ESMO SUMMIT AFRICA 2020

Current Standard of Care and Practice changing studies in Endometrial Cancers

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CONFLICT OF INTEREST DISCLOSURE

Consulting and advisory services, speaking or writing engagements, public presentations:
Roche, Astra Zeneca, MSD, Pharmamar, Tesaro- GSK, Clovis, Pfizer, Takeda, Immunogen, Biocad, Amgen

Institutional financial interests:
Roche, Pharmamar, Astra Zeneca, Pfizer

Non-financial interests:
Subject editor for gynecological cancer, ESMO clinical Guidelines
Endometrial cancer

The most common gynecological cancer in the developed world

- In 2018: 382,000 new cases of endometrial cancer diagnosed and 90,000 endometrial cancer-related deaths globally.
- Limited effective treatment options in women with advanced or recurrent disease
Estimated number of new cases in 2018, corpus uteri, females, all ages

- Asia: 148,764 (38.9%)
- Europe: 121,578 (31.8%)
- North America: 65,208 (17.1%)
- Latin America and the Caribbean: 29,353 (7.7%)
- Africa: 12,919 (3.4%)
- Oceania: 4,247 (1.1%)

Total: 382,069

Data source: GLOBOCAN 2018
Graph production: Global Cancer Observatory (http://gco.iarc.fr/)
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ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up†

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Endometrial cancer: Surgery

- **Standard surgery** is total hysterectomy with bilateral salpingo-oophorectomy without vaginal cuff.

- **Minimally invasive surgery** is recommended in the surgical management of low-and intermediate-risk endometrial cancer and can be considered in the management of high-risk endometrial cancer.

- **Ovarian preservation** can be considered in patients younger than 45 years old with grade 1 endometrioid endometrial cancer with myometrial invasion <50% and no obvious ovarian or other extrauterine disease.

- **Ovarian preservation** is not recommended for patients with cancer family history involving ovarian cancer risk (e.g. BRCA mutation, Lynch syndrome, etc.). Genetic counselling/testing should be offered.
Endometrial cancer: Surgery
Staging: Lymphadenectomy?

- If a lymphadenectomy is performed, a **systematic removal of pelvic and para-aortic nodes** up to the level of renal veins should be considered.
- **Sentinel lymph node** dissection is still experimental, but large series suggest that SLN is feasible.

- Lymphadenectomy is a staging procedure and allows tailoring of adjuvant therapy
  - **Not recommended** in Low risk (IA G1-2)
  - **Can be considered** in intermediate risk (deep myometrial invasion >50% or Grade 3 superficial myometrial invasion <50%)
  - **Should be recommended** in high risk patients (G3 with deep myometrial invasion >50%) lymphadenectomy
Optimal indications for fertility-sparing surgery

1. Histologically confirmed endometrioid type endometrial adenocarcinoma
2. Well-differentiated tumor
3. Disease confined to the endometrium
4. No evidence of myometrial invasion on imaging study
5. No clinical evidence of extrauterine spread of disease
6. Strong desire to preserve fertility
7. Age (≤40 years); relative indication
8. No contraindication for medical treatment
9. Informed consent with the understanding that this is not a standard treatment and carries a higher risk of recurrence
What is the current best definition of risk groups for adjuvant therapy (low risk versus (high) intermediate versus high risk)?

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Criteria</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Stage I Endometrioid + gr 1-2 + &lt;50% myometrial invasion + LVSI neg</td>
<td>I</td>
</tr>
<tr>
<td>Low Inter</td>
<td>Stage I Endometrioid + gr 1-2 + ≥50% myometrial invasion + LVSI neg</td>
<td>I</td>
</tr>
<tr>
<td>High Inter</td>
<td>Stage I Endometrioid + gr 3 + &lt;50% myometrial invasion, regardless of LVSI status</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>Stage I Endometrioid + gr 1-2 + LVSI unequivocal positive, regardless of depth of invasion</td>
<td>II</td>
</tr>
<tr>
<td>High Risk</td>
<td>Stage I Endometrioid + gr 3 + ≥50% myometrial invasion, regardless of LVSI status</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>Stage II &amp; stage III no residual disease</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>Non endometrioid (serous or clear cell or undifferentiated carcinoma, carcinosarcoma)</td>
<td>I</td>
</tr>
<tr>
<td>Adv M+</td>
<td>Stage III residual disease &amp; IVa</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>Stage IVB</td>
<td>I</td>
</tr>
</tbody>
</table>

FIGO 2009 staging used
Molecular factors were considered but not included
Tumor size was considered but not included
Nodal status may be considered for treatment recommendations
Adjuvant treatment: endometrial cancer

Miometrial infiltration

<table>
<thead>
<tr>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>&gt;1/2*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>No TX</td>
</tr>
<tr>
<td>&lt;1/2</td>
<td></td>
<td></td>
<td>VBT **</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No EBR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No VBT</td>
</tr>
</tbody>
</table>

Low risk (55%)
Risk of relapse = <5%

Intermediate (30%)
VBT **
No TX

High Risk (15%)
CT+RT
CT ?

*+stage II, III-IV, clear cell and serous histology

**Considered EBRT if LVI + and no nodal staging
High risk endometrial cancer: sequential chemo+RT vs RT

**Overall survival**
- HR 0.69, \( p = 0.07 \)
- OS 75 vs 82%

**Progression-free survival**
- HR 0.63, \( p = 0.009 \)
- PFS 69 vs 78%

Hogberg et al., EJC 46 (2010) 2422–243
• High risk Endometrial carcinoma
  • stage I grade 3, with deep invasion or LVSI+
  • stage II – III EC
  • stage I-III serous or clear cell cancers (>25%)
• WHO PS 0-2
• No residual macroscopic tumor after surgery
• Pathology review before randomisation

Stephanie de Boer: ASCO 2017
The Lancet Oncology: Vol 19, N3, p295–309, March 2018
The Lancet Oncology  July 22, 2019
PORTEC 3: UPDATED RESULTS
(72 months median F-UP)

A. Overall survival

- Radiotherapy
- Chemoradiotherapy

5-year overall survival: 81.4% (chemoradiotherapy) vs 76.4% (radiotherapy)
HR 0.70 (95% CI 0.51–0.97); P\text{,\textsubscript{median}}=0.034

B. Failure-free survival

The Lancet Oncology  July 22, 2019
PORTEC 3: UPDATED RESULTS
(72 months median F-UP)

The Lancet Oncology  July 22, 2019

Stage III

A Overall survival in stage III

B Failure-free survival in stage III

Serous

C Overall survival for serous cancers

D Failure-free survival for serous cancers
**Eligibility:**
Surgical Stage III or IVA EC (FIGO 2009)
Stage I or II clear cell or serous EC + cytology
GOG Performance Status of 0-2
Adequate organ function

**Ineligible Patients**
Carcinosarcoma
Recurrent EC
Residual tumor after surgery > 2 cm

Regimen 1: C-RT (n=407)
Cisplatin 50 mg/m² IV Days 1 and 29 plus **Volume-directed radiation therapy (45Gy +/- brachytherapy)** followed by
Carboplatin AUC 5* plus Paclitaxel 175 mg/m² q 21 days for 4 cycles with G-CSF support

Regimen 2: CT (N=406)
Carboplatin AUC 6 plus Paclitaxel 175 mg/m² q 21 days for 6 cycles

CT scans q 6months X 2 years, q 12 months X 3 years

Stratification:
Age >/= 65
Gross residual disease
Presented by: Daniela Matei, MD ASCO 2017

Vaginal Recurrence

- Incidence at 5 years
- C-RT vs. CT: HR = 0.36 (CI: 0.16-0.82)

Pelvic and PA Recurrence

- Incidence at 5 years
- C-RT vs. CT: HR = 0.43 (CI: 0.28-0.66)
Distant metastases were more frequent in the chemo-RT arm:

You should not compromise the dose and duration of chemotherapy when given together with radiotherapy.

FIG 3. Intention-to-treat analysis of overall survival (OS) by randomly assigned treatment. As of December 11, 2016, 76 deaths were reported. The median follow-up time was estimated to be 53 months. There was insufficient evidence to reject the null hypothesis of no superiority of vaginal cuff brachytherapy plus three cycles of carboplatin and paclitaxel chemotherapy (VCB/C) over radiation therapy (RT) with respect to OS. The log-rank test statistic was −0.756 (one-tailed test P = .57). The estimated treatment hazard ratio (HR) was 1.04 (regimen II relative to regimen I). The (1−α) × 100% Wald CI was 0.664 to 1.632 for a two-sided α = 0.05 (0.025 in each tail) and 0.713 to 1.518 for a two-sided α = 0.10 (0.05 in each tail). An effect size of 0.51 (49% decrease in hazard) was not contained in these CIs.

Published in: Marcus E. Randall; Virginia Filiaci; D. Scott McMeekin; Vivian von Gruenigen; Helen Huang; Catheryn M. Yashar; Robert S. Mannel; Jae-Weon Kim; Ritu Salani; Paul A. DiSilvestro; James J. Burke; Thomas Rutherford; Nick M. Spiritos; Keith Terada; Penny R. Anderson; Wendy R. Brewster; William Small; Carol A. Aghajanian; David S. Miller; Journal of Clinical Oncology 2019 37:1810-1818.
DOI: 10.1200/JCO.18.01575
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Consideration on High risk patients from PORTEC 3, GOG 249 and GOG 258

What has changed after PORTEC 3, GOG 249 and GOG 258?

- Sequential and concomitant chemo-RT superior to RT (FFS and OS in PORTEC 3): chemotherapy is needed in high risk patients
- Is RT needed?
  - In high risk stage I, 3 cycles of chemo/VBC similar to EBRT (GOG 249)
  - In stage III properly given chemotherapy similar to chemo-RT (GOG258)
ADVANCED AND RECURRENT DISEASE
Systemic Treatment of endometrial cancer

- Hormone therapy it is the preferred front-line systemic therapy for patients with hormone receptor positive tumours – grade 1 or 2 and without rapidly progressive disease.
- When chemotherapy is indicated, the standard of care is 6 cycles of three-weekly carboplatin and paclitaxel. This is based on the preliminary communication of a randomised trial showing similar efficacy and less toxicity compared to the triplet of cisplatin/doxorubicin/paclitaxel.
- There is no standard of care for second line chemotherapy.

Can Molecular profiling improve the systemic treatment of advanced/recurrent endometrial cancer
Integrated Genomic Characterization of Endometrial Carcinoma

The Cancer Genome Atlas Research Network

Potential therapeutic impact of TGCA classification

<table>
<thead>
<tr>
<th></th>
<th>POLE</th>
<th>MSI</th>
<th>Copy-number low</th>
<th>Copy-number high</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MSI/MLH methylation</strong></td>
<td>Mixed MSI high</td>
<td>MSI high</td>
<td>MSI stable</td>
<td>MSI stable</td>
</tr>
<tr>
<td><strong>Molecular profile</strong></td>
<td>POLE (100%)</td>
<td>PTEN (88%)</td>
<td>PTEN (77%)</td>
<td>TP53 (92%)</td>
</tr>
<tr>
<td></td>
<td>PTEN (94%)</td>
<td>RPL22 (37%)</td>
<td>CTNNB1 (52%)</td>
<td>PPP2R1A (22%)</td>
</tr>
<tr>
<td></td>
<td>PIK3CA (71%)</td>
<td>KRAS (35%)</td>
<td>PIK3CA (53%)</td>
<td>FBXW7 (22%)</td>
</tr>
<tr>
<td></td>
<td>FBXW7 (82%)</td>
<td>PIK3CA (54%)</td>
<td>ARID1A (42%)</td>
<td>PIK3CA (47%)</td>
</tr>
<tr>
<td></td>
<td>ARID1A (76%)</td>
<td>ARID1A (37%)</td>
<td>FGFR2 (10.9%)</td>
<td>PTEN (11%)</td>
</tr>
<tr>
<td></td>
<td>KRAS (53%)</td>
<td>PD1/PD-L1 overexpression</td>
<td></td>
<td>HER2 (25%)</td>
</tr>
<tr>
<td></td>
<td>PD1/PD-L1 overexpression</td>
<td></td>
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</tr>
</tbody>
</table>

**Potential drugs**

- PI3K/PTEN/AKT/mTOR pathway
- PARP-I
- Anti-PD1/PD-L1
- Hormones
- PI3K/PTEN/AKT/mTOR pathway
- PARP-I
- Anti-PD1/PD-L1
- Hormones
- HER2-I
- PI3K-I
- PARP-I
- Wee-1 I
- FGFR-I
# Phase II Clinical Trials With mTOR and PI3K-i in Women With EC

<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>RR</th>
<th>SD</th>
<th>PFS&gt; 6 Months</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>mTOR inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temsirolimus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Oza 2011) Chemo-naïve</td>
<td>29</td>
<td>14%</td>
<td>69%</td>
<td>-</td>
<td>7.3 months</td>
</tr>
<tr>
<td>Chemo-treated</td>
<td>25</td>
<td>4%</td>
<td>48%</td>
<td>-</td>
<td>3.2 months</td>
</tr>
<tr>
<td>Ridaforolimus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Colombo 2013) Chemo-treated</td>
<td>45</td>
<td>11%</td>
<td>18%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>Ridaforolimus</td>
<td>31a</td>
<td>8.8%</td>
<td>52.9%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ridaforolimus vs progestin or</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>investigator choice chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Oza 2015)</td>
<td>64 vs 66</td>
<td>4.6% vs 3% (P = NS)</td>
<td>56.3 vs 27.7 (P = .003)</td>
<td>-</td>
<td>5.6 months vs 1.9 months (HR, 0.39; 95% CI, 0.23 to 0.66; P&lt;.001)</td>
</tr>
<tr>
<td>Everolimus (Slomovitz 2010)</td>
<td>28</td>
<td>0%</td>
<td>43%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>PI3K inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pilasarilib (XL147) (Matulonis 2014)</td>
<td>67</td>
<td>6%</td>
<td>37.3%</td>
<td>11.9%</td>
<td>-</td>
</tr>
<tr>
<td>BKM120 NCT01289041</td>
<td>71</td>
<td>2.8%</td>
<td>36%</td>
<td>-</td>
<td>1.9 months</td>
</tr>
</tbody>
</table>

Randomized Phase II Trial of Ridaforolimus in Advanced Endometrial Carcinoma

Amit M. Oza, Sandro Pignata, Andres Poveda, Mary McCormick, Andrew Clancy, Benjamin Schwartz, Jonathan Cheng, Xiaoyun Li, Kriey Campbel, Porre Deole, and Frank C. Valiulis

Endometrial carcinoma

Integrated Genomic Characterization of Endometrial Carcinoma
The Cancer Genome Atlas Research Network

Hot tumors
Good Response to Immunotherapy

Cold tumors
Poor Response to Immunotherapy

MSI high and POLE mutated Endometrial Cancers display increased Neoantigen load, more TILs, and higher PD1/PD-L1 Expression

Howitt BE, Konstantinopoulos PA. Association of Polymerase e-Mutated and Microsatellite-Instable Endometrial Cancers With Neoantigen Load, Number of Tumor-Infiltrating Lymphocytes, and Expression of PD-1 and PD-L1. JAMA Oncol. 2015 Dec;1(9):1319-23
Can Immunotherapy improve the systemic treatment of advanced/recurrent endometrial cancer?
Clinical Evidence for Immune Checkpoint Inhibition in Endometrial Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>N</th>
<th>Patient Selection</th>
<th>ORR(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Le et al. (2017)</td>
<td>Pembro</td>
<td>15</td>
<td>MMRd EC</td>
<td>53%</td>
</tr>
<tr>
<td>Ott et al. (2017)</td>
<td>Pembro</td>
<td>24</td>
<td>PDL1+</td>
<td>13%</td>
</tr>
<tr>
<td>Fleming et al. (2017)</td>
<td>Atezo</td>
<td>15</td>
<td>All</td>
<td>13%</td>
</tr>
<tr>
<td>Hasegawa et al. (2018)</td>
<td>Nivo</td>
<td>23</td>
<td>All</td>
<td>23%</td>
</tr>
</tbody>
</table>
| Oaknin (2019)          | Dostarlimab | 125 | All               | 29.6% 
d-MMR 48.8%
p-MMR 20.3% |
| Antill (2019)          | Durvalumab | 70  | All               | d-MMR 43%
p-MMR 3% |
| Konstantinopoulos (2019)| Avelumab | 31  | All               | d-MMR 27%
p-MMR 6% |

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

Endometrial cohort (n=15)
CR: 3 (20)
PR: 5 (33)
SD: 3 (20)

GARNET part 2B: clinical activity of dostarlimab – best overall tumor response

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>Total (N=125)</th>
<th>MSI-H EC (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall response rate</strong></td>
<td>n (%) (95% CI)</td>
<td>37 (29.6%) (21.8, 38.4)</td>
</tr>
<tr>
<td>Complete response</td>
<td>n (%)</td>
<td>6 (4.8%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>n (%)</td>
<td>31 (24.8%)</td>
</tr>
<tr>
<td><strong>Disease control rate(^d)</strong></td>
<td>% (95% CI)</td>
<td>52.8% (43.7, 61.8)</td>
</tr>
<tr>
<td>Response ongoing</td>
<td>%</td>
<td>83.8%</td>
</tr>
</tbody>
</table>

Dostarlimab demonstrated clinically meaningful response rates regardless of MSI status, with an ORR of 49% and a DCR of 63% in the MSI-H cohort.

\(^a\)Based on central testing, MSI status could not be determined; \(^b\)17 confirmed and 1 still on treatment and yet to be confirmed; \(^c\)11 confirmed and 1 still on treatment and yet to be confirmed; \(^d\)irCR+irPR+uirPR+irSD. CI, confidence interval; EC, endometrial cancer; MSI-H, microsatellite instability-high; ORR, overall response rate. Data extraction date January 21, 2019. Oaknin A, et al. Presented at SGO; March 16–19, 2019; Honolulu, HI
GARNET part 2B: Duration of treatment-responding patients

- Responses were durable
- 85% are still on treatment
- Median DOR has not been reached; of responders:
  - 93% remained on treatment for >6 months
  - 50% remained on treatment for >1 year
- Median follow-up is 10 months

DOR, duration of response; irCR: immune-related complete response; irPR: immune-related partial response; irSD: immune-related stable disease; irPD: immune-related progressive disease. Stable disease (SD) is defined as at least one SD or Non-complete response/Non-progressive disease assessment (or better) ≥ 12 weeks - 10 days (≥74 days) after baseline and before progression (and not qualifying for a complete response or partial response). Oaknin A, et al. presented at SGO March 16-19, 2018; Honolulu, HI, USA.
Where are we going?
Rationale for Combining Cancer Immunotherapy with Anti-VEGF

Reduce TILs

Induces abnormal tumor vasculature
Reducing T-cell trafficking and infiltration into the tumor bed\(^5,6\)

Reduces lymphocyte adhesion to vessel walls
Decreases immune-cell recruitment to the tumor site\(^4\)

Immunosuppressive

Inhibits T-cell function
Binds to VEGFR2 on T cells\(^1\)
Kills T cells by tumor endothelium-produced FasL\(^2\)

Stimulates immunosuppressive regulatory T cells\(^2\)

Inhibits dendritic cell function
Drives them into an immature state\(^3\)

VEGF

Keynote 146: Study Design

Phase 2, Open-label, Single-arm Study (NCT02501096)

Key Eligibility Criteria
- Aged ≥18 years
- Pathologically confirmed and metastatic endometrial carcinoma
- ≤2 Prior systemic therapies
- Measurable disease by irRECIST
- ECOG performance status ≤1
- Life expectancy ≥12 weeks

Primary End Point*
- ORR at Week 24

Key Secondary End Points*
- Overall ORR
- DOR
- PFS
- OS
- DCR
- CBR
- Safety and tolerability

Prespecified Exploratory End Points
- Independent imaging review per irRECIST and RECIST v1.1
- Antitumor activity by PD-L1 status

Post Hoc Exploratory Analysis
- Antitumor activity by tumor histology
- Antitumor activity by MSI status

*Tumor responses for primary and secondary end points were assessed by the investigator per irRECIST.

Makker W. Lancet Oncol. 2019 Mar 25
Makker W, ESMO 2019
Levatinib is an oral multikinase inhibitor that targets VEGFR1-3, FGFR1-4, PDGFRα and the oncogenes RET and KIT.

In a phase 2 study of lenvatinib monotherapy in pts with advanced, previously treated endometrial cancer, 19 (14%) of 133 pts had a objective response and median PFS= 5.4 months.
Keynote 146: Primary endpoint: Tumor Response at 24 weeks (Investigator Assessment; irRECIST)

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Total (n = 108)</th>
<th>Not MSI-H or dMMR (n = 94)^a</th>
<th>MSI-H / dMMR (n = 11)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(complete response + partial response), n (%)^b</td>
<td>41 (38.0)</td>
<td>34 (36.2)</td>
<td>7 (63.6)</td>
</tr>
<tr>
<td>95% CI</td>
<td>28.8–47.8</td>
<td>26.5–46.7</td>
<td>30.8–89.1</td>
</tr>
</tbody>
</table>

^a Three patients could not be assessed for MSI or MMR status; ^b ORR wk24 and the exact 95% CIs were calculated with the Clopper-Pearson method, as was 95% CIs for ORR; ^c Duration of response was estimated with the Kaplan-Meier method, and 95% CIs were calculated with a generalized Brookmeyer and Crowley method; ^d Probabilities of patients achieving a duration of response ≥ 6 months or ≥ 12 months were calculated using the Kaplan-Meier product-limit method and Greenwood formula.

W. Makker, ESMO 2019
### Keynote 146: Tumor Response at Data Cut-off (Independent Imaging Review; RECIST version 1.1)

#### Endpoint

<table>
<thead>
<tr>
<th>Objective response rate (complete response + partial response)</th>
<th>Not MSI-H or dMMR (n = 94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>38.3 % (29,49)</td>
</tr>
<tr>
<td>Complete response</td>
<td>10.6 %</td>
</tr>
<tr>
<td>Partial response</td>
<td>27.7 %</td>
</tr>
</tbody>
</table>

#### Duration of response

<table>
<thead>
<tr>
<th>Median in months (range)</th>
<th>NR (1.2+,33.1+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with duration ≥ 6 months</td>
<td>69%</td>
</tr>
</tbody>
</table>

Data reported in the label

W. Makker, ESMO 2019
Accelerated approval

- The FDA, the Australian Therapeutic Goods Administration, and Health Canada granted simultaneous review decisions in all 3 countries on September 17, 2019
- Lenvatinib plus pembrolizumab was granted accelerated approval for the treatment of advanced endometrial carcinoma that is not MSI-H or dMMR
- Patients must have had disease progression following prior systemic therapy and must not be candidates for curative surgery or radiation

US food and Drug Administration assessed from https://www.fda.gov/drugs/resources-information-approved-drugs/simultaneous-review-decisions-pembrolizumab-plus-lenvatinib-austrailia-Canada-us.

Makker V, et al., Lancet Oncol 2019;20(5)711-718
Take home messages

- Minimally invasive surgery remains standard of care
- Adjuvant treatment based on grade, myometrial infiltration, stage and histology (molecular classification coming!!)
- Increased role of chemotherapy in the adjuvant treatment of high risk patients, with or without RT
- Primary treatment of advanced-recurrent disease includes hormonal therapy or chemotherapy with carboplatin-paclitaxel
- No standard second line treatment (weekly paclitaxel or antracyclines)
- Disappointing results with PI3K-M-Tor inhibitors
- Exciting preliminary data with Immune checkpoint inhibitors in ultramutated and hypermutated MMR tumors
- Exciting preliminary data with Pembrolizumab + Lenvatinib in MSS: confirmatory phase III trials ongoing
- Phase III trials ongoing with immune checkpoint inhibitors +/- chemotherapy in advanced endometrial cancer
The future is bright