Triple Negative Breast Cancer (TNBC)

Defined as lacking expression of:
1. estrogen receptor (ER)
2. progesterone receptor (PR)
3. human epidermal growth factor receptor 2 (HER2)

Histology:
• commonly infiltrating ductal carcinoma (IDC)
• but medullary carcinoma (rare) is generally triple negative
Epidemiology

- Premenopausal women
- African-American women
- BRCA mutation, ~20% of cases, mostly BRCA1

Carey, LA et al. JAMA, 2006
Parise CA et al. Breast J, 2009
TNBC patterns of recurrence


Distant Recurrence

Overall Survival

Breast Cancer Clinical Phenotype or Histologic Subtypes

Immunohistochemical analysis

Breast Cancer Genomic or Molecular or Intrinsic Subtypes

Gene expression array analysis
78 carcinomas, three benign tumors, and four normal tissues

- Luminal A (~40%) - ER expression genes, low HER2 or proliferation genes
- Luminal B (~20%) – lower ER, variable HER2 and higher proliferation genes
- HER2-enriched (~10-15%) – HER2 genes
- Basal-like – low luminal and HER2 genes.

Sorlie T et al. PNAS, 2001
Triple-negative BC x Basal-like BC
Clinical phenotype x Molecular Subtype

**TNBC**
but not basal-like
10-30%
(can include “claudine-low” subtype, stem cells rich)

**Basal**
but not TNBC
15-40% can be ER+, PR+, HER2+

TNBC and Basal-like
~80%

TNBC Molecular Subtypes

Gene Expression Profiles
587 TNBC cases

Basal-like 1: BRCA pathway
Basal-like 2: PI3K, PTEN, EGFR
Immunomodulatory: CTLA4 pathway
Mesenchymal-like: WNT, ALK
Mesenchymal stem-like: ECM, ALK
Luminal AR: Androgen, Estrogen

Lehmann et al. JCI, 2011
Patient diagnosed at 60 years or younger with a TNBC undergo BRCA mutation testing regardless of family history.

In metastatic TNBC, results of BRCA testing have therapeutic implications.
TNBC stage and treatment plan

Early stage breast cancer:
- Non-metastastic
- Surgery and radiation similar to other breast cancer subtypes
- Chemotherapy if tumor >0.5cm or node positive
- Neoadjuvant or adjuvant?

Metastatic breast cancer:
- Palliative chemotherapy
- PARP (Poly (ADP-ribose) polymerase inhibitors
- Immune checkpoint inhibitors
Neoadjuvant versus Adjuvant chemotherapy in breast cancer

Meta analysis of 9 trials, 3946 patients

Mauri et al. JNCI, 2005
Neoadjuvant chemotherapy in TNBC

• Improve surgery cosmetic outcomes
• Evaluate response to treatment *in vivo*
• Avoid delays in systemic therapy
• Evidence of benefit for adjuvant Capecitabine in TNBC with residual tumor after neoadjuvant chemotherapy - CREATX
TNBC neoadjuvant or adjuvant therapy

Preferred regimens:
- Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel (every 2 weeks or weekly)
- TC (docetaxel/cyclophosphamide)
- In residual disease after adjuvant therapy – capecitabine

Useful in certain circumstances:
- Dose-dense AC
- AC (every 3 weeks)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- AC followed by weekly paclitaxel

Other:
- AC followed by docetaxel every 3 weeks
- EC (epirubicin/cyclophosphamide)
- TAC (docetaxel/doxorubicin/cyclophosphamide)
- Selected patient in preoperative setting only:
  - Weekly paclitaxel and carboplatin
  - Docetaxel and carboplatin

• NCCN Guidelines 1.2020
Triple Negative Breast Cancer

Neoadjuvant Chemotherapy pathological Complete Response (pCR)

Symmans WF et al. JCO, 2017
Neoadjuvant chemotherapy TNBC

CALGB 40603 ddAC+T +/- Carboplatin or Bevacizumab

454 patients

Sikov WM, et al. JCO, 2015
Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy – CREATE-X

Masuda N et al., NEJM, 2017

- HER2 negative breast cancer (included both ER+ and TNBC)
- Neoadjuvant therapy with anthracycline +/- taxane
- Residual disease or positive nodes
- Randomized to capecitabine or standard therapy
  - 1250 mg/m2 BID on days 1 through 14 of a 21 day cycle
- Primary Endpoint PFS
- All patients were enrolled in Asia (Japan and South Korea)

DFS 69.8 vs 56.1 %
OS 78.8 vs 70.3%

Hazard ratio for recurrence, second cancer, or death, 0.58
95% CI, 0.39–0.87

Hazard ratio for death, 0.52
95% CI, 0.30–0.90
Metastatic TNBC

- Repeat biopsy:
  - ER, PR and HER2 may change
  - Test tumor PDL1
- Similar chemotherapy regimens, goal palliation, combination regimens pending of volume of disease
- PDL1+ -> atezolizumab + abraxane
- Germinative BRCAmut -> PARPi
Anti-PDL1 antibody

Mechanism of action

Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer – IMpassion130

902 patients
First line metastatic treatment

Schmid P et al. NEJM, 2018
### Table 3. Key Adverse Events.*

<table>
<thead>
<tr>
<th>Event</th>
<th>Atezolizumab + Nab-Paclitaxel (N = 452)</th>
<th>Placebo + Nab-Paclitaxel (N = 438)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Alopecia</td>
<td>255 (56.4)</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>208 (46.0)</td>
<td>5 (1.1)</td>
</tr>
<tr>
<td>Cough</td>
<td>112 (24.8)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>98 (21.7)</td>
<td>25 (5.5)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>94 (20.8)</td>
<td>37 (8.2)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>85 (18.8)</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>62 (13.7)</td>
<td>0</td>
</tr>
</tbody>
</table>

*number of patients with event (percent)*

*Schmid P et al. NEJM, 2018*
PARP (Poly ADP-ribose polymerase) inhibitors

Mechanism of action

**FIGURE** Illustration of Olaparib Mechanism Specifically in *BRCA*-Deficient Cells Compared With Normal Cells[1]

PARP = poly (ADP-ribose) polymerase.

Davis CC and Caulfield S. Cancer Network, 2019
Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation

302 BRCAmut randomized 2:1
Olaparib vs Standard 2nd line therapy (capecitabine, eribulin, vinorelbine)
TNBC 49%, HR+ 50%

Robson M et al. NEJM, 2017
Robson M et al. Annals of Oncology, 2019
Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation

302 BRCAmut randomized 2:1
Olaparib vs Standard 2nd line therapy (capecitabine, eribulin, vinorelbine)

Table 2. Summary of Adverse Events.ox

<table>
<thead>
<tr>
<th>Variable</th>
<th>Olaparib Group (N = 205)</th>
<th>Standard-Therapy Group (N = 91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Adverse event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>199 (97.1)</td>
<td>75 (36.6)</td>
</tr>
<tr>
<td>Anemia†</td>
<td>82 (40.0)</td>
<td>33 (16.1)</td>
</tr>
<tr>
<td>Neutropenia‡</td>
<td>56 (27.3)</td>
<td>19 (9.3)</td>
</tr>
<tr>
<td>Decreased white-cell count</td>
<td>33 (16.1)</td>
<td>7 (3.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>119 (58.0)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>61 (29.8)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>42 (20.5)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>33 (16.1)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>59 (28.8)</td>
<td>6 (2.9)</td>
</tr>
<tr>
<td>Headache</td>
<td>41 (20.0)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>29 (14.1)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>35 (17.1)</td>
<td>0</td>
</tr>
<tr>
<td>Increased alanine aminotransferase level</td>
<td>23 (11.2)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase level</td>
<td>19 (9.3)</td>
<td>5 (2.4)</td>
</tr>
<tr>
<td>Palmar–plantar erythrodysthesia</td>
<td>1 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Dose reduction owing to adverse event</td>
<td>52 (25.4)</td>
<td>NA</td>
</tr>
<tr>
<td>Treatment interruption or delay owing to adverse event</td>
<td>72 (35.1)</td>
<td>NA</td>
</tr>
<tr>
<td>Treatment discontinuation owing to adverse event</td>
<td>10 (4.9)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Robson M et al. NEJM, 2017
Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation

431 BRCAmut randomized 2:1
Talazoparib vs Standard 2nd line therapy (capecitabine, eribulin, gemcitabine, vinorelbine)
44% TNBC, 55% HR+

Litton JK et al. NEJM, 2018
Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation

431 BRCAmut randomized 2:1
Talazoparib vs Standard 2nd line therapy (capecitabine, eribulin, gemcitabine, vinorelbine)
44% TNBC, 55% HR+

Table 3. Summary of Adverse Events.*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Talazoparib Group (N=286)</th>
<th>Standard-Therapy Group (N=126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>282 (98.6)</td>
<td>123 (97.6)</td>
</tr>
<tr>
<td>Serious adverse event†</td>
<td>91 (31.8)</td>
<td>37 (29.4)</td>
</tr>
<tr>
<td>Serious and drug-related adverse event</td>
<td>26 (9.1)</td>
<td>11 (8.7)</td>
</tr>
<tr>
<td>Grade 3 or 4 serious adverse event</td>
<td>73 (25.5)</td>
<td>32 (25.4)</td>
</tr>
<tr>
<td>Adverse event resulting in permanent drug discontinuation</td>
<td>17 (5.9)</td>
<td>11 (8.7)</td>
</tr>
</tbody>
</table>

Litton JK et al. NEJM, 2018
Initial treatment of metastatic triple-negative breast cancer

- **Rapidly progressive visceral disease?**
  - Yes
  - Combination chemotherapy
  - BRCA germline mutation?
    - Yes
    - Prior chemotherapy (either for early-stage or metastatic disease)?
      - Yes
      - PD-L1 expression ≥1%?
        - Yes
        - Options include:
          - PARP inhibitor
          - Atezolizumab plus nabpaclitaxel
        - No
        - Single-agent chemotherapy Options include:
          - Taxane
          - Platinum agent
      - No
      - Atezolizumab plus nabpaclitaxel
    - No
    - Options include:
      - Taxane
      - Anthracycline
  - No
- No

Investigational agents

- Anti-Trop2 antibody-drug conjugate:
  - sacituzumab govitecan, IMMU-132 (SN-38 irinotecan metabolite)
- Androgen receptor inhibitor:
  - bicalutamide, enzalutamide
- Immunotherapy
Phase I/II study of the anti-programmed death ligand-1 antibody MEDI4736 in combination with olaparib for advanced triple negative breast cancer

Metastatic TNBC (measurable / biopsiable)

Cohort 1 – BRCA wt
Step 1 N=16, if >=2 responses
Step 2 N=25

Pilot Cohort – BRCA mut
N=10, early stop 0/5 responses

Durvalumab 1500mg IV Q28d
Olaparib 300mg PO BiD

• Primary endpoint: Response Rate
• Secondary endpoints: duration response, PFS, OS, toxicity

correlatives
images Q2 cycles
**ONC201 - Phase II for metastatic breast/endometrial cancer**

**Cohort 2:**
TNBC, biopsiable, measurable*

**Cohort 3:**
Endometrial cancer, biopsiable, measurable

**ONC201 weekly**
28 days cycles

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>625mg orally weekly</td>
</tr>
<tr>
<td>-1</td>
<td>500mg orally weekly</td>
</tr>
<tr>
<td>-2</td>
<td>375mg orally weekly</td>
</tr>
<tr>
<td>-3</td>
<td>250mg orally weekly</td>
</tr>
</tbody>
</table>

* at least 1 chemotherapy line in metastatic setting

**Correlatives**

Radiographic assessment every 8 weeks

0 biopsy 4 biopsy 8 12 16 weeks Biopsy PD
Incidence of brain metastases

• Breast cancer:
  • Most common cancer in women - 271,260 new cases in USA in 2019
  • Second most common cause of brain metastases in USA
• Autopsy studies – 15 to 35% patients with breast cancer presented brain metastases
• Risk subtype specific:

Brain metastases
- Up to 50%
- 25-40%
- 7.6%

References:
Siegel RL et al. CA Cancer J C. 2019
Barnholz-Sloan JS et al. JCO. 2004
Stemmler HJ et al. Breast. 2006
Lin NU et al. Cancer. 2008
Nam BH et al. Breast Cancer Res. 2008
Lee YT. J Surg Oncol. 1983
Cummings MC et al. J Pathol. 2014
Tsukada Y et al. Cancer. 1984
Kennecke H et al. JCO. 2010
Pestalozzi et al. Lancet Oncol. 2013
Kennecke H et al. JCO. 2010
Survival from diagnosis of CNS metastases by breast cancer subtype

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Number of patients</th>
<th>Median survival</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal</td>
<td>343</td>
<td>9.3</td>
<td>(7.2–11.3)</td>
</tr>
<tr>
<td>Luminal-HER2</td>
<td>162</td>
<td>16.5</td>
<td>(11.9–21.1)</td>
</tr>
<tr>
<td>HER2</td>
<td>270</td>
<td>11.5</td>
<td>(9.1–13.8)</td>
</tr>
<tr>
<td>TN</td>
<td>337</td>
<td>4.9</td>
<td>(3.9–5.9)</td>
</tr>
</tbody>
</table>

1256 patients with brain metastases
2001-2012 Japan

*Niikura N et al. Breast Cancer Res Treat, 2014*

119 patients with brain metastases
1998-2008 North Carolina, US

*Anders CK et al. Cancer, 2011*
# Brain metastases

## TNBC survival

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Number patients (period)</th>
<th>Median Survival after CNS mets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eichler AF et al. Cancer, 2008.</td>
<td>21 patients (2001-2005)</td>
<td>4.0 months</td>
</tr>
<tr>
<td>Kaplan MA et al. Oncology, 2012</td>
<td>73 patients (2001-2011)</td>
<td>5.4 months</td>
</tr>
<tr>
<td>Oehrlich NE et al. Oncol Letter, 2017</td>
<td>22 patients (2004-2010)</td>
<td>4.9 months</td>
</tr>
</tbody>
</table>
Phase I/II Study of Metronomic Temozolomide in Secondary Prevention of TNBC Brain Metastases Following Local Therapy

**Phase I design**

**Dose declasation for Phase I**

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Temozolomide mg/m2 daily for 21 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>-1</td>
<td>40</td>
</tr>
<tr>
<td>-2</td>
<td>30</td>
</tr>
</tbody>
</table>

**Endpoints:**

**Phase I:** Safety and maximum tolerated dose (MTD)

**Phase II:** Freedom from distant brain metastases at 4-6 months

**Secondary endpoints:** Time to WBRT, Overall survival (OS)
Thank you!

Questions?