A Phase 2 Trial of Pembrolizumab combined with chemoradiation for Patients with $^{18}\text{F}$-FDG PET/CT-defined Poor-prognostic Cervical Cancer

AGOG18-005

Chun-Chieh Wang, MD and Feng-Yuan Liu, MD/
Prof. Chyong-Huey Lai, MD
Poor survival for advanced cervical cancer (FIGO Annual Report)

<table>
<thead>
<tr>
<th>FIGO Stage</th>
<th>5-Year Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIB</td>
<td>55.9%</td>
</tr>
<tr>
<td>IIIIB</td>
<td>23.7%</td>
</tr>
<tr>
<td>IVA</td>
<td>16.7%</td>
</tr>
</tbody>
</table>

AGOG 09-001 Trial

• CCRT with single-agent cisplatin (arm C) versus cisplatin plus gemcitabine (arm CG)

Gynecologic Oncology 137 (2015) 462–467

A randomized trial comparing concurrent chemoradiotherapy with single-agent cisplatin versus cisplatin plus gemcitabine in patients with advanced cervical cancer: An Asian Gynecologic Oncology Group study

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AGOG 09-001 Eligibility criteria

- New pathological diagnosis of cervical cancer with squamous cell carcinoma
- FIGO stage III–IVA or any stage with $^{18}$F-FDG PET-defined positive pelvic or para-aortic lymph node
- Between 35 and 70 years old
- ECOG performance status 0 or 1
- Adequate bone marrow, liver and renal function
- **Exclusion** criteria
  - prior pelvic radiation
  - prior systemic chemotherapy
  - evidence of distant metastasis other than PALN
Assessed for eligibility (N = 89)

Random assignment (n = 74)

Allocated to Arm C (n = 37)
- Excluded before intervention begin (n = 5)
  - Patient withdraw consent (n = 3)
  - Schizophrenia (n = 1)
  - Death from other causes (n = 1)
- Efficacy analysis
  - Analyzed (n = 37)
  - Safety analysis
    - Analyzed (n = 32)
    - Excluded from analysis (n = 5)
- LTFU by end of study (n = 1)

Allocated to Arm CG (n = 37)
- Excluded before intervention begin (n = 1)
  - Foreign patient (n = 1)
- Efficacy analysis
  - Analyzed (n = 37)
  - Safety analysis
    - Analyzed (n = 36)
    - Excluded from analysis (n = 1)
- LTFU by end of study (n = 1)
3-year PFS of stage IIIB 69.6% in AGOG09-001
Arm C: 3-year PFS 65.1%  
Arm CG: 3-year PFS 71.0%  

$P = 0.71$
Utility of $^{18}$F-FDG PET/CT in patients with advanced squamous cell carcinoma of the uterine cervix receiving concurrent chemoradiotherapy: a parallel study of a prospective randomized trial

Feng-Yuan Liu$^{1,2}$ · Chyong-Huey Lai$^{2,3}$ · Lan-Yan Yang$^{4,5}$ · Chun-Chieh Wang$^{2,6}$ · Gigin Lin$^{2,7}$ · Chee-Jen Chang$^{5,8}$ · Wei-Yang Chang$^{3}$ · Shu-Hua Huang$^9$ · Yu-Erh Huang$^{10}$ · Nan-Jing Peng$^{11}$ · Ji-Hong Hong$^{2,6}$ · Angel Chao$^{2,3}$ · Hung-Hsueh Chou$^{2,3}$ · Yu-Chen Chang$^{1,2,12}$ · Tzu-Chen Yen$^{1,2}$

https://doi.org/10.1007/s00259-017-3884-0

Comparison of positron emission tomography/computed tomography and magnetic resonance imaging for posttherapy evaluation in patients with advanced cervical cancer receiving definitive concurrent chemoradiotherapy

Tzu-Pei Su$^1$ · Gigin Lin$^{2,3}$ · Yu-Ting Huang$^{2,4}$ · Feng-Yuan Liu$^{2,5}$ · Chun-Chieh Wang$^{2,6}$ · Angel Chao$^{2,7}$ · Hung-Hsueh Chou$^{2,7}$ · Tzu-Chen Yen$^{2,5,7}$ · Chyong-Huey Lai$^{2,7}$
Pre-treatment
$^{18}\text{F}]$-FDG PET/CT

- Para-aortic LNs
- Regional LNs
- Primary Tumor
## Pre-treatment PET/CT-defined Prognostic Factors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>N</th>
<th>3-year PFS</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PALN</td>
<td>Negative</td>
<td>42</td>
<td>83.3%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>13</td>
<td>23.1%</td>
<td></td>
</tr>
<tr>
<td>Pre-treatment MTV (mL)</td>
<td>&lt; 90</td>
<td>38</td>
<td>81.6%</td>
<td>.003</td>
</tr>
<tr>
<td></td>
<td>≥ 90</td>
<td>17</td>
<td>39.7%</td>
<td></td>
</tr>
<tr>
<td>Pre-treatment SUVnode</td>
<td>&lt; 6.6 or negative</td>
<td>35</td>
<td>85.6%</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>≥ 6.6</td>
<td>20</td>
<td>40.0%</td>
<td></td>
</tr>
<tr>
<td>Low-risk group</td>
<td>None of above</td>
<td>24</td>
<td>100.0%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>High-risk group</td>
<td>Any of above</td>
<td>31</td>
<td>44.7%</td>
<td></td>
</tr>
</tbody>
</table>

Real data from AGOG09-001
Will Novel Therapy including Pembrolizumab Improve the Outcome and Survival?
Phase 2 Trial Proposal

• Based on AGOG09-001, only 44.7% of PET/CT-defined advanced cervical SCC (not including ScLN mets) can be free of persistent or recurrent disease at 3-y (1-y PFS of 54.8%)

• The survival of cervical cancer patients with persistent or recurrent disease after primary treatment remains dismal.

• We thus propose a phase II trial of primary CCRT plus pembrolizumab and post-CCRT immunochemotherapy to improve 1-y PFS for such high-risk patients.
Eligibility criteria

- New pathological diagnosis of cervical cancer with SCC
- $^{18}$F-FDG PET/CT-defined high-risk factors (any one)
  - Positive PALN
  - Pre-treatment MTV ≥ 90 mL
  - Pre-treatment SUVnode ≥ 6.6
- Between 35 and 70 years old
- ECOG performance status 0 or 1
- Adequate bone marrow, liver and renal function
- Exclusion criteria
  - prior pelvic radiation
  - prior systemic chemotherapy
  - evidence of distant metastasis other than PALN
Study design

• Multicenter, single-arm, phase II study
• Primary end point: Progression-free survival
• Secondary end points:
  1. Tolerability
  2. Overall survival
  3. Quality of life

Exploratory: Biomarkers related to outcomes
Estimated patient number (n = 55)

- Test for one exponential mean
- For alpha = 0.05 and power = 0.80

<table>
<thead>
<tr>
<th>Ref 1-y PFS</th>
<th>Ref Mean survival (yr)</th>
<th>Trt. 1-y PFS</th>
<th>Trt. Mean survival (yr)</th>
<th>Duration of observation (yr)</th>
<th>single-arm N</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>2</td>
<td>70%</td>
<td>3.33</td>
<td>1.0</td>
<td>97</td>
</tr>
<tr>
<td>50%</td>
<td>2</td>
<td>75%</td>
<td>4.0</td>
<td>1.0</td>
<td>58</td>
</tr>
<tr>
<td>50%</td>
<td>2</td>
<td>70%</td>
<td>3.33</td>
<td>2.0</td>
<td>55</td>
</tr>
<tr>
<td>50%</td>
<td>2</td>
<td>75%</td>
<td>4.0</td>
<td>2.0</td>
<td>32</td>
</tr>
<tr>
<td>50%</td>
<td>2</td>
<td>70%</td>
<td>3.33</td>
<td>3.0</td>
<td>42</td>
</tr>
<tr>
<td>50%</td>
<td>2</td>
<td>75%</td>
<td>3</td>
<td>4.0</td>
<td>25</td>
</tr>
</tbody>
</table>
Trial Treatment-1

• Pembrolizumab 200 mg IV 3-weekly and combination chemotherapy with cisplatin 40mg/m² D1, D8 with topotecan (0.7 mg/m²) D1-D3 or paclitaxel (135 mg/m²) D1 3-weekly for concurrent RT limited to pelvis, chemotherapy regimen can be determined at the physician’s discretion according to local health insurance coverage. Those with extended field RT only single agent cisplatin will be given. Combination chemotherapy and pembrolizumab can be started before RT is commenced.

• Target volume RT (conformal or IMRT with or without brachytherapy) concurrently with chemotherapy
Trial Treatment-2

• If treatment delay > 2 week for G3/4 toxicity, chemotherapy will be given with single agent **cisplatin** alone with pembrolizumab continued.

• Post-CCRT **combination chemotherapy with pembrolizumab** will continued for 4 courses.
Status

• It was approved by AGOG Board meeting on September 16, 2018.
• It is assigned AGOG18-005.
• The MSD global review is ongoing and will have results in 2 weeks.
THANK YOU