Efficacy & Safety of Single Agent Immunotherapy & Immune Checkpoint Inhibitors in Gynecologic Cancer

FDA-AACR-SGO Workshop on Drug Development in Gynecologic Malignancies

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## Clinical Trial Research Funding:

- Astra Zeneca
- Pfizer
- Genentech
- Clovis
- Syndax
- Tesaro

## Consultant/Advisory Board:

- Cue Biopharma

**Unlabeled/Unapproved use:** I will discuss use of immune checkpoint inhibitors for currently unlabeled uses
Outline

- Endometrial Cancer
- Cervical cancer
  - Other HPV-associated gyn cancers
- Ovarian cancer
MMR Defects in Endometrial Cancer

- Loss of DNA mismatch repair is a common event in endometrial cancer
  - 22-37%, most frequent in endometrioid histology
- Most MMR defects in endometrial cancer are somatic, not inherited
  - Less than 5% overall due to germline mutations (Lynch)
  - Due to epigenetic silencing via methylation
    - Predominantly MLH1
  - Due to somatic mutations in the gene(s)
    - MSH6, MSH2, PMS2, MLH1
DNA mismatches occur during normal DNA synthesis (about one in every $10^6$ bases)

DNA mismatches commonly occur in regions of repetitive nucleotide sequences called microsatellites

A characteristic feature of loss of mismatch repair in tumors is the expansion or contraction of these microsatellite regions in the tumor compared with normal tissue

This genetic alteration is termed microsatellite instability (MSI)
- First defined by Papadopolous and Vogelstein in 1990’s
Patients divided into TCGA subgroups

100 hypothetical newly diagnosed endometrial cancer patients

POLE sequencing

100

POLE hotspot or exonuclease domain mutation

95

POLE (~5%)

PMS2 or MSH6 loss

MSI (~25%)

TP53 Wildtype

Copy-Number Low (~40%)

TP53 Mutant

Copy-Number High (~30%)

2 marker IHC (PMS2 and MSH6)

70

TP53 sequencing or IHC
Endometrial Cancer (EC) – Four molecular subtypes
(Integrated genomic, transcriptomic and proteomic characterization)

POLE ultra-mutated
(15x > vs MSI)

MSI hyper-mutated
(8x > vs MSS)

Copy number low
- endometrioid -
(MSS group)

Copy number high
- serous-like -

Mutations per Mb

POLE

MSI / MLH1

CN Cluster

Microsatellite Instability (MSI)

DNA methylation

Copy Number Cluster

Histology

Grade

Histology

Grade

Tumor grade

Cold tumors

Hot tumors

Kandoth et al., Nature 2013

Presented By Hans Nijman at 2017 ASCO Annual Meeting
Alexandrov et.al. Nature 2013
Potential Mechanisms of Action of Anti-PD-1 Therapy in Mismatched Repair-Deficient Tumors

(A) MMR deficiency results in a more diverse neo-antigen repertoire, increasing the chances of a tumor-specific T cell response.

(B) MMR deficiency is associated with the activation of signaling pathways, which leads to a more inflammatory tumor micro-environment.

(C) MMR deficiency leads to cellular stress, which, for instance, promotes T or NK cell accumulation or tumor recognition.

Response to Anti-PD1 (Pembrolizumab) in MMR Deficient Tumors

<table>
<thead>
<tr>
<th></th>
<th>MMR-deficient CRC</th>
<th>MMR-proficient CRC</th>
<th>MMR-deficient non-CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>13</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Objective Response Rate</td>
<td>62%</td>
<td>0%</td>
<td>60%</td>
</tr>
<tr>
<td>Disease Control Rate</td>
<td>92%</td>
<td>16%</td>
<td>70%</td>
</tr>
</tbody>
</table>

Le et al, *NEJM*, 2015
Endometrial Cancer Cohort

• Nine 9 patients with MSI-high recurrent or progressive endometrioid endometrial cancer enrolled
• Median – 2 prior therapies
• Overall response rate is 56% (95% CI: 21-86%, N=5/9)
  – CR 1, PR 4
  – 3 pts with prolonged SD
• Disease control rate, or “clinical benefit” rate (CR + PR + stable disease) is 88.9% (8/9 patients)
• 12-month OS rate is 89%

Fader, AN et.al. SGO 2016
Overall Survival After Pembrolizumab
Durability of Disease Control
Pembrolizumab in PD-L1 Positive Endometrial Cancer KEYNOTE-028

3/24 responders (13%)
- 1 POLE mutation
- 1 MSI low
- 1 MS unknown

36/75 (48%) screened were PD-L1 positive

Ott et al. J Clin Oncol, 2017
Mismatch repair deficiency across 12,019 tumors. Proportion of tumors deficient in mismatch repair in each cancer subtype, expressed as a percentage. Mismatch repair deficient tumors were identified in 24 out of 32 tumor subtypes tested.

Le D, et al. Science June 8, 2017
Overall, MSI-H was found in 33% (203/621) of EECs

<table>
<thead>
<tr>
<th>Grade</th>
<th>MSI High</th>
<th>TMB High</th>
<th>PD-L1 Pos</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>25</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>113</td>
<td>113</td>
<td>107</td>
</tr>
<tr>
<td>%</td>
<td>22%</td>
<td>13%</td>
<td>1%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>55</td>
<td>39</td>
<td>5</td>
</tr>
<tr>
<td>Moderately diff</td>
<td>172</td>
<td>171</td>
<td>169</td>
</tr>
<tr>
<td>%</td>
<td>32%</td>
<td>23%</td>
<td>3%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>58</td>
<td>53</td>
<td>18</td>
</tr>
<tr>
<td>Poorly Diff</td>
<td>156</td>
<td>156</td>
<td>153</td>
</tr>
<tr>
<td>%</td>
<td>37%</td>
<td>34%</td>
<td>12%</td>
</tr>
</tbody>
</table>

Figure 1. Overview of Immune Biomarker Phenotypes in EECs.

N.L. Jones et al. Immune checkpoint expression, microsatellite instability, and mutational burden: Identifying immune biomarker phenotypes in uterine cancer. Poster 84 SGO 2018
Immune Checkpoint Inhibition: Endometrial Cancer

- MSI is a biomarker for EndoCa response to anti PD-L1 therapy
  - 22-37% of endometrioid histology will have MSI-high phenotype
- PD-L1 expression alone appears to be less robust than MSI as an independent biomarker for response to pembrolizimab in EndoCa
- Need to further identify molecular characteristics that predict response to immunotherapy (POLE, POLD, MSI + PD-L1, etc)
- Multiple ongoing and pending trials of single agent ICI in MSI and MSS EndoCa
- MMR IHC or MSI testing should be done in all endometrial cancers
Rationale for Immunotherapy in Cervical Cancer

- Presence of foreign viral antigens
- Higher expression of PD-L1 in virus-associated cancers
- Upregulation of PD-1 in CIN
An Open-Label, Multicohort, Phase 1/2 Study of Nivolumab in Patients With Virus-Associated Tumors (CheckMate 358): Efficacy and Safety in Recurrent or Metastatic Cervical, Vaginal, and Vulvar Cancers

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CheckMate 358 Study Design: Metastatic Monotherapy Cohort

• CheckMate 358 (NCT02488759) is an ongoing, open-label, phase 1/2, multicohort study

Eligibility

Eligible tumor types
• EBV+ gastric carcinoma
• HPV+ SCCHN
• Cervical, vaginal, and vulvar cancers
• Merkel cell carcinoma
• Nasopharyngeal carcinoma

Key eligibility criteria
• ≤2 prior treatments for R/M disease
• ≥1 target lesion
• ECOG PS: 0–1
• PD-L1 unselected

Treatment

Nivolumab 240 mg Q2W until progression or unacceptable toxicity

Assessments

• Imaging Q8W for the first year of treatment
• Imaging Q12W thereafter

Follow-up

• Minimum follow-up: 12 weeks
• Survival follow-up

Primary endpoints: ORR
Secondary endpoints: DOR, PFS, OS

• Enrollment dates: October 2015 to February 2016
• Data cut-off: July 2016 (median follow-up, 31 weeks)

aPer investigator-assessed RECIST 1.1 criteria
DOR = duration of response; EBV = Epstein Barr Virus; OS = overall survival; QXW = every X weeks; SCCHN = squamous cell carcinoma of the head and neck
## Best Overall Response
### CheckMate 358: Nivolumab Monotherapy in R/M Cervical, Vaginal, and Vulvar Cancers

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N = 24)</th>
<th>Cervical (n = 19)</th>
<th>Vaginal/Vulvar (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best overall response, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (4.2)</td>
<td>1 (5.3)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>4 (16.7)</td>
<td>4 (21.1)</td>
<td>0</td>
</tr>
<tr>
<td>Stable disease</td>
<td>12 (50.0)</td>
<td>8 (42.1)</td>
<td>4 (80.0)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>7 (29.2)</td>
<td>6 (31.6)</td>
<td>1 (20.0)</td>
</tr>
<tr>
<td><strong>ORR, n (%)</strong></td>
<td>5 (20.8)</td>
<td>5 (26.3)</td>
<td>0</td>
</tr>
<tr>
<td>[95% CI]</td>
<td>[7.1, 42.2]</td>
<td>[9.1, 51.2]</td>
<td>[0.0, 52.2]</td>
</tr>
<tr>
<td><strong>Disease control rate, n (%)</strong></td>
<td>17 (70.8)</td>
<td>13 (68.4)</td>
<td>4 (80.0)</td>
</tr>
<tr>
<td><strong>Duration of response, median (range), months</strong></td>
<td>NR&lt;sup&gt;a&lt;/sup&gt; (0.0, 5.8+)</td>
<td>NR&lt;sup&gt;a&lt;/sup&gt; (0.0, 5.8+)</td>
<td>NA</td>
</tr>
</tbody>
</table>

+ Ongoing response; NA = not applicable; NR = not reached
<sup>a</sup>All responses ongoing as of the data cut-off
Duration of Treatment
CheckMate 358: Nivolumab Monotherapy in R/M Cervical, Vaginal, and Vulvar Cancers

Patients

- On treatment – cervical cancer
- On treatment – vaginal/vulvar cancer
- Off treatment

- Ongoing response
- Progression
- Death

Weeks Since Treatment Initiation

0 6 12 18 24 30 36 42
## Best Overall Response by PD-L1 and HPV

**CheckMate 358: Nivolumab Monotherapy in R/M Cervical, Vaginal, and Vulvar Cancers**

<table>
<thead>
<tr>
<th>PD-L1 Expression</th>
<th>HPV Status&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best overall response, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td>Partial response</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>6 (60.0)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2 (20.0)</td>
</tr>
<tr>
<td><strong>ORR, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>[95% CI]</td>
<td>2 (20.0) [2.5, 55.6]</td>
</tr>
<tr>
<td><strong>Disease control rate, n (%)</strong></td>
<td>8 (80.0)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Per local site testing
Conclusions
CheckMate 358: Nivolumab Monotherapy in R/M Cervical, Vaginal, and Vulvar Cancers

• Nivolumab demonstrated encouraging clinical activity in patients with R/M cervical, vaginal, and vulvar cancers
  – 20.8% ORR (all 5 responses in patients with cervical cancer at time of data cut-off)
    • Responses observed across tumor PD-L1 expression
      – 70.8% disease control rate
      – Median OS was not reached; 6-month OS rate was 87.1%
• The observed safety profile was manageable and consistent with previous results seen with nivolumab monotherapy in other tumor types
## Immunotherapy Trials: Cervical Cancer

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ORR n (%)</th>
<th>Eligibility</th>
<th>Med PFS</th>
<th>Med OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab(^1)</td>
<td>1/32 (3%)</td>
<td>PD-L1+</td>
<td>2.5 M</td>
<td>8.5 M</td>
</tr>
<tr>
<td>Pembrolizumab (KN-28)(^2)</td>
<td>4/24 (17%)</td>
<td></td>
<td>2.0 M</td>
<td>11 M</td>
</tr>
<tr>
<td>Pembrolizumab (KN-158)(^3)</td>
<td>8/47 (17%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab (CM 358)(^4)</td>
<td>5/19 (26%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Lheureux, J Clin Oncol, Nov 2017
2. PD-L1 pos, Frenel, J Clin Oncol, Dec 2017
3. Unselected for PD-L1, Schellens, ASCO 2017, Abs 5514
4. Hollebecque, ASCO 2017, Abs 5504
Lymphopenia and its association with survival in patients with locally advanced cervical cancer

Emily S. Wu a,*,1, Titilope Oduyebob,1, Lauren P. Cobb a, Diana Cholakian a, Xiangrong Kong b, Amanda N. Fader a, Kimberly L. Levinson a, Edward J. Tanner III a, Rebecca L. Stone a, Anna Piotrowski c, Stuart Grossman c, Kara Long Roche a

a Kelly Gynecologic Oncology Service, Department of Gynecology and Obstetrics, Johns Hopkins Hospital, Baltimore, MD, USA
b Department of Epidemiology, Johns Hopkins Hospital School of Public Health, Baltimore, MD, USA
c The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD, USA
Fig. 1. Total lymphocyte count prior to treatment and in the first 12 months after initiating chemoradiation.
Figure 3. PDL-1 Expression via IHC in GYN Cancers. PD-L1 expression was observed in only 7% of uterine and ovarian tumors but in 28% cervical, 63% vulvar and 47% of vaginal cancers. This figure represents those tumors with >5% PDL-1 expression.
Immune Checkpoint Inhibition: Cervical Cancer

- Single agent ICIs have variable activity in cervical cancer
  - Response rates range from 3-26%
- PD-L1 expression alone does not appear to be a robust, independent biomarker for response in cervical cancer
- Epidemiologic and therapeutic factors in cervical cancer may inhibit response to ICI
  - Lymphocyte depletion after chemoradiation may blunt ability to respond to ICI
  - T-cell exhaustion, associated with chronic viral infection, may contribute
Ovarian Cancer
<table>
<thead>
<tr>
<th><strong>Treatment</strong></th>
<th><strong>ORR n (%)</strong></th>
<th><strong>DCR</strong>*</th>
<th><strong>6 M PFS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti PD-L1</td>
<td>1/16 (6%)</td>
<td>3/17 (18%)</td>
<td>25%</td>
</tr>
<tr>
<td>Avelumab</td>
<td>12/124 (10%)</td>
<td>54%</td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab (KN-28)</td>
<td>3/26 (11.5%)</td>
<td>9/26 (35%)</td>
<td></td>
</tr>
<tr>
<td>Nivolumab</td>
<td>3/20 (15%)</td>
<td>9/20 (45%)</td>
<td></td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>2/9 (22%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab (KN-100)</td>
<td>30/376 (8%)</td>
<td>37%</td>
<td></td>
</tr>
</tbody>
</table>

*Disease control rate (CR+PR+SD)*

1Brahmer NEJM 2012
2Disis ASCO 2016
3PD-L1-pos, Varga ASCO 2015
4Plat-Resistant, Hamanashi JCO 2015
59/12 evaluable, Infante, ESGO 2016
6Matulonis ASCO 2018
Figure 3. PDL-1 Expression via IHC in GYN Cancers. PD-L1 expression was observed in only 7% of uterine and ovarian tumors but in 28% cervical, 63% vulvar and 47% of vaginal cancers. This figure represents those tumors with >5% PDL-1 expression.
Mismatch repair deficiency across 12,019 tumors. Proportion of tumors deficient in mismatch repair in each cancer subtype, expressed as a percentage.

Le D, et.al. Science June 8, 2017
Tumor Mutational Burden (TMB) in GYN Cancers. TMB was studied in GYN cancers with overall levels noted in A. High TMB (TMB-H) was noted in 2% of ovarian cancers (9% germ cell, 6% endometrioid, 3% low grade, 7% mucinous, 4% clear cell, 3% carcinosarcoma, 1% serous).

I.S. Winer et al. Mutational burden, tumor PDL-1 expression, and microsatellite instability in gynecologic malignancies: Implications for immune Immune checkpoint expression, Poster 85 SGO 2018
Correlation between Tumor Mutational Burden and Objective Response Rate with Anti–PD-1 or Anti–PD-L1 Therapy in 27 Tumor Types. Yarchoan M, NEJM 2017
Immune Checkpoint Inhibition: Ovarian Cancer

- Low level biomarkers of Response to ICI in OvCa
  - Low level PD-L1 expression
  - Low level of MSI
  - Lowest TMB of all gyn cancers
- Effective immunotherapy with ICI will likely require combination approaches to transform tumors from cold to hot
  - With other ICI
  - With cancer vaccines
  - With adoptive cell therapy