BRAF/MEK inhibitor rechallenge in advanced melanoma patients

Not, O.J. van; Eertwegh, A.J.M. van den; Haanen, J.B.; Rijn, R.S. van; Aarts, M.J.B.; Berkmortel, F.W.P.J. van den; ... ; Suijkerbuijk, K.P.M.

Received: 24 August 2023 | Revised: 12 October 2023 | Accepted: 16 October 2023

DOI: 10.1002/cncr.35178

ORIGINAL ARTICLE

BRAF/MEK inhibitor rechallenge in advanced melanoma patients

Olivier J. Van Not MD[1,2] | Alfons J. M. van den Eertwegh MD, PhD[3] | John B. Haanen MD, PhD[4] | Rozemarijn S. van Rijn MD, PhD[5] | Maureen J. B. Aarts MD, PhD[6] | Franchette W. P. J. van den Berkmortel MD, PhD[7] | Christian U. Blank MD, PhD[4,8] | Marye J. Boers-Sonderen MD, PhD[9] | Jan Willem W. B. de Groot MD, PhD[10] | Geke A. P. Hospers MD, PhD[11] | Ellen Kapiteijn MD, PhD[12] | Manja Bloem MD[1,13,14] | Djura Piersma MD, PhD[15] | Marion Stevense-den Boer MD, PhD[16] | Rik J. Verheijden MSc[2] | Astrid A. M. van der Veldt MD, PhD[17] | Michel W. J. M. Wouters MD, PhD[1,13,14] | Willeke A. M. Blokx MD, PhD[18] | Karijn P. M. Suijkerbuijk MD, PhD[2]

[1]Scientific Bureau, Dutch Institute for Clinical Auditing, Leiden, The Netherlands

[2]Department of Medical Oncology, University Medical Centre Utrecht, Utrecht University, Utrecht, The Netherlands

[3]Department of Medical Oncology, Amsterdam UMC, VU University Medical Center, Cancer Center Amsterdam, Amsterdam, The Netherlands

[4]Department of Molecular Oncology & Immunology, Netherlands Cancer Institute, Amsterdam, The Netherlands

[5]Department of Internal Medicine, Medical Centre Leeuwarden, Leeuwarden, The Netherlands

[6]Department of Medical Oncology, GROW School for Oncology and Developmental Biology, Maastricht University Medical Centre+, Maastricht, The Netherlands

[7]Department of Medical Oncology, Zuyderland Medical Centre Sittard, Sittard-Geleen, The Netherlands

[8]Department of Medical Oncology & Immunology, Netherlands Cancer Institute, Amsterdam, The Netherlands

[9]Department of Medical Oncology, Radboud University Medical Centre, Nijmegen, The Netherlands

[10]Isala Oncology Center, Zwolle, The Netherlands

[11]Department of Medical Oncology, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

[12]Department of Medical Oncology, Leiden University Medical Centre, Leiden, The Netherlands

[13]Department of Biomedical Data Sciences, Leiden University Medical Centre, Leiden, The Netherlands

[14]Department of Surgical Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands

[15]Department of Internal Medicine, Medisch Spectrum Twente, Enschede, The Netherlands

[16]Department of Internal Medicine, Amphia Hospital, Breda, The Netherlands

[17]Department of Medical Oncology and Radiology & Nuclear Medicine, Erasmus Medical Centre, Rotterdam, The Netherlands

[18]Department of Pathology, University Medical Centre Utrecht, Utrecht University, Utrecht, The Netherlands

Correspondence
Karijn P. M. Suijkerbuijk, Postbus 85500, Utrecht, 3508 GA, The Netherlands.
Email: k.suijkerbuijk@umcutrecht.nl

Abstract

Background: Effectivity of BRAF(/MEK) inhibitor rechallenge has been described in prior studies. However, structured data are largely lacking.

Methods: Data from all advanced melanoma patients treated with BRAFi(/MEKi) rechallenge were retrieved from the Dutch Melanoma Treatment Registry. The authors analyzed objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) for both first treatment and rechallenge. They performed a multivariable logistic regression and a multivariable Cox proportional hazards model to assess factors associated with response and survival.

Results: The authors included 468 patients in the largest cohort to date who underwent at least two treatment episodes of BRAFi(/MEKi). Following rechallenge, ORR was 43%, median PFS was 4.6 months (95% confidence interval [CI], 4.1–5.2), and median OS was 8.2 months (95% CI, 7.2–9.4). Median PFS after rechallenge for patients who discontinued first BRAFi(/MEKi) treatment due to progression was 3.1 months (95% CI, 2.7–4.0) versus 5.2 months (95% CI, 4.5–5.9) for patients who discontinued treatment for other reasons. Discontinuing first treatment due to progression and lactate dehydrogenase (LDH) levels greater than two times the upper limit of normal were associated with lower odds of response and worse PFS and OS. Symptomatic brain metastases were associated with worse survival, whereas a longer treatment interval between first treatment and rechallenge was associated with better survival. Responding to the first BRAFi(/MEKi) treatment was not associated with response or survival.

Conclusions: This study confirms that patients benefit from rechallenge. Elevated LDH levels, symptomatic brain metastases, and discontinuing first BRAFi(/MEKi) treatment due to progression are associated with less benefit from rechallenge. A prolonged treatment interval is associated with more benefit from rechallenge.

KEYWORDS
melanoma, rechallenge, response, survival, targeted therapy

INTRODUCTION

The *BRAF* gene is a proto-oncogene encoding B-Raf kinase, which is important for cell signaling and growth. Activating mutations in this *BRAF* gene are the most frequent driver mutations in melanoma, present in nearly half of the patients with advanced melanoma.[1,2] This mutation can be a target for systemic therapy, such as BRAF inhibitors (BRAFi), which have been approved by the Food and Drug Administration as a treatment option for *BRAF* mutant melanoma since 2011.[3,4] The addition of MEK inhibitors to BRAF inhibition has been shown to improve outcomes.[5] Synchronous to the development of targeted therapies, other therapeutic options have been developed and introduced, such as immune checkpoint inhibitors (ICIs), and talimogene laherparepvec.[6–10] The treatment of advanced melanoma is still developing, and new treatment options are being investigated.[11,12] Although several recent studies have indicated that BRAFi/MEKi is not the preferred first-line treatment for most advanced melanoma patients,[13–15] a proportion of patients does derive long-term benefit from BRAF/MEKi.[16]

Still, most patients with *BRAF*-mutant melanoma develop resistance to targeted therapy, leading to disease progression.[5,17] This is why new treatment strategies are being investigated, an example of which is switching to immune checkpoint inhibition on response to targeted therapy.[18] Another treatment strategy is to retreat patients with BRAFi(/MEKi) after prior treatment with BRAFi(/MEKi), also called rechallenge. Between two BRAFi(/MEKi) treatment episodes, the patient is usually exposed to another treatment, such as immunotherapy or experimental treatment. Rechallenge with the same treatment has been shown to be effective in other types of cancer.[19,20] However, studies investigating BRAFi(/MEKi) rechallenge in melanoma are scarce and lack the power to structurally analyze factors associated with outcomes.[21–23] In this nationwide study, we aim to investigate the objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) of patients with unresectable melanoma rechallenged with targeted therapy. Moreover, we try to identify factors associated with response to rechallenge.

MATERIALS AND METHODS

Data were retrieved from the Dutch Melanoma Treatment Registry (DMTR). Data from all systemically treated stage III and IV melanoma patients in the Netherlands have been registered in the DMTR since 2012.[24] All included patients were registered in the DMTR between

2013 and 2022. We analyzed all patients with advanced (i.e., unresectable or metastatic) cutaneous melanoma who were treated with targeted therapy (BRAFi or BRAFi/MEKi) after prior targeted treatment, regardless of treatment line. Rechallenge was defined as a treatment break of at least 30 days between the first treatment and rechallenge with targeted therapy. We included both patients who received other treatments during this break and patients who received rechallenge as an immediate sequential systemic treatment line without intervening therapy. We analyzed the ORR, PFS, and OS for both the first treatment episode with targeted therapy and rechallenge and assessed factors associated with response to rechallenge and survival outcomes following rechallenge.

The medical ethical committee approved research using DMTR data and concluded that it was not deemed subject to the Medical Research Involving Human Subjects Act in compliance with Dutch regulations. For this study, the data set cutoff date was December 5, 2022.

Patient, tumor, and treatment characteristics

Patient and tumor characteristics analyzed for all patients were: age at diagnosis, sex, Eastern Cooperative Oncology Group Performance Status (ECOG PS), lactate dehydrogenase (LDH) levels, primary melanoma location, liver metastasis, brain metastasis, number of organ sites with metastases, stage according to American Joint Committee on Cancer (AJCC) 8th edition,[25] and *BRAF* mutation status. Treatment characteristics were treatment duration in days defined from the start date of BRAFi(/MEKi) until the stop date of BRAFi(/MEKi), reason for BRAFi(/MEKi) discontinuation and number of patients with grade ≥3 toxicity according to the Common Terminology Criteria for Adverse Events.

Statistical analysis

Descriptive statistics were used to analyze baseline characteristics. Categorical variables were compared using the McNemar test; continuous variables were compared using the paired *t*-test or Wilcoxon signed-rank test depending on their distribution. Median follow-up was estimated using the reversed Kaplan–Meier method.[26] We calculated the ORR for the first and second treatment with targeted therapy for advanced melanoma. The treating physician determined the response evaluation according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[27] The ORR was defined as the proportion of evaluable patients who achieved a complete response (CR) or partial response (PR). Patients who did not have a response evaluation registered or who died from no melanoma-related causes before their first response evaluation were excluded from the analysis of ORR. The association of patient, tumor and treatment-related factors with response (CR/PR vs. other) to rechallenge therapy was analyzed using a multivariable logistic regression model. Covariates used for the multivariable logistic regression and multivariable Cox proportional hazards models were age, sex, ECOG PS, LDH levels, brain metastasis, liver metastasis, response (CR/PR) to the first BRAFi(/MEKi) treatment, treatment with immune checkpoint inhibitors (ICIs) between the first treatment and rechallenge, progression as reason for treatment discontinuation of the first BRAFi(/MEKi) treatment, and duration of treatment interval between the two BRAFi(/MEKi) treatment episodes in years. The treatment interval was defined as the time between the stop date of the first BRAFi(/MEKi) treatment and the start date of the rechallenge. Patients with missing values in the covariates were excluded from the multivariable analyses. PFS was defined as time between start of systemic therapy for advanced melanoma to first progression, regardless of treatment line or death. OS was defined as start of systemic therapy to death by any cause. Patients not experiencing an event were right-censored at the date of the last contact. The Kaplan–Meier method was used to calculate the median PFS and OS. Comparisons were considered statistically significant for two-sided p values <0.05. Statistical software used was R studio version 4.0.2[28]: packages tableone,[29] survival,[30] and survminer.[31]

RESULTS

After excluding one patient with mucosal melanoma, a total of 468 patients were included. Median follow-up time from the start of rechallenge was 42.6 months (95% CI, 34.5–51.3). The first treatment with BRAFi(/MEKi) was most frequently during the first treatment line (n = 345; 74%), followed by the second line (n = 85; 18%), and third line (n = 31; 7%). Ninety-four patients received ICIs before their first treatment with BRAFi(/MEKi). Most patients had a reintroduction of BRAF/MEKi in the third treatment line (n = 273; 58.3%), followed by the fourth (n = 102; 21.8%), the fifth (n = 43; 9.2%), and the second (n = 36; 7.7%). Of the 468 patients, most patients (n = 357; 76.3%) received ICIs in the treatment line before their rechallenge. Information regarding all systemic treatment lines before rechallenge is shown in Table S1. Sixty-five patients were rechallenged with BRAFi/MEKi after initial BRAFi monotherapy, and 16 patients were rechallenged with BRAFi monotherapy after BRAFi/MEKi. Sixty-three patients were treated with BRAFi monotherapy twice, and 324 were treated with BRAFi/MEKi twice.

Patient, tumor, and treatment characteristics

Patients, tumor and treatment characteristics at first BRAFi(/MEKi) treatment and at rechallenge can be found in Table 1. Additional information can be found in Table S2. The median age of the included patients at rechallenge was 59 years. When comparing the patient characteristics at baseline to the time of rechallenge, we saw a significant increase in ECOG PS ≥2 (16.7% vs. 19.7%; $p < .001$) and more patients with brain metastases (31.1% vs. 50.7%; $p < .001$). During the first treatment with targeted therapy, treatment discontinuation was most frequently planned (42.5%). Progression was the

TABLE 1 Patient, tumor, and treatment characteristics of advanced melanoma patients treated with a rechallenge of targeted therapy at the time of first BRAFi(/MEKi) treatment and the time of BRAFi(/MEKi) rechallenge.

	First BRAFi(/MEKi) treatment	BRAFi(/MEKi) rechallenge	*p*
No.	468	468	
Age, years			
<70	382 (81.6)	369 (78.8)	<.001
>70	86 (18.4)	99 (21.2)	
Median age (IQR)	58.0 (51.0, 67.0)	59.0 (52.0, 68.0)	<.001
Sex			
Male	261 (55.8)	—	—
Female	207 (44.2)	—	
ECOG PS			
0	181 (38.7)	115 (24.6)	<.001
1	166 (35.5)	162 (34.6)	
≥2	78 (16.7)	92 (19.7)	
Unknown	43 (9.2)	99 (21.2)	
LDH levels			
Not determined	6 (1.3)	6 (1.3)	.392
Normal	257 (54.9)	257 (54.9)	
1–2× ULN	125 (26.7)	124 (26.5)	
>2× ULN	77 (16.5)	74 (15.8)	
Unknown	3 (0.6)	7 (1.5)	
Liver metastases			
No	301 (64.3)	292 (62.4)	.153
Yes	159 (34.0)	162 (34.6)	
Unknown	8 (1.7)	14 (3.0)	
Brain metastases			
No	317 (67.7)	223 (47.6)	<.001
Yes, asymptomatic	62 (13.2)	86 (18.4)	
Yes, symptomatic	84 (17.9)	151 (32.3)	
Unknown	5 (1.1)	8 (1.7)	
Organ sites			
<3	189 (40.4)	175 (37.4)	.222
≥3	278 (59.4)	291 (62.2)	
Unknown	1 (0.2)	2 (0.4)	
AJCC stage (8th edition)			
IIIc unresectable	16 (3.4)	7 (1.5)	<.001
IV-M1a	34 (7.3)	22 (4.7)	
IV-M1b	29 (6.2)	20 (4.3)	
IV-M1c	238 (50.9)	174 (37.2)	
IV-M1d	146 (31.2)	237 (50.6)	
Unknown	5 (1.1)	8 (1.7)	
Type of *BRAF* mutation			
V600E	371 (79.3)	—	—
V600K	33 (7.1)	—	
Other/unknown	64 (13.7)	—	
Type of targeted therapy			
BRAF inhibitor	128 (27.4)	79 (16.9)	<.001
BRAF/MEK inhibitors	340 (72.6)	389 (83.1)	
Median treatment duration BRAFi (/MEKi) in days (IQR)	103.0 (68.0, 180.5)	126.0 (52.0, 224.0)	.314
Reason for BRAFi(/MEKi) treatment discontinuation			
Planned	199 (42.5)	22 (4.7)	<.001
Progression or death	117 (25.0)	294 (62.8)	
Toxicity	78 (16.7)	43 (9.2)	
Still on treatment	0 (0.0)	64 (13.7)	
Unknown	74 (15.8)	45 (9.6)	

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Score; IQR, interquartile range; LDH, lactate dehydrogenase; ULN, upper limit of normal.

reason for treatment discontinuation in 117 (25.0%) patients during first BRAFi(/MEKi) treatment and 294 (72.8%) of the 404 patients who finished rechallenge therapy. Treatment was discontinued due to toxicity in 78 (16.7%) patients during first treatment and 43 (10.6%) patients during rechallenge. Patients more often experienced grade ≥3 toxicity during the first BRAFi(/MEKi) treatment than during the rechallenge (21.2% vs. 10.9%; $p < .001$). However, 64 patients were still on rechallenge treatment. Patients who did not tolerate targeted therapy well in the first episode might have received an adjusted or lower dose of targeted therapy. This could explain the lower number of patients experiencing grade ≥3 toxicity.

ORR

The majority of patients (71%) achieved a CR/PR during the first BRAFi(/MEKi) treatment. Of this 71%, only 6% had a complete response, and 65% had a partial response. The percentage of patients achieving CR/PR during rechallenge was lower: 43%. Again, most patients had a partial response (40%) (Table 2). Logistic regression of ORR of the rechallenge showed that LDH levels greater than two times the upper limit of normal (ULM) at rechallenge were associated

with a lower odds of achieving a response (adjusted odds ratio [OR_{adj}], 0.30; 95% CI, 0.12–0.69).[Table 3] Moreover, discontinuing the first BRAFi(/MEKi) episode due to progression was significantly associated with a lower odds of responding to rechallenge therapy (OR_{adj}, 0.54; 95% CI, 0.31–0.93). A longer treatment interval was not associated with a higher odds of response (OR_{adj}, 1.24; 95% CI, 0.90–

TABLE 2 Objective response rate of advanced melanoma patients treated with a rechallenge of targeted therapy at the time of first BRAFi(/MEKi) treatment and the time of BRAFi(/MEKi) rechallenge.

	First BRAFi(/MEKi) treatment		BRAFi(/MEKi) rechallenge	
Response to therapy	**No.**	**%**	**No.**	**%**
Complete response	26	6	14	3
Partial response	301	65	175	40
Stable disease	108	23	84	19
Progressive disease or death	26	6	164	38
Not evaluable[b]	7	—	31	—
Total no. of evaluable patients	461	100	437	100
Objective response rate[a]	327	71	189	43

[a]Objective response rate $= \frac{(\text{complete response}+\text{partial response})}{(\text{total number of evaluable patients})}$.

[b]Patients who died due to nonmelanoma–related causes or who did not have a registered response rate were excluded from this analysis.

TABLE 3 Logistic regression of objective response rate of advanced melanoma patients treated with a rechallenge of targeted therapy at the time of BRAFi(/MEKi) rechallenge.

	95% CI	OR_{adj}	*p*
(Intercept)	0.48–20.9	1.01	.985
Age, <70 years			
Age, >70 years	0.37–1.25	0.68	.221
Sex, male			
Sex, female	0.65–1.66	1.04	.871
ECOG, 0–1			
ECOG, 2–4	0.52–1.59	0.91	.734
LDH, normal			
LDH, 1–2× ULN	0.41–1.25	0.72	.245
LDH, >2× ULN	0.12–0.69	0.30	.006
Brain metastasis: no			
Brain metastasis: yes, asymptomatic	0.76–2.60	1.40	.284
Brain metastasis: yes, symptomatic	0.36–1.08	0.63	.096
Liver metastasis: no			
Liver metastasis: yes	0.55–1.57	0.92	.769
Response (CR/PR) to first BRAFi(/MEKi) treatment: no			
Response (CR/PR) to first BRAFi(/MEKi) treatment: yes	0.86–2.42	1.44	.168
Progression as reason for treatment discontinuation first BRAFi(/MEKi) treatment: no			
Progression as reason for treatment discontinuation first BRAFi(/MEKi) treatment: yes	0.31–0.93	0.54	.029
Immune checkpoint inhibitors before rechallenge: no			
Immune checkpoint inhibitors before rechallenge: yes	0.54–1.78	0.98	.950
Treatment interval per year	0.91–1.73	1.24	.178

Abbreviations: CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; OR_{adj}, adjusted odds ratio; PR, partial response; ULN, upper limit of normal.

1.73). The presence of a *BRAF* V600E or V600K mutation was not significantly associated with response.

Among patients who stopped first BRAFi(/MEKi) treatment due to progression, ORR of response was 33% (2% CR and 31% PR) versus 47% (4% CR and 43% PR) for patients who did not discontinue treatment due to progression (Table S3).

Survival outcomes

Median PFS was 6.8 months (95% CI, 6.5–7.3) after first BRAFi (/MEKi) treatment compared to 4.8 months (95% CI, 4.3–5.5) after rechallenge (Figure 1). Response to first BRAFi(/MEKi) and receiving ICI before rechallenge were not associated with a higher hazard of progression during rechallenge in both univariable and multivariable analyses. However, progression as the reason for treatment discontinuation of the first BRAFi(/MEKi) episode was significantly associated with a higher hazard of progression (adjusted hazard ratio [HR_{adj}], 1.80; 95% CI, 1.36–2.37). Other factors that were significantly associated with progression or death were LDH levels at rechallenge of one to two times the upper limit of normal (ULN) (HR_{adj}, 1.56; 95% CI, 1.17–2.07) and greater than two times ULN (HR_{adj}, 2.31; 95% CI, 1.55–3.45), and symptomatic brain metastasis (HR_{adj}, 1.44; 95% CI, 1.08–1.94) at rechallenge. Even though a longer treatment interval was not associated with a higher odds of response, it was associated with a lower hazard of progression after rechallenge (HR_{adj}, 0.75; 95% CI, 0.62–0.91) (Figure 2). When dichotomizing the treatment interval into <3 months and >3 months, the HR_{adj} for progression for a treatment interval >3 months was 0.80 (95% CI, 0.61–1.04). When dichotomizing into <6 months and >6 months, the HR_{adj} for progression for a treatment interval >6 months was 0.74 (95% CI, 0.57–0.95). When dichotomizing into >12 months and <12 months, the HR_{adj} for a treatment interval >12 months was 0.62 (95% CI, 0.45–0.86). Patients who discontinued the first BRAFi(/MEKi) treatment due to progression had a median PFS of 3.1 months (95% CI, 2.7–4.0) to rechallenge versus 5.4 months (95% CI, 4.7–6.2) for patients who did not discontinue treatment because of progression (Figure 3).

Calculated from initiation of the first BRAFi(/MEKi) treatment, median OS was 21.1 months (95% CI, 20.2–23.7). Following rechallenge, median OS was reduced to 8.2 months (95% CI, 7.2–9.4) (Figure S1). The multivariable Cox model for OS showed a nonsignificant trend of a higher hazard of death for patients who discontinued the first BRAFi(/MEKi) treatment due to progression (HR_{adj}, 1.32; 95% CI, 0.99–1.76). Again, response to first BRAFi (/MEKi) and receiving ICI before rechallenge were not associated with a higher hazard of death. Patients over 70 years old, with ECOG scores ≥2, LDH levels one to two times ULN and/or greater than two times ULN, and symptomatic brain metastasis also had a significantly higher hazard of death following rechallenge. A prolonged treatment interval was significantly associated with a lower hazard of death (HR_{adj}, 0.69; 95% CI, 0.55–0.87) (Figure S2). To further assess the

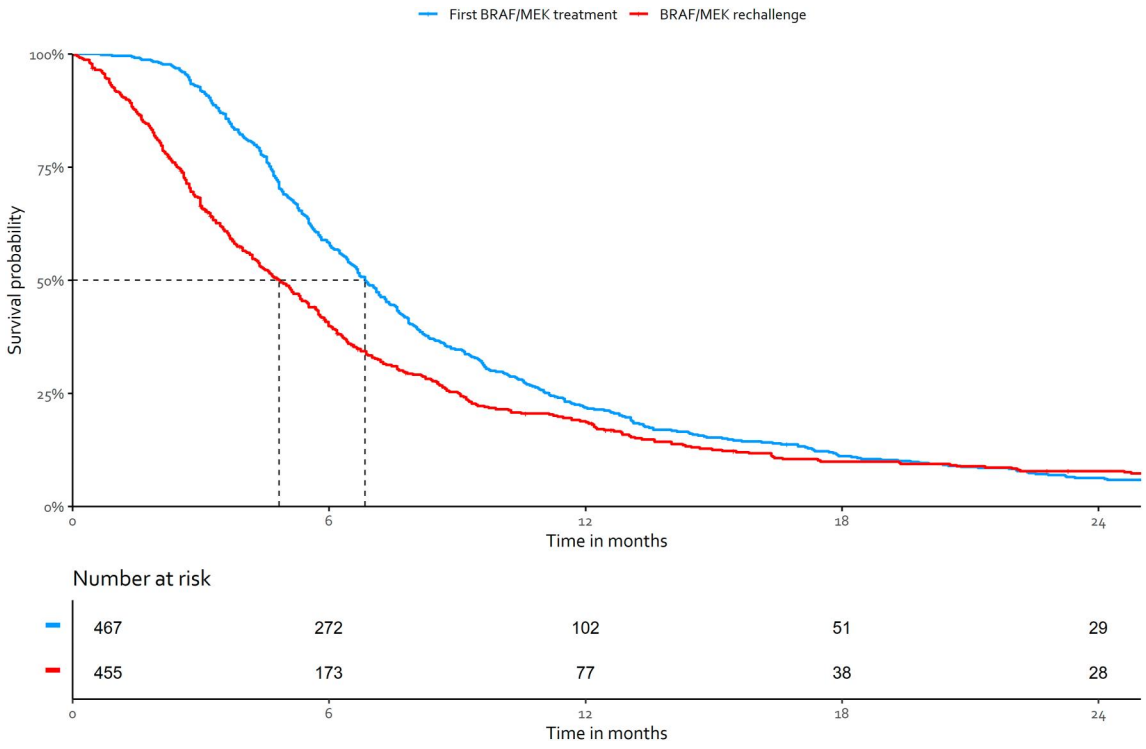

FIGURE 1 Kaplan–Meier curve of progression-free survival of patients with a BRAFi(/MEKi) rechallenge at the time of first BRAFi(/MEKi) treatment and BRAFi(/MEKi) rechallenge.

Variable		N	Hazard ratio	p
Age	0-69	258	Reference	
	>70	60	1.18 (0.87, 1.59)	0.288
Sex	Male	182	Reference	
	Female	136	0.96 (0.75, 1.22)	0.714
ECOG	0-1	236	Reference	
	2-4	82	1.35 (1.01, 1.79)	0.040
LDH	Normal	190	Reference	
	250-500 U/l	90	1.56 (1.17, 2.07)	0.002
	>500 U/l	38	2.31 (1.55, 3.45)	<0.001
Liver metastasis	No	209	Reference	
	Yes	109	1.13 (0.86, 1.48)	0.374
Brain metastasis	No	153	Reference	
	Yes, asymptomatic	65	0.92 (0.66, 1.27)	0.601
	Yes, symptomatic	100	1.44 (1.08, 1.94)	0.014
Response to first BRAFi(/MEKi)	No	98	Reference	
	Yes	220	1.07 (0.81, 1.40)	0.638
Reason stop first BRAFi(/MEKi)	Other reason	234	Reference	
	Progression	84	1.80 (1.36, 2.37)	<0.001
ICIs before rechallenge	No	66	Reference	
	Yes	252	1.00 (0.73, 1.38)	0.998
Treatment interval		318	0.75 (0.62, 0.91)	0.003

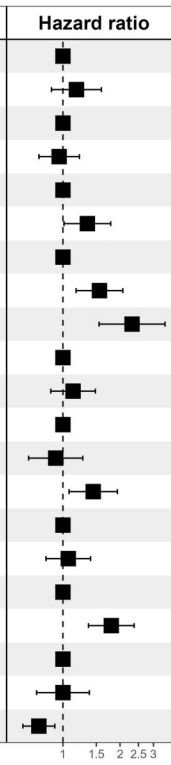

FIGURE 2 Multivariable Cox proportional hazards model of progression-free survival following BRAFi(/MEKi) rechallenge.

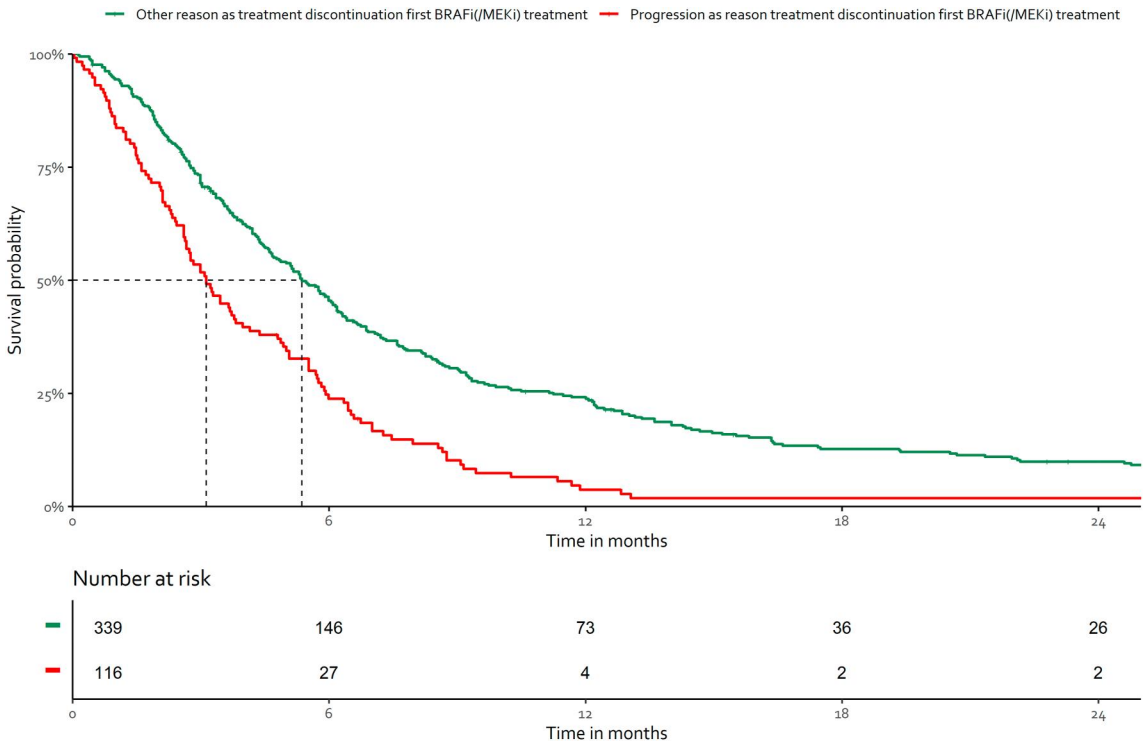

FIGURE 3 Kaplan–Meier curve of progression-free survival following rechallenge of advanced melanoma patients stratified by progression versus other reason for treatment discontinuation of first BRAFi(/MEKi) treatment.

association of the treatment interval with the HR_{adj} for PFS and OS, we flexibly plotted the HR_{adj} for (progression or) death over the time of the treatment interval in months (Figures S3 and S4). These figures suggest that a longer treatment interval between discontinuation of first BRAFi(/MEKi) is linearly associated with prolonged PFS and OS.

Second rechallenge, induction therapy patients, and rechallenge for patients with brain metastases

Fifty-one patients received a second rechallenge. Of these patients, 21 (41%) experienced progression during their first treatment episode with BRAFi(/MEKi) and 26 (51%) experienced progression during their first rechallenge due to progression. The ORR for this cohort was 39% (14% CR and 25% PR). Median PFS following second rechallenge was 6.2 months (95% CI, 4.4–9.2), and median OS following second rechallenge was 9.5 months (95% CI, 6.7–21.3). We separately analyzed 83 patients who received their first BRAFi(/MEKi) episode as an "induction treatment" aimed to improve chance of response to subsequent ipilimumab-nivolumab treatment. These patients had planned discontinuation of their first BRAFi(/MEKi) treatment, followed by ipilimumab-nivolumab treatment. Following BRAF/MEKi rechallenge, the ORR for this group was 55% (1% CR and 54% PR) and median PFS was 5.3 months (95% CI, 4.6–7.1).

For patients with asymptomatic or symptomatic brain metastases, ORR was 42% (1% CR, 41% PR). Median PFS was 5.8 months (95% CI, 5.2–6.5) after first treatment and 4.3 months (95% CI, 3.7–5.2) after rechallenge. Median OS was 18.5 months (95% CI, 14.3–22.0) after first treatment and 6.8 months (95% CI, 5.9–8.2) after rechallenge.

DISCUSSION

In this study, we present the outcomes for rechallenge therapy with BRAFi(/MEKi) in the largest cohort to date of patients with unresectable melanoma. Median PFS following first BRAFi(/MEKi) treatment was 6.8 months, which is lower than reported in trials. This can be explained by the fact that 94 patients already received ICIs before first treatment with BRAFi(/MEKi). Moreover, 31% of our included patients had brain metastases, 17% had an ECOG PS of ≥2, and 17% had LDH levels greater than two times ULN. These factors have been shown to be associated with poorer treatment outcomes.[32] Although response rate and duration in the rechallenge setting are lower than in the first episode, patients do derive benefit from rechallenge, even after previous progression. One of our goals was to identify factors associated with response and survival following rechallenge. We found known predictive factors of BRAFi(/MEKi) primary treatment, such as a high ECOG PS, elevated LDH levels, and the presence of symptomatic brain metastasis to be associated with poorer survival after rechallenge. This aligns with previous research investigating factors associated with survival in BRAFi/MEKi therapy outside of the rechallenge setting.[16,33,34] In our cohort, 199 patients had a planned discontinuation of first BRAFi(/MEKi) treatment. Of these patients, 178 started ICI treatment after first BRAFi(/MEKi) treatment, indicating that a planned switch to treatment with ICIs can explain this relatively high percentage of planned discontinuation. Not surprisingly, patients who had discontinued first BRAFi(/MEKi) treatment because of progression had a lower odds of responding to rechallenge therapy and a higher chance of progression or death. Responding to the first BRAFi(/MEKi) treatment or receiving ICIs before rechallenge was not associated with better outcomes, but a longer treatment interval between the targeted therapies was. When dichotomizing the treatment interval at 3 months, the HR_{adj} for PFS was not significant (HR_{adj}, 0.80; 95% CI, 0.61–1.04). The treatment interval did become significant when dichotomized at 6 and at 12 months. A longer treatment interval seems associated with better outcomes.

Sun et al.[35] raised the hypothesis based on preclinical and translational data that some patients who develop resistance to BRAFi(/MEKi) therapy may benefit from a period free of targeted therapy. This was preceded by a report of Seghers et al.[36] who described successful clinical rechallenge, but the exact mechanism behind this finding is yet to be fully elucidated. It has been suggested that the phenotype switching of melanoma cells to acquire resistance to targeted therapy could be reversible when withdrawing the driving stimulus.[21,37–39] Several other studies have investigated rechallenge with BRAFi(/MEKi) in advanced melanoma. Schreuer et al.[23] conducted a prospective clinical trial including 25 patients who had previously progressed on BRAFi(/MEKi). After an off-treatment period of at least 12 weeks, they were treated with dabrafenib/trametinib. The authors found a partial response in eight patients (32%) and no ORR in patients with an elevated baseline LDH. Valpione et al.[40] included 116 patients with metastatic melanoma who received BRAFi and were rechallenged with BRAFi (/MEKi). They reported comparable outcomes to our present study: the response rate to rechallenge therapy was 43%, mainly consisting of PR (39%). Median PFS after rechallenge was 5.0 months and median OS was 9.8 months. They found an increase in the number of metastatic sites and elevated LDH to be associated with worse OS and combination of BRAFi/MEKi with better OS compared to BRAFi alone. Tietze et al.[41] reported a lower ORR of 28% (8% CR and 20% PR) in 60 advanced melanoma patients who were rechallenged, but a comparable PFS of 5.0 months. The only predictive factor for response to rechallenge therapy they found was responding to the first targeted therapy. Cybulska et al.[42] included 51 patients who were rechallenged with BRAFi/MEKi after progressing on prior BRAFi/MEKi and found a median OS rate of 29.7 following the first BRAFi/MEKi therapy and 9.3 months after rechallenge. OS following BRAFi/MEKi rechallenge was negatively influenced by male sex, presence of brain metastases, elevated LDH levels, and an ECOG ≥2.

The present study has some limitations. Population-based studies are more prone to missing data than clinical trials. However, DMTR data is registered by regularly trained, independent data managers. Registered data is checked by treating physicians to warrant the quality. Moreover, the online registry in which patients are registered warns data managers of inconsistent or missing values. The high quality and low number of missing values in the DMTR have been demonstrated in an earlier study.[24] Observational studies, such as the current study, are also prone to biases, including bias by indication. Although we have tried to adjust for

potential confounders in our multivariable analysis, residual confounding as a potential explanation for the findings of this study cannot be ruled out.

The present study shows that patients can derive benefit from rechallenge with BRAFi(/MEKi). Response to rechallenge was not associated with response to or duration of the first BRAFi(/MEKi) treatment. However, patients with elevated LDH levels, symptomatic brain metastases, and those who discontinued prior BRAFi(/MEKi) due to progression benefit less from rechallenge. In contrast, a prolonged treatment interval is associated with better outcomes after BRAF/MEKi rechallenge. Future studies should focus on finding the optimal rechallenge strategy in terms of treatment interval and intermittent treatment to optimize survival after rechallenge in advanced melanoma patients.

AUTHOR CONTRIBUTIONS

Olivier J. Van Not: Conceptualization, methodology, writing–original draft, writing–review and editing, project administration, formal analysis, data curation, and investigation. **Alfons J. M. van den Eertwegh**: Investigation, project administration, and writing–review and editing. **John B. Haanen**: Writing–review and editing, project administration, and investigation. **Rozemarijn S. van Rijn**: Investigation, writing–review and editing, and project administration. **Maureen J. B. Aarts**: Project administration, writing–review and editing, and investigation. **Franchette W. P. J. van den Berkmortel**: Investigation, writing–review and editing, and project administration. **Christian U. Blank**: Project administration, writing–review and editing, and investigation. **Marye J. Boers-Sonderen**: Investigation, writing–review and editing, and project administration. **Jan Willem W. B. de Groot**: Project administration, writing–review and editing, and investigation. **Geke A. P. Hospers**: Investigation, writing–review and editing, and project administration. **Ellen Kapiteijn**: Project administration, writing–review and editing, and investigation. **Manja Bloem**: Investigation, writing–review and editing, and project administration. **Djura Piersma**: Project administration, writing–review and editing, and investigation. **Marion Stevense-den Boer**: Investigation, writing–review and editing, and project administration. **Rik J. Verheijden**: Investigation, writing–review and editing, formal analysis, and methodology. **Astrid A. M. van der Veldt**: Investigation, writing–review and editing, and project administration. **Gerard Vreugdenhil**: Project administration, writing–review and editing, and investigation. **Michel W. J. M. Wouters**: Investigation, project administration, writing–review and editing, conceptualization, methodology, and supervision. **Willeke A. M. Blokx**: Conceptualization, writing–review and editing, investigation, project administration, data curation, and methodology. **Karijn P. M. Suijkerbuijk**: Data curation, project administration, writing–review and editing, investigation, conceptualization, and methodology.

ACKNOWLEDGMENTS

For the Dutch Melanoma Treatment Registry (DMTR), the Dutch Institute for Clinical Auditing foundation received a start-up grant from governmental organization The Netherlands Organization for Health Research and Development (ZonMW, project number 836002002). The DMTR is structurally funded by Bristol-Myers Squibb, Merck Sharpe & Dohme, Novartis, and Roche Pharma. Roche Pharma stopped funding in 2019, and Pierre Fabre started funding the DMTR in 2019. For this work, no funding was granted. The medical ethical committee approved research using DMTR data and concluded that it was not deemed subject to the Medical Research Involving Human Subjects Act in compliance with Dutch regulations.

CONFLICT OF INTEREST STATEMENT

Alfons J. M. van den Eertwegh has advisory relationships with Amgen, Bristol-Myers Squibb, Roche, Novartis, MSD, Pierre Fabre, Sanofi, Pfizer, Ipsen, and Merck; has received research study grants not related to this article from Sanofi, Roche, Bristol-Myers Squibb, Idera, and TEVA; has received travel expenses from MSD Oncology, Roche, Pfizer and Sanofi; and has received speaker honoraria from Bristol-Myers Squibb and Novartis. John B. Haanen has advisory relationships with Achilles Therapeutics, AstraZeneca, Bristol-Myers Squibb, BioNTech, CureVac, Imcyse, Immunocore, Iovance Biotherapeutics, Instil Bio, Ipsen, MSD, Merck Serono, Molecular Partners, Novartis, Neogene Therapeutics, Pfizer, PokeAcel, Roche/Genentech, Sanofi, T-Knife, and Third Rock Ventures; and has received research grants not related to this article from Asher Bio, Amgen, BioNTech, Bristol-Myers Squibb, MSD, Novartis, and Sastra Cell Therapy (all grants were paid to the institutions). Christian U. Blank has/had advisory roles with Bristol-Myers Squibb, MSD, Roche, Novartis, GSK, Astra-Zeneca, Pfizer, Lilly, GenMab, Pierre Fabre, and Third Rock Ventures; has received research funding from Bristol-Myers Squibb, Novartis, NanoString, and 4SC; has stock ownership and is a cofounder of Immagene BV and Signature Oncology; and has patents (including submitted) WO 2021/177822 A1, N2027907, and P091040NL2. Maureen J. B. Aarts has received advisory board/consultancy honoraria from Amgen, Bristol-Myers Squibb, Novartis, MSD-Merck, Merck-Pfizer, Pierre Fabre, Sanofi, Astellas, and Bayer; and has received research grants from Merck-Pfizer (not related to current work and paid to institute). Jan Willem W. B. de Groot has consultancy and/or advisory relationships with Bristol-Myers Squibb, Pierre Fabre, Servier, MSD, and Novartis. Geke A. P. Hospers has consultancy/advisory relationships with Amgen, Bristol-Myers Squibb, Roche, MSD, Pfizer, Novartis, and Pierre Fabre; and has received research grants not related to this article from Bristol-Myers Squibb and Seerave (all grants were paid to the institution). Ellen Kapiteijn has consultancy/advisory relationships with Bristol-Myers Squibb, Novartis, Merck, Pierre Fabre, Lilly, and Bayer not related to current work and paid to the institution; and received research grants not related to this article from Bristol-Myers Squibb, Delcath, and Pierre-Fabre. Rozemarijn S. van Rijn has advisory board/consultancy honoraria from Pfizer and an expert meeting fee from Roche. Astrid A. M. van der Veldt has consultancy relationships with Bristol-Myers Squibb, MSD, Roche, Novartis, Pierre Fabre, Pfizer, Sanofi, Ipsen, Eisai, and Merck (all paid to the institution). Marye J. Boers-Sonderen has consultancy/advisory relationships with Pierre

Fabre, MSD, and Novartis. Karijn P. M. Suijkerbuijk has advisory relationships with Bristol-Myers Squibb, Novartis, MSD, Pierre Fabre, and AbbVie; received honoraria from Novartis, MSD, and Roche; and received research funding from BMS, Philips, and TigaTx. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are not publicly available but can be shared on reasonable request from the corresponding author.

ORCID

Karijn P. M. Suijkerbuijk https://orcid.org/0000-0003-3604-5430

REFERENCES

1. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. *Nature*. 2002;417(6892):949-954. doi:10.1038/nature00766
2. van Not OJ, Blokx WAM, van den Eertwegh AJM, et al. BRAF and NRAS mutation status and response to checkpoint inhibition in advanced melanoma. *JCO Precis Oncol*. 2022(6):1-11. doi:10.1200/po.22.00018
3. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med*. 2011;364(26):2507-2516. doi:10.1056/nejmoa1103782
4. Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600–mutant advanced melanoma treated with vemurafenib. *N Engl J Med*. 2012;366(8):707-714. doi:10.1056/nejmoa1112302
5. Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2018;19(5):603-615. doi:10.1016/S1470-2045(18)30142-6
6. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363(8):711-723. doi:10.1056/NEJMoa1003466
7. Wolchok JD, Hodi FS, Weber JS, et al. Development of ipilimumab: a novel immunotherapeutic approach for the treatment of advanced melanoma. *Ann N Y Acad Sci*. 2013;1291(1):1-13. doi:10.1111/nyas.12180
8. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med*. 2015;372(26):2521-2532. doi:10.1056/nejmoa1503093
9. Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med*. 2013;369(2):122-133. doi:10.1056/NEJMoa1302369
10. Andtbacka RHI, Kaufman HL, Collichio F, et al. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. *J Clin Oncol*. 2015;33(25):2780-2788. doi:10.1200/JCO.2014.58.3377
11. Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. *N Engl J Med*. 2022;386(1):24-34. doi:10.1056/nejmoa2109970
12. Rohaan MW, Borch TH, van den Berg JH, et al. Tumor-infiltrating lymphocyte therapy or ipilimumab in advanced melanoma. *N Engl J Med*. 2022;387(23):2113-2125. doi:10.1056/NEJMoa2210233
13. Ascierto PA, Mandalà M, Ferrucci PF, et al. Sequencing of ipilimumab plus nivolumab and encorafenib plus binimetinib for untreated BRAF-mutated metastatic melanoma (SECOMBIT): a randomized, three-arm, open-label phase II trial. *J Clin Oncol*. 2023;41(2):212-221. doi:10.1200/JCO.21.02961
14. Atkins MB, Lee SJ, Chmielowski B, et al. Combination dabrafenib and trametinib versus combination nivolumab and ipilimumab for patients with advanced BRAF-mutant melanoma: the DREAMseq Trial - ECOG-ACRIN EA6134. *J Clin Oncol*. 2023;41(2):186-197. doi:10.1200/JCO.22.01763
15. van Breeschoten J, Wouters MWJM, Hilarius DL, et al. First-line BRAF/MEK inhibitors versus anti-PD-1 monotherapy in BRAFV600-mutant advanced melanoma patients: a propensity-matched survival analysis. *Br J Cancer*. 2021;124(7):1222-1230. doi:10.1038/s41416-020-01229-1
16. Ismail RK, Suijkerbuijk KPM, De Boer A, et al. Long-term survival of patients with advanced melanoma treated with BRAF-MEK inhibitors. *Melanoma Res*. 2022;32(6):460-468. doi:10.1097/CMR.0000000000000832
17. Kakadia S, Yarlagadda N, Awad R, et al. Mechanisms of resistance to BRAF and MEK inhibitors and clinical update of us food and drug administration-approved targeted therapy in advanced melanoma. *Onco Targets Ther*. 2018;11:7095-7107. doi:10.2147/OTT.S182721
18. Schouwenburg MG, Suijkerbuijk KPM, Koornstra RHT, et al. Switching to immune checkpoint inhibitors upon response to targeted therapy; the road to long-term survival in advanced melanoma patients with highly elevated serum LDH? *Cancers*. 2019;11(12):1940. doi:10.3390/cancers11121940
19. Zama IN, Hutson TE, Elson P, et al. Sunitinib rechallenge in metastatic renal cell carcinoma patients. *Cancer*. 2010;116(23):5400-5406. doi:10.1002/cncr.25583
20. Santini D, Vincenzi B, Addeo R, et al. Cetuximab rechallenge in metastatic colorectal cancer patients: how to come away from acquired resistance? *Ann Oncol*. 2012;23(9):2313-2318. doi:10.1093/annonc/mdr623
21. Valpione S, Carlino MS, Mangana J, et al. Rechallenge with BRAF-directed treatment in metastatic melanoma: a multi-institutional retrospective study. *Eur J Cancer*. 2018;91:116-124. doi:10.1016/j.ejca.2017.12.007
22. Chen G, McQuade JL, Panka DJ, et al. Clinical, molecular, and immune analysis of dabrafenib-trametinib combination treatment for braf inhibitor-refractorymetastatic melanoma a phase 2 clinical trial. *JAMA Oncol*. 2016;2(8):1056-1064. doi:10.1001/jamaoncol.2016.0509
23. Schreuer M, Jansen Y, Planken S, et al. Combination of dabrafenib plus trametinib for BRAF and MEK inhibitor pretreated patients with advanced BRAFV600-mutant melanoma: an open-label, single arm, dual-centre, phase 2 clinical trial. *Lancet Oncol*. 2017;18(4):464-472. doi:10.1016/S1470-2045(17)30171-7
24. Jochems A, Schouwenburg MG, Leeneman B, et al. Dutch Melanoma Treatment Registry: quality assurance in the care of patients with metastatic melanoma in the Netherlands. *Eur J Cancer*. 2017;72:156-165. doi:10.1016/j.ejca.2016.11.021
25. Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017;67(6):472-492. doi:10.3322/caac.21409
26. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Contr Clin Trials*. 1996;17(4):343-346. doi:10.1016/0197-2456(96)00075-X
27. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247. doi:10.1016/j.ejca.2008.10.026
28. R Core Team. R: A language and environment for statistical computing; 2017.
29. Yoshida K, Bartel A. tableone: Create "Table 1" to Describe Baseline Characteristics with or without Propensity Score Weights; 2020.
30. Therneau TM, Grambsch PM. *Modeling Survival Data: Extending the Cox Model*. Springer; 2000.

31. Kassambra A, Kosinski M, Biecek P. Survminer: Drawing Survival Curves using 'ggplot2; 2020.
32. Schouwenburg MG, Jochems A, Leeneman B, et al. Vemurafenib in BRAF-mutant metastatic melanoma patients in real-world clinical practice: prognostic factors associated with clinical outcomes. *Melanoma Res*. 2018;28(4):326-332. doi:10.1097/CMR.0000000000000453
33. Robert C, Grob JJ, Stroyakovskiy D, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. *N Engl J Med*. 2019;381(7):626-636. doi:10.1056/nejmoa1904059
34. Ismail RK, Sikkes NO, Wouters MWJM, et al. Postapproval trials versus patient registries: comparability of advanced melanoma patients with brain metastases. *Melanoma Res*. 2021;31(1):58-66. doi:10.1097/CMR.0000000000000707
35. Sun C, Wang L, Huang S, et al. Reversible and adaptive resistance to BRAF(V600E) inhibition in melanoma. *Nature*. 2014;508(1):118-122. doi:10.1038/nature13121
36. Seghers AC, Wilgenhof S, Lebbé C, Neyns B. Successful rechallenge in two patients with BRAF-V600-mutant melanoma who experienced previous progression during treatment with a selective BRAF inhibitor. *Melanoma Res*. 2012;22(6):466-472. doi:10.1097/CMR.0b013e3283541541
37. Levesque MP, Cheng PF, Raaijmakers MIG, Saltari A, Dummer R. Metastatic melanoma moves on: translational science in the era of personalized medicine. *Cancer Metastasis Rev*. 2017;36(1):7-21. doi:10.1007/s10555-017-9658-0
38. Kemper K, De Goeje PL, Peeper DS, Van Amerongen R. Phenotype switching: tumor cell plasticity as a resistance mechanism and target for therapy. *Cancer Res*. 2014;74(21):5937-5941. doi:10.1158/0008-5472.CAN-14-1174
39. Gebhardt C, Ascierto P, Atkinson V, Corrie P, Dummer R, Schadendorf D. The concepts of rechallenge and retreatment in melanoma: a proposal for consensus definitions. *Eur J Cancer*. 2020;138:68-76. doi:10.1016/j.ejca.2020.07.016
40. Valpione S, Carlino MS, Mangana J, et al. Rechallenge with BRAF-directed treatment in metastatic melanoma: a multi-institutional retrospective study. *Eur J Cancer*. 2018;91:116-124. doi:10.1016/j.ejca.2017.12.007
41. Tietze JK, Forschner A, Loquai C, et al. The efficacy of re-challenge with BRAF inhibitors after previous progression to BRAF inhibitors in melanoma: a retrospective multicenter study. *Oncotarget*. 2018;9(76):34336-34346. doi:10.18632/oncotarget.26149
42. Cybulska-Stopa B, Rogala P, Czarnecka AM, et al. BRAF and MEK inhibitors rechallenge as effective treatment for patients with metastatic melanoma. *Melanoma Res*. 2020;30(5):465-471. doi:10.1097/CMR.0000000000000662

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Van Not OJ, van den Eertwegh AJM, Haanen JB, et al. BRAF/MEK inhibitor rechallenge in advanced melanoma patients. *Cancer*. 2024;1-11. doi:10.1002/cncr.35178