Current Pharmaceutical Design, 2023, *29*, 3312-3323

RESEARCH ARTICLE

Treatment of Metastatic Renal Cell Carcinoma with Checkpoint Inhibitors in Clinical Practice in the Volga-Ural Region of the Eurasian Continent

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ARTICLE HISTORY

Received: June 09, 2023
Accepted: October 09, 2023

DOI:
10.2174/0113816128262498231122072050

Abstract: ***Introduction*:** Renal cancer ranks 10th in the mortality structure of the Russian Federation. The introduction of checkpoint inhibitors has changed the paradigm of treatment of patients with malignant neoplasms.

***Methods*:** Data from clinical trials have shown good progression-free median and median overall survival. Each cancer center has been accumulating its own experience in treating patients with renal cell cancer by applying modern target drugs and immunotherapy.

***Results*:** In routine clinical practice, oncologists do not get the results that have been demonstrated in clinical trials when evaluating the effectiveness of the therapy.

***Conclusion*:** In this single-center clinical study, we discuss the results of using nivolumab as mono-therapy and the combination of nivolumab with ipilimumab in metastatic renal parenchyma cancer patients.

Keywords: Oncology, renal cancer, immunotherapy, checkpoint inhibitors, nivolumab, ipilimumab.

1. INTRODUCTION

In the structure of general morbidity, renal cancer ranks 10th in terms of morbidity in the Russian Federation. The absolute number of renal cancer patients in the Russian Federation in 2021 made up 12333 cases. In the rate of men's cases, kidney cancer ranked 8th, and in the rate of women's cases, kidney cancer ranked 12th. The average age of patients diagnosed with renal cancer for the first time is 62.8 years. The absolute number of renal cancer patients in Bashkortostan Republic in 2021 made up 454 cases. The crude morbidity rate is 11.33 per 100 000 population. The standardized incidence rate in the Bashkortostan Republic is 4.14. The mortality rate of renal cancer has tended to decrease over the past 5 years. The "crude" mortality rate in Bashkortostan Republic in 2021 was 5.14 per 100,000 population, which is lower than that of the Russian Federation. The standardized mortality rate is 2.91 per 100,000 people in the Republic of Bashkortostan, which is slightly higher than the all-Russian rate [1].

Anticancer drug therapy for metastatic renal cancer is based on the target drug and immunotherapy. Chemotherapy is not used in routine practice. Target drug therapy and immunotherapy are the most advanced methods of treatment in cancer patients [2, 3].

Targeted drugs considered in our study selectively target tyrosine kinase and include sunitinib, pazopanib, soraphenib, lenvatinib (in combination with everolimus), axitinib, and cabozantinib.

Nivolumab is also a targeted drug that represents a monoclonal antibody that selectively binds to the biologically active vascular endothelial growth factor (VEGF) [4, 5]. The next step in the development of anticancer drug therapy is the creation of checkpoint inhibitors. These drugs inhibit T-lymphocytes [6, 7]. Tumor cells express PD-L1/PD-L2 ligands on their surfaces that help cancer cells to avoid immune control. The checkpoint inhibitors help the immune system to destroy cancer cells. Nivolumab and a combination of nivolumab with ipilimumab belong to this group [8, 9].

However, the next level of anticancer drug therapy is the combination of checkpoint inhibitors with tyrosine kinase inhibitors (nivolumab with cabozantinib, pembrolizumab and axitinib, pembrolizumab with lenvatinib, avelumab and axitinib) [10, 11]. Each step of anticancer drug therapy evolution showed a considerable increase in progression-free survival and overall survival [12, 13].

This study aimed to investigate the efficacy of immune checkpoint inhibitors in renal cancer treatment in real clinical practice.

2. MATERIALS AND METHODS

During the period of 2019-2021, 86 patients with metastatic renal cancer were treated in the Republic Clinical Oncology Dispensary (Bashkortostan Republic).

Inclusion criteria were the following: metastatic cancer of renal parenchyma and treatment with nivolumab and ipilimumab. Exclusion criteria included malignant neoplasms of any localization other than renal parenchyma, metastatic cancer of any localization with renal involvement, treatment with drugs other than nivolumab and ipilimumab, and primary multiple metachronous or synchronous cancer.

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1873-4286/23 $65.00+.00

PD-L1 expression was not determined in any patient according to the clinical guidelines of the Association of Oncologists of Russia and the practical guidelines of the Russian Society of Clinical Oncology (RUSSCO) [14]. Progression-free survival and overall survival were monitored in 2022. Statistic calculations were performed in the first months of 2023. Analysis of progression-free survival and overall survival were calculated by the Kaplan-Meier method in the XL STAT 2023 program.

Group A consisted of eleven patients (12.8%) who received a combination of nivolumab 3 mg/kg on the 1st day and ipilimumab 1 mg/kg on 1st day every 21 days, followed by nivolumab 3 mg/kg every 14 days. The average age was 60 (30-73) years old. Six (54.5%) patients were male and five (45.5%) were female. Eight (72.7%) patients had previously undergone nephrectomy.

Nine patients (81.8%) had a histological picture of clear cell renal cell carcinoma. In 18.2% of cases, there was an excellent histological picture other than clear renal cell carcinoma. One patient (9.1%) had spindle cell leiomyosarcoma of the kidney, and one patient (9.1%) had papillary renal cell carcinoma. Three patients (27.3%) had 3rd stage of renal cancer, and seven patients (63.6%) were registered with the stage IV. One patient (9.1%) had the 1st stage of parenchymal renal cancer. Metastases to the lungs were found in 45%, bones in 45%, distant lymph nodes in 27.2%, brain in 9.1%, peritoneal carcinomatosis in 18.2%, pleural carcinomatosis in 9.1%, right adrenal gland in 9.1%, and pancreas in 9.1%. Two patients (18.2%) had a favorable prognosis according to IMDC, seven patients (63.6%) had an intermediate prognosis, and 2 patients (18.2%) had a poor prognosis.

A total of 100 courses of immunotherapy were administered, with an average number of 9.1 (range 3-29) courses per patient. Nivolumab and ipilimumab were introduced, on average, as the second line of chemotherapy (range 1-5). Five patients received a combination of these drugs as the first line of treatment.

Group B included twenty-six (30.2%) patients who received nivolumab 3 mg/kg or 240 mg on the 1st day every two weeks. The average age was 63 (33-84) years old; eighteen (69.2%) patients were male and eight (30.8%) were female.

Clear cell renal cell carcinoma was found in 16 (61.5%) patients. Other histological variants of kidney cancer were observed in 38.5% of cases, including synovial sarcoma in 2 (7.7%) cases, chromophobe renal cell carcinoma in 2 (7.7%) patients, papillary renal cell carcinoma in 2 (7.7%) patients, leiomyosarcoma of the kidney in 3 (11.5%) patients, and clear cell papillary renal cell carcinoma in one patient (3.9%). Eight patients (30.7%) were in stage one, two patients had stage two, five patients were in stage three, and 11 patients had stage four, according to TNM classification.

Metastases were found in the lungs in 84.6%, bones in 38.5%, distant lymph nodes in 46.2%, brain in 11.5%, liver in 11.5%, soft tissues in 11.5%, pancreas in 7.7%, and adrenal gland in 3.8%.

Nine (34.6%) patients had a favorable prognosis according to IMDC, twelve patients (46.2%) had an intermediate prognosis, and five (19.2%) patients had a poor prognosis.

A total of 312 courses of nivolumab 3 mg/kg or 240 mg every 2 weeks were administered, with each patient receiving 12 courses (range: 2-59). Nivolumab at a dose of 240 mg was prescribed as the second line (2-4) treatment.

Group C included 49 patients who received nivolumab 480 mg on 1st day every 28 days. The average age was 63.5 (30-86) years old; thirty-six (73.5%) patients were male and thirteen (26.5%) were female. Clear cell renal cell carcinoma was found in 37 patients (75.4%). Other histological variants of renal cancer were observed in 24.6% of cases, including chromophobe renal cell carcinoma in four (8.2%) patients, papillary renal cell carcinoma in four (8.2%) patients, and leiomyosarcoma of the kidney in four (8.2%) patients.

Metastases were found in the lungs in 65.3%, bones in 40.8%, distant lymph nodes in 38.8%, brain in 8.2%, liver in 6.1%, soft tissues in 10.2%, pancreas in 6.1%, adrenal gland in 16.3%, peritoneal carcinomatosis in 2%, and pleural carcinomatosis in 2%.

Nine (32.6%) patients had a favorable prognosis according to IMDC, thirteen (46.9%) patients had an intermediate prognosis, and ten (20.5%) patients had a poor prognosis.

A total of 416 courses of nivolumab 480 mg every 28 days were administered, with each patient receiving an average of 8.5 courses (range: 3-26). Nivolumab at a dose of 480 mg was prescribed as the second line (2-4) treatment.

A total of 828 courses of immunotherapy with nivolumab and ipilimumab were administered to patients from three subgroups with metastatic kidney cancer.

3. RESULTS

3.1. Group A

In Group A, the complete response was not registered in any patient. Partial response was observed in two patients (18.2%). Stabilization of renal cancer was observed in six (54.5%) patients. Progression occurred in three (27.2%) patients. The median progression-free survival was 7.7 months (Fig. **1**).

The median overall survival was 16.1 months (Fig. **2**).

3.2. Adverse Events

Weakness was observed in four (36.3%) patients. Grade 2 diarrhea was noted in two (18.2%) patients. Grade 3 hepatotoxicity was observed in one (9.1%) case. Immune-mediated pneumonitis was observed in one (9.1%) patient. Hypothyroidism was registered in two (18.2%) patients. All adverse effects of the drugs were managed. There were no fatal outcomes caused by checkpoint inhibitors.

3.3. Group B

There were no patients who achieved a complete response to the treatment. Partial response was observed in six (23.1%) patients. Stabilization of renal cancer was observed in 10 (61.5%) cases. Progression was observed in four (15.4%) patients. The median progression-free survival was 10.7 months (Figs. **3** and **4**).

3.4. Adverse Events

Fatigue was observed in four (36.3%) patients. Grade 2 diarrhea was noted in two (18.2%) patients. Grade 3 hepatotoxicity was observed in one (9.1%) case. Immune-mediated pneumonitis was observed in one (9.1%) patient. Hypothyroidism was registered in two (18.2%) patients. All adverse effects of the drugs were managed. There were no fatal outcomes caused by checkpoint inhibitors.

3.5. Group C

No complete response to treatment with nivolumab 480mg was observed in any patient. Partial response was seen in 7 (14.3%) patients. Stabilization was noted in 32 (65.3%) patients. Progression

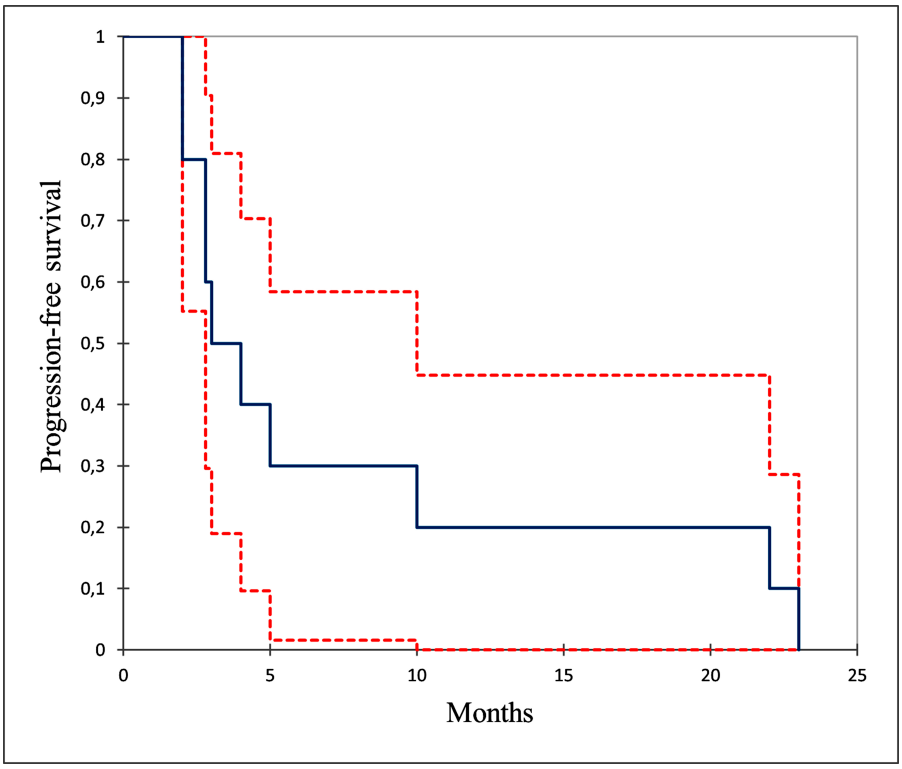

Fig. (1). Group A. Progression-free survival in renal cancer patients of group A. Nivolumab 3 mg/kg on day 1 and ipilimumab 1 mg/kg on day 1 every 21 days with subsequent nivolumab 3 mg/kg administration every 14 days. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

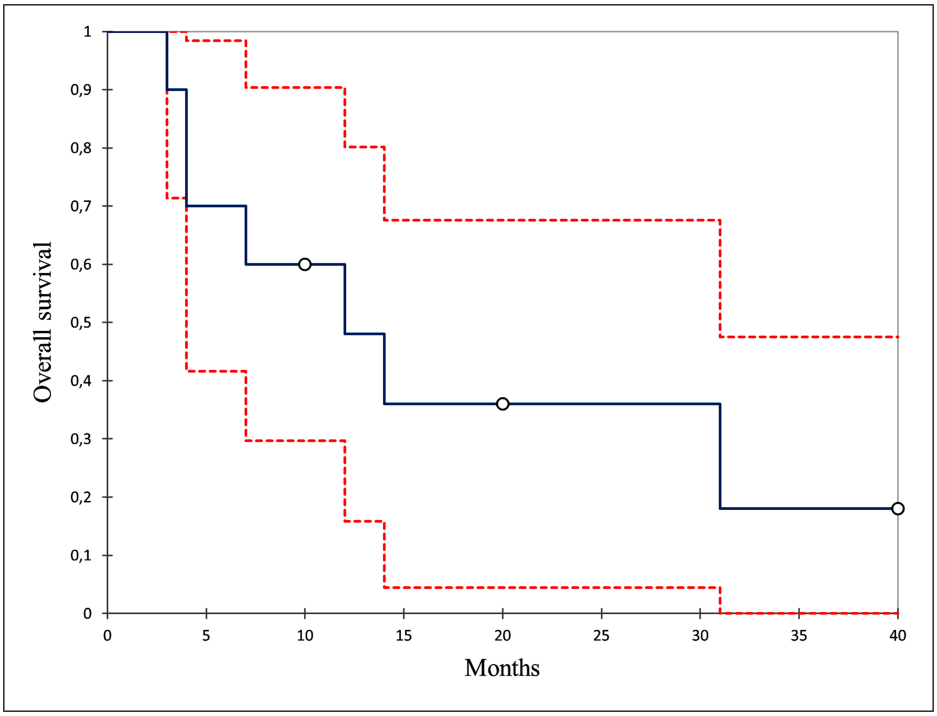

Fig. (2). Group A. Overall survival. The regimen was nivolumab 3 mg/kg on day 1 and ipilimumab 1 mg/kg on day 1 every 21 days with subsequent nivolumab 3 mg/kg administration every 14 days cycle. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

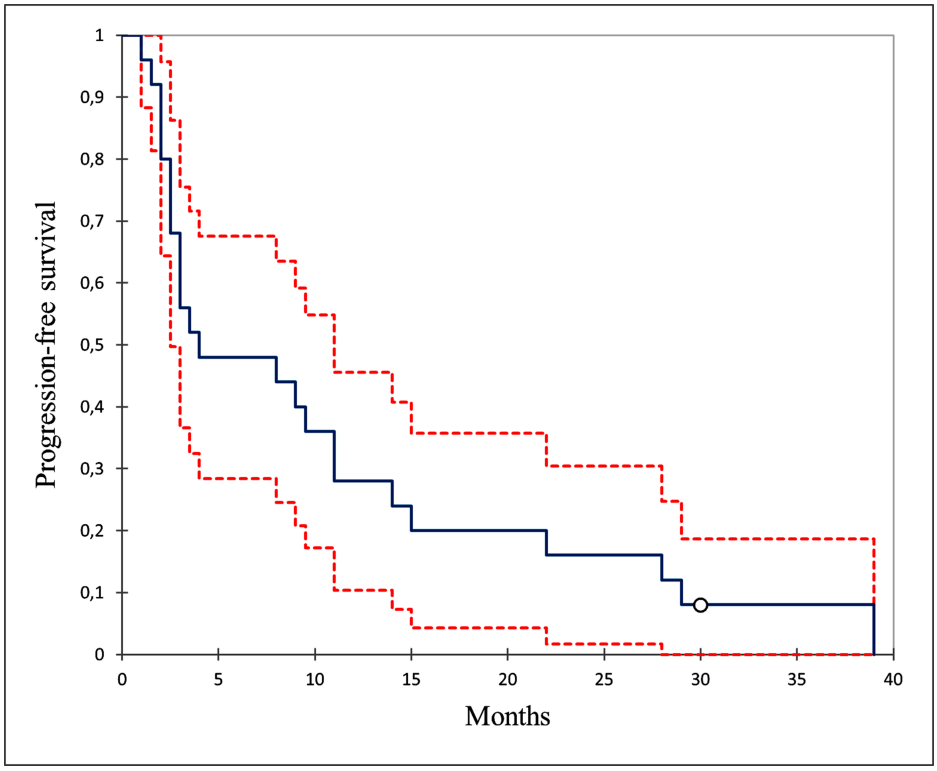

Fig. (3). Group B. Progression-free survival. The regimen was nivolumab 3 mg/kg or 240 mg every 14 days. The median overall survival was 17.8 months (Fig. **4**). (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

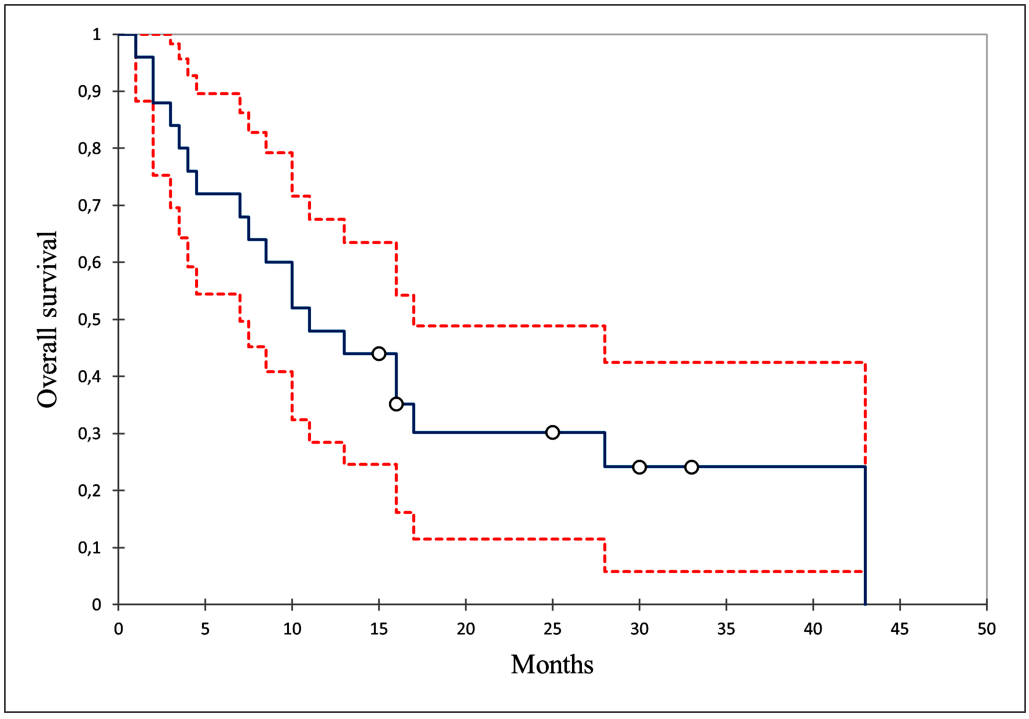

Fig. (4). Group B. Overall survival. The regimen was nivolumab 3 mg/kg or 240 mg every 14 days. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

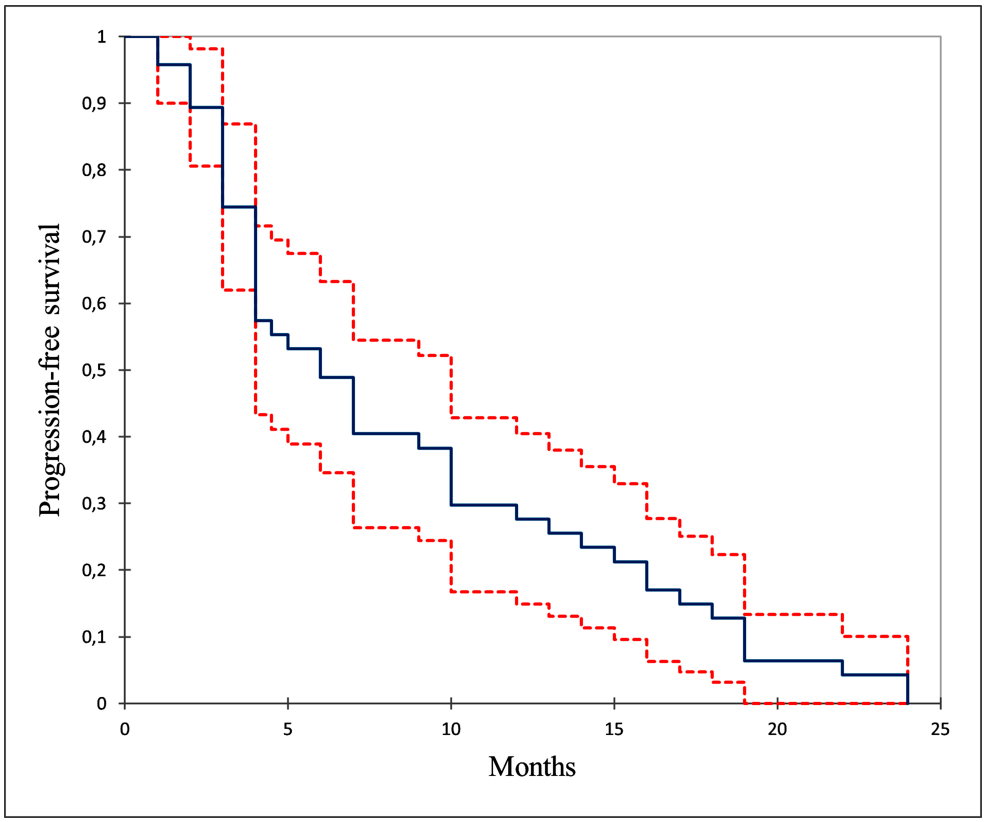

Fig. (5). Group C. Progression-free survival. Nivolumab regimen of 480 mg every 28 days. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

of renal cancer was detected in ten (20.4%) patients. The median progression-free survival was 8.7 months (Fig. **5**).

The median overall survival was 14.3 months (Fig. **6**).

3.6. Adverse Events

Weakness was reported in 17 (34.7%) patients. Diarrhea was observed in 9 (18.4%) cases. Grade 3 hepatotoxicity occurred in 3 (6.1%) patients. Immune-mediated pneumonitis was present in 2 (4.1%) cases. Hypothyroidism was documented in 8 patients (16.3%). Immune-mediated gastritis was observed in one case (2%). All adverse events were managed. There were no deaths related to checkpoint inhibitors.

There were separately analyzed cases of treatment in patients with clear cell renal cell carcinoma and other histological types of renal parenchymal cancer. Due to the small sample size in Group A, where patients received nivolumab and ipilimumab, survival analysis without progression and overall survival with clear cell renal cell carcinoma and other histological variants was not performed in this group.

Group B. The median progression-free survival of patients with clear cell renal cell carcinoma was 11.7 months (Fig. **7**).

The median overall survival was 18.5 months (Fig. **8**).

The median progression-free survival of patients with clear cell renal cell carcinoma was 6.1 months (Fig. **9**).

The median overall survival was 9.1 months (Fig. **10**).

3.7. Group C

Median progression-free survival in patients with clear cell renal cell carcinoma was 8.7 months (Fig. **11**).

Median overall survival was 14.4 months (Fig. **12**).

The median progression-free survival for patients with non-clear cell kidney cancer was 8.7 months (Fig. **13**).

Median overall survival was 12.0 months (Fig. **14**).

4. DISCUSSION

4.1. Group A

The low frequency of objective responses (18.2%), shorter progression-free survival (7.7 months), and lower overall survival (16.1 months) may be due to the small number of patients studied. We suppose that a search for biomarkers is needed to better select this effective treatment option for patients with kidney cancer [15-17]. There may be resistance to checkpoint inhibitors, so real-world clinical practice data do not agree with the CheckMate 214 registry clinical trial.

In the CheckMate 214 phase 3 clinical trial, weakness was found in 38%, and grade 3-4 weakness was reported in 4% of patients. In our observations, weakness was reported in four patients (36.3%) from Group A. These data are comparable with the previously mentioned registry study. Grade 2 diarrhea was noted in two patients (18.2%). This adverse event was less common in patients from the Republic of Bashkortostan compared to the CheckMate

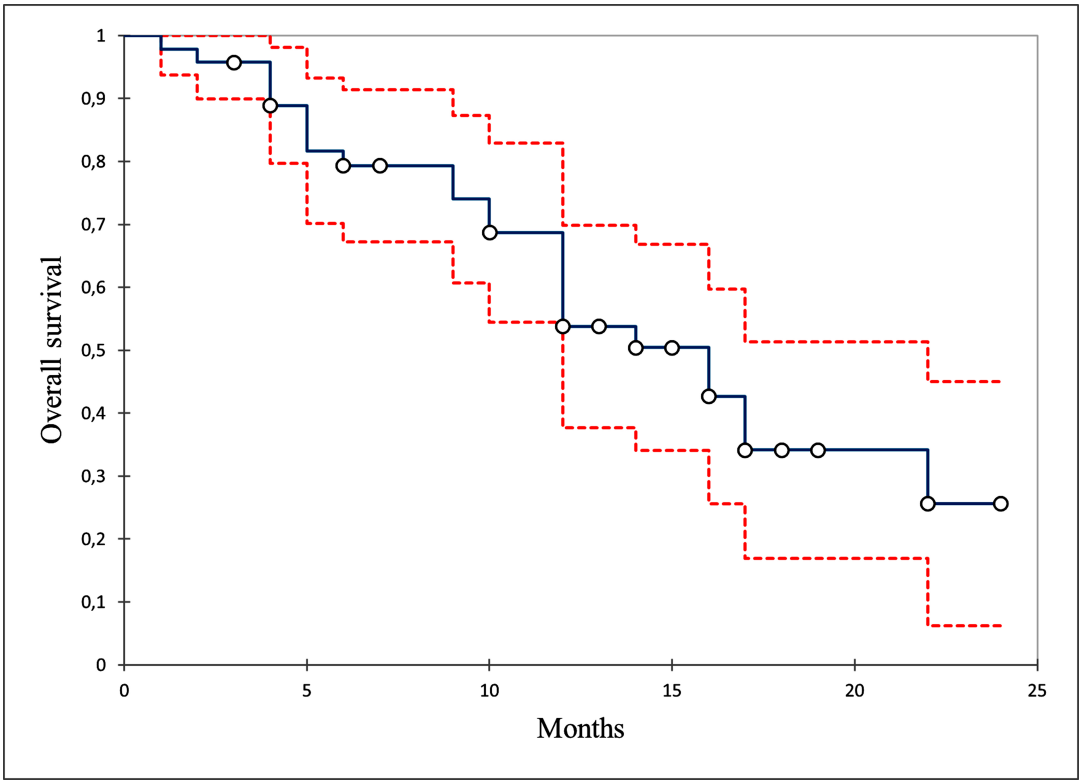

Fig. (6). Group C. Overall survival. The regimen was nivolumab 480 mg every 28 days. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

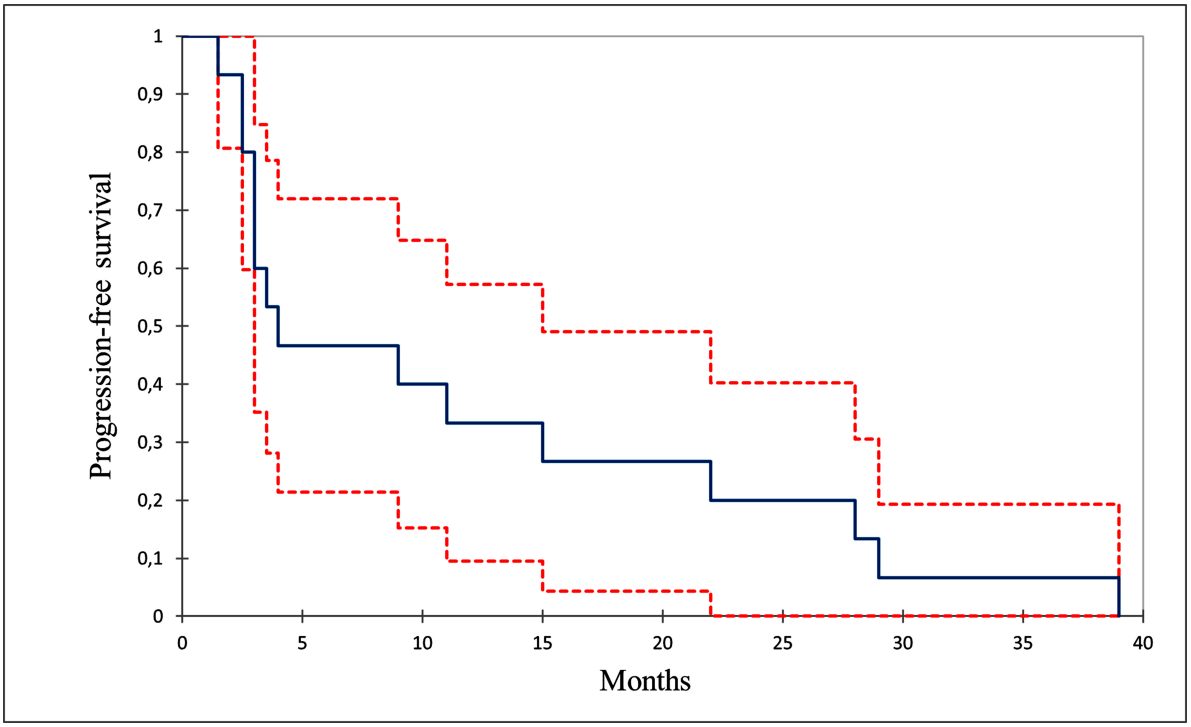

Fig. (7). Group B. Progression-free survival. Nivolumab regimen of 3 mg/kg or 240 mg every 14 days (clear cell renal cell carcinoma). (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

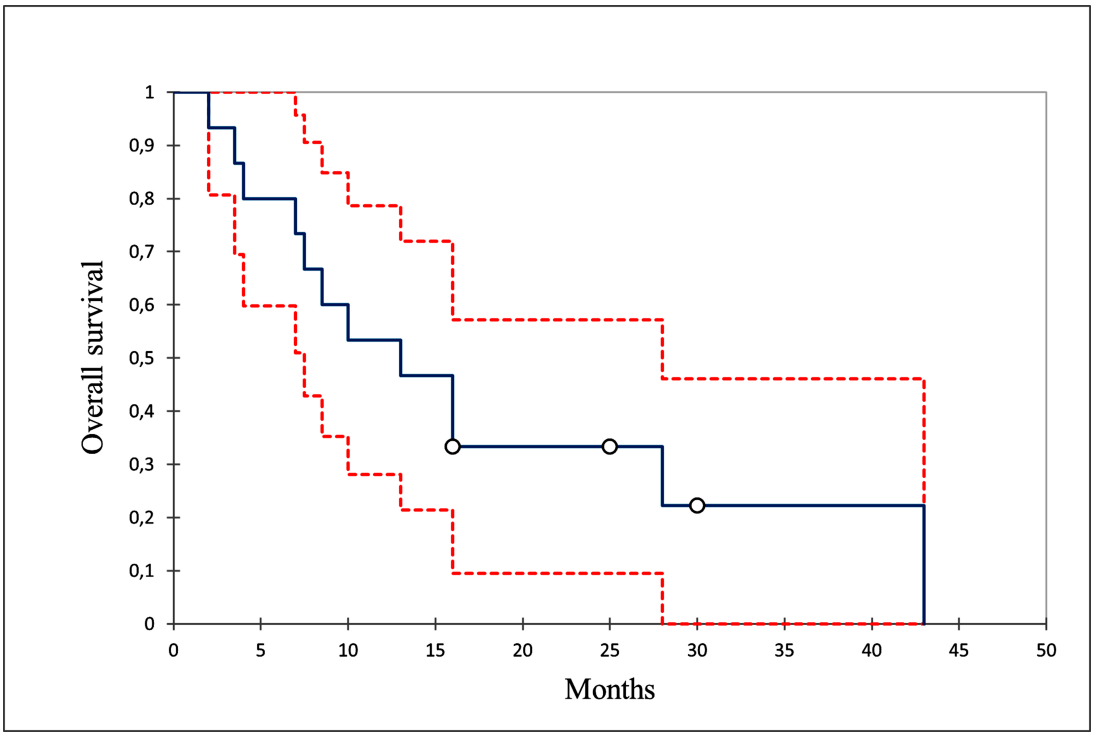

Fig. (8). Group B. Overall survival. Nivolumab regimen of 3 mg/kg or 240 mg every 14 days (clear cell renal cell carcinoma). (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

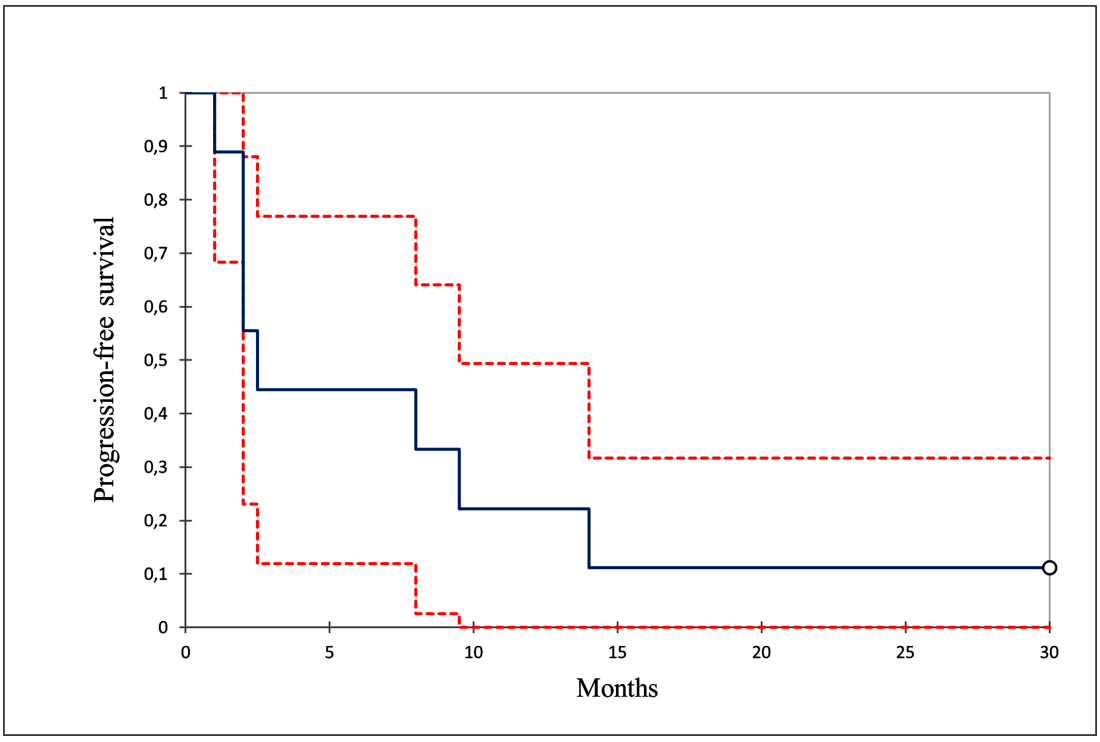

Fig. (9). Group B. Progression-free survival. The regimen was nivolumab of 3 mg/kg or 240 mg every 14 days (non-clear cell renal cell carcinoma). (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

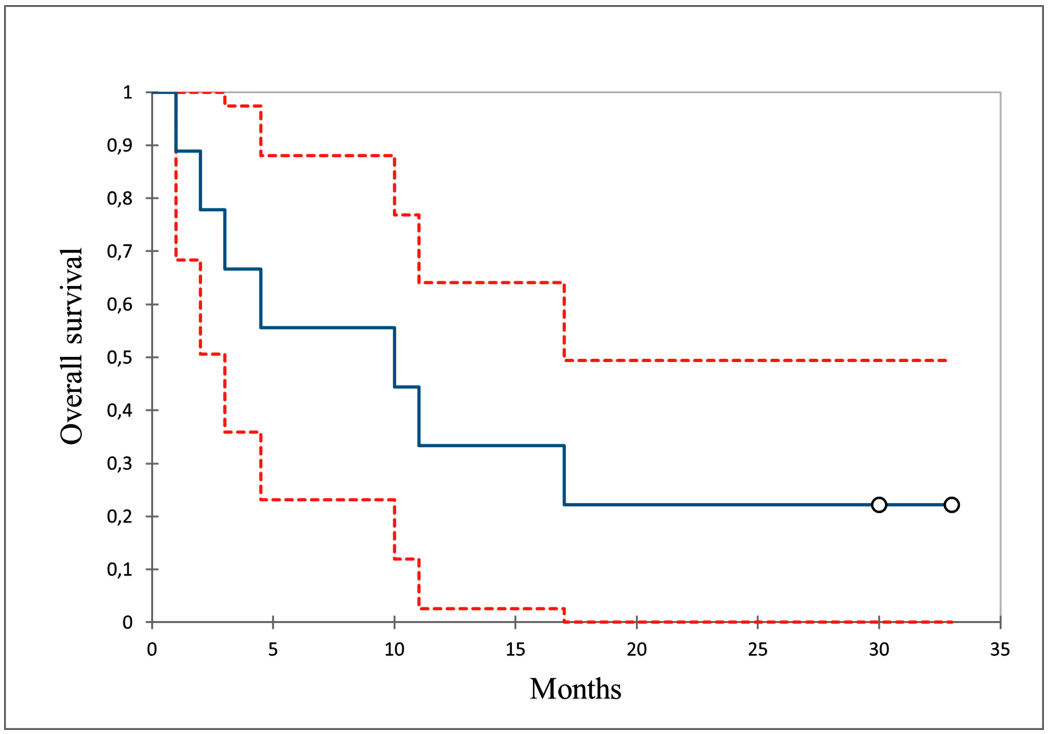

Fig. (10). Group B. Overall survival. The regimen was nivolumab 3 mg/kg or 240 mg every 14 days (non-clear cell carcinoma of the kidney). (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

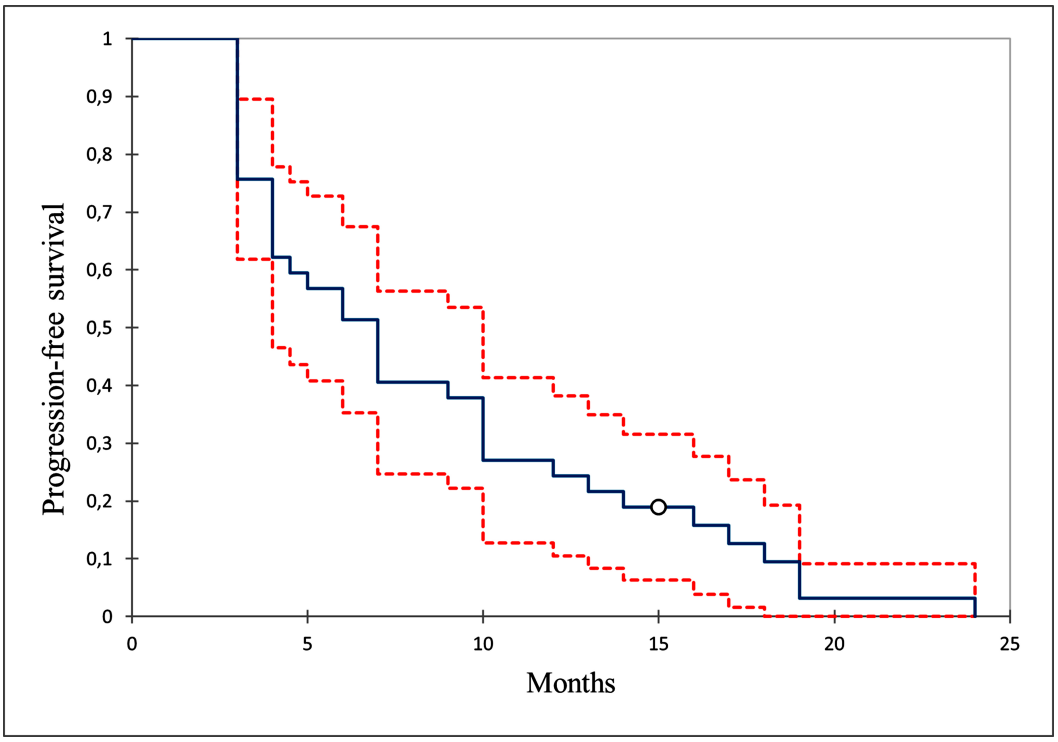

Fig. (11). Group C. Progression-free survival. Nivolumab 480 mg every 28 days (clear cell renal cell carcinoma). (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

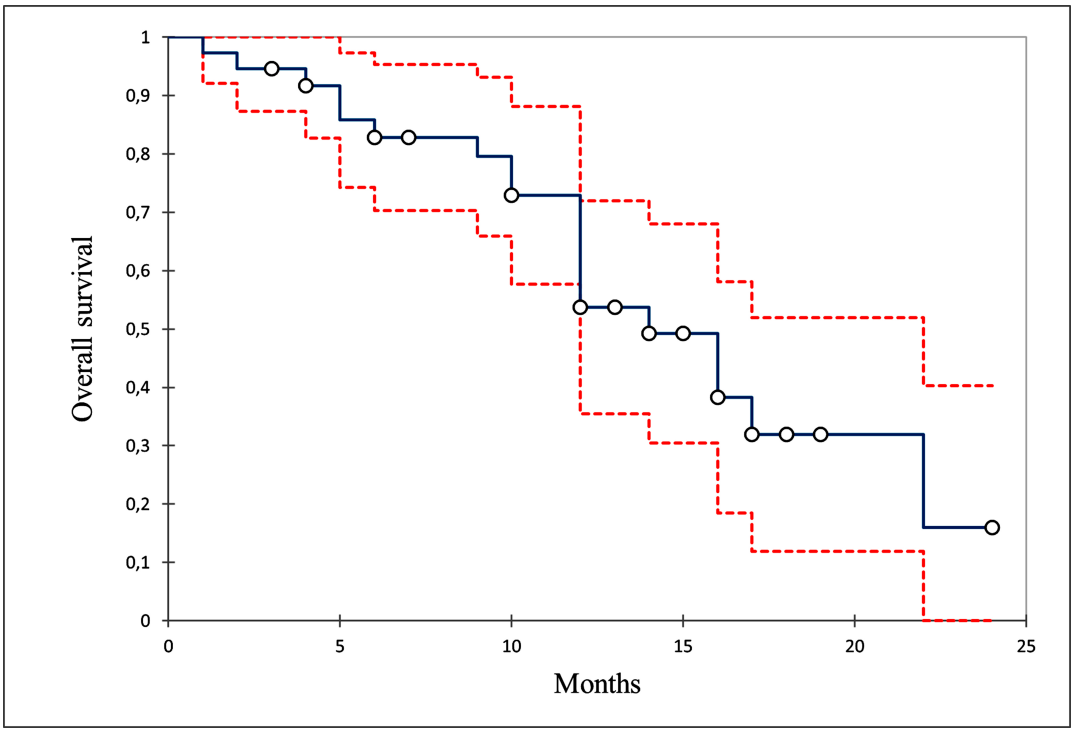

Fig. (12). Group C. Overall survival. Nivolumab 480 mg every 28 days (clear cell renal cell carcinoma). (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

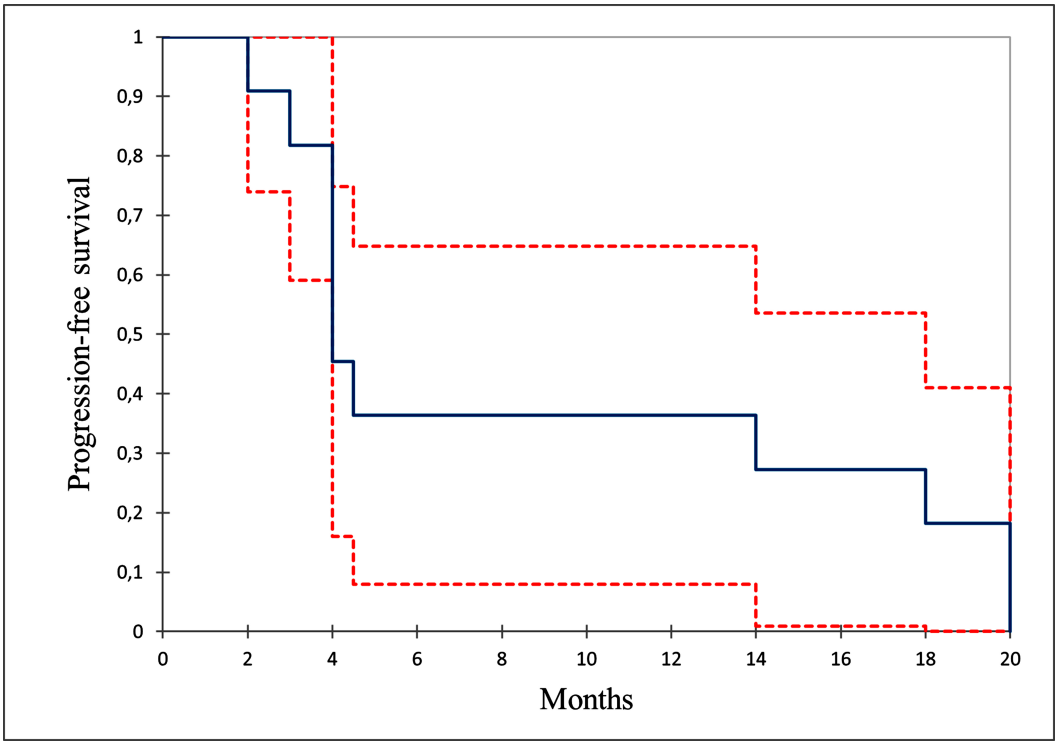

Fig. (13). Group B. Progression-free survival. Nivolumab 480 mg every 28 days (non-clear cell renal cell carcinoma). (*A higher resolution/ colour version of this figure is available in the electronic copy of the article*).

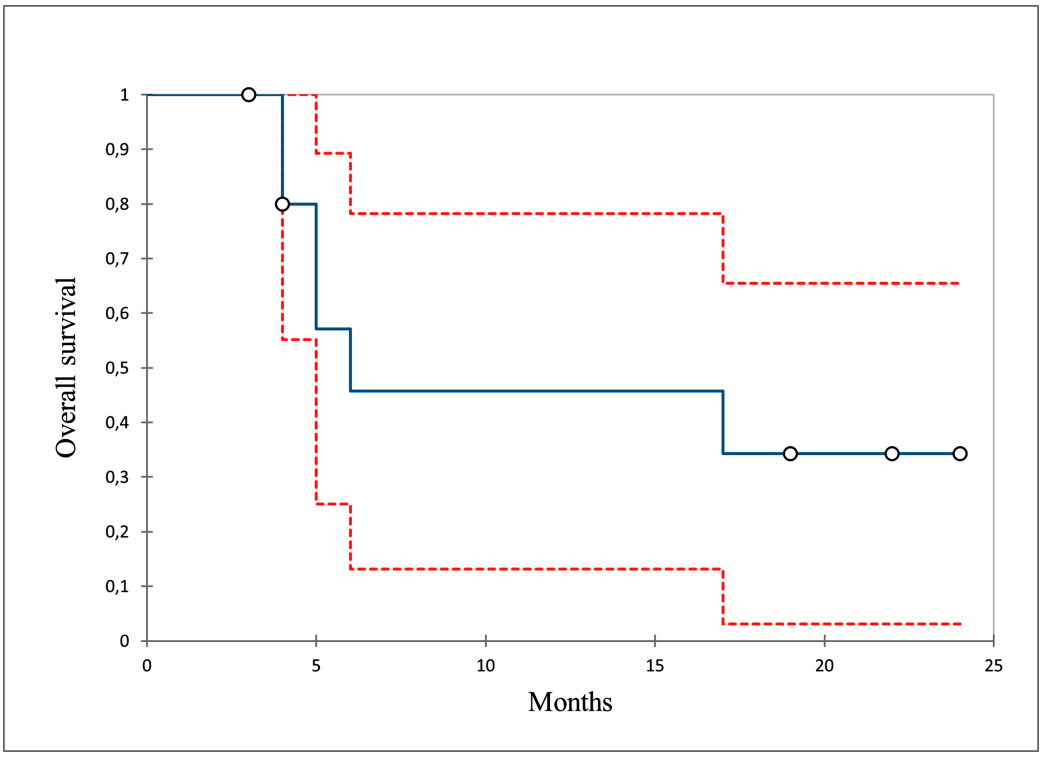

Fig. (14). Group B. Overall survival. Nivolumab 480 mg every 28 days (non-clear cell renal cancer). (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

214 clinical trial, where diarrhea was noted in 28% and 3-4-degree diarrhea in 4%. Immune-mediated grade 3 hepatitis occurred in 9% of patients in the study. Our data are equivalent. Grade 3 hepatotoxicity occurred in 1 patient (9.1%). Immune-mediated pulmonitis occurred in 1 patient (9.1%). Hypothyroidism was reported in 2 patients (18.2%). These adverse events occurred more frequently, which may be caused by a small sample size [7, 18, 19]. There were no lethal outcomes caused by checkpoint inhibitors.

4.2. Group B

Partial response was observed in 6 (23.1%) patients. This indicator was comparable to the registration trial CheckMate 025. Stabilization of renal cancer was observed in 10 (61.5%) patients. Disease stabilization was almost twice as high as in the CheckMate 025 trial. Progression was observed in 4 (15.4%) patients. It occurred less frequently than in the CheckMate 025 trial. The median progression-free survival was 10.7 months. This was higher than in the CheckMate 025 clinical trial. However, not all patients were able to maintain the effect of nivolumab treatment at a dose of 3 mg/kg or 240 mg every two weeks for a long time. This led to a decrease in overall survival. The median overall survival was 17.8 months. These indicators in our observation were lower than in the clinical trial. It is possible that this may be related to the presence of histological variants of renal cancer other than clear cell renal cell carcinoma (38.5%). The mechanism of resistance to immunotherapy cannot be excluded [20, 21].

4.3. Group C

There have been no clinical trials studying the efficacy of a 480 mg dose of nivolumab, so the results of our experience will be compared to the CheckMate 025 clinical trial, which used a 240 mg dose of nivolumab every two weeks [11, 22]. Similar median progression-free survival and overall survival rates were observed in the CheckMate 384 clinical trial at doses of 240 mg and 480 mg of nivolumab for non-small cell lung cancer [23, 24]. X. Zhao also demonstrated the effectiveness of a 480 mg dose of nivolumab for various malignancies.

In Group B, the partial response rate was lower than in the CheckMate 025 clinical trial. However, cases of stabilization and progression of renal cancer were almost twice higher than in the trial. The median progression-free survival was 8.7 months. A larger sample size showed a more modest progression-free survival rate. However, it was higher than that in the CheckMate 025 clinical trial. Progression of patients on subsequent lines of therapy for metastatic renal cancer prevented them from achieving an overall survival of 25.8 months (CheckMate 025 clinical trial). The median overall survival was 14.3 months in Group B. The histological type of the tumor may also be important when prescribing checkpoint inhibitors for metastatic renal cancer [25, 26].

According to a single-center study on the efficacy of metastatic non-clear cell renal cell carcinoma, the median progression-free survival was 4.9 months, and the median overall survival was 21.7 months. In Group B with non-clear cell renal cancer, the median progression-free survival was slightly higher (6.1 months). In Group C, this indicator was even higher, *i.e.*, 8.7 months. However, overall survival in non-clear cell parenchymal renal cancer was significantly lower, *i.e.*, 9.1 months in Group B and 12 months in Group C [27, 28].

Taking into consideration the contradictory results and the lack of clarity in anti-tumor immunity when using checkpoint inhibitors, there is a need to search for biomarkers for personalized prescriptions of immune-oncological drugs. The presence of PD-L1 expression is not always an indicator of the effectiveness of check-

point inhibitors used in the treatment of metastatic renal cancer. Some studies provide data on biomarkers, such as exosomal microRNA expressions, which are promising nowadays. Perhaps in the future, practicing physicians will use them in routine practice [29].

CONCLUSION

Immunotherapy remains the most advanced method of anti-tumor drug therapy. Checkpoint inhibitors show efficacy in renal cancer patients' treatment. However, clinical practice data differ from registration trial results. Immune-oncological drugs have an acceptable toxicity profile.

LIST OF ABBREVIATIONS

RUSSCO	=	Russian Society of Clinical Oncology
VEGF	=	Vascular Endothelial Growth Factor

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethics Committee of the Institute of Biochemistry and Genetics-Subdivision of the Ufa Federal Research Centre of the Russian Academy of Sciences (protocol code 11 and date of approval 27th October, 2014).

HUMAN AND ANIMAL RIGHTS

All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committee and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

Informed consent was obtained from all participants.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this research are available within the article.

FUNDING

This study was funded by the Russian Science Foundation grant Nº 23-25-00392, https://rscf.ru/project/23-25-00392/.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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