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- О ВОЗМОЖНОСТЯХ СОВМЕЩЕНИЯ АНАЛИЗА «ВЛИЯНИЯ НА БЮДЖЕТ» И АНАЛИЗА «ЗАТРАТЫ-ЭФФЕКТИВНОСТЬ» - СОЗДАНИЕ «3D» ФАРМАКОЭКОНОМИЧЕСКОЙ МОДЕЛИ

- ФАРМАКОЭКОНОМИКА САХАРНОГО ДИАБЕТА, РАКА ПОЧКИ, ПОСТИНСУЛЬТНОЙ СПАСТИЧНОСТИ

- СОЦИАЛЬНЫЕ АСПЕКТЫ ТАБАКОКУРЕНИЯ

PHARMACOECONOMIC EVALUATION OF MEDICINAL PRODUCTS USED AS FIRST-LINE TARGETED THERAPY OF METASTATIC KIDNEY CANCER

Kolbin A.S. [1,2], Kurylev A.A.[2], Pavlysh A.V.[1], Proskurin M.A.[2], Balykina Yu.E.[2]

[1] *Academician I.P. Pavlov First Saint-Petersburg State Medical University.*

[2] *Saint-Petersburg State University.*

Abstract: *A pharmacoeconomic evaluation of sunitinib as the first-line metastatic renal-cell carcinoma targeted agent in the Russian healthcare settings was performed in comparison with sorafenib and bevacizumab + interferon. A pharmacoeconomic Markov model was created and used to assess the costs and effectiveness (including mean overall survival in months) of each therapeutic regimen. The evaluation presented also includes a probabilistic multivariate sensitivity analysis. The results show that sunitinib-based treatment is dominant over sorafenib and bevacizumab + interferon, which makes it the most cost-effectiveness treatment option.*

Keywords: *pharmacoeconomics, metastatic renal cell carcinoma, sunitinib.*

Background

Cancer remains the leading cause of death worldwide. One of the most serious issues in oncology is kidney cancer and particularly renal cell carcinoma (RCC) [1-3]. There is a range of logistical, medical and social reasons due to which clinical oncologists often have to deal with the metastatic disease (mRCC) [4]. mRCC treatment uses targeted agents which include antiangiogenic agents: VEGF (vascular endothelial growth factor) tyrosine kinase inhibitors - sunitinib, sorafenib, axitinib, pazopanib; anti-VEGF monoclonal antibodies - bevacizumab; mTOR (mammalian target of rapamycin) kinase inhibitors – everolimus, temsirolimus [2;3;5-7]. According to the available international guidelines, disease prognosis and the choice of first-line treatment is of key importance for the best sequential system therapy of mRCC patients [8]. However, medication cost-effectiveness data are needed besides the information on its clinical efficacy and safety. Consequently, we have conducted a clinical & economic evaluation of sunitinib, one of the antiangiogenic agents, in the Russian healthcare settings. According to international and Russian guidelines (level IA evidence), sunitinib is the first-line treatment of choice for favorable and intermediate prognostic risk patients with mRCC. Alternative treatments were sorafenib and bevacizumab + interferon that occupy the greatest market share in the Russian Federation.

Methods

The Industry Guidance for Clinical & Economic Studies and expert guidelines used in the Russian Federation were utilized for the clinical & economic evaluation methodology [9-12]. Cost-effectiveness analysis was used that implied calculating the cost-effectiveness ratio (CER). Cost and effectiveness data were obtained using a Markov model. When the effectiveness and costs of one of the investigated treatments exceeded any other, an increment analysis was performed with the calculation of incremental cost-effectiveness ratios (ICERs). This analysis was conducted to determine extra costs for an additional life year gained. The study results were evaluated against the parameter of the societal willingness to pay (cost-effectiveness threshold) which is calculated as a 3-fold gross domestic product value per person [13].

Efficacy

A systematic literature review was performed to collect mRCC effectiveness data. The analysis included randomized clinical trials (RCTs) with sunitinib, sorafenib, bevacizumab and everolimus as second-line treatment in mRCC patients. The analysis excluded retrospective and observational studies with less than 50 subjects due to the high risk of the efficacy estimate bias in these studies. The following clinical trial parameters were entered into the database for a further systematic analysis: design; number of subjects; drugs used; therapeutic indications; dosage (mg/kg/day); efficacy endpoints; subject baseline characteristics [8]. We also took into account that disease progression is determined by the RECIST (Response to treatment in solid tumors) criteria, which are based on the evaluation of the changes in the number of lesions and other parameters determined by imaging studies (computerized and magnetic resonance tomography) [14]. Progression-free survival (PFS) in months and overall survival (OS) in years were also one of the efficacy endpoints in mRCC clinical trials. The efficacy data collected with different drugs used as first- and second-line treatments are provided in Table 1.

Table 1. Median progression-free survival and overall survival in first-line targeted therapy (treatment-naïve patients).

Drug	PFS, months	OS, months	Subject distribution by prognosis			Reference
			Favorable prognostic risk, %	Intermediate prognostic risk, %	Poor prognostic risk, %	
Sunitinib	11,0	26,4	38	56	6	[15;16]
Bevacizumab + IFN	10,2	23,3	27	56	9 (+9 % with unknown prognostic risk)	[17;18]
Sorafenib	5,7	Not evaluated in CTs	53,6	45,4	1	[19]

As the data in Table 1 show, the trials selected had different subject distribution by the prognostic risk. The proportion of subjects in the favorable prognostic risk group was the highest in the sorafenib trial; however, the efficacy analysis results were the poorest. At the same time, sunitinib and bevacizumab + interferon clinical trials did not have any significant differences in subject prognostic risks.

Model Structure

Pharmacoeconomic decision tree model was generated where costs and effectiveness were analyzed in a group of 100 subjects within each model branch. A PFS model for first-line treatment and for everolimus, and then a palliative care duration model were created based on efficacy data for the therapeutic options evaluated. The criterion for the subsequent treatment need was disease progression [2;3;5-7;20]. The total treatment cost per patient was then calculated within each group. The flow-chart for a model patient is provided on Figure 1.

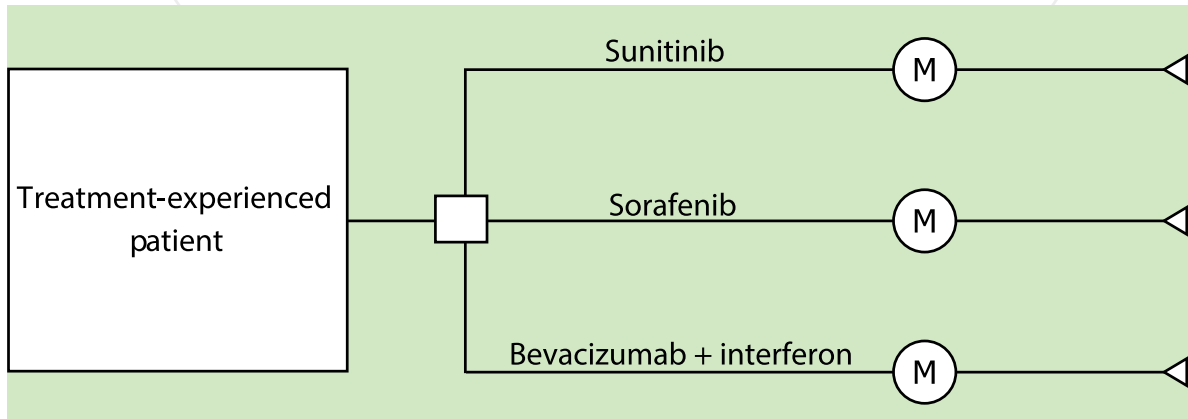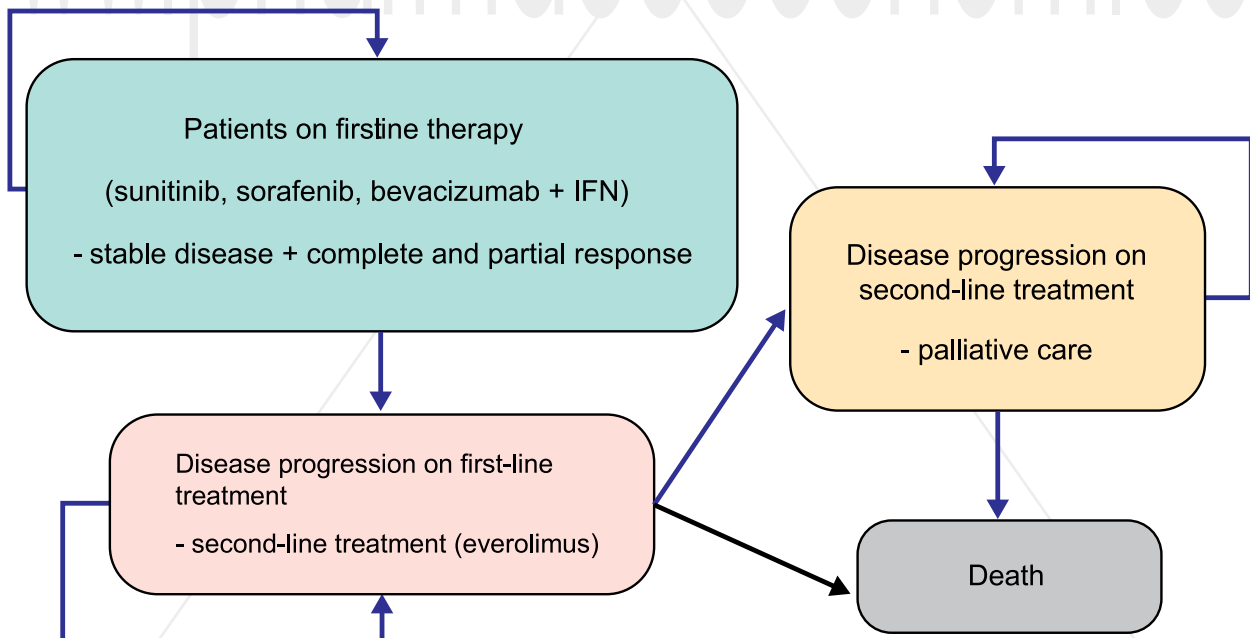Figure 1. **Decision tree model structure for mRCC first-line treatment.**

Figure 2. **. Flow-chart for Markov model sequential therapy.**

As the data in Table 1 show, the model cohort includes subjects in favorable and intermediate prognostic risk groups, which is why deaths during the first-line treatment are relatively unlikely and were not taken into account in this evaluation.

Cost Characterization

A direct cost evaluation for mRCC treatment was performed at the next stage and included:

- Underlying disease treatment cost analysis:
  o Cost of drugs for the first-line treatment and management of treatment-related adverse events (AEs)
  o Cost of drugs for the second-line treatment (everolimus) and management of treatment-related AEs
- Supportive care cost analysis, including palliative care
- Patient hospice stay cost analysis
- Laboratory and imaging diagnostic procedure cost analysis.

Costs of targeted therapeutic agents were evaluated based on the information provided in the State Register of Maximum Sale Prices [21].

AE management cost was calculated as the sum of costs for the drugs needed, taking into account the number of doses per cycle and administration frequency [15;17;19-21;23-25;], as well as the cost for hospital stay, out-patient doctor visits evaluated according to the AE severity [26]. The assumption when calculating the cost for AE therapy in treatment groups was that two out-patient oncologist visits were needed on the average with mild and moderate AEs (< Grade 3) [27], while severe anemia and leukopenia (≥ Grade 3) necessitated the patient's stay at the hospital for 14 days (including the ambulance call) and appropriate drug treatment. Treatment of other severe AEs included two out-patient oncologist visits on the average and the use of appropriate medications for their management, determined by the standard of care in renal cancer patients.

Palliative and supportive care occupied a special place in the cost analysis structure. Since no current standard of care for end-stage cancer patients in the Russian Federation was found in open sources, the cost of one bed day at a hospice (2915.67 rubles in 2014 [28]) was used for calculating the cost of palliative and supportive care. At this stage, we assumed that an end-stage renal cancer patient receiving palliative care needs 8 home visits by an oncologist per month (one visit cost is 507.10 rubles [28]).

The calculation of costs for laboratory and imaging diagnostic procedures in mRCC patients was based on the RECIST criteria [14], according to which the treatment effectiveness evaluation was performed every 3 months. Therefore, according to the standard of medical care for renal cancer patients and compulsory health insurance system rate agreement, the cost for a set of diagnostic procedures is 7825.00 rubles [23;24;29].

Analysis

A disease cost analysis per patient of the target group was performed for each treatment strategy. If a less expensive strategy was also more effective, it was regarded as a "dominant" therapeutic option. All the costs and treatment outcomes were discounted at 5 % annually. Multiple one-way sensitivity analyses were conducted in the range of 75 % to 125 % to verify the robustness of the study results against the changes in the key variables such as estimated drug efficacy parameters and their cost.
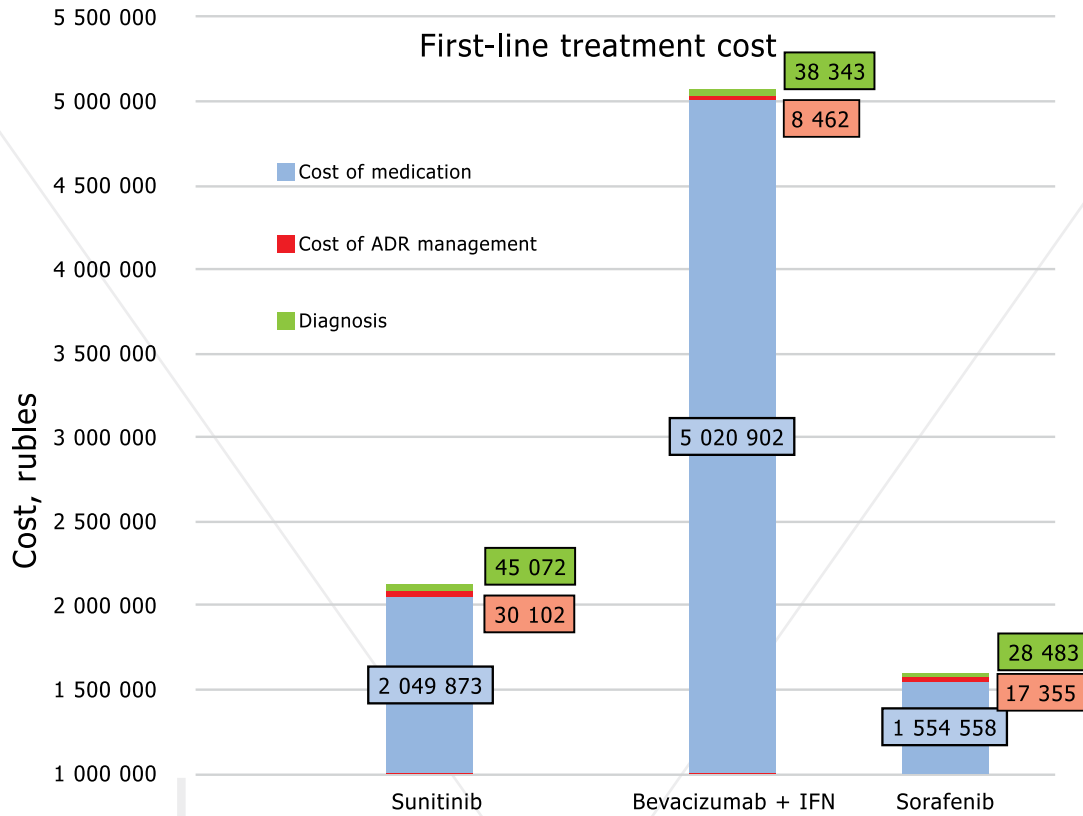
Results

A disease cost analysis was performed for each treatment strategy for one patient of the target group (model horizon was 6 years). Figure 3 shows the costs associated with the first-line treatment for the overall model period per one mRCC patient in case of effective therapy with no disease progression.

Table 2. Costs of targeted therapeutic agents.

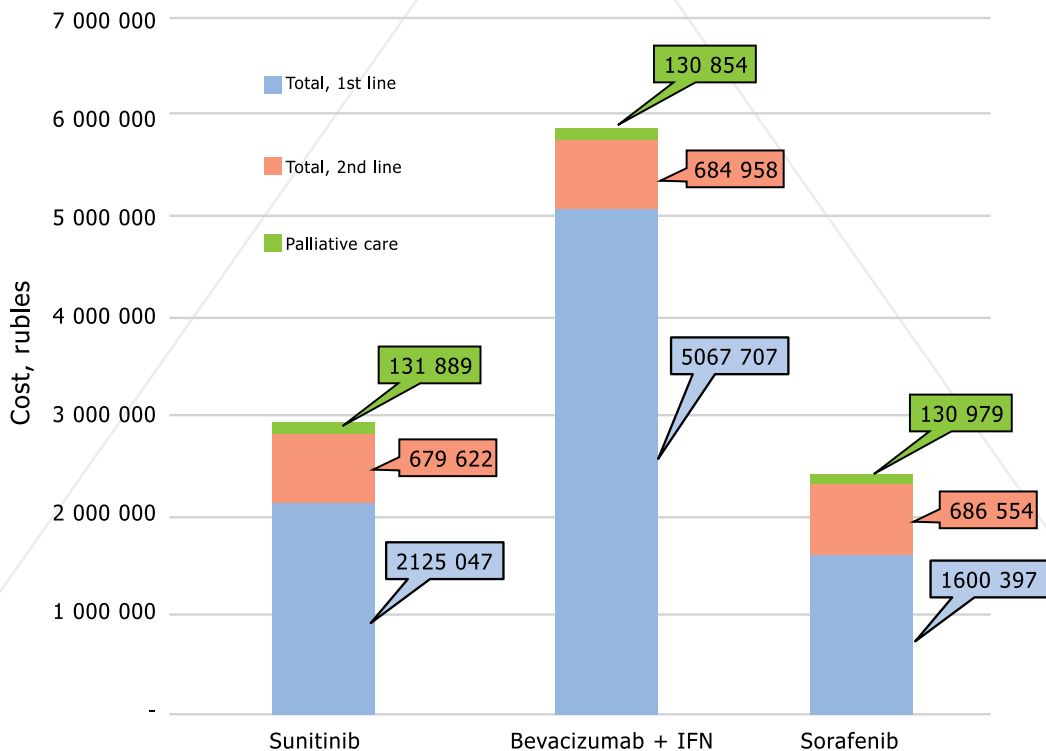| Drug (trade name)	Daily dose (mg)	Treatment cycle duration (weeks)	Formulation	Vital & Essential Drug List status	Price [22], rubles	Cost for one treatment day, rubles
Sunitinib (Sutent)	50	4 week with a 2-week interruption until progression	50 mg capsules, 28 cc	Yes	176279	4197
Sorafenib (Nexavar)	800	Daily until progression	200 mg oral tablets, 112 cc	Yes	145821	5207
Bevacizumab (Avastin) + Interferon alpha (Alfaferone)	0.72 mg/kg (10 mg/kg once every other week) 3.85 MU/day (9 MU three times weekly)	Until disease progression	400 mg/16 mL concentrate, 16 mL 3 MIU/mL solution for injections, 1 pc - 1 mL ampoules	Yes	69028 1859	9861 2390
Everolimus (Afinitor)	10	Until progression	10 mg tablets, 30-cc	Yes	174559	5818

Figure 3. **First-line therapy costs per patient treated for mRCC (overall model period).**

First-line treatment cost

Legend:
- Cost of medication
- Cost of ADR management
- Diagnosis

Sunitinib: 2 049 873; 30 102; 45 072
Bevacizumab + IFN: 5 020 902; 8 462; 38 343
Sorafenib: 1 554 558; 17 355; 28 483

As the data presented show, direct costs for sunitinib-based treatment strategy exceeded those for sorafenib treatment, resulting in 2,125,047 rubles over the patient's lifetime. At the same time, the highest costs for the first-line treatment were associated with bevacizumab + IFN, amounting up to 5,067,707 rubles. It should be noted that these expenses related to different life expectancies. For instance, the less effective treatment regimen which included sorafenib was the less expensive and amounted up to 1,600,397 rubles for the first-line mRCC targeted therapy. Further, total direct costs for each strategy over the model period was evaluated, taking into account the first- and second-line treatment efficacy, potential AEs and their severity, as well as palliative care. The cost analysis results are presented on Figure 4.

Figure 4. **Total cost of the therapeutic strategies compared per patient for the overall model period (6 years).**

Legend:
- Total, 1st line
- Total, 2nd line
- Palliative care

Sunitinib: 2125 047; 679 622; 131 889
Bevacizumab + IFN: 5067 707; 684 958; 130 854
Sorafenib: 1600 397; 686 554; 130 979

As the data on Figure 4 show, the sunitinib-based treatment strategy required more total direct costs than sorafenib therapy (2,936,558 rubles versus 2,417,929 rubles, respectively). However, the greater sum for the sunitinib-based treatment was due to a greater overall survival. The most expensive treatment strategy was bevacizumab + IFN therapy (5,883,519 rubles), which is twice as high as the sunitinib treatment cost. The efficacy of each strategy compared was also evaluated based on the Markov model results and expressed as the mean overall survival; the results are presented on Figure 5 and Figure 6.

Figure 5. **Efficacy of the mRCC treatment strategies evaluated – progression-free survival (months).**
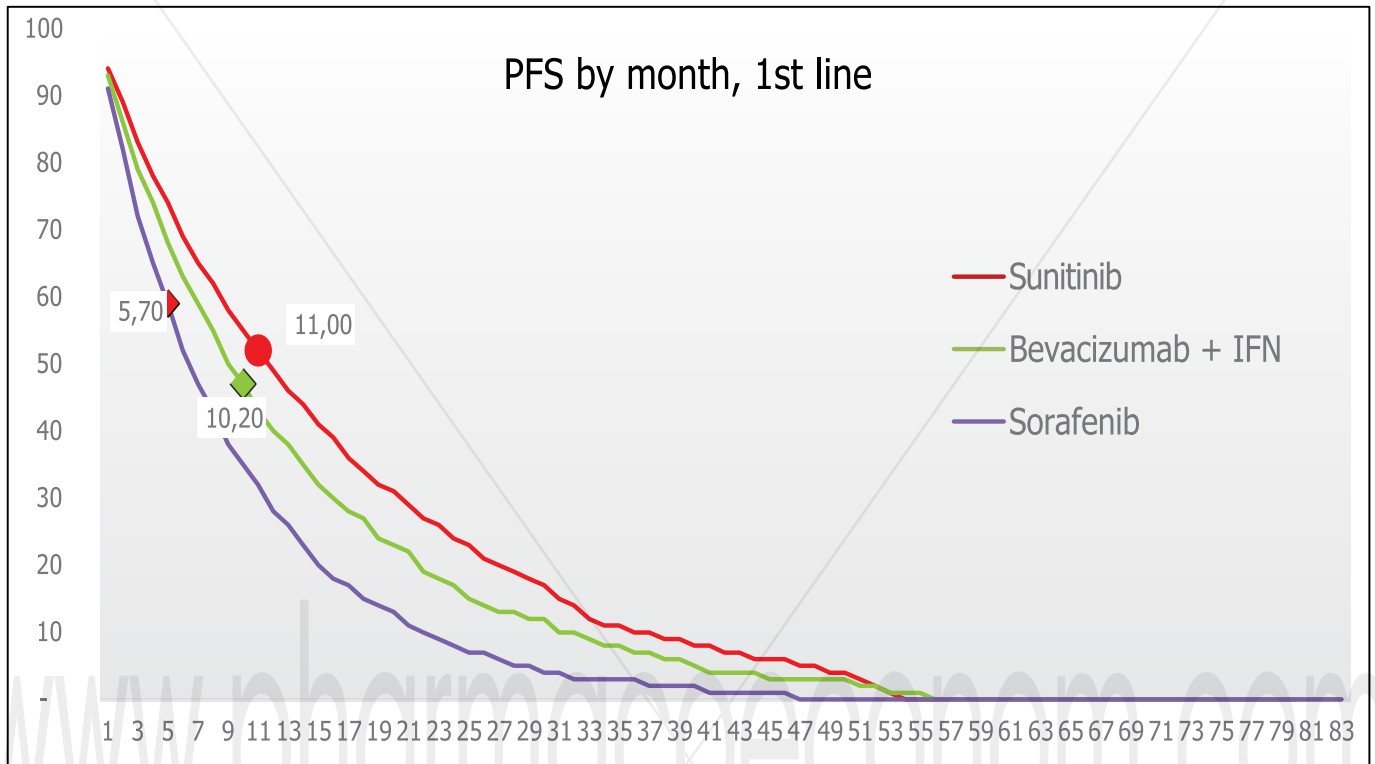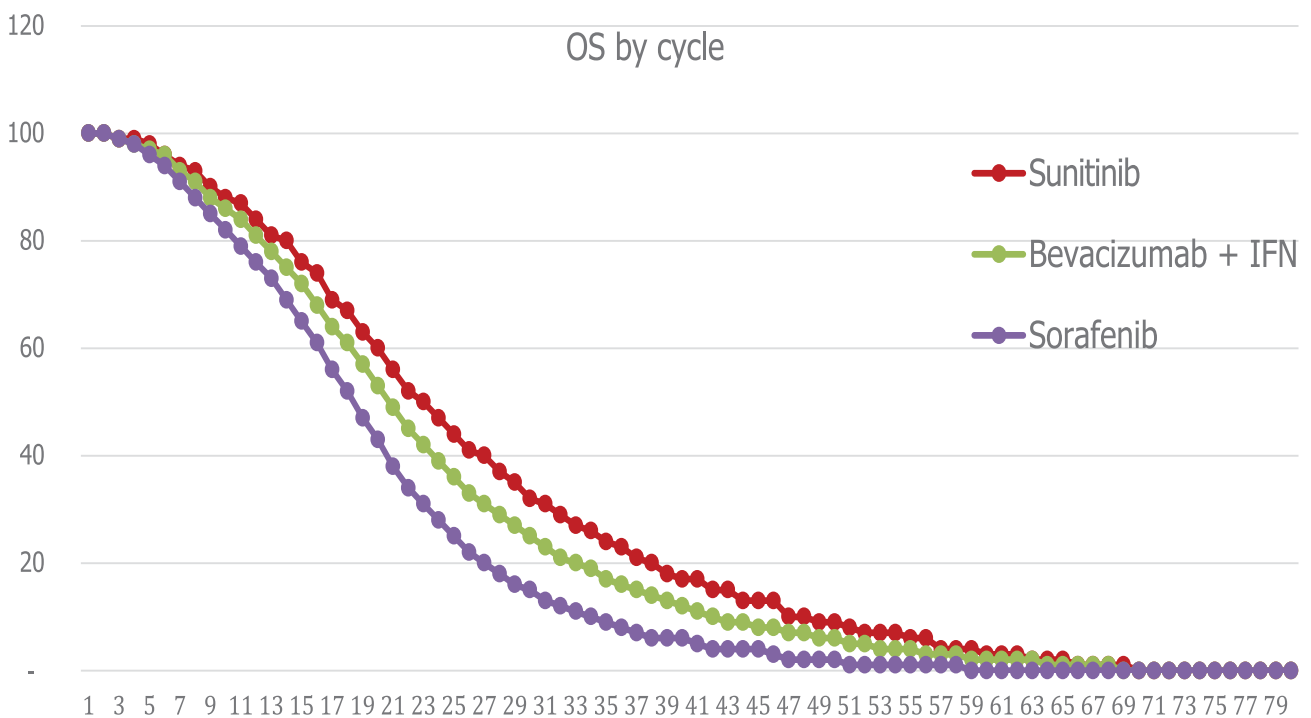

Figure 6. **Efficacy of the mRCC treatment strategies evaluated – life years gained (overall survival).**

As the analysis of the Markov model results (Figures 5 and 6) shows, sunitinib-based mRCC treatment was the most effective of the therapeutic options compared: median PFS was 11 months, which is 1.9 times as great as PFS with sorafenib (5.7 months). In terms of overall survival, sunitinib was also the most effective treatment strategy, achieving the mean OS up to 35.61 months, which is 8.8 months and 3.8 months longer than therapies including sorafenib and bevacizumab + IFN, respectively. The cost-effectiveness results for different mRCC treatment strategies are shown graphically on Figure 7.

Figure 7. **Cost-effectiveness in case of effective treatment according to the efficacy variables indicated. Cost effectiveness ratio (CER) is the mean monthly treatment cost in rubles.**
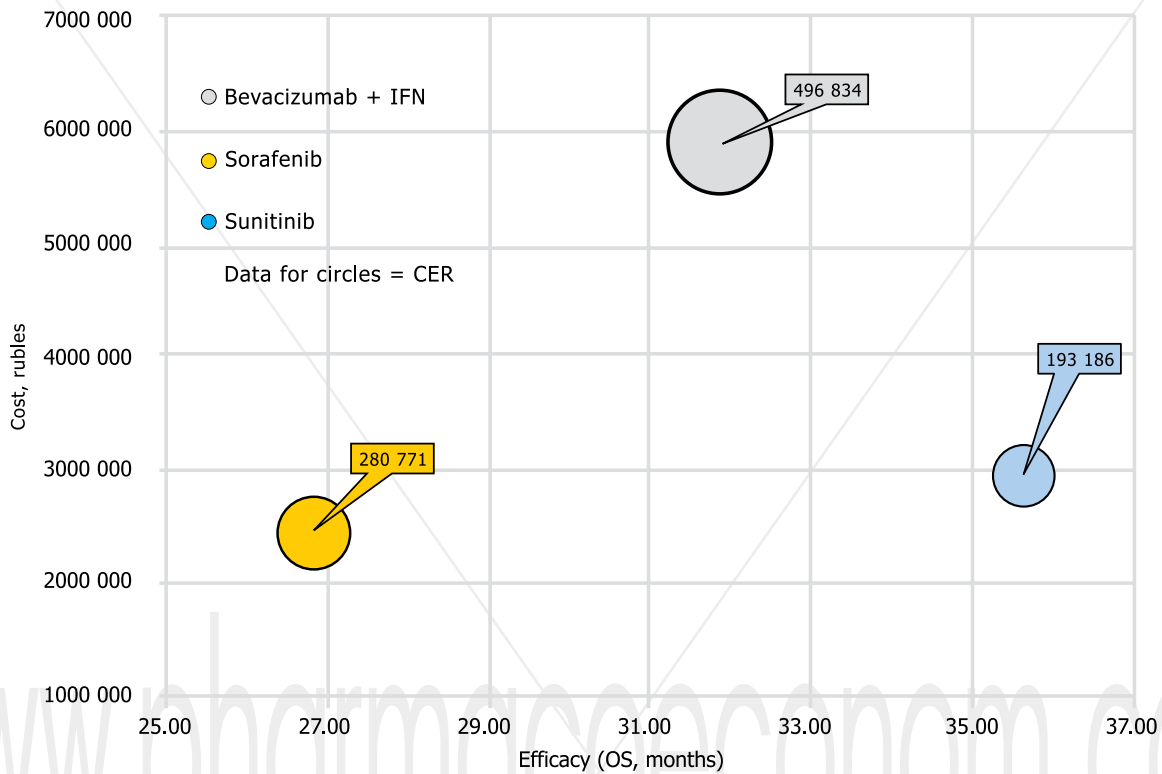
As can be seen from the data shown on Figure 7 that demonstrate the cost effectiveness ratio for the treatment strategies evaluated, sunitinib use allowed to achieve the highest efficacy among the medical interventions investigated. This therapeutic option was also less expensive than bevacizumab + IFN. Sorafenib use required less direct costs, but at the same time demonstrated the lowest treatment efficacy, i.e. higher expenses for sunitinib therapy compared to sorafenib are due to the superior efficacy of sunitinib that leads to a better overall survival and, consequently, to longer use of healthcare resources. This is confirmed by values of cost effectiveness ratios (CERs) that show the mean mRCC treatment cost of 280,771 rubles and 193,186 rubles for sorafenib and sunitinib treatment strategies, respectively.

The incremental cost effectiveness ratio (ICER) (Table 3) that reflects total additional costs per life year gained was also calculated in order to perform an economic analysis of sunitinib as mRCC first-line targeted treatment.

Table 3. ICER calculation for the strategies compared.

Treatment strategy	Total direct costs	Cost increment	OS (months)	Efficacy increment (months)	ICER
Sunitinib	2 936 558 rubles	- 2 946 960 rubles	35,61	3,75	Dominant
Bevacizumab + IFN	5 883 519 rubles	-----	31,86	-----	-----
Sunitinib	2 936 558 rubles	518 629 rubles	35,61	8,82	58 805 rubles
Sorafenib	2 417 929 rubles	-----	26,79	-----	-----

As can be seen from the data in Table 3, the comparison of treatment strategies that included sunitinib and bevacizumab + IFN showed that sunitinib-based therapy is dominant: it led to less significant treatment costs with the overall survival increment of 3.8 months. When sunitinib was compared to sorafenib, the total sunitinib-based treatment costs were 518,629 rubles higher, but an additional mean OS benefit of 8.8 months was achieved. The corresponding ICER for sunitinib was 58,805 rubles per month or 705,660 rubles per year, which is twice as low as the willingness-to-pay threshold in the Russian Federation [13]. Therefore, it can be concluded that additional costs for sunitinib use compared to sorafenib are acceptable and economically viable in the Russian healthcare settings. Additionally, the use of sunitinib requires a smaller amount of expenses per one life year.

The conclusions above were preliminary. A pharmacoeconomic sensitivity analysis was performed to confirm the cost-effectiveness results with different input data.

Sensitivity Analysis
Probabilistic multivariate sensitivity analysis was conducted by the multiple simultaneous changes in parameters such as targeted drug efficacy and cost. The results of simultaneous multiple changes in the variables showed that sunitinib-based treatment strategy is more effective than the other therapeutic options. The sensitivity analysis also demonstrated that the sunitinib and sorafenib use cost ranges overlap sufficiently to indicate that there is no essential difference between the cost of these treatments.

Discussion

A pharmacoeconomic evaluation of mRCC first-line targeted treatments (sunitinib, sorafenib and bevacizumab + IFN) has been performed for the first time in the Russian healthcare settings. A disease cost analysis has been conducted, with the evaluation of the efficacy of these treatments expressed as the estimated overall survival (in months) that was based on RCT results. A pharmacoeconomic model was then generated with treatment-naïve patients included in the decision tree and receiving one of the targeted agents investigated: sunitinib, sorafenib or bevacizumab + IFN (Figure 1). The patients were further included in the Markov cycle; second-line targeted therapy (everolimus) was used in case of disease progression, and palliative and supportive care was taken into account with further progression. The end state in the Markov cycle was the patient's death. The duration of the Markov cycle was one month with the maximum model horizon of 6 years (Figure 2). The final study stage involved a multivariate sensitivity analysis that allowed to evaluate the robustness of the results obtained and to account for a potential bias when calculating efficacy parameters and total direct costs.

The pharmacoeconomic results for medications used as targeted first-line mRCC therapy demonstrated that the treatment based on bevacizumab + IFN was the most expensive and of inferior efficacy compared to sunitinib, tyrosine kinase inhibitor recommended as targeted first-line mRCC treatment of choice. Whereas the costs associated with sorafenib-based treatment were lower, they were significantly less effective in terms of a mean monthly treatment cost: the cost of one life month was 280,771 rubles and 193,186 rubles for sorafenib- and sunitinib-based treatments, respectively. The cost of one additional life year with sunitinib treatment was as low as 705,660 rubles per year which is twice as low as the willingness-to-pay threshold in the Russian Federation.

Conclusions

The pharmacoeconomic results for medications used as targeted first-line mRCC therapy show that:

1) Sunitinib-based treatment allows to achieve the greatest overall survival. Mean overall survival on sunitinib therapy was 8.82 months which is 3.75 months longer than on sorafenib and bevacizumab + IFN, respectively.

2) With greater clinical efficacy, sunitinib use is almost twice as cheap as the combination of bevacizumab and IFN. In this case sunitinib treatment is the dominant option.

3) Sorafenib-based treatment demonstrated the lowest cost for mRCC therapy; however, this advantage was due to the shortest overall survival. The cost-effectiveness analysis conducted showed that the least expensive monthly treatment was sunitinib. Additional costs for sunitinib use were twice as low as the willingness-to-pay threshold in the Russian Federation, which is the evidence for the economic viability of these expenses.

Based on the results above, it can be concluded that sunitinib-based mRCC treatment is the most advantageous among the therapeutic options compared in terms of cost effectiveness.

Study limitations

Treatment efficacy data were based on the results of clinical trials with patients receiving the best supportive care besides the targeted treatment, which is not wholly included in the Russian standard of care. Supportive care had a certain impact on the overall survival of these patients.

Since we do not have full risk factor-dependent efficacy information, some efficacy data are estimates. A multivariate sensitivity analysis was performed in order to reduce the impact of this factor.

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