Translating Trials to Clinic: Understanding Treatment Options for your Patients

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## SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

### Adjuvant Treatment When Used for Uterine-Confined Disease

**Preferred Regimens**
- Carboplatin/paclitaxel

### Recurrent, Metastatic, Or High-Risk Disease\(^{a,b}\)

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
<th>Other Recommended Regimens</th>
<th>Useful In Certain Circumstances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic therapies(^{a,b})</td>
<td>• Carboplatin/docetaxel(^{d})</td>
<td>N/A</td>
</tr>
<tr>
<td>• Carboplatin/paclitaxel (category 1 for carcinosarcoma)(^{1})</td>
<td>• Carboplatin/doxorubicin(^{3})</td>
<td></td>
</tr>
<tr>
<td>• Carboplatin/paclitaxel/trastuzumab(^{e}) (for stage III/IV or recurrent HER2-positive uterine serous carcinoma)(^{2})</td>
<td>• Carboplatin/doxorubicin/paclitaxel(^{F,3})</td>
<td></td>
</tr>
<tr>
<td>• Carboplatin/paclitaxel/bevacizumab(^{e,9,4})</td>
<td>• Carboplatin</td>
<td></td>
</tr>
<tr>
<td>• Doxorubicin</td>
<td>• Carboplatin</td>
<td></td>
</tr>
<tr>
<td>• Liposomal doxorubicin</td>
<td>• Paclitaxel(^{9})</td>
<td></td>
</tr>
<tr>
<td>• Albumin-bound paclitaxel(^{h})</td>
<td>• Topotecan</td>
<td></td>
</tr>
<tr>
<td>• Bevacizumab(^{9,1})</td>
<td>• Temsirolimus(^{7})</td>
<td></td>
</tr>
<tr>
<td>• Docetaxel(^{1}) (category 2B)</td>
<td>• Docetaxel(^{1})</td>
<td></td>
</tr>
<tr>
<td>• Ifosfamide (for carcinosarcoma)</td>
<td>• Ifosfamide/paclitaxel (for carcinosarcoma)(^{8})</td>
<td></td>
</tr>
<tr>
<td>• Ifosfamide</td>
<td>• Nivolumab(^{n,12})</td>
<td></td>
</tr>
<tr>
<td>• Carboplatin/paclitaxel/bevacizumab(^{e,9,4})</td>
<td>• Pembrolizumab(^{1}) (for TMB-H(^{10}) or MSI-high [MSI-H]/MMR deficient [dMMR] tumors(^{m,11}))</td>
<td></td>
</tr>
<tr>
<td>• Nivolumab(^{n,12})</td>
<td>• Nivolumab/gemcitabine(^{o,13})</td>
<td></td>
</tr>
<tr>
<td>• Dostarlimab-gxly(^{o,13})</td>
<td>• Larotrectinib or entrectinib for NTRK gene fusion-positive tumors (category 2B)(^{p})</td>
<td></td>
</tr>
</tbody>
</table>

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https://www.nccn.org/professionals/physician_gls/default.aspx
**MODEL:** MOlecular Driven Endometrial Cancer Therapy for Recurrent Disease – Post Pem/Len

1. **Genomic Profiling &/or IHC**
   - MSI; MMR; TMB Testing
   - MSS; pMMR; TMB-L
   - Hormonal therapy (Check for ESR1 mutation consider fulvestrant)

2. **Progression**
   - IO
   - Pembrolizumab + lenvatinib
   - HER2 directed therapy
       - ERBB2 &/or ERBB3
   - B-Catenin mutation (CTNNB1)
       - Bevacizumab containing therapy
   - PI3K/AKT/mTOR pathway activation or TSC2 mutation
       - mTOR inhibitor
   - Other activating alterations
   - Pathway directed therapy

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1. Chemotherapy added at the discretion of the treating physician
2. Everolimus + letrozole

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Adapted from MODEL paradigm. Alvarez Secord, A. *et al.*, SGO Annual Meeting 2019

CONFIDENTIAL
Case 1

- Postmenopausal Black female with Stage IVB grade 2 endometrioid endometrial cancer diagnosed in 2013 s/p surgical debulking and paclitaxel/carboplatin.
- PET/CT: Bilateral inguinal adenopathy left 9.3 x 7.0 cm with right 4.1 x 2.0 cm, avid bilateral iliac lymph nodes, and hypermetabolic soft sacral tissue mass 2.3 x 3.4.
- **Declined chemotherapy.**
- Completed BL groin and whole pelvic radiation.
- 9/2016: Started on megestrol acetate and aromatase inhibitor
Case 1

- **9/2016**: Started on megestrol acetate and aromatase inhibitor
  - Exam partial response and imaging demonstrated stable disease.

Response rates to hormonal therapy vary based on ER/PR receptor status and grade.

Progestin only regimens: 2.4-40% response rates

van Weelden *et al.* conducted systematic review reported response rates tamoxifen (10 to 53%), other SERMs and SERDs (9–31%), aromatase inhibitors (8 to 9%), and combined tamoxifen/progestin treatment (19–58%).

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### Hormonal Therapy Efficacy

<table>
<thead>
<tr>
<th>Agent</th>
<th>RR (%)</th>
<th>PFS months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Megestrol acetate&lt;sup&gt;1&lt;/sup&gt;</td>
<td>24</td>
<td>2.5</td>
</tr>
<tr>
<td>Tamoxifen&lt;sup&gt;1&lt;/sup&gt;</td>
<td>10</td>
<td>1.9</td>
</tr>
<tr>
<td>MA alt Tamoxifen&lt;sup&gt;1&lt;/sup&gt;</td>
<td>22-38</td>
<td>2.7</td>
</tr>
<tr>
<td>Letrozole&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>9</td>
<td>3.9&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anastrozole&lt;sup&gt;1&lt;/sup&gt;</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Letrozole + Everolimus&lt;sup&gt;1,3&lt;/sup&gt;</td>
<td>24-32</td>
<td>3-6.3</td>
</tr>
</tbody>
</table>

### Grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>%</th>
<th>Progestin vs MA/Tam RR (%)&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>84</td>
<td>37-40 / 38</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>17.5 / 24</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>2.4 / 22</td>
</tr>
</tbody>
</table>

<sup>1</sup>UpToDate.com Accessed 3/4/2021; 2Ma BBY IJGC 2004; 3Slomovitz B SGO Annual Meeting 2018; 4van Weeden WJ Frontier Oncol 2019
**Case 1**

- **10/2017:** Symptomatic progressive disease.
- MRI demonstrated 12 cm left groin mass;

**Tumor testing:** MSI-H, MMR-D with loss of MLH1 and PMS2, methylated MLH1 alleles

**May 23, 2017**

**FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication**

**April 22, 2021**

**FDA grants accelerated approval for dostarlimab-gxly for women with recurrent or advanced dMMR endometrial cancer**

11/2017: Initiated pembrolizumab 200 mg IV q3 wk

Pre-Pembrolizumab Treatment

One Month Post-Pembrolizumab Treatment
Case 1

- Rapid evidence of clinical partial response confirmed on imaging with sustained response.
- **5/2018**: Pembrolizumab discontinued due to CHF and acute on chronic renal failure possibly related to IO therapy. Etiology uncertain.
- **2/2019**: Groin biopsy x2; NED
- **7/2021**: Clinically NED

Pre-Pembrolizumab Treatment

Five Months Post-Pembrolizumab Treatment

3.5 years Post-Pembrolizumab Treatment Initiation
MSI-H and dMMR Endometrial Cancers

Pembrolizumab vs Pembrolizumab + Lenvatinib

• Is there any role to adding lenvatinib to pembrolizumab in patients with recurrent endometrial cancer?
• Single agent therapy
  • Pembrolizumab 57%
  • Dostarlimab 44.7%
• Combination therapy
  • Pembrolizumab+lenvatinib 63.6%

Important question that hopefully will be addressed in RCT:
Need to determine if combination therapy adds clinically meaningful improvement in response rate and survival outcomes without negatively impacting QoL compared to IO monotherapy.

Case 2

- Postmenopausal Black female with Stage IIIB uterine serous cancer diagnosed in 2015 s/p TLH/USO/LND s/p WPRT with VCB and paclitaxel/carboplatin.
- 1/2018: symptomatic recurrence 2.7 cm periaortic mass with mild left hydronephrosis; and pulmonary metastases largest 1.3 cm.
- Treated with paclitaxel/carboplatin x 6 cycles with evidence of PR. Stopped due to side effects

Tumor testing:
**Foundation One**: unable to be completed due to insufficient tissue

**Molecular testing**: MSS; MMR-P; ER+(ALLRED SCORE = 8); PR+(ALLRED SCORE = 5); HER2/neu NEGATIVE (1+)
Case 2

- Initiation megestrol acetate alternating with tamoxifen with stable disease on CT imaging. X 6 months then progressed.
- 8/2019 Offered KEYNOTE-775 but she declined opted for treatment holiday given asymptomatic state.
- Follow-up CT scan demonstrated significant progression retroperitoneal, pulmonary, and pericardial mets.
- Treatment options reviewed.
- Medical issues notable for BP 156/94, creatinine 1.2, negative proteinuria, and normal TSH. Started amlodipine 5 mg daily.
- **5/8/2020** pembrolizumab started; followed later by 10 mg lenvatinib on **May 19th, 2020** (delayed start due to HTN).
  - Counseled about BP control, diarrhea management, and precautions.

Pre-Pembrolizumab/Lenvatinib Treatment

September 17, 2019 Accelerated Approval

FDA Approval Summary: Pembrolizumab plus Lenvatinib for Endometrial Carcinoma, a Collaborative International Review under Project Orbis

July 22, 2021 Full Approval

FDA Grants Full Approval for lenvatinib and pembrolizumab combination for advanced endometrial cancer that is not MSI-H or MMR-D with disease progression after systemic therapy
Case 2

- Pembrolizumab/lenvatinib
  - Partial response with 34% decrease in disease at first imaging
  - BP 121-135/80-94; increased amlodipine to 10 mg daily with adequate DBPs in the 70-80’s
  - Diarrhea controlled with imodium and BRAT diet
  - TSH normal until cycle #6 increased to 7.23; T3/FT4 normal. Remained stable and never required thyroid replacement.

Thyroid screening questions:
Increased sensitivity to cold. - no
Constipation. no
Dry skin. - yes
Weight gain. yes
Puffy face. no
Hoarseness. no
Muscle weakness. no
Elevated blood cholesterol level. Checked 3/2021 normal
Muscle aches, tenderness and stiffness. no

- 17 cycles of therapy until new pulmonary nodule and pleural effusion
Thank You