I SIMPOSIO NACIONAL
de ONCOLOGÍA de PRECISIÓN

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

Tumores Cutáneos

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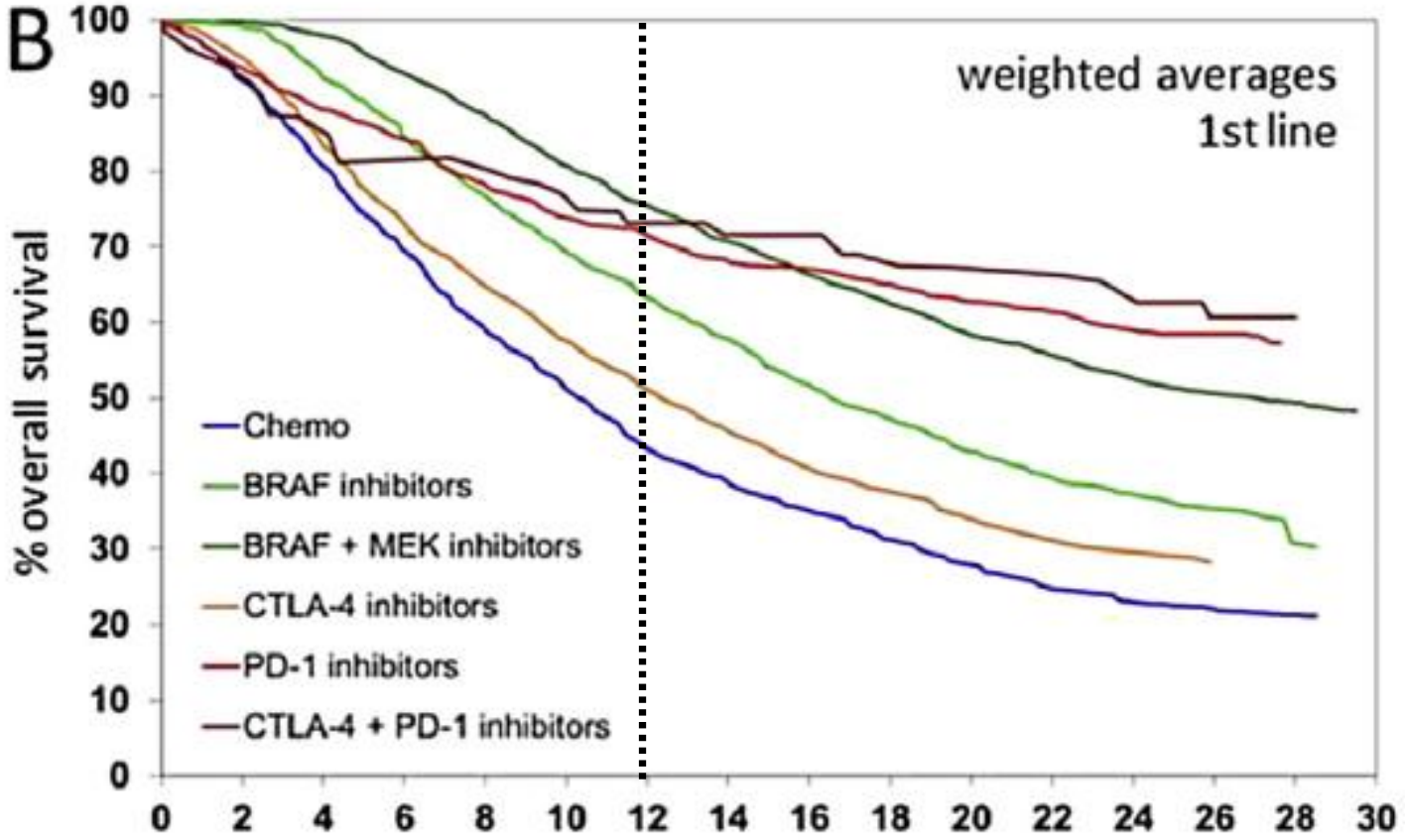
Summary of OS accross clinical trials in patients with metastatic melanoma

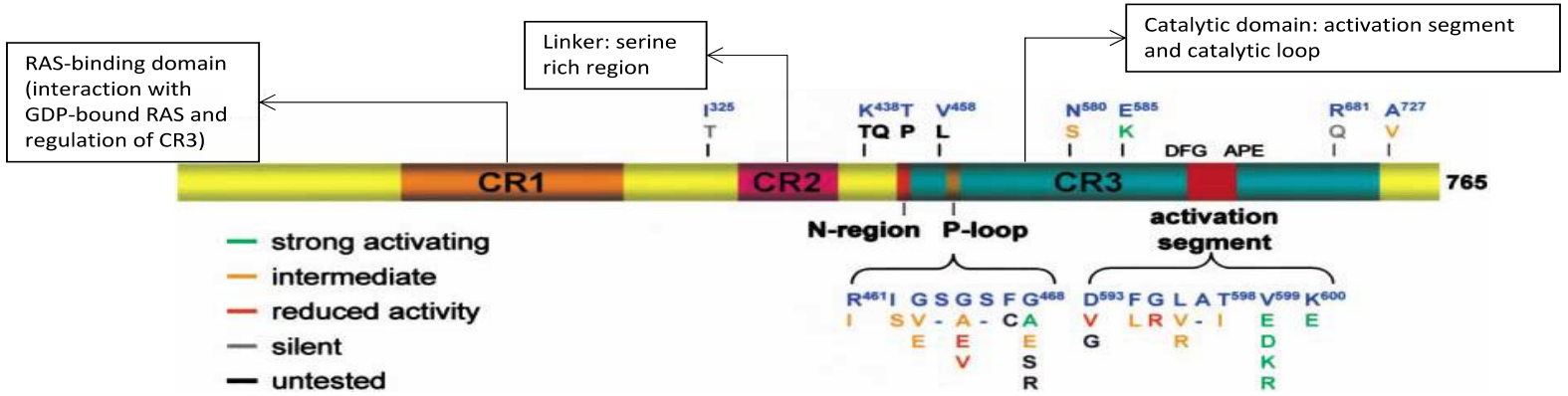


Ugurel et al. Eur J Cancer 2017

BRAF mutant Melanoma

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

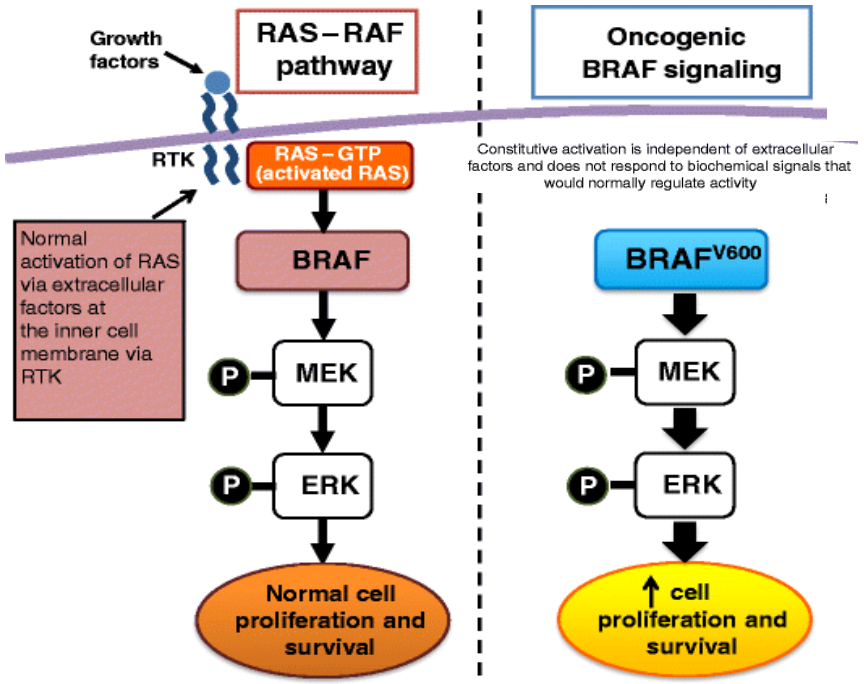
BRAF Mutation, %	
All	45-55%
V600E (val-glu)	70-80%
V600K (val –lys)	15-30%
Other (V600D/R, K601E, G469A, D594G, L597V...)	<5%



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

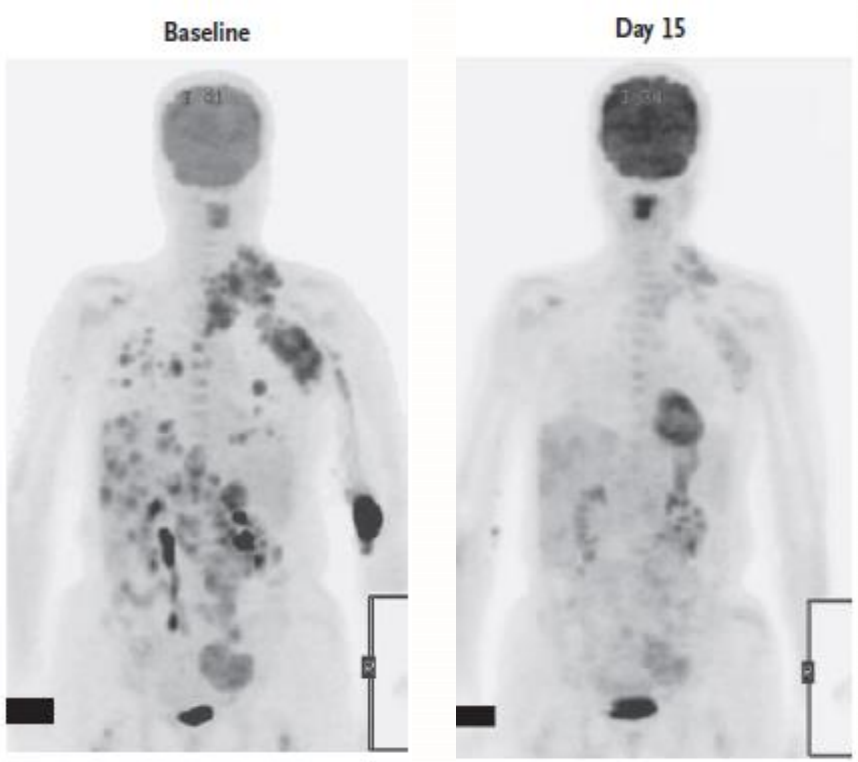
BRAF and MAPK pathway

- 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

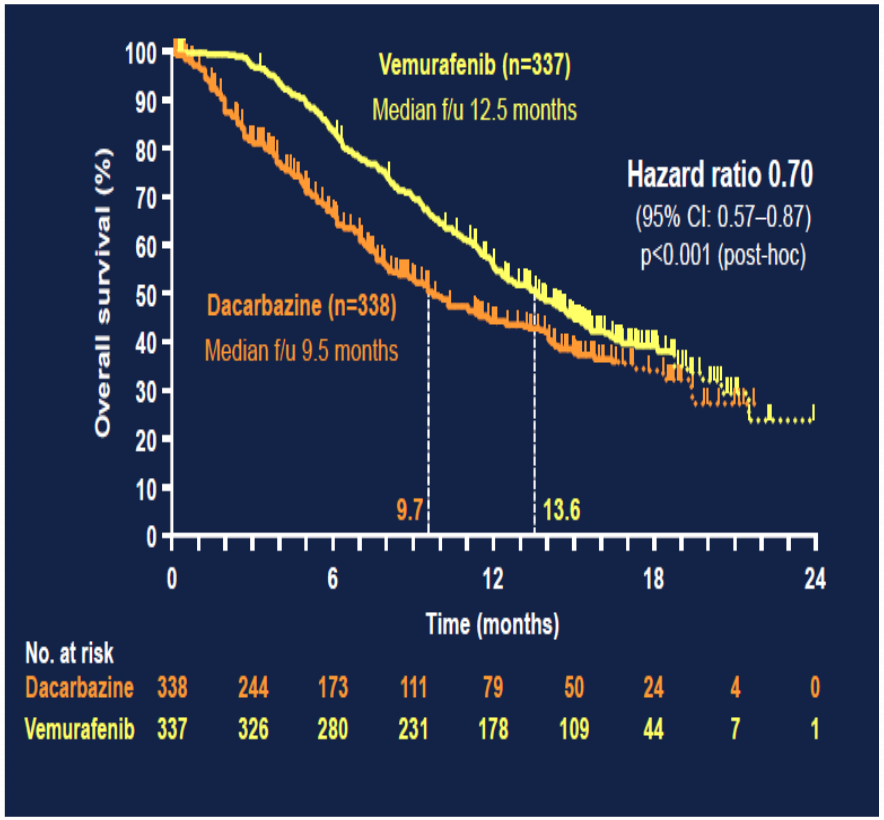


Ascierto PA, et al; Journal of Translational Medicine 2012, 10:85

BRAFi induce early responses

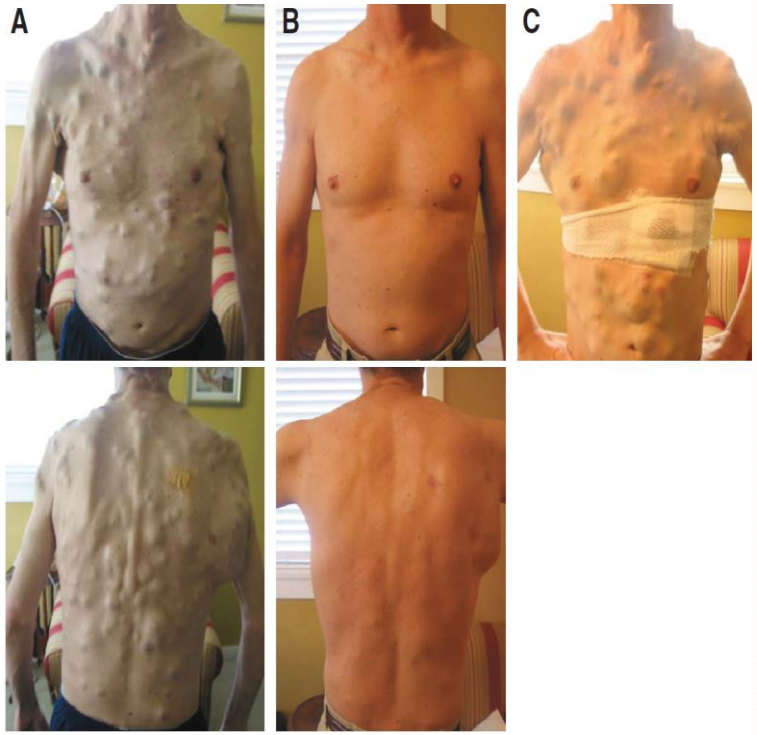


Improved OS in MelanomaBRAFV600



Resistance to BRAFi

mDoR = 6.7 months

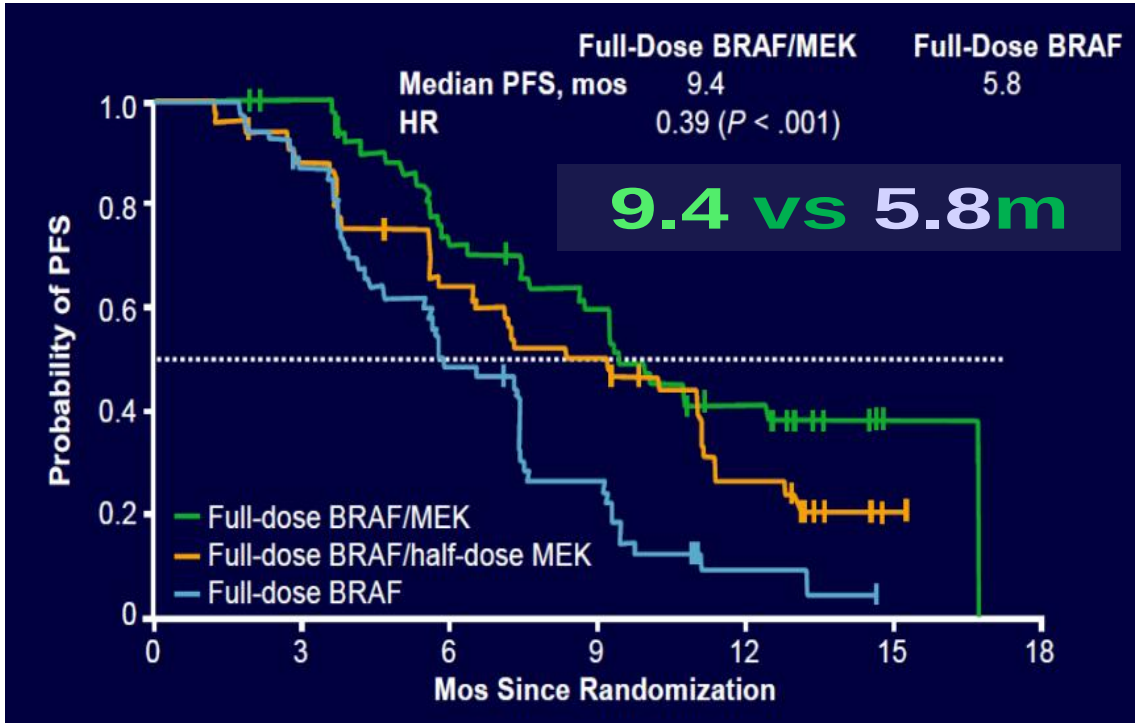


Basal iBRAF PD

Flaherty FT, et al. N Engl J Med 2010;363:809-19; Mc Arthur et al. J Clin Oncol 2012; Chapman P.B. N Engl J Med , June 2011; Lancet Oncol 2014; 15: 323–32; J Clin Oncol 29:3085-3096. 2011

Delayed Resistance with BRAFi/MEKi combo *vs* Single Agent BRAFi

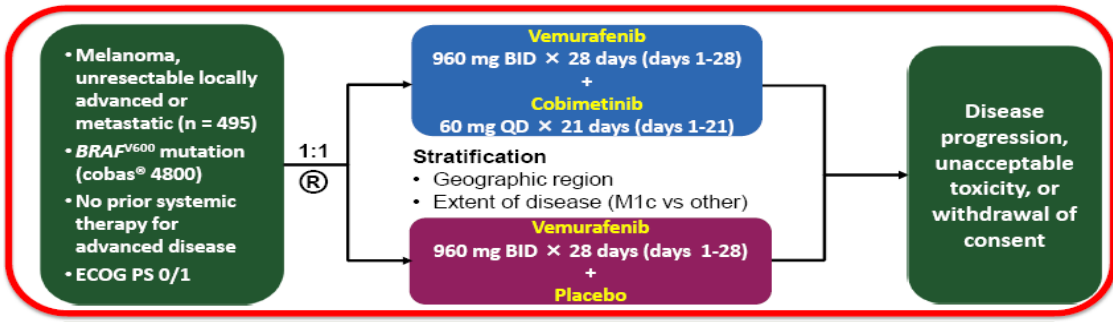
N=162



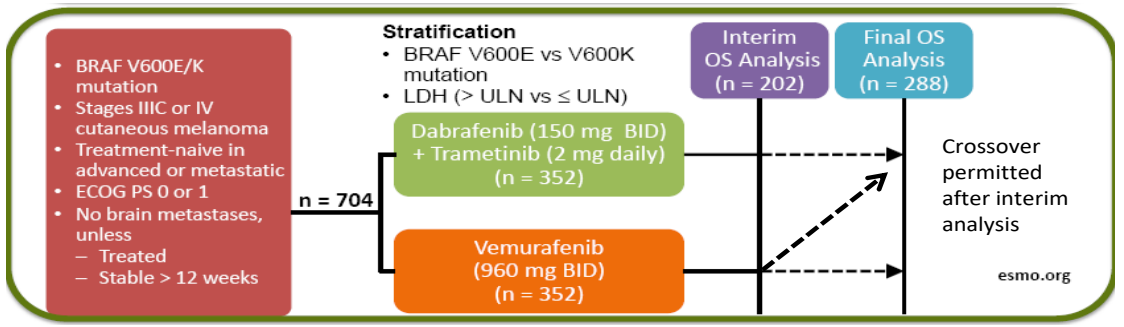
Flaherty KT, et al. N Engl J Med. 2012;367:1694-1703.

Phase 3 studies BRAFi/MEKi *vs* BRAFi

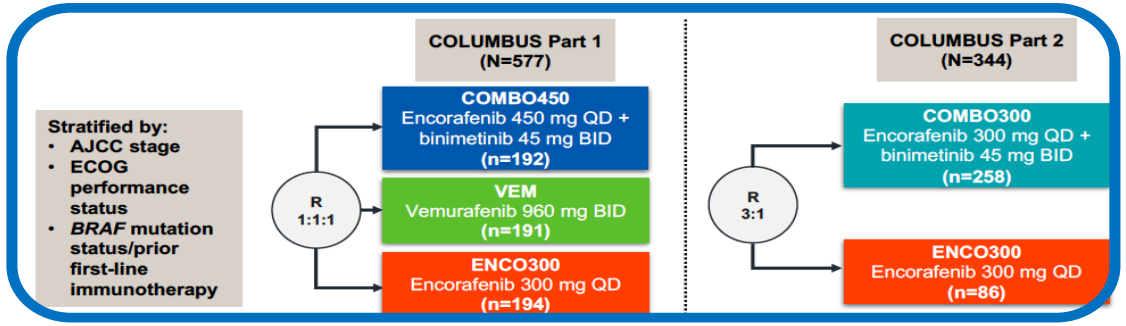
coBRIM (PFS)



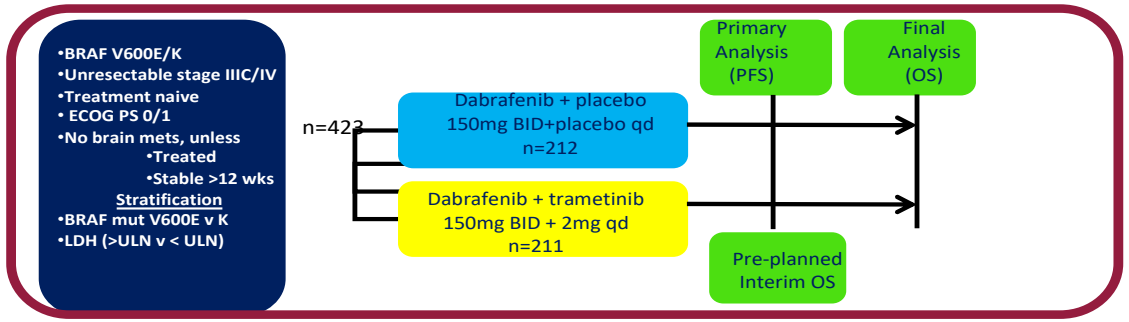
COMBI-v (OS)



COLUMBUS (PFS)



COMBI-d (PFS)

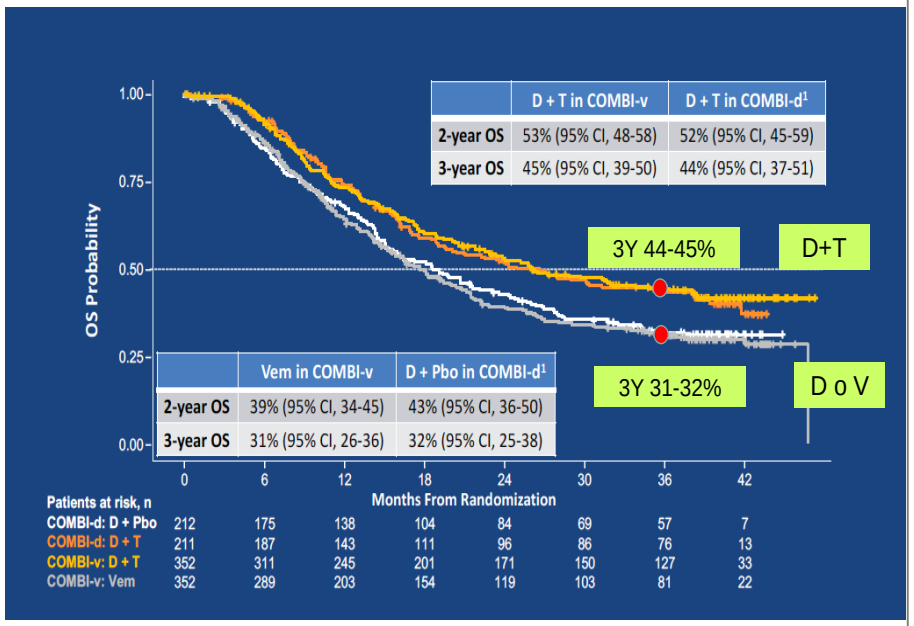


BRAFi/MEKi : Response

Trial	ORR (%)		mDoR, m	
	iBRAF/MEK	iBRAF	iBRAF/MEK	iBRAF
Combi-V	66	53	13.8	8.5
Combi-D	69	53	12.9	10.6
Cobrim	70	50	12.9	9.3
Columbus	64	41	18.6	6.7

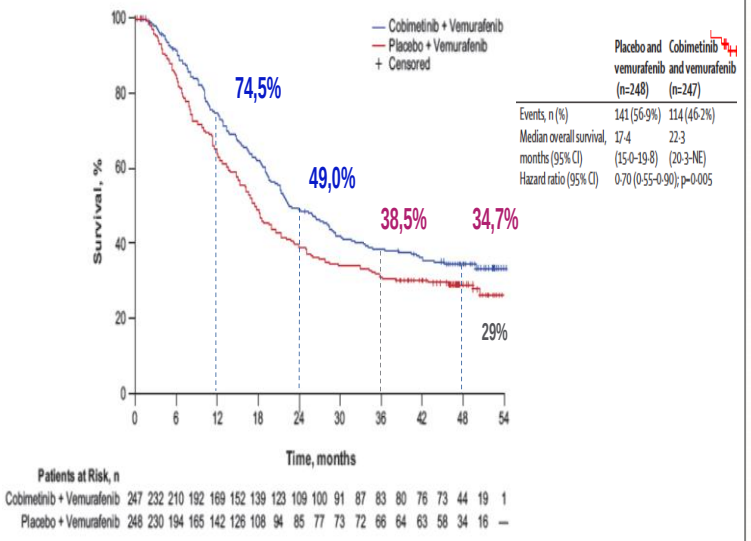
Robert C et al, ESMO 2014. Long GV, et al. N Engl J Med 2014. Larkin J, et al. N Engl J Med 2014. Robert et al. ESMO 2015; Long et al. ASCO 2015. Larkin et al. ASCO 2015; Mc Arthur et al. J Clin Oncol 2012

COMBI-v and COMBI-d
Dabrafenib + Trametinib SG



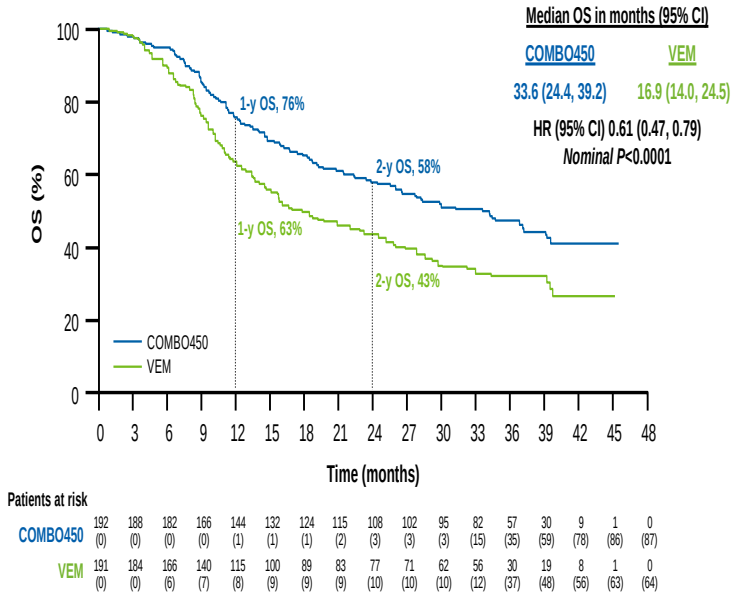
Robert C, *et al*. Oral presentation at ESMO 2016

coBRIM: Supervivencia Global



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

COLUMBUS Part 1: OS – COMBO450 vs VEM



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

Summary of efficacy data

	COMBI-v[1,2] FU 23 months		CoBRIM[3,4] FU 21.2 months		COLUMBUS[5–7] FU 36.8 months[+]	
	DAB + TRAM (n=352)	VEM (n=352)	**VEM + COBI** (n=247)	VEM (n=248)	**ENCO + BINI** (n=192)	VEM (n=191)
Median PFS (months)	**12.1**	7.3	**12.3**	7.2	**14.9[#]**	7.3[#]
	HR 0.61 (95% CI 0.51, 0.73)		HR 0.58 (95% CI 0.46, 0.72)		HR 0.51 (95% CI 0.39, 0.67)	
Median OS (months)	**26.1**	17.8	**22.5**	17.4	**33.6**	16.9
	HR 0.68 (95% CI 0.56, 0.83)		HR 0.78 (95% CI 0.62, 0.97)		HR 0.61 (95% CI 0.47, 0.79)	
1-year survival (%)	**72**	65	**75**	64	**75**	63
2-year survival (%)	**53**	39	**49**	39	**58**	43
3-year survival (%)	**45**	31	**39**	31	**47[†]**	32[†]

*data overview deriving from different studies; direct comparative conclusions are not possible

BINI, binimetinib; COBI, cobimetinib; DAB, dabrafenib; ENCO, encorafenib; FU, follow-up (related to OS of the combo); OS, overall survival; PFS, progression-free survival; TRAM, trametinib; VEM, vemurafenib; [+]reverse Kaplan-Meier-analysis; [†]data not mature yet; # according to central review

1. Robert C. et al., N Engl J Med 2015;372:30-9; 2. Robert C. et al., Ann Oncol 2016;27:1-36: #LBA40 and presentation; 3. Ascierto P. et al., Lancet Oncol 2016;17:1248–1260; 4. Dréno B. et al., J Clin Oncol 2018;36(suppl.): #9522 and poster; 5. Dummer R. et al., J Clin Oncol 2018;36(suppl.): #9504 and presentation; 6. Dummer R. et al.,Lancet Oncol 2018;19:1315–1327; 7. Dummer R. et al. Lancet Oncol 2018;19:603–615

Safety

	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%)

Event	Dabrafenib plus Trametinib (N=209)		Dabrafenib Alone (N=211)	
	Any Grade†	Grade 3	Any Grade†	Grade 3
	number of patients (percent)			
Any adverse event	199 (95)	66 (32)	203 (96)	72 (34)
Pyrexia‡	107 (51)	12 (6)	59 (28)	4 (2)
Fatigue	74 (35)	4 (2)	74 (35)	2 (1)
Headache	63 (30)	1 (<1)	62 (29)	3 (1)
Nausea	63 (30)	0	54 (26)	3 (1)
Chills	62 (30)	0	33 (16)	0
Arthralgia	51 (24)	1 (<1)	58 (27)	0
Diarrhea	51 (24)	2 (1)	30 (14)	2 (1)
Rash	48 (23)	0	46 (22)	2 (1)
Hypertension	46 (22)	8 (4)	29 (14)	10 (5)
Vomiting	42 (20)	2 (1)	29 (14)	1 (<1)

	Encorafenib 450 mg plus binimetinib 45 mg group (n=192)			Encorafenib 300 mg group (n=192)			Vemurafenib 960 mg group (n=186)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Nausea	76 (40%)	3 (2%)	0	66 (34%)	8 (4%)	0	60 (32%)	3 (2%)	0
Diarrhoea	65 (34%)	4 (2%)	1 (1%)	23 (12%)	3 (2%)	0	59 (32%)	4 (2%)	0
Vomiting	54 (28%)	3 (2%)	0	43 (22%)	9 (5%)	0	26 (14%)	2 (1%)	0
Fatigue	51 (27%)	4 (2%)	0	47 (24%)	1 (1%)	0	53 (28%)	4 (2%)	0
Arthralgia	48 (25%)	1 (1%)	0	66 (34%)	18 (9%)	0	72 (39%)	11 (6%)	0
Blood creatine phosphokinase increased	31 (16%)	11 (6%)	2 (1%)	2 (1%)	0	0	4 (2%)	0	0
Constipation	42 (22%)	0	0	27 (14%)	0	0	11 (6%)	0	1 (1%)
Headache	39 (20%)	3 (2%)	0	46 (24%)	6 (3%)	0	34 (18%)	1 (1%)	0
Asthenia	32 (17%)	2 (1%)	1 (1%)	32 (17%)	5 (3%)	0	26 (14%)	8 (4%)	0
Pyrexia	28 (15%)	7 (4%)	0	27 (14%)	2 (1%)	0	52 (28%)	0	0
Abdominal pain	27 (14%)	5 (3%)	0	9 (5%)	4 (2%)	0	11 (6%)	1 (1%)	0

Ascierto et al. Lancet Oncology 2016; Dummer et al. Lancet Oncol 2018; Long et al NEJM 2014

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:

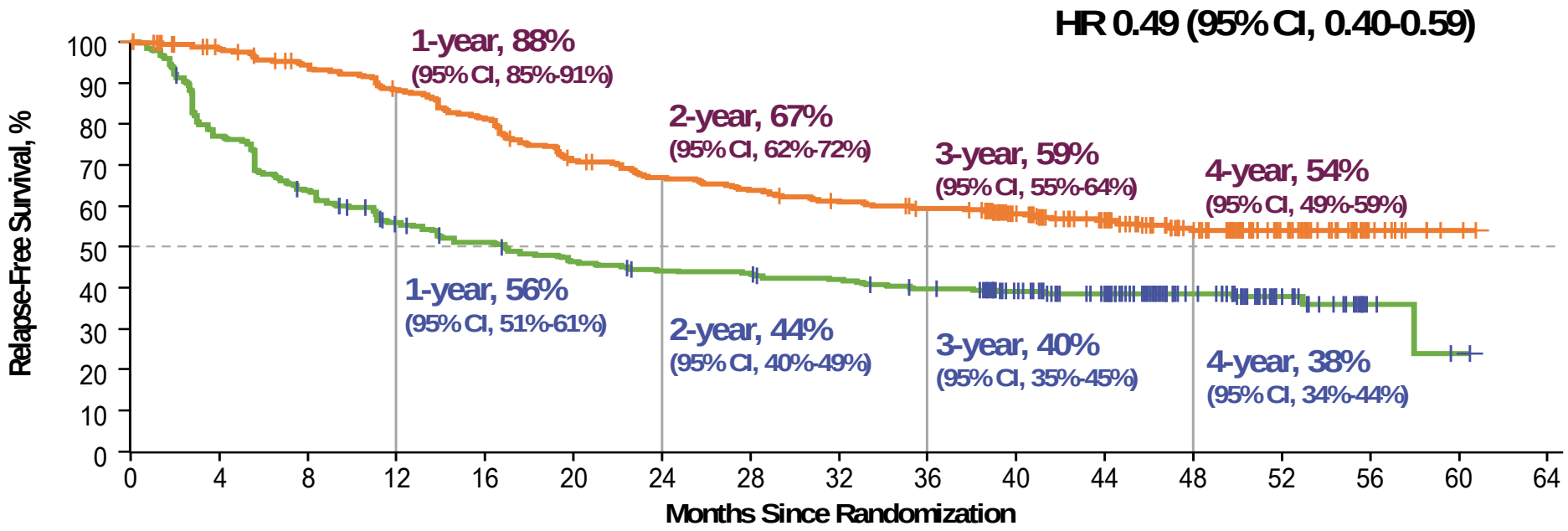
- Treated or untreated
- Asymptomatic or symptomatic brain M1

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

Adjuvant Setting

COMBI-AD: Dabrafenib + Trametinib was associated with improved RFS

Stage IIIA (>1mm), IIIB, IIIC completely resected

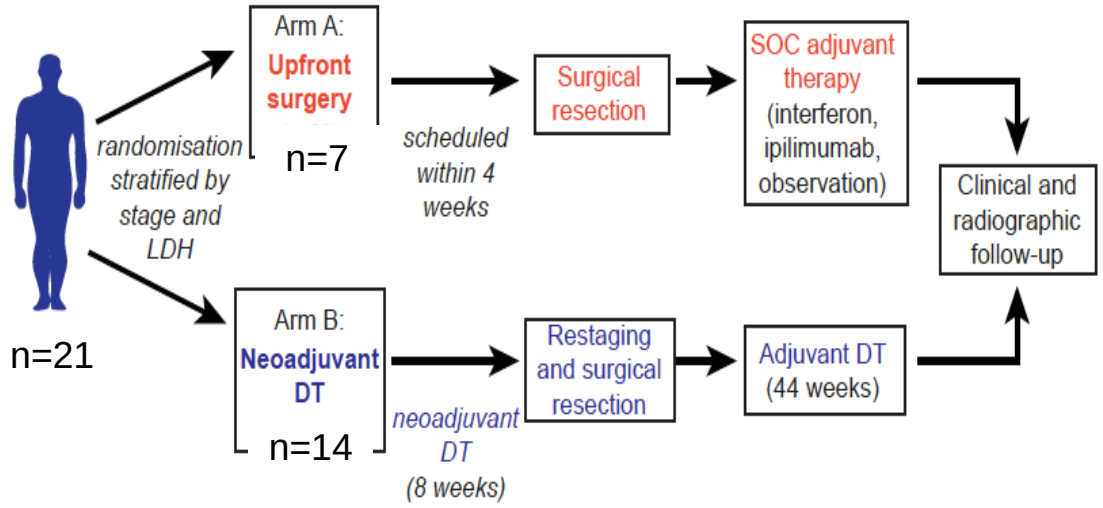


No. at risk																	
Dabrafenib + trametinib	438	405	381	354	324	281	262	249	236	227	183	148	92	47	13	2	0
Placebo	432	322	263	219	198	178	168	164	157	147	128	107	63	27	4	1	0

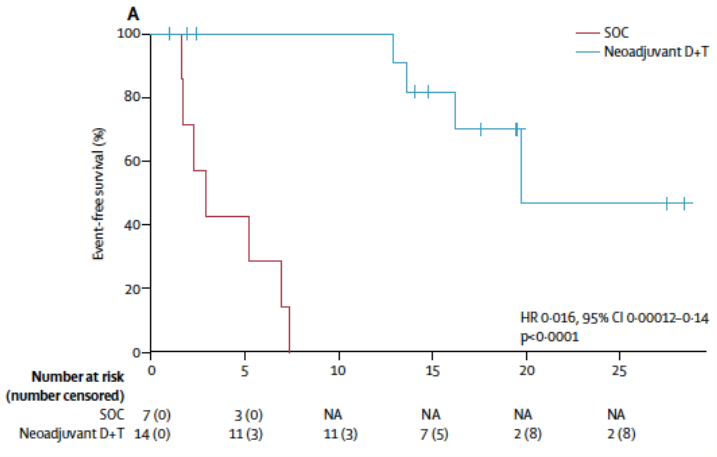
Long GV, et al. *N Engl J Med*. 2017;377:1813-1823; Hauschild et al. J Clin Oncol 2018

Neo-Adjuvant Setting

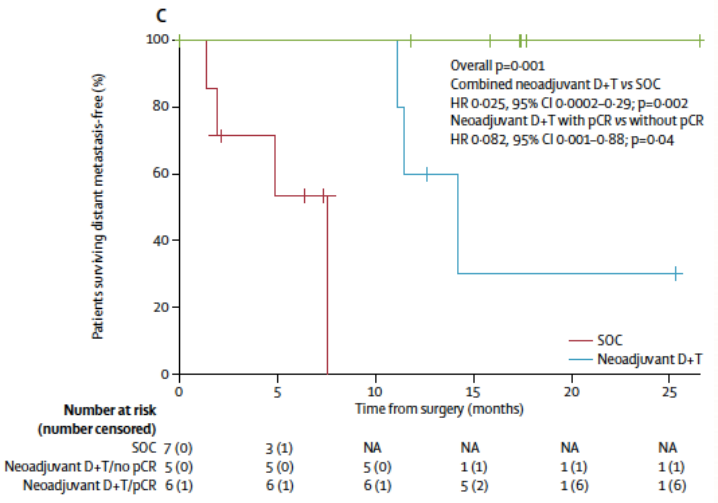
- Clinical Stage III and oligometastatic stage IV BRAFV600 melanoma:
  - N> 1.5cm or 1cm intransit M1
  - < 4 sites of M1



Objective: Event-free survival

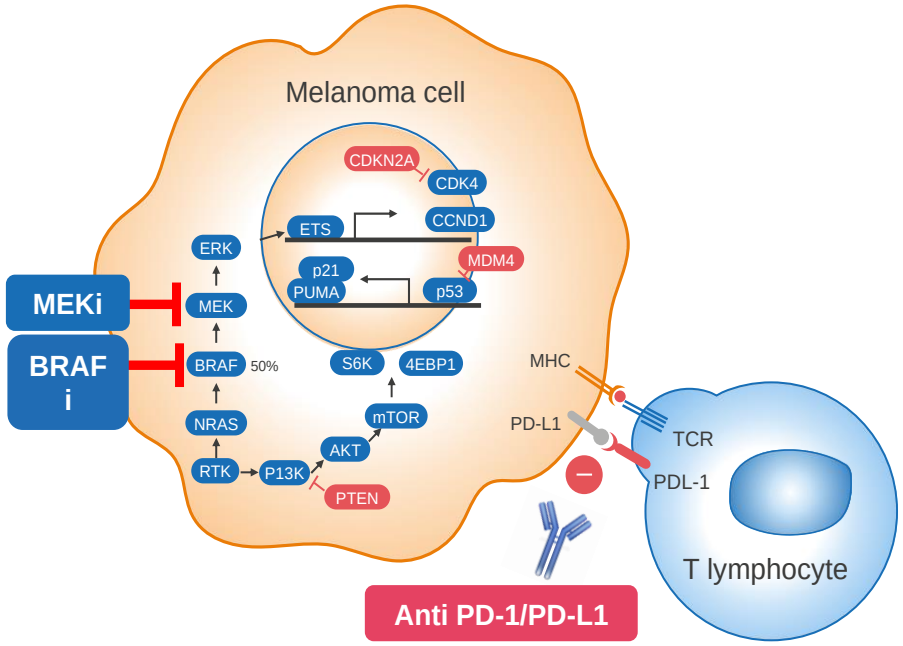


7/12 (58%) pCR
2/12 (17%) pPR



Amaria et al. Lancet Oncol 2018; 19: 181–93

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

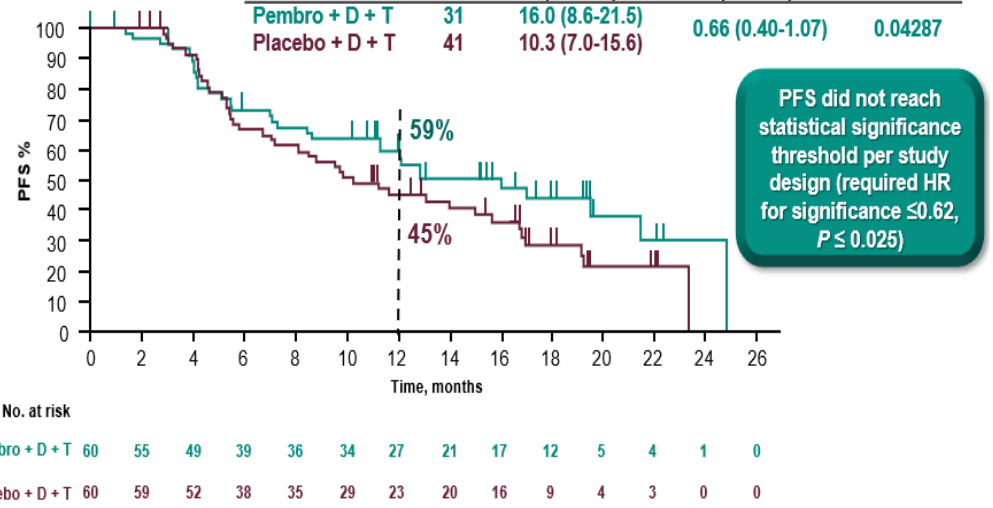
Triplets

Dabrafenib + Trametinib + Pembrolizumab or Placebo Keynote 022

N=120

Progression-Free Survival

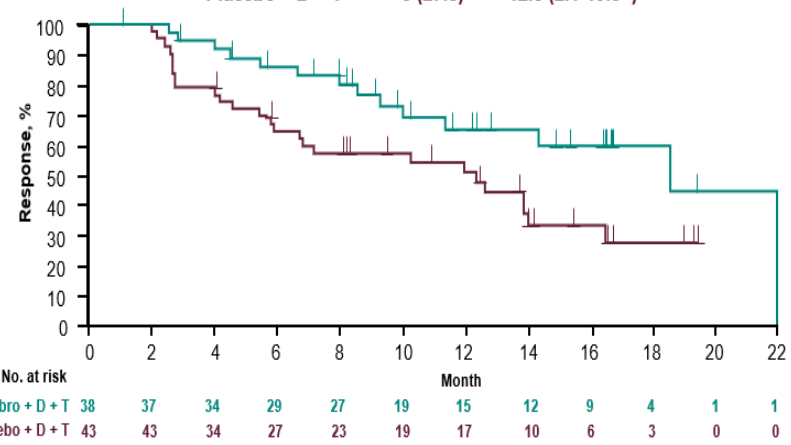
	Events, n	Median,[a] mo (95% CI)	HR[b] (95% CI)[b]	*P* Value[c]
Pembro + D + T	31	16.0 (8.6-21.5)	0.66 (0.40-1.07)	0.04287
Placebo + D + T	41	10.3 (7.0-15.6)		



PFS did not reach statistical significance threshold per study design (required HR for significance ≤0.62, $P \leq 0.025$)

Kaplan-Meier Analysis of Duration of Response[a]

DOR	DOR[b] ≥18 mo n (%)	Median (range),[b] mo
Pembro + D + T	4 (59.8)	18.7 (1.9+-22.1)
Placebo + D + T	3 (27.8)	12.5 (2.1-19.5+)



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

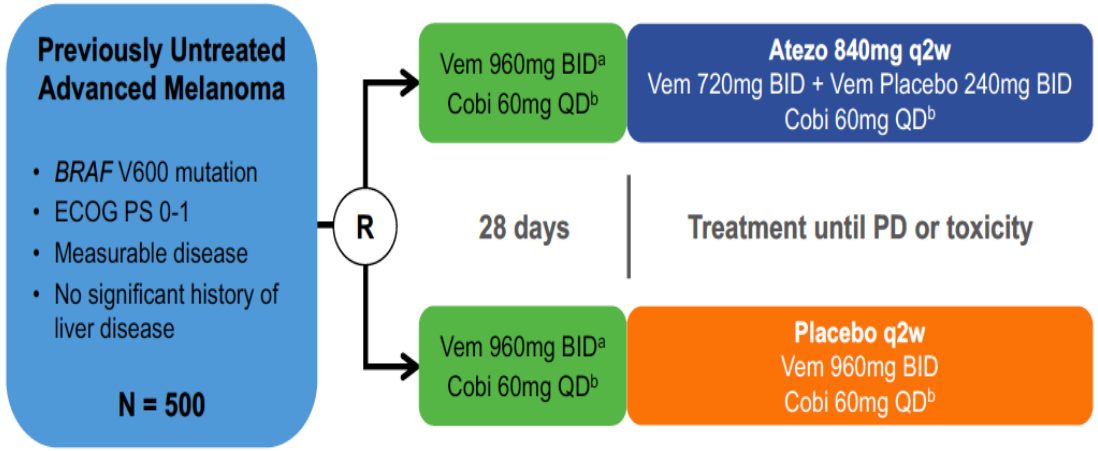
PDR001 (RP3R identified in part 1) dabrafenib 150mg BID + trametinib 2mg QD

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)

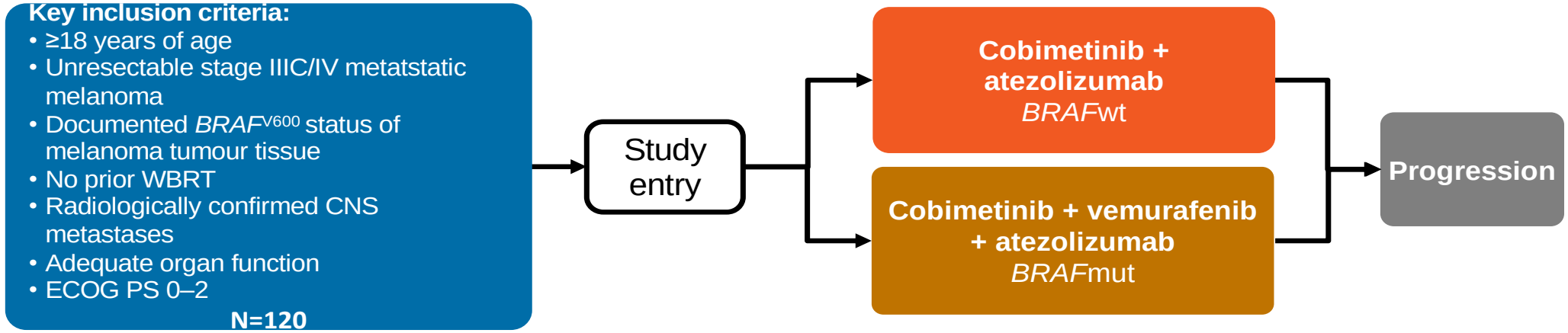
Primary endpoints: PFS[RECIST]



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

TRICOTEL study: atezolizumab, cobimetinib and vemurafenib in metastatic melanoma

Phase II, cohort, multi-centre study evaluating the efficacy and safety of the addition of atezolizumab to cobimetinib and vemurafenib in advanced metastatic melanoma



Primary endpoint:

- Intracranial response rate as per IRC

Secondary endpoints:

- PFS, DOR, CBR, OS, PRO, safety

CBR, clinical benefit rate; CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PFS, progression free survival; PRO, patient-reported outcomes; WBRT, whole brain radiotherapy.

Sequential Therapy

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

Conclusiones

- BRAF inhibitors have changed the treatment paradigm for a 50% of melanoma patients whose tumours habour the BRAFV600 mutation
- All patients with advanced melanoma and with stage III melanoma completely resected should be tested for the BRAFV600 mutation
- Combination of BRAFi + MEKi has been validated as standard of care in BRAFV600 melanoma
- Building on BRAF/MEK inhibition will proceed:
  - in optimizing MAPK-targeted therapy
  - Combination/sequencing with immunotherapy to maximize survival and QoL
- Development of predictive biomarkers should be a priority to best select patients for targeted *vs* immunotherapy

Muchas Gracias

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