

*Original article*

# Single Center Experience Study with Pembrolizumab in Patients with BRAF Mutant Negative Metastatic Melanoma

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## SUMMARY

The aim of the paper was to determine the efficacy, toxicity and progression free survival with anti-PD-1 immunotherapy pembrolizumab in BRAF wild type metastatic melanoma patients with good performance status (ECOG PS 0–1).

From February 2017 to April 2018, 17 patients with BRAF mutant wild type metastatic melanoma were enrolled in the study. Only 3/17 patient had received chemotherapy previously. The aim of the study was to confirm the efficacy of pembrolizumab immunotherapy in patients with good performance status (ECOG 0-1). Treatment consisted of pembrolizumab 2 mg/kg Q3 weeks continued until disease progression or intolerable toxicity. Secondary end points included toxicity and progression-free survival (defined as the time from randomization to documented disease progression according to RECIST).

The overall response rate (ORR) was 11/17 (53.0 %), with complete response (CR) 0, partial response (PR) 3 (18 %), stable disease (SD) 8 (47%), and progressive disease (PD) 6 (35%). A total number of 97 consecutive cycles were administered. Adverse effects were mild. The most common toxicity was pneumonitis grade 1. None of the patients in the study demonstrated grade 2, 3 and 4 toxicity. No treatment-related deaths occurred. The median time to disease progression was 5.8 months.

Anti-PD-1 pembrolizumab immunotherapy appeared to be a beneficial therapeutic approach with less toxicity for metastatic BRAF wild type melanoma patients with good PS.

*Key words:* immunotherapy, pembrolizumab, metastatic melanoma

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## INTRODUCTION

Metastatic melanoma is an aggressive and difficult to treat cancer. While surgery and radiation therapy play a vital role in the palliation of symptoms, systemic therapy remains the cornerstone of treatment. It is rather disappointing to see how little, if any, progress has been made over the last three decades in the systemic treatment of metastatic melanoma (1). The 10-year survival rate for patients with metastatic melanoma is < 10% (2). In recent years there have been dramatic changes in the landscape of metastatic melanoma treatment. Molecular target therapy with BRAF and MEK inhibitors and immunotherapy with "checkpoint inhibitors" have been documented as a new treatment paradigm for metastatic disease.

Checkpoint inhibitors and other cancer immunotherapy treatments aim to "wake up" the immune system, which recognizes and kills malignant cells. When it works, immunotherapy is less toxic to normal cells than chemotherapy. The emergence of immune "checkpoint inhibitors" such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death receptor 1 (PD-1), has revolutionized the treatment of melanoma.

The programmed death 1 (PD-1) pathway limits immune responses to melanoma cells and can be blocked with the humanized anti-PD-1 monoclonal antibody pembrolizumab. Ribas and al. were excited to see that pembrolizumab was effective in previously untreated patients (1).

Around 40-60% patients with skin melanoma have a mutation in BRAF gene, and it has been marked as V600 (3, 4).

The aim of the study was to characterize the association of pembrolizumab with tumor response and progression free survival (PFS) among patients with metastatic BRAF wild type melanoma.

Treatment consisted of pembrolizumab in dose schedule of 2 mg/kg Q3 weeks continued until disease progression or intolerable toxicity.

The primary end point was to determine the objective response rate (best overall response or complete response or partial response) in patients with measurable disease at baseline per independent central review. Secondary end points included toxicity and PFS (defined as the time from randomization to documented disease progression according to the Response Evaluation Criteria In Solid Tumors- RECIST).

## PATIENTS AND METHODS

Seventeen adult patients (18 years or older) were enrolled in the study. The recruitment period lasted from February 2017 to April 2018. All patients were treated at the Oncology Clinic, Clinical Centre Niš. Eligibility criteria included BRAF wild type gene, stage IV (metastatic) melanoma,  $\geq 1$  measurable lesion per RECIST version 1.1 (RECIST v 1.1), and Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1 (on a 5-point scale).

Three patients (3/17) received systemic chemotherapy because of the metastatic disease (one patient received monoagent Dacarbazine, one of the enrolled patient received Temozolamide and one patient received Dacarbazine as a front line therapy and then underwent Vinblastin, Bleomycin and Cisplatin (VBD) regimen).

Clinically validated test of BRAF status was made in the Institute for Oncology and Radiology of Serbia as a referent clinical laboratory (Cobas 4800 BRAF V 600 Mutation test).

Clinical staging was based on the American Joint Committee on Cancer (AJCC) Eight Edition (8<sup>th</sup> Ed.).

Treatment consisted of pembrolizumab in the dose schedule of 2 mg/kg Q3 weeks continued until disease progression or intolerable toxicity. Pembrolizumab infusions were administered intravenously during a 30-minute period.

Toxicity grading was assessed in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events version 4 (NCI-CTCAE v.4).

The obtained results were analyzed according to the methods of descriptive and analytic statistics. The analysis of PFS was done according to Kaplan-Meier (5).

## RESULTS

Seventeen patients with clinically validated metastatic melanoma with BRAF V600E wild type gene were enrolled in the study. Patient's characteristics were summarized in Table 1.

In accordance with AJCC staging system, two patients were in clinically M1a1 stage, 4 were in M1b1, 1 had M1c0 disease, 8 were in M1c1 stage, while 1 patient had M1d0 and 1 had M1d1 stage. Overall, 97 cycles of pembrolizumab were administered. Six patients progressed during the course of immune therapy. Median time of the disease progression was noticed at 3<sup>rd</sup> to 4<sup>th</sup> cycle

of pembrolizumab. The patients that did not progress received from 2 to 13 cycles of therapy.

Objective response and adverse events are sum-

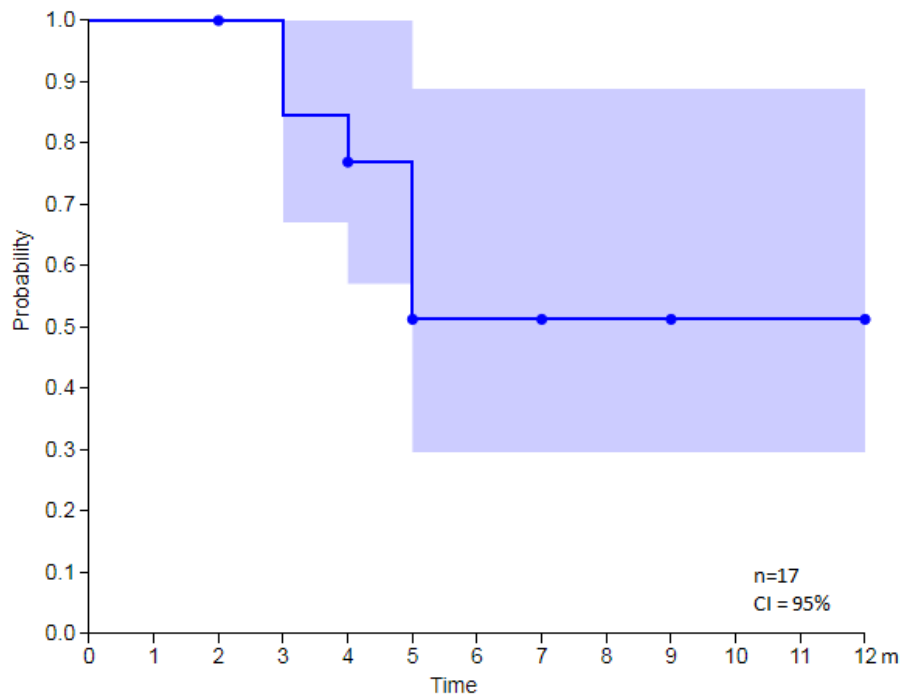
marized in Table 2. Progression free survival is summarized in Graph 1.

**Table 1. Patient's characteristics on pembrolizumab therapy**

Median age	67.5 (48-79)
Sex	
Male	11
Female	6
PS (ECOG)	
0	9
1	8
Number of metastatic sites	
1	2
2	5
3	5
≥4	5

**Table 2. Objective response and adverse events on pembrolizumab therapy**

Overall response rate	
CR	0
PR	3 (18%)
SD	8 (47%)
PD	6 (35%)
Toxicity	Number of patients
No toxicity	13
Pneumonitis gr.1	2
Heart arrhythmio gr.1	1
Hypothyroidism gr.2	1



Graph 1. Kaplan-Meier curve for pembrolizumab progression-free survival

## DISCUSSION

Through this low-volume study we addressed the scientific community, presenting our first preliminary results of immune check point inhibitor pembrolizumab use in Serbia at Niš Oncology Clinic. The use of pembrolizumab, in our study, was limited to BRAF V600E wild type gene metastatic melanoma patients regarding our Health Found limitation for treatment indications for this specific and highly expensive treatment modality. The median duration time of a 15-month follow up period was too short for higher volume reproducible data, so we only analyzed a period of PFS, while overall survival (OS) was not our primary or secondary end point.

By searching relevant indexed bases (PubMed, Scopus, etc.) we have found a number of published studies in which pembrolizumab was shown to produce durable responses with an estimated ORR ranging from 26–40% (6, 7). In our cohort of patients, there were 3 (18%) patients who demonstrated PR as a therapeutic response. However, if we involve additional 8 (47%) patients who achieved SD as a therapeutic response, it can be concluded that the objective favorable response rate was obtained in 65% of patients. This raw data of higher percentage of favorable outcome can be explained by a

short period of follow-up, which in the aforementioned studies was longer, so the results were poorer.

Median PFS for pembrolizumab was 5.4–6.0 months (8). In our case series, the median PFS duration ranged for 5.8 months, which is in accordance with literature data.

PD-1 inhibitors have proven to be less toxic in patients with established, unresectable or metastatic melanoma (9).

Overall, pembrolizumab was well tolerated, with adverse events that were consistent with other clinic trials of this therapy. The most common treatment-related adverse events, reported in studies, were fatigue (40%), pruritus (28%), and rash (23%), and only 8% of patients have been discontinued from pembrolizumab because of serious side effects (9). In our study, after the overall 97 cycles of therapy, there were not any adverse events of grade 3–4. Only 3 patients exhibited mild to moderate adverse reactions, which were not the reason for the treatment interruption, delay or discontinuation.

## CONCLUSION

In this early evaluation of pembrolizumab, as a potent targeted humanized anti PD1 monoclonal antibody, in patients with BRAF wild type metastatic

Melanoma, favorable effects considering therapeutic response, PFS and favorable toxicity profile have been shown. In the future, by including a larger number of

patients and a longer follow up evaluation, we expect this trend to continue and to demonstrate clear clinical benefit of this therapy.

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## Prva iskustva u primeni pembrolizumaba kod BRAF negativnog metastatskog melanoma

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### SAŽETAK

Cilj rada bio je utvrditi efikasnost, toksičnost i slobodni period do progresije bolesti kod bolesnika na anti-PD1 imunoterapiji pembrolizumabom, a koji su oboleli od BRAF nemutiranog metastatskog melanoma i sa dobrim "performance status" (ECOG PS 0-1).

U studiju je uključeno 17 bolesnika sa BRAF nemutiranim metastatskim melanomom u periodu od februara 2017.godine do aprila 2018. godine. Samo je 3/17 bolesnika primalo hemioterapiju u prethodnom periodu. Cilj studije bio je da utvrdi aktivnost imunoterapije pembrolizumabom kod bolesnika sa dobrim "performance status" (ECOG 0-1). Tretman se sastojao od pembrolizumaba 2 mg/kg, sa ponavljanjem na tri sedmice do progresije bolesti ili neprihvatljive toksičnosti. Naredni cilj bio je određivanje toksičnosti i slobodnog perioda do progresije bolesti (koji se definiše kao vreme od randomizacije do potvrđene progresije bolesti u skladu sa RECIST kriterijumima).

Ukupni terapijski odgovor (ORR) bio je 11/17 (53,0%), uz kompletni odgovor (CR) 0, parcijalni odgovor (PR) 3 (18%), stabilnu bolest (SD) 8 (47%) i progresiju bolesti (PD) 6 (35%). Ukupno je ordinirano 97 ciklusa terapije. Uzgredni efekti bili su srednjeg intenziteta. Najčešći oblik toksičnosti bio je pneuomonitis gradusa 1. Nije bilo bolesnika sa toksičnošću gradusa 2, 3 ili 4. Nije bilo egzzitusa uzrokovanog tretmanom. Srednje vreme do progresije bolesti bilo je 5,8 meseci.

Zaključeno je da anti-PD-1 imunoterapija predstavlja delotvorni terapijski tretman sa niskom toksičnošću kod bolesnika sa metastatskim BRAF negativnim melanomom koji su sa dobrim PS.

**Ključne reči:** imunoterapija, pembrolizumab, metastatski melanom