A prospective phase 2 trial (GOG-0265) of the *Listeria*-based HPV immunotherapy axalimogene filolisbac (AXAL) in second- and third-line metastatic cervical cancer: An NRG Oncology Group trial

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Disclosures

- **W. Huh**: Consulting or advisory role – TheVax, Invio (DSMB)
- **W.E. Brady**: No conflicts of interest to disclose
- **D. Dizon**: No conflicts of interest to disclose
- **M.A. Powell**: No conflicts of interest to disclose
- **C.A. Leath III**: Research funding – Novartis, AstraZeneca, Plexxikon, and Celsion. Supported in part by NIH 3P30CA013148-43S3
- **L.M. Landrum**: No conflicts of interest to disclose
- **E. Tanner**: No conflicts of interest to disclose
- **R. Higgins**: No conflicts of interest to disclose
- **S. Ueda**: No conflicts of interest to disclose
- **M. McHale**: Consulting or advisory role – Ethicon, for new homeostatic product. Research funding – Navidea, funded clinical trial, with no principal investigator compensation. Travel, accommodation, expenses – Ethicon
- **C. Aghjanian**: No conflicts of interest to disclose.
Background: Persistent/recurrent metastatic cervical cancer (PRmCC)

• Lethal disease
  – No approved therapy following failure of first-line treatment
  – Survival only 4–7 months\(^1\)

• From 1998–2015, GOG conducted >20 phase 2 studies in PRmCC
  – Never has the 12-month OS rate exceeded 30%
  – Only 1 study met the predefined efficacy and safety threshold to progress to second stage of enrollment (GOG-227C)\(^1\)
  – Bev median OS = 7.3 months and 12-month OS = 30%

GOG, Gynecologic Oncology Group, now NRG Oncology; OS, overall survival; SOC, standard of care.
The GOG experience: 12-month milestone survival rates in pretreated PRmCC

GOG, Gynecologic Oncology Group, now NRG Oncology; PRmCC, persistent/recurrent metastatic cervical cancer.

Rationale for axalimogene filolisbac (AXAL) in metastatic cervical cancer

- **AXAL immunotherapy**: A live, highly attenuated *Listeria monocytogenes* (Lm) targeted immunotherapy bioengineered to secrete an HPV-16 E7 protein fused with a truncated fragment of listeriolysin O (tLLO)

- AXAL immunotherapy targets HPV-transformed cells, inducing antitumor T-cell immunity and breaking immune tolerance in the tumor microenvironment

- Phase 2 randomized study of AXAL +/- cisplatin in Indian patients with PRmCC (0–2 prior lines of therapy) demonstrated promising activity (12-month milestone survival rate of 32%) and acceptable toxicity
  - Activity observed across all HPV types (16, 18, 45, other)

- We now present results from the GOG/NRG-0265 study of AXAL in patients with PRmCC with at least 1 prior line of systemic-dose chemotherapy
**Lm Technology™ overview: Harnessing unique life cycle of Lm in APCs**

- *Lm*-LLO agent taken up only by phagocytic dendritic cells/APCs

- *Lm*-LLO stimulates a strong innate multi-pathway immune response (e.g., STING) in APC

- *Lm*-LLO expresses LLO-TAA fusion protein, which is processed by stimulated APC and activates TAA-specific T cells

- Robust T-cell response generated toward TAA, allowing tumor-specific immune response

- Immune activation can overcome checkpoint inhibition and negative regulators of cellular immunity

**APC**, antigen-presenting cell; *Lm, Listeria monocytogenes*; MHC, major histocompatibility complex; STING, stimulator of interferon genes; TAA, tumor-associated antigen; tLLO, truncated listeriolysin O.
GOG/NRG-0265: Study design and eligibility

- \( N = \sim 63 \): Simon two-stage design
- \( \geq 18 \) years
- Persistent/recurrent metastatic (PRmCC) squamous/non-squamous cervical cancer
- \( \geq 1 \) 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 \( \geq 1 \) target lesion (RECIST 1.1)

### Treatment

**AXAL Monotherapy**

- \( 1 \times 10^9 \) CFU \( \times 3 \) doses \( q 28 \) days (month 1, 2, 3) as a 250-mL infusion over 60 min

<table>
<thead>
<tr>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>AXAL Day 0</td>
<td>AXAL Day 28</td>
<td>AXAL Day 56</td>
</tr>
</tbody>
</table>

### Co-primary Endpoints:

- 12-month survival rate
- Tolerability/safety of AXAL

### Secondary Endpoints:

- PFS
- OS
- ORR

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*\( N = \) total 54 enrolled, as a result of clinical hold interruption during Stage 2.

*Stage 2 amended to allow continuous (\( > 3 \)) dosing of AXAL.

AXAL, axalimogene filolisbac; CFU, colony-forming units; GOG PS, Gynecologic Oncology Group performance status; HPV, human papillomavirus; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRmCC, persistent/recurrent metastatic cervical cancer; RECIST, Response Evaluation Criteria In Solid Tumors.
Statistical methodology

- Sample size calculation was based on the expected null proportion of patients surviving 12 months across historical trials = 20%
  - 90% power to detect a 15% increase in 12-month survival (20% to 35%) at a one-sided significance level of 0.10; targeted sample size for Stage 1 = 27 and Stage 2 = 36

- Trial proceeded to Stage 2 enrollment, as conditional power at the end of Stage 1 was >20%

- A logistic model-based estimation of expected 12-month survival rate of patients treated with an inactive agent was 21%
  - Calculated using data from ~500 PRmCC patients from 17 previous GOG/NRG studies of “inactive” agents

- The 12-month survival estimate was further refined to 24.5%
  - Based on model-identified key prognostic factors (age, performance status, and race), prospectively applied to the 0265 study population
Stage 1 completed; Stage 2 enrollment initiated

Stage 1
Enrollment period: 1/6/2012 – 5/6/2014
N = 29 consented
N = 26 treated

<table>
<thead>
<tr>
<th>Doses</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 dose</td>
<td>4</td>
</tr>
<tr>
<td>2 doses</td>
<td>4</td>
</tr>
<tr>
<td>3 doses</td>
<td>18</td>
</tr>
<tr>
<td>&gt;3 doses</td>
<td>NA*</td>
</tr>
</tbody>
</table>

Stage 2†
Enrollment period: 2/25/2015 – 9/24/2015
N = 25 consented
N = 24 treated

<table>
<thead>
<tr>
<th>Doses</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 dose</td>
<td>5</td>
</tr>
<tr>
<td>2 doses</td>
<td>7</td>
</tr>
<tr>
<td>3 doses</td>
<td>10</td>
</tr>
<tr>
<td>&gt;3 doses</td>
<td>2</td>
</tr>
</tbody>
</table>

†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.
## Demographics and baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Overall (N = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range), years</strong></td>
<td>46 (29–70)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>37 (74)</td>
</tr>
<tr>
<td><strong>GOG PS, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>0 vs 1</td>
<td>31 (62) vs 19 (38)</td>
</tr>
<tr>
<td><strong>FIGO stage at diagnosis, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>1 (2)</td>
</tr>
<tr>
<td>IB</td>
<td>18 (36)</td>
</tr>
<tr>
<td>IIA</td>
<td>3 (6)</td>
</tr>
<tr>
<td>IIB</td>
<td>14 (28)</td>
</tr>
<tr>
<td>IIIB</td>
<td>4 (8)</td>
</tr>
<tr>
<td>IV</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Not available</td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>Prior lines of systemic-dose therapy, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>24 (48)</td>
</tr>
<tr>
<td>2</td>
<td>22 (44)</td>
</tr>
<tr>
<td>3</td>
<td>4 (8)</td>
</tr>
<tr>
<td><strong>Prior bevacizumab, n (%)</strong></td>
<td>28 (56)</td>
</tr>
<tr>
<td><strong>Prior pelvic radiation, n (%)</strong></td>
<td>43 (86)</td>
</tr>
</tbody>
</table>

Note: Prior lines of therapy do not include chemotherapy given as part of curative treatment. FIGO, International Federation of Gynecology and Obstetrics; GOG PS, Gynecologic Oncology Group performance status.
Treatment-emergent adverse event summary

- 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>Chills</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Fever</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)

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.
Diagnosis: Squamous cell carcinoma of the cervix

Radical hysterectomy

Pelvic recurrence

Treated with:
- Paclitaxel/carboplatin
- Bevacizumab
- Pelvic radiation

Systemic recurrence

June 2015
Enrolled in GOG-0265

Dose 1
Dose 2
Dose 3

July | Aug | Sept

Dose 2
Axalimogene filolisbac

May 2016
Complete response

Study GOG-0265: 66-year-old patient treated with AXAL – durable complete response

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

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

*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.

TRAEs: Grade 1–2 fatigue, chills, fever, nausea, and grade 3 hypotension, cytokine release syndrome; no grade 4–5 TRAEs reported
GOG/NRG-0265 survival in the context of historical GOG PRmCC

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.
AXAL GOG/NRG-0265 and bevacizumab GOG-227C: 12-month overall survival curves

- **GOG-0265 (ADXS11-001)**
  - Number of patients: 50
  - Events: 43 (86%)
  - Censored: 8 (14%)
  - Median: 6.2 months
  - 95% CI: (4.4–12.3)

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

12-month survival = 38%

12-month survival = 30%

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

- Tissue samples from 41 patients were analyzed
- HPV-positive results were reported for 35 patient samples (85%)

<table>
<thead>
<tr>
<th></th>
<th>HPV-16 (n = 16)</th>
<th>HPV-18 (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-month OS, n (%)</td>
<td>7 (44)</td>
<td>7 (41)</td>
</tr>
<tr>
<td>Median OS for patients alive at 12 months, months (range)</td>
<td>17.8 (12.1–40.6)</td>
<td>15.7 (12.1–16.6)</td>
</tr>
</tbody>
</table>

HPV, human papillomavirus; OS, overall survival.
GOG-0265 results summary

- AXAL is an active therapy based on the mean 12-month survival of 38% (19/50) achieved in this study of a heavily pretreated population
  - Represents the highest 12-month survival to date, with a compelling CR of 18.5 months
  - The probability of this survival advantage being detected by chance vs a true treatment effect was 0.02
  - The shape of the survival curve, with the characteristic raised tail indicating prolongation of patient survival, is representative of the delayed immunotherapy effect
- Results of GOG-0265 compare favorably to bevacizumab GOG-227C,¹ which subsequently gained regulatory approval in first-line combination with chemotherapy
  - This is significant given that ~50% of the 0265 patient population had received prior bevacizumab
- AXAL safety profile was consistent with previous clinical experience and generally well-tolerated, infusion-associated, low-grade, transient adverse events

AXAL, axalimogene filolisbac; CR, complete response.
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

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.
Conclusions

• Cervical cancer is the perfect disease to treat by leveraging the power of immunotherapy, as shown by the elongated survival curve in this study.

• Besides bevacizumab, AXAL is the only targeted agent to have been deemed active in metastatic cervical cancer, a significant result given the study population had received prior bevacizumab and it had failed.

• AXAL is being studied in the phase 3 setting in high-risk cervical cancer, and Advaxis plans to initiate a global, registrational phase 3 study in the metastatic setting later this year.