Cabozantinib in Patients with Advanced Renal Cell Carcinoma Primary Refractory to First-line Immunocombinations or Tyrosine Kinase Inhibitors

Cabozantinib in patients with advanced Renal Cell Carcinoma primary-refractory to first-line immuno-combinations or tyrosine kinase inhibitors

Matteo Santoni[1], Francesco Massari[2,*], Sergio Bracarda[3], Enrique Grande[4], Marc R Matrana[5], Mimma Rizzo[6], Ugo De Giorgi[7], Umberto Basso[8], Gaetano Aurilio[9], Lorena Incorvaia[10], Angelo Martignetti[11], Javier Molina-Cerrillo[12], Veronica Mollica[2], Alessandro Rizzo[2], Nicola Battelli[1]

[1]Oncology Unit, Macerata Hospital, via Santa Lucia 2, 62100, Macerata, Italy; [2]Medical Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Via Albertoni - 15, Bologna – Italia; [3]Azienda Ospedaliera Santa Maria, Terni, Italy; [4]Department of Medical Oncology, MD Anderson Cancer Center Madrid, Madrid, Spain; [5]Department of Internal Medicine, Hematology/Oncology, Ochsner Medical Center, New Orleans, LA, United States; [6]Division of Translational Oncology, IRCCS Istituti Clinici Scientifici Maugeri, Pavia, Italy; [7]Department of Medical Oncology, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy; [8]Department of Medical Oncology, Istituto Oncologico Veneto (IOV) IRCCS, Padova, Italy; [9]Medical Oncology Division of Urogenital and Head and Neck Tumours, IEO, European Institute of Oncology IRCCS, Milan, Italy; [10]Department of Surgical, Oncological and Oral Sciences, Section of Medical Oncology, University of Palermo, Palermo, Italy; [11]Dipartimento Oncologico USL Sud-Est Toscana-Area Senese, Località Campostaggia s.n.c., 53036 Poggibonsi, Italy; [12]Medical Oncology Departmentat Hospital Ramón y Cajal, Madrid, Spain.

***Correspondence to:**

Francesco Massari, MD

Medical Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Via Albertoni - 15, Bologna – Italia

Phone number: +390512142575; e-mail: francesco.massari@aosp.bo.it

Abstract

Context: A subset of patients with metastatic Renal Cell Carcinoma (mRCC), deemed as primary refractory, shows progressive disease as best response to first-line therapy even when treated with novel immune-based combos.

Objective: We aimed to assess the outcome of patients treated with second-line cabozantinib for mRCC primary refractory to first-line therapy defined as RECIST progression in the CT scan as best response to the upfront treatment.

Evidence Acquisition: We retrospectively collected data from 11 worldwide centers. Overall Survival (OS) and Progression-Free Survival (PFS) were analyzed using Kaplan-Meier curves. Cox proportional models were used at univariate and multivariate analyses.

Evidence Synthesis: We collected data from 108 patients with mRCC primary refractory to pembrolizumab plus axitinib(17%), nivolumab plus ipilimumab (36%) or tyrosine-kinase inhibitors (TKIs, 31% sunitinib, 16% pazopanib). The median OS with cabozantinib was 9.11 months and resulted 8.84 and 9.11 months in patients primary refractory to immuno-combinations or TKIs, respectively (p=0.952). A significant difference was found between patients primary refractory to pembrolizumab plus axitinib (OS not reached) and to nivolumab plus ipilimumab (mOS8.12 months, p=0.024). The median PFS with cabozantinib was 7.30 months, without significant differences between patients primary refractory to immuno-combinations or TKIs (6.90 vs 7.59 months, p=0.435) or between pembrolizumab plus axitinib or nivolumab plus ipilimumab (7.92 and 6.02, p=0.509). Investigator assessed Overall Response Rate (ORR) were 21% and 12% in patients primary refractory to first-line immuno-combinations or TKIs, respectively, with a clinical benefit of 48% in the overall population.

Conclusions: Our data show that cabozantinib is active in primary refractory mRCC patients regardless which treatment received as first-line therapy. Systemic options and prognosis of primary refractory

patients with mRCC, particularly those treated with novel immune-based combos is one of the major challenges we need to face in this field.

Patient Summary

Patients primary refractory to first-line therapy are characterized by poor prognosis. Herein, we aimed to assess the outcome of patients treated with second-line cabozantinib for mRCC primary refractory to first-line therapy defined as RECIST progression in the CT scan as best response to the upfront treatment. Our results suggest that cabozantinib is active in primary refractory mRCC patients.

Keywords: Cabozantinib; renal cell carcinoma; primary refractory; second-line; first-line.

1. Introduction

Renal Cell Carcinoma (RCC), the most frequent neoplasmof the kidney in adults, is progressively increasing in terms of global incidence [1,2]. The majority of these tumors are characterized by clear cell histology and accounts for approximately 75-85% of all RCC cases [3]. Surgery remains the main option for the majority of localized kidney cancers.

The advent of the combinations of immunotherapy with targeted therapies or other immunotherapy agents as the new standard of care for the first-line therapy of patients with metastatic RCC (mRCC) has provided higher tumor responserates and better survival outcomes, together with a fundamental improvement in terms of patients' Quality of Life (QoL) [4−13]. Since the era of targeted therapies [14,15], the quote of patients with complete responses (CR) and durable remissions has increased from 1% to more than 15% in specific subpopulations [16]. This event parallels with a reduction of the rate of patients deemed as "primary refractory" to first-line therapy, defined by progressive disease (PD) as their best response. This RCC subpopulation is characterized by a very poor prognosis and has not been fully characterized in terms of risk factors and outcome. In 2012, Heng DY and his group published the results of a retrospective study including 272 patients primary refractory to anti-Vascular Endothelial Growth Factor (VEGF) therapy [17]. The median Overall Survival (OS) for the entire cohort was 6.8 months; among those 40% of patients who received further systemic therapies, there were only 9% of responders with a median OS of 7.4 months. No statistical differences were found among those patients who received VEGF versus mammalian target of rapamycin (mTOR) inhibitors [17]. Therefore, no standard systemic approach is recommended in major guidelines for this subgroup of patients.

Cabozantinib was firstly approved for patients with previously treated mRCC and successively as a first-line therapy option. In 2019, we led an international retrospective real-world study including mRCC patients treated by cabozantinib as second- or third-line therapy [18]. In this setting, we observed that haemoglobin levels, International Metastatic renal cell carcinoma Database Consortium

(IMDC) criteria and Body Mass Index (BMI) were significantly correlated with the outcome of these patients [18,19].

The efficacy of cabozantinib in mRCC patients primary-refractory to first-line targeted therapy or immune-combinations has not been properly assessed so far. Thus, we first performed a retrospective international study aimed to assess the role ofthis drugin this RCC subpopulation with such a poor prognosis.

2. Evidence Acquisition

2.1. Study population

We retrospectively collected data from patients aged ≥18 years with a histologically confirmed diagnosis of RCC and histologically or radiologically confirmed metastatic disease, who resulted primary refractory to first-line therapies with nivolumab plus ipilimumab, pembrolizumab plus axitinib, sunitinib or pazopanib, and receiving cabozantinib as second-line therapy. We defined primary refractory to first-line therapy as RECIST progression in the CT scan as best response to the upfront treatment. This international real-world study included data from 11 International Institutions involved in the treatment of RCC from three different countries including Italy, Spain and the United States. Data collection included data from 1st January 2010 to 20st July 2021. We retrospectively extracted data from paper and electronic charts. For each patient, the following data were collected and analyzed by the database of each Institution and analyzed: histology, nephrectomy status, initial Eastern Cooperative Oncology Group (ECOG) performance status, IMDC criteria and sites of metastases. Patients without sufficient data on tumor assessment and response to therapy were excluded from this study.

The starting dose of cabozantinib was mainly 60 mg/daily. Dose reductions and treatment interruptions were managed basing on standard guidelines according to type and severity of drug-related adverse

events. Treatment with cabozantinib was performed till the evidence of radiological tumor progression on computed tomography (CT) or magnetic resonance imaging (MRI) scans, unacceptable adverse events, or death. Follow-up was commonly performed by periodical physical and laboratory assessment every 4–6 weeks. Imaging was carried out according to standard local procedures every 8–12 weeks.

2.2. Study endpoints

The primary objective of our retrospective study was to assess the OS of cabozantinib in primary refractory mRCC patients to standard approaches, and it was defined as the time from the start of cabozantinib to death from any cause. Tumor radiological assessment was led according to the RECIST 1.1 criteria [20] and data on tumor response (complete or partial responses, stable or progressive disease) were collected and analyzed.

Progression-Free Survival (PFS) was defined as the time from the start of treatment to progression or death from any cause. Patients without a tumor progression to following line of treatment or death or lost at follow-up at the time of analysis were censored at their last follow-up date.

2.3. Statistical Analysis

PFS and OS were estimated by Kaplan-Meier method with Rothman's 95% confidence intervals (CI) and compared by using the log-rank test.Univariate and multivariate analyses were performed by using Cox proportional hazards models. 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 statistical analysis was led by using MedCalc version 19.6.4 (MedCalc Software, Broekstraat 52, 9030 Mariakerke, Belgium).This project has been accepted by the "Comitato Etico Regionale delle Marche", the accepting number is 2019-403.

3. Evidence Synthesis

3.1. Study population

One hundred and eight patients were included in our study. The median age was 59y (range 38−79y); 71 patients (66%) were males. Tumour histology was predominantly clear cell (85, 79%). Among the 23 patients with non-clear RCC, tumor histology was papillary type I in 17, papillary type II in 5 and chromophobe in 1 patient. Number of metastatic sites was ≥ 2 in 64 patients (59%). Lung (66%), lymph nodes (50%),and bone (27%) were the most common sites of metastasis. According to IMDC criteria, 13 patients (12%) were at favourable-risk, 65 (60%) at intermediate-risk and 30 (28%) had poor-risk features.

Eighteen patients had resulted primary refractory to first-line pembrolizumab plus axitinib as first-line, 39 to nivolumab plus ipilimumab and 51 to TKIs (34 to sunitinib and 17 to pazopanib, respectively). Patients' characteristics are reported in Table 1. No significant differences were found in terms of clinico-pathological features between patients primary refractory to first-line immuno-combinations or TKI (Table 1).

3.2. Survival analysis

The median follow-up time from RCC diagnosis was 25.7 months (range 3.4−77.8). The median OS from the start of cabozantinib was 9.11 months (95%CI: 7.69−21.44, Figure 1). In terms of OS, no significant differences were found in terms of sex (9.96 monthsin males, 95%CI 7.69−14.07 vs 6.44 months in females, 95%CI 4.08−21.44, p=0.218), age ≥65y vs <65y (9.11 months, 95%CI 7.59−13.09 vs 9.60 months, 95%CI 3.75−21.44, p=0.493), number of metastatic sites ≥2 vs <2 (9.11 months, 95%CI 6.12−14.07 vs 8.84 months, 95%CI 7.69−21.44, p=0.738), and nephrectomy (yes vs no, 8.19 months, 95%CI 7.69−21.44 vs 9.60 months, 95%CI 5.82−14.07, p=0.702). The median OS was 9.96

months (95%CI: 8.15−9.96), 9.60 months (95%CI: 7.69−21.44) and 5.72 months (95%CI: 4.08−14.07) in patients with good, intermediate and poor IMDC risk criteria, respectively (p=0.105).

The median OS was 8.84 months in patients primary refractory to first-line immuno-combinations (95%CI 6.44−21.44), and 9.11 months (95%CI 7.69−10.95)in patients primary refractory to first-line TKIs (p=0.952, Figure 2). A significant difference was found between patients primary refractory to pembrolizumab plus axitinib (not reached, NR, 95%CI NR−NR) and to nivolumab plus ipilimumab (8.12 months, 95%CI 4.14−14.07, p=0.024, Figure 3). At univariate analysis, none of the analyzed factors resulted a significant predictor of OS (Table 2).

The median PFS from the start of cabozantinib was 7.30 months (95%CI: 4.87−7.59, Figure 1) and waslonger in males, without reporting a statistically significant difference (7.59 vs 4.87, p=0.167).

No significant PFS differences were also found basing on age ≥65y vs <65y (5.72 months, 95%CI 2.43−7.92 vs 7.59 months, 95%CI 6.02−7.99),nephrectomy (yes vs no, 7.59 months, 95%CI 5.72−7.59, vs 6.51 months, 95%CI 4.44−13.87, p=0.798), and number of metastatic sites ≥2 vs <2 (7.30 months, 95%CI 5.79−7.92 vs 7.59 months, 95%CI 4.44−9.70, p=0.449). The median PFS was 7.30 months (95%CI: 3.52−7.30), 7.59 months (95%CI: 4.87−7.92) and 5.79 months (95%CI: 3.58−13.87) in patients with good, intermediate and poor IMDC risk criteria, respectively (p=0.085).

No significant difference (p=0.435) was found between patients primary refractory to immuno-combinations (6.90 months, 95%CI 4.87−13.87) or TKIs (7.59 months, 95%CI 4.44−7.76, Figure 2).The median PFS was 7.92 months (NR, 95%CI 3.35−7.92) in patients primary refractory to pembrolizumab plus axitinib and 6.02 months (95%CI 4.21−13.87) in patients primary refractory to nivolumab plus ipilimumab (p=0.509, Figure 3). Similarly to OS, at univariate analysis, none of the analyzed factors resulted a significant predictor of PFS (Table 2).

3.3. Response to therapy

In 16 patients (15%), cabozantinib was ongoing at the time of data cut-off. Sixty-two patients (57%) were died at time of data cut-off. Twenty-seven patients (25%) received third-line therapies; of them, 13 patients had been primary refractory to immuno-combinations and were treated with sunitinib (77%) or everolimus (23%), while the 14 patients primary refractory to TKIs received sunitinib (29%), nivolumab (36%) or everolimus (35%) as third-line therapy.

In the overall study population, cabozantinib was associated with partial responses in 18 patients (17%), stable disease in 34 (31%) and progressive disease as best response in 56 patients (52%). In patients primary refractory to immuno-combinations, patients treated with cabozantinibpresented 12 partial responses (21%), 14 stable diseases (25%) and 31 progressive diseases (54%) as best tumor response, leading to a clinical benefit rate of 46%. Five of the 12 partial responses were reported in patients primary refractory to pembrolizumab plus axitinib. In patients primary refractory to first-line TKIs, cabozantinib reported 6 partial responses (12%), 20 stable diseases (39%) and 25 progressive diseases (49%) as best tumor response, with a clinical benefit rate of 51%.

4. Discussion

Tumor heterogeneity constitutes one of the hallmarks of RCC [21,22], although it is likely common in many other cancers. This heterogeneity leads to a variety of biological and clinical behaviors including, for example, patients with metastases at diagnosis [23], late relapses [24], primary refractory to targeted therapy [25], hyper-progressions to immunotherapy [26] and long remissions [27].

To the best of our knowledge, we first focused on the efficacy of cabozantinib in mRCC patients primary refractory to immuno-combinations or targeted therapies. We showed that cabozantinib resulted active in this setting, with median OS and PFS of 9.11 and 7.30 months, respectively. No significant differences in terms of cabozantinib efficacy were found between patients primary refractory to immuno-combinations or targeted therapies. Otherwise, the median OS with cabozantinib

was longer in patients primary refractory to pembrolizumab plus axitinib compared to patients primary refractory to nivolumab plus ipilimumab but this findings may be conditioned by the low number of patients analyzed.

In the study published by Heng DY *et al.* in 2012 [17], the 40% of patients primary refractory to anti-VEGF therapy received further systemic therapies (anti-VEGF or mTOR inhibitors), showing 9% of tumor responses and a median OS of 7.4 months.In addition, median PFS from initiation of second-line targeted therapy was only 2.5 months. In our analysis, tumor responses to cabozantinib were reported in 21% and 12% of patients primary refractory to immuno-combinations or targeted therapies, some results that further confirm that second-line therapy in these patients is associated with dismal outcomes. Although several step forward have been made, understanding the mechanisms of primary and acquired resistance to targeted therapy and immunotherapy still remains a hot topic for cancer researchers. Several studies indicate that both tumor cell intrinsic and extrinsic factors contribute to the resistance mechanisms and include, for example, the lack of recognition by T cells due to the absence of tumor antigens or to their avoided presentation on the surface restricted by MHC, either related to altered antigen presenting machinery (proteasome subunits, transporters associated with antigen processing, beta-2-microglobulin or MHC itself) [28]. The possibility to assess the risk of primary resistance in a single patient pass through the optimization of laboratory techniques and to a progressive integration of these methodologies within daily clinical practice and in the context of randomized clinical trials.

Our data support the need for novel therapeutic approaches for patients primary refractory to first-line therapies, being the percentage of progressive diseases during second-line therapy between 49% and 54%.The impressive clinical responses obtained by the administration of cytotoxic T lymphocytes genetically modified to express a chimeric antigen receptor (CAR) in hematologic malignancies that do not respond to chemotherapy and prior immunotherapy [29] and the more recent results reported by

CAR-macrophages [30] support their investigation also in the context of RCC.

Our study presents several limitations, mainly due to its retrospective nature. Firstly, we did not perform a centralized review of radiological imaging and follow-up was not standardized. Secondly, we did not have available data on the concomitant use medications that could influence the efficacy of cabozantinib therapy. Lastly, 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 consequence, our findings should be interpreted with caution and are in need of a larger prospective validation. At this regard, the results from ongoing phase 2 trial CaboPoint (NCT03945773) will be of great interest to confirm our findings.

Nevertheless, our data suggest that cabozantinib results active in a subgroup of mRCC patients primary refractory to first-line therapy. Choosing the optimal treatment in the population of primary refractory patients remains an unmet need in this setting, where no clear standard exists; thus, the current study has the merit of shedding light to this timely topic and to raise some questions regarding sequence therapies. In particular, a crucial present and future point will be sequencing available therapies in order to enable a balance of clinical and benefit and safety, something that is even more important in primary refractory mRCC patients. The recent discovery of the genomic landscape of this tumor may help the identification of novel therapeutic targets in this context and pave the way to personalized approaches for this subpopulation in next years.

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References

[1] http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2020; [accessed on 15th July 2021].

[2] Santoni M, Piva F, Porta C, Bracarda S, Heng DY, Matrana MR, et al. Artificial Neural Networks as a way to predict future Kidney Cancer incidence in the United States. Clin Genitourin Cancer 2020;S1558-7673(20)30250-0.

[3] Moch H, Cubilla AL, Humphrey PA, Reuter VE, Ulbright TM. The 2016 WHO classification of tumours of the urinary system and male genital organs—part A: renal, penile, and testicular tumours. EurUrol2016;70:93–105.

[4] Rizzo A, Mollica V, Santoni M, Ricci AD, Rosellini M, Marchetti A, Montironi R, Ardizzoni A, Massari F. Impact of Clinicopathological Features on Survival in Patients Treated with First-line Immune Checkpoint Inhibitors Plus Tyrosine Kinase Inhibitors for Renal Cell Carcinoma: A Meta-analysis of Randomized Clinical Trials. Eur Urol Focus 2021; S2405-4569(21)00058-4.

[5] Santoni M, Rizzo A, Mollica V, Rosellini M, Marchetti A, Fragomeno B, Battelli N, Massari F. Pembrolizumab plus lenvatinib or axitinib compared to nivolumab plus ipilimumab or cabozantinib in advanced renal cell carcinoma: a number needed to treat analysis.Expert Rev Pharmacoecon Outcomes Res. 2021 Jun 15:1-7.

[6] Massari F, Rizzo A, Mollica V, Rosellini M, Marchetti A, Ardizzoni A, Santoni M. Immune-based combinations for the treatment of metastatic Renal Cell Carcinoma: a meta-analysis of randomized clinical trials. Eur J Cancer 2021; 154: 120-127.

[7] Rizzo A, Mollica V, Dall'Olio FG, Ricci Ad, Maggio I, Marchetti A, Rosellini M, Santoni, Ardizzoni A, Massari F. Quality of life assessment in RCC phase II and III clinical trials published between 2010 and 2020: a systematic review. Future Oncol 2021; in press.

[8] Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med 2018;378:1277-1290.

[9] Motzer RJ, Penkov K, HaanenJ,Rini B, Albiges L, Campbell MT, et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med 2019;380:1103-1115.

[10] Rini BI, Powles T, Atkins MB, Escudier B, McDermott DF, Suarez C, Bracarda S, Stadler WM, Donskov F, Lee JL, Hawkins R, Ravaud A, Alekseev B, Staehler M, Uemura M, De Giorgi U, Mellado B, Porta C, Melichar B, Gurney H, Bedke J, Choueiri TK, Parnis F, Khaznadar T, Thobhani A, Li S, Piault-Louis E, Frantz G, Huseni M, Schiff C, Green MC, Motzer RJ; IMmotion151 Study Group. Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial. Lancet. 2019 Jun 15;393(10189):2404-2415.

[11] Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al; KEYNOTE-426 Investigators. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med 2019;380:1116-1127.

[12] Motzer R, Alekseev B, Rha SY, Porta C, Eto M, Powles T, et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. N Eng J Med 2021; doi: 10.1056/NEJMoa2035716

[13] Choueiri TK, Powles T, Burotto M, Escudier B, Bourlon MT, Zurawski B, et al. Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2021;384(9):829-841.

[14] Iacovelli R, Alesini D, Palazzo A, Trenta P, Santoni M, De Marchis L, Cascinu S, Naso G,

Cortesi E. Targeted therapies and complete responses in first line treatment of metastatic renal cell carcinoma. A meta-analysis of published trials. CancerTreat Rev. 2014;40(2):271-5.

[15] Santini D, Santoni M, Conti A, Procopio G, Verzoni E, Galli L, et al. Risk of recurrence and conditional survival in complete responders treated with TKIs plus or less locoregional therapies for metastatic renal cell carcinoma.Oncotarget. 2016;7(22):33381-90.

[16] Zambrana F, Carril-Ajuria L, Gómez de Liaño A, Martinez Chanza N, Manneh R, Castellano D, de Velasco G. Complete response and renalcell carcinoma in the immunotherapy era: The paradox of good news. CancerTreat Rev. 2021;99:102239.

[17] Heng DY, Mackenzie MJ, Vaishampayan UN, Bjarnason GA, Knox JJ, Tan MH, et al. Primary anti-vascular endothelial growth factor (VEGF)-refractory metastatic renal cell carcinoma: clinical characteristics, risk factors, and subsequent therapy. Ann Oncol. 2012;23(6):1549-55.

[18] Santoni M, Heng DY, Bracarda S, Procopio G, Milella M, Porta C, 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;12:84.

[19] Santoni M, Massari F, Bracarda S, Procopio G, Milella M, De Giorgi U, et al. Body Mass Index in Patients Treated with Cabozantinib for Advanced Renal Cell Carcinoma: A New Prognostic Factor? Diagnostics (Basel). 2021;11:138.

[20] Schwartz LH, Litière S, de Vries E, Ford R, Gwyther S, MandrekarS, et al. RECIST 1.1-Update and clarification: From the RECIST committee. Eur J Cancer 2016;62:132-7.

[21] GerlingerM,RowanAJ,HorswellS,etal.Intratumorheterogeneityandbranchedevolutionrevealedbymultiregionsequencing.N EnglJ Med.2012;366(10):883–892.

[22] Santoni M, Santini D, Massari F, et al. Heterogeneous drug targetexpression as possible basis for different clinical and radiologicalresponse to the treatment of primary and metastatic renal

cellcarcinoma: suggestions from bench to bedside. Cancer Metastasis Rev.2014;33(1):321–331.

[23] Garcia JA, Cowey CL, Godley PA. Renal cell carcinoma. Curr Opin Oncol.2009;21(3):266–271.

[24] Santoni M, Conti A, Porta C, et al. Sunitinib, pazopanib or sorafenib for the treatment of patients with late relapsing metastatic renal cell carcinoma. J Urol.2015;193(1):41–47.

[25] Porta C, Sabbatini R, Procopio G, et al. Primary resistance to tyrosine kinase inhibitors in patients with advanced renal cell carcinoma: state-of-the-science. Expert RevAnticancerTher. 2012;12(12):1571–1577.

[26] SoriaF, Beleni AI, D'Andrea D, et al. Pseudoprogression and hyper-progression during immune checkpoint inhibitor therapy for urothelial and kidney cancer. World J Urol. 2018;36(11):1703–1709.

[27] Tannir NM, Figlin RA, Gore ME, et al. Long-term response to sunitinib treatment in metastatic renal cell carcinoma: a pooled analysis of clinical trials. Clin Genitourin Cancer. 2017;S1558-7673(17)30171–4.

[28] Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy. Cell. 2017 Feb 9;168(4):707-723.

[29] Boyiadzis MM, Dhodapkar MV, Brentjens RJ, Kochenderfer JN, Neelapu SS, Maus MV, et al. Chimeric antigen receptor (CAR) T therapies for the treatment of hematologic malignancies: clinical perspective and significance. J. Immunother. Cancer 2018;6:137.

[30] Santoni M, Massari F, Santoni G, Cimadamore A, Montironi R, Battelli N. Re: Human chimeric antigen receptor macrophages for cancer immunotherapy. Eur Urol 2021; S0302-2838(21)00064-6.

Table Legends

Table 1. Patient characteristics.

Table 2. Univariate and multivariate analyses of predictors of Overall Survival and Progression-Free Survival in patients with mRCC primary refractory to first-line therapy.

Figure Legends

Figure 1. Overall Survival (OS) and Progression-Free Survival (PFS) of mRCC patients primary refractory to first-line therapy treated with second-line cabozantinib. Median OS and median PFS from the start of cabozantinib were 9.11 months (95%CI: 7.69−21.44) and 7.30 months (95%CI: 4.87−7.59), respectively.

Figure 2. Overall Survival (OS) and Progression-Free Survival (PFS) of cabozantinib as second-line therapy in mRCC patients primary refractory to first-line immunocombinations or TKIs. Median OS was 8.84 months in patients primary refractory to first-line immuno-combinations (95%CI 6.44−21.44), and 9.11 months (95%CI 7.69−10.95) in patients primary refractory to first-line TKIs (p=0.952); as regards PFS, no significant difference (p=0.435) was found between the two groups - 6.90 months (95%CI 4.87−13.87) and 7.59 months (95%CI 4.44−7.76), respectively.

Figure 3. Overall Survival and Progression-Free Survival of cabozantinib as second-line therapy in mRCC patients primary refractory to the first-line combination of pembrolizumab plus axitinib or nivolumab plus ipilimumab.A significant difference was found between patients primary refractory to pembrolizumab plus axitinib (not reached, NR, 95%CI NR−NR) and to nivolumab plus ipilimumab (8.12 months, 95%CI 4.14−14.07, p=0.024); median PFS was 7.92 months (NR, 95%CI 3.35−7.92) and 6.02 months (95%CI 4.21−13.87), respectively (p=0.509). Axi = axitinib; Ipi = ipilimumab; Nivo = nivolumab; Pembro = pembrolizumab.