Sequencing Therapies for Cervical Cancer and Future Directions Beyond IO

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Division of Gynecologic Oncology
Virginia Commonwealth University
Cervical Cancer Trials Advisor, GOG Partners

Thursday, September 9, 2021
Cervical Cancer: Summary of Current High-Risk Disease Treatment

1. **Locally Advanced Disease**
   - FIGO I_B3/I_B/I_B: Chemoradiotherapy (preferred) Surgery if Feasible
   - FIGO IV_A: Chemoradiotherapy (preferred) Surgery if Feasible

2. **Metastatic Disease**
   - FIGO IV_B: Platinum-based Chemotherapy +/- Bevacizumab
   - Pembrolizumab (PD-L1+/ MSIh/dMMR/TMBh) or Single-agent Chemotherapy

1. **Est. 1999**
2. **Est. 2014**
3. **Est. 2018**

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1. NCCN Cervical Cancer Guidelines v2.2019
2. SEER Cancer Stat Facts: Cervical Cancer, National Cancer Institute. Bethesda, MD
Locally Advanced, Metastatic and Recurrent Cervical Cancer: A HIGH UNMET CLINICAL NEED!

- New drug strategy-find activity in later lines of treatment
- Special FDA new drug approval pathways
- Accelerated approval when no standard of care exists
- For cervical ca-after 1\textsuperscript{st} chemotherapy (2L or greater)
- Requires confirmatory trial in earlier line of therapy
## Single-agent anti PD-(L)1 activity, 2L+

<table>
<thead>
<tr>
<th>Agent</th>
<th>N</th>
<th>ORR (95% CI)</th>
<th>ORR PD-L1+ (95% CI)</th>
<th>ORR PD-L1- (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab¹</td>
<td>98</td>
<td>14.3% (8.0-22.8)</td>
<td>17.1% (9.7-27.0)</td>
<td>0% (0-21.8)</td>
</tr>
<tr>
<td>Cemiplimab²</td>
<td>304</td>
<td>16.4% (12.5-21.1)</td>
<td>18.3% (10.6-28.4)</td>
<td>11.4% (3.8-24.6)</td>
</tr>
<tr>
<td>Balstilimab³</td>
<td>140</td>
<td>15% (10.0-21.8)</td>
<td>20.0% (12.9-29.7)</td>
<td>7.9% (NR)</td>
</tr>
<tr>
<td>Socazolimab⁴</td>
<td>94</td>
<td>18.1% (10.9-27.4)</td>
<td>19.6% (10.2-32.4)</td>
<td>20.7% (8.0-39.7)</td>
</tr>
</tbody>
</table>

1. Chung et al. Virtual SGO 2021  
2. Tewari KS et al. Virtual IGCS 2021  
# Randomized phase III ICI trials in metastatic/recurrent setting

<table>
<thead>
<tr>
<th>Frontline ICI trial</th>
<th>Agent (n)</th>
<th>Design</th>
<th>Stratification factors</th>
<th>Primary endpoint(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keynote-826 (NCT03635567)</td>
<td>Pembro (600)</td>
<td>2 arm 1:1 GOG 240 control MD choice bev</td>
<td>• Stage • +/- Bev • PD-L1 status</td>
<td>• PFS BICR • OS</td>
</tr>
<tr>
<td>BEATcc (NCT03556839)</td>
<td>Atezo (404)</td>
<td>2 arm 1:1 GOG 240 control Mandatory bev</td>
<td>• Prior CRT • Histology • Chemotherapy Backbone: Cis v Carbo</td>
<td>• OS</td>
</tr>
<tr>
<td>FERMATA (NCT03912415)</td>
<td>BCD-100 (316)</td>
<td>2 arm 1:1 GOG 240 control MD choice bev</td>
<td>• Stage • +/- Bev • PDL1 status • Ethnicity</td>
<td>• OS</td>
</tr>
</tbody>
</table>
KEYTRUDA® (pembrolizumab) Plus Platinum-Based Chemotherapy With or Without Bevacizumab Significantly Improved OS and PFS Compared to Platinum-Based Chemotherapy With or Without Bevacizumab Alone as First-Line Treatment, Regardless of PD-L1 Status

KENILWORTH, N.J., Jun 22, 2021--(BUSINESS WIRE)--Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced that the pivotal Phase 3 KEYNOTE-826 trial investigating KEYTRUDA, Merck's anti-PD-1 therapy, in combination with platinum-based chemotherapy (paclitaxel plus cisplatin or paclitaxel plus carboplatin) with or without bevacizumab, met its primary endpoints of overall survival (OS) and progression-free survival (PFS) for the first-line treatment of patients with persistent, recurrent or metastatic cervical cancer. Based on an interim analysis conducted by an independent Data Monitoring Committee, KEYTRUDA plus platinum-based chemotherapy with or without bevacizumab demonstrated statistically significant and clinically meaningful improvements in OS and PFS compared to the same platinum-based chemotherapy regimens with or without bevacizumab alone, regardless of PD-L1 status; KEYTRUDA is the first anti-PD-1/PD-L1 therapy to demonstrate this. The safety profile of KEYTRUDA in this trial was consistent with that observed in previously reported studies. Results will be presented at an upcoming medical meeting and will be submitted to regulatory authorities.

https://www.businesswire.com/news/home/20210622005214
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
- Available tissue (archival or fresh)
- N=404 pts

**Control Arm**

Cis- or carboplatin + paclitaxel + bevacizumab (GOG 240) until disease progression, unacceptable toxicity, death or withdrawal of consent

**Experimental Arm**

Cis- or carboplatin + paclitaxel + bevacizumab + atezolizumab until disease progression, unacceptable toxicity, death or withdrawal of consent

**Stratification Factors:**
- Prior ChemoRT
- Histology: SCC vs Adeno (including AdenoSquamous)
- Chemotherapy Backbone: Cisplatin vs Carboplatin

**Primary Endpoint:**
Overall survival (OS)

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

ClinicalTrials.gov Identifier: NCT03556839
**PACIFIC: Phase III Trial of Durvalumab Post-CRT Maintenance for Locally-advanced, Unresectable NSCLC**

<table>
<thead>
<tr>
<th>Study Population</th>
<th></th>
<th>2.1</th>
<th></th>
<th>Efficacy Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>• NSCLC Stage 3 Unresectable</td>
<td></td>
<td></td>
<td></td>
<td>Primary:</td>
</tr>
<tr>
<td>• Prior ≥2 cycles of platinum-based Tx</td>
<td></td>
<td></td>
<td></td>
<td>PFS, OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Secondary:</td>
</tr>
<tr>
<td>• N= 713</td>
<td></td>
<td></td>
<td></td>
<td>12 mo PFS, 18 mo PFS, 24 mo OS, ORR, DOR,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Time to death, Time to distant metastasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Durvalumab</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>R</td>
<td></td>
<td>10 mg/kg IV Q2W, up to 12 months Vs</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>arms</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Efficacy Endpoints**
- Primary: PFS, OS
- Secondary: 12 mo PFS, 18 mo PFS, 24 mo OS, ORR, DOR, Time to death, Time to distant metastasis

### Efficacy Results

<table>
<thead>
<tr>
<th></th>
<th>Durvalumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of Events/ No of Patients</td>
<td>214/476</td>
<td>157/237</td>
</tr>
<tr>
<td>PFS (95% CI)</td>
<td>16.8 (13-18.1)</td>
<td>5.6 (4.6-7.6)</td>
</tr>
<tr>
<td>OS (95% CI)</td>
<td>NR (34.7-NR)</td>
<td>28.7 (22.9-NR)</td>
</tr>
<tr>
<td>12 mo PFS (95% CI)</td>
<td>55.9 (51-60.4)</td>
<td>35.3 (29-41.7)</td>
</tr>
<tr>
<td>18 mo PFS (95% CI)</td>
<td>44.2 (37.7-50.5)</td>
<td>27 (19.9-34.5)</td>
</tr>
<tr>
<td>24 mo OS (95% CI)</td>
<td>66.3 (61.7-70.4)</td>
<td>55.6 (48.9-61.8)</td>
</tr>
</tbody>
</table>

*Antonia et al, NEJM 2017; Antonia et al, NEJM 2016*
GOG 9929: CRT + ipilimumab (anti-CTLA4)

Figure 3. Progression-Free and Overall Survival in Patients Receiving 2 or More Cycles of Ipilimumab

On-treatment T-cell activation anti-CTLA4

Duska, et al, SGO 2020: Randomized phase 2 translational study of pembrolizumab during and after CRT

**Primary Carcinoma of the Cervix:**
Squamous, adenosquamous, adenocarcinoma
Stages IB2-IVA or IB1 with positive nodes (FIGO 2009)

PET/CT and MRI pelvis
Tissue biopsy and peripheral blood collection

**Randomized 1:1**

**ARM1 (sequential):**
CDDP 40 mg/m² weekly for 5-6 weeks
Concurrent XRT: EBRT plus brachytherapy
3 cycles of consolidative pembrolizumab: 200 mg every 21 days beginning week 9 for 3 cycles

**ARM2 (concurrent):**
CDDP 40 mg/m² weekly for 5-6 weeks
3 cycles of concurrent pembrolizumab: 200 mg every 21 days beginning day 1 for 3 cycles
Concurrent XRT: EBRT plus brachytherapy

PET/CT required
MRI pelvis (optional)
Tissue biopsy and peripheral blood collection

CRT was SOC per institution, complete in 8 weeks
<table>
<thead>
<tr>
<th>Frontline ICI trial</th>
<th>Population</th>
<th>Agent (n)</th>
<th>Design</th>
<th>Primary endpoint(s)</th>
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</thead>
</table>
| **CALLA (NCT03830866)** | • FIGO 2009 IB2-IIB node+  
• IIIA-IVA any nodal status  
• Measurable RECIST v1.1  
• ECOG PS: 0-1 | Durva (714) | 2 arm 1:1 CRT control 24 months | • PFS |
| **ENGOT cx11/GOG 3047/KEYNOTE-A18 (NCT04221945)** | • FIGO 2009 IB2-IIB node+  
• IIIA-IVA any nodal status  
• Measurable RECIST v1.1  
• ECOG PS: 0-1 | Pembro (980) | 2 arm 1:1 CRT control 24 months | • PFS  
• OS |

CRT, chemoradiotherapy; durva, durvalumab; ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics; ICI, immune checkpoint inhibitor; OS, overall survival; pembro, pembrolizumab; RECIST, Response Evaluation Criteria in Solid Tumours
Cervical Cancer: Projection of Treatment

Locally Advanced Disease
- Chemoradioimmunotherapy (preferred)

Metastatic Disease
- Platinum-based Chemoimmunotherapy +/- Bevacizumab
  - LN-145 (lifileucel) TILs?
    - NEED non-IO options
  - Clinical trial Assay-directed Chemotherapy

Recurrent Disease (post CRT +/- IO)
- No Prior IO
  - Platinum-based Chemoimmunotherapy +/- Bevacizumab
- Prior IO
  - Platinum-based Chemotherapy +/- Bevacizumab
    - Will need non-IO options
  - LN-145 (lifileucel) TILs?
    - URGENT NEED non-IO, post-IO options
  - Clinical trial Assay-directed Chemotherapy
No proof of concept to date

LN-145 (lifileucel) TILs

Combinations likely key

Best response and time to progression on or after initial checkpoint will likely matter

As urgent as PARPi after PARPi in HGSOC
LN-145 Phase II Trial in Recurrent and/or Metastatic Cervical Carcinoma

A phase II, multicenter study to evaluate the efficacy and safety of adoptive cell therapy using autologous tumor-infiltrating lymphocytes (LN-145) in patients with recurrent, metastatic, or persistent cervical carcinoma

N = 47; Simon’s two-stage design

Key Inclusion Criteria:

• Measurable metastatic disease and ≥1 lesion resectable for TIL generation
• At least one prior systemic therapy, checkpoint-naïve
• Age ≥18
• ECOG PS 0-1
• Adequate hematologic, cardiac, pulmonary, hepatic, and renal function

Endpoints:

• Efficacy and safety

Autologous TILs (LN-145) 2L+ FDA Breakthrough Designation

- ORR = 44.4%
- CR = 11.1%

- 78% of patients had a reduction in tumor burden
- Median follow up is 7.4 months
- Mean number of TIL cells infused: $28 \times 10^9$
- Median number of IL-2 doses administered was 6.0

# I/O combinations in the pipeline, 2L+

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>N</th>
<th>ORR (%) (95% CI)</th>
<th>ORR PD-L1+ (95% CI)</th>
<th>ORR PD-L1- (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab + ipilimumab</td>
<td>26</td>
<td>23% (9-43.6)</td>
<td>40% (12.2-73.8)</td>
<td>9.1% (0.2-41.3)</td>
</tr>
<tr>
<td>Nivolumab + ipilimumab</td>
<td>22</td>
<td>36% (17.2-59.3)</td>
<td>16.7% (2.1-48.4)</td>
<td>57.1% (18.4-90.1)</td>
</tr>
<tr>
<td>Balstilimab + Zalifrelimab</td>
<td>143</td>
<td>22% (16-29)</td>
<td>27% (19-37)</td>
<td>11% (4-25)</td>
</tr>
<tr>
<td>AK-104 (PD1i/CTLA4i bispecific)</td>
<td>40</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Bintrafusp alfa (PDL1i/TGFbi bispecific)</td>
<td>39</td>
<td>28.2% (15-44.9)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Tiragolumab (+atezolizumab)</td>
<td>160</td>
<td>--</td>
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<td>--</td>
</tr>
<tr>
<td>Socazolimab</td>
<td>94</td>
<td>18.1% (10.9-27.4)</td>
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Balstilimab +/- Zalifrelimab

Two Parallel, Single-arm Trials Testing Balstilimab Alone and with Zalifrelimab in Recurrent/Metastatic Cervical Cancer (for up to 24 mon)

Population

- Histologically confirmed SCC, ASC, AC of the cervix relapsed after platinum-based treatment
- Measurable baseline dx
- ECOG PS 0–1

Treatment

Bal (n = 161)
3 mg/kg q2w
(NCT03104699)

Bal + Zal (n = 155)
Bal 3 mg/kg q2w + Zal 1 mg/kg q6w
(NCT03495882)

Follow-up

Imaging every 6 wks through 2 yrs

• Primary endpoint: Independent Review Committee (IRC) ORR by RECIST 1.1
• Secondary endpoints: OS, PFS, DOR

O'Malley et al, ESMO 2020
Tumor Response with Bal stilimab Monotherapy

• Patients with ≥1 prior chemotherapy

<table>
<thead>
<tr>
<th>PD-L1 Status</th>
<th>Negative</th>
<th>Positive</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR [95% CI]</td>
<td>18/138 (13%) [8, 20]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>3/138 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>15/138 (11%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOR (mon)</td>
<td>15.4 [1.3+, 15.4]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-L1 (+) (%) [95% CI]</td>
<td>15/84 (18%) [11, 27]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-L1 (-) (%) [95% CI]</td>
<td>3/37 (8%) [3, 21]</td>
<td></td>
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</tr>
</tbody>
</table>
Tumor Response with Balstilimab plus Zalifrelimab

- Patients with ≥1 prior chemotherapy

<table>
<thead>
<tr>
<th>PD-L1 Status</th>
<th>ORR [95% CI] 24/119 (20%) [14, 28]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>6/119 (5%)</td>
</tr>
<tr>
<td>PR</td>
<td>18/119 (15%)</td>
</tr>
<tr>
<td>DOR (mon)</td>
<td>NR [1.3+,15.4+]</td>
</tr>
<tr>
<td>PD-L1 (+) (%) [95% CI]</td>
<td>16/61 (26%) [17, 38]</td>
</tr>
<tr>
<td>PD-L1 (-) (%) [95% CI]</td>
<td>3/33 (9%) [3, 24]</td>
</tr>
</tbody>
</table>

O’Malley et al, ESMO 2020
FDA Grants Balstilimab/Zalifrelimab Dual Immunotherapy Fast Track Designation in Cervical Cancer

March 12, 2020
Jason M. Broderick

The FDA has granted a Fast Track designation to the combination of the PD-1 inhibitor balstilimab and the CTLA-inhibitor zalifrelimab for the treatment of patients with relapsed or refractory metastatic cervical cancer.
GOG-3028 - A Two Arm, Randomized, Non Comparative Blinded Phase 2 Trial of AGEN2034 (anti PD-1) as a Monotherapy or in Combination Therapy with AGEN1884 (anti-CTLA4) or with Placebo in Women with Recurrent Cervical Cancer (Second Line) – RaPiDS

Patient Eligibility

- Cervical cancer that has relapsed after a platinum-based treatment (first line) regimen for advanced (recurrent, unresectable, or metastatic) disease
- Measurable disease on imaging based on RECIST version 1.1
- ECOG PS ≤1
- Sufficient and adequate formalin-fixed paraffin embedded (FFPE)

Randomization 1:1

Treatment up to 24 months

Balstilimab (300 mg) every 3 weeks
Placebo every 6 weeks

Balstilimab (300 mg) every 3 weeks
Zalifrelimab (1 mg/kg) every 6 weeks

Primary Endpoint
- ORR according to RECIST 1.1
6 Completely Enrolled Studies in Cervical Cancer as of Feb 2021

1. Phase 3: CALLA (Durvalumab with chemotherapy and radiation)*
2. Phase 3: KN-826 (Pembrolizumab added to chemotherapy +/-bevacizumab in 1-L)*
3. Phase 3: EMPOWER-CERVICAL 1 (Cemiplimab vs chemotherapy in 2-L)*
4. Phase 2: innovaTV 204 (Tisotumab vedotin in 2-L)
5. Phase 2: (LN-145 in 2-L)*
6. Phase 2: SKYSCRAPER-04 (Tiragolumab plus atezolizumab in 2-L)*

* Results Pending
6 Completely Enrolled Studies in Cervical Cancer as of April 2021

1. Phase 3: CALLA (Durvalumab with chemotherapy and radiation)*
2. Phase 3: KN-826 (Pembrolizumab added to chemotherapy +/- bevacizumab in 1-L)*
3. Phase 3: EMPOWER- CERVICAL 1 (Cemiplimab vs chemotherapy in 2-L)**
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5. Phase 2: (LN-145 in 2-L)*
6. Phase 2: SKYSCRAPER-04 (Tiragolumab plus atezolizumab in 2-L)*

*Results Pending
**Results announced
***BLA pending
6 Completely Enrolled Studies in Cervical Cancer as of September 2021

1. Phase 3: CALLA (Durvalumab with chemotherapy and radiation)*
2. Phase 3: KN-826 (Pembrolizumab added to chemotherapy +/- bevacizumab in 1-L)**
3. Phase 3: EMPOWER- CERVICAL 1 (Cemiplimab vs chemotherapy in 2-L)**
4. Phase 2: innovaTV 204 (Tisotumab vedotin in 2-L)***
5. Phase 2: (LN-145 in 2-L)*
6. Phase 2: SKYSCRAPER-04 (Tiragolumab plus atezolizumab in 2-L)*

**Results announced
Thank You!!

lrandall@gog.org