Comprometidos Contigo

ASPECTOS GENÉTICOS EN LA INDIVIDUALIZACIÓN FARMACOTERAPÉUTICA

CONGRESO NACIONAL
SOCIEDAD ESPAÑOLA DE FARMACIA HOSPITALARIA

sefh

Javier Milara; PhD; PharmD;
Hospital General Universitario de Valencia.

Individualización de la farmacoterapia

FARMACOGENÉTICA

- ¿ Sirve para ajustar las dosis de los medicamentos ?
- ¿ Sirve para Evitar Reacciones Adversas ?
- ¿ Sirve para seleccionar el tratamiento óptimo?

¿Cómo prescribimos?

¿Cómo individualizamos los tratamientos?

Cambio de fármaco

No responde

Muy poco

Dosis

No responde

Dosis

Cambio de fármaco

Toxicidad

demasiado

↓ Dosis

Toxicidad

↓ Dosis

Se trata una enfermedad, no al individuo.

• ¿ Sirve para ajustar las dosis de los medicamentos ?

Clinical Pharmacogenetics Implementation Consortium

De los aproximadamente 1000 medicamentos aprobados por la FDA, menos de 100 son candidatos para el análisis farmacogenético y su decisión clínica asociada

Fármaco	Gen	Fenotipo	Nivel de evidencia
Warfarina/Acenocumarol	VKORC/CYP2C9	Eficacia/ Dosificación	1A/1B
Clopidogrel	CYP2C19	Eficacia/ dosificación	1A
Peg-Interferon	IL-28B	Eficacia	1A
Abacavir	HLA-B*5701	Toxicidad	1A
Alopurinol	HLA-B*58:01	Toxicidad	1A
Mercaptopurina/ Azatioprina	TPMT	Toxicidad/ dosificación	1A
Simvastatina	SLCO1B1	Toxicidad/ dosificación	1A
Irinotecan	UGT1A1	Toxicidad/ dosificación	3
5-FU/ Capecitabina	DPYD/ TYMS	Toxicidad/ dosificación	1B
Metotrexato	MTHFR/ SLCO1B1	Toxicidad/ dosificación	1B
Tacrólimus	CYP3A5	Eficacia/ dosificación	1B
Maraviroc	CCR5/gp120	Eficacia	1A
Tamoxifeno	CYP2D6	Eficacia/ dosificación	2A
Metoprolol	CYP2D6	Eficacia/ dosificación	3
Ivacaftor	**CFTR**	**Eficacia**	**1A**
Codeina	CYP2D6	Toxicidad/ eficacia	1A
Nilotinib	UGT1A1	Toxicidad/eficacia	3
Efavirenz	CYP2B6	Toxicidad/ dosificacion	2
Antipsicóticos (doxepina)	CYP2D6, CYP2C19	Toxicidad/ dosificacion	1A
Antidepresivos tricíclicos	CYP2D6/ CYP2C19/ CYP2C9	Toxicidad/ dosificación	1A
Antidepresivos (sertralina etc..)	CYP2C19	Toxicidad/ dosificación	1A
Voriconazol	CYP2C19	Farmacocinética	3
Carbamacepina	HLA-A*3103	Toxicidad	1A
Fenitoina	CYP2C9/ HLA-B*15:02	Toxicidad	1A

• ¿ Sirve para ajustar las dosis de los medicamentos ?

ACENOCUMAROL Sintrom®

MÚLTIPLES ESTUDIOS

CYP2C9 1*/2*/3*; rs1057910, rs1799853

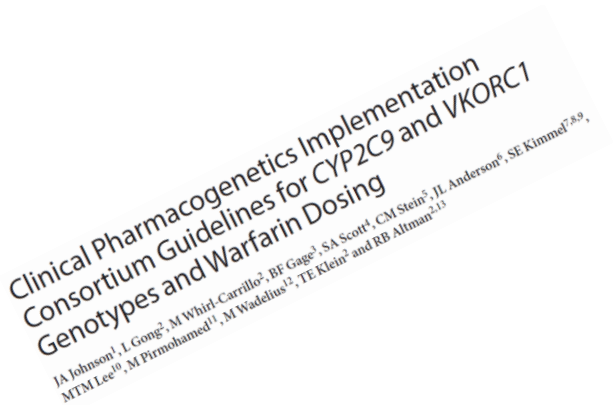
VKORC1; rs9923231

CYP4F2; rs2108622

APOE; rs7412, rs429358

Explican 30% de la variabilidad

Explican 45-50% de la variabilidad


Clinical Pharmacogenetics Implementation Consortium Guidelines for *CYP2C9* and *VKORC1* Genotypes and Warfarin Dosing

JA Johnson[1], L Gong[2], M Whirl-Carrillo[3], BF Gage[3], SA Scott[4], CM Stein[5], JL Anderson[6], SE Kimmel[7,8,9], MTM Lee[10], M Pirmohamed[11], M Waddelius[12], TE Klein[3] and RB Altman[2,13]

Table 1 Recommended daily warfarin doses (mg/day) to achieve a therapeutic INR based on *CYP2C9* and *VKORC1* genotype using the warfarin product insert approved by the US Food and Drug Administration

VKORC1: −1639G>A	*CYP2C9*1/*1*	*CYP2C9*1/*2*	*CYP2C9*1/*3*	*CYP2C9*2/*2*	*CYP2C9*2/*3*	*CYP2C9*3/*3*
GG	5–7	5–7	3–4	3–4	3–4	0.5–2
GA	5–7	3–4	3–4	3–4	0.5–2	0.5–2
AA	3–4	3–4	0.5–2	0.5–2	0.5–2	0.5–2

Reproduced from updated warfarin (Coumadin) product label.

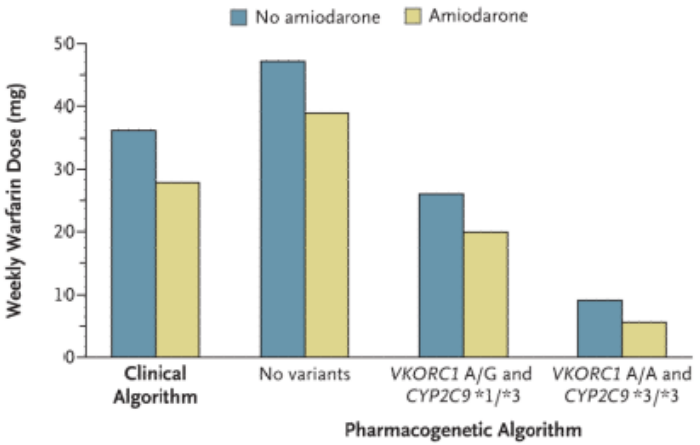
Johnson JA . Clin Pharmacol Ther. 2011. 90(4):625-9

• ¿ Sirve para ajustar las dosis de los medicamentos ?

Box 1 Patient characteristics utilized in the Gage algorithm,[17] the International Warfarin Pharmacogenetics Consortium[18] algorithm, or both

Age
Sex
Race
Weight
Height
Smoking status
Warfarin indication
Target international normalized ratio
Interacting drugs
- Inhibitors: amiodarone, statins, sulfamethoxazole, azole antifungals
- Inducers: rifampin, phenytoin, carbamazepine

Genetic variables
- *CYP2C9* genotype
- *VKORC1* genotype
- The Gage algorithm can also incorporate *CYP4F2* and *GGCX* genotypes



Algoritmo de dosificación: basado en características clínicas y genotipo

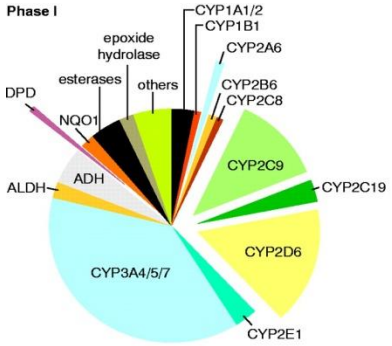
- VKORC1, CYP2C9 y CYP4F2
  +
- Características clínicas

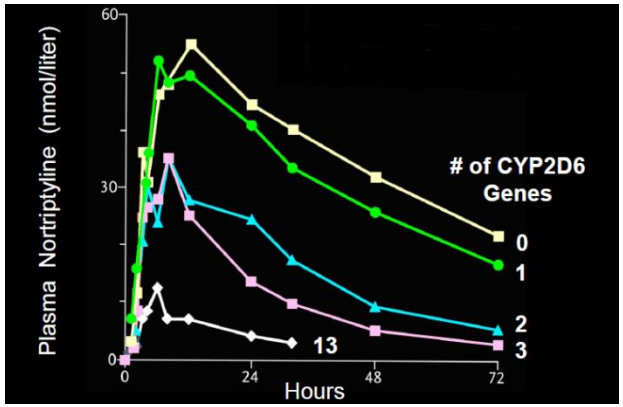
} Ajuste de dosis según INR deseado

International Warfarin Pharmacogenetics Consortium N Engl J Med. 2009 Feb 19;360(8):753-64

• ¿ Sirve para ajustar las dosis de los medicamentos ?

Antidepresivos/ antipsicóticos





- **Fármacos en psiquiatría**
  - Los efectos secundarios son causa frecuente de interrupción o fracaso del tratamiento
  - El tiempo requerido para obtener el efecto óptimo es muy prolongado (3-8 semanas), necesitándose contínuos ajustes de la dosis.
  - La selección del fármaco y la dosis se hace en gran medida de modo empírico
  - Las dosis pueden variar considerablemente entre individuos
  - No es posible una monitorización del fármaco

- **CYP2D6 : uno de los responsables de las diferencias de respuesta entre individuos**
  - El enzima CYP2D6 metaboliza muchos fármacos utilizados en psiquiatría
  - Alta variabilidad entre individuos y poblaciones
  - Entre el 7-10% de los Europeos tienen actividad del CYP2D6 reducida (metabolizadores lentos)

Molecular Psychiatry (2004) 9, 442–473

www.nature.com/mp

FEATURE REVIEW

Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response

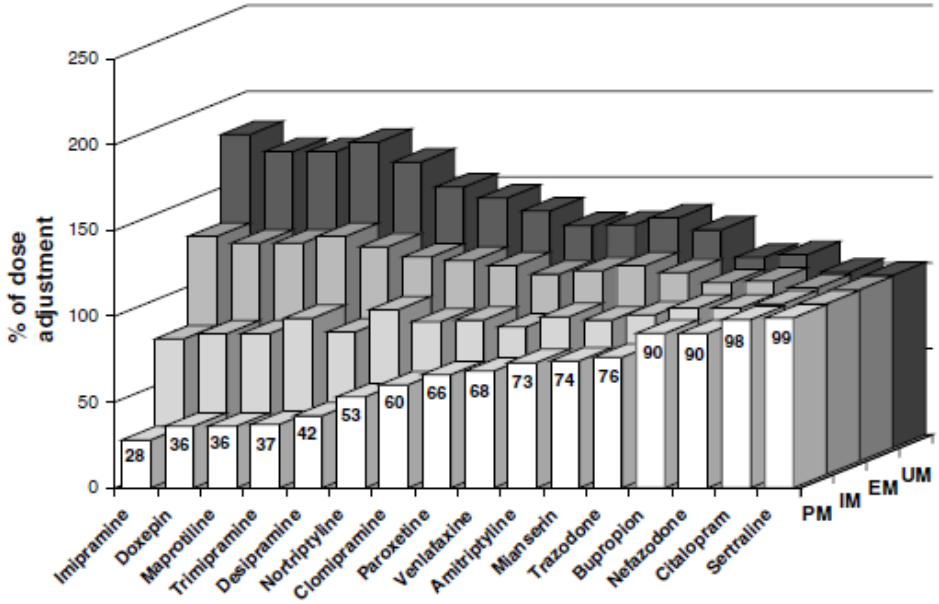
J Kirchheiner[1], K Nickchen[1], M Bauer[2], M-L Wong[3], J Licinio[3], I Roots[1] and J Brockmöller[4]

[1]*Institute of Clinical Pharmacology, Campus Charité Mitte, University Medicine Berlin, Berlin, Germany;* [2]*Department of Psychiatry and Psychotherapy, Campus Charité Mitte, University Medicine Berlin, Berlin, Germany;* [3]*Center for Pharmacogenomics and Interdepartmental Clinical Pharmacology Center, Neuropsychiatric Institute, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA;* [4]*Department of Clinical Pharmacology, Georg August University, Göttingen, Germany*

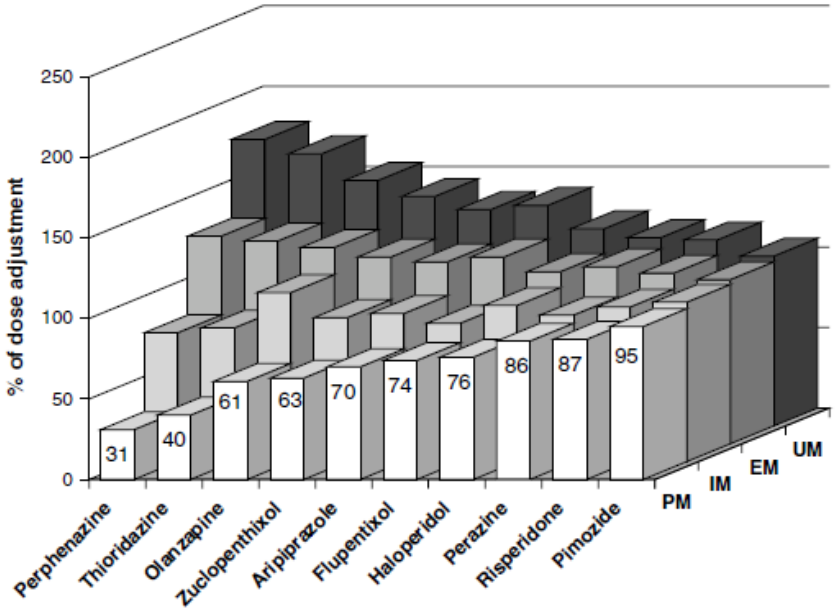
• ¿ Sirve para ajustar las dosis de los medicamentos ?

AJUSTE DE DOSIS EN FUNCION DEL GENOTIPO CYP2D6; % de la dosis de ficha técnica

Antidepresivos



Antipsicóticos



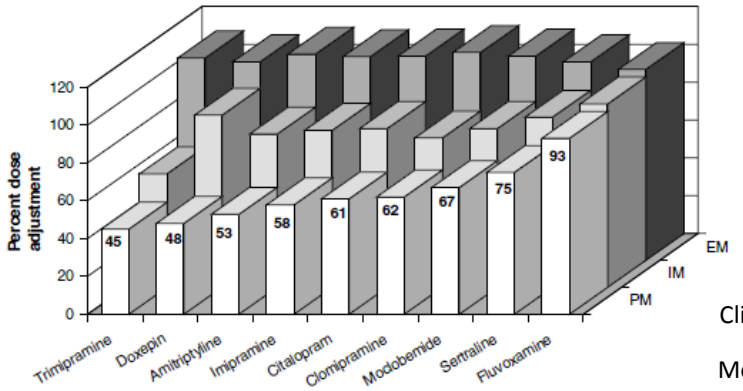
AJUSTE DE DOSIS EN FUNCION DEL GENOTIPO CYP2C19; % de la dosis normal

CPIC GUIDELINES

nature publishing group

Clinical Pharmacogenetics Implementation Consortium Guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Tricyclic Antidepressants

JK Hicks[1], JJ Swen[2], CF Thorn[3], K Sangkuhl[3], ED Kharasch[4], VL Ellingrod[5,6], TC Skaar[7], DJ Müller[8], A Gaedigk[9] and JC Stingl[10]



Clin Pharmacol Ther. 2013 May;93(5):402-8.

Mol Psychiatry. 2004 May;9(5):442-73

• ¿ Sirve para ajustar las dosis de los medicamentos ?

TACRÓLIMUS

Optimization of Initial Tacrolimus Dose Using Pharmacogenetic Testing

E Thervet[1,2], MA Loriot[3], S Barbier[4], M Buchler[5], M Ficheux[6], G Choukroun[7], O Toupance[8], G Touchard[9], C Alberti[10], P Le Pogamp[11], B Moulin[12], Y Le Meur[13], AE Heng[14], JF Subra[15], P Beaune[3] and C Legendre[1,2]

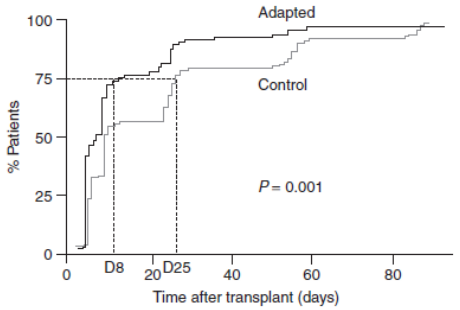


Figure 3 Time to achieve tacrolimus C_0 target range (10–15 ng/ml).

Algoritmo de decisión: Test pre-tratamiento

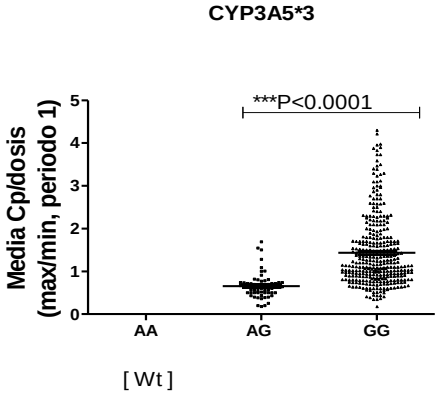
- Variaciones CYP3A5*1 / CYP3A5*1*3 en transplante renal; comenzar inmunosupresion con tacrólimus 0,3 mg/kg/día

- Variaciones CYP3A5*3*3 en transplante renal; comenzar inmunosupresion con tacrólimus 0,15 mg/kg/día

Table 1: Dosing recommendations for tacrolimus based on CYP3A5 phenotype:

Adapted from Tables 1 and 2 of the 2015 guideline manuscript.

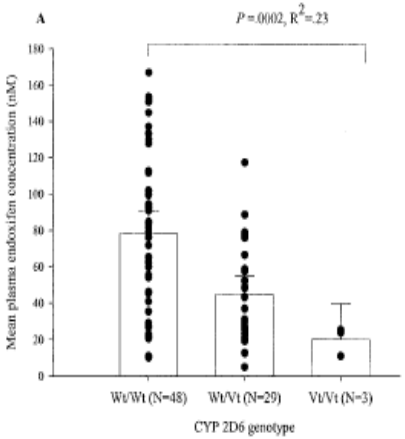
Likely phenotype [a]	Genotypes	Examples of diplotypes [b]	Implications for tacrolimus pharmacologic measures	Therapeutic Recommendations [c]	Classification of recommendations [e]
Extensive metabolizer (CYP3A5 expresser)	An individual carrying two functional alleles	*1/*1	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations	Increase starting dose 1.5 to 2 times recommended starting dose [d]. Total starting dose should not exceed 0.3mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments	Strong
Intermediate metabolizer (CYP3A5 expresser)	An individual carrying one functional allele and one non-functional allele	*1/*3, *1/*6, *1/*7	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations	Increase starting dose 1.5 to 2 times recommended starting dose [d]. Total starting dose should not exceed 0.3mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments	Strong
Poor metabolizer (CYP3A5 non-expresser)	An individual carrying two non-functional alleles	*3/*3, *6/*6, *7/*7, *3/*6, *3/*7, *6/*7	Higher ("normal") dose-adjusted trough concentrations of tacrolimus and increased chance of achieving target tacrolimus concentrations	Initiate therapy with standard recommended dose. Use therapeutic drug monitoring to guide dose adjustments	Strong



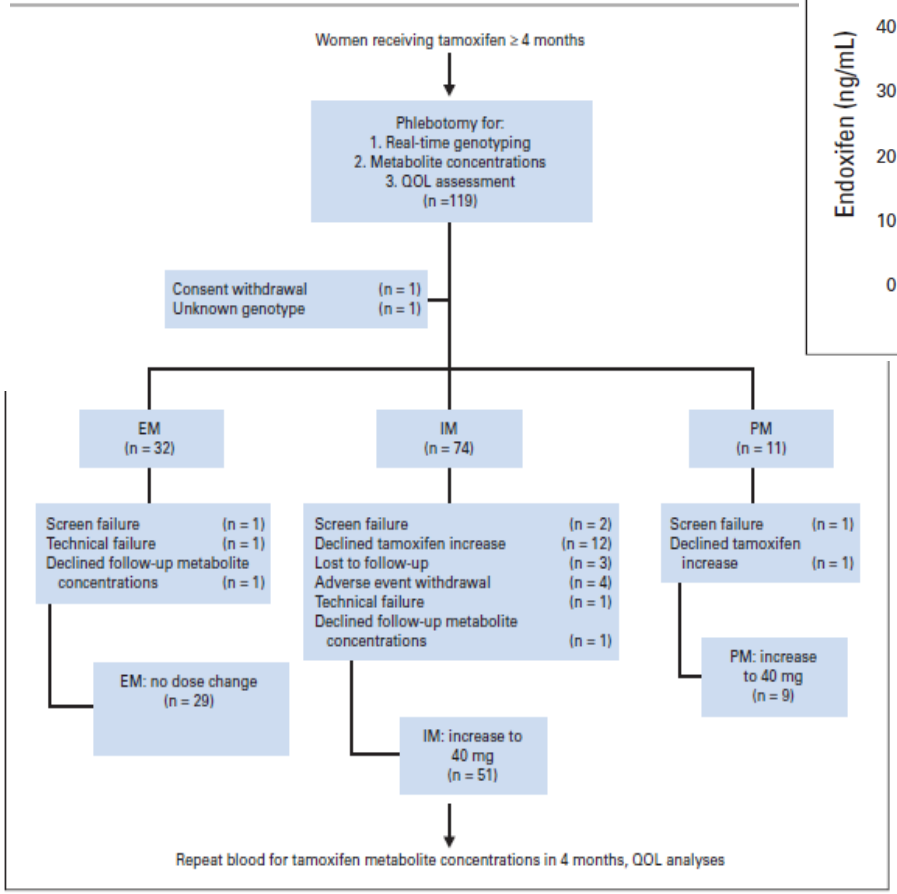
• ¿ Sirve para ajustar las dosis de los medicamentos ?

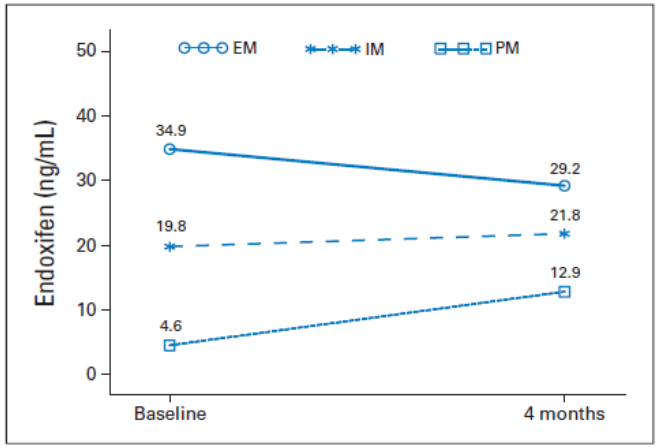
TAMOXIFENO

El estado polimórfico CYP2D6 metabolizador lento PUEDE AFECTAR a las concentraciones plasmáticas de endoxifeno así como a la supervivencia libre de enfermedad en mujeres postmenopáusicas ER+ en tratamiento adyuvante con tamoxifeno 20mg/día durante 5 años.



J Natl Cancer Inst. 2005 Jan 5;97(1):30-9





J Clin Oncol. 2011 Aug 20;29(24):3232-9.

The Pharmacogenomics Journal. 2013. 13, 1–11

J Natl Cancer Inst. 2012. *104:452–460*

J Natl Cancer Inst. 2012. *104:441–451*

• ¿ Sirve para evitar Reacciones Adversas ?

AZATIOPRINA/ 6-MP

		Number		Frequency		
		Subjects	Alleles	*1	*3A	*3C
Mayo Study	Caucasican	271	542	0.958	0.037	0.006
	Chinese	253	506	0.982	0	0.018
Aberdeen Study*	Caucasican	199	398	0.952	0.045	0.003
	Chinese	192	384	0.977	0	0.023

*Collie-Dugid et al., Pharmacogenetics 9:37-42, 1999

Algoritmo de decisión: Test pre-tratamiento

- TPMT*2, *3A, *3C: Disminución de dosis/ retirada de medicación

Table 2 Recommended dosing of thiopurines by thiopurine methyltransferase phenotype

	MP			Azathioprine		TG		
Phenotype	Implications for MP and azathioprine pharmacologic measures	Dosing recommendations for MP	Classification of recommendations[a]	Dosing recommendations for azathioprine	Classification of recommendations[a]	Implications for pharmacologic measures after TG	Dosing recommendations for TG	Classification of recommendations[a]
Homozygous wild-type or normal, high activity	Lower concentrations of TGN metabolites, higher methylTIMP, this is the "normal" pattern	Start with normal starting dose (e.g., 75 mg/m^2/d or 1.5 mg/kg/d) and adjust doses of MP (and of any other myelosuppressive therapy) without any special emphasis on MP compared to other agents. Allow 2 weeks to reach steady state after each dose adjustment.[4,25,29]	Strong	Start with normal starting dose (e.g., 2–3 mg/kg/d) and adjust doses of azathioprine based on disease-specific guidelines. Allow 2 weeks to reach steady state after each dose adjustment.[4,27,29]	Strong	Lower concentrations of TGN metabolites, but note that TGN after TG are 5–10× higher than TGN after MP or azathioprine	Start with normal starting dose. Adjust doses of TG and of other myelosuppressive therapy without any special emphasis on TG. Allow 2 weeks to reach steady state after each dose adjustment.[4,16]	Strong
Heterozygote or intermediate activity	Moderate to high concentrations of TGN metabolites; low concentrations of methylTIMP	Start with reduced doses (start at 30–70% of full dose e.g., at 50 mg/m^2/d or 0.75 mg/kg/d) and adjust doses of MP based on degree of myelosuppression and disease-specific guidelines. Allow 2–4 weeks to reach steady state after each dose adjustment. In those who require a dosage reduction based on myelosuppression, the median dose may be ~40% lower (44 mg/m^2) than that tolerated in wild-type patients (75 mg/	Strong	If disease treatment normally starts at the "full dose", consider starting at 30–70% of target dose (e.g., 1–1.5 mg/kg/d), and titrate based on tolerance. Allow 2–4 weeks to reach steady state after each dose adjustment.[4,27,29,31]	Strong	Moderate to high concentrations of TGN metabolites; but note that TGN after TG are 5–10× higher than TGN after MP or azathioprine	Start with reduced doses (reduce by 30–50%) and adjust doses of TG based on degree of myelosuppression and disease-specific guidelines. Allow 2–4 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, and depending on other therapy, emphasis should be	Moderate

• ¿ Sirve para evitar Reacciones Adversas ?

5-Fluoracilo/ capecitabina

- **Más de 40 variaciones diferentes en DPYD dan lugar a la deficiencia de DPD.**

- Las más frecuentes son IVS14+1 G>A, D949V, y I560S

- ***Variaciones en TYMS***
  - **2R/2R**
  - **2R/3R**
  - **3R/3R**
  - **4R**

DPYD – 5%

TYMS – 15-20%

Algoritmo de decisión: Test pre-tratamiento

- Variaciones DPYD + variaciones TYMS: Disminución de dosis al 50% o retirada

Table 2 Recommended dosing of fluoropyrimidines by DPD phenotype

Phenotype (genotype)	Implications for phenotypic measures	Dosing recommendations	Classification of recommendations[a]
Homozygous for wild-type allele, or normal, high DPD activity	Normal DPD activity and "normal" risk for fluoropyrimidine toxicity	Use label-recommended dosage and administration	Moderate
Heterozygous, or intermediate activity	Decreased DPD activity (leukocyte DPD activity at 30–70% that of the normal population) and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs	Start with at least a 50% reduction in starting dose, followed by titration of dose based on toxicity[b] or pharmacokinetic test (if available)	Moderate
Homozygous, or deficient activity	Complete DPD deficiency and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs	Select alternative drug	Strong

Clin Pharmacol Ther. 2013 Dec;94(6):640-5.

***Mol Cancer Ther* 2006. 5(11): 289-291.**

***Pharmacogenomics J* 2001.1(1): 65-70.**

***Mol Cancer Ther* 2006. 5(11): 289-291.**

- ¿ Sirve para ajustar las dosis de los medicamentos ?
- ¿ Sirve para evitar Reacciones Adversas ?

Table 1 GWAS pharmacogenomics responses

	Drug	Response	Cases	Gene	Genotype OR (95% CI)	Genome-wide significance/ replication	Reference
Efficacy	Metformin	Glycemic response	3,960	*ATM*	1.35 (1.22–1.49)	Yes/Yes	30
	Interferon α (Pegasys)	Sustained hepatitis C genotype 1 viral response	1,137; 142; 293; 1,015	*IL28B*	37.7 (16.7–83.9)	Yes/Yes	13–16
	Clopidogrel (Plavix)	Anti-platelet responsiveness	429	*CYP2C19*	2.42 (1.18–4.99)	Yes/Yes	21
	Warfarin (Coumadin)	Maintenance dose	181; 1,053	*VKORC1CYP2C9CYP4F2*	1.11 (1.00–1.22)	Yes/Yes	65,66
	Glucocorticoids	Response to glucocorticoid therapy in asthma	935 418	*GLCC11T*	2.36 (1.27–4.41)	No	31,32
	Thiazide	Diastolic blood pressure change	389	*12q15 region*	–	Yes/No	67
	Candesartan (Atacand)	Diastolic blood pressure change	198	*FUT4*	–	No	68
	Dabigatran (Pradaxa)	Bleeding	1,490	*CES1*	0.67 (0.55–0.82)	No	69
ADR	Simvastatin (Zocor)	Skeletal myopathy	85	*SLCO1B1*	17.4 (4.8–62.9)	Yes/Yes	45
	Ximelagatran	Hepatotoxicity	74; 10	*HLA-DRB1*0701 HLA-DQA1*0201*	4.4 (2.2–8.9) 4.4 (2.2–8.1)	No	70
	Flucloxacillin (Floxapen)	Hepatotoxicity	51	*HLA-B*5701*	80.6 (22.8–284.9)	Yes/Yes	40
	Lumiracoxib (Prexige)	Hepatotoxicity	41 51	*HLA-DRB1*1501 HLA-DQB1*0602*	7.5 (5.0–11.3)	Yes/Yes	
	Amoxicillin-clavulanate (Augmentin)	Hepatotoxicity	201	*HLA-DRB1*1501 HLA-DQB1*0602*	2.8 (2.1–3.8)	Yes/Yes	41
	Carbamazepine (Tegretol)	SJS	12; 53	*HLA-A*3103*	25.93 (4.93–116.18)	Yes/Yes	71,72
	Interferon α2b/ribavirin	Hemolytic anemia	988	*ITPA*	–	Yes/Yes	73
	Methotrexate (Trexall)	Drug clearance and toxicity in pediatric leukemia patients	434	*SLCO1B1*	16.4 (8.7–26.7)	Yes/Yes	74

SJS, Stevens–Johnson syndrome.

Proyecto 1000 genomas

nature International weekly journal of science

Search Go

Advanced search

Home | News & Comment | Research | Careers & Jobs | Current Issue | Archive | Audio & Video | For Authors

Archive > Volume 526 > Issue 7571 > Articles > Article

NATURE | ARTICLE OPEN

日本語要約

An integrated map of structural variation in 2,504 human genomes

Peter H. Sudmant, Tobias Rausch, Eugene J. Gardner, Robert E. Handsaker, Alexej Abyzov, John Huddleston, Yan Zhang, Kai Ye, Goo Jun, Markus Hsi-Yang Fritz, Miriam K. Konkel, Ankit Malhotra, Adrian M. Stütz, Xinghua Shi, Francesco Paolo Casale, Jieming Chen, Fereydoun Hormozdiari, Gargi Dayama, Ken Chen, Maika Malig, Mark J. P. Chaisson, Klaudia Walter, Sascha Meiers, Seva Kashin, Erik Garrison + *et al.*

Affiliations | Contributions | Corresponding authors

Nature **526**, 75–81 (01 October 2015) | doi:10.1038/nature15394

Received 19 February 2015 | Accepted 20 August 2015 | Published online 30 September 2015

PDF | Citation | Reprints | Rights & permissions | Article metrics

Editor's summary العربية

The Structural Variation Analysis Group of The 1000 Genomes Project reports an integrated structural variation map based on discovery and genotyping of eight major structural variation classes in geno…

Associated links

News & Views
Human genomics: The end of the start for population sequencing
by Birney and Soranzo

Article
A global reference for human genetic variation
by Auton *et al.*

Related audio

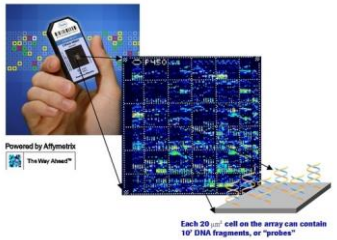
Adam Levy investigates the huge progress made in the 25 years since Human Genome Project began.

00:00

FARMACOGENÉTICA CLÍNICA PREVENTIVA

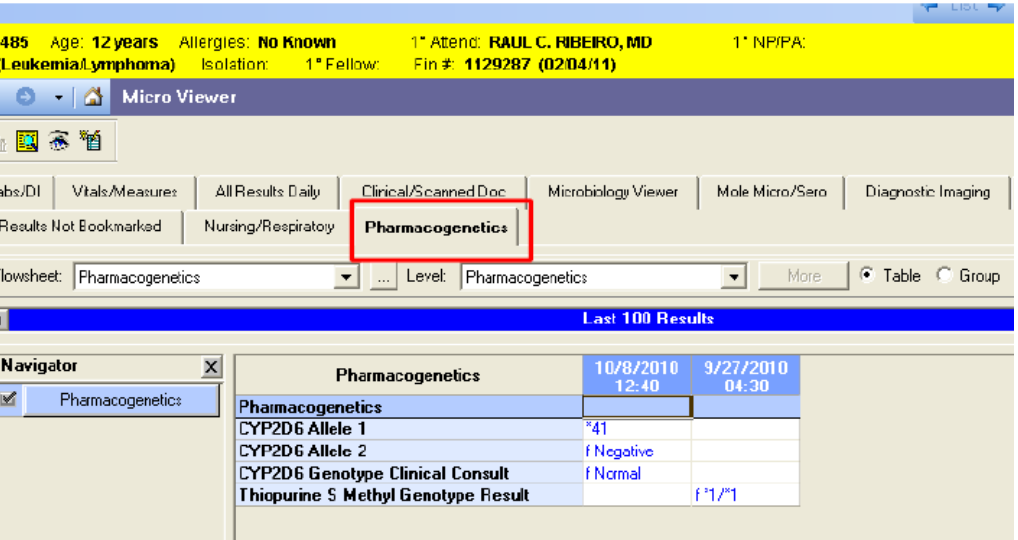
- eMERGE-PGx project (9000 individuos)
- 1200 Patients Project
- Translational Pharmacogenetic Program (TPP) 1500 individuos

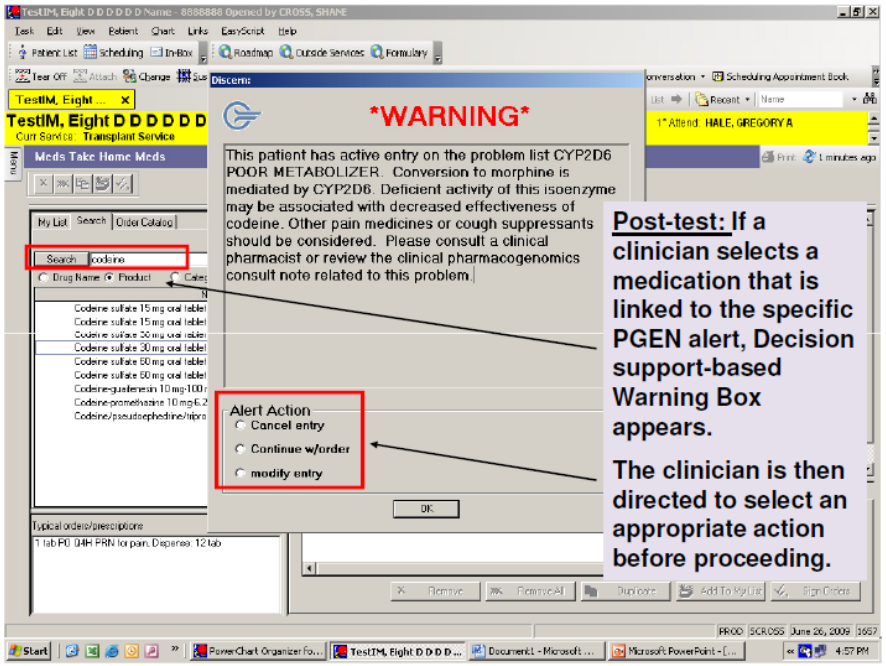
Institution (reference)	Genotyping platform	Number of genes assayed
Mayo Clinic (43)	PGRNseq	84
Mount Sinai Medical Center (42)	Sequenom iPLEX ADME PGx	36
St. Jude Children's Research Hospital (65)	Affymetrix DMET Plus Array	230
University of Florida and Shands Hospital (35)	Life Technologies Quant Studio Open Array	120
Vanderbilt University Medical Center (69)	VeraCode ADME Core Panel	34



Barriers	Solutions
• PGx test availability • Delay in obtaining results	• All relevant PGx variants • Preemptive CLIA genotyping
• Lack of physician knowledge • Physician concerns regarding interpretation, translation	• Creation of an interactive consultation portal • Instantaneous availability of patient-specific results • Delivered as individualized PGx summaries
• Clinical relevance of current PGx evidence	• Relevance determined by patient-specific/setting-specific physician assessment of utility
• Cost	• Comprehensive, preemptive approach reduces marginal cost

Pharmacogenetics tab added to EMR; all clinically eligible genotypes are entered with a gene-specific consult





Post-test: If a clinician selects a medication that is linked to the specific PGEN alert, Decision support-based Warning Box appears.

The clinician is then directed to select an appropriate action before proceeding.

• ¿ Sirve para seleccionar el tratamiento óptimo?

LOS BIOMARCADORES GENÉTICOS DE EFICACIA MÁS DESARROLLADOS PERTENECEN AL TRATAMIENTO DEL CÁNCER

VARIANTES GENÓMICAS ADQUIRIDAS O SOMÁTICAS

Fármaco	Gen	Fenotipo	Nivel de evidencia
Cetuximab/ Panitumumab	KRAS/ NRAS/ BRAF/ EGFR/ HER2 …….	Eficacia	1A
Crizotinib/ Ceritinib	EML4-ALK; ROS1	Eficacia	1A
Erlotinib/ Gefitinib/ Afatinib	EGFR…….	Eficacia	1A
Imatinib	ABL1, BCR, FIP1L1, KIT, PDGFRB	Eficacia	1A
Dasatinib	ABL1, BCR	Eficacia	1A
Nilotinib	UGT1A1	Toxicidad/eficacia	3
trastuzumab, pertuzumab y lapatinib	HER2	Eficacia	1A
Vemurafenib, Dabrafenib , Trametinib	BRAF	Eficacia	1A
Anastrozol/ exemestano/ everolimus	ESR1/ PGR	Eficacia	1A
Cisplatino	TPMT/ COMP	Toxicidad	3
Abiraterona/ Enzalutamida	Variante 7 del receptor de andrógeno	Eficacia	2

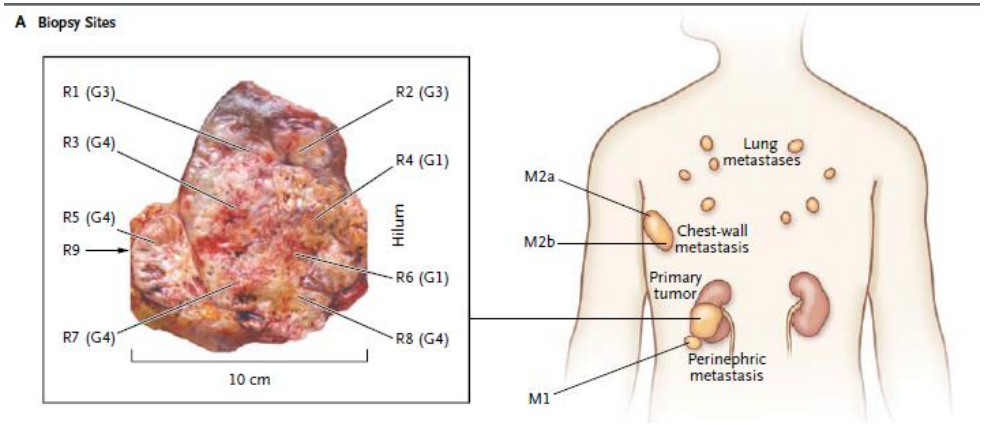
• ¿ Sirve para seleccionar el tratamiento óptimo?

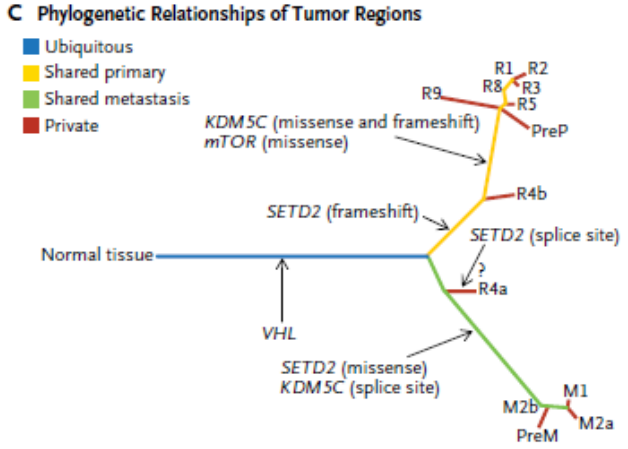
LOS TUMORES EVOLUCIONAN Y MODIFICAN SU ESTRUCTURA GENÉTICA

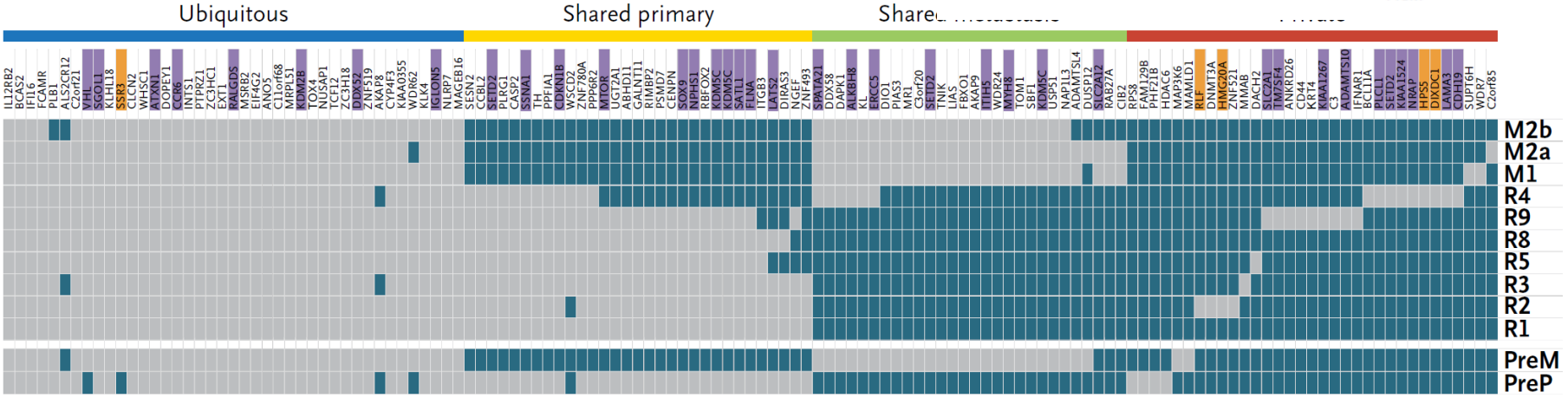
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 8, 2012 VOL. 366 NO. 10

Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing





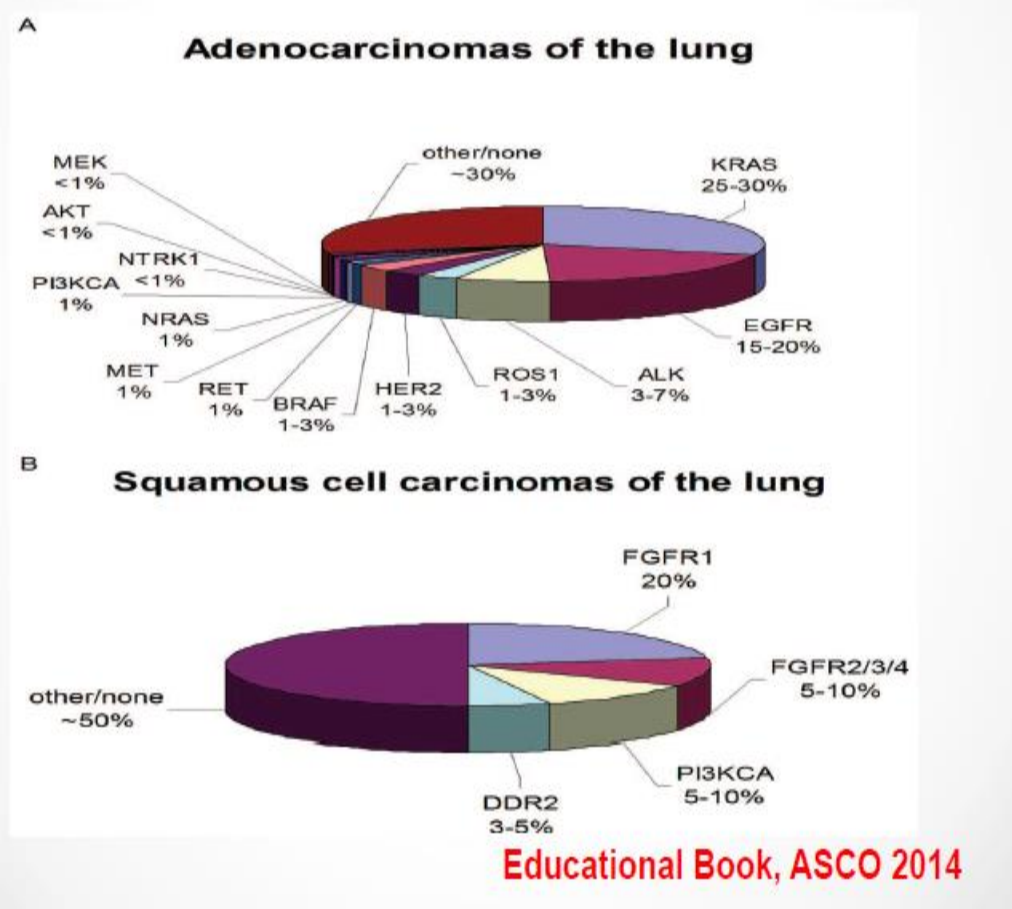


• ¿ Sirve para seleccionar el tratamiento óptimo?

¿ TODAS LAS MUTACIONES SON IGUALES ?

¿ BIOPSIA ÚNICA ?

ANORMALIDADES MOLECULARES EN EL CANCER DE PULMÓN NO MICROCÍTICO

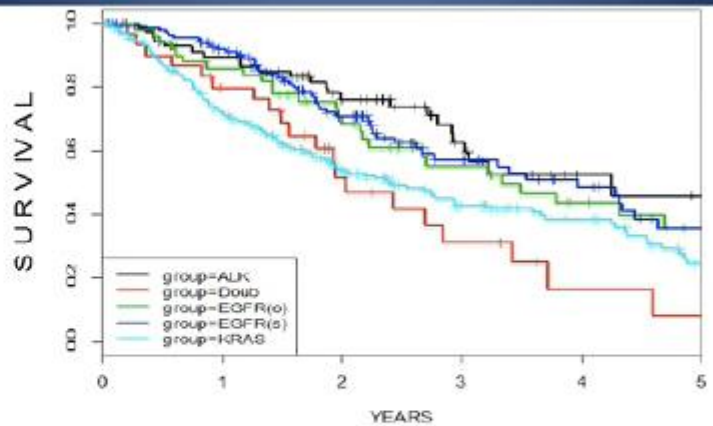


Therapies Matched to Oncogenic Drivers
Lung Cancer Mutation Consortium (LCMC)

Survival of Patients with Drivers: Targeted Therapy vs No Targeted Therapy

Group	N	Median Survival (95% CI)
Driver, no targeted therapy (A)	313	2.4 years (1.8 to 2.9)
No driver (B)	361	2.1 years (1.8 to 2.5)
Driver, targeted therapy (C)	264	3.5 years (3.2 to 4.6)

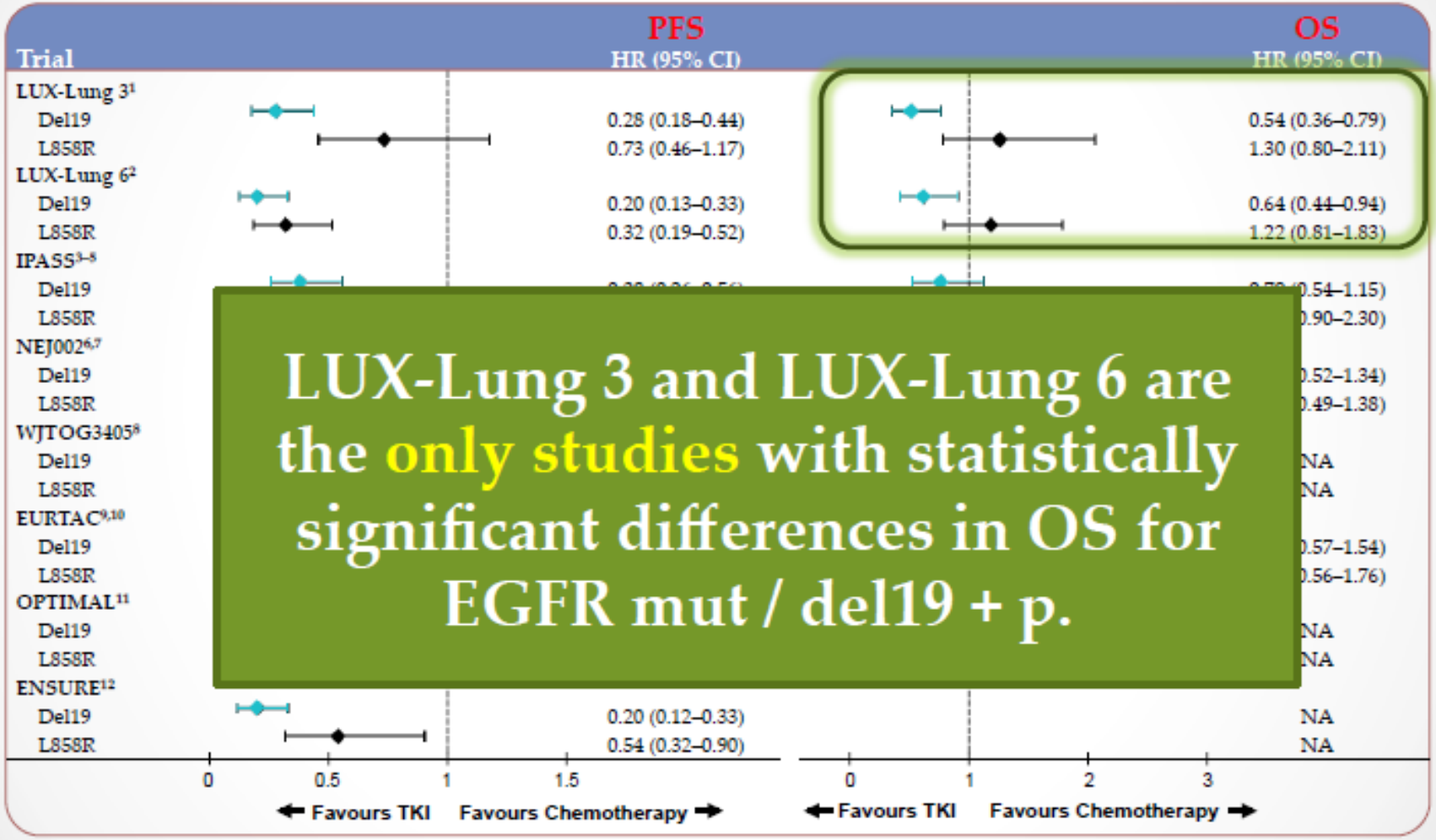
Survival with the five most frequent oncogenic drivers (n=526)



Altered Gene	N	Median Survival (95% CI)
EGFR (sensitizing)	140	4.0 years (2.7 to 5.4)
EGFR (other)	50	3.3 years (2.2 to 6.2)
ALK	73	4.3 years (3.0 to NA)
KRAS	231	2.4 years (1.9 to 3.6)
Two Drivers	32	2.0 years (1.6 to 4.6)

p=0.001

HRs for PFS and OS in Del19 and L858R



LUX-Lung 3 and LUX-Lung 6 are the only studies with statistically significant differences in OS for EGFR mut / del19 + p.

1. Sequist et al. *J Clin Oncol*. 2013;31:3327; 2. Wu et al. *Lancet Oncol*. 2014;15:213; 3. Mok et al. *N Engl J Med*. 2009;361:947; 4. Fukuoka et al. *J Clin Oncol*. 2011;29:2866; 5. Yang et al. *Eur J of Cancer*. 2011 (suppl1;S633); 6. Maemondo et al. *N Engl J Med*. 2010;362:2380; 7. Inoue et al. *Ann Oncol*. 2013;24:54; 8. Mitsudomi et al. *Lancet Oncol*. 2010;11:121; 9. Rosell et al. *Lancet Oncol*. 2012;13:239; 10. TARCEVA® (erlotinib) prescribing information, 2013; 11. Zhou et al. *Lancet Oncol*. 2011;12:735; 12. Wu et al. *J Thorac Oncol*. 2013;8:suppl 2 (P1.11-021).

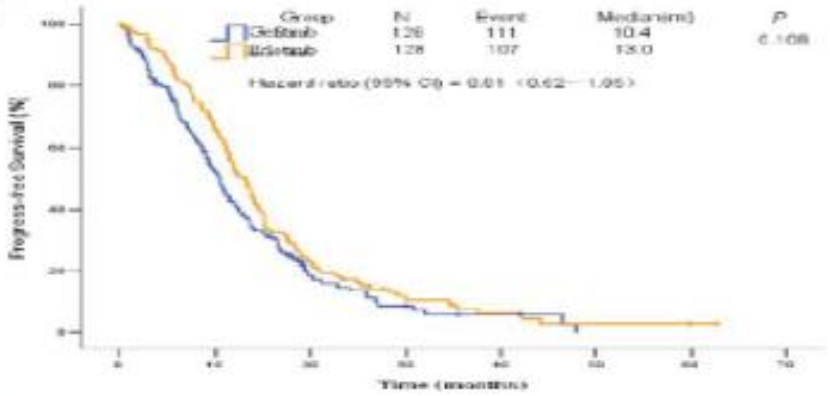
Presented by Yang et al. ASCO 2014. Abstract 8004.

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
16TH WORLD CONFERENCE ON LUNG CANCER
SEPTEMBER 6–9, 2015 — DENVER, COLORADO, USA

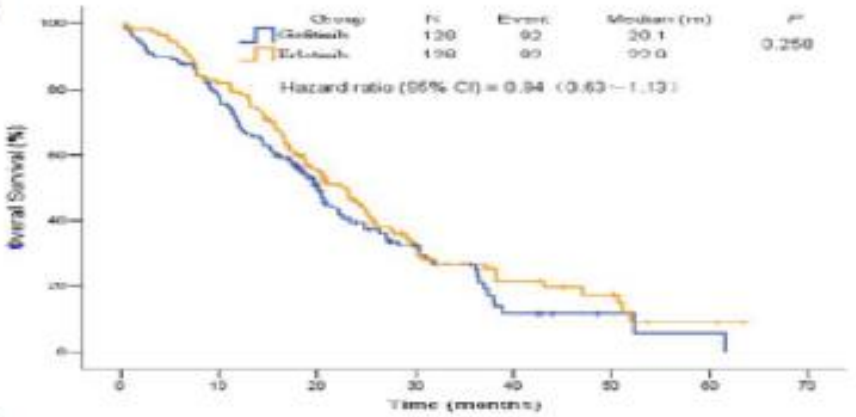
A randomized controlled trial of erlotinib versus gefitinib in advanced non-small-cell lung cancer harboring EGFR exon 19 or 21 mutations (CTONG0901)

Jin-Ji Yang, Qing Zhou, Hong-Hong Yan, Xu-Chao Zhang, Hua-Jun Chen, Hai-Yan Tu, Zhen Wang, Chong-Rui Xu, Jian Su, Yi-Sheng Huang, Bin-Chao Wang, Ben-Yuan Jiang, Xiao-Yan Bai, Wen-Zhao Zhong, Xue-Ning Yang, Yi-Long Wu*.

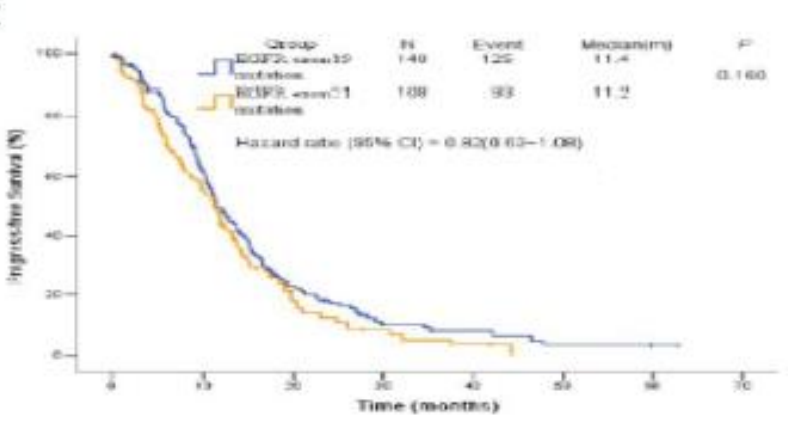
A



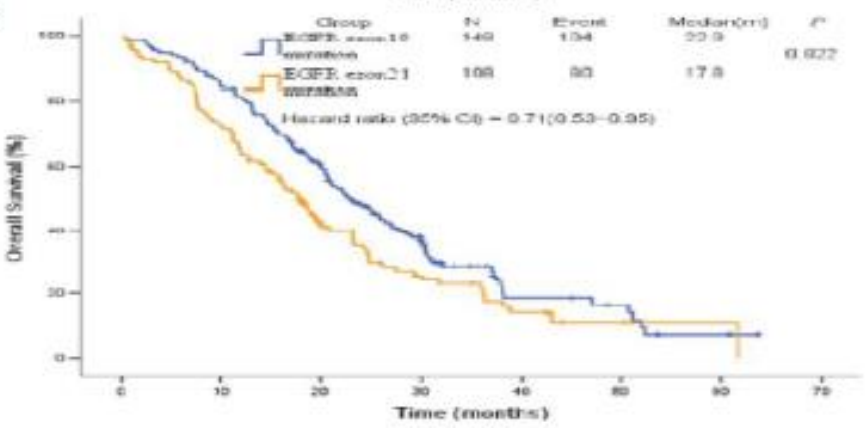
B



C

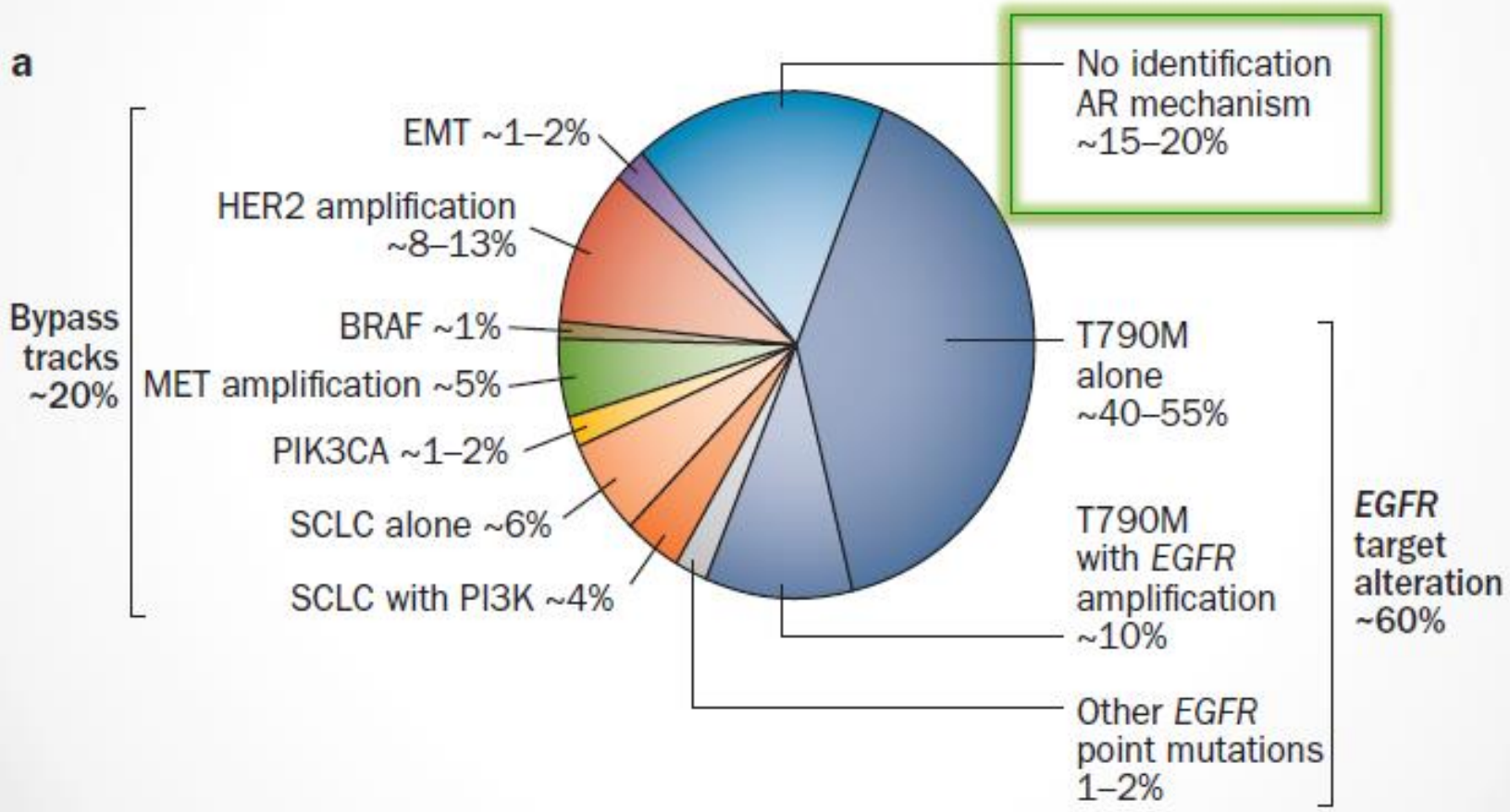


D



Acquired resistance to TKIs in solid tumours: learning from lung cancer

D. Ross Camidge, William Pao and Lecia V. Sequist

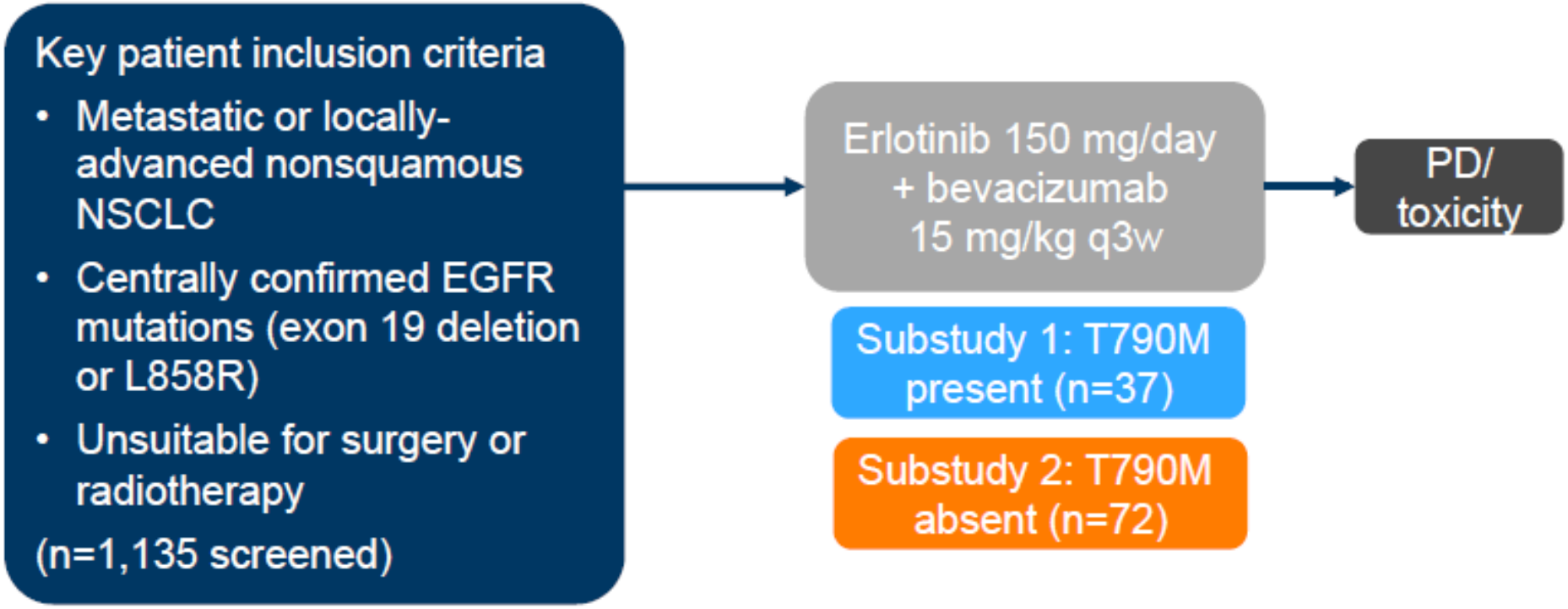


Nat Rev Clin Oncol 2014

3BA: A phase II trial of erlotinib (E) and bevacizumab (B) in patients with advanced non-small-cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations with and without T790M mutation. The Spanish Lung Cancer Group (SLCG) and the European Thoracic Oncology Platform (ETOP) BELIEF trial – Stahel RA et al

Study objective

- To estimate PFS in patients with nonsquamous NSCLC with or without EGFR T790M mutation, treated with first-line bevacizumab and erlotinib



Primary endpoint(s)

- PFS

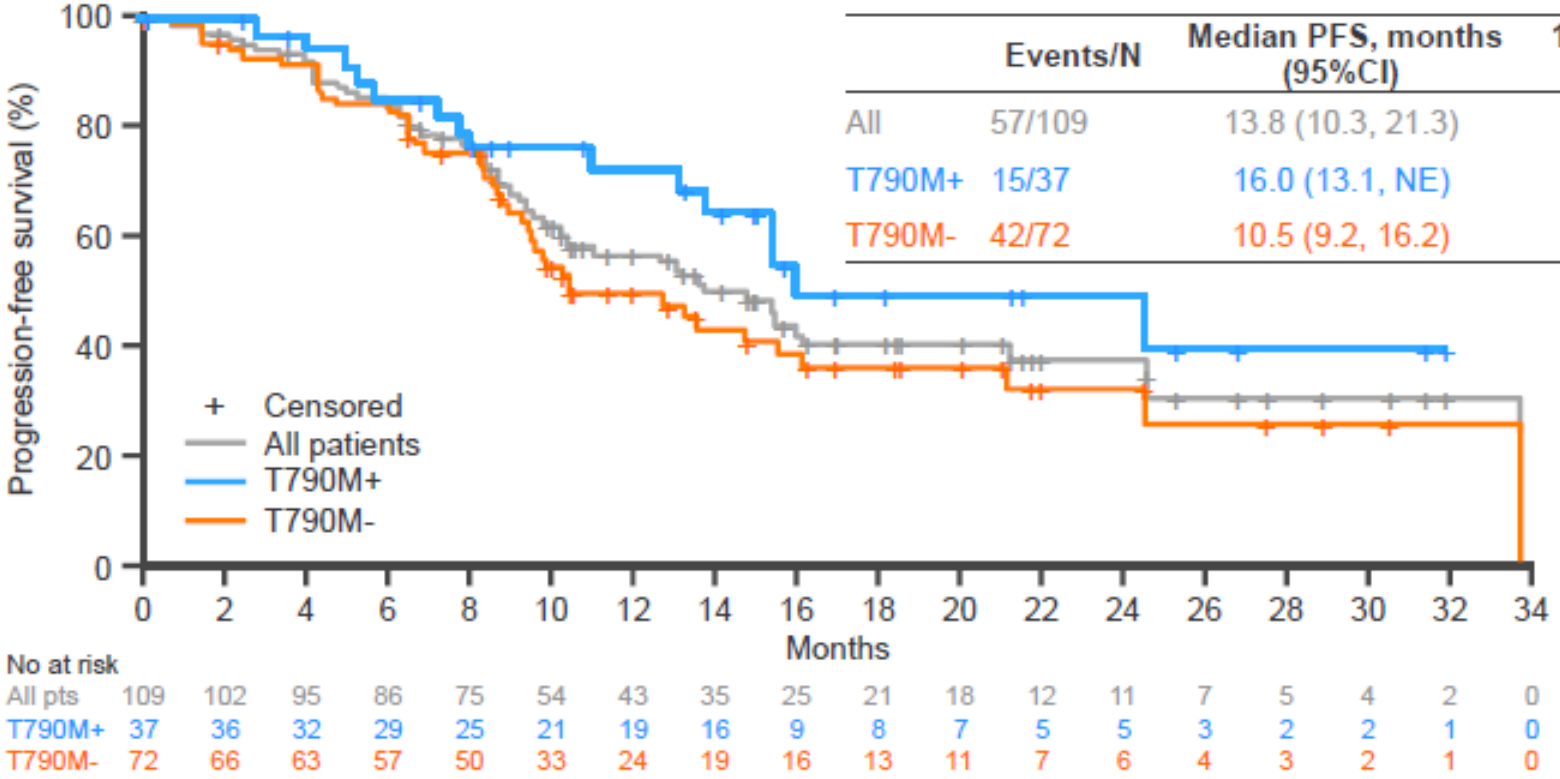
Secondary endpoints

- Safety, correlation of PFS with mutations

Stahel et al. Ann Oncol 2015; 26 (suppl 6): abstr 3BA

3BA: A phase II trial of erlotinib (E) and bevacizumab (B) in patients with advanced non-small-cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations with and without T790M mutation. The Spanish Lung Cancer Group (SLCG) and the European Thoracic Oncology Platform (ETOP) BELIEF trial – Stahel RA et al

- **Key results (cont.)**
  - Erlotinib plus bevacizumab resulted in an overall 1-year PFS of 56.7% and median PFS of 13.8 months compared with 72.4% and 16.0 months, respectively, in T790M+ patients



	Events/N	Median PFS, months (95%CI)	12-month PFS, % (95%CI)
All	57/109	13.8 (10.3, 21.3)	56.7 (46.0, 66.0)
T790M+	15/37	16.0 (13.1, NE)	72.4 (53.4, 84.7)
T790M-	42/72	10.5 (9.2, 16.2)	49.4 (36.6, 61.0)

Stahel et al. Ann Oncol 2015; 26 (suppl 6): abstr 3BA

Targeting T790M resistance

Third-generation EGFR TKIs have been designed to specifically target *EGFR* resistance mutants, including T790M

AZD9291 (phase I)[1,2]

Advanced NSCLC with confirmed radiological PD on prior EGFR TKI

Dose escalation based on safety and PK
(rolling 6 design, with cohort expansion up to n=30)

20mg	40mg	80mg	160mg	240mg
T790M+	T790M+	T790M+	T790M+	T790M+
	T790M–	T790M–	T790M–	

Primary endpoints
Safety and tolerability in EGFR TKI-resistant patients

CO-1686 (phase I/II)[3]

Advanced or metastatic *EGFR* mut+ NSCLC

Previously treated with EGFR TKI

(n=170)

→ Phase I
Dose escalation

→ Phase II*
Expansion in T790M+

Primary endpoints
Incidence of grade 3/4 AEs, PK, ORR and DoR

AE = adverse event; DoR = duration of response
ORR = overall response rate; PK = pharmacokinetics

1. Janne, et al. ASCO 2014; 2. Yang, et al. ESMO 2014
3. Sequist, et al. ASCO 2014

Third-generation TKIs in *EGFR* Mut+ NSCLC

	CO-1686[1]	AZD9291[2]
ORR, %	58% in T790M+ pts	21% in T790M- pts 61% in T790M+ pts
Median PFS	Not reached (current estimate >12 months in T790M+)	2.8 months (T790M-) 9.6 months (T790M+)
Any drug-related AE, %	NR	80
Any drug-related AE grade ≥3, %	NR	13
Most frequent AEs	Hyperglycaemia and IGT (53%), nausea (35%) and diarrhoea (24%)	Diarrhoea (47%), rash* (40%) and nausea (22%)

Studies are ongoing

*Grouped term
NR = not reported; IGT = impaired glucose tolerance
Cross-trial comparison. Data should be interpreted with caution
CO-1686 and AZD9291 are not approved in Malaysia for the treatment of patients with NSCLC

1. Sequist, et al. ASCO 2104; 2. Yang, et al. ESMO 2014

Mechanisms of acquired resistance to AZD9291 in EGFR T790M positive lung cancer

Geoffrey R. Oxnard[1], Kenneth S. Thress[2], Cloud P. Paweletz[1], Daniel Stetson[2], Brian Dougherty[2], Zhongwu Lai[2], Aleksandra Markovets[2], Enriqueta Felip[3], Ana Vivancos[3], Yanan Kuang[1], Lynette Sholl[4], Amanda J. Redig[1], Mireille Cantarini[5], J. Carl Barrett[2], Rathi N. Pillai[6], Byoung Chul Cho[7], David Planchard[8], Jean-Charles Soria[8], Pasi A. Jänne[1]

- **Study objective**
  - To investigate the molecular mechanisms underlying acquired resistance to AZD9291
- **Study design**
  - In patients with T790M-positive lung cancer treated in the AURA trial (phase 1 and 2 components), acquired resistance to AZD9291 was studied using 3 complementary strategies: cell-free DNA (cfDNA) genotyping using droplet digital PCR (ddPCR); next-generation sequencing (NGS) of cfDNA; and molecular analysis of post-AZD9291 disease progression in biopsies
- **Key results**
  - Of 67 patients who met eligibility criteria for resistance, 15 (**22%**) had detectable **C797S** on ddPCR, all **with detectable T790M**
  - C797S was more common with EFGR exon 19 del (13/43 [30%] vs. those with L858R (2/24 [8%]; p=0.06)
  - 32/67 (48%) had **no detectable T790M** in plasma despite the presence of the EGFR-TKI-sensitising mutation, suggesting overgrowth of an **alternate resistance mechanism**
- **Conclusions**
  - At resistance, most patients with resistance to AZD9291 maintain T790M, at times acquiring a new C797S mutation, particularly in those with EGFR exon 19 deletion
  - At progression, loss of T790M may be mediated by outgrowth of a competing resistance mechanism (e.g. **MET or HER2 amplification or BRAF V600E**)

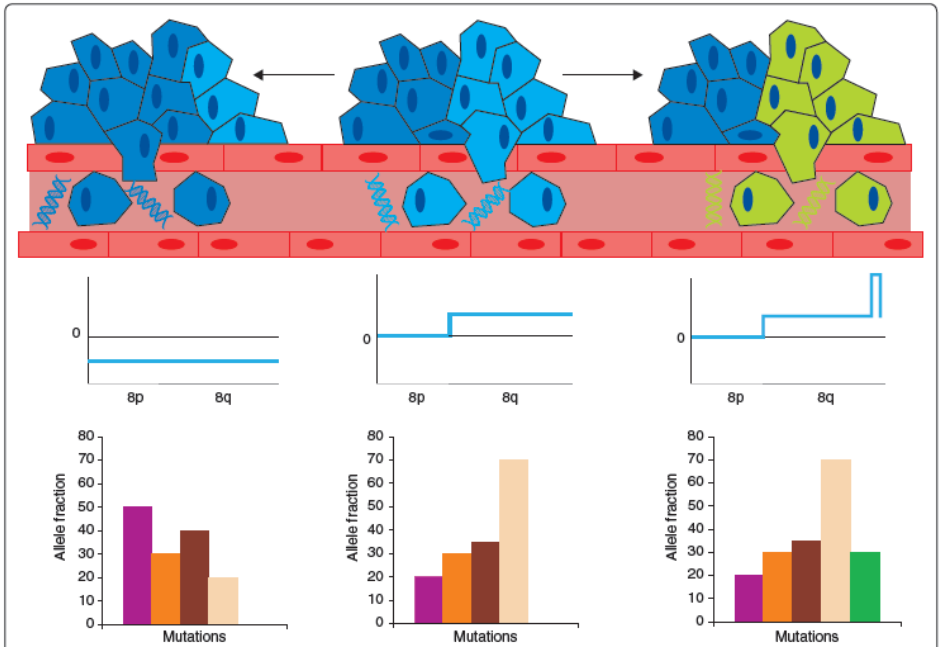
Oxnard et al. J Thorac Oncol 2015; 10 (suppl 2): ORAL17.07

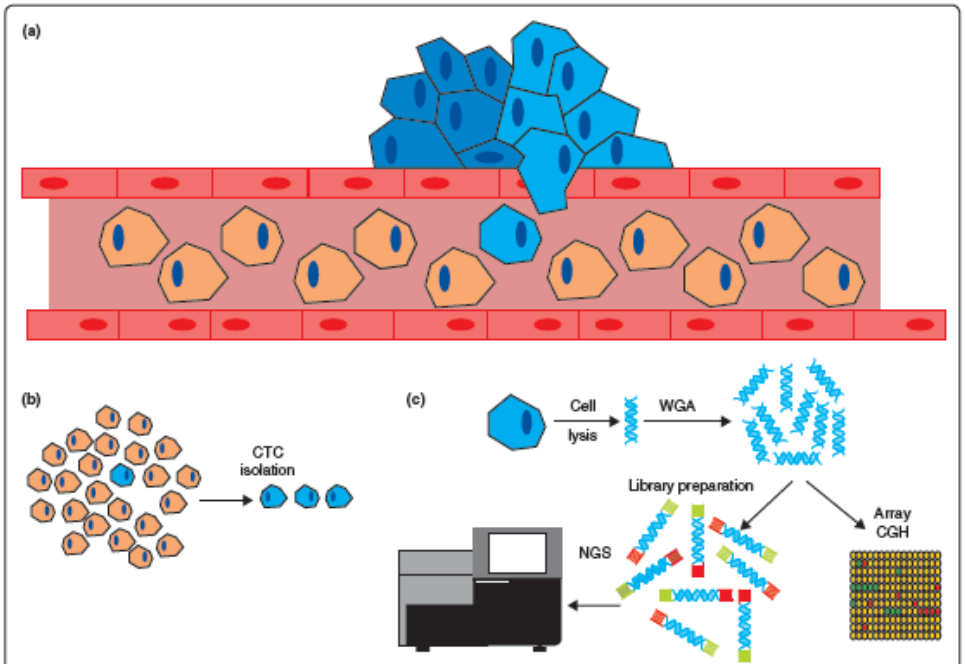
BIOMARCADORES DE EFICACIA

BIOPSIAS LÍQUIDAS

•Las nuevas técnicas mas sensibles van a favorecer la realización de biopsias liquidas de forma mas generalizada.

•La análisis de las CTC o del ctDNA permite la caracterización molecular de la enfermedad y la monitorización de la evolución del tumor a lo largo del tratamiento

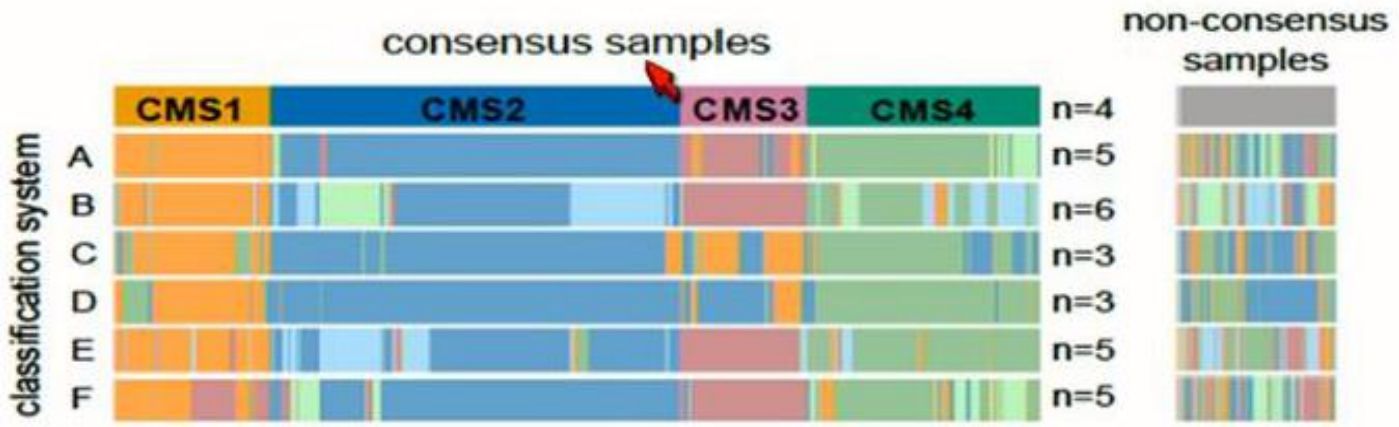


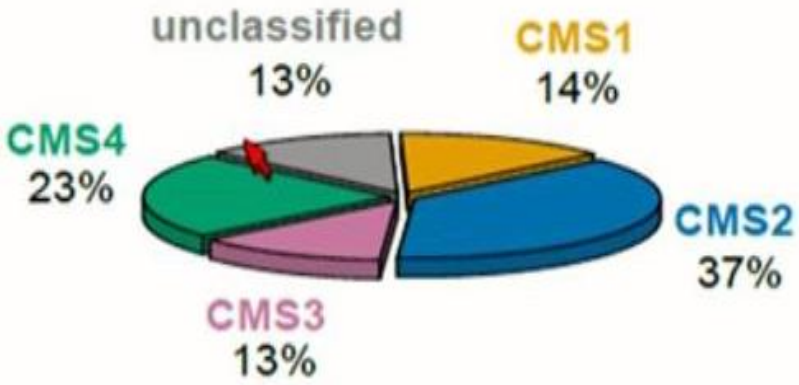


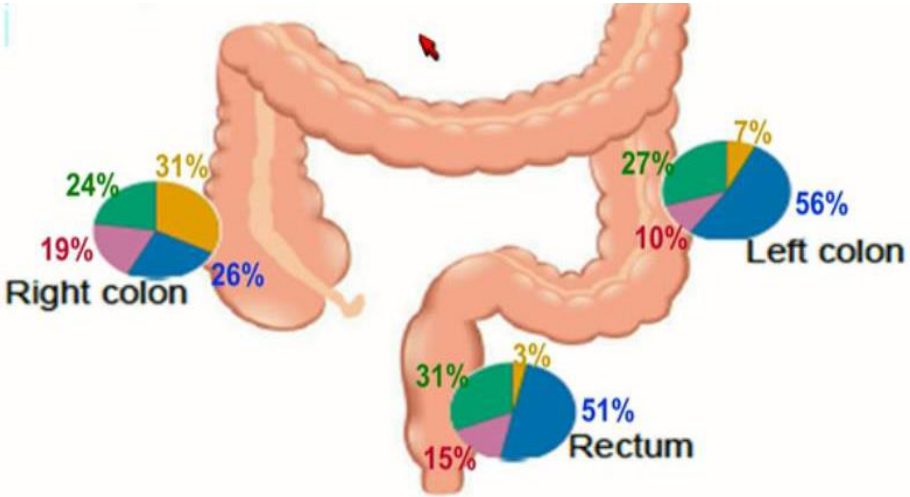
BIOMARCADORES DE EFICACIA: CANCER COLORECTAL

Network of samples

Colorectal Cancer Subtyping Consortium (CRCSC) identification of a consensus of molecular subtypes.

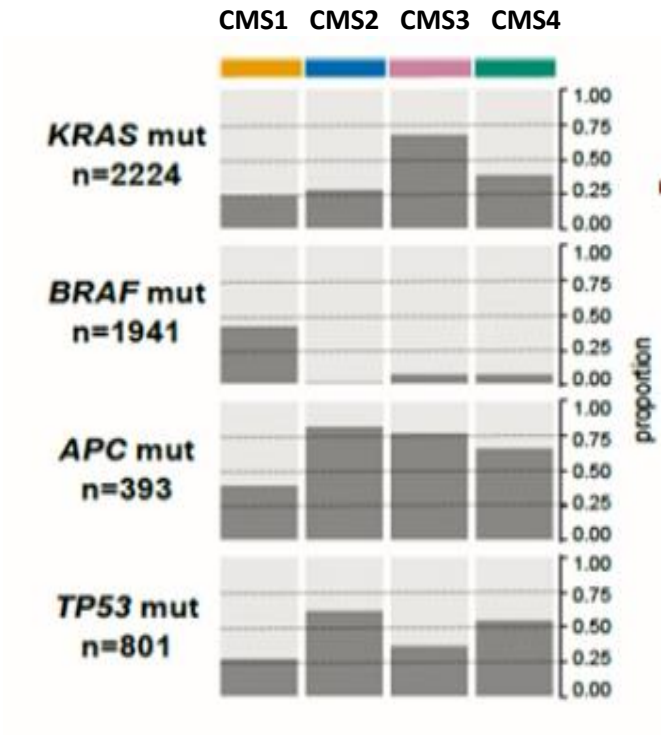




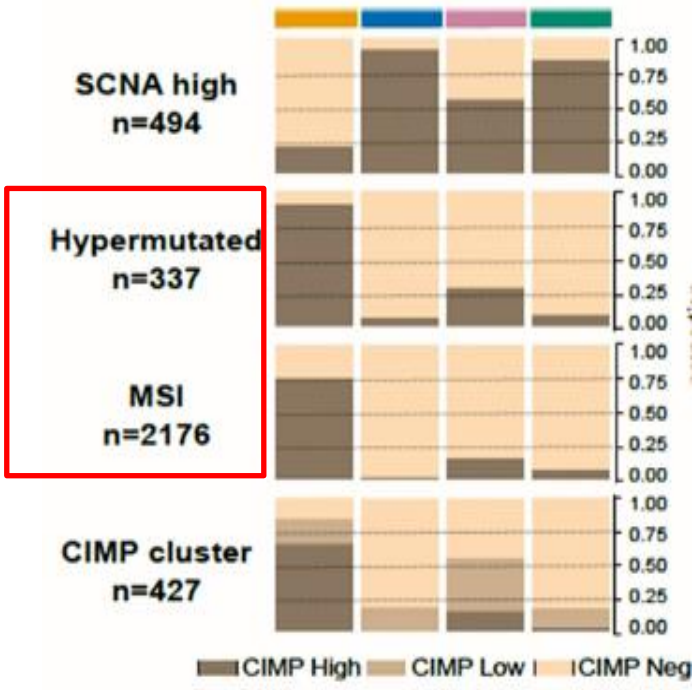


Presented by Sabine Tejpar, at ASCO GI 2015

Molecular associations of CMS groups in CRC



SCNA: Somatic copy number alteration
MSI: Microsatelite inestability



CMS1	14%	MSI, immune pathway activation/expression, right-side tumors, older age at diagnosis, females, hypermutation, *BRAF* mut, intermediate survival
CMS2	41%	High CIN, MSS, strong WNT/MYC pathway activation, left-side tumors, *TP53* mut, *EGFR* amplification/overexpression, better survival
CMS3	8%	Low CIN, moderate WNT/MYC pathway activation, *KRAS* mut, *PIK3CA* mut, IGFBP2 overexpression, intermediate survival
CMS4	20%	CIN/MSI heterogeneous, mesenchymal/TGF-beta activation, younger age at diagnosis, NOTCH3/VEGFR2 overexpression, worse survival

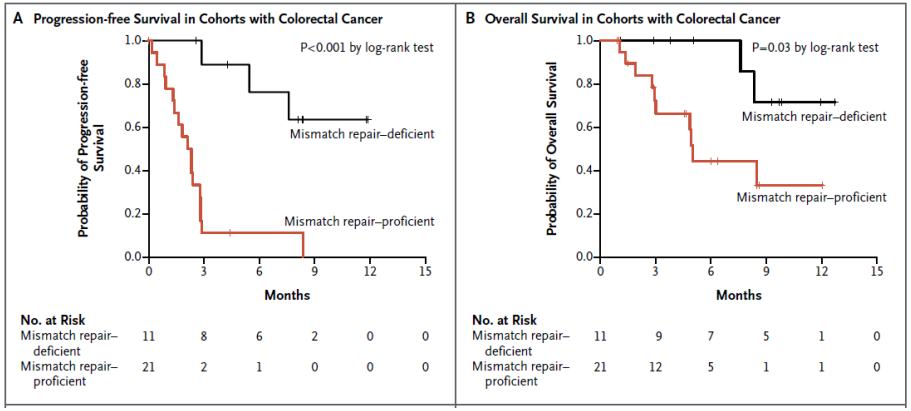
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

1782Mutaciones somáticas por tumor en el grupo reparador deficiente de DNA

73 Mutaciones somáticas por tumor en el grupo reparador efifiente de DNA



NIVOLUMAB, PEMBROLIZUMAB

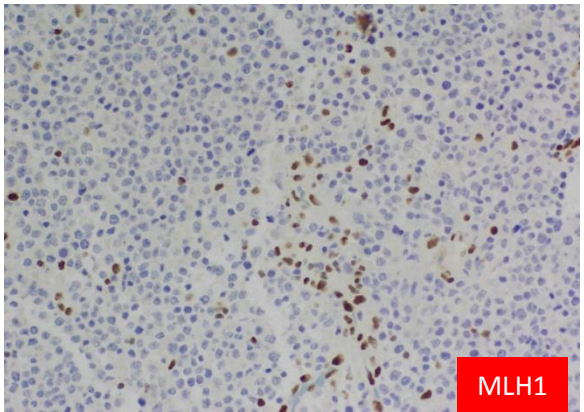
Inestabilidad de microsatélites elevada

Déficit de expresión de genes reparadores del DNA

MLH1, MSH2, MSH6, PMS1, PMS2

Genoma HIpermutado grupo reparador deficiente de DNA

Sindrome de Lynch



CONCLUSIONES

- ¿ SIRVE PARA AJUSTAR LAS DOSIS DE LOS MEDICAMENTOS ? MUCHO CUIDADO ¡¡¡

- ¿ SIRVE PARA EVITAR REACCIONES ADVERSAS ? AJUSTE DE PRIMERA DOSIS Y SOLO PARA CAMBIAR DE TRATAMIENTO EN CASOS DE VARIANTES MONOGÉNICAS

- ¿ SIRVE PARA SELECCIONAR EL TRATAMIENTO ÓPTIMO? SI, PRINCIPALMENTE EN EL CÁNCER