# A prospective randomized trial evaluating gene expression arrays to select neoadjuvant chemotherapy regimen for operable breast cancer: first report of the REMAGUS04 trial


- J-Y. Pierga[1], B. Asselain[1], S. Alsafadi[2], E. Brain[3], F. Lerebours[3], S. Delaloge[2], D. Gentien[1], N. Servant[1], B. Sigal-Zafrani[1], F. André[2]

[1]Institut Curie Paris, [2]Institut Gustave Roussy Villejuif,

[3]Institut Curie St Cloud

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# Disclosure slide

- No Conflicts of Interest to declare

# Background

- There is a need to develop robust and high throughput biotechnologies for biomarker determination for clinical use
- DNA arrays allow quantifying gene expression at the whole genome level and could improve prediction of the benefit from a specific chemotherapy.

# Rationale

- Diagonal Linear Discriminant Analysis–30 (DLD-30) probe set model predicts resistance to neoadjuvant chemotherapies with a better sensitivity than standard parameters[1]

- Topoisomerase 2 (TOP2A) amplification has been reported as a predictor for the efficacy of anthracyclines-based chemotherapy[2]

- We evaluated whether whole genome array approach is feasible in the context of daily practice, and whether the use of a genomic score (DLD-30) combined with TOP2A level could improve neoadjuvant chemotherapy efficacy.

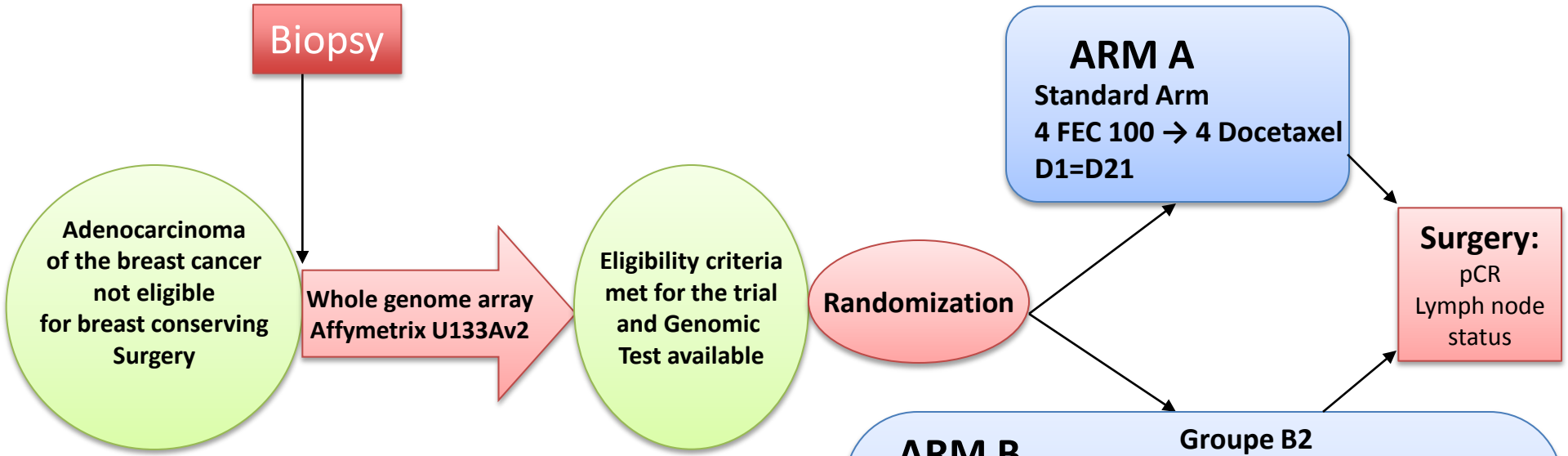


*1 Hess et al, J Clin Oncol 2006*

*2 Di Leo A et al, Lancet Oncol 2011*

# Trial design

Phase III randomized trial : standard neoadjuvant chemotherapy vs a genomic-driven neoadjuvant chemotherapy




Clinical Eligibility criteria

- **HER2 negative**
- no multifocality
- cT1-cT3 tumor
- no metastases
- normal lab value
- LVEF >50%

Sample Eligibility criteria

- 30% cancer cells
- RIN>6,
- RNA content > 2ug

**TOP2A >500 (sensitive to anthracyclines)**

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(N° EudraCT: 2008-005534-70).

# Statistical hypotheses and analyses

- Primary endpoint:
  - To evaluate whether genomic driven chemotherapy increased the likelihood of pathological complete response (pCR , tumor and lymph nodes) as compared to standard chemotherapy.
  - The trial as designed to improve pCR rates from 13% to 28%.
  - The hypothesis to increase was based on an expected rate of 19% pCR rate in patients with DLD30-neg score and a 50% PPV for the DLD30.
- With 300 patients, the study had 80% power to detect such difference.
- Stopping rule for futility:
  - An interim analysis was planned after 20 patients included in the docetaxel/capecitabine arm (DLD30-negative / TOP2A-negative).
  - If less than 3 patients presented a pCR, the study was stopped by the steering committee.

# Cancer centers involved in Remagus04

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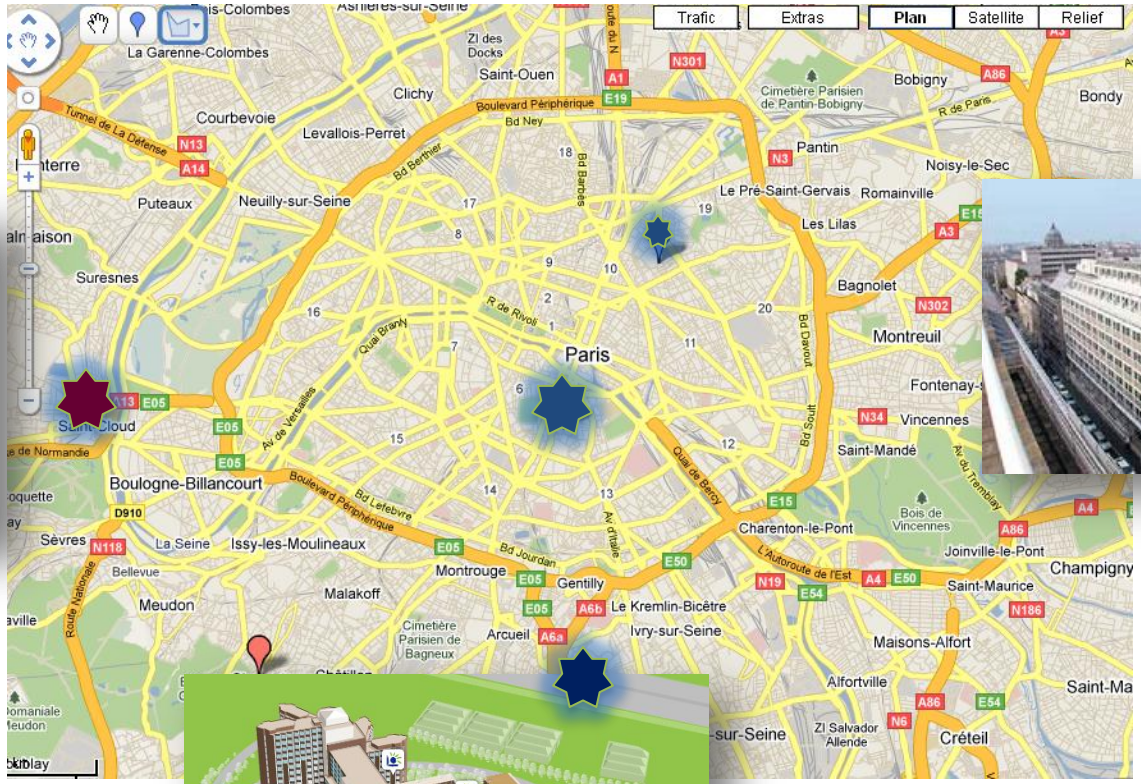
VILLEJUIF - www.igr.fr

100 ans 1909 2009
institutCurie
Ensemble, prenons le cancer de vitesse.



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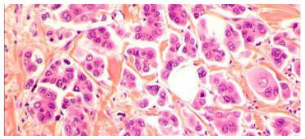
# From 1st visit to neoadjuvant chemotherapies: The "genomic journey"

Monday-Wednesday

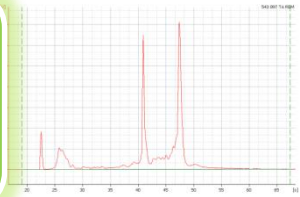
Biopsy in cancer centers



Thursday-Friday

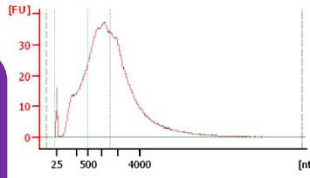
Tumor cell analysis

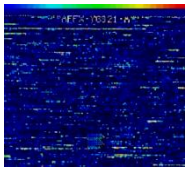
RNA extraction and QC



Monday-Thursday

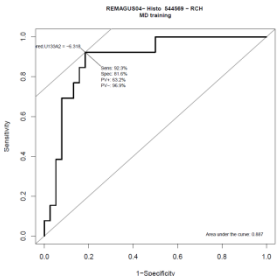
Target preparation and U133Av2 hybridization



Friday

DLD30 procedure

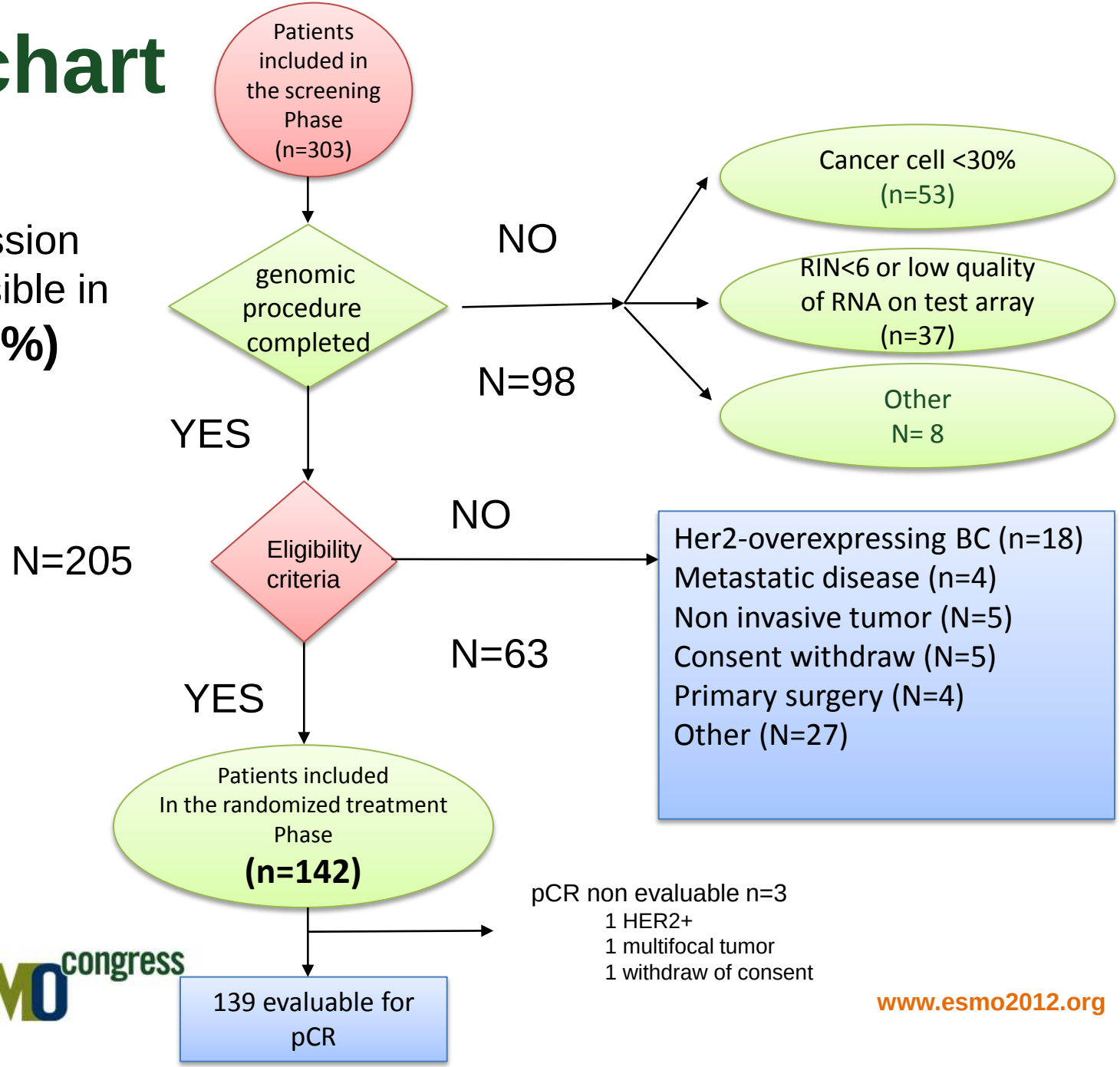


Monday

Results to clinicians

# Flow chart

Gene expression profiling feasible in 205/303 **(67%)**



# Patients' characteristics N=142

| | | Arm A (standard) (70 patients) | Arm B (Genomic) (72 patients) |
|---|---|---|---|
| Age | Median | 48.9 | 46.9 |
| T | 1 | 1 (1.5%) | 2 (3%) |
| | 2 | 42 (60%) | 40 (56%) |
| | 3 | 24 (34%) | 23 (32%) |
| | 4 | 1 (1.5%) | 6 (8%) |
| | NA | 2 (3%) | 1 (1%) |
| N | 0 | 26 (37%) | 35 (49%) |
| | 1 | 33 (47%) | 33 (46%) |
| | 2 | 8 (11%) | 4 (5%) |
| | 3 | 1 (1.5%) | 0 |
| | NA | 2 (3%) | 0 |
| ER- PgR- | Triple neg | 24(34%) | 28 (39%) |
| ER- PgR+ | | 2(3%) | 1 (1%) |
| ER+ PgR- | | 10 (14%) | 4 (6%) |
| ER+PgR+ | | 34 (49%) | 39 (54%) |
| Grade | I | 3 (4%) | 2 (3%) |
| | II | 27 (39%) | 25 (35%) |
| | III | 39 (56%) | 42 (58%) |
| | Non-assessable | 1 (1%) | 2 (3%) |
| | NA | 0 | 1 (1%) |
| DLD30 | - | 32 (46%) | 32 (44%) |
| | + | 38 (54%) | 40 (56%) |
| pCR | yes | 14 (21%) | 16 (22%) |
| | no | 53 | 56 |
| | NA | 3 | 0 |

# pCR according to treatment group

| Group | | Genomic profile | Neoadjuvant Chemotherapy | pCR | | | |
|---|---|---|---|---|---|---|---|
| | | | | 0 | 1 | % pCR | *TOTAL* |
| **Standard ARM A** | Group A2 | DLD30+ | 4FEC 4 Doc | 24 | 13 | 35% | ***37*** |
| | Group A3 | DLD30- TOPA2+ | 4FEC 4 Doc | 4 | 0 | 0% | ***4*** |
| | Group A4 | DLD30- TOPA2 - | 4FEC 4 Doc | 25 | 1 | 4% | ***26*** |
| **Genomic ARM B** | Group B2 | DLD30+ | 12w Pacli 4FEC | 25 | 15 | 38% | ***40*** |
| | Group B3 | DLD30- TOPA2+ | 4FEC 4 Doc | 5 | 0 | 0% | ***5*** |
| | Group B4 | DLD30- TOPA2 - | 6 Doc Cape | 26 | 1 | 4% | ***27*** |
| | ***TOTAL*** | | | ***109*** | ***30*** | | ***139*** |

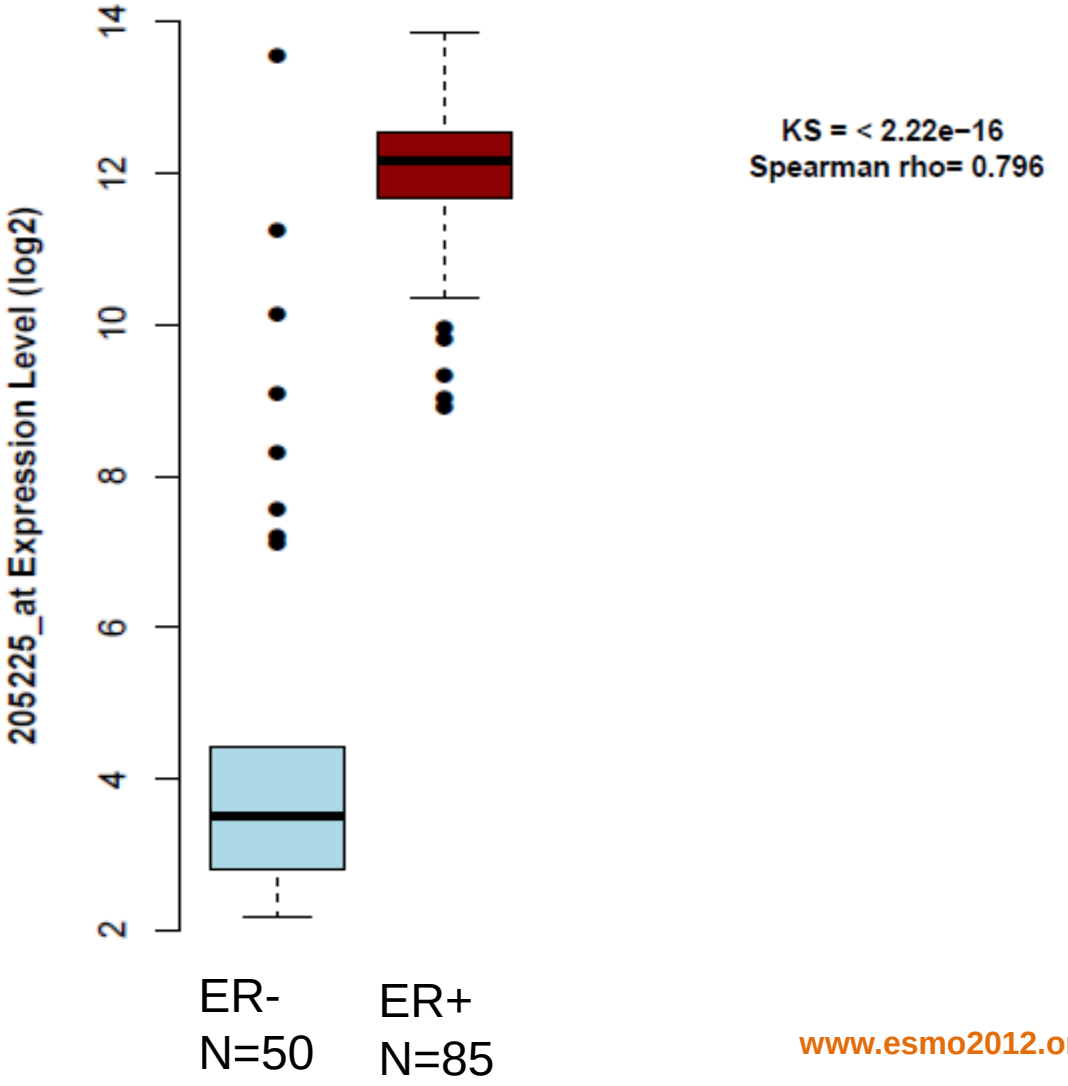
The trial, designed to include 300 pts, was stopped after a preplanned interim analysis showing < 2 pathological Complete Response (pCR) out of 20 in the Docetaxel Capecitabine Group (B4)

# pCR Correlation with biological parameters

| | | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|
| | | OR | IC 95% | p | OR | IC 95% | p |
| **ER** | + | 1 | - | $<10^{-4}$ | 1 | - | 0.06 |
| | - | 10.53 | [4.14 – 30.78] | | 3.23 | [1.03 – 11.72] | |
| **DLD30** | - | 1 | - | 0.0002 | 1 | - | 0.09 |
| | + | 17.14 | [4.82 – 109.49] | | 4.7 | [0.87 – 35.9] | |
| **Grade** | **I & II** | 1 | - | 0.0007 | 1 | - | 0.14 |
| | **III** | 8.83 | [2.89 – 38.56] | | 2.88 | [0.77 – 13.99] | |

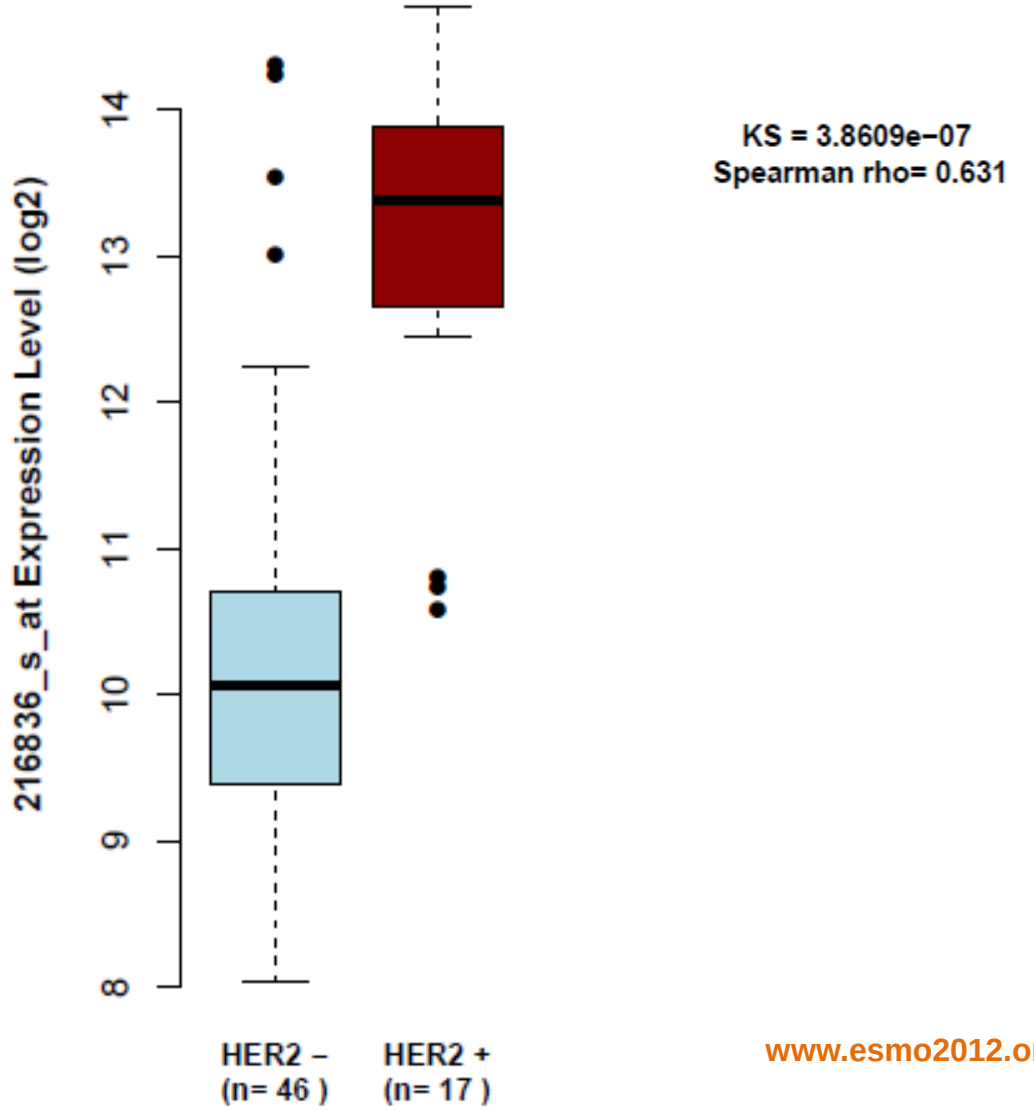
# Good correlation between probeset expression and ER by ImmunoHistoChemistry

Probeset 205225_at for Estrogen Receptor



# Good correlation between probeset expression and HER2 by ImmunoHistoChemistry

Probeset
216836_s_at
forHER2



# Conclusions (1)

- This is the first prospective trial showing that whole genome array is feasible in the context of daily practice within 15 days
- The success rate for genomic analysis was 61% (142/232) for the clinically eligible patients and 67% (205/303) for the screened population.
- Main sources of loss of samples are low % tumor cell in biopsy and RNA poor quality
- Microarray accurately quantified gene expression (r=0.80 correlation with IHC for ER expression).

# Conclusions (2)

- No difference was observed between genomic driven arm and standard chemotherapy arm
  - (pCR rates: 22 % and 21% respectively).
- This clinical trial validates predictive value of DLD30 score:
  - DLD30+ score was associated with an increased likelihood of pCR (36% versus 3% for DLD30-).
  - at multivariate analysis, pCR was associated with
    - DLD30+ at OR= 4.7 (0.87 – 35.9, p=0.09)
    - And ER negativity

# Conclusions (3)

- We have identified a group of patients (DLD30&TOP2A negative) with a very low rate of response which need specific strategies
  - No neoadjuvant chemotherapy
  - or Clinical trials for new drugs
- Gene expression arrays could be a solution in the future to propose an all-in-one assay for personalized medicine.

# Perspectives

- Determining new gene signatures
  - for chemosensitivity ,
  - functional pathways for targeted therapies (mTOR signature , PIK3CA signatures etc…)
  - single gene expressions, in addition to some already validated prognostic signatures (genomic grade…) and targets (ESR1, ERBB2)

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