EMRseq: Registry based outcome analysis on 1,000 patients with BRAF V600 mutated metastatic melanoma in Europe treated with either immune checkpoint or BRAF-/MEK inhibition

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Background

In BRAF mutated metastatic melanoma, potential outcome differences for different first line choices of treatments including immunotherapy or BRAF-/MEK inhibition are not completely understood. We therefore analyzed the treatment patterns and outcome of systemic therapies for patients with BRAF mutated metastatic melanoma.

Study objectives

Primary outcomes of interest were overall survival (OS) and second progression free survival (PFS-2), stratified for upfront treatment decision of immunotherapy (IO) versus targeted therapy (TT). PFS-2 was defined as the interval from start of first line treatment to a progression after a 2nd line systemic treatment or death of any cause. Further endpoints regarding treatment patterns and outcome were evaluated including time on treatment (ToT), time to next treatment (TTNT) and second line treatments.

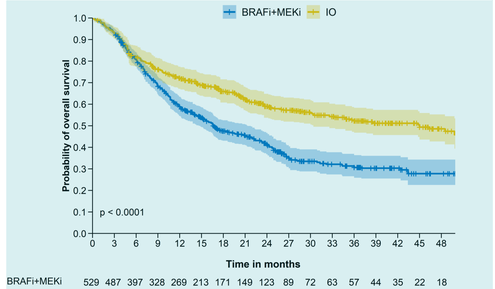
Methods

From the EUMelaReg treatment registry, patients fulfilling the following inclusion criteria were consecutively included until a number of 1,000 evaluable cases was reached. 1) Patients with unresectable metastatic melanoma and BRAF V600 mutation 2) First line treatment with either combined BRAF-/MEK inhibitor treatment (BRAF/MEK-i) or immune checkpoint inhibition (ICI) with PD-1 single agent or combined PD-1/CTLA-4 antibodies. Multivariable cox regression analysis as well as propensity score-based weighting were applied to control for bias from baseline imbalances.

Results

In total 529 (52.9 %) of the patients received BRAF/MEK-i, and 471 (47.1%) ICI. For various co-variates there were significant imbalances between strata, including number of metastatic sites, AJCC substage, serum LDH and ECOG performance status, with more favorable prognostic variables for patients receiving IO. The overall response rate (ORR) for BRAF/MEKi was significantly higher than for ICI (53.3% vs. 42.0%; p=0.0004), but for OS and PFS-2 the adjusted hazard ratios (HR) were significantly in favor for ICI (HR 0.62 and 0.66, respectively; p <0.0001). In 2nd line, patients switching from ICI to BRAF/MEK-i had again markedly higher ORR than patients switching vice versa (57.7% vs. 19.9%; P<0.0001), and also significantly longer unadjusted PFS (8.1 vs. 3.1 months; p <0.0001) and OS (15.7 vs. 10.6 months; p=0.01) after start of 2nd line treatment.

Figure 1: Adjusted OS grouped by 1st line therapy



OS: overall survival. BRAFi+MEKi: therapy with BRAF/MEK inhibitors. IO: Immuno-oncology. IPSW: inverse propensity score weighting for age, AJCC stage, ECOG, gender, LDH, melanoma subtype and no. of metastatic sites.

Table 1: Baseline patient characteristics

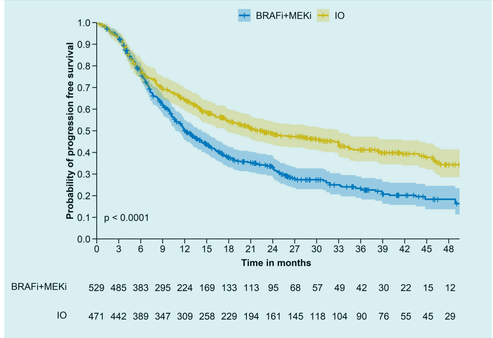
	BRAFi+MEKi (N=529)	IO (N=471)
Age at start of 1st line (years)		
Mean (SD)	61.6 (14.2)	62.5 (13.7)
Median [Min, Max]	61.0 [23.0, 95.0]	64.0 [25.0, 93.0]
Gender		
Female	222 (42.0%)	212 (45.0%)
Male	307 (58.0%)	259 (55.0%)
Charlson comorbidity score		
Mean (SD)	2.50 (1.52)	2.75 (1.66)
Median [Min, Max]	2.50 [0, 7.00]	3.00 [0, 7.00]
ECOG at start of 1st line		
0	204 (38.6%)	272 (57.7%)
1	130 (24.6%)	96 (20.4%)
≥ 2	90 (17.0%)	16 (3.4%)
Unknown	105 (19.8%)	87 (18.5%)
Prior adjuvant treatment		
No	474 (89.6%)	435 (92.4%)
Yes	55 (10.4%)	36 (7.6%)
Follow up		
Median follow-up (95% CI)	27.4 (25.8-31.7)	30.9 (28.7.34.6)

Table 2: Baseline tumor characteristics

	BRAFi+MEKi (N=529)	IO (N=471)
Brain metastases at start of 1st line		
Yes	142 (26.8%)	104 (22.1%)
No	387 (73.2%)	367 (77.9%)
AJCC Stage at start of 1st line		
Stage III, non-resectable	25 (4.7%)	13 (2.8%)
Stage IV M1a	73 (13.8%)	122 (25.9%)
Stage IV M1b	55 (10.4%)	71 (15.1%)
Stage IV M1c	234 (44.2%)	161 (34.2%)
Stage IV M1d	142 (26.8%)	104 (22.1%)
LDH at start of 1st line		
Normal	185 (35.0%)	238 (50.5%)
Increased	229 (43.3%)	155 (32.9%)
Unknown	115 (21.7%)	78 (16.6%)
Number of metastatic sites at start of 1st line		
1	141 (26.7%)	167 (35.5%)
2	128 (24.2%)	134 (28.5%)
≥ 3	260 (49.1%)	170 (36.1%)
T reatment regime		
BRAFi+MEKi	529 (100%)	0 (0%)
Anti-PD1	0 (0%)	303 (64.3%)
Ipi/Nivo	0 (0%)	168 (35.7%)

AJCC: American Joint Committee on Cancer. BRAFi+MEKi: therapy with BRAF/MEK inhibitors. IO: Immuno-oncology. ECOG: Eastern Cooperative Oncology Group. LDH: lactate dehydrogenase.

Figure 2: Adjusted PFS-2 grouped by 1st line therapy



PFS-2: Second PFS (progression free survival). BRAFi+MEKi: therapy with BRAF/MEK inhibitors. IO: Immuno-oncology. IPSW: inverse propensity score weighting for age, AJCC stage, ECOG, gender, LDH, melanoma subtype and no. of metastatic sites.

Table 2: Study outcomes grouped by 1st line therapy

	BRAFi+MEKi (N = 529)	IO (N = 471)	P value
Objective Remissions	282 (53.3%)	198 (42.0%)	0.0004
Median PFS-2 (95% CI)* [months]	12.3 (11.3-14.8)	21.9 (17.6-33.0)	< 0.0001
Median OS (95% CI)* [months]	16.9 (15.2-22.3)	45.0 (30.2-NA)	< 0.0001

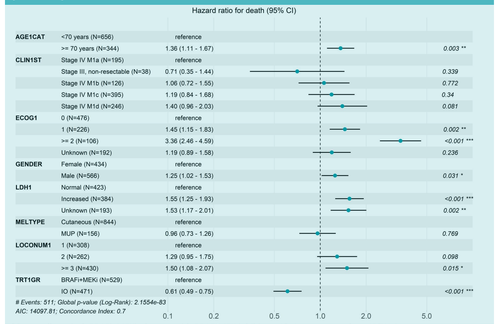
*Adjusted by inverse propensity score weighting for confounding factors (age, AJCC stage, ECOG, gender, LDH, melanoma subtype and no. of metastatic sites). BRAFi+MEKi: therapy with BRAF/MEK inhibitors. IO: Immuno-oncology. CI: confidence interval. OS: overall survival. PFS-2: Second PFS (progression free survival).

Table 3: Study outcomes grouped by 2nd line therapy

	BRAFi+MEKi (N = 213)	IO (N = 256)	P value
Objective Remissions	123 (57.7%)	51 (19.9%)	< 0.0001
Median PFS (95% CI) from start of 2nd line [months]	8.1 (6.7-9.8)	3.1 (2.7-4.4)	< 0.0001
Median OS (95% CI) from start of 2nd line [months]	15.7 (12-24.5)	10.6 (7.2-16.3)	0.01

BRAFi+MEKi: therapy with BRAF/MEK inhibitors. IO: Immuno-oncology. CI: confidence interval. OS: overall survival. PFS: progression free survival.

Figure 3: Multivariable cox regression for Adjusted OS (IPSW)



OS: overall survival. BRAFi+MEKi: therapy with BRAF/MEK inhibitors. IO: Immuno-oncology. IPSW: inverse propensity score weighting for age, AJCC stage, ECOG, gender, LDH, melanoma subtype and no. of metastatic sites. CLIN1ST: Clinical stage at start of 1st line therapy. ECOG1: ECOG performance status at start of 1st line therapy. LDH1: LDH at 1st line therapy. MELTYPE: melanoma subtype. LOCONUM1: number of metastatic sites at start of 1st line therapy. TRT1GR: treatment regimen of 1st line therapy.

Figure 4: Multivariable cox regression for adjusted OS (IPSW) by 1st line therapy option

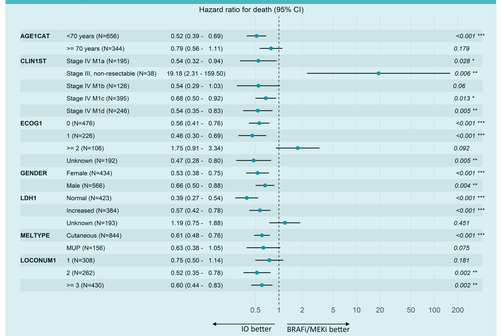


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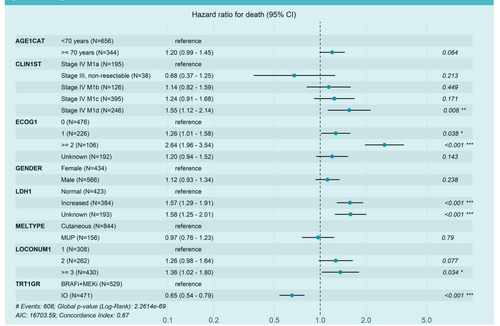
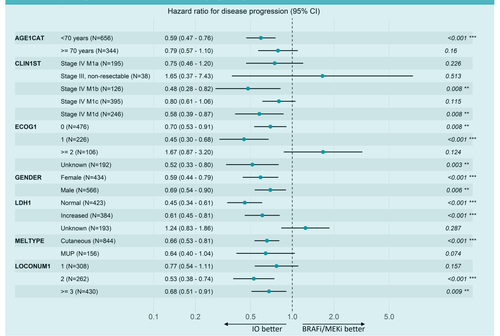
Figure 5: Multivariable cox regression for adjusted PFS-2 (IPSW)



PFS-2: Second PFS (progression free survival). BRAFi+MEKi: therapy with BRAF/MEK inhibitors. IO: Immuno-oncology. IPSW: inverse propensity score weighting for age, AJCC stage, ECOG, gender, LDH, melanoma subtype and no. of metastatic sites. CLIN1ST: Clinical stage at start of 1st line therapy. ECOG1: ECOG performance status at start of 1st line therapy. LDH1: LDH at 1st line therapy. MELTYPE: melanoma subtype. LOCONUM1: number of metastatic sites at start of 1st line therapy. TRT1GR: treatment regimen of 1st line therapy.

Figure 6: Multivariable cox regression for adjusted PFS-2 (IPSW) by 1st line therapy option



PFS-2: Second PFS (progression free survival). BRAFi+MEKi: therapy with BRAF/MEK inhibitors. IO: Immuno-oncology. IPSW: inverse propensity score weighting for age, AJCC stage, ECOG, gender, LDH, melanoma subtype and no. of metastatic sites. CLIN1ST: Clinical stage at start of 1st line therapy. ECOG1: ECOG performance status at start of 1st line therapy. LDH1: LDH at 1st line therapy. MELTYPE: melanoma subtype. LOCONUM1: number of metastatic sites at start of 1st line therapy. TRT1GR: treatment regimen of 1st line therapy.

Conclusions

The two BRAF V600 mutated cohorts had imbalances on key prognosis variables. After adjustment for these imbalances, upfront ICI resulted in significantly longer overall survival and PFS-2 as compared to BRAF/MEKi. Due to the nature of real-world observational data causing inherent imbalances in the treatments cohorts and being unable to account for potential unknown confounders, outcome parameters may still be biased despite adjustment efforts.