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- АНАЛИЗ ФАРМАКОЭКОНОМИЧЕСКИХ И КЛИНИКО-ЭКОНОМИЧЕСКИХ ИССЛЕДОВАНИЙ, ОПУБЛИКОВАННЫХ НА БАЗЕ НАУЧНОЙ ЭЛЕКТРОННОЙ БИБЛИОТЕКИ «ELIBRARY.RU» (РИНЦ) ЗА ПЕРИОД С 2005 ПО 2015 гг.
- РЕЗУЛЬТАТЫ РОССИЙСКИХ ФАРМАКОЭКОНОМИЧЕСКИХ ИССЛЕДОВАНИЙ

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RELATIVE VALUE ASSESSMENT OF IPILIMUMAB USAGE IN PATIENTS WITH METASTATIC MELANOMA

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Summary:
Melanoma is a malignant tumor that develops from transformed melanocytes, located mainly in the skin. According to Russian statistics, the incidence of melanoma in 2014 was 9,390 new cases [4]. In 2004-2014, melanoma prevalence rate per 100,000 population increased on average by 4.2% per year. High prevalence of melanoma and frequent poor prognosis necessitate search of innovative treatment methods and use of high-tech drugs. The unmet need for oncology therapies is substantial. The introduction of innovative, high-cost treatments, coupled with mounting budgetary pressures, will necessitate value trade-offs across cancer types. Defining value will be critical to informing decision-making.
The purpose of this study was to perform relative value analysis (RVA) of the ipilimumab use in patients with metastatic melanoma among the entire group of oncology products selected for comparison. Relative value analysis (RVA) can be used to benchmark the clinical and economic value delivered by one product versus others in a broad therapeutic class, using acceptable statistical methods applied to clinical and economic measures. These are naive comparisons with no adjustment for differences in trial characteristics or patient populations. The analysis could not be consider as a substiture for ITC/NMA or more sophisticaled cost effectiveness modeling.

Keywords: *clinical and economic analysis, cost analysis, relative value analysis, immuno-oncology, metastatic melanoma, long-term survival.*

Introduction

Melanoma is a malignant tumor of neuroectodermal origin that develops from transformed melanocytes, located mainly in skin [1]. Over 90% of cases of melanoma are skin melanoma, therefore it is the most well studied in terms of prognosis and treatment options [1].

According to Russian statistics, the incidence of melanoma in 2014 was 9,390 new cases [4]. Melanoma prevalence rate per 100,000 population and the accumulation index of patients with malignant tumors increase with each year. (Fig. 1) In 2004-2014, melanoma prevalence rate per 100,000 population increased on average by 4.2% per year.

Melanoma accounts for not more than 10% in the structure of malignant skin tumors, but 80% of deaths in this group of diseases occurs because of it [6].

Ipilimumab (Yervoy®) is a recombinant human monoclonal antibody that selectively binds to a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), which is the key regulator of T-lymphocytes activation. Ipilimumab inhibits CTLA-4 and blocks inhibiting signals of CTLA-4 cascade by increasing the amount of anti-tumor T-helpers, which in turn induce an increase in the amount of direct T-killers. It has been shown that CTLA-4 blockade reduces the regulatory function of T-cells, which can lead to increased anti-tumor immune response. Furthermore, ipilimumab selectively reduces the amount of regulatory T cells in the tumor, resulting in increase in the ratio of antitumor T-helpers to T regulators, which promotes death of cancer cells.

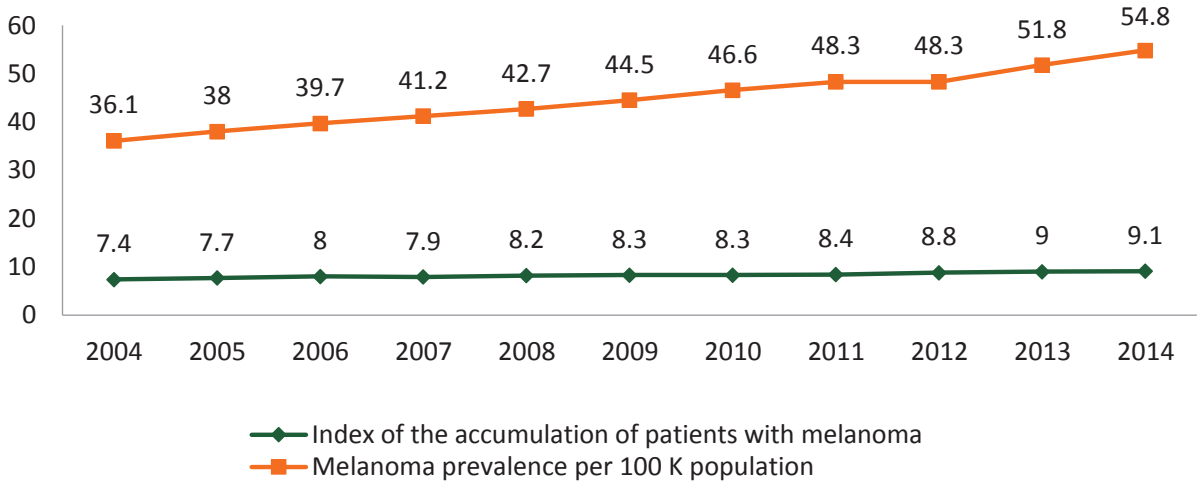

Figure 1. Melanoma prevalence rate per 100,000 population and accumulation index of patients with melanoma in Russian Federation

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Currently, in Russia ipilimumab is indicated for the treatment of unresectable or metastatic melanoma in adult patients after failure or intolerance to prior therapy. According to the results of 12 randomized phase II and III clinical trials, ipilimumab has become the first immuno-oncological drug that demonstrated long-term overall survival of patients. According to the research, ipilimumab showed a 3-year survival in 22% of patients with the expected 5- and 7-year survival rate of 17-20% [9].

Due to its mechanism of action, ipilimumab has no direct antitumor action and its effect develops through the activation of antitumor immunity, which takes time. One of the distinctive features of ipilimumab survival curve is the formation of a plateau after 3- year follow-up, which has not been previously demonstrated in any antitumor drug. However, this plateau appears below the median of overall survival, that is why the traditional efficacy criterion "median of overall survival" may not be the key parameter for evaluation of the efficacy of the immuno-oncological therapy. Thus, for example, in phase III study of ipilimumab (MDX010-020) the OS median among patients treated by ipilimumab alone was 10.1 months (n=137) compared to 6.4 months in the control group (n=136). At the same time, long-term results provide evidence that among patients, in which the follow-up period was over 3 years at the time of slice data, 13 of 53 patients (25%) in ipilimumab group were alive for 3 years or more compared to 5 of 50 patients in the control group (10%), which is absolutely not reflected in the assessment of OS median [10, 11]. Since enduring and long-term survival rates are the major differences of immuno-oncological therapy, it is reasonable to use the parameter of mean OS as the main criteria of treatment efficacy. The use of alternative evaluation criteria, such as the mean OS, 1-year survival rate and 2-year survival rate also allow to evaluate the efficacy of immuno-oncological therapy.

Goal of the study

The goal of this study was to perform to provide value assessment of the ipilimumab use in patients with metastatic melanoma among the entire group of oncology products selected for comparison.

Study objectives:

1. Information search and selection of performance criteria.
2. Determination of the list of drugs for comparison.
3. Calculation of the drugs use cost.
4. Relative value analysis

Results

Determination of the list of drugs for comparison.

To compile the list of drugs for comparison [see Table 1], the following criteria were used:

- registration in the Russian Federation during the period 2005-2015;
- The metastatic and/or unresectable tumors therapy including refractory onco-hematology diseases ;
- availability of phase III clinical trials, in which the overall survival parameter was used to assess the efficacy as a one of the primary or secondary endpoints;
- availability of Kaplan-Meier OS curve.

Table 1. List of drugs

Avastin - Bevacizumab	Zelboraf - Vemurafenib
Alimta - Pemetrexed	Zytiga - Abiraterone
Afinitor - Everolimus	Inlyta - Axitinib
Beyodaym - Pertuzumab + Trastuzumab	Iressa - Gefitinib
Vidaza - Azacitidin	Kadcyla - Trastuzumab emtansin
Vectibix - Panitumumab	Xalkori - Crizotinib
Votrient - Pazopanib	Nexavar - Sorafenib
Herceptin - Trastuzumab	Revlimid - Lenalidomide
Giotrif - Imatinib	Sutent - Sunitinib
Jevtana - Cabazitaxel	Tyverb - Lapatinib
Yervoy - Ipilimumab	Tarceva - Erlotinib
Javlor - Vinflunin	Tafinlar - Dabrafenib
Zaltrap - Aflibercept	Erbitux - Cetuximab

The final list of drugs for comparison includes 26 trade names of drugs [see Table 1], and some drugs were considered from the perspective of different indications. For example, bevacizumab was considered for the treatment of patients with colorectal cancer, patients with non-small cell lung cancer and patients with metastatic renal cell carcinoma. RVA calculation was carried out for each nosology separatedly. Figure 2 shows proportional distribution of drugs within oncological nosologies: drugs for the treatment of non-small cell lung cancer take the leading position; drugs for the treatment of melanoma account for 8% of the overall structure.

Efficacy analysis

Efficacy data used in the study were drawn from the foreign model of Relative Value Analysis developed by the clinical research organization Parexel [3]. There are traditionally used oncology endpoints such as

- median overall survival - the time when 50% of the patients are alive,
- mean overall survival,
- 1-year survival rate,
- 2-year survival rate.

The RVA for ipilimumab in metastatic melanoma provides support to show the full value of the long-term survival data of ipilimumab by use of relevant comparators and oncology indications. This analysis is necessary because the survival difference of ipilimumab over control was shown early and was sustained for responding patients, therefore median overall survival (OS) does not capture the durable long-term survival that a proportion of patients have achieved by being treated with ipilimumab . – Long term survival data to the right of that point not captured.

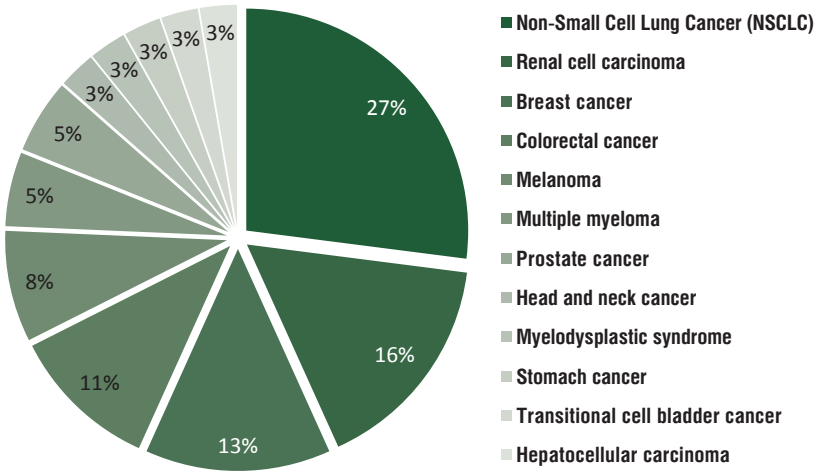


Figure 2. Proportional distribution of drugs within the oncological nosologies

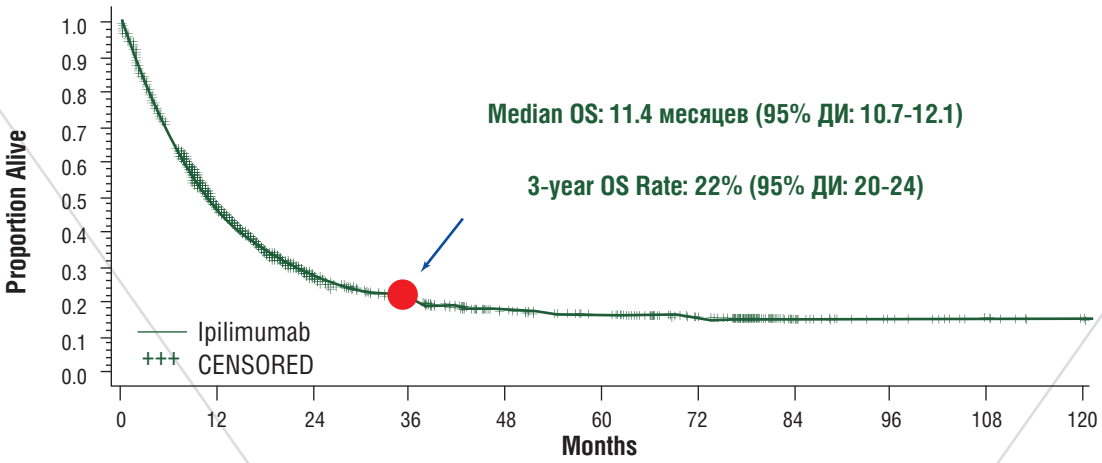


Figure 3. Ipilimumab has shown median OS improvement over control and durable long-term survival in a proportion of patients [9]

Thus there were the following endpoints:

- mean overall survival (mean OS);
- 1-year survival rate;
- 2-year survival rate;

Cost analysis

Regarding clinical endpoints ipilimumab showed improvement in mean OS, improvement in 1-year survival and improvement in 2-year survival as well compared with control in the range of improvements reported for comparators.

The next stage of the RVA included a cost analysis. Since the drugs from the defined list are used for a variety of indications, it was decided to consider only direct costs, namely the market value of drugs.To compare the relative value for ipilimumab cost with that of other comparators, treatment costs were calculated for each product, including cost per month and total treatment cost. Cost per month was calculated by determining the cost of one cycle of therapy at the indicated dose and dividing the days per month (an assumption of 30.4 days per month) by the cycle duration (in days) to determine the monthly cost. For certain products, mostly injectables, indicated doses and subsequent costs were based on patient weight or body surface area both of which were sourced from a relevant product label. To calculate the cost, the data from the essencial drug list (EDL) (www.grls.rosminzdrav.ru) including VAT (10%) or the prices from public tenders for not EDL drugs, the price for ipilimumab was taken from Bristol-Myers Squibb company price list. We used the following assumptions: the average predicted body weight - 70 kg, the average calculated body surface area - 1.7 m^2.

For comparison of the relative economic value of ipilimumab *vs* other comparators, the clinical metrics were plotted against monthly treatment costs and total treatment costs. For each comparator monthly and total treatment costs were estimated using data on the dosing, therapy cycle duration, and treatment duration (obtained from the product labels, or published studies - attachment 1) and unit costs (pricing assumptions using publicly available data). To assess the relative value of ipilimumab *vs* other oncology products each product was plotted, with the x-axis reflecting total treatment cost, and the y-axis reflecting improvement *vs* comparator clinical metric. A regression line highlighted in red indicating an average cost-to-benefit ratio was used to divide the products in 'above average' and 'below average' value groups and to identify products with highest relative value per metric.

Table 3 shows the course cost of drugs calculated based on the assumptions.

The course cost of ipilimumab amounted to 5,064,880 rubles in the second-line therapy. Moreover, among the entire group of drugs for comparison, the highest course cost amounted to 10,503,731 rubles for lenalidomide for the treatment of multiple myeloma; the lowest course cost amounted to 25,813 rubles for pemetrexed for the treatment of non-small cell lung cancer.

Table 3. Results of the cost analysis, rubles[1]

Trade name	INN	Tumour type	Therapeutic line	Therapy cost, rubles
Avastin	Bevacizumab	Colorectal cancer (CRC)	1L	1,457,444
Avastin	Bevacizumab	Non-Small Cell Lung Cancer (NSCLC)	1L	1,326,738
Avastin	Bevacizumab	Renal cell carcinoma (RCC)	1L	2,698,659
Alimta	Pemetrexed	Non-Small Cell Lung Cancer (NSCLC)	1L	32,266
Alimta	Pemetrexed	Non-Small Cell Lung Cancer (NSCLC)	2L	25,813
Alimta	Pemetrexed	Non-Small Cell Lung Cancer (NSCLC)	Supporting treatment	32,266
Afinitor	Everolimus	Renal cell carcinoma (RCC)	2L	41,785
Afinitor	Everolimus	Breast cancer (BC)	2L+	70,270
Beyodaym	Pertuzumab + Trastuzumab	Breast cancer (BC)	1L	9,244,390
Vidaza	Azacitidin	Myelodysplastic syndrome (MDS)	1L	4,137,046
Vectibix	Panitumumab	Colorectal cancer (CRC)	1L	2,232,644
Votrient	Pazopanib	Renal cell carcinoma (RCC)	1L/2L	809,641
Herceptin	Trastuzumab	Breast cancer (BC)	1L	562,126
Herceptin	Trastuzumab	Stomach cancer (SC)	1L	573,301
Giotrif	Afatinib	Non-Small Cell Lung Cancer (NSCLC)	1L	1,131,130
Jevtana	Cabazitaxel	Prostate cancer (PCa)	2L	1,955,013
Yervoy	Ipilimumab	Melanoma	2L	5,064,880
Javlor	Vinflunine	Transitional cell bladder cancer (TCBC)	2L	413,751
Zaltrap	Aflibercept	Colorectal cancer (CRC)	2L	1,760,786
Zelboraf	Vemurafenib	Melanoma	1L	4,389,003
Zytiga	Abiraterone	Prostate cancer (PCa)	2L/3L	1,673,872
Inlyta	Axitinib	Renal cell carcinoma (RCC)	2L	53,066
Iressa	Gefitinib	Non-Small Cell Lung Cancer (NSCLC)	1L	497,960
Kadcyla	Trastuzumab emtansin	Breast cancer (BC)	2L+	3,200,968
Xalkori	Crizotinib	Non-Small Cell Lung Cancer (NSCLC)	2L	4,711,842
Nexavar	Sorafenib	Hepatocellular carcinoma (HCC)	1L	772,722
Nexavar	Sorafenib	Renal cell carcinoma (RCC)	2L	801,881
Revlimid	Lenalidomide	Multiple myeloma (MM)	2L+	5,783,662
Revlimid	Lenalidomide	Multiple myeloma (MM)	1L	10,503,731
Sutent	Sunitinib	Renal cell carcinoma (RCC)	1L	1,689,993
Tyverb	Lapatinib	Breast cancer (BC)	1L	1,322,662
Tarceva	Erlotinib	Non-Small Cell Lung Cancer (NSCLC)	1L	778,240
Tarceva	Erlotinib	Non-Small Cell Lung Cancer (NSCLC)	2L/3L	151,200
Tarceva	Erlotinib	Non-Small Cell Lung Cancer (NSCLC)	Maintenance	229,600
Tafinlar	Dabrafenib	Melanoma	1L	1,398,400
Erbitux	Cetuximab	Colorectal cancer (CRC)	1L	3,473,097
Erbitux	Cetuximab	Head and neck cancer (HNC)	1L	1,636,432

[1] 1L - first-line therapy, 2L - second-line therapy

Improvement in Mean overall survival (OS)

Figure 4 shows the relative value of drugs of the entire comparison group in terms of the criterion improvement in **mean OS**. Ipilimumab is above the regression trend line, i.e. at a given course cost, the parameter of improvement in mean OS exceeds the corresponding predicted average based on data included value.

Necessity to note that for most drugs the market value of the drugs is in the range of 2 million rubles, and the level of improvement in mean overall survival is 4 months.

After comparing the relative value of ipilimumab on improvement in mean overall survival with the other drugs indicated for melanoma therapy (vemurafenib and dabrafenib), the following conclusions can be made:

- Ipilimumab efficacy during the second-line melanoma therapy is four times higher than vemurafenib efficacy in the first-line melanoma therapy, while ipilimumab course cost is only 15% higher.
- Dabrafenib efficacy in terms of improvement in mean OS is significantly lower than the expected one having the given course cost.

Improvement in 1-year survival

Figure 5 shows relative-value for drugs of the comparison group on improvement in 1-year survival endpoint. For most drugs the course cost is in the range of 2 mln rubles and their efficacy on improvement in 1-year survival endpoint for over 50% of the drugs exceeds mean expected value.

Efficacy ratio on improvement in 1-year survival endpoint for ipilimumab is comparable with this parameter for vemurafenib. At the same time, ipilimumab efficacy on improvement in 1-year survival endpoint significantly exceeds the corresponding vemurafenib efficacy, whereas ipilimumab course cost is only 15% higher.

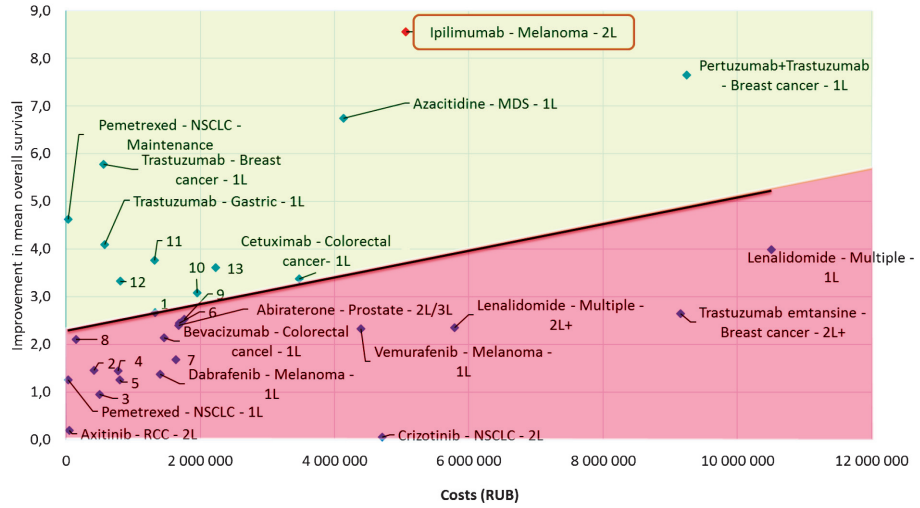
It worths to emphasize that the figure 5 suggests that more costly treatments are generally less effective so, greater investment not worh-while for some indications.

Improvement in 2-year survival

Figure 6 shows relative-value for drugs of the comparison group on improvement in 2-year survival endpoint . Considering this criterion, ipilimumab efficacy exceeds the corresponding mean value along with the following drugs: erlotinib, trastuzumab, cabazitaxel, azacitidin, aflibercept, pemetrexed, trastuzumab emtansin, pertuzumab + trastuzumab. For vemurafenub and dabrafenib, which are also indicated for melanoma therapy, there are no data on efficacy on improvement in 2-year survival, which makes their comparison based on this parameter impossible.

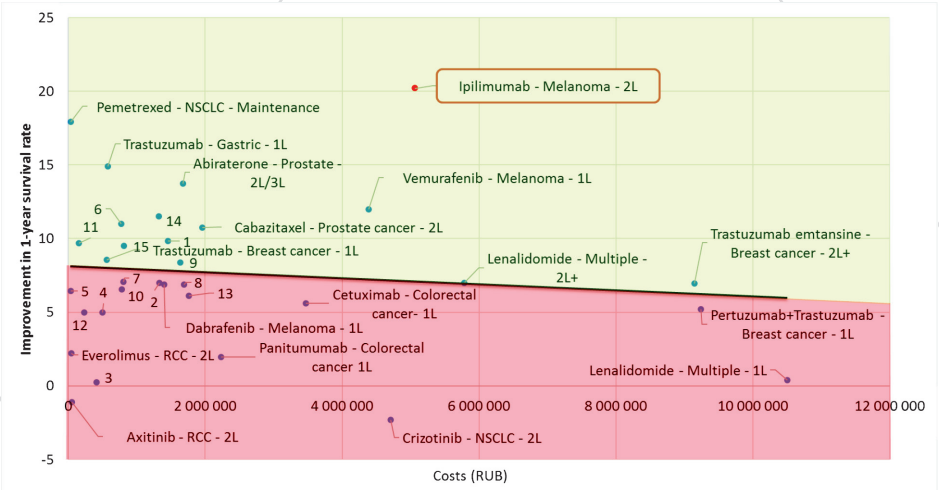
Conclusions

1. For ipilimumab the improvement in mean overall survival exceeds the corresponding predicted average value based on data included within the established course cost for the comparison group.
2. Considering the improvement in mean overall survival , ipilimumab – melanoma 2L efficacy is four times higher than vemurafenib-melanoma



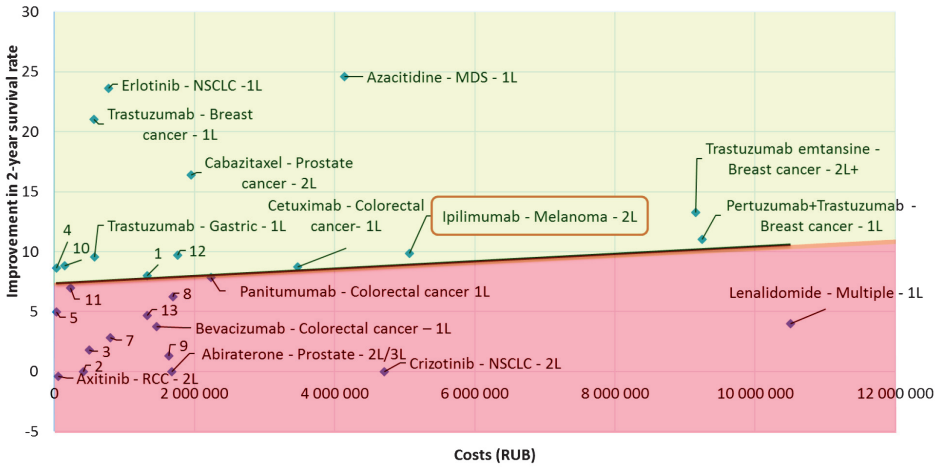
Note: 1 – Bevacizumab - NSCLC - 1L; 2 – Vinflunin - TCBC - 2L; 3 – Gefitinib - NSCLC - 1L; 4 – Sorafenib - RCC - 1L; 5 – Sorafenib - RCC - 2L; 6 – Sunitinib - RCC - 1L; 7 – Cetuximab - HNC - 1L; 8 – Erlotinib - NSCLC - 2L/3L; 9 – Aflibercept - CRC - 2L; 10 – Cabazitaxel - PCa - 2L; 11 – Lapatinib - BC - 1L; 12 – Pazopanib - RCC - 1L/2L; 13 – Panitumumab - CRC - 1L.

Figure 4. Ipilimumab relative-value analysis on improvement in mean overall survival.



Note: 1 – Bevacizumab - CRC - 1L; 2 – Bevacizumab - NSCLC - 1L; 3 – Gefitinib - NSCLC - 1L; 4 – Pemetrexed - NSCLC - 1L; 5 - Sorafenib - RCC - 1L; 6 – Sorafenib - RCC - 2L; 7 – Sunitinib - RCC - 1L; 8 - Trastuzumab - BC - 1L; 9 – Cetuximab - HNC - 1L; 10 - Everolimus - RCC - 2L; 11 – Erlotinib - NSCLC - 1L; 12 – Erlotinib - NSCLC - 2L/3L; 13 – Erlotinib - NSCLC - Maintenance therapy; 14 - Aflibercept - CRC - 2L; 15 – Lapatinib - BC - 1L; 16 – Pazopanib - RCC - 1L/2L.

Figure 5. Ipilimumab relative-value analysis on improvement in 1-year survival



Note: 1 – Bevacizumab - NSCLC - 1L; 2 – Vinflunin - TCBC - 2L; 3 – Gefitinib - NSCLC - 1L; 4 – Pemetrexed - NSCLC - 1L; 5 - Pemetrexed - NSCLC - Maintenance therapy; 6 - Sorafenib - RCC - 1L; 7 – Sorafenib - RCC - 2L; 8 – Sunitinib - RCC - 1L; 9 – Cetuximab - HNC - 1L; 10 – Everolimus - RCC - 2L; 11 - Erlotinib - NSCLC - 2L/3L; 12 - Erlotinib - NSCLC - Maintenance therapy; 13 – Aflibercept - CRC - 2L; 14 – Lapatinib - BC - 1L.

Figure 6. Ipilimumab relative-value analysis on improvement in 2-year survival

1L while the course cost difference is only +15%.

3. Efficacy and course cost ratio on improvement in 1-year survival for ipilimumab is comparable with this parameter for vemurafenib-melanoma 1L. At the same time ipilimumab-melanoma 2L efficacy on improvement in 1-year survival while the course cost difference is only +15% .
4. Considering cost-effectiveness of the drugs of the comparison group on improvement in 2-year survival , ipilimumab efficacy exceeds the corresponding mean value for erlotinib, trastuzumab, cabazitaxel, azacitidin, aflibercept, pemetrexed, trastuzumab emtansin, pertuzumab + trastuzumab.

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Attachment 1

Azacitidine - MDS - 1L	http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(09)70003-8/abstract
Bevacizumab - Colorectal Cancer – 1L	http://theoncologist.alphamedpress.org/content/14/1/22.full.pdf+html
Bevacizumab – NSCLC - 1L	http://www.nejm.org/doi/full/10.1056/NEJMoa061884
Bevacizumab - RCC - 1L	http://jco.ascopubs.org/content/23/16/3697.full.pdf
Vinflunine - Transitional cell carcinoma of urothelial tract - 2L	http://annonc.oxfordjournals.org/content/24/6/1466.long
Gefitinib- NSCLC - 1L	https://www.scottishmedicines.org.uk/SMC_Advice/Advice/615_10_gefinitib_Iressa/gefitinib_Iressa_Resubmission
Ipilimumab - Melanoma - 2L	https://clinicaltrials.gov/ct2/show/study/NCT00094653?sect=X01256
Lenalidomide - Multiple - 1L	http://www.nejm.org/doi/full/10.1056/NEJMoa1402551?fromsource=nelm
Lenalidomide - Multiple - 2L+	http://www.nature.com/leu/journal/v23/n11/full/leu2009147a.html
Pemetrexed - NSCLC - 1L	http://jco.ascopubs.org/content/26/21/3543.long
Pemetrexed - NSCLC - 2L	http://jco.ascopubs.org/content/22/9/1589.full.pdf+html
Pemetrexed - NSCLC - Maintenance	http://theoncologist.alphamedpress.org/content/15/12/1352.full.pdf+html
Sorafenib - HCC - 1L	http://www.nejm.org/doi/pdf/10.1056/NEJMoa0708857
Sorafenib - RCC - 2L	http://jco.ascopubs.org/content/27/20/3312.long
Sunitinib - RCC - 1L	http://jco.ascopubs.org/content/27/22/3584.full.pdf+html http://www.nejm.org/doi/pdf/10.1056/NEJMoa065044 (baseline only)
Trastuzumab - Gastric Cancer - 1L	http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736%2810%2961121-X.pdf
Trastuzumab - Breast Cancer - 1L	http://www.roche-trials.com/studyResultGet.action?studyResultNumber=M77001 http://jco.ascopubs.org/content/23/19/4265.long
Cetuximab - Colorectal cancer- 1L	http://jco.ascopubs.org/content/29/15/2011.long
Cetuximab - Head & Neck - 1L	http://www.nejm.org/doi/pdf/10.1056/NEJMoa0802656
Everolimus - RCC - 2L	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4142675/
Everolimus - Breast cancer - 2L+	https://www.scottishmedicines.org.uk/SMC_Advice/Advice/872_13_everolimus_Afinitor/everolimus_Afinitor
Erlotinib - NSCLC -1L	http://www.sciencedirect.com/science/article/pii/S147020451170393X#
Erlotinib - NSCLC - 2L/3L	http://www.nejm.org/doi/pdf/10.1056/NEJMoa050753
Erlotinib - NSCLC – Maintenance	https://clinicaltrials.gov/ct2/show/results/NCT00556712?sect=X4301256#othr
Abiraterone - Prostate Cancer - 2L/3L	http://www.sciencedirect.com/science/article/pii/S1470204512703790
Axitinib - RCC - 2L	http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045%2813%2970093-7/abstract
Afatinib - NSCLC - 1L	http://jco.ascopubs.org/content/31/27/3327.full.pdf+html
Aflibercept – Colorectal Cancer - 2L	http://www.scottishmedicines.org.uk/files/advice/aflibercept_Zaltrap_Resubmission_FINAL_February_2014_for_website.pdf
Vemurafenib - Melanoma - 1L	http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(14)70012-9/abstract
Dabrafenib - Melanoma - 1L	http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2812%2960868-X/abstract https://clinicaltrials.gov/ct2/results?term=01227889&Search=Search
Cabazitaxel - Prostate cancer - 2L	http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736%2810%2961389-X.pdf
Crizotinib - NSCLC - 2L	http://www.nejm.org/doi/full/10.1056/NEJMoa1214886
Lapatinib - Breast cancer- 1L	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3227947/pdf/onc122.pdf
Pazopanib - RCC - 1L/2L	http://jco.ascopubs.org/content/28/6/1061.long https://clinicaltrials.gov/ct2/show/NCT00334282?term=00334282&rank=1
Panitumumab - Colorectal cancer - 1L	Final results from ASPECCT: Randomized phase 3 non-inferiority study of panitumumab (pmab) vs cetuximab (cmab) in chemorefractory wild-type (WT) KRAS exon 2 metastatic colorectal cancer (mCRC).
Pertuzumab+Trastuzumab - Breast cancer - 1L	http://www.nejm.org/doi/pdf/10.1056/NEJMoa1113216
Trastuzumab emtansine - Breast cancer - 2L+	http://www.nejm.org/doi/pdf/10.1056/NEJMoa1209124