Cost-Effectiveness of Everolimus for Second-Line Treatment of Metastatic Renal Cell Carcinoma in Serbia

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ABSTRACT

Background: New targeted therapeutics for metastatic renal cell carcinoma (mRCC) enable an increment in progression-free survival (PFS) ranging from 2 to 6 months. Compared with best supportive care, everolimus demonstrated an additional PFS of 3 months in patients with mRCC whose disease had progressed on sunitinib and/or sorafenib. The only targeted therapy for mRCC currently reimbursed in Serbia is sunitinib.

Objective: The aim of this study was to estimate the cost-effectiveness and the budget impact of the introduction of everolimus in Serbia in comparison to best supportive care, for mRCC patients refractory to sunitinib.

Methods: A Markov model was designed corresponding with Serbian treatment protocols. A health care payer perspective was taken, including direct costs only. Treated and untreated cohorts were followed up over 18 cycles, each cycle lasting 8 weeks, which covered the lifetime horizon of mRCC patients refractory to the first-line treatment. Annual discounted rates of 1.5% for effectiveness and 3% for costs were applied. Transitions between health states were modeled by time-dependent probabilities extracted from published Kaplan-Meier curves of PFS and overall survival (OS). Utility values were obtained from the appraisals of other mRCC treatments. One-way and probabilistic sensitivity analyses were done to test the robustness and uncertainty of the base–case estimate. Lastly, the potential impacts of everolimus on the overall health care expenditures on annual and 4-year bases were estimated in the budget-impact analysis.

Results: The incremental cost-effectiveness ratio for everolimus was estimated at €86,978 per quality-adjusted life-year. Sensitivity analysis identified the hazard multiplier, a statistical approximator of OS gain, as the main driver of everolimus cost-effectiveness. Furthermore, probabilistic sensitivity analyses revealed a wide 95% CI around the base–case incremental cost-effectiveness ratio estimate (€32,594–€425,258 per quality-adjusted life-year). Finally, an average annual budgetary impact of everolimus in first 4 years after its potential reimbursement would be around €270,000, contributing to <1% of the total budget in Serbian oncology.

Conclusions: Everolimus as a second-line treatment of mRCC is not likely to be a cost-effective option under the present conditions in Serbia, with a relatively limited impact on its budget in oncology. A major constraint on the estimation of the cost-effectiveness of everolimus relates to the uncertainty around the everolimus effect on extending OS. However, prior to a final decision on the acceptance/rejection of everolimus, reassessment of the whole therapeutic group might be needed to construct an economically rational treatment strategy within the mRCC field. (*Clin Ther*. 2013;▮:▮▮▮–▮▮▮)

Key words: cost-effectiveness, everolimus, renal cell carcinoma, Serbia.

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INTRODUCTION

Kidney cancer is the 14th most common cancer worldwide, accounting, in 2008, for ~270,000 new cancer cases (~2% of all adult malignancies).[1] Renal cell carcinoma (RCC) is the most prevalent histologic type of kidney cancer, with an increasing trend in age-standardized incidence over the past 3 decades.[2] Although this increase was accompanied by considerable progress in surgical and pharmaceutical treatments, the mortality-to-incidence ratio for RCC remained significantly higher than in other urologic malignancies.[3] In the United States, between 1988 and 2002, the 5-year survival for all stages of RCC significantly improved (from 64% to 74%), yet no notable change in the 5-year overall survival (OS) of metastatic RCC (mRCC) was observed (~12%).[4] As the population ages, it is expected that RCC will be not only a serious health issue but also an important issue in health care expenditures.[5]

Advanced and/or metastatic RCC is a practically incurable disease. Therefore, the primary objectives of an adjuvant medical treatment are delay of disease progression, relief of physical symptoms, and maintenance of vital functions.[6] Until recently, drugs that affect the immune system, such as interferon-alfa and interleukin 2, have been the cornerstones of mRCC therapy. However, because these molecules are linked to serious adverse effects, they are of limited benefit to patients.[7] Recent advances in the understanding of the molecular biology of kidney cancer have led to the development of treatments that specifically target angiogenesis through the inhibition of the vascular endothelial growth factor (VEGF) and the mammalian target of rapamycin (mTOR).[8] European guidelines recommend sunitinib, pazopanib (a VEGF inhibitor), bevacizumab (a VEGF antibody), and temsirolimus (an mTOR inhibitor) for the first-line therapy of mRCC.[9,10] Although these pharmaceuticals can provide an increment in progression-free survival (PFS) ranging from 2 to 6 months,[11–14] they also create a need for sequential therapy in patients who failed to respond.

Everolimus is an oral, once-daily selective inhibitor of the mTOR protein that controls tumor cell division, growth, and angiogenesis.[15] In RECORD-1 (Renal Cell Cancer Treatment With Oral RAD001 Given Daily),[16] a Phase III randomized clinical trial in patients with mRCC who had progressed on sunitinib and/or sorafenib, the median PFS was 4.9 months in everolimus-treated patients compared with 1.9 months in the best supportive care (BSC) group. In a number of national and international guidelines,[9,10,17] everolimus is indicated as a second-line treatment option in those refractory to sunitinib and/or sorafenib.

Cost-effectiveness analysis (CEA) is broadly used in appraisals of new health technologies throughout developed countries. Concerning reimbursement of new oncologic drugs, CEA is one of the most decisive elements.[18] The cost-effectiveness of everolimus has been assessed in the United Kingdom, where it was not found to be cost-effective compared with BSC,[19] and in the United States, where it was more cost-effective than sorafenib as a second-line treatment of mRCC.[20]

Although pharmacoeconomic evaluation has only recently been introduced into the Serbian health care system, it commonly relies on studies originally designed for other socioeconomic settings, and its influence remains rather advisory. This might be one of the reasons why no CEAs of everolimus or any other mRCC-targeted therapies have been published from Serbia to date. Currently, the only treatment option for mRCC that is reimbursed in Serbia is sunitinib, with no second-line options for patients without clinical response to sunitinib.[21]

The primary goal of these cost-effectiveness and the budget-impact analyses was to assess the application of everolimus in Serbia in mRCC patients refractory to sunitinib. The chosen comparator was BSC, which corresponds to current Serbian clinical practice. The results of this analysis might help decision-makers to design economically rational clinical guidance for mRCC.

MATERIALS AND METHODS

Model Overview

A decision analytical Markov model was developed to estimate the cost-effectiveness of everolimus in addition to BSC in comparison to BSC alone as a second-line treatment of mRCC. The model was designed with respect to the treatment protocols defined by the clinical experts from Serbian oncology clinics (personal communication, Dr. Davorin Radosavljević, 2013), and a Serbian health care payer perspective was taken. The model comprised 3 discrete health states: stable disease (SD), progressed disease (PD), and death (Figure 1).

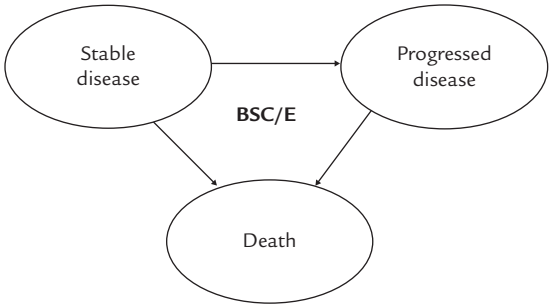

Figure 1. Markov model scheme for both compared alternatives. Arrows represent transition probabilities. BSC = best supportive care; E = everolimus.

We followed up a hypothetical group of 1000 mRCC patients who were distributed evenly between the 2 treatment arms. All patients entered the model in the SD state. Once disease progressed, patients remained in the PD state until death. The latter was considered as an absorbing state. The cohorts were modeled in 8-week cycles that corresponded to the period of assessment within the trial[16] and were followed up over the expected lifetime horizon of the mRCC patients eligible for the second-line treatment. Annual discounted rates of 1.5% for health and 3% for cost outcomes (or 0.23% and 0.46% per cycle, respectively) were applied from the second cycle on. A differential discount accounted for an expectedly increasing value of health through time and was in accordance with the official guidelines in Serbia.[22] The analysis was conducted using the statistical software R version 2.13.2.[23]

Transition Probabilities

The transitions through the health states of the model were defined by time-dependent probabilities, extracted from published estimates of PFS and OS.[16] Namely, different distributions (exponential, Weibull, log-normal, log-logistic, and logistic) were used to fit published trial data. The best-fitting distribution, based on the Akaike information criterion, was chosen as the best option. Hence, the probability of remaining in the SD state was estimated using a log-normal distribution fitted over PFS Kaplan-Meier curves from the RECORD-1 trial (Figure 2A). The probability of OS for everolimus across time was extracted from the OS Kaplan-Meier curve of the same trial, fitting a Weibull distribution (Figure 2B). The transition probabilities from the SD to the PD state were calculated using the estimates of PFS and OS for each arm of the trial. No

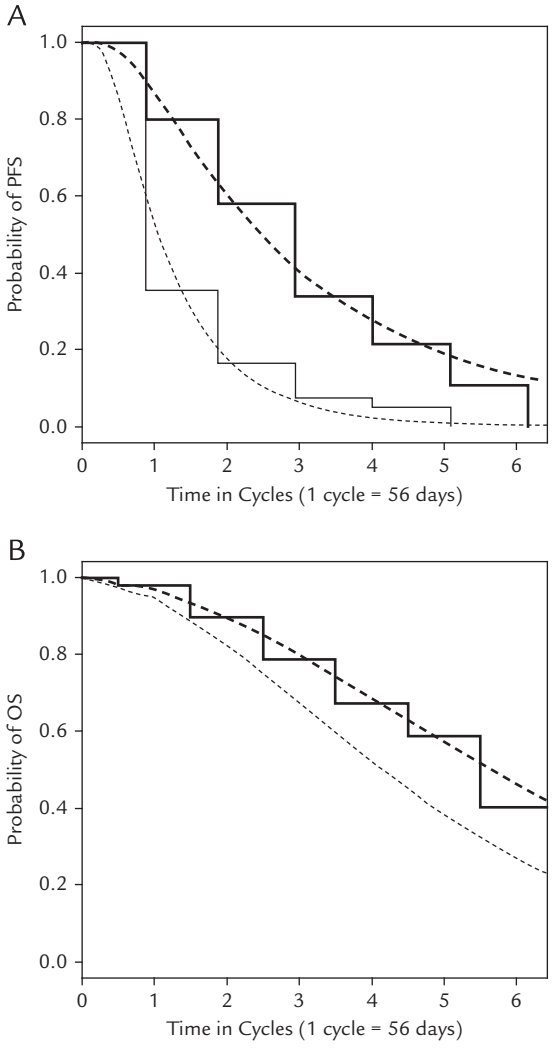

Figure 2. Estimated survival functions over progression-free survival (PFS) (A) and overall survival (OS) (B) Kaplan-Meier curves. Bold lines represent observed survival with everolimus from RECORD-1 (Renal Cell Cancer Treatment With Oral RAD001 Given Daily[16]). Light solid lines = observed PFS of best supportive care (BSC) from RECORD-1; dashed lines = estimated log-normal (A) and Weibull (B) survival functions of everolimus; dotted lines = the estimated lognormal (A) and Weibull (B) survival functions of BSC.

state-specific information regarding the proportions of patients transitioning to death could be extracted from the available trial data.[16,24] For that reason, we made the assumption of equal probabilities of death from both health states.

Because the design of the trial allowed the crossover of BSC patients to the everolimus arm, direct fitting of a distribution on the trial results on OS, in the BSC arm, was not possible. Instead, probabilities of all-cause mortality in the BSC arm were estimated using the inverse probability of censoring weight (IPCW) method. Briefly, in the IPCW method, a constant hazard ratio of mortality between the 2 arms was initially estimated. This ratio was subsequently applied to the time-dependent mortality rates for everolimus to estimate the mortality rates for BSC. In a recent appraisal, the National Institute for Health and Clinical Excellence estimated the hazard ratio of the 2 arms using the IPCW method,[19] and utilizing the same RECORD-1 trial,[16] we extracted the hazard estimate from this published appraisal report. The parameters of all fitted distributions are presented in Table I.

Costs

The CEA was conducted from a Serbian health care payer perspective, including only direct costs of drug treatment and other medical interventions. Acquisition costs of everolimus were obtained from the *Official Gazette of Republic of Serbia*[25] and were adjusted to 91.8% of full dosage (10 mg once daily) in accordance with the RECORD-1 trial data.[24] Because the BSC for mRCC patients is not explicitly defined by the Serbian health care system, stable and progressed disease treatment were firstly identified by clinical experts (personal communication, Dr. Davorin Radosavljević, 2013) and subsequently their costs were sourced out from hospital invoices and the Republic Healthcare Fund (RFZO) price lists (Table II).[26–28] Briefly, SD costs consisted of regular follow-up visits to the oncologist and computed tomography diagnostics. Additional to these, the PD health state bared only costs of treatment of painful metastases (radiotherapy and pain management) (personal communication, Dr. Davorin Radosavljević, 2013).

The same approach was followed for the estimation of the costs of treating adverse events. These cost estimates were combined with the probabilities of their occurrence as extracted from the RECORD-1 trial,[24] to provide adjusted cost estimates for the SD state in the everolimus arm (Table II). Only adverse events of grade 3 or 4, with a difference in occurrence of at least 1% between the 2 arms, were considered in the model. All adverse events were assumed to have resolved within 1 cycle.

Table I. Parameters used in survival probability models.

Parameter	Everolimus	BSC
PFS (log-normal)		
Shape-log (SE)	0.9047 (0.0582)	0.0495 (0.0658)
Scale-log (SE)	−0.2146 (0.0636)	0.3646 (0.0779)
Covariance ($\times 10^{-4}$)	9.3372	−1.5407
OS (Weibull)		
Shape-log (SE*)	1.8852 (0.0351)	NA
Scale-log (SE)	−0.6064 (0.0475)	NA
Covariance ($\times 10^{-4}$)	−5.3607	NA
Hazard multiplier	NA	1.82

BSC = best supportive care; NA = not applicable; OS = overall survival; PFS = progression-free survival; SE = standard error.

Utilities

In the absence of quality-of-life estimates for mRCC patients in the RECORD-1 trial, we used utility values from published appraisals of other mRCC treatments.[29] Hence, the incremental cost-effectiveness ratio (ICER) estimates were expressed in euros per life-year gained (€/LYG), as well as in euros per quality-adjusted life-year gained (€/QALY). Additionally, the quality-of-life estimates for the PD and SD states for both treatment options were adjusted for the presence of potential adverse events. The rates of adverse events were extracted from the RECORD-1 trial, as indicated earlier.[24]

One-Way and Probabilistic Sensitivity Analysis

The sensitivities of the CEA estimates to the uncertainty around all transition probabilities used, the hazard multiplier, the cost of everolimus, other costs incurred in the SD and PD states, utilities, and adverse-events rates were assessed using univariate sensitivity analyses. Each parameter was independently varied to the upper and lower limits of its 95%

Table II. Estimates of all costs, their structure, and proportion of patients covered.

Cost Item	Price per Item Unit*	Price per DDD	DDD/Frequency per Cycle	Proportion of Patients, %†	Cost per Cycle
Drug acquisition					
Everolimus (30 × 10 mg)[25]	3328.26	110.94	56.00	91.8	5703.31
Total cost per cycle	—	—	—	—	5703.31
SD[26]					
Oncologist's examination	1.66	—	1.00	100.0	1.66
CT scan	97.68	—	0.61	100.0	59.95
Total cost per cycle	—	—	—	—	61.61
PD					
Oncologist's examination[26]	1.66	—	1.00	100.0	1.66
CT scan[26]	97.68	—	0.61	100.0	59.95
Treatment					
Radiotherapy[26]	672.22	—	1.00	5.6	37.48
Megestrol (100 × 160 mg)[27]	128.48	1.28	56.00	100.0	71.95
Morphine sulfate (20 × 10 mg/5 mL)[27]	10.87	5.43	56.00	6.6	20.08
Hydromorphone (14 × 16 mg)[27]	40.46	3.61	56.00	6.6	13.35
Fentanyl (5 × 4.2 mg, transdermal)[27]	9.72	0.56	56.00	6.6	2.05
Total cost per cycle	—	—	—	—	206.53
Adverse events					
Anemia[26]					
Blood transfusion	7.54	—	2.00	5.1	0.77
Hospitalization	21.99	—	2.00	5.1	2.24
Anorexia[27]					
Megestrol (100 × 160 mg)	128.48	1.28	7.00	1.5	0.13
Nausea[27]					
Metoclopramide (30 × 10 mg)	1.19	0.12	7.00	3.7	0.03
Dexamethasone (50 × 0.5 mg)	2.73	0.16	7.00	3.7	0.04
Dyspnea					
Oxygen therapy[26]	4.56	—	1.00	4.8	0.22
Morphine sulfate (20 × 10 mg/5 mL)[27]	10.87	5.43	2.00	4.8	0.52
Dexamethasone (50 × 0.5 mg)[27]	2.73	0.16	2.00	4.8	0.02
Ranitidine (20 × 150 mg)[25]	2.48	0.25	2.00	4.8	0.02
Hospitalization[26]	21.99	—	2.00	4.8	2.11
Infection					
Ceftazidime (1 × 1 g)[28]	11.57	52.04	7.00	3.0	10.93
Hospitalization[26]	21.99	—	7.00	3.0	4.62
Pneumonitis (noninfectious)					
Dexamethasone (50 × 0.5 mg)[27]	2.73	0.16	7.00	2.6	0.03
Total cost per cycle‡	—	—	—	—	21.69

CT = computed tomography; DDD = defined daily dose; PD = progressed disease; SD = stable disease.

*All costs are expressed in euros, using exchange rate from National Bank of Serbia for June 3, 2013 (€1 = 112.51 dinars), the date when the latest update of everolimus price was accepted.

†Proportions of patients receiving radiotherapy, morphine, hydromorphone, and fentanyl in the PD state were defined by a clinical expert (personal communication, Dr. Davorin Radosavljević, 2013); proportions of patients per adverse event present the between-treatment differences in proportions in RECORD-1.[24]

‡Incremental for everolimus.

CI when these were defined (transition probabilities, hazard multiplier, and utilities) or to an arbitrary ±20% of the parameter value when CIs were not defined (all costs, adverse-events rates). Additionally, to investigate the uncertainty around the distribution choice for the PFS and OS curves, we examined the change in the ICER when the second-best–fitting distributions were applied. Therefore, next to the base case, we offer the additional scenarios in which: (1) a Weibull distribution was fitted on PFS in the everolimus and the BSC arms (scenario 1); (2) a log-normal distribution was fitted on OS in the everolimus arm (scenario 2); and (3) a Weibull distribution was fitted on PFS in the everolimus and BSC arms while a log-normal distribution was fitted on OS in the everolimus arm (scenario 3). The results of the sensitivity analyses were visualized through a tornado diagram.

Parameter uncertainty was jointly assessed through a probabilistic sensitivity analysis (PSA). The PSA incorporated the uncertainty surrounding the hazard multiplier; distribution parameters estimated for PFS and OS; as well as the parameters related to all costs, utilities, and the adverse-effects estimates. The hazard multiplier as well as the PFS and the OS parameters were assumed to have been normally distributed. Triangular distributions were ascribed to all costs, normal distributions to all utility values, and β distribution to the adverse-events rates. After distributional assumptions were made for all parameters, 10,000 Monte Carlo simulations were performed. A simple percentile method was employed to create 95% CIs for incremental costs, incremental effectiveness, and ICER.[30] The outcomes of the simulations were firstly ordered by their value, after which the 250th and 9750th estimates were taken for the construction of the lower and upper limits of the 95% CIs. The same simulations of ICER enabled plotting of the cost-effectiveness acceptability curves.

Budget-Impact Analysis

The influences of a potential reimbursement of everolimus on the annual and 4-year RFZO spending (2013–2016) were estimated through a budget-impact analysis. Firstly, we calculated the number of patients who would have been eligible for everolimus treatment. The starting point was the number of new kidney cancer cases in Serbia per year, taken from national cancer registries (670 in the year 2009).[31,32] Predictions of the number of new kidney cancer cases for the years 2013 to 2016 were based on the trends observed in the period 1999–2009.[31,32] The proportions of kidney cancer patients who had RCC and mRCC were based on information from published surveillance studies.[33,34] The proportions of patients eligible for the first- and second-line mRCC and everolimus treatment were based on clinical experts' opinions (personal communication, Dr. Davorin Radosavljević, 2013) because this type of data was not available for Serbia. It was assumed that everolimus would be gradually introduced through time after a potentially positive decision on its reimbursement. Particularly, 25% of the patients eligible for second-line treatment would have been treated with everolimus in the first year, 50% in the second year, and 75% in the third and fourth years after the decision (Table III).

The average incremental cost per patient-year in the everolimus arm was extracted from the CEA model. Because a small proportion of patients were expected to have been alive in the second and third year of the model, we separately analyzed the average incremental costs for all 3 years of the model. The average (per-patient) incremental cost for a certain year was always calculated as a sum of all incremental costs among living patients in that year, divided by the total number of patients in the model. Finally, the annual budget impact for a given year represented the sum of: (1) patients eligible for treatment in a given year, multiplied by the average incremental costs of the first year; (2) patients eligible in the previous year, multiplied by the average incremental costs of the second year; and (3) patients eligible 2 years before a given year, multiplied by the average incremental costs of the third year.

Together with the base–case budget-impact estimate (prediction A), we presented the budget-impact estimates with the lowest (prediction B) and highest (prediction C) budget impacts. These two extreme predictions were the result of setting all parameters on the edges of their 95% CIs (incidence increase, RCC and mRCC proportions) or ±20% of their base–case estimates (incremental costs, proportions of patients for first- and second-line treatments, and proportion of second-line patients selected for everolimus). The values of parameters used in the extreme predictions are presented in Table III. Incremental cost parameter was estimated through the CEA model.

Table III. List of assumptions made in the estimation of the number of patients in budget-impact analysis.

Parameter	Assumptions Made in Prediction A*	Assumptions Made in Prediction B†	Assumptions Made in Prediction C‡	Range of Parameter Variation
Increase in kidney cancer incidence,[28,29] new cases/y	12.8	16.9	8.7	Within 95% CI
Kidney cancer patients having RCC,[30] %	82.5	83.1	81.8	Within 95% CI
RCC patients having mRCC,[31] %	22.7	22.9	22.5	Within 95% CI
mRCC patients eligible for first-line treatment,§ %	66.0	79.2	52.8	Within ±20%
Patients treated in first line eligible for second-line treatment,§ %	33.0	39.6	26.4	Within ±20%
Eligible second-line patients selected for everolimus,§ %				Within ±20%
1st year	25	30	20	
2nd year	50	60	40	
3rd and 4th years	75	90	60	

mRCC = metastatic renal cell carcinoma; RCC = renal cell carcinoma.
*Prediction A: base-case budget-impact estimate.
†Prediction B: highest budget-impact estimate.
‡Prediction C: lowest budget-impact estimate.
§Personal communication, Dr. Davorin Radosavljević, 2013.

RESULTS

In the base case, an additional lifetime cost of €16,188 per mRCC patient for second-line everolimus treatment was estimated. The average gain in life-years with everolimus treatment was ~0.2455 LYG, or 90 days of life per patient. When utilities of these years were taken into consideration, it resulted in 0.1861 QALYs, or 68 days of full-quality life per patient. Thus, the ICER was estimated at €65,926/LYG or €86,978/QALY (Table IV).

Sensitivity analysis indicated that the hazard multiplier was the most influential parameter of the model when varied within its CIs (change of ICER from €553,766/QALY to €54,205/QALY). Also, the choices of distributions fitted over the PFS and OS curves were found to be influential on the overall uncertainty of the CEA, but to a considerably smaller extent. Particularly, ICER estimates were €123,322/QALY for scenario 3 and €108,126/QALY for scenario 1. Comparably important appeared to be uncertainties around the probabilities of OS and PFS in the everolimus arm. Setting them to the limits of the 95% CI changed the ICER from €68,176/QALY to €117,152/QALY and from €74,861/QALY to €102,718/QALY, respectively. The cost of everolimus showed similar impact on the base-case result—its variation of ±20% changed the ICER from €104,260/QALY to €69,696/QALY. The variation

Table IV. Base-case results.

Outcome	Everolimus	BSC	Difference
Costs, €	16,828	640	16,188
Effectiveness	0.8113	0.5658	0.2455
LYG			
QALY	0.5804	0.3943	0.1861
ICER	—	—	65,926
€/LYG			
€/QALY	—	—	86,978

BSC = best supportive care; LYG = life year gained; QALY = quality-adjusted life-year.

of all other parameters (scenario 2, probability of PFS in BSC arm, all costs estimates, utilities, and adverse-events rates) was not found to be significantly influential on the ICER estimates (Figure 3 and Table V).

Assessment of parameter uncertainty through the PSA showed a wide variation of incremental costs (95% CI, €10,057–€17,422) and incremental effectiveness (95% CI, 0.0008–0.2767 QALY), which led to an uncertainty of the ICER from €32,594/QALY to €425,258/QALY in the 95% CI. Estimation of a cost-effectiveness acceptability curves revealed that the probability of the cost-effectiveness of everolimus was 54% when the threshold was put at the base–case ICER estimate (€86,978/QALY); however, this probability was zero when the threshold was 3-fold the domestic gross national product per capita (€12,402/QALY) which corresponds with the limit of cost-effectiveness defined by the World Health Organization (WHO[35,36]) (Figure 4).

If everolimus were to be officially introduced as a second-line therapy for mRCC, the estimated cost for the state (RFZO) would be €1,065,152 for 4 years, or €379,775 in the last year (prediction A). In the economically most favorable case (prediction B), total expenses were €391,966, with €139,143 to be spent in the last year, whereas the economically least favorable case (prediction C) calculated €3,015,413 of 4-year spending and €1,079,396 in the last year (Table VI).

DISCUSSION

This study is the first to estimate the cost-effectiveness of everolimus as a second-line treatment of mRCC in Serbia and is one of the first CEAs in Serbian therapeutic oncology. The results of the analysis indicate that everolimus as a second-line treatment of mRCC might be an effective, albeit costly, therapeutic alternative, with an ICER estimated around €87,000/QALY. When this ICER was placed in the perspective of the current Serbian economic surroundings by using a willingness-to-pay threshold suggested by WHO, everolimus was not found to be cost-effective.

Sensitivity analysis identified the uncertainty around the OS estimates in the BSC arm as the most influential parameter on the cost-effectiveness of everolimus. Furthermore, it pinpointed the importance of the choice of distributions, OS and PFS probabilities in everolimus arm, and the drug acquisition cost for the ICER estimate. On the contrary, the expenses of treating stable and progressed mRCC in Serbia did not significantly influence the ICER estimate. Overall, PSA analysis revealed a considerable uncertainty around the incremental costs and effectiveness estimates.

Potential reimbursement of everolimus in Serbia would compose ~0.4% of the country's annual spending in oncology (€64 million in 2009).[37] This base–case estimate was markedly affected by the simultaneous

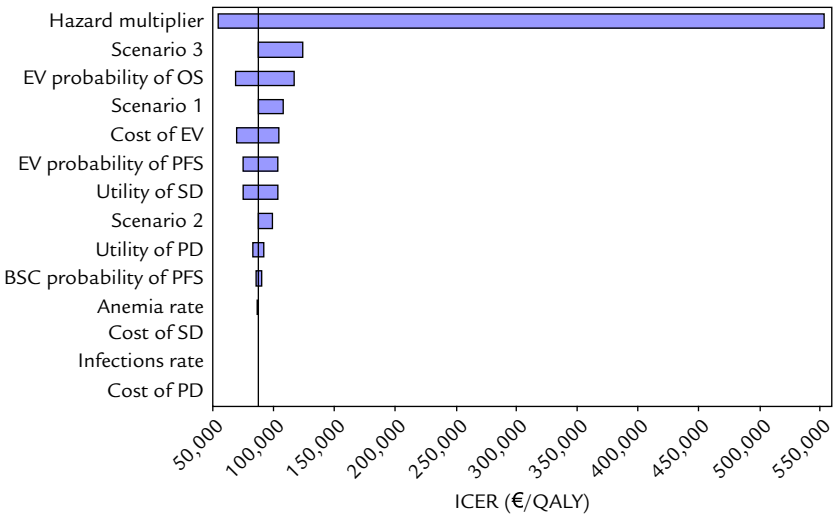

Figure 3. Sensitivity analysis on tornado diagram. BSC = best supportive care; EV = everolimus; ICER = incremental cost-effectiveness ratio; OS = overall survival; PD = progressed disease; PFS = progressive-free survival; QALY = quality-adjusted life-year; SD = stable disease.

Table V. One-way sensitivity analysis.

Parameter	Variation Range	ICER With Upper Parameter Limit	ICER With Lower Parameter Limit
Hazard multiplier	Within 95% CI	54,205	553,766
Scenario 3*	No variation	123,322	—
EV probability of OS	Within 95% CI	68,176	117,152
Scenario 1†	No variation	108,126	—
Cost of EV	Within ±20%	104,260	69,696
EV probability of PFS	Within 95% CI	74,861	102,718
Utility of SD	Within ±20%	74,974	103,558
Scenario 2‡	Within ±20%	99,161	—
Utility of PD	Within ±20%	91,377	82,983
BSC probability of PFS	Within 95% CI	85,341	89,675
Anemia rate	Within ±20%	87,205	86,752
Cost of SD	Within ±20%	87,111	86,845
Infection rate	Within ±20%	87,086	86,870
Cost of PD	Within ±20%	86,882	87,074

BSC = best supportive care; EV = everolimus; ICER = incremental cost-effectiveness ratio; OS = overall survival; PD = progressive disease; PFS = progression-free survival; SD = stable disease.
*Scenario 3: Weibull distribution was fitted on PFS in the everolimus and BSC arms while a log-normal distribution was fitted on OS in the everolimus arm.
†Scenario 1: Weibull distribution was fitted on PFS in the everolimus and the BSC arms.
‡Scenario 2: log-normal distribution was fitted on OS in the everolimus arm.

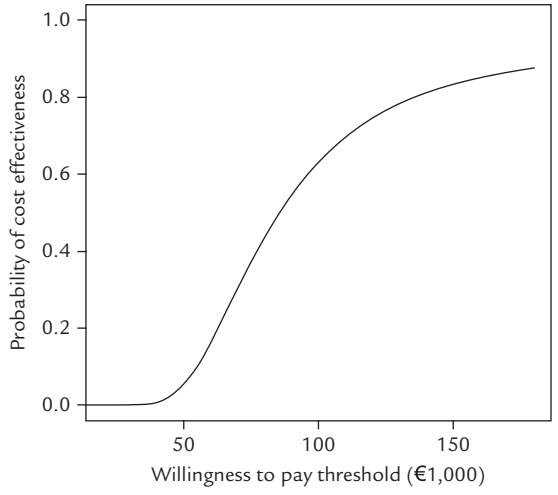

Figure 4. Probabilistic sensitivity analysis on cost-effectiveness acceptability curve.

change in parameters within their CI limits. Among the analyzed parameters, an increase in kidney cancer incidence seems to be the least controllable, due to aging of the population[38] and a lack of adequate prevention methods.[39] On the other hand, the criteria for selecting patients eligible for first- and second-line mRCC treatments are under the control of the health authorities and are controllable to a certain extent.

To the authors' knowledge, CEAs of everolimus or other mRCC therapeutic alternatives in the Serbian setting have not been published previously. Previous studies in the United States and the United Kingdom have identified comparable estimates of the cost-effectiveness of everolimus. Particularly, in the United Kingdom, a CEA similar to the one in the present analysis estimated an ICER for everolimus versus BSC of £76,070/QALY,[19] whereas in the United States, a CEA based on the indirect comparison of everolimus to sorafenib resulted in an ICER estimate of $89,160/QALY.[20] Finally, a CEA conducted in the United Kingdom, but with a different correction for the

Table VI. Everolimus budget-impact analysis.*

	Base-Case Prediction				Lowest Prediction				Highest Prediction			
Parameter	2013	2014	2015	2016	2013	2014	2015	2016	2013	2014	2015	2016
No. of patients												
With kidney cancer	721	734	747	760	664	672	681	690	762	779	796	813
With RCC	595	605	616	627	543	550	557	565	633	647	661	675
With mRCC	135	137	140	142	122	124	126	127	145	148	151	155
For 1st-line mRCC therapy	89	91	92	94	65	65	66	67	115	117	120	122
For 2nd-line mRCC therapy	29	30	30	31	17	17	17	18	57	59	60	61
Selected for everolimus	7	15	23	23	3	7	10	11	17	35	54	55
Incremental costs of everolimus arm, €												
1st year of treatment	14,142	14,142	14,142	14,142	11,314	11,314	11,314	11,314	16,971	16,971	16,971	16,971
2nd year of treatment	1959	1729	1729	1729	1567	1567	1567	1567	2351	2351	2351	2351
3rd year of treatment	428	428	428	428	342	342	342	342	513	513	513	513
Budget impact per year	103,923	224,300	352,024	374,523	38,599	83,474	130,750	139,143	291,989	637,452	1,006,576	1,079,396
Total budget impact		1,054,771				391,966				3,015,413		

*Patient flow through the budget-impact analysis model was regulated by the parameters presented in Table III.

crossover in the BSC arm, resulted in an ICER estimate of £61,330/QALY.[19] All cited studies, similarly to our analysis, identified the uncertainty around the gain in OS for everolimus as the main source of the uncertainty in cost-effectiveness. Having in mind the significantly lower costs of disease maintenance, but quite comparable ICER estimates, in Serbia, it could be argued that the incremental cost estimations depend predominantly on the price of everolimus.

The main purpose of this analysis was to advise decision makers on the affordability and consequences of potential reimbursement of everolimus in mRCC patients. Given the assumptions and the estimations presented here, we conclude that everolimus treatment might not be a cost-effective option for Serbia. Nonetheless, the incremental cost-effectiveness of new oncologic treatments, especially of those that postpone disease progression without changing prognosis, commonly overpasses regularly defined thresholds,[40,41] supporting the belief that treatment of metastatic/advanced cancers might justify a higher threshold. This is in accordance with clinicians' ethical standpoint that patients should be offered the most effective available option regardless of price or cost-effectiveness ratio.[42] Common solutions proposed for such situations are imposing special appraisal recommendations for end-of-life therapies of incurable diseases or applying risk-sharing schemes with the manufacturer.[43–45] Therefore, prior to making decisions on reimbursement of mRCC pharmaceuticals, health authorities need to construct a reasonable cost-effectiveness policy within the oncology field, balancing between financial constraints and patients' best interests.

An additional issue that could affect the estimated cost-effectiveness of everolimus in the future might be the inclusion of an existing (sorafenib) or a novel second-line mRCC treatment in the Serbian health care system. Given these circumstances, a new CEA that would incorporate all relevant therapeutics as comparators might be needed. However, existing data on the comparison of everolimus versus sorafenib, conducted in a different economical setting, suggested that everolimus would remain a more cost-effective option.[20]

Everolimus has been designated as an orphan drug in some European countries.[46] Such a designation is given to treatments of life-threatening rare diseases with a prevalence of $<5/10{,}000$ people.[47] According to the epidemiologic parameters presented in our analysis, this could be applicable to everolimus, as well as to any other mRCC treatment in Serbia. Still, the impact of the potential orphan drug designation on everolimus economic appraisal remains arguable, due to the controversy of whether higher cost-effectiveness thresholds should be allowed for these medicines.[48,49] Moreover, the orphan drugs' funding in Serbia has not been clearly defined.

Study Limitations

One of the main limitations of our analysis was data unavailability for a number of parameters. Probably the most influential unknown parameter was the allocation of OS between patients in the SD and PD states. Because the available data on the probability of OS did not distinguish between PD and SD in the 2 arms, we ascribed the same probability of death to both health states. Sensitivity analysis, however, indicated that the influence of this assumption on the final outcome of the CEA is relatively moderate. The lack of reliable resource-utilization costs from Serbia might have led to an underestimation of hospitalization fees and palliative care expenses. We tried to resolve the issue through the consultation of clinical experts (ie, personal communication with Dr. Radosavljević) and the use of secondary sources for pricing. Furthermore, because our ICER estimates were rather inelastic on changes in price, more precise reporting of prices in the future is not expected to excessively change these ICER estimates. As far as the model itself is concerned, a different choice of hazard multiplier could have been applied, as well as a different choice of fitted distributions to the PFS and OS curves. For the former, the authors had no access to the patient-level data that are required for the estimation of another form of crossover correction. In the case of fitted distributions, we provided scenarios with the second-best goodness-of-fit in the sensitivity analysis. Consistent with the conclusions from previous studies,[50] the choice of fitted distributions seems to influence the final outcome. Yet, in our analysis, this was not enough to affect overall cost-effectiveness.

CONCLUSIONS

An unmet need exists in mRCC patients refractory to first-line treatment. This analysis revealed that everolimus as a second-line treatment for mRCC is not likely to be a cost-effective option under the present circumstances in Serbia, while its budgetary impact

remains relatively small. The major source of variation around the cost-effectiveness outcome was the uncertainty of the relative benefit of everolimus on OS. Efforts should be undertaken to perform an integral assessment of the economic attractiveness of all current and new therapeutics in mRCC.

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CONFLICTS OF INTEREST

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