CERVICAL CANCER: SYSTEMIC TREATMENT

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Disclosure

Advisory board for

Roche
Tesaro
Merck
Astra Zeneca
Clovis Oncology

Institutional Research Support from

Pharma Mar, Clovis Oncology and Merck
The Global Burden of Cancer to Women Worldwide

- 9% of all new cancer cases (53 million new cases/year)
- 8% of total cancer deaths (27.5 million deaths/year)
- 85% of new cases and 87% of deaths occur in developing countries

CHEMOTHERAPY IN ADVANCED CERVICAL CANCER

- Radiosensitizer
- Neoadjuvant
- Exclusive
- Salvage treatment
February 1999 NCI Clinical announcement on concurrent chemo-radiation for cervical cancer

“.........strong consideration should be given to the incorporation of concurrent cisplatin based chemotherapy in women who require radiation for treatment of cervical cancer....”
### CONCURRENT CHEMORADIATION FOR CERVICAL CANCER: RESULTS OF FIVE RANDOMIZED TRIALS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Figo Stage</th>
<th>#pts</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 85</td>
<td>IIB- IVA</td>
<td>388</td>
<td>5FU and cisplatin vs Hydroxiurea + RT</td>
</tr>
<tr>
<td>RTOG 9001</td>
<td>IIB-IVA</td>
<td>390</td>
<td>5-FU and cisplatin + RT vs RT</td>
</tr>
<tr>
<td>GOG 120</td>
<td>IIB- IVA</td>
<td>526</td>
<td>CDDP vs 5FU, Cis, HY vs HY + RT</td>
</tr>
<tr>
<td>SWOG 8797</td>
<td>IA2, IB IIA</td>
<td>250</td>
<td>cisplatin -5-FU infusion + RT vs RT</td>
</tr>
<tr>
<td>GOG 123</td>
<td>IB Bulky</td>
<td>365</td>
<td>RT + weekly cisplatin, followed by surgery vs RT followed by surgery</td>
</tr>
</tbody>
</table>
Long-term complications in LACC patients submitted to chemoradiotherapy

- Sexual: 50%
- Bladder: 45%
- Bowel: 25%
- Others: 10%
Health-Related Quality of Life in Locally Advanced Cervical Cancer Patients After Definitive Chemoradiation Therapy Including Image Guided Adaptive Brachytherapy: An Analysis From the EMBRACE Study

744 pts
Concomitant CT/RT for cervical cancer: A meta-analysis using individual patient data (IPD) from randomised controlled trials
15 RCT’s, 3452 pts

**OS gain**
- 10%
- 7%
- 3%

**OS HR:** 0.81 Absolute 5 yrs OS improvement 6%
**DFS HR:** 0.78 Absolute 5 yrs DFS improvement 8%

Cochrane 2010
# Chemotherapy Plus Radiotherapy vs Radiotherapy

Cochrane Database Syst Rev: 2 trials; 368 pts

**Survival (OS)**
- HR: 0.56

**Progression-Free Survival (PFS)**
- HR: 0.47

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Rosa D et al 2014
OUTBACK

A Phase III trial of adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone

Primary Endpoint:
Overall Survival

Planned accrual = 900
INTERLACE – induction chemotherapy followed by standard chemoradiation vs standard chemoradiation alone in patients with locally advanced cervical cancer

Randomise

Carboplatin AUC2 & Paclitaxel 80mg/m²
Weeks 1-6

Standard CRT

Weeks 7-13
Standard CRT

Standard CRT: 40–50.4 Gy in 20-28 fractions plus Intracavitary brachytherapy to give total EQD2 dose of 78-86 Gy to point A/volume. Weekly cisplatin 40 mg/m² x 5 weeks
CHEMOTHERAPY IN ADVANCED CERVICAL CANCER

- RADIOSENSITIZER
- NEOADJUVANT
- EXCLUSIVE
- SALVAGE TREATMENT
NEOADJUVANT CHEMOTHERAPY

RATIONALE

NACT

- SHRINKAGE OF PRIMARY TUMOR
- TREATMENT OF LOCO-REGIONAL AND DISTANT MICROMETASTASES
- REDUCED RISK FACTORS AND IMPROVED NEGATIVE SURGICAL MARGINS
- BETTER DISEASE CONTROL
- REDUCED NEED FOR ADJUVANT TREATMENTS (about 30%)
- INCREASED OVERALL SURVIVAL (data inconsistency)
**Neoadjuvant Chemotherapy followed by surgery vs RT for Locally Advanced Cervical Cancer: a systematic review and meta-analysis of individual patient data from 5 randomised trials and 872 patients**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Nr. of events/patient</th>
<th>HR (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>368/872</td>
<td>0.65 (0.00004)</td>
</tr>
<tr>
<td>Loco-regional DFS</td>
<td>414/872</td>
<td>0.68 (0.0001)</td>
</tr>
<tr>
<td>Metastases-free survival</td>
<td>402/872</td>
<td>0.68 (0.0001)</td>
</tr>
<tr>
<td></td>
<td>381/872</td>
<td>0.63 (0.00001)</td>
</tr>
</tbody>
</table>

**Absolute OS improvement: 15%**

*Cochrane Database Syst Rev. 2007*
Abstract No. 3395 / 928O_PR

Neoadjuvant chemotherapy followed by surgery versus concomitant cisplatin and radiation therapy in patients with stage IB2, IIA or IIB squamous carcinoma of cervix: A randomized controlled trial

Sudeep Gupta, MD, DM, on behalf of

Pallavi Parab, Rajendra Kerkar, Umesh Mahantshetty, Amita Maheshwari, Supriya Sastri, Reena Engineer, Rohini Hawaldar, Jaya Ghosh, Seema Gulia, Swati Godbole, Neha Kumar, Malliga Jeyaraman, Renuka Dalvi, Yogesh Kembhavi, Madhuri Gaikar, Rohit Ranade, Hemant Tongaonkar, Rajendra Badwe and Shyam Shrivastava

Gynaecologic Oncology Group, Tata Memorial Centre, Mumbai

Funded by Tata Memorial Centre, Department of Atomic Energy, Government of India
Study Design

- Squamous carcinoma
- Stage IB2, IIA, or IIB
- ECOG 0-1
- No prior treatment
- Adequate hematological & renal function

Stratify by stage

Experimental
NACT X 3 cycles followed by surgery

N = 317

Control
Concurrent chemoradiation.

N = 318

- Planned cross-over from NACT-Surgery to CTRT
  - Unresectable disease after 2nd or 3rd cycle NACT
  - Intraoperative unresectability
  - Lymph node positive on frozen section intraoperative
- Postoperative adjuvant RT
  - T > 4 cm, LVI +, deep cervical stromal invasion, (any two)
- Postoperative adjuvant CTRT
  - LN +, parametrium +, surgical margin +, (any one)

- Neoadjuvant chemotherapy
  Paclitaxel (175 mg/m2) + Carboplatin: (AUC 5-6) every 3 weeks X 3 cycles
- Concomitant chemotherapy
  Cisplatin (40/m2/week) X 5 weeks
- Radiation therapy
  EBRT: 40 Gy/20 fr/5 weeks + HDR: 7Gy/5 application
Disease free survival in intention-to-treat population

Hazard ratio for relapse or death due to cancer: 1.38 (95% CI, 1.02-1.87); log-rank p=0.038

- **NACT + Surgery**: 5-year disease-free survival 69.3% (95% CI, 63.8 to 74.8)
- **CTRT**: 5-year disease-free survival 76.7% (95% CI, 71.6 to 81.8)

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months since Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>NACT + Surgery</td>
<td>316</td>
</tr>
<tr>
<td>CTRT</td>
<td>317</td>
</tr>
</tbody>
</table>
Overall survival in intention-to-treat population

Hazard ratio, 1.03 (95% CI, 0.75 -1.40)  
P=0.87

No. at Risk
NACT+Surgey  316  286  264  215  171  127  95  58
CTRT  317  297  277  223  176  120  86  60

Months since Randomization

Probability of Overall Survival
<table>
<thead>
<tr>
<th>Site</th>
<th>NACT-Surgery (N=316)</th>
<th>CTRT (N=317)</th>
<th>All (N=633)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal</td>
<td>7 (2.2%)</td>
<td>11 (3.5%)</td>
<td>17 (2.8%)</td>
<td>0.474</td>
</tr>
<tr>
<td>Bladder</td>
<td>5 (1.6%)</td>
<td>11 (3.5%)</td>
<td>16 (2.5%)</td>
<td>0.204</td>
</tr>
<tr>
<td>Vaginal</td>
<td>38 (12.0%)</td>
<td>81 (25.6%)</td>
<td>119 (18.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>17 (5.4%)</td>
<td>11 (3.5%)</td>
<td>28 (4.4%)</td>
<td>0.334</td>
</tr>
</tbody>
</table>
### Treatment in NACT-Surgery Group

<table>
<thead>
<tr>
<th>Surgical resection</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>227 (71·8%)</td>
</tr>
<tr>
<td>No</td>
<td>89 (28·2%)</td>
</tr>
</tbody>
</table>

#### Loco-regional treatment in NACT-surgery group *

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical resection</td>
<td>227 (71·8%)</td>
</tr>
<tr>
<td>Definitive CTRT</td>
<td>68 (21·5%)</td>
</tr>
<tr>
<td>Adjuvant CTRT</td>
<td>42 (13·3%)</td>
</tr>
<tr>
<td>Adjuvant RT</td>
<td>31 (9·8%)</td>
</tr>
</tbody>
</table>

- Numbers are more than group total because some surgical patients received adjuvant radiation or concomitant chemotherapy and radiotherapy.
## Subgroup Analysis for DFS

<table>
<thead>
<tr>
<th>Stage</th>
<th>NACT+surgery</th>
<th>CTRT</th>
<th>Hazard ratio (95% CI)</th>
<th>p value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB2</td>
<td>16/57</td>
<td>15/56</td>
<td></td>
<td>0.14</td>
</tr>
<tr>
<td>IIA</td>
<td>22/80</td>
<td>23/78</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>IIB</td>
<td>57/179</td>
<td>36/183</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Haemoglobin</th>
<th>NACT+surgery</th>
<th>CTRT</th>
<th>Hazard ratio (95% CI)</th>
<th>p value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;11</td>
<td>60/206</td>
<td>44/203</td>
<td></td>
<td>0.78</td>
</tr>
<tr>
<td>≤11</td>
<td>35/110</td>
<td>30/114</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pelvic lymph node status</th>
<th>NACT+surgery</th>
<th>CTRT</th>
<th>Hazard ratio (95% CI)</th>
<th>p value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>82/270</td>
<td>58/272</td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>Positive</td>
<td>13/46</td>
<td>16/45</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ECOG performance status</th>
<th>NACT+surgery</th>
<th>CTRT</th>
<th>Hazard ratio (95% CI)</th>
<th>p value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>30/290</td>
<td>71/293</td>
<td></td>
<td>0.79</td>
</tr>
<tr>
<td>1</td>
<td>5/26</td>
<td>3/24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All patients: 95/316 vs 74/317

Hazard ratio: NACT+surgery better than CTRT better.
EORTC prot.55994

Cervical Cancer
IB2; IIA>4cm; IIB

RANDOMIZATION

NACT + SURGERY

Exclusive Chemoradiation

Final OS data (primary end point): June 2019
CHEMOTHERAPY IN ADVANCED CERVICAL CANCER

- RADIOSENSITIZER
- NEOADJUVANT
- EXCLUSIVE
- SALVAGE TREATMENT
<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Stage</th>
<th>Patients (n)</th>
<th>Type study</th>
<th>Comparison</th>
<th>CT regimen</th>
<th>CT cycles (n)</th>
<th>F/U time (y)</th>
<th>DF adjuvant (%)</th>
<th>First recurrence (%)</th>
<th>OS (%)</th>
<th>BRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sardi et al. (1998)</td>
<td>Ib-IIa</td>
<td>56</td>
<td>P</td>
<td>NACT + RS + CT</td>
<td>CDDP 50 mg/m² + methotrexate 30 mg/m² + cyclophosphamide 500 mg/m²</td>
<td>3</td>
<td>6</td>
<td>88.7 (&gt;4 cm)</td>
<td>19</td>
<td>67.7 (&gt;4 cm)</td>
<td>None</td>
</tr>
<tr>
<td>Lai et al. (1989)</td>
<td>Ib-IIb</td>
<td>388 (172 high risk)</td>
<td>P</td>
<td>RS + CT</td>
<td>PV8</td>
<td>3</td>
<td>75% for high risk</td>
<td>12.5</td>
<td>-</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Iwasaka et al. (1994)</td>
<td>Ib-IIb</td>
<td>101 (53 high risk)</td>
<td>P</td>
<td>RS + CT</td>
<td>PVM</td>
<td>5</td>
<td>-</td>
<td>24</td>
<td>89.1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Lahousen et al. (1999)</td>
<td>Ib-IIb</td>
<td>76 high risk</td>
<td>R</td>
<td>RS + CT</td>
<td>CDDP 40 mg/m² + BLM 30 mg</td>
<td>6</td>
<td>5</td>
<td>10</td>
<td>84</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Takeshima et al. (2006)</td>
<td>Ib-IIa</td>
<td>65 (35 high risk)</td>
<td>P</td>
<td>RS + CT</td>
<td>PVM</td>
<td>4</td>
<td>5</td>
<td>85.7</td>
<td>14.3</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Mossa et al. (2010)</td>
<td>Ib-IIa</td>
<td>127</td>
<td>P</td>
<td>RS + CT</td>
<td>PV8</td>
<td>3</td>
<td>10</td>
<td>59.8</td>
<td>40.2</td>
<td>69.3</td>
<td>Yes</td>
</tr>
<tr>
<td>Hosaka et al. (2012)</td>
<td>Ib-IIB</td>
<td>125</td>
<td>RTP</td>
<td>RS + CT</td>
<td>CDDP 50 mg/m² + paclitaxel 135 mg/m²</td>
<td>6</td>
<td>3</td>
<td>78.1</td>
<td>30</td>
<td>92.8</td>
<td></td>
</tr>
<tr>
<td>Gong et al. (2012)</td>
<td>Ib2-IIB</td>
<td>414 (202 CT adj)</td>
<td>RTP</td>
<td>NACT + RS + CT</td>
<td>BP or FIP</td>
<td>3</td>
<td>2</td>
<td>83</td>
<td>-</td>
<td>95.5</td>
<td>None</td>
</tr>
<tr>
<td>Angioli et al. (2012)</td>
<td>Ib-IIb</td>
<td>115</td>
<td>RTP</td>
<td>NACT + RS + CT</td>
<td>TP</td>
<td>3</td>
<td>5</td>
<td>70</td>
<td>16</td>
<td>81</td>
<td>None</td>
</tr>
</tbody>
</table>
CHEMOTHERAPY IN ADVANCED CERVICAL CANCER

- RADIOSENSITIZER
- NEOADJUVANT
- EXCLUSIVE
- SALVAGE TREATMENT
# Recurrent and Metastatic Cervical Cancer

## Systemic Treatment

<table>
<thead>
<tr>
<th>Trial (year)</th>
<th>n</th>
<th>Regimen</th>
<th>OS, months</th>
<th>PFS, months</th>
<th>RR, %</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG-0169</td>
<td>264</td>
<td>Cisplatin</td>
<td>8.8</td>
<td>2.8</td>
<td>19</td>
<td>Improvement in ORR and PFS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cisplatin + paclitaxel</td>
<td>9.7</td>
<td>4.8</td>
<td>22</td>
<td>No significant OS improvement</td>
</tr>
<tr>
<td>GOG-0179</td>
<td>364</td>
<td>Cisplatin</td>
<td>6.5</td>
<td>2.9</td>
<td>13</td>
<td>Supports cisplatin-topotecan label</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cisplatin + topotecan</td>
<td>9.4</td>
<td>4.6</td>
<td>27</td>
<td>Some argue that OS in the cisplatin-control arm was low due to high radiotherapy-cisplatin use</td>
</tr>
<tr>
<td>GOG-0204</td>
<td>513</td>
<td>Cisplatin + paclitaxel</td>
<td>12.9</td>
<td>5.8</td>
<td>29</td>
<td>Study consolidated cisplatin-paclitaxel as SoC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cisplatin + topotecan</td>
<td>10.3</td>
<td>4.6</td>
<td>23</td>
<td>No other combination was better</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cisplatin + gemcitabine</td>
<td>10.3</td>
<td>4.7</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cisplatin + vinorelbine</td>
<td>10.0</td>
<td>4.0</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>JGOG-0505</td>
<td>253</td>
<td>Cisplatin + paclitaxel</td>
<td>18.3</td>
<td>6.9</td>
<td>n/a</td>
<td>Carboplatin-paclitaxel was non-inferior to cisplatin-paclitaxel in overall population</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carboplatin + paclitaxel</td>
<td>17.5</td>
<td>6.2</td>
<td>n/a</td>
<td>For patients who had not received prior platinum, OS was better with cisplatin-paclitaxel</td>
</tr>
</tbody>
</table>

Phase III Trial of Four Cisplatin-Containing Doublet Combinations in Stage IVB, Recurrent, or Persistent Cervical Carcinoma: A Gynecologic Oncology Group Study

Bradley J. Monk, Michael W. Sill, D. Scott McMeekin, David E. Cohn, Lois N. Ramondetta, Cecelia H. Boardman, Jo Benda, and David Cella

Median PFS 5.5 months
Median OS 12 months
Paclitaxel Plus Carboplatin Versus Paclitaxel Plus Cisplatin in Metastatic or Recurrent Cervical Cancer: The Open-Label Randomized Phase III Trial JCOG0505

Ryo Kitagawa, Noriuki Katsumata, Taro Shibata, Toshiharu Kamura, Takahiro Kasamatsu, Toru Nakanishi, Sadako Nishimura, Kimio Ushijima, Masashi Takano, Toyomi Satoh, and Hiroyuki Yoshikawa

<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 1.35</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>Microscopic 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>1.89</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>0.36 to 1.41</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>

A: Overall Survival (probability)

B: Progression-Free Survival (probability)
Recurrent and Metastatic Cervical Cancer
Systemic Treatment: How to improve beyond Platinum Doublets?

1. Anti-Angiogenesis Therapy:
   • The role of Anti-VEGF(Bevacizumab): GOG#240

2. Immunotherapy: Next Frontier
   • Checkpoint inhibitors: Anti-PD1/PD-L1
Rationale for Targeting VEGF in Treatment of Cervical Cancer

• Angiogenesis is critical in tumor growth and survival and has been generally considered a very attractive target for cancer therapy.

• Overexpression of VEGF has been associated with tumor progression and poor prognosis in several tumors, including cervical cancer.

• More specifically, intratumoral protein levels of VEGF have been shown to be increased in cervical cancer compared to normal cervical tissue, and higher VEGF levels correlate with higher stage increased risk of lymph nodes metastasis, poor disease-free and overall survival.


GOG 240: Disegno dello studio

Carcinoma of the cervix
• Primary stage IVB
• Recurrent/persistent
• Measureable disease
• GOG PS 0–1
• No prior chemotherapy for recurrence (N=452)

Randomize

I
Paclitaxel 135 or 175 mg/m² IV
Cisplatin 50 mg/m² IV

II
Paclitaxel 135 or 175 mg/m² IV
Cisplatin 50 mg/m² IV
Bevacizumab 15 mg/kg IV

III
Paclitaxel 175 mg/m² IV
Topotecan 0.75 mg/m² d1-3
Bevacizumab 15 mg/kg IV

IV
Paclitaxel 175 mg/m² IV
Topotecan 0.75 mg/m² d1-3
Bevacizumab 15 mg/kg IV

Q21d Rx to PD, toxicity, CR

Chemo alone

Chemo + Bev
GOG 240: Interim Analysis

- Topotecan + paclitaxel shown to not be superior or inferior to cisplatin + paclitaxel

<table>
<thead>
<tr>
<th></th>
<th>Cis + Pac (n= 229)</th>
<th>Topo + Pac (n= 223)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>81 (35)</td>
<td>93 (42)</td>
</tr>
<tr>
<td>Median OS, mos</td>
<td>15</td>
<td>12.5</td>
</tr>
<tr>
<td>HR=1.20 (98.74% CI; 0.82–1.76)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P$ (one-sided)=0.880</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
GOG 240: PFS 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>184 (82)</td>
<td>183 (81)</td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>5.9</td>
<td>8.2</td>
</tr>
<tr>
<td>HR</td>
<td>0.67 (95% CI, 0.54-0.82)</td>
<td>2-sided P=0.0002</td>
</tr>
<tr>
<td>2-sided</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR, %</td>
<td>36 (CR, n=14)</td>
<td>48 (CR, n=28)</td>
</tr>
<tr>
<td>2-sided</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.00807</td>
<td></td>
</tr>
</tbody>
</table>

5th ESO-ESMO Latin American Masterclass in Clinical Oncology
GOG 240: OS for Chemo vs Chemo + Bev

**Chemotherapy**
(n=225)

**Chemotherapy + Bev**
(n=227)

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>140 (62)</th>
<th>131 (58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mos</td>
<td>13.3</td>
<td>17.0</td>
</tr>
</tbody>
</table>

HR=0.71 (97% CI, 0.54-0.94)

*P*=0.0035

Median follow-up 20.8 mos

Presented by: Krishnansu S. Tewari, MD, FACOG, FACS
GOG 240: Eventi Avversi di particolare interesse

<table>
<thead>
<tr>
<th>Adverse Event, n (%)</th>
<th>Chemo Alone (n=219)</th>
<th>Chemo + Bev (n=220)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment cycles, median (range)</td>
<td>6 (0-30)</td>
<td>7 (0-36)</td>
</tr>
<tr>
<td>Grade 5 AE(s)</td>
<td>4 (1.8)</td>
<td>4 (1.8)</td>
</tr>
<tr>
<td>GI events, non-fistula (grade ≥2)</td>
<td>96 (44)</td>
<td>114 (52)</td>
</tr>
<tr>
<td>GI fistula (grade ≥3)*</td>
<td>0 (0)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>GI perforation (grade ≥3)</td>
<td>0 (0)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>GU fistula (grade ≥3)*</td>
<td>1 (0)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Hypertension (grade ≥2)*</td>
<td>4 (2)</td>
<td>54 (25)</td>
</tr>
<tr>
<td>Proteinuria (grade ≥3)</td>
<td>0 (0)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Pain (grade ≥2)</td>
<td>62 (28)</td>
<td>71 (32)</td>
</tr>
<tr>
<td>Neutropenia (grade ≥4)*</td>
<td>57 (26)</td>
<td>78 (35)</td>
</tr>
<tr>
<td>Febrile neutropenia (grade ≥3)</td>
<td>12 (5)</td>
<td>12 (5)</td>
</tr>
<tr>
<td>Thromboembolism (grade ≥3)*</td>
<td>3 (1)</td>
<td>18 (8)</td>
</tr>
<tr>
<td>Bleeding CNS (any grade)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Bleeding GI (grade ≥3)</td>
<td>1 (0)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Bleeding GU (grade ≥3)</td>
<td>1 (0)</td>
<td>6 (3)</td>
</tr>
</tbody>
</table>

*p<0.05
Patients receiving bevacizumab reported 1.2 points lower on average (not significant)

98.75% CI -4.1 – 1.7

P=0.3

Assessment Time

Score

Pre-cycle 1  Pre-cycle 2  Pre-cycle 5  5 mos post cycle 1  9 mos post cycle 1


Presented at ASCO 2013 by: Krishnansu S. Tewari, MD, FACOG, FACS

bradley.monk@chw.edu
Progress in Survival in Advanced and Recurrent Cervical Cancer

- GOG 64 Cisplatin
- GOG 110 Cisplatin + Ifosfamide
- GOG 149 Cisplatin + Ifosfamide + Bleomycin
- GOG 169 Cisplatin + Palitaxel
- GOG 179 Cisplatin + Topotecan
- GOG 240 Cisplatin + Palcitaxel + Bevacizumab

Year:

Months:
0, 2, 4, 6, 8, 10, 12, 14, 16, 18
2. Immunotherapy: The Next Frontier
Anti-programmed death (PD)-1 therapy for cervical cancer

Rationale

- Human papillomavirus (HPV) infection is the cause of more than 90% of cervical cancers
- PD-L1 has been shown to be a solid biomarker of HPV infection of the cervix
- PD-L1 is significantly up-regulated in cervical cancer and detectable by immunohistochemistry in tumor cells:
  - Squamous Cervical cancer between 54%- 80% according to different series
  - Adenocarcinoma: 14%
- PD-L1 expression reduces the immune response since it is able to bind to PD1 on T lymphocytes, thereby inhibiting their function.
- These findings suggest that targeting the PD-1/PD-L1 pathway may be therapeutically effective and should be considered in the treatment of cervical cancer patients.

KEYNOTE-158:
Phase II basket study, single-agent pembrolizumab, cervical cancer cohort

- **Key eligibility criteria**:
  - ECOG: 0 or 1
  - Advanced cervical squamous carcinomas on progression or intolerance to ≥1 line of standard therapy
- **Main Demographics and Disease Characteristics**:
  - 65% ≥2 prior therapies for recurrent/metastatic CC
  - 84% PD-L1-positive; 77/98 (79%) had CPS ≥1*
- **Treatment**: pembrolizumab 200 mg once every 3 weeks (Q3W) for 2 years or until disease progression, intolerable toxicity, patient withdrawal, or investigator decision

**Primary endpoint**: IRC-assessed ORR (RECIST v1.1)

**Secondary endpoints**: DoR, IRC-assessed PFS, OS, safety

<table>
<thead>
<tr>
<th>Response</th>
<th>All patients (n=98)</th>
<th>PD-L1 positive (n=82)</th>
<th>PD-L1-negative (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>12.2%</td>
<td>14.6% (8–24)</td>
<td>0% (0–22)</td>
</tr>
<tr>
<td>CR</td>
<td>3%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>PR</td>
<td>9%</td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td>SD</td>
<td>18%</td>
<td>18%</td>
<td>20%</td>
</tr>
</tbody>
</table>

*CPS (Combined Positive Score): number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100

- **Median time to response**: 2.1 months (range 1.6–4.1)
- **Median DoR**: not reached (range 3.7+–18.6+)
- Six out of 12 responses ongoing at data cut-off

Hyun Cheol Chung et al; J Clin Oncol 36, 2018 (suppl; abstr 5522)  
ClinicalTrials.gov:NCT02628067
KEYNOTE-158: Phase II basket study, single-agent pembrolizumab, cervical cancer cohort: Outcomes (cont’d)

- At data cut-off (median follow-up 10.2 months): PFS events in 86%, OS events in 69%

FDA approval (June 2018): patients with recurrent or metastatic cervical cancer who had progressed on or after platinum-based chemotherapy and whose tumors express CPS ≥1 as determined by an FDA-approved test.

Overall Survival (OS)
- mOS: 9.4 months (95% CI 7.7–13.1)
- 6-month OS rate: 75%

CPS (Combined Positive Score): number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.
CHECKMATE-358
Single-agent nivolumab in virus-associated tumours

- CheckMate 358 (NCT02488759) is an ongoing, open-label phase 1/2, multicohort study
  - Eligibility
    - CheckMate 358
      - SCC of the cervix, vagina or vulva
        - Eligible tumor types
          - EBV+ gastric carcinoma
          - HPV+ SCCHN
        - Key eligibility criteria
          - ≤2 prior treatments for R/M disease
          - ≥1 target lesion
          - ECOG PS: 0–1
          - PD-L1 unselected
  - Treatment
    - Nivolumab 240 mg Q2W until progression or unacceptable toxicity
  - Assessments
    - Imaging Q8W for the first year of treatment
      - Imaging Q12W thereafter
  - Follow-up
    - Minimum follow-up: 12 weeks
      - Survival follow-up
    - Primary endpoints: ORR
      - Secondary endpoints: DOR, PFS, OS
  - Enrollment dates: October 2015 to February 2016
  - Data cutoff: July 2016 (median follow-up: 31 weeks)

Max treatment duration: 2 years


ClinicalTrials.gov: NCT02488759
CHECKMATE-358: Single-agent nivolumab in virus-associated tumours

1º End-Point: Overall Response Rates (ORR)

<table>
<thead>
<tr>
<th></th>
<th>All patients (N = 24)</th>
<th>Cervical (n = 19)</th>
<th>Vaginal/Vulvar (n = 5)</th>
<th>0 prior systemic therapies in R/M setting (n = 7)</th>
<th>≥1 prior systemic therapies in R/M setting (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best overall response</strong>, n (%)</td>
<td>Complete response</td>
<td>1 (4.2)</td>
<td>1 (5.3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Partial response</td>
<td>4 (16.7)</td>
<td>4 (21.1)</td>
<td>0</td>
<td>2 (28.6)</td>
</tr>
<tr>
<td></td>
<td>Stable disease</td>
<td>12 (50.0)</td>
<td>8 (42.1)</td>
<td>4 (80.0)</td>
<td>3 (42.9)</td>
</tr>
<tr>
<td></td>
<td>Progressive disease</td>
<td>7 (29.2)</td>
<td>6 (31.6)</td>
<td>1 (20.0)</td>
<td>2 (28.6)</td>
</tr>
<tr>
<td><strong>ORR, n (%)</strong></td>
<td></td>
<td>5 (20.8)</td>
<td>3 (26.3)</td>
<td>0</td>
<td>2 (28.6)</td>
</tr>
<tr>
<td>[95% CI]</td>
<td></td>
<td>[7.1, 42.2]</td>
<td>[9.1, 51.2]</td>
<td>[0.0, 52.2]</td>
<td>[3.7, 71.0]</td>
</tr>
<tr>
<td><strong>Disease control rate</strong>, n (%)</td>
<td></td>
<td>17 (70.8)</td>
<td>13 (68.4)</td>
<td>4 (80.0)</td>
<td>5 (71.4)</td>
</tr>
<tr>
<td><strong>Duration of response, median (range), months</strong></td>
<td></td>
<td>NR (0.0–5.8+)</td>
<td>NR (0.0–5.8+)</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

ClinicalTrials.gov: NCT02488759
CHECKMATE-358: Single-agent nivolumab in virus-associated tumours

2º End-Point: Progression Free Survival (PFS) and Overall Survival (OS)

Median PFS (95%CI): 5.5 months (3.5-NR)

Median OS: NR
6-months OS rate: 87.1%

NR: Not Reached

ClinicalTrials.gov: NCT02488759

Cemiplimab Phase I First-in-Human (FIH) Study

Cemiplimab (REGN2810) is a high-affinity, highly potent, human monoclonal antibody directed against PD-1

- **Phase I data N=60 patients** presented at ASCO 2016:
  - Monotherapy as well as in combination with hypofractionated radiation
  - **Safety**: No DLTs. Most common related AEs were fatigue (28%), arthralgia (12%), nausea/vomiting (12%), flu-like illness (8%), and rash (8%)
  - **Efficacy**: Overall response rate **18.6%** in dose escalation
  - 3 mg/kg REGN2810 every two weeks selected for further study

- FDA /EMA approved cemiplimab for the treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or who are not candidates for surgery

Recurrent and/or metastatic cervical cancer progressed after platinum-based chemotherapy given to treat recurrent or metastatic cervical cancer

N=436

Investigators’ choice

Options:
- Antifolate: Pemetrexed
- Nucleoside analogue: Gemcitabine
- Topoisomerase 1 inhibitor: Topotecan or Irinotecan
- Vinca Alkaloid: Vinorelbine

Cemiplimab

- Primary Endpoint: OS
- Secondary Endpoints: PFS, ORR

Statistical Considerations for Study Design

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power</td>
<td>90%</td>
</tr>
<tr>
<td>Median Survival</td>
<td>7 mos.</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.7</td>
</tr>
<tr>
<td>Timing of Final Anal. (Ha)</td>
<td>30.5 mos.</td>
</tr>
</tbody>
</table>

Cemiplimab 350 mg IV every 3 weeks

All treatment regimens are for up to 96 weeks, with option for re-treatment

GOG PI: K. Tewari
ENGOT PI on behalf of GEICO: A. Oaknin

Actively Recruiting: N= 205 pts enrolled so far

ClinicalTrials.gov:NCT03257267
BEATcc Trial: ENGOT-Cx10 / GEICO 68-C /GOG#3030/ JGOG1084

This is a phase III, randomized, open-label, multi-center study to assess the efficacy of Atezolizumab administered concurrent to the combination of Cisplatin and Paclitaxel plus Bevacizumab in previously untreated patients with metastatic (stage IVB), persistent, or recurrent carcinoma of the cervix.

- This study is designed to test the hypothesis that breaking of immune tolerance by PD-1/PD-L1 blockade will enhance the efficacy of anti-VEGF therapy in the treatment of patients with metastatic, persistent or recurrent cervical cancer.

Global PI: Ana Oaknin, MD PhD on behalf of GEICO

ClinicalTrials.gov Identifier: NCT03556839
Primary Stage IVB, persistent or recurrent carcinoma of the cervix

- Measurable disease by RECIST v1.1
- ECOG-PS: 0-1
- No previous systemic chemotherapy for advanced or recurrent disease
- N=404 pts

Control Arm

Cisplatin + paclitaxel + bevacizumab
(GOG#240) until disease progression, unacceptable toxicity, death or withdrawal of consent

Experimental Arm

Cisplatin + paclitaxel + bevacizumab + atezolizumab
until disease progression, unacceptable toxicity, death or withdrawal of consent

Primary Endpoint:
Overall survival (OS)

Secondary Endpoints:
- PFS
- ORR
- DOR
- Safety
- HR-QOL

Stratification Factors:
- Prior concurrent Cisplatin-RDT
- Histology: SCC vs ADK (including AdenoSquamous)
- Chemotherapy Backbone: Cisplatin vs Carboplatin

Safety run-in cohort: First 12 patients after 2 cycles of treatment

ClinicalTrials.gov Identifier: NCT03556839

A tumor specimen is mandatory at study entry. This may be an archival biopsy or, in its absence, a tumor biopsy obtained within 3 months of randomization from a non-irradiated lesion.
KEYNOTE-826:
Efficacy and Safety Study of First-line Treatment With Pembrolizumab (MK-3475) Plus Chemotherapy Versus Placebo Plus Chemotherapy in Women With Persistent, Recurrent, or Metastatic Cervical Cancer

Investigator choice of chemotherapy:
- Paclitaxel 175 mg/m² + cisplatin 50 mg/m² +/- BEV OR
- Paclitaxel 175 mg/m² + carboplatin AUC 5 +/- BEV
  + placebo on d1 Q3W

Up to 35 cycles

Actively Recruiting

Co-primary endpoints: PFS, OS
Secondary endpoints:
- ORR and DoR
- 12-month PFS
- Safety
- QoL

ClinicalTrials.gov: NCT03635567
CONCLUSIONS

- Cervical Cancer still represents a burden in terms of incidence and mortality particularly in developing countries.

- Role of chemotherapy is evolving over time:
  - Radiosensitizer
  - Neoadjuvant
  - Exclusive
  - Metastatic Disease

- The best treatment in locally advanced disease (CHT-RT vs NACHT+S) need to be addressed.

- Bevacizumab is the only treatment able to increase OS during the last 20 years in the metastatic setting.

- Immunotherapy promising.