Results from the INMUNOSUN-SOGUG trial: a prospective phase II study of sunitinib as a second-line therapy in patients with metastatic renal cell carcinoma after immune checkpoint-based combination therapy

E. Grande1*, T. Alonso-Gordoa2, O. Reig3, E. Esteban4, D. Castellano5, X. Garcia-del-Muro6, M. J. Mendez7, J. García-Donas8, M. González Rodríguez9, J. A. Arranz-Arija1, P. Lopez-Criado1, J. Molina-Cerrillo5, B. Mellado10, C. Alvarez-Fernandez4, G. De Velasco5, M. A. Cuéllar-Rivas6, R. M. Rodríguez-Alonso7, J. F. Rodríguez-Moreno8 & C. Suarez-Rodriguez9

1Medical Oncology, MD Anderson Cancer Center Madrid, Madrid; 2Medical Oncology, Hospital Universitario Ramón y Cajal, Madrid; 3Medical Oncology, Hospital Clinic and Translational Genomics and Targeted Therapies in Solid Tumors Group, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona; 4Medical Oncology, Hospital Universitario Central de Asturias, Oviedo; 5Medical Oncology, Hospital Universitario 12 de Octubre, Madrid; 6Medical Oncology, Institut Català d’Oncologia (ICO Bellvitge) Idiibell, University of Barcelona, Barcelona; 7Medical Oncology, Maimonides Institute for Biomedical Research of Córdoba (IMIBIC) Hospital Universitario Reina Sofia (HURS), Córdoba; 8Medical Oncology, Clara Campal Comprehensive Cancer Center, Madrid; 9Medical Oncology, Vall d’Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d’Hebron, Barcelona; 10Medical Oncology, Hospital Clinic of Barcelona, Barcelona, Spain

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Background: The INMUNOSUN trial had the objective of prospectively evaluating the efficacy and safety of sunitinib as a pure second-line treatment in patients with metastatic renal cell carcinoma (mRCC) who have progressed to first-line immune checkpoint inhibitor (ICI)-based therapies.

Patients and methods: A multicenter, phase II, single-arm, open-label study was carried out in patients with a histologically confirmed diagnosis of mRCC with a clear-cell component who had progressed to a first-line regimen of ICI-based therapies. All patients received sunitinib 50 mg once daily orally for 4 weeks, followed by a 2-week rest period following package insert instructions. The primary outcome was the objective response rate.

Results: Twenty-one assessable patients were included in the efficacy and safety analyses. Four patients (19.0%, 95% confidence interval (CI) 2.3% to 35.8%) showed an objective response (OR), and all of them had partial responses. Additionally, 14 (67%) patients showed a stable response, leading to clinical benefit in 18 patients (85.7%, 95% CI 70.7% to 100%). Among the four assessable patients who showed an OR, the median duration of the response was 7.1 months (interquartile range 4.2-12.0 months). The median progression-free survival (PFS) was 5.6 months (95% CI 3.1-8.0 months). The median overall survival (OS) was 23.5 months (95% CI 6.3-40.7 months). Patients who had better antitumor response to first-line ICI-based treatment showed a longer PFS and OS with sunitinib. The most frequent treatment-emergent adverse events were diarrhea (n = 11, 52%), dysgeusia (n = 8, 38%), palmar-plantar erythrodysesthesia (n = 8, 38%), and hypertension (n = 8, 38%). There was 1 patient who exhibited grade 5 pancytopenia, and 11 patients experienced grade 3 adverse events. Eight (38%) patients had serious adverse events, four of which were considered to be related to sunitinib.

Conclusion: Although the INMUNOSUN trial did not reach the pre-specified endpoint, it demonstrated that sunitinib is active and can be safely used as a second-line option in patients with mRCC who progress to new standard ICI-based regimens.

Key words: metastatic renal carcinoma, immune checkpoint inhibitors, second-line treatment, sunitinib

INTRODUCTION

Immune checkpoint inhibitor (ICI)-based combinations have replaced tyrosine kinase inhibitors (TKIs) as single agents as the first-line treatment of metastatic renal cell carcinoma (mRCC). Due to a remarkable improvement in overall survival (OS), these novel combinations have rapidly been added to the main international guidelines as preferable options.1-3 Both double ICI blockade with nivolumab plus ipilimumab4 and the combination of an ICI plus a TKI, including pembrolizumab plus axitinib,5 avelumab plus axitinib,6 cabozantinib plus nivolumab,7 and pembrolizumab plus lenvatinib,8 have demonstrated significant clinical benefit over sunitinib as comparators replacing TKIs as a
standard of care. Despite the wave of data for ICI-based combinations, angiogenesis remains the most important biologically altered factor in mRCC. The rapid adoption of new upfront combinations limits the prospective assessments of activity and safety in subsequent lines of treatment. In this context, the selection of treatment for second and subsequent lines after progression to ICI-based therapies is also evolving but is currently largely based on retrospective or subgroup analyses of randomized controlled trials. The median progression-free survival (PFS) reported in trials with TKIs in this setting ranges between 5.6 and 14.7 months, and up to 45% of the patients experienced an objective response (OR) after ICI-based treatment. The INMUNOSUN trial had the objective of prospectively evaluating the efficacy and safety of sunitinib as a pure second-line treatment in patients with mRCC who have progressed to a first-line ICI-based upfront approach.

PATIENTS AND METHODS

Study design
This was a multicenter, phase II, single-arm, open-label study conducted in 10 centers in Spain belonging to the Spanish Oncology Genitourinary Group (SOGUG). The study was approved by the Ethics Committee of the Ramon y Cajal University Hospital (Madrid, Spain), and all subjects provided written informed consent before being included in the study. This study was registered at ClinicalTrials.gov with the number NCT03066427.

Participants
Eligible patients were 18 years or older, with a histologically confirmed diagnosis of mRCC with a clear-cell component, who had progressed to a first-line regimen containing a programmed death-1 receptor inhibitor, programmed death-ligand 1 inhibitor, or a cytotoxic T-lymphocyte-associated antigen 4 ICI, either as monotherapy or combined with any antiangiogenic drug. Patients were required to have evidence of measurable disease according to Response to Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (v1.1), an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, and adequate hematological and end-organ function, and they could not be candidates for curative surgery, radiotherapy, or combined treatment. Patients were excluded if they had received previous sunitinib or had uncontrolled central nervous system metastases.

Study procedures
All patients received sunitinib 50 mg once daily orally for 4 weeks, followed by a 2-week rest period (4/2) according to package insert instructions. Sunitinib dose interruptions and/or dose reduction by one and, if needed, two (one dose level decrease at a time) dose levels were allowed depending on the type and severity of toxicity encountered, providing that criteria for patient withdrawal had not been met. The investigator could modify the sunitinib schedule to 2 weeks on and 1 week off (2/1). Treatment had to be permanently discontinued if >2 toxicity-related dose reductions of sunitinib were required or if the treatment delay was longer than 4 weeks.

At baseline and within 28 days before treatment initiation, a computed tomography (CT) scan of the brain, chest, abdomen, and pelvis and bone scintigraphy were carried out. CT chest, abdomen, and pelvis scans were carried out every 8 weeks for the first 24 weeks and every 12 weeks thereafter until the end-of-treatment visit. If the patient had bone or brain metastases at baseline or it was clinically indicated during the study, bone imaging or CT head scans were carried out after baseline every 12 weeks for the first 24 weeks and every 24 weeks thereafter until treatment discontinuation. Physical exam, ECOG performance status, and a standard blood work-up were carried out at baseline, on day 15 of cycles 1 and 3, and on day 1 of every cycle thereafter until the final visit. Toxicities were evaluated at each clinical visit and graded with Common Toxicity Terminology Criteria for Adverse Events version 4.03. The end-of-treatment visit was carried out at disease progression, unacceptable toxicity, or consent withdrawal. After treatment discontinuation, patients were followed up for survival every 8 weeks.

Outcomes
The primary outcome was the OR rate (ORR), defined as the proportion of patients who had a confirmed best response of complete response or partial response according to RECIST v1.1 based on the investigators’ assessment. Secondary outcomes included PFS, defined as the time from treatment initiation to first RECIST v1.1 evidence of progression or death; time to progression, defined as the time from treatment initiation to first RECIST v1.1 evidence of progression; duration of response, defined as the time from the first occurrence of response (complete or partial response) to disease progression according to RECIST v1.1 or death, whichever occurs first; and OS, defined as the time from treatment initiation to death from any cause.

Statistical analysis
Sample size estimation was based on a single-stage phase II Fleming’s design. An ORR of 30% was expected with sunitinib. This improvement of ~20% with respect to the ORR obtained with standard second-line treatment required 20 patients to achieve 80% statistical power with a significance level of 0.05. Considering a drop-out rate of 10%, the sample size was increased to 23 patients.

The ORR is described using the absolute and relative frequencies and the corresponding 95% confidence interval (95% CI). Continuous outcomes, including duration of response, are described with the median and the interquartile range (IQR). Time-to-event outcomes were analyzed using the Kaplan–Meier method. We carried out several subgroup analyses for the efficacy outcomes, including a preplanned analysis according to the best
response to first-line immunotherapy and post hoc analyses according to previous surgery, previous antiangiogenic treatment, duration of the first-line treatment, or time from the last dose of previous first-line ICI-based combination to sunitinib initiation. All analyses were carried out using SPSS v.22 (IBM, Chicago, IL).

**RESULTS**

**Patient disposition and characteristics**

Twenty-three patients were recruited from May 2017 to October 2019. Two patients were excluded from any analysis: one because the patient died during the screening period and one because the patient did not meet the selection criteria (the patient had active central nervous system involvement). Therefore, 21 patients were included in the efficacy and safety analyses. Most patients were male, with an ECOG performance status of 1, and with an intermediate prognosis according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic criteria; the most common metastatic sites were the lung and lymph nodes. The most important demographic and clinical features of the sample are described in Table 1. The median follow-up was 15.0 months (IQR 7.6-24.1 months).

The most common ICIs used in the first-line therapy were the combination of atezolizumab and bevacizumab (n = 6, 29%), pembrolizumab monotherapy (n = 3, 14%), and the combination of ipilimumab and nivolumab (n = 3, 14%). The activity of the first-line ICI-based combination was remarkable before being recruited in the IMMUNOSUN trial, with a median time on treatment with the first-line approach of 10 months and a radiological response observed in 10 (50% of the 20 assessable patients) patients (Table 1). Among the 19 patients receiving first subsequent anticancer therapy, 11 received cabozantinib, 2 nivolumab, 2 everolimus, 1 axitinib, and 3 clinical trial medication; second subsequent anticancer therapy included 1 patient treated with cabozantinib, 1 with nivolumab, and 2 with clinical trial medication.

**Efficacy results**

When treated with sunitinib, four patients (19%, 95% CI 2.3% to 35.8%) showed an OR, and all of them were partial responses; additionally, 14 (67%) patients showed a stable response, leading to a clinical benefit in 18 patients (85.7%, 95% CI 70.7% to 100%). A waterfall plot showing the best percentage change in the sum of the diameters of the target lesions is presented in Figure 1. Bivariate analysis showed no difference in the best response to sunitinib according to previous cytoreductive nephrectomy, previous antiangiogenic treatment, duration of first-line immunotherapy, or time from previous first-line immunotherapy to sunitinib initiation (data not shown). Among the four assessable patients who showed an OR, the median duration of response was 7.1 months (IQR 4.2-12.0 months).

Median PFS was 5.6 months (95% CI 3.1-8.0 months) (Figure 2A). PFS significantly differed according to the best antitumor response achieved with first-line immunotherapy, being longer for those who had an OR (median 7.3 months, 95% CI 0.0-20.1 months) and stable disease (median 7.7 months, 95% CI 3.1-12.2 months) than for those who showed progressive disease (median 2.7 months, 95% CI 0.5-5.0 months) [log-rank (Mantel-Cox) \( P < 0.001 \) (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2022.100463)]. Post hoc analyses showed

### Table 1. Baseline demographic and clinical characteristics

| Characteristic                                | n  |
|-----------------------------------------------|----|
| Age (years), median (IQR)                     | 21 |
| Sex, n (%)                                    | 21 |
| Male                                          | 18 (85.7) |
| Female                                        | 3 (14.3) |
| ECOG performance status, n (%)                | 17 |
| 1                                             | 16 (94.1) |
| 2                                             | 1 (5.9) |
| Predominant histology, n (%)                  | 21 |
| Pure clear-cell carcinoma                     | 19 (90.5) |
| Non-clear-cell predominant histology          | 2 (9.5) |
| Heng risk score, n (%)                        | 16 |
| Favorable prognosis                           | 1 (6.2) |
| Intermediate prognosis                        | 15 (93.8) |
| Most common metastatic sites, n (%)           | 21 |
| Lung                                          | 10 (47.6) |
| Lymph node                                    | 8 (38.1) |
| Bone                                          | 5 (23.3) |
| Liver                                         | 5 (23.3) |
| Most common comorbidities, n (%)              | 21 |
| Hypertension                                  | 15 (71.4) |
| Dyslipidemia                                   | 8 (38.1) |
| Diabetes mellitus                             | 3 (14.3) |
| Previous nephrectomy, n (%)                   | 21 |
| Radical                                       | 13 (61.9) |
| Partial                                       | 5 (23.8) |
| Previous pharmacologic treatment, n (%)       | 21 |
| Atezolizumab + bevacizumab                    | 6 (28.6) |
| Pembrolizumab                                 | 3 (14.3) |
| Ipilimumab + nivolumab                        | 3 (14.3) |
| Pembrolizumab + lenvatinib                    | 2 (9.5) |
| Atezolizumab                                  | 2 (9.5) |
| Pembrolizumab + lenvatinib + everolimus       | 1 (4.8) |
| Nivolumab                                     | 1 (4.8) |
| Atezolizumab + RO6874281 (IL-2V)              | 1 (4.8) |
| Atezolizumab + unknown investigational product| 1 (4.8) |
| Atezolizumab + bevacizumab + RO6874281 (IL-2V)| 1 (4.8) |
| Duration on previous immunotherapy (months), median (IQR) | 21 10.4 (3.5-16.7) |
| Best response on previous treatment, n (%)    | 21 |
| Complete response                             | 1 (5.0) |
| Partial response                              | 9 (45.0) |
| Stable disease                                 | 5 (25.0) |
| Progressive disease                           | 5 (25.0) |
| Time from first-line treatment discontinuation to sunitinib initiation (months), median (IQR) | 21 1.1 (0.8-1.7) |

ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; n, number of assessable patients.
no difference in PFS according to previous cytoreductive nephrectomy, previous antiangiogenic treatment, duration of first-line immunotherapy, or time from previous first-line immunotherapy to sunitinib initiation (data not shown).

The median OS was 23.5 months (95% CI 6.3-40.7 months) (Figure 2B). A significant difference in OS with sunitinib was observed according to the best radiological response to first-line immunotherapy treatment. Those with an OR did not reach the median; among those with stable disease, the median was 23.5 months (95% CI, not estimable); and among those who showed progressive disease, the median was 6.8 months (95% CI 0.0-17.5 months); the differences were statistically significant [log-rank (Mantel–Cox) \( P = 0.008 \)] (Supplementary Figure S2, available at

![Figure 1. Best percentage change in size of target lesions with sunitinib.](https://doi.org/10.1016/j.esmoop.2022.100463) The number of patients included in this analysis was 19. Two patients did not have a measurement of the sum of the diameters of the lesions after baseline.

![Figure 2. Time-to-event outcomes with sunitinib.](https://doi.org/10.1016/j.esmoop.2022.100463) (A) Progression-free survival. (B) Overall survival.
Most frequent (>10% overall frequency) treatment-emergent adverse events

| Adverse event                      | Grade 1* | Grade 2* | Grade 3* | Total  |
|-----------------------------------|----------|----------|----------|--------|
| Diarrhea                          | 8 (38.1) | 3 (14.3) | 0 (0.0) | 11 (52.4) |
| Dysgeusia                         | 5 (23.8) | 3 (14.3) | 0 (0.0) | 8 (38.1)  |
| Palmar—plantar erythrodysesthesia | 6 (28.6) | 2 (9.5)  | 0 (0.0) | 8 (38.1)  |
| Hypertension                      | 2 (9.5)  | 3 (14.3) | 3 (14.3) | 8 (38.1)  |
| Mucosal inflammation              | 3 (14.3) | 4 (19.0) | 0 (0.0) | 7 (33.3)  |
| Decreased appetite                | 3 (14.3) | 3 (14.3) | 1 (4.8)  | 7 (33.3)  |
| Neutropenia                       | 0 (0.0)  | 3 (14.3) | 3 (14.3) | 6 (28.6)  |
| Anemia                            | 1 (4.8)  | 1 (4.8)  | 2 (9.5)  | 4 (19.0)  |
| Nausea                            | 2 (9.5)  | 2 (9.5)  | 0 (0.0)  | 4 (19.0)  |
| Dyspepsia                         | 3 (14.3) | 0 (0.0)  | 0 (0.0)  | 3 (14.3)  |
| Abdominal pain                    | 3 (14.3) | 0 (0.0)  | 0 (0.0)  | 3 (14.3)  |
| Peripheral edema                  | 3 (14.3) | 0 (0.0)  | 0 (0.0)  | 3 (14.3)  |
| Thrombocytopenia                  | 0 (0.0)  | 1 (4.8)  | 2 (9.5)  | 3 (14.3)  |
| Epistaxis                         | 2 (9.5)  | 1 (4.8)  | 0 (0.0)  | 3 (14.3)  |
| Back pain                         | 1 (4.8)  | 1 (4.8)  | 0 (0.0)  | 3 (14.3)  |

*There were no grade 4 or 5 adverse events except for one patient who exhibited grade 5 pancytopenia.

An additional patient reported back pain without grading.

Sunitinib treatment and toxicity

The median duration of sunitinib treatment was 5.1 months (IQR 2.7-11.0 months), and the median dose intensity was 30.6 mg/day (IQR 25.0-32.1 mg/day). Five (24%) patients required at least one dose reduction. The main reasons for dose reductions were drug-unrelated issues (n = 2), hematouria, impaired renal function, hematological toxicity (n = 3), asthenia (n = 1), general physical health deterioration (n = 1), and diarrhea and fragility (n = 1). Twelve (57%) patients required at least one treatment interruption while on sunitinib; overall, there were 19 interruptions, split into 16 due to nonhematological toxicity (asthenia (n = 3), mucositis (n = 2), hypertension (n = 2), proteinuria (n = 2), impaired renal function (n = 1), acute lower limb ischemia (n = 1), epistaxis (n = 1), palmar—plantar erythrodysesthesia (n = 1), anorexia (n = 1), dysphagia (n = 1), and poor tolerability (n = 1)) and 3 due to hematological toxicity.

The most frequent treatment-emergent adverse events were diarrhea (n = 11, 52%), dysgeusia (n = 8, 38%), palmar—plantar erythrodysesthesia (n = 8, 38%), and hypertension (n = 8, 38%) (Table 2). There was 1 patient who exhibited grade 5 pancytopenia, and there were 11 grade 3 adverse events (3 patients each with neutropenia and hypertension, 2 patients each with anemia and thrombocytopenia, and 1 patient with decreased appetite). Eight (38%) patients had serious adverse events, and four patients had serious adverse events that were considered related to sunitinib: bilateral thrombosis (n = 1), oral mucositis (n = 1), pancytopenia (n = 1), and rectal bleeding (n = 1); all patients with serious adverse events recovered, except for the patient who exhibited pancytopenia who died.

**DISCUSSION**

In this phase II, prospective, single-arm trial, second-line sunitinib showed antitumor activity in patients with mRCC previously treated with an ICI-based regimen as a first-line treatment. However, this trial failed to demonstrate the pre-specified endpoint (i.e. a 30% ORR). Toxicity was consistent with that previously described.

The proportion of patients who achieved an OR (19%) was lower than expected (30%) but in line with the activity observed with other TKIs in the same setting.10-16 The limited data available with sunitinib in this setting showed somewhat mixed results. In a retrospective study of 33 patients treated with ipilimumab—nivolumab in the Checkmate 214 study who were treated with a second-line vascular endothelial growth factor receptor (VEGFR) TKI [mainly sunitinib (n = 17)], the median PFS (8 months) was longer than in our study.3 In a retrospective real-world study of 102 patients of the International mRCC Database Consortium who had received first-line ICI-based treatment with ipilimumab—nivolumab (61%), a combination of immunotherapy and VEGFR TKI (26%), or single immunotherapy (13%), the ORR with second-line sunitinib among assessable patients was 22.5% (all partial responses).17 Other retrospective studies providing results for all combined second-line TKIs generally showed higher ORRs, ranging from 22% to 36%.18-21 However, the results of these studies are difficult to put into perspective as, in addition to being retrospective, the activity of second-line TKIs appears to differ depending on prior first-line ICI-based regimens,22,23 and seems especially remarkable after the combination of ipilimumab—nivolumab.24-26 It is important to note that the results of second-line sunitinib reported by Auvray et al.,9 which are better than ours in terms of PFS, were achieved in patients who previously received first-line treatment with ipilimumab—nivolumab and in our study that prior combination was only administered in three patients, while the majority had received a combination of an ICI plus an antiangiogenic (mostly bevacizumab or lenvatinib).

Most studies reporting individual results for second-line or subsequent VEGFR TKIs have also reported better results than those achieved in our study (Table 3).12-16,24-26 Rini et al.,13 in a phase III, randomized, open-label trial, reported similar results with third-line tivozanib (an ORR of 18% and a PFS of 5.6 months) and poorer results with third-line sorafenib (an ORR of 8% and a PFS of 3.9 months). On the other hand, in a prospective phase II study with axitinib in 40 patients who had received an ICI (mostly nivolumab monotherapy and less frequently the combination of ipilimumab—nivolumab), 18 (45%) achieved an OR—17 of them had partial responses—and a median PFS of 8.8 months; in a post hoc analysis, the authors did not find an association between previous type of ICI-based therapy and

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response to axitinib, nor with previous nivolumab mono-
therapy versus ipilimumab plus nivolumab.12

Our subgroup analyses suggest that the outcomes achieved with sunitinib could be better in patients who showed better results with first-line ICI-based therapy. Thus, patients who had a better antitumor response with first-line therapy showed a longer PFS and OS with sunitinib. These results are somewhat consistent with those previously reported by the IMDC using a prognostic model in patients who received second-line targeted therapy after a mostly TKI-based first-line therapy.27 According to the IMDC risk stratification, the authors of that analysis found median OS of 35.3, 16.6, and 5.4 months for those patients in the favorable-, intermediate-, and poor-risk groups, respectively.27

Despite a relatively short median PFS of 5.6 months, in our trial the median OS was 23.5 months. Several factors may have influenced these results in terms of OS, including the access to subsequent lines of therapy, particularly cabozantinib, that have already shown an important impact on OS after failure to a TKI-based therapy.28 In our trial, 12 (57%) of the 21 patients treated received subsequent treatment with cabozantinib, 11 of them immediately after failure to sunitinib. In patients who progress on a VEGFR TKI, there is evidence supporting that treatment with a second VEGFR TKI provides an additional benefit.29 Another factor that could have influenced the OS is that patients recruited in the trial tend to have better prognosis than those treated in the real-world setting, and long-term activity after first-line immune-based approach is something that is difficult to weigh up in a non-randomized trial such as the IMMUNOSUN.

The toxicity with sunitinib was similar to that reported in other second-line sunitinib trials, with over 50% of the patients exhibiting grade 3 or greater adverse events and a similar profile of adverse events.30,31 Importantly, there were 12 patients who required 19 dose interruptions, and the dose intensity had a median of 30 mg/day. In our trial, patients received sunitinib 50 mg/day (4 weeks on, 2 weeks off). A recent systematic review has shown that an alternative treatment schedule of 2 weeks on and 1 week off compared to the traditional schedule 4/2 could be associated with better treatment outcomes, with a greater proportion of patients with a stable disease and a reduced frequency of several adverse events.32 Therefore, it would be worth testing whether schedule 2/1 in this second-line setting is associated with a better safety profile, fewer dose interruptions, greater dose intensity, and eventually increased treatment response.

Our trial has some limitations, including the uncontrolled design and the heterogeneous profile of the first-line treatments, the small sample population recruited, and the few patients recruited with prior ICI plus TKI-based treatment. Despite these limitations, the activity observed with sunitinib, particularly in terms of responses (19%), is remarkable, although the median PFS looks shorter than that with other similar alternatives in the same setting.

Current recommendations of clinical practice guidelines for the selection of second-line treatment after progression to ICI-based therapies are based on a low level of evidence.1,2 The INMUNOSUN trial is one of the few prospective trials conducted thus far to assess the activity of a single agent TKI after failure of one ICI-based combination as an upfront treatment for mRCC. In this trial, the activity of sunitinib seems to mirror the efficacy of first-line treatment. The safety profile of sunitinib was consistent with prior experience in the first line. Although the INMUNOSUN trial did not reach the pre-specified endpoint, it demonstrated that sunitinib is active and can be used safely as a second-line option in patients with mRCC who progress to new standard ICI-based regimens.

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**Table 3. Second-line tyrosine kinase inhibitors following immune checkpoint inhibitors in patients with metastatic renal cell carcinoma**

| Author (year) | Design | Treatment | n  | Median follow-up (months) | ORR (%) | Median PFS (months) |
|---------------|--------|-----------|----|---------------------------|---------|---------------------|
| Present study | Phase II, prospective, single arm | Sunitinib | 21 | 15.0 | 19 | 5.6 |
| Auveray et al. (2019)9 | Retrospective | Sunitinib | 17 | 22.0 | NR | 8 |
| Wells et al. (2021)17 | Retrospective | Sunitinib | 102 | NR | 22.5 | NR (TTD 5.4 months) |
| Ormstein et al. (2019)12 | Retrospective | Sunitinib | 40 | 8.7 | 45 | 8.8 |
| McGregor et al. (2020)14 | Retrospective | Cabozantinib | 86 | 12.0 | 36 | 6.5 |
| Iacovelli et al. (2020)13 | Retrospective | Cabozantinib | 84 | (75 for ORR) | NR | 52 | 11.5 |
| Procopio et al. (2021) | Phase II, prospective (n = 30) and retrospective (n = 19) | Cabozantinib | 48 | 8.0 | 43 | 9.3 |
| Cao et al. (2020)15 | Retrospective | Pazopanib | 182 (second line) | NR | NR | 16 |
| Powles et al. (2020)26 | Phase II, prospective, single arm | Pazopanib | 47 (second line) | NR | NR | 12 |
| Pal et al. (2020)16 | Phase II, randomized, noninferiority trial | Lenvatinib 14 mg | 343 (FAS) | ? | 32.1 34.8 | 11.1 14.7 |
| Rini et al. (2019) | Phase III, randomized, open-label trial | Tivozanib | 175 | 19.0 | 18 | 5.6 |
| Sorafenib | 175 | 8 | 3.9 |

FAS, full analysis set; NR, not reported; ORR, objective response rate; PFS, progression-free survival; TTD, time to treatment discontinuation.

*Investigator assessment.*
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DATA SHARING
The clinical trial data are available from the corresponding author upon reasonable request.

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