EFFICACY AND SAFETY OF BOSUTINIB IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA – SYSTEMATIC REVIEW AND META-ANALYSIS

P. Siderova, M. Kamusheva, K. Mitov

Medical University – Sofia, Faculty of Pharmacy, Department of Organization and Economics of Pharmacy, 2 Dunav str., 1000 Sofia, Bulgaria

Abstract. Internet based search of published clinical trials for Bosutinib is conducted for the purposes of the study. The $\chi 2$ method for comparison of proportions and meta-analysis are applied using MedCalc. A fixed effect is determined for major cytogenetic response 33.725% (p=0.3552 (>0.05)) and for the adverse drug reactions thrombocytopenia – 23.576% (P = 0.4637), nausea – 43.108% (P = 0.6908) and neutropenia – 18.323%, (P = 0.9816). The results from the heterogeneity test showed random effect on the percentage of patients with diarrhea – 84.975%, (p=0.0158) and rashes – 40.003%, (p < 0.0001). There is a statistical significant difference for the efficacy $\chi 2$=21.475, neutropenia ($\chi 2$=25.686), diarrhea ($\chi 2$=281.338) and rashes ($\chi 2$=21.639), (p<0.0001) between Bosutinib and Imatinib. There is no difference for efficacy, neutropenia, thrombocytopenia and nausea of Bosutinib among the clinical trials. The efficacy and the frequency of diarrhea and rashes of Bosutinib are statistically significantly higher and the frequency of nausea is statistically significantly lower than Imatinib.

Key Words: Bosutinib, meta-analysis, efficacy, safety, CML

INTRODUCTION

Approximately 6% of the population in the world is affected by rare diseases. These patients are in front of a lot of difficulties associated with the symptoms as well as with the lack of appropriate treatment or due to no adequate access to treatment. [1,2] The development of new medicinal products for the unmet medical needs of these patients is associated with a lot of financial resources and there is also uncertainty about the expected return on the investments. Due to this reason European and American legislation define several incentives for the development and placing onto the market of designated orphan medicines. [3, 4]

So called 'small' clinical trials conducted among patients with rare diseases cannot often demonstrate a statistically significant difference between the new observed therapy and the existing one. [5] Applying meta-analysis as a quantitative approach, which combines the results from several independent clinical trials and thus the significant benefit from the new therapy could be proved. Meta-analysis includes a statistical test of heterogeneity of the results of the eligible trials selected through a precise systematic review. [6, 7, 8]

Chronic myeloid leukemia (CML) is a rare disease whose rate of incidence is reported as between 1 and 2 cases/100 000 per year. Inclusion in the clinical practice of thyrosine kinase inhibitors (TKIs) Inatinib, Dasatinib, Nilotinib, Bosutinib leads to better control of the symptoms and longer survival. The pharmacotherapy costs are significant and cost-effectiveness of the therapy with TKIs should be assessed from the perspective of every healthcare system using objective effectiveness data obtained from meta-analysis applied. [9, 10, 11]

More and more studies about the effectiveness of the treatment of the patients with rare diseases with the innovative products called orphan drugs should be performed and more precise techniques and approaches as meta-analysis should be applied.

The purposes of the current study are to evaluate the efficacy and safety of Bosutinib in patients with CML and to compare its safety and efficacy with the safety and efficacy of the first generation TKI Imatinib.

MATERIALS AND METHODS

Systematic review

Internet based search of clinical trials concerning Bosutinib was performed for the aims of the current study. Systematic review was conducted in the following Internet based scientific data basis: Pub Med, ClinicalTrials.gov, EU Clinical Trials Register. The key words used were efficacy, safety and Bosutinib. A particular consistency was followed:

1. Defining the study question: What is the existing evidence for the efficacy and safety of Bosutinib in patients with CML?

2. Input of the key words in the data base PubMed Clinical Queries - BOSUTINIB EFFICACY SAFETY CML;

3. The search for the available clinical studies was started and the details shown by the system were: Therapy/Broad[filter] AND ((“bosutinib”[Supplementary Concept] OR “bosutinib”[All Fields]) AND EFFICACY[All Fields] AND (“safety”[MeSH Terms] OR “safety”[All Fields]) AND CML[All Fields]).

4. The studies were copied and analyzed. The duplicated studies were withdrawn from the analysis.

5. The technological scheme PRISMA Flow Diagram was applied. This diagram presents the flow of information during different phases of the systematic review. It shows the number of the identified, included and excluded studies and the reasons for exclusion as well. [12]

Meta-analysis

The data from the studies are analyzed by statistical software MedCalc used for statistical analysis of medical research. The $\chi 2$-method for comparison of proportions and meta-analysis were applied.

Particular steps are applied in MedCalc: Statistics -> Meta-analysis -> Proportions. The input data were major cytogenetic response, overall survival (OS), progression free survival (PFS), adverse drug reactions (ADRs): anemia, diarrhea, nausea, thrombocytopenia, neutropenia. A heterogeneity test was performed and the conclusions were based on the level of significance of the results. Forest plot diagram was designed for each of the observed variables.

Comparison of proportions

$\chi 2$ method is applied for hypothesis testing about association between categorical variables. The null hypothesis says that there is no statistically significant association between the variables - the proportions for a particular variable are equal for all observed groups. The alternative hypothesis claims for existing of such association. High value for $\chi 2$ corresponds to a low probability of occurrence of the event ($p<0.05$), which is verification for statistically significant difference between the variables observed.

RESULTS AND DISCUSSION

21 studies about efficacy and safety of Bosutinib were identified. 6 of them were excluded due to duplication, 9 were without results published and 1 was an article. Only 1 of the last 5 was a randomized clinical trial which had led to its exclusion from the qualitative analysis. Only one study did not give enough information about all ADRs object of the study and its role was assessed only for the purposes of com-

Table. 1 Data extracted from the analyzed studies

STUDY	*Total_N	MCyR+	MCyR_N	OS %	OS_N	PFS %	PFS_N	D %	D_N	R %	R_N	T %	T_N	A %	A_N	N %	N_N	NEO %	NEO_N
1	118	32%	38	83	98	73	86	81	96	22	26	25	30	8	9	43	51	19	22
2	63	36%	23	96	60	94	59	95	60	57	36	18	11		0	38	24	18	11
3	288	31%	89	92	265	79	228	84	242	44	127	24	69	13	37	44	127	18	52
4	143	39%	56					90	129										

***Total_N** – total number of the patients; **MCyR+** - patients with major cytogenetic response in %; **MCyR_N** – patients with major cytogenetic response in absolute number; **OS** – overall survival in %; **OS_N** - overall survival in absolute number; **PFS** –progression-free survival in %; **PFS_N** –progression-free survival in absolute number; **D** – patients with diarrhea in %; **D_N** – patients with diarrhea in absolute number*; **R** - patients with rashes in %; **R_N** - patients with rashes in absolute number; **T** – patients with thrombocytopenia in %; **T_N** - patients with thrombocytopenia in absolute number; **A** - patients with anemia in %; **A_N** - patients with anemia in absolute number; **N** - patients with nausea in %; **N_N** - patients with nausea in absolute number; **NEO** – patients with neutropenia in %; **NEO_N** patients with neutropenia in absolute number.*

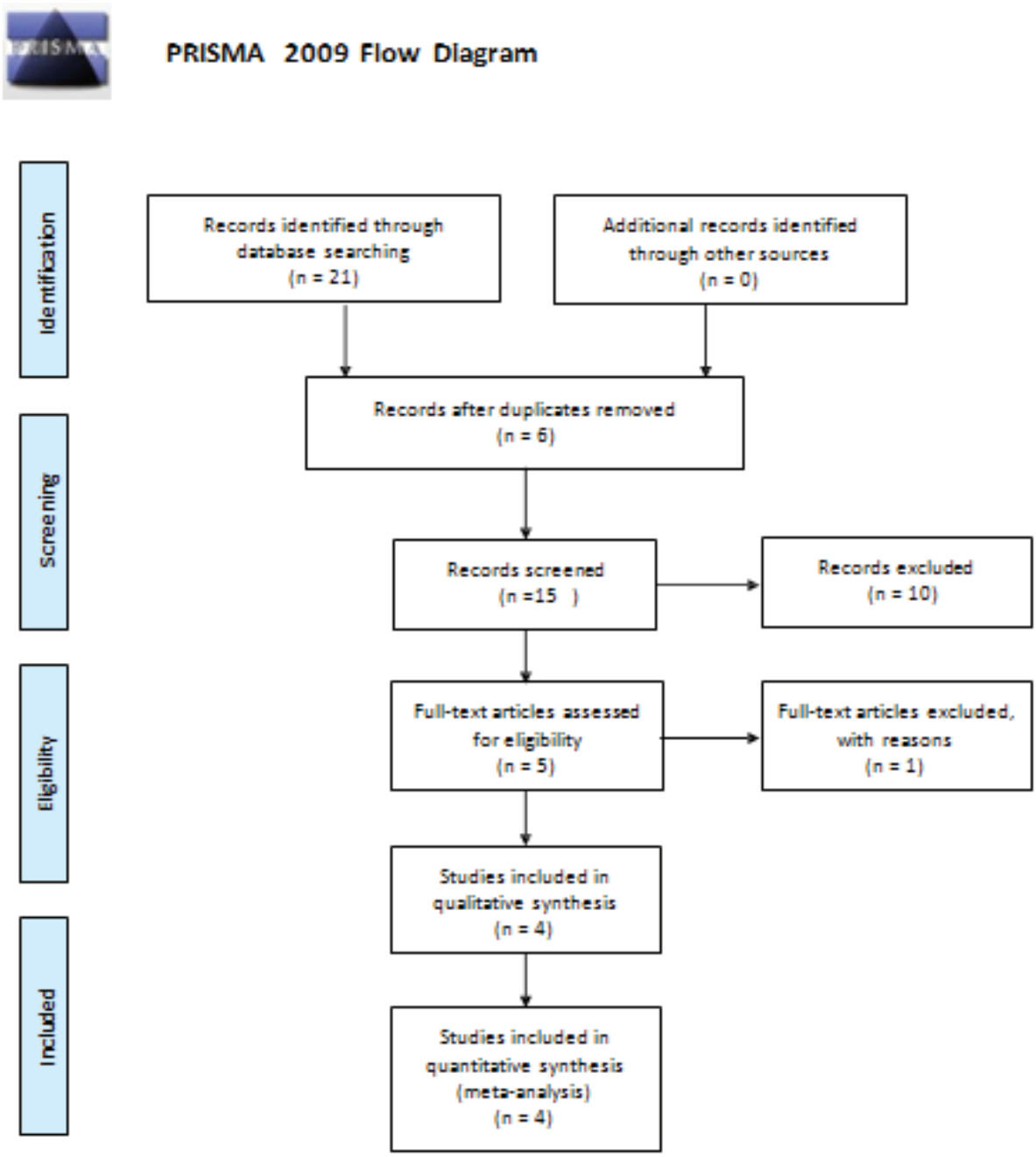

Fig. 1. PRISMA flow diagram
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta- Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

parison of Bosutinib efficacy. **Figure 1** represents the adapted PRISMA flow diagram which gives information about the flow of information during the performed systematic review. 3 clinical trials were included in the meta-analysis and one additional only for efficacy as well. [13, 14, 15, 16]

The data from the included studies are presented in **table 1**. Efficacy was defined by the percentage of the patients who have achieved major cytogenetic response. The most common ADRs in these groups of patients treated with TKIs were nausea, diarrhea, thrombocytopenia, anemia, neutropenia, rashes.

Efficacy of Bosutinib

A meta-analysis of the data collected about major cytogenetic response of Bosutinib in patients

with CML was performed. The total number of the patients was 612, and the number of the patients with **major cytogenetic response** were 33,725%, 95% CI (29,996 - 37,611). The performed test of heterogeneity showed that the level of significance is p=0,3552 (>0,05), which rejected the null hypothesis for presence of a significant difference between the results of the different studies. There is no statistically significant difference in the effects. Therefore a fixed effect was found which means that there is a lack of differences between the effects from the different samples. (**Table 2, fig.2**)

Table 2. Heterogeneity test for efficacy data

Q	3,2461
DF	3
Significance level	P = 0,3552
I^2 (inconsistency)	7,58%
95% CI for I^2	0,00 to 88,07

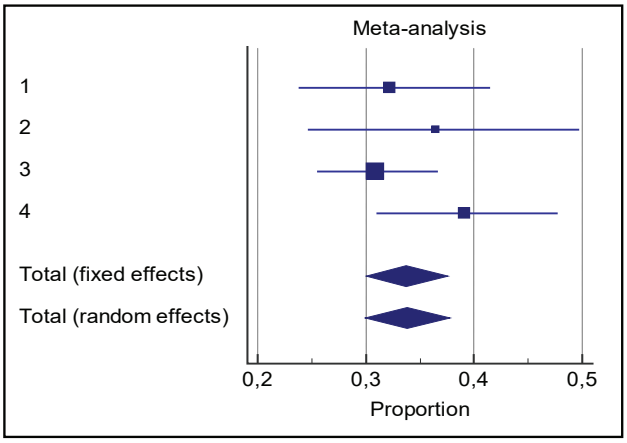

Fig. 2. Forest Plot diagrma for efficacy data of Bosutinib

Analyses of the other effects: overall survival ***(OS)*** (**table. 3, fig. 3**) and progression free survival ***(PFS)*** were performed (**table 4, fig. 4**). The results show that the level of significance p=0.0145 (<0.05) for OS and p = 0.0012 (<0.05) for PFS are 90.06 (95% CI 83.034-95.367) and 81.928 (95% CI 70.883-90.798), respectively. A random effect was defined which proves that there is a difference in the effects among different samples.

Safety of Bosutinib

A meta-analysis of Bosutinib safety regarding the

Table 3. Heterogeneity test for OS data

Q	**8,4605**
DF	**2**
Significance level	**P = 0,0145**
I2 (inconsistency)	**76,36%**
95% CI for I2	**22,53 to 92,79**

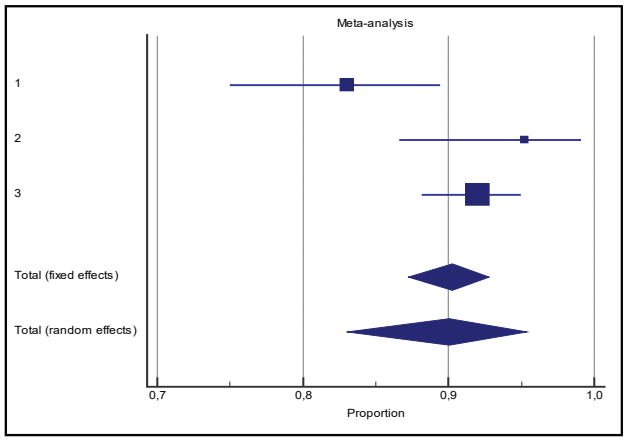

Fig. 3. Forest Plot diagram for OS

Table. 4. Heterogeneity test for PFS

Q	**13,4859**
DF	**2**
Significance level	**P = 0,0012**
I2 (inconsistency)	**85,17 %**
95% CI for I2	**56,30 to 94,97**

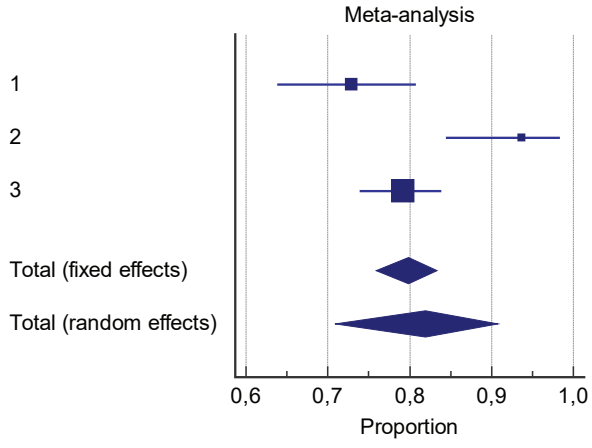

Fig. 4. Forest Plot diagram for PFS

ADRs – diarrhea, rashes, nausea, neutropenia, thrombocytopenia and anemia was performed. A random effect was defined about the following ADRs: diarrhea (p=0,0158, 84,975%, 95% CI 81,427 -88,077) (**fig.5**) and rashes (p < 0,0001, 40,003%, 95% CI 35,552 - 44,580) (**fig.6**). There are statistically significant differences regarding the number of patients with diarrhea and rashes in the observed samples.

A fixed effect was determined in patients who experienced thrombocytopenia (P = 0,4637, 23,576% , 95% CI 19,817 - 27,671) (**fig.7**); nausea (P = 0,6908, 43,108%, 95% CI, 38,590 - 47,713) (**fig.8**) and neutropenia (P = 0,9816, 18,323%, 95% CI, 14,935 - 22,114) (**fig. 9**), which proves lack of statistically significant differences regarding the number of patients with thrombocytopenia, nausea and neutropenia.

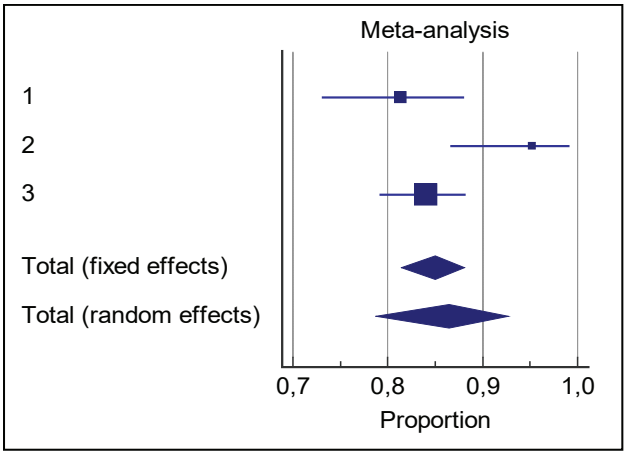

Fig. 5. Forest Plot diagram for diarrhea

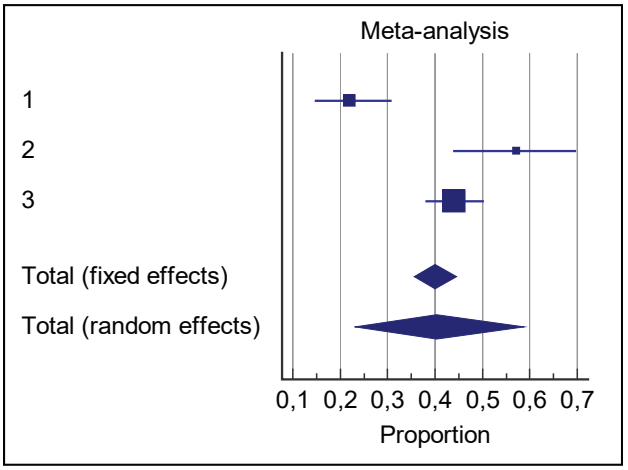

Fig. 6. Forest Plot diagram for rash

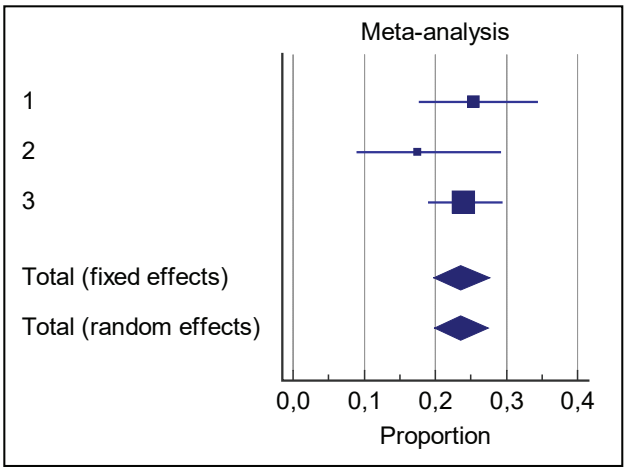

Fig. 7. Forest Plot diagram for thrombocytopenia

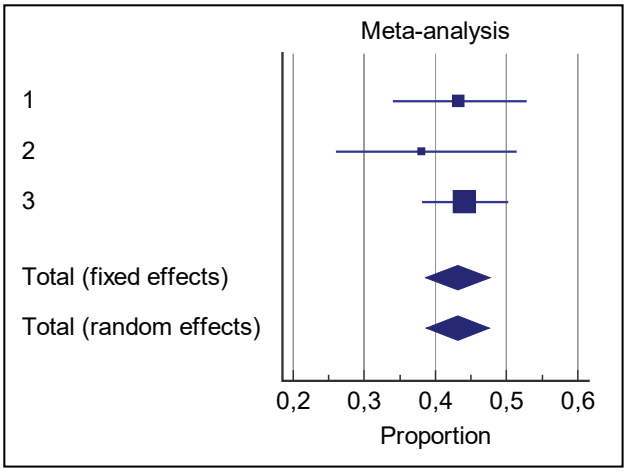

Fig. 8. Forest Plot diagram for nausea

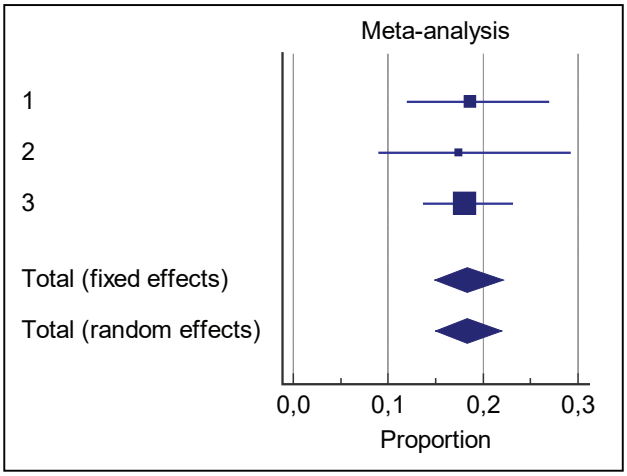

Fig. 9. Forest Plot diagram for neutropenia

Table 5. Data for efficacy and safety of Bosutinib and Imatinib

STUDY	Total_N	MCyrR+	D	R	T	A	N	NEO
Imatinib	260	16%	24%	23%	29%	41%	63%	16%
Bosubinib		33.725%	84.975%	40.003%	23.576%		43.108%	18.323%

Comparison of proportions

The pooled results for efficacy and safety of Bosutinib after conduction of the described meta-analysis were compared with efficacy and safety of first generation TKI Imatinib. The data for Imatinib were extracted from a study in Phase II conducted among 260 patients with CML in blast phase. [17] In 16% of the patients Imatinib has induced major cytogenetic response and in 7% – complete cytogenetic response. 24% of the patients experienced diarrhea, 23% – rashes, 29% – thrombocytopenia, 41% – anemia, 63% – nausea, 16% – neutropenia. (**Table 5)**

Statistically significant difference (p<0.0001) was determined for:

1. Efficacy – Chi-squared=21.475, 16.0830% difference, 95% CI, 9.5239% – 22.2168%;
2. ADR nausea – Chi-squared=25.686, 19.8920% difference, 95% CI, 12,1738% – 27,3183%;
3. ADR diarrhea – Chi-squared = 281.338, 62.4760% difference, 95% CI, 55.8534% – 68.3403%;
4. ADR rashes – Chi-squared = 21.639, 17,3570% difference, 95% CI, 10.1891% – 24.129%;

No statistically significant difference *(p>0,05)* was defined for:

1. ADR thrombocytopenia – p = 0.4908, Chi-squared = 0.475, 2.3230% difference, 95% CI, – 3,7496% – 8,0176%;
2. ADR neutropenia – p = 0.1284, Chi-squared = 2.312, 5.4240% difference, 95% CI, – 1,393% to 12,4483%.

CONCLUSION

The total number of clinical trials which observe efficacy and safety of Bosutinib in CML patients is limited. No difference between the data about Bosutinib efficacy was defined and the total fixed effect for efficacy was approximately 34% which proves the efficacy of Bosutinib regarding major cytogenetic response. Differences were observed for ADRs nausea and diarrhea and more evidence should be obtained about these ADRs. The efficacy of Bosutinib is greater than Imatinib and the differences were determined to be approximately 16%. The safety profile of Bosutinib and Imatinib is acceptable and the frequencies of diarrhea and rashes are higher in the sample treated with Bosutinib. Additional studies should be conducted for the purposes of investigation of Bosutinib safety compared with other TKIs. Individual treatment approach should be applied according to patient's tolerability.

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✉ **Corresponding author:**
Maria Stefanova Kamusheva, PhD
Department of Organization and Economics of Pharmacy
Faculty of Pharmacy, Medical University – Sofia
Dunav str. 2, 1000 Sofia, Bulgaria
E-mail: maria.kamusheva@yahoo.com