Recent advances in triple negative breast cancer

22\textsuperscript{nd} Annual Breast Cancer Update
April 10, 2019

Rishi Sawhney, MD
Bayhealth Cancer Institute
What is triple negative breast cancer?
TNBC—the basics

**Epidemiology**

- 200,000 cases/year worldwide
- Younger age
  - 50% under age 50 at diagnosis
- Premenopausal
- More common in African-American race
- BRCA mutation

**Clinical features**

- Rapid growth
- Often diagnosed clinically
- High tumor grade
- ER/PR/Her2 negative
- More sensitive to chemo
  - Particularly platinum
Natural History of TNBC

TNBC recurrences peak at 1 – 3 years; Sharp decline thereafter....
Recurrence Patterns of TNBC

TNBC recurrences more likely to be Visceral – involving Lung and brain; less likely Bone only recurrences
Estimated Cancer Deaths per year in the USA

Women 270,290

- 26% Lung & bronchus
- 10% Breast Luminal
- 9% Colon & rectum
- 7% Pancreas
- 5% Ovary
- **5% Triple-Negative BC (ER-, PR-, HER2-)**

- 4% Non-Hodgkin lymphoma
- 3% Leukemia
- 3% Uterine corpus
- 2% Liver & intrahepatic bile duct
- 2% Brain/Other nervous system
- 24% All other sites
Triple Negative Breast Cancer
Heterogeneity of TNBC
Not just one disease
Different subtypes likely have different ’’driver’’ pathways and targets
Novel ‘druggable’ pathways in TNBC

- Sacituzumab
- Trop2
- AR
- AR antagonist
How can we use these drugs to make a difference in TNBC?

- **Localized disease**
  - Neoadjuvant—give systemic therapy BEFORE surgery with goal of shrinking the tumor, and eliminating microscopic spread of tumor
  - Adjuvant—give systemic therapy AFTER surgery with goal of eradicating any microscopic spread of tumor that may have already occurred

- **Metastatic disease**
  - Use systemic therapy long term, with the goals of
    - Achieve/maintain control of disease
    - Improve symptoms and quality of live
    - Extend patient survival
Druggable targets in TNBC

- Chemotherapy
- PARP inhibitors
- Immunotherapy
- PI3K inhibitors
- Androgen receptor antagonists
- Antibody-drug conjugates
Neoadjuvant paradigm for TNBC (systemic therapy)

Surgery
Assess for residual cancer
Surveillance
Neoadjuvant chemo for TNBC

• Among the highest pCR rates are seen in TNBC
• pCR associated with excellent outcomes

Neoadjuvant paradigm for TNBC—new standard of care

Surgery
If YES residual cancer

Capecitabine
Druggable targets in TNBC

- Chemotherapy
- **PARP inhibitors**
- Immunotherapy
- PI3K inhibitors
- Androgen receptor antagonists
- Antibody-drug conjugates
# NCCN Guidelines Version 1.2019
## Invasive Breast Cancer

### CHEMOTHERAPY REGIMENS FOR RECURRENT OR STAGE IV (M1) DISEASE\(^a, b\)

#### HER2-Negative

<table>
<thead>
<tr>
<th>Preferred regimens</th>
</tr>
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<tbody>
<tr>
<td>Anthracyclines</td>
</tr>
<tr>
<td>Doxorubicin</td>
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</tr>
<tr>
<td>Eribulin</td>
</tr>
</tbody>
</table>

   - PARP inhibitors (options for patients with HER2-negative tumors and germline *BRCA1/2* mutation)\(^d\)
   - Olaparib\(^d\) (category 1)
   - Talazoparib\(^d\) (category 1)

#### HER2-Positive\(^g\)

<table>
<thead>
<tr>
<th>Preferred regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pertuzumab + trastuzumab + docetaxel (category 1)(^h)</td>
</tr>
<tr>
<td>Pertuzumab + trastuzumab + paclitaxel(^g)</td>
</tr>
</tbody>
</table>

### Other recommended regimens:

- Ado-trastuzumab emtansine (T-DM1)
- Trastuzumab + paclitaxel\(^h\) ± carboplatin
- Trastuzumab + docetaxel\(^h\)
- Trastuzumab + vinorelbine\(^h\)
- Trastuzumab + capecitabine
- Lapatinib + capecitabine
- Trastuzumab + lanatinib (without cytotoxic therapy)

### FDA approves olaparib for germline BRCA-mutated metastatic breast cancer

**FDA D.I.S.C.O. podcast**

On January 12, 2018, the Food and Drug Administration granted regular approval to olaparib tablets (Lynparza, AstraZeneca Pharmaceuticals LP), a poly (ADP-ribose) polymerase (PARP) inhibitor, for the treatment of patients with deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*m), HER2-negative metastatic breast cancer who have been treated with chemotherapy either in the neoadjuvant, adjuvant, or metastatic setting.
Druggable targets in TNBC

- Chemotherapy
- PARP inhibitors
- Immunotherapy
- PI3K inhibitors
- Androgen receptor antagonists
- Antibody-drug conjugates
Immune checkpoint inhibitors—How they work

- PD1 is an inhibitory protein on T-cells
- PD1 is activated by interacting with PDL-1 protein on other cells
Immune checkpoint inhibitors in metastatic TNBC

Immune checkpoint inhibitors have shown durable responses in heavily pretreated patients with metastatic TNBC

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab (n = 32)</th>
<th>Atezolizumab (n = 71)</th>
<th>Avelumab (n=58 /9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>PD-1</td>
<td>PD-L1</td>
<td>PD-L1</td>
</tr>
<tr>
<td>Tumour PD-L1</td>
<td>≥1% (58%+)</td>
<td>≥5%</td>
<td>All / ≥1%</td>
</tr>
<tr>
<td>ORR</td>
<td>18.5%</td>
<td>13%</td>
<td>8.6% / 44.4%</td>
</tr>
<tr>
<td>SD</td>
<td>25.9%</td>
<td>18%</td>
<td>22.4%</td>
</tr>
</tbody>
</table>
Phase 1b Study of Atezolizumab + nab-Paclitaxel in Metastatic TNBC

Metastatic TNBC 0 to 3 prior lines Tx (N = 32)

Atezolizumab 800 mg on d1, 15 + nab-paclitaxel 125 mg/m² on d1, 8, 15 28-d cycles

After nab-P discontinued, maintenance atezolizumab allowed until loss of clinical benefit

- Confirmed ORR
  - All pts (n = 32): 38%
  - First-line (n= 13): 46%
  - Second-line (n = 9): 22%
  - Third-line (n = 10): 40%

- PD-L1 status was not predictive of response
- Responding patients tended to have higher baseline levels of TILs

**IMpassion130: Atezolizumab in 1st line mTNBC**

**Design:** Double-blind | Multicentre | Randomized | Placebo-controlled

**Central testing for PD-L1 status**

**Patients with incurable advanced/metastatic TNBC (N=900)**

**Stratification:**
- Tumour tissue PD-L1 expression (IHC 0 vs IHC 1,2,3)
- Liver metastases (Yes vs No)
- Prior taxane treatment (Yes vs No)

**Study treatment phase**

- Atezolizumab (840mg q2w) + nab-paclitaxel (100mg/m² qw)
- Placebo + nab-paclitaxel (100mg/m² qw)

**Until loss of Clinical Benefit**

**Until PD**

**Survival Follow-Up**

**Presented at:** ASCO Annual Meeting ’17 | #ASCO17
Progression-free survival

ALL patients

A Progression-free Survival in the Intention-to-Treat Population

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Events/No. of Patients</th>
<th>Median Progression-free Survival (95% CI)</th>
<th>1-Yr Rate of Progression-free Survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab+Nab-Paclitaxel</td>
<td>358/451</td>
<td>7.2 (5.6–7.5)</td>
<td>23.7 (19.6–27.9)</td>
</tr>
<tr>
<td>Placebo+Nab-Paclitaxel</td>
<td>378/451</td>
<td>5.5 (5.3–5.6)</td>
<td>17.7 (14.0–21.4)</td>
</tr>
</tbody>
</table>

Stratified hazard ratio for progression or death, 0.80 (95% CI, 0.69–0.92)
P=0.0025

No. at Risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No.</th>
<th>451</th>
<th>360</th>
<th>226</th>
<th>164</th>
<th>77</th>
<th>34</th>
<th>20</th>
<th>11</th>
<th>6</th>
<th>1</th>
<th>NE</th>
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<td>327</td>
<td>183</td>
<td>130</td>
<td>57</td>
<td>29</td>
<td>13</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>NE</td>
<td>NE</td>
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Overall survival

ALL patients
# NCCN Guidelines Version 1.2019
Invasive Breast Cancer

## Chemotherapy Regimens for Recurrent or Stage IV (M1) Disease

### HER2-Negative

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<tr>
<td>Anthracyclines</td>
<td>Pertuzumab + trastuzumab + docetaxel (category 1)&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Pertuzumab + trastuzumab + paclitaxel&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>Liposomal doxorubicin</td>
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<td>Taxanes</td>
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<tr>
<td>Paclitaxel</td>
<td></td>
</tr>
<tr>
<td>Anti-metabolites</td>
<td>Ado-trastuzumab emtansine (T-DM1)</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Trastuzumab + paclitaxel&lt;sup&gt;h&lt;/sup&gt; ( \pm ) carboplatin</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Trastuzumab + docetaxel&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td>Microtubule inhibitors</td>
<td>Trastuzumab + vinorelbine&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>Trastuzumab + capecitabine</td>
</tr>
<tr>
<td>Eribulin</td>
<td>Lapatinib + capecitabine</td>
</tr>
</tbody>
</table>

### Other recommended regimens

- Cyclophosphamide
- Docetaxel
- Albumin-bound paclitaxel
- Epirubicin/cyclophosphamide
- Eribulin
- Ixabepilone

### Useful in certain circumstances

- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel
- GT (gefrelecin)
- Gemcitabine
- Paclitaxel

**FDA approves atezolizumab for PD-L1 positive unresectable locally advanced or metastatic triple-negative breast cancer**

On March 8, 2019, the Food and Drug Administration granted accelerated approval to atezolizumab (TECENTRIQ, Genentech Inc.) in combination with paclitaxel protein-bound for adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] of any intensity covering \( \geq 1\% \) of the tumor area), as determined by an FDA-approved test.
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>

* Shown are the single most frequent adverse event of any grade, adverse events of any grade for which the rates differed by at least 5 percentage points between groups, and adverse events of grade 3 or 4 for which the rates differed by at least 2 percentage points between groups.
Druggable targets in TNBC

- Chemotherapy
- PARP inhibitors
- Immunotherapy
- **PI3K inhibitors**
- Androgen receptor antagonists
- Antibody-drug conjugates
The PI3K/AKT pathway is one of the most frequently altered pathways in breast cancer and is key for survival and growth of tumors.

AKT can be activated by:

- **Loss of function of negative regulators:**
  - PTEN
  - INPP48
  - PHLPP
  - PP2A

- **Gain of function of positive regulators:**
  - PI3K
  - AKT
  - Receptor tyrosine kinases (HER2)

- **Therapy-induced survival response**
  - Chemotherapy
  - Hormone therapy

• AKT inhibitors
  – 2 phase II trials demonstrated improved PFS and OS with an oral AKT inhibitor combined with paclitaxel as first-line therapy for metastatic TNBC
    • AZD5363 (Capivasertib), n = 140 (Schmid et al, #1007)
    • Ipatasertib, n = 124 (LOTUS trial, Dent et al, #1008)
      – Trend toward 5 month improvement in OS
  – A phase III trial is underway
    • IPATunity130 (NCT03337724)


Druggable targets in TNBC

- Chemotherapy
- PARP inhibitors
- Immunotherapy
- PI3K inhibitors
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- Antibody-drug conjugates
Feasibility study of adjuvant enzalutamide in AR+ TNBC

TNBC following (neo)adjuvant Chemotherapy AR-positive

Enzalutamide 180mg daily X 52-weeks

Primary endpoint: treatment adherence

NCT02750358
Druggable targets in TNBC

- Chemotherapy
- PARP inhibitors
- Immunotherapy
- PI3K inhibitors
- Androgen receptor antagonists
- Antibody-drug conjugates
Antibody-drug conjugates
Sacituzumab Govitecan Antibody-Drug Conjugate

Humanized anti-Trop-2 antibody
• Targets Trop-2, an epithelial antigen expressed on many solid cancers, including mTNBC

Linker for SN-38
• Hydrolysable linker for payload release
• High drug-to-antibody ratio (7.5:1)

SN-38 payload
• SN-38 more potent than parent compound, irinotecan
• ADC delivers up to 136-fold more SN-38 than irinotecan in vivo

Response rate: 33%
Clinical benefit: 45%
## Antibody-Drug Conjugates in Development for TNBC

<table>
<thead>
<tr>
<th>ADCs</th>
<th>Glembatumumab Vedotin(^1)</th>
<th>Ladiratuzumab Vedotin(^2)</th>
<th>Sacituzumab Govitecan(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Other name</strong></td>
<td>CDX-011</td>
<td>SGN-LIV1A</td>
<td>IMMU-132</td>
</tr>
<tr>
<td><strong>Target</strong></td>
<td>gpNMB</td>
<td>LIV-1</td>
<td>Trop-2</td>
</tr>
<tr>
<td><strong>Tumor expression</strong></td>
<td>~40%</td>
<td>71%</td>
<td>88%</td>
</tr>
<tr>
<td><strong>Cytotoxin</strong></td>
<td>MMAE</td>
<td>MMAE</td>
<td>SN-38</td>
</tr>
<tr>
<td><strong>Single-agent activity (ORR)</strong></td>
<td>28%</td>
<td>37%</td>
<td>30%</td>
</tr>
<tr>
<td><strong>Registrational trials</strong></td>
<td>METRIC 1(^{st})-3(^{rd}) line</td>
<td>Active arm in ISPY-2 Phase II trial 2018</td>
<td>ASCENT (\geq 3^{rd}) line</td>
</tr>
</tbody>
</table>

### ABT 414: depatuxizimab mafodotin, targets EGFR linked to MMAF

Doc, I have triple negative breast cancer. How can you help me?

We have no specific targets. Let’s talk chemo.
Potential approach to TNBC in 2019 & beyond

- Germline BRCA1/2 and HR pathway gene mutation testing
  - Somatic BRCA mutation testing
  - HRD score, HRD scar biomarkers

- Histologic examination for tumor-infiltrating lymphocytes (?)
  - Immune signature by gene expression microarray

- IHC for androgen receptor (?)
  - Androgen-related gene signature by genomic diagnostic assay

- Sequencing for PIK3CA/AKT1/PTEN alterations

- IHC for targetable cancer epithelial antigens

- Defective DNA repair:
  - Platinums and PARP inhibitors

- Inflamed phenotype:
  - Immunotherapy

- Androgen receptor–positive:
  - Androgen blockade

- PI3K/AKT/PTEN altered:
  - AKT inhibitors
  - Antibody-drug conjugates

- Unique antigen-expressing:

- Unclassified TNBCs:
  - Chemotherapy and clinical trials
Thank you!