Breakthroughs in Breast Cancer Treatment

Living Beyond Cancer (LBBC)
Webinar January 16, 2018

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Department of Breast Medical Oncology
The University of Texas MD Anderson Cancer Center
Key Recent Advances In Breast Cancer

- Improvements in breast imaging (not necessarily screening, but in staging cancer)
- Minimizing surgery (particularly less lymph node surgery)
- Better decision-making for adjuvant medical (systemic) therapy using gene profiling
- Using neoadjuvant (pre-operative) therapy to accelerate drug discovery
- Immunotherapy!!
- Improved hormonal-biotherapy for advanced breast cancer
- Newer HER2-targeted drugs
- PARP Inhibition for BRCA mutation-related breast cancer
- Integrative therapies and improvements in quality of life
Gene Expression Array Profiling

Next Generation Sequencing
Supervised Classification on Prognostic Signatures on 78 Tumors

van't Veer LJ et al. Nature 2002

- Expression Data Matrix of 70 Prognostic Genes
- Differentiating Between Recurrent and Non-Recurrent Cases

(a) Sporadic breast tumours
patients <55 years
tumour size <5 cm
lymph node negative (LN0)

(b) Correlation to average good prognosis profile

(c) Prognosis reporter genes
Distant metastases <5 years
No distant metastases >5 years
21-Gene Recurrence Score
NSABP B-20 Tam +/- CMF: Absolute % Increase in DRFS at 10 Years

RS
Low
RS < 18
n = 353 (54%)

Int
RS 18-30
n = 134 (21%)

High
RS > 30
n = 164 (25%)

% Increase in DRFS at 10 Yrs (mean ± SE)

Paik S, et al, JCO 2006
Outcome Based on pCR: Impact of Receptor Subsets

**Luminal A**
HR+, low grade

**Basal**
ER/PR/HER2-Neg

**HER2+**

**I-SPY 2 TRIAL:**
Learn, Drop, Graduate, and Replace Agents Over Time

**Patient is on Study**

**Randomize**

- **HER 2 (++)**
  - Paclitaxel + Trastuzumab
  - Paclitaxel + Trastuzumab* + New Agent A
  - Paclitaxel + Trastuzumab* + New Agent B
  - Paclitaxel + Trastuzumab* + New Agent C

- **HER 2 (--)**
  - Paclitaxel
  - Paclitaxel + New Agent E
  - Paclitaxel + New Agent F
  - Paclitaxel + New Agent GH

**Surgery**

**Learn and adapt from each patient as we go along**

**Key**
- **MRI**
- **Residual Disease (Pathology)**

**AC**
MK-2206 I-SPY 2 Efficacy Results

**All**
- Control: 21% (n=57)
- MK2206: 37% (n=87)
- Prob(>Ctl) = 0.99
- Prob(Ph3) = 0.76

**HR+**
- Control: 16%
- MK2206: 24%
- Prob(>Ctl) = 0.87
- Prob(Ph3) = 0.49

**HR- (Signature 2)**
- Control: 26%
- MK2206: 50%
- Prob(>Ctl) = 0.99
- Prob(Ph3) = 0.88

**HER2+ (Signature 3)**
- Control: 29%
- MK2206: 53%
- Prob(>Ctl) = 0.97
- Prob(Ph3) = 0.83

**HR+/HER2+**
- Control: 22%
- MK2206: 38%
- Prob(>Ctl) = 0.89
- Prob(Ph3) = 0.68

**HR-/HER2+ (Signature 1)**
- Control: 36%
- MK2206: 67%
- Prob(>Ctl) = 0.98
- Prob(Ph3) = 0.91

Tripathy D, et al. ASCO 2015 Abstr 524
Antitumour immunity enhanced by inhibiting PD-L1/PD-L1 and identifying mutant neoantigens.
Immunogenic Cancers
General Approaches for Cancer Immunotherapy

Active immunotherapy
- Peptide vaccine
- DC vaccine
- Genetic vaccine
- IL-2
- IFN
- IL-15
- IL-21

Adoptive cell transfer immunotherapy
- T cell cloning
- TCR or CAR genetic engineering

Checkpoint Inhibition
- CD40
- CD137
- OX40
- CTLA-4
- PD-1

Co-stimulation
Tumor Infiltrating Lymphocytes (TILs) and Outcome

All Patients

BIG 02-98 Trial

Loi S, et al. JCO 2013

ECOG 2197 and 1199 – TNBC Cases

Adams S, et al. JCO 2015
Novel Cancer Immunotherapies in Clinical Trials

Diagram showing various receptors and pathways involved in cancer immunotherapies, including T-cell activation and interactions with dendritic cells and antigen-presenting cells.
Pembrolizumab (Anti-PD1) Keynote-012 Phase Ib Study for Triple Negative Breast Cancer

All patients had ≥ 1% PD-L1 expression on stroma or tumor cells

Overall Response Rate 18.5%

Pembrolizumab (Anti-PD1) Keynote-012 Phase Ib Some Responses are Durable on Longer Term Follow-up

Nanda R et al. SABCS 2016
## Anti-PD-L1 Antibody Avelumab – Phase Ib Cohort Expansion

<table>
<thead>
<tr>
<th>Best overall response</th>
<th>Overall population (n=168)</th>
<th>Patients with TNBC (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR, n (%)</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>7 (4.2)</td>
<td>5 (8.6)</td>
</tr>
<tr>
<td>SD, n (%)</td>
<td>39 (23.2)</td>
<td>13 (22.4)</td>
</tr>
<tr>
<td>PD, n (%)</td>
<td>106 (63.1)</td>
<td>38 (65.5)</td>
</tr>
<tr>
<td>Non-evaluable, n (%)</td>
<td>15 (8.9)</td>
<td>2 (3.4)</td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>4.8 (2.1, 9.2)</td>
<td>8.6 (2.9, 19.0)</td>
</tr>
<tr>
<td>DCR, %</td>
<td>28.0</td>
<td>31.0</td>
</tr>
</tbody>
</table>

### Subtype

<table>
<thead>
<tr>
<th>Subtype</th>
<th>n/N1* (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNBC</td>
<td>5/58 (8.6)</td>
<td>2.9, 19.0</td>
</tr>
<tr>
<td>HER2−/ER+ or PR+</td>
<td>2/72 (2.8)</td>
<td>0.3, 9.7</td>
</tr>
<tr>
<td>HER2+</td>
<td>1/26 (3.8)</td>
<td>0.1, 19.6</td>
</tr>
</tbody>
</table>

SWOG S1418/NRG BR006 Trial Schema

- TNBC
- > 1cm residual cancer or any + LN after 3rd generation neoadjuvant chemotherapy
- N = 1000

Randomization (R 1:1)

Pembrolizumab 200mg IV q3wk x 1 year

Projected HR 0.65

Observation

Up to 10 year f/u

Primary outcome measures
- DFS in overall and PD-L1+ populations (co-primary)

Secondary outcome measures
- OS, distant DFS, toxicities, Patient-related outcomes
- Correlative studies

Post operative chemotherapy (up to 24 weeks) allowed

PI: Lajos Pusztai
NCT02954874
Activated 11/15/2016
CDK 4/6 Inhibition Works in an Rb-Dependent Fashion and is Most Effective in ER+/Luminal Breast Cancer Cells

Dickson MA Clin Cancer Res 2014
CDK 4/6 Inhibition Doubles Progression-Free Survival

**PFS (BIRC)**

<table>
<thead>
<tr>
<th></th>
<th>Ribociclib + tamoxifen/NSAI</th>
<th>Placebo + tamoxifen/NSAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events, n (%)</td>
<td>40 (30.1)</td>
<td>72 (53.7)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>NR (19.9–NR)</td>
<td>11.1 (7.4–16.9)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.427 (0.288–0.633)</td>
<td></td>
</tr>
</tbody>
</table>

Tripathy D et al San Antonio Breast Cancer Symposium 2017
Trastuzumab, Pertuzumab, Lapatinib, T-DM1:

Trastuzumab:
- Inhibits ligand-independent HER2 signaling
- Prevents HER2 ECD shedding
- Activates ADCC

Pertuzumab:
- Inhibits ligand-dependent HER2 dimerization and signaling
- Activates ADCC
- Prevents HER2 ECD shedding

Lapatinib:
- Inhibits intracellular kinase domain of HER2, HER1 (EGFR)
- Activates ADCC
- Inhibits ligand-dependent HER2 dimerization and signaling

T-DM1:
- Immunoconjugate with emtansine
- Few molecules kill cell
- Internalizes and dissociates
- Few molecules kill cell

Complementary Mechanisms
HER2+ Metastatic Breast Cancer:
Serial Improvements in Survival with Newer Agents and Combinations
BUT.... No Cures

Verma S, et al.
Oncologist
2013

CLEOPATRA
Swain et al. 2013

EGF30008
Johnston et al. 2009

TAnDEM
Kaufman et al. 2009

EGF104535
Guan et al. 2013

Slamon et al. 2001

EMILIA
Verma et al. 2012

GBG26/BIG3-05
von Minckwitz et al. 2011

EGF100151
Cameron et al. 2010

EGF104900
Blackwell et al. 2012

Median OS (months) 0 10 20 30 40 50

First-Line

Second-Line Plus

Third-Line Plus

Pert+Tras+Doc\textsuperscript{a} \( p = .0008 \)

Tras+Doc

Lap+Let \( p = .113\textsuperscript{b} \)

Let

Tras+Ana \( p = .325 \)

Ana

Lap+Pac \( p = .0124 \)

Pac

Trast+CT \( p = .046 \)

CT

T-DM1 \( p = .0006 \)

Lap+Cap

Tras+Cap \( p = .73 \)

Cap

Lap+Cap \( p = .206 \)

Cap

Tras+Lap \( p = .026 \)

Lap

Verma S, et al.
Oncologist
2013
PARP Inhibitors - active in DNA repair-deficient cells (eg. BRCA mutant)

EMBRACA Trial Compare Talazoparib to Standard Chemotherapy

Primary Endpoint: PFS by Blinded Central Review

<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, 95% CI, 0.41, 0.71</td>
<td>P &lt; .0001</td>
</tr>
</tbody>
</table>

1-Year PFS 37% vs 20%  Median follow-up time: 11.2 months

Clinical Practice Guidelines on the Evidence-Based Use of Integrative Therapies During and After Breast Cancer Treatment

Heather Greenlee, ND, PhD, MPH\textsuperscript{1,2}; Melissa J. DuPont-Reyes, MPH, MPhil\textsuperscript{3}; Lynda G. Balneaves, RN, PhD\textsuperscript{4}; Linda E. Carlson, PhD\textsuperscript{5}; Misha R. Cohen, OMD, LAc\textsuperscript{6,7}; Gary Deng, MD, PhD\textsuperscript{8}; Jillian A. Johnson, PhD\textsuperscript{9}; Matthew Mumber, MD\textsuperscript{10}; Dugald Seely, ND, MSc\textsuperscript{11,12}; Suzanna M. Zick, ND, MPH\textsuperscript{13,14}; Lindsay M. Boyce, MLIS\textsuperscript{15}; Debu Tripathy, MD\textsuperscript{16}

Modified US Prevention Services Task Force (USPSTF) Grades

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
<th>Suggestions for Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Recommends the modality. There is high certainty that the net benefit is substantial.</td>
<td>Offer/provide this modality.</td>
</tr>
<tr>
<td>B</td>
<td>Recommends the modality. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.</td>
<td>Offer/provide this modality.</td>
</tr>
<tr>
<td>C</td>
<td>Recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.</td>
<td>Offer/provide this modality for selected patients depending on individual circumstances.</td>
</tr>
<tr>
<td>D</td>
<td>Recommends against the service. There is moderate or high certainty that the modality has no net benefit.</td>
<td>Discourage the use of this modality.</td>
</tr>
<tr>
<td>H</td>
<td>Recommends against the service. There is moderate or high certainty that the harms outweigh the benefits.</td>
<td>Discourage the use of this modality.</td>
</tr>
<tr>
<td>I</td>
<td>Concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.</td>
<td>If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.</td>
</tr>
<tr>
<td>CLINICAL OUTCOMES</td>
<td>RECOMMENDED THERAPY</td>
<td>STRENGTH OF EVIDENCE GRADE</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Acute radiation skin reaction</td>
<td>Aloe vera and hyaluronic acid cream should not be recommended for improving acute radiation skin reaction.</td>
<td>D</td>
</tr>
<tr>
<td>Anxiety/stress reduction</td>
<td>Meditation is recommended for reducing anxiety.</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Music therapy is recommended for reducing anxiety.</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Stress management is recommended for reducing anxiety during treatment, but longer group programs are likely better than self-administered home programs or shorter programs.</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Yoga is recommended for reducing anxiety.</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Acupuncture, massage, and relaxation can be considered for reducing anxiety.</td>
<td>C</td>
</tr>
<tr>
<td>Chemotherapy-induced nausea and vomiting</td>
<td>Acupressure can be considered as an addition to antiemetics drugs to control nausea and vomiting during chemotherapy.</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Electroacupuncture can be considered as an addition to antiemetics drugs to control vomiting during chemotherapy.</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Ginger and relaxation can be considered as additions to antiemetic drugs to control nausea and vomiting during chemotherapy.</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Glutamine should not be recommended for improving nausea and vomiting during chemotherapy.</td>
<td>D</td>
</tr>
<tr>
<td>Depression/mood disturbance</td>
<td>Meditation, particularly MBSR, is recommended for treating mood disturbance and depressive symptoms.</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Relaxation is recommended for improving mood disturbance and depressive symptoms.</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Yoga is recommended for improving mood and depressive symptoms.</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Massage is recommended for improving mood disturbance.</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Music therapy is recommended for improving mood.</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Acupuncture, healing touch, and stress management can be considered for improving mood disturbance and depressive symptoms.</td>
<td>C</td>
</tr>
<tr>
<td>CLINICAL OUTCOMES</td>
<td>RECOMMENDED THERAPY</td>
<td>STRENGTH OF EVIDENCE GRADE</td>
</tr>
<tr>
<td>--------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Hypnosis and ginseng can be considered for improving fatigue during treatment.</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Acupuncture and yoga can be considered for improving post-treatment fatigue.</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Acetyl-L-carnitine and guarana should not be recommended for improving fatigue during treatment.</td>
<td>D</td>
</tr>
<tr>
<td>Lymphedema</td>
<td>Low-level laser therapy, manual lymphatic drainage, and compression bandaging can be considered for improving lymphedema.</td>
<td>C</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>Acetyl-L-carnitine is not recommended for the prevention of chemotherapy-induced peripheral neuropathy in patients with BC due to potential harm.</td>
<td>H</td>
</tr>
<tr>
<td>Pain</td>
<td>Acupuncture, healing touch, hypnosis, and music therapy can be considered for the management of pain.</td>
<td>C</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Meditation is recommended for improving quality of life.</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Yoga is recommended for improving quality of life.</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Acupuncture, mistletoe, qigong, reflexology, and stress management can be considered for improving quality of life.</td>
<td>C</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>Gentle yoga can be considered for improving sleep.</td>
<td>C</td>
</tr>
<tr>
<td>Vasomotor/ hot flashes</td>
<td>Acupuncture can be considered for improving hot flashes.</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Soy is not recommended for hot flashes in patients with BC due to lack of effect.</td>
<td>D</td>
</tr>
</tbody>
</table>

Greenlee H, et al. CA Cancer J Clin 2017
THANK YOU