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CLINICAL AND ECONOMIC EVALUATION OF ATEZOLIZUMAB + VEMURAFENIB + COBIMETINIB COMBINATION AND NIVOLUMAB + IPILIMUMAB COMBINATION: ADMINISTRATION IN METASTATIC MELANOMA TREATMENT WITH BRAF-CONFIRMED MUTATION IN ADULT PATIENTS

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The aim of the study was to conduct a pharmacoeconomic evaluation of the atezolizumab, vemurofenib and cobimetinib (ATZ+VM+COB) combination and the nivolumab and ipilimumab (NIVO+IPI) combination for the treatment of BRAF-confirmed metastatic melanoma in adult patients.
Materials and methods. With the help of mathematical modeling methods, a pharmacoeconomic "cost-effectiveness" analysis; a "budget impact" analysis; a sensitivity analysis to the changes in the initial parameters of the model, were carried out.
Results. The analysis of literature sources made it possible to conclude that the combination of ATZ+VM+COB compared with the combination of NIVO+IPI (15.1 and 11.2 months, respectively) has a greater clinical efficacy in terms of a progression-free survival (PFS) in patients with metastatic melanoma. When choosing the ATZ+VM+COB combination, the total cost of treatment for one adult patient with metastatic melanoma per course was lower, compared to the NIVO+IPI combination (RUB 8 326 864.89 vs RUB 7 172 751.68); the difference amounted to 1 154 113.21 rubles. When calculating the "cost-effectiveness" ratio for a year of a progression-free survival, the advantage of the ATZ + VM + COB combination in comparison with the NIVO + IPI combination, remained (5 700 200.01 rubles vs 8 942 400.10 rubles); the difference amounted to 3 242 200.09 rubles. The sensitivity analysis demonstrated the developed model stability to an increase in the cost of the ATZ + VM + COB course up to + 16%, a decrease in the cost of the NIVO + IPI course to –13%, and a reduction in the PFS to –37% against the background of the ATZ + VM + COB course. The "budget impact" analysis showed the possibility of reducing costs by 8 655 849.11 rubles with an increase from 5% to 20% in the proportion of the patients administrated with the ATZ+VM+COB combination, and with a decrease from 95% to 80% in the proportion of the patients administrated with the NIVO+IPI combination.
Conclusion. The results of the work have shown that within the healthcare system of the Russian Federation, the triple combination of ATZ+VM+COB is a clinically cost-effective option for the treatment of adult metastatic melanoma patients with a confirmed BRAF mutation.
Keywords: metastatic melanoma; BRAF mutations; melanoma treatment; "cost-effectiveness" analysis; "budget impact" analysis; atezolizumab; vemurafenib; cobimetinib
Abbreviations: ATZ – atezolizumab; COB – cobimetinib; IPI – ipilimumab; NIVO – nivolumab; VM – vemurafenib; PFS – progression-free survival; OS – overall survival; RR – relative risk; RCT – randomized clinical trial; AE – adverse event; CEA – "cost-effectiveness" analysis; BIA – "budget impact" analysis; OS – overall survival.

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КЛИНИКО-ЭКОНОМИЧЕСКАЯ ОЦЕНКА ПРИМЕНЕНИЯ КОМБИНАЦИИ АТЕЗОЛИЗУМАБ, ВЕМУРАФЕНИБ И КОБИМЕТИНИБ С КОМБИНАЦИЕЙ НИВОЛУМАБ И ИПИЛИМУМАБ В ТЕРАПИИ МЕТАСТАТИЧЕСКОЙ МЕЛАНОМЫ С ПОДТВЕРЖДЕННОЙ BRAF-МУТАЦИЕЙ У ВЗРОСЛЫХ ПАЦИЕНТОВ

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Цель. Провести фармакоэкономическую оценку применения комбинации препаратов атезолизумаб, вемурофениб и кобиметиниб (ATZ+VM+COB) с препаратами ниволумаб и ипилимумаб (NIVO+IPI) для терапии метастатической меланомы с подтвержденной BRAF-мутацией у взрослых пациентов.

Материалы и методы. С помощью методов математического моделирования был проведен фармакоэкономический анализ «затраты-эффективность»; анализ «влияния на бюджет»; анализ чувствительности к изменениям исходных параметров модели.

Результаты. Проведенный анализ литературных источников позволил сделать вывод о большей клинической эффективности в отношении выживаемости без прогрессирования (ВБП) у пациентов с метастатической меланомой для комбинации ATZ+VM+COB по сравнению с комбинацией NIVO+IPI (15,1 и 11,2 мес. соответственно). Общие затраты на курс лечения одного взрослого пациента с метастатической меланомой при выборе комбинации ATZ+VM+COB были ниже в сравнении с комбинацией NIVO+IPI (8 326 864,89 руб. против 7 172 751,68 руб.); разница составила 1 154 113,21 руб. При расчете коэффициента «затраты-эффективность» на год жизни без прогрессирования сохранялось преимущество комбинации ATZ+VM+COB в сравнении с комбинацией NIVO+IPI (5 700 200,01 руб. против 8 942 400,10 руб.); разница составила 3 242 200,09 руб. Анализ чувствительности продемонстрировал устойчивость разработанной модели к увеличению стоимости курса ATZ+VM+COB до +16%, снижению стоимости курса NIVO+IPI до –13%, сокращению ВБП на фоне курса ATZ+VM+COB до –37%. Анализ «влияние на бюджет» показал возможность снижения затрат на 8 655 849,11 руб. при увеличении доли пациентов, получающих комбинацию ATZ+VM+COB, с 5 до 20%, и при снижении доли пациентов, получающих комбинацию NIVO+IPI, с 95 до 80%.

Заключение. Результаты проведенной нами работы показали, что тройная комбинация ATZ+VM+COB является клинически эффективным и экономически предпочтительным вариантом терапии пациентов с метастатической меланомой с подтвержденной BRAF-мутацией у взрослых пациентов в рамках системы здравоохранения Российской Федерации.

Ключевые слова: метастатическая меланома; BRAF-мутации; лечение меланомы; анализ «затраты-эффективность»; анализ «влияния на бюджет»; атезолизумаб; вемурафениб; кобиметиниб

Список сокращений: ATZ – атезолизумаб; COB – Кобиметиниб; IPI – ипилимумаб; NIVO – ниволумаб; VM – вемурафениб; ВБП – выживаемость без прогрессирования; ОВ – общая выживаемость; ОР – относительный риск; РКИ – рандомизированное клиническое исследование; НЯ – нежелательные явления; CEA – анализ «затраты-эффективность»; BIA – анализа «влияния на бюджет»; ОВ – общая выживаемость.

INTRODUCTION

Melanoma is a malignant tumor originating from melanocytes, pigment skin cells that produce melanin [1]. The treatment of melanoma requires an interdisciplinary approach that includes surgery, radiation therapy, chemotherapy, immunotherapy, and targeted therapy[1] [2]. There is a distinct increase in the incidence of melanoma. According to the data of Herzen Moscow Scientific and Research Oncological Institute, since 2010, the prevalence rate has increased from 46.6:100 000 to 69.1:100 000 of the population (at the beginning of 2021)[2].

Melanoma is one of the most aggressive oncological diseases, which quickly and often metastasizes. The rate of neglect at the time of the disease detection in skin melanoma is quite high and amounts to 19.6% (i.e. the detection in late III-IV stages). The mortality within a year after this disease registration is 8.2% [3, 4].

In some cases, only distant metastases can be detected, and the primary lesion on the skin (or in other organs) cannot be detected (for example, due to the spontaneous regression of the primary tumor or removal of the lesion during medical or cosmetic manipulations without morphological examinations) [5, 6].

While surgery and adjuvant cytokine therapy are the mainstay of the treatment for resectable melanoma, the treatment for unresectable or metastatic melanoma is based on the use of the drug therapy [7–10]. The agents available for the unresectable/metastatic malignant melanoma treatment, can be divided into three classes: immunotherapy (e.g., nivolumab, pembrolizumab, ipilimumab, cytokines); BRAF/MEK inhibitors (e.g., vemurafenib, dabrafenib, cobimetinib, trametinib); chemotherapy (temozolomide) [2, 11, 12].

The development of immunotherapeutic agents over the past decade has dramatically changed the prognosis for melanoma patients, significantly increasing survival and improving their quality of life [13]. However, BRAF/MEK inhibitors, like immunotherapy, are expensive kinds of treatment that carry a large financial burden on the healthcare budget, so it is important to conduct a pharmacoeconomic evaluation of the therapy for melanoma patients with a confirmed BRAF mutation in the Russian Federation [3].

At the moment, the combination of immunodrugs nivolumab and ipilimumab NIVO+IPI has shown its high efficacy in the treatment of melanoma [1, 2]. However, a randomized clinical trial (RCT) showed that this therapy regimen had to be canceled in 42% due to the development of drug-related adverse events (AEs) [14].

The search for new therapeutic options led to the development of the atezolizumab, vemurofenib, and cobimetinib (ATZ+VM+COB) combination, the only triple treatment regimen included in international and Russian clinical guidelines for the treatment of melanoma [1, 2] and available on the Russian market since 2020. The triple combination has proven its high effectiveness in RCTs, as well as a better tolerability [15].

THE AIM of the study was to conduct a pharmacoeconomic evaluation of the atezolizumab, vemurofenib and cobimetinib (ATZ+VM+COB) combination and the nivolumab and ipilimumab (NIVO+IPI) combination for the treatment of BRAF-confirmed metastatic melanoma in adult patients.

MATERIALS AND METHODS

The design of the study consisted of a pharmacoeconomic "cost-effectiveness" analysis (CEA), a "budget impact" analysis (BIA), a sensitivity analysis of the changes in the initial parameters of the model. A hypothesis that the triple combination of ATZ+VM+COB is clinically and cost-effective for the treatment of metastatic melanoma with a confirmed BRAF mutation in adult patients within the healthcare system of the Russian Federation was formulated.

The ATZ+VM+COB combination under study includes: 1) Atezolizumab – Tecentriq® (F.Hoffmann-La Roche, Ltd, Switzerland) concentrate for the infusion solution, 60 mg/ml in 1200 mg/20 ml vials and 840 mg/14 ml vials; 2) Vemurafenib – Zelboraf® (F. Hoffmann-La Roche, Ltd, Switzerland) film-coated tablets, 240 mg; 3) Cobimetinib – Cotellic® (F. Hoffmann-La Roche, Ltd, Switzerland) film-coated tablets, 20 mg.

The NIVO+IPI comparison combination includes 1) Ipilimumab – Yervoy® (Bristol-Myers Squibb, USA) concentrate for the infusion solutions, 5 mg/ml, in 10.7 ml vials; 2) Nivolumab – Opdivo® (Bristol-Myers Squibb, USA) concentrate for the infusion solutions, 10 mg/ml, in 4 ml and 10 ml vials.

Description of research methodology

At the preliminary stage of the investigation, an information search for studies on the efficacy and safety of ATZ + VM + COB and NIVO + IPI combinations in adults with metastatic melanoma according to the PICOS and PRISMA criteria in the Cochrane, Pubmed and eLIBRARY databases, was carried out [16, 17].

The analysis included 7 publications: five – on the clinical efficacy and safety of the NIVO+IPI combination, two – on the ATZ+VM+COB combination. The following works were included in the analysis: 1) RCT IMspire150, Gutzmer R. et al., 2020 [15]; 2) RCT CheckMate 067, Wolchok J.D. et al., 2017 [18]; 3) RCT CheckMate 067, Hodi F.S. et al., 2018 [19]; 4) RCT CheckMate 067, Larkin J. et al., 2019 [14]; 5) RCT CheckMate 069, Hodi F.S. et al., 2016 [20]; 6) RCT CheckMate 511, Lebbe C. et al., 2019 [21]; 7) Network meta-analysis by Lee J. et al., 2022 [22].

[1] The Association of Russian Oncologists (AOR), Russian melanoma professional association the Russian Society of Clinical Oncology (RUSSCO). Melanoma kozhi i slizistyh obolochek [Melanoma of the skin and mucous membranes]. Clinical guidelines. 2022: 136 p. Russian

[2] Kaprin AD, Starinsky VV, Shakhzadova AO. Sostoyanie onkologicheskoj pomoshchi naseleniyu Rossii v 2020 godu [The state of oncological care for Russian population in 2020]. M.: MNIOI im. P.A. Herzen – branch of "NMITs Radiology". 2021: 239 p. Russian

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Table 1 – Model of patient treatment according to ATZ + VM + COB protocol

Preparations	Pharmaceutical form	Dosing regimen
Introductory period		
VM	240 mg, 56 tab. per pack	960 mg twice a day for 21 days, then – 720 mg twice a day for 7 days
COB	20 mg, 63 tab. per pack	60 mg per day for 21 days, 7 days off
Maintenance period (from the 29th day on) for 9.2 months		
ATZ	60 mg/ml, 1200 mg/20 ml or 850 mg/14 ml, 1 pc. in pack	1200 mg once every 21-st day or 840 mg once every 14-th day
VM	240 mg, 56 tab. per pack	720 mg twice a day
COB	20 mg, 63 tab. per pack	60 mg a day for 21 days, 7 days off

Note: ATZ – atezolizumab; COB – cobimetinib; IPI – ipilimumab; NIVO – nivolumab; VM – vemurafenib.

Table 2 – Model of patient treatment according to NIVO + IPI protocol

Preparations	Pharmaceutical form	Dosing regimen
Introductory period		
NIVO	10 mg/ml, 4 ml vials, 1 pc. per pack	1 mg/kg – 80 mg once every 21-st day
IPI	5 mg/ml, 10.7 ml, 1 pc. per pack	3 mg/kg – 240 mg once every 21-st day
Maintenance period (from the 22-nd day) for 7.5 months		
NIVO	NIVO Opdivo® 10 mg/ml, 10 ml and 4 ml vials, 1 pc. per pack	3 mg/kg – 240 mg once every 14-th day

Note: ATZ – atezolizumab; COB – cobimetinib; IPI – ipilimumab; NIVO – nivolumab; VM – vemurafenib.

Table 3 – Prices for individual drugs included in combinations under study

MP (INN)	Pharmaceutical form (mg)	Cost per pack (rub.)	Trade mark-ups and VAT (rub.)
Tecentriq® (ATZ)	1200 mg/20 ml per vial, No.1	215 930.09	265 657.71
Tecentriq® (ATZ)	840 mg/14 ml per vial, No.1	151 151.06	185 960.39
Zelboraf ® (VM)	960 mg, 56 tab.	43 185.94	53 131.44
Kotellik® (COB)	20 mg, 63 tab.	141 335.82	173 884.75
Opdivo® (NIVO)	10mg/1ml, 4 ml per vial, No.1	31 076.23	38 232.93
Opdivo® (NIVO)	10mg/1ml, 10 ml per vial, No.1	77 691.35	95 583.27
Yervoy® (IPI)	5mg/1ml, 10.7 ml per vial, No.1	186 134.59	229 00.46

Note: the prices are indicated in rubles, including trade mark-ups and VAT.

Table 4 – Calculation of treatment costs according to ATZ + VM + COB protocol per metastatic melanoma patient

Preparation	Dosing regimen	Requirement (pcs/pack)	Cost per pack (rub.)	Cost per course (rub.)
Introductory period 1–28 days				
Zelboraf®, 240 mg	960 mg twice a day for 21 days.	168 / 3	53 131.4461	159 394.34
	Then 720 mg twice a day	42 / 1	53 131.4461	53 131.45
Kotellic®, 20 mg	60 mg/day for 21 days. Then a 7-day break	63 / 1	173 884.753	173 884.75
Maintenance phase up to 9.2 months				
Tecentriq®, 1200 mg/20 ml	1200 mg once every 21-st day	13 / 13	265 657.71	3 453 550.23
Zelboraf®, 240 mg	720 mg twice a day	1,656 / 30	53 131.4461	1 593 943.38
Kotellic®, 20 mg	60 mg per day for 21 days. Then a 7-day break	630 / 10	173 884.753	1 738 847.53
Course costs		7, 172, 751.68		

Note: the prices are indicated in rubles, including trade mark-ups and VAT.

Table 5 – Calculation of treatment costs according to NIVO + IPI protocol per metastatic melanoma patient

Preparation	Dosing regimen	Requirement (pcs/pack)	Cost per pack (rub.)	Cost per course (rub.)
Introductory period				
Opdivo®, 10 mg/ml – 4 ml	1mg/kg – 80 mg once every 21 days	8	38 232.93	305 863.44
Yervoy®, 5 mg/ml – 10.7 ml	60 mg once a day, 21 days, 7 days break	20	229 000.45	4 580 009.11
Maintenance phase:				
Opdivo®, 10 mg/ml – 10 ml	3 mg/kg – 240 mg once every 14 days	10 ml 30 vials	95 583.27	2 867 498.38
Opdivo®, 10 mg/ml – 4 ml		4 ml 15 vials	38 232.93	573 493.96
Course costs		8 326 864.89		

Note: the prices are indicated in rubles, including trade mark-ups and VAT.

Table 6 – "Cost-effectiveness" ratios

Index number	ATZ+VM+COB	NIVO+IPI
Cost analysis		
Costs for a treatment course (rubles)	7 172 751.68	8 326 864.89
Therapy costs per month (rubles/patient)	788 214.47	1 110 248.65
Effectiveness analysis		
Progression-free survival (months)	15.1	11.2
"Cost-effectiveness" ratio, rub/year progression-free survival	5 700 200.01	8 942 400.10
Difference (rub.)	3 242 200.09	

Table 7 – Sensitivity analysis

Value	ATZ+VM+COB (rub.)	NIVO+IPI (rub.)	Economic benefit (rub.)
Initial	7 172 751.68	8 326 864.89	1 154 113,21
Sensitivity to price increases for ATZ+VM+COB rate			
Value +10%	7 890 026.84	8 326 864.89	436 838.05
Value +15%	8 248 664.42	8 326 864.89	78 200.47
Value +20%	8 607 302.01	8 326 864.89	–280 437.12
Sensitivity to price reduction for NIVO+IPI course			
Value –5%	7 172 751.68	7 910 521.64	737769.96
Value –10%	7 172 751.68	7 494 178.40	321 426.72
Value –15%	7 172 751.68	7 077 835.15	–94 916.53

Table 8 – Results of "budget impact" analysis

Region: Russian Federation		Number of patients: 50	
Distribution	ATZ + VM + COB	NIVO +IPI	Total
Share 1 (%)	5.00%	95.00%	100.00%
Share 2 (%)	20.00%	80.00%	100.00%
Expenses			
Budget 1 (rub.)	17 931 879.19	395 526 082.30	413 457 961.49
Budget 2 (rub.)	71 727 516.76	333 074 595.62	404 802 112.38
Savings (rub.)			8 655 849.11

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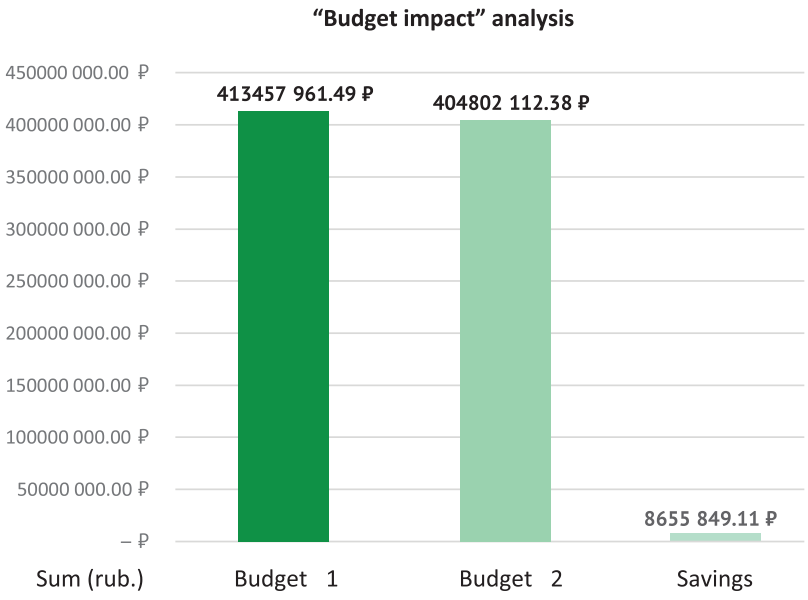

Figure 1 – Savings in administration of ATZ + VM + COB combination

Next, the data on marginal prices for the drugs from the Russian State Register[3] included in the ATZ + VM + COB and NIVO + IPI combinations, were copied.

Based on the current clinical guidelines[4], a model for the treatment of a metastatic melanoma patient with a confirmed BRAF mutation for the triple ATZ+VM+COB (Table 1) and dual NIVO+IPI (Table 2) combinations was developed. The duration of the treatment was calculated based on the clinical studies in real practice (IMspire 150 [16] and Checkmate 511 [21]), where the average treatment period was 9.2 months for the triple combination and 7.5 months for the double one.

At the next stage of the study, a comparative "cost-effectiveness"[5] analysis of the triple ATZ + VM + COB combination and the dual NIVO + IPI combination was carried out. A progression-free survival (PFS) derived from a systematic meta-analysis was selected as an efficacy criterion. The cost-effectiveness ratio was calculated using the formula[6]:

$$CER = DC/Ef,$$

where: CER (cost-effectiveness ratio) is the ratio of costs and effectiveness; DC – direct costs; Ef (effectiveness) – an indicator of the effectiveness which the drugs are compared by.

Next, a sensitivity analysis to determine the sensitivity of the model (cost-effectiveness ratio) to the changes in the main initial parameters – the costs of a therapy course per patient with metastatic melanoma and PFS[7], was performed.

At the final stage of the study, a "budget impact" analysis (BIA)[8] was carried out.

RESULTS

Effectiveness evaluation according to the literature data

At the first stage of the investigation, an information search for the studies on the efficacy and safety of the ATZ + VM + COB and NIVO + IPI combinations in adults with metastatic melanoma was conducted.

The efficacy of atezolizumab in combination with cobimetinib and vemurafenib was evaluated in the double blind, randomized (1:1), placebo-controlled, multicenter trial (IMspire150) of phase 3 [15]. The group consisted of 514 IIIC-IV melanoma patients at the unresectable stage with a positive BRAF V600 mutation. The treatment was carried out in 28-day cycles. After the first cycle of COB+VM (prescribed in the both groups), the study participants, while on-going the COB+VM therapy, were administrated with either ATZ or placebo. The duration of the course was determined on the basis of the data from the IMspire 150 [15] and CheckMate 511 [21] studies.

In the both cases, the treatment was carried out until progression or unacceptable toxicity. For the triple com-

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bination, the duration of the maintenance phase was 9.2 months, for the double combination –7.5 months (the median of 15 injections).

The primary evaluation standard of efficacy in the IMspire 150 protocol was the PFS, measured as the time from randomization to the first occurrence of the disease progression or death from any cause. Secondary endpoints included an objective response, a duration of response, an overall survival (OS), the time to the global health status deterioration, and the time to the deterioration in physical functions. In the ATZ group, the median PFS was 15.1 months (95% CI: 11.4, 18.4) and in the placebo group it was 10.6 months (95% CI: 9.3, 12.7) (the relative risk (RR) was 0.78; 95% CI: 0.63, 0.97; p=0.0249). At the time of this interim OS analysis, 205 patients died: 93 (36%) of 256 patients in the atezolizumab group and 112 (43%) of 258 patients in the control group (the hazard ratio was 0.85; 95% CI: 0.64–1 .11; p = 0.23 in the Logrank test) [15].

Common treatment-related adverse events (AEs) (the incidence >30%) in the ATZ group were: elevated blood creatine phosphokinase (51.3%), diarrhea (42.2%), rash (40.9%), arthralgia (39.1%), pyrexia (38.7%), increased alanine aminotransferase (33.9%) and increased lipase (32.2%). The discontinuation of the therapy due to AEs was observed in 13% of patients in the ATZ group and in 16% of patients in the placebo group [13]. According to the search results, the IMspire150 trial is currently the only protocol that has examined the combination of ATZ+VM+COB in patients with metastatic melanoma. The NIVO+IPI combination has been used for a relatively longer period and therefore has a broader evidence base, which is founded on the CheckMate study cycle.

CheckMate 067 is a phase 3 double-blind RCT [14, 18, 19]. The protocol included patients with previously untreated advanced melanoma, with a confirmed BRAF V600 mutation, aged 18 and older. The primary endpoints were defined as PFSs and OSs. Randomization occurred in three groups in the ratio of 1:1:1. The main group patients were administrated with a combination of NIVO + IPI (NIVO at the dose of 1 mg/kg body weight, once in 21 days, 4 infusions + IPI 3 mg/kg body weight, once in 21 days, 4 infusions; then NIVO at the dose of 3 mg/kg body weight every 14 days). The comparison groups' patients were administrated with either NIVO (at the dose of 3 mg/kg body weight every 14 days) + placebo or IPI (at the dose of 3 mg/kg body weight, once in 21 days, 4 infusions) + placebo. The treatment continued until the progression, unacceptable toxic effects, or withdrawal of the consent.

In the work by Larkin J. et al. (2019) the results of the CheckMate 067 study after a five-year follow-up (60 months) have been presented. In the NIVO+IPI group, the OS median was not reached for 38.2 months, in the NIVO group it was 36.9 months, in the IPI group – 19.9 months. The RR of death with NIVO+IPI compared with IPI, was 0.52. No persistent deterioration in the health-related quality of life was observed during or after the treatment with NIVO+IPI or NIVO. No new late toxic effects were notified. The authors concluded that among the advanced melanoma patients, a sustained long-term survival of 5 years was observed in a large percentage of patients treated with the NIVO+IPI combination [14].

In a multicenter, double-blind, phase 2 RCT CheckMate 069 (Hodi F.S. et al., 2016) [20], which also included adult patients with previously untreated, unresectable stage III or IV melanoma, the primary endpoint was the proportion of patients with wild-type melanoma BRAF V600 who had achieved an objective response assessed by the investigator. The main group patients were administrated with a combination of NIVO + IPI (NIVO at the dose of 1 mg/kg body weight, once in 21 days, 4 infusions + IPI 3 at the dose of mg/kg body weight, once in 21 days, 4 infusions; then NIVO at the dose of 3 mg/kg body weight once in 14 days). The comparison group patients were administrated with IPI + placebo (IPI 3 at the dose of mg/kg m body, once in 21 days, 4 infusions, then placebo once in 14 days). The protocol included 142 patients (95 patients in the NIVO+IPI group and 47 patients in the IPI group). At the median follow-up of 24.5 months (the interquartile interval of 9.1-25.7), a 2-year OS was 63.8% (95% CI 53.3–72.6) in the NIVO+IPI group and 53.6% (95% CI 38.1–66.8) in the IPI group.

The aim of the phase IIIb/IV CheckMate 511 study (Lebbe C. et al., 2019) [21] was to determine the safety of the NIVO+IPI combination at different dosages. A complete response was observed in 15.0% and 13.5% of patients, respectively. The median PFS was 9.9 months in the NIVO3+IPI1 group and 8.9 months in the NIVO1+IPI3 group. The median OS was not reached in any of the groups [21].

A network meta-analysis using a Bayesian model by Lee J. et al., 2022 [22] compared the efficacy and safety of the ATZ+VM+COB combination vs other therapies for unresectable or metastatic melanoma in adults. The endpoints included PFS, an objective response, the frequency and proportion of patients who had discontinued the treatment due to AEs.

The meta-analysis included 11 studies (not only ATZ+VM+COB and NIVO+IPI combinations, but also other approved regimens). The result was that in the general population, the use of the ATZ + VM + COB combination significantly increases the PFS compared with all comparators. This result was statistically significant for most comparators, including NIVO+IPI [RR 95% CI: 0.75 (0.58–0.97)]. An indirect comparison of IMspire-150 and CheckMate 067 study data showed a better PFS with ATZ+VM+COB (15.1 months) compared to NIVO+IPI (11.147 months). The ATZ+VM+COB combination was rated as the best treatment option in terms of the PFS and an objective response to the treatment.

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Cost analysis results

When copying the data on marginal prices for medicines from the Russian State Register of Maximum Selling Prices for Medicines, the prices for the medicines included in the ATZ+VM+COB and NIVO+IPI combinations, which are the subject of interest of this study, were included in the analyzes. Since there is only one price for each pharmaceutical and dosage form in the SRMRs, the median was not calculated. In the analysis, trade mark-ups and VAT were taken into account (Table 3).

Based on clinical guidelines the treatment models for a single patient with a BRAF-confirmed metastatic melanoma were constructed for the triple ATZ+VM+COB combination and the dual NIVO+IPI combination. The cost analysis results for the ATZ+VM+COB treatment course are presented in Table 4. The cost analysis results for the NIVO+IPI treatment course are presented in Table 5.

In the calculation shown in Table 4, the dosing regimen of atezolizumab 1200 mg once every three weeks was used. According to the Clinical guidelines[9], within the ATZ+VM+COB protocol, atezolizumab can be also administered at the dose of 840 mg once every two weeks.

According to this dosing regimen, one patient undergoing the ATZ + VM + COB protocol will require 19 packs per course (atezolizumab 840 mg / 14 ml), which increases the cost of ATZ up to 3 533 247.47 rubles and the entire course up to 7 252 448.92 rubles. Thus, the use of atezolizumab (840 mg every 14 days) increases the cost of the therapy by 79 697.24 rubles compared with atezolizumab (1200 mg once every 21 days).

With the choice of the ATZ+VM+COB combination, the total course treatment costs for one adult patient with metastatic melanoma was lower compared to the NIVO+IPI combination (8 326 864.89 rubles vs 7 172 751.68 rubles); the difference was 1 154 113.21 rubles.

Results of “cost-effectiveness” analysis

At the next stage of the study, a comparative “cost-effectiveness” analysis on the use of the triple ATZ + VM + COB combination and the dual NIVO + IPI combination was carried out. The PFS indicators obtained from an indirect comparison were chosen as an efficiency criterion.

When calculating the “cost-effectiveness” ratio for a year of a progression-free life, the advantage of the ATZ + VM + COB combination in comparison with the NIVO + IPI combination remained (5 700 200.01 rubles vs 8 942 400.10 rubles). The difference was significant and amounted to 3 242 200.09 rubles (Table 6). Thus, the combination of ATZ+VM+COB has shown an economic advantage.

Sensitivity analysis results

At the next stage of the study, a sensitivity analysis was carried out. Its aim was to determine the sensitivity of the model (“cost-effectiveness” ratio) to the changes in the main initial parameters – the cost of a therapy course per patient with metastatic melanoma and the PFS indicator (Table 7).

The sensitivity analysis demonstrated the stability of the developed model to an increase in the cost of the ATZ + VM + COB course up to + 16%; the reduction in the cost of the NIVO + IPI course up to –13%; the reduction in the PFS against the backdrop of the ATZ + VM + COB rate up to –37% (Table 7).

"Budget impact" analysis

At the final stage of the study, the budget impact analysis of 50 patients with a possible cohort of melanoma was carried out. The analysis showed a potential opportunity to reduce the budget costs by 8 655 849.11 rubles, with an increase in the proportion of the patients administrated with the ATZ + VM + COB combination from 5% to 20% and a decrease in the proportion of the patients administrated with the NIVO + IPI combination from 95% to 80% in public procurement. The data are presented in Table 8 and Fig. 1.

DISCUSSION

The Russian epidemiological data of the State Register of Medicinal Remedies[10] (SRMRs) on the prevalence of metastatic melanoma raise certain concerns – there is an increase in the incidence and pathology often detected at late stages, and associated with high mortality.

The implementation of new treatment regimens into practice, in particular, combinations of modern classes of drugs – BRAF/MEK inhibitors and an anti-PD-L1 immune preparation – can significantly improve the prognosis of such patients, increasing the relapse-free period compared to the previously existing therapy regimens.

Herewith, immunological drugs are highly likely to cause the development of immune-mediated AEs and are characterized by high costs, which emphasize a great importance of identifying the most clinically effective, safe and cost-effective combinations.

The NIVO+IPI combination has been shown in clinical studies to achieve good results in adult patients with metastatic melanoma, providing the longest overall survival among existing therapy regimens. However, a recent study has found out the benefits of the ATZ+VM+COB combination in this group due to the lower complication rate [22].

According to the results of the CheckMate 067 study [14], when prescribing an NIVO+IPI course, in 42% of cases the patients had to interrupt the therapy due to the drug-related AEs. For comparison, in the coBRIM study [10], against the background of the

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VM+COB course, the treatment was interrupted in only 11% of subjects, which is comparable to the data of the IMspire150 study (16% of cases) [15]. When the ATZ component was added to the dual VM+COB combination, the number of withdrawals amounting to 13%, did not increase [15]. The difficulties in using the NIVO+IPI combination, in addition, are due to the high costs for the healthcare system, as noted by foreign authors [19, 25]. For 2017-2018, the costs of the NIVO + IPI course per patient per year reached the amount equal to 226 thousand pounds in the UK, 258 thousand euros in Germany, 234 thousand dollars in America [25].

To date, there are no direct comparative studies on the benefits of one or another combination; in this regard, in the study, indirect comparison data were used and the costs analysis of these treatment regimens were performed. When comparing the endpoints of large clinical trials with a similar methodology, the ATZ + VM + COB combination was found out superior to the NIV + IPI combination in terms of the PFS median, lower costs per therapy course and, as a result, a lower "cost-effectiveness" ratio was notified.

The results of the work have shown that the triple ATZ+VM+COB combination is a clinically cost-effective option for the treatment of metastatic melanoma with a confirmed BRAF mutation in adult patients within the healthcare system of the Russian Federation.

CONCLUSION

The analysis of the literature sources made it possible to conclude that the ATZ+VM+COB combination was more clinically effective than the NIVO+IPI combination in relation to the PFS, which was 15.1 and 11.2 months, respectively, in the patients with metastatic melanoma.

With the choice of the ATZ+VM+COB combination, the total course treatment costs for one adult patient with metastatic melanoma was lower compared to the NIVO+IPI combination (8 326 864.89 rubles vs 7 172 751.68 rubles); the difference was 1 154 113.21 rubles.

The calculation of the "cost-effectiveness" ratio for a year of progression-free life showed the advantage of the ATZ + VM + COB combination in comparison with the NIVO + IPI combination (5 700 200.01 rubles vs 8 942 400.10 rubles); the difference was 3 242 200.09 rub.

The sensitivity analysis demonstrated the stability of the developed model to increase the costs of the ATZ+VM+COB course to +16%, to reduce the costs of the NIVO+IPI course to –13%, and to reduce the PFS against the backdrop of the ATZ+VM+COB course to –37%.

The "budget impact" analysis showed the possibility of reducing costs by 8 655 849.11 rubles with an increase in the proportion of the patients administrated with the ATZ+VM+COB combination from 5% to 20%, and with a decrease in the proportion of the patients administrated with the NIVO+IPI combination from 95% to 80%.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

ISK – concept development and study design, carrying out calculations; EVM – development of research models, carrying out calculations, text writing; VYuE – information search and analysis, editing of article.

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