Systemic Management of Locally Advanced or Metastatic Cervical and Endometrial Cancer

Jan B. Vermorken, MD, PhD
Department of Medical Oncology
Antwerp University Hospital
Edegem, Belgium
Conflict of Interest Disclosure

- Participates in Advisory Boards of:
  Carrick Therapeutics Limited, Cue Biopharma, Debiopharm, Immunomedics, Innate Pharma, Merck-Serono, Merck Sharp & Dome Corp, PCI Biotech, Synthon Biopharmaceuticals, WntResearch

- Lecturer fee from:
  Merck-Serono, BMS, MSD
Cervical Cancer: Epidemiology

- Third most common cause of female mortality
- Incidence 13.2/100,000 women/yr in Europe
- Mortality 5.9/100,000 women/yr
- Incidence and mortality higher in developing countries (85% of cases, 90% of deaths)

Etiological factors
- High risk HPV persistent infection

Predisposing factors
- Early age first intercourse, genetic predisp.
- Early pregnancies, nutrition, smoking e.a.

Squamous 80%
Adenocarcinoma 10-20%
Prognostic Factors in Cervical Cancer

- Stage (FIGO)
  - IIB, IIIA/B, IV (advanced)
  - IB, IIA (early)

- Histology
- Tumor size
- Tumor grade
- LI / VI
- Dept of stromal infiltration
- Level of SCC-antigen
- Nodal metastases*

*Predominant adverse prognostic factor
Management of Invasive Cervical Cancer

- Early stages (I – IIA): surgery (open or MIS) or radiotherapy postop CCRT in case of LN+

- Bulky stage I (IB2)
  Locally advanced (II-IVA)
  Any stage (except IVB) with LN+
  Concurrent CRT standard
  NACT → surgery*
  CCRT → ACT*

- Recurrent and/or metastatic cervical cancer
  Surgery, RT, CT, TT, IT or BSC alone

CT=chemotherapy, TT=targeted therapy, IT=immunotherapy, NACT=neoadjuvant chemotherapy, ACT adjuvant chemother.
MIS in Early-Stage Cervical Cancer

- **LACC prospective multi-institutional trial**\(^1\)
  Stages 1A1 +LVSI, 1A2 or IB1: MIS vs open (2008)
  Primary endpoint: DFS at 4.5 yrs, noninf. margin -7.2%
  740 patients planned, halted at 631 (2017)
  DFS 3-yr rate 91.2% vs 97.1% (MIS vs open)
  OS 3-yr rate 93.8% vs 99.0% (MIS vs open)
  Several limitations and criticisms

- **Retrospective epidemiologic study**\(^2\)
  Stages 1A2 or 1B1: MIS vs open
  National Cancer Database: 2461 patients underwent RH (2010-2013): 49.8% MIS
  79.8% of whom had robot assisted laparoscopy
  Median follow-up was 45 months
  Mortality at 4 yr 9.1% (MIS) vs 5.3% (open, p=0.002)

# Practice Changing Data for Cervical Cancer leading to NCI-Clinical Announcement in 1999

<table>
<thead>
<tr>
<th>Study</th>
<th>Drugs</th>
<th>No.</th>
<th>Comb.</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 9001¹</td>
<td>PF</td>
<td>388</td>
<td>73%</td>
<td>58%</td>
<td>0.004</td>
</tr>
<tr>
<td>GOG 123²</td>
<td>P</td>
<td>369</td>
<td>83%</td>
<td>74%</td>
<td>0.008</td>
</tr>
<tr>
<td>SWOG 8797³</td>
<td>PF</td>
<td>243</td>
<td>80%</td>
<td>63%</td>
<td>0.01</td>
</tr>
<tr>
<td>GOG 0085⁴</td>
<td>PF</td>
<td>368</td>
<td>55%</td>
<td>43%</td>
<td>0.018</td>
</tr>
<tr>
<td>GOG 120⁵</td>
<td>P</td>
<td>526</td>
<td>64%</td>
<td>39%</td>
<td>0.002</td>
</tr>
<tr>
<td>GOG 120⁵</td>
<td>PF+HU</td>
<td></td>
<td>66%</td>
<td>39%</td>
<td>0.002</td>
</tr>
</tbody>
</table>

**CCRT in Advanced-Stage Cervical Cancer 2020**

**Standard therapy**: cisplatin 40 mg/m² x6 during RT

**Ongoing trials aiming for improvement**

**TACO trial**  
CCRT (40 mg/m² x6) vs CCRT (75 mg/m² x3)

**Interlace trial**  
CCRT (40 mg/m² x5) vs NACT→CCRT

**Outback trial**  
CCRT (40 mg/m² x5) vs CCRT→ACT

**AIM2CERV trial**  
CCRT (40 mg/m² x4) →placebo IV up to 1 yr  
CCRT (40 mg/m² x4) →AXAL& (1x10⁹ CFU) 1 yr

---

&ADXS11-001 (live attenuated *Listeria Monocytogenes* bioengineered molecule secreting a HPV-16-E7 fusion protein)
Trials with Impact on the Management of R/M Cervical Cancer

- Randomized trials (US & Europe) comparing platinum-based combinations vs cisplatin alone

- **GOG 204**: 4-arm trial comparing different cisplatin combinations (PP, VP, GP, TP) → PP better regimen

- **GOG 240**: 4-arm trial (2 platinum-based and 2 non-platinum based; w/wo bevacizumab) → significant OS↑ with Bev.

- **JCOG0505**: comparing cis vs carbo combined with paclitaxel → cisplatin the superior drug in platinum-naive patients
GOG 204 Overall Survival

By Treatment Group

Proportion Surviving

0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0

Months on Study

0
12
24
36

Treatment

CIS+PAC

CIS+VIN

CIS+GEM

CIS+TOP

Alive

29
23
20
22

Dead

74
85
92
89

Total

103
108
112
111

Monk BJ et al, J Clin Oncol 2009; 4649-4655

Do not duplicate or distribute without permission of ESO and the author.
GOG 240: OS for Chemo vs Chemo + Bev

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy (n=225)</th>
<th>Chemotherapy + Bev (n=227)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>140 (62)</td>
<td>131 (58)</td>
</tr>
<tr>
<td>Median OS, mos</td>
<td>13.3</td>
<td>17.0</td>
</tr>
<tr>
<td>HR</td>
<td>0.71 (97% CI, 0.54-0.94)</td>
<td>P=0.0035</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>20.8 mos</td>
<td></td>
</tr>
</tbody>
</table>

Presented by: Krishnansu S. Tewari, MD, FACOG, FACS
Published in New Engl J Med 2014; 370: 734-43
TC versus TP in Advanced Cervical Cancer
JCOG 0505

Kitagawa et al, JCO 2015

Overall survival

Subgroup analysis of overall survival
Management of R/M Cervical Cancer: Summary

• No gold standard for R/M disease: cisplatin alone and cisplatin plus paclitaxel ± bevacizumab are good options. Patients preferably should be treated in trials

• The addition of bevacizumab to cisplatin plus paclitaxel leads to a survival advantage of 3.7 mo at the cost of 3-8% more serious adverse events¹

• Pazopanib, brivanib and sunitinib (RR 0-9%; mPFS ≤4.1 mo)*
  Gefitinib, erlotinib, lapatinib, cetuximab (RR 0-5%; mPFS ≤3.9 mo)*
  Temsirolimus (RR 3%, PFS 3.5 mo)*

*Hacker NF, Jackson M, Vermorken JB. Cervical Cancer: in Gynecologic Oncology (Berek J & Hacker NF, eds), 7th Edition, 2020
## Immunotherapy for Cervical Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Agent</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single agent ICI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KEYNOTE 028(^1)</td>
<td>PD-L1(^+), recurrent</td>
<td>Pembrolizumab</td>
<td>ORR, 17.0%; DOR, 6 mo</td>
</tr>
<tr>
<td>KEYNOTE 158(^2)</td>
<td>PD-L1(^+), recurrent</td>
<td>Pembrolizumab</td>
<td>ORR, 14.3%, DOR, &gt;11.7mo</td>
</tr>
<tr>
<td>Lheureux et al(^3)</td>
<td>Recurrent</td>
<td>Ipilimumab</td>
<td>ORR, 2.9%</td>
</tr>
<tr>
<td>CheckMate 358(^4)</td>
<td>Recurrent</td>
<td>Nivolumab</td>
<td>ORR, 5.0%</td>
</tr>
<tr>
<td>NRG-GY002(^5)</td>
<td>Recurrent</td>
<td>Nivolumab</td>
<td>ORR, 4.0%</td>
</tr>
<tr>
<td><strong>Adoptive T-cell therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stevanovic et al(^6)</td>
<td>Recurrent</td>
<td>HPV TILS</td>
<td>ORR, 28.0% (5/18), 2CR</td>
</tr>
<tr>
<td><strong>Vaccine therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huh et al(^7)</td>
<td>Recurrent</td>
<td>Axalimogene filolisbac</td>
<td>12-month OS, 38.5%</td>
</tr>
</tbody>
</table>

\(^1\)Frenel et al, JCO 2017; \(^2\)Chung et al, JCO 2018; \(^3\)Lheureux et al, JAMA Oncol 2018; \(^4\)Hollebecque et al, JCO 2017; \(^5\)Santin et al, JCO 2018; \(^6\)Stevanovic et al, Science 2017; \(^7\)Huh et al, JCO 2016

*Modified from Levison et al. 2019 ASCO Educational Book*
Take-Home Messages for Cervical Cancer 2020

Advanced-stage cervical cancer
- Chemoradiation is the standard
- NACT and ACT experimental (and under study)
- Trials on optimal RT and optimal cisplatin dose during RT ongoing
- T-cell based immunotherapy under study

Recurrent/metastatic cervical cancer
- No gold standard for R/M disease: cisplatin alone and cisplatin plus paclitaxel ± bevacizumab are good options. Patient preferably should be treated in trials
- Cisplatin plus paclitaxel is the control arm in randomized trials in the USA. The addition of bevacizumab to cisplatin plus paclitaxel leads to a survival advantage of 3.7 months at the cost of 3-8% more serious adverse events.
Surgical management of apparent stage I endometrial cancer

Surgery is the cornerstone in the treatment of endometrial cancer (MIS is recommended in the management of low- and intermediate-risk EC and can be considered in patients with high-risk EC)
Endometrial Cancer: Epidemiology

- The most common gynecologic cancer in Western countries
- Incidence 13/100,000 women/yr in Europe
- Mortality 2-3/100,000 women/yr in Europe
- >90% is over 50 years; 5% is <40 yrs old (median age 63 years
  - 80% stage I; 5-year survival >95% (with regional spread 68%)
  - 10% stage IV; 5-year survival 17%

Etiological factors: unopposed / excessive estrogen exposure
Predisposing factors: nulliparity, early menarche/late menopause
                     obesity, diabetes, hypertension,
                     treatment with tamoxifen

Genetic susceptibility: Lynch type II syndrome

## Endometrial Cancer: Pathology and Biology

<table>
<thead>
<tr>
<th></th>
<th>Type I (80-90%)*</th>
<th>Type II (10-20%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histotype</strong></td>
<td>endometrioid adenocarcinoma</td>
<td>papillary serous; clear cell</td>
</tr>
<tr>
<td><strong>Precursor lesions</strong></td>
<td>atypical hyperplasia</td>
<td>endometrial CIN</td>
</tr>
<tr>
<td><strong>Hormone sensitivity</strong></td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td><strong>Grading</strong></td>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td><strong>Initial stage</strong></td>
<td>early 70%</td>
<td>advanced 60%</td>
</tr>
<tr>
<td><strong>Behavior</strong></td>
<td>favorable</td>
<td>aggressive</td>
</tr>
<tr>
<td><strong>Recurrence</strong></td>
<td>local</td>
<td>abdominal, lymphatic</td>
</tr>
<tr>
<td><strong>Molecular alterations</strong></td>
<td>MSI with MMR defects (20%)</td>
<td>p53 mut (90%)</td>
</tr>
<tr>
<td></td>
<td>PTEN deletion (80%)</td>
<td>HER2 overexpress. (45%)</td>
</tr>
<tr>
<td></td>
<td>KRAS, β-catenin mut (40%)</td>
<td>amplific. (70%)</td>
</tr>
<tr>
<td></td>
<td>PI3K mut (39%)</td>
<td></td>
</tr>
<tr>
<td><strong>5 yr survival</strong></td>
<td>85%</td>
<td>43%</td>
</tr>
</tbody>
</table>

* Include also: adenocarcinoma, adenosquamous, undiff., squamous, mucinous. (ESMO-ESGO-ESTRO Consensus Conference Ann Oncol 2016; 27: 16-41) ; MSI= microsatellite instability; MMR= mismatch repair deficiency
Endometrial Cancer
Surgery is (still) the cornerstone of treatment

• Hysterectomy + BSO is the cornerstone in the therapy of endometrial carcinoma*

• The uterus should be removed whenever feasible

• Hysterectomy enhances twofold the chances of cure

• Uterus pathology provides the best information on the risk factors of this tumor: histologic grade and myometrial invasion

*Mangioni C, 1988
Indications for Adjuvant Radiotherapy in Endometrial Carcinoma

- Risk factors LN invasion: stage, histotype, grade, MI, LVSI
- Two types of RT: EBRT for locoregional control
  VBT for vaginal vault control
- RT not indicated in low risk cases (gr 1-2 + <50% invasion)
- VBT (or EBRT*) indicated in intermediate risk (2 risk factors)
- EBRT and/or CT indicated in high-risk cases (3 risk factors, stages II and III)

* If PLND not performed
Indications for Adjuvant Systemic Therapy in Endometrial Carcinoma

• Cytotoxic chemotherapy not standard, but in study
  - Can be considered for HR patients and/or with nodal metastases
  - Evaluated in combination with RT (PORTEC 3 study in HR patients*: EBRT vs EBRT + CDDP→4xTC): Overall no improvement in FFS or OS, but in stage III it did: FFS↑ (11% at 5 years)

• Hormonal therapy not standard. Several negative trials

*PORTEC 3: eligible are FIGO stage I, grade 3 ± LVSI; stage II or III; serous/clear cell tumors
Hormonal therapy in recurrent/metastatic disease

1. Hormone therapy (HT) indicated (100% consensus)

2. HT likely more effective in G1 or 2 endometrioid ca or with ER+ or PgR+ status (100% consensus)

3. Biopsy of recurrent disease could be considered, as there might be differences in receptor status in primary and metastatic tumor (100% consensus)

4. HT is the preferred frontline systemic therapy for patients with HR positive tumors, grade 1 or 2 and without rapidly progressive disease. Progestins are generally recommended (100% consensus)

# Cytotoxic Chemotherapy in EC Chemononaive patients

<table>
<thead>
<tr>
<th>Agent</th>
<th># Pts</th>
<th>% RR</th>
<th>% CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclofosfamide</td>
<td>23</td>
<td>9</td>
<td>-</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>65</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>196</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>24</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>95</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>76</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>28</td>
<td>36</td>
<td>14</td>
</tr>
</tbody>
</table>

Vermorken JB, Baekelandt M, 2004
## Cytotoxic Chemotherapy in EC Randomized Studies

<table>
<thead>
<tr>
<th>Regimen</th>
<th># Pts</th>
<th>% RR</th>
<th>% CR</th>
<th>MS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin (A)(^1)</td>
<td>150</td>
<td>25</td>
<td>8</td>
<td>9.2</td>
</tr>
<tr>
<td>A + cisplatin (P)</td>
<td>131</td>
<td>42</td>
<td>17</td>
<td>9.0</td>
</tr>
<tr>
<td>Doxorubicin (A)(^2)</td>
<td>87</td>
<td>17</td>
<td>9</td>
<td>7.0*</td>
</tr>
<tr>
<td>A + cisplatin (P)</td>
<td>90</td>
<td>43</td>
<td>14</td>
<td>9.0*</td>
</tr>
<tr>
<td>A + cisplatin (P)(^3)</td>
<td>266</td>
<td>+</td>
<td>34 **</td>
<td>7</td>
</tr>
<tr>
<td>AP + paclitaxel (T)</td>
<td>57</td>
<td>**</td>
<td>22</td>
<td>15.3#</td>
</tr>
</tbody>
</table>

\(^*\)Intent-to-treat analysis (p = 0.0654; stratified for PS, HR 1.46; p=0.024); + eligible pts randomized. \(^{**}\) p < 0.001; \(^{#}\) p=0.037

Cytotoxic Chemotherapy in EC
GOG 209: study design

- Number of patients included in 1381 (from 2003-2009)

Recurrent or metastatic endometrial cancer

Randomize

T: 160 mg/m² (day 2)
A: 45 mg/m² (day 1)
P: 50 mg/m² (day 1)

T: 175 mg/m² (day 1)*
C: AUC 6 (day 1)*

Both regimens given every 3 weeks for 7 cycles
Results presented from 2nd planned interim analysis (551 deaths)
Median PFS TC vs TAP, 14 v 14 months (HR = 1.03)
Median OS TC vs TAP, 32 vs 38 months (HR = 1.01)

*in 2008 TC doses were reduced in patients pelvic/spine irradiation to 135 mg/m² and AUC 5
Miller et al, Gynecol Oncol 2012: 125; 771-773 (LBA #1)
# GOG 209: Tolerance and Toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>TAP</th>
<th>TC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation for toxicity</td>
<td>18%</td>
<td>12%</td>
</tr>
<tr>
<td>Numbers receiving 7 cycles</td>
<td>62%</td>
<td>69%</td>
</tr>
<tr>
<td>Neurologic toxicity (&gt;grade1)</td>
<td>26%</td>
<td>19%</td>
</tr>
<tr>
<td>Neutropenia (&gt;grade 2)</td>
<td>52%</td>
<td>79%</td>
</tr>
<tr>
<td>Thrombocytopenia (&gt;grade 2)</td>
<td>23%</td>
<td>12%</td>
</tr>
<tr>
<td>Other hematologic (&gt;grade 2)</td>
<td>30%</td>
<td>22%</td>
</tr>
<tr>
<td>Vomiting (&gt;grade 2)</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Diarrhea (&gt;grade 2)</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Metabolic (&gt;grade 2)</td>
<td>14%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Modified from Miller et al. Gynecol Oncol 2012
Interesting Targets in Endometrial Cancer

- PI3K/PTEN/AKT/mTOR pathway
- PTEN
- RAS-MAPK
- Angiogenesis
- ER/PgR
- MSI/MMR deficiency

- Single agent bevacizumab
- Phase II of TC plus bevacizumab (and postprotocol data)
- GOG-86P: TC + bev vs TC + tem vs ixabepilone/C + bev
- MITO END-2: bevacizumab added to TC in REC (PFS↑)
## Bevacizumab as Single Agent and Combined with Paclitaxel/Carboplatin

<table>
<thead>
<tr>
<th>First author</th>
<th>Drug dose</th>
<th>No.</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aghajanian et al</td>
<td>Bevacizumab</td>
<td>52</td>
<td>RR 13.5%, 6-mo PFS 40%</td>
</tr>
<tr>
<td>2015</td>
<td>15 mg/kg/3wks</td>
<td></td>
<td>Median: PFS 4.2 mo; OS 10.5 mo</td>
</tr>
<tr>
<td>Simpkins et al</td>
<td>T (175 mg/m²) C (AUC 5)</td>
<td>15</td>
<td>RR 73.0%, 6-mo PFS 93%</td>
</tr>
<tr>
<td>2015</td>
<td>Bev (15 mg/kg)</td>
<td></td>
<td>Median: PFS 18 mo; OS 58 mo</td>
</tr>
<tr>
<td>Rose et al</td>
<td>TC-B (as above)</td>
<td>34</td>
<td>RR 82.8% (in 29 evaluable pts)</td>
</tr>
<tr>
<td>2017</td>
<td>every 3 weeks</td>
<td></td>
<td>Median: PFS 20 mo; OS 56 mo</td>
</tr>
</tbody>
</table>
## Randomized Studies with Bevacizumab in Advanced Endometrial Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>GOG-86P</th>
<th>MITO-END 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CP-B, CP-TEM, IC-B n=329*</td>
<td>CP-B vs CP n=108*</td>
</tr>
<tr>
<td>OR (%)</td>
<td>60 vs 55 vs 53</td>
<td>71 vs 54</td>
</tr>
<tr>
<td>Median PFS (mo)</td>
<td>12, 8, 9</td>
<td>13 vs 8.7</td>
</tr>
<tr>
<td>HR</td>
<td>0.81 (0.63-1.02)</td>
<td>0.59 (0.35-0.98)</td>
</tr>
<tr>
<td>Median OS (mo)</td>
<td>34, 25, 25</td>
<td>23.5 vs 18</td>
</tr>
<tr>
<td></td>
<td>0.71 (0.55-0.91)</td>
<td>0.65 (0.31-1.36)</td>
</tr>
</tbody>
</table>

CP-B had favorable safety profile and promising antitumor activity (confirmation needed)

*Initial therapy for measurable stage III or IVA, stage IVB or recurrent endometrial cancer (courtesy of Dr. Sessa)
Mismatch-Repair Deficiency Predicts Response of Solid Tumors to PD-1 Blockade

A. Tumor type among 86 patients
B. Waterfall plot of all radiographic responses across 12 different tumor types at 20 weeks. RR 53%, CR rate 21%
C. Confirmed radiographic response at 20 weeks (blue) vs the best radiographic response in the same patient (red)
E. KM estimates of PFS (at 1/2 yrs 64%/53%)
F. KM estimates of OS (at 1/2 yrs 76%/64%)

Le et al, Science, 2017
Endometrial cancer

Cancer Genome Atlas Research Network

Comprehensive genomic and transcriptomic analysis of endometrial cancer

Four genomic classes

<table>
<thead>
<tr>
<th>Copy-number aberrations</th>
<th>POLE (ultramutated)</th>
<th>MSI (hypermutated)</th>
<th>Copy-number low (endometrioid)</th>
<th>Copy-number high (serous-like)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>

| MSI/MLH1 methylation    | Mixed MSI high, low, stable | MSI high           | MSI stable                    | MSI stable                    |

| Mutation rate           | Very high (232 × 10^6 mutations/Mb) | High (18 × 10^6 mutations/Mb) | Low (2.9 × 10^4 mutations/Mb) | Low (2.3 × 10^4 mutations/Mb) |

<table>
<thead>
<tr>
<th>Genes commonly mutated (prevalence)</th>
<th>POLE (100%)</th>
<th>PTEN (38%)</th>
<th>RPL22 (37%)</th>
<th>CTNNB1 (52%)</th>
<th>TP53 (92%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PTEN (94%)</td>
<td>KRAS (35%)</td>
<td>PIK3CA (54%)</td>
<td>PIK3CA (53%)</td>
<td>PPP2R1A (22%)</td>
</tr>
<tr>
<td></td>
<td>PIK3R1 (65%)</td>
<td>PIK3R1 (40%)</td>
<td>ARID1A (42%)</td>
<td>ARID1A (42%)</td>
<td>PIK3CA (47%)</td>
</tr>
<tr>
<td></td>
<td>FBXW7 (82%)</td>
<td>ARID5B (47%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ARID1A (75%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>KRAS (53%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histological type</th>
<th>Endometrioid</th>
<th>Endometrioid</th>
<th>Endometrioid</th>
<th>Serous, endometrioid, and mixed serous and endometrioid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour grade</td>
<td>Mixed (grades 1-3)</td>
<td>Mixed (grades 1-3)</td>
<td>Grades 1 and 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Progress-free survival</td>
<td>Good</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Poor</td>
</tr>
</tbody>
</table>

Murali R, Lancet Oncol, 2014
# Checkpoint Inhibitors in Endometrial Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Agent</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single agent CPI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Le et al(^1)</td>
<td>MMRd tumors (2 EC pts)</td>
<td>Pembro</td>
<td>ORR, 71%</td>
</tr>
<tr>
<td>KEYNOTE 028(^2)</td>
<td>24 PD-L1(^+) EC patients</td>
<td>Pembro</td>
<td>ORR, 13%</td>
</tr>
<tr>
<td>KEYNOTE 158,028,016(^3)</td>
<td>MSI-H, 17 EC patients</td>
<td>Pembro</td>
<td>ORR, 37.7%</td>
</tr>
<tr>
<td>Fader et al(^4)</td>
<td>MMRd tumors, recurrent</td>
<td>Pembro</td>
<td>ORR, 56%; DCR 89%</td>
</tr>
<tr>
<td>Santin et al(^5)</td>
<td>MMRd tumors, recurrent 2 pts (POLE &amp; MSI-H)</td>
<td>Nivo</td>
<td>Resp. &gt; 7 months</td>
</tr>
<tr>
<td>Hasegawa et al(^6)</td>
<td>23 metastatic EC pts</td>
<td>Nivo</td>
<td>ORR, 23%; PFS 3.6 m</td>
</tr>
<tr>
<td>Fleming et al(^7)</td>
<td>15 metastatic EC pts</td>
<td>Atezo</td>
<td>ORR, 13% (1 MSI-H)</td>
</tr>
<tr>
<td>GARNET(^8)</td>
<td>MSI-H recurrent/adv.EC</td>
<td>TSR-042</td>
<td>ORR, 52%</td>
</tr>
<tr>
<td><strong>Antiangiogenesis + CPI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KEYNOTE 775(^9)</td>
<td>Metastatic EC</td>
<td>Lenvat+pembro</td>
<td>ORR, 48%; DCR 96%</td>
</tr>
</tbody>
</table>


*Modified from Levinson et al. 2019 ASCO Educational Book*
Take-Home Messages for Endometrial Cancer 2020

- No routine adjuvant hormonal or chemotherapy

- Hormonal therapy first choice for recurrence in HR-positive patients
  - Progestins: 200 mg/d MPA
  - SERMS (selective estrogen receptor modulators)

- Chemotherapy for hormone failures
  - Standard: paclitaxel/carboplatin
  - Alternative: doxorubicin + cisplatin

- MisMatch-Repair deficient cancers are predicted to have a very large number of mutation-associated neoantigens that might be recognized by the immune system. In case of MSI positive endometrial carcinoma, CPI treatment should be considered
Thank you
Checkpoints Inhibitors in Endometrial Cancer
Selected patient (MSI/MMR deficiency)

• Phase Ib trial KEYNOTE-028 evaluating response rate in patients with refractory PD-L1+ solid tumors
  - Cohort endometrial cancer patients (N=24)
    RR: 13% (in unselected patients); PR+SD=26%

• Phase Ib trials KEYNOTE-028/016/158 evaluating response rate in patients with MSI or MMR deficient solid tumors
  - Cohort endometrial cancer patients (N=14)
  - Objective response rate 36% (in selected patients)
  - Duration of response 4.2+ to 17.6+ months

Ott PA et al. JCO 2017
Management Issues for Endometrial Cancer

Systemic therapy

• No routine adjuvant hormonal or chemotherapy. CRT not standard for high risk FIGO stages I and II, should be discussed in stage III (PORTEC-3)

• Hormonal therapy first choice for recurrence in HR-positive patients
  – Progestins: 200 mg/d MPA
  – SERMS (selective estrogen receptor modulators)

• Chemotherapy for hormone failures
  – Standard: paclitaxel/carboplatin (w/wo Bev)
  – Alternative: doxorubicin + cisplatin

• MisMatch-Repair deficient cancers are predicted to have a very large number of mutation-associated neoantigens that might be recognized by the immune system. In case of MSI positive endometrial carcinoma, CPI treatment should be considered