Pharmacoeconomic aspects of using enzalutamide for treatment of patients with nonmetastatic castration-resistant prostate cancer

N.A. Avxentyev[1, 2], M.Yu. Frolov[3, 4], Yu.V. Makarova[1]

[1]*Research Institute of Finance; Build 2, 3 Nastas'inskiy Pereulok, Moscow 127006, Russia;*
[2]*Institute of Social Analysis and Prognosis, Russian Presidential Academy of National Economy and Public Administration; Build. 1, 82 Vernadskogo Prospekt, Moscow 119571, Russia;*
[3]*Volgograd State Medical University, Ministry of Health of Russia; 1 Pavshikh Bortsov Ploshchad', Volgograd 400131, Russia;*
[4]*Volgograd Medical Scientific Center; 1 Pavshikh Bortsov Ploshchad', Volgograd 400131, Russia*

Background. *Prostate cancer is one of the most common malignant diseases among men. Until recently, the most common treatment of nonmetastatic castration-resistant prostate cancer (nmCRPC) in Russia was to continue previously started hormonal therapy. Enzalutamide is a second-generation anti-androgen indicated for treatment of castration-resistant prostate cancer (CRPC), regardless of a patient's metastatic status, which significantly increases metastasis-free survival in nmCRPC compared with androgen deprivation therapy (ADT).*

Objective: *to evaluate the incremental cost–effectiveness ratio (ICER) of enzalutamide use in patients with nmCRPC and the ICER of abiraterone as the first-line therapy for mCRPC from the Russian healthcare system perspective.*

Materials and methods. *Standard ADT regimens for nmCRPC were used as a comparator as it was the only approved treatment for nmCRPC in Russia. We proposed a Markov model of CRPC progression on enzalutamide plus ADT (hereinafter enzalutamide) or ADT based on PROSPER trial data. Model was used to calculate progression-free life years and costs of nmCRPC and post-progression CRPC treatment during. Simulation period was 5 years with one cycle of 1 month. In the "cost–effectiveness" analysis, we calculated enzalutamide ICER compared to ADT. In addition, we calculated ICER for abiraterone plus ADT and prednisolone (hereinafter abiraterone) vs ADT + prednisolone in the first-line therapy of metastatic CRPC (mCRPC) as a benchmark. In both cases, time to disease progression over a 5-year period was used as an efficacy criteria.*

Results. *According to the Markov model, progression-free life-years gained for enzalutamide were 3.12 years compared to 1.79 for ADT within a 5-year period. The average enzalutamide therapy costs were 7,989,475.8 rubles/1 patient for 5 years, which were 5,716,983.5 rubles higher than when using ADT (2,272,492.3 rubles). ICER for enzalutamide (vs ADT) was 4,307,136.3 rubles per one progression-free life-year gained. ICER for abiraterone in the first line of mCRPC treatment (vs ADT + prednisolone) was 6,191,617.4 rubles per one progression-free life-year gained.*

Conclusion. *In the Russian healthcare system, ICER for enzalutamide in nmCRPC was 4,307,136.3 rubles and ICER for abiraterone in mCRPC was 6,191,617.4 rubles.*

Key words: *prostate cancer, enzalutamide, pharmacoeconomic analysis, "cost–effectiveness" analysis*

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Background

Prostate cancer (PC) is a malignant neoplasm arising from prostatic epithelial cells. PC is one of the most common malignant diseases in men: about 1.6 million new cases are diagnosed annually in the world, about 366 thousand men die from the disease annually [1]. The incidence of PC among malignant neoplasms in male population of Russia was 14.9 % in 2018, which is second highest (after 16.9 % for trachea, bronchus and lung cancer). In 2018, 42,518 new cases of all-stages PC were detected, which is 4.3 % higher than in 2017, while the number of new detected cases for all malignant neoplasms increased only by 1.5 % [2]. Mortality rate from prostate cancer was third highest among male population of Russia in 2018, – 13,007 cases (after 41,501 deaths from trachea, bronchus, lung cancer and 16,572 deaths from stomach cancer) [2].

Prostate cancer exhibits androgen dependence and responds to the suppressed activity of androgen receptors. Enzalutamide is a potent androgen receptors inhibitor that blocks several stages of the androgen receptors signaling pathway. The drug is used once a day orally, a daily dose is 160 mg . In Russia enzalutamide is indicated for the treatment of castration-resistant prostate cancer (CRPC), regardless of a patient's metastatic status [3]. It is registered in Russia and included in the list of vital and essential drugs (Vital and Essential Drugs list). Domestic clinical guidelines recommend it for the treatment of metastatic and non-metastatic CRPC (mCRPC and nmCRPC, respectively) [1].

Currently, the results of a pharmacoeconomic evaluation of enzalutamide use as the first- [4–6] and second-line [7, 8] therapy for mCRPC are published in Russia. Pharmacoeconomic analysis of enzalutamide use to treat nmCRPC in Russia has not been conducted previously.

Objective – the cost–effectiveness analysis of enzalutamide use in nmCRPC patients in comparison against the cost-effectiveness of abiraterone as the first-line therapy for mCRPC as benchmark within Russian healthcare system.

Materials and methods

Mathematical model of the study

For pharmacoeconomic analysis, we developed a heterogeneous Markov model for the following nmCRPC treatment regimens:

- enzalutamide (160 mg once per day) in combination with standard androgen deprivation therapy (ADT), the regimens are described below (hereinafter – "enzalutamide" regimen);
- standard ADT (hereinafter – "ADT" regimen), including the following treatment regimens:
  - goserelin subcutaneously 3.6 mg once every 28 days or 10.8 mg subcutaneously once every 3 months,
  - tripotrelin intramuscularly 3.75 mg once every 28 days or 11.25 mg once every 3 months,
  - leuprorelin intramuscularly or subcutaneously 7.5 mg once every 28 days, or 22.5 mg once every 3 months, or 45 mg once every 6 months,
  - buserelin intramuscularly 3.75 mg once every 28 days,
  - degarelix subcutaneous 240 mg in the 1st month, then 80 mg monthly.

In all cases, flutamide (orally 250 mg 3 times a day) or bicalutamide (orally 50 mg once a day) were supposed to be administered as well. Thus, we considered 18 alternative ADT regimens. All of them were assumed to be of equal market share (each regimen in 5.6 % of cases). ADT regimen is consistent with domestic clinical recommendations [1]*.

Simulation period was 5 years with one cycle of 1 month, since by the end of this period more than 70 % of patients progressed in both treatment arms. Patients' states are sequentially shown in fig. 1.

All patients are initially in "stable phase", where, depending on the treatment regimen, enzalutamide + ADT or ADT are administered. In each subsequent cycle of the model, patients can remain in this state, change to the docetaxel or abiraterone ("abiraterone 1"), first-line therapy for mCRPC.

Second-line therapy includes abiraterone, docetaxel or cabazitaxel, depending on the first-line therapy. In addition, in some patients second-line therapy is not administered (such patients immediately change to "palliative" state).

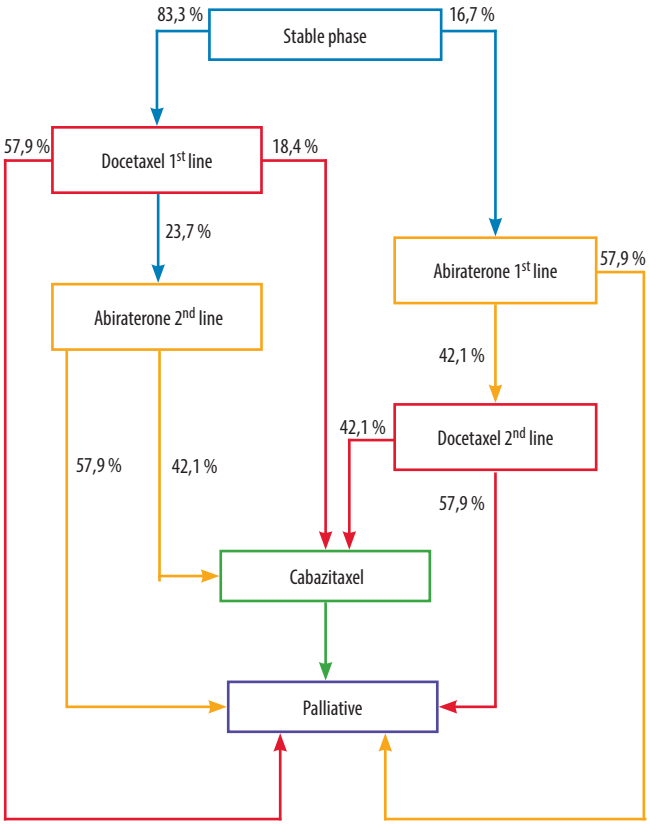

Fig. 1. *Treatment flow diagram used for Markov model of non-metastatic castration-resistant prostate cancer progression (based on data [9])*

Third-line therapy includes only cabazitaxel, however, after completing second-line therapy some patients directly change to "palliative" state.

Patients' distribution between subsequent treatment options of the model did not depend on nmCRPC treatment tactics and was determined based on the data of real clinical practice of treating mCRPC patients in Russia [9]. For example, to distribute patients from the "stable phase" between "abiraterone 1" and "docetaxel 1", it was taken into account that 239 out of 321 registered patients received docetaxel as the first-line therapy for mCRPC, while other 48 received abiraterone. Thus, if we consider only 2 treatment options for the first-line therapy (abiraterone and docetaxel), 16.7 % (48 of 287) patients receive the first one, 83.3 % (239 of 287) patients – the second one. According to the register, the second-line therapy was planned in 135 (42.1 %) of 321 patients, therefore, the remaining 57.9 % received palliative care. It was assumed that the numbers for the third-line therapy were the same. Full information on frequency of each of the considered mCRPC treatment options after withdrawing the previous treatment, which was taken into account in the model, is presented in fig. 1.

*Modern clinical guidelines [1] do not recommend flutamide and bicalutamide, but their use was recommended in the previous version of 2018 [11] and, according to an expert opinion, it remains a common practice in Russia.

Lethal outcome in the model is possible only in the "palliative" state.

Estimating probability of withdrawal from the model state

PROSPER [10], a pivotal Phase 3 clinical study which assessed the safety and efficacy of enzalutamide in patients with non-metastatic prostate cancer , estimated metastasis-free survival, which was defined as time from randomization to radiographic progression or death. The study included 1401 men with nmCRPC, prostate-specific antigen doubling time ≤10 ms and prostate-specific antigen ≥2 ng/mL at screening. The patients were randomized 2:1 to enzalutamide 160 mg or placebo. Study results showed that enzalutamide significantly reduced risk of metastasis or death than placebo with hazard ratio (HR) of 0.29 (95 % confidence interval (CI) 0.24–0.35). The current pharmacoeconomic study considered efficacy of placebo + ADT equal to that of ADT only.

The probability of patients withdrawing the "stable phase" was simulated based on the metastasis-free survival in the corresponding group of a randomized controlled trial (RCT) PROSPER [10] using the generalized gamma distribution, which was selected based on AIC.

The probability of withdrawal the subsequent treatment options did not depend on prior therapy. Except for palliative state, these probabilities were estimated based on median therapy duration with discussed mCRPC drugs in corresponding RCT. The treatment time was assumed to be distributed exponentially*. For example, the probability of withdrawing "docetaxel 1" or "docetaxel 2" during the 1st cycle of the model was estimated based on docetaxel median therapy duration in RCT TAX237 [12], which amounted 9.5 cycles, equivalent to 7.125 months. Thus, the parameter of this exponential distribution can be estimated by the formula:

$$\lambda = \frac{\ln 2}{7{,}125} = 0{,}097.$$

To simulate the probability of abiraterone discontinuation, we used 13.8 months and 8 months, its median therapy duration as the first-line treatment (for "abiraterone 1") according to RCT COU-AA-302 data [13] and as the second-line treatment (for "abiraterone 2") according to RCT COU-AA-301 data [14], respectively. To simulate the probability of cabazitaxel discontinuation, we used the median number of treatment cycles in RCT TROPIC [15] (6 cycles), which is equivalent to 4.5 months.

The probability of lethal outcome from the "palliative" state was assessed based on data of overall survival of control group in RCT TROPIC [15]. Data was extrapolated using a generalized gamma distribution.

Estimated expenses

Expenses were estimated within Russian healthcare system in 2020 and per patient. All expenses were discounted at a rate of 5 % per annum.

Expenses on basic therapy (enzalutamide, ADT, abiraterone, docetaxel, cabazitaxel). Therapy regimens in nmCRPC corresponded to those described in the section "Mathematical model of the study". We assumed all patients receive treatment until disease progression. Therapy duration in the basic version of the model was assumed to be equal to metastasis-free survival when using the appropriate comparison option.

For other mCRPC medications therapy regimens used in the model comply with the clinical recommendations [1]: for abiraterone – 1000 mg/day, for docetaxel – 75 mg/m^2 once every 21 days, for cabazitaxel – 25 mg/m^2 once every 21 days (all medications in combination with prednisolone 5 mg twice a day).

Prices, used for calculations, are presented in table. 1. Further prices included 10 % value added tax.

Expenses for docetaxel and cabazitaxel therapy were estimated in accordance with the Guidelines on the ways of payment for medical care using compulsory health insurance [16]:

- cost coefficient for docetaxel chemotherapy of 75 mg/m^2 once every 3 weeks in case of hospitalization to a day hospital (DH) is 3.34, to a twenty-four-hour hospital (TFH) – 2.42;
- cost coefficient for cabazitaxel chemotherapy of 25 mg/m^2 once every 3 weeks in case of hospitalization to a DH is 15.87, to a TFH – 8.91.
- Hospitalization was assumed equally probable both to DH and TFH. Financial standard rates from the Program of state guarantees of free medical care for citizens for 2020 were used as the base rates for medical care in DH and TFH [17], with additional correction coefficients reflecting the lowest base rates (the average cost of completed treatment in DH and TFH included in clinical and statistical groups):
- 60 % adjusted standard of 20,454.4 rubles for DH (12,272.64 rubles);
- 65 % adjusted standard of 34,713.7 rubles for TFH (22,563.91 rubles).

Expenses for the most common and costly adverse events of grade III and higher. Expenses for adverse events (AE) treatment during nmCRPC treatment were estimated only for the most expensive and frequently occurring AE of grade III and higher that occurred during docetaxel and cabazitaxel treatment (table 2).

*An important distribution property is that outcome probability does not depend on the time spent in the model state. This allows using the distribution to determine the probability of withdrawing of a state in which different cohorts of patients spend different amount of time.

Table 1. *Prices for the most used medications*

International nonproprietary name	Price (without VAT), rubles	Package	Source
Enzalutamide	155 740,00	40 мг № 112 40 mg No. 112	Медиана зарегистрированных в ГРЛС цен* Median SRMR price*
Goserelin	3367,47	3,6 мг № 1 3.6 mg No. 1	
Triptorelin	6852,02	3,75 мг № 1 3.75 mg No. 1	
Leuprorelin	5668,74	3,75 мг № 1 3.75 mg No. 1	
Buserelin	3399,38	3,75 мг № 1 3.75 mg No. 1	
Degarelix	6420,26	80 мг № 1 80 mg No. 1	
Bicalutamide	1330,19	50 мг № 28 50 mg No. 28	
Flutamide	316,00	250 мг № 20 250 mg No. 20	
Abiraterone	179 700,00	250 мг № 120 250 mg No. 120	
Prednisone	92,96	30 мг/мл № 10 30 mg/ml No. 10	

**To determine the price of the indicated package for each medication we calculated median SRMR price per 1 mg of active substance for all relevant drug forms (duplicate and irrelevant entries were excluded from the analysis). It was then multiplied by the amount of active substance containing in the package indicated in the corresponding column.*
Note. *VAT – value added tax; SRMR – State Register of Medicinal Remedies.*

Table 2. *Frequency of grade III–IV adverse events taken into account in the model during docetaxel and cabazitaxel therapy, %*

Adverse event	Docetaxel	Cabazitaxel
Neutropenia	32	82
Anemia	5	11
Thrombocytopenia	1	4
Leukocytopenia	0	68
Febrile neutropenia	3	8
Source	[12]	[15]

It was assumed that AE could be treated in DH and TFH with equal probability. To determine its cost, we used charge-to-cost ratios from the Guidelines on the ways of payment for medical care using compulsory health insurance for 2020 [17] (table 3).

The indicated charge-to-cost ratios were multiplied by the corresponding base hospitalization rates in DH and TFH calculated above.

The total treatment cost for one grade III–IV AE was calculated as the product of corresponding base hospitalization rate into the corresponding charge-to-cost ratio given in table 3. Due to the equal probability for each AE to be treated in DH or TFH, obtained values were additionally multiplied by 0.5. Further, calculated hospitalization costs for each AE were multiplied by its frequency for corresponding treatment (see table 2).

At the next step, obtained weighted cost for AE treatment per patient was divided by the median treatment duration: 7.125 months with docetaxel [12] and 4.5 months with cabazitaxel [15].

Expenses for AE therapy per 1 month (table 4) in each cycle of the model were charged to all patients in an appropriate state.

Expenses for other medications. Other expenses, estimated in the model, included expenses for bone metastasis therapy, pain management, necessary for docetaxel, cabazitaxel and palliative therapy.

To treat bone metastases, 90 % of patients receive 4 mg of zoledronic acid once every 3 weeks, 10 % – 120 mg of denosumab once every 4 weeks.

For pain relief during docetaxel therapy, tramadol is prescribed in 100 % of cases at 400 mg/day, for a long time; during cabazitaxel therapy – morphine (in 90 % of cases) or tramadol (in 10 % of cases) are prescribed both at 400 mg/day, for a long time. For pain relief in palliative patients, morphine is used (in 100 % of cases) at 400 mg/day, for a long time.

Table 3. *Service intensity weight to treat III–IV grade adverse events*

Adverse event	Service intensity weight		Diagnosis related group	
	Day-patient treatment facility	All-day patient treatment facility	Day-patient treatment facility	All-day patient treatment facility
Anemia	0,91	0,94	ds05.001	st05.001
Neutropenia	0,91	1,09	ds05.001	st05.004
Febrile neutropenia	0,91	2,93	ds05.001	st19.037
Thrombocytopenia	2,41	4,50	ds05.002	st05.003
Leukocytopenia	0,91	1,09	ds05.001	st05.004

Table 4. *Estimated expenses at different model stages to treat III–IV grade adverse events (authors' calculations), rubles*

Adverse event	Docetaxel	Cabazitaxel
Neutropenia	1105	4465
Anemia	107	371
Thrombocytopenia	82	519
Leukocytopenia	0	3717
Febrile neutropenia	278	1175
Total	*1571*	*10247*

The corresponding prices used for calculations are presented in table 5. Further prices included 10 % value added tax.

Expenses on outpatient visits to oncologist for treatment monitoring. According to the clinical guidelines [1] frequency of outpatient visits for treatment monitoring in nmCRPC patients is once in 3 months.

According to abiraterone package insert, during the first 3 months of treatment outpatient visits are necessary every 2 weeks to monitor patients' condition, after 3 months of therapy – every month [18]. Accordingly, for patients receiving abiraterone, the frequency of outpatient visits during the first 3 months was assumed to be 2.17 times per month and from the 4th month of therapy – 1 time per month. For patients receiving docetaxel and cabazitaxel and palliative patients, the frequency of outpatient visits was assumed to be 3 times per month [4]. The cost of 1 outpatient visit to an oncologist in the model is 272.9 rubles, which corresponds to an average cost of 1 preventive and other visits from the Program of state guarantees for 2020 when providing medical care on an outpatient basis by medical organizations (by their structural units) at the expense of compulsory medical insurance [17].

Expenses on palliative care. The model also includes expenses on palliative care in a hospital. It was estimated that 13.4 % of patients in "palliative" state receive such care (ratio of the total number of cases of palliative care in hospitals in 2018 (n = 39 362) [19] to cancer mortality (n = 293 704) [2]). These expenses were calculated as the product of the average length of hospital stay for palliative care (10.4 days [19]) into the financial standard stipulated by the Program of state guarantees in 2020 and equaled 2099.8 rubles [17].

"Cost–effectiveness" analyses

During the "cost–effectiveness" analysis, the incremental "cost–effectiveness" ratio was calculated for enzalutamide therapy compared to "ADT" therapy:

$$ICER = \frac{ICost_5}{IEffect_5},$$

Table 5. *Prices for other medications*

International nonproprietary name	Price (without VAT), rubles	Package	Source
Zoledronic acid	8501,54	0.8 mg/ml, 5 ml No. 1	Median SRMR price*
Tramadol	148,78	50 mg/ml, 2 ml No. 10	
Morphine	225,83	10 mg No. 10	
Denosumab	17 800	120 mg No. 1	

**To determine the price of the indicated package for each medication we calculated median SRMR price per 1 mg of active substance for all relevant drug forms (duplicate and irrelevant entries were excluded from the analysis). It was then multiplied by the amount of active substance containing in the package indicated in the corresponding column.*
Note. *VAT – value added tax; SRMR – State Register of Medicinal Remedies.*

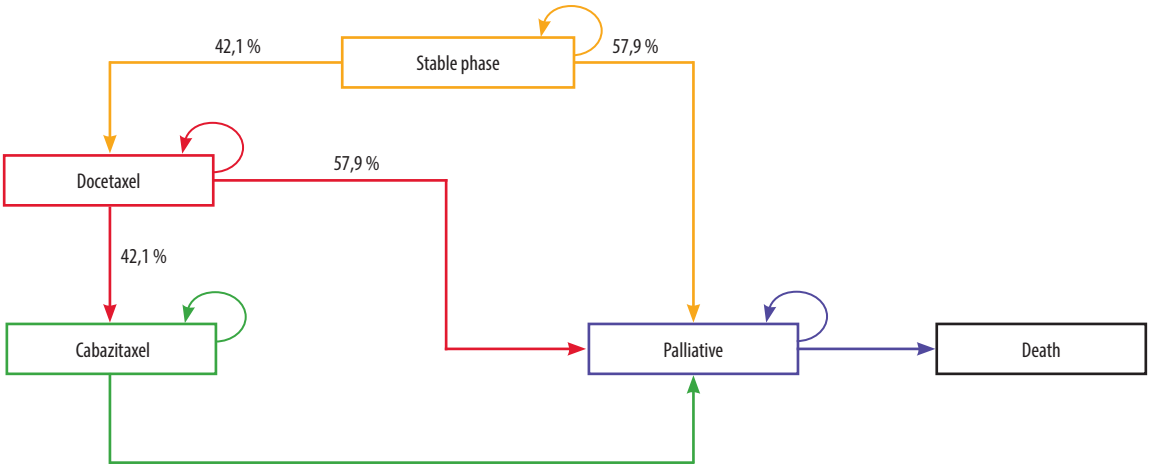

Fig. 2. *Markov model of metastatic castration-resistant prostate cancer progression (based on data [9])*

where $ICost_5$ – incremental direct medical costs associated with enzalutamide use compared with ADT use per 1 patient for 5 years; $IEffect_5$ – parameter reflecting 5-year incremental effectiveness of enzalutamide + ADT compared with ADT.

To assess incremental efficacy we used the incremental life expectancy without progression during the simulating period, as RCT PROSPER revealed significant differences on this parameter [10].

In addition, for each comparison option, we also calculated cost/effectiveness ratio by dividing direct medical expenses by the average number of years without progression.

To verify the results reliability, we carried out one-factor sensitivity analysis and evaluated change of incremental "cost–effectiveness" ratio for enzalutamide + ADT compared with that for ADT using the number of years without progression during the simulation period as the efficacy criteria. Parameters, which were assessed during the sensitivity analysis, as well as their fluctuations are presented further in the "Discussion" section.

Enzalutamide is the only one in its class recommended by domestic clinical guidelines [1] for the treatment of nmCRPC, and also the only one in the list of essential drugs that can be used to treat the disease. Moreover, according to the Rules for the formation of lists of medicines [20]: "incremental "cost/effectiveness" ratio for the proposed drug is compared with the incremental "cost/effectiveness" ratio for drugs included in the lists and used for diseases from the same class of the International Statistical Classification of Diseases and Related Health problems. Incremental "cost–effectiveness" ratios are compared for the same clinical effect (achieving recovery, remission, year of saved life, year of preserved quality of life, etc.)".

Domestic clinical guidelines [1] for mCRPC treatment recommend an androgen biosynthesis inhibitor – abiraterone, which is included in the List of Essential Medicines. Considering close clinical patterns for nmCRPC and mCRPC, to calculate "cost–effectiveness" "reference" ratio, we studied clinical and economic effectiveness of abiraterone as the first-line therapy for mCRPC.

RCT COU-AA-302 conducted a direct comparison of abiraterone + prednisolone and monotherapy with prednisolone as first-line therapy for mCRPC [13, 21, 22]. It showed that adding abiraterone to prednisolone allows to significantly increase progression-free survival (HR 0.52; 95 % CI 0.45–0.61).

This allows us to compare the incremental "cost/effectiveness" ratio for abiraterone + prednisolone with that of prednisolone using the time difference to radiographic progression as an incremental effect, and the difference in direct medical expenses per 1 patient as 5-year incremental effect. In this case, the parameter will be calculated for the same clinical effect (the average number of years without progression over 5 years), as in the case of "cost–effectiveness" analysis when using enzalutamide + ADT compared with ADT to treat nmCRPC.

The simulating technique, as well as the list of medical expenses in this part of the study corresponded to those previously proposed for enzalutamide as nmCRPC treatment. Model structure for mCRPC is consistent with that proposed before and is presented in fig. 2. As in the previous model the following treatment options may be used in the "stable phase": abiraterone (1000 mg/day) + prednisolone (10 mg/day) or prednisolone (10 mg/day).

The main difference of the model here is including data on survival without radiographic progression when using abiraterone + prednisolone or prednisolone from the COU-AA-302 study [13, 21].

Results

According to the results, enzalutamide therapy allows to increase the number of years without progression during the simulating period: 3.12 years compared to 1.79 years when using ADT.

Assessment of direct medical expenses per 1 patient within compared treatment options is presented in table. 6. When using enzalutamide, 5-year costs are 7,989,475.8 rubles per 1 patient, which is 5,716,983.5 rubles higher than when using ADT. The main expenses in "enzalutamide" treatment options are for the basic drug therapy in the "stable phase", while the main expenses in "ADT" option are for the first-line mCRPC therapy.

Results of "cost–effectiveness" analysis for enzalutamide compared with ADT using the efficacy criteria (number of life years without progression over the simulating period) are presented in table 7. The incremental cost of progression-free life year for enzalutamide compared with ADT is 4,307,136.3 rubles/year.

The average number of life years without progression when using abiraterone + prednisolone as the first-line therapy in mCRPC patients during the simulating period was 1.84 years compared to 1.06 years with prednisolone monotherapy. Moreover, average 5-year direct medical expenses per patient in the first case amounted 5,922,075.4 rubles, which is 4,799,347.6 rubles higher than with prednisolone monotherapy (table 8).

The incremental "cost–effectiveness" ratio when using abiraterone + prednisolone as the first-line mCRPC therapy was 6,191,617.4 rubles for an additional year of saved life without progression compared to prednisolone monotherapy (table 9).

Discussion

Obtained results almost do not depend on fluctuations of the main parameters of the model (fig. 3). The variability of incremental "cost–effectiveness" ratio is the highest for enzalutamide prices change, ADT effectiveness on survival without metastases, and for the method to simulate survival without metastases when using enzalutamide. When all parameters fluctuate, enzalutamide incremental "cost–effectiveness" ratio was lower than the benchmarked value for abiraterone.

When interpreting the obtained results, it is necessary to take into account the limitations of our approach. First, to simulate mCRPC treatment options, we used data of mCRPC patients registered during 2016–2018. As time passed since the results' publication, approaches for

Table 6. *Results of assessing 5-year discounted direct medical costs per 1 patient (authors' calculations), rubles*

Cost	Option 1 (enzalutamide)	Option 2 (androgen deprivation therapy)	Difference (option 1 – option 2)
Stable phase	*6 637 891,0*	*195 901,3*	*6 441 989,7*
Main therapy	6 634 811,4	194 097,5	6 440 713,9
Outpatient visits	3079,6	1803,8	1275,8
First-line therapy for mCRPC	*721 254,3*	*1 056 729,5*	*–335 475,2*
Main therapy	631 675,0	928 641,2	–296 966,1
Therapy of bone metastases	68 281,5	97 607,2	–29 325,7
Pain relief	9496,0	13 574,4	–4078,4
Outpatient visits	4312,6	6201,1	–1888,5
Adverse events	7489,2	10 705,6	–3216,5
Second-line therapy for mCRPC	*387 937,2*	*608 133,7*	*–220 196,5*
Main therapy	356 610,4	559 169,7	–202 559,3
Therapy of bone metastases	10 804,6	16 990,8	–6186,2
Pain relief	14 140,7	21 639,0	–7498,3
Outpatient visits	884,3	1893,7	–1009,3
Adverse events	5497,2	8440,6	–2943,4
Third-line therapy for mCRPC	*86 503,8*	*149 617,3*	*–63 113,6*
Main therapy	73 053,6	126 353,8	–53 300,2
Therapy of bone metastases	3648,9	6311,1	–2662,2
Pain relief	6983,1	12 078,0	–5094,9
Outpatient visits	208,5	360,6	–152,1
Adverse events	2609,7	4513,8	–1904,1
Palliative care	*155 889,5*	*262 110,4*	*–37 931,6*
Inpatient treatment	9442,7	15 876,8	–6434,1
Therapy of bone metastases	46 225,7	77 723,3	–31 497,5
Pain relief	97 579,7	164 069,1	–66 489,4
Outpatient visits	2641,4	4441,3	–1799,8
Total	*7 989 475,8*	*2 272 492,3*	*5 716 983,5*

Note. *mCRPR – metastatic castration-resistant prostate cancer.*

Table 7. *"Cost–effectiveness" analysis of enzalutamide use to treat non-metastatic castration-resistant prostate cancer compared with androgen-deprivation therapy; efficacy criteria – number of life years without progression during the modeling period (authors' calculations)*

Parameter	Enzalutamide	Androgen-deprivation therapy
Discounted costs, rubles/person	7 989 475,8	2 272 492,3
Progression-free life-years gained	3,12	1,79
"Cost/effectiveness" ratio, rubles/progression-free life-years gained	*2 564 429,1*	*1 270 847,6*
Incremental costs, rubles/person	5 716 983,5	
Incremental life expectancy without progression, years	1,33	
Incremental "cost/effectiveness" ratio, rubles/additional progression-free life-year gained	*4 307 136,3*	

Table 8. *Assessment of 5-year discounted direct medical costs per 1 patient (authors' calculations), rubles*

Cost	Option 1 (abiraterone + prednisone)	Option 2 (prednisone)	Difference (option 1 – option 2)
Stable phase	*4 977 429,9*	*6429,1*	*4 971 000,8*
Main therapy	4 969 727,8	1770,9	4 967 956,9
Outpatient visits	7702,1	4658,2	3043,9
Docetaxel (progression 1)	*305 369,7*	*348 902,3*	*–43 532,6*
Drug therapy	240 434,9	274 710,7	–34 275,7
Therapy of bone metastases	49 724,3	56 812,9	–7088,6
Pain relief	6915,2	7901,1	–985,8
Outpatient visits	2841,4	3246,4	–405,1
Adverse events	5453,8	6231,3	–777,5
Cabazitaxel (progression 2)	*299 054,2*	*350 070,3*	*–51 016,1*
Drug therapy	251 551,4	294 463,9	–42 912,5
Therapy of bone metastases	13 753,2	16 099,4	–2346,2
Pain relief	24 045,4	28 147,4	–4101,9
Outpatient visits	718,0	840,4	–122,5
Adverse events	8986,3	10 519,3	–1533,0
Palliative care	*340 221,6*	*417 326,1*	*–77 104,5*
Inpatient treatment	20 045,8	24 588,8	–4543,0
Therapy of bone metastases	107 416,3	131 760,1	–24 343,8
Pain relief	207 151,9	254 098,8	–46 946,9
Outpatient visits	5607,5	6878,3	–1270,8
Total	*5 922 075,4*	*1 122 727,8*	*4 799 347,6*

Table 9. *"Cost–effectiveness" analysis for abiraterone (authors' calculations)*

Parameter	Abiraterone + prednisone	Prednisone
Discounted costs, rubles/person	5 922 075	1 122 728
Progression-free life-years gained	1,84	1,06
"Cost/effectiveness" ratio, rubles/progression-free life-years gained	*3 222 691*	*1 056 703*
Incremental costs, rubles/person	4 799 348	
Incremental life expectancy without progression, years	0,78	
Incremental "cost/effectiveness" ratio, rubles/additional progression-free life-year gained	*6 191 617,4*	

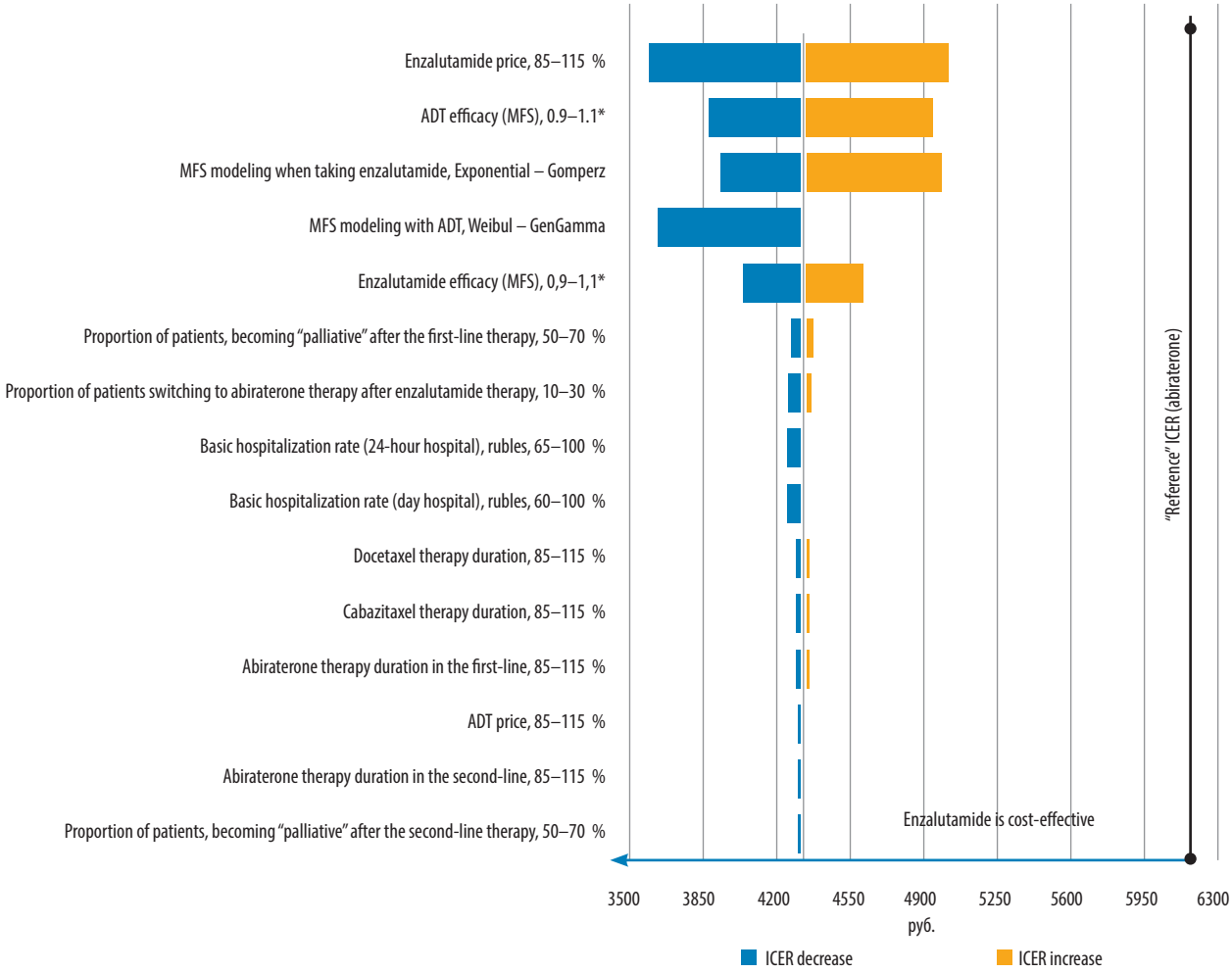

Fig. 3. *Results of sensitivity analysis of the incremental "cost/effectiveness" ratio (ICER) for enzalutamide compared with androgen deprivation therapy (ADT) using the efficacy criteria (authors' calculations), rubles/additional progression-free life-year gained. *The parameters adjust the MFS score by appropriately exponentiating values in each period of the model. MFS – metastatic free survival*

patients' treatment in Russia could change. In addition, the published data did not include information on the third-line mCRPC therapy, so we made an assumption that after the first- and second-line therapy patients with the equal probability continue active antitumor treatment (42.1 %). At the same time, sensitivity analysis shows that these parameters have a little impact on incremental "cost–effectiveness" ratio for enzalutamide use for nmCRPC.

Secondly, as there were no data on the frequency of different ADT administration, we accepted that patients were equally distributed between them. In reality this may be incorrect, however, as the sensitivity analysis showed, ADT cost almost does not affect the final calculations.

Thirdly, the study suggested a lethal outcome only in patients who have completed active treatment, that is, in a "palliative" state. This approach allows us to assess possible differences in the overall survival of nmCRPC patients receiving enzalutamide + ADT or ADT, which were not shown in the first results of RCT PROSPER [10] due to the short observation period. According to the simulation results, 5-year overall survival of nmCRPC patients receiving enzalutamide + ADT was 54 %, while when using ADT, it was only 28 %.

In June 2020, the results of RCT PROSPER were updated, it was revealed that overall survival in enzalutamide + ADT group was significantly higher than in the control group (HR of death 0.73; 95 % CI 0.61–0.89) [23]. The 5-year overall survival of patients receiving enzalutamide + ADT was 59 % (compared to 54 % in our model), while for ADT it was only 44 % (compared to 28 % in our model). Thus, our model made it possible to predict enzalutamide + ADT overall survival with high accuracy, but the prognosis of ADT overall survival was underestimated. This may be explained by the fact that in RCT PROSPER a significant part of metastatic CRPC patients apart from ADT therapy (36 %) received enzalutamide for mCRPC treatment [23], while in our model it was not prescribed in the late stages.

New significant data on the advantages of enzalutamide + ADT compared with ADT to treat nmCRPC theoretically allow analyzing "cost–effectiveness" from the point of view of overall survival. Moreover, this analysis allows us to take information about differences of patients' overall survival directly from RCT PROSPER [23]. However, this approach may not fully take into account possible differences between treatment options, since a part of enzalutamide positive effect for nmCRPC treatment will be "hidden" due to patients cross-over in RCT PROSPER control group [23] after the disease progression to metastatic form.

Conclusion

Enzalutamide in combination with ADT allows to significantly increase survival without metastases compared with ADT in patients with nmCRPC (HR 0.29; 95 % CI 0.24–0.35). Moreover, according to the results of the mathematical model, the average lifetime without metastatic progression over a 5-years period when using enzalutamide + ADT is 3.12 years compared to 1.79 years when using ADT.

The average expenses for enzalutamide + ADT therapy are 7,989,475.8 rubles/patient for 5 years, which is 5,716,983.5 rubles higher than when using ADT (2,272,492.3 rubles).

Progression-free life year when using enzalutamide to treat nmCRPC compared with ADT costs 4,307,136.3 rubles.

Progression-free life year when using abiraterone to treat mCRPC compared with prednisolone costs 6,191,617.4 rubles.

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Authors' contributions
N.A. Avxentyev: development of research design;
M.Yu. Frolov: analysis of data;
Yu.V. Makarova: obtaining data, article writing.

ORCID of authors
N.A. Avxentyev: https://orcid.org/0000-0002-2686-1330
M.Yu. Frolov: https://orcid.org/0000-0002-0389-560X
Yu.V. Makarova: https://orcid.org/0000-0001-5129-8175

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