5th ESO-ESMO Eastern Europe and Balkan Region Masterclass in Medical Oncology

Cervical and endometrial Cancer

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IOSI Bellinzona, Switzerland

Belgrade, June 19th, 2018
Presenter Disclosures

None
Cervical Cancer
Estimated Incidence, Mortality and Prevalence Worldwide in 2012
CERVICAL CANCER

Epidemiology

- In female in less developed countries
  second most commonly diagnosed
  third leading cause of cancer death
- Third most common cause of female mortality
- In 2012 worldwide
  527’600 new cases
  265’700 deaths
- In 2012 in Europe
  58’000 new cases
  24’000 cancer deaths
- Incidence and mortality higher in developing countries
  (85% of cases, 90% of deaths)
Cervical Cancer

Diagnosis and staging

- Bimanual P/V examination, colposcopy, biopsy and/or endocervical currettage (ECC)

- MRI: to determine tumor size, degree of stromal penetration, vaginal and corpus extension.

- CT: to detect pathologic lymphnodes

- Chest xray

- Cystoscopy, rectoscopy (stages IIB-IV)
FIGO Staging is based on the extent of tumor lesion

| Extent of Tumor | Stage 0                  | Stage 1                   | Stage 2                                             | Stage 3                                             | Stage 4                                            |
|-----------------|--------------------------|---------------------------|*****************************************************|*****************************************************|*****************************************************|
| Carcinoma in situ | Confined to cervix       | Disease beyond cervix but not to pelvic wall or lower 1/3 of vagina | Disease to pelvic wall or lower 1/3 of vagina        | Invades bladder, rectum or metastasis              |

- **Stage at presentation**
  - Stage 0: 0%
  - Stage 1: 47%
  - Stage 2: 28%
  - Stage 3: 21%
  - Stage 4: 4%

- Tumor locations:
  - Fallopian tube
  - Uterine cavity
  - Uterine wall
  - Internal OS
  - External OS
  - Corpus
  - Fundus
  - Cervix
  - Vagina
  - Pelvic side wall
  - Rectum
  - Bladder
Survival by FIGO stage

Proportion surviving

Years after diagnosis

Stage Ia1 (n = 787)
Stage Ia2 (n = 313)
Stage Ib1 (n = 986)
Stage Ib (n = 2470)
Stage Ib2 (n = 440)
Stage IIA (n = 993)
Stage IIB (n = 2775)
Stage IIIa (n = 131)
Stage IIIb (n = 2271)
Stage IVA (n = 258)
Stage IVb (n = 196)
CERVICAL CANCER

Histopathological assessment

Timer size stromal invasion / depth of the wall involved, tumour differentiation, LVSI, status of resection margin, status of parametrial and vaginal cuff, number and status of lymph nodes

**Risk factors**

- Tumour size
- Deep stromal invasion
- LVSI

Intermediate-risk

- Positive margins
- Positive lymph nodes
- Microscopic parametrial involvement

High-risk
CERVICAL CANCER

ESMO algorithm for cervical cancer

Locally advanced disease

- RGO Ia / Ib / IIa
  - CRT standard of care

- RGO IVA
  - CT (C) RT
  - Pelvic exenteration

Metastatic disease

- RGO IVB
  - CT + bevacizumab
  - standard of care
CERVICAL CANCER
2/22/99: NCI alert on cervical cancer

The results of 5 large studies have shown that women with bulky IB₂-IVA cervical cancer have better survival when they receive chemotherapy which includes the drug cisplatin along with radiation therapy.
CERVICAL CANCER

Concurrent chemoradiotherapy for cervical cancer: a meta-analysis of 18 randomized trials

- Greater effect for stage IB2-IIA/IIB with 10% survival improvement, 3% for stage III / IVA

- Better results for platinum based therapy (40mg / m² / wk)

- Greater benefit in overall survival with additional adjuvant CT (to be confirmed in ongoing studies: INTERLACE)
CISPLATIN CHEMORADIOThERAPY VS RADIOThERAPY IN FIGO STAGE IIIB SQUAMOUS CELL CARCINOMA OF THE UTERINE CERVIX
A RANDOMIZED CLINICAL TRIAL

SHRIVSTAVA S. ET AL

Jama Oncol, 2018
STUDY DESIGN
Open label phase randomized III Trial

INCLUSION CRITERIA
- FIGO Stage IIIB
- Squamous carcinoma histology
- Age > 18 years and < 65 years
- WHO performance status : 0 or 1
- Hemoglobin > 10 gm %
- Normal WBC and platelet counts
- Normal renal functions

Exclusion Criteria
- Bilateral Hydronephrosis
- HIV positive
- Medical Renal Disease
- Gross PA nodes on Imaging

1 : 1 randomization
N = 424

STUDY ARM
Concomitant Chemoradiation
(Cisplatin weekly 40 mg/m² for 5 cycles atleast)

N = 426

STANDARD ARM
Definitive Radiation

Definitive Radiation:
- External Beam : 50 Gy / 25 # (MLB at 40 Gy when ever feasible)
- Brachytherapy : LDR (25- 30 Gy to point ‘A’ 1# ) or HDR (7 Gy to point ‘A’ x 3# once weekly)
- Total RT (Physical) Doses : 76 Gy – 81 Gy (LDR Equivalent) to Point ‘A’ *

Overall Survival by Arms: ITT Analysis

Overall survival at 5 years
- Chemo-radiation arm: 54% (95% CI, 53.95 – 54.05)
- Radiation Arm: 46% (95% CI, 45.95 – 46.05)

HR=0.82 (95% CI = 0.68 - 0.98), p=0.033

<table>
<thead>
<tr>
<th></th>
<th>chemoradiation</th>
<th>definitive radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>424</td>
<td>426</td>
</tr>
<tr>
<td>12</td>
<td>345</td>
<td>347</td>
</tr>
<tr>
<td>24</td>
<td>289</td>
<td>264</td>
</tr>
<tr>
<td>36</td>
<td>246</td>
<td>220</td>
</tr>
<tr>
<td>48</td>
<td>219</td>
<td>187</td>
</tr>
<tr>
<td>60</td>
<td>194</td>
<td>157</td>
</tr>
<tr>
<td>72</td>
<td>161</td>
<td>125</td>
</tr>
</tbody>
</table>
CONCLUSIONS

- Our study is the largest trial in a homogenous group of advanced stage (IIIB) cervical cancer to prove the benefit of relatively simple and well tolerated concomitant cisplatin chemotherapy regimen over adequately delivered radiation therapy.

Our study confirms that concomitant weekly cisplatin based chemo-radiation should be the standard of care in FIGO Stage IIIB Squamous Cell Cervical Cancer
CERVICAL CANCER

ESMO algorithm for cervical cancer

Locally advanced disease

- FIGO Ia / Ib / IIa
  - CRT standard of care

- FIGO IVA
  - CT (C) RT
    - Pelvic exenteration

Metastatic disease

- FIGO IIIB
  - CT + bevacizumab
    - standard of care

ESMO Guidelines
CERVICAL CANCER

Phase III trial four cisplatin-containing doublet combinations in stage IVB, recurrent or persistent cervical carcinoma

Conclusion: Experimental arms NOT superior – Trend favors control arm of cisplatin/paclitaxel

Monk et al, JCO, 2009
CERVICAL CANCER

GOG 240: final protocol-specified Overall survival
Cisplatin-Paclitaxel versus Cisplatin-Paclitaxel-Bevacizumab

bev, bevacizumab; CI, confidence interval; cis, cisplatin; HR, hazard ratio; OS, overall survival; pac, paclitaxel.

Tewari et al ESMO Madrid 2014
CERVICAL CANCER

Randomised trial comparing cisplatin/paclitaxel with carboplatin/paclitaxel: a non inferiority study (JCOG 0505)

Stage IV B, persistent or recurrent cervical cancer, not amenable to curative surgery radiotherapy

Balancing factors:
- Tumors outside of the prior irradiation field (yes or no)
- PS 0-1 or 2
- SCC or non SCC
- Institution

Randomize

Standard: TP
- Paclitaxel 135 mg/m² 24h d1
- Cisplatin 50 mg/m² d2

Every 21 days for 6 cycles

Experimental: TC
- Paclitaxel 175 mg/m² 3h d1
- Carboplatin AUC 5 d1
Cisplatin / paclitaxel versus carboplatin/paclitaxel in metastatic or recurrent cervical cancer

Overall survival

Kitagawa et al, JCO, 2015.
Cisplatin / paclitaxel versus carboplatin/paclitaxel in metastatic or recurrent cervical cancer

Subgroups analysis of overall survival

<table>
<thead>
<tr>
<th>Category</th>
<th>TP (n)</th>
<th>TC (n)</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 50</td>
<td>56</td>
<td>48</td>
<td>1.16</td>
<td>0.77 to 1.75</td>
</tr>
<tr>
<td>≥ 51</td>
<td>67</td>
<td>73</td>
<td>0.94</td>
<td>0.65 to 1.36</td>
</tr>
<tr>
<td>Performance status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>94</td>
<td>91</td>
<td>0.90</td>
<td>0.65 to 1.24</td>
</tr>
<tr>
<td>1 or 2</td>
<td>29</td>
<td>30</td>
<td>1.44</td>
<td>0.84 to 2.47</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCC</td>
<td>102</td>
<td>100</td>
<td>0.96</td>
<td>0.71 to 1.29</td>
</tr>
<tr>
<td>Non-SCC</td>
<td>21</td>
<td>21</td>
<td>1.28</td>
<td>0.66 to 2.48</td>
</tr>
<tr>
<td>Nonirradiated tumor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one tumor is nonirradiated</td>
<td>79</td>
<td>73</td>
<td>0.97</td>
<td>0.69 to 1.37</td>
</tr>
<tr>
<td>All the tumors are irradiated</td>
<td>44</td>
<td>48</td>
<td>1.03</td>
<td>0.65 to 1.64</td>
</tr>
<tr>
<td>Prior platinum therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (most CDDP)</td>
<td>59</td>
<td>68</td>
<td>0.69</td>
<td>0.47 to 1.02</td>
</tr>
<tr>
<td>No</td>
<td>64</td>
<td>53</td>
<td>1.57</td>
<td>1.06 to 2.32</td>
</tr>
<tr>
<td>Platinum-free interval, months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 6</td>
<td>20</td>
<td>12</td>
<td>1.69</td>
<td>0.78 to 3.65</td>
</tr>
<tr>
<td>≥ 6, &lt; 12</td>
<td>18</td>
<td>22</td>
<td>0.57</td>
<td>0.29 to 1.11</td>
</tr>
<tr>
<td>≥ 12</td>
<td>21</td>
<td>34</td>
<td>0.71</td>
<td>0.38 to 1.38</td>
</tr>
<tr>
<td>No prior platinum therapy</td>
<td>64</td>
<td>53</td>
<td>1.57</td>
<td>1.06 to 2.32</td>
</tr>
<tr>
<td>Overall</td>
<td>123</td>
<td>121</td>
<td>0.99</td>
<td>0.76 to 1.31</td>
</tr>
</tbody>
</table>

Kitagawa et al, JCO, 2015.
Immunotherapy for cervical cancer

Several T cell based immunotherapy approaches in early clinical trials

- **Checkpoint inhibitors / immune modulators**
- Therapeutic vaccines
  - Bacterial vector
  - Viral vector
  - Peptide / protein based
- Adoptive T cell therapy
Emerging strategies in recurrent cervical cancer immune checkpoint inhibitors

Pembrolizumab in patients with advanced cervical Ca

Phase 1b Keynote-028 study

Key eligibility criteria
- Unresectable or metastatic Cervical Ca
- Failure of standard therapy
- PD-L1 positive

Primary endpoints
- ORR (Recist)

Pembrolizumab
- 10mg/Kg IV
- q 2 wks

CR, PR, SD
Continue for 24 mos or PD

PD Unacceptable toxicity
Off study

Frenel, JCO 2017
# Pembrolizumab in advanced cervical cancer

## KEY NOTE 028 results

<table>
<thead>
<tr>
<th>Patients treated (%) (n=24)</th>
<th>Antitumor activity (%)</th>
<th>Grade 3 TRAE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic disease</td>
<td>100 ORR 17</td>
<td>Any 75</td>
</tr>
<tr>
<td>Prior RT</td>
<td>92 PR 17</td>
<td>Rash 21</td>
</tr>
<tr>
<td>Prior lines CT (≥3)</td>
<td>38 SD 13</td>
<td>Colitis 4</td>
</tr>
<tr>
<td>Prior Bev</td>
<td>42 PD 67</td>
<td>Guillain Barrè 4</td>
</tr>
<tr>
<td>Median response:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median OS:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>duration: 5.4 mo (4.1-7.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>duration: 11 mo (95% CI: 4-15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median follow up:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 mo (1.3-32.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Frenel, JCO 2017
Pembrolizumab in advanced cervical cancer

Phase II KEY NOTE 158 results

<table>
<thead>
<tr>
<th>Patients treated (n=82)</th>
<th>Antitumor activity (pts number)</th>
<th>PD–L1+ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>CR</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>PR</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>SD</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>PD</td>
<td>44</td>
<td>37</td>
</tr>
</tbody>
</table>

ASCO, 2017

Pembrolizumab granted FDA approval for PD–L1+ Cervical Cancer 12 June 2018
Pembrolizumab in advanced cervical cancer

FDA approved DAKO PD–L1 IHC 22C3 pharmDx assay as companion diagnostic test 12 June 2018
Endometrial cancer

Epidemiology

- The most common gynaecologic cancer in Western countries
- Incidence 13/100,000 women/yr Europe
- Mortality 2-3/100,000 women/yr
- 80-90% post menopausal; 5% in <40 yrs old
- Median age 63 yrs
- 80% Stage I 5yr survival 95%
- 10% stage IV 5yr survival 17%

- unopposed / excessive oestrogen exposure
- metabolic syndrome (obesity, hypertension):

Risk factors

- RR 1.89
- nulliparity, early menarche/late menopause, diabetes
treatment with tamoxifen in postmenopause

Genetic susceptibility

- Lynch syndrome/ Hereditary Non-Polyposis Colorectal Cancer: 40-60% lifetime risk of both endometrial and CRC
### Obesity-related cancers

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Relative risk* with BMI of 25–30 kg/m²</th>
<th>Relative risk* with BMI of ≥ 30 kg/m²</th>
<th>PAF (%) for US population ‡</th>
<th>PAF (%) for EU population §</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal (men)</td>
<td>1.5</td>
<td>2.0</td>
<td>35.4</td>
<td>27.5</td>
</tr>
<tr>
<td>Colorectal (women)</td>
<td>1.2</td>
<td>1.5</td>
<td>20.8</td>
<td>14.2</td>
</tr>
<tr>
<td>Female breast (postmenopausal)</td>
<td>1.3</td>
<td>1.5</td>
<td>22.6</td>
<td>16.7</td>
</tr>
<tr>
<td>Endometrial</td>
<td>2.0</td>
<td>3.5</td>
<td>56.8</td>
<td>45.2</td>
</tr>
<tr>
<td>Kidney (renal-cell)</td>
<td>1.5</td>
<td>2.5</td>
<td>42.5</td>
<td>31.1</td>
</tr>
<tr>
<td>Oesophageal (adenocarcinoma)</td>
<td>2.0</td>
<td>3.0</td>
<td>52.4</td>
<td>42.7</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>1.3</td>
<td>1.7</td>
<td>26.9</td>
<td>19.3</td>
</tr>
<tr>
<td>Liver</td>
<td>ND</td>
<td>1.5–4.0</td>
<td>ND III</td>
<td>ND II</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>1.5</td>
<td>2.0</td>
<td>35.5</td>
<td>27.1</td>
</tr>
<tr>
<td>Gastric cardia (adenocarcinoma)</td>
<td>1.5</td>
<td>2.0</td>
<td>35.5</td>
<td>27.1</td>
</tr>
</tbody>
</table>

*estimated from the literature

Calle, Nat Rev Can 2004
## Endometrial cancer

<table>
<thead>
<tr>
<th>Clinical, endocrinological, and morphological components (Bokhman classification)</th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution</td>
<td>60–70%</td>
<td>30–40%</td>
</tr>
<tr>
<td>Reproductive function</td>
<td>Decreased</td>
<td>No disturbances</td>
</tr>
<tr>
<td>Onset of menopause</td>
<td>After age 50 years</td>
<td>Younger than age 50 years</td>
</tr>
<tr>
<td>Background endometrium</td>
<td>Hyperplasia</td>
<td>Atrophy</td>
</tr>
<tr>
<td>Oestrogen associated</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Associated obesity, hyperlipidaemia, and diabetes mellitus</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Tumour grade</td>
<td>Low (grades 1–2)</td>
<td>High (grade 3)</td>
</tr>
<tr>
<td>Myometrial invasion</td>
<td>Superficial</td>
<td>Deep</td>
</tr>
<tr>
<td>Potential for lymphogenic metastatic spread</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Favourable</td>
<td>Unfavourable</td>
</tr>
<tr>
<td>Sensitivity to progestagens</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Outcome (5-year survival)</td>
<td>86%</td>
<td>59%</td>
</tr>
<tr>
<td>Prototypical histological type</td>
<td>Endometrioid</td>
<td>Serous</td>
</tr>
<tr>
<td>Oestrogen-receptor or progesterone-receptor expression</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Stage at diagnosis</td>
<td>Early (FIGO stage I–II)</td>
<td>Advanced (FIGO stage III–IV)</td>
</tr>
</tbody>
</table>
Endometrial cancer

Cancer Genome Atlas Research Network

Comprehensive genomic and transcriptomic analysis of endometrial cancer

Four genomic classes

<table>
<thead>
<tr>
<th></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>Copy-number aberrations</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>MSI/MLH1 methylation</td>
<td>Mixed MSI high, low, stable</td>
<td>MSI high</td>
<td>MSI stable</td>
<td>MSI stable</td>
</tr>
<tr>
<td>Mutation rate</td>
<td>Very high (232 × 10^6 mutations/Mb)</td>
<td>High (18 × 10^6 mutations/Mb)</td>
<td>Low (2.9 × 10^6 mutations/Mb)</td>
<td>Low (2.3 × 10^6 mutations/Mb)</td>
</tr>
<tr>
<td>Genes commonly mutated (prevalence)</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>KRA5 (35%)</td>
<td>PIK3CA (53%)</td>
<td>PIK3CA (47%)</td>
</tr>
<tr>
<td></td>
<td>PIK3R1 (65%)</td>
<td>PIK3CA (54%)</td>
<td>PIK3R1 (33%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FBXW7 (82%)</td>
<td>PIK3R1 (40%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ARID1A (76%)</td>
<td>ARID1A (37%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>KRAS (53%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ARID5B (47%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histological type</td>
<td>Endometrioid</td>
<td>Endometrioid</td>
<td>Endometrioid</td>
<td>Serous, endometrioid, and mixed serous and endometrioid</td>
</tr>
<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>Progression-free survival</td>
<td>Good</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Poor</td>
</tr>
<tr>
<td></td>
<td>7%</td>
<td>28%</td>
<td>39%</td>
<td>26%</td>
</tr>
</tbody>
</table>

Murali R, Lancet Oncol, 2014
## ENDOMETRIAL CANCER

### Risk factors for adjuvant therapy

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

Phase III trial comparing concurrent chemo radiation (CTRT) and adjuvant CT with pelvic RT alone in high-risk and advanced stage endometrial carcinoma (EC) S. de Boer et al.

Question

Is the combination of RT and CT better than RT alone in improving PFS and OS in high-risk EC patients?

ASGO 2017
HIGH RISK ENDOMETRIAL CANCER (HREC)

- Pelvic RT 48.6 Gy + 2x Cisplatin 50mg/m2
- 4x Carboplatin AUC5 Paclitaxel 175mg/m2

- Uniform treatment schedule
- Upfront pathology review
- Quality of life analysis

5 weeks - 2 weeks - 12 weeks
PORTEC 3

Inclusion criteria

- Endometrial carcinoma
  - stage I grade 3, with deep invasion or LVSI+
  - stage II - III
  - stage I-III serous or clear cell cancers (>25%)
- WHO PS 0-2
- No residual macroscopic tumor after surgery
- Pathology review before randomisation
PORTEC 3

Survival (Os and FFS)

5 yr OS: 82% (CTRT) versus 77% (RT)

HR 0.79 [0.57-1.12], p=0.18

5 yr FFS: 76% (CTRT) versus 69% (RT)

HR 0.77 [0.58-1.03], p=0.078
PORTEC 3
Conclusions

- Risk reduction of 7% (FFS) and 5% (OS)
- **Significant 11% FFS benefit with CTRT for stage III → Recommended**
- Significant more toxicity with CTRT in the first 12 mos
- Good pelvic control with RT alone
- OS analysis may need a longer follow up
ENDOMETRIAL CANCER

Adjuvant treatment algorithm stage I

- **Low risk (stage I endometrioid G1-G2, <50% myometrial invasion)**
  - No adjuvant treatment

- **Intermediate risk (stage I endometrioid, G1-G2, >50% myometrial invasion, LVSI neg.)**
  - Adjuvant BT
  - No adjuvant BT is an option in younger patients

  - Surgical nodal staging performed, node negative: adjuvant BT, no BT is an option

  - No surgical node staging: adjuvant EBRT

- **High intermediate risk (stage I endometrioid, G3, <50% myometrial invasion or G1-G2 LVSI positive)**
  - Surgical nodal staging performed, node negative: adjuvant EBRT with limited fields

  - If LVSI positive adjuvant BT for G3 and LVSI negative

- **High risk: stage I EEC (G3, >50% myometrial invasion)**
  - No surgical nodal staging: adjuvant EBRT, adjuvant CT can be considered

ESMO Guidelines

**BT** = brachytherapy; **EBRT** = radiotherapy; **LVSI**: lymphovascular space invasion; **CT**: chemotherapy

ESMO Guidelines
ENDOMETRIAL CANCER

Adjuvant treatment algorithm stage II-III high-risk pts

High risk stage II

High risk stage III EEC
no residual disease

High risk non endometrioid
(serous or clear cell or undifferentiated or carcinosarcoma)

Hysterectomy, surgical nodal staging performed node negative:
G1-G2, LVSI negative vaginal BT
G3 or LVSI positive limited EBRT

No surgical nodal staging:
adjuvant EBRT; G3 or LVSI positive consider adjuvant CT

III A, III B, III C1
CT + EBRT

III C2 CT + EBRT

Serous and clear cell after staging: stage I A, LVSI negative: vaginal BT
stage ≥ IB: EBRT + CT

Carcinosarcoma: CT, consider EBRT

ESMO Guidelines

RT green
CT + RT
light blue
PORTEC 3

BT = brachytherapy; EBRT = radiotherapy; LVSI: lymphovascular space invasion; CT: chemotherapy
ENDOMETRIAL CANCER
Advanced / recurrent disease treatment algorithms

<table>
<thead>
<tr>
<th>Isolated vaginal relapse</th>
<th>Central local relapse</th>
<th>Advanced / metastatic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only if optimal cytoreduction (RO) can be achieved</td>
<td>Exenteration considered for stage III A and central local relapse after RT</td>
<td>Resection of oligometastases if feasible</td>
</tr>
<tr>
<td>Resection of oligometastases if feasible</td>
<td>Palliative surgery to alleviate specific symptoms</td>
<td>Standard treatment curative RT</td>
</tr>
<tr>
<td>Standard treatment curative RT</td>
<td>Radical RT for primary unresectable disease</td>
<td>CT + RT can be considered for high risk vaginal or pelvic nodal relapse</td>
</tr>
<tr>
<td>CT + RT can be considered for high risk vaginal or pelvic nodal relapse</td>
<td>Standard of care CT 6 cy carbo / tax</td>
<td>Hormonal treatment for G1 / G2 endometrioid hormone receptor positive in PTS without visceral involvement or rapidly PD</td>
</tr>
<tr>
<td>No biomarker approved for clinical use; biomarker driven clinical trials needed</td>
<td>Palliative RT to alleviate specific symptoms</td>
<td>ESMO Guidelines</td>
</tr>
</tbody>
</table>

Surgery purple; RT green; medical treatment dark blue; CT + RT light blue
Rationale - Hypothesis

Hypermutated endometrial cancers (MSI and POLE) →

More tumor-specific neoantigens →

More tumor-infiltrating lymphocytes →

Compensatory upregulation of immune checkpoints including of the PD-1/PD-L1 pathway →

Good response to PD-1/PD-L1 blockade

*Howitt et al. JAMA Onc, 2015*
Study Schema

Patients with Recurrent or Persistent Endometrial Cancer → Screening Registration

MSI or POLE-mutated cohort → IV Avelumab q2weeks until disease progression

MSS cohort → IV Avelumab q2weeks until disease progression

One cycle = 28 days

MSI/MSS status: Determined by immunohistochemistry for ALL tumors

Primary endpoints: PFS at 6mo and ORR
Key Eligibility Criteria

- Recurrent or persistent endometrial cancer of any histology
- Unlimited lines of prior therapies
- Measurable disease per RECIST 1.1
- Life expectancy of greater than 6 months
- ECOG performance status 0 or 1
- Participants must have normal organ and marrow function
- Availability of a formalin fixed paraffin embedded (FFPE) block of cancer tissue from diagnosis or most recent biopsy
- No previous immunotherapy targeting the PD-1/PD-L1 pathway
MSS Cohort

ORR: 6.3%
PFS6: 6.3%

- 16 patients enrolled
- 2 patients removed from study before 1st scan because of clinical progression
- 1 patient with confirmed PR, currently on Cycle 15 and ongoing
- 15 patients: Off study with no RECIST PFS6 or ORR
- MSS cohort did not meet criteria for 2nd stage
MSI/POLE Cohort

**ORR:** 21.4%

**PFS6:** 33.3%

- 16 patients enrolled (no POLE)
- 1 pt never received avelumab
- 1 pt is on study without first scan
- 3 pts removed for clinical progression before 1st scan (2 before completing 1st cycle)
- 3 confirmed PRs, all ongoing
- 5 pts with PFS6, all ongoing
- Met criteria for 2nd stage
- All PR and PFS6 responses in pts with ≥3 prior cytotoxic lines
MSI/POLE Cohort - Swimmer’s plot
Conclusions

- Avelumab **did not meet prespecified criteria to move to 2nd stage in the MSS cohort**
- All 5 PFS6 and 3 PRs in MSI/POLE cohort pts with ≥ 3 prior lines of cytotoxic therapy
- This is consistent with the FDA approval of pembrolizumab in MSI/MMR deficient tumors
- **Pembrolizumab in endometrial MSI:** ORR in 5 of 14 (36%), DOR (4.2+ months, 17.6+ months)
- Correlative work (TILs, PD-L1, MMR by PCR, mutational load and signatures) is ongoing
Microsatellite instability (MSI)

Condition of genetic hypermutability due to defect of DNA mismatch repair (MMR) with accumulation of incorrected INDEL in repetitive DNA tracts.
Microsatellite instability testing

Immunohistochemistry

To detect the presence / absence of the protein products of the MMR genes (MLH1, MSH2, MSH6 and PMS2)

83% sensitivity; 89% specificity

Preceed sequencing analysis to identify MMR gene to be searched for germline alteration
Molecular testing for Lynch Syndrome

- autosomal dominant familiar cancer risk syndrome
- due to a germline mutation in one of MMR genes in the tumor
  (MLH1, MSH2, PMS2, MSH6)
- 42-54% risk of endometrial and 6 – 12% risk of OvCa

Tumors from individuals should be tested for MSI in the following situations:

i) Colorectal cancer diagnosed in a patient who is <50 years of age.

ii) Presence of synchronous, metachronous colorectal, or other Lynch syndrome-related tumors, regardless of age.

iii) Colorectal cancer with the MSI-high histology diagnosed in a patient who is <60 years of age.

iv) Colorectal cancer diagnosed in one or more first-degree relatives with an Lynch syndrome-related tumor, with one of the cancers being diagnosed under age 50 years.

v) Colorectal cancer diagnosed in two or more first- or second-degree relatives with Lynch syndrome-related tumors, regardless of age.

1 Lynch syndrome-related tumors include colorectal, endometrial, gastric, ovarian, pancreatic, ureteral and renal pelvis, biliary tract, and brain (usually glioblastoma as observed in Turcot syndrome) tumors, sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.

2 Presence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern. MSI.
## Prevention and screening strategies for Lynch syndrome

<table>
<thead>
<tr>
<th>MLH1, MSH2, MSH6, EPCAM and PMS2 mutations</th>
<th>Screening</th>
<th>Prevention/risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Annual colonoscopy from age 20-25</td>
<td></td>
<td>1) Consider risk-reducing hysterectomy and RRSO after completion of childbearing</td>
</tr>
<tr>
<td>2) Annual neurological examination for screening of CNS tumours may be considered</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3) Annual endometrial ultrasound + biopsies from age 30-35 may be considered</td>
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</tbody>
</table>
EASTERN EUROPE AND BALKAN REGION REFRESHER COURSE ON GYNAECOLOGICAL TUMOURS

11-12 October 2018
Sarajevo, Bosnia-Herzegovina

Chairs: S. Beslija, BA - C. Sessa, CH

ATTENDANCE TO THE COURSE IS BY APPLICATION ONLY
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