Breast Cancer Immunotherapy: Are We There Yet?

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Financial Disclosures

- I do not currently have any relevant financial relations to disclose
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UK 1950–2009 and USA (to 2008):
Breast cancer mortality at ages 35–69

Death rate / 100 000 women, age standardised*

- UK
- USA

LARGE effect on UK/USA breast cancer mortality by combining several MODERATE effects.

Further MODERATE effects are still worthwhile and achievable.

*Mean of annual rates in the seven component 5-year age groups

WHO (& 2008 US NCHS) mortality and UN population estimates
Breast Cancer: Facts and Figures

ESTIMATES IN US (2015)
- 231,840 new cases
- 40,290 deaths

ESTIMATES IN WEST VIRGINIA (2015)
- 1430 new cases
- 270 deaths

ESTIMATES WORLDWIDE (2012)
- 1,676,000 new cases
- 521,900 deaths

ACS, Facts and Figures 2015
World-wide Burden of Cancer in Women

- Breast
- Cervix
- Colon / rectum
- Lung
- Stomach
- Ovary etc
- Corpus uteri
- Liver

Globocan 2012
Cancer Immunotherapy

• Goal of cancer immunotherapy is to activate a patient’s immune system to recognize and kill their cancer cells

• An enhanced understanding of the immune response to malignancy over the past 5 years have translated into several successes of a number of immunotherapy agents leading to the FDA approving these agents
FDA Approved Immunotherapy Agents

• 2010- Sipuleucel-T, a vaccine that has shown to prolong overall survival in metastatic castrate resistant prostate cancer

Three immune checkpoint inhibitors:

• 2011- Ipilimumab, monoclonal antibody that targets T-lymphocyte associated protein4 (CTLA-4)-Melanoma

• 2014– Pembrolizumab and Nivolumab- Melanoma

• 2015- Pembrolizumab and Nivolumab- metastatic NSCLC (both squamous and non-squamous)
Breast Cancer Immunotherapy

• Relevance of host immune response to breast cancer has long been debated

• Unlike melanoma and renal cell carcinoma, breast cancer was thought to be non-immunogenic

• Robust body of literature now suggests that breast cancer, particularly the more aggressive subtypes of Her-2 positive and TNBC, does elicit host antitumor immune responses and the robustness of the response correlates with prognosis.
Breast Cancer Immunotherapy

Monoclonal Antibodies

Trastuzumab (*Herceptin*™)

- a monoclonal antibody targeting the extracellular portion of the HER2 protein
- Utilized in treatment of HER2- positive breast cancer
- While its benefit is mainly attributed to inhibition of HER2- mediated signaling, there is increased appreciation of its immune mediated mechanisms of action

- Humanized IgG antibody with a conserved Fc portion, and data show a role for antibody-dependent, cell mediated cytotoxicity mediated by NK cells

- A subset of patients with high expression of TIL-associated genes were observed to have greater benefit than those with low to intermediate expression (NSABP B-31)
Breast Cancer Immunotherapy

*Immune Checkpoint Inhibitors*

- Avelumab- anti-PD-L1 (JAVELIN)
- Pembrolizumab- anti-PD-1 (KEYNOTE-028)
- Atezolizumab- anti-PD-L1
Dizon et Al, JCO 2016
JAVELIN: Phase Ib Study Design

- Primary endpoint: DLT
- Secondary endpoints: clinical activity, immune response, safety
- PD-L1 expression assessed by IHC

Pts with refractory or progressive locally advanced or MBC (N = 168)*

Avelumab 10 mg/kg IV Q2W

Dosing until progression

*Pts eligible if ≤ 3 previous cytotoxic regimens, previous treatment with taxane + anthracycline, biopsy/tissue sample taken within 90 days of avelumab initial dose, ECOG PS 1 or 2, ≥ 1 quantifiable lesion, life expectancy ≥ 3 mos.

Pts unselected for PD-L1 expression, HER2/ER/PR subtype.

# JAVELIN: Antitumor Activity

<table>
<thead>
<tr>
<th>Best Overall Response, %</th>
<th>All Pts (N = 168)</th>
<th>Pts With TNBC (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0.6</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>4.2</td>
<td>8.6</td>
</tr>
<tr>
<td>SD*</td>
<td>23.2</td>
<td>22.4</td>
</tr>
<tr>
<td>PD</td>
<td>63.1</td>
<td>65.5</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>8.9</td>
<td>3.4</td>
</tr>
<tr>
<td>ORR</td>
<td><strong>4.8</strong> (95% CI: 2.1-9.2)</td>
<td><strong>8.6</strong> (95% CI: 2.9-19.0)</td>
</tr>
<tr>
<td>DCR†</td>
<td>28.0</td>
<td>31.0</td>
</tr>
</tbody>
</table>

*Defined as SD at first assessment after 6 wks.
†Defined as response plus SD.

Median follow-up – 10 months

JAVELIN: ORR According to PD-L1 Expression

• ORR increased in pts with PD-L1–positive tumors
  - Pts with PD-L1 expression on immune cells showed greater response than pts with PD-L1–negative immune cells (33.3% [4/12] vs 2.4% [3/124])
  - PD-L1 expression also appeared associated with response in subgroup with TNBC (44% [4 of 9] PD-L1 positive vs 2% [1/39] PD-L1 negative)

• Median DoR- 28.7 weeks

JAVELIN: Potential Autoimmune TEAEs

- Treatment-related discontinuation occurred in 8 pts (4.8%)
- Death in 2 pts considered treatment related (1.2%)
  - Acute liver failure (autoimmune hepatitis in pt w/ liver metastasis)
  - Respiratory distress (prior/ongoing history respiratory disorders)

<table>
<thead>
<tr>
<th>Pts, %</th>
<th>TEAEs, % (N = 168)</th>
<th>Grade (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts with any event</td>
<td>10.1</td>
<td>1/2 (13); 3/4 (4)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>4.8</td>
<td>1/2 (8)</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>1.8</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1.8</td>
<td>1/2 (2); 3 (1)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1.2</td>
<td>1 (1); 4 (1)</td>
</tr>
</tbody>
</table>

KEYNOTE-028 Breast Cancer Cohort: Study Design

• Phase Ib multicohort study

Pts with locally advanced or metastatic PD-L1*, ER+/HER2- breast cancer; failed or ineligible for standard therapy; ECOG PS 0-1; ≥ 1 measurable lesion; (N = 25)

Pembrolizumab 10 mg/kg IV Q2W

CR, PR, or SD

PD or unacceptable toxicity

Tx to 24 mos or PD or toxicity

Discontinue

*defined as ≥ 1% tumor cell membranous or any stroma staining

• Primary endpoint: ORR
• Secondary endpoints: PFS, OS, DoR

Slide credit: clinicaloptions.com

Rugo HS, et al. SABCS 2015. Abstract S5-07
KEYNOTE-028 Breast Cancer Cohort: Antitumor Activity

<table>
<thead>
<tr>
<th>Characteristic, % (95% CI)</th>
<th>Pembrolizumab (N = 25)</th>
</tr>
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<tbody>
<tr>
<td>ORR</td>
<td>12 (2.5-31.2)</td>
</tr>
<tr>
<td>CR</td>
<td>0 (0-13.7)</td>
</tr>
<tr>
<td>PR*</td>
<td>12 (2.5-31.2)</td>
</tr>
<tr>
<td>SD</td>
<td>16 (4.5-36.1)</td>
</tr>
<tr>
<td>Clinical benefit rate (CR + PR + SD for ≥ 24 wks)</td>
<td>20 (6.8-40.7)</td>
</tr>
<tr>
<td>PD</td>
<td>60 (38.7-78.9)</td>
</tr>
<tr>
<td>No assessment†</td>
<td>12 (2.5-31.2)</td>
</tr>
</tbody>
</table>

• In 22 pts with ≥ 1 scan after BL
  - ORR: 14%
  - CBR: 23%

• DoR- 8.7 weeks to >44 weeks
  (3 responders remained on study >26 weeks at the time of data reporting)

*All had received ≥ 3 lines of prior therapy in metastatic setting.
†Includes pts who discontinued therapy before first post-BL scan.

**KEYNOTE-028 Breast Cancer Cohort: Treatment-Related AEs**

- Median follow-up: 7.3 mos (range: 0.7-14.3)
- No treatment-related deaths

<table>
<thead>
<tr>
<th>AEs ≥ 5%, %</th>
<th>Pembrolizumab (N = 25)</th>
</tr>
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<tbody>
<tr>
<td>Any</td>
<td>60</td>
</tr>
<tr>
<td>Nausea</td>
<td>20</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>8</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>8</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>8</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8</td>
</tr>
<tr>
<td>Rash</td>
<td>8</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 3/4 AE, %</th>
<th>Pembrolizumab (N = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 autoimmune hepatitis</td>
<td>4</td>
</tr>
<tr>
<td>Grade 3 nausea</td>
<td>4</td>
</tr>
<tr>
<td>Grade 3 muscular weakness</td>
<td>4</td>
</tr>
<tr>
<td>Grade 3 $\gamma$-glutamyltransferase</td>
<td>4</td>
</tr>
<tr>
<td>Grade 4 septic shock</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immune-Related AE, %</th>
<th>Pembrolizumab (N = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 autoimmune hepatitis*</td>
<td>4</td>
</tr>
<tr>
<td>Grade 2 hyperthyroidism†</td>
<td>4</td>
</tr>
<tr>
<td>Grade 2 hypothyroidism†</td>
<td>12</td>
</tr>
<tr>
<td>Grade 1 pneumonitis‡</td>
<td>4</td>
</tr>
</tbody>
</table>

*Resulted in tx interruption.
†Managed with oral steroids.
‡No tx indicated.

Atezolizumab + Albumin-Bound Paclitaxel in mTNBC Cohort: Study Design

• Phase Ib multicohort study

Pts with locally advanced or metastatic TNBC; 1-2 previous cytotoxic chemotherapy regimens; ECOG PS 0-1 (N = 32)

Atezolizumab 800 mg Q2W + Albumin-bound paclitaxel 125 mg/m² IV QW (3 wk on/1 wk off)*

*D1 and D8 of cycle 1 in pts in the serial biopsy cohort (n = 24)

• Primary endpoint: Safety/tolerability
• Other endpoints: ORR, DoR, PFS

Slide credit: clinicaloptions.com

Atezolizumab + Albumin-Bound Paclitaxel in mTNBC Cohort: Antitumor Activity

- 11 of 17 (65%) responses ongoing at time of reporting
- Responses reported in both PD-L1+ (77.8%; IC1/2/3) and PD-L1- (57.1%; IC 0) patients

<table>
<thead>
<tr>
<th>Best Overall Response, %</th>
<th>All pts (N = 24)</th>
<th>1st-line pts (n = 9)</th>
<th>2nd-line pts (n = 8)</th>
<th>3rd-line + pts (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>70.8</td>
<td>88.9</td>
<td>75.0</td>
<td>42.9</td>
</tr>
<tr>
<td>CR</td>
<td>4.2</td>
<td>11.1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>65.7</td>
<td>77.8</td>
<td>75.0</td>
<td>42.9</td>
</tr>
<tr>
<td>SD</td>
<td>20.8</td>
<td>11.1</td>
<td>25.0</td>
<td>28.6</td>
</tr>
</tbody>
</table>

Atezolizumab + Albumin-Bound Paclitaxel in mTNBC Cohort: Safety

• Median follow-up of 5.2 mos

<table>
<thead>
<tr>
<th>Treatment-related AEs in &gt; 1 pt, %</th>
<th>All grades (N = 32)</th>
<th>Grade 3/4 (N = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>100</td>
<td>56</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>53</td>
<td>41</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Anemia</td>
<td>19</td>
<td>8</td>
</tr>
</tbody>
</table>

- No treatment related deaths.

Ongoing Phase III IMpassion 130 trial

• Comparing nab-paclitaxel + atezolizumab vs. Nab-paclitaxel + placebo

• Previously untreated metastatic TNBC (350 patients)

• Primary endpoint: PFS

• Secondary endpoints: OS, ORR, DoR
Vaccines

PRESENT Trial

(Prevention of Recurrence in Early Stage Node Positive Breast Cancers with Low to Intermediate HER-2 Expression with NeuVax Treatment)

- Phase III registration trial evaluating nelipepimut-S, a (HLA)-A2/A3-restricted immunogenic peptide derived from the HER-2 protein.

[Initial phase I/II clinical studies evaluating nelipepimut-S combined with GM-CSF vaccine administered in adjuvant setting to prevent disease recurrence in high risk breast cancer. 5-yr DFS rate was 89.7% in vaccinated patients versus 80.2% in controls (p=.08); DFS higher in optimally dosed patients, 94.6% vs. controls p=.05).

- Completed enrollment in April 2015 with 758 patients in intent-to-treat population

- Primary endpoint results anticipated in 2018 after 36 months of follow-up.
SUMMARY AND FUTURE DIRECTIONS

• Preliminary results from recent studies suggest that immune checkpoint blockade may be a viable option for LA or metastatic breast cancer particularly in combination with other active agents.

• Potential combination strategies are currently ongoing such as the PANACEA phase Ib/II trial combining pembrolizumab and trastuzumab in patients with HER-2 positive ds. progressed on trastuzumab.

• Interest in identifying immunotherapeutic approach to treat breast cancer will continue to grow which will include monoclonal antibodies, vaccines, checkpoint blockade, adoptive T-cell therapy, immunomodulating agents or Toll-like receptor agonists.
“We are not there yet but definitely on our way.”

- Me
Thank you for your attention.