CLÍNIC
BARCELONA
Hospital Universitari

Terapias a dianas moleculares en melanoma

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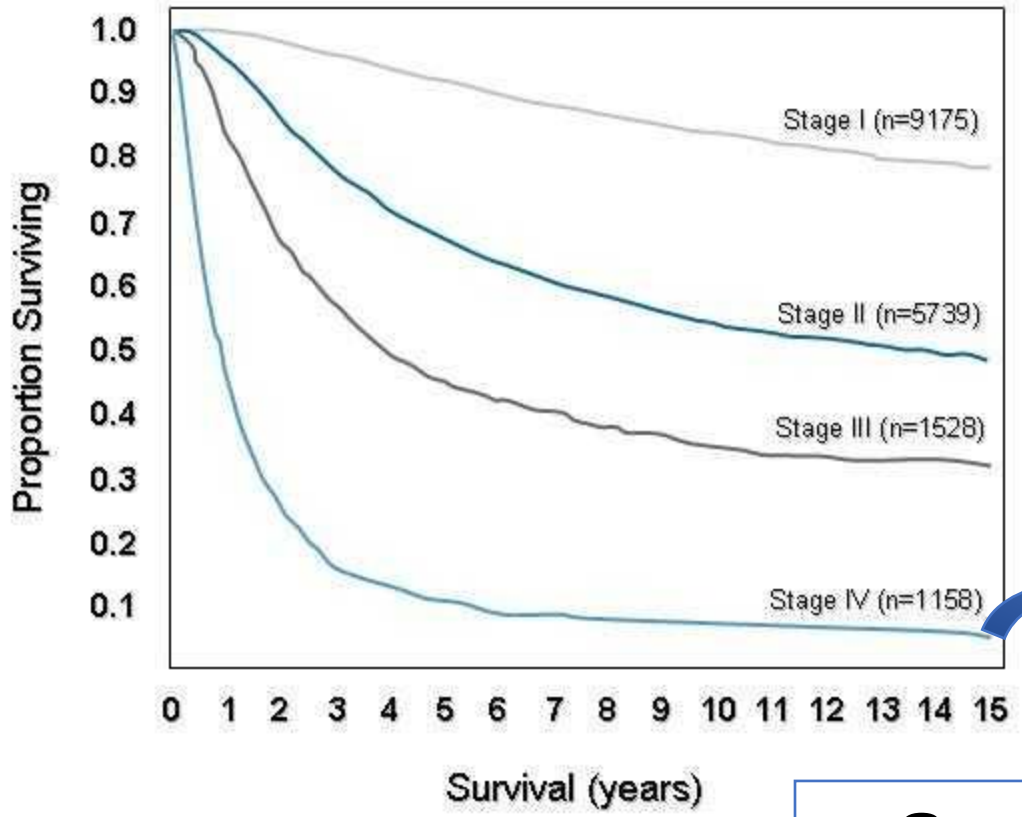
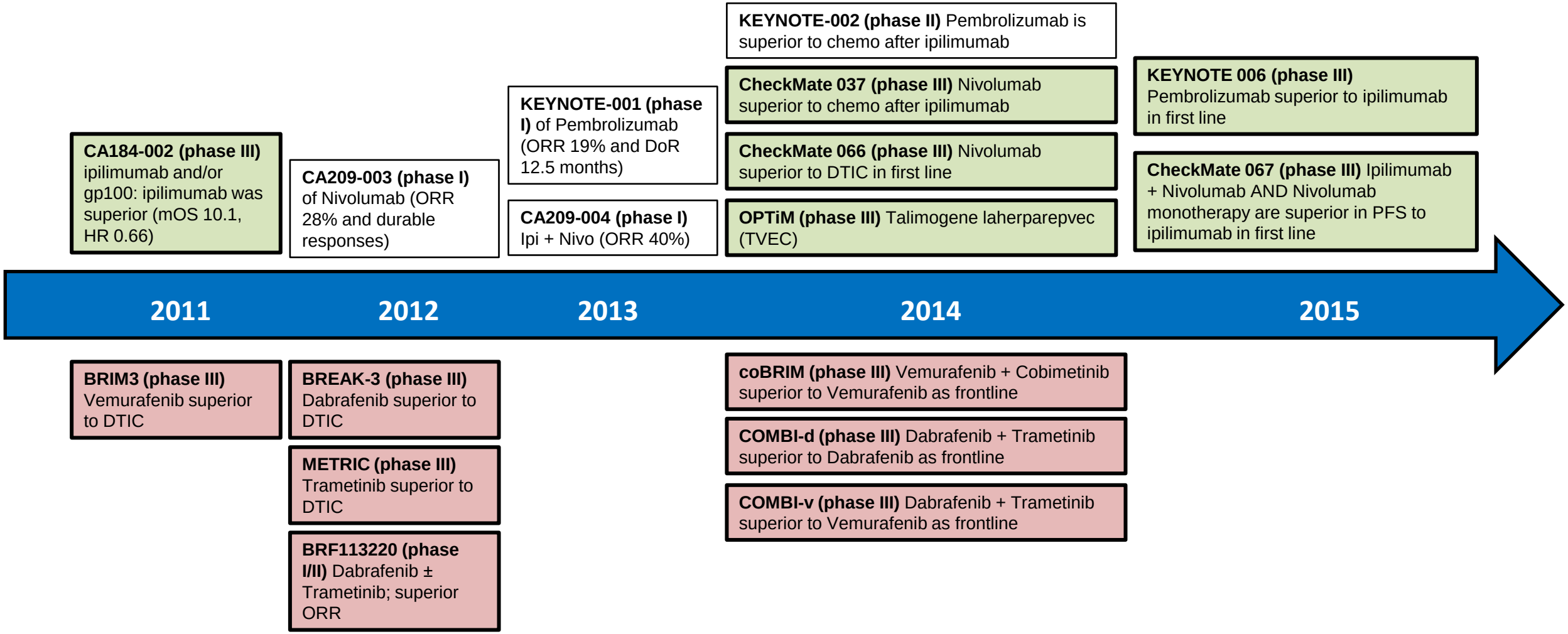
Survival in Melanoma by Stage



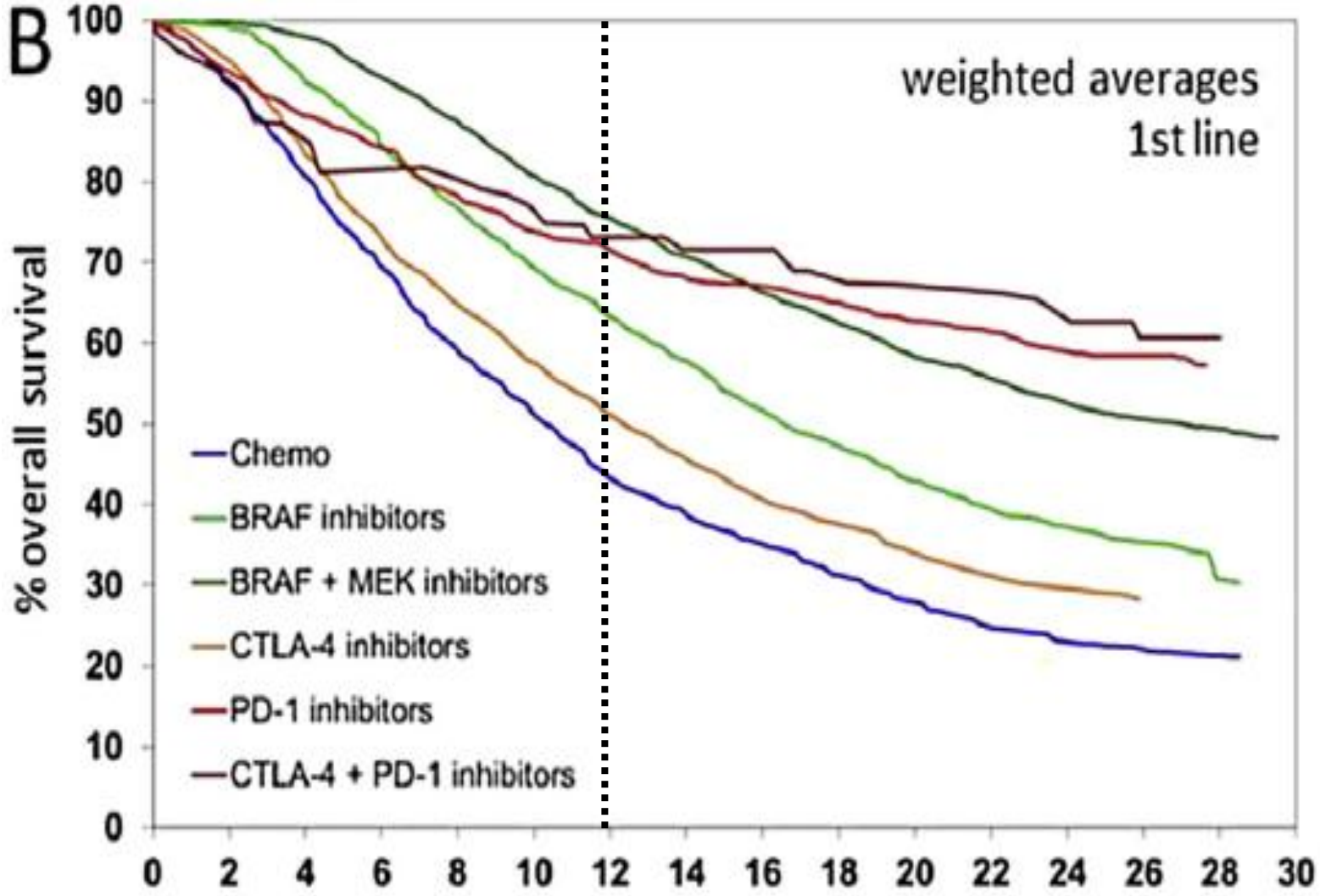
Balch CM, et al. *J Clin Oncol*. 2001;19:3635-3648.

Supervivencia mediana
6-9 meses

Metastatic Melanoma: Treatment Advances



Summary of OS accross clinical trials in patients with metastatic melanoma

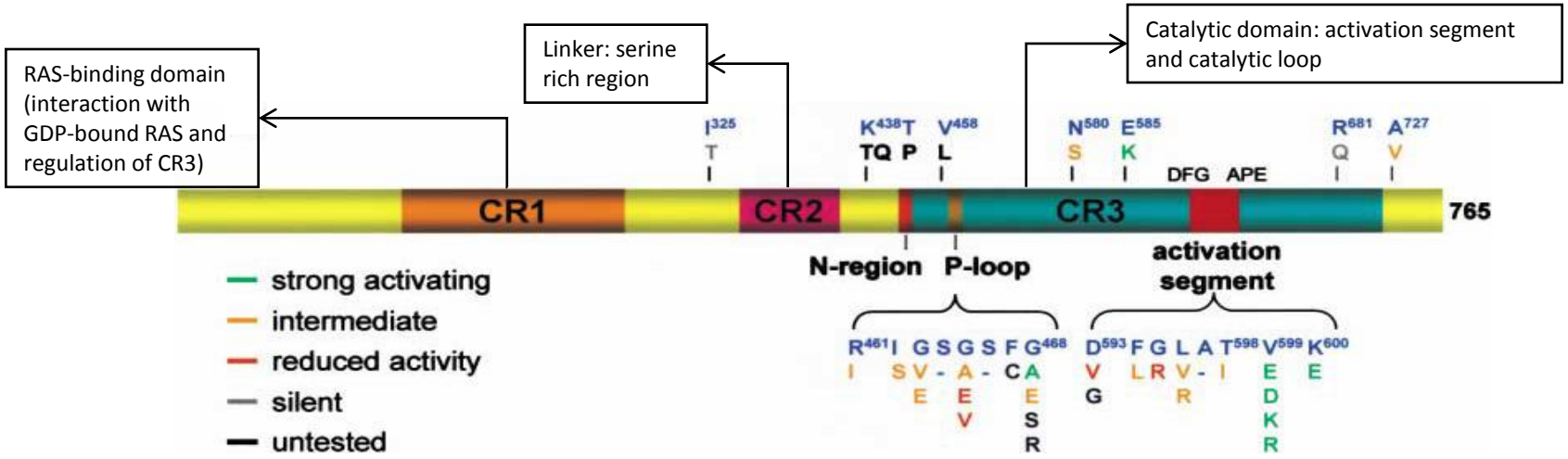


Ugurel et al. Eur J Cancer 2017

BRAF mutant Melanoma

- *BRAF* mutation present in ~50% of melanomas
- *BRAF* gene encodes a serine-threonine kinase

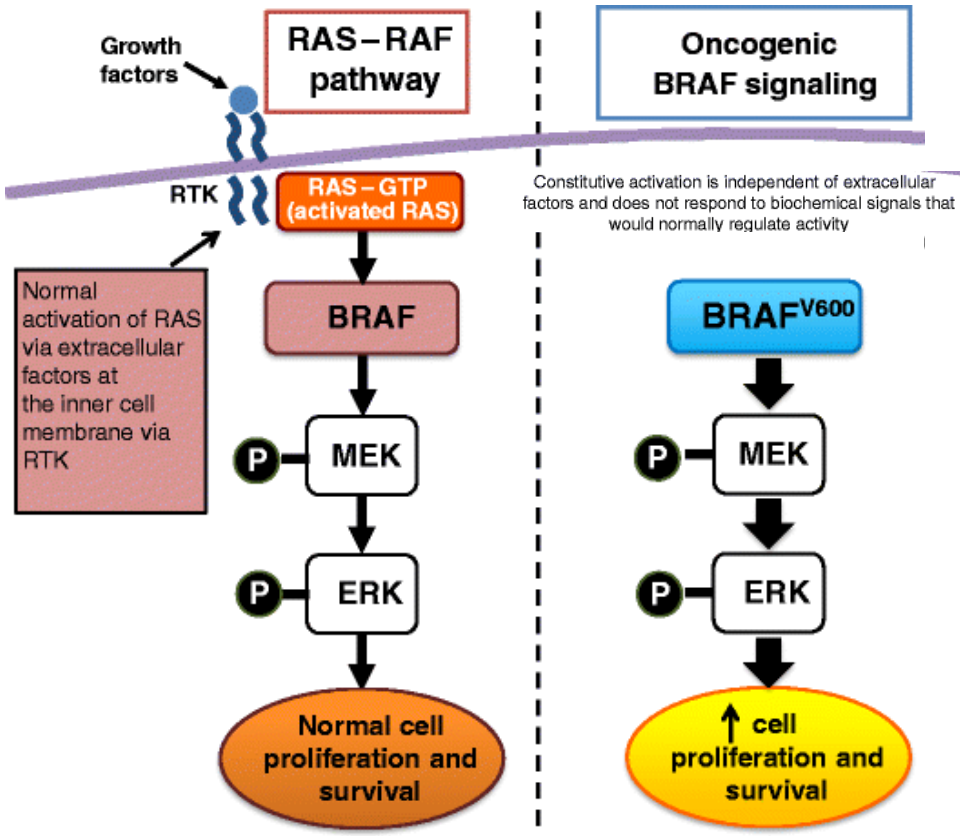
BRAF Mutation, %	
All	45-55%
V600E (val-glu)	70-80%
V600K (val –lys)	15-30%
Other (V600D/R, K601E, G469A, D594G, L597V...)	<5%



Davies H, et al. Nature 2002;417:949-954; Wan PTC, et al. Cell 2004;116:855-867

BRAF and MAPK pathway

- Activating BRAF mutations result in constitutive signaling that leads to oncogenic cell proliferation
- V600 increases the kinase activity (130- 700 fold)
- Other mutations, with reduced ability to activate MEK, promote dimerization with CRAF proteins and increase signaling activity
- BRAF mutations also impacts on microenvironment
  - Immune evasion
  - vascularity



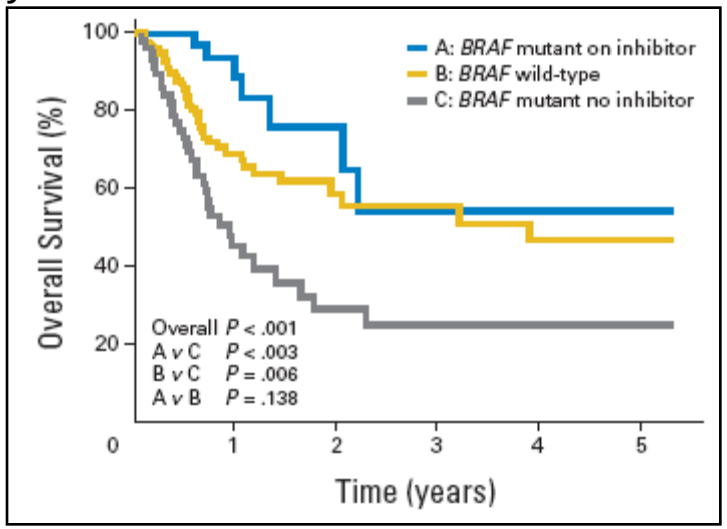
Ascierto PA, et al; Journal of Translational Medicine 2012, 10:85

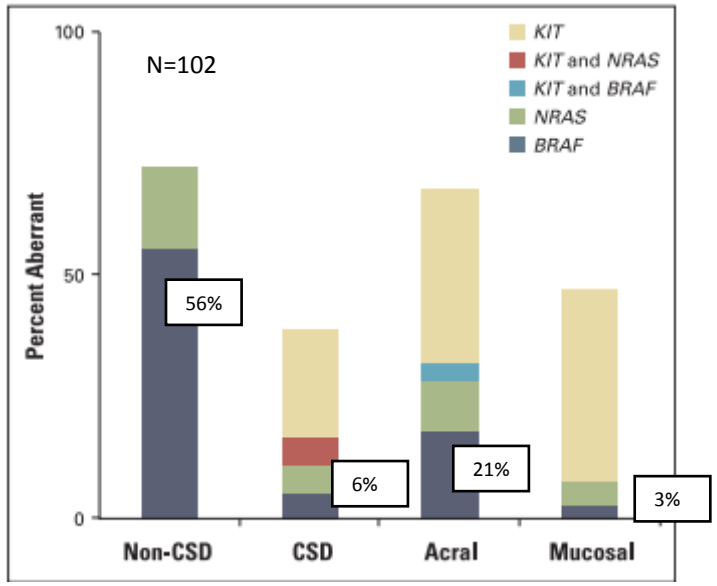
Clinicopathological features

- More common in:
  - younger patients: 55.8 years *BRAF*m vs 63.1 years *BRAF*wt (p<0.001)
  - histopathologic subtype (superficial spreading or nodular melanoma)
  - occult primary melanoma or truncal location
  - Skin without evidence of CSD

Age	No.	BRAF mutant	V600E	V600K
20-30	14	86%	83%	0%
31-40	30	80%	92%	8%
41-50	42	50%	76%	14%
51-60	58	41%	67%	29%
61-70	103	48%	71%	24%
>70	65	22%	50%	21%

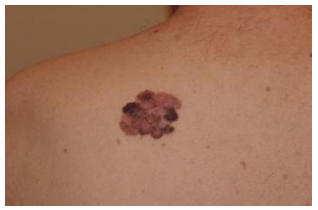
- Unfavorable prognosis in the absence of anti-BRAF directed therapy



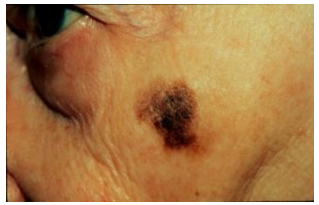


Curtin JA, et al. J Clin Oncol 2006;24:4340-4346; Long GV, et al. J Clin Ocol 2011 29:1239-1246; Menzies AM, et al. J Clin Oncol 29: 2011 (suppl; abstr 8507)

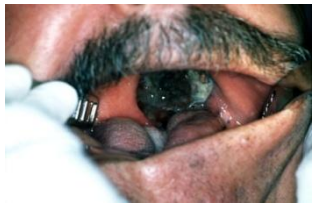
Driver Oncogenic Mutations Define Clinically Relevant Melanoma Molecular Subsets



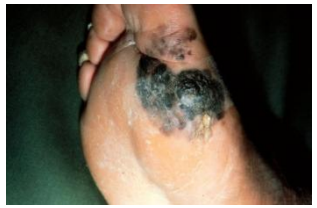
Arising from Skin Without Chronic Sun Damage → 50% BRAF, 20% NRAS, 0% KIT



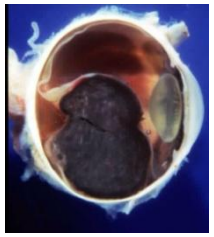
Arising from Skin With Chronic Sun Damage → 10% BRAF, 10% NRAS, 2% KIT



Arising from Mucosal Surfaces → 5% BRAF, 15% NRAS, 20% KIT



Arising from Acral Surfaces → 15% BRAF, 15% NRAS, 15% KIT



Uveal Melanoma → 25% GNAQ, 55% GNA11

Curtin *et al*. NEJM 2005; Curtin *et al*. JCO 2006; Van Raamsdonk *et al*., NEJM 2010

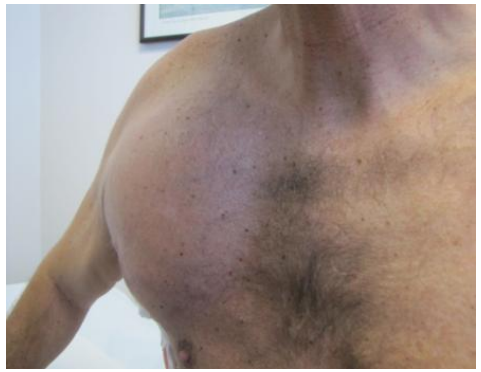
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 AUGUST 26, 2010 VOL. 363 NO. 9

Inhibition of Mutated, Activated BRAF in Metastatic Melanoma

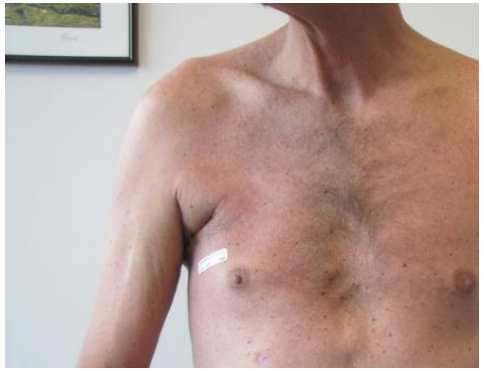
Keith T. Flaherty, M.D., Igor Puzanov, M.D., Kevin B. Kim, M.D., Antoni Ribas, M.D., Grant A. McArthur, M.B., B.S., Ph.D., Jeffrey A. Sosman, M.D., Peter J. O'Dwyer, M.D., Richard J. Lee, M.D., Ph.D., Joseph F. Grippo, Ph.D., Keith Nolop, M.D., and Paul B. Chapman, M.D.

- Phase I study
  - N=49 patients dose escalation + 32 patients extension phase
  - **MTD: 960mg bid**
  - DLT: g2-3 rash, fatigue and arthralgia (4/6 patients in 1120mg bid)
  - Tumor shrinkage **81%**; mPFS 7 months

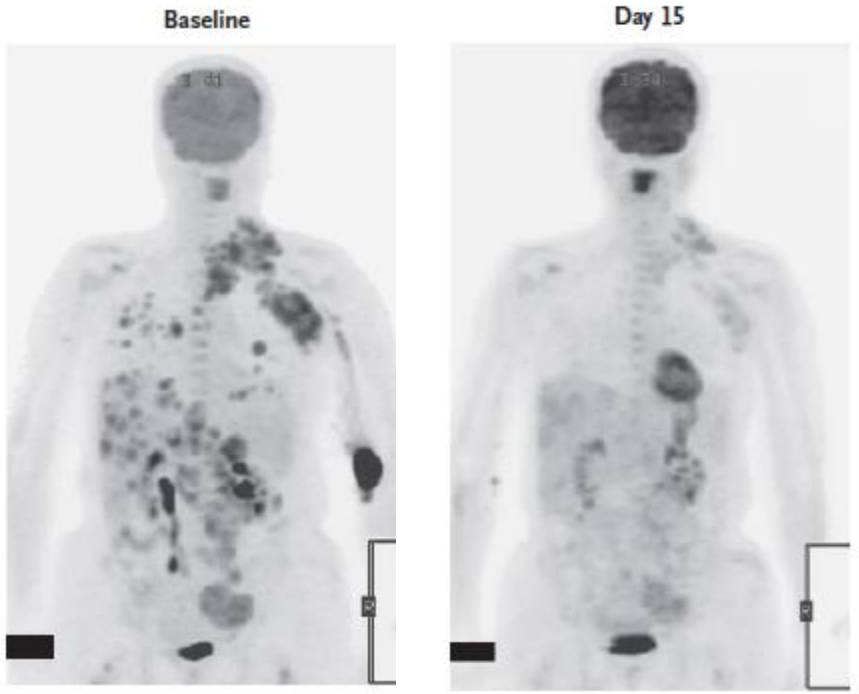
Baseline, 3/2011



Cycle 4 Day 1, 6/2011



BRAFi induce early responses



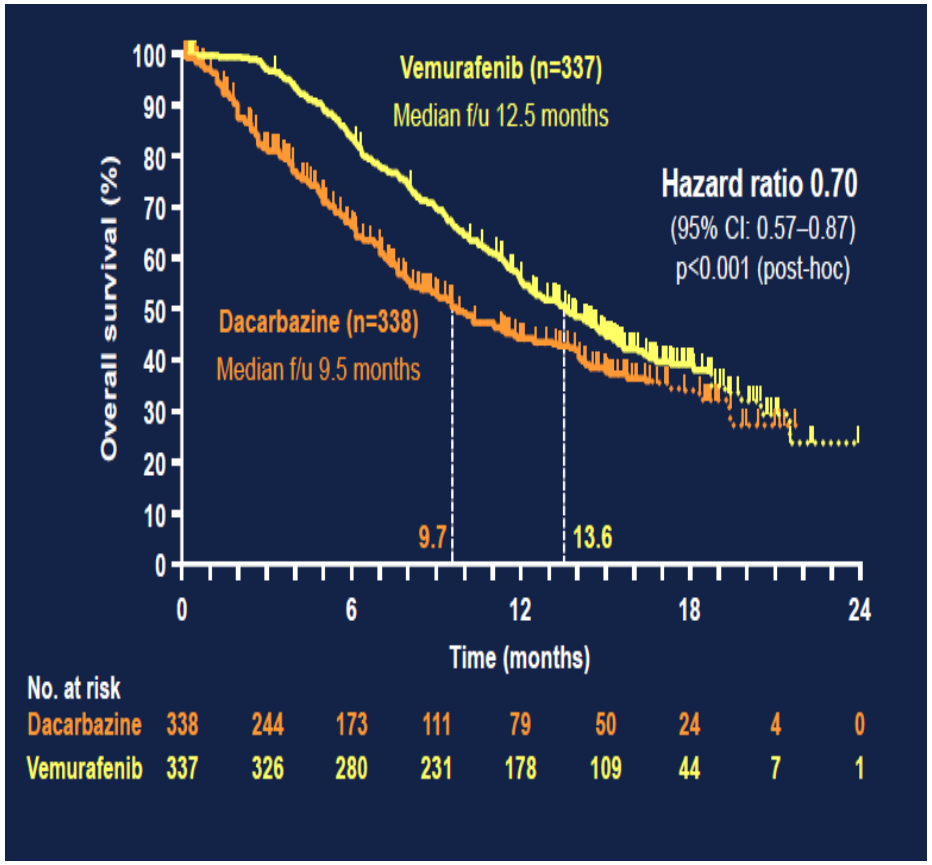
Flaherty FT, et al. N Engl J Med 2010;363:809-19; Mc Arthur et al. J Clin Oncol 2012

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

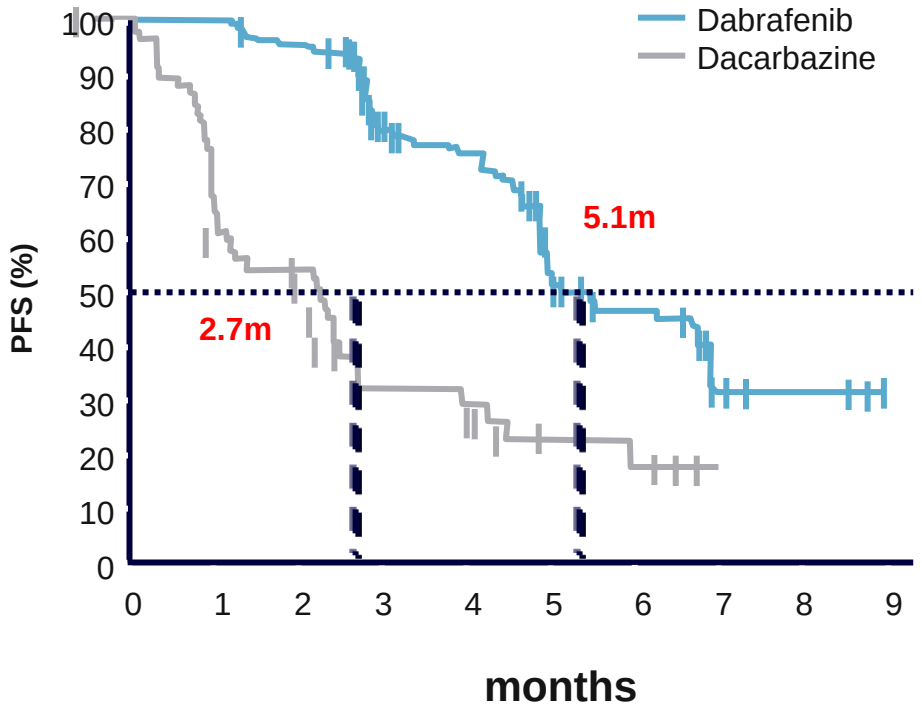
Paul B. Chapman, M.D., Axel Hauschild, M.D., Caroline Robert, M.D., Ph.D., John B. Haanen, M.D., Paolo Ascierto, M.D., James Larkin, M.D., Reinhard Dummer, M.D., Claus Garbe, M.D., Alessandro Testori, M.D.,



Chapman P.B. N Engl J Med , June 2011; Lancet Oncol 2014; 15: 323–32

Dabrafenib in *BRAF*-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial

Axel Hauschild, Jean-Jacques Grob, Lev V Demidov, Thomas Jouary, Ralf Gutzmer, Michael Millward, Piotr Rutkowski, Christian U Blank, Wilson H Miller Jr, Eckhart Kaempgen, Salvador Martin-Algarra, Boguslawa Karaszewska, Cornelia Mauch, Vanna Chiarion-Sileni, Anne-Marie Martin, Suzanne Swann, Patricia Haney, Beloo Mirakhur, Mary E Guckert, Vicki Goodman, Paul B Chapman



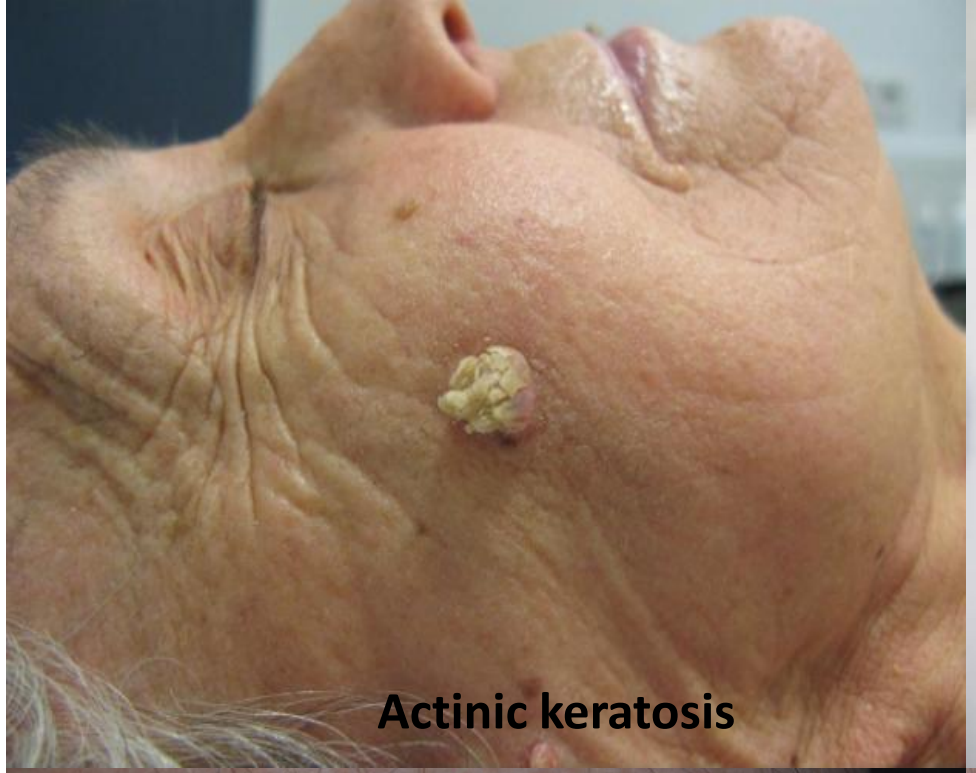
Hauschild A, et al. Lancet Oncol. 2012;380:358-365.

Common toxicities with Vemurafenib and Dabrafenib

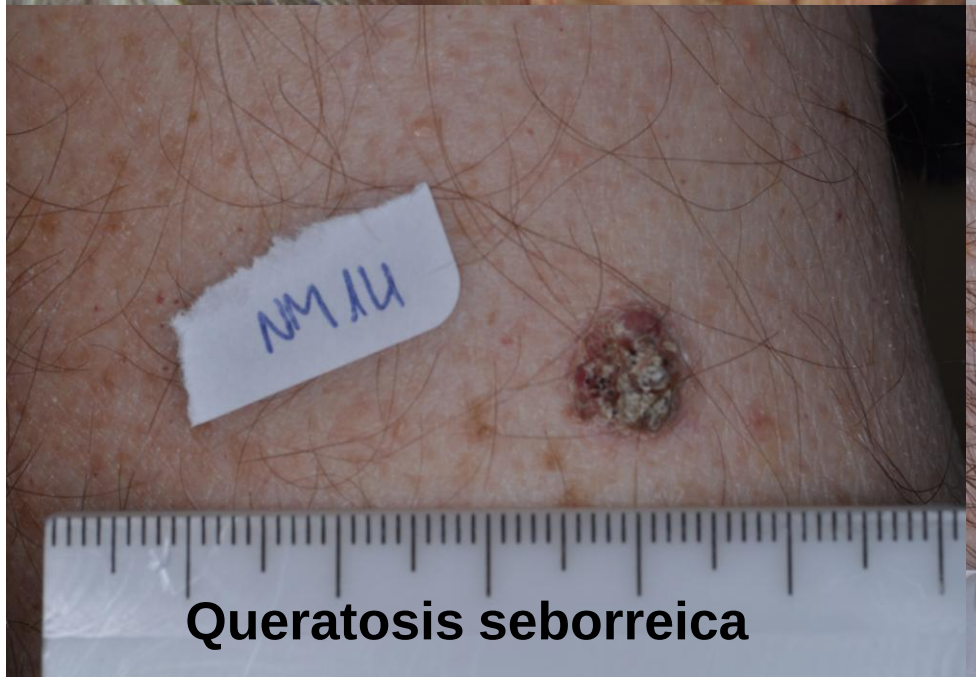
Vemurafenib Adverse Event[1]	Patients With Toxicity, %
Rash	68
Arthralgia	48
Photosensitivity	42
Fatigue	32
Cutaneous squamous cell carcinoma (keratoacanthoma)	23/7

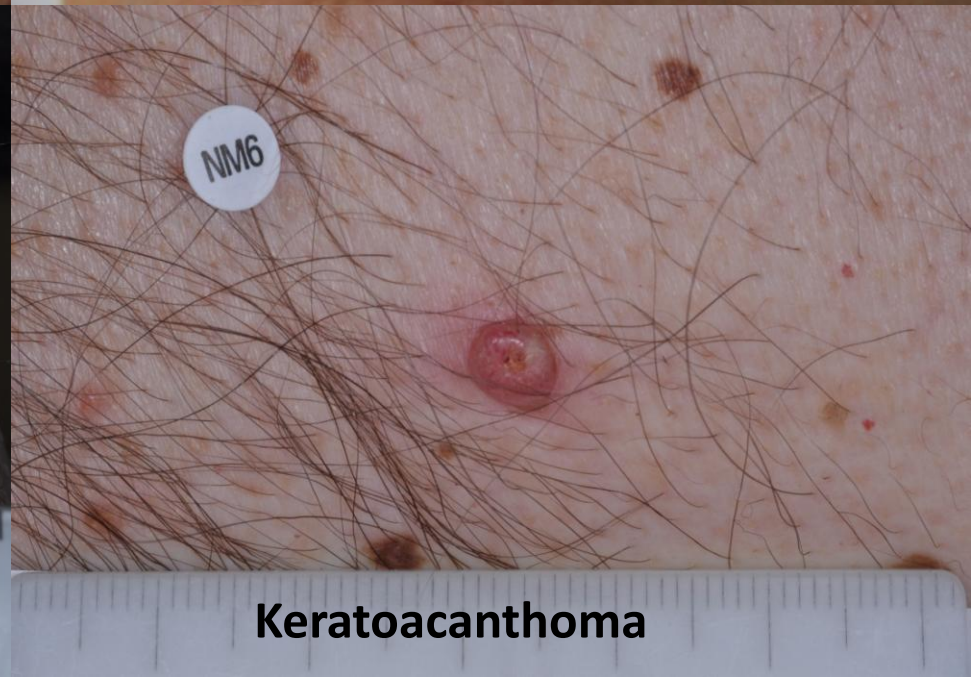
Dabrafenib Adverse Event[2]	Patients With Toxicity, %
Pyrexia	43
Rash	30
Headache	26

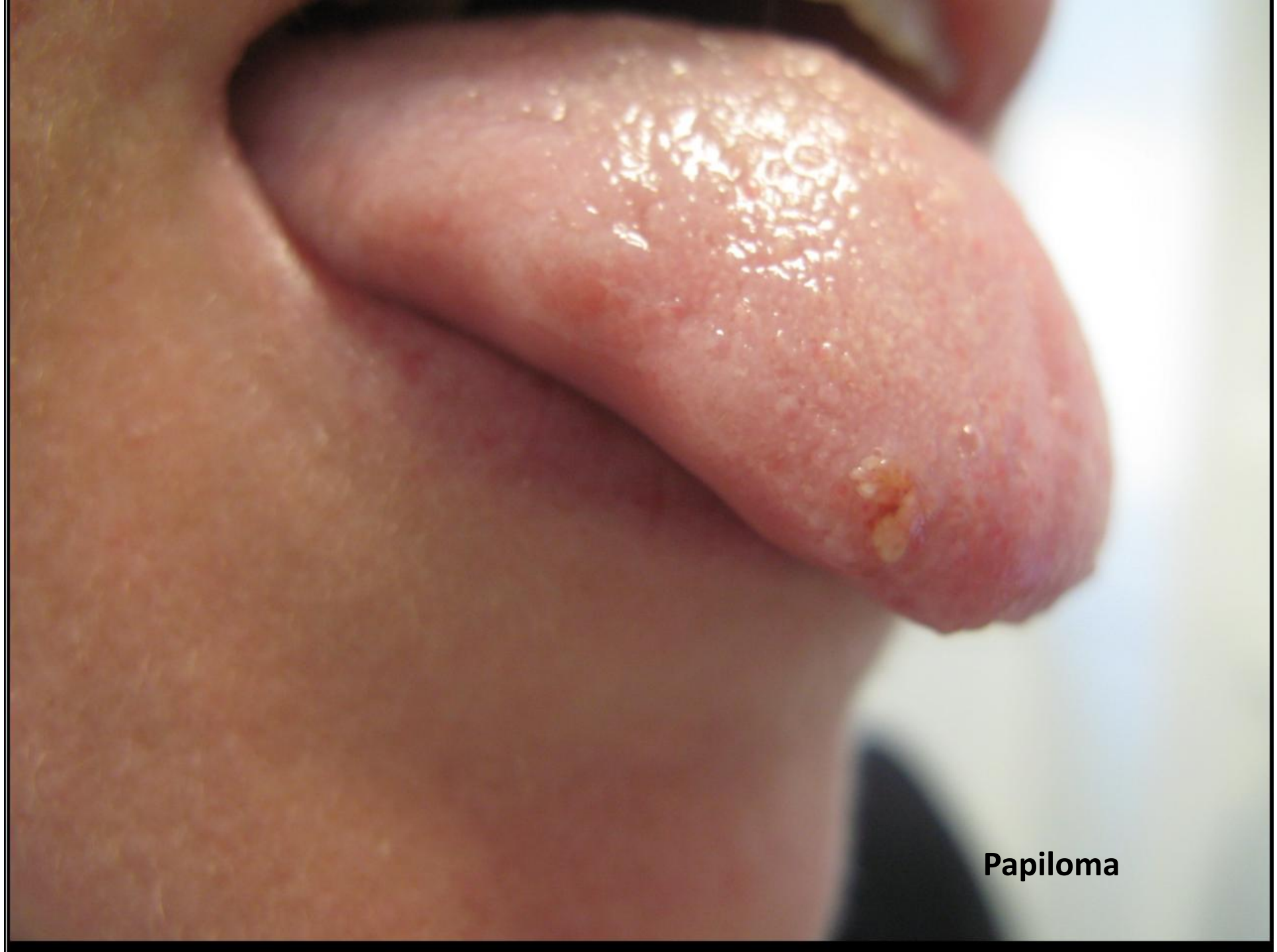
1. Flaherty KT, et al. N Engl J Med. 2010;363:809-819.
2. Kefford R, et al. Society for Melanoma Research Congress 2010. Abstract 100.

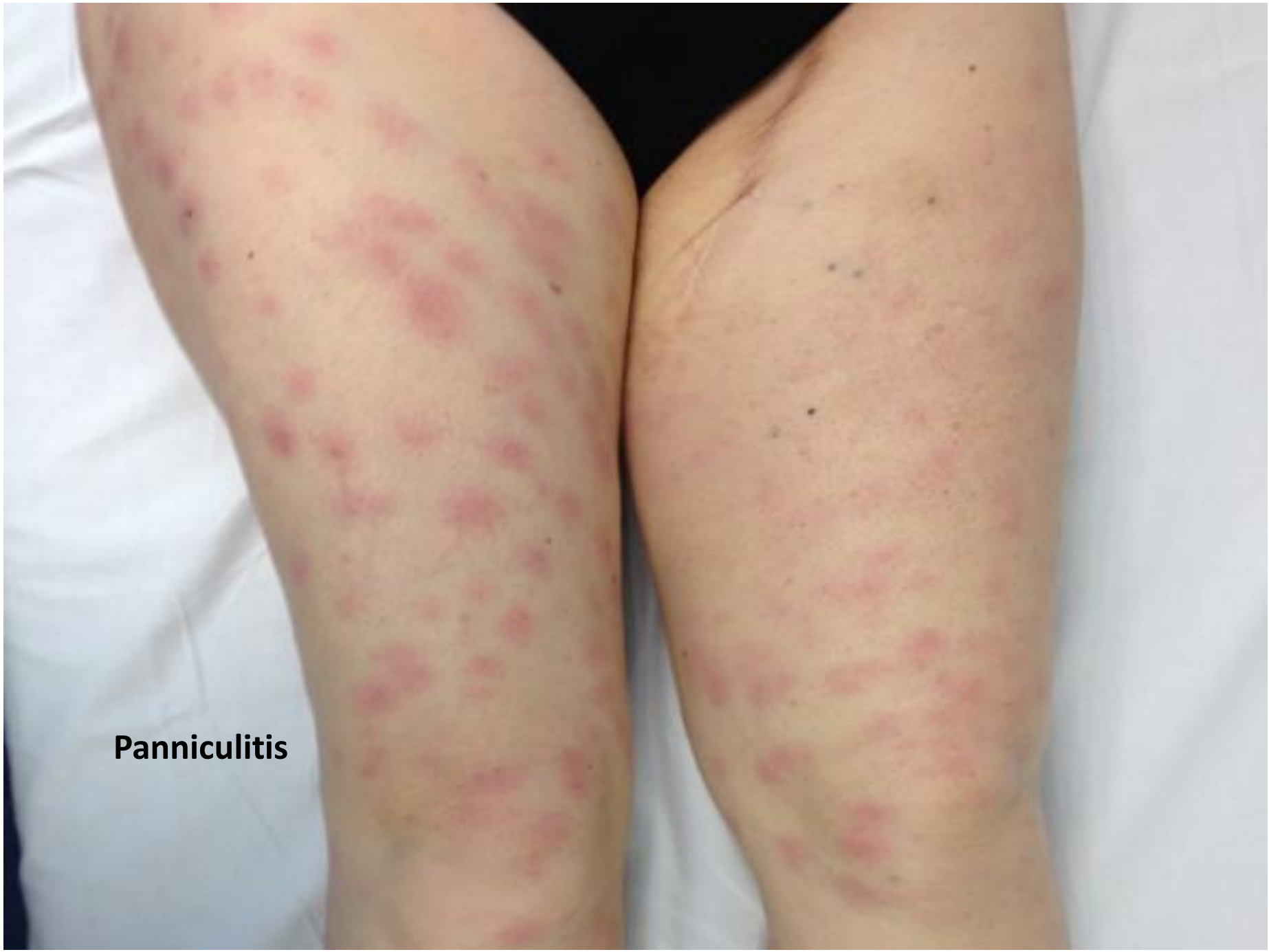

Actinic keratosis

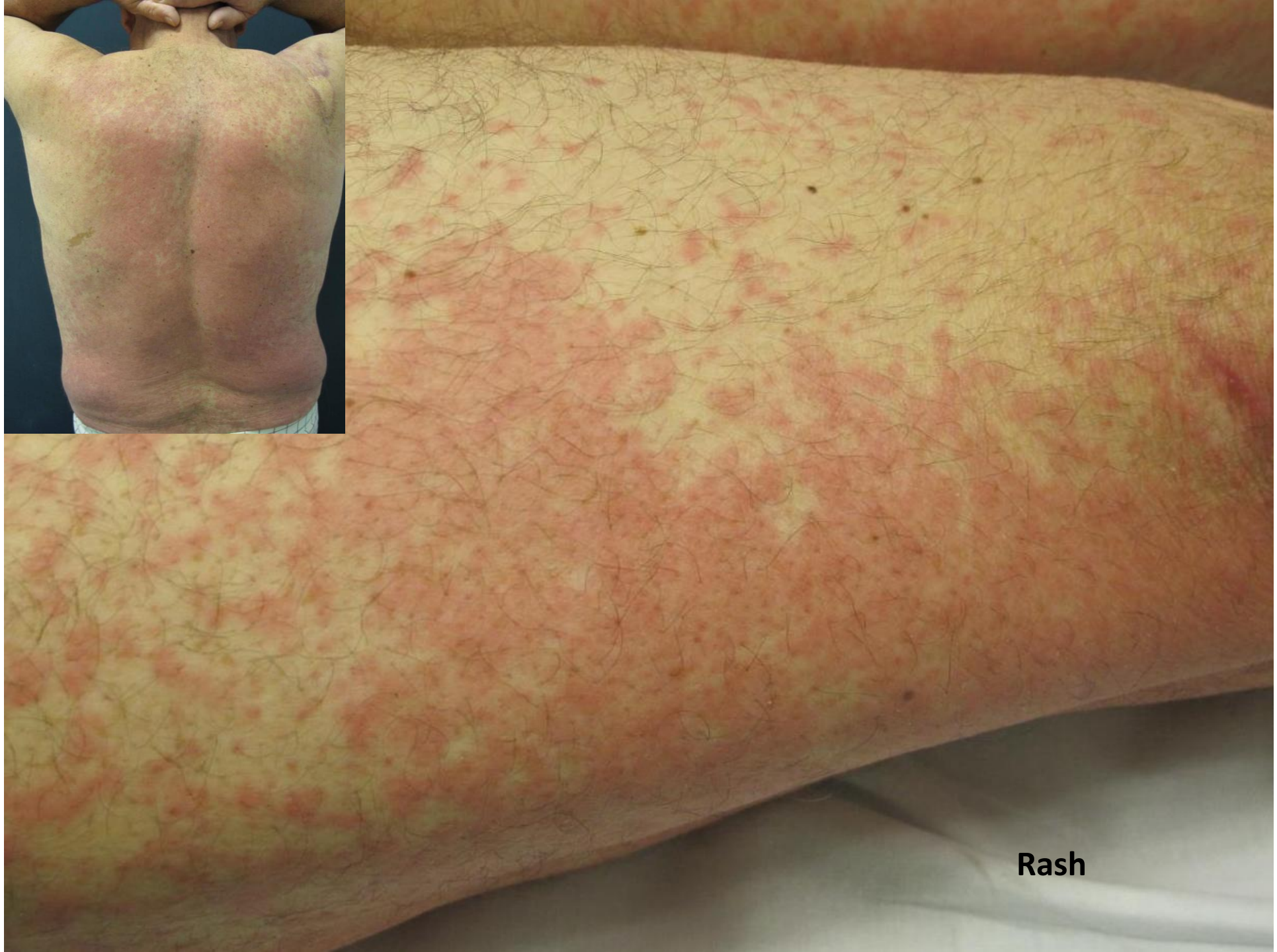

Keratoacanthoma


Queratosis seborreica

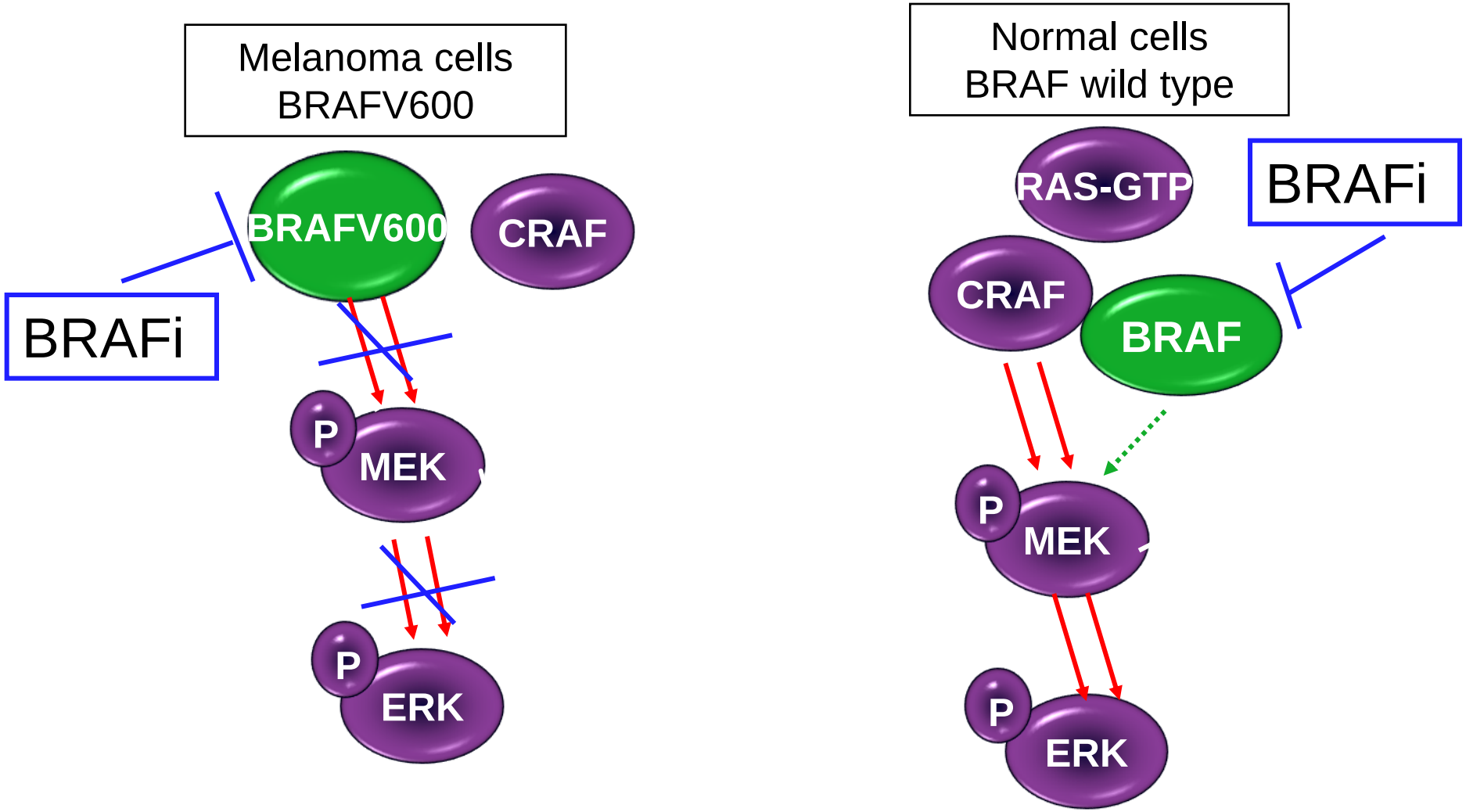

NM6
Keratoacanthoma


Papiloma


Panniculitis


Rash

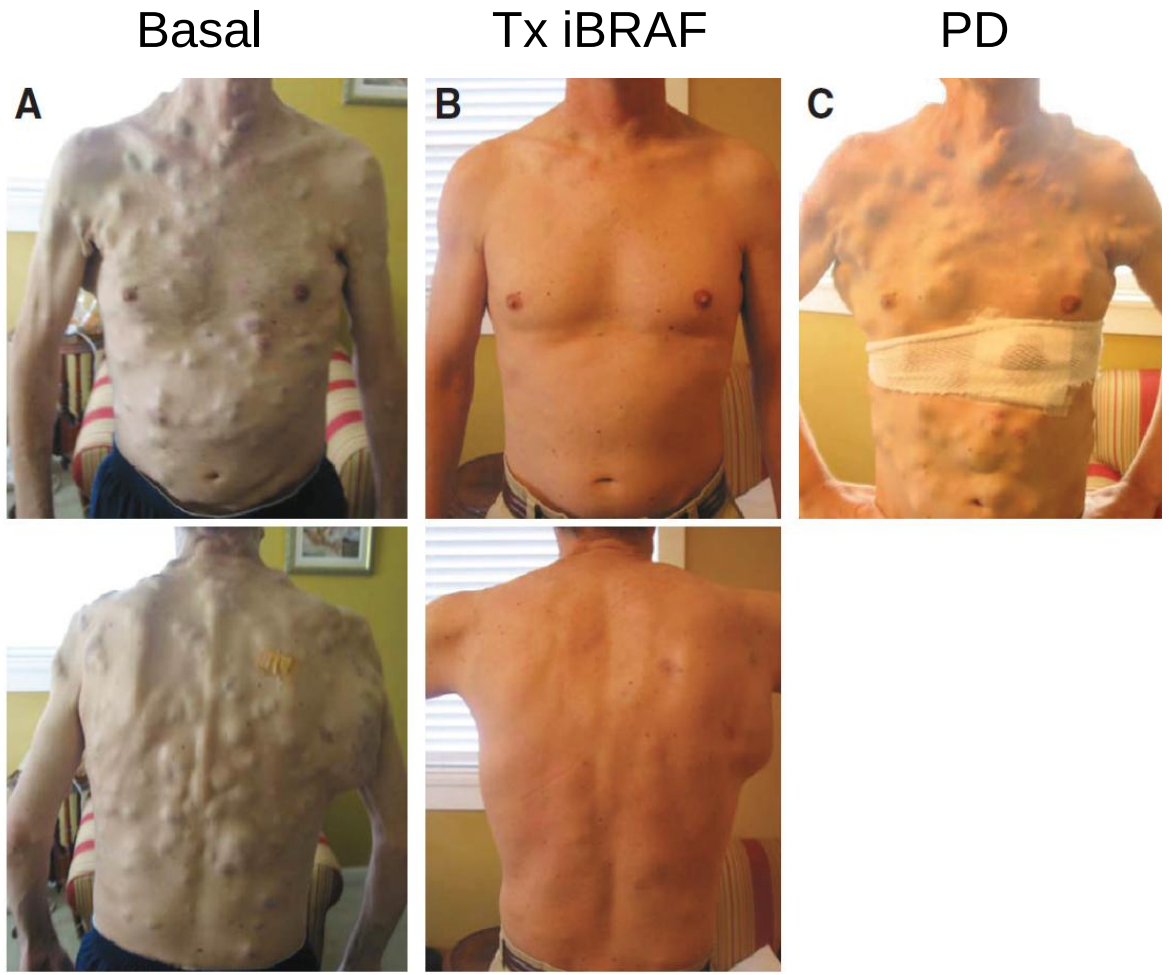
BRAFi only inhibit in the context of *BRAF* mutation



Heidorn SJ, et al. Cell. 2010;140:209-221. Poulikakos PI, et al. Nature. 2010; 464:427-430.
Hatzivassiliou G, et al. Nature. 2010;464:431-435.

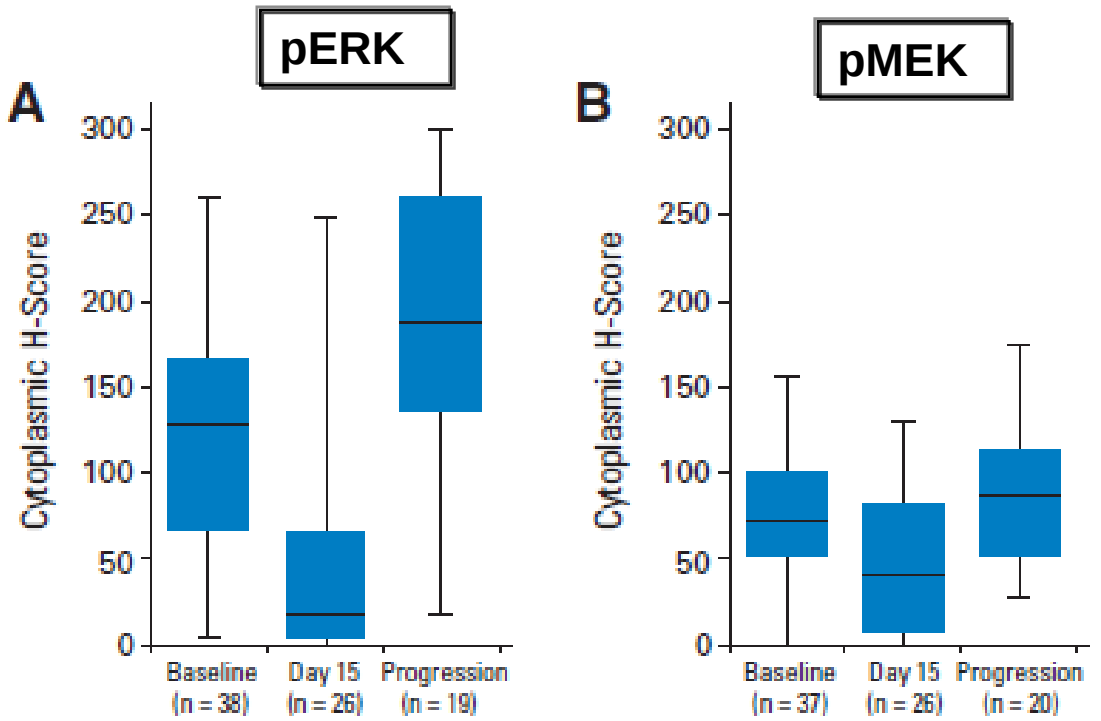
Resistance to BRAF inhibitors

Median duration of response = 6.7 months (95% CI: 5.6, 9.8; range 1.3–12.7)



J Clin Oncol 29:3085-3096. 2011

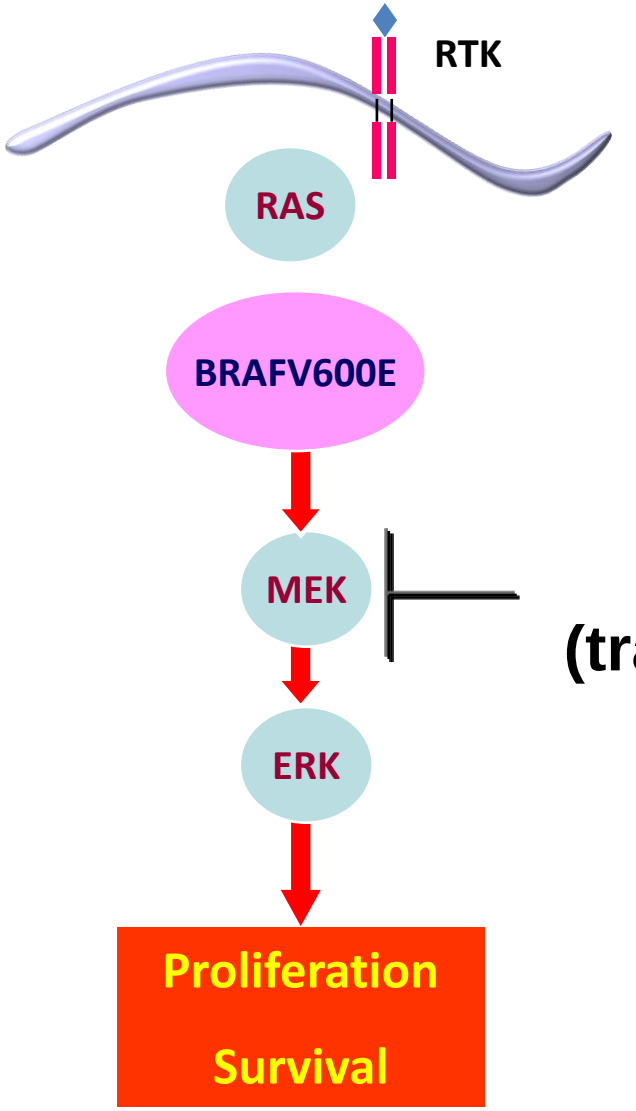
Características farmacodinámicas de la Progresión



- Reactivación de la vía MAPK-ERK
- No nuevas mutaciones activadoras en *BRAF*

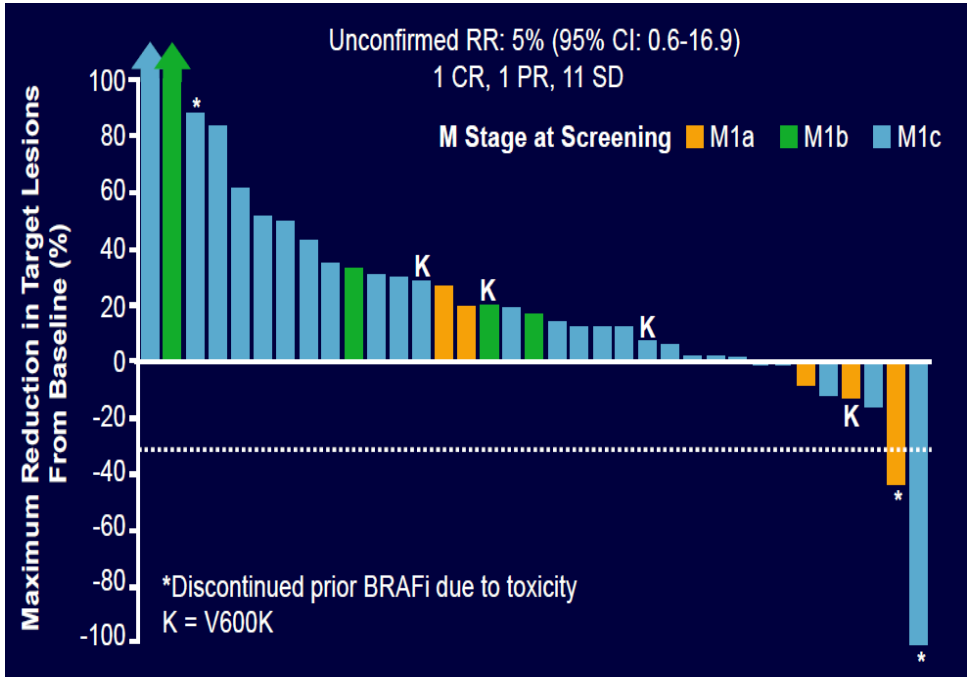
Flaherty. J Clin Oncol 31:1767-1774, 2013

Actividad iMEK en pacientes refractarios a iBRAF



iMEK

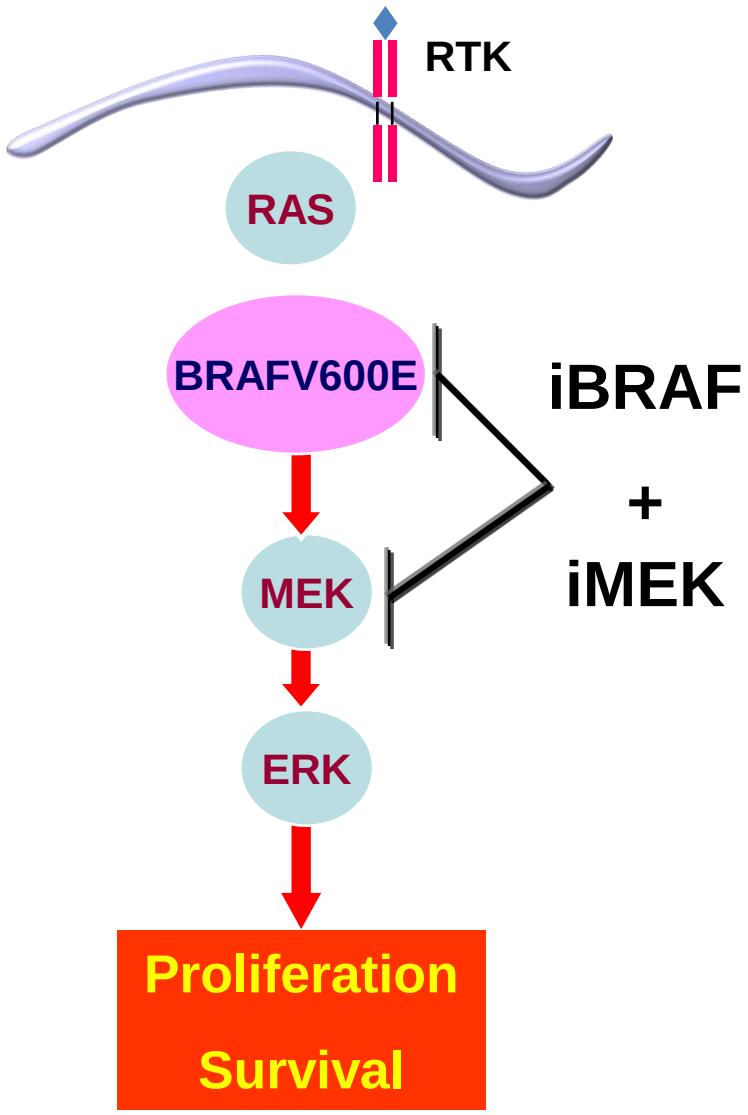
(trametinib)

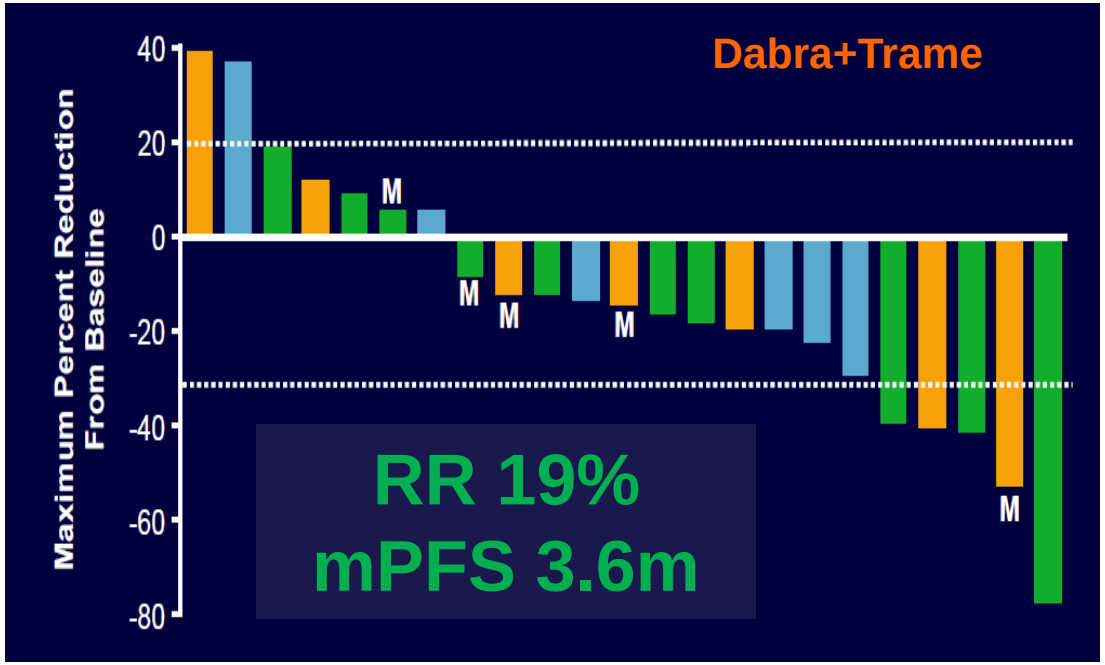


RR 5%

Kim KB, et al. J Clin Oncol. 2013;31:482-489

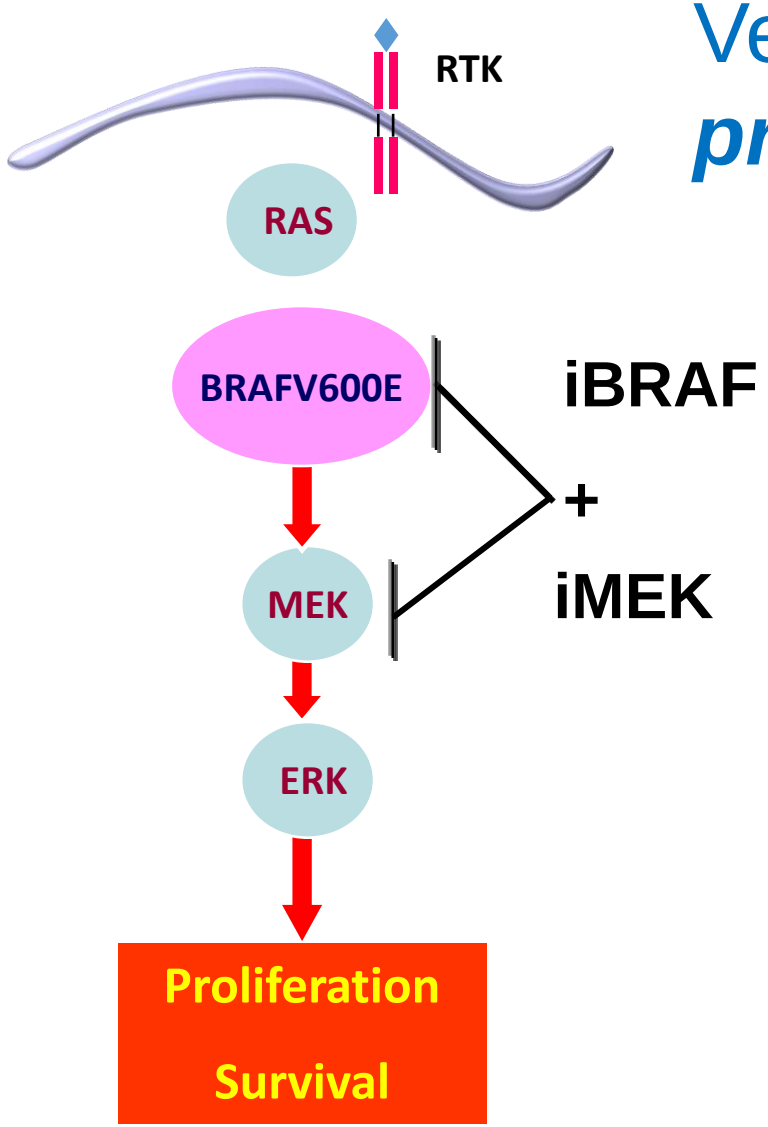
Actividad combo Dabrafenib/Trametinib en pacientes refractarios a iBRAF

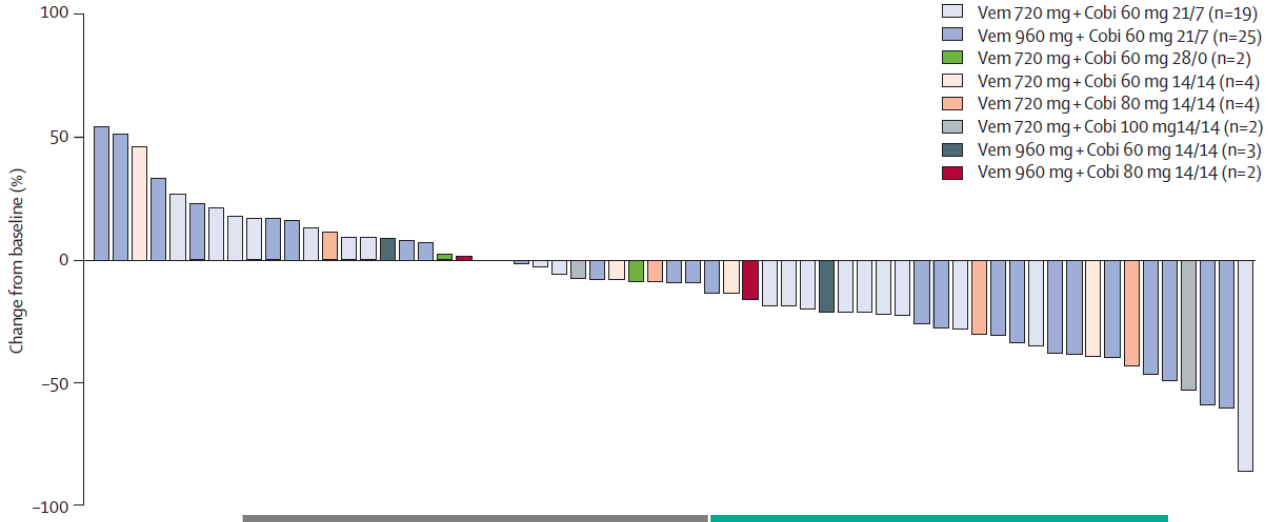




Johnson et al. J Clin Oncol 32. 2014

Fase Ib BRIM7: Actividad Vemurafenib+Cobimetinib en pacientes ***con progresión*** a Vemurafenib

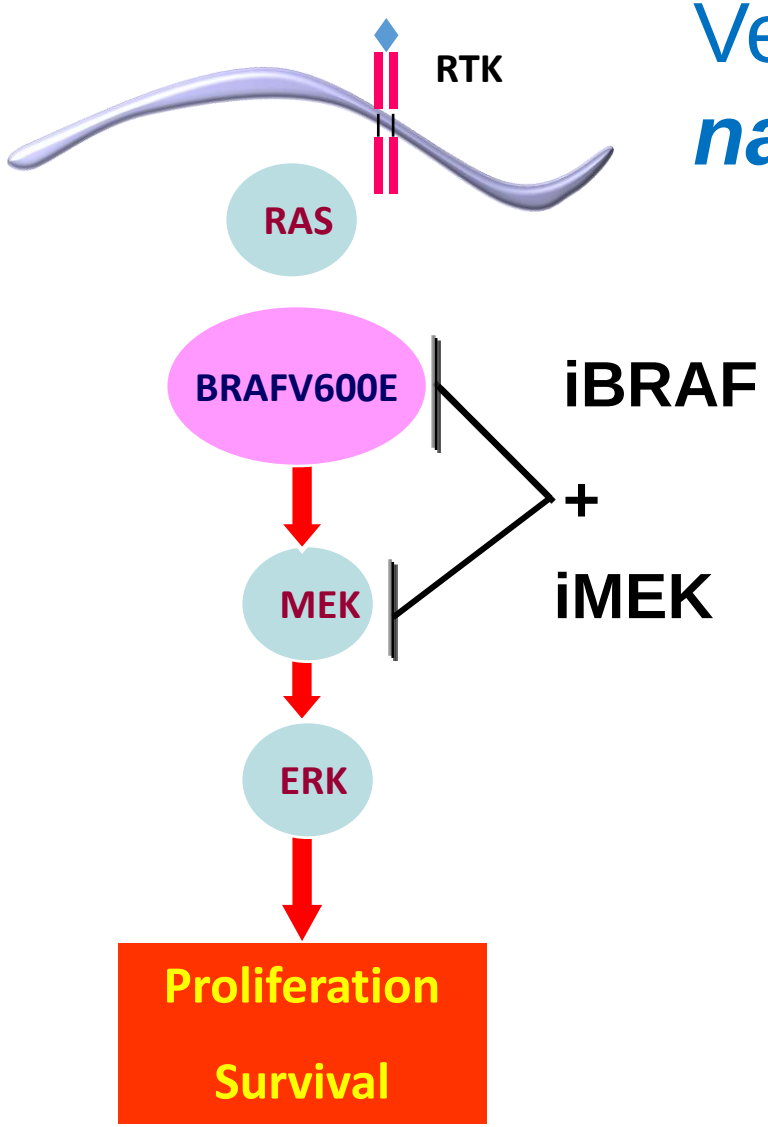


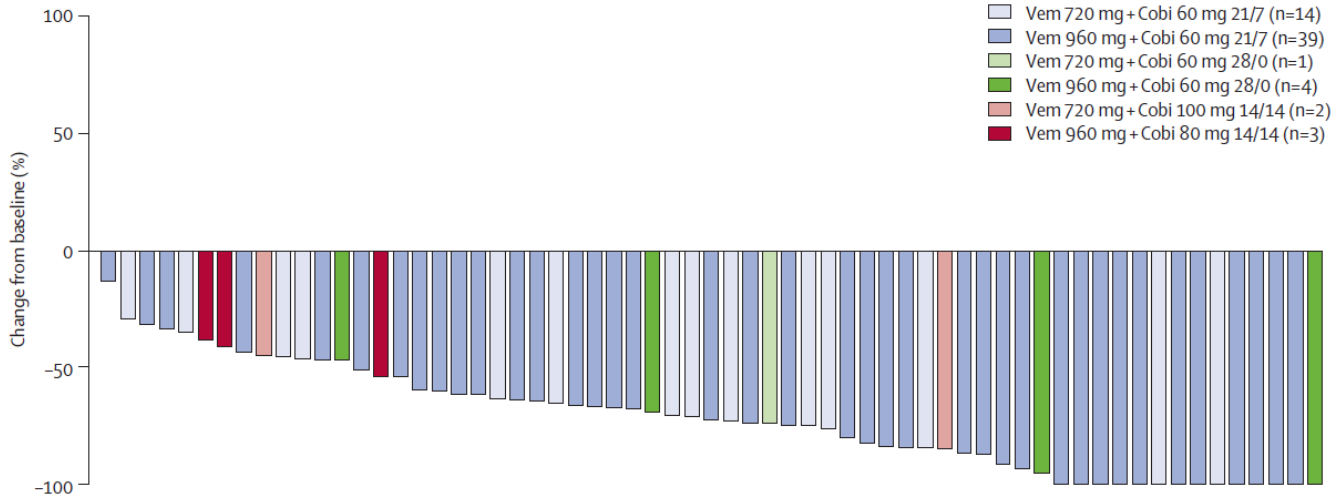


ORR por RECIST 1.1	n=66
ORR	**10 (15,2%)**
RC	1 (1,5%)
RP	9 (13,6%)
EE	28 (42,4%)
PD	24 (36,4%)
No Evaluable	4 (6,0%)

Ribas A, et al. Lancet Oncology. 2014; Daud et al. ASCO 2016

Fase Ib BRIM7: Actividad Vemurafenib+Cobimetinib en pacientes ***naïve para*** iBRAF

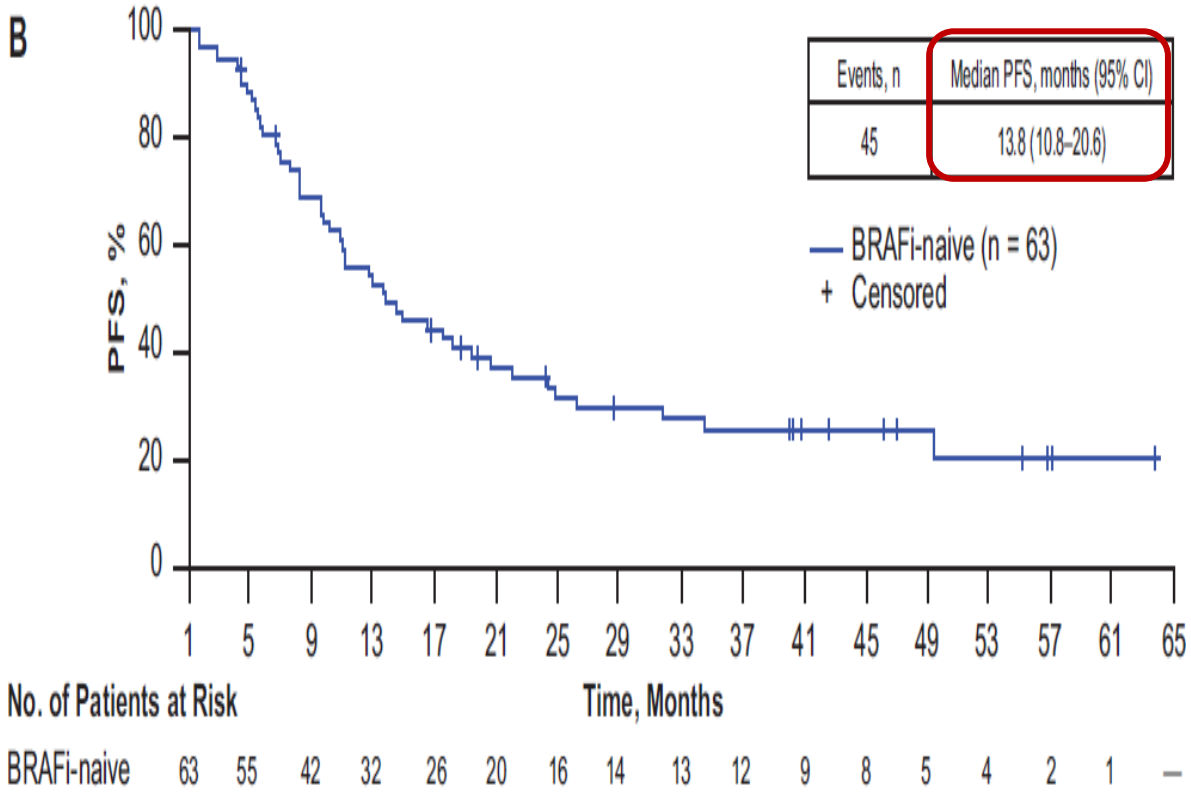




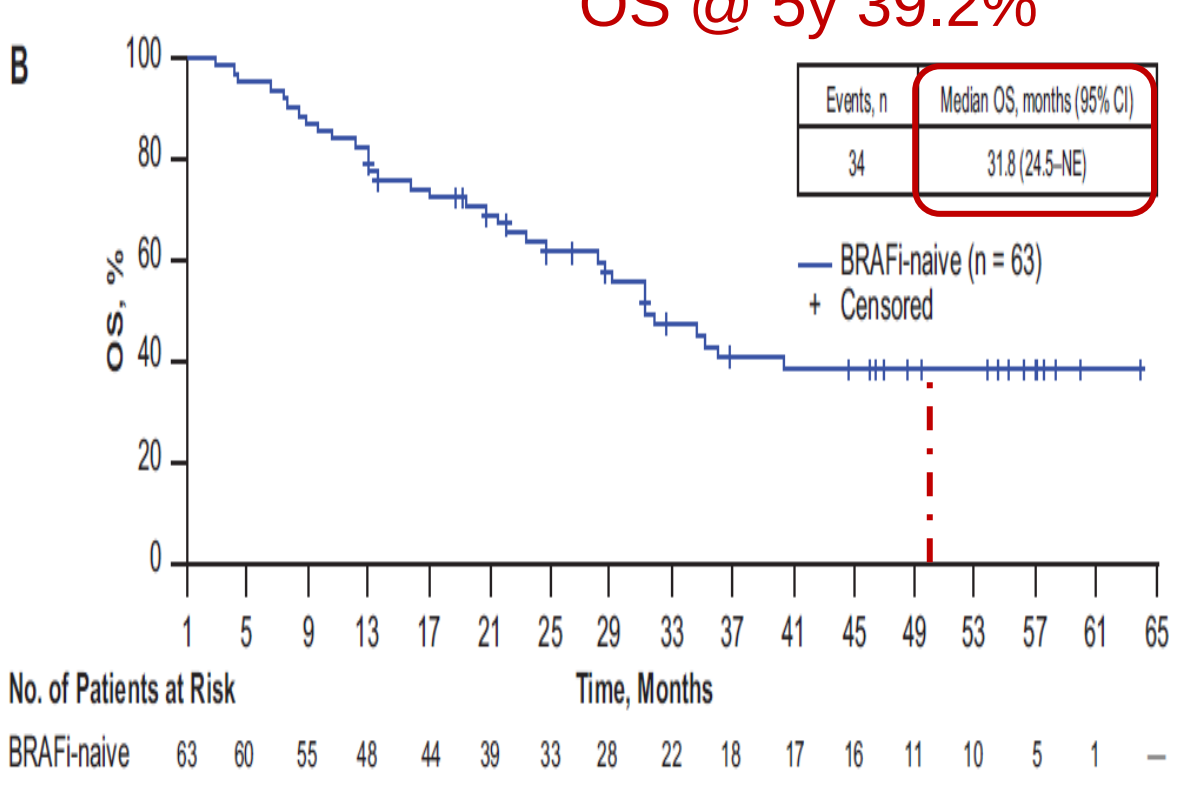
ORR por RECIST 1.1	n=63
ORR (IC 95%)	**87,3% (76-94,4%)**
RC	12 (19%)
RP	43 (68,3%)
EE	6 (9,5%)
PD	2 (3,2%)

Ribas A, et al. Lancet Oncology. 2014; Daud et al. ASCO 2016

Fase Ib BRIM7: PFS & OS @ 5 years Vemurafenib+Cobimetinib en pacientes ***naïve para*** iBRAF



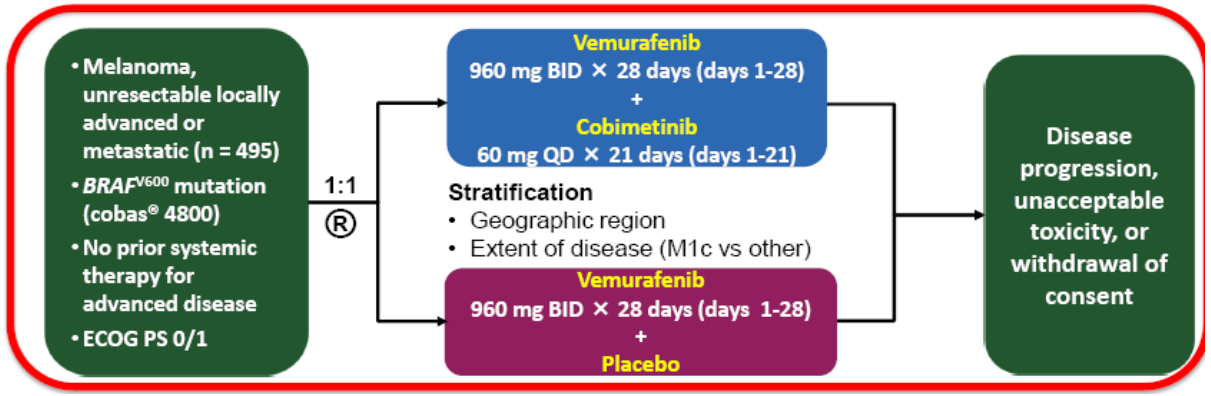
OS @ 5y 39.2%



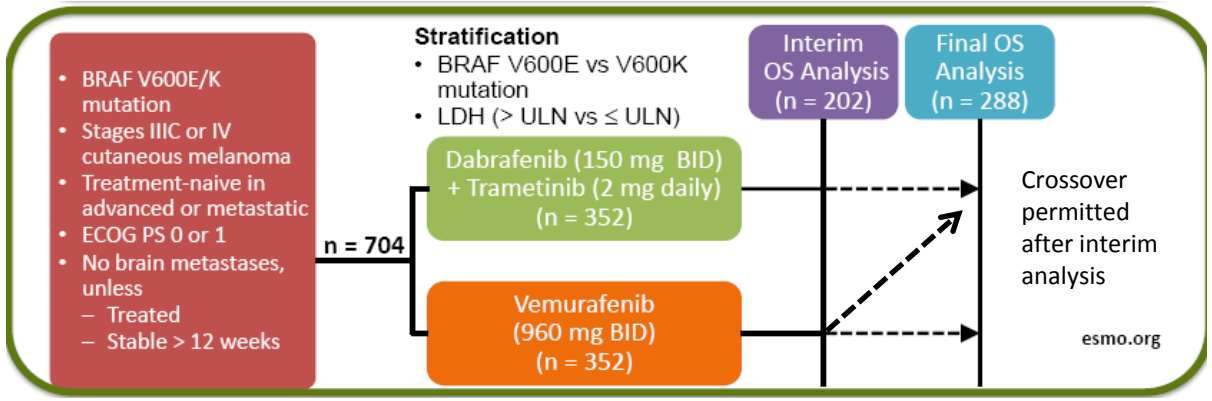
Daud et al ASCO 2016; Dreno et al ASCO 2018

Phase 3 studies BRAFi/MEKi *vs* BRAFi

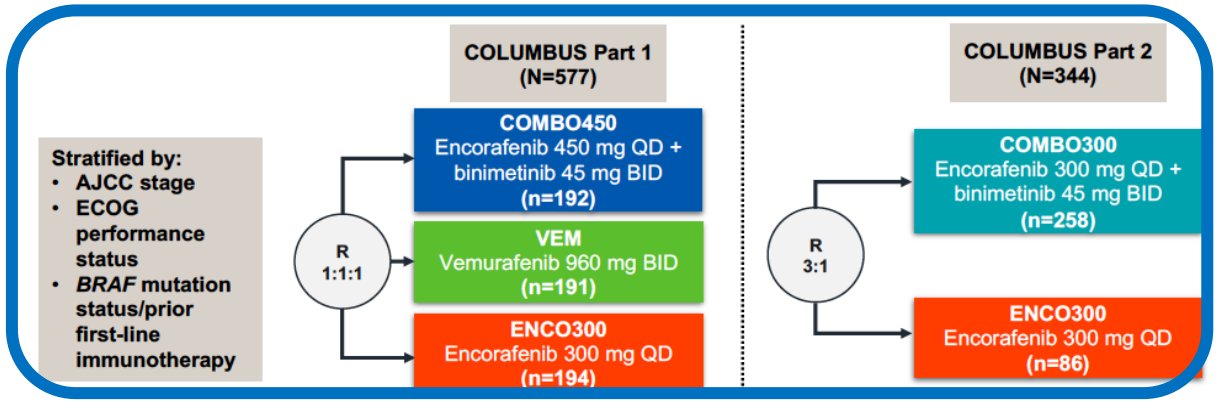
coBRIM (PFS)



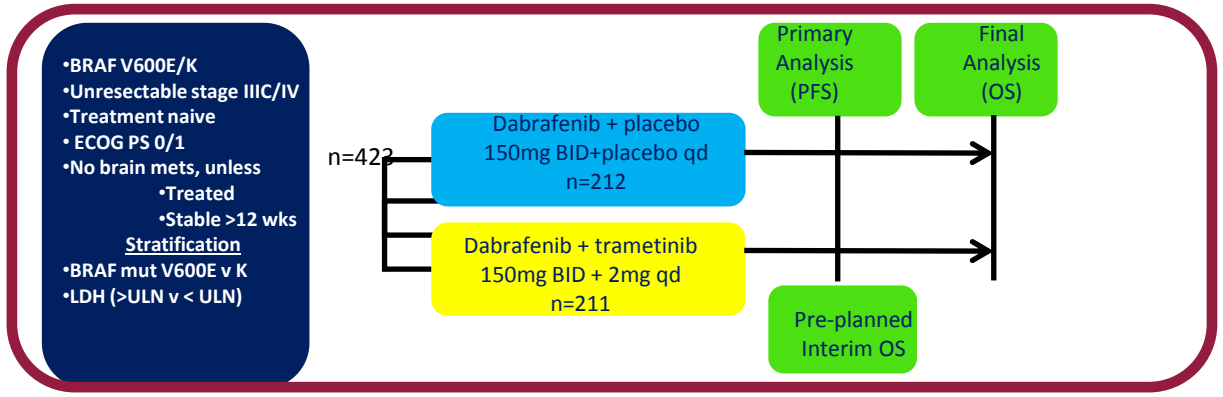
COMBI-v (OS)



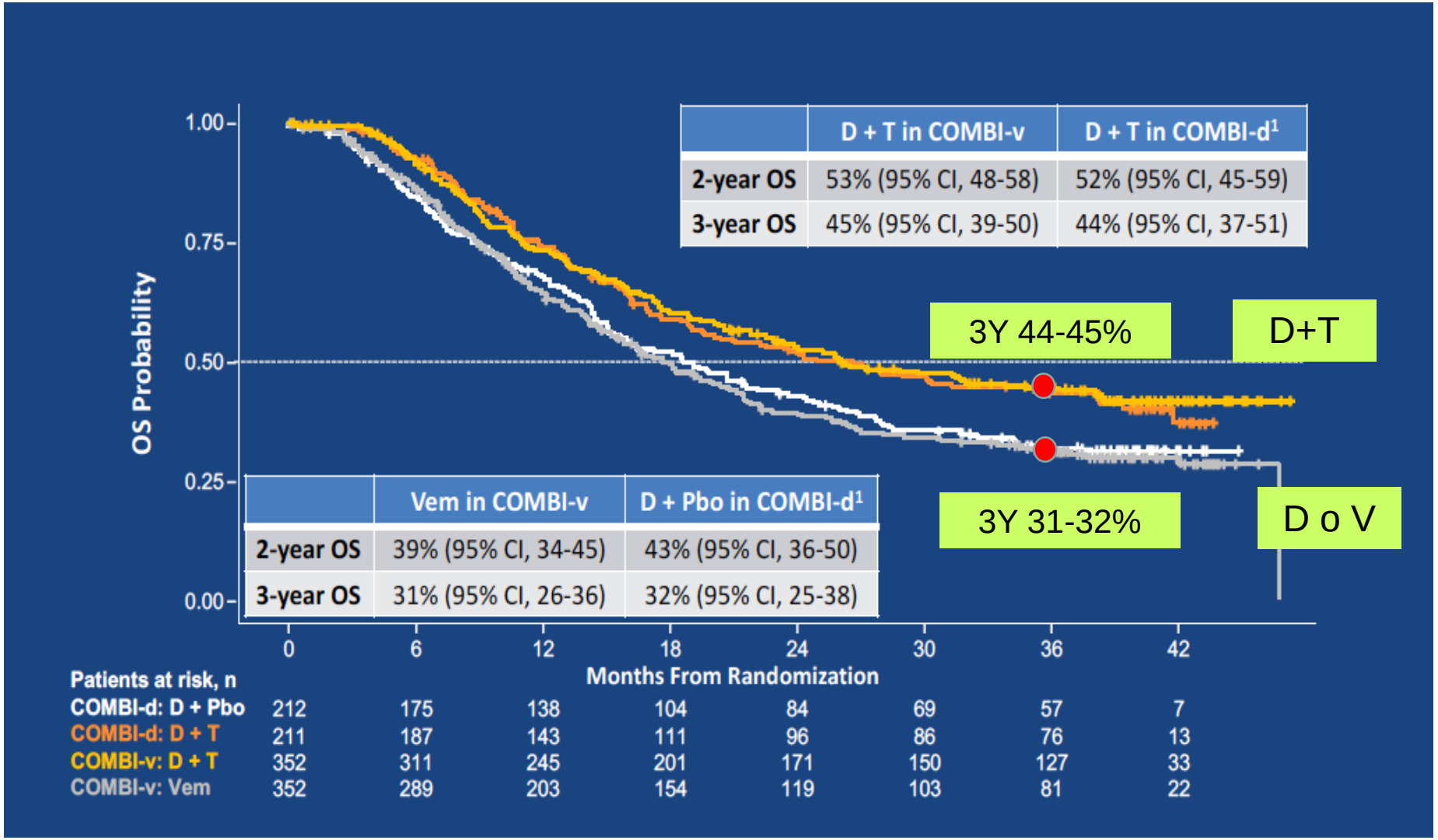
COLUMBUS (PFS)



COMBI-d (PFS)

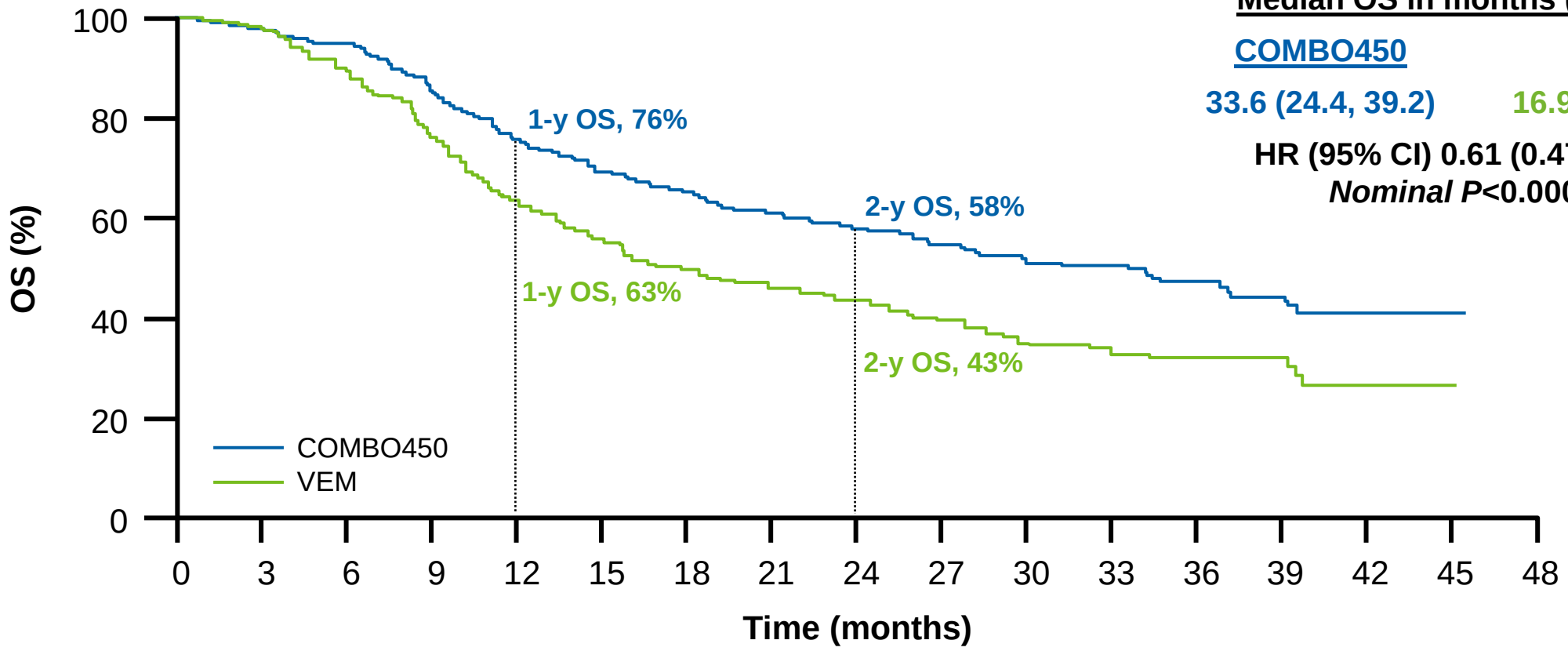


COMBI-v and COMBI-d
Dabrafenib + Trametinib SG



Robert C, *et al*. Oral presentation at ESMO 2016

COLUMBUS Part 1: OS – COMBO450 vs VEM



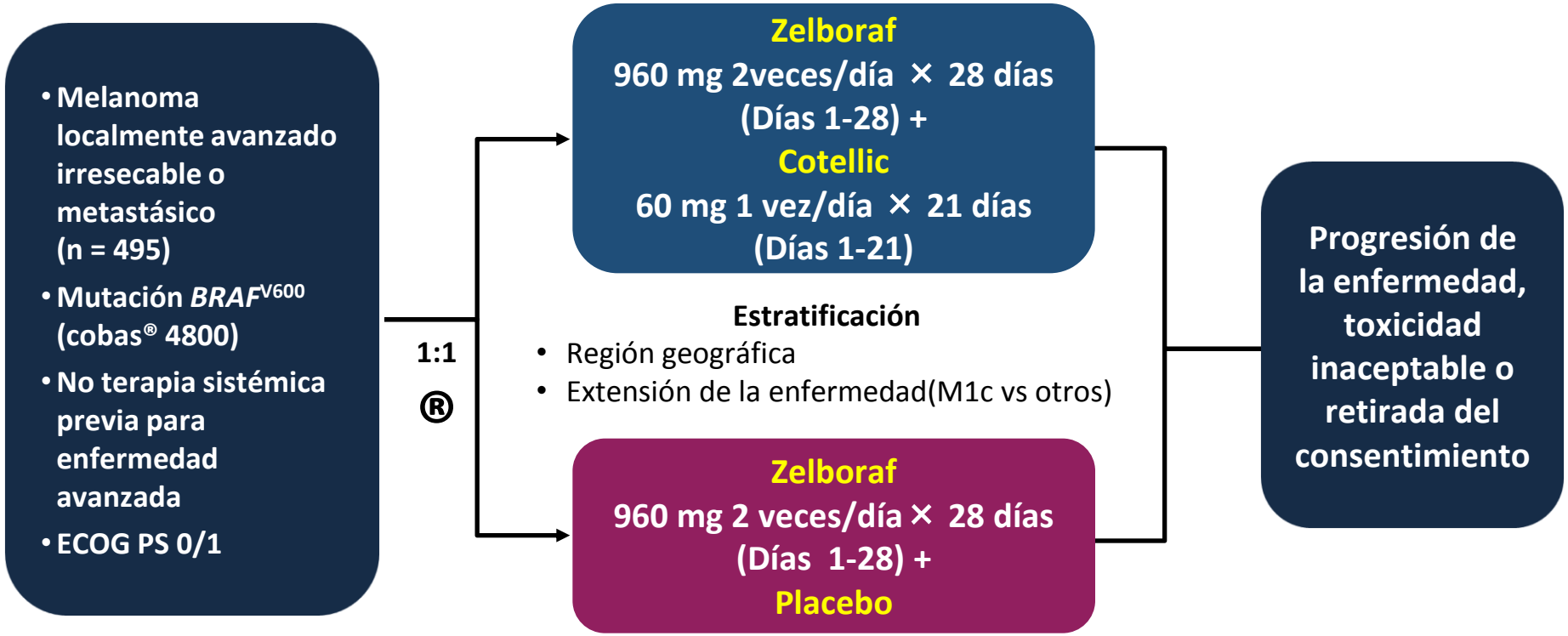
Patients at risk

COMBO450	192 (0)	188 (0)	182 (0)	166 (0)	144 (1)	132 (1)	124 (1)	115 (2)	108 (3)	102 (3)	95 (3)	82 (15)	57 (35)	30 (59)	9 (78)	1 (86)	0 (87)
VEM	191 (0)	184 (0)	166 (6)	140 (7)	115 (8)	100 (9)	89 (9)	83 (9)	77 (10)	71 (10)	62 (10)	56 (12)	30 (37)	19 (48)	8 (56)	1 (63)	0 (64)

BID, twice daily; COMBO450, encorafenib 450 mg QD + binimetinib 45 mg BID; OS, overall survival; QD, once daily; VEM, vemurafenib 960 mg BID

Adapted from: Dummer R, et al. Lancet Oncol 2018;19:1315–1327

coBRIM: diseño



Objetivos primarios
SLP evaluada por el investigador

Objetivos secundarios
SG, TRO, duración de la respuesta, SLP por CRI, seguridad, farmacocinética, calidad de vida (QLQ-C30 y EQ-5D)

Larkin J et al. *N Engl J Med.* 2014;371:1867-1876

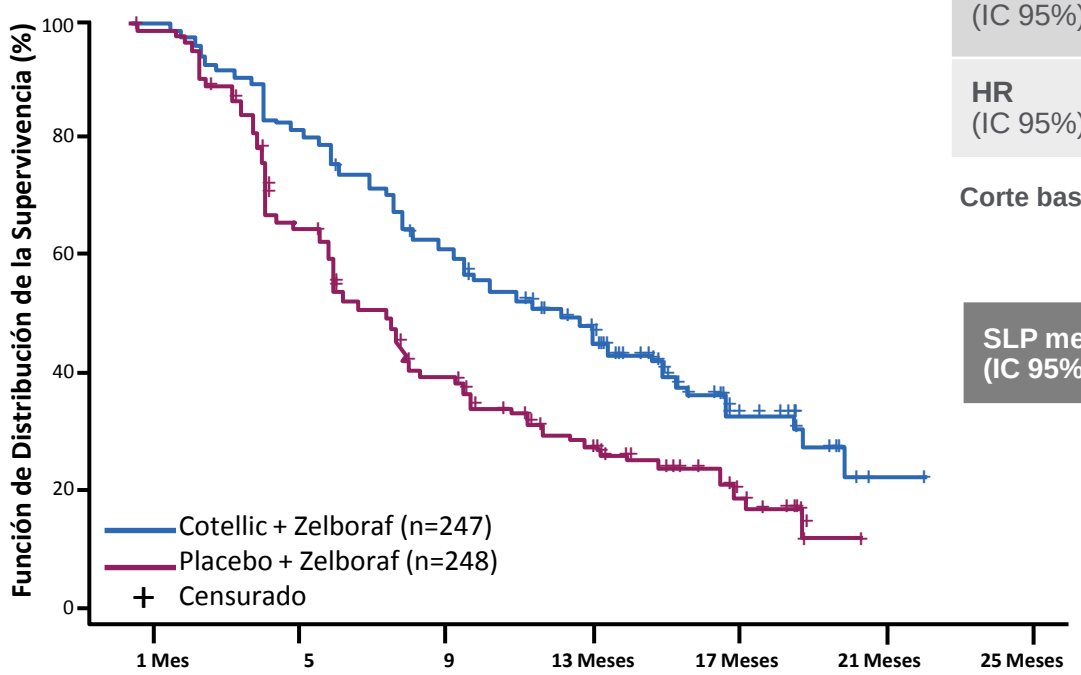
coBRIM: características basales población

	Cotellic + Zelboraf n=247	Zelboraf + Placebo N=248
Mediana de edad (intervalo), años	56 (23-88)	55 (25-85)
Sexo, n (%) Hombre Mujer	 146 (59) 101 (41)	 140 (57) 108 (44)
Región geográfica, n (%) Australia/Nueva Zelanda/Otros* Europa Norte América	 40 (16) 182 (74) 25 (10)	 38 (15) 184 (74) 26 (11)
ECOG, n (%) PS 0 PS 1 PS 2	 184 (76) 58 (24) 1 (<1)†	 164 (67) 80 (33) 0
Metástasis cerebrales previamente tratadas, n (%)	1 (<1)	2 (0.8)
Estado en la randomización, n (%) Estadio IIIc irresecable Estadío IV, M1a Estadío IV, M1b Estadío IV, M1c	 21 (9) 40 (16) 40 (16) 146 **(59)**	 13 (5) 40 (16) 42 (17) 153 **(62)**
LDH elevada, n (%)	**112 (46)**	**104 (43)**

† ECOG PS 1 en la inclusión y PS 2 en la primera administración de la combinación

1. Larkin J et al. *N Engl J Med.* 2014;371:1867-1876.

coBRIM: Supervivencia Libre de Progresión



N. de pacientes en riesgo

Zelboraf + Cotellic	238	215	190	168	142	116	79	46	21	8	1
Zelboraf + placebo	240	205	150	115	87	67	45	30	17	3	

Corte base de datos: 16 enero 2015.

Población ITT	Cotellic + Zelboraf n = 247	Zelboraf+Placebo n = 248
SLP mediana, meses (IC 95%) [1]	12.3 (9.5-13.4)	7.2 (5.6-7.5)
HR (IC 95%)	0.58 (0.46-0.72) p<0001	

Corte base de datos: 16 enero 2015.

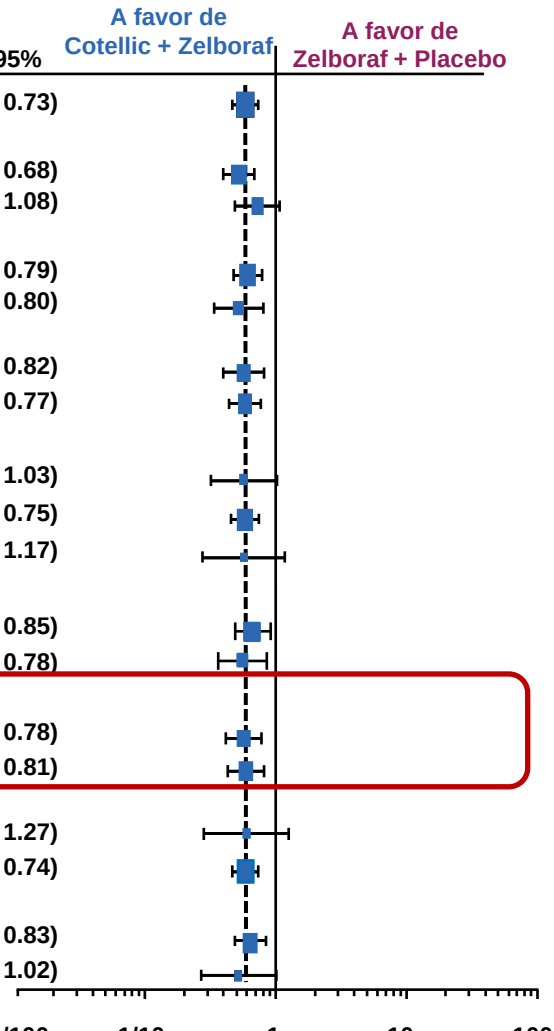
SLP mediana, meses (IC 95%) [2]	12.6 (9.5-14.7)	7.2 (5.6-7.5)

Corte base de datos: 13 Octubre 2017

1. Ascierto et al. Lancet Oncol. 2016 Sep;17(9):1248-60. 2. Dreno et al. J Clin Oncol 36, ASCO 2018 (suppl; abstr 9522)

coBRIM: SLP por subgrupos

Factores de Riesgo Basales	Total n	Zelboraf + Placebo (n=248) n	Eventos	Mediana (meses)	Cotellic + Zelboraf (n=247) n	Eventos	Mediana (Meses)	Hazard Ratio	IC 95%
Todos los pacientes	495	248	180	7.2	247	143	12.3	0.59	(0.47, 0.73)
Estadío de la Enfermedad (IIIc/M1a/M1b, or M1c)									
M1C	299	153	128	5.5	146	94	9.5	0.52	(0.40, 0.68)
Estadío irresecable IIIC/M1A/M1B	196	95	52	11.0	101	49	13.4	0.73	(0.49, 1.08)
Grupo de edad (años)									
< 65	362	179	128	7.2	183	107	12.6	0.61	(0.47, 0.79)
≥ 65	133	69	52	5.6	64	36	11.2	0.52	(0.34, 0.80)
Género									
Mujer	209	108	72	7.5	101	52	12.9	0.57	(0.40, 0.82)
Hombre	286	140	108	5.7	146	91	11.1	0.58	(0.44, 0.77)
Region Geográfica									
Australia/Nueva Zelanda/Otros	78	38	26	7.4	40	20	13.3	0.57	(0.32, 1.03)
Europa	366	184	138	6.0	182	107	11.2	0.58	(0.45, 0.75)
N. America	51	26	16	7.5	25	16	11.2	0.57	(0.28, 1.17)
ECOG Performance Status									
0	348	164	110	7.6	184	100	12.9	0.65	(0.49, 0.85)
1	138	80	66	5.5	58	41	10.0	0.53	(0.35, 0.78)
Niveles de LDH en suero									
Elevado	216	104	85	5.4	112	78	8.2	0.57	(0.42, 0.78)
Normal	268	138	90	7.8	130	65	13.4	0.59	(0.43, 0.81)
Terapia Adyuvante Previa									
Sí	48	24	16	7.2	24	12	16.5	0.60	(0.28, 1.27)
No	447	224	164	7.2	223	131	11.2	0.59	(0.47, 0.74)
Estado Mutacional $BRAF^{V600}$									
V600E	344	174	126	7.2	170	102	10.6	0.64	(0.49, 0.83)
V600K	56	32	24	6.0	24	14	12.4	0.52	(0.27, 1.02)



Corte base de datos: 16 enero 2015.

1. Ascierto P et al. Lancet Oncol. 2016;17(9):1248-60

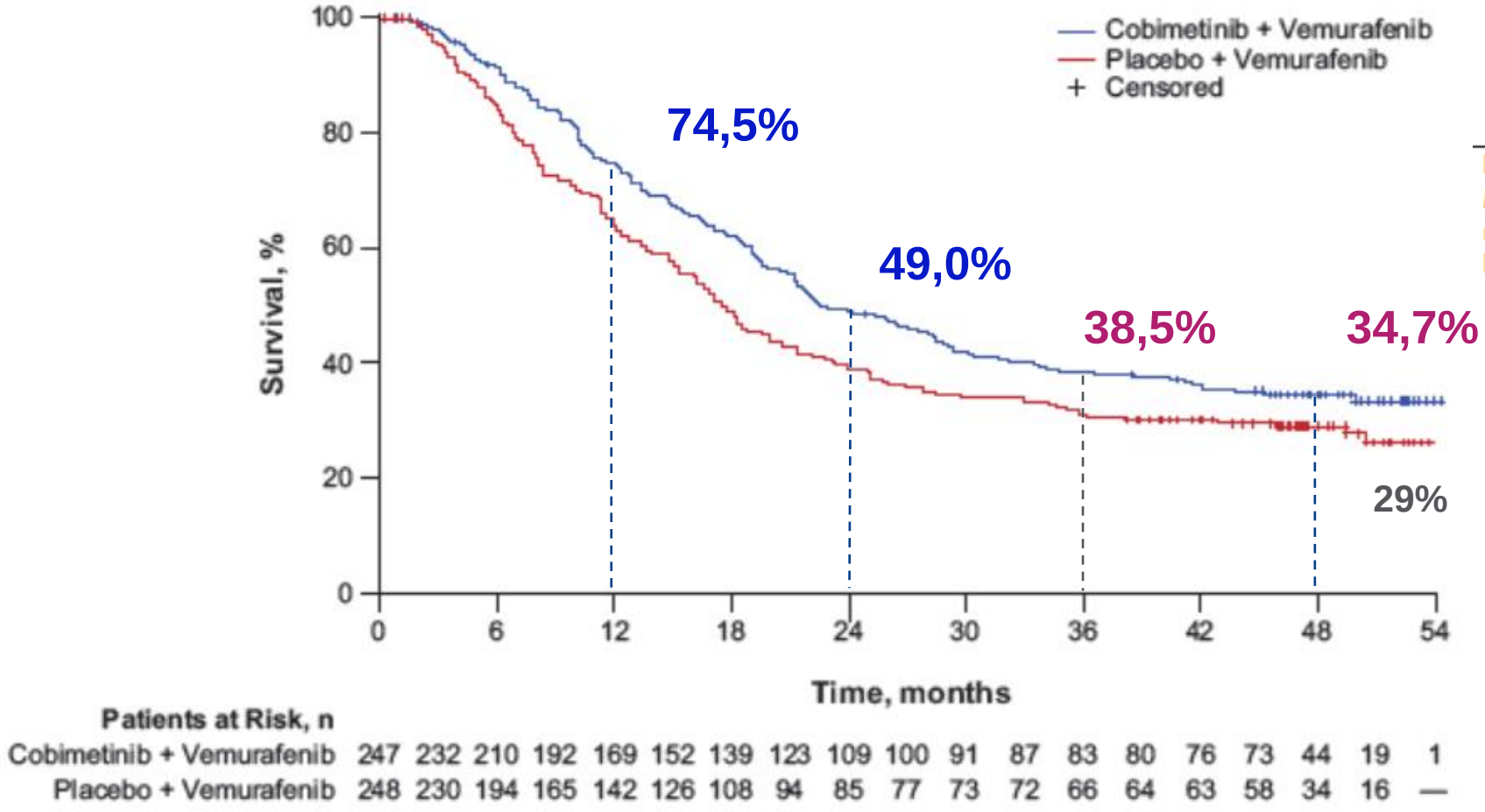
coBRIM: Tasas y Duración de Respuesta

	Cotellic + Zelboraf n = 247	Zelboraf + placebo n = 248
Respuestas Completas (RC), % (n)	16% (39)	10% (26)
Respuestas Parciales (RP), % (n)	54% (133)	40% (98)
ORR, %	**70%**	**50%**
(n)	(172)	(124)
(IC 95%)	(63.5-75.3)	(43.6-56.4)
Duración de la Respuesta		
Pacientes con evento, n (%)	84 (49)	73 (59)
Mediana, meses	**13.0**	**9.2**
(IC 95%)	(11.1-16.6)	(7.5-12.8)

Corte base de datos: 16 enero 2015.

Ascierto P et al. Lancet Oncol. 2016;17(9):1248-60

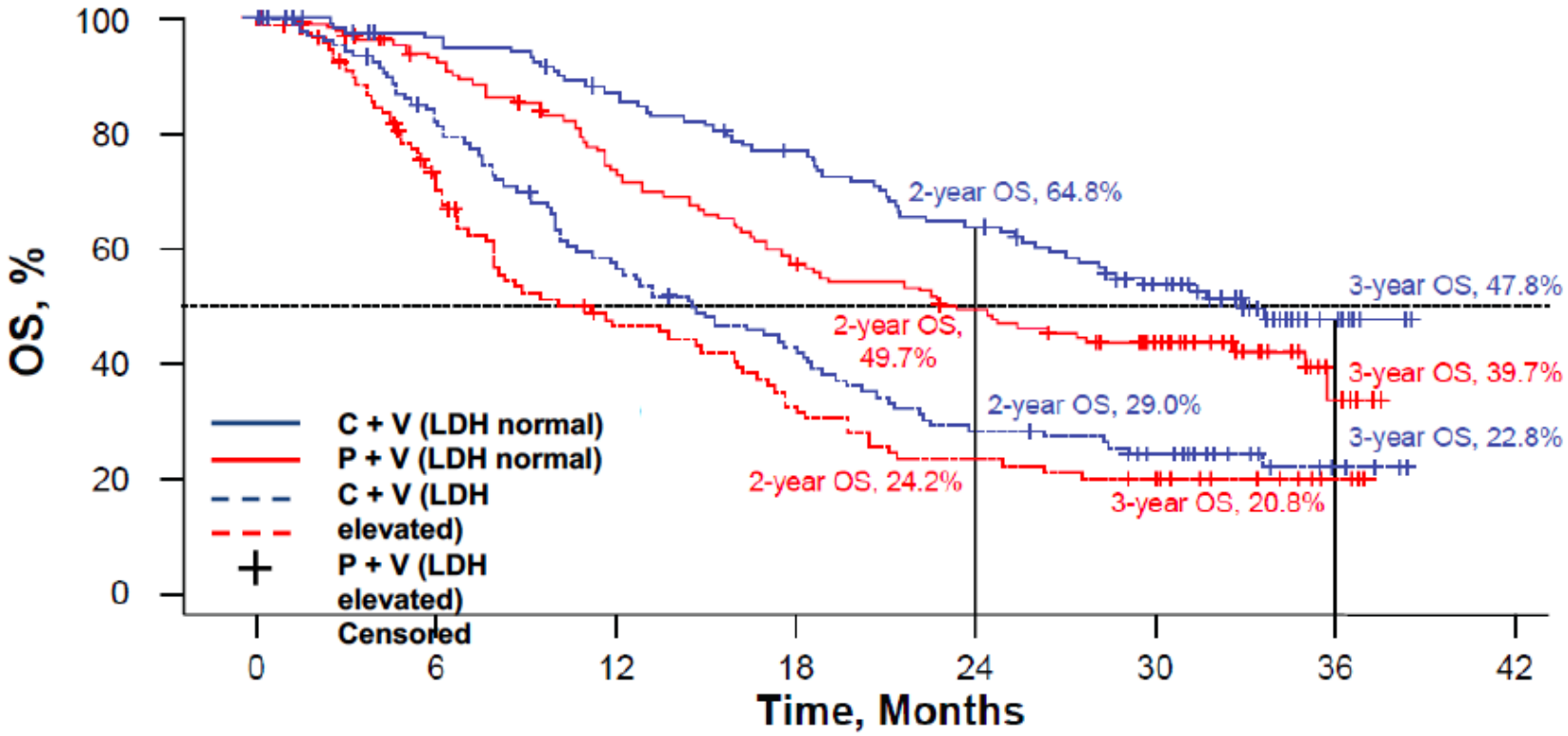
coBRIM: Supervivencia Global



	Placebo and vemurafenib (n=248)	Cobimetinib and vemurafenib (n=247)
Events, n (%)	141 (56·9%)	114 (46·2%)
Median overall survival, months (95% CI)	17·4 (15·0–19·8)	22·3 (20·3–NE)
Hazard ratio (95% CI)	0·70 (0·55–0·90); p=0·005	

Dreno et al. J Clin Oncol 36, ASCO 2018 (suppl; abstr 9522)

coBRIM:
Supervivencia superior en pacientes con LDH normal

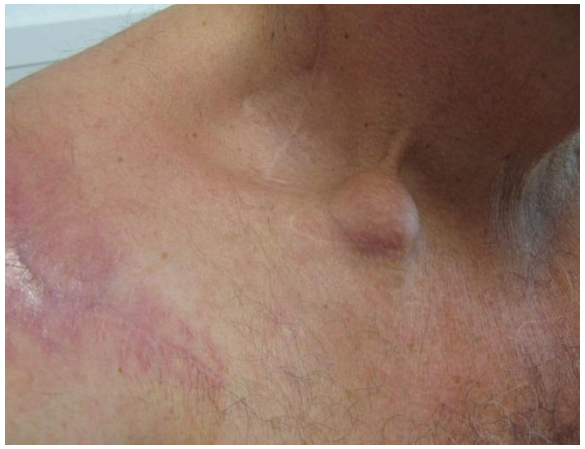
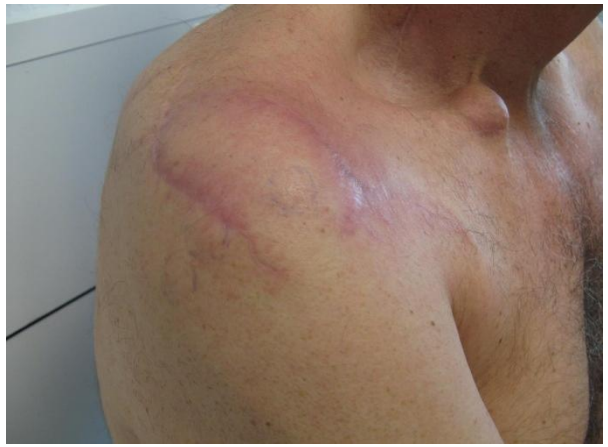
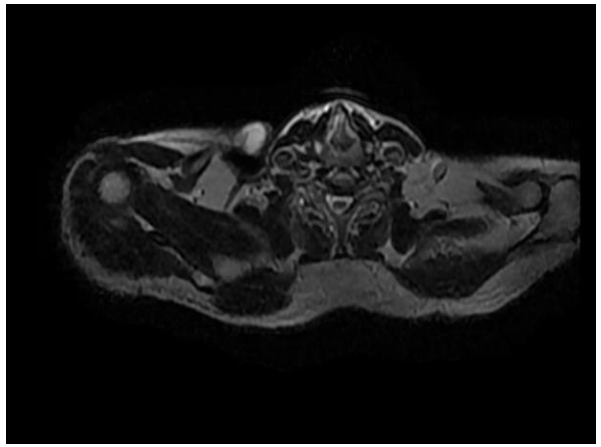


Patients at risk, n													
C + V (LDH normal)	130	122	116	112	103	96	89	82	74	66	57	33	10
P + V (LDH normal)	138	134	123	113	98	87	77	69	62	56	49	27	10
C + V (LDH elevated)	112	105	89	75	61	51	45	36	30	28	21	13	6
P + V (LDH elevated)	104	92	68	49	41	37	29	23	21	19	16	10	5

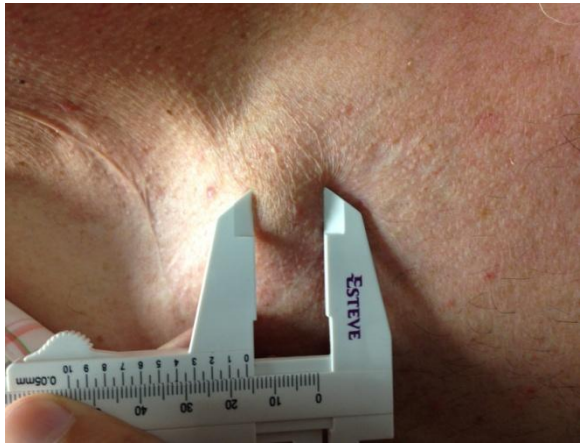
Vemurafenib + Cobimetinib
coBRIM

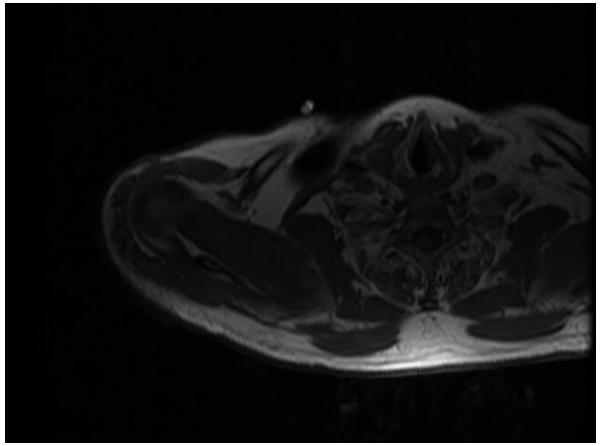
67 y old male stage IV-M1a Melanoma BRAF mut, LDH N

Baseline: **31/Jul/2013**

Last FUP control: **SEPT/2018** (Complete Response since 24/Jan/2014)





coBRIM: Seguridad

	Placebo and vemurafenib (n=246)		Cobimetinib and vemurafenib (n=247)	
	All grades	Grade ≥3	All grades	Grade ≥3
Most common adverse events (occurring in ≥20% of patients in either group)				
Rash*	166 (68%)	40 (16%)	179 (73%)	42 (17%)
Arthralgia	103 (42%)	12 (5%)	94 (38%)	6 (3%)
Diarrhoea	82 (33%)	2 (1%)	150 (61%)	16 (7%)
Fatigue	82 (33%)	7 (3%)	91 (37%)	11 (5%)
Alopecia	75 (31%)	1 (<1%)	41 (17%)	1 (<1%)
Hyperkeratosis	67 (27%)	6 (3%)	25 (10%)	1 (<1%)
Nausea	64 (26%)	2 (1%)	105 (43%)	3 (1%)
Pyrexia	59 (24%)	0	71 (29%)	3 (1%)
Decreased appetite	50 (20%)	1 (<1%)	50 (20%)	0
Photosensitivity reaction	48 (20%)	0	84 (34%)	8 (3%)
Alanine aminotransferase concentration increase	44 (18%)	15 (6%)	65 (26%)	28 (11%)
γ-glutamyltransferase concentration increase	44 (18%)	25 (10%)	54 (22%)	36 (15%)
Vomiting	34 (14%)	2 (1%)	63 (26%)	4 (2%)
Aspartate aminotransferase concentration increase	31 (13%)	5 (2%)	60 (24%)	22 (9%)
Serous retinopathy†	9 (4%)	0	67 (27%)	7 (3%)
Blood creatine phosphokinase level increase	7 (3%)	1 (<1%)	87 (35%)	30 (12%)
Other selected adverse events (selected based upon known association with BRAF or MEK inhibition)				
Cutaneous squamous cell carcinoma	31 (13%)	31 (13%)	10 (4%)	9 (4%)
Keratoacanthoma	23 (9%)	21 (9%)	4 (2%)	3 (1%)
Decreased ejection fraction	13 (5%)	3 (1%)	29 (12%)	5 (2%)
QT prolongation	13 (5%)	3 (1%)	11 (5%)	3 (1%)

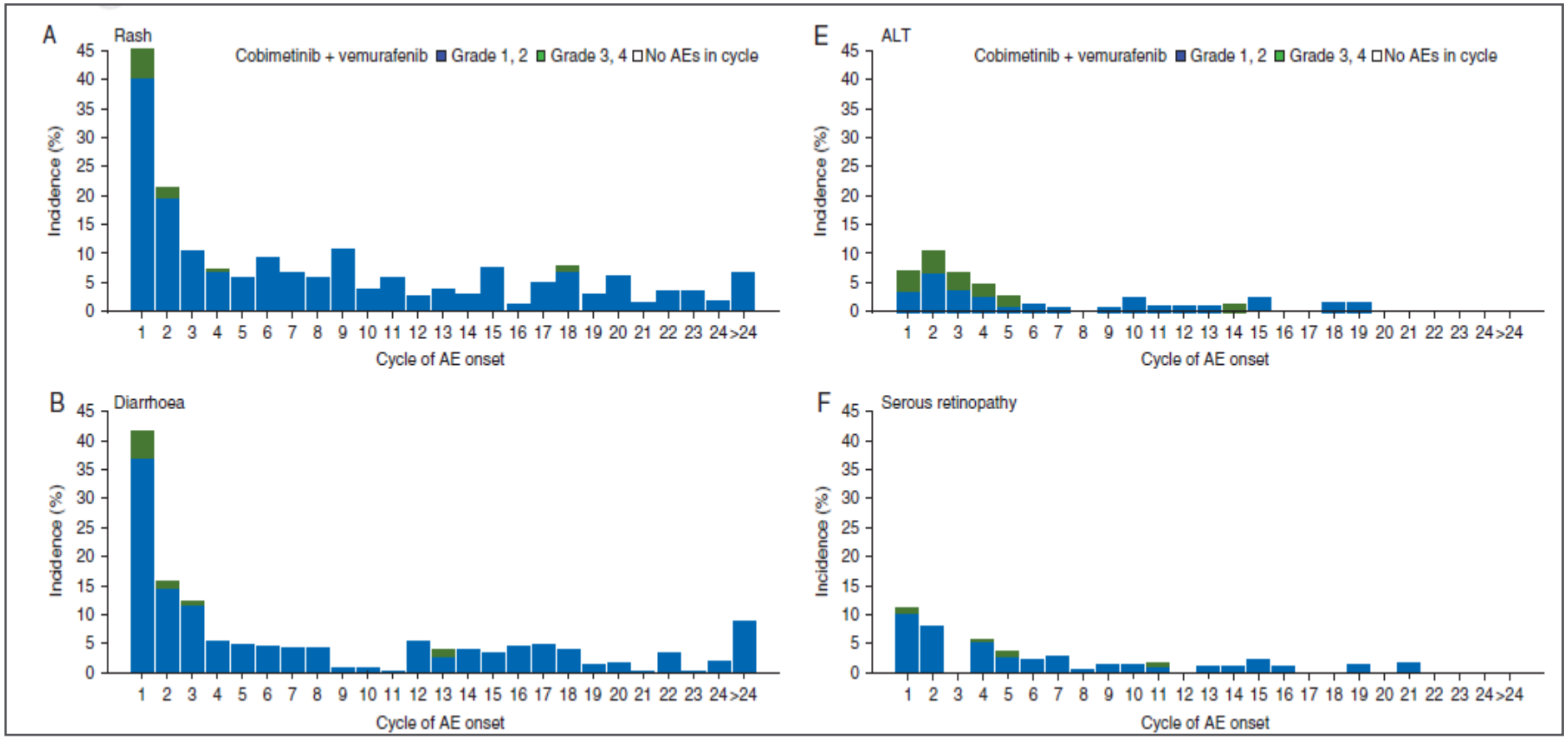
Table 2. Incidence of discontinuation and dose modification (reduction or interruption) at any time on study by AE in the cobimetinib plus vemurafenib arm (*n* = 247)

AE, *n* (%)	Cobimetinib dose		Vemurafenib dose		Both doses	
	Discontinued	Modified[a]	Discontinued	Modified[a]	Discontinued	Modified[a]
Any	53 (21.5)	141 (57.1)	44 (17.8)	152 (61.5)	41 (16.6)	116 (47.0)
Rash[b]	8 (3.2)	37 (15.0)	8 (3.2)	44 (17.8)	7 (2.8)	32 (13.0)
Diarrhoea	0	22 (8.9)	0	23 (9.3)	0	20 (8.1)
Photosensitivity[c]	1 (0.4)	5 (2.0)	0	7 (2.8)	0	4 (1.6)
Pyrexia	3 (1.2)	14 (5.7)	3 (1.2)	18 (7.3)	3 (1.2)	14 (5.7)
Serous retinopathy[d]	9 (3.6)	30 (12.1)	4 (1.6)	26 (10.5)	4 (1.6)	25 (10.1)
Elevated CPK level[e]	3 (1.2)	13 (5.3)	1 (0.4)	3 (1.2)	1 (0.4)	3 (1.2)
Elevated AST level	6 (2.4)	9 (3.6)	6 (2.4)	20 (8.1)	5 (2.0)	8 (3.2)
Elevated ALT level	4 (1.6)	9 (3.6)	5 (2.0)	25 (10.1)	4 (1.6)	9 (3.6)
Elevated GGT level	4 (1.6)	9 (3.6)	5 (2.0)	22 (8.9)	4 (1.6)	8 (3.2)
Cutaneous neoplasms	0	2 (0.8)	0	2 (0.8)	0	2 (0.8)
LVEF reduction	4 (1.6)	8 (3.2)	1 (0.4)	1 (0.4)	1 (0.4)	0

	V + P (n = 246) 30 Sept 2015	P + V (n = 245) 20 June 2016	C + V (n = 247) 30 Sep 2015	C + V (n = 248) 20 June 2016
Discontinued both V and C/P	216 (88)	225 (92)	193 (78)	209 (84)
Disease Progression	180 (73)	185 (76)	127 (51)	135 (54)
Adverse Events	21 (8.5)	21 (8.6)	36 (14.6)	38 (15.3)
Deaths	2 (0.8)	3 (1.2)	3 (1.2)	4 (1.6)
Other[a]	13 (5.3)	16 (6.5)	27 (10.9)	32 (12.9)

Ascierto et al. Lancet Oncology 2016; Dréno et al. Ann Oncol 2017

coBRIM:
Tras el primer Ciclo, la incidencia de Acontecimientos Adversos disminuye en el tiempo



Con Zelboraf & Cotellic la mayoría de los EAs son tolerables , de grado 1 o 2 ,y se manejan con tratamiento de soporte o modificación de dosis [1]

1. Ascierto PA, Lancet Oncol. 2016 Sep;17(9):1248-60. 2. Dréno B et al, Ann Onc 2017 **Corte base de datos: 30 Septiembre 2015** .

La doble inhibición de BRAF/MEK es superior a la inhibición de BRAF con monoterapia

En pacientes con Melanoma M1 BRAFV600

M1 SNC

COMBI-MB: Activity CNS

	No local therapy	+ local therapy	+/- local therapy
	V600E N=76	V600E N=16	V600D/K/R N=16
	Asymptomatic		
IC RR	58%	56%	44%
	+/- local therapy V600D/E/K/R N=17		
	Symptomatic		
IC RR	59%		

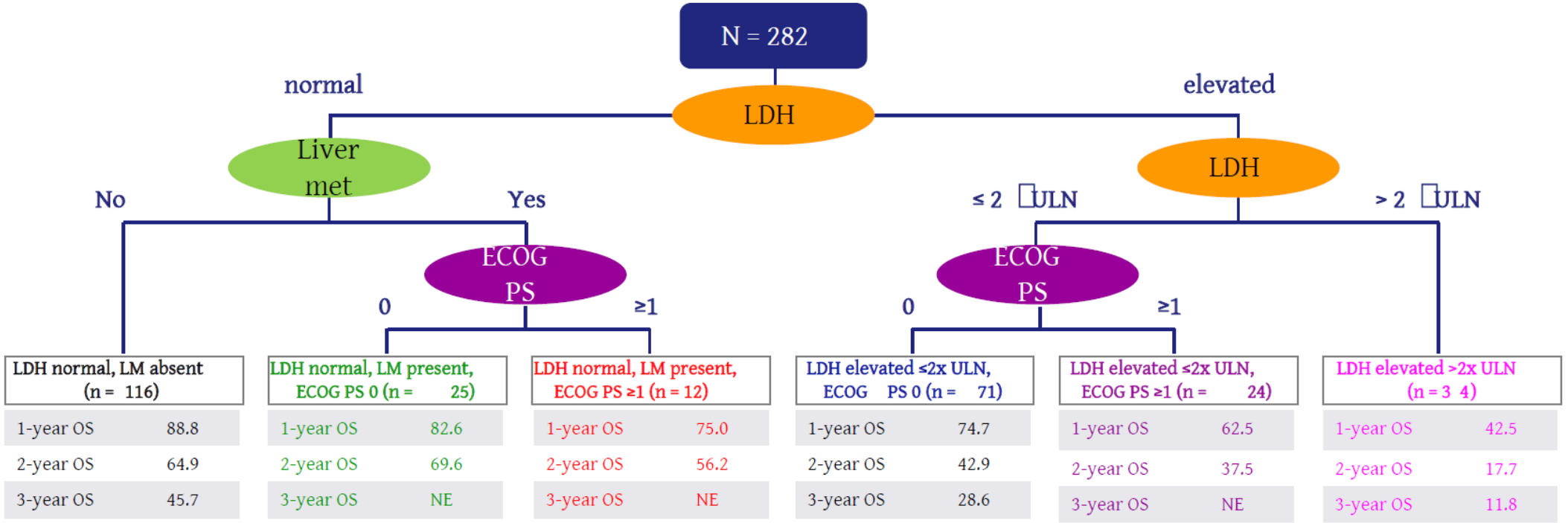
BRAF/MEKi Can be safely used in patients with:

- Treated or untreated
- Asymptomatic or symptomatic brain M1

Davies et al. Lancet Oncol 2017; 18(7):863-73

Is Immunotherapy less effective after failure of BRAF/MEKi?

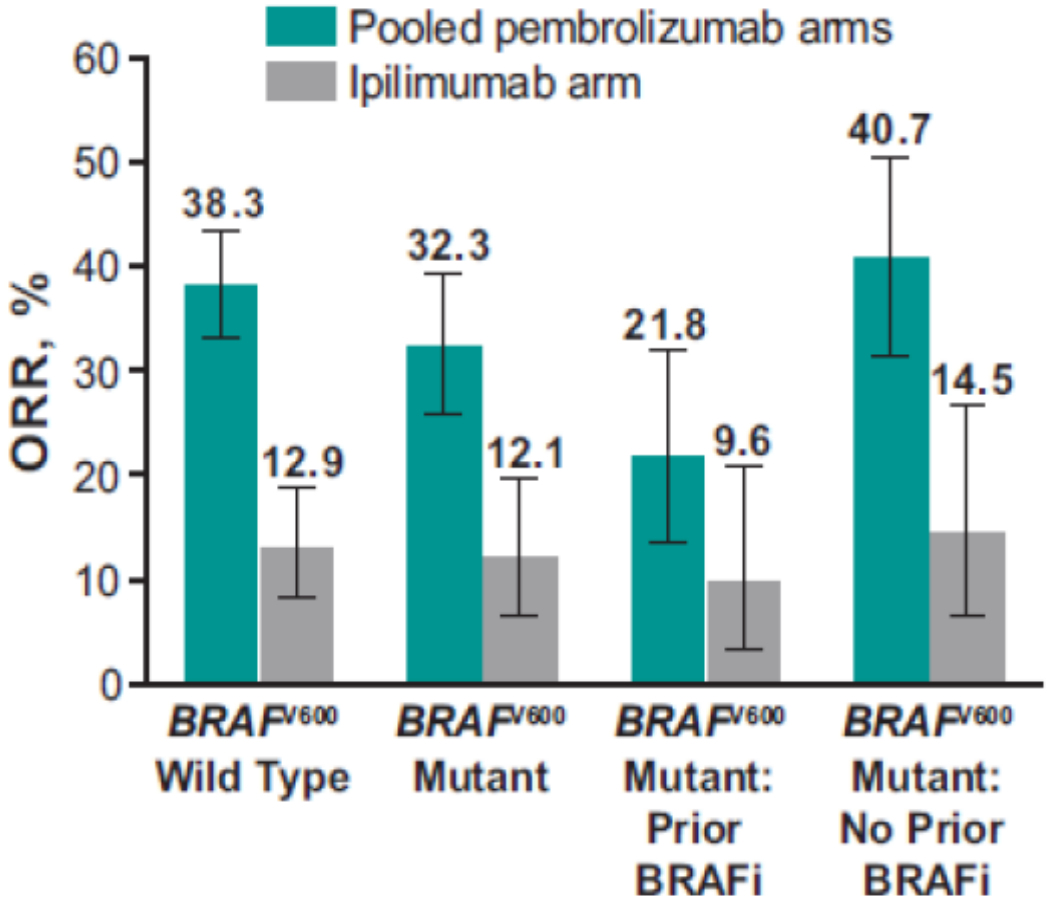
Análisis conjunto BRIM7 y coBRIM: Efectos características basales



Distribución ramificada de SG en todos los pacientes tratados con Z + C

1. Hauschild A. et al, Identification of prognostic subgroups for overall survival in patients with BRAF V600 -mutated metastatic melanoma treated with vemurafenib ± cobimetinib : a pooled exploratory analysis of the BRIM-2 , BRIM-3, BRIM-7, and coBRIM studies. Presented at EADO 2016.

Is anti-PD-1 therapy less effective after failure of BRAFi?



Puzanov et al. SMR 2015

Keynote 006: Baseline characteristics of BRAFV600 patients

	BRAF wild-type	BRAF mutant	BRAF mutant without prior BRAF inhibitor	BRAF mutant with prior BRAF inhibitor
Received 1 line of prior therapy	24%	52%	11%	100%
ECOG 1	34%	27%	21%	34%
M1c stage	66%	65%	58%	73%
Elevated LDH	36%	26%	17%	37%
Brain metastases	8%	11%	8%	15%
Baseline tumor size, mean (mm) and median (mm)	86 61	72 54	57 51	89 62
PD-L1 negative	17%	20%	12%	28%

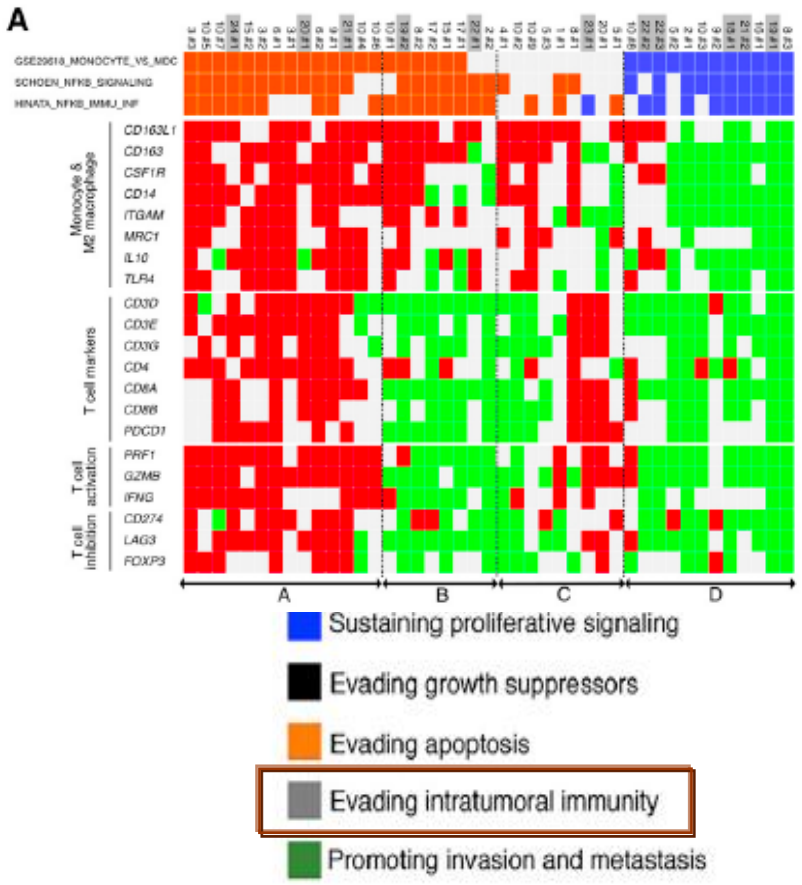
~18% BRAFV600 treatment naive

Pembrolizumab Assessment report EMEA/H/C/003820/0000

Shared mechanisms of resistance with immunotherapy and MAPKi

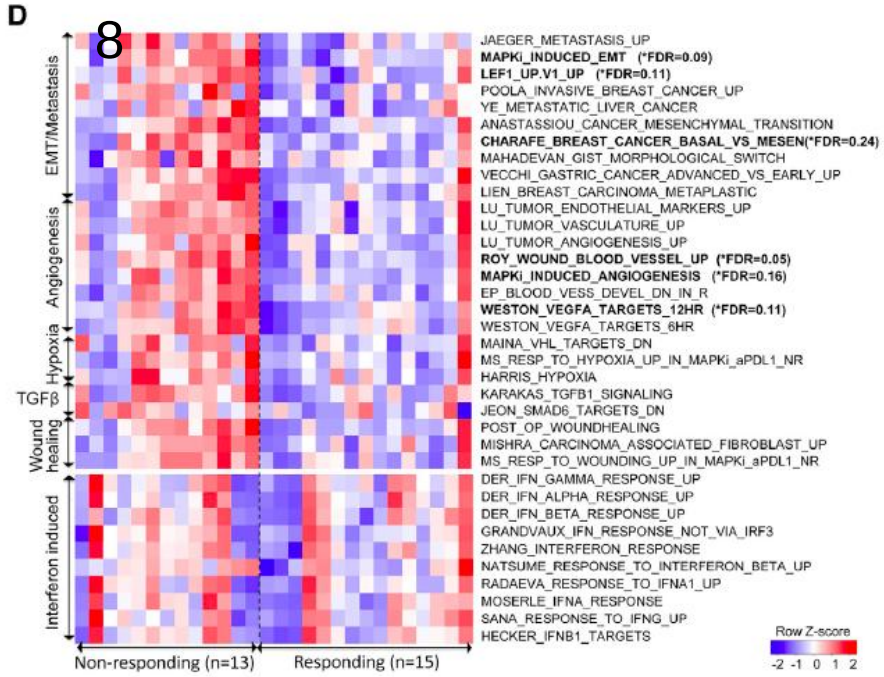
N=38

50% resistant melanomas



Hugo et al. Cell 162: 1271–1285, 2015

N=28



The transcriptomic signature that defines resistance to BRAF/MEKi is contained within the IPRES signatures associated to innate resistance to anti-PD-1

Hugo et al. Cell 165: 35-44, 2016

Factors influencing outcome to Immunotherapy after BRAF/MEKi failure:

- Clinical characteristics
- Tumor biology

SEquential COMBo Immuno and Target therapy (SECOMBIT) Study

ECCO

- Prospective randomized phase II study to evaluate the best sequential approach with combo immunotherapy (ipilimumab/nivolumab) followed by combo target therapy (dabrafenib/ trametinib) and vice-versa
- Patients with metastatic BRAF V600 mutated melanoma
- Sample size 230 pts

ARM A
Combo T
LGX 450 mg
MEK 162 45 mg
→ PD → Combo I until PD

ARM B
Combo I
Ipilimumab 3 mg/Kg
Nivolumab 1mg /Kg
→ PD → Combo T until PD

ARM C
Sandwich
LGX 450 mg
MEK 162 45 mg for 8 weeks
→ Combo I until PD → Combo T until PD

This study is designed as a phase II randomized trial with no formal comparative test.

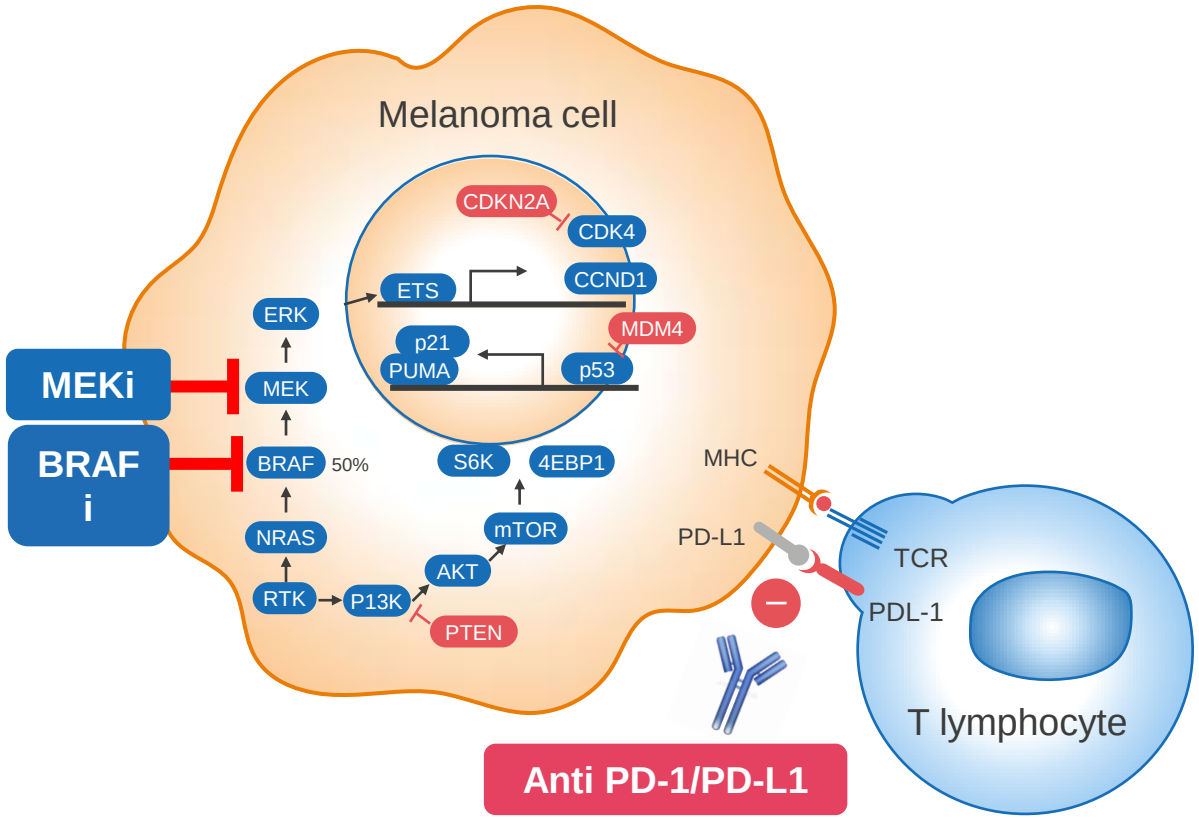
Endpoints:

Primary – OS

Secondary – PFS, Total PFS (TPFS): the time to the second progression, % patients alive at 2-3 years, BORR;
Duration of Response, Toxicity, Biomarkers study

P I : P. Ascierto
NCT02631447

Dual MAPK pathway inhibition changes the tumour environment, making tumours more susceptible to cancer immunotherapy



MAPKi-induced changes[1,2]

- Increased melanoma antigen expression
- Decreased immunosuppressive cytokine production
- Increased CD8+ T-cell infiltration
- Increased T-cell clonality
- Increased PD-L1 expression
- Class I MHC upregulation

Enhanced tumour cell death

T cells are activated and live longer

Tumour cells are more visible

Tumours are more susceptible to cancer immunotherapy

Number represents percentage of patients who have altered protein expression or mutation
MHC, major histocompatibility complex; PD-1, programmed death 1; PD-L1, programmed death ligand 1; TCR, T-cell receptor

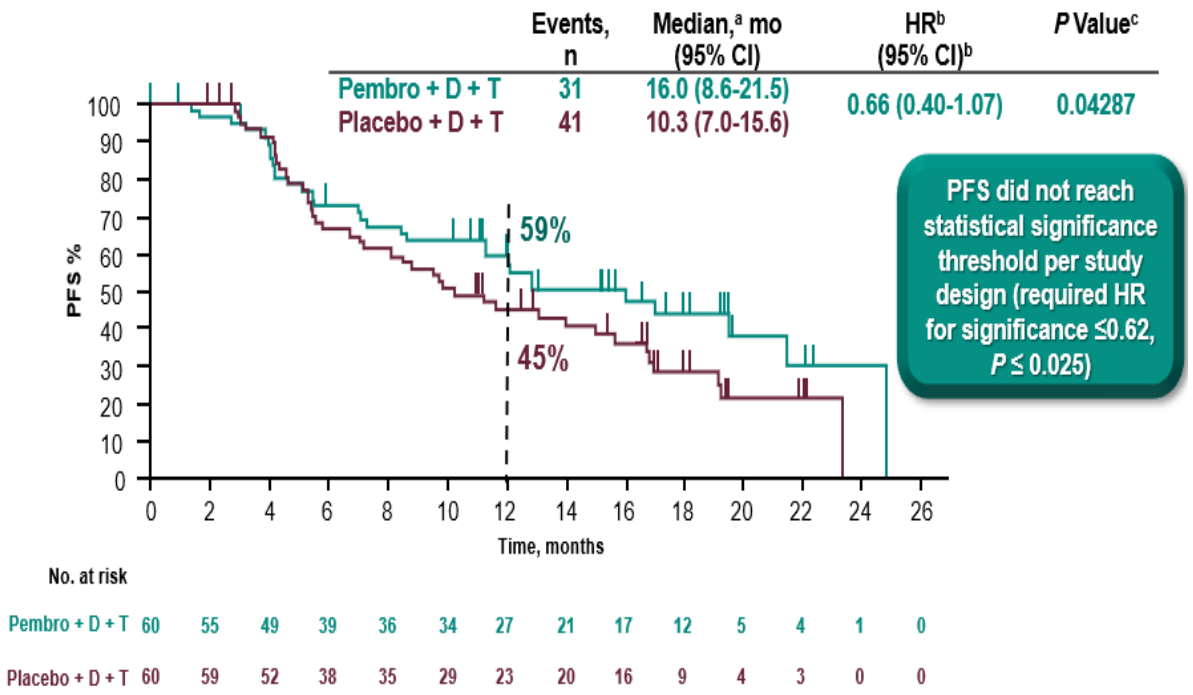
Image modified from McArthur and Ribas, J Clin Oncol, 2014

1. Frederick et al. Clin Cancer Res 2013; 2. Ebert et al. Immunity 2016

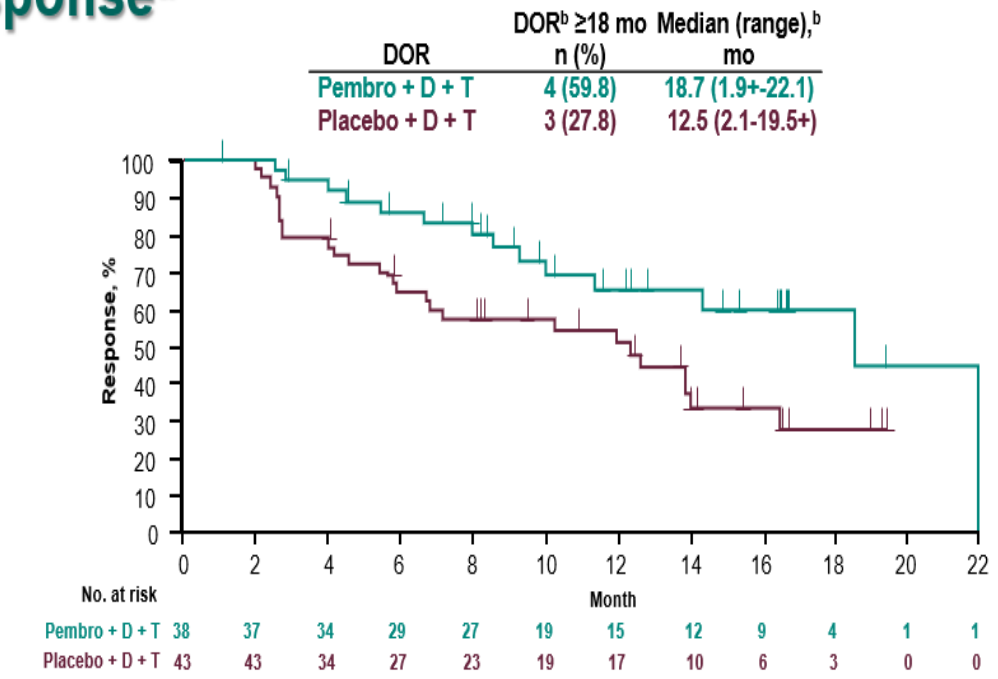
Dabrafenib + Trametinib + Pembrolizumab or Placebo Keynote 022

N=120

Progression-Free Survival



Kaplan-Meier Analysis of Duration of Response[a]



Ascierto et al ESMO 2018

Phase III clinical trials BRAF/MEKi + Anti-PD-1/PDL-1

Overview of Study Design PDR001: Double-blind, Randomized, Placebo-controlled

N = 500

Unresectable or metastatic BRAF V600 mutant melanoma (stage IIIC/IV)

- Previously untreated
- No active brain mets
- ECOG **PS ≤ 2**

R 1:1

PDR001 (RP3R identified in part 1) dabrafenib 150mg BID + trametinib 2mg QD

Placebo IV dabrafenib 150mg BID + trametinib 2mg QD

PD^{RECIST} or unacceptable toxicity*

Randomization Stratification

- ECOG PS (0 vs 1 vs 2)
- LDH (< 1 x ULN vs ≥ 1 to < 2 x ULN vs ≥ 2 x ULN)

Primary endpoints: PFS^{RECIST}

Previously Untreated Advanced Melanoma

- *BRAF* V600 mutation
- ECOG PS 0-1
- Measurable disease
- No significant history of liver disease

N = 500

R

Vem 960mg BID[a] Cobi 60mg QD[b]

Atezo 840mg q2w Vem 720mg BID + Vem Placebo 240mg BID Cobi 60mg QD[b]

28 days | Treatment until PD or toxicity

Vem 960mg BID[a] Cobi 60mg QD[b]

Placebo q2w Vem 960mg BID Cobi 60mg QD[b]

- **Key study objectives**
  - Primary: investigator-assessed PFS
  - Secondary: PFS (IRF-assessed), OS, ORR, DOR, Safety, PK

FINAL REMARKS

- BRAF inhibitors have changed the treatment paradigm for a 50% of melanoma patients whose tumours habour the BRAFV600 mutation

- All patients with advanced melanoma should be tested for the presence/absence of the BRAFV600 mutation

- Combination of BRAFi + MEKi has been validated as a new standard of care in BRAFV600 melanoma

- Building on BRAF/MEK inhibition will proceed:
  - in optimizing MAPK-targeted therapy
  - combination targeted therapy antagonizing pathways essential for melanomagenesis
  - Combination/sequencing with immunotherapy to maximise survival and QoL

- Translational research will be the key to guide us rationally and efficiently in the large number of trials ahead of us

Muchas Gracias

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coBRIM
Seguridad

	Vemurafenib + placebo (n=239)				Vemurafenib + cobimetinib (n=254)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Any AE, n (%)*[1,2]	233 (98)†				250 (98)†			
	21 (9)	70 (29)	117 (49)	22 (9)	19 (7)	66 (26)	125 (49)	34 (13)
Most common AEs, occurring in ≥20% of patients in either study group, n (%)[2]								
Diarrhoea	51 (21)	16 (7)	0	0	99 (39)	29 (11)	16 (6)	0
Nausea	43 (18)	12 (5)	2 (1)	0	75 (30)	22 (9)	2 (1)	0
Vomiting	21 (9)	6 (3)	2 (1)	0	41 (16)	10 (4)	3 (1)	0
Rash	46 (19)	27 (11)	12 (5)	0	55 (22)	29 (11)	13 (5)	2 (1)
Photosensitivity reaction	25 (10)	12 (5)	0	0	48 (19)	18 (7)	6 (2)	0
Hyperkeratosis	49 (21)	14 (6)	5 (2)	0	23 (9)	3 (1)	0	0
Fatigue	42 (18)	24 (10)	7 (3)	0	48 (19)	24 (9)	9 (4)	0
Pyrexia	43 (18)	10 (4)	0	0	49 (19)	13 (5)	4 (2)	0
Arthralgia	53 (22)	31 (13)	12 (5)	0	54 (21)	23 (9)	6 (2)	0
Alopecia	55 (23)	14 (6)	1 (<1)	0	33 (13)	1 (<1)	1 (<1)	0
Increased ALT	17 (7)	11 (5)	14 (6)	1 (<1)	16 (6)	15 (6)	28 (11)	1 (<1)
Increased AST	15 (6)	10 (4)	4 (2)	1 (<1)	17 (7)	18 (7)	21 (8)	0
Increased CK	6 (3)	1 (<1)	0	0	23 (9)	27 (11)	17 (7)	9 (4)
Selected AEs[2]								
cuSCC	0	0	27 (11)	0	0	1 (<1)	6 (2)	0

McArthur G, *et al*. Oral presentation at ESMO 2014; Abstract LBA5_PR;
Larkin J, *et al*. *N Engl J Med* 2014;371:1867−76.

Chorioretinopathy <1 vs 13%
Retinal detachment 0 vs 9%

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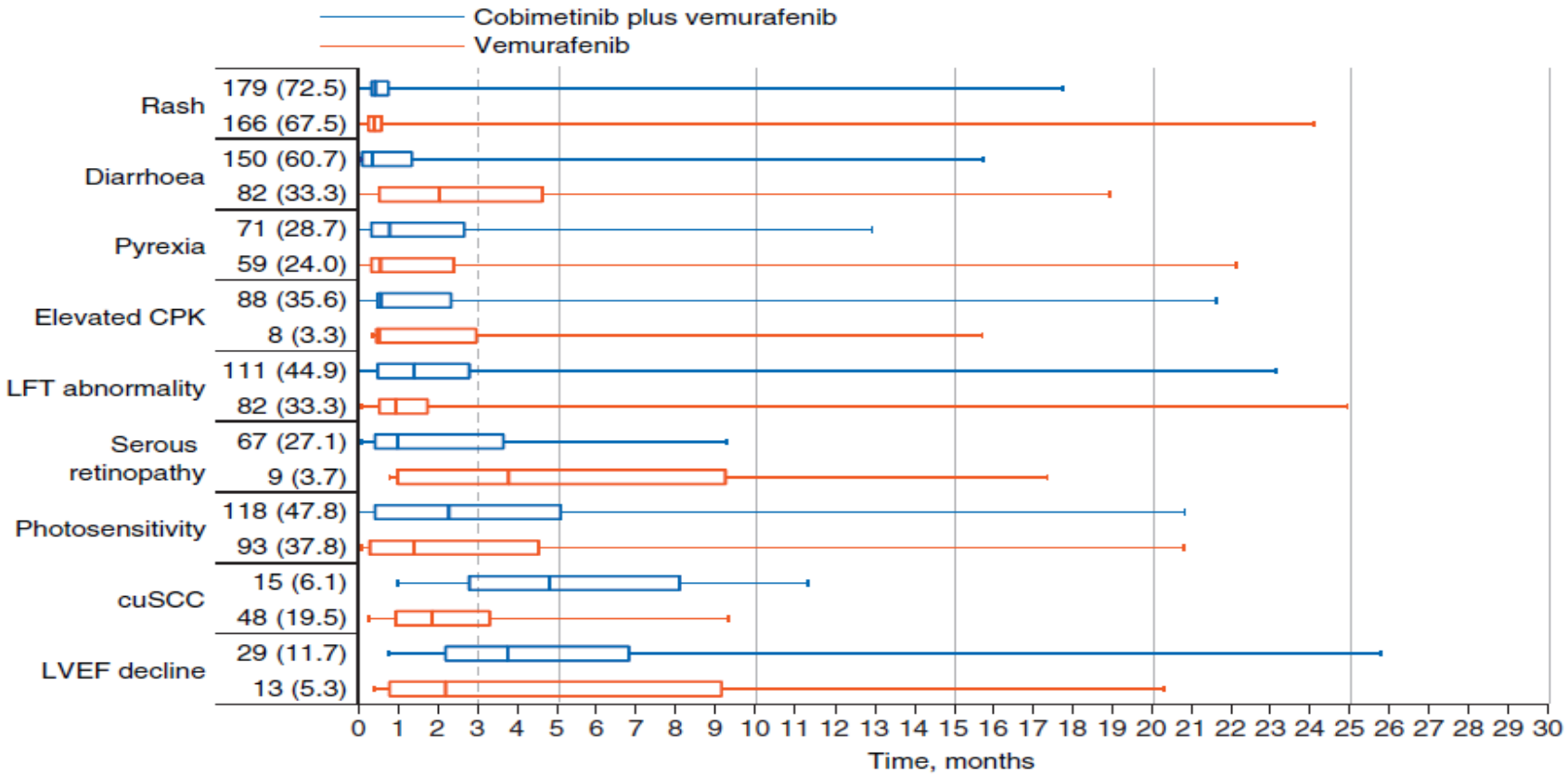
coBRIM: discontinuaciones de tratamiento

	V + P (n = 246) 30 Sept 2015	P + V (n = 245) 20 June 2016	C + V (n = 247) 30 Sep 2015	C + V (n = 248) 20 June 2016
Discontinued both V and C/P	216 (88)	225 (92)	193 (78)	209 (84)
Disease Progression	180 (73)	185 (76)	127 (51)	135 (54)
Adverse Events	21 (8.5)	21 (8.6)	36 (14.6)	38 (15.3)
Deaths	2 (0.8)	3 (1.2)	3 (1.2)	4 (1.6)
Other[a]	13 (5.3)	16 (6.5)	27 (10.9)	32 (12.9)

Mc Arthur, SMR 2016

coBRIM: Tiempo hasta 1ª aparición de EAs de interés

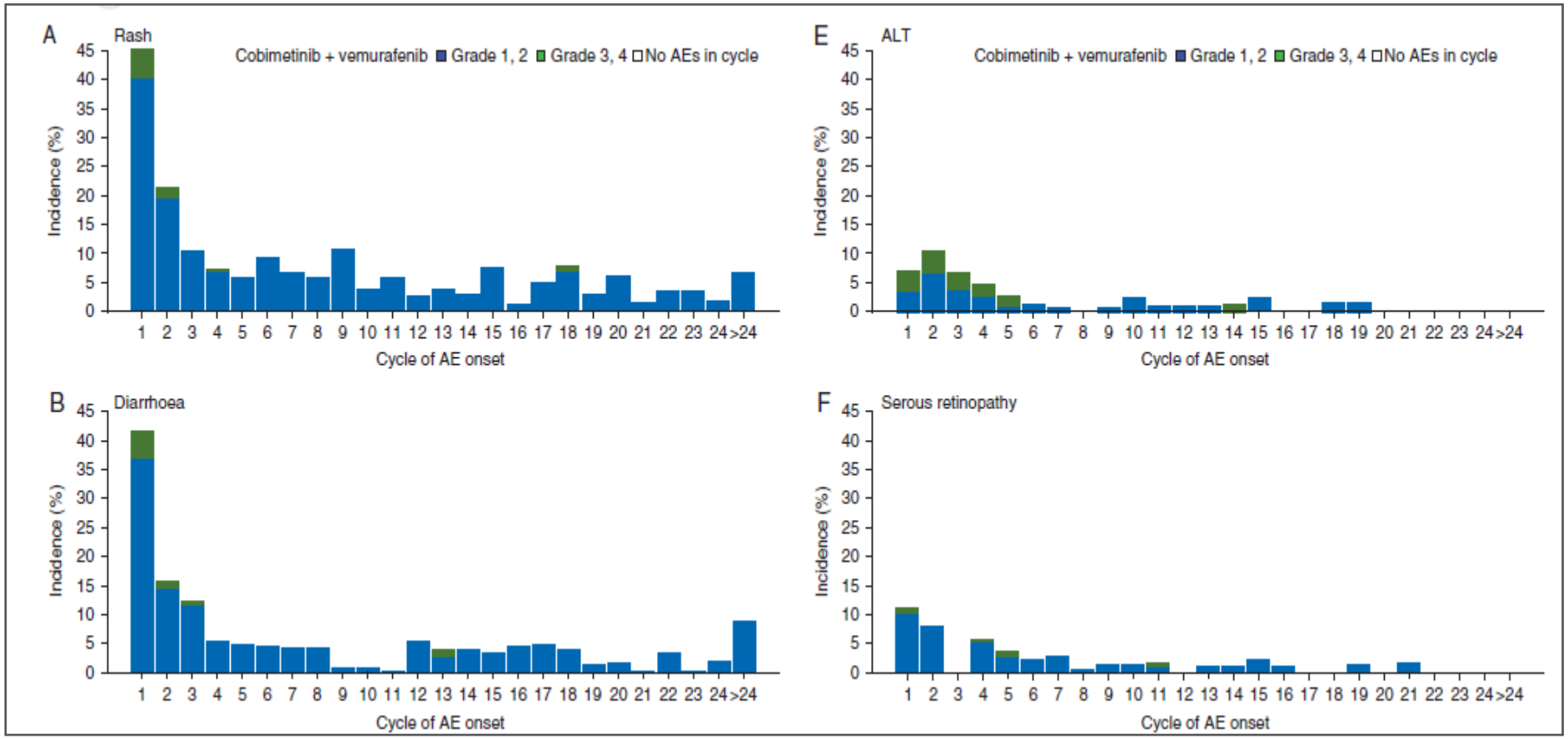
La mayoría de EAs comunes de interés tuvieron una aparición temprana, en los primeros 3 ciclos de tratamiento [1]



La línea refleja el rango, y la caja el 1er cuartil, la mediana y el 3er cuartil para la primera aparición de EAs

1. Dréno B et al, Ann Onc 2017

coBRIM:
Tras el primer Ciclo, la incidencia de Acontecimientos Adversos disminuye en el tiempo



Con Zelboraf & Cotellic la mayoría de los EAs son tolerables , de grado 1 o 2 ,y se manejan con tratamiento de soporte o modificación de dosis [1]

Corte base de datos: 30 Septiembre 2015 .

1. Ascierto PA, Lancet Oncol. 2016 Sep;17(9):1248-60. 2. Dréno B et al, Ann Onc 2017

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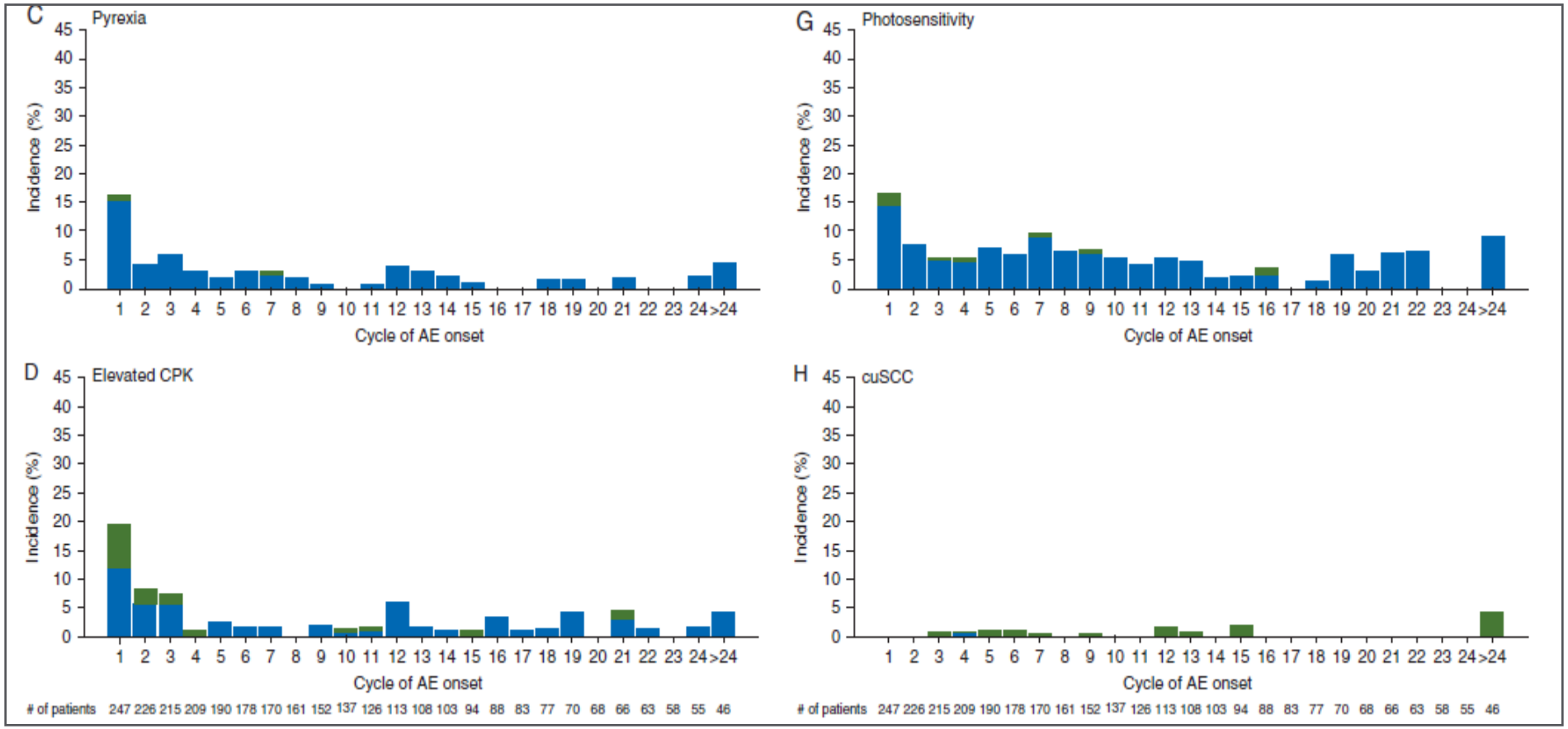

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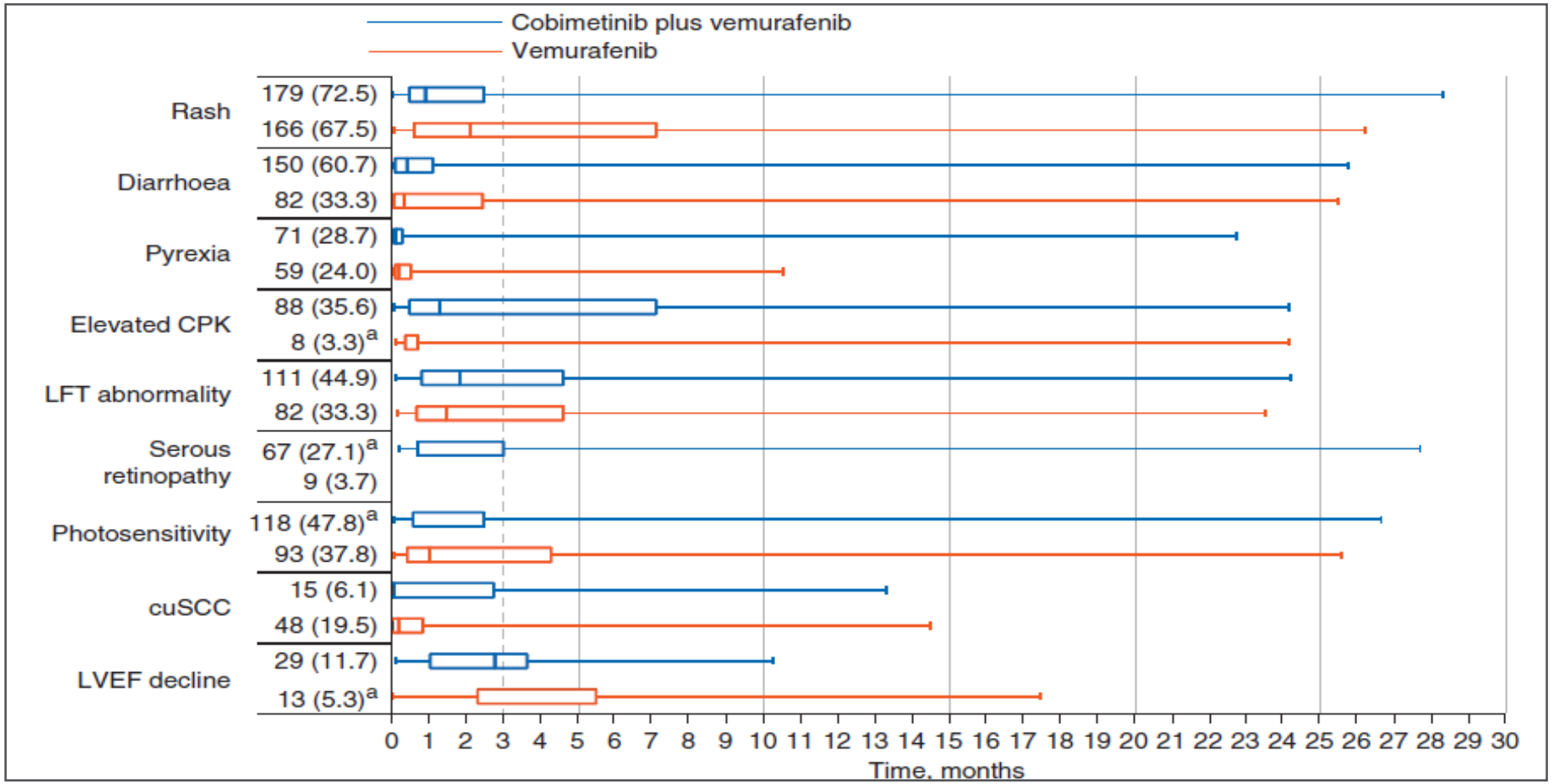
Corte base de datos: 30 Septiembre 2015 .

coBRIM:
Tiempo hasta resolución de EAs de interés

La mayoría de los EAs comunes se resolvió con una mediana de tiempo inferior a 2 meses[1]

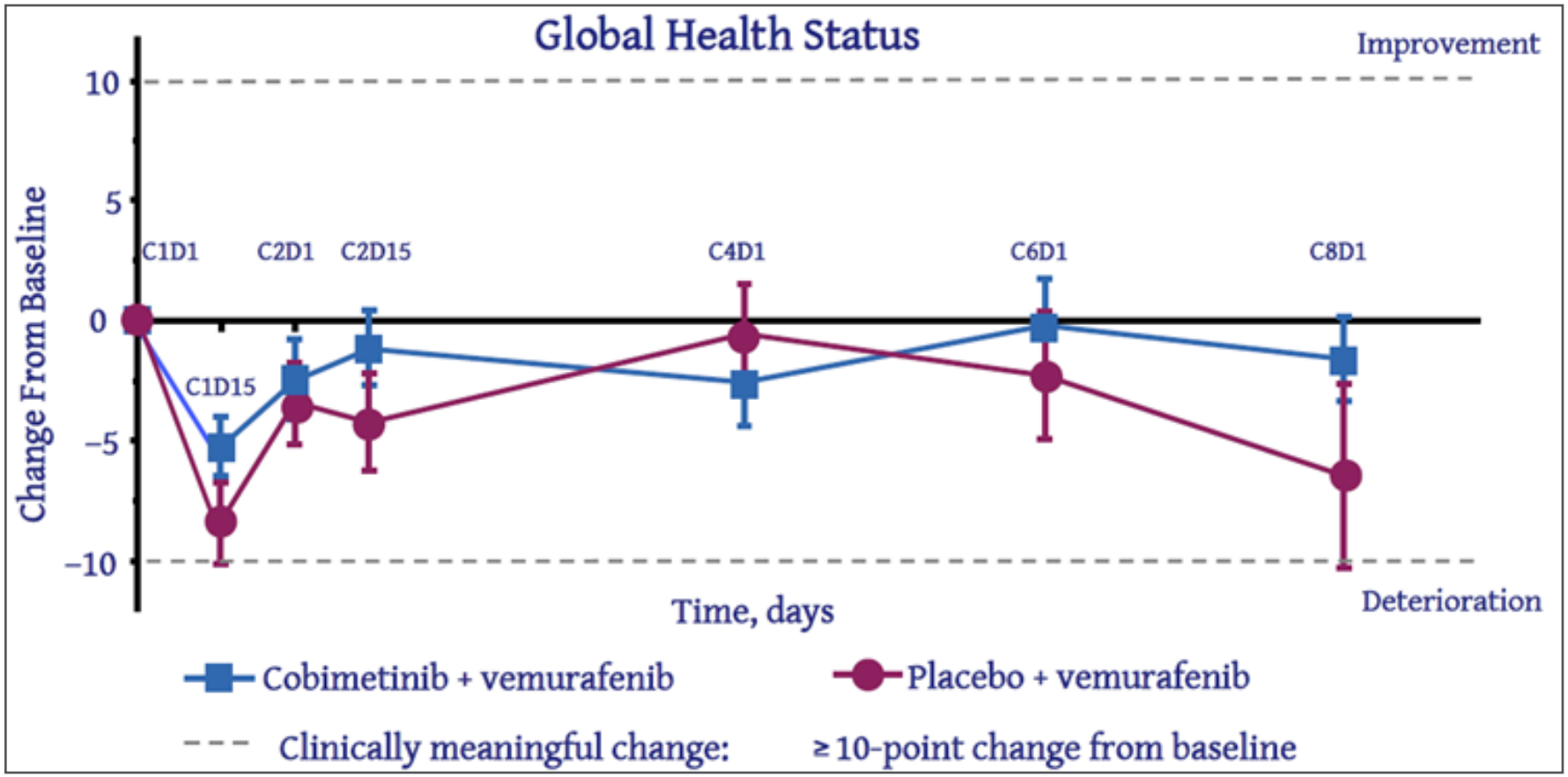


La línea refleja el rango, y la caja el 1er cuartil, la mediana y el 3er cuartil hasta la resolución de la primera aparición de EAs de cualquier grado

1. Dréno B et al, Ann Onc 2017

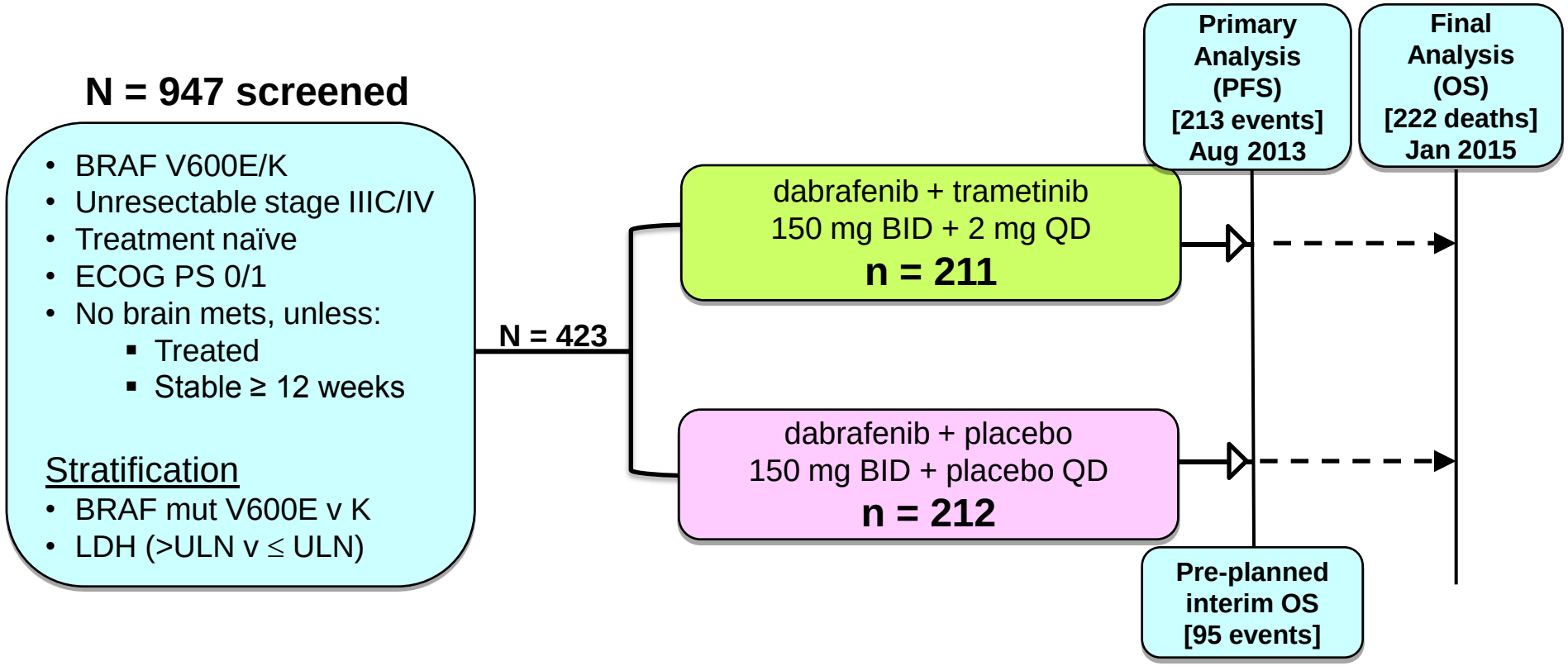
coBRIM:
Calidad de vida

Zelboraf + Cotellic mantuvo la Calidad de vida de los pacientes[1]



1. Dréno B et al. EADO 2015.

COMBI-d
Dabrafenib + Trametinib *vs* Dabrafenib

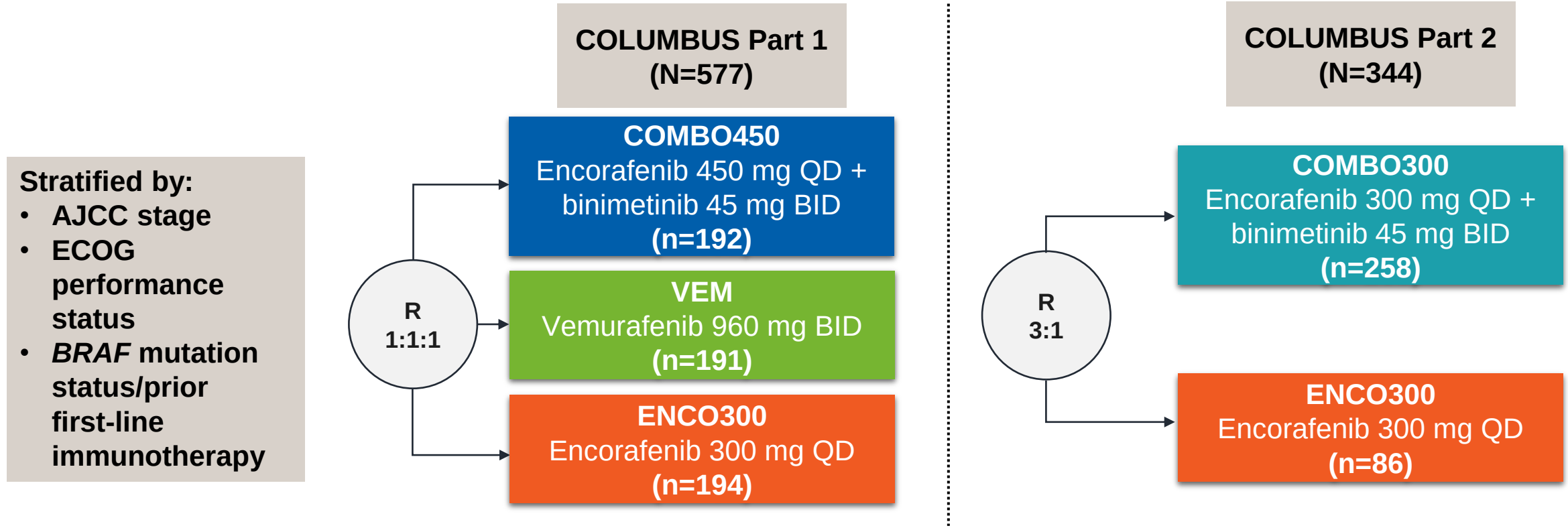


Primary Endpoint: Investigator-assessed PFS

Secondary Endpoints: OS, overall response rate (ORR), duration of response, safety

Long GV, et al. *Lancet* epub 31 May 2015.

COLUMBUS Part 1 and 2: study design



Primary endpoint:
PFS* for COMBO450 vs VEM

Select secondary endpoints:
OS, ORR, DoR and QoL across all arms

*PFS determined based on blinded independent radiology assessment

AJCC, American Joint Committee on Cancer; BID, twice daily; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; QoL, quality of life; R, randomisation

Dummer R. et al. SMR2016: presentation; Dummer R. et al. Ann Oncol 2017;28(suppl.5): v428-48 (#1215O and presentation); Dummer R, et al. Lancet Oncol 2018;19:603–615; Dummer R, et al. Lancet Oncol 2018;19:1315–1327; Novartis study protocol CMEK162B2301, version 04, 04.11.2014