Efficiency of second-line BRAF/MEK inhibitors in BRAF^{V600} mutated metastatic melanoma patients after first-line immunotherapy failure. A EUMelaReg real-world study.

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BACKGROUND

- The use of BRAF/MEK inhibitors (BRAF/MEKi) in the first-line (1L) treatment has recently been deprioritized due to inferior outcomes compared to upfront immune checkpoint inhibitor (ICI) therapy. However, BRAF/MEKi are still the treatment of choice for BRAF mutated melanoma patients who have failed from 1L ICI.
- Efficacy benchmark data for second-line (2L) BRAF/MEKi therapy are sparse as the combination was initially developed for 1L use, lacking estimates for the impact of prior ICI therapy.
- We hence initiated a retrospective, non-interventional registry study to evaluate effectiveness of 2L BRAF/MEKi therapy following progression after upfront, anti-PD1-inhibitor based ICI therapy in one of the largest real-world populations available

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 2L compared to 1L BRAF/MEKi therapy.

SUMMARY AND CONCLUSION

- The use of BRAF/MEKi in the 2L after ICI failure does not compromise key outcomes, affirming the clinical benefit in this sequencing approach for BRAF^{V600} mutated melanoma.
- The results provide additional support for a preferred sequencing of 1L ICI and 2L BRAF/MEKi for BRAF^{V600} mutated melanoma patients.

METHODS

- **Study population:** Patients with BRAF^{V600} mutated non-resectable stage III or metastatic stage IV cutaneous melanoma who either received BRAF/MEKi in 2L after failure of 1L ICI or who received BRAF/MEKi in 1L were retrieved from the **European Melanoma Registry (EUMelaReg)** database. Patients pre-treated with adjuvant ICI or BRAF/MEKi were excluded.
- **Matching:** For adjustment of imbalances of prognostic factors between 1L and 2L patients, a 1:1 inverse propensity score-based matching for several prognostic factors was performed. Samples were matched for sex, age, melanoma type, type of prior ICI, ECOG, AJCC stage, baseline serum LDH, number of metastatic sites, Charlson comorbidity score and brain metastases.

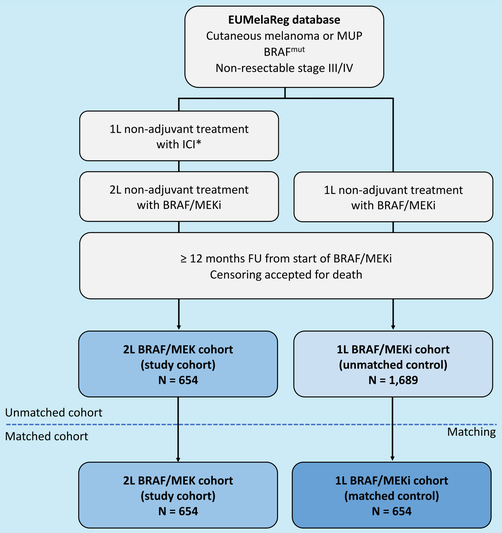


Figure 1: Flow chart illustrating the selected populations for analysis using real-world data from the EUMelaReg. BRAF/MEKi: BRAF/MEK inhibitor therapy; FU: follow-up; ICI: immune checkpoint inhibitor therapy; MUP: melanoma of unknown primary; mut: mutated; 1L/2L: first/second line. *ICI treatment includes anti-PD1 and/or anti-PD1/anti-CTLA4 antibodies. Matching was performed with an optimal matching algorithm using inverse propensity score matching.

RESULTS

- We identified 654 patients with 2L BRAF/MEKi therapy following prior frontline ICI therapy and 1,689 patients who received 1L BRAF/MEKi therapy and subsequent ICI therapy. These 654 patients were furthermore matched 1:1 to patients from the 1L cohort (**Table 1**).
- Kaplan-Meier estimates for PFS and TOT demonstrated slightly better outcomes for 2L BRAF/MEKi therapy with a longer **median PFS** (8.4 months vs. 7.7 months; p=0.01) and a longer median TOT (7.8 months vs. 6.2 months; p=0.002) for compared to 1L BRAF/MEKi (**Figure 2, Table 2**).
- **Median OS** measured either from start of 2L BRAF/MEKi (17.2 months) or from start of 1L BRAF/MEKi (16.0 months) was similar (p=0.73).
- 2L BRAF/MEKi resulted in an equal efficiency compared 1L with **ORR** of 56% vs. 54% and a **DCR** of 73% vs. 71%, respectively (**Table 2**).

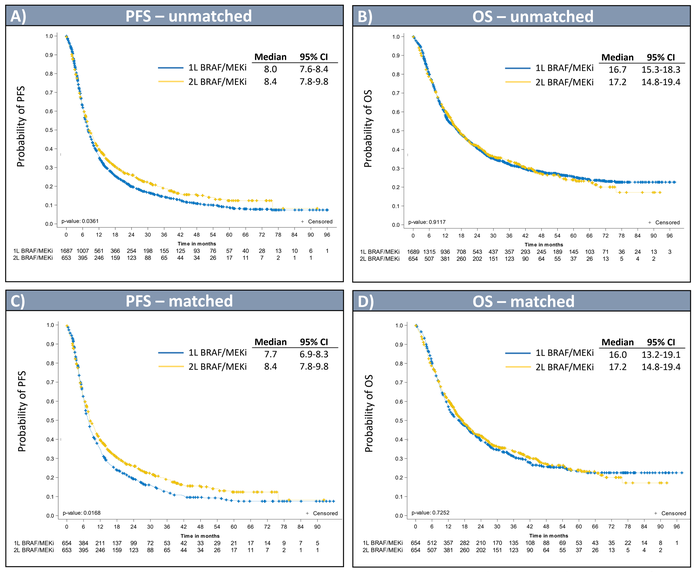
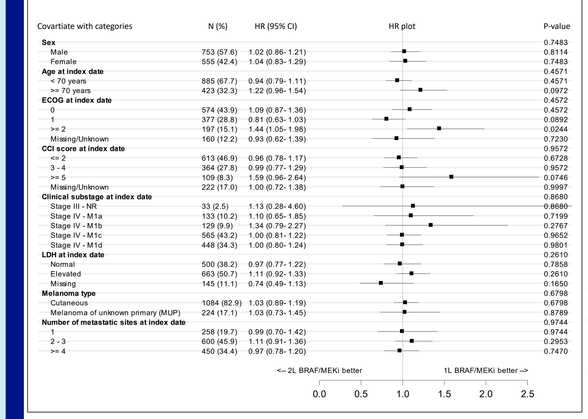


Figure 2: Kaplan-Meier curves of PFS and OS for patients treated with 2L (yellow lines) or 1L BRAF/MEKi (blue) for unmatched (A and B) and matched (C and D) cohorts. PFS, progression-free survival; OS, overall survival; 1L/2L, first/second line; CI, confidence interval.

	1L BRAF/MEKi Unmatched control (N = 1,689)	P-value	2L BRAF/MEKi Study cohort (N = 654)	P-value	1L BRAF/MEKi Matched control (N = 654)
Best response		0.61		0.61	
CR	229 (13.6%)		85 (13.0%)		81 (12.4%)
PR	678 (40.1%)		284 (43.4%)		269 (41.1%)
SD	333 (19.7%)		113 (17.3%)		122 (18.7%)
PD	308 (18.2%)		118 (18.0%)		137 (20.9%)
Not assessable	122 (7.2%)		44 (6.7%)		39 (6.0%)
Unknown/Missing	19 (1.1%)		10 (1.5%)		6 (0.9%)
ORR	907 (53.7%)	0.25	369 (56.4%)	0.32	350 (53.5%)
DCR	1,191 (70.5%)	0.17	480 (73.4%)	0.13	454 (69.4%)
Survival (95% CI; months)					
Median OS	16.7 (15.3-18.3)	0.91	17.2 (14.8-19.4)	0.73	16.0 (13.2-19.1)
Median PFS	8.0 (7.6-8.4)	0.04	8.4 (7.8-9.8)	0.02	7.7 (6.9-8.3)
Median TOT	6.1 (6.3-6.9)	0.003	7.8 (6.6-8.6)	0.002	6.2 (5.8-6.9)

Table 2: Therapy outcome post-ICI of 2L BRAF/MEKi and 1L BRAF/MEKi therapy (matched/unmatched cohort). N, Number of patients; CR, complete response; PR, partial remission; SD, stable disease; PD, progressive disease; DCR, disease control rate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TOT, time on treatment; CI, confidence interval.



Subgroup Analysis

Analyzing various subgroups for overall survival outcome in 1L vs. 2L using multivariate hazard ratios from Cox regression showed strong homogeneity for equality, except for patients with an ECOG-PS ≥2, elderly or severely comorbid patients, who might benefit less from 2L BRAF/MEKi after ICI failure.

Figure 3: Hazard ratios for OS for patients treated with 1L or 2L BRAF/MEKi. HRs and 95% CI from a multivariate cox regression model are reported for various subpopulations in patients treated with 2L BRAF/MEKi in comparison to 1L BRAF/MEKi. Stratified analyses in each category are adjusted for all other variables in the model. N: number of patients, ECOG, Eastern Cooperative Oncology Group; CCI, Charlson comorbidity index; NR, non-resectable; LDH, lactate dehydrogenase.

Table 1: Demographics and clinical characteristics for 2L and unmatched/matched 1L BRAF/MEKi cohort

	1L BRAF/MEKi Unmatched control (N = 1,689)	P-value	2L BRAF/MEKi Study cohort (N = 654)	P-value	1L BRAF/MEKi Matched control (N = 654)
Sex		0.35		0.74	
Male	1,018 (60.3%)		380 (58.1%)		373 (57.0%)
Female	671 (39.7%)		274 (41.9%)		281 (43.0%)
Age (years)		0.93		0.87	
Mean (SD)	61.4 (14.3)		61.4 (14.3)		61.4 (14.2)
Median [Min, Max]	62.0 [19, 95]		62.5 [17, 95]		61 [19, 94]
Melanoma type		0.46		0.16	
Cutaneous	1,403 (83.1%)		552 (84.4%)		532 (81.3%)
MUP	286 (16.9%)		102 (15.6%)		122 (18.7%)
BRAF mutation type		0.005		0.33	
V600D positive	36 (2.1%)		1 (0.2%)		6 (0.9%)
V600E positive	1067 (63.2%)		442 (67.6%)		441 (67.4%)
V600K positive	141 (8.4%)		63 (9.6%)		56 (8.6%)
V600R positive	11 (0.7%)		4 (0.6%)		3 (0.5%)
Other mutation	76 (4.5%)		23 (3.5%)		16 (2.4%)
Positive, unknown variant	358 (21.2%)		121 (18.5%)		132 (20.2%)
ECOG		0.76		0.84	
0	742 (43.9%)		292 (44.7%)		282 (43.1%)
1	503 (29.8%)		181 (27.7%)		196 (30.0%)
≥ 2	250 (14.8%)		100 (15.3%)		97 (14.8%)
Missing/Unknown	194 (11.5%)		81 (12.4%)		79 (12.1%)
LDH		0.13		0.41	
Normal	686 (40.6%)		261 (39.9%)		239 (36.5%)
Elevated	767 (45.4%)		320 (48.9%)		343 (52.4%)
Missing	236 (14.0%)		73 (11.2%)		72 (11.0%)
Charlson comorbidity score		0.25		0.41	
≤ 2	835 (49.4%)		294 (45.0%)		319 (48.8%)
3 - 4	445 (26.3%)		184 (28.1%)		180 (27.5%)
≥ 5	147 (8.7%)		61 (9.3%)		48 (7.3%)
Unknown/Missing	262 (15.5%)		115 (17.6%)		107 (16.4%)
AJCC stage		0.003		0.62	
Stage III - NR	102 (6.0%)		17 (2.6%)		16 (2.4%)
Stage IV - M1a	209 (12.4%)		74 (11.3%)		59 (9.0%)
Stage IV - M1b	208 (12.3%)		68 (10.4%)		61 (9.3%)
Stage IV - M1c	675 (40.0%)		275 (42.1%)		290 (44.3%)
Stage IV - M1d	495 (29.3%)		220 (33.6%)		228 (34.9%)
Number of metastatic sites		0.0009		0.38	
1	445 (26.4%)		139 (21.3%)		119 (18.2%)
2	454 (26.9%)		153 (23.4%)		157 (24.0%)
≥ 3	790 (46.8%)		362 (55.4%)		378 (57.8%)
Brain metastases		0.05		0.68	
Yes	495 (29.3%)		220 (33.6%)		228 (34.9%)
No	1,194 (70.7%)		434 (66.4%)		426 (65.1%)

N, number of patients; SD, standard deviation; MUP, melanoma of unknown primary; ECOG, Eastern Cooperative Oncology Group; LDH, Lactate dehydrogenase; AJCC, American Joint Committee on Cancer staging; NR, non-resectable.

- An exploratory stratification according to the best overall response of 1L ICI therapy shows that patients who primarily achieved a response to 1L ICI had significantly better outcomes for subsequent BRAF/MEKi.
- 69% of these achieved a partial or complete response with 2L BRAF/MEKi compared to 53.6% (p=0.003) in 535 1L ICI non-responders (**Table 3**).
- 1L ICI responders (n=119) patients had a median 2L PFS of 11.2 months (vs. 8.0 in non-responders; **Figure 4**).

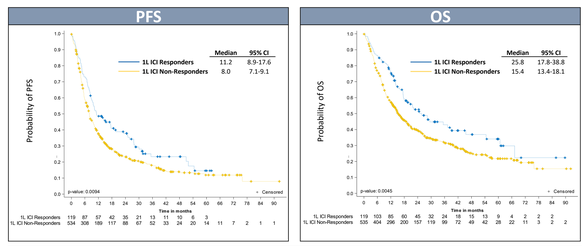


Figure 4: Subgroup analysis for PFS and OS: impact of best overall response to frontline ICI therapy for patients responding (blue lines) and not responding (yellow lines) to prior ICI therapy. PFS, progression-free survival; OS, overall survival; 1L, first line; ICI, immune checkpoint inhibitors; CI, confidence interval.

	1L ICI Responders (N = 119)	1L ICI Non-Responders (N = 535)	P-value
Best response 2L BRAF/MEKi			0.02
CR	25 (21.0%)	60 (11.2%)	
PR	57 (47.9%)	227 (42.4%)	
SD	14 (11.8%)	99 (18.5%)	
PD	16 (13.4%)	102 (19.1%)	
Not assessable	5 (4.2%)	39 (7.3%)	
Unknown/Missing	2 (1.7%)	8 (1.5%)	
ORR	82 (68.9%)	287 (53.6%)	0.003
DCR	96 (80.7%)	384 (71.8%)	0.05
Survival (95% CI; months) from start of 2L			
Median OS	25.8 (17.8-38.8)	15.4 (13.4-18.1)	0.005
Median PFS	11.2 (8.9-17.6)	8.0 (7.1-9.1)	0.01
Median TOT	9.7 (7.3-14.7)	7.2 (6.1-8.3)	0.13

Table 3: Outcome of 2L BRAF/MEKi stratified by 1L ICI Response. N, Number of patients; CR, complete response; PR, partial remission; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate; OS, overall survival; PFS, progression-free survival; TOT, time on treatment; 1/2L, first/second line; CI, confidence interval.

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European Melanoma Registry (EUMelaReg; www.eumelareg.org): This registry is a multi-center database run by a cross-national consortium of academic groups in Europe collecting and evaluating real-world melanoma cases with non-resectable stage III or metastatic stage IV melanoma. Data has been captured since 2018 entered voluntarily into the system by participating centers.