mo

### Graphs
- **PFS Chart**
  - Pembrolizumab: 54% at 24 mo
  - Chemotherapy: 73% at 24 mo
- **24-mo response duration**
  - Pembrolizumab: 33%
  - Chemotherapy: 38%
- **Median DOR**
  - Pembrolizumab: NR, 10.8 (2.8 to 37.5+)
  - Chemotherapy: NR, 10.4 (2.5 to 41.4+)

### Table

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab (N = 153)</th>
<th>Chemotherapy (N = 154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>67 (43.8)</td>
<td>51 (33.1)</td>
</tr>
<tr>
<td>Difference, estimate (95% CI)</td>
<td>10.7 (-0.2 to 21.3)</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.0273</td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>17 (11.1)</td>
<td>6 (3.9)</td>
</tr>
<tr>
<td>Partial response</td>
<td>50 (32.7)</td>
<td>45 (29.2)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>32 (20.9)</td>
<td>65 (42.2)</td>
</tr>
<tr>
<td>Disease control rate (CR+PR+SD)</td>
<td>99 (64.7)</td>
<td>116 (75.3)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>45 (29.4)</td>
<td>19 (12.3)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>3 (2.0)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>No assessment</td>
<td>6 (3.9)</td>
<td>17 (11.0)</td>
</tr>
<tr>
<td>Median time to response, mo</td>
<td>2.2 (1.8-18.8)</td>
<td>2.1 (1.7-24.9)</td>
</tr>
</tbody>
</table>
GOG-3064/ENGOT en15/KN-C93: A phase 3, randomized, open-label study of first-line pembrolizumab versus platinum-doublet chemotherapy in mismatch repair deficient advanced or recurrent endometrial carcinoma

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
- No previous chemo for adjuvant or first line except as part of radiosensitizing
- ECOG 0-1

**Stratification:**
- Newly diagnosed advanced EC vs Recurrent EC
- Histology – endometrioid vs. non-endometrioid

**Dual Primary Endpoints**
- PFS (by BICR)
- OS

**Key Secondary Endpoint**
- ORR (by BICR)

1:1

N=350

Pembro Monotherapy
Q6W (up to 18 Cycles)

Pembrolizumab
Q6W (18 Cycles)

Standard of Care
Carboplatin+Paclitaxel
(Q3W, up to 6 cycles)

*Participants who were randomized to Arm 2 (chemotherapy) and experience BICR-assessed disease progression per RECIST 1.1, will have an opportunity to participate in the Crossover Phase to receive up to 18 cycles of pembrolizumab 400 mg Q6W, upon Sponsor consultation*
The Future is Bright