DOI: https://doi.org/10.17650/1726-9776-2023-19-3-80-93

Impact of using novel antitumor drugs in adult patients with locally advanced or metastatic urothelial carcinoma on reducing cancer mortality in Russia

N.A. Avxentyev[1, 2, 3], B.Ya. Alekseev[4, 5], I.I. Andreyashkina[6], Yu.V. Makarova[1]

[1]Financial Research Institute, Ministry of Finance of Russia; Build 2, 3 Nastas'inskiy Pereulok, Moscow 127006, Russia;
[2]Institute of Applied Economic Studies, Russian Presidential Academy of National Economy and Public Administration; 82 Vernadskogo Prospekt, Moscow 119571, Russia;
[3]Health Market Access; Build. 1, 157 Volgogradskiy Prospekt, Moscow 109378, Russia;
[4]National Medical Research Radiological Center, Ministry of Health of Russia; 3 2nd Botkinskiy Proezd, Moscow 125284, Russia;
[5]Medical Institute of Continuing Education, Russian Biotechnological University; 11 Volokolamskoe Shosse, Moscow 125080, Russia;
[6]A.S. Loginov Moscow Clinical Scientific Center, Moscow Healthcare Department; Build. 1, 1 Novogireevskaya St., Moscow 111123, Russia

Contacts: Nikolay Aleksandrovich Avxentyev *na@nifi.ru*

Background. Standard first-line therapy options for patients with locally advanced or metastatic urothelial carcinoma (UC) is platinum-based chemotherapy. Currently, patients also have access to immune checkpoint inhibitors (ICIs) such as pembrolizumab, nivolumab, and atezolizumab, along with avelumab, which, unlike other drugs in this class, can be used as maintenance therapy after first-line platinum-based chemotherapy.
Aim. To evaluate the effects of using ICIs in treating adult patients with locally advanced or metastatic UC on reducing overall and one-year cancer mortality in Russia.
Materials and methods. A mathematical model based on overall survival and progression-free survival data from clinical trials has been proposed. This model describes duration of therapy and treatment outcomes for cases of treatment without ICIs (routine clinical practice); with pembrolizumab, nivolumab, and atezolizumab in first and second-line therapy according to real-life clinical practice (current practice); and with avelumab as maintenance therapy after platinum-based chemotherapy (proposed practice) over a 3-year period. The model was used to estimate the number of lives saved and healthcare system costs when transitioning from historical to current practice, and from current to proposed practice over a three-year horizon, considering the number of locally advanced or metastatic UC patients who may start platinum-based therapy annually in Russia.
Results. Annually, up to 4,182 patients with locally advanced or metastatic UC in Russia can start platinum-based chemotherapy. Compared to historical practice, the use of pembrolizumab, nivolumab, and atezolizumab in the first and second lines of therapy in accordance with the routine clinical practice allows to reduce mortality from malignant neoplasms by 553 cases over a 3-year horizon. Over the same period, avelumab-based treatment would additionally save 2,506 lives. Moreover, the cost of saving one life with the use of avelumab amounts to 6.0 million rubles, which is 9 % lower than the cost of saving one life with the use of other ICIs (6.6 million rubles).
Conclusion. The use of avelumab as maintenance therapy after platinum-based chemotherapy in the 1st line in patients with locally advanced or metastatic UC has a significant and quantifiable impact on reducing cancer-related mortality in Russia.

Keywords: urothelial carcinoma, avelumab, overall survival, cancer mortality

For citation: Avxentyev N.A., Alekseev B.Ya., Andreyashkina I.I., Makarova Yu.V. Impact of using novel antitumor drugs in adult patients with locally advanced or metastatic urothelial carcinoma on reducing cancer mortality in Russia. Onkourologiya = Cancer Urology 2023;19(3):80–93. (In Russ.). DOI: https://doi.org/10.17650/1726-9776-2023-19-3-80-93

Introduction

Cancer is the second leading cause of death after cardiovascular diseases. Since 2019, Russia has been implementing the Federal Project "Cancer control" (hereinafter referred to as the "Federal project"), focusing mainly on reducing neoplasm (including malignant neoplasm)-related mortality to 195.1 cases per 100,000 population by 2024 [1].

In recent years, a range of novel and highly effective drugs have become available, which are able to significantly improve the prognosis for patients in certain clinical situations and hence contribute to the attainment

of the target indicators of the Federal project. There has been progress in treating locally advanced or metastatic urothelial carcinoma (UC), which can now be treated in the 1st and 2nd lines with immune checkpoint inhibitors (ICIs) such as pembrolizumab, nivolumab and atezolizumab. Along with those, Russian patients now have access to avelumab, which, unlike other drugs in this class, can be used as maintenance therapy upon taking the disease under control after 1st-line platinum drugs.

Several clinical studies have demonstrated that these treatment options can help to achieve a statistically significant increase in the overall survival rate compared to the standard therapy. As an example, the results of the randomized clinical study JAVELIN Bladder 100 have shown that adult patients with locally advanced or metastatic UC whose disease did not progress after platinum-based induction chemotherapy had the hazard ratio of death 0.77 compared to placebo when using avelumab as 1st-line maintenance therapy (95 % confidence interval (CI) 0.64–0.92 %) [2]. In another clinical situation featuring patients with locally advanced or metastatic UC who were treated with pembrolizumab as a 2nd-line therapy, the hazard ratio of death versus chemotherapy was 0.71 (95 % CI 0.59–0.86) [3], and 0.82 (95 % CI 0.71–0.94) when using atezolizumab [4].

So far, the literature has no answer as to the impact of ICIs on the key indicators of the Federal project, which are cancer mortality and one-year mortality.

The aim of the study is to estimate the impact of using novel ICIs to treat adult patients with locally advanced or metastatic UC on reducing overall and one-year cancer mortality in Russia.

Materials and methods

Characteristics and size of target patient population

Adult patients with locally advanced or metastatic UC who are eligible for platinum-based chemotherapy were considered in this study.

The patient number was determined as indicated in Fig. 1, considering only bladder cancer (BC), which accounts for up to 90 % of urothelial carcinomas (UCs) [5]. This restriction is due to the lack of statistical data on the incidence of other types of UC in Russia.

The year 2021 saw 14,352 morphologically confirmed new BC cases registered [6]. According to the literature, UC accounts for up to 90 % of BC cases [6]. The clinical guidelines [7] stipulate that patients with non-muscle-invasive cancer (stage I) have an indication for transurethral resection, after which the disease progresses to the muscle-invasive form in about 25 % cases [8], requiring radical cystectomy. In 50–90 % of those cases (70 % on average), the disease progresses to locally advanced or metastatic UC over a certain time [8]. The recurrence rate in patients with status post radical cystectomy performed for newly identified muscle-invasive cancer in stages II–IIIa is about 50 % [7].

Up to 90 % of patients with locally advanced or metastatic UC can be treated using platinum-based drugs [9]. Thus, the target population of patients with locally advanced or metastatic UC who have an indication for platinum-based chemotherapy is 4,182 people in Russia annually.

Comparators

To attain the aim of the study, which was to estimate the impact of using novel ICIs to treat adult patients

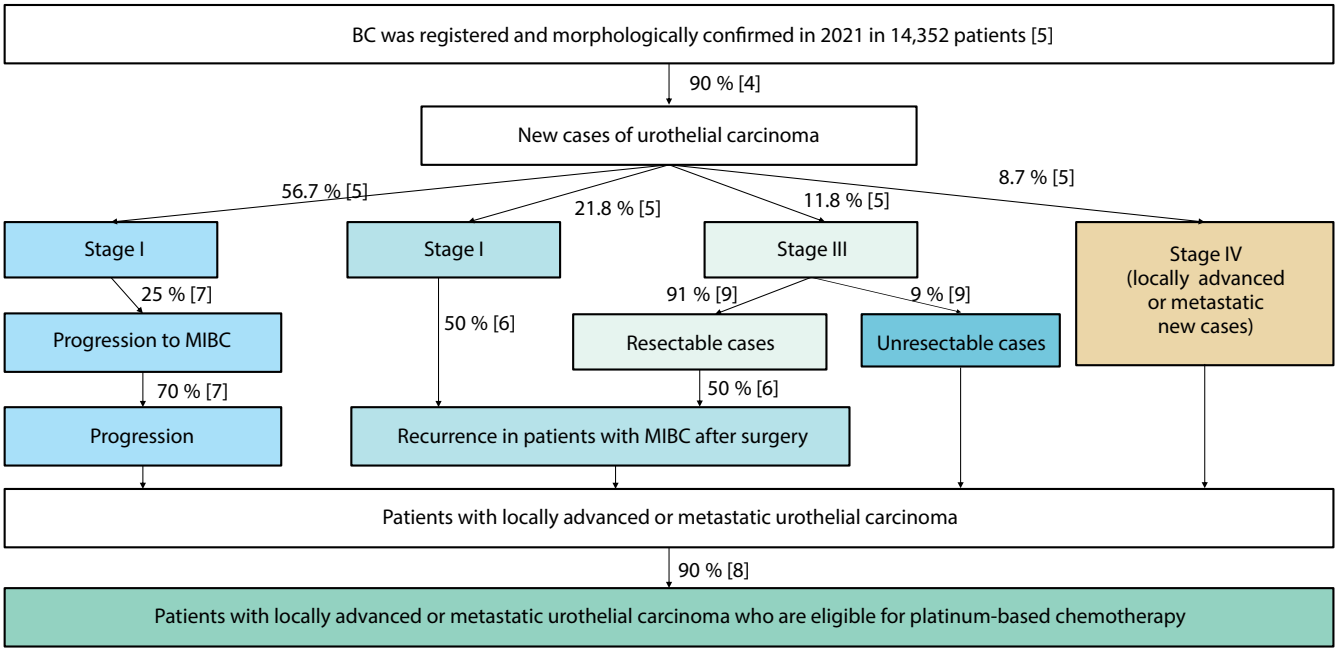


Fig. 1. *Estimation of the size of the target patient population. BC – bladder cancer; MIBC – muscle-invasive bladder cancer (source [5–10])*

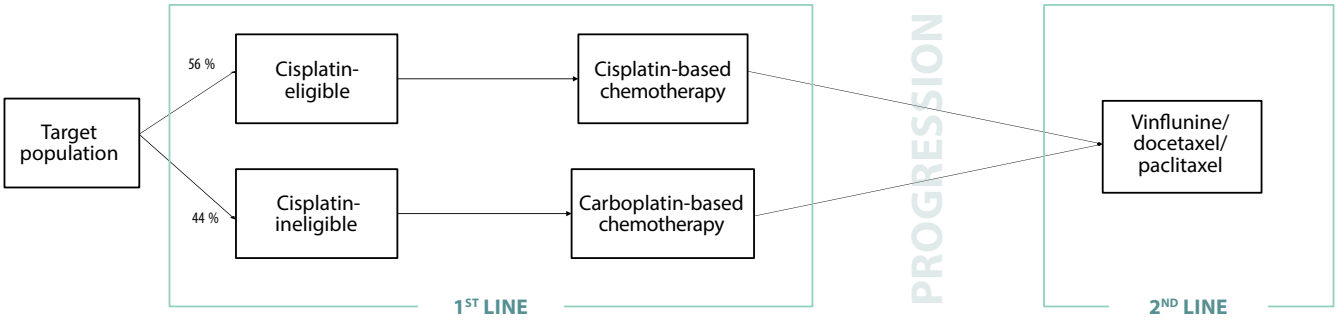


Fig. 2. *Historical therapy practice (compiled by the authors)*

with locally advanced or metastatic UC, the 1st comparison option chosen was the historical approach of managing such patients without using ICIs (Fig. 2). It was assumed in historical approach that all patients received either cisplatin or carboplatin as 1st-line therapy (combined with gemcitabine in either case), while the patients were distributed between the platinum-based chemotherapy options according to an expert estimation [9]. In case of progression, it was assumed that vinflunine, docetaxel, or paclitaxel were used in all living patients.

As the 2nd comparison option, we considered the current approach of treating the target patient population using atezolizumab or pembrolizumab (in some patients with PD-L1 ≥5 % or CPS ≥10 and contraindicated for cisplatin), as well as atezolizumab, pembrolizumab, or nivolumab in 2nd-line therapy in some patients without history of using ICIs (Fig. 3). The frequency of PD-L1 ≥5 % or CPS ≥10 (30 %) was estimated based on patient characteristics from the randomized clinical studies IMvigor210 [11], IMvigor211 [4], KEYNOTE-052 [3], and CheckMate 275 [12]. The frequency of prescription of the drugs in 1st- and 2nd-line therapy was determined based on the IPSOS materials on the actual practice of treating patients in the clinical situation in question. Data on 2nd-line therapy were obtained from a survey conducted among doctors in 2021, who were treating 127 patients in total. Data on 1st-line therapy were obtained from a survey of doctors in 2021, who were treating 650 patients in total.

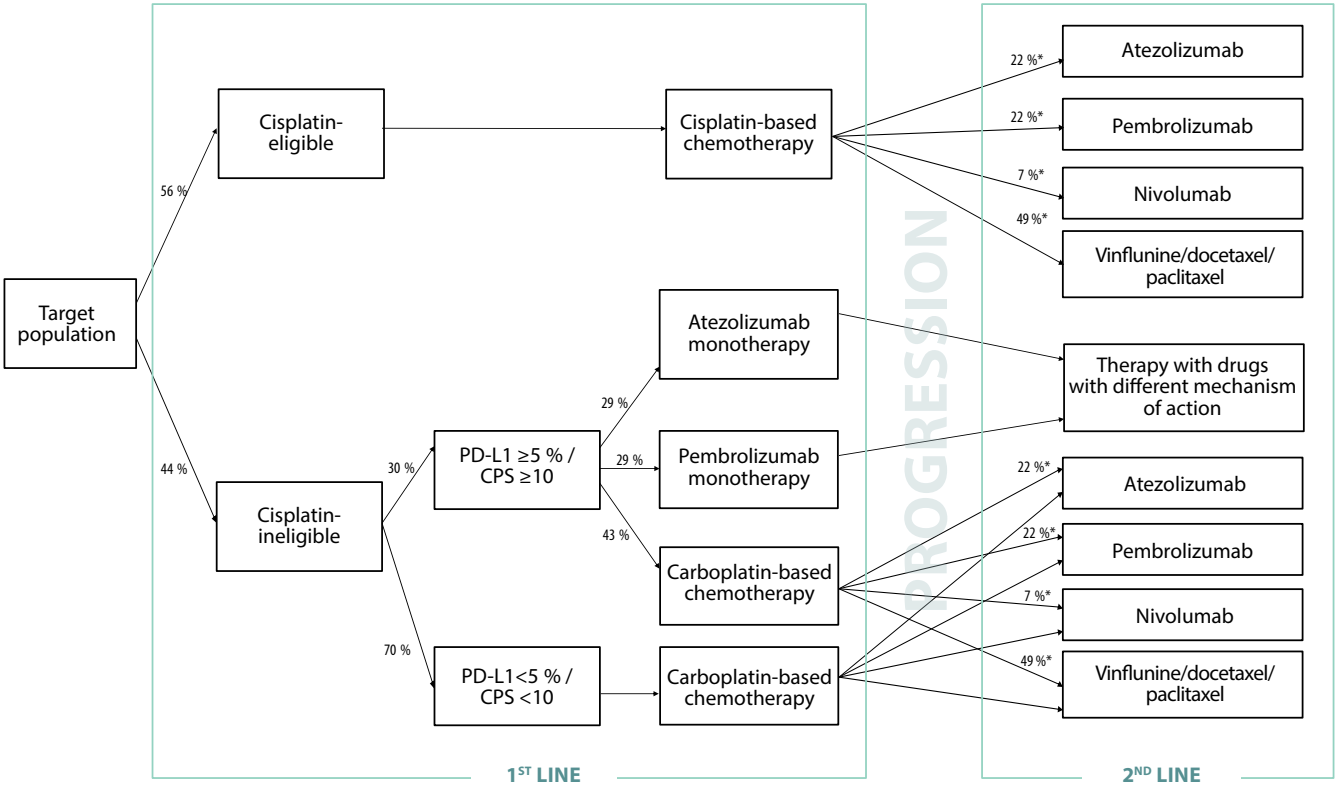


Fig. 3. *Current therapy practice (compiled by the authors). *Relative to the number of individuals starting therapy*

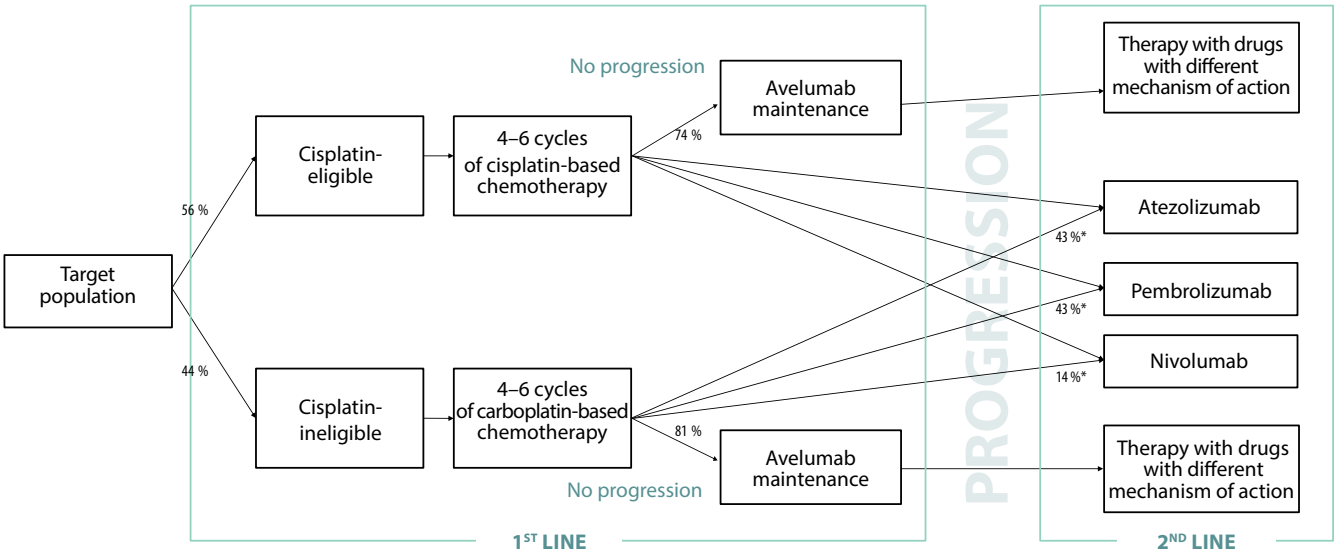


Fig. 4. *Proposed therapy practice (compiled by the authors). *Relative to the number of individuals starting therapy*

Finally, the 3rd comparison option was used to study the using of avelumab as maintenance therapy upon taking the disease under control after platinum-based therapy (provided that there were no signs of progression observed after chemotherapy was completed), as well as atezolizumab, pembrolizumab, or nivolumab in all patients refractory to platinum drugs who survived to receive 2nd-line therapy (proposed approach) (Fig. 4). In order to determine the share of patients eligible to start maintenance therapy with avelumab, whose disease did not progress upon completion of 4–6 cycles of platinum-based chemotherapy, literature data was used concerning progression-free survival under platinum-based treatment after 4–6 therapy cycles in the studies of IMvigor130 (in the carboplatin group) [13] and by H. von der Maase et al. [14] for the cisplatin group. Ultimately, avelumab can be prescribed after cisplatin to 74 % patients; after carboplatin, to 81 %.

In every case, the drug administration regimens corresponded to the clinical guidelines [7] and the prescribing information of the respective drug.

Overall survival assessment

As each comparison option constitutes a sequence of using various drugs at certain frequencies, conducting the study required creating a model of overall survival of the patients when the comparators are used.

This was done using a mathematical model developed from the data on overall survival and progression-free survival in clinical studies of the drugs in question (Table 1). The modeling horizon was 3 years; the modeling step, 1 month.

All comparators had models consisting of 2 blocks, namely 1st- and 2nd-line therapy, with the respective drugs used at certain frequencies in each model (Fig. 5). The options of the 1st- and 2nd-line therapy and the frequency of their prescription are presented above in Fig. 2–4.

All patients start 1st-line therapy with a duration that corresponds in the model to the median progression-free survival in the clinical study of the respective drug, except for platinum drugs before the prescription of avelumab, which are used over 4–6 cycles of therapy (see Table 1).

Afterwards, the patients with no recurrence on chemotherapy were switched to treatment with avelumab in the proposed approach. A patient may die under therapy with any drug; the probability of death was estimated from the data on overall survival in the study of the respective drug.

After 1st-line therapy was completed and the disease progressed, the surviving patients who did not receive ICIs in the 1st line were switched to 2nd-line therapy with a duration that corresponded to the median progression-free survival, and the mortality to the overall survival of the patients when this drug was used in the respective study (see Table 1).

Patients who became refractory to platinum and who were not eligible for avelumab in the proposed practice were switched to the 2nd-line therapy as well. After ICIs were prescribed in 1st-line therapy, the subsequent treatment lines were not modeled separately; the mortality for those patients was estimated from the data on overall survival in the 1st-line therapy studies.

The share of patients outside the state of death was considered an estimate of the overall survival of the patients in the historical, current, and proposed approaches.

Table 1. *Overall survival and progression-free survival for different therapies used in the study*

Line of therapy	Option		Therapy duration (median progression-free survival), months	Source of therapy duration data	Source of overall survival data
1st	Cisplatin + gemcitabine	Prior to avelumab	4.6	Calculation*	H. von der Maase et al., 2005 [14]
		Without avelumab	7.7	H. von der Maase et al., 2005 [14]	
	Carboplatin + gemcitabine	Prior to avelumab	3.5	Calculation*	EORTC-30986 [15]
		Without avelumab	5.8	EORTC-30986 [15]	
	Avelumab maintenanc	After cisplatin	5.7	JAVELIN Bladder 100 [16]	JAVELIN Bladder 100** [2]
		After carboplatin	3.7	JAVELIN Bladder 100 [16]	JAVELIN Bladder 100** [2]
	Atezolizumab		4.1***	IMvigor210 [11]	
	Pembrolizumab		4.9***	KEYNOTE-052 [3]	
2nd	Atezolizumab		2.1	IMvigor211 [4]	
	Pembrolizumab		2.1	KEYNOTE-045 [3]	
	Nivolumab		2.0	CheckMate 275 [12]	CheckMate 275 [17]
	Vinflunine/docetaxel/paclitaxel		4.0	IMvigor211 [4]	

**Calculated value for 5 cycles (mean of 4–6 cycles taking into account cycle duration for the considered therapy type).*
***In the final report from the randomized clinical trial JAVELIN Bladder 100 [2], overall survival included both chemotherapy period (with cisplatin or carboplatin) and avelumab maintenance, therefore the data was corrected taking into account duration of chemotherapy.*
****For populations with PD-L1 ≥5 % (in case of atezolizumab) and CPS ≥10 (in case of pembrolizumab), respectively.*

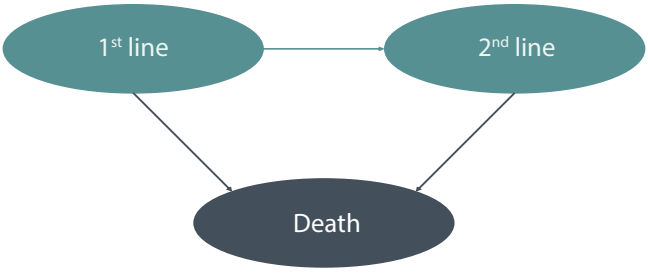


Fig. 5. *Mathematical model (compiled by the authors)*

Estimation of costs

Only the costs for drug therapy using the considered drugs were estimated. This was done according to the drug administration regimens as stated in the clinical guidelines [7] and the prices determined from the State Registry of Maximum Sale Prices or average prices in public procurement (for vinflunine) (Table 2).

Estimation of contribution to reducing overall and one-year mortality

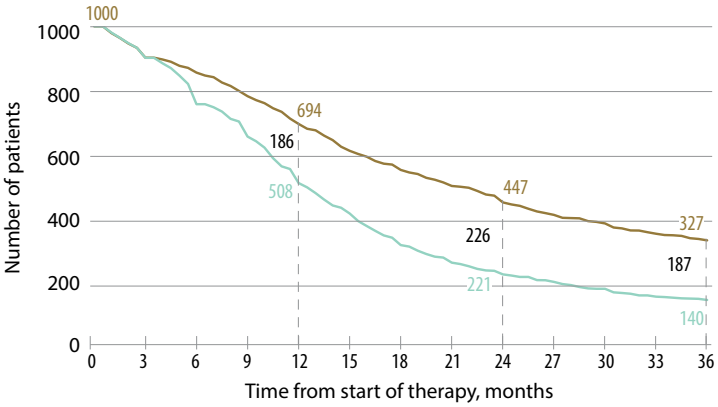
The number of prevented deaths (saved lives) using ICIs was estimated using the method proposed before [18, 19], where the number of saved lives was estimated for the case of transitioning from the historical (not using ICIs) to the current approach (using atezolizumab, nivolumab, and pembrolizumab in some of the eligible patients in 1st- and 2nd-line therapies according to the frequency of prescription of those drugs in actual practice), and from the current to the proposed approach (using avelumab as maintenance therapy in all patients who were not refractory to platinum, as well as atezolizumab, nivolumab, and pembrolizumab in 2nd-line therapy in patients who became refractory). Likewise, the horizon of analysis was 3 years (2023–2025).

The method is based on the estimations of the patient number and overall survival when each of the compared options are used. Let us illustrate this estimation by supposing that there are 1,000 patients who can start therapy annually (Fig. 6). Considering overall survival for the respective

Table 2. *Drug prices (compiled by the authors)*

International nonproprietary name	Price (without value added tax), rubles	Price (with value added tax), rubles	Pack size
Avelumab	49,800.00	54,780.0	20 mg/mL, 10 mL
Cisplatin	76.56	84.2	1 mg/mL, 10 mL
Gemcitabine	699.05	768.9	200 mg, No. 1
Carboplatin	354.92	390.4	10 mg/mL, 5 mL, No. 1
Atezolizumab	215,930.09	237,523.1	1200 mg/20 mL, No. 1
Pembrolizumab	135,605.30	149,165.8	25 mg/mL, 4 mL, No. 1
Nivolumab	31,076.23	34,183.9	10 mg/mL, 4 mL, No. 1
	77,691.35	85,460.5	10 mg/mL, 10 mL, No. 1
Docetaxel	2482.94	2731.2	10 mg/mL, 2 mL, No. 1
Paclitaxel	2213.39	2434.7	6 mg/mL, 5 mL, No. 1
Vinflunine	15,390.52	16,929.6	25 mg/mL, 2 mL, No. 1

Note. *Prices are calculated as median registered prices in the National Registry of Maximal Selling Prices (with removed duplicates). Vinflunine price was determined as mean price within the state procurement system.*



Estimation of the number of prevented deaths in 3 years

	2023	2024	2025
Cohort 2023	186	40	–39
Cohort 2024		186	40
Cohort 2025			186
Total	186	226	187

Fig. 6. *Diagram of the contribution of an innovative drug to reduction of mortality from neoplasms, including malignant tumors (calculated by the authors)*

practice option (share of patients outside the state of death), it can be determined how many patients from this cohort will survive through the end of the 1st year. This amounts to 694 patients in the proposed approach when avelumab is used, and 508 patients in the cohort of those receiving therapy using other ICIs in the current approach. Thus, the number of prevented deaths in the 1st year will amount to 694 – 508 = 186 cases.

By the end of the 2nd year, this cohort will contain 447 living patients when therapy with avelumab is used according to the proposed approach, and 221 patients when therapy with other ICIs is used according to the current approach. This means that 694 – 447 = 247 patients will die in the 2nd year in the first case, and 508 – 221 = 287 patients will die in the 2nd year in the second case. Thus, the number of prevented deaths in the 2nd year will amount to 287 – 247 = 40 cases. This should be complemented by the number of prevented deaths under treatment using avelumab according to the proposed approach in patients who started therapy in the 2nd year, which is 186 cases. Thus, the total prevented deaths in the 2nd year will amount to 40 + 186 = 226 cases.

The same method is used for estimation of the subsequent years and for comparison of the current approach using atezolizumab, pembrolizumab, and nivolumab against the historical approach when no ICIs were used.

In order to estimate the contribution of novel drugs for the treatment of UC to attaining the aims of the Federal project to reduce the mortality of the population from MNs (as percentage), the total number of saved lives when transitioning from one approach to another was divided by the number

of deaths to be prevented in 2023–2025 (in reference to 2021) in order to achieve the aims of the Federal project*, which is 4,670 cases in 2023 and 7,075 in each of 2024 and 2025.

Finally, the contribution to the one-year mortality indicator was estimated, considering the reduction in mortality in the cohort of patients diagnosed within one year before that, which is 1,266 out of 4,182 patients. This estimation was compared to the actual one-year mortality indicators in the 1st year after the diagnosis was established, for all cancer types and specifically for the BC as of 2021, according to [6].

Sensitivity analysis

This work included an sensitivity analysis of the total lives saved when transitioning to avelumab as maintenance therapy (compared with the current approach) to the changes in the basic premises of the model, which are therapy duration and overall survival of the drugs, frequency of prescription in current approach, patient number, and share of patients who are switched to therapy using avelumab (which is, in the base case, 100 % of the patients who are not refractory to platinum).

Results

Overall survival

The results of estimating the overall survival of the patients in the considered options are presented in Fig. 7. The most favorable prognosis is observed in patients receiving therapy using avelumab according to the proposed approach (median overall survival is about 20.8 months from the start of platinum-based therapy), and the worst, in patients receiving therapy without ICIs according to the historical approach (median overall survival is about 12 months). If other ICIs are used as part of the current approach , the median overall survival is 12.4 months.

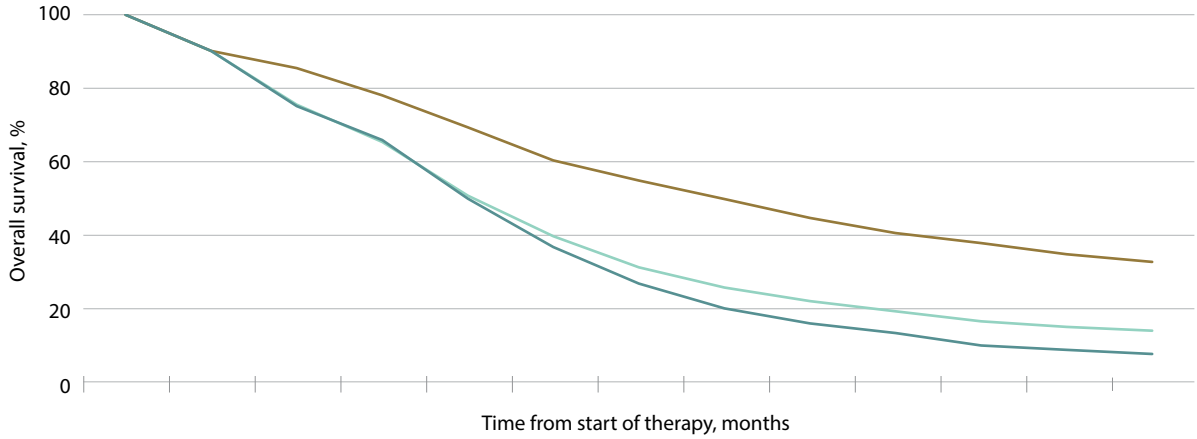
By the end of the 3rd year, the overall survival under therapy of locally advanced or metastatic UC using avelumab according to the proposed approach is 33 %; if other ICIs are used according to the current approach, 14 %; if no ICIs are used according to the historical approach, 8 %.

Estimation of lives saved and reduction in one-year mortality

Transitioning to atezolizumab, pembrolizumab, and nivolumab in some of the patients in the 1st- and 2nd-line therapy (to the current approach) is estimated to save 553 lives over 3 years, or prevent from 0.7 to 3.7 % deaths, to attain the aims of the Federal project (Table 3).

Using avelumab in this category of patients over the same period additionally saves up to 4.5 times more lives: in addition to 553 cases, it can prevent up to 2,506 deaths, which is 11.1 to 16.6 % of the reduction in mortality necessary to attain the aims of the Federal project (see Table 3).

The differences are even greater when examining the contribution of the drugs in question to the reduction of one-year mortality, as using avelumab may help reduce this indicator from 13.8 to 12.1 % for BC and from 20.3 to 20.25 %



	0	3	6	9	12	15	18	21	24	27	30	33	36
Current practice	100	91	77	67	52	40	32	26	22	20	17	15	14
Proposed practice	100	91	86	78	70	61	55	50	45	41	38	35	33
Historical practice	100	91	76	67	51	38	27	20	16	14	10	9	8

Fig. 7. *Overall survival prediction for patients receiving therapy in accordance with the considered treatment practices for locally advanced or metastatic urothelial carcinoma (calculated by the authors)*

**Adjusted target values of the mortality indicator for 2023–2024 were used, analogous to those presented in N.A. Avxentyev et al. [19]. The adjustment is necessary as the goal for mortality from MNs set for 2024 was attained for Russia in 2021.*

Table 3. *Estimation of the number of prevented deaths and contribution to the target values of the Fight against Oncological Diseases federal project (federal oncoproject) (compiled by the authors)*

Year	Number of deaths that must be prevented relative to 2021 to achieve the target of the federal oncoproject	Transition from the current practice to the proposed practice		Transition from the historical practice to the current practice	
		Number of prevented deaths	Percent of contribution to the target value	Number of prevented deaths	Percent of contribution to the target value
2023	4670	777	16.6	34	0.7
2024	7075	946	13.4	254	3.6
2025	7075	783	11.1	265	3.7
Total		2506		553	

Table 4. *Estimation of the changes in one-year mortality (calculated by the authors, data [6])*

Malignant tumor	One-year mortality (factual in 2021), %	Transition from the current practice to the proposed practice		Transition from the historical practice to the current practice	
		One-year mortality, %	Change, p.p.	One-year mortality, %	Change, p.p.
All malignant tumors	20.300	20.252	–0.05	20.298	–0.002
Bladder cancer	13.800	12.120	–1.680	13.726	–0.074

Note. *P.p. – percentage points.*

for all cancer types, while the contribution from using other ICIs is insignificant (Table 4).

Estimation of additional costs and the cost of one saved life

In the historical approach, the cost of treating the target population of patients with locally advanced or metastatic UC is estimated to amount to 2,287 million rubles annually. In the current approach, when ICIs are used in some of the eligible patients in 1st- and 2nd-line therapy, the expenses to treat the same patients have increased by 53 %, or by 1,217 million rubles annually, and amount to 3,504 million rubles. Transitioning to therapy using avelumab will require an additional 5,029 million rubles annually (Fig. 8).

The cost of one saved life was determined considering the number of prevented deaths and the need for additional funding when transitioning from the no-ICI option (historical approach) to using atezolizumab, pembrolizumab, and nivolumab in some of the patients in 1st- and 2nd-line therapy (current approach), and from using these ICIs (current approach) to using avelumab (proposed approach) (Table 5). When transitioning from historical approach-to using other ICIs, the average cost of one saved life over 3 years amounts to 6.6 million rubles; when transitioning from current approachto using avelumab, 6.0 million rubles.

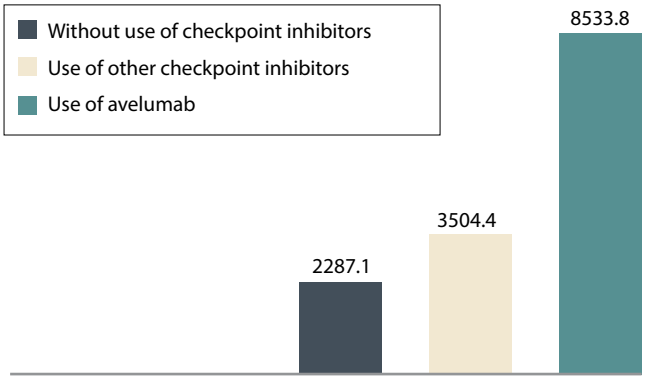


Fig. 8. *Comparison of annual budget spending, millions of rubles (calculated by the authors)*

Sensitivity analysis

When transitioning from the current to the proposed approach, the number of averted deaths is most influenced by the premises as to the share of patients who are switched to therapy with avelumab and as to the patient number (Fig. 9).

The other parameters of the model have almost no influence on the estimations obtained, therefore these results can be considered reasonably stable.

Table 5. *Estimation of the cost of 1 saved life (calculated by the authors)*

Year	Transition from the historical practice to the current practice			Transition from the current practice to avelumab use		
	Number of saved lives, *n*	Additional costs, millions of rubles	Cost of 1 saved life, millions of rubles	Number of saved lives, *n*	Additional costs, millions of rubles	Cost of 1 saved life, millions of rubles
2023	34	1217	35.8	777	5029	6.5
2024	254	1217	4.8	946	5029	5.3
2025	265	1217	4.6	783	5029	6.4
2023–2025	553	3652	6.6	2506	15,088	6.0

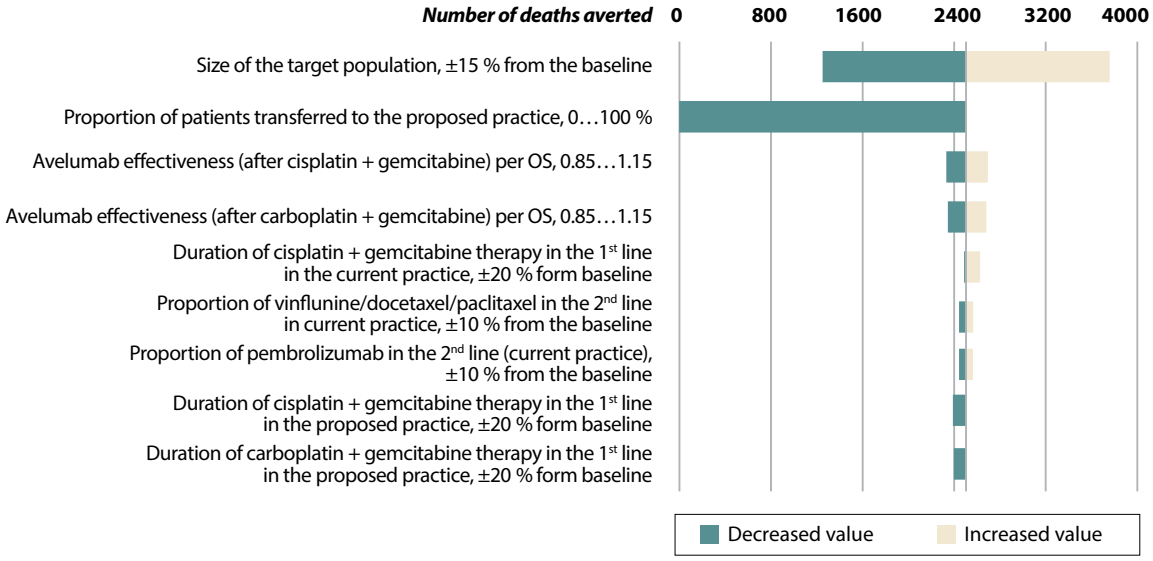


Fig. 9. *Results of the sensitivity analysis for the number of prevented deaths in 3 years due to transition to avelumab use (calculated by the authors). OS – overall survival*

Discussion

The results obtained in this study give reason to believe that the potential contribution from using avelumab to treat adult patients with locally advanced or metastatic UC in the Russian Federation to the reduction of the mortality of MNs and one-year mortality at the national level will be significant.

Using avelumab just on one indication alone can contribute up to 16 % to achieving the aim to reduce mortality as required by the Federal project. Attaining such a contribution will require an additional 5 billion rubles annually, or 4 % of the total funds (140 billion rubles annually) allocated for the project.

Even though using avelumab to treat the target patient population requires additional funding compared to what is being currently spent, the effect per ruble spent turns out to be greater than with other ICIs, since the cost of one saved life when transitioning to the treatment with avelumab is 9 % lower than when transitioning from the historical to the current approach.

It should be noted that the method proposed by us in this study has certain limitations to be considered when interpreting the results.

First, literature presents no data on direct comparison of the comprehensive options of treating patients with locally advanced or metastatic UC in 1st- and 2nd- line therapies, only comparing the individual therapeutic options within certain clinical situations. Therefore, conducting this study required modelling overall survival of the patients when using various approaches to treating locally advanced or metastatic UC as 1st- and 2nd-line therapies. It must be considered that the estimations obtained in the modeling are not as accurate or reliable as a direct comparison, but it does not appear possible to directly compare the comprehensive approaches in question.

It should also be noted that modeling the therapy duration and patient survival was based on data from foreign clinical studies and actual foreign clinical practice. The conclusions obtained in foreign studies may not always be applicable in the Russian healthcare system.

Second, we estimated the number of patients based on the assumption that 1st- and 2nd-line therapies can be prescribed to every living patient. However, data exists suggesting that only 22.8 % of patients with metastatic UC in Russia received one line of therapy, and 12.2 % received two lines of therapy [20] (compared to 100 and 71–81 % respectively, depending on the 1st-line therapy option in current approach, the figures on which our model is based). Taking all of this into consideration will lead to a reduction in the absolute number of prevented deaths and additional costs; however, their ratio (the cost of one saved life) will remain unchanged.

Finally, our estimation of the patient number was based on BC alone, the only disease covered by the statistical data [6]. However, the literature demonstrates that BC accounts for 90 % of all UC cases, while urothelial cancer of the upper urinary tract is extremely rare [21].

Conclusion

Up to 4,182 patients with locally advanced or metastatic UC are eligible to start platinum-based therapy in Russia annually.

Compared to historical approach, using pembrolizumab, nivolumab, and atezolizumab in 1st- and 2nd-line therapies in some of these patients according to the actual frequency of prescription, reduces cancer mortality by 553 cases over a 3-year horizon, which amounts to 0.7 to 3.7 % of the number of deaths to be prevented to attain the aims of the Federal project.

Using avelumab over the same period will save an additional 2,506 lives, equivalent to the contribution of 11.1 to 16.6 % of the reduction in mortality to attain the aims of the Federal project. This will reduce one-year mortality of BC from 13.8 to 12.1 %, and from 20.3 to 20.25 % for all cancer types.

When avelumab is used, the cost of one saved life amounts to 6.0 million rubles, 9 % lower than that when other ICIs are used, which is 6.6 million rubles.

Using novel antineoplastic drugs to treat locally advanced or metastatic UC results in a quantifiable contribution to the reduction of cancer mortality in Russia.

REFERENCES

1. Постановление Правительства России от 31.03.2021 № 512 «О внесении изменений в государственную программу Российской Федерации «Развитие здравоохранения».
Resolution of the Government of the Russian Federation No. 512 dated 31.03.2021 “Amendments to the State Program of the Russian Federation “Development of healthcare”. (In Russ.).
2. Sridhar S.S., Powles T., Gupta S. et al. Avelumab first-line (1L) maintenance for advanced urothelial carcinoma: long-term follow-up from the JAVELIN Bladder 100 trial in subgroups defined by 1L chemotherapy regimen and analysis of overall survival from start of 1L chemothe, rapy. 2023 ASCO Genitourinary Cancers Symposium (February 16–18, 2023). San Francisco, CA, 2023, 21 p.
3. Balar A.V., Castellano D.E., Grivas P. et al. Efficacy and safety of pembrolizumab in metastatic urothelial carcinoma: results from KEYNOTE-045 and KEYNOTE-052 after up to 5 years of follow-up. Ann Oncol 2023;34(3):289–99.
DOI: 10.1016/elsevier_cm_policy
4. Van der Heijden M.S., Loriot Y., Durán I. et al. Atezolizumab *versus* chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma: a long-term overall survival and safety update from the phase 3 IMvigor211 clinical trial. Eur Urol 2021;80(1):7–11.
5. Котенко Д.В. Применение иммуноонкологических препаратов в лечении местно-распространенного и метастатического рака мочевого пузыря в качестве моно- и комбинированной терапии (обзор клинических исследований). Онкология. Журнал им. П.А. Герцена 2019;8(6):466–70.
Kotenko D.V. The use of cancer immunology drugs as mono- and combined therapy for locally advanced and metastatic bladder cancer (a review of clinical trials). Onkologiya. Zhurnal imeni P.A. Gertsena = P.A. Herzen Journal of Oncology 2019;8(6):466–70. (In Russ.).
6. Состояние онкологической помощи населению России в 2021 году. Под ред. А.Д. Каприна, В.В. Старинского, А.О. Шахзадовой. М.: МНИОИ им. П.А. Герцена – филиал ФГБУ «НМИЦ радиологии» Минздрава России, 2022. 239 с.
State of oncological care in Russia in 2021. Eds.: A.D. Kaprin, V.V. Starinskiy, A.O. Shachzadova. Moscow: MNIOI im. P.A. Gertsena – filial FGBU “NMITS radiologii” Minzdrava Rossii, 2022. 239 p. (In Russ.).
7. Клинические рекомендации. Рак мочевого пузыря, 2020. Доступно по: https://cr.minzdrav.gov.ru/recomend/11_2 (дата обращения 20.05.2023).
Clinical Guidelines. Bladder cancer, 2020. Available at: https://cr.minzdrav.gov.ru/recomend/11_2 (accessed on 20.05.2023). (In Russ.).
8. Старцев В.Ю., Балашов А.Е., Мерзляков А.С. и др. Молекулярные детерминанты рецидива уротелиальной опухоли человека. Онкоурология 2021;17(3):130–9.
DOI: 10.17650/1726-9776-2021-17-3-130-139
Startsev V.Yu., Balashov A.E., Merzlyakov A.S. et al. Molecular determinants of recurrences of the human urothelial tumor. Onkourologiya = Cancer Urology 2021;17(3):130–9. (In Russ.).
DOI: 10.17650/1726-9776-2021-17-3-130-139
9. Калпинский А.С. РМП: иммунотерапия для всех? Доступно по: https://roou.ru/blog/rmp-immunoterapiya-dlya-vseh/ (дата обращения 20.05.2021).
Kalpinsky A.S. Bladder cancer: immunotherapy for all? Available at: https://roou.ru/blog/rmp-immunoterapiya-dlya-vseh/ (accessed on 20.05.2021). (In Russ.).
10. David K.A., Milowsky M.I., Ritchey J. et al. Low incidence of perioperative chemotherapy for stage III bladder cancer 1998 to 2003: a report from the National Cancer Data Base. J Urol 2007;178(2):451–4.
11. Balar A.V., Galsky M.D., Rosenberg J.E. et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally

advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet 2017;389(10064):67–76.
12. Sharma P., Retz M., Siefker-Radtke A. et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol 2017;18(3): 312–22. DOI: 10.1016/S1470-2045(17)30065-7
13. Galsky M.D., Arranz Arija J.Á., Bamias A. et al. Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial. Lancet 2020;395(10236):1547–57. DOI: 10.1016/S0140-6736(20)30230-0
14. Von der Maase H., Sengelov L., Roberts J.T. et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol 2005;23(21):4602–8.
15. De Santis M., Bellmunt J., Mead G. et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol 2012;30(2):191.
16. Powles T., Park S.H., Caserta C. et al. Avelumab first-line maintenance for advanced urothelial carcinoma: results from the JAVELIN Bladder 100 Trial After ≥2 years of follow-up. J Clin Oncol 2023;41(19):3486–92. DOI: 10.1200/JCO.22.01792
17. Galsky M.D., Saci A., Szabo P.M. et al. Nivolumab in patients with advanced platinum-resistant urothelial carcinoma: efficacy, safety, and biomarker analyses with extended follow-up from CheckMate 275. Clin Cancer Res 2020;26(19):5120–8. DOI: 10.1158/1078-0432.CCR-19-4162
18. Авксентьев Н.А., Сисигина Н.Н., Фролов М.Ю., Макаров А.С. Оценка вклада применения современных противоопухолевых лекарственных препаратов в достижение целей федерального проекта по борьбе с онкозаболеваниями. Вопросы онкологии 2021;67(6):768–76. DOI: 10.37469/0507-3758-2021-67-6-768-776
Avksentyev N.A., Sisigina N.N., Frolov M.Yu., Makarov A.S. Analysis impact of using novel antineoplastic drugs on cancer mortality in Russia. Voprosy onkologii = Problems in Oncology 2021;67(6):768–76. (In Russ.).
19. Авксентьев Н.А., Макаров А.С., Сисигина Н.Н. Обновленная оценка влияния применения современных лекарственных препаратов для лечения рака легкого на ключевые показатели Федерального проекта «Борьба с онкологическими заболеваниями». Вопросы онкологии 2023;69(2):538–48. DOI: 10.37469/0507-3758-2023-69-3-538-548
Avxentyev N.A., Makarov A.S., Sisigina N.N. Impact assessment of expanding the utilization of novel antineoplastic drugs for lung cancer treatment on key performance indicators of the Federal project "Cancer control". Voprosy onkologii = Problems in Oncology 2023;69(2):538–48. (In Russ.). DOI: 10.37469/0507-3758-2023-69-3-538-548
20. Тимофеев И.В., Алексеева Г.Н., Петкау В.В. и др. Продолжительность жизни больных метастатическим раком мочевого пузыря в Российской Федерации: результаты многоцентрового регистрового исследования URRU. Онкоурология 2021;17(3):102–9. DOI: 10.17650/1726-9776-2021-17-3-102-109
Tsimafeyeu I.V., Alekseeva G.N., Petkau V.V. et al. Survival of patients with metastatic bladder cancer in the Russian Federation: results of a multicenter registry study URRU. Onkourologiya = Cancer Urology 2021;17(3):102–9. (In Russ.). DOI: 10.17650/1726-9776-2021-17-3-102-109
21. Ищенко К.Б. Эпидемиология, клиника и диагностика уротелиальных опухолей почечной лоханки и мочеточника: современное состояние проблемы. Злокачественные опухоли 2016;2(18):66–71. DOI: 10.18027/2224-5057-2016-2-66-71
Ishhenko K.B. Epidemiology, clinical picture and diagnosis of urothelial tumors of the renal pelvis and ureter: current state of the problem. Zlokachestvennye opuholi = Malignant Tumours 2016;2(18):66–71. (In Russ.). DOI: 10.18027/2224-5057-2016-2-66-71

Authors' contributions
N.A. Avxentyev, B.Ya. Alekseev, I.I. Andreyashkina, Yu.V. Makarova: developing the research design, analysis of the obtained data, article writing. All authors made an equivalent contribution to the preparation of the publication.

ORCID of authors
N.A. Avxentyev: https://orcid.org/0000-0002-2686-1330
B.Ya. Alekseev: https://orcid.org/0000-0002-3398-4128
I.I. Andreyashkina: https://orcid.org/0000-0003-2646-499X
Yu.V. Makarova: https://orcid.org/0000-0001-5129-8175

Conflict of interest. The authors are responsible for the contents of the publication and editorial decisions. The authors declare no conflict of interest and confirm accuracy, independence and objectivity of the data presented in the publication.

Funding. The study was performed without external funding.

Article submitted: 22.08.2023. **Accepted for publication:** 14.09.2023.