ReFORMÚLaTE

LAS NUEVAS REGLAS DEL JUEGO

"NUEVOS DISEÑOS DE EECC"

Fernando Gutiérrez Nicolás

Farmacéutico Hospitalario

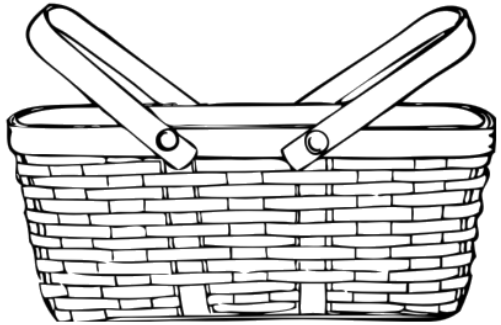
Hospital Universitario de Canarias

¿Porqué esta charla?

Todo cambia…

¿De qué estamos hablando?

Umbrella



Basket

Ajustar el tratamiento en función de una mutación…


E=mc²

67 CONGRESO NACIONAL · 24-26 NOVIEMBRE · BARCELONA 2022

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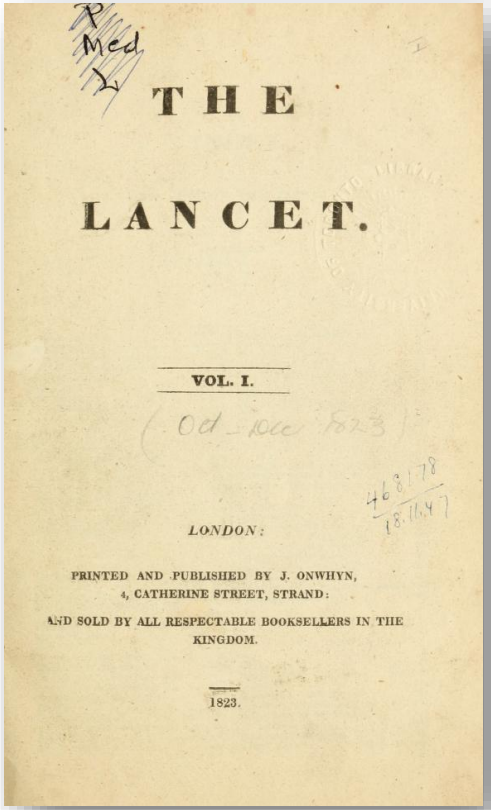

THE

LANCET.

VOL. I.

LONDON:

PRINTED AND PUBLISHED BY J. ONWHYN,
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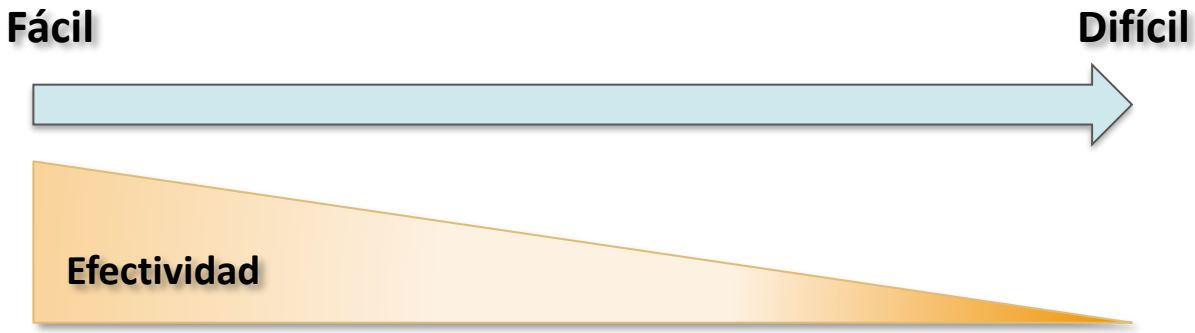
AND SOLD BY ALL RESPECTABLE BOOKSELLERS IN THE KINGDOM.

1823.

Tratar un tumor por su localización anatómica



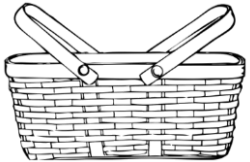
Lógica…

$$\left.\begin{array}{l} A \rightarrow B \\ B \rightarrow C \end{array}\right\} A \rightarrow C$$

¿El cáncer es una enfermedad genética?

SI

Umbrella



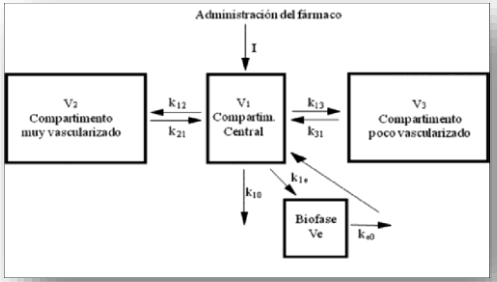
Basket

¿El cáncer es una enfermedad genética?

PK/PD Vd

$t_{1/2}$ Cl

monocompartimental

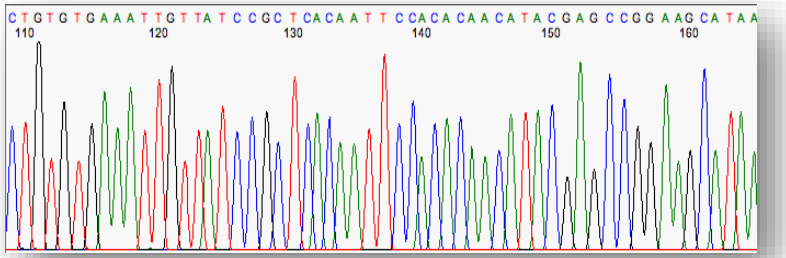


Germinal Recombinación

Somática

Homóloga

Trapping Heteróloga



¿Tengo que saber genética?

depende…

Varon de 36 años que lleva 4 días ingresado en urgencias por neumonía.
Desde el ingreso los neutrófilos han descendido a valores normales y lleva 24 horas sin fiebre. El valor de la PCR se encuentra en descenso desde la última analítica. El paciente presenta ingestas normales.

TA:110/80
Aclaramiento renal de 34 ml/min mantenido
K=3,9 meq/l
Na=142 meq/l
Resto de valores analíticos dentro de la normalidad

Tratamiento prescrito al ingreso

Levofloxacino IV 500mg/24h
Paracetamol IV 1g/8h
Fragmin 5.000 SC/24h
Omeprazol IV 40 mg/24h
1.500 ml de suero fisiológico/24h
Simvastativa 40mg/24h (medicación domiciliaria)

La validación requiere conocimientos:

Microbiología
Hematología
Nefrología
Fisiología

Validar esta prescripción

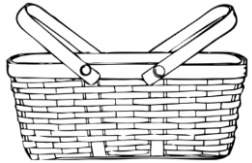
¿Tengo que saber genética?

depende…

Los nuevos EECC requieren conocimientos den BM…

El cáncer es una enfermedad genética

Umbrella



Basket

Lo importante de un tumor no es dónde está sino lo que lo hace tumor…

Mutación driver

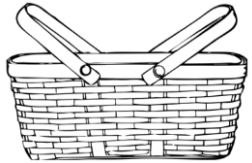
…cuya potencia driver sea decisiva diversos tipos de tumores

Esta situación es una EXCEPCIÓN

Un tumor cuando se diagnostica tiene múltiples potenciales drivers…

El cáncer es una enfermedad genética

Umbrella



Basket

Lo importante de un tumor no es dónde está sino lo que lo hace tumor…

TUMOR AGNÓSTICO

Entender BM….

Mutación driver

“tipos” de mutación

Somática

Germinal

Drug	Gene target	information	
Erlotinib	EGFR	None response Test not required	no tumoral EGFR expression
Cetuximab	EGFR	None response Test required	no tumoral EGFR expression
Panitumumab	EGFR	None response Test required	no tumoral EGFR expression
Trastuzumab	HER2	None response Test required	no tumoral HER2 expression
tamoxifene	ER	None response Test required	no tumoral ER expression
anastrozole	ER	None response Test required	no tumoral ER expression
Exemestane	ER	None response Test required	no tumoral ER expression
Letrozole	ER	None response Test required	no tumoral ER expression
Cetuximab	K-RAS	None response Test required	Tumoral K-RAS mutations
Panitumumab	K-RAS	None response Test required	Tumoral K-RAS mutations
Imatinib	c-Kit	None response Test required	Absence of activating tumoral c-Kit mutations

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DPYD genotype-guided dose individualization to improve patient safety of fluoropyrimidine therapy: call for a drug label update

Efectividad

Seguridad

Entender BM….

El cáncer es una enfermedad genética

Concepto de tumor agnóstico

Mutaciones som y germinales

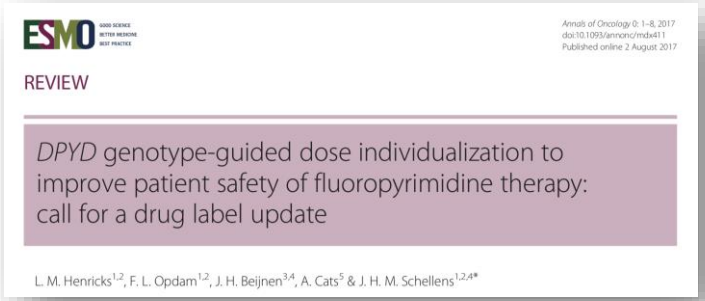
Fácil → Difícil

Efectividad

A → B

B → C

A → C



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doi:10.1093/annonc/mdx411
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REVIEW

DPYD genotype-guided dose individualization to improve patient safety of fluoropyrimidine therapy: call for a drug label update

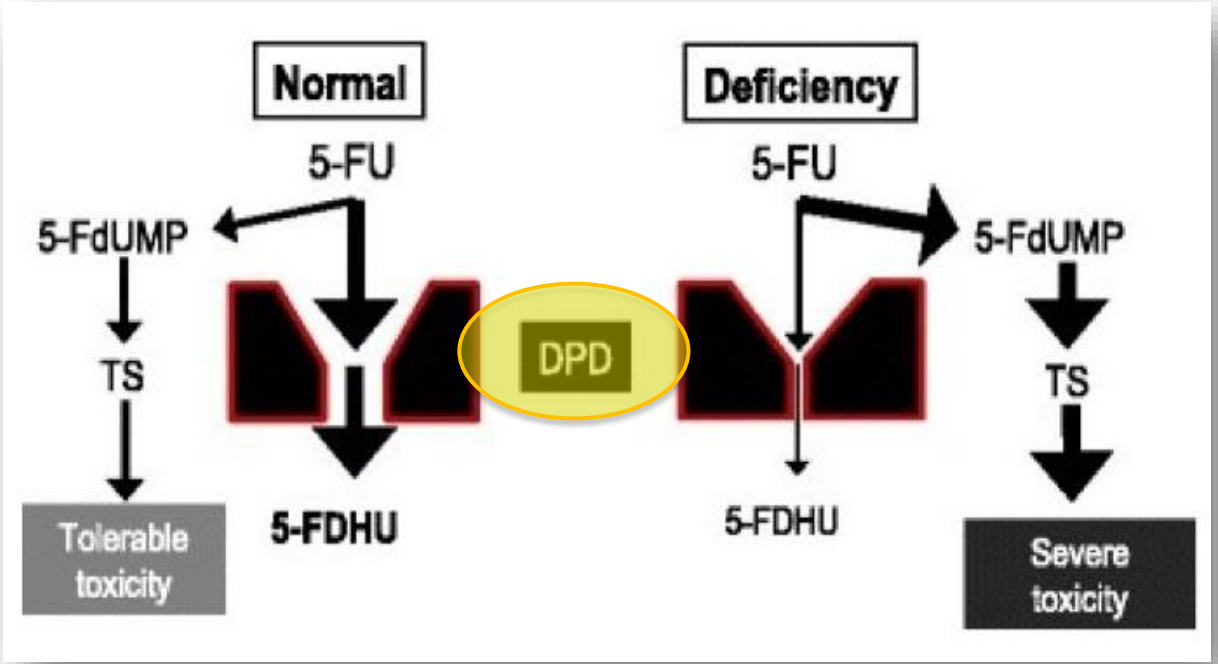
L. M. Henricks[1,2], F. L. Opdam[1,2], J. H. Beijnen[3,4], A. Cats[5] & J. H. M. Schellens[1,2,4*]

DPYD genotype-guided dose individualization to improve patient safety of fluoropyrimidine therapy: call for a drug label update

Table 1. Initial dose recommendations for heterozygous *DPYD* variant allele carriers [29]

***DPYD* variant**	**% of standard fluoropyrimidine dose[a]**
*DPYD**2A (rs3918290)	50
c.1679T>G (rs55886062)	50
c.2846A>T (rs67376798)	75
c.1236G>A/HapB3 (rs56038477)	75

[a]For patients with complete DPD deficiency (for example homozygous *DPYD* variant allele carriers) selection of alternative treatment is recommended.


Normal
5-FU
5-FdUMP
TS
Tolerable toxicity
5-FDHU
DPD
Deficiency
5-FU
5-FdUMP
TS
5-FDHU
Severe toxicity

ESMO
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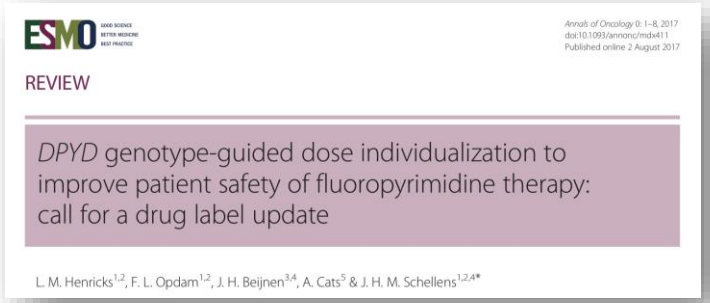
Pharmacogenetics of Capecitabine in Advanced Breast Cancer Patients

Rémy Largillier,[1] Marie-Christine Etienne-Grimaldi,[1] Jean-Louis Formento,[1] Joseph Ciccolini,[2] Jean-François Nebbia,[1] Aurélie Ginot,[1] Mireille Francoual,[1] Nicole Renée,[1] Jean-Marc Ferrero,[1] Cyril Foa,[1] Moise Namer,[1] Bruno Lacarelle,[2] and Gérard Milano[1]

Abstract **Purpose:** Germinal gene polymorphisms can explain a part of the interpatient pharmacodynamic variability of anticancer drugs, particularly fluoropyrimidines. Genes for which polymorphisms may potentially influence pharmacodynamics of fluoropyrimidines, including capecitabine, are *thymidylate synthase* (*TS*), *methylenetetrahydrofolate reductase* (*MTHFR*), and *dihydropyrimidine dehydrogenase* (*DPD*).
Experimental design: The aim of this prospective pilot study was to analyze the effect of *TS, MTHFR*, and *DPD* gene polymorphisms on toxicity and efficacy in advanced breast cancer patients receiving capecitabine as monotherapy. Germinal polymorphisms of TS (6 bp deletion in the 3′ region and 28 bp repeats, including G>C mutation in the 5′ region), MTHFR (677C>T and 1298A>C), and DPD (IVS14 + 1G>A) were determined in 105 consecutive patients.
Results: A trend toward a higher global toxicity grade 3 and 4 was observed in patients homozygous for the TS 3RG allele compared with patients heterozygous for the 3RG allele or patients not carrying the 3RG allele (50% versus 19% versus 13% respectively, $P = 0.064$). The sole patient bearing the DPD IVS14 + 1G>A mutation (heterozygous) deceased from hematologic toxicity. The median response duration was 5.8 months (95% confidence interval, 4.3-7.2). Duration of response was significantly shortened in patients homozygous for the 3RG allele compared with others ($P = 0.037$).
Conclusions: The present data suggest that 3RG3RG breast cancer patients are not good candidates for capecitabine therapy. In addition, attention should be paid to DPD deficiency in breast cancer patients receiving capecitabine. These preliminary data require further confirmation on a larger number of patients.

¿Realizamos el ajuste de dosis en función de la localización?

A nadie se le ocurre en un paciente homocigoto mutado DPyD con CaMama prescribir/validar dosis plenas de capecitabina…



ESMO

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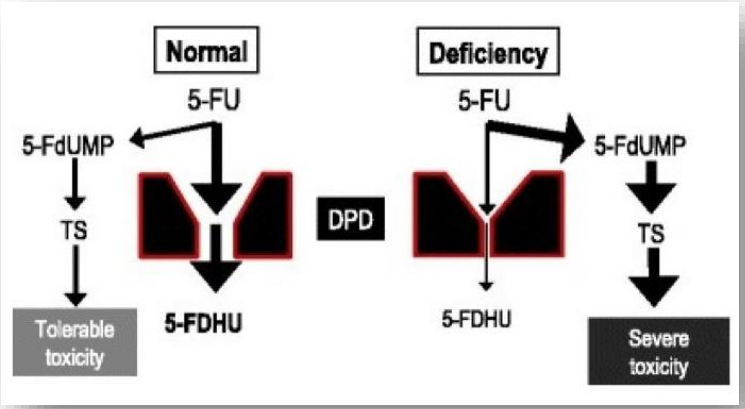

Estamos ajustando un tratamiento en función de una mutación…

Tratar un tumor por su

localización anatómica

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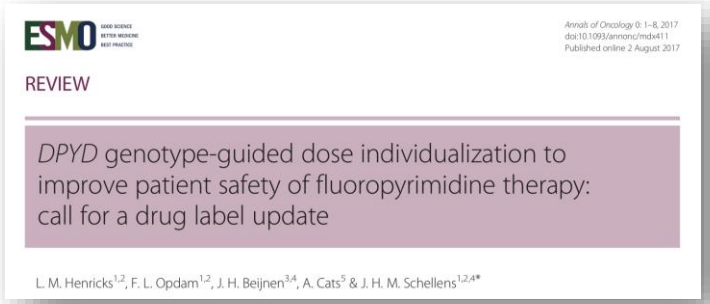
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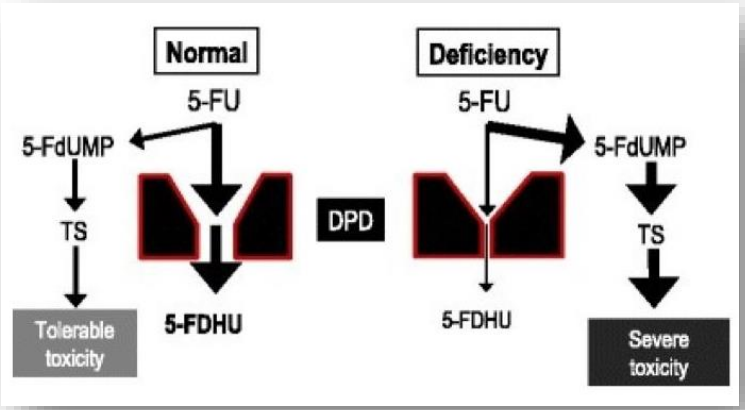

Estamos ajustando un tratamiento en función de una mutación…

De otra forma sería imposible…

El cambio es difícil

NO!!!

Ese ajuste está demostrado en colon pero no en gástrico…

Y se requiere de una demostración por patología…

Trastuzumab in combination with chemotherapy versus
HER2-positive
al junction cancer
ised controlled trial

waki, Florian Lordick, Atsushi Ohtsu, Yasushi Omuro,
-Koo Kang, for the ToGA Trial Investigators†

20 %

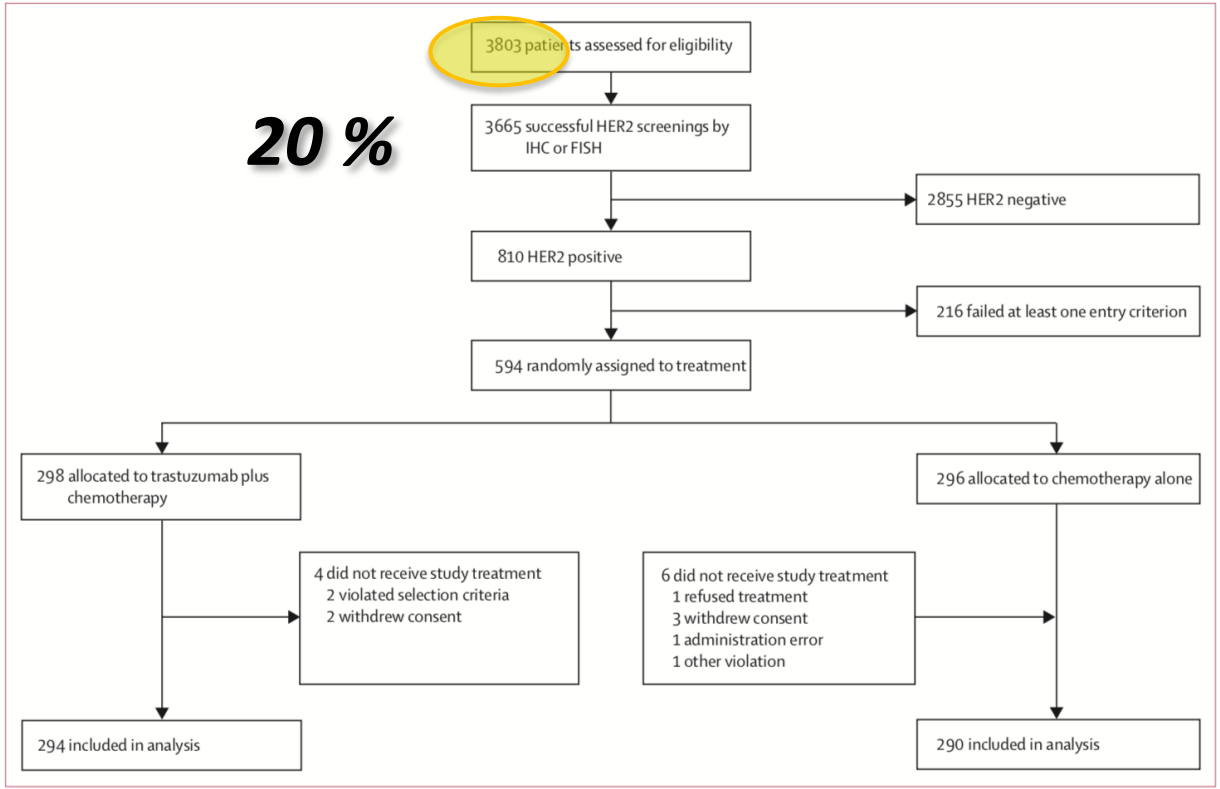

Figure 1: **Trial profile**
HER2=human epidermal growth factor receptor 2 (also known as ERBB2). IHC=immunohistochemistry. FISH=fluorescence in-situ hybridisation.

Si aplicamos el desarrollo clásico…

95.000 pacientes

20 %

0,8 %

Trastuzumab in combination with chemotherapy versus
HER2-positive
al junction cancer
ised controlled trial

waki, Florian Lordick, Atsushi Ohtsu, Yasushi Omuro,
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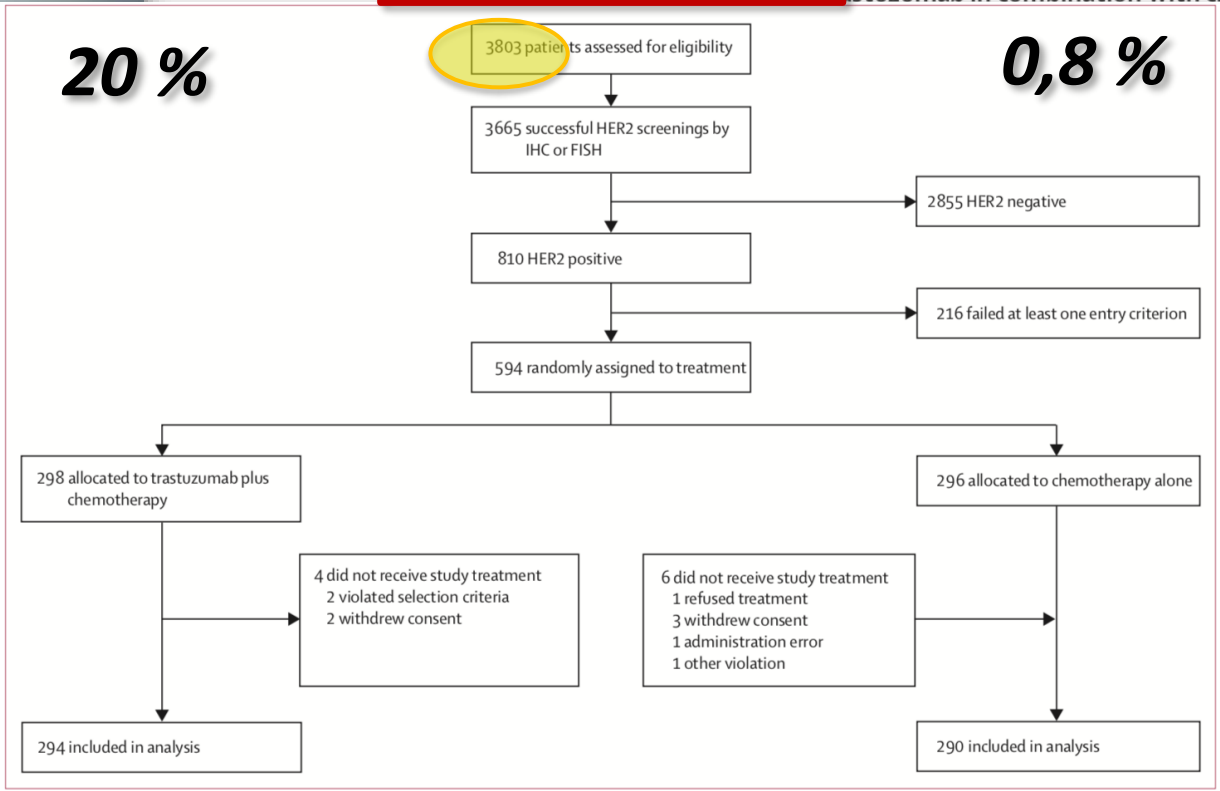
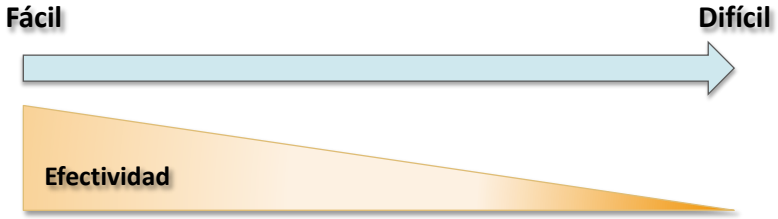
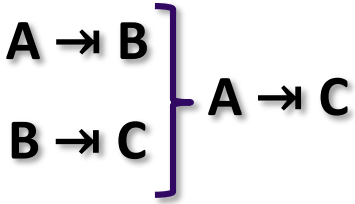


Figure 1: **Trial profile**
HER2=human epidermal growth factor receptor 2 (also known as ERBB2). IHC=immunohistochemistry. FISH=fluorescence in-situ hybridisation.

¿Tiene sentido reclutar 95.000 pacientes para analizar la conveniencia de ajuste de DPyD en gástrico?





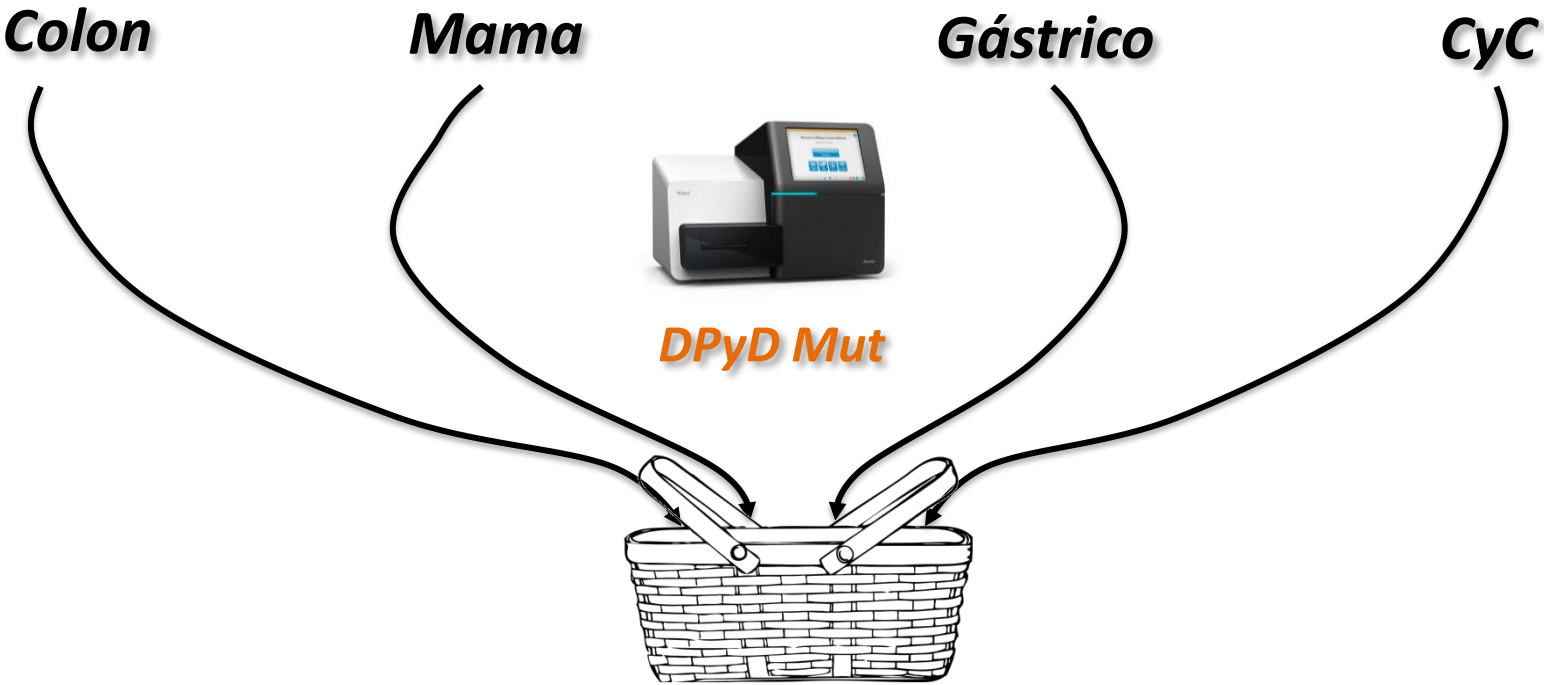
Assessment of feasibility for tumour-specific RCTs in NTRK+ cancers

	Minimum sample size	Time to study results (years)	Feasible?
Colorectal cancer	215	55	✗
MASC	207	31	✗
Papillary thyroid	255	87	✗
Anaplastic thyroid	206	104	✗
Squamous NSCLC	206	104	✗
Non-squamous NSCLC	206	27	✗
Pancreatic cancer	206	70	✗
Sarcoma	209	17	✗
Neuroendocrine	222	76	✗
Secretory breast cancer	207	53	✗
Non-secretory breast cancer	207	105	✗

MASC: Mammary analogue secretory carcinoma; NSCLC: non-small cell lung cancer.

An Overview of Precision Oncology Basket and Umbrella Trials for Clinicians

Jay J. H. Park, MSc[1]; Grace Hsu, MSc[2]; Ellie G. Siden, MD[1]; Kristian Thorlund, PhD[2,3]; Edward J. Mills, FRCP(Edin)[2,3]



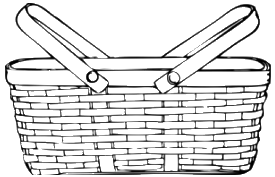
An Overview of Precision Oncology Basket and Umbrella Trials for Clinicians

Jay J. H. Park, MSc[1]; Grace Hsu, MSc[2]; Ellie G. Siden, MD[1]; Kristian Thorlund, PhD[2,3]; Edward J. Mills, FRCP(Edin)[2,3]

Ajustamos el plan fármaco-terapéutico a la mutación

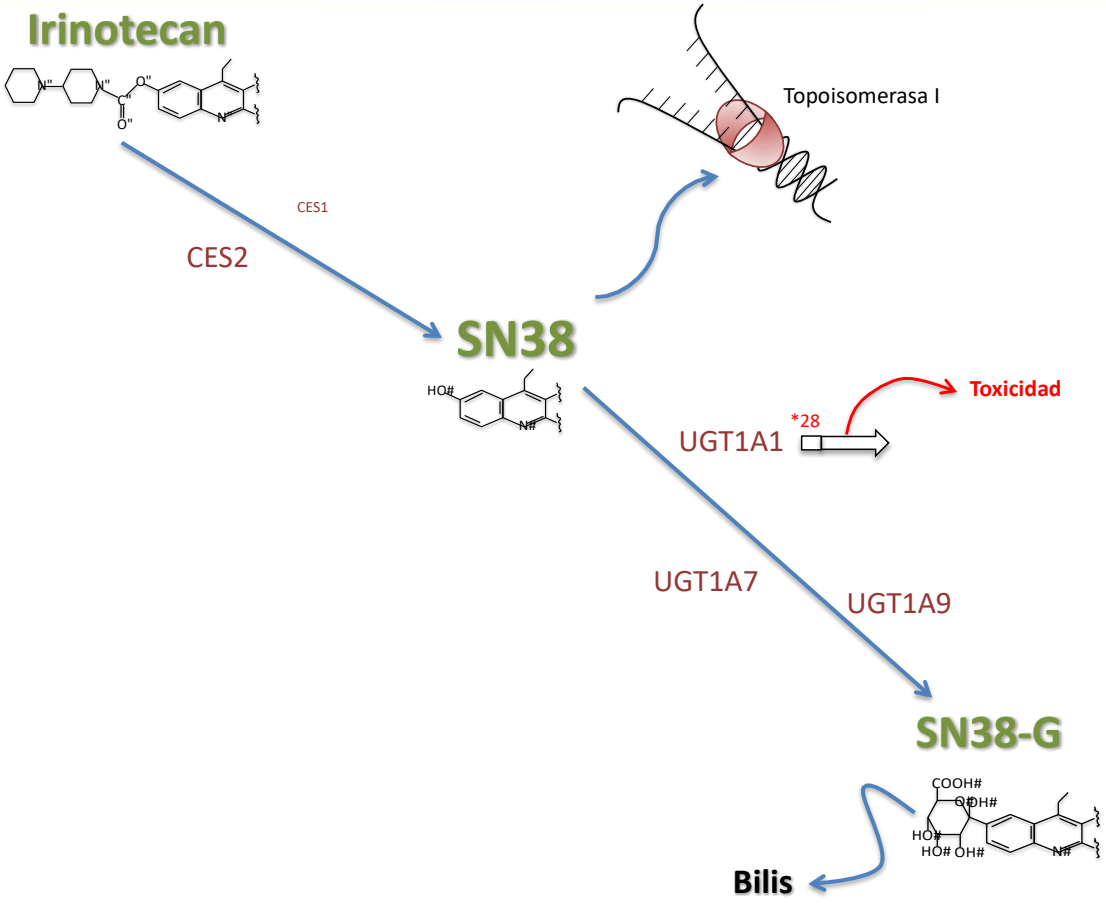
¿De qué estamos hablando?

Umbrella



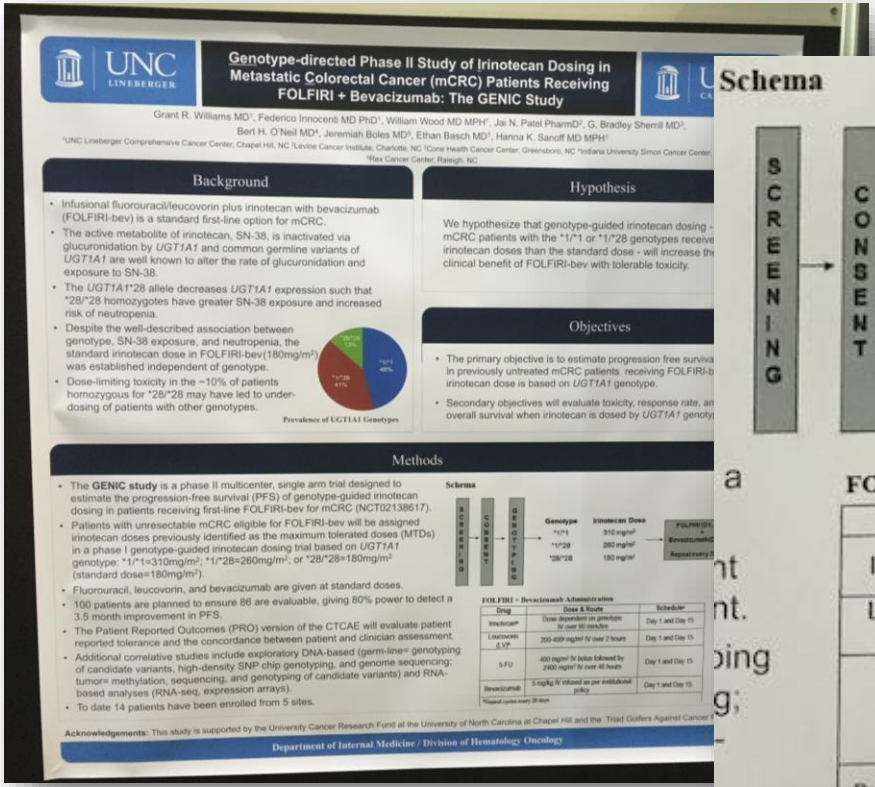
Basket

Ajustar el tratamiento en función de una mutación…


Irinotecan
Topoisomerasa I
CES1
CES2
SN38
Toxicidad
*28
UGT1A1
UGT1A7
UGT1A9
SN38-G
Bilis

Aprovechando que el río pasa…

La inercia en farmacia es… bajar dosis!!



UNC LINEBERGER

Genotype-directed Phase II Study of Irinotecan Dosing in Metastatic Colorectal Cancer (mCRC) Patients Receiving FOLFIRI + Bevacizumab: The GENIC Study

Grant R. Williams MD[1], Federico Innocenti MD PhD[1], William Wood MD MPH[1], Jai N. Patel PharmD[2], G. Bradley Sherrill MD[3], Bert H. O'Neil MD[4], Jeremiah Boles MD[5], Ethan Basch MD[3], Hanna K. Sanoff MD MPH[1]

[1]UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC [2]Levine Cancer Institute, Charlotte, NC [3]Cone Health Cancer Center, Greensboro, NC [4]Indiana University Simon Cancer Center, [5]Rex Cancer Center, Raleigh, NC

Background

- Infusional fluorouracil/leucovorin plus irinotecan with bevacizumab (FOLFIRI-bev) is a standard first-line option for mCRC.
- The active metabolite of irinotecan, SN-38, is inactivated via glucuronidation by *UGT1A1* and common germline variants of *UGT1A1* are well known to alter the rate of glucuronidation and exposure to SN-38.
- The *UGT1A1*28* allele decreases *UGT1A1* expression such that *28/*28 homozygotes have greater SN-38 exposure and increased risk of neutropenia.
- Despite the well-described association between genotype, SN-38 exposure, and neutropenia, the standard irinotecan dose in FOLFIRI-bev(180mg/m²) was established independent of genotype.
- Dose-limiting toxicity in the ~10% of patients homozygous for *28/*28 may have led to under-dosing of patients with other genotypes.

Prevalence of UGT1A1 Genotypes

Hypothesis

We hypothesize that genotype-guided irinotecan dosing - mCRC patients with the *1/*1 or *1/*28 genotypes receive irinotecan doses than the standard dose - will increase the clinical benefit of FOLFIRI-bev with tolerable toxicity.

Objectives

- The primary objective is to estimate progression free survival in previously untreated mCRC patients receiving FOLFIRI-b irinotecan dose is based on *UGT1A1* genotype.
- Secondary objectives will evaluate toxicity, response rate, an overall survival when irinotecan is dosed by *UGT1A1* genoty

Methods

- The **GENIC study** is a phase II multicenter, single arm trial designed to estimate the progression-free survival (PFS) of genotype-guided irinotecan dosing in patients receiving first-line FOLFIRI-bev for mCRC (NCT02138617).
- Patients with unresectable mCRC eligible for FOLFIRI-bev will be assigned irinotecan doses previously identified as the maximum tolerated doses (MTDs) in a phase I genotype-guided irinotecan dosing trial based on *UGT1A1* genotype: *1/*1=310mg/m²; *1/*28=260mg/m²; or *28/*28=180mg/m² (standard dose=180mg/m²).
- Fluorouracil, leucovorin, and bevacizumab are given at standard doses.
- 100 patients are planned to ensure 86 are evaluable, giving 80% power to detect a 3.5 month improvement in PFS.
- The Patient Reported Outcomes (PRO) version of the CTCAE will evaluate patient reported tolerance and the concordance between patient and clinician assessment.
- Additional correlative studies include exploratory DNA-based (germ-line= genotyping of candidate variants, high-density SNP chip genotyping, and genome sequencing; tumor= methylation, sequencing, and genotyping of candidate variants) and RNA-based analyses (RNA-seq, expression arrays).
- To date 14 patients have been enrolled from 5 sites.

Schema

SCREENING → CONSENT → GENOTYPING

Genotype	Irinotecan Dose
*1/*1	310 mg/m²
*1/*28	260 mg/m²
*28/*28	180 mg/m²

→ FOLFIRI (D1, D15) + Bevacizumab (D1, D15) Repeat every 28 days

FOLFIRI + Bevacizumab Administration

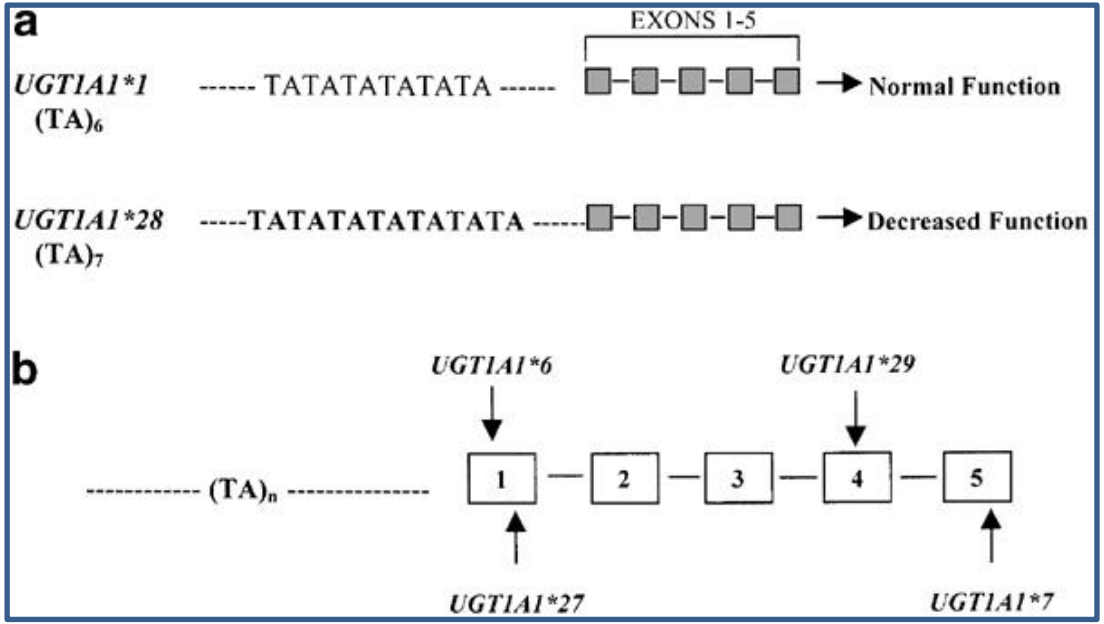
Drug	Dose & Route	Schedule[a]
Irinotecan[b]	Dose dependent on genotype IV over 90 minutes	Day 1 and Day 15
Leucovorin (LV)[b]	200-400[c] mg/m² IV over 2 hours	Day 1 and Day 15
5-FU	400 mg/m² IV bolus followed by 2400 mg/m² IV over 46 hours	Day 1 and Day 15
Bevacizumab	5 mg/kg IV infused as per institutional policy	Day 1 and Day 15

[a]Repeat cycles every 28 days

Acknowledgements: This study is supported by the University Cancer Research Fund at the University of North Carolina at Chapel Hill and the Triad Golfers Against Cancer

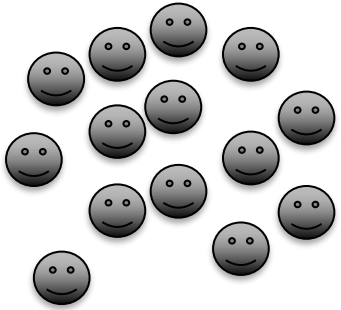
Department of Internal Medicine / Division of Hematology Oncology

¿Irinotecan?



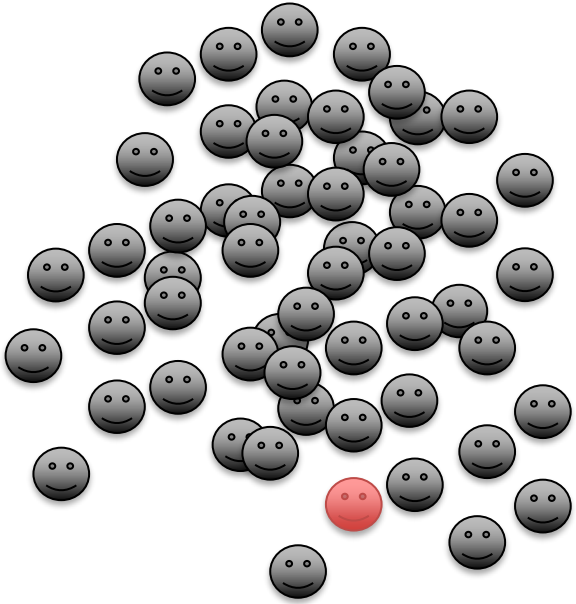
*28 = 30%

FASE I



DPyD = 1%

FASE II



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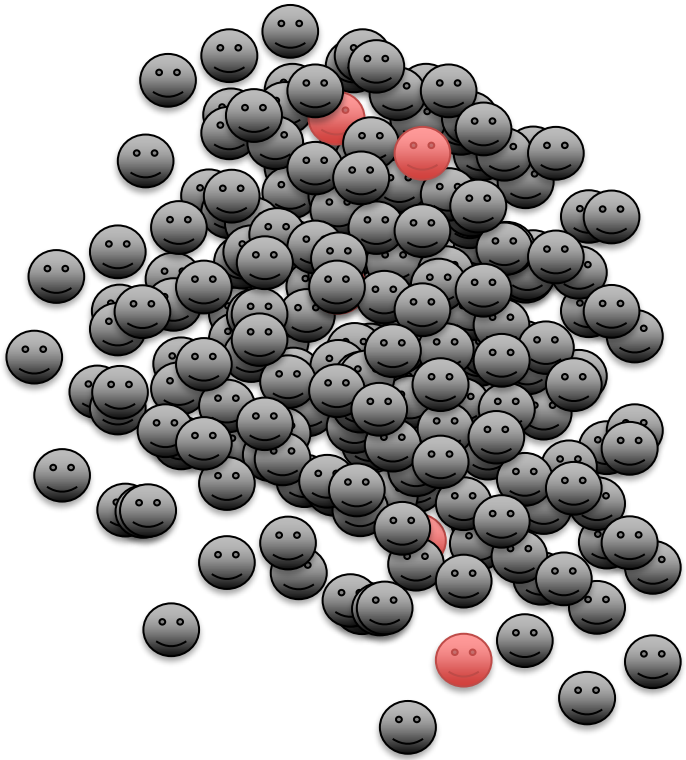
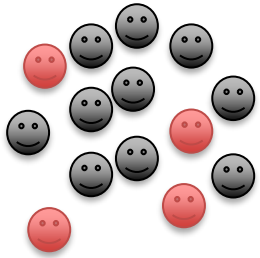
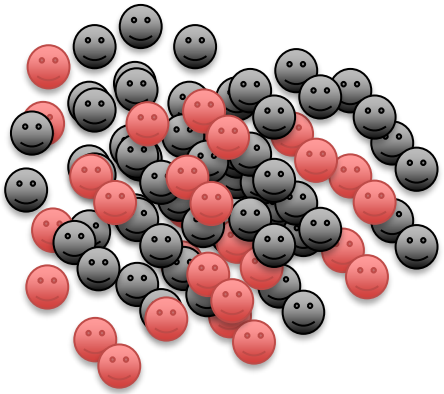


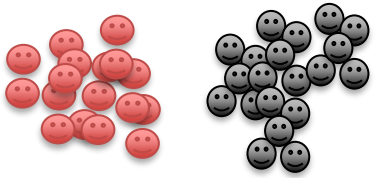
FASE I



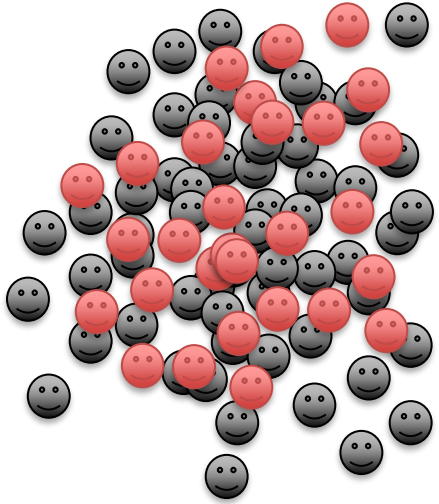
*28 = 30%

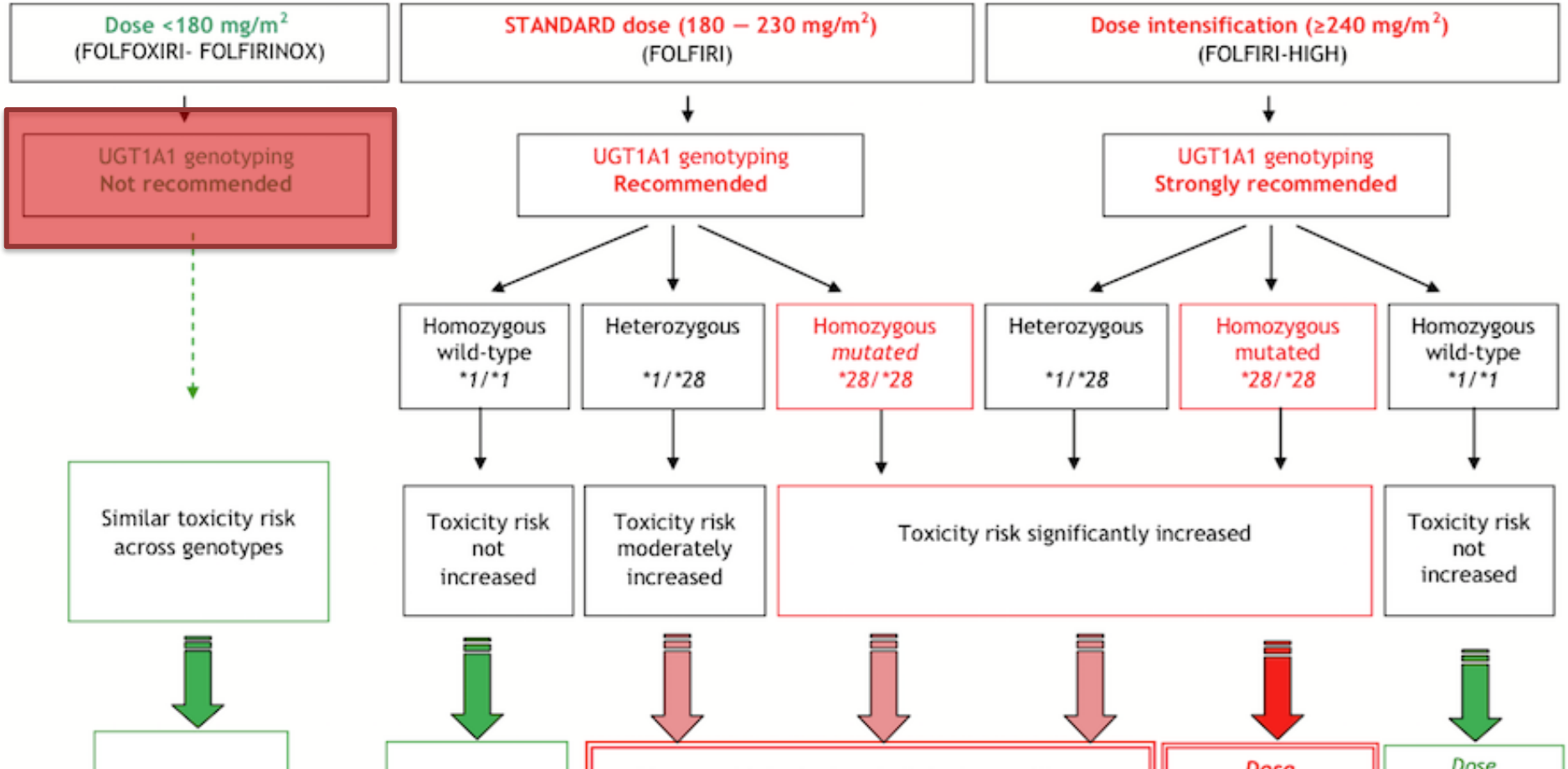
FASE II





FASE III

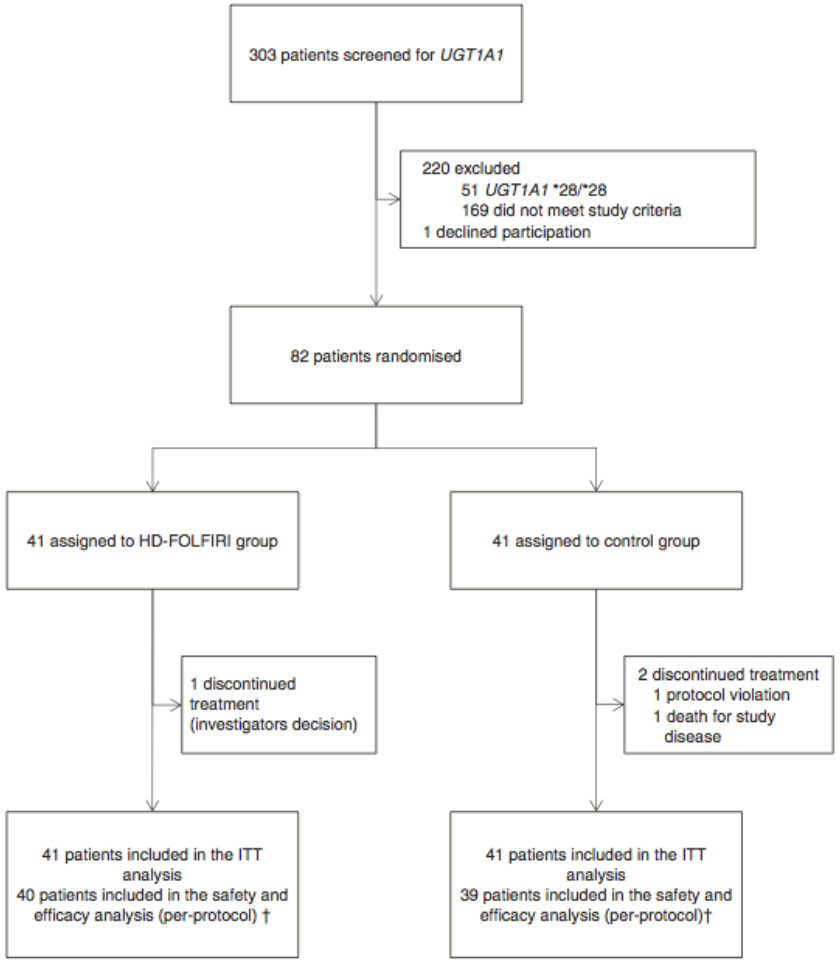



Dose <180 mg/m2
(FOLFOXIRI- FOLFIRINOX)
STANDARD dose (180 – 230 mg/m2)
(FOLFIRI)
Dose intensification (≥240 mg/m2)
(FOLFIRI-HIGH)
UGT1A1 genotyping
Not recommended
UGT1A1 genotyping
Recommended
UGT1A1 genotyping
Strongly recommended
Homozygous wild-type *1/*1
Heterozygous *1/*28
Homozygous mutated *28/*28
Heterozygous *1/*28
Homozygous mutated *28/*28
Homozygous wild-type *1/*1
Similar toxicity risk across genotypes
Toxicity risk not increased
Toxicity risk moderately increased
Toxicity risk significantly increased
Toxicity risk not increased
Dose

PHENOTYPE (GENOTYPE)	THERAPEUTIC DOSE RECOMMENDATION	LEVEL OF EVIDENCE	CLINICAL RELEVANCE
*1/*28	None.	Published controlled studies of moderate quality* relating to phenotyped and/or genotyped patients or healthy volunteers, and having relevant pharmacokinetic or clinical endpoints..	Clinical effect (S): death; arrhythmia; unanticipated myelosuppression.
*28/*28	Dose >250mg/m^2: reduce initial dose by 30%. Increase dose in response to neutrophil count. Dose <=250mg/m^2: no dose adjustment.	Published controlled studies of moderate quality* relating to phenotyped and/or genotyped patients or healthy volunteers, and having relevant pharmacokinetic or clinical endpoints.	Clinical effect (S): Failure of lifesaving therapy e.g. anticipated myelosuppression; prevention of breast cancer relapse; arrhythmia; neutropenia < 0.5x10^9/l; leucopenia < 1.0x10^9/l; thrombocytopenia < 25x10^9/l; life-threatening complications from diarrhea.

Pharmacogenetic clinical randomised phase II tr
the efficacy and safety of FOLFIRI with high-d
(HD-FOLFIRI) in metastatic colorectal cancer
according to their *UGT1A 1* genotype

David Páez[1,2], María Tobeña[1], Julen Fernández-Plana[3], Ana Sebio[1], Anna C. Virgili[1,4], Lluís Cirera[3], Ag
Ivana Sullivan[1] and Juliana Salazar[2,5]

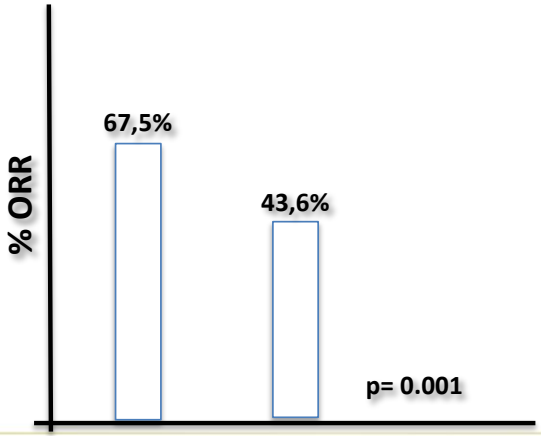


1*/1*
1*/28*

- **Experimental**
  - **1*/28*** 260 mg/m²
  - **1*/1*** 300 mg/m²
- **Control**
  - **1*/28*** 180 mg/m²
  - **1*/1*** 180 mg/m²

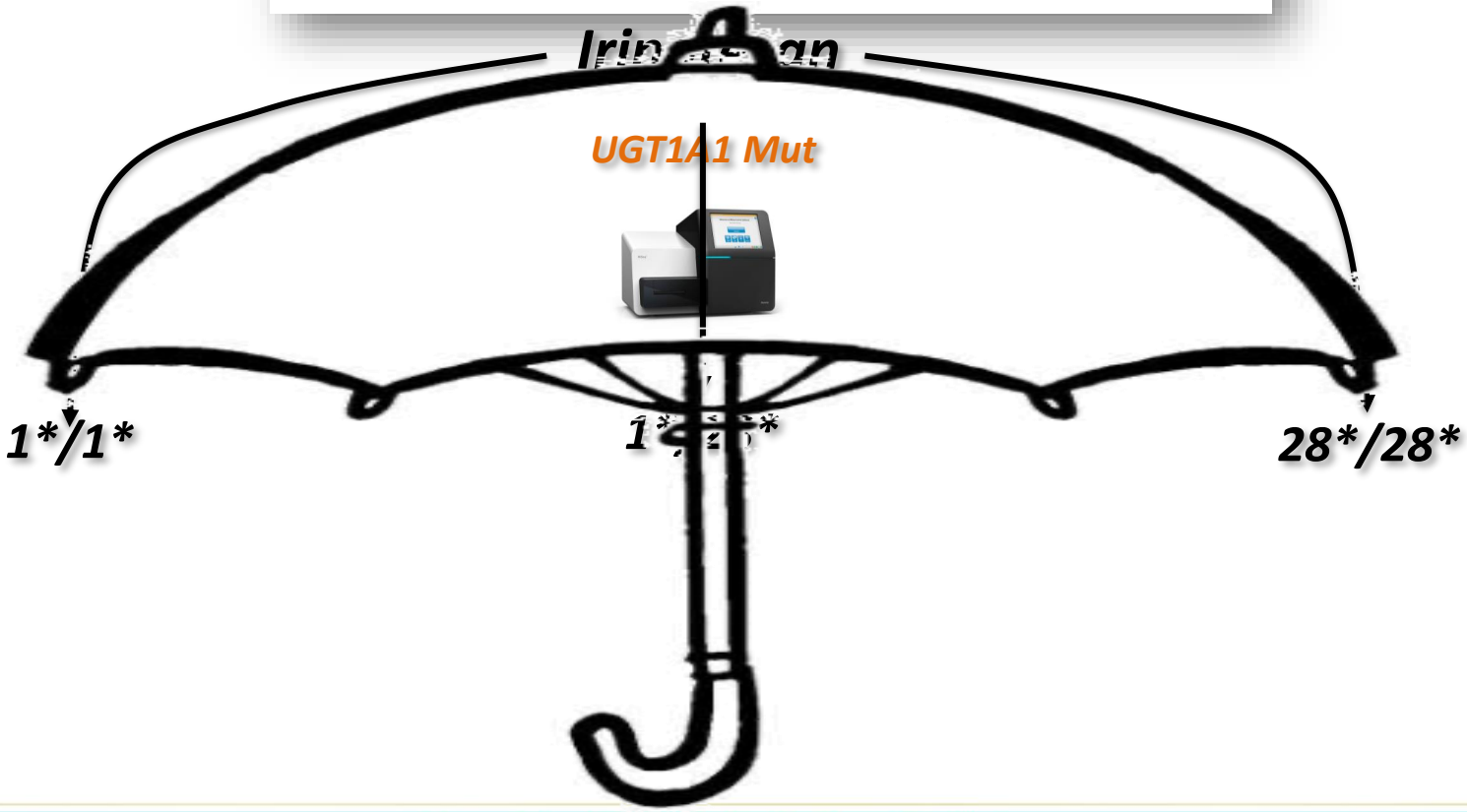
Table 2. Efficacy data: response rate in the overall population and according to *UGT1A1* and *RAS/BRAF* genotypes

	Response rate			*p* Value
	CR + PR (%)	SD (%)	PD (%)	
Overall population, N = 79	44 (55.7)	20 (25.3)	15 (19)	0.001
HD-FOLFIRI group, *N* = 40	27 (67.5)	3 (7.5)	10 (25)	
Control group, *N* = 39	17 (43.6)	17 (43.6)	5 (12.8)	
UGT1A1 genotype				
*1/*1 and *1/*28 N = 79	44 (55.7)	20 (25.3)	15 (19)	0.147
*1/*1 N = 37	17 (46)	13 (35.1)	7 (18.9)	
*1/*28 N = 42	27 (64.3)	7 (16.7)	8 (19)	
RAS and BRAF genotype				
Wild type N = 36	21 (58.3)	9 (25)	6 (16.7)	0.648
RAS mutant N = 30	17 (56.7)	6 (20)	7 (23.3)	
BRAF mutant N = 12	5 (41.7)	5 (41.7)	2 (16.6)	



An Overview of Precision Oncology Basket and Umbrella Trials for Clinicians

Jay J. H. Park, MSc[1]; Grace Hsu, MSc[2]; Ellie G. Siden, MD[1]; Kristian Thorlund, PhD[2,3]; Edward J. Mills, FRCP(Edin) [2,3]



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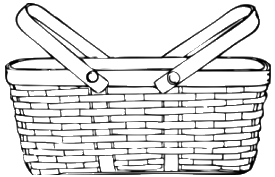
Ajustamos el plan fármaco-terapéutico a la mutación

¿De qué estamos hablando?

Umbrella



Basket

Ajustar el tratamiento en función de una mutación…

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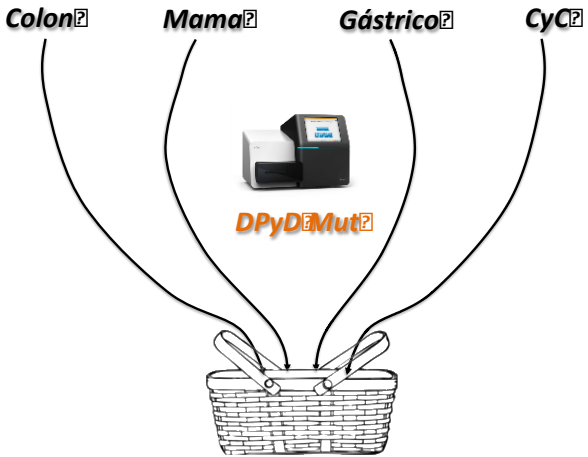
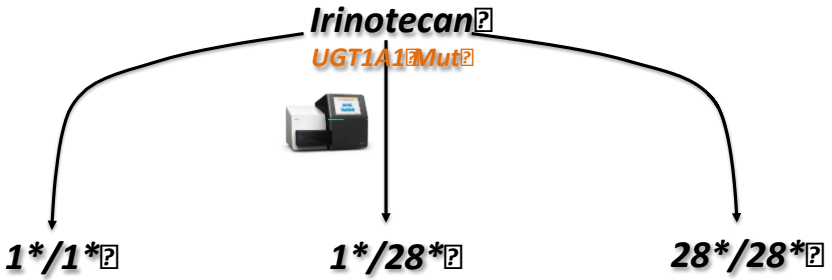
Jay J. H. Park, MSc[1]; Grace Hsu, MSc[2]; Ellie G. Siden, MD[1]; Kristian Thorlund, PhD[2,3]; Edward J. Mills, FRCP(Edin)[2,3]

Ajustamos el plan fármaco-terapéutico a la mutación





Consenso internacional de tratamientos con indicación tumor-agnóstica

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

JSCO—ESMO—ASCO—JSMO—TOS: international expert consensus recommendations for tumour-agnostic treatments in patients with solid tumours with microsatellite instability or *NTRK* fusions

T. Yoshino[1*], G. Pentheroudakis[2], S. Mishima[1], M. J. Overman[3], K.-H. Yeh[4], E. Baba[5], Y. Naito[6], F. Calvo[7], A. Saxena[8], L.-T. Chen[9], M. Takeda[10], A. Cervantes[11], H. Taniguchi[1], K. Yoshida[12], Y. Kodera[13], Y. Kitagawa[14], J. Tabernero[15], H. Burris[16] & J.-Y. Douillard[17]

Table 1. The six identical clinical questions (CQs) formulated for the treatment and management of patients with MSI/dMMR or *NTRK* fusion-positive tumours from which two separate series of recommendations were developed, i.e. one series of clinical recommendations for each clinical situation

CQ no.	CQs
CQ1	Should all patients with solid tumours be tested for MSI/MMR or *NTRK* fusions?
CQ2	When is the optimal timing for tests for MSI/MMR or for *NTRK* fusions?
CQ3	Which tests are recommended for determining MSI/MMR status or *NTRK* fusions?
CQ4	What is the appropriate biospecimen for testing for MSI/MMR or *NTRK* fusions?
CQ5	Which treatment is recommended for MSI/dMMR patients or patients with *NTRK* fusions?
CQ6	Where in the treatment algorithm should immunotherapy be used in the treatment of patients with MSI/dMMR solid tumours or a TRK inhibitor be used in the treatment of patients with *NTRK* fusion-positive solid tumours?

dMMR, deficient in (DNA) mismatch repair; MSI, microsatellite instability; *NTRK*, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase.

Table 2. Summary of the expert recommendations for the treatment of patients with MSI/dMMR solid tumours

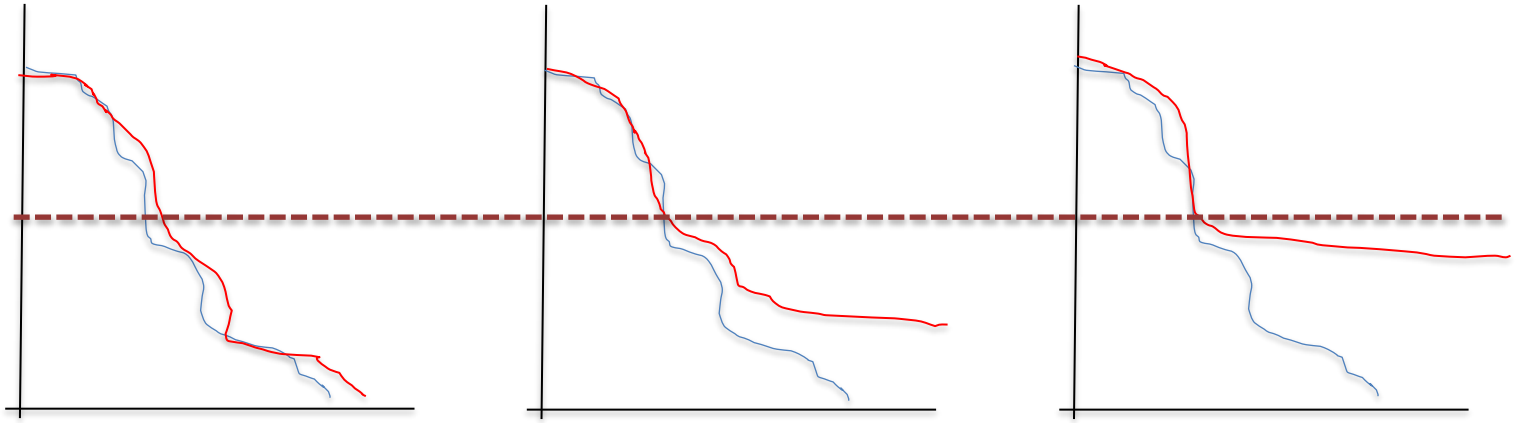
CQ1. Should all patients with solid tumours be tested for MSI/MMR?	
1-1	Patients with **advanced (unresectable or metastatic)** solid tumours **with a high incidence** of MSI/dMMR should be tested for their MSI/MMR status. [LoE: III, GoR **for testing: A, LoA: A = 100%**]
1-2	Patients with advanced (**unresectable or metastatic)** solid tumours with a **low incidence of MSI/dMMR** should be **considered** for MSI/MMR **testing**. [LoE: III, GoR **for testing: B, LoA: A = 100%**]
1-3	Patients with **localised resectable non-colorectal tumours should** not be considered for MSI/MMR testing outside of a clinical trial, **unless Lynch syndrome is clinically suspected**. [LoE: V, GoR **for testing: D, LoA: A = 100%**]
CQ2. When is the optimal timing for tests for MSI/MMR?	
	MSI/MMR should be tested before or during the standard treatment of advanced **(unresectable or metastatic**) solid tumours. [LoE: V, GoR: A, **LoA: A = 100%**]
CQ3. Which tests are recommended for determining MSI/MMR status?	
3-1	IHC is highly recommended for testing. [LoE: III, GoR for testing: A, **LoA: A = 100%**]
3-2	PCR is recommended for testing **either upfront or when IHC is equivocal or not available**. [LoE: III, GoR **for testing: B, LoA: A = 75%, B = 25%**]
3-3	**Validated** NGS is recommended for testing **either upfront or when IHC is equivocal or not available**. [LoE: III, GoR **for testing: B, LoA: A = 75%, B = 25%**]
CQ4. What is the appropriate biospecimen for testing for MSI/MMR?	
	Formalin-fixed, paraffin-embedded tissue blocks are appropriate for testing. [LoE: V, GoR: A, **LoA: A = 100%**]
CQ5. Which treatment is recommended for MSI/dMMR patients?	
	PD-1/PD-L1 inhibitors are strongly recommended for patients with MSI/dMMR tumours. [LoE: III, GoR: A, **LoA: A = 100%**]
CQ6. Where in the treatment algorithm should immunotherapy be used in MSI/dMMR solid tumours?	
	We recommend immunotherapy for patients with MSI/dMMR during the course of their therapy when no other satisfactory treatment options exist depending on the clinical context. [LoE: III, GoR: **A, LoA: A = 100%**]

Table 3. Summary of the expert recommendations for the treatment of patients with solid tumours with *NTRK* fusions

CQ1. Should all patients with solid tumours be tested for *NTRK* fusion?	
1-1	Patients with **advanced (unresectable or metastatic)** solid tumours with**out** actionable and **driver gene mutations/ fusions/amplifications** should be tested for *NTRK* fusion. [LoE: V, GoR: B, **LoA: A = 100%**]
1-2	Patients with **advanced (unresectable or metastatic)** solid tumours which are **highly likely to harbour *NTRK* fusions** should be tested for *NTRK* fusion, especially *ETV6-NTRK3* fusion. [LoE: V, GoR: A, **LoA: A = 100%**]
1-3	Patients with **advanced (unresectable or metastatic)** solid tumours other than above (CQ1-1 and 1-2) should be considered for testing for *NTRK* fusions. [LoE: V, GoR: A, **LoA: A = 100%**]
1-4	**Patients with locally-advanced tumours with a high incidence of *NTRK* fusions should be tested when considering neoadjuvant therapy before resection**. [LoE: V, GoR: **B, LoA: A = 100%**]
CQ2. When is the optimal timing for tests for *NTRK* fusion?	
	NTRK fusion **testing** should be **considered** before or during the standard treatment of advanced (unresectable or metastatic) solid tumour. [LoE: V, GoR: **B, LoA: A = 100%**]
CQ3. Which tests are recommended for determining *NTRK* fusions?	
3-1	IHC is not recommended for confirming *NTRK* fusion. It may be used for screening to enrich patients with *NTRK* fusion. [LoE: V, GoR: B, **LoA: A = 100%**]
3-2	*In situ* hybridisation (ISH, e.g. FISH) for *ETV6-NTRK3* fusion is recommended for patients with tumours which are highly likely to harbour *NTRK* fusions. ISH is not recommended for patients other than the above. [LoE: V, GoR: B, **LoA: A = 100%**]
3-3	RT-PCR for *ETV6-NTRK3* fusion is recommended for patients with tumours which are highly likely to harbour *NTRK* fusions. [LoE: V, GoR: B, **LoA: A = 100%**]
3-4	NGS which detects *NTRK* fusion is recommended for testing for *NTRK* fusion. [LoE: V, GoR: C, **LoA: A = 100%**]
CQ4. What is the appropriate biospecimen for testing for *NTRK* fusions?	
	Both fresh samples as well as archival tissue samples properly fixed and preserved are appropriate for testing. [LoE: V, GoR: B, **LoA: A = 100%**]
CQ5. Which treatment is recommended for patients with *NTRK* fusions?	
	TRK inhibitors are strongly recommended for patients with *NTRK* fusions. [LoE: III, GoR: A, **LoA: A = 100%**]
CQ6. Where in the treatment algorithm should a TRK inhibitor be used in the treatment of patients with *NTRK* fusion-positive solid tumours?	
	We recommend TRK inhibitors for patients with *NTRK* fusions during the course of therapy, when no other satisfactory treatment options exist, depending on the clinical context. [LoE: III, **GoR: A, LoA: A = 100%**]

¿Por qué cambiar la mentalidad?

Una mira al pasado en ocasiones ayuda…

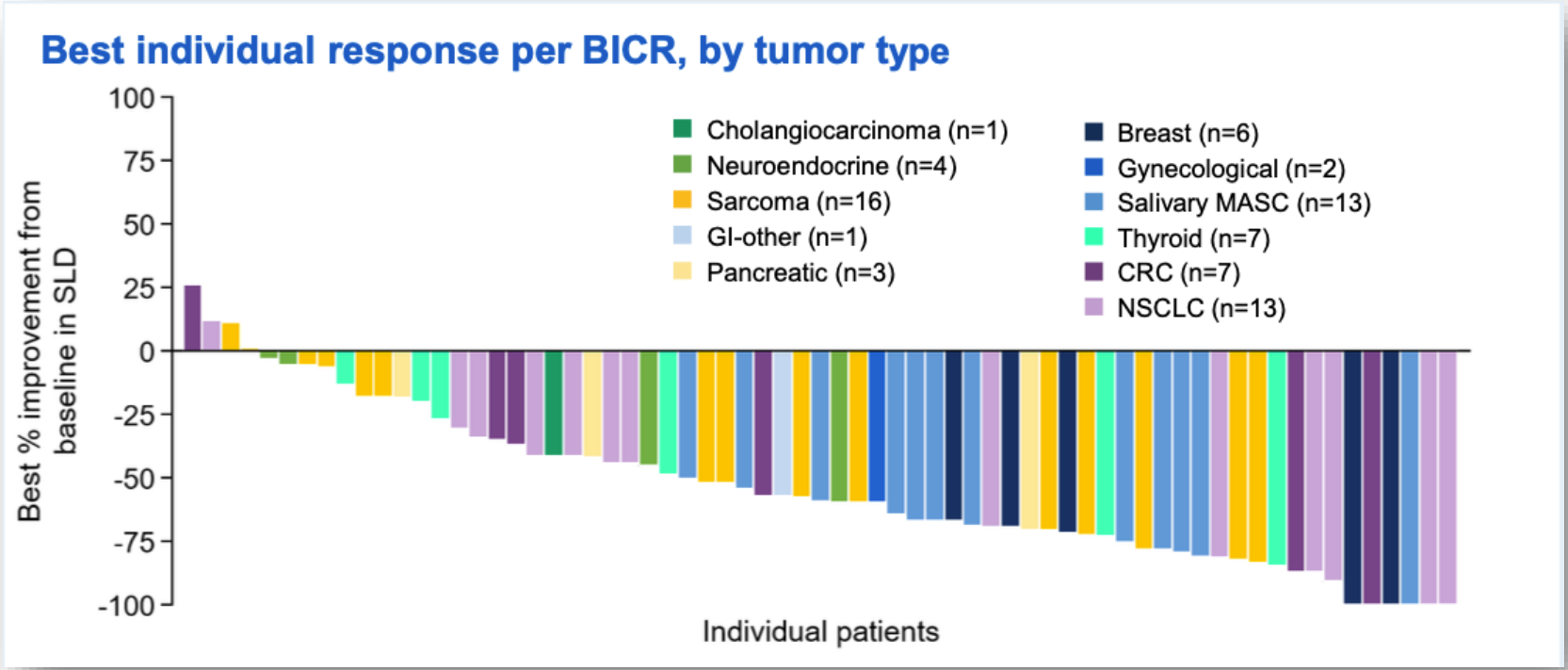


La mediana es insensible a la eficacia de la inmunoterapia

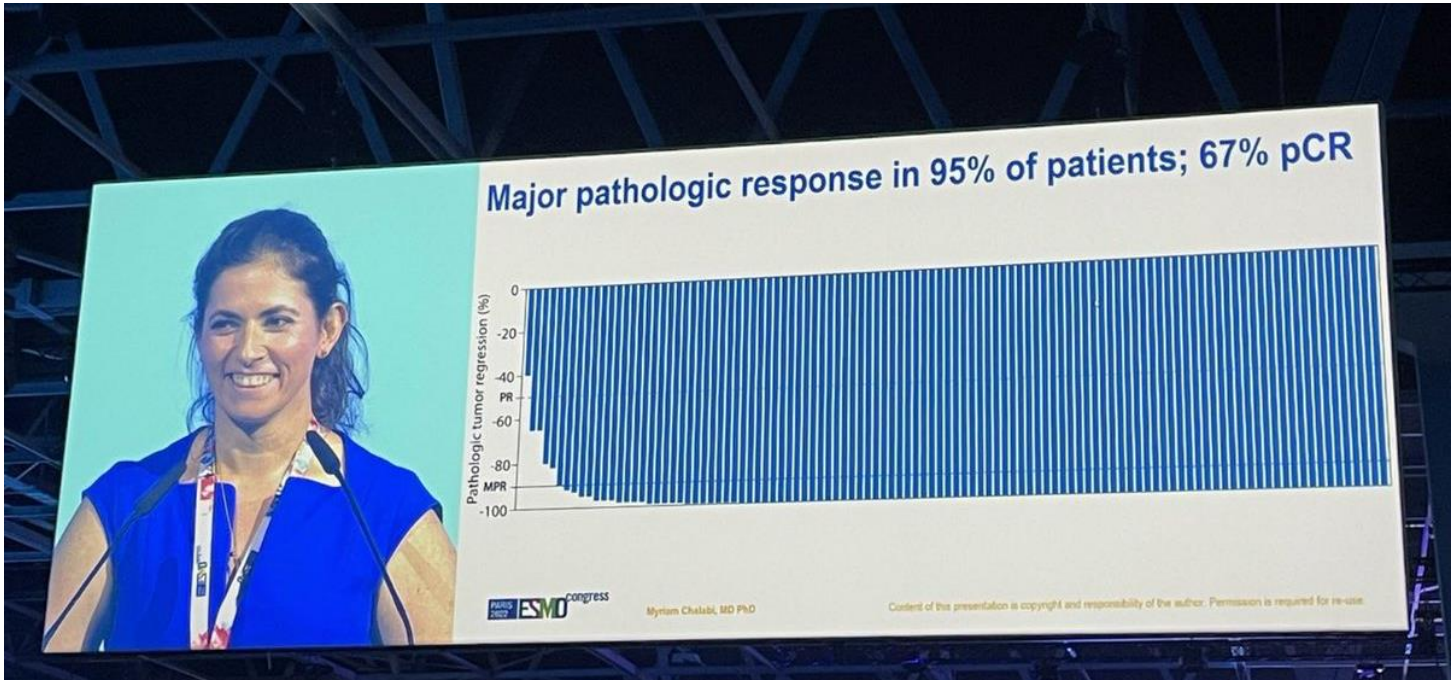
PARA EL DEBATE

No tienen brazo comparador

¿Qué hacemos con estás respuestas?



¿Qué hacemos con estás respuestas?

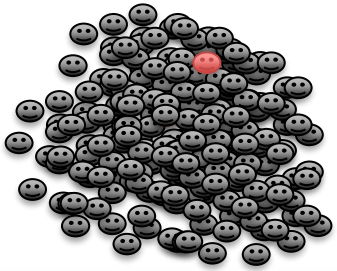


PARA EL DEBATE

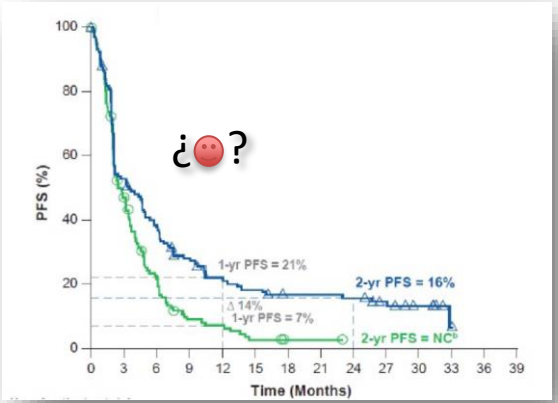
No tienen brazo comparador

No puede tenerlo

La evidencia actual no permite comparar con lo anterior…



Son tumores biológicamente diferentes
NO responden a inmunoterapia
NO responden a quimioterapia



Habría que comparar con la respuesta que tuvieron los tumores mutados en los ensayos originales

PARA EL DEBATE

No tienen brazo comparador

No puede tenerlo

Pero…

Tienen elevadísimas TRO

El dato más "limpio" es TRO

¿Quién es subrogada de quién?

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Gracias por su atención

Gràcies per la seva atenció

Eskerrik asko zure arretagatik

Grazas pola súa atención

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