Results of NEMO: A Phase 3 Trial of Binimetinib (BINI) vs Dacarbazine (DTIC) in *NRAS*-Mutant Cutaneous Melanoma

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Disclosures

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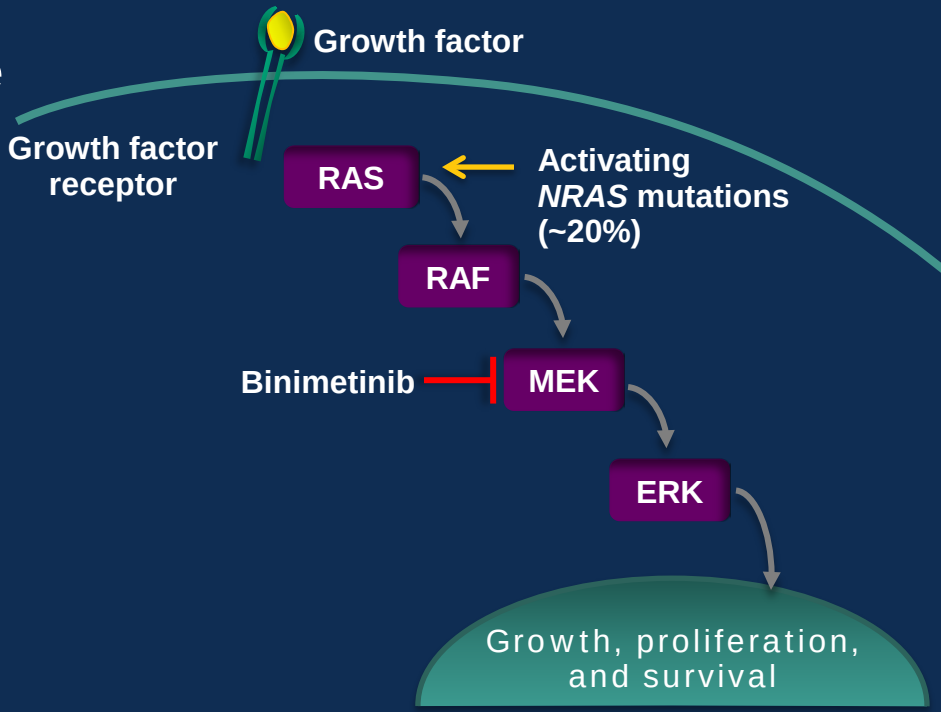
NRAS Mutations in Melanoma

- *NRAS* mutations present in ~20% of patients with metastatic melanoma[1,2]
- May constitutively activate the MAPK pathway, driving cell proliferation and inhibiting apoptosis[2-4]
- Preclinical studies: *NRAS*-mutant melanoma is sensitive to MEK inhibition[5,6]
- *NRAS*-mutant melanoma → more aggressive subtype, less favorable prognosis[1]
- Substantial unmet clinical need, particularly after failure of immunotherapy

1. Jakob JA, et al. *Cancer*. 2012;118(16):4014-4023
2. Krauthammer M, et al. *Nat Genet*. 2015;47(9):996-1002
3. Johnson DB and Puzanov I. *Curr Treat Options Oncol*. 2015;16(4):15
4. Richman J, et al. *Expert Opin Pharmacother*. 2015;16(9):1285-1297
5. Solit DB, et al. *Nature*. 2006;439(7074):358-362
6. Lee PA, et al. *Cancer Res*. 2010;70(8 suppl):abstract 2515

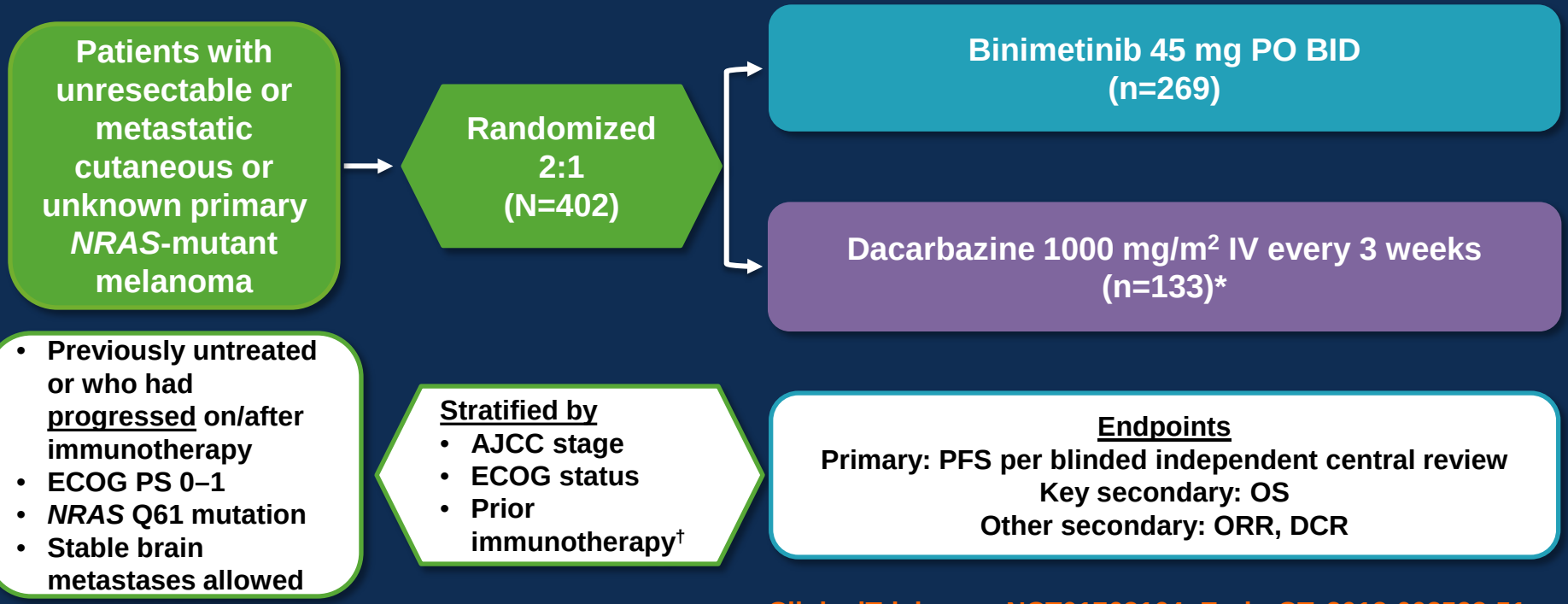
Binimetinib (MEK162)

- Oral, selective, ATP-uncompetitive inhibitor of MEK1 and MEK2[1]
- Inhibits in vitro growth of tumors with driver mutations in *NRAS* genes[1]
- Phase 2 study demonstrated clinical activity of binimetinib in *NRAS*-mutant metastatic melanoma[2]
  - 15% confirmed response rate[3]



1. Lee PA, et al. *Cancer Res.* 2010;70(8 suppl):abstract 2515
2. Ascierto PA, et al. *Lancet Oncol.* 2013;14(3):249-256
3. van Herpen, et al. *Ann Oncol*. 2014;25(suppl 5):abstract LBA35

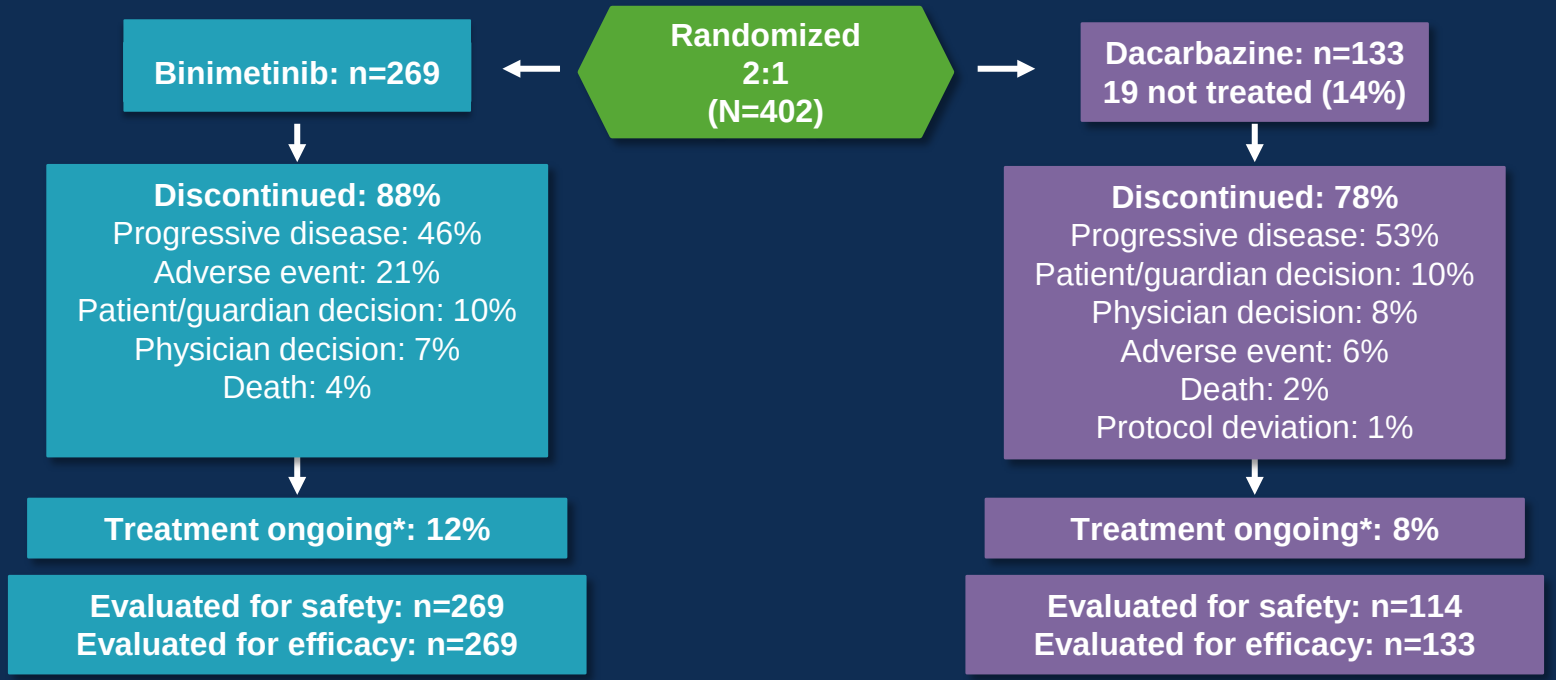
Phase 3 NEMO Trial: Study Design



ClinicalTrials.gov, NCT01763164; EudraCT, 2012-003593-51

*19 patients not treated
†Prior immunotherapy for unresectable/metastatic disease
AJCC=American Joint Committee on Cancer; BID=twice daily; DCR=disease control rate; ECOG=Eastern Cooperative Oncology Group; IV=intravenous; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PO=by mouth; PS=performance status

Disposition and Median Exposure



Median (range) duration of exposure was 13 (0–73) weeks with binimetinib and 9 (3–57) weeks with dacarbazine

*As of August 24, 2015
Efficacy evaluated in all randomized patients; safety analyzed in all patients who received ≥1 dose of study drug and had ≥1 valid postbaseline safety evaluation

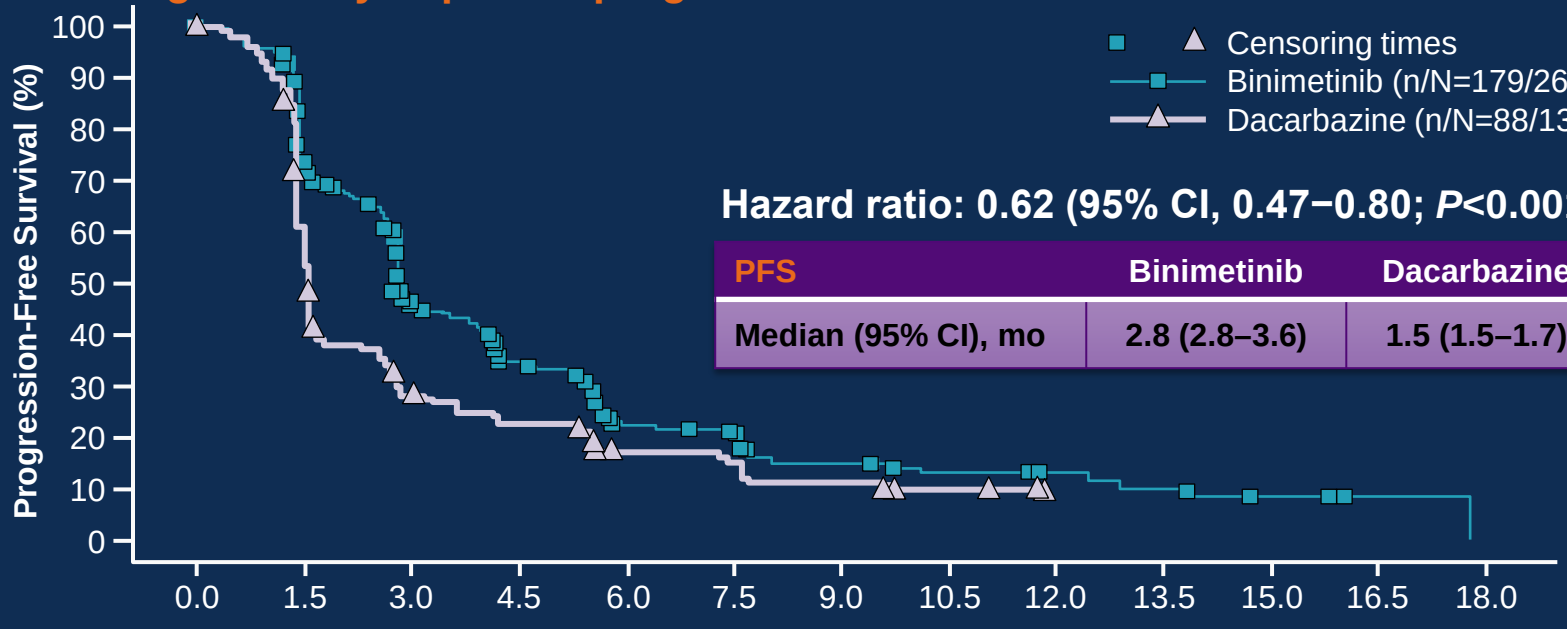
Baseline Characteristics

Characteristic	Binimetinib (n=269)	Dacarbazine (n=133)
Median age, y	65	62
Male sex, %	62	64
ECOG performance status 0,* %	72	72
LDH level >ULN, %	26	24
NRAS mutation, %	100	99
Q61K	37	38
Q61L	12	13
Q61R	51	48
IIIC, IVM1a, or IVM1b tumor stage at study entry, %	30	36
Prior immunotherapy stratum, %	21	21
Prior ipilimumab,† %	13	13
Prior anti–PD-1 or anti–PD-L1,† %	6	5

*All other patients had ECOG performance status 1, except for 1 patient with a performance status of 2 in the dacarbazine arm
†Metastatic setting
ECOG=Eastern Cooperative Oncology Group; LDH=lactate dehydrogenase; PD=programmed death; PD-L=PD ligand; ULN=upper limit of normal

Progression-Free Survival

Binimetinib significantly improves progression-free survival



Hazard ratio: 0.62 (95% CI, 0.47−0.80; *P*<0.001)

PFS	Binimetinib	Dacarbazine
Median (95% CI), mo	2.8 (2.8–3.6)	1.5 (1.5–1.7)

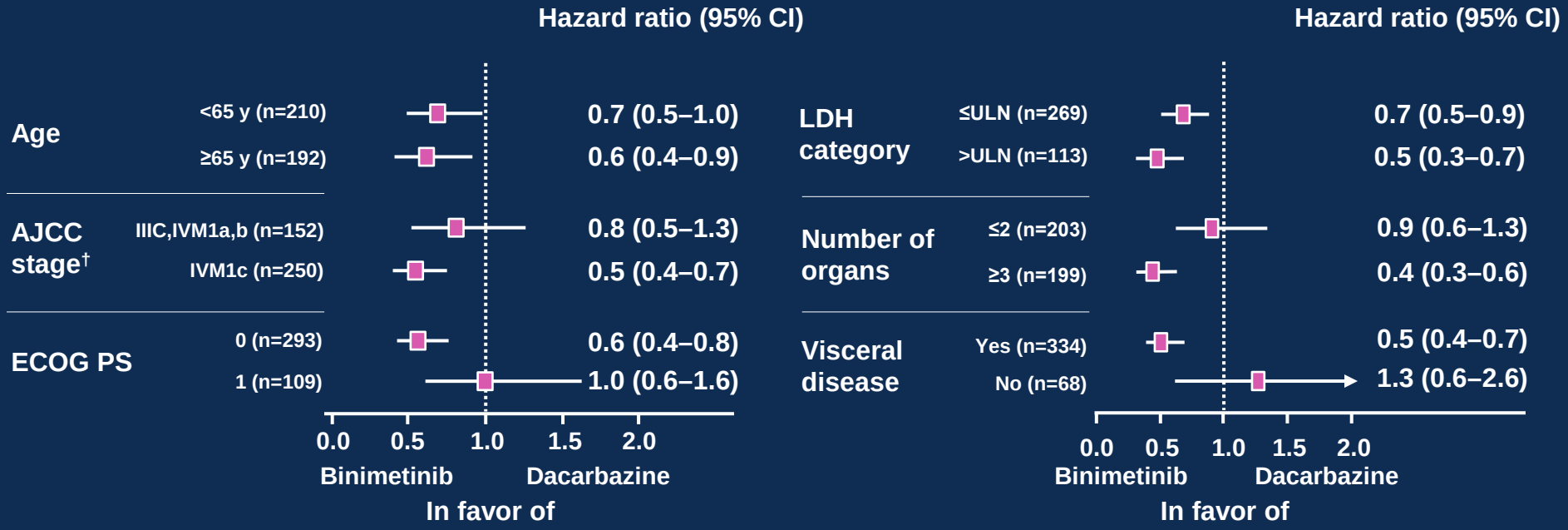
Number still at risk

Time (mo)	0.0	1.5	3.0	4.5	6.0	7.5	9.0	10.5	12.0	13.5	15.0	16.5	18.0
Binimetinib	269	175	90	56	30	25	15	11	9	7	4	1	0
Dacarbazine	133	56	27	21	9	8	6	3	0	0	0	0	0

Stratified log-rank test and stratified Cox model using strata defined by AJCC stage, prior line immunotherapy, and ECOG performance status

AJCC=American Joint Committee on Cancer; ECOG=Eastern Cooperative Oncology Group; PFS=progression-free survival

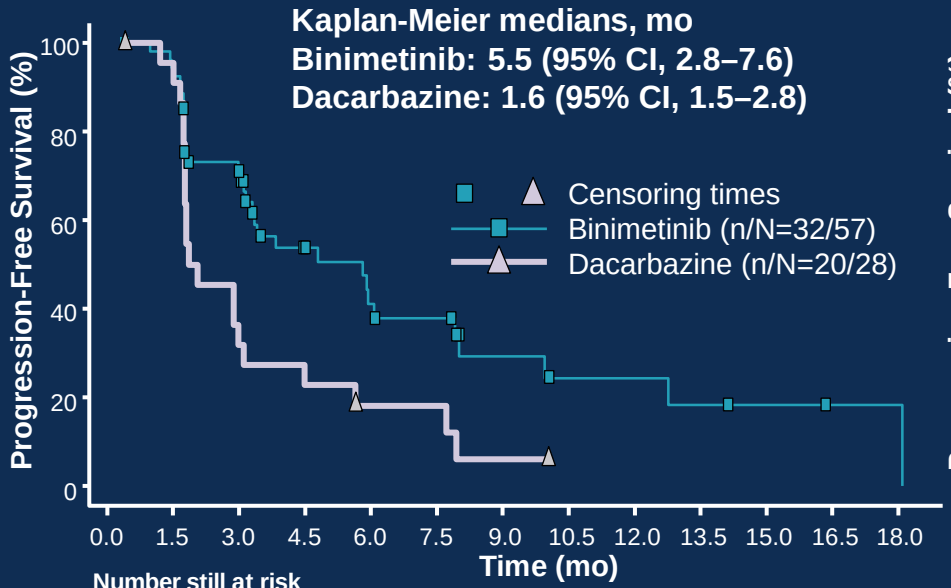
Progression-Free Survival by Subgroups (All Subgroups With >30 Patients*)



*Except race and sex
†IIIC,IVM1a,b=IIIC, IVM1a, or IVM1b
Hazard ratios for subgroups obtained from unstratified proportional hazards model
AJCC=American Joint Committee on Cancer; ECOG=Eastern Cooperative Oncology Group; LDH=lactate dehydrogenase; PS=performance status; ULN=upper limit of normal

Progression-Free Survival by Prior Immunotherapy Stratum

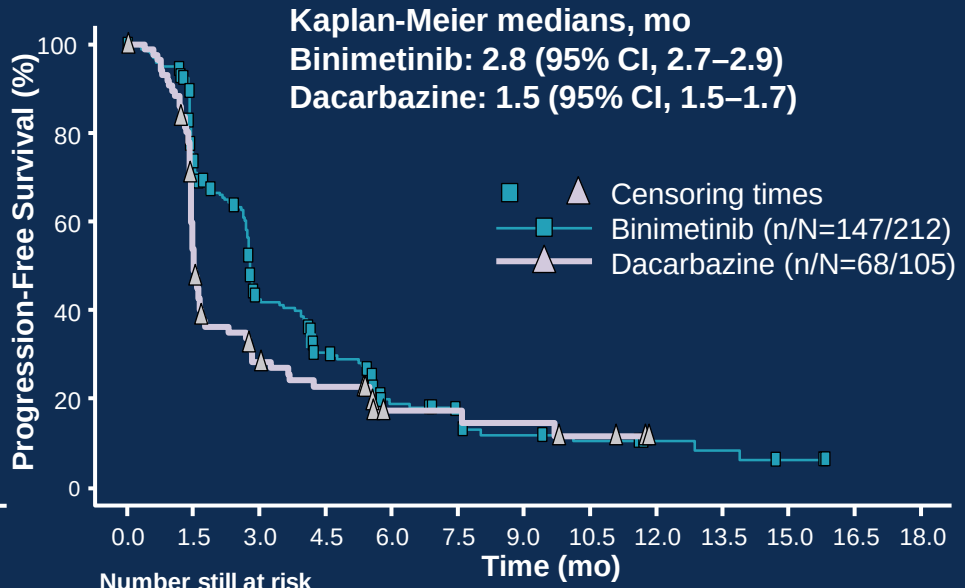
Stratum: Prior immunotherapy



Number still at risk

Months	0.0	1.5	3.0	4.5	6.0	7.5	9.0	10.5	12.0	13.5	15.0	16.5	18.0
BINI	57	36	24	16	11	11	6	4	4	3	2	1	0
DTIC	28	12	6	5	3	2	1	0	0	0	0	0	0

Stratum: No prior immunotherapy

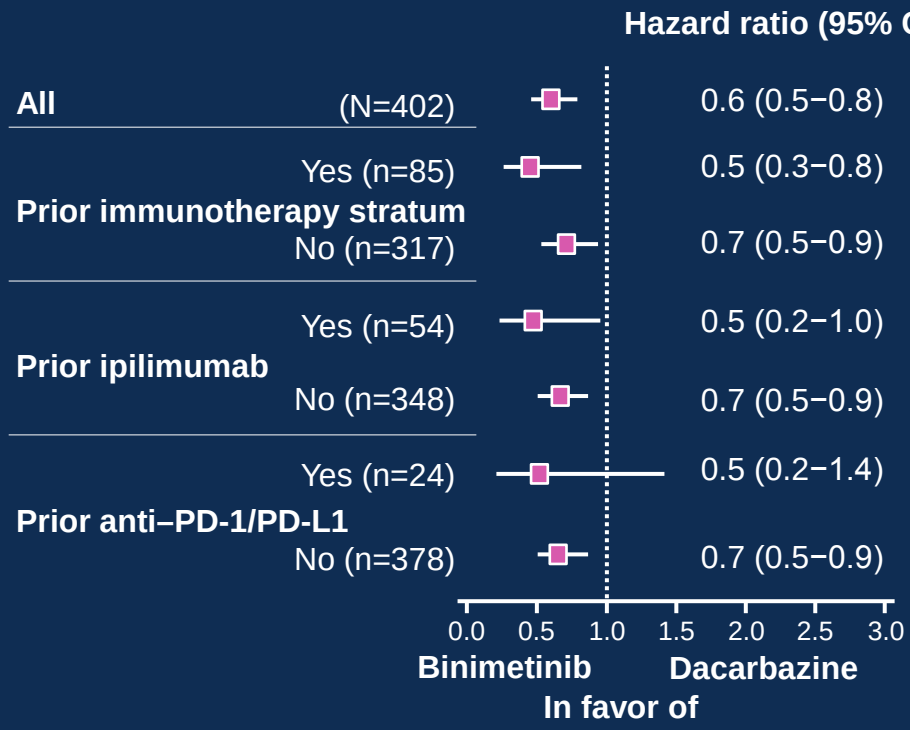


Number still at risk

	0.0	1.5	3.0	4.5	6.0	7.5	9.0	10.5	12.0	13.5	15.0	16.5	18.0
	212	139	66	40	19	14	9	7	5	4	2	0	0
	105	44	21	16	6	6	5	3	0	0	0	0	0

BINI=binimetinib; DTIC=dacarbazine

Progression-Free Survival by Prior Immunotherapy



Patients in the prior immunotherapy stratum who received binimetinib*:

- Confirmed overall response rate: 16%
- Median duration of response: 11.1 months

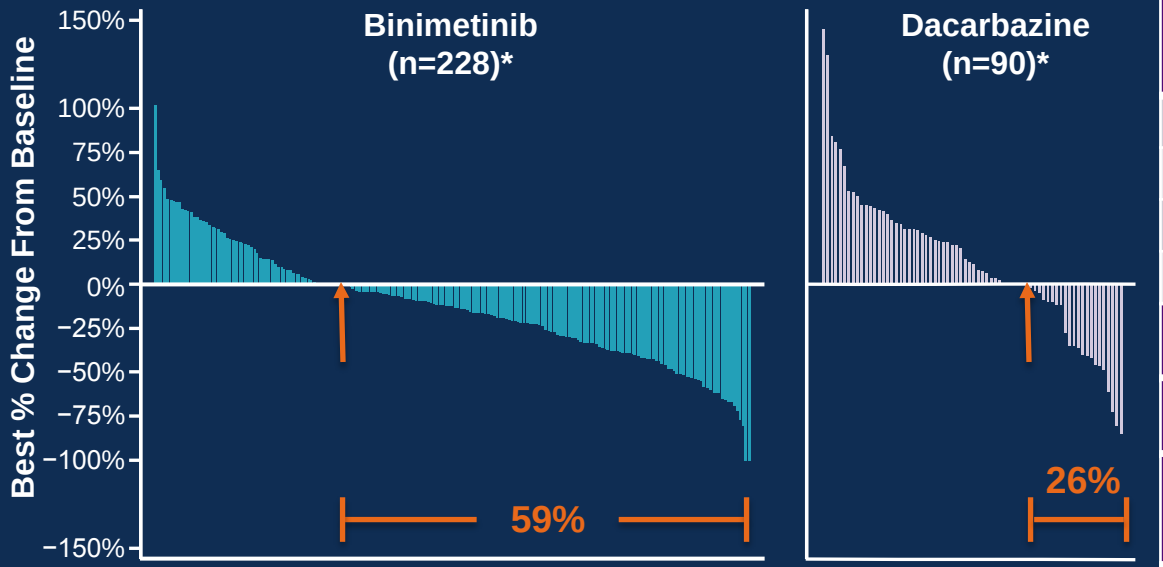
All patients in the binimetinib arm:

- Confirmed overall response rate: 15%
- Median duration of response: 6.9 months

*Post hoc analysis
Hazard ratios for subgroups obtained from unstratified proportional hazards model

Tumor Response as per Central Blinded Independent Review

Decrease in best percentage change from baseline: binimetinib, 135 patients (59%); dacarbazine, 23 patients (26%)



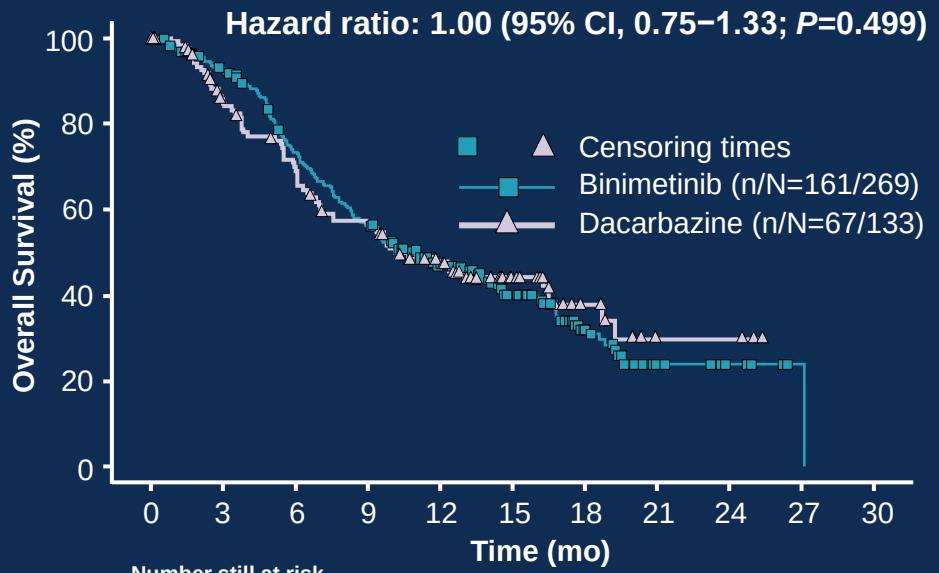
Confirmed Best Overall Response, %	Binimetinib† (n=269)	Dacarbazine† (n=133)
CR	1	0
PR	14	7
SD	41	17
PD	27	44
ORR, % (95% CI)	15 (11–20)	7 (3–13)
DCR, % (95% CI)	58 (52–64)	25 (18–33)
Median response duration (range), mo	6.9 (4.2–11.1)	NE (4.1–NE)

*Patients whose best % change from baseline was contradicted by an overall response of progressive disease (binimetinib, 13%; dacarbazine, 22%) not presented

†As of the data cutoff (Aug 24, 2015), 32 patients were ongoing in the binimetinib arm and 10 in the dacarbazine arm

CR=complete response; DCR=disease control rate; NE=not evaluable; ORR=overall response rate; PD=progressive disease; PR=partial response; SD=stable disease

Overall Survival



Number still at risk

Time (mo)	0	3	6	9	12	15	18	21	24	27	30
Binimetinib	269	240	185	141	96	58	26	9	5	1	0
Dacarbazine	133	98	76	62	44	26	11	3	3	0	0

Overall survival	Binimetinib	Dacarbazine
Median (95% CI), mo	11.0 (8.9–13.6)	10.1 (7.0–16.5)

Use of immunotherapy* after study treatment discontinuation:

%	Binimetinib (n=269)	Dacarbazine (n=133)
Any immunotherapy	46	44
Ipilimumab	33	36
Nivolumab	13	9
Pembrolizumab	12	7

*Ipilimumab, nivolumab, or pembrolizumab.
Stratified log-rank test and stratified Cox model using strata defined by AJCC stage, prior line immunotherapy, and ECOG performance status
AJCC=American Joint Committee on Cancer; CI=confidence internal; ECOG=Eastern Cooperative Oncology Group

Safety: All-Cause AEs and Grade 3/4 AEs

Preferred Term, %	Binimetinib (n=269)		Dacarbazine (n=114)	
	All Grades*	Grade 3/4†	All Grades*	Grade 3/4†
Total	100	68	91	46
Skin-related				
Rash	36	4	1	0
Dermatitis acneiform	35	3	1	0
Gastrointestinal				
Diarrhea	40	1	11	1
Nausea	29	1	32	1
Vomiting	21	2	12	0
Muscle-related				
Blood CPK increased	42	19	3	0
Other				
Peripheral edema	36	<1	3	0
Fatigue	22	2	32	3
Asthenia	18	3	17	4

*>15% of patients in any treatment group; †>2.0% of patients in any treatment group
AE=adverse event; CPK=creatine phosphokinase

Safety: All-Cause AEs and Grade 3/4 AEs (cont'd)

Preferred Term, %	Binimetinib (n=269)		Dacarbazine (n=114)	
	All Grades*	Grade 3/4†	All Grades*	Grade 3/4†
Other (cont'd)				
Hypertension	14	7	4	2
AST increased	13	2	4	0
Decreased appetite	12	1	16	1
Ejection fraction decreased	11	4	2	1
ALT increased	8	3	6	2
General physical health deterioration	7	4	2	0
Anemia	7	2	10	5
GGT increased	3	1	5	3
Lymphopenia	3	1	5	3
Neutropenia	1	1	18	9
Thrombocytopenia	1	<1	15	4
Neutrophil count decreased	<1	0	7	3
Leukopenia	0	0	7	4

*>15% of patients in any treatment group; †>2.0% of patients in any treatment group
AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma-glutamyltransferase

Safety: AEs Leading to Discontinuation*

Preferred Term, %	Binimetinib (n=269)		Dacarbazine (n=114)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Total	25	17	8	5
Ejection fraction decreased	4	2	0	0
Blood CPK increased	2	2	0	0
Retinal vein occlusion	2	1	0	0
Retinal detachment	1	0	0	0
ALT increased	1	1	0	0
AST increased	1	1	1	0
Dermatitis acneiform	1	1	0	0
General physical health deterioration	1	1	0	0
Muscular weakness	1†	1‡	0	0

*>1.0% of patients in any treatment group, all grades
†1 patient with grade 1 muscular weakness also experienced grade 1 and grade 2 CPK elevation
‡1 patient with grade 3 muscular weakness also experienced grade 1 and grade 2 CPK elevations and grade 1 myalgia
AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase

Summary and Conclusions

- NEMO is the largest controlled study to date in patients with *NRAS*-mutant melanoma
- Binimetinib significantly prolonged PFS and improved response rates vs dacarbazine in patients with *NRAS*-mutant melanoma
  - Median PFS: 2.8 vs 1.5 months, respectively
- Benefit with binimetinib was seen in treatment-naive patients and in those who received prior immunotherapy
  - In a prespecified analysis of patients randomized to the stratum of patients with prior immunotherapy (n=85), a benefit was observed with binimetinib vs dacarbazine (PFS 5.5 vs 1.6 months)
- The safety profile of binimetinib was consistent with other currently marketed MEK inhibitors[1,2]
- Binimetinib represents a new effective therapy in patients with unmet clinical needs

PFS=progression-free survival

1. Mekinist (trametinib) tablets. Full Prescribing Information, Novartis Pharmaceuticals Corporation, East Hanover, NJ, 2015
2. Cotellic (cobimetinib) tablets. Full Prescribing Information, Genentech, Inc., South San Francisco, CA, 2015

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