ESMO SUMMIT RUSSIA 2019

Current standards & practice changing studies in Endometrial Cancer

Domenica Lorusso on behalf of Mansoor Raza Mirza
Advisory board for Roche Tesaro, Merck, Astra Zeneca, Clovis Oncology, Genmab, Immunogen

Consultant Roche, Pharmamamar

Institutional Research Support from Roche, Pharma Mar, Clovis Oncology and Merck

Travel support Pharmamamar, Tesaro, Roche, Astra Zeneca
2015 ESMO-ESGO-ESTRO Consensus

**ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up.**

**ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: Diagnosis, Treatment and Follow-up.**

**ESMO-ESGO-ESTRO consensus conference on endometrial cancer: Diagnosis, treatment and follow-up.**
Radiother Oncol. 2015 Dec;117(3):559-81.
Presentation Outline

- Adjuvant Hormonal Therapy
- Adjuvant Radiation Therapy
- Adjuvant EBRT + Chemotherapy
- Adjuvant Chemotherapy
- Management of Locally Advanced/Metastatic Disease
- Targeted Therapy
Adjuvant Hormonal Therapy

- Systemic review of 9 randomized trials
- The available evidence does not demonstrate any benefit for adjuvant hormonal therapy
- The use of hormonal therapy is not recommended as adjuvant treatment

Level one evidence for adjuvant radiotherapy in endometrial cancer?
Cochrane Meta-analysis of 8 clinical trials (n = 3628)
Aalders; ASTEC; GOG99; PORTEC1; PORTEC2; Soderini2003; Sorbe2009; Sorbe 2011

Overall Survival

Cochrane Meta-analysis

Locoregional Control

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Total</th>
<th>No EBRT</th>
<th>Total</th>
<th>Weight</th>
<th>Hazard Ratio</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBRT vs no additional treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOG 99</td>
<td>-1.77</td>
<td>0.63</td>
<td>190</td>
<td>202</td>
<td>9.3%</td>
<td>0.17 [0.05, 0.59]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PORTEC-1</td>
<td>-1.12</td>
<td>0.34</td>
<td>354</td>
<td>360</td>
<td>31.9%</td>
<td>0.33 [0.17, 0.64]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>544</td>
<td>562</td>
<td>41.2%</td>
<td>0.28 [0.16, 0.51]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.82, df = 1 (P = .36); I² = 0%
Test for overall effect: Z = 4.23 (P < .0001)

EBRT vs no additional treatment (VBT balanced across groups)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Total</th>
<th>No EBRT</th>
<th>Total</th>
<th>Weight</th>
<th>Hazard Ratio</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASTEC/EN.5 (1)</td>
<td>-0.78</td>
<td>0.34</td>
<td>452</td>
<td>453</td>
<td>31.9%</td>
<td>0.46 [0.24, 0.89]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorbe 2011 (2)</td>
<td>-1.11</td>
<td>0.5</td>
<td>264</td>
<td>263</td>
<td>14.7%</td>
<td>0.33 [0.12, 0.88]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>716</td>
<td>716</td>
<td>46.6%</td>
<td>0.41 [0.24, 0.72]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 1 (P = .59); I² = 0%
Test for overall effect: Z = 3.15 (P = .002)

EBRT vs VBT

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Total</th>
<th>No EBRT</th>
<th>Total</th>
<th>Weight</th>
<th>Hazard Ratio</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>PORTEC-2 (3)</td>
<td>-0.73</td>
<td>0.55</td>
<td>214</td>
<td>213</td>
<td>12.2%</td>
<td>0.48 [0.16, 1.42]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>214</td>
<td>213</td>
<td>12.2%</td>
<td>0.48 [0.16, 1.42]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 1.33 (P = .18)

Total (95% CI)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Total</th>
<th>No EBRT</th>
<th>Total</th>
<th>Weight</th>
<th>Hazard Ratio</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1474</td>
<td>1491</td>
<td>100.0%</td>
<td>0.36 [0.25, 0.52]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 2.31, df = 4 (P = .88); I² = 0%
Test for overall effect: Z = 5.33 (P < .00001)
Test for subgroup differences: Chi² = 1.19, df = 2 (P = .55), I² = 0%
1) 54% in EBRT group and 52% in the No EBRT group received VBT
2) All women received VBT. This trial expressed HRs in terms of VBT; we have expressed the HR in terms of EBRT.
3) This trial expressed HRs in terms of VBT (VBT vs EBRT); we have expressed the HR in terms of EBRT.

Cochrane Meta-analysis

Long-Term Follow-up

Radiotherapy deteriorates overall survival

• PORTEC 1 & Aalders
• HR=1.26; CI=1.03-1.54

Toxicity & QoL

• Acute grade 3-4 (5) toxicity
  • 2 trials; n=1328; HR=4.68; CI=1.35-16.16
  • Fatal complications: 4

• Late grade 3-4 toxicity
  • 6 trials; n=3501; HR=2.58; CI=1.61-4.11

• Deteriorated Quality of Life
  • Urinary incontinence, diarrhea, feecal leakage limited daily activities
  • Worsen physical functioning
  • Bodily pain

Kong et al. JNCI 2012
Long Term Outcomes after External Beam Radiation (EBRT) For Early Stage Endometrial Cancer: Oslo Trial – revisited!

Overall survival in patients <60 years - ITT

Risk of Secondary Malignancy

Level one evidence for adjuvant radiotherapy with chemotherapy in endometrial cancer?
## Phase III Trials of Adjuvant Radiotherapy with Chemotherapy

| Population (Stage) | GOG 34  
|-------------------|--------|
|                   | Morrow et al.  
|                   | Finnish Study  
|                   | Kuoppala et al.  
|                   | GOG184  
|                   | Homeslay et al.  
|                   | NSGO9501  
|                   | Hogberg et al.  
|                   | PORTEC 3  
|                   | De Boer et al.  
| n | 181  
| 157  
| 586  
| 534  
| 660  
| Regimen | RT  
|        | RT➔Doxo8  
|        | RT (split)  
|        | CEP/RT/CEP/RT/CEP  
|        | RT➔AP6  
|        | RT➔TAP6  
|        | RT  
|        | RT+CT  
|        | RT  
|        | CTRT  
| PFS | -  
| NS  
| NS  
| NS  
| 69/78  
| HR 0.63*  
| 69/76  
| HR 0.77 (NS) **  
| OS | NS  
| NS  
| NS  
| -  
| HR 0.69 (NS)  
| 77/82  
| HR 0.79 (NS)  


** POSITIVE RESULTS ONLY IN STAGE III (11% increase in PFS)**
Pelvic lymph node metastases (%)

<table>
<thead>
<tr>
<th>Depth of invasion</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No invasion</td>
<td>0</td>
<td>3-4</td>
<td>0</td>
</tr>
<tr>
<td>&lt; 50%</td>
<td>0-3</td>
<td>5-10</td>
<td>7-9</td>
</tr>
<tr>
<td>&gt; 50%</td>
<td>0-11</td>
<td>17-19</td>
<td>28-34</td>
</tr>
</tbody>
</table>

LNE not mandatory in NSGO-EC-9501 or in PORTEC-3
Is the difference in survival due to effect on node-positive patients only (stage IIIC)?

Level one evidence for adjuvant chemotherapy in endometrial cancer?
## Phase III Trials of Adjuvant Chemotherapy

<table>
<thead>
<tr>
<th>Population (Stage)</th>
<th>GOG: Randall et al. JCO '06</th>
<th>Italian Study: Maggi et al. BJC '06</th>
<th>JGOG 2033: Susumu et al. Gyn Oncol '08</th>
<th>GOG 249: SGO 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>III-IV</td>
<td>IC (26%)</td>
<td>IC (61%; 55% grade 1)</td>
<td>IB G1 &amp; G2 (50%) IB G3; II (50%)</td>
</tr>
<tr>
<td>n</td>
<td>396</td>
<td>345</td>
<td>385</td>
<td>601</td>
</tr>
<tr>
<td>Regimen</td>
<td>WART A(^{60}) P(^{50}) x 8</td>
<td>RT C(^{600}) A(^{45}) P(^{50}) x 5</td>
<td>RT C(^{333}) A(^{40}) P(^{50}) x 3</td>
<td>RT TC x 3</td>
</tr>
<tr>
<td>PFS</td>
<td>Significant</td>
<td>-</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>OS</td>
<td>Significant</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>
## GOG 249 & PORTEC3

### 5-year survival - FIGO

<table>
<thead>
<tr>
<th>Stage</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage I</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ia</td>
<td>93</td>
<td>91</td>
<td>80</td>
</tr>
<tr>
<td>Ib</td>
<td>92</td>
<td>93</td>
<td>82</td>
</tr>
<tr>
<td>Ic</td>
<td>91</td>
<td>86</td>
<td>75</td>
</tr>
<tr>
<td><strong>Stage II</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIa</td>
<td>90</td>
<td>84</td>
<td>68</td>
</tr>
<tr>
<td>IIb</td>
<td>81</td>
<td>77</td>
<td>65</td>
</tr>
</tbody>
</table>

**Grade 1 & 2 tumors**
- GOG 249: ≈50%
- PORTEC3: ≈39%

Creasman et al., IJGO, 2007
<table>
<thead>
<tr>
<th>Stage</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>93</td>
<td>91</td>
<td>80</td>
</tr>
<tr>
<td>Ib</td>
<td>92</td>
<td>93</td>
<td>82</td>
</tr>
<tr>
<td>Ic</td>
<td>91</td>
<td>86</td>
<td>75</td>
</tr>
<tr>
<td>IIa</td>
<td>90</td>
<td>84</td>
<td>68</td>
</tr>
<tr>
<td>IIb</td>
<td>81</td>
<td>77</td>
<td>65</td>
</tr>
</tbody>
</table>

Creasman et al., IJGO, 2007
A phase III Trial of postoperative chemotherapy or no further treatment for patients with node-negative stage I-II intermediate or high risk endometrial cancer.

**ENGOT-EN2-DGCG**

NCT01244789

### 1:1 randomization

**Endometrioid:**
- Stage I - G3; II
- **Non-endometrioid:**
  - Stage I-II

#### Chemotherapy

Carboplatin-Paclitaxel x 6 + Brachytherapy

#### Observation

+ Brachytherapy

Sponsor: DGCG
Study Chair: Mirza MR

Recruitment Completed
Management of locally advanced/metastatic endometrial cancer?
### Phase III Trials in Advanced/Metastatic Disease Chemotherapy

<table>
<thead>
<tr>
<th>Population (Stage)</th>
<th>RT agent vs. Doublet</th>
<th>Single agent vs. Doublet</th>
<th>Doublet vs. Doublet</th>
<th>Doublet vs. Triplet</th>
<th>TAP vs. TC</th>
</tr>
</thead>
<tbody>
<tr>
<td>III-IV</td>
<td>GOG Randall et al. JCO ’06</td>
<td>EORTC55872 Van Wijk Ann Onc ’03</td>
<td>GOG107 Thigpen JCO ’04</td>
<td>GOG Fleming Ann Onc ’04</td>
<td>GOG209 Miller SGO ’12</td>
</tr>
<tr>
<td>n</td>
<td>396</td>
<td>177</td>
<td>299</td>
<td>317</td>
<td>273</td>
</tr>
<tr>
<td>Regimen</td>
<td>WART A^{60} P^{50} x 8</td>
<td>Dox vs. Dox-Cisplat</td>
<td>Dox vs. Dox-Cisplat</td>
<td>Dox-Cisplat vs. Dox-Paclitax</td>
<td>Dox-Cisplat vs. Dox-Cisplat-Tax</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Carbo-Tax vs. Dox-Cisplat-Tax</td>
</tr>
<tr>
<td>PFS</td>
<td>Signif HR 0.71</td>
<td>NS</td>
<td>Signif HR 0.73</td>
<td>NS</td>
<td>Signif P &lt; 0.01</td>
</tr>
<tr>
<td>OS</td>
<td>Signif HR 0.68</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>Signif P &lt; 0.037</td>
</tr>
</tbody>
</table>
GOG-258: Randomized Phase III Trial of Cisplatin and Tumor Volume-Directed Irradiation Followed by Carboplatin and Paclitaxel vs Carboplatin and Paclitaxel for Optimally Debulked, Advanced EC

*first dose of Carboplatin will be at AUC of 5, in subsequent cycles the dose will be escalated to AUC 6, as described in Section 6.2

GOG-258 Recurrence-Free Survival

GOG-258 Overall Survival

OS, overall survival
Target therapy:
Anti-angiogenic therapy
Randomized Phase II Trial of Carboplatin-Paclitaxel compared to Carboplatin-Paclitaxel Bevacizumab in advanced or recurrent endometrial cancer

Patients with advanced (stage III-IV) or recurrent type 1 or type 2 (no carcinosarcoma) endometrial cancer; 0-1 previous CHT lines; Measurable or evaluable disease (n~108)

Carboplatin AUC 5 + Paclitaxel 175 mg/mq d1 q 21 x 6-8 cycles

Carboplatin AUC 5 + Paclitaxel 175 mg/mq d1 q 21 x 6-8 cycles + Bevacizumab 15 mg/kg in combination with chemotherapy and maintenance until PD

R

Events, n
CT (N=54) 34
CT-B (N=54) 32

Median PFS, months (95% CI)
CT (6.3-11.2)
CT-B (9.2-16.8)

HR (stratified) (95% CI)
0.59 (0.35–0.98)
0.036

Lorusso et al. ASCO 2015

Phase 2

EUDRACT 00330116

n = 108
GOG-86-P

**ARM 1:**
- Paclitaxel
- Carboplatin
- Bevacizumab

**ARM 2:**
- Paclitaxel
- Carboplatin
- Temsirolimus

**ARM 3:**
- Ixabepilone
- Carboplatin
- Bevacizumab

**NCT00977574**

*Phase 3*

**GOG86P: OS**

**Aghaganian et al. ASCO 2015**

\[ n = 349 \]
ENGOT-EN1 / FANDANGO

A randomized double-blind placebo-controlled phase II trial of first-line combination chemotherapy with Nintadenib for patients with advanced or recurrent endometrial cancer

Recruitment Completed

**Randomization: 1:1**

ARM A
Carboplatin + Paclitaxel + Nintedanib
followed by maintenance Nintedanib

Treat to PD/toxicity

Investigator’s choice

ARM B
Carboplatin + Paclitaxel + Placebo
followed by maintenance Placebo

Treat to PD/toxicity

Endometrial Cancer
Stage 3C2
or
Stage 4
or
First relapse

**Randomization Completed**

NCT02730416
Phase 2

Study Chair: Mirza MR

n = 148
PI3K/AKT pathway

Metabolic pathways
## mTOR and PI3K inhibitors

<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 (Oza 2011)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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 (Colombo 2013)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemo-treated</td>
<td>45</td>
<td>11%</td>
<td>18%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>Ridaforolimus (Tsoref 2014)</td>
<td>31*</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>64</td>
<td>4.6%</td>
<td>56.3</td>
<td>27.7 (P = .003)</td>
<td></td>
</tr>
<tr>
<td>(Oza 2015)</td>
<td>66</td>
<td>3%</td>
<td></td>
<td></td>
<td></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 Clamp, Benjamin Schwartz, Jonathan Cheng, Xiaojun Li, Kristy Campbell, Perre Duchesne, and Frank C. Hilsidea

A

Median, months
(95% CI)
Ridaforolimus 3.6 (2.7 to 7.3)
Comparator 1.9 (1.9 to 2.3)
P 0.53 (0.31 to 0.90) .008

B

Median, months
(95% CI)
Ridaforolimus 10.0 (8.1 to 12.4)
Comparator 9.6 (7.5 to 12.2)
P 1.06 (0.70 to 1.59) .604

A randomized phase II trial of Everolimus and Letrozole or hormonal therapy for patients with advanced, persistent or recurrent endometrial cancer

**GOG 3007**

**NCT02228681**

**ARM A**
Everolimus + Letrozole

**ARM B**
Tamoxifen + MPA

Randomize

Treat to PD/toxicity

Investigator’s choice

Slomovitz et al.
GOG 3007

PFS by prior treatment

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Events</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Prior Chemo or Chemoradiotherapy</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Prior Chemo or Chemoradiotherapy</td>
<td>10</td>
<td>22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Events</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Prior Chemo or Chemoradiotherapy</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Prior Chemo or Chemoradiotherapy</td>
<td>20</td>
<td>22</td>
</tr>
</tbody>
</table>

Everolimus/Letrozole – NPC: PFS 21.6 mos.
Everolimus/Letrozole – Prior chemo: PFS 3.3 mos.

HT – NPC: PFS 6.6 mos.
HT– prior ctx: PFS 3.2 mos.

Slomovitz et al.
A Phase II, Single-Arm Study of Everolimus, Letrozole, and Metformin in Patients With Advanced or Recurrent Endometrial Carcinoma

NCT01797523
Cyclin-Dependent Kinase (CDK) Inhibitors
A randomized phase II trial of Palbociclib in combination with letrozole versus letrozole for patients with oestrogen receptor positive recurrent endometrial cancer.

**ENGOT-EN3-NSGO/PALEO**

**Endometrial Cancer**
- Primary stage 4 or relapsed incurable disease
- ER positive endometrioid adenocarcinoma

**Randomization: 1:1**
- **ARM A**
  - Letrozole, 2.5mg d 1-28 every 28 days
  - Placebo d 1-21 every 28 days
  - Until progression

- **ARM B**
  - Letrozole, 2.5mg d 1-28 every 28 days
  - Palbociclib 125mg d 1-21 every 28 days
  - Until progression

**Stratification:**
- Number of prior lines of therapy (primary advanced disease vs. 1st relapse vs. ≥2 relapses)
- Measurable vs. evaluable disease
- Prior use of MPA/Megace (prior MPA/Megace use capped to a maximum of 50%)

**NCT02730429**

**Recruitment Completed**
Novel Agents
Selective Inhibitor of Nuclear Export Proteins
Exportin 1 (XPO1) is the major nuclear export protein for tumor suppressor proteins (TSPs)

- All neoplasms tested to date overexpress XPO1 2-4 fold, with higher levels correlating with poorer outcomes
- Selective Inhibitors of Nuclear Export (SINE) compounds inhibit XPO1, leading to nuclear retention and reactivation of TSPs, inducing selective tumor cell apoptosis
- Selinexor is a novel oral SINE compound currently being evaluated in solid and hematological cancers

Rationale for Gynecological malignancies are a rationale indication for selinexor

- Elevated XPO1 expression is found in ovarian and cervical cancers, correlating with poorer outcomes
- Multiple TSPs are mislocalized to the cytoplasm (and often degraded) in gynecological cancers
- HPV E7 (and E6) proteins associated with strains that cause cervical cancer stimulate the XPO1 mediated nuclear to cytoplasmic transport of p53 and pRB, leading to their degradation

NCT02025985
SIGN study

Primary endpoint – Disease Control Rate (CR + PR + SD≥12 Weeks)

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Dose</th>
<th>N</th>
<th>DCR (%)</th>
<th>PR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian</td>
<td>35 mg/m² (BIW)</td>
<td>18</td>
<td>11 (61%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td></td>
<td>50 mg/m² (BIW)</td>
<td>22</td>
<td>10 (45%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td></td>
<td>50 mg/m² (QW)</td>
<td>19</td>
<td>8 (42%)</td>
<td>3 (16%)</td>
</tr>
<tr>
<td></td>
<td><strong>All Doses</strong></td>
<td>59</td>
<td><strong>29 (49%)</strong></td>
<td><strong>8 (14%)</strong></td>
</tr>
<tr>
<td>Endometrial</td>
<td>50 mg/m² (BIW)</td>
<td>20</td>
<td>9 (45%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Cervical</td>
<td>50 mg/m² (BIW)</td>
<td>23</td>
<td>6 (26%)</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

Responses were adjudicated according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1) based on interim unaudited data = DCR=Disease Control Rate (CR+PR+SD≥12)

ENGOT-EN5 / BGOG / SIENDO
Maintenance with Selinexor/ Placebo After Combination Chemotherapy for Patients with Advanced or Recurrent Endometrial Cancer.

Chemotherapy for advanced (Stage IV) or recurrent endometrial cancer (prior adjuvant for Stage I-III is not counted as a line of chemotherapy unless the relapse occurred within 6 months after the last adjuvant course of chemotherapy for stage I-III disease

**SELEXINOR**
Oral
80mg once weekly

2:1 Randomization

**Placebo**
Oral
Once weekly

N = 161

ENGOT model: C
Lead group: BGOG
Sponsor: Karyopharm
Planned No. of patients: 172
Status: enrolling

**Stratification:**
- 1 vs. 2 prior lines of chemotherapy for advanced (Stage IV) or recurrent endometrial cancer
- Disease status after chemotherapy (PR vs. CR)

Primary endpoint: Progression-Free Survival (PFS)

**Study Chair: Vergote I**
Novel Agents
Immune Check-Point Inhibitors
Immunotherapy

- POLE ultramutated & MSI have
  - high mutation load
  - Tumor-infiltrating lymphocytes (TILs)
  - counterbalanced by overexpression of PD-1 & PD-L1
  - Checkpoint (PD-1 & PD-L1) inhibitors can “re-activate” our TILs

Dostarlimab in Endometrial Cancer: Change in Tumor Size

>50% reduction in total tumor burden in 85% of MSI-H and 69% of MSS responders

Primary objective: OTRR (iRECIST)

<table>
<thead>
<tr>
<th></th>
<th>dMMR (n =35)</th>
<th>pMMR (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OTRR</strong></td>
<td>15 (43%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td><strong>DCR</strong></td>
<td>23 (66%)</td>
<td>10 (29%)</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>5 (14%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>10 (29%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>8 (23%)</td>
<td>9 (26%)</td>
</tr>
<tr>
<td>Non-evaluable*</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

1 non-evaluable as no RECIST assessment after registration

dMMR- MMR deficient, pMMR- MMR proficient
**Confirmed Objective Response and PFS6**

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MMRD cohort (N=15)</td>
</tr>
<tr>
<td>Best Overall Response</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>1</td>
</tr>
<tr>
<td>PR</td>
<td>3</td>
</tr>
<tr>
<td>SD</td>
<td>4</td>
</tr>
<tr>
<td>PD</td>
<td>4</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>3</td>
</tr>
<tr>
<td><strong>ORR, % (95% CI)</strong></td>
<td><strong>26.7 (7.8-55.1)</strong></td>
</tr>
<tr>
<td>PFS6 Response</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>No</td>
<td>9</td>
</tr>
<tr>
<td><strong>PFS6 Response, %</strong></td>
<td><strong>40 (16.3-66.7)</strong></td>
</tr>
</tbody>
</table>
PFS and OS in both cohorts (median follow up 18.6 months)

**PROGRESSION FREE SURVIVAL**

- Median PFS
  - MMRD: 4.4 months
  - MMRP: 1.9 months
  - /non-POLE

**OVERALL SURVIVAL**

- Median OS
  - MMRD: not reached
  - MMRP: 6.6 months
  - /non-POLE

Presented By Panagiotis Konstantinopoulos at 2019 ASCO Annual Meeting
ENGOT-EN6 /NSGO - RUBY

Trial Design

Eligible Subjects
Recurrent or Primary
Advanced (stage III or IV) Endometrial Cancer or first recurrent endometrial cancer (see International Federation of Gynecology and Obstetrics staging in Appendix 4) with a low potential for cure by radiation therapy or surgery alone or in combination

N = 470
Randomization 1:1

Stratification:
By microsatellite instability (MSI) status (MSI-high [MSI-H] or microsatellite stable [MSS]), prior external pelvic radiotherapy (yes or no), and disease status (recurrent, primary Stage III, or primary Stage IV).

Dostarlimab 500 mg
Carboplatin AUC 5mg/mL/min
Paclitaxal 175 mg/m² Q3W for 6 cycles

Dostarlimab 1.000 mg Q6W up to 3 years*

Placebo
Carboplatin AUC 5mg/mL/min
Paclitaxal 175 mg/m² Q3W for 6 cycles

Placebo Q6W up to 3 years*

Follow-up

*Treatment ends after 3 years, progression of disease, toxicity, withdrawal of consent, Investigator’s decision, or death, whichever occurs first. Continued treatment with dostarlimab or placebo beyond 3 years may be considered following discussion between the Sponsor and the Investigator.
AtTEnd

Atezolizumab Trial in Endometrial cancer - MaNGO

Stage III/IV with residual disease or recurrent endometrial cancer

Paclitaxel 175mg/m² carboplatin AUC 5 or 6 placebo
Maintenance placebo

Paclitaxel 175mg/m² carboplatin AUC 5 or 6 atezolizumab 1200mg
Maintenance atezo 1200mg

Confirmed PD

Stratified by:
- Country
- Histological type
- Disease (recurrent disease vs advanced disease at primary diagnosis)
- MS status

Principal Investigator: Nicoletta Colombo, Istituto Europeo di Oncologia - Milan
Sponsor(s): MaNGO- Istituto di Ricerche Farmacologiche Mario Negri IRCCS - Milan
Planned No. of patients: 550

- FIGO stage III, stage IV or recurrent endometrial carcinoma
- No prior chemotherapy (except chemoradiation)
- ECOG 0 or 1
- 612 pMMR plus approximately 108 dMMR patients

Stratify:
MMR status (pMMR vs. dMMR),
- If pMMR,
  - ECOG (0 vs. 1)
  - Measurable disease (y/n)
  - And prior chemoradiation (y/n)

Model C

Pembrolizumab 200 mg IV infusion Q3W15 mg/kg q3w
Up to 35 infusions

Lenvatinib 20mg orally QD

Carboplatin AUC 6* IV infusion Q3W
Up to 7 cycles

Paclitaxel 175 mg/m² IV infusion Q3W
Up to 7 cycles

* Carboplatin AUC 5 may be administered in accordance with local practice
NRG-GY018

Randomized phase II/III study of carboplatin + paclitaxel vs. carboplatin + paclitaxel + pembrolizumab in patients with advanced stage (stage 3 or 4) or recurrent endometrial cancer

Stage III & IV or recurrent endometrial cancer
(Stage 3 or 4A: measurable disease; Stage 4B or recurrent whether there is measurable disease or not)
MMR-proficient vs. MMR-deficient

C/T + placebo
C/T + pembrolizumab + maintenance pembrolizumab x 12 months

Patients may have received prior radiation therapy or hormonal therapy. Patients in whom both radiation and chemotherapy are planned must receive radiation prior to entry on study. C = Carboplatin; T = Paclitaxel

Stratification factors: MMR-proficient vs. MMR-deficient, performance status, measurable disease status

N=590 pMMR patients
N=185 deficient MMR (dMMR)
Management of endometrial cancer is going to be improved considerably