

Real-world effectiveness of dabrafenib and trametinib in patients with BRAF-positive melanoma treated in routine Bulgarian clinical practice

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Abstract

Malignant melanoma is among the leading forms of cancer on a global scale, accounting for 1 in 5 skin cancers. Over the past decades, the treatment of melanoma has significantly improved following the development of therapies such as MAPK molecular therapy targeted at BRAF and MEK signaling pathways. We present real-world evidence from clinical practice in Bulgaria on the treatment of malignant melanoma with dabrafenib and trametinib from 2018 to 2022. Treatment outcomes from the real-world data are compared against the pivotal clinical trials, namely COMBI-d and COMBI-v. Outcomes are compared on the basis of metrics, including overall survival, progression-free survival, and clinical benefit. Further, iterational proportional fitting is performed to control for differences in characteristics across the patient cohorts. Results show that real-world overall survival and progression-free survival outperform results from the clinical trials, particularly with respect to COMBI-d.

Keywords

Dabrafenib, Trametinib, melanoma, Bulgaria, real-world data, outcomes

Introduction

Skin cancers are the most common form of cancer, with more than 1.5 million new diagnoses recorded in 2020 (Arnold et al. 2022). Melanoma accounts for approximately 1 in 5 of these cases. On a global scale, in 2020, approximately 325,000 new patients were diagnosed and 57,000 deaths occurred. Incidence rates have been increasing, particularly in light-skinned populations of European ancestry (Erdmann et al. 2013). It is likely that this trend is primarily attributable to increased exposure to UV radiation. According to estimates, more than 3 in 4 cases of melanoma are attributable to UV radiation on a global scale (Arnold et al. 2018). The incidence of malignant melanoma is rapidly increasing worldwide, and this increase is occurring at a faster rate than that of any other cancer except lung cancer in women. Melanoma is more common in Whites than in Blacks and Asians. Overall, melanoma is the fifth most common malignancy in men and the seventh most common malignancy in women, accounting for 5% and 4% of all new cancer cases, respectively. The average age at diagnosis is 57 years, and up to 75% of patients are younger than 70 years of age. (Donley et al. 2019; Ghazawi et al. 2019) Unlike other solid tumors, mainly affecting older adults, melanoma is also presented in young and middle-aged people. It is commonly found in patients younger than 55 years, and it accounts for the third-highest number of lives lost across all cancers. The five-year relative survival rate for patients in Europe with melanoma is 83%, with the highest values in Northern and Central Europe (88%), while the lowest survival was in Eastern Europe around 74% (Crocetti et al. 2015).

Apart from UV exposure, other risk factors include age, with incidences being greater among the older population. However, melanoma is also among the most common cancers in the young adult population (Fidler et al. 2017).

Melanoma arises from transformations in the melanocytes and can arise in various locations throughout the body, but it is most common in the skin in the context of UV injury. Melanoma in most cases arises on healthy skin, although 25% of melanomas are associated with a preexisting nevus. The number of moles and the dysplastic appearance are associated with higher risk (Zalaudek et al. 2020). Approximately half of cutaneous melanomas show mutations in BRAF (Cancer Genome Atlas Network 2015).

Over the past several decades, the treatment of melanoma patients has significantly improved following the developments of immune checkpoint blockers (targeting PD-1 and CTLA-4) and MAPK molecular therapy targeted at BRAF and MEK signaling pathways. Both approaches have been proved effective in the treatment of advanced melanoma (Jenkins and Fisher 2021).

The combination of dabrafenib (Tafinlar®) (European Medicines Agency 2023a) and trametinib (Mekinist®)

(European Medicines Agency 2023b) was the first BRAF-MEK combination approved for metastatic melanoma. Together, dabrafenib and trametinib target the AS/RAF/MEK/ERK pathway that is prevalently hyperactivated in cancers. The combination dabrafenib and trametinib is indicated for: the treatment of patients with unresectable (or metastatic) melanoma with BRAF V600E or V600K mutations; adjuvant treatment for patients with BRAF V600E or V600K mutations.

Approval of the treatment for melanoma was based on the two-phase III clinical trials COMBI-d (Long et al. 2014; Long et al. 2015) and COMBI-v (Robert et al. 2015). The conclusions from trial COMBI-d show that the combination with trametinib and dabrafenib improves progression-free survival and overall survival compared with dabrafenib alone. The median progression-free survival was 9.3 months, and the median overall survival was 25.1 months. In the second study, the median overall survival was 11.0 months, and the overall survival rate was 74% after 12 months and 51% after 24 months, compared with 68% and 42%, respectively, in patients with dabrafenib monotherapy. Results from the COMBI-v trial show significant improvement in progression-free survival, overall survival, and objective response rate. The overall survival rate was 72% after 12 months in the dabrafenib-trametinib group compared with 65% in the vemurafenib monotherapy group. The difference is observed in median progression-free survival: 11.4 months for the combination therapy group and 7.3 months for vemurafenib monotherapy. The observed objective response rate was 64% for combination therapy and 51% for vemurafenib monotherapy.

The objective of this study is to perform an in-depth analysis of the treatment outcomes based on real-world data (RWD) from the Bulgarian population and to compare with the pivotal clinical trials COMBI-v and COMBI-d.

Materials and methods

Data sources

The primary data source for this study consists of electronic health records (EHRs) collected from 57 hospitals (university, multispecialty, and oncology hospitals) in Bulgaria. The retrospective analysis includes data ranging from 1 January 2018 to 31 December 2022. Some partial data from 2017 and from 2023 is also included. The data includes both reimbursed and donated therapy prescriptions. The data was extracted from structured and unstructured text through the implementation of NLP algorithms. The analysis of this data was conducted via the Danny Platforms (Squiline Health, Sofia, Bulgaria; <https://squiline.com/products/danny-platform/>), which is an analytic platform that integrates large amounts of RWD from EHRs using embedded machine learning and NLP algorithms to facilitate the extraction of information from free

text in different languages. For this report, the data was further manually checked and/or annotated for consistency, errors, and missing values, wherever applicable.

The randomized control trials (RCTs) used for comparison were COMBI-d and COMBI-v. COMBI-d compares the combination of dabrafenib and trametinib vs. dabrafenib and placebo in BRAF V600E/K-positive patients with unresectable stage IIIC or stage IV cutaneous melanoma as first-line therapy. COMBI-v compares the combination of dabrafenib and trametinib vs. a baseline of vemurafenib monotherapy in BRAF V600E/K-positive patients with metastatic cutaneous melanoma as first-line therapy.

Inclusion and exclusion criteria

The present RWD study included patients comparable to COMBI-v and COMBI-d.

Included are patients who have started treatment with the combination dabrafenib + trametinib between 01 January 018 and 31 December 2022. Only patients who have received at most (neo)adjuvant past therapies are included. Only patients with a positive BRAF V600 mutation are included.

Outcome measures

The study evaluates treatment outcomes using several endpoints, including PFS (defined as probability of receiving treatment during the period of observation without disease progression or censoring for reason other than death), OS (defined as probability of receiving treatment during the period of observation without censoring for death from any cause), and CBR (defined as complete plus partial remission [CR + PR] plus stable disease [SD]).

Statistical considerations

For treatment outcomes, the survival functions of OS and PFS were estimated using the Kaplan-Meier (product-limit) estimator. The confidence interval was calculated using Greenwood's method.

In comparison between RWD and clinical trial treatment outcomes, one of the challenges is that the underlying baseline characteristics between the two groups can be different. This can result in a bias in the comparison and hence interpretation if these different baselines are not taken into account. For instance, a difference in the PFS may not be the result of a difference in drug effectiveness but rather due to an older patient group in the real-world. To account for such differences, we applied iterative proportional fitting (IPF) (El-Khorazaty et al. 2014) to balance a set of chosen characteristics prior to our survival analyses. IPF works by, for a given characteristic, deriving weights to adjust the underlying distributions in order to match a target distribution. For instance, if a RCT cohort consists of 50% men and 50% women but the real-world

data has a different proportion (60% vs. 40%), then IPF will derive weights in such a way (e.g., more weights for the female patients) that the weighted sum would result in 50:50 as seen in the RCT. The characteristics considered were: sex, ECOG, age, and having had prior immunotherapy (in a neo- or adjuvant setting).

The Wilson score method was utilized to calculate 95% confidence intervals (CIs) for binominal variables.

The hazard ratio was calculated using the Cox regression models in alignment with the corresponding RCTs to enable comparison. In the COMBI-d clinical trial, the dabrafenib + trametinib combination was compared against a dabrafenib + placebo control group. We similarly did this comparison by constructing the RWD cohorts for each of these two corresponding treatment arms. We do a comparison against a control group of RWD patients on dabrafenib 1st line monotherapy. In the COMBI-v clinical trial, the dabrafenib + trametinib combination was compared against a vemurafenib control group. We similarly did this comparison by constructing the RWD cohorts for each of the two corresponding treatment arms. We compared against a control group of RWD patients on first-line vemurafenib.

Results

Patient disposition

In total, the RWD dataset consists of 335 patients who were treated with dabrafenib and trametinib. In order to ensure a meaningful comparison to the RCTs, the patients are divided into 3 groups, as follows:

1. Initial treatment group: About 57% (190/335) of the total patients examined are taking the combination who were 1st line, i.e., previously untreated in the advanced or metastatic setting. These patients are closest in terms of inclusion/exclusion criteria to the RCTs (COMBI-d and COMBI-v), and they will be the main focus of most of the report sections below.
2. Overtreated group: About 20% (68/335) of the total patients examined are taking the combination as the 2nd or above line of therapy after progression on another regimen in the advanced or metastatic setting.
3. Adjuvant group: About 23% (77/335) patients are taking the combination in the adjuvant setting.

The patients in the initial treatment group are closest in terms of inclusion/exclusion criteria to the RCTs (COMBI-d and COMBI-v). Therefore, they will be the main focus of most of the analysis. In comparison to the sample size of 190 patients within the Initial Treatment group, the COMBI-d cohort is of a relatively similar size, consisting of 211 patients. The COMBI-v cohort consists of 352 patients. A detailed comparison of the number of patients at risk for OS and PFS by months is exhibited in Table 1.

Table 1. Patients at risk by months, progression-free survival, and overall survival.

months	PFS			OS		
	RWD	COMBI-d	COMBI-v	RWD	COMBI-d	COMBI-v
0	190	211	352	190	211	352
2	168	196	310	182	208	342
4	134	164	270	169	200	336
6	108	137	228	150	187	310
8	82	125	194	136	174	283
10	72	96	142	124	159	232
12	58	84	83	110	144	157
14	44	80	39	93	135	85
16	38	71	10	81	124	46
18	32	70	7	72	112	15
20	27	65	0	64	106	2
22	23	61	0	58	103	
24	18	38		51	88	
26	13	26		48	53	
28	13	6		43	21	
30	12	0		37	3	
32	12			31	0	
34				26	0	

Patient demographics and disease characteristics

Table 2 presents the demographic characteristics of the patients in the initial treated group. Overall, the profiles are mostly comparable. We observe that age and sex distributions are similar to the RCTs. The real-world patients are a bit older but, overall, still within the expected range. The ECOG values are not as good as in the RCT, but both values of 0 and 1 indicate a positive overall condition. All the patients have a BRAF V600 mutation to be eligible for the dabrafenib + trametinib combination, but in many patients the exact subtype of the V600 mutation is not mentioned. We include only patients who have not yet received a systemic treatment for melanoma, i.e., only (neo) adjuvant prior therapies were permitted—most common is immunotherapy with interferon alfa-2a or BCG vaccine. We observe a proportion very close to the RCTs. The majority of the patients in the trial were metastatic in stage IV. In contrast, in RWD we observe a much broader distribution across the TNM stages. This needs to be interpreted with caution, as the TNM stage status refers to the staging at the time of diagnosis as opposed to the status at which the combination was given.

The 190 patients in the initial treatment group, by definition, have at most (neo)adjuvant as prior regimens. Table 3 exhibits their treatment history. We observe that the majority (72%) have no documented regimens before the dabrafenib + trametinib combination. For the remainder, by far the most common adjuvant treatment is interferon alfa-2a (55% of all prior therapies). Also, 41% of patients in the initial treatment group have a subsequent treatment after dabrafenib + trametinib (due to progression or another reason for discontinuation, such as intolerance or adverse events). Fig. 1 illustrates the mobility of patients across different therapies. Immunotherapy is the preferred course of treatment in such cases (either pembrolizumab, nivolumab, or a combination of nivolumab + ipilimumab).

Table 2. Patient characteristics of the initial treatment group.

Characteristic	Values	N = 190	%	COMBI-d % (N = 211)	COMBI-v % (N = 352)
Sex		N = 190		% (N = 211)	% (N = 352)
	F	69	36.3	47	41
	M	121	63.7	53	59
ECOG¹		N = 190	%	% (N = 210)	% (N = 350)
	0	71	41.5	74	71
	1	95	55.6	26	29
	2	3	1.8		
	3	2	1.2		
Age (at start)		N = 190	years	N = 211	N = 352
	Median	64		55	55
	Mean ± SD	62.4 ± 13.1			
	Q1 – Q3	52.3–73.8			
	Min – Max	30–89		22–89	18–91
BRAF status²		N = 189	%	% (N = 211)	% (N = 346)
				By def.	By def.
	V600E	5	2.6	85	90
	V600K	3	1.6	15	10
	V600R	1	0.5		
	V600-mut	33	17.5		
	BRAF+	147	77.8		
Previous therapies³		N = 190	%	% (N = 210)	% (N = 352)
	No priors documented	137	72.1		
	Immunotherapy	53	27.9	27	17
TNM Stage⁴		N = 189	%	% (N = 211)	% (N = 351)
	I*	21	11.1		
	II*	43	22.8		
	III	3	1.6		
	IIIA	11	5.8		
	IIIB	10	5.3		
	IIIC	12	6.3	33 (IIIC, IVM1a/b)	37 (IIIC, IVM1a/b)
	IV	89	47.1	67 (IVM1c)	63 (IVM1c)
TNM-M⁴		N = 185	%	% (N = 211)	% (N = 351)
	M0	83	44.9	2	4
	M1	53	28.6		
	M1a	5	2.7	9	16
	M1b	1	0.5	21	17
	M1c	7	3.8	67	63
	MX	36	19.5		
LDH⁵		N = 53	U/L	% (N = 210)	% (N = 351)
	Median	270			
	Mean ± SD	336.1 ± 215.7			
	Q1 – Q3	189–442			
	Min – Max	6–983			
	<= ULN	–	–	63	66
	> ULN	–	–	37	34

¹ – ECOG data is taken from available clinical documentation closest to the time that the combination dabrafenib + trametinib is first prescribed.

² – The entire available information from medical documents is used—from diagnosis until present day. The mutation status is either in a structured field or extracted from free text (epicrisis).

³ – The initial treatment group of patients has either no priors or (neo)adjuvant regimens before 1st line dabrafenib + trametinib.

⁴ – The earliest available information from medical documentation is used. In most cases, this indicates a stage at diagnosis.

⁵ – The LDH value is taken from available clinical documentation closest to the time that the combination dabrafenib + trametinib is first prescribed.

In the case of the overtreated group, Table 4 shows there are several different types of previous therapies. Pembrolizumab (39 regimens), Interferon alfa-2a (21 regimens), and vemurafenib (12 regimens) are the most common

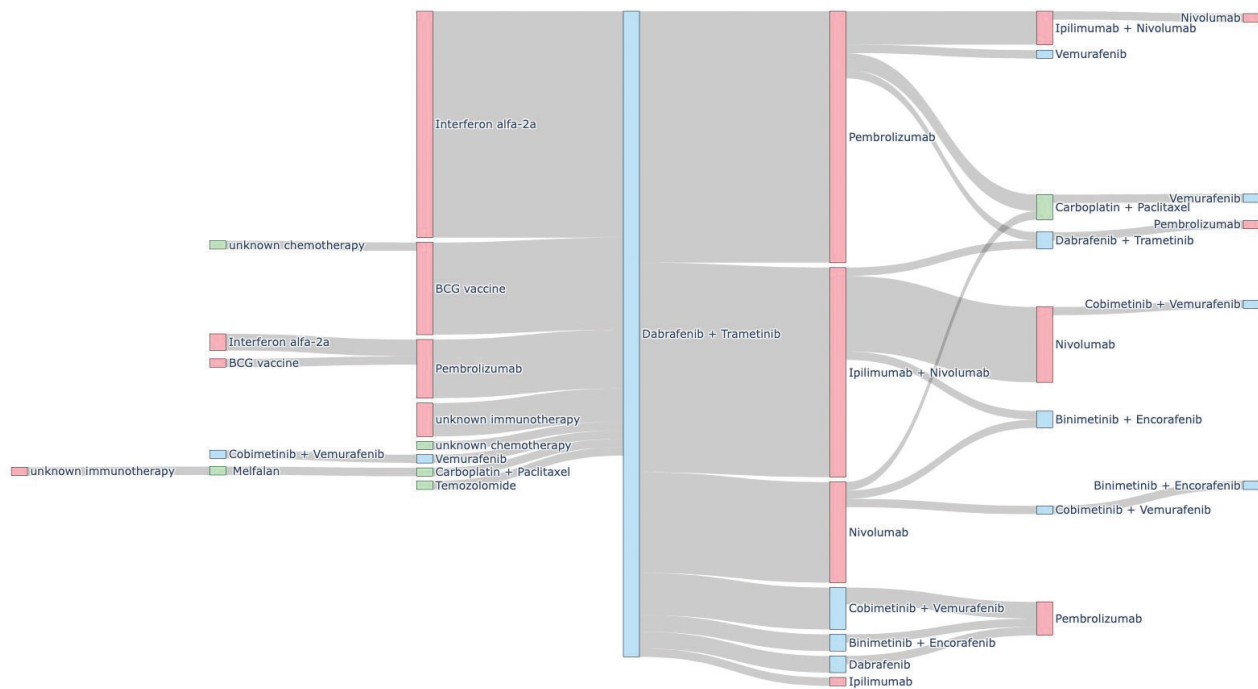


Figure 1. Treatment history of initial treatment group patients.

Table 3. Treatment history of the initial treatment group.

Regimen	All previous regimens (N = 190)		Regimen directly preceding Dabrafenib + Trametinib (N = 53)		All subsequent Regimens (N = 190)		Regimen directly after Dabrafenib+ Trametinib (N = 77)	
	Number	%	Number	%	Number	%	Number	%
BCG vaccine	12	6.3	11	20.8				
Binimetinib + Encorafenib					5	2.6	2	2.6
Carboplatin + Paclitaxel	1	0.5	1	1.9	3	1.6		
Cobimetinib + Vemurafenib	1	0.5			7	3.7	5	6.5
Dabrafenib					2	1.1	2	2.6
Dabrafenib + Trametinib					2	1.1		
Interferon alfa-2a	29	15.3	27	50.9				
Ipilimumab					1	0.5	1	1.2
Ipilimumab + Nivolumab					29	15.3	25	32.5
Melfalan	1	0.5						
Nivolumab					22	11.6	12	15.6
Pembrolizumab	7	3.7	7	13.2	35	18.4	30	39
Temozolomide	1	0.5	1	1.9				
Unknown chemotherapy	2	1.1	1	1.9				
Unknown immunotherapy	5	2.6	4	7.5				
Vemurafenib	1	0.5	1	1.9	2	1.1		

drugs used in the past. Overall, immunotherapy is most frequently observed in past regimens (79.4% of patients), followed by targeted therapy (38.5%) and chemotherapy (17.6%). The mobility of therapies for patients in this group is illustrated in Fig. 2. We observe that most patients in this group, as in the previous subsection, still have ongoing therapy and have not been prescribed a subsequent regimen. Immunotherapy and dabrafenib monotherapy are the most common subsequent therapies.

Clinical benefit rate

There are 149 out of 190 patients (78%) with explicitly documented assessments in the dabrafenib + trametinib combination. Some regimens have not yet been evaluated, as insufficient time may have passed since the start. Table 5 summarizes the responses given to the dabrafenib

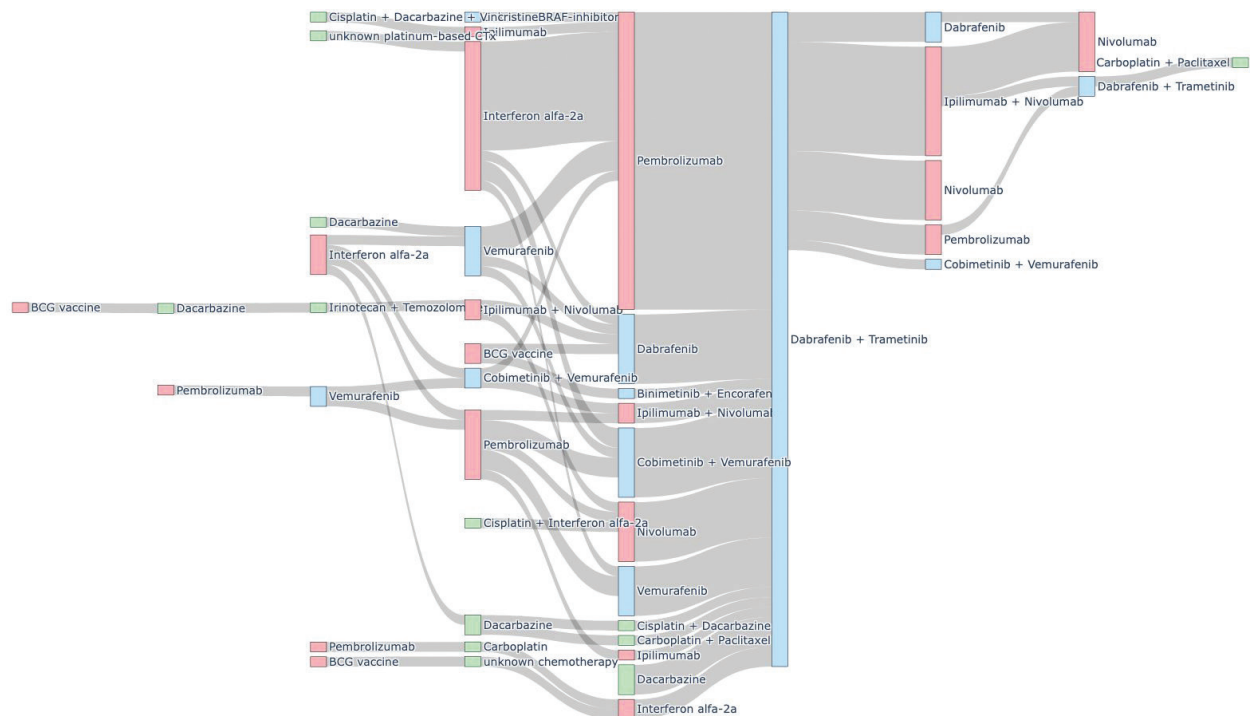
+ trametinib regimens. We observe comparable results: RWD is 84.6% (95% CI: 77.9–89.5) vs. 92% for COMBI-d and 90% for COMBI-v.

Progression-free survival

Comparisons between RWD and the RCTs for PFS are exhibited in Table 6. In the case of COMBI-d, estimates are based on a similar number of events: 95 events for the RWD and 103 events for the RCT. We notice that for PFS the probabilities are consistently higher for RWD in comparison to the RCT. The median PFS based on RWD is 16.1 (95% CI: NC–NC) months in comparison to 9.3 months from RCT. For the 4th month, probabilities are 91% (95% CI: 86–95%) and 81% for RWD and RCT, respectively. For the 6th month, they are 85% (95% CI: 78–90%) and 68%, respectively. The trends continue to

Table 4. Treatment history of the overtreated group.

Previous Regimen	All previous regimens (N = 68)		Regimen directly preceding Dabrafenib+Tra metinib (N = 68)		All subsequent regimens (N = 68)		Regimen directly after Dabrafenib+Tr ametinib (N = 24)	
	Number	%	Number	%	Number	%	Number	%
BCG vaccine	4	5.9						
Binimetinib + Encorafenib	1	1.5	1	1.5				
Carboplatin	1	1.5						
Carboplatin + Paclitaxel	1	1.5	1	1.5	1	1.5		
Cisplatin + Dacarbazine	1	1.5	1	1.5				
Cisplatin + Dacarbazine + Vincristine	1	1.5						
Cisplatin + Interferon alfa- 2a	1	1.5						
Cobimetinib + Vemurafenib	9	13.2	7	10.6	1	1.5	1	4.2
Dabrafenib	7	10.3	7	10.6	3	4.4	3	12.5
Dabrafenib + Trametinib					2	2.9		
Dacarbazine	7	10.3	3	4.5				
Interferon alfa-2a	21	30.9	3	4.5				
Ipilimumab	2	2.9	1	1.5				
Ipilimumab + Nivolumab	4	5.9	2	3	11	16.2	11	45.8
Irinotecan + Temozolomide	1	1.5						
Nivolumab	6	8.8	6	9.1	12	17.6	6	25
Pembrolizumab	39	57.4	30	45.5	3	4.4	3	12.5
unknown BRAF-inhibitor	1	1.5						
Unknown chemotherapy	1	1.5						
Unknown platinum-based CTx	1	1.5						
Vemurafenib	12	17.6	6	9.1				

**Figure 2.** Treatment history of the overtreated group patients. The Sankey diagram presents the history of patient treatments in the cohort chronologically from left to right.**Table 5.** Clinical benefit rate.

	N = 190	RWD with response % (N = 149)	COMBI-d % (N = 211)	COMBI-v % (N = 351)
CBR	126	84.6	92	90
(Clinical Benefit Rate)		(77.9–89.5)		

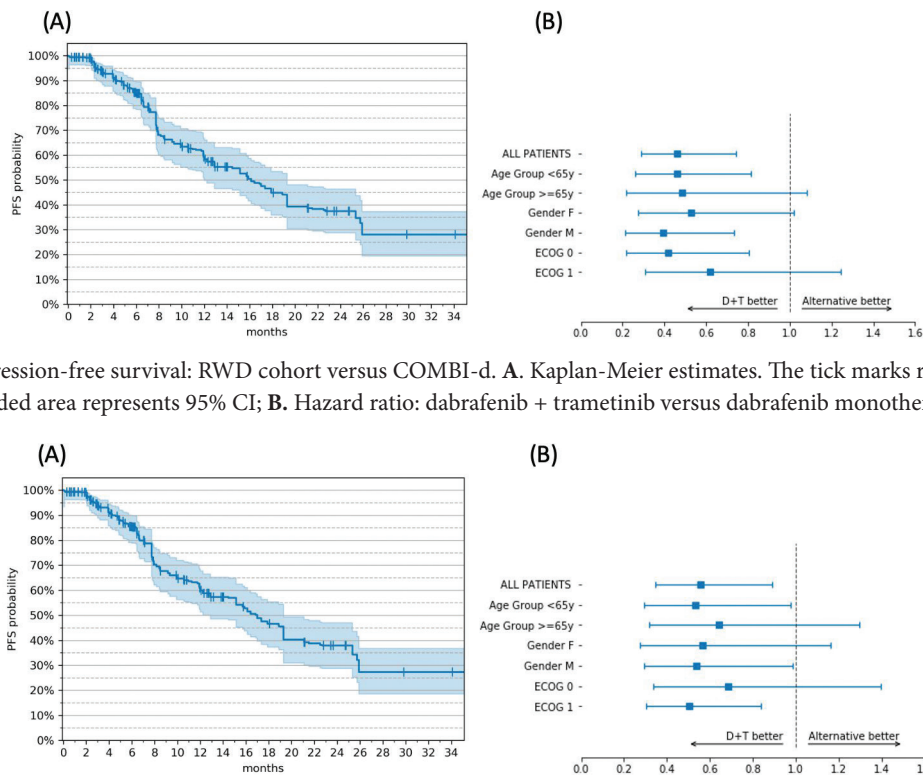
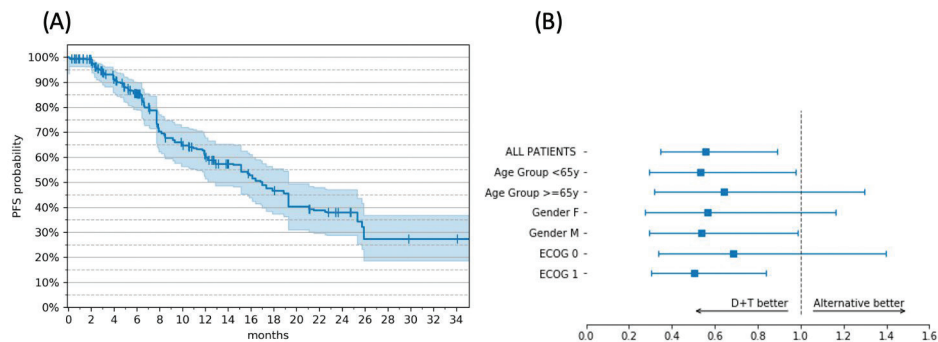
diverge to month 12 to 58% (95% CI: 50–66%) and 34%, respectively. A Kaplan-Meier curve of RWD is illustrated in Fig. 3A. After the 24th month, confidence intervals of the curve for RWD data are rather large due to the small number of patients at risk.

The weight-adjusted hazard ratio of PFS in the RWD cohort receiving dabrafenib + trametinib was 0.46 (95% CI: 0.29–0.74), exhibited in Table 8. In COMBI-d, the hazard ratio for dabrafenib + trametinib versus the control group was 0.75. In the RWD group, all subgroups across age, gender, and ECOG show more favorable results in comparison to the RCT (Fig. 3B).

Comparison of PFS against COMBI-v (see Table 6) shows that probabilities for RWD are consistently higher than the RCT. The median probability rate for RWD is higher than for RCT at 17.0 (95% CI: NC-NC) months

Table 6. Progression-free survival: RWD vs. RCT.

COMBI-d					COMBI-v			
	RWD		Clinical Trial		RWD		Clinical Trial	
PFS	Patients at risk	N = 190	Patients at risk	N = 211	Patients at risk	N = 190	Patients at risk	N = 352
# events		95 (50.0%)		103 (48.8%)		95 (50.0%)		–
Median		16.1 mo. (NC –NC)		9.3 mo.		17 mo. (NC –NC)		11.4 mo.
@4 mo.	134	91% (86–95)	164	~81%	168	91% (86–95)	270	~83%
@6 mo.	108	85% (78–90)	138	~68%	108	85% (79–90)	228	~71%
@8 mo.	82	68% (60–75)	82	~58%	82	70% (62–77)	194	~63%
@12 mo.	58	58% (50–66)	9	~34%	58	60% (51–68)	83	~48%
@24 mo.	18	38% (29–46)	–	–	18	38% (29–47)	–	–

**Figure 3.** Progression-free survival: RWD cohort versus COMBI-d. **A.** Kaplan-Meier estimates. The tick marks represent censored patients; the shaded area represents 95% CI; **B.** Hazard ratio: dabrafenib + trametinib versus dabrafenib monotherapy.**Figure 4.** Progression-free survival: RWD cohort versus COMBI-v. **A.** Kaplan-Meier estimates. The tick marks represent censored patients, the shaded area represents 95% CI; **B.** Hazard ratio: dabrafenib + trametinib versus vemurafenib therapy.

vs. 11.4 months. At the 4th month, probabilities are 91% (95% CI: 86–95%) vs. 83% for RWD and RCT, respectively. At the 6th month, they diverge significantly and stand at 85% (95% CI: 79–90%) and 71%, respectively. By the 12th month, probabilities stand at 60% (95% CI: 51–68%) vs. 48%, respectively. A Kaplan-Meier curve of RWD is illustrated in Fig. 4A. By the 24th month, confidence intervals become rather large due to the small number of remaining patients at risk. Results should therefore be interpreted with caution.

The weight-adjusted hazard ratio of PFS in the RWD cohort receiving dabrafenib + trametinib was 0.56 (95% CI: 0.35–0.89) (Table 8, Fig. 4B). In COMBI-v, the hazard ratio for dabrafenib + trametinib versus the control group was also 0.56. By the subgroups analyzed, more favorable

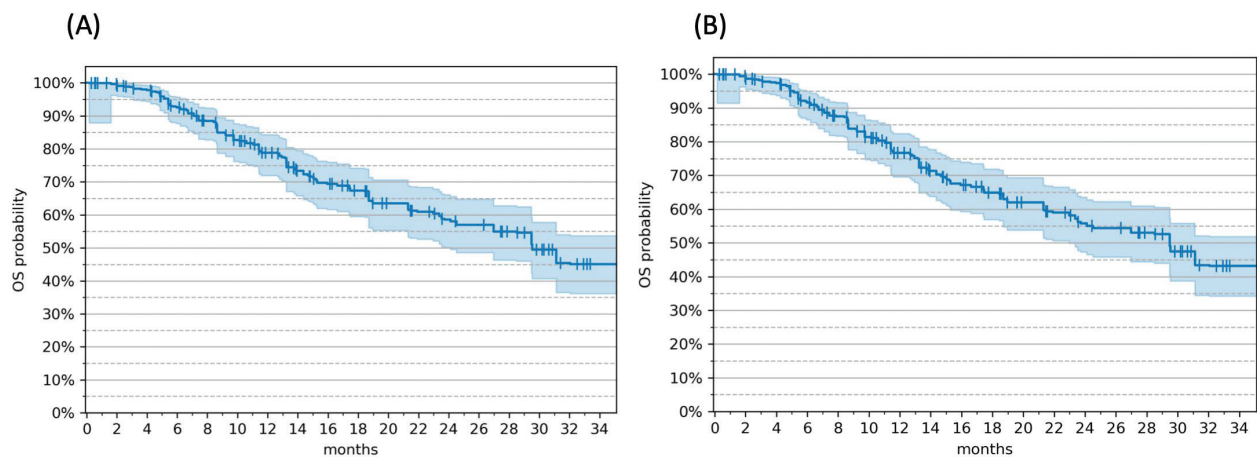
results for the RWD group are estimated for patients below 65 years of age, males, and ECOG 1.

Overall survival

Comparisons between RWD and RCTs for OS are exhibited in Table 7. Comparison against COMBI-d shows that probabilities for RWD are consistently higher throughout the observed period. Calculations are based on 88 events for RWD in comparison to 40 for the RCT. A median of 29.5 (95% CI: 24.1–51.4) months is calculated for RWD, while in the case of RCT it is not reached. For the 4th month, RWD and RCT results are 98% (95% CI: 94–99%) and 97%, respectively. For the 6th month, results are 93% (95% CI: 88–96%) and 92%, respectively. For the 8th month,

Table 7. Overall survival: RWD vs. RCT.

COMBI-d					COMBI-v			
RWD		Clinical Trial			RWD		Clinical Trial	
OS	Patients at risk	N = 190	Patients at risk	N = 211	Patients at risk	N = 190	Patients at risk	N = 352
# events		88		40		88		100 (28.0%)
		(46.3%)		(19.0%)		(46.3%)		
Median		29.5 mo.		NC		29.5 mo.		NC
		(24.1–51.4)				(23.0–43.1)		
@4 mo.	169	98%	199	~97%	169	97%	336	~98%
		(94–99)				(94–99)		
@6 mo.	150	93%	185	~92%	150	92%	310	~92%
		(88–96)				(86–95)		
@8 mo.	136	88%	160	~85%	136	87%	283	~85%
		(83–92)				(82–92)		
@12 mo.	110	79%	44	~74%	110	77%	157	~72%
		(72–84)				(69–82)		
@24 mo.	51	59%	–	–	51	56%	–	–
		(50–66)				(47–64)		

**Figure 5.** Overall survival: Kaplan-Meier estimates. **A.** IPF based on COMBI-d. The tick marks represent censored patients; the shaded area represents 95% CI; **B.** IPF based on COMBI-v. The tick marks represent censored patients; the shaded area represents 95% CI.**Table 8.** Hazard ratios: RWD vs. RCT.

Feature/ Value	COMBI-d				COMBI-v			
	RWD	RCT	RWD	RCT	RWD	RCT	RWD	RCT
	n/N	HR	N	HR	n/N	HR	N	HR
All patients	138/253	0.46 b (0.29–0.74)	423	0.75	148/293	0.56 (0.35–0.89)	704	0.56
Age								
<65y	77/133	0.46 (0.26–0.81)	305	0.71	82/145	0.53 (0.29–0.98)	538	0.57
≥65y	61/120	0.48 (0.22–1.08)	118	1.09	66/148	0.64 (0.32–1.29)	166	0.50
Gender								
Female	53/95	0.53 (0.27–1.02)	198	0.73	55/113	0.56 (0.27–1.16)	316	0.44
Male	85/158	0.40 (0.21–0.73)	225	0.86	93/180	0.54 (0.29–0.99)	388	0.65
ECOG								
0	52/95	0.42 (0.22–0.80)	305	0.75	48/103	0.69 (0.34–1.40)	496	0.50
1	63/122	0.62 (0.31–1.24)	116	0.93	75/149	0.5 (0.30–0.84)	206	0.75

results are 88% (95% CI: 83–92%) and 85%, respectively. For the 12th month, results are 79% (95% CI: 72–84%) and 74%, respectively. A Kaplan-Meier curve of RWD is illustrated in Fig. 5A. After the 24th month, confidence intervals of the curve are rather large due to the small number

of patients at risk. Thus, comparison with RCT results after that time should be interpreted with caution.

A comparison against COMBI-v (see Table 7) is made based on 88 events for RWD and 100 events for the RCT. Results show a median value of 29.5 (95% CI: 23–43.1) months for RWD, while in the case of Combi-v the median is not reached. For the 4th month, results show 97% (95% CI: 94–99%) vs. 98% for RWD vs. RCT, respectively, and for the 6th month, both cohorts report 92% OS (RWD, 95% CI: 86–95%). The curves begin to exhibit a notable divergence from each other beyond the 8th month, with RWD rates remaining higher than RWD for the observable period. At 12th month, rates stand at 77% (95% CI: 69–82%) vs. 72% for RWD and RCT, respectively. A Kaplan-Meier curve illustrating OS for RWD over the entire observable period is illustrated in Fig. 5B.

Discussion

The present analysis compared the outcomes of patients receiving dabrafenib and trametinib within Bulgarian clinical practice. Outcomes from RWD with respect to OS, PFS, OBR, CBR, and HR were compared to the

outcomes of each of the RCTs, namely COMBI-v and COMBI-d.

With respect to certain of the considered patient characteristics, such as age, sex, and previous therapies, the distributions observed in RWD were comparable to those of the RCTs. With respect to other indicators, such as TNM Stage, differences were observed. In order to control for the possible impact of differences in patient characteristics on the outcome comparison, the RWD was weight-adjusted in to match the distributions of the RCTs.

We compared OS and PFS from RWD to COMBI-d and COMBI-v. In comparison to COMBI-d, RWD outcomes were overall more favorable: OS for RWD was consistently higher than RCT over the first 24 months; the median PFS was 16.1 (95% CI: NC-NC) months for RWD versus 9.3 months in the RCT. Similarly, in comparison to COMBI-v, RWD outcomes were more favorable: OS was close to or higher than the RCT; the median PFS was 17 months (95% CI: NC-NC) for RWD versus 11.4 months in the RCT. Hazard ratios also show that patients receiving treatment with dabrafenib and trametinib respond more favorably in the RWD as opposed to the RCTs in comparison to the control group.

With respect to CBR outcomes, similar rates are observed in both RWD and RCTs (84.6% (95% CI: 77.9–89.5%) for RWD vs. 92 and 90% for COMBI-d and COMBI-v, respectively).

A few studies analyzing the effectiveness of the combined targeted therapy dabrafenib+trametinib in real-world settings are available. The results from the reviewed analyses confirm the effectiveness of dabrafenib + trametinib in real-world clinical practice despite the unselected population.

The results from our study correspond with the Italian retrospective observational analysis conducted for BRAF+ patients with metastatic melanoma, where 729 patients were treated with targeted therapy (TT) (n = 671 with TT as first line) (Marcon et al. 2023). The TT consists of dabrafenib + trametinib, or vemurafenib + cobimetinib, or binimetinib + encorafenib. The demographic characteristics of the patients included in the Italian retrospective analysis are similar to those of the Bulgarian population. Around 60% of patients treated with TT were male, and the mean age at start of first-line treatment was 60 years (59.4 years in dabrafenib + trametinib). The median OS after initiating first-line TT is 27 months, which is comparable with our findings. Median time to discontinuation was 10.6 months for first line (11.0 months for dabrafenib + trametinib), with a proportion of discontinuing patients of 62% overall (Marcon et al. 2023).

The results of the present study are consistent with the results of an observational retrospective ADMIRE study that involved 382 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma who received targeted therapy (TT) in twelve medical centers in Russia (Orlova et al. 2021). The characteristics of patients are similar between the two analyses in terms of ECOG status. There are some differences in the distribution of patients in the TNM stage. The BRAFi+MEKi cohort consists of 54 (31.4%) M1c patients and 70 (40.7%) M1d patients.

The mean age of the patients in the BRAFi+MEKi cohort is 49.0 +/- 13.4 years. 55.2% (n = 211) patients received a combination of BRAFi and MEKi (dabrafenib (D) plus trametinib (T) or vemurafenib (V) plus cobimetinib (C)). Most patients (138/225, 61.3%) received combined TT (dabrafenib (D) plus trametinib (T) or vemurafenib (V) plus cobimetinib (C)) as the first-line therapy. The median PFS in the ADMIRE study for the patients receiving combined first-line therapy was 9.2 months versus 11.1 months in the pooled COMBI-v/d data analysis (dabrafenib + trametinib). The median OS in ADMIRE for the first-line combined TT group was 22.6 months versus 25.9 months in the pooled COMBI-v/d data analysis (dabrafenib + trametinib). The ORR of patients on the first-line combination treatment is 59.4% (Orlova et al. 2021).

DESCRIBE II is a retrospective study, conducted with patients with BRAF V600-mutated unresectable stage III/IV melanoma treated with dabrafenib + trametinib (Atkinson et al. 2020).

The EGOG status of patients included in the study is similar to the ECOG status of our patients. Patients in stage IV melanoma are 92.6% of the total 271. Patients treated with dabrafenib + trametinib as first-line therapy are 171 (63.1%). The median OS for BRAFi-naïve patients is 20.0 months, and the PFS is 7.5 months (Atkinson et al. 2020).

A retrospective analysis conducted at the Maria Skłodowska-Curie National Research Institute of Oncology Cracow Branch, Poland, assessed current trends and treatment effects of patients with advanced/disseminated melanoma through real-world results (Cybulska-Stopa et al. 2020). The cohort of patients treated with TT as first-line treatment (n = 111) has a median age of 60 years, and ECOG is mainly 1–84 (76%), which is similar to our cohort. There are differences in the TNM distribution of the patients; the Poland cohort consists of 40 (36%) patients in M1c and 40 (36%) patients in M1d. In the retrospective analysis, 65 out of 111 patients are treated with BRAFi + MEKi (consisting of vemurafenib ± cobimetinib or dabrafenib ± trametinib). Based on the first-line treatment, the median OS is 12.6 months for TT, 6-month OS is 77%, 1-year OS is 50%, and 2-year OS is 22%. The median PFS is 7.3 months. The reported ORR of first-line TT is 64% (Cybulska-Stopa et al. 2020).

Our findings differ from the above mentioned, and the explanation could be in the number of the patients in the cohorts (65 patients against 190 patients), patient distribution in the TNM stage, as well as the fact that in the Poland cohort the therapies include not only dabrafenib + trametinib but also vemurafenib + cobimetinib.

DATUM-NIS is a noninterventional, postmarketing, observational study designed to prospectively investigate the day-to-day clinical routine treatment of patients with unresectable/metastatic melanoma receiving dabrafenib + trametinib by prescription across 12 sites in Austria (Richtig et al. 2024). In the study are included 79 adult patients with BRAF V600-mutant, unresectable/metastatic melanoma. The median age of patients is 60 years; 61% of them are male. The cohort with ECOG 0 is 50 (63%) patients and with ECOG 1 is 20 (25%). Most patients 59

(75%) have M1c disease. Median PFS for the overall population was 9.1 months. The 6-, 12-, and 18-month PFS rates were 76%, 30.6%, and 16.2%, respectively. The median OS was 17.93 months with a survival rate of 62.7% and 26.8% after 12 and 24 months, respectively (Richtig et al. 2024).

Patients with unresectable, advanced BRAF V600-mutant melanoma were included in phase IIb, a single-arm multicenter French study (Saiag et al. 2021). A total of 856 patients are included in the study, with a mean age of 58.5 years. Patients with ECOG 0 are 62% and with ECOG 1 are 28.3%. Most of the patients (92%) had stage IV melanoma, and 72% have M1c TNM stage. Patients are treated with trametinib in combination with dabrafenib. The reported progression events (including death) are 401. Median PFS is 8.02 months and the ORR is 50.2% (Saiag et al. 2021).

Our study demonstrates highly comparable efficacy of the combined targeted therapy dabrafenib+trametinib in everyday clinical practice when compared to COMBI-d and COMBI-v clinical trials. In addition, the reported results of the Bulgarian patients are close to the results reported in some of the reviewed analyses.

Conclusion

We present an analysis of RWD data on patients receiving a combination treatment of dabrafenib and trametinib collected from clinical practice in Bulgaria. IPF was implemented in order to control for potential impacts from differences in patient characteristics. Results show that patients achieve more favorable OS and PFS outcomes in RWD in comparison to RCTs COMBI-d and COMBI-v. CBR outcomes were comparable between RWD and RCTs. Hazard ratios also indicate that patients on a combination of dabrafenib and trametinib achieve more favorable results in RWD vs. RCTs in comparison to the control group.

Additional information

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study. This study was based on secondary usage of anonymized data using hospital-integrated software. Ethics committee approval or patient-informed consent were not required for this type of research as per local Bulgarian regulations.

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Data availability

All of the data that support the findings of this study are available in the main text.

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