Outcome of adjuvant BRAF and MEK inhibition with dabrafenib and trametinib in BRAF V600K- compared to V600E-mutated melanoma

Michael Weichenthal[1], Eva Ellebaek[2], Peter Mohr[3], Mirna Situm[4], Joanna Mangana[5], Vanna Chiarion Sileni[6], Imke von Wasielewski[7], Christoffer Gebhardt[8], Piotr Rutkowski[9], Friedegund Elke Meier[10], Paolo A. Ascierto[11], Ralf Gutzmer[12], Inge Marie Svane[13], Dirk Schadendorf[14], Helen Gogas[15], the EUMelaReg Research Group*

[1]University of Kiel, Kiel, Germany; [2]National Center for Cancer Immune Therapy (CCIT-DK), Department of Oncology, Copenhagen University Hospital Herlev, Herlev, Denmark; [3]Elbe Medical Center, Buxtehude, Germany; [4]"Sestre milosrdnice" University Hospital Centre, Zagreb, Croatia; [5]Department of Dermatology, University Hospital Zurich, Zurich, Switzerland; [6]Istituto Oncologico veneto IOV-IRCCS, Padova, Italy; [7]Skin Cancer Center Hannover, Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany; [8]Department of Dermatology/Skin Cancer Center, University Medical Center Hospital Hamburg-Eppendorf, Hamburg, Germany; [9]Narodowy Instytut Onkologii im, Warsaw, Poland; [10]Department of Dermatology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany; SkinCancer Center at the University Cancer Centre Dresden National Center for Tumor Diseases, Dresden, Germany; [11]Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy; [12]Johannes Wesling Medical Center, Ruhr University Bochum, Minden, Germany; [13]Herlev Hospital, Herlev, Denmark; [14]University of Essen and the German Cancer Consortium, Partner Site, Essen, Germany; [15]National and Kapodistrian University of Athens,Athens, Greece

BACKGROUND

- Patients with resected stage III BRAF V600 mutated melanoma can be treated with combined dabrafenib and trametinib (D/T) with significant improvement of recurrence-free survival (RFS). The results of the pivotal Combi-AD study showed overall survival (OS) improvement only for patients with BRAF V600E mutations, while for V600K there was even an OS impairment as compared to placebo, although not statistically significant.

OBJECTIVES

- Primary objective was overall survival (OS) from start of 2L BRAF/MEKi therapy.
- Secondary objective included OS, progression-free survival (PFS), overall response rate (ORR), and time on treatment (TOT) for 1L compared to 2L BRAF/MEKi therapy.

METHODS

- **Study population:** We analysed EUMelaReg data for patients with adjuvant D/T therapy for resected stage III melanoma. Only patients with V600E and V600K mutations were selected, where n = 93 from a total of 1,033 patients (9.0 %) harboured V600K.
- Overall, recurrence-free, and melanoma specific survival were calculated by Kaplan-Meier analysis and multivariable cox regression.

RESULTS

- After excluding three cases for not being valid as djuvant treatments, 1.030 cases could be analysed.
- Baseline characteristics differed in V600K patients being significantly older, more often male, and a slightly different pattern of primary tumors. (Tab1)
- V600K patients had a shorter mean duration of treatment owing to a higher rate of early termination due to a mix of reasons including more toxicity, patient's wish and a slightly higher early recurrence rate.
- Overall survival, RFS, and MSS were not significantly different.

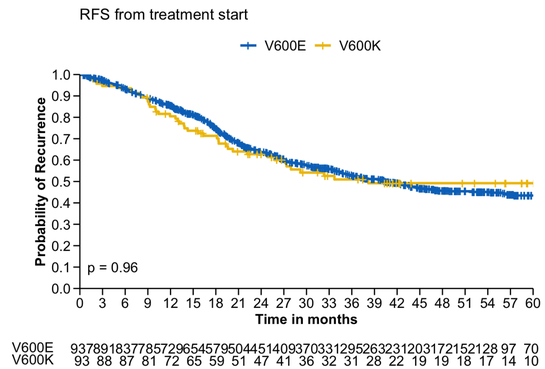
Table 1. Baseline

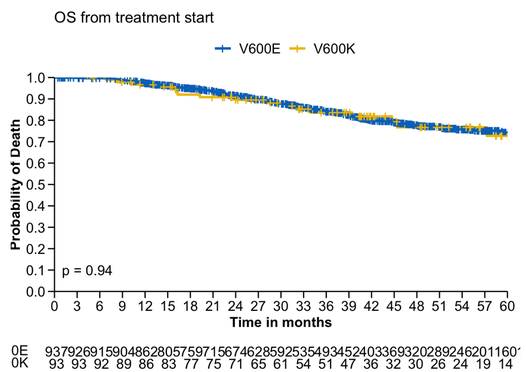
	V600E (N=937)	V600K (N=93)	P-value	Overall (N=1030)
SEX				
Female	425 (45.4%)	31 (33.3%)	0.034	456 (44.3%)
Male	512 (54.6%)	62 (66.7%)		574 (55.7%)
AGE [Years]				
Mean (SD)	57.5 (13.8)	65.6 (11.9)	<0.001	58.2 (13.8)
Median [Min, Max]	58.0 [17.0, 90.0]	67.0 [28.0, 87.0]		59.0 [17.0, 90.0]
ECOG				
0	817 (87.2%)	80 (86.0%)	0.23	897 (87.1%)
1	51 (5.4%)	5 (5.4%)		56 (5.4%)
2	4 (0.4%)	2 (2.2%)		6 (0.6%)
UK	65 (6.9%)	6 (6.5%)		71 (6.9%)
Baseline Stage				
IIIA	123 (13.1%)	7 (7.5%)	0.41	130 (12.6%)
IIIB	289 (30.8%)	29 (31.2%)		318 (30.9%)
IIIC	455 (48.6%)	52 (55.9%)		507 (49.2%)
IIID	40 (4.3%)	2 (2.2%)		42 (4.1%)
OTH	30 (3.2%)	3 (3.2%)		33 (3.2%)
Diagnosis Type				
Primary Melanoma Stage 3	620 (66.2%)	61 (65.6%)	1	681 (66.1%)
Locoregional Relapse	317 (33.8%)	32 (34.4%)		349 (33.9%)
Melanoma subtype				
ALM	31 (3.3%)	0 (0%)	0.001	31 (3.0%)
NMM	314 (33.5%)	44 (47.3%)		358 (34.8%)
SSM	358 (38.2%)	26 (28.0%)		384 (37.3%)
LMM	4 (0.4%)	3 (3.2%)		7 (0.7%)
MUP	49 (5.2%)	4 (4.3%)		53 (5.1%)
UK/NOS	181 (19.3%)	16 (17.2%)		197 (19.1%)

Table 2. Outcome

	V600E (N=937)	V600K (N=93)		Overall (N=1030)
Duration of Treatment				
Mean (SD)	9.70 (4.37)	8.68 (4.65)	0.03	9.61 (4.40)
Median [Min, Max]	11.8 [0.1, 43.5]*	11.7 [0.1, 17.1]*		11.8 [0, 43.5]
End of Treatment				
Regular/completed	590 (63.0%)	48 (51.6%)	0.18	638 (61.9%)
Recurrence	65 (6.9%)	10 (10.8%)		75 (7.3%)
Toxicity	180 (19.2%)	21 (22.6%)		201 (19.5%)
Patient's wish	53 (5.7%)	9 (9.7%)		62 (6.0%)
Other/unknown	47 (5.0%)	5 (5.4%)		52 (5.0%)
Recurrence				
No	526 (56.1%)	51 (54.8%)	0.90	577 (56.0%)
Yes	411 (43.9%)	42 (45.2%)		453 (44.0%)
Type of recurrence				
Stage III	166 (17.7%)	17 (18.3%)	0.907	183 (17.8%)
Stage IV	228 (24.3%)	24 (25.8%)		252 (24.5%)
UK	6 (0.6%)	1 (1.1%)		7 (0.7%)
Tumor related death				
No	762 (81.3%)	76 (81.7%)	1	838 (81.4%)
Yes	175 (18.7%)	17 (18.3%)		192 (18.6%)

* Few Patients had longer than 12 mth TOT, partly also beyond Recurrence





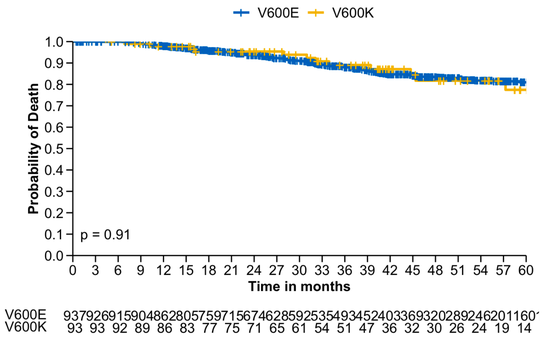


Table 3. Multivariable Cox Regression for Overall Survival

	Univariate cox regression		Multivariate, full model		backward selection*	
	HR (95% CI)	pvalue	HR (95% CI)	p-value	HR (95% CI)	p-value
AGE	1.03 (1.02-1.04)	<0.001	1.02 (1.01-1.04)	<0.001	1.02 (1.01-1.04)	<0.001
SEX						
M	1.26 (0.94-1.69)	0.116	1.11 (0.83-1.5)	0.474		
ECOG						
1	2.68 (1.69-4.23)	<0.001	1.95 (1.2-3.17)	0.007	1.92 (1.19-3.1)	0.007
2	12.56 (4.59-34.37)	<0.001	8.5 (3.06-23.57)	<0.001	8.14 (2.95-22.47)	<0.001
UK	1.35 (0.81-2.27)	0.251	1.24 (0.73-2.12)	0.432	1.25 (0.73-2.12)	0.421
VISTYPE						
Relapse	1.12 (0.83-1.5)	0.464	1.12 (0.82-1.51)	0.486		
BLST						
IIIB	2.24 (1-5.01)	0.049	1.82 (0.8-4.12)	0.15	1.92 (0.86-4.3)	0.113
IIIC	4.59 (2.14-9.83)	<0.001	3.58 (1.65-7.76)	0.001	3.74 (1.74-8.05)	<0.001
IIID	8.61 (3.54-20.94)	<0.001	6.58 (2.67-16.23)	<0.001	7.05 (2.89-17.21)	<0.001
OTH	5.43 (2.06-14.27)	<0.001	4.77 (1.78-12.74)	0.002	4.89 (1.83-13.06)	0.002
BRAF						
V600K	0.98 (0.6-1.62)	0.944	0.74 (0.45-1.24)	0.252		

SUMMARY AND CONCLUSION

- V600E and V600K mutations are not associated with a different outcome from adjuvant treatment with combined D/T.
- The findings offer no explanation for differences found in the Combi-AD trial, although part of these differences may have resulted from a different natural course of V600K^{mut} melanomas the placebo group.
- Longer follow-up will help to further confirm these results and also analyse the possible role of further treatments in the metastatic setting.

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