The Role of Immunotherapy in Breast Cancer: Teaching an Old Dog New Tricks?

Hope S. Rugo, MD
Professor of Medicine
Director, Breast Oncology and Clinical Trials Education
UCSF Helen Diller Family Comprehensive Cancer Center
Immunogenicity of Breast Cancer

• Not traditionally thought to be immunogenic
  – Risk is not increased in patients who are immunosuppressed
    • But outcome is overall worse in patients on long-term immunosuppression
  – Spontaneous remissions are highly uncommon

• Differential response?
  – Evidence of extensive inflammatory infiltrate in more aggressive tumors
  – Perhaps we looked at the wrong tumors......
TIL are prognostic in TNBC treated with adjuvant chemotherapy (BIG 02-98)

RCT 2009 N+ patients (256 TNBC) A-CMF/AC-CMF vs. AT-CMF/A-T-CMF

Highest TIL in HER2 and TNBC

Prognostic correlation in TNBC
Continuous: better with each 10%
Binary: LPBC (>50% better)
DDFS correlated to TILS (n=8390)

TILs as a Predictive and Prognostic Biomarker in Different Subtypes of BC Treated with Neoadjuvant Rx: Meta-Analysis of 3771 Pts

- Metaanalysis of 3771 patients (GBG)
  - High TILS are more frequent in TNBC (30%) >HER2 (19%) >luminal (13%)

Denkert et al, SABCS 2016
TILS are linked to increased pCR rates in all subtypes.

High TILS associated with OS for TNBC and HER2; low TILS associated with OS for luminal.

High TILS after neoadjuvant chemotherapy associated with better outcome for TNBC.

Targeting the PD-1 Pathway in Breast Cancer

TNBC and other rapidly proliferative BC subtypes are attractive candidates for cancer immunotherapy:

- Higher rate of mutational complexity, genomically unstable
- Presence of PD-1$^+$ TIL
- Higher rates of PD-L1$^+$ expression by tumor cells and immune cells
- No current targeted therapy options


# Overall Response Rates by PD-L1 Status in Phase I Trials

<table>
<thead>
<tr>
<th>Agent</th>
<th>Subtype</th>
<th>ORR</th>
<th>ORR (PD-L1+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>TNBC</td>
<td>18.5%</td>
<td>18.5%</td>
</tr>
<tr>
<td></td>
<td>ER+/HER2-</td>
<td>12.0%</td>
<td>12.0%</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>TNBC</td>
<td>19.0%</td>
<td>19.0%</td>
</tr>
<tr>
<td></td>
<td>TNBC</td>
<td>41.7%</td>
<td>77.8%</td>
</tr>
<tr>
<td>Avelumab</td>
<td>All</td>
<td>3.0% (1 CR, 4PR)</td>
<td>immune cells&gt;10%</td>
</tr>
<tr>
<td></td>
<td>ER+/HER2-TNBC</td>
<td>4.8% unconfirmed</td>
<td>16.7% (n=2/12)</td>
</tr>
<tr>
<td></td>
<td>TNBC</td>
<td>2.8%</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>TNBC</td>
<td>5.2% (3/58)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>TNBC</td>
<td>22.2% (n=2/9)</td>
<td>NR</td>
</tr>
</tbody>
</table>

Studies used different antibodies and cutoffs for determining PD-L1 positivity

Nanda, JCO 2016, Emens, AACR 2015, Adams, ASCO 2016; Dirix et al, BCRT 2017; Rugo SABCS
Pembrolizumab Antitumor Activity in Previously Treated and Previously Untreated mTNBC

Cohort A (N = 170):
Previously Treated, Regardless of PD-L1 Expression

Cohort B (N = 52):
Previously Untreated, PD-L1 Positive

ORR, %

Total PD-L1
Positive
Partial response
Complete response

Adams S et al. ASCO 2017
Numerically higher ORRs were observed in IC2/3 and 1L subgroups

- irRC criteria captured non-classical responses to atezolizumab

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Overall</th>
<th>IC2/3</th>
<th>IC0/1</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (%)</td>
<td>13%</td>
<td>17%</td>
<td>8%</td>
</tr>
<tr>
<td>CI (%)</td>
<td>5%</td>
<td>9%</td>
<td>18%</td>
</tr>
<tr>
<td>n</td>
<td>112</td>
<td>71</td>
<td>37</td>
</tr>
</tbody>
</table>

ORR 95% CI: 5%, 17%, 8%  

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>1L</th>
<th>2L</th>
<th>3L+</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (%)</td>
<td>26%</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>CI (%)</td>
<td>9%</td>
<td>18%</td>
<td>17%</td>
</tr>
<tr>
<td>n</td>
<td>19</td>
<td>28</td>
<td>65</td>
</tr>
</tbody>
</table>

ORR 95% CI: 9%, 51%, 9%, 51%, 0%, 18%, 2%, 28%, 3%, 17%, 4%, 21%

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Objective response–evaluable patients. Four patients had unknown PD-L1 status. Confirmed, investigator-assessed responses are plotted. Patients with missing or unevaluable responses are included (16 per RECIST v1.1 and 23 per irRC). ORR 95% CI was estimated using Clopper-Pearson method. Data cutoff: March 31, 2016.
Immune Sculpting of the TNBC Genome:
Good prognosis (i.e. immune rich/low inflammation) TNBC has low mutation and neoantigen loads

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>immune rich TNBC</th>
<th>immune poor TNBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognosis</td>
<td>good</td>
<td>poor</td>
</tr>
<tr>
<td>Mutation load</td>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td>Neoantigen load</td>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td>Clonal heterogeneity</td>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td>Negative association of heterogeneity and T-cell presence</td>
<td>strong</td>
<td>weak</td>
</tr>
<tr>
<td>Potential state of immuno editing hypothesis</td>
<td>equilibrium phase with pruning of clonal diversity</td>
<td>lack of immunogenicity / immune escape, clonal diversification</td>
</tr>
</tbody>
</table>

No correlation with mutational load and TIL infiltration

Hypothesis: Genomic instability is important to activate the immune response; increasing genomic complexity suppresses the immune response

Karn et al, SABCS 2016, Luen et al, 2016 courtesy of Loi
TNBC and Immunotherapy: Response to Single Agent Anti-PD-L1/PD-1 by Line of Therapy

Anti-PD-L1/PD-1 single agent in mTNBC ≥1L, PDL1+/-

Atezolizumab (n=115)
- 26% overall response rate
  - 11% CR
  - 15% PR

Pembrolizumab (n=222)
- 23% overall response rate
  - 4.7% CR
  - 18.3% PR

No clear relationship with PD-L1 positivity

Overall Survival by Best Response

Pembrolizumab single agent in mTNBC ≥1L, PDL1+/-

Atezolizumab single agent in mTNBC ≥1L, PDL1+/-
High sTILs are Associated with Improved Response Particularly in the First-Line Setting

<table>
<thead>
<tr>
<th>Objective Response Rate (%)</th>
<th>Atezolizumab (Cohort A: &gt;2nd line)</th>
<th>Pembrolizumab (Cohort B: 1st line)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIL high</td>
<td>19%</td>
<td>39.1%</td>
</tr>
<tr>
<td>TIL low</td>
<td>9%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

Different levels by source of sample (archival vs new) and organ site sampled: LN>lung>liver

Metastatic breast cancer is a low TIL disease

## Immune Checkpoint Inhibitors in ER+ Disease

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab (n = 25)</th>
<th>Avelumab (n=2/72)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>PD-1</td>
<td>PD-L1</td>
</tr>
<tr>
<td><strong>Tumour PD-L1</strong></td>
<td>≥1%</td>
<td>All</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>12%</td>
<td>2.8%</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>16%</td>
<td>25% in entire study population</td>
</tr>
</tbody>
</table>

Rugo et al. SABCS 2015, Dirix et al SABCS 2015
Enhancing Response to Immunotherapy

- Immune agonists: preclinical data suggests increased immune infiltration and enhanced response to immune checkpoint inhibition
- DNA damage upregulates PD-L1 expression, immune infiltration?
- Strategies
  - Combinations with chemotherapy
    - Nab-paclitaxel, paclitaxel, others
  - Combinations with immune agonists
  - Combinations with other targeted agents
    - PARPi, MEKi
  - Combinations with radiation therapy

Jeong Kim, Genentech, Unpublished data
Atezolizumab in Combination with nab-Paclitaxel in TNBC: Phase Ib Trial

*Best Objective Response per RECIST v1.1 by line of therapy*

- 32 pts were evaluable for response
  - Median no. (range) of prior systemic cancer therapies: 5 (1-10)
  - Prior taxane use: 88%
- Responses seen regardless of PD-L1 tumor status
- Baseline levels TILs showed a trend with increased response

<table>
<thead>
<tr>
<th>BestOR</th>
<th>1L n = 13</th>
<th>2L n = 9b</th>
<th>3L+ n = 10c</th>
<th>All N = 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR (95% CI)a</td>
<td>46% (19, 75)</td>
<td>22% (3, 60)</td>
<td>40% (12, 74)</td>
<td>38% (21-56)</td>
</tr>
<tr>
<td>CR</td>
<td>8%</td>
<td>0</td>
<td>0</td>
<td>3%</td>
</tr>
<tr>
<td>PR</td>
<td>38%</td>
<td>22%</td>
<td>40%</td>
<td>34%</td>
</tr>
<tr>
<td>SD</td>
<td>38%</td>
<td>67%</td>
<td>30%</td>
<td>44%</td>
</tr>
</tbody>
</table>

Adams, et al. ASCO 2016

TILs as a percentage of total tumor area.
I-SPY2 Neoadjuvant Trial: Pembrolizumab graduated in all HER2- signatures: Both HR+/HER2- and TN

- Neoadjuvant paclitaxel x 12 +/- pembrolizumab followed by AC x 4
- Adaptive randomization on I-SPY 2

<table>
<thead>
<tr>
<th>Signature</th>
<th>Estimated pCR rate (95% probability interval)</th>
<th>Probability pembro is superior to control</th>
<th>Predictive probability of success in phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pembro</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>All HER2-</td>
<td>0.46 (0.34 – 0.58)</td>
<td>0.16 (0.06 – 0.27)</td>
<td>&gt; 99%</td>
</tr>
<tr>
<td>TNBC</td>
<td>0.60 (0.43 – 0.78)</td>
<td>0.20 (0.06 – 0.33)</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>HR+/HER2-</td>
<td>0.34 (0.19 – 0.48)</td>
<td>0.13 (0.03 – 0.24)</td>
<td>&gt;99%</td>
</tr>
</tbody>
</table>

The Bayesian model estimated pCR rates adjust to characteristics of the I-SPY 2 population. The raw pCR rates are higher than the model estimate of 0.604 in TNBC.

Nanda et al, ASCO 2017, Abstract 506
Toxicity: Immune Checkpoint Inhibitors

- Related to enhanced immune activity
  - Thyroid disorders, colitis, hepatitis, pneumonitis, hypophysitis, adrenal insufficiency, myocarditis, rash, and ?
  - Serious toxicity generally at 1-2%
- Enhanced when chemotherapy given after checkpoint inhibition?
  - Late toxicities reported
    - Up to 120 days after last dose
    - ISPY2: AC given after paclitaxel/pembrolizumab
      - 6 cases with adrenal insufficiency
      - None when pembrolizumab was continued through AC
Ongoing Trials (examples)

Metastatic disease (all comers)
- First line trials
  - Pembrolizumab and gem/carbo vs paclitaxel/nab-P
  - Atezolizumab and nab-paclitaxel (completed accrual)
- Additional combinations
  - With alternate chemotherapy (eribulin, platinum, etc)
  - With PARP inhibitors, targeted agents (MEK, etc)
  - In ER+ disease: with CDK 4/6 inhibitors, HDAC inhibitors
  - In HER2+ disease

Adjuvant
- Various neoadjuvant combination studies
- Continuing through AC (ISPY-2, KEYNOTE Ph III)
- Post-neoadjuvant pembrolizumab (SWOG 1418)
New Directions: Example

• Combination immunotherapy
  – Combine PD-L1 or PD-1 inhibitors with immune agonists, or agents targeted to related pathways
  – For example:
    • ‘Tumor cell-autonomous’ pathways that may promote host antitumor immune evasion
    • Therapeutic cooperation between MEK and PD-1/PD-L1 immune checkpoint inhibitors (Loi et al, Clin Cancer Res 2016, Dushyanthen et al (Loi), Nature Comm 2017)
OX-40 and 4-1BB antibodies are immune agonists

Binimetinib: MEK 1/2 inhibitor

Avelumab: PD-L1 inhibitor

Tumor biopsy
Blood collection

Tumor biopsy
Blood collection

15 day lead-in

1 Cycle = 4 weeks
Tumor assessments and PRO every 8 weeks

Blood collection
(at 8 weeks and Disease Progression)
Additional Studies

- Gene signatures to predict TILs?
  - 4-gene expression signature to predict high TILs after neoadjuvant therapy (HLF, CXCL13, SULT1E1, and GBP1)

- Vaccines

- CAR-T cells
  - HER2 CARS containing 4-1BB c-stimulatory domain in brain mets improve tumor targeting and reduce T cell exhaustion

- Targeting MSI/mismatch repair deficiency

- Optimal sequencing strategies (TONIC trial)
  - 50 pts with TNBC: 2 week lead in with RT, metronomic dox or cyclo, cisplatin or no Rx followed by nivolumab
  - ORR 22%, PFS 3.4 mo, DOR 9 mo; correlated with TIL/CD8 in baseline sample

Tailoring Immunotherapy to Tumor Biology: Personalized Immunotherapy?

Immunologically hot tumors

- PD-L1/checkpoints
- CD8 T cells/IFNγ
- Mutational load
- TILs

Excluded infiltrate

- Angiogenesis, MDSCs, Reactive stroma, Mutational load

Immunologically cold tumors

- Low T cells, Low MHC class I, Proliferating tumours

Single agent immune checkpoint inhibitors

- Attract T-cells to tumor bed

Priming & activation

- (e.g. CTLA-4, OX40)

Influence infiltration?

- (e.g. VEGF, MEKi)

Make tumor more immunogenic

- Priming, activation & infiltration

- Neoantigen expression?
  - (e.g. epigenetic modulation)
  - Adoptive Cell Therapy?
  - Vaccination

Adapted from Ribas and Schmid
Thanks to:

- Our many clinical collaborators
- The TBCRC
- The BCRF
- Our patients and their families
- Fatima Cardoso
- The ESO staff