Endometrial Cancer: Highlight Reel

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Director, Gynecologic Oncology, Mount Sinai Medical Center
Member, Board of Directors, GOG Foundation
Uterine Cancer Lead, GOG Partners

November 19, 2021
## Systemic Therapy for Endometrial Carcinoma

### Primary or Adjuvant Treatment When Used for Uterine-Confined High-Risk Disease

**Preferred Regimens**
- Carboplatin/paclitaxel

### Recurrent or Metastatic Disease

#### Systemic Therapies

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
<th>Other Recommended Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin/paclitaxel (category 1 for carcinosarcoma)¹</td>
<td>Carboplatin/docetaxel²</td>
</tr>
<tr>
<td>Carboplatin/paclitaxel/trastuzumab³ (for stage III/IV or recurrent HER2-positive uterine serous carcinoma)²</td>
<td>Cisplatin/doxorubicin²</td>
</tr>
<tr>
<td></td>
<td>Cisplatin/doxorubicin/paclitaxel⁴,⁵</td>
</tr>
<tr>
<td></td>
<td>Carboplatin/paclitaxel/bevacizumab⁶,⁷,⁸</td>
</tr>
<tr>
<td></td>
<td>Cisplatin</td>
</tr>
<tr>
<td></td>
<td>Carboplatin</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin</td>
</tr>
<tr>
<td></td>
<td>Liposomal doxorubicin</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel⁵</td>
</tr>
<tr>
<td></td>
<td>Albumin-bound paclitaxel⁹</td>
</tr>
<tr>
<td></td>
<td>Topotecan</td>
</tr>
<tr>
<td></td>
<td>Bevacizumab⁵,⁶,⁷</td>
</tr>
<tr>
<td></td>
<td>Temsirolimus⁷</td>
</tr>
<tr>
<td></td>
<td>Docetaxel⁵ (category 2B)</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide (for carcinosarcoma)</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide/paclitaxel (for carcinosarcoma)⁸</td>
</tr>
<tr>
<td></td>
<td>Cisplatin/ifosfamide (for carcinosarcoma)</td>
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</table>

#### Biomarker-directed Systemic Therapy for Second-line Treatment

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
<th>Other Recommended Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenvatinib/pembrolizumab (category 1) for non–MSI-high [MSI-H]/non–MMR-deficient [dMMR] tumors⁹,¹⁰</td>
<td>Nivolumab for dMMR/MSI-H tumors¹²</td>
</tr>
<tr>
<td>pembrolizumab¹¹ for TMB-H¹² or MSI-H/dMMR tumors¹¹</td>
<td>Dostarlimab-gxly for dMMR/MSI-H tumors¹³,¹⁴</td>
</tr>
<tr>
<td></td>
<td>Larotrectinib or entrectinib for NTRK gene fusion-positive tumors (category 2B)⁶</td>
</tr>
<tr>
<td></td>
<td>Avelumab for dMMR/MSI-H tumors</td>
</tr>
<tr>
<td></td>
<td>Cabozantinib</td>
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</tbody>
</table>

### Footnotes on page ENDO-D 3 of 4

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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References

**Continued**

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# SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

## Preferred Regimens

- Carboplatin/paclitaxel

### Recurrent or Metastatic Disease

<table>
<thead>
<tr>
<th>Systemic therapies&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Preferred Regimens</th>
<th>Other Recommended Regimens</th>
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<tbody>
<tr>
<td>• Carboplatin/paclitaxel (category 1 for carcinosarcoma)&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td>• Carboplatin/docetaxel&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>• Carboplatin/paclitaxel/trastuzumab&lt;sup&gt;c&lt;/sup&gt; (for stage III/IV or recurrent HER2-positive uterine serous carcinoma)&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td>• Cisplatin/doxorubicin&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Carboplatin/doxorubicin/paclitaxel&lt;sup&gt;e,f,3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Carboplatin/paclitaxel/bevacizumab&lt;sup&gt;e,g,4&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cisplatin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Carboplatin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Doxorubicin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Liposomal doxorubicin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Paclitaxel&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Albumin-bound paclitaxel&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Topotecan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Bevacizumab&lt;sup&gt;i,j,6&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>• Temsirolimus&lt;sup&gt;7&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>• Docetaxel&lt;sup&gt;i&lt;/sup&gt; (category 2B)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Ifosfamide (for carcinosarcoma)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Ifosfamide/paclitaxel (for carcinosarcoma)&lt;sup&gt;8&lt;/sup&gt;</td>
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</tr>
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<td></td>
<td>Pembrolizumab (for MMR-H/dMMR tumors)&lt;sup&gt;1,11&lt;/sup&gt;</td>
<td>• Dostarlimab-gxly for dMMR/MSI-H tumors&lt;sup&gt;m,i,13&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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**References Continued**

**ENDO-D 1 OF 4**
NCCN Guidelines Version 1.2022
Endometrial Carcinoma

SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

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• Carboplatin/paclitaxel

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<tr>
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</tr>
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<td>• Nivolumab for dMMR/MSI-H tumors&lt;sup&gt;12&lt;/sup&gt; • Dostarlimab-gxly for dMMR/MSI-H tumors&lt;sup&gt;m&lt;/sup&gt; • Pembrolizumab&lt;sup&gt;k&lt;/sup&gt; for MSI-H/dMMR-tumors&lt;sup&lt;l&lt;/l&gt;&gt;&lt;sup&gt;11&lt;/sup&gt; • Avelumab for dMMR/MSI-H tumors • Cabozantinib</td>
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References

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## SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

### Hormone Therapy

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
<th>Other Recommended Regimens</th>
<th>Useful in Certain Circumstances</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Medroxyprogesterone acetate/tamoxifen (alternating)</td>
<td>• Everolimus/letrozole (for endometrioid histology)</td>
<td>N/A</td>
</tr>
<tr>
<td>• Megestrol acetate/tamoxifen (alternating)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Progestational agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▸ Medroxyprogesterone acetate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▸ Megestrol acetate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▸ Levonorgestrel intrauterine device (IUD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(for select fertility-sparing cases)</td>
<td></td>
<td></td>
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<tr>
<td>• Aromatase inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Tamoxifen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fulvestrant</td>
<td></td>
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</tr>
</tbody>
</table>
A multicenter, open-label, randomized, phase 3 study to compare the efficacy and safety of lenvatinib in combination with pembrolizumab vs treatment of physician’s choice in patients with advanced endometrial cancer: Study 309/KEYNOTE-775

Vicky Makker¹; Nicoletta Colombo²; Antonio Casado Herráez³; Alessandro D. Santin⁴; Emeline Colomba⁵; David S. Miller⁶; Keiichi Fujiwara⁷; Sandro Pignata⁸; Sally Baron-Hay⁹; Isabelle Ray-Coquard¹⁰; Ronnie Shapira-Frommer¹¹; Kimio Ushijima¹²; Jun Sakata¹³; Kan Yonemori¹⁴; Yong Man Kim¹⁵; Eva M. Guerra¹⁶; Ulus A. Sanli¹⁷; Mary M. McCormack¹⁸; Jie Huang¹⁹; Alan D. Smith²⁰; Stephen Keefe²¹; Lea Dutta¹⁹; Robert J. Orlowski²¹; Domenica Lorusso²²

¹Memorial Sloan Kettering Cancer Center, New York, NY, USA; ²University of Milan-Bicocca, European Institute of Oncology IRCCS, Milan, Italy; ³San Carlos University Teaching Hospital, Madrid, Spain; ⁴Yale University School of Medicine, New Haven, CT, USA; ⁵Gustave Roussy Cancerology Institute, Villejuif, GINECO group, France; ⁶University of Texas Southwestern Medical Center, Dallas, TX, USA; ⁷Saitama Medical University International Medical Center, Hidaka, Japan; ⁸Istituto Nazionale Tumori IRCCS-Fondazione G. Pascale, Naples, Italy; ⁹Royal North Shore Hospital, St. Leonards, Australia; ¹⁰Centre Léon-Bérard, University Claude Bernard, Lyon, GINECO group, France; ¹¹Sheba Medical Center, Ramat, Israel; ¹²Kurume University School of Medicine, Kurume, Japan; ¹³Aichi Cancer Center Hospital, Nagoya, Japan; ¹⁴National Cancer Center Hospital: Kokuritsu Gan Kenkyu Center Chuo Byoin, Tokyo, Japan; ¹⁵Asan Medical Center, University of Ulsan, Seoul, Korea; ¹⁶Hospital Universitario Ramón y Cajal, Madrid, Spain; ¹⁷Ege University, Izmir, Turkey; ¹⁸University College London Hospitals NHS Foundation Trust, London, United Kingdom; ¹⁹Eisai Inc., Woodcliff Lake, NJ, USA; ²⁰Eisai Ltd., Hatfield, United Kingdom; ²¹Merck & Co., Inc., Kenilworth, NJ, USA; ²²Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
Study Design

**Key eligibility criteria**
- Advanced, metastatic, or recurrent endometrial cancer
- Measurable disease by BICR
- 1 Prior platinum-based CT<sup>a</sup>
- 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 (Y vs N)

**Primary endpoints**
- PFS by BICR
- Overall survival

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

**Key exploratory endpoint**
- Duration of response

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<sup>a</sup>Patients may have received up to 2 prior platinum-based CT regimens if 1 is given in the neoadjuvant or adjuvant treatment setting.  
<sup>b</sup>Maximum of 35 doses.  
<sup>c</sup>Maximum cumulative dose of 500 mg/m².  
BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; IV, intravenous; PFS, progression-free survival; pMMR, mismatch repair-proficient; ORR, objective response rate; PO, per os (by mouth); QD, once daily; Q3W, every 3 weeks; QW, once weekly.
Progression-free Survival

**pMMR**

- Median (95% CI)
  - LEN + pembro: 6.6 mo (5.6, 7.4)
  - TPC: 3.8 mo (3.6, 5.0)

**All-comers**

- Median (95% CI)
  - LEN + pembro: 7.2 mo (5.7, 7.6)
  - TPC: 3.8 mo (3.6, 4.2)

**HR (95% CI) and P-value**

<table>
<thead>
<tr>
<th></th>
<th>LEN + pembro</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pMMR</td>
<td>247</td>
<td>0.60 (0.50, 0.72)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TPC</td>
<td>238</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-comers</td>
<td>281</td>
<td>0.56 (0.47, 0.66)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TPC</td>
<td>286</td>
<td></td>
<td></td>
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</table>

*By BICR per Response Evaluation Criteria in Solid Tumors version 1.1.*
Overall Survival

### pMMR

<table>
<thead>
<tr>
<th>Median (95% CI)</th>
<th>LEN + pembro</th>
<th>TPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.4 mo (14.2, 19.9)</td>
<td>165 events</td>
<td>203</td>
</tr>
<tr>
<td>12.0 mo (10.8, 13.3)</td>
<td>HR (95% CI)</td>
<td>0.68 (0.56, 0.84)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.0001</td>
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</table>

### All-comers

<table>
<thead>
<tr>
<th>Median (95% CI)</th>
<th>LEN + pembro</th>
<th>TPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.3 mo (15.2, 20.5)</td>
<td>188 events</td>
<td>245</td>
</tr>
<tr>
<td>11.4 mo (10.5, 12.9)</td>
<td>HR (95% CI)</td>
<td>0.62 (0.51, 0.75)</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; 0.0001</td>
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</table>
## Treatment Exposure, Safety, and Discontinuation in All-comers

<table>
<thead>
<tr>
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<th>LEN + pembro (n = 406)</th>
<th>TPC (n = 388)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of treatment (range), days</td>
<td>231 (1-817)</td>
<td>104.5 (1-785)</td>
</tr>
<tr>
<td>Patients with any TEAEs, %</td>
<td>99.8</td>
<td>99.5</td>
</tr>
<tr>
<td>Grade ≥ 3</td>
<td>88.9</td>
<td>72.7</td>
</tr>
<tr>
<td>Patients with any TEAEs leading to dose reductions, %(^a)</td>
<td>66.5</td>
<td>12.9</td>
</tr>
<tr>
<td>Patients with any-grade TEAEs leading to interruption, %(^b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEN(^c)</td>
<td>58.6</td>
<td>--</td>
</tr>
<tr>
<td>Pembro(^c)</td>
<td>50.0</td>
<td>--</td>
</tr>
<tr>
<td>LEN + pembro</td>
<td>30.8</td>
<td>--</td>
</tr>
<tr>
<td>Patients with any-grade TEAEs leading to discontinuation, %(^b)</td>
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</tr>
<tr>
<td>LEN(^c)</td>
<td>30.8</td>
<td>--</td>
</tr>
<tr>
<td>Pembro(^c)</td>
<td>18.7</td>
<td>--</td>
</tr>
<tr>
<td>LEN + pembro</td>
<td>14.0</td>
<td>--</td>
</tr>
</tbody>
</table>

\(^a\)Includes LEN only or TPC. \(^b\)Includes LEN or pembro or LEN + pembro or TPC. \(^c\)Regardless of action taken with the other drug in the combination arm.
Outcomes by Histology and Prior Therapy With Lenvatinib Plus Pembrolizumab vs Treatment of Physician’s Choice in Patients With Advanced Endometrial Cancer (Study 309/KEYNOTE-775)

Nicoletta Colombo¹; Domenica Lorusso²; Antonio Casado Herráez³; Alessandro D. Santin⁴; Emeline Colomba⁵; David S. Miller⁶; Keiichi Fujiiwara⁷; Sandro Pignata⁸; Anne Floquet⁹; Bradley J. Monk¹⁰; Susana Banerjee¹¹; Richard T. Penson¹²; Rebecca Kristeleit¹³; Michel Fabbro¹⁴; Mauro Orlando¹⁵; Helen Mackay¹⁶; Erin Jensen¹⁷; Lea Dutta¹⁸; Robert Orlowski¹⁷; Vicky Makker¹⁹

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Progression-Free Survival<sup>a</sup> by Histology: pMMR

<table>
<thead>
<tr>
<th>Endometrioid</th>
<th>Serous</th>
<th>Clear cell</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Events, n (%)</strong></td>
<td><strong>HR (95% CI)</strong></td>
<td><strong>Events, n (%)</strong></td>
</tr>
<tr>
<td>Len + pembro</td>
<td>188</td>
<td>122 (64.9)</td>
</tr>
<tr>
<td>TPC</td>
<td>198</td>
<td>131 (66.2)</td>
</tr>
</tbody>
</table>

Median (95% CI)

- Endometrioid: 7.6 mo (5.9–9.1) (Len + pembro) 5.0 mo (3.7–5.7) (TPC)
- Serous: 5.7 mo (4.9–7.6) (Len + pembro) 3.6 mo (2.0–5.1) (TPC)
- Clear cell: 3.9 mo (2.1–7.4) (Len + pembro) 2.0 mo (1.9–4.6) (TPC)

No. at risk

- **Len + pembro**
  - Endometrioid: 188, 152, 98, 70, 34, 25, 19, 17, 7, 2, 0
  - Serous: 99, 76, 45, 31, 16, 10, 7, 2, 2, 0
  - Clear cell: 29, 17, 11, 6, 6, 2, 2, 1, 1, 0

- **TPC**
  - Endometrioid: 198, 113, 59, 24, 10, 7, 3, 1, 1, 0
  - Serous: 112, 48, 22, 11, 3, 1, 0, 0, 0, 0
  - Clear cell: 17, 6, 1, 1, 1, 0, 0, 0, 0, 0

<sup>a</sup>Per RECIST v1.1 by BICR. Randomization was stratified by MMR status.

HRs for other histologic types: mixed cell (n = 31): HR (95% CI), 0.90 (0.35–2.29); other (n = 23): HR (95% CI), 0.38 (0.12–1.19).

Progression-Free Survival\textsuperscript{a} by Histology: All-Comers

### Endometrioid

<table>
<thead>
<tr>
<th></th>
<th>Events, n (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Len + pembro</td>
<td>243 150 (61.7)</td>
<td>0.52 (0.41–0.65)</td>
</tr>
<tr>
<td>TPC</td>
<td>254 173 (68.1)</td>
<td></td>
</tr>
</tbody>
</table>

Median (95% CI)
7.6 mo (6.3–9.3)
3.9 mo (3.7–5.6)

No. at risk
len + pembro 243 196 128 98 56 39 29 12 3 0
TPC 254 142 69 28 12 9 4 1 1 0

### Serous

<table>
<thead>
<tr>
<th></th>
<th>Events, n (%)</th>
<th>HR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Len + pembro</td>
<td>103 81 (78.6)</td>
<td>0.53 (0.38–0.72)</td>
</tr>
<tr>
<td>TPC</td>
<td>115 80 (69.6)</td>
<td></td>
</tr>
</tbody>
</table>

Median (95% CI)
5.7 mo (4.9–7.6)
3.6 mo (2.1–5.0)

### Clear cell

<table>
<thead>
<tr>
<th></th>
<th>Events, n (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Len + pembro</td>
<td>30 24 (80.0)</td>
<td>0.47 (0.24–0.92)</td>
</tr>
<tr>
<td>TPC</td>
<td>17 15 (88.2)</td>
<td></td>
</tr>
</tbody>
</table>

Median (95% CI)
3.9 mo (2.1–7.4)
2.0 mo (1.9–4.6)

\textsuperscript{a}Per RECIST v1.1 by BICR.

HRs for other histologic types: mixed cell (n = 38): HR (95% CI), 0.90 (0.38–2.17); other (n = 27): HR (95% CI), 0.57 (0.21–1.54).

# PFS\textsuperscript{a} by Prior Therapy and PFI: pMMR and All-Comers

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Events/N</th>
<th>HR for OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 prior line of platinum</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pMMR</td>
<td>370/526</td>
<td>0.54 (0.44–0.67)</td>
</tr>
<tr>
<td>All-comer</td>
<td>446/641</td>
<td>0.50 (0.41–0.61)</td>
</tr>
<tr>
<td><strong>&gt;1 prior line of platinum</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pMMR</td>
<td>114/170</td>
<td>0.75 (0.52–1.09)</td>
</tr>
<tr>
<td>All-comer</td>
<td>120/185</td>
<td>0.69 (0.48–0.99)</td>
</tr>
<tr>
<td>Received (neo)adjuvant therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pMMR</td>
<td>190/258</td>
<td>0.58 (0.43–0.78)</td>
</tr>
<tr>
<td>All-comer</td>
<td>217/303</td>
<td>0.55 (0.42–0.73)</td>
</tr>
<tr>
<td>No (neo)adjuvant therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pMMR</td>
<td>295/439</td>
<td>0.60 (0.47–0.76)</td>
</tr>
<tr>
<td>All-comer</td>
<td>350/524</td>
<td>0.54 (0.44–0.67)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Events/N</th>
<th>HR for OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFI ≥6 months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pMMR</td>
<td>158/240</td>
<td>0.59 (0.43–0.81)</td>
</tr>
<tr>
<td>All-comer</td>
<td>173/270</td>
<td>0.55 (0.41–0.75)</td>
</tr>
<tr>
<td><strong>PFI &lt;6 months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pMMR</td>
<td>323/451</td>
<td>0.57 (0.45–0.71)</td>
</tr>
<tr>
<td>All-comer</td>
<td>390/550</td>
<td>0.51 (0.42–0.63)</td>
</tr>
<tr>
<td><strong>PFI ≥12 months</strong></td>
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</tr>
<tr>
<td>pMMR</td>
<td>67/99</td>
<td>0.74 (0.45–1.20)</td>
</tr>
<tr>
<td>All-comer</td>
<td>70/111</td>
<td>0.72 (0.45–1.16)</td>
</tr>
<tr>
<td><strong>PFI &lt;12 months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pMMR</td>
<td>414/592</td>
<td>0.56 (0.46–0.68)</td>
</tr>
<tr>
<td>All-comer</td>
<td>493/709</td>
<td>0.50 (0.42–0.60)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} PFS, platinum-free interval from most recent platinum-containing regimen. \textsuperscript{b} Per RECIST v1.1 by BICR.

Summary

- Lenvatinib + pembrolizumab provided a PFS and OS benefit compared with TPC in patients with previously treated, advanced endometrial cancer, including in patients with pMMR status and all-comers and regardless of
  - Histology, including difficult-to-treat histologies (i.e., clear cell carcinoma)
  - Prior (neo)adjuvant treatment
  - PFI
- Patients with 1 prior line of platinum therapy had more favorable HRs for OS and PFS than those with >1 prior line of platinum therapy, supporting earlier use of lenvatinib + pembrolizumab
- Because these were post hoc analyses, the results should be interpreted with caution
Randomized Phase 3 Study of Lenvatinib Plus Pembrolizumab for Advanced Endometrial Cancer: Subgroup Analysis of Patients with DNA Mismatch Repair-Deficient Tumors

Vicky Makker¹, Nicoletta Colombo², Antonio Casado Herráez³, Alessandro D. Santin⁴, Emeline Colomba⁵, David S. Miller⁶, Keiichi Fujiwara⁷, Sandro Pignata⁸, Susana Banerjee⁹, Bradley J. Monk¹⁰, Kimio Ushijima¹¹, Richard T. Penson¹², Rebecca Kristeleit¹³, Michel Fabbro¹⁴, Mauro Orlando¹⁵, Helen Mackay¹⁶, Min Ren¹⁷, Robert J. Orlowski¹⁸, Lea Dutta¹⁹, and Domenica Lorusso²⁰

¹Department of Medicine, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical Center, New York, NY, USA; ²Gynecologic Oncology Program, University of Milan-Bicocca, European Institute of Oncology IRCCS, Milan, Italy; ³Department of Medical Oncology, San Carlos University Teaching Hospital, Madrid, Spain; ⁴Department of Obstetrics, Gynecology & Reproductive Sciences, Yale University School of Medicine, New Haven, CT, USA; ⁵Department of Cancer Medicine, Gustave Roussy Cancerology Institute, Villejuif, GINECO group, France; ⁶Gynecologic Oncology, University of Texas Southwestern Medical Center, Dallas, TX, USA; ⁷Department of Gynecologic Oncology, Saitama Medical University International Medical Center, Hidaka, Japan; ⁸Department of Urology & Gynecology, Istituto Nazionale Tumori IRCCS-Fondazione G. Pascale, Naples, Italy; ⁹Gynaecology Unit, The Royal Marsden NHS Foundation Trust, London, UK; ¹⁰Gynecologic Oncology, Obstetrics and Gynecology, Arizona Oncology, Phoenix, AZ, USA; ¹¹Department of Obstetrics and Gynecology, Kurume University School of Medicine, Kurume, Japan; ¹²Division of Hematology and Oncology, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA; ¹³Department of Oncology, Guy’s and St Thomas’ NHS Foundation Trust, London, UK; ¹⁴Service de radiothérapie, Institut Régional du Cancer de Montpellier, Montpellier, France; ¹⁵Oncologo Medico, Instituto Alexander Fleming, Buenos Aires, Argentina; ¹⁶Medical Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Canada; ¹⁷Biostatistics, Oncology Business Group, Eisai Inc., Woodcliff Lake, NJ, USA; ¹⁸Late Stage Clinical Development, Merck & Co., Inc., Kenilworth, NJ, USA; ¹⁹Clinical Research, Eisai Inc., Woodcliff Lake, NJ, USA; ²⁰Division of Gynecologic Oncology, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy.
Progression-free Survival of the dMMR Population

- **Median HR (95% CI):**
  - LEN + pembrolizumab: 0.36 (0.23, 0.57)
  - TPC: NR
  - **P-value:** <0.0001

- **Events:**
  - LEN + pembrolizumab: 34
  - TPC: 40

- **Follow-up (range):** 12.0 months (0.4, 25.1)

Overall Survival of the dMMR Population

- **Median HR (95% CI):**
  - NR: 2.6 (1.5, 4.3)
  - LEN + pembrolizumab: 0.37 (0.22, 0.56)
  - TPC: NR
  - **P-value:** <0.0001

- **Events:**
  - NR: 23
  - LEN + pembrolizumab: 40
  - TPC: 40

- **Follow-up (range):** 12.0 months (0.4, 25.1)

**Note:**
- By blinded independent central review per RECIST version 1.1.
- dMMR, DNA mismatch repair-deficient; LEN + pembrolizumab, lenalidomide plus pembrolizumab; NR, not reached; TPC, treatment of physician’s choice.
Conclusions

• Efficacy in the dMMR population of patients with aEC appeared to improve with LEN + pembro, at least consistent with that of patients in both the pMMR and all-comers populations previously reported\(^1\)
  o PFS, OS, and ORR were improved with LEN + pembro compared to treatment of physician’s choice
  o Notably, \(\sim\)14% of patients treated with LEN + pembro had a complete response

• LEN + pembro had a manageable safety profile in the dMMR population and was generally consistent with that observed in the all-comers population and the established safety profiles of the individual monotherapies\(^1\)

aEC, advanced endometrial cancer; dMMR, DNA mismatch repair-deficient; LEN + pembro, lenvatinib plus pembrolizumab; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; pMMR, DNA mismatch repair-proficient

What’s Next for Lenvatinib/Pembrolizumab: LEAP-001: First-line metastatic recurrent Phase 3

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

Carboplatin and Paclitaxel
N=360

Lenvatinib and Pembrolizumab
N=360

Dual Primary Endpoints
- PFS
- OS

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

Stratification factors:
- MMR status (pMMR v dMMR), if pMMR:
  - Measurable disease (yes or no)
  - ECOG (0 vs 1)
  - Prior chemotherapy and/or chemoradiation (yes or no)

PI: C. Marth
ClinicalTrials.gov: NCT04865289
Activated October 22, 2019
Accrual complete except for China expansion
Analysis of Antitumor Activity of Dostarlimab by Tumor Mutational Burden in Patients with Endometriatal Cancer in the GARNET Trial

Ana Oaknin, Lucy Gilbert, Anna V. Tinker, Jubilee Brown, Cara Mathews, Joshua Z. Press, Renaud Sabatier, David M. O’Malley, Vanessa Samouëlian, Valentina Boni, Linda Duska, Sharad Ghamande, Prafull Ghatage, Rebecca Kristeleit, Charles Leath III, Xinwei Han, Sujatha Kumar, Tao Duan, Ellie Im, Bhavana Pothuri

Objective:
To examine the antitumor activity of dostarlimab in patients with dMMR/MSI-H or MMRp/microsatellite stable (MSS) EC by TMB status
Conclusions

- TMB-high (TMB-H) status and dMMR/MSI-H status show substantial overlap in the patient populations with EC
- TMB-H and dMMR/MSI-H EC have similar response rates
- Notably, the objective response rate (ORR) of patients with mismatch repair proficient (MMRp) and TMB-H EC was comparable to the ORR of patients with dMMR/MSI-H and TMB-H EC
- TMB-H status in the patients with MMRp EC was not due to MSI-H (hypermutated) or POLε-mutated (ultramutated) status
- The study was not powered to assess antitumor activity by TMB status, and interpretation is limited by the small sample size
Pembrolizumab in Patients With Microsatellite Instability-High (MSI-H) Advanced Endometrial Cancer: Updated Results From KEYNOTE-158

David M. O’Malley¹; Giovanni Mendonca Bariani²; Philippe A. Cassier³; Aurelien Marabelle⁴; Aaron R. Hansen⁵; Ana De Jesus Acosta⁶; Wilson H. Miller, Jr⁷; Tamar Safran⁸; Antoine Italiano⁹; Linda Mileshkin¹⁰; Lei Xu¹¹; Fan Jin¹¹; Kevin Norwood¹¹; Michele Maio¹²

¹The Ohio State University Wexner Medical Center and The James Comprehensive Cancer Center, Columbus, OH, USA; ²Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, São Paulo, Brazil; ³Centre Léon Bérard, Lyon, France; ⁴Gustave Roussy, Institut National de la Santé et de la Recherche Médicale U1015, Villejuif, France; ⁵Princess Margaret Cancer Centre, Toronto, ON, Canada; ⁶Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; ⁷Segal Cancer Centre, Jewish General Hospital, Rosy Cancer Network, and McGill University, Montreal, QC, Canada; ⁸Tel Aviv Medical Center, Tel Aviv and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; ⁹Early Phase Trials and Sarcoma Units, Institut Bergonie, Bordeaux, France; ¹⁰Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; ¹¹Merck & Co., Inc., Kenilworth, NJ, USA; ¹²Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy
Summary

- Pembrolizumab demonstrated robust and clinically meaningful antitumor activity in patients with previously treated MSI-H/dMMR advanced endometrial cancer
  - ORR, 48%
  - Estimated DOR ≥3 years, 68%

- Survival outcomes after treatment with pembrolizumab were encouraging, with 60% estimated to be alive at 4 years

- Toxicity was manageable and consistent with that previously observed for pembrolizumab in patients with advanced solid tumors

- Pembrolizumab monotherapy represents a promising treatment option for patients with previously treated MSI-H/dMMR advanced endometrial cancer
What’s Next for dMMR:
GOG 3064/ ENGOT–en15/MK KN-C93 Proposed Study Design 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 (radiologically apparent)
• dMMR
• No previous chemo for adjuvant or first line except as part of radiosensitizing
• ECOG 0-1

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

PI: B. Slomovitz
co-PI: F. Backes
Clinicaltrials.gov #: TBD
Shared with permission from sponsor
To compare with a randomized trial an intensive (INT) vs minimalist (MIN) 5-year follow-up regimen in endometrial cancer patients in terms of overall survival (OS)
CONCLUSIONS

INTENSIVE FOLLOW-UP IN ENDOMETRIAL CANCER TREATED PATIENTS DOES NOT IMPROVE OS, EVEN IN HIR PATIENTS

THE HRQL, IN OUR STUDY, IS NOT INFLUENCED BY DIFFERENT REGIMENS OF FOLLOW-UP

ACCORDING TO OUR DATA THERE IS NO NEED TO ROUTINELY ADD VAGINAL CYTOLOGY, LABORATORY OR IMAGING INVESTIGATIONS TO THE MINIMALIST REGIMENS USED IN THIS TRIAL
“The best way to predict the future is to create it”

Abraham Lincoln
Endometrial Cancer: Active Trials

- 2 trials of immunotherapy in the adjuvant setting
- 5 first line trials
  - 3 trials chemo vs. chemo and I/O (and PARP)
  - LEAP trial: combination I/O vs chemotherapy
  - 3064/c93: single agent I/O vs chemotherapy
  - Selinexor maintenance trial
- Multiple I/O and biomarker second line trials
Current Standard of Care

• Adjuvant:
  • Chemotherapy +/- XRT

• First-line metastatic or recurrent:
  • Chemotherapy (+ trastuzumab for HER2 + USC)

• Second-line:
  • dMMR: single agent I/O
  • pMMR: pembrolizumab and Lenvatinib

• Third-line and beyond:
  • Hormonal therapy (mTOR, CDK 4/6)
  • 2nd line chemotherapy
## Predicting Future in First Line Recurrent

<table>
<thead>
<tr>
<th>Scenario #1</th>
<th>Chemo + I/O +/- PARP</th>
<th>LEAP-001</th>
<th>B21 or GY020 – Adjuvant Pembro in HR</th>
<th>IMPACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>I/O 1&lt;sup&gt;st&lt;/sup&gt; line</td>
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<tr>
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<tr>
<td>Positive or Negative</td>
<td>Positive or Negative</td>
<td>Positive</td>
<td>I/O adjuvant</td>
<td></td>
</tr>
</tbody>
</table>

- I/O after I/O?
- May move Biomarker/Hormonal therapy to 2<sup>nd</sup> line?
- MSI-H/dMMR in adjuvant setting
  - In MSI/dMMR, do we need chemo?
The Future is Bright