Targeted Oncology (2022) 17:571–581
https://doi.org/10.1007/s11523-022-00907-9

ORIGINAL RESEARCH ARTICLE

Concomitant Use of Statins, Metformin, or Proton Pump Inhibitors in Patients with Advanced Renal Cell Carcinoma Treated with First-Line Combination Therapies

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Accepted: 25 July 2022 / Published online: 10 August 2022
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Abstract

Background Drug–drug interactions are a major concern in oncology and may potentially affect the outcome of patients with cancer.

Objective In this study, we aimed to determine whether the concomitant use of statins, metformin, or proton pump inhibitors affects survival in patients with metastatic renal cell carcinoma treated with first-line combination therapies.

Methods Medical records of patients with documented metastatic renal cell carcinoma between January 2016 and November 2021 were reviewed at 17 participating centers. This research was conducted in ten institutions, including both referral centers and local hospitals. Patients were assessed for overall survival, progression-free survival, and overall clinical benefit. Univariate and multivariate analyses were conducted to explore the association of variables of interest with overall survival and progression-free survival.

Results A total of 304 patients receiving dual immunotherapy (51%) or immunotherapy/vascular endothelial growth factor-tyrosine kinase inhibitor (49%) combinations were eligible for inclusion in this retrospective study. Statin use was a significant prognostic factor for longer overall survival in a univariate analysis (hazard ratio 0.48, 95% confidence interval 0.26–0.87; $p = 0.016$) and a multivariate analysis (hazard ratio 0.48, 95% confidence interval 0.31–0.74; $p < 0.001$) and was significantly associated with an overall clinical benefit (83% in statin users vs 71% in non-users; $p = 0.045$). Otherwise, the use of metformin or proton pump inhibitors did not affect the outcome of these patients.

Conclusions Our study suggests a prognostic impact of statin use in patients receiving first-line immuno-oncology combinations. The mechanism of this interaction warrants further elucidation.

1 Introduction

The incidence of renal cell carcinoma (RCC) is increasing worldwide, with approximately 76,000 new cases estimated in 2021 in the USA [1, 2]. The prognosis of patients with metastatic RCC (mRCC) has been completely changed by the advent of immune checkpoint inhibitors. These agents are directed against the cytotoxic T-lymphocyte antigen-4 or programmed cell death-1 axis and are able to counteract

Key Points

Drug–drug interactions are a major concern in oncology and may potentially affect the outcome of patients with cancer.

In this study, we aimed to determine whether the concomitant use of statins, metformin, or proton pump inhibitors affects survival in patients with metastatic renal cell carcinoma treated with first-line combination therapies.

Our study suggests a prognostic impact of statin use in patients receiving first-line immuno-oncology combinations.

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tumor-induced T-cell immune suppression, a key mechanism for RCC growth and metastasis [3, 4]. A variety of immuno-oncology (IO) combinations have been developed for patients with mRCC, rapidly becoming the new standard of care as first-line therapy. These combinations consist of dual IO-IO agents (anti-programmed cell death-1 nivolumab plus anti-cytotoxic T-lymphocyte antigen-4 ipilimumab) or in IO plus anti-vascular endothelial growth factor tyrosine kinase inhibitors, such as pembrolizumab plus axitinib, avelumab plus axitinib, nivolumab plus cabozantinib, or pembrolizumab plus lenvatinib [5–9].

The majority of patients with RCC receive concomitant medications for the treatment of cancer-related symptoms or co-morbidities. Drug–drug interactions have become an area of increasing interest. This evidence can be explained by the ability of some concomitant medications to exert immune-modulatory effects, thus influencing the efficacy of immunotherapy in this context [10]. A more classic example is represented by steroids, whose immunosuppressive capability, which might dampen the activity of immunotherapies, has resulted in their more routine use to manage immune-related adverse effects [11]. Two other examples are represented by antibiotic treatment, which has demonstrated to influence the efficacy of immune checkpoint inhibitors and to modulate acute and chronic pain by altering the normal bacterial microenvironment in several retrospective and few prospective studies [12–15] and by proton pump inhibitors (PPIs), which seem to not affect the outcome of patients treated with immunotherapy [16, 17]. Based on this scenario, we aimed to first assess the impact of commonly used concomitant medications, such as statins, metformin, and PPIs, on the outcome of patients with mRCC treated with first-line combination therapies.

2 Patients and Methods

2.1 Study Population

We retrospectively analyzed data from patients aged ≥18 years with a histologically confirmed diagnosis of RCC and a histologically and/or radiologically diagnosis of metastatic disease, treated with first-line immune-oncology combinations. First-line therapies included nivolumab plus ipilimumab, pembrolizumab plus axitinib, axitinib plus avelumab, nivolumab plus cabozantinib, or pembrolizumab plus lenvatinib.

This international real-world study collected data from 17 international institutions from Italy, Spain, and the USA involved in the treatment of patients with RCC. Data collection included data from 1 January, 2016 to 30 November, 2021.We retrospectively reviewed data from paper and electronic charts. For each patient, we collected data including: tumor histology, nephrectomy status, initial Eastern Cooperative Oncology Group performance status, International Metastatic RCC Database Consortium (IMDC) criteria, sites of metastases, and concomitant use of statins, PPIs, or metformin. Patients without sufficient data on tumor assessment and response to first-line therapy were excluded from this analysis.

First-line therapy was generally performed till the evidence of radiological tumor progression on computed tomography or magnetic resonance imaging scans, unacceptable adverse events, or death. Follow-up was generally performed by periodical physical and laboratory assessment every 4–6 weeks. Imaging was carried out according to standard local procedures every 8–12 weeks. Dose reductions and treatment interruptions were managed basing on standard guidelines according to the type and severity of drug-related adverse events. Statin, metformin, and PPI users were defined as those who had been prescribed continuous oral medications over a period of ≥30 days and were receiving at least one of these concomitant medications at the time of first-line therapy.

2.2 Study Endpoints

The primary objective of our retrospective study was to assess the influence on the oncological outcome of concomitant statins, PPIs, or metformin in patients treated with first-line immune combinations for advanced RCC. Tumor radiological assessment was led according to the RECIST 1.1 criteria [18] and data on tumor response (complete or partial responses, stable or progressive disease) were collected and analyzed.

Overall survival (OS) was defined as the time from the start of treatment to death or lost at follow-up. Progression-free survival (PFS) was defined as the time from the start of treatment to progression or death from any cause, whichever occurred first. Patients without a tumor progression to a following line of treatment or death or lost at follow-up at the time of analysis were censored at their last follow-up date. Overall clinical benefit (OCB) was defined by the percentage of patients who experienced complete responses (CR), partial responses (PR), or stable diseases (SD).

2.3 Statistical Analysis

Progression-free survival and OS were estimated by using the Kaplan–Meier method with Rothman's 95% confidence intervals (CIs), and comparisons were performed by the log-rank test. Cox proportional hazards models were used for univariate and multivariate analyses. Categorical endpoints were compared by the chi-square test. Significance levels

Table 1 Patients' characteristics in the overall study population and stratified by concomitant medications

Patients	Overall 304 (%)	Statin users 93 (%)	Statin non-users 211 (%)	*p* value	PPI users 153 (%)	PPI non-users 151 (%)	*p* value	Metformin users 53 (%)	Metformin non-users 251 (%)	*p* value
Sex										
Male	224 (74)	69 (74)	155 (73)	0.894	113 (74)	111 (74)	0.945	37 (70)	187 (75)	0.482
Female	80 (26)	24 (26)	56 (27)		40 (26)	40 (26)		16 (30)	64 (25)	
Age, years										
≥ 70	104 (34)	33 (35)	71 (34)	0.756	56 (37)	48 (32)	0.377	18 (34)	86 (34)	0.967
Synchronous metastatic RCC	149 (49)	40 (43)	109 (52)	0.165	69 (45)	80 (53)	0.17	29 (55)	120 (48)	0.361
Previous nephrectomy	190 (63)	59 (63)	131 (62)	0.147	95 (62)	95 (63)	0.883	27 (51)	163 (65)	0.056
Clear cell histology	261 (86)	81 (87)	180 (85)	0.681	137 (90)	124 (82)	0.064	46 (87)	215 (86)	0.83
IMDC risk stratification										
Favorable risk	51 (17)	18 (19)	33 (16)	0.717	28 (18)	23 (15)	0.669	5 (9)	46 (18)	0.161
Intermediate risk	184 (61)	54 (58)	130 (62)		89 (58)	95 (63)		32 (61)	152 (61)	
Poor risk	69 (22)	21 (23)	48 (22)		36 (24)	33 (22)		16 (30)	53 (21)	
Common sites of metastasis										
Lung	210 (69)	70 (75)	140 (66)	0.088	105 (69)	105 (70)	0.864	40 (81)	170 (67)	0.268
Lymph nodes	164 (54)	43 (46)	121 (57)	0.074	82 (54)	82 (54)	0.901	25 (47)	139 (55)	0.277
Bone	94 (31)	25 (27)	69 (33)	0.313	51 (33)	43 (28)	0.36	16 (30)	78 (31)	0.899
Liver	49 (16)	13 (14)	36 (17)	0.501	28 (18)	21 (14)	0.298	12 (23)	37 (15)	0.156
Brain	19 (6)	6 (6)	13 (6)	0.923	12 (8)	7 (5)	0.249	3 (6)	16 (6)	0.846
≥ 2 metastatic sites	220 (72)	68 (73)	152 (72)	0.846	113 (74)	107 (71)	0.56	41 (77)	179 (71)	0.372
First-line therapy										
IO + IO	155 (51)	44 (47)	111 (53)	0.396	67 (44)	88 (58)	**0.012**	30 (57)	125 (50)	0.369
IO + TKI	149 (49)	49 (53)	100 (47)		86 (56)	63 (42)		23 (43)	126 (50)	
Second-line therapy										
Sunitinib	30 (10)	6 (6)	24 (11)	0.186	12 (8)	18 (12)	0.234	9 (17)	21 (8)	0.056
Cabozantinib	48 (16)	5 (5)	43 (20)	**0.001**	19 (12)	29 (19)	0.105	7 (13)	41 (16)	0.571
Other	9 (3)	1 (1)	8 (4)	0.199	4 (3)	5 (3)	0.721	1 (2)	8 (3)	0.612

Bold indicates statistically significant values

IMDC International Metastatic RCC Database Consortium, *IO* immune-oncology, *PPI* proton pump inhibitor, *RCC* renal cell carcinoma, *TKI* tyrosine kinase inhibitor

were set at a 0.05 value and all *p* values were two sided. The statistical analysis was performed using MedCalc version 19.6.4 (MedCalc Software, Mariakerke, Belgium).

3 Results

3.1 Study Population

Three hundred and four patients were included in our retrospective study. The median age was 65 years (range 29–89 years); 224 patients (74%) were male (Table 1). Tumor histology was clear cell in 261 subjects (86%). Tumor histology among the 43 patients with non-clear RCC included 12 patients (4%) with papillary RCC, six (2%) with sarcomatoid differentiation, six (2%) with unclassified tumors, four (1%) with poorly differentiated disease, three (1%) with chromophobe RCC, and 12 (4%) patients with other non-clear cell histologies. The number of metastatic sites was two or more in 220 patients (72%). Lung (69%), lymph nodes (54%), and bone (31%) were the most common metastatic sites (Table 1). According to IMDC criteria, 51 patients (17%) had favorable-risk features, 184 (61%) had intermediate-risk features, and 69 (22%) had poor-risk features (Table 1).

Fig. 1 Overall survival in patients treated with immuno-oncology combinations. *IMDC* International Metastatic RCC Database Consortium, *PPI* proton pump inhibitor ▶

First-line therapy consisted of dual immunotherapy in 155 patients (51%); 149 (49%) patients treated with the IO-TKI combination, 110 (36%) received pembrolizumab plus axitinib, 24 (8%) received axitinib plus avelumab, eight (3%) received pembrolizumab plus lenvatinib, and seven (2%) received nivolumab plus cabozantinib. Eighty-seven patients (29%) received second-line therapies, which consisted of sunitinib or cabozantinib in 90% of patients (Table 1).

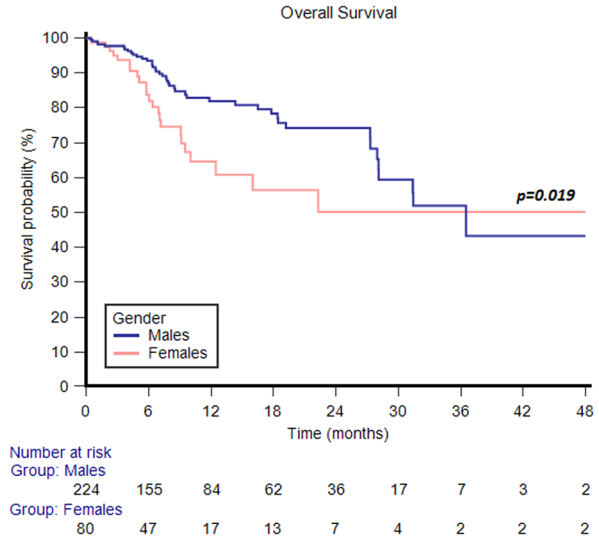
Concomitant use of statins, PPIs, or metformin was reported in 31%, 50%, and 17% of patients, respectively (Table 2). Patients' characteristics are summarized in Tables 1 and 2. The use of PPIs was significantly more frequent in patients treated with the IO plus TKI combination than the IO plus IO combination (Table 1). No significant

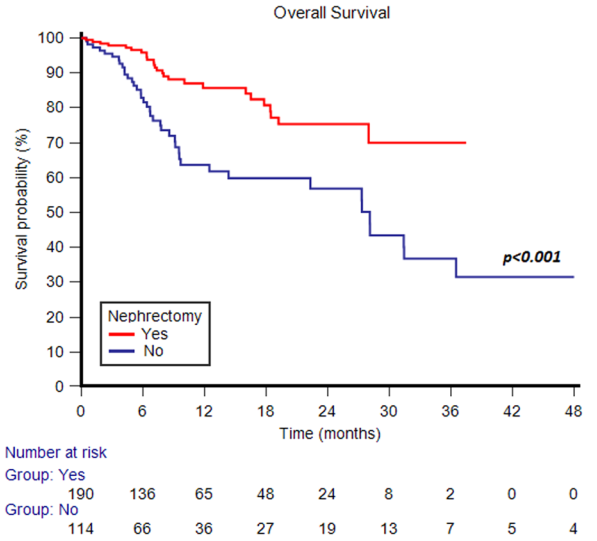
Table 2 Patients' characteristics stratified by the type of first-line therapy

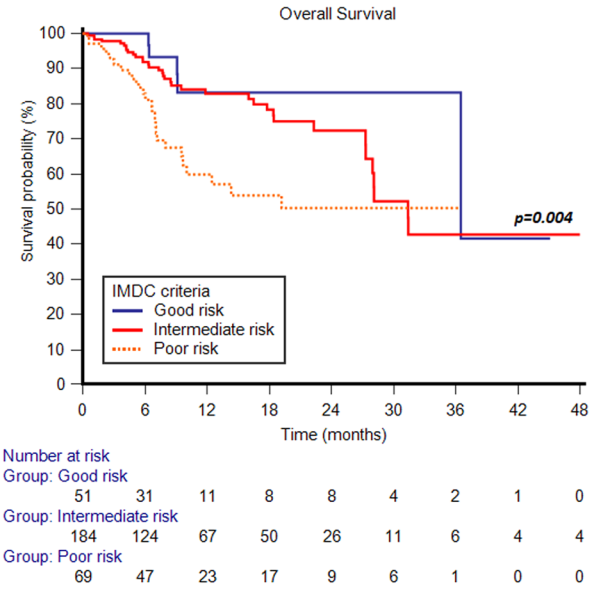
Patients	Overall 304 (%)	IO + IO 155 (%)	IO + TKI 149 (%)	*p* value
Sex				
Male	224 (74)	121 (78)	103 (69)	0.077
Female	80 (26)	34 (22)	46 (31)	
Age, years				
≥ 70	104 (34)	48 (31)	56 (38)	0.225
Median	65	66	65	–
Synchronous metastatic RCC	149 (49)	80 (52)	69 (46)	0.356
Previous nephrectomy	190 (63)	100 (65)	90 (60)	0.460
Clear cell histology	261 (86)	134 (86)	127 (85)	0.761
IMDC risk stratification				
Favorable risk	51 (17)	8 (5)	43 (36)	**< 0.001**
Intermediate risk	184 (61)	99 (64)	75 (50)	
Poor risk	69 (22)	48 (31)	21 (14)	
Common sites of metastasis				
Lung	210 (69)	111 (72)	99 (66)	0.330
Lymph nodes	164 (54)	90 (58)	74 (50)	0.143
Bone	94 (31)	48 (31)	46 (31)	0.986
Liver	49 (16)	25 (16)	24 (16)	0.996
Brain	19 (6)	8 (5)	11 (7)	0.425
≥ 2 Metastatic sites	220 (72)	111 (72)	110 (74)	0.638
Concomitant medications				
Statins	93 (31)	44 (28)	49 (33)	0.396
PPIs	153 (50)	67 (43)	86 (58)	**0.012**
Metformin	53 (17)	30 (19)	23 (15)	0.369

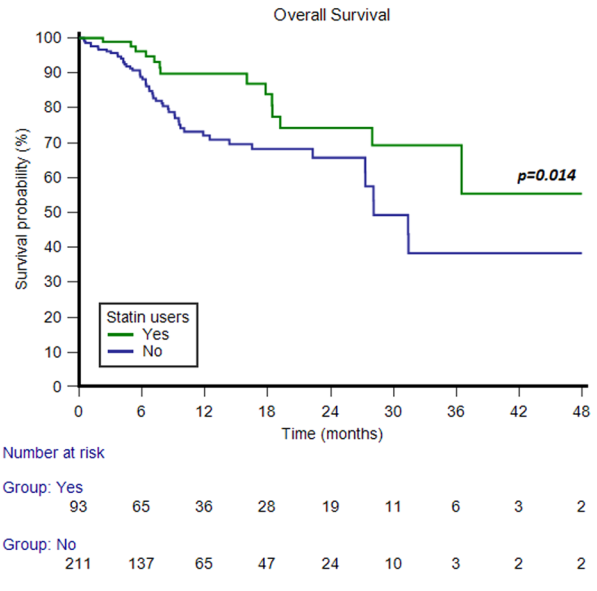
Bold indicates statistically significant values

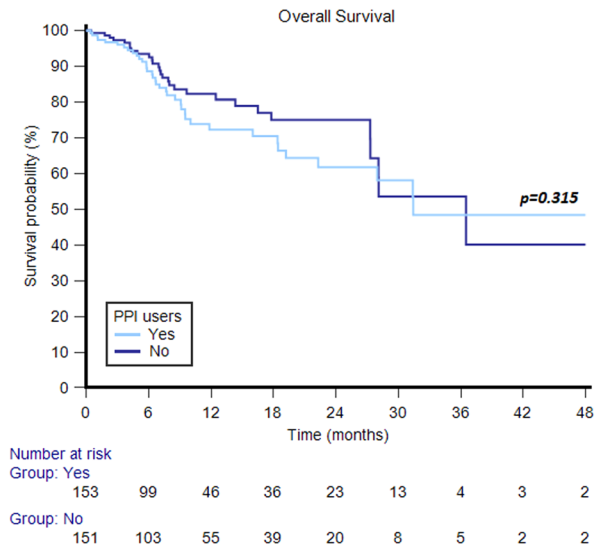
IMDC International Metastatic RCC Database Consortium, *IO* immune-oncology, *PPIs* proton pump inhibitors, *RCC* renal cell carcinoma, *TKIs* tyrosine kinase inhibitors

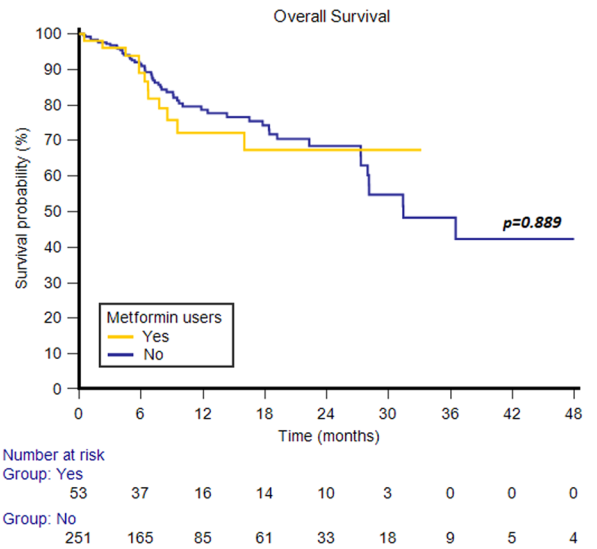

Overall Survival
Survival probability (%)
p=0.019
Gender
Males
Females
Time (months)
Number at risk
Group: Males
224 155 84 62 36 17 7 3 2
Group: Females
80 47 17 13 7 4 2 2 2

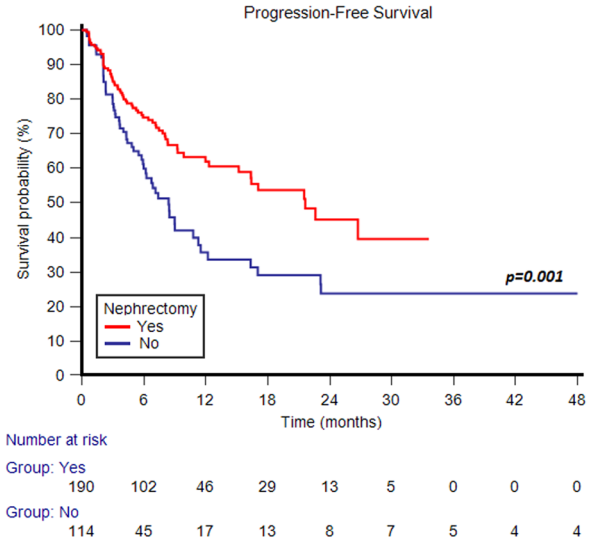

Overall Survival
Survival probability (%)
p<0.001
Nephrectomy
Yes
No
Time (months)
Number at risk
Group: Yes
190 136 65 48 24 8 2 0 0
Group: No
114 66 36 27 19 13 7 5 4

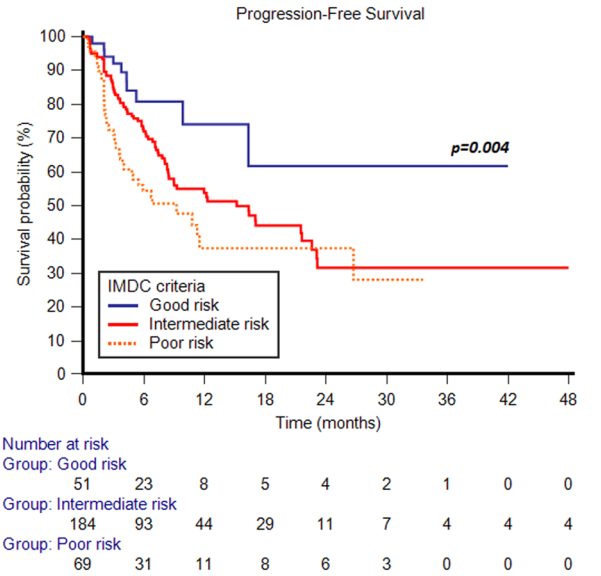

Overall Survival
Survival probability (%)
p=0.004
IMDC criteria
Good risk
Intermediate risk
Poor risk
Time (months)
Number at risk
Group: Good risk
51 31 11 8 8 4 2 1 0
Group: Intermediate risk
184 124 67 50 26 11 6 4 4
Group: Poor risk
69 47 23 17 9 6 1 0 0

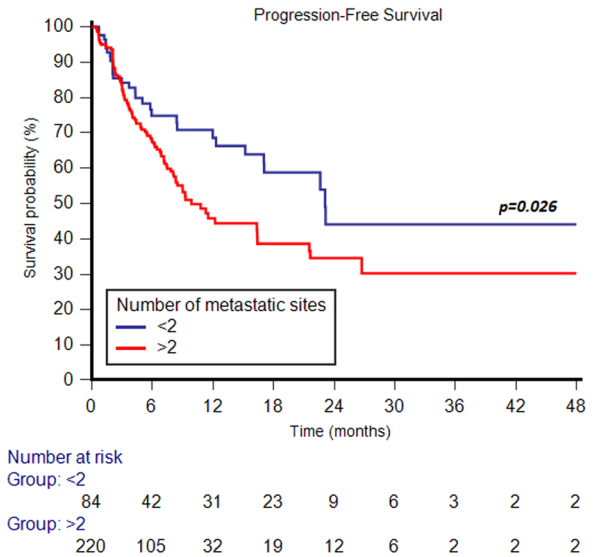

Overall Survival
Survival probability (%)
p=0.014
Statin users
Yes
No
Time (months)
Number at risk
Group: Yes
93 65 36 28 19 11 6 3 2
Group: No
211 137 65 47 24 10 3 2 2

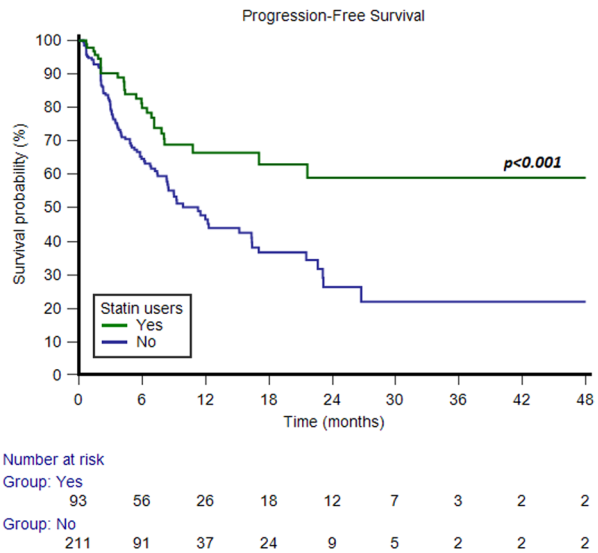

Overall Survival
Survival probability (%)
p=0.315
PPI users
Yes
No
Time (months)
Number at risk
Group: Yes
153 99 46 36 23 13 4 3 2
Group: No
151 103 55 39 20 8 5 2 2

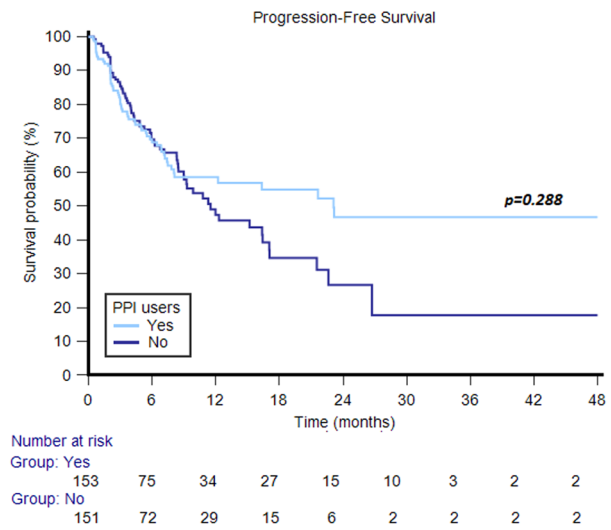

Overall Survival
Survival probability (%)
p=0.889
Metformin users
Yes
No
Time (months)
Number at risk
Group: Yes
53 37 16 14 10 3 0 0 0
Group: No
251 165 85 61 33 18 9 5 4

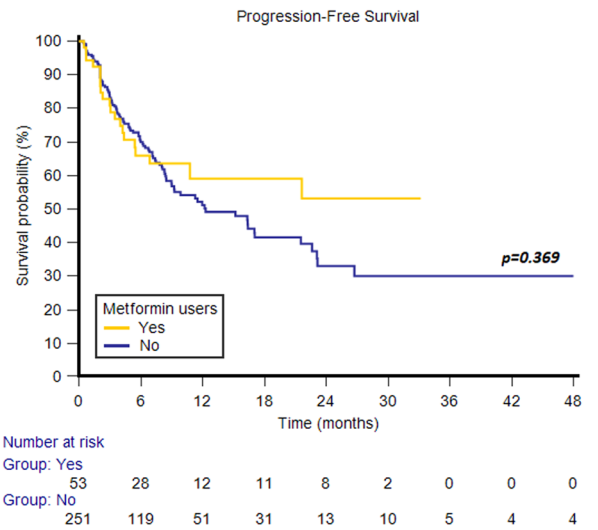

Progression-Free Survival
Survival probability (%)
Time (months)
p=0.001
Nephrectomy
Yes
No
Number at risk
Group: Yes
190 102 46 29 13 5 0 0 0
Group: No
114 45 17 13 8 7 5 4 4


Progression-Free Survival
Survival probability (%)
Time (months)
p=0.004
IMDC criteria
Good risk
Intermediate risk
Poor risk
Number at risk
Group: Good risk
51 23 8 5 4 2 1 0 0
Group: Intermediate risk
184 93 44 29 11 7 4 4 4
Group: Poor risk
69 31 11 8 6 3 0 0 0


Progression-Free Survival
Survival probability (%)
Time (months)
p=0.026
Number of metastatic sites
<2
>2
Number at risk
Group: <2
84 42 31 23 9 6 3 2 2
Group: >2
220 105 32 19 12 6 2 2 2


Progression-Free Survival
Survival probability (%)
Time (months)
p<0.001
Statin users
Yes
No
Number at risk
Group: Yes
93 56 26 18 12 7 3 2 2
Group: No
211 91 37 24 9 5 2 2 2


Progression-Free Survival
Survival probability (%)
Time (months)
p=0.288
PPI users
Yes
No
Number at risk
Group: Yes
153 75 34 27 15 10 3 2 2
Group: No
151 72 29 15 6 2 2 2 2


Progression-Free Survival
Survival probability (%)
Time (months)
p=0.369
Metformin users
Yes
No
Number at risk
Group: Yes
53 28 12 11 8 2 0 0 0
Group: No
251 119 51 31 13 10 5 4 4

◂**Fig. 2** Progression-free survival in patients treated with immuno-oncology combinations. *IMDC* International Metastatic RCC Database Consortium, *PPI* proton pump inhibitor

differences were found in terms of clinicopathological features based on the concomitant use of statins, PPIs, or metformin (Table 1) or stratified by the type of first-line combination, except for the IMDC group distribution (Table 2).

3.2 Survival Analysis in the Overall Study Population

The median follow-up time from RCC diagnosis was 35.8 months (range 33.9–39.5 months). The median OS from the start of first-line therapy was 36.5 months (95% CI 28.1–36.5). In 176 patients (58%), first-line therapy was ongoing at the time of the data cut-off. Sixty-six patients (22%) had died at the time of the data cut-off.

A significant difference was found in terms of sex, with male patients showing longer OS compared with female patients (36.5 months, 95% CI 29.6–50.0 vs not reached [NR], 95% CI 28.1–36.5, $p = 0.019$, Fig. 1). Nephrectomy was associated with longer OS (NR, 95% CI NR–NR vs 28.1 months, 95% CI 12.5–36.5, $p < 0.001$, Fig. 1). The median OS was 36.5 months (95% CI 36.5–36.5), 31.4 months (95% CI 27.3–31.4), and NR (95% CI NR–NR) in patients with good, intermediate, and poor IMDC risk criteria, respectively ($p = 0.004$, Fig. 1).

Statin users, compared with non-users, showed longer OS (NR, 95% CI NR–NR vs 28.1 months, 95% CI 27.3–31.4, $p = 0.014$, Fig. 1). Otherwise, concomitant use of PPIs (31.4 months, 95% CI 22.3–31.4 vs 36.5 months in non-users, 95% CI 27.3–36.5, $p = 0.315$, Fig. 1) or metformin (NR, 95% CI NR–NR vs 31.4 months in non-users, 95% CI 28.0–36.5, $p = 0.889$, Fig. 1) was not significantly associated with OS.

The median PFS from the start of first-line therapy was 16.30 months (95% CI 9.3–22.6), without reporting a significant difference between sexes (15.2 months in male patients, 95% CI 9.2–23.1, 21.5 months in female patients, 95% CI 5.9–22.6, $p = 0.763$). As for OS, nephrectomy (21.6 months, 95% CI 15.2–26.7 vs 8.4 months, 95% CI 6.0–11.3, $p = 0.001$, Fig. 2), and IMDC criteria (NR, 95% CI NR–NR in the good risk subgroup; 15.2 months, 95% CI 8.5–21.6 in patients with intermediate risk criteria; 9.2 months, 95% CI 3.9–26.7 in patients with poor risk features, $p = 0.004$, Fig. 2) were associated with PFS. Furthermore, two or more metastatic sites was correlated with the worst PFS (9.9 months, 95% CI 8.1–16.4, vs 23.1 months, 95% CI 17.0–23.2, $p = 0.026$, Fig. 2).

Similarly, concomitant statin use was correlated with longer PFS (NR, 95% CI NR–NR vs 11.3 months, 95% CI 8.3–16.3, $p < 0.001$, Fig. 2), in contrast to both PPIs (23.1 months, 95% CI 8.1–23.2 vs 11.5 months, 95% CI 9.0–17.0, $p = 0.288$, Fig. 2) or metformin (NR, 95% CI NR–NR vs 12.3 months, 95% CI 9.0–21.5, $p = 0.369$, Fig. 2).

In the univariate analysis, sex (HR = 0.55, 95% CI 0.33–0.91, $p = 0.021$), nephrectomy (HR = 0.38, 95% CI 0.23–0.63, $p < 0.001$), IMDC criteria (HR = 1.90, 95% CI 1.26–2.86, $p = 0.002$), and statin use (HR = 0.48, 95% CI 0.26–0.87, $p = 0.016$) were significantly associated with OS. Their prognostic role was confirmed in a multivariate analysis (Table 3). Regarding PFS, nephrectomy, two or more metastatic sites, IMDC criteria, and statin use were significant predictors in both univariate and multivariate analyses (Table 3).

3.3 Response to Therapy

In the overall study population, responses to first-line therapy consisted of eight CR (3%), 128 PR (42%), 94 SD (31%), and progressive disease (PD) as best responses in 74 patients (24%), with an OCB of 76% (Fig. 3). Overall clinical benefit was 83% (CR = 2%, PR = 51%, SD = 30%, PD = 17%) in statin users and 71% (CR = 2%, PR = 38%, SD = 31%, PD = 29%) in non-users ($p = 0.045$, Fig. 3). No significant differences were found between PPI users (OCB = 74%, CR = 4%, PR = 37%, SD = 33%, PD = 26%) and non-users (OCB = 76%, CR = 1%, PR = 47%, SD = 28%, PD = 24%, $p = 0.639$, Fig. 3). Similarly, in the 53 metformin users, OCB was 68% (CR = 4%, PR = 49%, SD = 15%, PD = 32%) compared with 77% (CR = 2%, PR = 41%, SD = 34%, PD = 23%) in non-users ($p = 0.150$, Fig. 3).

3.4 Role of Concomitant Statins, PPIs, or Metformin in Patients with RCC Stratified by First-Line IO-IO or IO-TKI Combinations

In patients treated with the first-line IO-IO combination, the median OS and PFS were NR (95% CI NR–NR) and 11.3 months (95% CI 7.2–16.4), respectively. Statin administration was significantly associated with PFS (21.6 months, 95% CI 7.8–21.6, vs 9.2 months, 95% CI 5.9–15.2, $p = 0.038$, Fig. S1 of the Electronic Supplementary Material [ESM]) but not with OS (NR, 95% CI NR–NR vs NR, 95% CI NR–NR, $p = 0.710$, Fig. S1 of the ESM). The concomitant use of PPIs was associated with neither OS (28.0 months, 95% CI 18.4–28.0 vs NR, 95% CI NR–NR, $p = 0.118$, Fig. S1 of the ESM) nor PFS (8.1 months, 95% CI 6.4–21.6 vs 11.5, 95% CI 7.1–17.0, $p = 0.618$, Fig. S1 of the ESM). Similarly, metformin intake did not correlate with OS (NR, 95% CI NR–NR vs NR, 95% CI NR–NR, $p = 0.229$, Fig. S1 of the ESM) and PFS

Table 3 Univariate and multivariate analyses for overall survival (OS) and progression-free survival (PFS)

	Univariate Cox regression		Multivariable Cox regression	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
OS				
Sex (M/F)	0.55 (0.33–0.91)	**0.021**	0.52 (0.31–0.86)	**0.012**
Age, years (≥ 70 vs < 70)	1.55 (0.96–2.53)	0.076		
Nephrectomy (Y vs N)	0.38 (0.23–0.63)	**< 0.001**	0.41 (0.25–0.68)	**< 0.001**
Histology (clear cell vs non-clear cell)	0.76 (0.40–1.46)	0.407		
Number of metastatic sites (≥ 2 vs < 2)	1.34 (0.78–2.31)	0.289		
IMDC prognostic group	1.90 (1.26–2.86)	**0.002**	1.78 (1.18–2.68)	**0.006**
Concomitant PPIs (Y vs N)	1.28 (0.79–2.09)	0.316		
Concomitant statins (Y vs N)	0.48 (0.26–0.87)	**0.016**	0.53 (0.29–0.97)	**0.039**
Concomitant metformin (Y vs N)	1.05 (0.56–1.96)	0.899		
PFS				
Sex (M/F)	0.94 (0.63–1.40)	0.764		
Age, years (≥ 70 vs < 70)	1.17 (0.82–1.66)	0.397		
Nephrectomy (Y vs N)	0.57 (0.40–0.80)	**0.001**	0.58 (0.41–0.82)	**0.002**
Histology (clear cell vs non-clear cell)	0.94 (0.58–1.52)	0.800		
Number of metastatic sites (≥ 2 vs < 2)	1.60 (1.05–2.44)	**0.027**	1.55 (1.01–2.39)	**0.045**
IMDC prognostic group	1.62 (1.22–2.16)	**0.001**	1.38 (1.03–1.85)	**0.032**
Concomitant PPIs (Y vs N)s	0.83 (0.58–1.18)	0.291		
Concomitant statins (Y vs N)	0.48 (0.31–0.74)	**< 0.001**	0.48 (0.32–0.74)	**< 0.001**
Concomitant metformin (Y vs N)	0.80 (0.50–1.30)	0.371		

CI confidence interval, *F* female, *HR* hazard ratio, *IMDC* International Metastatic RCC Database Consortium, *M* male, *N* no, *PPIs* proton pump inhibitors, *Y* yes

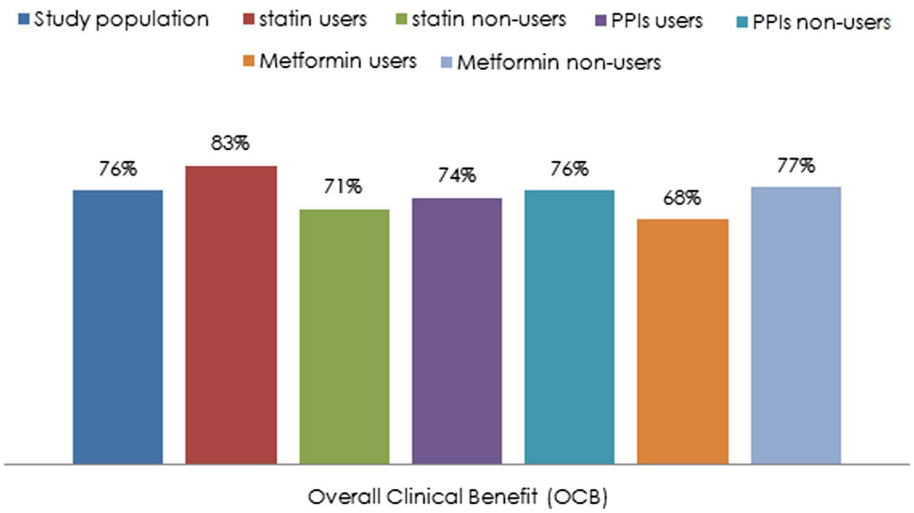


Fig. 3 Overall clinical benefit in patients treated with first-line immune-oncology combinations for advanced renal cell carcinoma. *PPI* proton pump inhibitor

(21.6 months, 95% CI 3.1–21.6, vs 9.9 months, 95% CI 7.5–16.4, $p = 0.618$, Fig. S1 of the ESM).

Patients treated with the IO-IO combination reported 5% CR, 40% PR, 26% SD, and 29% PD (OCB = 71%). No significant differences were found between patients treated or not treated with concomitant medications (statins: OCB = 75% vs 69%, $p = 0.488$; PPIs: OCB = 67% vs 73%, $p = 0.581$; metformin: OCB = 60% vs 74%, $p = 0.142$).

In patients treated with the IO-TKI combinations, the median OS and PFS were 31.4 (95% CI 28.1–36.5) and 23.2 months (95% CI 10.8–23.2), respectively. Statin use was associated with both improved OS (NR, 95% CI NR–NR, vs 28.1, 95% CI 27.3–31.4, $p < 0.001$, Fig. S2

of the ESM) and PFS (NR, 95% CI NR−NR, vs 23.1, 95% CI 8.5−23.2, $p = 0.006$, Fig. S2 of the ESM). Otherwise, no significant differences were observed between PPI users and non-users (median OS: NR, 95% CI NR−NR, vs 28.1, 95% CI 27.3−36.5, $p = 0.703$; median PFS: NR, 95% CI NR−NR, vs 10.8, 95% CI 8.5−10.8, $p = 0.805$; Fig. S2 of the ESM) or between metformin users and non-users (median OS: NR, 95% CI NR−NR, vs 31.4, 95% CI 27.3−36.5, $p = 0.183$; median PFS: NR, 95% CI NR−NR, vs 23.2, 95% CI 9.0−23.2, $p = 0.387$; Fig. S2 of the ESM).

In the patients treated with IO-TKI combinations, we registered one CR (1%), 65 PR (44%), 54 SD (36%), and 29 PD (19%), with on OCB of 81%. A significant difference was found between statin users and non-users (OCB = 90% vs 76%, $p = 0.046$), while no differences were reported with the other two concomitant medications (PPIs: OCB = 79% vs 83%, $p = 0.598$; metformin: OCB = 74% vs 82%, $p = 0.385$).

4 Discussion

Concomitant medications are known to potentially influence the outcomes of patients with cancer treated with immunotherapy or targeted therapy. The mechanisms underlying this evidence include drug–drug interactions, activity on gut microbiota, and alterations of drug pharmacokinetics [10, 19]. In this scenario, we investigated the impact of concomitant statins, PPIs, or metformin in patients with mRCC treated with first-line IO-IO or IO-TKI combinations. In our analysis, we showed that statin exposure was associated with longer OS and PFS and improved OCB, while PPIs and metformin did not affect the outcome in patients with mRCC. These results are in line with the results from the meta-analysis published by Luo et al. [20], in which statin intake was a predictor of OS in RCC, bladder cancer, and prostate cancer. Statin administration has shown antitumor activity in both in vitro and in vivo RCC models [21] and has been associated with increased OS in patients who underwent surgery for localized RCC [22–24]. Statin users showed better outcomes when treated with anti-vascular endothelial growth factor or mammalian target of rapamycin inhibitors for mRCC but not with interferon-α [25]. Furthermore, a pilot trial led by Manoukian et al. [26] designed to assess the efficacy and safety of combining a bisphosphonate and a statin in patients with RCC metastatic to bone observed treatment responses in 4 of the 11 patients enrolled, with the development of sclerosis in lytic bone lesions and improved deoxypyridinoline and N-telopeptide bone biomarkers. Moreover, our results are also in line with those recently published by our group on the positive impact of statin use in patients with mRCC treated with nivolumab [27].

Our study presents several limitations, mainly owing to its retrospective nature. First, we did not perform a centralized review of radiological imaging. Second, we did not have available data on both comorbidities and concomitant use of other medications that could influence the efficacy of first-line therapy. Furthermore, dose, type, and duration of concomitant statins, PPIs, or metformin as well as patients' cholesterol levels were not available at the time of the data analysis.

Nevertheless, our data clearly show that statin administration is associated with the outcome of patients with mRCC treated with first-line immune-oncology combinations. A better comprehension of this interaction and a prospective validation of these data are needed in order to optimize the outcome of these patients and guide clinicians' choices in daily clinical practice.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11523-022-00907-9.

Declarations

Funding No external funding was used in the preparation of this article.

Conflict of interest All the authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this article.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Data are available upon reasonable request.

Code availability Not applicable.

Author contributions Conception and design: MS, JMC, FM, CP; acquisition of data: MS, FM; analysis and interpretation of data: all authors; drafting of the manuscript: FM, MS; statistical analysis: MS; supervision: CM, NB.

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