Immune Targeting in Breast Cancer

Ashley Cimino-Mathews, MD
Associate Professor of Pathology and Oncology
The Johns Hopkins Hospital
March 5, 2017

International Society of Breast Pathology
“Molecular diagnostics in breast cancer”
USCAP 2017 Annual Meeting

Disclosure of Relevant Financial Relationships

USCAP requires that all planners (Education Committee) in a position to influence or control the content of CME disclose any relevant financial relationship WITH COMMERCIAL INTERESTS which they or their spouse/partner have, or have had, within the past 12 months, which relates to the content of this educational activity and creates a conflict of interest.

Speaker Disclosures

• No relevant disclosures or conflicts of interest.

OBJECTIVES

1. DEFINE THE TUMOR MICROENVIRONMENT

2. EXAMINE THE ROLE OF TILS (TUMOR INFILTRATING LYMPHOCYTES) AS PROGNOSTIC AND PREDICTIVE MARKERS

3. DISCUSS THE USE OF IMMUNE CHECKPOINT INHIBITION IN BREAST CANCER

What are the elements of the tumor immune microenvironment?

The components of the tumor microenvironment are:
1) the cells
2) the proteins they express and secrete
Cytokines

The cells of the inflamed tumor microenvironment

Cytotoxic granules
CD8+ T lymphocyte
FoxP3+ Regulatory T lymphocyte
CD20+ B lymphocyte
Tertiary lymphoid structure

Macrophage


These cells participate in cancer immune surveillance

<table>
<thead>
<tr>
<th>Tumor elimination</th>
<th>Immune evasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system recognizes tumor neo-antigens as &quot;foreign&quot;</td>
<td>Tumor cells gain immune resistance mechanisms and immune cells shift to pro-tumorigenic milieu</td>
</tr>
</tbody>
</table>

Tissue Antigen Presenting Cell

Antigen Presenting Cell

INHIBITORY "IMMUNE CHECKPOINT" SIGNALS

Antigen presenting cells can stimulate or inhibit the anti-tumor immune response.

CHECKPOINT INHIBITORS: Result in anti-tumor T cell activation

Cytokines

Proteins expressed by tumor and immune cells can stimulate or inhibit the anti-tumor immune response.

What do we already know about tumor infiltrating lymphocytes (TILs) and breast carcinomas?

TILs are emerging as a promising biomarker in breast cancer.
Triple negative (TNBC) and HER2+ carcinomas are more immunogenic than luminal (ER+) carcinomas:
- increased TIL infiltrate
- increased “immune” gene signatures

How should we score TILs in breast carcinoma?

Morphology, definitions, biological and diagnostic relevance of the different immune infiltrates found in breast cancer.

Stromal TILs vs. Intratumoral TILs

Standardized approach for TILs evaluation in breast cancer.
“Lymphocyte-predominant breast cancer”

- In studies, most look at TIL in deciles
- Use cut-off of > 50-60% TIL for “lymphocyte predominant breast carcinoma” (LPBC) (i.e., more TIL than carcinoma cells)
Can TIL be reliably assessed on core needle biopsy?

"T and B lymphocytes show more heterogeneity across a single section than between different sections... This observation suggests that the average lymphocyte score from a single biopsy of a tumor is reasonably representative of the whole cancer."

What is the role of TILs as a **prognostic** biomarker?

Medullary carcinomas have a favorable prognosis... but what is the association of TIL with survival in invasive ductal carcinomas?

The presence of TIL and tertiary lymphoid structures are associated with improved survival in TNBC and HER2+ carcinomas:

- independent prognostic factor for overall survival, decreased metastasis, and increased metastasis free survival in TNBC [1-6]
- improved overall survival in HER2+ carcinomas [1]

What is the role of TILs as a prognostic biomarker in residual disease after neoadjuvant therapy?

The presence of TIL in the tumor bed after neoadjuvant chemotherapy is favorable, primarily in TNBC:
- improved recurrence-free survival
- improved overall survival


What is the role of TILs as a predictive biomarker?
The presence of TIL predicts a favorable response to neoadjuvant therapy, particularly in TNBC and HER2+ tumors.

Table 4 Neoadjuvant trials that have assessed TILs

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased TILs</td>
<td>LPBC have highest pCR</td>
</tr>
<tr>
<td>Lacking TILs</td>
<td>All cases</td>
</tr>
<tr>
<td></td>
<td>~1000 patients</td>
</tr>
</tbody>
</table>

Understanding the components of the tumor microenvironment enables the development and investigation of immunotherapies.
In breast carcinomas, the ligand PD-L1 is expressed by the TIL and the breast carcinoma cells. The PD-1 receptor is expressed on the TIL.

Inhibitory “immune checkpoint” signals:

Proteins expressed by tumor and immune cells can stimulate or inhibit the anti-tumor immune response.

**Triple negative and HER-2+ carcinomas** contain more TIL and are more likely to be PD-L1+ than luminal (ER+) carcinomas, and thus are the most attractive candidates for immunotherapy.

**FDA-approved PD-1/PD-L1 checkpoint inhibitors in solid organ tumors**

- Nivolumab (Bristol-Myers Squibb)
  - Anti-PD-1
  - Melanoma, non-small cell lung carcinoma, renal cell carcinoma, urothelial carcinoma, and head & neck squamous cell carcinoma (and classical Hodgkin lymphoma)
- Pembrolizumab (Merck)
  - Anti-PD-1
  - Melanoma, non-small cell lung carcinoma, and head & neck squamous cell carcinoma
- Atezolizumab (Genentech/Roche)
  - Anti-PD-L1
  - Urothelial carcinoma, NSCLC

**PD-1/PD-L1 Blockade in Breast Cancer**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Target</th>
<th>Subtype (all metastatic)</th>
<th>Patients</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avelumab</td>
<td>PD-L1</td>
<td>All</td>
<td>168</td>
<td>4.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PD-L1+ All</td>
<td>12</td>
<td>33.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TNBC</td>
<td>58</td>
<td>8.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PD-L1+ TNBC</td>
<td>9</td>
<td>44.4%</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD-L1</td>
<td>PD-L1+ TNBC</td>
<td>20</td>
<td>18.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PD-L1+ ER+HER-2-</td>
<td>21</td>
<td>12%</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>PD-L1</td>
<td>PD-L1+ TNBC</td>
<td>21</td>
<td>19%</td>
</tr>
</tbody>
</table>


Slide courtesy of Dr. Leisha Emens, Johns Hopkins Oncology and Immunology

**PD-1/PD-L1 Blockade in Breast Cancer**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Target</th>
<th>Subtype (all metastatic)</th>
<th>Patients</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avelumab</td>
<td>PD-L1</td>
<td>All</td>
<td>168</td>
<td>4.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PD-L1+ All</td>
<td>12</td>
<td>33.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TNBC</td>
<td>58</td>
<td>8.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PD-L1+ TNBC</td>
<td>9</td>
<td>44.4%</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD-L1</td>
<td>PD-L1+ TNBC</td>
<td>20</td>
<td>18.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PD-L1+ ER+HER-2-</td>
<td>21</td>
<td>12%</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>PD-L1</td>
<td>PD-L1+ TNBC</td>
<td>21</td>
<td>19%</td>
</tr>
</tbody>
</table>


Slide courtesy of Dr. Leisha Emens, Johns Hopkins Oncology and Immunology


### PD-1/PD-L1 Blockade in Breast Cancer

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Target</th>
<th>Subtype (all metastatic)</th>
<th>Patients</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avelumab</td>
<td>PD-L1</td>
<td>All</td>
<td>168</td>
<td>4.8%</td>
</tr>
<tr>
<td></td>
<td>PD-L1+ All</td>
<td></td>
<td>12</td>
<td>33.3%</td>
</tr>
<tr>
<td></td>
<td>TNBC</td>
<td></td>
<td>58</td>
<td>8.6%</td>
</tr>
<tr>
<td></td>
<td>PD-L1+ TNBC</td>
<td></td>
<td>9</td>
<td>44.4%</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD-L1</td>
<td>PD-L1+ TNBC</td>
<td>20</td>
<td>18.5%</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>PD-L1</td>
<td>PD-L1+ TNBC</td>
<td>21</td>
<td>19%</td>
</tr>
</tbody>
</table>


**Avelumab (anti-PD-L1) activity in unselected patients**

- ORR in breast cancer = 4.8%
- 1 CR, 7 PRs, 39 patients with SD; Disease control rate (DCR) = 28%
- Ref: Dirix L et al SABCS 2015

**Change in Target Lesion Size**

**Combination therapy:**
Can we convert a non-immunogenic tumor into a tumor with an active immune microenvironment?

- ORR = 19%
- Median duration of response has not yet been reached (range: 18 to 56+ wks)
- Ref: Emens LA et al, AACR, 2015

**“Immunogenic cell death” stimulates an antitumor T cell response**

- [1] Radiation therapy or chemotherapy
- [2] Immune checkpoint inhibition

Slide content courtesy of Dr. Leisha Emens, Johns Hopkins Oncology and Immunology
Atezolizumab (anti-PD-L1) and Nab-Paclitaxel (taxane) activity in PD-L1 unselected, metastatic TNBC

Changes in Tumor Burden Over Time

1st line patients: n = 9 (ORR ~ 67%)

Adams S, et al SABCS 2015

Summary of Responses to Atezolizumab with Nab-Paclitaxel in metastatic TNBC

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>First Line (n = 9)</th>
<th>Second Line (n = 8)</th>
<th>&gt; Third Line (n = 7)</th>
<th>All Patients (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR</td>
<td>66.7%</td>
<td>25%</td>
<td>28.6%</td>
<td>41.7%</td>
</tr>
<tr>
<td>ORR</td>
<td>88.9%</td>
<td>75%</td>
<td>42.9%</td>
<td>70%</td>
</tr>
<tr>
<td>CR</td>
<td>11.1%</td>
<td>0</td>
<td>0</td>
<td>4.2%</td>
</tr>
<tr>
<td>PR</td>
<td>77.8%</td>
<td>75%</td>
<td>42.9%</td>
<td>66.7%</td>
</tr>
<tr>
<td>SD</td>
<td>11.1%</td>
<td>25%</td>
<td>28.6%</td>
<td>20.8%</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8.3%</td>
</tr>
</tbody>
</table>


The optimal biomarker to use for overall prognosis, prediction and inclusion for immunotherapies is still not clear.

The degree tumor infiltrating lymphocytes (TIL)?
The number of CD8 versus FoxP3 T cells?
The PD-1 or PD-L1 expression by the tumor cells?
The PD-1 or PD-L1 expression by the TIL?
The ER/PR/HER2 status of the tumor?

Understanding the tumor microenvironment characteristics may help guide treatment algorithms and selecting patients for whom immunotherapeutic strategies might be considered.

References:

Figure 2 Possible trial design using tumour-infiltrating lymphocyes as a biomarker

Nature Reviews | Clinical Oncology
Future considerations

- Is assessing TIL on H&E alone enough information?
- What is the role of multiplex assays (CD8, PD-L1)?
- What is the impact of the cancer mutational load?
- How do we standardize PD-L1 assessment?
- Is TIL scoring ready for primetime implementation?

SUMMARY

1. BREAST CARCINOMAS HAVE ACTIVE TUMOR MICROENVIRONMENTS (ESPECIALLY TNBC AND HER-2+)
2. TILS ARE PROGNOSTIC AND PREDICTIVE (PARTICULARLY IN TNBC)
3. IMMUNE CHECKPOINT INHIBITORS ARE UNDER CLINICAL INVESTIGATION IN BREAST CANCER, WITH PROMISING EARLY RESULTS

ACKNOWLEDGEMENTS

JHH Oncology and immunology
Leisha Emens, MD PhD

JHH Dermatopathology
Janis Taube, MD
Helen Xu

JHH Pathology
Robert Anders, MD PhD
Pedram Argani, MD
Tamara Lotan, MD PhD
Alan Meeker, PhD
Rajni Sharma, PhD
Elizabeth Thompson, MD PhD

THANK YOU