Locally Advanced and Recurrent Cervical Cancer: Current Landscape

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Thursday, September 9, 2021
# Faculty Disclosure

<table>
<thead>
<tr>
<th>Company Name</th>
<th>Honoraria/Expenses</th>
<th>Consulting/Advisory Board</th>
<th>Funded Research</th>
<th>Royalties/Patent</th>
<th>Stock Options</th>
<th>Ownership/Equity Position</th>
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Cervical Cancer is an International Health Concern
An Estimated 14,480 Cases of Invasive Cervical Cancer in the US in 2020

- Death rate in 2016 (2.2 per 100,000) was less than half that in 1975 (5.6 per 100,000)

- From 2007 to 2016, the death rate decreased by about 1% per year in women >50 years of age and older, but was stable in <50
### FIGO staging systems: differences between the 2009 and 2018 FIGO staging systems for cervical cancer

<table>
<thead>
<tr>
<th></th>
<th>FIGO 2009</th>
<th>FIGO 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Cervical carcinoma confined to the uterus (extension to the corpus should be disregarded)</td>
<td>Cervical carcinoma confined to the uterus (extension to the corpus should be disregarded)</td>
</tr>
<tr>
<td>IA</td>
<td>Invasive carcinoma diagnosed only by microscopy, with a maximum depth of invasion ≤5.0 mm and largest extension ≥7.0 mm</td>
<td>Invasive carcinoma diagnosed only by microscopy, with a maximum depth of invasion &lt;5 mm</td>
</tr>
<tr>
<td>IA1</td>
<td>Measured stromal invasion with a depth of ≤3.0 mm and a horizontal spread of ≤7.0 mm</td>
<td>Measured stromal invasion with a depth of &lt;3 mm</td>
</tr>
<tr>
<td>IA2</td>
<td>Measured stromal invasion &gt;3.0 mm and &lt;5.0 mm, with a horizontal spread of ≤7.0 mm</td>
<td>Measured stromal invasion ≥3 mm, and &lt;5 mm in depth</td>
</tr>
<tr>
<td>IB</td>
<td>Clinically visible lesion confined to the cervix or microscopic lesion greater than Stage IA</td>
<td>Invasive carcinoma with a maximum depth of invasion ≥5 mm (greater than Stage IA), lesion limited to the cervix uteri</td>
</tr>
<tr>
<td>IB1</td>
<td>Clinically visible lesion ≤4.0 cm in greatest dimension</td>
<td>Invasive carcinoma ≥5 mm depth of stromal invasion, and &lt;2 cm in greatest dimension</td>
</tr>
<tr>
<td>IB2</td>
<td>Clinically visible lesion &gt;4.0 cm in greatest dimension</td>
<td>Invasive carcinoma ≥2 cm and &lt;4 cm in greatest dimension</td>
</tr>
<tr>
<td>IB3</td>
<td>N/A</td>
<td>Invasive carcinoma ≥4 cm in greatest dimension</td>
</tr>
<tr>
<td>II</td>
<td>Cervical carcinoma invading beyond the uterus but not to the pelvic wall or lower third of the vagina</td>
<td>Cervical carcinoma invading beyond the uterus but not to the pelvic wall or lower third of the vagina</td>
</tr>
<tr>
<td>IIA</td>
<td>Tumour without parametrial invasion</td>
<td>Tumour without parametrial invasion</td>
</tr>
<tr>
<td>IIA1</td>
<td>Clinically visible lesion ≤4.0 cm in greatest dimension</td>
<td>Invasive carcinoma &lt;4 cm in greatest dimension</td>
</tr>
<tr>
<td>IIA2</td>
<td>Clinically visible lesion &gt;4.0 cm in greatest dimension</td>
<td>Invasive carcinoma ≥4 cm in greatest dimension</td>
</tr>
<tr>
<td>IIB</td>
<td>Tumour with parametrial invasion</td>
<td>Tumour with parametrial invasion</td>
</tr>
<tr>
<td>III</td>
<td>Tumour extending to the pelvic sidewall and / or involving the lower third of the vagina and / or causing hydronephrosis or non-functioning kidney</td>
<td>Tumour extending to the pelvic sidewall and / or involving the lower third of the vagina and / or causing hydronephrosis or non-functioning kidney and / or involves PLN and / or PALNs</td>
</tr>
<tr>
<td>IIIA</td>
<td>Tumour involving the lower third of the vagina but not extending to the pelvic wall</td>
<td>Tumour involving the lower third of the vagina but not extending to the pelvic wall</td>
</tr>
<tr>
<td>IIIB</td>
<td>Tumour extending to the pelvic wall and / or causing hydronephrosis or non-functioning kidney</td>
<td>Tumour extending to the pelvic wall and / or causing hydronephrosis or non-functioning kidney</td>
</tr>
<tr>
<td>IIIIC1/2</td>
<td>N/A</td>
<td>Involvement of the PLN and / or PALNs, irrespective of tumour size and extent (with r and p notations*)</td>
</tr>
<tr>
<td>IVA</td>
<td>Spread to adjacent pelvic organs</td>
<td>Spread to adjacent pelvic organs</td>
</tr>
<tr>
<td>IVB</td>
<td>Spread to distant organs</td>
<td>Spread to distant organs</td>
</tr>
</tbody>
</table>

*Notations of r (imaging) and p (pathology) indicate the findings that are used to allocate the case to Stage IIIC. Pecorelli S. *Int J Gynaecol Obstet* 2009;105:103–104; Bhatla N, et al. *Int J Gynaecol Obstet* 2019;145:129–135.
Cervical cancer: summary of treatment

Initial Diagnosis
Colposcopy / Biopsy

Early Disease
46%2
- FIGO IA1
- FIGO IA2
- FIGO IB2 + IIA

Surgery Followed by
Adjuvant Treatment Depending on Risk Factors

Locally Advanced Disease
36%2
- FIGO IB3/IIIB/IIIB

Chemoradiotherapy (preferred)
Surgery if Feasible

Metastatic Disease
15%2
- FIGO IVB

Platinum-based Chemotherapy
+/- Bevacizumab

Pembrolizumab (PD-L1+/ MSIH/dMMR) or Single-agent Chemotherapy

LEEP: Loop Electrosurgical Excision Procedure; PD-L1: Programmed Cell Death Ligand-1; MSIH: Microsatellite Instability High; dMMR: deficient Mismatch Repair
External Beam Radiation

APP/PA Fields

3D Conformal

IMRT
Treatment timing

- Treatment delay has been correlated with higher rates of pelvic failure, and current guidelines stipulate completion of EBRT plus brachytherapy within 8 weeks.\(^1\)
- Treatment extended beyond 8 weeks is associated with poorer outcomes.\(^1\)
  - It is possible that prolonging treatment beyond 8 weeks allows increased repopulation of cancer cells, resulting in reduced local control rates.\(^2\)

Effect of treatment time on pelvic control and survival.\(^3\)

Brachytherapy

- Brachytherapy is the only method demonstrated to provide the high dose of radiation needed to control cervical cancer while minimizing adverse effects on normal tissue\textsuperscript{1,2}

- Imaging can improve the efficacy of brachytherapy\textsuperscript{3}

A radioactive source is placed in or near the tumor, which allows for the tumor to receive a concentrated dose while relatively sparing the surrounding normal tissue\textsuperscript{1}

Underutilization of Brachytherapy

- SEER data shows brachytherapy utilization decreased from 83% in 1988 to 58% in 2009 ($p<0.001$)$^1$

- Brachytherapy treatment was associated with higher 4-year cause-specific survival (64.3% vs 51.5%, $p<0.001$) and overall survival (58.2% vs 46.2%, $p<0.001$)$^1$

- A study of patients with cervical cancer in California showed 45% brachytherapy utilization during the study period (2004–2014), with a subsequent decrease in survival outcomes (HR, 1.16; 95% CI, 1.01–1.34; $p=0.0330$) in patients who did not receive brachytherapy$^2$

- There was also a disparity in patients treated with brachytherapy$^2$:
  - Brachytherapy utilization was lower in patients aged >80 years and in patients at Stage IVA
  - Black patients and those in low socioeconomic situations had worse survival

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OUTBACK: randomized Phase 3 trial of adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared with chemoradiation alone

Patients with cervical cancer suitable for chemoradiation with curative intent:
• FIGO 2008 Stage IB1+LN, IB2, II, IIIB, IVA
• ECOG 0–2
• Squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma
• No nodal disease above L3/4

Concurrent chemoradiation (CRT)

Concurrent chemoradiation (CRT)

Adjuvant chemoradiation (ACT)
Carboplatin + paclitaxel

Primary endpoint:
• Overall survival

Secondary endpoints:
• Progression-free survival
• Adverse events
• Sites of disease recurrence
• Radiation protocol compliance
• Patient-reported outcomes

Stratification factors:
• Pelvic or common iliac nodal involvement
• Requirement for extended-field radiotherapy
• FIGO 2008 stage: IB / IIA or IIB or IIIB / IVA
• Age <60 or ≥60 years
• Hospital / site

OUTBACK: Key Efficacy Outcomes

ACT did not significantly improve PFS or OS
Sites of disease progression were not significantly different between the treatment arms and about two-thirds of women did not experience recurrence.
### OUTBACK: Sensitivity Analysis

<table>
<thead>
<tr>
<th>Survival Rates at 5 years (%)</th>
<th>Hazard ratios from Cox regressions</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT +ACT Difference (95% CI)</td>
<td>(95% CI) Interaction P</td>
</tr>
<tr>
<td>Overall survival</td>
<td></td>
</tr>
<tr>
<td>Completed CRT 71% 74% +3.3 (-4 to 11) 0.37</td>
<td>0.81 (0.60-1.08) 0.15 0.11</td>
</tr>
<tr>
<td>Did not complete CRT 73% 64% -9.2 (-24 to 5) 0.21</td>
<td>1.32 (0.77-2.25) 0.32</td>
</tr>
<tr>
<td>Progression-Free Survival</td>
<td></td>
</tr>
<tr>
<td>Completed CRT 62% 66% +4.8 (-3 to 12) 0.22</td>
<td>0.78 (0.60-1.00) 0.05 0.12</td>
</tr>
<tr>
<td>Did not complete CRT 60% 51% -8.6 (-23 to 6) 0.26</td>
<td>1.16 (0.75-1.80) 0.49</td>
</tr>
</tbody>
</table>

There was an **absolute difference of 3% for OS**, which was not greater than expected by chance alone.
Lessons Learned from OUTBACK Trial

1. High drop out rate with switch maintenance strategy
2. With long post-progression survival, preferred endpoint is PFS
3. With almost 100% crossover, OS is not the preferred endpoint
4. Newer agents such as antiangiogenics and immunotherapy not studied
Advanced/Recurrent Cervical Cancer: A HIGH UNMET CLINICAL NEED!

Stage IVB Cervical Cancer

Cervical cancer has spread to other parts of the body:

- Lymph nodes
- Lung
- Liver
- Intestinal tract
- Cervix
- Bone
- Abdominal wall

GOG-204: Study Design

A Phase III trial to assess the toxicity and efficacy of cisplatin doublet combinations in advanced and recurrent cervical cancer

Patients (N=434)
- Primary stage 4b or recurrent/persistent CC
- Measurable disease
- GOG PS 0-1
- No CNS disease
- No prior chemotherapy (unless CRT)

Randomize

Regimen 1
Paclitaxel 135 mg/m^2 over 24 hours and CDDP 50 mg/m^2 q3w, 6 cycles

Regimen 2
Vinorelbine 30 mg/m^2 IV bolus day 1 and 8 and CDDP 50 mg/m^2 q3w, 6 cycles

Regimen 3
Gemcitabine 1000mg/m^2 IV day 1 and 8 and CDDP 50 mg/m^2 IV day q3w, 6 cycles

Regimen 4
Topotecan 0.75 mg/m^2 over 30 min days 1, 2, 3 CDDP 50 mg/m^2 IV day 1, q3w, 6 cycles

Quality of life was assessed for all regimens

GOG-204: Results

- Response rates for PC, VC, GC and TC were 29.1%, 25.9%, 22.3%, and 23.4%.
- Comparable toxicity except for leukopenia, neutropenia, infection and alopecia.

Stage IVB, persistent or recurrent cervical cancer; not amenable to curative surgery / radiotherapy

*Balancing factors:
- Tumors outside of the prior irradiation field (yes or no)
- PS 0-1 or 2
- SCC or non-SCC
- Institution

**Standard arm: TP**
- Paclitaxel 135 mg/m² 24h d1
- Cisplatin 50 mg/m² 2h d2

**Experimental arm: TC**
- Paclitaxel 175 mg/m² 3h d1
- Carboplatin AUC 5 1h d1

ClinicalTrials.gov Identifier:NCT00295789
Overall Survival

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Events</th>
<th>Median(m)</th>
<th>1-yr</th>
<th>2-yr</th>
<th>3-yr</th>
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</thead>
<tbody>
<tr>
<td>TP</td>
<td>123</td>
<td>106</td>
<td>18.3 m</td>
<td>72.4%</td>
<td>38.8%</td>
<td>18.3%</td>
</tr>
<tr>
<td>TC</td>
<td>121</td>
<td>98</td>
<td>17.5 m</td>
<td>67.6%</td>
<td>31.5%</td>
<td>21.3%</td>
</tr>
</tbody>
</table>

HR: 0.994 [90% CI: 0.789-1.253 (<1.29)]
noninferiority one-sided $P = .032$

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

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

United States, Canada & Spain

Paclitaxel 135 or 175 mg/m² IV
Cisplatin 50 mg/m² IV
Paclitaxel 135 or 175 mg/m² IV
Cisplatin 50 mg/m² IV
Bevacizumab 15 mg/kg IV
Paclitaxel 175 mg/m² IV
Topotecan 0.75 mg/m² d1-3
Bevacizumab 15 mg/kg IV
Paclitaxel 175 mg/m² IV
Topotecan 0.75 mg/m² d1-3
Bevacizumab 15 mg/kg IV

Chemo alone
q 21 d Rx to PD, toxicity, CR

Chemo + bevacizumab

GOG-0240: Final OS/PFS

HR: 0.71 (95% CI: 0.54-0.95)  
*P*=0.004

Follow up: 20.8 months

HR: 0.67 (95% CI: 0.54-0.82)  
*P*=0.002

## GOG 240: Toxicity

### Table: Adverse Events by Grade

<table>
<thead>
<tr>
<th>Event</th>
<th>Chemotherapy (n=219)</th>
<th>Chemotherapy + Bevacizumab (n=220)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GI events (grade ≥2)</strong></td>
<td>96 (44)</td>
<td>114 (52)</td>
</tr>
<tr>
<td>Fistula:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI</td>
<td>0</td>
<td>7 (3)</td>
</tr>
<tr>
<td>GU</td>
<td>1 (&lt;1)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Total b</td>
<td>1 (&lt;1)</td>
<td>13 (6)</td>
</tr>
<tr>
<td><strong>Hypertension (grade ≥2)</strong></td>
<td>4 (2)</td>
<td>54 (25)</td>
</tr>
<tr>
<td><strong>Proteinuria (grade ≥3)</strong></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><strong>Febrile neutropenia (grade ≥3)</strong></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><strong>CNS bleeding (grade ≥3)</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GI bleeding (grade ≥3)</td>
<td>1 (&lt;1)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>GU bleeding (grade ≥3)</td>
<td>1 (&lt;1)</td>
<td>6 (3)</td>
</tr>
</tbody>
</table>

- **a** Excluding fistulas. Fistulas were mainly managed supportively; one patient underwent colostomy, and another received nephrostomy tubes.
- **b** Hypertension of grade 2 or higher was defined as recurrent or continuous hypertension for a period of more than 254 hours or a symptomatic increase in blood pressure by more than 20 mm Hg diastolic or to <150/100 mm Hg if the blood pressure was previously normal.
- **c** Bleeding was primarily managed with supportive therapy and transfusions of packed RBCs, most commonly in the outpatient setting.

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- CNS, central nervous system; GI, gastrointestinal; GU, genitourinary; RBC, red blood cells.
# Improving OS in Recurrent or Metastatic Cervical Cancer

**How do we move forward?**

<table>
<thead>
<tr>
<th>Year</th>
<th>OS (months)</th>
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<tbody>
<tr>
<td>1989</td>
<td>GOG 110 Cisplatin + Ifosfamide</td>
</tr>
<tr>
<td>1997</td>
<td>GOG 169 Cisplatin + Paclitaxel</td>
</tr>
<tr>
<td>2002</td>
<td>GOG 149 Cisplatin + Ifosfamide + Bleomycin</td>
</tr>
<tr>
<td>2004</td>
<td>GOG 179 Cisplatin + Topotecan</td>
</tr>
<tr>
<td>2005</td>
<td>GOG 179 Cisplatin + Topotecan</td>
</tr>
<tr>
<td>2009</td>
<td>GOG 169 Cisplatin + Paclitaxel</td>
</tr>
<tr>
<td>2013</td>
<td>GOG 240 Cisplatin + Paclitaxel + Bevacizumab</td>
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</tbody>
</table>

**Graph:**
- **GOG 110 Cisplatin + Ifosfamide**
- **GOG 169 Cisplatin + Paclitaxel**
- **GOG 149 Cisplatin + Ifosfamide + Bleomycin**
- **GOG 179 Cisplatin + Topotecan**
- **GOG 240 Cisplatin + Paclitaxel + Bevacizumab**
Rationale for Immunotherapy

• TCGA data
  - Amplifications in PD-L1/L2
    • Correlates with key immune cytolytic effectors
    • Can limit protective immunity

• Immunotherapy
  - PD-1/L1 inhibition
    • Promote T-cell activation against tumors
  - CTLA-4 inhibition
    • Enhances tumor-specific CD8+ T-cell responses

Mutational Burden Compared With Other Tumors

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

Median follow-up: 36.9 months
Range: 34.3-41.0 months

Baseline characteristic, n (%) N=98

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>46.0 (24-75)</td>
</tr>
<tr>
<td>ECOG PS 1</td>
<td>64 (65)</td>
</tr>
<tr>
<td>PD-L1+ tumor^a</td>
<td>82 (84)</td>
</tr>
<tr>
<td>Number of prior therapies</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>44 (45)</td>
</tr>
<tr>
<td>2</td>
<td>31 (32)</td>
</tr>
<tr>
<td>3</td>
<td>13 (13)</td>
</tr>
<tr>
<td>≥4</td>
<td>8 (8)</td>
</tr>
</tbody>
</table>

^CPS ≥1
KEYNOTE-158: Safety and Efficacy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Overall(^a) N=98</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR(^d), % (95% CI)</td>
<td>14.3 (8.0-22.8)</td>
</tr>
</tbody>
</table>

Best overall response, n (%)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>5 (5.1)</td>
</tr>
<tr>
<td>PR</td>
<td>9 (9.2)</td>
</tr>
<tr>
<td>SD</td>
<td>16 (16.3)</td>
</tr>
<tr>
<td>PD</td>
<td>55 (56.1)</td>
</tr>
<tr>
<td>Non-evaluable(^e)</td>
<td>4 (4.1)</td>
</tr>
<tr>
<td>No assessment(^f)</td>
<td>9 (9.2)</td>
</tr>
</tbody>
</table>

Safety Summary

- 65% of patients experienced any TRAE
- 12% had grade ≥3 TRAEs
- 4% had TRAEs leading to discontinuation
- ~25% of patients had any irAE; ~4% were grade ≥3, ~50% resolved
- 2% of patients discontinued pembrolizumab due to irAEs (hepatitis, n=2)

Pembrolizumab received FDA approval for the treatment of PD-L1+ r/m cervical cancer; q6w dosing approved in April 2020

\(^{a}\text{Includes 1 patient with unknown PD-L1 expression level.}
\(^{b}\text{CPS ≥1.}
\(^{c}\text{CPS <1.}
\(^{d}\text{At the time of analysis, all responses were confirmed.}
\(^{e}\text{Target lesions not captured on ≥1 post-baseline imaging assessment.}
\(^{f}\text{Post-baseline tumor assessment not performed.}
\(^{g}\text{TRAEs leading to discontinuation included hepatitis (n=2), diarrhea (n=1), and stomatitis (n=1).}

US FDA Accelerated Approval of Pembrolizumab (June 12, 2018)

FDA approves pembrolizumab for advanced cervical cancer with disease progression during or after chemotherapy

On June 12, 2018, the Food and Drug Administration approved pembrolizumab (Keytruda, Merck and Co. Inc.) for patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

Pembrolizumab was investigated in 98 patients with recurrent or metastatic cervical cancer enrolled in a single cohort of KEYNOTE 158 (NCT02628067), a multicenter, non-randomized, open-label, multi-cohort trial. Patients were treated with pembrolizumab intravenously at a dose of 200 mg every 3 weeks until unacceptable toxicity or documented disease progression. Among the 98 patients, approval was based on 77 (79%) patients who had tumors that expressed PD-L1 with a CPS ≥1 and who had received at least one line of chemotherapy for metastatic disease. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx Kit.


Companion Diagnostic
PD-L1 IHC 22C3
CPS≥1
# NCCN Guidelines: Systemic Therapy for Cervical Cancer

<table>
<thead>
<tr>
<th>Preferred regimens</th>
<th>Other recommended regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemoradiation</td>
<td>N/A</td>
</tr>
<tr>
<td>Cisplatin, carboplatin if cisplatin intolerant</td>
<td>Cisplatin/paclitaxel, Carboplatin/paclitaxel, Topotecan/paclitaxel ± bevacizumab, Cisplatin/topotecan</td>
</tr>
<tr>
<td>First-line combinations</td>
<td></td>
</tr>
<tr>
<td>Cisplatin/paclitaxel/bevacizumab</td>
<td></td>
</tr>
<tr>
<td>Carboplatin/paclitaxel/bevacizumab</td>
<td></td>
</tr>
<tr>
<td>Cisplatin/paclitaxel</td>
<td></td>
</tr>
<tr>
<td>Carboplatin/paclitaxel</td>
<td></td>
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<tr>
<td>Topotecan/paclitaxel ± bevacizumab</td>
<td></td>
</tr>
<tr>
<td>Cisplatin/topotecan</td>
<td></td>
</tr>
<tr>
<td>Possible first-line monotherapy</td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td></td>
</tr>
<tr>
<td>Carboplatin or paclitaxel</td>
<td></td>
</tr>
<tr>
<td>Second-line therapy</td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab (for PD-L1+ or MSI-H/dMMR tumors)</td>
<td>Bevacizumab, albumin-bound paclitaxel, docetaxel, fluorouracil, gemcitabine, ifosfamide, irinotecan, mitomycin, pemetrexed, topotecan, vinorelbine Pembrolizumab for TMB-H tumors Larotrectinib or entrectinib for NTRK+ gene fusion positive tumors</td>
</tr>
</tbody>
</table>
EMPOWER-CERVICAL 1/GOG-3016/ENGOT-CX9: RESULTS OF PHASE 3 TRIAL OF CEMIPLIMAB VS INVESTIGATOR’S CHOICE (IC) CHEMOTHERAPY (CHEMO) IN RECURRENT/METASTATIC (R/M) CERVICAL CARCINOMA

Krishnansu S Tewari,* Bradley J Monk,* Ignace Vergote, Austin Miller, Andreia Cristina de Melo, Hee Seung Kim, Yong Man Kim, Alla Lisyanskaya, Vanessa Samouélian, Domenica Lorusso, Fernanda Damian, Chih-Long Chang, Evgeniy A Gotovkin, Shunji Takahashi, Daniella Ramone, Joanna Pikiel, Beata Mackowiak-Matejczyk, Eva Maria Guerra, Nicoletta Colombo, Yulia Makarova, Jingjin Li, Shaheda Jamil, Vladimir Jankovic, Chieh-I Chen, Frank Seebach, David M Weinreich, George D Yancopoulos, Israel Lowy, Melissa Mathias, Matthew G Fury, and Ana Oaknin

12 May 2021

*Contributed equally to this presentation.

This study (NCT03257267) was sponsored by Regeneron Pharmaceuticals, Inc. and Sanofi.
EMPOWER: Interim Analysis of a Phase 3 trial of Cemiplimab versus Investigator’s Choice Chemotherapy in R/M Cervical Carcinoma

- **Opened:** Sept 2017
- **Closed:** June 2020
- **N = 590**
- **Sites = 105**
Overall Survival

SCC Population

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Median OS (95% CI), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cemiplimab</td>
<td>239 11.1 (95% CI, 9.2–13.4)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>238 8.8 (95% CI, 7.6–9.8)</td>
</tr>
</tbody>
</table>

HR (95% CI) = 0.73 (0.58–0.91)*
one-sided P=0.00306

Median duration of follow-up‡: 16.8 months (range: 6.0–38.2)

AC Population

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Median OS (95% CI), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cemiplimab</td>
<td>65 13.3 (95% CI, 9.6–17.6)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>66 7.0 (95% CI, 5.1–9.7)</td>
</tr>
</tbody>
</table>

HR (95% CI) = 0.56 (0.36–0.85)*
one-sided P<0.005†

Median duration of follow-up‡: 21.9 months (range: 6.9–36.6)

Data cutoff date: 4 Jan 2021

*Stratified by geographic region (North America vs Asia vs ROW) according to interactive web response system. †One-sided nominal P value, not adjusted for multiplicity.
‡From randomisation to data cutoff date.

AC, adenocarcinoma or adenosquamous carcinoma; CI, confidence interval; HR, hazard ratio; mo, month; OS, overall survival; ROW, rest of world; SCC, squamous cell carcinoma.
Overall Survival

- At second interim analysis (85% of total OS events), IDMC recommended trial be stopped early for efficacy

### Overall Population

**No. of patients**

<table>
<thead>
<tr>
<th></th>
<th>Med. OS (95% CI), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cemiplimab</td>
<td>12.0 (95% CI, 10.3–13.5)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>8.5 (95% CI, 7.5–9.6)</td>
</tr>
</tbody>
</table>

**HR (95% CI) = 0.69 (0.56–0.84)**

One-sided *p*=0.00011

**Median duration of follow-up**: 18.2 months (range: 6.0–38.2)

*Stratified by geographic region (North America vs Asia vs ROW) and Histology (SCC vs AC) according to interactive web response system.

†From randomisation to data cutoff date.

AC, adenocarcinoma or adenosquamous carcinoma; CI, confidence interval; HR, hazard ratio; IDMC, Independent Data Monitoring Committee; mo, month; ROW, rest of world; OS, overall survival.

---

Data cutoff date: 4 Jan 2021
Progression-free Survival

### SCC Population

- **No. of patients:**
  - Cemiplimab: 65
  - Chemotherapy: 66

- **Median PFS (95% CI), mo:**
  - Cemiplimab: 2.7 (95% CI, 2.3–4.0)
  - Chemotherapy: 2.8 (95% CI, 2.0–3.2)

- **HR (95% CI):**
  - Cemiplimab vs Chemotherapy: 0.91 (0.62–1.34)*

### AC Population

- **No. of patients:**
  - Cemiplimab: 239
  - Chemotherapy: 238

- **Median PFS (95% CI), mo:**
  - Cemiplimab: 2.8 (95% CI, 2.6–4.0)
  - Chemotherapy: 2.9 (95% CI, 2.7–3.9)

- **HR (95% CI):**
  - Cemiplimab vs Chemotherapy: 0.71 (0.58–0.86)*

*Stratified by geographic region (North America vs Asia vs ROW) according to interactive web response system.

AC, adenocarcinoma or adenosquamous carcinoma; CI, confidence interval; HR, hazard ratio; mo, month; PFS, progression-free survival; ROW, rest of world; SCC, squamous cell carcinoma.

Data cutoff date: 4 Jan 2021
## Objective Response Rate

### ORR of SCC population
- **Cemiplimab:** 17.6% (95% CI: 13.0–23.0)
- **Chemotherapy:** 6.7% (95% CI: 3.9–10.7)

### ORR of AC population
- **Cemiplimab:** 12.3% (95% CI: 5.5–22.8)
- **Chemotherapy:** 4.5% (95% CI: 0.9–12.7)

### Table: Overall population

<table>
<thead>
<tr>
<th>By investigator assessment</th>
<th>Cemiplimab (n=304)</th>
<th>Chemotherapy (n=304)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Objective response rate (ORR:CR+PR)</td>
<td>50 (16.4)</td>
<td>19 (6.3)</td>
</tr>
<tr>
<td>95% CI for ORR(^a)</td>
<td>(12.5, 21.1)</td>
<td>(3.8, 9.6)</td>
</tr>
<tr>
<td><strong>Best overall tumour response, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response (CR)(^b)</td>
<td>10 (3.3)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Partial response (PR)(^b)</td>
<td>40 (13.2)</td>
<td>16 (5.3)</td>
</tr>
<tr>
<td>Stable disease (SD)(^c)</td>
<td>125 (41.1)</td>
<td>148 (48.7)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>105 (34.5)</td>
<td>88 (28.9)</td>
</tr>
<tr>
<td>Not evaluable (NE)</td>
<td>24 (7.9)</td>
<td>49 (16.1)</td>
</tr>
<tr>
<td><strong>Stratified CMH test one-sided P-value(^d)</strong></td>
<td>0.00004</td>
<td></td>
</tr>
<tr>
<td><strong>Odds ratio (95% CI)(^d)</strong></td>
<td>2.984 (1.707, 5.215)</td>
<td></td>
</tr>
<tr>
<td><strong>KM estimated median DOR, months (95% CI)(^e)</strong></td>
<td>16.4 (12.4, NE)</td>
<td>6.9 (5.1, 7.7)</td>
</tr>
<tr>
<td><strong>Median observed time to response, months (range)</strong></td>
<td>2.7 (1.2–11.4)</td>
<td>1.6 (1.2–9.0)</td>
</tr>
</tbody>
</table>

\(^a\)Clopper-Pearson exact confidence interval (CI); \(^b\)CR/PR must be confirmed by repeated assessments no less than 4 weeks apart; \(^c\)SD criteria must be met at least once for a minimum duration of 4 weeks after first dose date; \(^d\)One-sided P-value and odds ratio using geographic region and histology stratified Cochran-Mantel-Haenszel (CMH) test. Due to the low response rate in the chemotherapy arm, the results from CMH test should be interpreted with caution; \(^e\)Based on patients with confirmed CR or PR.

AC, adenocarcinoma or adenosquamous carcinoma; DOR, duration of response; KM, Kaplan-Meier; SCC, squamous cell carcinoma.

Data cutoff date: 4 Jan 2021
Mean Change From Baseline In GHS/QoL Scale

- MMRM Estimates

- Overall population: nominally significant difference in favour of cemiplimab over IC chemotherapy

- Patients receiving cemiplimab improved or maintained GHS/QoL from baseline

- Patients receiving chemotherapy generally showed deterioration in these scores

Overall (SE)
Cemiplimab: 1.01 (1.54)
Chemotherapy: –6.81 (2.12)
Difference: 7.81, one-sided nominal P=0.00040

Data cutoff date: 4 Jan 2021

LS mean (95% CI) for change from baseline

No. at risk: Cemiplimab 215 215 152 115 102 88 67 59
Chemotherapy 181 179 111 69 39 32 16 12

C, cycle; CI, confidence interval; D, day; GHS, Global Health Status; IC, investigator’s choice; LS, least squares; MMRM, mixed-model repeated measure; QoL, quality of life; SE, standard error.

Clinically meaningful threshold
The Future is Bright