I SIMPOSIO NACIONAL
de ONCOLOGÍA de PRECISIÓN

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

CÁNCER DE ORIGEN DIGESTIVO

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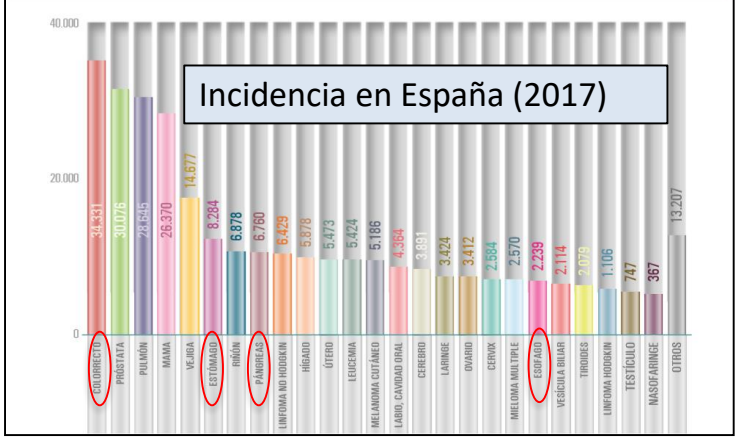
Disclosure Information

- Consultant or Advisory Role: Roche, Merck-Serono, Amgen, MSD, BMS, Lilly, Celgene, Sanofi-Aventis, Servier, Astra-Zeneca, Bayer
- Research Funding: Roche, Merck-Serono, Amgen, MSD, Lilly, Celgene, Sanofi-Aventis, Bayer
- Speaking: Roche, Merck-Serono, Amgen, MSD, BMS, Lilly, Celgene, Sanofi-Aventis, Servier, Bayer
- Grant support: Amgen

TUMORES DIGESTIVOS: C colorectal, esófagico, gástrico y pancreático

Figura 2. Incidencia estimada de los tumores más frecuentes en España en el año 2017 (ambos sexos).
Datos procedentes de GLOBOCAN 2012, desglosados por edad y sexo, y extrapolados a los datos de la población española para el año 2017 proporcionada por el INE.



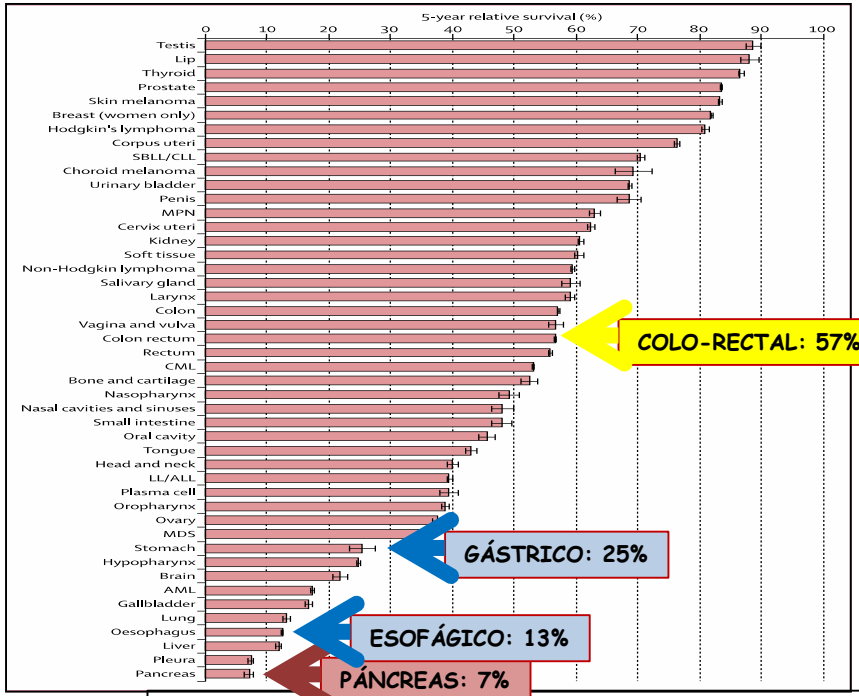
49.375 pts/año → 24 % de los cánceres en España

Las cifras del cáncer en España, 2018, 2019. SEOM

Mortalidad en España (2017)

29 282 muertes/año → 26 % de las muertes por cáncer en España

Sv a 5 años en Europa según tumor



Eurocare 5 (De Angelis R et al. EUROCARE-5. Lancet Oncol 2014; 15: 23-34

GUION

.- Cáncer Colorectal

BM rutinarios *(CAP-I)*	BM recomendables (IIA)	BM investigación (IIB)
- RAS	- HER2	- CMS
- BRAF	- NTRK	- Genetic signatures
- MSI/MMRD	- Alk, Ros1	- CDX2

.- Adenoca Esófago-Gástrico

BM rutinarios	BM recomendables	BM investigación
- HER2	- PD-L1 (CPS)	- TCGA
- MSI/MMRD		

.- Cáncer Epidermoide de Esofago

BM recomendables

- PD-L1 (CPS)

.- Adenoca Pancreático

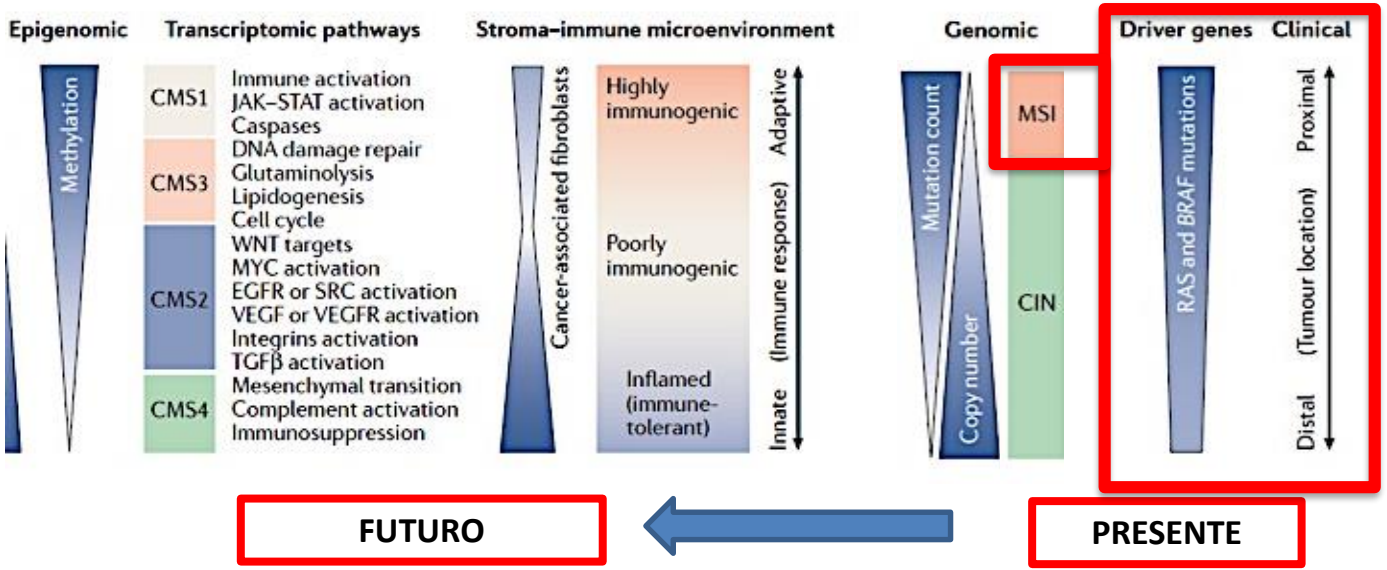
BM rutinarios	BM recomendables	BM investigación
- MSI/MMRD	- BRCA/BRCAness	- Alk, Ros1
	- NTRK	- HA

.- BM predict. Tox

BM recomendables

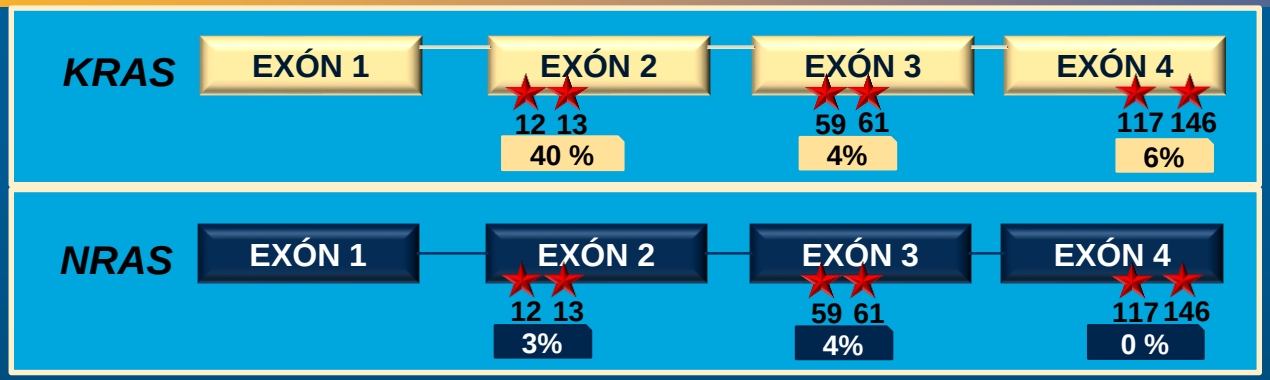
- DPD ; -UGT1A1

Medicina de precisión en CCR: Integración de toda la información



Adpated from Dienstmann R.- Nat Cancer Rev 2017

K-N Ras mutations prevalence



→**50%** K-NRAS mut
No benefit with anti EGFR moAb

50% K-NRAS wt
More benefit with antiEGFR moAb

Douillard, J. Y., et al.(2013). "Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer." N Engl J Med **369**(11): 1023-1034.

Determinación de mutaciones de Ras como predictor de respuesta a anti EGFR (n = 161). **SELECCIÓN PUNTO DE CORTE en tejido**

		THERASCREEN PYRO (5%)		COBAS (1%)		NGS 454 GS JUNIOR (1%)	
		MUT	WT	MUT	WT	MUT	WT
KRAS 2	n	17	144	16	145	49	112
	Median (mut/wt), month	4.14	7.10	4.14	7.1	7.92	5.82
	HR (95% CI)	0.78 (0.45-1.33)		0.74 (0.42-1.06)		1.13 (0.77-1.66)	
	P	0.354		0.299		0.540	
All RAS	n	49	112	50	111	82	79
	Median (mut/wt), month	4.44	7.20	4.73	7.2	7.03	6.97
	HR (95% CI)	**0.59** (0.40-0.87)		0.77 (0.52-1.15)		0.83 (0.58-1.19)	
	P	0.007		0,203		0.315	
All RAS* or *BRAF	n	61	100	59	102	87	74
	Median (mut/wt), month	4.11	7.92	4.44	7.56	6.97	7.03
	HR (95% CI)	**0.48** (0.33-0.69)		**0.67** (0.45-0.98)		0.79 (0.55-1.14)	
	P	0.000		0.036		0.204	
All RAS* or *BRAF* or *PiK3CA	n	68	93	71	90	95	66
	Median (mut/wt), month	4.14	8.84	4.14	8.08	5.91	7.20
	HR (95% CI)	**0.52** (0.37-0.73)		**0.52** (0.36-0.75)		**0.67** (0.46-0.97)	
	P	0.0001		0.001		0.033	

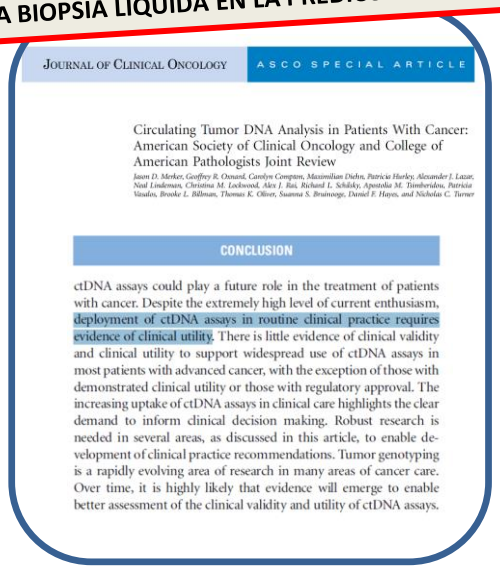
Adjusted for age, gender, and chemotherapy lines

- *Increasing detection sensitivity to 1% MAF in tissue samples did not improve patients' selection to anti-EGFR therapy compared to SOC*
- *A 5% mutational threshold in tissue RAS testing was the best cutoff to predict response to anti-EGFR therapy in mCRC*

Vidal et al. WCGIC 2018. Abstract 576

Futuro: BIOPSIA LIQUIDA

¿ PUNTO DE CORTE ÓPTIMO DE MAF (¿1%? ¿0,1%?) ?'
¿PAPEL DE LA BIOPSIA LIQUIDA EN LA PREDICCIÓN PRECOZ DE RESPUESTA Y DE RESISTENCIA AL TRATAMIENTO ?



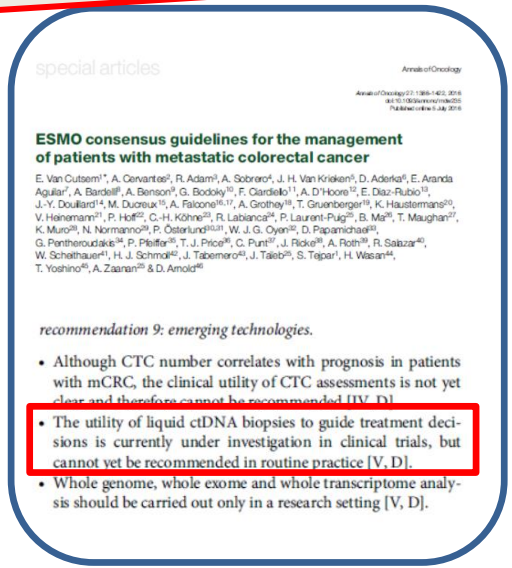
JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Circulating Tumor DNA Analysis in Patients With Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review

Jason D. Merker, Geoffrey R. Oxnard, Carolyn Compton, Maximilian Diehn, Patricia Hurley, Alexander J. Lazar, Neal Lindeman, Christina M. Lockwood, Alex J. Rai, Richard L. Schilsky, Apostolia M. Tsimberidou, Patricia Vasalos, Brooke L. Billman, Thomas K. Oliver, Suanna S. Bruinooge, Daniel F. Hayes, and Nicholas C. Turner

CONCLUSION

ctDNA assays could play a future role in the treatment of patients with cancer. Despite the extremely high level of current enthusiasm, deployment of ctDNA assays in routine clinical practice requires evidence of clinical utility. There is little evidence of clinical validity and clinical utility to support widespread use of ctDNA assays in most patients with advanced cancer, with the exception of those with demonstrated clinical utility or those with regulatory approval. The increasing uptake of ctDNA assays in clinical care highlights the clear demand to inform clinical decision making. Robust research is needed in several areas, as discussed in this article, to enable development of clinical practice recommendations. Tumor genotyping is a rapidly evolving area of research in many areas of cancer care. Over time, it is highly likely that evidence will emerge to enable better assessment of the clinical validity and utility of ctDNA assays.



special articles | Annals of Oncology

ESMO consensus guidelines for the management of patients with metastatic colorectal cancer

E. Van Cutsem[1*], A. Cervantes[2], R. Adam[3], A. Sobrero[4], J. H. Van Krieken[5], D. Aderka[6], E. Aranda Aguilar[7], A. Bardelli[8], A. Benson[9], G. Bodoky[10], F. Ciardiello[11], A. D'Hoore[12], E. Diaz-Rubio[13], J.-Y. Douillard[14], M. Ducreux[15], A. Falcone[16,17], A. Grothey[18], T. Gruenberger[19], K. Haustermans[20], V. Heinemann[21], P. Hoff[22], C.-H. Köhne[23], R. Labianca[24], P. Laurent-Puig[25], B. Ma[26], T. Maughan[27], K. Muro[28], N. Normanno[29], P. Österlund[30,31], W. J. G. Oyen[32], D. Papamichael[33], G. Pentheroudakis[34], P. Pfeiffer[35], T. J. Price[36], C. Punt[37], J. Ricke[38], A. Roth[39], R. Salazar[40], W. Scheithauer[41], H. J. Schmoll[42], J. Tabernero[43], J. Taieb[25], S. Tejpar[1], H. Wasan[44], T. Yoshino[45], A. Zaanan[25] & D. Arnold[46]

recommendation 9: emerging technologies.

- Although CTC number correlates with prognosis in patients with mCRC, the clinical utility of CTC assessments is not yet clear and therefore cannot be recommended [IV, D].
- The utility of liquid ctDNA biopsies to guide treatment decisions is currently under investigation in clinical trials, but cannot yet be recommended in routine practice [V, D].
- Whole genome, whole exome and whole transcriptome analysis should be carried out only in a research setting [V, D].

Merker J.D., et al. J Clin Oncol 2018;36.
http://ascopubs.org/doi/10.1200/JCO.2017.76.8671

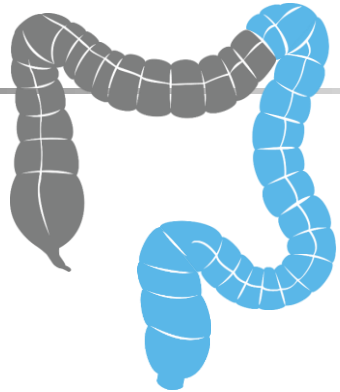
Van Cutsem, E, et al. Ann Oncol 2016;27:1386-422

BRAF mut are more frequent in Right CRC [1,2]

1. Yamauchi M, et al. Gut 2012;61:847–54;
2. Missiaglia E, Ann Oncol 2014;25:1995–2001;.

Right colon

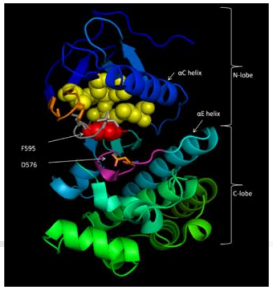
BRAF mut 30 %



Left colorectum

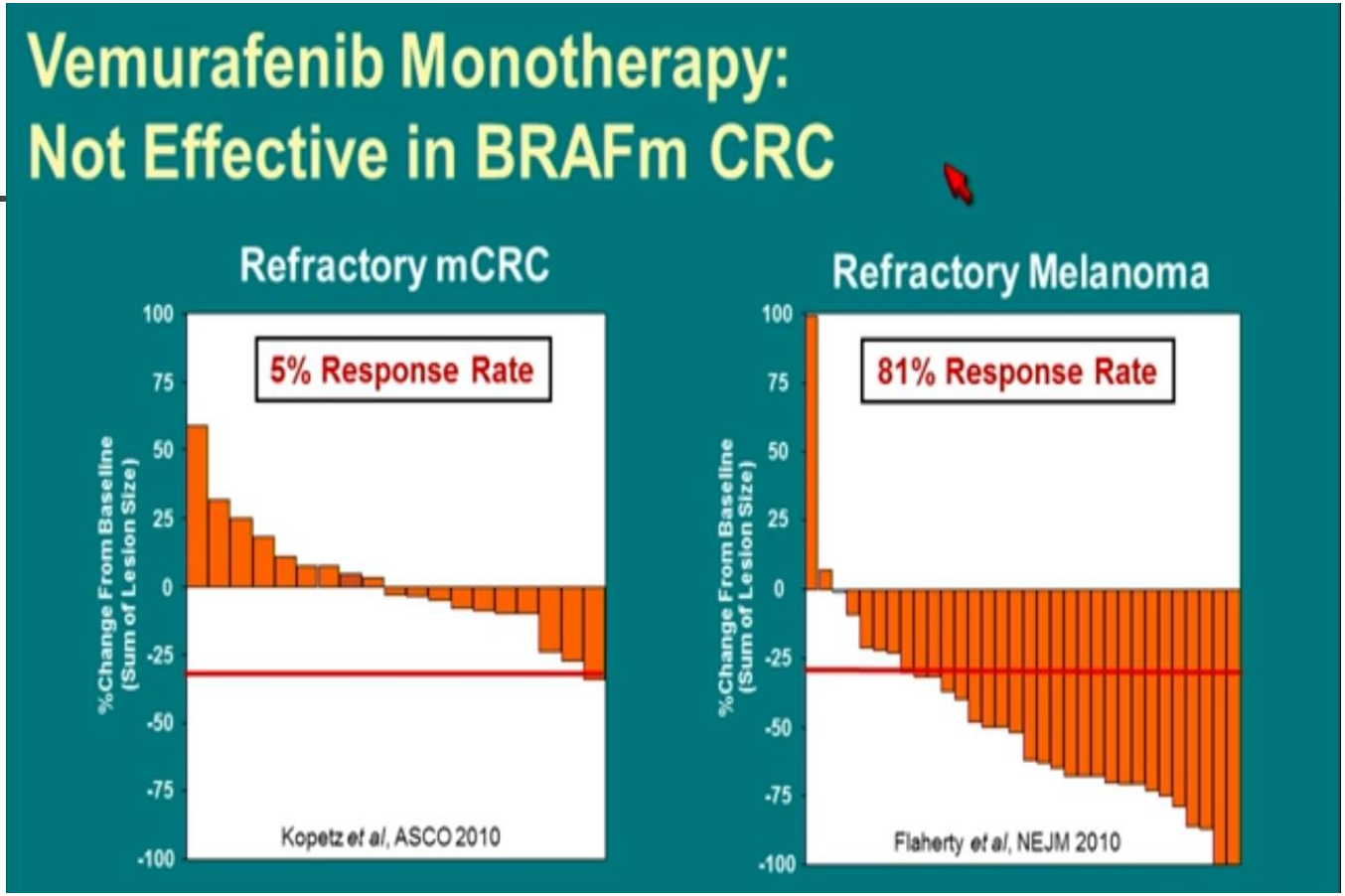
BRAF mut <5 %

Mut BRAF in mCRC

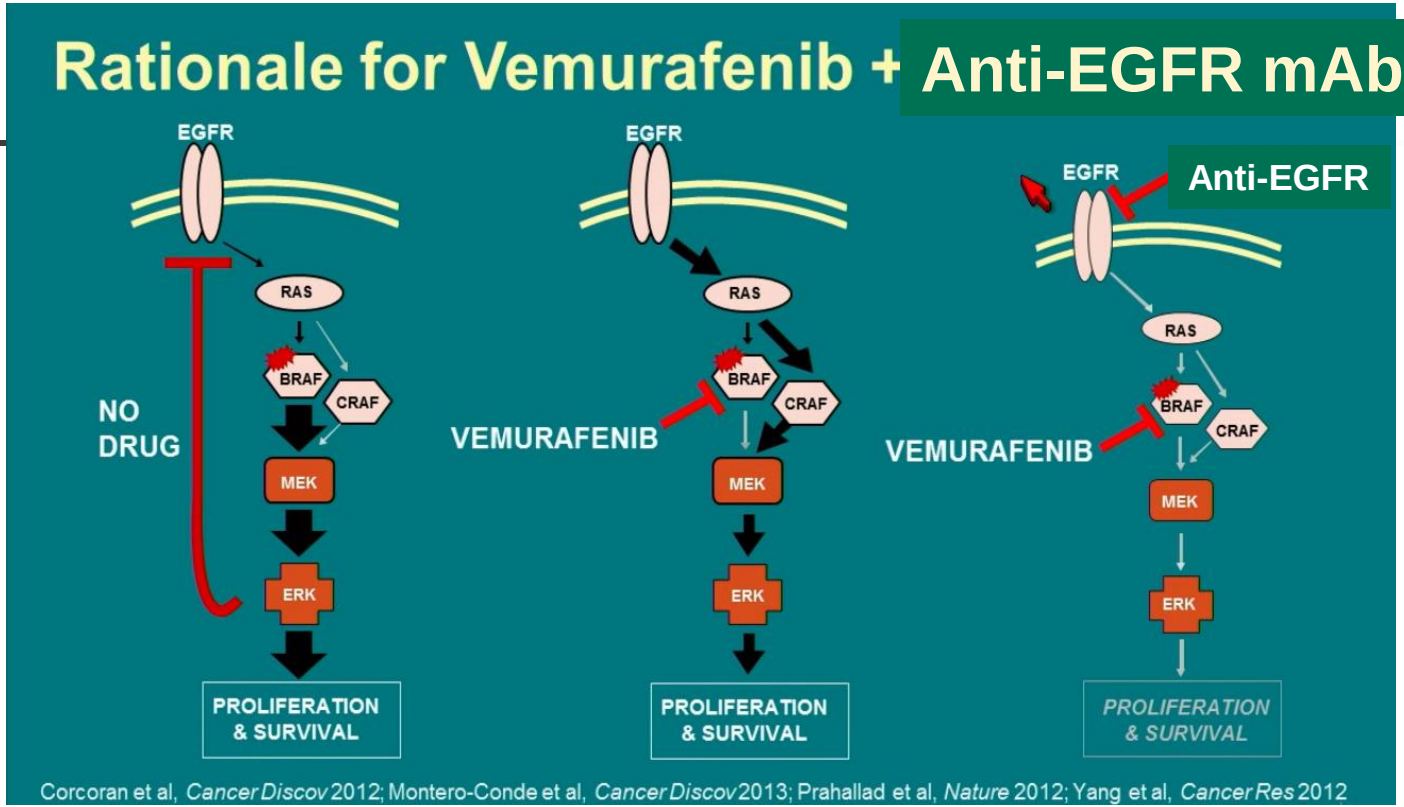


- Mut B-RAF ^{V600E} in 5 % of mCRC (10% of RAS wt)
- Associated with Sporadic MSI (35%)
- More frequent in right colon (30%) than in left colon (5%)
- Poor prognosis (mOS in BRAF mut 11 m vs 30 m in BRAF wt)
- No Benefit (or small) with antiEGFR mAb
- No predictive for antiangiogenics

Vemurafenib Monotherapy: Not Effective in BRAFm CRC

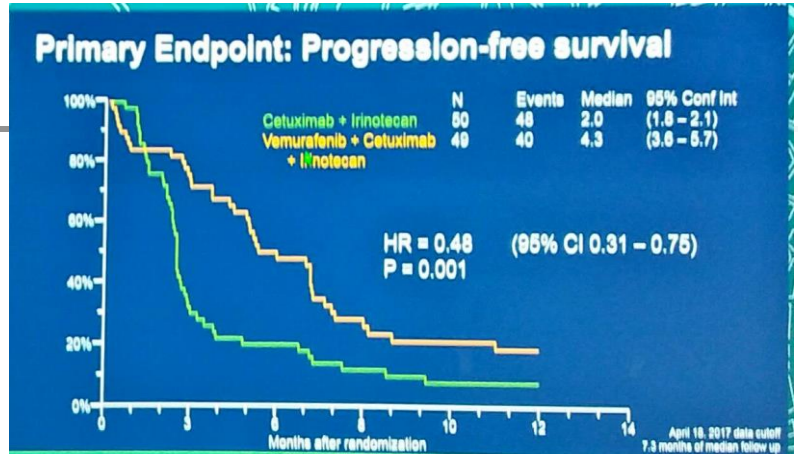


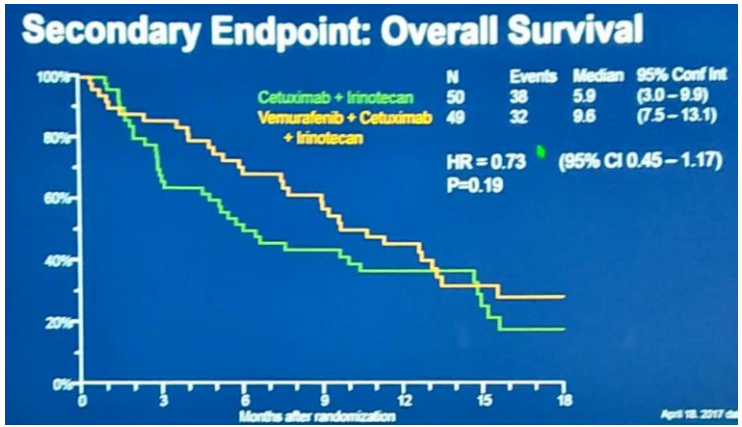
Rationale for Vemurafenib + Anti-EGFR mAb



Corcoran et al, *Cancer Discov* 2012; Montero-Conde et al, *Cancer Discov* 2013; Prahallad et al, *Nature* 2012; Yang et al, *Cancer Res* 2012

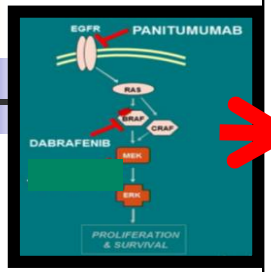
Rand P II: Cetuxi-Irinotecan +/- Vemurafenib



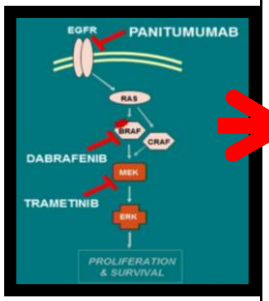


Kopetz S et al, ASCO 2017

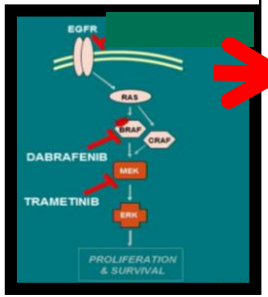
Dabrafenib, Panitumumab + Trametinib –Phase 1/2 2010221 Study BRAF^{V600E} Cohort (Van Cutsem et al)



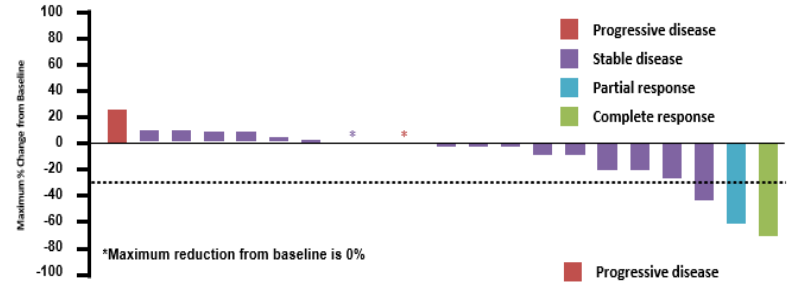
D+P (N = 20)
CR+PR: [redacted] (10%)
Stable disease: 16 (80%)

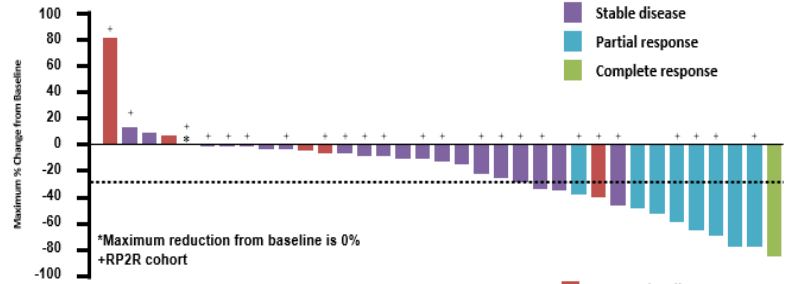


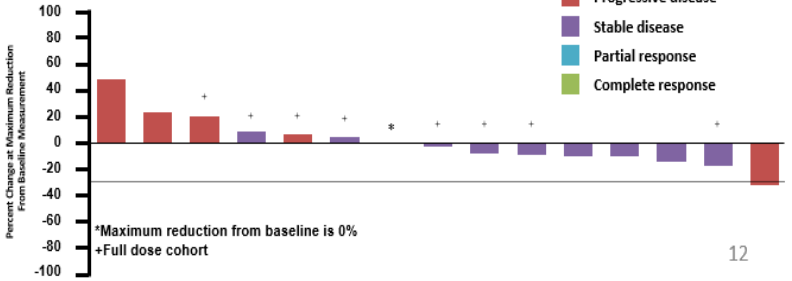
D+P+T (N = 35)
CR+PR: [redacted] (26%)
Stable disease: 21 (60%)

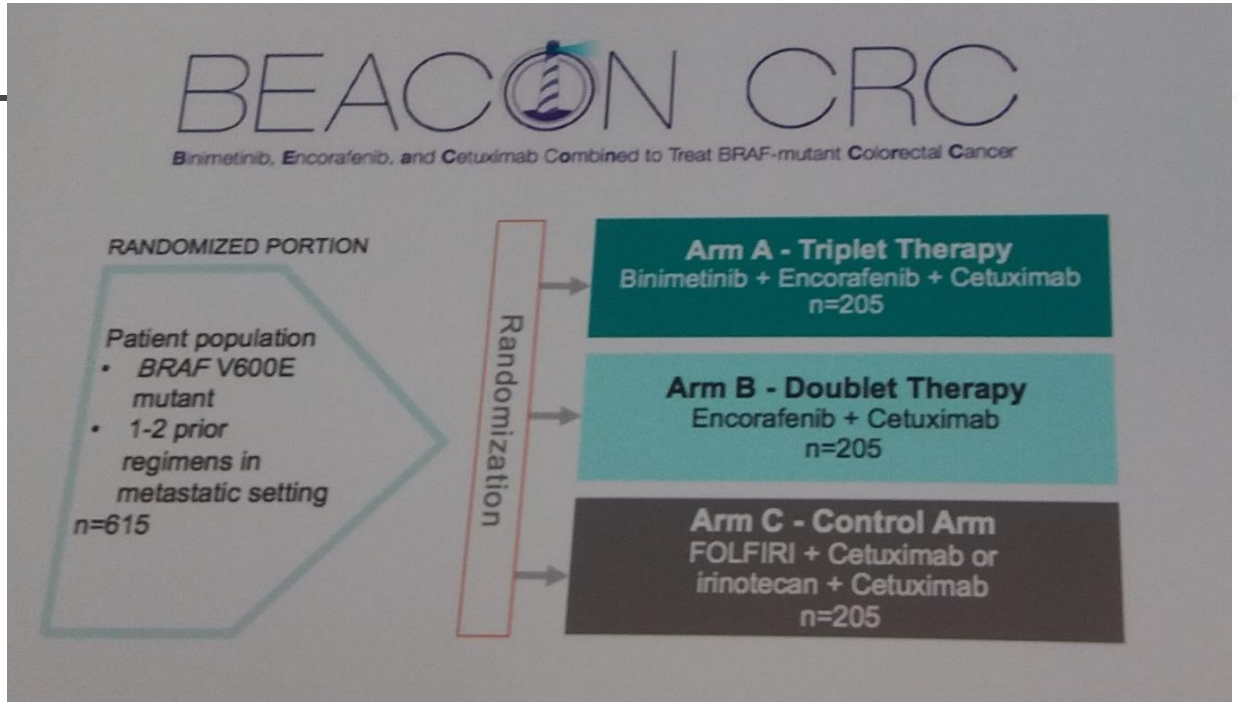


P+T (N = 19)
CR+PR: [redacted] (0%)
Stable disease: 10 (53%)







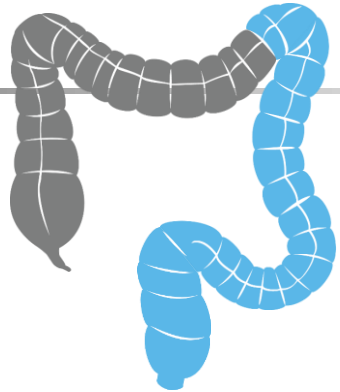

BEACON CRC
Binimetinib, Encorafenib, and Cetuximab Combined to Treat BRAF-mutant Colorectal Cancer
RANDOMIZED PORTION
Patient population
• BRAF V600E mutant
• 1-2 prior regimens in metastatic setting
n=615
Randomization
Arm A - Triplet Therapy
Binimetinib + Encorafenib + Cetuximab
n=205
Arm B - Doublet Therapy
Encorafenib + Cetuximab
n=205
Arm C - Control Arm
FOLFIRI + Cetuximab or
irinotecan + Cetuximab
n=205

MSI is more frequent in Right CRC [1,2]

1. Yamauchi M, et al. Gut 2012;61:847–54;
2. Missiaglia E, Ann Oncol 2014;25:1995–2001;.

Right colon

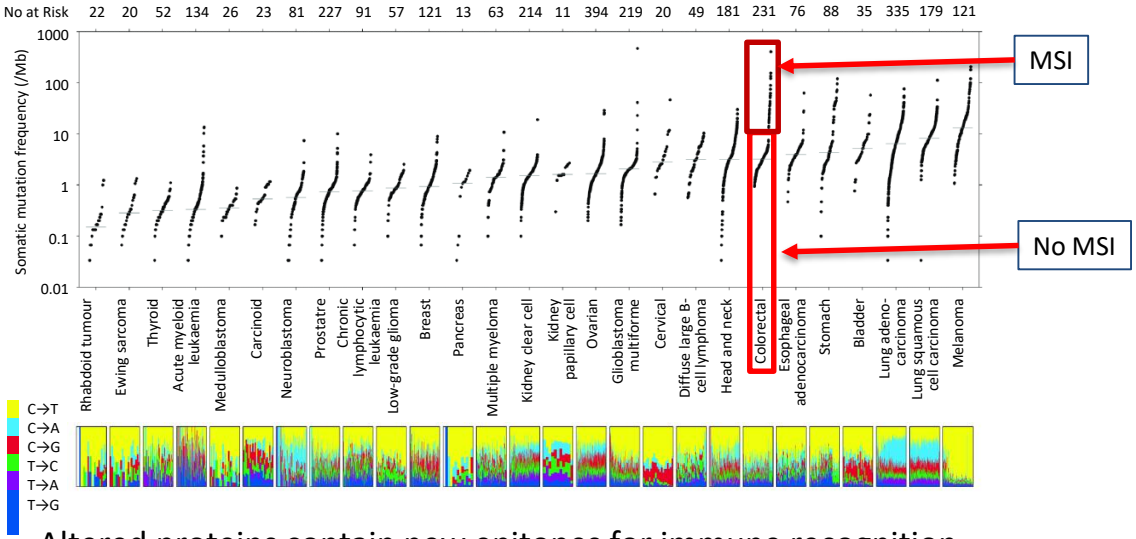
MSI / MMRD 30 %



Left colorectum

MSI / MMRD <5 %

Frequency of genetic somatic mutations in cancer



Altered proteins contain new epitopes for immune recognition, providing a common denominator for cancer immunotherapy

Lawrence Nature 2013

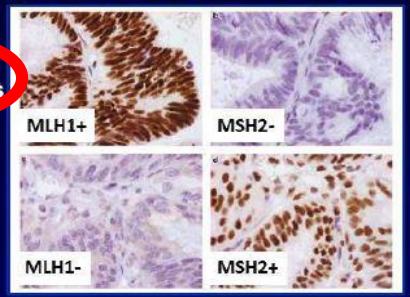
Mismatch Repair Deficiency (MMR-D): Unique Biological Subgroup of Colon Cancer

Metilaciones en el promotor

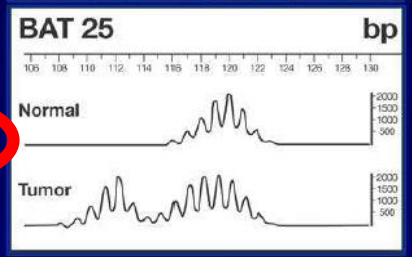
somáticas

Germinales: Lynch

IHC for MMR protein status



PCR on tumor DNA for MSI (microsatellite instability)



MMR-D = MSI-H
MMR-P = MSI-L/MSS

Imai K, et al. *Carcinogenesis.* 2008;29(4):673-680. Umetani N, et al. *Ann Surg Oncol.* 2000;7(4):276-280. Rosen DG, et al. *Mod Pathol.* 2006;19(11):1414-1420.

MMR-D / MSI in CRC

In 15% of CRC pts

- Sporadic CRC: in 13% of pts (in 20-50% BRAF mut)
- Lynch syndrom CRC: >95% of pts (no BRAF mut)

- St II: 15-20% pts / St III: 10% of pts
  - → Good prognosis
  - → no benefit with adjuvant fluoropyrimidines
- St IV: 4 % of pts
  - → Poor prognosis
  - → Important activity of Immunotherapy

P. II KEYNOTE-164

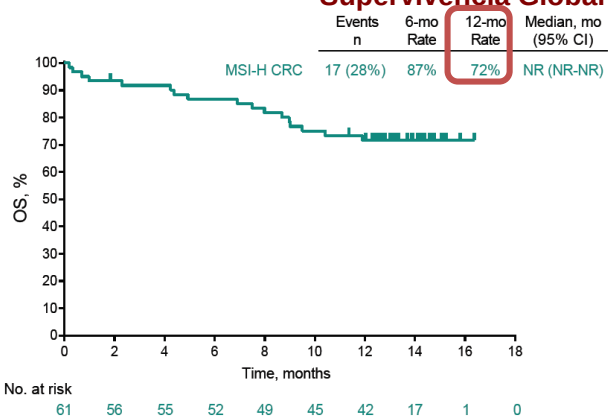
mCRC , **MSI-H or dMMR**
2nd, 3rd line

→ Pembrolizumab

- **63 pts**
- **RR 32% ; DC: 57%**

Le et al ASCO 2018

Supervivencia Global



P. III KEYNOTE-177

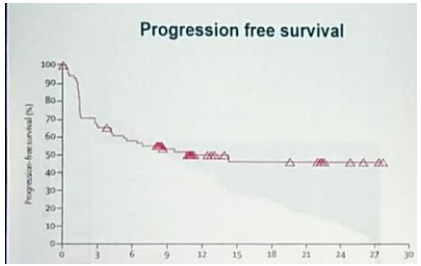
mCRC , **MSI-H or dMMR**
1st line

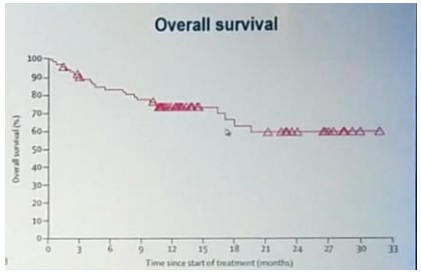
→ Standard Chemo/biologic

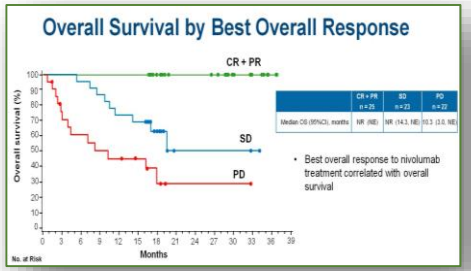
→ Pembrolizumab

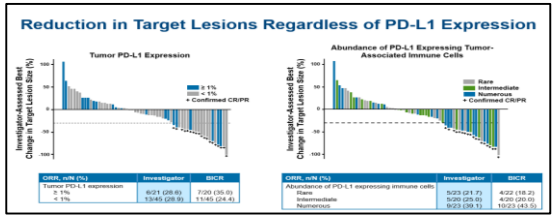
CheckMate 142: MMR-D pts treated with Nivo (74 pts)

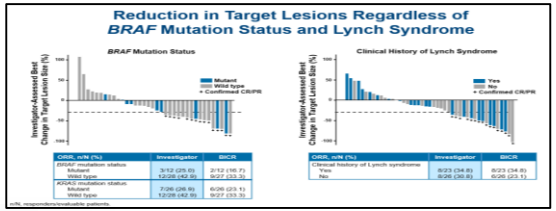
RR: 33% (CR 9%, PR 24%)
DC: 62%





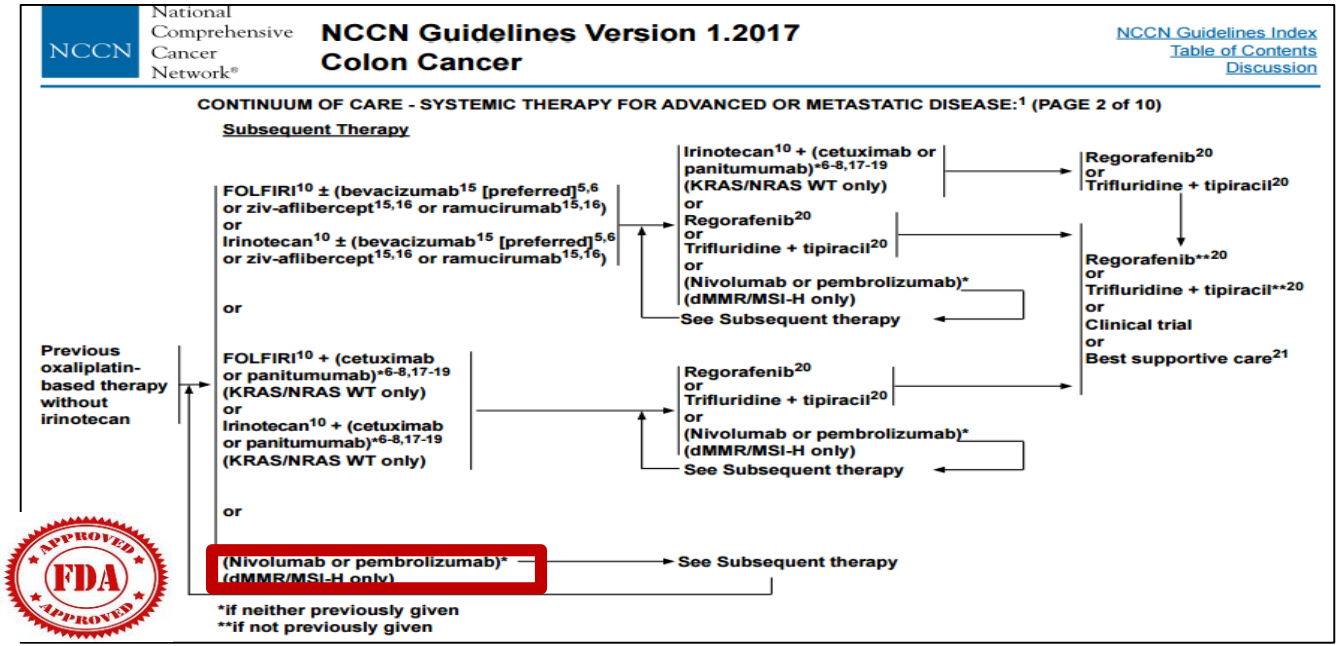






	Objective response	Disease control for ≥12 weeks
Tumour PD-L1 expression		
≥1% (n=21)	6 (29%)	11 (52%)
<1% (n=47)	13 (28%)	35 (75%)
Immune cell PD-L1 expression		
Rare (n=24)	5 (21%)	14 (58%)
Intermediate (n=21)	5 (24%)	17 (81%)
Numerous (n=23)	9 (39%)	15 (65%)
Mutation status		
BRAF mutant (n=12)	3 (25%)	9 (75%)
KRAS mutant (n=26)	7 (27%)	16 (62%)
Both *BRAF* and *KRAS* wild type (n=29)	12 (41%)	23 (79%)
Clinical history of Lynch syndrome*		
Yes (n=27)	9 (33%)	19 (70%)
No (n=28)	8 (29%)	21 (75%)

Overman, Lancet Oncol 2017


NCCN
National Comprehensive Cancer Network®
NCCN Guidelines Version 1.2017
Colon Cancer
NCCN Guidelines Index
Table of Contents
Discussion
CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:1 (PAGE 2 of 10)
Subsequent Therapy
Previous oxaliplatin-based therapy without irinotecan
FOLFIRI10 ± (bevacizumab15 [preferred]5,6 or ziv-aflibercept15,16 or ramucirumab15,16)
or
Irinotecan10 ± (bevacizumab15 [preferred]5,6 or ziv-aflibercept15,16 or ramucirumab15,16)
or
FOLFIRI10 + (cetuximab or panitumumab)*6-8,17-19 (KRAS/NRAS WT only)
or
Irinotecan10 + (cetuximab or panitumumab)*6-8,17-19 (KRAS/NRAS WT only)
or
(Nivolumab or pembrolizumab)* (dMMR/MSI-H only)
Irinotecan10 + (cetuximab or panitumumab)*6-8,17-19 (KRAS/NRAS WT only)
or
Regorafenib20
or
Trifluridine + tipiracil20
or
(Nivolumab or pembrolizumab)* (dMMR/MSI-H only)
See Subsequent therapy
Regorafenib20
or
Trifluridine + tipiracil20
or
(Nivolumab or pembrolizumab)* (dMMR/MSI-H only)
See Subsequent therapy
Regorafenib20
or
Trifluridine + tipiracil20
Regorafenib**20
or
Trifluridine + tipiracil**20
or
Clinical trial
or
Best supportive care21
See Subsequent therapy
*if neither previously given
**if not previously given
APPROVED
FDA
APPROVED

GUION

.- Cáncer Colorectal

BM rutinarios *(CAP-I)*	BM recomendables (IIA)	BM investigación (IIB)
- RAS	- HER2	- CMS
- BRAF	- NTRK	- Genetic signatures
- MSI/MMRD	- Alk, Ros1	- CDX2

.- Adenoca Esófago-Gástrico

BM rutinarios	BM recomendables	BM investigación
- HER2	- PD-L1 (CPS)	- TCGA
- MSI/MMRD		

.- Cáncer Epidermoide de Esofago

BM recomendables

- PD-L1 (CPS)

.- Adenoca Pancreático

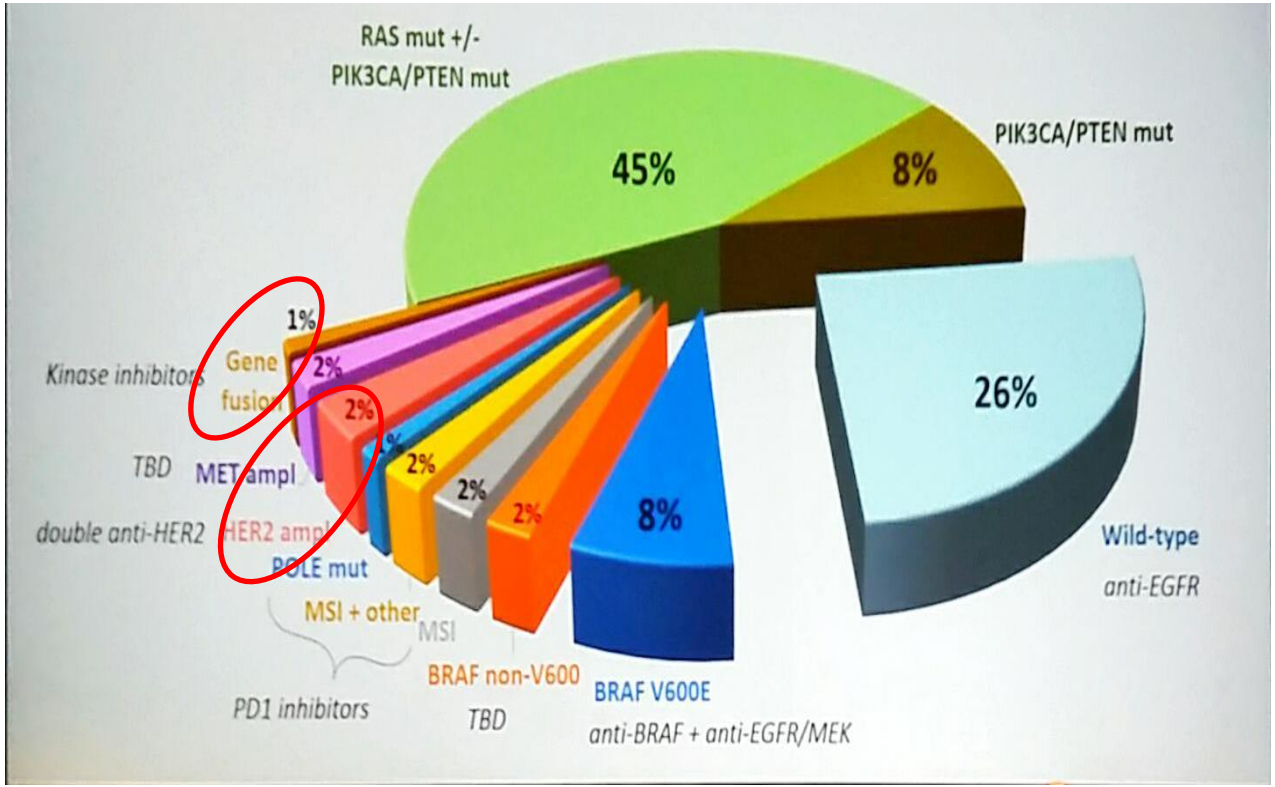
BM rutinarios	BM recomendables	BM investigación
- MSI/MMRD	- BRCA/BRCAness	- Alk, Ros1
	- NTRK	- HA

.- BM predict. Tox

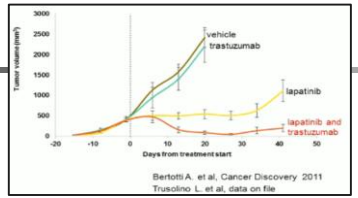
BM recomendables

- DPD ; -UGT1A1

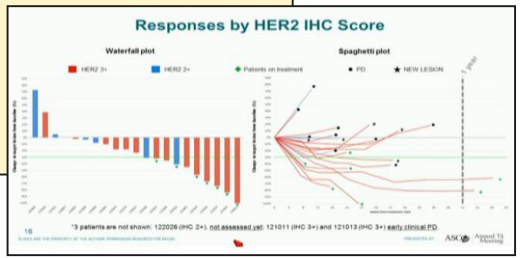
mCRC: Genomic classification



HERACLES Study: Trastuzumab + Lapatinib in mCRC



- 914 pts, KRAS wt mCRC, EGFR pre-treated
  → 48 **(5%) were HER2+**
  → **27 pts** included
- RR: 30%
- DCR: 74%
- mTTP: 5.5 m (3.7-7.8+ m)



Sartore-Bianchi A et al. 2016

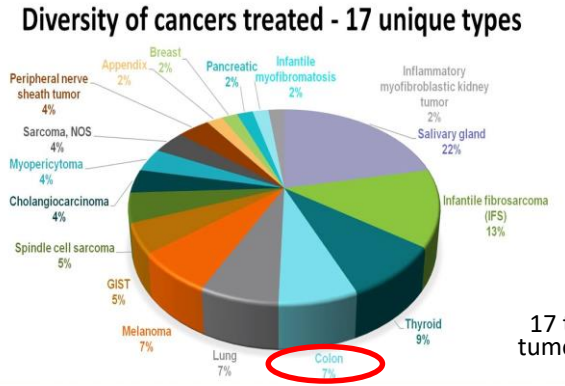
NTRK (fusiones)

NTRK: neurotropic tropomyosin receptor kinase

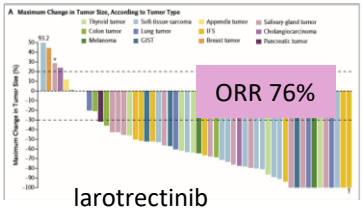
2017

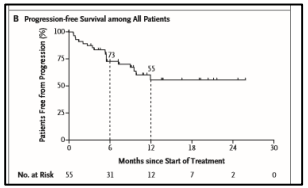
FDA grants orphan drug designation to entrectinib for NTRK fusion-positive solid tumors

FDA grants orphan drug designation to larotrectinib for solid tumors with NTRK gene fusions



17 tipos tumorales





larotrectinib

Vaishnavi A, et al. Nature Medicine 2013; Drilon A et al, NEJM 2018

GUION

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.- Cáncer Epidermoide de Esofago

BM recomendables

- PD-L1 (CPS)

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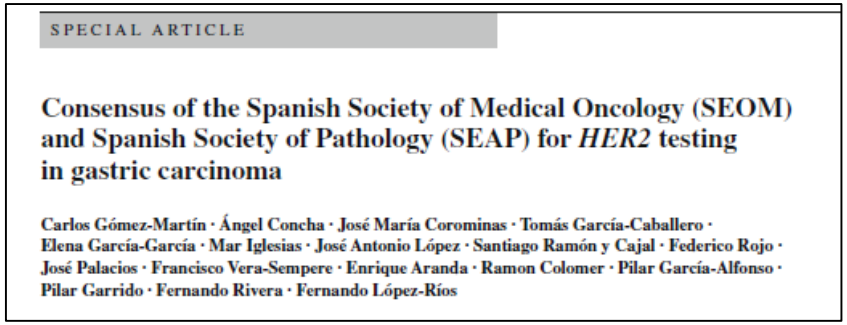
BM recomendables
- DPD ; -UGT1A1

HER-2 en Adenoca esófago gástrico. Uso rutinario

- **Métodos de medición:**
  - Determinación de la expresión de la proteína mediante IHC.
  - Determinación de la amplificación del gen (FISH, CISH).



SPECIAL ARTICLE

Consensus of the Spanish Society of Medical Oncology (SEOM) and Spanish Society of Pathology (SEAP) for *HER2* testing in gastric carcinoma

Carlos Gómez-Martín · Ángel Concha · José María Corominas · Tomás García-Caballero · Elena García-García · Mar Iglesias · José Antonio López · Santiago Ramón y Cajal · Federico Rojo · José Palacios · Francisco Vera-Sempere · Enrique Aranda · Ramon Colomer · Pilar García-Alfonso · Pilar Garrido · Fernando Rivera · Fernando López-Ríos

- **Sobreexpresado** (IHQ 3+ o IHQ 2+/FISH+) **en 20% de pts**
  - Tipo intestinal: 30%, tipo difuso: 6 %;
  - Unión esófago gástrica: 25% estómago: 15%.

P. III TOGA (C-X/F vs C-X/F-Trastuzumab)

3807 scrined pts →810 HER2+. → **584 pts included**

97% M1; 32% EGJ; 10% ECOG 2

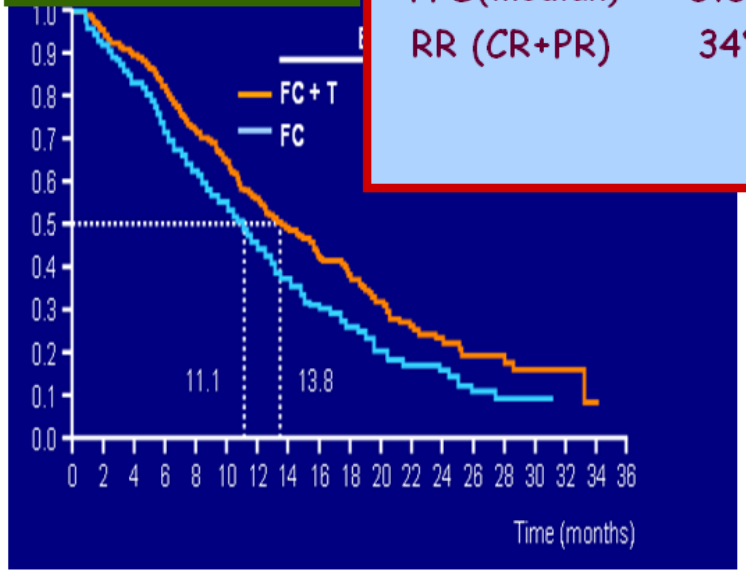
CX(87%)**/F**(13%)

CX(87%)**-/F**(13%)**-Trast**

8→6mg/kg/3w

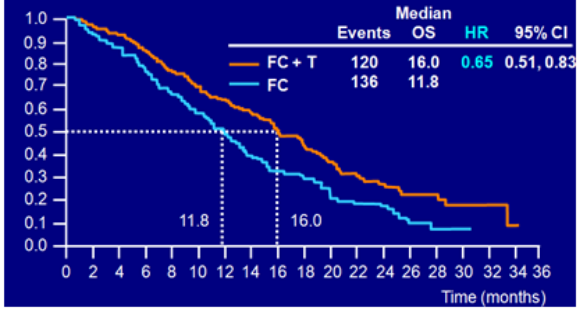
Primary endpoint OS

OS (median)	11.1 m	*HR 0.74*	*p 0.004*	13.8 m
PFS(median)	5.5 m	*HR 0.71*	*p 0.0002*	6.7 m
RR (CR+PR)	34%		*p 0.001*	47%



Bang IJ, Lancet 2010

OS in IHC2+/FISH+ or IHC3+
(exploratory analysis)



Gastric Cancer: Other anti HER-2

T-DM1, Pertuzumab

Phase II/III **GATSBY** → **T-DM1** / Taxane
2nd line
345 pts, HER2 +
Primary endpoint: P.II: efficacy, tox
P.III: OS

Phase III JACOB

→ **780 pts**

1st line M1; HER-2+ (67% IHC 3+) ; **27% EGJ**

CX/F-Hercep-Pertu

CX/F-Hercep-Pcb

Kang Y-K et al. ASCO GI San Francisco 2016

P III trials with Lapatinib

P. III TYTAN *Yung-Jue Bang et al. ASCO-GI 2013*

Asia, 2nd line HER2+. → **261 pts**

Taxol → Taxol-Lapatinib

P. III LOGIC *ASCO 2013*

1st line, HER2+.

→ **540 pts** (Asian 40%)

CapOx → CapOx-Lapatinib

P. III EORTC 40071 *ASCO -GI, 2015*

1st line, HER2+ or EGFR+

→ **69 pts** (planned 350)

ECF/X-Pcb → ECF/X-Lapatinib

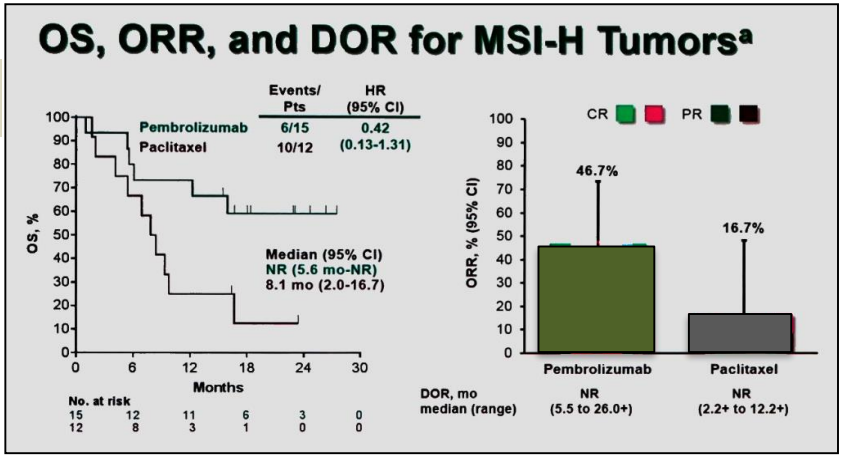
MSI advanced esophago-gastric adenocarcinoma Pembrolizumab

P. II KN 059 (Cohort 1) [1] **: Pembro in >2nd line GC**

10 pt with MSI: RR 57% DC 71%

P. III KN 061 [2] **: Pembro vs Paclitaxel in 2nd line GC**

27 pts MSI



1- Fucks CS et al, JAMA Oncol, 2018 ; 2.- Fuchs CS et al, ASCO 2018

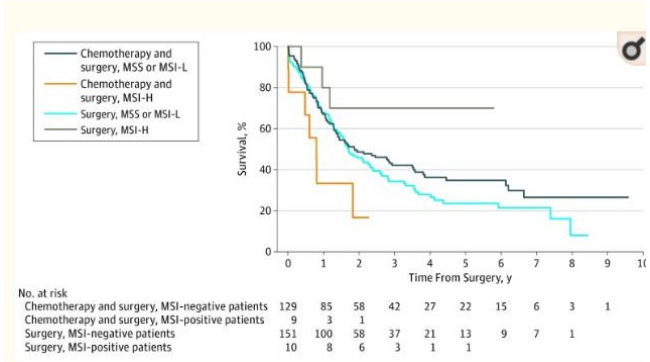
Chemotherapy (periop) and MSI

MAGIC-1 [1]: ECF→Sx→ECF vs Sx

MSI 6.6% of pts:
→ better OS with Sx alone and no benefit with Periop CT

Clinicopathologic Characteristics of Patients With MMRD vs MMRP[a]

Characteristic	MMRP (n = 246)	MMRD (n = 22)	*P* Value
Age, median (IQR) [range], y	61 (54-69) [23-79]	66 (61-68) [36-76]	.19
Sex			
Male	190 (77.2)	18 (81.8)	.79
Female	56 (22.8)	4 (18.2)	
Site of tumor			
Stomach	183 (74.4)	22 (100)	.02
Esophagus	34 (13.8)	0	
Gastroesophageal junction	29 (11.8)	0	
Histologic subtype			
Diffuse	67 (27.2)	2 (9.1)	.07[b]
Intestinal	138 (56.1)	17 (77.3)	
Mixed or other	32 (13.0)	1 (4.5)	
Missing	9 (3.7)	2 (9.1)	
T stage			
T1	10 (4.1)	0	.18[b]
T2	72 (29.3)	11 (50.0)	
T3	151 (61.4)	9 (40.9)	
T4	5 (2.0)	0	



1.- Smyh EC et al. JAMA Oncol 2017

GUION

.- Cáncer Colorectal

BM rutinarios *(CAP-I)*	BM recomendables (IIA)	BM investigación (IIB)
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.- Adenoca Esófago-Gástrico

BM rutinarios	BM recomendables	BM investigación
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- MSI/MMRD		

.- Cáncer Epidermoide de Esofago

BM recomendables

- PD-L1 (CPS)

.- Adenoca Pancreático

BM rutinarios	BM recomendables	BM investigación
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	- NTRK	- HA

.- BM predict. Tox

BM recomendables

- DPD ; -UGT1A1

PD-L1: predictive value in AGC

- **Pembrolizumab (CPS >1: 40-57%)[1]**
  - Más actividad (Rta, Dur Rta) en PD-L1+
  - …pero tbn hay actividad en PD-L1-
  - KN-061: ¿Sólo beneficio en CPS>10??

PD-L1 positive was defined as combined positive score (CPS) ≥1 (previously reported as and equivalent to CPS ≥1%), where CPS = the number of PD-L1–positive cells[b] (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells × 100
- PD-L1 IHC 22C3 pharmDx (Agilent Technologies)

- **Nivolumab (Tumor cells > 1%: 14-33%)[2]**
  - No valor predictivo

Retrospective determination of tumor PD-L1 expression, defined as positive if staining in ≥1% (or ≥5%) of tumor cells, was performed in a central laboratory using immunohistochemistry (28-8 pharmDx assay) for patients with available tumor samples

1.- Fuchs CS. ASCO 2018
2.- Lancet. 2017 Dec 2;390(10111):2461-2471

Advanced EG adenocarcinoma: Pembrolizumab

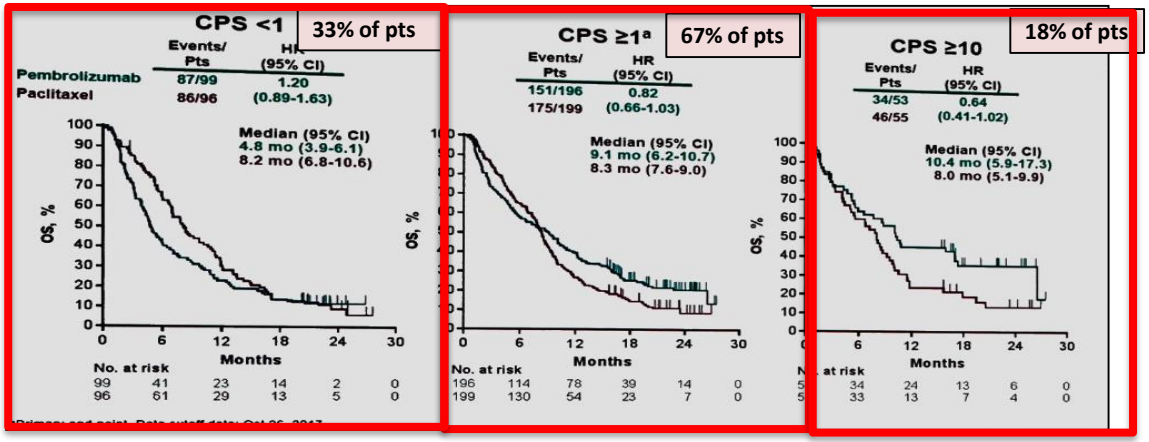
P. II KN 059 (Cohort 1)[1] : Pembro in >2nd line GC

259 pts: PD-L1 CPS>1% : 57%		
Higher activity in	**PD-L1+** vs	**PD-L1-**
RR:	15%	6%
DC	33%	19%
Dur of Resp	16,3 m	6,9 m

FDA: aprobación pembro en CPS>1%

P. III KN 061[2] : Pembro vs Paclitaxel in 2nd line GC

OS



1- Fucks CS et al, JAMA Oncol, 2018 ; 2.- Fuchs CS et al, ASCO 2018

GUION

.- Cáncer Colorectal

BM rutinarios *(CAP-I)*
- RAS
- BRAF
- MSI/MMRD

BM recomendables (IIA)
- HER2
- NTRK
- Alk, Ros1

BM investigación (IIB)
- CMS
- Genetic signatures
- CDX2

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BM rutinarios
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- MSI/MMRD

BM recomendables
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BM investigación
- TCGA

.- Cáncer Epidermoide de Esofago

BM recomendables
- PD-L1 (CPS)

.- Adenoca Pancreático

BM rutinarios
- MSI/MMRD

BM recomendables
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- NTRK

BM investigación
- Alk, Ros1
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.- BM predict. Tox

BM recomendables
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GUION

.- Cáncer Colorectal

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BM recomendables

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BM recomendables

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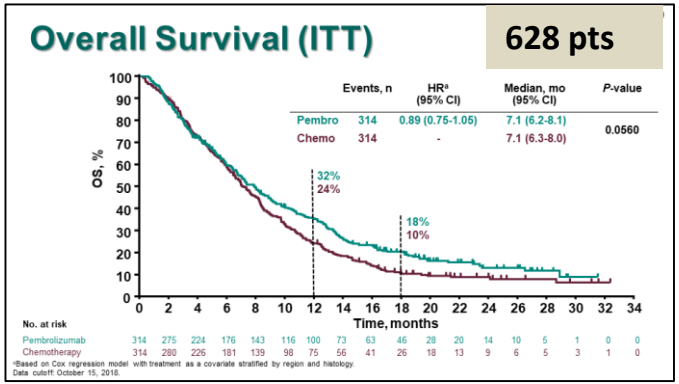
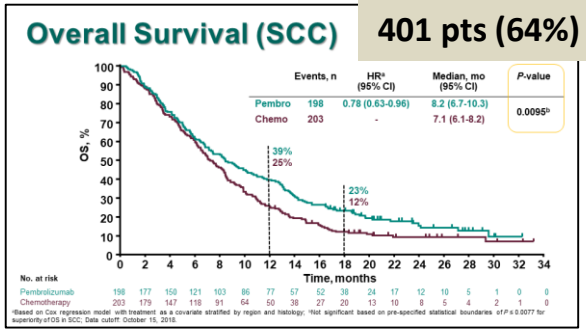
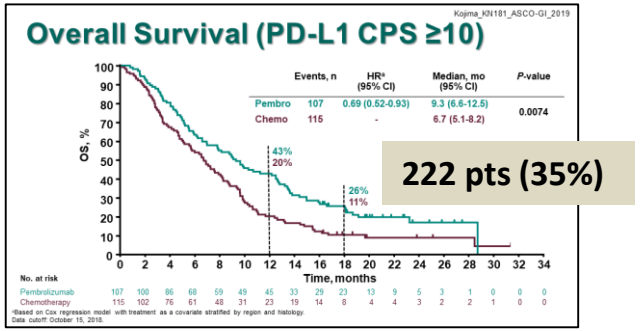
Advanced Esophageal Cancer: Pembrolizumab

P. III KN 181 [1]: Pembro vs Chemo in 2nd line Esop.Cancer







1- Kojima et al. ASCO-GI 2019

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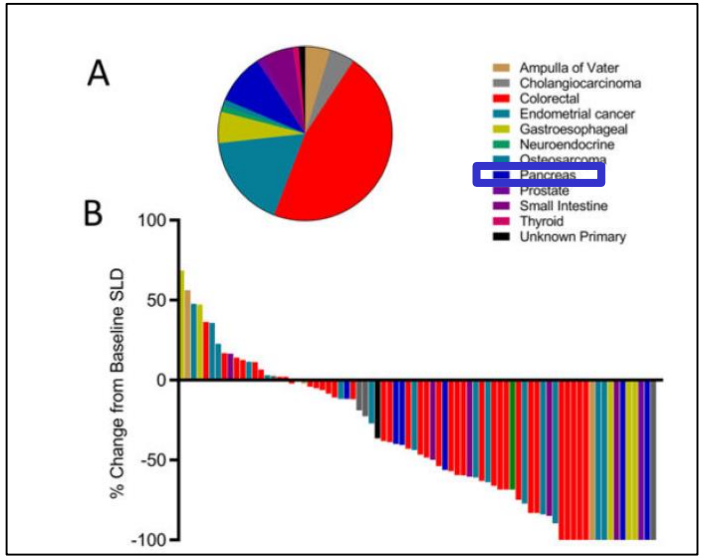
Mismatch-repair deficiency predicts response of solid tumours to PD-1 blockade [1]



N 86 patients with 12 tumor types MSI-H; Pembrolizumab

FDA News Release

FDA approves first cancer treatment for any solid tumor with a specific genetic feature

1% of pts with PC are MSH-H [2]
How we can identify this patients?
KRAS WT?
Different hystological subtype?

1.- Le et al, Science 2017 2.- Humphris et al, Gastroenterology 2017

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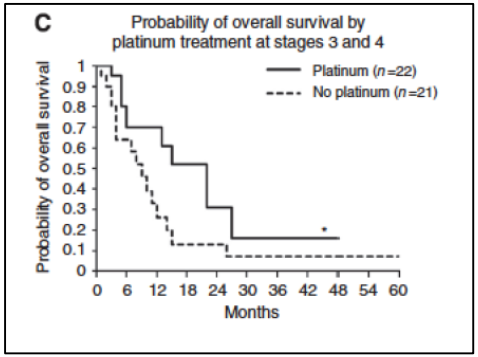
BRCA mutations and platinum sensitivity in PC

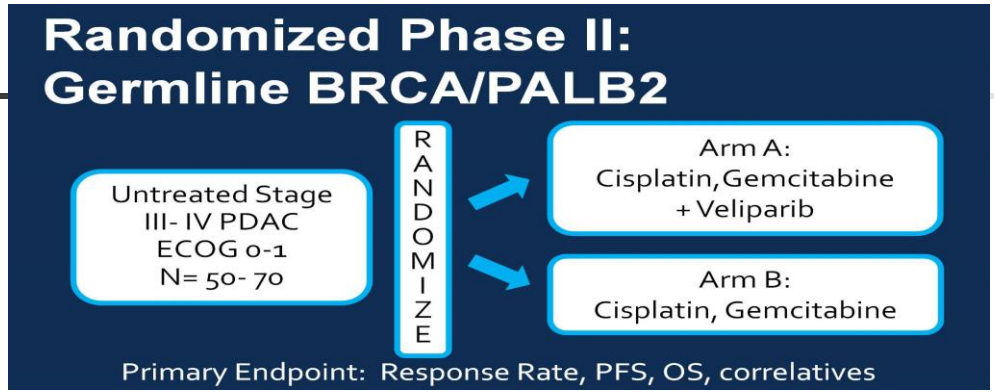
- 5-7 % of PC → BRCA-2 mutations [1].
- Defects in BRCA-1-2, PALB-B2, FANC

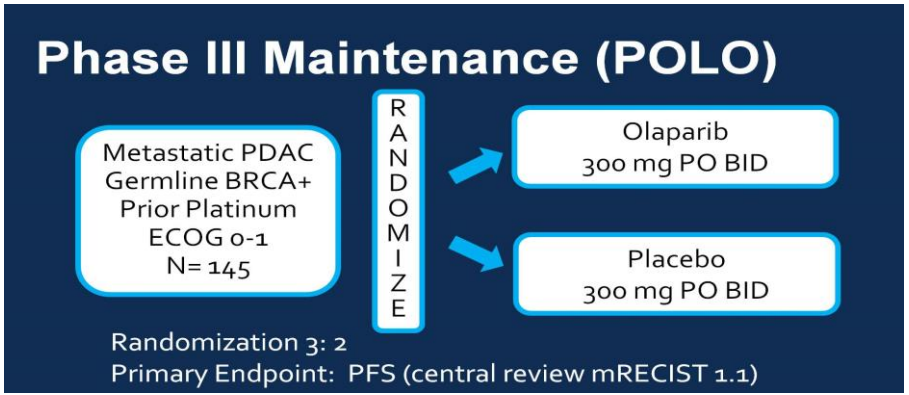
  → Increase sensibility to **platinum** [2].



1 -Goggins, Cancer Res 1996, 2- Golan, Br. J Cancer 2014.

PARP-I in APC: Veliparib, Olaparib





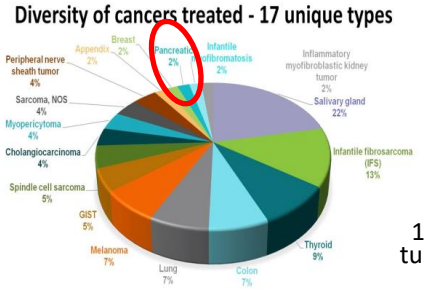
A shift of paradigm : ‘One drug fits all’
molecular alterations shared in several cancers

FDA grants orphan drug designation to entrectinib for NTRK fusion–positive solid tumors

2017

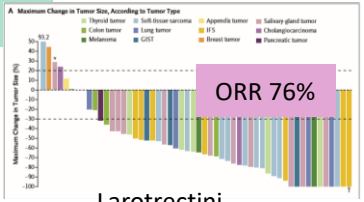
FDA grants orphan drug designation to larotrectinib for solid tumors with NTRK gene fusions

NTRK: neurotropic tropomyosin receptor kinase

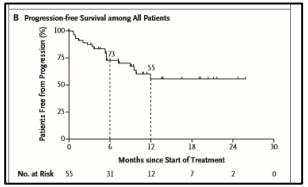


17 tipos tumorales

Aprobación de fármacos en base a la alteración molecular



ORR 76%



Larotrectinib

Vaishnavi A, et al. Nature Medicine 2013; Drilon A et al, NEJM 2018

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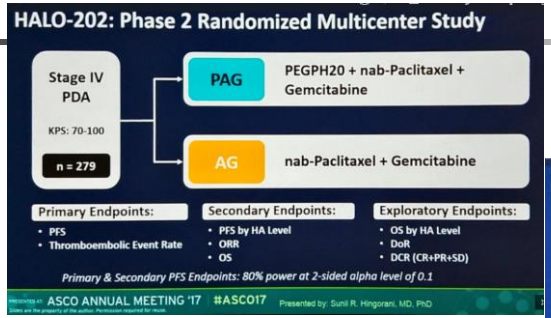
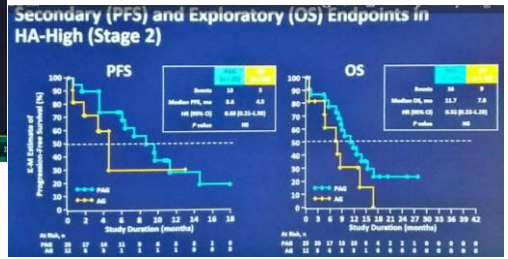
BM recomendables

- DPD ; -UGT1A1

PEGPH20 (PEGylated Recombinant Human Hyaluronidase) in PC



279 pts
→ HA hight 84 pts (30%)



P III HALO 301

mPC; HA hight — **420 PTS**

Primary endpoints:
PFS / OS

PEGPH20-Gem-Abx

Placebo-Gem-Abx

GUION

.- Cáncer Colorectal

BM rutinarios *(CAP-I)*	BM recomendables (IIA)	BM investigación (IIB)
- RAS	- HER2	- CMS
- BRAF	- NTRK	- Genetic signatures
- MSI/MMRD	- Alk, Ros1	- CDX2

.- Adenoca Esófago-Gástrico

BM rutinarios	BM recomendables	BM investigación
- HER2	- PD-L1 (CPS)	- TCGA
- MSI/MMRD		

.- Cáncer Epidermoide de Esofago

BM recomendables
- PD-L1 (CPS)

.- Adenoca Pancreático

BM rutinarios	BM recomendables	BM investigación
- MSI/MMRD	- BRCA/BRCAness	- Alk, Ros1
	- NTRK	- HA

.- BM predict. Tox

BM recomendables
- DPD ; -UGT1A1

Biomarcadores Tox recomendables: DPD (dihidropirimidín deshidrogenasa)

- **Métodos de determinación:**
  - –ELISA.
  - –IHQ.
  - –Nivel de expresión (mARN) por PCR.
  - –Polimorfismos/mutaciones.
  - –Test de inhalación de uracilo.

- **Utilidad clínica:** valor pronóstico y valor predictivo. Está bastante establecido su valor como predictor de toxicidad con las fluoropirimidinas.

- **Recomendación: no se puede considerar su utilización como rutinaria de inicio. Sí recomendable si se sospecha déficit de DPD (Tox previa) y se precisan fluoropirimidinas**

Biomarcadores Tox recomendables: UGT1A1 (UDP-glucuronosiltransferasa 1 A1)

- **Métodos de determinación: polimorfismos.**
- **Utilidad clínica:** valor pronóstico y valor predictivo. El número más habitual de repeticiones de TA es de seis, siendo la mayor parte de los individuos homocigotos 6/6. Cuando hay siete repeticiones en uno de los alelos (heterocigotos 7/6), pero sobre todo cuando esto sucede en los dos alelos (homocigotos 7/7), se reduce la expresión del gen y, por tanto, se glucuroniza menos el SN-38, acumulándose y produciéndose una mayor exposición al mismo con el consiguiente aumento en la toxicidad.

- **Recomendación: sería recomendable determinar los polimorfismos en UGT1A1*28 en aquellos pacientes que van a ser tratados con CPT-11 a dosis superiores a 200 mg/m2 y utilizar dosis reducidas en aquellos que fuesen homocigotos 7/7.**

Gracias