MADRID 2014 ESMO congress

COMBI-v: A Randomized, Open-Label, Phase III Study Comparing the Combination of Dabrafenib (D) and Trametinib (T) With Vemurafenib (Vem) as First-Line Therapy in Patients (pts) With Unresectable or Metastatic BRAF V600E/K Mutation-Positive Cutaneous Melanoma

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Disclosure Slide

C. Robert – Consultant: GSK, Roche, BMS, Amgen, Novartis, Merck.

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Study describes investigational use of dabrafenib/trametinib.

Study Objective

To evaluate the superiority of dabrafenib and trametinib combination therapy over vemurafenib with respect to overall survival (OS) for subjects with advanced/metastatic BRAF V600E/K mutation-positive cutaneous melanoma

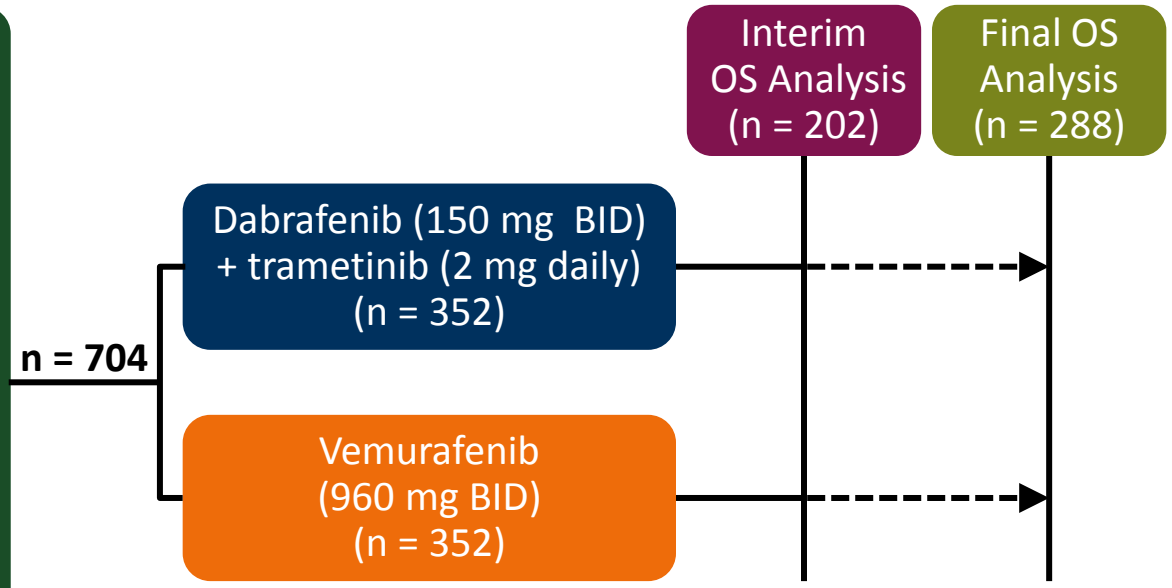
Study Design and Endpoints

N = 1,644 screened

- BRAF V600E/K mutation
- Stages IIIC or IV cutaneous melanoma
- Treatment-naive in advanced or metastatic
- ECOG PS 0 or 1
- No brain metastases, unless
  - Treated
  - Stable > 12 weeks

Stratification

- BRAF V600E vs V600K mutation
- LDH (> ULN vs ≤ ULN)



Primary endpoint: OS

Secondary endpoints: progression-free survival (PFS), overall response rate (ORR), duration of response (DoR), safety

BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ULN, upper limit of normal

Protocol Planned Interim and Final Analyses

Interim OS analysis:

- Timing: 202 observed death events
  (70% of n = 288 events required for final analysis)
- There were 222 (77%) observed death events at data cut-off
- Protocol allows stopping for efficacy as well as futility at the interim
  - Stop for efficacy if two-sided *P*-value < 0.0214 and stop for futility if two-sided *P*-value > 0.2210
- If Independent Data Monitoring Committee (IDMC) recommends stopping at interim, interim becomes final

IDMC recommendation:

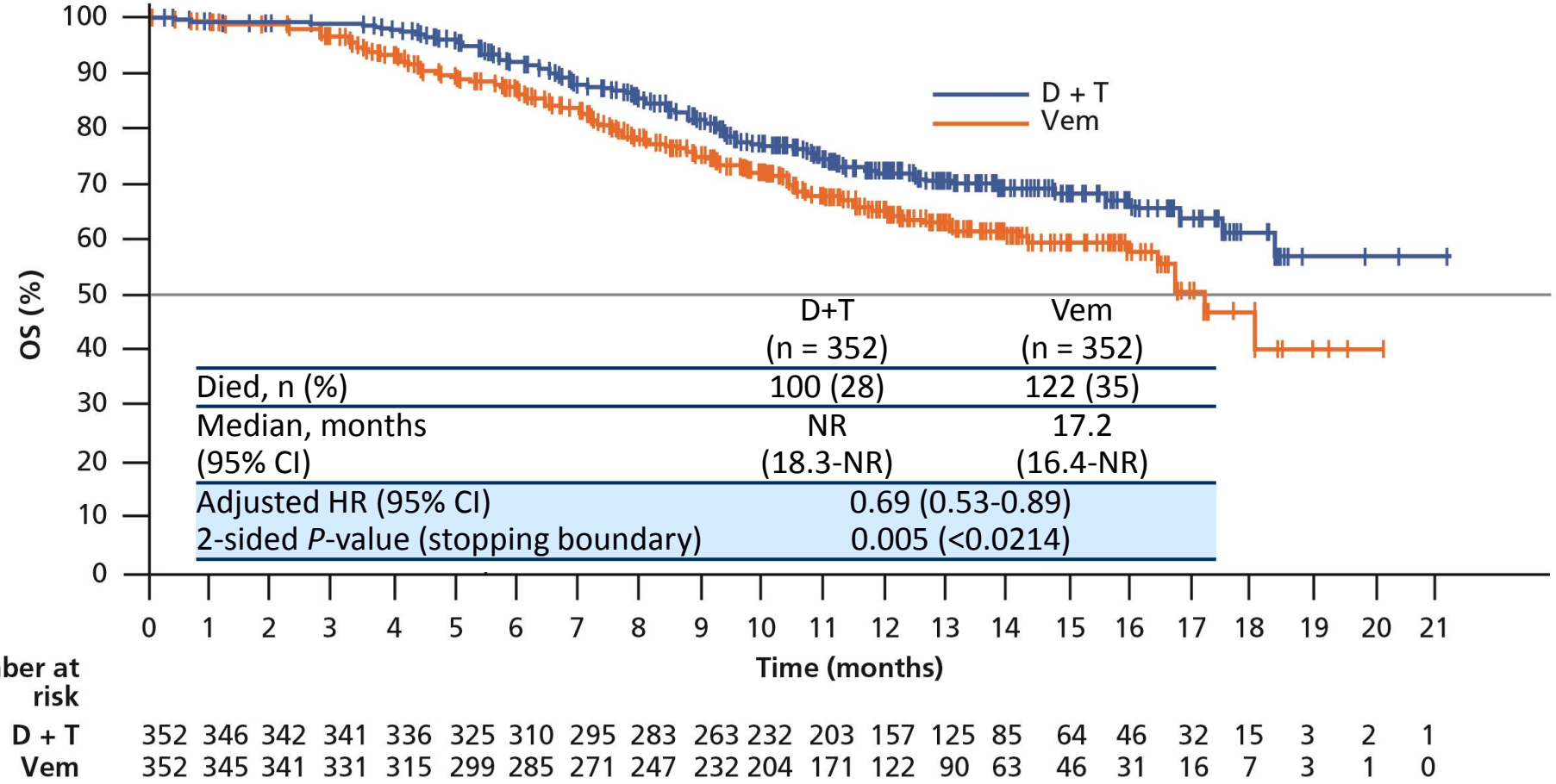
- Stop for efficacy at interim
- Interim is the final OS analysis

Baseline Patient Characteristics

	Dabrafenib + trametinib (n = 352)	Vemurafenib (n = 352)
Median age, years (range)	55 (18–91)	54 (18–88)
Male, n (%)	208 (59)	180 (51)
LDH > ULN , n (%)	118 (34)	114 (32)
Stage, n (%)		
IV	337 (96)	326 (93)
M1a	55 (16)	50 (14)
M1b	61 (17)	67 (19)
M1c	221 (63)	208 (59)
ECOG PS 0, n (%)	248 (70)	248 (70)
BRAF mutation, n (%)		
V600E	312 (89)	317 (90)
V600K*	34 (10)	34 (10)

*5 pts (dabrafenib + trametinib) and 1 pt (vemurafenib) were both V600E and V600K

Overall Survival

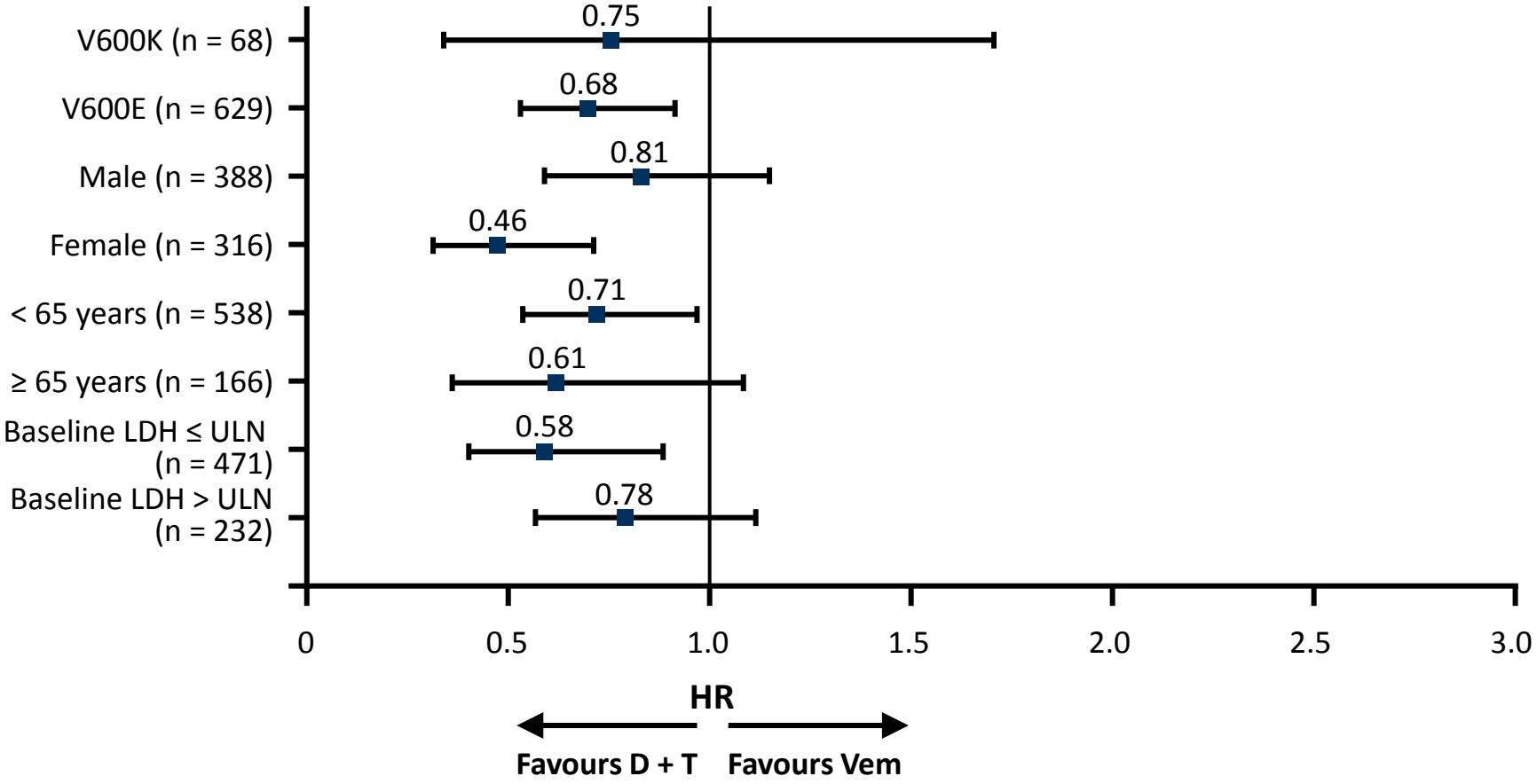


	D+T (n = 352)	Vem (n = 352)
Died, n (%)	100 (28)	122 (35)
Median, months (95% CI)	NR (18.3-NR)	17.2 (16.4-NR)
Adjusted HR (95% CI)	0.69 (0.53-0.89)	
2-sided *P*-value (stopping boundary)	0.005 (<0.0214)	

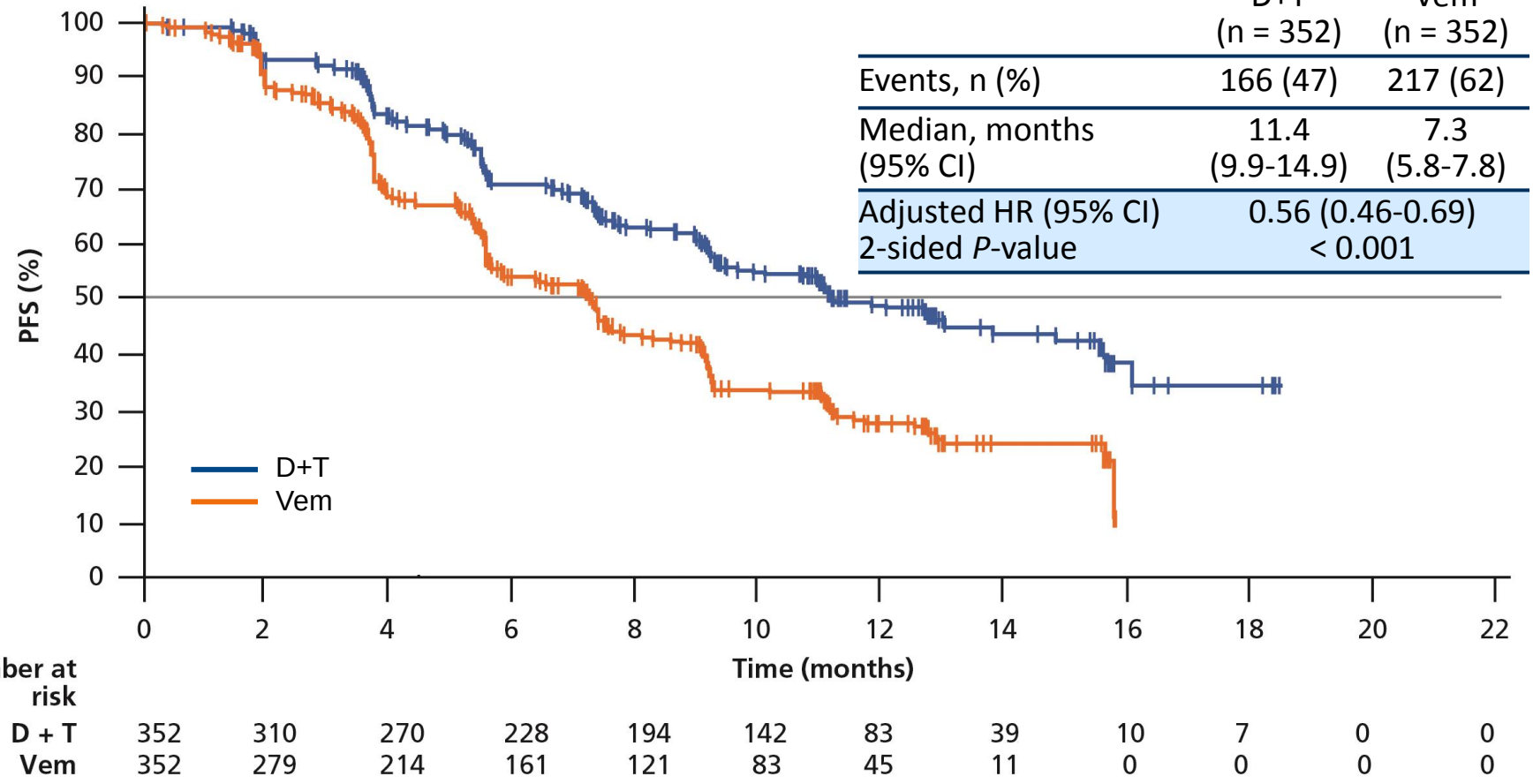
D + T, dabrafenib + trametinib; Vem, vemurafenib

Median Follow-up: D + T = 11 months and Vem = 10 months

Overall Survival Subgroup Analyses (ITT)



Progression-Free Survival



	D+T (n = 352)	Vem (n = 352)
Events, n (%)	166 (47)	217 (62)
Median, months (95% CI)	11.4 (9.9-14.9)	7.3 (5.8-7.8)
Adjusted HR (95% CI)	0.56 (0.46-0.69)	
2-sided *P*-value	< 0.001	

Number at risk												
D + T	352	310	270	228	194	142	83	39	10	7	0	0
Vem	352	279	214	161	121	83	45	11	0	0	0	0

D + T, dabrafenib + trametinib; Vem, vemurafenib

Best Confirmed Response

Best confirmed response	Dabrafenib + trametinib (n = 351)	Vemurafenib (n = 350)
Complete response, n (%)	47 (13)	27 (8)
Partial response, n (%)	179 (51)	153 (44)
Stable disease, n (%)	92 (26)	106 (30)
Progressive disease, n (%)	22 (6)	38 (11)
Not evaluable, n (%)	11 (3)	26 (7)
Response rate, n (%) (95% CI)	226 (64) (59.1–69.4)	180 (51) (46.1–56.2)
Difference in ORR, % (95% CI)	13 (5.7–20.2)	
P-value	< 0.001	
DoR, months (95% CI)	13.8 (11.0–NR)	7.5 (7.3–9.3)

NR, not reached

Adverse Events Overview

Category	Dabrafenib + trametinib (n = 350*)	Vemurafenib (n = 349*)
Any AE, n (%)	343 (98)	345 (99)
AEs leading to dose interruption, n (%)	192 (55)	197 (56)
AEs leading to dose reduction, n (%)	115 (33)	136 (39)
AEs leading to permanent discontinuation, n (%)	44 (13)	41 (12)
Any SAE, n (%)	131 (37)	122 (35)
Fatal SAEs,† n (%)	3 (< 1)	3 (< 1)

AE, adverse event; SAE, serious adverse event;
*2 patients (dabrafenib + trametinib) and 3 patients (vemurafenib) were excluded from safety population because they were randomized but not dosed;
†Fatal SAEs (all deemed unrelated to study treatment) included:
D + T arm - 2 cerebral haemorrhages, 1 brain stem haemorrhage;
Vem arm - 1 acute coronary syndrome, 1 cerebral ischaemia, and 1 pleural infection

Adverse Events in > 20% of Patients

AE, n (%)	Dabrafenib + trametinib (n = 350)		Vemurafenib (n = 349)	
	All Grades	Grade 3	All Grades	Grade 3
All events	343 (98)	167 (48)	345 (99)	198 (57)
Pyrexia	184 (53)	15 (4)	73 (21)	2 (< 1)
Nausea	121 (35)	1 (< 1)	125 (36)	2 (< 1)
Diarrhoea	112 (32)	4 (1)	131 (38)	1 (< 1)
Chills	110 (31)	3 (< 1)	27 (8)	0
Fatigue	101 (29)	4 (1)	115 (33)	6 (2)
Headache	101 (29)	3 (< 1)	77 (22)	2 (< 1)
Vomiting	101 (29)	4 (1)	53 (15)	3 (< 1)
Hypertension	92 (26)	48 (14)	84 (24)	32 (9)
Arthralgia	84 (24)	3 (< 1)	178 (51)	15 (4)
Rash	76 (22)	4 (1)	149 (43)	30 (9)
Pruritus	30 (9)	0	75 (21)	3 (< 1)
Alopecia	20 (6)	0	137 (39)	1 (< 1)
Hyperkeratosis	15 (4)	0	86 (25)	2 (< 1)
Photosensitivity	13 (4)	0	78 (22)	1 (< 1)
Skin papilloma	6 (2)	0	80 (23)	2 (< 1)

Grade 4 events:
D + T arm - All events: 16 (5%) and headache 1 (< 1%); Vem arm - All events: 23 (7%) and hypertension 1 (< 1%)

BRAF Inhibitor-Related Adverse Events

AE, n (%)	Dabrafenib + trametinib (n = 350)	Vemurafenib (n = 349)
BRAF inhibitor-related AEs*		
Pyrexia	184 (53)	73 (21)
Cutaneous small-cell carcinoma and keratoacanthoma	5 (1)	63 (18)
Hyperkeratosis	15 (4)	86 (25)
Skin papilloma	6 (2)	80 (23)
Hand-Foot syndrome†	14 (4)	87 (25)
Alopecia	20 (6)	137 (39)
Photosensitivity + sunburn	15 (4)	124 (36)
Non-cutaneous malignancy	3 (< 1)	2 (< 1)
New primary melanoma	2 (< 1)	7 (2)

*AEs indicated are those typically associated with BRAF inhibitors
†Hand–Foot syndrome = palmoplantar keratoderma and palmar plantar erythrodysaesthesia

MEK Inhibitor-Related Adverse Events

AE, n (%)	Dabrafenib + trametinib (n = 350)	Vemurafenib (n = 349)
MEK inhibitor-related AEs*		
Diarrhoea	112 (32)	131 (38)
Hypertension	92 (26)	84 (24)
Acneiform rash	22 (6)	20 (6)
Ejection fraction decrease	29 (8)	0
Chorioretinopathy	2 (< 1)	1 (< 1)

*AEs indicated are those typically associated with MEK inhibitors

Conclusions

Significant improvement across all efficacy endpoints in favor of D+T combination

- OS: 31% reduction in the risk of death; median OS not reached for combination vs 17.2 months (95% CI 16.4–NR) for vemurafenib
- PFS: 44% reduction in the risk of progression or death; median PFS 11.4 months (95% CI 9.9–14.9) for combination vs 7.3 months (95% CI 5.8–7.8) for vemurafenib
- ORR: 64% for combination vs 51% for vemurafenib; p-value < 0.001
- DoR : 13.8 mo (95% CI 11.0–NR) for combination vs 7.5 mo (95% CI 7.3–9.3) for vemurafenib

Safety profile of the combination arm was consistent with previously reported studies

- In general, similar rates of AEs and SAEs across both arms:

↑ Incidence of pyrexia and ejection fraction decrease for combination vs. vemurafenib

↓ Incidence of cutaneous malignancies, hyperproliferative events, and photosensitivity for combination vs vemurafenib

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