TARGETED THERAPY IN CERVICAL CANCER

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CREIGHTON UNIVERSITY SCHOOL OF MEDICINE AT ST. JOSEPH’S HOSPITAL AND MEDICAL CENTER, A DIGNITY HEALTH MEMBER
UNIVERSITY OF ARIZONA CANCER, ARIZONA USA

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Verbal Disclosure

• My institution has received grants for me from Amgen, Genentech, Eli Lilly, Array, TESARO Inc., Morphotek, and Janssen/Johnson & Johnson.
• I have received honoraria for speakers’ bureaus from Genentech, Roche, AstraZeneca, Myriad, and Janssen/Johnson & Johnson.
• I have received honoraria for my consulting with Merck, TESARO Inc., Gradalis, Advaxis, Amgen, Bayer, Insys, Clovis, Mateon (formally OxiGENE), Roche, Genentech, AstraZeneca, Pfizer and PPD.

• I agree that content of this presentation will be well balanced, unbiased, and evidence-based. Opinions that are not supported by evidence, or are supported by limited or preliminary evidence will be so identified.
Recurrent/Persistent and Metastatic Disease: A HIGH UNMET CLINICAL NEED!
HPV Infection + Angiogenesis = Progressive Cervical Neoplasia

Transient infection

<table>
<thead>
<tr>
<th>Normal</th>
<th>Precancerous, potential to regress or persist to severe disease</th>
<th>Invasive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>CIN 1,2</td>
<td>CIN 2,3¹</td>
</tr>
<tr>
<td>HPV infection</td>
<td>CIN 1,2</td>
<td>CIN 2,3¹</td>
</tr>
<tr>
<td>7-10 years¹</td>
<td>≥10 years²</td>
<td></td>
</tr>
</tbody>
</table>

Colposcopy demonstrates abnormal vasculature and angiogenesis dependent progression of cervical neoplasia

CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus

Complete Remission of Metastatic Cervical Cancer With the Angiogenesis Inhibitor TNP-470

Potent fungal metabolite first isolated from *Aspergillus fumigatus* with anti-angiogenesis properties

The Angiogenesis Map

**Anti-VEGF Out Performs Anti-EGF**

**Progression-free survival (PFS): ITT**

<table>
<thead>
<tr>
<th>Median PFS, weeks</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapatinib</td>
<td>17.1</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>18.1</td>
</tr>
</tbody>
</table>

**HR (90% CI)**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.66</td>
</tr>
<tr>
<td>(90% CI)</td>
<td>(0.48,0.91)</td>
</tr>
</tbody>
</table>

**P value**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>P value</td>
<td>P = .013</td>
</tr>
</tbody>
</table>

**The CI are 90% (alpha = 10%) naïve CIs. *Wald normal approximation is used to calculate the 1-sided P value. ***Stratified log-rank P value and hazard ratio (Pike) adjusted only for one of the stratification factors – prior chemotherapy.**

VEGF, vascular endothelial growth factor; EGF, epidermal growth factor; ITT, intent-to-treat

Anti-VEGF Out Performs Anti-EGF

Maximum decrease in target lesion diameter: Lapatinib vs Pazopanib

GOG 227C
Phase II Bevacizumab, Recurrent Cervical Cancer

PFS of Bev versus GOG historical database (failing one or two cytotoxic regimens, not including chemo-radio-therapy (RT))

GOG 227C
Phase II Bevacizumab, Recurrent Cervical Cancer

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

Stratification factors:
• Stage IVB vs recurrent/persistent disease
• Performance status
• Prior cisplatin Rx as radiation-sensitizer

1:1:1:1

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 (Topo) 0.75 mg/m² d1-3

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

q21d Rx to PD, toxicity, CR

CR, complete response; PD, progressive disease; PS, performance status; q21d, every 21 days; Rx, treatment

United States, Canada & Spain

Activated: 4/6/09
Closed to accrual: 1/3/12

GOG 240: Publications

- GOG 240.1: Non-platinum chemotherapy backbone.  
- GOG 240.5: Circulating tumor cells.  
- GOG 240.6: Prognostic significance of smoking.  
- GOG 240.7: Mature survival.  
- GOG 240.8: Prognostic significance tumor histology.  
- GOG 240.9: Fistula data.  
- GOG 240.10: Complete responder data.  
Phase III Randomized Clinical Trial of Cisplatin Plus Paclitaxel vs the Non-Platinum Chemotherapy Doublet of Topotecan Plus Paclitaxel in Women With Recurrent, Persistent, or Metastatic Cervical Carcinoma: A Gynecologic Oncology Group Study

KS Tewari, M Sill, HJ Long III, L Ramondetta, L Landrum, A Oaknin, T Reid, M Leitao, H Michael, BJ Monk

Presented at: The Society of Gynecologic Oncology’s (SGO) 2013 Annual Meeting on Women’s Cancer
Abstract 1

SGO Presidential Award for Most Outstanding Scientific Abstract
Hugh Barber Lectureship Designation
GOG 240.1: Schema

Carcinoma of the cervix
- Primary stage IVB
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Activated: 4/6/09
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United States, Canada & Spain

Cis-paclitaxel backbone

Topotecan-paclitaxel backbone

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

## GOG 240.1: Results
Demographics & Treatment Allocation

<table>
<thead>
<tr>
<th></th>
<th>Cis + Pac Backbone</th>
<th>Topo + Pac Backbone</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>46 (20-85)</td>
<td>48 (22-82)</td>
<td>NS</td>
</tr>
<tr>
<td>Squamous</td>
<td>71%</td>
<td>67%</td>
<td>.308</td>
</tr>
<tr>
<td>Adenocarcinoma, unspecified</td>
<td>20%</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>78%</td>
<td>77%</td>
<td>.800</td>
</tr>
<tr>
<td>African American</td>
<td>13%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>5%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>0.4%</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Recurrent</td>
<td>75%</td>
<td>69%</td>
<td>.298</td>
</tr>
<tr>
<td>Persistent</td>
<td>9%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Advanced</td>
<td>16%</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>PS 0</td>
<td>57%</td>
<td>59%</td>
<td>.703</td>
</tr>
<tr>
<td>PS 1</td>
<td>43%</td>
<td>41%</td>
<td></td>
</tr>
<tr>
<td>Prior platinum</td>
<td>76%</td>
<td>74%</td>
<td>.666</td>
</tr>
<tr>
<td>TOTAL</td>
<td>229</td>
<td>223</td>
<td>NS</td>
</tr>
</tbody>
</table>

GOG 240.1: Results
Planned Interim Analysis

• February 2012
  – 174 deaths

• NCI DSMB convened
  – Recommended release of topotecan plus paclitaxel data
  – ‘Dear Investigator’ and ‘Dear Patient’ letters drafted
GOG 240.1: Interim Analysis SGO 2013
Overall Survival: Cis-Pac Backbone vs Topo-Pac Backbone

- February 2012 study results released comparing non-platinum doublet vs platinum-doublet
  - 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, months</td>
<td>15</td>
<td>12.5</td>
</tr>
<tr>
<td>HR</td>
<td>1.20 (98.74% CI, 0.82-1.76)</td>
<td></td>
</tr>
<tr>
<td>P (1-sided)</td>
<td>.880</td>
<td></td>
</tr>
</tbody>
</table>

Incorporation of Bevacizumab in the Treatment of Recurrent and Metastatic Cervical Cancer

GOG 240: A Phase III Randomized Trial of the Gynecologic Oncology Group


Presented at: ASCO Annual Meeting 2013
Abstract 3
Carcinoma of the cervix
• Primary stage IVB
• Recurrent/persistent
• Measureable disease
• GOG PS 0-1
• No prior chemotherapy for recurrence (N = 452)

Stratification factors:
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Cisplatin 50 mg/m² IV
Paclitaxel 175 mg/m² IV
Topotecan 0.75 mg/m² d1-3
Paclitaxel 175 mg/m² IV
Topotecan 0.75 mg/m² d1-3
Bevacizumab 15 mg/kg IV
Bevacizumab 15 mg/kg IV

q21d Rx to PD, toxicity, CR
Chemo alone
Chemo + Bev

Activated: 4/6/09
Closed to accrual: 1/3/12
United States, Canada & Spain

GOG 240.2: Second Interim Analysis
OS for Chemo vs Chemo + Bev

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy (n = 225)</th>
<th>Chemotherapy + Bev (n = 227)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>140 (62)</td>
<td>131 (58)</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>13.3</td>
<td>17.0</td>
</tr>
<tr>
<td>HR</td>
<td>0.71 (97% CI, 0.54-0.94)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>.0035</td>
<td></td>
</tr>
</tbody>
</table>

Median follow-up 20.8 months

GOG 240.2: Second Interim Analysis
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, months</td>
<td>5.9</td>
<td>8.2</td>
</tr>
<tr>
<td>HR = 0.67 (95% CI, 0.54-0.82)</td>
<td>2-sided $P = .0002$</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 $P = .00807$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### GOG 240.2: Treatment Exposure and Specific Adverse Events (AEs)

<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><strong>GI fistula (grade ≥3)</strong></td>
<td>0 (0)</td>
<td>7 (3)</td>
</tr>
<tr>
<td><strong>GI perforation (grade ≥3)</strong></td>
<td>0 (0)</td>
<td>5 (2)</td>
</tr>
<tr>
<td><strong>GU fistula (grade ≥3)</strong></td>
<td>1 (0)</td>
<td>6 (2)</td>
</tr>
<tr>
<td><strong>Hypertension (grade ≥2)</strong></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><strong>Neutropenia (grade ≥4)</strong></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><strong>Thromboembolism (grade ≥3)</strong></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<.05

GOG 240: Bevacizumab Increased the Risk of Vaginal Fistulae

In a separate analysis of the GOG 240 study, all fistulae events were re-graded, and the results showed that:

- None of the fistulae were associated with peritonitis, sepsis or death. Among the patients who developed GI-vaginal fistulae, all (100%) had received prior pelvic radiation therapy compared to 80% in the overall population.

CT, chemotherapy; GI, gastrointestinal; GU, genitourinary
Improved Survival with Bevacizumab in Advanced Cervical Cancer

Krishnansu S. Tewari, M.D., Michael W. Sill, Ph.D., Harry J. Long III, M.D., Richard T. Penson, M.D., Helen Huang, M.S., Lois M. Ramondetta, M.D., Lisa M. Landrum, M.D., Ana Oaknin, M.D., Thomas J. Reid, M.D., Mario M. Leitao, M.D., Helen E. Michael, M.D., and Bradley J. Monk, M.D.

Abstract

CIRCCa: (Cediranib In Recurrent Cervical Cancer)

A Randomised Double Blind Phase II Trial of Carboplatin-Paclitaxel Plus Cediranib Versus Carboplatin-paclitaxel Plus Placebo in Metastatic/Recurrent Cervical Cancer

P Symonds, C Gourley, S Davidson, C West, C Dive, J Paul, K Carty, E McCartney, D Rai, S Banerjee, D Jackson, R Lord, M McCormack, E Hudson, N Reed, M Flubacher, P Jankowska, M Powell
Cedirinib—Randomized Phase II
Recurrent Cervical Cancer

**Design**
Randomized double-blind phase II. Patients randomized (1:1) to:

- **Cediranib** 20 mg daily or matched **Placebo**
  *in combination with Carboplatin AUC5 + Paclitaxel 175 mg/m² 3 weekly (max 6 cycles) and then until progression/lack of tolerability*

**Primary Endpoint**
PFS

<table>
<thead>
<tr>
<th>Response Rate</th>
<th>CR (9.4%)</th>
<th>PR (56.3%)</th>
<th>Overall (80% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cediranib</td>
<td>3</td>
<td>18</td>
<td>66% (53% to 77%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>0 (0.0%)</td>
<td>13 (41.9%)</td>
<td>42% (30% to 55%)</td>
</tr>
</tbody>
</table>

\[ P \ (1\text{-sided}) \text{-} .030 \]

**Median change in log_{10} VEGFR-2 from baseline at 28 days**

- **Cediranib**: -0.036 (iqr* -.097 to .048, n = 18)
- **Placebo**: 0.067 (iqr* .016 to .134, n = 22) *interquartile range

\[ P \ (1\text{-sided}) <.001 \]

Cedirinib—PFS

Immunotherapy: The Next Frontier

HPV-Targeted Tumor-Infiltrating Lymphocytes for Metastatic Cervical Cancer

Presenting Author: Christian S. Hinrichs

Sanja Stevanović, Lindsey Draper, Robert Somerville, John Wunderlich, Nicholas P. Restifo, Richard Sherry, Giao Q. Phan, Udai S. Kammula, James C. Yang, Steven A. Rosenberg; National Cancer Institute, Bethesda, MD

Abstract LBA3008 (ASCO 2014)

Treatment Schema for HPV-Targeted Tumor-Infiltrating Lymphocytes (HPV-TIL)

1. Tumor excision
2. T cells cultured from tumor fragments
3. Testing for E6 and E7 reactivity
4. T cell rapid expansion
5. Cyclophosphamide 60 mg/Kg x 2 + fludarabine 25 mg/m² x 5 followed by aldesleukin
6. T cell infusion

## Patient Characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Histology</th>
<th>HPV Type</th>
<th>Prior Systemic Therapy</th>
<th>Cell Dose (x10⁹)</th>
<th>Response (Duration in Months)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>Adeno-squamous</td>
<td>HPV-18</td>
<td>Cisplatin</td>
<td>101</td>
<td>PD</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>Squamous</td>
<td>HPV-18</td>
<td>Cisplatin, paclitaxel, carboplatin, topotecan, ixabepilone, phase I trial</td>
<td>126</td>
<td>PR (3)</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>Squamous</td>
<td>HPV-16</td>
<td>Bleomycin, vincristine, cisplatin, gemcitabine, topotecan, paclitaxel</td>
<td>152</td>
<td>CR (22+)</td>
</tr>
<tr>
<td>4</td>
<td>55</td>
<td>Squamous</td>
<td>HPV-16</td>
<td>Carboplatin, 5-FU, irinotecan</td>
<td>80</td>
<td>PD</td>
</tr>
<tr>
<td>5</td>
<td>44</td>
<td>Squamous</td>
<td>HPV-18</td>
<td>Cisplatin</td>
<td>90</td>
<td>PD</td>
</tr>
<tr>
<td>6</td>
<td>36</td>
<td>Adeno</td>
<td>HPV-18</td>
<td>Cisplatin</td>
<td>75</td>
<td>CR (15+)</td>
</tr>
<tr>
<td>7</td>
<td>59</td>
<td>Adeno</td>
<td>HPV-18</td>
<td>Cisplatin, carboplatin, paclitaxel, bevacizumab</td>
<td>33</td>
<td>PD</td>
</tr>
<tr>
<td>8</td>
<td>31</td>
<td>Adeno-squamous</td>
<td>HPV-18</td>
<td>Cisplatin, paclitaxel</td>
<td>46</td>
<td>PD</td>
</tr>
<tr>
<td>9</td>
<td>37</td>
<td>Adeno</td>
<td>HPV-18</td>
<td>Carboplatin, paclitaxel, ipilimumab</td>
<td>70</td>
<td>PD</td>
</tr>
</tbody>
</table>

* Duration measured in months from cell infusion.

Prolonged Tumor Regression Following a Single Infusion of Cells

Patient 6

• 36-year-old woman
• Adenocarcinoma (HPV-18+)
• Cisplatin + radiation
• Refractory primary tumor
• Salvage surgery identified pelvic and extrapelvic progression

HPV-Targeted Tumor-Infiltrating Lymphocytes: Summary of the Findings

- Objective tumor responses in 3/9 patients
  - 1 PR (3 months), 2 CR (22+ months and 15+ months)
- HPV-reactive infused T cells in 6/8 patients
  - 3/6 patients with reactivity had responses
  - 0/2 patients without reactivity had responses
- Repopulation of peripheral blood with HPV reactive T cells in 2/4 patients
  - 2/2 with repopulation had tumor responses
  - 0/2 without repopulation had tumor responses

Checkpoint Inhibition: Overcoming Immune Tolerance

Lebbé C, et al. Presented at: 33rd European Society for Medical Oncology Congress; September 12-16, 2008; Stockholm, Sweden. Abstract 769O.
A Phase I/II Study of Ipilimumab in Metastatic or Recurrent Cervical Carcinoma

• 10 mg/kg every 21 days for four cycles; followed by four cycles of maintenance therapy (same dose) every 12 weeks
• 42 patients, median age of 49 years (23-78)
  – 29 squamous, 13 adenocarcinoma
  – 35 had prior radiation completed
  – 21 had received 2/3 prior regimens
• 34 evaluable patients: 2 PR (6%), 9 SD and 23 PD
• Median PFS was 2.5 months (95% CI: 2.3-3.2)
• Grade 3 toxicities included diarrhea (4 patients) and colitis (3 patients)
• Did not meet the objective of 4 responders
Programmed Cell Death 1 (PD-1) and Programmed Death-Ligand 1 (PD-L1)

Longoria TC, Tewari KS. Drugs. 2015 Oct 16 [Epub ahead of print].
Pembrolizumab in Patients with Advanced Cervical Cancer: Preliminary Results From the Phase 1b KEYNOTE-028 Study

Jean-Sebastien Frenel,1 Christophe Le Tourneau,2 Bert O’Neil,3 Patrick A. Ott,4 Sarina Piha-Paul,5 Carlos Gomez-Roca,6 Emilie van Brummelen,7 Hope Rugo,8 Shari Thomas,9 Sanatan Saraf,9 Mei Chen,9 Andrea Varga10

1Institut de Cancerologie de l’Ouest, Centre René Gauducheau, Saint-Herblain, France; 2Institut Curie, Paris, France; 3Indiana University Health University Hospital, Indianapolis, IN; 4Dana-Farber Cancer Institute, Boston, MA; 5The University of Texas MD Anderson Cancer Center, Houston, TX; 6Institut Claudius Regaud, Toulouse, France; 7The Netherlands Cancer Institute, Amsterdam, Netherlands; 8University of California, San Francisco, San Francisco, CA; 9Merck & Co., Inc., Kenilworth, NJ; 10Gustave Roussy, Villejuif, France
KEYNOTE-028 (NCT02054806): Phase 1b Multicohort Study of Pembrolizumab for PD-L1–positive Advanced Solid Tumors

Patients
- Unresectable or metastatic cervical cancer
- Failure of or inability to receive standard therapy
- ECOG PS 0 or 1
- Measurable disease (RECIST v1.1)
- PD-L1 positive†

Pembrolizumab
10 mg/kg IV Q2W

Complete response, partial response, or stable disease

Treat for 24 months, or until progression§ or intolerable toxicity

Confirmed progressive disease§ or unacceptable toxicity

Discontinue pembrolizumab

‡Response assessment: Every 8 weeks for the first 6 months; every 12 weeks thereafter

Primary end points: ORR per RECIST v1.1 and safety
Secondary end points: PFS, OS, duration of response

†Membranous PD-L1 expression in ≥1% of tumor or stromal cells using a prototype immunohistochemistry assay and 22C3 antibody (Merck). §Clinically stable patients were allowed to remain on pembrolizumab until progressive disease was confirmed on a second scan performed ≥4 weeks later. Patients who experienced progression after discontinuing pembrolizumab were eligible for up to 1 year of additional treatment if no other anticancer therapy was received.

Presented By Jean-Sebastien Frenel at 2016 ASCO Annual Meeting
# Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>N = 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>41 (26–62)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>15 (63)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Not specified</td>
<td>8 (33)</td>
</tr>
<tr>
<td>ECOG performance status of 1, n (%)</td>
<td>18 (75)</td>
</tr>
<tr>
<td>Histology, n (%)</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>23 (96)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Metastatic stage, n (%)</td>
<td></td>
</tr>
<tr>
<td>MX</td>
<td>1 (4)</td>
</tr>
<tr>
<td>M0</td>
<td>6 (25)</td>
</tr>
<tr>
<td>M1</td>
<td>15 (63)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>N = 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior radiotherapy</td>
<td>23 (96)</td>
</tr>
<tr>
<td>Prior lines of therapy for advanced disease</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9 (38)</td>
</tr>
<tr>
<td>2</td>
<td>6 (25)</td>
</tr>
<tr>
<td>≥3</td>
<td>9 (38)</td>
</tr>
<tr>
<td>Prior platinum</td>
<td>23 (96)</td>
</tr>
<tr>
<td>Prior bevacizumab</td>
<td>10 (42)</td>
</tr>
</tbody>
</table>
# Treatment-Related Adverse Events

## Any Grade Occurring in ≥2 Patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>N</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>18</td>
<td>(75)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4</td>
<td>(17)</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>(13)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>(8)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>2</td>
<td>(8)</td>
</tr>
<tr>
<td>Constipation</td>
<td>2</td>
<td>(8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>(8)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2</td>
<td>(8)</td>
</tr>
<tr>
<td>Anemia</td>
<td>2</td>
<td>(8)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>2</td>
<td>(8)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>2</td>
<td>(8)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2</td>
<td>(8)</td>
</tr>
</tbody>
</table>

## Grade 3 Occurring in ≥1 Patient

<table>
<thead>
<tr>
<th>Condition</th>
<th>N</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>5</td>
<td>(21)</td>
</tr>
<tr>
<td>Rash</td>
<td>2</td>
<td>(8)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1</td>
<td>(4)</td>
</tr>
<tr>
<td>Colitis</td>
<td>1</td>
<td>(4)</td>
</tr>
<tr>
<td>Guillain-Barre syndrome</td>
<td>1</td>
<td>(4)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>1</td>
<td>(4)</td>
</tr>
</tbody>
</table>

- Median follow-up duration: 43 weeks (range, 6–92)
- No grade 4 treatment-related AEs
- No treatment-related mortality
- 2 treatment-related discontinuations: grade 3 colitis; grade 3 Guillain-Barre syndrome
## Antitumor Activity
(RECIST v1.1, Investigator Review)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR†</td>
<td>4</td>
<td>17</td>
<td>5–37</td>
</tr>
<tr>
<td>Partial response</td>
<td>4</td>
<td>17</td>
<td>5–37</td>
</tr>
<tr>
<td>Stable disease</td>
<td>3</td>
<td>13</td>
<td>3–32</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>16</td>
<td>67</td>
<td>45–84</td>
</tr>
<tr>
<td>No assessment‡</td>
<td>1</td>
<td>4</td>
<td>&lt;1–21</td>
</tr>
</tbody>
</table>

N = 24

---

Data cutoff date: Feb 17, 2016. Only confirmed responses are included. Patients who received ≥1 dose of pembrolizumab and had a baseline scan with measurable disease per RECIST v1.1 are included. †There were no complete responses. ‡Patient did not have a postbaseline response evaluation.
Longitudinal Change From Baseline in Tumor Size (RECIST v1.1, Investigator Review)

Change From Baseline, %

Nonresponder
Responder

+20% increase
-30% decrease

Time, weeks

0 8 16 24 32 40 48 56 64 72

Data cutoff date: Feb 17, 2016. Patients who received ≥1 dose of pembrolizumab, had a baseline scan with measurable disease per RECIST v1.1, and a post-baseline assessment are included (n = 20). One patient was excluded due to 2 scans for the same assessment out of window.
Progression-Free Survival† and Overall Survival

Progression-Free Survival
Median (95% CI),
2 months (2–4)
6-month, 21%
12-month, 8%

Overall Survival
Median (95% CI),
9 months (4–12)
6-month, 67%
12-month, 33%

Presented By Jean-Sebastien Frenel at 2016 ASCO Annual Meeting
AN OPEN-LABEL, RANDOMIZED, PHASE 3 CLINICAL TRIAL OF REGN2810* VERSUS PHYSICIANS CHOICE CHEMOTHERAPY (PCC)

- Recurrent squamous or adenocarcinoma of the cervix
- Measurable disease by RECIST 1.1
- Tumor progression or recurrence within 6 months of last dose of platinum therapy used to treat metastatic, persistent or recurrent cancer

PCC:
- Pemetrexed
- Topotecan or Irinotecan
- Vinorelbine until progression

REGN2810:
- IV 350 mg q3w for 48 weeks or until progression

Primary endpoint: OS
Secondary endpoints: PFS, Overall Response Rate, Adverse events, Quality of life
Statistics: Sample size = 414, 1-sided alpha = 0.025, 90% power, target HR = 0.7, stratification factors (region, PCC, histology)

*REGN2810 is a high affinity hinge-stabilized IgG4 human antibody to the PD-1 receptor that blocks PD-1/PD L1-mediated T cell inhibition
T-cells target TAA on tumor cells and tLLO inhibits Treg and MDSC in the TME, reducing the tumor’s protective shield.

Attenuated *Lm* trigger a robust immune response and *bioengineered plasmids* generate a fusion protein, tLLO-TAA.

TAA activates cytotoxic T-cells targeted against the tumor.

T-cells target TAA on tumor cells and tLLO inhibits Treg and MDSC in the TME, reducing the tumor’s protective shield.

**Source:** Advaxis; used with permission

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*APC*, antigen presenting cell; *Lm*, *Listeria monocytogenes*; MHC, major histocompatibility complex; TCR, T-cell receptor; MDSC, myeloid-derived suppressor cells; TAA, tumor-associated antigen; tLLO, truncated listeriolysin O; Treg, regulatory T cell; TME, tumor microenvironment.
Stage 1 completed; Stage 2 enrollment initiated

†In October 2015 all trials of AXAL were placed on a brief clinical hold by the US Food and Drug Administration, for investigation of an isolated safety concern; the hold was subsequently lifted in Dec 2015.

*Maximum 3 doses allowed by protocol.

AXAL, axalimogene filolisbac; NA, not applicable.
All treated patients (N = 50) experienced ≥1 AE; safety findings from both stages of the study were consistent.

<table>
<thead>
<tr>
<th>AE</th>
<th>Grade 1–4</th>
<th>Grade 1–2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥1 TRAE, n (%)</td>
<td>48 (96)</td>
<td>28 (56)</td>
<td>18 (36)</td>
<td>2 (4)*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TRAEs occurring in ≥30% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>26 (52)</td>
</tr>
<tr>
<td>26 (52)</td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td>Chills</td>
</tr>
<tr>
<td>26 (52)</td>
</tr>
<tr>
<td>26 (52)</td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>24 (48)</td>
</tr>
<tr>
<td>19 (38)</td>
</tr>
<tr>
<td>5 (10)</td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>16 (32)</td>
</tr>
<tr>
<td>16 (32)</td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>15 (30)</td>
</tr>
<tr>
<td>15 (30)</td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td>-</td>
</tr>
</tbody>
</table>

*The observed grade 4 TRAEs recorded in 2 patients were considered possibly related (lung infection [klebsiella related] and sepsis; same patient) or probably related (hypotension and cytokine related symptoms; same patient) to treatment.

AE, adverse event; TRAE, treatment-related AE.
12-month and median overall survival

- Represents a 52% improvement vs logistic model-predicted milestone survival rate of 24.5%
- The probability of this survival advantage being detected by chance vs a true treatment effect was 0.02
- 8 patients remain alive as of January 31, 2017

12-month OS rate: 38%, range 12.02–40.6 months (n = 19/50; primary endpoint)

Number of patients: 50
Events: 42 (84%)
Censored: 8 (16%)
Median OS: 6.2 months
95%CI: (4.4–12.3)

No. at risk:
50  47  35  25  22  21  19  13  9  4  3  3  3  3  3  3  2  1  1  1  1  1  0

CI, confidence interval; OS, overall survival.
Objective response rates

- Investigator assessment of tumor best response was reported in 38 patients (76%)

<table>
<thead>
<tr>
<th>Tumor Best Response</th>
<th>Overall (N = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>1 (2)</td>
</tr>
<tr>
<td>SD</td>
<td>15 (30)</td>
</tr>
<tr>
<td>PD</td>
<td>22 (44)</td>
</tr>
<tr>
<td>NE</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Missing post-baseline scan</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

Note: These are unconfirmed.
CR, complete response; NE, no evaluation; OR, objective response; PD, progressive disease; SD, stable disease.

Huh W et al SGO 2017
Study GOG-0265: 66-year-old patient treated with AXAL – durable complete response

Diagnosis: Squamous cell carcinoma of the cervix

Radical hysterectomy

Pelvic recurrence

Treated with
- Paclitaxel/carboplatin
- Bevacizumab
- Pelvic radiation

Pelvic recurrence

Systemic recurrence

Enrolled in GOG-0265

June 2015

Dose 1

Dose 2

Dose 3

2015

July | Aug | Sept

Axalimogene filolisbac

May 2016

Complete response

Survival to date – second-line metastatic squamous cell cervical carcinoma (post-bevacizumab): 18.5 months*

TRAEs: Grade 1–2 fatigue, chills, fever, nausea, and grade 3 hypotension, cytokine release syndrome; no grade 4–5 TRAEs reported

*Calculated from date of first AXAL dose (July 16, 2015) to data cut-off (Jan 31, 2017)
Results may not be typical; further study is warranted.

AXAL, axalimogene filolisbac; TRAE, treatment-related adverse event.

Huh W et al SGO 2017
GOG/NRG-0265 Survival in the Context of Historical GOG Trials in Second-line

*There are 2 patients with >24 months follow up (~31 and 41 months, respectively).

GOG, Gynecologic Oncology Group; OS, overall survival; PRmCC, persistent/recurrent metastatic cervical cancer.

12-month survival of 38% (n=19/50; Primary Endpoint)

12-month milestone survival rate exceeds historical data and represents highest rate achieved

*There are 2 patients with >24 months follow up (~31 and 41 months, respectively).

GOG, Gynecologic Oncology Group; OS, overall survival; PRmCC, persistent/recurrent metastatic cervical cancer.

Huh W et al SGO 2017
AXAL GOG/NRG-0265 and bevacizumab GOG-227C: 12-month overall survival curves

12-month survival = 38%

GOG-0265 (ADXS11-001)
GOG-227C (Bevacizumab)

GOG-0265 OS
Number of patients: 50
Events: 43 (86%)
Censored: 8 (14%)
Median: 6.2 months
95% CI: (4.4–12.3)

GOG-227C OS
Number of patients: 46
Events: 38 (83%)
Censored: 8 (17%)
Median: 7.3 months
95% CI: (6.1–10.4)

AXAL, axalimogene filolisbac; CI, confidence interval; OS, overall survival.

Next steps: Phase 3 AIM2CERV studies – AXAL as adjuvant monotherapy to prevent recurrence in high-risk cervical cancer

- HRLACC
- FIGO stage I–II with positive pelvic nodes
- FIGO stage III–IVA
- Any FIGO stage with para-aortic nodes

Treatment with cisplatin (at least 4-wk exposure) and radiation (minimum 40-Gy external beam radiation therapy)

Randomize

Placebo IV
Up to 1 year
N = 150

Axalimogene filolisbac
(1 × 10⁹ CFU)
Up to 1 year
N = 300

Primary endpoint:
DFS

Baseline tumor imaging must be performed within 28 days before the first study treatment infusion

ClinicalTrials.gov Identifier: NCT02853604

AIM2CERV – Axalimogene Filolisbac Immunotherapy Following Chemo/Radiation in Patients Who Have High-Risk Locally Advanced Cervical Cancer (HRLACC)

CFU, colony-forming unit; DFS, disease-free survival; FIGO, International Federation of Gynecology and Obstetrics; HRLACC, high-risk locally advanced cervical cancer; IV, intravenous.

AIM2CERV Sites – Asia Map (May 2017)

MALAYSIA (n = 5)
- Abdullah (Kota Bharu) – May ‘17
- Wan Mohd. Nazri (Kelantan) – May ‘17
- Yong Chee Ming (Ampang) – May ‘17
- Mat Adenan (Kuala Lumpur) – May ‘17
- Appalanaido (Pulau Pinang) – May ‘17

SOUTH KOREA (n = 8)
- Choi (Seoul) – June ‘17
- Kim Gun Min (Seoul) – June ‘17
- Kim Byong-Gie (Seoul) – June ‘17
- Kim Jae-Hoon (Seoul) – June ‘17
- Moon (Seongnam) – Aug ‘17
- Nam (Seoul) – June ‘17
- Ryu (Seoul) – June ‘17
- Song (Gyeongsangnam) – June ‘17

TAIWAN (n = 6)
- Cheng Wen-Fang (Taipei)
- Chung, Chi-Feng (Taipei)
- Ho (Taipei)
- Lu (Taichung)
- Chang (Taoyuan) – May ‘17
- Chou (Tainan)

VIETNAM (n = 1)
- Linh (Ho Chi Minh City) – Nov ‘17

LEGEND
- Open site (n = 5)
- Opening pending (n = 15)

* Site selection in China pending
Summary and Conclusions

- Antiangiogenesis was the first validated targeted intervention in cervical cancer
- Immunotherapy is the next frontier
  - Checkpoint inhibitors (PD-1, PDL-1, CTLA4)
  - Listeria-based vectors
Thank You

Bradley.monk@usoncology.com