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Original Research

Statin use improves the efficacy of nivolumab in patients with advanced renal cell carcinoma

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Abstract ***Background:*** Statins are widely used in an ageing population, including subjects with solid malignancies. However, no conclusive evidence is currently available on their potential influence on patients' outcome. We aimed to assess whether statin exposure affects the survival of patients with metastatic renal cell carcinoma (mRCC) treated with nivolumab.
Patients and methods: Medical records of patients with documented mRCC treated with second- or third-line nivolumab were reviewed at ten institutions from Italy, Spain and the USA. Patients were assessed for overall survival (OS), progression-free survival (PFS), and overall

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clinical benefit. Univariate and multivariate analyses were used to explore the association of variables of interest with survival.

Results: A total of 219 patients with mRCC receiving nivolumab between January 2016 and September 2021 were eligible for inclusion in this study; 59 (27%) were statin users. The median OS (34.4 versus 18.6 months, $p = 0.017$) and PFS (11.7 versus 4.6 months, $p = 0.013$) resulted apparently longer in statin users. Stratified by age, longer median OS and PFS were associated with statin exposure in both patients aged ≥70 y (median OS: 21.4 versus 10.1 months, $p = 0.047$; median PFS: 16.4 versus 4.6 months, $p = 0.022$) and <70 y (median OS: 34.4 versus 21.4 months, $p = 0.043$; median PFS: 10.3 versus 4.6 months, $p = 0.042$). Overall clinical benefit resulted higher in statin users than non-users (71% versus 54%, $p = 0.030$).

Conclusions: Our study suggests a prognostic impact of statin use in patients receiving nivolumab for mRCC.

1. Introduction

Renal cell carcinoma (RCC) is one of the most frequent urinary malignancies worldwide and it has been predicted that its incidence will increase in the coming years [1,2]. Metastasis and recurrence are important biological characteristics of this tumour and occur in about 30% of patients after curative treatment for the primary renal tumour [3]. With the development of targeted therapy and immunotherapy, a novel era has started, characterised by prolonged survival and maintained, or even improved, quality of life [4–12]. Nevertheless, still a not negligible rate of patients is a primary refractory to these therapeutic approaches, or develop resistance during therapy [4–12], highlighting the need for identifying potential factors associated with their prognosis, as well as their response to therapy.

The influence of concomitant medications has become a hot topic in patients treated by immunotherapy [13–15]. In particular, the use of broad-spectrum antibiotics has been demonstrated to have a negative predictive impact on patients with cancer receiving immune checkpoint inhibitors through the modulation of the gut microbiome [16].

Statins are commonly used for the prevention of cardiovascular events and their use is recommended in adults aged 40–75 years without a history of cardiovascular disease who have one or more risk factors, including dyslipidemia, diabetes, hypertension or smoking, and a calculated 10-year cardiovascular disease event risk ≥10% [17].

In the last years, a series of studies have focused on the potential role of statins in modulating the risk of developing RCC. Indeed, the use of statins has been correlated with a reduction of the risk of RCC in both sexes [18], independently from the presence of obesity and smoking attitude [19], although these results are still controversial [20–22]. Moreover, statin use has been correlated with improved OS in patients with localised RCC who underwent surgery [23,24] and resulted in a predictor of PFS and OS in surgically treated patients with RCC and with dyslipidemia [25,26].

In patients with metastatic RCC (mRCC), the use of statins has been shown to affect the outcome of patients receiving anti-vascular endothelial growth factor, or mammalian target of rapamycin inhibitors, but not Interferon-(IFN)-α [27]. However, a study by Fiala *et al.* [28] reported no differences in terms of oncological outcomes between statin users and non-users treated with first-line sunitinib or pazopanib.

Presently, data on the effect of concomitant statin administration in patients with mRCC treated with immunotherapy or immuno-combinations are still unclear. In this study, we retrospectively collected data from ten Institutions from Italy, Spain and the USA in order to assess the relationship between statin exposure and the efficacy of nivolumab in patients with pretreated mRCC.

2. Patients and methods

2.1. Study population

We retrospectively collected data from patients aged ≥18 years with a cytologically and/or histologically confirmed the diagnosis of mRCC treated with nivolumab monotherapy as second- or third-line therapy.

This international real-world study collected data from ten International Institutions from Italy, Spain and the USA involved in the treatment of patients with mRCC. Data collection lasted from 1st January 2016 to 30th September 2021. We retrospectively extracted data from paper and electronic charts, and for each patient, we collected, within a database from each Centre, data on histology, nephrectomy status, initial Eastern Cooperative Oncology Group performance status, International mRCC Database Consortium (IMDC) criteria, sites of metastases and statin exposure. Patients without

sufficient data on tumour assessment, statin exposure or response to therapy were excluded from our study.

Statin users were defined as those who had been prescribed continuous oral statin over a period of ≥30 days and were receiving concomitant statins at the time of Nivolumab initiation and during all the time of Nivolumab therapy. Nivolumab was administered intravenously at a dose of 240 mg every two weeks or 480 mg every four weeks, according to local practice. Treatment interruptions were carried out following standard guidelines according to type and severity of adverse events, especially immune-related ones. Treatment was continued till the evidence of clinical or radiological tumour progression on computed tomography or magnetic resonance imaging scans, unacceptable toxicities or death. Follow-up was commonly carried out by means of physical and laboratory tests every 4–6 weeks, while imaging was performed following standard local procedures every 8–12 weeks.

2.2. Study end-points

Disease status was evaluated using standard RECIST 1.1 criteria [29]. Overall Survival (OS) was defined as the time from the start of therapy to death from any cause, while 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 tumour progression or death or lost at follow-up at the time of the analysis were censored at the last follow-up visit. Data on tumour response (complete or partial responses, stable or progressive disease) were collected and analysed.

2.3. Statistical analysis

We used the Kaplan–Meier method with Rothman's 95% confidence intervals (CI) to estimate PFS and OS. Comparisons were carried out by using the log-rank test. Univariate and multivariate analyses were performed by Cox proportional hazards models. Variables of interest included age, gender, previous nephrectomy, histology, number of metastatic sites and time to metastatic disease, IMDC prognostic group and statin exposure. The chi-square test was used to compare categorical end-points. Significance levels were set at a 0.05 value, and all p values were two-sided. The MedCalc version 19.6.4 (MedCalc Software, Broekstraat 52, 9030 Mariakerke, Belgium) was used for the statistical analysis.

3. Results

3.1. Study population

Two hundred and nineteen consecutive patients were included in our analysis. The median follow-up time from was 25.7 months (95% CI 3.4–77.8). Eighty patients (37%) were aged ≥70 y; 151 patients (69%) were males. Tumour histology was predominantly clear cell (183, 84%); in the 36 non-clear cell RCC patients, histology showed a papillary type I or II RCC in 35 cases, and chromophobe RCC in the remaining case.

Number of metastatic sites was ≥2 in 113 patients (52%). Lung (54%), lymph nodes (48%) and bone (31%) were the most common sites of metastasis. Stratifying by IMDC criteria, 41 patients (19%) were at favourable-risk, 136 (62%) patients were at intermediate-risk and 42 (19%) patients were at poor-risk. One hundred and thirty-two patients (60%) received sunitinib as first-line therapy. Nivolumab was administered as second- and third-line therapy in 156 (71%) and 63 (29%) patients, respectively.

Fifty-nine patients (27%) were statin users and 160 (73%) were non-users. Patients' characteristics are summarised in Table 1. No significant differences were found in terms of clinico-pathological features between statin users and non-users, except for the rate of patients aged ≥70 y, which (as expected) resulted significantly higher in statin users (49% versus 32%, $p = 0.019$, Table 1).

3.2. Survival analysis

In the overall study population, the median OS and PFS were 20.8 months (95% CI 15.8–26.0) and 5.8 months (95% CI 4.6–8.6), respectively (Fig. 1). The median OS and PFS were apparently longer in statin users than non-users, 34.4 versus 18.6 months ($p = 0.017$) and 11.7 versus 4.6 months ($p = 0.013$), respectively (Fig. 2). Basing on the statistically significant imbalance of patients aged ≥70 y in the group of statin users (Table 1), we stratified the study population by age, with the aim to assess the prognostic role of statin exposure in both older and younger patients. In accordance with the overall study population, longer median OS and PFS were statistically associated with statin exposure in both patients aged ≥70 y (median OS: 21.4 versus 10.1 months, $p = 0.047$; median PFS: 16.4 versus 4.6 months, $p = 0.022$) and <70 y (median OS: 34.4 versus 21.4 months, $p = 0.043$; median PFS: 10.3 versus 4.6 months, $p = 0.042$) (see Fig. 3).

In the overall study population, longer PFS was observed in patients with clear cell histology (7.1 versus 4.6 months, $p = 0.015$) and with metachronous mRCC (7.6 versus 4.1 months, $p = 0.006$). In terms of OS, a significant difference was found between patients with metachronous and synchronous mRCC (26.8 versus 13.0 months, $p = 0.001$) and among IMDC prognostic groups. Indeed, patients with good, intermediate and poor risk criteria showed a median OS of 36.3, 18.6 and 11.7 months, respectively ($p = 0.047$).

At univariate analysis, non-clear cell histology (HR = 1.60; 95% CI: 1.09–2.35, $p = 0.016$) and

Table 1
Patients' characteristics. Statistically significant values were reported in bold. IMDC = International mRCC Database Consortium; RCC = Renal Cell Carcinoma.

Patients	Overall 219 (%)	Statin users 59 (%)	Statin non-users 160 (%)	*p*
Gender				
Male	151 (69)	43 (73)	108 (68)	0.446
Female	68 (31)	16 (27)	52 (32)	
Age, years (y)				
≥70 y	80 (37%)	29 (49%)	51 (32%)	**0.019**
Synchronous metastatic RCC	135 (62)	33 (56)	102 (64)	0.292
Previous nephrectomy	171 (78)	48 (81)	123 (77)	0.478
Clear cell histology	183 (84)	51 (86)	132 (83)	0.486
IMDC risk stratification				
Favourable risk	41 (19)	12 (20)	29 (18)	0.710
Intermediate risk	136 (62)	37 (63)	99 (62)	0.910
Poor risk	42 (19)	10 (17)	32 (20)	0.612
Common sites of metastasis				
Lung	119 (54)	29 (49)	90 (56)	0.351
Lymph nodes	105 (48)	26 (44)	79 (49)	0.487
Bone	68 (31)	14 (24)	54 (34)	0.156
Liver	38 (17)	7 (12)	31 (19)	0.194
Brain	9 (4)	1 (2)	8 (5)	0.275
≥2 Metastatic sites	113 (52)	29 (49)	84 (53)	0.661
First-line therapy				
Sunitinib	132 (60)	33 (55)	99 (62)	0.426
Pazopanib	64 (29)	18 (31)	46 (29)	0.800
Other	23 (11)	8 (14)	15 (9)	0.372
Second-line therapy				
Nivolumab	156 (71)	41 (69)	115 (72)	0.703
Cabozantinib	25 (11)	8 (14)	17 (10)	0.546
Axitinib	15 (7)	4 (7)	11 (7)	0.980
Everolimus	13 (6)	2 (3)	11 (7)	0.334
Other	10 (5)	4 (7)	6 (4)	0.342
Third-line therapy				
Nivolumab	63 (29)	18 (31)	45 (28)	0.730
Cabozantinib	47 (21)	14 (24)	33 (21)	0.620
Other	17 (8)	4 (7)	13 (8)	0.742

synchronous metastatic disease (HR = 1.54; 95% CI: 1.13–2.11, $p = 0.006$) were significant predictors of worst PFS, while statin use (HR = 0.55; 95% CI: 0.38–0.80, $p = 0.002$) was associated with longer PFS. At multivariate analysis, synchronous metastatic disease and, again, statin exposure proved to be significantly associated with PFS (Table 2).

As for OS, synchronous metastatic disease (HR = 1.85; 95% CI: 1.28–2.69, $p = 0.001$), IMDC prognostic group (HR = 1.44; 95% CI: 1.08–1.92,

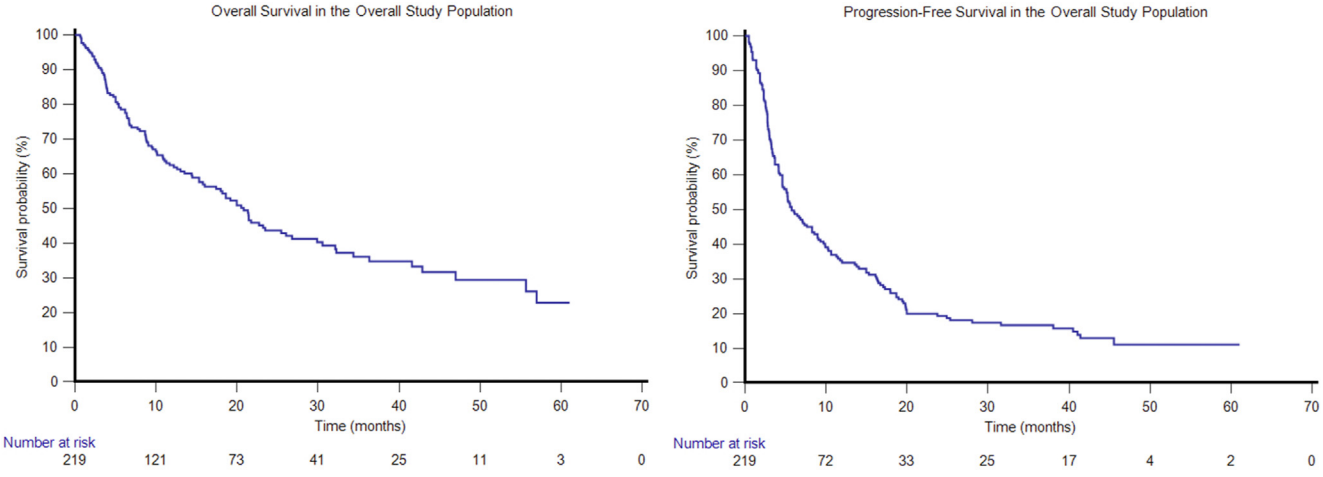

Fig. 1. Median overall survival and progression-free survival in patients with metastatic renal cell carcinoma treated with nivolumab.

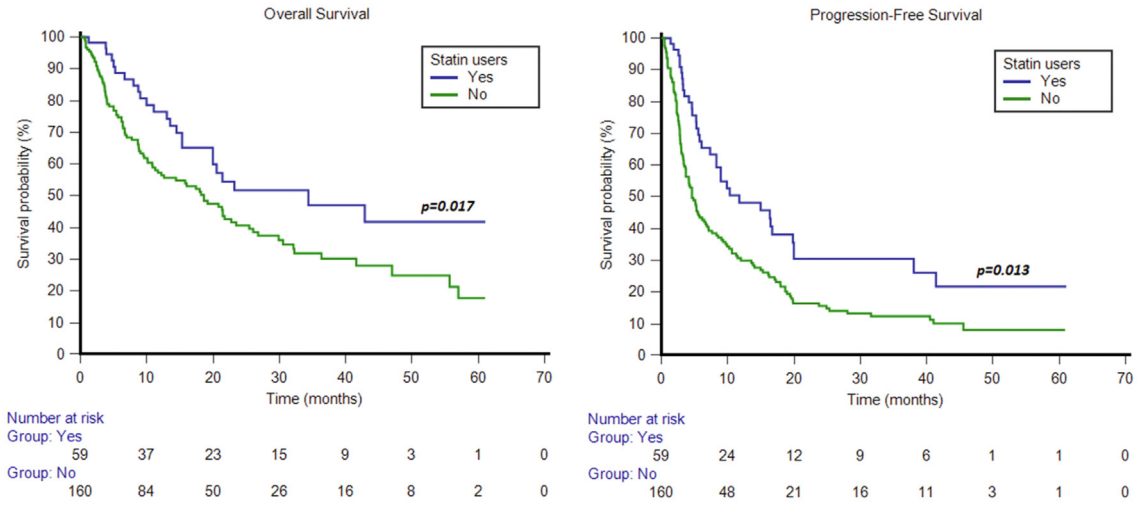

Fig. 2. Median overall survival and progression-free survival in patients with metastatic renal cell carcinoma treated with nivolumab stratified by statin exposure.

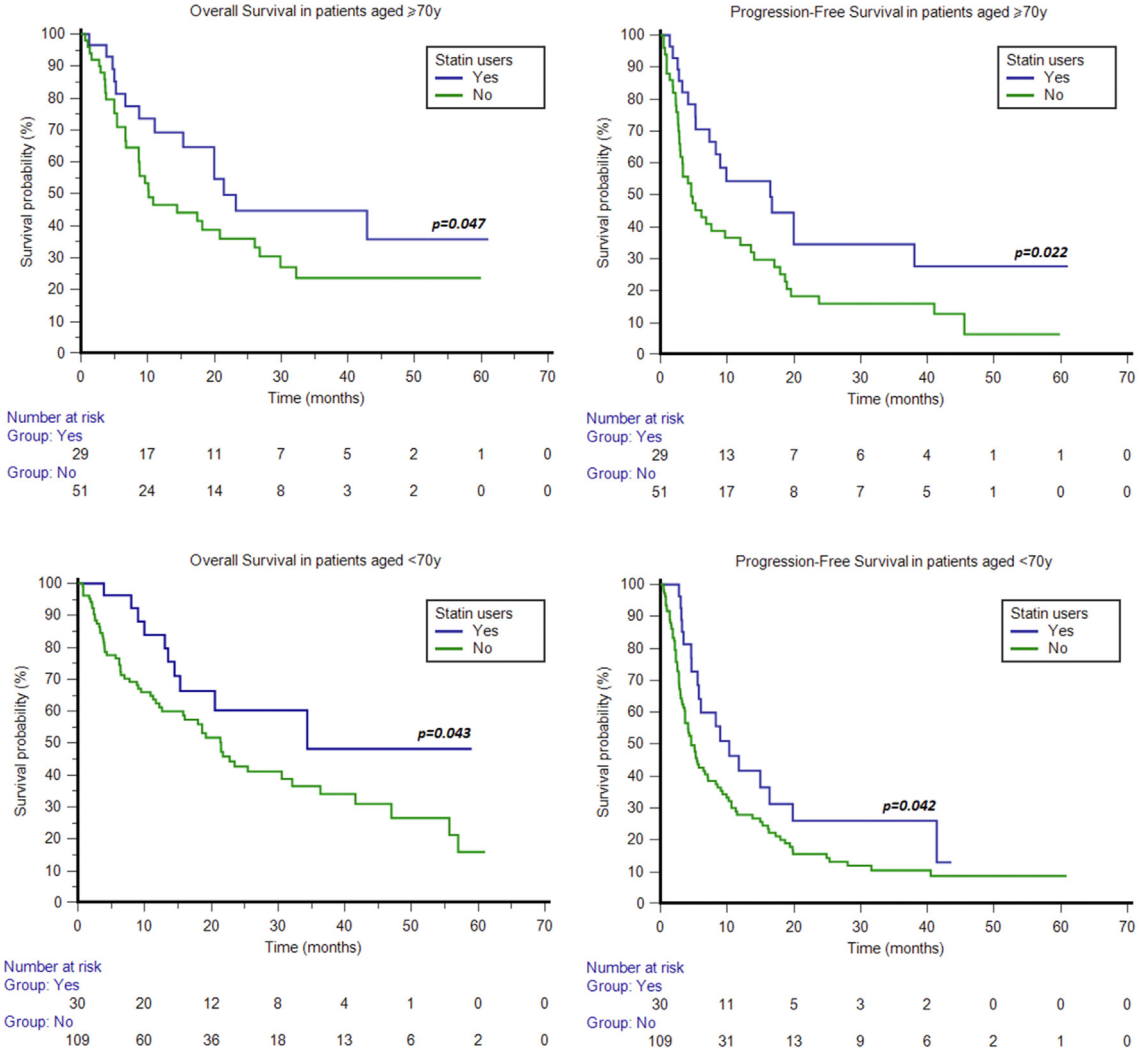

Fig. 3. Median overall survival and progression-free survival in patients with metastatic renal cell carcinoma treated with nivolumab stratified by age and statin exposure.

Table 2
Univariate and multivariate analyses of predictors of progression-free survival and overall survival in metastatic renal cell carcinoma patients treated with nivolumab. Statistically significant values were reported in bold.

PFS	Univariate Cox Regression		Multivariate Cox regression	
	HR (95% CI)	*p-value*	HR (95% CI)	*p-value*
Age (≥70 y vs <70 y)	0.81 (0.59–1.11)	0.201		
Gender (M/F)	0.99 (0.71–1.38)	0.962		
Previous nephrectomy	1.15 (0.85–1.57)	0.369		
Histology (nccRCC vs ccRCC)	1.60 (1.09–2.35)	**0.016**	1.44 (0.98–2.11)	0.065
Synchronous metastatic RCC	1.54 (1.13–2.11)	**0.006**	1.55 (1.13–2.12)	**0.006**
Number of metastatic sites	1.10 (0.81–1.49)	0.556		
IMDC prognostic group	1.14 (0.89–1.46)	0.285		
Statin users (Y vs N)	0.55 (0.38–0.80)	**0.002**	0.56 (0.38–0.81)	**0.002**
OS	Univariate Cox Regression		Multivariate Cox regression	
	HR (95% CI)	*p-value*	HR (95% CI)	*p-value*
Age (≥70 y vs <70 y)	1.21 (0.84–1.76)	0.306		
Gender (M/F)	1.03 (0.70–1.52)	0.888		
Previous nephrectomy	1.34 (0.91–1.95)	0.136		
Histology (nccRCC vs ccRCC)	1.48 (0.96–2.30)	0.078		
Synchronous metastatic RCC	1.85 (1.28–2.69)	**0.001**	1.73 (1.18–2.54)	**0.005**
Number of metastatic sites	0.96 (0.67–1.39)	0.832		
IMDC prognostic group	1.44 (1.08–1.92)	**0.014**	1.24 (0.92–1.69)	0.158
Statin users (Y vs N)	0.58 (0.37–0.91)	**0.019**	0.62 (0.39–0.98)	**0.042**

ccRCC = clear cell Renal Cell Carcinoma; CI = confidence interval; HR = hazard ratio; mRCC = metastatic Renal Cell Carcinoma; nccRCC = non-clear cell Renal Cell Carcinoma; OS = overall survival; PFS = progression-free survival.

$p = 0.014$) and statin use (HR = 0.58; 95% CI: 0.37–0.91, $p = 0.019$) were significantly associated with OS. As for PFS, at multivariate analysis, synchronous metastatic disease and statin exposure were significantly associated with improved OS (Table 2).

3.3. Response to therapy

At the time of data cut-off, nivolumab was ongoing in 41 patients (19%), while 129 patients (59%) were died. Of all the patients treated with nivolumab in second-line, 64 (29%) patients received third line therapies, as reported in Table 1.

In the overall study population, nivolumab was associated with partial responses in 53 patients (27%), stable disease in 62 patients (31%), and progressive disease in 82 patients (42%). In the statin user group, 15 partial responses (29%), 22 stable diseases (42%) and 15 progressive diseases (29%) were observed in nivolumab-treated patients, leading to an OCB of 71% (Table 3). Among statin non-users, nivolumab yielded 38 partial responses (26%), 40 stable diseases (28%) and 67 progressive diseases (46%), leading to an OCB of 54%. The difference in terms of OCB between statin users and non-users resulted statistically significant ($p = 0.030$).

4. Discussion

Statins are well-known cholesterol-depleting agents. Their extensive use for the prevention of cardiovascular events in a wide population of subjects, especially the elderly, suggest the need for investigating their potential effects in modulating the risk of developing a series of diseases, including cancer, and the interactions between these drugs and concomitant therapies. From these considerations, we aimed to assess the effects of statin exposure on the efficacy of nivolumab, administered as second- or third-line therapy in a retrospective study cohort of 219 patients with mRCC. We found that the median OS and PFS were apparently improved in statin users.

Taking into account the presence of a higher rate of elderly patients in the statin user group, we stratified patients by age, observing a survival advantage in both patients aged ≥70 y and <70 y. Furthermore, the positive prognostic role of statin exposure was confirmed at

Table 3
Overall clinical benefit in metastatic renal cell carcinoma patients treated with nivolumab according to statin exposure. Statistically significant values were reported in bold.

Tumour response according to RECIST 1.1 criteria	Overall 197 (%)	Statin users 52 (%)	Statin non-users 145 (%)	*p*
Complete/Partial responses (CR/PR)	53 (27)	15 (29)	38 (26)	–
Stable diseases (SD)	62 (31)	22 (42)	40 (28)	
Progressive diseases (PD)	82 (42)	15 (29)	67 (46)	
Overall Clinical Benefit (CR + PR + SD)	115 (58)	37 (71)	78 (54)	**0.030**

multivariate analyses for both OS and PFS. Notably, improved OCB (+17%) was reported in patients receiving nivolumab and concomitant statins.

Since the early 1990s, it has been evident that statins could play some role in treating patients with solid tumours [30], but the exact mechanisms of statin activity have not been completely elucidated so far. Statin exert a series of activities that modulate cancer cell metabolism. In particular, statins have been shown to (1) inhibit the cell cycle by modulating the expression and activity of cyclins, cyclin-dependent kinases, and/or inhibitors of cyclin-dependent kinases, (2) induce both intrinsic and extrinsic pathways of cancer cell apoptosis, (3) destabilise the tumour (or leukaemic) cell membrane by inhibiting the synthesis of the lipid bilayer of cell membranes from cholesterol, and (4) change the arrangement of the anion exchanger Organic Anion Transporting Polypeptide 1, the localisation of 3-hydroxy-3-methylglutaryl-CoA reductase and (5) induce conformational changes in glucose transporters [30]. Statins have demonstrated antitumour effects in both *in vitro* and *in vivo* models of RCC [31,32]. In particular, it has been shown that statins inhibit the phosphorylation of AKT, mammalian target of rapamycinc and ERK in a time- and dose-dependent manner and suppress interleukin (IL)-6-induced the phosphorylation of JAK2 and STAT3 [33], which are essentials for RCC cell metabolism, growth and survival [34,35]. Moreover, statins modulate the immune response at different levels, including T-cell signalling, antigen presentation, immune cell migration and cytokine production [36].

Our study presents several limitations, mainly due to its retrospective nature. Furthermore, we did not perform a centralised review of radiological imaging, did have neither available data on the concomitant use of medications beyond statins that could influence the efficacy of nivolumab therapy nor available data on the type of statin and duration of exposure, which may influence the interaction between these drugs and nivolumab activity. Finally, the sample size could have played a role in determining the OS difference between some treatments, and a relatively high number of censored events was observed in some groups.

As a consequence of all the above, our findings should be interpreted with caution and are in need of a larger prospective validation.

Nevertheless, our data suggest that statin exposure is apparently associated with better outcomes in patients with mRCC receiving nivolumab. Prospective clinical trials investigating the role of statins in patients with mRCC treated by immunotherapy or immuno-oncology combinations are thus needed.

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Author contributions

- **Conceptualisation**: Matteo Santoni.
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- **Supervision**: Camillo Porta, Nicola Battelli.
- **Writing - original draft**: Matteo Santoni, Francesco Massari, Gaetano Aurilio.
- **Writing - review & editing**: Camillo Porta.

Conflict of interest statement

The authors declare to have no conflicts of interest.

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