



**Society for Melanoma Research
2016 Congress
November 6–9, 2016
Boston, Massachusetts**

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

Reinhard Dummer, Paolo A. Ascierto, Helen J. Gogas, Ana Arance,
Mario Mandala, Gabriella Liskay, Claus Garbe, Dirk Schadendorf,
Ivana Krajsova, Ralf Gutzmer, Vanna Chiarion Sileni,
Caroline Dutriaux, Jan Willem B. de Groot, Naoya Yamazaki,
Carmen Loquai, Laure A. Moutouh-de Parseval, Michael D. Pickard,
Victor Sandor, Caroline Robert, Keith T. Flaherty

Disclosures

KT Flaherty: Honoraria from and consulting/advisory role for Novartis and Array BioPharma; research funding from Novartis

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

PA Ascierio: Consulting fees from BMS, Roche/Genentech, MSD, Ventana, Novartis, Amgen, and Array BioPharma; research funding from BMS, Roche/Genentech, Ventana, and Array BioPharma

HJ Gogas: Consultant for Roche, BMS, MSD, Novartis, and Amgen

A Arance: Honoraria from and consulting/advisory role and speakers bureau for Novartis, Roche, MSD, and BMS; travel expenses from Roche and BMS

M Mandala: Honoraria from Novartis, GSK, BMS, MSD, and Roche; speakers bureau for Novartis, GSK, Roche, and BMS; advisory board member for Novartis, Amgen, MSD, and BMS; research funding from Roche

C Garbe: Honoraria and travel expenses from and served in a consulting/advisory role and speakers bureau member for Amgen, BMS, MSD, Novartis, Roche, and Philogen; has received research funding for University Hospital Tübingen from BMS, Novartis, and Roche

D Schadendorf: Honoraria and travel expenses from and consulting/advisory role and speakers bureau for Amgen, BMS, Novartis, Roche, and MSD; research funding for University Hospital Essen from Amgen, BMS, Novartis, Roche, and MSD

I Krajsova: Advisory board member for BMS, Novartis, Roche, MSD; travel expenses from BMS and MSD

R Gutzmer: Consulting fees from Roche, BMS, MSD, GSK, Novartis, Almirall, LEO, Amgen, and Pfizer; honoraria from Roche, BMS, GSK, Novartis, MSD, Merck Serono, Almirall, Amgen, and Boehringer Ingelheim; research funding from Roche, Novartis, Pfizer, and Johnson & Johnson; travel expenses from BMS and Roche

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

JWB de Groot: Consulting/advisory role for Amgen, Bayer, Celgene, Roche, BMS, GSK, MSD, and Merck Serono

N Yamazaki: Advisory role for Chugai Pharma, Bristol-Myers Squibb Japan, and Ono Pharmaceutical; honoraria from Chugai Pharma, Bristol-Myers Squibb Japan, Ono Pharmaceutical, GlaxoSmithKline, Takeda, AstraZeneca Japan, Boehringer Ingelheim, and Maruho

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

LA Moutouh-de Parseval: Employee of Novartis Pharma AG; may own stock or stock options

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 Liskay, 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 profile³
 - 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 MEK1/2⁴
 - Shorter half-life than other MEK1/2 inhibitors; may provide more rapid resolution of toxicity upon interruption⁵

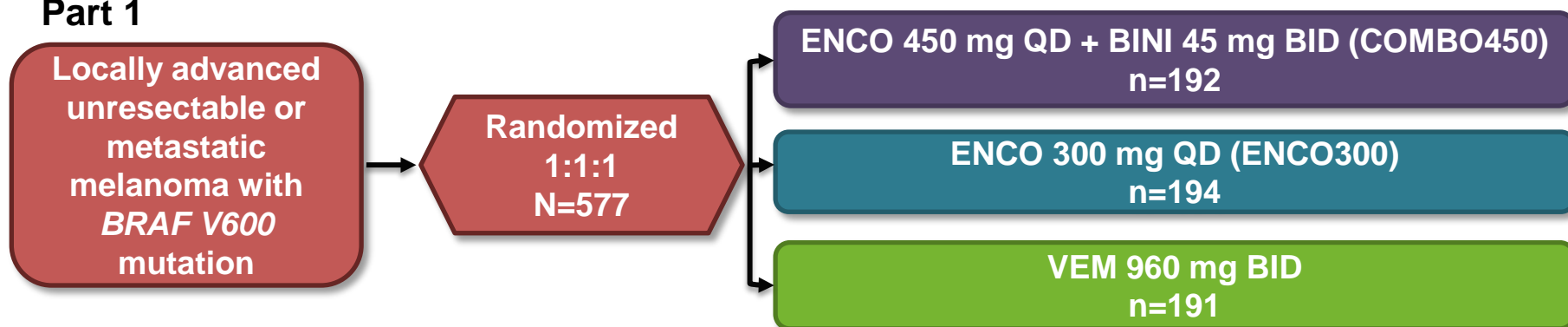
IC_{50} =half-maximal inhibitory concentration.

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

Part 1



- 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*

- | | |
|---|---|
| <ul style="list-style-type: none">• Primary endpoint:• Key secondary endpoint (tested sequentially):• Patient-reported outcomes: | <p>PFS[†] for COMBO450 vs VEM</p> <p>PFS[†] for COMBO450 vs ENCO300</p> <p>FACT-M, EORTC QLQ-C30</p> |
| <ul style="list-style-type: none">• 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.

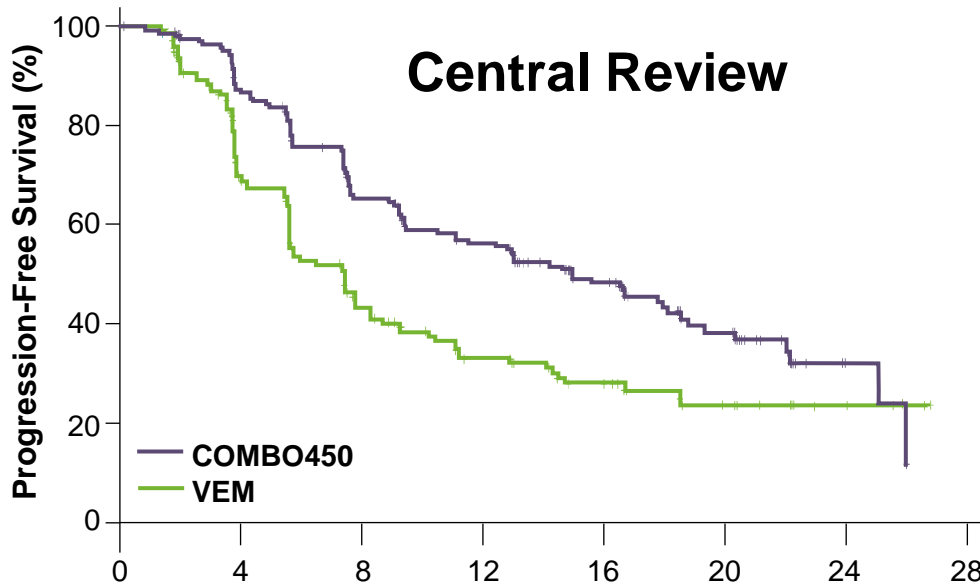
Baseline Characteristics

| 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 \geq ULN, % | 29 | 24 | 27 |
| <i>BRAF</i> mutation status (<i>V600E/V600K</i>), % | 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 |
| \geq 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



| Patients at risk | | Time (mo) | | | | | | | |
|------------------|-----|-----------|-----|----|----|----|----|----|----|
| | | 0 | 4 | 8 | 12 | 16 | 20 | 24 | 28 |
| COMBO450 | 192 | 151 | 107 | 87 | 57 | 28 | 4 | | |
| VEM | 191 | 101 | 56 | 36 | 23 | 13 | 4 | | |

Median PFS in months (95% CI)

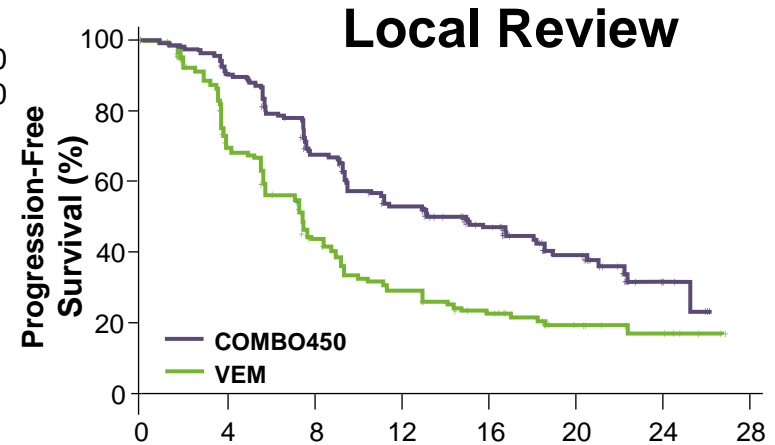
| COMBO450 | VEM |
|------------------|---------------|
| 14.9 (11.0–18.5) | 7.3 (5.6–8.2) |

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*

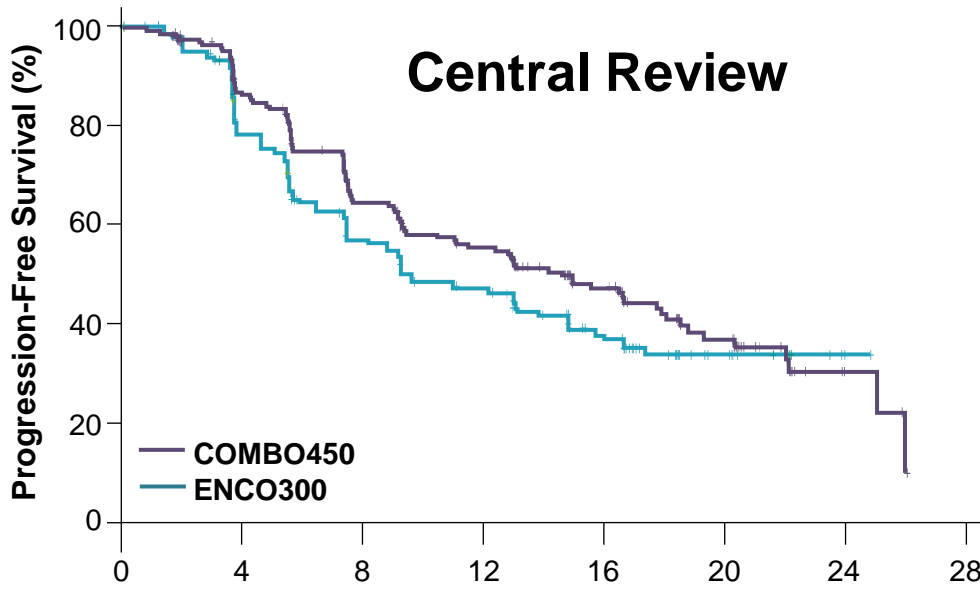


| Patients at risk | | Time (mo) | | | | | | | |
|------------------|-----|-----------|-----|----|----|----|----|----|----|
| | | 0 | 4 | 8 | 12 | 16 | 20 | 24 | 28 |
| COMBO450 | 192 | 160 | 116 | 88 | 63 | 30 | 5 | 0 | |
| VEM | 191 | 111 | 61 | 40 | 27 | 14 | 6 | 0 | |

*Nominal P value.

BINI=binimetinib; CI=confidence interval; COMBO450=ENCO 450 mg QD + BINI 45 mg BID

Progression-Free Survival: COMBO450 vs ENCO300



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

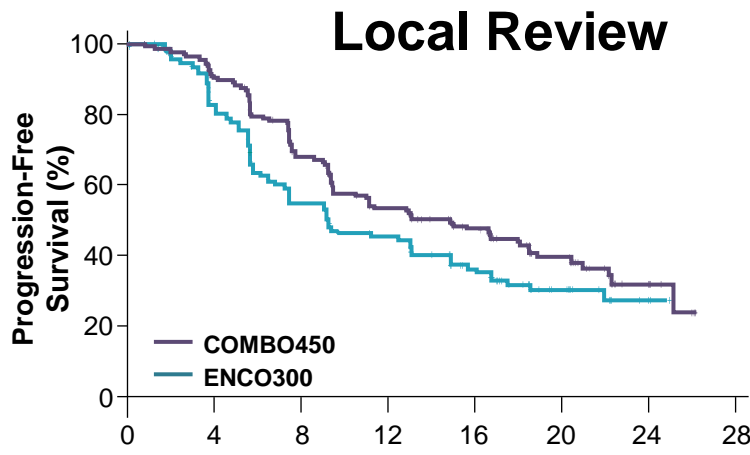
Patients at risk

| | | | | | | | | |
|----------|-----|-----|-----|----|----|----|----|----|
| | 0 | 4 | 8 | 12 | 16 | 20 | 24 | 28 |
| 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 |
| 14.8 (10.4–18.4) | 9.2 (7.4–12.9) |

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

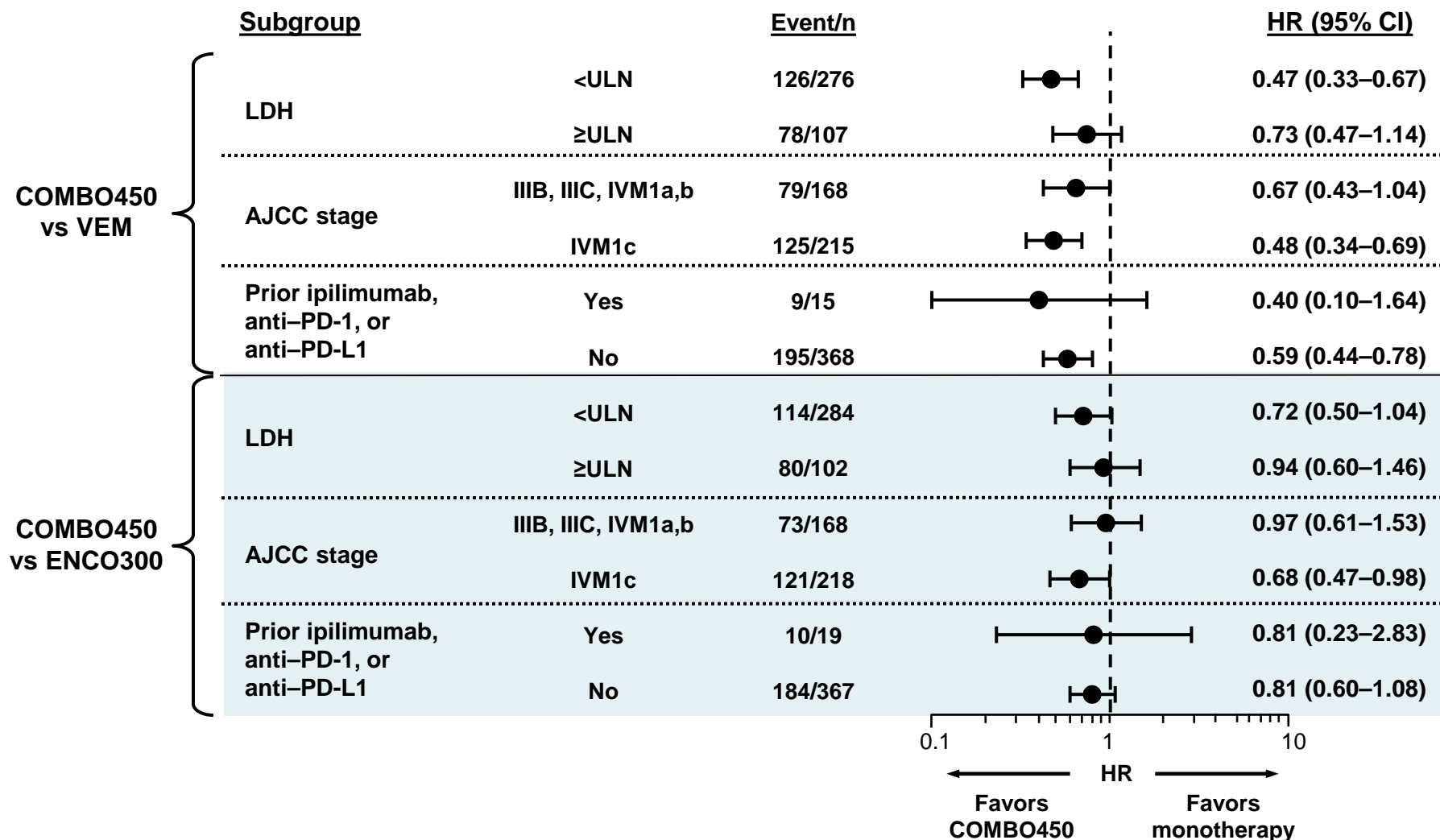


Patients at risk

| | | | | | | | | |
|----------|-----|-----|-----|----|----|----|----|----|
| | 0 | 4 | 8 | 12 | 16 | 20 | 24 | 28 |
| COMBO450 | 192 | 160 | 116 | 88 | 63 | 30 | 5 | 0 |
| ENCO300 | 194 | 133 | 87 | 70 | 42 | 17 | 1 | 0 |

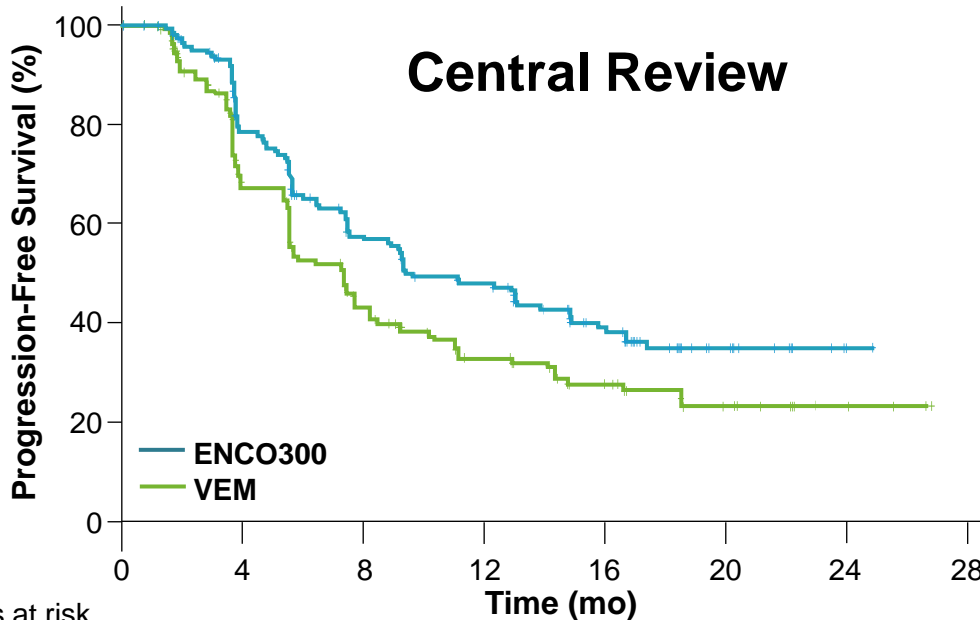
*Nominal P value.
BINI=binimetinib; CI=confidence interval; COMBO450=ENCO 450 mg QD + BINI 45 mg BID; ENCO=encorafenib

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



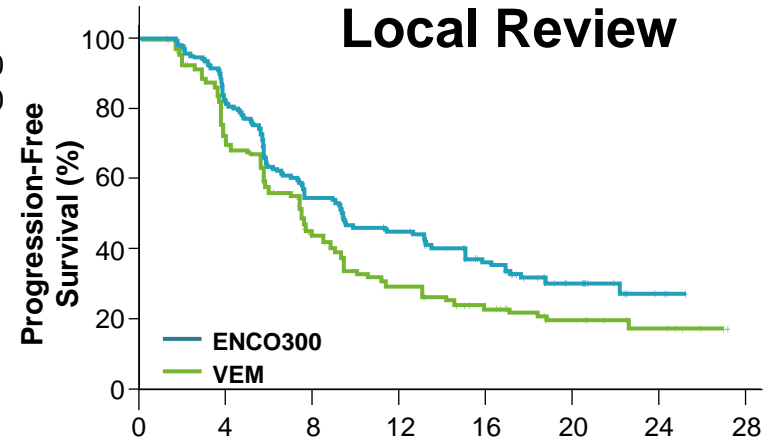
Median PFS in months (95% CI)

| <u>ENCO300</u> | <u>VEM</u> |
|-------------------------------|---------------|
| 9.6 (7.5–14.8) | 7.3 (5.6–8.2) |
| HR (95% CI), 0.68 (0.52–0.90) | |
| P=0.007* | |

| Patients at risk | | 0 | 4 | 8 | 12 | 16 | 20 | 24 | 28 |
|------------------|-----|-----|----|----|----|----|----|----|----|
| ENCO300 | 194 | 125 | 84 | 68 | 41 | 17 | 1 | 0 | 0 |
| VEM | 191 | 101 | 56 | 36 | 23 | 13 | 4 | 0 | 0 |

Median PFS in months (95% CI)

| <u>ENCO300</u> | <u>VEM</u> |
|-------------------------------|---------------|
| 9.2 (7.4–12.9) | 7.3 (5.7–8.5) |
| HR (95% CI), 0.70 (0.54–0.91) | |
| P=0.008* | |



| Patients at risk | | 0 | 4 | 8 | 12 | 16 | 20 | 24 | 28 |
|------------------|-----|-----|----|----|----|----|----|----|----|
| ENCO300 | 194 | 133 | 87 | 70 | 42 | 17 | 1 | 0 | 0 |
| VEM | 191 | 111 | 61 | 40 | 27 | 14 | 6 | 0 | 0 |

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.

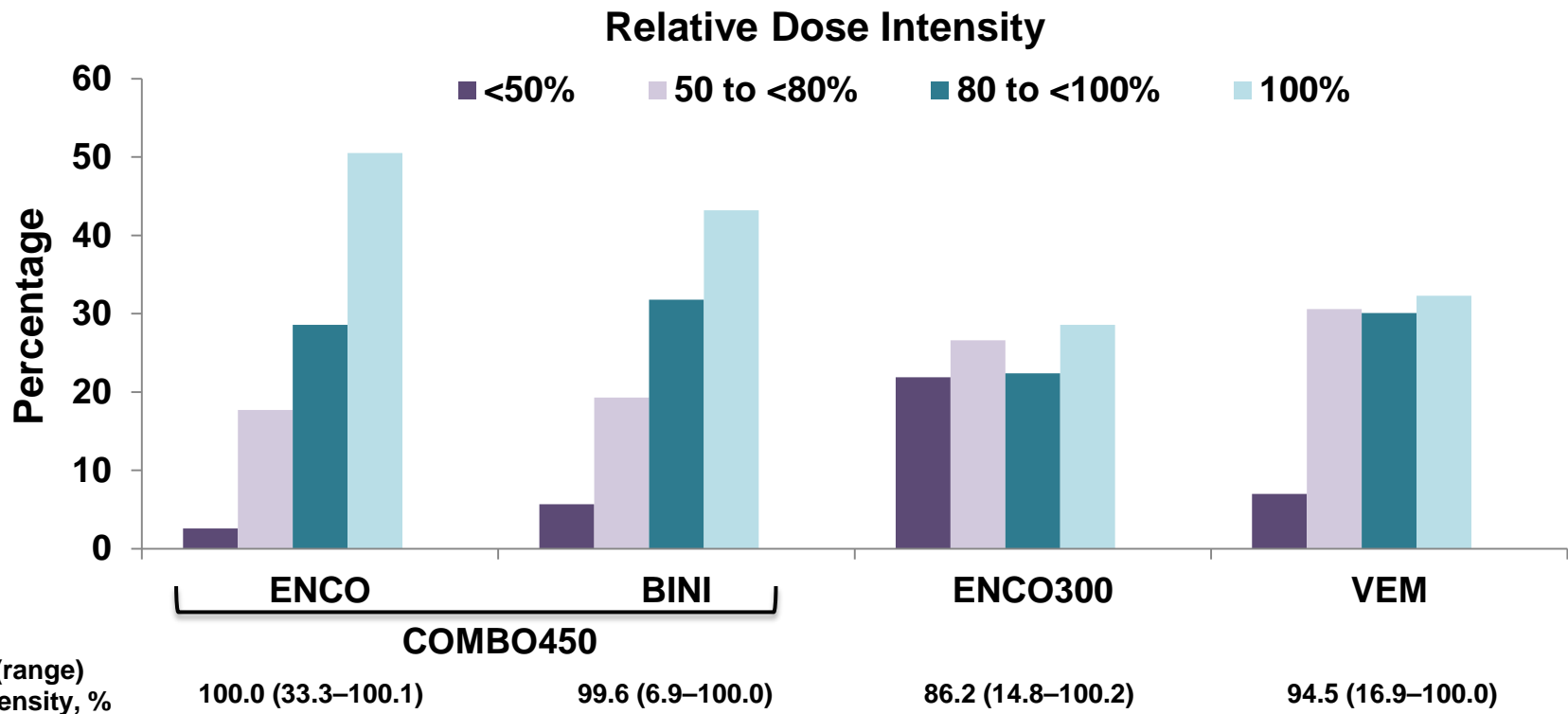
[†]Includes patients with only nontarget lesions with best response of non-CR/non-PD.

[‡]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) |



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%])

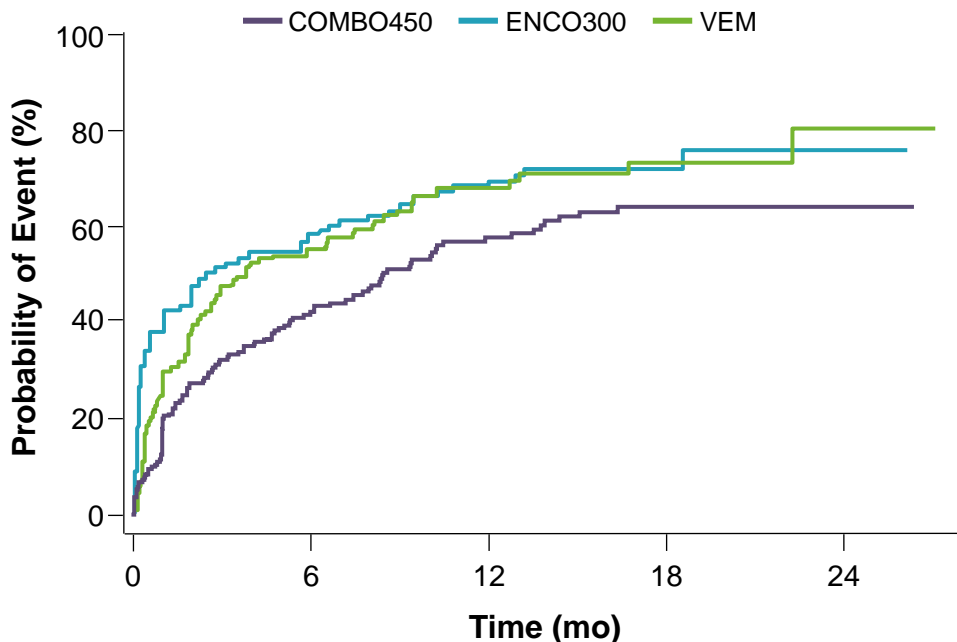
- Adverse events leading to discontinuation: ALT increased (3%), AST increased (3%)
- Adverse events requiring dose interruption: nausea (7%), vomiting (7%), ejection fraction decreased (5%), GGT increased (5%), pyrexia (4%), ALT increased (4%), diarrhea (3%), AST increased (3%), blood creatine phosphokinase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

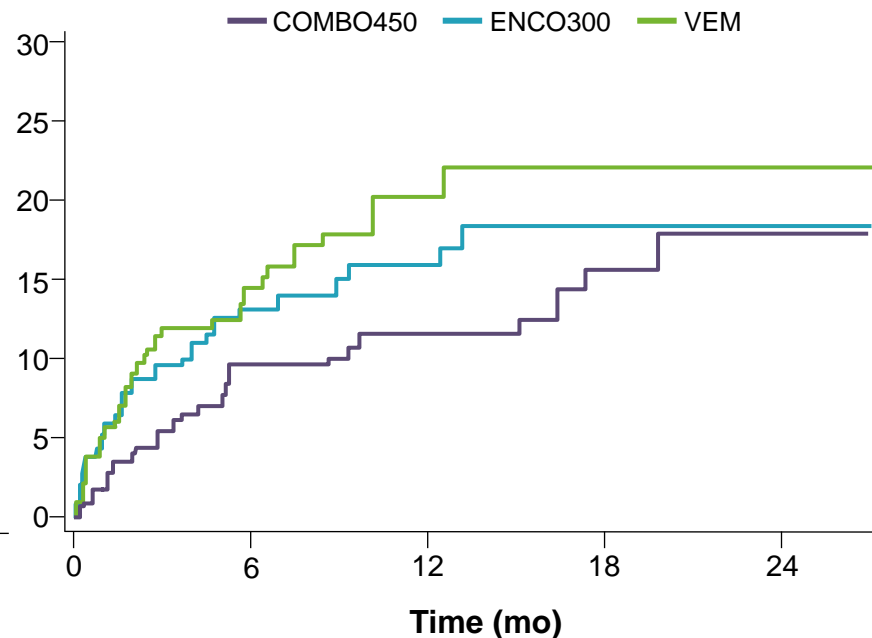
[†]Includes on-treatment deaths and deaths within 30 days of stopping study treatment.

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=creatinine 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=creatinine 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=creatinine 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.

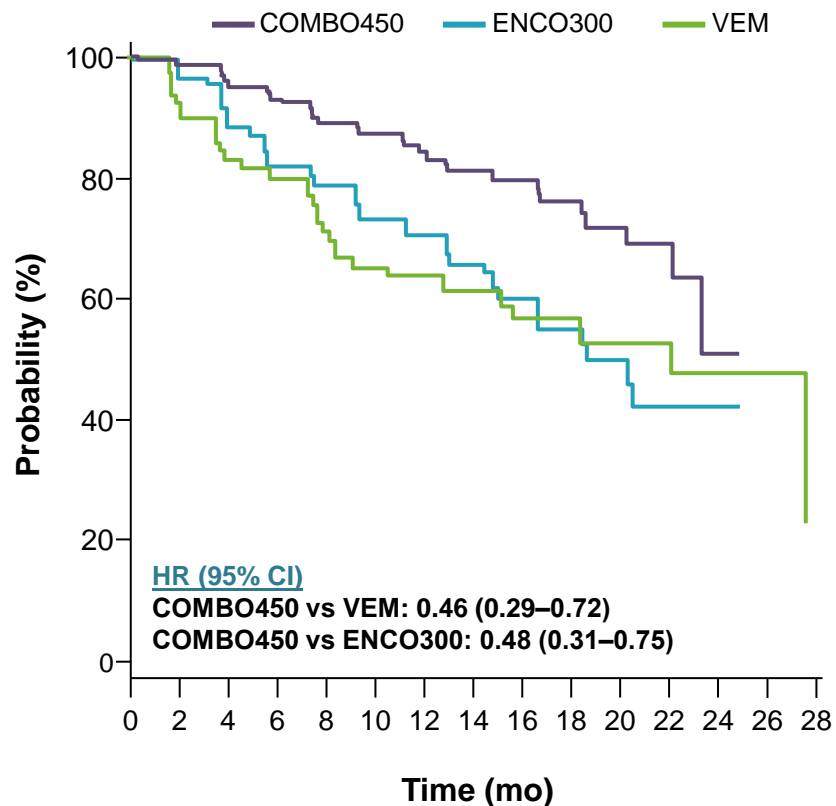
§Includes chorioretinopathy, detachment of macular retinal pigment epithelium, detachment of retinal pigment epithelium, retinal detachment, and subretinal fluid.

|| Includes ejection fraction decreased, cardiac failure, left ventricular dysfunction, and left ventricular failure.

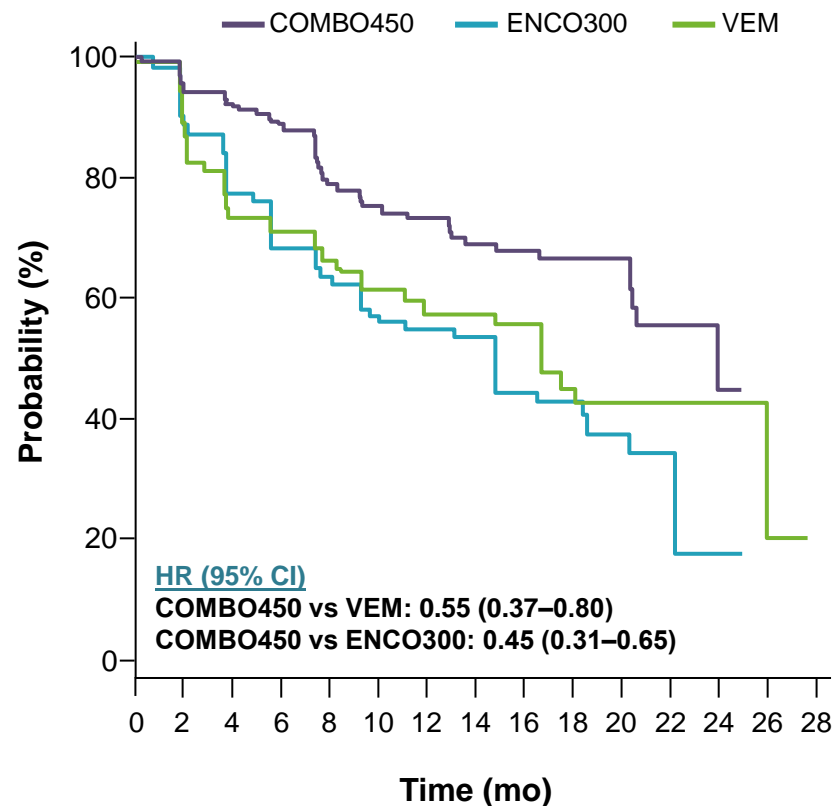
¶Includes alanine aminotransferase increased, aspartate aminotransferase increased, and transaminases increased.

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.

Acknowledgments

- **The authors thank the patients and their families and the sites participating in this study.**

This study was sponsored by Array BioPharma Inc.,
with funding support from Novartis Pharmaceuticals Corporation.