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« Modern Management of Breast Cancer »

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Director, Division of Clinical Research,
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Founder and Past Chairman, Breast Cancer International Research Group (BCIRG)
Breast Cancer

• Worldwide:
  – 1,390,000 new cases/year
  – > 450,000 deaths/year

• Early disease: Curable
  – Cure rates
    • Stable from 1930 until 1990
    • Improvement in the 1990’s
      (Screening, Adjuvant therapy)
    • Ageing population in Europe: Absolute No of deaths still rising (2004: 130,000 / 2006: 132,000)

• Metastatic disease: Non Curable
  • Concept of chronic disease
Recent reduction of mortality (ages: 35-69 years)
United Kingdom and USA 1950 - 2004

Source: WHO mortality & UN population estimates

SABCS 2007 – according to Peto R et al., Key note lecture 1.
Breast Cancer Screening

Self-Examination

Examination by Physician

Mammography/Ultrasound
Screening

- Main reason for improved survival, proportional to increased incidence
- Survival benefit around 30%
- Recognised method: mammography + clinical examination
- Organized screening: 1 mammography/2 years from 50 to 74 years
- Problems: dense breasts, women <50 ans
- Extension to all territory difficult
Les diverses étapes d’un programme de dépistage des cancers du sein

Population cible

Invitation à participer

Participants
Non-participants

Assurance de qualité

Test mammographique
Communication des résultats

Résultats normaux
Invitation dans deux ans

Résultats anormaux
Examens diagnostiques

Cancer
Bénin

Traitement
Breast Cancer Therapies

- Local:
  - Surgery
  - Radiation Therapy
- Systemic:
  - Chemotherapy
  - Hormone therapy
  - Biologic modifiers
Breast Cancer Therapies

- Surgery
- Hormonotherapy
- Radiation therapy
- Chemotherapy
- Biologics


Rayter & Mansi. Medical Therapy of Breast Cancer 2003
Rationale for Breast Cancer Therapy

From Prognostic to predictive Approaches
Classical Prognostic Factors

TNM Classification

- Tumor (T)
- Nodes (N)
- Metastasis (M)

Age

Histo Type

Histo Grade

Hormonal Receptors

“First Generation” Factors
First Generation Factors

- Used in Consensus Conferences for therapeutic decisions.
- **Tumor size** with threshold of 1 cm (NCI) or 2 cm (St Gallen) for adjuvant chemotherapy decision
- Number of **positive nodes** [0 ; 1-3 ; 4-9 et ≥ 10]
- **Age**, histologic type, **histoprognostic grade** (American college of pathologists)
- **Hormonal receptors**
• **Grade SBR**

• Prognostic index based upon
  – Glandular differentiation
  – Cellular abnormalities
  – Mitosis

• Used for therapeutic decision (chemotherapy / hormonetherapy)
ER+ MBC: Anti-endocrine or cytotoxic therapy? Hints for hormone sensitivity

- **HR-status (ER+PR+, ER+,PR-, ER-,PR+)**

<table>
<thead>
<tr>
<th>Receptor status</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER + PR +</td>
<td>n = 963 (55.3%)</td>
</tr>
<tr>
<td>ER + PR -</td>
<td>n = 272 (15.6%)</td>
</tr>
<tr>
<td>ER - PR +</td>
<td>n = 60 (3.4%)</td>
</tr>
<tr>
<td>ER - PR -</td>
<td>n = 448 (25.7%)</td>
</tr>
</tbody>
</table>

Rakha ED J Clin Oncol 25 (2007)
Recurrence hazard rate

Long-Term Risk of Breast Cancer Recurrence Remains High in ER/PR+ Patients

PgR = progesterone receptor.
<table>
<thead>
<tr>
<th></th>
<th>Hormono</th>
<th>Chimio</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 ans</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+</td>
<td>25%</td>
<td>25%</td>
<td>45%</td>
</tr>
<tr>
<td>ER-</td>
<td>0%</td>
<td>35%</td>
<td>---</td>
</tr>
<tr>
<td>&gt; 50 ans</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+</td>
<td>25%</td>
<td>10%</td>
<td>35%</td>
</tr>
<tr>
<td>ER-</td>
<td>0%</td>
<td>20%</td>
<td>---</td>
</tr>
</tbody>
</table>
First Generation Factors

• Frequent problems
  – High risk patients with long survival
  – Low risk patients relapsing quickly…

Need for new prognostic factors => Better knowledge of tumor biology
Breast Cancer Subtypes

Cancers du sein
ER/PR+

HER-2 +++

"Basal-like" (Array)
- "Triple negative"
- ER/PR-

BRCA1
p53mut
Breast Cancer is an Heterogeneous Group of Diseases

Luminal A = ER+, HER2-, KI67 low (<15%)
Luminal B = ER+, HER2-, KI67 high (>15%)
HER2+ = ER- and HER2+ (IHC 3+ or FISH+)
Basal-like = ER-, HER2-, CK5/6+ and/or HER1+
Unclassified = negative for all 4 markers
### Intrinsic Classification of Breast Cancer: ER + Tumors

<table>
<thead>
<tr>
<th>Luminal A</th>
<th>Luminal B</th>
</tr>
</thead>
<tbody>
<tr>
<td>60% Breast Cancers</td>
<td>20% Breast Cancers</td>
</tr>
<tr>
<td>High expression ER</td>
<td>Lower expression ER</td>
</tr>
<tr>
<td>High expression of genes</td>
<td>Lower expression of genes</td>
</tr>
<tr>
<td>regulated by ER (Gata-3, FOX</td>
<td>regulated by ER (Gata-3, FOX</td>
</tr>
<tr>
<td>A1...)</td>
<td>A1...)</td>
</tr>
<tr>
<td>Low proliferation</td>
<td>High proliferation</td>
</tr>
<tr>
<td>Mutated P53: 13%</td>
<td>Mutated P53: 66%</td>
</tr>
</tbody>
</table>
Ki67 Index, HER2 Status, and Prognosis of Patients With Luminal B Breast Cancer

Maggie C. U. Cheang, Stephen K. Chia, David Voduc, Dongxia Gao, Samuel Leung, Jacqueline Snider, Mark Watson, Sherri Davies, Philip S. Bernard, Joel S. Parker, Charles M. Perou, Matthew J. Ellis, Torsten O. Nielsen

Ki67 predicts Luminal B

Clinical Outcome

HER2+/ER- Tumors
1. 15-25% of tumors
2. prognostic/predictive
3. two types (ER -/+)

HER2

GRB7

17q11-12 amplification

Basal

Luminal

Proliferation

AR
General Algorithm to test HER2

FISH / CISH

HER2/Cent 17
1,8→2,2
Check more cells with FISH or retest with IHC

Equivocal HER2 status

Réf. : HERA, BCIRG, NSABP B31, FIN HER
ER+ MBC: Anti-endocrine or cytotoxic therapy? Hints for hormone sensitivity

- HER2 status

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<table>
<thead>
<tr>
<th>ERBB2 status (endocrine treatment)</th>
<th>N</th>
<th>Events</th>
<th>4-year DFS, % (±SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative (letrozole)</td>
<td>1648</td>
<td>178</td>
<td>90 (1)</td>
</tr>
<tr>
<td>Negative (tamoxifen)</td>
<td>1646</td>
<td>240</td>
<td>86 (1)</td>
</tr>
<tr>
<td>Positive (letrozole)</td>
<td>134</td>
<td>27</td>
<td>79 (4)</td>
</tr>
<tr>
<td>Positive (tamoxifen)</td>
<td>105</td>
<td>32</td>
<td>70 (5)</td>
</tr>
</tbody>
</table>

Number at risk
- ERBB2 negative: 3294, 3235, 3120, 2424, 1472, 899
- ERBB2 positive: 239, 228, 208, 151, 98, 58

Rasmussen Lancet Oncol 2008; 9: 23–28
TNBC clinical characteristics

- Young age
- More prevalent in:
  - African-American (>30%)
  - Hispanic (>30%)
  - North African women (>30%)
- >75% of BRCA1 carriers
- Relapse:
  - High risk of relapse
  - Early (<2 years)
  - Atypical (lung 40% and brain 30%)

Foulkes WD et al, New England J Med 2010
The Picture of Basal-like Breast Cancer

- Low ER (and related genes) expression
- Low HER2 cluster expression → usually “triple negative”
- High basal cluster
  - basal cytokeratins
  - EGFR
  - c-kit
  - others...
- Very proliferative
- Often p53 mutant
- Evidence of genomic instability
Heterogeneity of “triple negative” B.C.

Triple-negative and basal show a 65% pCR rate to neoadj. CTX

Basal, non triple-negative

Basal, non triple – have a 50% pCR to neoadj. CTX

Triple-negative non-basal

Show a 20% pCR to neoadj. CTX

« Claudin-low »

- Low-expression of cell-cell junction proteins
- Sometimes metaplastic features
- Stem cell features
- Does it exist?

C. Perou, SABCS 2009
Most cancers in BRCA1 mutation carriers are basal-like.

Most basal-like breast cancers are not in BRCA1 carriers.

Association between BRCA1 mutations and basal-like cancers

Intrinsic gene list applied to Van’t Veer dataset (Nature 2002)

BRCA1 mutation carriers

Sorlie T et al. PNAS 03
Clinical implications

• Luminal A breast cancer could be treated by hormonal treatment only?

• Luminal B breast cancer could benefit from adjuvant chemotherapy?
Clinical implications

• Poor prognosis of HER2+
• Traztuzumab treatment ++++
• HER2+, ER+: choice of hormonal treatment is important (ER deprivation, castration, LH-RH analogs, anti aromatase)
Clinical implications

• Triple negative BC
  – Heterogeneity ++++
  – Chemotherapy only…
Predictive Factors

HER2+++:
- RH+:
  - Trastuzumab
  - Chemotherapy
  - Hormonetherapy
- RH-:
  - Trastuzumab
  - Chemotherapy

HER2-:
- RH+:
  - Trastuzumab
- RH-:
  - Chemotherapy

Chimiothérapie

HER2+++

Hormonetherapy
Breast Cancer Therapies

- Surgery
- Hormonotherapy
- Radiation therapy
- Chemotherapy
- Biologics

- 3000 BC
- 1500’s
- 1800’s
- 1937
- 1950-1970
- 1997
Surgery

Towards less...
Surgery

• Halsted
• Mastectomy
• Conservative surgery
• Sentinel node biopsy…
Chirurgie axillaire et Récidives axillaires
**Avant l’ère du GS (Ganglion Sentinelle Node)**

<table>
<thead>
<tr>
<th>Étude (année)</th>
<th>Patientes</th>
<th>pT1 (%)</th>
<th>pN+ (si curage)</th>
<th>Suivi</th>
<th>Curage et récidive axil.</th>
<th>Pas de curage Récidive axil.</th>
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<tr>
<td>Guy I (1987)</td>
<td>232</td>
<td>17</td>
<td>24%</td>
<td>60-120</td>
<td>0,9%</td>
<td>18,8%</td>
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<tr>
<td>Guy II (1987)</td>
<td>258</td>
<td>38</td>
<td>-</td>
<td>60-120</td>
<td>1,4%</td>
<td>12,5%</td>
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<td>NSABP B04</td>
<td>727</td>
<td>39</td>
<td>39</td>
<td>120</td>
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- **En l’absence de toute chirurgie axillaire**
  - Le risque de récidive axillaire
    - Dépend de la taille de la tumeur
      - Si 40% de pT1: risque de 5 à 10 ans de **20%**
Avant l’ère du GS

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- **En cas de curage axillaire**
  - **Le risque de récidive axillaire**
    - Dépend de la taille de la tumeur
      - Si 40% de pT1: risque de 5 à 10 ans de **1,4%**
Avant l’ère du GS

• Pas de curage axillaire

– Essai AXIL 95
  • Schéma de l’étude (1995-2005):
    – Patientes >50 ans, carcinome infiltrant <10mm, N0
    – Groupe n°1:
      » 297 patientes: pas de curage
    – Groupe n°2:
      » 310 patientes: curage (pN+=14%)

• Résultats
  – Récidive axillaire
    » Groupe n°1: 2% (6 patientes)
    » Groupe n°2: 0% (0 patientes),

Avril A et al, EJSO 2010
A l’ère du GS

- GS et curage axillaire

- **Essai NSABP B32**
  - Schéma de l’étude:
    - Groupe n°1:
      » 2619 patientes: GS+curage
    - Groupe n°2:
      » 2697 patientes: GS +/- curage
  - Suivi moyen 95 mois

- **Résultats**
  - Récidive axillaire
    » Groupe n°1: 0,3% (8 patientes)
    » Groupe n°2: 0,5% (14 patientes), [p=0,22]

Krag D et al, Lancet Oncol 2010
A l’ère du GS

• GS pN- sans curage axillaire

### Résultats
- Récidive axillaire (suivi de 20 à 48 mois)
  - 0,1% à 1,2%

<table>
<thead>
<tr>
<th>Auteur (année)</th>
<th>Patientes</th>
<th>T1 (%) ou T médian</th>
<th>Suivi</th>
<th>Récidives axillaires</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veronesi (2009)</td>
<td>3548</td>
<td>84%</td>
<td>48 mois</td>
<td>0,9%</td>
</tr>
<tr>
<td>Bergvist (2008)</td>
<td>2246</td>
<td>14mm</td>
<td>37 mois</td>
<td>1,2%</td>
</tr>
<tr>
<td>Christiansen 2008</td>
<td>3717</td>
<td>71%</td>
<td>20 mois</td>
<td>0,5%</td>
</tr>
<tr>
<td>Naik (2004)</td>
<td>2340</td>
<td>89%</td>
<td>31 mois</td>
<td>0,1%</td>
</tr>
</tbody>
</table>
A l’ère du GS

- GS pN+ sans curage axillaire

- Cohortes
  - National cancer data base
    - 1981 patientes
      » GS micro-métastase: 530
      » GS macro-métastase: 1458

- Résultats
  - Suivi 64 mois

  - Taux de récidive axillaire
    » GS micro-métastase: 0,6%
    » GS macro-métastase: 1,2%

Bilimoria et al, JCO 2009
A l’ère du GS

• GS pN+ sans curage axillaire

– Essai Randomisé
  • American College of Surgeon Oncology Group Z0011
    – Patientes T1-T2, tumorectomie, GS pN+ (pré sélectionnées / Z0010)
      » GS seul: 445 (44% micro-métastase)
      » GS et curage: 446 (37% micro-métastase)

• Résultats
  – Suivi 6,3 ans
    – Taux de récidive axillaire
      » GS seul: 0,9%
      » GS et curage: 0,5%

Giuliano et al, Ann Surg 2010
Radiation Therapy

Critical for local control

May be more…
Chemotherapy

Towards less...?
### Development of Chemotherapy Breast Cancer

#### 1970s
- **Before anthracyclines**
  - CMF, CMFVP

#### 1980s
- **With anthracyclines**
  - Combinations: AC, FAC, AVCMF, FEC, CEF
  - Sequence and Alternating (Milan A & B)
  - Dose intensity, dose density, HDCT

#### 1990s
- **Taxanes (Paclitaxel/Docetaxel)**
  - Sequential: A $\Rightarrow$ T $\Rightarrow$ C or AC $\Rightarrow$ T
  - Combinations: TA, TAC

#### 2000s
- **Biologic Modifiers (Herceptin)**
  - Integration in chemotherapy strategies
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Reduction of Annual Odds, %</th>
<th>Absolute Improvement, %</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relapse</td>
<td>Death</td>
<td>Death</td>
</tr>
<tr>
<td>PolyCT vs. no CT (1995)</td>
<td>23.5</td>
<td>15</td>
<td>3.0%</td>
</tr>
<tr>
<td></td>
<td><em>(P &lt; .00001)</em></td>
<td><em>(P &lt; .00001)</em></td>
<td><em>(P &lt; .00001)</em></td>
</tr>
<tr>
<td>Anthracyclines vs. CMF (2000)</td>
<td>10.8</td>
<td>15.7</td>
<td>4.3%</td>
</tr>
<tr>
<td></td>
<td><em>(P &lt; .0005)</em></td>
<td><em>(P &lt; .00001)</em></td>
<td><em>(P &lt; .00001)</em></td>
</tr>
<tr>
<td>Agent</td>
<td>Année de publication</td>
<td>CR + PR (%)</td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
<td>----------------------</td>
<td>--------------</td>
<td></td>
</tr>
<tr>
<td>Taxotere (75-100mg/m²)</td>
<td>1993 - 95</td>
<td>48 - 68</td>
<td></td>
</tr>
<tr>
<td>Taxol (175 - 250 mg/m² : 3-24hr)</td>
<td>1991 - 95</td>
<td>29 - 63</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin (60-75mg/m²)</td>
<td>1974 - 94</td>
<td>43 - 54</td>
<td></td>
</tr>
<tr>
<td>Navelbine</td>
<td>1992 - 94</td>
<td>30 - 41</td>
<td></td>
</tr>
<tr>
<td>Capecitabine</td>
<td>1995 - 98</td>
<td>30-41</td>
<td></td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>1995-97</td>
<td>25-37</td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>1978 -88</td>
<td>9 - 50</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>1959 - 68</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>1961 - 81</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>1952 - 81</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>1976 - 85</td>
<td>32</td>
<td></td>
</tr>
</tbody>
</table>

## Adjuvant Chemotherapy

### Taxanes vs Anthracyclines

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Risk reduction %</th>
<th>Absolute Benefit, %</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relapse</td>
<td>Death</td>
<td>Death</td>
</tr>
<tr>
<td>Anthra vs.</td>
<td>18</td>
<td>15</td>
<td>3.0%</td>
</tr>
<tr>
<td>CT-Paclitaxel</td>
<td>($P &lt; .001$)</td>
<td>($P &lt; .01$)</td>
<td>($P &lt; .01$)</td>
</tr>
<tr>
<td>Anthra vs.</td>
<td>27</td>
<td>21</td>
<td>5.1%</td>
</tr>
<tr>
<td>CT-Docetaxel</td>
<td>($P &lt; .001$)</td>
<td>($P &lt; .005$)</td>
<td>($P &lt; .00001$)</td>
</tr>
</tbody>
</table>
Benefits of Adjuvant Chemotherapy

BC Mortality at 10 Years

Taxanes > anthra > CMF > No Chemotherapy

Mortalité par Cancer du Sein

Death rates (% / year: total – rate in women without recurrence) & logrank analyses

Peto et al, SABCS 2007
Hormonetherapy

Changes in dogmas...
# Efficacy of Endocrine Agents in Women With Advanced Breast Cancer

Response data from comprehensive reviews

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Response Rate (%)</th>
</tr>
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<tbody>
<tr>
<td>Ablative</td>
<td></td>
</tr>
<tr>
<td>Oophorectomy</td>
<td>33</td>
</tr>
<tr>
<td>Adrenalectomy</td>
<td>32</td>
</tr>
<tr>
<td>Hypophysectomy</td>
<td>36</td>
</tr>
<tr>
<td>Radiationtherapy</td>
<td>32</td>
</tr>
<tr>
<td>Inhibitive</td>
<td></td>
</tr>
<tr>
<td>Aminoglutethimide + HC</td>
<td>31</td>
</tr>
<tr>
<td>Additive</td>
<td></td>
</tr>
<tr>
<td>Estrogens</td>
<td>26</td>
</tr>
<tr>
<td>Progestins</td>
<td>29</td>
</tr>
<tr>
<td>Androgens</td>
<td>21</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>25</td>
</tr>
<tr>
<td>Competitive</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td></td>
<td>32</td>
</tr>
</tbody>
</table>

Tamoxifen was Gold Standard in Adjuvant Breast Cancer.
Aromatase Inhibitors

- **Nonselective**
  - Aminogluthethimide (competitive)

- **Selective: Discovery Late 80’s**
  - Competitive (nonsteroidal)
    - Anastrozole
    - Letrozole
    - Vorozole
    - Fadrozole
  - Noncompetitive (steroidal)
    - Exemestane
    - Formestane
# Efficacy of Endocrine Agents in Women With Advanced Breast Cancer

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<td>Adrenalectomy, Hypophysectomy</td>
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<tr>
<td>Radiation therapy</td>
<td>32</td>
</tr>
<tr>
<td><strong>Additive</strong></td>
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</tr>
<tr>
<td>Progestins</td>
<td>29</td>
</tr>
<tr>
<td>Androgens</td>
<td>21</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>25</td>
</tr>
<tr>
<td><strong>Competitive</strong></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>32</td>
</tr>
<tr>
<td><strong>Inhibitive</strong></td>
<td></td>
</tr>
<tr>
<td>Aminoglutethimide + HC</td>
<td>31</td>
</tr>
<tr>
<td>Al 3rd generation</td>
<td>40-45</td>
</tr>
</tbody>
</table>
Third Generation Aromatase Inhibitors

Adjuvant Breast Cancer
ADDITIONAL EFFECTS OF AROMATASE INHIBITORS IN EARLY BREAST CANCER

38% relapse rates without adjuvant Tt (EBCTCG)

50% risk decrease with tamoxifen

20% more with AIs
## Efficacy of Endocrine Agents in Women With Advanced Breast Cancer

Response data from comprehensive reviews

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Response Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ablative</strong></td>
<td></td>
</tr>
<tr>
<td>Oophorectomy</td>
<td>33</td>
</tr>
<tr>
<td>Adrenalectomy, Hypophysectomy</td>
<td>32</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>32</td>
</tr>
<tr>
<td><strong>Additive</strong></td>
<td></td>
</tr>
<tr>
<td>Estrogens</td>
<td>26</td>
</tr>
<tr>
<td>Progestins</td>
<td>29</td>
</tr>
<tr>
<td>Androgens</td>
<td>21</td>
</tr>
<tr>
<td>Glucocorticoids</td>
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<tr>
<td>Al 3rd generation</td>
<td>40-45</td>
</tr>
<tr>
<td><strong>ER down Regulators</strong></td>
<td></td>
</tr>
<tr>
<td>Fulvestrant</td>
<td>45-50</td>
</tr>
</tbody>
</table>
Antibody anti HER-2

Herceptin
Amplification of HER-2 Oncogène

Overexpression of Her-2 Oncoprotein

Decreased survival

**Median survival**

- HER-2 alterations: 3 years
- HER-2 normal: 6 - 7 years

Slamon et al, 1987
**Chimetherapy ± Herceptin: 1st line Therapy MBC Registration Trial (H0648g): Results**

<table>
<thead>
<tr>
<th></th>
<th>H + CT (n = 235)</th>
<th>CT (n = 234)</th>
<th>Valeur P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS Median, mo</td>
<td>7.4</td>
<td>4.6</td>
<td>.0001</td>
</tr>
<tr>
<td>Response rates, %</td>
<td>50</td>
<td>32</td>
<td>.0001</td>
</tr>
<tr>
<td>Duration of response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, mo</td>
<td>9.1</td>
<td>6.1</td>
<td>.0001</td>
</tr>
<tr>
<td>TTF Median, mo</td>
<td>6.6</td>
<td>4.5</td>
<td>.0001</td>
</tr>
</tbody>
</table>

Overall Survival

Probability Alive

Months

0.2
0.4
0.6
0.8
1.0

20.3 mo
25.1 mo

Herceptin + CT
CT

RR = .80
p = .046

65 % of CT group crossed over to Herceptin
FISH/Overall Survival H0648g

Chemotherapy +/- Herceptin, 1st Line

FISH+
- Herceptin + Chemo (n = 169)
- Chemo alone (n = 176)

Risk ratio = 0.70
p = 0.007
95% CI = 0.54, 0.91

FISH-
- Herceptin + Chemo (n = 50)
- Chemo alone (n = 56)

Risk ratio = 1.13
p = ns
95% CI = 0.72, 1.79
Adjuvant Trastuzumab Disease-Free Survival

**• B-31**
- N: 872
- Events: 171
- HR = 0.45, 2P = 1x10^-9
- 5-year survival: 87% for AC -> T, 74% for AC -> TH

**• N9831**
- N: 807
- Events: 90
- HR = 0.55, 2P = 0.0005
- 5-year survival: 87% for AC -> T, 78% for AC -> TH

**• HERA**
- N: 1694
- Events: 127
- HR = 0.54, p < 0.0001
- 5-year survival: 85.8% for Chimio, 77.4% for Chimio -> H

**ASCO 2005**
BCIRG 006
Breast Cancer Adjuvant HER-2 Positive by FISH

HER2 + FISH
N=3150

4 x AC
60/600 mg/m²

4 x Docétaxel
100 mg/m²

1 an Trastuzumab

Nabholtz JM, Slamon D et al
BCIRG 006: DFS

% patients

<table>
<thead>
<tr>
<th>Years</th>
<th>AC → TH</th>
<th>AC → T</th>
<th>TCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>93</td>
<td>92</td>
<td>87</td>
</tr>
<tr>
<td>1</td>
<td>87</td>
<td>86</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>83</td>
<td>82</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HR 0.61 [0.48;0.76] p<0.0001 Absolute Benefit 6%

HR 0.67 [0.54;0.83] p=0.0003 Absolute Benefit 7%

D. Slamon et al., SABCS 2007, abst. 13
BCIRG 006: DFS no Co-Amplification Gene Topo IIa
(2/3 of patient population)

% patients

AC → TH
AC → T
TCH

P<0.001
P<0.001

Years

D. Slamon et al., SABCS 2007, abst. 13
BCIRG 006: DFS Co-Amplified Gene Topo IIa

(1/3 of patient population)

% Disease Free

- Treatment
  - AC->T
  - AC->TH
  - TCH

Logrank P<0.01
Logrank P= 0.24

Months

0 6 12 18 24 30 36 42 48 54
Overall Survival According to HER status and Herceptin treatment

S.S. Dawood et al. ASCO 2008. Abstract 1018
“From humans to the lab, back to humans” instead of “from the lab to humans”

- Identification of abnormalities in humans: Prognostic value
- Confirmation of relevance in human cancers (Xenografts)
- Identification of a therapy targeting the anomalies
- Development of tests for targeting patient subpopulations: Confirmation of predictive value
- Pivotal clinical development (Phase II, III) in selected population of patients
Role of Neoadjuvant Strategies in Breast Cancer Therapeutics

Two generations so far
Neoadjuvant strategies
First generation (1990s)

Question: What is the role of Neoadjuvant (systemic treatment before surgery) versus Adjuvant strategies (systemic therapy after surgery)?
Neoadjuvant strategies
First generation

Answers:
1. Neoadjuvant similar to adjuvant (Survival)
2. Increase rates of conservative surgery
3. pCR correlated with survival
Neoadjuvant strategies
Second generation

The Quest for Pathologic Complete Response (pCR)
Single Agent Neoadjuvant Taxotere After 4 Cycles CVAP

First Phase

All Patients

4 cycles of CVAP

Second Phase

4 cycles of Taxotere

Final Assessment / Surgery

Randomize

No Response

Response

4 cycles of Taxotere

4 cycles of CVAP

### Objective Response after Eight Cycles of Chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>4CVAP (162)</th>
<th>No response → 4Docetaxel (N=55)</th>
<th>Randomized to 4 CVAP (N=52)</th>
<th>Randomized to 4Docetaxel (N=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cCR+cPR</td>
<td>56%</td>
<td>47%</td>
<td>64%</td>
<td>85%</td>
</tr>
<tr>
<td>Clinical complete response</td>
<td>14%</td>
<td>11%</td>
<td>33%</td>
<td>56%</td>
</tr>
<tr>
<td>PCR: In breast and Axilla.</td>
<td>2%</td>
<td>15%</td>
<td>31%</td>
<td></td>
</tr>
</tbody>
</table>

Breast conserving surgery: CVAP = 48% Docetaxel = 67% P=0.01
Higher Five yr DFS 90% vs 72% P=0.04

Neoadjuvant strategies
Second generation

Answers:

1. Neoadjuvant allows to select “in vivo sub-populations” of patients based upon their sensitivity to therapy...

2. Potential model for predictivity of efficacy or non efficacy of therapy.

3. Potential human model for biologic developments
Neoadjuvant strategies
Second generation

1. No information for optimization of adjuvant therapy, based upon biologic modifications induced by exposition to therapy in neoadjuvant setting (individualized therapy)

2. Limited biologic data from neoadjuvant trials...
Neoadjuvant strategies
Third Generation (2010s)

From Neoadjuvant to adaptive Adjuvant therapies
Neoadjuvant strategies
Third Generation (2010s)

“From humans to the lab, back to humans” instead of “from the lab to humans”

- Identification of abnormalities in biologically defined sub-populations: Prognostic value with confirmation of relevance in human cancers (Xenografts).
- Exposition to new therapies targeting the abnormalities.
- Development of tests for targeting patient sub-populations: Confirmation of potential predictive value.
- Study of mechanisms of resistance to therapy: predictive tests
- Prerequisite to pivotal clinical development (Phase II, III) in selected sub-populations.
  - Towards the concept of adaptative adjuvant strategies instead of “blind adjuvant approaches”
The future?

Already Present..

Biologic revolution
Targeting HER-2, Her-1 (EGFR), IGRF...
Multiple signaling pathways in breast cancer cells: Multiple targets
Lapatinib

1+1
2+2
1+2

Down stream signal

Erlotinib

Erbitux

Signal

Cell division/ tumor growth

1+1
2+2

Herceptine

lapatinib

gefitinib
Herceptin + Lapatinib vs Lapatinib (Etude EGF104900)

Phase III Randomized trial

ABC HER2-positive (FISH)

PFS

Lapatinib 1000 mg/j
+ maintien
Herceptin 2 mg/kg/sem
(n = 148)

Lapatinib 1500 mg/j
(n = 148)

Cross over if progression after 4 weeks (73 pts)

Primary Endpoint: PFS

O’Shaughnessy et al. ASCO 2008
**Herceptin + Lapatinib vs Lapatinib**

**Progression-free Survival**

- **Herceptin + Lapatinib**
- **Lapatinib**

**HR = 0.73 ; p = 0.008**

**Patients**

<table>
<thead>
<tr>
<th></th>
<th>L (148)</th>
<th>LH (148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>148</td>
<td>148</td>
</tr>
<tr>
<td>10</td>
<td>53</td>
<td>73</td>
</tr>
<tr>
<td>20</td>
<td>21</td>
<td>42</td>
</tr>
<tr>
<td>30</td>
<td>13</td>
<td>27</td>
</tr>
<tr>
<td>40</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>50</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

*O’Shaughnessy et al. ASCO 2008*
Herceptin and Pertuzumab target 2 distinct epitopes of the HER2 extracellular domain:

- Activate cellular antibody-dependent cytotoxicity
- Inhibit HER2 Clavage and formation of p95 fragments
- Inhibit HER2 signaling pathway

- Block receptor dimerazation
- Strong inhibition of HER2 signaling pathway
- Activate cellular antibody-dependent cytotoxicity

Hubbard 2005
Combination Herceptin + Pertuzumab: Breast cancer Xemografts

Friess et al. ESMO 2006

6 / 10 cured animals
**Herceptin + Pertuzumab after progression on herceptin (phase II)**

<table>
<thead>
<tr>
<th>Response</th>
<th>n (%)</th>
<th>n = 66</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>5 (7,6 %)</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>11 (16,7 %)</td>
<td></td>
</tr>
<tr>
<td>Global response</td>
<td>16 (24,2 %)</td>
<td></td>
</tr>
<tr>
<td>Stabilisation ((≥ 6) months)</td>
<td>17 (25,8 %)</td>
<td></td>
</tr>
<tr>
<td>((≥) cycle 8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical benefit</td>
<td>33 (50,0 %)</td>
<td></td>
</tr>
<tr>
<td>Progression</td>
<td>33 (50,0 %)</td>
<td></td>
</tr>
</tbody>
</table>

Gelmon et al. ASCO 2008
Primay endpoint : PFS
Secondary endpoints : OS, RR, toxicity quality of life.
International study
Highly potent cytotoxic agent

Monoclonal antibody: Trastuzumab

Systemically stable

Target expression: HER2

Cytotoxic agent: DM1

Highly potent cytotoxic agent

Linker: MCC

Systemically stable

T-DM1

Targeted Chemotherapy

Average drug: antibody ratio $\approx 3.5:1$
Targeting the Angiogenesis...

Bevacizumab (Avastin) = Anti-VEGF Antibody
Méta-analyse E2100, AVADO et Ribbon-1

Design des études

- E2100
  - Paclitaxel

- AVADO
  - Docetaxel

- RIBBON-1
  - Capécitabine, Taxane, ou Anthracycline

RANDOMISATION

- Chimio + non-BV
- Chimio + BV

Chimio + BV en 2ème ligne facultatifs (AVADO et RIBBON-1 uniquement)

Traitement jusqu'à progression

O'Shaughnessy J. et al. ASCO 2010
Méta-analyse E2100, AVADO et Ribbon-1
Survie sans progression, population poolée

<table>
<thead>
<tr>
<th>Patientes à risque (n)</th>
<th>Durée de survie sans progression (mois)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Bev (n = 1 008)</td>
<td>210 111 38 18 9 1 0 0</td>
</tr>
<tr>
<td>Bev (n = 1 439)</td>
<td>491 292 134 67 22 8 2 1</td>
</tr>
</tbody>
</table>

O'Shaughnessy J. et al. ASCO 2010
Triple negative BC
Inhibitors of PARP
Mechanisms of DNA Repair

DNA DAMAGE

MAJOR DNA REPAIR PATHWAYS

Replication Lesions
- Base excision repair
- PARP1

DNA Adducts/Base Damage
- Alkyltransferases
- Nucleotide excision repair
- Base excision repair
- PARP1

Cell Death
Phase II TNBC Study: Treatment Schema

Metastatic TNBC
N = 120

RANDOMIZE

21-Day Cycle

Gemcitabine (1000 mg/m², IV, d 1, 8)
Carboplatin (AUC 2, IV, d 1, 8)

BSI-201 (5.6 mg/kg, IV, d 1, 4, 8, 11)
Gemcitabine (1000 mg/m², IV, d 1, 8)
Carboplatin (AUC 2, IV, d 1, 8)

RESTAGING
Every 2 Cycles

* Patients randomized to gem/carbo alone could crossover to receive gem/carbo + BSI-201 at disease progression
Progression-Free Survival

BSI-201 + Gem/Carbo (n = 57)
Median PFS = 6.9 months

Gem/Carbo (n = 59)
Median PFS = 3.3 months

\( P < 0.0001 \)

HR = 0.342 (95% CI, 0.200-0.584)
Overall Survival

BSI-201 + Gem/CARBO (n = 57)
Median OS = 9.2 months

Gem/CARBO (n = 59)
Median OS = 5.7 months

P = 0.0005
HR = 0.348 (95% CI, 0.189-0.649)
BRCA1 and PARP Abnormalities Synergize to Kill Cells

“SYNTHETIC LETHALITY”
Cell death by dual targeting of pathways that in isolation are not lethal

HR = homologous recombination (BRCA1-dependent)
BER = base excision repair (PARP-dependent)

Chemo, X-rays, other insults → DNA damage

Normal cell
- BER
- HR → Viable

BRCA loss
- BER
- HR → Viable

PARP deficient
- BER
- HR → Viable

BRCA lost + PARP deficient
- BER
- HR → Dead
### PARP Inhibitors in Development

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Phase*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABT-888</td>
<td>Oral</td>
<td>II</td>
</tr>
<tr>
<td>AG-014699</td>
<td>IV</td>
<td>II</td>
</tr>
<tr>
<td>Olaparib (AZD2281)</td>
<td>Oral</td>
<td>II</td>
</tr>
<tr>
<td>Iniparib (BSI-201)</td>
<td>IV</td>
<td>III</td>
</tr>
<tr>
<td>INO-1001</td>
<td>IV</td>
<td>II</td>
</tr>
<tr>
<td>GPI 15427</td>
<td>Oral</td>
<td>I</td>
</tr>
<tr>
<td>MK4827</td>
<td>Oral</td>
<td>I/II</td>
</tr>
<tr>
<td>CEP-9722</td>
<td>Oral</td>
<td>II</td>
</tr>
</tbody>
</table>

*Highly heterogeneous regarding tumor types and combinations/single agents
Chemotherapyimiothérapies et Thérapies ciblées des HER2- and anti_PARP Triple negative BC…

O’Shaughnessy, ASCO 2011
Combination of Hormonotherapy with biologic modifiers
Estrogen Receptors

Genes involved in proliferation, inhibition of apoptosis, angiogenesis and invasion metastasis

Co-activators involved in the expression of different genes such as proliferation, metastasis (IGF-1, myc, cycline D1, Bcl-2, collagenase)

Cytoplasmic and membrane levels

"Cross-talks" with type 1 tyrosine kinase GPR30 et calveline receptors. Activation of ER-E2 complex with activation of membrane growth factor receptors such as IGF-1R, ErbB2/HER-2, and ErbB1/EGFR, with activation of ER at the nuclear level via Akt and MAPK ....
Resistence to hormonotherapy

- 40 à 50% of tumors will not express ER at time of progression on hormonotherapy

- Epigenetic « silencing » epigénetique of ER via methylation of CpG in the promoting region of ERα gene (DNA methylation inhibitors → reexpression de ER)

- Suppression of ER expression by activation of signal transduction pathways (EGFR – HER2) via MAPK which suppress the expression of ERα.

10 patients with advanced BC ER-/HER2+ treated with herceptine 2-6 mois → new expression of ER in 3 patients (Munzone 2006)

- hypersensibility to low levels of œstradiol
- « crosstalks » between signal transduction growth factors (EGFR, HER2, IGFR) and activation of ER-dependant transcription genes ER via phosphorylation of ER and/or its association to coactivators of transcription such as AIB1
Cross-talk and endocrine resistance

- Increased EGFR and HER2 signalling is associated with the development of resistance to endocrine agents.
- Targeting growth factor signalling pathways may delay the onset of endocrine-resistant disease.

EGFR, epidermal growth factor receptor
HER2, human EGFR 2 (also known as c-erbB-2 / neu)
Conclusions

- Significant improvement of breast cancer prognosis
  - Screening programs
  - Better and more adapted therapies with less toxicity

- Evolution towards individualized strategies based upon the tumor biology and the patient

- Future:
  - Less chemotherapy
  - Explosion of biology understanding and biologic therapies
    ....Concept of “Biologic cocktails”