

EFFICACY OF COMBINED TARGETED THERAPY AND IMMUNOTHERAPY IN BRAF-MUTATED PATIENTS WITH ADVANCED MELANOMA AND PROGNOSTIC SIGNIFICANCE OF LACTATE DEHYDROGENASE ACTIVITY: EXPERIENCE OF A TERTIARY CENTER

EFIKASNOST KOMBINOVANE CILJANE TERAPIJE I IMUNOTERAPIJE KOD PACIJENATA SA BRAF MUTIRANIM UZNAPREDOVALIM MELANOMOM I PROGNOSTICKI ZNAČAJ AKTIVNOSTI LDH: ISKUSTVO TERCIJARNOG CENTRA

Mirjana Bakić^{1,2}, Aleksandar Popović³, Aleksandra Klisić^{*,1,4}

¹University of Montenegro-Faculty of Medicine, Podgorica, Montenegro

²Clinic of Dermatovenereology, Clinical Centre Podgorica, Montenegro

³Clinic of Oncology, University Clinical Centre Niš, Serbia

⁴Primary Health Care Centre, Podgorica, Montenegro

Summary

Background: To evaluate the efficacy of combined targeted therapy and immunotherapy in patients with BRAF-mutated melanoma, and to assess the prognostic significance of lactate dehydrogenase (LDH) activity.

Methods: This retrospective study included 68 patients (mean age 57.4 ± 13.6 years), with advanced melanoma treated at a tertiary centre between 2019 and 2024. Patients were divided into two groups: immunotherapy (nivolumab/pembrolizumab) and combined BRAF/MEK-targeted therapy (dabrafenib/trametinib or vemurafenib/cobimetinib). Clinical outcomes were analysed according to LDH values.

Results: Median progression-free survival (PFS) was 15.97 months, while median overall survival (OS) reached 38.57 months in our patient population. No statistically significant differences were observed between treatment groups, although numerically longer survival was noted in the immunotherapy group. Elevated LDH activity was detected in 41% of patients, more frequently among those receiving targeted therapy. Patients with normal LDH ac-

Kratak sadržaj

Uvod: Cilj je bio da se ispita efikasnost kombinovane ciljane terapije i imunoterapije kod pacijenata sa BRAF-mutiranim melanomom, kao i prognostički značaj aktivnosti laktat dehidrogenaze (LDH).

Metode: Retrospektivna studija obuhvatila je 68 pacijenata (starosti $57,4 \pm 13,6$ godina), sa uznapredovalim melanomom, lečenih inovativnim terapijama u tercijarnom centru između 2019–2024. Pacijenti su bili podeljeni u dve grupe: imunoterapija (nivolumab/pembrolizumab) i kombinovana BRAF/MEK terapija (dabrafenib/trametinib ili vemurafenib/cobimetinib). Analizirani su klinički ishodi u odnosu na LDH aktivnost.

Rezultati: Medijana progresije bez bolesti (PFS) iznosila je 15,97 meseci, dok je medijana ukupnog preživljavanja (OS) bila 38,57 meseci u ispitivanoj populaciji. Nije bilo statistički značajnih razlika između terapijskih grupa, iako je numerički duže preživljavanje zabeleženo kod pacijenata na imunoterapiji. Povišena LDH aktivnost je registrovana kod 41% pacijenata i bila je značajno češća u grupi na ciljanoj terapiji. Pacijenti sa normalnom LDH aktivnošću

Address for correspondence:

Aleksandra Klisić, MD, PhD

University of Montenegro-Faculty of Medicine,
Podgorica, Montenegro

Centre for Laboratory Diagnostics, Primary Health Care Centre,
Podgorica, Montenegro

Address: No. 6, Nikole Kovačevića Square,
81000 Podgorica, Montenegro

Phone and Fax: +382 20 481 999

e-mail: aleksandrklisic@gmail.com

tivity had significantly longer OS than those with elevated LDH (NR vs 16.6 months; $p=0.009$).

Conclusion: Established prognostic value of LDH was confirmed in our patient population. Patients with LDH activity within the reference range had significantly longer overall survival, underscoring LDH's importance as a routine biomarker in clinical practice. Immunotherapy showed numerically better outcomes than combined BRAF/MEK therapy, highlighting the need for further prospective studies to validate these findings.

Keywords: BRAF mutation, melanoma, lactate dehydrogenase, prognosis

Introduction

Melanoma is a malignant tumour of melanocytes that has shown a continuous increase in incidence among white populations over the past four decades, as well as a rise among younger individuals (1). The most common subtype is cutaneous melanoma, while rarer forms include mucosal and ocular melanomas (1.3%), which exhibit distinct clinico-pathological characteristics (2). According to data from the GLOBOCAN global cancer statistics network, which compiles information from 185 countries, an estimated 331,711 new cases were diagnosed in 2022, with cutaneous melanoma accounting for 1.7% of all cancer diagnoses worldwide (3).

Advanced melanoma, defined as unresectable or metastatic disease, has historically been associated with poor prognosis (4). Before the introduction of targeted and immune therapies, the median overall survival (mOS) of patients with advanced melanoma was approximately 6 months (5). In contrast, current data demonstrate that 50% of patients with metastatic melanoma now survive beyond 5 years, compared to only 5% a decade ago (6, 7). For patients with BRAF-mutated melanoma, treatment options currently include targeted therapy and immune checkpoint inhibitors (ICI) (8).

Conventional prognostic factors for survival outcomes in metastatic melanoma include disease stage, serum lactate dehydrogenase (LDH) activity, the sum of the longest diameters of target lesions (SLD), performance status (ECOG PS), and the presence or absence of liver and central nervous system metastases (9, 10). LDH is an enzyme present in all cells of the body that catalyses the reversible conversion of lactate to pyruvic acid. Cancer cells, including melanoma, adopt altered metabolic strategies to meet their energy demands and sustain proliferation. The association between elevated LDH activity and melanoma, particularly metastatic disease – where approximately 40% of patients present with serum LDH above the upper reference limit (11) – has been well established.

imali su značajno duže OS u poređenju sa onima sa povišenom LDH aktivnošću (NR vs 16,6 meseci; $p=0,009$).

Zaključak: Prognostička vrednost LDH je potvrđena u našoj populaciji pacijenata. Pacijenti sa normalnim LDH vrednostima imaju značajno duže ukupno preživljavanje, što naglašava važnost LDH kao rutinskog biomarkera u kliničkoj praksi. Imunoterapija pokazuje numerički povoljnije ishode u poređenju sa kombinovanom BRAF/MEK terapijom, što ukazuje na potrebu za daljim prospektivnim istraživanjima radi potvrde ovih nalaza.

Gljučne reči: BRAF mutacija, melanom, laktat dehidrogenaza, prognoza

Since 2009, LDH has been incorporated into the American Joint Committee on Cancer (AJCC) TNM classification for melanoma, specifically stage IV, underscoring its prognostic significance (12). Monitoring LDH activity as a biomarker may therefore provide valuable prognostic information regarding recurrence and distant metastases, especially to the liver and lungs (13).

For patients with unresectable or metastatic BRAF-mutated melanoma, the U. S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved three combinations of BRAF and Mitogen-activated protein kinase (MEK) inhibitors: dabrafenib plus trametinib, vemurafenib plus cobimetinib, and encorafenib plus binimetinib. In addition, three immune checkpoint inhibitors – ipilimumab, nivolumab, and pembrolizumab – are approved for this indication as monotherapy or in combination (8).

This analysis aimed to evaluate the prognostic significance of LDH values in patients with melanoma treated with innovative agents.

Material and Methods

Study design and patients

This retrospective clinical study included 68 patients, with a mean age of 57.4 ± 13.6 years, who had BRAF-mutated, inoperable stage III and metastatic stage IV melanoma, and were treated with innovative therapies between 2019 and 2024 at the University Clinical Centre in Niš.

Inclusion criteria

Eligible patients had cutaneous unresectable stage III or stage IV metastatic melanoma, confirmed BRAF mutation, ECOG performance status 0–1 (Eastern Cooperative Oncology Group performance status), and were ≥ 18 years of age. None had received prior systemic therapy.

Mutation testing

BRAF mutational status was assessed using the COBAS BRAF Mutation Test, the first FDA-approved companion diagnostic for patients with advanced melanoma harbouring the mutation.

Tumour assessment

Baseline tumour evaluation was performed before therapy initiation and subsequently every 12 weeks using the same imaging modality – computed tomography or magnetic resonance imaging (in cases of contrast allergy) – according to RECIST criteria (version 1.1).

Safety evaluation

Safety assessments were conducted before each treatment cycle and within 30 days after therapy completion. Adverse events were graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, version 5.0).

Treatment groups

Patients were divided into two groups based on therapeutic modality:

Mono-immunotherapy group: pembrolizumab or nivolumab (n=34);

Combined targeted therapy group: dabrafenib/trametinib or vemurafenib/cobimetinib (n=34).

Sub-analyses were performed according to the presence or absence of elevated LDH activity, both within therapeutic subgroups and across the overall population.

LDH activity was measured on an automatic biochemistry analyser (Cobas pro, Roche, Mannheim, Germany). The reference range for LDH is considered to be <250 U/L.

Follow-up and ethics

Patients were followed for up to 5 years (2019–2024) to assess treatment efficacy and survival outcomes. The study protocol was approved by the Ethics Committee of the University Clinical Centre in Niš.

Statistical analysis

The chi-square test or Fisher's exact test was used to compare the two groups, depending on category size. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Mei-

er method (95% CI; $p < 0.05$), and the log-rank test was applied to compare PFS and OS based on LDH level. The primary endpoint of the study was investigator-assessed progression-free survival according to RECIST [version 1.1]. The secondary endpoint was to evaluate the prognostic significance of LDH values. Progression-free survival and overall survival were estimated using the Kaplan-Meier method, and subgroup comparisons were performed using the log-rank test. All analyses were conducted using Stata software, version 17. A p-level <0.05 was regarded as statistically significant.

Results

A total of 68 patients with melanoma were included in the study, with a median follow-up of 20.5 months, comprising 38 males and 30 females (Table I). The largest proportion of patients was in the 61–70 age group (28%), followed by the 51–60 age group (25%) and the 41–50 age group (24%). The youngest group (<40 years) accounted for 9%, while the oldest group (>70 years) represented 15%. Detailed patient characteristics are presented in Table I.

Half of the patients received targeted therapy (dabrafenib/trametinib or vemurafenib/cobimetinib), while the other half were treated with immunotherapy (pembrolizumab or nivolumab). Elevated LDH activity was observed in 41% of patients, whereas 59% had LDH activity within the reference range (Table II).

Table I Baseline demographic and clinical characteristics of melanoma patients.

Parameter	Criterion	N (%)
Sex	Male/female	38/30 (56/44)
Age (years)	Mean $\pm$ SD (57.4 $\pm$ 13.6) Range (27–90)	
Age groups	<40 41–50 51–60 61–70 >71	6 (9) 16 (23) 17 (25) 19 (28) 10 (15)
ECOG	0 $\geq$ 1	37 (54.4) 31 (45.4)
BRAF mutation	Mutated Wild type	47 (69) 21 (31)
Presence of brain metastasis	Yes No	16 (23.5) 52 (76.5)

Table II Distribution of therapy types and LDH activity in melanoma patients.

Therapy	Targeted/immunotherapy	34/34 (50/50)
Type of drug	Dabrafenib/ trametinib	21 (30.9)
	Nivolumab	15 (22.1)
	Pembrolizumab	19 (27.9)
	Vemurafenib/ cobimetinib	13 (19.1)
LDH activity	Activity:	
	within reference range (<250 U/L)	40 (59)
	elevated (>250 U/L)	28 (41)

Table III Distribution of patients by clinical stage of melanoma.

Clinical stage	Number	Percentage
IIIC	6	8.9
IIID	5	7.4
M1a	11	16.1
M1b	9	13.2
M1c	21	30.9
M1d	16	23.5

Table IV Distribution of melanoma patients according to treatment response.

Response	Number	Percentage
Complete response	6	9
Progressive disease	15	22
Partial response	30	44
Stable disease	17	25

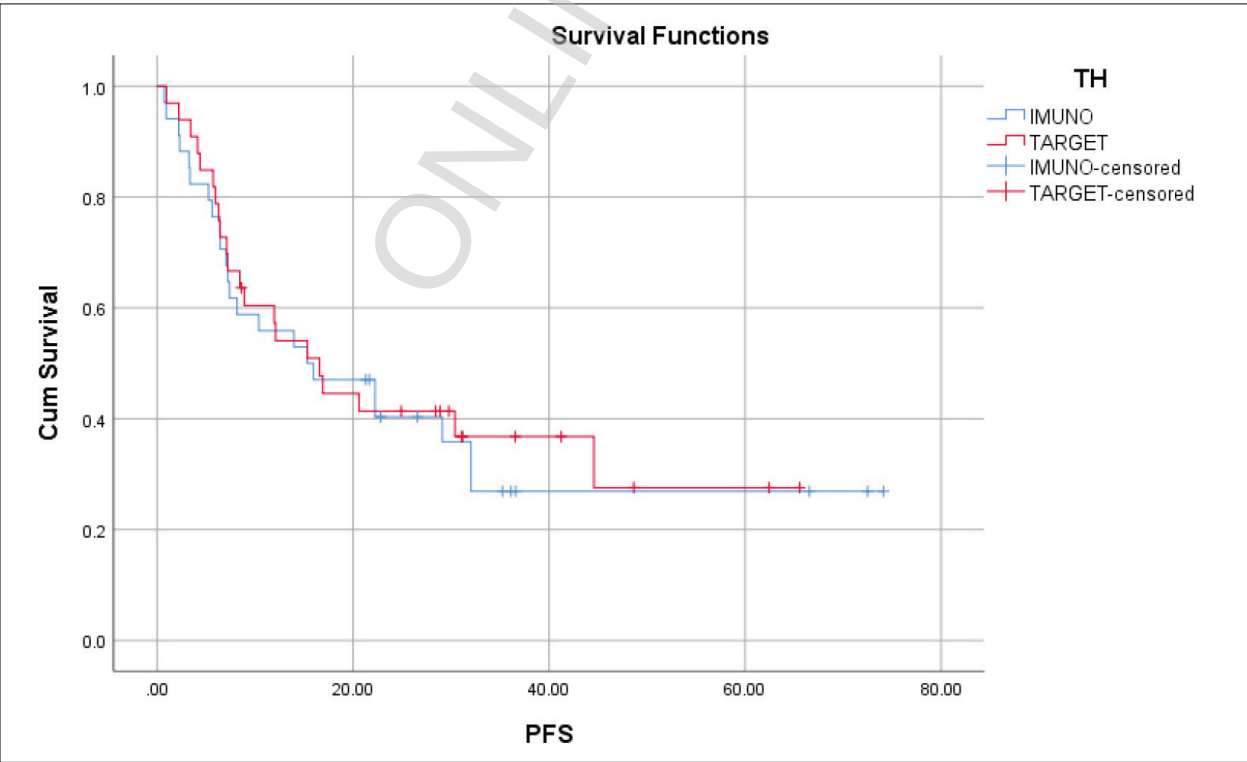


Figure 1 The median progression-free survival (mPFS) for patients treated with novel therapy.

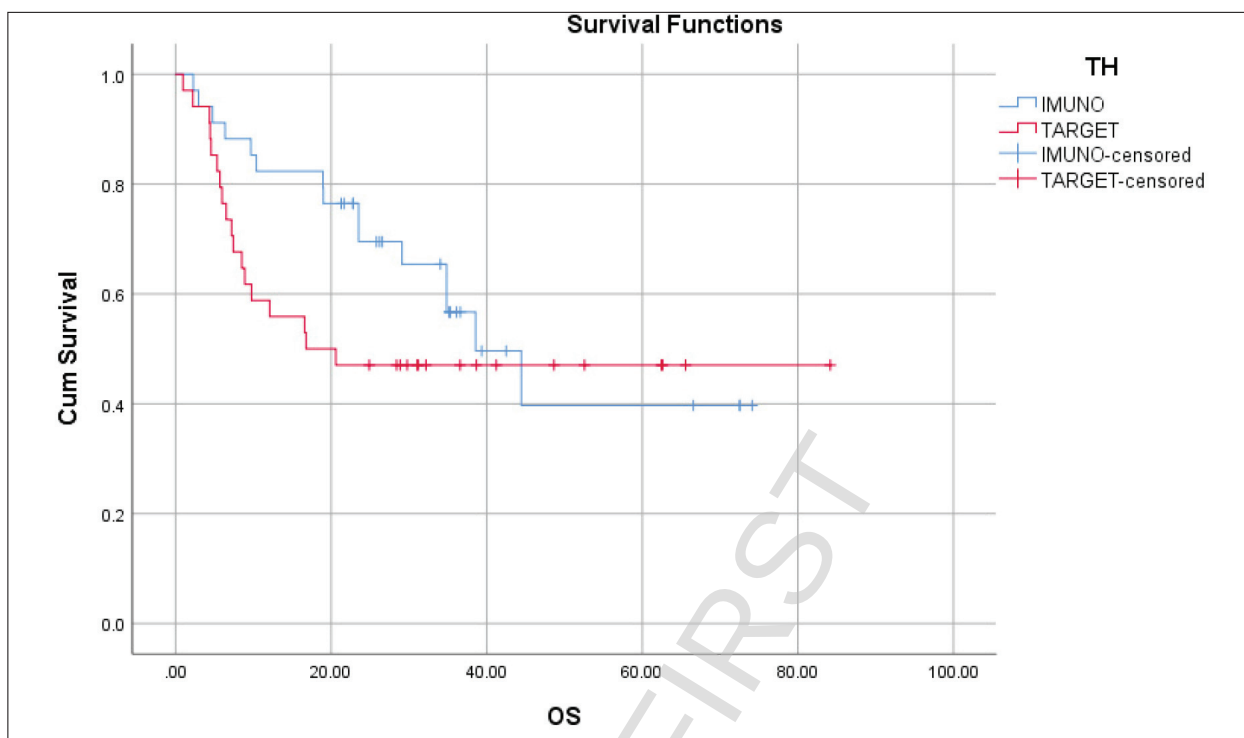


Figure 2 The median overall survival (mOS) for patients treated with novel therapy.

Table V Comparison of the proportion of patients with elevated LDH enzyme activity across therapy subgroups.

LDH activity	Immunotherapy n (%)	Targeted therapy n (%)	χ^2 , P
Within reference range (< 250 U/L)	24 (71)	16 (47)	3.9; 0.042
Elevated (> 250 U/L)	10 (29)	18 (53)	

The majority of patients were classified as stage M1c (30.9%), while the smallest proportion was in stage IIID (7.4%). The distribution of patients according to clinical stage is shown in *Table III*.

Treatment response analysis (*Table IV*) revealed that the largest proportion of patients achieved a partial response (44%), followed by stable disease (25%) and progressive disease (22%). Complete response was observed in 9% of patients.

The median progression-free survival (mPFS) for patients treated with novel therapy was 15.97 months (*Figure 1*), while the median overall survival (mOS) was 38.57 months (*Figure 2*). Comparison between the two therapeutic groups (immunotherapy vs targeted therapy) did not demonstrate statistically significant differences in mPFS (15.3 vs 16.6 months; $p=0.77$) or mOS (38.5 vs 16.8 months;

$p=0.245$). However, numerically longer survival was observed in the immunotherapy group.

In the immunotherapy group, there were significantly fewer patients with elevated LDH (29% vs 53%) compared with the targeted therapy group (*Table V*). Elevated LDH values were observed in 41% of patients overall. When comparing patients with LDH activity within the reference range to those with elevated LDH activity, no statistically significant difference in progression-free survival (PFS) was observed (16.0 vs 12.1 months; $p=0.37$). However, a statistically significant longer overall survival (OS) was observed in patients with LDH activity within the reference range (NR vs 16.6 months; $p=0.009$) (*Figures 3 and 4*).

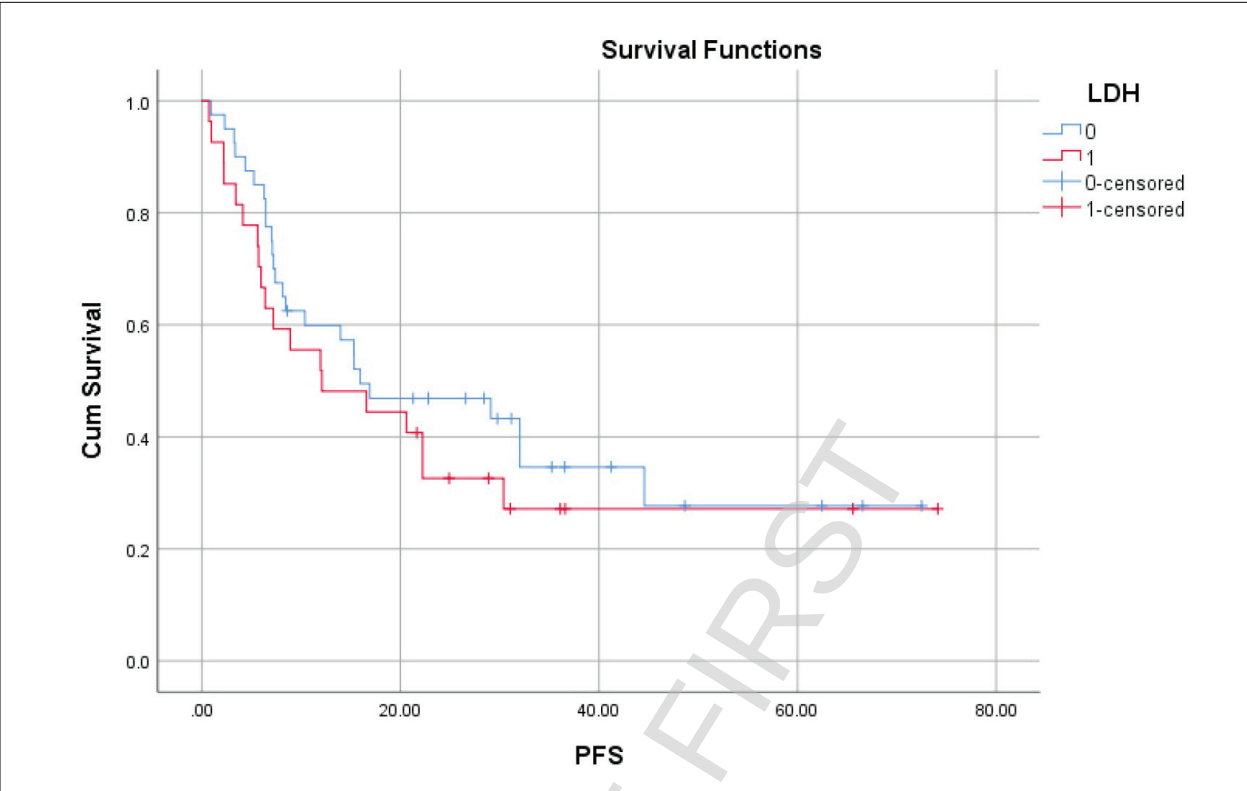


Figure 3 Progression-free survival by LDH status.

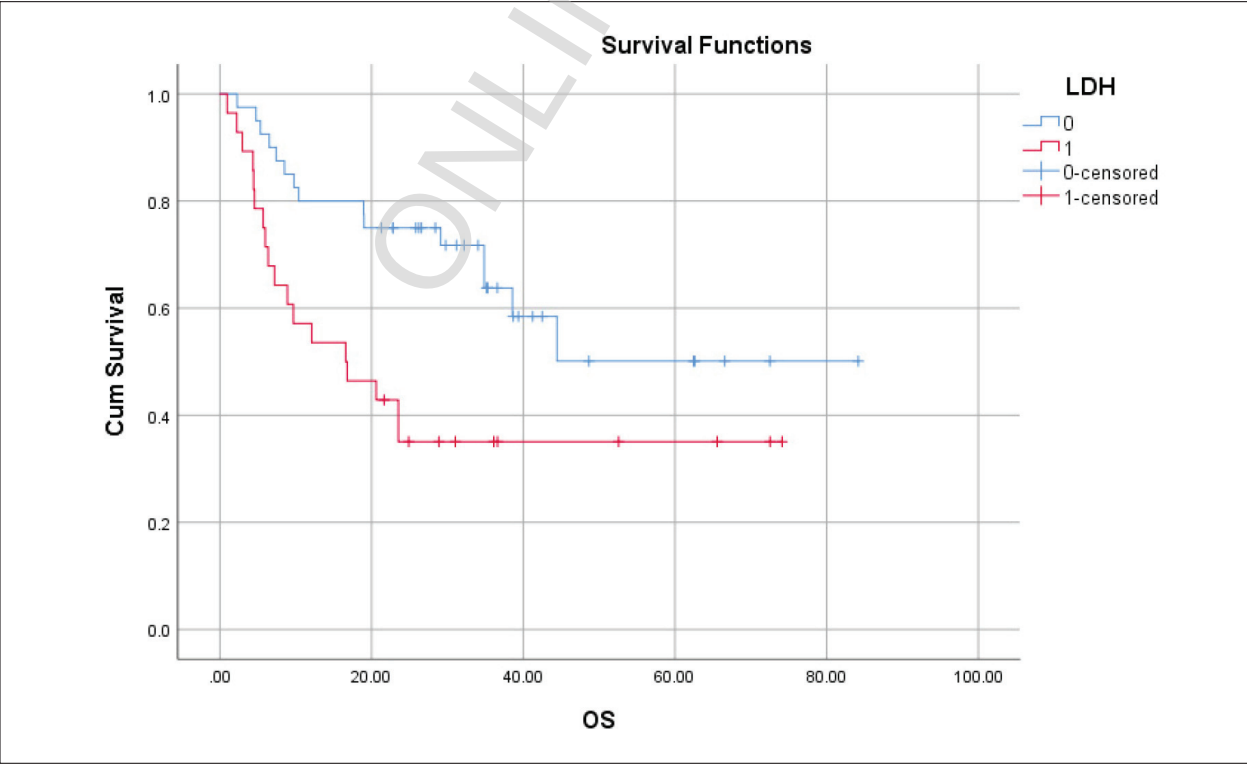


Figure 4 Overall survival by LDH status.

Discussion

In our study, the majority of patients presented with metastatic melanoma, while the smallest proportion had unresectable advanced-stage disease. When analysing treatment response to immunotherapy and targeted therapy, partial response was the most frequent outcome, followed by stable disease and progressive disease, whereas complete response was observed in the lowest percentage of patients. No statistically significant differences in median progression-free survival (mPFS) or median overall survival (mOS) were observed between the two treatment groups. However, numerically longer survival was observed in patients treated with immunotherapy. Elevated serum LDH activity was more frequently detected in patients receiving targeted therapy.

The introduction of novel therapies, particularly immune checkpoint inhibitors and BRAF/MEK-targeted therapy, has markedly improved overall survival in advanced melanoma (14). The literature indicates that anti-PD-1 therapy (nivolumab/pembrolizumab) achieves 5-year overall survival (OS) rates of approximately 34–44% (15). In our 5-year cohort, the median OS for patients treated with immunotherapy was 38.57 months. Combination targeted therapy with BRAF/MEK inhibitors has demonstrated overall response rates (ORR) of 60–70%, with median OS ranging from 22 to 33 months and 3-year survival rates of 30–45%. While targeted therapy provides a rapid onset of response, resistance develops more commonly (16). In our study, patients treated with BRAF/MEK inhibitors had a median OS of 16.8 months. No statistically significant differences were observed between immunotherapy and targeted therapy in mPFS (15.3 vs 16.6 months; $p=0.77$) or mOS (38.5 vs 16.8 months; $p=0.245$). Nonetheless, patients receiving immunotherapy demonstrated numerically longer survival.

According to current guidelines from the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO), immunotherapy is preferred in patients with BRAF-mutant melanoma, except in cases of high tumour burden that require a rapid therapeutic effect. This preference is based on the durability of responses (17), as reflected in our analysis, albeit only numerically, likely due to the limited sample size.

LDH remains one of the most reliable serum biomarkers and prognostic factors in metastatic melanoma (18). In our study, elevated LDH activity was verified in 41% of patients. A statistically significantly lower proportion of patients with increased LDH activity was observed in the immunotherapy group compared to those receiving targeted therapy. This

finding may be attributed to current therapeutic guidelines, which recommend immunotherapy in patients with lower tumour burden (19). When comparing patients with normal versus elevated LDH activity, no statistically significant difference in progression-free survival (PFS) was observed. However, patients with normal LDH activity demonstrated significantly longer overall survival (OS). These results are consistent with previous reports indicating that elevated LDH activity correlates with poorer survival outcomes in metastatic melanoma (20) and serves as a negative predictor of treatment response (21).

Mechanistic studies suggest that in patients with metastatic disease treated with immunotherapy, lactate accumulation promotes immune evasion by reducing the survival and cytolytic capacity of CD8+ T cells and natural killer cells (22). This may explain the poorer therapeutic response observed in patients with elevated LDH activity in our cohort. Accordingly, high LDH activity in cancer patients is thought to antagonise the effects of anti-PD-1/PD-L1 antibodies, leading to unfavourable prognosis (23). Long-term survival outcomes from the CoBRIM trial with cobimetinib and vemurafenib demonstrated the most favourable results in patients with normal baseline LDH activity and low tumour burden, with 5-year OS rates of 52% in the subgroup defined by normal LDH activity and SLD ≤ 45 mm, and 68% in the subgroup defined by LDH activity within the reference range and fewer than three organ sites involved (24).

The potential prognostic value of LDH has been confirmed in several melanoma studies, which demonstrated that elevated pre-treatment LDH was significantly associated with reduced OS and PFS in patients with advanced melanoma treated with nivolumab (25), as well as in other investigations (26) examining the relationship between LDH activity and survival in metastatic melanoma. However, whether LDH can serve as a predictive biomarker of response to anti-PD-1/PD-L1 antibodies remains uncertain, as some evidence suggests no significant correlation between baseline LDH levels and OS or PFS.

Our study has certain limitations. First, the relatively small number of participants included in the analysis. Second, unknown side effects or adverse events of the applied therapy, as well as the types and numbers of comorbidities among our patients, may have influenced the results. Third, an LDH imbalance between the examined groups might introduce selection bias. The strengths of this study include a homogeneous group of patients with confirmed BRAF mutation and good performance status, which allowed clearer comparison of treatment outcomes. The study is based on real-world clinical data from a tertiary centre, making the results more reflective of everyday practice. A significant con-

tribution is the analysis of the prognostic value of LDH activity, which highlights its clinical relevance for melanoma management, course, and treatment outcome.

Conclusion

The prognostic value of LDH remains relevant in the era of novel agents, as observed in our study population. Patients with LDH activity within the reference range had significantly longer overall survival, underscoring LDH's importance as a routine biomarker in clinical practice. Immunotherapy showed numerically more favourable outcomes compared to combined BRAF/MEK therapy, highlighting the need for further prospective studies to validate these findings and enhance our understanding of predictive biomarkers and their role in the management of metastatic melanoma.

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Authors' contribution

All the authors contributed to the study conception and design. MB and AP performed material preparation, data collection and laboratory analyses. AK and AP performed statistical analysis. MB wrote the first draft of the manuscript. All the authors have read and approved the final version of the manuscript.

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Ethics approval

The study protocol was approved by the Ethics Committee of the University Clinical Centre in Niš. The investigation was conducted in accordance with the Declaration of Helsinki.

Consent to participate

Each participant provided informed consent.

Consent for publication

Written consent for publication was obtained from all participants. Each participant gave explicit permission for the use of their anonymised data in this study and its dissemination in scientific publications.

Data availability statement

All data generated or analysed during this study are included in this article. The data will be available from the corresponding author upon reasonable request.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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