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Original research

Efficacy of combined BRAF-MEK inhibitor second-line therapy in patients with non-resectable or metastatic BRAFV600-positive melanoma after prior immunotherapy: A retrospective EUMelaReg multicenter study

Eva Ellebaek [a,1], Michael Weichenthal [b,*,1], Iva Gavrilova [c], Nethanel Asher [d], Patrick Terheyden [e], Jochen Utikal [f], Amina Jalovčić Suljević [g], Claudia Pföhler [h], Igor Stojkovski [i], Rudolf Alexander Herbst [j], Selma Ugurel [k], Christina Ruhlmann [l], Alfonso Berrocal [m], Margarita Majem [n], Branko Dujovic [o], Viktor Šabarić [p], Tomislav Duvancic [q], Ainara Soria [r], Marco Donia [s], Henrik Schmidt [t], Rasmus B. Friis [t], Alexander Gerasimov [c], Gergana Shalamanova-Deleva [u], Ahmed Kontilev [v], Shaked Lev-Ari [w], Ronnie Shapira [w], Luisa Piccin [x], Alessandro Minisini [y], Berna C. Özdemir [z], Pawel Teterycz [aa], Anna Mariuk-Jarema [ab], Dimitrios Ziogas [ac], Amalia Anastasopoulou [ac], Dimitra Stefanou [ac], Lourdes Gutiérrez [ad], Christoffer Gebhardt [ae], Reinhard Dummer [af], Axel Hauschild [b], Peter Mohr [ag], Imke von Wasielewski [ah], Friedegund Meier [ai], John Haanen [aj], Inge Marie Svane [a], Paolo A. Ascierto [ak], Joanna Mangana [af], Piotr Rutkowski [ab], Helen Gogas [ac], Lars Bastholt [al], Dirk Schadendorf [am]

[a] National Center for Cancer Immune Therapy (CCIT-DK), Department of Oncology, Copenhagen University Hospital, Herlev, Denmark
[b] Skin Cancer Center Kiel, University Hospital Schleswig-Holstein, Kiel, Germany
[c] Prof. Ivan Chernozemski University Hospital of Oncology, Sofia, Bulgaria
[d] Skin Cancer and Melanoma Center at Davidoff Cancer Center, Rabin Medical Center, Petah Tikva, Israel
[e] Department of Dermatology, University of Lubeck, Lubeck, Germany
[f] German Cancer Research Center (DKFZ) and University Medical Center Mannheim, Heidelberg University, Heidelberg, Germany
[g] Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina
[h] Department of Dermatology, Saarland University Medical School, Homburg, Germany
[i] University Clinic of Radiotherapy and Oncology, Skopje, North Macedonia
[j] Department of Dermatology, Helios Klinikum Erfurt, Erfurt, Germany
[k] Department of Dermatology, Bielefeld University, Medical School and University Medical Center OWL, Klinikum Bielefeld Rosenhöhe, Bielefeld, Germany
[l] Department of Oncology, Odense University Hospital, Odense, Denmark
[m] Medical Oncology Department, Hospital General Universitario Valencia, Valencia, Spain
[n] Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
[o] Military Medical Academy Belgrade, Belgrade, Serbia
[p] Medical Oncology Resident at University Hospital Centre Zagreb, Zagreb, Croatia
[q] Clinical Center Sisters of Mercy, Zagreb, Croatia
[r] Hospital Universitario Ramón y Cajal, Madrid, Spain
[s] National Center for Cancer Immune Therapy (CCIT-DK), Department of Oncology, Copenhagen University Hospital, Herlev, Denmark
[t] Department of Oncology, Aarhus University Hospital, Aarhus, Denmark
[u] Complex Oncology Center Plovdiv, Plovdiv, Bulgaria
[v] Acibadem CityClinic Tokuda Hospital, Sofia, Bulgaria
[w] The Ella Lemelbaum Institute for Immuno-Oncology and Melanoma, Ramat-Gan, Israel
[x] Istituto Oncologico Veneto, Padova, Italy
[y] Department of Oncology, ASUFC "Santa Maria della Misericordia", Udine, Italy
[z] Department of Medical Oncology, Inselspital Bern, Bern University Hospital, Bern, Switzerland
[aa] Department of Soft Tissue/Bone Sarcoma and Melanoma, Department of Computational Oncology, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[ab] Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[ac] First Department of Medicine, National and Kapodistrian University of Athens, Athens, Greece

* Correspondence to: Skin Cancer Center Kiel, Arnold-Heller-Str.3, 24105 Kiel, Germany for the EUMelaReg European Melanoma Registry Consortium, Germany.
E-mail address: MWeichenthal@dermatology.uni-kiel.de (M. Weichenthal).

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[ad] Hospital Universitario Puerta de Hierro, Madrid, Spain
[ae] Department of Dermatology and Venereology, University Skin Cancer Center Hamburg, University Medical Center Hamburg-Eppendorf (UKE), Hamburg, Germany
[af] University Hospital of Zurich, Zurich, Switzerland
[ag] Department of Dermatology, Elbekliniken Buxtehude, Buxtehude, Germany
[ah] Skin Cancer Center Hannover, Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany
[ai] Department of Dermatology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
[aj] Division of Medical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands
[ak] Department of Melanoma, Cancer Immunotherapy and Development Therapeutics - Istituto Nazionale Tumori IRCCS Fondazione "G. Pascale", Napoli, Italy
[al] Department of Oncology, Odense University Hospital, Odense, Denmark
[am] Department of Dermatology, Venereology and Allergology, University Hospital Essen, Essen, Germany

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ABSTRACT

Background: Randomised trials recently showed that sequencing of first-line (1 L) immune checkpoint inhibitor (ICI) and second-line (2 L) BRAF-MEK-inhibitor (BRAF/MEKi) combination therapy provides better clinical outcomes in *BRAF*^{V600}-mutated, irresectable/metastatic melanoma than the inverse sequence. However, efficacy benchmark data for 2 L BRAF/MEKi are limited as the combination was developed for 1 L use, lacking estimates for the impact of prior ICI.
Methods: This retrospectively study analysed 2343 patients from the EUMelaReg registry with *BRAF*^{V600}-mutated melanoma who received BRAF/MEKi either as 2 L after failing 1 L ICI (n = 654) or as 1 L treatment (n = 1689). Patients with prior adjuvant ICI or BRAF/MEKi were excluded. Prognostic imbalances between the two groups were adjusted using 1:1 inverse propensity score matching. Key efficacy outcomes included overall survival (OS), progression-free survival (PFS), overall response rate (ORR), and time on treatment (TOT).
Results: Patients in the 2 L cohort achieved outcomes from start of treatment at least equivalent to the matched 1 L BRAF/MEKi cohort. Kaplan-Meier estimates demonstrated longer median PFS (8.4 vs 7.7 months; p = 0.01) and longer median TOT (7.8 vs 6.2 months; p = 0.002) for patients treated with 2 L BRAF/MEKi compared to 1 L. Median OS from start of 2 L (17.2 months) or 1 L (16.0 months) BRAF/MEKi was similar (p = 0.73) despite inherent bias from differing index dates. ORR among both groups (56.4 % vs 53.5 %; p = 0.32) was equal.
Conclusion: This study further supports the recommended sequencing of ICI as 1 L and BRAF/MEKi as 2 L therapy for patients with *BRAF*^{V600}-mutated melanoma. It shows that prior failure of ICI does not compromise the efficacy of BRAF/MEKi treatment.

1. Introduction

Approximately 50 % of cutaneous melanomas present mutations of the *BRAF* gene [1,2]. Due to their high incidence, *BRAF*^{V600} mutations became a promising target for systemic anti-cancer therapy in stage III or IV melanoma. Although studies initially did not reveal a worse outcome for *BRAF*-mutated melanoma [2–4], a systematic review found an association among the presence of such mutations and shorter overall survival (OS) compared to *BRAF* wild-type melanoma [5].

Since 2010, the fate of patients with irresectable or metastatic *BRAF*-mutated melanoma was much improved by novel therapies targeting the mitogen-activated protein kinase (MAPK) pathway with BRAF and MEK as downstream signalling targets. The combinations of vemurafenib and cobimetinib [6], dabrafenib and trametinib [7,8] and later on encorafenib and binimetinib [9] emerged as frontline therapy standard with extended follow-up confirming their long-term clinical benefit [10–12]. Of note, the rapid onset of responses and unprecedented overall response rates (ORR) particularly helped to improve outcomes in *BRAF*-mutated patients with rapidly evolving or symptomatic metastatic disease.

In parallel, immune checkpoint inhibitors (ICI) acting on the PD-(L)1 axis, alone or in combination with anti-CTLA-4 or anti-LAG3 directed antibodies, have demonstrated significant clinical activity in metastatic melanomas, independently from patients' mutational status [1,13]. Due to previously unachieved survival rates, combined ICI therapy was rapidly established as standard-of-care in *BRAF* wild-type melanoma, with comparable efficacy observed in *BRAF*-mutated melanoma [14].

The frequent acquisition of resistance to BRAF/MEK inhibitor (BRAF/MEKi) combination therapy raised the question of the adequate frontline and the best use of BRAF/MEKi therapy. In absence of head-to-head comparisons, indirect treatment comparisons attempted to inform on the most active regimen for first-line (1 L) therapy in advanced, *BRAF*-mutated melanoma [15–17]. Then two randomised-controlled trials investigated the best sequencing approach for BRAF/MEKi and ICI therapy [18–20]. Both trials, *SECOMBIT* and *DREAMSeq*, demonstrated higher 2-year OS rates for upfront ICI therapy followed by BRAF/MEKi therapy after clinical progression, compared to the inverse sequence.

Since, clinical practice guidelines recommend for *BRAF*^{V600}-mutated, advanced melanoma to use ICI therapy as upfront therapy of choice, exempting some well-defined clinical situations [21–23]. While the clinical evidence for the BRAF/MEKi therapies had been established for frontline use in advanced melanoma, data however remain quite limited regarding their efficacy for second-line (2 L), post-ICI use.

We hence initiated a retrospective, non-interventional registry study collecting and analysing data from the European Melanoma Registry (EUMelaReg) to describe the efficiency of 2 L BRAF/MEKi therapy following progression after upfront, anti-PD-1 inhibitor-based ICI therapy in a real-world setting.

2. Methods

2.1. Study design and patient selection

This retrospective study analysed data on patients selected from the EUMelaReg (www.eumelareg.org) database with cutaneous melanoma or melanoma of unknown primary (MUP). Patients eligible for inclusion were *BRAF*^{V600}-mutation positive and had advanced, non-resectable stage III/IV disease according to the American Joint Committee on Cancer's 8th edition for melanoma staging (AJCC v8) [24]. Patients were either treated with BRAF/MEKi after failure of 1 L therapy with ICI – anti-PD-1 directed monotherapy or anti-PD-1/CTLA-4 directed combined immunotherapy – or with 1 L BRAF/MEKi. Treatment with these regimens was done in accordance with medicinal products' respective Summary of Product Characteristics (SmPC) or, for centres outside the

[1] *Eva Ellebaek and Michael Weichenthal contributed equally to this work.

European Union, in line with applicable prescription information inside their authorised labels and indication. All patients eligible for inclusion must have had a documented follow-up time of at least 12 months calculated from the start date of the indexed treatment, i.e. begin of BRAF/MEKi therapy for either 2 L or for 1 L use. Patients with inadequate information on stage and baseline characteristics were excluded from inclusion as well as any patients who had received either BRAF/-MEKi or ICI therapy for adjuvant treatment. Case documentation in the registry and informed consent procedures had been done according to applicable national laws for such registry studies.

Assessment of OS from start of 2 L BRAF/MEKi treatment was the primary study objective. Secondary objectives included the assessment of OS, progression-free survival (PFS), overall response rate (ORR) and time-on-treatment (TOT) for 1 L compared to 2 L BRAF/MEKi therapy. The description of demographic and clinical characteristics for both cohorts constituted another secondary objective. Exploratory objectives included correlation analyses of factors which might impact on outcomes of patients receiving 2 L BRAF/MEKi therapy.

2.2. Statistical considerations and analysis

Time-to-event variables were defined as the period from the start of the respective BRAF/MEKi treatment (1 L or 2 L) until death for any cause (for OS), death for any cause or disease progression before a new therapy line began (for PFS), or the best overall response (BOR) achieved prior to it. In case events had not yet occurred, OS, PFS and TOT were censored at the last date, the patient was known to be alive. Complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were assessed in line with established criteria/definitions [25].

The study intended to analyze data from at least 500 patients who received 2 L BRAF/MEKi therapy after failure of frontline ICI therapy (i.e. targeted therapy 2 L set, TT2) and as a benchmark for comparison 500 patients who received 1 L BRAF/MEKi therapy (i.e. targeted therapy 1 L set, TT1). The TT2 cohort also formed the basis for covariate-based matching to provide an identical-in-size cohort for comparisons of effectiveness across both treatment settings. The optimal matching algorithm used inverse propensity score matching (IPSW) accounting for prognostic factors like sex, age, Eastern Cooperative Oncology Group performance status (ECOG-PS), lactate dehydrogenase (LDH) status, AJCC v8 substage, melanoma type, number of metastatic sites and Charlson comorbidity index (CCI) score to address anticipated baseline imbalances and eliminate selection bias. For statistical analyses, SAS statistical software (version 9.4 or higher) and R Statistical Software 4.3 were used.

We used descriptive statistics to summarize cohort characteristics at baseline. Survival plots and estimate median time in months with 95 % confidence intervals (CI) and event rates with 95 % CI applied the Kaplan-Meier method to analyze time-to-event variables like OS, PFS or TOT; p-Values were derived by Log-Rank-statistics. For regression analyses, the models assessed the influence of covariates of interest on the primary outcome variable, applying univariable and multivariable logistic regression analysis. The primary endpoint OS was assessed in an univariable and multivariable Cox regression analysis.

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. All covariates remaining at the end of the selection process were used for multivariate regression.

3. Results

Between October 2024 and February 2025, we extracted cases from the EUMelaReg, identifying 654 patients with 2 L BRAF/MEKi therapy following prior frontline ICI therapy and 1689 patients who received 1 L BRAF/MEKi therapy, all fulfilling the inclusion and exclusion criteria (for CONSORT diagram, see Suppl. Figure S1).

The demographics and clinical characteristics of the 2 L and of the unmatched 1 L cohort are displayed in Table 1 (left and middle column). Reported *p*-values indicate line-specific imbalances among both cohorts: the 2 L cohort comprised a higher proportion of patients with stage IV M1c or M1d disease, ≥ 3 sites of metastases or elevated LDH. After covariate-based matching, baseline characteristics were more adequately balanced (Table 1, right column).

Kaplan-Meier curves for PFS demonstrated better outcomes for BRAF/MEKi therapy when used after ICI therapy. Median PFS was 8.4 months (95 % CI 7.8–9.8); for the 1 L BRAF/MEKi control, medians were significantly lower for both, the unmatched and the matched cohort (Fig. 1A and C). Median OS tended, for 2 L BRAF/MEKi, to be at least equivalent with 17.2 months (95 % CI 14.8–19.4). For the unmatched and matched 1 L cohorts, medians (95 % CI) were 16.7 months (15.3–18.3) respectively 16.0 months (13.2–19.2) despite earlier setoff of the index date, beginning at start of 1 L BRAF-MEKi therapy control cohorts (Fig. 1B and D).

Outcomes of sensitivity analysis for OS – i.e., multivariate Cox regression with sub-stratification for hazard ratio – are provided in Suppl. Table S1. The analysis did not allow to discriminate any of the presumed confounders except significance ($p < 0.05$) found for age (<70 years) and ECOG-PS of 1.

Focused sensitivity analyses for OS are provided for the matched cohorts comparison. The respective Cox regression analysis – displayed as a Forest plot (Fig. 2) – shows that only for patients with an ECOG-PS ≥ 2, elevated LDH, a high CCI score, or for patients ≥ 70 years 2 L therapy results tended to be worse than in treatment-naive patients. Of note, neither the presence of brain metastases (M1d) or visceral metastases (M1c) nor a very high number of metastatic sites were associated with a worse outcome in 2 L BRAF/MEKi therapy.

Landmark PFS rates at 6- months, 12-months and 24-months were 61.8 % (95 % CI 57.9–65.4), 39.9 % (36.1–43.7) and 25.9 % (22.4–29.5) for 2 L BRAF/MEKi therapy. Respective OS landmark rates were 78.6 % (95 % CI 38.2–43.1), 60.8 % (75.3–81.6) and 42.2 % (44.2–52.1) (Table 2). PFS rates at 24 months did not reach 20 % for both, the unmatched and matched 1 L control; in terms of OS, their 2-year rates similarly remained with 40.7 % and 39.5 % below the 2 L rates too (Table 2).

2 L use of BRAF/MEKi resulted in an ORR of 56 % and a DCR of 73 %, hence demonstrating equal efficacy compared to use in treatment-naive advanced melanoma (Table 2). Median TOT for BRAF/MEKi when used as 2 L therapy was with 7.8 months (95 % CI 6.6–8.6) significantly longer than for use as 1 L therapy (Suppl. Figure S2). Medians were 6.1 months (95 % CI 6.3–6.9) and 6.2 months (5.8–6.9) for the unmatched and matched controls; the respective *p*-values for comparison were 0.003 and 0.002 (Table 2).

The analysis of follow-up times (Suppl. Table S2) between investigational and control cohorts (prior and post matching) indicated an average 25 % longer median follow-up time for the 1 L BRAF/MEKi control cohort; median (95 % CI) follow-up was 39.6 months (32.8–44.1) for the BRAF/MEKi 2 L cohort and 48.5 months (44.9–50.9) and 49.3 months (43.2–53.2) for the unmatched respectively matched BRAF/MEKi 1 L control cohorts.

Further insights into the efficiency of 2 L BRAF/MEKi therapy were gained when exploratorily stratifying this primary analysis cohort according to the BOR observed during precedent 1 L ICI therapy. Fig. 3 demonstrates that patients who achieved a response to prior ICI therapy had significantly better outcomes for subsequent BRAF/MEKi therapy. Median PFS was 10.2 months (95 %CI 8.4–17.4) in the 112 patients who had responded to prior ICI therapy. 66.9 % of these responders achieved a partial or complete response with 2 L BRAF/MEKi; the DCR rate was 79.5 %; the 472 non-responders to frontline ICI therapy achieved an ORR of 54.4 % only ($p = 0.02$) (Suppl. Table S3). Median follow-up was 31.8 and 43.5 months for 1 L responders and non-responders,

Table 1
Demographics and clinical characteristics for 2 L and unmatched/matched 1 L cohort.

	1 L BRAF/MEKi (unmatched control) (N = 1689)	P-value	2 L BRAF/MEKi (primary cohort) (N = 654)	P-value	1 L BRAF/MEKi (matched control) (N = 654)
Sex		0.35		0.74	
Male	1018 (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]		61.0 [19, 94]
Age		0.62		0.72	
< 70 years	1152 (68.2 %)		439 (67.1 %)		446 (68.2 %)
≥ 70 years	537 (31.8 %)		215 (32.9 %)		208 (31.8 %)
Adjuvant treatment		0.31		0.48	
Yes	155 (9.2 %)		69 (10.5 %)		78 (11.9 %)
No	1534 (90.8 %)		585 (89.5 %)		576 (88.1 %)
Type of adjuvant treatment		1.00			
anti-CTLA-4	6 (0.4 %)		2 (0.3 %)		4 (0.6 %)
Other	151 (8.9 %)		68 (10.4 %)		76 (11.6 %)
Melanoma type		0.46		0.16	
Cutaneous	1403 (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 %)
CCI 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 %)
No. of metastatic sites		0.001		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	1194 (70.7 %)		434 (66.4 %)		426 (65.1 %)

N, number of patients; 1 L/2 L, first/second line; MUP, melanoma of unknown primary; ECOG, Eastern Cooperative Oncology Group; LDH, Lactate dehydrogenase; CCI, Charlson comorbidity index; stage, American Joint Committee on Cancer 8th version; NR, non-resectable.

respectively ($p = 0.33$).

An *ad hoc* analysis investigated the impact of the type of 1 L ICI failure on outcomes of 2 L BRAF/MEKi therapy. Suppl. Figure 3 indicates that patients experiencing a PD whilst still on ICI therapy tended to have a, although not statically significant, shorter median PFS and OS (8.3 and 15.8 months), compared to patients with PD after end of ICI therapy (median for PFS 9.7 months, for OS 24.6 months).

4. Discussion

Second-line BRAF/MEKi therapy used after failure of frontline ICI therapy is an efficacious treatment option for $BRAF^{V600}$-mutated, advanced melanoma. With a median OS of 17.2 months (14.8–19.4) from start of BRAF/MEKi therapy and a 2-year survival rate of 42.2 % (38.2–46.2), survival equalled with outcomes of the parallelly assessed 1 L BRAF/MEKi treatment despite the earlier index date for that control cohort (Table 2). In terms of PFS and ORR, the outcome of BRAF/MEKi 2 L therapy in this real-world study was moderately better than for comparable patients receiving BRAF/MEKi therapy upfront. We hence conclude that the previous use of anti-PD-1-based ICI therapy does not affect patients' susceptibility to provide meaningful clinical responses to subsequent targeted therapy. The overall outcome for median OS medians after 2 L BRAF/MEKi was slightly better, with differences of 1.2 months and 0.7 months respectively among the matching cohorts (Fig. 1).

Compared with pivotal phase III trials, which were all conducted in 1 L, the outcome of our study was less favourable for both the 1 L and 2 L treatments. The CoBRIM, COMBI-d, COMBI-v and COLUMBUS trials revealed ORRs of 67 %, 68 %, 64 % and 64 %, respectively. The according median PFS was 12.6, 11.0, 12.1, and 14.9 months, and the median OS 22.5, 32.7, 26.1, and 33.6 months, respectively [6,8,9,26].

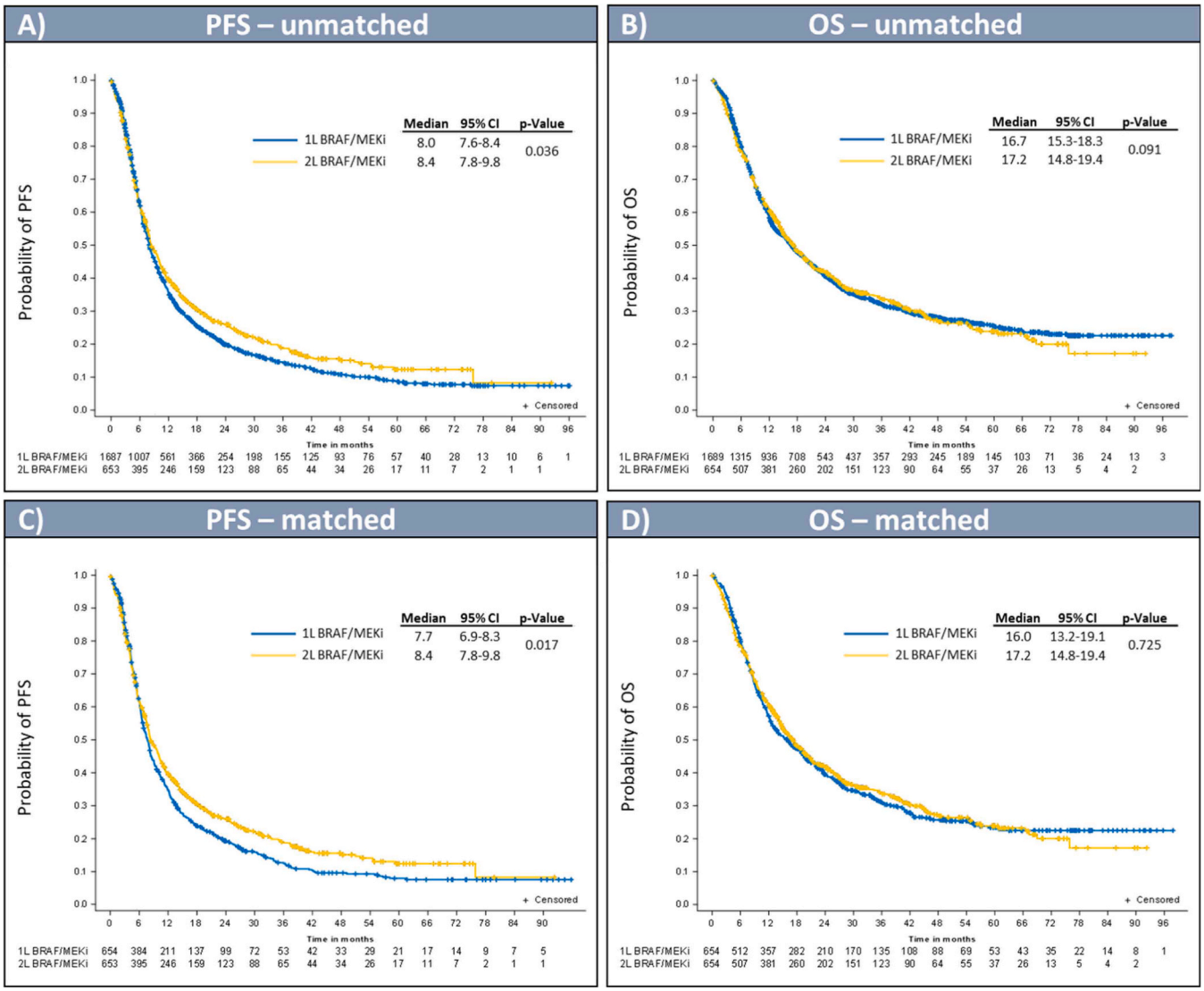

Fig. 1. Kaplan-Meier curves of PFS (left side) and OS (right side) for BRAF/MEKi second-line treatment (yellow lines). Comparisons with the unmatched (Panels A and B) and matched (Panels C and D) first-line BRAF/MEKi cohorts (blue lines) show significantly longer median PFS for second-line use. PFS, progression-free survival; OS, overall survival; BRAF/MEKi, BRAF/MEK inhibitor therapy; CI, confidence interval.

This typically reflects the selection effect of clinical trial exclusion criteria, such as unfavourable prognostically factors like brain metastases, impaired performance status, and various comorbidities, which are much more prevalent in real-world studies [27].

The same contrast is also seen in other observational and phase IV studies when compared to registrational trail results. In the non-interventional COMBI-r phase IV study, median OS was 17.5 months and median PFS 7.7 months [28]. In various retrospective analyses, the characteristic ORRs - apart from outliers - ranged from 58 % to 71 %, median PFS from 7.5 to 12.0 months, and median OS from 15.1 to 20.0 months [16,29–35]. Some of these studies have also evaluated BRAF/-MEKi therapy specifically in the 2 L setting, revealing results that are predominantly similar to those in our study. In the COMBI-r study, median OS for 2 L BRAF/MEKi therapy in patients with advanced melanoma was 19.0 months (95 % CI 12.8–14.6). PFS also mirrored our results with 8.8 months (95 % CI 6.9–11.3) for 2 L use. In this study, more than 80 % of the 2 L BRAF/MEKi patients had received prior ICI therapy; nearly all of them either in form of anti-PD-1 monotherapy (49 %) or of combined anti-PD-1/anti-CTLA-4 therapy (31 %) [28].

A retrospective Polish study investigating the outcomes of 2 L targeted therapy following frontline ICI therapy reported a median OS of 12.8 months and a median PFS of 7.7 months since initiation of BRAF/MEKi therapy in a cohort of 97 patients [34]. Rogala et al. reported an ORR of 58 %, a PFS of 7.5 months and an OS of 12.8 months in 97 patients receiving BRAF/MEKi in 2 L, while two other studies reported ORRs of 74 % and 78 %, respectively, without detailing PFS and OS for 2 L [31,35].

The two randomised phase II and III trials investigating the impact of sequencing in advanced melanoma also partially allow to contextualise our study results. In the phase III *DREAMSeq* trial, the reported ORR in the 2 L BRAF/MEKi treatment following ICI failure was 70 %, which was remarkably higher than in 1 L (51 %), and the median PFS from 2 L BRAF/MEKi was 11.2 months. Both outcomes are more favourable than those observed in most real-world data studies. This is likely due to some degree of selection bias inherent in the phase III trial design [20]. The phase II *SECOMBIT* trial reported an ORR of 61 % for 2 L BRAF/MEKi treatment, while the PFS for this line of treatment was not reported [19].

The uncompromised efficacy of BRAF/MEKi 2 L therapy might be partly explained by a patient selection effect: generally, mainly the fit stage IV patients are candidates for 2 L or even late-line therapy, and those with rapidly progressive disease may not survive long enough to receive 2 L. Second, it was postulated that immune checkpoint blockade

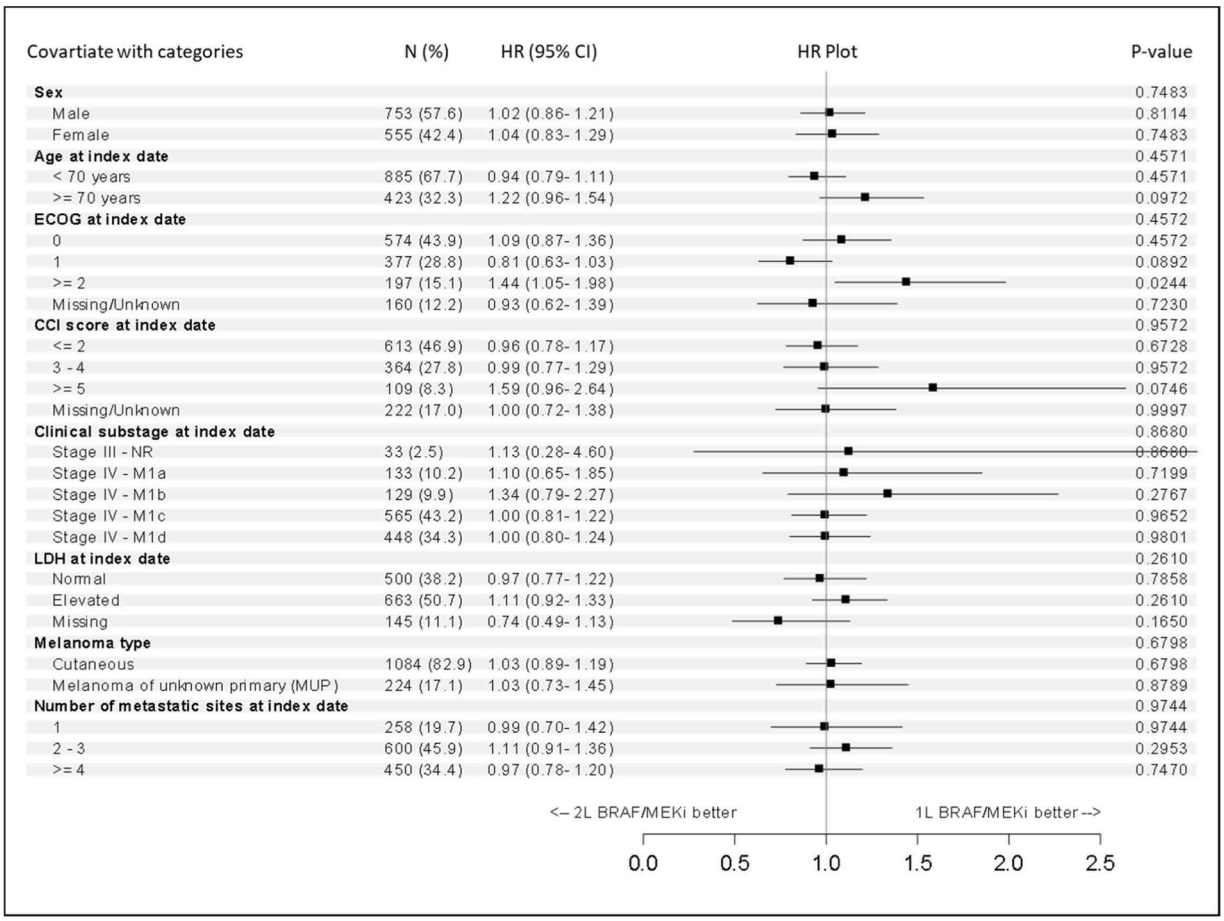

Fig. 2. Forest plot - Sensitivity analysis for OS from index date via multivariable Cox regression with sub-stratification for hazard ratios regarding index treatment after propensity score matching (1:1). The reference for the comparison is first-line BRAF/MEKi therapy. N, number of patients; OS, overall survival; CI, confidence interval; HR, hazard ratio; ECOG, Eastern Cooperative Oncology Group performance score; CCI, Charlson comorbidity score; stage, American Joint Committee on Cancer 8th edition; NR, non-resectable; LDH, serum lactate dehydrogenase.

might have had a positive 'priming' effect on subsequent therapies including targeted therapy. For *BRAF*^{V600}-mutant melanoma, the priming hypothesis has been backed mechanistically by *in vivo* data [36]. In more detail, ICI therapy appears to prime a more durable BRAF/MEKi response and BRAF/MEKi combination helps to overcome primary ICI resistance. ICI optimize BRAF/MEKi response by promoting pro-inflammatory polarization of macrophages and clonal expansion of interferon-γ^{hi}, and CD8 + cytotoxic and proliferative T cells. At least for chemotherapy given as post-ICI melanoma treatment, two small retrospective studies could sustain this hypothesis [37,38]; one retrospective study found such an effect in melanoma patients treated with dabrafenib plus trametinib, who showed an improved ORR if they had received prior ICI therapy [39].

On the other hand, the commonly perceived clinical experience that the efficacy of anti-cancer therapy decreases with each line of systemic therapy is lacking systematic evaluation. Although sporadic data sets exist indicating such a correlation [40–42], the overall evidence is lacking. Selection effects – usually only fit patients (ECOG 0–1) are candidates for further line of therapy – and pattens of multiplied, acquired resistance may counterbalance each other, resulting as well in opposite observations [43,44].

Independently from the above reflections, the subgroup analyses in Fig. 2 support another clinical recommendation as specified in the current EADO guideline for example [22]: 1 L therapy with BRAF/MEKi for 6–12 weeks prior to immunotherapy can be offered to patients with a poor performance status, high LDH levels, a high tumour burden, an aggressive disease course or symptomatic metastases. Our registry data (Fig. 2) point in the same direction.

Of note, the results of our exploratory analysis, shown above, indicate that factors other than the line of therapy impact on treatment outcomes for 2 L BRAF/MEKi therapy. These factors include the type of BOR prior to the failure of 1 L ICI therapy. In our subgroup analysis (Fig. 3), response to immunotherapy is generally associated with particularly good outcomes. However, the correlation between ORR and PFS/OS is not considered particularly strong [45–48]. Although our study shows that patients with PR or CR to prior ICI have a somewhat better outcome with 2 L BRAF/MEKi therapy, sensitivity analysis for OS did not indicate any further patient subgroups which would particularly benefit from 2 L BRAF/MEKi therapy (Suppl. Table 1).

Similarly, the timepoint of progression (i.e. during or after ICI 1 L therapy) may affect the observed efficiency patterns. Whilst several studies have investigated time to response under IC therapy [49–51], little data is available regarding the impact of early, on-therapy PD versus progression after discontinuation of ICI therapy [52]. The results from our *ad hoc* sensitivity analysis support the initiation of 2 L BRAF/MEKi therapy particularly in those patients who progressed after the 1 L ICI therapy had ended.

Our study has strengths and limitations. A major advantage of our analysis is the large sample size combined with high quality, detailed clinical information. The external validity of this study analysing real-world evidence represents a strength, as such an analysis includes also patients who were not included in pivotal trials [53]. The convergence of the results with the outcomes of the above-described observational studies and prospective trials, providing further enhances evidence that

Table 2
Efficiency outcomes post-ICI BRAF/MEKi 2 L and 1 L therapy (matched and unmatched).

	1 L BRAF/MEKi (unmatched control) (N = 1689)	P-value	2 L BRAF/MEKi (primary cohort) (N = 654)	P-value	1 L 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	1191 (70.5 %)	0.17	480 (73.4 %)	0.13	454 (69.4 %)
Survival (95 % CI)					
Median OS (months)	16.7 (15.3–18.3)	0.91	17.2 (14.8–19.4)	0.73	16.0 (13.2–19.1)
6-months rate	79.9 % (77.9–81.8)		78.6 % (75.3–81.6)		80.2 % (76.9–83.1)
12-months rate	58.4 % (56.0–60.8)		60.8 % (56.9–65.5)		57.2 % (53.3–61.0)
24-months rate	40.7 % (38.2–43.1)		42.2 % (38.2–46.2)		39.5 % (35.6–43.4)
Median PFS (months)	8.0 (7.6–8.4)	0.04	8.4 (7.8–9.8)	0.02	7.7 (6.9–8.3)
6-months rate	62.5 % (60.1–64.8)		61.8 % (57.9–65.4)		61.7 % (57.8–65.4)
12-months rate	35.8 % (33.5–38.1)		39.9 % (36.1–43.7)		34.8 % (31.1–38.6)
24-months rate	19.9 % (17.9–22.0)		25.9 % (22.5–29.6)		19.3 % (16.2–22.6)
Median TOT (months)	6.1 (6.3–6.9)	0.003	7.8 (6.6–8.6)	0.002	6.2 (5.8–6.9)
6-months rate	54.2 % (51.8–56.6)		56.3 % (52.4–60.0)		51.8 % (47.9–55.5)
12-months rate	28.6 % (26.5–30.8)		35.7 % (32.0–39.3)		26.6 % (23.3–30.0)
24-months rate	14.3 % (12.7–16.1)		21.3 % (18.1–24.6)		13.6 % (11.1–16.4)

N, number of patients; 1 L/2 L, first/second line; 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.

patients with advanced melanoma harbouring *BRAF*^{V600}-mutations benefit from the recommended treatment sequence involving ICI frontline therapy and subsequent BRAF/MEKi treatment.

The known limitations of this study are due to its retrospective design and the methodological constraints in performing such indirect comparisons among independent, although matched cohorts [54]. In addition, the comparison of a 2 L with a 1 L therapy in a registry implies potentially differing follow-up times – here in fact an approximately 25 % longer follow-up for the control cohort – introducing some allocation bias.

The comparison of outcome data from 2 L with data from a 1 L treatment with matched co-variates still carries the potential for inherent bias from hidden confounders. Although these confounders may principally act in different directions, it is likely that most of them would act in favour of the 1 L treatment. In particular, comparing OS from different time zero starting points would create at least some lead-time bias in favour of 1 L BRAF/MEKi, backing the hypothesis that patients failing 1 L immunotherapy have an OS benefit from 2 L BRAF/MEKi therapy.

5. Conclusion

The results of this study support the preferred sequencing of ICI in 1 L and BRAF/MEKi therapy in 2 L for patients with melanoma harboring *BRAF*^{V600}-mutation. The study demonstrates that the use of BRAF/MEKi in the 2 L does not compromise key outcomes, affirming their clinical benefit in this sequencing approach.

CRediT authorship contribution statement

Peter Mohr: Writing – review & editing. **Tomislav Duvancic:** Writing – review & editing. **Axel Hauschild:** Writing – review & editing. **Reinhard Dummer:** Writing – review & editing. **Christoffer Gebhardt:** Writing – review & editing. **Margarita Majem:** Writing – review & editing. **Lourdes Gutiérrez:** Writing – review & editing. **Alfonso Berrocal:** Writing – review & editing. **Dimitra Stefanou:** Writing – review & editing. **Christina Ruhlmann:** Writing – review & editing. **Amalia Anastasopoulou:** Writing – review & editing. **Selma Ugurel:** Writing – review & editing. **Dimitrios Ziogas:** Writing – review & editing. **Rudolf Alexander Herbst:** Writing – review & editing. **Anna Mariuk-Jarema:** Writing – review & editing. **Igor Stojkovski:** Writing – review & editing. **Pawel Teterycz:** Writing – review & editing. **Claudia Pföhler:** Writing – review & editing. **Berna C. Özdemir:** Writing – review & editing. **Amina Jalovčić Suljeviić:** Writing – review & editing. **Viktor Šabarić:** Writing – review & editing. **Branko Dujovic:** Writing – review & editing. **Alessandro Minisini:** Writing – review & editing. **Dirk Schadendorf:** Writing – review & editing. **Luisa Piccin:** Writing – review & editing. **Lars Bastholt:** Writing – review & editing. **Helen Gogas:** Writing – review & editing. **Shaked Lev-Ari:** Writing – review & editing. **Piotr Rutkowski:** Writing – review & editing. **Ahmed Kontilev:** Writing – review & editing. **Nethanel Asher:** Writing – review & editing. **Joanna Mangana:** Writing – review & editing. **Gergana Shalamanova-Deleva:** Writing – review & editing. **Paolo A. Ascierto:** Writing – review & editing. **Alexander Gerasimov:** Writing – review & editing. **Iva Gavrilova:** Writing – review & editing. **Inge Marie Svane:** Writing – review & editing. **Rasmus B. Friis:** Writing – review & editing. **Eva Ellebaek:** Writing – review & editing, Conceptualization. **John Haanen:** Writing – review & editing. **Henrik Schmidt:** Writing – review & editing. **Michael Weichenthal:** Conceptualization, Data curation, Formal analysis, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft. **Friedegund Meier:** Writing – review & editing. **Marco Donia:** Writing – review & editing. **Imke von Wasielewski:** Writing – review & editing. **Ainara Soria:** Writing – review & editing. **Jochen Utikal:** Writing – review & editing. **Patrick Terheyden:** Writing – review & editing. **Ronnie Shapira:** 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

E. Ellabaek: honoraria: Bristol Myers and Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre. Travel/accommodations/expenses: Pierre Fabre, Merck Sharp & Dohme.

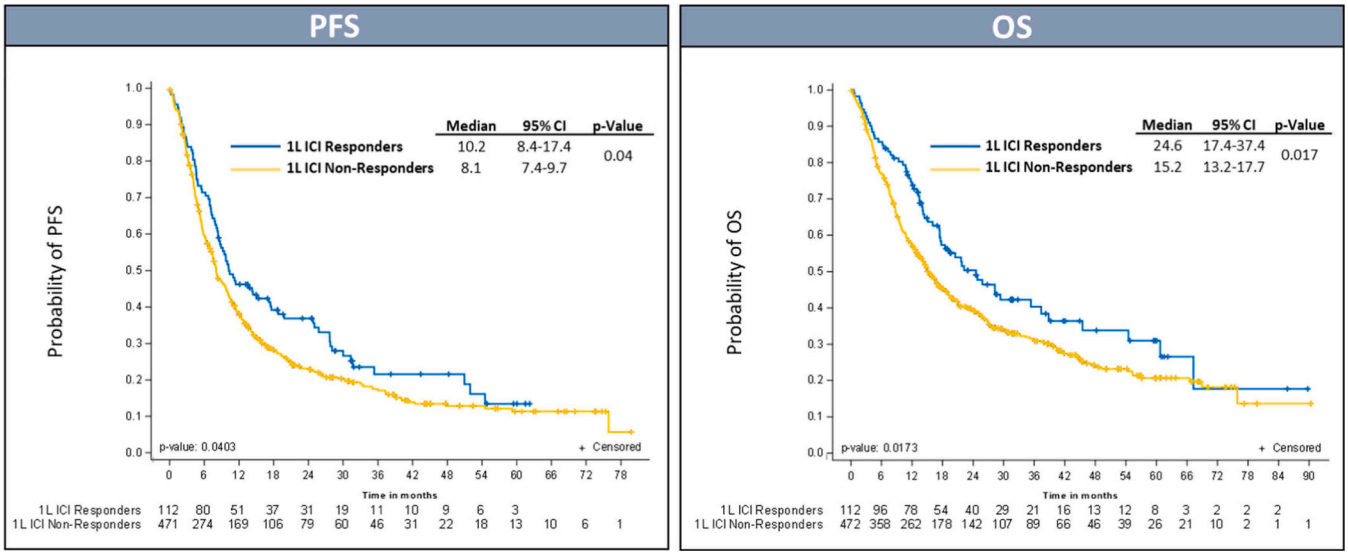

Fig. 3. Protocol-prespecified subgroup analysis for PFS and OS: impact of best overall response to frontline immunotherapy. Patients responding to prior ICI therapy (blue lines) had significantly longer PFS and OS when receiving second-line BRAF/MEKi therapy compared to patients having not responded to first-line ICI (yellow lines). Patients without progression before start of BRAF/MEKi treatment were excluded from the analysis. PFS, progression-free survival; OS, overall survival; ICI, immune checkpoint inhibitor therapy; CI, confidence interval.

M. Weichenthal: consulting/advisory roles: Merck Sharp & Dohme, Roche, Novartis, Bristol Myers and Squibb, Sun Pharma, Sanofi, Pierre Fabre. Honoraria: Merck Sharp & Dohme, Roche, Novartis, Bristol Myers and Squibb, Sanofi. Research funding: institutional funding from Merck Sharp & Dohme, Bristol Myers and Squibb, Novartis, 4SC, Innate Pharma.

I. Gavrilova: consulting/advisory roles: Merck Sharp & Dohme, Bristol Myers and Squibb, Pierre Fabre, Medison. Honoraria: Roche, Novartis, Merck Sharp & Dohme, Bristol Myers and Squibb, Sanofi, Merck, Pierre Fabre, Medison. Speaker's bureau: Roche, Novartis, Merck Sharp & Dohme, Bristol Myers and Squibb, Sanofi, Merck, Pierre Fabre, Medison. Travel/accommodations/expenses: Merck Sharp & Dohme, Bristol Myers and Squibb, Pierre Fabre.

N. Asher: honoraria payments: Novartis, Merck Sharp & Dohme, Bristol Myers and Squibb, Medison, Taro, Sanofi. Research funding: Bristol Myers and Squibb.

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C. Pföhler: served as consultant and/or has received honoraria from Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Sanofi, Sunpharma, Pierre Fabre, AbbVie, Kyona Kirin and Amgen and received travel support from Amgen, Merck Sharp & Dohme , Bristol-Myers Squibb , Pierre Fabre, Sunpharma and Novartis, outside the submitted work.

I. Stojkovski: Advisory Board: Immunocore, Novartis. Invited Speaker: MSD, Roche.

S. Ugurel: consulting/advisory roles: Bristol Myers and Squibb, Merck Sharp & Dohme, Merck, Novartis. Honoraria payments: Almirall, Bristol Myers and Squibb, IGEA Clinical Biophysics, Merck Sharp & Dohme, Novartis, Pierre Fabre, Sun Pharma. Travel/accommodations/expenses: Pierre-Fabre, Sun Pharma. Research funding: Bristol Myers and Squibb, Merck.

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V. Šabarić: Honoraria: Novartis, Bristol Myers Squibb. Travel/Accommodation/Expenses: MSD, Novartis.

A. Soria: Advisory Board/Consultancy/Speaker: Novartis Pharma, BMS, MSD, Piuerre Fabre, Regeneron, Pfizer.

M. Donia: received payments for advisory to Achilles Therapeutics, and is member of the external expert network of Guidepoint Global LLC and Alphasights.

G. Shalamanova: Consulting/advisory roles: MSD, BMS, Roche, Novartis and Merck. Honoraria: MSD, BMS, Roche, Novartis, Merck.

S. Lev-Ari: Travel/accommodations/expenses: BMS/ MSD/ Medison. Research funding: BMS.

R. Shapira: Honoraria: Novartis, BMS, MSD, Roche, Astra-Zeneca.

L. Piccin: Invited Speaker:BMS, MSD, Novartis, Pfizer, Pierre Fabre, Sunpharma. Travel/accommodations/expenses: BMS, MSD, Novartis, Pfizer, Pierre Fabre, Sunpharma.

A. Minisini: Speaker's bureaux: Daiichi Sankio, Novartis. Honoraria payments: Consulting/advisory roles: Astra Zeneca, Daiichi Sankio, Pfizer, Novartis, MSD, BMS, Regeneron, Pierre Fabre, Genomic health, Gilead, Merk, Sunpharma. Travel/accommodations/expenses: Lilly, Gilead, MSD, Pierre Fabre, BMS.

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P. Teterycz: Travel/accommodations/expenses: Pierre-Fabre.

A. Mariuk-Jarema: Research funding: Bristol Myers Squibb, MSD, Novartis, Pierre Fabre.

D. Ziogas: Consulting/advisory roles: Roche, Winmedica. Honoraria payments: Amgen, Astra-Zeneca, Bristol Myers Squibb, Merck Sharp & Dohme, Genesis, Gilead, Ipsen, Pierre Fabre.

C. Gebhardt: Consulting/advisory roles: Beiersdorf, BioNTech, Bristol-Myers Squibb, Immunocore, Merck Sharp & Dohme, Novartis, Pierre-Fabre Pharma, Roche, Sanofi Genzyme, SUN Pharma, Sysmex. Travel/accommodations/expenses: Bristol-Myers Squibb, Pierre Fabre Pharma, SUN Pharma. Speaker's bureau: Almirall, Bristol-Myers Squibb, Immunocore, Janssen, Merck Sharp & Dohme, Novartis, Onkowissen, Pierre-Fabre Pharma, Regeneron, Roche, Sanofi Genzyme, SUN Pharma. Honoraria payments: Beiersdorf, BioNTech, Bristol-Myers Squibb, Immunocore, Merck Sharp & Dohme, Novartis, Pierre-Fabre Pharma, Regeneron, Sanofi Genzyme, SUN Pharma, Sysmex. Research funding: Novartis, Regeneron, Sanofi Genzyme. Stocks/shares: Dermagnostix,

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R. Dummer: intermittent, project focused consulting and/or advisory relationships with Novartis, Merck Sharp & Dhome (MSD), Bristol-Myers Squibb (BMS), Roche, Amgen, Takeda, Pierre Fabre, Sun Pharma, Sanofi, Catalym, Second Genome, Regeneron, T3 Pharma, MaxiVAX SA, Pfizer and Simcere outside the submitted work.

A. Hausschild: Consulting/advisory roles: Bristol Myers and Squibb, Merck Pfizer, Merck Sharp & Dohme/Merck, Philogen, Pierre Fabre, Regeneron, Roche, Sanofi-Genzyme, Novartis Pharma, Eisai, Immunocore, Replimune, Seagen, IO Biotech, Dermagnostix, Incyte, NeraCare, Highlight Therapeutics, Iovance. Honoraria payments: Amgen, Bristol Myers and Squibb, Merck Pfizer, Merck Sharp & Dohme/Merck, Philogen, Pierre Fabre, Regeneron, Roche, Sanofi-Genzyme, Novartis Pharma, Eisai, Immunocore, Replimune, Seagen, IO Biotech, Dermagnostix, Incyte, NeraCare, Highlight Therapeutics, Huya Biosciences, Kyowa Kirin, Iovance. Research funding: Bristol Myers and Squibb, Merck Pfizer, Merck Sharp & Dohme/Merck, Philogen, Pierre Fabre, Regeneron, Roche, Sanofi-Genzyme, Novartis Pharma. Stocks/shares: Melagenix.

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I. von Wasielewski: Consulting/advisory roles: BMS, MSD, Sanofi. Honoraria payment: Novartis, BMS, MSD, Sanofi, Stemline, Kyowa Kirin. Travel/accommodations/expenses: Novartis, BMS, MSD, Sanofi, Stemline, Kyowa Kirin.

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J. Haanen: Consulting/advisory boards: Achilles Tx, AZ, BioNTech, Bristol Myers and Squibb, CureVac, GSK, Immunocore, Instil Bio, Iovance Bio, Merck Serono, Molecular Partners, Merck Sharp & Dohme, Neogene Tx, Novartis, Pfizer, Roche, Serono, Sastra Cell Therapy, Scenic, T-knife. TRV. Stock options: Neogene Tx, Sastra Cell Therapy. Grant support: Amgen, Asher Bio, BioNTech, Bristol Myers and Squibb, Novartis, Sastra Cell Therapy.

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J. Mangana: consultant/advisory roles: Merck/Pfizer, Merck Sharp & Dohme, Novartis, Roche, Pierre Fabre, Amgen, Bristol Myers and Squibb. Travel/accommodations/expenses: Ultrasun, L' oreal, Merck Sharp & Dohme, Bristol Myers and Squibb und Pierre Fabre.

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H. Gogas: consulting/advisory roles: Bristol-Myers Squibb, Merck Sharp & Dohme Oncology, Pierre Fabre, Sanofi/Regeneron. Honoraria: Bristol-Myers Squibb, Merck Sharp & Dohme Oncology, Pierre Fabre, Sanofi/Regeneron. Travel/accommodations/expenses: Merck Sharp & Dohme, Pfizer, Sanofi. Research funding: institutional funding from Bristol-Myers Squibb, Roche, Merck Sharp & Dohme Oncology, Amgen, Novartis, Iovance Biotherapeutics.

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D. Schadendorf: consulting/advisory roles: Astra-Zeneca, Daiichi Sankyo, Erasca, Haystack, Anaevon, Immatics, Immunocore, InFlarX, Innovent, Merck-Serono, Nektar, Neracare, NoviGenix, PamGene, Philogen, Pfizer, Regeneron, BioNTech, Replimune, Roche, Sanofi, Seagen, UltimoVacs, Bristol Myers and Squibb, Merck Sharp & Dohme, Novartis, Pierre-Fabre, Sun Pharma. Honoraria: Bristol Myers and Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre, Sun Pharma. Travel/accommodations/expenses: Pierre-Fabre. Research funding: institutional funding from Bristol Myers and Squibb, Merck Sharp & Dohme, Novartis, Amgen, Roche and Pfizer.

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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.2025.100773.

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