Body mass index in patients treated with cabozantinib for

advanced Renal Cell Carcinoma: a new prognostic factor?

**Matteo Santoni1\*, Francesco Massari2, Sergio Bracarda3, Giuseppe Procopio4, Michele Milella5, Ugo De Giorgi6, Umberto Basso7,Gaetano Aurilio**8**, Lorena Incorvaia9, Angelo Martignetti10, Mimma Rizzo11, Giacomo Cartenì12, Enrique Grande13, Marc R Matrana14, Simon J Crabb15, Nuno Vau16, Giulia Sorgentoni1, Alessia Cimadamore17, Rodolfo Montironi17, Nicola Battelli1**

|  |
| --- |
|  |

1. Oncology Unit, Macerata Hospital, via Santa Lucia 2, 62100, Macerata, Italy; [mattymo@alice.it](mailto:mattymo@alice.it) (MS); [giulia.sorgentoni@libero.it](mailto:giulia.sorgentoni@libero.it) (GS); [nicola.battelli@sanita.marche.it](mailto:nicola.battelli@sanita.marche.it)(NB)
2. Oncologia Medica, Azienda Ospedaliero-Universitaria di Bologna, Via Albertoni - 15, Bologna – Italia;[fmassari79@gmail.com](mailto:fmassari79@gmail.com)(FM)
3. Medical and Translational Oncology Unit, Department of Oncology, AziendaOspedaliera Santa Maria, Terni, Italy;[sergio.bracarda@gmail.com](mailto:sergio.bracarda@gmail.com)(SG)
4. Department of Medical Oncology, IstitutoNazionaledeiTumori IRCCS, Milan, Italy;[giuseppe.procopio@istitutotumori.mi.it](mailto:giuseppe.procopio@istitutotumori.mi.it)(GP)
5. U.O.C. Oncology, Azienda Ospedaliera Universitaria Integrata, University and Hospital Trust of Verona, Verona, Italy; [michele.milella@univr.it](mailto:michele.milella@univr.it)(MM)
6. Department of Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy; [ugo\_degiorgi@yahoo.com](mailto:ugo_degiorgi@yahoo.com)(UDG)
7. Department of Medical Oncology, IstitutoOncologico Veneto (IOV) IRCCS, Padova, Italy; [umberto.basso@iov.veneto.it](mailto:umberto.basso@iov.veneto.it)(UB)
8. Medical Oncology Division of Urogenital and Head and Neck Tumours, IEO, European Institute of Oncology IRCCS, Milan, Italy; [gaetano.aurilio@ieo.it](mailto:gaetano.aurilio@ieo.it)(GA)
9. Department of Surgical, Oncological and Oral Sciences, Section of Medical Oncology, University of Palermo, Palermo, Italy; [lorena.incorvaia@unipa.it](mailto:lorena.incorvaia@unipa.it)(LI)
10. Dipartimento oncologico usl sud-est toscana-area senese, Località Campostaggia s.n.c. 53036 Poggibonsi, Italy; [angelo.martignetti@uslsudest.toscana.it](mailto:angelo.martignetti@uslsudest.toscana.it)(AM)
11. Medical Oncology, I.R.C.C.S. San Matteo University Hospital Foundation, Pavia, Italy; [rizzo.mimma@gmail.com](mailto:rizzo.mimma@gmail.com)(MR)
12. Department of Medical Oncology, AO "A. Cardarelli," Naples, Italy;[cartenigiacomo@gmail.com](mailto:cartenigiacomo@gmail.com)(GC)
13. Department of Medical Oncology, MD Anderson Cancer Center, Madrid, Spain;[egrande@mdanderson.es](mailto:egrande@mdanderson.es)(EG)
14. Department of Internal Medicine, Hematology/Oncology, Ochsner Medical Center, New Orleans, LA, United States;[mamatrana@ochsner.org](mailto:mamatrana@ochsner.org)(MRM)
15. Southampton Clinical Trials Unit, University of Southampton, Southampton, United Kingdom;[S.J.Crabb@southampton.ac.uk](mailto:S.J.Crabb@southampton.ac.uk)(SJC)
16. Urologic Oncology, Champalimaud Clinical Center, Lisbon, Portugal;[nuno.vau@fundacaochampalimaud.pt](mailto:nuno.vau@fundacaochampalimaud.pt)(NV)
17. Section of Pathological Anatomy, Polytechnic University of the Marche Region, School of Medicine, United Hospitals, Ancona, Italy; [a.cimadamore@staff.univpm.it](mailto:a.cimadamore@staff.univpm.it)(AC); [r.montironi@staff.univpm.it](mailto:r.montironi@staff.univpm.it)(RM)

\* Correspondence: Matteo Santoni, MD, Phone number: +3907332572553; e-mail: [mattymo@alice.it](mailto:mattymo@alice.it)

**Abstract:** We analyzed the clinical and pathological features of RCC patients treated with cabozantinib stratified by Body Mass Index (BMI). We retrospectively collected data from 16 worldwide centers involved in the treatment of RCC. Overall survival (OS) and progression-free survival (PFS) were analyzed using Kaplan-Meier curves. Cox proportional models were used at univariate and multivariate analyses. We collected data from 224 patients with advanced RCC receiving Cabozantinib as second (113, 5%) or third-line (111, 5%) therapy. The median PFS was significantly higher in patients with BMI ≥ 25 (9.9 vs 7.6 months, p <0.001). The median OS resulted higher in the BMI ≥ 25 subgroup (30.7 vs 11.0 months, p=0.003). As third-line therapy, both median PFS (9.2 months, vs 3.9 months, p = 0.029) and OS (39.4 vs 11.5 months, p = 0.039) were longer in patients with BMI ≥ 25. BMI was a significant predictor for both PFS and OS at multivariate analysis. We showed that a BMI ≥ 25 correlates with longer survival in patients receiving cabozantinib. BMI can be easily carried out and should be included into current prognostic criteria for advanced RCC.

**Keywords:** Body Mass Index; Cabozantinib; Obesity; Prognosis; Real-world data; Renal Cell Carcinoma; Targeted therapy;

1. Introduction

The American Cancer Society has estimated a total of 73,750 new cases of kidney tumours (45,520 men and 28,230 women) in 2020 in the United States,with more than 14000 cancer-related deaths [1]. Recently, we reported the results of an Artificial Neural Networks (ANN) model to predict the incidence of Renal Cell Carcinoma (RCC) in the United States for the future decades [2]. We showed that RCC incidence will increase in the next years, thus supporting the necessity of more accurate studies on the prevention of RCC-related risk factors in order to reduce future tumour burden [2].

Beyond its well known role as a risk factor for the development of RCC, obesity is emerging also as a potential key factor for response to therapy [3]. A growing body of evidences suggests that being overweight and obesity are associated with better outcome in cancer patients treated with immunotherapy [4,5]. At this regard, Sanchez et al. investigated the angiogenic and immunologic transcriptomic profiles of the primary tumor and perinephric adipose tissue in normal weight and obese RCC patients. They reported that tumours from obese patients were enriched in the expression of Vascular Endothelial Growth Factor (VEGF) and related proteins. Moreover, a higher proportion of plasmacytoid dendritic cells (pDCs) and mast cells and a lower proportion of innate lymphoid cells (NK\_CD56bright\_cells) were observed in obese RCC patients [6]. In this context, leptin levels in obese subjects have been correlated to higher T cell Programmed Death (PD)-1 expression and improved response to anti-PD-1 therapy [7,8].

Cabozantinib is an orally administered tyrosine kinase inhibitor (TKI) acting mainly on VEGFR2(VEGF receptor 2), MET (mesenchymal epithelial transition receptor) and AXL (anexelekto pathway) [9]. Currently, cabozantinib is approved for the treatment of patients with metastatic RCC in treatment-naïve adults with intermediate or poor-risk features and for adults progressed to prior vascular endothelial growth factor/receptor inhibitors. In 2019, we reported the results of an international retrospective real-world analysis on cabozantinib in previously treated patients with metastatic RCC, aimed at investigating the presence of prognostic factors in this context [10]. We observed that both haemoglobin (Hb) levels and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic modelswere associated with the outcome of patients receiving cabozantinib [10]. Furthermore, the median Time to Strategy Failure (TTSF) was 11.57 months with the sequence cabozantinib–nivolumab and 25.64 months with nivolumab–cabozantinib [10].

On this latter scenario, may we classify being overweight and obesity as eventual predictive factors of tumour response to immunotherapy in metastatic RCC? Hence, as a consequence, can we base our choice between Cabozantinib and Nivolumab as second or third-line therapy on patient weight or Body Mass Index (BMI)? To answer this question, we performed an international multicentre retrospective study to investigate BMI as a potential predictive factor of response in patients with advanced RCC receiving Cabozantinib as second or third-line therapy in respect mainly to nivolumab.

2. Materials and Methods

*2.1 Study population*

We analyzed data from adult patients (aged 18 years and above) with a histologically confirmed diagnosis of RCC and histologically or radiologically confirmed metastatic disease treated with cabozantinib as second or third-line therapy. Stage and grade were assigned by the local pathologist according to the American Joint Committee on Cancer (AJCC) TNM system and to the ISUP/WHO grading system, respectively [11-12].

Standard biopsy procedures were followed according to the international EAU guidelines [13]. This international multi-center retrospective study included data from sixteen Institutions between 1st January, 2008 and 1st October, 2019. Data were retrospectively collected from paper and electronic charts. Patients were excluded from this study if they had missing data regarding the site of metastasis and response to therapy.

*2.2 Treatment Regimens and Statistical Analysis*

Cabozantinib was administered orally, mainly with a starting dose of 60 mg once daily. In patients with comorbidities, cabozantinib was initiated at a reduced dose of 40 mg once daily. Dose reductions and treatment interruptions were performed depending on type and severity of adverse events according to standard guidelines. Treatment with cabozantinib was continued till the evidence of disease progression on computed tomography (CT) or magnetic resonance imaging (MRI) scans, unacceptable toxicity, or death. Follow-up commonly consisted of regular physical and laboratory assessment every 4–6 weeks. Imaging was carried out according to local procedures every 8–12 weeks.

Body mass index (BMI) was defined as weight expressed in kilograms divided by the square of the height in meters. Progressive disease was defined as a ≥ 20% increase in the sum of diameters of target lesions or by the appearance of one or more new lesions according to the Response evaluation criteria in solid tumors (RECIST) 1.1 criteria [11]. Progression free survival (PFS) was defined as the time from the start of cabozantinib therapy to progression or to death from any cause. Patients without tumor progression or death at the time of the data cutoff were censored at their last follow-up date. Overall Survival (OS) was defined as the time from the start of treatment to death from any cause. Patients alive or lost to follow-up were censored.

PFS and OS were estimated using Kaplan-Meier method with Rothman’s 95% confidence intervals (CI) and compared across the groups using the log-rank test.

Cox proportional hazards models were used to investigate patients’ characteristics predictors of survival univariate and multivariate analyses. Chi-square test was used to compare categorical end-points. All the significance levels were set at a 0.05 value and all p values were two-sided. The statistical analysis was performed by MedCalc version 11.4.4.0 (MedCalc Software, Broekstraat 52, 9030Mariakerke, Belgium). This project was performed in accordance with the approval by the Ethical Committee of our Institutions.

3. Results

*3.1 Study population*

We retrospectively collected data from 224 patients with advanced RCC receiving Cabozantinib as second (113, 5%) or third-line (111, 5%) therapy. The median age was 63y (range 25−86). One hundred and sixty of them were males (71%). Tumour histology was predominantly clear cell (193, 9%); 51% of patients were metastatic at RCC diagnosis. Number of metastatic sites was ≥ 2 in 135 patients (60%). Lung (65%), lymph nodes (51%) and bone (28%) were the most common metastatic sites. According to IMDC criteria, 50 patients (22%) were at favourable-risk, 134 (60%) at intermediate-risk and 40 (18%) had poor-risk features. The complete list of patients’ characteristics is reported in Table 1.

**Table 1.** Patient demographic and disease characteristics.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Patients | Overall  224 (%) | BMI ≥ 25  119 (%) | BMI < 25  105 (%) | *p* |
| **Gender**  Male  Female | 160 (71)  64 (29) | 87 (73)  32 (27) | 73 (70)  32 (30) | 0.657 |
| **Age, years (y)**  Range | 63  25 − 86 | 63  31 − 86 | 63  25 − 85 | - |
| **Karnofsky performance status**  Score > 70 | 211 (94) | 114 (96) | 97 (92) | 0.421 |
| **Metastatic at diagnosis** | 114 (51) | 57 (48) | 57 (54) | 0.412 |
| **Past nephrectomy** | 173 (77) | 92 (77) | 81 (77) | 0.897 |
| **Clear cell histology** | 193 (86) | 99 (83) | 94 (90) | 0.240 |
| **IMDC risk stratification**  Favorable risk  Intermediate risk  Poor risk | 50 (22)  134 (60)  40 (18) | 29 (24)  65 (55)  25 (21) | 21 (20)  69 (66)  15 (14) | 0.219 |
| **Common sites of metastasis**  Lung  Lymph nodes  Bone  Liver  Brain | 145 (65)  115 (51)  63 (28)  42 (19)  17 (8) | 77 (65)  63 (53)  34 (29)  15 (13)  7 (6%) | 68 (65)  52 (50)  29 (28)  20 (19)  10 (10) | 0.896  0.706  0.993  0.254  0.439 |
| **≥ 2Metastatic sites** | 135 (60) | 69 (58) | 66 (63) | 0.458 |

The median BMI was 26 (range 18−36). BMI was ≥ 25 in 119 patients (53%), where15 patients (13%) had a BMI ≥ 30. Among the 105 patients with BMI < 25, 17 (16%) had a BMI ≤ 20. As reported in Table 1, no statistically significant differences in terms of demographic and disease characteristics were found between patients with BMI ≥ 25 and < 25.

*3.2 Response to therapy and Survival analysis*

The median follow-up time from diagnosis was 182.79 months (95% CI 131.00 to not reached; NR). During the follow-up, 78 patients (35%) died. First-line therapy was sunitinib in 121 patients (54%), pazopanib in 73 (33%) and immunocombinations in 9 (4%). A total of 113 patients (50%) were treated with cabozantinib as second-line therapy, while 111 (50%) received cabozantinib in the third-line setting. In 21 patients (19%), second-line cabozantinib was ongoing at the time of data analysis. Among the 92 patients progressed on second-line cabozantinib, 51 (55%) received a third-line therapy, which was nivolumab in 36 patients. Drug distribution is reported in Table 2.

**Table 2**. Drug distribution and response to cabozantinib. In bold statistically significant values.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Patients | Overall  224 (%) | BMI ≥ 25  119 (%) | BMI < 25  105 (%) | *p* |
| **First-line therapy**  Sunitinib  Pazopanib  Immunocombinations  Other | 121 (54)  73 (33)  9 (4)  21 (9) | 64 (54)  38 (32)  5 (4)  12 (10) | 57 (54)  35 (33)  4 (4)  9 (9) | 0.979 |
| **Second-line therapy**  Cabozantinib  Nivolumab  Other | 113 (50)  89 (40)  22 (10) | 62 (52)  46 (39)  11 (9) | 51 (49)  43 (41)  11 (10) | 0.862 |
| **Third-line therapy**  Cabozantinib  Nivolumab  Other | 111 (50)  36 (16)  15 (7) | 57 (48)  19 (16)  8 (7) | 54 (51)  17 (16)  7 (6) | 0.982 |
| **Response to 2nd-line cabozantinib**  CR/PR  SD  PD | 31 (27)  54 (48)  28 (25) | 18 (15)  29 (26)  15 (13) | 13 (12)  25 (22)  13 (12) | 0.916 |
| **Response to 3rd-line cabozantinib**  CR/PR  SD  PD | 32 (29)  37 (33)  42 (38) | 18 (16)  14 (13)  25 (17) | 14 (13)  23 (20)  17 (21) | 0.127 |
| **1y-OS (second-line cabozantinib)** | 73 (65) | 47 (76) | 27 (53) | **0.019** |
| **1y-OS (third-line cabozantinib)** | 22 (20) | 16 (28) | 6 (11) | **0.045** |

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease

The median PFS of cabozantinib as second-line therapy was 7.8 months (95%CI: 7.6−9.9) in the overall study population. The median PFS was significantly higher in patients with BMI ≥ 25 (9.9 months, 95%CI: 7.9−19.1, vs 7.6 months, 95%CI: 5.9−12.3, p <0.001, Figure 1).



**Figure 1.** Progression-Free Survival of patients receiving cabozantinib as second-line therapy stratified by Body Mass Index.

The median OS was 12.5 months (95% CI: 11.1−30.7) in all patients and resulted higher in the BMI ≥ 25 subgroup (30.7 months, 95%CI: 11.6−44.8, vs 11.0 months, 95%CI: 9.7−11.2, p=0.003, Figure 2).



**Figure 2.** Overall Survival of patients receiving cabozantinib as second-line therapy stratified by Body Mass Index.

In terms of 1y-OS rate, 76% of patients with BMI ≥ 25 were alive at 1 year, compared to 53% of BMI < 25 (p = 0.019, Table 2). No significant differences were found concerning tumour response to cabozantinib as a second-line option (Table 3).

**Table 3**. Univariate and multivariate analyses of predictors of Progression-Free Survival and Overall Survival in patients treated with cabozantinib as second-line therapy.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| PFS |  | Univariate Cox Regression | |  | Multivariable Cox regression | |
|  | **HR (95%CI)** | ***p-value*** |  | **HR (95%CI)** | ***p-value*** |
| Age (≥70y vs <70y) |  | 1.31 (0.78−2.21) | 0.306 |  |  |  |
| Gender (M/F) |  | 1.17 (0.69−2.00) | 0.563 |  |  |  |
| Number of metastatic sites | 0.99 (0.78−1.27) | 0.930 |  |  |
| Lung metastases | 0.86 (0.59−1.47) | 0.783 |  |  |
| Liver metastases | 1.42 (0.77−2.51) | 0.459 |  |  |
| Bone metastases | 1.99 (1.08−3.18) | 0.112 |  |  |
| IMDC prognostic group | 2.08 (1.26−3.44) | **0.004** | 2.09 (1.29−3.37) | **0.003** |
| BMI (≥25 vs <25) | 0.90 (0.84−0.97) | **0.005** | 0.37 (0.20−0.68) | **0.002** |
|  |  |  |  |  |
| **OS** |  | **Univariate Cox Regression** | |  | **Multivariable Cox regression** | |
|  | **HR (95%CI)** | ***p-value*** |  | **HR (95%CI)** | ***p-value*** |
| Age (≥70y vs <70y) |  | 0.78 (0.41−1.49) | 0.459 |  |  |  |
| Gender (M/F) |  | 1.46 (0.80−2.67) | 0.219 |  |  |  |
| Number of metastatic sites |  | 1.08 (0.81−1.44) | 0.613 |  |  |  |
| Lung metastases | 0.82 (0.51−1.33) | 0.424 |  |  |
| Liver metastases | 1.39 (0.80−2.39) | 0.244 |  |  |
| Bone metastases | 2.11 (1.32−3.40 | 0.051 |  |  |
| IMDC prognostic group | 1.85 (1.02−3.34) | **0.042** | 2.09 (1.29−3.37) | **0.003** |
| BMI (≥25 vs <25) | 0.90 (0.83−0.98) | **0.018** | 0.38 (0.22−0.69) | **0.046** |
|  |  |  |  |  |
| BMI = Body Mass Index;CI=confidence interval; HR=hazard ratio; OS=overall survival;PFS= progression-free survival. | | | | | | |

At multivariate analysis, IMDC prognostic group (HR = 2.09; 95%CI: 1.29–3.37, p = 0.003) and BMI (HR = 0.37; 95%CI: 0.20–0.68 p = 0.002) were significant predictors of PFS. Similarly, IMDC prognostic group (HR = 2.09; 95% CI, 1.29–3.37, p = 0.003) and BMI (HR = 0.38; 95%CI: 0.22–0.69, p = 0.046) were significantly correlated with OS at multivariate analysis.

As third-line therapy, we registered median PFS and OS of 6.7 (95% CI: 4.9−18.0) and 39.4 months (95%CI: 11.2–39.4), respectively. Both median PFS (9.2 months, 95%CI: 4.8–16.3, vs 3.9 months, 95%CI: 3.0–18.0, p = 0.029, Figure 3) and OS (39.4 months, 95%CI: 11.2–39.4, vs 11.5 months, 95%CI: 4.9–11.5, p = 0.039, Figure 4) were longer in patients with BMI ≥ 25. 1y-OS rate was 28% and 11% in patients with BMI ≥ 25 vs <25, respectively (p = 0.045, Table 4). Similarly to second-line, no differences were reported in terms of tumour response to third-line cabozantinib (Table 4).

**Table 4.** Univariate and multivariate analyses of predictors of Progression-Free Survival and Overall Survival in patients treated with cabozantinib as third-line therapy.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| PFS |  | Univariate Cox Regression | |  | Multivariable Cox regression | |
|  | **HR (95%CI)** | ***p-value*** |  | **HR (95%CI)** | ***p-value*** |
| Age (≥70y vs <70y) |  | 0.59 (0.31−1.11) | 0.102 |  |  |  |
| Gender (M/F) |  | 0.86 (0.46−1.61) | 0.645 |  |  |  |
| Number of metastatic sites | 1.40 (1.10−1.80) | **0.007** | 1.35 (1.04−1.74) | **0.021** |
| Lung metastases | 0.86 (0.67−1.91) | 0.672 |  |  |
| Liver metastases | 1.75 (0.84−2.88) | 0.594 |  |  |
| Bone metastases | 1.87 (0.96−3.98) | 0.317 |  |  |
| IMDC prognostic group | 1.18 (0.76−1.82) | 0.458 |  |  |
| BMI (≥25 vs <25) | 0.55 (0.32−0.95) | **0.031** | 0.52 (0.32−0.95) | **0.020** |
|  |  |  |  |  |
| **OS** |  | **Univariate Cox Regression** | |  | **Multivariable Cox regression** | |
|  | **HR (95%CI)** | ***p-value*** |  | **HR (95%CI)** | ***p-value*** |
| Age (≥70y vs <70y) |  | 0.34 (0.12−0.96) | **0.042** |  | 0.70 (0.51−1.05) | 0.074 |
| Gender (M/F) |  | 1.12 (0.52−2.39) | 0.776 |  |  |  |
| Number of metastatic sites |  | 1.29 (0.94−1.76) | 0.120 |  |  |  |
| Lung metastases | 0.91 (0.64−1.57) | 0.458 |  |  |
| Liver metastases | 1.82 (0.73−2.86) | 0.632 |  |  |
| Bone metastases | 1.91 (1.08−3.41) | 0.351 |  |  |
| IMDC prognostic group | 1.51 (0.87−2.64) | 0.144 |  |  |
| BMI (≥25 vs <25) | 0.35 (0.18−0.70) | **0.003** | 0.32 (0.16−0.65) | **0.002** |
|  |  |  |  |  |
| BMI = Body Mass Index; CI = confidence interval; HR = hazard ratio; OS = overall survival; PFS = progression-free survival. | | | | | | |



**Figure 3.** Progression-Free Survival of patients receiving cabozantinib as third-line therapy stratified by Body Mass Index.



**Figure 4.** Overall Survival of patients receiving cabozantinib as third-line therapy stratified by Body Mass Index.

For both PFS (HR = 0.52; 95% CI, 0.32–0.95, p = 0.020) and OS (HR = 0.32; 95% CI, 0.16–0.695, p = 0.002) BMI was a significant predictor at multivariate analysis. Number of metastatic sites (≥ 2 vs <2) was significantly associated with PFS (HR = 1.35; 95% CI, 1.04–1.74, p = 0.021) at multivariate analysis, while age (≥ 70y vs <70y) was significantly correlated with OS at univariate (HR = 0.34; 95% CI, 0.12–0.96, p = 0.042) but not at multivariate analysis (HR = 0.70; 95% CI, 0.51–1.05, p = 0.074).

4. Discussion

The search for prognostic or predictive factors in patients with advanced RCC has become even more essential due to the evidence that immune combos could perform differently based on Memorial Sloan-Kettering Cancer Center (MSKCC)risk stratification [12−14]. Interestingly, while treatment with nivolumab plus ipilimumab [12] or avelumab [13] do consider patient weight for a drug dose calculation, cabozantinib and other TKIs do not take care about this parameter. In this view, we focused on the eventual role of BMI in RCC patients treated with cabozantinib. Our results clearly show that BMI strongly correlates with the outcome of patients treated with second or third-line cabozantinib. Interestingly, no differences were reported in terms of histopathological and clinical features (i.e. number of type of metastatic sites and IMDC criteria) as well as tumor response. Our data are in line with those published by Martini et al. [15], who reported no differences in terms of adverse events between obese and non-obese patients receiving cabozantinib for advanced RCC.

Together with the published results on the correlation between obesity and response to immunotherapy [16], our results support a prognostic but not predictive role for BMI in RCC patients, even if the results in patients with BMI < 25 receiving cabozantinib as third-line (median PFS = 3.7 months) seem to merit careful consideration. Nevertheless, our study presents several limitations (i.e. the lack of data on causes of death and comorbilities), mainly due to the biased characteristic of retrospective studies and should be confirmedby prospective clinical studies.

As reported above, the “obesity paradox” in RCC patients receiving immunotherapy has been partially clarified by the evidence of different signatures and tumour infiltrating immune cells between obese and non-obese subjects [8]. A potential explanation for the role of being overweight and obesity in this setting of antiangiogenic therapies may be provided by the emerging data on the role of adipocytes in renal carcinogenesis. Indeed, adipose microenvironment can regulate the proliferation and migration of tumoural and non tumoural human renal epithelial cells [17]. Increased levels of leptin could enhance the invasive potential of renal epithelial cell lines and could modulate the progression of the disease [18,19]. Furthermore, higher Hypoxia Induced Factor (HIF)-1 levels (which stimulates angiogenesis by deregulating the production of Tumour Necrosis Factor-α, VEGF, and angiopoietin) have been reported in the adipose tissue of obese patients [20]. Moreover, adiponectin levels are higher in non-obese subjects [21], and exposure of RCC cell lines to adiponectin inhibits the secretion of VEGF [22].

5. Conclusions

We showed that a BMI ≥ 25 correlates with longer survival in patients receiving cabozantinib. BMI can be easily carried out and monitored during patients’ management, supporting its role as a tool for the decision-making process of advanced RCC. Further prospective studies should be provided in order to validate BMI among RCC prognostic criteria.

**Author Contributions:** Conceptualization, M.S.; investigation, S.B., G.P., M.M., U.D.G., U.B., G.A., L.I., A.M., M.R., G.C., E.G., M.R.M., S.J.C., N.V.; writing—original draft preparation, M.S., F.M.; writing—review and editing, M.S., A.C..; supervision, G.S., A.C.; project administration, R.M., N.B. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the "ComitatoEticoRegionaledelle Marche", the accepting number is 2019-403.

**Informed Consent Statement:**Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** please refer to suggested Data Availability Statements in section “MDPI Research Data Policies” at https://www.mdpi.com/ethics.

**Conflicts of Interest:** The authors declare no conflict of interest.

References

1. http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2020; [accessed on 22th October 2020].
2. Santoni, M.; Piva, F.; Porta, C., et al. Artificial Neural Networks as a way to predict future Kidney Cancer incidence in the United States. *ClinGenitourin Cancer***2020**; in press.
3. Aurilio, G.; Piva, F.; Santoni, M.; et al. The Role of Obesity in Renal Cell Carcinoma Patients: Clinical-Pathological Implications. *Int J Mol Sci***2019**, 20, 5683.
4. Rutkowski, P.; Indini, A.; De Luca, M.; et al. Body mass index (BMI) and outcome of metastatic melanoma patients receiving targeted therapy and immunotherapy: a multicenter international retrospective study. *J Immunother Cancer***2020**, *8(2)*, e001117.
5. Cortellini, A.; Ricciuti, B.; Tiseo, M.; et al. Baseline BMI and BMI variation during first line pembrolizumab in NSCLC patients with a PD-L1 expression ≥ 50%: a multicenter study with external validation. *J Immunother Cancer***2020**, *8(2)*, e001403.
6. Sanchez, A.; Furberg, H.; Kuo, F.; et al. Transcriptomic signatures related to the obesity paradox in patients with clear cell renal cell carcinoma: a cohort study. *Lancet Oncol***2020**, *21(2)*, 283-293.
7. Wang, Z.; Aguilar, EG.; Luna, JI.; et al. Paradoxicaleffects of obesityon T cell functionduring tumor progression and PD-1 checkpoint blockade. *Nat Med***2019**, *25(1)*, 141-51.
8. Santoni, M.; Cortellini, A.; Buti, S. Unlocking the secret of the obesity paradox in renal tumours. *Lancet Oncol***2020**, *21(2)*, 194-196.
9. Di Nunno, V.;Cubelli, M.;Massari, F. The role of the MET/AXL pathway as a new target for multikinase inhibitors in renal cell carcinoma. *Expert Rev. Precis. Med. Drug Dev* **2017**, *2*, 169-175.
10. Santoni, M.; Heng, D.Y.; Bracarda, S.; et al. Real-World Data on Cabozantinib in Previously Treated Patients with Metastatic Renal Cell Carcinoma: Focus on Sequences and Prognostic Factors. *Cancers (Basel***2019**;12(1):84.
11. Amin, M.B.; Edge, S.; Greene, F.; et al. AJCC Cancer Staging Manual **2017** © Springer International Publishing. ISBN 978-3-319-40617-6
12. Moch, H.; Cubilla, A.L.; Humphrey, P.A.; Reuter, V.E.; Ulbright, T.M. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part A: Renal, Penile, and Testicular Tumours. *Eur Urol*. **2016**;*70*(1):93-105. doi: 10.1016/j.eururo.2016.02.029.
13. Ljungberg, B.; Albiges, L.; Abu-Ghanem, Y.; Bensalah, K.; Dabestani, S.; Fernández-Pello, S.; Giles, R.H.; Hofmann, F.; Hora, M.; Kuczyk, M.A.; et al. European Association of Urology Guidelines on Renal Cell Carcinoma: The 2019 Update. *Eur Urol.* **2019**;*75*(5):799-810. doi: 10.1016/j.eururo.2019.02.011.
14. Schwartz, L.H.; Litière, S.; de Vries, E.; et al. RECIST 1.1-Update and clarification: From the RECIST committee. *Eur J Cancer***2016**, *62*, 132-7.
15. Motzer, R.J.; Tannir, N.M.; McDermott, D.F.; et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. *N Engl J Med***2018**,*378(14)*, 1277-1290.
16. Motzer, R.J.; Penkov, K.; Haanen, J.; et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med***2019**, *380(12)*,1103-1115.
17. Rini, B.I.; Plimack, E.R.; Stus, V.; et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med***2019**,*380(12)*,1116-1127.
18. Martini, D.J.;  Shabto, J.M.;  Liu, Y.; et al. Body mass index (BMI) and toxicities and association with clinical outcomes (CO) in metastatic renal cell carcinoma (mRCC) patients (pts) treated with cabozantinib (cabo). *J ClinOncol***2019**, *37:7\_suppl*, 613-613.
19. De Giorgi, U.; Procopio, G.; Giannarelli, D.; et al. Association of Systemic Inflammation Index and Body Mass Index with Survival in Patients with Renal Cell Cancer Treated with Nivolumab. *Clin Cancer Res***2019**, *25(13)*, 3839-3846.
20. Bruna, F.A.; Romeo, L.R.; Campo-Verde-Arbocco, F.; et al. Human renal adipose tissue from normal and tumor kidney: its influence on renal cell carcinoma.  **2019**, *10(52)*, 5454-5467.
21. Campo-Verde-Arbocco, F.; López-Laur, J.D.; Romeo, L.R.; et al. Human renal adipose tissue induces the invasion and progression of renal cell carcinoma. *Oncotarget***2017**, *8(55)*, 94223-94234.
22. Horiguchi, A.; Sumitomo, M.; Asakuma, J.; et al. Increased serum leptin levels and over expression of leptin receptors are associated with the invasion and progression of renal cell carcinoma. *J Urol* **2006**, *176*, 1631-1635.
23. Cancello, R.; Henegar, C.; Viguerie, N.; et al. Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss. *Diabetes***2005**, *54*, 2277–2286.
24. Gariballa, S.; Alkaabi, J.; Yasin, J.; Al Essa, A. Total adiponectin in overweight and obese subjects and its response to visceral fat loss. *BMC EndocrDisord***2019**, *19(1)*, 55.
25. Kleinmann, N.; Duivenvoorden, W.C.; Hopmans, S.N.; et al. Underactivation of the adiponectin-adiponectin receptor 1 axis in clear cell renal cell carcinoma: implications for progression. *ClinExp Metastasis* **2014**, *31(2)*, 169-83.