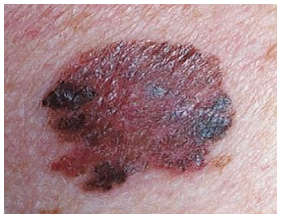
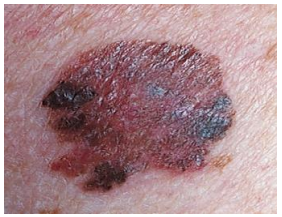
Inhibiting signalling pathways Clinical Applications in Melanoma

Caroline Robert, MD, PhD
Gustave Roussy and Paris-Sud University
France

Eggermont, Spatz , Robert, Lancet 2013



RTK
KIT
MC1R
Cell membrane
Cytoplasm
NRAS
G protein
BRAF
40-50%
PI3K
PTEN
Adenyl-cyclase
MEK
AKT1
MITF
ERK
mTOR
IκB
p14/p16
Cyclin D
NFκB
cAMP
CDK4/6
Differentiation
Apoptosis/survival
HDM2
Rb
p53
E2F
Proliferation
CREB
Transcription
Nucleus



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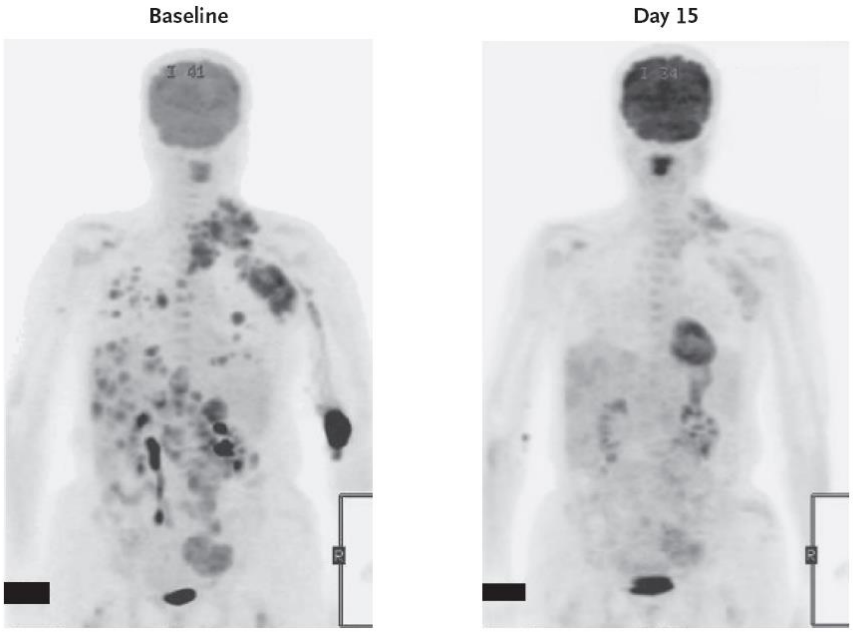
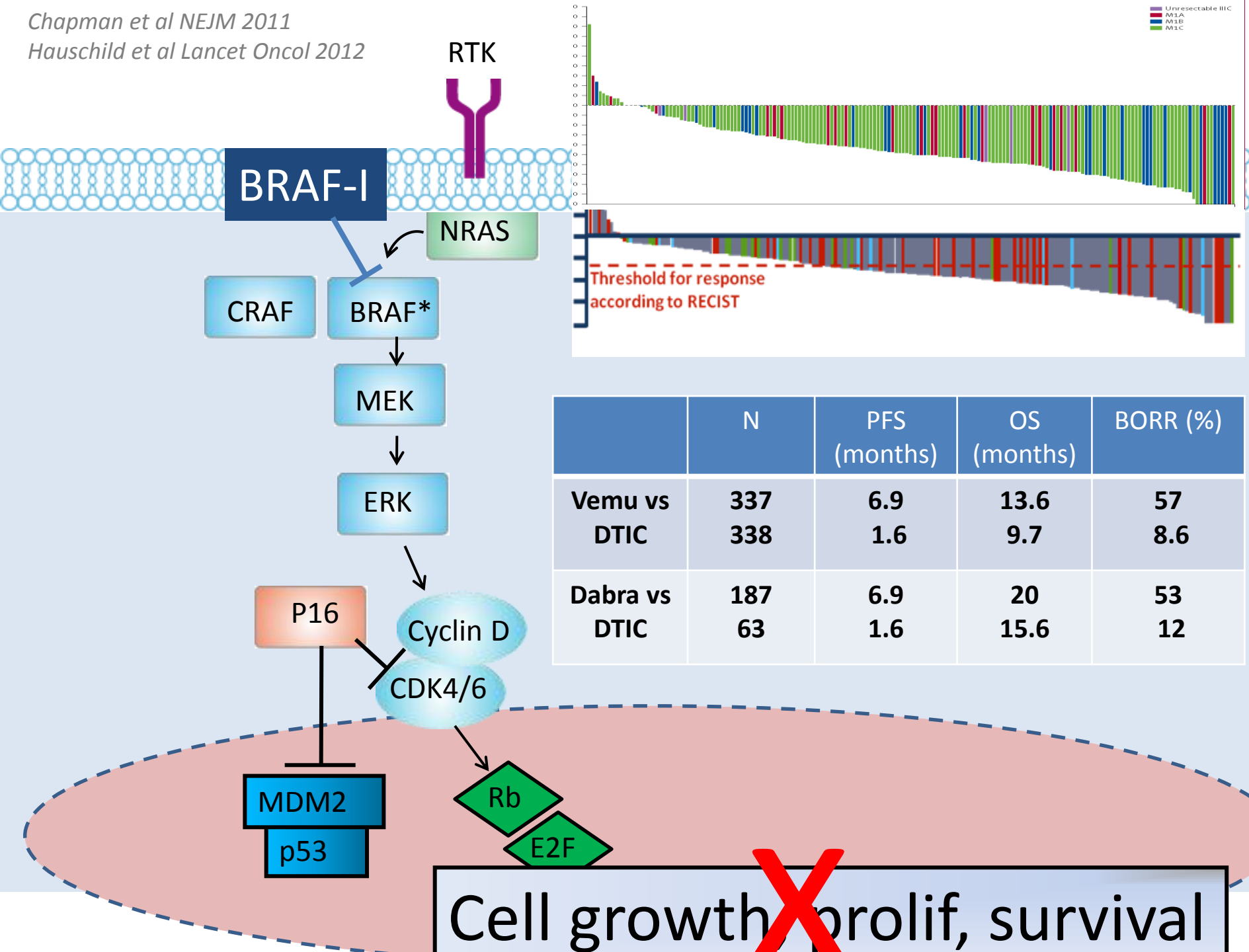


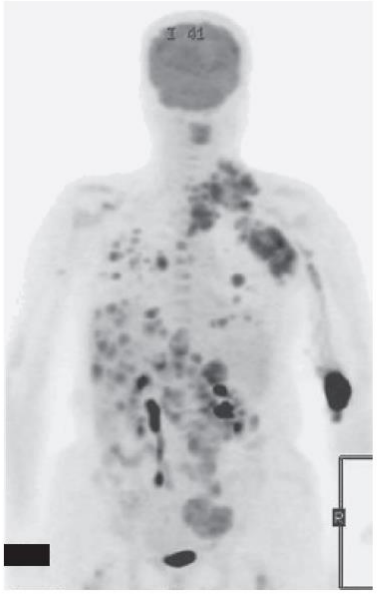
Flaherty KT et al. Inhibition of mutated, activated *BRAF* in metastatic melanoma. N Engl J Med 2010;363:809

Chapman et al NEJM 2011
Hauschild et al Lancet Oncol 2012



	N	PFS (months)	OS (months)	BORR (%)
Vemu vs DTIC	**337 338**	**6.9 1.6**	**13.6 9.7**	**57 8.6**
Dabra vs DTIC	**187 63**	**6.9 1.6**	**20 15.6**	**53 12**

Baseline



Day 15

Flaherty KT et al. Inhibition of mutated, activated *BRAF* in metastatic melanoma. N Engl J Med 2010;363:809

Flaherty KT et al. Inhibition of mutated, activated *BRAF* in metastatic melanoma. N Engl J Med 2010;363:809

Reynolds et al, *Am J Med Genet 1986*;
Jeffries et al, *Pediatr Dermatol* 2009
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Cardiofaciocutaneous Syndrome

Reynolds et al, *Am J Med Genet 1986*;
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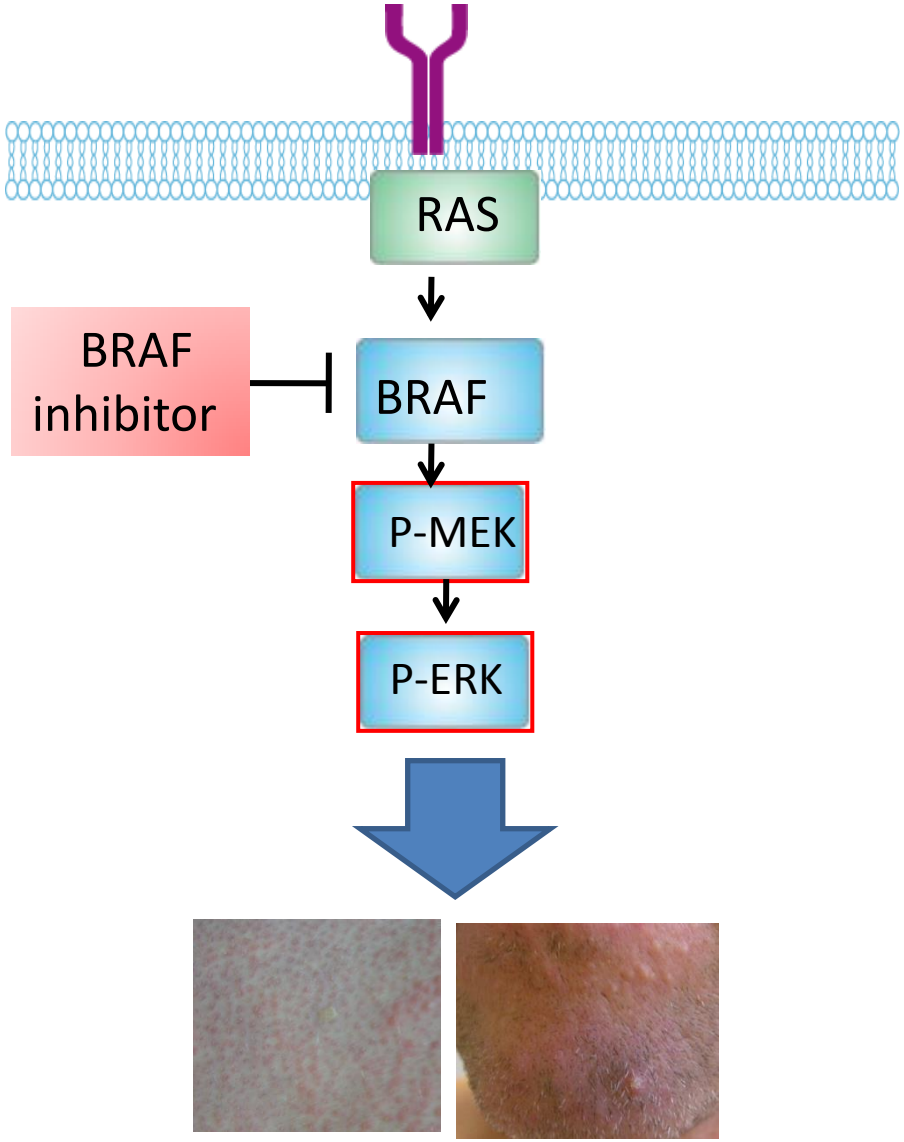
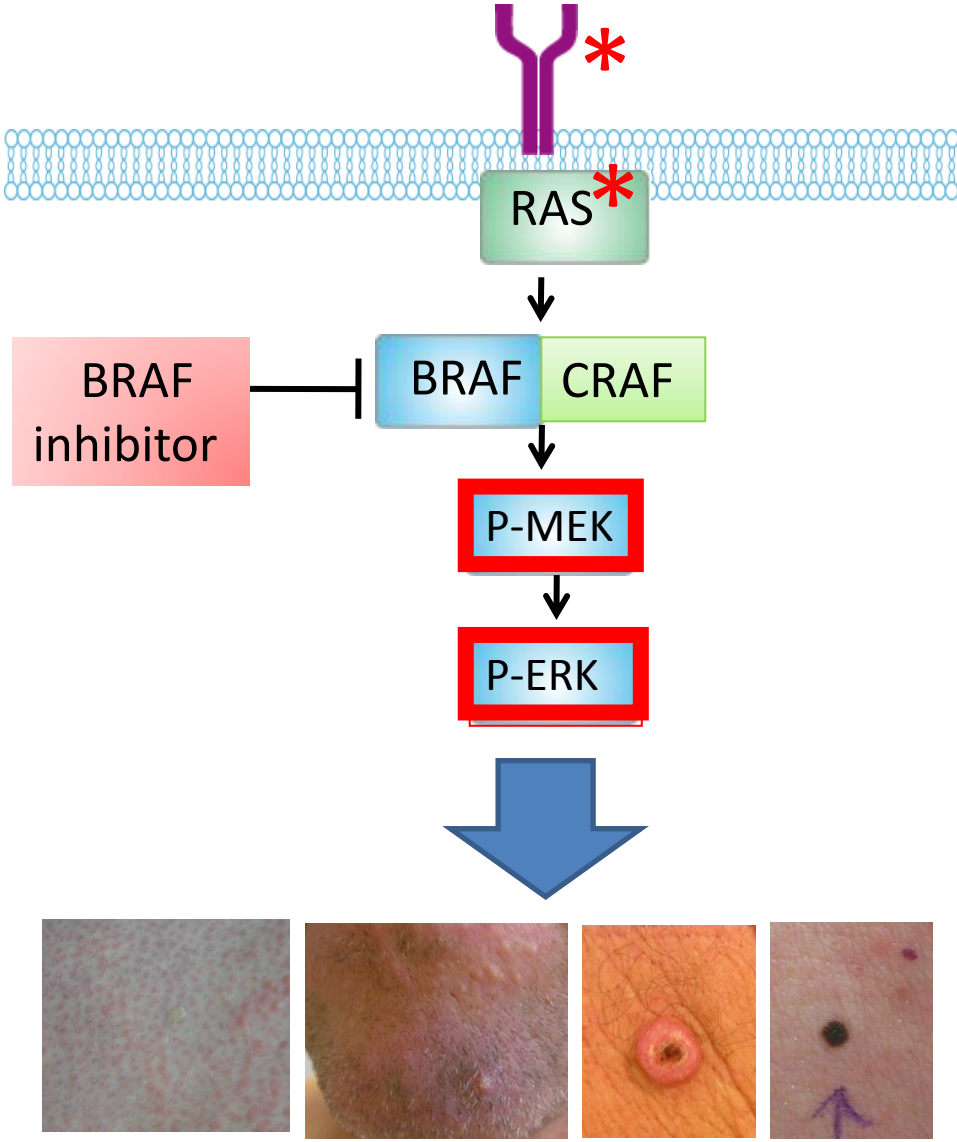
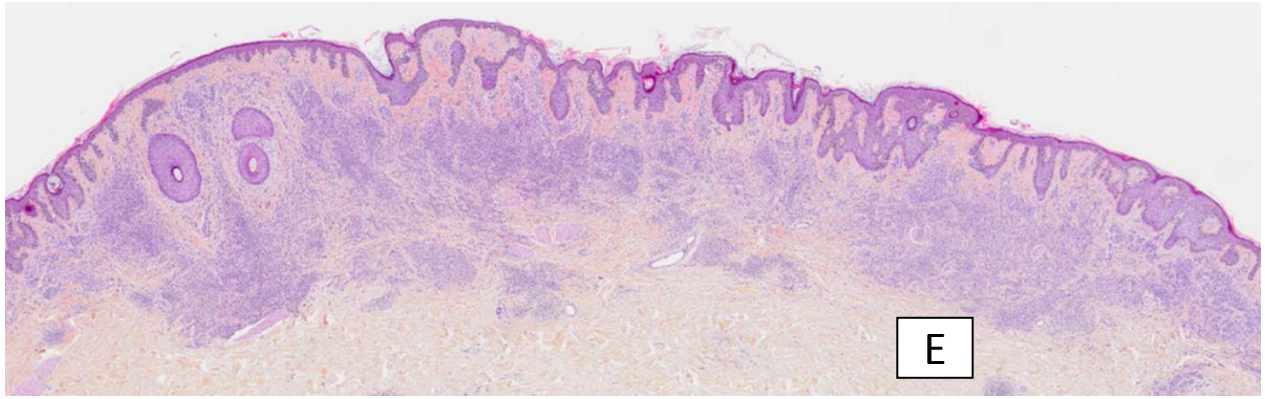
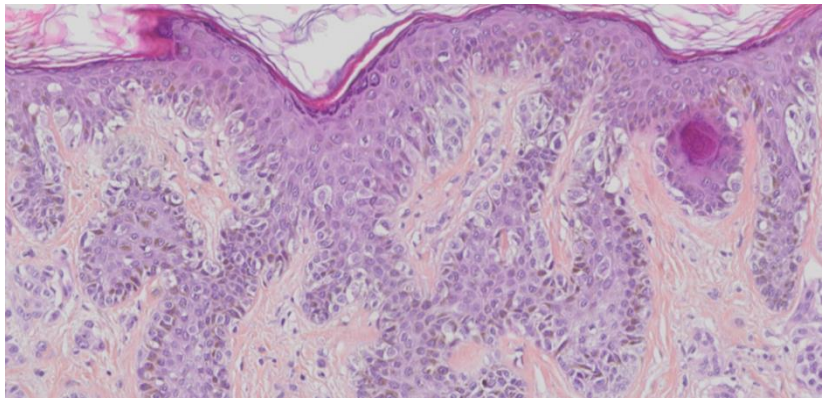
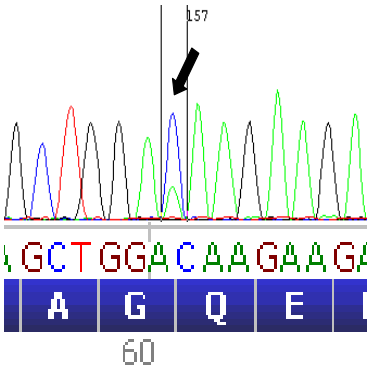

RAS
BRAF inhibitor
BRAF
P-MEK
P-ERK


RAS*
BRAF inhibitor
BRAF
CRAF
P-MEK
P-ERK



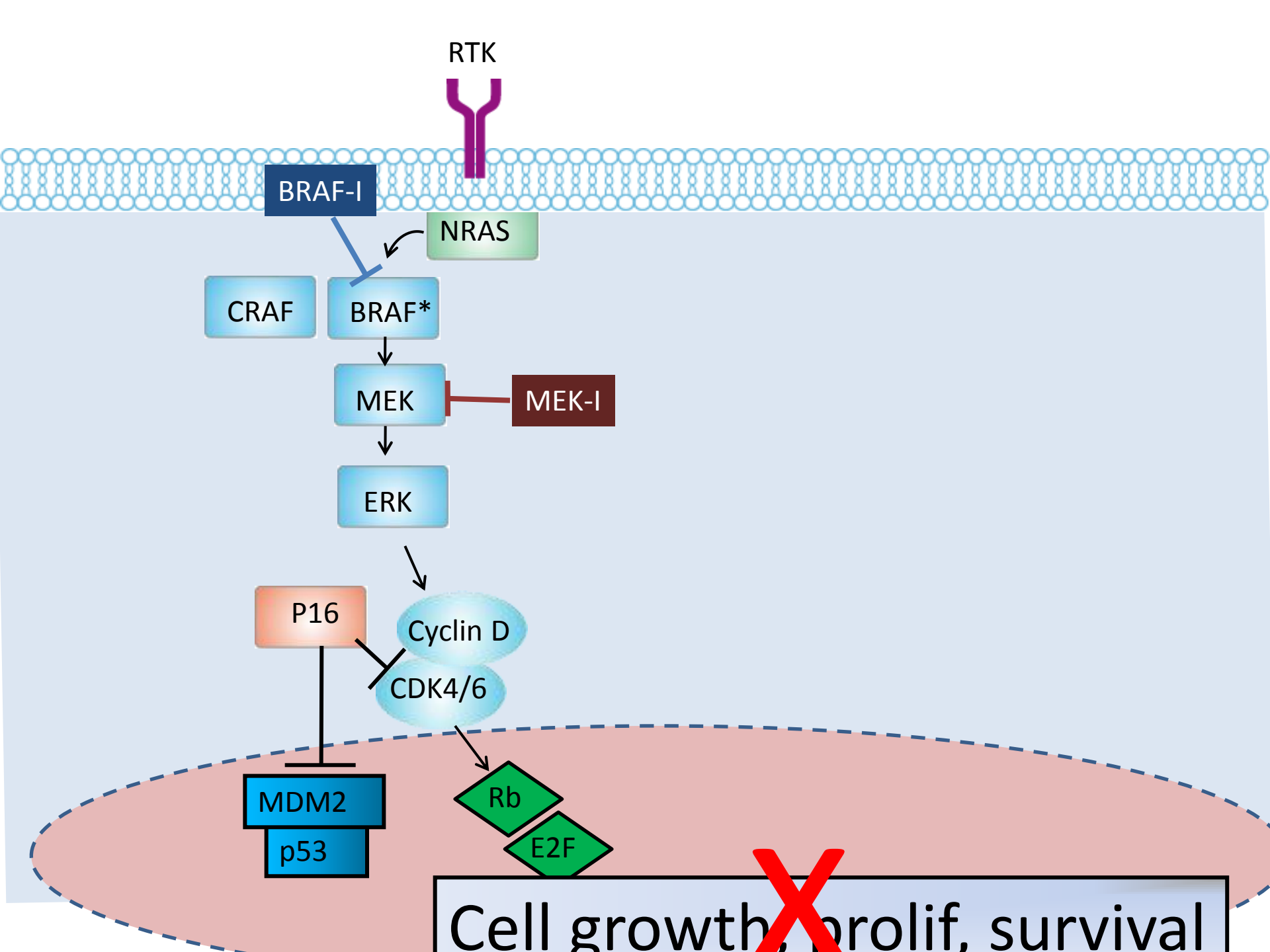




NRAS^{Q61}

Main issue :
secondary resistance to BRAFI

Wagle et al JCO 2011


RTK
BRAF-I
NRAS
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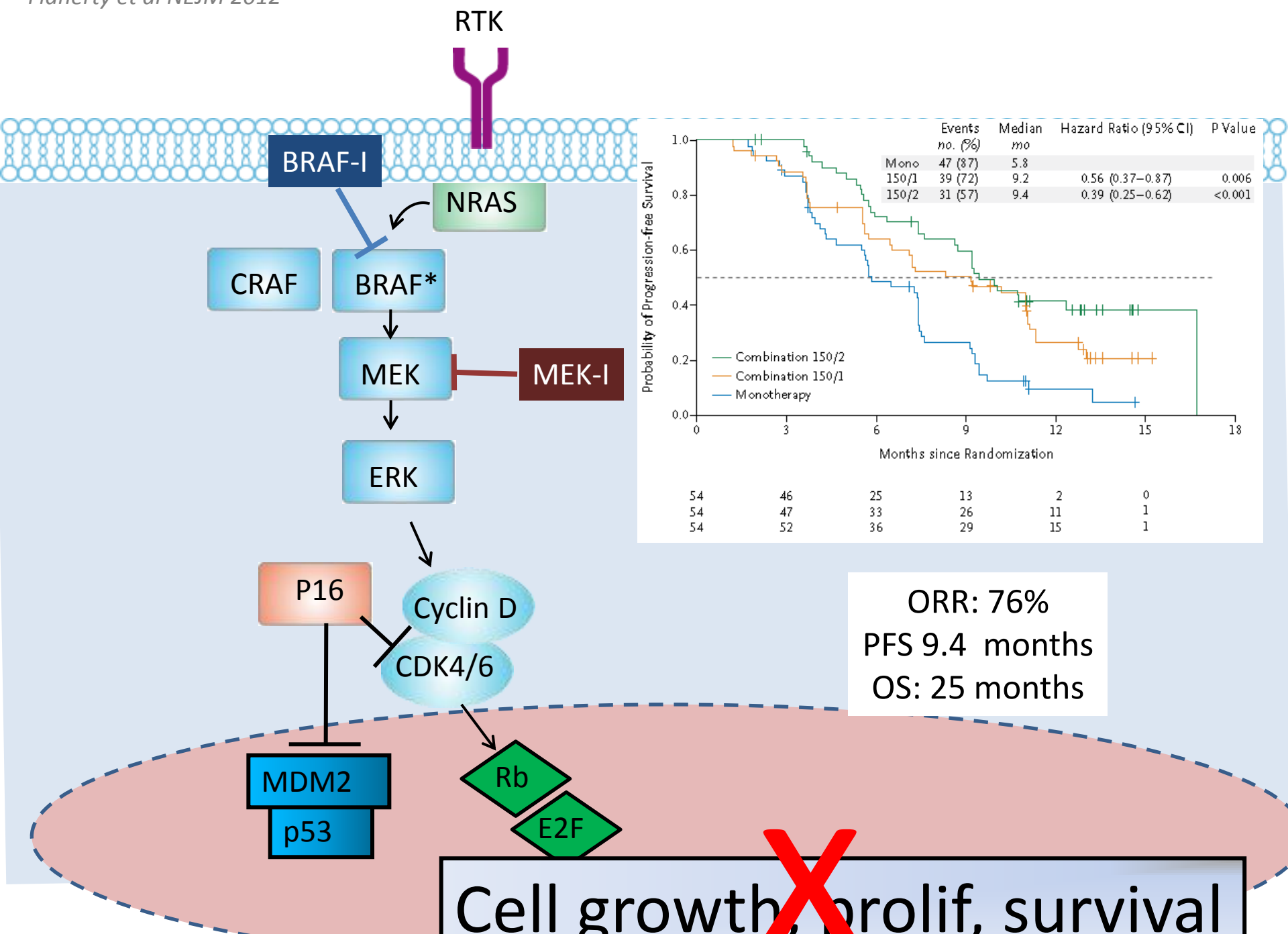
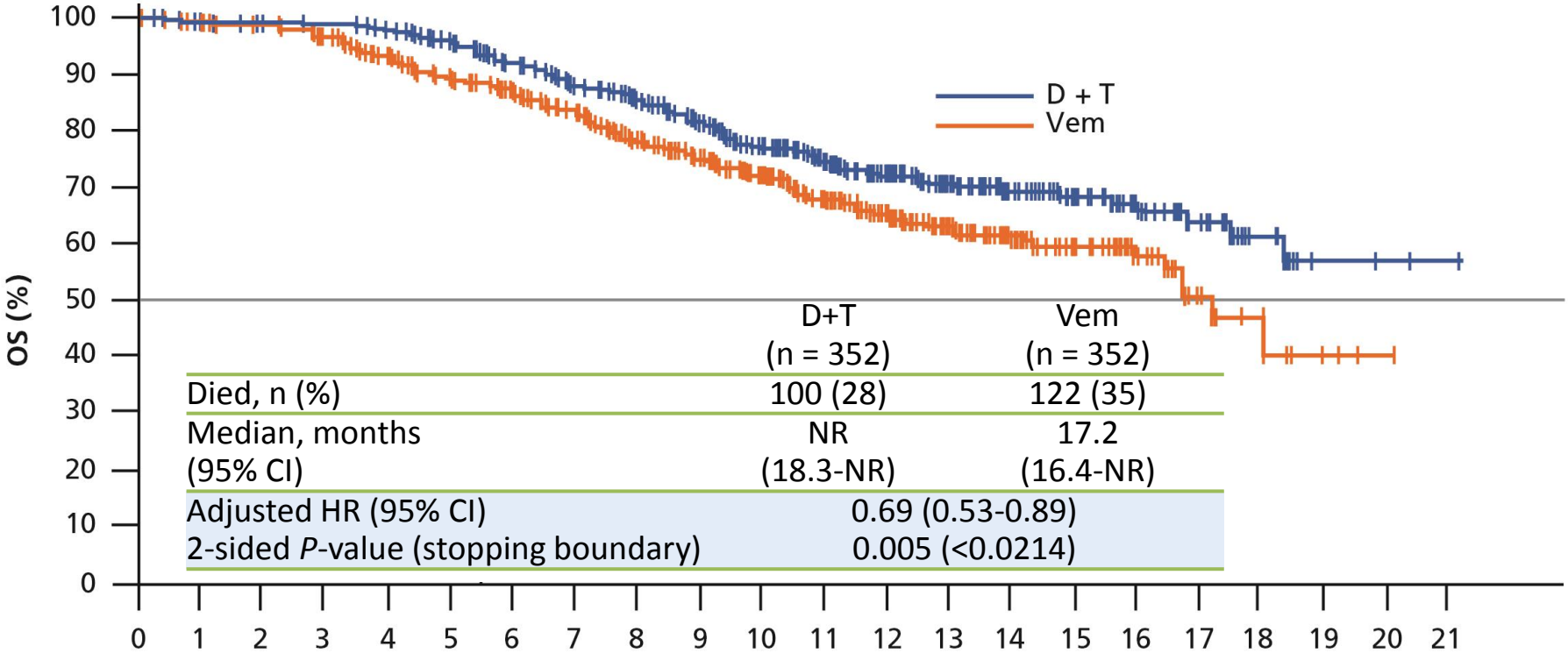
E2F
Cell growth, prolif, survival

Flaherty et al NEJM 2012



COMBI-v study
Overall Survival



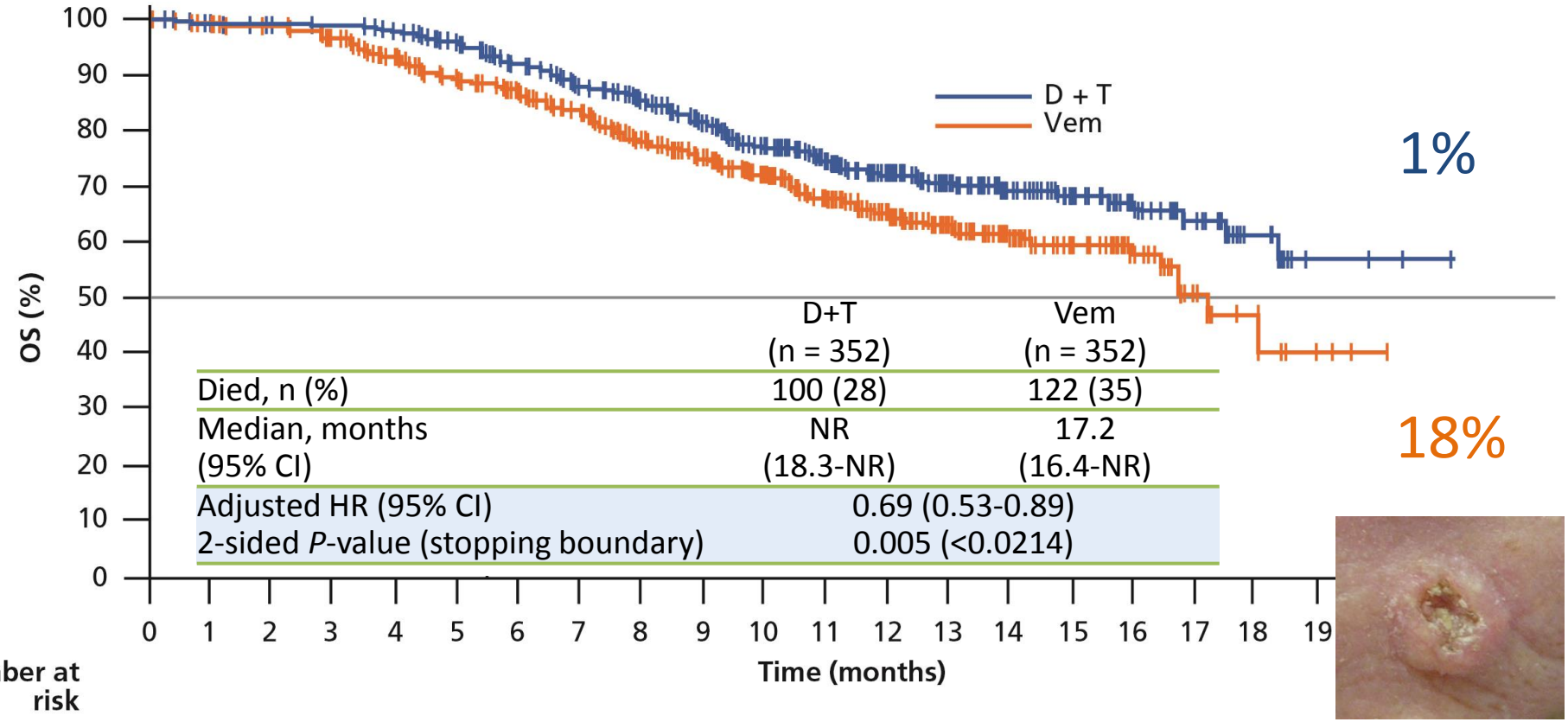
	D+T (n = 352)	Vem (n = 352)
Died, n (%)	100 (28)	122 (35)
Median, months (95% CI)	NR (18.3-NR)	17.2 (16.4-NR)
Adjusted HR (95% CI)	0.69 (0.53-0.89)	
2-sided *P*-value (stopping boundary)	0.005 (<0.0214)	

Number at risk																						
D + T	352	346	342	341	336	325	310	295	283	263	232	203	157	125	85	64	46	32	15	3	2	1
Vem	352	345	341	331	315	299	285	271	247	232	204	171	122	90	63	46	31	16	7	3	1	0

D + T, dabrafenib + trametinib; Vem, vemurafenib

Median Follow-up: D + T = 11 months and Vem = 10 months

C ROBERT et al ESMO 2014



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D + T, dabrafenib + trametinib; Vem, vemurafenib

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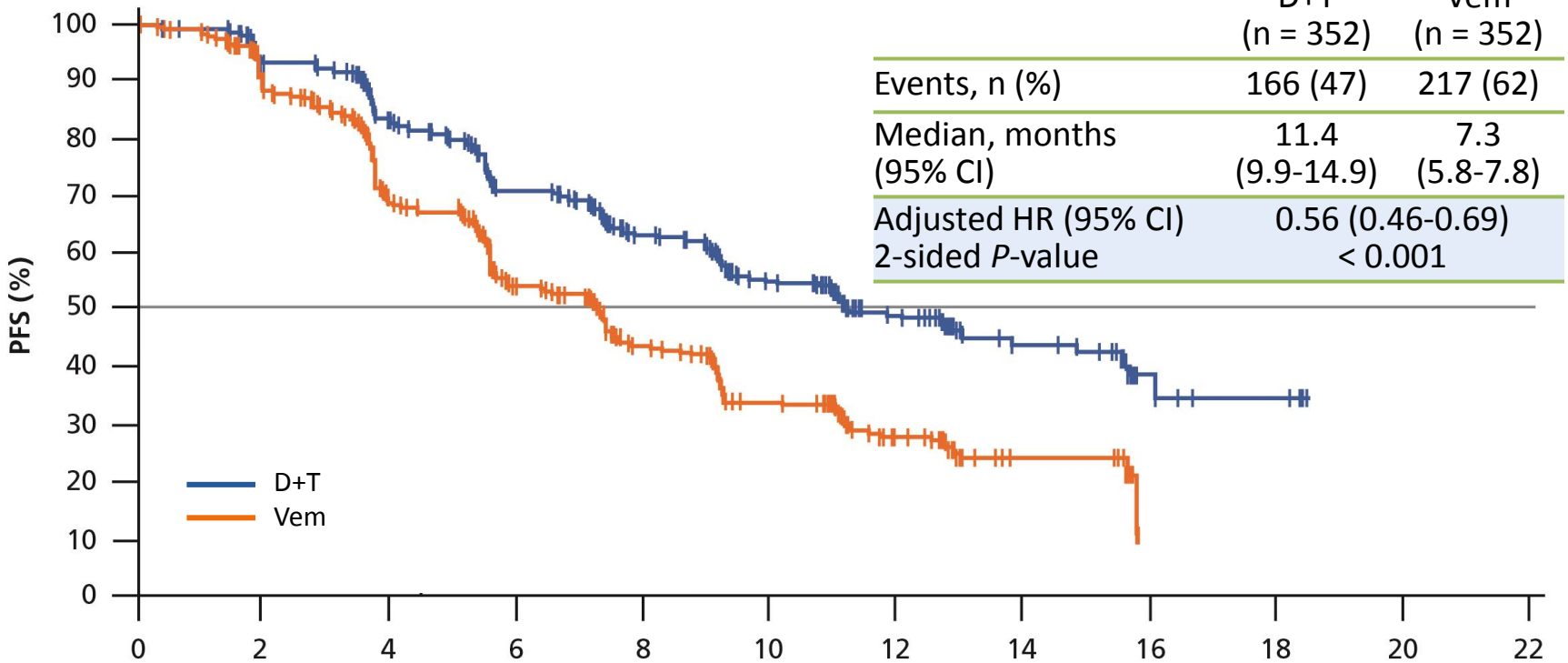
Robert et al. N Engl J Med. 2015;372:30-39

Progression-Free Survival



	D+T (n = 352)	Vem (n = 352)
Events, n (%)	166 (47)	217 (62)
Median, months (95% CI)	11.4 (9.9-14.9)	7.3 (5.8-7.8)
Adjusted HR (95% CI) 2-sided *P*-value	0.56 (0.46-0.69) < 0.001	

Number at risk												
D + T	352	310	270	228	194	142	83	39	10	7	0	0
Vem	352	279	214	161	121	83	45	11	0	0	0	0

D + T, dabrafenib + trametinib; Vem, vemurafenib

C ROBERT et al ESMO 2014

Best Confirmed Response

Best confirmed response	Dabrafenib + trametinib (n = 351)	Vemurafenib (n = 350)
Complete response, n (%)	47 (13)	27 (8)
Partial response, n (%)	179 (51)	153 (44)
Stable disease, n (%)	92 (26)	106 (30)
Progressive disease, n (%)	22 (6)	38 (11)
Not evaluable, n (%)	11 (3)	26 (7)
Response rate, n (%) (95% CI)	226 (64) (59.1–69.4)	180 (51) (46.1–56.2)
Difference in ORR, % (95% CI)	13 (5.7–20.2)	
P-value	< 0.001	
DoR, months (95% CI)	13.8 (11.0–NR)	7.5 (7.3–9.3)

NR, not reached

C ROBERT et al ESMO 2014

Adverse Events in > 20% of Patients

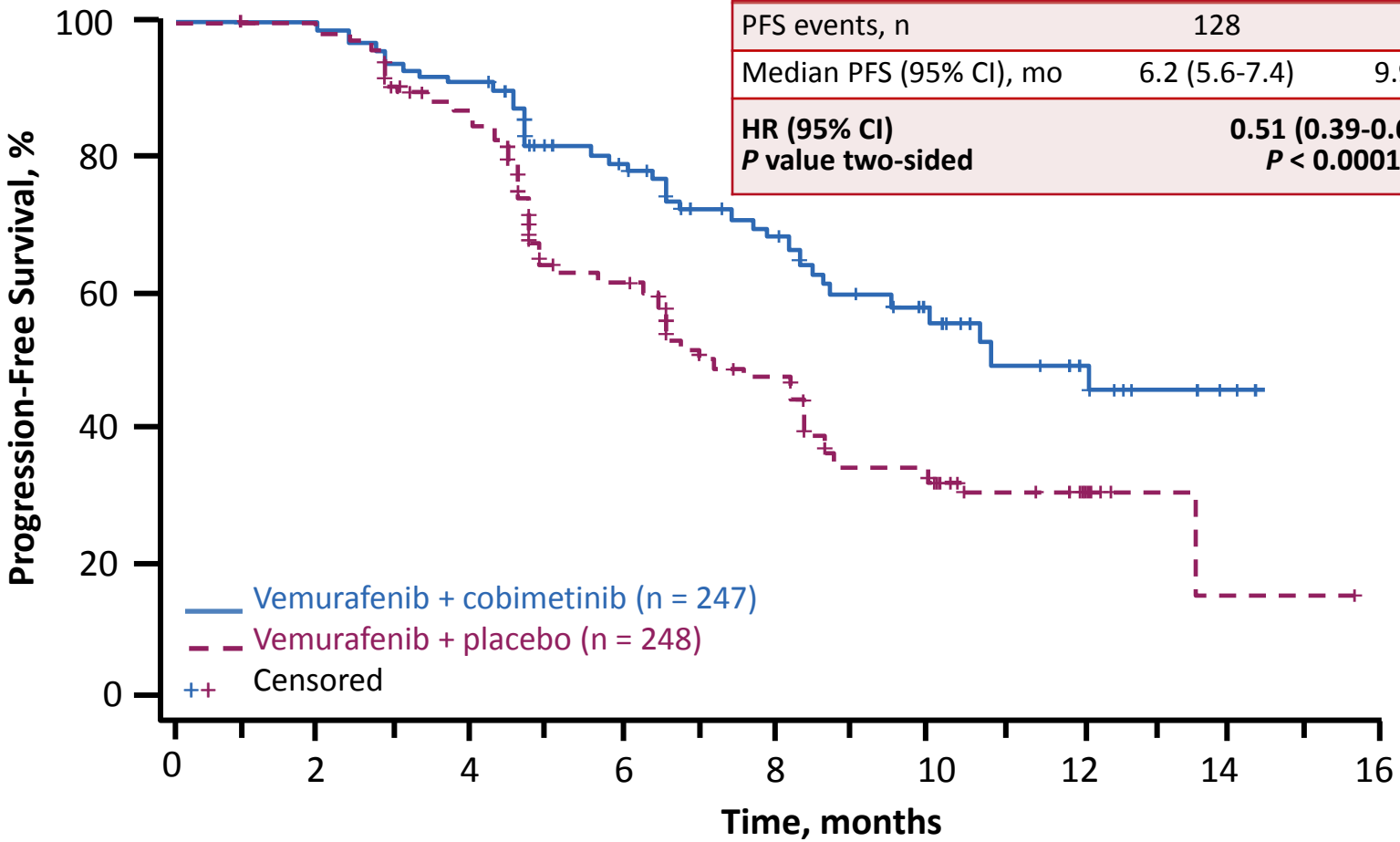
AE, n (%)	Dabrafenib + trametinib (n = 350)		Vemurafenib (n = 349)	
	All Grades	Grade 3	All Grades	Grade 3
All events	343 (98)	167 (48)	345 (99)	198 (57)
Pyrexia	184 (53)	15 (4)	73 (21)	2 (< 1)
Nausea	121 (35)	1 (< 1)	125 (36)	2 (< 1)
Diarrhoea	112 (32)	4 (1)	131 (38)	1 (< 1)
Chills	110 (31)	3 (< 1)	27 (8)	0
Fatigue	101 (29)	4 (1)	115 (33)	6 (2)
Headache	101 (29)	3 (< 1)	77 (22)	2 (< 1)
Vomiting	101 (29)	4 (1)	53 (15)	3 (< 1)
Hypertension	92 (26)	48 (14)	84 (24)	32 (9)
Arthralgia	84 (24)	3 (< 1)	178 (51)	15 (4)
Rash	76 (22)	4 (1)	149 (43)	30 (9)
Pruritus	30 (9)	0	75 (21)	3 (< 1)
Alopecia	20 (6)	0	137 (39)	1 (< 1)
Hyperkeratosis	15 (4)	0	86 (25)	2 (< 1)
Photosensitivity	13 (4)	0	78 (22)	1 (< 1)
Skin papilloma	6 (2)	0	80 (23)	2 (< 1)

Grade 4 events:
D + T arm - All events: 16 (5%) and headache 1 (< 1%); Vem arm - All events: 23 (7%) and hypertension 1 (< 1%)

C ROBERT et al ESMO 2014

COBRIM phase III study

	Vemurafenib+ Placebo	Vemurafenib + Cobimetinib
PFS events, n	128	79
Median PFS (95% CI), mo	6.2 (5.6-7.4)	9.9 (9.0-NE)
HR (95% CI) ***P* value two-sided**	**0.51 (0.39-0.68)** ***P* < 0.0001**	



No. at Risk

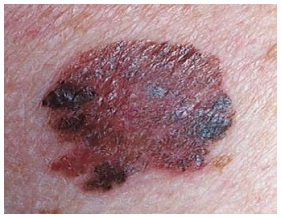
Vemurafenib + cobimetinib	**238**	**215**	**152**	**96**	**46**	**14**	**3**
Vemurafenib + placebo	**240**	**200**	**118**	**68**	**34**	**12**	**1**

CI, confidence interval; NE, not estimable.

Data Cutoff: May 9, 2014

G McArthur et al ESMO 2014; Larkin et al NEJM 2014

	trial	N	PFS (months)	OS (months)	BORR (%)
Vemu vs DTIC	BRIM 3	337/338	6.9 vs 1.6	13.6 vs 9.7	57 vs 8.6
Dabra vs DTIC	BREAK 3	187/63	6.9 vs 1.6	20 vs 15.6	53 vs 12
Trame vs chemo	METRIC	214/108	4.8 vs 1.5	-	22 vs 8
Vemu + Cobimet	COBRIM	247/248	9.9 vs 6.2	NR	68 vs 45
Dabra + trame vs Dabra	COMBI-d	210/210	9.3 vs 8.8	NR	67 vs 51
Dabra + trame vs Vemu	COMBI-v	352/352	11.4 vs 7.3	? vs 17.3	64 vs 51



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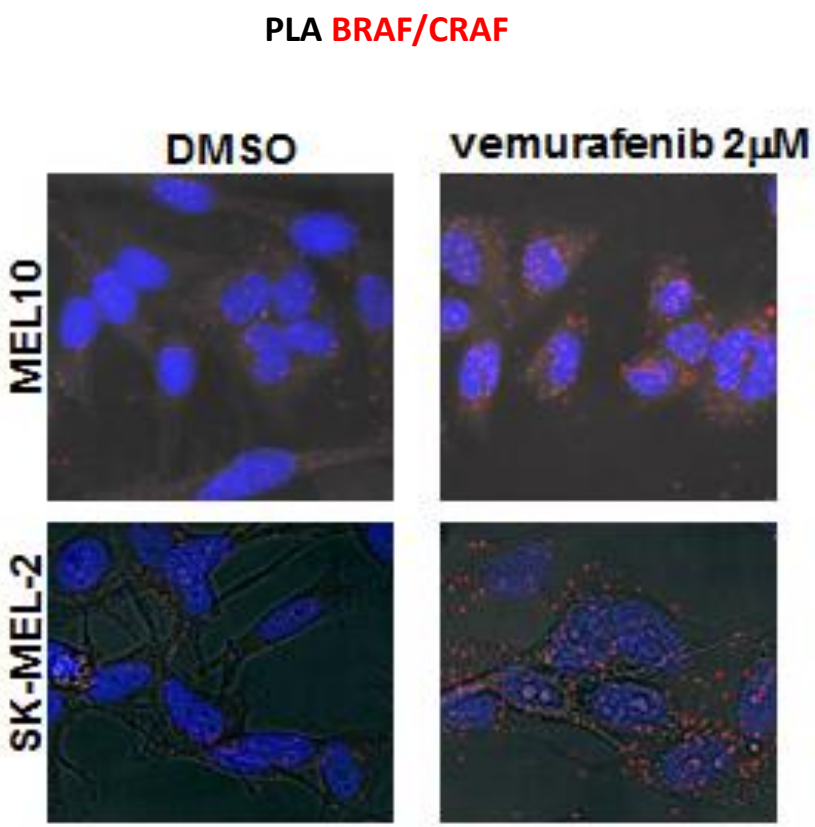
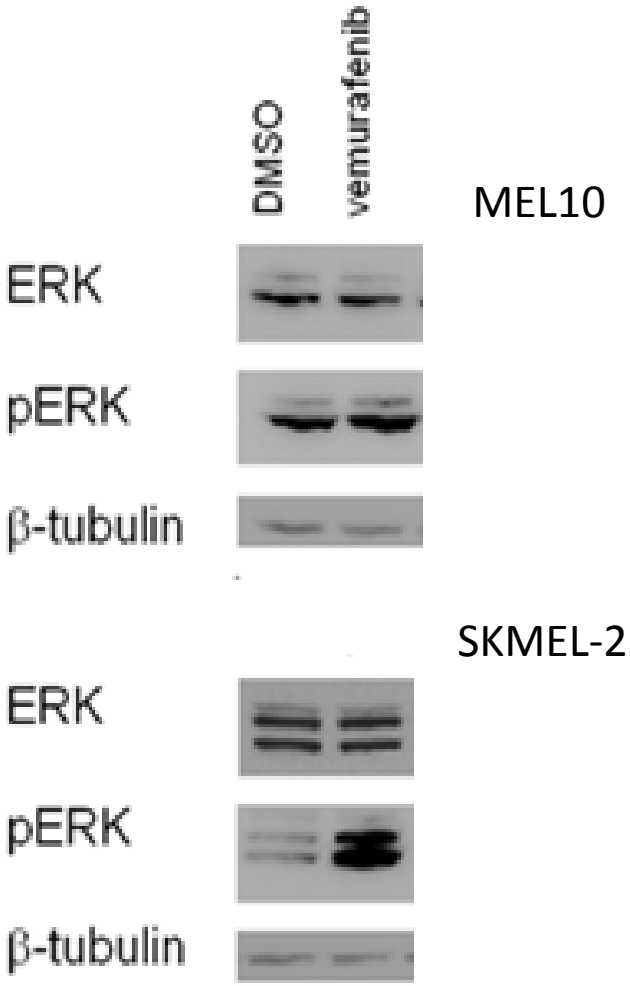
Proliferation

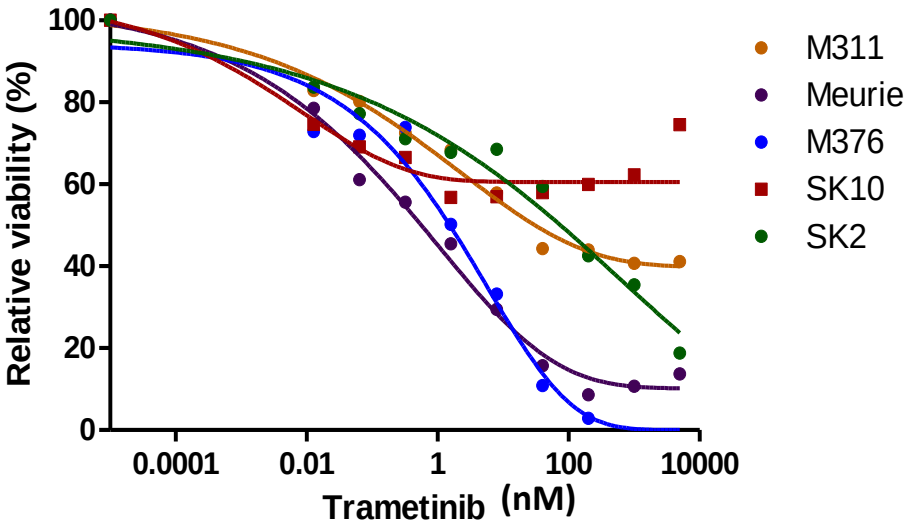
NRAS mutant melanoma cell lines Do not respond to BRAF-inhibitors

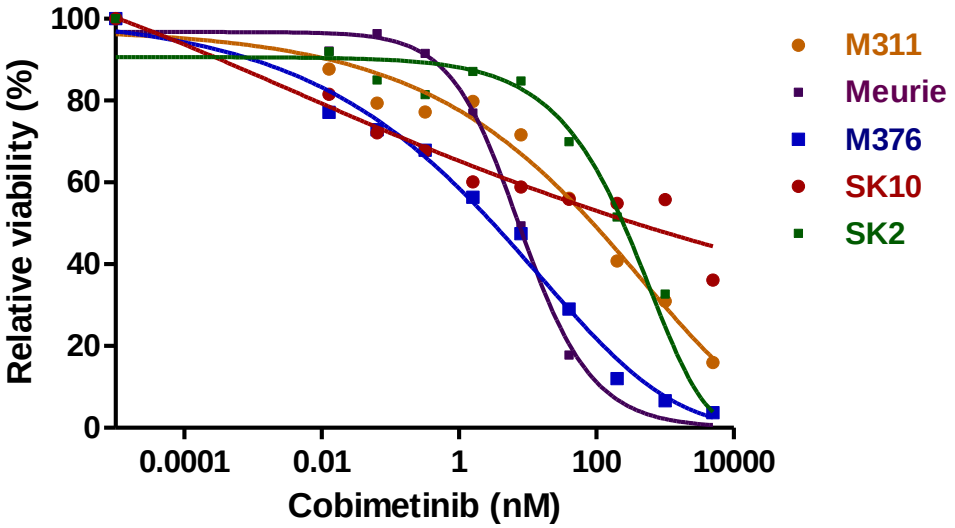




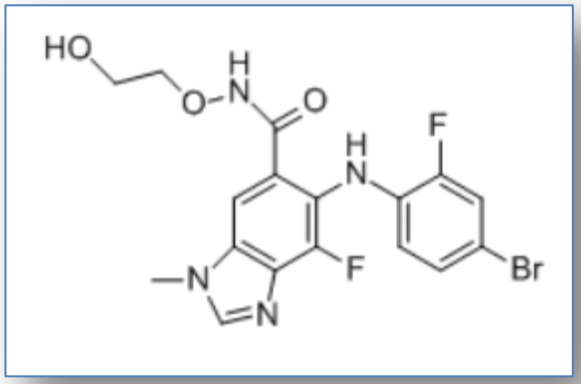
NRAS mutant cell lines variable sensitivities to MEK inhibitors

Lignée	Mutation
SKMel2	NRAS(Q61R)
SKMel10	NRAS(Q61R)
M311	NRAS(Q61L) homozygous
Meurie	NRAS(Q61K)
M376	NRAS(Q61K) heterozygous BRAF(V600E) heterozygous





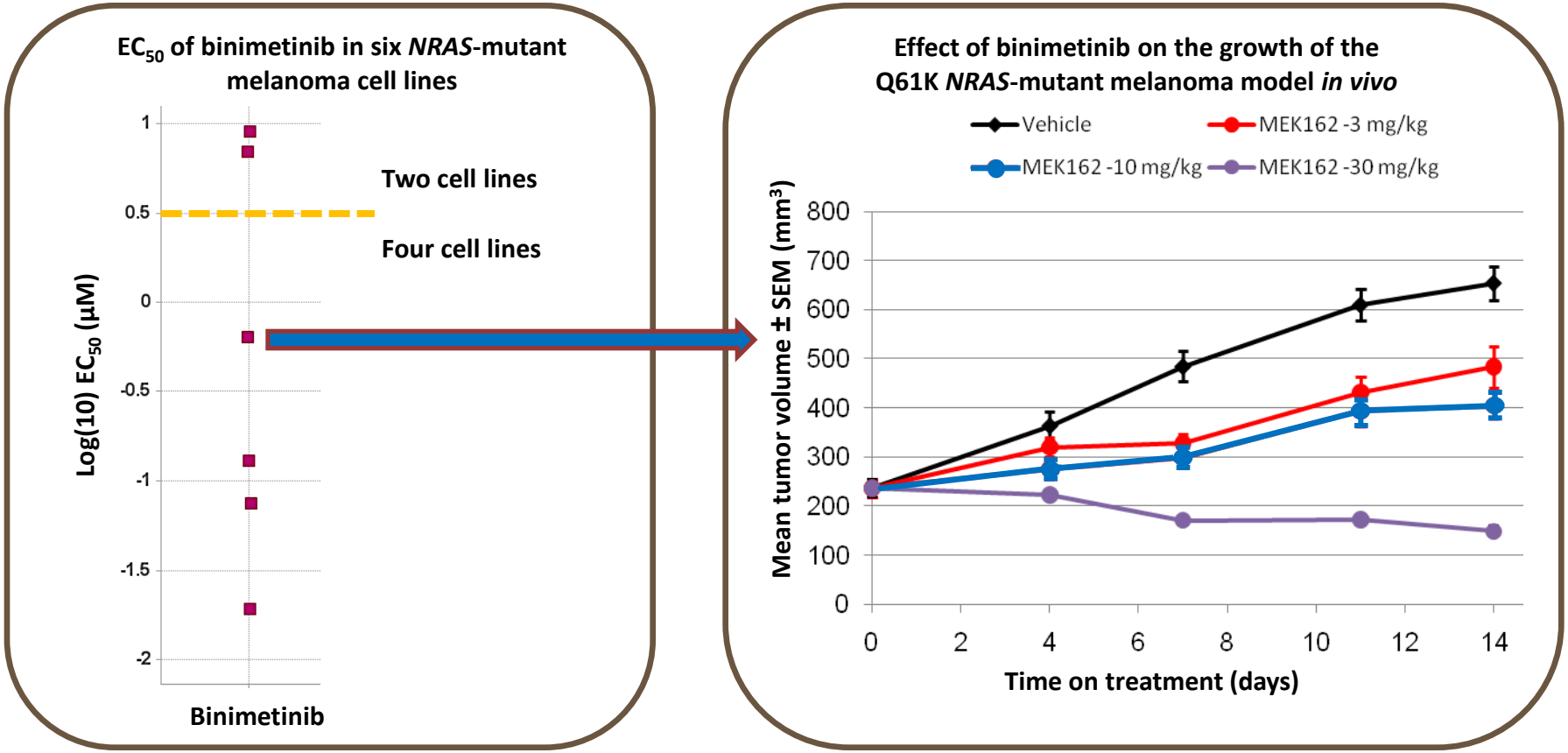
Binimetinib (MEK162) is a potent and specific, allosteric inhibitor of MEK1/2



Potency	
MEK enzyme IC_{50}	12 nM
Cellular pERK Inhibition IC_{50} (Malme-3M)	11 nM
***In Vitro* Selectivity and Safety**	
Kinase Panel of 220 enzymes	No activity @ 10 μM
Profile Screen of 30 Receptors/Ion Channels	No activity @ 10 μM
hERG (patch clamp)	28% @ 10 μM
P450 Inhibition (7 isoforms except CYP2B6)	No inhibition @ 10 μM
Genotoxicity (Ames, Micronucleus, Chrom Abb)	Negative

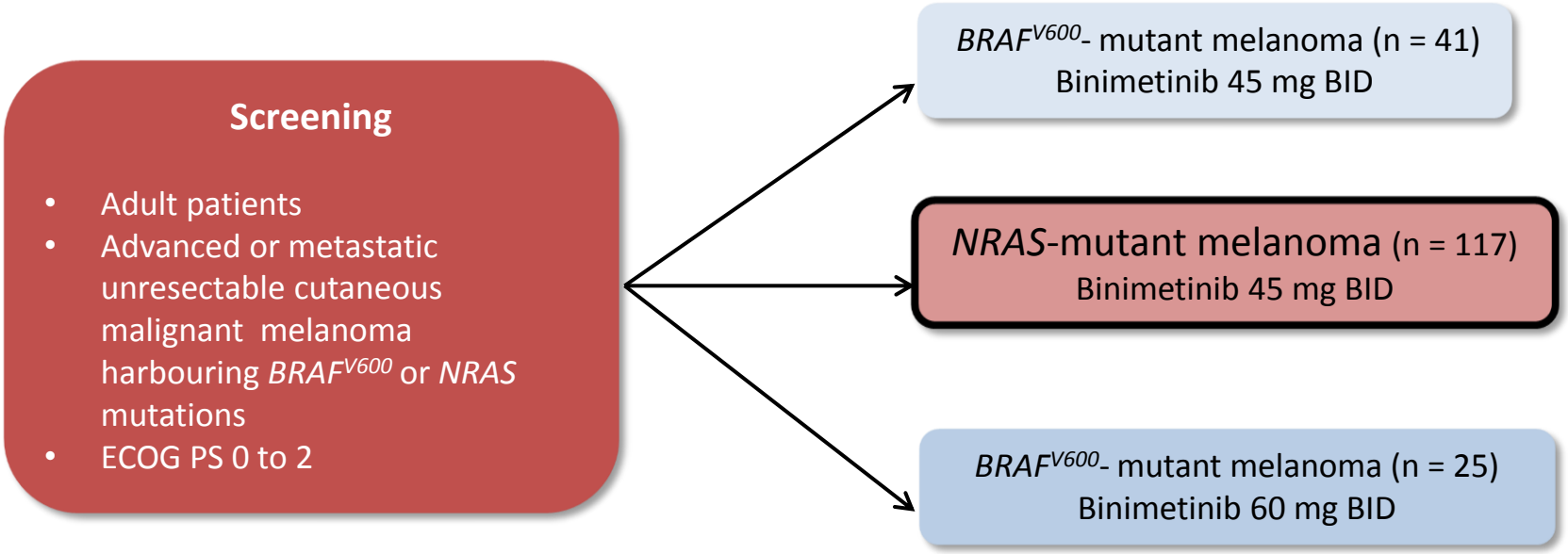
Lee P, et al. *AACR.* 2010 [abstract 2515].

Binimetinib (MEK162) is Active Against *NRAS*-mutant Melanoma Cell Lines *in vitro* / *in vivo*



Ascierto P et al, ASCO 2012 [Abstract 8511].

Study X2201:



Primary endpoint: ORR according to RECIST 1.0
Secondary endpoints: PFS (key), OS, safety,[a] pharmacodynamics analysis (pERK, DUSP6)
Exploratory endpoint: Biomarker analysis

ECOG PS, Eastern Cooperative Oncology Group Performance Status; BID, twice a day; ORR, objective response rate; PFS, progression-free survival; OS, overall survival.

[a] Adverse events assessed according to CTCAE v4.03.

Van Herpen C. et al ESMO 2014 [abstract LBA35].

Study X2201: Patient Demographics and Baseline Characteristics

	NRAS-mutant Binimetinib 45 mg n = 117
Age, median (range), years	62 (26–84)
Sex, n (%) Male Female	 84 (71.8) 33 (28.2)
WHO performance status, n (%) 0 1 2	 82 (70.1) 30 (25.6) 5 (4.3)
Melanoma type, n (%) Cutaneous Non-cutaneous[a] Missing	 111 (94.9) 4 (3.4) 2 (1.7)
Elevated LDH (U/L) at baseline, n (%)	45 (38.5)
Prior lines of therapy, n (%) 1-4 > 4	 79 (67.5) 5 (4.3)
No prior therapy, n (%)	33 (28.2)

[a] Of the four patients with non-cutaneous melanoma, 3 had mucosal melanoma and 1 had unknown primary site of melanoma.

Van Herpen C. et al ESMO 2014 [abstract LBA35].

Study X2201: Adverse Events Suspected to be Drug Related (All grades

Preferred term	NRAS-mutant patients (n = 117)	
	All grades n (%)	Grade 3/4 n (%)
Total	117 (100)	73 (62.4)
Skin-related		
Dermatitis acneiform	63 (53.8)	1 (0.9)
Rash	23 (19.7)	1 (0.9)
Pruritus	20 (17.1)	2 (1.7)
Dry skin	18 (15.4)	0
Alopecia	14 (12.0)	0
Fluid retention		
Peripheral edema	49 (41.9)	1 (0.9)
Gastrointestinal		
Diarrhea	44 (37.6)	3 (2.6)
Nausea	27 (23.1)	0
Vomiting	14 (12.0)	0
Constipation	13 (11.1)	0
Blood creatine phosphokinase increased	60 (51.3)	29 (24.8)
Aspartate aminotransferase increased	19 (16.2)	1 (0.9)
Alanine aminotransferase increased	15 (12.8)	1 (0.9)
Fatigue	27 (23.1)	4 (3.4)
Hypertension	18 (15.4)	6 (5.1)
Chorioretinopathy	16 (13.7)	1 (0.9)

Van Herpen C. et al ESMO 2014 [abstract LBA35].

folliculitis

Xerosis/Fissuration/paronychia

Study X2201: Clinical Response

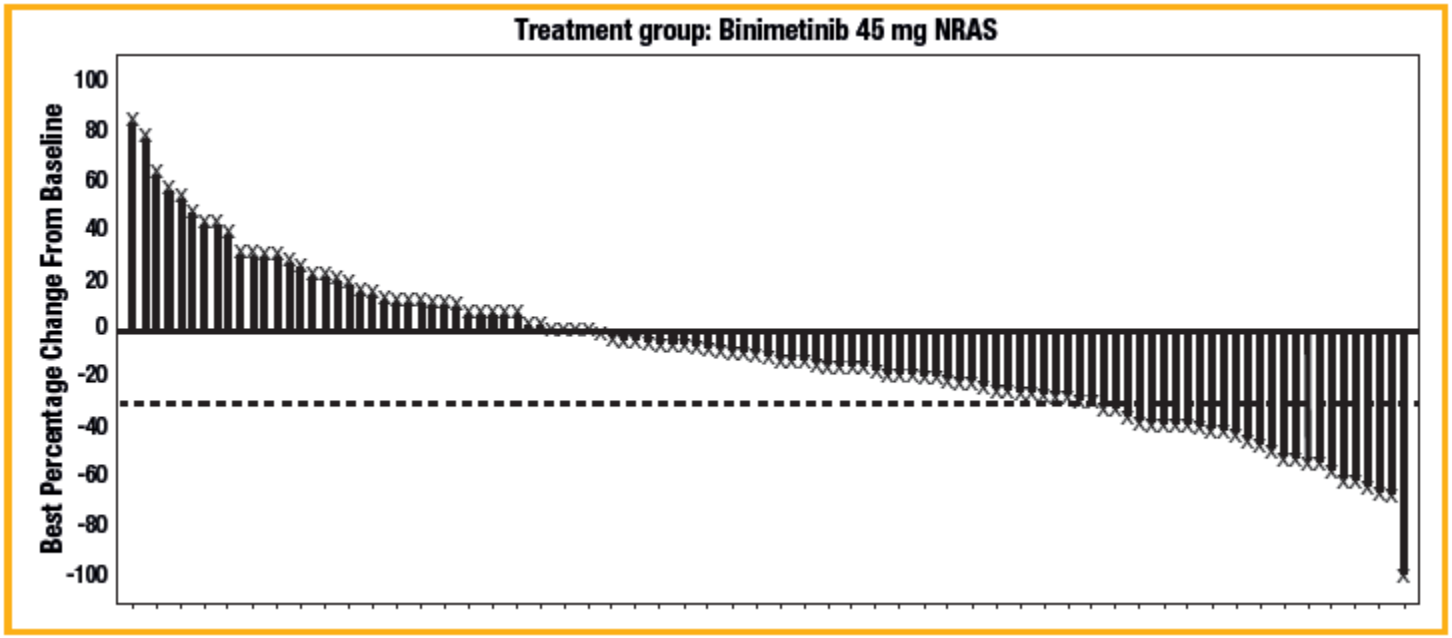
	NRAS-mutant Binimetinib 45 mg n = 117 n (%)
Best overall response, n (%)	
Complete response	1 (0.9)
Partial response	16 (13.7)
Stable disease	49 (41.9)
Progressive disease	39 (33.3)
Unknown[a]	12 (10.3)
ORR (CR + PR)	17 (14.5)
DCR (≥ SD)	66 (56.4)

[a] In six patients, post-baseline assessment was missing. In four patients, metastases (bone, brain or both) were not followed up. For each of the remaining two patients, post-baseline scan showed stable disease; however, the post-baseline CT scan was taken before 6 weeks following the first dose (not performed as per RECIST guidelines).

Van Herpen C. et al ESMO 2014 [abstract LBA35].

Study X2201: Best Percentage Change in Target Lesions

Best Percentage Change from Baseline in Target Lesions, by Response, *NRAS*-mutant Patients[a]

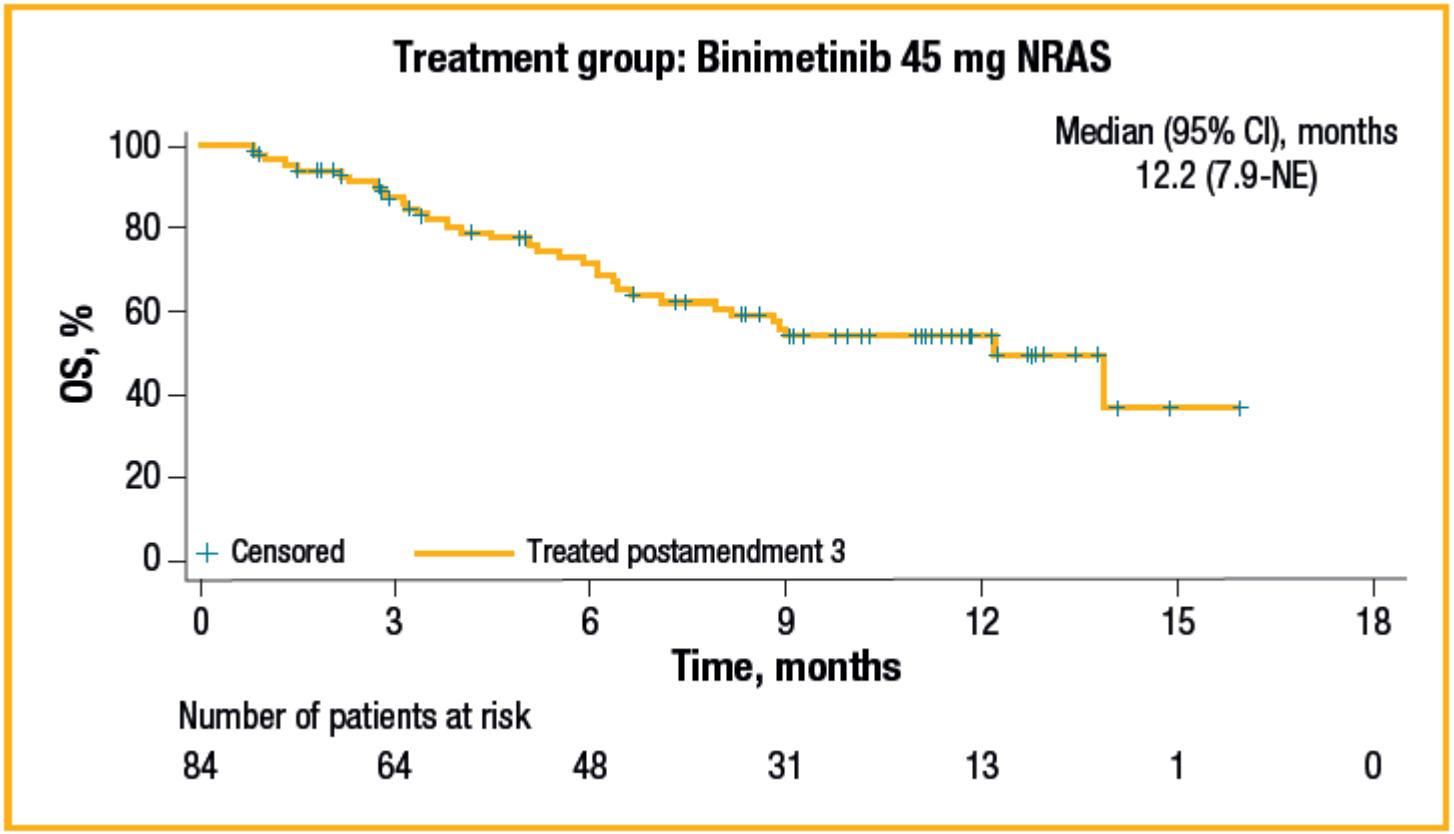


n = number of patients in the treatment group with the baseline and at least 1 evaluable postbaseline assessment of target lesions based on investigator's assessment

[a] Thirteen patients were ongoing at the time of data cutoff.

Van Herpen C. et al ESMO 2014 [abstract LBA35].

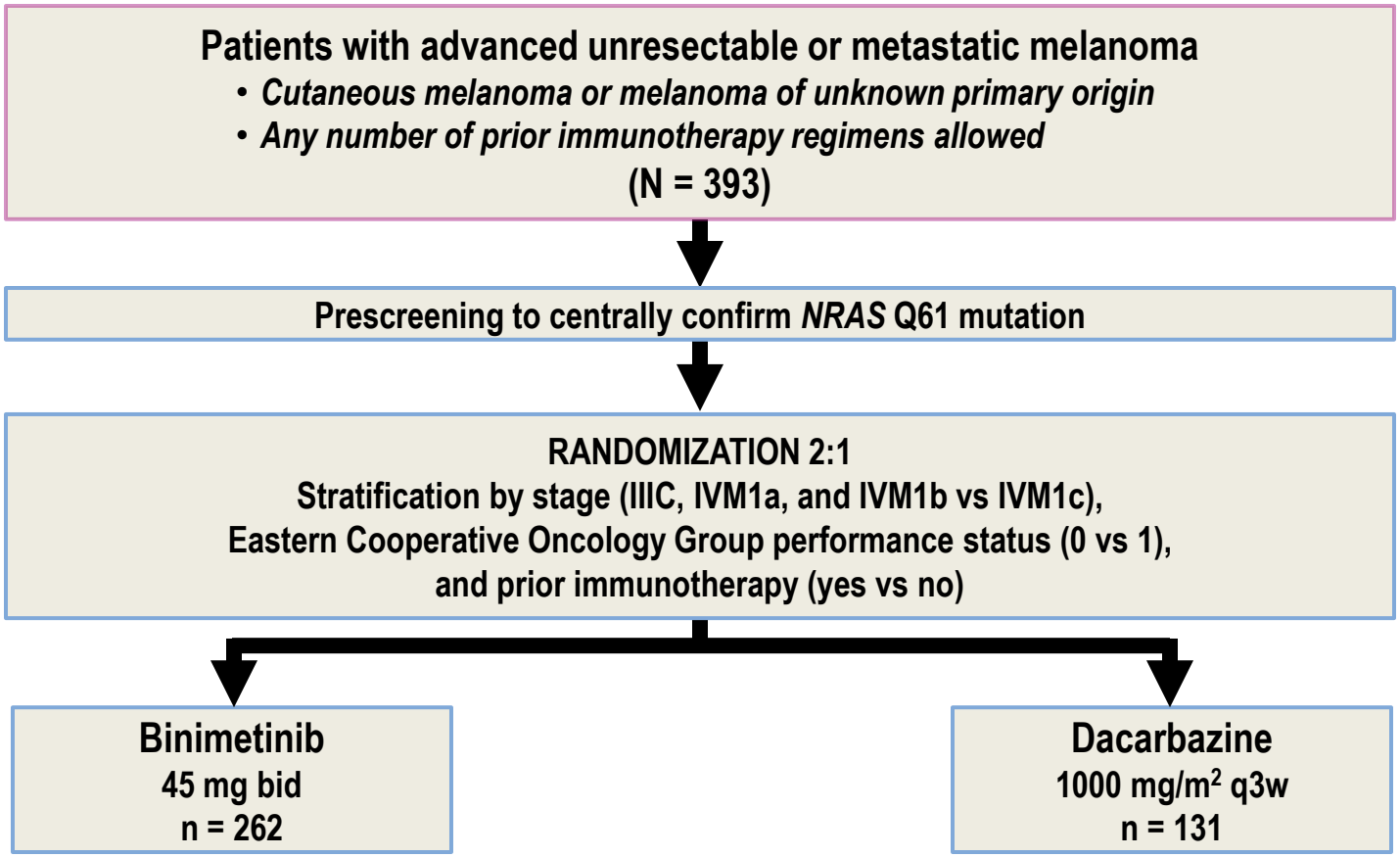
Study X2201: Overall Survival in Patients with *NRAS*-mutant Melanoma[a]



[a] Data represents patients who received their first treatment dose after protocol amendment 3 was implemented.
NE, not estimable.

Van Herpen C. et al ESMO 2014 [abstract LBA35].

NEMO (CMEK162A2301): Phase 3 Pivotal Study of Binimetinib in *NRAS*-Mutant Melanoma

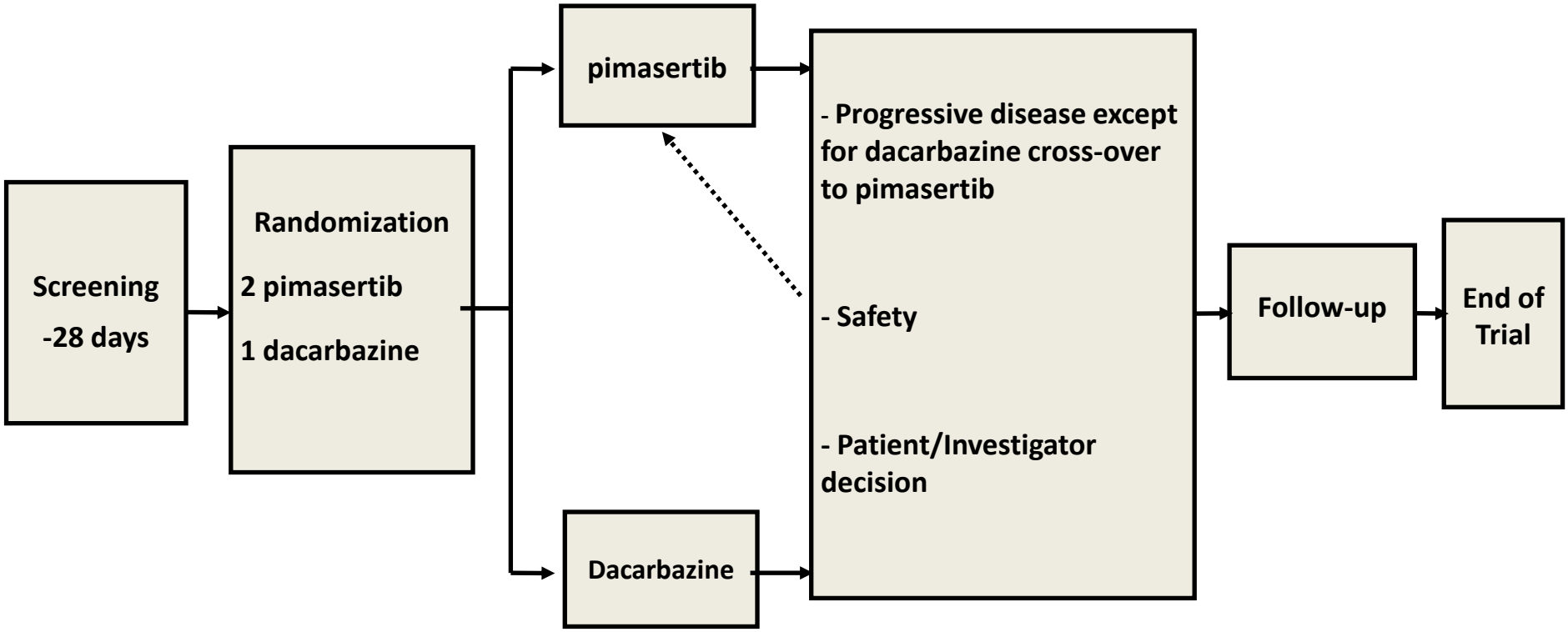


- **Primary endpoint:** progression-free survival
- **Secondary endpoints:** overall survival, objective response rate, time to response, duration of response, disease control rate, safety, quality of life

bid, twice daily; q3w, every 3 weeks.

www.clinicaltrials.gov; NCT01763164. Accessed May 30, 2014.

Pimasertib : Trial design



Conclusion

- New standard of care for $BRAF^{V600}$ mutant melanoma: combination of BRAF and MEK-inhibitors
- For NRAS mutant melanoma: ongoing phase 3 trials with anti-MEK monotherapies
- Immunotherapies with checkpoint inhibitors can also be used in patients with BRAF or NRAS mutations
- Efforst need to be continued: combinations, sequential treatments, new targets