MEDICAL UNIVERSITY SOFIA
FACULTY OF PUBLIC HEALTH
„PROF. DR. TSEKOMIR VODENICHAROV, MD, PHD“

AUTHOR'S ABSTRACT

MIROSLAV KIRILOV TSONKOV

Socio-medical aspects and comparative analysis of the use of generic versus innovative EGFR tyrosine kinase inhibitors in the treatment of lung cancer

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Research supervisors:

Prof. Dr. Angelika Velkova, MD, DSc

Prof. Dr. Assena Serbezova, MSc Pharm, PhD

Reviewers:

Prof. Dr. Georgi Momekov, MSc Pharm, DSc

Prof. Dr. Nonka Mateva, MD, PhD

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in of the Faculty of Public Health "Prof. Dr. Tsekomir Vodenicharov, MD", Medical University - Sofia, 8 "Bialo more" str. University Hospital "Tsaritsa Yoanna - ISUL", Sofia in accordance with the Regulations for the Conditions and Procedures for Acquisition of Scientific Degrees and Holding Academic Positions at the Faculty of Public Health "Prof. Dr. Tsekomir Vodenicharov, MD", Medical University, Sofia. Sofia and on the basis of order No. PK36 - 589 of 27.03.2023, before a scientific jury of 5 habilitated persons in the relevant scientific field on the topic of the dissertation:

1. **Prof. Dr. Lidia Mladenova Georgieva, MD, PhD – internal Member** for Medical University – Sofia, Department of Social Medicine at the Faculty of Public Health "Prof. Dr. Tsekomir Vodenicharov, DSc" at MU – Sofia
2. **Prof. Dr. Georgi Tsvetanov Momekov, DSc – internal Member** of the Medical University – Sofia, Department of Pharmacology, Pharmacotherapy and Toxicology, Faculty of Pharmacy at MU – Sofia
3. **Prof. Dr. Sashka Rumenova Popova, MD, PhD – external member** of the Medical University – Sofia, retired lecturer for more than five years from the academic staff of the Faculty of Public Health "Prof. Dr. Tsekomir Vodenicharov, DSc" at MU – Sofia
4. **Prof. Dr. Yuliana Krumova Marinova, MD, PhD – external member** of MU – Sofia, Medical Faculty of Trakia University – Stara Zagora
5. **Prof. Dr. Nonka Georgieva Mateva, MD, PhD – external Member** for Medical University – Sofia, Faculty of Public Health at Medical University – Plovdiv

Backup members:

1. **Prof. Dr. Ralitsa Zlatanova Zlatanova-Velikova, MD, PhD – internal Member** for Medical University – Sofia, Department of Health Policy and Management at the Faculty of Public Health "Prof. Dr. Tsekomir Vodenicharov, DSc" at MU – Sofia
2. **Prof. Dr. Maria Anastasova Semerdzhieva, MD, PhD – external member** of the Medical University – Sofia, Dean of the Faculty of Public Health at the Medical University – Plovdiv

The materials are available at the Scientific Department, Faculty of Public Health "Prof. Dr. Tsekomir Vodenicharov, MD, PhD", Medical University - Sofia, 6 Bialo pole Str

CONTENT

1. INTRODUCTION

Globally according to GLOBOCAN, lung cancer remains an important public health and economic burden, based on its high incidence and mortality. Lung cancer is the leading cause of cancer-related death and its incidence has been increasing rapidly since the early 20th century.

Treatment outcomes and survival in cancer are known to have a very important social gradient, and lung cancer is no exception. Factors such as socioeconomic status, race, ethnicity, and place of residence have been found to create social disparities and reflect different cancer-related outcomes. Among these, socioeconomic status is a complex factor that can encompass several dimensions of individuals' social and economic life circumstances and is often measured based on information regarding education, income, and/or occupation.

The last two decades have led to important improvements in the diagnosis and treatment of lung cancer. However, recent evidence suggests that people of lower socioeconomic status are less likely to benefit from such improvements. For example, in the US, lower socioeconomic status is associated with poorer access to lung cancer screening and lower rates of use of innovative therapies. There is evidence that people of lower socioeconomic status are less likely to undergo lung cancer screening and more likely to be diagnosed with complications of the disease as an emergency. A large body of evidence suggests that people from lower socioeconomic backgrounds have 20-30% lower odds of receiving traditional treatments, such as surgery and chemotherapy, also have about 30% lower odds of receiving next-generation treatments, such as targeted therapies.

Overall, these results regarding access to new therapies are consistent with the counterfactual equity hypothesis that innovations, based on their high cost and access issues, would initially reach and benefit only the financially independent and thus widen

socioeconomic disparities in outcomes. In this context, lower socioeconomic status is associated with lower lung cancer survival. There are therefore widespread socioeconomic inequalities in lung cancer incidence, mortality and survival.

Average total health-related costs are higher for lung cancer patients both before and after diagnosis of the disease with an expected peak around diagnosis and treatment. Hospital treatment accounts for the bulk of total health costs before and after diagnosis.

Publicly funded sickness benefits were significantly higher for lung cancer patients, correlating with a greater burden of comorbidity. When estimating the economic burden of lung cancer, the European Respiratory Society (ERS) reported a cost of 1 873 000 disability-adjusted life years (DALYs), equivalent to over €100 billion in disability and premature mortality. A greater economic burden than for COPD patients (amounting to approximately €93 billion per year).

It is an undeniable fact that the socio-economic impact of lung cancer is growing in prospect and access to costly therapies is becoming increasingly difficult for a large proportion of sufferers. This is why governments and health funds are turning to the opportunities that generic medicines provide to reduce the economic burden on private and public health systems. Logically, the economic burden of treatment on patients and society correlates with the importance of using generic medicines to contain treatment costs while maintaining clinical effectiveness.

2. OWN STUDY

2.1. Aims and objectives of the study

The analysis of the literature revealed the need to conduct modern studies for the attitudes of medical professionals and pharmacists in Bulgaria regarding the position of generic drugs in the treatment of lung cancer, as well as to determine the financial parameters and costs of targeted therapy for lung cancer in Bulgaria, based on which we set the following aim and objectives:

Aim:

To analyze the positioning of generic versus innovative TKIs for the treatment of lung cancer in the Bulgarian clinical practice and to assess the financial burden of cancer therapies in Bulgaria.

To achieve this aim, we set the following OBJECTIVES (tasks):

1. To investigate the attitudes and preferences of healthcare professionals regarding the use of generic and innovative targeted drugs in lung cancer therapy.

2. To analyze the choice of generic or innovative drugs in oncology practice.

3. To evaluate the financial parameters and costs of targeted therapy for lung cancer patients by analyzing the costs of TKI used in the treatment of lung cancer.

4. To compare the prices of TKIs in the treatment of lung cancer and to analyze the cost-benefit correlation of TKI administration.

5. To analyze the financial burden of cancer therapies in the country by assessing the cost of oncology drugs in Bulgaria in order to position and justify the use of generic drugs.

Considering the set of tasks the following hypotheses can be formulated:

Hypothesis 1. Oncologists have a negative attitude towards the use of generic drugs in the treatment of patients with lung cancer.

Hypothesis 2. Pharmacists working in oncology care have a positive attitude towards the use of generic medicines in the treatment of lung cancer patients.

Hypothesis 3. The introduction of new therapies in the medical treatment of cancer multiply the burden on the healthcare budget.

Hypothesis 4. The widespread positioning of generic drugs in cancer care would dramatically reduce the financial pressure on the healthcare system.

2.2 Subject, object, time and place of the study

The object of the study is the social effectiveness of drug therapy in cancer patients.

The subject of this dissertation is the effects of generic versus innovative drugs in the treatment of patients with lung cancer.

Time and place of the study:

The study was conducted between April 2021 and April 2022 .

Study sites are:

- The study sites were pharmacies in the city of Sofia, Pleven, Plovdiv, Varna, Stara Zagora
- Comprehensive oncology centers in the country, clinics and oncology departments treating patients with lung cancer.

2.3 Materials and methods

Setting of the study: a complex socio-medical study was conducted, including a cross-sectional survey among pharmacists and oncologists from the cities where lung cancer patients are treated; an economic evaluation of the therapy with generic and innovative medicines for the treatment of lung cancer and a cost-benefit determination.

I. A cross-sectional study

A survey was conducted among pharmacists and oncologists in cities with university oncology clinics, Comprehensive Cancer Centers and private oncology facilities between April 2021 and April 2022. A survey questionnaire was developed, collecting information on professionals' opinions on aspects of the topic presented as 12 statements/questions. The level of awareness of physicians and pharmacists about these drugs, as well as preferences towards their use in clinical practice, was also investigated.

The survey results for the included individuals were obtained on the basis of descriptive statistics in the analysis of relative shares across the map:

Distribution based on gender: 49 (40.8%) males and 71 (59.2%) females participated in the survey among health professionals (Figure 1).

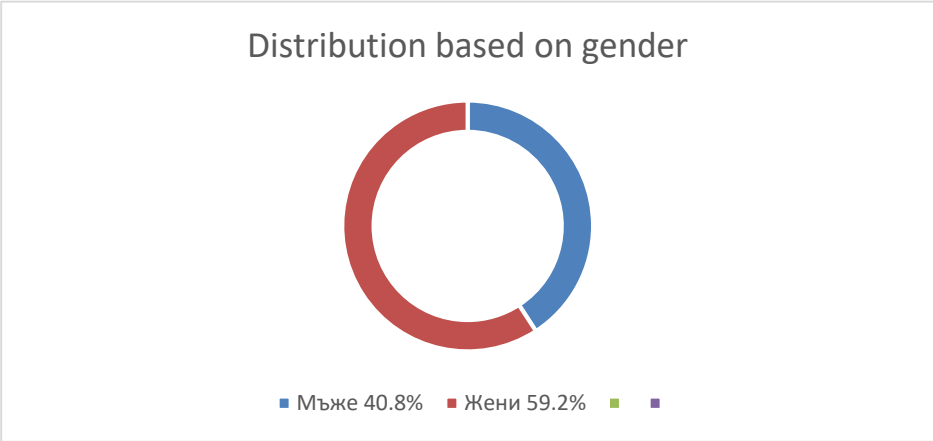

Fig. 1 Gender distribution of participants in the representative sample survey

Despite the lack of definitive national statistics in recent years on the characteristics of oncologists and pharmacists working in oncology practice, this distribution is broadly consistent with the distribution in the general population. Women outnumber men by a very small margin-51.9%. In the profession of oncologists, the female gender is predominant in Bulgaria, which could also be correlated with the profession of pharmacists working in oncology practice, although not to such a high degree.

Distribution by age groups

Fig. 2 reflects the age distribution of responders. The meadian age of corespondents is 45 and the most common age is 55. The two values are drawn to the right in the distribution, reflecting an aging of the occupational population studied.

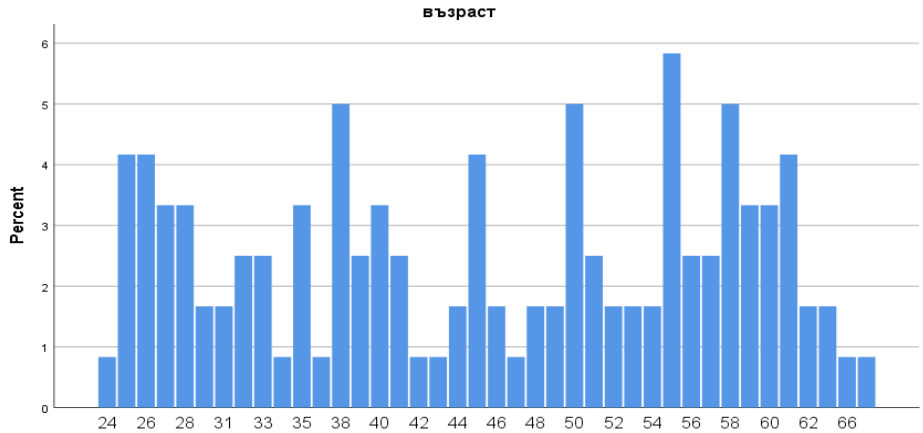

Fig. 2 Age distribution of correspondents in the survey.

The structure of the study participants by age groups is presented in Tabl. 1, with the predominance of people over 50 years of age. This is consistent with the general trend of ageing of the population in the country, and in particular the ageing of the healthcare profesionals.

Table 1 Structure of survey participants by age group

	Frequency	Percent
Up to 35 years old	34	28.3
Between 36-50 years	39	32.5
Over 51 years	47	39.2
Total	120	100.0

Distribution by profession

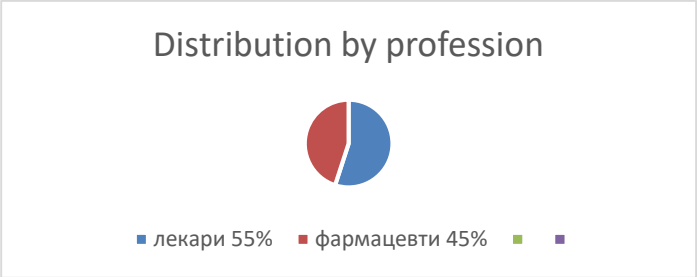

Fig. 3 The structure of the corespondents by profession

In the survey, physicians had a higher relative proportion than pharmacists, which is explained by the increasing number of physicians (including postgraduate students) working with cancer patients, based on the increased interest in medical oncology in the last few years.

Distribution by seniority (years of service into the specialty)

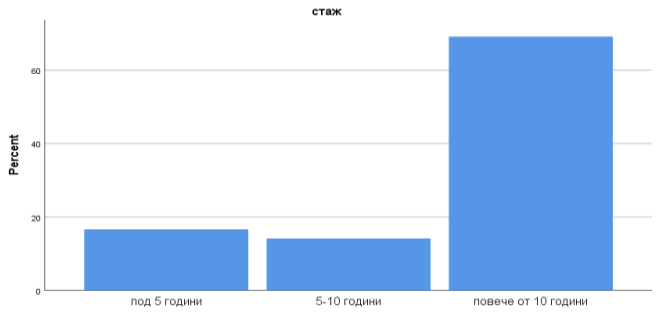

Fig. 4 The structure of the corespondents in relation to the professional experience

The results show that the vast majority of corespondents (69.2%) had more than 10 years of experience. This directly links to the analysis of the age group question we comment above.

Distribution by place of work

Those who participated in the study work mainly in clinics or departments - 49.2% (59 corespondents) of all. Those working in pharmacies come in second position - 32.5% (39 corespondents). The smallest proportion was of those working in pharmaceutical companies - 18.3% (22 corespondents) (Figure 5).

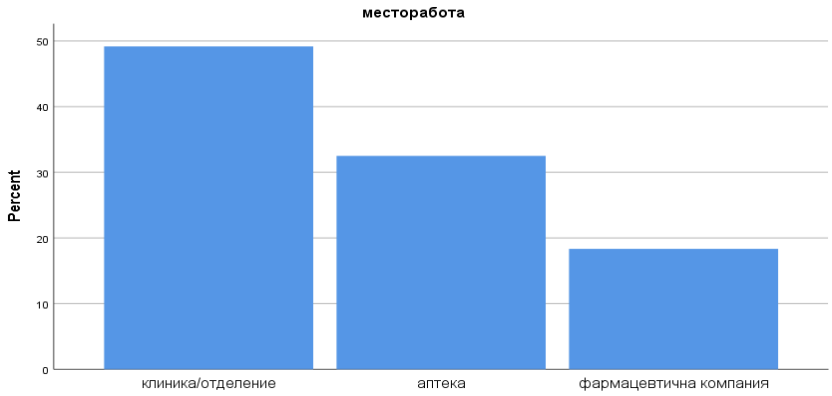

Fig. 5 Distribution of survey participants by place of work

Distribution of responses based on the form of ownership of the place of work

The corespondents who participated in the study were distributed with a certain prevalence of those from private structures, respectively 42.5% (51corespondents) from state and 57.5% (69co respondents) from private institutions, which corresponds to the trends in recent years in Bulgaria for the increasing overlap of private oncology centers and clinics, whose share in oncology until 10 years ago was completely monopolized by state and municipal oncology

structures. It is the trend over the last 15 years that shows an increase in the staff of private health structures (Table 2).

Table 2 Distribution of responses based on the form of ownership of the place of work

	Frequency	Percent
private	69	57.5
public	51	42.5
total	120	100.0

Distribution of responses by location of place of work

Cancer care in Bulgaria has been planned as decentralised structure since its inception with one National Oncology Centre in Sofia and 13 oncology dispensaries across the country, one of which is also in Sofia. In recent years and with the expansion of private structures, although many of them are located in the capital, the presence of complex oncological structures has been maintained in the countryside, where many physicians and pharmacists, respectively, continue to practice (Table 3).

Table 3 Distribution of responses by location of place of work

	Number	Percents
Sofia	52	43.3
Outside Sofia	63	52.5
Total	115	95.8
No answer	5	4.2
	120	100.0

Methodology: The techniques for analysis used include sociological methods - survey and documentary methods, comparative economic analysis and statistical methods.

Sociological methods

Method of the survey

Primary individual information was collected through a direct individual survey. The survey questionnaire was given to the respondents at their workplace by the doctoral student and was collected after completion at a time and place convenient to them. A total of 126 medical professionals were invited to participate in the study, of whom 120 (95.2%) responded.

A questionnaire with 12 statements (questions) was constructed to accomplish the first task of the study. For each statement, respondents were asked to express their agreement with it using a five-point Likert scale from "Strongly Agree" to "Strongly Disagree". The questionnaire explored participants' familiarity with the medication and preference for the innovative or generic drug. From the demographic characteristics, the variables of gender, age, occupation, years of experience in the occupation, place of work, form of ownership of the medical/pharmacy facility and location of the medical/pharmacy facility were studied.

Scale reliability

The 12 statements that make up the scale measuring attitudes towards innovative and generic medicines were subjected to reliability analysis. The calculated value of the Cronbach's alpha coefficient was 0.608. This value indicates relatively good reliability for the small number of scale statements. In a subsequent administration, the content of questions numbers 4 and 8 could be edited, which reduce the reliability of the scale to some extent.

Documentary method

Information was collected from sources classified as written documents - data from self-administered questionnaires completed by participants. Qualitative and quantitative content analysis was conducted. Content analysis and summary of the documents and the rationale for the conclusions was conducted.

Statistical method

Classical and modern statistical methods were used to analyze the collected data, applied with IBM SPSS Statistics version 26.0 statistical package.

Descriptive analysis was applied to examine the distribution of relative proportions and dispersion; cross-tabulation analysis to determine the relationship between demographic characteristics and responses to statements; t-test to compare means and ANOVA to determine differences between groups; factor analysis to reduce variables and infer profiles; Alpha-Cronbach analysis for scale reliability and correlation analysis to determine relationships between factor components and demographic characteristics.

Chapter 3

RESULTS

3. Results of own studies

3.1. Survey of attitudes towards originator and generic medicines

Distribution of responses on the scale assessing attitudes towards innovative and generic drugs.

Based on the results of the distribution of responses reported in the subsequent figures, the distribution of responses for each question is presented and illustrated graphically:

The first statement of the questionnaire explores the respondents' opinion on the therapeutic equivalence of generic medicines with the corresponding innovative products. 45% of respondents fully agreed, 39.2% partially agreed. Every tenth corespondent has a neutral position against the statement. 5% of respondents disagreed with the statement, with only 0.8% completely disagreeing that each generic medicinal product is therapeutically equivalent to the corresponding innovative one (Figure 6).

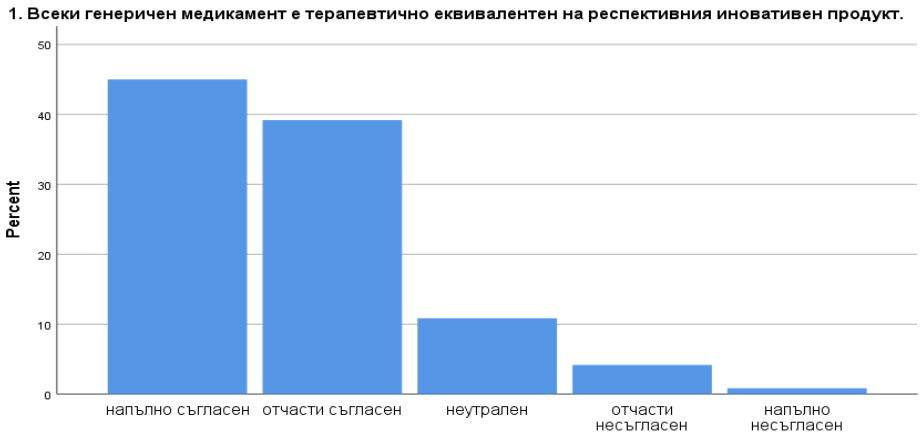

Fig. 6 Distribution of responses to statement 1

Participants' opinion on the therapeutic equivalence of each generic drug product with each other generic drug product was determined by the second statement. It is noteworthy that 45.6% of the respondents partially agreed with the statement and nearly one-fifth were neutral (Fig. 7).

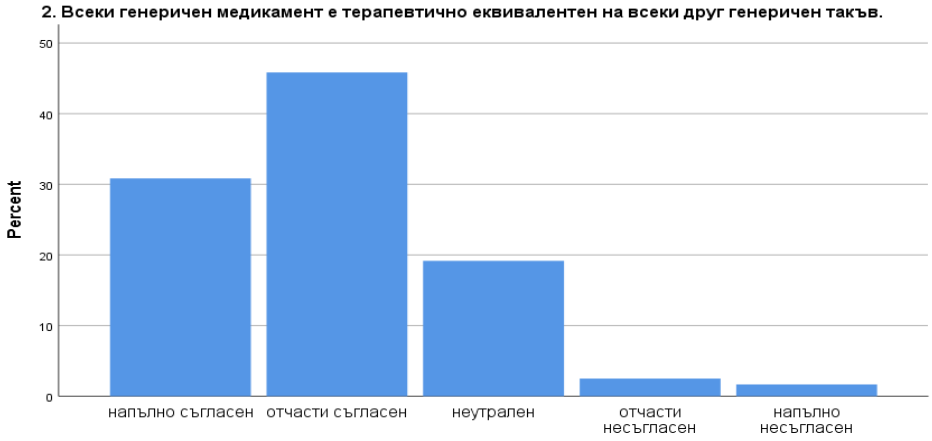

Fig. 7 Distribution of responses to statement 2

Regarding the bioequivalence of each generic drug product relative to the respective innovative product, it is noteworthy that half of the respondents (50%) partially agreed with the statement, almost one-third (34.2%) strongly agreed, 11% were neutral, and only about 4% overall expressed complete or partial disagreement (Fig. 8).

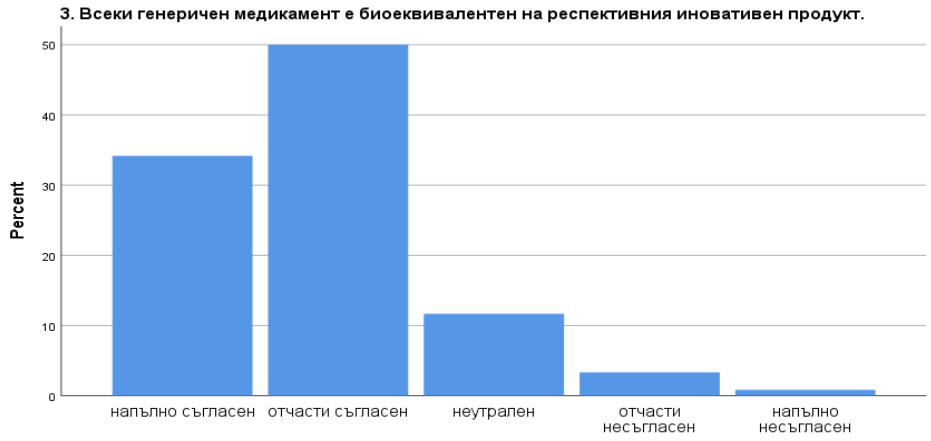

Fig. 8 Distribution of responses to statement 3.

Fully or partially agree with the need for more information on the bioequivalence results of generic medicines were 23.3% and 38.3% of respondents, respectively, 24.2% were neutral, and 10.8% and 3.3% of respondents expressed partial or complete disagreement, respectively *(Fig. 9).*

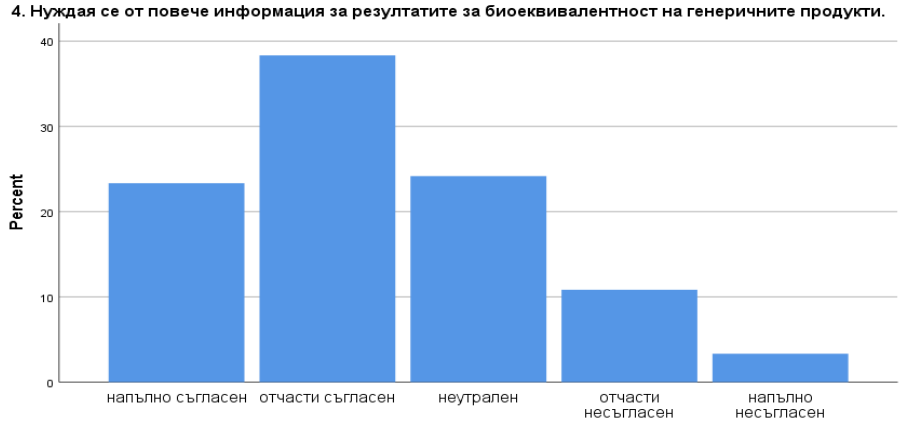

Fig. 9 Distribution of responses to statement 4

With regard to the statement that each generic medicinal product should have the same dosage form (tablets, capsules) as the respective innovative product, again just over half of the respondents partially agreed with the statement, 18.3% strongly agreed, 15% abstained from taking a side, and 6.7% and 7.5% partially and completely disagreed respectively (Fig. 10) .

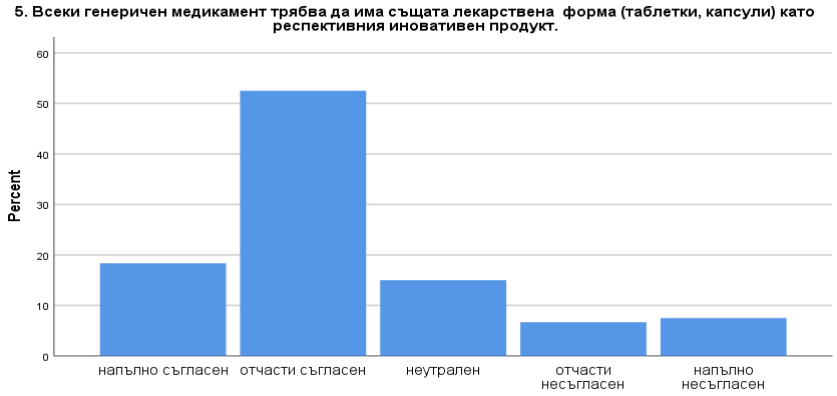

Fig. 10 Distribution of responses to statement 5

This is not such proportion of responses to the question about the lower quality of generic medicines compared to the corresponding innovative medicines. Here the majority of respondents partially or completely disagreed, 30.8% and 25.8% respectively. Fully or partially agreed were 5.8% and 20%, and neutral were 17.5% (Figure 11).

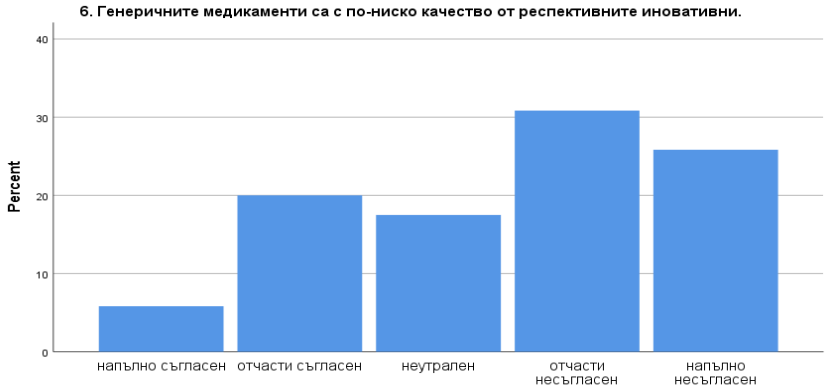

Fig. 11 Distribution of responses to statement 6.

A similar trend is observed in the responses to the seventh statement that generic medicines are less effective than the corresponding innovative products. 37.5% and 27.5% of corespondents disagreed partially or completely, respectively

Fig. 12 Distribution of responses to statement 7.

The safety of generic medicines continues to be a subject of more discussions and doubt, it is addressed in statement 8 of the questionnaire, namely: generic medicines cause more AEs (adverse events) than the corresponding innovative products. It is noteworthy that a quarter of correspondents partially or completely agreed with the statement, while 45% and 20% partially or completely disagreed, respectively (Figure 13).

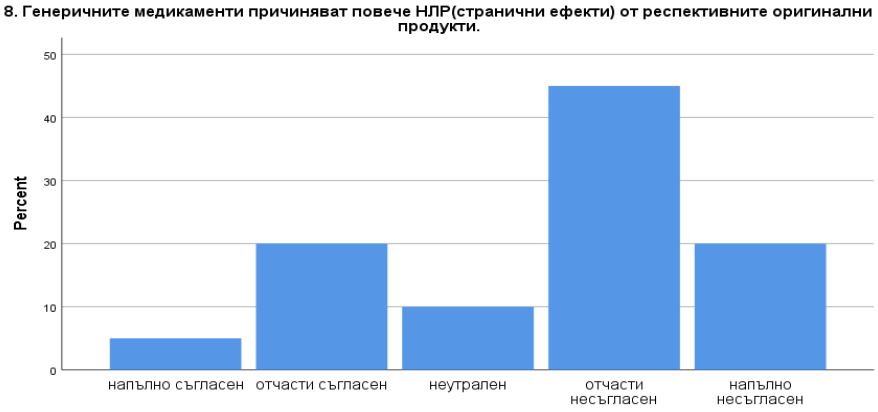

Fig. 13 Distribution of responses to statement 8.

Regarding the lower cost of generic drugs compared to the corresponding innovative medicines, most of the corespondents (64.2%) were aware of this fact and strongly supported the statement.

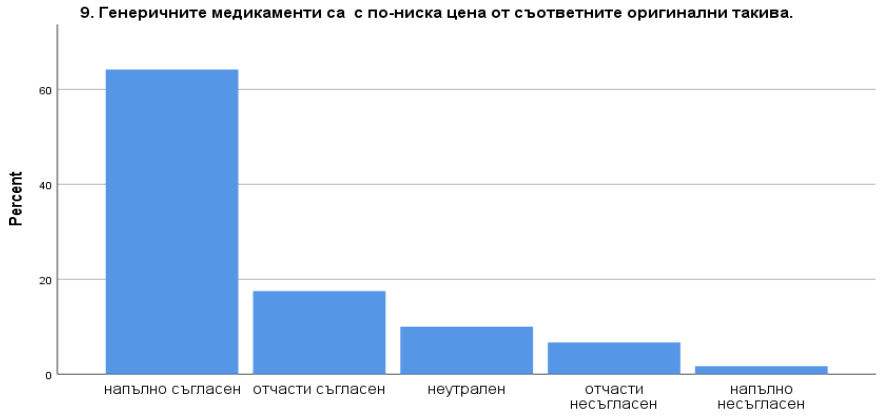

Fig. 14 Distribution of responses to statement 9.

Safety is the key point to decide using of any medical product, and accordingly it is expected that the law applies the same safety requirements to generic as to innovative products. This statement is fully or partially supported by 43.3% and 38.3% of responders respectively. 15.8% were neutral and less than 3% disagreed with this statement (Figure 15).

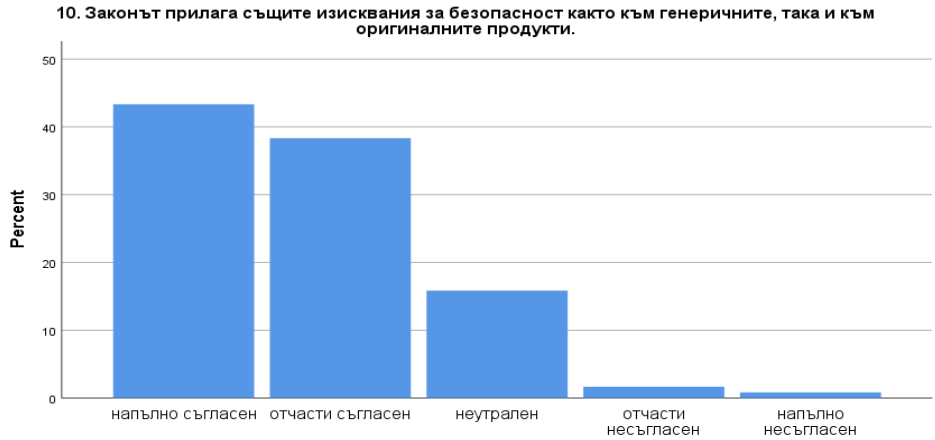

Fig. 15 Distribution of responses to statement 10.

Another important point regarding the substitutability of an innovative with a generic drug is the bioavailability of the active ingredient, which has a direct bearing on manufacturing requirements and standards. Regarding the same manufacturing quality assurance required for both generic and originator medicines, 78.3% of responders agreed with the statement, one-fifth maintained a neutral position, and less than 2% disagreed.

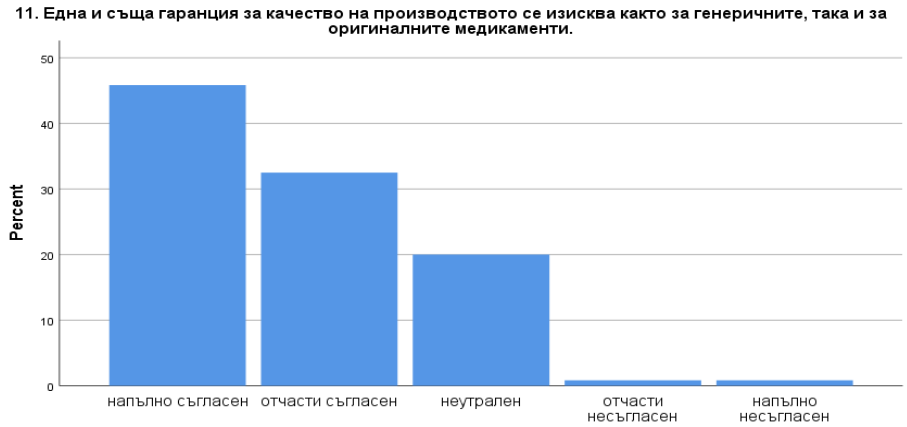

Fig. 16 Distribution of responses to statement 11.

It is an undeniable fact that generic substitution reduces the cost of treatment for patients, logically 90% of respondents agree with this statement, 5.8% are neutral and only 4.2% express their complete disagreement, which is not based on data from economic analyses on the issue, but in most cases due to personal opinion and ignorance of drug prices (Fig. 17).

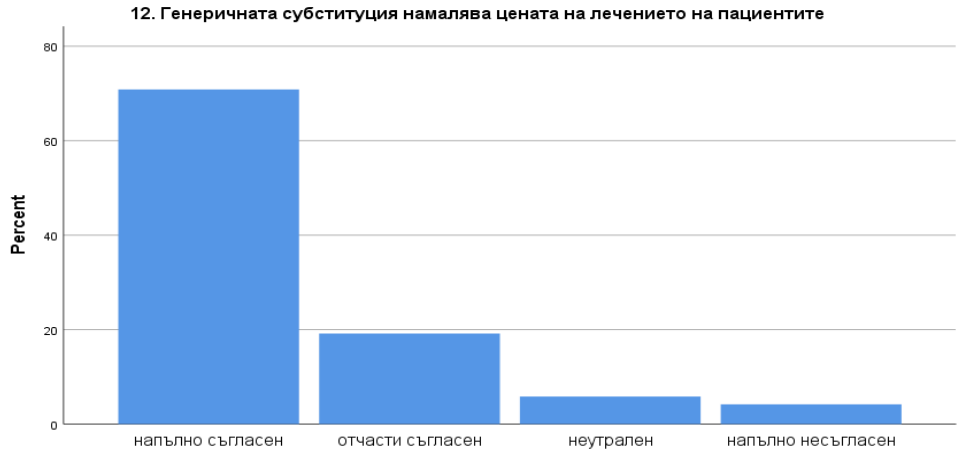

Fig. 17 Distribution of responses to statement 12.

The means of the quantification of individuals' opinions on the statements about generic medicines are arranged on a scale from 1 - strongly agree to 5 - strongly disagree, and the standard deviation indicates how large the spread of responses is. The larger the value of the standard deviation, the greater the dispersion i.e. the less the agreement. Table 3 presents the median and standard deviation for the twelve statements used.

Tab. 3. Central tendency and variance in quantifying respondents' opinions

Statement	Median value	Standard deviation
1. Each generic drug shall be therapeutically equivalent to the corresponding innovative product.	1,77	0,867
2. Each generic drug is therapeutically equivalent to any other generic drug.	1,98	0,869
3. Each generic drug shall be bioequivalent to the corresponding innovative product.	1,87	0,809
4. I need more information on the bioequivalence results of generic products.	2,33	1,055
5. Each generic product must have the same dosage form (tablets, capsules) as the corresponding innovative product.	2,33	1,086
6. Generic products are of lower quality than innovative ones.	3,51	1,237
7. Generic drugs are less effective than the corresponding innovative products.	3,65	1,207
8. Generic drugs cause more AEs (adverse events) than the corresponding innovative products.	3,55	1,166
9. Generic drug products are lower in price than the corresponding innovative ones.	1,64	1,019
10. The law applies the same safety requirements to generic as to innovative products.	1,78	0,832
11. The same manufacturing quality assurance is required for both generic and innovative products.	1,78	0,852
12. Generic substitution reduces the cost of treatment for patients	1,48	0,935

The results in the table show that the opinion of the study subjects was located between neutral and partly disagree when comparing the quality, effectiveness and adverse drug reactions, with

the dispersion being the largest, compared to the other statements. For question 10, there was agreement with the statement that the same manufacturing quality assurance is required for both generic and innovative drugs, with a mean of 1.78, which was located between strongly agree and agree. Moreover, the dispersion of responses is relatively small, with a standard deviation of 0.852 (less than 1, which is set as the range between values on the scale).

Distribution of responses for knowing innovative products

The subsequent part of the questionnaire examines the recognition of generic and innovative medicines by the surveyed physicians and pharmacists.

Since the introduction of TKIs, the treatment of lung cancer has seen a new upsurge for patients with EGFR activating mutations and provides oncologists with a potentially highly effective new option for durable and significantly greater outcomes compared to previously known therapeutic options. Logically, TKIs have established themselves as the standard approach for these patients and knowing them is essential for the good oncology practice, hence it is understandable why around 90% of respondents were familiar with the innovative and the generics. It is noteworthy that the 13% who do not know it are mainly pharmacists who work in outpatient pharmacies and do not have direct access to these medicinal products, as currently standard oncology therapy is presumptively prescribed by the hospital pharmacies of the respective cancer center and these therapies as costly ones are only prescribed by oncologists and therefor outpatient pharmacies do not work with them.

Regarding gefitinib, it is notebly that the majority of responders 86.7% (104 corespondents) were familiar with the original drug and its generic. Only 13.3% (16 corespondents) had no knowledge of the subject, and these were mostly pharmacists working in out-of-hospital care, in pharmacy settings where there is no direct handling of oncology medicines (Figure 18).

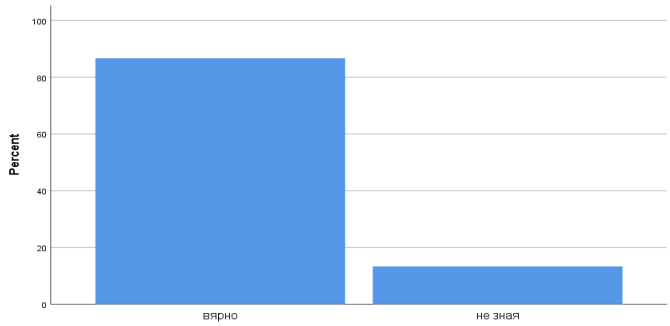

Fig. 18 Generic and innovative drug knowledge scores for gefitinib.

Absolutely similar distributions were found for erlotinib, with 86.7% (104 corespondents) being familiar with the innovative and generic drug, and 13.3% (16 corespondents) not (Fig. 19).

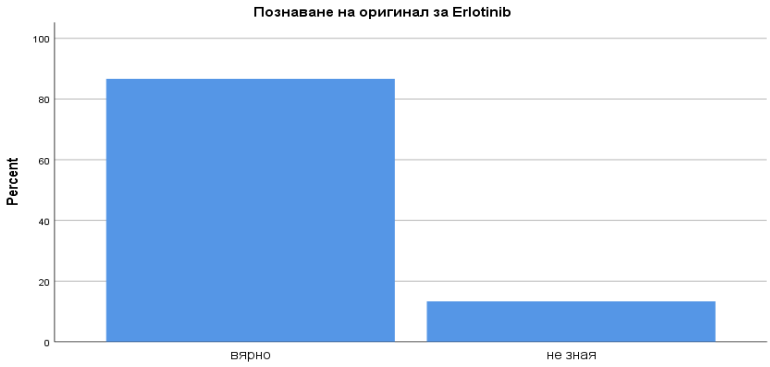

Fig. 19 Generic and innovaive drug knowledge scores for erlotinib.

Preference for use of an innovative or generic product

Of particular interest in this study are the results on preferences among physicians and pharmacists regarding the administration of an innovative medical product or its generic equivalent.

Preferences for the use of tarceva/erlotinib

In terms of prescribing preferences for Tarceva (innovative drug) or erlotinib (generic equivalent), there was a slight preponderance of preference for erlotinib (52.5%, 63 respondents) versus 46.7% (56 respondents) for Tarceva. One corespondent (0.8%) did not provide a response (Figure 20).

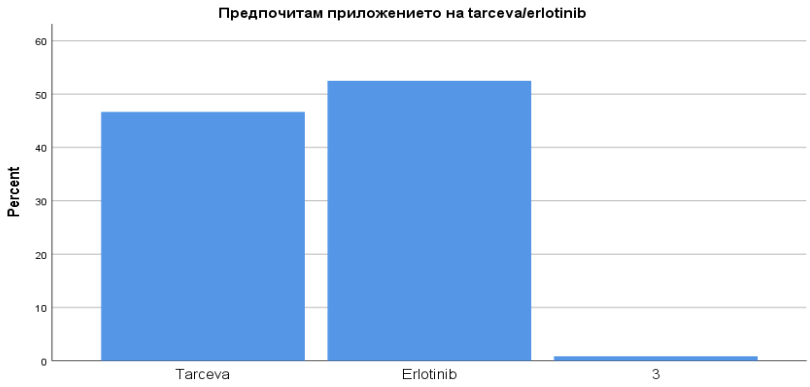

Fig. 20 Preference for administration of Tarceva versus erlotinib.

Preferences for administration of Iressa/gefitinib

Similar to Tarceva/erlotinib was the distribution for Iressa/gefitinib. 54.2% of respondents (65 corespondents) preferred the generic equivalent (gefitinib) over the innovative product (Iressa) 45.8% (55 corespondents) respectively (Fig. 21).

Fig. 21 Preference for administration of Iressa versus gefitinib.

It is also noteworthy that the preferences for generic or innovative product administration are comparable for the two groups of drugs, iressa/gefitinib and tarceva/erlotinib, respectively. Although it is generally accepted that generic medicines are comparable in efficacy to innovative ones (but at a lower cost, which justifies their greater use in the face of the increasing financial burden of cancer therapies), innovative medicines are still preferred by a not insignificant proportion of interviewees - the subgroup analysis shows that these are mainly physicians versus pharmacists. Related to this distribution is the lesser knowledge of structure, ingredients, manufacturing methodology and bioavailability by physicians versus pharmacists, and their purely personal preference to work with innovative drug products, on which relevant clinical trials are also based in the light of evidence-based medicine.

3.2. Analysis of the choice of generic or innovative therapy in oncology practice

Analysis of interrelationships and differences - Profile identification

By examining the opinions of medical professionals regarding generic and innovativemedicines, a significant research problem for us was to determine the influence of demographic and sub-occupational variables in shaping attitudes towards generic products. To this end, the relationships of the responses to the demographic block questions and the responses to the questions on the attitudes toward originator and generic drug products scale were analyzed.

Only on the variable "gender" no correlations and differences were found. This allows to accept the null hypothesis that there is no difference in the attitudes and opinions of men and women towards originator and generic medicines.

The largest number (in terms of quantity) of correlations was found with respect to the variable 'occupation'.

When differences in means were tested (t-test for independent samples), differences were found in responses to 10 out of 12 scale items and questions on knowledge of originator medicines and preference for use of specific originator and generic ones.

Physicians were more likely to disagree with the statement that "Any generic drug product is therapeutically equivalent to the corresponding innovative product." than pharmacists. The difference between the two groups was statistically significant at the sig level of significance. 0.0001.

A similar result was found when determining agreement with the statement "Any generic drug product is therapeutically equivalent to any other generic drug product. "Pharmacists showed a higher level of agreement with this statement, with a significance level of sig. 0.0001.

With the statement "Each generic drug product is bioequivalent to the corresponding innovative product." a higher level of agreement was again given by pharmacists. The difference was statistically significant with a t criterion value of 5.164 and a significance level of 0.0001.

It is more important for physicians to have additional information about generic medicines. They are more in agreement with the statement "I need more information about the bioequivalence results of generic products". The difference between their responses and pharmacists' responses were statistically different with a significance level of 0.002.

Physicians were more in agreement with the statement "Generic medicines are of lower quality than the corresponding innovative medicines.". The difference between their responses and those of pharmacists is statistically significant at the 0.007 level of significance

There was also a difference in the agreement with the statement that "Generic medicines cause more AEs than the corresponding original products.". Physicians are more in agreement with this statement than pharmacists. The level of significance of the difference is strictly sig. 0.0001.

Among pharmacists, there is a greater degree of agreement with the statement that "Generic drug products are less expensive than the corresponding innovative ones.".

The statement "The law applies the same safety requirements to both generic and innovative products." is more popular among pharmacists. Their agreement with this statement is statistically significantly different from physicians' agreement at the 0.000 significance level

Again, pharmacists are more in agreement with the statement that "Generic substitution reduces the cost of treatment for patients."

An examination of the influence of the profession practiced on responses to the scale questions revealed a relationship for most questions (at .0001 level of significance) and a strength of relationship (as measured by Cramar`s V) between medium and strong.

Here are the responses to question 9, "Generic medicines are less expensive than the corresponding innovative medicines" (Cramar`s V 0.585) for physicians and pharmacists (Figures 22 and 23).

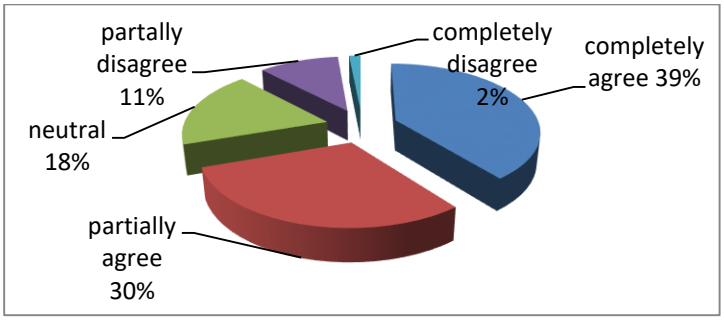

Fig. 22 Distribution of responses to question 9 for physicians

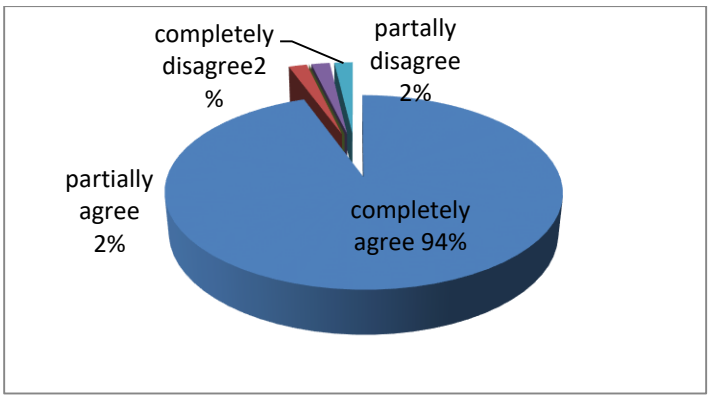

Fig. 23 Distribution of responses to question 9 for pharmacists.

Similar relationships were found for the other questions in the scale (see table below):

Твърдение	**Cramar`s V with variable "profession"**	**Level of significance**
Each generic drug shall be therapeutically equivalent to the corresponding innovative product.	0,480 (strong)	0,001
Each generic drug is therapeutically equivalent to any other generic drug.	0,497 (strong)	0,001
Each generic drug shall be bioequivalent to the corresponding innovative product.	0,551 (strong)	0,001
I need more information on the bioequivalence results of generic products.	0,335 (median)	0,009
Each generic product must have the same dosage form (tablets, capsules) as the corresponding innovative product.	0,459 (median)	0,001
Generic products are of lower quality than innovative ones.	0,526 (strong)	0,001
Generic drugs are less effective than the corresponding innovative products.	0,509 (strong)	0,001
Generic drugs cause more AEs (adverse events) than the corresponding innovative products.	0,452 (median)	0,001
Generic drug products are lower in price than the corresponding innovative ones.	0,585 (strong)	0,001
The law applies the same safety requirements to generic as to innovative products.	0,494 (strong)	0,001
The same manufacturing quality assurance is required for both generic and innovative products.	0,448 (median)	0,001
Generic substitution reduces the cost of treatment for patients	0,522 (strong)	0,001

Ultimately, this reflects the preference for the innovative drug towards the generic. Physicians show a preference for innovative products and pharmacists for generics. In the figures below (Fig. 24 and Fig. 25) the distributions of preferences can be seen.

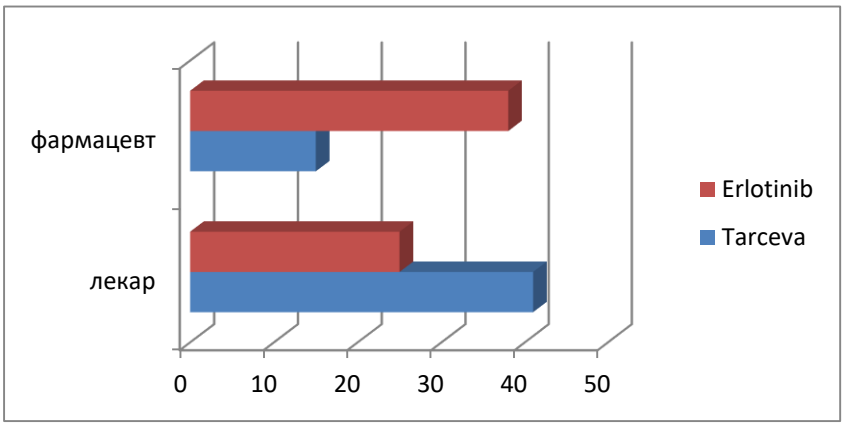

Fig. 24 Physician versus pharmacist preferences for erlotinib and Tarceva

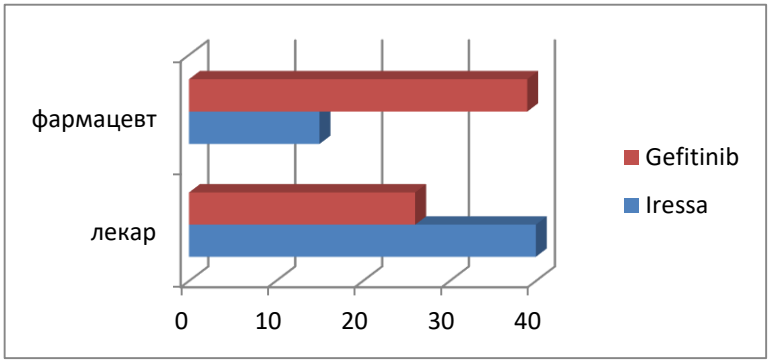

Fig. 25 Physician versus pharmacist preferences for gefitinib and Iressa.

Multiple relationships are also found between responses to the scale questions and the workplace location characteristic. There is a statistically significant difference between the responses depending on whether the respondents practice in Sofia or in other locations outside the capital.

Comparisons of the level of agreement with the proposed statements on where the professional practices showed statistically significant differences.

For example, the statement "Any generic medicinal product is therapeutically equivalent to the corresponding innovative product." was agreed with a greater extent by specialists practicing in Sofia compared to their counterparts practicing outside the capital. The new significance level of the difference is 0.001.

The responses to the statement "Each generic drug product is therapeutically equivalent to the corresponding generic." are distributed in the same way. Here again, practitioners in the capital city are more likely to agree than their counterparts elsewhere in the country.

The metropolitan practitioners are more in agreement with the statement that "Each generic drug product is bioequivalent to the corresponding innovator product." The difference is statistically significant with a t criterion value of -5.815 and a significance level of 0.0001.

Practitioners practicing outside the capital city were more in agreement with the statements "Generic medicines are of lower quality than the reference innovative products.", "Generic medicines are less effective than the reference innovative products." and "Generic medicines cause more AEs than the reference innovative products." For all statements, the significance level of the differences found with the opinion of practitioners in the capital city was significant ($p = 0.0001$).

Practitioners who have practices in the city were more likely to agree with the statement "Generic medicines are lower priced than the corresponding innovative ones." They are more agreeable with the generic medicines. The significance level of the difference is 0.012.

Professionals practicing in the capital also showed a higher level of agreement with the statements "The law applies the same safety requirements to both generic and innovative products." and "The same manufacturing quality assurance is required for both generic and innovative products."

It can be seen that, in addition to differences in responses to the scale's items, there is also a difference in preference for an innovative drug and a generic drug product.

Figure 26 presents how the professionals' preferences for the administration of Iressa/gefitinib are distributed. Notable is the significantly larger difference in the preference of those working outside the capital city for the original Iressa administration.

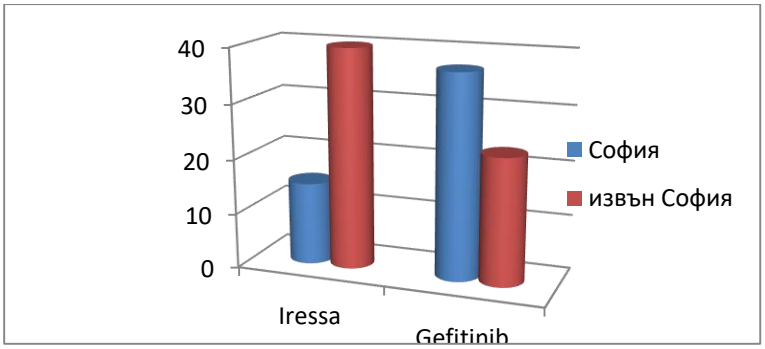

Fig. 26 Distribution of specialists' preferences for the use of Iressa and gefitinib according to practice location.

The following figure shows the distribution of corespondents' preferences for Tarceva/erlotinib administration according to their practice location.

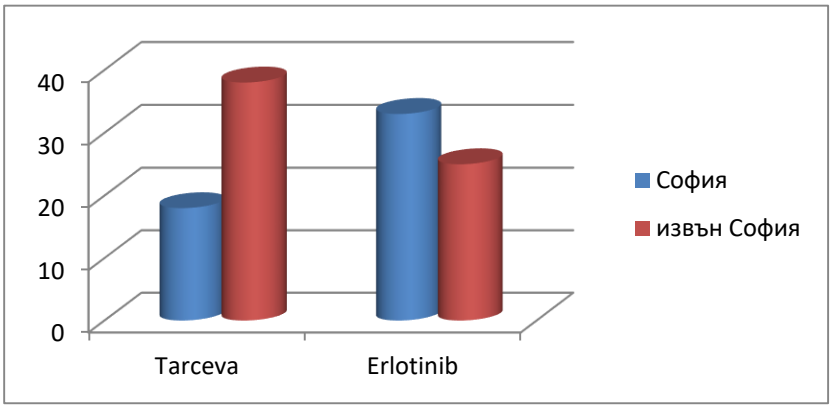

Fig. 27 Distribution of specialist preferences for Tarceva and erlotinib administration by practice location.

The figure illustrates the preferences of the practitioners in Sofia for generic drugs, and the observed differences are statistically significant (p = 0.02).

Factor analysis

In order to cluster corespondents' answers, the data were subjected to factor analysis using VARIMAX rotation method, with a limitation of clustering to three factors. In the factor analysis performed, three factors in particular emerged that were associated with higher levels of agreement with the following statements.

Factor 1 "Generic supporters" - agreement with the statements:

1. Each generic product is therapeutically equivalent to the respective innovative product.

2. Each generic medical product is therapeutically equivalent to the corresponding other generic (with the same INN).

3. Each generic medical product is bioequivalent to the reference innovative product.

5. Each generic medical product must have the same dosage form (tablets, capsules) as the reference innovative product.

9. Generic medical products shall have a lower price than the corresponding original ones.

12. Generic substitution reduces the cost of treatment for patients

Factor 2 "Opponents of generic medicines" - agreement with the statements:

6. Generic medicines are of lower quality than the corresponding innovative ones.

7. Generic medical products are less effective than corresponding innovative products.

8. Generic medicines cause more AEs (adverse events) than the corresponding innovative products.

Factor 3 "Undecided" - agreement with the statements:

4. I need more information about the bioequivalence results of generic products.

10. The law applies the same safety requirements to both generic and innovative products.

11. The same manufacturing quality assurance is required for both generic and innovative products.

The three factors resulting from the analysis delineate groups of responders that can be called "Generic Supporters" (Factor 1), "Hesitators" (Factor 3) and "Generic Opponents" (Factor 2).

Supporters are oriented entirely towards the positive effects of generic medicines. Opponents - to adverse events, and hesitators - to control and verification.
Factorization of the results allows for conditional profiles of the medical professionals who fall into each group. To this end, the results of the factor analysis were linked to demographic characteristics through correlation analysis. The table below shows the results obtained (only data highlighted in yellow are relevant for the profile).

Based on the results of the analysis, the following profiles can be distinguished:

- **Profile of generic supporters**: These are primarily pharmacists who work in pharmacies or pharmaceutical companies no matter what form of ownership, located mainly in Sofia.
- **Profile of opponents of generic medicines**: mainly physicians who work in wards, in state-owned medical institutions, located outside Sofia.
- **Profile of the hesitants**: mainly pharmacists working in Sofia.

Gender and age variables showed no influence on the factors and are not included in the profiles.

3.3 The financial parameters and costs of targeted therapy

The financial parameters and costs of targeted therapies in oncology have been steadily increasing in recent years with the introduction of new innovative molecules and the expansion of indications. The situation is similar in the treatment of lung cancer in particular. Task 3 aims to assess the financial parameters and costs of targeted therapy for lung cancer patients by applying a cost analysis to the administration of TKIs in the treatment of lung cancer. In Task 4, in addition and specificity, we aim to analyze the cost-benefit correlation of TKI administration when comparing TKI prices.

Results from a number of studies indicate that the cost of oncology drugs is increasing worldwide. Added to the high prices of anti-tumour drugs is the fact that many newly approved drugs have weak or uncertain evidence of their real clinical value. In the face of constrained healthcare budgets, the provision of cost-effective and accessible cancer care is becoming increasingly important. Unlike the US, many European countries have regulations that allow national authorities to negotiate drug prices directly with manufacturers**.**

Methods

Identification of investigational medicinal products

For the purposes of our study and in response to objectives 3 and 4, we identified all new tyrosine kinase inhibitors with initial indications for the treatment of solid tumors (specifically lung cancer) in adults approved by the U.S. Food and Drug Administration (FDA) between January 1, 2004, and December 31, 2020, from the publicly available FDA database. In our cohort, we also included antitumor drugs that were also approved by the European

Medicines Agency (EMA) for the same period by searching European public evaluation reports. Drug prices were extracted from publicly available databases in the US and in five European countries (National Health Service database for England, Spezialitätenliste for Switzerland, Lauer-Taxe database for Germany, VIDAL database for France, and NHIS database for Bulgaria), and monthly treatment costs for each individual drug were calculated based on intake (dosing) information from the CHP and the corresponding price value. Following this in-depth analysis, the relationship between the cost of drug treatment for lung cancer and clinical benefit was assessed based on both the American Society of Clinical Oncology (ASCO-Value Framework) and the European Society of Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale.

Data sources and information output

For this cost-benefit analysis, we used the Drugs@FDA11 public database to identify all TKIs for the treatment of lung cancer approved by the FDA between January 1, 2004, and December 31, 2020, with initial indications for solid tumors (advanced and metastatic lung cancer) in adults, and included in our cohort all TKIs also approved by the European Medicines Agency (EMA) for the same period by searching the EMA's European Public Assessment Reports (EPAR) database.

Average US sales prices (and, if unavailable, wholesale acquisition costs) for drugs in our cohort were extracted from the US Centers for Medicare and Medicaid Services and the RedBook database (IBM Micromedex, Armonk, NY, USA) and compared with currency-adjusted post-manufacturing drug costs for England, Switzerland, Germany, France and Bulgaria. European prices were derived from the National Health Service of England, the positive list (Spezialitätenliste) published by the Swiss Federal Office of Public Health, the Lauer-Taxe database for Germany, the VID database. Statutory rebates were also included in the analysis, as well as any additional negotiated rebates where these were publicly available (available for Germany and Switzerland).

All costs were reported in US dollars, and to estimate the clinical benefit of the respective antitumor medications included in our cohort, we applied two established cost-benefit scales: ESMO-MCBS version 1.116 and ASCO-VF version 2.17. The outcomes evaluated were those provided by the pivotal registration clinical trials supporting FDA and EMA approval. There is evidence that the FDA and EMA typically consider the same set of clinical studies when approving new drugs. Consistent with the rating scale development

methodology and previous studies, high benefit is defined as a score of 45 or more for ASCO-VF and a palliative thalapies score of 4-5 for ESMO-MCBS. Low benefit is defined as any other score. Unlike ESMO-MCBS, ASCO-VF is not designed to evaluate single-arm studies and therefore applies only to randomized clinical trials.

Statistical analysis

We calculated the average cost of treatment per month for all drugs in our cohort for which cost information was available. For each drug, we compared monthly treatment costs in the United States with average monthly costs in England, Switzerland, Germany, and France and then correlated the resulting cost differences with high versus low clinical benefit.

To assess the relationship between drug treatment costs and clinical benefit, we first used a hierarchical linear regression model to compare monthly treatment costs with high versus low clinical benefit, treating monthly treatment costs across the six different countries as repeated measures. We then calculated the Spearman's rank correlation coefficient (r) between monthly drug treatment costs and benefit (according to ASCO-VF and ESMO-MCBS) for each country for TKIs in lung cancer treatment, respectively. We calculated the average cost of treatment per month for all drugs in our cohort for which cost information was available. For each drug, we compared monthly treatment costs in the United States with average monthly costs in England, Switzerland, Germany, France, and Bulgaria and then analyzed the correlation between the resulting cost differences with high versus low clinical benefit (Table 4).

Table 4 TKIs in the treatment of lung cancer with price distribution.

Медикамент	Първоначална индикация, одобрена от FDA и EMA	Година на одобрение FDA	Година на одобрение EMA	Цена в САЩ $	Цена в Англия $	Цена в Швейцария $	Цена в Германия $	Цена във Франция $	Цена в България $	ASCO-VF†‡	ESMO-MCBS score
Gefitinib	НДБК	2003	2009	8 141	8	-	4 185	4 532	2 496	49.1	4
Erlotinib	НДБК	2004	2005	8 832	7 102	7 345	6 208	5 987	3 005	42.1	4
Crizotinib	НДБК	2011	2012	16 859	5 710	5 412	4 835	4 866	3 580	63.37	4
Afatinib	НДБК	2013	2013	8 807	2 112	2 689	1 764	1 667	3 273	53.81 31.7?	4
Ceritinib	НДБК	2014	2015	10 554	3 597	3 513	2 943	3 253	4 001	NA	2
Osimertinib	НДБК	2015	2016	14 763	7 026	6 481	5 108	6 640	6 630	NA	3
Alectinib	НДБК	2015	2017	14 947	6 565	5 871	5 312	5 432	4 980	NA	3
Brigatinib	НДБК	2017	2018	15 946	6 393	...	6 529	...	3 903	NA	3
Nintedanib	НДБК	2014	2014	11 302	6 890	6 430	6 023	5 702	4 903		3

Results

Our analysis was conducted in January-February 2021 and subsequently updated as of May 1, 2021. Our cohort of study medications includes 9 medications that had initial regulatory approval from the FDA and EMA for the study period. All drugs are approved for solid tumors and are tyrosine kinase inhibitors (TKIs) in the treatment of non-small cell lung cancer (Table 1). Our cohort for statistical analysis included these 9 drugs with prices available in at least one of the assessed countries (USA, England, Switzerland, Germany, France and Bulgaria, respectively).

The results for the average prices of the respective TKIs are presented in the table. It is noteworthy that oncology drug costs per month in the USA were on average 2.31 times higher than their corresponding average costs in the five European countries considered (IQR (interquartile range) 1.79-3.17). In repeated measures analyses of these drugs approved for the treatment of non-small cell lung cancer collected in all countries assessed, we found no significant difference in monthly treatment costs between drugs with high clinical benefit compared with low benefit according to ASCO-VF and ESMO-MCBS.

There was no association between the difference in prices between the US and European average price lists and ASCO-VF or ESMO.

3.4 Analysis of the financial burden of cancer therapies in Bulgaria

Through Task 5 we aim to analyse the financial burden of cancer therapies in the country by assessing the cost of cancer drugs in Bulgaria in order to position and justify the use of generic drugs.

Methods

Identification of the costs of oncology drugs in Bulgaria

For the purpose of our study and in response to the set task 5, we conducted an analysis of the costs of oncology therapies for the last 5 years (the period 2017 - 2020) and a comparison with the data from 2015 was also made. In our cohort, we included the anti-tumour medicines (including chemotherapy and targeted and immunotherapies) that have and have been authorised for use in Bulgaria for the relevant period and are reimbursed (fully paid) by the National Health Insurance Fund (NHIF). Following this in-depth analysis, the trend in the cost

of oncology drugs and the burden on the budget of the healthcare system in Bulgaria was assessed, as well as attempts to optimize them.

Data sources and information output

For this cost analysis, we used the public database published on the NHIF website regarding the costs of treatment of diseases in the country, filtering those that concern cancer patients and in particular their drug treatment for the period 2017 - 2021 by comparing them with the data from the National Institute of Statistics on the population in Bulgaria, the incidence of cancer in Bulgaria and worldwide according to the current Globocan data.

The case of price increases of oncology drugs usually involves several parties: pharmaceutical companies as suppliers of the respective drugs, the NHIF or the health system as regulators and payers of the respective therapies, and last but not least, patients and society as users of the respective services. According to the pharmaceutical companies, these rising costs are due to completely objective reasons: the ageing population, the increased number of patients diagnosed with cancer, increased life expectancy, including thanks to new medicines. At the same time, the development of any new drug is subject to huge investment and expenditure on the part of the innovative companies, and therefore the molecules that reach the market have to recoup the investment both for these molecules and for the unsuccessful developments, logically their cost is high. However, according to the health authorities, along with objective reasons, costs are rising due to the lack of adequate optimisation of drug dispensing and administration, which predisposes to stimulate the financial burden on the health system. For their part, patients and the public expect timely, precise treatment in line with current therapeutic trends, regardless of the cost, especially when it comes to a vulnerable group of patients such as oncology patients.

In recent years, many legislative changes have been introduced, including health technology assessment and rebates, with pharmaceutical companies sharing the risk of rising drug costs and returning money back to the treasury. In 2017, for example, pharmaceutical companies returned 168 million leva back to the NHIF budget compared to 87 million leva in 2016 and 47 million leva in 2015. In view of the lifted moratorium, the rebates for 2018 are even higher, with the trend continuing until 2021.

At the same time, new and novel molecules are entering the therapeutic aspect, generating hundreds of millions of leva in expenditure and, given the growing number of patients, the

NHIF continues to face the growing needs and increasing financial burden of oncology therapies.

Results

Population of Bulgaria based on the NSI data has been decreasing in recent years with 7.1 million in 2017 and 6.8 million in 2021. However, in spite of the decrease in population, funds for cancer therapies and hospitals for active treatment of cancer diseases in Bulgaria have been increasing over the years. These data do not fully correlate with better survival outcomes for cancer in Bulgaria. According to the European Cancer Registry (ENCR), in 2012 the average standardised mortality rate (ASR (En)) in the country of all ages and both sexes was - 245.0, and in 2020 - 258.4. In terms of absolute numbers, the number of cancer deaths in 2012 was 17.9 thousand and in 2020 - 19.3 thousand.

At the same time, funds for oncology drugs and the number of treatment facilities have increased significantly. Expenditure on oncology drugs is increasing, having almost tripled from 2015 (when it was around 246 million BGN) to 2021 to 708 million BGN (actually 571 million BGN after the rebates from the industry that the NHIF is obliged to provide). In 2015, there were 16 health care facilities that provided drug treatment, and in 2021 there are 42 health care facilities. This is largely due to the entry of private oncology facilities, which work with and report to the NHIF the treatment of oncology patients. Before 2015, the treatment of oncology patients was carried out in 13 complex oncology centers in the country, 2 oncology centers for Sofia city and Sofia region in Sofia and the National Oncology Centre in Sofia. Today, private structures operate throughout the country and report activity to the NHIF, bringing the number of hospitals providing active treatment to oncology patients to 42.

Double growth of drug therapy costs in the last 5 years

The growth in the NHIF's spending on drugs is mainly due to the entry of new drugs in the fields of oncology, rheumatological diseases and rare diseases. Oncology has seen an increase in the number of patients for whose chemotherapy the NHIF pays. The number in different years ranges from 34,000 to just over 62,000, with a decrease in cancer patients diagnosed and treated in 2020 in the face of the COVID-19 pandemic, offset by newly diagnosed and treated cases in 2021 (Table 5).

Table 5 Number of cancer and cancer haematology patients whose drug treatment was paid for by the NHIF under Annex 2 of the PPS in the period 2017-2021 (includes patients receiving active therapy including chemotherapy, targeted therapy and immunotherapy)

Year	**2017**	**2018**	**2019**	**2020**	**2021**
Number of patients	34275	31022	41804	36 636	62692

Spending on oncology drugs has been rising, almost tripling from 2015 (when it was around 246 million BGN) to 708 million BGN in 2021 . According to NHIF data, over the last five

years - from 2017 to 2021 - NHIF spending on treating patients with cancer has roughly doubled, from BGN 364m to BGN 708m (actually BGN 571m after industry rebates, which NHIF is obliged to pay for), and this has been associated with an increase in patients receiving therapy (Table 6).

Table 6 NHIF spending on cancer patient treatment for the period 2017-2021.

year	2017	2018	2019	2020	2021
Cost in BGN	364.056 / 327 million BGN	415.713 million BGN	496.960 million BGN	632.580 million BGN	708.210 million BGN

For different therapies, the rise in costs is due to different reasons. The average cost of treating a cancer patient has risen from 5 thousand. In 2013, to BGN 10 thousand in 2017, subsequently increasing to more than BGN 16 thousand in 2019, with the upward trend continuing in subsequent years (Table 7).

Tab. 7 Average cost for oncology or oncohaematology patient in a hospital

Year	**2013**	**2017**	**2019**
Cost in BGN	5240	10622	16349

And if the average cost of treating a patient in 2017 is 10 000 leva in general, the average cost of treating a patient with the new molecules in oncology for the last five years reaches 40 000 leva.

The cost alone is not the most important thing, as it is far more important whether the new therapy is superior and produces a qualitatively better therapeutic result than the old one, i.e. whether it increases survival compared to standard therapy or whether it leads to a complete cure, which was not possible before, etc.

Equally important, however, is how it is prescribed, whether it is preferred to the old one solely because of certain benefits in terms of therapeutic outcomes or because of other subjective factors on the part of the doctors prescribing the therapy in question in the increased number of medical oncology clinics and departments in the country.

Furthermore, an analysis by the NHIF last year showed large differences of up to ten times in the cost of treating a cancer patient in different hospitals in the country, with the most expensive treatment not being in university hospitals.

The costs of new molecules have increased several times since their introduction

Specifically in oncology, the rise in costs is undoubtedly due to the entry of innovative and costly therapies that drive up the cost of treating patients. The NHIF data show that after the

first year of their entry, the costs of new molecules in the next two to three years increase by a factor of 2 to 6. Therefore, it is quite logical that, against the background of such pronounced financial toxicity, the NHIF should look for various options to optimise the budget in order to cut costs, and given that the moratorium on new molecules has been lifted, and new and more expensive molecules are coming with each passing year.

In 2014, for example, new molecules in the field of oncology generated a cost of nearly 4.5 million leva. These same molecules in their second year of entry, due to the increase in the number of patients treated with them, generated 11.6 million leva. Although the number of patients treated with the respective "new" molecules increased in the following years, the costs generated are now slightly decreasing due to price erosion caused by internal and external competition - BGN 10.6 million and BGN 9.7 million for the third and fourth years respectively.

Naturally, the jump in the cost of oncology therapies is not unambiguous, as the appointment of the new innovative therapies frees up resources from the old ones that would have treated the patient. However, the doubling of the cost of treating a cancer patient in 5 years is itself telling enough of the trend.

Innovation in oncology should lead to better outcomes in terms of treatment effect and therefore survival. But based on the 2020 data, it can be assumed that this does not always correspond to the actual facts given the correlations for morbidity, mortality, DALYs, YLDs, YLLs.

4. DISCUSSION

Today, a number of innovative drugs promise us an improvement in therapeutic results, and in most cases the facts support this thesis. In the era of innovation in oncology, it is innovative therapies that hold the key to better treatment strategies. Increasingly, a new generation of antitumor cancer drugs is leading to durable remissions and potentially cures. In particular, the development of new cancer drugs leads to more favorable toxicity profiles, increased convenience especially associated with the use of oral agents. Thus, the changing treatment algorithm found its place in the therapeutic behavior of non-small cell lung carcinoma, giving new hope for improving survival.

However, the enthusiasm of physicians and patients is often tempered by the real financial burden these expensive drugs place on the healthcare system, often with the price not always

proportional to the results. Although drug costs can be high, they are only one of the many costs that cancer patients face. It is the term financial toxicity that describes the negative impact of cancer treatment costs on patients' well-being.

Globally, cost is one of the main reasons why patients are denied access to newer cancer drugs. Therefore, methods for cost optimization are being sought in real practice. Here, as such, the European and American Oncology Societies (ESMO, ASCO) scales, respectively the ESMO-MCBS and ASCO-VF clinical benefit scales, are used to clearly show which drugs provide the greatest benefit to patients. By showing which drugs are most likely to be worth the higher price, we can hope to improve access to the most expensive drugs so that patients receive standardized, optimal therapy wherever they live. Regarding tyrosine kinase inhibitors in the treatment of lung carcinoma impresses with an extremely high score on both scales, which is associated with more advantages and benefits for patients, and thus with better outcomes, despite the high cost.

The entry of generic drugs into the market usually has a significant impact on the cost-effectiveness of the drug and is another method of cost optimization. The use of generic alternatives to original drugs has already been identified as a key area for reimbursement in non-oncology healthcare settings, such as primary care and cardiology, and is already a fact in oncology clinical practice, although some bias still exists among healthcare professionals. Considering the high incidence and mortality from lung cancer in Bulgaria, it is logical that the treatment of these patients, in addition to being a therapeutic and diagnostic challenge for doctors, against the background of expensive innovative treatment strategies, also represents a serious financial resource for the health system. This makes the analysis of the positioning of generic versus innovative TKIs for the treatment of lung cancer in Bulgarian clinical practice extremely valuable in parallel with the assessment of the financial toxicity of oncology therapies in Bulgaria.

Generic medicines play an important role in the European healthcare system and economy. Not only do generic medicines affect the market (contribution to market supply), the budget (significant cost savings) and the macroeconomic sector (employment, investment), but they also positively affect patients by improving their health outcomes and adherence the treatment.

Based on our analysis, it seems that the preferences for the application of a generic or original product are comparable for the two studied tyrosine kinase inhibitors - Iressa/gefitinib and Tarceva/erlotinib respectively. Although it is generally accepted that generic products are

comparable in effectiveness to the original medicinal products (however, their price is lower, which justifies their greater use against the background of the growing financial burden of oncology therapies), the innovative medical product is still preferred by a considerable part of the interviewees – from the subgroup analysis it is clear that these are mainly doctors over pharmacists. Related to this distribution is the lesser knowledge of the structure, ingredients, production methodology and bioavailability of the drug on the part of the physicians compared to the pharmacists and their purely personal preference to work with innovative medicinal products on which the relevant clinical studies are based and taken into account evidence-based medicine.

As healthcare systems are under increasing pressure to deliver improvements in healthcare, costs are becoming prohibitive and budgets are under pressure. In order to create financial flexibility, it is necessary to develop, implement and gradually increase the use of a new replacement model for innovative medicines (where possible).

Modifying conventional analytical cost-effectiveness models to be broadly applicable is a potential solution to meet the needs of policy and decision makers to evaluate innovative therapies on a case-by-case basis, which in turn addresses persistent resource constraints of skilled labor and financing. Various economic evaluation models implemented in a number of European countries can be disseminated as efficient and accessible tools requiring less user experience to provide meaningful value-based information from locally applicable and population-based baselines.

Most European countries regulate the prices of generic medicines using policy instruments such as external and internal reference pricing, mainly to reduce drug costs and generate savings that can be used to expand access to both innovative and generic medicines .

Bulgaria's healthcare system faces several major challenges at the same time. The country's population has the lowest life expectancy in the EU in 2021 and an alarmingly high prevalence of behavioral risk factors (smoking, alcohol abuse, rising obesity), as well as a highly aging population, labor shortages and low healthcare costs. Bulgaria will have to choose wisely how to strategically spend its limited resources and maintain the sustainability of the health system. The health system is not effective in reducing susceptible or preventable mortality, which is reflected in persistently high mortality from diseases such as cardiovascular disease and increasing mortality from cancer, diabetes and non-communicable diseases.

Healthcare financing is characterized by low total costs as well as very high patient out-of-pocket payments. Although health spending growth has outpaced the economy as a whole in

recent years, the revenue base needs to expand to protect against economic shocks, low employment, a large informal sector and a worsening dependency ratio due to aging.

It remains a challenge for the health system in Bulgaria how to adequately minimize the repeatedly increased costs of drugs in oncology in order to reduce the burden of financial toxicity and improve control. In view of all these factors and the growing need for improvements in health care and its financing, the health authorities are undertaking a number of activities to reduce costs, among which is tracking the therapeutic effect of new molecules in order to collect data on these medicinal products from their use in practice and subsequently, the results should be used to assess whether to continue to be paid by the health fund and, last but not least, generic substitution, including in relation to oncology therapies, as long as it is therapeutically justified and possible.

5. CONCLUSIONS

For task 1:

1.1 Supporters of generic substitution in the application of EGFR TKI in the treatment of lung cancer are entirely oriented towards the positive effects of generic medicinal products. Opponents - to adverse events, and those hesitating - to control and verification.

1.2 Conditional profiles of the medical specialists who fall into each group are defined, and based on the results of the analysis, the following profiles can be distinguished:

• Profile of supporters of generic products: These are primarily pharmacists who work in pharmacies or pharmaceutical companies regardless of the form of ownership, located mainly in Sofia.

• Profile of the opponents of generic medicinal products: First of all, physicians who work in departments, in public medical institutions, located outside Sofia.

• Profile of hesitators: pharmacists working in Sofia.

For task 2:

2.1 A large part of the respondents prefer a generic to an innovative product, but among the supporters of the original product prevail mainly physicians.

2.2 Regarding preferences for prescribing Tarceva (original drug) or erlotinib (generic equivalents), there was a slight predominance of preferences for erlotinib over Tarceva. The distribution is similar for Iressa and gefitinib.

For task 3:

3.1 Oncology drug costs per month in the US were on average 2.31 times higher than their corresponding average costs in the five European countries examined.

3.2 There is no connection between the price difference between the US and the average European price lists and ASCO-VF or ESMO-MCBS.

For task 4:

4.1 In multiple analyzes of measures of these drugs approved for the treatment of non-small cell lung cancer pooled across all evaluated countries, we found no significant difference in monthly treatment costs between drugs with high clinical benefit compared with low benefit according to ASCO-VF ($p = 0.25$) and ESMO-MCBS ($p = 0.25$).

According to task 5:

5.1 Despite the decrease in the population in Bulgaria, the tendency to increase the newly diagnosed cases of oncological diseases is maintained.

5.2 There is a tendency to increase the number of private medical facilities where oncology therapy is being given and used accordingly.

5.3 For the last five years, a double increase in the costs of drug therapy has been reported.

5.4 Costs for new molecules increase several times after their entry.

5.5 The visible increase in costs necessitates the introduction and application of generic drugs in oncology.

6. CONTRIBUTIONS

1. The opinion of two professional groups with the greatest influence in determining drug policy and the therapy of patients with lung cancer - physicians and pharmacists - was examined and the demographic and professional profiles of the proponents and opponents of generic drugs were identified.

2. The trends for the development of oncology care in Bulgaria have been studied, including those for costs of oncology drugs, and based on them, key statements have been formulated for positioning generic substitution in oncology and reducing drug costs.

3. Based on in-depth analysis, generic products in oncology are positioned as an adequate model for replacing innovative medicines and for the implementation and gradual increase of their use (where possible).

7. RECOMMENDATIONS

Drug policy has a strategic impact on public health. It is related to providing the population with sufficient volume and necessary for treatment medicinal products, as well as creating a favorable environment for the development of the necessary pharmaceutical care. Modern drug policy approaches are an important factor in managing public spending in healthcare, ensuring access to therapy for patients in need, and ensuring the financial stability of health systems. These recommendations aim to improve the quality of life of Bulgarian citizens by improving access to medicines.

Bulgaria has not yet adopted drug policies that ensure long-term results in improving cost-effectiveness by regulating the supply and demand of medicinal products – changes in the prescribing model to accelerate generic uptake, pharmaceutical generic substitution, risk-sharing agreements, reverse pay policies, etc.

The lack of a comprehensive set of drug strategies in Bulgaria leads to undesirable results of a continuous significant increase in public spending on medicinal products. The recommendations for updating drug policies in Bulgaria in order to reduce public and private spending on medicinal products are as follows:

1. Recommendations to the Bulgarian Drug Agency (BDA)

In Bulgaria, the body that evaluates the safety, quality and efficacy of medicinal products with a view to granting a marketing authorisation is the Bulgarian Drug Agency (BDA). BDA takes over the main organization of the processes of regulation, registration of new drugs at management level.

The following recommendations are outlined:

- When including innovative medicinal products in the Positive Drug List, risk-sharing agreements must be concluded. In cases where post-marketing studies do not confirm the therapeutic efficacy and safety results of randomised clinical trials, marketing authorisation holders shall reimburse public resources for medicinal products.

- Innovative medicinal products with unfavourable cost-effectiveness indicators (cost-benefit ratio and therapeutic outcome) not to be included in a Positive Drug List and not reimbursed by the public health system.

- Establishment of a specialized structure with functions in health technology assessment and pharmaco-economic analysis in our country, which has the status of a State Agency in order to achieve independence and impartiality.

2. Recommendations to the National Health Insurance Fund (NHIF)

The NHIF should, as a payer, be involved in the process of introducing new generic drugs, the level of their reimbursement and their accessibility to patients. Recommendations to the institution:

- The inclusion of innovative therapies is associated with high costs. In this regard, it is necessary to introduce contracts and risk-sharing schemes in order to limit the budgetary impact to be concluded by the payer in the event of agreeing on acceptable terms and to be a prerequisite for the inclusion of therapy in the reimbursement system.
- A constant process of evaluation of current treatments, information on costs, etc. This information is currently difficult to access, and difficult to make analysis and evaluation without the participation of experts from the NHIF.
- A permanent process of evaluation of existing medicinal products, their alternatives, accessibility and availability in the country.
- -The NHIF should support the process through joint activities with public health training institutions in order to expand knowledge and collaboration between future experts and the institution.

3. Recommendations to the Ministry of Health

- Need for changes in the legal and regulatory framework - the prescription of medicinal products is carried out mainly by trade name both in hospitals and in outpatient care, and substitution is not allowed in the pharmacy for prescription drugs that are covered by the National Health Insurance Fund (NHIF). As a result, many prescriptions are written and dispensed by trade names that are more expensive than the reference or comparative price, which increases the cost to patients and the health system. Consideration should be given both

to mandatory prescription under an international nonproprietary name (INN) and to give pharmacists the right to replace an original trademark with a generic drug on dispensing. In cases where a prescription is written for a drug that has a generic competitor, patients should have the right to receive it.

4. Recommendations to the media

- For an active generics policy, awareness campaigns also need to be undertaken to encourage widespread acceptance of generic medicines among patients and prescribers. A programme should be developed to promote the safety and quality of generic medicines, to raise awareness of the actual cost of medicines and to save money by choosing generic options in the pharmacy.
- In order for the public to benefit most effectively from the periodic reduction in the prices of medicinal products, it is necessary to establish a mechanism to ensure that every patient is informed about the cheapest medicinal product belonging to the international non-proprietary name necessary for its treatment.

8. SCIENTIFIC STATEMENTS

DISSERTATION RELATED PUBLICATIONS

M. Tsonkov, A. Velkova. Economic Impact of Oncological Therapies on Public Funds for Healthcare, Journal of Clinical and Surgical Oncology, BCI, Volume 2, Issue 1, 2022, p. 18

M. Tsonkov, A. Velkova, N. Chilingirova. EGFR tyrosine kinase inhibitors in the treatment of lung cancer, journal Nauka OncoHematology, Arbilis, issue 1, 2022, p. 14

M. Tsonkov, A. Velkova, A. Serbezova, N. Chilingirova. Financial and Economic Burden of Antitumor Drugs in Oncology, Rheumatology Journal, Bulgarian Rheumatological Society (in press)