Impact of Breast Cancer Molecular Subtypes on Clinical Decision-Making

Krembil Knowledge Gaps in Parkinson’s Disease Symposium

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Disclosures

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• Advisory Boards (Uncompensated)
  – Bristol-Myers Squibb, Genentech/Roche, Pfizer, Sanofi
Overview

- To discuss how breast cancer treatment has been advanced through biology-driven clinical trials driven by understanding role of

  - Estrogen Receptor
  - HER2 Receptor
  - Intrinsic Molecular Subtypes
  - Rare Driver Genomic Alterations
Breast Cancer in 2019

23,000 new diagnoses/year (1 in 8)
5,300 deaths/ year (1 in 28)

≈ 1.5 million women diagnosed
≈ 500,000 breast cancer deaths
EARLY DISEASE

Stage 1
Node negative

Stage 2
Node positive

Stage 3

Stage 4

ADVANCED DISEASE

Adjuvant therapy

≈ 30%

≈ 50%

≈ 70%

INCURABLE
Types of Systemic Therapy

Chemotherapy

Endocrine therapy

Trastuzumab (Herceptin®)

Dividing Cells
Cells with ER expression
Cells with HER2/neu expression

Breast Cancer Population

100% 70% 20%
Hormonal Therapy for Advanced Breast Cancer Milestones

- 1896: Oophorectomy and Response to Advanced Disease (George Beatson)
- 1951: Estrogen Drives Breast Cancer
- 1977: Estrogen Receptor Identified, Tamoxifen Approved
- 1990's: First Selective Aromatase Inhibitor (AI) Approved for Metastatic Breast Cancer
- 1999: Immuno-histochemistry Developed for ER and PR Analysis
- 2002: ER Downregulator Approved, AI Approved as Adjuvant Therapy
- 2010: HER2-based Plus AI Approved
- 2012: mTOR Inhibitor Plus AI Approved
- 2015: CDK 4/6 Inhibitor Plus AI Approved
Benefit of Tamoxifen for Five Years According to Hormone Receptor Status

ER+/PgR+  ER-/PgR-

Mechanisms of Endocrine Therapy

GnRH agonists

Gonadotrophins (FSH + LH)

Pituitary gland

ACTH

Adrenal glands

Androgens

Ovary

Tamoxifen

SERDs

Estrogens

Aromatase Inhibitors

Peripheral conversion (aromatase enzyme)

ACTH = adrenocorticotropic hormone;
FSH = follicle-stimulating hormone;
LH = luteinising hormone;
LHRH = LH-releasing hormone
Duration of Endocrine Therapy

**Duration of Endocrine Therapy**

**Annual recurrence rate (%)**

**Years**

- ATAC
- BIG 1-98
- ABCSG 8, TEAM
- IES, ITA, ARNO

**Randomisation**

- Node+
- Node−

**AI = aromatase inhibitor.**

Abstract 582; Untch and Jackisch. *Onkologie.* 2007;30:55.
Estrogen Receptor (ER) is a Target for Endocrine Resistance

- Loss of ER protein expression
  - Detected in 5-10% metastatic biopsies

- Somatic mutation of ESR1 in ligand-binding domain
  - Detected in 35-40% (circulating tumor DNA)
  - Frequently polyclonal
  - May be sensitive to novel ER targeted drugs (oral SERDS)

- Gene fusion of ESR1
  - Occur in 1-2%, aggressive clinical course
HER2 and Breast Cancer

- Overexpressed in 15-20% breast cancer
- Associated with 2-fold increased risk of recurrence
Cloning of HER-2 (Semba et al., Coussens et al.)

Anti-HER-2 MoAb inhibits neu-transformed cells (Drebin et al.)

Humanization of an anti HER-2 MoAb = Herceptin® (Carter et al.)

Identification of the HER-2 neu oncogene (Schechter et al.)

Correlation of HER-2/neu amplification and prognosis (Slamon et al.)

Phase II trial as monotherapy in MBC (Baselga et al.)

Phase II trial in MBC, in combination with chemo (Pegram et al.)

Pivotal phase III trial in metastatic HER2+ breast cancer

Herceptin®-enhanced chemosensitivity: impressive synergy in pre-clinical models (Pietras et al.)

Reporting of Adjuvant Herceptin® Trials

Trastuzumab reduces the risk of recurrence by 40-50%.

<table>
<thead>
<tr>
<th>Study</th>
<th>DFS benefit</th>
<th>Median follow-up, years</th>
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<tbody>
<tr>
<td>HERA CTx→H 1 year</td>
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<td>B-31 / N9831 AC→PH</td>
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<td>BCIRG 006 AC→DH</td>
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<td>BCIRG 006 DCarboH</td>
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**HR**

0  Favours Trastuzumab  1  Favours no Trastuzumab  2

*Based on small subgroups of patients with HER2-positive breast cancer; \(^b\)relapse-free survival; V, vinorelbine CEF, cyclophosphamide, epirubicin, 5-fluorouracil

Joensuu et al 2006; Slamon et al 2006
Perez et al 2007; Smith et al 2007
Spielmann et al 2007
Trastuzumab and Pertuzumab induce more potent HER2 blockade

Trastuzumab binds to subdomain IV and inhibits downstream signalling

Pertuzumab binds to a specific domain II and inhibits ligand-activated dimerization

HER2

Cell membrane

HER1-4
Pertuzumab Improves Metastatic Breast Cancer Survival

Overall Survival

Hazard ratio, 0.68 (95% CI, 0.56–0.84)
P<0.001

No. at Risk
- Pertuzumab: 402, 371, 318, 268, 226, 104, 28, 1, 0
- Control: 406, 350, 289, 230, 179, 91, 23, 0

Swain S et al NEJM 2015
Novel Treatment Paradigm: Response Adapted Therapy

No Residual Cancer (pCR) → De-Escalate

Chemo HER2 therapy

Residual Cancer (non pCR) → Novel HER2-targeted treatment
Trastuzumab-DM1 Mechanism of Action

DM1 is a highly potent antimicrotubule agent

T-DM1 undergoes receptor-mediated internalization

Free DM1 is released within the cell
T-DM1 reduces recurrence risk for patients with residual disease

Unstratified hazard ratio for disease recurrence or death, 0.50 (95% CI, 0.39–0.64)

P<0.001
Adjuvant Chemotherapy: Benefits versus Risks

Decreases risk of recurrence by 25-45%

Short-term side effects
- Hair Loss
- Nausea/Vomiting
- Febrile Neutropenia
- Inability to work

Long-term risks
- Secondary leukemia
- Cardiomyopathy
- Early menopause
- Cognitive impairment
“Intrinsic” Molecular Subtypes

- Basal-like
- HER2 +
- Luminal B
- Luminal A

PROLIFERATION

- LOW
  - Good Prognosis
  - Endocrine Sensitive

- HIGH
  - Poor Prognosis
  - Chemosensitive

Adapted from Sotiriou and Pusztai *NEJM* 2009; 360: 790-800
TAILORx Methods: Treatment Assignment & Randomization
Accrued Between April 2006 - October 2010

Preregister – Oncotype DX RS (N=11,232)

Register (N=10,273)

ARM A: Low RS 0-10 (N=1629 evaluable)
ASSIGN
Endocrine Therapy (ET)

Mid-Range RS 11-25 (N=6711 evaluable)
RANDOMIZE
Stratification Factors: Menopausal Status, Planned Chemotherapy, Planned Radiation, and RS 11-15, 16-20, 21-25

ARM B: Experimental Arm (N=3399)
ET Alone

ARM D: High RS 26-100 (N=1389 evaluable)
ASSIGN
ET + Chemo

ARM C: Standard Arm (N=3312)
ET + Chemo

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TAILORx Results - ITT Population: All Arms (A,B,C & D)

9-Year Event Rates

IDFS Decreases as RS Increases
P<0.001

- **Arm A**: ET alone (RS 0-10)
  - 3% Distant recurrence rate
- **Arms B & C**: Randomized (RS 11-25)
  - 5% Distant recurrence rate overall
- **Arm D**: Chemoendocrine (RS 26-100)
  - 13% Distant recurrence rate despite chemotherapy + endocrine therapy

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**TAILORx Results - ITT Population: All Arms (A,B,C & D)**

9-Year Event Rates

- **Arm A**: RS 0-10: Assigned to ET Alone
- **Arm B**: RS 11-25: Randomized to ET Alone
- **Arm C**: RS 11-25: Randomized to CHEMO + ET
- **Arm D**: RS 26-100: Assigned to CHEMO + ET

**IDFS Probability**

- **Arm A**: ET alone (RS 0-10)
- **Arm B**: RS 11-25: Randomized to ET Alone
- **Arm C**: RS 11-25: Randomized to CHEMO + ET
- **Arm D**: RS 26-100: Assigned to CHEMO + ET

**Months**

- 0
- 12
- 24
- 36
- 48
- 60
- 72
- 84
- 96
- 108

**DFS Probability**

- 1.0
- 0.8
- 0.6
- 0.4
- 0.2
- 0.0

**IDFS Decreases as RS Increases**
P<0.001

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Next-Generation Clinical Trials

- Small, focussed trials in rare genomic subpopulations
- Broad molecular screening
- Novel trial designs
  - Umbrella
  - Basket
  - “Seamless” Phase I/II
- Randomized trials may not be feasible
What has been learned in Breast Cancer?

- Advances driven by biology-based trials
  - Largely abandoned “one size fits all” approach
  - Drugging “driver” alterations that define disease subtype
  - Standardization of molecular testing
- Future treatment strategies will incorporate response-adapted therapy & account for rare molecular alterations