Triple-Negative Breast Cancer: Recent Updates and Ongoing Research

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Living Beyond Breast Cancer Webinar
November 1, 2018
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 more common in young women and in those with a BRCA1 germline mutation
• There are different types of TNBC
TNBC Subtypes

Before 2011 to 2011:
- 587 TNBC tumors
- TNBCtype: M, LAR, MSL, BL1, BL2, IM

2011 to 2016:
- 767 TNBC tumors
- TNBCtype-4: M, BL1, BL2, LAR

4 TNBC Subtypes, plus immune descriptor
TNBC Subtypes

- Luminal/Androgen receptor (LAR)
  Androgen-receptor signaling and PIK3CA mutations
- Mesenchymal (M)
  Trans-differentiation features and growth factor signaling (FGFR, PDGFR, NOTCH, TGFβ)
- Basal-like 1 (BL1)
  Elevated expression of cell cycle and DNA damage response genes
- Basal-like 2 (BL2)
  Enriched in select growth factors (MET & EGFR) and myoepithelial cell features

N=767

Lehmann, Chen, Shyr, Pietenpol; PLoS One, June, 2016
Other Methods of Classification

• Germline testing
  – To look for mutations in BRCA1/2

• Next generation sequencing (NGS)
  – To look for mutations in tumor DNA

• Expression of proteins
  – To look for expression of nuclear hormone receptors or cell surface receptors
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
Systemic Treatment for Metastatic Breast Cancer

Evaluation for systemic treatment

HR Positive → Hormone Therapy

HER-2+ → Biologic Therapy

HR+ and HER2+ → Biologic Therapy + Hormone Therapy

Triple-negative → Chemotherapy
Targeted Therapies
Showing Promise for Advanced TNBC

• Drugs that target DNA repair
  – PARP inhibitors (approved in BRCA1/2 mutation carriers)

• Drugs that target the immune system
  – Immune checkpoint inhibitors (PD-1/PD-L1 inhibitors)

• Drugs that target other receptors
  – Androgen receptor
  – Antibody drug conjugates (gpNMB, Trop2, LIV1A)

• Drugs that target pathways that lead to chemo resistance
  – AKT/PI3K/mTOR inhibitors
PARP Inhibitors

- Talazoparib
- Niraparib
- Rucaparib
- Olaparib
- Veliparib
OlympiAD study design

- HER2-negative metastatic BC
  - ER+ and/or PR+ or TNBC
- Deleterious or suspected deleterious gBRCAm
- Prior anthracycline and taxane
- ≤2 prior chemotherapy lines in metastatic setting
- HR+ disease progressed on ≥1 endocrine therapy, or not suitable
- If prior platinum use
  - No evidence of progression during treatment in the advanced setting
  - ≥12 months since (neo)adjuvant treatment

2:1 randomization

Primary endpoint:
- Progression-free survival (RECIST 1.1, BICR)

Secondary endpoints:
- Time to second progression or death
- Overall survival
- Objective response rate
- Safety and tolerability
- Global HRQoL (EORTC-QLQ-C30)

Olaparib 500 mg tablets bd

Chemotherapy treatment of physician’s choice (TPC)
- Capecitabine
- Erlotinib
- Vinorelbine

BICR, blinded independent central review; ER, estrogen receptor; HRQoL, health-related quality of life; PR, progesterone receptor; RECIST, response evaluation criteria in solid tumors; TNBC, triple-negative breast cancer
Primary endpoint: progression-free survival by BICR

Progression/deaths, n (%)
Olaparib 300 mg bd: 163 (79.5)
Chemotherapy TPC: 71 (73.2)

Median PFS, months
Olaparib 300 mg bd: 7.0
Chemotherapy TPC: 4.2

HR 0.58
95% CI 0.43 to 0.80; P=0.0009
EMBRACA Study Design

Primary endpoint
- Progression-free survival by RECIST by blinded central review

Key secondary efficacy endpoints
- Overall survival (OS)
- ORR by investigator
- Safety

Exploratory endpoints
- Duration of response (DOR) for objective responders
- Quality of life (QoL; EORTC QLQ-C30, QLQ-BR23)

Patients with locally advanced or metastatic HER2-negative breast cancer and a germline BRCA1 or BRCA2 mutation

Stratification factors:
- Number of prior chemo regimens (0 or ≥ 1)
- TNBC or hormone receptor positive (HR+)
- History of CNS mets or no CNS mets

Physician's choice of therapy (PCT): capecitabine, eribulin, gemcitabine, or vinorelbine

Phase 3, international, open-label study randomized
431 patients in 16 countries and 145 sites

Talazoparib 1 mg PO daily
Primary Endpoint: PFS

<table>
<thead>
<tr>
<th> </th>
<th>TALA (n = 287)</th>
<th>Overall PCT (n = 144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, no. (%)</td>
<td>186 (65%)</td>
<td>83 (58%)</td>
</tr>
<tr>
<td>Median, mo (95% CI)</td>
<td>8.6 (7.2, 9.3)</td>
<td>5.6 (4.2, 6.7)</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.54</td>
<td>95% CI, 0.41, 0.71</td>
</tr>
<tr>
<td>P</td>
<td>&lt; .0001</td>
<td></td>
</tr>
</tbody>
</table>

**Graph:**
- **TALA**
- **Overall PCT**

**Table:**

<table>
<thead>
<tr>
<th>Duration of PFS, mo</th>
<th>No. at risk (events/cumulative events)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>287 (0/0)</td>
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<tr>
<td>1</td>
<td>229 (50/50)</td>
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<tr>
<td>2</td>
<td>148 (53/103)</td>
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<tr>
<td>3</td>
<td>91 (34/137)</td>
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<td>4</td>
<td>55 (17/154)</td>
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<tr>
<td>5</td>
<td>42 (9/163)</td>
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<td>6</td>
<td>29 (9/172)</td>
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<tr>
<td>7</td>
<td>23 (2/174)</td>
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<tr>
<td>8</td>
<td>16 (5/179)</td>
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<tr>
<td>9</td>
<td>12 (4/183)</td>
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<tr>
<td>10</td>
<td>5 (2/185)</td>
</tr>
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<td>11</td>
<td>3 (0/185)</td>
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<td>13</td>
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<td>14</td>
<td>0 (0/186)</td>
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<tr>
<td>15</td>
<td>144 (0/0)</td>
</tr>
<tr>
<td>16</td>
<td>68 (41/41)</td>
</tr>
<tr>
<td>17</td>
<td>34 (20/61)</td>
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<tr>
<td>18</td>
<td>22 (8/69)</td>
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<tr>
<td>19</td>
<td>9 (7/76)</td>
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<tr>
<td>20</td>
<td>8 (0/76)</td>
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<tr>
<td>21</td>
<td>4 (3/79)</td>
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<td>22</td>
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<td>23</td>
<td>2 (0/81)</td>
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<tr>
<td>27</td>
<td>0 (0/83)</td>
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<tr>
<td>28</td>
<td>0 (0/83)</td>
</tr>
</tbody>
</table>
KEYNOTE-086: Phase 2 Study of Pembrolizumab Monotherapy For mTNBC

**Cohort A**
- ≥1 prior systemic treatment for mTNBC with documented PD
- PD-L1 positive or negative

**Cohort B**
- No prior systemic treatment for mTNBC
- PD-L1 positive

**All Patients**
- Centrally confirmed TNBC
- ECOG PS 0-1
- LDH <2.5 x ULN
- Tumor biopsy sample
- No radiographic evidence of CNS metastases

Pembrolizumab 200 mg IV Q3W for 2 years or until PD, intolerable toxicity, patient withdrawal, or investigator decision

Protocol-specified follow-up

- Primary end points: ORR and safety
- Secondary end points: DOR, DCR, PFS, OS

Adams et al. ASCO 2017; Loi et al. ESMO 2017
KEYNOTE-086: Antitumor Activity

Cohort A (N = 170)\(^1\):
Previously Treated mTNBC,
Regardless of PD-L1 Expression

Cohort B (N = 52)\(^2\):
Previously Untreated mTNBC, 
PD-L1 Positive

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>PD-L1 Positive</th>
<th>PD-L1 Negative</th>
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</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>4.7%</td>
<td>4.8%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Partial response</td>
<td>23.1%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Adams S et al. Presented at ASCO 2017; Jun 2-6, 2017; Chicago, IL, USA; abstr 1008.
2. Adams S et al. Presented at ASCO 2017; Jun 2-6, 2017; Chicago, IL, USA; abstr 1088.
**IMpassion130 study design**

**Key IMpassion130 eligibility criteria**:  
- Metastatic or inoperable locally advanced TNBC  
  - Histologically documented
- No prior therapy for advanced TNBC  
  - Prior chemo in the curative setting, including taxanes, allowed if TFI ≥ 12 mo  
- ECOG PS 0-1

**Stratification factors**:  
- Prior taxane use (yes vs no)  
- Liver metastases (yes vs no)  
- PD-L1 status on IC (positive [≥ 1%] vs negative [< 1%])

**Atezo + nab-P arm:**  
- Atezolizumab 840 mg IV  
  - On days 1 and 15 of 28-day cycle  
- *nab*-paclitaxel 100 mg/m² IV  
  - On days 1, 8 and 15 of 28-day cycle

**Plac + nab-P arm:**  
- Placebo IV  
  - On days 1 and 15 of 28-day cycle  
- *nab*-paclitaxel 100 mg/m² IV  
  - On days 1, 8 and 15 of 28-day cycle

**Double blind; no crossover permitted**

**RECIST v1.1**

**PD or toxicity**

- Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations  
  - Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated
Primary PFS analysis: ITT population

Stratified HR = 0.80
(95% CI: 0.69, 0.92)
$P = 0.0025$

<table>
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<th>Atezo (N = 451)</th>
<th>Plac (N = 451)</th>
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<tbody>
<tr>
<td>PFS events, n</td>
<td>358</td>
<td>378</td>
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<tr>
<td>1-year PFS</td>
<td>24% (20, 28)</td>
<td>18% (14, 21)</td>
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<tr>
<td>(95% CI), %</td>
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No. at risk:

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<td>226</td>
<td>183</td>
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<td>9</td>
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<td></td>
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</table>
Primary PFS analysis: PD-L1+ population

Stratified HR = 0.62
(95% CI: 0.49, 0.78)

PFS events, n

Atezo (n = 185) Plac (n = 184)

PFS events, n 138 157

1-year PFS (95% CI), % 29% (22, 36) 16% (11, 22)

No. at risk:

<table>
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<tr>
<th></th>
<th>Atezo</th>
<th>Plac</th>
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</thead>
<tbody>
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</table>

Progression-free survival

5.0 mo (3.8, 5.6)
7.5 mo (6.7, 9.2)
Interim OS analysis: ITT population

**Stratified HR = 0.84**
*(95% CI: 0.69, 1.02)*

*P = 0.0840*

<table>
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<th></th>
<th>Atezo (N = 451)</th>
<th>Plac (N = 451)</th>
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<tr>
<td>OS events, n</td>
<td>181</td>
<td>208</td>
</tr>
<tr>
<td>2-year OS</td>
<td>42% (34, 50)</td>
<td>40% (33, 46)</td>
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**Overall survival**

<table>
<thead>
<tr>
<th>Months</th>
<th>Overall survival</th>
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<tbody>
<tr>
<td>0</td>
<td>100</td>
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<tr>
<td>3</td>
<td>80</td>
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No. at risk:

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<tr>
<td>426</td>
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<td>146</td>
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<tr>
<td>3</td>
<td>NE</td>
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</table>
Interim OS analysis: PD-L1+ population

Stratified HR = 0.62 (95% CI: 0.45, 0.86)

<table>
<thead>
<tr>
<th></th>
<th>Atezo (n = 185)</th>
<th>Plac (n = 184)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS events, n</td>
<td>64</td>
<td>88</td>
</tr>
<tr>
<td>2-year OS</td>
<td>54% (42, 65)</td>
<td>37% (26, 47)</td>
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</table>

No. at risk:

<table>
<thead>
<tr>
<th></th>
<th>Atezo + nab-P</th>
<th>Plac + nab-P</th>
</tr>
</thead>
<tbody>
<tr>
<td>185 177 160 142 113 61 36 22 15</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>184 170 147 129 89 44 27 19 13</td>
<td>6</td>
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</tr>
</tbody>
</table>
Immunotherapy Drug Combinations

• Hormone Receptor Positive Breast Cancer
  – CDK4/6 inhibitors

• HER2 Positive Breast Cancer
  – HER2 directed therapy

• Triple-Negative Breast Cancer
  – PARP Inhibitors
  – Chemotherapy
  – Radiation therapy
  – Immunotherapy combinations
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 has being tested in women with AR+ TNBC

Traina et al, ASCO 2015
**MDV3100-11: Study Schema**

**AR Testing**
- Optional consent for AR testing
- IHC results reported as:
  - “Positive” (AR > 0%)
  - “Negative” (AR = 0%)

**Screening**
- AR “positive” TNBC*
- ECOG-PS ≤ 1
- Sufficient tissue to enable biomarker discovery
- No CNS metastases
- Any number of prior therapies permissible
- Evaluable bone-only disease allowed

**Endpoints**
- **Primary**
  - CBR16

  **Secondary**
  - CBR24
  - Response rate
  - PFS
  - OS
  - Safety

- **Exploratory**
  - AR biomarker discovery

**Treatment**
- Enzalutamide 160 mg/day

**Stage 1**
- “Go” to Stage 2
- ≥ 3 of 26 Evaluable have CBR16

**Stage 2**
- Rejection of H₀
- ≥ 9 of 62 Evaluable have CBR16

Treat to progression

**Definitions**
- Evaluable = AR IHC ≥ 10% and ≥ 1 post-baseline tumor assessment
- ITT = any AR “positive” by central assessment and received ≥ 1 dose of drug

**Statistical considerations**
- 85% power to detect true CBR16 = 8% tested against 1-sided alternative (CBR16 ≥ 20%); alpha = 5%

**Traina et al, ASCO 2015**
### Clinical Benefit in Evaluable and ITT Populations

<table>
<thead>
<tr>
<th></th>
<th>Evaluable (n = 75)</th>
<th>ITT (n = 118)</th>
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<tbody>
<tr>
<td><strong>CBR16, n (%)</strong></td>
<td>26 (35%)</td>
<td>29 (25%)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(24, 46)</td>
<td>(17, 33)</td>
</tr>
<tr>
<td><strong>CBR24, n (%)</strong></td>
<td>22 (29%)</td>
<td>24 (20%)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(20, 41)</td>
<td>(14, 29)</td>
</tr>
<tr>
<td><strong>CR or PR, n</strong></td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

Evaluable = AR IHC ≥ 10% and ≥ 1 post-baseline tumor assessment; ITT = any AR “positive” by central assessment and received ≥ 1 dose of drug.

Traina et al, ASCO 2015
Antibody Drug Conjugates

1. Monoclonal antibody specific for a tumor antigen with little/no expression on normal cells

2. Linker that is stable in circulation but releases the cytotoxic agent in target cells

3. Potent cytotoxic agent designed to induce target cell death when internalized and released
IMMU-132

- **Target:** Trop2 (EGP-1)
  - Pan-epithelial cancer antigen
  - Related to but distinct from EpCAM (EGP-2) – less expression on normal tissues.
  - Oncogene which signaling leading to increased tumorigenicity, aggressiveness, and metastasis.
  - Prognostic marker in several cancer types

- **Linker:** pH sensitive linker (CL2A)
- **Cytotoxic:** SN-38 (Irinotecan active metabolite)
Efficacy and Safety of Anti-Trop-2 Antibody Drug Conjugate Sacituzumab Govitecan (IMMU-132) in Heavily Pretreated Patients With Metastatic Triple-Negative Breast Cancer


Table 3. Treatment Efficacy in Intention-to-Treat Data Set (N = 69)

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Best Overall Response, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>2 (3)</td>
</tr>
<tr>
<td>PR</td>
<td>19 (28)</td>
</tr>
<tr>
<td>SD</td>
<td>31 (45)</td>
</tr>
<tr>
<td>PD</td>
<td>17 (25)</td>
</tr>
<tr>
<td>Confirmed objective response (CR + PR)</td>
<td>21 (30)</td>
</tr>
<tr>
<td>95% CI</td>
<td>20 to 43</td>
</tr>
<tr>
<td>Clinical benefit (CR + PR + SD ≥ 6 months)</td>
<td>32 (46)</td>
</tr>
<tr>
<td>95% CI</td>
<td>34 to 59</td>
</tr>
<tr>
<td>Median duration of objective response, months (95% CI)</td>
<td>8.9 (6.1 to 11.3)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>6.0 (5.0 to 7.3)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>16.6 (11.1 to 20.6)</td>
</tr>
</tbody>
</table>

J Clin Oncol 35:2141-2148.
Select trials of Antibody-Drug Conjugates in Metastatic TNBC

<table>
<thead>
<tr>
<th>Name</th>
<th>Phase</th>
<th>Arms</th>
<th>Clinicaltrials.gov</th>
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<tbody>
<tr>
<td>IMMU-132</td>
<td>III</td>
<td>Sacituzumab govitecan Capecitabine, eribulin, gemcitabine, vinorelbine</td>
<td>NCT02574455</td>
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<tr>
<td>CDX-011</td>
<td>II</td>
<td>Glembatumumab Capecitabine</td>
<td>NCT01997333</td>
</tr>
<tr>
<td>LIV1A</td>
<td>I/II</td>
<td>SGN-LIV1A</td>
<td>NCT01969643</td>
</tr>
</tbody>
</table>
PI3K/AKT Pathway and Breast Cancer

• PI3K/AKT signaling pathway plays a crucial role in carcinogenesis, promoting cell survival and growth\(^1,2\)
• Activated in 15-20% of TNBC\(^3\)
• Ipatasertib is an oral, ATP-competitive inhibitor of all three isoforms of Akt
• LOTUS trial
  — evaluate efficacy and safety of paclitaxel +/- ipatasertib in advanced TNBC

---

The LOTUS Trial

Co-primary endpoints:
• PFS in the ITT population
• PFS in the PTEN-low subgroup (IHC 0 in ≥50% tumour cells)

Dent et al. ASCO 2017
PFS in PIK3CA/AKT1/PTEN-altered Tumors

Dent et al. ASCO 2017
I-SPY 2 TRIAL Schema: HER2- Signatures

Adaptive Randomization

Paclitaxel

Paclitaxel + Pembro

Other HER2- Arms

12 weeks

Doxorubicin
60 mg/m2

Cyclophosphamide
600 mg/m2
X 4

8-12 weeks

SURGERY

Control
Paclitaxel 80 mg/m2 every wk x 12

Experimental
Paclitaxel 80 mg/m2 every wk x 12
Pembro 200 mg every 3 wks x 4

Nanda et al, ASCO 2017
Pembrolizumab graduated in all HER2- signatures:
Both HR+/HER2- and TN

<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</td>
<td>0.16</td>
<td>&gt; 99%</td>
</tr>
<tr>
<td></td>
<td>(0.34 – 0.58)</td>
<td>(0.06 – 0.27)</td>
<td></td>
</tr>
<tr>
<td>TNBC</td>
<td>0.60</td>
<td>0.20</td>
<td>&gt;99%</td>
</tr>
<tr>
<td></td>
<td>(0.43 – 0.78)</td>
<td>(0.06 – 0.33)</td>
<td></td>
</tr>
<tr>
<td>HR+/HER2-</td>
<td>0.34</td>
<td>0.13</td>
<td>&gt;99%</td>
</tr>
<tr>
<td></td>
<td>(0.19 – 0.48)</td>
<td>(0.03 – 0.24)</td>
<td></td>
</tr>
</tbody>
</table>
Select ongoing phase II and III adjuvant/neoadjuvant trials in HER2 negative early stage breast cancer

<table>
<thead>
<tr>
<th>Name</th>
<th>Phase</th>
<th>Arms</th>
<th>Clinicaltrials.gov</th>
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</thead>
<tbody>
<tr>
<td>S1418</td>
<td>III</td>
<td>observation pembro x 1 year</td>
<td>NCT02954874</td>
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<tr>
<td>ISPY2</td>
<td>II</td>
<td>paclitaxel —→ AC paclitaxel + pembro → pembro</td>
<td>NCT01042379</td>
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<tr>
<td>KEYNOTE 522</td>
<td>III</td>
<td>carboplatin/taxol→AC carboplatin/taxol + pembro → AC + pembro</td>
<td>NCT03036488</td>
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<tr>
<td>IMpassion031</td>
<td>III</td>
<td>nab-paclitaxel→AC nab-paclitaxel + atezo → AC + atezo</td>
<td>NCT02425891</td>
</tr>
</tbody>
</table>
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
How can I find out about clinical trials in my area?

• Treating oncologist
• ClinicalTrials.gov
• Triple-negative breast cancer foundation
  www.tnbcfoundation.org
Future Promise

• Much research is ongoing for mets TNBC
  – Understand mechanisms of resistance to standard treatments
  – Develop more personalized therapy

• New therapies are being developed and tested in clinical trials specifically for patients with MBC

• Hope for the future
  – More effective therapies
  – Fewer side effects