Ovarian Cancer: Contemporary Management & Clinical Trial Endpoint Considerations

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Relevant financial relationships in the past twelve months by presenter or spouse/partner.

Other: Scientific AD Board (AZ, Roche, Caris, Clovis, Tesaro)

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Strategies Targeting Hallmarks of Cancer

Avoiding immune destruction is a hallmark of cancer


Cancer-immunity cycle = immune system recognises, targets and kills cancer cells

Tumors can inhibit the anti-tumour immune response by disrupting the balance of the cancer-immunity cycle via immune checkpoints. 

Cancer-Immunity Cycle

1. Release of cancer cell antigens (cancer cell death)
2. Cancer antigen presentation (dendritic cells/ APCs)
3. Priming and activation (APCs & T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells into tumors (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (Immune and cancer cells)
Tregs vs. CD8 T cells

Smyth et al. Immunology and Cell Biology 2017
Cold & Hot immune tumors: Clinical implications

“Non-T cell inflamed” Tumor

CD3 Tumor

“T cell inflamed” Tumor

COLD

HOT

Immunoscore

0 1 2 3 4
OC carries significant levels of mutational load

Red line indicates the threshold for samples with a high mutational burden (13.8 mutations/Mb)

Mb, megabase

Zehir et al. Nat Med 2017
### Key studies Establishing Immune Response in OC

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Immune cell type</th>
<th>Outcomes</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang et al.</td>
<td>186</td>
<td>CD3+ TILs</td>
<td>PFS, OS</td>
<td>Presence of TILs positively correlates with PFS, OS</td>
</tr>
<tr>
<td>Mariya et al.</td>
<td>122</td>
<td>CD3+, CD4+, CD8+ TILs</td>
<td>OS</td>
<td>CD8+ TIL presence correlates with platinum response</td>
</tr>
<tr>
<td>The Cancer Genome Atlas</td>
<td>489</td>
<td>Exome, mRNA, miRNA sequencing, somatic copy number analysis</td>
<td>NA</td>
<td>Immunoreactive subset of ovarian cancers identified by mRNA expression of chemokines and receptors</td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Curiel et al.</td>
<td>70</td>
<td>CD4+CD25+FOXP3+ Treg cells in ascites and tumor slices</td>
<td>OS</td>
<td>Tumor recruitment of immunosuppressive Tregs predicts decreased OS</td>
</tr>
<tr>
<td>Sato et al.</td>
<td>117</td>
<td>CD8+ TILs, CD4+TILs, CD4+ CD25+ FOXP3+ Tregs</td>
<td>OS</td>
<td>High CD8 TIL to Treg ratio associated with improved OS</td>
</tr>
<tr>
<td>Hamanishi et al.</td>
<td>70</td>
<td>Tumor cells expressing PD-L1, CD8+ TILs</td>
<td>OS</td>
<td>PD-L1 expression on tumors predicts decreased OS, and CD8 TILs are associated with improved OS</td>
</tr>
</tbody>
</table>

**Turner et al. Gynecologic Oncology, 2016**
Blockade of PD-1/PD-L1 or CTLA-4 Signaling

Ipilimumab*  
Tremelimumab  
Nivolumab*  
Pembrolizumab*  
Atezolizumab*  
Avelumab  
Durvalumab

* FDA-approved
Checkpoint Inhibition
## Immune Checkpoint Inhibitors Overview

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Nivolumab&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Pembrolizumab&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Avelumab&lt;sup&gt;4&lt;/sup&gt;</th>
<th>Atezolizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brand Name Mfg</strong></td>
<td>BMS</td>
<td>BMS</td>
<td>Merck</td>
<td>Pfizer</td>
<td>Genentech</td>
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<tr>
<td><strong>Isotype</strong></td>
<td>IgG1</td>
<td>IgG4</td>
<td>IgG4</td>
<td>IgG1</td>
<td>IgG1</td>
</tr>
<tr>
<td><strong>Targets</strong></td>
<td>CTLA-4</td>
<td>PD-1</td>
<td>PD-1</td>
<td>PD-L1</td>
<td>PD-L1</td>
</tr>
<tr>
<td><strong>ADCC</strong></td>
<td>Yes&lt;sup&gt;5&lt;/sup&gt;</td>
<td>No&lt;sup&gt;6&lt;/sup&gt;</td>
<td>No/Minimal&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

## Ovarian Immune Checkpoint Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab&lt;br&gt;¹</th>
<th>Nivolumab&lt;br&gt;²</th>
<th>Pembrolizumab&lt;br&gt;³</th>
<th>Avelumab&lt;br&gt;⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>9</td>
<td>20</td>
<td>26</td>
<td>124</td>
</tr>
<tr>
<td><strong>Patient population</strong></td>
<td><strong>Metastatic ovarian carcinoma</strong></td>
<td><strong>Platinum-resistant, post-taxane</strong></td>
<td><strong>Failure or inability to receive standard Tx; PD-L1+</strong></td>
<td><strong>Recurrent post-platinum</strong></td>
</tr>
<tr>
<td><strong>Prior therapies</strong></td>
<td>NR</td>
<td>≥4: 55%</td>
<td>≥4: 80.8%</td>
<td>≥3: 65.3% (not including adjuvant)</td>
</tr>
<tr>
<td><strong>PD-L1+ prevalence</strong></td>
<td>NR</td>
<td>80% (IC 2/3)</td>
<td>100% (≥1% TC)</td>
<td>77% (≥1% TC)</td>
</tr>
<tr>
<td><strong>Median follow-up</strong></td>
<td>NR</td>
<td>11 months</td>
<td>NR</td>
<td>12.4 months</td>
</tr>
<tr>
<td><strong>TRAE, any</strong></td>
<td>22%</td>
<td>95%</td>
<td>69.2%</td>
<td>66.1%</td>
</tr>
<tr>
<td><strong>TRAE, Gr 3+</strong></td>
<td>NR</td>
<td>40%</td>
<td>3.8%</td>
<td>6.5%</td>
</tr>
<tr>
<td><strong>ORR (95% CI)</strong></td>
<td>NR</td>
<td>15% (3.2-37.9)</td>
<td>11.5% (2.4-30.2)</td>
<td>9.7% (5.1-16.3)</td>
</tr>
<tr>
<td><strong>DCR (95% CI)</strong></td>
<td>NR</td>
<td>45% (23-69)</td>
<td>34.6% (17-56)</td>
<td>54% (45-63)</td>
</tr>
<tr>
<td><strong>mPFS</strong></td>
<td>NR</td>
<td>3.5 months</td>
<td>NR</td>
<td>2.6 months</td>
</tr>
<tr>
<td><strong>mOS</strong></td>
<td>NR</td>
<td>20 months</td>
<td>NR</td>
<td>10.8 months</td>
</tr>
</tbody>
</table>

DCR, disease control rate; NR, not reached; TC, tumor cell; TRAE, treatment-related adverse event.

Potential Impact of Immuno-Oncology Agents on Ovarian Cancer Treatment Paradigm

Neoadjuvant therapy – 3-4 cycles

Debulking surgery

1st-line platinum-based chemotherapy

Response

1st-line maintenance

Lack of response or early recurrence (<6 mo)

Lack of response or early recurrence (>6 mo) = platinum sensitive

Re-treat with platinum

Response

2nd-line maintenance

Late recurrence (>6 mo) = platinum sensitive

Re-treat with platinum

Response

= Frontline

- Javelin Ovarian 100 (avelumab)
- Pembrolizumab + chemotherapy

PS recurrence

- Atalante (atezolizumab)
- Keynote 100 (pembrolizumab)
- Pembrolizumab + bevacizumab

Resistant

- Javelin Ovarian 200 (avelumab)
- NRG GY-009 (atezolizumab)
- Keynote 100 (pembrolizumab)
- Pembrolizumab + bevacizumab
- EORTC-1508 (atezolizumab)

PS, platinum sensitive.

**JAVELIN Ovarian 100**
Avelumab Platinum Combo + Maintenance (Frontline)

**Enrollment Criteria**
- Previously untreated
- Stage III-IV
- Prior debulking surgery or plan for neoadjuvant chemotherapy
- ECOG PS 0 or 1
- Mandatory archival tissue

**Primary Endpoint:**
- PFS

**Secondary Endpoints:**
- Maintenance PFS, OS, ORR, duration of response, pCR, PROs, safety, PK

**Patients with SD or better will be allowed to continue to maintenance**
- Chemotherapy: Choice of Q3W carboplatin-paclitaxel OR carboplatin + weekly paclitaxel
- Maintenance avelumab up to 2 years

Enrollment Criteria

- High-grade ovarian cancer
- No prior treatment
- Disposition to neoadjuvant chemotherapy
- Peripheral neuropathy Grade 0 or 1
- Measurable disease
- ECOG PS 0 or 1
- Mandatory archival tissue or new tissue sample

Primary Endpoint: PFS

- Participants receive carboplatin IV on day 1 and paclitaxel 80 mg/m² IV on days 1, 8, and 15 every 21 days for 3 cycles of therapy
- After observation, participants without evidence of progression will undergo interval cytoreductive surgery
- After surgery, participants will restart chemotherapy as previously prescribed, with the addition of pembrolizumab 200 mg IV on day 1 every 21 days for 3 cycles
- Pembrolizumab maintenance therapy (200 mg IV every 21 days) will be given for a total of 20 cycles or until progression

Enrollment Criteria
• Recurrent ovarian cancer
• Measurable disease
• ECOG PS 0 or 1
• Mandatory submission of tumor tissue samples

Pembrolizumab, Bev, & Cyclophosphamide in Recurrent Ovarian Cancer
Phase 2 Study (NCT02853318)

Primary Endpoint: Safety, PFS
Secondary Endpoints: OS, antitumor immune response, objective tumor response

Chemotherapeutic agents
- Pembrolizumab
- Bevacizumab
- Cyclophosphamide

n = ~40

• Patients receive pembrolizumab IV and bevacizumab IV on day 1 and cyclophosphamide PO QD on days 1-21
• Treatment repeats every 3 weeks for up to 17 courses in the absence of disease progression or unacceptable toxicity
Ex vivo TIL Expansion

1. Excise tumour
2. Plate fragments
3. Culture with 6,000 IU/ml IL2
4. Assay for specific tumour recognition
5. Select and expand to $10^{10}$ cells
6. Reinfuse post-lymphodepletion
Estimates of the Worldwide Incidence of Cervical Cancer

Source: GLOBOCAN 2014; IARC
Human Papillomavirus

Non enveloped Icosahedral DNA Virus
Upstream reg region -reg viral proteins

L1 encodes for major capsid proteins
-Often integrated in Cx Ca

6 open reading frames
Categories of HPV Vaccines

• **Prophylactic**
  – Induce neutralizing antibodies to the L1 capsid protein
  – Protect against transmission and acquisition of HPV infection

• **Therapeutic**
  – Induce immunity to the E6/ E7 and other antigens expressed in HPV-infected epithelial cells
  – Induce Type 1 T-cell responses

Kadish and Einstein, *Curr Opin Oncol* 2005
Vaccine Approaches

- Autologous
- Allogenic
- Dendritic Cell
- Peptide
- Viral
- Bacterial
- RNA/DNA
<table>
<thead>
<tr>
<th>Company/Institution</th>
<th>Antigen</th>
<th>Type</th>
<th>HPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zycos/MGI/Eisai</td>
<td>E6, E7</td>
<td>Microparticle delivered DNA</td>
<td>16, 18</td>
</tr>
<tr>
<td>Stressgen</td>
<td>E7</td>
<td>Fusion Protein: mycobacterial heat shock protein/E7 (Hsp E7)</td>
<td>16</td>
</tr>
<tr>
<td>Johns Hopkins</td>
<td>E7</td>
<td>pNGVLa-Sig/E7(detox)/HSP70</td>
<td>16</td>
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<tr>
<td>Transgene/Roche</td>
<td>E6,E7, IL2</td>
<td>Live rVaccinia virus (TA-HPV)</td>
<td>16</td>
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<tr>
<td>Xenova/Cantab</td>
<td>E6,E7</td>
<td>Live rVaccinia virus (TA-HPV)</td>
<td>16, 18</td>
</tr>
<tr>
<td>Xenova/Cantab</td>
<td>L2/E6/E7</td>
<td>Fusion Protein (TA-CIN)</td>
<td>16</td>
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<tr>
<td>Cantab</td>
<td>L2/E7</td>
<td>Fusion Protein (TA-GW)</td>
<td>6</td>
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<tr>
<td>CSL</td>
<td>E6/E7</td>
<td>Fusion Protein (CerVax 16)</td>
<td>16</td>
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<tr>
<td>Cytel</td>
<td>E7</td>
<td>Peptide</td>
<td>16</td>
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<tr>
<td>Medigene</td>
<td>L1, E7</td>
<td>Chimeric VLPs</td>
<td>16</td>
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<tr>
<td>University of Leiden</td>
<td>E7</td>
<td>Peptide</td>
<td>16</td>
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<tr>
<td>Inovio</td>
<td>E6, E7</td>
<td>DNA Vaccine-Electroporation</td>
<td>16, 18</td>
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<tr>
<td>Aduro</td>
<td>E7</td>
<td>Listeria monocytogenes</td>
<td>16</td>
</tr>
<tr>
<td>Advaxis</td>
<td>E7</td>
<td>Listeria monocytogenes</td>
<td>16</td>
</tr>
</tbody>
</table>
Tailoring selection of immunotherapy based on detecting adaptive immune resistance

Ribas et al, Cancer Discov 2015
Adoptive T-cell Transfer Therapy

- Infusion of transduced T-cells
- Leukapheresis
- T-cell expansion
- T-cell transduction

- TCR-gene therapy
- TILs
- Vaccines
- Checkpoint inhibitors

- Intracellular antigens
  - MHC-dependent
  - APM-dependent
  - Endogenous costimulatory signals

- Surface antigens
  - MHC-independent
  - APM-independent
  - Costimulation on antigen recognition

Rodriguez-Garcia A et al Gyn Onc 2017
Frequency of Somatic Mutations Across Tumor Types

Adoptive T Cell Therapy: Schema for HPV-Targeted Tumor-Infiltrating Lymphocytes (HPV-TIL)

Testing for E6 and E7 reactivity

T cell rapid expansion

T cells cultured from tumor fragments

T cell infusion

Cyclophosphamide 60 mg/Kg x 2 + fludarabine 25 mg/m² x 5 followed by aldesleukin

Tumor excision

Prolonged Tumor Regression Following Single Infusion of Autologous Tumor-Targeted T Cells

Stevanovic S, et al. LBA3008 (ASCO 2014)
A Phase I/II Study of Ipilimumab in Metastatic or Recurrent Cervical Carcinoma

- 10 mg/kg q 21 d for x4 cycles; followed by 4 cycles of maintenance therapy (same dose) q 12 wks
- 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 pts: 2 PR (6%), 9 SD & 23 PD
- Median PFS was 2.5 months (95% CI: 2.3-3.2)
- Gr 3 toxicities included diarrhea (4 pts) & colitis (3 pts)
- Did not meet the objective of 4 responders


ClinicalTrials.gov Identifier: NCT01693783
Pembrolizumab in Adv Cervical Cancer: Ph Ib

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

**Response Assessment†**
- 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).

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

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>N = 24</th>
<th>Characteristic, n (%)</th>
<th>N = 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>41 (26–62)</td>
<td>Prior radiotherapy</td>
<td>23 (96)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td>Prior lines of therapy for advanced disease</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>15 (63)</td>
<td>1</td>
<td>9 (38)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (4)</td>
<td>2</td>
<td>6 (25)</td>
</tr>
<tr>
<td>Not specified</td>
<td>8 (33)</td>
<td>≥3</td>
<td>9 (38)</td>
</tr>
<tr>
<td>ECOG performance status of 1, n (%)</td>
<td>18 (75)</td>
<td>Prior platinum</td>
<td>23 (96)</td>
</tr>
<tr>
<td>Histology, n (%)</td>
<td></td>
<td>Prior bevacizumab</td>
<td>10 (42)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>23 (96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>1 (4)</td>
<td></td>
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<tr>
<td>Metastatic stage, n (%)</td>
<td></td>
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</tr>
<tr>
<td>MX</td>
<td>1 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>6 (25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>15 (63)</td>
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<tr>
<td>Unknown</td>
<td>2 (8)</td>
<td></td>
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</tbody>
</table>
# Pembrolizumab in Adv Cervical Cancer: Ph Ib

## 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><strong>ORR^†</strong></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)

-30% decrease
+20% increase

Change From Baseline, %

Time, weeks

0  8  16  24  32  40  48  56  64  72

Nonresponder
Responder

Presented By Jean-Sebastien Frenel at 2016 ASCO Annual Meeting

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%

Data cutoff date: Feb 17, 2016.
Patients who received ≥1 dose of pembrolizumab and had a baseline scan with measurable disease per RECIST v1.1 are included. †RECIST v1.1 by investigator review.
NRG GY002
Nivolumab in Persistent, Recurrent, or Metastatic Cervical Cancer

- Measurable disease
- only 1 prior systemic regimen for management of persistent, recurrent or metastatic disease
- Nivolumab 3 mg/kg IV every 2 weeks
- 2 stage design
  - First stage: n = 12
  - Second stage (if warranted): n = 13
  - Activated May 18, 2015
  - Temporarily Closed August 2015 after first stage
    - 1 response needed to move to second stage
  - Closed June 2016

PI: Alessandro Santin ClinicalTrials.gov Identifier: NCT02257528
NRG GY002
Nivolumab in Persistent, Recurrent, or Metastatic Cervical Cancer

Figure 1
Cumulative Accrual for NRG GY002 - Data as of 11/3/2015

Cumulative Number of Patients Enrolled

Month and Year

Projected Accrual
Observed Accrual

PI: Alessandro Santin ClinicalTrials.gov Identifier: NCT02257528
Ph I GOG (NRG) 9929: Schema

Chemoradiation (weekly for 6 weeks)
Concurrent Weekly Cisplatin 40mg/m²/week (max dose 70 mg)
AND

Extended Field Radiation: pelvis + para-aortics
4500 cGy in 25 fractions to the para-aortic nodes (180 cGy/fraction)
4500 cGy in 25 fractions to the pelvis (180 cGy/fraction)

Note: All radiation is to be completed within 56 ± 3 days.

Intracavitary Brachytherapy
LDR 4000cGy
OR
HDR 3000cGy

~2 weeks

Adjuvant Immunotherapy
Ipilimumab will be given ~2 weeks following completion of all chemoradiation and be given every 3 weeks x 4 doses total. Patients may commence ipilimumab up to 6 weeks following completion of all chemoradiation to allow resolution of chemoradiation associated acute toxicities.

Dose Escalation Schema

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Ipilimumab</th>
<th>Rx Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Starting Dose)</td>
<td>3 mg/kg</td>
<td>q3 weeks x 4*</td>
</tr>
<tr>
<td>2</td>
<td>10 mg/kg</td>
<td>q3 weeks x 4*</td>
</tr>
<tr>
<td>1a§</td>
<td>6 mg/kg</td>
<td>q3 weeks x 4*</td>
</tr>
</tbody>
</table>

†Once the MTD is estimated, the expansion cohort will start.
§Dose level 1a will be used if 10 mg/kg is found to exceed the MTD.

ClinicalTrials.gov Identifier:
NCT01711515
**Lm Technology™: Harnessing Unique Life Cycle of Lm in APCs**

- **Lm-LLO & HPV E7 antigen** presented & taken up by dendritic cells (antigen presenting cells or APCs)
- Dendritic cells activated & generate immune response through both the MHC I & II pathways
- Robust T-cell response generated towards antigen secreted by Lm-LLO & redirected to tumors expressing the same HPV E7 antigen
- "Perceived" acute listeriosis causes immune response
- Over-rides checkpoint inhibitors & negative regulators of cellular immunity

MHS, major histocompatibility complex
12-month Survival Rates in Pre-treated PRmCC

GOG/NRG 0265 Study Design & Eligibility

- N = ~67 Simon 2 Stage design
- > 18 years
- Persistent/recurrent metastatic (PRmCC) squamous/non-squamous cervical cancer
- > 1 prior line of systemic dose therapy for PRmCC, *excluding that received as a component of primary curative treatment*
- Prior bevacizumab allowed, but not required
- GOG PS 0/1
- Measurable disease > 1 target lesion (RECIST 1.1)

**Co-Primary Endpoints:**
- 12-month survival rate
- Tolerability/safety of ADXS11-001

**Secondary Endpoints:**
- Progression-free survival (PFS)
- Overall survival (OS)
- Objective response rate (ORR)

**ADXS11-001 Monotherapy**
1x10^9 cfu x 3 doses q 28 days (month 1, 2, 3) as an 80 ml infusion over 15 min

- ADXS11-001 Day 0
- ADXS11-001 Day 28
- ADXS11-001 Day 56

https://www.clinicaltrials.gov/ct2/show/NCT01266460
NRG 0265- 12 mos. Overall Survival vs. Historical Cohorts

Historical Perspective of 12-Month Survival Rates in GOG Phase II Trials for Recurrent/Metastatic Cervical Cancer

Axalimogene Filolisbac (ADXS-HPV): Phase 3 AIM2CERV Study Schema

High risk, locally advanced cervical cancer
- FIGO stage I-II with positive pelvic nodes
- FIGO stage III-IV
- Any FIGO stage with para-aortic nodes

• N = 450

Cisplatin (at least 4 wks exposure) and Radiation (min. 40 Gy external beam radiation)

2:1 RANDOMIZE

Reference Group
Placebo IV Up to 1 yr

Treatment Group
ADXS11-001 (1 x 10^9 cfu) Up to 1 yr

Primary Endpoint: PFS
Ph I/II CervIISA:

- Advanced Cervical Cancer
- ISA101 vaccine = 13 overlapping HPV16 (E6 & 7) synthetic long peptides
- N = 60 pts 4 dose levels of vaccine; strong association btw HPV-specific T-cell response measured via ELISpot
- Med OS not reached for 2 highest doses

Melief CJ et al ASCO –SITC 2017
# Em Ca IO Trials

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Eligibility</th>
<th>Study</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durvalumab, Vigil (bi-shRNAfurin &amp; GMCSF Aug. Autologous Tumor Cell Immunotherapy)</td>
<td>Locally advanced or metastatic EM, uterine, breast, ovarian, FT, primary peritoneal, cervical</td>
<td>NCT02725489</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Durvalumab; Durvalumab, Tremelimumab</td>
<td>Persistent or recurrent endometrial carcinoma (endometrioid, serous, undifferentiated, dedifferentiated, clear cell, mixed, other adenocarcinoma) or carcinosarcoma</td>
<td>NCT03015129</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Persistent or recurrent EM CA (endometrioid, serous, clear cell, undifferentiated, mixed, other adenocarcinoma) or CS that is hypermutated (MMR gene defect) or ultra-mutated (POLE mutation) on NGS</td>
<td>NCT02899793</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Avelumab</td>
<td>Persistent or recurrent EM CA that are either 1) POLE mutated or MMR loss or 2) microsatellite stable on IHC</td>
<td>NCT02912572</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Nivolumab; Nivolumab, Cabozantinib</td>
<td>Advanced, recurrent, or metastatic endometrial carcinoma or carcinosarcoma with MSI/MMR results available</td>
<td>NCT03367741</td>
<td>Not yet recruiting</td>
</tr>
<tr>
<td>Atezolizumab, Carboplatin, Cyclophosphamide</td>
<td>Advanced gynecologic cancer (endometrial, cervical, ovarian) or advanced breast cancer</td>
<td>NCT02914470</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td>Pembrolizumab, IMGN853</td>
<td>Advanced endometrial, epithelial ovarian, primary peritoneal, or fallopian tube cancer with folate receptor alpha positive tumor expression</td>
<td>NCT02606305</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Nivolumab, Ipilimumab</td>
<td>Advanced or metastatic endometrial cancer (grade 3 endometrioid, serous, clear cell, or mixed high grade) or bone/soft tissue sarcoma; all must have MMR expression loss on IHC</td>
<td>NCT02982486</td>
<td>Not yet recruiting</td>
</tr>
<tr>
<td>Pembrolizumab, Carboplatin, Ptx</td>
<td>Advanced or recurrent endometrial carcinoma</td>
<td>NCT02549209</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Durvalumab, Radiation Therapy; Durvalumab, Tremelimumab, Radiation Therapy</td>
<td>Advanced or recurrent endometrial, ovarian, fallopian tube, primary peritoneal, cervical, vaginal, or vulvar cancer</td>
<td>NCT03277482</td>
<td>Not yet recruiting</td>
</tr>
</tbody>
</table>
## Em Ca IO Trials

<table>
<thead>
<tr>
<th>Trial Name</th>
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<th>Study Code</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>Metastatic or recurrent EM CA, carcinosarcoma, LMS, undiff. sarcoma, high grade endometrial stroma sarcoma, or ovarian/fallopian tube carcinosarcoma that are MSI-high, MMR-deficient, or hypermutated</td>
<td>NCT03241745</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Vesicular stomatitis virus-human interferon beta-sodium iodide symporter (VSV-hIFNbeta-NIS)</td>
<td>Stage IV or recurrent EM CA (endometrioid, serous, undiff., clear cell, mixed, or other adenocarcinoma)</td>
<td>NCT03120624</td>
<td>Suspended (per study design)</td>
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<tr>
<td>Pembrolizumab, Immune Modul Cocktail (Vitamin D, Lansoprazole Teva, Cyclophosphamide, Aspirin), Radiation Therapy, Curcumin</td>
<td>Persistent or recurrent endometrial carcinoma, cervical carcinoma, or uterine sarcoma</td>
<td>NCT03192059</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Spartalizumab, MCS110 (Anti-M-CSF Monoclonal Antibody)</td>
<td>Advanced EM CA, melanoma, pancreatic, or triple negative breast cancer</td>
<td>NCT02807844</td>
<td>Recruiting</td>
</tr>
</tbody>
</table>
FDA Grants Priority Review to Pembrolizumab for New Indication in Microsatellite Instability–High Cancer

By The ASCO Post
Posted: 11/29/2016 1:11:44 PM
Conclusions

• Immuno-oncology: exciting, emerging & extremely complex
• NextGen technologies & systems biology will dynamically profile vulnerabilities
• PD-1 blockade may unleash diverse antitumor T cell re-activities.
• Multiple I/O trials in Gyn Cancers
• MSI High is Universal target
Thank You