V SIMPOSIO GETHI | 18/19 noviembre de 2019

Ilustre Colegio Oficial de Médicos de Madrid. Aula Jiménez Díaz. Madrid

BLOQUE 5: BRAF Y MEK EN TUMORES SÓLIDOS Y CÁNCER RARO

16:40h – 17:00h Resultados clínicos de los inhibidores a través de histologías

Dr. David Gutiérrez

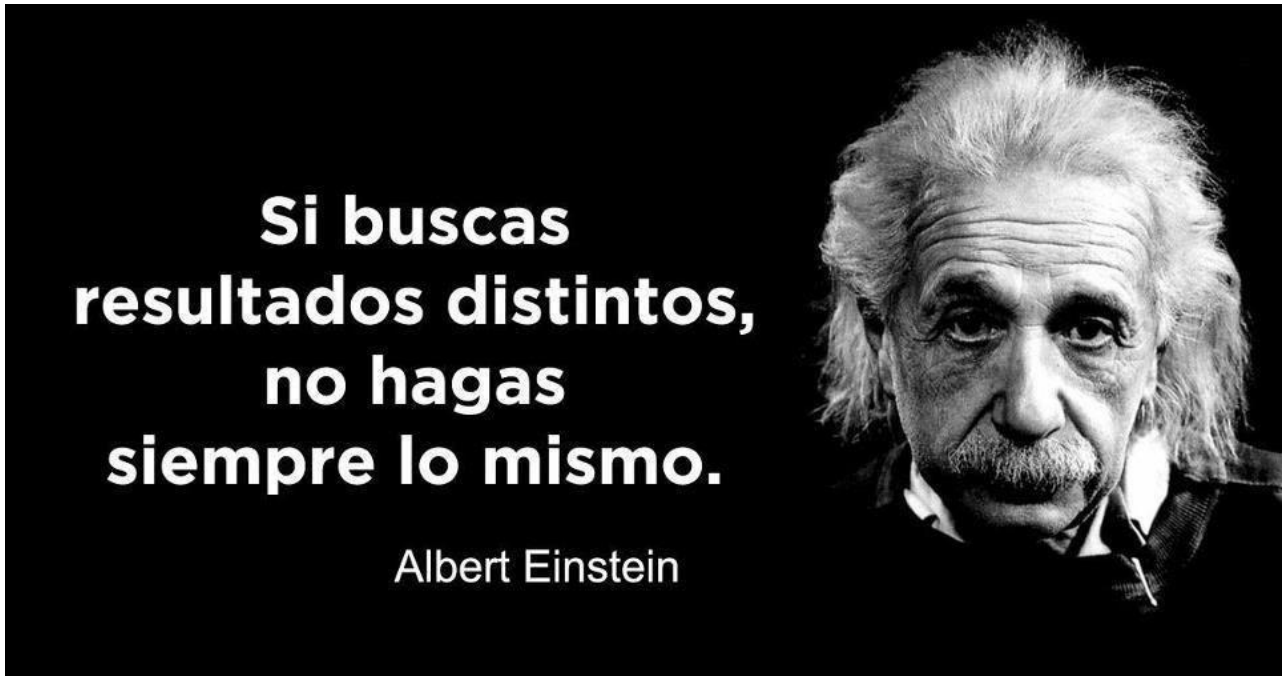
Hospital Universitario de Fuenlabrada

grupo Gethi
Grupo Español de Tumores Huérfanos e Infrecuentes

Disclosures

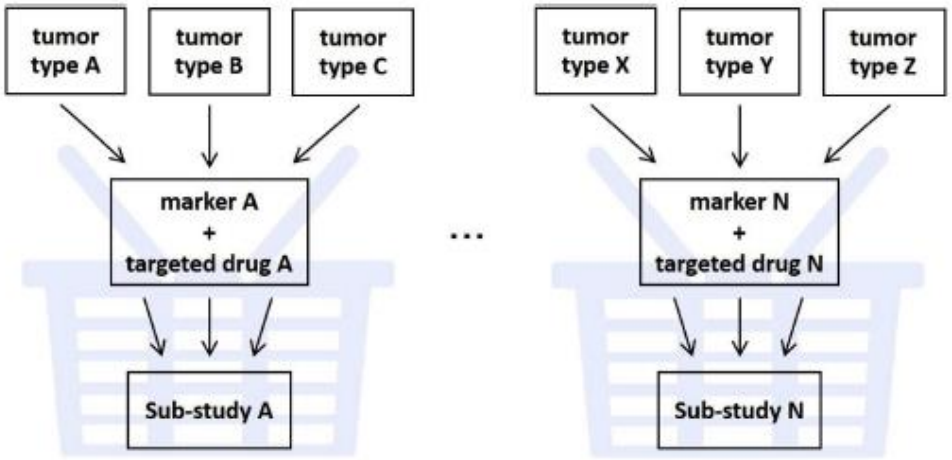
- Oncólogo médico Hospital Universitario de Fuenlabrada
- Recibo honorarios como consultor en programas de formación de cáncer colorrectal de Roche
- Los comentarios de la presentación presentada reflejan mi punto de vista como oncólogo médico basados en la evidencia clínica expuesta
- Para la actual presentación no recibo honorarios de ningún laboratorio

Cambio de mentalidad



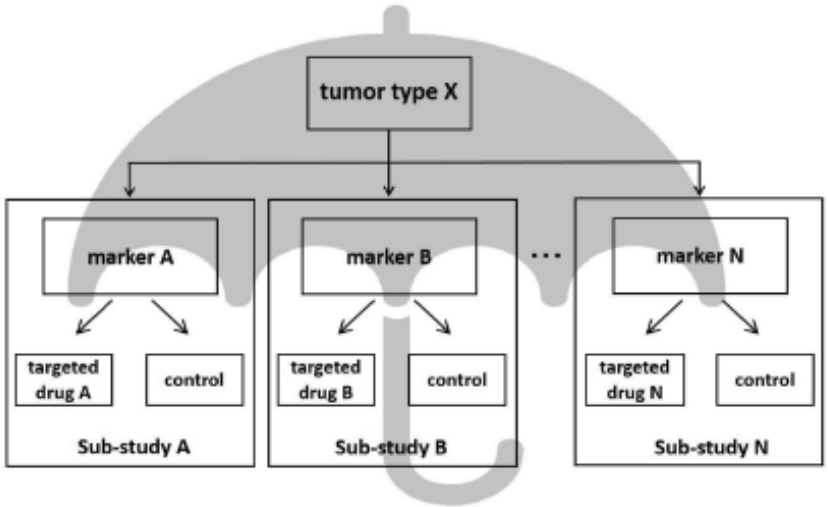
Master protocol trials in oncology: Review and new trial designs

Akihiro Hirakawa[a,*], Junichi Asano[b], Hiroyuki Sato[b], Satoshi Teramukai[c]



Basket trials

A basket trial **evaluates one targeted therapy** on multiple diseases or multiple disease subtypes.



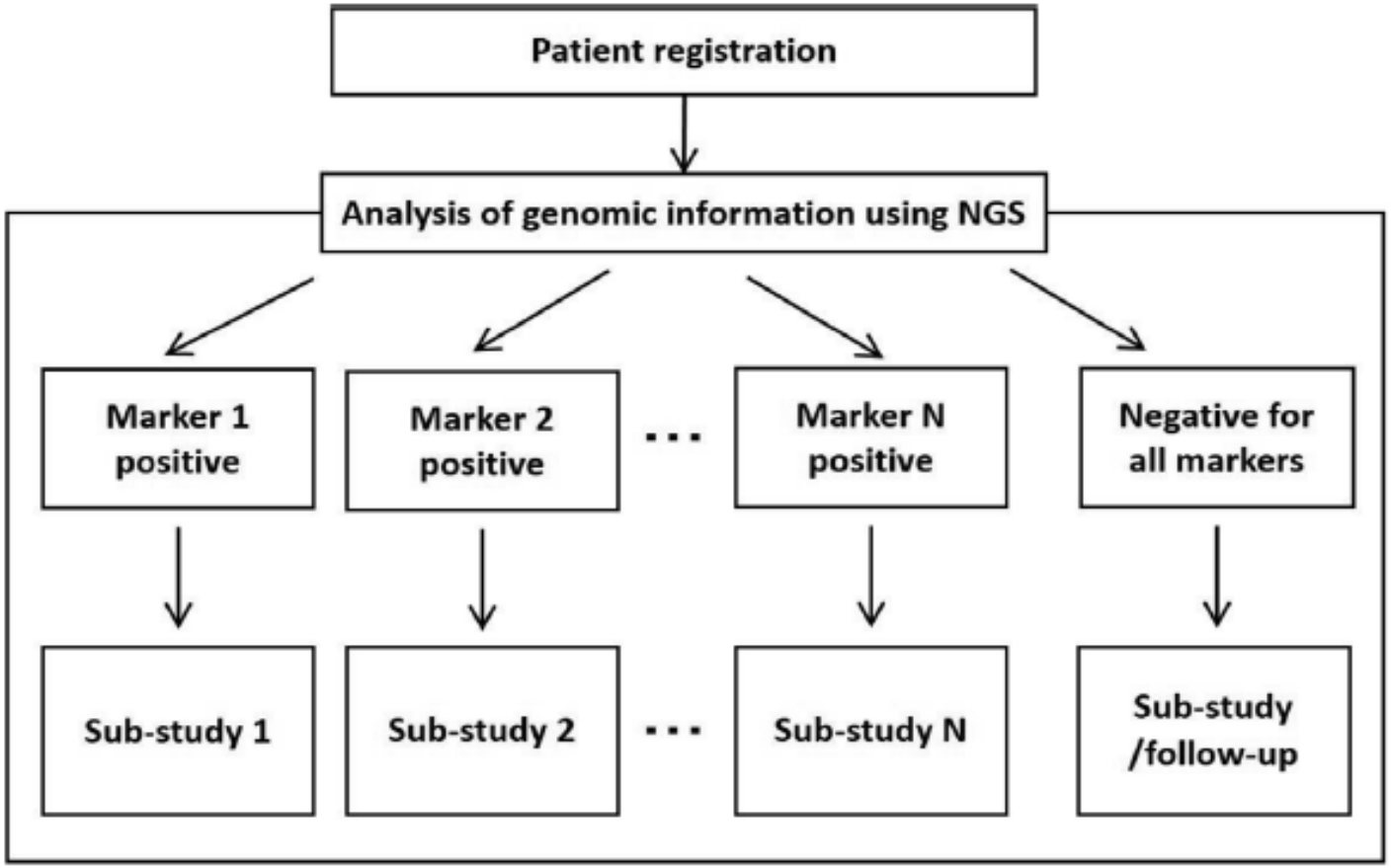
Umbrella trials

Umbrella trials **evaluate multiple targeted therapies** for one disease or several diseases

Contemporary Clinical Trials Communications 12 (2018) 1–8

-K.M. Cunanan, et al., Basket trials in oncology: a trade-off between complexity and efficiency, J. Clin. Oncol. 35 (2017) 271–273.
-J. Woodcock, L.M. LaVange, Master protocols to study multiple therapies, multiple diseases, or both, N. Engl. J. Med. 377 (2017) 62–70.
-L.A. Renfro, D.J. Sargent, Statistical controversies in clinical research: basket trials, umbrella trials, and other master protocols: a review and examples, Ann. Oncol. 28 (2017) 34–43.

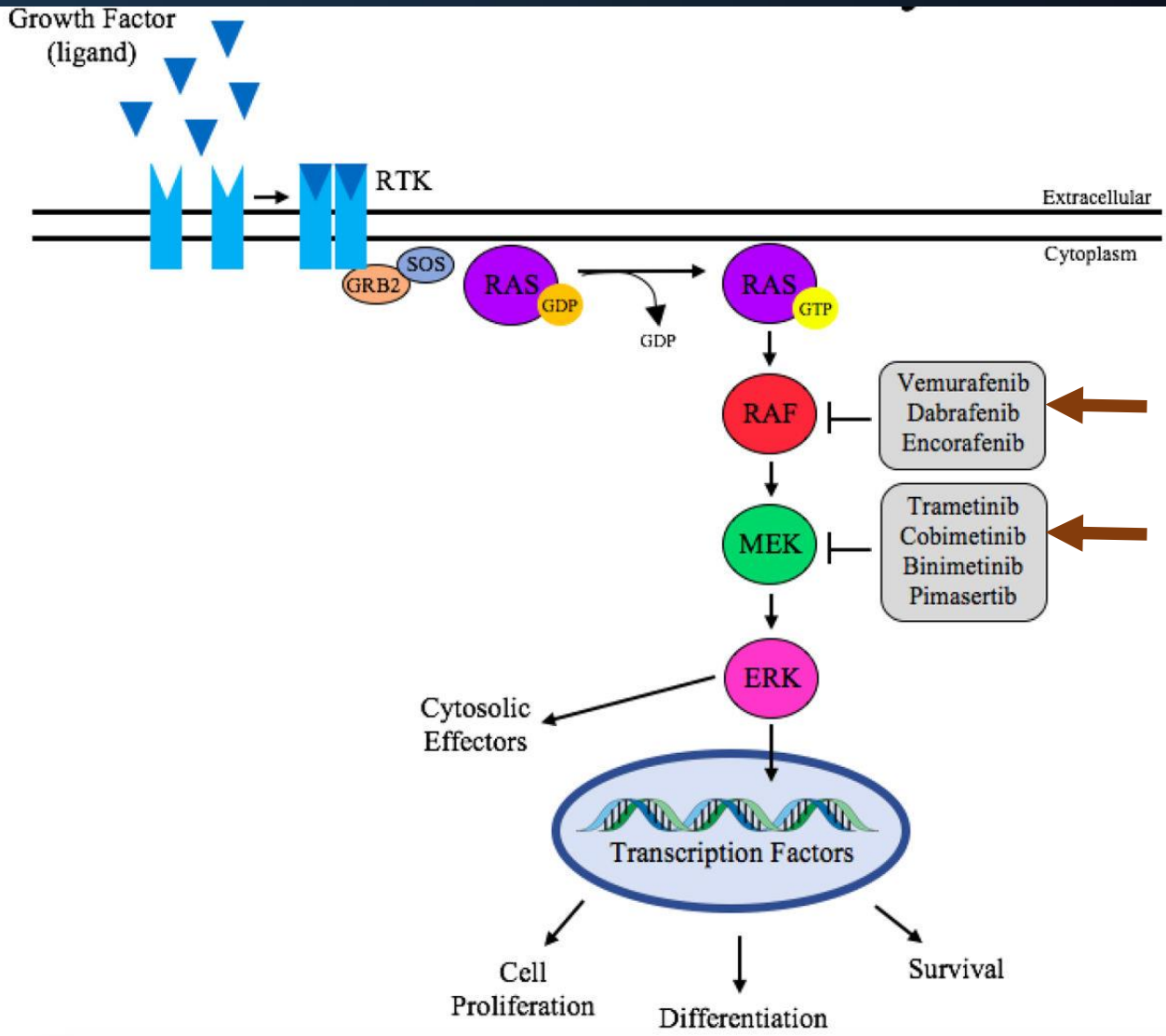
Diseño de los futuros estudios



Contemporary Clinical Trials Communications 12 (2018) 1–8

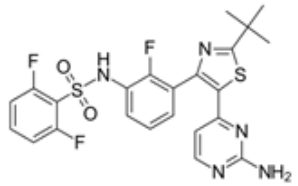
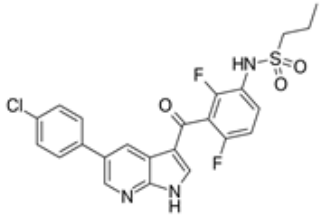
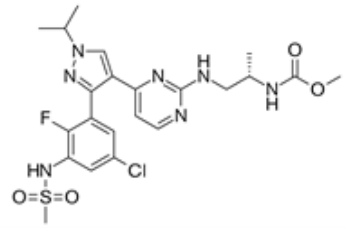
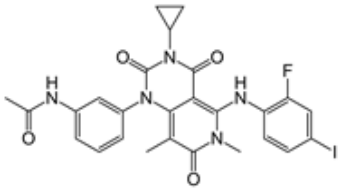
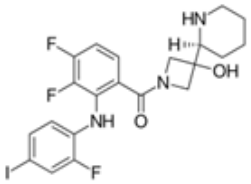
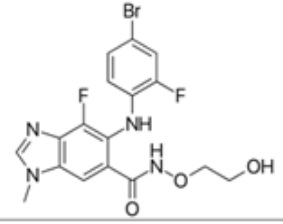
vía MAPK/ERK

Esta vía de señalización se activa cuando un factor de crecimiento (ligando) se une a su respectivo receptor.
El RTK activado transmite la señal extracelular al interior de la célula a través de la via de la proteína GRB2, RAS, RAF, MEK y finalmente se activa ERK que actúa sobre efectores nucleares.



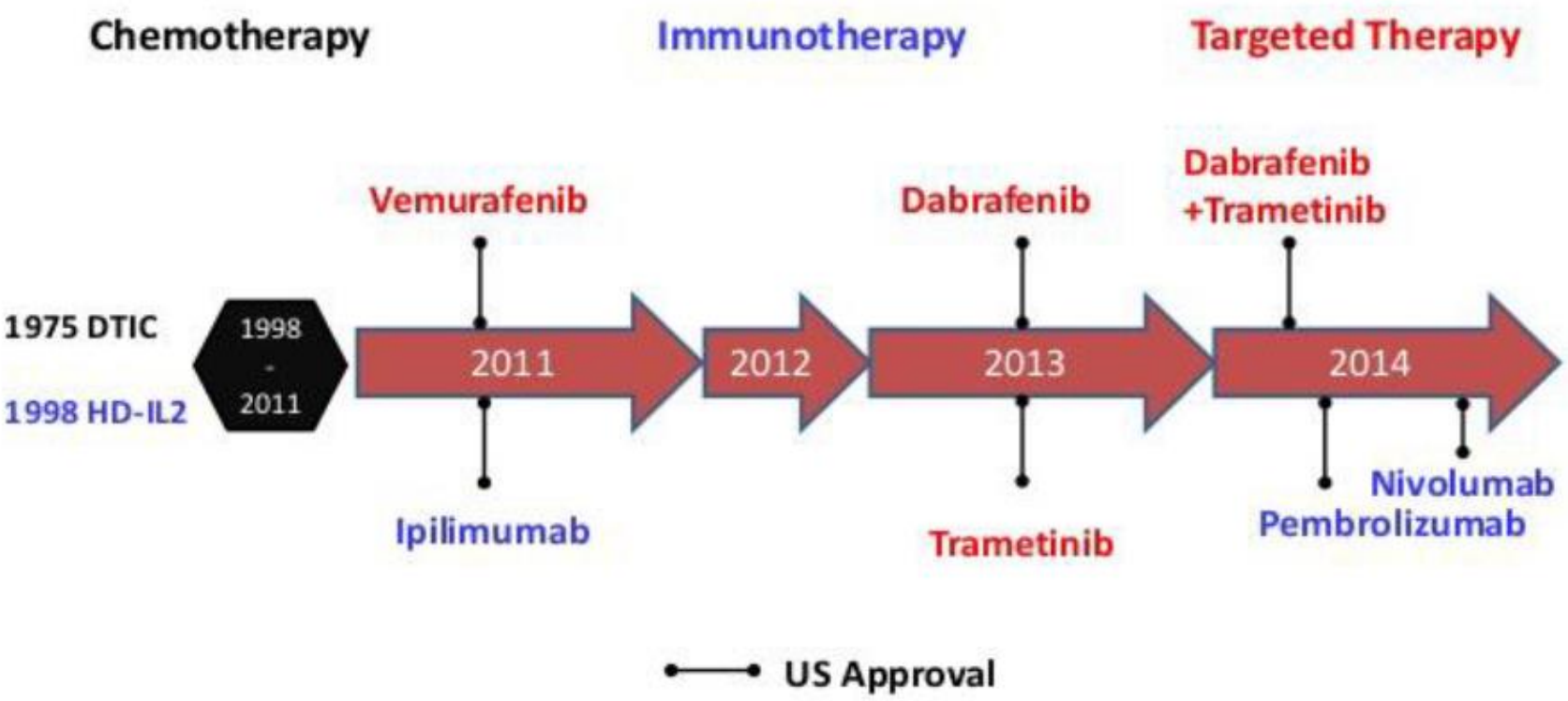
Drugs. 2018 April ; 78(5): 549–566

Inhbidores de vía **MAPK/ERK**

	Dabrafenib / Trametinib	**Vemurafenib / Cobimetinib**	**Encorafenib / Binimetinib**
BRAF Inhibitors **Dab.** (GSK2118436) **/** **Vem.** (PLX4032,RG7204) **/** **Enc.** (LGX818)			
	RP2D: **150 mg td** (MTD not reached) * BCS class: II (high permeability, low solubility) Food effect: Intake 1h prior or 2 h after meal Absorption (t_{max}): **1.9 h** Time to steady-state ($t_{max,ss}$): **14 d** $AUC_{0\text{-}24,ss}$: **4.3 h*µg/mL** (38 %CV_b) $C_{max,ss}$: **1478 ng/mL** (37 %CV_b) Clearance (CL/F): **17.3 L/h** (nc) Elimination half-life (t½): **8.4 h** (nc)	RP2D: **960 mg td** (=MTD) BCS class: IV (low permeability, low solubility) Food effect: none (Intake with/without food) Absorption (t_{max}): ~**4 h** Time to steady-state ($t_{max,ss}$): **15-22 d** $AUC_{0\text{-}8,ss}$: **380.2 h*µg/mL** (38 %CV_b) $C_{max,ss}$: **56,700 ng/mL** (38 %CV_b) Clearance (CL/F): **1.2 L/h** (32 CV_b%) Elimin. half-life (t½): **56 h** [30-120]	RP2D: **300 mg od** (MTD: 450 mg od) BCS class: *nr* Food effect: None (Intake with/without food) Absorption (t_{max}): **2.0 h** Time to steady-state ($t_{max,ss}$): **15 d** $AUC_{0\text{-}24,ss}$: **12.3 h*µg/mL** (med.) $C_{max,ss}$: **3100 ng/mL** (med.) Clearance (CL/F): **24.4 L/h** (med.) Elimination half-life (t½):**6.3 h** [3.7-8.1]
MEK Inhibitors **Tra.** (GSK1210212) **/** **Cob.** (RG7420) **/** **Bin.** (MEK162)			
	RP2D: **2 mg od** (MTD: 3 mg od) BCS class: II (high permeability, low solubility) Food effect: Intake 1h prior or 2 h after meal Absorption (t_{max}): **1.5 h** Time to steady-state ($t_{max,ss}$): **15 d** $AUC_{0\text{-}24,ss}$: **0.4 h*µg/mL** (22 %CV_b) $C_{max,ss}$: **22 ng/mL** (28 %CV_b) Clearance (CL/F): **5.4 L/h** (nc) Elimination half-life (t½): **90 h** [58-183]	RP2D: **60 mg od** (d1-21 q4w) (=MTD) BCS class I: (high permeability, high solubility) Food effect: none (Intake with/without food) Absorption (t_{max}): **2.4 h** Time to steady-state ($t_{max,ss}$): **10 d** $AUC_{0\text{-}24,ss}$: **4.3 h*µg/mL** (61 %CV_b) $C_{max,ss}$: **273 ng/mL** (60 CV_b%) Clearance (CL/F): **13.8 L/h** (61% CV) Elimination half-life (t½): **44 h** [23-69]	RP2D: **45 mg td** (MTD: 60 mg td) BCS class: *nr* Food effect: none (Intake with/without food) Absorption (t_{max}): **2.0 h** (1.5 h at 60 mg td) Time to steady-state ($t_{max,ss}$): **15 d** $AUC_{0\text{-}8,ss}$: **1.5 h*µg/mL** (nc) $C_{max,ss}$: **273 ng/mL** (65 %CV_b) Clearance (CL/F): *nr* Elimination half-life (t½): **8.7 h** (nc)

Inhbidores de vía MAPK/ERK

Evolución histórica de aprobaciones de inhibidores de BRAF y MEK EN MELANOMA METASTASICO (incidencia de mutaciones de BRAF v600E del 40-50%)



Estudio VE-BASKET

Basket trial en tumores sólidos no melanomas

- ***BRAF está mutado en alrededor de* 15% de todos los cánceres (1,2)**
- **Para algunos cánceres, la mutación *BRAF se detecta en un alto porcentaje*: melanoma (40%–60% de pacientes) y en leucemia de celulas peludas (3,4)**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vemurafenib in Multiple Nonmelanoma Cancers with *BRAF* V600 Mutations

David M. Hyman, M.D., Igor Puzanov, M.D., Vivek Subbiah, M.D., Jason E. Faris, M.D., Ian Chau, M.D., Jean-Yves Blay, M.D., Ph.D., Jürgen Wolf, M.D., Ph.D., Noopur S. Raje, M.D., Eli L. Diamond, M.D., Antoine Hollebecque, M.D., Radj Gervais, M.D., Maria Elena Elez-Fernandez, M.D., Antoine Italiano, M.D., Ph.D., Ralf-Dieter Hofheinz, M.D., Manuel Hidalgo, M.D., Ph.D., Emily Chan, M.D., Ph.D., Martin Schuler, M.D., Susan Frances Lasserre, M.Sc., Martina Makrutzki, M.D., Florin Sirzen, M.D., Ph.D., Maria Luisa Veronese, M.D., Josep Tabernero, M.D., Ph.D., and José Baselga, M.D., Ph.D.

Hyman, DM et al, NEJM 373;8 August 20, 2015

Estudio VE-BASKET

VE-BASKET: a histology-independent, flexible, early phase 2 study of vemurafenib in patients with non-melanoma cancers harboring BRAF V600 mutations

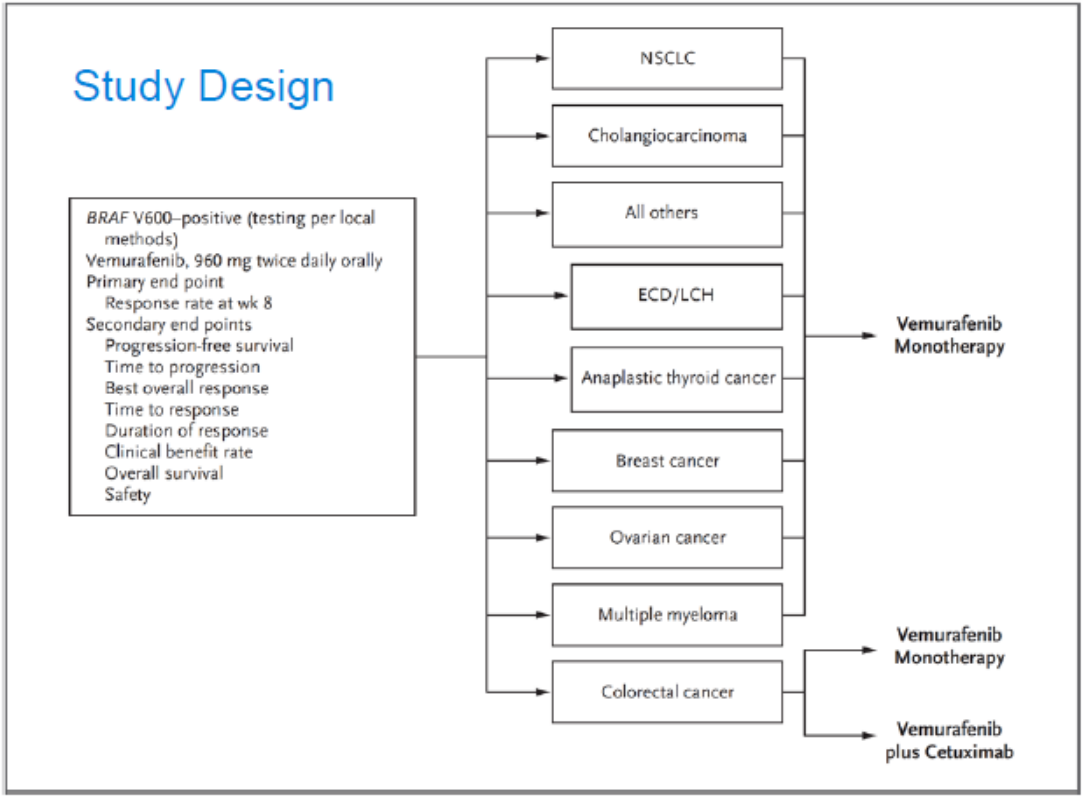
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vemurafenib in Multiple Nonmelanoma Cancers with *BRAF* V600 Mutations

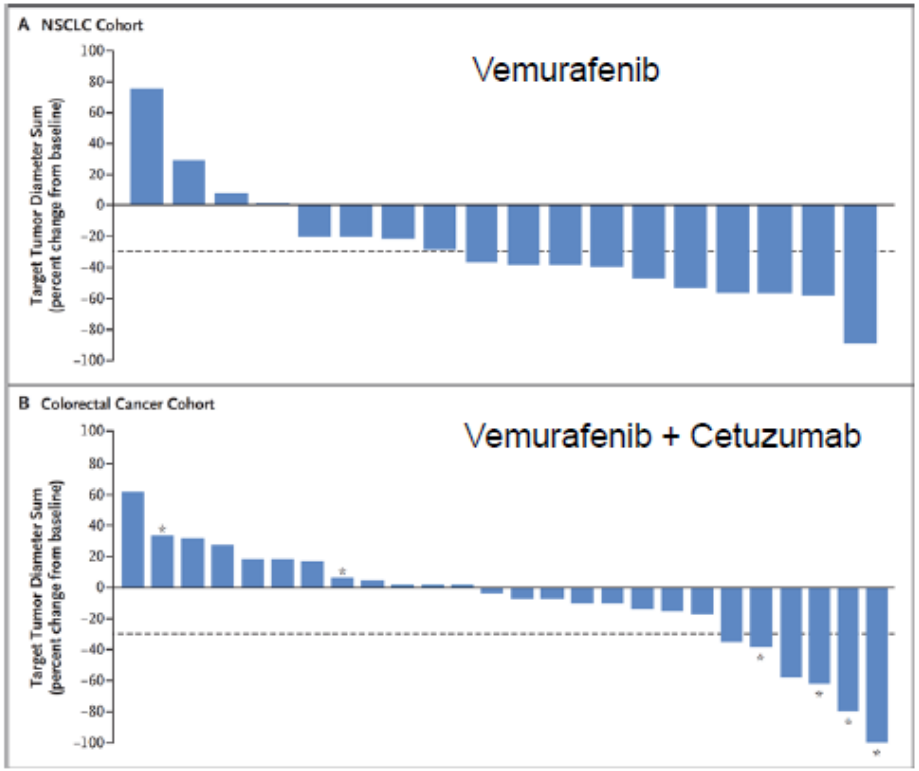
David M. Hyman, M.D., Igor Puzanov, M.D., Vivek Subbiah, M.D., Jason E. Faris, M.D., Ian Chau, M.D., Jean-Yves Blay, M.D., Ph.D., Jürgen Wolf, M.D., Ph.D., Noopur S. Raje, M.D., Eli L. Diamond, M.D., Antoine Hollebecque, M.D., Radj Gervais, M.D., Maria Elena Elez-Fernandez, M.D., Antoine Italiano, M.D., Ph.D., Ralf-Dieter Hofheinz, M.D., Manuel Hidalgo, M.D., Ph.D., Emily Chan, M.D., Ph.D., Martin Schuler, M.D., Susan Frances Lasserre, M.Sc., Martina Makrutzki, M.D., Florin Sirzen, M.D., Ph.D., Maria Luisa Veronese, M.D., Josep Tabernero, M.D., Ph.D., and José Baselga, M.D., Ph.D.

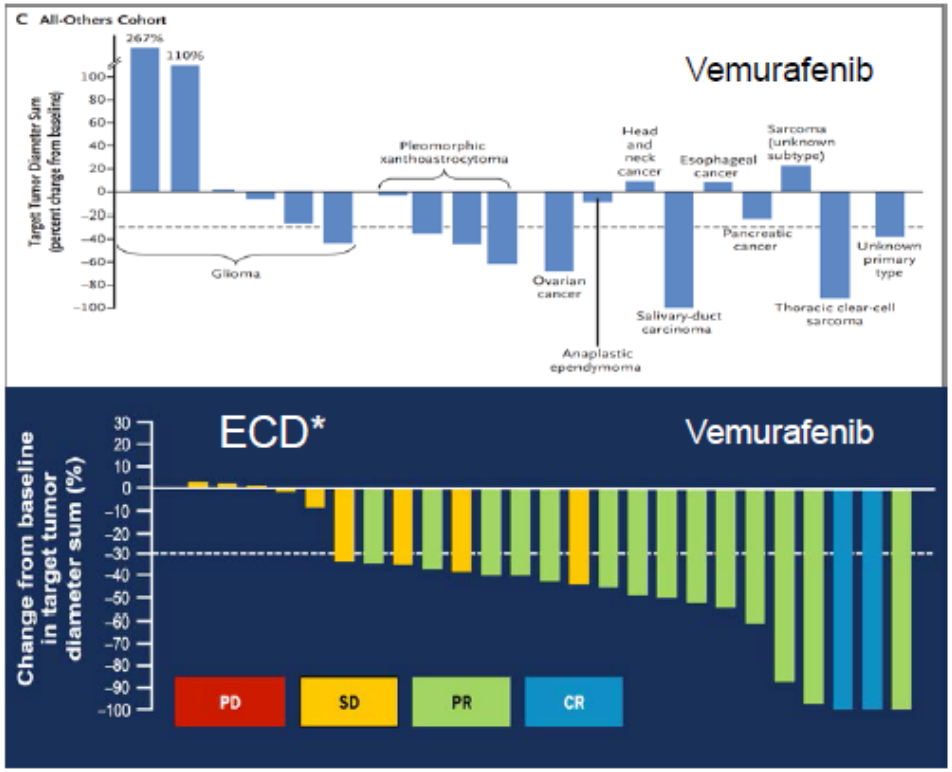
Hyman, DM et al, NEJM 373;8 August 20, 2015



Estudio VE-BASKET: parámetros de sensibilidad tumoral

Percent change from baseline by RECIST1.1





The histologic context is an important determinant of response in BRAF V600–mutated

Hyman, DM et al, NEJM 373;8 August 20, 2015 Diamond· E et al, ASH 2016

Estudios e Indicaciones de inhibidores de vía MAPK/ERK en Combinacion

- **Melanoma**

- **Colorectal Cancer**

- **Non-Small Cell Lung Cancer**

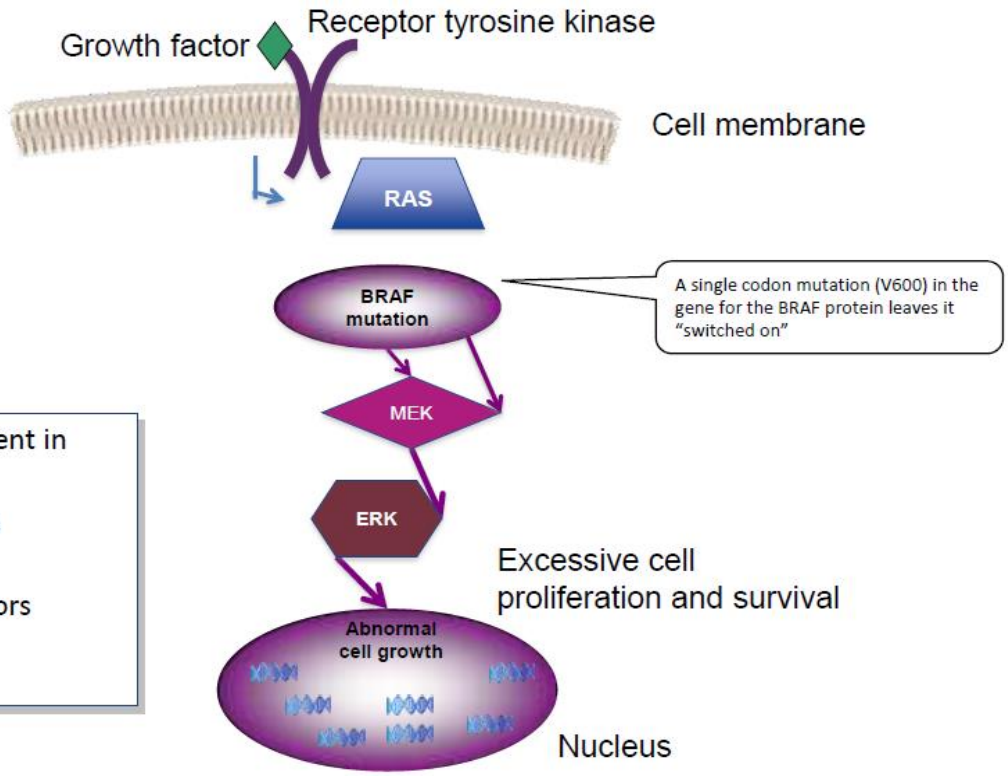
- **Thyroid Cancer**

Mutated BRAF

The role of "V600"

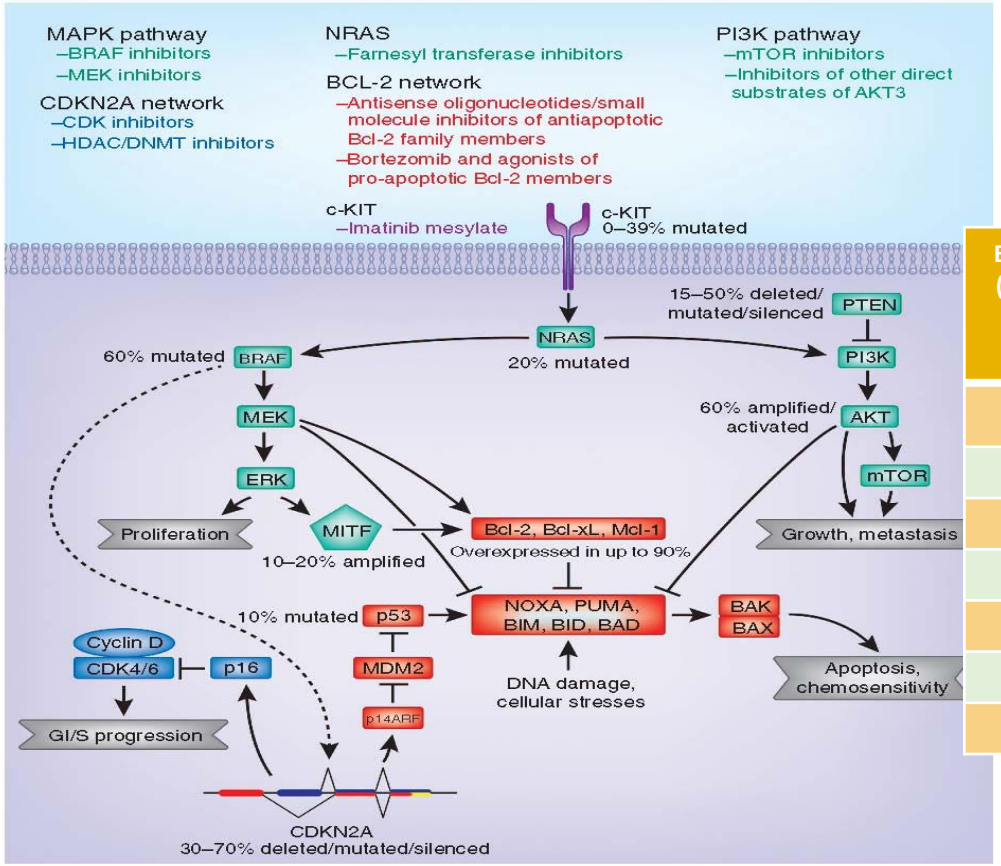
Mutated BRAF is present in many cancers:

- >50% melanomas
- ~10% colorectal
- ~8% all solid tumors



Estudios e Indicaciones de inhibidores de vía MAPK/ERK en Combinacion

- **Melanoma metastásico**



Frecuencia relativa de mutaciones BRAF

BRAF mutation location (by amino acid position and substitution)	% of all BRAF mutations
V600E	**97.3%**
V600K	1.0%
K601E*	0.4%
G469A*	0.4%
D594G*	0.3%
V600R	0.3%
L597V*	0.2%

Hocker, et al. 2008 The Society for Investigative Dermatology

Estudios e Indicaciones de inhibidores de vía MAPK/ERK en Combinacion

- **Melanoma metastásico**

Comparison of Major Clinical End Points for BRAF Monotherapy with Combined BRAF and MEK Inhibition.

Table 1. Comparison of Major Clinical End Points for BRAF Monotherapy with Combined BRAF and MEK Inhibition.

End Point	Larkin et al. Study[9]		Long et al. Study[10]	
	Vemurafenib	Vemurafenib and Cobimetinib	Dabrafenib	Dabrafenib and Trametinib
Objective response (%)	45	68	51	67
Complete response (%)	4	10	9	10
Median progression-free survival (mo)	6.2	9.9	8.8	9.3
Survival at 9 mo (%)*	73	81	77	85
Toxic events leading to treatment withdrawal (%)	12	13	5	9

* Survival at 9 months in the study by Long et al. was estimated from Figure 2A of the article.

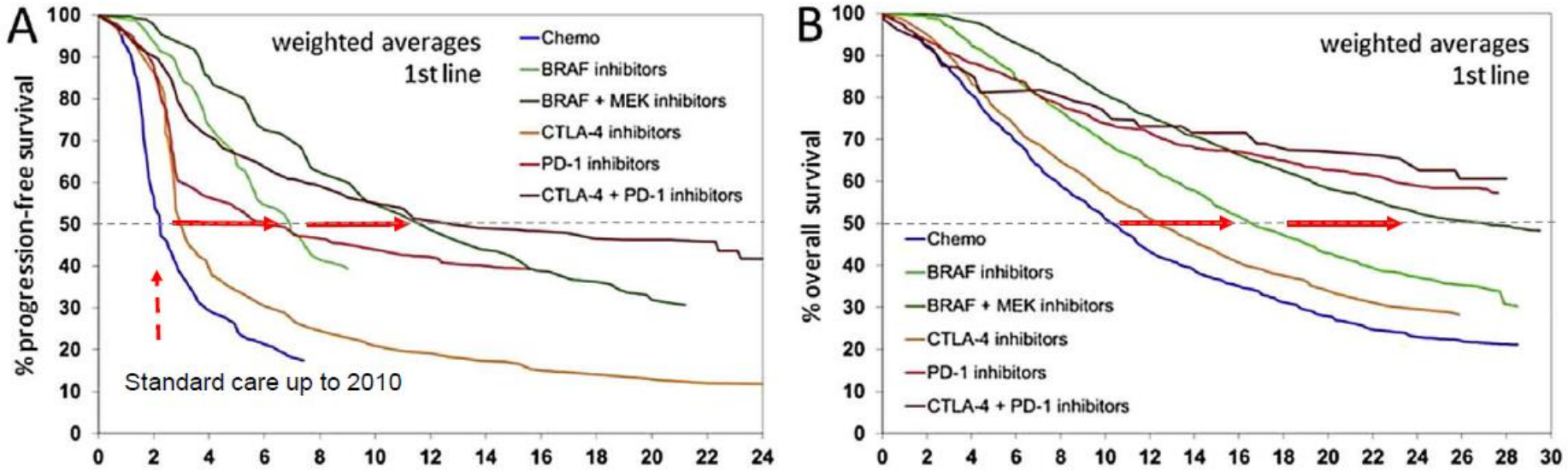
Curti BD. N Engl J Med 2014;371:1929-1930.

The NEW ENGLAND JOURNAL of MEDICINE

Estudios e Indicaciones de inhibidores de vía MAPK/ERK en Combinacion

- **Melanoma metastásico**

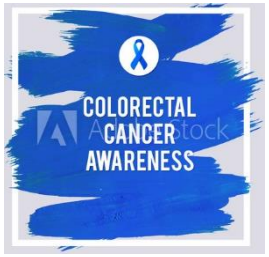
En melanoma metastásico el tratamiento en primera línea con inhibidores BRAF y MEK aporta un beneficio en SLP y SG

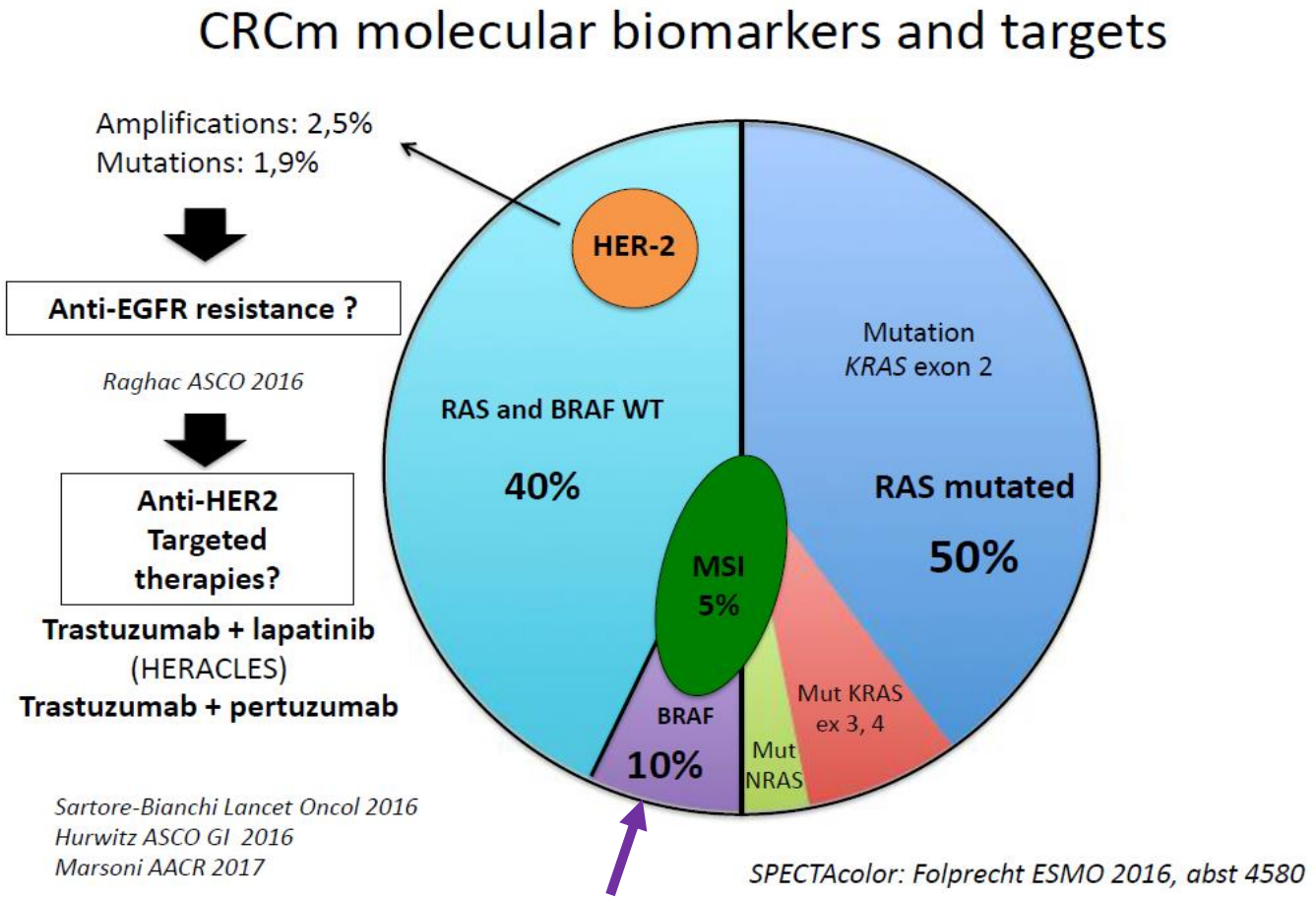


Selma Ugurel, et al; European Journal of Cancer 83 (2017) 247e25

Estudios e Indicaciones de inhibidores de vía MAPK/ERK en Combinacion

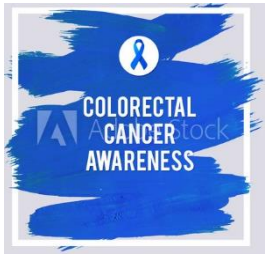
- **Cáncer colorrectal metastásico**





Estudios e Indicaciones de inhibidores de vía MAPK/ERK en Combinacion

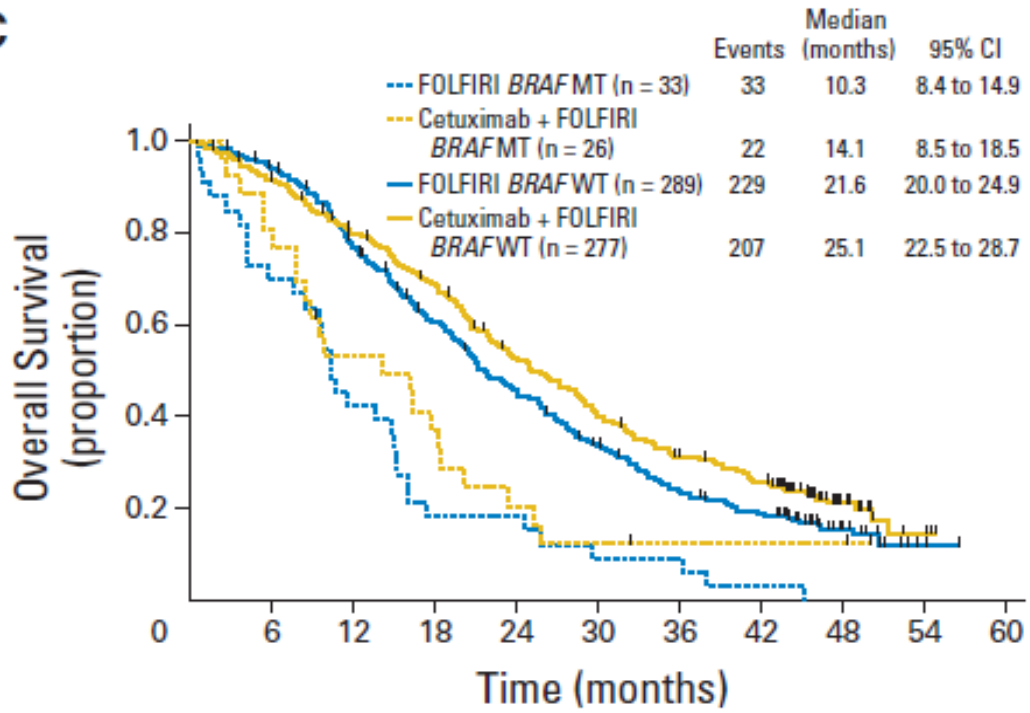
- **Cáncer colorrectal metastásico**



- **La mutación BRAF V600E como biomarcador?**
- En estadios avanzados de de mCRC indica mal pronóstico
- Efecto predictivo negative para EGFR MoAbs en algunos estudios:

-Cetuximab: refractory (European cons.)1,2 & first-line setting (CRYSTAL study)3

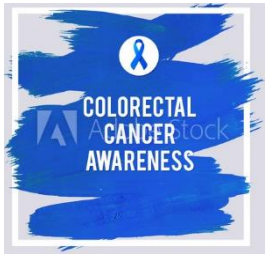
-Panitumumab: 2nd line setting (PICCOLO study)4



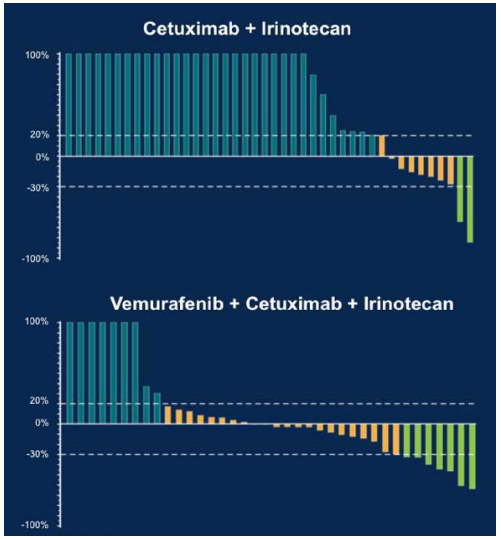
1 Di Nicolantonio F, J Clin Oncol 2018; 2 De Roock et al. Lancet Oncol 2010; 3 Van Cutsem et al, J Clin Oncol 2011;
4 Seymour MT et al, Proc ASCO 2011

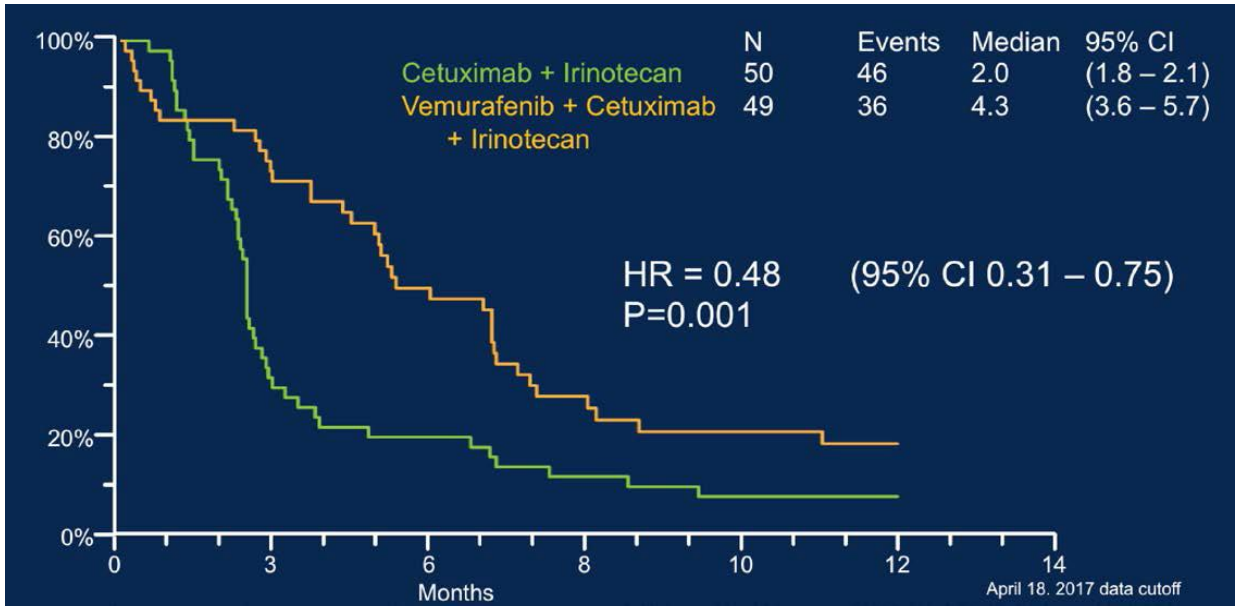
Estudios e Indicaciones de inhibidores de vía MAPK/ERK en Combinacion

- **Cáncer colorrectal metastásico**



Tasa de respuestas y control de la enfermedad más altas en el brazo de vemurafenib (16% versus 4% y 67% versus 22% respectivamente)

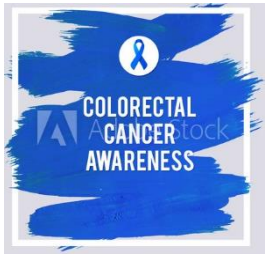


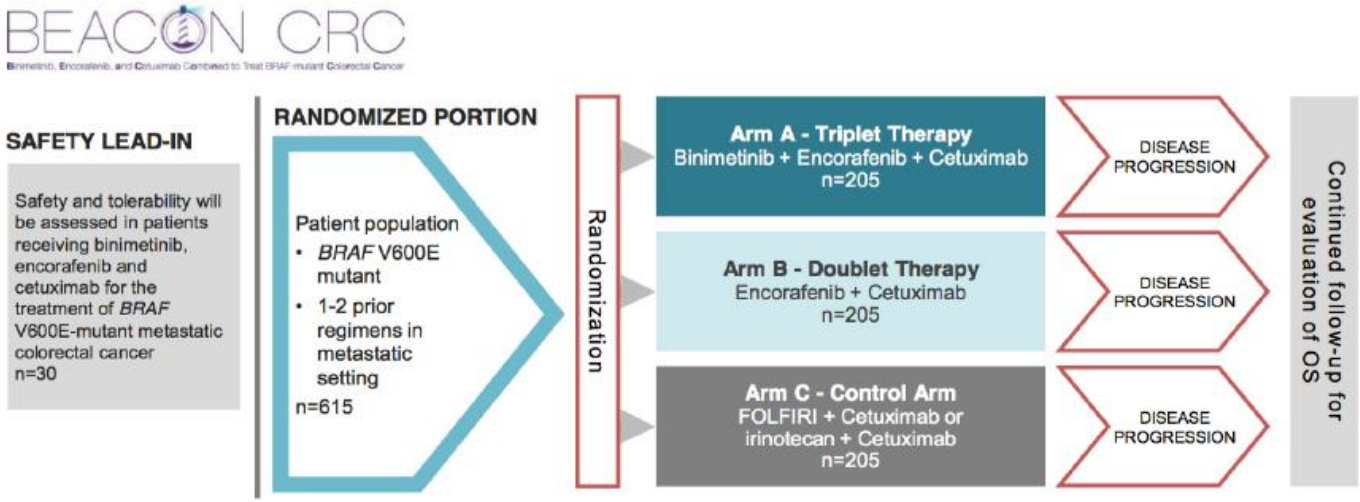


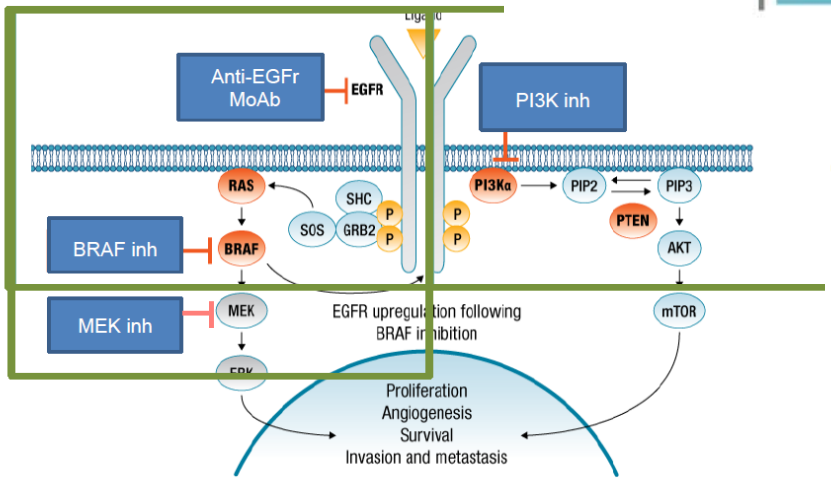
Scott Kopetz et al, ASCO 2017

Estudios e Indicaciones de inhibidores de vía MAPK/ERK en Combinacion

- **Cáncer colorrectal metastásico**



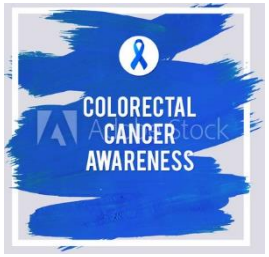




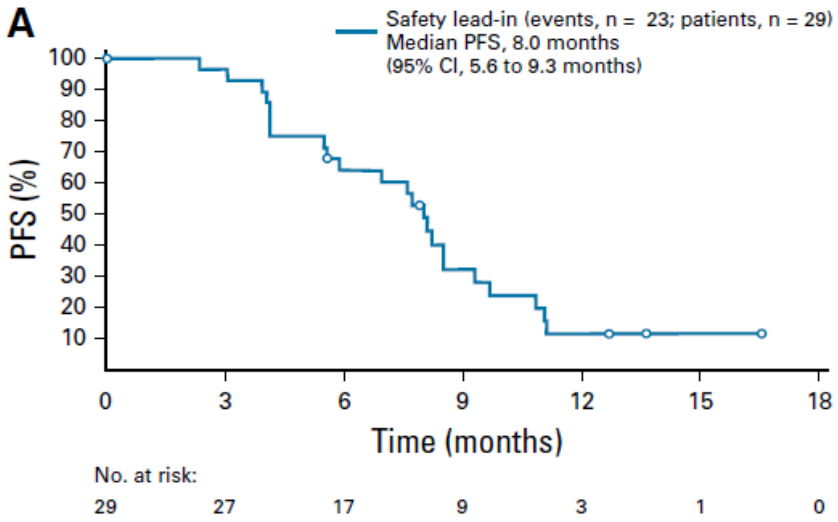
Binimetinib, Encorafenib, and Cetuximab Triplet Therapy for Patients With *BRAF* V600E–Mutant Metastatic Colorectal Cancer: Safety Lead-In Results From the Phase III BEACON Colorectal Cancer Study

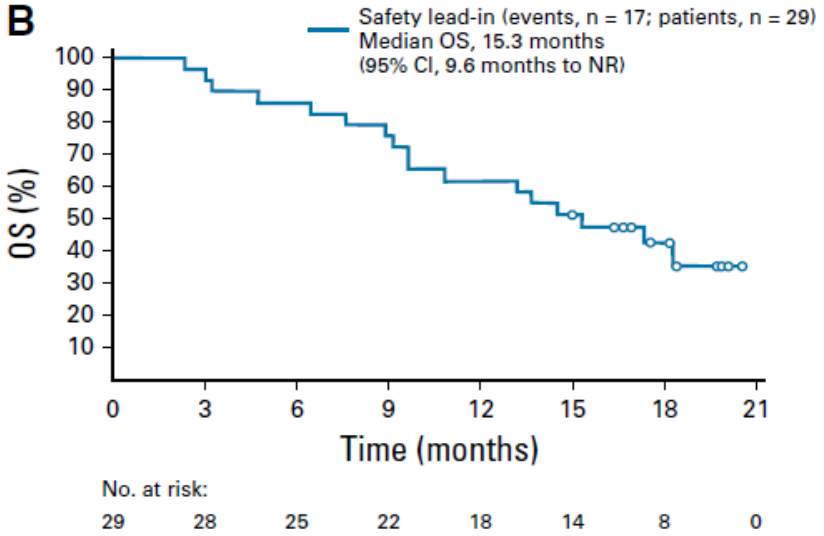
Estudios e Indicaciones de inhibidores de vía MAPK/ERK en Combinacion

- **Cáncer colorrectal metastásico**



Binimetinib, Encorafenib, and Cetuximab Triplet Therapy for Patients With *BRAF* V600E–Mutant Metastatic Colorectal Cancer: Safety Lead-In Results From the Phase III BEACON Colorectal Cancer Study

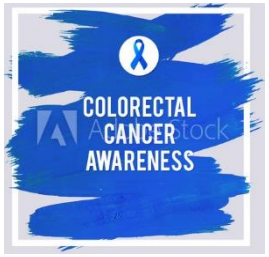




J Clin Oncol 37:1460-1469.

Estudios e Indicaciones de inhibidores de vía MAPK/ERK en Combinacion

- **Cáncer colorrectal metastásico**

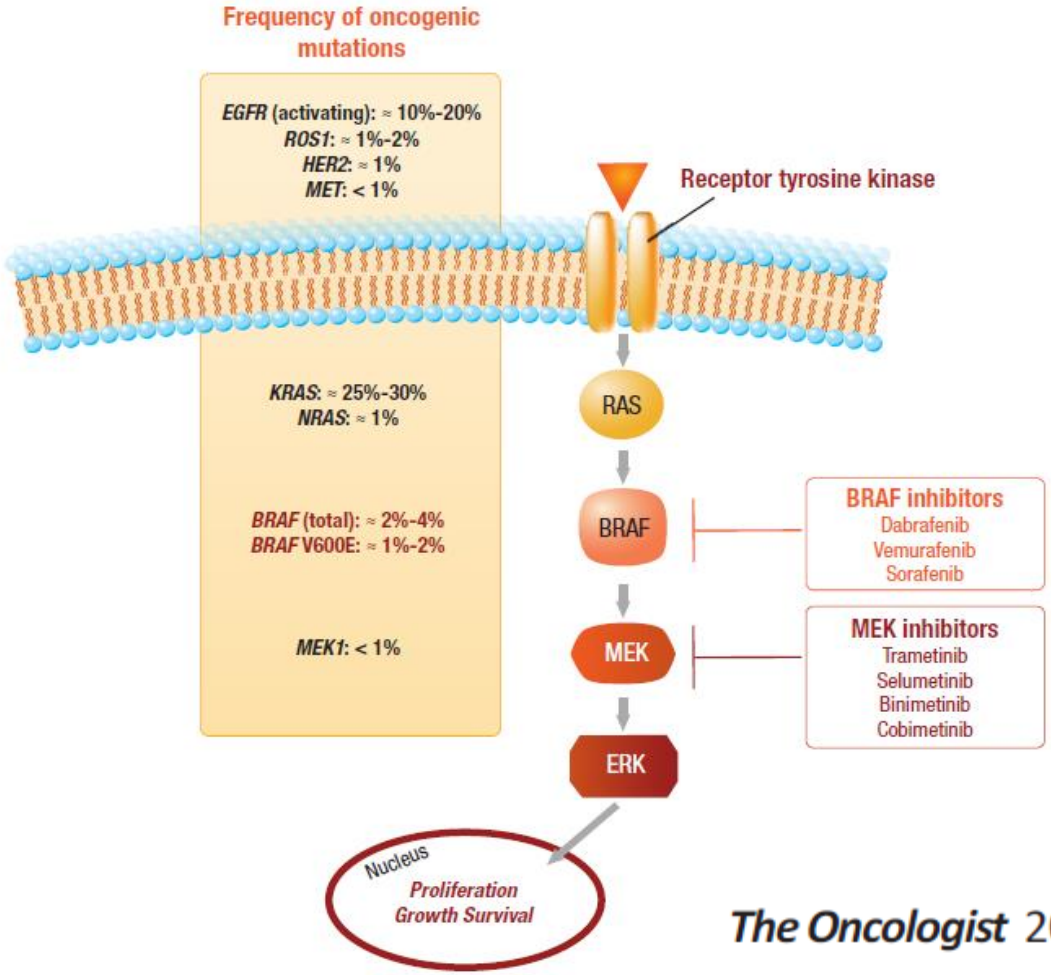


El *Estudio (ANCHOR-CRC)* está reclutando pacientes para investigar el efecto de la triple terapia en primera linea de mCRC *BRAF* V600E-mutado

Tabernero et al. ESMO GI 2016

Estudios e Indicaciones de inhibidores de vía MAPK/ERK en Combinacion

- **Cáncer pulmón metastásico célula no pequeña**



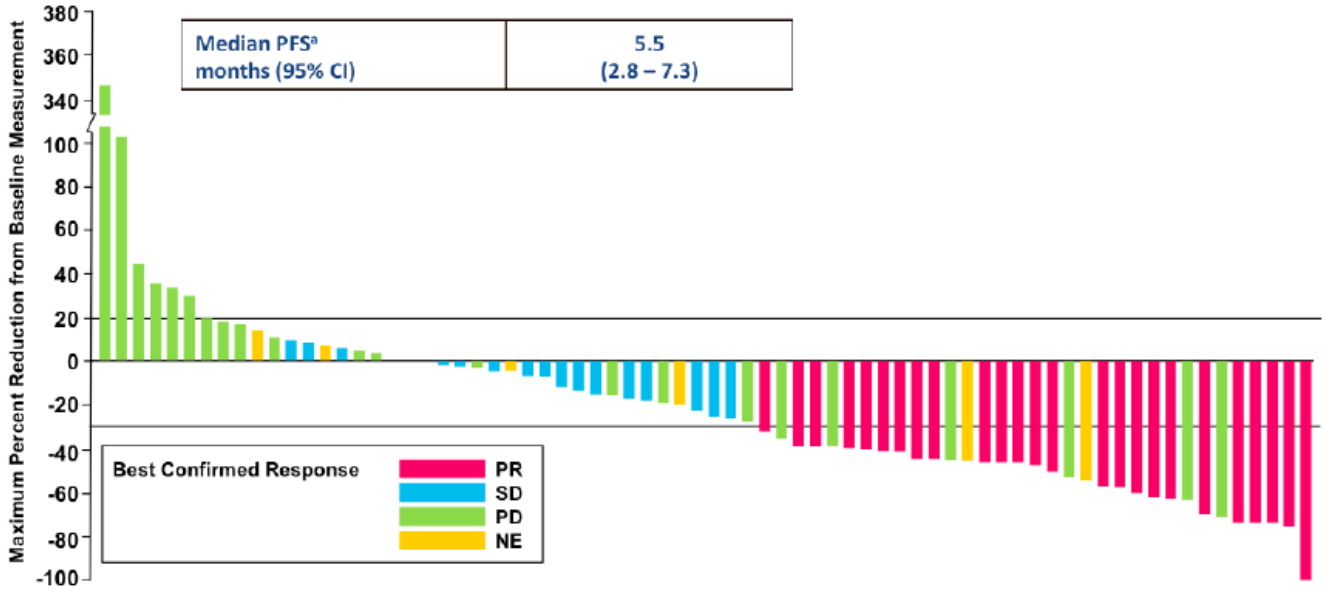
The Oncologist 2017;22:786–796

Estudios e Indicaciones de inhibidores de vía MAPK/ERK en Combinacion

- **Cáncer pulmón metastásico célula no pequeña**

Estudio fase 2 con inhibidor de BRAF en NSCLC

Maximum Reduction of Sum of Lesion Diameters By Best Confirmed Response in ≥ 2nd Line (N = 78)



Planchard, ASCO 2014

Estudios e Indicaciones de inhibidores de vía MAPK/ERK en Combinacion

- **Cáncer pulmón metastásico célula no pequeña**

Clinical activity	Vemurafenib[a]	Dabrafenib	Dabrafenib + trametinib
Overall response rate, %	42	33	63
Complete response	0	0	4
Partial response	42	33	60
Disease control rate,[b] %	84	58	79
Stable disease[c]	42	24	16
Median DOR, months	NR	9.6	9.0[d]
Median PFS, months	7.3	5.5	9.7

[a]Responses did not require second post-baseline scan for confirmation.
[b]Disease control rate is defined as complete response + partial response + stable disease.
[c]Includes patients with a response of stable disease at week 8 for vemurafenib or at least 12 weeks for dabrafenib and dabrafenib + trametinib.
[d]Half of responses were ongoing at data cutoff.
Abbreviations: DOR, duration of response; NR, not reported; PFS, progression-free survival.

The Oncologist 2017;22:786–796

Estudios e Indicaciones de inhibidores de vía MAPK/ERK en Combinacion

- **Cáncer pulmón metastásico célula no pequeña**

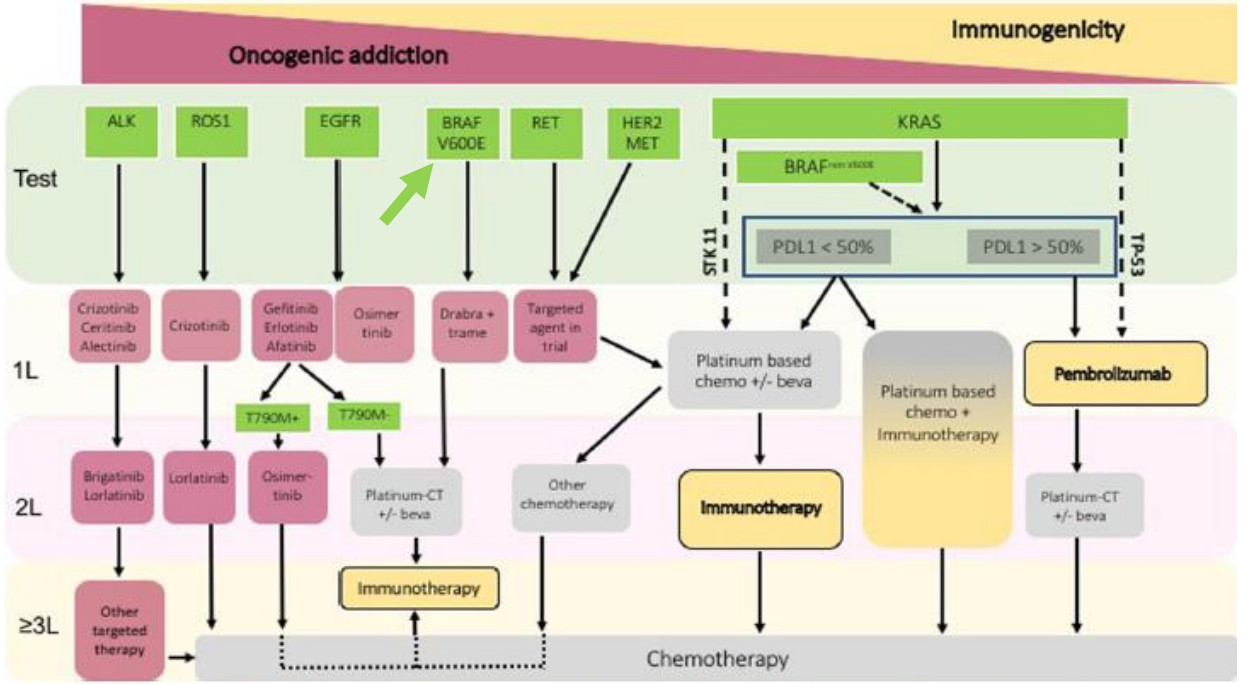
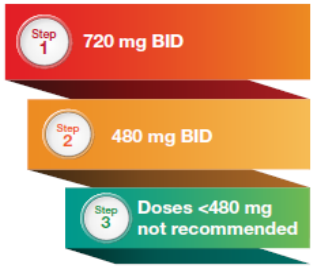


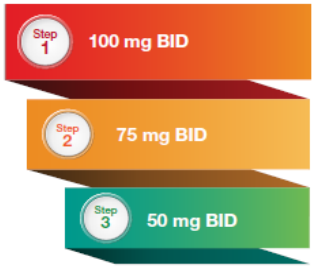
Fig. 3. Proposed algorithm of integration of immunotherapy in the management of patients with oncogenic addiction.

Dose Reduction

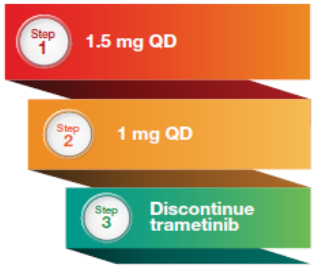
Vemurafenib
(Recommended dose 960 mg BID)*



Dabrafenib
(Recommended dose 150 mg BID)*



Trametinib
(Recommended dose 2 mg QD)*



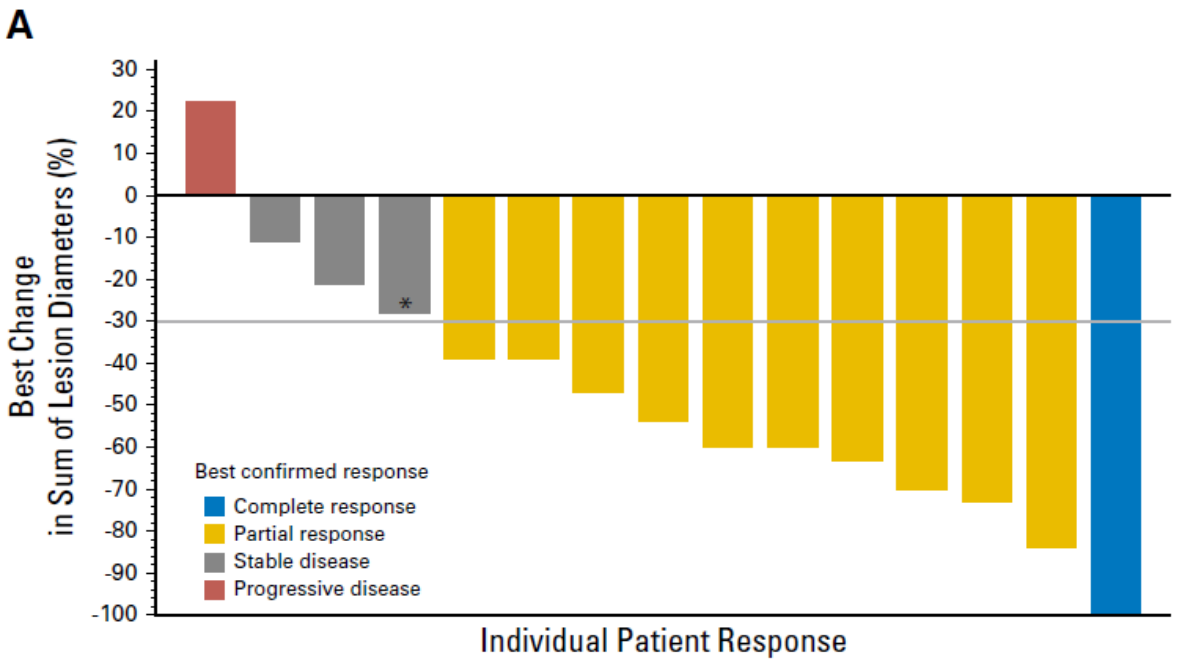
Curr. Treat. Options in Oncol. (2019) 20: 60
The Oncologist 2017;22:786–796

Estudios e Indicaciones de inhibidores de vía MAPK/ERK en Combinacion

- **Cáncer de tiroides metastásico**

Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic *BRAF* V600–Mutant Anaplastic Thyroid Cancer

Vivek Subbiah, Robert J. Kreitman, Zev A. Wainberg, Jae Yong Cho, Jan H.M. Schellens, Jean Charles Soria,



J Clin Oncol 36:7-13. © 2017

Estudios e Indicaciones de inhibidores de vía MAPK/ERK en Combinacion

- **Cáncer de tiroides metastásico**

Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic *BRAF* V600–Mutant Anaplastic Thyroid Cancer

Vivek Subbiah, Robert J. Kreitman, Zev A. Wainberg, Jae Yong Cho, Jan H.M. Schellens, Jean Charles Soria,

Table 2. Best Overall Response to Therapy in Anaplastic Thyroid Cancer

	Intent-to-Treat (n = 16)		*BRAF* V600E Centrally Confirmed Patient Population (n = 15)	
Radiology Review Type	Investigator	Independent	Investigator	Independent
Best response*				
Complete response	1 (6)	0	1 (7)	0
Partial response	10 (63)	10 (63)	10 (67)	10 (67)
Stable disease	3 (19)	3 (19)	2 (13)	2 (13)
Progressive disease	2 (13)	3 (19)	2 (13)	3 (20)
Not evaluable	0	0	0	0
Overall response rate [95% CI]†	11 (69) [41.3 to 89.0]	10 (63) [35.4 to 84.8]	11 (73) [44.9 to 92.2]	10 (67) [38.4 to 88.2]

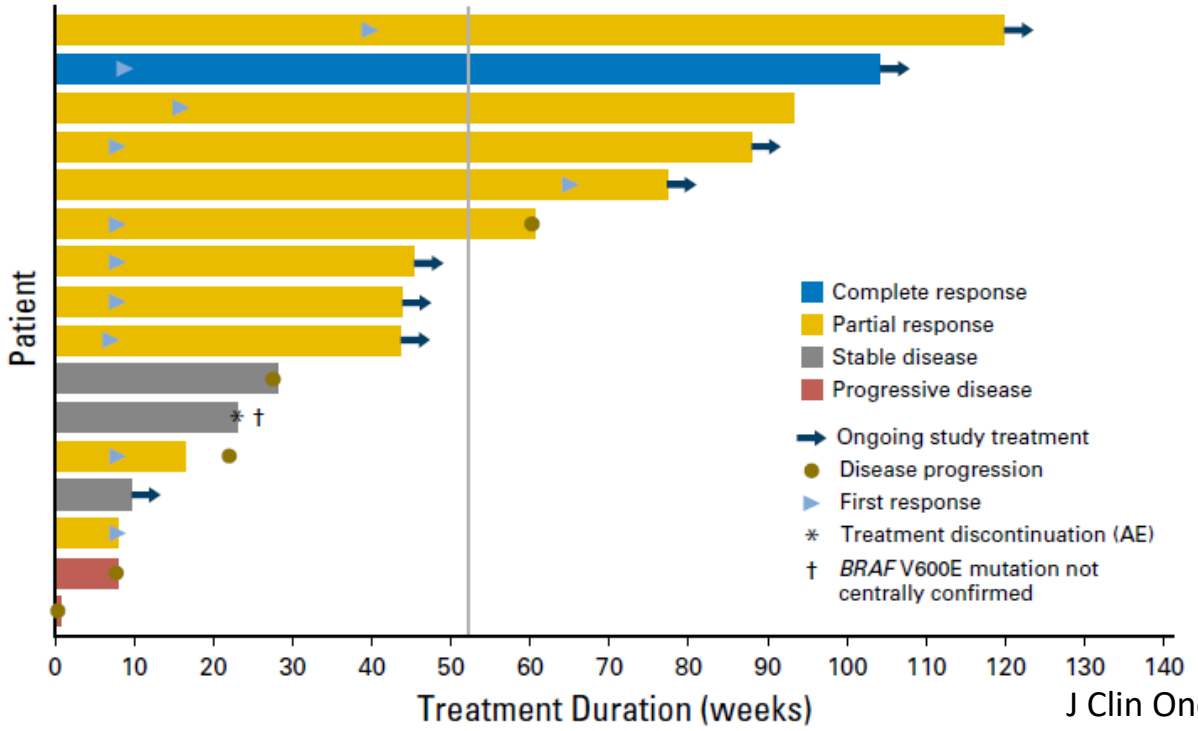
J Clin Oncol 36:7-13. © 2017

Estudios e Indicaciones de inhibidores de vía MAPK/ERK en Combinacion

- **Cáncer de tiroides metastásico**

Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic *BRAF* V600–Mutant Anaplastic Thyroid Cancer

Vivek Subbiah, Robert J. Kreitman, Zev A. Wainberg, Jae Yong Cho, Jan H.M. Schellens, Jean Charles Soria,



J Clin Oncol 36:7-13. © 2017

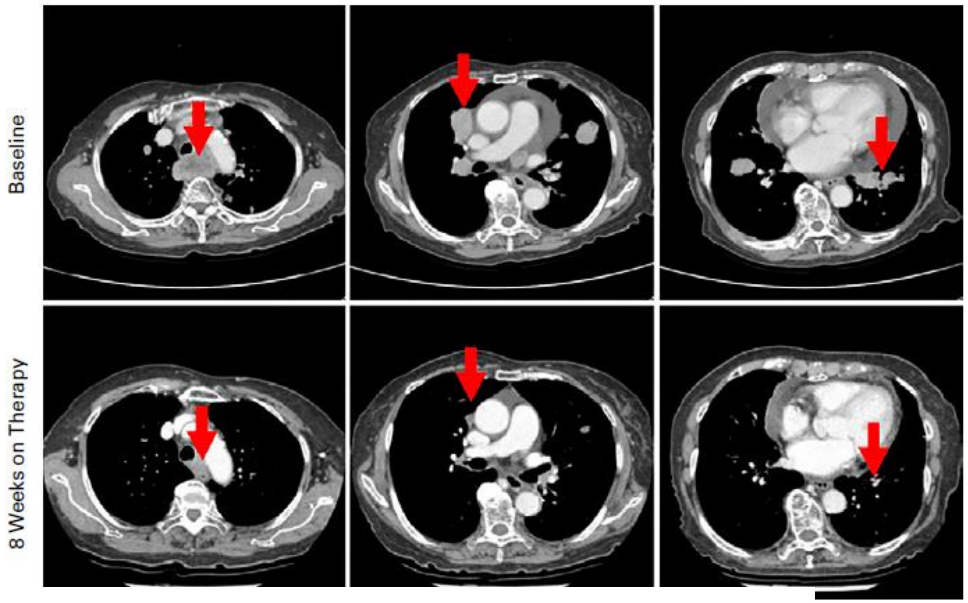
Estudios e Indicaciones de inhibidores de vía MAPK/ERK en Combinacion

- **Cáncer de tiroides metastásico**

Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic *BRAF* V600–Mutant Anaplastic Thyroid Cancer

Vivek Subbiah, Robert J. Kreitman, Zev A. Wainberg, Jae Yong Cho, Jan H.M. Schellens, Jean Charles Soria,

TRAS 8 SEMANAS DE TRATAMIENTO →



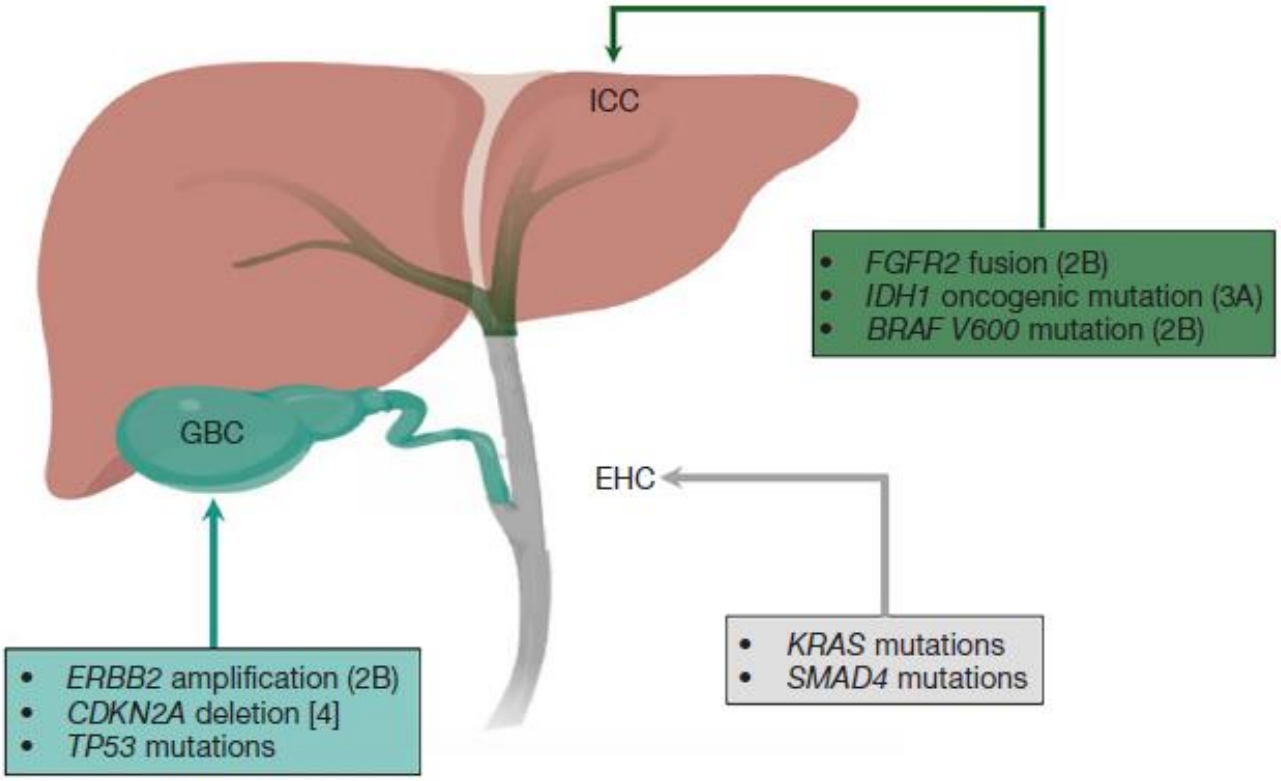
Conclusion

Dabrafenib plus trametinib is the first regimen demonstrated to have robust clinical activity in *BRAF* V600E–mutated anaplastic thyroid cancer and was well tolerated. These findings represent a meaningful therapeutic advance for this orphan disease.

J Clin Oncol 36:7-13. © 2017

Estudios e Indicaciones de inhibidores de vía MAPK/ERK en Combinacion

- **Cáncer de vías biliares**



Mondaca et al. BTC prognostic and predictive genomics

Estudios e Indicaciones de inhibidores de vía MAPK/ERK en Combinacion

- **Cáncer de vías biliares**

187: Efficacy and safety of dabrafenib (D) and trametinib (T) in patients (pts) with BRAF V600E-mutated biliary tract cancer (BTC): A cohort of the ROAR basket trial – Wainberg ZA, et al

Study objective

- To assess the efficacy and safety of dabrafenib (a BRAF inhibitor) + trametinib (a MEK inhibitor) in the cohort of patients with BRAF V600E-mutated BTC in the ROAR basket trial

Key patient inclusion criteria
- Advanced or metastatic BTC
- BRAF V600E mutated
- Progression on gemcitabine
- ECOG PS ≤2 (n=35)

PRIMARY ENDPOINT
- ORR (RECIST v1.1)

Dabrafenib 150 mg bid + trametinib 2 mg/day

PD/ toxicity/ death

SECONDARY ENDPOINTS
- DoR, PFS, OS, biomarkers, safety

Wainberg ZA, et al. J Clin Oncol 2019;37(Suppl):Abstr 187

Estudios e Indicaciones de inhibidores de vía MAPK/ERK en Combinacion

- **Cáncer de vías biliares**

187: Efficacy and safety of dabrafenib (D) and trametinib (T) in patients (pts) with BRAF V600E-mutated biliary tract cancer (BTC): A cohort of the ROAR basket trial – Wainberg ZA, et al

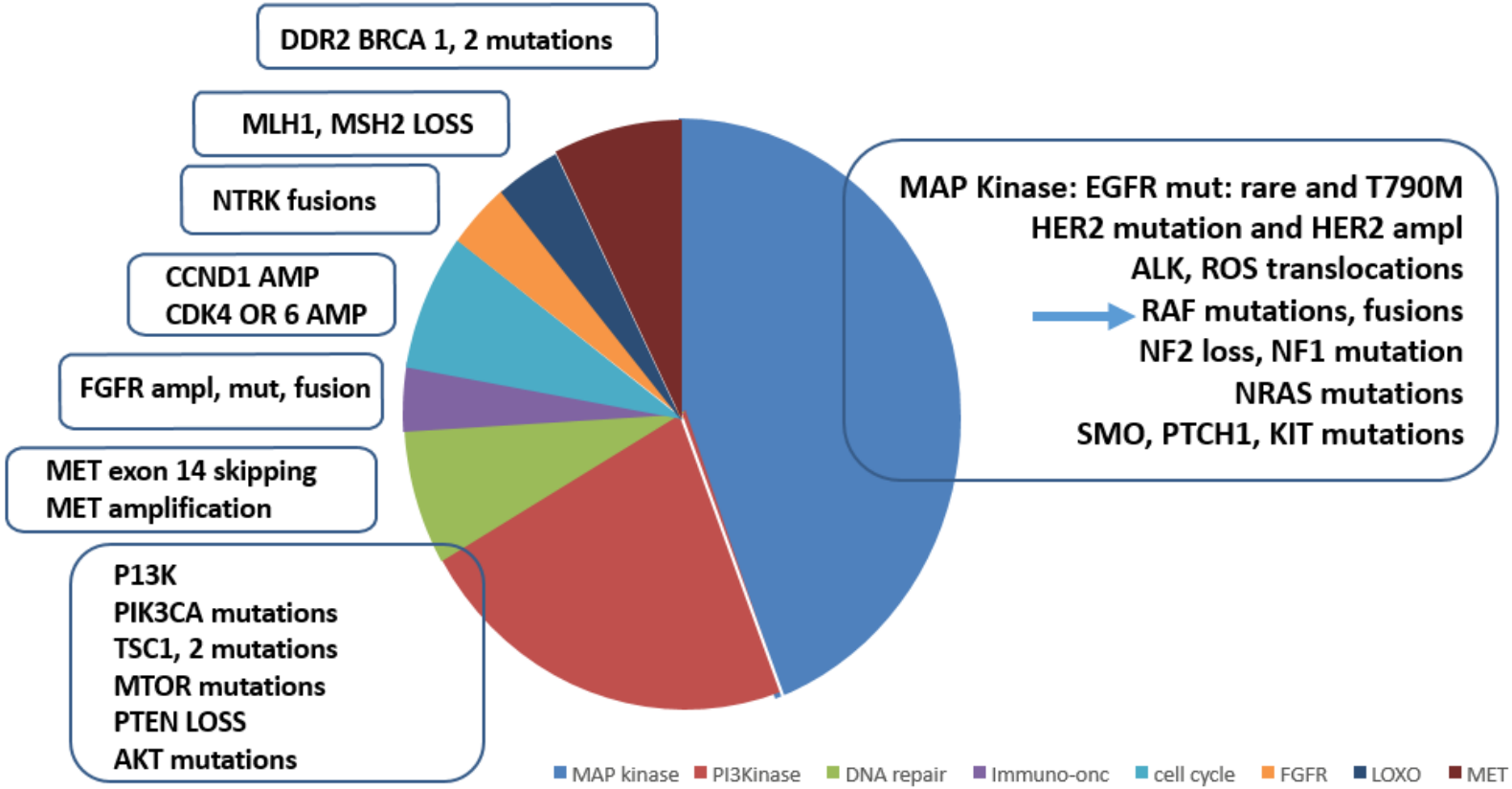
Response	Investigator-assessed	Independent review
BOR, n (%)		
CR	0	0
PR	14 (42)	12 (36)
SD	15 (45)	13 (39)
PD	4 (12)	4 (12)
NE/missing	0	4 (12)
ORR, n (%) [95%CI]	14 (42) [25.5, 60.8]	12 (36) [20.4, 54.9]

Wainberg ZA, et al. J Clin Oncol 2019;37(Suppl):Abstr 187

NCI-MATCH TRIAL (ARM H)

- NCI-MATCH trial (NCT02465060) is the largest precision medicine trial of its kind, was launched in August 2015 by NCI and the ECOG-ACRIN Cancer Research Group.
- Patients are assigned to receive treatment based on the genetic changes found in their tumors
- There are 40 different treatment arms for a 6000 patients with solid tumors, lymphoma or mieloma.
- Arm H (EAY131-H) evaluated the combination of the BRAF inhibitor dabrafenib and the MEK inhibidor, trametinib, in pts with BRAF V600E/K mutations
- The primary endpoint was objective response rate (ORR).
- The secondary endpoints were progression-free survival, 6-month progression-free survival, and overall survival.

Treatment Arms NCI-MATCH by Molecular Pathway



NCI-MATCH TRIAL (ARM H)

- A total of 35 patients were enrolled
- Over 17 distinct tumor histologies were represented.
  - 58% of were female,
  - median age was 63 (range 21-85),
  - 94% were Caucasian
  - 48% of pts had received at least 3 prior therapies (range 1- 8).

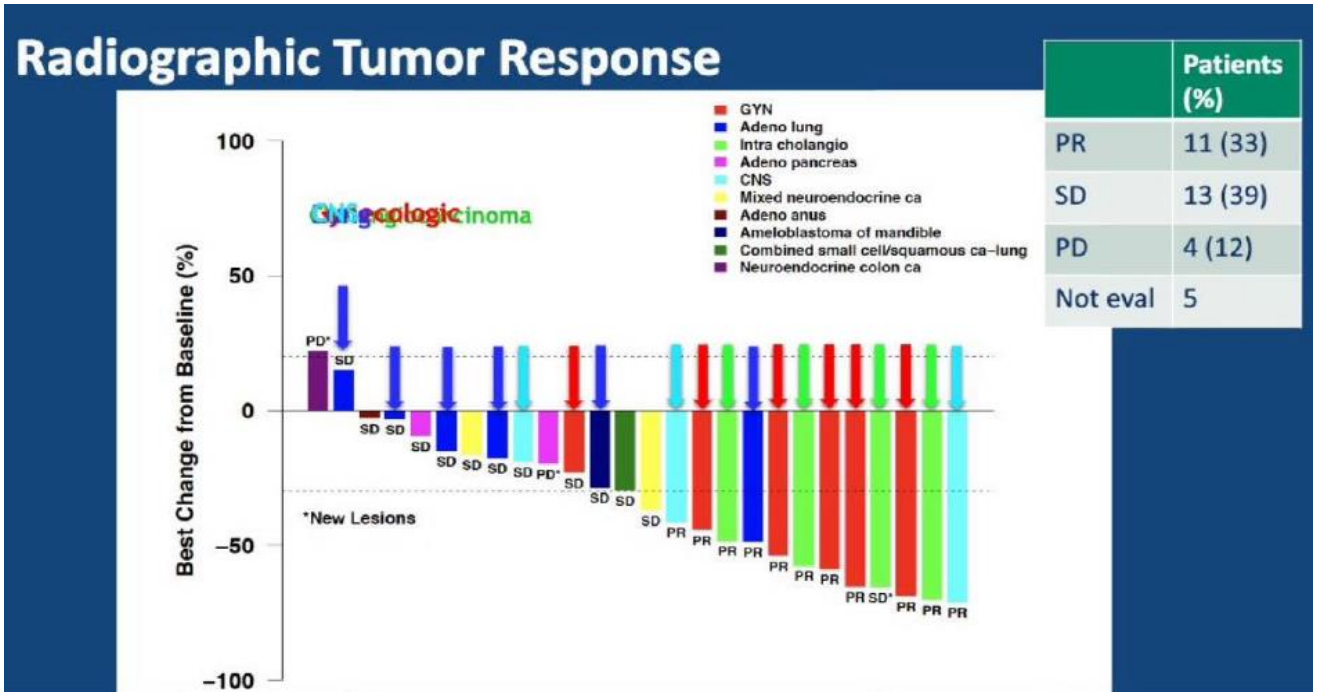
	Number
Gastrointestinal tract:	12
Adenocarcinoma of pancreas	3
Intrahepatic cholangiocarcinoma	4
Mixed ductal/adeno-neuroendocrine carcinoma	2
Neuroendocrine carcinoma of colon	2
Adenocarcinoma of anus	1
Lung:	7
Adenocarcinoma	6
Combined small cell-squamous cell carcinoma	1
Gynecologic:	6
Low-grade papillary serous adenocarcinoma of ovary	5
Mucinous-papillary serous adenocarcinoma of peritoneum	1
Central nervous system:	5
BRAF-mutated epithelioid glioblastoma of corpus callosum	1
Pilocytic astrocytoma of optic nerve	1
Anaplastic astroblastoma of temporal lobe	1
Pleomorphic xanthoastrocytoma of parietal lobe	1
Histiocytic sarcoma of parietal-occipital lobes	1
Hematologic malignancy:	2
Extramedullary plasmacytoma/myeloma, kappa type	1
Plasma cell myeloma, IgA kappa type	1
Ameloblastoma of mandible	1

April K.S. Salama. Journal of Clinical Oncology 2019 37:15_suppl, 3002-3002

NCI-MATCH TRIAL (ARM H)

RESULTS

- The confirmed **ORR was 33.3%** (90% CI 19.9%, 49.1%),
- **Median duration of response (DoR) was 12 months**.
- **Median PFS was 11.4 months**;
  - 6 months PFS rate was 70.6% (90% CI 58.2%-85.5%),
  - additional 10 pts had a PFS > 5.5 months.
- **Median OS was 28,8 months**.



	Patients (%)
PR	11 (33)
SD	13 (39)
PD	4 (12)
Not eval	5

April K.S. Salama. Journal of Clinical Oncology 2019 37:15_suppl, 3002-3002

Mecanismos de Resistencia a inhibidores de vía MAPK/ERK

Mecanismos de Resistencia a inhibidores de vía MAPK/ERK

- **Resistencia Primaria (Intrinseca):**

-En melanoma BRAF mutado (V600E o V600K) 20% del total de pacientes tienen Resistencia primaria a inhibidores selectivos de BRAF y no responden.

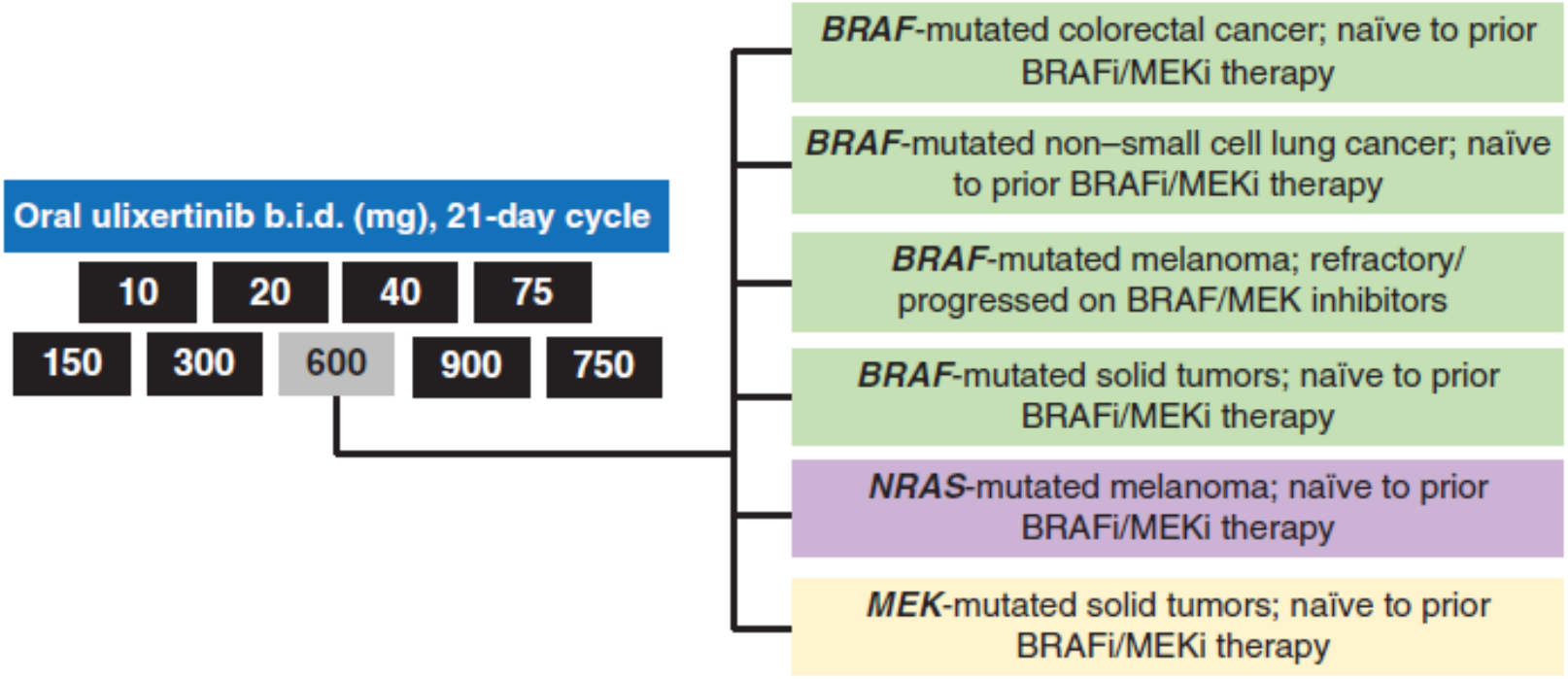
-En cáncer colorectal con la misma mutación de BRAF, la Resistencia intrinseca a estos inhbidores se debe a una activación de EGFR por un mecanismo de feedback

- **Resistencia Secundaria (Adquirida):**

-En los pacientes que incialmente responden a inhibidores de BRAF, pero que en pocos meses muestran progresión, los mecanismos de Resistencia pueden ser clasificados en dependientes o independientes de la vía MAPK/ERK

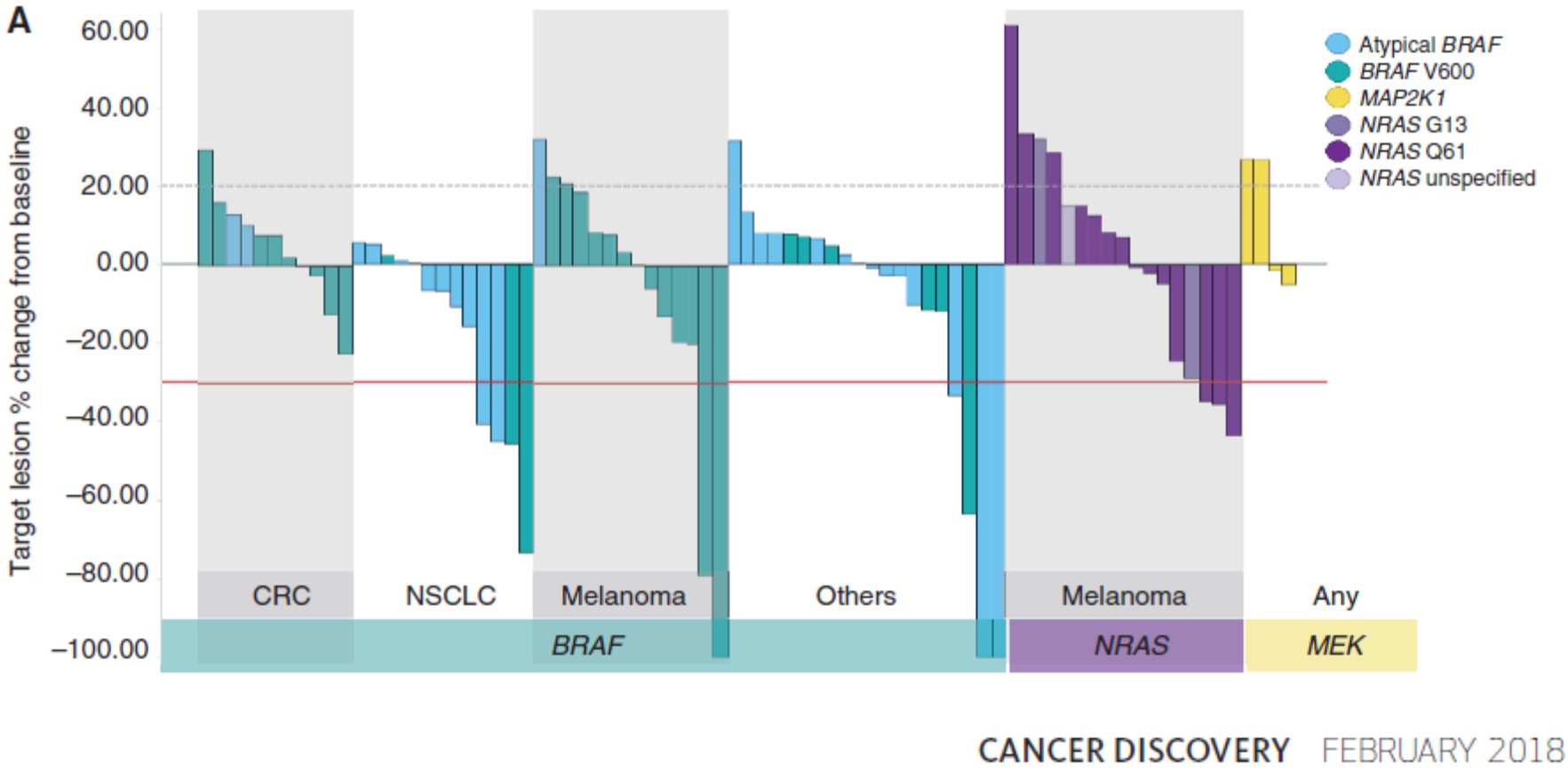
-Manzano JL, Layos L, Buges C, et al. Resistant mechanisms to BRAF inhibitors in melanoma. Ann Transl Med. 2016; 4(12):237.
-Prahallad A, Sun C, Huang S. Unresponsiveness of colon cancer to BRAF (V600E) inhibition through feedback activation of EGFR. Nature. 2012; 483(7387):100–3.
-OncoTargets and Therapy 2018:11 7095–7107

TRATAMIENTOS PARA MUTACIONES BRAF ATIPICAS (NO V600E)



CANCER DISCOVERY FEBRUARY 2018

TRATAMIENTOS PARA MUTACIONES BRAF ATIPICAS (NO V600E)



CANCER DISCOVERY FEBRUARY 2018

Evolución y metástasis en el cáncer

El estudio de la evolución de las células tumorales hacia la metástasis *está arrojando luz sobre las bases moleculares, genéticas y biológicas de este proceso, proporcionando estrategias para poder combatirla.*

Uno de los marcos conceptuales que ha permitido este desarrollo se basa en Darwin y su planteamiento sobre los procesos evolutivos.

Joan Massagué

Darwin
EXPEDITIONS