RESULTS OF COLUMBUS PART 2:

A Phase 3 Trial of Encorafenib Plus Binimetinib Versus Encorafenib in *BRAF*-Mutant Melanoma

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Disclosures

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Background

- BRAF/ MEK inhibitor combination therapy is standard of care in *BRAF V600*-mutant locally advanced or metastatic melanoma,[1] based on improved survival with manageable tolerability.[2,3]
- **Binimetinib (BINI):** potent, selective allosteric, ATP-uncompetitive inhibitor of MEK1/2[4] with shorter half-life than other MEK1/2 inhibitors; may provide more rapid resolution of toxicity upon interruption[5]
  - MTD 45 mg BID
- **Encorafenib (ENCO):** ATP-competitive BRAFi with unique pharmacologic profile[6]
  - Single agent MTD 300 mg QD[7]
  - Dose able to be increased to 450 mg QD when combined with BINI[8]

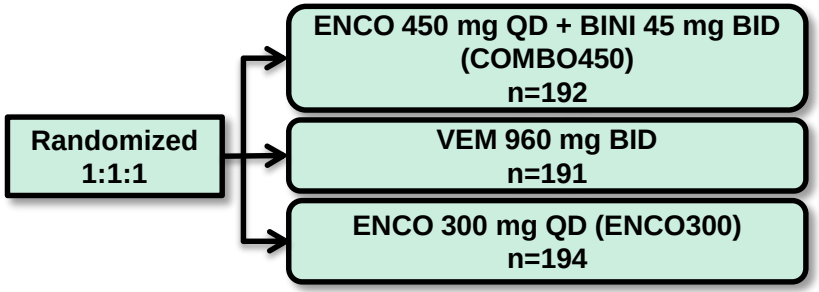
IC_{50}=half-maximal inhibitory concentration; MTD=maximum tolerated dose.

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. Long GV, et al. *Lancet*. 2015;386(9992):444-451.
4. Ascierto PA, et al. *Lancet Oncol*. 2013;14(3):249-256.
5. Data on File. Array BioPharma Inc.
6. Stuart DD, et al. *Cancer Res*. 2012;72(8 suppl):3790.
7. Delord JP, et al. *Clin Cancer Res*. 2017:[Epub ahead of print]
8. Sullivan RJ, et al. *Journal of Clinical Oncology*. 2015;33(15)..

COLUMBUS Part 1

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

PART 1
N=577 randomized



Efficacy endpoints:

- **Primary: PFS* for COMBO450 vs VEM**
- **Key secondary (tested sequentially):** **PFS* for COMBO450 vs ENCO300 (Part 1: n=191)**
- **Other secondary:** **OS, ORR, QoL**

***PFS determined based on blinded independent radiology assessment.**

BINI=binimetinib; ECOG PS=Eastern Cooperative Oncology Group performance status; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; QoL=quality of life; VEM=vemurafenib.

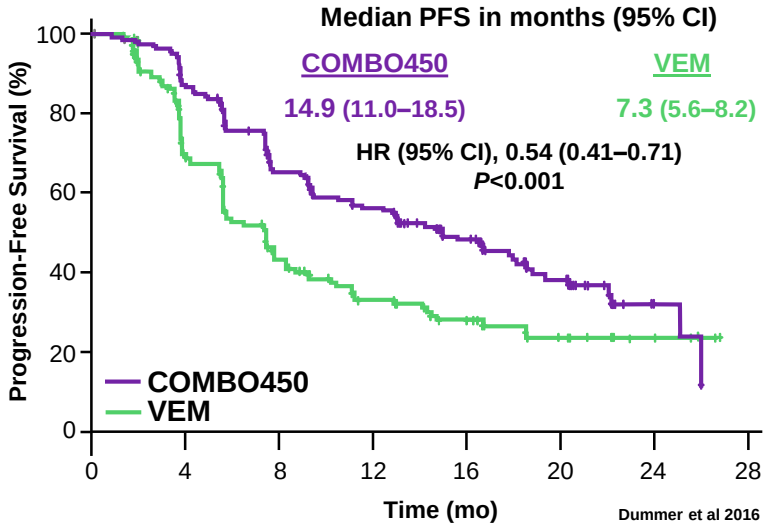
COLUMBUS Part 1

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

PART 1
N=577 randomized

Randomized 1:1:1

- ENCO 450 mg QD + BINI 45 mg BID (COMBO450) n=192
- VEM 960 mg BID n=191
- ENCO 300 mg QD (ENCO300) n=194



Efficacy endpoints:

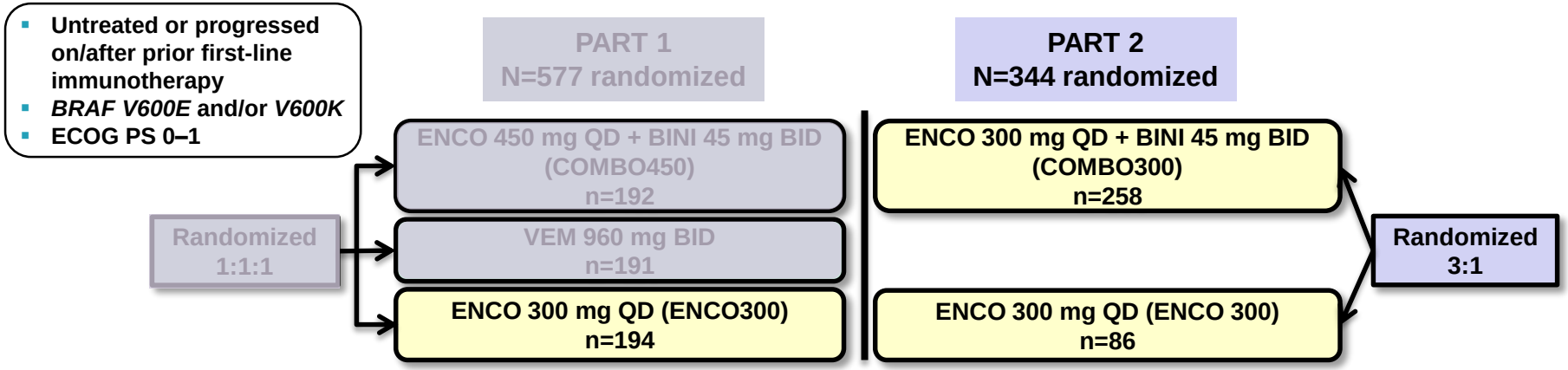
- **Primary: PFS* for COMBO450 vs VEM**
- **Key secondary (tested sequentially): PFS* for COMBO450 vs ENCO300 (Part 1: n=191)**
- **Other secondary: OS, ORR, QoL**

*PFS determined based on blinded independent radiology assessment.

BINI=binimetinib; ECOG PS=Eastern Cooperative Oncology Group performance status; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; QoL=quality of life; VEM=vemurafenib.

COLUMBUS Part 2

- Designed to isolate the contribution of BINI to combination therapy by maintaining the same dose of ENCO in the combination (COMBO300) and comparator arms (ENCO300)



Efficacy endpoints:

- **Primary: PFS* for COMBO450 vs VEM**
- **Key secondary (tested sequentially):** **PFS* for COMBO450 vs ENCO300 (Part 1: n=191)**; **PFS* for COMBO300 vs ENCO300 (Part 1 + Part 2: n=280)**
- **Other secondary:** **OS, ORR, QoL**

*PFS determined based on blinded independent radiology assessment.

BINI=binimetinib; ECOG PS=Eastern Cooperative Oncology Group performance status; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; QoL=quality of life; VEM=vemurafenib.

Baseline Characteristics

Characteristic	COMBO300 n=258	ENCO300 (Parts 1+2) n=280
Median age (range), y	58 (20–94)	55 (19–88)
Male sex, %	59	54
ECOG performance status 0, %	73	72
LDH ≥ ULN, %	31	28
IVM1c tumor stage at study entry, %	67	64
≥3 organs involved, %	44	45
Prior checkpoint inhibitor, %		
Ipilimumab	7	5
Prior anti–PD1 or anti–PDL1	<1	1
Primary cancer site, %		
Cutaneous melanoma	93	97
Unknown	7	3

BINI=binimetinib; COMBO300=ENCO 300 mg QD + BINI 45 mg BID; ECOG=Eastern Cooperative Oncology Group; ENCO=encorafenib; ENCO300=ENCO 300 mg QD; LDH=lactate dehydrogenase; PD=programmed death; PD-L=PD ligand; ULN=upper limit of normal.

Baseline Characteristics

Characteristic	COMBO300 n=258	ENCO300 (Parts 1+2) n=280	ENCO300 (Part 2) n=86
Median age (range), y	58 (20–94)	55 (19–88)	57 (19–81)
Male sex, %	59	54	51
ECOG performance status 0, %	73	72	72
LDH ≥ ULN, %	31	**28**	**37**
IVM1c tumor stage at study entry, %	67	64	67
≥3 organs involved, %	44	45	48
Prior checkpoint inhibitor, %			
Ipilimumab	7	5	5
Prior anti–PD1 or anti–PDL1	<1	1	2
Primary cancer site, %			
Cutaneous melanoma	93	97	92
Unknown	7	3	8

BINI=binimetinib; COMBO300=ENCO 300 mg QD + BINI 45 mg BID; ECOG=Eastern Cooperative Oncology Group; ENCO=encorafenib; ENCO300=ENCO 300 mg QD; LDH=lactate dehydrogenase; PD=programmed death; PD-L=PD ligand; ULN=upper limit of normal.

Baseline Characteristics

Characteristic	COMBO450 n=192	COMBO300 n=258	ENCO300 (Parts 1+2) n=280	ENCO300 (Part 2) n=86
Median age (range), y	57 (20-89)	58 (20–94)	55 (19–88)	57 (19–81)
Male sex, %	60	59	54	51
ECOG performance status 0, %	**71**	**73**	72	72
LDH ≥ ULN, %	**29**	**31**	28	37
IVM1c tumor stage at study entry, %	**64**	**67**	64	67
≥3 organs involved, %	**45**	**44**	45	48
Prior checkpoint inhibitor, %				
Ipilimumab	4	7	5	5
Prior anti–PD1 or anti–PDL1	1	<1	1	2
Primary cancer site, %				
Cutaneous melanoma	99	93	97	92
Unknown	1	7	3	8

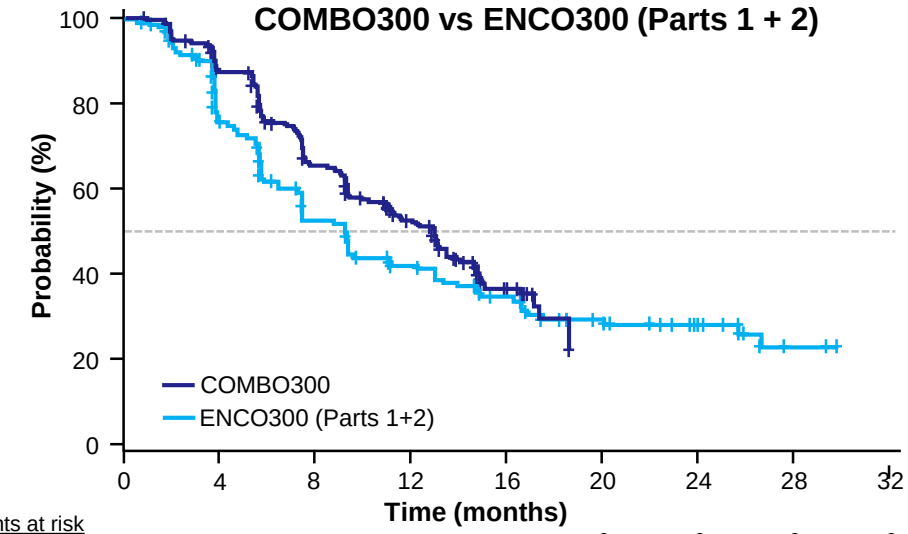
BINI=binimetinib; COMBO300=ENCO 300 mg QD + BINI 45 mg BID; COMBO450=ENCO 450 mg QD + BINI 45 mg BIDECOG=Eastern Cooperative Oncology Group; ENCO=encorafenib; ENCO300=ENCO 300 mg QD; LDH=lactate dehydrogenase; PD=programmed death; PD-L=PD ligand; ULN=upper limit of normal.

Patient Disposition

Variable, n (%)	COMBO300 n=258§	ENCO300 (Parts 1+2) n=280§
Discontinued treatment	**156 (60)**	**221 (79)**
Progressive disease	96 (37)	134 (48)
Adverse event	22 (9)	32 (11)
Physician or patient decision*	30 (12)	51 (18)
Death**	8 (3)	2 (<1)
Other†	0	2 (<1)
Treatment ongoing‡	**101 (39)**	**55 (20)**

*Physician or patient/guardian decision.
†Includes protocol violation and lost to follow-up.
‡As of the data cutoff date of November 9, 2016.
§1 patient in COMBO300 and 4 patients in ENCO300 (Parts 1 + 2) not treated.
**Includes only deaths leading to treatment discontinuation. On-treatment deaths 10% vs. 8% see Safety Summary slide.
BINI=binimetinib; COMBO300=ENCO 300 mg QD + BINI 45 mg BID; ENCO=encorafenib; ENCO=encorafenib; ENCO300=ENCO 300 mg QD.

PFS: COMBO300 vs ENCO300 by Central Review

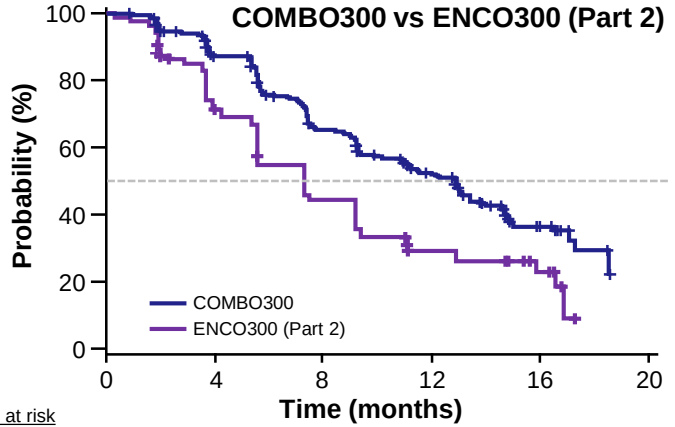


Patients at risk									
COMBO300	258	204	144	92	27	0	0	0	0
ENCO300 (Parts 1+2)	280	177	114	85	62	40	18	5	0

Median PFS in months (95% CI)

COMBO300	ENCO300 (Parts 1 + 2)*
12.9 (10.1–14.0)	9.2 (7.4–11.0)

HR (95% CI), 0.77 (0.61–0.97)
P=0.029†



Patients at risk						
COMBO300	258	204	144	92	27	0
ENCO300 (Part 2)	86	52	30	17	9	0

Median PFS in months (95% CI)

COMBO300	ENCO300 (Part 2)
12.9 (10.1-14.0)	7.4 (5.6-9.2)

HR (95% CI), 0.57 (0.41-0.78)
P<0.001†

*Median duration of potential follow-up approximately 5 months longer than with COMBO300 due to longer duration in study of ENCO300 Part 1 patients.
†Nominal *P*-value.
BINI=binimetinib; COMBO300=ENCO 300 mg QD + BINI 45 mg BID; ENCO=encorafenib; PFS=progression-free survival.

Confirmed Response Rates

Confirmed Response	COMBO300 n=258		ENCO300 (Parts 1+2) n=280		ENCO300 (Part 2) n=86	
	Central Review	Local Review	**Central Review**	Local Review	**Central Review**	Local Review
ORR* (95% CI†), %	**66 (60–72)**	73 (67–78)	**50 (44–56)**	56 (50–62)	**50 (39–61)**	54 (42–64)
CR, %	8	11	5	8	3	3
PR, %	58	62	45	49	47	50
Median DOR (95% CI), mo	12.7 (9.3–15.1)	13.1 (10.8–16.6)	12.9 (8.9–15.5)	13.0 (9.5–15.0)	7.5 (5.6–14.0)	9.2 (7.4–14.8)
SD,‡ %	25	22	32	29	29	29
PD,¶ %	9	5	18	15	21	17
DCR§ (95% CI), %	91 (87–94)	95 (91–97)	83 (78–87)	85 (81–89)	79 (69–87)	83 (73–90)

*ORR = CR + PR.
†95% CI for the frequency distribution of each variable was computed using Clopper-Pearson's method.
‡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.
BINI=binimetinib; CI=confidence interval; COMBO300=ENCO 300 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; SD=stable disease.

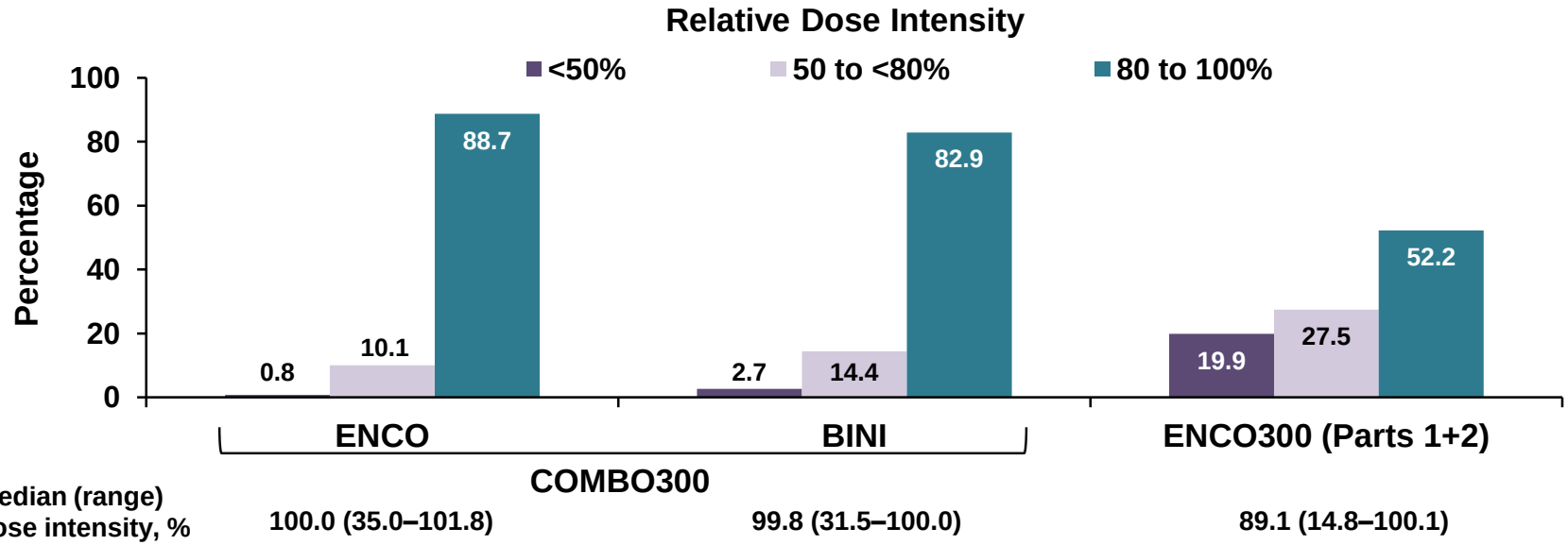
Confirmed Response Rates

Confirmed Response	COMBO300 n=258		ENCO300 (Parts 1+2) n=280		ENCO300 (Part 2) n=86	
	Central Review	**Local Review**	Central Review	**Local Review**	Central Review	**Local Review**
ORR* (95% CI†), %	66 (60–72)	**73 (67–78)**	50 (44–56)	**56 (50–62)**	50 (39–61)	**54 (42–64)**
CR, %	8	11	5	8	3	3
PR, %	58	62	45	49	47	50
Median DOR (95% CI), mo	12.7 (9.3–15.1)	13.1 (10.8–16.6)	12.9 (8.9–15.5)	13.0 (9.5–15.0)	7.5 (5.6–14.0)	9.2 (7.4–14.8)
SD,‡ %	25	22	32	29	29	29
PD,¶ %	9	5	18	15	21	17
DCR§ (95% CI), %	91 (87–94)	95 (91–97)	83 (78–87)	85 (81–89)	79 (69–87)	83 (73–90)

*ORR = CR + PR.
†95% CI for the frequency distribution of each variable was computed using Clopper-Pearson's method.
‡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.
BINI=binimetinib; CI=confidence interval; COMBO300=ENCO 300 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; SD=stable disease.

Dose Exposure

Duration of exposure, weeks	COMBO300 n=257			ENCO300 (Parts 1+2) n=276
	ENCO	BINI	ENCO + BINI	
Mean (SD)	47.6 (21.3)	47.3 (21.3)	47.6 (21.3)	43.8 (35.1)
Median (range)	52.1 (2.7–85.9)	50.6 (2.7–85.9)	52.1 (2.7–85.9)	31.5 (0.1–138.1)

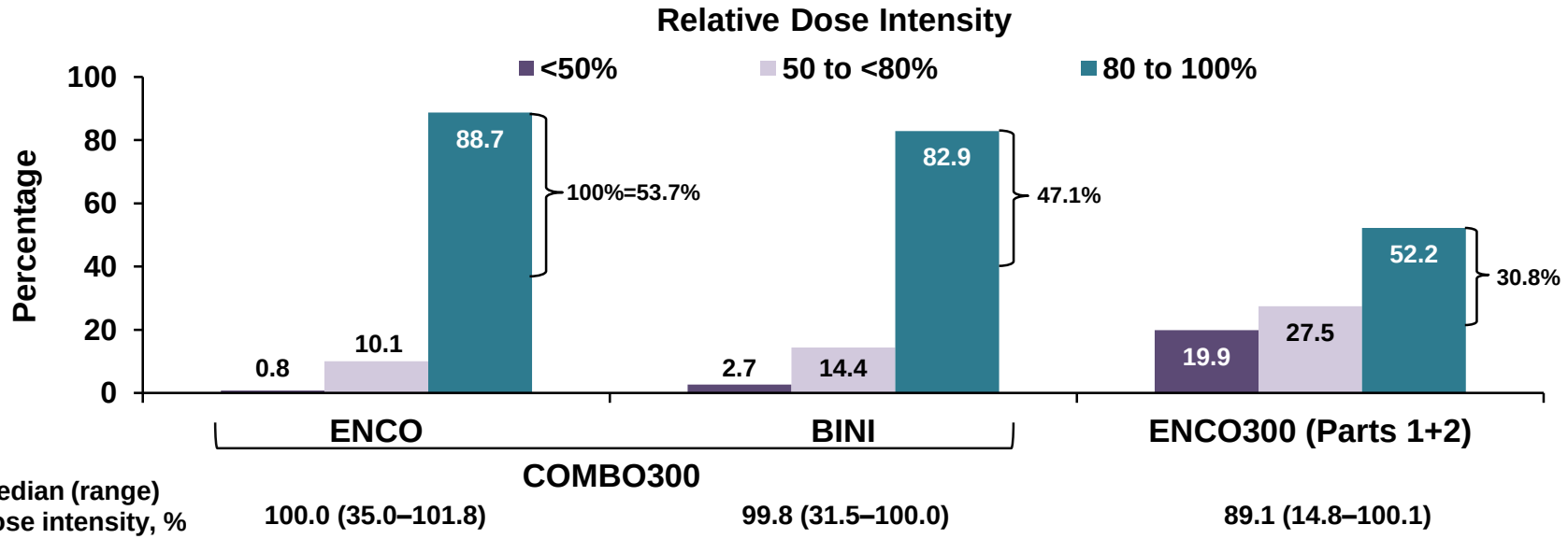


Includes only patients receiving ≥1 dose of study drug.

BINI=binimetinib; COMBO300=ENCO 300 mg QD + BINI 45 mg BID; ENCO=encorafenib; SD=standard deviation.

Dose Exposure

Duration of exposure, weeks	COMBO300 n=257			ENCO300 (Parts 1+2) n=276
	ENCO	BINI	ENCO + BINI	
Mean (SD)	47.6 (21.3)	47.3 (21.3)	47.6 (21.3)	43.8 (35.1)
Median (range)	52.1 (2.7–85.9)	50.6 (2.7–85.9)	52.1 (2.7–85.9)	31.5 (0.1–138.1)



Includes only patients receiving ≥1 dose of study drug.

BINI=binimetinib; COMBO300=ENCO 300 mg QD + BINI 45 mg BID; ENCO=encorafenib; SD=standard deviation.

Overall Summary of Safety

	COMBO300 n=257	ENCO300 (Parts 1+2) n=276	ENCO300 (Part 2) n=84
Median duration of exposure, weeks	**52.1**	**31.5**	**31.5**
AEs, %	98	99	96
Grade 3/4 AEs, %	47	63	55
SAEs, %	29	33	30
Grade 3/4 SAEs, %	25	28	26
AEs leading to discontinuation, %	12	13	10
AEs leading to dose interruption/change, %	45	69	63
On-treatment deaths[†], %	10	8	7

[†]Includes on-treatment deaths and deaths within 30 days of stopping study treatment. All but 3 (1%) deaths in the COMBO300 arm and all but 2 (<1%) deaths in the ENCO300 (Parts 1+2) arm were considered due to disease progression.

BINI=binimetinib; COMBO300=ENCO 300 mg QD + BINI 45 mg BID; ENCO=encorafenib; ENCO300=ENCO 300 mg QD; SAE=serious AE.

Most Common AEs Regardless of Causality*

	COMBO300 n=257		ENCO300 (Parts 1+2) n=276	
Median duration of exposure, weeks	**52.1**		**31.5**	
Preferred Term, %	**All Grades**	**Grades 3/4**	**All Grades**	**Grades 3/4**
Diarrhea	28	2	12	1
Nausea	27	2	36	3
Arthralgia	22	1	43	8
Fatigue	22	1	26	1
Increased CK	20	5	1	0
Vomiting	15	<1	25	4
Increased GGT	14	5	11	4
Myalgia	14	<1	27	8
Alopecia	13	0	49	<1
Headache	12	<1	26	3
Increased ALT	11	5	4	1
Pain in extremity	11	<1	20	1
Hyperkeratosis	10	0	39	3
Dry skin	8	0	28	0
Rash	7	1	23	3
Palmoplantar keratoderma	7	<1	24	1
Palmar-plantar erythrodysesthesia syndrome	4	<1	47	11

*All-cause AEs (≥20% in any treatment group for all grades or ≥5% in any group for grade 3/4 AEs).

ALT=alanine aminotransferase; BID=twice daily; BINI=binimetinib; CK=creatine phosphokinase; COMBO300=ENCO 300 mg QD + BINI 45 mg BID; ENCO=encorafenib; GGT=gamma-glutamyltransferase.

Selected AEs of Interest

	COMBO300 n=257		ENCO300 (Parts 1+2) n=276	
Median duration of exposure, weeks	**52.1**		**31.5**	
Event, %	**All Grades**	**Grades 3/4**	**All Grades**	**Grades 3/4**
Pyrexia*	17	0	16	1
Rash†	15	1	43	5
Transaminases increased‡	14	5	5	1
Retinal pigment epithelial detachment¶	9	<1	1	0
Left ventricular dysfunction§	6	1	3	1
Secondary skin neoplasms‖	6	1	10	1
Skin papilloma	6	0	12	0
Dermatitis acneiform	2	0	4	0
Photosensitivity#	2	0	4	0
Blood bilirubin increased	1	<1	0	0

*Includes pyrexia, body temperature increased, and hyperthermia.
†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 alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased, hepatic function abnormal, and hepatic enzyme increased.
¶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, left ventricular failure, cardiac output decreased, and ventricular hypokinesia.
‖Includes basal cell carcinoma, Bowen's disease, keratoacanthoma, lip squamous cell carcinoma, neoplasm skin, squamous cell carcinoma, and squamous cell carcinoma of skin.
#Includes photosensitivity reaction, solar dermatitis, and sunburn.
BINI=binimetinib; COMBO300=ENCO 300 mg QD + BINI 45 mg BID; ENCO=encorafenib.

Efficacy

	COMBO450 N=192		COMBO300 n=258		ENCO300 (Parts 1+2) n=280		VEM n=191	
	Central Review	Local Review	Central Review	Local Review	Central Review	Local Review	Central Review	Local Review
Median PFS, months (95% CI)	14.9 (11.0–18.5)	14.8 (10.4–18.4)	12.9 (10.1–14.0)	12.9 (10.9, 14.8)	9.2 (7.4–11.0)	9.2 (7.4, 11.1)	7.3 (5.6–8.2)	7.3 (5.7–8.5)
ORR* (95% CI†), %	63 (56–70)	75 (68–81)	66 (60–72)	73 (67–78)	50 (44–56)	56 (50–62)	40 (33–48)	49 (42–57)
CR, %	8	16	8	11	5	8	6	7
PR, %	55	59	58	62	45	49	35	42
Median DOR (95% CI), mo	16.6 (12.2–20.4)	16.2 (11.1–20.4)	12.7 (9.3–15.1)	13.1 (10.8–16.6)	12.9 (8.9–15.5)	13.0 (9.5–15.0)	12.3 (6.9–16.9)	8.4 (5.8–11.0)

BINI=binimetinib; COMBO300=ENCO 300 mg QD + BINI 45 mg BID; COMBO450=ENCO 450 mg QD + BINI45 mg BID; CR=complete response; DOR=duration of response; PFS=progression-free survival;; PFS=progression-free survival; PR=partial response; VEM=vemurafenib.

Tolerability of COMBO450 and COMBO300

- Similar tolerability with ENCO 450 mg QD and ENCO 300 mg QD in combination with BINI 45 mg BID

Tolerability		
	COMBO450	**COMBO300**
Median duration of treatment, weeks	51.2	52.1
AEs, %	98	98
Grade 3/4 AEs, %	58	47
AEs leading to discontinuation, %	13	13
AEs leading to dose interruption/change, %	48	45

BINI=binimetinib; COMBO300=ENCO 300 mg QD + BINI 45 mg BID; COMBO450=ENCO 450 mg QD + BINI45 mg BID; QD=once daily.

AEs with a Difference in Incidence Rates >5.0% (All Grades) between COMBO450 and COMBO300*

	COMBO450 n=192			COMBO300 n=257		
Preferred Term, %	**Grade 1**	**Grade 2**	**Grade 3/4**	**Grade 1**	**Grade 2**	**Grade 3/4**
Vomiting	18	10	2	10	5	<1
Nausea	24	15	2	21	5	2
Headache	12	8	2	8	4	<1
Diarrhea	24	10	3	20	7	2
Rash	13	1	1	5	1	1
Fatigue	21	6	2	15	7	1
Abdominal pain	9	5	3	7	2	1
Dry skin	13	2	0	7	1	0
Anemia	3	8	4	2	4	3
Vision blurred	16	0	0	9	1	<1
Macular edema	4	2	1	<1	0	0
Constipation	17	5	0	13	4	0

*Values in red represent differences of ≥5% and/or doubling of rates between COMBO450 and COMBO300.
BINI=binimetinib; COMBO300=ENCO 300 mg QD + BINI 45 mg BID; COMBO450=ENCO 450 mg QD + BINI45 mg BID; ENCO=encorafenib.

Conclusions

- There was a meaningful improvement in PFS and ORR with COMBO300 vs ENCO300 providing evidence of the direct contribution of BINI to the combination
- COMBO300 was better tolerated than ENCO300, resulting in greater relative dose intensity, fewer grade 3/4 AEs and fewer AEs requiring discontinuation
- Patient and disease characteristics in the COMBO450 and COMBO300 arms were similar; PFS and duration of response with COMBO450 from COLUMBUS Part 1 were longer compared to PFS and duration of response with COMBO300 from Part 2
- The safety and tolerability of COMBO300 was similar to that of COMBO450 from COLUMBUS Part 1, suggesting that the higher ENCO dose does not expose patients to a significantly greater burden of toxicity when combined with BINI
- Future reports will include OS, updated PFS, and long-term safety data

Conclusions:

- COMBO300 improved PFS, ORR, and tolerability vs ENCO300, confirming the contribution of BINI to both efficacy and tolerability
- Results support that a higher dose of encorafenib may result in improved efficacy

BINI=binimetinib; CI=confidence interval; COMBO300=ENCO 300 mg QD + BINI 45 mg BID; ENCO=encorafenib; NE=not evaluable; ORR=overall response rate; OS=overall survival; PFS=progression-free survival.

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