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Genitourinary Cancer

# Sunitinib: Ten Years of Successful Clinical Use and Study in Advanced Renal Cell Carcinoma

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*Disclosures of potential conflicts of interest may be found at the end of this article.*

**Key Words.** Sunitinib • Renal cell carcinoma • Study design • Treatment management • Drug development

## Abstract

The oral multikinase inhibitor sunitinib malate was approved by the U.S. Food and Drug Administration in January 2006 for use in patients with advanced renal cell carcinoma (RCC). Since then, it has been approved globally for this indication and for patients with imatinib-resistant or -intolerant gastrointestinal stromal tumors and advanced pancreatic neuroendocrine tumors. As we mark the 10-year anniversary of the beginning of the era of targeted therapy, and specifically the approval of sunitinib, it is worthwhile to highlight the progress that has been made in advanced RCC as it relates to the study of sunitinib. We present the key trials and data for sunitinib that established it as a reference standard of care for first-line advanced RCC therapy and, along with other targeted agents, significantly altered the treatment landscape in RCC. Moreover, we discuss the research with sunitinib that has sought to refine its role via patient selection and prognostic markers, improve dosing and adverse event management, and identify predictive efficacy biomarkers, plus the extent to which this research has contributed to the overall understanding and management of RCC. We also explore the key learnings regarding study design and data interpretation from the sunitinib studies and how these findings and the sunitinib development program, in general, can be a model for successful development of other agents. Finally, ongoing research into the continued and future role of sunitinib in RCC management is discussed. ***The Oncologist*** 2017;22:41–52

**Implications for Practice:** Approved globally, sunitinib is established as a standard of care for first-line advanced renal cell carcinoma (RCC) therapy and, along with other targeted agents, has significantly altered the treatment landscape in RCC. Research with sunitinib that has sought to refine its role via patient selection and prognostic markers, improve dosing and adverse event management, and identify predictive efficacy biomarkers has contributed to the overall understanding and management of RCC. Key learnings regarding study design and data interpretation from the sunitinib studies and the sunitinib development program, in general, can be a model for the successful development of other agents.

## Introduction

Worldwide, approximately 338,000 patients are newly diagnosed each year with kidney cancer, with renal cell carcinoma (RCC) the most common type, and more than 143,000 patients die of this disease [1]. Of those newly diagnosed patients, up to 30% will present with metastatic disease, and up to 40% of patients initially treated for localized disease will eventually develop metastatic disease [2–4].

Historically, before the introduction of targeted therapies, cytokine-based therapy with interferon-α (IFN) and/or interleukin-2 (IL-2) was considered standard first-line treatment for patients with metastatic RCC (mRCC). However, the response rates were low (only approximately 15%), survival was limited (Fig. 1), and treatment-related toxicities restricted their usage [14]. In addition, previous studies of other therapies for cytokine-refractory patients with RCC were unable to show benefit [15].

RCC has several subtypes, but clear cell carcinoma is the most common (~70%–80% of all tumors) and is usually associated with inactivation of the von Hippel-Lindau *(VHL)* tumor-suppressor gene [16]. This leads to elevated levels of the transcription factor hypoxia-inducible factor *1*α (HIF-1α) and subsequent overexpression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), which promote tumor angiogenesis. Correspondingly, these pathways were logical therapeutic targets for drug development [16, 17] and led to U.S. Food and Drug Administration (FDA) approval of the receptor tyrosine kinase inhibitors (TKIs) sorafenib and sunitinib for use in patients with advanced RCC (Nexavar prescribing information,

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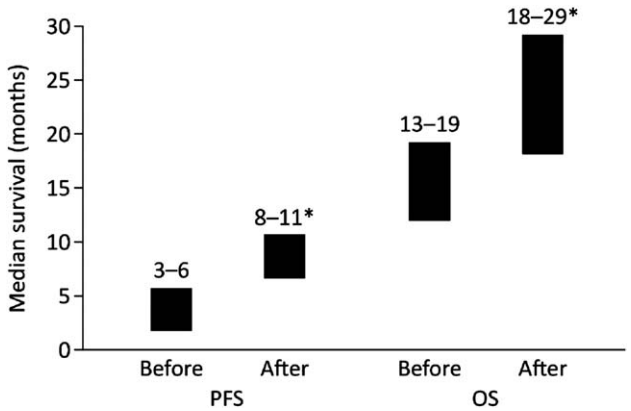


**Figure 1.** Range of median PFS and OS values in advanced RCC, before and after the era of targeted therapies. *, With TKIs as first-line mRCC therapy in primarily good- or intermediate-risk patients [5–13].

Abbreviations: mRCC, metastatic renal cell carcinoma; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; TKIs, tyrosine kinase inhibitors.

http://labeling.bayerhealthcare.com/html/products/pi/Nexavar_PI.pdf, and SUTENT prescribing information, http://labeling.pfizer.com/ShowLabeling.aspx?id=607, respectively).

Sunitinib malate (SUTENT; Pfizer Inc., New York, NY, http://www.pfizer.com) is an oral receptor TKI of VEGF receptor 1 (VEGFR-1), VEGFR-2, VEGFR-3, PDGF receptor-α (PDGFR-α), PDGFR-β, and other receptor tyrosine kinases. Sunitinib was first approved by the U.S. FDA in January 2006 for advanced RCC (SUTENT prescribing information). Since then, it has been approved globally for this indication and for patients with imatinib-resistant or -intolerant gastrointestinal stromal tumors and advanced pancreatic neuroendocrine tumors.

As we mark the 10-year anniversary of the beginning of the era of targeted therapy, and specifically the approval of sunitinib, it is worthwhile to highlight the progress that has been made in advanced RCC (evident by the improved survival times; Fig. 1) as related to the study of sunitinib. The purpose of the present report is to detail the key trials and data for sunitinib that established it as a reference standard of care for first-line advanced RCC therapy and, along with other targeted agents, significantly altered the treatment landscape in RCC. Moreover, we discuss the research with sunitinib that has sought to refine its role via patient selection and prognostic markers, improve dosing and adverse event management, and identify predictive efficacy biomarkers, plus the extent to which this research has contributed to the overall understanding and management of RCC. We also explore the key learnings regarding the study design and data interpretation from the sunitinib studies and how these findings, and the sunitinib development program in general, can be a model for successful development of other agents. Finally, ongoing research into the continued and future role of sunitinib in RCC management is discussed.

## Key Clinical Trials of Sunitinib in Advanced RCC

### Phase II Studies

In January 2006, the U.S. FDA granted accelerated approval for sunitinib in advanced RCC. Its approval was based on two consecutive open-label phase II studies in which treatment with sunitinib 50 mg/day on schedule 4/2 (4 weeks taking the drug and 2 weeks not taking it) resulted in unprecedented antitumor activity in patients with cytokine-refractory mRCC (Table 1) [18–20]. These studies represented a turning point in RCC therapy. The key efficacy and safety results from these two trials and others in the sunitinib clinical development program in RCC are summarized in Table 1.

In the initial phase II study ($n = 63$), 25 patients achieved a partial response according to investigator assessment, yielding an objective response rate (ORR), the primary endpoint, of 40% (Table 1) [18]. Adverse events (AEs) were mostly grade 1 or 2, with grade 4 AEs uncommon. In the second, larger phase II study ($n = 106$), the ORR by independent third-party assessment, the primary endpoint, was 33% (Table 1) [20].

### Pivotal Phase III Study

Interim results from the pivotal phase III trial of sunitinib in treatment-naïve mRCC patients [12, 13] established sunitinib as a reference standard of care for first-line mRCC therapy. In the trial, 750 treatment-naïve patients with mRCC were randomized 1:1 to either sunitinib 50 mg/day on schedule 4/2 or IFN 9 million units given subcutaneously three times weekly. The primary endpoint, progression-free survival (PFS), was significantly longer with sunitinib than with IFN (median, 11 vs. 5 months, respectively; hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.32–0.54; $p < .001$; Figure 2; Table 1). At the final analysis, the median overall survival (OS) was 26.4 versus 21.8 months for sunitinib versus IFN, respectively (HR, 0.821; 95% CI, 0.673–1.001; $p = .051$).

### Expanded-Access Program

Given the lack of active agents available in 2005 to treat advanced RCC, a global, expanded-access trial was implemented to provide sunitinib to patients in countries where its approval had not yet been granted and to those patients ineligible for registration-directed trials [27, 28]. For the 4,543 patients who received sunitinib in 50 countries, the ORR was 16% and the median PFS and OS were 9.4 and 18.7 months, respectively (Table 1). In addition, clinical benefit was observed in both treatment-naïve and previously treated patients, both older and younger patients, and patients traditionally with a poor prognosis, including patients with brain metastases.

In subpopulation analyses of patients from six different geographic regions, efficacy in each region was broadly similar to that in the overall expanded-access population, although the median OS appeared longer in Italy (27.2 months) and Central and Eastern Europe (30.7 months) [29–34]. In addition, most regions also reported efficacy (based on ORR) in patients from the poor prognosis groups. Finally, the safety profile of sunitinib in each region was consistent with that for the overall study population.

### Other Studies

In a phase II multicenter study of patients with bevacizumab-refractory mRCC ($n = 61$), sunitinib demonstrated antitumor activity with a tolerability safety profile [24]. The ORR, the primary endpoint, was 23.0% (Table 1).

In a phase II study of Japanese patients with treatment-naïve ($n = 25$) or cytokine-refractory ($n = 26$) mRCC and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 [23], the median OS exceeded 2.5 years (Table 1).

**Table 1.** Summary of key efficacy and safety results from the sunitinib clinical development program in RCC

| Study | Design (sunitinib dosing schedule; no. of patients) | Key efficacy results | Key safety results |
|---|---|---|---|
| 014 [18] | Phase II, cytokine-refractory mRCC (schedule 4/2; $n = 63$) | ORR, 40%[a]<br>Median TTP, 8.7 mo<br>Median OS, 16.4 mo | Most common grade 3 treatment-related AEs: fatigue (11%), nausea (3%), diarrhea (3%), and vomiting (3%)<br>Most frequent grade 3–4 laboratory abnormalities: increased lymphopenia (32%), elevated lipase (21%), neutropenia (13%), and anemia (10%) |
| 1006 [19, 20] | Phase II, cytokine-refractory mRCC (schedule 4/2; $n = 106$) | ORR, 33%[a,b]<br>Median PFS, 8.8 mo<br>Median OS, 23.9 mo | Most common AEs: fatigue (28%) and diarrhea (20%)<br>Most common laboratory abnormalities: neutropenia (42%), lipase elevation (28%), and anemia (26%) |
| 1061 [21] | Phase II, cytokine-refractory mRCC (CDD; $n = 107$) | ORR, 20%[a]<br>Median PFS, 8.2 mo<br>Median OS, 19.8 mo | Most common grade 3 treatment-related AEs: asthenia/fatigue (16%), diarrhea (11%), hypertension (11%), hand-foot syndrome (9%), and anorexia (8%) |
| 1110 [22] | Phase II, treatment-naïve mRCC (CDD; $n = 119$) | ORR, 35.3%[a]<br>Median PFS at 1 yr, 9 mo<br>1-yr survival probability, 67.8% | Most common treatment-related AEs: diarrhea (50%) and hand-foot syndrome (43%)<br>Most common grade 3–4 treatment-related AEs: hand-foot syndrome (13%), neutropenia (11%), and diarrhea (9%) |
| 1072 [23] | Phase II, treatment-naïve and cytokine-refractory mRCC, Japanese patients (schedule 4/2: $n = 51$) | ORR, 52.0% and 53.8%[a]<br>Median PFS, 12.2 and 10.6 mo<br>Median OS, 33.1 and 32.5 mo | Acceptable tolerability, with a favorable risk/benefit profile, similar to results from Western studies |
| 1038 [24] | Phase II, bevacizumab-refractory mRCC (schedule 4/2; $n = 61$) | ORR, 23.0%[a]<br>Median PFS, 30.4 wk<br>Median OS, 47.1 wk | Most treatment-related AEs were mild to moderate intensity |
| 1034 [12, 13] | Phase III, treatment-naïve mRCC, sunitinib vs. IFN (schedule 4/2; $n = 750$) | ORR, 31% vs. 6% ($p < .001$)[b]<br>Median PFS, 11 vs. 5 mo (HR, 0.42; $p < .001$)[a]<br>Median OS, 26.4 vs. 21.8 mo (HR, 0.821; $p$ 5 .051) | Most common grade 3–4 treatment-related AEs with sunitinib and IFN included hypertension (12% vs. 1%) and fatigue (11% vs. 13%) |
| 1065, Renal EFFECT [25] | Phase II, treatment-naïve advanced RCC (schedule 4/2 vs. CDD; $n = 292$) | ORR, 32.2% vs. 28.1% ($p = .444$)<br>Median TTP, 9.9 vs. 7.1 mo (HR, 0.77; $p = .090$)[a]<br>Median OS, 23.1 vs. 23.5 mo (HR, 1.09; $p = .615$) | No significant difference was observed in commonly reported AEs |
| 1132 [26] | Phase IV, treatment-naïve mRCC, Chinese patients (schedule 4/2; $n = 105$) | ORR, 31.1%<br>Median PFS, 61.7 wk (14.2 mo)[a]<br>Median OS, 133.4 wk (30.7 mo) | Most treatment-emergent AEs were grade 1–2 severity and were manageable using standard approaches |
| 1037 [27, 28] | Expanded-access program, cytokine-refractory or treatment-naïve mRCC (schedule 4/2 and CDD; $n = 4,543$) | ORR, 16%<br>Median PFS, 9.4 mo<br>Median OS, 18.7 mo | Most common grade 3–4 treatment-related AEs: thrombocytopenia (10%), fatigue (9%), and asthenia, neutropenia, and hand-foot syndrome (7% each) |

[a]Primary endpoint.
[b]Independent third-party assessment.
Abbreviations: AE, adverse event; CDD, 37.5 mg/day on a continuous daily dosing schedule; HR, hazard ratio; IFN, interferon-ff; mRCC, metastatic renal cell carcinoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; schedule 4/2, 50 mg/day on a 4-weeks-on/2-weeks-off schedule; TTP, time to tumor progression.

With acceptable tolerability, treatment with sunitinib showed a favorable risk/benefit profile in that study, similar to that in Western studies.

An open-label, multicenter, phase IV study of sunitinib was conducted in treatment-naïve Chinese patients with mRCC ($n = 105$) [26]. In the first prospective study to assess sunitinib treatment in this population, sunitinib showed activity and had a manageable AE profile as first-line therapy. The median PFS (the primary endpoint) was 61.7 weeks (Table 1).

## Prognostic Factors and Patient Selection for Sunitinib

The identification of various prognostic factors, including clinical and molecular markers, and the subsequent development

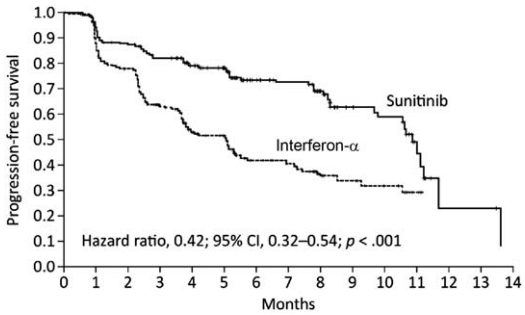


**Figure 2.** Kaplan-Meier estimates of PFS from the pivotal phase III trial. From *New England Journal of Medicine*, Motzer RJ, Hutson TE, Tomczak P et al., Sunitinib Versus Interferon Alfa in Metastatic Renal-Cell Carcinoma, 356,115–124, © 2007 Massachusetts Medical Society [12]. Reprinted with permission.

Abbreviation: CI, confidence interval; PFS, progression-free survival.

of risk models, such as the Memorial Sloan Kettering Cancer Center (MSKCC) model and, more recently, the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model, have given clinicians the ability to classify an individual patient according to the patient's risk of progression (i.e., favorable, intermediate, or poor risk), providing guidance regarding the selection and sequencing of therapy [35–38]. The investigation of such factors using patient data from sunitinib trials has allowed better selection of mRCC patients who are most likely to benefit from sunitinib treatment and provided further validation of the established risk models.

Using pooled data from 1,059 mRCC patients who received sunitinib in six clinical trials in the first-line ($n = 783$; 74%) or cytokine-refractory ($n = 276$; 26%) setting, retrospective analyses of potential baseline prognostic variables for PFS, OS, and long-term OS (i.e., OS $\geq$30 months) with sunitinib were conducted [39]. The results of a multivariate Cox regression model found that independent predictors for PFS and OS with sunitinib include ethnic origin, ECOG performance status, time from diagnosis to treatment, previous cytokine use, hemoglobin, lactate dehydrogenase (LDH), and corrected calcium level, neutrophil and platelet counts, and bone metastases (OS only). Survival did not significantly differ between white and Asian patients but did differ between white versus nonwhite, non-Asian patients. Finally, specific independent predictors of long term OS included ethnic origin (median, 50.2 vs. 38.4 months in white vs. nonwhite patients, respectively; HR, 0.339; $p = .0257$), bone metastases (median, 42.7 vs. 54.5 months for patients with vs. without metastases; HR, 2.337; $p = .0061$), and corrected calcium (median, 41.7 vs. 50.2 months for patients with $>10$ vs. $\leq 10$ mg/dL calcium; HR, 4.356; $p = .0028$).

These findings were similar to those for an earlier retrospective multivariate analysis of prognostic factors using data from sunitinib-treated patients in the pivotal phase III trial only, which confirmed the applicability of the MSKCC model in the era of targeted therapy [37]. The following five factors were identified as independent predictors for PFS with sunitinib: serum LDH level, the presence of two or more metastatic sites, no previous nephrectomy, ECOG performance status, and baseline platelet count. The serum LDH level, corrected serum calcium level, time from diagnosis to treatment, hemoglobin level, ECOG performance status, and presence of bone metastases were identified as independent predictors of OS with sunitinib.

The prognostic significance of bone metastases has been established in multiple analyses of sunitinib and VEGF therapies [40, 41]. For example, in a retrospective analysis of patients from the sunitinib expanded-access program with ($n = 1,147$) versus without ($n = 2,817$) baseline bone metastases who did not receive bisphosphonates, the median OS was 14.1 versus 22.0 months (HR, 0.7004; $p < .0001$; and HR, 0.841; $p < .001$ by univariate and multivariate analysis, respectively) [41]. The IMDC prognostic model was externally validated using the final patient data from the sunitinib expanded-access program—the largest contemporary patient population evaluated to date using an RCC prognostic model [28].

Current treatment recommendations for mRCC are based on the prognostic risk groups defined by combinations of the factors described above. Correct risk profiling of the individual patient is therefore critical in the overall treatment of the patient. For its part, sunitinib is included in all the major U.S. and European Union mRCC treatment guidelines (i.e., the European Urology Association, European Society of Medical Oncology [ESMO], European Organization for Research and Treatment of Cancer Genito-Urinary Group [EORTC-GU], and U.S. National Comprehensive Cancer Network [NCCN]) [42–46]. Across all guidelines, sunitinib is recommended as first-line therapy for good- or intermediate-risk patients and, with varying degrees of evidence, as a nonstandard or alternative treatment option for poor-risk patients in the ESMO and EORTC-GU guidelines, respectively. In the NCCN guidelines, sunitinib is also recommended as second-line therapy for patients with cytokine-refractory disease or for those who have previously received another first-line TKI therapy.

## Optimizing Treatment With Sunitinib

Maximal clinical effect with sunitinib is achieved through maximal exposure to the drug; however, this can lead to an increase in the risk of AEs [47, 48]. Long-term survival is therefore achieved through proactive and ongoing therapy management, which encompasses optimized dosing, proactive management of AEs, and maximized duration of treatment [49], as well as the potential use of predictive efficacy biomarkers and various treatment strategies.

### Dose and Schedule

Before its approval, sunitinib was assessed in phase I solid tumor studies at doses ranging from 25 to 150 mg/day using three different cycles: 2 weeks on/1 week off (schedule 2/1), 2 weeks on/2 weeks off (schedule 2/2), and 4 weeks on/2 weeks off (schedule 4/2) [16]. The frequency and severity of AEs generally correlated with greater drug exposure. The primary dose-limiting toxicity (DLT) associated with sunitinib in these studies was fatigue/asthenia, which occurred approximately 1–2 weeks after the start of therapy but was reversible during the off-treatment period within each cycle.

Based on these studies, the recommended dose and schedule for use in the phase II RCC trials was 50 mg/day using schedule 4/2, the dosing regimen subsequently approved for

use. However, additional studies have assessed alternative dosing schedules to determine whether the clinical benefit with sunitinib in patients with advanced RCC can be maintained while improving the associated safety profile and health-related quality of life (QoL).

In a phase II study of patients with cytokine-refractory mRCC ($n = 107$), sunitinib 37.5 mg administered as a continuous once-daily dosing regimen in the morning or evening had a manageable safety profile, providing flexible dosing (Table 1) [21]. The efficacy, tolerability, and QoL results were similar between patients dosed in the morning or evening.

In a phase II study of treatment-naïve patients with mRCC, sunitinib 37.5 mg continuous daily dosing (CDD) was active, with a manageable safety profile as first-line mRCC therapy, providing further evidence of the feasibility of this dosing regimen [22]. The ORR (the primary endpoint) was 35.3% (Table 1). The patient-reported outcomes were largely maintained, although fatigue appeared to worsen after treatment started, with improvement over time.

A randomized phase II study (the Renal EFFECT trial [randomized phase II study of the efficacy and safety of sunitinib malate schedule 4/2 vs. sunitinib malate continuous dosing as first-line therapy for metastatic renal cell cancer]) compared the outcomes for treatment-naive patients with advanced RCC who received sunitinib, schedule 4/2 versus CDD [25]. The median time to tumor progression (TTP; the primary endpoint) was numerically longer with schedule 4/2 than with CDD (Table 1). In addition, schedule 4/2 was superior to the CDD schedule according to a composite endpoint of time to deterioration, which included death, disease progression, and progression of disease-related symptoms ($p = .034$). No benefit was seen in the efficacy or safety for continuous dosing of sunitinib compared with the approved 50 mg/day dose on schedule 4/2. Also, given the numerically longer TTP with the approved 50-mg dose on schedule 4/2, the investigators concluded that adherence to this dose and schedule should remain the treatment goal for patients with advanced RCC.

Several studies, however, including the RAINBOW, RESTORE (randomized phase II trial of sunitinib four weeks on and two weeks off vs. two weeks on and one week off in metastatic clear-cell type renal cell carcinoma), and single-center studies, have investigated sunitinib on schedule 2/1 or other alternative schedules (in both Western and Asian patients with advanced RCC). The results from these studies suggest that schedule 2/1 might have an improved safety profile compared with schedule 4/2 but with similar efficacy [50–57]. Patients experiencing AEs with schedule 4/2 might tolerate treatment better when switched to schedule 2/1. Prospective studies with this schedule will allow a better understanding of its efficacy.

## Treatment Duration and Exposure

As might be expected, a longer treatment duration was associated with increased response rates in the pivotal phase III trial [12, 13, 58]. Moreover, in an exploratory pharmacokinetic/pharmacodynamic meta-analysis of 639 RCC and gastrointestinal stromal tumor patients with available pharmacodynamic data (443 with pharmacokinetic data), increased exposure to sunitinib was associated with longer TTP and OS and a greater chance of antitumor response [47].

## Adverse Event Management

The commonly reported AEs with sunitinib in patients with mRCC include diarrhea, fatigue, nausea, mucositis/stomatitis, vomiting, dyspepsia, hypertension, abdominal pain, rash, and hand-foot syndrome (SUTENT prescribing information), many of which are common with all targeted agents, including both TKIs and mammalian target of rapamycin (mTOR) inhibitors. However, some AEs are specific to TKIs, including sunitinib, such as hepatotoxicity with aspartate transaminase/alanine transaminase elevation and hypertension.

Proactive AE assessment and management can ensure optimal benefit with sunitinib [59]. Sunitinib has a predictable and manageable tolerability profile, which facilitates proactive and effective therapy management interventions, ensuring that patients receive optimal clinical benefit from their treatment and maintain their QoL [13, 27, 48, 49, 60, 61].The intermittent dosing schedule (schedule 4/2), for example, is associated with a predictable "on-off" effect. Moreover, the extensive clinical experience now available with sunitinib after several years of use has enabled clinicians to avoid discontinuation of treatment by controlling most AEs with appropriate supportive and prophylactic measures, to achieve long-term benefits.

Retrospective interval and cumulative time period analyses of long-term safety with sunitinib using pooled data from mRCC patients from nine trials ($n = 5,739$) have shown that prolonged use of sunitinib (up to 6 years) is not associated with new types or increased severity of treatment-related AEs [62]. Except for hypothyroidism, which can be monitored and treated per standard medical practice, toxicity is not cumulative. Clinicians may, therefore, be able to prescribe long-term sunitinib for as long as patients continue to derive clinical benefit, without unnecessary additional risk.

The use of TKIs is associated with an elevated risk of congestive heart failure (CHF), and sunitinib is no exception. In a meta-analysis of 6,935 sunitinib-treated patients (with and without RCC), the incidence of all- and high-grade CHF was 4.1% and 1.5%, respectively [63]. Also, in a retrospective analysis, nearly 20% of patients taking sunitinib had a reduction in their left ventricular ejection fraction (LVEF) by $\geq$15% [64]. In addition, patients with underlying risk factors, such as a history of coronary artery disease or hypertension, have an increased risk of cardiotoxicity from sunitinib [65]. However, the relative risk of CHF among approved TKIs is similar [66], and a comprehensive adjudicated database analysis of 1,090 sunitinib-treated patients from two phase III clinical trials demonstrated reversibility of clinically meaningful cardiovascular AEs [67]. In addition, in a prospective analysis of cardiotoxicity in patients with resected high-risk RCC who had received adjuvant sunitinib (or sorafenib) versus placebo, the incidence of LVEF decline ($>$15% and less than the institutional lower limit of normal) with sunitinib did not significantly differ versus placebo (1.8% vs. 0.9%; $p = .28$). Similarly, no difference was found in the incidence of symptomatic heart failure, arrhythmia, or myocardial ischemia [68].

The safety profile of sunitinib has been investigated in special subpopulations, such as those with a traditionally poor prognosis. In the final report of the sunitinib expanded-access program, it was shown that the incidence of non hematological, treatment-related AEs of any grade was comparable among

patients aged ≥65 years (33% of the total population), those with non-clear cell histologic features (12%), and the overall population. Also, the incidence was lower in patients with an ECOG performance status ≥2 (14%) or with baseline brain metastases (7%) compared with the overall population [28]. Similarly, in a phase II study of patients with mRCC and previously untreated brain metastases ($n = 16$), the tolerability with the standard regimen of sunitinib was acceptable [69]. In addition, in a retrospective analysis of outcome with sunitinib as a function of age (<70 vs. ≥70 years) in mRCC patients, based on the safety profile (and comparable efficacy), the investigators concluded that advanced age should not be a deterrent to sunitinib therapy [70].

### Predictive Efficacy Biomarkers of Sunitinib

Several areas of research have investigated the potential predictive biomarkers of efficacy with sunitinib in patients with mRCC, including biological (e.g., serum- and tissue-based biomarkers) and clinical (e.g., mechanism-based AEs and response status) correlates, shedding light on potential areas of research for further investigation with sunitinib and other therapies [71–76]. Some of the early studies explored potential biomarkers of sunitinib pharmacological activity via serial assessment of plasma levels of four soluble proteins from patients in the initial phase II study of cytokine-refractory advanced RCC, all of which are components of the angiogenesis system: VEGF, soluble VEGFR-2 (sVEGFR-2), placenta growth factor, and a novel soluble variant of VEGFR-3 (sVEGFR- 3) [71]. Overall, significantly larger changes in VEGF, sVEGFR-2, and sVEGFR-3 levels were observed in patients with an objective tumor response compared with those with stable disease or disease progression ($p < .05$ for each analyte). These findings suggested that these proteins could be of value as biomarkers of clinical activity of sunitinib in patients with RCC and of angiogenic processes in cancer and other diseases. Similarly, the plasma levels of VEGF-A, VEGF-C, sVEGFR-3, and IL-8 were investigated as potential biomarkers using patient data from the pivotal phase III trial in the first-line setting [75]. The findings suggested that baseline VEGF-A and IL-8 might have prognostic value (both were significantly associated with OS by univariate analysis in both treatment arms [$p < .05$] and remained independent predictors of a lower risk of death by multivariate analysis in the sunitinib arm; $p < .05$). In addition, baseline sVEGFR-3 might predict sunitinib efficacy (in the sunitinib arm, this analyte was significantly associated with both PFS and OS by univariate analysis [$p < .05$] and was an independent predictor of OS by multivariate analysis [$p < .05$]).

Clear cell RCC is usually associated with inactivation of the *VHL* tumor-suppressor gene, which leads to elevated levels of the transcription factor HIF-1α and subsequent over expression of VEGF and PDGF. Thus, HIF-1α expression has also been a focus of biomarker studies [16], with early promising preclinical data for sunitinib [77]. Subsequently, tumor samples from mRCC patients receiving sunitinib and other targeted agents have been analyzed via immunohistochemistry (IHC) and other methods to examine HIF-1α as a potential marker [76]. Using patient data from the Renal EFFECT study and relying on Kaplan-Meier-derived statistical significance, the HIF-1α percentage of tumor expression, as assessed by IHC, was significantly associated with PFS to sunitinib [76]. In the same study, circulating angiopoietin-2 (Ang-2) and matrix metalloproteinase-2 (MMP-2), identified via two independent multiplex platforms, were also significantly associated with outcome (tumor response). In contrast, germline single nucleotide polymorphisms in VEGF-related genes and *VHL* inactivation mechanisms were not associated with the outcome, despite previous studies indicating a potential role. However, using the same data set, a more stringent performance assessment that incorporated sensitivity and specificity characteristics, a receiver operating characteristics model, concluded that neither Ang-2 nor MMP-2, nor the HIF-1α percentage of tumor expression, performed appropriately from a patient-selection standpoint [78].

Genome-wide association studies (GWASs) have also been used to detect genetic variants potentially useful in predicting both clinical outcome and toxicity to cytotoxic chemotherapy and targeted agents [79]. The variant (rs34231037/C482R) was shown to be associated with both lower baseline sVEGFR2 levels and a greater decline in sVEGFR2 in response to pazopanib treatment in patients with RCC [80]. In addition, in what the investigators concluded was the largest GWAS for response and toxicity to antiangiogenesis therapies in RCC reported to date ($n = 1{,}099$ RCC patients treated with pazopanib or sunitinib) [81], genetic markers were found to be significantly associated with combined efficacy endpoints (a common variant intronic in *LOXL2* and *ENTPD4* with PFS, OS, and best response) and safety endpoints (common variants near *UGT1A1* with bilirubin elevation in pazopanib-treated patients and a common variant intergenic between *ANAPC4* and *SLC34A2* with hand-foot syndrome).

Next-generation sequencing (NGS) has been used to identify prevalent mutations in epigenetic regulators with prognostic significance in RCC. In a study of patients from the RECORD-3 (efficacy and safety comparison of RAD001 [everolimus] vs. sunitinib in the first-line and second-line treatment of patients with metastatic renal cell carcinoma) trial [82], somatic mutations in the epigenetic regulator *KDM5C* (an HIF-dependent transcription target that functions as a tumor suppressor) were identified by NGS assay and found to be associated with longer PFS with sunitinib.

To date, none of these biomarkers have been validated for use with targeted therapies or integrated into a prognostic model. An alternative to biological correlates as biomarkers of efficacy are mechanism-based AEs that reflect "on-target" effects of molecularly targeted agents and are common, manageable, and readily and systematically measurable. Using a pooled database of five prospective clinical trials, a retrospective combined AE model identified on-treatment neutropenia and hypertension as independent biomarkers of sunitinib efficacy in patients with mRCC [72, 73]. Patients with sunitinib-induced hypertension, defined by maximum systolic blood pressure (BP) ≥140 mmHg, had significantly longer PFS (12.5 vs. 2.5 months) and OS (30.9 vs. 7.2 months) than patients without treatment-induced hypertension ($p < .001$ for both). Similar results were obtained when comparing patients with and without sunitinib-induced hypertension, defined by a maximum diastolic BP of ≥90 mmHg [72]. A recently reported combined AE model subsequently assessed the relative strength and independence of each biomarker in a final

combined multivariate analysis using the same database ($n = 770$) and identified on-treatment neutropenia and hypertension as independent biomarkers of sunitinib efficacy [73]. In addition, the incorporation of both AEs into the IMDC prognostic model improved its prognostic accuracy.

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A pooled retrospective analysis of mRCC patients treated in phase II and III Pfizer-sponsored studies between 2003 and 2011 ($n = 2,749$, of whom 1,059 had received sunitinib) found that tumor response was an independent prognostic factor for both PFS and OS (even with patients stratified by first-or second-line therapy and ECOG performance status). In addition, the depth of remission was an independent prognostic factor, with major tumor shrinkage of 60% or more associated with a median OS of 54.5 months [74].

### Treatment Strategies

Current evidenced-based treatment guidelines provide recommendations for targeted therapies by treatment setting and patient risk profile. Within this framework, choices can remain regarding the optimal sequence of therapies or algorithm for a given patient, prompting the study of sunitinib in sequence with other agents (and as rechallenge therapy) [83–85]. Based on the compelling rationale to combine targeted agents in order to inhibit multiple tumor pathways (e.g., VEGF and mTOR), several studies have investigated sunitinib in combination with other targeted agents [86].

The open-label phase III SWITCH study ($n = 365$) [83] prospectively evaluated sequential use of sorafenib followed by sunitinib versus sunitinib followed by sorafenib in patients with mRCC. The total PFS (the primary endpoint) was not superior with the sorafenib-sunitinib versus the sunitinib-sorafenib arm (12.5 vs. 14.9 months, respectively; HR, 1.01; $p = .5$), and OS was comparable in both arms (31.5 vs. 30.2 months, respectively; HR, 1.00; $p = .5$). The safety profiles were as expected.

The randomized phase II RECORD-3 study ($n = 471$) [84] compared first-line everolimus followed by sunitinib at progression with the standard sequence of first-line sunitinib followed by everolimus in mRCC patients. Everolimus did not demonstrate noninferiority in PFS (the primary endpoint) compared with sunitinib (7.9 vs. 10.7 months; HR, 1.4), supporting the standard treatment paradigm of first-line sunitinib followed by everolimus at progression.

In an observational study of 61 mRCC patients, sunitinib rechallenge in the third-line or later setting was found to be a feasible treatment option with potential clinical benefit in mRCC patients who experienced disease progression with first-line sunitinib [85]. With first-line sunitinib and rechallenge, the median PFS was 18.4 and 7.9 months and the ORR was 54% and 15%, respectively; the median OS was 55.9 months overall. The sunitinib rechallenge safety profile was as expected, with no new AEs reported. The investigators therefore concluded that disease progression with first-line sunitinib might not be associated with complete or irreversible resistance to therapy.

The results of sunitinib as combination therapy with other targeted agents have been disappointing, largely because of issues of intolerable toxicity. Sunitinib has been studied in two separate phase I combination studies with the FDA-approved mTOR inhibitors temsirolimus and everolimus in patients with mRCC [87, 88]. In the first study with temsirolimus, DLT was observed at low starting doses of both agents, and in the second study with everolimus, the combination was associated with significant acute and chronic toxicities and only tolerated at attenuated doses.

Sunitinib was also studied in a phase I study as combination therapy with the VEGF inhibitor bevacizumab in mRCC patients [89]. However, this combination was also intolerable, with patients experiencing a high degree of hypertension and vascular and hematologic toxicities at the maximum tolerated dose of both agents.

An open-label phase II study of sunitinib plus the investigational recombinant peptide-Fc fusion protein trebananib ($n = 85$) suggested a potential benefit in efficacy. However, again, despite this finding, the toxicity at the tested doses seemed to increase with the combination [90].

In contrast, sunitinib has shown promising results in combination with the cytotoxic chemotherapy gemcitabine in patients with sarcomatoid and/or poor-risk mRCC [91]. In a single-arm phase II study ($n = 39$), the combination appeared to be more efficacious than either therapy alone (e.g., the ORR was 26% and 24% for patients with sarcomatoid RCC and poor-risk RCC, respectively) and was tolerated in such a patient population. In addition, a phase II study of sunitinib plus AGS-003, an autologous immunotherapy, as first-line therapy in patients with intermediate and poor-risk mRCC ($n = 21$) found that the combination was well tolerated and yielded supportive immunologic responses with extended survival [92]. No patients experienced a complete response (the primary endpoint) but nine patients had a partial response and four, stable disease. The median PFS and OS from registration were 11.2 and 30.2 months, respectively.

These positive findings for combination therapy, in particular for sunitinib plus AGS-003, which is the subject of an ongoing phase III trial and could ultimately change the standard of care for intermediate- and poor-risk patients [93], warrant further investigation. However, it should be noted that a recent phase III trial combining sunitinib with the IMA901 multipeptide vaccine failed to show benefit compared with sunitinib alone [94].

## Key Insights in Trial Design and Data Interpretation for Sunitinib

Starting with its preclinical models and phase I study to the two phase II studies and pivotal phase III trial, resulting in accelerated and standard FDA approval, respectively, the clinical development program for sunitinib in RCC has been a paradigm of "bench to bedside" research, setting an example for the

**Table 2.** Ongoing phase III trials with sunitinib in RCC

| Study | Design (estimated enrollment) | Estimated primary completion date (ClinicalTrials.gov ID) |
|---|---|---|
| S-TRAC (1109) | Adjuvant sunitinib vs. placebo ($n = 600$) | April 2016 (NCT00375674) |
| ASSURE (ECOG 2805) | Adjuvant sunitinib vs. sorafenib vs. placebo (nonmetastatic RCC; $n = 1,923$) | April 2016 (NCT00326898) |
| SURTIME | Sunitinib + immediate vs. deferred nephrectomy ($n = 458$) | December 2015 (NCT01099423) |
| CARMENA | Sunitinib + nephrectomy vs. sunitinib ($n = 576$) | September 2019 (NCT00930033) |
| STAR | Conventional continuation vs. drug-free interval strategy with sunitinib or pazopanib ($n = 1,000$) | April 2018 (ISRCTN06473203)[a] |
| CHECKMATE 214 | Nivolumab + ipilimumab vs. sunitinib ($n = 1,070$) | November 2017 (NCT02231749) |
| ADAPT | AGS-003 autologous immunotherapy + sunitinib ($n = 450$) | April 2016 (NCT01582672) |
| IMPRINT | IMA901 multipeptide cancer vaccine + sunitinib vs. sunitinib ($n = 330$) | Completed (NCT01265901) |
| RAPID | Atezolizumab + bevacizumab vs. atezolizumab vs. sunitinib ($n = 305$) | January 2016 (NCT01984242) |
| ECOG-E1808[b] | Sunitinib + gemcitabine vs. sunitinib (advanced RCC with sarcomatoid features; $n = 100$) | June 2021 (NCT01164228) |

[a]Registered at http://www.controlled-trials.com.
[b]Phase II study.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ID, identification; RCC, renal cell carcinoma.

development of other drugs [95]. However, the clinical trial program for sunitinib also exemplifies some of the challenges associated with development of targeted agents (rather than, for example, with the newer immunotherapies), necessitating novel statistical approaches to address these issues. Moreover, as the reference standard of care in the first-line setting, sunitinib has become not only the comparator arm for other agents, in terms of clinical benefit, but also for economic evaluation.

## Survival Analysis

In the phase III trial of treatment-naïve patients with mRCC, the median OS—traditionally the reference standard for evaluation of cancer therapies—did not significantly differ between the two treatment arms [13]. At that time, the investigators proposed that this was likely due to both crossover from the IFN arm to the sunitinib arm and to the confounding influence of post-study cancer treatment (33% and 32% of patients randomized to the IFN arm received post-study sunitinib and other VEGF inhibitors, respectively). Therefore, exploratory analyses were conducted to separately censor the crossover patients and any patients who received post-study treatment. As a result, statistically significant improvement in OS with sunitinib versus IFN was demonstrated (the latter method demonstrated a twofold increase in median OS, 28.1 vs. 14.1 months, respectively; HR, 0.647; $p = .003$). However, such methods could be associated with selection bias [96].

Because of the survival results for sunitinib (and similar findings for other targeted agents), attention turned to the viability of PFS as a standard endpoint for evaluating new therapies [97]. The general consensus has been that, despite inherent biases, PFS is a valid and acceptable outcome measure in mRCC (e.g., acceptable to regulatory authorities) if its improvement is of sufficient magnitude to be considered clinically relevant. In addition, it should be concordant with, and linked to, the OS and QoL data [97].

To determine the suitability of PFS as a surrogate endpoint for OS, the relationship between PFS and postprogression survival (PPS; the difference between PFS and OS) was studied using data from the phase III study [98]. In a Weibull parametric model, longer PFS was significantly predictive of longer PPS ($p < .001$). The model also allowed the prediction of an estimated median PPS duration from the actual PFS times. As a result of the positive relationship found between PFS and PPS, the investigators concluded that PFS could act as a surrogate endpoint for OS.

Using data from the phase III trial, researchers have also shown that sunitinib, compared with IFN, reduced the tumor growth rate in treatment-naïve patients with mRCC and that this rate correlated with OS, suggesting its potential use as an important clinical trial endpoint [99].

Finally, two statistical modeling techniques that have been used to correct for crossover in oncology trials and are considered relevant by health technology assessment authorities are the inverse probability of censoring weighting model and the rank-preserving structural failure time model [100]. Both models were used to reanalyze data from the phase III sunitinib trial, determining new HR values for OS. The variation in HR from the two models compared with the previously reported intent-to-treat and censored HR values was not as pronounced as the findings from a separate analysis using data from a phase III sunitinib trial in gastrointestinal stromal tumor [96]. However, this work resulted in specific recommendations for the use of these models in future studies and highlighted the potential impact of such modeling on subsequent cost-effectiveness analyses. As further described in the next section, choices in study design can have major implications for real-world evaluation (e.g., cost effectiveness).

## Economic Evaluation

Using data from the phase III trial, the cost effectiveness and cost utility of sunitinib as first-line mRCC therapy compared with IFN and IL-2 were assessed from a U.S. societal perspective [101]. Treatment with sunitinib was associated with estimated gains in progression-free life years (PFLYs) of 0.41 and 0.35, life-years (LYs) of 0.11 and 0.24, and quality-adjusted life years (QALYs) of 0.14 and 0.20 compared with IFN and IL-2, respectively. In addition, both IFN and sunitinib treatment dominated IL-2 treatment. The incremental cost-effectiveness ratio of sunitinib versus IFN was $18,611 per PFLY gained and $67,215 per LY gained, and the cost-utility ratio was $52,593 per QALY gained (at a 5% discount rate). The results indicated that

sunitinib was cost effective compared with IFN as first-line mRCC therapy. Similarly, an analysis of the economic value of sunitinib as first-line mRCC therapy in the Spanish health care system found that sunitinib was a cost-effective alternative to other targeted therapies, specifically sorafenib and bevacizumab plus IFN [102].

The cost effectiveness of sunitinib has been compared with other agents in both first- and second-line mRCC settings across numerous countries (e.g., Sweden, Canada, United Kingdom, Colombia, Mexico, Israel, Brazil, Finland, Belgium). Based on a systemic data search of these studies, the investigators concluded that in most economic evaluations sunitinib can be considered a cost-effective treatment option compared with other treatments [103]. The incremental cost-effectiveness ratio was most often in a range considered acceptable for novel cancer treatments, and, as first-line therapy, sunitinib demonstrated cost savings compared with some other targeted treatments.

## The Future of Sunitinib in RCC

As evidenced by the number of ongoing phase III studies (Table 2), a key area of future research remains the role of nephrectomy, which remains unclear in the setting of sunitinib treatment and other targeted agents, and adjuvant use of sunitinib. Regarding the latter, preliminary results from the placebo-controlled phase III ASSURE trial ($n = 1{,}943$), designed to assess adjuvant use of sunitinib versus sorafenib in patients with resected RCC, were not promising [104]. At the interim analysis, no significant differences were found in disease-free survival (DFS; the primary endpoint) with sunitinib or sorafenib versus placebo (5.6 and 5.6 vs. 5.7 years, respectively; HR, 1.00, $p = .96$; and HR, 0.97, $p = .74$ vs. placebo, respectively). The investigators concluded that adjuvant treatment with sorafenib or sunitinib should not be pursued. However, it was recently reported that the phase III S-TRAC trial of sunitinib versus placebo in the adjuvant setting had met its primary endpoint of improved DFS. That study of RCC patients at high risk of recurrence after surgery is the first such trial of the use of a TKI to prolong DFS in the adjuvant setting [105].

Potential neoadjuvant use of sunitinib has also been studied, with several case series reporting tumor responses and reduction in primary tumor size, allowing surgical excision. However, routine preoperative use of sunitinib and other targeted therapies for patients with otherwise resectable disease is not currently recommended, until further research has defined the most appropriate scenarios for their use [106].

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Methods to optimize the dosing schedule with sunitinib continue to be explored. The phase III STAR trial (Table 2) is investigating the use of a conventional continuation strategy (i.e., standard dose and schedule) versus a drug-free interval strategy (i.e., standard dose and schedule for four 6-week cycles, followed by a planned treatment break until progressive disease) with sunitinib or pazopanib (which has demonstrated noninferiority to sunitinib for PFS [9]) in treatment-naïve mRCC patients.

Several other ongoing trials (CHECKMATE 214, ADAPT, IMPRINT, and RAPID; Table 2) in which sunitinib is either compared against or combined with immunotherapy reflect the heightened and renewed interest in such treatments. These treatments have shown promising clinical activity in advanced RCC, including nivolumab, which was recently approved by the U.S. FDA for use in patients with advanced RCC who have received previous antiangiogenic therapy (OPDIVO prescribing information, http://packageinserts.bms.com/pi/pi_opdivo.pdf). Finally, the phase III ECOG-E1808 study is following up on the promising phase II results with sunitinib combined with gemcitabine for patients with advanced RCC with sarcomatoid features.

## Conclusion

Beginning with the two phase II studies of sunitinib in patients with cytokine-refractory mRCC, which demonstrated previously unseen tumor response rates, to the pivotal phase III trial of treatment-naïve mRCC patients, which established sunitinib as a reference standard of care, these early milestones marked the beginning of a revolution in the treatment of advanced RCC. The development of sunitinib and other targeted therapies significantly improved the treatment landscape in mRCC and has certainly extended survival for many patients. Moreover, the research conducted during the past 10 years, which continues in ongoing trials, represents the lasting commitment in the development program for sunitinib to maximize its clinical benefit and shed further light on issues affecting the overall management of RCC.

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## Disclosures

**Robert J. Motzer**: Pfizer, Novartis, Eisai Inc. (C/A), Pfizer, Novartis, Eisai Inc., Roche-Genentech, Bristol-Myers Squibb (RF); **Bernard Escudier**:

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