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Results of COLUMBUS Part 1: A Phase 3 Trial of Encorafenib (ENCO) Plus Binimetinib (BINI) Versus Vemurafenib (VEM) or ENCO in *BRAF*-Mutant Melanoma

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Disclosures

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R Dummer: Honoraria from and consulting/advisory role for Roche, BMS, GSK, MSD, Novartis, and Amgen; research funding from Roche, BMS, GSK, MSD, and Novartis

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V Chiarion Sileni: Honoraria received from Novartis, GSK, BMS, MSD, and Roche; speakers bureau for Novartis, GSK, Roche, and BMS; advisory board member for Novartis, Amgen, MSD, BMS, and Roche

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C Loquai: Advisory board member for Roche, Novartis, BMS, MSD, Biontech, and Amgen; speakers fees from Roche, Novartis, BMS, and MSD; travel expenses from Roche, Novartis, BMS, MSD, and Amgen

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MD Pickard: Employee of Array BioPharma; may own stock or stock options

V Sandor: Employee/leadership role at Array BioPharma; stock or other ownership of Array BioPharma and Incyte Corp

C Robert: Consultant for Roche, Novartis, BMS, MSD, and Amgen

G Liszkay, C Dutriaux: Nothing to disclose

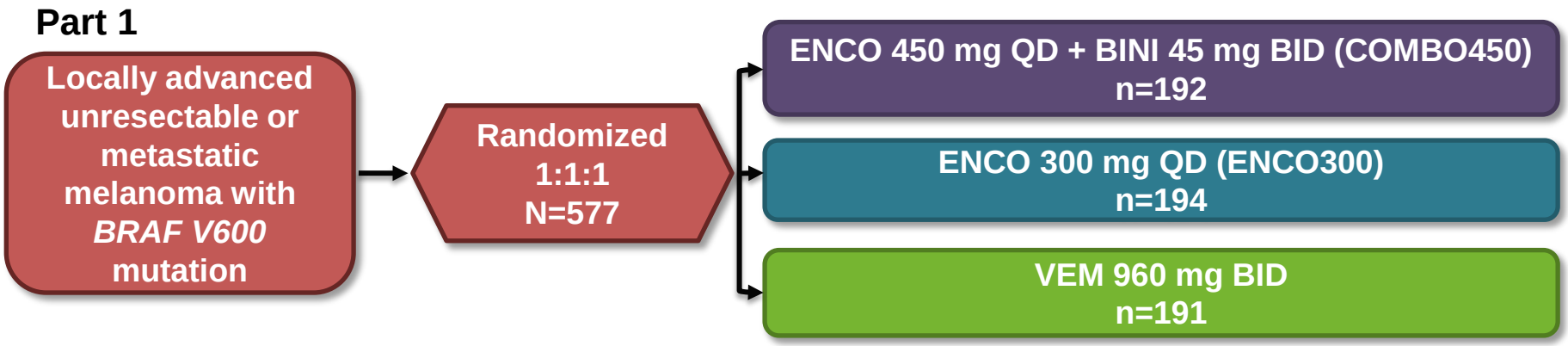
Background

- Although BRAF inhibitor (BRAFi) monotherapy is effective in *BRAF V600*-mutant locally advanced or metastatic melanoma,[1] the addition of a MEK inhibitor has been shown to improve survival and attenuate some BRAFi-associated toxicities.[2]
- **Encorafenib (ENCO):** ATP-competitive BRAF kinase inhibitor
  - Unique pharmacologic profile[3]
    - Potent inhibition of proliferation in cells with *BRAF V600* mutations
    - Highly selective with no significant activity observed against a panel of 100 kinases (IC_{50} >900 nM)
    - Dissociation half-life >24 hours, leading to sustained target inhibition
- **Binimetinib (BINI):** potent, selective allosteric, ATP-uncompetitive inhibitor of MEK1/2[4]
  - Shorter half-life than other MEK1/2 inhibitors; may provide more rapid resolution of toxicity upon interruption[5]

IC_{50}=half-maximal inhibitory concentration.

1. Chapman PB, et al. *N Engl J Med*. 2011;364(26):2507-2516.
2. Robert C, et al. *N Engl J Med*. 2015;372(1):30-39.
3. Stuart DD, et al. *Cancer Res*. 2012;72(8 suppl):3790.
4. Ascierto PA, et al. *Lancet Oncol*. 2013;14(3):249-256.
5. Data on File. Array BioPharma Inc.

Study Design and Objectives



- **Untreated or progressed on/after prior first-line immunotherapy**
- ***BRAF V600E* and/or *V600K***
- **ECOG PS 0–1**

Stratified by
- **AJCC stage**
- **ECOG status**
- ***BRAF* mutation status/prior first-line immunotherapy***

- **Primary endpoint:** **PFS† for COMBO450 vs VEM**
- **Key secondary endpoint (tested sequentially):** **PFS† for COMBO450 vs ENCO300**
- **Patient-reported outcomes:** **FACT-M, EORTC QLQ-C30**

- Key secondary endpoint of overall survival for COMBO450 vs VEM not yet mature

Part 2 (ongoing): the primary objective is to further evaluate the contribution of BINI to combination therapy by comparing a lower dose of ENCO (300 mg QD) + BINI to single-agent ENCO (300 mg QD).

AJCC=American Joint Committee on Cancer; BID=twice daily; BINI=binimetinib; COMBO450=ENCO 450 mg QD + BINI 45 mg BID; ECOG=Eastern Cooperative Oncology Group; ENCO=encorafenib; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACT-M=Functional Assessment of Cancer Therapy-Melanoma; PFS=progression-free survival; PS=performance status; QD=once daily; VEM=vemurafenib.
*Prior first-line immunotherapy replaced *BRAF* mutation status as a stratification factor after protocol amendment 2.
†PFS determined based on blinded independent radiology assessment.

Disposition

Variable, n (%)	COMBO450 n=192	ENCO300 n=194	VEM n=191
Untreated	**0**	**2 (1)**	**5 (3)**
Discontinued treatment	**124 (65)**	**146 (75)**	**159 (83)**
Progressive disease	83 (43)	87 (45)	101 (53)
Adverse event	16 (8)	24 (12)	26 (14)
Physician or patient decision*	15 (8)	32 (16)	28 (15)
Death†	7 (4)	1 (1)	4 (2)
Other‡	3 (2)	2 (1)	0
Treatment ongoing§	**68 (35)**	**46 (24)**	**27 (14)**

BID=twice daily; BINI=binimetinib; COMBO450=ENCO 450 mg QD + BINI 45 mg BID; ENCO=encorafenib; QD=once daily; VEM=vemurafenib.
*Physician or patient/guardian decision.
†Deaths that occurred while patient was receiving study drug.
‡Includes protocol violation and lost to follow-up.
§As of the data cutoff date of May 19, 2016.

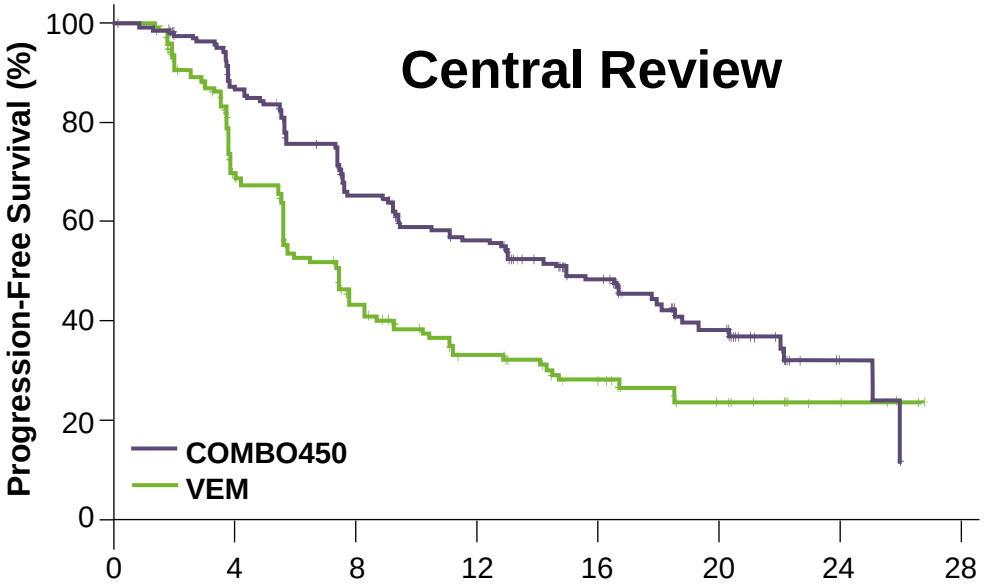
Baseline Characteristics

Characteristic	COMBO450 n=192	ENCO300 n=194	VEM n=191
Median age (range), y	57 (20–89)	54 (23–88)	56 (21–82)
Male sex, %	60	56	58
ECOG performance status 0, %	71	72	73
LDH ≥ULN, %	29	24	27
BRAF mutation status (*V600E*/*V600K*), %	89/11	89/10*	88/12
Tumor stage at study entry, %			
IIIB/IIIC	5	3	6
IVM1a	14	15	13
IVM1b	18	20	16
IVM1c	64	62	65
Number of organs involved, %			
1	24	29	24
2	30	27	31
≥3	45	44	46
Prior checkpoint inhibitor, %			
Ipilimumab	4	5	4
Prior anti–PD-1 or anti–PD-L1	0.5	1	0

BID=twice daily; BINI=binimetinib; COMBO450=ENCO 450 mg QD + BINI 45 mg BID; ECOG=Eastern Cooperative Oncology Group; ENCO=encorafenib; LDH=lactate dehydrogenase; PD=programmed death; PD-L=PD ligand; QD=once daily; ULN=upper limit of normal; VEM=vemurafenib.
*2 observations were indeterminate.

Progression-Free Survival: COMBO450 vs VEM

Central Review



Patients at risk

COMBO450	192	151	107	87	57	28	4	0
VEM	191	101	56	36	23	13	4	0

Median PFS in months (95% CI)

COMBO450	VEM
14.9 (11.0–18.5)	7.3 (5.6–8.2)

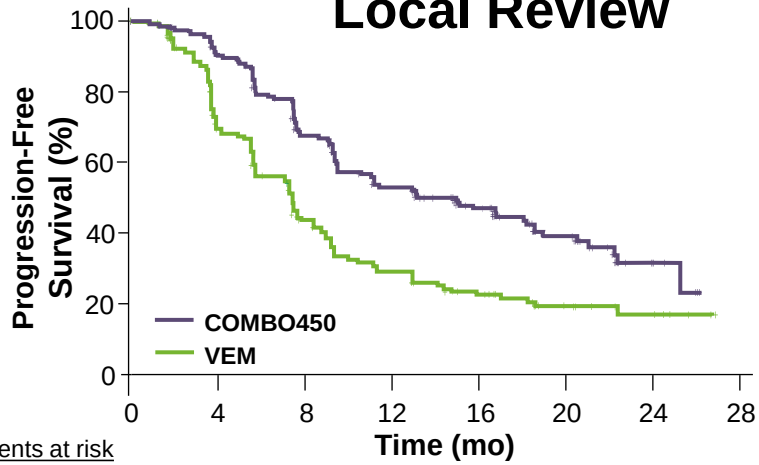
HR (95% CI), 0.54 (0.41–0.71)
***P*<0.001**

Median PFS in months (95% CI)

COMBO450	VEM
14.8 (10.4–18.4)	7.3 (5.7–8.5)

HR (95% CI), 0.49 (0.37–0.64)
P*<0.001

Local Review



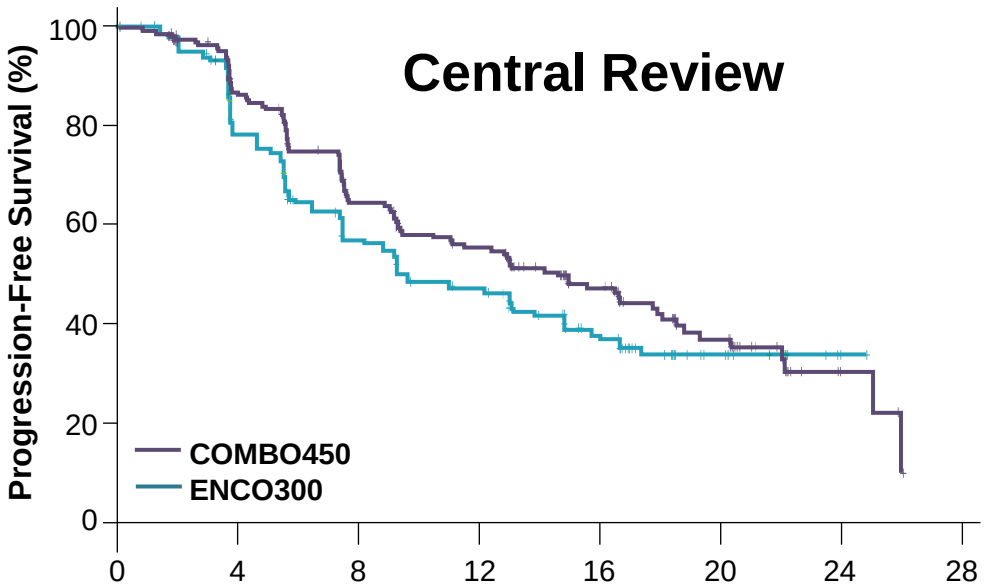
Patients at risk

COMBO450	192	160	116	88	63	30	5	0
VEM	191	111	61	40	27	14	6	0

*Nominal *P* value.
BINI=binimetinib; CI=confidence interval; COMBO450=ENCO 450 mg QD + BINI 45 mg BID

Progression-Free Survival: COMBO450 vs ENCO300

Central Review



Patients at risk

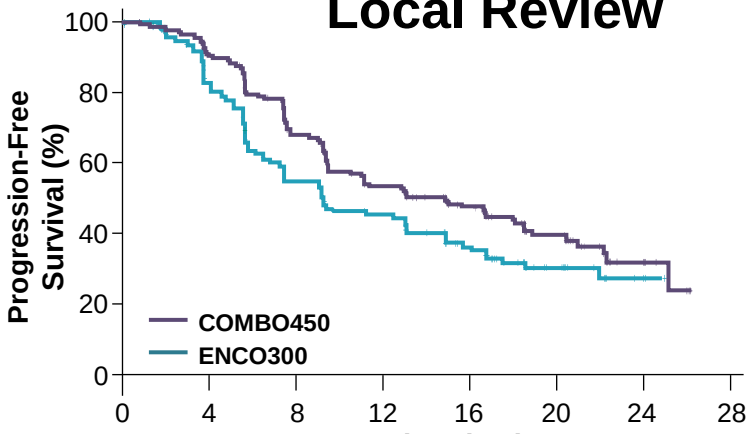
COMBO450	192	151	107	87	57	28	4	0
ENCO300	194	125	84	68	41	17	1	0

Median PFS in months (95% CI)

COMBO450	ENCO300
14.9 (11.0–18.5)	9.6 (7.5–14.8)

HR (95% CI), 0.75 (0.56–1.00)
***P*=0.051**

Local Review



Patients at risk

COMBO450	192	160	116	88	63	30	5	0
ENCO300	194	133	87	70	42	17	1	0

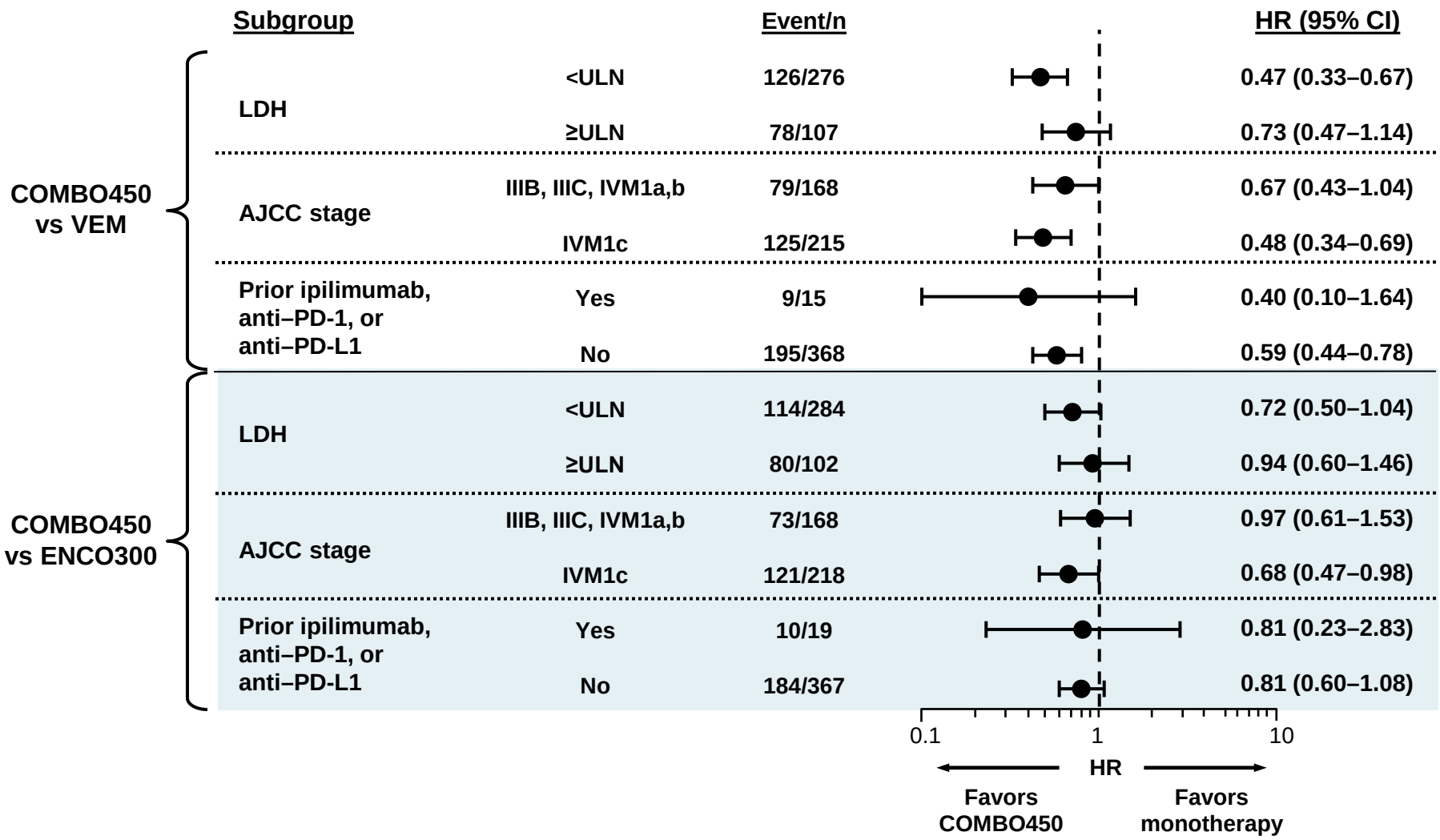
Median PFS in months (95% CI)

COMBO450	ENCO300
14.8 (10.4–18.4)	9.2 (7.4–12.9)

HR (95% CI), 0.68 (0.52–0.90)
P*=0.006

*Nominal *P* value.
BINI=binimetinib; CI=confidence interval; COMBO450=ENCO 450 mg QD + BINI 45 mg BID; ENCO=encorafenib

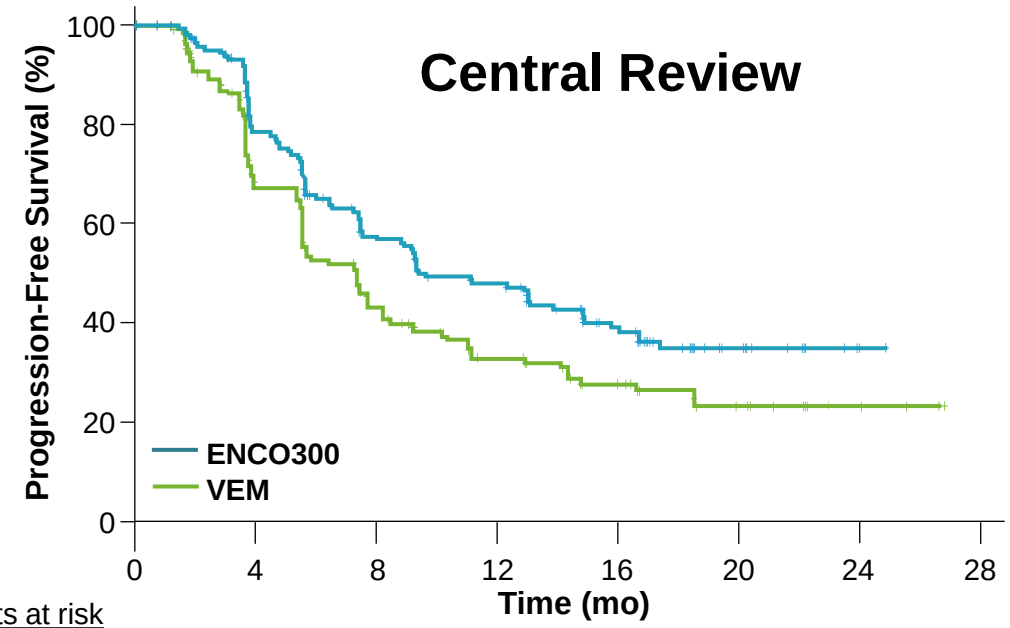
Progression-Free Survival by Central Review in Patient Subgroups



AJCC=American Joint Committee on Cancer; BID=twice daily; BINI=binimetinib; CI=confidence interval; COMBO450=ENCO 450 mg QD + BINI 45 mg BID; ENCO=encorafenib; HR=hazard ratio; LDH=lactate dehydrogenase; PD=programmed death; PD-L=PD ligand; QD=once daily; ULN=upper limit of normal; VEM=vemurafenib.

Progression-Free Survival: ENCO300 vs VEM

Central Review



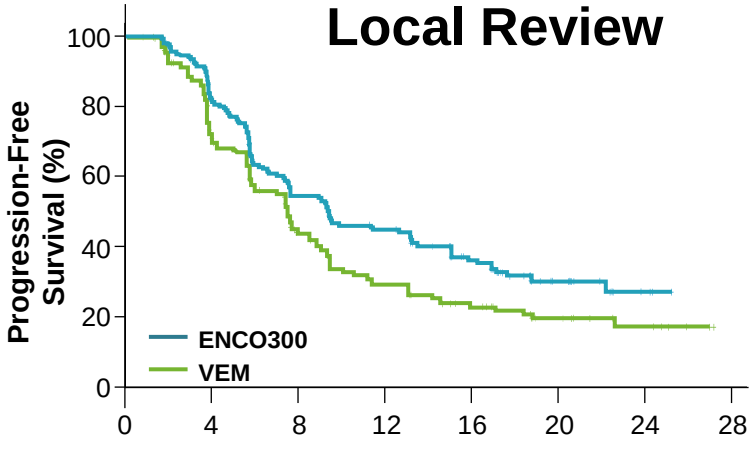
Patients at risk								
ENCO300	194	125	84	68	41	17	1	0
VEM	191	101	56	36	23	13	4	0

Median PFS in months (95% CI)

ENCO300	VEM
9.6 (7.5–14.8)	7.3 (5.6–8.2)

HR (95% CI), 0.68 (0.52–0.90)
P*=0.007

Local Review



Patients at risk								
ENCO300	194	133	87	70	42	17	1	0
VEM	191	111	61	40	27	14	6	0

Median PFS in months (95% CI)

ENCO300	VEM
9.2 (7.4–12.9)	7.3 (5.7–8.5)

HR (95% CI), 0.70 (0.54–0.91)
P*=0.008

CI=confidence interval; ENCO=encorafenib; HR=hazard ratio; PFS=progression-free survival; VEM=vemurafenib.
*Nominal *P* value.

Confirmed Response Rates

Confirmed Response	COMBO450 n=192		ENCO300 n=194		VEM n=191	
	Central Review	Local Review	**Central Review**	Local Review	**Central Review**	Local Review
ORR (95% CI),* %	**63 (56–70)**	75 (68–81)	**51 (43–58)**	58 (50–65)	**40 (33–48)**	49 (42–57)
CR, %	8	16	5	9	6	7
PR, %	55	59	45	49	35	42
Median DOR (95% CI), mo	16.6 (12.7–20.4)	16.2 (11.1–20.4)	14.9 (11.0–NE)	14.8 (11.0–NE)	12.5 (6.9–16.9)	8.4 (5.8–11.0)
SD,† %	29	18	34	29	41	35
PD,‡ %	8	7	16	13	18	16
DCR (95% CI),§ %	92 (87–96)	93 (89–96)	84 (78–89)	87 (81–91)	82 (75–87)	84 (78–89)

BID=twice daily; BINI=binimetinib; CI=confidence interval; COMBO450=ENCO 450 mg QD + BINI 45 mg BID; CR=complete response; DCR=disease control rate; DOR=duration of response; ENCO=encorafenib; NE=not evaluable; ORR=overall response rate; PD=progressive disease; PR=partial response; QD=once daily; SD=stable disease; VEM=vemurafenib.

*ORR = CR + PR.

†Includes patients with only nontarget lesions with best response of non-CR/non-PD.

‡Includes patients with best response of unknown or no assessment.

§DCR = CR + PR + SD.

Confirmed Response Rates

Confirmed Response	COMBO450 n=192		ENCO300 n=194		VEM n=191	
	Central Review	**Local Review**	Central Review	**Local Review**	Central Review	**Local Review**
ORR (95% CI),* %	63 (56–70)	**75 (68–81)**	51 (43–58)	**58 (50–65)**	40 (33–48)	**49 (42–57)**
CR, %	8	16	5	9	6	7
PR, %	55	59	45	49	35	42
Median DOR (95% CI), mo	16.6 (12.7–20.4)	16.2 (11.1–20.4)	14.9 (11.0–NE)	14.8 (11.0–NE)	12.5 (6.9–16.9)	8.4 (5.8–11.0)
SD,† %	29	18	34	29	41	35
PD,‡ %	8	7	16	13	18	16
DCR (95% CI),§ %	92 (87–96)	93 (89–96)	84 (78–89)	87 (81–91)	82 (75–87)	84 (78–89)

BID=twice daily; BINI=binimetinib; CI=confidence interval; COMBO450=ENCO 450 mg QD + BINI 45 mg BID; CR=complete response; DCR=disease control rate; DOR=duration of response; ENCO=encorafenib; NE=not evaluable; ORR=overall response rate; PD=progressive disease; PR=partial response; QD=once daily; SD=stable disease; VEM=vemurafenib.

*ORR = CR + PR.

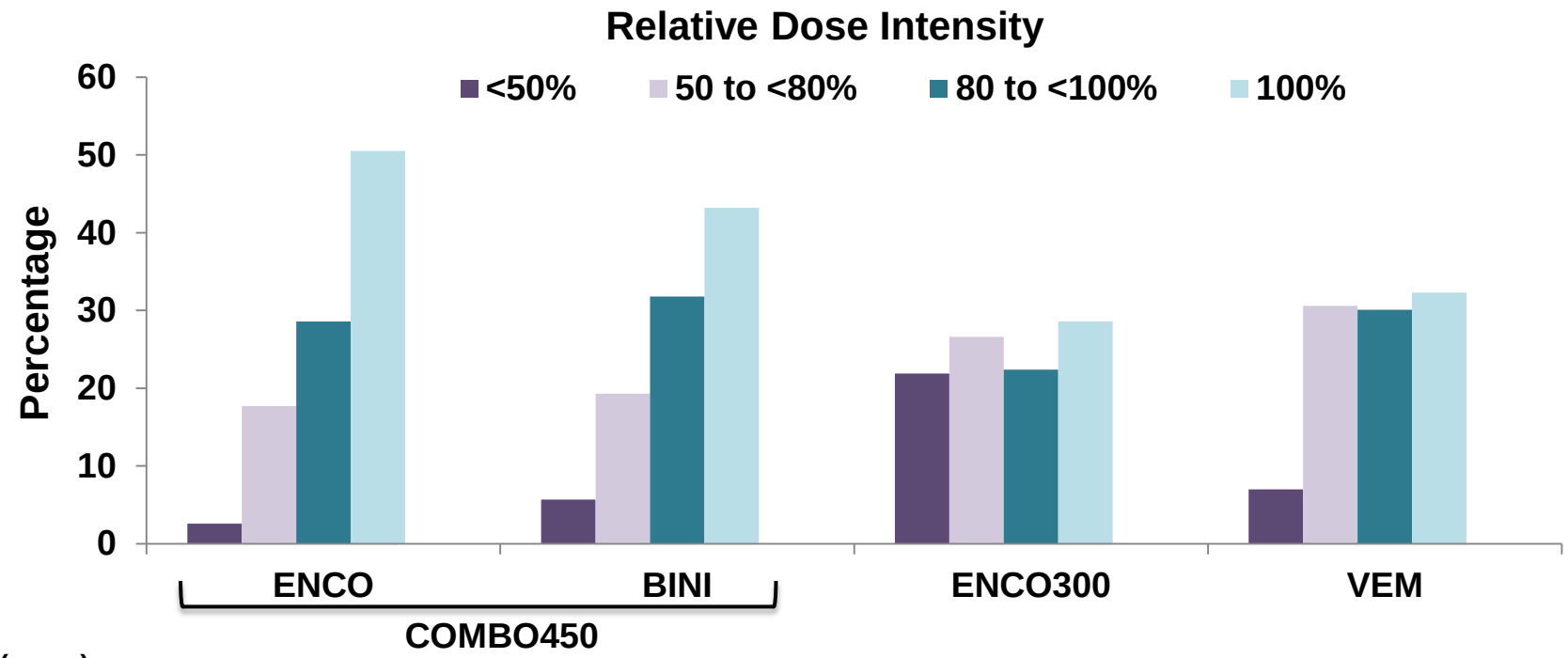
†Includes patients with only nontarget lesions with best response of non-CR/non-PD.

‡Includes patients with best response of unknown or no assessment.

§DCR = CR + PR + SD.

Dose Exposure

Duration of exposure, weeks	COMBO450 n=192		ENCO300 n=192	VEM n=186
	ENCO	BINI		
Mean (SD)	54.3 (30.9)	53.8 (31.3)	42.4 (31.2)	35.9 (29.5)
Median (range)	51.2 (0.4–116.0)	50.6 (0.4–116.0)	31.4 (0.1–113.3)	27.1 (0.9–121.6)



Median (range) dose intensity, %	COMBO450		ENCO300	VEM
	ENCO	BINI		
	100.0 (33.3–100.1)	99.6 (6.9–100.0)	86.2 (14.8–100.2)	94.5 (16.9–100.0)

BINI=binimetinib; COMBO450=ENCO 450 mg QD + BINI 45 mg BID; ENCO=encorafenib; VEM=vemurafenib.
Includes only patients receiving ≥1 dose of study drug.

Overall Summary of Safety

Event, %	COMBO450 n=192 Median Duration of Exposure: 51 weeks	ENCO300 n=192 Median Duration of Exposure: 31 weeks	VEM n=186 Median Duration of Exposure: 27 weeks
Adverse events	98	>99	>99
Grade 3/4 adverse events	58	66	63
Adverse events leading to discontinuation	13	14	17
Adverse events leading to dose interruption	46	64	53
Adverse events requiring dose reduction	11	27	23
On-treatment deaths†	9	7	10

COMBO450 most common events (occurring in ≥5 patients [3%])

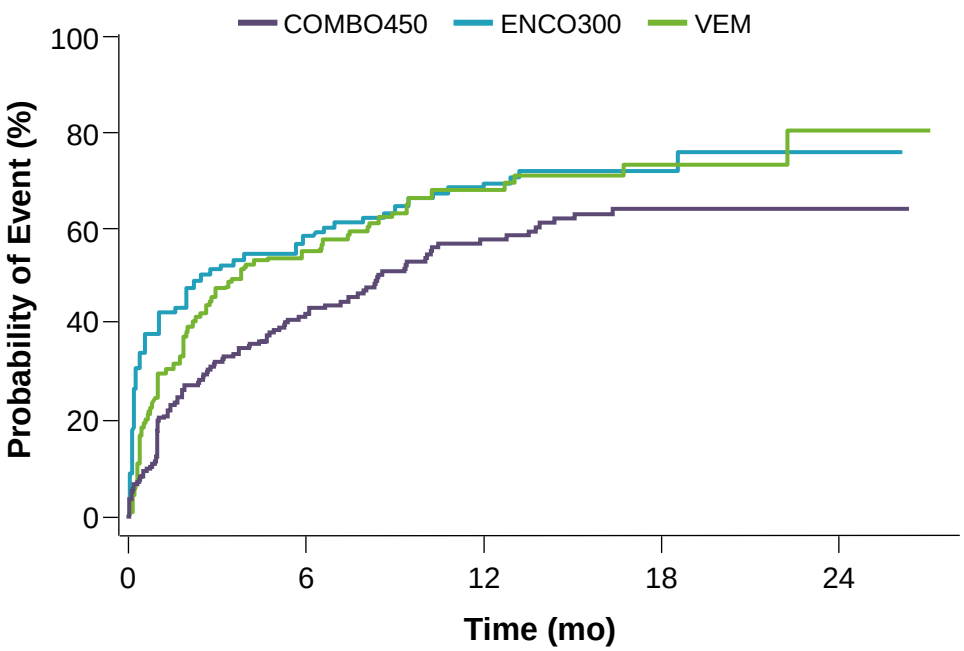
- Adverse events leading to discontinuation: ALT increased (3%), AST increased (3%)
- Adverse events requiring dose interruption: nausea (7%), vomiting (7%), ejection fraction decreased (5%), GGT increased (5%), pyrexia (4%), ALT increased (4%), diarrhea (3%), AST increased (3%), blood creatine phosphokinase increased (3%), abdominal pain (3%)
- On-treatment death: malignant melanoma (5%)

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BID=twice daily; BINI=binimetinib; COMBO450=ENCO 450 mg QD + BINI 45 mg BID; ENCO=encorafenib; GGT=gamma-glutamyltransferase; QD=once daily; VEM=vemurafenib.

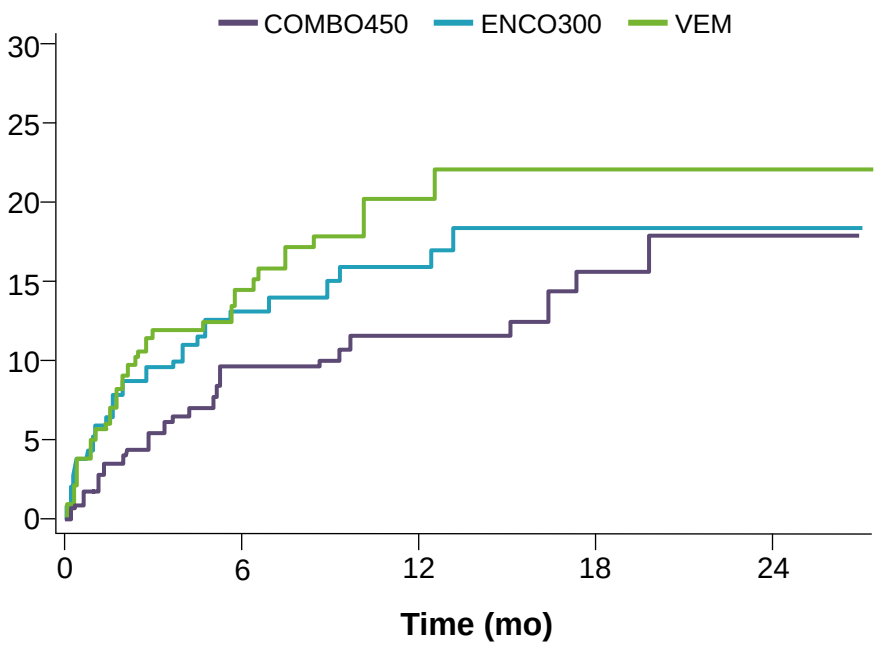
†Includes on-treatment deaths and deaths within 30 days of stopping study treatment.

Time to First Grade 3 or 4 Adverse Event and Discontinuation Due to Adverse Events

Time to First Grade 3/4 AE (All Patients)



Time to AE-Related Discontinuation (All Patients)



First Grade 3/4 AE Among Patients Having an Event	
Treatment	**Median months (95% CI)**
COMBO450	2.5 (1.4–3.7)
ENCO300	0.4 (0.2–0.9)
VEM	1.3 (0.9–1.8)

AE-Related Discontinuation Among Patients Having an Event	
Treatment	**Median months (95% CI)**
COMBO450	3.8 (1.8–5.6)
ENCO300	1.8 (0.9–4.0)
VEM	1.8 (1.0–2.9)

AE=adverse event; BID=twice daily; BINI=binimetinib; CI=confidence interval; COMBO450=ENCO 450 mg QD + BINI 45 mg BID; ENCO=encorafenib; QD=once daily; VEM=vemurafenib.

Most Common Adverse Events Regardless of Assessed Causality*

Preferred Term, %	COMBO450 n=192 Median Duration of Exposure: 51 weeks		ENCO300 n=192 Median Duration of Exposure: 31 weeks		VEM n=186 Median Duration of Exposure: 27 weeks	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Total	98	58	>99	66	>99	63
Nausea	41	2	39	4	34	2
Diarrhea	36	3	14	2	34	2
Vomiting	30	2	27	5	15	1
Fatigue	29	2	25	1	31	2
Arthralgia	26	1	44	9	45	6
Blood CK increased	23	7	1	0	2	0
Headache	22	2	27	3	19	1
Pyrexia	18	4	15	1	28	0
GGT increased	15	9	11	5	11	3
Alopecia	14	0	56	0	37	0
Hyperkeratosis	14	1	38	4	29	0
Dry skin	14	0	30	0	23	0
Myalgia	14	0	28	10	18	1
Rash	14	1	21	2	29	3
Hypertension	11	6	6	3	11	3
Palmoplantar keratoderma	9	0	26	2	16	1
Palmar-plantar erythrodysesthesia syndrome	7	0	51	14	14	1

AE=adverse event; BID=twice daily; BINI=binimetinib; CK=creatine phosphokinase; COMBO450=ENCO 450 mg QD + BINI 45 mg BID; ENCO=encorafenib; GGT=gamma-glutamyltransferase; QD=once daily; VEM=vemurafenib.
*All-cause AEs (>25% in any treatment group) or grade 3/4 AEs (>5% in any treatment group).

Most Common Adverse Events Regardless of Assessed Causality*

Preferred Term, %	COMBO450 n=192 Median Duration of Exposure: 51 weeks		ENCO300 n=192 Median Duration of Exposure: 31 weeks		VEM n=186 Median Duration of Exposure: 27 weeks	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Total	98	58	>99	66	>99	63
Nausea	41	2	39	4	34	2
Diarrhea	36	3	14	2	34	2
Vomiting	30	2	27	5	15	1
Fatigue	29	2	25	1	31	2
Arthralgia	**26**	**1**	**44**	**9**	**45**	**6**
Blood CK increased	23	7	1	0	2	0
Headache	22	2	27	3	19	1
Pyrexia	**18**	**4**	**15**	**1**	**28**	**0**
GGT increased	15	9	11	5	11	3
Alopecia	**14**	**0**	**56**	**0**	**37**	**0**
Hyperkeratosis	**14**	**1**	**38**	**4**	**29**	**0**
Dry skin	**14**	**0**	**30**	**0**	**23**	**0**
Myalgia	14	0	28	10	18	1
Rash	**14**	**1**	**21**	**2**	**29**	**3**
Hypertension	11	6	6	3	11	3
Palmoplantar keratoderma	**9**	**0**	**26**	**2**	**16**	**1**
Palmar-plantar erythrodysesthesia syndrome	**7**	**0**	**51**	**14**	**14**	**1**

AE=adverse event; BID=twice daily; BINI=binimetinib; CK=creatine phosphokinase; COMBO450=ENCO 450 mg QD + BINI 45 mg BID; ENCO=encorafenib; GGT=gamma-glutamyltransferase; QD=once daily; VEM=vemurafenib.
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Most Common Adverse Events Regardless of Assessed Causality*

Preferred Term, %	COMBO450 n=192 Median Duration of Exposure: 51 weeks		ENCO300 n=192 Median Duration of Exposure: 31 weeks		VEM n=186 Median Duration of Exposure: 27 weeks	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Total	98	58	>99	66	>99	63
Nausea	41	2	39	4	34	2
Diarrhea	36	3	14	2	34	2
Vomiting	**30**	**2**	**27**	**5**	**15**	**1**
Fatigue	29	2	25	1	31	2
Arthralgia	26	1	44	9	45	6
Blood CK increased	**23**	**7**	**1**	**0**	**2**	**0**
Headache	22	2	27	3	19	1
Pyrexia	18	4	15	1	28	0
GGT increased	15	9	11	5	11	3
Alopecia	14	0	56	0	37	0
Hyperkeratosis	14	1	38	4	29	0
Dry skin	14	0	30	0	23	0
Myalgia	14	0	28	10	18	1
Rash	14	1	21	2	29	3
Hypertension	11	6	6	3	11	3
Palmoplantar keratoderma	9	0	26	2	16	1
Palmar-plantar erythrodysesthesia syndrome	7	0	51	14	14	1

AE=adverse event; BID=twice daily; BINI=binimetinib; CK=creatine phosphokinase; COMBO450=ENCO 450 mg QD + BINI 45 mg BID; ENCO=encorafenib; GGT=gamma-glutamyltransferase; QD=once daily; VEM=vemurafenib.
*All-cause AEs (>25% in any treatment group) or grade 3/4 AEs (>5% in any treatment group).

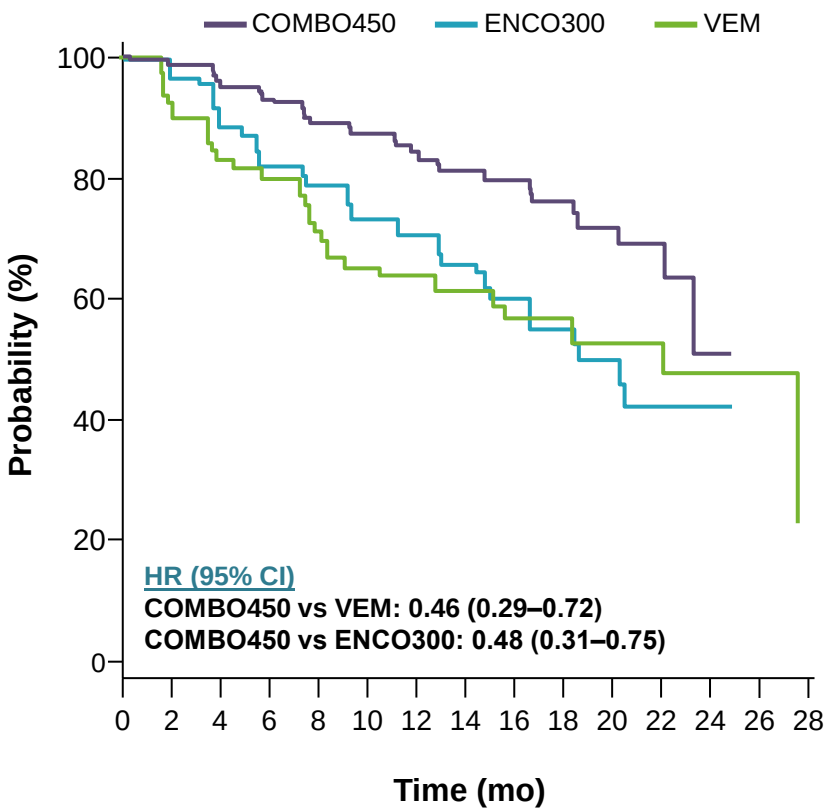
Selected Adverse Events of Interest

Event, %	COMBO450 n=192 Median Duration of Exposure: 51 weeks		ENCO300 n=192 Median Duration of Exposure: 31 weeks		VEM n=186 Median Duration of Exposure: 27 weeks	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Rash*	23	1	45	5	56	13
Dermatitis acneiform	3	0	4	0	4	0
Photosensitivity†	5	1	4	0	30	1
Secondary non-melanoma skin neoplasms‡	4	0	9	1	18	7
Skin papilloma	6	0	9	0	17	0
Retinal pigment epithelial detachment§	13	2	1	0	1	0
Left ventricular dysfunction‖	8	2	2	1	1	0
Transaminases increased¶	13	6	7	2	9	2
Blood bilirubin increased	1	0	0	0	8	0

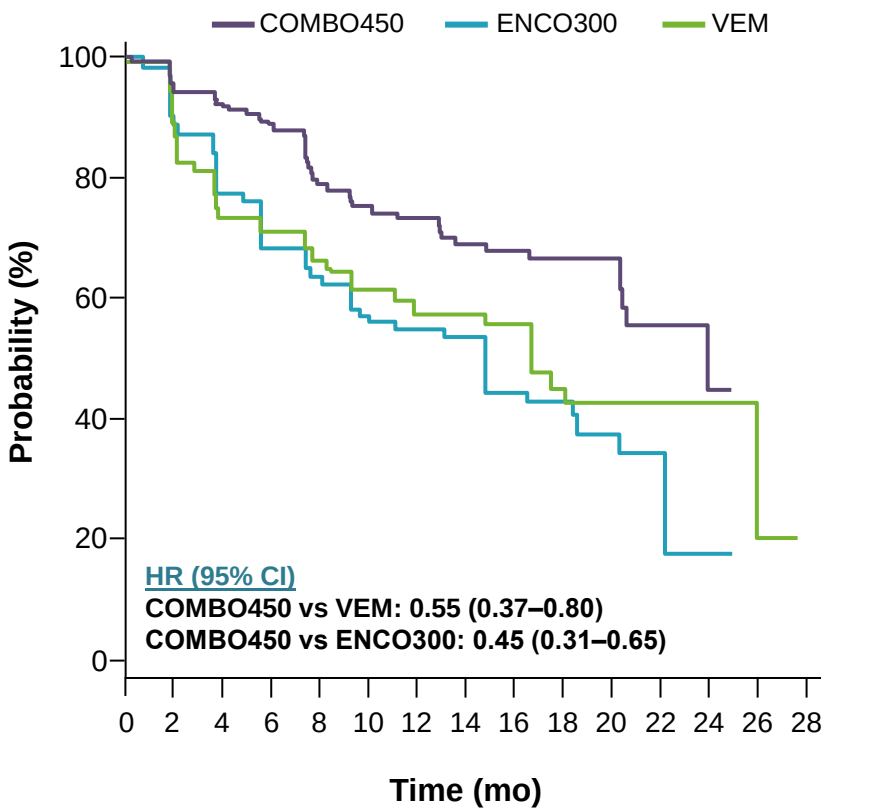
BID=twice daily; BINI=binimetinib; COMBO450=ENCO 450 mg QD + BINI 45 mg BID; ENCO=encorafenib; QD=once daily; VEM=vemurafenib.
*Includes rash, rash generalized, rash erythematous, rash maculo-papular, dermatitis, rash follicular, rash macular, rash papular, rash pruritic, generalized erythema, rash vesicular, dermatitis psoriasiform, and rash pustular.
†Includes photosensitivity reaction and solar dermatitis.
‡Includes basal cell carcinoma, Bowen's disease, keratoacanthoma, lip squamous cell carcinoma, neoplasm skin, squamous cell carcinoma, and squamous cell carcinoma of skin.
§Includes chorioretinopathy, detachment of macular retinal pigment epithelium, detachment of retinal pigment epithelium, retinal detachment, and subretinal fluid.
‖ Includes ejection fraction decreased, cardiac failure, left ventricular dysfunction, and left ventricular failure.
¶Includes alanine aminotransferase increased, aspartate aminotransferase increased, and transaminases increased.

Maintenance of Quality of Life*

FACT-Melanoma Scale Score



EORTC QLQ-C30 Global Health Status/QoL Scale Score



- EORTC QLQ-C30 subscale scores showed a similar pattern

BINI=binimetinib; CI=confidence interval; COMBO450=ENCO 450 mg QD + BINI 45 mg BID; ENCO=encorafenib; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACT=Functional Assessment of Cancer Therapy; HR=hazard ratio; QD=once daily; QoL=quality of life; VEM=vemurafenib.
*As measured by time to 10% deterioration in score, defined as the time from the date of randomization to the date of at least 10% worsening of the corresponding scale score (without subsequent improvement) or death

Conclusions

COMBO450 demonstrated a favorable efficacy and safety profile in patients with *BRAF*-mutant melanoma:

- COMBO450 significantly improved PFS vs VEM alone.
  - Median PFS: 14.9 months for COMBO450 vs 7.3 months for VEM
  - HR (95% CI), 0.54 (0.41–0.71); *P*<0.001
- Performance of VEM was consistent with prior trials using VEM as a control in this patient population.[1,2]
- COMBO450 improved PFS vs ENCO300 alone, but results by blinded independent assessment did not meet predefined criteria for statistical significance.
  - Median PFS: 14.9 months for COMBO450 vs 9.6 months for ENCO300
    - HR (95% CI), 0.75 (0.56–1.00); *P*=0.051
  - Local assessment of PFS was consistent with the result by blinded independent assessment. HR (95% CI), 0.68 (0.52–0.90); *P*=0.006.*

BID=twice daily; BINI=binimetinib; CI=confidence interval; COMBO450=ENCO 450 mg QD + BINI 45 mg BID; ENCO=encorafenib; HR=hazard ratio; PFS=progression-free survival; QD=once daily; VEM=vemurafenib.
*Nominal *P* value.

1. Ascierto PA, et al. *Lancet Oncol.* 2016;17(9):1248-1260.
2. Robert C, et al. *N Engl J Med*. 2015;372:30-39.

Conclusions (cont'd)

- The tolerability profile of COMBO450 was favorable compared with monotherapy with VEM or ENCO300, resulting in higher relative dose intensity for COMBO450.
- ENCO 300 mg QD alone improved PFS vs VEM.
  - HR (95% CI), 0.68 (0.52–0.90); *P*=0.007*
- ORR and DOR were greater in the COMBO450 arm, whether assessed by central review or local review.
- Maintenance of QoL was improved with COMBO450 compared with VEM alone and ENCO alone as measured by the FACT-Melanoma scale and the EORTC QLQ-C30 Global Health Status score.

COMBO450 represents a potential new treatment option for patients with *BRAF*-mutant melanoma, with a favorable efficacy and safety profile.

*Nominal *P* value.
BINI=binimetinib; CI=confidence interval; COMBO450=ENCO 450 mg QD + BINI 45 mg BID; DOR=duration of response; ENCO=encorafenib; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACT=Functional Assessment of Cancer Therapy; VEM=vemurafenib.

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