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Original research

BRAF/MEK inhibitor rechallenge in patients with non-resectable or metastatic BRAF V600-mutated melanoma: A stratified, controlled, retrospective EUMelaReg multicenter study

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ABSTRACT

Background: Therapeutic options for BRAF^{V600}-mutant melanoma in patients who progress on BRAF/MEK-inhibitors (BRAF/MEKi) and immune-checkpoint-inhibitor (ICI) therapy, are limited. We conducted a retrospective registry study to investigate post-ICI rechallenge with BRAF/MEKi, stratified by type of initial BRAF/MEKi therapy.

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Real-world-data
Rechallenge

Methods: This retrospective study analysed patients from the EUMelaReg registry, who received adjuvant or first-line (1 L) BRAF/MEKi in the advanced setting, followed by ICI therapy and were later retreated with BRAF/MEKi. Overall response rate (ORR) for rechallenge served as primary endpoint, disease-control rate (DCR), progression-free survival (PFS), and overall survival (OS) were further endpoints. A covariate-matched control group of patients who received BRAF/MEKi only after 1 L ICI failure was selected for comparison.
Results: Among patients previously treated with adjuvant (n = 42) or non-adjuvant (n = 142) BRAF/MEKi, rechallenge after one interim ICI line resulted in ORRs of 26.2 % and 30.3 % and DCRs of 42.9 % and 61.8 %, respectively. Median PFS was 8.4 and 5.1 months, median OS 13.8 and 8.6 months, respectively. Overall, the rechallenge group had a 1-year OS of 43.2 %, lower than the matched control (58.9 %). The adjuvant subgroup was similar to control (55.4 %), while the advanced subgroup showed notably poorer survival (39.9 %). Subgroup analyses showed that both the pre-ICI response to BRAF/MEKi treatment and progressive disease prior to ICI were associated with outcome of the BRAF/MEKi rechallenge.
Conclusion: Rechallenge with BRAF/MEKi therapy under real-world conditions for advanced melanoma provides a valid treatment option. For patients who received their initial BRAF/MEKi therapy as adjuvant therapy there seems to be only limited impairment of outcomes.

1. Introduction

Around 330,000 cases of melanoma are diagnosed worldwide each year, resulting in approximately 58,000 deaths. In Europe, the 5-year prevalence is around 570,000 patients who either live with melanoma or are melanoma survivors. Around 50 % of patients with melanoma have *BRAF* mutations resulting in constitutive activation of MEK and ERK signalling, providing therefore a rationale for combined BRAF-MEK inhibitor (BRAF/MEKi) therapy [1]. *BRAF*-targeting combination therapy with tyrosine kinase inhibitors and anti-PD-1 and anti-CTLA-4 immune checkpoint inhibitor (ICI) therapy have revolutionized treatment of cutaneous melanoma, following a series of landmark approvals from 2011 onward [1,2]. Recently, the optimal sequencing strategy of both approaches has been elucidated by two randomised controlled trials, *DREAMSeq* and *SECOMBIT* [3–5]. Based on these trials, ICI therapy is recommended as the first-line (1 L) therapy of choice for advanced melanoma, regardless of *BRAF* mutational status. For patients with $BRAF^{V600}$-mutated melanoma, second-line (2 L) BRAF/MEKi therapy is current standard of care [6–9]. For resectable stage III melanoma, BRAF/MEKi and ICI therapy are generally considered to be equivalent treatment options for patients with $BRAF^{V600}$-mutant melanoma [6–8].

The 1 L use of BRAF/MEKi is currently limited to patients who require a rapid tumour response. This includes patients with poor performance status, high levels of lactate dehydrogenase (LDH), high tumour burden, an aggressive course of the disease, or symptomatic metastases particularly in the brain. Similarly, patients with contraindications for ICI or with prior adjuvant ICI therapy remain candidates for 1 L BRAF/MEKi therapy. However, regardless of the sequential approach chosen, there is no established, evidence-based therapy for patients who progress after both treatment options. Clinical trials or rechallenge are recommended options, as late-line chemotherapy e.g. with dacarbazine resulted in very modest response rates of 5–12 % only [6,7].

The rationale for rechallenge with BRAF/MEKi is based on the hypothesis that, in patients developing resistance, repeated treatment after a break ('drug holidays') or an intermittent, distinct therapy may result in clinical benefit due to melanoma cells' ability to re-switch or alter their resistance phenotype [10–13]. Small, prospective phase II trials investigating BRAF/MEKi rechallenge with only short breaks after initial BRAFi-monotherapy or BRAF/MEKi therapy yielded overall response rates (ORR) of 10–32 % with a median progression-free survival (PFS) of 2–5 months [14–16]. Higher ORR (28 % and 43 %) and equal PFS medians (5.0 months) were reported in two retrospective studies with longer BRAF/MEKi-free intervals and, in part, intermittent therapies [17,18]. Recent retrospective studies have reported ORRs in the range of 28–43 % and median PFS of 4.4–4.8 months for subsequent third-line (3 L) BRAF/MEKi rechallenge, presupposing intermittent, 2 L ICI therapy [19–22].

Here, we report real-world efficacy data from a retrospective, controlled, international registry study evaluating BRAF/MEKi rechallenge after a sequence of upfront BRAF/MEKi treatment follows by ICI. We further stratified in our analysis whether the initial BRAF/MEKi therapy was given either as 1 L therapy for non-resectable or metastatic melanoma, or as adjuvant therapy for resectable stage III melanoma. BRAFi-naive patients receiving 2 L BRAF/MEKi therapy after prior 1 L ICI therapy served as an internal benchmarking control cohort.

2. Methods

2.1. Study design and patient selection

This retrospective non-interventional, multicentre registry study included patients from the European Melanoma Registry, (EUMelaReg; www.eumelareg.org) database with $BRAF^{V600}$-mutation positive cutaneous melanoma or melanoma of unknown primary (MUP). At time of selection, all patients had stage III/IV non-resectable or metastatic melanoma according to the American Joint Committee on Cancer's (AJCC) 8th edition for melanoma staging [23]. Patients were eligible for inclusion if they had been rechallenged with combined BRAF/MEKi therapy following ICI therapy given as 1 L or 2 L therapy for non-resectable or metastatic melanoma. Eligible patients were also required to have a documented follow-up of at least 12 months after BRAF/MEKi rechallenge. ICI therapy comprised either anti-PD-1 monotherapy or anti-PD-1/CTLA-4 combination therapy. Patients had received their initial BRAF/MEKi treatment course either as adjuvant therapy for resectable stage III melanoma, or as 1 L therapy for advanced melanoma.

The primary outcome variable was ORR of BRAF/MEKi rechallenge in terms of achieved complete responses (CR) or partial responses (PR). Overall survival (OS) and PFS as well as the disease control rate (DCR) constituted secondary outcomes. CR and PR rates and time-to-event endpoints were analysed separately for patients who received their initial BRAF/MEKi either in the adjuvant setting, or as a 1 L therapy for advanced melanoma. Patients' demographic and clinical characteristics were described and – as an explorative objective – analysed in relation to response rates and time-to-event outcomes. For patients who received initial BRAF/MEKi as 1 L therapy for advanced melanoma, best overall response and reason for end of treatment (progressive disease [PD] or other) were assessed for sub-stratification purposes too. The study did not assess safety outcomes.

CR, PR, stable disease (SD), and PD were assessed according to clinical practice in line with established criteria, but not always strictly by RECIST definitions [24]. The start date of BRAF/MEKi rechallenge served as index date for the calculation of PFS (PD or death of any cause; censored in case of a documented next line of therapy without documented progression) and OS (death of any cause; censored at last date the patient was known to be alive).

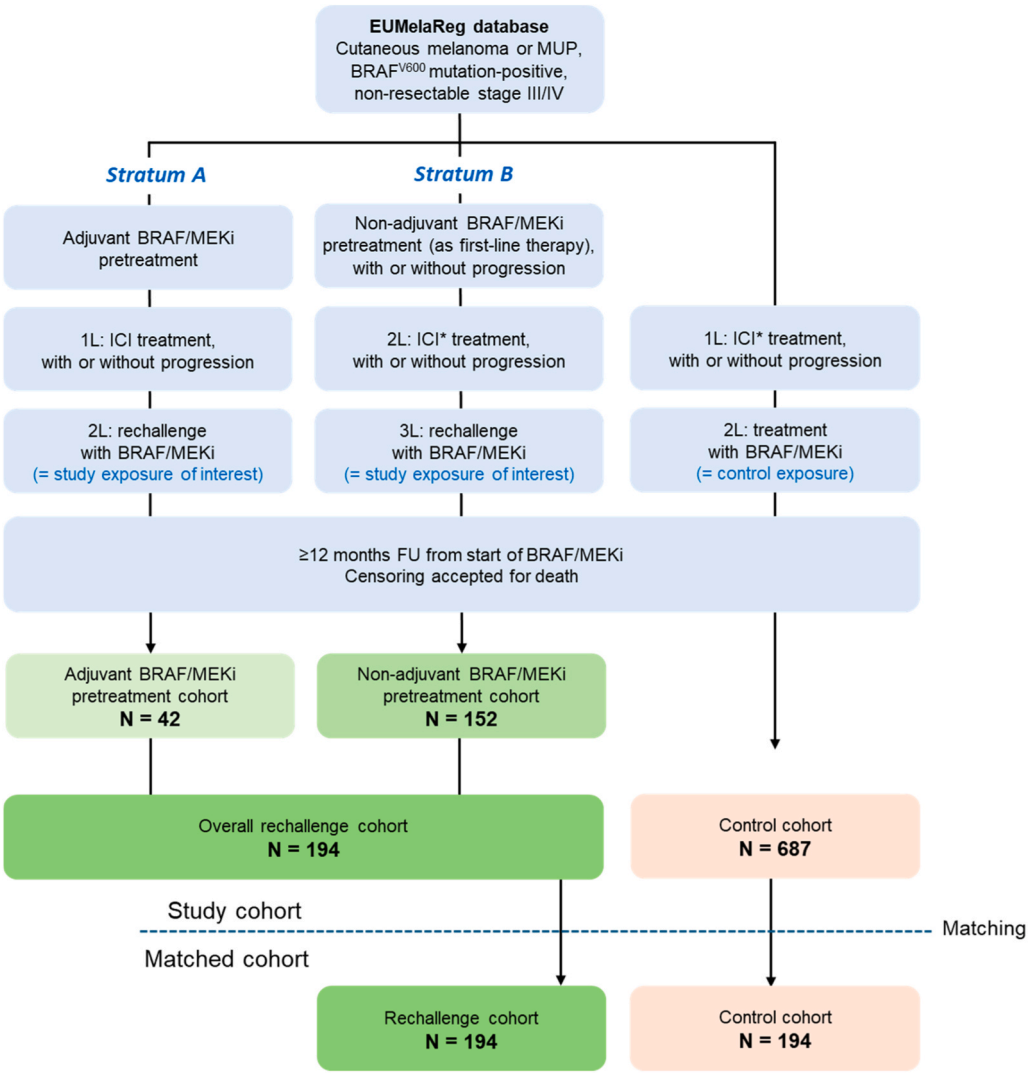

Fig. 1. Flow chart illustrating the selection criteria for this multicentre analysis using real-world data from the EUMelaReg. Eligible patients were stratified into those who received their first, initial BRAF or BRAF/MEK inhibitor (BRAF/MEKi) therapy as adjuvant treatment, and those who received such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

2.2. Statistical considerations and analysis

The planned sample size of the BRAF/MEKi rechallenge cohort was around 200 patients. For a protocol-defined sensitivity analysis (Suppl. Figure S2), an additional control cohort of at least 1000 patients was considered, to create a 1:1 matched control cohort identical in size to the rechallenge cohort.

For the control cohort, only patients who received 1 L ICI therapy and subsequent, BRAF/MEKi therapy as 2 L treatment were selected (Fig. 1). The index date for time-to-event evaluation of the control (i.e. non-rechallenge) cohort was accordingly defined as the start of 2 L BRAF/MEKi after 1 L ICI therapy in BRAF/MEKi-naive patients.

Descriptive statistics were used to summarize baseline study cohort characteristics. Statistics for time-to-event outcomes as OS, PFS or time-on-treatment (TOT) used Kaplan-Meier method to generate survival plots and estimate medians with 95 % confidence intervals (CI) and event rates with 95 % CI. P-values were derived by log-rank-statistics. Regression models assessed the impact of covariates of interest on the primary outcome variable, applying univariable and multivariable logistic regression analysis. OS as secondary outcome was assessed using univariable and multivariable Cox regression. For multivariable regression analyses, a stepwise backward selection was performed, starting with a full model, and using an entry level of $p = 0.2$ and a stay level of $p = 0.1$ for covariates to enter the variable selection and to stay in the model in each step of the process, respectively.

Covariate-based matching was performed for several prognostic factors at index date with an optimal matching algorithm using inverse propensity score weighting. Samples were matched 1:1 between the rechallenge set and the matching cohort for sex, age, Eastern Cooperative Oncology Group performance status (ECOG-PS), clinical stage, LDH status, melanoma type, number of metastatic sites and Charlson comorbidity index (CCI) score to address anticipated baseline imbalances and eliminate selection bias. SAS statistical software (version 9.4 or higher) and R Statistical Software 4.3 were used for all statistical analyses.

3. Results

3.1. Study population and treatment exposure

A total of 194 patients fulfilled the inclusion criteria for the study population. Of these patients, 42 (21.6 %) had received BRAF/MEKi as

Table 1
Demographics for rechallenge cohort (strata: [A] initial BRAF/MEKi as adjuvant pretreatment and [B] initial BRAF/MEKi pretreatment non-adjuvant) and for the unmatched control cohort (no BRAF/MEKi rechallenge).

	Adjuvant BRAF/MEKi pretreatment [A] (N = 42)	**Non-adjuvant BRAF/MEKi pretreatment [B] (N = 152)**	**P-value** (A vs B)	**BRAF/MEKi Rechallenge Total (N = 194)**	**TT naive Control (N = 687)**	**P-value** (Rechallenge vs. Control)
Sex			0.86			0.81
Male	23 (54.8 %)	87 (57.2 %)		110 (56.7 %)	397 (57.8 %)	
Female	19 (45.2 %)	65 (42.8 %)		84 (43.3 %)	290 (42.2 %)	
Age (years)			0.88			0.01
Mean (SD)	58.6 (13.7)	58.2 (13.9)		58.3 (13.8)	61.2 (14.4)	
Median [Min, Max]	60.0 [30, 82]	59.0 [20, 88]		59.0 [20, 88]	61.2 (14.4)	
Age at first BRAF/MEKi			0.67			0.0007
< 70 years	35 (83.3 %)	120 (79.0 %)		155 (79.9 %)	462 (67.2 %)	
≥ 70 years	7 (16.7 %)	32 (21.1 %)		39 (20.1 %)	225 (32.8 %)	
Age at index*			0.84			0.02
< 70 years	33 (78.6 %)	115 (75.7 %)		148 (76.3 %)	462 (67.2 %)	
≥ 70 years	9 (21.4 %)	37 (24.3 %)		46 (23.7 %)	225 (32.8 %)	
Type of prior ICI			1.00			< 0.0001
Anti-PD-1	13 (31.0 %)	49 (32.2 %)		62 (32.0 %)	392 (57.1 %)	
Anti-PD-1/anti-CTLA-4	29 (69.1 %)	103 (67.8 %)		132 (68.0 %)	295 (42.9 %)	
Melanoma type			0.21			1.00
Cutaneous	39 (92.9 %)	128 (84.2 %)		167 (86.1 %)	589 (85.7 %)	
MUP	3 (7.1 %)	24 (15.8 %)		27 (13.9 %)	98 (14.3 %)	
ECOG			0.21			0.63
0	17 (40.5 %)	62 (40.8 %)		79 (40.7 %)	308 (44.8 %)	
1	10 (23.8 %)	45 (29.6 %)		55 (28.4 %)	193 (28.1 %)	
≥ 2	5 (11.9 %)	28 (18.4 %)		33 (17.0 %)	109 (15.9 %)	
Unknown/Missing	10 (23.8 %)	17 (11.2 %)		27 (13.9 %)	77 (11.2 %)	
LDH			1.00			0.03
Normal	14 (33.3 %)	49 (32.2 %)		63 (32.5 %)	283 (41.2 %)	
Elevated	25 (59.5 %)	92 (60.5 %)		117 (60.3 %)	341 (49.6 %)	
Missing	3 (7.1 %)	11 (7.2 %)		14 (7.2 %)	63 (9.2 %)	
CCI			0.09			0.0002
≤ 2	29 (69.1 %)	86 (56.6 %)		115 (59.3 %)	305 (44.4 %)	
3–4	10 (23.8 %)	28 (18.4 %)		38 (19.6 %)	188 (27.4 %)	
≥ 5	2 (4.8 %)	20 (13.2 %)		22 (11.3 %)	63 (9.2 %)	
Unknown	1 (2.4 %)	18 (11.8 %)		19 (9.8 %)	131 (19.1 %)	
AJCC stage			0.26			< 0.0001
Stage III - NR	0 (0.0 %)	3 (2.0 %)		3 (1.6 %)	16 (2.3 %)	
Stage IV- M1a	3 (7.1 %)	7 (4.6 %)		10 (5.2 %)	74 (10.8 %)	
Stage IV- M1b	5 (11.9 %)	9 (5.9 %)		14 (7.2 %)	66 (9.6 %)	
Stage IV- M1c	15 (35.7 %)	41 (27.0 %)		56 (28.9 %)	295 (42.9 %)	
Stage IV- M1d	19 (45.2 %)	92 (60.5 %)		111 (57.2 %)	236 (34.4 %)	
N° of metastatic sites			0.21			0.86
1	12 (28.6 %)	26 (17.1 %)		38 (19.6 %)	137 (19.9 %)	
2	10 (23.8 %)	33 (21.7 %)		43 (22.2 %)	164 (23.9 %)	
≥ 3	20 (47.6 %)	93 (61.2 %)		113 (58.2 %)	386 (56.2 %)	
Brain metastases			0.08			< 0.0001
Yes	19 (45.2 %)	92 (60.5 %)		111 (57.2 %)	236 (34.4 %)	
No	23 (54.8 %)	60 (39.5 %)		83 (42.8 %)	451 (65.6 %)	

* index was BRAF/MEKi rechallenge and second-line BRAF/MEKi in the control group, respectively; N, number of patients; SD, standard deviation; ICI, immune checkpoint inhibition; MUP, melanoma of unknown primary; ECOG, Eastern Cooperative Oncology Group; LDH, Lactate dehydrogenase; CCI, Charlson comorbidity index; AJCC, American Joint Committee on Cancer staging version 8; *vs*, versus

initial adjuvant therapy following complete tumor resection of stage III melanoma (Fig. 1). The remaining 152 (78.4 %) patients were those who were rechallenged after 1 L BRAF/MEKi for non-resectable or metastatic melanoma. Baseline and clinical characteristics at the time of rechallenge with BRAF/MEKi treatment, as stratified, are shown in Table 1. In both strata, two-thirds of patients had received combined anti-PD-1/anti-CTLA-4 immunotherapy following the initial BRAF/MEKi treatment course, the remaining 31 % and 32 %, respectively, had been treated with anti-PD-1 monotherapy. Apart from differences in the CCI and the presence of brain metastases, mirroring both the worse prognosis of patients starting late with systemic therapy, both strata showed similar characteristics (Table 1).

Patients who were rechallenged and had received initial BRAF/MEKi as adjuvant therapy for stage III remained on treatment for a median (95 % CI) 7.4 months (4.3–11.4), compared with 4.9 months (4.3–5.9) for those who started BRAF/MEKi as a later line therapy (Suppl. Figure S1).

In 104 patients (53.6 %), disease progression was the main reason for discontinuation of BRAF/MEKi treatment, while 12 (6.2 %) patients stopped treatment due to toxicities (Suppl. Table S1).

3.2. *Treatment outcomes for rechallenge per stratum*

Rechallenge after prior adjuvant BRAF/MEKi therapy and subsequent 1 L ICI therapy represented a 2 L therapy approach, whilst rechallenge after' BRAF/MEKi for metastatic/non-resectable disease might be considered as a more advanced, 3 L or later therapy setting (Fig. 1). Kaplan-Meier estimates for PFS and OS of both strata accordingly showed longer medians for the adjuvant BRAF/MEKi rechallenge group (Fig. 2). In contrast, ORR was slightly higher (30.3 % versus

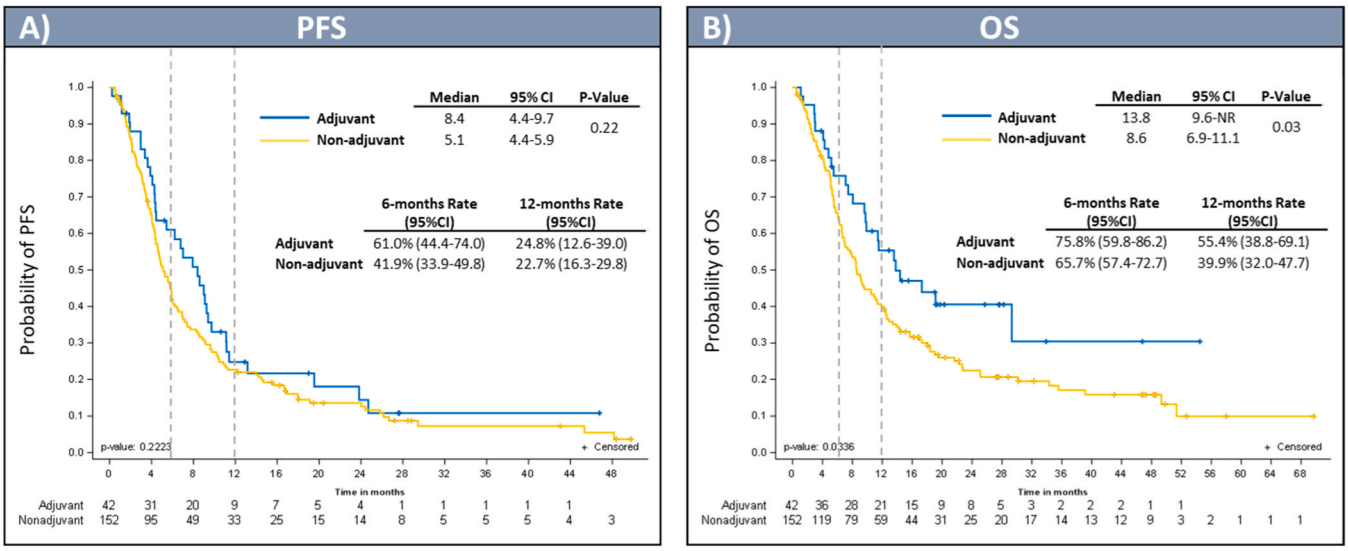

Fig. 2. Kaplan-Meier curves of (A) PFS and (B) OS stratified by adjuvant BRAF/MEKi pretreatment (blue) **or non-adjuvant** (i.e. for non-resectable or metastatic melanoma) **initial BRAF/MEKi treatment** (yellow). For both strata, rechallenge with BRAF/MEKi followed interim treatment lines with immune checkpoint inhibitor (ICI) therapy. PFS, progression-free survival; OS, overall survival; CI, confidence interval.

Table 2
Treatment outcomes for the rechallenge cohort (including strata: [A] "adjuvant pretreatment" as initial BRAF/MEKi therapy and [B] "non-adjuvant pretreatment" as initial BRAF/MEKi therapy) and for the matched control cohort.

	Adjuvant BRAF/MEKi pretreatment [A] (N = 42)	**Non-adjuvant BRAF/MEKi pretreatment [B] (N = 152)**	**P-value** (A vs B)	**BRAF/MEKi Rechallenge Total (N = 194)**	**TT naive matched control (N = 194)**	**P-value** (Rechallenge vs. control)
Best Response			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 (95 % CI)						
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

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; NR, not reached.

26.2 %) and DCR was significantly higher (61.8 % vs. 42.9 %, P = 0.03), when BRAF/MEKi rechallenge was initiated as 3 L or later treatment approach (Table 2). CR rates for both strata were, with around 9 %, nearly identical.

Protocol-defined, exploratory, subgroup analyses demonstrated that patients stopping their 1 L BRAF/MEKi therapy due to progression had less favourable outcomes through rechallenge than patients for whom 1 L BRAF/MEKi therapy was switched to ICI for other reasons, including toxicity. For PFS like for OS, Kaplan-Meier curves significantly diverged (Fig. 3). For patients who did not progress under initial BRAF/MEKi therapy, rechallenge resulted into a median PFS of 6.9 months (95 % CI 4.9–10.3) and a median OS of 12.6 months (95 % CI 8.6–19.5). PFS and OS were significantly longer and ORR significantly higher (41 % vs. 23 %; P = 0.02) than in patients having progressed on initial BRAF/MEKi therapy (Suppl. Table S2).

3.3. Treatment outcomes in context: rechallenge and control cohorts (unmatched/matched)

A total of 687 patients as identified in the EUMelaReg met the inclusion criteria for the unmatched control cohort. Apart from sex, ECOG-PS and number of metastatic sites, their clinical characteristics (Table 1) differed significantly from the 194 patients comprising the rechallenge cohort. Suppl. Figure S2 shows Kaplan-Meier curves of PFS and OS for the unmatched control cohort and rechallenge cohort.

Applying the protocol-defined, covariate-based matching procedure, 194 patients constituted the matching control cohort (Fig. 1). The matching using inverse propensity score weighting resulted in well-balanced clinical characteristics among both cohorts (Table 3). Median follow-up was 31.6 months (95 % CI 26.8–39.5) in the control and 28.8 months (95 % CI 27.2–46.7) in the rechallenge group. The distribution of the well-balanced follow-up times is displayed in Suppl. Figure S3.

Kaplan-Meier estimates for PFS and OS of both cohorts indicate more favourable outcomes for the control in line with expectations for a population of patients with advanced melanoma who received ICI therapy as 1 L and BRAF/MEKi as 2 L therapy. In contrast, 78 % of patients in the rechallenge cohort had received a total of three lines of therapy for advanced disease (Fig. 4). Median (95 % CI) PFS for rechallenge was 5.6 months (4.6–6.6) and median OS 9.6 months

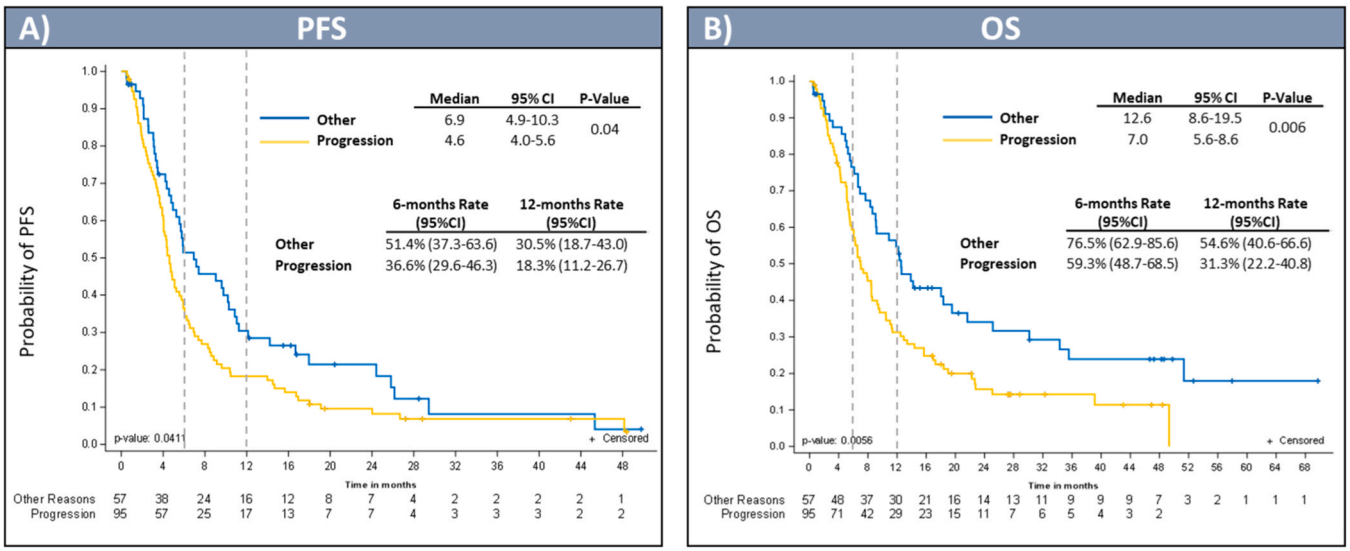

Fig. 3. Subgroup analysis displaying the impact of the reason of end-of-therapy (EoT) of the initial BRAF/MEKi therapy: Kaplan-Meier curves of (A) PFS and (B) OS display progression (N = 95, yellow) **versus 'other reasons'** (N = 57, blue) **as reason for EoT in the rechallenge cohort.** Reasons for EoT were documented for 152 patients undergoing rechallenge. PFS, progression-free survival; OS, overall survival; CI, confidence interval.

(8.0–12.2). The median (95 % CI) PFS for the control cohort was 7.6 months (5.9–8.6), the median OS 16.9 months (15.2–19.3).

A total of 4.6 % of patients in the control cohort had stopped their 2 L BRAF/MEKi therapy due to toxicities, compared to the above reported 6.2 % for rechallenge patients (Suppl. Table S1). Comparisons of the distribution of the initial BRAF/MEKi therapy start dates and the study exposure index dates (BRAF/MEKi rechallenge) versus the control exposure (2 L BRAF/MEKi) did not indicate any distribution or analysis bias among the matched cohorts.

The comparison of responses to treatment, primary outcome variable in this study, indicated a significantly better ORR for the control cohort. 106 (54.6 %) versus 57 (29.4 %) patients achieved an objective response ($p < 0.0001$); the DCR was 145 (74.7 %) versus 112 (57.7 %) patients also significantly higher ($P = 0.0006$). The CR rates were equal between both cohorts (9.3 %, N = 18 and 8.8 %, N = 17), whereas PR rates for controls were considerably higher (45.5 %, N = 88 and 20.6 %, N = 40).

Logistic regression analysis models on ORR (Suppl. Table S3) and Cox regression analysis on OS (Suppl. Table S4) showed that LDH and ECOG-PS (for OS only) were the only variables confounding patients' outcomes significantly in the adjusted models.

4. Discussion

Our study results confirm that BRAF/MEKi rechallenge provides a meaningful clinical benefit to patients with advanced melanoma who have failed ICI after an initial BRAF/MEKi therapy. The ORR was 26 % for patients with initial adjuvant BRAF/MEKi treatment and 30 % for those with 1 L BRAF/MEKi treatment in the advanced setting. Median PFS in the two strata was 8.4 and 5.1 months, and median OS 13.8 and 8.6 months, respectively. Apart from a small subgroup (n = 5) in a recent publication [25], to our knowledge, our study is the first to provide data for such a 'post-adjuvant double-sequence' setting with a reasonable sample size. For this stratum, the reported ORR of 26 % seems comparatively low. However, four out of 42 patients achieved a CR with BRAF/MEKi rechallenge after intermediate ICI therapy, and the survival outcomes appear promising with a median OS of 13.8 months and a 1-year survival rate of 55 %. Thus, post-ICI BRAF/MEKi rechallenge is a clinically valid option after initial, adjuvant BRAF/MEKi therapy.

The outcomes of (3 L) rechallenge after 1 L (non-adjuvant) BRAF/MEKi following by ICI very well match with data from two retrospective studies published in 2018 [17,18], and more recent reports [19–22]. A systematic review and meta-analysis based on seven identified studies reported a pooled ORR of 34 % (95 % CI 29–40), a DCR of 65 % (95 % CI 57–73), an overall median PFS of 5 months (95 % CI 4–6) and a median OS of 9.8 months (95 % CI 9.3–20.4) for patients rechallenged with BRAF/MEKi [26]. One other retrospective study was identified, which evaluated outcomes of sequential therapies after adjuvant BRAF/MEKi therapy [27]. However, no details on the third sequential therapy and its outcomes had been provided.

The control cohort in the 2 L treatment setting for advanced disease of our study served to validate the study results internally. With an ORR of 54 % and DCR of 75 % these figures indicate the real-world effectiveness of standard 2 L BRAF/MEKi in a BRAF/MEKi-naive population. Interestingly, in terms of PFS (7.6 months; 95 % CI 5.9–8.6), the control cohort did not outperform BRAF/MEKi rechallenge (8.4 months, 95 % CI 6.9–11.1) after adjuvant initial BRAF/MEKi pretreatment.

Few data exist on the best therapeutic approach for patients with non-resectable disease after adjuvant targeted treatment [6,7]. A phase II trial showed favourable outcome for ICI, either as single agent anti-PD-1 or in combination with anti-CTLA-4 (63 % and 62 %, respectively) [28]. With an ORR of 25 %, re-treatment with direct BRAF/MEKi was clinically inferior. In line with current clinical recommendations [6–8], single agent or combined ICI therapy are considered as clinically appropriate [29]. The open clinical question is what to do when such post-adjuvant ICI therapy fails.

The pivotal *KeyNote-006* trial provided the basis for some of the data on BRAF/MEKi therapy in ICI-refractory patients [30]. Of 59 patients who received BRAFi or BRAF/MEKi therapy following ICI, 22 had previously undergone BRAF- or BRAF/MEKi-based therapy before 1 L pembrolizumab treatment. However, only one patient experienced a CR or PR after 2 L BRAF/MEKi therapy (ORR 9 %). Rechallenge-like outcomes were also reported in the *SECOMBIT* and *ImmunoCobiVem* trials, in which an investigational study arm consisted of a short, 2-or 3-months course of BRAF/MEKi therapy, followed by a seamless switch to ICI therapy prior to progression and then cross-over BRAF/MEKi therapy after ICI failure [4,31]. In the so-called 'sandwich approach', re-exposure to BRAF/MEKi resulted in ORRs of 62 % (95 % CI not reported (NR)) and 43 % (95 % CI 28–59), respectively, and DCRs of 70 % (95 % CI NR) and 54 % (95 % CI 38–69). This is in accordance with our finding of an ORR of 42.1 % for patients who stopped their 1 L

Table 3
Demographics for rechallenge cohort and for the matched control cohort (i.e. BRAF/MEKi naive patients).

	Rechallenge (N = 194)	**TT naive Control (N = 194)**	**P-value** (Rechallenge vs Control)
Sex			0.84
Male	110 (56.7 %)	107 (55.2 %)	
Female	84 (43.3 %)	87 (44.8 %)	
Age at index treatment* **(years)**			0.78
Mean (SD)	58.3 (13.8)	57.9 (14.8)	
Median [Min, Max]	59.0 [20.0, 88.0]	57.0 [17.0, 91.0]	
Age at first BRAF/MEKi			0.33
< 70 years	155 (79.9 %)	146 (75.3 %)	
≥ 70 years	39 (20.1 %)	48 (24.7 %)	
Type of prior ICI			1.00
Anti-PD1	62 (32.0 %)	62 (32.0 %)	
Anti-PD1/anti-CTLA4	132 (68.0 %)	132 (68.0 %)	
Melanoma type			1.00
Cutaneous	167 (86.1 %)	166 (85.6 %)	
MUP	27 (13.9 %)	28 (14.4 %)	
ECOG			0.96
0	79 (40.7 %)	78 (40.2 %)	
1	55 (28.4 %)	59 (30.4 %)	
≥ 2	33 (17.0 %)	33 (17.0 %)	
Unknown/Missing	27 (13.9 %)	24 (12.4 %)	
LDH			0.82
Elevated	117 (60.3 %)	114 (58.8 %)	
Normal	63 (32.5 %)	68 (35.1 %)	
Missing	14 (7.2 %)	12 (6.2 %)	
CCI			0.99
≤ 2	115 (59.3 %)	116 (59.8 %)	
3–4	38 (19.6 %)	38 (19.6 %)	
≥ 5	22 (11.3 %)	20 (10.3 %)	
Unknown	19 (9.8 %)	20 (10.3 %)	
AJCC stage			0.73
Stage III- NR	3 (1.5 %)	1 (0.5 %)	
Stage IV- M1a	10 (5.2 %)	6 (3.1 %)	
Stage IV- M1b	14 (7.2 %)	15 (7.7 %)	
Stage IV- M1c	56 (28.9 %)	60 (30.9 %)	
Stage IV- M1d	111 (57.2 %)	112 (57.7 %)	
N° of metastatic sites			0.53
1	38 (19.6 %)	32 (16.5 %)	
2	43 (22.2 %)	51 (26.3 %)	
≥ 3	113 (58.2 %)	111 (57.2 %)	
Brain metastases			1.00
Yes	111 (57.2 %)	112 (57.7 %)	
No	83 (42.8 %)	82 (42.3 %)	

* index treatment was BRAF/MEKi rechallenge and second-line BRAF/MEKi in the control group; N, number of patients; TT, targeted therapy; 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; *vs*, versus.

BRAF/MEKi treatment for reasons other than progression, and it supports the concept of a "calculated switch" in patients receiving upfront targeted therapy for various reasons [3,32].

Nevertheless, the long-term outcome for patients who have failed both immunotherapy and targeted treatment remains poor, and there is an urgent need for better options. Lifileucel, the first cellular therapy approved for non-resectable or metastatic melanoma previously treated with an anti-PD-1-directed antibody and, if $BRAF^{V600}$-mutation positive, also a BRAFi (±MEKi), demonstrated an ORR of 31 % and a median PFS of 4.1 months (95 % CI 2.8–4.4) [33]. In the pivotal phase II trial (*C144–01*), most patients had received this therapy based on tumour infiltrating lymphocytes as third or higher line therapy. Today, an ORR of approximately 30 %, with median PFS of 4–5 months, seem to represent the overall benchmark for 3 L therapy in patients with advanced $BRAF^{V600}$-mutated melanoma who have previously received BRAF/MEKi and ICI treatment.

As a real-world registry study, our study has inherent limitations, partly due to its retrospective nature and partly due to the low level of monitoring and scrutiny, which makes it more susceptible for bias. Nevertheless, quality assessment tools in place to improve completeness, validity and accuracy can mitigate bias and enhance internal validity. Another limitation arises from the fact, that not all comparators (e.g. patients receiving only best supportive care after two lines of treatments) could be included in this study. Strengths of this study are the use of real-world data with high external validity, as well as the provision of a large control cohort for internal benchmarking and validation.

5. Conclusion

Rechallenge with BRAF/MEKi therapy for advanced melanoma under real-world conditions provides meaningful clinical benefit in patients who received their initial BRAF/MEKi therapy for advanced disease, or as prior adjuvant therapy. With promising 1-year survival rates of 40 % and 55 %, for prior 1 L or adjuvant BRAF/MEKi pre-treatment, respectively, further follow-up is needed. In particular, for patients which initial response to ICI, BRAF/MEKi rechallenge seems the

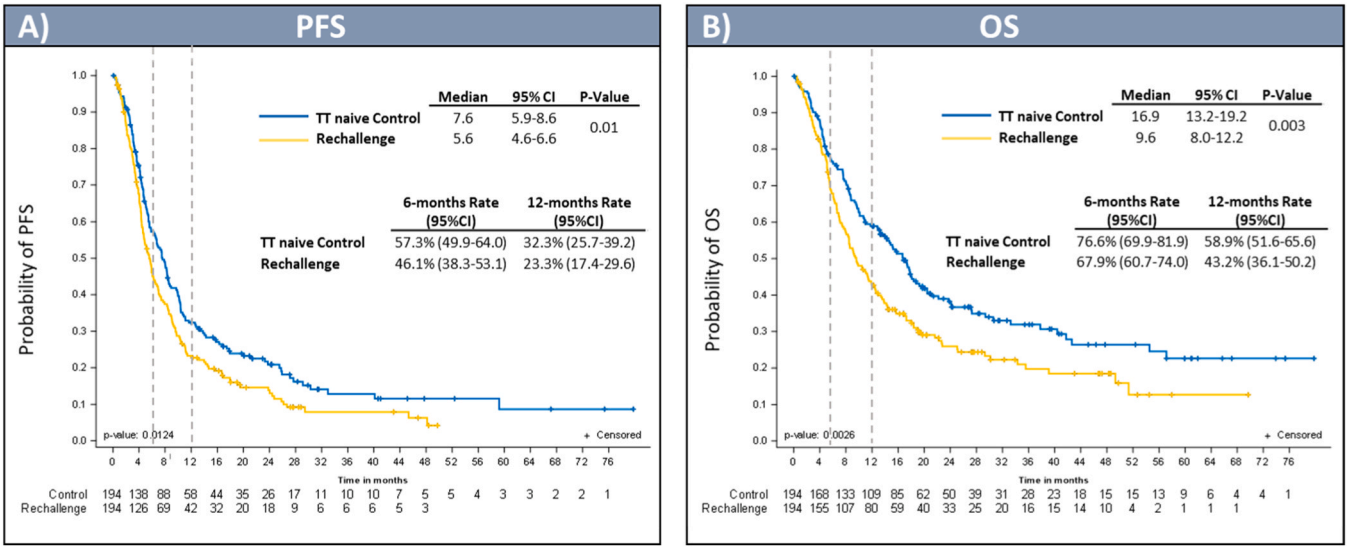

Fig. 4. Kaplan-Meier curves of (A) PFS and (B) OS for the unstratified rechallenge cohort (N = 194, yellow) **and the matching TT naive control cohort** (N = 194, blue). PFS, progression-free survival; OS, overall survival; TT, targeted therapy; CI, confidence interval.

favourable option. Our data provide benchmarks for novel drugs developed for patient's refractory to the current TT/ICI sequences.

CRediT authorship contribution statement

Eva Ellebaek: Writing – review & editing. **Nethanel Asher:** Writing – review & editing. **Berna C. Özdemir:** Writing – review & editing. **Peter Mohr:** Writing – review & editing. **Almudena García Castaño:** Writing – review & editing. **Edgar Dippel:** Writing – review & editing. **Iva Gavrilova:** Writing – review & editing. **Michael Weichenthal:** Writing – original draft, Visualization, Validation, Supervision, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Ronnie Shapira:** Writing – review & editing. **Gergana Shalamanova-Deleva:** Writing – review & editing. **Dirk Debus:** Writing – review & editing. **Katarzyna Kozak:** Writing – review & editing. **Luisa Piccin:** Writing – review & editing. **Dimitrios Ziogas:** Writing – review & editing. **Egle Ramelyte:** Writing – review & editing. **Henrik Schmidt:** Writing – review & editing. **Ascierto Paolo:** Writing – review & editing. **Inge Marie Svane:** Writing – review & editing. **John Haanen:** Writing – review & editing. **Shaked Lev-Ari:** Writing – review & editing. **Igor Stojkovski:** Writing – review & editing. **Christina Ruhlmann:** Writing – review & editing. **Aleksander Popovic:** Writing – review & editing. **Alexander Kreuter:** Writing – review & editing. **Jens Ulrich:** Writing – review & editing. **Lorena Bellido Hernández:** Resources, Writing – review & editing. **Dirk Schadendorf:** Writing – review & editing. **Lars Bastholt:** Writing – review & editing. **Joanna Mangana:** Writing – review & editing. **Helen Gogas:** Writing – review & editing. **Piotr Rutkowski:** Writing – review & editing.

Ethics approval and consent to participate

This study is a retrospective database analysis. Submission of this study to an Institutional Review Board/Independent Ethics Committee was not required.

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Declaration of Competing Interest

The author Professor Schadendorf is the Editor-in-Chief of EJC Skin Cancer and was not involved in the editorial review or the decision to publish this article.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejcskn.2026.100776.

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