The role of BRAF/MEKi rechallenge in BRAF^{V600} mutated melanoma patients. Insights from a EUMelaReg real-world study.

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BACKGROUND

- For patients with advanced BRAF^{V600} mutated melanoma who have completed both BRAF-plus-MEK-inhibitor (BRAF/MEKi) therapy and immune-checkpoint-inhibitor (ICI) therapy, treatment options are limited.
- Rechallenging patients with BRAF/MEKi in later-lines can be successful in patients with BRAF^{V600} mutated melanoma who have progressed on other treatments.
- We conducted a retrospective registry study evaluating BRAF/MEKi rechallenge following prior ICI therapy, stratified by BRAF/MEKi pre-treatment (as either none, adjuvant, or non-adjuvant pre-treatment). BRAF/MEKi naive patients receiving second-line (2L) BRAF/MEKi therapy after prior ICI therapy served as a control cohort.

OBJECTIVES

- Overall response rate (ORR) for BRAF/MEKi rechallenge after ICI failure served as primary endpoint.
- Secondary endpoints were progression-free survival (PFS), overall survival (OS) and disease-control rates (DCR) from start of BRAF/MEKi rechallenge.

SUMMARY AND CONCLUSION

- Rechallenge with BRAF/MEKi therapy for BRAF^{V600} mutated melanoma under real-world conditions lead to clinically meaningful benefit in terms of ORR and survival outcomes in patients who already received an initial BRAF/MEKi therapy for advanced disease, or as an adjuvant pre-treatment.
- Although response rates were inferior compared to BRAF/MEKi naive patients in general, patients with adjuvant BRAF/MEKi pre-treatment achieved survival outcomes comparable to BRAF/MEKi naive patients.
- Rechallenging patients with BRAF/MEKi therapy represents a viable treatment option for patients who have failed on immunotherapy.

METHODS

- **Study population:** Patients with BRAF^{V600} mutated non-resectable stage III or metastatic stage IV melanoma who were rechallenged with combined BRAF/MEKi therapy following ICI therapy (single-agent anti-PD1 or combination therapy) were retrieved from the **European Melanoma Registry (EUMelaReg)** database.
- These patients had all failed ICI following prior treatment with either adjuvant BRAF/MEKi (adjuvant pre-treated cohort) or non-adjuvant BRAF/MEKi (non-adjuvant pre-treated cohort) treatment.
- **Matching:** Sensitivity analyses compared rechallenged patients with BRAF/MEKi-naive patients treated with non-adjuvant BRAF/MEKi after ICI failure (control cohort). In order to prevent statistical bias from selection of patients, a 1:1 covariate-based matching of the rechallenge and control populations was performed on several prognostic factors.
- Statistics are provided with nominal p-value throughout, no multiplicity adjustment was performed

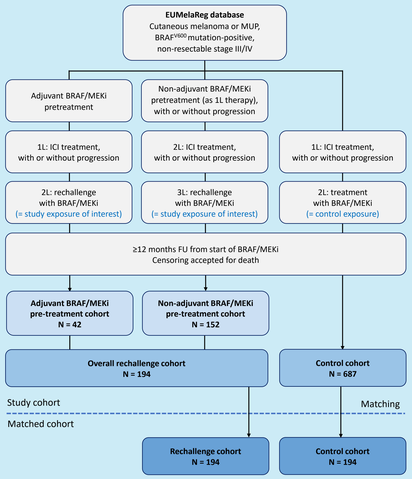
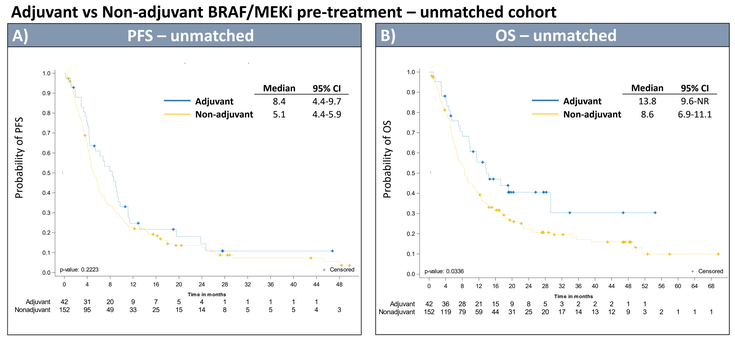


Figure 1: Flow chart illustrating the selection criteria for this multicentre analysis using real-world data from the EUMelaReg. Eligible patients were stratified into those who received their first, initial BRAFi or BRAF/MEKi therapy as adjuvant (adjuvant pre-treatment cohort), and those who received such pre-treatment for advanced, non-resectable or metastatic melanoma (non-adjuvant pre-treatment cohort). Patients from the EUMelaReg registry treated with 2L BRAF/MEKi served as a pool for a matching control cohort. N, number of patients; MUP, melanoma of unknown primary; ICI, immune checkpoint inhibitor; FU, follow-up; 1L/2L/3L, first/second/third line.

RESULTS

- We identified 42 (21.6%) patients in the adjuvant and 152 (78.4%) in the non-adjuvant BRAF/MEKi pre-treatment cohort with ORRs of 30.3% and 26.2%, and DCRs of 61.8% and 42.9%, respectively (**Table 1 and 2**).
- Kaplan-Meier estimates showed a significantly longer median OS (13.8 months vs 8.6 months; p=0.03) and a (non-significant) longer median PFS (8.6 months vs 5.1 months) for patients in the adjuvant compared to the non-adjuvant BRAF/MEKi pre-treatment cohort (**Figure 2 Panel A, B**).
- Comparison of rechallenged patients with BRAF/MEKi-naive patients (control cohort) revealed significantly shorter median PFS (5.6 months vs 8.3 months; p<0.0001) and OS (9.6 months vs 16.7 months; p<0.0001) for the rechallenge group (**Figure 2 Panel C, D**).

Adjuvant vs Non-adjuvant BRAF/MEKi pre-treatment – unmatched cohort



Rechallenge vs 2L BRAF/MEKi control (BRAF/MEKi-naive) – unmatched cohort

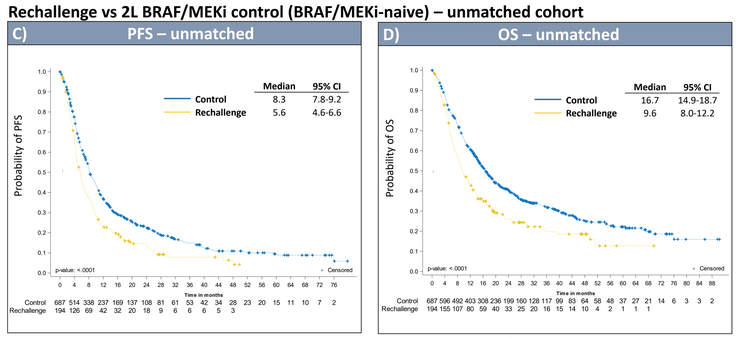


Figure 2: Kaplan-Meier curves of PFS and OS stratified by (A+B) adjuvant BRAF/MEKi pre-treatment (blue) or non-adjuvant BRAF/MEKi pre-treatment (yellow) cohort and (C+D) control (blue) or rechallenge (yellow) cohort. cohort. PFS, progression-free survival; OS, overall survival; CI, confidence interval.

- In order to prevent statistical bias from selection of patients, a protocol-defined, covariate-based 1:1 matching procedure was applied. 194 patients constituted the matching control cohort with BRAF/MEKi-naive population. The matching using inverse propensity score weighting resulted in well-balanced clinical characteristics among both cohorts (**Table 1**).
- The outcomes were significantly better in BRAF/MEKi-naive patients compared to the rechallenge cohort with ORR 54.6% (p<0.0001), median OS (16.9 months, p=0.0026) and PFS (7.6 months; p=0.012) (**Figure 3**).

Rechallenge vs 2L BRAF/MEKi control (BRAF-naive) – matched cohort

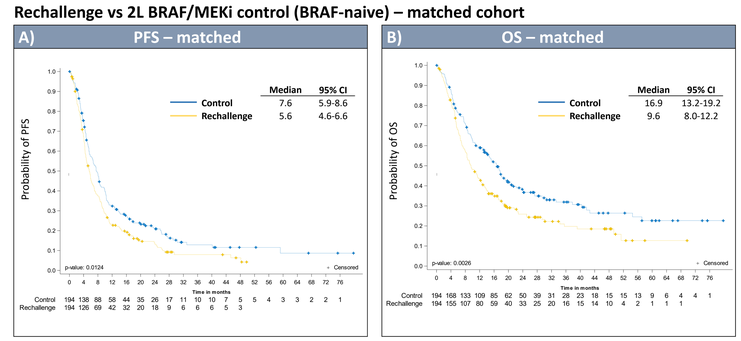


Figure 3: Kaplan-Meier curves of (A) PFS and (B) OS for the rechallenge cohort (yellow) and the matching control cohort (blue). PFS, progression-free survival; OS, overall survival; CI, confidence interval.

	Adjuvant BM pre-treatment (N = 42)	Non-adjuvant BM pre-treatment (N = 152)	P-value	BRAF/MEKi Rechallenge Total (N = 194)	No rechallenge: Matched control (N = 194)	P-value
BOR to rechallenge			0.15			<0.0001
CR	4 (9.5%)	13 (8.6%)		17 (8.8%)	18 (9.3%)	
PR	7 (16.7%)	33 (21.7%)		40 (20.6%)	88 (45.4%)	
SD	7 (16.7%)	48 (31.6%)		55 (28.4%)	39 (20.1%)	
PD	18 (42.9%)	38 (25.0%)		56 (28.9%)	35 (18.0%)	
Missing	6 (14.3%)	20 (13.2%)		26 (13.4%)	14 (7.2%)	
DCR	18 (42.9%)	94 (61.8%)	0.03	112 (57.7%)	145 (74.7%)	0.0006
ORR	11 (26.2%)	46 (30.3%)	0.70	57 (29.4%)	106 (54.6%)	<0.0001
Survival analysis (95% CI) from date of rechallenge						
Median OS	13.8 (9.6-NR)	8.6 (6.9-11.1)	0.03	9.6 (8.0-12.2)	16.9 (13.2-19.2)	0.003
Median PFS	8.4 (4.4-9.7)	5.1 (4.4-5.9)	0.22	5.6 (4.6-6.6)	7.6 (5.9-8.6)	0.01
Median TOT	7.4 (4.3-11.4)	4.9 (4.3-5.9)	0.11	5.5 (4.6-6.4)	7.3 (5.7-9.0)	0.02

Table 2: Treatment outcomes for the adjuvant/non-adjuvant and rechallenge/matched control cohort. N, Number of patients; BM, BRAF/MEKi; BOR, best overall response; 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; NR, not reached.

Table 1: Demographics for the adjuvant/non-adjuvant and rechallenge/unmatched/matched control cohort (BRAF/MEKi-naive)

	Adjuvant vs Non-adjuvant BRAF/MEKi pre-treatment			Rechallenge vs BRAF naive 2L Control unmatched			Rechallenge vs BRAF naive 2L Control matched		
Demographic variables at date of re-challenge	**Adjuvant BM pre-treatment (N = 42)**	**Non-adjuvant BM pre-treatment (N = 152)**	**P-value**	**Rechallenge Total (N = 194)**	**No rechallenge: Unmatched Control (N = 687)**	**P-value**	**Rechallenge Total (N = 194)**	**No rechallenge: Matched Control (N = 194)**	**P-value**
Sex			0.86			0.81			0.84
Male	23 (54.8%)	87 (57.2%)		110 (56.7%)	397 (57.8%)		110 (56.7%)	107 (55.2%)	
Female	19 (45.2%)	65 (42.8%)		84 (43.3%)	290 (42.2%)		84 (43.3%)	87 (44.8%)	
Age (years)			0.88			0.01			
Mean (SD)	58.6 (13.7)	58.2 (13.9)		58.3 (13.8)	61.2 (14.4)		58.3 (13.8)	57.9 (14.8)	
Median [Min, Max]	60.0 [30, 82]	59.0 [20, 88]		59.0 [20, 88]	61.2 (14.4)		59.0 [20.0, 88.0]	57.0 [17.0, 91.0]	
Type of prior ICI			1.00			<0.0001			1.00
Anti-PD1	13 (31.0%)	49 (32.2%)		62 (32.0%)	392 (57.1%)		62 (32.0%)	62 (32.0%)	
Anti-PD1/anti-CTLA4	29 (69.1%)	103 (67.8%)		132 (68.0%)	295 (42.9%)		132 (68.0%)	132 (68.0%)	
Melanoma type			0.21			1.00			1.00
Cutaneous	39 (92.9%)	128 (84.2%)		167 (86.1%)	589 (85.7%)		167 (86.1%)	166 (85.6%)	
MUP	3 (7.1%)	24 (15.8%)		27 (13.9%)	98 (14.3%)		27 (13.9%)	28 (14.4%)	
ECOG			0.21			0.63			0.96
0	17 (40.5%)	62 (40.8%)		79 (40.7%)	308 (44.8%)		79 (40.7%)	78 (40.2%)	
1	10 (23.8%)	45 (29.6%)		55 (28.4%)	193 (28.1%)		55 (28.4%)	59 (30.4%)	
≥2	5 (11.9%)	28 (18.4%)		33 (17.0%)	109 (15.9%)		33 (17.0%)	33 (17.0%)	
Unknown/Missing	10 (23.8%)	17 (11.2%)		27 (13.9%)	77 (11.2%)		27 (13.9%)	24 (12.4%)	
LDH			1.00			0.03			0.82
Normal	14 (33.3%)	49 (32.2%)		63 (32.5%)	283 (41.2%)		117 (60.3%)	114 (58.8%)	
Elevated	25 (59.5%)	92 (60.5%)		117 (60.3%)	341 (49.6%)		63 (32.5%)	68 (35.1%)	
Missing	3 (7.1%)	11 (7.2%)		14 (7.2%)	63 (9.2%)		14 (7.2%)	12 (6.2%)	
Charlson comorbidity score*			0.09			0.0002			0.99
≤2	29 (69.1%)	86 (56.6%)		115 (59.3%)	305 (44.4%)		115 (59.3%)	116 (59.8%)	
3-4	10 (23.8%)	28 (18.4%)		38 (19.6%)	188 (27.4%)		38 (19.6%)	38 (19.6%)	
≥5	2 (4.8%)	20 (13.2%)		22 (11.3%)	63 (9.2%)		22 (11.3%)	20 (10.3%)	
Unknown	1 (2.4%)	18 (11.8%)		19 (9.8%)	131 (19.1%)		19 (9.8%)	20 (10.3%)	
AJCC stage			0.26			<0.0001			0.73
Stage III – NR	-	3 (2.0%)		3 (1.6%)	16 (2.3%)		3 (1.5%)	1 (0.5%)	
Stage IV- M1a	3 (7.1%)	7 (4.6%)		10 (5.2%)	74 (10.8%)		10 (5.2%)	6 (3.1%)	
Stage IV- M1b	5 (11.9%)	9 (5.9%)		14 (7.2%)	66 (9.6%)		14 (7.2%)	15 (7.7%)	
Stage IV- M1c	15 (35.7%)	41 (27.0%)		56 (28.9%)	295 (42.9%)		56 (28.9%)	60 (30.9%)	
Stage IV- M1d	19 (45.2%)	92 (60.5%)		111 (57.2%)	236 (34.4%)		111 (57.2%)	112 (57.7%)	
Number of metastatic sites			0.21			0.86			0.53
1	12 (28.6%)	26 (17.1%)		38 (19.6%)	137 (19.9%)		38 (19.6%)	32 (16.5%)	
2	10 (23.8%)	33 (21.7%)		43 (22.2%)	164 (23.9%)		43 (22.2%)	51 (26.3%)	
≥3	20 (47.6%)	93 (61.2%)		113 (58.2%)	386 (56.2%)		113 (58.2%)	111 (57.2%)	

N, number of patients; BM, BRAF/MEKi; SD, standard deviation; ICI, immune checkpoint inhibition; MUP, melanoma of unknown primary; ECOG, Eastern Cooperative Oncology Group; LDH, Lactate dehydrogenase; AJCC, American Joint Committee on Cancer staging version 8; NR, non-resectable; 2L, second line. *CCI not considering current metastatic disease.

- An exploratory subgroup analysis showed that patients who discontinued initial BRAF/MEKi therapy due to disease progression experienced less favorable outcomes upon rechallenge compared to those who stopped treatment for other reasons, including side effects.
- Patients without progression had significantly longer median PFS (6.9 months vs 4.6 months; p=0.04) and median OS (12.6 months vs 7.0 months; p=0.006) compared to patients perceiving progression as best overall response of initial BRAF/MEKi therapy.

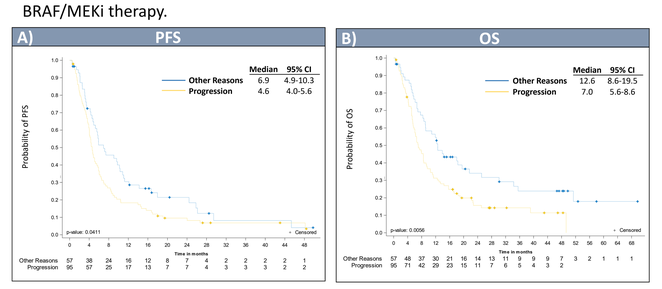


Figure 4: Subgroup analysis displaying the impact of the reason of end-of-therapy of the initial BRAF/MEKi therapy. Survival outcome calculated for 152 patients undergoing rechallenge after earlier non-adjuvant BRAF/MEKi pre-treatment. PFS, progression-free survival; OS, overall survival; CI, confidence 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.