e-ISSN 2083–4640
ISSN 1507–1367

RESEARCH PAPER

Reports of Practical Oncology and Radiotherapy
2025, Volume 30, Number 1, pages: 34–43
DOI: 10.5603/rpor.104389
Submitted: 04.06.2024
Accepted: 10.12.2024

Exploring the efficacy of nivolumab and ipilimumab in renal cell carcinoma: insights from a district hospital cohort study

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ABSTRACT

Background: Nivolumab and ipilimumab combination is recommended as a first-line treatment for metastatic renal cell carcinoma (mRCC) in patients without life-threatening symptoms. This study aims to assess the efficacy and safety of this treatment regimen administered in the one-day chemotherapy unit of a district hospital.

Materials and methods: We conducted a retrospective study involving 36 patients diagnosed with mRCC who had received combined immunotherapy at the Department of Chemotherapy, District Hospital in Sucha Beskidzka, Poland. We evaluated treatment response and adverse events (AEs). Laboratory parameters were recorded, and we calculated neutrophil-lymphocyte ratios (NLR), platelet-lymphocyte ratios (PLR), and lymphocyte-monocyte ratios (LMR) at baseline, after 3 months of treatment, and prior to disease progression.

Results: After a median follow-up of 11 months (7.5–17.5 months), the median overall survival was not reached (NR, 6.7-NR), while the median progression-free survival was 11.5 months (6.7-NR). The objective response rate was 30.6% (n = 11), and the disease-control rate was 66.7% (n = 24). Hemoglobin and eosinophil levels varied at three checkpoints, without differences in NLR, PLR, and LMR. AEs of any grade were observed in 23 patients (63.9%) with a median onset time of 3 months (2–4 months), and serious AEs in 13.8% of patients (n = 5).

Conclusions: Our analysis suggests that the combination of nivolumab and ipilimumab for mRCC has an acceptable toxicity profile and can be effectively managed in a district hospital's outpatient clinic. This approach requires close patient monitoring and collaboration with other hospital departments to ensure patient safety and treatment efficacy.

Keywords: immunotherapy; renal cell carcinoma; nivolumab and ipilimumab; adverse events; treatment efficacy

Rep Pract Oncol Radiother 2025;30(1):34–43

Introduction

Renal cell carcinomas (RCCs) originating from the renal cortex constitute 80–85% of primary kidney neoplasms [1]. The highest prevalence is observed in the Czech Republic and North America [2], whereas in Poland, there are approximately 5,000 cases annually, with 2,500 deaths [1]. RCC is twice as common in men as in women, with a median age at diagnosis of approximately 64 years [3].

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The primary treatment approach for RCCs is surgical resection in locally advanced stages I–III. However, up to one-third of patients experience disease recurrence, and around 15% present with metastatic disease at the time of diagnosis [4]. Treatment decisions in such cases are guided by risk stratification using the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic model [5], which considers clinical factors (Karnofsky performance status < 80%, time from diagnosis to treatment onset < 1 year) and laboratory results (hemoglobin below the normal limit, elevated serum calcium, neutrophil, and platelet counts). Patients are categorized into favorable, intermediate, or poor-risk groups based on the absence or presence of these risk factors.

Management of metastatic disease typically involves antiangiogenic therapy using tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) [4]. Monotherapy is recommended as the first-line treatment for the favorable risk group, while combinations of TKIs and ICIs are preferred for intermediate- and poor-risk groups with substantial disease burden. Combined immunotherapy with the anti-programmed cell death 1 protein (PD-1) antibody nivolumab and the cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor ipilimumab is recommended for patients without life-threatening symptoms in these risk groups [6].

In Poland, reimbursement for combined immunotherapy with nivolumab and ipilimumab in the first-line treatment of metastatic RCCs began in May 2022, with inclusion criteria regulated by the National Drug Program of the Polish Ministry of Health [7]. When a combination of TKIs and ICIs is unavailable, patients in the intermediate/poor-risk group may receive combined immunotherapy, monotherapy with cabozantinib (TKI), or, rarely, temsirolimus [mammalian target of rapamycin (mTOR) inhibitor]. Typically, such treatments are conducted in high-volume centers across the country. This study presents our single-center experience in which patients were treated in the one-day chemotherapy unit of the district hospital.

Materials and methods

Patients and data collection

We conducted a retrospective cohort study including patients who were diagnosed with advanced RCCs and who received combined immunotherapy between 1st May 2022 and 1st April 2024 at the Department of Chemotherapy, District Hospital in Sucha Beskidzka, Poland. The study protocol was approved by the Bioethics Committee of the Jagiellonian University Medical College (decision number 118.0043.1.115.2024).

All patients treated with a combined immunotherapy regimen who met the criteria outlined by the National Drug Program [7] were included in the analysis, provided they had undergone at least one assessment via computer tomography (CT) scan. Therefore, we included patients with good performance status, as assessed by the Eastern Cooperative Oncology Group (ECOG) score ranging from 0–1; patients who were diagnosed with clear cell RCCs with or without sarcomatous features; and patients who presented with unresectable disease. Previous nephrectomy was considered optional. Additionally, laboratory test results had to align with summary product characteristics [8, 9]. Patients with brain metastases were required to be asymptomatic or had undergone local treatment (surgery or radiation therapy). Pregnancy and breastfeeding served as exclusion criteria.

Treatment regimen

Treatment was administered at standard doses, with 4 cycles of ipilimumab at 1 mg/kg and nivolumab at 3 mg/kg given every 3 weeks as induction therapy. Subsequently, patients received nivolumab at a flat dose of 480 mg every 4 weeks until disease progression (PD), the occurrence of unacceptable toxicity, or withdrawal of patient consent.

Evaluation of treatment efficacy

The patient's response to treatment was assessed through CT scans of adequate regions following either the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) or immune RECIST (iRECIST) criteria [10], which were conducted every 12 weeks or upon clinical suspicion of PD. In cases of pseudoprogression (immune unconfirmed progressive disease—iUPD), defined by iRECIST as an increase in lesion size or the appearance of new lesions that do not present at baseline [11], a subsequent CT scan was performed 4-8 weeks later, with the final assessment recorded thereafter. Immune-confirmed progressive disease (iCPD) was noted when the target tumor burden increased

by at least 5 millimeters or a new target lesion appeared [10]. In instances of oligoprogression, where PD occurred in no more than 5 lesions across no more than 3 organs (as outlined in the National Drug Program [7]), treatment continuation was feasible following radical treatment of these lesions via surgery or stereotactic radiotherapy, provided that the patient benefited from such intervention and that the remaining metastases were stable.

Treatment efficacy was analyzed by evaluating overall survival (OS), defined as the duration from the initiation of combined immunotherapy to the patient's death; progression-free survival (PFS), denoting the period from the onset of combined immunotherapy to PD on CT scan or patient death; and time to treatment failure (TTF), calculated as the time from treatment onset to termination due to PD/patient death/toxicity. Additionally, we assessed the overall response rate (ORR), comprising complete remission (CR) or partial response (PR), as well as the disease control rate (DCR), encompassing CR, PR, and stable disease (SD) (both according to RECIST 1.1 [10]). Adverse events (AEs) occurring from the initiation of combined immunotherapy until the conclusion of the observation period on 1st April 2024 were documented. The severity of AEs was graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [13], and diagnosis and management followed the European Society for Medical Oncology guidelines [14]. Additionally, we recorded laboratory parameter results obtained before each treatment, 3 months after treatment onset, and before PD and calculated the neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), and lymphocyte–monocyte ratio (LMR).

Statistical analysis

We conducted a statistical analysis using PS Imago Pro 9 (SPSS). Continuous variables were found to be nonnormally distributed based on the Shapiro–Wilk test and are thus presented as medians and interquartile ranges. Categorical variables were represented as percentages. Treatment outcomes were estimated and visualized using the Kaplan–Meier method. Additionally, single and multiple Cox regressions were performed to assess factors influencing PFS and OS. Furthermore, a log-rank test was employed to compare survival distributions among selected factors. Laboratory parameters at baseline, after 3 months of treatment and before PD were compared using ANOVA and the Friedman test. In cases of statistical significance, we conducted a post hoc analysis using the Wilcoxon test with Bonferroni correction (statistical significance was defined as a p-value < 0.017). The cutoff points for the NLR, PLR, and LMR were determined using reference data from meta-analyses [12–14], followed by ROC curve construction based on the obtained results. A p-value < 0.05 indicated statistical significance.

Results

Baseline characteristics

As of the data cutoff on April 1st, 2024, a total of 40 patients had undergone treatment with nivolumab and ipilimumab, 36 of whom were included in this analysis. Four patients were excluded due to a short observation period and the absence of CT scan results. The detailed patient characteristics are shown in Table 1. Notably, 2 patients were diagnosed with hepatitis B and intestinal lung disease at baseline (classified as having autoimmunologic diseases) and showed no signs of disease exacerbation during treatment with ICIs. Among other sites of metastatic disease, 3 patients had metastasis to serous membranes (peritoneum, pleura), and other 3 had metastasis to skin/soft tissues. Additionally, metastases to the pancreas, orbit, and greater psoas muscle were observed.

Survival analysis

The flow chart presents the patients' distributions after 3 and 12 months of follow-up (Fig. 1). After 3 months of treatment with the induction phase with nivolumab and ipilimumab, 72.2% (n = 26) of patients continued maintenance therapy with nivolumab, and 27.8% had withdrawn treatment due to PD (70% of them) or toxicity (30% of them). Almost half of the patients (44%) continued treatment after 12 months. Overall, ten of the patients received second-line therapy with cabozantinib (27.8%), and the other five died (13.9%).

After a median follow-up time of 11 months (range: 7.5–17.5), a median OS was not reached (NR, range: 6.7-NR, Fig. 2A). We observed a median TTF of 8.6 months (range: 5.6-NR), whereas the median PFS was 11.5 months (range: 6.7-NR, Fig. 2B). The distribution of PFS according to CT

Table 1. Baseline clinical characteristics of the enrolled patients (n = 36)

Demographics		
Age		64 (53.8–73.3)
Males, n(%)		27 (75)
Time of follow-up (months)		11 (7.5–17.5)
Comorbidities		
Hypertension, n(%)		14 (38.9)
Ischemic heart disease, n(%)		3 (8.3)
Heart failure, n(%)		1 (2.8)
Hypercholesterolemia, n(%)		2 (5.6)
Autoimmunologic diseases, n(%)		2 (5.6)
Hypothyroidism, n(%)		1 (2.8)
Diabetes mellitus type 2, n(%)		7 (19.4)
Venous thromboembolism n(%)		2 (5.6)
Baseline characteristics		
Performance status, n(%)	0	8 (22.2)
	1	28 (77.8)
Nephrectomy, n(%)	Yes	30 (83.3)
	No	6 (16.7)
Time from nephrectomy to treatment initiation (months)		4 (1.4- 9.6)
T stage after nephrectomy*, n(%)	T1	2 (5.6)
	T2	2 (5.6)
	T3	31 (86.1)
	T4	1 (2.8)
Histologic grade, n(%)	G1	0
	G2	7 (19.4)
	G3	9 (25)
	G4	20 (55.6)
Histologic subtype, n(%)	Clear cell	36 (100)
	Sarcomatous components	3 (8.3)

Baseline characteristics		
Primary metastatic, n(%)		14 (38.9)
Number of disease sites, n(%)	≤ 2	26 (72.2)
	> 2	10 (27.8)
Site of metastasis at the baseline computer tomography scan, n(%)	Nonregional lymph nodes	12 (33.3)
	Kidney	4 (11.1)
	Suprarenal gland	3 (8.3)
	Liver	9 (25)
	Central nervous system	4 (11.1)
	Lungs	25 (69.4)
	Bones	10 (2.8)
	Other	13 (36.1)
IMDC risk group, n(%)	Intermediate	27 (75)
	Poor	9 (25)
Number of risk factors, n(%)	1	16 (44.4)
	2	11 (30.6)
	3	9 (25)
No of patients with risk categories, n(%)	Time from the diagnosis to treatment onset	30 (83.3)
	Karnofsky Score < 80%	7 (19.4)
	Hemoglobin level < unl	18 (50)
	Corrected calcium > unl	3 (7.7)
	Neutrophils > unl	1 (2.6)
	Platelets >unl	8 (22.2)

*American Joint Committee on Cancer 8th edition. Categorical variables are presented as numbers (percentages), and continuous variables are presented as medians and interquartile ranges. n — number; IMDC — The International Metastatic Renal Cell Carcinoma Database Consortium; unl — upper normal limit

scan results is presented in Figure 2D. Importantly, radiographic response (CR + PR *vs.* SD *vs.* PD) was significantly related to treatment efficacy (OS and PFS) according to pairwise comparisons (log-rank test $p < 0.001$). We observed an ORR in 30.6% of patients (n = 11) and a DCR in 66.7% (n = n 24). One patient achieved CR (2.8%), and 4 patients with iUPD achieved an iCPD in subsequent CT scans. Patients with central nervous system metastases had a significantly greater risk of treatment failure [hazard ratio (HR) 18.2, 95% CI: 2.5–134.9, $p = 0.005$), as shown in Figure 2C. In a pairwise comparison, IMDC risk factor, number of metastatic sites (≤ 2 *vs.* > 2), and previous nephrectomy did not influence treatment outcome. According to the multiple Cox regression model ($p < 0.001$ for the model), the only factors that influenced TTF were the central nervous system (HR: 73.8, 95% CI: 7.8–698.8), $p < 0.001$) and liver metastases (HR: 4.2, 95% CI: 1–17, $p = 0.04$).

Eleven patients (30.6%) received radiotherapy during treatment with ICIs, and 2 (5.6%) required transfusions of blood and blood products, with no influence on survival ($p = 0.9$ for both log-rank test).

Laboratory parameters

Table 2 shows the median values of selected laboratory parameters obtained at baseline, after 3 months of treatment, and before PD. Hemoglobin

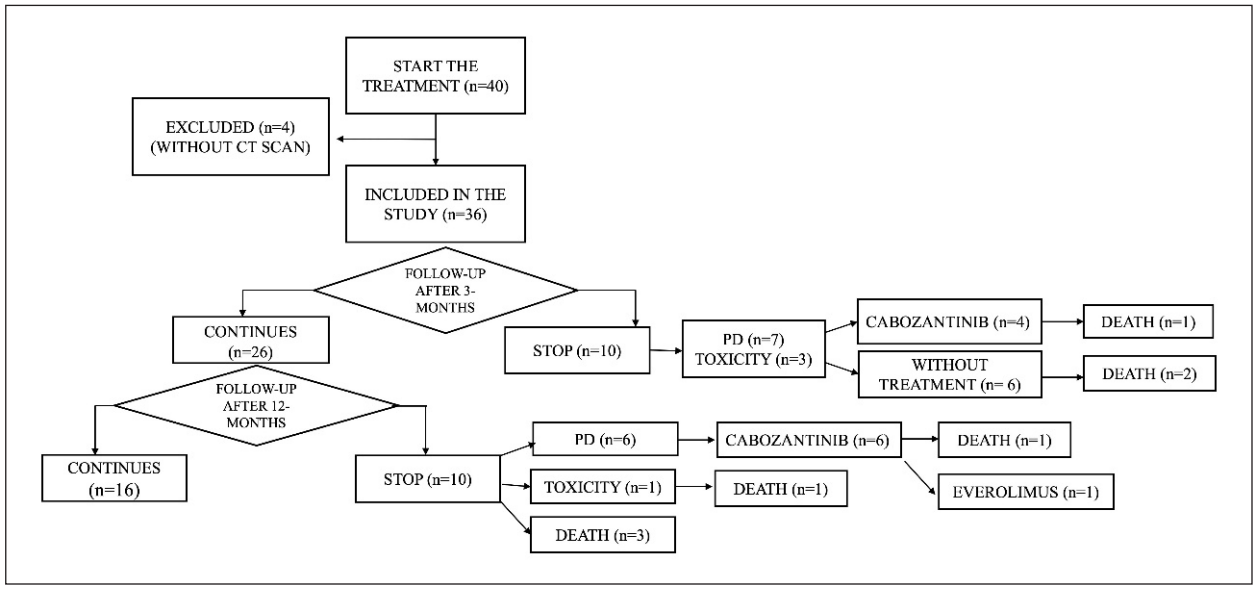

Figure 1. Patient distribution during treatment

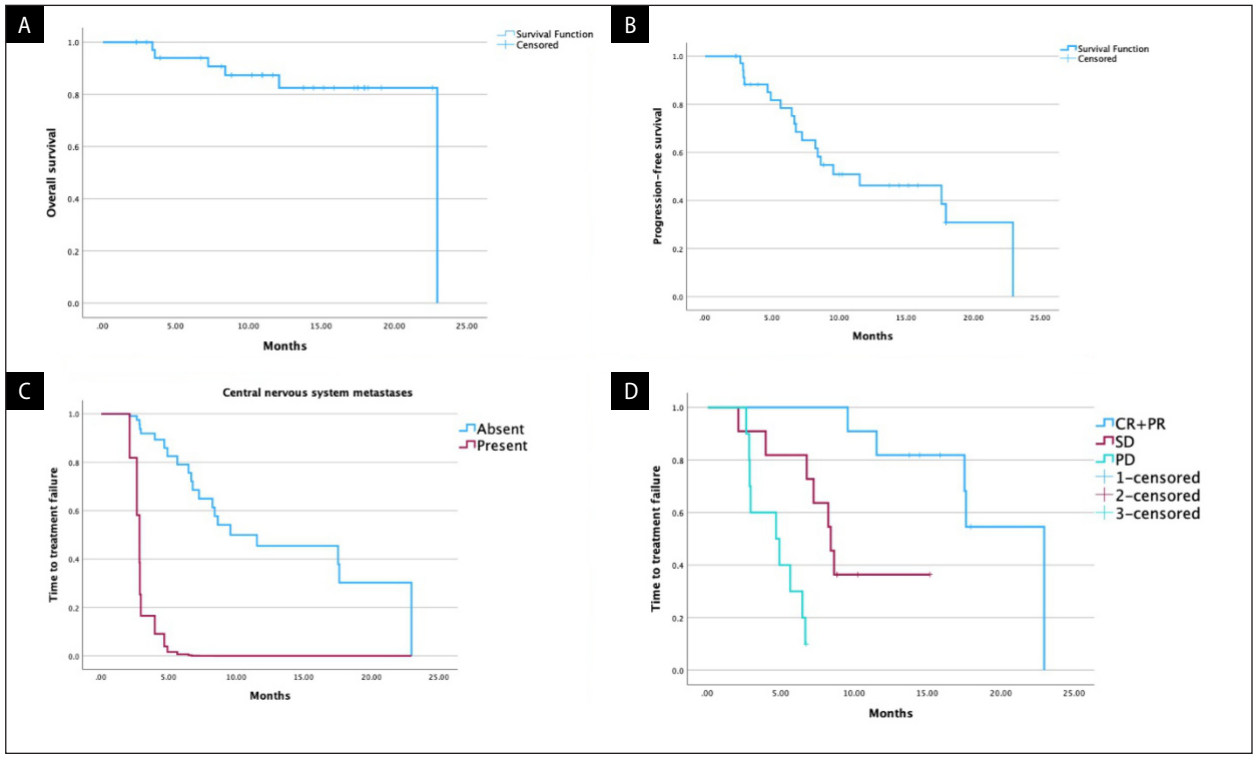

Figure 2. Kaplan-Meyer curves of overall survival (**A**), progression-free survival (**B**), survival distribution based on central nervous system metastasis (**C**), and progression-free survival in relation to treatment efficacy, as shown by computed tomography scan results (**D**)

and eosinophil levels are different at these checkpoints. However, in the post-hock analysis, only eosinophils at baseline and after 3 months were significantly different ($p < 0.001$). In pairwise comparisons, a higher pre-PD monocyte count was associated with a greater risk of treatment failure (log-rank test $p = 0.04$, Fig. 3B). Another finding was that patients with a higher NLR pre-PD were at

Table 2. Summary of selected laboratory parameters at three different checkpoints

Parameter	Baseline	After 3 months	Before progressive disease	p-value
NLR	2 (1.6– 2.73)	2.34 (1.7–2.54)	2.63 (2.1–3.23)	0.53
PLR	155.2 (111.3–224.1)	145.9 (106.8–195.7)	137.6 (102–205.2)	1
LMR	3.2 (2.4–4.5)	2.8 (2.2–3.4)	2.9 (2.2–3.8)	0.3
Hemoglobin [g/dL]	13.7 (11.2–14.7)	11.8 (10.9–14.1)	12.4 (10.9–14.9)	0.02*
Lymphocytes [10^3/uL]	2.35 (1.9–3.1)	2.3 (2–2.9)	2.4 (1.9–3.1)	0.9
Neutrophils [10^3/uL]	4.4 (4.1–5.7)	5 (4.6–5.9)	4.8 (4.3–7.3)	0.3
Platelets [10^3/uL]	348 (276.5–413.8)	306 (262.5–472.3)	310.5 (249.3–410.8)	0.5
Eosinophils [10^3/uL]	0.2 (0.1–0.4)	0.5 (0.1–0.8)	0.3 (0.1–0.6)	0.02*
Monocytes [10^3/uL]	0.7 (0.6–0.9)	0.9 (0.6–1.1)	0.7 (0.6–0.9)	0.3

Variables are presented as medians and interquartile ranges. LMR — lymphocyte–monocyte ratio; NLR — neutrophil–lymphocyte ratio; PLR — platelet–lymphocyte ratio. Statistically significant values are marked as *

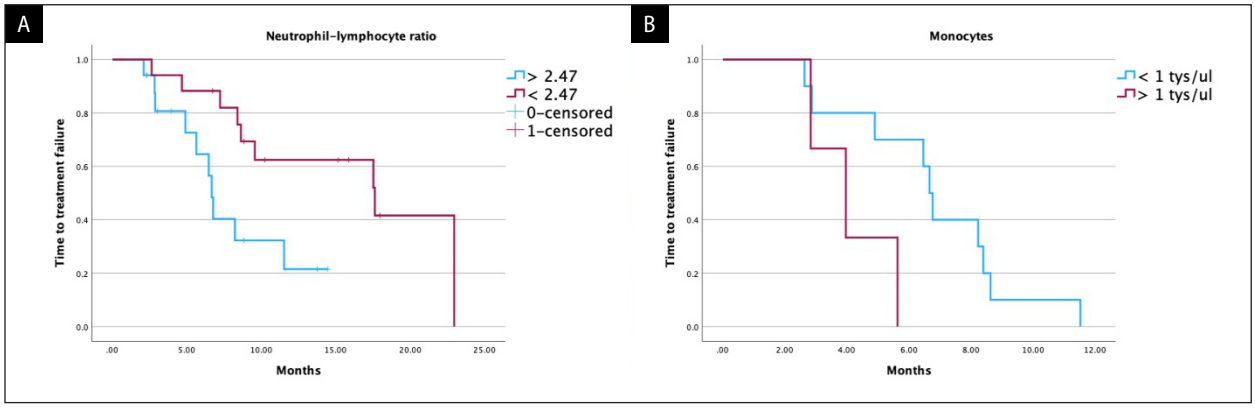

Figure 3. Kaplan Meyer curves of the influence of the neutrophil-lymphocyte ratio (**A**) and monocyte count (**B**) before PD on the time to treatment failure according to computed tomography (CT) scan results (pre-PD)

risk of treatment failure, but the difference was not statistically significant (p = 0.06, Fig. 3A). Other laboratory parameters did not influence treatment outcome.

Adverse events

During the observation period of 11 months (range: 7.5–17.5), AEs of any grade occurred in 23 patients (63.9%) after a median time of 3 months (range: 2–4). In total, 35 events were recorded. The distribution of AEs is depicted in Figure 4. The most common AE was fatigue, which was reported in 25% of patients (n = 9); thyroid dysfunction, which was reported in 20% (n = 7); and cutaneous dysfunction, which was reported in 17% (n = 6). Thirteen patients experienced 1 AE, three patients experienced 2 AEs, and other three patients experienced 3 AEs. The severity of the reported AEs was as follows: 15 (42.9%) were G1, 15 (42.9%) were G2, and 3 (8.6%) were G3. We observed 2 episodes of G4 AEs (5.6%), including one case of G4 neutropenia and one case of G4 hepatotoxicity. This yielded a serious (G3 + G4) AE incidence of 13.8% (n=5). One patient with G3 neutropenia did not receive steroids due to rapid neutrophil count recovery, whereas four patients required systemic steroids at maximum doses: 0.5 mg/kg, 1 mg/kg, 1 mg/kg, and 4 mg/kg of prednisone, respectively. These individuals experienced treatment withdrawal due to toxicity (discontinuation rate of 11%). One patient with G4 hepatotoxicity was steroid-resistant and required mycophenolate mofetil. The occurrence of AEs did not influence progression-free survival in pairwise comparisons (log-rank test p = 0.6). Similarly, the number of AEs did not impact treatment outcome (log-rank test p = 0.1).

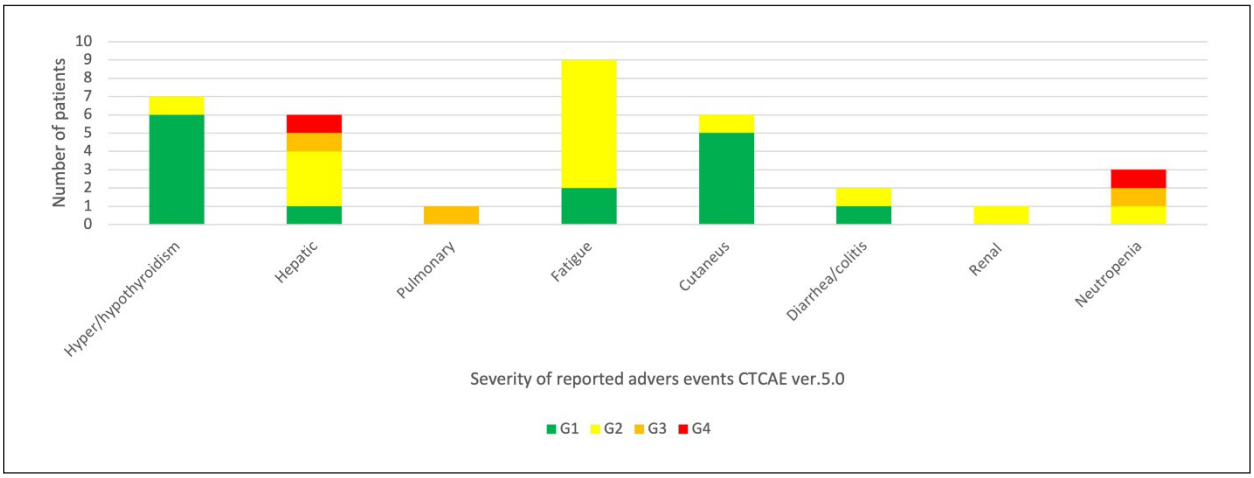

Figure 4. Prevalence and grade [according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0] of immunotherapy-related adverse events

Discussion

In this study, we revealed that combined immunotherapy with nivolumab and ipilimumab in patients with metastatic RCCs achieved an ORR in one-third of treated patients and controlled the disease in two-thirds. Although AEs occurred in 64% of treated individuals, most were of G1–G2 severity and were reported early in treatment, during the induction phase when nivolumab is administered with ipilimumab. Serious AEs were noted in 14% of patients, but only one patient required immunosuppressive agents other than steroids, and two patients were hospitalized in the internal medicine unit.

The efficacy of the nivolumab and ipilimumab combination was demonstrated in the phase III Checkmate 214 trial [15]. In this study, 1096 treatment-naive patients with metastatic RCCs were randomized to receive either nivolumab plus ipilimumab or sunitinib (TKI). After a median of 68 months of follow-up, patients with intermediate- or poor-risk disease treated with ICIs had improved OS (medians, NR *vs.* 26 months; $p < 0.001$), PFS (medians, 11.6 *vs.* 8.4 months; $p = 0.03$), ORR (42% *vs.* 27%; $p < 0.001$), and CR rates (9% *vs.* 1%). However, there was no OS benefit observed in the favorable risk group, albeit with lower PFS and ORR [16]. Another report with extended 4-year follow-up data [17] revealed CR in 10% of treated patients, with almost half remaining alive and 30% showing no progressive disease in the intermediate/poor-risk group. This underscores the durable clinical benefit of combined immunotherapy.

According to real-world data from the IMDC study [18], the median OS of patients treated with this regimen was 47.8, 51.1, and 18.3 months for those with favorable, intermediate, and poor risk, respectively. Interestingly, patients who survived for 6 months had an 81% likelihood of surviving an additional year and a 68% likelihood of surviving two years. CR was reported in 3–6% of patients, depending on the risk group. According to other data, the median OS was 26.6 months [19]. In a Japanese report [20], the median duration of combination therapy was 7.2 months, and OS and PFS were NR after a median observation period of 16 months. Doshi et al. [21] reported a median PFS of 17.1 months and an ORR of 43.2%. The results of our study align with the aforementioned results and data from the pivotal study.

In the Checkmate 214 study [15], AEs of any grade occurred in 93% of patients, with serious AEs in 46% and a discontinuation rate of 22%. The most common toxicities were fatigue, rash/pruritus, and diarrhea. Data from a meta-analysis [22] of different first-line regimens for metastatic RCCs indicated that the most favorable OS was for patients treated with nivolumab + cabozantinib, the highest ORR was for patients treated with lenvatinib + pembrolizumab, and the lowest toxicity was for patients treated with the nivolumab + ipilimumab combination. In a Japanese study [20], 70.8% of patients experienced AEs, of them 40.3% were G3–4 AEs; the most frequent AEs were hepatotoxicity and en-

docrine and skin toxicities. The median time for AE onset was 3 months. In this study, discontinuation due to AEs did not lead to shorter PFS. In another real-world study [21], AEs were reported in 47.2% of patients, the most frequent of them being fatigue, rash, and diarrhea; 5.5% of patients required hospitalization. Another study [23] revealed endocrine toxicity to be the most common (in 66% of patients), with most occurring within 3 months of initiating therapy. In our study, we reported a lower incidence of serious adverse events (AEs), but the aforementioned studies confirmed that AEs usually occur at the beginning of treatment.

Data from other malignancies indicate that the occurrence of AEs may positively impact treatment results [24, 25]. Washino et al. [26] reported that patients with multiple AEs had longer OS and PFS. In a study by Nukaya [27], patients with immune-related adverse events (AEs) had prolonged OS and PFS. Similarly, in the study by Ueda [28], the OS of patients with AEs was greater in the NR group than in the control group (23.6 months; $p = 0.004$), and the PFS was greater in the NR group than in the control group (25 months *vs.* 5 months; $p = 0.0002$). Conversely, Ikeda et al. [29] reported prolonged PFS (28.2 months *vs.* 2.6 months, $p < 0.0001$) without an impact on OS. Thyroid dysfunction and skin reactions were found to be predictive of PFS [30]. We did not observe similar relationships between AE occurrence and treatment results, possibly due to the small sample size.

Study strengths and limitations

The main limitation of our study is its retrospective nature. It was conducted on a small sample size, with patients from a single center. However, we plan to extend our analysis by comparing this data with results from other sites in Poland. As mentioned earlier, most real-world data on RCCs come from the Japanese population. We believe that every report from a daily practice is valuable as part of post-registration studies, known as phase IV trials. Our study is notable because it demonstrates that patients can be successfully treated in an outpatient clinic outside of an academic or high-volume center. The key factors for success include organized workflows, trained staff, and cooperation with the internal medicine ward. As we detailed in another report [31], collaboration with physicians from various specialties is essential during immunotherapy treatment.

Conclusions

Our analysis indicated that treatment with the combination of nivolumab and ipilimumab in metastatic RCCs has an acceptable toxicity profile, with the rate of serious AEs even lower than that in the pivotal trial. Most AEs occur during the first 3 months of treatment, as confirmed by other real-world reports, highlighting the necessity of careful monitoring, especially at the beginning of treatment. G3–G4 AEs can be successfully managed with steroids, even in outpatient clinics, as only 2 patients required hospitalization in our daily practice. The key message from our study is that such treatment can be conducted in a district hospital's outpatient clinic with close patient monitoring and cooperation with other hospital units.

Conflict of interests

The Authors declare that there is no conflict of interest.

Funding

None declared.

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