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coBRIM: Phase 3, Double-Blind, Placebo-Controlled Study of Vemurafenib + Cobimetinib Versus Vemurafenib in Previously Untreated *BRAF*^{V600} Mutation–Positive Metastatic Melanoma

Grant McArthur, Paolo Ascierto, James Larkin, Antoni Ribas,
Gabriella Liszkay, Michele Maio, Mario Mandalà,
Lev Demidov, Daniil Stoyakovskiy, Luc Thomas,
Luis de la Cruiz Merino, Victoria Atkinson, Caroline Dutriaux,
Claus Garbe, Ilsung Chang, Stephen P. Hack, Brigitte Dréno

Disclosure Slide

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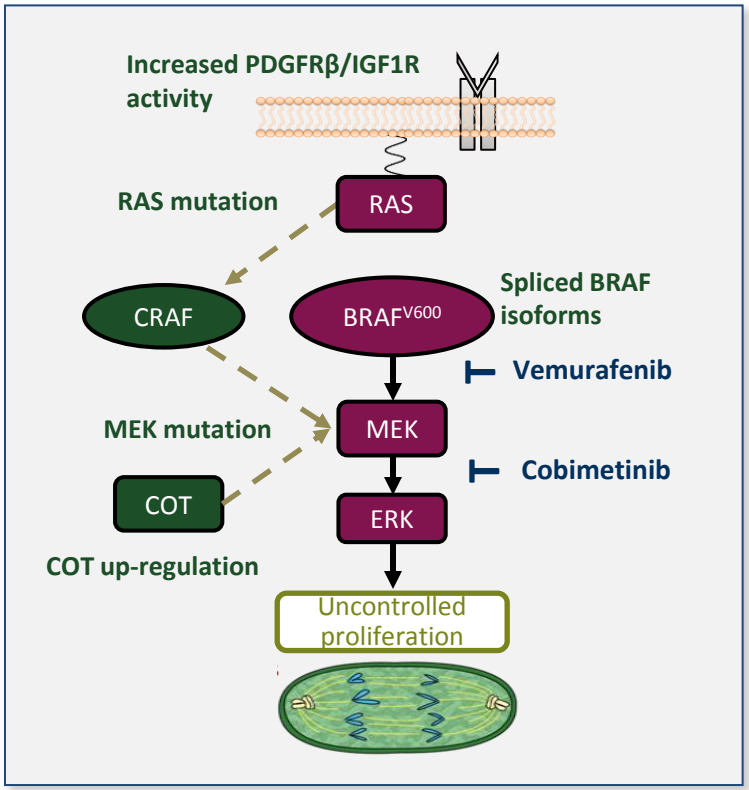
Rationale for Coinhibition of BRAF and MEK



Adapted with permission from AACR.[1]

Cobimetinib Overview	
Molecule type	Small molecule
Mechanism of action	Highly selective, allosteric inhibitor of MEK
Route of delivery	Oral
Half Life	48.8 hours

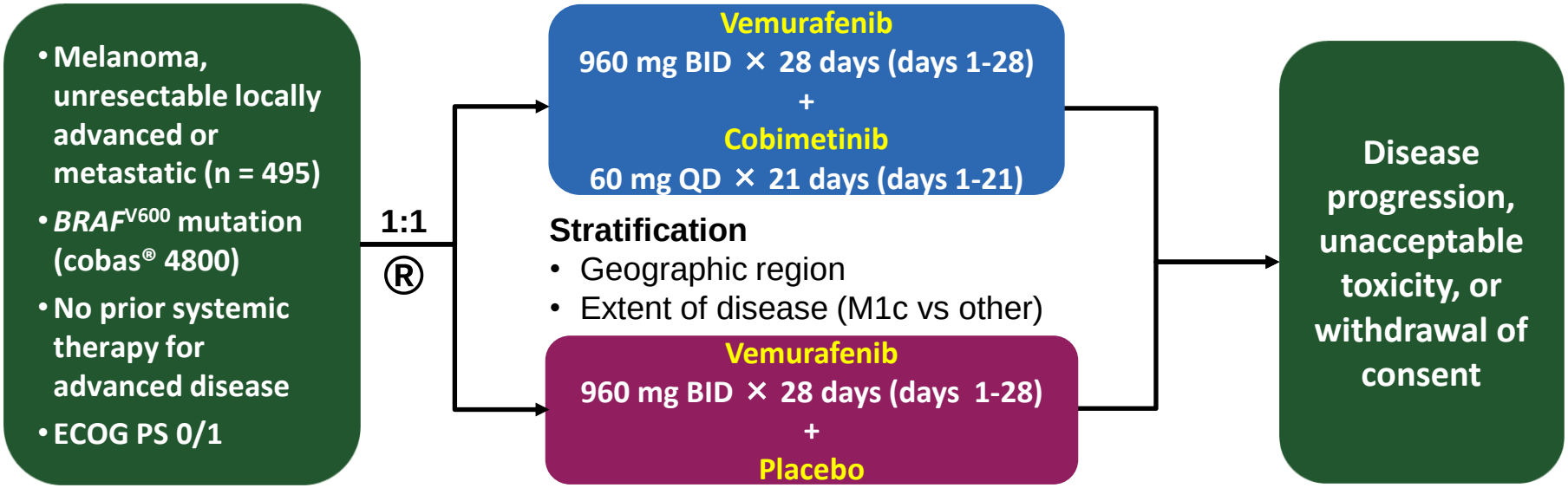
Rationale

- Most common mechanism of acquired resistance to vemurafenib is MAPK reactivation through MEK[1,2]
- MEK + BRAF inhibition prevents the development of acquired resistance in preclinical models[3]
- MEK + BRAF inhibition (dabrafenib + trametinib[4] phase 3 and vemurafenib + cobimetinib phase 1/2)[5] improved response rates and PFS in BRAF inhibitor–naive melanoma patients
- Reduced incidence of hyperproliferative lesions by blocking paradoxical activation of the MAPK pathway from RAF inhibition[6]

PFS, progression free survival.

1. Shi H et al. *Cancer Discov.* 2014;4:69-79. 2. Trunzer K et al. *J Clin Oncol.* 2013;31:1767-1774. 3. Paraiso K et al. *Br J Cancer.* 2010;102:1724-1730. 4. Long GV et al. *J Clin Oncol.* 2014;32(5S):9011. 5. Ribas A et al. *Lancet Oncol.* 2014;15:954-965. 6. Su F et al. *New Engl J Med* 2012;366:207-215.

Study Design



Primary end point
- PFS, investigator assessed

Secondary end points
- OS
- Objective response rate
- Duration of response
- PFS, IRC assessed
- Safety
- Pharmacokinetics
- Quality of life: QLQ-C30 and EQ-5D

Statistical assumptions
- 95% power to detect an improvement in median PFS from 6 to 11 months (HR = 0.55)
- 80% power to detect an improvement in median OS from 15 to 20 months (HR = 0.75)

BID, two times daily; ECOG, Eastern Cooperative Oncology Group; EQ, EuroQol; HR, hazard ratio; IRC, independent review committee; OS, overall survival; PS, performance status; QD, once daily; QLQ, quality of life questionnaire.

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Patient Characteristics

	Vemurafenib + Placebo (n = 248)	Vemurafenib + Cobimetinib (n = 247)
Median age (range), years	55 (25-85)	56 (23-88)
Sex, n (%)		
Male	140 (57)	146 (59)
Female	108 (44)	101 (41)
Geographic region, n (%)		
Australia/New Zealand/Other*	38 (15)	40 (16)
Europe	184 (74)	182 (74)
North America	26 (11)	25 (10)
ECOG, n (%)		
PS 0	164 (67)	184 (76)
PS 1	80 (33)	58 (24)
PS 2	0	1 (<1)†
Previously treated brain metastasis, n (%)	2 (0.8)	1 (<1)
Stage at randomization, n (%)		
Unresectable stage IIIc	13 (5)	21 (9)
Stage IV, M1a	40 (16)	40 (16)
Stage IV, M1b	42 (17)	40 (16)
Stage IV, M1c	153 (62)	146 (59)
Elevated LDH, n (%)	104 (43)	112 (46)
Median follow-up (range), months	7.2 (0.5-16.5)	7.4 (1.4-14.7)

LDH, lactate dehydrogenase.

Data Cutoff: May 9, 2014

*Other = Israel. †One patient was ECOG PS 1 at enrollment and ECOG PS 2 prior to first combination administration.

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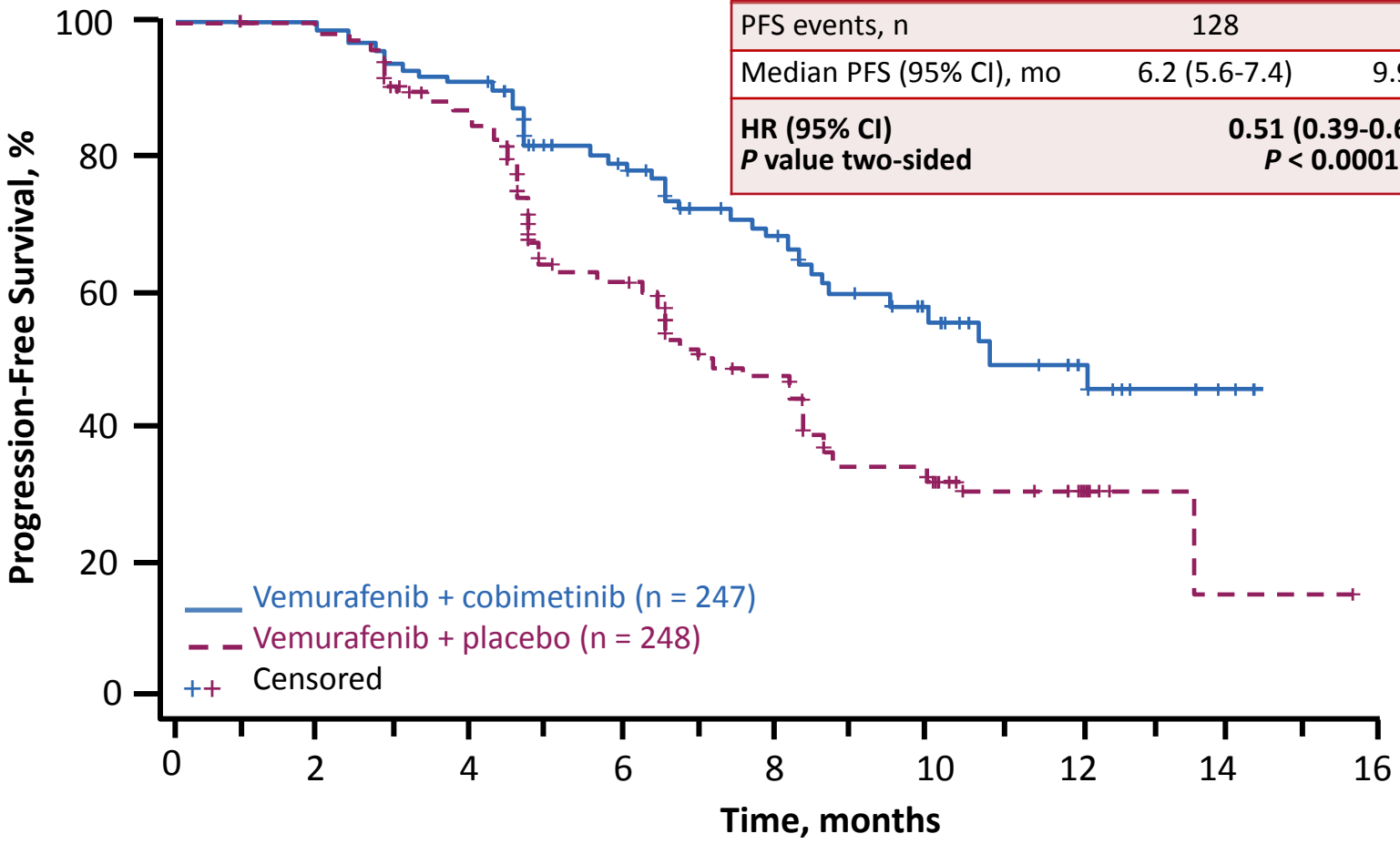
Investigator-Assessed PFS

	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

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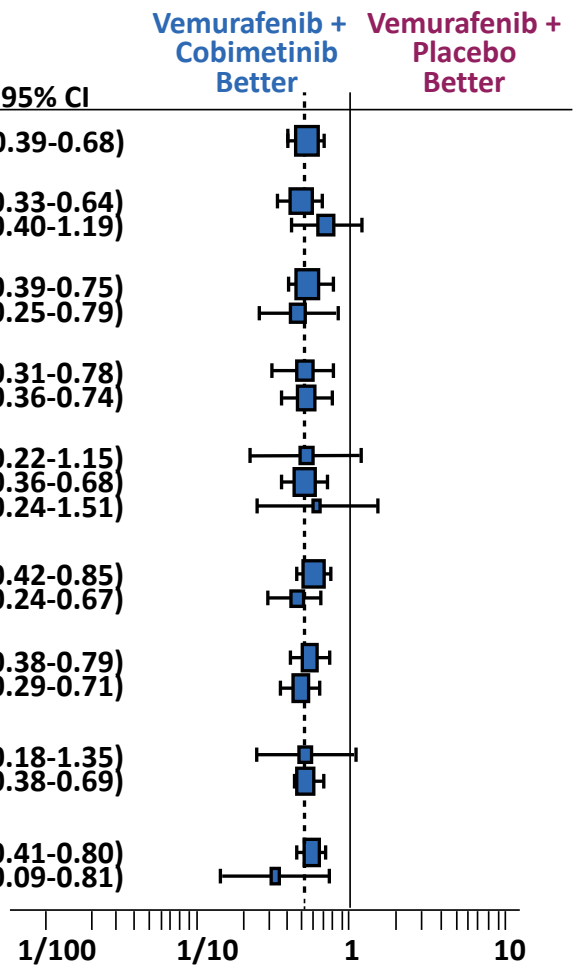
Investigator-Assessed PFS by Selected Subgroups

Baseline Risk Factors	Total N	Vemurafenib + Placebo (n = 248) n	No. Events	Median, mo	Vemurafenib + Cobimetinib (n = 247) n	No. Events	Median, mo	HR	95% CI
All patients	495	248	128	6.2	247	79	9.9	0.51	(0.39-0.68)
Disease stage									
M1c	299	153	99	5.3	146	55	9.1	0.46	(0.33-0.64)
Unresect. IIIc/M1a/ M1b	196	95	29	NE	101	24	NE	0.69	(0.40-1.19)
Age group									
<65 years	362	179	92	6.5	183	61	9.9	0.54	(0.39-0.75)
≥65 years	133	69	36	5.5	64	18	NE	0.45	(0.25-0.79)
Sex									
Female	209	108	51	7.2	101	27	NE	0.49	(0.31-0.78)
Male	286	140	77	5.6	146	52	9.8	0.52	(0.36-0.74)
Geographic region									
Australia/NZ/Other*	78	38	16	NE	40	9	NE	0.51	(0.22-1.15)
Europe	366	184	101	5.7	182	62	9.9	0.50	(0.36-0.68)
North America	51	26	11	7.4	25	8	NE	0.60	(0.24-1.51)
ECOG PS									
0	348	164	75	7.5	184	57	9.9	0.60	(0.42-0.85)
1	138	80	51	5.5	58	21	11.1	0.40	(0.24-0.67)
Baseline LDH									
≥ Upper limit of normal	216	104	67	4.7	112	51	7.7	0.55	(0.38-0.79)
< Upper limit of normal	268	138	57	7.5	130	28	NE	0.45	(0.29-0.71)
Prior adjuvant therapy									
Yes	48	24	11	7.2	24	6	NE	0.50	(0.18-1.35)
No	447	224	117	6.0	223	73	9.9	0.51	(0.38-0.69)
BRAF^{V600} mutation status									
V600E	344	174	88	6.5	170	58	NE	0.57	(0.41-0.80)
V600K	56	32	17	5.3	24	4	NE	0.27	(0.09-0.81)



CI, confidence interval; HR, hazard ratio; No, number; NZ, New Zealand; Unresect, unresectable.
*Other = Israel.

Data Cutoff: May 9, 2014

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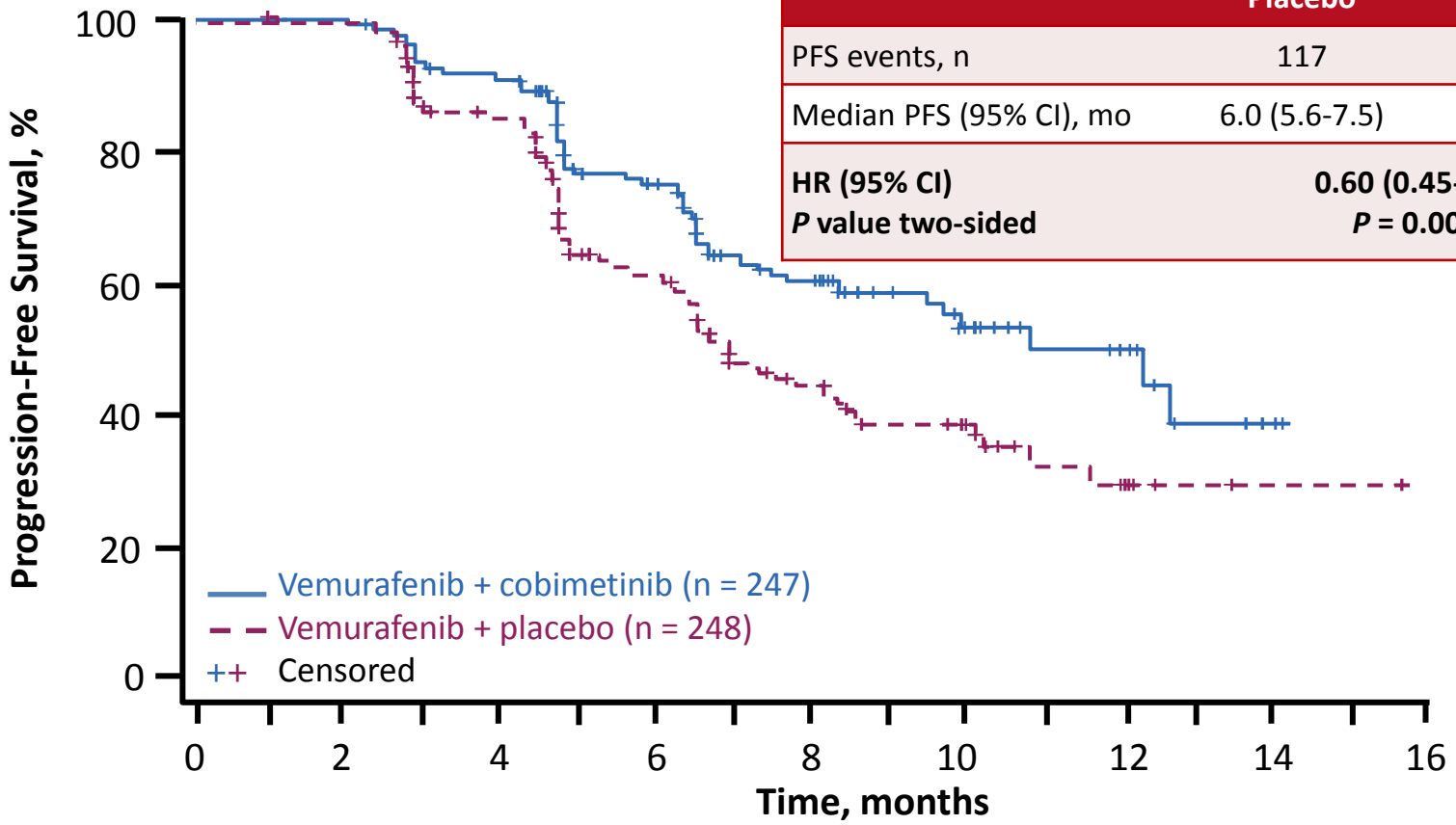
PFS by Independent Review Facility

	Vemurafenib + Placebo	Vemurafenib + Cobimetinib
PFS events, n	117	82
Median PFS (95% CI), mo	6.0 (5.6-7.5)	11.3 (8.5-NE)
HR (95% CI)	**0.60 (0.45-0.79)**	
***P* value two-sided**	***P* = 0.0003**	



No. at Risk

Vemurafenib + cobimetinib	228	201	138	81	39	13	3
Vemurafenib + placebo	235	189	112	61	32	11	1

CI, confidence interval; NE, not estimable.

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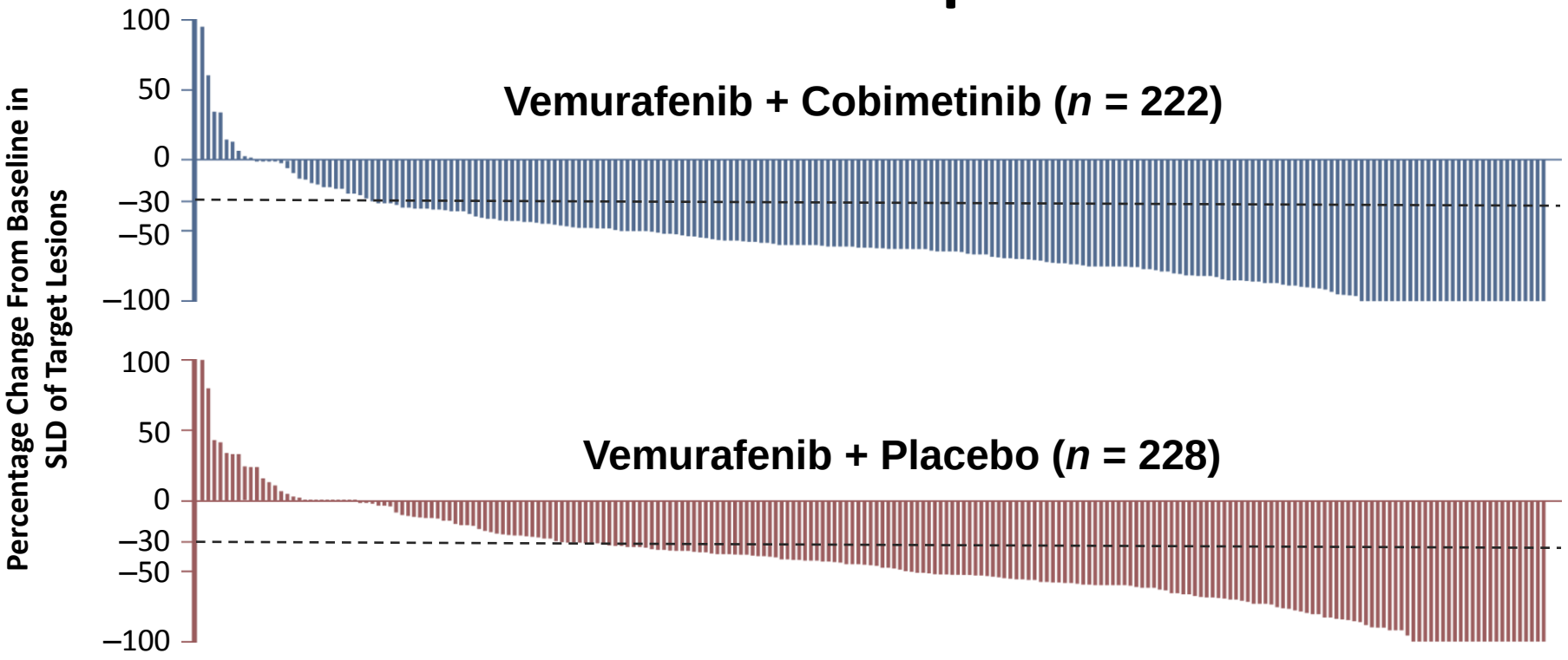
Best Tumor Response



	Vemurafenib + Placebo (n = 248)	Vemurafenib + Cobimetinib (n = 247)
Patients with confirmed objective response (95% CI), %*	45 (38.5-51.2)	68 (61.4-73.4)
Complete response, n (%)	11 (4)	25 (10)
Partial response, n (%)	100 (40)	142 (58)
Stable disease, n (%)	105 (42)	49 (20)

SLD is defined as the sum of the diameters of investigator identified target lesion per RECIST v 1.1.
*Only patients who had both pre and post tumor evaluations are included.

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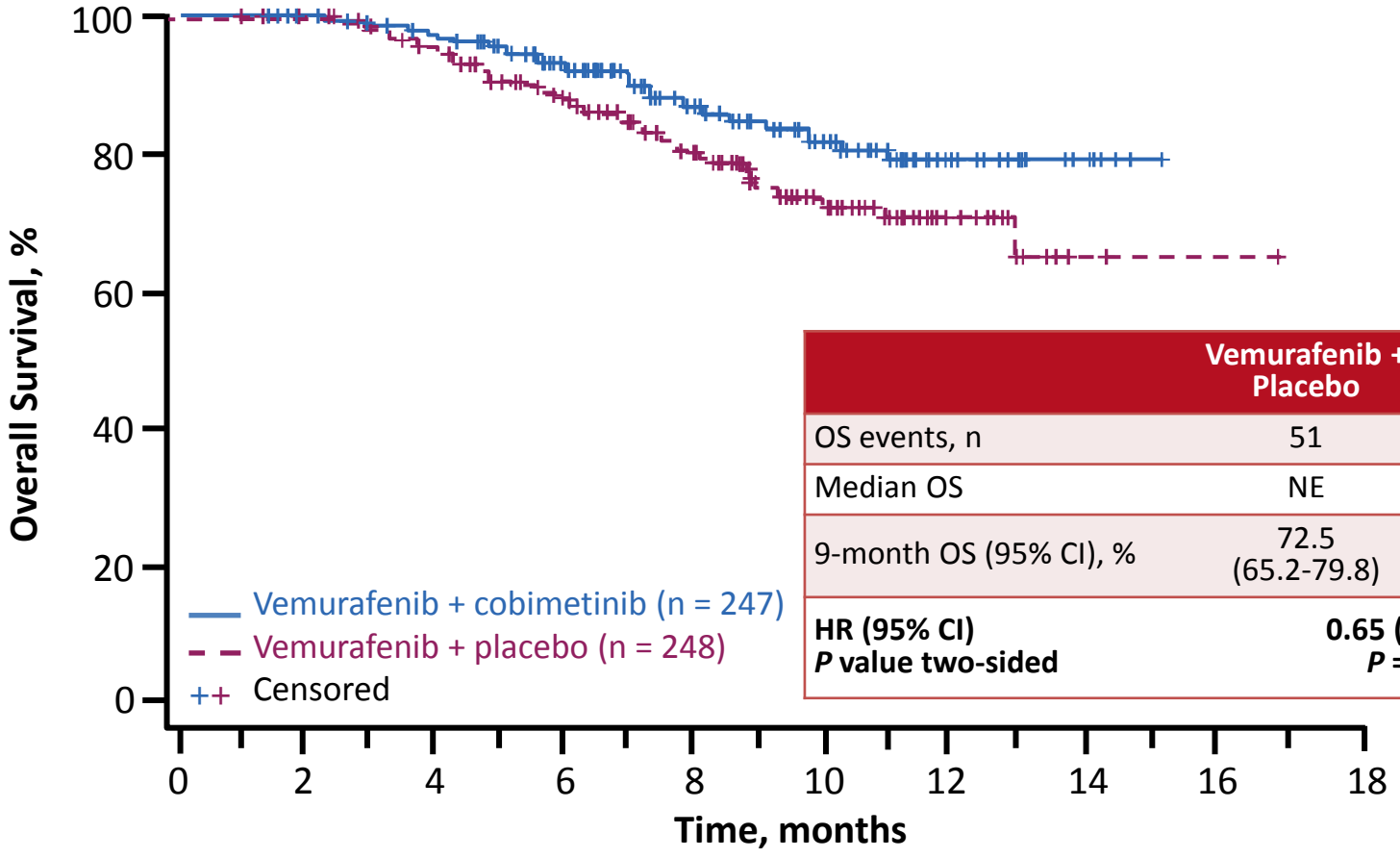
Overall Survival



	Vemurafenib + Placebo	Vemurafenib + Cobimetinib
OS events, n	51	34
Median OS	NE	NE
9-month OS (95% CI), %	72.5 (65.2-79.8)	81.1 (74.7-87.5)
HR (95% CI)	**0.65 (0.42-1.00)**	
***P* value two-sided**	***P* = 0.046***	

No. at Risk

Vemurafenib + cobimetinib	243	229	182	112	62	20	6	
Vemurafenib + placebo	245	227	166	101	53	21	2	1

CI, confidence interval; NE, not estimable.

Data Cutoff: May 9, 2014

* Descriptive p-value. Did not cross the pre-specified stopping boundary for the interim analysis (boundary p <0.0000015)

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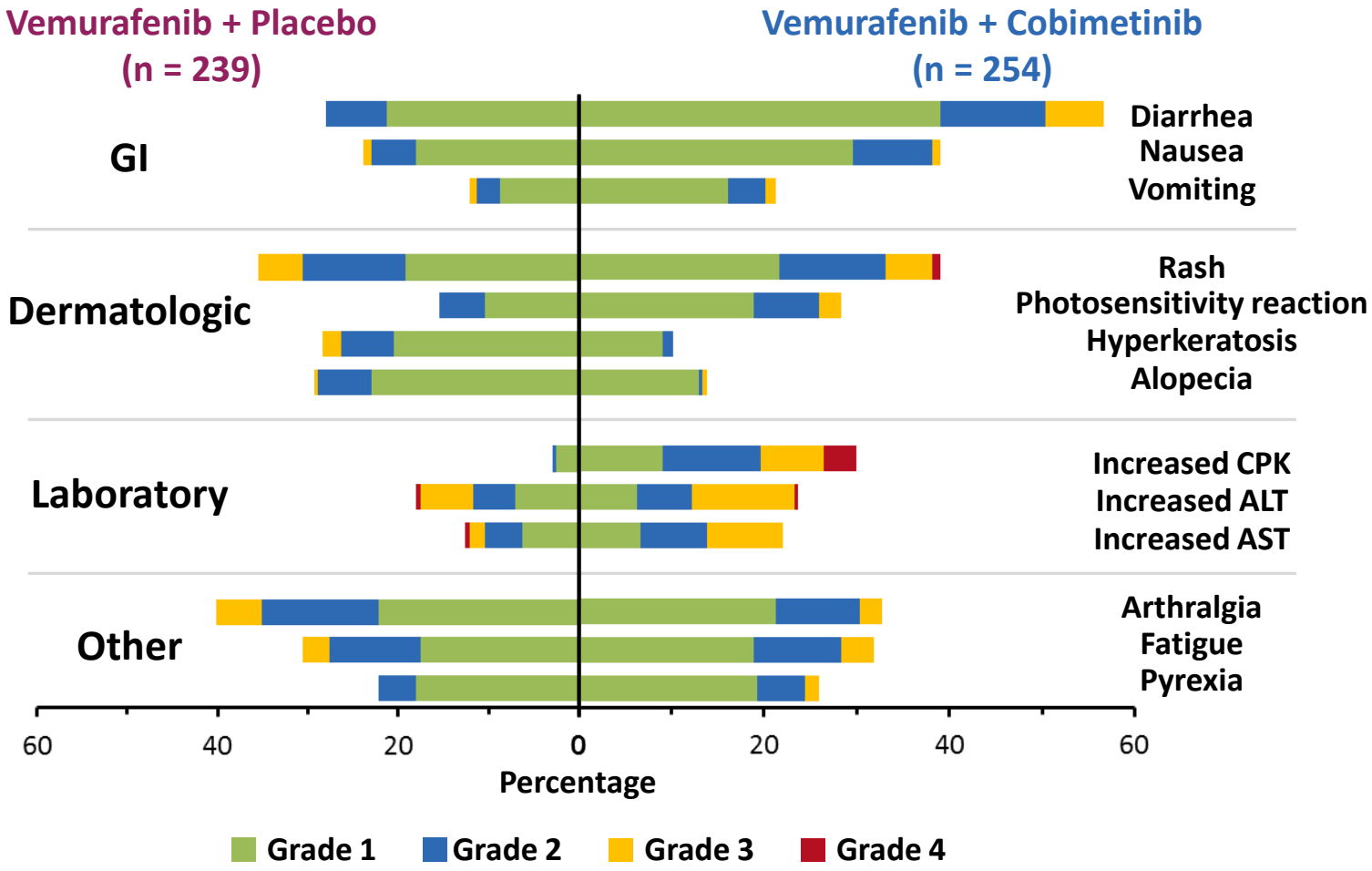
Overall Safety Summary

	Vemurafenib + Placebo (n = 239)	Vemurafenib + Cobimetinib (n = 254)
Patients with at least 1 AE, n (%)	233 (98)	250 (98)
Patients with at least 1 of the following:		
Grade ≥ 3 AE, n (%)	142 (59)	165 (65)
Grade 5 AE, n (%)	3 (1)	6 (2)
Serious AE, n (%)	60 (25)	75 (30)
AE leading to withdrawal of vemurafenib, n (%)	32 (13)	35 (14)
AE leading to withdrawal of cobimetinib/placebo, n (%)	33 (14)	42 (17)
AE leading to withdrawal of both cobimetinib and vemurafenib, n (%)	28 (12)	32 (13)

AE, adverse event.
Safety analyses included all patients who had received at least one dose of a study drug

Data Cutoff: May 9, 2014

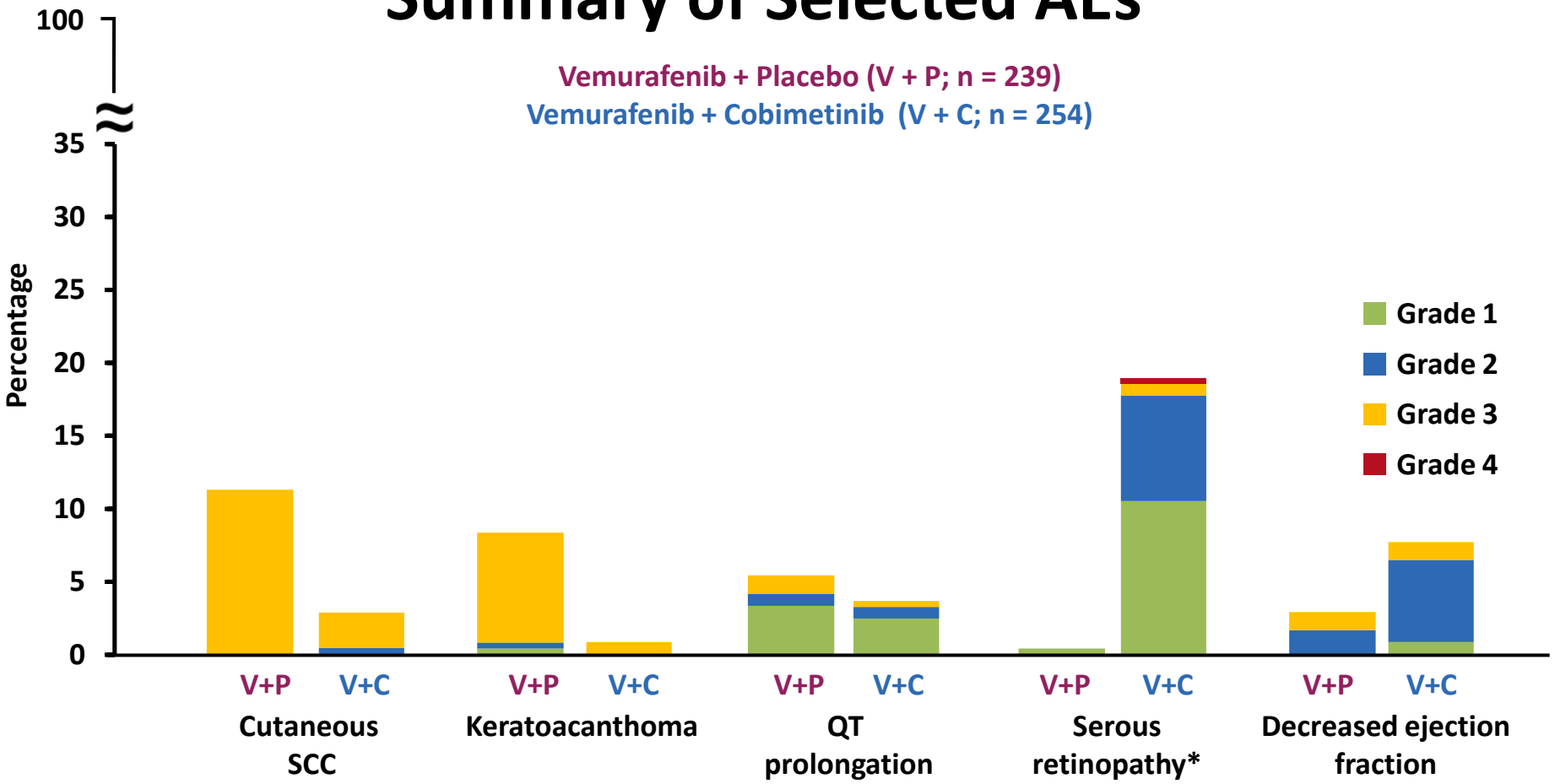
AEs Occurring in ≥20% of Patients



ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase.
*Multiple occurrences of a specific AE for a patient were counted once at the highest NCI CTCAE grade of the occurrence.

Data Cutoff: May 9, 2014

Summary of Selected AEs



No cases of retinal vein occlusion were reported.

***Includes specific terms chorioretinopathy and retinal detachment.**

SCC, squamous cell carcinoma.

Data Cutoff: May 9, 2014

Summary of Selected AEs

Adverse Event, n (%)	Vemurafenib + Placebo (n=239)				Vemurafenib + Cobimetinib (n=254)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Cutaneous squamous cell carcinoma	0	0	27 (11)	0	0	1 (<1)	6 (2)	0
Keratoacanthoma	1 (<1)	1 (<1)	18 (8)	0	0	0	2 (1)	0
Serous retinopathy*	1 (<1)	0	0	0	26 (10)	18 (7)	6 (2)	1 (<1)
Decreased ejection fraction	0	4 (2)	3 (1)	0	2 (1)	14 (6)	3 (1)	0
QT interval prolongation	8 (3)	2 (1)	3 (1)	0	6 (2)	2 (1)	1 (<1)	0

*Includes specific terms chorioretinopathy and retinal detachment.

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Conclusions

The coBRIM study provides clear and definitive evidence that cobimetinib combined with vemurafenib results in improved PFS and increased ORR; preliminary OS analysis is promising

Vemurafenib plus cobimetinib vs. vemurafenib:

- 49% reduction in risk of progression or death (HR = 0.51; 95% CI, 0.39 to 0.68; P<0.0001)
  - ORR 68% versus 45% (P<0.0001); CR rate 10% v 4%
  - Interim OS analysis showed a reduction in risk of death of 35% (HR of 0.65; 95% CI, 0.42 to 1.00)
- Tolerable and manageable AE profile consistent with previous trials of the combination
  - Grade ≥ 3 toxicity was 65% vs. 59%
  - No difference in the rate of study drug discontinuation between arms
- coBRIM is ongoing in order to evaluate mature OS

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