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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Real-world treatment patterns and outcomes in patients with metastatic melanoma

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SUMMARY

Introduction/Objective The purpose of this study was to assess the effectiveness of different approaches in the treatment of metastatic melanoma in daily clinical practice in a situation with limited and late availability of new drugs in a resource-limited country and to compare these parameters with those reported in clinical studies and from other real-world data.

Methods Main methods included assessment of overall survival (OS) and progression-free survival (PFS). Patients were included in the study if they were treated with first or second-line systemic therapy for radiologically/pathologically confirmed metastatic melanoma. Patients were divided into four groups based on the type of therapy they received: chemotherapy (dacarbazin), BRAF inhibitor (vemurafenib), BRAF/MEK inhibitors (vemurafenib/cobimetinib and trametinib/dabrafenib) and anti PD-1 therapy with pembrolizumab.

Results Regardless of the line of therapy, the calculated median OS in chemotherapy and vemurafenib group was nine months. The median OS in the BRAF/MEK inhibitor group was 14 months and 15 months in the pembrolizumab group. Median PFS in the chemotherapy group was four months, seven months for vemurafenib, in the BRAF/MEK inhibitor group nine months and in the pembrolizumab group six months. There was a statistically significant difference in survival between first and second-line therapy in the pembrolizumab group.

Conclusion Our results showed lower median OS and PFS in comparison to reported data from clinical trials. Compared to other real-world data from countries with similar problems related to the late reimbursement of new drugs, our research has shown similar results.

Keywords: metastatic melanoma; immunotherapy; targeted therapy; chemotherapy; survival; real-world data

INTRODUCTION

When we look at the not-so-distant history, patients with advanced melanoma had a poor prognosis and overall survival (OS). Chemotherapy had limited success in metastatic melanoma, with responses observed in 13.7% of patients, median OS ranging from 6.6 to 15.6 months and median PFS ranging from 1.5 to 5.6 months [1]. Significant progress in the treatment of metastatic melanoma has occurred in recent years with the introduction of MAP kinase inhibitors and immunotherapy which have shown an impressive effect on OS. Two-year survival rates have reached 50% in cases with either anti-PD1 immunotherapy (immune checkpoint inhibitor) or the BRAF/MEK inhibitors combination, compared with < 10% of patients treated with chemotherapy [2, 3]. Programmed cell death 1 (PD-1) blockade along with BRAF/MEK inhibitors is now a standard of first line care for all advanced and metastatic melanoma patients [4]. It is still unclear whether these remarkable results are also achieved in daily clinical practice. However, there are significant differences in the access to novel drugs across European countries, therefore differences in patient survival are possible [5]. This study aims to assess the effectiveness of different approaches in the treatment of metastatic melanoma in daily clinical practice in a situation with limited and late availability of new drugs in a resource-limited country and to compare these parameters with those reported in clinical studies and from other real-world data.

METHODS

This was a retrospective observational study evaluating real-world treatment and patient outcomes for metastatic melanoma. The main objectives included OS and PFS assessment. This study was conducted at the Oncology Clinic, University Clinical Centre of the Republic of Srpska, Bosnia and Herzegovina (BiH), in the period from January 2015 to December 2020. Patients were included in our analysis if they were treated with first or second-line systemic therapy for radiologically/pathologically confirmed metastatic melanoma.

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Table 1. Demographic and disease characteristics of the patients

Patients' characteristic	Chemotherapy	BRAF inhibitor	BRAF/MEK inhibitors	Anti PD-1	Total population
Number of cases (%)	52 (48.60)	17 (15.90)	27 (25.20)	11 (10.30)	107 (100)
Median age in years	66.50 (35–85)	54 (31–79)	56 (33–81)	55 (28–67)	62 (28–85)
Male gender n (%)	28 (53.85)	10 (58.80)	20 (74)	8 (72.70)	66 (61.70)
The Eastern Cooperative Oncology Group performance status – n (%)					
0	27 (51.90)	8 (47.10)	19 (70.40)	7 (63.60)	61 (57)
1	15 (28.80)	6 (35.30)	6 (22.20)	1 (9.10)	28 (26.20)
2	8 (15.40)	2 (11.80)	2 (7.40)	2 (18.20)	14 (13.10)
3	2 (3.80)	1 (5.90)	0 (0)	1 (9.10)	4 (3.70)
4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Anatomic site of primary n (%)					
Cutaneous	43(82.70)	17(100)	23(85.20)	9(82)	92(86)
Ocular	2(3.85)	0 (0)	0 (0)	0 (0)	2(2)
Mucosal	1(1.90)	0 (0)	0 (0)	1(9)	2(2)
Primary unknown	6(11.55)	0 (0)	4(16.80)	1(9)	11(10)
BRAF status (%)					
Wild type	19 (36.55)	0 (0)	0 (0)	10 (91)	29 (27.10)
V600E mutated	14 (26.90)	17 (100)	27 (100)	1 (9)	59 (55.15)
Not evaluated	19 (36.55)	0 (0)	0 (0)	0 (0)	19 (17.75)
Elevated baseline lactat dehidrogenase level (> 280 U/L) n (%)	29 (48.30)	11 (18.30)	13 (21.7)	7 (11.7)	60 (56)
Organs with metastatic involvement – n (%)					
1	24 (46.15)	0 (0)	1(3.70)	0(0)	25(29.90)
2	17 (32.70)	4 (23.50)	5(18.50)	5(45.45)	31(32.70)
3	7 (13.45)	8 (47)	11(40.75)	2(18.20)	28(23.40)
> 3	4 (7.70)	5 (29.50)	10(37.05)	4(36.35)	23(14)
First-line therapy n (%)	52 (100)	9 (53)	11 (40.70)	6 (54.55)	78 (73)

The disease stage was determined by using the eight version of the American Joint Committee on Cancer, the tumor, node, metastases classification system [6]. Patients were excluded if they were enrolled in clinical trials, had another cancer diagnosis besides basal cell carcinoma and some in situ carcinomas and patients that were in two different treatment groups. All relevant data were collected from medical files and entered into a data-base. Patients were divided into four groups according to the therapy they have received: chemotherapy (dacarbazin based chemotherapy), BRAF inhibitor (vemurafenib), BRAF/MEK inhibitors (vemurafenib/cobimetinib and trametinib/dabrafenib) and anti PD-1 therapy with pembrolizumab. Therapy was applied according to the valid recommendations for each protocol. Also, we collected other data related to the patient: age, sex, anatomic site of primary melanoma, BRAF mutation, baseline serum Lactat dehidrogenase (LDH), The Eastern Cooperative Oncology Group (ECOG) performance status and the number of organs with detected metastases. The efficacy of therapy was evaluated according to the response evaluation criteria in solid tumors (RECIST, version 1.1) by using computed tomography scan, positron emission tomography using 18F-fluorodeoxyglucose, magnetic resonance imaging, clinical examination and laboratory tests [7].

Statistical analysis

Statistical data was obtained using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to assess absolute values and percentages. The survival rate was calculated by the Kaplan–Meier method and compared using the log-rank test. A p value of ≤ 0.05 was considered statistically significant. OS was calculated from the date of the initiation of specific treatment until the date of death due to any cause. Patients who did not die were censored for OS on the last visit date available in the database. PFS is the interval from treatment initiation until the date of physician-documented assessed disease progression. Patients who did not progress and were still alive were censored for PFS on the last visit date available in the database. Last visit date available in database was December 31, 2020. The relationship of certain baseline characteristics was examined using Cox hazard proportional model. The study was approved by the Institutional Review Board Committee number 01.19-321-2/21 and was conducted in accordance with the ethical standards defined by the Helsinki Declaration.

RESULTS

Demographic and disease characteristics of 107 patients included in analysis are presented in more detail in Table 1. All patients were Caucasian. The median age was 62 years (range 28–85), the majority of patients (61.7%) were males, and in ECOG performance status 0 (57%). Among all of the patients, 92 (86%) had the cutaneous subtype of melanoma. A total of 59 patients (55.15%) had a BRAF V600E mutation, 29 (27.1%) were wild type, and

19 (17.75%) patients did not have a BRAF status evaluated. Normal baseline LDH was found in 42 (39.3%) of the patients, elevated LDH in 60 (56%) of the patients and in five (4.7%) of the patients LDH was not evaluated. In total, 31 (32.7%) of the patients – had two organs with metastatic involvement. In total, 52 (48.6%) of patients received chemotherapy. BRAF/MEK inhibitors were received by 27 patients (25.2%), BRAF inhibitors by 17 (15.9%) and 11 (10.3%) patients received pembrolizumab. All patients in the chemotherapy group received dacarbasine-based chemotherapy as a first-line treatment. In the mono BRAF inhibitor group, nine patients received the BRAF inhibitor as first-line therapy. First-line therapy with BRAF/MEK inhibitors were received by 11 out of 27 patients. Six patients in the pembrolizumab group received it as a first line treatment.

Survival analysis

We conducted a survival analysis for cutaneous metastatic melanoma. Regarding the efficacy of different therapies, at data cut-off, all patients in the chemotherapy group and in the BRAF inhibitor group progressed. In the BRAF inhibitor group all of the patients died, and in the chemotherapy group one patient is still alive. Seven (30.45%) patients in BRAF/MEK inhibitor group and three (33.35%) patients in the pembrolizumab group are still undergoing treatment. In the BRAF/MEK inhibitor group eight (34.8%) patients are alive, as are five (55.55%) of the patients in the pembrolizumab group. In all the treatment groups, regardless of the therapy line, there is a statistically significant difference in OS and PFS (Figure 1 and 2). The calculated median OS in both the chemotherapy group and in the vemurafenib group were nine months. The median OS in the BRAF/MEK inhibitor group was 14 months and in the pembrolizumab group 15 months. The calculated median PFS in the chemotherapy group was four months and in the vemurafenib group seven months. Median PFS in the BRAF/MEK inhibitor group was nine months and in the pembrolizumab group nine months (Table 2). Table 3 shows the results of the first and second-line of therapy for different treatment groups. In 15 patients (14%) with non-cutaneous melanoma, median OS was seven months, while PFS was four months. The survival rate differences were statistically significant ($p = 0.04$) in all of the patients, according to whether baseline LDH was elevated or not. The median OS for patients with normal LDH was 16 months (95% CI, 10.35–21.65), while patients with elevated baseline LDH had the median OS of nine months (95% CI, 6.35–11.65). We used the Cox proportional hazard model to evaluate the nominal explanatory variable – elevated LDH values were considered a prognostic factor of disease progression and death. Elevated LDH was a statistically significant prognostic factor of disease progression ($p = 0.037$) and patient death ($p = 0.007$). The risk of disease progression in patients with elevated LDH values was 1.57 times higher compared to patients with normal values of LDH. Also, patients with elevated LDH values were found to be in a statistically significant higher risk of death (HR 1.84) compared to patients

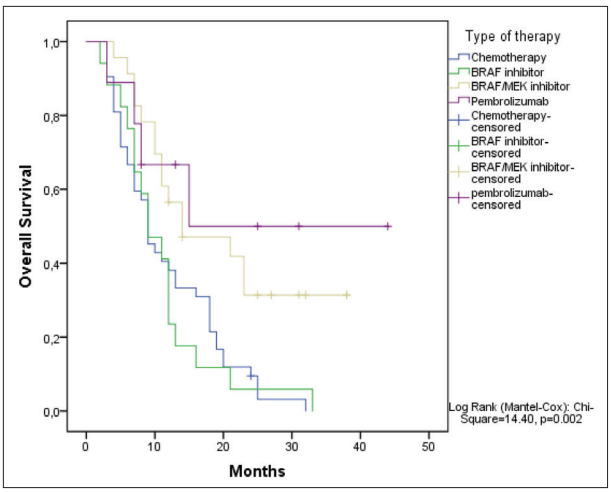

Figure 1. Caplan–Meier curve showing overall survival in different treatment groups for cutaneous melanoma

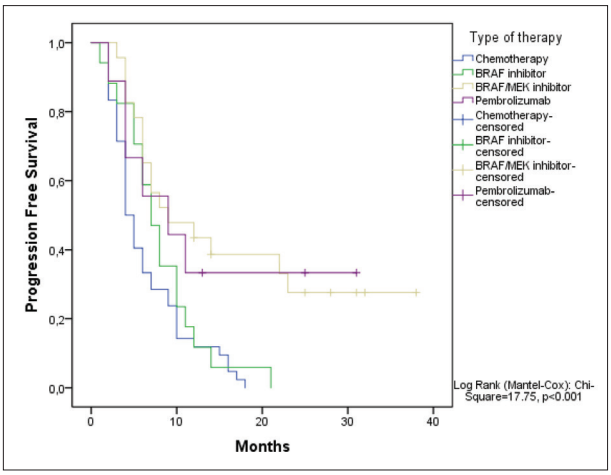

Figure 2. Caplan–Meier curve showing progression-free survival in different treatment groups for cutaneous melanoma

with normal LDH values. Similarly, the differences in survival rate according to the ECOG status were statistically significant in all patients ($p < 0.001$).

As for subsequent lines of therapy, 15 of the patients in chemotherapy group received second-line therapy. Five of them received any of the novel therapeutics available as second-line therapy. In the other three groups, only seven patients managed to receive the further line of therapy.

DISCUSSION

Public financing of new drug therapy in the Republic of Srpska and the whole BiH is usually performed within a separate financial path – the so-called "drug programmes". By a decision made by the Ministry for Health and Health Insurance Fund, a drug programme is to be performed by referent hospitals. The drug programmes provide a financing path for new drugs under strictly specified conditions. Sometimes the quantity of the new drug received is not enough for all patients, so some patients with metastatic melanoma continue to receive chemotherapy as a first-line

Table 2. Survival statistics for different treatment protocols

Type of therapy	Overall survival	95% CI	Progression-free survival	95% CI	Patients alive	Ongoing treatment
Chemotherapy (dacarbasin)	9	6.9–11.1	4	3–5	1	0
BRAF inhibitor (vemurafenib)	9	4.9–13	7	5–9	0	0
BRAF/MEK inhibitors (vemurafenib/cobimetinib, dabrafenib/trametinib)	14	3.4–26.7	9	1.2–16.8	8	7
Immunotherapy (pembrolizumab)	15	1.3–26.1	9	0.7–17.7	5	3

Table 3. Median overall survival and progression-free survival for first and second-line therapy for different protocols

Overall survival						
Type of therapy	Therapy Line	Median				p value (Log-Rank)
		Estimate	Std. Error	95% CI		
				Lower Bound	Upper Bound	
BRAF inhibitor	First-line	9	0.7	7.5	10.5	0.913
	Second-line	8	2.8	2.5	13.5	
BRAF/MEK inhibitors	First-line	23	7.7	7.8	38.2	0.294
	Second-line	12	1.8	8.4	15.6	
Pembrolizumab	First-line	Not reached	0	0	0	0.032
	Second-line	8.0	1.8	4.5	11.5	
Progression-free survival						
BRAF inhibitor	First-line	7.0	0.7	5.5	8.5	0.676
	Second-line	5.0	4.2	0	13.3	
BRAF/MEK inhibitors	First-line	12.0	7.2	0	26.1	0.084
	Second-line	8.0	2	4.1	11.9	
Pembrolizumab	First-line	Not reached	0	0	0	0.005
	Second-line	4	0.4	3.1	4.9	

therapy. This is one of the reasons why most of the patients are in the chemotherapy group. Another reason is the late reimbursement of new drugs. Results from this one-country, single-center analysis showed differences in the median OS and PFS between different groups of melanoma patients receiving these four types of therapy, compared to reported data from clinical studies. As previously mentioned, chemotherapy has limited success in metastatic melanoma [1]. Also, high dose Interleukin-2 has been used to treat metastatic melanoma with modest responses, but those who achieve complete response (< 10%) tend to have extremely durable responses and high rates of long-term survival [8]. Compared to the efficacy of different protocols of chemotherapy, our results showed similar results, with a nine-month median OS and a median PFS of four months.

Another study that was using real-world data was performed in Poland [9]. This retrospective analysis included 287 patients treated from 2013 to 2019. All enrolled patients were treated with immunotherapy (pembrolizumab/nivolumab or ipilimumab), targeted therapy (vemurafenib/cobimetinib or dabrafenib/trametinib) or chemotherapy in at least one treatment line. Brain metastases were detected in 64 (22%) patients. The first-line treatment of patients involved immunotherapy, targeted therapy, or chemotherapy, and the median OS reached 19.2, 12.6, and 15.9 months, respectively [9]. In this analysis, the unexpected finding was that the median OS for targeted therapy is lower than that in chemotherapy group. This is probably due to the high incidence of poor prognostic factors, and because the BRAF mono- and BRAF combo-therapy were analyzed as one group. Our results showed better median OS in all groups in the first line, with the exemption of the chemotherapy group.

Atkinson et al. [10] conducted a retrospective study, DESCRIBE II, consisting of a chart review of the patients with BRAF V600-mutated unresectable stage III/IV melanoma receiving dabrafenib plus trametinib as compassionate use. Treatment patterns and duration, clinical outcomes, and tolerability were evaluated. The total number of enrolled patients was 271. Stage IV melanoma had 92.6% of them, including 36.5% with brain metastases. More than half, 162 patients (59.8%) were BRAF inhibitor naive. These patients achieved an overall response rate (ORR) in 67.3% cases, median OS reached 20 months, and median PFS was 7.5 months. The number of BRAF inhibitor-naive patients with detected brain metastases was 62, ORR was 61.3%, median OS was 15.5 months, and median PFS was 6.2 months [10].

In a study evaluating real-world data efficacy of pembrolizumab in 532 patients pembrolizumab was administered to 315 (59%), 152 (29%), and 65 (12%) patients as first-, second-, and third-line/later therapy [11]. Median OS for first-line pembrolizumab was not reached, and for second-line and third-line/later was 13.9 and 12.5 months respectively, log-rank p = 0.0095 [11]. In comparison with this study, our result showed a shorter median OS in second-line therapy.

A retrospective observational multicenter study – Advanced Melanoma In Russia (Experience), evaluated a subset of patients with V600 BRAF-mutated unresectable or metastatic melanoma, who received targeted

therapy in a real-world setting. In 382 included patients, the ORR to the combined BRAF/MEK inhibitor and to the BRAF inhibitor mono-therapy were 57.4% and 39.8%, respectively. The median PFS and OS were 9.2 months and 22.6 months, respectively, for the combined first-line therapy; 9.4 months and 16.1 months, respectively, for the combined second-line therapy; and 7.4 months and 17.1 months, respectively, for the combined third or higher-line therapy [12]. The results of this study were similar to those in clinical trials and better than those in other real-world data studies. Also, it showed solid results when the drugs were applied in the second line. In the case of the mono vemurafenib group, our data of nine months median OS and seven months of median PFS, where slightly lower than results found in the BRIM-3 trial. In final overview of the BRIM-3 study, median OS, censored at crossover, was significantly longer for vemurafenib - 13.6 months, than for dacarbasine - 9.7 months [13]. Despite high initial ORR, half of the patients treated with BRAF targeted monotherapies relapsed within six months, due to the development of drug resistance and other various reasons [14, 15, 16].

Trametinib, cobimetinib, and binimetinib, targeting the MAP kinase pathway, are overcoming resistance to BRAF inhibitor therapy. They are oral small-molecule inhibitors of MEK1 and MEK2, signaling molecules downstream of BRAF in the MAP kinase pathway. When compared with either single-agent dabrafenib or single agent vemurafenib, BRAF/MEK inhibitor combination therapy with dabrafenib and trametinib, vemurafenib plus cobimetinib and encorafenib plus binimetinib showed improved ORR, duration of response, PFS, and OS [17, 18, 19]. Results are significantly better then mono BRAF inhibition, with median OS ranging from 22 to 33 months and PFS from 11 to 15 months. Our results for patients treated with BRAF/MEK inhibition with two available combinations showed inferior OS and PFS with median OS of 14 months and median PFS of nine months. Two complete responses are currently being observed, as well as three partial responses and two stable diseases in this treatment group.

In the matter of the efficacy of pembrolizumab, it showed a lower median OS of 15 months, but a similar PFS of nine months. One complete response is still ongoing, as well as two partial responses in the pembrolizumab group. A recent publication of outcomes and survival from a randomized, phase 3 trial Keynote-006 of pembrolizumab for ipilimumab naive advanced or metastatic melanoma patients, showed a median OS of 32.7 months (95% CI 24.5–41.6), median PFS of 8.4 months (95% CI 6.6–11.3) [20]. Nivolumab is another PD-1 inhibitor that is indicated for the treatment of advanced or metastatic melanoma. In a five-year outcome analysis in trial with Nivolumab CheckMate 066, the median OS was 37.3 months (95% CI, 25.4–51.6) and median PFS 5.1 months (95% CI, 3.5–12.2) [21].

There are more possible reasons for these results. Firstly, medium follow-up in our analysis was shorter in comparison to published clinical trials. Secondly, the characteristics of our patients differ from those in the mentioned clinical trials. Our patients were mainly in an ECOG performance status of 0, but there are 18 of them that were ECOG 2 or 3, which is often within the exclusion criteria in clinical trials. There were 14 (13.1%) patients with initially detected brain metastases, some of them had symptomatic brain metastases, which was an exclusion criterion in some clinical trials. We know that patients with active brain metastases not only have a poor survival rate due to their disease, but also require systemic glucocorticoids [22]. Ultimately, perhaps the most significant reason for the poor efficacy of targeted therapy and immunotherapy is that a huge number of patients did not start therapy as a first-line treatment. These patient groups received chemotherapy before starting targeted therapy or immunotherapy, which had a detrimental effect on performance status and perhaps induced drug resistance. However, at the time of initiation of the first-line treatment, the tumor burden was lower, as well as the number of metastatic sites.

The limitations of this study include a small number of patients is insufficient for definitive conclusion, as well as the retrospective design of the study results and a short follow-up time compared to recent publications. Our future perspective is to update the data, especially regarding the survival rate and the responses to immunotherapy and BRAF/MEK inhibitors. We hope to see better antitumor activity of these drugs. In October 2018, when PD-1 inhibitor pembrolizumab was available for melanoma patients in BiH, this was the only PD-1 inhibitor reimbursed by medical insurance. Even today, Nivolumab is not fully reimbursed and neither the combination of nivolumab with ipilimumab, which presents another treatment option for this group of patients, with an exceptional survival [23]. BRAF/MEK inhibitors were reimbursed in 2017, and BRAF inhibitor in 2015. Based on this, in BiH there is still a lot of space for improvement when it comes to systemic melanoma treatment. Providing faster reimbursement for new drugs, different financing options for this kind of treatment, procurement of larger quantities of these drugs so patients do not have to wait and including patients in clinical trials should be priorities. The lack of focus on these priorities is possibly reflected in the data showing an increase in the mortality-to-incidence ratios in Eastern European countries compared to Western Europe [24].

CONCLUSION

Our results show lower median OS and PFS compared to reported data from clinical studies. Compared to other real-world data in countries with similar problems, our research has shown similar results. This gives us an insight into real-life patient care and represents an important contribution to the oncology community, with the hope that it will enable a better care for our patients in the future.

Conflict of interests: None declared.

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Обрасци и исходи лечења болесника са метастатским меланомом – подаци из стварног света

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САЖЕТАК

Увод/Циљ Сврха овог истраживања је да се процени ефикасност различитих приступа у лечењу метастатског меланома у свакодневној клиничкој пракси у ситуацији са ограниченом и касном доступношћу нових лекова у земљи са ограниченим ресурсима и да се ови параметри упореде са оним објављеним у клиничким студијама и са другим подацима из стварног света.

Методе Главни методе су укључивале процену укупног преживљавања и преживљавања без прогресије болести. Анализирани су болесници који су били лечени првом или другом линијом системске терапије за радиолошки/патохистолошки потврђени метастатски меланом. Болесници су подељени у четири групе према терапији коју су примали: хемотерапију (дакарбазин), БРАФ инхибитор (вемурафениб), БРАФ/МЕК инхибиторе (вемурафениб/цобиметиниб и траметиниб/дабрафениб) и анти ПД-1 терапију пембролизумабом.

Резултати Без обзира на терапијску линију, израчуната медијана укупног преживљавања у групи која је примала хемиотерапију и вемурафениб била је девет месеци. Медијана укупног преживљавања у групи која је примала БРАФ/МЕК инхибитор била је 14 месеци, а у групи која је примала терапију пембролизумабом 15 месеци. Преживљавање без прогресије болести у хемиотерапијској групи било је четири месеца, у групи која је примала вемурафениб седам месеци, у групи која је примала БРАФ/МЕК инхибитор девет месеци и у групи која је имала терапију пембролизумабом шест месеци. Постоји статистички значајна разлика у преживљавању између прве и друге линије у групи која је имала терапију пембролизумабом.

Закључак Наши резултати показују нижу медијану укупног преживљавања и преживљавања без прогресије болести у поређењу са пријављеним подацима из клиничких испитивања. У поређењу са другим подацима из стварног света у земљама са сличним проблемима са касним увођењем нових лекова, наше истраживање је показало сличне резултате. Нове терапије значајно су продужиле преживљавање, али још много тога треба да се уради како би болесници постигли веће стопе преживљавања.

Кључне речи: метастатски меланом; имунотерапија; циљана терапија; хемиотерапија; преживљавање; подаци из стварног света