PHARMACIA

Pharmacia 71: 1–19
DOI 10.3897/pharmacia.71.e126016

Research Article

Analysis of the pharmacoeconomic effectiveness of the tyrosine kinase inhibitors therapy in patients with chronic myeloid leukemia in a Single Hematology Center in Plovdiv, Bulgaria

Veselina Goranova-Marinova[1], Daniela Grekova-Kafalova[2], Kalina Andreevska[3], Vania Georgieva[4], Yana Gvozdeva[2], Margarita Kassarova[2], Zhanet Grudeva-Popova[5], Evelina Gavazova[2], Valentina Petkova[6]

1 *Section of Hematology, First Department of Internal Medicine, Faculty of Medicine, Medical University – Plovdiv, Plovdiv, Bulgaria*
2 *Department of Pharmaceutical Sciences, Faculty of Pharmacy, Medical University - Plovdiv, Plovdiv, Bulgaria*
3 *Educational-Scientific Laboratory of Social Pharmacy, Department of Physical Chemistry, Faculty of Chemistry and Pharmacy, Sofia University "St. Cl. Ohridski", Sofia, Bulgaria*
4 *Department of Health Care Organization and Management, Faculty of Public Health and Health Care, "Prof. Dr. As. Zlatarov" University, Burgas, Bulgaria*
5 *Department of Clinical Oncology, Faculty of Medicine, Medical University – Plovdiv, Plovdiv, Bulgaria*
6 *Department of Social Pharmacy, Faculty of Pharmacy, Medical University - Sofa, Sofia, Bulgaria*

Corresponding author: Valentina Petkova (veselina.goranova@ mu-plovdiv.bg)

Received 23 April 2024 ♦ **Accepted** 5 May 2024 ♦ **Published** 26 June 2024

Citation: Goranova-Marinova V, Grekova-Kafalova D, Andreevska K, Georgieva V, Gvozdeva Y, Kassarova M, Grudeva-Popova Z, Gavazova E, Petkova V (2024) Analysis of the pharmacoeconomic effectiveness of the tyrosine kinase inhibitors therapy in patients with chronic myeloid leukemia in a Single Hematology Center in Plovdiv, Bulgaria. Pharmacia 71: 1–19. https://doi.org/10.3897/pharmacia.71.e126016

Abstract

Summary: Chronic myelogenous leukemia (CML) is a pluripotent hemopoietic stem cell malignancy characterized by the presence of a BCR-ABL1 fusion gene derived from a balanced translocation between the long arms of chromosomes 9 and 22 [t(9;22) (q34; q11)] known as the Philadelphia (Ph) chromosome. CML is an acquired hematopoietic stem cell disease common to myelo- and lymphopoiesis, characterized by uncontrolled proliferation of granulopoiesis (Shuvaev et al. 2015; Yordanov and Varbanova 2019).

Relevance and goals: Second-generation tyrosine kinase inhibitors (TKIs) (nilotinib, dasatinib, and bosutinib) have an advantage over imatinib (first-generation) in the frequency and speed of achieving cytogenetic and molecular responses in the treatment of chronic myelogenous leukemia (CML), but they cause severe adverse effects and are much more expensive than imatinib, especially if we compare them to the prices of the registered generic products of Imatinib and Dasatinib. "Novartis Tasigna® trial shows superior results to Glivec® in patients with early-stage chronic myeloid leukemia", reported on 10/20/2021 by Pierre Perrin-Montlouis. In the first direct comparison of these two oral therapies back in 2009 (Tasigna (nilotinib) 2009), as first-line treatment for CML, the results of Tasigna showed statistically significant improvement over Glivec in every measure of efficacy, including major molecular response (MMR), complete cytogenetic response (CCyR) and prevention of progression to accelerated or blast phase, with responses achieved faster in the Tasigna group than in the Glivec group. Furthermore, in the last ten years, CML patients who have achieved a stable deep molecular response for at least 2 years have been included in clinical trials for the management of treatment-free remission (TFR) (Kim et al. 2013; Saußele et al. 2016).

On the other hand, the ever-increasing costs of diagnosis, treatment and monitoring of the response of CML to the various therapeutic strategies require conducting pharmacoeconomic analyses of the cost-effectiveness and cost-utility types in order to evaluate which are the cost-effective strategies with a view to introducing them into therapeutic practice. The present study aims to analyze the pharmacoeconomic efficiency of the TKI inhibitors used by the patients with CML-CP in the first and second lines, treated in the hematology clinic at UMHAT "St. George", MU- Plovdiv during the period 2018–2022.

Methods: An economic analysis of the medicinal use of TKIs for a 5-year period (2018–2022) was performed at the national level according to data from the National Health Insurance Fund and the availability, accessibility, and usability of original and generic TKIs in Bulgaria were evaluated. The direct medical costs for the therapy of all patients were calculated, including the costs of the TKI therapy, laboratory tests, and monitoring of the molecular response for the entire treatment period from the appointment of the TKI therapy until the end of 2022. A comparative analysis was conducted to assess the cost-effectiveness of the different therapeutic strategies with TKIs on the first and second lines of treatment of patients with CML-CP in the hematology clinic at UMHAT "St. George" Medical University, Plovdiv, using the decision analysis method and conducting one-way and probalistic sensitivity analyses.

Results: The sensitivity analyzes of all pharmacoeconomic models showed the robustness and reliability of the obtained results. The threshold limits of medical costs and the frequency of achieving a deep molecular response determining the choice of first- and second-generation tyrosine kinase inhibitors as first- and second-line therapy for patients with chronic myeloid leukemia in the chronic phase have been determined. Prescribing doctors prefer the original MPs to generic analogues, which is also assumed by the current regulations, according to which even for expensive MPs dispensing by protocols, the prescription is by trade and not by international non-proprietary names (INN), which is why the use of the much cheaper generic MPs is negligibly low compared to original MPs. A personalized approach to the patient's therapy and monitoring the patient's molecular response to it, as well as stopping therapy in 25–30% of patients suitable to stop it safely when in TFR phase with a probability of more than 50% of not having a relapse will save additional costs that, by improving the cost-effectiveness of therapy for patients with CML, will be directed towards the treatment of new patients with this or other diseases.

Conclusion: These pharmacoeconomic models can be applied to improve diagnostic and therapeutic standards in clinical practice and for the efficient use of the very limited resources for health care in countries like Bulgaria. The conducted cost-effectiveness analyses confirmed that the hematologists at the University Center in Plovdiv adhere to the recommendations of Leukemia Net and the Bulgarian Medical Society of Hematology and achieve not only good therapeutic but also pharmacoeconomic efficiency in the treatment of CML-CP patients in first- and second- line therapy.

Keywords

National Health Insurance Fund, National Price and Reimbursement Council, positive List of MPs, chronic myeloid leukemia, tyrosine kinase inhibitors, targeted therapy, pharmacoeconomics, cost-effectiveness

Introduction

In the case of chronic myeloid leukemia (CML), the association of a malignant disease with a specific genetic abnormality was shown for the first time. This characteristic abnormality is a chromosomal translocation called the Philadelphia chromosome. The mutant chromosome gets its name from its discoverers, Peter Knowell (University of Pennsylvania) and David Hungerford (Fox Chase Cancer Center), who first described it in 1960 in Philadelphia, USA (Kalmanti et al. 2015; Yordanov and Varbanova 2019). BCR-ABL1 protein activity is the pathophysiological cause of CML. Since the nature of the BCR-ABL protein and its tyrosine kinase activity have been studied in great detail, targeted therapies for specific inhibition of this activity have already been developed and successfully applied in clinical practice. In a previous study of ours (Goranova-Marinova et al. 2023) Analysis of the pharmacotherapeutic effectiveness of the tyrosine kinase, we found that the tyrosine kinase inhibitors approved in our country can contribute not only to improving the treatment results of patients with CML - prolonging their overall survival and progression-free survival, but even to achieving complete remission of CML, which confirms the leading role of BCR-ABL in the development of the disease (Yordanov and Varbanova 2019). In the chronic phase, CML shows a better response to treatment compared to the other two phases-accelerating phase (AP) and blast crisis (BC). Today, clinicians in our country have a rich arsenal of effective therapeutic options, and if the disease is diagnosed in an early phase and the European recommendations of Leukemia Net (ELN) (Efficace et al. 2011; Baccarani et al. 2013; Official Journal of the European Union 2020) and the Pharmacotherapeutic Guide for Hematology "Methodical Guidelines for Diagnosis and Treatment" of Hematological Diseases", a publication of the Bulgarian Medical Association of Hematology (Lucchesi et al. 2018; Pharmaco-therapeutic manual of hematology 2019) are followed, the survival rate of these patients and their quality of life are comparable to that of other people with chronic diseases. Invest-

ments in new health technologies that reduce mortality and extend years of life in good health preserve the economic and social activity of affected patients and improve demographic indicators nationally. If physicians have unlimited financial resources, they will implement the newest therapies and programs that are most beneficial to patients. However, given the high cost of new therapies on the one hand and limited resources on the other, comparing different therapeutic strategies in terms of their costs and benefits is imperative and especially useful for health managers at all levels (Lucchesi S et al. 2018). Although in the last decade the role of the PhEAs has been growing in the health sector when making decisions to include new targeted therapies and biological and biosimilar drugs in the Positive Drug List, which is a guarantee of patients' access to these innovative therapies, in our country there is very little data on conducted pharmacoeconomic analyzes that aim to determine the economic burden of the disease from the perspective of the patient, the medical facility and/or the payer (i.e. from the perspective of the National Health Insurance Fund (NHIF), which from 1.04. 2012 provides 100% reimbursed treatment with tyrosine kinase inhibitors for all patients with CML, according to the Ordinance published in State Gazette No. 97/9.12.2011, which new diseases, including C92.1-CML, are included in Appendix 1 of the Positive Drug List, for which the National Health Insurance Fund fully pays the MPs for home treatment).

This study aims to analyze the pharmacoeconomic efficiency of TKI inhibitors used by patients with CML-CP in the first and second lines, treated in the hematology clinic at UMHAT "St. George", MU- Plovdiv during the period 2018–2022.

Methods

Through an economic analysis of the medicinal use of TKIs for a 5-year period from 2018 to 2022 at the national level based on data from the National Health Insurance Fund, the availability, accessibility and usability of original and generic TKIs in Bulgaria were assessed. The medical costs for the treatment of all 188 patients with CML-CP, AP, and BC at the hematology clinic in Plovdiv for the period from the appointment of TKI therapy to the end of 2022 for all lines of therapy have been determined. Thanks to the successful attempts to stop therapy in CML-CP patients with persistent long-term molecular responses (Saußele et al. 2016) second-generation TKIs were introduced in first-line therapy in addition to imatinib, which is a first-generation TKI, because the faster achievement of large and the retention of a deep and very deep molecular response for more than 2 years will allow the completion and discontinuation of therapy with the preservation of the response to it for a longer time, while cumulative toxicity has not yet had time to manifest itself. For now, this strategy, called therapy-free remission (TFR), is being studied in large-scale clinical trials, but considered long-term, it will limit the annual accumulation of financial costs of CML treatment and provide funds from the saved costs of stopped therapy for months (in case of loss of a MMR) or years (in its maintenance) to be targeted for the diagnosis and treatment of newly discovered patients with this until recently deadly disease, and today, thanks to the development of targeted therapy against tumor cells alone, it has become a chronic disease. This hypothesis, which we will test through pharmacoeconomic modeling, based on data and results borrowed from publications in the specialized scientific literature of clinical trials, will most likely be confirmed in the future in clinical practice and tested on the basis of real data when we develop clear criteria, the observance of which will guarantee its safe and effective application at the request of patients. A comparative analysis was conducted to evaluate the cost-effectiveness of the different therapeutic strategies with TKIs using the decision tree analysis for patients with CML-CP treated in the first and second lines at the clinic. Sensitivity analyses were carried out to assess the reliability and stability of the obtained results.

Results and discussions

In our opinion, in economic analyses, in particular, and in pharmacoeconomic analyses it is difficult to separate the discussion of study results from their presentation in separate sections, so we decided to combine them.

Assessment of the availability and accessibility of TKIs for the treatment of CML in Bulgaria

In accordance with the Law on Medicinal Products in Human Medicine (LMPHM), medicinal products can be placed on the market only after they have received authorization for use in the relevant order and have a price registration, i.e., a medicinal product can be defined as available only if it is authorized for use and has a registered price. The same medicinal product is defined as affordable if it is available and included in the reimbursement system from the public fund. Therefore, we sought information on the original TKIs, marketing authorization holders, and manufacturers, as well as the date of expiry of patent protection, the availability of generic MPs for those TKIs whose patent protection has expired, and the costs that the NHIF reimbursed for a 5-year period (2018–2022). The data are presented in Tables 1–3. As can be seen from the Table 1 on the pharmaceutical market in our country there are already a large number of generic products of Imatinib and Dasatinib after the patents of the two original products, Glivec and Sprycel have expired. Delaying the first generic imatinib in the United States by about 6 months after the patent expiration of Gleevec, and in the EU Glivec (INN-imatinib), as well as pricing the generic product very close to the price of the patented drug for the next 6 months, has raised serious concerns that the advent

of affordable generic drugs will be delayed in the US. Potential solutions specific to generics include:

- monitoring and sanctioning anti-competitive late payment strategies;
- monitoring potential buyouts by generic firms of competing companies in order to establish a monopoly in small markets;
- reducing the procedures and costs of abbreviated applications for new drugs to encourage the availability of more generic drugs to prevent or alleviate shortages;
- establishing price limits for generic drugs to prevent their prices from increasing (e.g., the highest price of the first generic drug is less than 50% of the price of the original drug in the 6-month exclusivity period. According to the Bulgarian normative regulation, the price of the biosimilar medicinal products (BSMP) cannot exceed 80% of the registered price of the BSMP with the same INN due to the same considerations).

The prices of the original TKIs vary widely - the lowest is the price of Glivec (BGN 1120.38), and the highest is the price of Iclusig 45mg (BGN 18163.08) for 1 month of treatment, which continues non-stop until the end of the patients‘ lives (Table 2). Table 3 shows that the price of the generic versions of Imatinib varies from BGN 197.16 to BGN 980.80, and that of Dasatinib from BGN 1571.11 to BGN 3130.25, i.e., generic products are significantly cheaper than original products, but even for them the prices of a one-month therapeutic course significantly exceed the average income of Bulgarian citizens; therefore, these products, although available, can be considered affordable only after the inclusion in the reimbursement system. Based on this analysis, we can summarize that, in theory, all medicinal products, original and generic, once authorized for use could be considered available on the market in Bulgaria from the date of the authorization. In practice, this is not the case, because the Ordinance on the conditions, rules, and procedure for regulating and registering the prices of medicinal products, introduces a mandatory condition that a „medicinal product can be sold on the territory of the country only after the entry into force of a decision on approval of a price issued by the National Council for Pricing and Reimbursement of Medicinal Products (NCPRMP)“ (Council Directive 2020; EMA 2020; National Council of Price and Reimbursement of Medicinal Products 2020; National Health Insurance Fund 2021; Lex.bg 2020a, 2020b) and in case of non-compliance with this condition, the National Law on Medicinal Products in Human Medicine provides administrative penalties.

Table 1. Issued authorization for use and expiration date of the patent of the original TKI MPs.

MPs & AH	INN	Manufacturer	Permission to use	Patent
Glivec, Film-coated tablet, 100, mg, Pack: 120 in blister (Novartis, Ireland)	Imatinib	Novartis Pharma GmbH, Germany	EU and FDA - 2001	Expired 07.2015 there are 18 versi ons of generic MPs
Sprycel, Film-coated tablet, 50, mg, (Bristol-Myers Squibb Pharma EEIG, Ireland)	Dasatinib	Catalent Anagni S.r.l., Italy; Swords Labora tories T/A Bristol-Myers Squibb, Ireland	EU and FDA - 2006	Expired there are 6 versi ons of generic MPs
Tasigna, Capsule, hard, 200 mg, Pack: 28 (Novartis, Ireland)	Nilotinib	Novartis Pharma GmbH, Germany; Lek d.d., Slovenia	EU and FDA- 2012	until 7.10.2032
Bosulif, Film-coated tablet, 100, mg, Pack: 28 in blister (Pfizer Europe MA EEIG, Belgium)	Bosutinib	Pfizer Manufacturing Deutschland GmbH, Betriebsstatte Freiburg Mooswal dallee 1 Freiburg, Germany	EU and FDA - 2012 Approved in BG in 2013	until 28.02.2034
Iclusig, Film-coated tablet, 15, mg, Pack: 60 (Incyte Biosciences Distribution B.V., The Netherlands)	Ponatinib	Haupt Pharma-AMAREG GmbH, Germany; Penn Pharmaceutical Services Limited,UK	EU and FDA -2013 Approved in BG in 2018	until 22.12.2026

MPs: medicinal products; AH: authorization holder.

Table 2. Original TKIs authorized for use in Bulgaria and their wholesale prices.

MPs and AH	INN	Manufacturer	WP
Glivec, Film-coated tablet, 100, mg, Pack: 120 in blister (Novartis Europharm Limited, Ireland)	Imatinib	Novartis Pharma GmbH, Germany	1,120.38
Sprycel, Film-coated tablet, 50, mg, (Bristol-Myers Squibb Pharma EEIG, Ireland)	Dasatinib	Catalent Anagni S.r.l., Italy; Swords Laboratories T/A Bristol-Myers Squibb , Ireland	6,249.29
Tasigna, Capsule, hard, 200 mg, Pack: 28 (Novartis, Ireland)	Nilotinib	Novartis Pharma GmbH, Germany; Lek d.d., Slovenia	1,519.21
Tasigna, Capsule, hard, 150 mg, Pack: 28 (Novartis, Ireland)	Nilotinib	Novartis Pharma GmbH, Germany; Lek d.d., Slovenia	1,268.26
Bosulif, Film-coated tablet, 100, mg, Pack: 28 in blister (Pfizer Europe MA EEIG, Belgium)	Bosutinib	Pfizer Manufacturing Deutschland GmbH,Freiburg Mooswaldallee 1 Freiburg, Germany	1,188.31
Bosulif, Film-coated tablet, 500, mg, Pack: 28 in blister (Pfizer Europe MA EEIG, Belgium)	Bosutinib	Pfizer Manufacturing Deutschland GmbH,Freiburg Mooswaldallee 1 , Germany;	5,893.57
Iclusig, Film-coated tablet, 15, mg, Pack: 60 The Netherlands	Ponatinib	Haupt Pharma-AMAREG GmbH ,Germany; Penn Pharmaceuti cal Services , Limited, UK	12,108.72

Table 3. Generic TKI medicinal products with authorization for use in Bulgaria and retail prices.

MPs and AH	INN	Manufacturer	RP
Imatinib Accord, Film-coated tablet, 100, mg, Pack: 120 (Accord Healthcare S.L.U.), Spain	Imatinib	Accord Healthcare Polska Sp.z o.o.,Poland	197.16
Meaxin, Film-coated tablet, 100, mg, Pack: 120 (KRKA, d.d.) Slovenia	Imatinib	KRKA, d.d., Novo Mesto,; Lek d.d., Slovenia; TAD Pharma GmbH, Germany ; KRKA-Farma d.o.o., Croatia	232.06
Nibix, Capsule, hard, 100, mg, Pack: 120 (Blister PA/Al/PVC/Al) (Adamed Pharma S.A.), Poland	Imatinib	Adamed Pharma S.A.,Poland; UAB Norameda, Lithuania; Gedeon Richter Plc., Hungary	980.80
Dasatinib Sandoz, Film-coated tablet, 50, mg, Pack: 60 (Sandoz d.d.,) Slovenia	Dasatinib	Remedica Ltd., Cyprus; Lek Pharmaceuticals d.d., Slovenia	3,130.25
Dasatinib Teva, Film-coated tablet, 50, mg, Pack: 30 (Teva B.V.) The Netherlands	Dasatinib	Merckle GmbH, Blaubeuren,Германия; PLIVA Hrvatska d.o.o. (PLIVA Croatia Ltd.), Croatia	1,571.11
Dasatinib Zentiva, Film-coated tablet, 50, mg, Pack: 60 (Zentiva k.s.,) Czech Republic	Dasatinib	Zentiva k.s., Czech Republic	2,644.87

Notes: 1. There are 10 MPs with the INN Imatinib with the code of the National Health Insurance Fund (NHIF)for the period 2018-2022, for some of which the reimbursed amounts are for a short period of time.
2. Imatinib Actavis received a marketing authorization valid for the EU on 17 Apr. 2013, with a term of 5 years and in 2017, the company Actavis Group PTC ehf, the holder of the permit, received an indefinite use permit, but from 16 Dec. 2021, at its request, the same was terminated as the ATC code was changed to the ATC Vet code.
3. There are already several registered generic drugs with INN Dasatinib, as can be seen from table 3, but we do not have information about their share in the total costs of drugs with INN Dasatinib.

Economic analysis of CML treatment costs at the national level for the period 2018–2022

We requested from the NHIF with an application for access to public information (entry no. 24-01-90/ 21. 07.2023) data at the national level on the number of health insured patients with CML for the period 2018–2022 and on the costs incurred for their treatment. With the decision RD -19-245/3.08.2023 of the NHIF, we received the information we requested, presented in Tables 4–9. Table 4 presents information on the number of patients with CML and the costs of their drug therapy outside the value of the Clinical Pathway (CP) for the period 2018–2022.

Table 4. Health insured persons with ICD C92.1-CML and the costs of the NHIF for their treatment.

Year	Health insured persons with ICD C92.1 turned to the NHIF system (number of patients)	Expenditures of the NHIF for drug therapy beyond the value of CP for ICD C92.1(Bg lv)
2018	618	27,254,295.45
2019	665	28,003,052.05
2020	706	28,394,271.98
2021	711	27,687,505.35
2022	702	26,320,727.09
		Total: 137,659,851.92

The analysis of the data from Table 4 shows that the number of health insured persons with ICD diagnosis C 92.1 – CML increased in 2019 and 2020 by more than 40 patients, which is the average annual number of newly diagnosed CML patients. In 2021 the increase was only by 5 patients, and in the last year of the period it even decreased by 9 people. The NHIF spent for the entire 5-year period the sum of BGN 137,659,851.92, and recalculated in US dollars at an average annual exchange rate of BGN 1.861798 for 1 US dollar, the costs of drug therapy amounted to $73,939,197. The annual costs for the same period (2018–2022) for all TKI drugs with international non-proprietary names (INN): Imatinib, Dasatinib, Nilotinib, Bosutinib, and Ponatinib are presented in Table 5. The analysis of the data in Table 5 shows that the total costs for TKI therapies remain around $27.5 million per year with slight fluctuations according to the number of patients. However, there is a serious trend of decreasing costs for Imatinib from nearly BGN 4 million in the first year of the period to around BGN 1.5 million in the second year, and with a continued decrease in the next 3 years, costs fall below BGN 400,000. This major change can be explained by the lack of data on the reimbursed costs of Glivec c INN Imatinib for the last 2 years and the introduction of cheaper generic versions compared to the price of the original Glivec, with the development of mutations and intolerance to this therapy, as well as the fact that second-generation TKIs are approved for use as a first treatment strategy for CML-CP patients and as replacement therapy after failure of Imatinib therapy. Therefore, the total amount of costs for the last 3 years of the period decreased, a trend that did not correspond to the increased number of patients with CML due to increased survival and better therapeutic strategies. A minor fluctuation is observed in the costs of MPs with INN Nilotinib, which remains around BGN 20 million with a slight downward trend, and with Dasatinib, which increased from BGN 3,200,000 in 2018 to over BGN 4 million in the following years. The most significant increase is in the costs of Bosutinib, which, from nearly 1 million at the beginning of the period already exceed 1.5 million BGN. However, a real spike in costs was seen with Ponatinib, the highest-priced 3rd-generation TKI but the only MP approved by the EMA in 2013 for use as Second-line treatment for CML with the T315I mutation, which data show from the literature is often found (National Statistical Institute in Bulgaria 2023).

In our country, this product was proposed for inclusion in the positive list at the end of 2017, but was approved in 2018. According to the authors of the PACE study (Council Directive 2020; EMA 2020; Lex.bg 2020a, 2020b; NCPRMP 2020; National Health Insurance Fund 2021), the use of Ponatinib in the earliest stages of the disease can prevent the emergence of resistance caused by mutations. The costs for this MP which were a little over BGN 300,000 in 2018, will reach nearly BGN 2 million in 2022 with a tendency to increase. (EMA, Availability of medicines, for regulators-on-public-communicationsection, 2020; Electronic registers of National Council of Price and Reimbursement of Medicinal Products. Bulgaria, 2020; Website of the National Health Insurance Fund, Bulgaria, 2021; Lex.bg. Bulgarian Law on Medicinal Products in Human Medicine, in force since 13. Apr. 2007, 2020; Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems, 2020; Ordinance on terms, rules, and procedure for regulation and registration of prices for medicinal products, in force since 30. Apr. 2013, 2020).

The analysis of the data from Table 6 shows that only two codes according to the National Health Insurance Fund were present during the 5 years of the period LH 401 (Imatinib Teva Pharma) and LH 324 (Imatinib Meaxin)

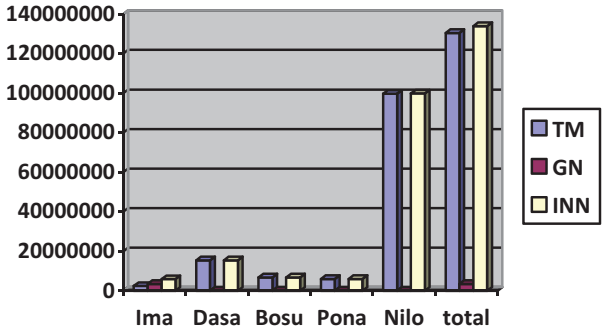

Figure 1. Graphic presentation of the costs of the NHIF for original and generic medicinal products for the period 2018-2022. as a total amount and distribution by INN in BGN. Legend: TM-trademark, GN- generic name, INN- international non-proprietary name.

as generic drugs. It lacks cost data for the original Glivec (INN Imatinib) for the past several years, as well as the cost of generic products with the INN Dasatinib. The total costs of treatment with TKI MPs, distributed by INN for the five-year period, are BGN 133,874,624.62. Of them, the share of original TKI MPs is 97.32%, while the share of generic medicinal products is only 2.68% (Table 7 and Fig. 1)

From the reports presented (Tables 8, 9) on the number of cases of patients with a diagnosis of C2.1 and the amounts paid for their treatment in outpatient and in-hospital medical care, it can be seen that the economic burden

Table 5. Expenditures of the NHIF for TKI MPs by INN and years.

INN	2018	2019	2020	2021	2022
Imatinib	3,934,671.45	1,486,106.84	491,537.13	382,424.16	335,703.62
Nilotinib	19,331,677.97	21,267,071.48	20,119,458.62	20,119,458.62	18,998,841.09
Dasatinib	3,165,643.79	3,466,528.67	4,023,366.22	4,392,682.06	3,714,033.48
Bosutinib	934,703.38	1,383,388.11	1,466,485.53	1,427,555.13	1,529,775.15
Ponatinib	132,436.62	653,325.01	1,713,358.14	1,512,881.15	1,951,643.06
Total	27,499,133.21	28,256,419.11	27,814,205.64	27,834,981.12	26,529,996.40

Table 6. Costs for all LPs with INN Imatinib (in BGN).

NHIF code		2018	2019	2020	2021	2022
LH 203	Glivec, Novartis	2,012,233.73	275,520.62	0.00	0.00	0.00
LH 270	Imakrebin, Alvogen	61,133.97	42,666.85	12,455.17	0.00	0.00
LH 278	Glivec Novartis	2,442.24	4,731.84	0.00	0.00	0.00
LH 285	Imatinib Acord	10,066.17	9,944.57	0.00	0.00	0.00
LH 324	Imatinib Meaxin	188,428.97	174,538.32	118,481.07	19,662.77	28,863.27
LH 377	Imatinib Actavis	16,657.45	24,828.65	17,538.32	0.00	0.00
LH 401	Imatinib Teva Pharma	1,642,637.06	939,592.30	241,878.06	138,974.07	44,423.91
LH 402	Imatinib Teva Pharma	1,011.86	0.00	0.00	215,118.52	236,309.55
LH 475	Imatinib Meaxin	0.00	0.00	0.00	8,668.80	6,538.32
LH 627	Imatinib Acord	0.00	0.00	0.00	0.00	19,538.57
	Total:	3,934,671.45	1,486,106.84	491,537.13	382,424.16	335,703.62

Table 7. Expenses of the NHIF for original and generic medicinal products for the period 2018-2022 as a total amount and distribution by INN in BGN.

Medicinal product (INN)	Costs of INN	Costs of original MPs	Costs of generic MPs
Imatinib	5,912,315.42	2,411,184.42	3,501,131.00
Nilotinib	99,836,505.00	99,836,505.00	–
Dasatinib	15,419,253.00	15,419,253.00	–
Bosutinib	6,741,907.30	6,741,907.30	–
Ponatinib	5,963,643.90	5,963,643.90	–
Total costs	133,874,624.62	130,373,493.62	3,501,131.00
Relative share	100%	97.32%	2.68%

Table 8. Patients with CML were examined, and amounts paid for outpatient care in BGN.

Out of hospital care	2018	2019	2020	2021	2022
Number of cases	358	411	400	423	438
Amounts paid	6,778.37	6,965.51	6,962.08	7,440.59	9,773.65

Table 9. Treated patients with a diagnosis of C2.1 and paid amounts for hospital care.

In-hospital care	2018	2019	2020	2021	2022
Number of cases	1959	1866	947	1094	1001
Amounts paid	1,665,955	1,587,670	4,556,017	3,732,947	10,895,635

of CML is increasing progressively. Regardless of the fact that in out-of-hospital care the number of cases increased by 22% over the 5-year period, but the amounts paid increased by 44%, and in in-hospital care due to the good quality of life of patients treated on an outpatient basis at home with the new TKI tablets and hard capsules, easy to take, the cases have almost halved in the same period, but the amounts have increased more than 6.5 times.

Under the terms of Bulgaria's membership in the EU, Bulgarian citizens have guaranteed availability of quality, safe, and efficient modern medicinal products, equal to other EU citizens. Regardless of the fact that Bulgaria has been a member of the EU since January 1, 2007, our population has the lowest incomes; the number of pensioners is over 2 million, and half of them receive pensions of less than BGN 1,000 (about 500 euros), which is why all approved TKI MPs are included in the positive list and their costs are fully covered by the National Health Insurance Fund/ NHIF/ with public funds. This gives clinicians the opportunity to prescribe the most suitable therapy for the patient, even when the disease is diagnosed. All TKIs are prescribed every month according to a protocol issued by a specialized hematology center. Although they fall into a higher price range, the original MPs are preferred for prescribing, dispensing, and treatment in Bulgaria, even when generic alternatives are available. In accordance with the established rules for prescribing and dispensing in our country, prescribing is still by trade name and not by INN, even when a protocol for expensive treatment is issued by special order. Bulgarian pharmacists do not have the right to replace the prescribed drug with another cheaper one with the same INN, as is the case in most developed countries in the world. It is not surprising to find that the share of generic TKI MPs is at a negligible low level. On the other hand, many medical specialists lack confidence and knowledge about the quality and effectiveness of generic drugs in order to achieve rational drug use for the benefit of patients. In Bulgarian therapeutic practice, there is a lack of uniform and adequate standards for the replaceability and interchangeability of commercial drugs with generic drugs and of biological drugs with biosimilar drugs, which are of equal quality, safety, and efficacy. We are fully convinced that it is imperative to introduce the criteria for rational drug use in clinical practice as a mandatory element of our national drug policy (WHO Resolution 2020)

Evaluation of the costs of the treatment of patients with CML and of the achieved molecular response as an indicator of the effectiveness of the therapy in the hematology clinic at UMHAT„St. George" at the MU-Plovdiv

At the local level, we calculated the costs for all 188 patients with CML treates in CP, AP, and BC for the period 2005–2022. On the Table 10 presents the data on the number of patients diagnosed in a 5-year interval, the phase of the disease and the number of deaths. As can be seen from the data in Table 10, at the beginning of the period, the new targeted therapy was prescribed to only 6 patients, and in 2006–2010, their number gradually increased by 42 patients to reach 188 patients included in the study, of which during the period 2009–2022, 40 patients died, including 8 out of 10 patients in the CML blast crisis (CML-BC). The first patient was diagnosed with CML-CP on 1 March 2000, at the age of 55, received the first TKI therapy in 2005, and, as included in the present study, underwent four lines of TKI therapies, but failed to achieve MR. He died at the age of 74 in 2019, when he finally lost the battle with the disease. The youngest of the last 8 patients included in the study in the second half of 2022 is a newly diagnosed 22-year-old patient with a diagnosis of CML-CP, who has the chance to soon be put into long-term remission if he complies with the prescribed therapy and manages to achieve a large and deep molecular response.

BGN 18,792,814 was spent for the treatment of all 188 first-line patients with various TKIs for 12,691 months; BGN 6,749,213 was spent for second-line treatment over 2,398 months; and BGN 6,749,213 for 3+ lines amounts to BGN 2,404,925 for 417 months, or only for the tyrosine kinase inhibitor drugs; the total amount is BGN 22,946,040. Adding to it are the costs of laboratory tests, molecular response monitoring, and other tests. According to clinical path 242 for CML, the total costs are worth BGN 31,458,542 for the entire period of their treatment from the start of TKI therapy until the end of 2022. Fig. 2 presents the cumulative incidence of progression-free survival of patients on the 1st, 2nd, and 3rd lines of treatment.

Obviously, the earlier the disease is detected in the chronic phase and, based on a personalized approach, the patient is assigned the appropriate TKI therapy, to which he achieves a rapid MMR and a subsequent long-term DMR, the more he will feel "cured" and the quality of his life will be close to 1. In the message we quoted above (Li et al. 2018) the unit QALY, which combines two indicators at the same time (year, prolonged life with improved quality) for CML-CP is 0.92, and for CML-AP and CML-BC is much lower. Progression of the disease in a higher line of therapy and/or phase of the disease (AP and BC) leads to an increase in costs due to switching to more expensive drugs, a deterioration in the quality of life, a decrease in survival, and an increase in mortality (Table 10 and Fig. 2).

Table 10. Distribution of patients with CML according to the period of diagnosis, phase of the disease and death.

Period of diagnosis	Number of patients	Start of the TKI therapy	Phase			Year of death
			CP	AP	BC	
2000–2005	10	2004-1; 2005-5; 2006-3; 2007-1.	7	2	1	2011-1; 2017-1; 2018-1; 2019-2.
2006–2010	38	2006-10; 2007-4; 2008-9; 2009-5; 2010- 10.	34	1	3	2009-1; 2016-1; 2019-1; 2020-3; 2021-4.
2011–2015	43	2011-5;2012-6; 2013- 8; 2014-10; 2015-11; 2017 -1; 2018- 2.	32	9	2	2018-1; 2019-3; 2020-4;2022-1.
2016–2020	83	2016 -15; 2017- 15; 2018 -22; 2019-14; 2020-17.	66	14	3	2019-2; 2020-4; 2021-6; 2022-3.
2021–2022	14	2021-6; 2022-8.	12	1	1	2022-1
Total	188		151	27	10	40

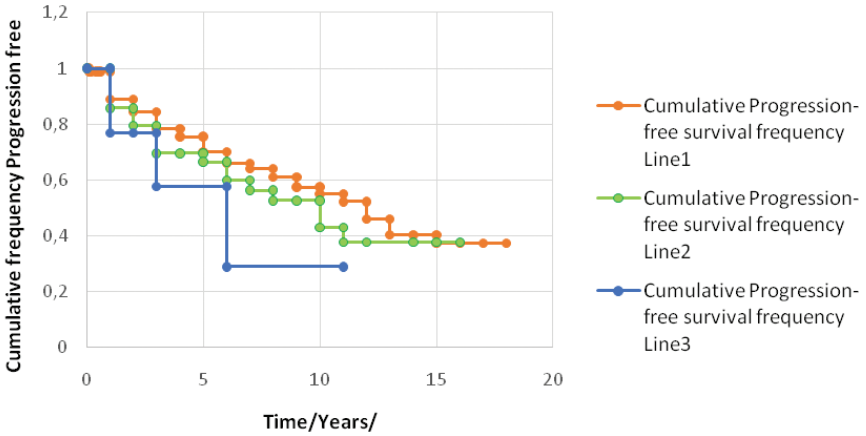

Figure 2. Cumulative rate of progression-free survival of CML patients on first-, second-, and third- line TKI therapy.

A study conducted in Bulgaria evaluated the quality of life of patients with three rare diseases, among them CML (Kamusheva et al. 2013).

Only 10 patients with CML, without an established disease phase, with a mean age of 50 years were surveyed, and based on their responses to the SF 36 short form (WHO) their estimated quality of life was 67.7 out of a maximum value of 100. A statistical relationship was sought between the domains of health-related quality of life and the costs incurred for the treatment of these patients, including co-payments by the patients themselves. The authors conclude that the study is not a long-term analysis, but only a snapshot of the current state, and further studies should be done to assess the long-term HQoL for patients with these three rare diseases in Bulgaria (Kamusheva et al. 2013).

On October 29, 2021, the US Food and Drug Administration granted accelerated approval of asciminib (Scemblix, Novartis AG) for patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP) previously treated with two or more tyrosine kinase inhibitors (TKIs) and approved asciminib for adult patients with Ph+ CML in CP with the T315I mutation. Over the past 20 years, the development of TKIs has changed the treatment paradigm for patients with CML; accordingly, the survival outcomes of CML patients have also improved dramatically. However, a significant proportion of patients still experience resistance or intolerance to TKI treatment, resulting in a discontinuation rate of approximately 30% for 1st-line TKI, which gradually increases with treatment lines (Bonifacio et al. 2022; Yeung et al. 2022).

Because patients who fail to respond to multiple lines of TKIs show poorer outcomes, more effective therapy is needed for CML patients with treatment failure. Asciminib is a first-in-class allosteric inhibitor that binds to the myristoyl pocket of ABL1. Preclinical data support the specificity and potent efficacy of asciminib in CML cells with or without BCR:ABL1 mutations, as well as the synergistic effects of asciminib and conventional TKIs, particularly in overcoming resistance. In phase 1 and phase 3 clinical trials, asciminib showed a significantly improved and durable response with a favorable safety profile, even when enrolled patients were pretreated with multiple

Table 11. Results of the MR analyzes of first- and second-line CML-CP patients.

	TKI MPs First line of therapy Second line of therapy							
INN	Analyzes № / %	MMR	DMR + VDMR	No MR No data	Analyzes № / %	MMR	DMR + VDMR	No MR No data
IMATINIB	98 100%	11 11.2%	46 46.9%	41 41.9%	3 100%	1 33.3%	2 66.7%	–
NILOTINIB	41 41.9%	5 11.4%	28 63.6%	11 25%	26 100%	2 7.7%	14 53.9%	10 38.4%
DASATINIB	9 100%	–	4 44.4%	5 55.6%	8 100%	–	6 75%	2 25%
BOSUTINIB	–	–	–	–	3 100%	–	1 33.3%	2 66.7%
Total :	151	16	78	57	40	3	23	14
%	100%	10.6%	51.7%	37.7%	100%	7.5%	57.5%	35%

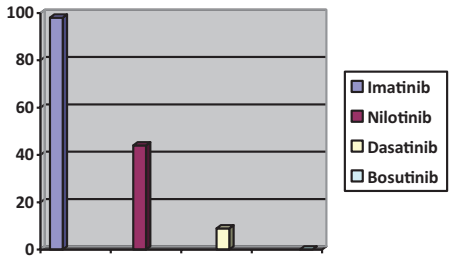

Figure 3. Distribution of patients with CML-CP in the first line according to therapy (INN).

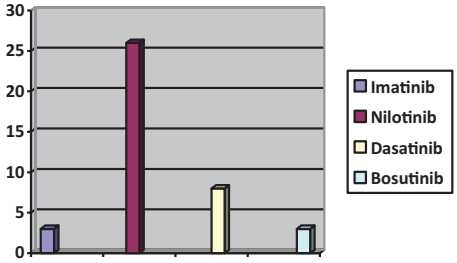

Figure 4. Distribution of second-line CML-CP patients according to therapy (INN).

TKIs. It is also effective in patients with the T315I mutation. Research efforts today aim to determine whether the use of asciminib as a first-line treatment compared to conventional TKIs, as add-on therapy to achieve DMR, or as consolidation therapy for successful TFR can improve patient outcomes in various clinical scenarios, including CML (Cortes et al. 2013; Kim et al. 2019; Yeung et al. 2022).

The distribution of CML-CP patients (whose numbers are respectively 151 patients for the first line and 40 patients for the second line) according to the line and type of TKI therapy is presented in Figs 3, 4, and the results for the achieved molecular response to the respective therapies are presented in Table 11.

Among the treated 151 first-line CML-CP patients, of 98 (64.9%) patients receiving Glivec (Imatinib) 400 mg, 11 (11.2%) patients achieved a major molecular response / MMR 3logs/, 46 (46.9%) patients had deep and very deep molecular response/DMR 4logs and 4.5logs and VDMR 5logs/ and 41 (41.9%) patients had no response. A total of 58.1% of patients treated with first-line Imatinib in chronic phase CML achieved the primary goal of therapy. The remaining 53 (35.1%) first-line patients were treated with 2nd generation TKI therapies, with the following results: 5 (9.4%) patients achieved MMR, 32 (60.4%) patients had DMR and VDMR and 16 (30.2%) - had no molecular response. Among the 44 (29.1%) first-line patients treated with nilotinib, 5 (11.4%) patients achieved MMR and 28 (63.6%) patients - DMR and VDMR, and 11 (25%) - had no response. Among dasatinib-treated 9 (6%) patients, 4 (44.4%) achieved DMR and VDMR, and 5 (55.6%) patients had no response. Thus, nilotinib administered to 44 patients in the first line, i.e. over twice as many patients as those on imatinib had better outcomes-33 (75%) patients achieved MMR, DMR, and VDMR versus 57 (58.1%) patients on imatinib and only 11 (25%) patients vs. 41 (41.9%) treated with imatinib had no response. The total contribution of the 2nd generation TKI MPs in the first line is two times greater compared to that of imatinb; 37 (69.8%) patients achieved a molecular response and 16 (30.2%) did not while 57 (58.1%) patients on imatinib achieved MR and 41 (41.9%) had no response. In summary, of 151 CML-CP patients on first-line therapy, 94 (62.3%) patients achieved a large and deep molecular response, but 57 (37.7%) patients did not respond to therapy.

40 patients were treated on the second line of therapy, of which 3 (7.5%) patients received Imatinib (2 patients × 400 mg daily and 1 patient × 600 mg daily), 26 (65%) patients - Nilotinib, 8 (20%) patients - Dasatinib and 3 (7.5%) patients - Bosutinib. The results for the achieved MR for the respective therapies are as follows:

- 3 (7.5%) imatinib-treated patients achieved MR: 1 patient achieved MMR, 1-DMR and 1-VDMR; Among 26 (65%) Nilotinib-treated patients, 2 (7.5%) achieved MMR, 14 (54%) patients had DMR and VDMR, and 10 (38.5%) had no response;
- Among 8 (20%) patients treated with Dasatinib, 6 (75%) patients had DMR and VDMR and 2(25%) had no response;
- Among the 3 (7.5%) patients treated with bosutinib, 1 patient had a DMR and 2 had no response. There are 8 patients in the third line of therapy, as MR data is available for only 2 of them, and in the fourth line, there are two patients who have not achieved MR. Overall, second-line outcomes were slightly better than first-line outcomes - 65% of patients achieved MR and 35% did not.

For the treatment of all 151 patients with CML-CP in the first line with various TKIs during 11066 months, 16 106 444 BGN were spent for their drug therapy with TKIs. For the treatment of all 40 patients with CML-CP on the second line during 2315 months, BGN 6,475,294 was spent on drug therapy with TKI medicinal products, or only on TKI MPs. The total amount for the first and second lines is BGN 22,581,738. We add to it the costs of laboratory tests, monitoring of the molecular response, and other tests. According to clinical path 242 for CML, the total costs are worth BGN 23,274,501 for the entire period of their treatment from the start of TKI therapy for each patient until 31 Dec. 2022.

Cost data included the following items: costs of diagnostic procedures, costs of drug therapy, costs of laboratory tests, and costs of monitoring the molecular response to therapy. The prices of TKI MPs were taken from the Register of the National Council for Prices and Reimbursement of MPs in the Republic of Bulgaria/NSCRRB/ (Electronic registers of National Council of Price and Reimbursement of Medicinal Products. Bulgaria 2020) and from the Positive Drug List, and the costs for laboratory tests and monitoring of the molecular response were taken from Clinical Pathway 242 for ICD diagnosis C2.1.-CML.

Table 12. The average annual value of each strategy applied in the first line of treatment for patients with CML-CP in the hematology clinic at the Medical University of Plovdiv (2018-2022) TM.

Results	Costs per 1 year in leva	Probabilities	Costs x Probabilities in leva
A. First strategy Glivec 400mg daily			
Success - stay on this MP	1,120.38 × 12 = 13,444.56	0.58 × 1.0 = 0.58	7,797.84
Success - replace with another TKI	13,444.56	0.58 × 0.0 = 0.00	–
Failure - stay on this MP	13,444.56	0.42 × 0.24 = 0.10	1,344.46
Failure- replace with another TKI	13,444.56	0.42 × 0.76 = 0.32	4,302.26
Total for strategy Imatinib Nibix 400 mg	1.00		13,444.56
B. Second strategy Tasigna 300mg 2 x daily			
Success - stay on this MP	5,073.04 × 12 = 60,876.48	0.75 × 1.0 = 0.75	45,657.36
Success - replace LP with another one	60,876.48	0.75 × 0.0 = 0.00	–
Failure - stay on this MP	60,876.48	0.25 × 0.45 = 0.11	6,848.61
Failure- replace MP with another one	60,876.48	0.25 × 0.55 = 0.14	8,370.52
Total for strategy Tasigna 300 mg	1.00		60,876.49
C. Third strategy Sprycel 100 mg daily			
Success - stay on this MP	6,249.29 × 12 = 74,991.48	0.45 × 1.0 = 0 45	33,746.17
Success–replace with another TKI	74,991.4	0.45 × 0.0 = 0 ,0	–
Failure -stay on this MP	74,991.48	0.55 × 0.40 = 0.22	16,498.12
Failure- replace with another TKI	74,991.48	0.55 × 0.60 = 0.33	24,747.19
Total for strategy Sprycel 100 mg	1.00		74,991.48

Pharmacoeconomic analyses of the cost-effectiveness of TKI therapies in the first- and second- lines of treatment for patients with CML-CP

A comparative evaluation of the cost-effectiveness of individual TKI therapies for the treatment of patients with CML-CP on first- and second- line therapy using the Decision Analysis method

We applied the Decision Tree methodology because it is suitable for comparing two or more alternatives (new innovative therapy compared with standard therapy or therapy with no treatment) and is ideally applied for comparative cost-effectiveness evaluation of new innovative therapies, such as targeted TKI therapies for the treatment of CML. Starting from real clinical practice, we can build a decision tree for first- and second- lines therapy based on the data for patients with CML-CP in the hematology clinic at the Medical University of Plovdiv and consider the results of clinical studies described in the brief characteristics of all TKI products.

The prescribed dose of Glivec should be taken orally with a meal and with a large glass of water to minimize the risk of gastrointestinal irritation. Doses of 400 mg or 600 mg should be administered once daily, while a daily dose of 800 mg should be administered as 400 mg twice daily, morning, and evening. Treatment with Glivec (imatinib) is continued until disease progression. Dose escalation from 400 mg to 600 mg or 800 mg in patients with chronic phase disease or from 600 mg to a maximum of 800 mg (given as 400 mg twice daily) in patients in acceleration phase or with blast crisis may be considered in the absence of severe adverse drug reactions and severe non-leukemia-related neutropenia and thrombocytopenia in the following circumstances: disease progression (at any time); failure to achieve a satisfactory hematological response after at least 3 months of treatment; failure to achieve a cytogenetic response after 12 months of treatment; or loss of a previously achieved hematological and/or cytogenetic response (EMA, Glivec 2012).

Tasigna dosage in adult patients with Philadelphia chromosome-positive CML. The recommended dose is: – 300 mg twice daily in newly diagnosed patients with CML in the chronic phase, and – 400 mg twice daily in patients in the chronic phase or in the acceleration phase of CML, who are resistant to or do not tolerate previous therapy well (EMA, Tasigna 2019).

The recommended starting dose for chronic phase CML in adult patients is 100 mg of Sprycel once daily. The recommended starting dose for advanced, myeloid or lymphoid blast phase (advanced phase) CML or Ph^+ ALL is 140 mg once daily. (EMA, Sprycel 2019)

Newly diagnosed Ph^+ CML -CP: The recommended dose is 400 mg of bosutinib once daily. Ph^+ CML (CP, AP or BC) with resistance or intolerance to prior therapy: The recommended dose is 500 mg of bosutinib once daily. (EMA, Bosulif 2022)

Iclusig is indicated in adult patients with:

- chronic myeloid leukemia (CML) in the chronic phase, acceleration phase, or blast phase that are resistant to dasatinib or nilotinib; who are intolerant of dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.
- Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph^+ALL) that are resistant to dasatinib; who are intolerant of dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.

The recommended starting dose is 45 mg of Iclusig (ponatinib) once daily. Treatment should be continued until the patient shows evidence of disease progression or unacceptable toxicity (EMA, Ponatinib 2013)

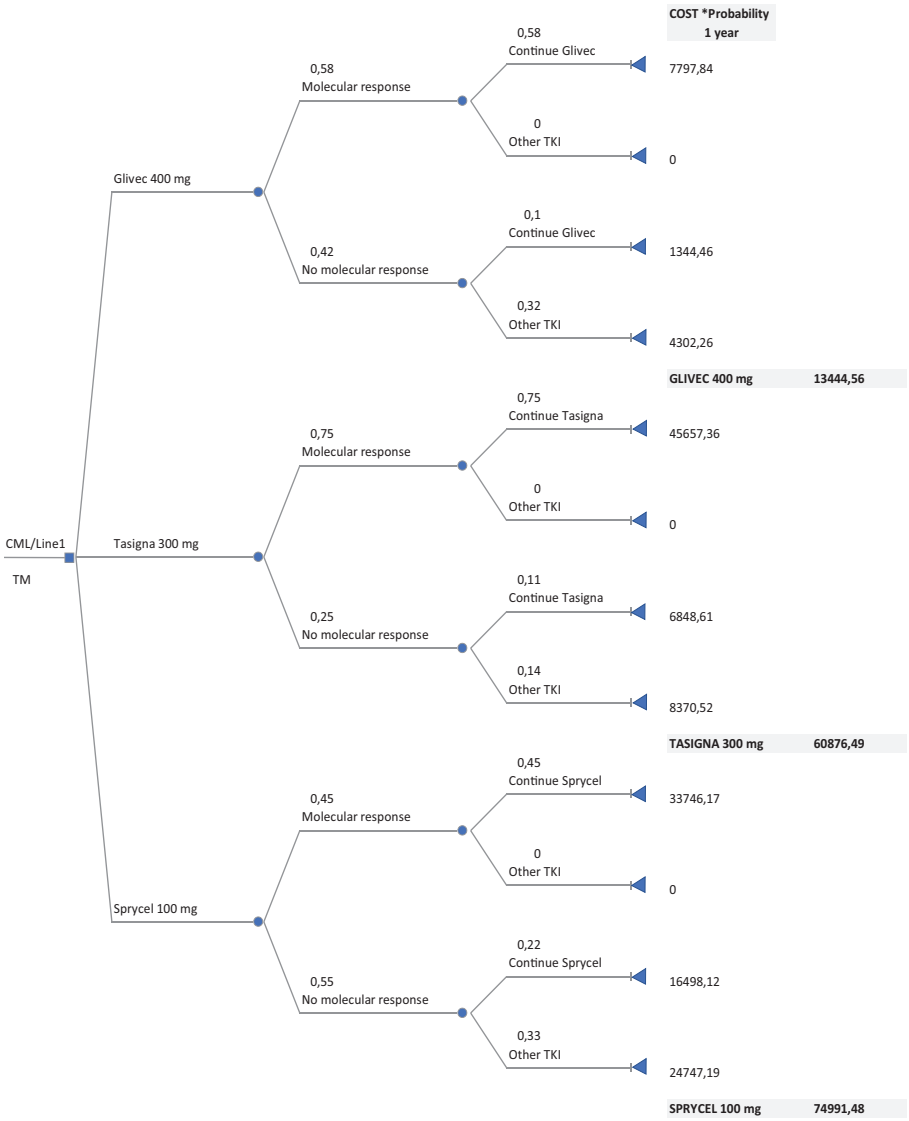

Figure 5. Decision tree for patients with CML –CP in the first-line of therapy with trademarks (TM).

The next two figures present decision tree models comparing the main TKI MPs used to treat patients with CML-CP in the first line of therapy (Figs 5, 6).

In the first line of therapy, Glivec 400mg daily, Tasigna 300mg twice daily and Sprycel 100mg once daily are prescribed, or these are the 3 therapies in the node of choice. Each has different clinical success and failure rates. By the end of the first year, with successful therapy, it is expected to achieve MMR; in the second year, it is expected to achieve DMR and VDMR, which will last for at least 2 years, which is a guarantee of maintaining a long-term remission of the patient. Failure to achieve MR or its loss is considered a failure and is a signal of disease progression, resistance, or intolerance, as well as the need to replace the medicinal product with another more effective one. These are the two nodes of chance for any type of TKI therapy; clinical success and failure. The third type of terminal node for each chance node includes remaining on treatment with the same MP or switching to another more effective TKI MP.

Another TKI MP, Bosulif 100mg, is included in the decision tree for the second line of therapy. In addition, the doses of MP-Glivec 600–800mg daily, and Tasigna 400mg twice a day have increased. To facilitate calculations, tables containing probability data for each node on each branch and cost data are compiled. In the terminal nodes, the calculated probabilities are multiplied by the costs, summed for each therapy, and finally an incremental cost-benefit ratio is calculated according to the formula, where the measure of the effectiveness of the therapeutic strategies is the achieved molecular response to the respective therapy:

$$\text{ICER} = \frac{[\text{cost (strategyA)} - \text{cost (strategyB)}]}{[\text{effectiveness (strategy A)} - \text{effectiveness (strategy B)}]}$$

All published articles on the use of Markov models for PHEA cost-effectiveness use the QALY as the measure of effectiveness, which is appropriate for a long study horizon. When constructing a decision tree for the therapeutic management of patients with CML-CP after successful

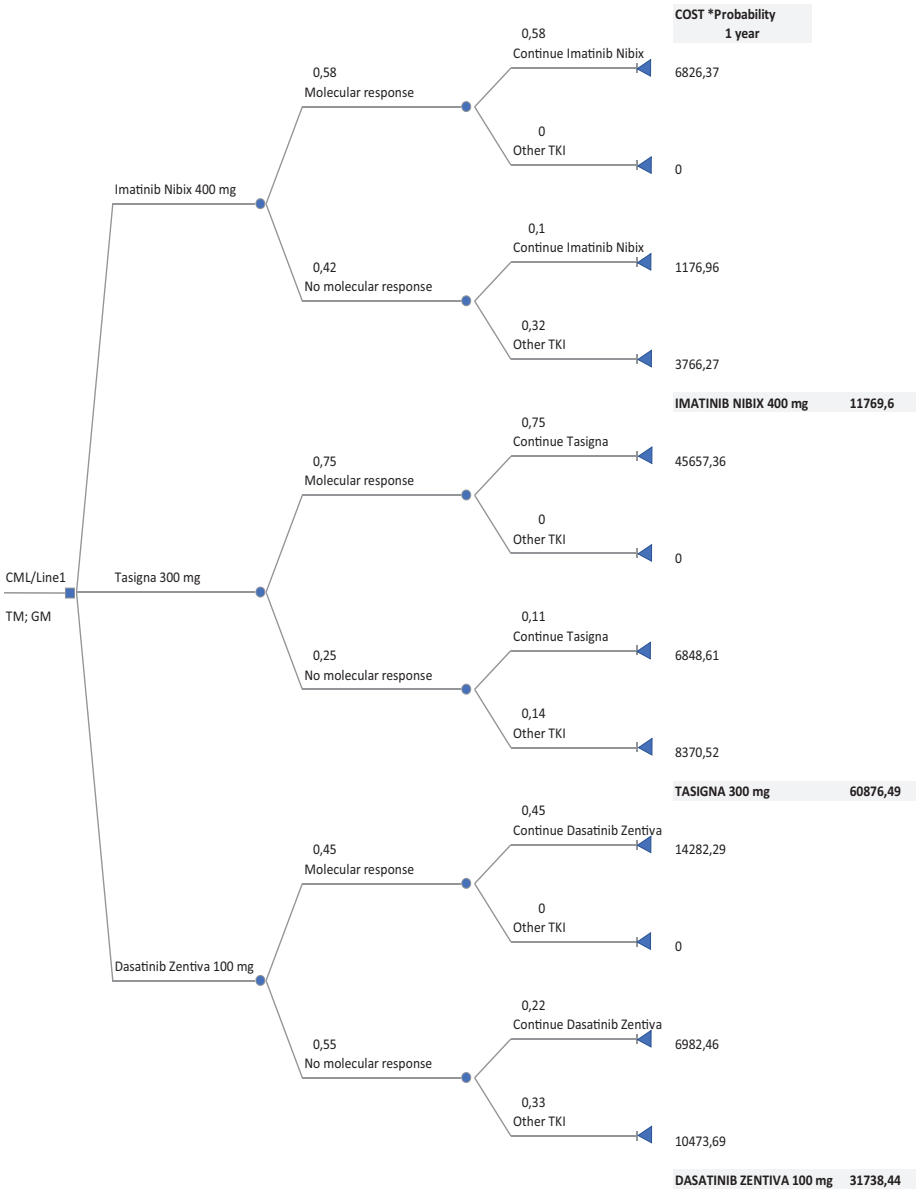

Figure 6. Decision tree for CML-CP patients in the 1st-line of therapy with TKIs (TM; GM).

or unsuccessful treatment (intolerance, lack of response to therapy, need to change TKI MP to a more expensive but more effective one) we decided to use as a measure of effectiveness of different pharmacotherapeutic strategies the molecular response achieved by patients (Eichler et al. 2004; Saglio et al. 2010; Bonifacio et al. 2022). Table 12 presented the average annual value of each strategy applied in the first line of treatment for patients with CML-CP in the hematology clinic at the Medical University of Plovdiv (2018-2022) TM (Table 12).

Regardless of the fact that trademarks are preferred over generic analogues, based on the fact that there are such available in the country, as well as data on reimbursed amounts from the NHIF, we built two variants of the decision tree for the first and second lines of therapy.

The first strategy with Glivec 400 mg daily has a high probability of success of 58% and it is the cheap est with an average cost per year of BGN 13,444.56. If any other generic product is used instead of the original Glivec, the treatment will become even cheaper (Table 13). With close data on average annual costs, the third strategy with Sprycel 100 mg daily is ranked second, if Dasatinib Zentiva (Czech Republic) is used with a price of a monthly therapeutic course of BGN 2644.87 instead of the original Sprycel (Bristol-Myers Squibb Pharma EEIG, Ireland), whose monthly price of therapy is BGN 6,249.29. The second strategy with Tasigna 300mg 2× daily is the most expensive; as the MP is protected by a patent, there are no generic analogues, but it has the highest first-line clinical success (75%).

Additionally, a total of 846 patients were randomized to Tasigna 400 mg twice daily (n=281), Tasigna 300 mg twice daily (n=282) in 220 global sites in the ENESTnd study (Kamusheva et al. 2013), and Glivec 400 mg once daily (n=283). The primary endpoint was MMR at 12 months; the secondary endpoint was CCyR up to 12 months. The planned follow-up period is five years. MMR rates at 12

Table 13. Determining the average annual value of each strategy applied in the first line of treatment for patients with CML-CP in the hematology clinic at the Medical University of Plovdiv (2018–2022) GN; TM.

Results	Costs per 1 year in leva	Probabilities	Costs x Probabilities in leva
A. First strategy Imatinib Nibix 400 mg daily			
Success - stay on this MP	980.80 × 12 = 11,769.60	0.58 × 1.0 = 0.58	6,826.37
Success - replace LP with another one	11,769.60	0.58 × 0.0 = 0.00	–
Failure - stay on this MP	11,769.60	0.42 × 0.24 = 0.10	1,176.96
Failure- replace MP with another one	11,769.60	0.42 × 0.76 = 0.32	3,766.27
Total for strategy Imatinib Nibix 400 mg		1.00	11,769.60
B. Second strategy Tasigna 300mg 2 x daily			
Success - stay on this MP	5,073.04 × 12 = 60,876.48	0.75 × 1.0 = 0.75	45,657.36
Success - replace with another TKI	60,876.48	0.75 × 0.0 = 0.00	–
Failure - stay on this MP	60,876.48	0.25 × 0.45 = 0.11	6,848.61
Failure- replace MP with another one	60,876.48	0.25 × 0.55 = 0.14	8,370.52
Total for strategy Tasigna 300 mg		1.00	60,876.49
C. Third strategy Dasatinib Zentiva 100 mg daily			
Success - stay on this MP	2,644.87 × 12 = 31,738.44	0.45 × 1.0 = 0 45	14,282.29
Success - replace MP with another one	31,738.44	0.45 × 0.0 = 0.00	–
Failure - stay on this MP	31,738.44	0.55 × 0.40 = 0.22	6,982.46
Failure- replace MP with another one	31,738.44	0.55 × 0.60 = 0.33	10,473.69
Total for strategy Dasatinib Zentiva 100 mg	1.00	31,738.44	

months were statistically twofold higher in patients in the Tasigna 300 mg or 400 mg twice daily groups compared with Glivec 400 mg once daily (44% vs. 22%, $p < 0.0001$ and 43% vs. 22%, $p<0.0001$, respectively). The median time to MMR was shorter for Tasigna 300 mg or 400 mg twice daily (5.7 and 5.8 months, respectively) compared to Glivec 400 mg once daily (8.3 months). A complete cytogenetic response (CCyR) was achieved by 80% of patients with Tasigna versus 65% with Glivec 400 mg daily ($p < 0.0001$). Progression to advanced disease was much lower with Tasigna 300 mg twice daily (2 patients) and with Tasigna 400 mg twice daily (1 patient) compared with Glivec 400 mg once daily (11 patients).

ICER = (74,991.49 – 13,444.56) / (0.45 – 0.58) = 615,456.93 / -0.13 = -4,173,437.9

ICER = (74,991.49 -60,876.49) / (0.45–0.75) = 14,115 / -0.30 = -47,050

When the ICER is a negative number, as in the above case when comparing the Sprycel 100 mg strategy to the Glivec 400 mg and Tasigna 300 mg strategies, it is not cost-effective because it is more expensive and has a lower clinical success rate than them. The Glivec strategy with 400 mg is dominant because it is cheaper and has higher clinical success.

ICER1 = (60,876.49 - 11,769.60) / (0.75–0.58) = 49,106.89 / 0.17 = 288,864.05

ICER2= (60,876.49 - 31,738.44) / (0.75 – 0.45) = 29,138.05 / 0.30 = 97,126.83

When the ICER is a positive number, as in the above two cases when we compare the Tasigna strategy against the Imatinib Nibix 400 mg strategy and against the Dasatinib Zentiva 100 mg strategy, it only means that the Tasigna 300 mg strategy has the highest costs, but also the most good clinical outcome, i.e. it is the most expensive and therapeutically most effective, but to understand whether the additional benefit justifies the additional cost we need to calculate the incremental net benefit (INB) for certain cost limits.

If we use three times the gross domestic product per capita (GDP) in Bulgaria in 2022 (BGN 24,252 × 3 = BGN 72,756/ under BGN 100,000/ or USD 13,026 × 3 = $39,078) as an efficiency threshold of costs according to WHO recommendations in pharmacoeconomic analyses of conventional drugs, in both cases negative numbers for INB are obtained at this cost-effectiveness threshold (Murray 2000). In 2022, GDP reached a nominal value volume of BGN 165.384 billion. Converted into US dollars at an average annual exchange rate of BGN 1.861798 for 1 US dollar, GDP amounts to 88.83 billion dollars. Recalculated in euros, the GDP is 84.559 billion euros, or 24,252 BGN per person of the indicator amount, or 13,026 dollars and 12,400 euros, respectively (Murray CJ, Evans DB, Acharya A, Baltussen RM. 2000)

If we take BGN 100,000 (€100,000 is the threshold in other EU countries) as the lower threshold of efficiency for TKI MP costs, which fall into the higher price range, then INB will be a positive number, i.e., the Tasigna 300 mg strategy will be cost-effective compared to the Dasatinib Zentiva 100 mg strategy at a minimum threshold of BGN 100,000.

INB = (difference in results × performance threshold) – difference in costs; or

INB_1 = (0.30 × 100,000) – 29,138.05 = 30,000 – 29,138.05 = 861.95 BGN.

The next two figures present decision tree models comparing the main TKI MPs used to treat patients with CML-CP in the second line (Figs 7, 8).

Of the strategies applied in the second line of drug therapy for patients with CML-CP, the first strategy with Glivec 600mg daily has a high probability of success and is the cheap-

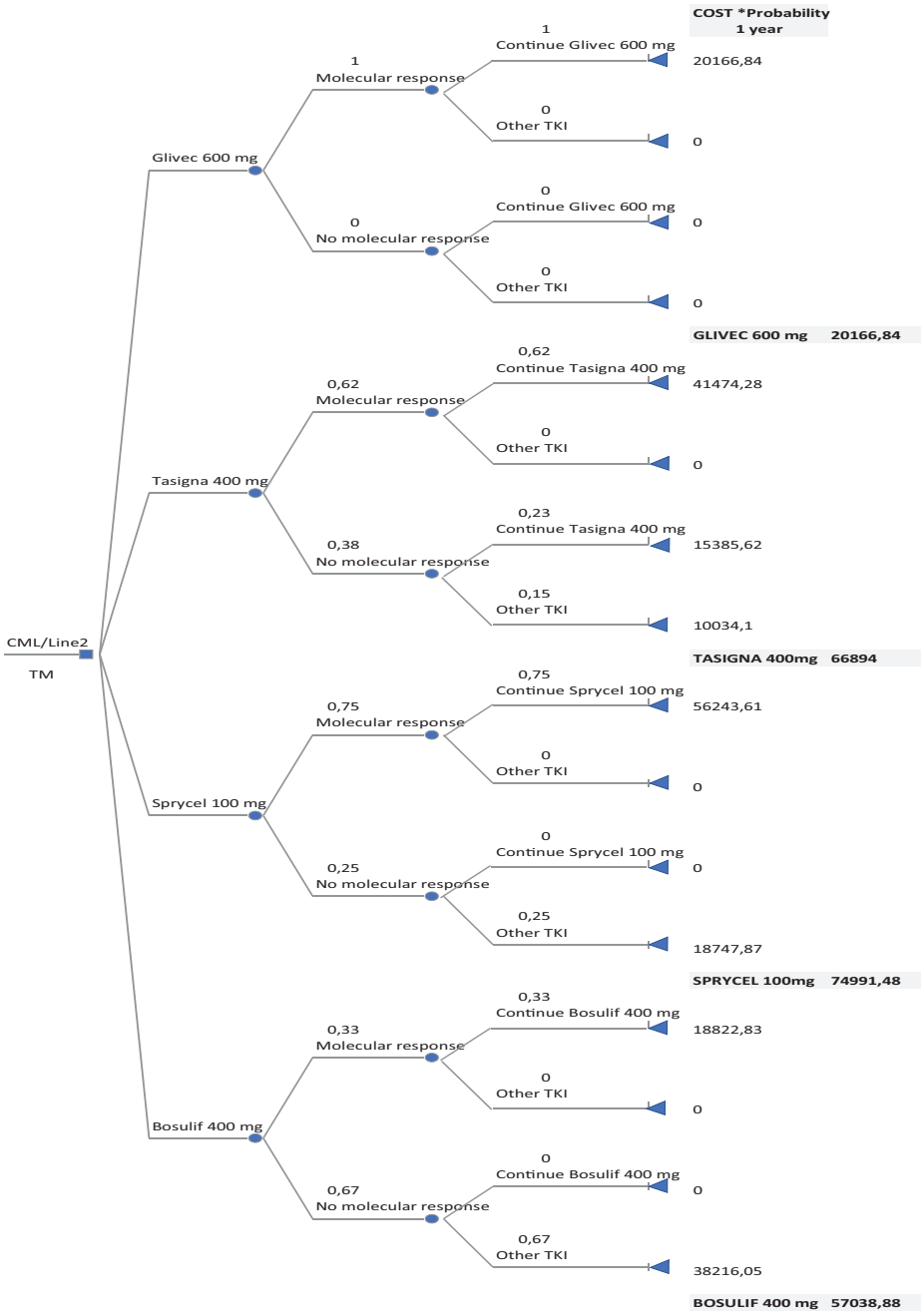

Figure 7. Decision tree for patients with CML – CP in second-line therapy with TKI trademarks (TM).

est, with an average cost per year of BGN 20,166.84 (Table 14) However, the number of patients with this second-line strategy is very small, due to the numerous mutations and the development of resistance and intolerance. If any other generic product is used instead of the original Glivec, the treatment will become even cheaper. (Table 15) The Glivec 600 mg strategy is dominant because it is the cheapest and has the highest probability of clinical success. The ICERs of all other strategies with original MPs compared to this strategy are negative. With almost two times higher average annual costs of BGN 31,738.40 compared to the Imatinib Nibix 600 mg strategy and a high probability of success of 75%, it is the third strategy with the generic Dasatinib Zentiva 100 mg daily, which is dominant compared to the 2nd generation TKI strategies MP- Bosulif 400 mg and Tasigna 400 mg.

$$ICER_1 = (74{,}991.48 - 57{,}038.88) / (0.75 - 0.33) = 17{,}952.60 / 0.42 = 42{,}744.85.$$

$$ICER_2 = (74{,}991.48 - 66{,}894.00) / (0.75 - 0.62) = 8{,}097.48 / 0.13 = 62{,}288.31.$$

The Sprycel 100 mg strategy is the most expensive, but due to its highest second-line success, it has a positive ICER value compared to Bosulif 400 mg and Tasigna 400 mg. ($ICER_1$ and $ICER_2$ in BGN).

The second strategy Tasigna (300mg or 400 mg 2× daily) is expensive, because the drug is protected by a patent, there are no generic analogues, but it has a high clinical success rate and in the second line - 62%. The ICER of Tasigna versus Bosulif 400 mg is also a positive number, but to under-

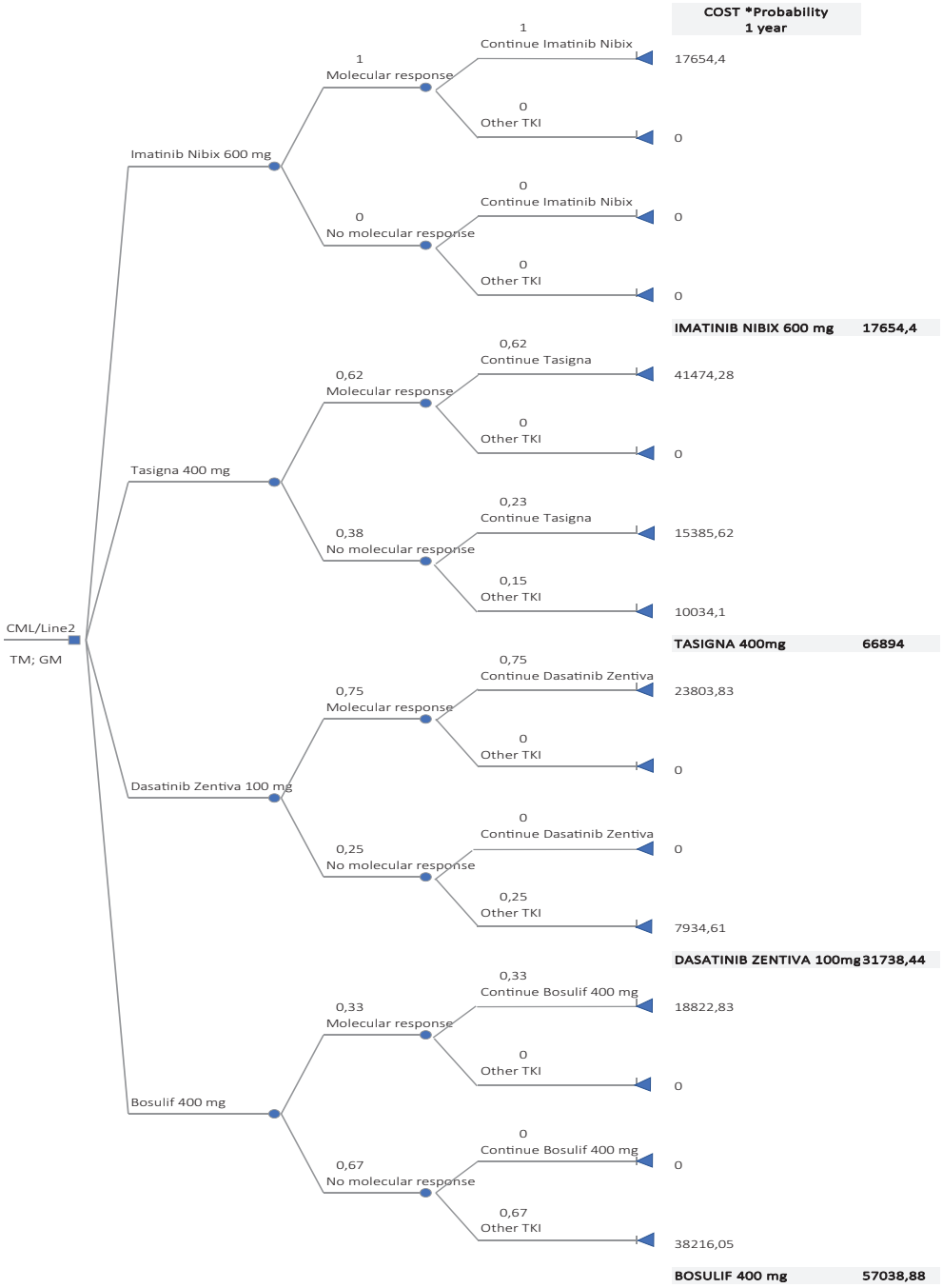

Figure 8. Decision tree for patients with CML –CP in second-line therapy with TKI (TM;GM).

stand whether the additional benefit justifies the additional cost we need to calculate the incremental net benefit (INB) for certain cost ranges for the three positive ICERs.

$$ICER_3 = (66{,}894.00 - 57{,}038.88) / (0.62 - 0.33) = 9{,}855.12 / 0.29 = 33{,}983.17.$$

Since we have taken BGN 100,000 as the lower threshold of efficiency for the costs of TKI LP, which fall in the higher price range, the calculated INB are positive numbers at this threshold, i.e.: the Sprycel 100 mg strategy is cost-effective compared to Bosulif 400 mg and Tasigna 400 mg., and the Tasigna 400 mg strategy is cost-effective over the Bosulif 400mg strategy.

INB = (difference in results × performance threshold) – difference in costs; or

$$INB_1 = (0.42 \times 100{,}000) - 17{,}952.60 = 42{,}000 - 17{,}952.60 = 24{,}047.40$$

$$INB_2 = (0.13 \times 100{,}000) - 8{,}097.48 = 13{,}000 - 8{,}097.48 = 4{,}902.52$$

$$INB_3 = (0.29 \times 100{,}000) - 9{,}855.12 = 29{,}000 - 9{,}855.12 = 19{,}144.88.$$

We performed the followed sensitivity analyses: we varied the cost of TKIs by 400 mg ± 25% and the cohort of

Table 14. Determining the average annual value of each strategy applied in the second line of treatment of patients with CML-CP in the hematology clinic at the Medical University of Plovdiv (2018–2022) TM.

Results	Costs per 1 year	Probabilities	Costs x Probabilities
A. First strategy Glivec 600 mg daily			
Success - stay on this MP	1,680.57 × 12 = 20,166.84	1.00 × 1.0 = 1.0	20,166.84
Total for strategy Glivec 600 mg		1.0	20,166.84
B. Second strategy Tasigna300 mg or 400mg 2 x daily			
Success - stay on this MP Average price	5,574.5 × 12 = 66,894	0.62 × 1.00 = 0.62	41,474.28
Success - replace with another TKI	66,894	0.62 × 0.00 = 0	–
Failure - stay on this MP	66,894	0.38 × 0.6 = 0.23	15,385.62
Failure- replace MP with another one	66,894	0.38 × 0.40 = 0.15	10,034.1
Total for strategy Tasigna		1.00	66,894.00
C. Third strategy Sprycel 100 mg daily			
Success - stay on this MP	6,249.29 × 12 = 74,991.48	0.75 × 1.0 = 0.75	56,243.61
Success - replace with another TKI	74,991.48	0.75 × 0.0 = 0	–
Failure - stay on this MP	74,991.48	0.25 × 0.0 = 0	–
Failure- replace MP with another one	74,991.48	0.25 × 1.00 = 0.25	18,747.87
Total for strategy Sprycel 100 mg		1.0	74,991.48
D. Forth strategy Bosulif 400mg daily			
Success - stay on this MP	4,753.24 × 12 = 57,038.88	0.33 × 1.0 = 0.33	18,822.83
Success -replace with another TKI	57,038.88	0.33 × 0.0 = 0	–
Failure - stay on this MP	57,038.88	0.66 × 0.0 = 0	–
Failure- replace MP with another one	57,038.88	0.67 x1.0 = 0.67	38,216.05
Total for strategy Bosulif 400mg		1.00	57,038.88

Table 15. The annual value of each strategy applied to the second line of treatment for patients with CML-CP in the hematology clinic at the Medical University of Plovdiv (2018-2022) GN; TM.

Results	Costs per 1 year	Probabilities	Costs x Probabilities
A. First strategy Imatinib Nibix 600 mg daily			
Success - stay on this MP	1,471.20 × 12 = 17,654.40	1.00 × 1.0 = 1.0	17,654.40
Total for strategy Imatinib Nibix 600 mg		1.0	17,654.40
B. Second strategy Tasigna300 mg or 400 mg 2 x daily			
Success -stay on this MP	5,574.5 × 12 = 66,894	0.62 × 1.00 = 0.62	41,474.30
Success - replace with another TKI	66,894	0.62 × 0.00 = 0	–
Failure - stay on this MP	66,894	0.38 × 0.6 = 0.23	15,385.62
Failure- replace with another TKI	66,894	0.38 × 0.40 = 0.15	10,034.10
Total for strategy Tasigna		1.00	66,894.00
C. Third strategy Dasatinib 100 mg daily			
Success- stay on this MP	2644.87 × 12 = 31,738.44	0.75 × 1.0 = 0.75	23,803.83
Success - replace with another TKI	31,738.44	0.75 × 0.0 = 0	–
Failure - stay on this MP	31,738.44	0.25 × 0.0 = 0	–
Failure- replace with another TKI	31,738.44	0.25 × 1.00 = 0.25	7,934.61
Total for strategy Dasatinib 100 mg	31,738.44		
D. Forth strategy Bosulif 400 mg daily			
Success - stay on this MP	4,753.24 × 12 = 57,038.88	0.33 × 1.0 = 0.33	18,822.83
Success - replace with another TKI	57,038.88	0.33 × 0.0 = 0	–
Failure - stay on this MP	57,038.88	0.66 × 0.0 = 0	–
Failure- replace MP with another one	57,038.88	0.67 × 1.0 = 0.67	38,216.05
Total for strategy Bosulif 400 mg		1.00	57,038.88

patients with failure switching to a more effective second- or third-generation TKI (Fig. 9).

The results of the one-way sensitivity analysis proved to be stable. As presented in Fig. 7 the costs of treatment with tyrosine kinase inhibitors in first- and second-line chronic phase myeloid leukemia were significantly influenced by the cost of treatment with Tasigna 400 mg, Tasigna 300 mg, Glivec 400 mg and Sprycel 100 mg. Under the scenario analysis and assumption, the annual costs for generic Dasatinib 100 mg and Imatinib 400mg are lower than the set threshold.

One-way sensitivity analysis of treatment costs for Tyrosine kinase inhibitors of the fraction of patients without a molecular response who continue therapy with TKI in the first- and second- lines treatment of chronic phase of CML (Fig. 8) revealed an increase in the costs of Glivec 600 mg, Imatinib 600 mg, Tasigna 400 mg and Bosulif 400 mg, while the costs of Dasatinib 100 mg and Tasigna 300 mg under the adopted scenario of varying the probabilities by ± 50% remain lower.

A one-way sensitivity analysis of treatment costs for tyrosine kinase inhibitors in first- and second-line therapy of patients with CML–CP and one-way sensitivity analysis of treatment costs for tyrosine kinase inhibitors of fraction of patients without a molecular response who continue targeted therapy with tyrosine kinase inhibitors in first- and sec-

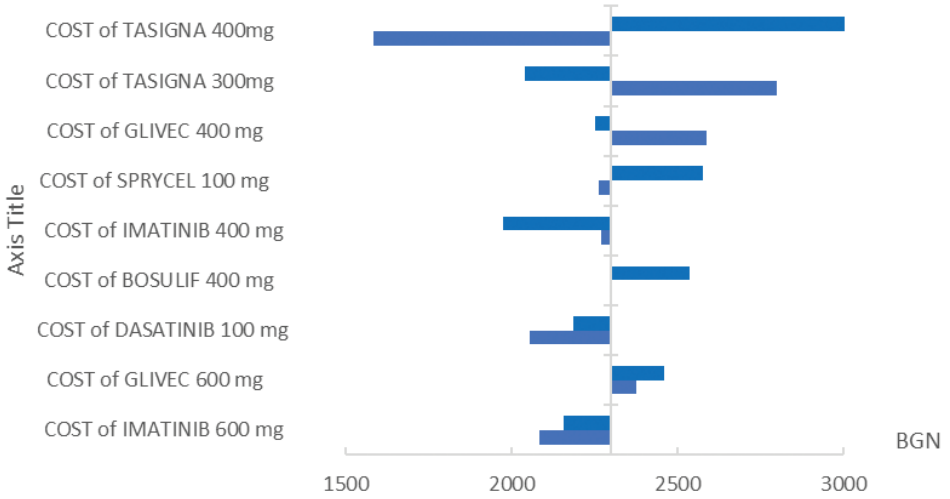

Figure 9. One-way sensitivity analysis of treatment costs for tyrosine kinase inhibitors in first- and second- lines therapy of patients with CML–CP (Tornado diagram). Variation of the drug costs with ± 25% of the prices. The values are presented in Bulgarian monetary currency /BGN/.

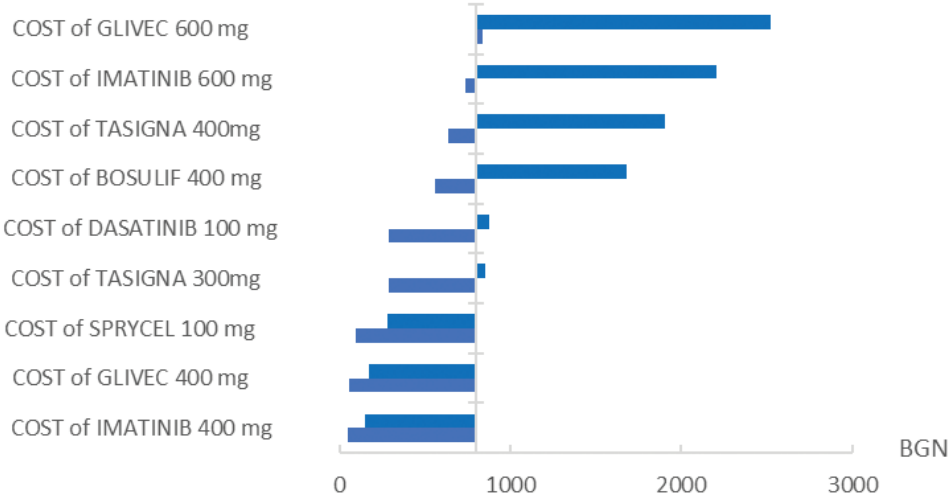

Figure 10. One-way sensitivity analysis /Tornado diagram/ of treatment costs for tyrosine kinase inhibitors of the fraction of patients without a molecular response who continue targeted therapy with Tyrosine kinase inhibitors in first- and second- lines treatment of the chronic phase of CML. Variation of the fraction of the patients with ± 50% of the probabilities. The values are presented in Bulgarian monetary currency /Leva/.

ond- lines treatment of chronic phase of CML in Bulgarian monetary currency /BGN, Leva/ are presented in Figs 9, 10.

2G and 3G TKIs will lose patent protection by 2026-2034. Although costs are likely to decrease, it is difficult to predict the scale and timing of future changes. For this reason, we did not model specific cost scenarios for 2GTKI. Instead, we performed a price sensitivity analysis of 2GTKI by changing the price by ± 25%. The sensitivity analysis may cover some scenarios, but cost assumptions for 2GTKIs are likely not to apply once patent protection lapses and generics enter.

Conclusion

Sensitivity analyses of the pharmacoeconomic models showed their robustness. The thresholds for the cost of TKI drugs and the frequency of achieving a deep molecular response were determined, determining the economic feasibility of choosing first- and second-generation tyrosine kinase inhibitors in the first- and second-line treatment of patients with CML-CP. The results show that the Glivec 400 mg strategy is dominant in the first line and the Glivec 600 mg in the second- lines of therapy because it is cheaper and has higher clinical success. At a lower cost-effectiveness threshold for TKI MPs that fall in the higher price range, BGN 100 000, the Tasigna 300 mg strategy will be cost-effective compared to the Dasatinib Zentiva 100 mg strategy on first line of therapy, the Sprycel 100 mg strategy is cost-effective compared to Bosulif 400 mg, and Tasigna 400 mg and the Tasigna400 mg strategy is cost-effective over the Bosulif 400mg strategy in the second line of therapy of patients with CML-CP. With almost two times higher average annual costs of BGN 31,738.40 compared to the Imatinib Nibix 600 mg strategy and with a high probability of success of 75%, it is the third strategy

with the generic Dasatinib Zentiva 100 mg daily, which is dominant compared to the 2nd generation TKI strategies LP- Bosulif 400mg and Tasigna 400 mg.

Author Contributions

Conceptualization, VGM, MKT, and ZhGP; Data curation, DG, VG, KA, EG, and YG; Formal analysis, DG, VG, KA, EG, YG, and MKT; Investigation, VGM, and MKT; Methodology, KA, YG, and MKT; Resources VGM, KA, YG, EG, MKT, and ZGP; Software, VG, KA, and YG; Validation, VGM; Visualization, VG; Writing – original draft, DG; Writing – review and editing, VGM, EG, MKT, and ZGP.

Funding

This research is realized with the financial support of the Project BG05M2OP001-1.002-0005-C03, Competence Center „Personalized Innovative Medicine (PERIMED)“, work packs 1, 2, 3, 8, financed by the Operational Program „Science and Education for Smart Growth“, co-financed by the European Union through the European Structural and Investment Funds.

Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the Medical University of Plovdiv , Protocol 3/2018

Informed consent statement

Informed consent was obtained from all subjects involved in the study

Data availability statement

Data were taken from the electronic information system and patient medical records at Clinic of Clinical Hematology, University Hospital “Sv. Georgi”.

References

Baccarani M, Deininger MW, Rosti G, Hochhaus A, Soverini S, Apperley JF, Cervantes F, Clark RE, Cortes JE, Guilhot F, Hjorth-Hansen H, Hughes TP, Kantarjian HM, Kim DW, Larson RA, Lipton JH, Mahon FX, Martinelli G, Mayer J, Müller MC, Niederwieser D, Pane F, Radich JP, Rousselot P, Saglio G, Saußele S, Schiffer C, Silver R, Simonsson B, Steegmann JL, Goldman JM, Hehlmann R (2013) European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood 122: 872–884. https://doi.org/10.1182/blood-2013-05-501569

Bonifacio M, Maheshwari V, Tran D, Agostoni G, Filioussi K, Viana R (2022) Economic Model to Evaluate the Cost-Efectiveness of Second-Line Nilotinib Versus Dasatinib for the Treatment of Philadelphia Chromosome-Positive Chronic Myeloid Leukemia (CML-CP) in Italy. PharmacoEconomics - Open 6: 95–104. https://doi.org/10.1007/s41669-021-00286-3

Cortes JE, Kim DW, Pinilla-Ibarz J, le Coutre P, Paquette R, Chuah C, Nicolini FE, Apperley JF, Khoury HJ, Talpaz M, DiPersio J, DeAngelo DJ, Abruzzese E, Rea D, Baccarani M, Müller MC, Gambacorti-Passerini C, Wong S, Lustgarten S, Rivera VM, Clackson T, Turner CD, Haluska FG, Guilhot F, Deininger MW, Hochhaus A, Hughes T, Goldman JM, Shah NP, Kantarjian H (2013) A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. The New England Journal of Medicine 369: 1783–1796. https://doi.org/10.1056/NEJMoa1306494

Council Directive (2020) 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems. OJ L 40, 11.2.1989, p. 8–11 (ES, DA, DE, EL, EN, FR, IT, NL, PT) In force. [Cited 2020 June 23]. http://data.europa.eu/eli/dir/1989/105/oj

Efficace F, Baccarani M, Breccia M, Alimena G, Rosti G, Cottone F, Deliliers GL, Baratè C, Rossi AR, Fioritoni G, Luciano L, Turri D, Martino B, Di Raimondo F, Dabusti M, Bergamaschi M, Leoni P, Simula MP, Levato L, Ulisciani S, Veneri D, Sica S, Rambaldi A, Vignetti M, Mandelli F (2011) Health-related quality of life in chronic myeloid leukemia patients receiving long-term therapy with imatinib compared with the general population. Blood 118: 4554–4560. https://doi.org/10.1182/blood-2011-04-347575

Eichler HG, Kong SX, Gerth WC, Mavros P, Jonsson B (2004) Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? Value Health 7(5): 518–528. https://doi.org/10.1111/j.1524-4733.2004.75003.x

EMA (2012) European Medicines Agency. https://www.ema.europa.eu/en/medicines/human/EPAR/glivec

EMA (2020) Availability of medicines, for regulators-on-public-communication-section. https://www.ema.europa.eu/en/human-regulatory/postauthorisation/availabilitymedicines#guidance

EMA, Bosulif (2022) European Medicines Agency. https://www.ema.europa.eu/en/medicines/human/EPAR/bosulif

EMA, Glivec (2012) European Medicines Agency. https://www.ema.europa.eu/en/medicines/human/EPAR/glivec;

EMA, Ponatinib (2013) European Medicines Agency. https://www.ema.europa.eu/en/medicines/human/EPAR/iclusig

EMA, Sprycel (2019) European Medicines Agency. https://www.ema.europa.eu/en/medicines/human/EPAR/sprycel

EMA, Tasigna (2019) European Medicines Agency. https://www.ema.europa.eu/en/medicines/human/EPAR/tasigna

Goranova-Marinova V, Grekova D, Georgieva V, Andreevska K, Gvozdeva Y, Kassarova M, Grudeva-Popova Z (2023) Analysis of the pharmacotherapeutic effectiveness of the tyrosine kinase inhibitors

therapy in patients with Chronic Myeloid Leukemia in a single hematology center in Plovdiv, Bulgaria. Pharmacia 70(4): 1355–1362. https://doi.org/10.3897/pharmacia.70.e111923

Kalmanti L, Saussele S, Lauseker M, Müller MC, Dietz CT, Heinrich L, Hanfstein B, Proetel U, Fabarius A, Krause SW, Rinaldetti S, Dengler J, Falge C, Oppliger-Leibundgut E, Burchert A, Neubauer A, Kanz L, Stegelmann F, Pfreundschuh M, Spiekermann K, Scheid C, Pfirrmann M, Hochhaus A, Hasford J, Hehlmann R (2015) Safety and efficacy of imatinib in CML over a period of 10 years: data from the randomized CML-study iv. Leukemia 29: 1123–1132. https://doi.org/10.1038/leu.2015.36

Kamusheva M, Georgieva S, Lakic D, Mitov K, Savova A, Stoimenova A, Petrova G (2013) A health-related quality of life and pharmacotherapy costs study for patients with cystic fybrosis, gaucher disease and chronic myeloid leukemia in Bulgaria. Biotechnology & Biotechnological Equipment 27(3): 3896–3900. https://doi.org/10.5504/bbeq.2013.0029

Kim K, McMillin GA, Bernard PS, Tantravahi S, Walker BS, Schmidt RL (2019) Cost effectiveness of therapeutic drug monitoring for imatinib administration in chronic myeloid leukemia. PLOS ONE 14(12): e0226552. https://doi.org/10.1371/journal.pone.0226552

Kim TD, Rea D, Schwarz M, Grille P, Nicolini FE, Rosti G, Levato L, Giles FJ, Dombret H, Mirault T, Labussière H, Lindhorst R, Haverkamp W, Buschmann I, Dörken B, le Coutre PD (2013) Peripheral artery occlusive disease in chronic phase chronic myeloid leukemia patients treated with nilotinib or imatinib. Leukemia 27: 1316–1321. https://doi.org/10.1038/leu.2013.70

Lex.bg (2020a) Ordinance on terms, rules and procedure for regulation and registration of prices for medicinal products (in force since 30.04.2013) [Cited 2020 June 23]. https://www.lex.bg/laws/ldoc/2135852669

Lex.bg (2020b) Bulgarian Law on Medicinal Products in Human Medicine, (in force since 13.04.2007) [Cited 2020 June 23]. http://www.lex.bg/bg/laws/ldoc/2135549536

Li N, Zheng B, Cai H-F, Yang J, Luo X-F, Weng L-Z, Zhan F-M, Liu M-B(2018) Cost effectiveness of imatinib, dasatinib, and nilotinib as first line treatment for chronic-phase chronic myeloid leukemia in China. Clinical Drug Investigation 38(1): 79–86. https://doi.org/10.1007/s40261-017-0587-z

Lucchesi S, Marciano I, Panagia P, Intelisano R, Randazzo MP, Sgroi C, Altavilla G, Santarpia M, Adamo V, Franchina T, Ferrau F, Reitano P, Trifiro G (2018) Prevalence of Use and Cost of Biological and Non-Biological Targeted Therapies for Cancer Treatment: A 5-Year Picture from Southern Italy. Clinical Drug Investigation 38(3): 269–278. https://doi.org/10.1007/s40261-017-0591-3

Murray CJ, Evans DB, Acharya A, Baltussen RM (2000) Development of WHO guidelines on generalized cost-effectiveness analysis. Health Economics 9(3): 235–251. https://doi.org/10.1002/(SICI)1099-1050(200004)9:3%3C235::AID-HEC502%3E3.0.CO;2-O

National Health Insurance Fund (2021) National Health Insurance Fund ,Bulgaria. [Cited 2021 Feb. 21] https://www.nhif.bg/page/218

National Statistical Institute in Bulgaria (2023) Administrative division by GDP per capita. http://www.nsi.bg [Accessed 2, October 2023]

NCPRMP [National Council of Price and Reimbursement of Medicinal Products] (2020) Electronic registers of National Council of Price and Reimbursement of Medicinal Products, Bulgaria. [Cited 2020 June 02] https://portal.ncpr.bg/registers/pages/register/list-medicament.xhtml

Official Journal of the European Union (2020) Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. [Cited 2020 June 30] http://data.europa.eu/eli/reg/2004/726/oj

Pharmaco-Therapeutic Manual of Hematology (2024) Methodological guidelines for diagnosis and treatment of hematological diseases. Publication of the Bulgarian Medical Society of Hematology, 2019, version 3, 160–181. https://bulgarian-hematology.com/rakovodstva-na-bmsh/

Saglio G, Kim DW, Issaragrisil S, le Coutre P, Etienne G, Lobo C, Pasquini R, Clark RE, Hochhaus A, Hughes TP, Gallagher N, Hoenekopp A, Dong M, Haque A, Larson RA, Kantarjian HM (2010) ENESTnd Investigators. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. The New England Journal of Medicine 362(24): 2251–2259. https://doi.org/10.1056/NEJMoa0912614

Saußele S, Richter J, Hochhaus A, Mahon F-X (2016) The concept of treatment-free remission in chronic myeloid leukemia. Leukemia 30: 1638–1647. https://doi.org/10.1038/leu.2016.115

Shuvaev V, Abdulkadyrov K, Turkina A, Martynkevic i, Chelysheva E, Fominykh M, Martchenko V (2015) Pharmacoeconomical analysis of chronic myelogenous leukemia treatment free remission. Blood 126(23): 3293. [Health services and outcomes research malignant diseases: poster ii / December 03, 2015)] https://doi.org/10.1182/blood.V126.23.3293.3293

WHO Resolution (2020) WHA60.16. Progress in the rational use of medicines. The Sixtieth World Health Assembly. [Cited 2020 June 23] https://apps.who.int/gb/ebwha/pdf_files/WHASSA_WHA60-Rec1/E/reso-60-en.pdf?ua=1#page=27

Yeung DT, Shanmuganathan N, Hughes TP (2022) Asciminib: a new therapeutic option in chronic- phase CML with treatment failure, Blood 139(24): 3474–3479. https://doi.org/10.1182/blood.2021014689

Yordanov A, Varbanova V (2019) Modern treatment of chronic myeloid leukemia. Medinfo 12: 1–5. https://medinfo.bg/ymoaltak/magazines/3042/article_pdf/16.pdf

Tasigna [nilotinib] (2009) Novartis AG. http://www.tasigna.com/en/tasigna-product-information.jsp#