V SIMPOSIO GETHI 18/19
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BRAF Y MEK en tumores sólidos y cáncer raro: ¿Qué alteraciones presentan y en qué tumores?

P. García Alfonso
Jefe de Sección de Oncología Médica
HGU Gregorio Marañón de Madridd

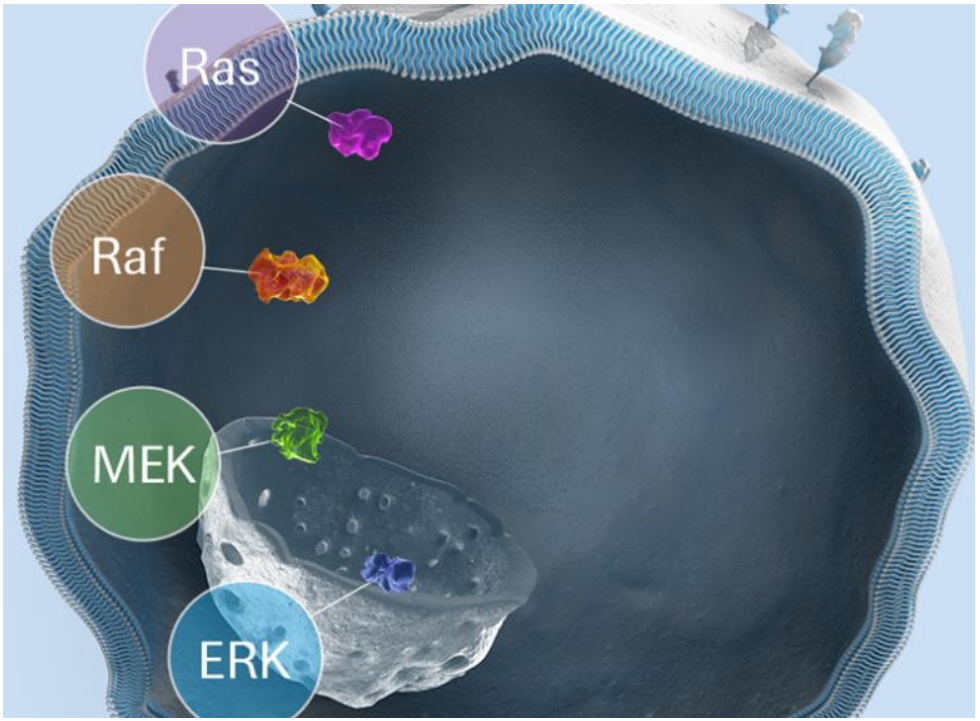
Disclosures

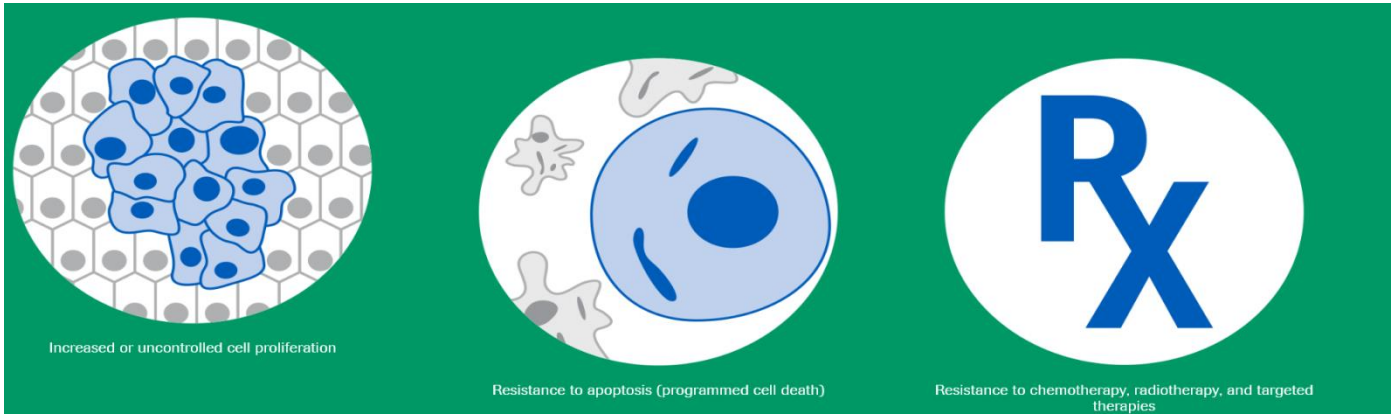
Advisory Boards and Speaker's fee

Amgen, Bayer, Bristol, Merck, MSD, Roche, Sanofi, Sirtex

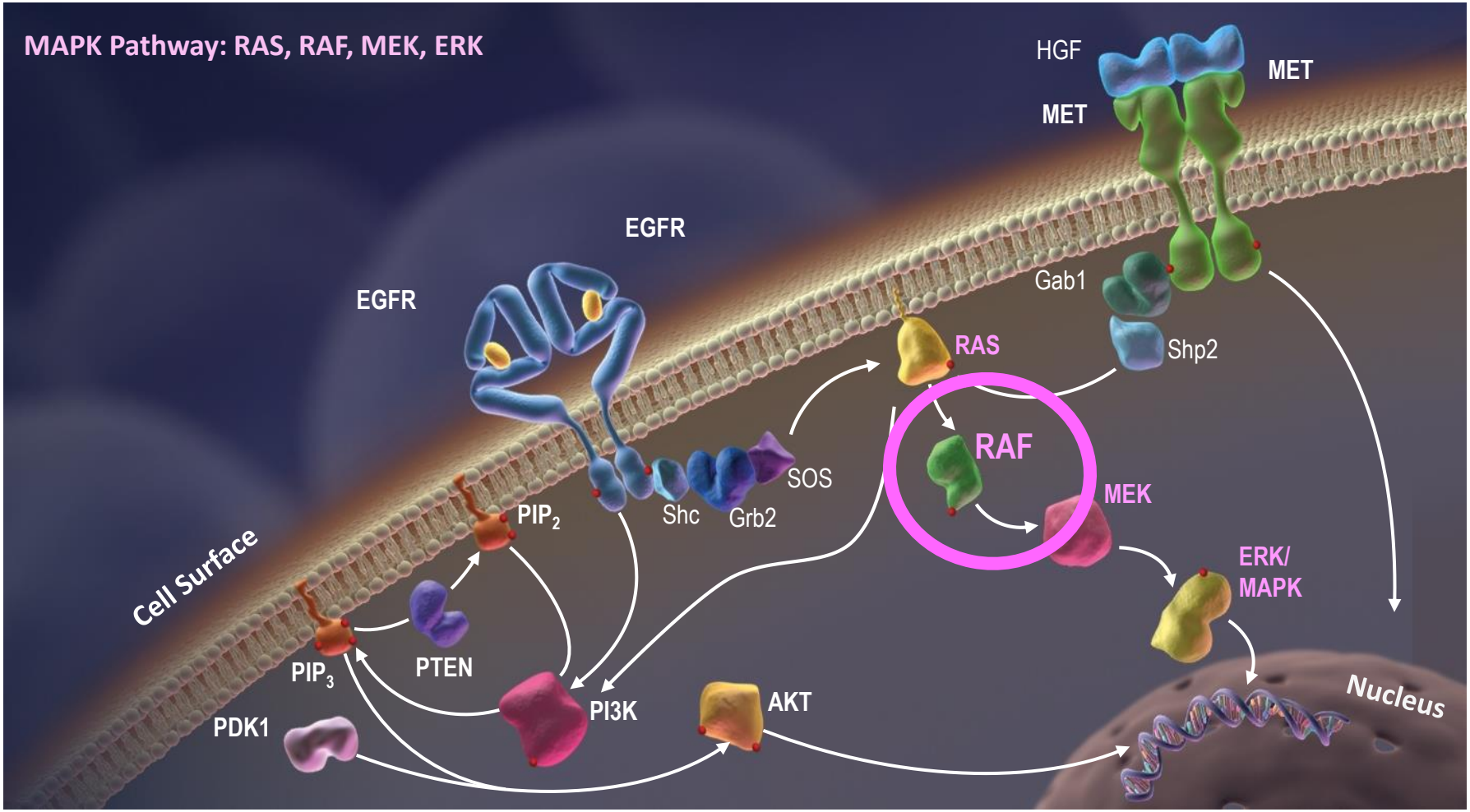
VIA MAPK

La cascada de señalización RAS/RAF/MEK/ERK, también conocida como la via MAPK (mitogen-activated protein kinase) está implicada en la proliferación, la diferenciación, la supervivencia y la apoptosis celular de los tejidos normales.





RAF Is a Key Downstream Component of EGFR Signaling[1-3]



- RAS/**RAF**/MEK signaling cascade (**MAPK pathwa**y)
- La disregulación de la vía MAPK afecta a un amplio rango de cánceres y ocurre a través de múltiples mecanismos, incluyendo la expresión anormal o la activación de mutaciones en los receptores y la activación de mutaciones en genes, incluyendo BRAF.

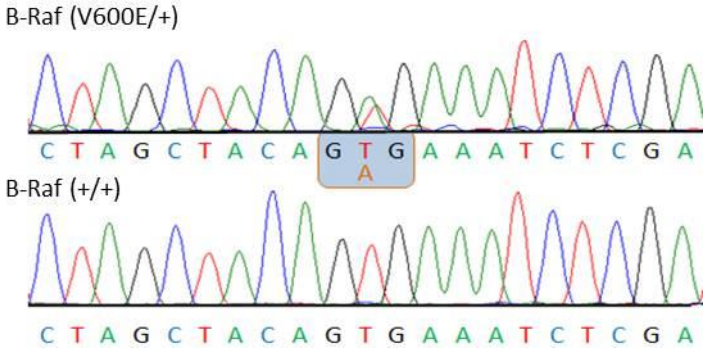
1. Birchmeier C. *Nat Rev Mol Cell Biol*. 2003;4:915-925; 2. Krasinskas AM. *Patholog Res Int*. 2011;932932:1-6; 3. Zenonos K. *World J Gastrointest Oncol*. 2013;5:97-101.

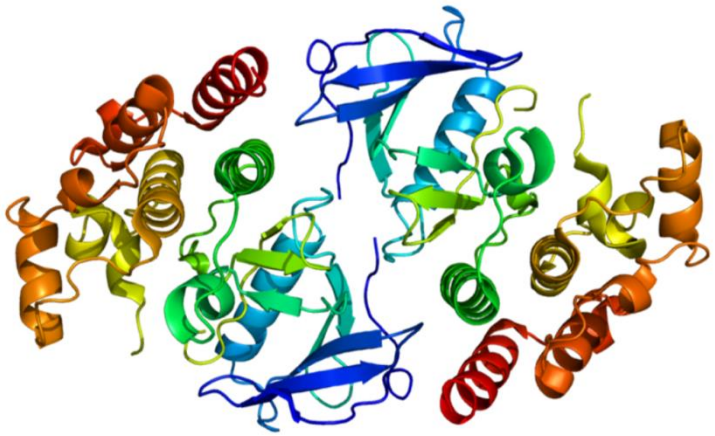
BRAF V600E Mutation

- Exon 15, T1799 point mutation (valine->glutamine) at codon 600
- Affecting the kinase domain of the BRAF protein

- This causes a conformational change in the G-loop activation segment of the kinase[1]

- The most common (50%) oncogenic driver mutation in melanoma[1].

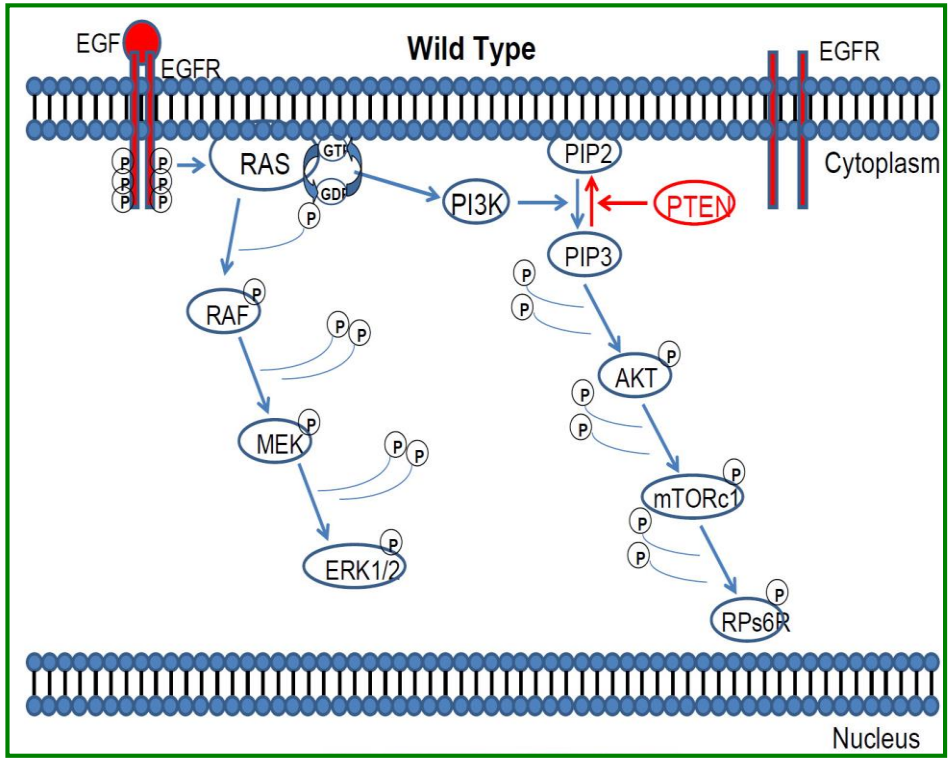


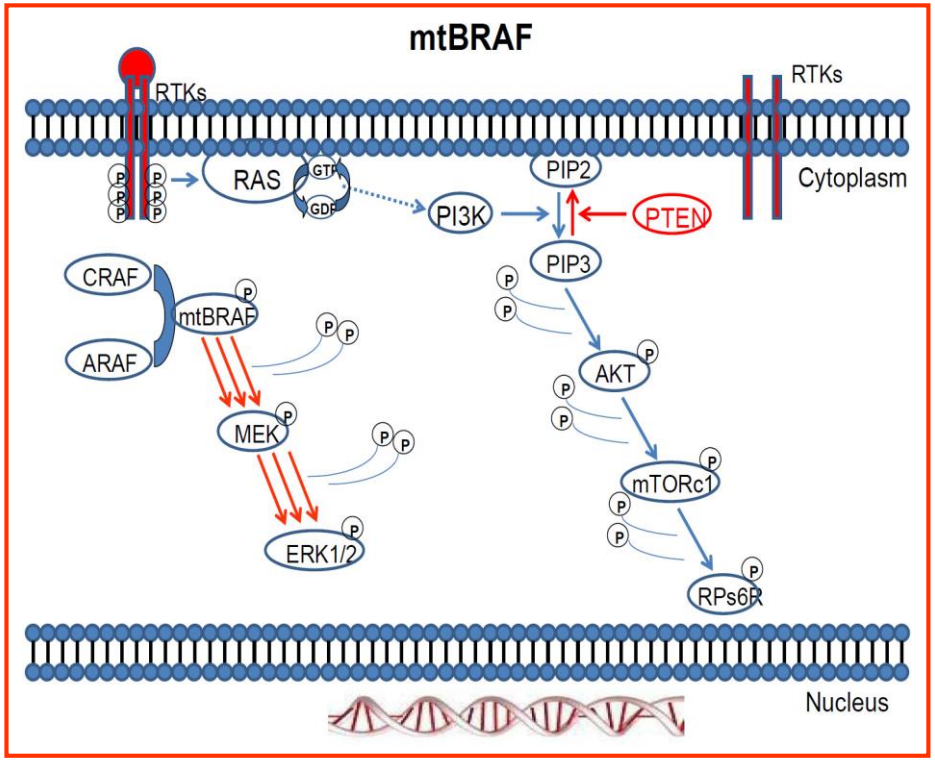


B-Raf proto-oncogene, serine/threonine kinase

1. Davies 2002 Nature

MAPK pathway activation in response to BRAF mutation





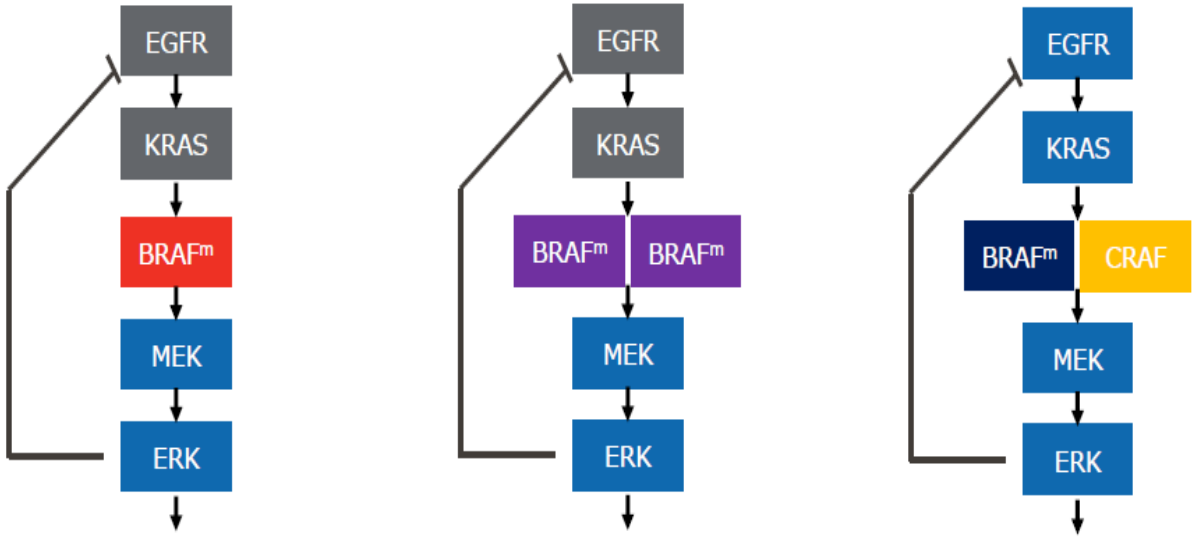
Ras/Raf/MEK/ERK pathway and the Ras/PI3K/PTEN/mTOR pathway are activated

La mutación de BRAF-V600 conlleva una actividad BRAF kinasa constitutiva, con fosforilización de MEK y ERK kinasa con una activacion de la via MAK-kinasa con un efecto de transformación oncogénicaBRAF V600E becomes constitutively active, able to bind MEK and ERK as a monomer,1 independent of upstream modulation2

E Oikonomou et al. Oncotarget 2014

Understanding Class II and Class III Non-V600E *BRAF*^{mut}

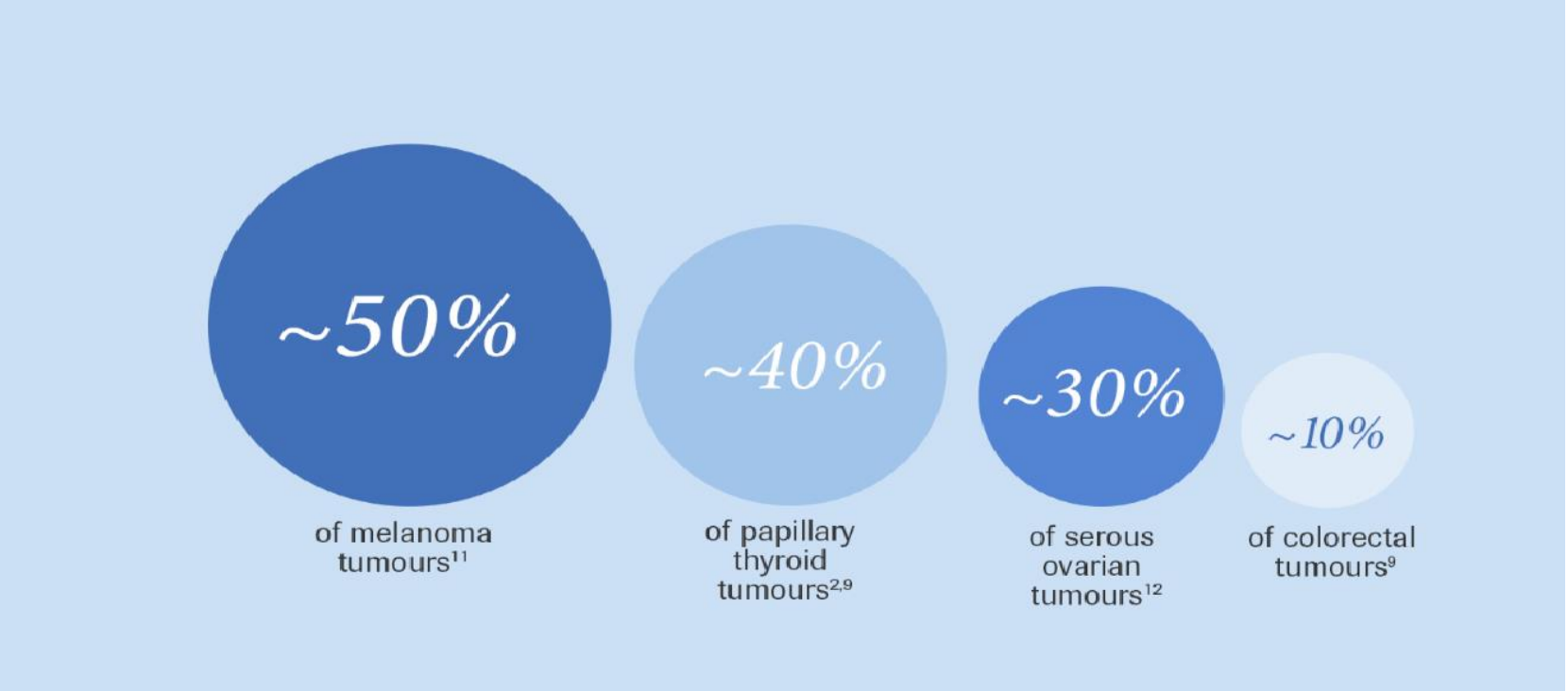
	BRAF V600E Class I	Class II BRAF	Class III BRAF
Structure	BRAF monomer	BRAF dimers	BRAF/CRAF dimers
RTK (EGFR) Dependency	No	No	Yes
Kinase activity	High	High/Intermediate	Low
EGFRi sensitivity	No	Unlikely	Likely
Potential Strategy	BRAF, MEK, EGFR	RAF dimer inhibitors	RTK, MAPK combinations



Yao et al Nature '17

Mutación BRAF

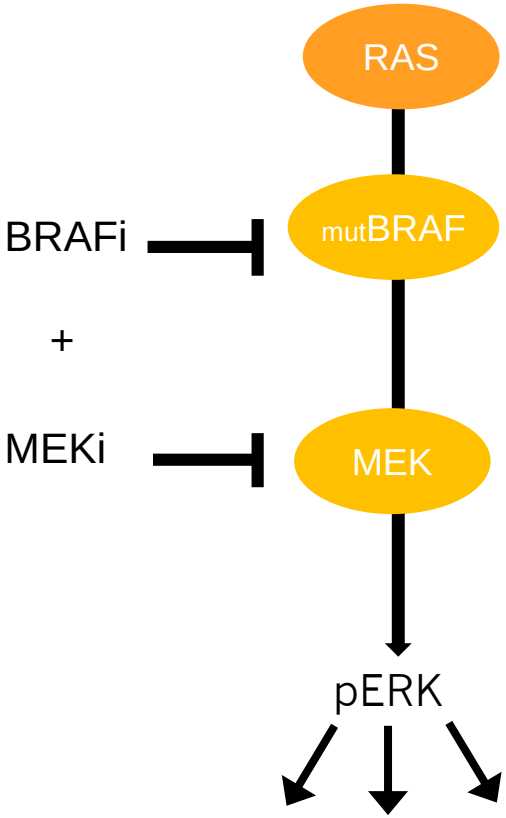
Ocurre en el 8% de todos los tumores

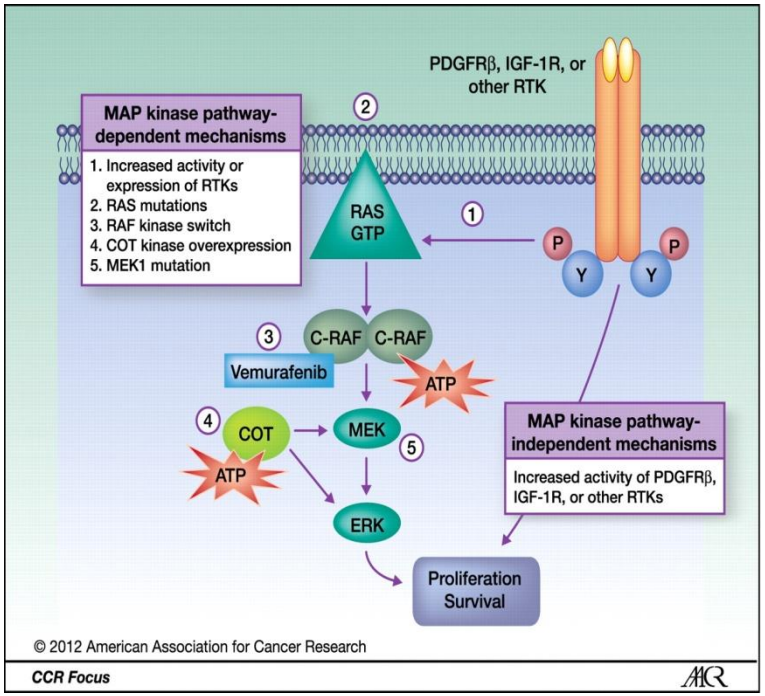


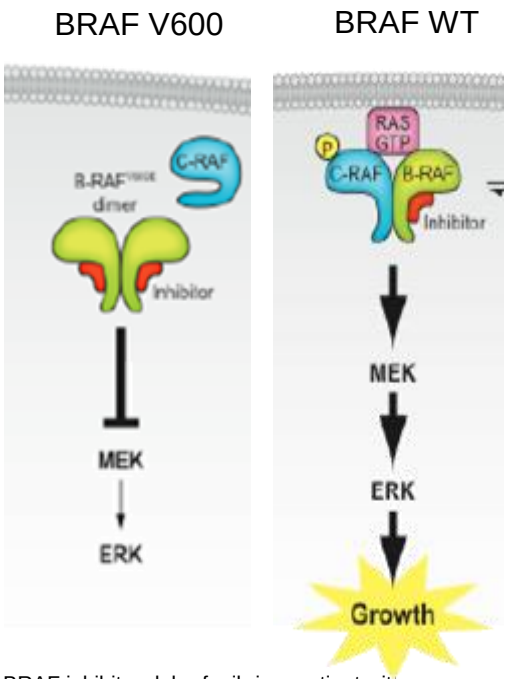
Cáncer de pulmón no células pequeñas, leucemia de células peludas, mieloma múltiple, cáncer seroso de ovario de bajo grado, colangiocarcinomas, cáncer de próstata y tumores de células germinales refractarios, histiocitosis, etcc

Rationale for the Combination of BRAF Inhibitor and MEK Inhibitor

- Sustained target inhibition to observe more prolonged and durable anti-tumor effect
- Delay and potentially prevent the development of resistance
- Prevent/delay hyperproliferative lesions and secondary malignancies (cuSCC)







Rudin CM, Hong K, Streit M. Molecular characterization of acquired resistance to the BRAF inhibitor dabrafenib in a patient with BRAF-mutant non-small-cell lung cancer. J Thorac Oncol. 2013;8(5):e41–2.. Lin L, Asthana S, Chan E, et al. Mapping the molecular determinants of BRAF oncogene dependence in human lung cancer. ProcNatl Acad Sci U S A. 2014;111(7):E748–57.

Melanoma

ALTERACIONES MOLECULARES EN MELANOMA

- Existe un gran número de alteraciones genéticas descritas en los pacientes con melanoma metastásico.
- Aproximadamente el 50% de pacientes presenta alteraciones en la vía de las MAPK, la más frecuente BRAFV600.
- La mutación de BRAF no confiere mal pronóstico en estadios precoces pero si en metastásicos
- BRAF V600 es una diana terapéutica reconocida en melanoma metastásico, con dos terapias dirigidas disponibles en la actualidad.

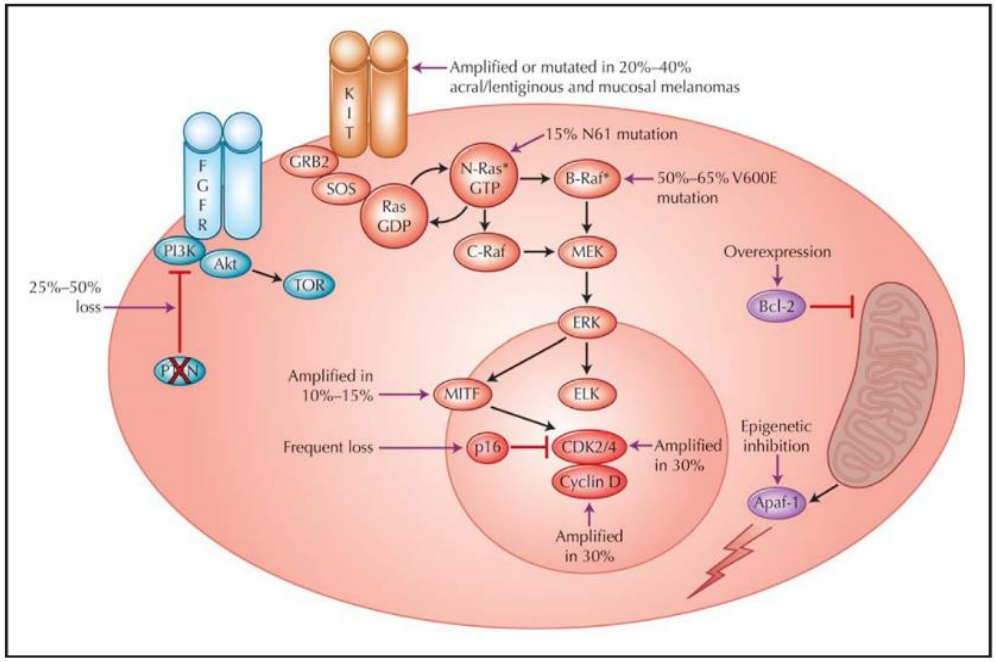


Figure 1. Molecular alterations prevalent in melanoma. CDK—cyclin-dependent kinase; FGFR—fibroblast growth factor receptor; GDP—guanosine diphosphate; GTP—guanosine triphosphate; MITF—micro-ophthalmia transcription factor; PI3K—phosphatidylinositol 3-kinase; TOR—target of rapamycin.

EL ANÁLISIS DEL ESTUDIO DEL TCGA HA DEFINIDO CUATRO SUBTIPOS MOLECULARES ESPECÍFICOS DE MELANOMA CUTÁNEO:

Sosman J, Margolin KA. Curr Oncol Rep. 2009;11(5):405-411

Melanoma BRAF mutado

- La mutación más frecuente ocurre en el codon 600 (50%)
- El 75-90% se deben a la sustitución de valina por ácido glutámico (V600E)
  - En el 11-20% hay sustitución de lisina por valina V600K
  - Las mutaciones BRAF V600R, V600D o presentes en otros codones (K601, V599) son muy poco frecuentes
- Las mutaciones de BRAF se adquieren en las células premalignas , al inicio del proceso de malignización. Estas mutaciones disregulan la via MAK e incrementan el riesgo de maliganización
- En melanomas primarios aparecen en el 35-45% y en metastásicos en un 40 to 55%.

Davies et al. Nature 2002;

Melanoma BRAF mutado

- Afectan a zonas expuestas al sol de tronco y extremidades
- Melanomas con extensión superficial o nodular
- Melanoma oculto o único
- Edad de diagnóstico < 50 años
- Leves signos de daño crónico inducido por el sol
- La mutación de *KIT* (c-kit receptor tyrosine kinase), es más frecuente en melanomas acrales y localizados en mucosa

Curtin JA et al. N Engl J Med 2005; Uguerel S. Plos One 2007

TRES FASE III COMBINACIÓN DEMUESTRAN SUPERIORIDAD EN PFS Y/O SG FRENTE A MONOTERAPIA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combined BRAF and MEK Inhibition versus BRAF Inhibition Alone in Melanoma

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Overall Survival in Melanoma with Combined Dabrafenib and Trametinib

ORIGINAL ARTICLE

Combined Vemurafenib and Cobimetinib in *BRAF*-Mutated Melanoma

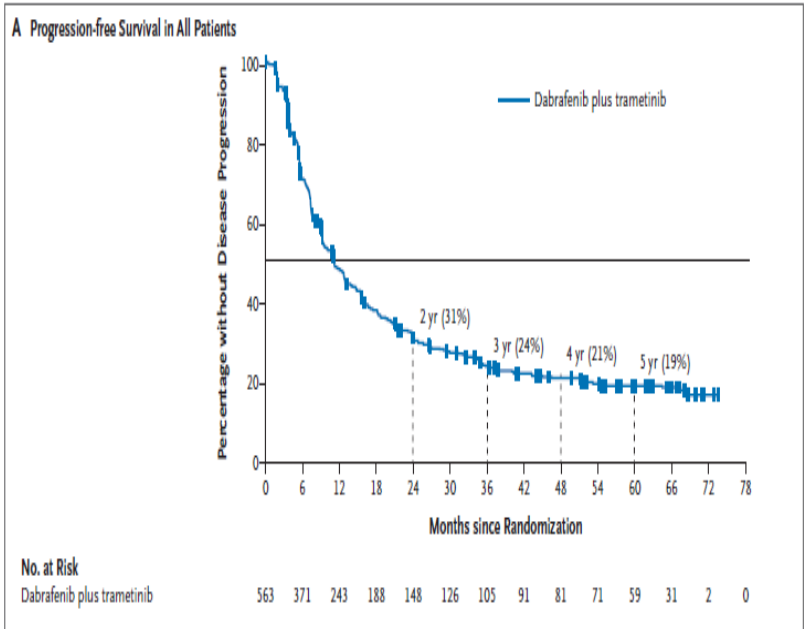
Long et al NEJM 2014
Robert et al NEJM 2014
Larkin et al NEJM 2014

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

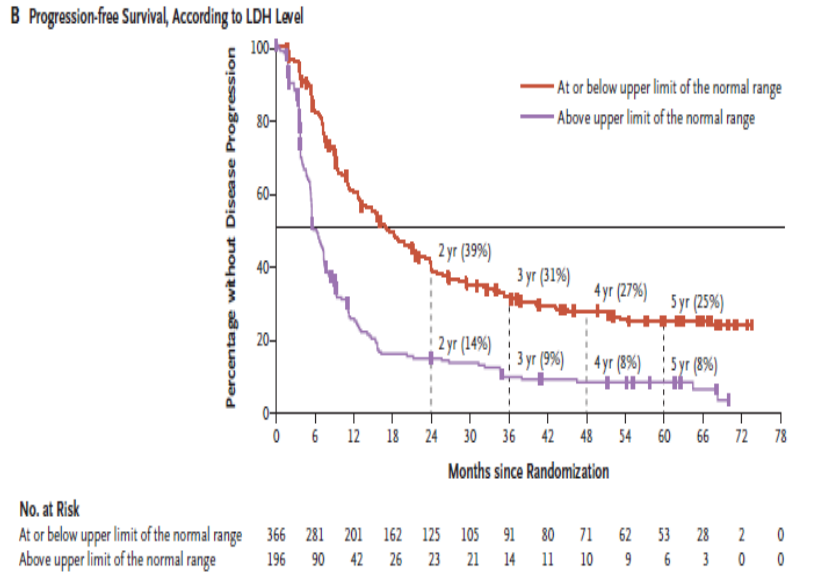
Five-Year Outcomes with Dabrafenib plus Trametinib in Metastatic Melanoma

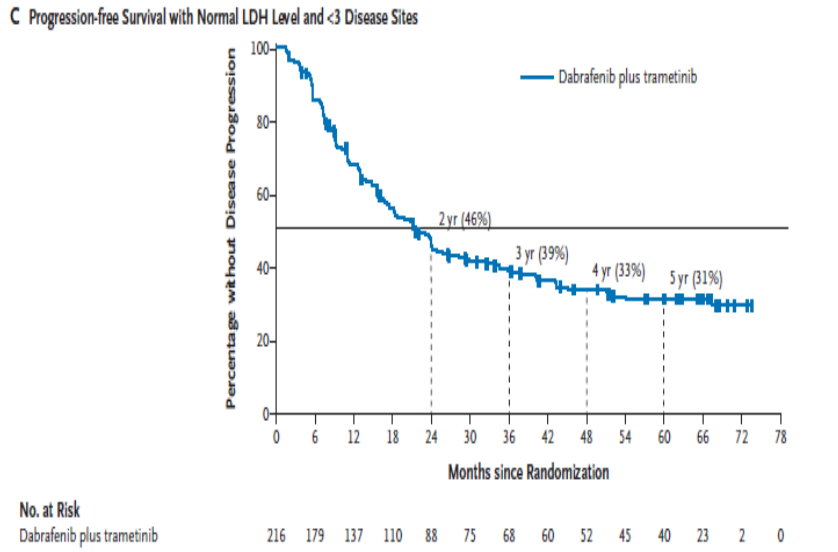
C. Robert, J.J. Grob, D. Stroyakovskiy, B. Karaszewska, A. Hauschild, E. Levchenko, V. Chiarion Sileni, J. Schachter, C. Garbe, I. Bondarenko, H. Gogas, M. Mandalá, J.B.A.G. Haanen, C. Lebbé, A. Mackiewicz, P. Rutkowski, P.D. Nathan, A. Ribas, M.A. Davies, K.T. Flaherty, P. Burgess, M. Tan, E. Gasal, M. Voi, D. Schadendorf, and G.V. Long



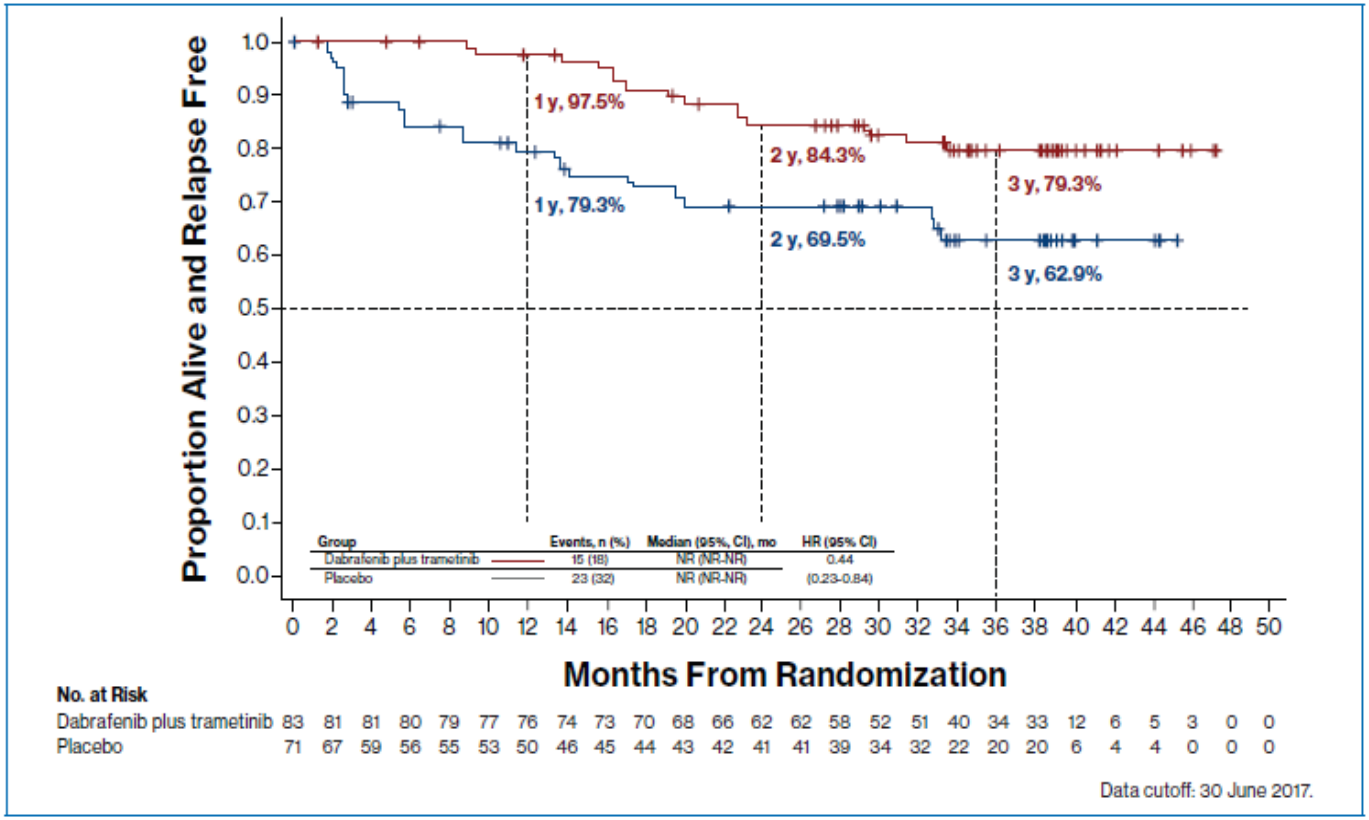
CONCLUSIONS

First-line treatment with dabrafenib plus trametinib led to long-term benefit in approximately one third of the patients who had unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation. (Funded by GlaxoSmithKline and Novartis; COMBI-d ClinicalTrials.gov number, NCT01584648; COMBI-v ClinicalTrials.gov number, NCT01597908.)





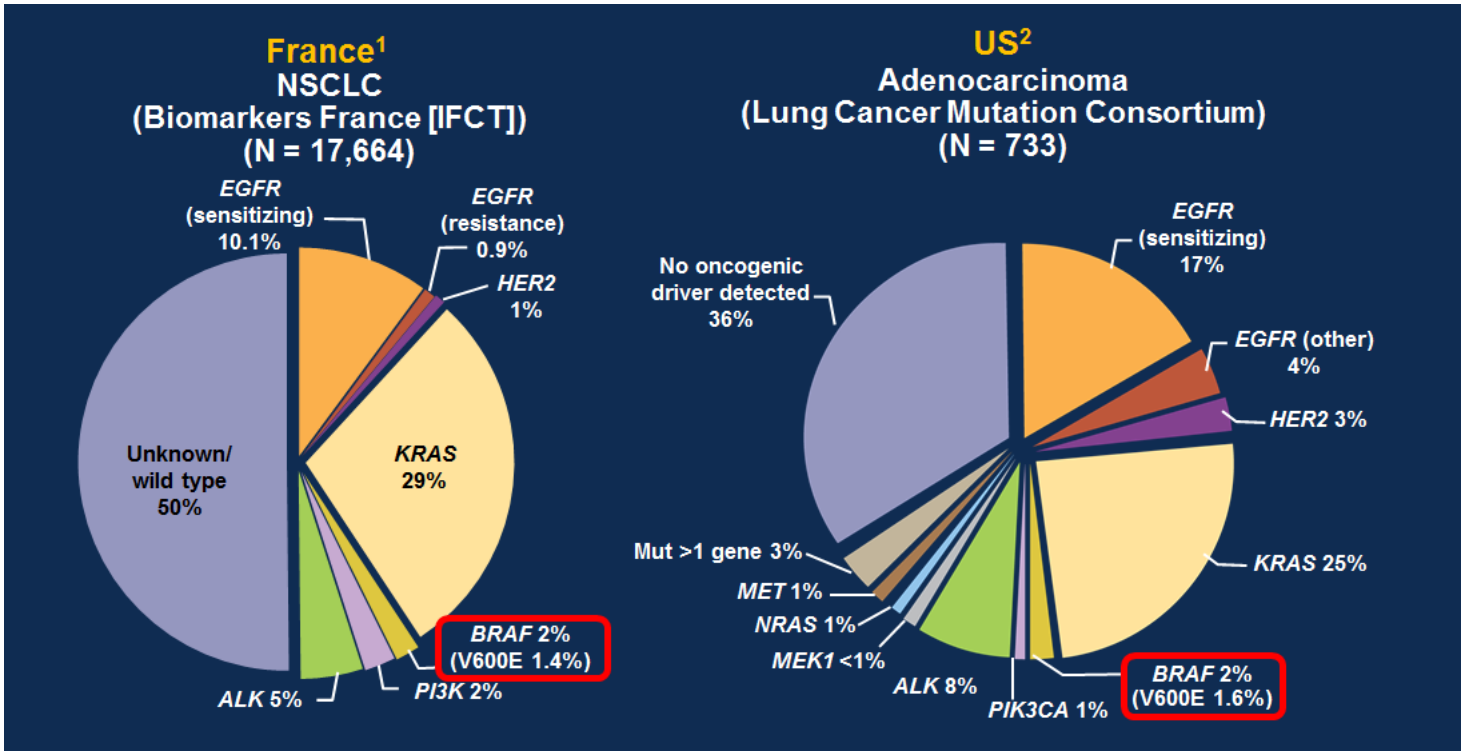
RFS en Melanoma estadio III con tratamiento adyuvante de Dabra más Trabetinib



Dummer R et al. ESMO 2019

Cáncer de Pulmón no células pequeñas

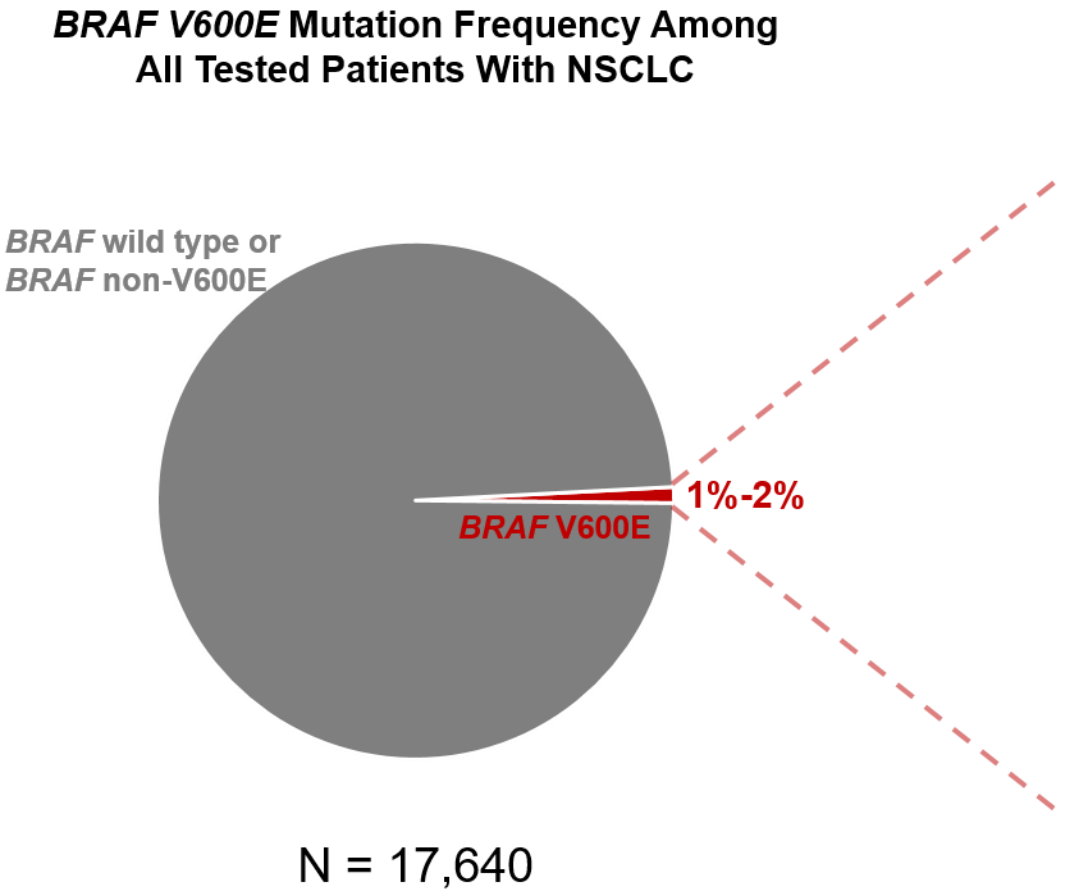
BRAF Mutations in NSCLC

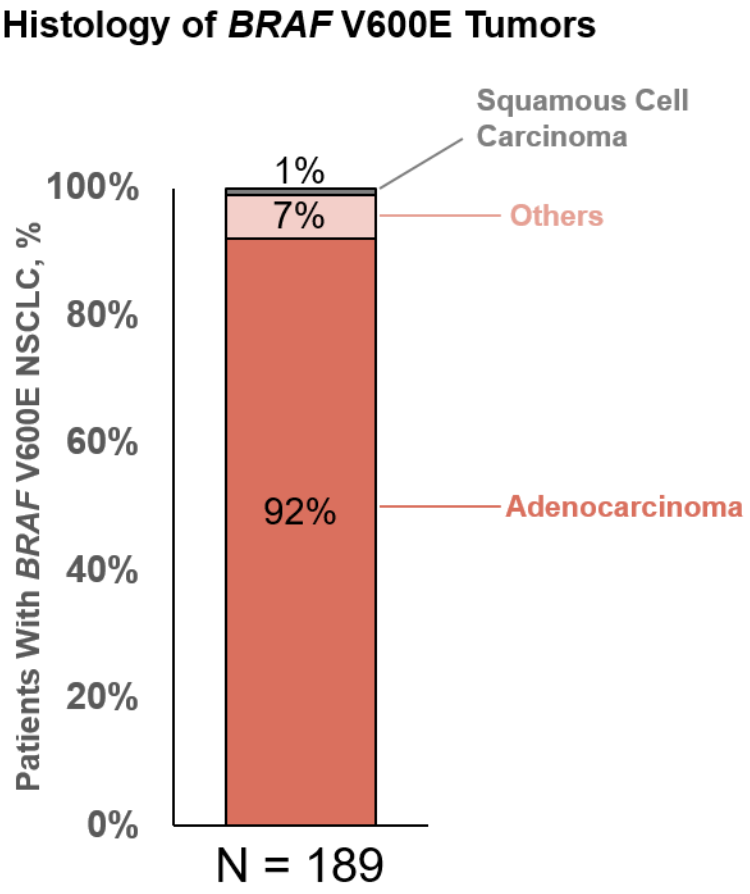


- NSCLC with *BRAF* V600E mutations has histological features suggestive of an aggressive tumor[3]
- Patients with *BRAF* V600E–mutant NSCLC demonstrated less-favorable outcomes with platinum-based chemotherapy[3,4]

1. Barlesi F, et al. *Lancet.* 2016;387:1415-1426;
2. 2. Kris MG, Johnson BE, et al. *JAMA*. 2014;311(19):1998-2006;
3. Marchetti A, et al. *J Clin Oncol*. 2011;29:3574-3579;
4. Cardarella S, et al. *Clin Cancer Res*. 19(16):4532-4540.

BRAF V600E mutations are most prevalent in lung adenocarcinoma





NSCLC, non-small cell lung cancer.

Intergroupe Francophone de Cancérologie Thoracique (IFCT) Biomarkers France Registry October 2015

BRAF NSCLC associated with aggressive histotype, shorter disease-free and overall survival

VOLUME 29 · NUMBER 26 · SEPTEMBER 10 2011

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Clinical Features and Outcome of Patients With Non–Small-Cell Lung Cancer Harboring *BRAF* Mutations

Antonio Marchetti, Lara Felicioni, Sara Malatesta, Maria Grazia Sciarrotta, Luigi Guetti, Antonio Chella, Patrizia Viola, Carmela Pullara, Felice Mucilli, and Fiamma Buttitta

- V600E mutations were significantly more prevalent in females (16 of 187 patients; 8.6%) than in males (five of 552 patients; 0.9%), as indicated by multivariate logistic regression analysis (hazard ratio [HR], 11.29; P .001).
- Retrospective analyses of patients with BRAF V600E mutations have shown inferior responses to platinum-based chemotherapy when compared to BRAF non-V600E-mutated patients or wild-type patients;
- V600E-mutated tumors showed an aggressive histotype characterized by micropapillary features in 80% of patients and were significantly associated with shorter disease-free and overall survival rates on both univariate (HR, 2.67; P .001 and HR, 2.97; P .001, respectively) and multivariate analyses (HR, 2.19; P .011 and HR, 2.18; P .014, respectively).
- All non-V600E mutations were found in smokers (P .015) and were associated with neither clinicopathologic parameters nor prognosis. BRAF and EGFR were concomitantly mutated in two tumors.

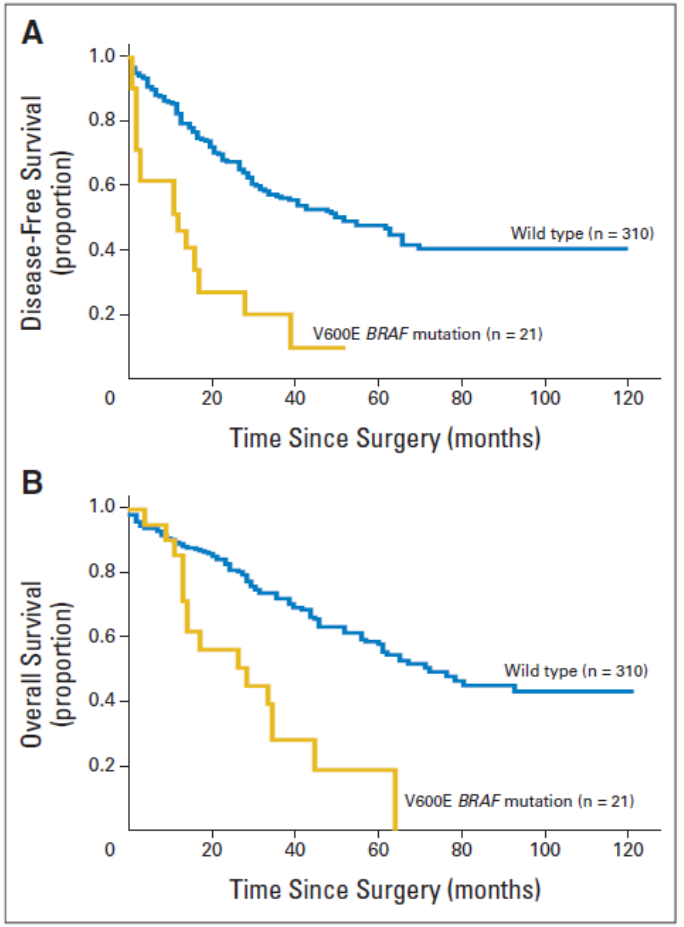
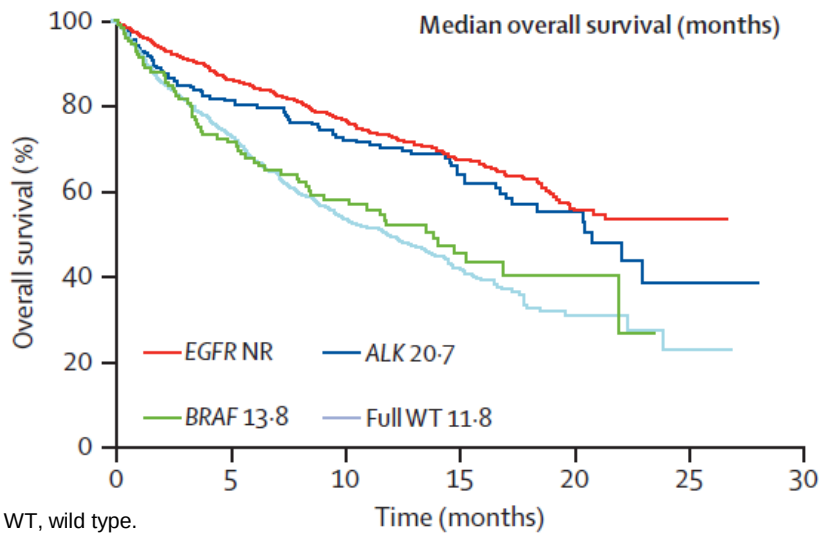


Fig 1. (A) Disease-free and (B) overall survival curves in 331 patients with lung adenocarcinoma based on presence or absence of V600E *BRAF* mutation. Curve differences are statistically significant.

An unmet need exists for patients with *BRAF*-mutant NSCLC

- Availability of targeted therapies (ie, EGFR-tyrosine kinase inhibitors, ALK inhibitors) for patients with known genetic alterations may lead to improved prognosis
  - However, some evidence suggests that the prognosis for patients with mutations in *BRAF* may remain relatively poor (13.8-month median overall survival)
  - Additionally, in a real-world second-line treatment setting, the majority of patients (57%) with *BRAF*-mutant NSCLC received only best supportive care, suggesting the lack of available treatment options in this population
- Additional clinical data are warranted to fully characterize the prognostic significance of *BRAF* mutations in patients with NSCLC



WT, wild type.
Barlesi F, et al. *Lancet*. 2016;387(10026):1415-1426.

Second-Line Treatment, n (%)	N = 106
Taxane	16 (15)
Pemetrexed	8 (8)
Erlotinib	9 (8)
Clinical trial[a]	5 (5)
Other[b]	8 (8)
Best supportive care only	60 (57)

[a] Usually based on targeted agents.
[b] Including, but not limited to, another type of chemotherapy, crizotinib via an expanded-access program before its registration, off-label targeted therapy, or a nonregistered combination of therapies.

BRAF mut Classes

- Clinicopathological :
  - class I patients less frequently harbor brain metastasis upon diagnosis (9 versus 29% and 31% for classes II and III, respectively).
  - PFS of patients with class I mutations was superior to classes II and III (n=14, n=5, and n=4, respectively) when treated with carboplatin and pemetrexed (5.1 versus 1.4 months and 4.9 months, respectively).
  - OS was also superior for class I when treated without targeted therapy compared to patients with classes II and III mutations (median OS of 40, 14, and 15.6 months, respectively).6

Bustamante Alvarez et al. Drugs in context 2019

BRAF targeted therapy trials

Drug	Phase	Treatment history	Sample size	ORR	DCR**	PFS	OS	NCT
Vemurafenib[9]	2	Previously treated and untreated patients	N=23	37%	79%	6.5 months	15.4 months	NCT01524978
Vemurafenib[10]	2	Previously treated	N=101	45%	64%	5.2 months	9.3 months	NCT02304809
Dabrafenib[11]	2	Previously treated and untreated patients.	N=84 Pretreated=78 Untreated=6	33%	58%***	5.5 months	12.7 months	NCT01336634
Dabrafenib + Trametinib[12]	2	Previously treated	N=57	63.2%	78%	8.6 and 9.7 months (independent and investigator assessment, respectively)	NE* 6 months OS was 82%	NCT01336634
Dabrafenib + Trametinib[13]	2	Previously untreated	N=36	64% (two patients had CR)	72–75% (independent and investigator assessment, respectively)	10.9 months	24.6 months	NCT01336634

Published in final edited form as:
Lancet Oncol. 2016 July ; 17(7): 984–993. doi:10.1016/S1470-2045(16)30146-2.

An open-label phase 2 trial of dabrafenib plus trametinib in patients with previously treated *BRAF* V600E–mutant metastatic non-small cell lung cancer

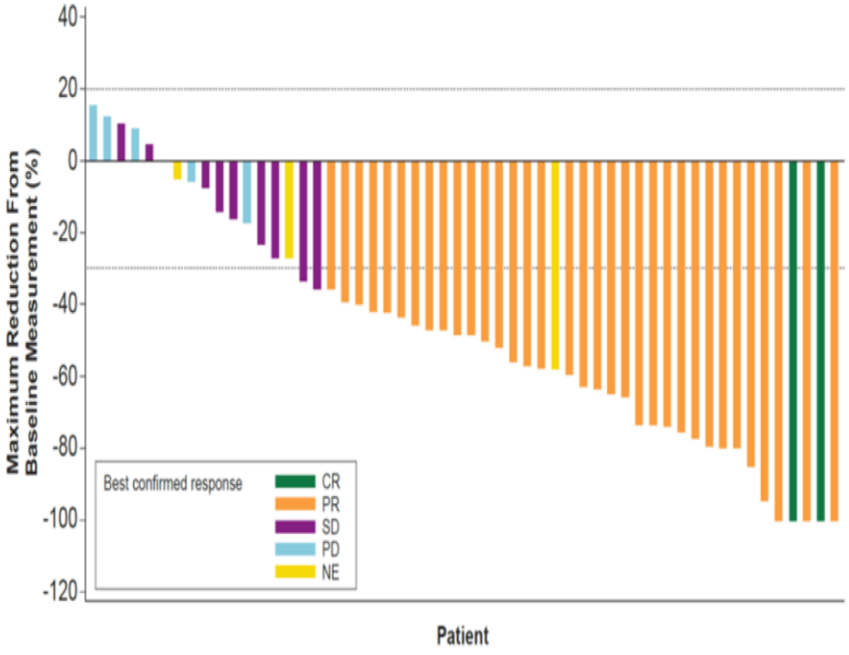


Figure 2. Tumor responses to dabrafenib + trametinib in *BRAF* V600E–mutant non-small cell lung cancer

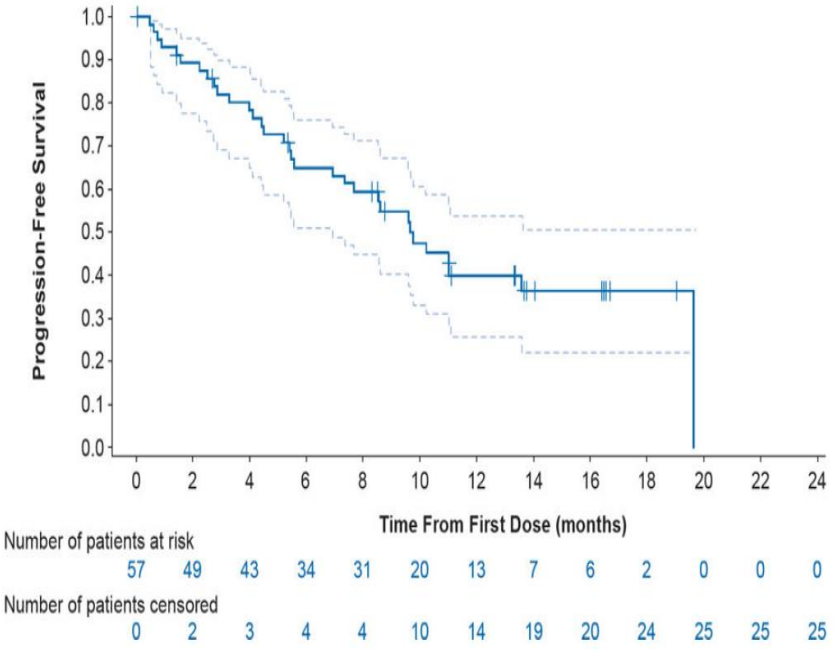
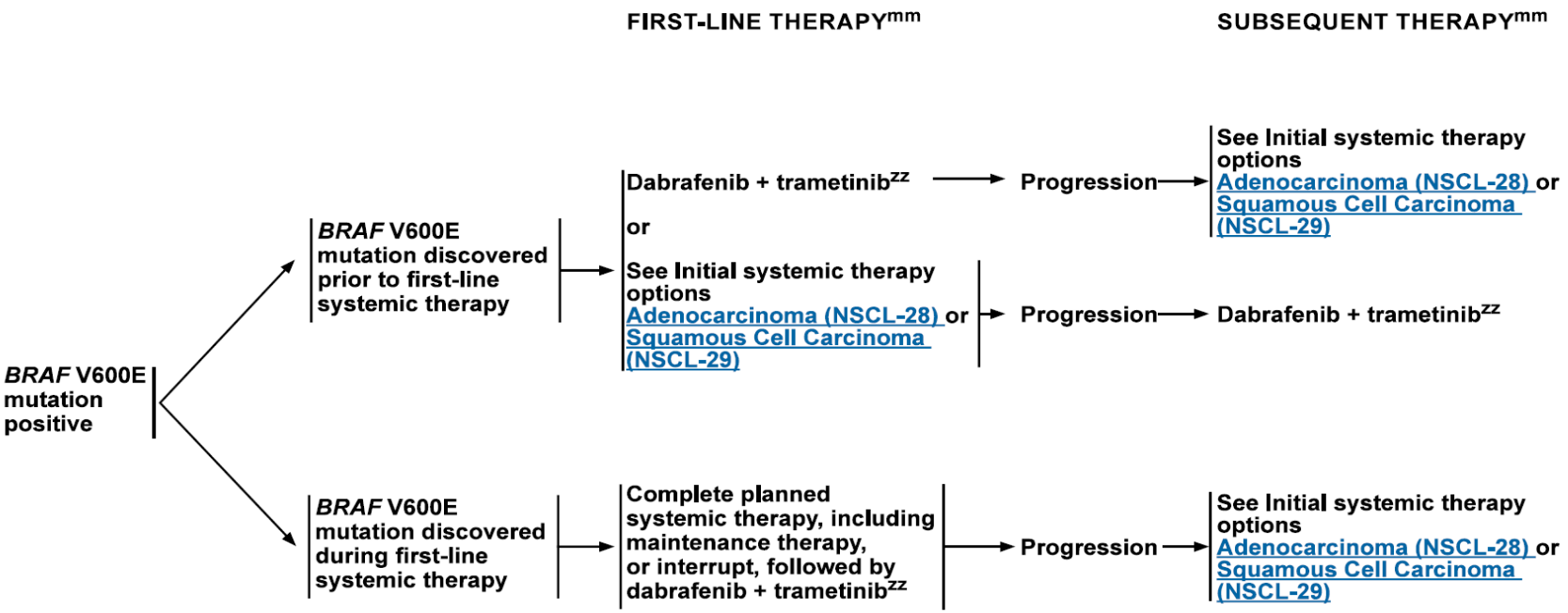


Figure 3. Kaplan-Meier curve of investigator-assessed progression-free survival in ≥ second-line patients

Dashed lines represent 95% CI. Number of patients censored represent cumulative totals.

BRAF V600E MUTATION POSITIVE[hh]



[hh]See Principles of Molecular and Biomarker Analysis (NSCL-G).
[mm]See Targeted Therapy for Advanced or Metastatic Disease (NSCL-I).
[zz]Single-agent vemurafenib or dabrafenib are treatment options if the combination of dabrafenib + trametinib is not tolerated.

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.

1. NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. 3.2019. http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed 28 Februray 2019

- Cáncer de Tiroides

Cáncer Anaplásico de Tiroides

- Carcinoma anaplásico de tiroides es un tumor indiferenciado, raro, y muy agresivos
- 1-2% cánceres de tiroides
- Más frecuente en mujeres y ancianos (mediana 70 años)
- Mediana supervivencia 5 a 12 meses.
- SV-1 año: 20% to 40%.
- OR% a tratamiento estándar 15%
- No hay tratamiento curativo
- 20%- 50% (BRAF) V600 m con significado pronóstico incierto
- Ca papilar de tiroides precede o coexiste con un 50% de CTI
- La mutación de BRAF V600 es un proceso precoz en la carcinogénesis. Aparecen en tumores bien diferenciados en los que promueven la desdiferenciacción

Subbiha V et al. JCO 2017

Genetic mutations in the treatment of anaplastic thyroid cancer: a systematic review

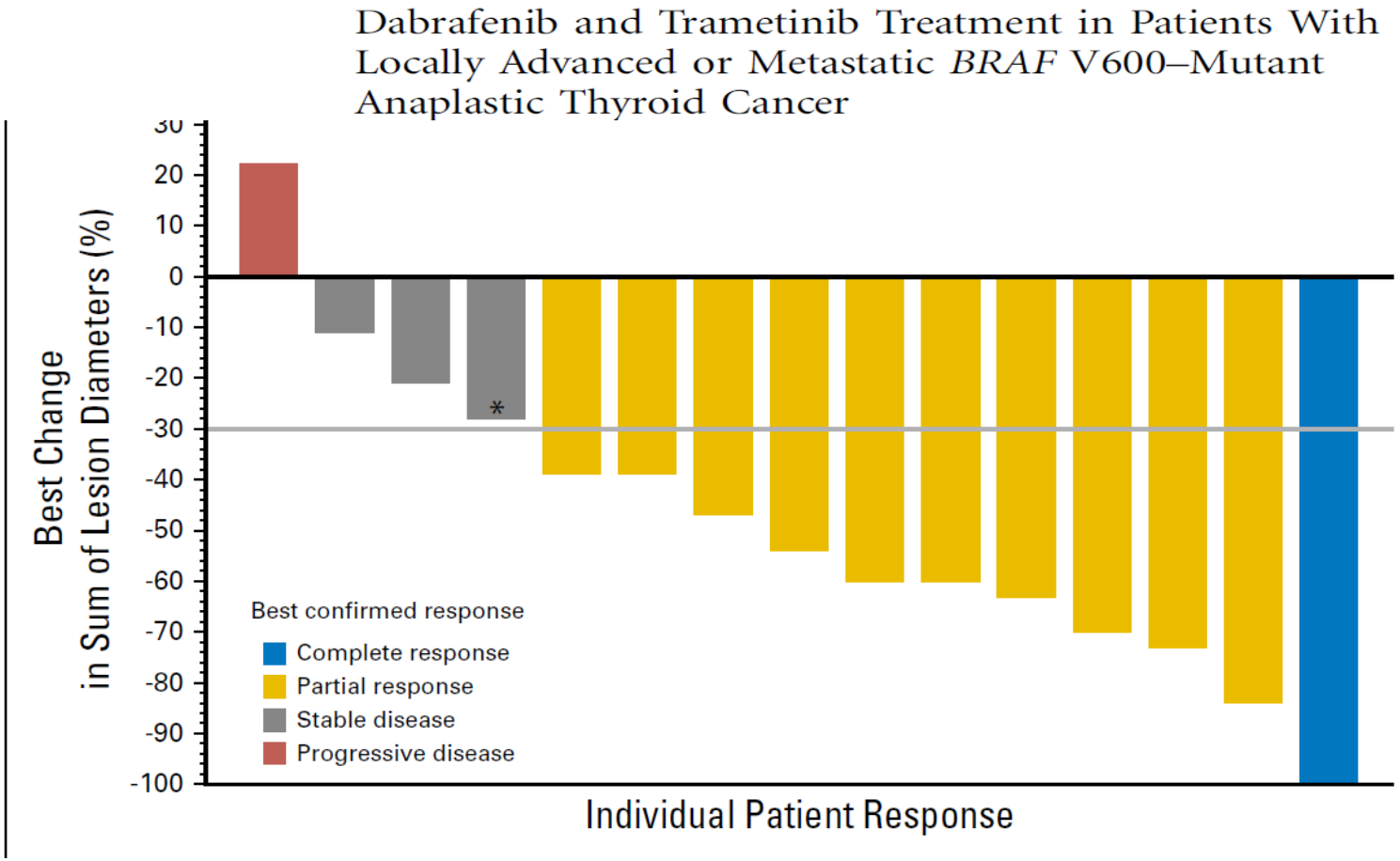
Anna Guerra[1], Vincenzo Di Crescenzo[1], Alfredo Garzi[1], Mariapia Cinelli[2], Chiara Carlomagno[3], Massimo Tonacchera[4], Pio Zeppa[1], Mario Vitale[1*]

Mutation	Positive/ total cases	Prevalence (%)	Reference
BRAF^{V600E}	0/7	0	[51]
	2/6	33	[52]
	3/29	10	[53]
	2/10	20	[54]
	8/16	50	[55]
	0/4	0	[56]
	6/17	35	[57]
Overall *BRAF*^{V600E}	21/89	23	
RAS	4/50	8	[44]
	2/18	11	[58]
	1/5	20	[59]
	4/18	23	[43]
	15/29	55	[60]
	4/50	8	[61]
	3/5	60	[62]
Overall *RAS* mutations	33/162	20	
RET/PTC	0/14	0	[63]
	3/51	6	[44]
	0/17	0	[64]
Overall *RET/PTC*	3/81	4	

APK

pathway in ATC

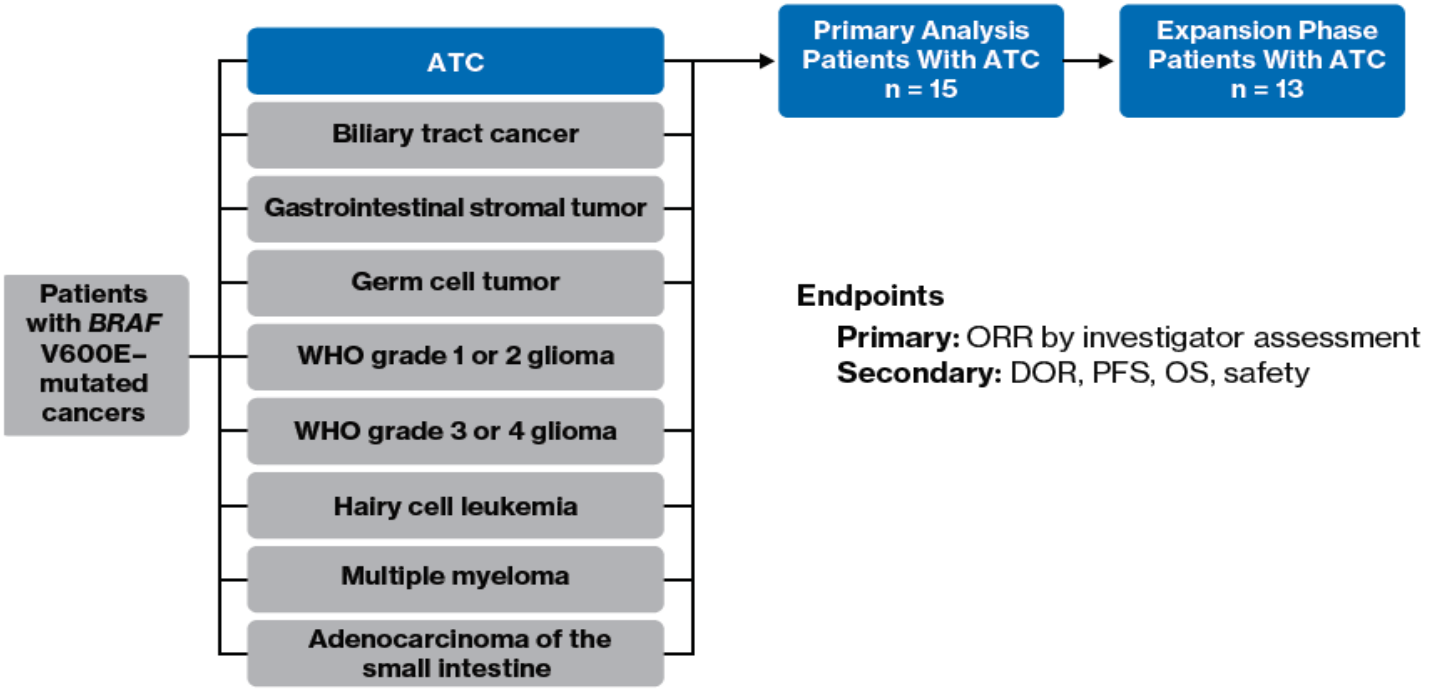
Mutation	Positive/ total cases	Prevalence (%)	Reference
PTEN	8/48	17	[44]
	8/50	16	[61]
	1/9	10	[65]
Overall *PTEN*	17/107	16	
PI3KCA	6/50	12	[44]
	4/18	22	[58]
	29/50	58	[61]
	16/70	23	[66]
Overall *PI3KCA*	45/188	24	
TP53	1/11	10	[67]
	5/7	71	[19]
	6/7	86	[68]
Overall *TP53*	12/25	48	



N= 17; OR: 69% (11 of 16; 95% CI, 41% to 89%)
Median duration of response, progression-free survival, and overall survival were not reached as a result of a lack of events

Subbiha V et al. JCO 2017

Updated Efficacy and Safety Data of Dabrafenib and Trametinib in Patients With *BRAF* V600–**Mutated Anaplastic Thyroid Cancer**



Keam B et al. ESMO 2018

Table 5. Best Overall Response in Patients With ATC

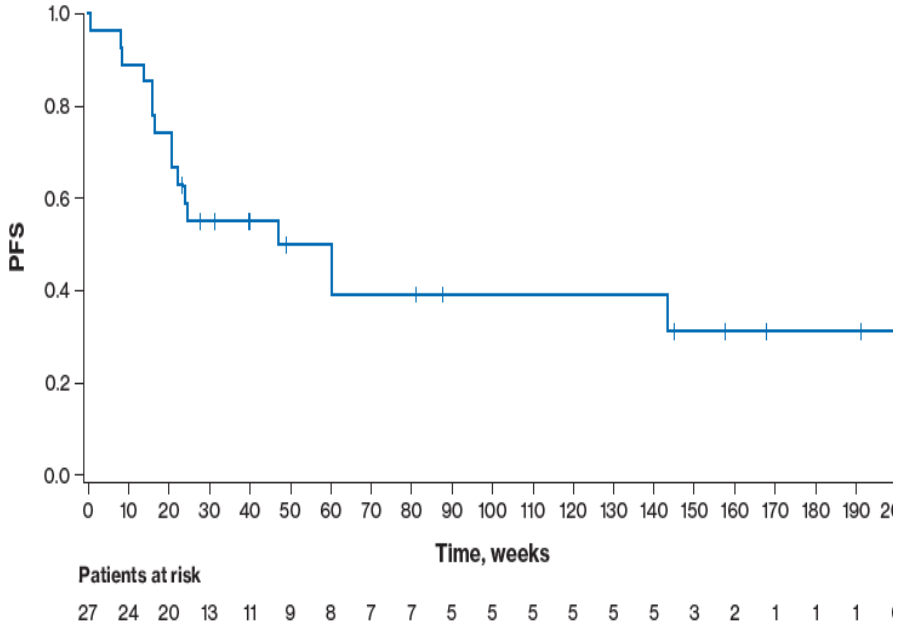
	ATC Cohort n = 28			
	ITT-Evaluable Population n = 27[a]		*BRAF* V600E-Evaluable Population n = 24[a,b]	
	Investigator Assessment	Independent Review	Investigator Assessment	Independent Review
Best overall response, n (%)				
CR	2 (7)	2 (7)	2 (8)	2 (8)
PR	16 (59)	13 (48)	16 (67)	13 (54)
SD	6 (22)	5 (19)	3 (13)	3 (13)
PD	3 (11)	6 (22)	3 (13)	5 (21)
Not evaluable	0	1 (4)	0	1 (4)
ORR (CR + PR), n (%)	**18 (67)**	**15 (56)**	**18 (75)**	**15 (63)**
95% CI	46-84	35-75	53-90	41-81

ITT, intention to treat; PD, progressive disease; PR, partial response SD, stable disease.

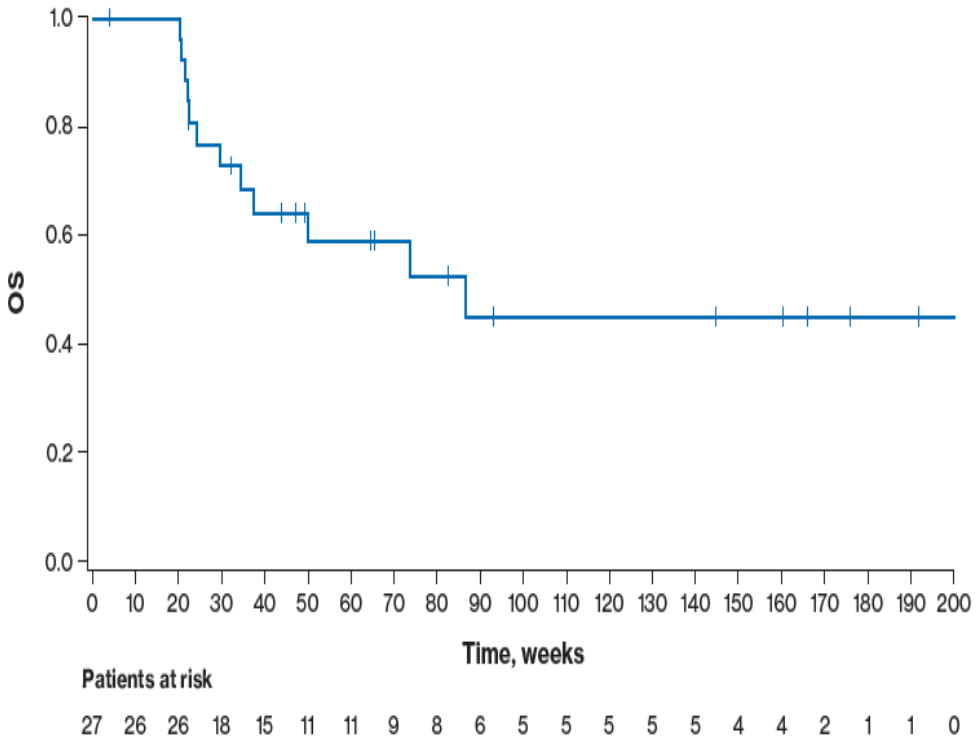
[a] The evaluable population excluded 1 patient with insufficient observation time at the interim data cutoff; 1 patient in the evaluable population had response data that were determined to be not evaluable by independent review; [b] Three patients did not have centrally-confirmed *BRAF* V600E mutations.

Updated Efficacy and Safety Data of Dabrafenib and Trametinib in Patients With *BRAF* V600–**Mutated Anaplastic Thyroid Cancer**

PFS: 60 w (95% CI, 20 weeks-not estimable)



OS: 86 weeks (95% CI, 35 weeks-NE



Keam B et al. ESMO 2018

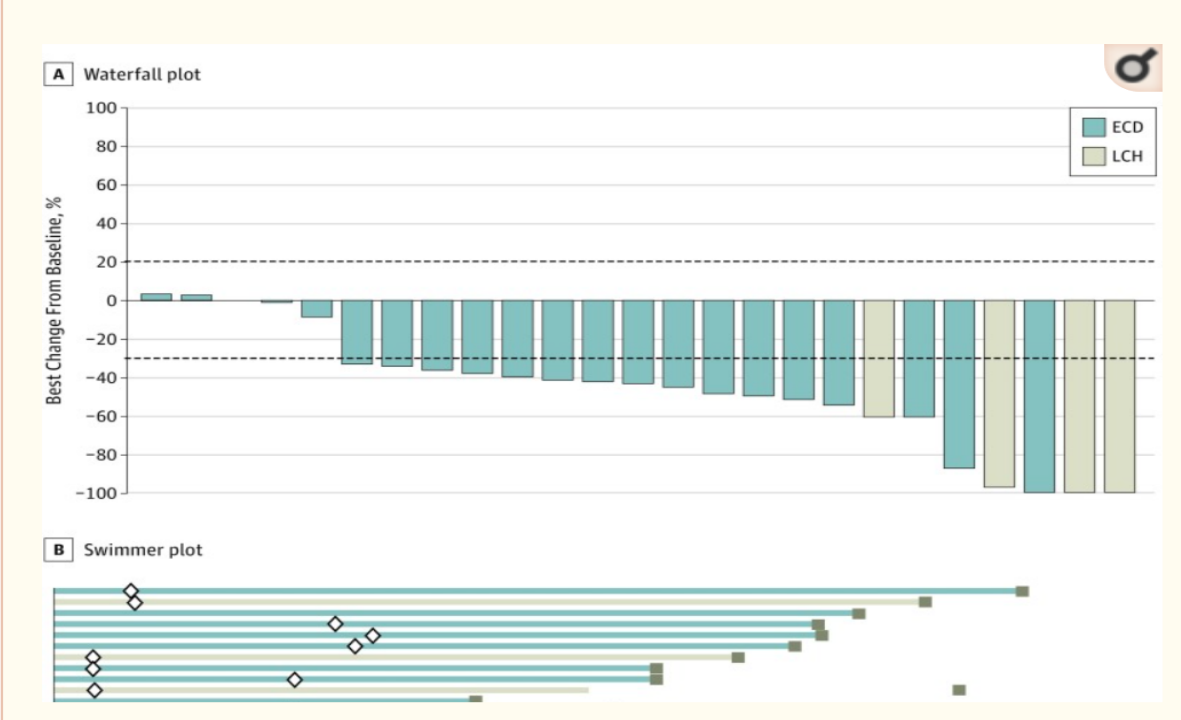
- **Histiocitosis**

JAMA Oncol. 2018 Mar; 4(3): 384–388.
Published online 2017 Nov 29. doi: 10.1001/jamaoncol.2017.5029
PMCID: PMC5844839
NIHMSID: NIHMS933869
PMID: 29188284

Vemurafenib for *BRAF* V600–Mutant Erdheim-Chester Disease and Langerhans Cell Histiocytosis

Analysis of Data From the Histology-Independent, Phase 2, Open-label VE-BASKET Study

BRAF mut: 50%



Efficacy of Vemurafenib in Patients With ECD or Langerhans Cell Histiocytosis[a]

Outcome	Patients With ECD (n = 22)	Overall Cohort (n = 26)
Objective response rate (95% CI), %	54.5 (32.2-75.6)	61.5 (40.6-79.8)
Best overall response		
Complete response	1 (5)	2 (8)
Partial response	11 (50)	14 (54)
Stable disease	9 (41)	9 (35)
Progressive disease	0	0
Not evaluable[b]	1 (5)	1 (4)
Clinical benefit rate, No. (%) (95% CI)[c]	16 (73) (49.8-89.3)	20 (77) (56.4-91.0)
Median PFS, % (95% CI)	NE	NE
At 1 year	83 (66-100)	86 (72-100)
At 2 years	83 (66-100)	86 (72-100)
Median OS, % (95% CI)	NE	NE
At 1 year	95 (85-100)	96 (87-100)
At 2 years	95 (85-100)	96 (87-100)

Vemurafenib demonstrated clinically meaningful long-term efficacy in patients with *BRAF* V600–mutant ECD and LCH in the VE-BASKET study. Based on these results, the US Food and Drug Administration has approved vemurafenib for patients with *BRAF* V600–mutant ECD and warrants consideration as a new standard of care for these patients.

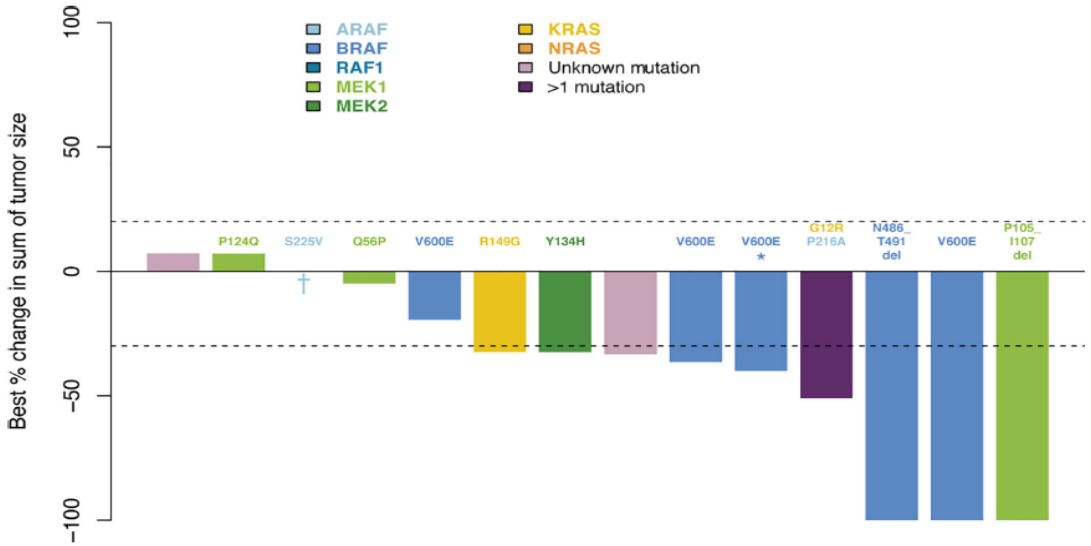
Published in final edited form as:

Nature. 2019 March ; 567(7749): 521–524. doi:10.1038/s41586-019-1012-y.

Efficacy of MEK Inhibition in Patients with Histiocytic Neoplasms

Eli L. Diamond[1,10,*], Benjamin H. Durham[2,3,*], Gary A Ulaner[4,10], Esther Drill[5], Justin Buthorn[1], Michelle Ki[3], Lillian Bitner[3], Hana Cho[3], Robert J. Young[4], Jasmine H Francis[6], Raajit Rampal[7], Mario Lacouture[8], Lynn A. Brody[4], Neval Ozkaya[2,11], Ahmet Dogan[2], Neal Rosen[7,9,10], Alexia Iasonos[5,10], Omar Abdel-Wahab[3,7,10,], and David M. Hyman[7,10,**]**

Extended Data



Extended Data Figure 1. Waterfall plot of maximum change in tumor size by RECIST following cobimetinib treatment in histiocytosis patients (n=14).

The upper and lower dotted lines represent cut-offs for progressive disease and partial response, respectively. Colors of bars indicate genomic alteration present. Notations above bars indicate specific mutation. One patient (asterisk) had prior BRAF inhibitor therapy that was discontinued due to intolerance. One patient (dagger) died due to underlying disease.

- **Carcinoma de Vía Biliar**

Genetic Targets in BTC

- Mutations in the *BRAF* gene have been found in 5% of biliary tumors[1,2]
  - *BRAF* mutations may be enriched in intrahepatic BTC[3]
- The combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib has demonstrated efficacy in *BRAF* V600E–mutated cancers, including metastatic melanoma and melanoma in the adjuvant setting,[4,5] non-small cell lung carcinoma,[6] and anaplastic thyroid cancer[7]

Intrahepatic cholangiocarcinoma

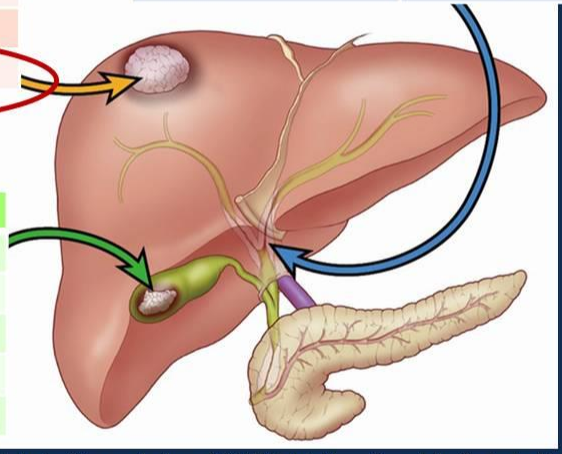
Targetable gene	Prevalence, %
FGFR2 (fusions)	10-20
IDH1/2	22-28
BAP1	15 to 25
BRAF V600 (mutation)[1,2]	5-7

Extrahepatic cholangiocarcinoma

Targetable gene	Prevalence, %
Her2/neu (mutation)	11-20
PRKACA and *PRKACB*	9
ARID1A	5-12

Gall bladder cancer

Targetable gene	Prevalence, %
EGFR	4-13
HER2/neu (amplification)	9
ERB3	0-12
PTEN	0-4
PIK3CA	6-13



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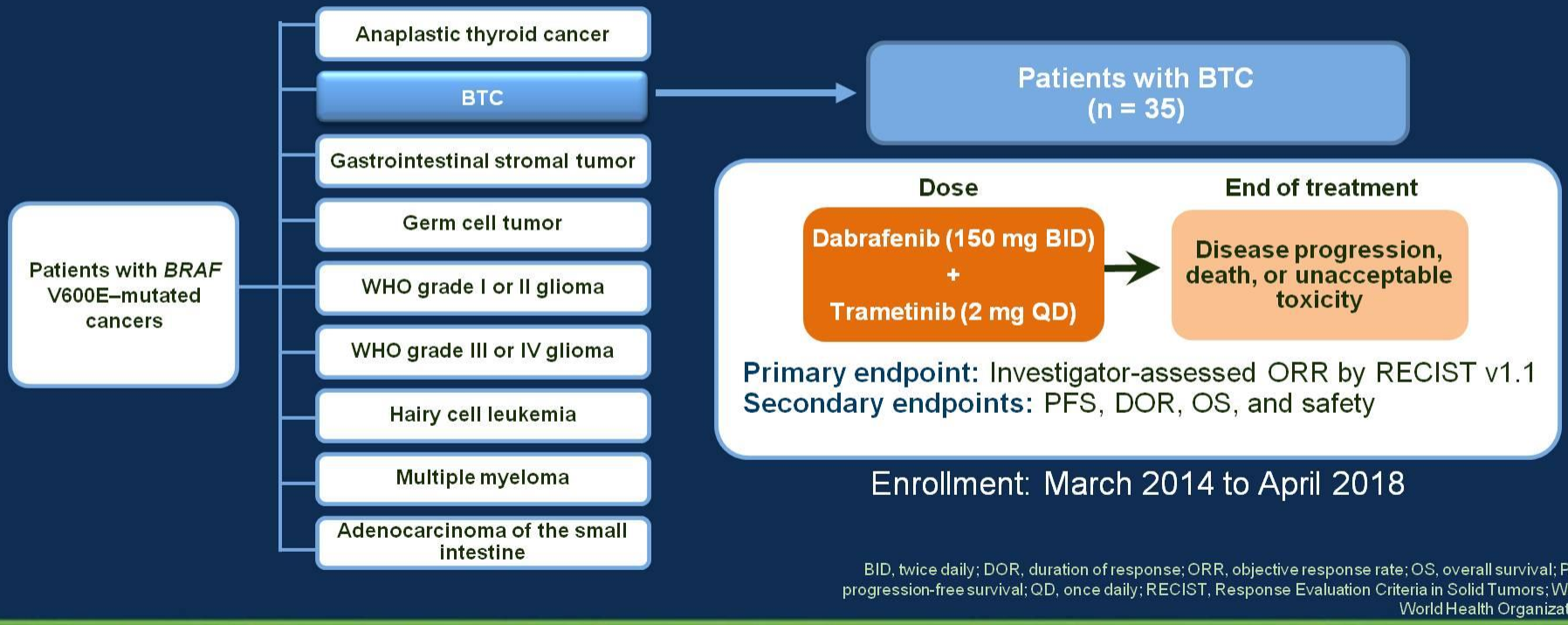
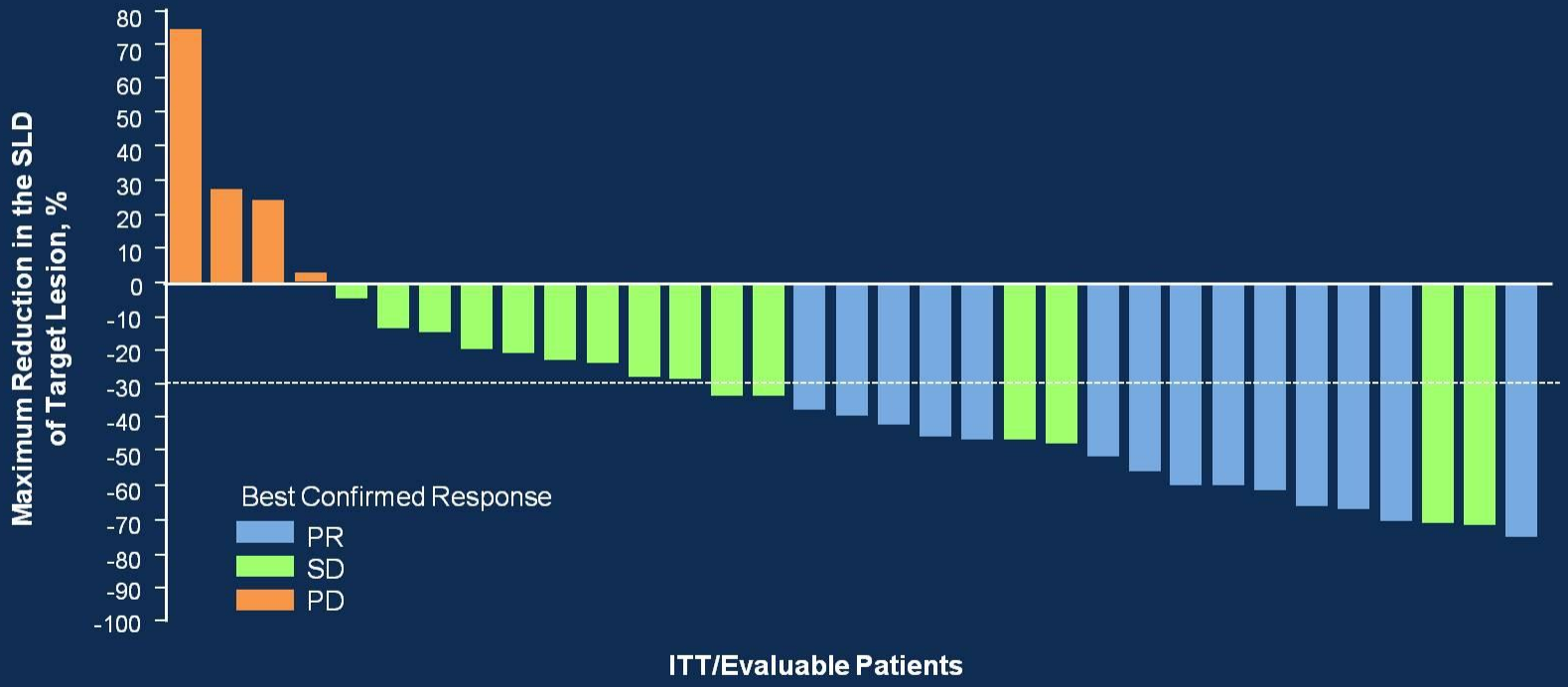
1. Ahn DH, et al. *J Gastrointest Oncol.* 2017;8(2):293-301. 2. Schrock AB, et al. *JAMA.* 2017;3(11):1546-1553. 3. Jain A, et al. *Curr Treat Options in Oncol.* 2016;17(11):58. 4. Long GV, et al. *Lancet.* 2015;386(9992):444-451. 5. Long GV, et al. *N Engl J Med.* 2017;377(19):1813-1823. 6. Planchard D, et al. *Lancet Oncol.* 2016;17(7):984-993. 7. Subbiah V, *et al. J Clin Oncol* 2018;36:7-13.

ROAR: A Phase 2, Open-Label, Multicenter Study (NCT02034110)



BID, twice daily; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization.

Investigator-Assessed Maximum Reduction in SLD of Target Lesions

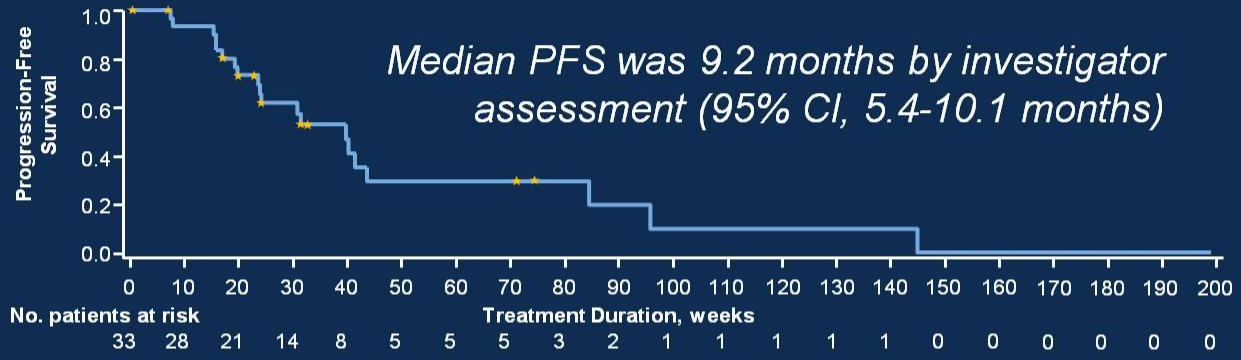


SLD, sum of the longest diameter of the target lesion.

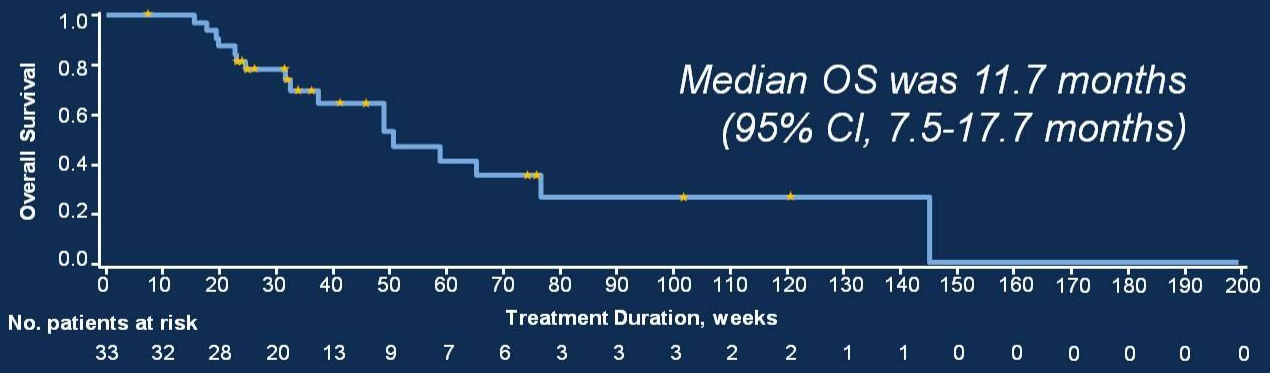
OR: 42%

Presented By Zev Wainberg at 2019 Gastrointestinal Cancer Symposium

PFS and OS in the ITT/Evaluable Population



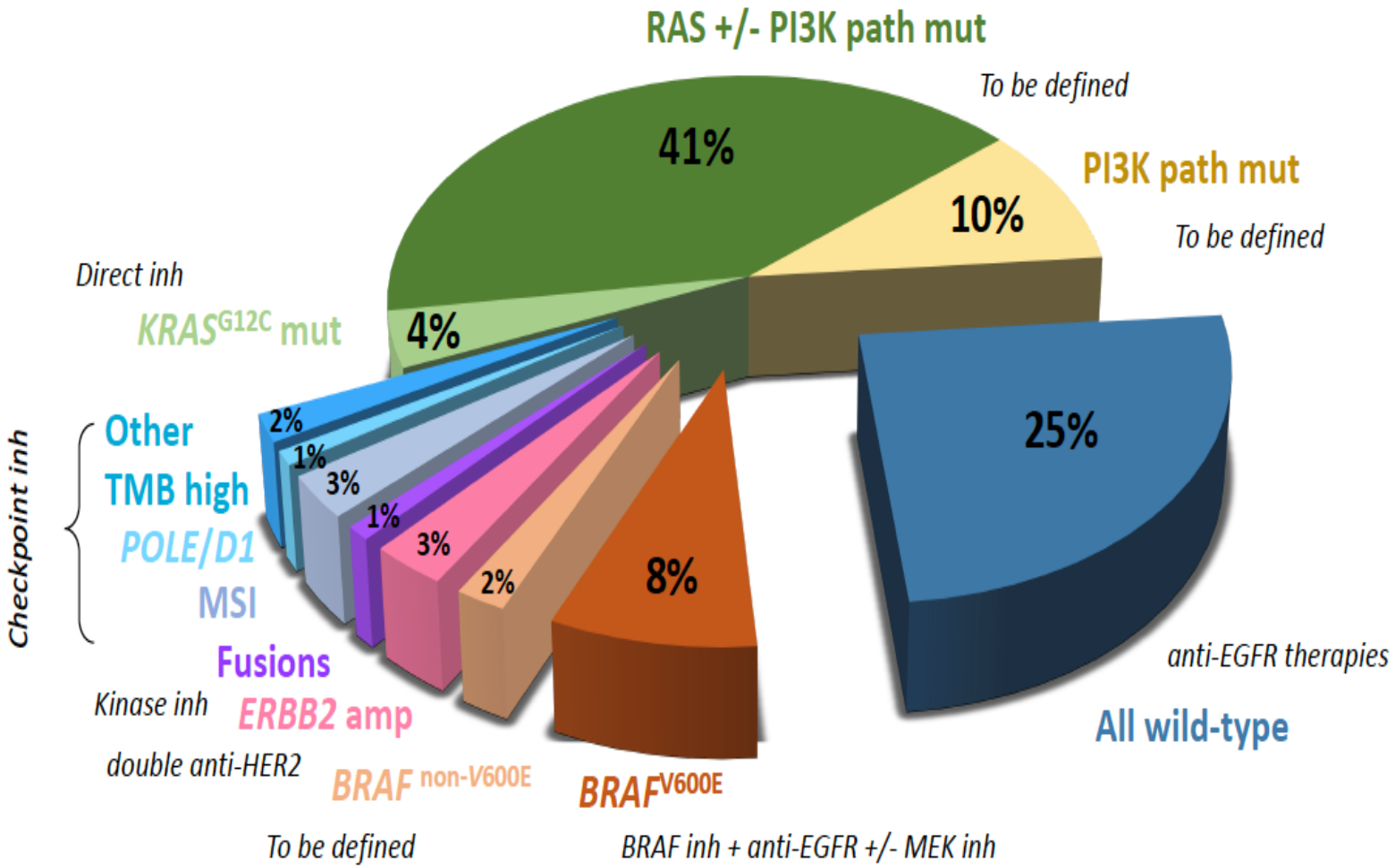
Median PFS was 9.2 months by investigator assessment (95% CI, 5.4-10.1 months)



Median OS was 11.7 months (95% CI, 7.5-17.7 months)

- **Cáncer Colorrectal**

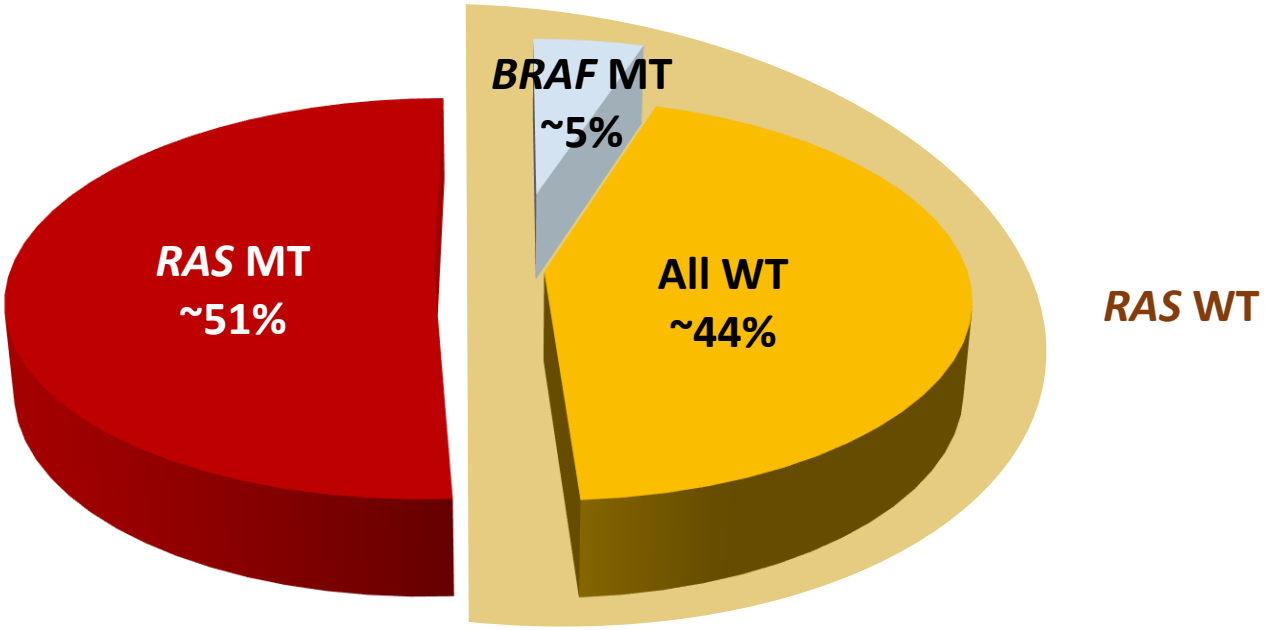
GENOMIC SUBTYPES OF CRC



Adapted from Dienstmann et al,
ASCO Educ Book 2018

BRAF and *RAS* Family Genes in CRC: Focus on mCRC

- Concomitant *KRAS* and *BRAF* tumor mutations are rare enough to be considered virtually mutually exclusive (but not entirely, as shown in anecdotal reports)[1,2]
- This relationship allows classification of patients with mCRC according to their multiple-mutation status[3]
  - Routine analysis for *BRAF* mutations in *KRAS* wild type tumors is not required for the selection of therapy[2]

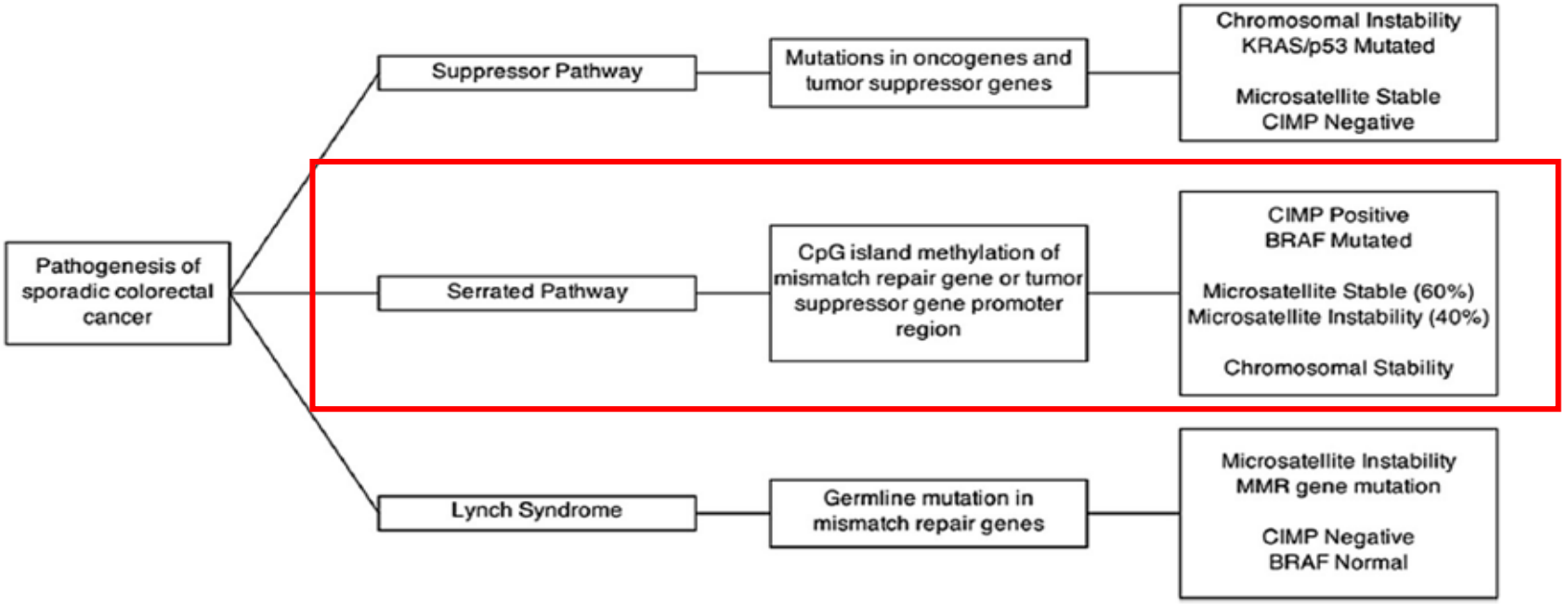


Schematic representation of the distribution of *RAS* and *BRAF* mutations in the mCRC population[3,4]

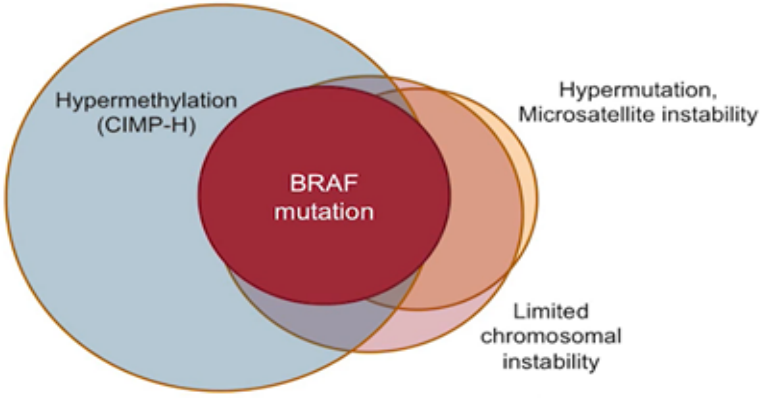
KRAS = Kirsten rat-associated sarcoma virus gene; WT = wild-type; MT = mutant.

1. Chen D, et al. *PLoS One*. 2014;9:e90607; 2. Sahin IH, et al. *J Cancer*. 2013;4:320-322; 3. Fakih M. *J Clin Oncol.* 2015;33:1809-24; 4. Douillard JY, et al. *N Engl J Med.* 2013;369:1023-34.

CLASSIC MECHANISMS OF CARCINOGENESIS IN COLORECTAL CANCER



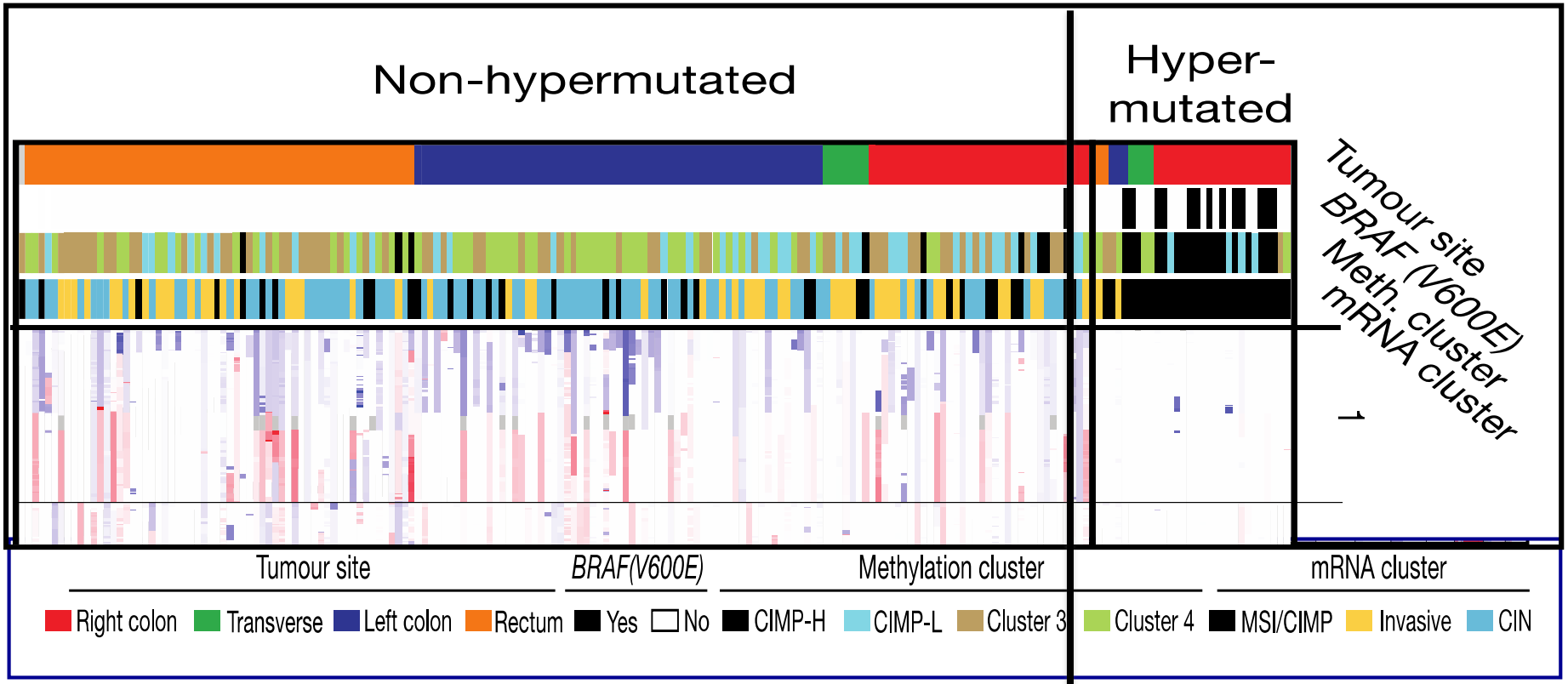
Landscape of BRAF^{mut} Colorectal Cancer



Lee GH et al. EJSO 2015

BRAF mut 3%

BRAF mut 47%



Left-sided

- Rectal / Sigmoid
- MSS
- *KRAS* mut
- CIN+

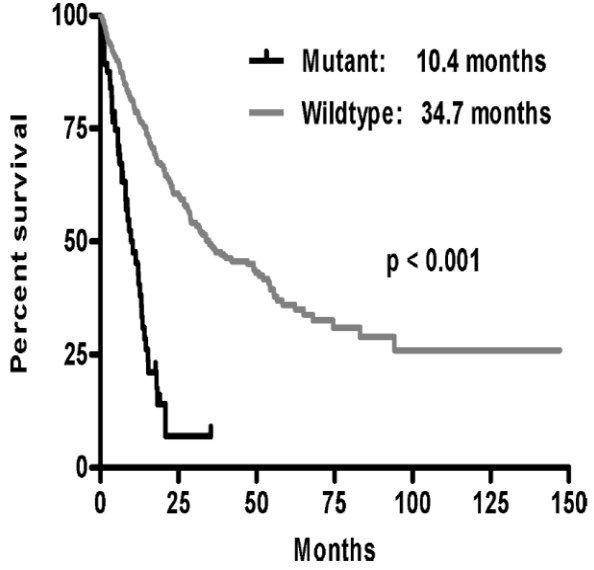
Right-sided

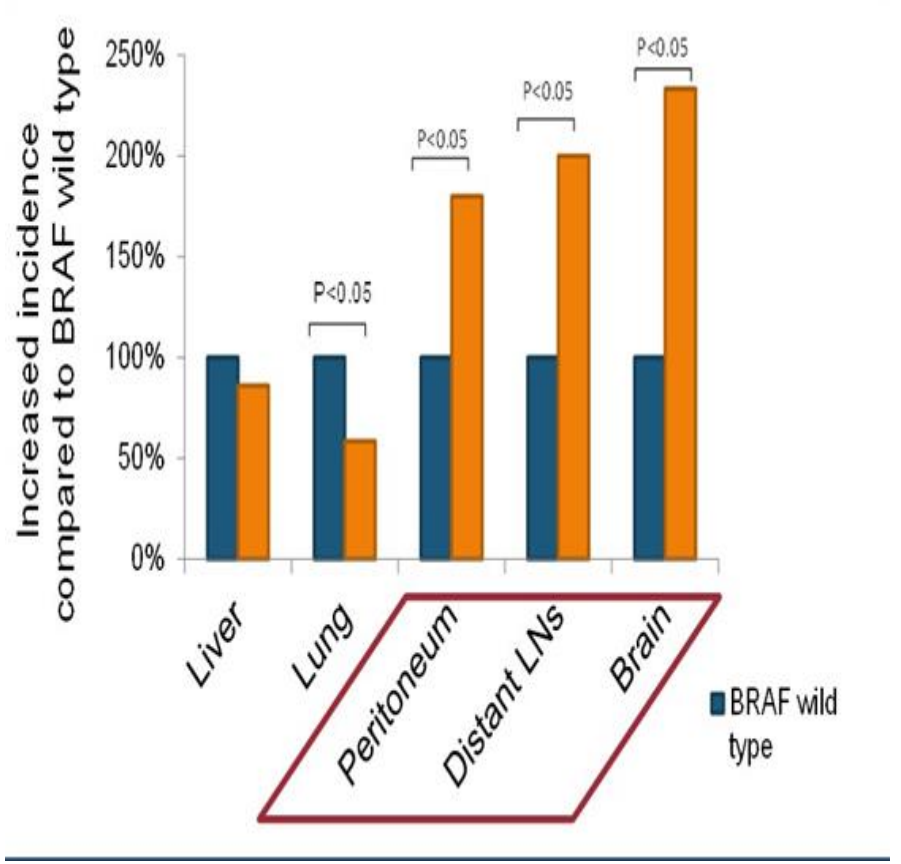
- MSI-H
- Hypermethylated
- ***BRAF* mut**
- Chromosomal stability

Adaptado de: The Cancer Genome Atlas Network *Nature* 487, 330-337 (2012)

Clínica

- Mujeres
- Ancianos
- Fumadores
- Colon derecho
- Localizaciones metastásicas atípicas
- Mal diferenciados y mucinosos
- Mal pronóstico





Morris et al , Clinical Colorectal Cancer ’13; Modest et al Ann Onc‘16

Riesgo de Enfermedad Tromboembólica

	VTE patients n=41/194
Mean age (+/- SD)	64.7 (+/- 12.3)
ECOG - no (%)	
0-1	30 (73.2%)
≥ 2	6 (14.6%)
Unknown	5 (12.2%)
Stage - no (%)	
Localized	4 (9.8%)
Metastatic	37 (90.2%)
Number of metastatic locations (+/- SD)	1.97 (+/-1.29)
Systemic treatment - no (%)	
Non treatment	11 (26.9%)
Chemotherapy	6 (14.6%)
Chemotherapy + anti-VEGF therapy	15 (36.6%)
Chemotherapy + anti-EGFR therapy	7 (17.1%)
Anti-EGFR therapy alone	1 (2.4%)
Unknown	1 (2.4%)
Khorana score - no (%)	
Low (0)	26 (63.4%)
Intermediate (1-2)	10 (24.5%)
High (≥ 3)	3 (7.3%)
Unknown	2 (4.8%)
Type venous thromboembolic event - no (%)	
PE	11 (26.9%)
Lower extremity DVT	15 (36.6%)
Visceral vein thrombosis	12 (29.3%)
Catheter-related thrombosis	2 (4.8%)
Unknown	1 (2.4%)

	All patients n=194 (%)	RAS mutated n=68 (35.1%)	BRAF mutated n=21 (10.8%)	Triple-WT n=105 (54.1%)
VTE	41 (21.1%)	13 (19.1%)	**6 (28.6%)**	22 (21%)

Risk factors	Univariate analysis p-value	Multivariate analysis OR (95% CI; p-value)
Age		1.01 (CI 95% 0.97-1.04; p=0.799)
Sex		0.89 (CI 95% 0.38-2.05; p=0.778)
Chronic kidney disease	**0.022**	3.87 (CI 95% 0.85-17.52; p=0.080)
ECOG ≥ 2	**0.038**	**8.73 (CI 95% 1.32-57.82; p=0.025)**
High-risk Khorana score	**0.011**	10.63 (CI 95% 0.87-129.97; p=0.064)
Metastatic disease	0.053	0.52 (CI 95% 0.24-1.15; p=0.104)
KRAS status	0.659	0.77 (CI 95% 0.31-1.90; p=0.57)
BRAF status	0.384	1.88 (CI 95% 0.60-5.91; p=0.278)

García Alfonso et al. *Journal of Clinical 2019 Oncology* 37, no. 15_suppl

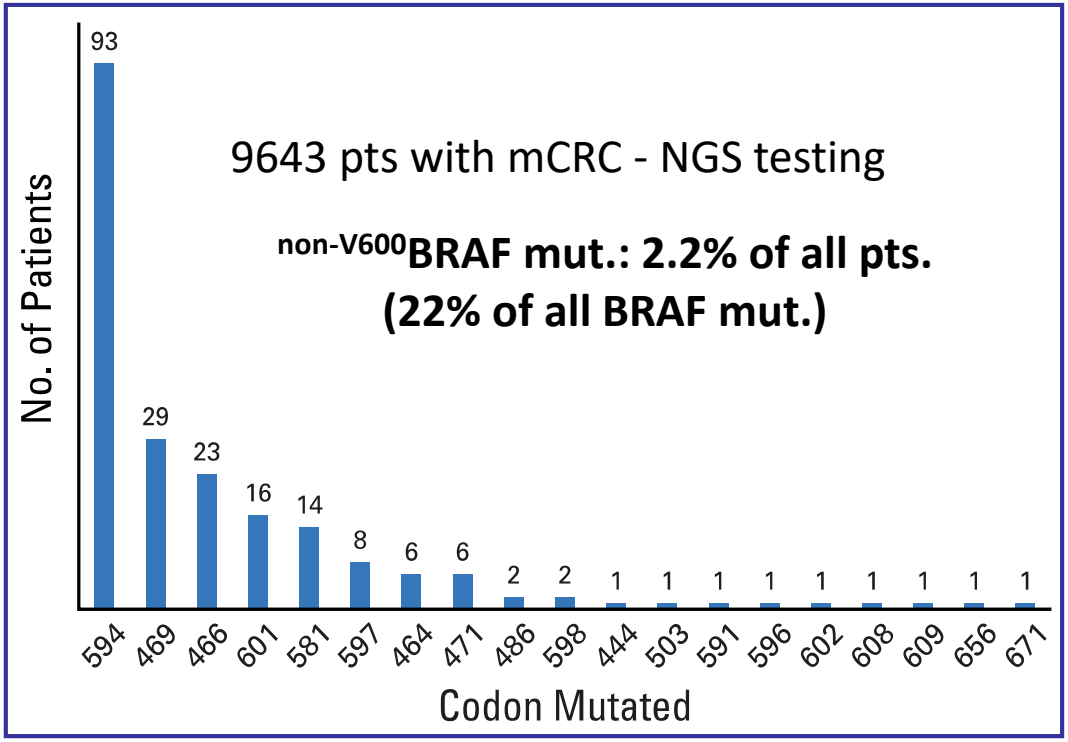
Non-V600 BRAF Mutations

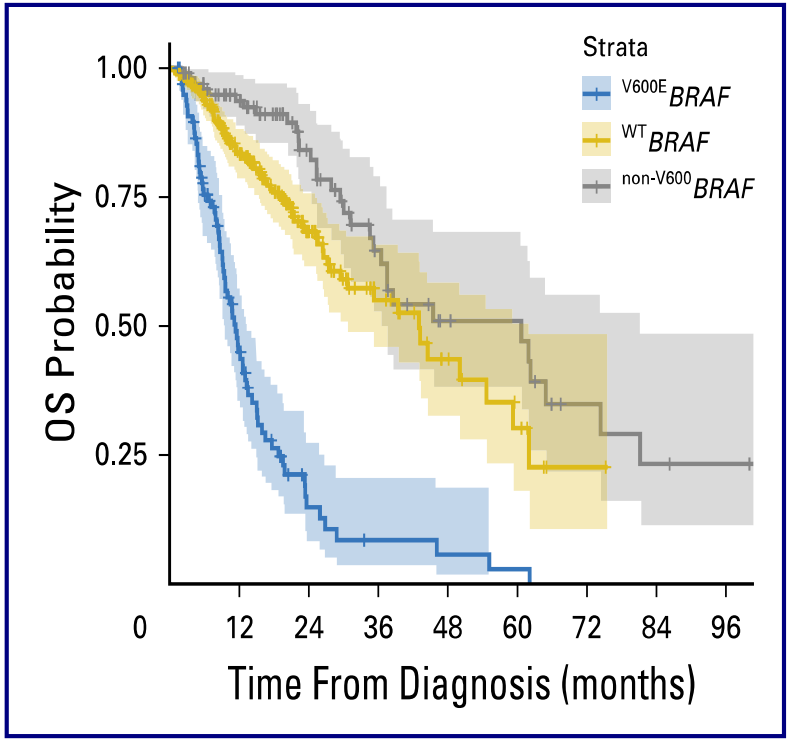
V600E BRAF-mutant CRC

Female predominance, older age, right-sided primary tumors, high-grade histology, MSI, and frequent peritoneal spread.

nonV600E BRAF mut. CRC (594 , 596)

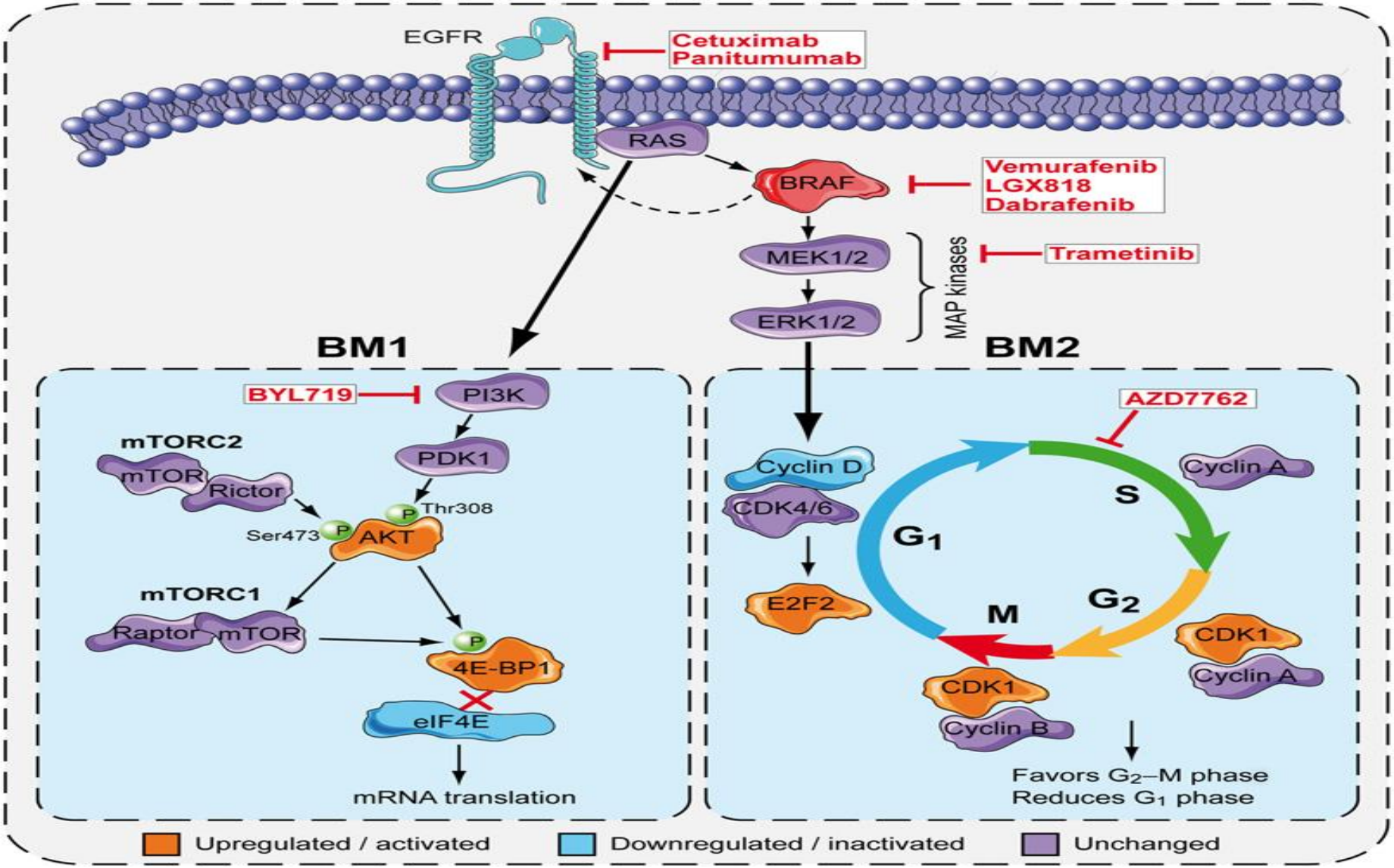
Younger, fewer female fewer high-grade or right-sided primary tumors





J.C. Jones et al. J Clin Oncol 2017

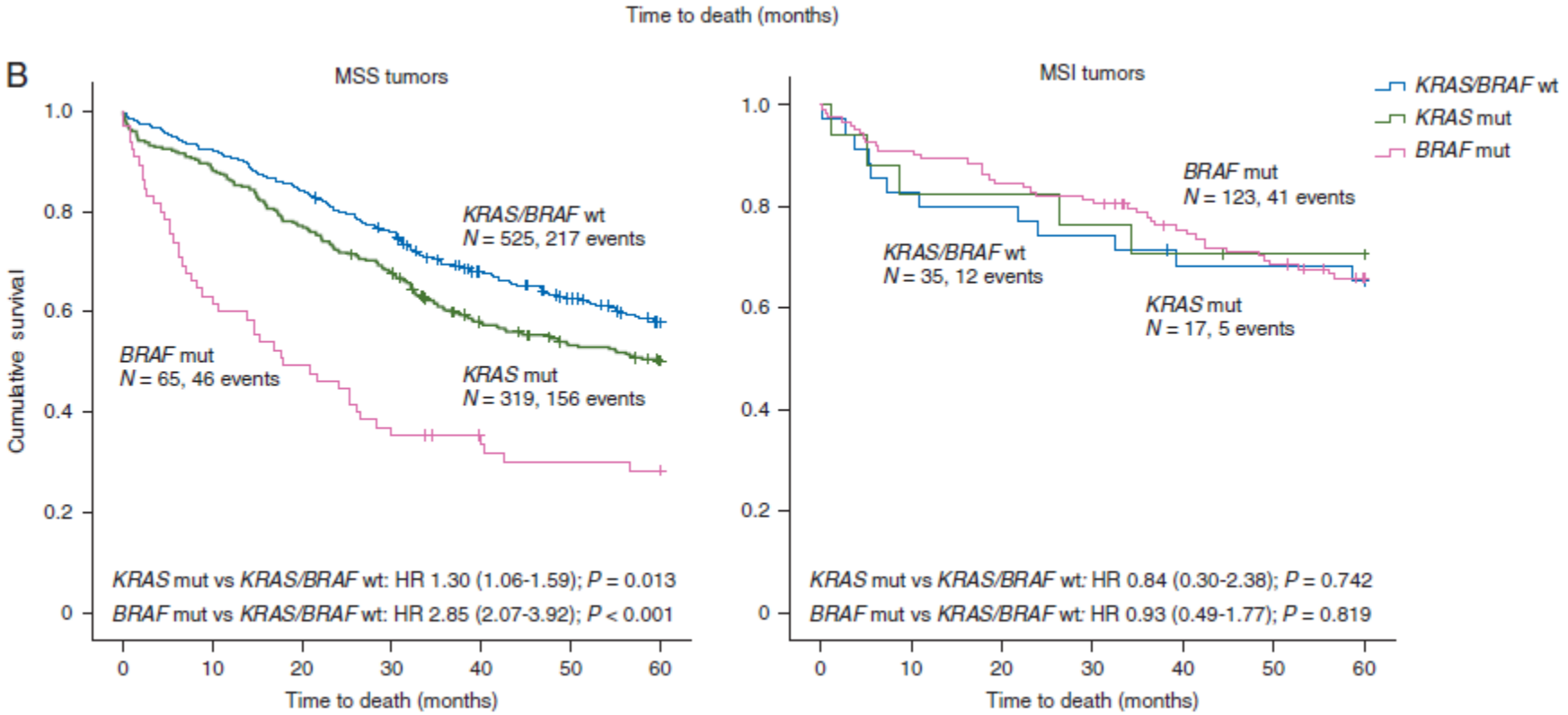
BRAF V600E mut. Colorectal Cancer Subtypes



D. Barras et al. Clin Cancer Res 2017

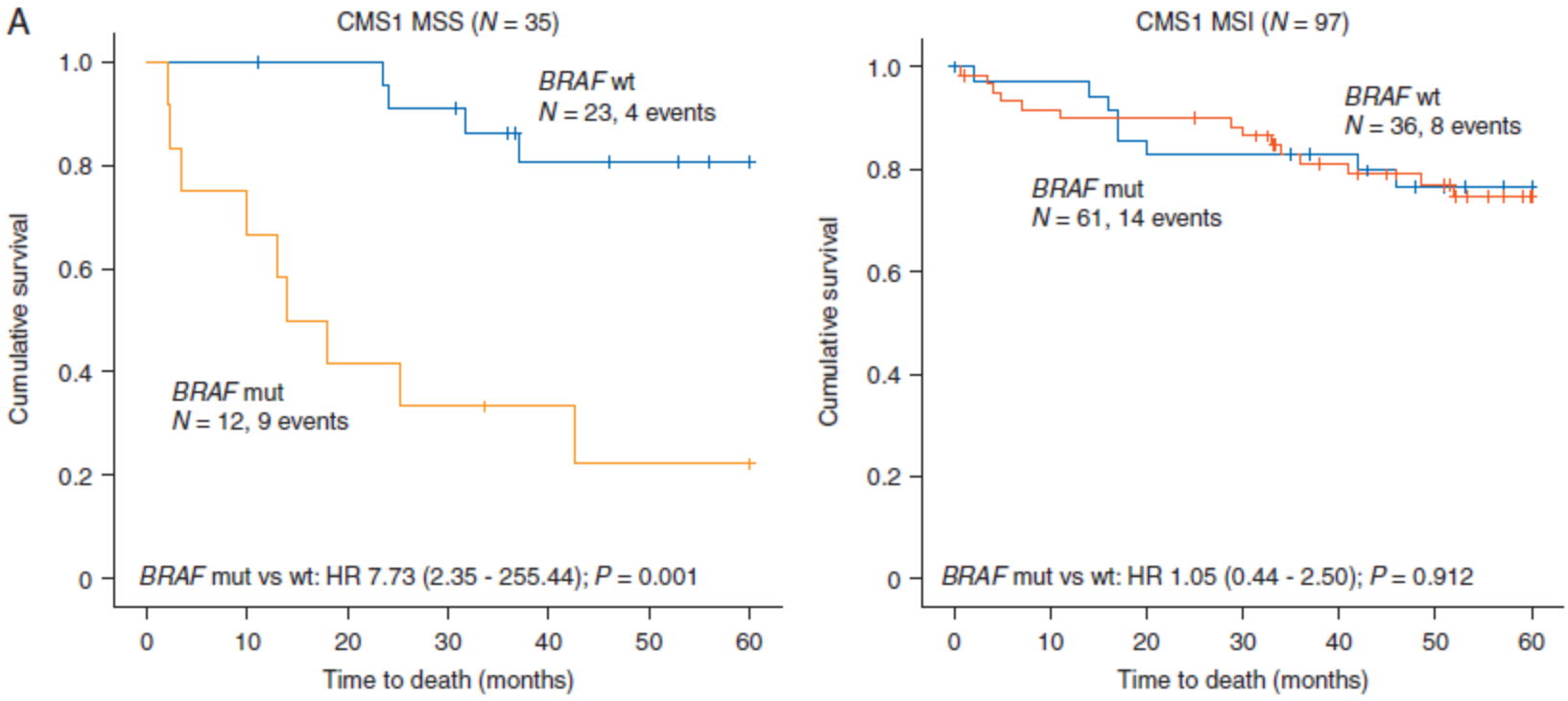
RAS/BRAF mut. en función de MSI y CMS-1 Factor Pronóstico varía

1197 tumores primarios E I-IV



J. Smeby et al. Annals of Oncology 2018

BRAF mut. en función de MSI y CMS-1 Factor Pronóstico varía



J. Smeby et al. Annals of Oncology 2018

Prognostic Effect of *BRAF V600E* Mutations in CRC

In stage II/III disease, the prognostic effect of *BRAF V600E* mutations on survival depends on the mismatch repair (MMR) proficiency context

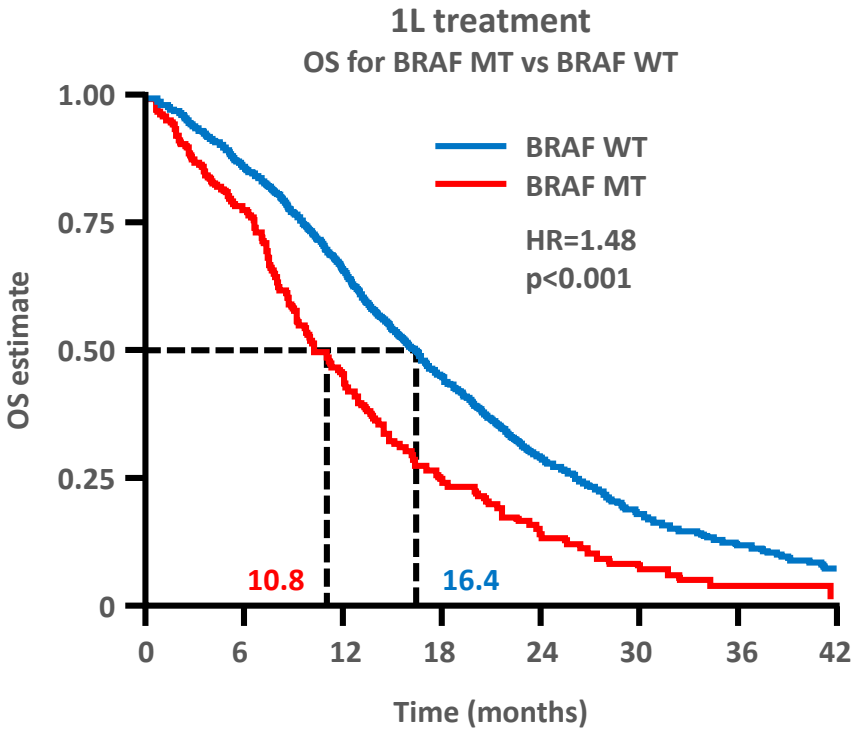
Key trials	MSI-High Tumors (deficient for MMR) *BRAF V600E* mutations do not affect overall prognosis	Microsatellite Stable (MSS) tumors (proficient for MMR) *BRAF V600E* mutations appear associated with poor prognosis
Phase 3 PETACC-3 trial[1] • Evaluating the addition of irinotecan to adjuvant fluoropyrimidine therapy • Stage II and III disease • Evaluable N = 1,307	• No outcome differences in *BRAF* WT or *V600E* were observed in the subgroup with high MSI • The number of evaluable patients in this group was low (n=190)	• In the group with low MSI or MSS, patients with *BRAF V600E* mutations had worse outcomes – Relapse-free survival (RFS): Hazard Ratio (HR) = 1.49; *P* = 0.067 – Overall survival (OS): HR = 2.19; *P* = 0.00034
Phase 3 NCCTG N0147[2] • Evaluating the addition of cetuximab to adjuvant FOLFOX therapy • Stage III disease • Evaluable N = 2,720	• No differences in outcomes in patients with MSI tumors, whether they had familial (*BRAF* WT) or sporadic (*BRAF V600E*) cancers	• Patients with *BRAF V600E* mutations had worse disease-free survival (DFS) (HR = 1.78; *P* < 0.0001)

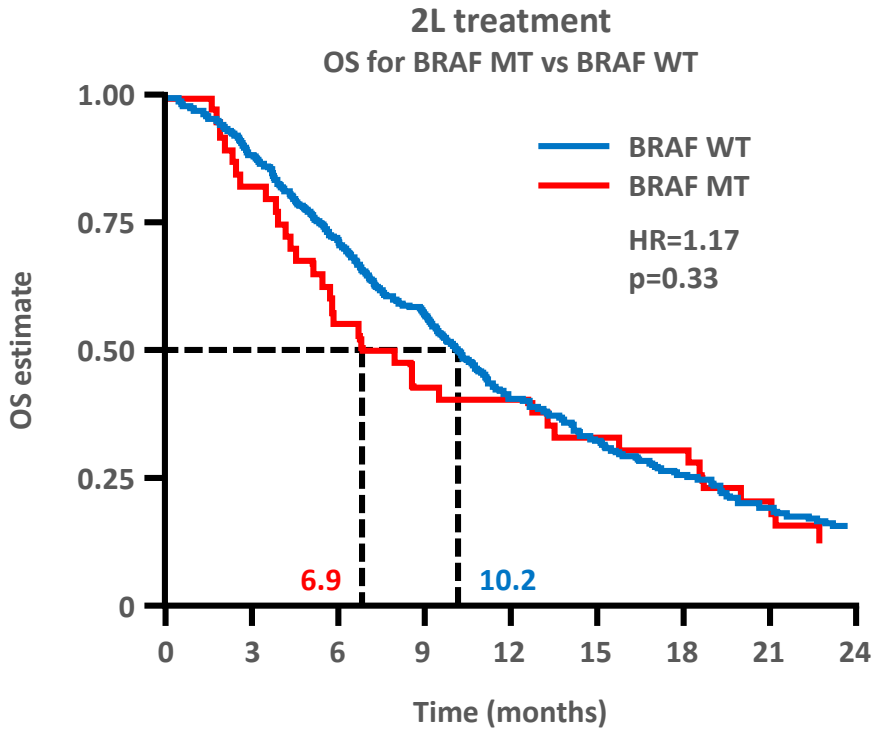
PETACC = Pan European Trial Adjuvant Colon Cancer; NCCTG = North Central Cancer Treatment Group.

1. Roth AD, et al. *J Clin Oncol*. 2010;28:466-474; 2. Sinicrope FA, et al. *Gastroenterology*. 2015;148:88-99.

BRAF MT associated with a poor prognosis

BRAF MT patients have a significantly shorter median OS in 1L;
only 39% of BRAF MT patients vs 60% BRAF WT received 2L treatment

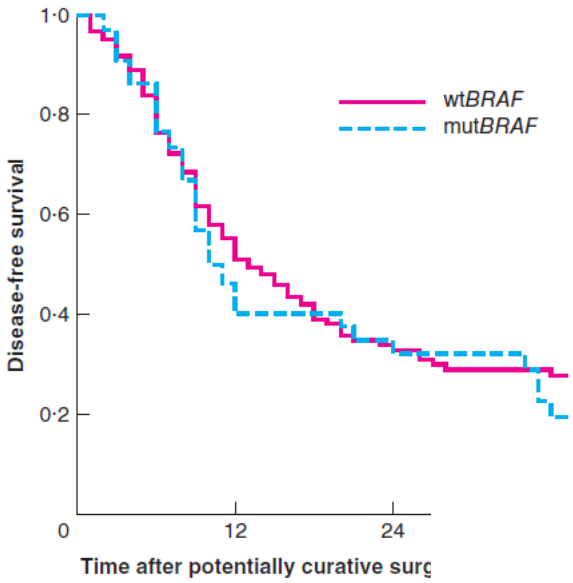




Seligmann, JF et al. et al. ASCO 2015
Seligmann JF et al. Ann Oncol 2017

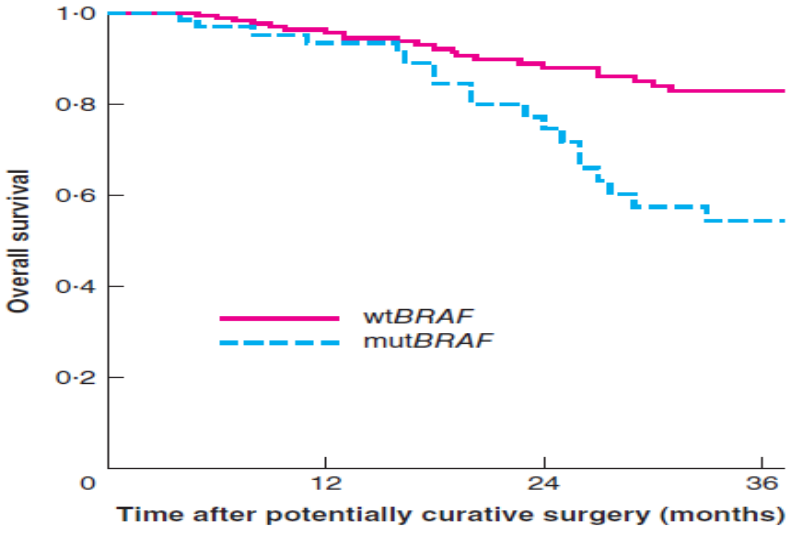
Cirugía de metástasis hepáticas en BRAF mutado

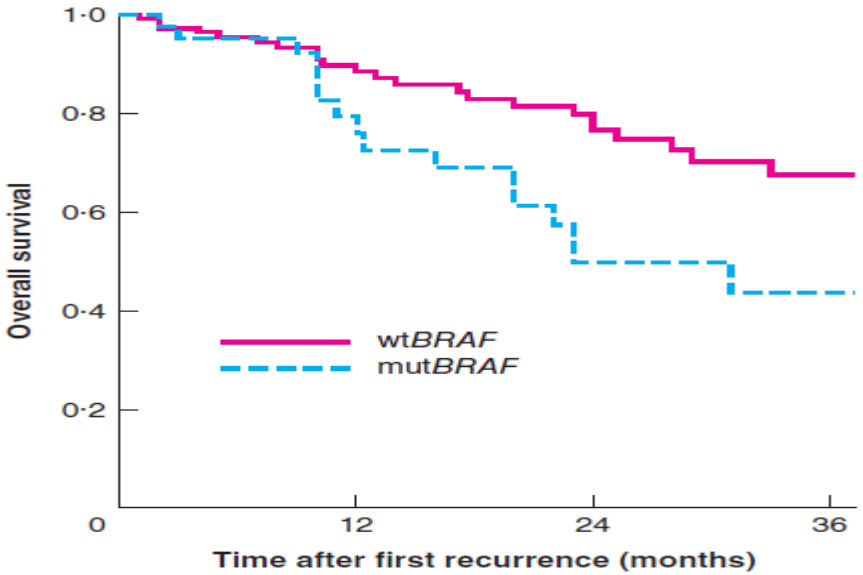
nationwide intergroup (ACHBT, FRENCH, AGEO 24 centros 2012-2016). BRAF mut 66; vs BRAF wt 183 ;



No. at risk

wt*BRAF*	183	85	34
mut*BRAF*	66	22	12



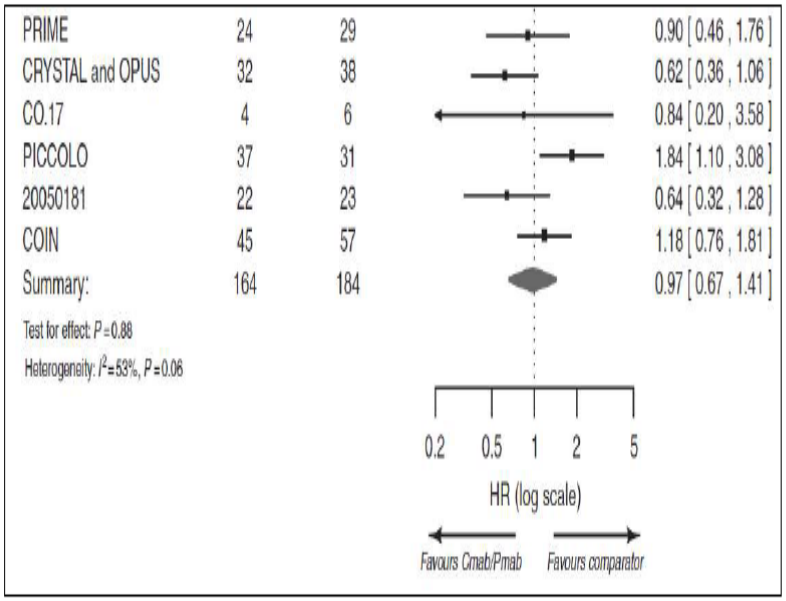


J.-B. Bachet et al. BJS 2019

Meta-análisis BRAF mutado

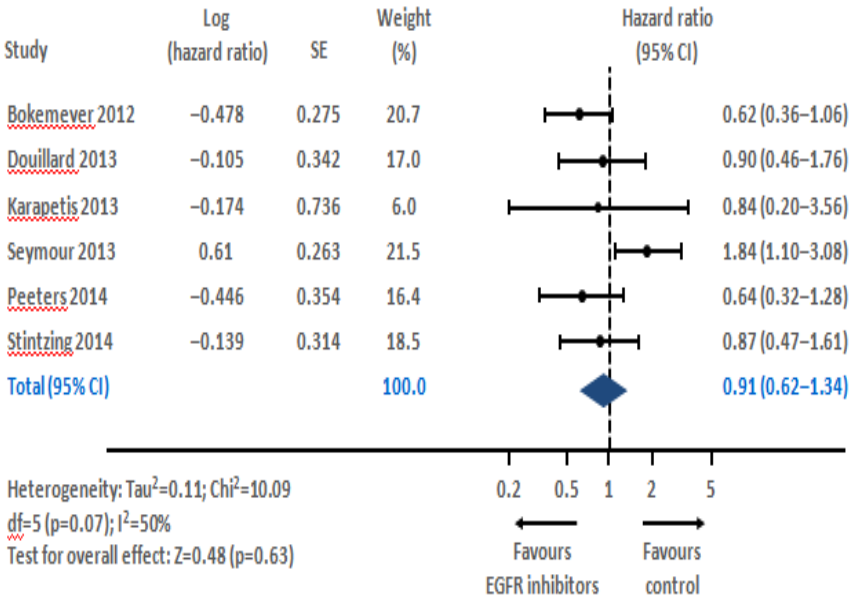
Meta-analysis, 7 Randomized, controlled trials

KRAS WT BRAF MT



Rowland A et al. 2015;112:1888-94

Meta-analysis of randomised clinical trials of cetuximab or panitumumab

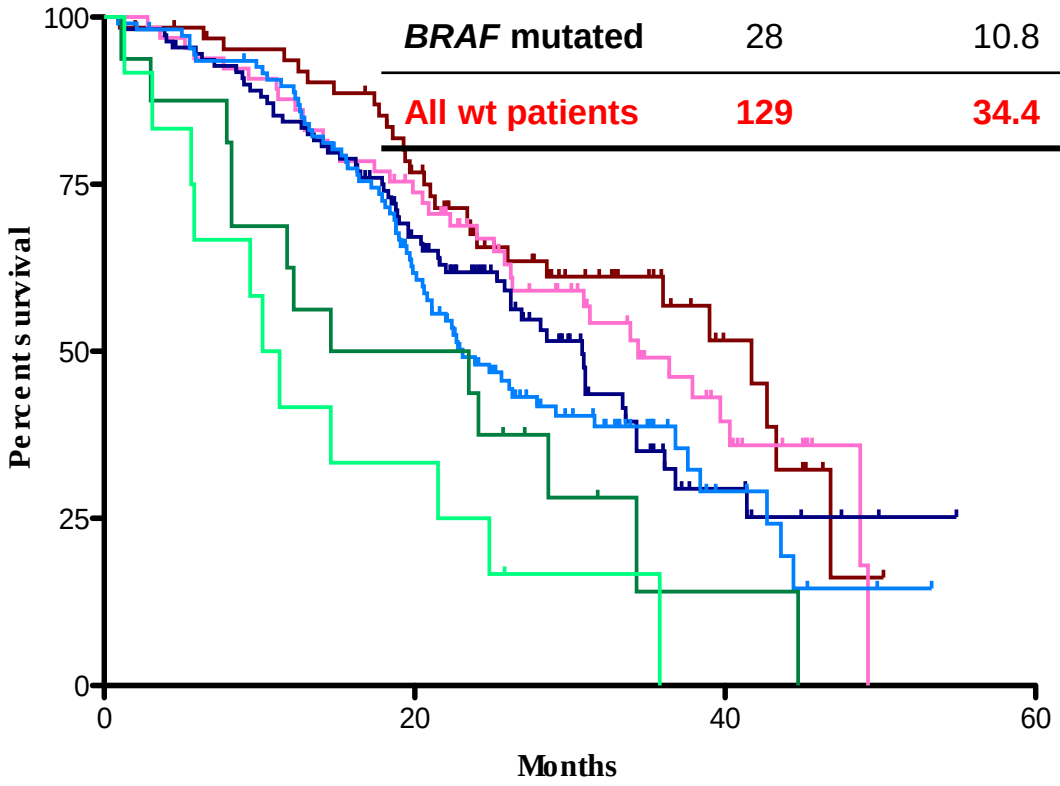


EGFR inhibitors are authorised only for RAS WT mCRC

Pietrantonio, et al. Eur J Cancer 2015

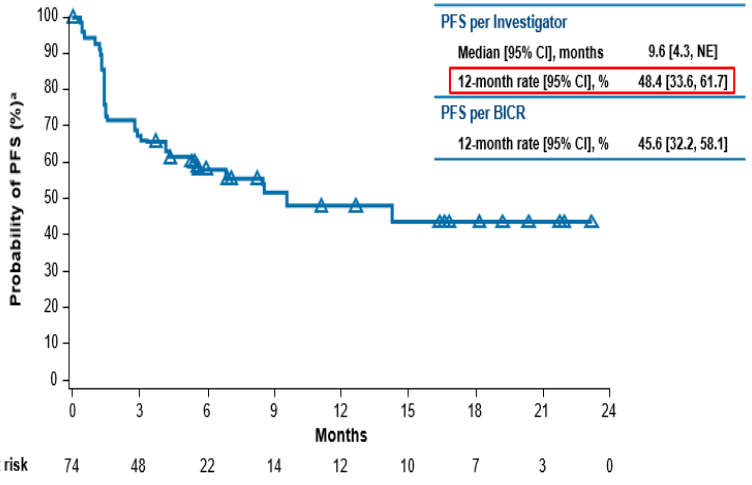
TRIBE Predictive impact - OS

	N	FOLFIRI + bev Arm A Median OS	FOLFOXIRI + bev Arm B Median OS	HR [95% CI]
ITT population	508	25.8	31.0	0.79 [0.63-1.00]
***R&B* evaluable**	375	25.8	31.0	0.86 [0.65-1.12]
***RAS* mutated**	218	23.1	30.8	0.86 [0.60-1.22]
***BRAF* mutated**	28	10.8	19.1	0.55 [0.24-1.23]
All wt patients	**129**	**34.4**	**41.7**	**0.85 [0.52-1.39]**



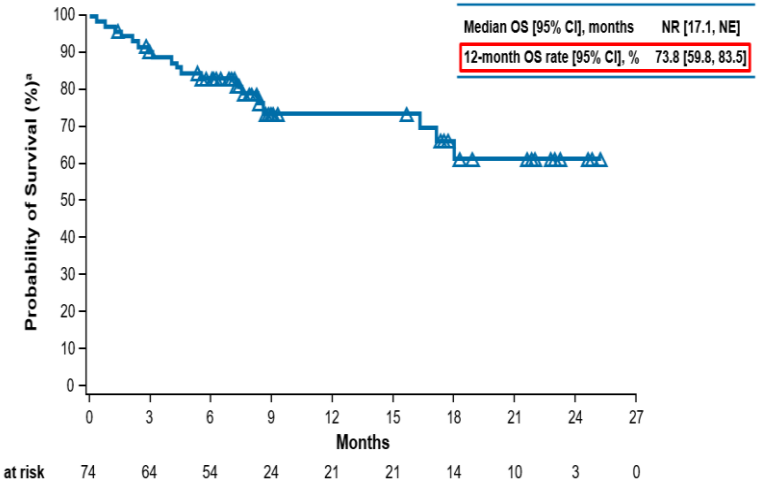
CheckMate 142: MMR-D pts treated with Nivo (74 pts)

Progression-Free Survival



PFS per Investigator	
Median [95% CI], months	9.6 [4.3, NE]
12-month rate [95% CI], %	48.4 [33.6, 61.7]
PFS per BICR	
12-month rate [95% CI], %	45.6 [32.2, 58.1]

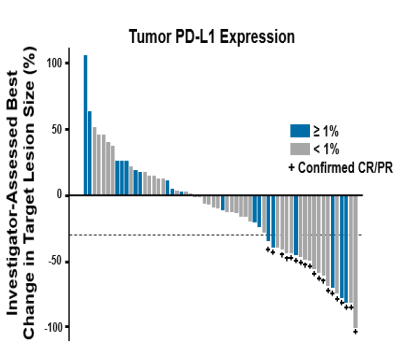
Overall Survival



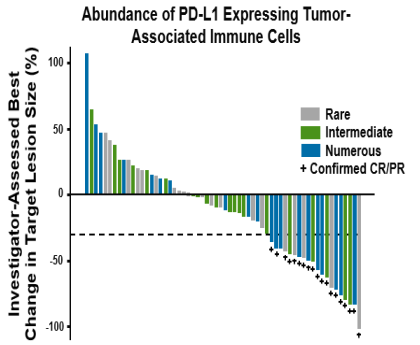
Median OS [95% CI], months	NR [17.1, NE]
12-month OS rate [95% CI], %	73.8 [59.8, 83.5]

Overman ASCO-GI 2017; Lancet 2017

Reduction in Target Lesions Regardless of PD-L1 Expression

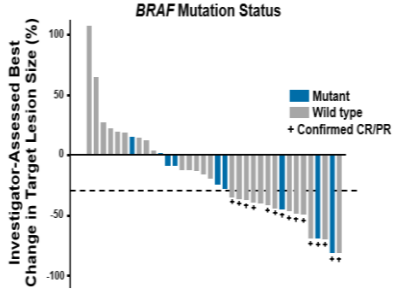


ORR, n/N (%)	Investigator	BICR
Tumor PD-L1 expression		
≥ 1%	6/21 (28.6)	7/20 (35.0)
< 1%	13/45 (28.9)	11/45 (24.4)

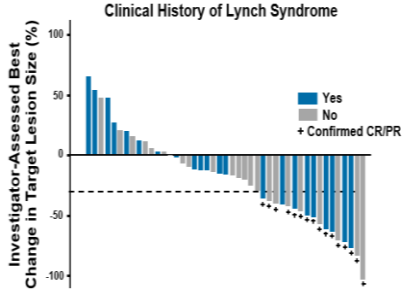


ORR, n/N (%)	Investigator	BICR
Abundance of PD-L1 expressing immune cells		
Rare	5/23 (21.7)	4/22 (18.2)
Intermediate	5/20 (25.0)	4/20 (20.0)
Numerous	9/23 (39.1)	10/23 (43.5)

Reduction in Target Lesions Regardless of *BRAF* Mutation Status and Lynch Syndrome



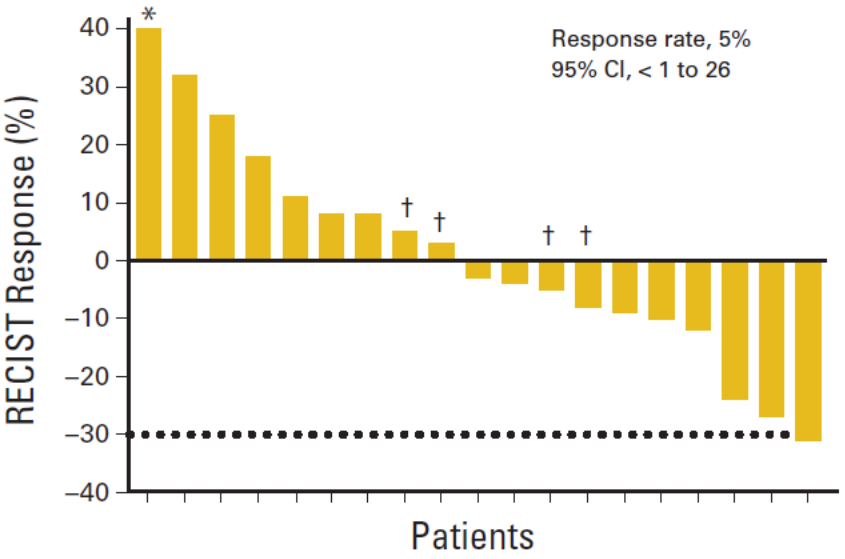
ORR, n/N (%)	Investigator	BICR
BRAF mutation status		
Mutant	3/12 (25.0)	2/12 (16.7)
Wild type	12/28 (42.9)	9/27 (33.3)
KRAS mutation status		
Mutant	7/26 (26.9)	6/26 (23.1)
Wild type	12/28 (42.9)	9/27 (33.3)

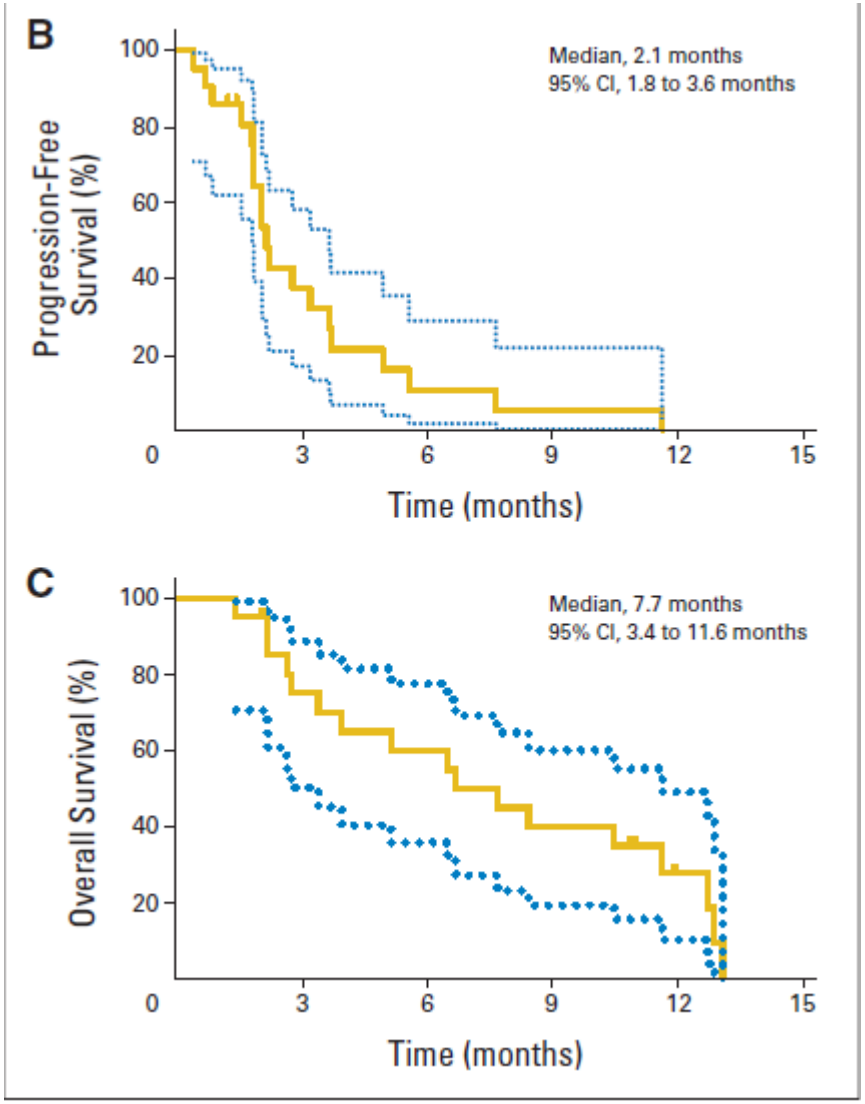


ORR, n/N (%)	Investigator	BICR
Clinical history of Lynch syndrome		
Yes	8/23 (34.8)	8/23 (34.8)
No	8/26 (30.8)	6/26 (23.1)

n/N, responders/evaluable patients.

Vemurafenib

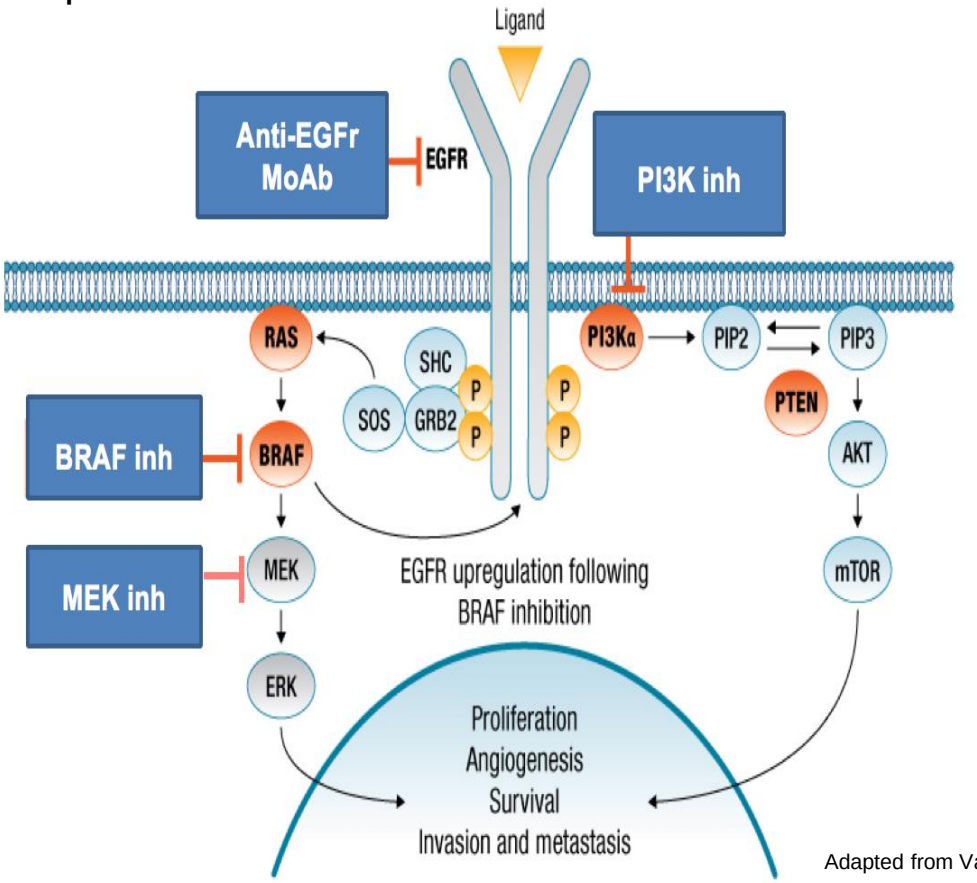




Kopets S et al. J Clin Oncol 2015

BRAF INHIBITION IN mCRC

EGFR signaling is inhibited by hyperactive BRAF. In the presence of BRAF inhibitor, EGFR signaling is reactivated either by the BRAF-MEK pathway or the PI3K-AKT pathway, resulting in cellular proliferation and survival[1,2]



Adapted from Van Geel et al. ASCO 2014

1. Corcoran et al. Nature 2012, 2. Prahallad et al. Cancer Discovery 2012

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Encorafenib, Binimetinib, and Cetuximab in *BRAF* V600E–Mutated Colorectal Cancer

S. Kopetz, A. Grothey, R. Yaeger, E. Van Cutsem, J. Desai, T. Yoshino, H. Wasan, F. Ciardiello, F. Loupakis, Y.S. Hong, N. Steeghs, T.K. Guren, H.-T. Arkenau, P. Garcia-Alfonso, P. Pfeiffer, S. Orlov, S. Lonardi, E. Elez, T.-W. Kim, J.H.M. Schellens, C. Guo, A. Krishnan, J. Dekervel, V. Morris, A. Calvo Ferrandiz, L.S. Tarpgaard, M. Braun, A. Gollerkeri, C. Keir, K. Maharry, M. Pickard, J. Christy-Bittel, L. Anderson, V. Sandor, and J. Tabernero

BEACON

Patients with *BRAF*^{V600E} mCRC with disease progression after 1 or 2 prior regimens; ECOG PS of 0 or 1; and no prior treatment with any RAF inhibitor, MEK inhibitor, or EGFR inhibitor

Safety Lead-in

ENCORAFENIB + BINIMETINIB + CETUXIMAB
N = 30

Encorafenib 300 mg PO daily
Binimetinib 45 mg PO bid
Cetuximab standard weekly dosing

Phase 3

R 1:1:1

Triplet therapy
ENCORAFENIB + BINIMETINIB + CETUXIMAB
n = 205

Doublet therapy
ENCORAFENIB + CETUXIMAB
n = 205

Control arm
FOLFIRI + CETUXIMAB, or irinotecan + CETUXIMAB
n = 205

Primary Endpoints:

Triplet vs Control

OS
(All randomized Pts)

ORR – Blinded Central Review
(1st 331 randomized Pts)

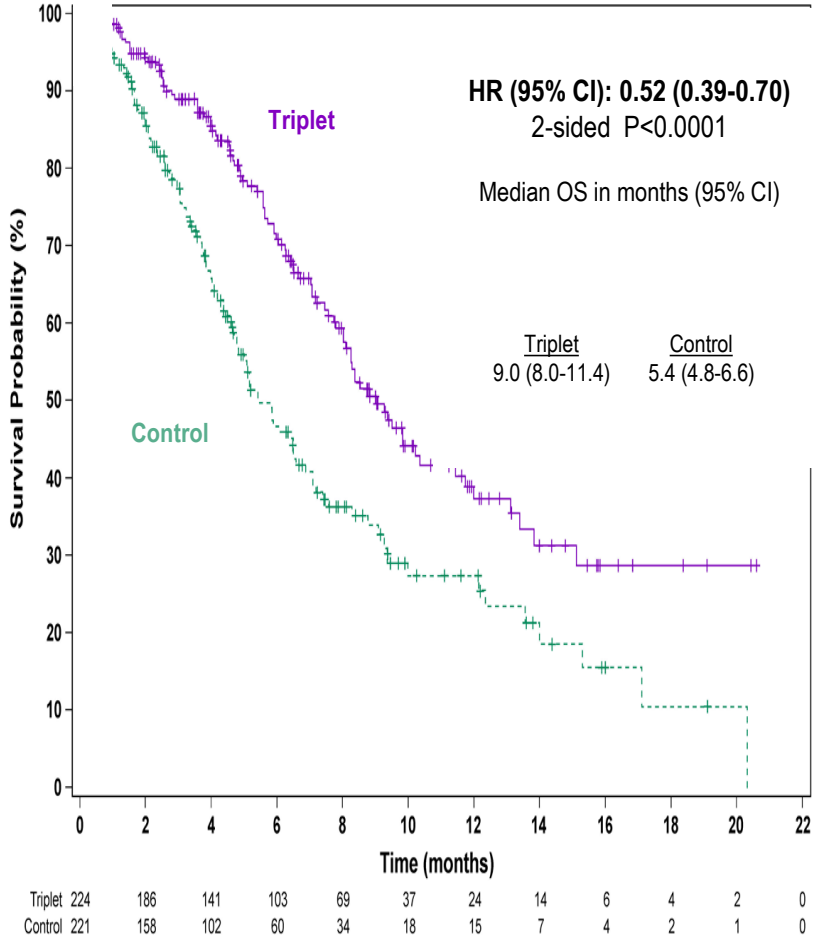
Randomization was stratified by ECOG PS (0 vs. 1), prior use of irinotecan (yes vs. no), and cetuximab source (US-licensed vs. EU-approved)

Secondary Endpoints: Doublet vs Control and Triplet vs Doublet - OS & ORR, PFS, Safety

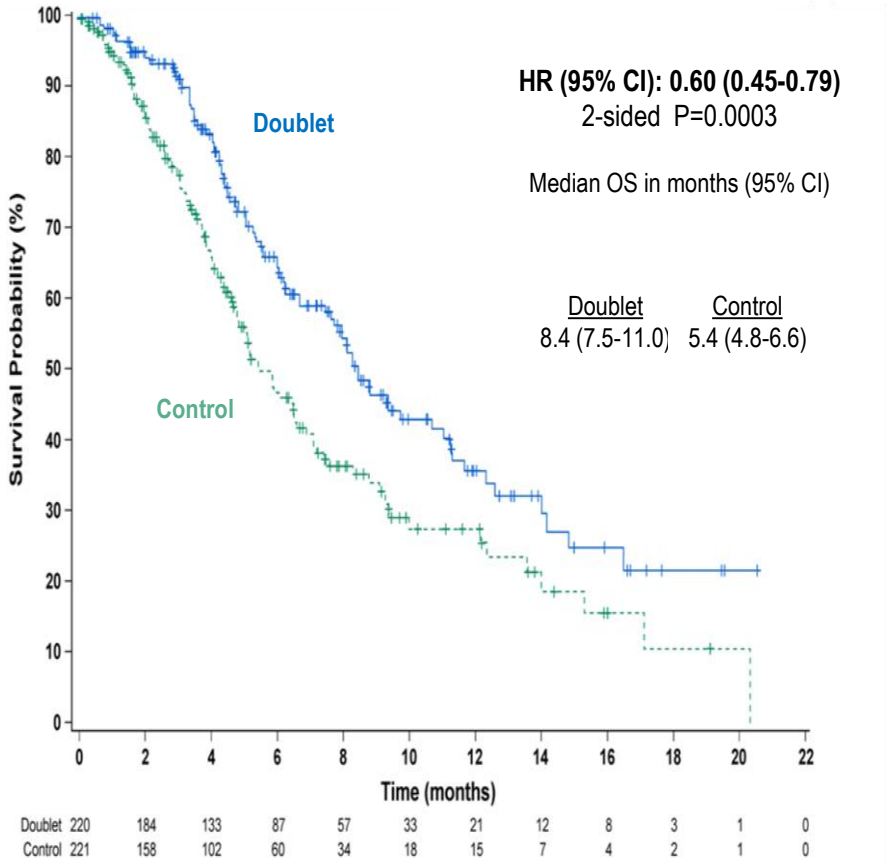
QOL Assessments: EORTC QOL Questionnaire (QLQ C30), Functional Assessment of Cancer Therapy Colon Cancer, EuroQol 5D5L, and Patient Global Impression of Change).

Overall Survival and Objective Response Rate

Triplet vs Control



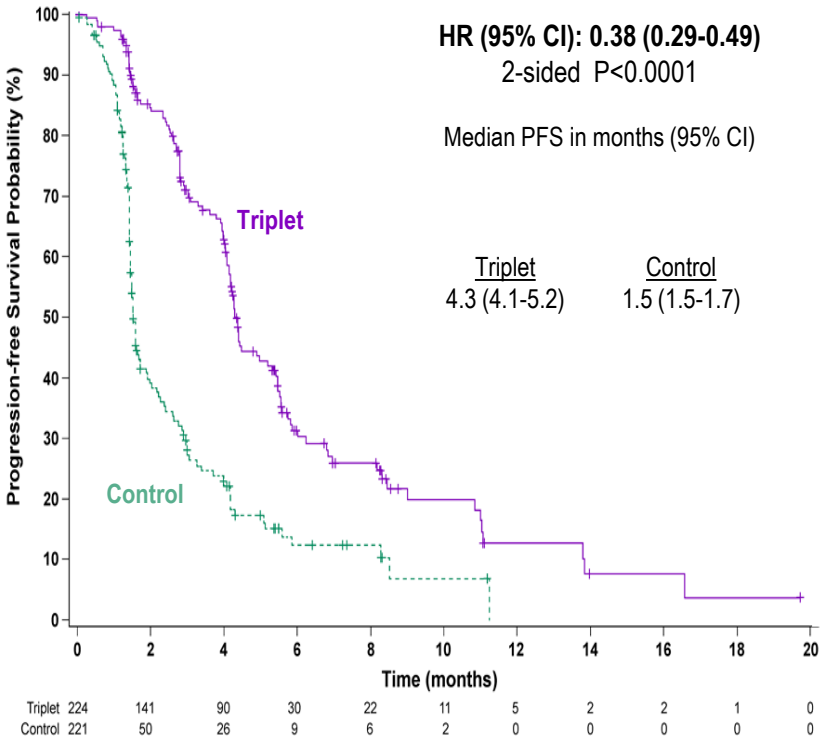
Doublet vs Control



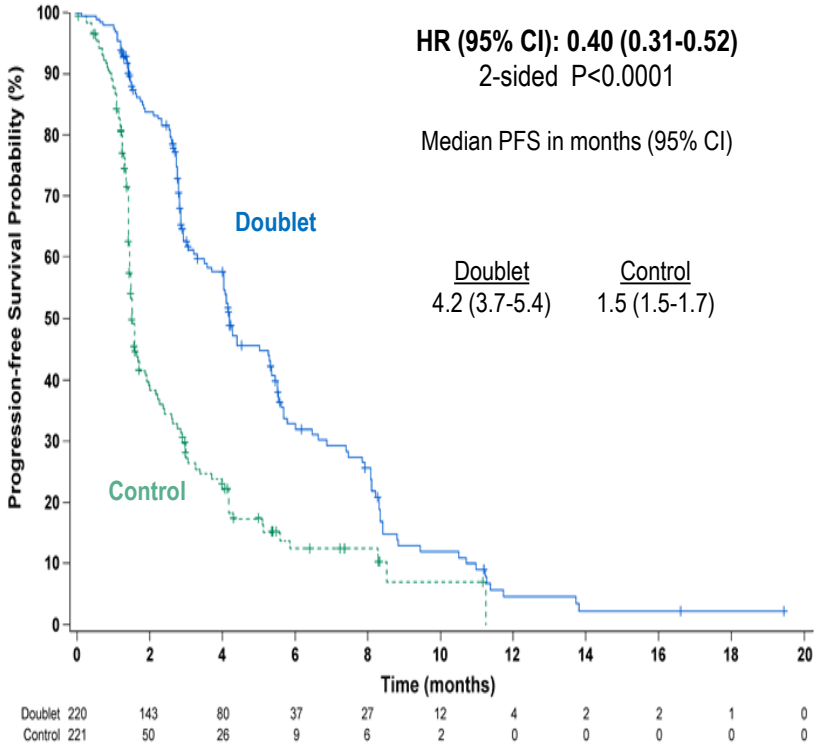
Kopetz et al. Ann Oncol 2019;30 (Supplement 4): iv137–iv151 (LBA-006).

Progression Free Survival (All Randomized Patients)*

Triplet vs Control



Doublet vs Control

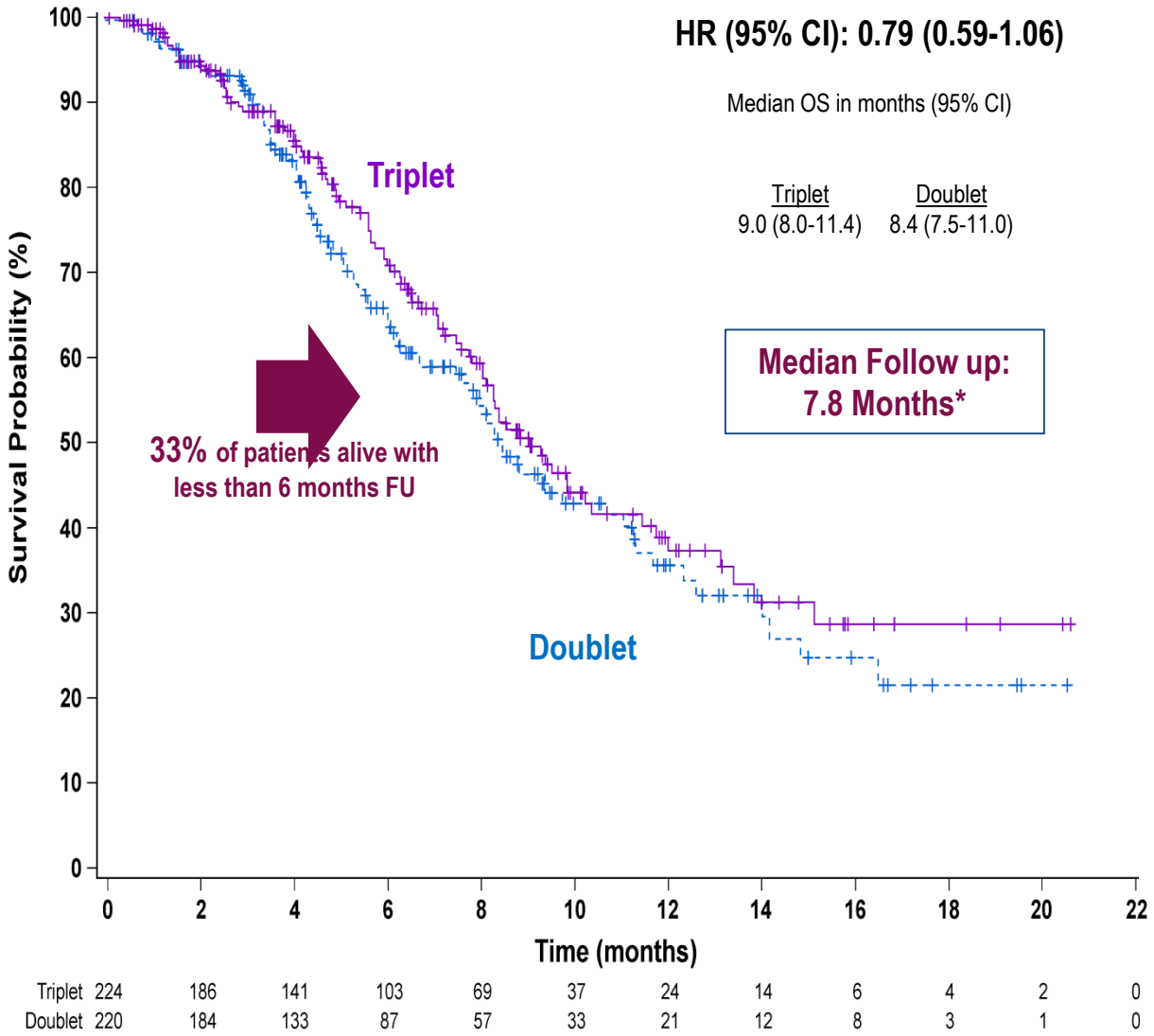


*PFS by BICR (blinded independent central review).

Kopetz et al. Ann Oncol 2019;30 (Supplement 4): iv137–iv151 (LBA-006).

Overall Survival: Triplet vs Doublet (All Randomized Patients)

Study not powered to formally compare the results of the triplet combination to the doublet combination



*all randomized patients.

Objective Response Rate (first 331 randomized patients)

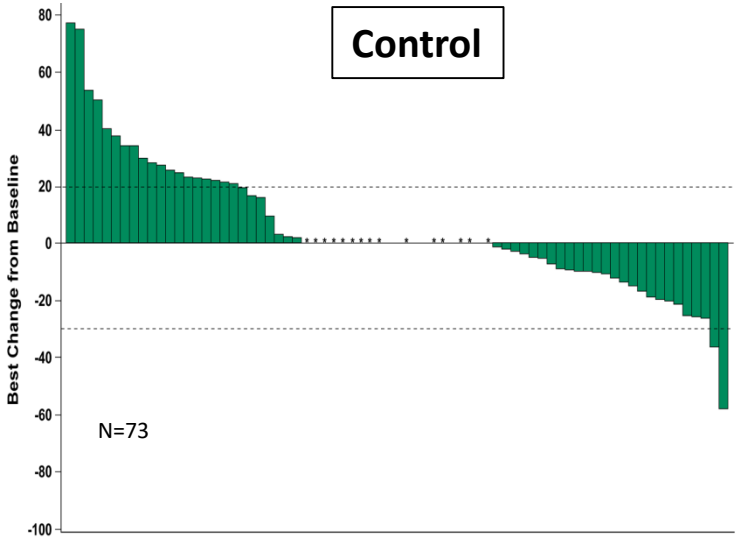
Confirmed Response by BICR	Triplet N=111	Doublet N=113	Control N=107
Objective Response Rate	**26%**	**20%**	**2%**
95% (CI)	(18, 35)	(13, 29)	(<1, 7)
p-value vs. Control	<0.0001	<0.0001	
Objective Response Rate			
1 prior line of therapy	**34%**	**22%**	**2%**
>1 prior line of therapy	14%	16%	2%
Best Overall Response			
Complete Response	4%	5%	0
Partial Response	23%	15%	2%
Stable Disease	42%	54%	29%
Progressive Disease	10%	7%	34%
Non Evaluable by RECIST	22%	19%	36%
Clinical progression or adverse event[a]	14%	17%	16%
Insufficient information to assess response[b]	8%	2%	20%

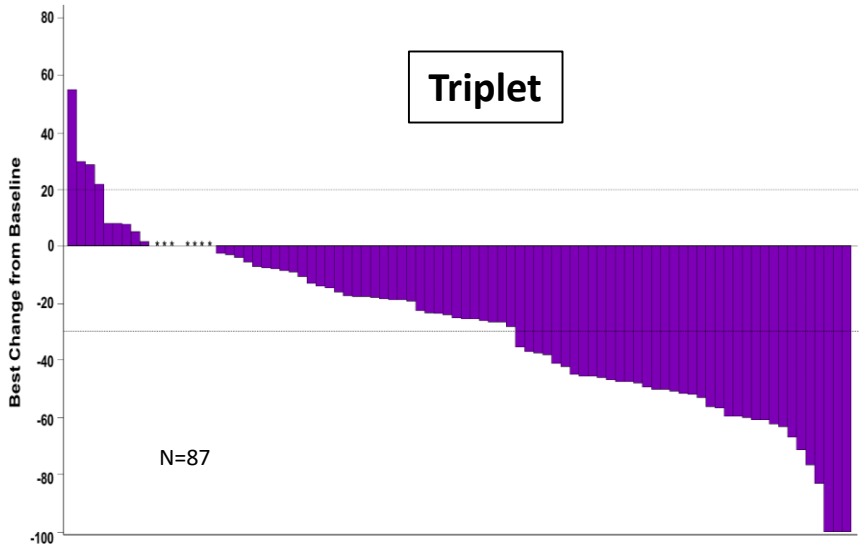
BICR=blinded independent central review.

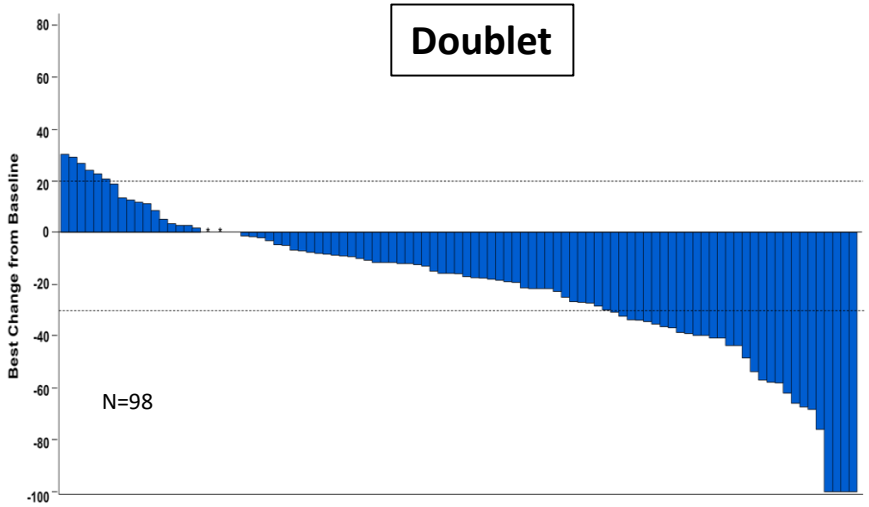
a. Includes patients considered not evaluable by central assessment with clinical progression or radiological progression by local assessment or discontinuation due to adverse event.

b. Includes patients who were untreated, withdrew consent, had stable disease < 42 days, had no baseline scans, or had no post-baseline scans without evidence of clinical progression or adverse event as the reason for missing scans.

Waterfall Plots of Best Change in Sum of Diameters
(based on central review)





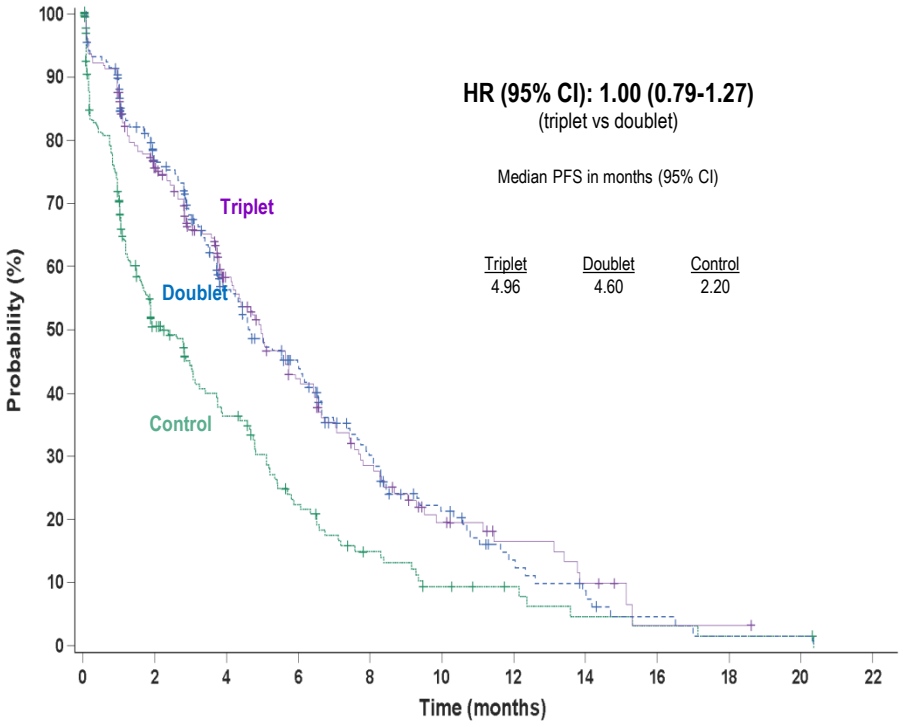


*Patients whose SoD was contraindicated by assessment of PD. SoD=sum of longest diameter. Includes patients with measurable disease with a baseline and at least one post-baseline scan.

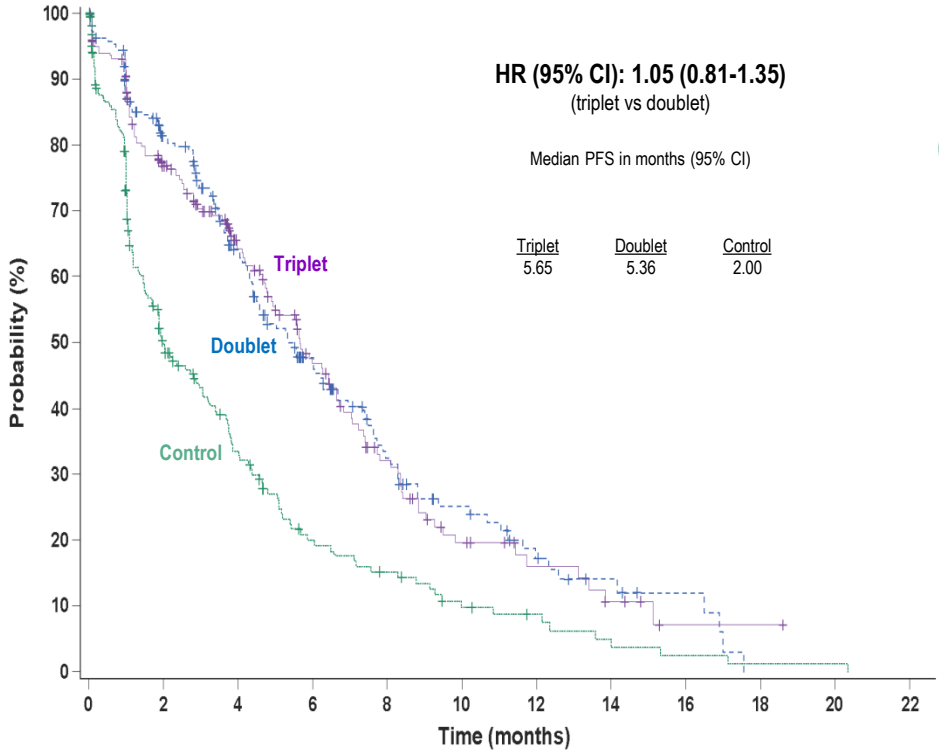
Maintenance of Quality of Life

QOL Assessments: EORTC QOL Questionnaire (QLQ C30), Functional Assessment of Cancer Therapy Colon Cancer, EuroQol 5D5L, and Patient Global Impression of Change.

Time to Definitive 10% Deterioration in EORTC QLQ-c30 Global Health Status



Time to Definitive 10% Deterioration in FACT-C Colorectal Cancer Subscale



- Similar results with all EORTC QLQ c30 and FACT-C subscales and PGIC

Conclusions

- In the BEACON CRC study, encorafenib, binimetinib and cetuximab (triplet), and encorafenib and cetuximab (doublet) regimens both significantly improved OS and ORR relative to standard of care (control) in patients with *BRAF*^{V600E} mutant mCRC, a population with historically dismal outcomes
- Triplet vs Doublet:
  - Data suggest that the triplet offers improved efficacy with some additional manageable toxicity and no relative impact on maintenance of QoL compared to the doublet
  - The safety and tolerability profile of both combinations allow maintenance of high dose intensity for most patients and are consistent with the known profiles of the component agents
  - Triplet regimen mitigated some BRAF associated toxicities

- **BEACON CRC study results provide a new standard of care in patients with previously treated *BRAF* V600E-mutant mCRC**
- **Data suggest the triplet regimen may have clinically relevant advantages over the doublet**
- **Further follow-up will better define the relative benefits of the two regimens**

Conclusiones

- La identificación de las alteraciones de la vía MAPK y en concreto de la mutación BRAF ha supuesto un avance en el conocimiento y en el tratamiento de estas neoplasias.
- La mutación de BRAF define a tumores muy agresivos con mala respuesta al tratamiento clásico
- Los resultados terapéuticos con inhibidores de BRAF y MEK son un ejemplo de terapia dirigida a oncogenes y validan la dependencia de estos tumores de la vía MAPK

¡ Muchas Gracias!

pgarcaalfonso@gmail.com

Alianza para la prevención
del cáncer de colon