# I SIMPOSIO NACIONAL de ONCOLOGÍA de PRECISIÓN

**Vigo,** del **28** de **febrero** al **1** de **marzo** de **2019**

GENERALITAT VALENCIANA

La Fe
Hospital Universitari i Politècnic

# Cáncer de mama y ginecológico

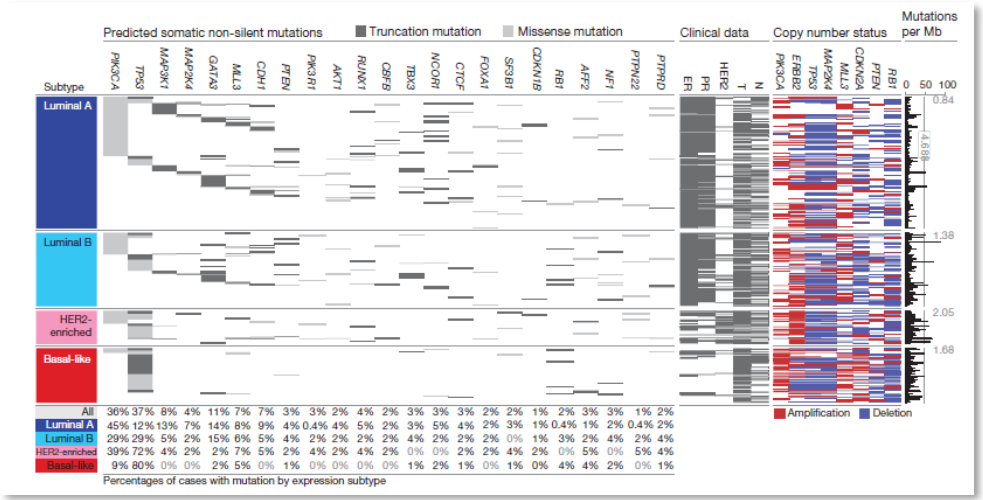
Ana Santaballa Bertrán, MD, PhD→ Mª Teresa Curiel, MD

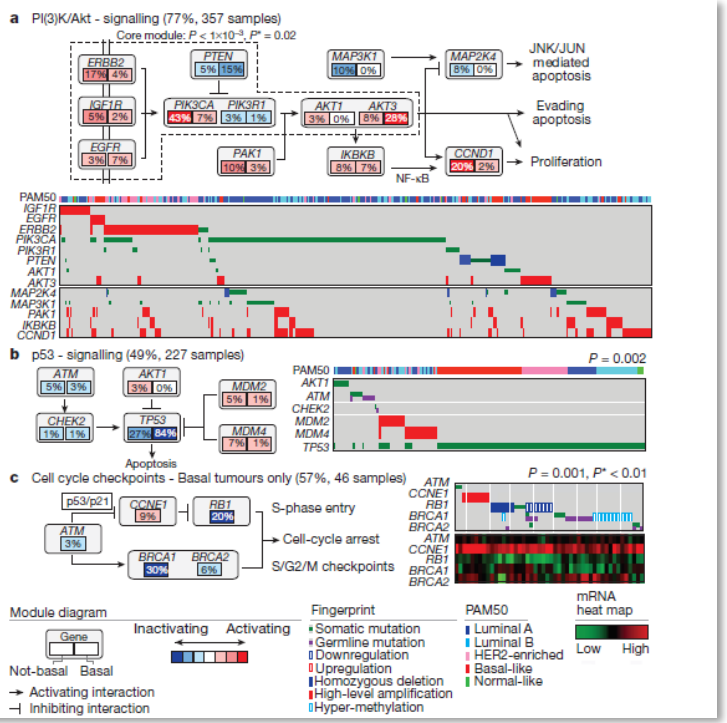
HOSPITAL HOSPITALES hm la esperanza

# CÁNCER DE MAMA

# Comprehensive molecular portraits of human breast tumours

The Cancer Genome Atlas Network*



# Plataformas genómicas en cáncer de mama precoz LUMINAL

## Oncotype®

- 21 genes
- Pronóstico recaída a distancia a 10 años tras HT
- **Predice beneficio de la QT con RS > 26**

## Mammaprint®

- 70 genes
- Pronóstico recaída a distancia 5 años tras HT

## Prosigna®

- **Subtipos intrínsecos**
- 50 genes
- Pronóstico recaída a distancia a 10 años tras HT
- Pronóstico de recaída tardía (5-10 años)

## Endopredict®

- 12 genes
- Pronóstico recaída a distancia a 10 años tras HT
- Pronóstico de recaída tardía (5-10 años)

# Potenciales aplicaciones de la genómica en el cáncer de mama metastásico

| Application of Genomics | Optimal Technology | Targets | Level of Evidence Associated with the Target[11] |
|---|---|---|---|
| Drivers (DNA) | Next-generation sequencing if multiple genes validated | ERBB2 amplification | I |
| | | PIK3CA mutations | II |
| | | AKT1 mutations | III |
| | | ERBB2 mutations | III |
| Drivers (RNA/ proteins) | Gene expression Phosphoprotein assays | ER expression | I |
| | | mTOR activation | ND |
| | | CDK4/6 activation | ND |
| Lethal subclone | Ultra-deep sequencing Circulating DNA | ESR1 mutations | III |
| DNA repair | Targeted sequencing Whole-exome sequencing SNP arrays | BRCA1/2 mutations | I/II |
| Immune system | Whole-exome sequencing RNA sequencing | PD-L1 overexpression | ND |
| | | Neoantigen | |

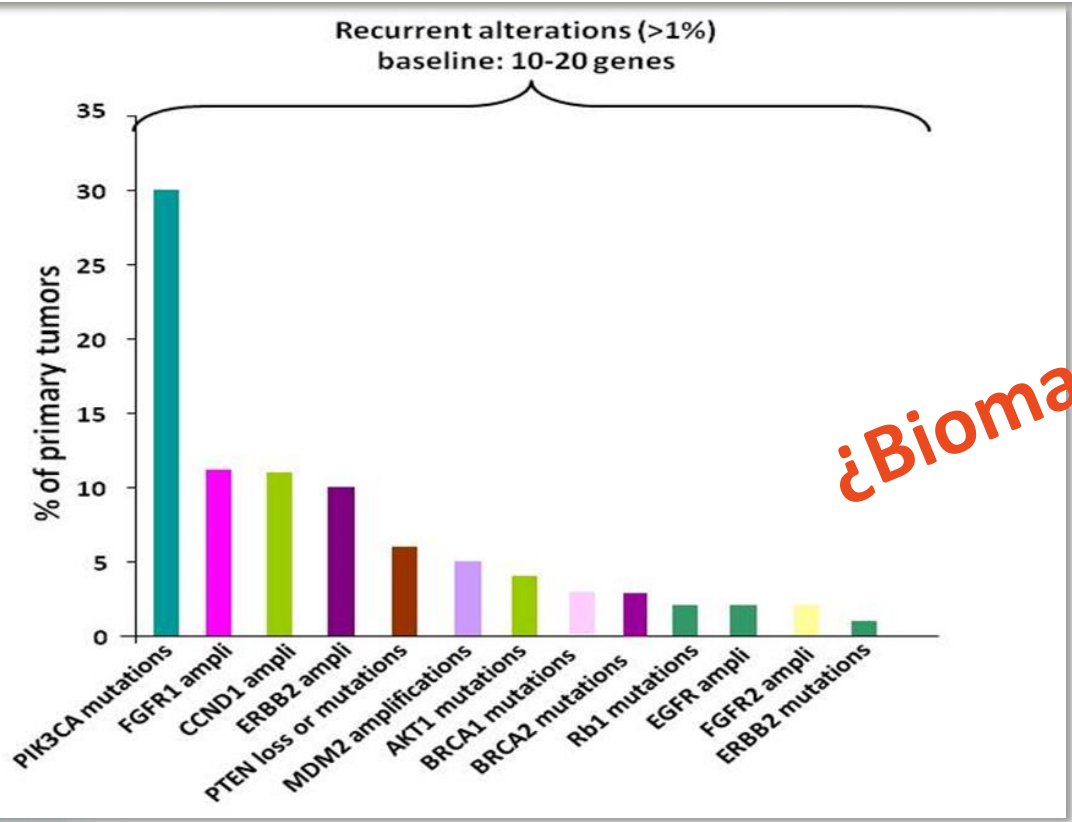
# Molecular profiling to capture tumor evolution and adaptation

| Molecular alteration | Evolution | Frequency | Candidate drug |
|---|---|---|---|
| ER expression | Primary to metastases | 14% | Endocrine therapy |
| Her2 expression | Primary to metastases | 5% | Her2 inh |
| ESR1 mut[1] | Resistance to AI | 10-30% | ER degraders |
| PTEN mut[2] | Resistance to alpha-specific PI3K inhibitors | unknown | PI3K + mTOR inh ? |
| Others | PIK3CA, TSC1/2 … | | |

## Which genomic tool could be useful to monitor appearance of genomic alteration ?

1. Toy, Nature Genetics 2013, 2. Juric, Nature 2014

## Identificar los “drivers”



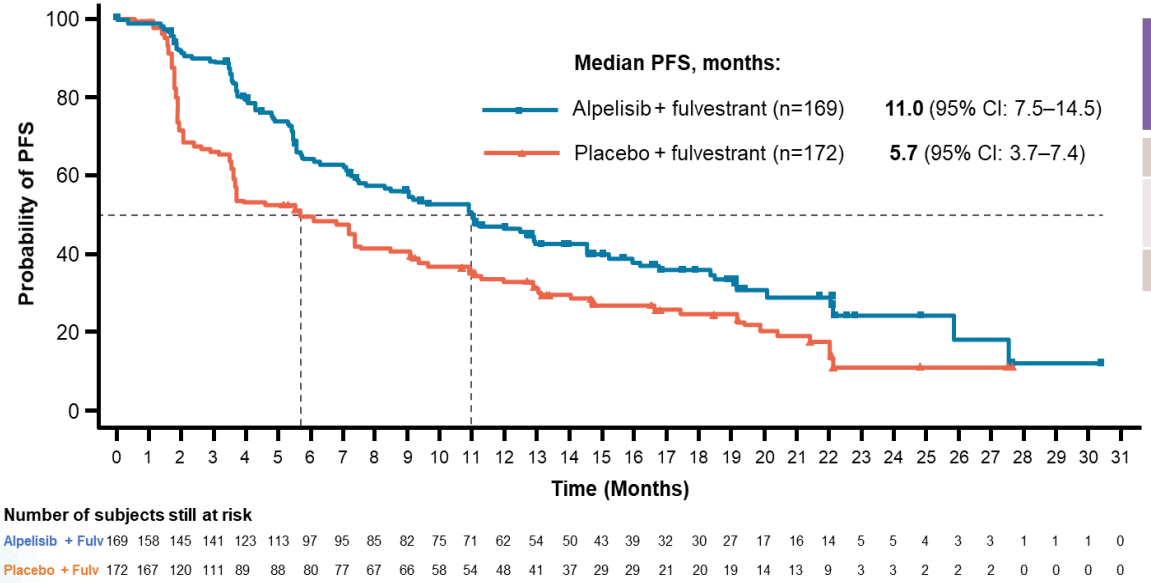

¿Biomarcadores predictivos?

# Which recurrent alterations predict drug efficacy ?

| Genomic alteration | Incidence | Drug / Efficacy |
|---|---|---|
| BRCA1/2 germline mutations | 3-5% | Sensitivity to carboplatin[1] (evidence lacking for ER+/BRCA2 mut)<br>Sensitivity to PARP inhibitors[2] |
| AKT1 mutations | 4-5% | mTOR/AKT inhibitors: 3/6 responders (SAFIR01)[3] |
| ERBB2 mutations | 2% | Neratinib: objective responses in phase II[4] |
| PIK3CA mutations | 25% | Alpha-selective PI3K inh (GDC-032 / BYL719):<br>BYL719 / fulvestrant: OR:24% / PFS:8.3 months[5] |
| FGFR1 amplification | 10% | No efficacy with specific inhibitors[6]<br>Objective responses with lucitanib (study lacks FGFR1- pats) [7] |
| AR expression | 55-79% TNBC | Clin benefit rate: 34% (enzalutamide)[8]<br>but the natural disease of the segment is unknown |
| CCND1 amplification | 10-15% | No predictive value for palbociclib[9] |
| Others | >30% | PTEN, NOTCH, FBXW7, EGFR, NF1, MYC ...:<br>No evidence for drug efficacy (yet) |

1.Tutt, SABCS, 2014, 2. Tutt, Lancet, 2010, 3. Andre, Lancet Oncol, 2014, 4. AACR/ASCO/FDA meeting, 2014 , 5. Janku, SABCS, 2014, 6. Andre, AACR, 2013, 7. Soria, Annals Oncol, 2014, 8. Traina, SABCS 2014, 9. Finn, Lancet Oncol, 2014

# Alpelisib + fulvestrant for HR+, HER2– advanced breast cancer: Results of the phase III SOLAR-1 trial

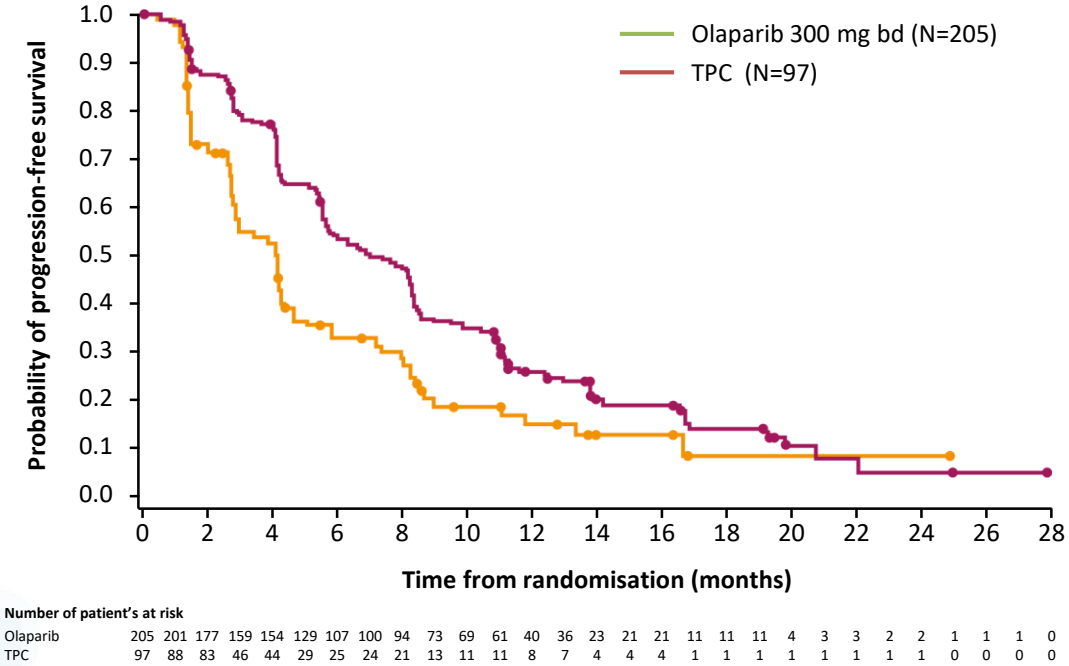



| Data cut-off: Jun 12, 2018 | Alpelisib + fulvestrant (N=85) | Placebo + fulvestrant (N=88) |
|---|---|---|
| Number of PFS events, n (%) | 43 (50.6) | 63 (71.6) |
| Median PFS (95% CI) | 11.1 (7.3–16.8) | 3.7 (2.1–5.6) |
| HR (95% CI) | 0.48 (0.32–0.71) | |

181061966

André, ESMO 2018

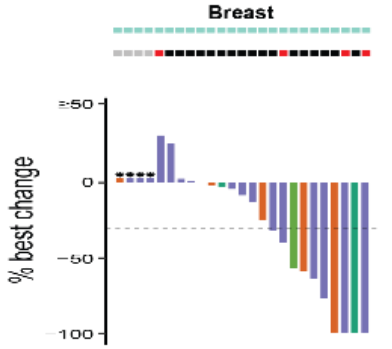
# Inhibidores de PARP BRCA mutadas



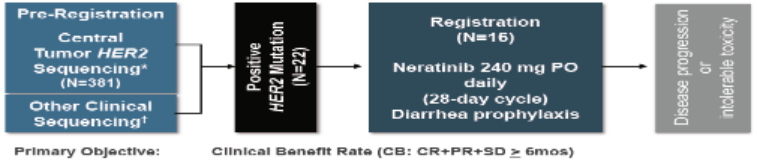

| | Olaparib | TPC |
|---|---|---|
| n | 205 | 97 |
| Events (%) | 163 (79.5%) | 71 (73.2%) |
| Median (m) | 7.0 | 4.2 |
| | **HR = 0.58**<br>95 % CI (0.43, 0.80)<br>p=0.0009 | |
| PFS free at 6m (%) | 54.1 | 32.9 |
| PFS free at 12m (%) | 25.9 | 15.0 |

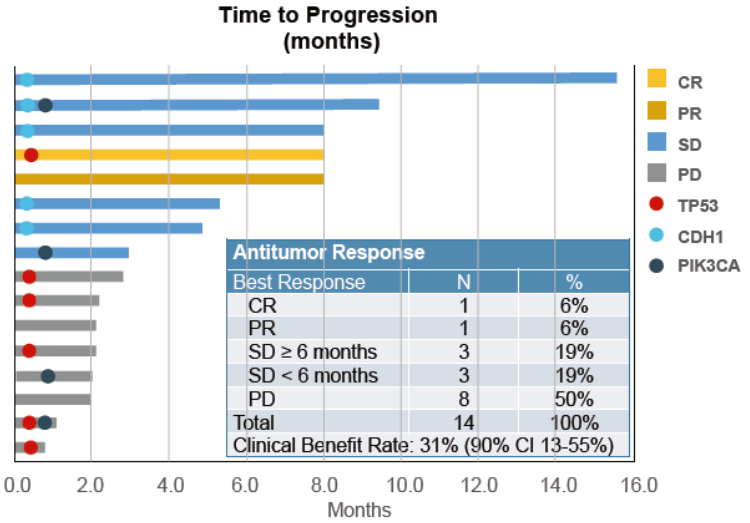
Robson et al. N Engl J Med. 2017; 377:523-533;

# Neratinib en HER2 mutadas



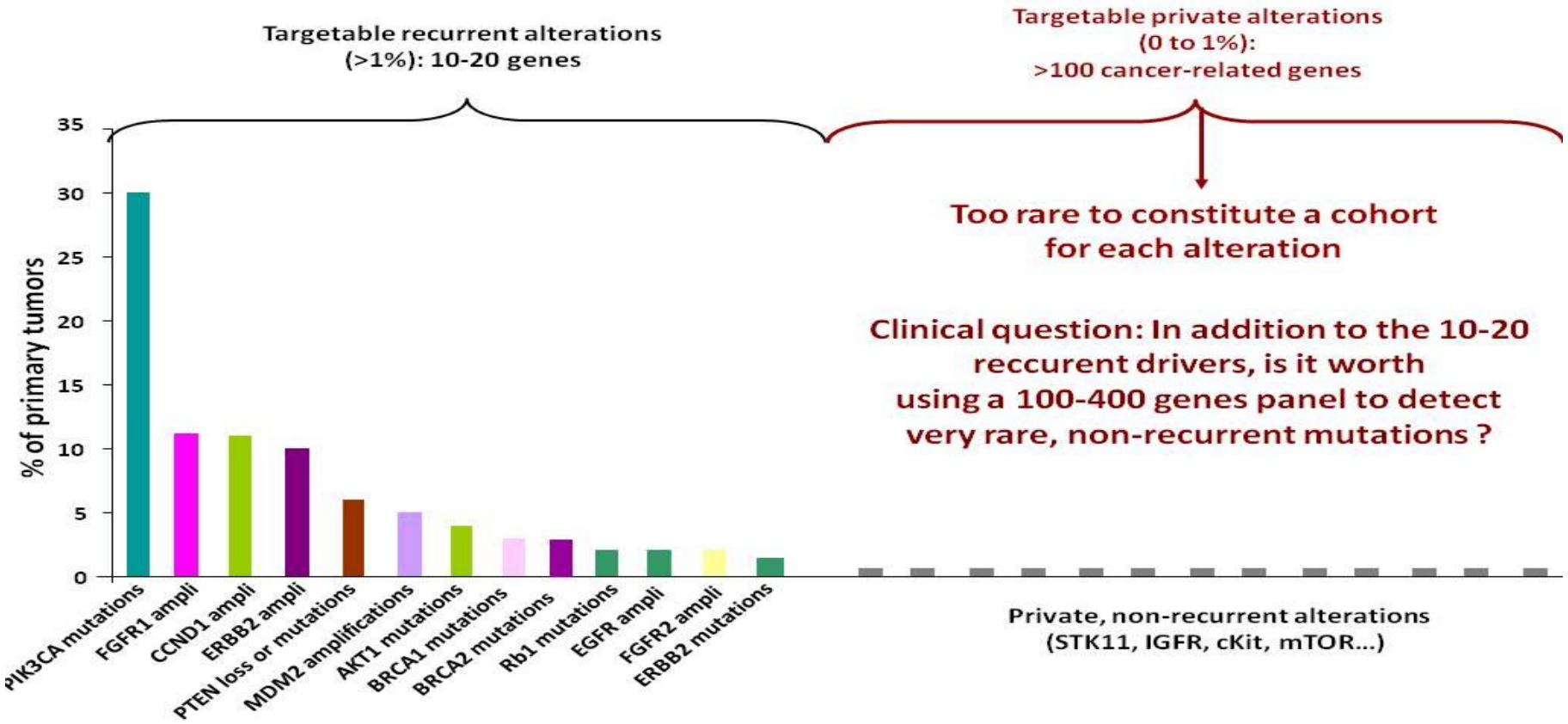

| | Breast (n=25) |
|---|---|
| **ORR at week 8, n (%)** [95% CI] | 8 (32.0) [14.9–53.5] |
| **ORR, n (%)** [95% CI] | 6 (24.0) [9.4–45.1] |
| **Clinical benefit rate, n (%)** [95% CI] | 10 (40.0) [21.1–61.3] |
| **Median PFS, months** (95% CI) | 3.5 (1.9–4.3) |




SUMMIT trial: Hyman D et al, AACR 2017; MUT-HER trial: . Ma C. et al, Clin Cancer Res 2017

# What is the clinical problem ?




Presented By Fabrice Andre at 2015 ASCO Annual Meeting

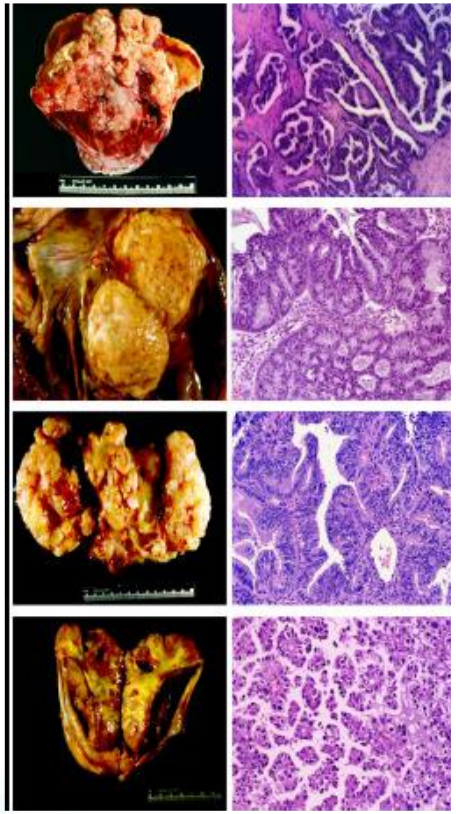
# CÁNCER DE OVARIO

# Comparative Meta-analysis of Prognostic Gene Signatures for Late-Stage Ovarian Cancer

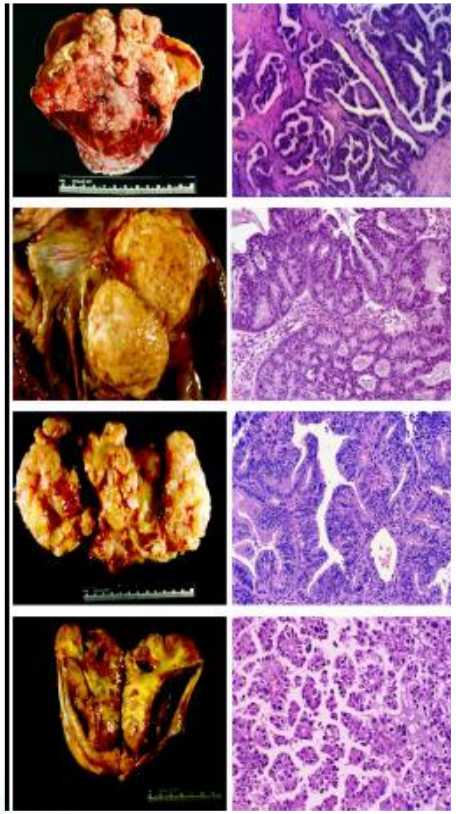
Levi Waldron, Benjamin Haibe-Kains, Aedín C. Culhane, Markus Riester, Jie Ding, Xin Victoria Wang, Mahnaz Ahmadifar, Svitlana Tyekucheva, Christoph Bernau, Thomas Risch, Benjamin Frederick Ganzfried, Curtis Huttenhower, Michael Birrer, Giovanni Parmigiani

**Conclusions** This analysis provides definitive support for a handful of prognostic models but also confirms that these require improvement to be of clinical value. This work addresses outstanding controversies in the ovarian cancer literature and provides a reproducible framework for meta-analytic evaluation of gene signatures.

JNCI J Natl Cancer Inst (2014) 106(5): dju049 doi:10.1093/jnci/dju049



| | |
|---|---|
| Seroso de alto grado | Inestabilidad genómica |
| Mucinoso | Via RAS aberrante |
| Endometrioide | Vía PTEN, PI3K, AKT aberrante |
| Células claras | ARID1A |



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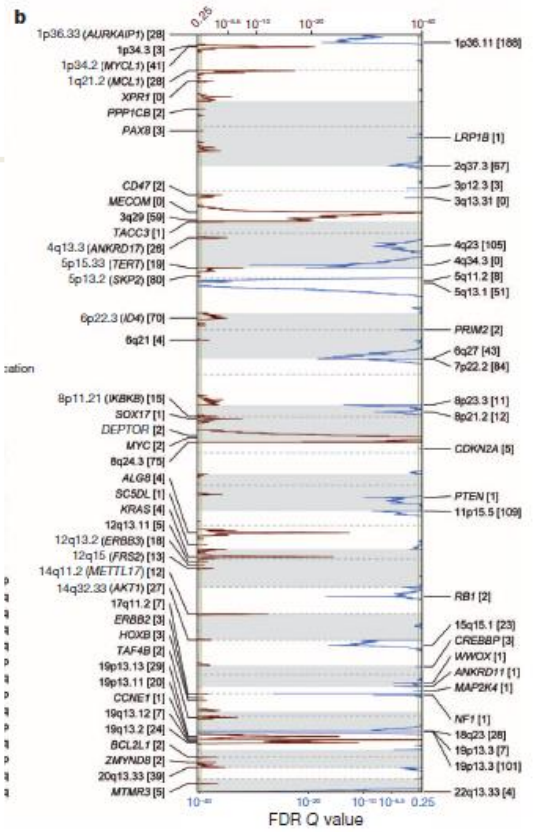
| Células claras | ARID1A |

# Integrated genomic analyses of ovarian carcinoma

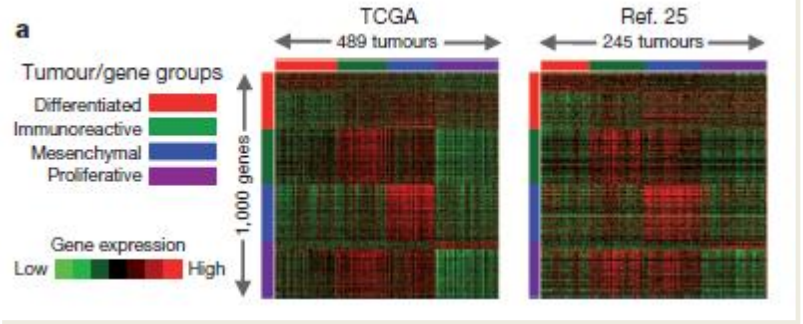
The Cancer Genome Atlas Research Network*

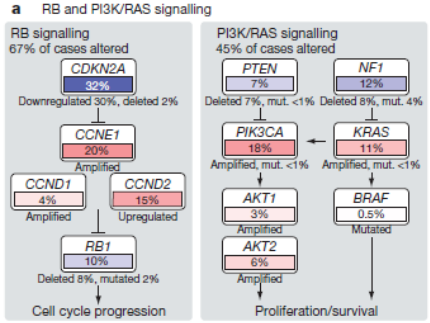
| Gene | No. of mutations | No. validated | No. unvalidated |
|---|---|---|---|
| *TP53* | 302 | 294 | 8 |
| *BRCA1* | 11 | 10 | 1 |
| *CSMD3* | 19 | 19 | 0 |
| *NF1* | 13 | 13 | 0 |
| *CDK12* | 9 | 9 | 0 |
| *FAT3* | 19 | 18 | 1 |
| *GABRA6* | 6 | 6 | 0 |
| *BRCA2* | 10 | 10 | 0 |
| *RB1* | 6 | 6 | 0 |

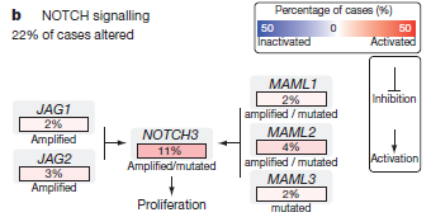


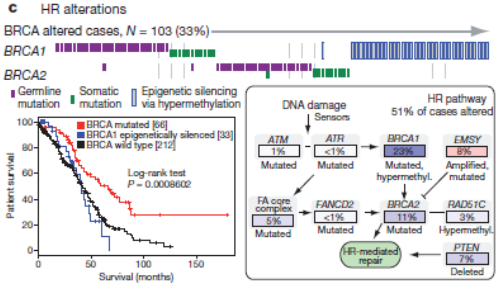
# Integrated genomic analyses of ovarian carcinoma

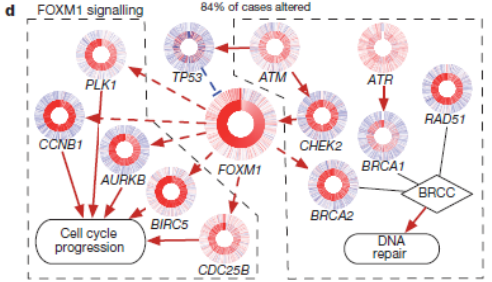
The Cancer Genome Atlas Research Network*



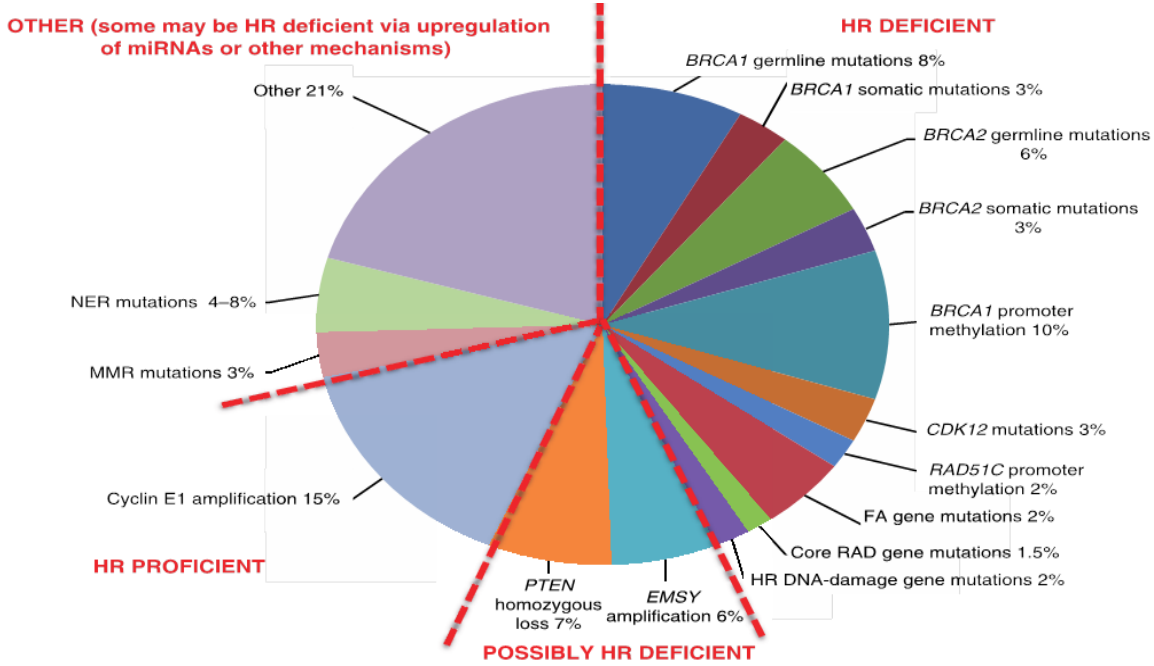



# Deficiencia de la recombinación homóloga



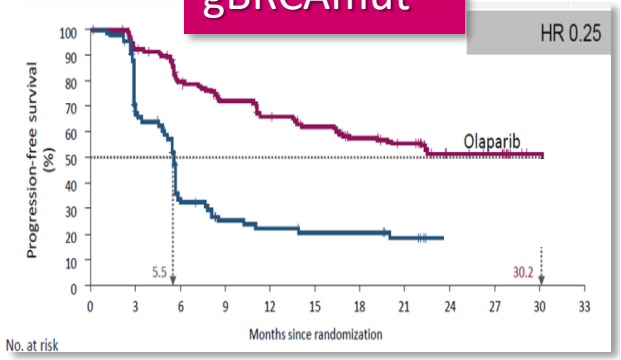

Cancer Discov; 5(11); 1137–54. 2015

# BRCA como factor predictivo de respuesta



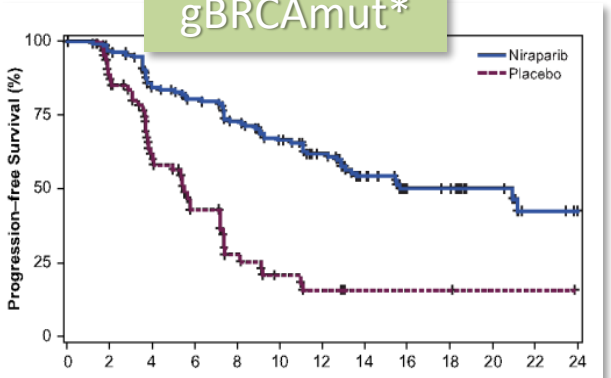
IPARP como mantenimiento en pacientes platino sensibles **BRCA mutadas (germinal y/o somática)**

## Olaparib SOLO 2 gBRCAmut



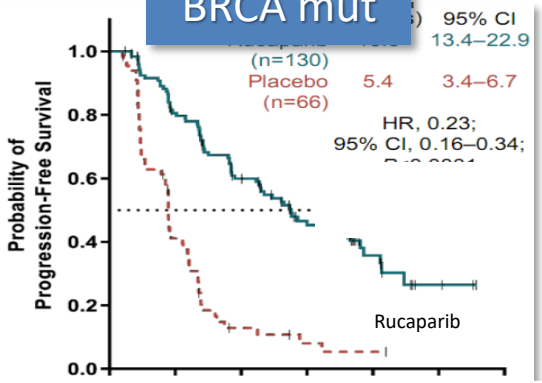

| | Olaparib (n=196) | Placebo (n=99) |
|---|---|---|
| Mediana PFS meses | 30.2 | 5.5 |
| HR (IC 95%) | 0.25 | |

## Niraparib NOVA gBRCAmut*




| | Niraparib (n=138) | Placebo (n=65) |
|---|---|---|
| Mediana PFS meses | 21 | 5,5 |
| HR (IC 95%) | 0,27 (0,17-0,41) p<0,01 | |

## Rucaparib ARIEL 3 BRCA mut



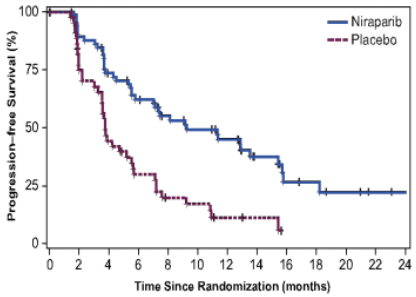

| | Rucaparib (n=130) | Placebo (n=66) |
|---|---|---|
| Mediana PFS meses | 16.6 | 5.4 |
| HR (IC 95%) | 0,23 (0,16-0,34) p<0,0001 | |

# IPARP como mantenimiento en pacientes platino sensibles

## BRCA no mutadas

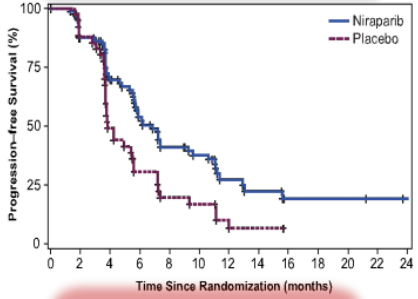
### Niraparib NOVA

HRD positivo*




HR 0.38
(0.231, 0.628)

HRD negativo

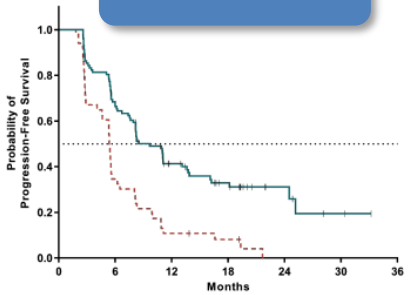



HR 0.58
(0.361, 0.922)

| | HRD positive | HRD negative |
|---|---|---|
| PFS placebo | 3.7 m | 3.8 m |
| PFS Niraparib | 9.3 m | 6.9 m |

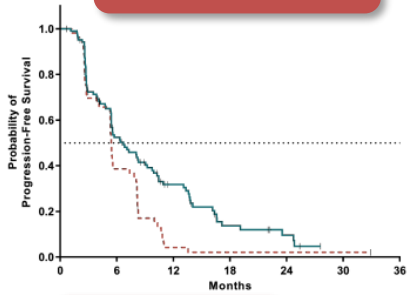
### Rucaparib ARIEL 3

LOH alto




HR 0.44
(0.29–0.66)

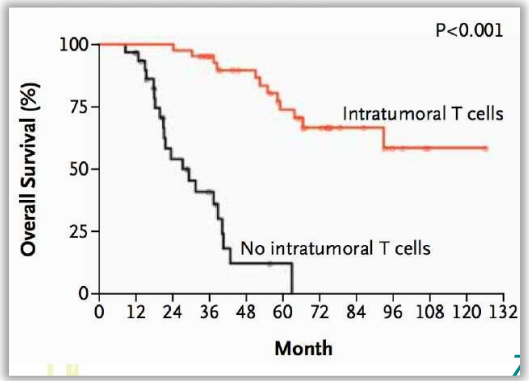
LOH bajo

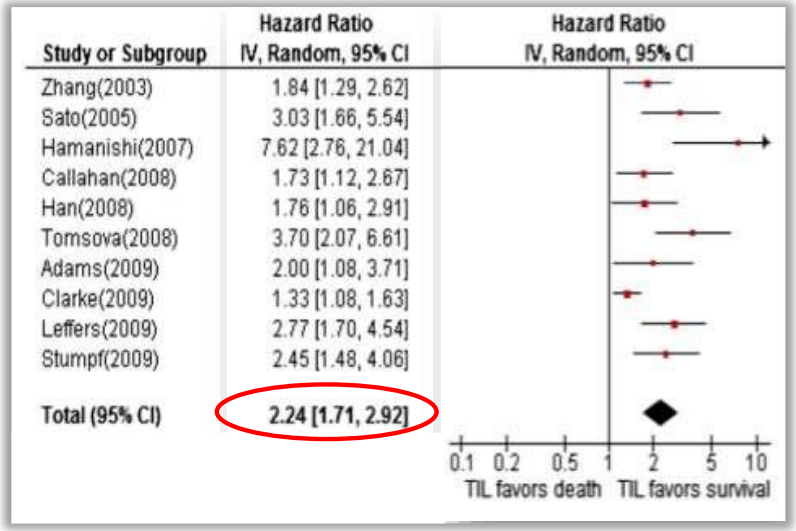



HR 0.58
(0.40–0.85)

| | LOH High | LOH Low |
|---|---|---|
| PFS placebo | 5.4 m | 5.4 m |
| PFS rucaparib | 9.7 m | 6.7 m |

# Significado pronóstico de los TILs en CO

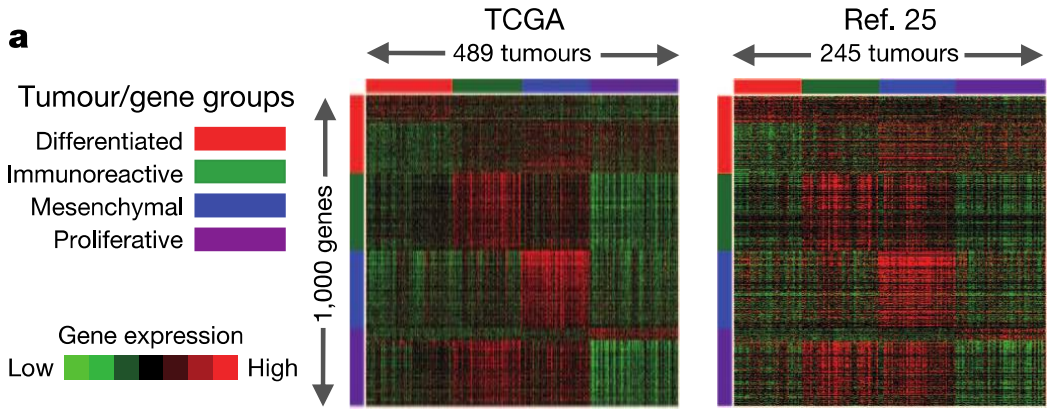





Zhang L, Conejo-Garcia JR, Katsaros D, Gimotty PA, Massobrio M, Regnani G, et al. Intratumoral T Cells, Recurrence, and Survival in Epithelial Ovarian Cancer. N Engl J Med. 2003;3483348:203–13.

Hwang WT, Adams SF, Tahirovic E, Hagemabn IS, Coukos G. Prognostic significance of tumor-infiltrating T cells in ovarian cancer: a meta-analysis. Gynecol Oncol 2012; 124(2): 192–198.

# Inmunogenicidad histotipos CEO




| Inmunoreactivo | Mesenquimal | Proliferativo |
|---|---|---|
| ↑↑↑ TILS | ↑↑ TILS | ↑ TILS |
| ↑ citocinas de cels. T (CXCL11, CXCL10,CXCP3) | ↑ HOX, miofibroblastos | ↑ HMGA2, SOX11, proliferación<br>↓ MUC1, MUC 16 |

Cancer Genome Atlas Research N. Integrated Genomic Analyses Of Ovarian Cance. Nature 474 (7353), 609–615; 2011.

# PRECISIÓN EN CÁNCER DE MAMA 2019

- Plataformas genómicas, ya instauradas en práctica clínica habitual
- Cambios moleculares entre primario y metástasis, qué pasa con la biopsia liquida?
- Es necesario homogeneizar las técnicas
- Alteraciones moleculares poco frecuentes: ensayos umbrella

# PRECISIÓN EN CA OVARIO 2019

- CEO resistente, seguimos sin identificarlo
- Clasificación CEO, debemos orientarla a características moleculares
- Validar biomarcadores predictivos para HGSC
- Desarrollo de EC para pacientes no HDR : firmas génicas con whole genomic sequencing?
- Insistir en la búsqueda de biomarcadores para antiangiogénesis