

13º Congreso de Pacientes con Cáncer

Avances en el tratamiento del Cáncer Colorrectal



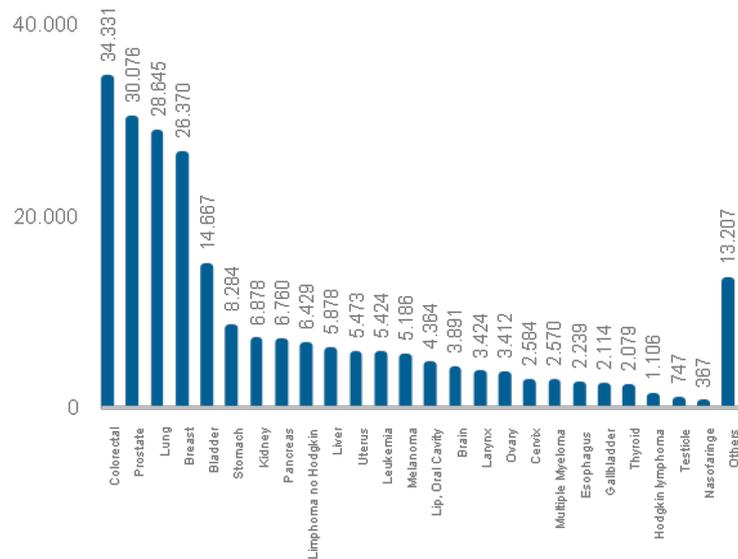
P. García Alfonso
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HGU Gregorio Marañón de Madrid

CCR en España

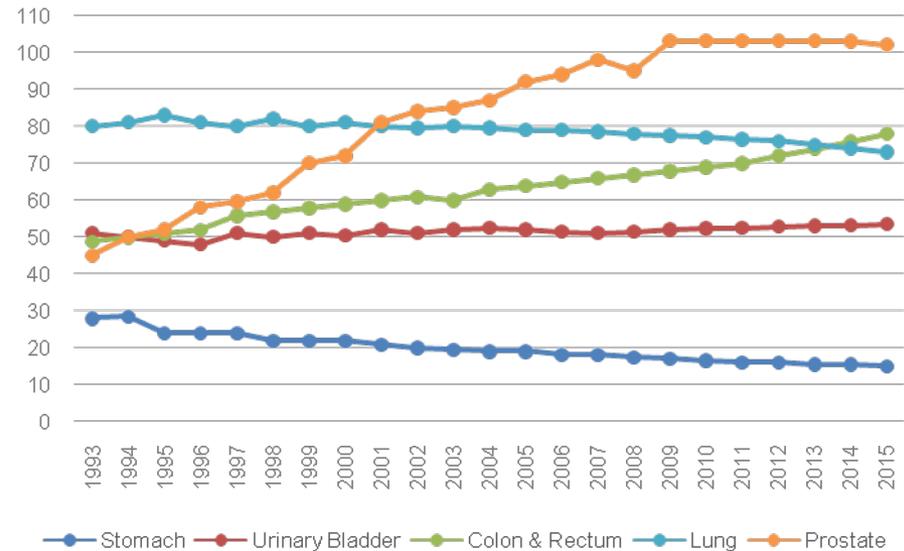
Incidencia

- CRC was the most common cancer in Spain in 2017 (both sexes)¹
- Third tumour in men after prostate and lung cancer¹
- Second in women after breast cancer¹

- The incidence of CRC has shown a steady increase in Spain^{1,2}



Estimated incidence of the most frequent tumours in Spain in 2017 (both sexes). Data from Globocan 2012, disaggregated by age and sex, and extrapolated to the data of the Spanish population for the year 2017 provided by the INE.



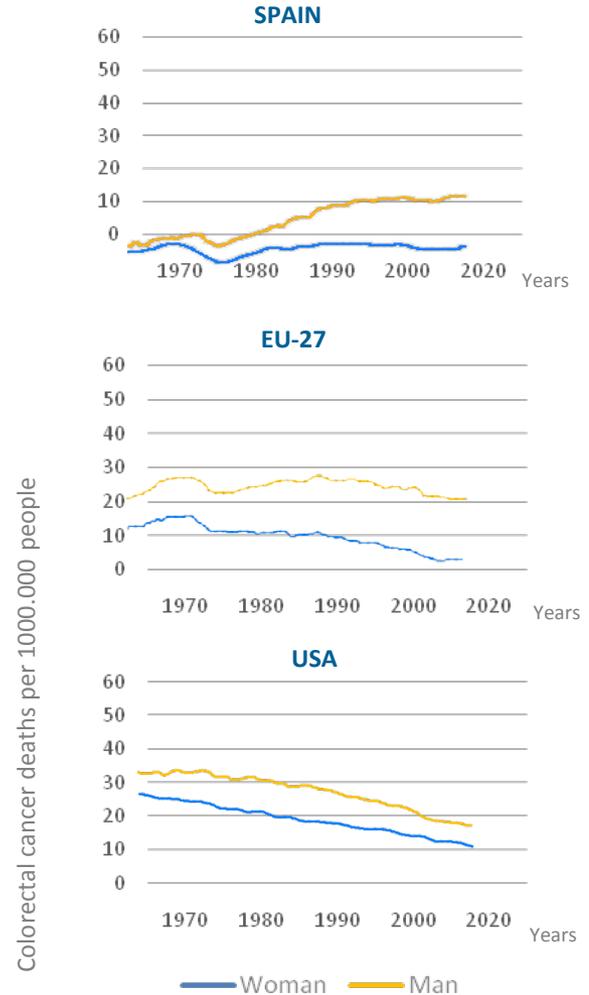
Trends in incidence rates 1993-2007 of five leading cancer types and projections until 2015 in Spain; men. Rates are standardized to the European standard population and expressed per 100,000 person-years.

CCR en España

Mortalidad

- CRC was the 2nd tumour in number of deaths in Spain in 2016 after lung cancer¹
- CRC mortality tends to slightly increase over time in Spain¹ probably associated with the changes in lifestyle²
- However in EU-27 and USA the CRC mortality tends to decrease²⁻⁵

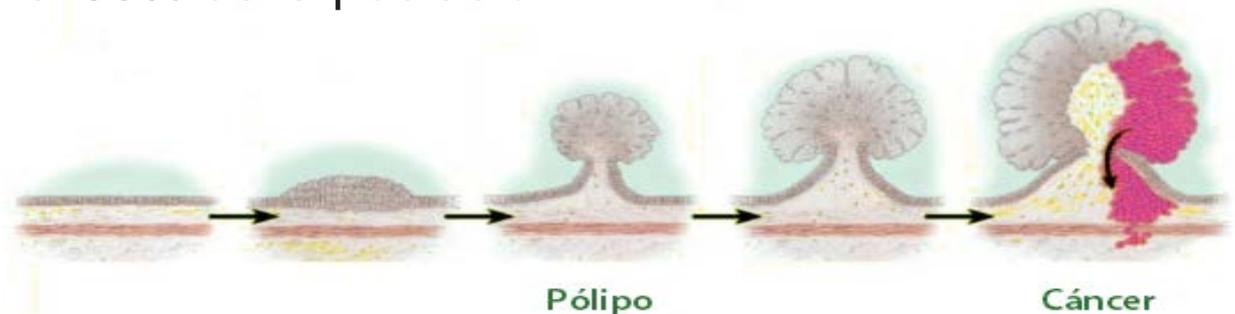
1. SEOM. Las cifras del cáncer en España 2018; 2. Ouakrim D.A. et al. British Med J 2015;351:h4970; 3. Torre A, et al. Cancer Epidemiol Biomarkers Prev; 2016; 25(1); 16–27; 4. Siegel R.L., et al. CA: A Cancer Journal for Clinicians 2017; 67(3):177-93; DOI: 10.3322/caac.21395; 5. Malvezzi M. et al. Ann Oncol 2018; doi:10-1093/annonc/mdy033



EU-27: 27 European Union member states

ETIOLOGÍA

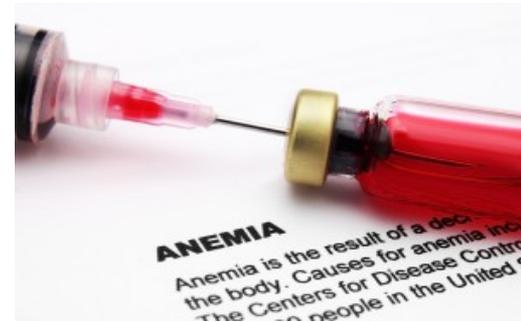
- La mayoría de los cánceres colorrectales se originan a partir de un crecimiento de la mucosa que forma un pólipo.
- Varios tipos de pólipos
- Tamaños variables, de 1-2 mm hasta 5-10 cm
- **Pólipos adenomatosos (adenomas):** son los más frecuentes (60-70%), lesiones premalignas.
 - Incidencia aumenta con la edad
 - Múltiples (30%)
 - Presentes en el 50% de la población



Factores de Riesgo

- Edad: Mas del 90% en mayores de 50 años
- **Presencia de pólipos (adenomatosos), pólipos vellosos o tubulovillosos**
- Enfermedades inflamatorias: Colitis ulcerosa: riesgo acumulado de 5-15 veces y enfermedad de Crohn
- Otros: obesidad, diabetes, inactividad física, alcohol, tabaco, Streptococcus bovis, factores dietéticos
- Haber tenido cáncer colorrectal, ovario o útero
- **Antecedentes familiares:** dos o más familiares directos (padres, hijos, hermanos) afectados, o algún caso menor de 50 años
- **Síndromes Genéticos:**
 - S. de Lynch: 3% de los casos. Trastorno autosómico dominante asociado a mutación de MMR (hMLH1, hMSH2, MSH6, PMS2). Aparece en colon derecho, edad media de 48, asociado con cáncer de endometrio o de ovario
 - Poliposis adenomatosa familiar < 1% de los casos. Trastorno autosómico dominante por mutación de APC. Aparece a los 16 años y ocurre en el 90% de los no tratados a los 45 años

CLÍNICA

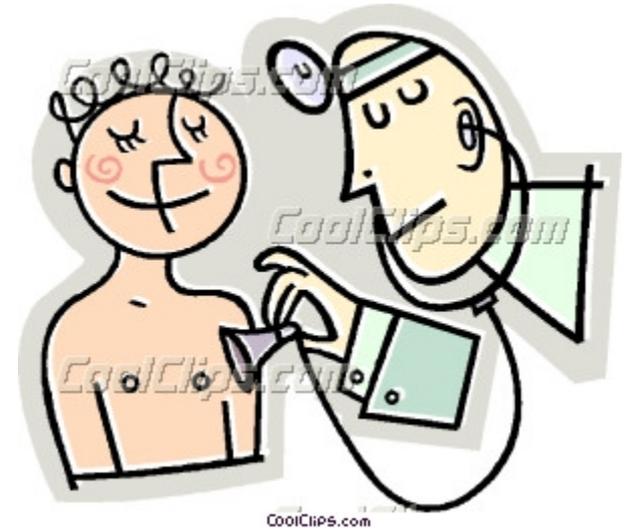


- Síntomas muy inespecíficos, crecimiento e invasión de estructuras vecinas
 - En estadios tempranos puede cursar de forma asintomática
 - Más frecuentes (asociados al tumor):
 - **Sangrado:** anemia ferropénica (colon derecho), melenas o rectorragia (unión recto-sigmoidea, recto)
 - **Alteración del ritmo intestinal:** diarrea, estreñimiento (colon izquierdo)
 - **Dolor**
 - **Obstrucción**
- aumenta

Tumores de recto: tenesmo, dolor rectal y disminución en el calibre de las heces

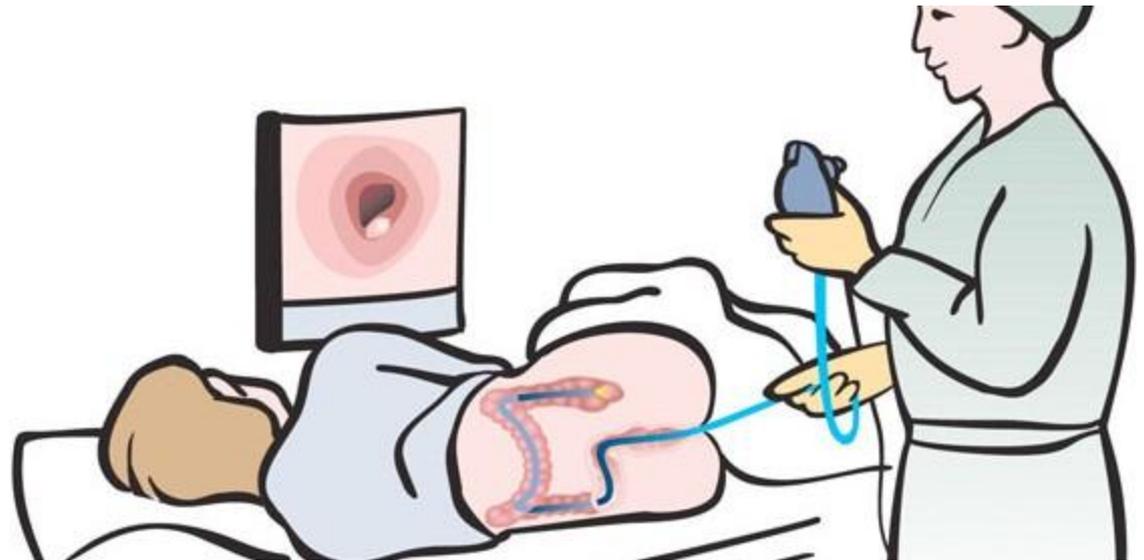
DIAGNÓSTICO

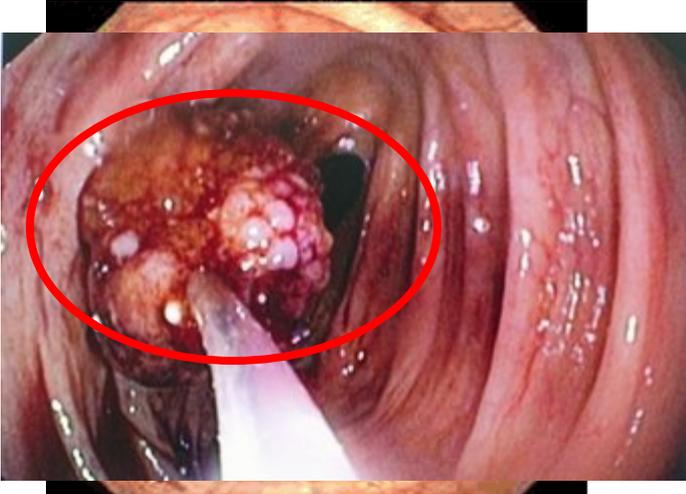
- **Examen físico completo**
 - Tacto rectal
- **Analítica de sangre**
 - Hemoglobina (anemia)
 - Perfil hepático (afectación hepática secundaria)
 - LDH
 - Marcadores tumorales: CEA
- **Sangre oculta en heces**
 - Sencilla y barata
 - Orientativa: detecta la presencia de sangre pero no el cáncer



COLONOSCOPIA

- Prueba más sensible y específica
- Puede ver y localizar lesiones
- Toma de **biopsias**
- Extirpar pólipos



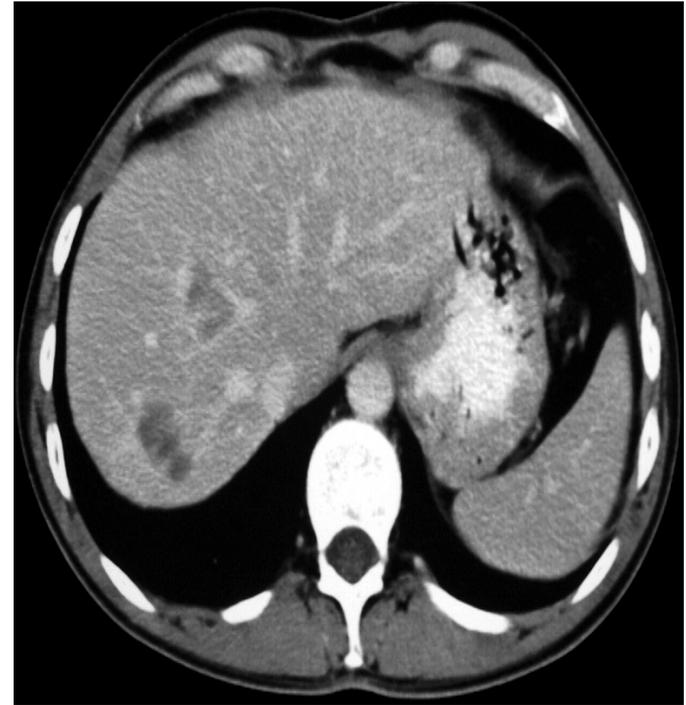


- Masas que crecen desde la mucosa y protruyen hacia la luz.
- Tamaño variable con obstrucción parcial o completa.
- Pueden ser lesiones necróticas, ulcerada o friables.

ANATOMIA PATOLÓGICA: la histología más común en el cáncer de colon y recto son los adenocarcinomas.

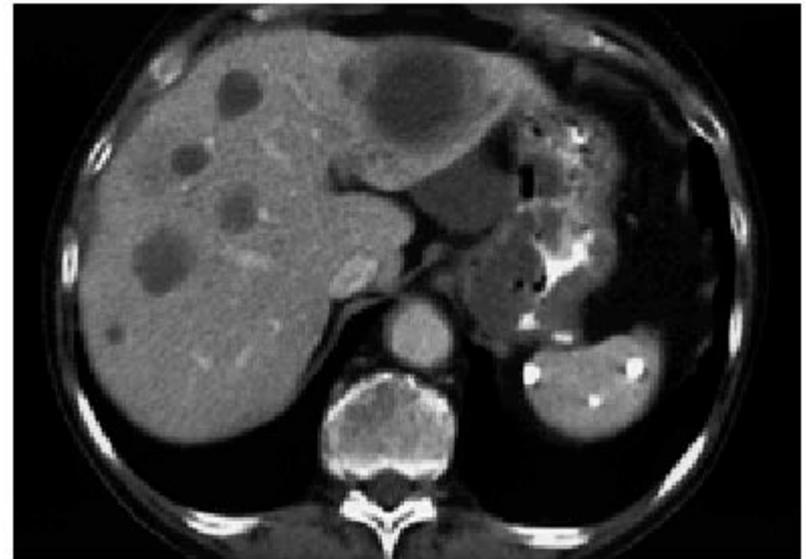
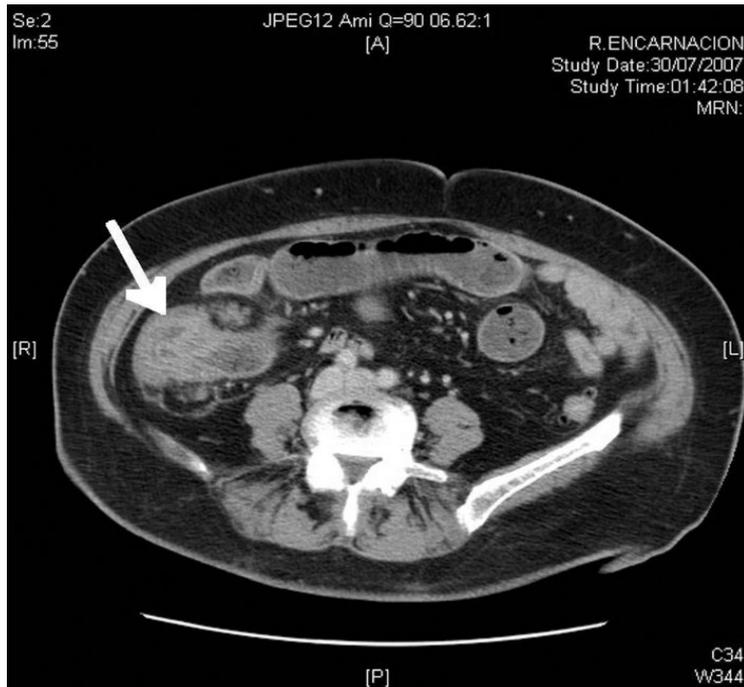
Estudio de Extensión en CCR

- TAC (abdomen-pelvis)
- Radiología simple (tórax)/ TAC torácico
- RM (pélvica, abdominal)
- Ultrasonografía (endorrectal, hepática)
- Marcadores tumorales (CEA, CA 19-9)
- PET/TAC



TOMOGRAFÍA (TAC)

- Útil para localizar el tumor y ver estructuras vecinas
- Ganglios regionales
- Estudio de extensión: afectación secundaria o metástasis



RESONANCIA MAGNÉTICA

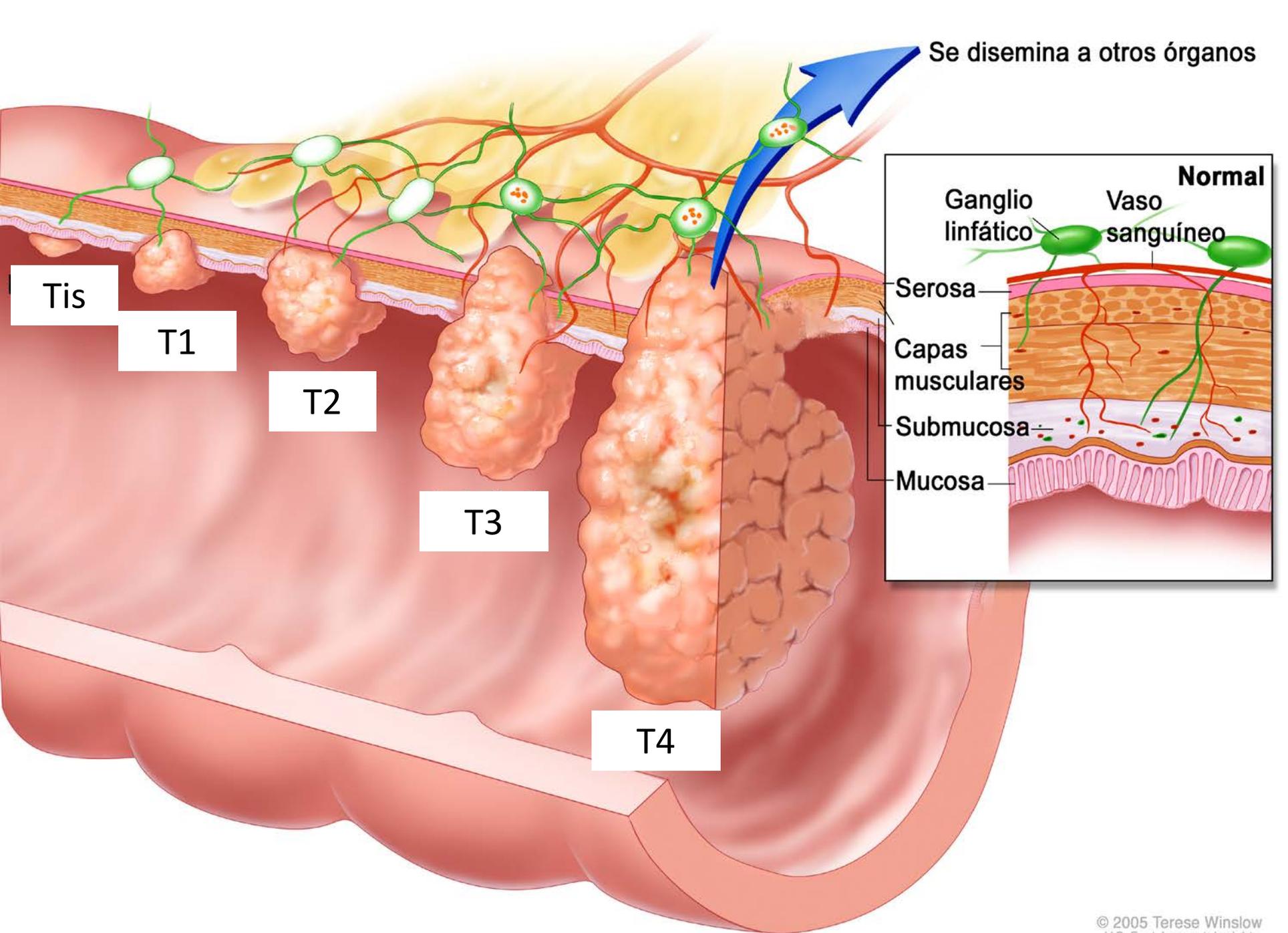
- Ayuda a identificar lesiones dudosas en TAC (hepáticas)
- Suele utilizarse en tumores rectales (grado de infiltración de estructuras vecinas y ganglios regionales)



- **Factores Pronósticos**

Clasificación TNM 7ª Ed AJCC

- T: tumor primario.
 - TX: tumor primario no puede encontrarse.
 - T0: sin evidencias de tumor primario.
 - Tis: carcinoma in situ intraepitelial o con compromiso lámina propia.
 - T1: tumor invade submucosa.
 - T2: tumor invade muscular propia.
 - T3: tumor invade la subserosa o tejido perirrectal o pericólico no peritonizado.
 - T4: tumor invade otros órganos o estructuras y/o perfora el peritoneo visceral.
 - T4d: invade órganos o estructuras vecinas



Se disemina a otros órganos

Tis

T1

T2

T3

T4

Normal

Ganglio linfático

Vaso sanguíneo

Serosa

Capas musculares

Submucosa

Mucosa

Clasificación TNM 7ª Ed AJCC

- N: ganglios linfáticos regionales.
 - NX: ganglios linfáticos no pueden determinarse.
 - N0: sin metástasis a ganglios linfáticos regionales.
 - N1a: metástasis en 1 ganglio linfático regionales
 - N1b: metástasis en 2 o 3 ganglios linfáticos.
 - N2a: metástasis en 4 a 6 ganglios linfáticos regionales.
 - N2b: metástasis en 7 o más ganglios linfáticos regionales.

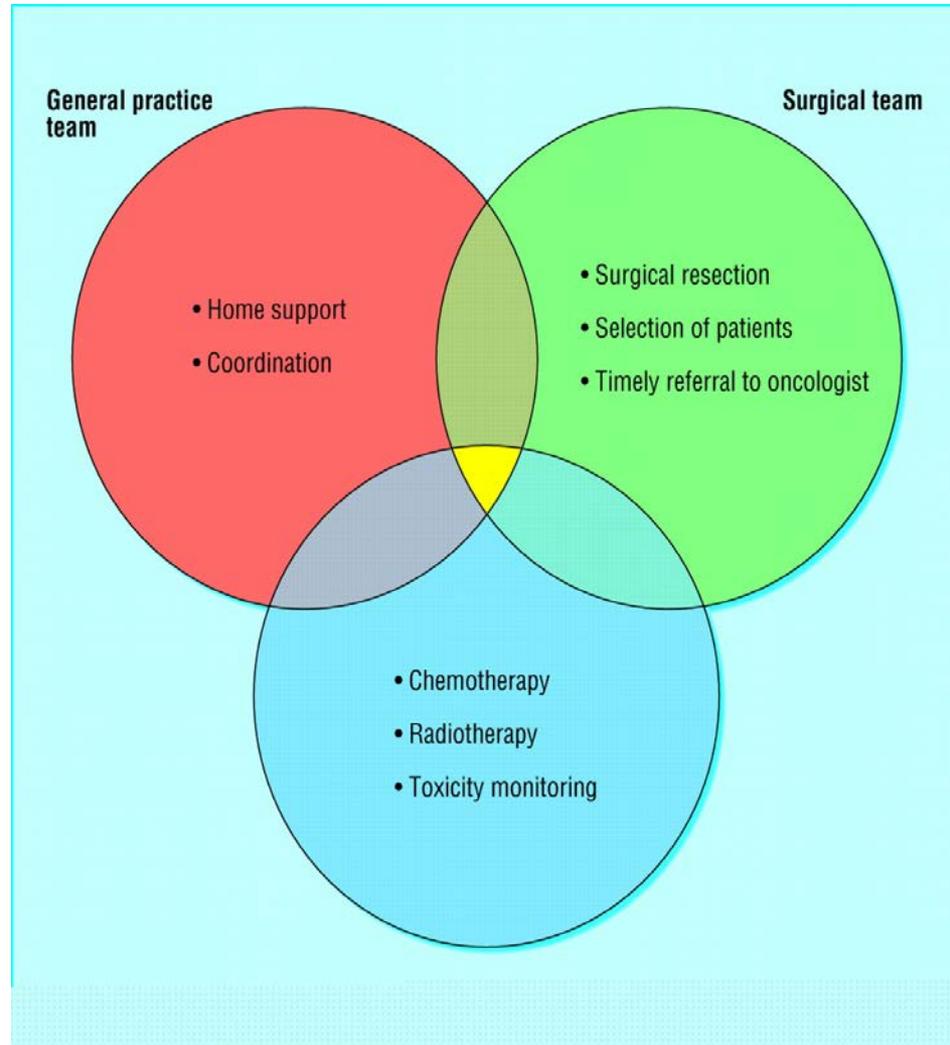
Clasificación TNM 7ª Ed AJCC

- M: metástasis a distancia.
 - MX: no puede determinarse presencia o ausencia de metástasis a distancia.
 - M0: sin metástasis a distancia.
 - M1a: con metástasis a distancia en una localización.
 - M1b: metástasis en más de una localización

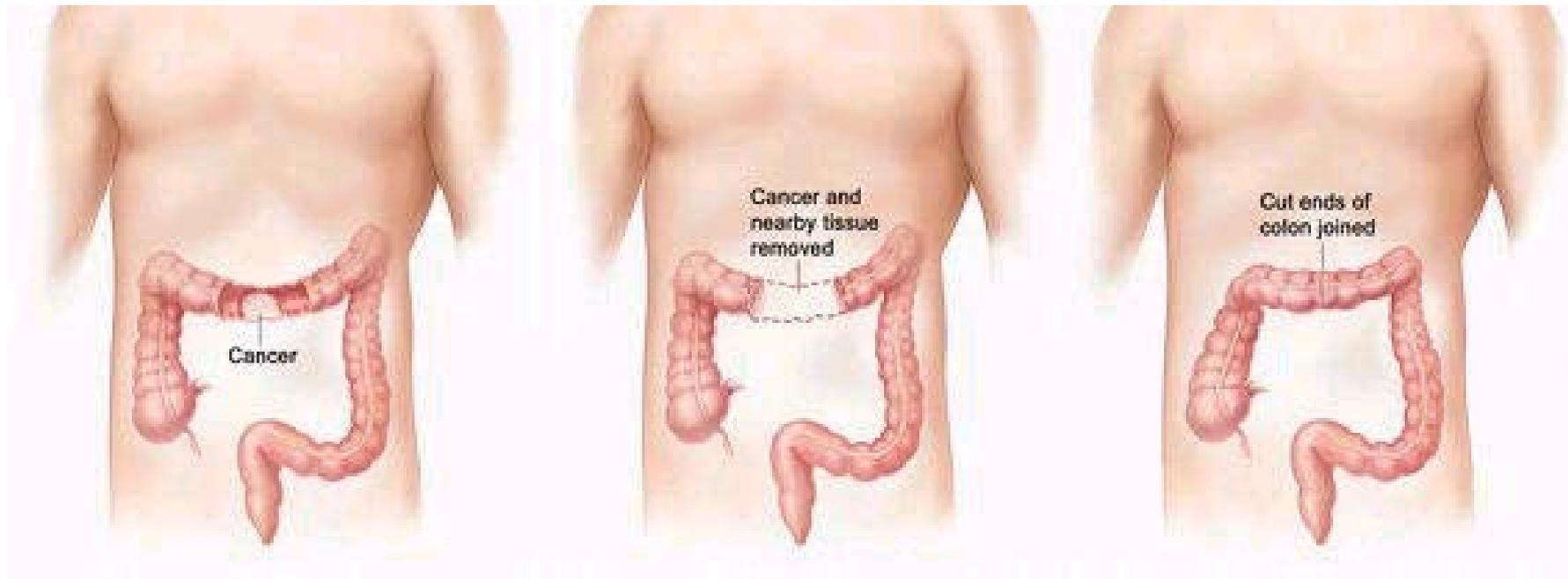
Tratamiento

Decisión multidisciplinaria

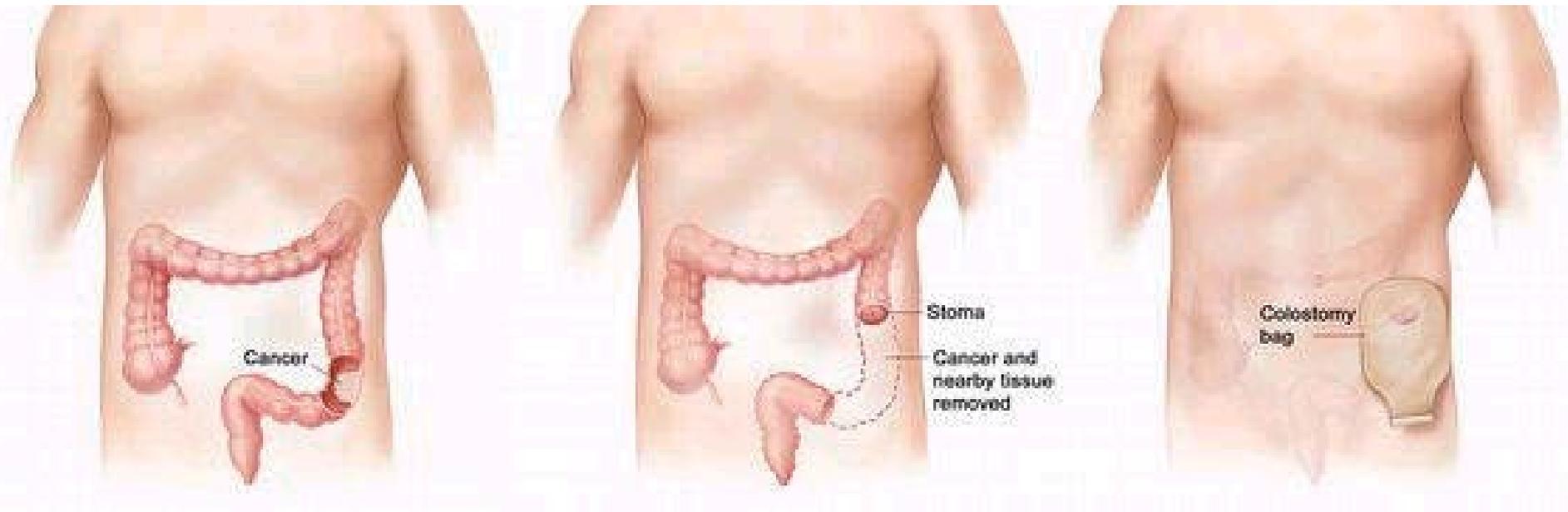
- Cirugía
- Oncología Médica
- Oncología Radioterápica
- Radiodiagnóstico
- Anatomía Patológica
- Aparato Digestivo
- Nutrición
- Anestesiología
- Enfermería



Cirugía del Cáncer de Colon



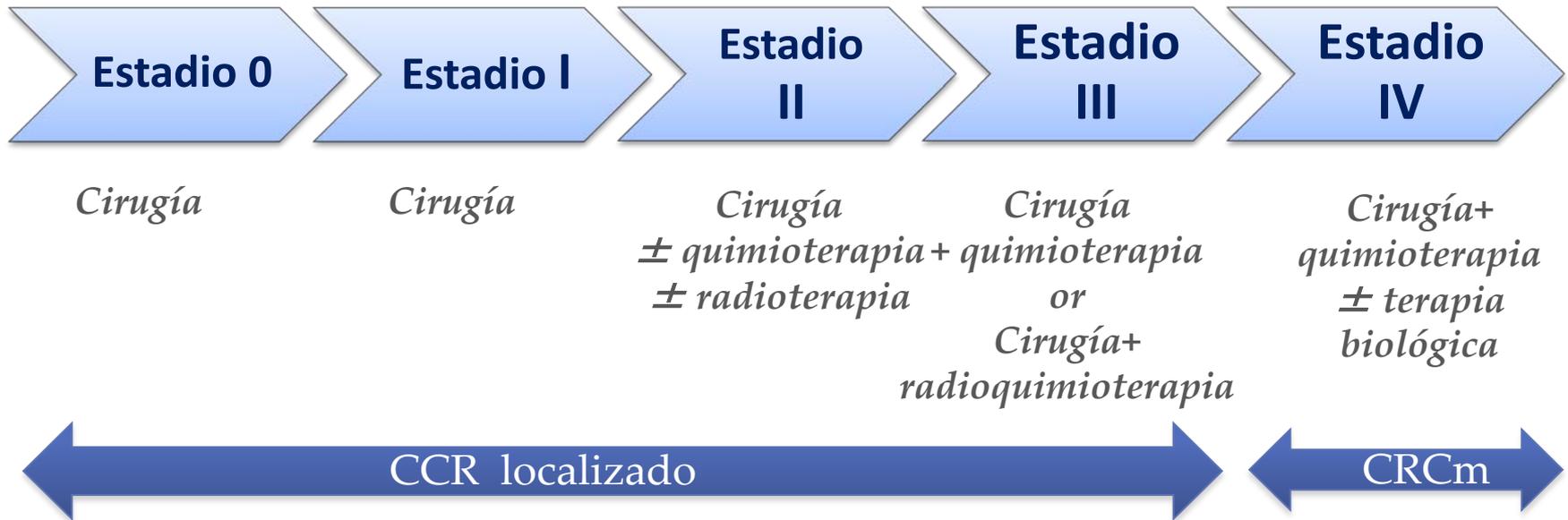
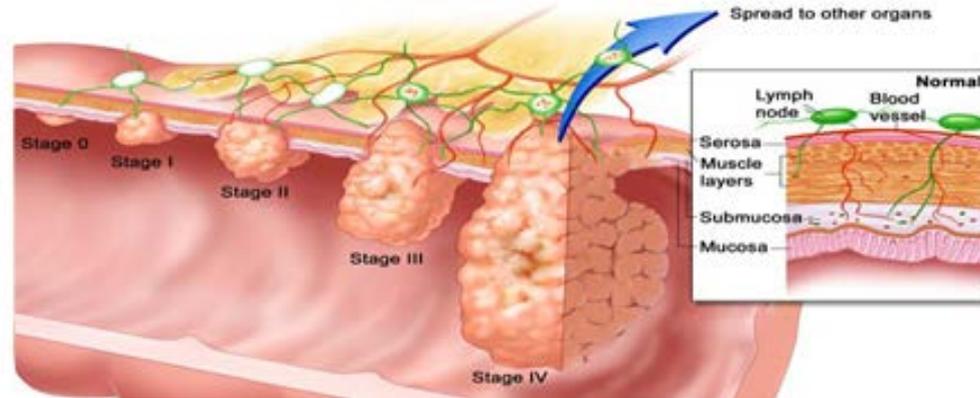
Cirugía del Cáncer de Colon



Cirugía del Cáncer de Colon

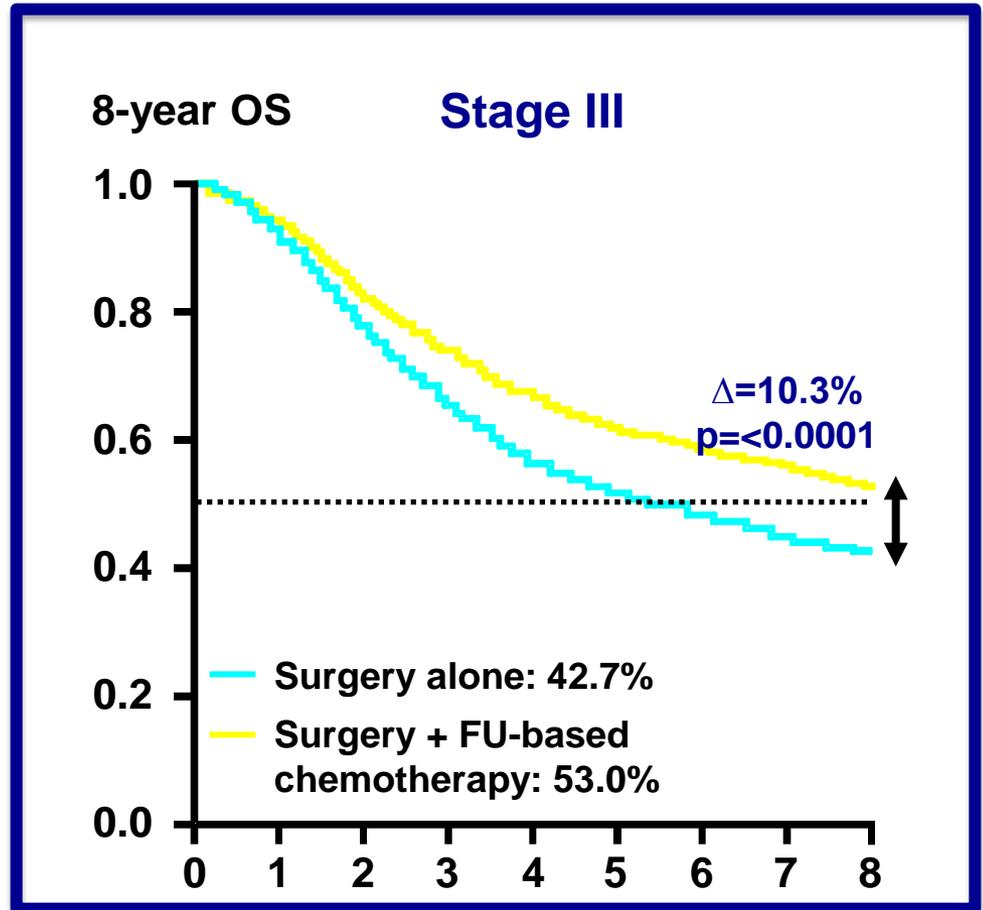
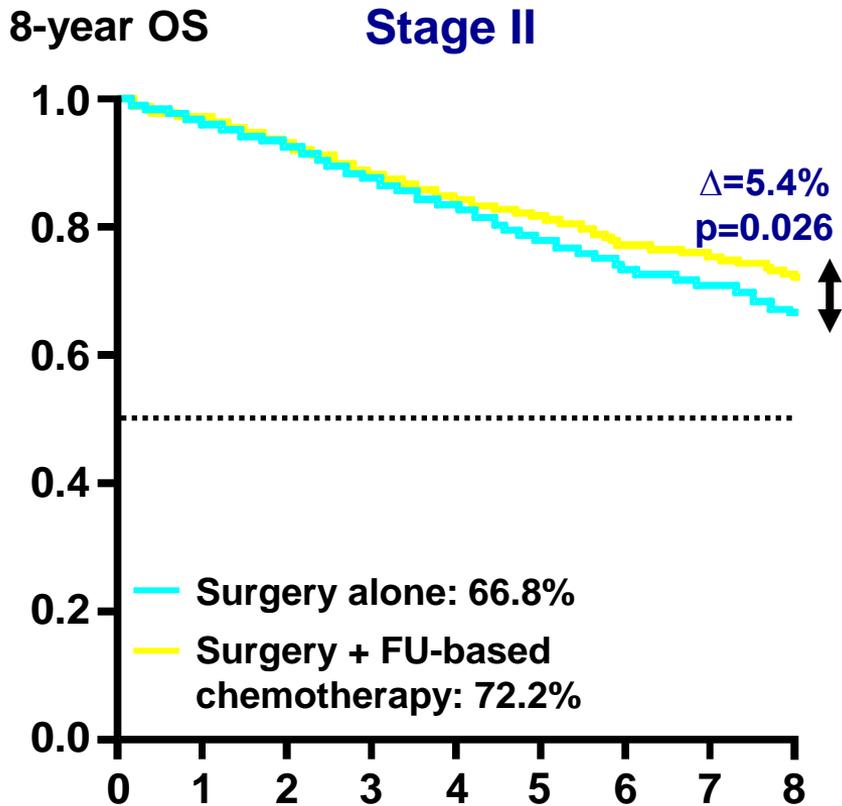


Tratamiento del CCR Metastásico



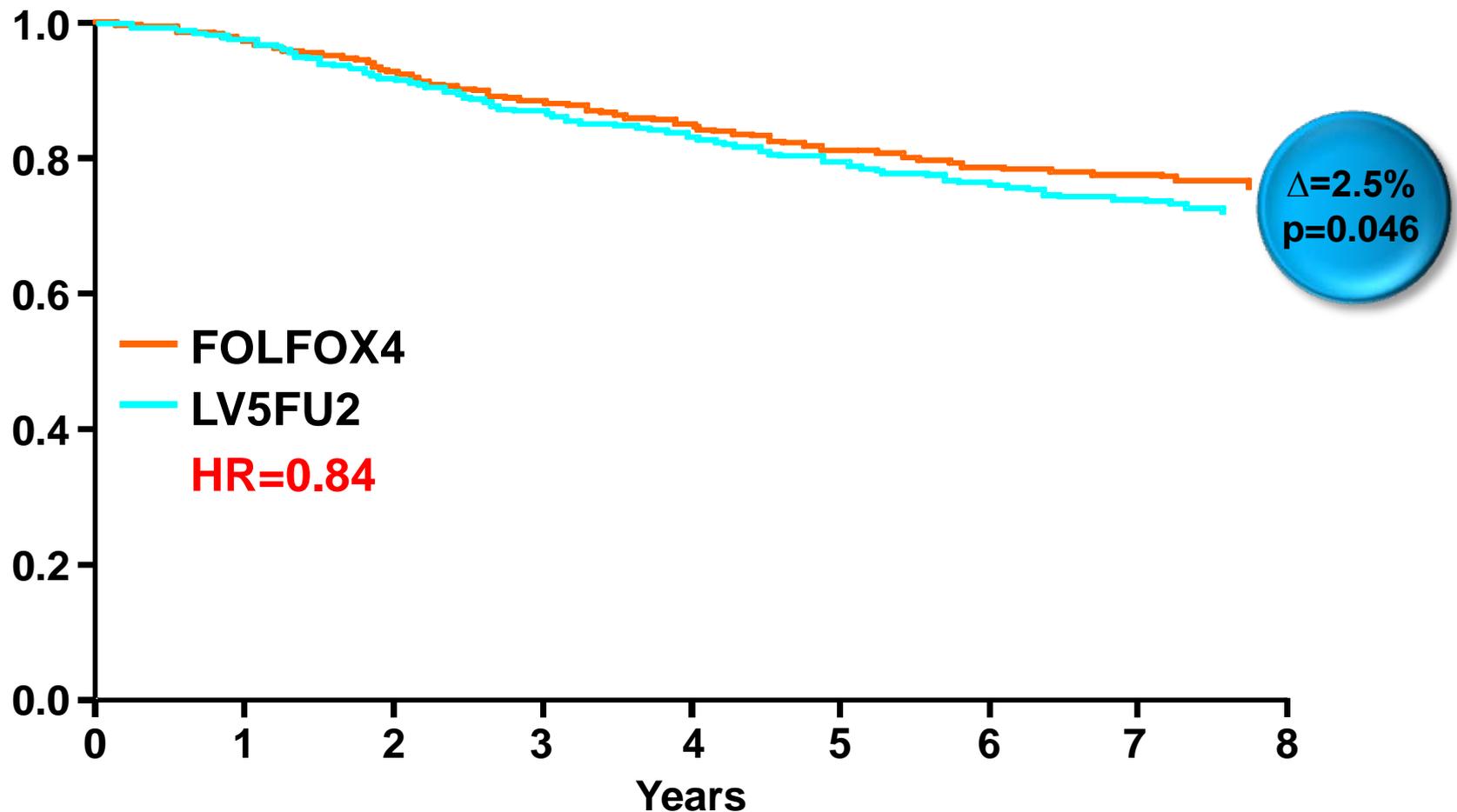
Tratamiento adyuvante

Adjuvant therapy increases survival: evidence from 20,898 patients



Follow-up (years)

MOSAIC: significantly improved 6-year OS in stage II/III



International Duration Evaluation of Adjuvant Chemotherapy (IDEA) Collaboration

Table 1 Randomized phase III trials that constitute the IDEA project

Study	Primary site	Stage	Regimen	Number of stage III colon cancer included in IDEA	Country
TOSCA	Colon	II and III	CAPOX/FOLFOX4	2,402	Italy
SCOT	Colon or Rectum	II and III	CAPOX/mFOLFOX6	3,983	UK, Denmark, Spain, Australia, Sweden, New Zealand
IDEA-France	Colon	III	CAPOX/mFOLFOX6	2,010	France
C80702	Colon	III	mFOLFOX6	2,440	USA, Canada
HORG	Colon	II and III	CAPOX/FOLFOX4	708	Greece
ACHIEVE	Colon	III	CAPOX/mFOLFOX6	1,291	Japan

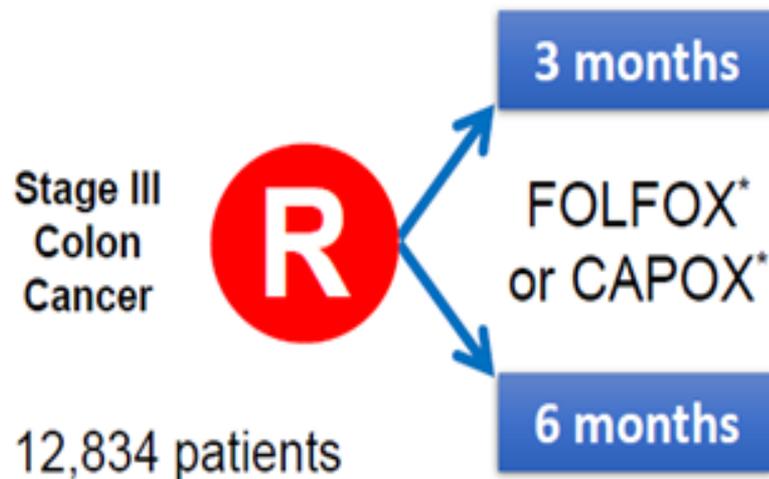
CAPOX, capecitabine plus oxaliplatin; FOLFOX, folinic acid, 5-FU, plus oxaliplatin.

Academic collaboration of clinicians and statisticians from six randomized phase III trials (12 countries)

- **SCOT** (UK, Denmark, Spain, Australia, Sweden, New Zealand), **TOSCA** (Italy), **Alliance/SWOG 80702** (US, Canada), **IDEA France**, **ACHIEVE** (Japan). **HORG** (Greece)

Grothey A et al. 2018

Study Overview



*Investigator's choice, no randomization

- **Objective:**

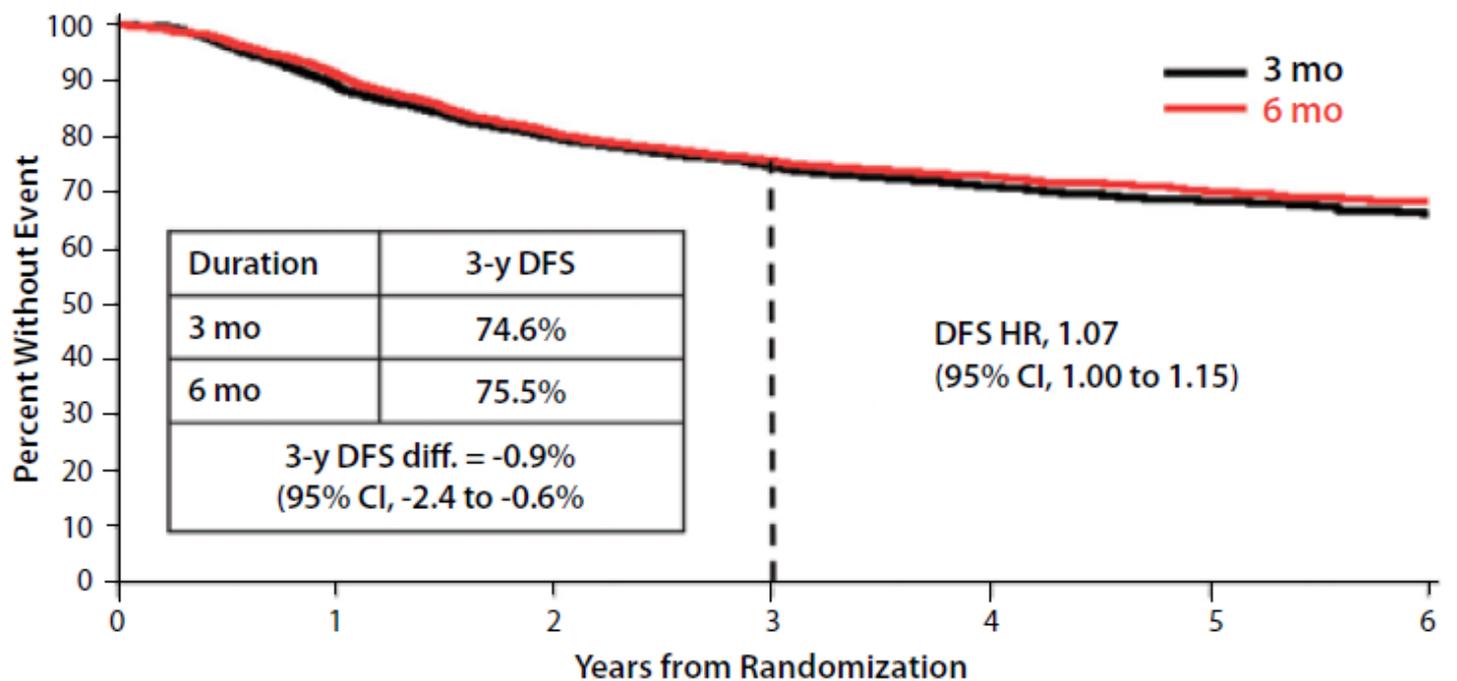
Reduce side-effects of therapy without giving up (too much) anti-cancer efficacy of therapy

- **Non-inferiority design:**

As agreed upon by patient advocates and oncologists, shorter duration of therapy should not sacrifice more than 12% of benefit of adjuvant therapy

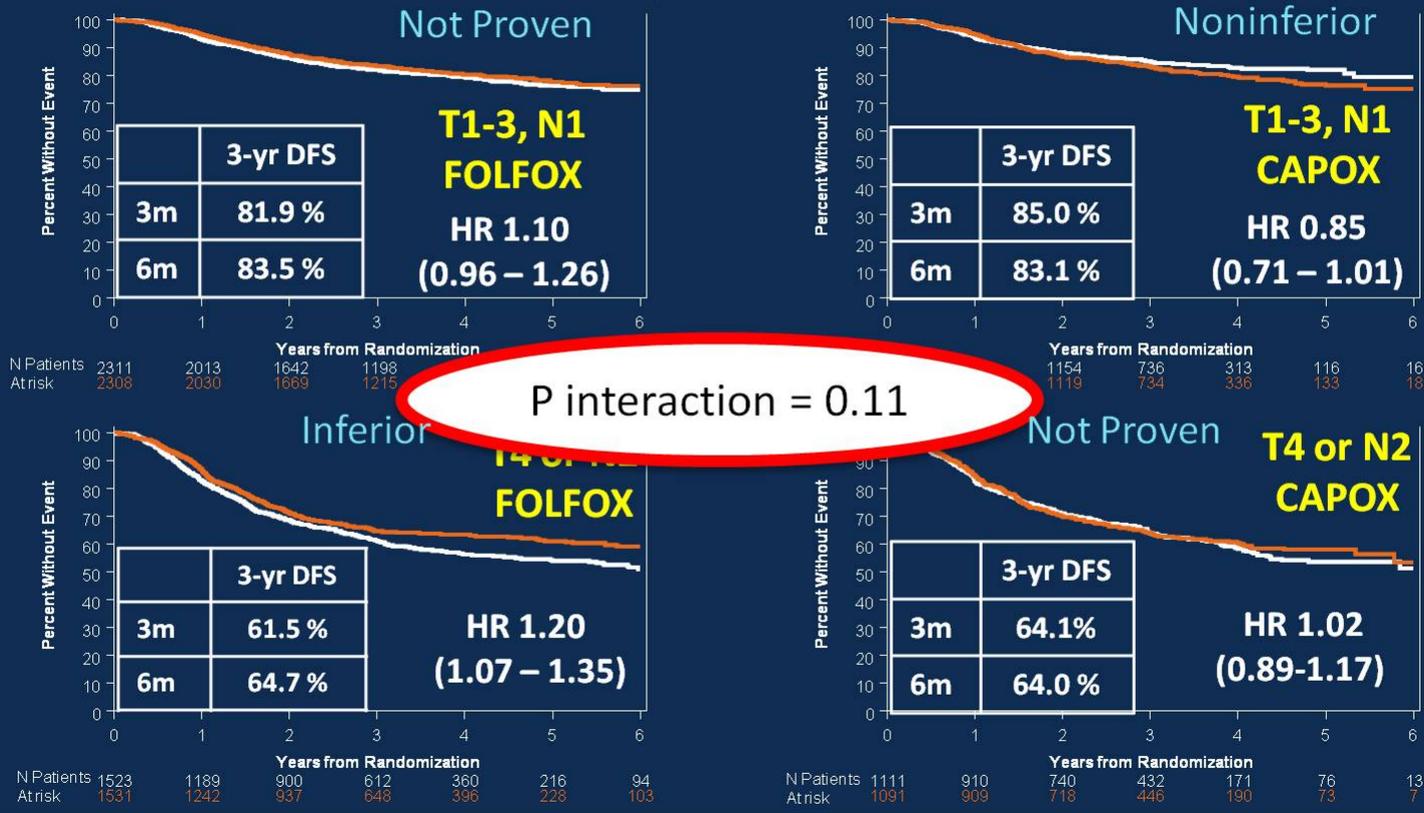
In statistical terms: upper 95% confidence interval of Hazard Ratio (HR) of disease free survival (DFS) should not exceed **1.12**

Primary Outcomes Analysis



N Patients	6424	5446	4464	3000	1609	826	321
At Risk	6410	5530	4477	3065	1679	873	334

DFS Comparison by Risk Group and Regimen in IDEA



Shi et al
ASCO
2017

PRESENTED AT: **ASCO ANNUAL MEETING '17** | **#ASCO17**
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Presented by: Jeffrey Meyerhardt, MD, MPH

IDEA Consensus: Risk-based approach to adjuvant chemotherapy in stage III colon cancer



Risk group

Recommended duration of adjuvant therapy

T1-3 N1

3 months

6 months

(~60% of stage III)

T4 and/or N2

(Or other high-risk factors)

Duration of therapy determined by

- tolerability of therapy
- patient preference
- assessment of risk of recurrence
- Regimen (CAPOX vs FOLFOX)

PRESENTED AT: **ASCO ANNUAL MEETING '17** | **#ASCO17**

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Presented by: Qian Shi, PhD on behalf of IDEA collaborators

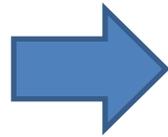
Inestabilidad microsatélite

- Los pacientes con CCR estadio II y con MSI tienen mejor supervivencia global y un beneficio limitado con quimioterapia basada en 5FU

Cáncer de recto estadio II/III



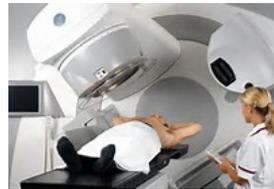
Estadificación local con **MRI** de pelvis
Ecoendoscopia



Radioterapia

(25 Gray, en 5 fracciones
en 1 semana)

OR



Chemoradiotherapy

Radioterapia con 46 - 50.4 Gray +
quimioterapia con 5FU o
capecitabina



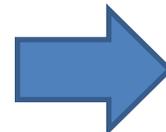
Inmediatamente



Cirugía

+/
+/-

Quimioterapia
adyuvante

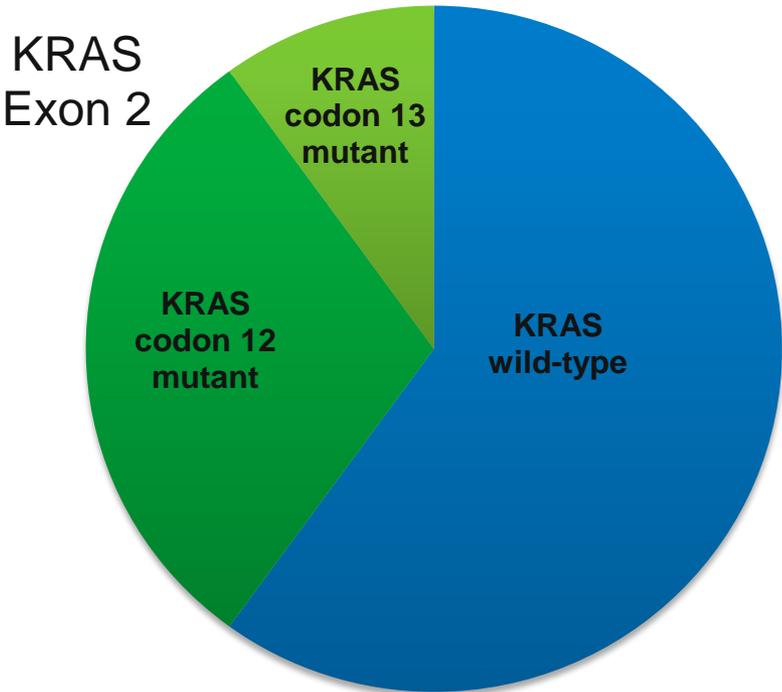


6-8 semanas

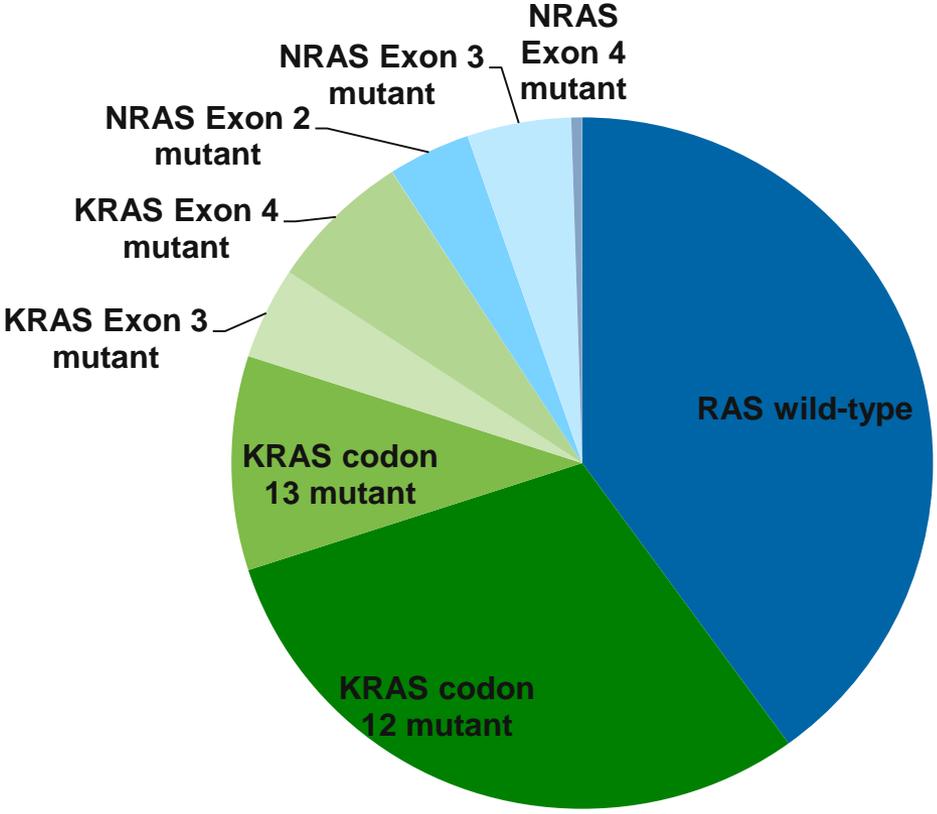
- **Biología Molecular**

Mutaciones RAS total

KRAS exon 2 wild-type (2008)

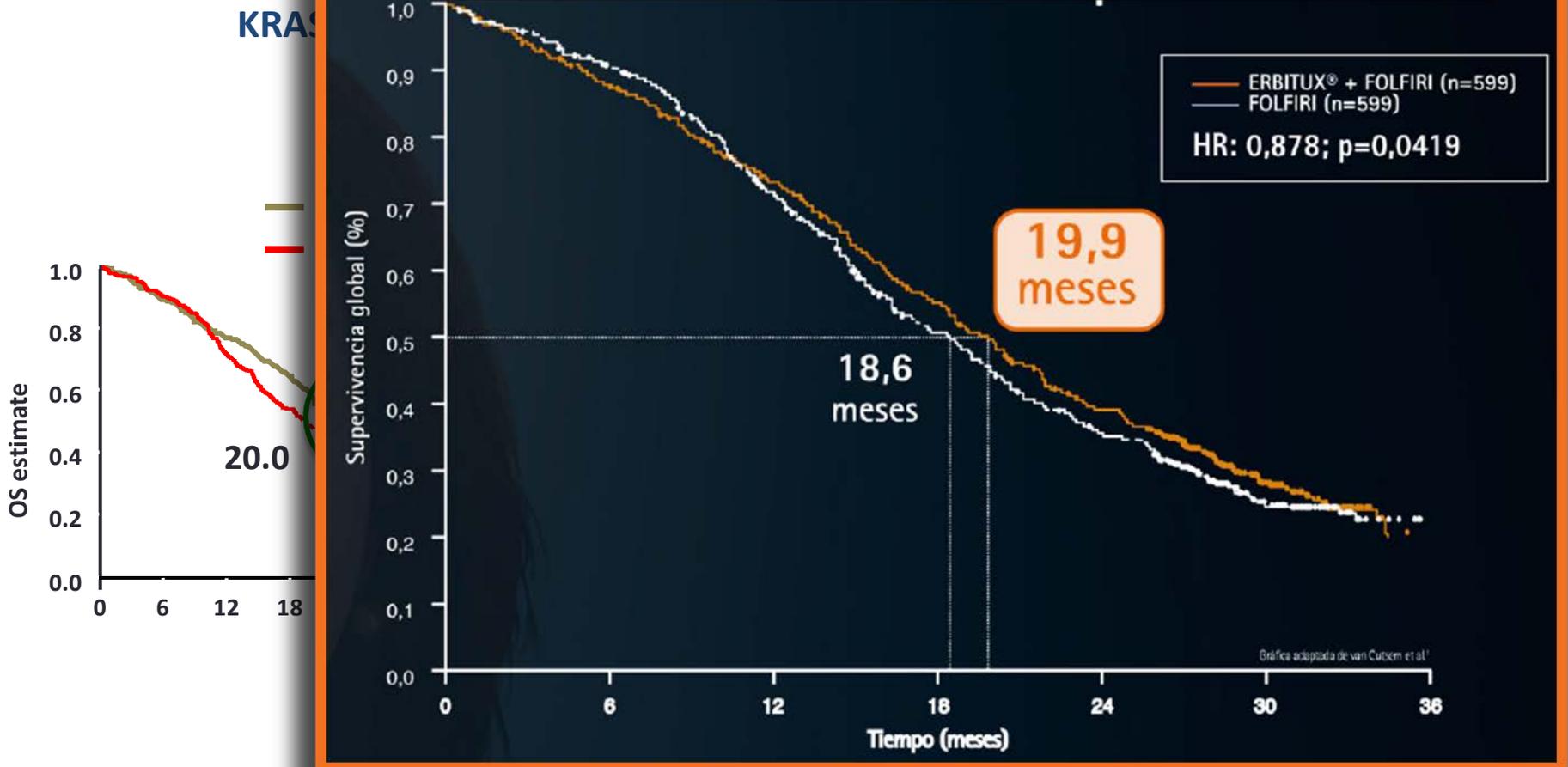


Extended RAS wild-type (2014)

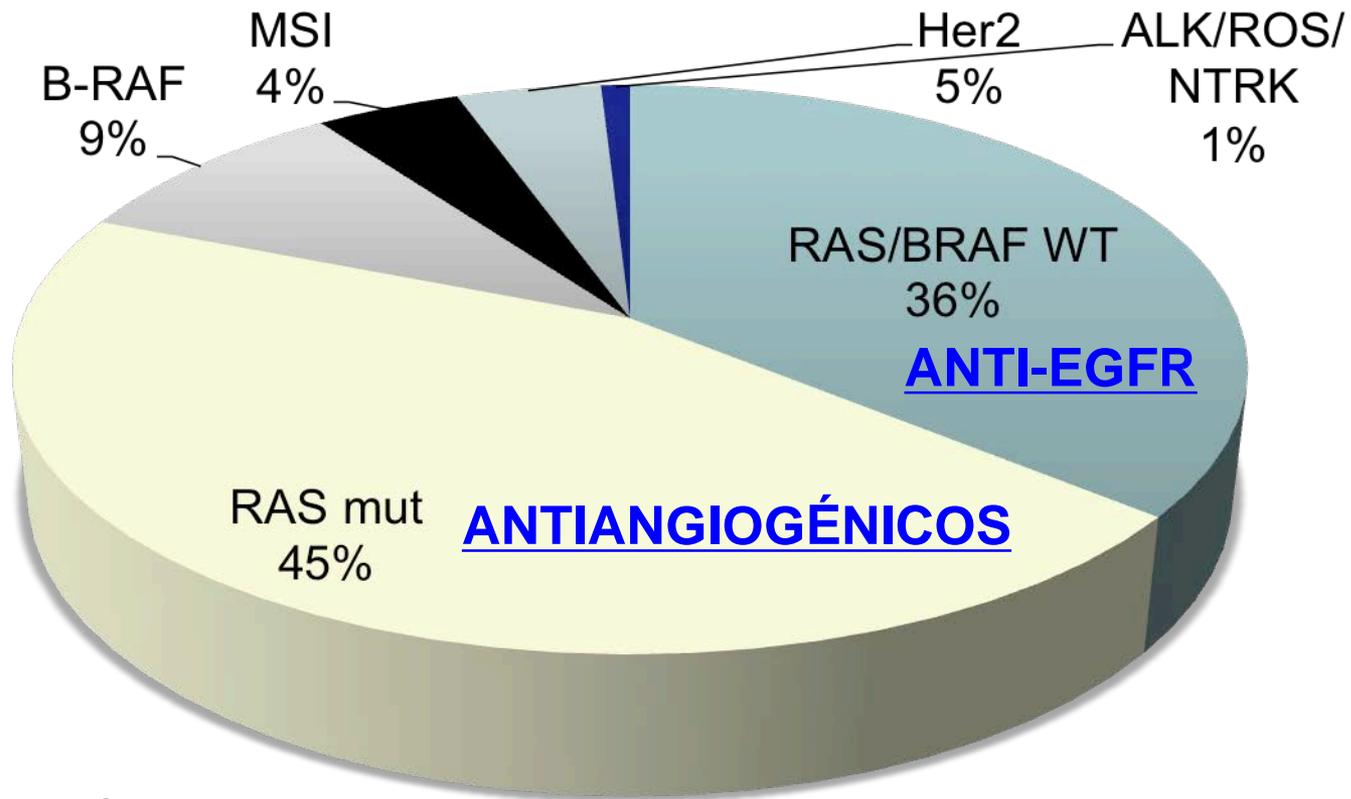


Douillard JY, et al. N Engl J Med 2013; 369:1023-34.

CRYSTAL study: OS



Adapted from 1. Van Cutsem E, et al. J Clin Oncol 2011;29:2011–2019 and 2. Ciardiello F, et al. ASCO 2014 (Abstract No. 3506)



Ras wt: anti-EGFR

RAS Mut: No anti-EGFR

MSI (dMMR): Anti-PD-1

BRAF:

- Tribe (FOLFOXIRI+Bv) GONO, JCO 2015
- SWOG S1406 (Kopetz ASCO GI) (Vem+Cetx+Iri)
- Vemurafenib+Cetx+Ir+Mek ?

HER2:

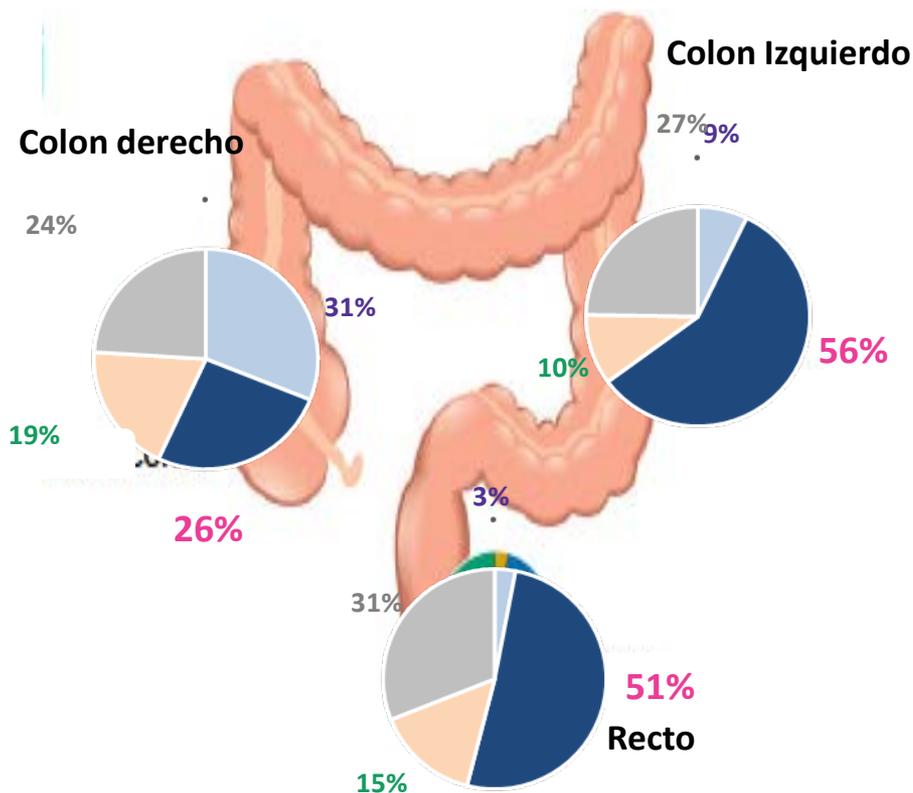
-Heracles (Trastuzumab+Lapatinib) Sartore Bianchi A, Lancet Oncol 2016

1ª Línea: RAS y RAF
2ª Línea: MSI, HER2, etc

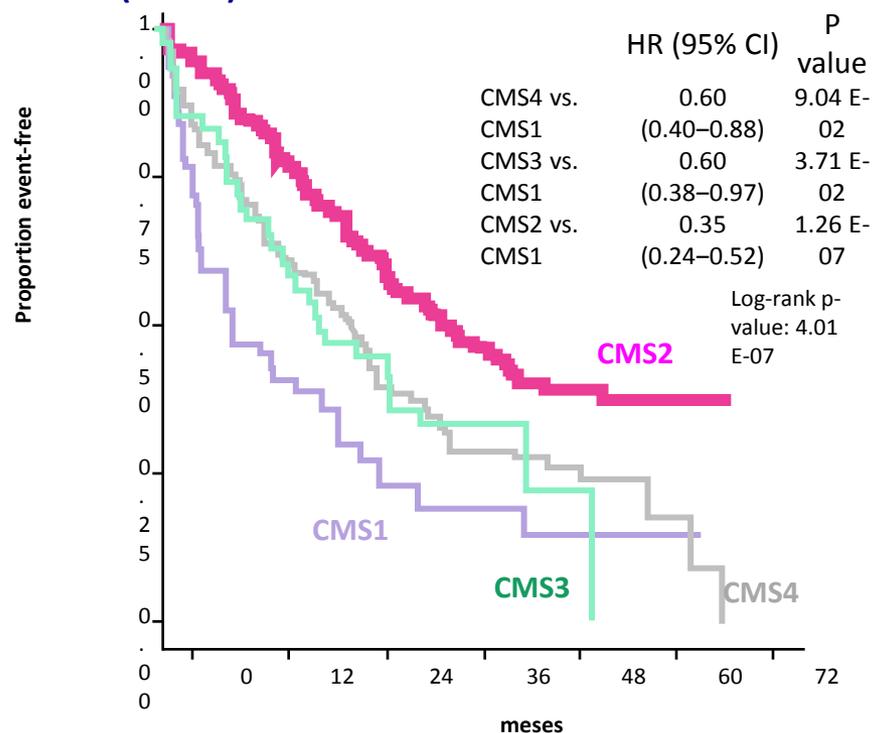
Características de los subgrupos moleculares

CMS1 MSI immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high, hypermethylation	SCNA high	Mixed MSI status, SCNA low, CIMP low	SCNA high
<i>BRAF</i> mutations		<i>KRAS</i> mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration, TGF- β activation, angiogenesis
Worse survival after relapse			Worse relapse-free and overall survival

Clasificación Molecular: CMS 2 es más frecuente en lado Izdo y es de mejor pronóstico



Supervivencia después de la Recurrencia (n=405)



Guinney J, et al. Nat Med 2015;21:1350–

*Tumor location data are in stage I–IV CRC; survival after relapse data are in stage I–III CRC 1356

Subgrupos del RAS WT

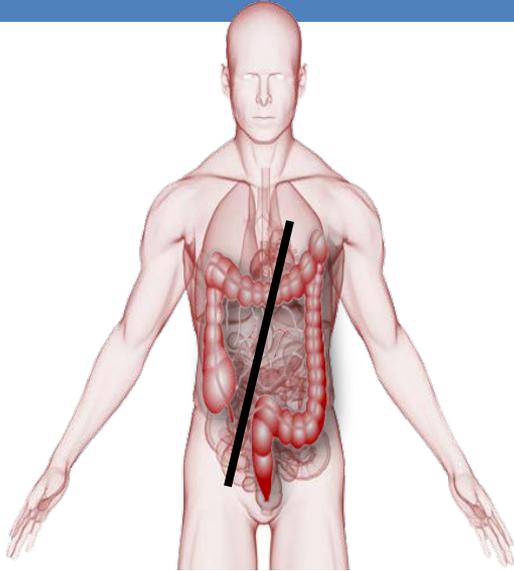
MSI

RAS WT

Colon Derecho

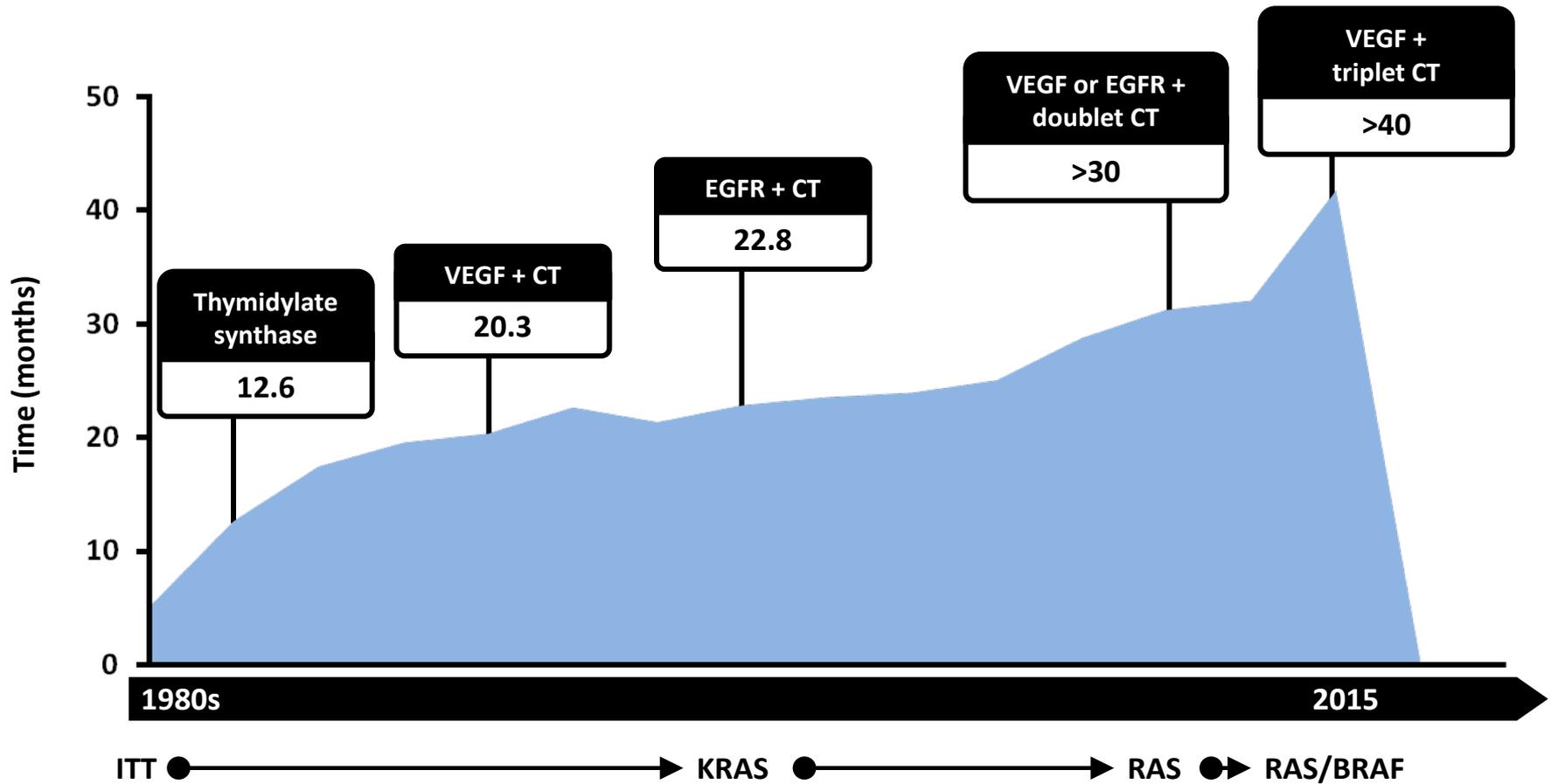
RAS/BRAF
WT

BRAF MUT



- **Tratamiento**

Mas opciones terapéuticas y mejor selección de pacientes incrementa sustancialmente la supervivencia



Scheithauer, et al. BMJ 1993; Saltz, et al. N Engl J Med 2000
 Douillard, et al. Lancet 2000; Goldberg, et al. J Clin Oncol 2004
 Hurwitz, et al. N Engl J Med 2004; Falcone, et al. J Clin Oncol 2007; Saltz, et al. J Clin Oncol 2008
 Bokemeyer, et al. Ann Oncol 2011; Van Cutsem, et al. J Clin Oncol 2011; Douillard, et al. Ann Oncol 2014
 Heinemann, et al. Lancet Oncol 2014; Lenz, et al. ESMO 2014; Loupakis, et al. ASCO 2015

Dobletes en el tratamiento del CCR metastásico

FOLFOX

FOL

F

OX

Folinic acid
(aka leucovorin)

5-**F**lurouracil (5-FU)

Oxaliplatin

FOLFIRI

FOL

F

IRI

Folinic acid
(aka leucovorin)

5-**F**lurouracil (5-FU)

Irinotecan

XELOX
(aka CapeOX)

XEL

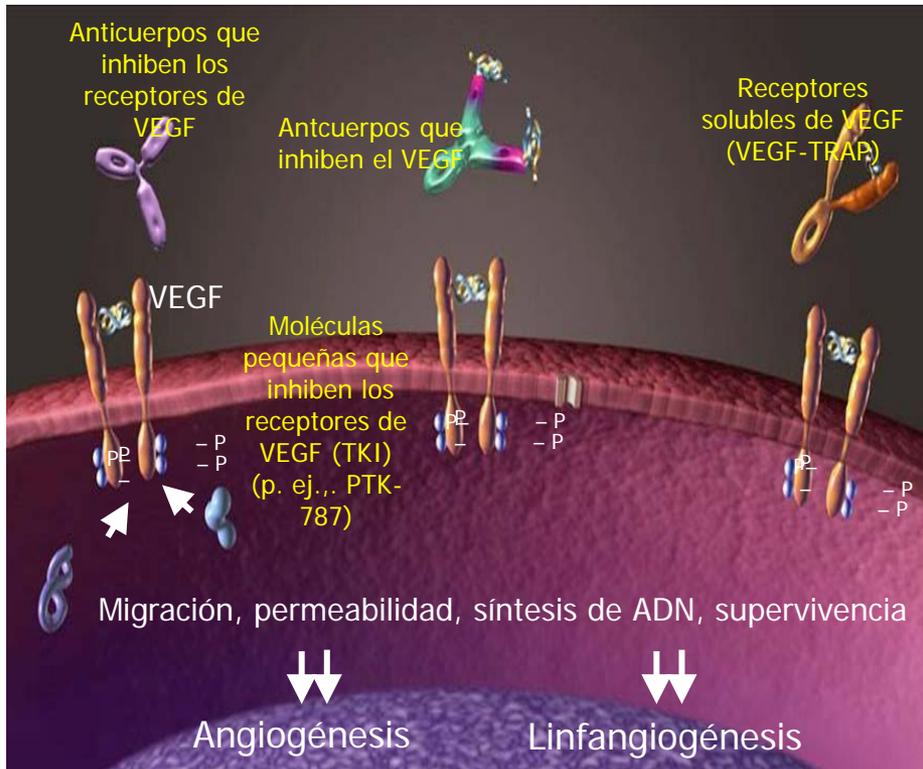
OX

Xeloda[®]
(**C**apecitabine)

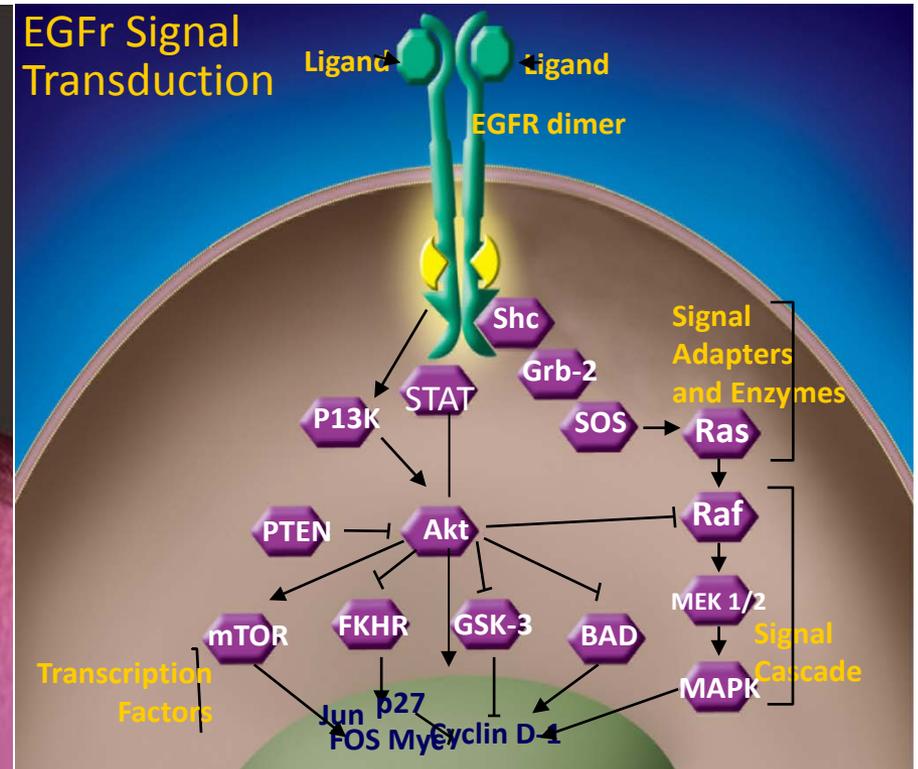
Oxaliplatin

Tratamiento Biológico

Fármacos anti-VEGF



Fármacos anti-EGFR



Bevacizumab for 1L treatment of mCRC: significant benefit with different chemotherapy regimens in phase III trials

Regimen	Tx line	N	Post-study therapy	ORR (%)	Median PFS (months)	Median OS (months)
IFL						
IFL + bevacizumab ¹	1L	813	2L: ~50% 2L: ~50%	35 45*	6.2 10.6*	15.6 20.3*
XELOX/FOLFOX						
XELOX/FOLFOX + bevacizumab ²	1L	1,401	2L: 53% 2L: 46%	38 38	8.0 9.4*	19.9 21.3
Capecitabine						
Capecitabine + bevacizumab ³	1L	313	68% 62%	30 38	5.7 8.5*	18.9 18.9
Capecitabine						
Capecitabine + bevacizumab ⁴	1L	280	37% 37%	10 19*	5.1 9.1*	16.8 20.7
FOLFOXIRI						
FOLFOXIRI + Bevacizumab	1L	508	-	53 65*	9.7 12.2*	25.8 31

1. Hurwitz, et al. NEJM 2004; 2. Saltz, et al. JCO 2008; 3. Tebbutt, et al. JCO 2010
4. Cunningham, et al. ASCO GI 2013; Falcone ASCO 2013

Bevacizumab for 1L treatment of mCRC: significant benefit with different chemotherapy regimens in phase III trials

Regimen	Tx line	N	Post-study therapy	ORR (%)	Median PFS (months)	Median OS (months)
IFL			2L: ~50%	35	6.2	15.6
IFL + bevacizumab ¹	1L	813	2L: ~50%	45*	10.6*	20.3*
XELOX/FOLFOX					8.0	19.9
XELOX/FOLFOX + bevacizumab ²					11.4*	21.3
Capecitabine						18.9
Capecitabine + bevacizumab ³						18.9
Capecitabine						16.8
Capecitabine + bevacizumab ⁴						20.7
FOLFOXIRI					9.7	25.8
FOLFOXIRI + Bevacizumab ⁴				65*	12.2*	31

La adicción de bevacizumab a cualquier esquema de quimioterapia incrementa su eficacia

1. Hurwitz, et al. NEJM 2004; 2. Saltz, et al. JCO 2008; 3. Tebbutt, et al. JCO 2010
4. Cunningham, et al. ASCO GI 2013; Falcone ASCO 2013

Results of Phase III trials with EGFR inhibitors

Trial	Fluoropyrimidine	Irinotecan or oxaliplatin	EGFR inhibitor	Significant improvement in		
				RR	PFS	OS
CRYSTAL	Inf + bolus 5-FU	Irinotecan	Cetuximab	+	+	+
COIN	Inf + bolus 5-FU	Oxaliplatin	Cetuximab	+	+	-
	Capecitabine	Oxaliplatin	Cetuximab	-	-	-
NORDIC	Bolus 5-FU	Oxaliplatin	Cetuximab	-	-	-
PRIME	Inf + bolus 5-FU	Oxaliplatin	Panitumumab	+	+	+

Results of Phase III trials with EGFR inhibitors

Trial	Fluoropyrimidine	Irinotecan or Oxaliplatin	EGFR	Significant improvement in		
				RR	PFS	OS
CRYSTAL					+	+
COIN						-
NORDIC					-	-
PRIME	Inf + bolus 5-FU	Oxaliplatin	Panitumumab	+	+	+

Añadir anti-EGFR a la quimioterapia incrementa la tasa de respuestas, la supervivencia libre de progresión y la supervivencia global

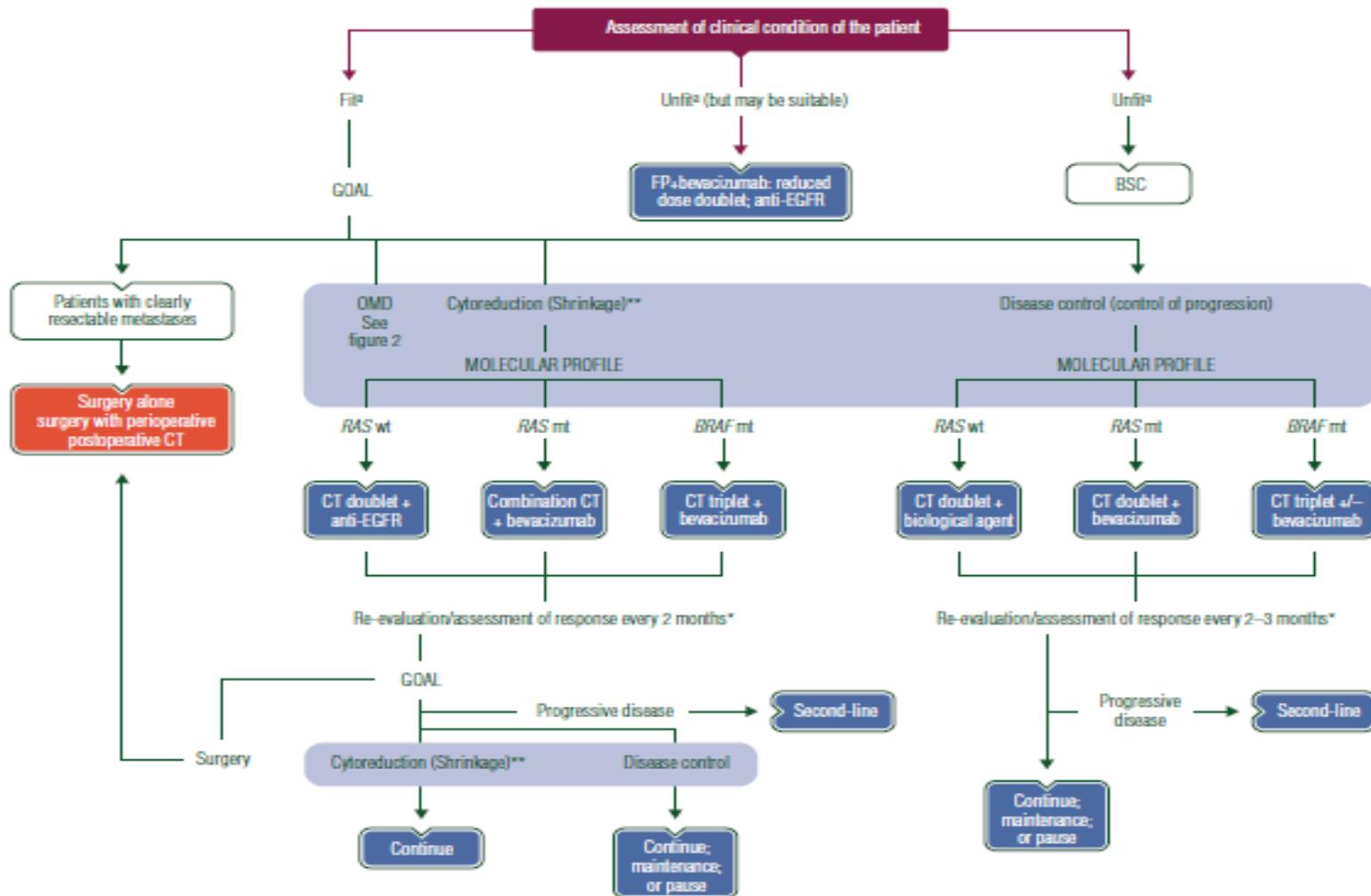
Selección de Tratamiento

Edad
PS
Comorbilidades
Volumen tumoral
- Posible cirugía
rescate
- Síntomas y
agresividad

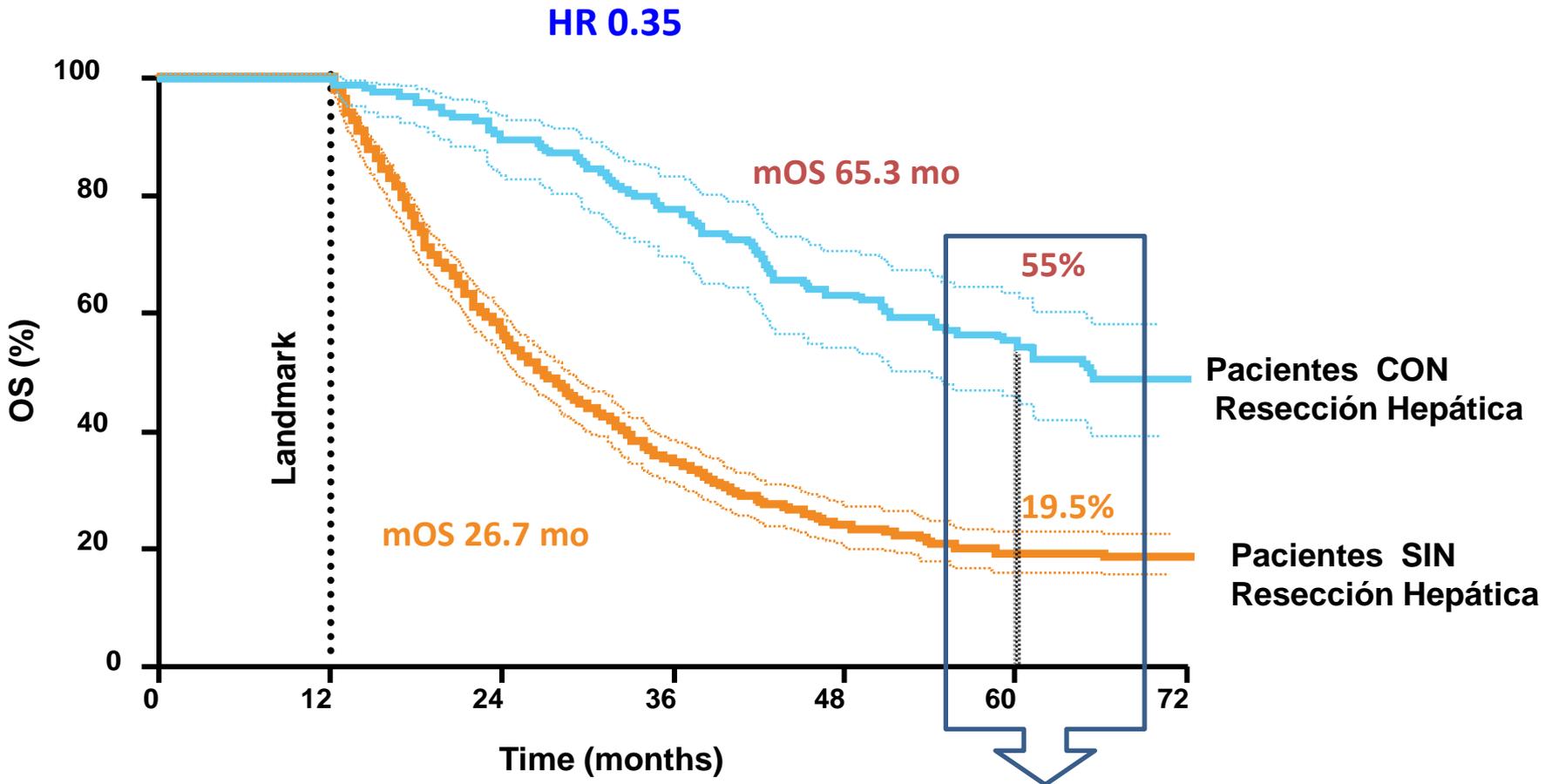


Grado histológico
CEA
MSI
KRAS
NRAS
BRAF

Guías ESMO 2016

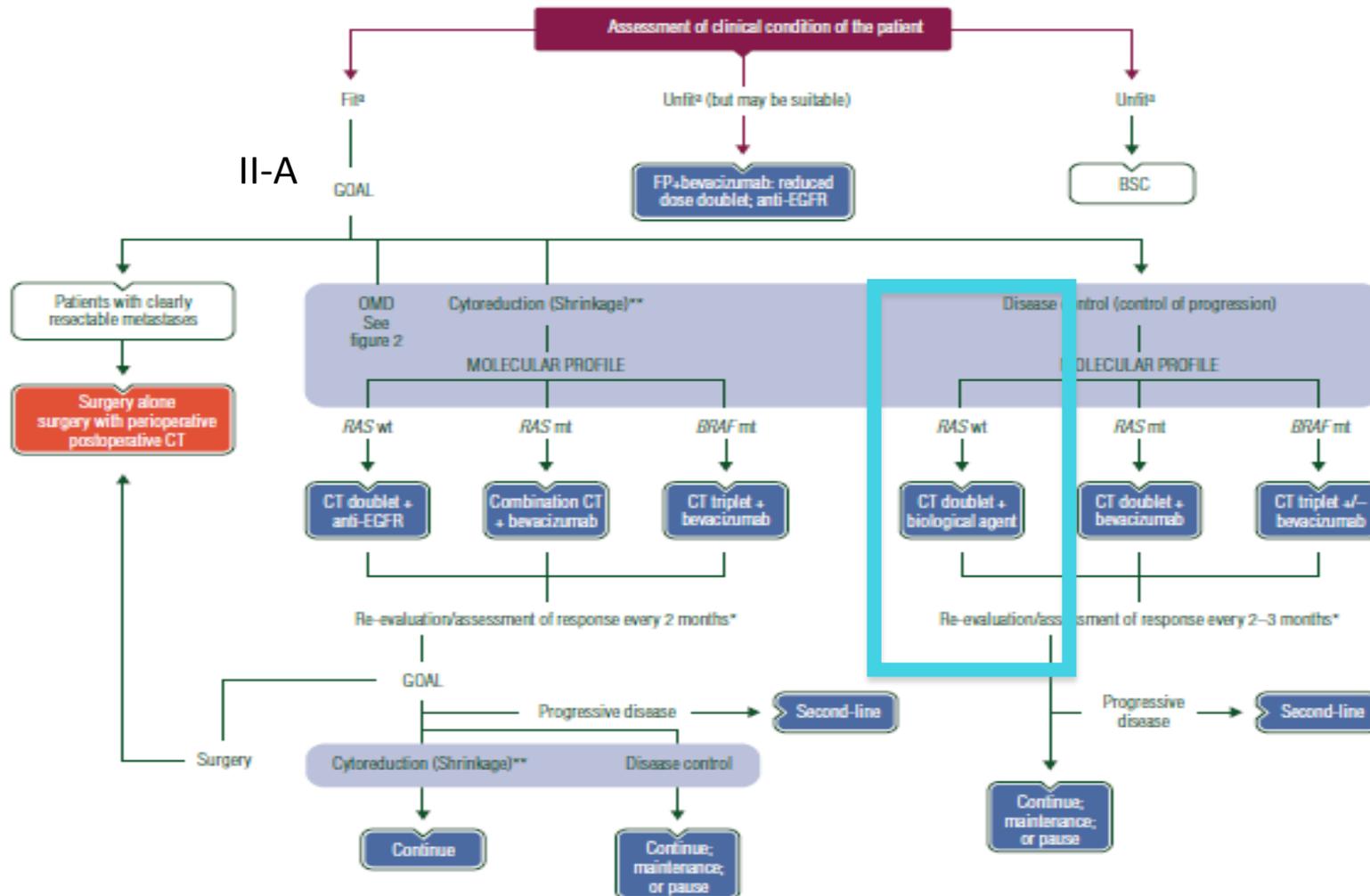


Papel de la resección... La curación



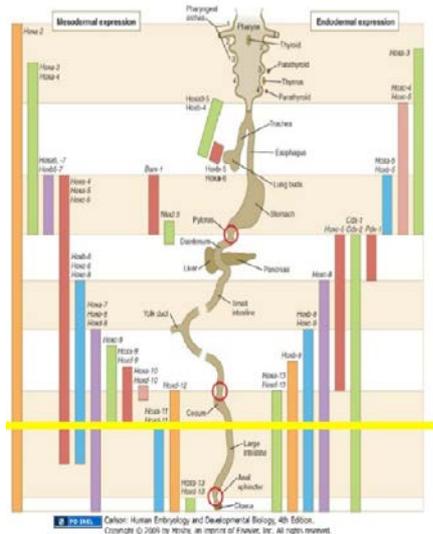


Guías ESMO 2016

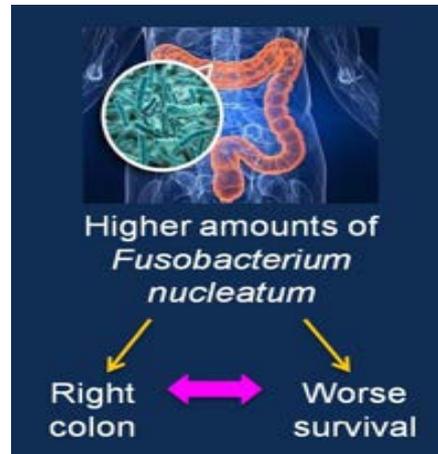


Diferencias del cáncer de colon derecho vs izquierdo

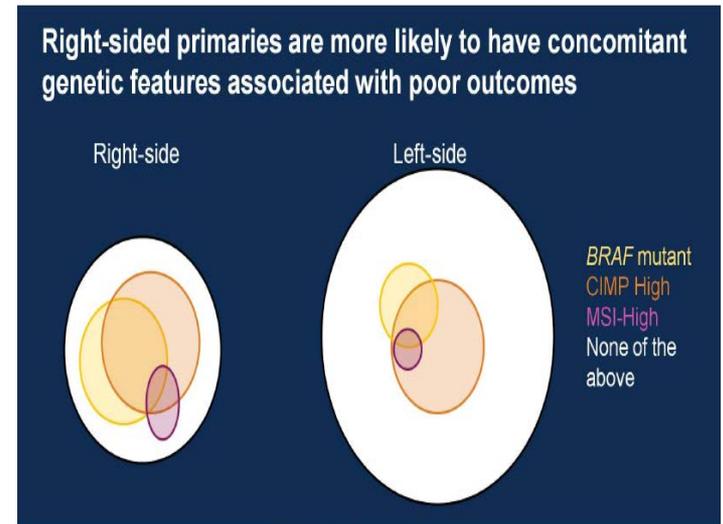
Embriología



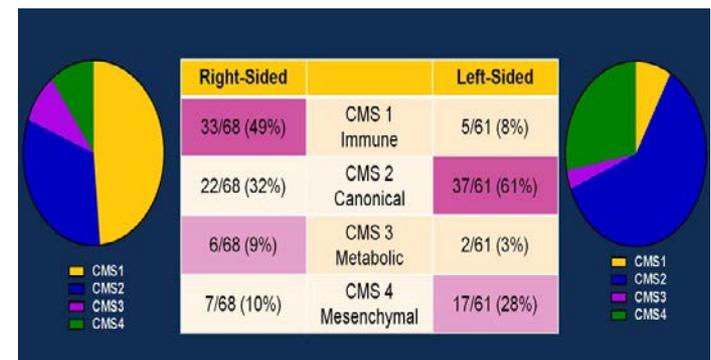
Factores ambientales



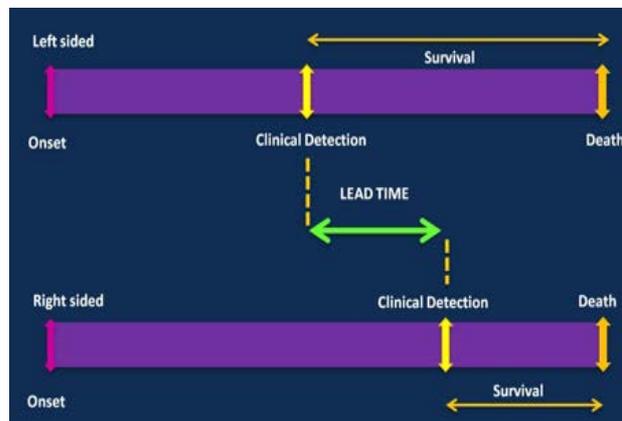
Factores genéticos



Distribución de subtipos moleculares

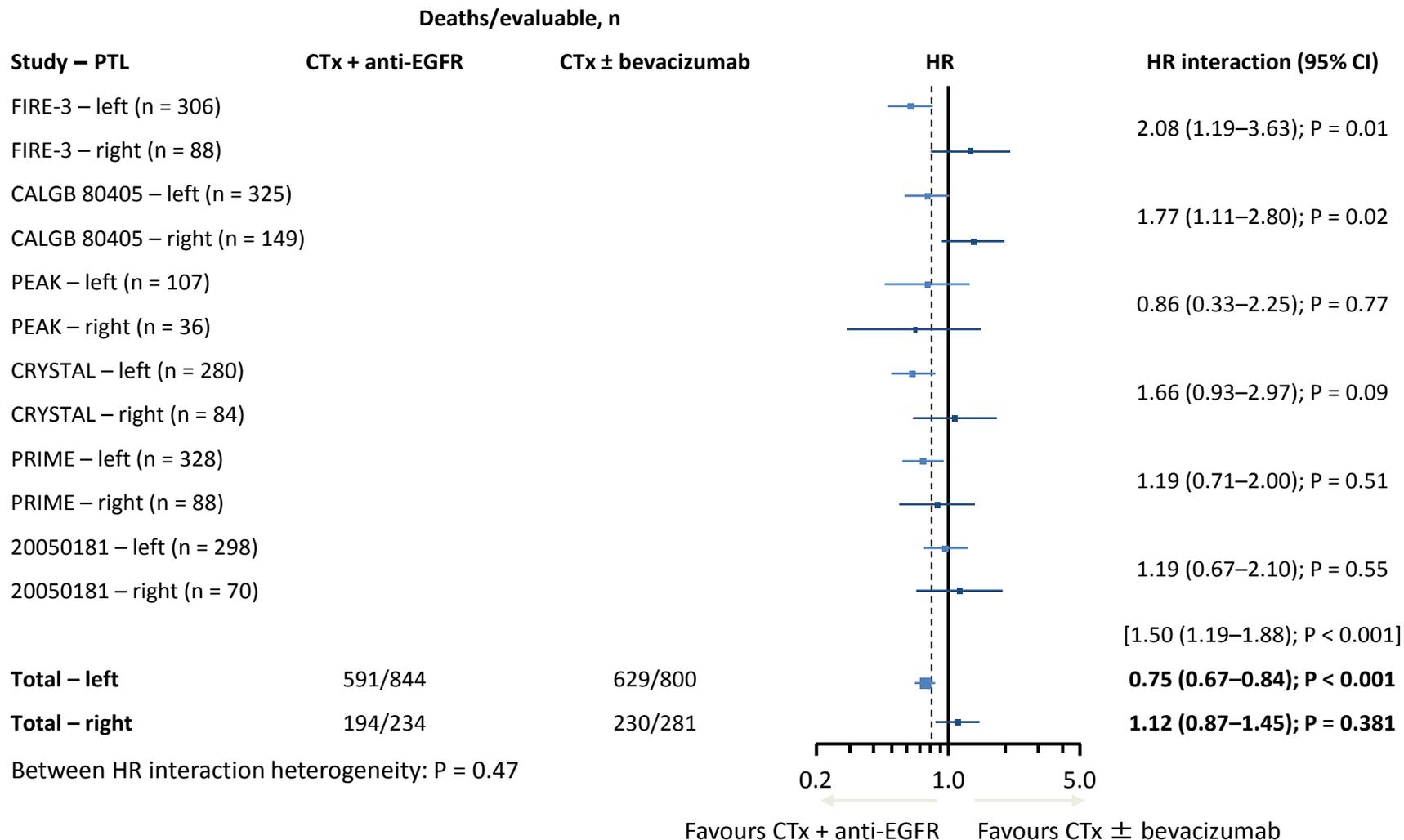


Clínica



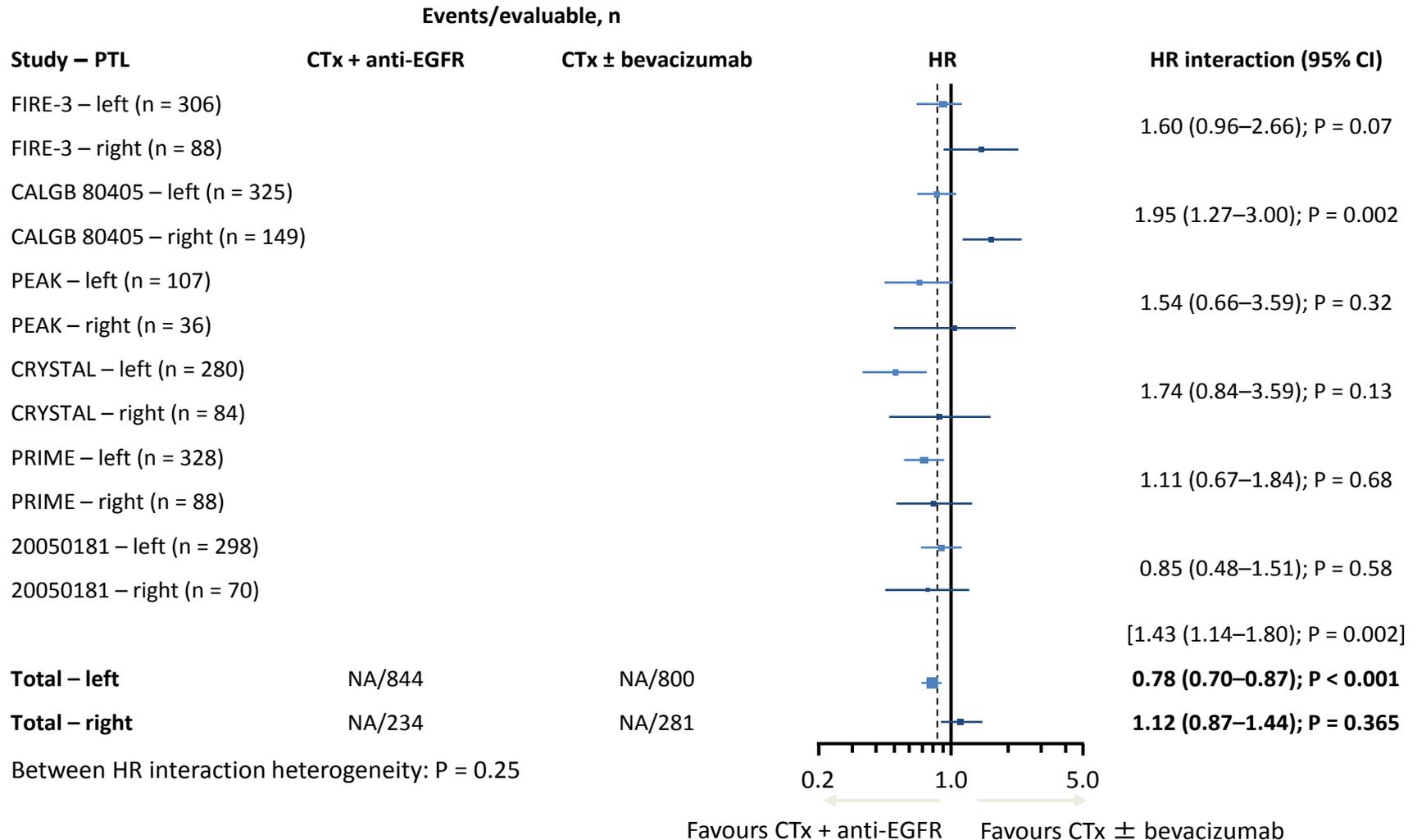
ESMO primary tumour location pooled analysis

Predictive analysis of tumour location for treatment effect on OS (pooled analysis, right vs left)



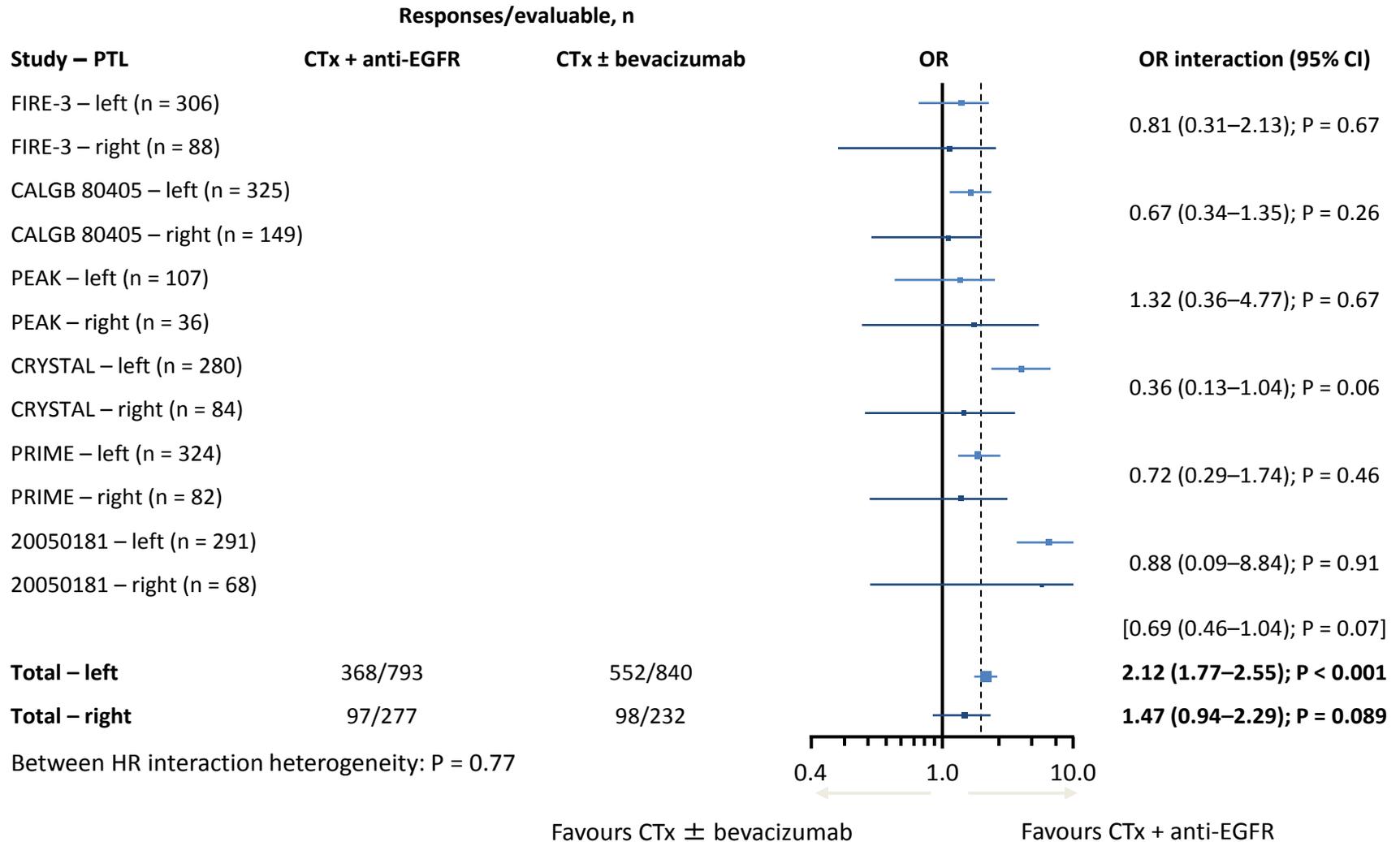
ESMO primary tumour location pooled analysis

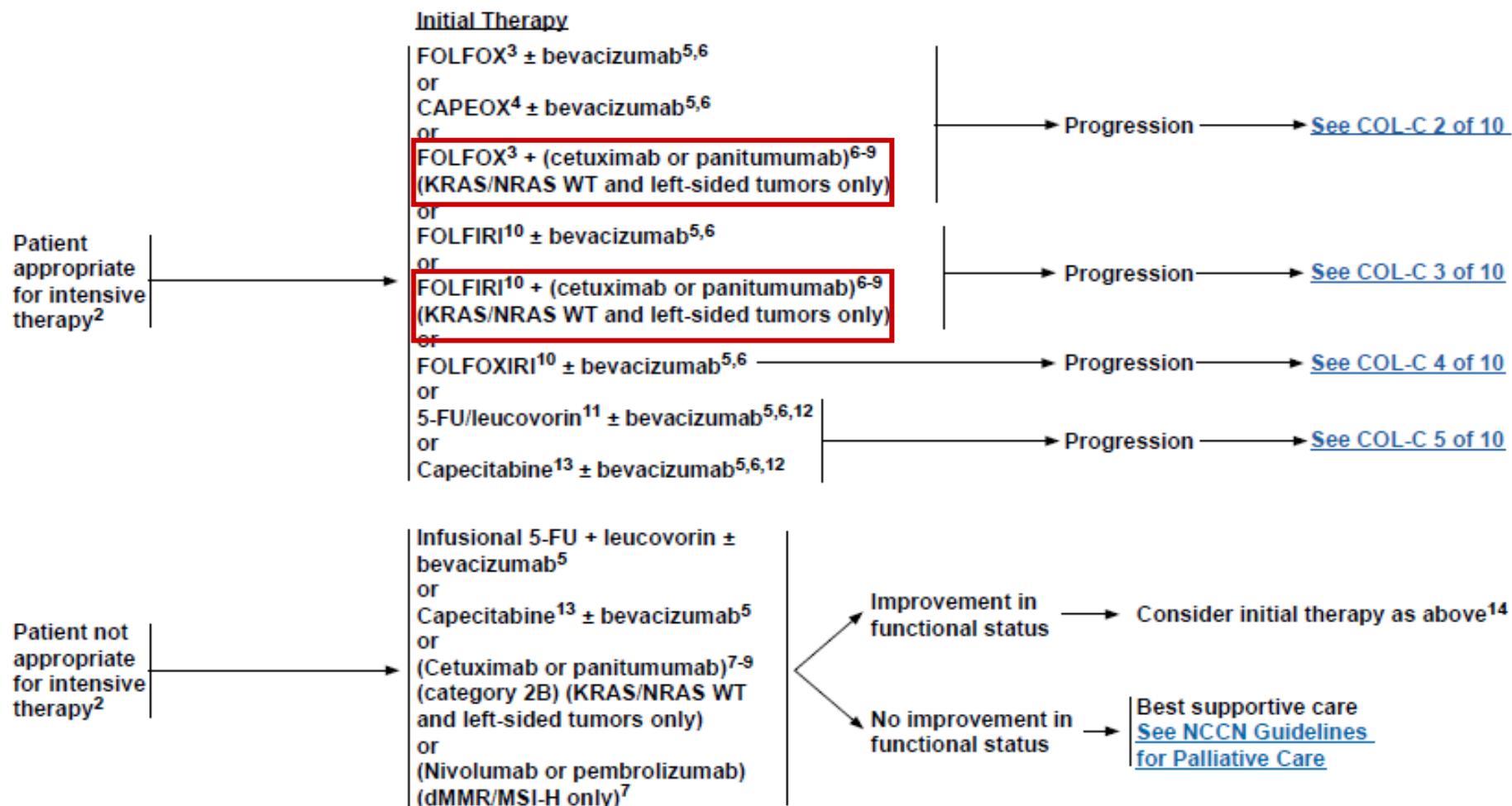
Predictive analysis of tumour location for treatment effect on PFS (pooled analysis, right vs left)



ESMO primary tumour location pooled analysis

Predictive analysis of tumour location for treatment effect on ORR (pooled analysis, right vs left)



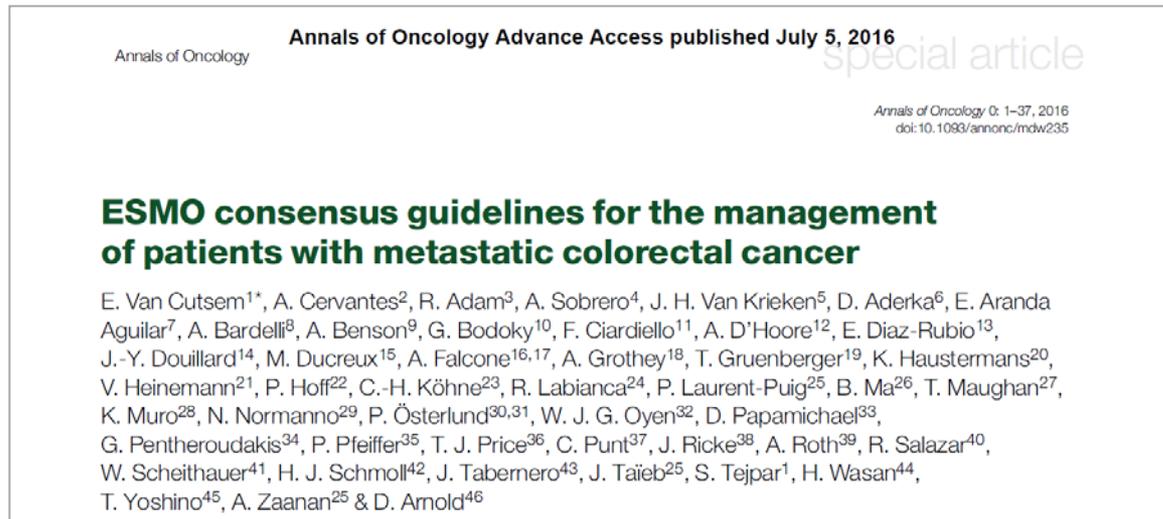
CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:¹ (PAGE 1 of 10)

See footnotes COL-C 6 of 10

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Tratamiento sistémico de 2ª línea



- En pacientes que han progresado a la quimioterapia de 1ª línea se debe cambiar a otro esquema de quimioterapia sin resistencia cruzada
- En paciente que no han recibido **bevacizumab en 1ª línea deben ser considerados para tratamiento con antiangiogénicos** (Bev or Afli) en 2ª línea
- Los pacientes que reciben bevacizumab en 1ª línea deben ser considerados para tratamiento con **antiangiogénicos** (Bev, Afli or Ramu) o con anti-EGFR (RAS WT).

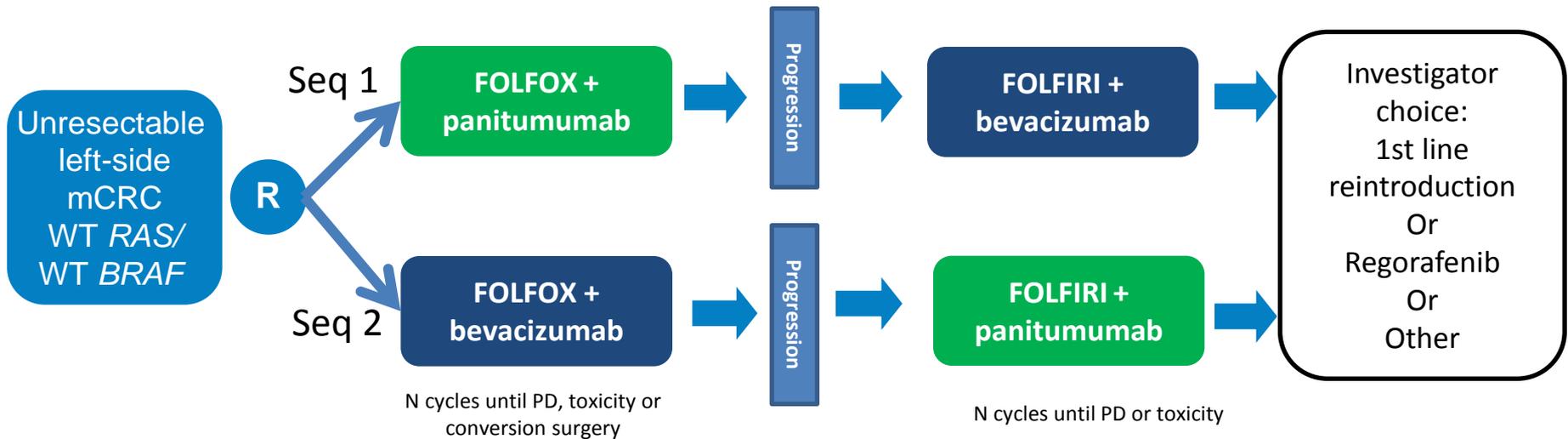
2ª línea Combinaciones con anti-VEGF

	E3200		TML		VELOUR		RAISE	
	Bev + FOLFOX (n=286)	FOLFOX (n=291)	Bev + CT (n=410)	CT (n=409)	Aflib + FOLFIRI (n=612)	Plac + FOLFIRI (n=614)	Ramu + FOLFIRI (n=536)	Plac + FOLFIRI (n=536)
Bev before?	<i>none</i>		<i>all</i>		<i>30%</i>		<i>all</i>	
mOS, months	12.9	10.8	11.2	9.8	13.5	12.1	13.3	11.7
	HR=0.75 p=0.0011		HR=0.81 p=0.0062		HR=0.82 p=0.0032		HR=0.84 p=0.022	
mPFS, months	7.3	4.7	5.7	4.1	6.9	4.7	5.7	4.4
	HR=0.61 p<0.0001		HR=0.68 p<0.0001		HR=0.76 p=0.00007		HR=0.79 p=0.0005	

2ª línea Combinaciones con anti-EGFR

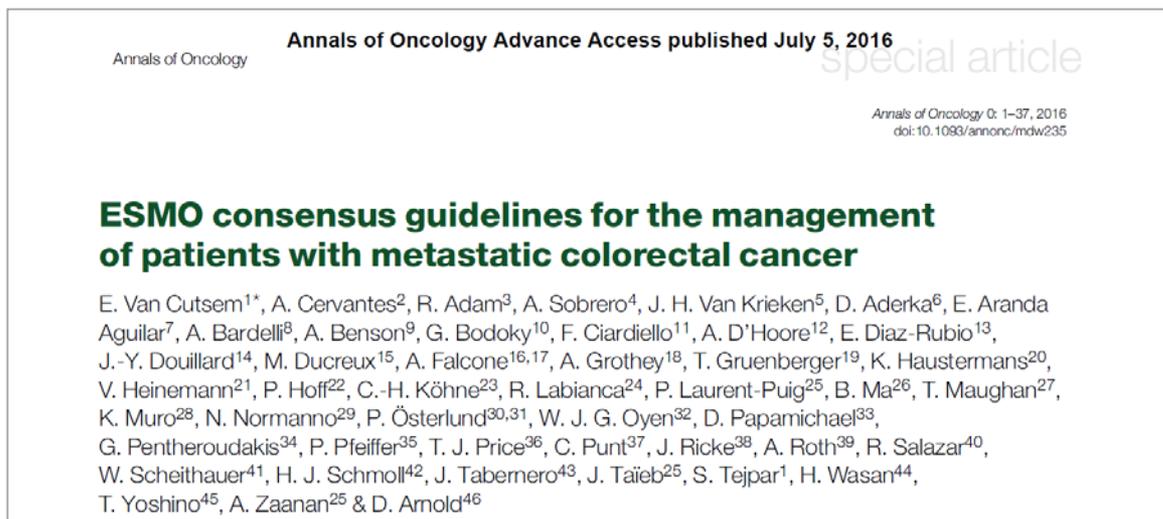
	BOND (phase 2)		EPIC		Peeters 2010		PICCOLO	
	Cetux + IRI (n=286)	IRI (n=291)	Cetux + IRI (n=648)	IRI (n=650)	Pani + FOLFIRI (n=303)	FOLFIRI (n=294)	Pani + IRI (n=230)	IRI (n=230)
mOS, months	8.6	6.9	10.7	10.0	14.5	12.5	10.5	10.4
	HR=0.91 p=0.48		HR=0.975 p=0.71		HR=0.85 p=0.12		HR=1.01 p=0.91	
mPFS, months	4.5	1.5	4.0	2.6	5.9	3.9		
	HR=0.54 p<0.001		HR=0.692 p<0.0001		HR=0.73 p=0.004		HR=0.78 p=0.015	

CR-SEQUENCE: Planned study design



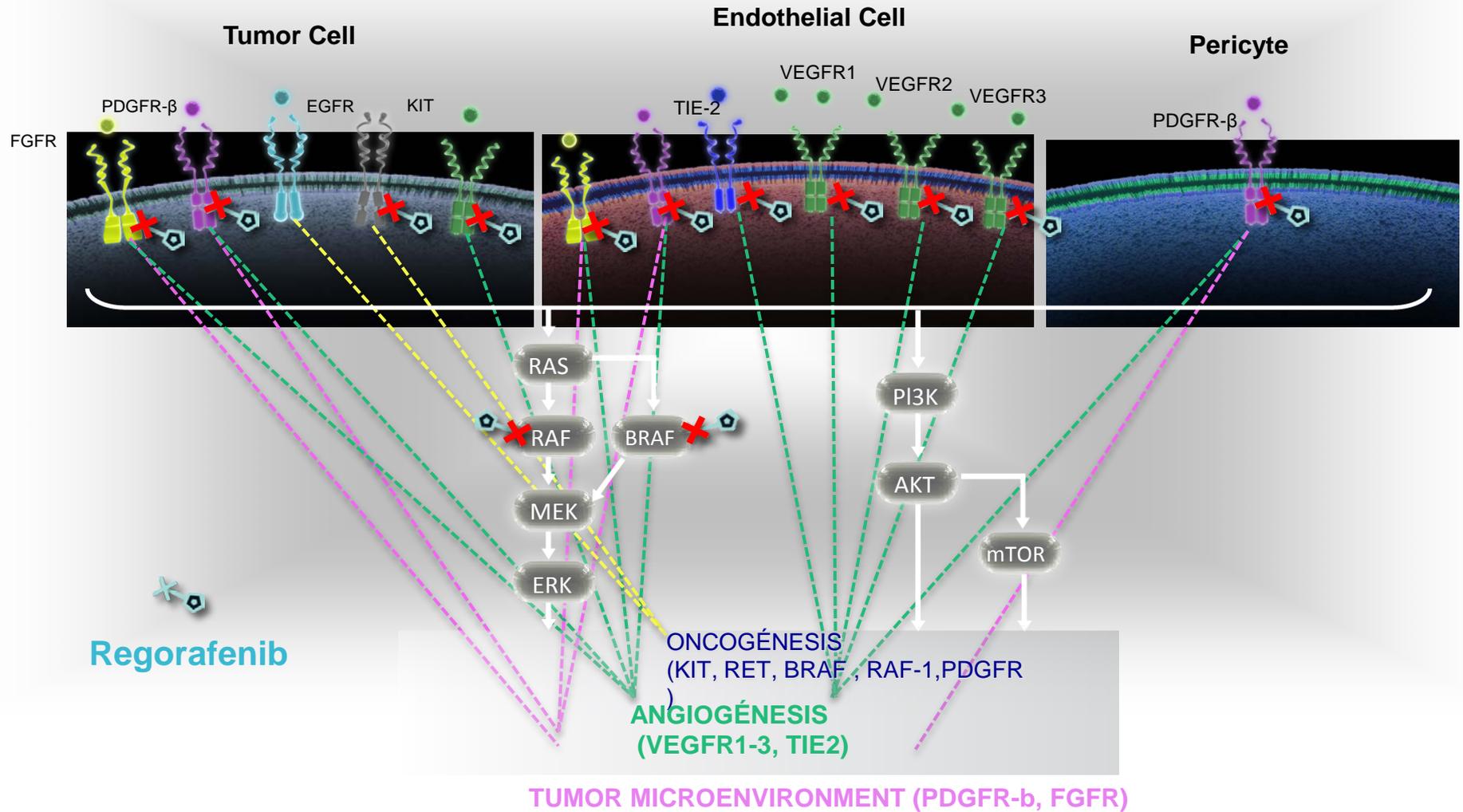
- New RCT have to stratify by location
- If all the sequence matters we need prospective RCT based on molecular characteristics, in a dynamic scenario
- Primary endpoint: 2nd progression/exitus free rate. (PFS1+PFS2): 30 vs 20 months. Total of 332 patients

Tratamiento Sistémico en 3ª línea

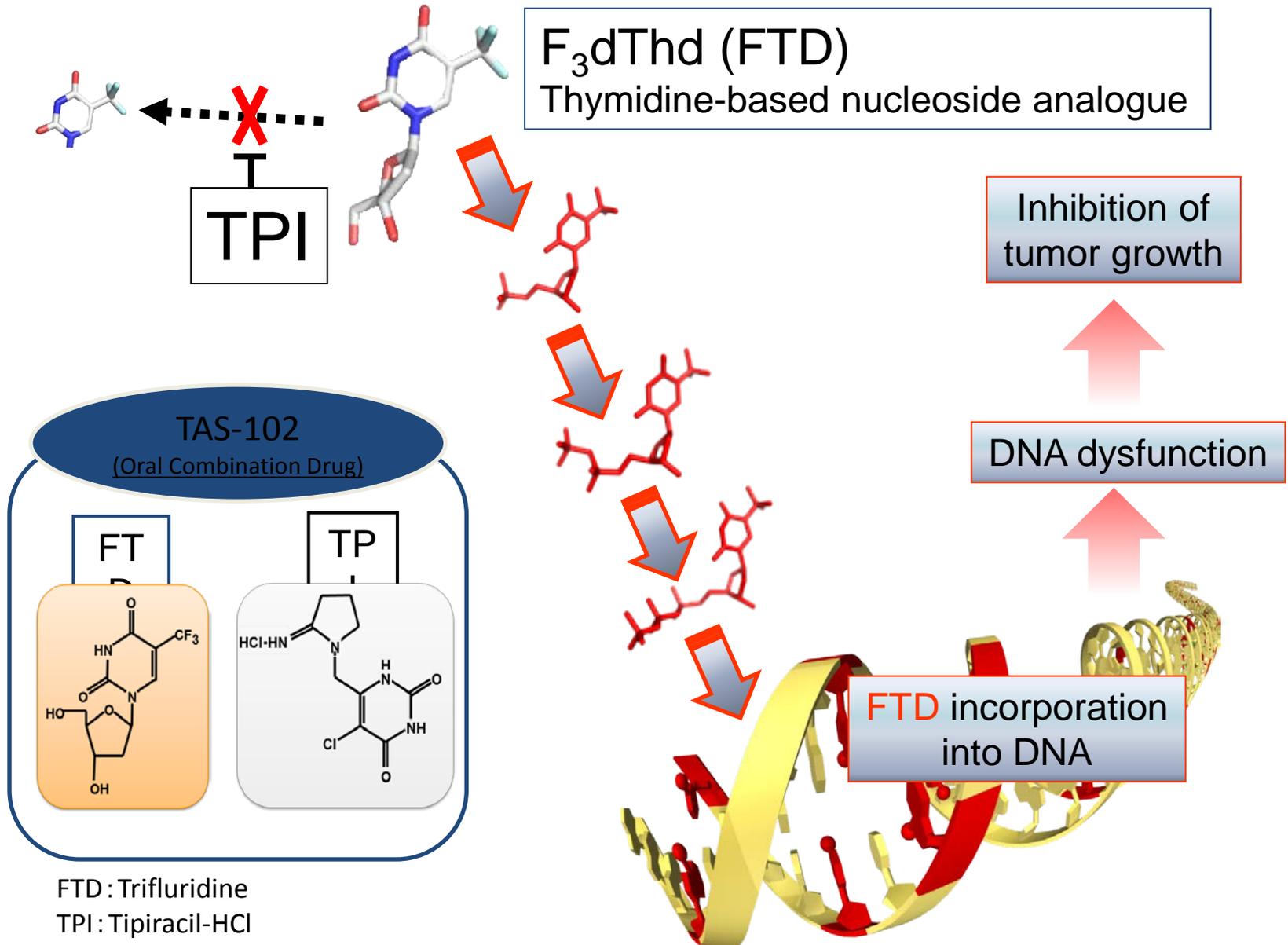


- In RAS WT and BRAF WT patients not previously treated with EGFR antibodies, **cetuximab or panitumumab** therapy should be considered
- **Regorafenib** is recommended in patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in RAS wild-type patients with EGFR antibodies. Regorafenib is superior to placebo in terms of OS, although there are **toxicity concerns in frail patients**.
- **Trifluridine/tipiracil** is recommended for patients pretreated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in RAS wild-type patients with EGFR antibodies.

MECANISMO DE ACCIÓN DE REGORAFENIB

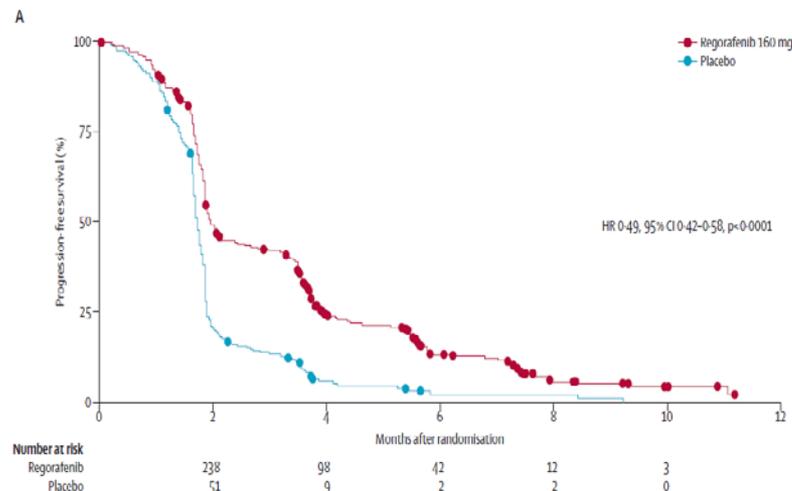
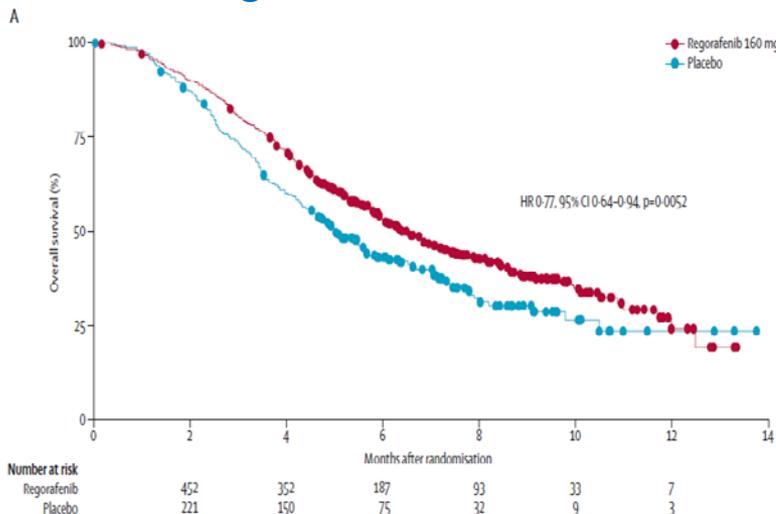


Trifluridine/tipiracil

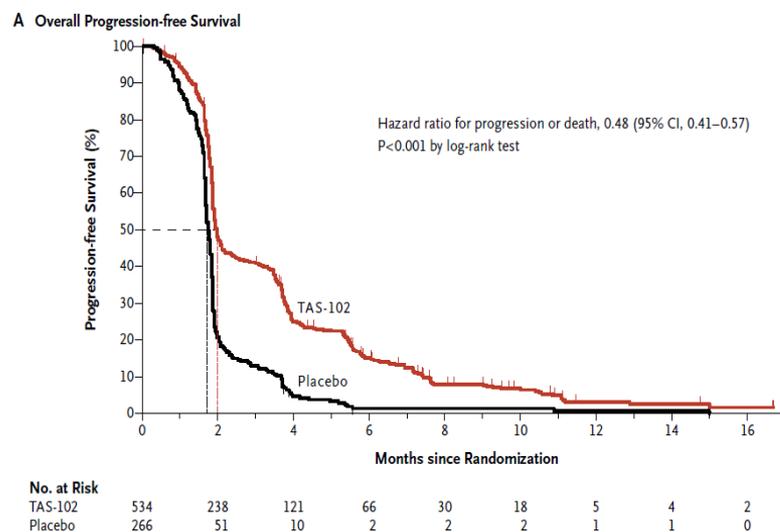
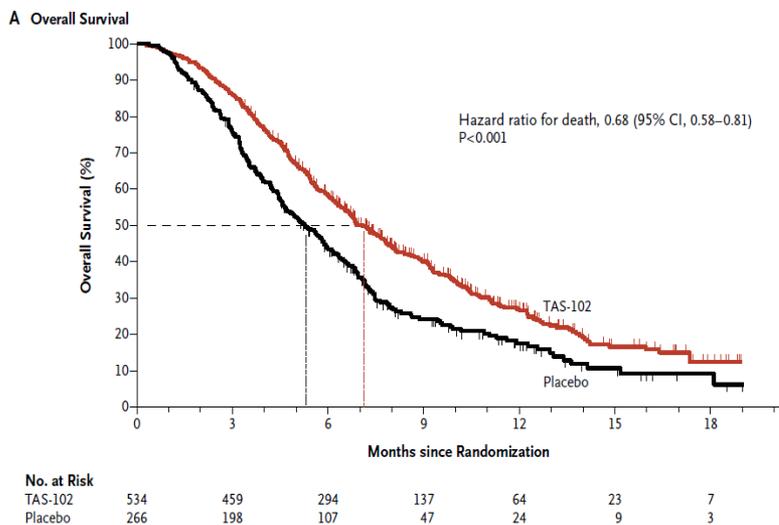


Regorafenib and trifluridine/tipiracil in refractory mCRC:

CORRECT: regorafenib



RECURSE: trifluridine/tipiracil



Desarrollo futuro en CCR

- Mejor selección de pacientes
- Identificación de grupos moleculares y dianas terapéuticas

BRAF^{V600E} predictive value in metastatic CRC

Prevalence ~ 8%

SWOG S1406

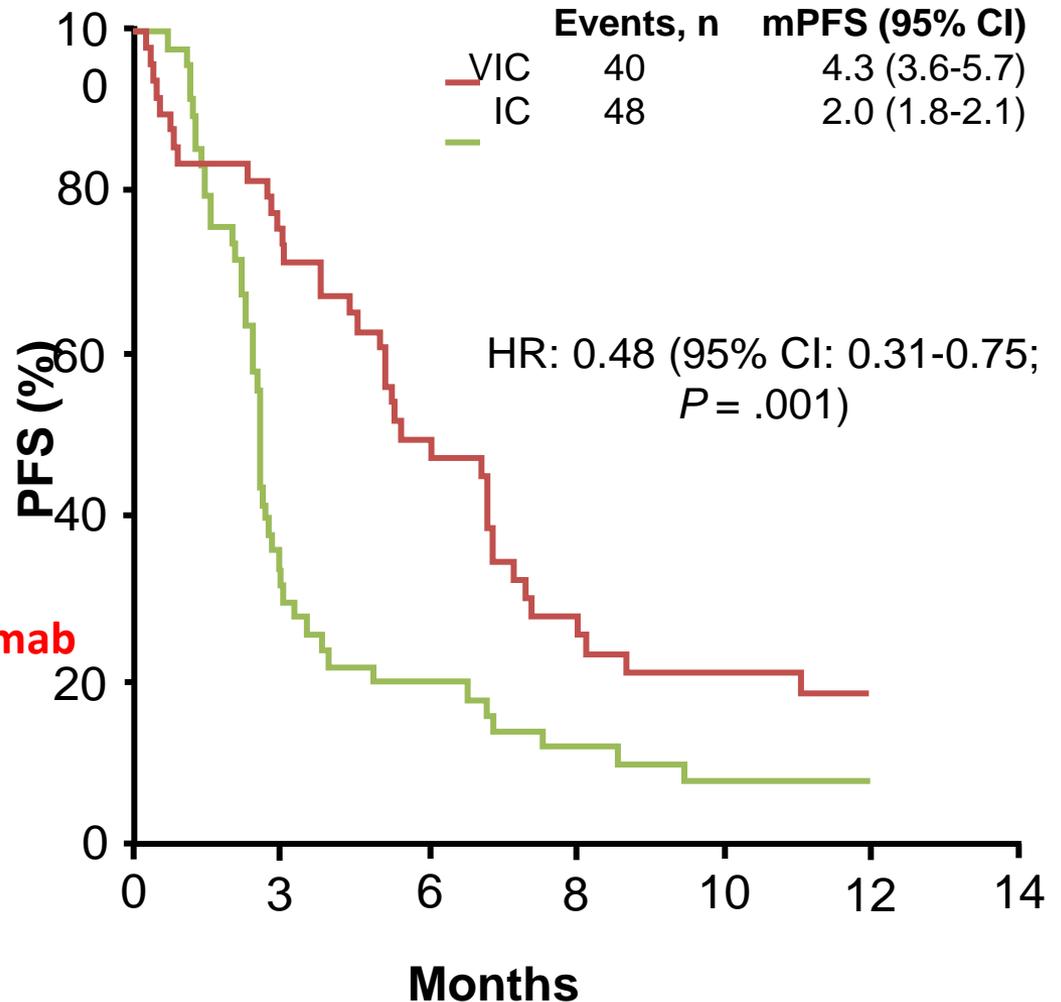
Phase II

1-2 prior lines

No prior anti-EGFR/BRAF/MEK

VIC – Vemurafenib, Irinotecan, Cetuximab

IC – Irinotecan, Cetuximab



Phase III Registration Trial of Encorafenib in BRAF V600E mutated CRC

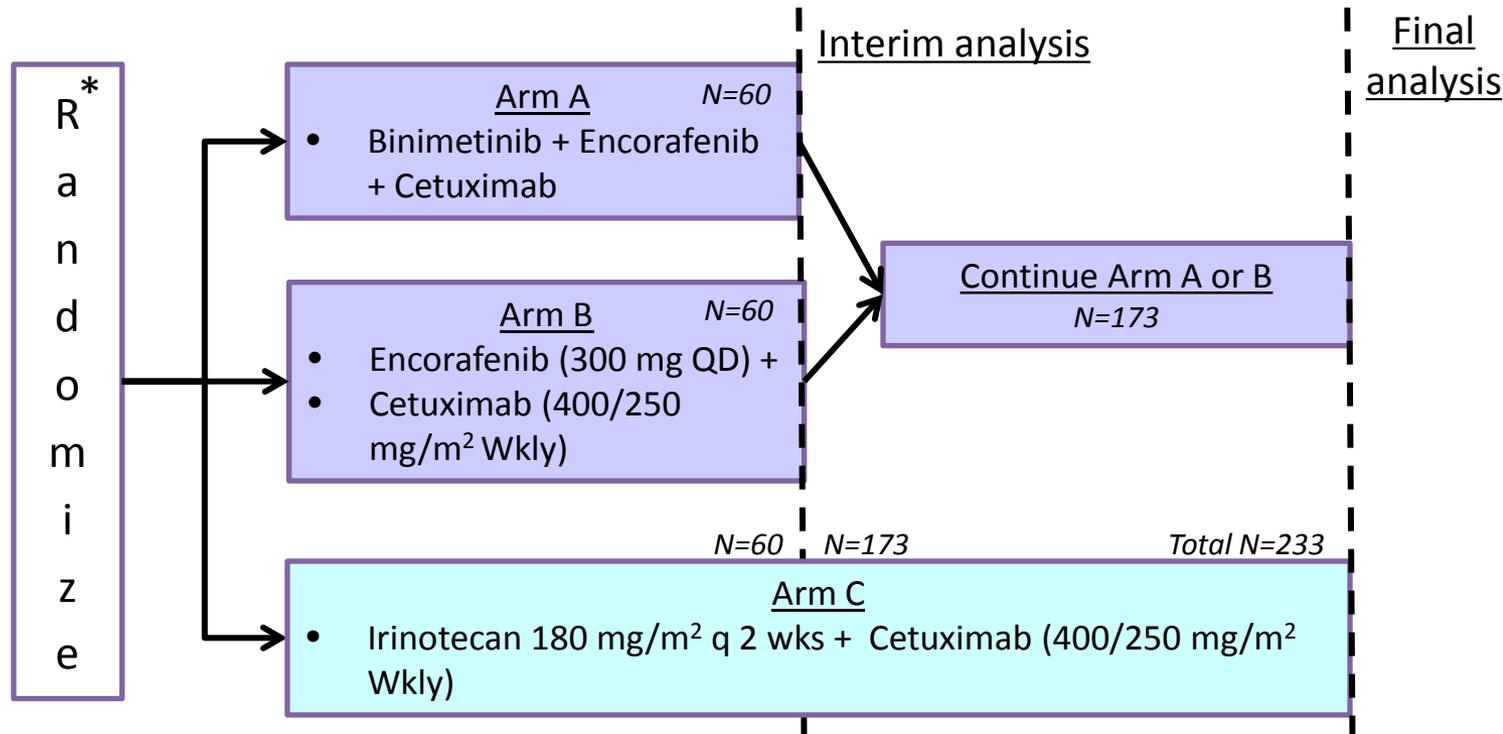
Safety Lead-in

- 1^o objective: confirm Phase 3 dose

- Binimetinib (45 mg BID) +
- Encorafenib (300 mg QD) +
- Cetuximab (400/250 mg/m² Wkly)
N=20

Phase 3

- 1^o objective: Overall Survival
- Key 2^o objective: ORR
- Other 2^o objectives: PFS, DOR, TTR



*Stratification factors: ECOG (0 vs. 1), prior irinotecan (yes vs. no), region (North America vs. rest of world)

HER2 como diana en CCRm: HERACLES trial: Lapatinib + Trastuzumab

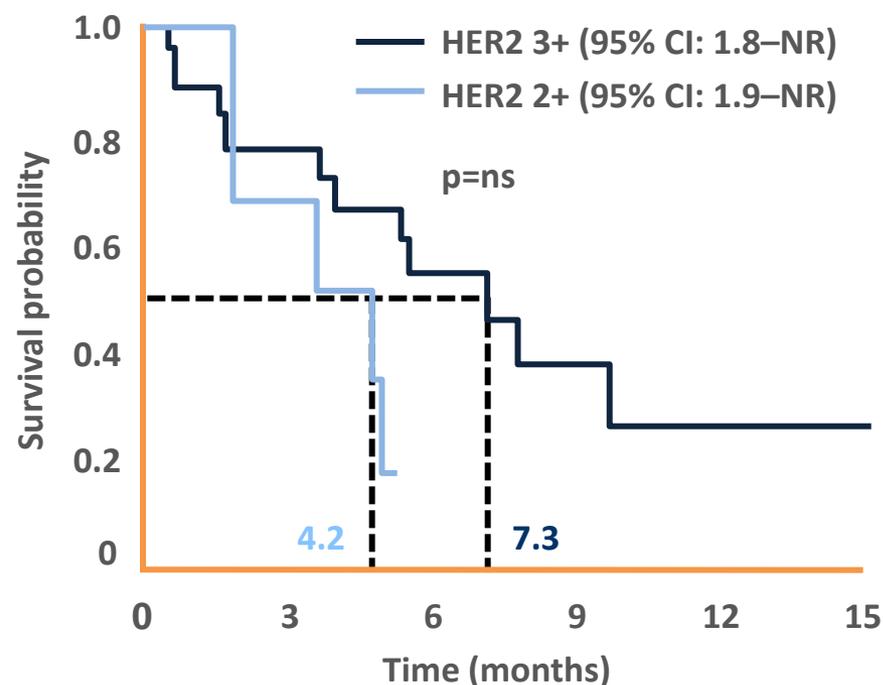
N: 54 previamente tratados HER2 +

Response rate

Response	n (%)
ORR	8 (34.7)
CR	1 (4.3)
PR	7 (30.4)
SD ≥4 months	7 (30.4)
SD <4 months	3 (13.0)
PD	5 (21.7)

- Primary endpoint was met with 8/23 objective responses (as per protocol, 6/27 needed to declare the study positive)
- Disease control rate (DCR): 78%

TTP



MSI

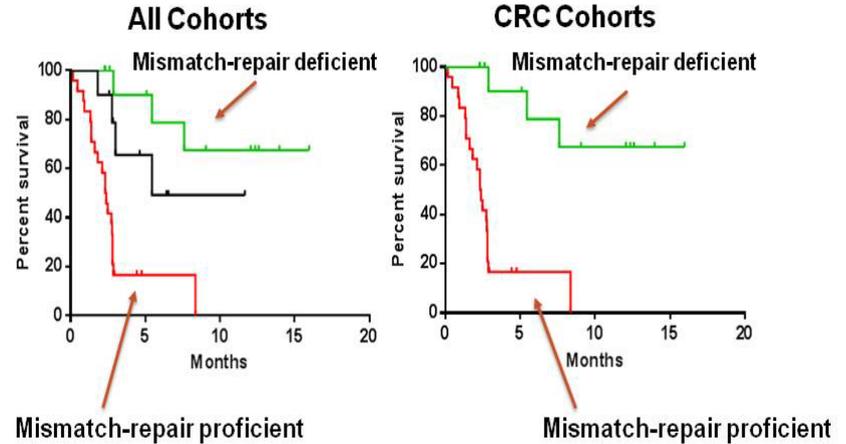
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

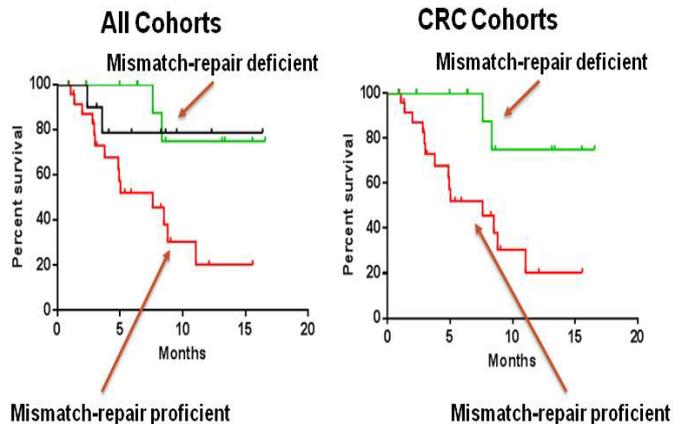
Objective Responses

	MMR-deficient CRC	MMR-proficient CRC	MMR-deficient non-CRC
N	13	25	10
Objective Response Rate	62%	0%	60%
Disease Control Rate	92%	16%	70%

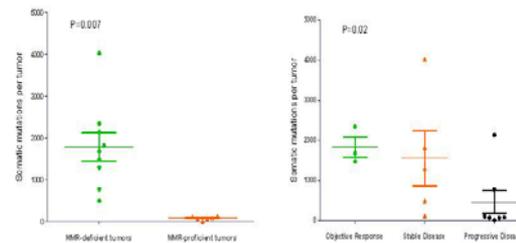
Progression-Free Survival



Overall Survival



Mutation Burden is Associated with Efficacy



Nivolumab in MMRD mCRC

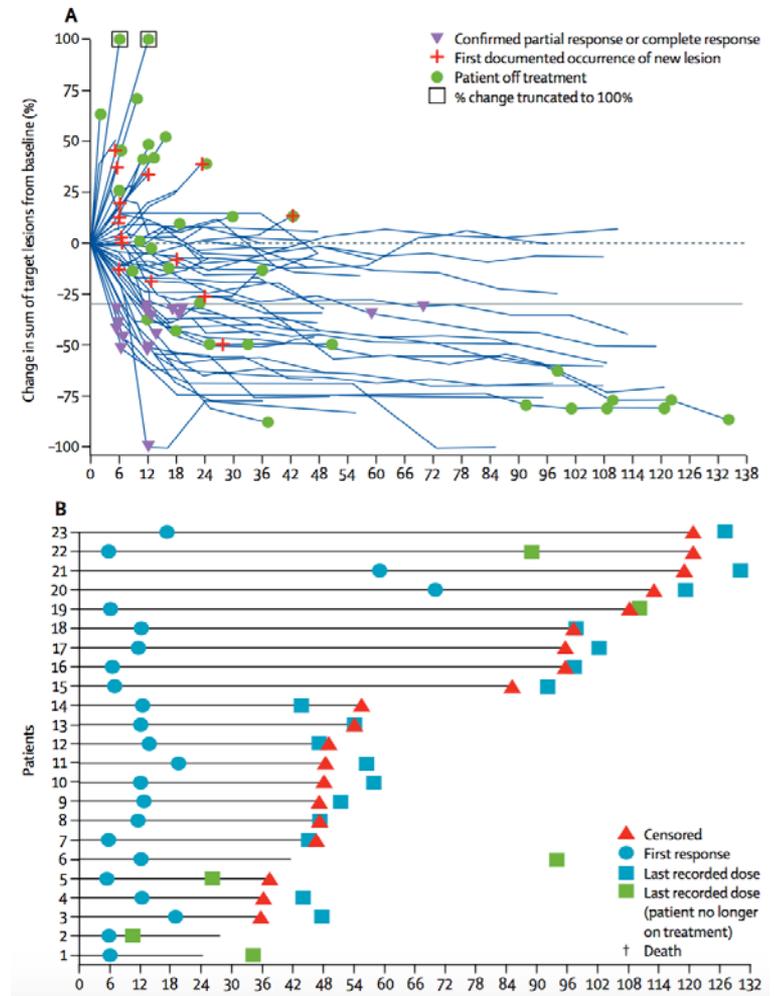
Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study

dMMR/MSI-H per local assessment (n=74)

	Investigator	Blinded independent central review
Objective response	23 (31.1%, 20.8–42.9)	24 (32%, 22–44)
Best overall response		
Complete response	0	2 (3%)
Partial response	23 (31%)	22 (30%)
Stable disease	28 (38%)	25 (34%)
Progressive disease	19 (26%)	21 (28%)
Not determined	4 (5%)	4 (5%)
Disease control for ≥12 weeks	51 (69%, 57–79)	47 (64%, 52–74)

Data are n (%; 95% CI) or n (%). dMMR/MSI-H=DNA mismatch repair deficient/microsatellite instability-high.

Table 2: Objective response, best overall response, and disease control per investigator and masked



Durable Clinical Benefit With Nivolumab Plus Low-Dose Ipilimumab as First-Line Therapy in Microsatellite Instability-High/Mismatch Repair Deficient Metastatic Colorectal Cancer

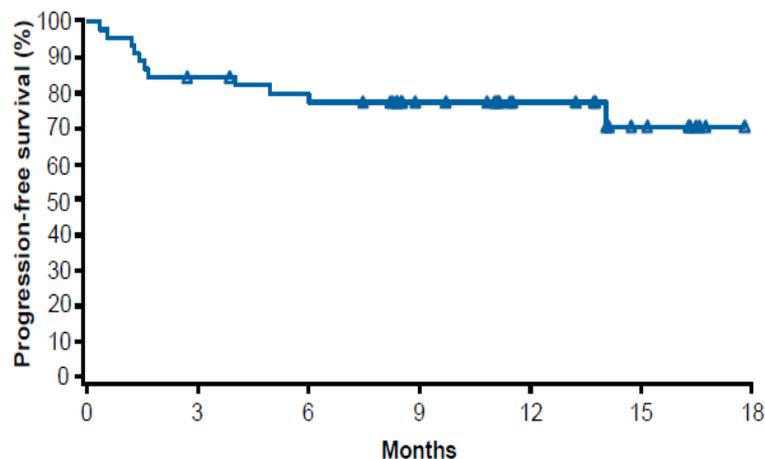
Heinz-Josef Lenz,¹ Eric Van Cutsem,² Maria Luisa Limon,³ Ka Yeung Mark Wong,⁴ Alain Hendlisz,⁵ Massimo Aglietta,⁶ Pilar García-Alfonso,⁷ Bart Neyns,⁸ Gabriele Luppi,⁹ Dana B. Cardin,¹⁰ Tomislav Dragovich,¹¹ Usman Shah,¹² Ajlan Atasoy,¹³ Roelien Postema,¹³ Zachary Boyd,¹³ Jean-Marie Ledéine,¹³ Michael James Overman,¹⁴ Sara Lonardi¹⁵

¹USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA; ²University Hospitals Gasthuisberg/Leuven and KU Leuven, Leuven, Belgium; ³Hospital Universitario Virgen del Rocío, Sevilla, Spain; ⁴Westmead Hospital, Sydney, Australia; ⁵Institut Jules Bordet, Brussels, Belgium; ⁶Candiolo Cancer Institute and University of Torino Medical School, Candiolo, Italy; ⁷Hospital Gral Universitario Gregorio Marañón, Madrid, Spain; ⁸University Hospital Brussels, Brussels, Belgium; ⁹University Hospital of Modena, Modena, Italy; ¹⁰Vanderbilt – Ingram Cancer Center, Nashville, TN, USA; ¹¹Banner MD Anderson Cancer Center, Gilbert, AZ, USA; ¹²Lehigh Valley Hospital, Allentown, PA, USA; ¹³Bristol-Myers Squibb, Princeton, NJ, USA; ¹⁴The University of Texas MD Anderson Cancer Center, Houston, TX, USA; ¹⁵Istituto Oncologico Vento IOV-IRCSS, Padova, Italy



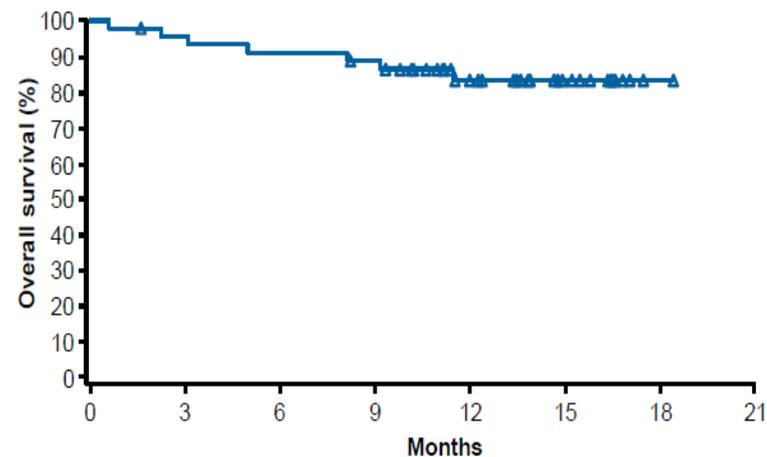
Progression-Free and Overall Survival

PFS ^a	NIVO3 (Q2W) + IPI1 (Q6W) N = 45
Median PFS, months (95% CI)	NR (14.1–NE)
9-mo rate (95% CI), %	77 (62.0–87.2)
12-mo rate (95% CI), %	77 (62.0–87.2)



No. at risk 45 37 34 24 15 7 7

OS ^a	NIVO3 (Q2W) + IPI1 (Q6W) N = 45
Median OS, months (95% CI)	NR (NE)
9-mo rate (95% CI), %	89 (74.9–95.1)
12-mo rate (95% CI), %	83 (67.6–91.7)



No. at risk 45 42 40 38 24 13 1 0



^aPer investigator assessment.
mo = month; NE = not estimable; NR = not reached

Lenz et al., ESMO 2018

¿Hacia donde vamos?

Biopsia Líquida

Aplicaciones de ctDNA

- Identificar alteraciones genómicas del tumor
- Monitorizar la respuesta a tratamiento
- Detectar resistencia terapéutica
- Detectar la evolución del tumor antes de ser detectable clínica o radiológicamente
- Caracterizar la heterogeneidad tumoral y mutaciones metastásicas que permitan adaptar el tratamiento del paciente

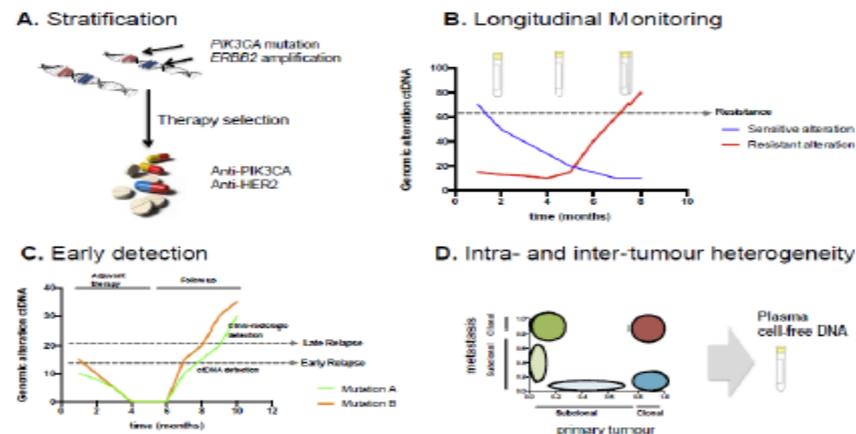
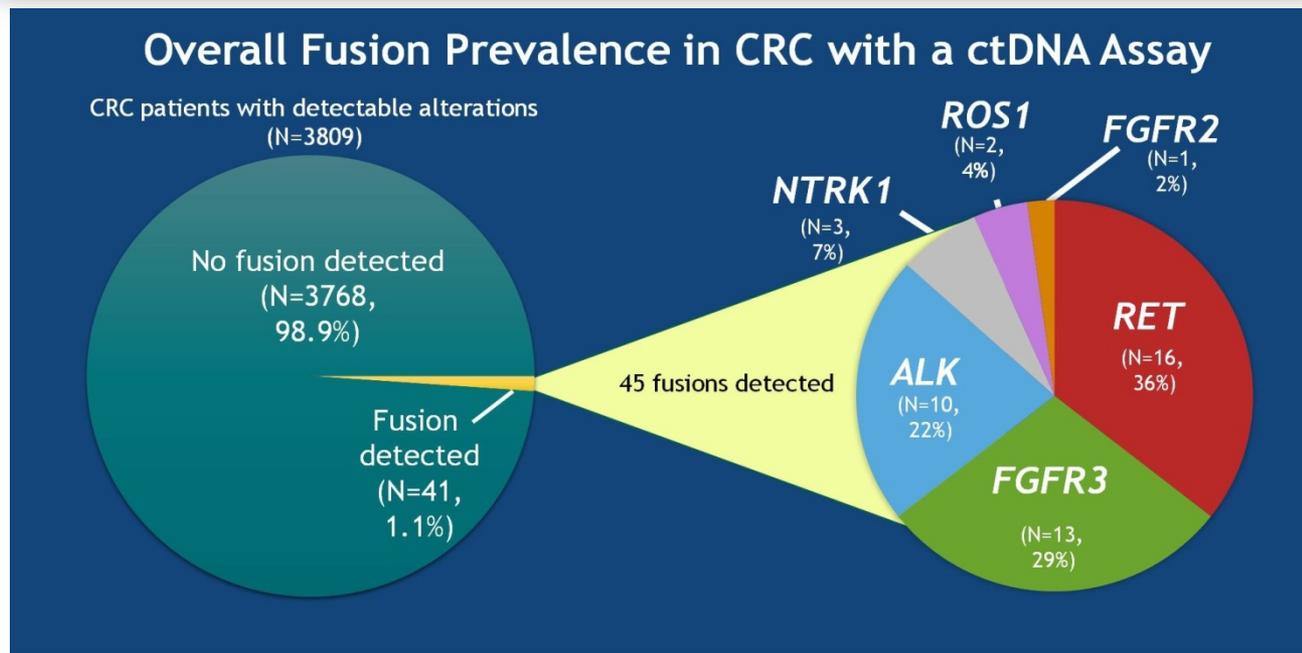


Figure 2 – The roles of cell-free circulating tumour DNA (ctDNA) in breast cancers. A. Genomic stratification of patients; B. Monitoring of tumour burden and mechanisms of therapeutic resistance; C. Early detection of recurrence; D. Deciphering intra- and inter-tumour heterogeneity. Clonal and subclonal events are depicted in both the x-axis and y-axis for primary tumour and metastasis. The red circle represents clonal events in both the primary tumour and metastasis.

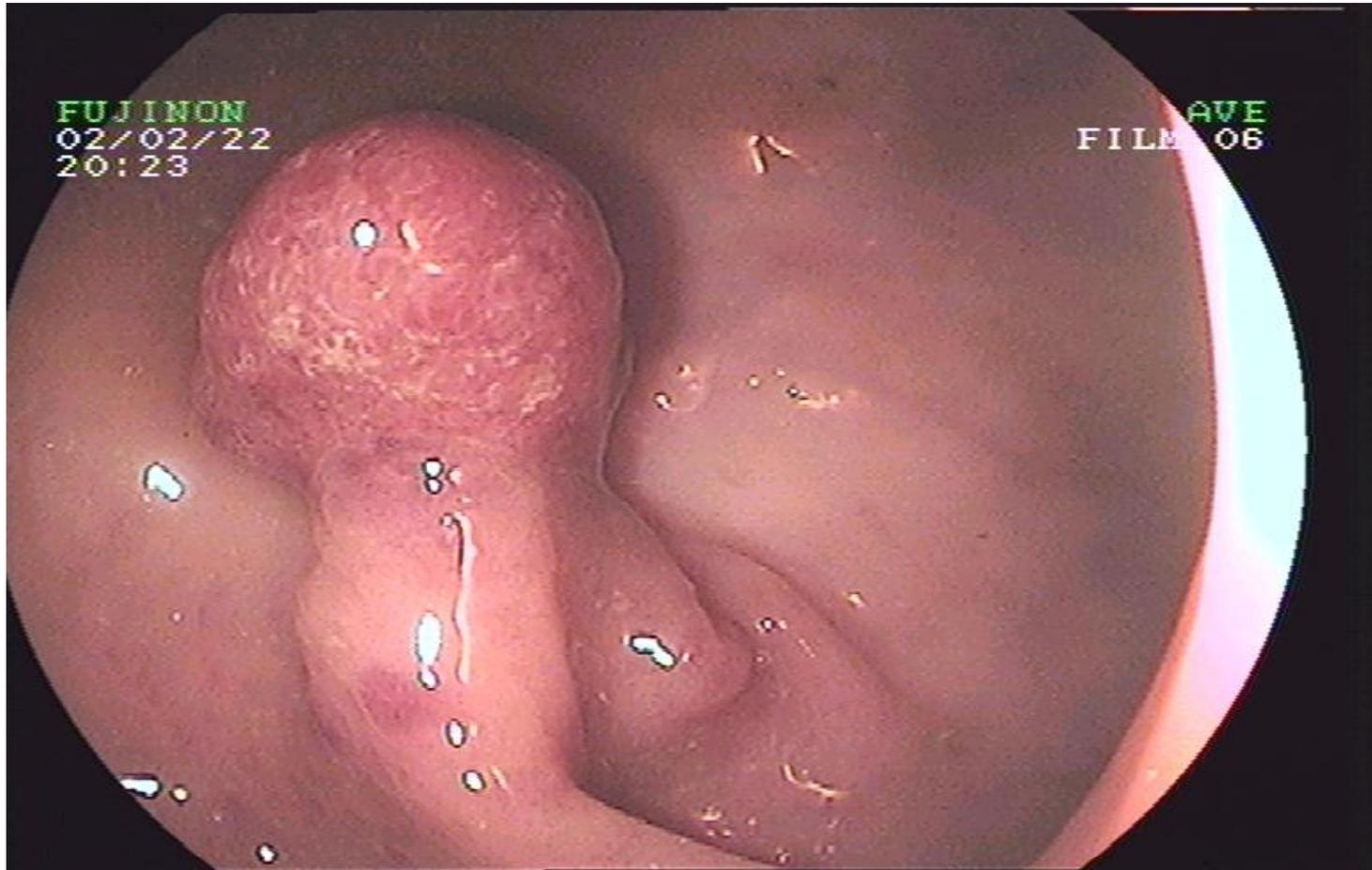
Alteration	Prevalence	Targetability evidence	Enrichment
<i>NTRK1</i> fusion	< 1%	Case reports	(> if right colon, <i>RAS/BRAF</i> wt, MSI) ¹
<i>ALK</i> fusion	< 1%	Case reports	(> if right colon, <i>RAS/BRAF</i> wt, MSI colitis-associated) ²
<i>ROS1</i> fusion	< 1%	No	(> if right colon, <i>RAS/BRAF</i> wt) ³
<i>RET</i> fusion	< 1%	No	(> if right colon, <i>RAS/BRAF</i> wt) ³

¹Russo et al, Cancer Discov 2016; ²Yaeger et al, Gastroenterology 2016; ³Kloosterman et al, Cancer Res 2017

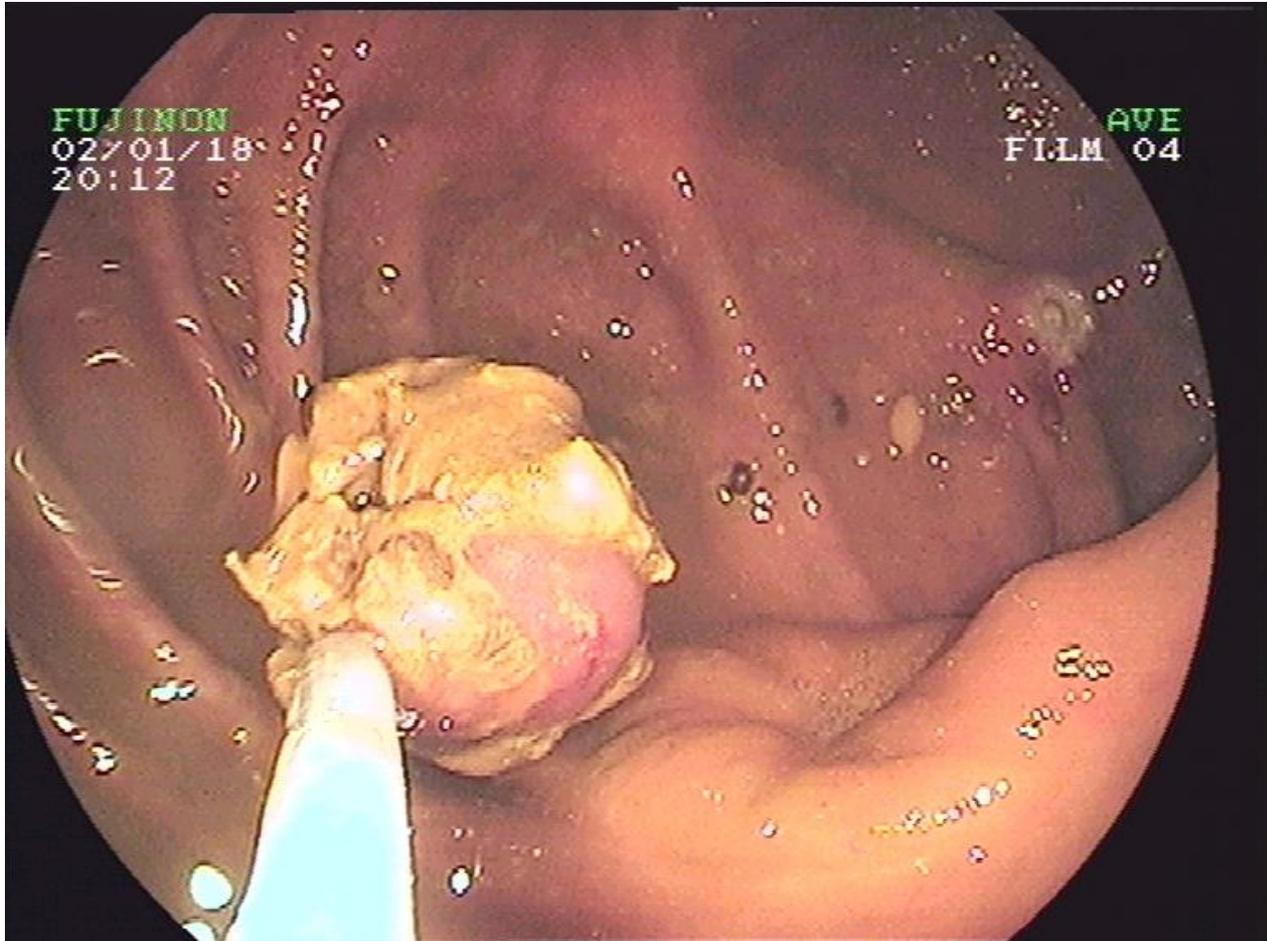


Screening

Adenoma avanzado



Poliectomía endoscópica

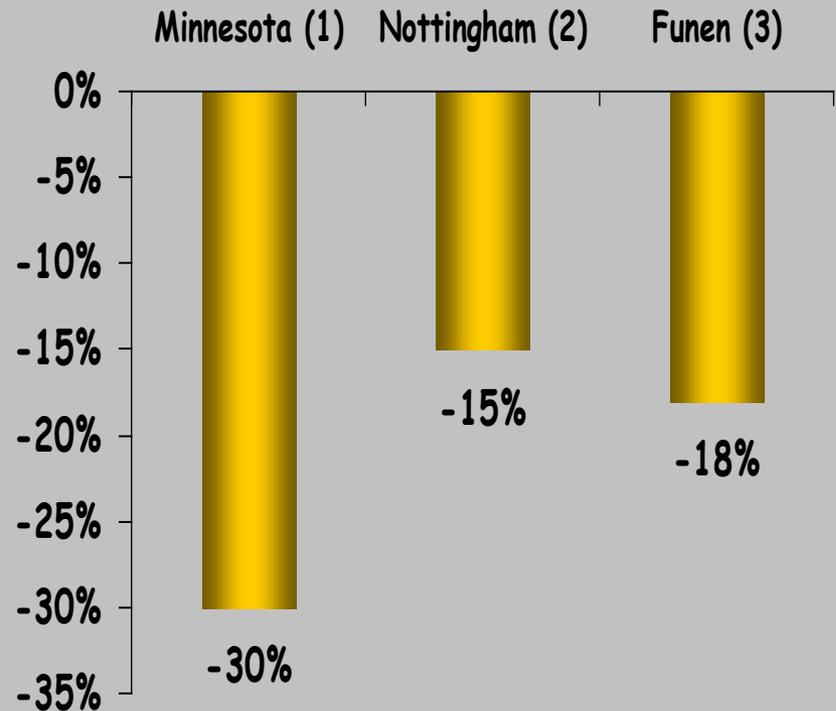


Screening



El intestino elimina habitualmente 0,6-1,2 ml de sangre al día (Hb fecal < 2 mg por gramo de heces).

Reducción de mortalidad por cáncer de color



Mandel, NEJM 1993
Hardcastle, Lancet 1996
Kronborg, Lancet 1996

En Julio 2013 el Ministerio de Sanidad decide la implantación nacional del screening del CCR



Alianza para la prevención del cáncer de colon

Madrid, 24 de mayo de 2012

Logos of participating organizations: aecc, AEG, European Association of Gastroenterology, FEDAO, FUNDACIÓN COFARÉS, FED, S&AP-IAP, GEDIA, SOCIEDAD ESPAÑOLA DE ENDOSCOPIA, semFYC, SEOM, SEOR, SEPD.



FRENTES EN LA LUCHA CONTRA EL CÁNCER

- Prevención primaria (Hábitos saludables, fármacos, cirugía, etc.)
- Prevención Secundaria (Diagnóstico precoz o screening)
- Mejorando el diagnóstico (Tecnología, Anatomía Patológica)
- Aumento de conocimientos sobre la biología del cáncer (Incremento de la investigación básica, traslacional y clínica)
- Mejorando el tratamiento: (A) Tratamientos individualizados, (B) realizados por profesionales bien entrenados. (C) Trabajo asistencial multidisciplinar. (D) Atención integral del paciente

¡ Muchas Gracias!
pgarcaalfonso@gmail.com



**Alianza para la prevención
del cáncer de colon**