Triple Negative Breast Cancer: Part 2
A Medical Update

April 29, 2015
Tiffany A. Traina, MD
Breast Medicine Service
Memorial Sloan Kettering Cancer Center
Weill Cornell Medical College
Overview

• What is TNBC?
• Today’s Standard Treatments for TNBC
  – Early Stage Breast Cancer
    • Pre-op platinum chemotherapy
  – Metastatic Breast Cancer
    • Taxanes
    • Platinum chemotherapy
    • Eribulin mesylate
• Ongoing Research to Find New Treatments
• How to Find a Clinical Trial
Triple Negative Breast Cancer

ER(-)  PR(-)  HER2(-)
How many women this year will get TNBC?

**Leading Sites of New Cancer Cases and Deaths – 2015**

<table>
<thead>
<tr>
<th>Estimated New Cases*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
</tr>
<tr>
<td>Prostate</td>
</tr>
<tr>
<td>220,800 (26%)</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
</tr>
<tr>
<td>115,610 (14%)</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
</tr>
<tr>
<td>69,090 (8%)</td>
</tr>
<tr>
<td>Urinary bladder</td>
</tr>
<tr>
<td>56,320 (7%)</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
</tr>
<tr>
<td>42,670 (5%)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>39,850 (5%)</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
</tr>
<tr>
<td>38,270 (5%)</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
</tr>
<tr>
<td>32,670 (4%)</td>
</tr>
<tr>
<td>Leukemia</td>
</tr>
<tr>
<td>30,900 (4%)</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
</tr>
<tr>
<td>25,510 (3%)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
</tr>
<tr>
<td>Breast</td>
</tr>
<tr>
<td>231,840 (29%)</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
</tr>
<tr>
<td>105,590 (13%)</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
</tr>
<tr>
<td>63,610 (8%)</td>
</tr>
<tr>
<td>Uterine corpus</td>
</tr>
<tr>
<td>54,870 (7%)</td>
</tr>
<tr>
<td>Thyroid</td>
</tr>
<tr>
<td>47,230 (6%)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>32,000 (4%)</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
</tr>
<tr>
<td>31,200 (4%)</td>
</tr>
<tr>
<td>Pancreas</td>
</tr>
<tr>
<td>24,120 (3%)</td>
</tr>
<tr>
<td>Leukemia</td>
</tr>
<tr>
<td>23,370 (3%)</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
</tr>
<tr>
<td>23,290 (3%)</td>
</tr>
<tr>
<td>All sites</td>
</tr>
<tr>
<td>810,170 (100%)</td>
</tr>
</tbody>
</table>

232,000 new breast cancers

15-20% are TN

~46,400 with TNBC
Observations about TNBC

Who gets TNBC?
• Younger women
• African-American or Hispanic ancestry
• Hereditary predisposition to breast cancer
  – BRCA1
• Discordant relationship to traditional risks:
  – Increased risk with increased number of pregnancies
  – Increased risk with earlier age at 1\textsuperscript{st} full term pregnancy

Characteristics
• Higher risk of recurrence than ER+ breast cancer
• Most recurrences occur in first 2-3 years
• More likely to spread to visceral organs
• Not all TNBC are the same...
The Faces of TNBC

Courtesy of Dilip Giri MD
Breast Cancers differ on the inside too!

Sorlie et al. PNAS. 2003.
Targeted Therapies Improve Survival

ER

Tamoxifen
Aromatase Inhibitors
Fulvestrant

HER2

Trastuzumab
Lapatinib
Pertuzumab
TDM1

TNBC

?
Early Stage Breast Cancer
GeparSixto: Does carboplatin increase response?

von Minckwitz et al Lancet Oncology 2014 Jun; 15(7)
Carboplatin increases pCR

pCR (ypToNo)

TNBC

<table>
<thead>
<tr>
<th></th>
<th>PM</th>
<th>PMCb</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>157</td>
<td>158</td>
</tr>
<tr>
<td>37.9%</td>
<td></td>
<td>58.7%</td>
</tr>
</tbody>
</table>

P < 0.05

von Minckwitz et al Lancet Oncology 2014 Jun; 15(7)
CALGB 40603: Does carboplatin increase pCR?

N = 443

2 x 2 Randomization

Key Eligibility
St II-III
ER/PR <10%
HER2 (-)

Primary Endpoint: pCR Breast (ypTo/is N any)

Paclitaxel 80 mg/m² wkly x 12  
ddAC x 4

Paclitaxel 80 mg/m² wkly x 12  
Bevacizumab 10 mg/kg q2wks x 9  
Surgery

Paclitaxel 80 mg/m² wkly x 12  
Carboplatin AUC 6 q3wks x 4

Paclitaxel 80 mg/m² wkly x 12  
Carboplatin AUC 6 q3wks x 4  
Bevacizumab 10 mg/kg q2wks x 9

Paclitaxel 80 mg/m² wkly x 12  
Carboplatin AUC 6 q3wks x 4

Carboplatin significantly improves pCR

46% (40-53%) vs. 60% (54-66%)

Odds Ratio: 1.76
p = 0.0018

41% (35-48%) vs. 54% (48-61%)

Odds ratio: 1.71
p = 0.0029
Metastatic Breast Cancer
How do we select treatment for TNBC?

The standard of care treatment for TNBC is chemotherapy.
Chemotherapy regimens for MBC

- Preferred single agents
  - Anthracyclines
    - Doxorubicin
    - Liposomal doxorubicin
  - Taxanes
    - Paclitaxel
  - Anti-metabolites
    - Capecitabine
    - Gemcitabine
  - Other microtubule inhibitors
    - Vinorelbine
    - Eribulin
- Other single agents
  - Cyclophosphamide
  - Carbo- or cisplatin
  - Docetaxel
  - Nab-paclitaxel
  - Epirubicin
  - Ixabepilone
- Off Label
  - Etoposide
  - Irinotecan
  - 5FU continuous infusion
  - Metronomic CM

NCCN Guidelines, v1.2014
CALGB 40502: Randomized Phase III trial of weekly paclitaxel vs. other chemotherapies

N = 799
Untreated
Stage IV
Strata:
Adj taxanes
ER/PR status

Randomize 1:1:1

nab-paclitaxel 150 mg/m² weekly + bevacizumab 10 mg/kg q 2 wks²
paclitaxel 90 mg/m² weekly + bevacizumab 10 mg/kg q 2 wks¹
ixabepilone 16 mg/m² weekly + bevacizumab 10 mg/kg q 2 wks³

Restage q 2 cycles until disease progression

Rugo H, JCO 2012, Abstract CRA 1002
CALGB 40502: weekly paclitaxel prevails

Rugo H, JCO 2012, Abstract CRA 1002
CALGB 40502: TNBC Subset

Triple Negative Disease

- No difference from overall study group
- Weekly paclitaxel less side effect than either of the others

<table>
<thead>
<tr>
<th>Comparison</th>
<th>HR</th>
<th>P-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>nab vs. pac</td>
<td>0.93</td>
<td>0.7354</td>
<td>0.62 – 1.40</td>
</tr>
<tr>
<td>ixa vs. pac</td>
<td>1.46</td>
<td>0.0647</td>
<td>0.98 – 2.18</td>
</tr>
</tbody>
</table>

Rugo H, JCO 2012, Abstract CRA 1002
TNT Study

Primary endpoint: response after 6 cycles of treatment

N=370

Current analysis done with median follow-up of 11 months
Response Overall & By \textit{BRCA} mutation status

---

**Randomised treatment - all patients (N=376)**

- **Carboplatin**
  - 59/188 (31.4%)
  - Absolute difference (C-D): -4.2% (95% CI -13.7 to 5.3)
  - Exact p = 0.44

- **Docetaxel**
  - 67/188 (35.6%)

**Germline \textit{BRCA} 1/2 Mutation (n=43)**

- **Carboplatin**
  - 17/25 (68.0%)
  - Absolute difference (C-D): 34.7% (95% CI 6.3 to 63.1)
  - Exact p = 0.03

- **Docetaxel**
  - 6/18 (33.3%)
Options after 1st line treatment? Eribulin improves overall survival by 20%

Eligibility (N = 762)
- Locally recurrent or mBC
- 2-5 prior chemotherapies
  - ≥2 for advanced disease
  - Prior anthracyclines and taxanes
- Progression ≤6 months of last chemotherapy
- Neuropathy ≤ Grade 2
- ECOG ≤ 2

Eribulin mesylate 1.4 mg/m², 2-5 min IV D1, 8 every 21 days

Treatment of Physician’s Choice (TPC)

2:1

Eribulin improves OS by 30% in patients with metastatic TNBC compared to capecitabine

**Patients (N=1102)**
- Locally advanced or MBC
  - ≤3 prior chemotherapy regimens (≤2 for advanced disease)
  - Prior anthracycline and taxane in (neo)adjuvant setting or for locally advanced or MBC

**Randomization 1:1**

**Eribulin mesylate**
- 1.4 mg/m² 2- to 5-min IV Day 1 & 8 q21 days

**Capecitabine**
- 1250 mg/m² BID orally Days 1-14, q21 days

**Co-primary endpoint**
- OS and PFS

**Secondary endpoints**
- Quality of life
- ORR
- Duration of response
- 1-, 2- and 3-year survival
- Tumor-related symptom assessments
- Safety parameters
- Population PK (eribulin arm only)

*Kaufmann P et al, SABCS 2012*
Ongoing Research to Find New Treatments
Some TNBCs behave like a hormone driven breast cancer


9/41 ER/PR(-) cluster with ER(+)
We can block androgen-driven growth!

![Graph showing cell growth over days with different treatments: R-1881, EtOH, R-1881 + Flutamide, Flutamide.](image)

- R-1881
- EtOH
- R-1881 + Flutamide
- Flutamide

Bicalutamide has activity in AR+ TNBC

<table>
<thead>
<tr>
<th>Best Response</th>
<th>No. of patients (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
</tr>
<tr>
<td>SD &gt; 6 months</td>
<td>5</td>
</tr>
<tr>
<td>SD &lt; 6 months</td>
<td>2</td>
</tr>
<tr>
<td>PD</td>
<td>19</td>
</tr>
</tbody>
</table>

Median # of cycles: 3 (2 – 84+)

Clinical Benefit Rate = 19% (95% CI 7-39%)

• 1 patient with SD > 7+yr
• 1 patient with SD > 1yr (13 mo)
• 1 patient with unresectable BC after neoadjuvant ddAC → T was able to proceed to curative surgery after >6mo on bicalutamide
• 1 patient with SD > 6 mo (8 mo)
• 1 patient with SD > 6 mo (10 mo)

Gucalp et al CCR 2013
Enzalutamide in AR+ TNBC

Figure 1. Enzalutamide directly binds the androgen receptor and has 3 sites of activity:

1. Inhibits binding of androgens to AR
2. Inhibits nuclear translocation of AR
3. Inhibits association of AR with DNA

AR = androgen receptor; T = testosterone.

404 tissue samples collected
368 analyzed via 2 antibody assays
289 (79%) with positive AR staining in some tumor cells
203 (55%) samples had AR+ staining in ≥ 10% of tumor cells
Enzalutamide shrinks AR+ TNBC

A. Case 1
- No prior therapies for advanced disease
- 5 target lesions and 4 non-target lesions with confirmed PR at Week 19
  - Baseline sum of longest diameter (SLD) = 107 mm
  - Week 8 SLD = 82 mm (24% reduction)
  - Week 16 SLD = 60 mm (44% reduction, PR)
  - Week 19 SLD = 54 mm (50% reduction, confirmed PR)
- Remains on study through Week 48

B. Case 2
- 71-year-old with initial diagnosis of TNBC in March 2006 and advanced disease diagnosed in June 2011
- 2 prior therapies for advanced disease
- 2 target lesions and 2 non-target lesions with confirmed PR at Week 16
  - Baseline SLD = 50 mm
  - Week 8 SLD = 22 mm (56% reduction)
  - Week 16 SLD = 0 mm (100% reduction)
- Remains on study through Week 32 with continued CR in target lesions

Traina et al, SABC 2014
Immunotherapy for TNBC

TNBC have high PD-L1

Early but encouraging results

Pembrolizumab (SABCS 2014)
- PD1 inhibitor. Blocks ability of tumor to deactivate immune system
- Small Phase 1 trial
- Responses in ~20% of women with PD-L1+ TNBC
- Well tolerated

MPDL3280A (AACR 2015)
- PD-1 inhibitor
- Small Phase 1 trial
- Responses in ~20% of patients
- Well tolerated
How to Find a Clinical Trial
Clinical Trial Resources

Advanced Search

Locations:

- **State 1:** Optional
- **Country 1:** Optional
- **State 2:** Optional
- **Country 2:** Optional
- **State 3:** Optional
- **Country 3:** Optional

Location Terms:

Additional Criteria:

- **Gender:** All Studies
  - Child (birth-17)
  - Adult (18-65)
  - Senior (66+)
- **Age Group:**
  - Phase 3
  - Phase 1
  - Phase 2
  - Phase 0
  - Phase 4
Clinical Trial Resource cont’d

Return: Triple Negative Breast Cancer Foundation

Clinical Trial Matching Service

Call us toll free: 1-877-769-4827

Se habla Español

TNBCF Clinical Trials Matching Service

We want you to be aware of all treatment options for triple negative breast cancer. The Triple Negative Breast Cancer Foundation is working with EmergingMed to offer you a way to take action - a free, confidential, personalized service that helps you understand which breast cancer clinical trials may be an option for you. Clinical trials are research studies that test how well new medical approaches work in people with early stage or advanced cancers. They can have an important place in your care as doctors strive to improve current breast cancer treatments and search for new and better ones.

How does the service work? We help you quickly search for clinical trials that match your specific diagnosis and treatment history. We recommend that you search for clinical trial options before you begin your first treatment and again at any time you are faced with a new treatment decision. The service is free and completely confidential.

We encourage you to call 877-769-4827 to find clinical trials that match your situation and to learn more about cancer research by creating your personal profile with a clinical trials navigator. You may also complete a profile online. Our clinical trial navigators are available Monday through Friday from 8:30am to 6:30pm ET.