Treatment Update: Metastatic Triple-Negative Breast Cancer

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Living Beyond Breast Cancer Conference for Women Living with Metastatic Disease
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Overview

- Triple-Negative Breast Cancer
- Current Treatment Options
- Importance of Clinical Trials
- Recent Advances
- Ongoing Research
Defining Triple-Negative Breast Cancer
Triple-Negative Breast Cancer

• Breast cancer is not one disease, and is categorized based on the expression of ER, PR, and HER2
• TNBC refers to a form of breast cancer which lacks expression of ER, PR and HER2/neu
• Approximately 15-20% of breast cancers
• No targeted therapies for TNBC
  – anti-estrogen therapy
  – anti-HER2 therapy
Breast Cancer Subtypes

Basal-like  HER-2  "Normal"  Luminal B  Luminal A

"Intrinsic" gene set on 78 single tumor samples

476 cDNA clones

85 Arrays

Sorlie et al, PNAS 2001
Risk Factors for TNBC

• More common in young women and women of African ancestry and Hispanic women
• More common in women with a *BRCA1* mutation
  – 75% with TNBC
• 15-20% of women with a *BRCA2* mutation develop TNBC
• Patients with TNBC should consider genetic testing if they have family history of breast/ovarian cancer or are diagnosed at a young age
How much of breast cancer is hereditary?

- Sporadic ~70%
- Familial ~15-20%
- Hereditary ~10%
When to suspect a hereditary cancer syndrome

- Cancer in two or more close relatives (on same side of family)
- Early age at diagnosis
- Multiple primary tumors in the same individual
- Bilateral or multifocal tumors
- Rare tumors/cancer
- Clustering of certain types of tumors consistent with specific cancer syndrome
- Evidence of autosomal dominant transmission
- From a population that has higher risk to carry certain cancer gene mutations (e.g., Ashkenazi Jewish)
Current Treatment Options for TNBC
Treatment Settings

- **Neoadjuvant**
  - Therapy prior to surgery
  - Treatment aimed at curing the cancer and preventing a recurrence

- **Adjuvant**
  - Therapy after surgery
  - Treatment aimed at curing the cancer and preventing a recurrence

- **Metastatic**
  - Treatment for advanced breast cancer
  - Treatment aimed at helping patients live longer and better
Systemic Treatment for Breast Cancer

Evaluation for systemic treatment

- Tumor Size
- Lymph node Status
- Distant Metastases

HR Positive
- Hormone Therapy

HER-2+
- Biologic Therapy

HR+ and HER2+
- Biologic Therapy + Hormone Therapy

Triple-negative
- Chemotherapy
Standard Treatments for Early-Stage TNBC

- Neoadjuvant/Adjuvant treatment
- Goal of therapy is curative
- Anthracycline and taxane-based chemotherapy
  - Typically administered for 8 cycles (4 of each)
  - Order doesn’t matter (T-AC vs AC-T)
  - Anthracycline doesn’t matter (A vs E)
- Surgery
  - Mastectomy vs Lumpectomy
- Radiation Therapy
  - To breast and/or lymph nodes
Recurrence Patterns of TNBC

• Most women with metastatic TNBC are first diagnosed with early stage breast cancer
• Recurrences are most common within 3 years of initial diagnosis
• Metastases are more common in
  – Lungs, Liver, Brain
• Metastases are less common in
  – Bone
Treatment for Metastatic TNBC

• Single-Agent Chemotherapy
  – Taxanes
  – Capecitabine
  – Eribulin
  – Liposomal doxorubicin
  – Other microtubule inhibitors (ixabepilone, vinorelbine)

• Combination Chemotherapy Regimens
  – Carboplatin+Gemcitabine
  – Ixabepilone+Capecitabine

• Clinical Trials

• No targeted agents are currently approved for TNBC
Importance of Clinical Trials
The Role of Clinical Trials

• Phases of Clinical Trials
  – Phase I, II, III

• Clinical trials are designed to build on the current standard of care

• Without clinical trials we cannot develop better treatment for the future
Clinical Trial Phases

• Phases I
  – Safety, dose finding
  – New drugs
  – New combinations of old drugs

• Phase II
  – Efficacy, specific for tumor type

• Phase III
  – Testing again standard treatment
  – +/- placebo
Pros and Cons of Clinical Trials

• Pros
  – Access to newer promising therapies before they are approved
  – Help to move the field forward
  – Potentially help future patients who are diagnosed with cancer

• Cons
  – No guarantee trial treatment is better
  – No guarantee that you will be assigned to study treatment
  – Treatment has to be at sponsoring institution
  – Additional time/visits/biopsies
Recent Advances
What we are learning about TNBC

• Research focused on TNBC is relatively recent
• TNBC is defined by characteristics it does not have
  – ER/PR negative
  – HER2 negative
• TNBCs are genetically unstable
  – Chromosomes are actively rearranging
  – Gene alterations are ongoing
  – Treatments to target this instability are being developed
• There are different types of TNBC
Triple Negative Subtype GE Patterns are Reproducible

Lehmann et al, JCI 2011
What does this mean for those with TNBC?

• Being able to subdivide triple-negative breast cancers into subcategories will help us identify new targets for therapy

• Clinical research is ongoing to target pathways that are implicated in TNBC and newer trials are being developed based on this work
Recent Clinical Trial Results
PD-1 Pathway and Immune Surveillance

- PD-1 is expressed primarily on activated T cells\(^1\)
- Binding of PD-1 to its ligands PD-L1 and PD-L2 impairs T-cell function\(^1\)
- PD-L1 is expressed on tumor cells and macrophages\(^2\)
- Tumors can co-opt the PD-1 pathway to evade immune surveillance\(^2\)

Pembrolizumab (MK-3475) Is a Humanized IgG4, High-Affinity, Anti-PD-1 Antibody

- High affinity for the PD-1 receptor (KD ≈ 29 pM)
- Dual ligand blockade of PD-L1 and PD-L2
- No cytotoxic (ADCC/CDC) activity
- PK supports dosing every 2 weeks (Q2W) or every 3 weeks (Q3W)
- Demonstrated clinical activity in multiple tumor types\(^1\)-\(^6\)
- Recently approved in the United States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor

KEYNOTE-012:
Triple-Negative Breast Cancer Cohort

• Recurrent or metastatic ER⁻/PR⁻/HER2⁻ breast cancer
• ECOG PS 0-1
• PD-L1⁺ tumor
• No systemic steroid therapy
• No autoimmune disease (active or history of)
• No active brain metastases

Pembro 10 mg/kg Q2W

Complete Response
Discontinuation Permitted
Partial Response or Stable Disease
Treat for 24 months or until progression or intolerable toxicity
Confirmed Progressive Disease
Discontinue

• PD-L1 positivity: 58% of all patients screened had PD-L1-positive tumors
• Treatment: 10 mg/kg IV Q2W
• Response assessment: Performed every 8 weeks per RECIST v1.1

[^a]: PD-L1 expression was assessed in archival tumor samples using a prototype IHC assay and the 22C3 antibody. Only patients with PD-L1 staining in the stroma or in ≥1% of tumor cells were eligible for enrollment.
[^b]: If clinically stable, patients are permitted to remain on pembrolizumab until progressive disease is confirmed on a second scan performed ≥4 weeks later. If progressive disease is confirmed, pembrolizumab is discontinued. An exception may be granted for patients with clinical stability or improvement after consultation with the sponsor.
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), years</td>
<td>51.9 (29-72)</td>
</tr>
<tr>
<td>Female</td>
<td>32 (100.0%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>7 (21.9%)</td>
</tr>
<tr>
<td>White</td>
<td>25 (78.1%)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>15 (46.9%)</td>
</tr>
<tr>
<td>1</td>
<td>16 (50.0%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>History of brain metastases</td>
<td>4 (12.5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. prior therapies for metastatic disease</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5 (15.6%)</td>
</tr>
<tr>
<td>1</td>
<td>6 (18.8%)</td>
</tr>
<tr>
<td>2</td>
<td>6 (18.8%)</td>
</tr>
<tr>
<td>3</td>
<td>5 (15.6%)</td>
</tr>
<tr>
<td>4</td>
<td>3 (9.4%)</td>
</tr>
<tr>
<td>≥5</td>
<td>7 (21.9%)</td>
</tr>
<tr>
<td>Previous neoadjuvant or adjuvant therapy</td>
<td>28 (87.5%)</td>
</tr>
<tr>
<td>Any previous chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Taxane</td>
<td>30 (93.8%)</td>
</tr>
<tr>
<td>Anthracycline</td>
<td>25 (78.1%)</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>21 (65.6%)</td>
</tr>
<tr>
<td>Platinum</td>
<td>19 (59.3%)</td>
</tr>
<tr>
<td>Eribulin</td>
<td>7 (21.9%)</td>
</tr>
</tbody>
</table>

Analysis cut-off date: November 10, 2014.
## Treatment-Related Adverse Events With Incidence ≥5%

<table>
<thead>
<tr>
<th>Condition</th>
<th>Any Grade</th>
<th>Grade 3-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>6 (18.8%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (18.8%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>5 (15.6%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (15.6%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>2 (6.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>AST increased</td>
<td>2 (6.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (6.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Erythema</td>
<td>2 (6.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (6.3%)</td>
<td>1 (3.1%)</td>
</tr>
</tbody>
</table>

- Adverse events of a potentially immune-mediated nature, regardless of attribution, included pruritus (n = 3; all grade 1-2), hepatitis\(^b\) (n = 1; grade 3), and hypothyroidism (n = 1; grade 2)

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\(^a\)Reported during treatment or within 30 days thereafter.

\(^b\)Not considered to be related to treatment by the investigator.

Analysis cut-off date: November 10, 2014.
Best Overall Response
(RECIST v1.1, Central Review)

<table>
<thead>
<tr>
<th>Patients Evaluable for Response(^a)</th>
<th>n = 27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>5 (18.5%)</td>
</tr>
<tr>
<td>Best overall response</td>
<td></td>
</tr>
<tr>
<td>Complete response(^b)</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td>Partial response(^b)</td>
<td>4 (14.8%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>7 (25.9%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>12 (44.4%)</td>
</tr>
<tr>
<td>No assessment(^c)</td>
<td>3 (11.1%)</td>
</tr>
</tbody>
</table>

\(^a\)Includes patients with measurable disease at baseline who received \(\geq 1\) pembrolizumab dose and who had \(\geq 1\) post-baseline scan or discontinued therapy before the first scan due to progressive disease or a treatment-related AE. 5 patients were excluded because they did not have any assessments per central review (n = 2) or because they did not have measurable disease per central review at baseline (n = 3).

\(^b\)Confirmed responses only.

\(^c\)“No assessment” signifies patients who discontinued therapy before the first post-baseline scan due to progressive disease or a treatment-related AE.

Analysis cut-off date: November 10, 2014.
# Best Overall Response By Previous Therapy (RECIST v1.1, Central Review)

<table>
<thead>
<tr>
<th>Evaluable Patients N = 27&lt;sup&gt;a&lt;/sup&gt;</th>
<th>CR or PR&lt;sup&gt;b&lt;/sup&gt;</th>
<th>SD</th>
<th>PD or No Assessment&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoadjuvant or adjuvant</td>
<td>24</td>
<td>4 (16.7%)</td>
<td>7 (29.2%)</td>
</tr>
<tr>
<td>No. of lines for metastatic disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4</td>
<td>0 (0.0%)</td>
<td>1 (25.0%)</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>1 (25.0%)</td>
<td>1 (25.0%)</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>0 (0.0%)</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>1 (25.0%)</td>
<td>1 (25.0%)</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>1 (33.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>≥5</td>
<td>6</td>
<td>2 (33.3%)</td>
<td>2 (33.3%)</td>
</tr>
</tbody>
</table>

- Previous therapy among the 5 patients with CR or PR
  - Capecitabine: 5 (100.0%)
  - Taxane: 5 (100.0%)
  - Anthracycline: 4 (80.0%)
  - Platinum: 3 (60.0%)
  - Eribulin: 1 (20.0%)

<sup>a</sup>Includes patients with measurable disease at baseline who received ≥1 pembrolizumab dose and who had ≥1 post-baseline scan or discontinued therapy before the first scan due to progressive disease or a treatment-related AE. 5 patients were excluded because they did not have any assessments per central review (n = 2) or because they did not have measurable disease per central review at baseline (n = 3).

<sup>b</sup>Confirmed responses only.

<sup>c</sup>“No assessment” signifies patients who discontinued therapy before the first scan due to progressive disease or a treatment-related AE.

Analysis cut-off date: November 10, 2014.
Time to and Durability of Response
(RECIST v1.1, Central Review)

- Median follow-up duration: 9.9 months (range, 0.4-15.1)
- Median time to response: 18 weeks (range, 7-32)
- Median duration of response\(^a\): not reached (range, 15 to 40+ weeks)

\(^a\)Kaplan-Meier estimate.
Analysis cut-off date: November 10, 2014.
Summary and Conclusions

- Pembrolizumab showed an acceptable safety and tolerability profile in patients with heavily pretreated, PD-L1-positive, advanced triple-negative breast cancer
- Pembrolizumab was associated with an ORR of 18.5%
- Responses were durable, with 3 of 5 responders on treatment for ≥11 months
- The acceptable safety and tolerability profile and promising antitumor activity support the further development of pembrolizumab in patients with advanced triple-negative breast cancer
- A phase II study of pembrolizumab for patients with advanced triple-negative breast cancer is planned to begin soon
Targeting the Androgen Receptor in TNBC

• The AR appears to be a driving force for a subset of TNBCs
• About 10% of TNBCs are AR+
• Bicalutamide has previously been shown to be effective at keeping AR+ TNBCs stable
• Enzalutamide binds to the AR with higher affinity than bicalutamide
• Enzalutamide is being tested in women with AR+ TNBC
Enzalutamide for Metastatic TNBC

• Small study of 118 pts with AR+ TNBC presented at the SABCS in 2014
• In first phase of study (42 pts), there were 2 responses seen, and 42% of pts had stable disease for at least 16 weeks
• In the second phase of the study (76 pts), an additional 4 responses were seen
• Final results are expected to be presented at ASCO in summer of 2015
Ongoing Research
Targeted Therapies Currently Under Investigation for Advanced TNBC

- Immune therapy (PD-1/PD-L1 inhibitors) +/- chemotherapy
- Androgen receptor
- PARP inhibitors
  - Mutation carriers (monotherapy)
  - TNBC (in combination with chemo)
- gpNMB
- Glucocorticoid receptor
- AKT/PI3K/mTOR inhibitors
- Jak2 inhibitors
- Macrophages (the tumor microenvironment)
How can I find out about clinical trials in my area?

- Treating oncologist
- ClinicalTrials.gov
- Triple-negative breast cancer foundation
  www.tnbcfoundation.org
Why has it been so hard to find a treatment?

• TNBC is not one disease
  – It is important to understand which type of TNBC will respond to which type of therapy

• Tumors are genetically unstable and are constantly undergoing changes

• Newer technologies and clinical trials hold great promise for the future
Future Promise

• Much research is ongoing in the field of breast cancer
  – Understand mechanisms of resistance
  – Develop more personalized therapy
• New therapies are being developed and tested in clinical trials specifically for TNBC
• Hope for the future
  – More effective therapies
  – Fewer side effects
Thank You!

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