PROGNOSTIC AND PREDICTIVE MARKERS FOR BREAST CANCER MANAGEMENT

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Villejuif, FRANCE

Cape Town, South Africa, 13-14 February 2020

ESMO preceptorship on breast cancer
OUTLINE

• Prognostic markers
  • Histopathological
  • Molecular
• Predictive markers
  • Early BC
  • Metastatic BC
• Conclusion and perspectives
HISTOPATHOLOGICAL PROGNOSTIC CRITERIA

- Histological type
- Histological grade
- Peritumoral lymphovascular invasion (20-30% BC)

- TILs (Tumor Infiltrating Lymphocytes)
- pTNM : Tumor size, Nodal status (AJCC 8th edition)
- Proliferation (mitotic activity, Ki67, molecular signature)
- ER/HER2 status (molecular subtype)
TUMOR INfiltrating lymphocytes

- RNA seq., TCGA n=1004, validated in independent cohort n=1954
- 4 immune phenotypes
  - ICR1: less immune activated
  - ICR4: Th1 immune signature, upregulation PDL1, FOXP3, CTLA4
- Heterogeneity according to molecular subtypes
- Th1 immune signature (ICR4) is associated with better survival
- Less clear in ER+/HER2- BC (poor prognosis in neoadjuvant setting) (Denkert C. Lancet oncol 2018)
- Predictive of pCR in neoadjuvant setting (Denkert C. JCO 2010, Denkert C. Lancet Oncol 2018)

Hendrickx W et al. Oncoimmunology 2017;6:e1253654
Stromal TILs

- Whole tumor area
- Assess (estimate) sTILs in % of stromal area occupied by mononuclear inflammatory cells
- Continuous variable (round up to the nearest 5%)

Surgical specimen
Biopsy
Stromal TILs

Review Article
Assessing Tumor-infiltrating Lymphocytes in Solid Tumors: A Practical Review for Pathologists and Proposal for a Standardized Method From the International Immunoooncology Biomarkers Working Group: Part 1: Assessing the Host Immune Response, TILs in Invasive Breast Carcinoma and Ductal Carcinoma In Situ, Metastatic Tumor Deposits and Areas for Further Research
Shona Hendry, MBBS, Trinidad Salgado, MD, Thomas Gruer, MD
Adv Anat Pathol 2017
PROGNOSTIC VALUE OF INTRINSIC SUBTYPES

ER neg

ER pos

C Perou & T Sorlie
ER+ HER2- TUMORS: LUMINAL A VS B??

Luminal ER+ HER2- BC is a spectrum!
PROLIFERATION: KI67 INDEX

- Expressed in G1, S, G2 and M
- Semi-quantitative assessed by IHC
- Prognostic factor
  \[ \text{Ki67}/ \text{MIB1} \leftrightarrow \text{size (+)} \]
  \[ \text{grade (+)} \]
  \[ \text{mitosis(+)} \]
  \[ \text{ER(-)} \]
- Predictive of response to CT in neoadjuvant setting
- Luminal A vs B, help to CT decision in ER+ BC
  (15-20% cut-off)
- …but lack of reproducibility, especially for intermediate values 10-30%

\[9\] Ki-67 scores should be interpreted in light of local laboratory values: as an example, if a laboratory has a median Ki-67 score in receptor-positive disease of 20%, values of 30% or above could be considered clearly high; those of 10% or less clearly low.

ESMO guidelines 2019
<table>
<thead>
<tr>
<th>70-gene signature</th>
<th>21-gene signature</th>
<th>PAM50 (prosigna)</th>
<th>Genomic grade</th>
<th>HOXB13:IL17BR 2-gene ratio</th>
<th>11-gene assay</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MammaPrint™</strong></td>
<td>Oncotype DX®</td>
<td>Prosigna (Prosigna)</td>
<td>MapQuant DX</td>
<td>BCI (Biotheranostics)</td>
<td>Endopredict®</td>
</tr>
<tr>
<td>Microarray</td>
<td>qRT-PCR</td>
<td>qRT-PCR</td>
<td>Microarray / qRT-PCR</td>
<td>RT-PCR</td>
<td>qRT-PCR</td>
</tr>
<tr>
<td>Centralized</td>
<td>Centralized</td>
<td>Local</td>
<td>Centralized</td>
<td>Local</td>
<td></td>
</tr>
<tr>
<td>-1 à +1</td>
<td>RS = 0 - 100</td>
<td>ROR = 0 - 100</td>
<td>0 - 10</td>
<td>0-15 (EP) 0-6(Epclin)</td>
<td></td>
</tr>
<tr>
<td><strong>High vs Low</strong></td>
<td><strong>High / Low / Intermediate</strong></td>
<td><strong>High / Low / Intermediate</strong></td>
<td><strong>High / Low</strong></td>
<td><strong>High / Low / Intermediate</strong></td>
<td><strong>High vs Low</strong></td>
</tr>
<tr>
<td>RSPC (→validation)</td>
<td>Molecular subtype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70 genes (growth, proliferation, angiogenesis, invasion, survival)</td>
<td><strong>ER, PR, BCL2, SCUBE2, Ki67, STK15, BIRC5, CCNB1, MYBL2, HER2, GRB7, MMP11, CTSL2, GSTM1, CD68, BAG1</strong></td>
<td>50 genes (prolif)</td>
<td>97 genes</td>
<td><strong>HOXB13, IL17BR, BUB1, CENPA, NEK2, RACGAP1, RRM2</strong></td>
<td></td>
</tr>
<tr>
<td>+ T</td>
<td>Simplified : <strong>MYBL2, KPNA2, CDC2, CDC20</strong></td>
<td>+ T with N</td>
<td></td>
<td>+ T and N</td>
<td></td>
</tr>
<tr>
<td>+ weight with N</td>
<td><strong>DHCR7, AZGP1, MGP, STC2, BIRC5, UBE2C, RBBP8, IL6ST</strong> (prolif, ER pathway)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cryo / FFPE</strong></td>
<td><strong>FFPE</strong></td>
<td><strong>FFPE</strong></td>
<td><strong>Cryo / FFPE</strong></td>
<td><strong>FFPE</strong></td>
<td><strong>FFPE</strong></td>
</tr>
<tr>
<td>→ M+ 5 and 10 yrs</td>
<td>→ M+ 10 yrs</td>
<td>→ M+ 10 yrs</td>
<td>→ M+ 10 yrs</td>
<td>→ M+ 5 and 10 yrs</td>
<td>→ M+ 10 yrs</td>
</tr>
<tr>
<td>ER+ / ER- HER2-/-+</td>
<td>ER+ with ET</td>
<td>ER+/HER2- with ET</td>
<td>ER+ with ET</td>
<td>ER+/HER2- with ET</td>
<td></td>
</tr>
<tr>
<td>pre/post-menop.</td>
<td>pre/post-menop.</td>
<td>post-menop.</td>
<td>ET adjuvant and CT neoadjuvant (high)</td>
<td>ET adj &gt; 5 yrs (high)</td>
<td></td>
</tr>
<tr>
<td>CT adjuvant (high)</td>
<td>CT adjuvant neoadjuvant (high)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**MINDACT** | **TAILORx** | **OPTIMA UK** | **ASTER 70s** | **RxPONDER** |
TNM AJCC STAGING

8th edition

- Applied in the US since January 1st 2018
- Includes 2 parts:
  - Anatomic TNM classification (similar to the one currently used, with some clarifications for pathologists)
  - Integrative prognostic classification = anatomic TNM + biology (ER, PR, HER2, grade and molecular prognostic signatures)
- Molecular signatures, LOE I or II (OncotypeDX®, mammaprint®, Breast Cancer Index®, EndoPredict®, PAM50®): these tests may be used in patients with ER+ HER2- N- (to avoid over-treatment)
- Tumor up to 5cm N0 M0, ER+ HER2-, with low molecular risk, whatever the histological grade, is in the same prognostic category as a pT1a/b N0 M0 (i.e. stage IA)
Gene expression profiles, such as MammaPrint (Agendia, Amsterdam, The Netherlands), Oncotype DX Recurrence Score (Genomic Health, Redwood City, CA), Prosigna (PAM 50; NanoString Technologies, Seattle, WA), Endopredict (Myriad Genetics Salt Lake City, UT) and Breast Cancer Index (Biotheranostics, Inc., San Diego, CA), may be used to gain additional prognostic and/or predictive information to complement pathology assessment and to predict the benefit of adjuvant ChT.

The choice of treatment strategy should be based on the tumour burden/location (size and location of primary tumour, number of lesions, extent of lymph node involvement) and biology (pathology, including biomarkers and gene expression), as well as the age, menopausal status, general health status and preferences of the patient [V, A].

**LoE**
- IA: MammaPrint, Oncotype DX
- IB: EndoPredict, PAM50

**Do NOT use genomic test if:**
- Clinico-pathological low risk (pT1a/b grade I strongly ER+ and pN0)
- Special subtype: encapsulated/solid papillary carcinoma, tubular
- 1-3N+ with other risk factors or ≥pN2
- Contraindications for CT (comorbidity)
ER+ HER2- N- (pN1mi included) Intermediate clinico-pathological risk

PREDICT: intermediate risk = absolute benefit at 10 yrs if +CT between 3 and 5%
Treatment Options

Hormone Therapy
- No
- Yes
Hormone (endocrine) therapy Available when ER-status is positive

Chemotherapy
- None
- 2nd gen
- 3rd gen

Trastuzumab (eg. Herceptin)
- No
- Yes
Available with chemotherapy when HER2 status is positive

Bisphosphonates
- No
- Yes
Available for post-menopausal women

Results

These results are for women who have already had surgery. This table shows the percentage of women who survive at least 5, 10, and 15 years after surgery, based on the information you have provided.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Additional Benefit</th>
<th>Overall Survival %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery only</td>
<td>-</td>
<td>82%</td>
</tr>
<tr>
<td>+ Hormone therapy</td>
<td>3.8% (2.2% – 4.7%)</td>
<td>86%</td>
</tr>
<tr>
<td>+ Chemotherapy</td>
<td>3% (2.2% – 3.7%)</td>
<td>89%</td>
</tr>
</tbody>
</table>

If death from breast cancer were excluded, 94% would survive at least 10 years, and 6% would die of other causes.
OUTLINE

• Prognostic markers
  • Histopathological
  • Molecular

• Predictive markers
  • Early BC
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• Conclusion and perspectives
PREDICTIVE BIOMARKERS
Systematically assessed for each invasive BC (early and metastatic)

ER/PGR

HR cut-off
• 10% in France
• 1-9% = 1.4% BC
• 1% ASCO

HER2

HER2 cut-off
• > 10%, ratio ≥2, HER2 ≥4
• ASCO 2018

Negative predictive value
HIGH 95%
(<5% chance to respond to anti-estrogens or trastuzumab)

Positive predictive value
30-50%
HORMONE RECEPTORS

• ER (Erα) and PR must be assessed by IHC for each invasive BC: 70-80% of BC are ER+
• Prognostic markers (molecular subtype) but also predictive of response to ET
• Cut-off for positivity: 1% (ASCO), 10% in a lot of European countries
  - ER 1-9% are rare (1.4% of BC in a French GEFPICS study in >14000 pts)
  - transcriptomic profile of these cases more similar to TNBC
  - limited data on ET benefit
  - ASCO 2020: should be reported as ER/PR low positive (check the IHC controls+++)

Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update

Kimberly H. Allison, MD1; M. Elizabeth H. Hammond, MD2; Mitchell Dowsett, PhD3; Shannon E. McKernan4; Lisa A. Carey, MD5; Patrick L. Fitzgibbons, MD6; Daniel F. Hayes, MD7; Sril R. Lakhani, MD8,9; Mariana Chavez-MacGregor, MSc2,10; Jane Perlmutter, PhD11; Charles M. Perou, PhD12; Meredith M. Regan, ScD13; David L. Rimm, MD, PhD13,14; W. Fraser Symmans, MD15; Emina E. Torlakovic, MD, PhD15,16; Letizia Varella, MD16, Giuseppe Viale, MD17,18, Tracey F. Weigberg, MD19; Lisa M. McShane, PhD20; and Antonio C. Wolff, MD21

Estrogen Receptor (ER) mRNA and ER-Related Gene Expression in Breast Cancers That Are 1% to 10% ER-Positive by Immunohistochemistry


JCO 2020
• HER2 overexpression in 10-15% of early BC (20-25% in metastatic setting)
• Prognostic marker and **predictive of response to HER2-targeted therapies**
• Cut-off for positivity:
  - IHC score 3+ (≥10% intense complete)
  - ISH HER2 amplified (HER2≥4 ± HER2/CEP17 ≥2)
• Score 2+ must be further assessed by ISH
• The report must clearly state the IHC score (new therapies for HER2<sub>low</sub>...)

Her2 testing (invasive component) by validated IHC assay

Batch controls and on-slide controls show appropriate staining

Circumferential membrane staining that is complete, intense, and in ≥10% of tumor cells

Weak to moderate complete membrane staining observed in ≥10% of tumor cells

Incomplete membrane staining that is faintly/barely perceptible and in ≥10% of tumor cells

No staining is observed or membrane staining that is incomplete and faintly/barely perceptible and in ≤10% of tumor cells

IHC 3+ positive

IHC 2+ equivocal

IHC 1+ negative

IHC 0 negative

Must order reflex test (same specimen using ISH) or order a new test (new specimen if available, using IHC or ISH)
Algorithm ISH (2 probes: HER2 and CEP17)

HER2 testing (invasive component) by validated dual-probe ISH assay

Batch controls and on-slide controls show appropriate hybridization

- **HER2/CEP17 ratio ≥ 2.0**
  - **Group 1**: Average HER2 copy number ≥ 4.0 signals/cell
    - ISH positive
  - **Group 2**: Average HER2 copy number < 4.0 signals/cell
    - Additional work-up required (see Fig 4)

- **HER2/CEP17 ratio < 2.0**
  - **Group 3**: Average HER2 copy number ≥ 6.0 signals/cell
    - Additional work-up required (see Fig 5)
  - **Group 4**: Average HER2 copy number ≥ 4.0 and < 6.0 signals/cell
    - Additional work-up required (see Fig 6)
  - **Group 5**: Average HER2 copy number < 4.0 signals/cell
    - ISH negative

Count additional cells (20 nuclei)

- **Negative**
- **Positive**
- **Negative**
<table>
<thead>
<tr>
<th>Initial Test Results</th>
<th>Laboratory</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HERA Central Laboratory</td>
<td>BCIRG Central Laboratory</td>
<td>USC Breast Cancer Analysis Laboratory</td>
<td>Mayo Clinic Cytogenetics Laboratory</td>
<td>UK NEOAS 2009-2016</td>
</tr>
<tr>
<td><strong>FISH distribution</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>6,018</td>
<td>10,468</td>
<td>7,526</td>
<td>2,851</td>
<td>11,116</td>
</tr>
<tr>
<td>Group 1 ratio ≥ 2.0; HER2 ≥ 4.0</td>
<td>55.0 (≥ 60.0, 48.7; ≥ 40.0, 6.3)</td>
<td>40.8</td>
<td>17.7</td>
<td>11.8</td>
<td>14.2</td>
</tr>
<tr>
<td>Group 2 ratio ≥ 2.0; HER2 &lt; 4.0</td>
<td>0.8</td>
<td>0.7</td>
<td>0.4</td>
<td>1.3</td>
<td>3.7</td>
</tr>
<tr>
<td>Group 3 ratio &lt; 2.0; HER2 ≥ 6.0</td>
<td>0.4</td>
<td>0.5</td>
<td>0.6</td>
<td>3.0</td>
<td>1.1</td>
</tr>
<tr>
<td>Group 4 ratio &lt; 2.0; HER2 ≥ 4.0</td>
<td>1.9</td>
<td>4.1</td>
<td>4.6</td>
<td>14.2 (7.5, 5.5, 1.3)</td>
<td>7.6</td>
</tr>
<tr>
<td>&lt; 6.0 (after alternative probe; pos, equivocal, neg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 5 ratio &lt; 2.0; HER2 &lt; 4.0</td>
<td>41.9</td>
<td>23.9</td>
<td>76.7</td>
<td>69.6</td>
<td>73.4</td>
</tr>
<tr>
<td><strong>IHC distribution</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>3,089</td>
<td>4,331</td>
<td>7,526</td>
<td>1,922</td>
<td>11,116</td>
</tr>
<tr>
<td>0</td>
<td>IHC 0:1+, 2.0</td>
<td>54.5</td>
<td>51.7</td>
<td>2.4</td>
<td>0.5</td>
</tr>
<tr>
<td>1+ (including 0 or 1+)</td>
<td></td>
<td>9.4</td>
<td>31.0</td>
<td>8.0</td>
<td>1.8</td>
</tr>
<tr>
<td>2+ (including 1+2+ or 2+3+)</td>
<td></td>
<td>41.8</td>
<td>13.7</td>
<td>9.0</td>
<td>87.1†</td>
</tr>
<tr>
<td>3+</td>
<td>36.2</td>
<td>22.4</td>
<td>8.4</td>
<td>2.5</td>
<td>1.3</td>
</tr>
</tbody>
</table>

**NOTE.** Data are presented as % unless otherwise indicated.

**Abbreviations.** BCIRG, Breast Cancer International Research Group; FISH, fluorescent in situ hybridization; HERA, Herceptin Adjuvant trial; neg, negative; pos, positive; UCSF, University of California, San Francisco; UK NEOAS, United Kingdom National External Quality Assessment Service; USC, University of Southern California; UWMCC, University of Washington Medical Center.

*Andrew Dodson, personal communication October 2016.
†IHC 1+ or 2+ and 2+ or 3+ were grouped together with IHC 2+. In each column for a specific laboratory or study, the top set of percentages describes the distribution of group 1 to 5 results when tested using a dual-probe FISH assay, while the bottom set of percentages describes the distribution of IHC tests results of the samples submitted to that laboratory or study for dual-probe ISH testing and as described in each publication.
OUTLINE

- Prognostic markers
  - Histopathological
  - Molecular
- Predictive markers
  - Early BC
  - Metastatic BC
- Conclusion and perspectives
**METASTATIC SITE BIOPSY**

Perform a biopsy of the metastatic localization if:
1. First diagnosis of metastatic relapse
2. Unusual clinical presentation (very early/late relapse, or if any doubt about the diagnosis of metastatic relapse)
3. Heterogeneous primary tumor (especially if multiple tumors with different phenotypes)
4. Phenotype of the primary tumor for HR and HER2 was evaluated more than 10 yrs ago
5. Primary tumor of unknown or negative phenotype

Avoid if possible:
- Bone sample (decalcification may impair IHC or molecular analysis)
- Cytological samples for IHC
HR AND HER2 DISCORDANCE AT METASTATIC DIAGNOSIS

<table>
<thead>
<tr>
<th>Comparison</th>
<th>ESME cohort (n=16703) N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histological report on met at metastatic diagnosis</td>
<td>2933 (17.6%)</td>
</tr>
<tr>
<td>HR and/or HER2 status on met at metastatic diagnosis (and also available on PT)</td>
<td>1677 (10.0%)</td>
</tr>
<tr>
<td>HR and/or HER2 status on met at 1st MBC progression (and also available on PT)</td>
<td>783 (4.7%)</td>
</tr>
</tbody>
</table>

PR discordance rate is twice (31.1%) the ER discordance rate (15.1%) with almost two thirds of loss of expression of both.

Sarah Lefèvre et al., SABCS 2018, P5-12-05
## PD-L1 IN LOCALLY ADVANCED/METASTATIC TNBC

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All</strong></td>
<td>902</td>
<td>0.80 (0.69, 0.92)</td>
</tr>
<tr>
<td>Baseline liver metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>244</td>
<td>0.79 (0.60, 1.03)</td>
</tr>
<tr>
<td>No</td>
<td>658</td>
<td>0.76 (0.65, 0.93)</td>
</tr>
<tr>
<td>Prior taxane use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>461</td>
<td>0.78 (0.64, 0.96)</td>
</tr>
<tr>
<td>No</td>
<td>441</td>
<td>0.81 (0.65, 1.00)</td>
</tr>
<tr>
<td>PD-L1 status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-L1+ (IC1/2/3)</td>
<td>369</td>
<td>0.62 (0.49, 0.79)</td>
</tr>
<tr>
<td>PD-L1– (IC0)</td>
<td>533</td>
<td>0.96 (0.79, 1.16)</td>
</tr>
</tbody>
</table>

- **PD-L1+**
  - Immune cells
  - ≥1% (IC1/2/3)
  - Clone SP142
  - Central testing

- **A + nab-Pac** ➸ **P + nab-Pac**

- FDA approval (8 March 2019), EMA
- ATU (early access program) in France for atezolizumab (Tecentriq) since 08/2019
PD-L1 TESTING
Sample specifications

- Accepted specimens
  - Formalin-fixed & paraffin embedded tissue (thickness 4-6µ, cut slides <2months)
  - Biopsy or surgical sample, primary or metastatic sites
  - Adequacy: at least 50 viable tumor cells

Presence of tumor associated stroma is essential for scoring IC
ANDROGEN RECEPTOR IN TNBC

- Apocrine carcinoma: phenotype ER- PR- AR+ HER2-/+ FOXA1+ GCDFP15+
- Poor prognosis (*Bonnefoi H et al. BJC 2019*)
- Tumor biology is AR dependent, *CHEK1/chk1* surexpression in non-responder patients (*Grellety T et al. CCR 2019*) → new therapeutic targets(s)
- Detected by IHC in triple-negative BC (88% concordance with molecular apocrine subtype) (*Bonnefoi H et al. BJC 2019*): positivity cut-off: ≥10%
- AR inhibitors: abiraterone acetate, darolutamide
- Clinical trials in metastatic setting:
  - AMA (UCBG 12-1): clinical benefit rate of 20% at 6 months (1 complete response and 5 stable diseases) (*Bonnefoi H et al. Ann Oncol 2016*)
  - START (darolutamide): open for enrollment
**PIK3CA MUTATIONS**

- Frequent (32%, n=10319), associated with ER+ status, age, low grade, small T size (p<0.001)
  - 18% ER-/HER2-
  - 22% HER2+
  - 37% ER+/HER2-

- Better prognosis (IDFS) (up-regulation of ER pathway)

- PI3Kα inhibitor: alpelisib
- Associated with fulvestrant
- n=572 ER+/HER2- treated by ET (341 \( \text{PIK3CA}^{\text{mut}} \))
- PFS 11mo vs 5.7mo in the \( \text{PIK3CA}^{\text{mut}} \) group
**BRCA1/2 AND HRD**

- Defect in repair of double-strand breaks by HR (HRD), especially (but not exclusively) in TNBC → DSB repair using other error-prone repair systems (NHEJ)
- PARP inhibitors (BER pathway): synthetic lethality

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**Olaparib**
- OlympiAD study
- mBC HER2-, gBRCA1/2\textsuperscript{mut}
- mPFS 7mo vs 4.2mo
- (Robson M et al. NEJM 2017)
- FDA in 2018

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**Talazoparib**
- EMBRACA study
- mBC HER2-, gBRCA1/2\textsuperscript{mut}
- PFS 8.6mo vs 5.6mo
- (Litton et al. NEJM 2018)
- FDA in 2018
- AMM Europe June 2019

➢ **BRCA1/2 germline mutation (but somatic screening possible)**
ERBB2 (HER2) MUTATIONS

Activating HER2 Mutations in HER2 Gene Amplification Negative Breast Cancer

Ron Bost, Shyam M. Kavuri, Adam C. Searleman, Wei Shen, Dong Shen, Daniel C. Koboldt, John Morsey, Nicholas Colet, Adam S. Aronson, Shunqiang Li, Cynthia X. Ma, Li Ding, Elaine R. Mardis, and Matthew J. Ellis

• 8 sequencing databases (1499 patients, HER2- in the vast majority of the cases)
→ **25 HER2 mutated cases (1.6%)** with some recurring mutations (13 mutations identified), HER2 non-amplified, ductal or lobular subtypes
• 2 major regions: 20% ECD, 68% kinase domain
• Expressed at the mRNA level
• 7 activating mutations
• 1 mutation (6 patients/25) lapatinib resistant (L755S)
• All sensitive to neratinib (irreversible TKI HER1/2/4)

**HER2 mutations**: 3 to 8%
• More frequent in peomorphic ILC
• Associated with HER2 negative status

**HER3 mutations**: 3.6%
TAKE-HOME MESSAGES

Role of the pathologist:
1) Classification and phenotype assessment of BC
   - Early BC
   - Relapse and metastatic setting (serial samples)
     → select the right biomarker on the right sample for an appropriate treatment

2) Active role in the development and implementation of new biomarkers
3) Development of new tools
   - Molecular biology approaches
   - Digital pathology and AI

<table>
<thead>
<tr>
<th>ER+/HER2-</th>
<th>ER-/HER2-</th>
<th>HER2+</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1 (IHC, SP142)</td>
<td>AR (IHC)</td>
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<tr>
<td>PIK3CA (tum or ctADN)</td>
<td>BRCA1/2</td>
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<td>BRCA1/2</td>
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Perspectives

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<tbody>
<tr>
<td>HRD panel</td>
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<tr>
<td>Target panel (ESR1, HER2, FGFR, NTRK...)</td>
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</tr>
</tbody>
</table>

Prognostic criteria
- Histological type and grade
- pTNM
- LVI
- ER/PR/HER2 and molecular subtype
- TILs
- Gene expression signatures
Thank you!