Advances in Immunotherapy for Breast and Ovarian Cancer
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## Estimated New Cancer Cases* in the US in 2017

<table>
<thead>
<tr>
<th></th>
<th>Males 836,150</th>
<th>Females 852,630</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>19%</td>
<td>30%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>14%</td>
<td>12%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>All other sites</td>
<td>23%</td>
<td>22%</td>
</tr>
</tbody>
</table>

*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.
Breast Cancer Subtypes

1. ER/PR+
   - HER2+
   - HER2-

2. ER/PR-
   - HER2+
   - HER2- (TNBC, Triple-negative breast cancer)
Gene Mutations that Increase Breast Cancer Risk

1. BRCA1/2
2. PALB2
3. p53
4. CHEK2
5. DNA repair genes (RAD51, ATM, etc.)
6. PTEN
7. CDH1
Innate Immunity

Molecular Biology of the Cell 4th Edition
Adaptive Immunity

Immature CD4+ T cell

Antigen

Immature CD8+ T cell

Antigen Presenting Cell

Mature helper T cell (Th1 or Th2)

CD4+

Mature cytotoxic T cell (Tc)

CD8+
What is Cancer Immunotherapy?

To Kill or Not To Kill, That is a Question!
Major Immune Cells for Cancer Immunotherapy

- B lymphocyte
- T lymphocyte
- Dendritic cells
- Natural killer cells
B Lymphocyte that Produce Antibodies
T Lymphocyte

- T cells that kill
  - Helper T cells
  - Cytotoxic T cells
  - Memory T cells
  - Regulatory T cells
Types of Cancer Immunotherapy

- **Monoclonal antibody**: Rituxan (rituximab) for B cell lymphoma
- **Cancer vaccines**: HPV vaccines for cervical, vulvar and anal cancer.
- **Immune Checkpoint Inhibitor**: ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, etc…
- **CAR-T**: Chimeric Antigen Receptor-T cells
- **Adoptive cell transfer**: tumor infiltrating T cells, autologous dendritic cells
Immune Checkpoint Regulation

- Cancer cells develop escape systems to evade immune detection and killing
- Immunotherapy is a type of targeted immune activation
How do Immune Checkpoint Inhibitors Work?

Chimeric Antigen Receptor T Cells (CAR-T)

Anti-CD19 antibody idioype

Co-stimulatory domain

CD19
Adoptive T Lymphocyte Transfer
Checkpoint Inhibitors Approved for:

- Melanoma
- Kidney cancer
- Non-small cell lung cancer
- Merkel cell carcinoma
- Hodgkin’s lymphoma
- Head and neck cancer
- Bladder cancer
- Gastric and esophageal cancer
- Hepatocellular carcinoma
- Any cancer with Mismatched Repair (MMR) Protein deficiency
Common side effects of checkpoint inhibitors

- Diarrhea
- Skin rash
- Pneumonitis
- Hypothyroidism
- Hemolysis
- Liver dysfunction
Checkpoint Inhibitors for Breast Cancer
Breast Cancer Subtypes

1. ER/PR+
   - HER2+
   - HER2-

2. ER/PR-
   - HER2+
   - HER2- (TNBC, Triple-negative breast cancer)
Clinical trials with checkpoint inhibitors

<table>
<thead>
<tr>
<th>Trial</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keynote-12</td>
<td>8% all Triple negative</td>
</tr>
<tr>
<td>Keynote-86</td>
<td>5% all PD-L1 +</td>
</tr>
<tr>
<td>Avelumab</td>
<td>5.4%, all but one PD-L1 +</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>26% 1\textsuperscript{st} line, 13% 2\textsuperscript{nd} line</td>
</tr>
<tr>
<td>Durvaluamb and Tremelizumab</td>
<td>3/18 responded, 3/7 TN, 0/11 ER+</td>
</tr>
<tr>
<td>Atezolizumab and Nab-Paclitaxel</td>
<td>67% 1\textsuperscript{st} line, 27% 2\textsuperscript{nd} line</td>
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</tbody>
</table>
Durable response to checkpoint inhibitor

I-SPY-2 Trial: Pembrolizumab plus Neoadjuvant Chemotherapy for Breast Cancer

Tumor size: 2.0 by imaging or 2.5 cm by exam
Taxol weekly plus Pembrolizumab for 12 weeks followed by AC x 4 cycles

<table>
<thead>
<tr>
<th>Signature</th>
<th>Current raw data: pCR/n [total assigned]</th>
<th>Estimated pCR rate (95% prob interval) [equivalent n]</th>
<th>Prob pembrol superior</th>
<th>Pred prob of success in phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR+/HER2−</td>
<td>7/25 (28.0%)</td>
<td>13/88 (14.8%) 34.2% (17-51%)</td>
<td>99.0%</td>
<td>86.8%</td>
</tr>
<tr>
<td>TNBC</td>
<td>15/21 (71.4%)</td>
<td>16/83 (19.3%) 62.4% (45-80%)</td>
<td>&gt;99.9%</td>
<td>99.3%</td>
</tr>
</tbody>
</table>

Nanda et al. ASCO Annual meeting Chicago 2017
NSABP-B59/GBGXX

- Atezolizumab plus neoadjuvant chemotherapy
- TN-BC
PD-L1 Expression in Breast Cancer

Adams et al. JCO 2014, 32, 2959.
PD-L1 Expression and Prognosis in Metastatic Breast Cancer

Adams et al. JCO 2014, 32, 2959
Primming Microenvironment for Checkpoint Inhibitor

Tonic Trial ESMO 2017

Group 1: Radiation Gy x 3
Group 2: Doxorubicin 15mg/m2 x 2 weeks
Group 3: Cyclophosphomide 50mg PO x 2 weeks
Group 4: Cisplatin 40mg/m2 x 2 weeks
Group 5: No treatment

Nivolumab

--50 patients
--ORR 26%
Checkpoint Inhibitors for Ovarian Cancer
Nivolumab for Ovarian Cancer

Hamanishi et al. JCO 2015
JAVELIN Ovarian 100

- Phase III
- First line platinum-based chemotherapy + Avelumab
- Stage III and IV
Factors Predictive of Benefit from Checkpoint Inhibitor

- Tumor biology
- PD-L1 expression
- MMR deficiency
- Tumor infiltrating T lymphocyte
- Gut microbial composition
- Systemic factors
Neutrophil Count Predictive of Progression in Melanoma Patients Treated with Pembrolizumab/Nivolumab

Neutrophils: Blue ≤3900 cells/µL; red 3901-5507 cells/µL; green ≥5501 cells/µL. P for difference <0.0001.
Platelet Count Also Predictive of Progression

Platelets: Blue $\leq 215,000$ cells/$\mu$L; red $216,000$-$303,000$ cells/$\mu$L; green $\geq 304,000$ cells/$\mu$L. P for difference $< 0.001$. 
What is the Future of Immunotherapy?

- Combination with chemotherapy
- Combination with targeted therapy
- Combination with different checkpoint inhibitor
- Identifying specific neoantigens for CAR-T
- Other novel approaches yet to be identified
- CRISPER gene editing
Acknowledgements

- Lisa Herrinton
- Mubarika Alavi
- Kaiser Permanente Cancer Program
- Our entire oncology team
- KP Public Affairs Office
Questions?