

Economic Evaluation of Sunitinib Malate for the First-Line Treatment of Metastatic Renal Cell Carcinoma

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ABSTRACT

Purpose

To assess the cost effectiveness and cost utility of sunitinib malate as a first-line treatment in metastatic renal cell carcinoma (mRCC) compared with interferon- α (IFN- α) and interleukin-2 (IL-2) from a US societal perspective.

Methods

A Markov model was developed to simulate disease progression and to determine progression-free survival, total life-years (LYs), and quality-adjusted life-years (QALYs) gained. Model parameters were derived from the pivotal trial of sunitinib, published literature, government sources, and clinical experts' opinions. The model included trial-based adverse events (AEs). Costs of drug treatment, routine follow-up, AEs, disease progression, and best supportive care (BSC) of terminally ill patients were included. Results were tested using probabilistic and deterministic sensitivity analyses.

Results

Treatment with sunitinib is associated with a gain in progression-free years of 0.41 and 0.35 over IFN- α and IL-2. The estimated gains over IFN- α were 0.11 LYs and 0.14 QALYs, and over IL-2 were 0.24 LYs and 0.20 QALYs. Both IFN- α and sunitinib treatments dominate IL-2 treatment; the incremental cost-effectiveness ratio of sunitinib versus IFN- α was \$18,611 per progression-free year gained and \$67,215 per LY gained, and the cost-utility ratio is \$52,593 per QALY gained (at a 5% discount rate). Sensitivity analyses found the results to be most sensitive to utility values during treatment, the cost of sunitinib, and the cost of BSC. Model results were robust to changes in other model variables.

Conclusion

These results suggest that sunitinib is a cost-effective alternative to IFN- α as a first-line treatment for mRCC.

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INTRODUCTION

Renal cell carcinoma (RCC), the most prevalent kidney cancer, is a relatively rare malignancy with a poor prognosis; fewer than 10% of patients with metastatic disease survive beyond 5 years.^{1,2} This is partly due to the lack of early symptoms; approximately 25% to 30% of patients present with metastases.³ RCC is frequently resistant to hormone, chemotherapeutic, and radiation therapies, which have failed to improve outcomes for patients with metastatic disease.² Cytokine therapies, including interferon- α (IFN- α) and interleukin-2 (IL-2), can be used for metastatic RCC (mRCC),⁴ but appear to be effective in a small patient subset and can lead to debilitating adverse effects.³⁻⁵ Studies of chemotherapy combined with cytokine therapy have been discourag-

ing. The increasing global incidence of RCC^{2,3} indicates a clear medical need for new treatments.

Sunitinib malate (SUTENT; Pfizer Inc, New York, NY) is a new orally administered small molecule with antitumor and antiangiogenic activity. Sunitinib inhibits the tyrosine kinase enzymatic activities of receptors overexpressed in mRCC, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). A pivotal, randomized, phase III trial of first-line treatment in patients with mRCC demonstrated median progression-free survival (PFS) of 11 months for sunitinib-treated patients versus 5 months for IFN- α -treated patients (hazard ratio [HR], 0.42; 95% CI, 0.32 to 0.54; $P < .001$).⁶ Evidence suggests that sunitinib offers clinical benefits; however, the financial implications of its use remain unclear.

Decisions regarding health care provision are based increasingly on economic evaluations to

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identify treatments that provide the greatest clinical benefit at acceptable costs. Cancer trials rarely collect enough data on treatment costs and consequences for rigorous economic assessment. Thus, mathematical modeling is required to support decision making. Used appropriately, modeling is a useful technique, particularly to extrapolate beyond trial durations, but bias associated with measuring overall survival (OS) after disease progression or treatment failure must be avoided.⁷ This analysis used OS before patients switching therapies to limit any bias.

This article aims to model the long-term cost effectiveness and cost utility of sunitinib as first-line therapy for mRCC compared with IFN- α and IL-2. A United States societal perspective was adopted to assist in determining the direct economic value of sunitinib in mRCC relative to commonly used therapies according to economic evaluation guidelines.^{7,8} The model assumes that patients' out-of-pocket expenses are zero, as they are likely to have reached the upper limit of their copayment at this disease stage. The model excludes indirect societal costs (productivity losses, premature deaths). A managed-care perspective has been explored in sensitivity analyses.

METHODS

A Markov model was developed in Microsoft Excel (Microsoft Corp, Redmond, WA) to simulate disease progression and determine outcomes over the lifetime (10 years) of a hypothetical cohort of 1,000 patients with mRCC receiving first-line treatment (in 6-week cycles) with sunitinib, compared with IFN- α or IL-2 (the most commonly used first-line treatments); sunitinib data were derived from the pivotal phase III trial.⁶ Patients were assumed to receive active treatment until an investigator's assessment of tumor progression was confirmed, when patients were switched to second-line treatment or best supportive care (BSC), defined as palliative care with tumor progression monitoring (Fig 1 and online-only Fig A1). The model was used to conduct a cost-effectiveness analysis (CEA) and a cost-utility analysis (CUA), using IFN- α as the base case to which sunitinib and IL-2 were compared. Outcomes were valued in the CEA in progression-free years (PFYs) and life-years (LYs) gained; in the CUA, outcomes were valued in quality-adjusted life-years (QALYs) gained, in accordance with economic assessment guidelines.^{7,8} The results of these analyses were expressed as an incremental cost-effectiveness ratio (ICER) and an incremental cost-utility ratio (ICUR), respectively. The

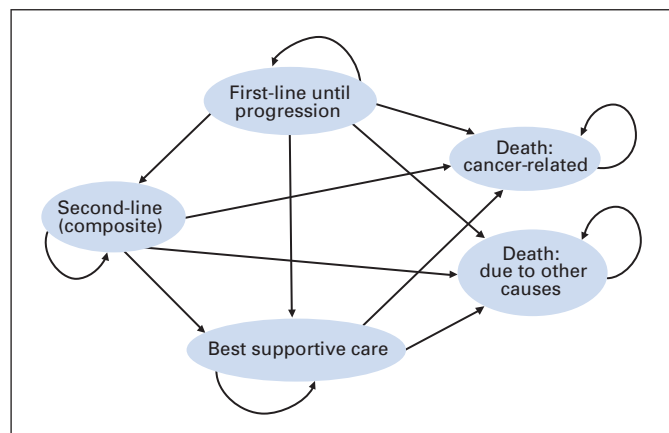


Fig 1. Structure of the 10-year Markov model for metastatic renal cell carcinoma.

model follows hypothetical patients with mRCC with a clear-cell histology component, radiographically measurable lesions, adequate organ function, and Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 (inclusion criteria of the pivotal sunitinib trial).⁶

In the sunitinib trial, patients received oral sunitinib 50 mg/d for 4 weeks followed by 2 weeks off-treatment in 6-week cycles, or IFN- α administered subcutaneously on 3 nonconsecutive days each week. The model used data from the second interim analysis of the trial (data cutoff date: November 15, 2005).⁶ IL-2 data were derived from a randomized, multicenter, phase III study of IL-2 versus IFN- α .⁹ As in the sunitinib trial, patients exhibited progressive mRCC (measured in two dimensions) and ECOG PS of 0 or 1.⁹

Kaplan-Meier survival curves for PFS and OS for IFN- α and sunitinib were available for the 66-week (11-cycle) maximum duration of follow-up.⁶ Weibull curves (used in life data analysis for their flexibility) were fitted to the Kaplan-Meier survival data using an SPSS 10.0 statistical package (SPSS, Chicago, IL). Estimated scale and shape parameters and their SEs and correlation coefficients are reported in Table 1. The shape parameter defines the underlying hazard rate of progression or death; a value of more than 1 indicates that the failure rate is increasing. The scale parameter is related to the measurement unit of time. Survival in the IL-2 arm was modeled on the survival curve for the IFN- α arm and the survival HR calculated by Négrier et al.⁹ For IL-2 and IFN- α , they reported PFS 1-year of 15% and 12% respectively, and median OS of 12 and 13 months, respectively.⁹ From these data, the following HR and 95% CI were calculated using simulation methods, based on trial sample sizes and beta distributions and assuming a constant hazard rate: PFS, 0.895 (95% CI, 0.680 to 1.202); OS, 1.083 (95% CI, 0.718 to 1.394).

OS data for sunitinib were derived from the interim trial analysis with a short time horizon (HR for sunitinib v IFN- α , 0.65; 95% CI, 0.449 to 0.942).⁶ Based on expert clinical opinion, long-term OS with sunitinib could be equal to, but not worse than, that with IFN- α at any time point. Length of second-line treatment was based on a median of 2.4 months (95% CI, 1.9 to 2.9), reported in a survival analysis of 251 patients with advanced RCC treated in 29 consecutive trials (1975 to 2002).¹⁰ Cumulative survival probabilities (eg, median survival) were converted to 6-week cycle probabilities.¹¹ The calculated cycle probability of failing second-line treatment was 32.96%, regardless of first-line treatment. The model predicted that less than 1% of patients would still be alive 10 years after the analysis began. Therefore, a 10-year time horizon was assumed to represent a life-time horizon.

The EuroQoL (EQ-5D) instrument was used in the sunitinib trial to collect quality of life (QOL) data.⁶ To model the change in QOL over one sunitinib treatment cycle, two utility values were used: the weighted average utility on day 28 was assumed to represent utility during the 4 weeks of sunitinib treatment; and the weighted average utility on day 1 of the next cycle was assumed to represent QOL during the 2-week off-treatment period. The utility for IFN- α -treated patients was calculated from the weighted average changes from baseline in EQ-5D scores measured on days 1 and 28 of each cycle.⁶ Patients receiving IL-2 were assumed to have the same utility as patients receiving IFN- α .¹² Utility values from a phase II trial of second-line sunitinib in mRCC¹³ were used to calculate utilities during second-line treatment and palliative care, regardless of treatment composition (Table 2).

Most adverse events (AEs) can be managed by dose reductions or interruptions. The model assumed sunitinib dose reductions from 50 mg/d to 37.5 mg/d for one cycle. The model incorporated the following treatment-related AEs (based on their reported incidences in the sourced clinical trials):^{6,9} fatigue/asthenia; stomatitis; hypertension; thrombocytopenia; neutropenia; abnormal ejection fraction; nausea/vomiting; diarrhea; anemia; hand-foot syndrome; and infection.

Direct medical costs included were: routine follow-up of treated patients (first and second line); managing treatment-related serious AEs (SAEs); diagnosis and treatment of progression; and BSC in the terminally ill. Indirect costs (eg, lost productivity or premature death) were not included; costs are reported in 2006 US dollars.

Table 1. Parameters of Weibull Curves Fitted to Kaplan-Meier Survival Data From a Pivotal Sunitinib Trial⁶

Treatment	Scale		Shape		Correlation Coefficient
	Mean	SE	Mean	SE	
PFS					
Investigator assessment					
IFN- α	0.030082	0.002793	1.053222	0.031467	-0.9854
Sunitinib	0.005588	0.000981	1.30184	0.051262	-0.9916
Core radiology assessment					
IFN- α	0.037583	0.003340	0.953442	0.030656	-0.9812
Sunitinib	0.00624	0.002072	1.246485	0.093471	-0.9914
OS					
IFN- α	0.004649	0.000337	1.125189	0.021001	-0.9895
Sunitinib	0.001434	0.000210	1.355542	0.040829	-0.9912

Abbreviations: IFN- α , interferon- α ; OS, overall survival; PFS, progression-free survival.

Drug treatment costs were based on the following schedules: IFN- α (first cycle): three injections/wk with 3 MU/injection in the first week, 6 MU/injection in the second week, and 9 MU/injection, thereafter.⁶ IFN- α (subsequent cycles): three injections/wk with 9 MU/injection.⁶ Sunitinib (full dose): 50 mg/d for 4 weeks followed by 2 weeks off treatment.⁶ Sunitinib (reduced dose): 37.5 mg/d for 4 weeks followed by 2 weeks off treatment.⁶ IL-2: infusion of 18 MU/m² body-surface area (BSA)/d for 5 days, once every 3 weeks (assuming 1.9 m² of BSA).⁹ Sorafenib (second-line treatment): 400 mg twice per day.

Based on expert opinion (S.N., R.M.), 66% of patients receive second-line treatment. Of those, 10% received IFN- α , 40% received sunitinib, 40% received sorafenib, and 10% received IL-2, regardless of first-line treatment. Expected follow-up for patients receiving active treatment, and health care resources required for BSC of terminally ill patients were obtained from clinical experts' opinions. Unit costs were based on Current Procedural Terminology (CPT) codes (online-only Table A1).¹⁴

Resource use associated with treatment-related SAEs (grade 3-4) was based on expert opinion and published sources.¹⁴⁻¹⁸ The national average length of a hospital stay associated with each AE was based on the Agency for Healthcare Research and Quality (AHRQ) Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) database, according to corresponding International Classification of Diseases (ICD)-9 codes.¹⁵ Hospital charges were converted to costs using the national average cost-to-charge ratio for routine inpatient days (0.56).¹⁶ A sensitivity analysis was conducted using full hospital charges. Treatment also included specialist visits, special procedures, and drug treatment, as necessary.

Expected treatment of patients with progression (based on expert opinion) included: 10% of patients hospitalized for malignant neoplasm of the kidney; four-to-five outpatient oncologist visits (4.5 visits used), and one general practitioner visit; five CBCs and two-to-three complete metabolic panels (2.5 tests used); one chest/pelvis computed tomography (CT) scan; one x-ray; and magnetic resonance imaging (MRI) in 50% of patients. Of patients

receiving BSC, 5% were assumed to require 5 days of hospice care, chosen as a conservative estimate, costing \$581.82/d.¹⁷ Model treatment phase costs were obtained by combining the quantity of resources used, the cost per unit of resource, and the probability of the events (Table 3).¹⁹ Costs and outcomes occurring after 1 year were discounted at 5% annually (with a sensitivity analysis using 3%).

The robustness of the results was tested by a probabilistic sensitivity analysis on the model parameters using a second-order Monte Carlo simulation (computational algorithm based on repeated random sampling). Distributions for model variables were chosen based on recommendations and in accordance with the nature of each variable.¹⁹ Patient proportions and utilities were assumed to follow a beta distribution (continuous distribution confined within the interval 0 to 1) based on trial sample sizes²⁰; HR for PFS and OS were represented using log-normal distributions according to calculated means and 95% CI,^{6,9} and health care resource utilization parameters and costs were assumed to follow gamma

Table 3. Costs Per 6-Week Treatment Cycle for Therapies, Adverse Events, and Model Treatment States

Treatment State in the Model	Cost Per Cycle (\$)	Source/Comment
IFN-α drug costs		
First cycle	1,903.10	Red Book ¹⁹
Subsequent cycles	2,254.20	Red Book ¹⁹
Sunitinib drug costs		
Full dose	5,985.00	Pfizer Inc
Reduced dose	4,488.75	Pfizer Inc
IL-2 drug costs		
Routine follow-up of patients with clinical benefit	2,421.49	Calculation
Progression	6,039.47	Calculation
Second-line composite drug costs		
BSC	16,011.17	Calculation
Serious adverse events		
With IFN- α	72.48*	Calculation
With sunitinib	160.13†	Calculation
With IL-2	312.62‡	Calculation

Abbreviations: IFN- α , interferon α ; IL-2, interleukin-2; BSC, best supportive care.

*Corresponds to the weighted average cost per adverse event (\$1,034) multiplied by the 6-week probability of any adverse event (7.3%).

†Corresponds to the weighted average cost per adverse event (\$1,098) multiplied by the 6-week probability of any adverse event (15.8%).

‡Corresponds to the weighted average cost per adverse event (\$1,911) multiplied by the 6-week probability of any adverse event (17.9%).

Table 2. Utilities for Metastatic Renal Cell Carcinoma Model States

Treatment	Utility
Interferon- α	0.71530
Sunitinib	
During treatment	0.72125
During rest	0.75987
During second-line treatment	0.63090
After termination of second-line treatment	0.55090

NOTE. Utilities were calculated based on utility values from a phase II trial of sunitinib as second-line treatment in metastatic renal cell carcinoma.¹³

distributions (continuous distribution defined by scale and shape parameters). Resource use counts follow discrete Poisson distribution (distribution based on the probability of a number of events occurring within a fixed time period), whose conjugate distribution to describe the mean is the gamma distribution.²⁰ For parameters without information on their variability, a 10% deviation of the mean was assumed. Drug acquisition costs are known and were not varied. The Monte Carlo simulation was run for 1,500 iterations. Results of the probabilistic analysis were used to calculate cost-effectiveness acceptability curves (CEACs).

To identify key model parameters, a one-way deterministic sensitivity analysis was conducted using extreme values (reference case estimates \pm 20%). Results were plotted as a tornado diagram based on the impact of the variable on the incremental net benefit, using \$100,000/QALY as the threshold. ICURs using the five most influential variables identified in the one-way analyses were examined.

RESULTS

The reference case results (Table 4) indicate a difference of \$7,534 in the total average per-patient lifetime cost of treatment with sunitinib versus IFN- α , and cost savings of \$3,441 versus IL-2. The acquisition cost of sunitinib largely explains its higher cost.

Sunitinib-treated patients spent an average of 0.92 years in a progression-free health state, compared with 0.51 years and 0.57 years for those receiving IFN- α and IL-2, respectively. Sunitinib treatment was associated with estimated gains in survival and QALYs over IFN- α and IL-2, respectively (Table 4). Both IFN- α and sunitinib were more effective but less costly

than IL-2. The probabilistic analysis showed that the incremental cost per progression-free year gained for sunitinib versus IFN- α was \$18,611, and the ICER and ICUR of sunitinib versus IFN- α were \$67,215 per LY gained and \$52,593 per QALY gained, respectively. At a 3% discount, the ratios were \$18,113, \$65,246, and \$51,130, respectively. Using full hospital charges resulted in ratios for sunitinib versus IFN- α of \$1,278, \$4,082, and \$3,434, respectively.

At thresholds of \$50,000/QALY and \$100,000/QALY, the probabilistic analyses indicated that sunitinib had 45.9% and 64.9% probability, respectively, of being cost-effective compared with IFN- α , and was the optimal treatment above a \$55,000/QALY threshold (Fig 2). Sunitinib has a more than 50% probability of being cost effective compared with IFN- α at any threshold above the ICUR calculated from the probabilistic analysis (\$57,619/QALY), and has a 65% probability of being cost effective at the \$100,000/QALY threshold.

The tornado analysis indicated that the most sensitive parameters were utility values, and costs of sunitinib and BSC (Fig A2). ICURs obtained from varying the most sensitive parameters ranged from \$1,470 using higher costs for BSC to \$136,783 using lower utility values for sunitinib during treatment (online-only Table A2). Reducing the time horizon from 10 years to 1 year increased the ICUR to \$120,304/QALY, while with a 2-year analysis, the ICUR fell to \$67,507/QALY.

Table 4. Incremental Cost-Effectiveness and Cost-Utility Ratios for Sunitinib Versus IFN- α and IL-2

Model Outcome	Treatment Strategy*		
	Sunitinib	IFN- α	IL-2
Cost, \$			
Deterministic mean	224,970	217,436	228,411
Probabilistic mean	227,830	218,415	231,795
SD	13,649	15,247	38,392
Progression-free years			
Deterministic mean	0.92	0.51	0.57
Probabilistic mean	0.93	0.51	0.57
SD	0.03	0.031	0.08
Life-years			
Deterministic mean	2.09	1.98	1.85
Probabilistic mean	2.11	1.98	1.88
SD	0.06	0.06	0.27
QALYs			
Deterministic mean	1.33	1.19	1.13
Probabilistic mean	1.36	1.20	1.14
SD	0.22	0.24	0.28
ICER: progression-free years gained, \$			
Deterministic mean		18,611	Dominated
Probabilistic mean		22,784	Dominated
ICER: LYs gained, \$			
Deterministic mean		67,215	Dominated
Probabilistic mean		72,510	Dominated
ICUR, \$			
Deterministic mean		52,593	Dominated
Probabilistic mean		57,619	Dominated

Abbreviations: IFN- α , interferon- α ; IL-2, interleukin-2; QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio; LY, life-year; ICUR, incremental cost-utility ratio; SD, standard deviation; dominated, less effective and more costly than another treatment strategy.

*All future costs discounted at 5%.

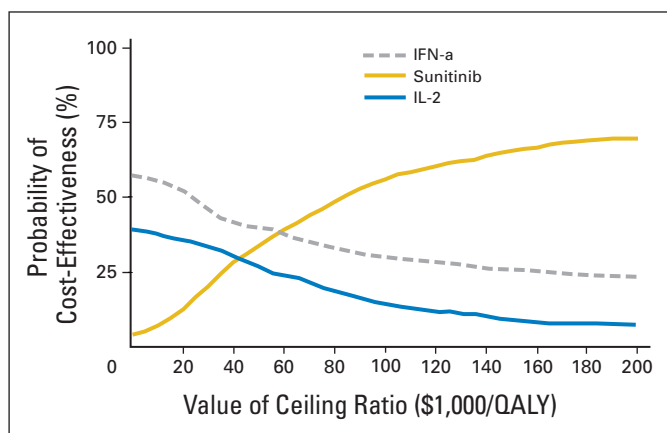


Fig 2. Cost effectiveness acceptability curves for sunitinib, interferon- α (IFN- α), and interleukin-2 (IL-2).

DISCUSSION

Data from the reference case analyses suggest that sunitinib provides health benefits for first-line treatment of mRCC. Compared with IFN- α , these benefits are achieved at an incremental cost per PF years of \$18,611. This end point, based on the largest number of patients meeting a trial end point, may reflect a more robust analysis and provide a better reflection of treatment benefits. The incremental cost per LY gained was \$67,215 and per QALY gained was \$52,593. These ratios are largely attributable to the higher cost associated with sunitinib. Both IFN- α and sunitinib were associated with gains compared with IL-2. Deterministic sensitivity analyses showed the results to be sensitive to the utility values associated with the treatments, and the costs of sunitinib and BSC. A 20% increase in the cost of sunitinib or a 20% decrease in the cost of BSC approximately doubled the ICUR from its reference case value. Increasing hospital costs and BSC resulted in low ICERs that were more favorable to sunitinib. Model results were robust to changes in other model variables.

Modeling to extrapolate outcomes beyond trial completion is an unavoidable limitation of this evaluation. Interim results from the pivotal sunitinib trial were favorable to sunitinib,⁶ and this model assumes that progression benefits are an appropriate surrogate measure of survival benefit. The greatest model uncertainty surrounds long-term survival rates. The model can be updated for sunitinib when long-term data are available. However, IFN- α -treated patients were offered open-label sunitinib at progression; therefore, long-term data for these patients will not be available.⁶ Consequently, it may be difficult to isolate the benefits of sunitinib in terms of OS in future analyses.

Another study limitation is the use of clinical trial data. These may not adequately reflect the efficacy and utility achievable in routine clinical practice. Also, the sensitivity analyses indicated that uncertainty in utility measurements had a major impact on the conclusion of this evaluation; the sunitinib trial was not powered to detect differences in EQ-5D scores between treatment groups.⁶ A number of assumptions regarding health care resource utilization were necessary

to fill information gaps. However, extensive sensitivity analyses were performed on resource use and the model was robust to these changes.

A narrow perspective was used, and only direct medical costs were included. Adding the burden of mRCC on family and caregivers and indirect costs to society would increase the costs of BSC, as would using full hospital charges. Thus, they would lead to more favorable results for treatments that prolong PFS, such as sunitinib.

Economic evaluations play an increasingly significant role in decision making regarding the funding of new drugs. Some researchers have recommended interpreting the results of economic evaluations by relating them to appropriate benchmarks. Hence, Laupacis et al²¹ suggested that an incremental cost per QALY gained of \$100,000 is beyond the limit of acceptable cost effectiveness. Others have recommended against the use of preset thresholds for various reasons.²² First, there is no empirical basis for deciding at what value a threshold should be set. Second, there may be circumstances where decision makers prefer to ignore a threshold (eg, for rare diseases or rescue treatments). Third, a set threshold would imply that efficiency has absolute priority over other objectives such as equity and fairness. We advocate decision making on a case-by-case basis.

Based on our economic evaluation, the health benefits of sunitinib are achieved at an incremental cost of \$18,611 per progression-free year gained, \$67,215 per LY gained, and \$52,593 per QALY gained, compared with IFN- α . These data suggest that sunitinib is a cost-effective alternative to IFN- α as first-line treatment for mRCC, with cost-effectiveness ratios within the established \$50,000 to \$100,000 per LY or QALY threshold that society is willing to pay for health benefits.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Conception and design: Edit Remák, Sylvie Négrier, Sindy T. Kim **Collection and assembly of data:** Edit Remák, Claudie Charbonneau, Sylvie Négrier, Sindy T. Kim **Data analysis and interpretation:** Edit Remák, Claudie Charbonneau, Sylvie Négrier, Robert J. Motzer **Manuscript writing:** Edit Remák, Claudie Charbonneau, Sylvie Négrier, Sindy T. Kim, Robert J. Motzer **Final approval of manuscript:** Edit Remák, Claudie Charbonneau

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Acknowledgment

The Acknowledgment is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).