BJC British Journal of Cancer

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ARTICLE

Clinical Study

First-line BRAF/MEK inhibitors versus anti-PD-1 monotherapy in BRAF^{V600}-mutant advanced melanoma patients: a propensity-matched survival analysis

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BACKGROUND: Anti-PD-1 antibodies and BRAF/MEK inhibitors are the two main groups of systemic therapy in the treatment of BRAF^{V600}-mutant advanced melanoma. Until now, data are inconclusive on which therapy to use as first-line treatment. The aim of this study was to use propensity score matching to compare first-line anti-PD-1 monotherapy vs. BRAF/MEK inhibitors in advanced BRAF^{V600}-mutant melanoma patients.

METHODS: We selected patients diagnosed between 2014 and 2017 with advanced melanoma and a known BRAF^{V600}-mutation treated with first-line BRAF/MEK inhibitors or anti-PD-1 antibodies, registered in the Dutch Melanoma Treatment Registry. Patients were matched based on their propensity scores using the nearest neighbour and the optimal matching method.

RESULTS: Between 2014 and 2017, a total of 330 and 254 advanced melanoma patients received BRAF/MEK inhibitors and anti-PD-1 monotherapy as first-line systemic therapy. In the matched cohort, patients receiving anti-PD-1 antibodies as a first-line treatment had a higher median and 2-year overall survival compared to patients treated with first-line BRAF/MEK inhibitors, 42.3 months (95% CI: 37.3-NE) vs. 19.8 months (95% CI: 16.7–24.3) and 85.4% (95% CI: 58.1–73.6) vs. 41.7% (95% CI: 34.2–51.0).

CONCLUSIONS: Our data suggest that in the matched BRAF^{V600}-mutant advanced melanoma patients, anti-PD-1 monotherapy is the preferred first-line treatment in patients with relatively favourable patient and tumour characteristics.

British Journal of Cancer https://doi.org/10.1038/s41416-020-01229-1

BACKGROUND

Over the last decade, new systemic treatment options have emerged in the treatment of metastatic melanoma. These approved treatments can be divided into two main groups: targeted therapy consisting of BRAF and MEK inhibitors[1,2] and immunotherapy, anti-PD-1 and anti-CTLA-4 monoclonal antibodies.[3–5] Their introduction has increased the overall survival of these patients.[2,6] Based on clinical consensus, treatment choice depends on several prognostic and predictive factors such as BRAF-mutation status, lactate dehydrogenase levels (LDH), performance status and the tumour stage.

As BRAF/MEK inhibitors have a rapid onset and a high overall response rate (ORR), they are often considered the preferred primary treatment for patients with extensive (symptomatic) disease and a BRAF^{V600}-mutation. However, in such patients, the response duration is relatively short due to acquired resistance.[7] As time to response for immunotherapy is generally longer and ORR lower, checkpoint inhibition is usually not the preferred treatment for BRAF-mutant patients with poor prognostic factors such as a poor performance score or elevated LDH.[8] Therefore, the perception that checkpoint inhibition leads to more durable responses could at least partially be explained by the fact that patients with better

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Received: 2 July 2020 Revised: 30 November 2020 Accepted: 10 December 2020
Published online: 26 January 2021

prognostic factors are being treated with immunotherapy. Although interstudy comparison suggests that immunotherapy results in more durable responses as compared to targeted therapy,[9] these results need to be interpreted with caution due to the potential biases associated with this type of analysis.

Due to the confounding by indication bias, a head-to-head comparison between both groups, based on real-world data is difficult. Propensity score matching, a statistical method developed by Rosenbaum and Rubins,[10] accounts for the unequal distribution of confounders. A propensity score is the chance of receiving the treatment, based on measured confounders such as age and tumour stage.[11,12] This method matches patients based on their propensity score, creating two groups with similar distribution of confounders.

In this study, we (1) compare OS of BRAF/MEK inhibitors and anti-PD-1 monotherapy in BRAF-mutant advanced melanoma patients, and (2) use propensity score matching to determine the overall survival in the BRAF/MEK inhibitors vs. anti-PD-1 monotherapy groups after matching.

METHODS

Study design and population

This longitudinal observational study used data from the Dutch Melanoma Treatment Registry (DMTR), a population-based, prospective registry capturing all patients with unresectable stage IIIc and IV melanoma in the Netherlands. Since the 1 July 2013, all patients with unresectable stage IIIC or stage IV melanoma seen in one of the 14 melanoma centres have been registered in the DMTR. Data are prospectively registered from diagnosis until death. Patients are followed every three months for changes in disease status, patients' characteristics or treatment characteristics by an independent trained data manager. A detailed description of the DMTR setup has been published by Jochems et al.[13]

All patients of 18 years and older, diagnosed between 2014 and 2017 (dataset cut-off date was 01-08-2019) with unresectable stage IIIC and IV melanoma, with a known $BRAF^{V600}$-mutation who used anti-PD-1 monotherapy (pembrolizumab or nivolumab) or BRAF/MEK inhibitors (dabrafenib + trametinib or vemurafenib + cobimetinib) as a first-line systemic therapy, were selected for analysis. Combination therapies of encorafenib + binimetinib and ipilimumab + nivolumab were not yet available during this time period. Line of therapy was defined as the start of a new drug class. Patients with uveal or mucosal melanoma were excluded from this analysis.

Statistical analysis

Baseline patient- and disease characteristics of $BRAF^{V600}$-mutant patients were analysed using descriptive statistics. Categorical variables were compared using the Chi-square test. Overall survival (OS) was defined as time from start systemic treatment until death from any cause with corresponding two-sided 95% confidence intervals and was estimated using the Kaplan–Meier method. TTNT was defined as the time until next treatment of a new drug class or death from any cause. OS and TTNT between subgroups was compared using log-rank tests for categorical variables. Patients alive or lost to follow-up were right-censored at the time of last registered contact.

In order to reduce confounding by indication, propensity score matching was used. As a first step, a multivariable logistic regression analysis was used to estimate propensity scores. Covariates used for the multivariable logistic regression were age at diagnosis (<75, ≥75), baseline ECOG-performance status (0–1 and ≥2), baseline lactate dehydrogenase (LDH) (normal, 250–500 U/L and >500 U/L), stage at diagnosis (unresectable IIIc, IV-M1a, M1b and IV-M1c), distant metastasis (<3 organ sites and ≥3 organ sites involved), brain metastases (none, asymptomatic, and symptomatic) and liver metastases (yes/no) and use of immunomodulating agents (corticosteroids, azathioprine and interferon). Covariates were chosen based on clinical practice and previous research identifying these prognostic risk factors.[14,15] A Monte Carlo simulation study has demonstrated that his method of selecting covariates for propensity score matching works very well.[16]

A multivariable Cox proportional hazards model was used to assess the association of prognostic factors with OS. Prognostic factors estimated were age at diagnosis (<75, ≥75), baseline ECOG-performance status (0–1 and ≥2), baseline lactate dehydrogenase (LDH; normal, 250–500 U/L and >500 U/L), distant metastases (<3 organ sites and ≥3 organ sites involved), brain metastases (none, asymptomatic and symptomatic) and liver metastases (yes/no). The proportional hazards assumption was tested with the scaled Schoenfeld residuals. None of the covariates violated the proportional hazards assumption.

For matching purposes, 1:1 nearest neighbour matching with a calliper set of 0.001 was used for propensity score matching. To assess the quality of matching, standardised mean differences for all covariates were calculated. Standardised mean differences of <0.1 were assumed to be negligible. After matching, a univariable Cox proportional hazards model with a robust variance estimator to account for the matched nature of the sample was used to estimate the relative change in hazard of survival.[17,18] To address potential biases due to incomplete matching, we compared our results to a second matched sample set using optimal matching. Optimal matching forms matched pairs to minimise the average within-pair difference in propensity scores.[19] We used both matching techniques in order to observe the influence of well-balanced prognostic factors across both groups in the nearest neighbour-matched group on OS and TTNT compared to the optimal matching method. Due to the matched nature, the use of a log-rank test comparing the survival curves will likely result in type I error rates that are artificially low,[20] stratified log-rank tests were used to compare the survival curves of the matched samples.[18] Statistical software used was R (version 3.5.2; packages car, tidyverse, survival and matchit).

RESULTS

Patient characteristics

Between 1-1-2014 and 31-12-2017, a total of 330 and 254 BRAF-mutant patients with unresectable stage IIIc or IV melanoma received BRAF/MEK inhibitors or anti-PD-1 monotherapy, respectively, as first-line systemic therapy (Fig. 1). Overall, patients receiving BRAF/MEK inhibitors as a first-line systemic treatment had a higher ECOG-performance status (≥2: 23.0% vs. 8.7%), elevated LDH levels, (50.3% vs 22.4%), IV-M1c disease (87.6% vs. 67.3%), brain metastases (41.8% vs. 18.5%), liver metastases (33.9% vs. 21.3%) and metastases in more organ sites (≥3 organ sites: 59.4% vs. 42.5%) (Table 1). There was no significant difference in age and gender between patients receiving first-line treatment with BRAF/MEK inhibitors and anti-PD-1 ligands. Median follow-up time, calculated with a reverse Kaplan–Meier was 28.3 months for the total population. Subsequent therapies are shown in Supplement 1 and subsequent therapies of progressive patients are shown in Supplement 2. Overall, progressive patients that received first-line BRAF/MEK inhibitors receive less second and third-line therapy compared to patients receiving first-line anti-PD-1, 61.3% vs. 94.2% and 6.5% vs.43.4%.

Predictors of receiving first-line BRAF/MEK inhibitors

To determine which factors were associated with receiving first-line BRAF/MEK inhibitors, a multivariable logistic regression was performed (Table 2). The results show that an ECOG-performance status of ≥2 (OR: 1.93, 95% CI: 1.11–3.44), elevated LDH (OR: 2.84, 95% CI: 1.86–4.38) and symptomatic brain metastases (OR: 3.84,

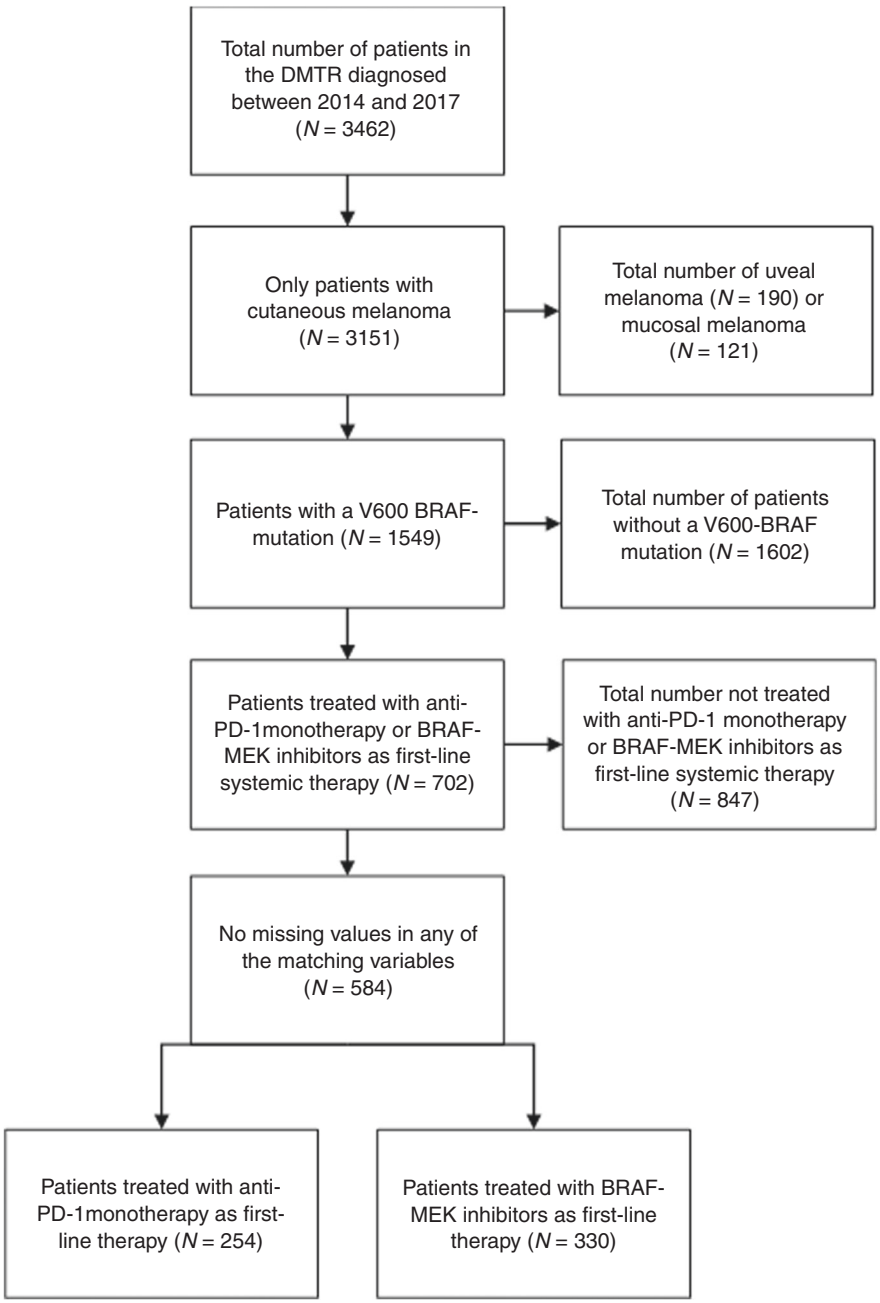

Fig. 1 Flow chart. Flow chart of the study population.

95% CI: 2.56–7.12) were all associated with higher odds of receiving first-line BRAF/MEK inhibitors. With unresectable stage IIIc as a reference, substage IV-M1b had lower odds of receiving first-line BRAF/MEK inhibitors (OR: 0.29, 95% CI: 0.11–0.74). Age ≥75 years, female gender, ≥3 organ sites, asymptomatic brain metastases and liver metastases were not significantly associated with receiving first-line BRAF/MEK inhibitors ($p > 0.05$).

Predictors of OS

In the multivariable Cox-regression on OS analysis age of ≥75 years (HR: 1.53, 95% CI: 1.10–2.13), ECOG-performance status ≥2 (HR: 2.30, 95% CI: 1.76–3.01), LDH > 500 U/L (HR: 3.38, 95% CI: 2.34–4.89) and symptomatic brain metastases (HR: 1.87, 95% CI: 1.44–2.43) were associated with a higher hazard of death. Female gender, asymptomatic brain metastases, liver metastases and ≥3 organ sites were not associated with a higher hazard of death (Table 3).

Propensity score matching

After 1:1 nearest neighbour propensity score matching, 310 patients were included in the final analysis: 155 patients who received first-line BRAF/MEK inhibitors (50%) and 155 patients who received first-line anti-PD-1 (50%). Groups did not differ with regards to age (median age: 62 vs. 62 years), gender (47.7% vs 47.7% female), ECOG-performance status ≥2 (7.1% vs. 7.1), elevated LDH > 250 U/L (30.3% vs. 30.3%), stage IV-M1c (77.4% vs. 77.4%), organ sites ≥3 (45.8% vs. 45.2%), brain metastases (22.6% vs. 22.6%), liver metastases (21.9% vs1 21.9%) and immunomodulating agents (13.5% vs. 13.5%). These results confirm satisfactory propensity score matching.

In total, 274 patients were not matched: 175 patients who received first-line BRAF-MEK and 99 patients receiving anti-PD-1 as a first-line treatment (Supplement 3). Overall, nonmatched patients who received BRAF/MEK inhibitors as first-line systemic

Table 1. Baseline characteristics.

	Original sample			Nearest neighbour-matched sample		
	BRAF-MEK	Anti-PD-1	*p* value	BRAF-MEK	Anti-PD-1	SMD
Baseline variable	(*N* = 330)	(*N* = 254)		(*N* = 155)	(*N* = 155)	
Age, median (range)	59 (19–91)	62 (22–87)	0.177	62 (19–91)	62 (25–87)	0.027
Gender						
Male	178 (53.9)	145 (57.1)	0.500	81 (52.3)	81 (52.3)	<0.001
Female	152 (46.1)	109 (42.9)		74 (47.7)	74 (47.7)	
ECOG-performance status						
0–1	254 (77.0)	232 (91.3)	<0.001	144 (92.9)	144 (92.9)	<0.001
≥2	76 (23.0)	22 (8.7)		11 (7.1)	11 (7.1)	
LDH						
Not determined/normal	164 (49.7)	197 (77.6)	<0.001	108 (69.7)	108 (69.7)	<0.001
250–500 U/L	108 (32.7)	55 (21.7)		45 (29.0)	45 (29.0)	
>500 U/L	58 (17.6)	2 (0.8)		2 (1.3)	2 (1.3)	
Stage (7th edition AJCC)						
Unresectable IIIc	15 (4.5)	14 (5.5)	<0.001	10 (6.5)	10 (6.5)	<0.001
IV-M1a	13 (3.9)	29 (11.4)		13 (8.4)	13 (8.4)	
IV-M1b	13 (3.9)	40 (15.7)		12 (7.7)	12 (7.7)	
IV-M1c	289 (87.6)	171 (67.3)		120 (77.4)	120 (77.4)	
Brain metastases						
No	192 (58.2)	207 (81.5)	<0.001	120 (77.4)	120 (77.4)	<0.001
Yes. asymptomatic	42 (12.7)	24 (9.4)		15 (9.7)	15 (9.7)	
Yes. symptomatic	96 (29.1)	23 (9.1)	<0.001	20 (12.9)	20 (12.9)	
Liver metastases						
No	218 (66.1)	200 (78.7)		121 (78.1)	121 (78.1)	<0.001
Yes	112 (33.9)	54 (21.3)		34 (21.9)	34 (21.9)	
Organ sites						
0–2	134 (40.6)	146 (57.5)	0.001	86 (55.5)	83 (53.5)	<0.001
≥3	196 (59.4)	108 (42.5)		69 (44.5)	72 (46.5)	
Immunomodulating agents						
No	242 (73.3)	224 (88.2)	<0.001	134 (86.5)	134 (86.5)	<0.001
Yes	88 (26.7)	30 (11.8)		21 (13.5)	21 (13.5)	<0.001
$BRAF^{V600}$-mutation						
V600E	274 (83.0)	212 (83.5)	0.833	130 (83.9)	132 (85.2)	0.073
V600K	44 (13.3)	35 (13.8)		19 (12.3)	19 (12.3)	
V600R/D/E2	12 (3.6)	7 (2.8)		6 (3.9)	4 (2.6)	

Comparison of baseline characteristics of patients receiving BRAF/MEK inhibitors or anti-PD-1 as a first-line treatment in the original sample and the matched sample.

therapy had poorer ECOG-performance status (ECOG-performance status ≥2 37.1% vs. 11.1%) and more often had elevated LDH levels (68.0% vs. 10.1%), stage IV-M1c (96.6% vs. 51.5%) more ≥3 organ sites affected (73.1% vs. 37.4%), brain metastases (58.8% vs. 12.1%), liver metastases (44.6% vs. 20.2%) and used immunomodulating agents (38.3% vs. 9.1%) compared to the unmatched patients who received anti-PD-1 monotherapy.

Clinical outcomes

In the cohort before matching, patients treated with BRAF/MEK inhibitors as first-line systemic treatment were more likely to die compared to patients treated with anti-PD-1 monotherapy ($p < 0.001$, log-rank test). Kaplan–Meier estimates are shown in Fig. 2. Median overall survival was 11.0 months (95% CI: 9.9–13.7) in patients receiving first-line BRAF/MEK inhibitors vs. 42.3 months (95% CI: 34.8-NE) in patients receiving anti-PD-1 ligands as first-line therapy. Median TTNT was 7.0 months (95% CI: 6.2–8.7) in patients receiving first-line BRAF/MEK inhibitors vs. 18.9 months (95%CI: 11.0–24.4) in patients receiving anti-PD-1 ligands as first-line therapy. Six and twelve-month OS were also lower for first-line BRAF/MEK inhibitors compared to anti-PD-1 monotherapy, 75.9% (95% CI: 71.4–80.7) and 47.7% (95% CI: 42.6–53.4) vs. 91.3% (95% CI: 87.9–94.8) and 81.7% (95% CI: 77.0–86.6) (Table 4).

Nearest neighbour propensity matching. In the nearest neighbour-matched cohort (*N* = 310), the overall survival of first-line BRAF/MEK inhibitors was significantly lower compared to anti-PD-1 (stratified log-rank $p < 0.001$). This matched cohort only included patients treated with anti-PD-1 and BRAF/MEK inhibitors in which the propensity score of both patients was within the pre-set calliper. Median OS of first-line BRAF/MEK inhibitors was lower compared to the anti-PD-1 cohort, 19.8 months (95% CI: 16.7–24.3) vs. 42.3 (95% CI 37.3-NE). Median TTNT of first-line BRAF/MEK

Table 2. Multivariable logistic regression.

Variables	OR	95% CI	*p* value
(Intercept)	0.84	(0.40–1.82)	0.659
Age (categories)			
<75 years	Ref		
≥75 years	1.54	(0.86–2.78)	0.149
Gender			
Male	Ref		
Female	1.34	(0.92–1.95)	0.132
ECOG-performance status			
0–1	Ref		
≥2	1.59	(0.89–2.89)	0.123
LDH			
Not determined/normal	Ref		
250–500 U/L	2.03	(1.86–4.38)	0.002
>500 U/L	30.73	(8.77–195.30)	<0.001
Stage (7th edition AJCC)			
Unresectable IIIc	Ref		
IV-M1a	0.47	(0.17–1.27)	0.140
IV-M1b	0.33	(0.12–0.88)	0.029
IV-M1c	0.58	(0.25–1.34)	0.201
Organ sites			
0–2	Ref		
≥3	1.52	(0.98–2.35)	0.063
Brain metastases			
No	Ref		
Yes, asymptomatic	1.40	(0.76–2.60)	0.279
Yes, symptomatic	3.97	(2.22–7.35)	<0.001
Liver metastases			
No	Ref		
Yes	0.89	(0.54–1.45)	0.629
Immunomodulating agents			
No	Ref		
Yes	1.41	(0.81–2.47)	0.222

Multivariable logistic regression of receiving first-line BRAF-MEK inhibitor treatment.
LDH lactate dehydrogenase, *OR* odds ratio, *CI* confidence interval.

Table 3. Multivariable Cox-regression analysis of OS.

	N	HR	95% CI	*p* value
Age				
<75 years	520	1		
≥75 years	64	1.53	(1.10–2.13)	0.012
Gender				
Female	323	1		
Male	261	0.94	(0.75–1.17)	0.585
ECOG-performance status				
0–1	486	1		
≥2	98	2.30	(1.76–3.01)	<0.001
LDH				
Normal	361	1		
250–500 U/L	163	1.28	(0.99–1.65)	0.065
>500 U/L	60	3.38	(2.34–4.89)	<0.001
Brain metastases				
No	399	1		
Yes, asymptomatic	66	1.36	(0.97–1.92)	0.076
Yes, symptomatic	119	1.87	(1.44–2.43)	<0.001
Liver metastases				
No	418	1		
Yes	166	1.18	(0.9–1.55)	0.241
Number of organ sites				
0–2	289	1		
≥3	295	1.25	(0.96–1.62)	0.096

LDH lactate dehydrogenase, *HR* hazard ratio, *CI* confidence interval.

inhibitors was not significantly lower compared to the anti-PD-1 cohort, 10.1 months (95% CI: 7.7–15.0) vs. 14.6 (95% CI 10.1–27.7). Six-, 12-and 24-month OS was also lower for BRAF/MEK inhibitors compared to anti-PD-1 monotherapy, 92.9% (95% CI: 89.9–97.0), 83.0% (95% CI: 77.3–89.2) and 65.4% (58.1–73.6) vs. 84.3% (95% CI: 78.7–90.3), 65.3% (95% CI: (58.2–73.3) and 41.7% (95% CI: 34.2–51.0) (Table 4). Kaplan–Meier estimates of the nearest neighbour-matched cohort are shown in Fig. 3. The estimated HR with a robust variance estimator was 0.50 (95% CI: 0.36–0.70) Thus, treatment with first-line anti-PD-1 ligands reduced the hazard of death by 50% in this matched sample. Overall survival of the nonmatched patients receiving BRAF/MEK inhibitors was significantly lower compared to anti-PD-1 (log-rank $p < 0.001$) (Supplement 4).

Optimal matching. In the optimal matched cohort ($N = 508$), overall survival was significantly lower for BRAF/MEK inhibitors compared to anti-PD-1 monotherapy (stratified log-rank $p < 0.001$). This matched cohort included all patients treated with first-line anti-PD-1 matched with the most alike set of patients treated with first-line BRAF/MEK inhibitors. Median OS of first-line BRAF/MEK inhibitors was lower compared to anti-PD-1 monotherapy, 15.6 months (95% CI: 12.4–19.1). vs. 42.3 months (95% CI: 34.4-NE). Median TTNT of first-line BRAF/MEK inhibitors was lower compared to anti-PD-1 monotherapy, 7.6 months (95% CI: 6.1–9.9). vs. 18.9 months (95% CI: 11.0–24.4). Six-, 12-and 24-month OS was also lower for BRAF/MEK inhibitors compared to anti-PD-1 monotherapy, 83.7% (95% CI: 79.3–88.4), 57.1% (95% CI: 51.3–63.6) and 34.4 (95% CI: 28.7–41.3) vs. 91.3% (95% CI: 87.9–94.8), 81.7% (95% CI: 77.0–86.6) and 64.0 (95% CI: 58.2–70.4) (Table 4). Kaplan–Meier estimates of the optimal matched cohort are shown in Fig. 4. The estimated HR with a robust variance estimator was 0.43 (95% CI: 0.34–0.56). Thus, treatment with first-line anti-PD-1 reduced the hazard of death by 57% in the optimal matched sample.

DISCUSSION

This report, based on real-world population-based data, describes the overall survival of $BRAF^{V600}$-mutant advanced melanoma patients after using first-line treatment with BRAF-MEK inhibitors or anti-PD-1 monotherapy. In total 310 patients were matched, resulting in 155 matched pairs. In the matched cohort, patients treated with anti-PD-1 monotherapy as a first-line treatment showed a higher 2-year survival compared to patients treated with first-line BRAF-MEK. Median OS in the anti-PD-1 monotherapy cohort was 42.3 months while the median OS was 19.8 months in patients receiving BRAF/MEK inhibitors as first-line treatment.

In the nearest neighbour-matched cohort, patients treated with anti-PD-1 as a first-line treatment have higher OS compared to patients treated with BRAF/MEK inhibitors as a first-line treatment. There were also patients who could not be matched. Overall, we matched patients with relatively good prognosis factors who

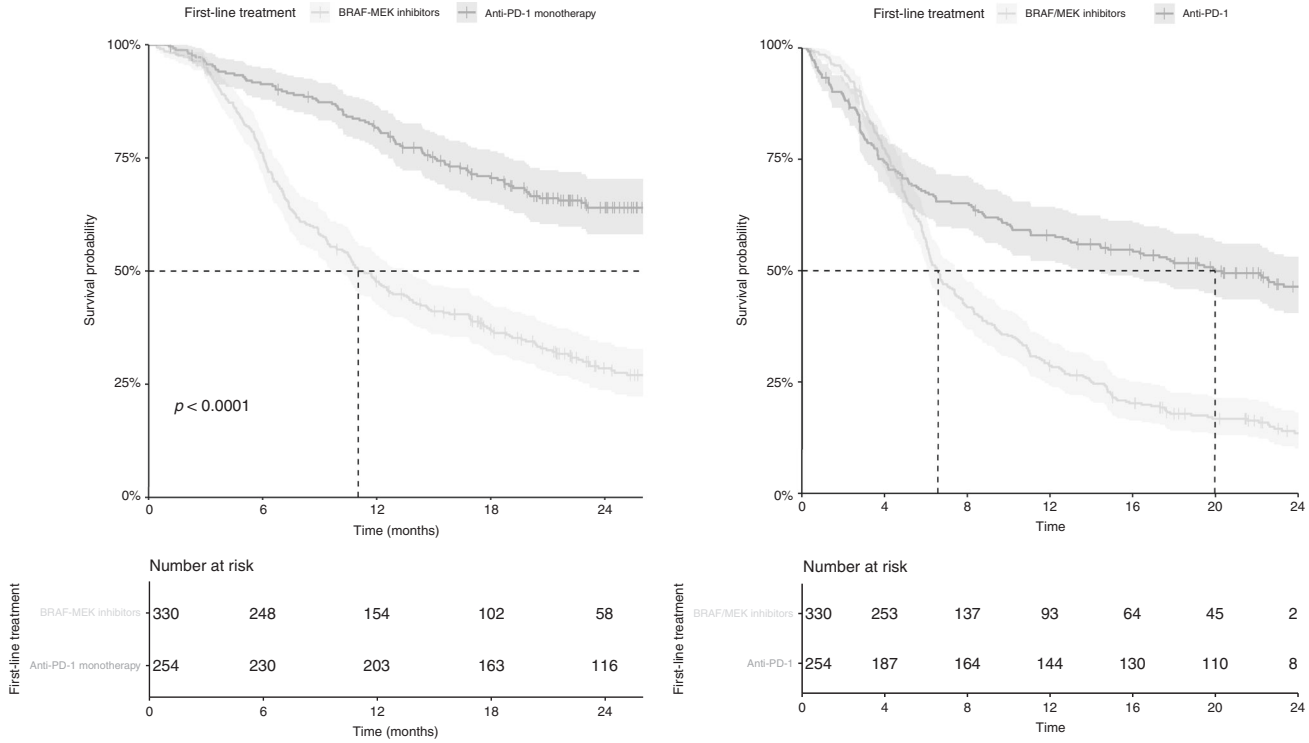

Fig. 2 Kaplan–Meier estimate of OS and TTNT of first-line BRAF/MEK inhibitors vs. anti-PD-1 monotherapy. Kaplan–Meier estimate of OS (left) and TTNT (right) of first-line BRAF/MEK inhibitors vs. anti-PD-1 monotherapy. Confidence interval is displayed by the shadow of both curves.

Table 4. TTNT and OS estimates of different methods.

	BRAF/MEK inhibitors	Anti-PD-1 monotherapy									
Overall	Median TTNT (months)	Median OS (months)	6 months (%)	12 months (%)	24 months (%)	Median TTNT (months)	Median (months)	6 months (%)	12 months (%)	24 months (%)	HR (95% CI)
Kaplan–Meier estimate	7.0 (6.2–8.7)	11.0 (9.9–13.7)	75.9 (71.4–80.7)	47.7 (42.6–53.4)	23.6 (19.0–29.3)	18.9 (11.0–24.4)	42.3 (34.8-NE)	91.3 (87.9–94.8)	81.7 (77.0–86.6)	57.9 (51.8–64.8)	0.36 (0.28–0.45)
Nearest neighbour matching	10.2 (7.7–15.0)	19.8 (16.7–24.3)	84.3 (78.7–90.3)	65.3 (58.2–73.3)	41.7 (34.2–51.0)	14.6 (10.1–27.7)	42.3 (37.3-NE)	92.9 (89.9–97.0)	83.0 (77.3–89.2)	65.4 (58.1–73.6)	0.50 (0.36–0.70)
Optimal matching	7.6 (6.1–9.9)	15.6 (12.5–19.1)	83.7 (79.3–88.4)	57.1 (51.3–63.6)	34.4 (28.7–41.3)	18.9 (11.0–24.4)	42.3 (34.8-NE)	91.3 (87.9–94.8)	81.7 (77.0–86.6)	64.0 (58.2–70.4)	0.43 (0.34–0.56)

TTNT and OS estimates shown as survival rates at 6,12 and 24 months and median overall survival stratified for first-line therapy (BRAF/MEK inhibitors vs. anti-PD-1 monotherapy).
NE non estimable.

received BRAF/MEK inhibitors with patients with relatively poor prognosis factors who received anti-PD-1 monotherapy as first-line systemic therapy. The unmatched patients consisted of patients with poor prognostic factors who received BRAF/MEK inhibitors as first-line therapy and the patients with good prognostic factors who received anti-PD-1 as first-line systemic therapy. In the optimal matching method, we matched all patients receiving first-line anti-PD-1, resulting in lower OS for BRAF/MEK inhibitors as sicker patients were matched, which could, in turn, lead to residual confounding.[18] Consequently, we cannot compare the efficacy of BRAF/MEK inhibitors or anti-PD-1 in the unmatched group. In BRAF-mutant patients with a very poor prognosis, BRAF-MEK inhibitors might be the preferred choice of first-line treatment as this treatment results in quick antitumour response.[21]

This study suggests that in the matched cohort, consisting of patients with relative favourable patient and tumour characteristics, anti-PD-1 monotherapy is the first-line treatment option of choice. However, the results need to be confirmed in randomised clinical trials to assess optimal front-line-and sequence therapy. Currently, several clinical trials are investigating the optimal front-line treatment of immunotherapy and targeted therapy. The COWBOY study evaluates a planned sequence vemurafenib and cobimetinib, followed by ipilimumab and nivolumab vs. ipilimumab and nivolumab (NCT02968303).[22] The DREAMseq study (NCT02224781) evaluates a sequence of dabrafenib and trametinib until progression, followed by ipilimumab and nivolumab or ipilimumab and nivolumab until progression followed by dabrafenib and trametinib. The SECOMBIT (NCT02631447) evaluates the sequence of encorafenib plus binimetinib followed by ipilimumab plus nivolumab or the opposite sequence or encorafenib plus binimetinib for 8 weeks followed by ipilimumab plus nivolumab until progression followed by encorafenib plus binimetinib.[23,24] These studies are expected to be completed by the end of 2021 and 2022.

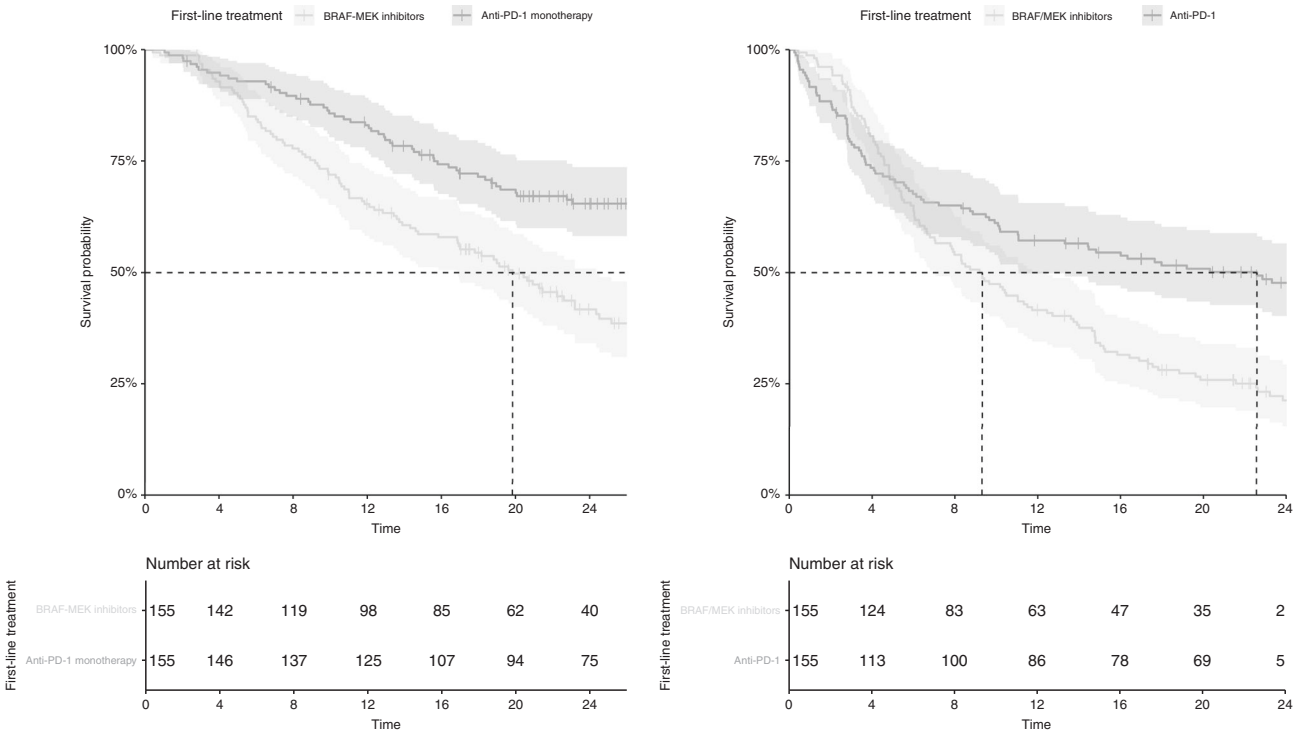

Fig. 3 Kaplan–Meier estimate OS and TTNT of the nearest neighbour-matched sample. Kaplan–Meier estimates of OS (left) and TTNT (right) for the nearest neighbour-matched cohort. Confidence interval is displayed by the shadow of both curves.

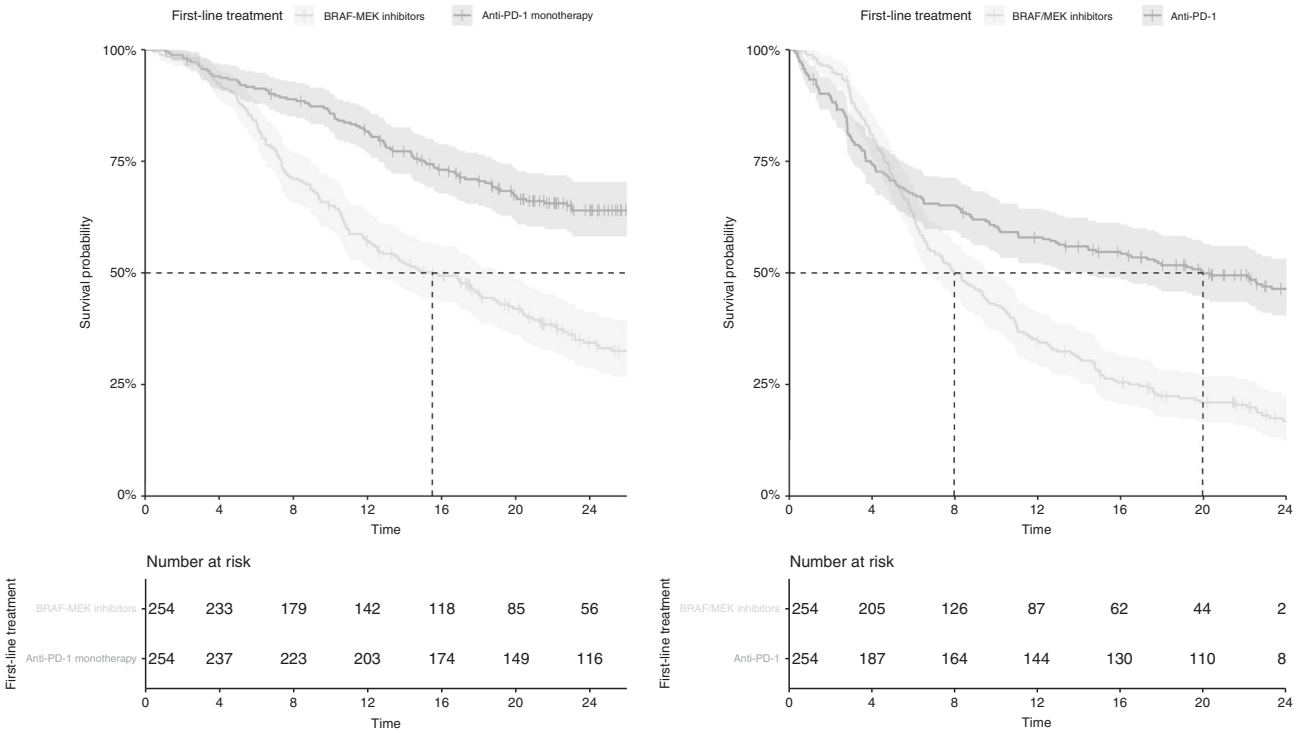

Fig. 4 Kaplan–Meier estimate of the optimal matched sample. Kaplan–Meier estimates of OS (left) and TTNT (right) for the optimal matched cohort. Confidence interval is displayed by the shadow of both curves.

In Phase 3 RCT's, 1-year survival was 74.1% for pembrolizumab and 72.9% for nivolumab.[4,25] Comparing the results of this study with the randomised clinical trials of both anti-PD-1 ligands, we find a higher 1-year survival (81.7%, 95% CI: 77.0–86.6). This is remarkable because we would expect 1-year survival of patients treated in clinical practice to be similar or worse due to unfavourable patient and tumour characteristics. However, in the CHECKMATE-066 study, only BRAF wild-type patients were included and the KEYNOTE-006 included only 35% of BRAF-mutant patients. These patients lack treatment options with BRAF/MEK inhibitors,

which may result in fewer treatment options available after progression on anti-PD-1 treatment. On the other hand, in our matched anti-PD-1 cohort, 7.1% of patients had a baseline ECOG-performance status of ≥2. These patients have been excluded from the previously mentioned RCT's and as a result, we would expect that the clinical outcomes of this study would be worse compared to RCT's. Compared to Phase 3 RCT's of BRAF/MEK inhibitors, one year survival was 71.2% for dabrafenib and trametinib and 74.5% for vemurafenib and cobimetinib.[2,26] Compared to the 1-year survival of this study, we find a lower 1-year survival of 65.3% (95% CI: 58.2–73.3). Differences in survival could be related to a higher age (62 vs. 55), inclusion of ECOG ≥ 2 (7.1%), more patients with IV-M1c disease (77% vs. 62–63%) and inclusion of patients with brain metastases (22.6%) in our matched sample.

Another real-world study investigating the outcomes of first-line immunotherapy and targeted therapy was performed by Luke et al.[27] Opposed to our current study, they find a lack of survival benefit for patients receiving first-line immunotherapy, despite a favourable imbalance of prognostic factors. These differences could be explained by the percentage of M1c patients (77.4%) in our study vs. 59.7% and 51.6% in the study by Luke et al. A direct comparison between both studies is hard due to differences in patient and tumour characteristics, study design and geographic location.

There are limitations to this study. First, this study did not include patients who received ipilimumab monotherapy or ipilimumab combined with nivolumab. Ipilimumab monotherapy is no longer given as first-line treatment since anti-PD-1 has proven superior efficacy.[28] However, combination therapy of ipilimumab and nivolumab has proven to be effective in metastatic melanoma patients in the CHECKMATE-067 trial.[29] We did not have enough patients who received combination therapy of ipilimumab and nivolumab to make a reliable analysis of this group. Second, the observational nature of the DMTR may have introduced bias. However, since the start of this registry, independent data managers have been trained annually and data are checked and confirmed by treating physicians. The online registration platform warns data managers of inconsistent or missing values in the registry. Previous studies have shown the quality and validity of the Dutch population-based registries.[30] We therefore argue that the data used in this study is of high quality. The third limitation is that we could not assess how subsequent therapies impact the outcome. By studying patients receiving second-line treatment, we would introduce a selection bias. Only patients fit enough would be able to receive second-line treatment. Studying the impact of subsequent therapies on outcomes would require a randomised controlled trial with several predefined arms. In the real-world, choice of type of subsequent therapy depends on patient and tumour characteristics as well as preference of the oncologist.

Based on the matched cohort, our data suggest that in $BRAF^{V600}$-mutant cutaneous metastatic melanoma patients, anti-PD-1 monotherapy should be the preferred treatment if a quick antitumour response, for example for symptom relief, is not the primary aim of treatment. Additional results from RCTs are necessary to confirm these results to determine optimal front-line and sequential therapy for BRAF-mutant cutaneous metastatic melanoma patients.

ACKNOWLEDGEMENTS

We thank all physicians and data managers who registered the patient data in the Dutch Melanoma Treatment Registry.

AUTHOR CONTRIBUTIONS

J.B. performed the analyses and wrote the manuscript. M.W. was responsible for the study conception and design, analysis and interpretation of data and drafting of the manuscript. D.H. was responsible for the study conception and design, analysis and interpretation of data and drafting of the manuscript. W.B. performed data acquisition, study conception, helped with the analysis and interpretation of the data, drafted the manuscript and performed critical revision and final approval of the manuscript. J.H. performed data acquisition, study conception, helped with the analysis and interpretation of the data, drafted the manuscript and performed critical revision and final approval of the manuscript. C.B. performed data acquisition, study conception, helped with the analysis and interpretation of the data, drafted the manuscript and performed critical revision and final approval of the manuscript. M.A. performed data acquisition, study conception, helped with the analysis and interpretation of the data, drafted the manuscript and performed critical revision and final approval of the manuscript. F.B. performed data acquisition, study conception, helped with the analysis and interpretation of the data, drafted the manuscript, performed critical revision and final approval of the manuscript. J.G. performed data acquisition, study conception, helped with the analysis and interpretation of the data, drafted the manuscript and performed critical revision and final approval of the manuscript. G.H. performed data acquisition, study conception, helped with the analysis and interpretation of the data, drafted the manuscript and performed critical revision and final approval of the manuscript. E.K. performed data acquisition, study conception, helped with the analysis and interpretation of the data, drafted the manuscript and performed critical revision and final approval of the manuscript. D.P. performed data acquisition, study conception, helped with the analysis and interpretation of the data, drafted the manuscript and performed critical revision and final approval of the manuscript. R.R. performed data acquisition, study conception, helped with the analysis and interpretation of the data, drafted the manuscript and performed critical revision and final approval of the manuscript. K.S. performed data acquisition, study conception, helped with the analysis and interpretation of the data, drafted the manuscript and performed critical revision and final approval of the manuscript. A.T. performed data acquisition, study conception, helped with the analysis and interpretation of the data, drafted the manuscript and performed critical revision and final approval of the manuscript. A.V. performed data acquisition, study conception, helped with the analysis and interpretation of the data, drafted the manuscript and performed critical revision and final approval of the manuscript. G.V. performed data acquisition, study conception, helped with the analysis and interpretation of the data, drafted the manuscript and performed critical revision and final approval of the manuscript. M.B. performed data acquisition, study conception, helped with the analysis and interpretation of the data, drafted the manuscript and performed critical revision and final approval of the manuscript. A.E. was responsible for the study conception and design, analysis and interpretation of data and drafting of the manuscript.

ADDITIONAL INFORMATION

Ethics approval and consent to participate In compliance with Dutch regulations, the DMTR was approved by a medical ethical committee (METC Leiden University Medical Center, 2013) and is not considered subject to the Medical Research Involving Human Subjects Act.

Data availability The datasets generated during and/or analysed during the current study are not publicly available due to privacy regulations in the Netherlands but are available from the corresponding author on reasonable request.

Competing interests A.J.M.V.D.E has consulting/advisory relationships with BMS, Roche, MSD, and Novartis. He received a study grant from Roche. J.W.D.G. has received personal fees outside the submitted work from Bristol-Myers Squibb, Pierre Fabre, Servier, MSD, Novartis. GH consultancy/advisory relationships with Amgen, Bristol-Myers Squibb, Roche, MSD, Pfizer, Novartis and has received research grants not related to this paper from Bristol-Myers Squibb, Seerave. E.K. has consultancy/advisory relationships with Amgen, Bristol-Myers Squibb, Novartis, Merck, Pierre Fabre, and received research grants not related to this paper from Bristol-Myers Squibb. K.P.M.S. has consulting/advisory relationships with BMS and MSD. She received honoraria from Novartis, Pierre Fabre, and Roche. A.V.D.V. has consultancy relationships with Bristol-Myers Squibb, MSD, Roche, Novartis, Pierre Fabre, Pfizer, Sanofi, Ipsen, Eisai. J.H. has advisory relationships with Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Celsius Therapeutics, GSK, Immunocore, Ipsen, MSD, Merck Serono, Novartis, Neon Therapeutics, Pfizer, Roche/Genentech, Sanofi, Seattle Genetics and has received research grants not related to this paper from Novartis, Bristol-Myers Squibb, MSD, Neon Therapeutics. C.U.B. has received commercial research grants from Novartis, Bristol-Myers Squibb, and NanoString; is a paid advisory board member for Bristol-Myers Squibb, MSD, Roche, Novartis, GlaxoSmithKline, AstraZeneca, Pfizer, Lilly, GenMab, and Pierre Fabre; and holds ownership interest in Uniti Cars, Neon Therapeutics, and Forty Seven. M.J.B.S. has consultancy relationships with Pierre Fabre, MSD and Novartis. All grants were paid to the institutions. The funders had no role in the writing of this article or decision to submit it for publication. All remaining authors have declared no conflicts of interest

Funding information For the Dutch Melanoma Treatment Registry (DMTR), the Dutch Institute for Clinical Auditing foundation received a start-up grant from governmental organisation 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 of the DMTR in 2019. For this work no funding was granted.

Supplementary information is available for this paper at https://doi.org/10.1038/s41416-020-01229-1.

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