# Adjuvant imatinib after resection of gastrointestinal stromal tumour – systematic review and meta-analysis

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## ABSTRACT

**Background**: Adjuvant therapy is recommended for the population of patients with high risk of recurrence of gastrointestinal stromal tumour after resection.

**The aim of the study**: Evaluation of the clinical efficacy and safety profile of imatinib used in adjuvant therapy in patients after complete resection of a gastrointestinal stromal tumour.

**Material and methods**: A systematic review of the literature published up to 30.03.2012 was performed, and a meta-analysis of identified studies was carried out. Databases were searched: PubMed, EMBASE, The Cochrane Library and others.

**Results**: Two randomised clinical trials regarding comparisons of: imatinib vs. placebo and 12 months of adjuvant imatinib vs. 36 months of adjuvant imatinib as well as 20 non-randomised trials fulfilled the established criteria. Adjuvant imatinib statistically significantly improves recurrence-free survival compared with placebo. Patients with high risk of recurrence benefit most from assigned treatment. Three years of adjuvant imatinib therapy improves recurrence-free state and overall survival compared with 1 year of imatinib in patients after resection of a gastrointestinal stromal tumour. The safety profile of imatinib in the analyzed population is acceptable.

**Conclusions**: For patients with a significant risk of recurrence adjuvant therapy with imatinib should be considered for every patient, due to the clinical benefits it brings.

KEY WORDS: adjuvant therapy, gastrointestinal stromal tumour, GIST, imatinib, systematic review

## INTRODUCTION

Gastrointestinal stromal tumours (GIST) are the most common mesenchymal tumours of the gastrointestinal tract. GISTs are thought to arise from interstitial cells of Cajal [1], which serve a pacemaker function in controlling the motility of the gastrointestinal tract [2, 3]. GISTs usually occur in the stomach (70%) and in the small intestine (20–30%), and are most frequently diagnosed in elderly people [4]. The neoplastic process is driven by activating mutations in the *KIT* gene (receptor for stem cell factor) or the *PDGFRA* gene (platelet-derived growth factor receptor alpha). The two genes encode receptor proteins acting as tyrosine kinases [2]. Mutations in *KIT* or *PDGFRA* genes lead to the constitutive activation of the receptor regardless of the presence of ligands, which results in continuous signal transduction to intracellular pathways (such as PI3K/AKT or MAPK), and disturbed cell proliferation processes [5, 6].

Gastrointestinal stromal tumours are stratified mainly based on the degree of potential malignancy according to the classification by the US National Institutes of Health (NIH) [2, 6]. A consensus approach adopted in 2001 by the NIH for defining the risk of aggressive behaviour in GISTs based on tumour size and mitotic count per 50 high-power fields allows for distinguishing low risk, moderate risk and high risk tumours [7], and through that for patient prognosis, including the risk of GIST recurrence or progression [8]. The modification of the NIH's classification system proposed in 2008 [9] and a classification system developed by the National Comprehensive Cancer Network – Armed Forces Institute of Pathology – American Joint Committee on Cancer (NCCN–AFIP–AJCC) [10] include the primary tumour site within the gastrointestinal tract as another prognostic factor for patients with GIST.

Radical surgery is the most successful treatment method for patients with primary GIST and offers five-year recurrence-free survival rates of 35–65% [11, 12]. Despite complete (radical) tumour resection, in many patients microscopic examination reveals positive margins (cancer cells present in the margins of the surgical incision). In the population of patients with high risk GIST (tumour size > 10 cm or mitotic count >10/50 HPF) disease recurs within 2 years following tumour resection, and the five-year overall survival rate is 20% [13]. Adjuvant therapy is used to reduce the risk of recurrence and to increase survival rates in patients [14], and is recommended for the population of patients with significant (high and moderate) risk of recurrence after the resection of GIST [15].

Imatinib is currently the only drug used and recommended for adjuvant therapy in patients with GIST. Imatinib is a signal-transducing inhibitor in cells that selectively binds with tyrosine kinases (including KIT and PDGFRA), expressed in cells of the gastrointestinal stromal tumour, and blocks the signalling pathway to inhibit uncontrolled proliferation of cancer cells [16]. Imatinib is a drug with proven efficacy in the treatment of unresectable and/or metastatic GISTs, and was also approved for the adjuvant treatment of adult patients who are at significant risk of relapse following resection of a KIT (CD117)-positive GIST [17]. Imatinib for the adjuvant treatment of GISTs has orphan drug status (being indicated for a very small population of patients), but was approved based on the results of a phase III randomised clinical trial [18–21].

## AIM OF THE STUDY

The aim of our study was to evaluate the clinical efficacy and safety profile of imatinib used in adjuvant therapy in patients after complete resection of GIST based on a systematic review of clinical trials presented in published medical literature.

## MATERIALS AND METHODS

To retrieve articles on primary clinical trials (randomised and non-randomised) and secondary studies (independent systematic reviews and reports evaluating medical technologies) on the use of imatinib in adjuvant therapy for patients after resection of GIST we carried out a systematic search in 16 medical databases, including MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews (CDSR), the Centre for Reviews and Dissemination (CRD), and the Trip Database. The search strategy was based on key terms identifying the analysed population (GIST OR gastrointestinal stromal tumour) in combination with the evaluated drug (imatinib), including synonyms of the above key terms included in MeSH (Medical Subject Reading) and Emtree (Elsevier's Life Science Thesaurus). We also searched references to retrieved articles, registries of clinical trials in progress (e.g. www.clinicaltrials.gov, http://www.novctrd.com), the drug registration dossier on the FDA website (Food and Drug Administration), and reports presented during international conferences of oncology: the American Society of Clinical Oncology (ASCO), the American Cancer Society (ASC), and the European Society of Medical Oncology (ESMO). We searched for articles published in English, French, German and Polish. The search timeframe for papers was not restricted, and we included all reports regardless of the date of their publication. The last search in databases was carried out on 30 March 2012. The systematic review was carried out in compliance with guidelines prepared by Cochrane Collaboration in 2011 [22].

Initial analysis included primary clinical trials found in identified evidence-based systematic reviews. Additionally, we included primary clinical trials not included in secondary reports but retrieved after the search of medical databases. Sources of clinical information were selected in a two-stage process. In the first stage we analysed study titles and abstracts, and based on these we shortlisted studies fulfilling the inclusion criteria for analysis. Next, we carried out a selection based on full versions of articles considering all inclusion criteria. Through this we established the final list of studies which were then evaluated in detail for the level of evidence. The selection of studies was carried out independently by two investigators. Contradicting opinions on the reviewed clinical trials, made based on full versions of papers, were finally resolved by consensus. The analysis of the methodological quality of the retrieved randomised clinical trials was conducted based on the Jadad scale (including the correctness of randomisation and blinding and the flow of patients). The level of clinical evidence regarding the results of studies included in our analysis was evaluated according to the GRADE scale.

Results for variables like *time to event* were presented as the *hazard ratio* (HR), together with a 95% confidence interval (95% CI) and p-value. The statistical significance in the carried out analyses was set at the significance level $p < 0.05$. When studies provided information on dichotomic variables, results were presented as *relative risk* (RR), with a 95% confidence interval. When a certain end point was not recorded in one of the treatment groups, results on dichotomic data were presented as an *odds ratio* (OR) calculated using the Peto method.

In our review we carried out an evaluation of the clinical and methodological heterogeneity of studies included in individual analyses. In the first stage we evaluated studies for their compliance in terms of population, intervention, end points and methodology. Homogeneous results of evaluated studies were included in the meta-analysis. Next, we analysed heterogeneity based on the results of clinical trials. We assumed that trials included in the analysis were homogeneous when in the statistical test for heterogeneity the p-value in the *Cochran`s Q* test was greater than 0.1 ($p > 0.1$). For clinical studies that were found homogeneous based on study results ($p > 0.1$) we accumulated data using the fixed effect method. Calculations were conducted using StatsDirect software.

## RESULTS

During the systematic review we retrieved 6 secondary reports and 25 primary clinical studies fulfilling the established inclusion criteria. From all the primary clinical studies included in the analysis two were randomised clinical trials with high levels of evidence regarding comparisons of imatinib vs. placebo [18–21] and 12 months of adjuvant imatinib vs. 36 months of adjuvant imatinib [23–26] for the treatment of patients after the resection of gastrointestinal stromal tumours. The review also identified 7 non-randomised clinical trials with moderate levels of evidence, regarding the use of imatinib in the analysed group of patients: 3 clinical trials with a control group receiving no intervention [27–31] and 4 clinical trials without any control group [32–42]. The analysis also included 13 studies that were clinical registries or multiple/single case reports on adjuvant therapy in patients after the resection of GIST [43–55]. Additionally, we found information on three pending clinical trials regarding the use imatinib in the analysed indication [56–59]. A diagram presenting the search process for primary clinical trials, including the number and reasons for exclusion of articles at individual stages of selection, is shown in figure 1.

## STUDIES WITH HIGH LEVEL OF EVIDENCE – RANDOMISED CLINICAL TRIALS

The ACOSOG Z9001 study was a phase III, randomised, double-blind, placebo-controlled clinical trial that compared 12 months of treatment with adjuvant imatinib vs. placebo in patients after the resection of KIT (CD 117)-positive gastrointestinal stromal tumour (GIST) [18–21]. The trial was designed in 2000, before risk stratification for disease recurrence was found important in planning therapeutic strategies for patients after the resection of GIST. For this reason the studied group [18–21] was not stratified with respect to the risk of disease recurrence, and included patients with very low risk, low risk, moderate risk and high risk of recurrence according to the NCCN–AFIP–AJCC classification system (the risk stratification was carried out retrospectively).

The SSG XVIII AIO study was a phase III, randomised, open-label clinical trial that included patients after the resection of primary GIST with a high or very high risk of disease recurrence. Patients included in the study were randomised to receive either 12 months or 36 months of treatment with adjuvant imatinib [23–26]. Because the control groups in the two studies did not receive identical treatments (patients received either placebo or imatinib), we were unable to carry out meta-analysis of results from these randomised clinical trials. Additionally, the analysis of methodology for these two randomised clinical trials revealed high heterogeneity, both with respect to methods (double-blind or open-label trial, differences in Jadad scores – 4 and 2 points, for studies [18–21] and [23–26], respectively), population of patients included (patients with undefined or high risk of disease recurrence), and the size of individual groups, as well

FIGURE 1.
Diagram representing the selection of primary clinical trials evaluating the clinical efficacy and safety of imatinib used in adjuvant therapy for patients after resection of GIST.

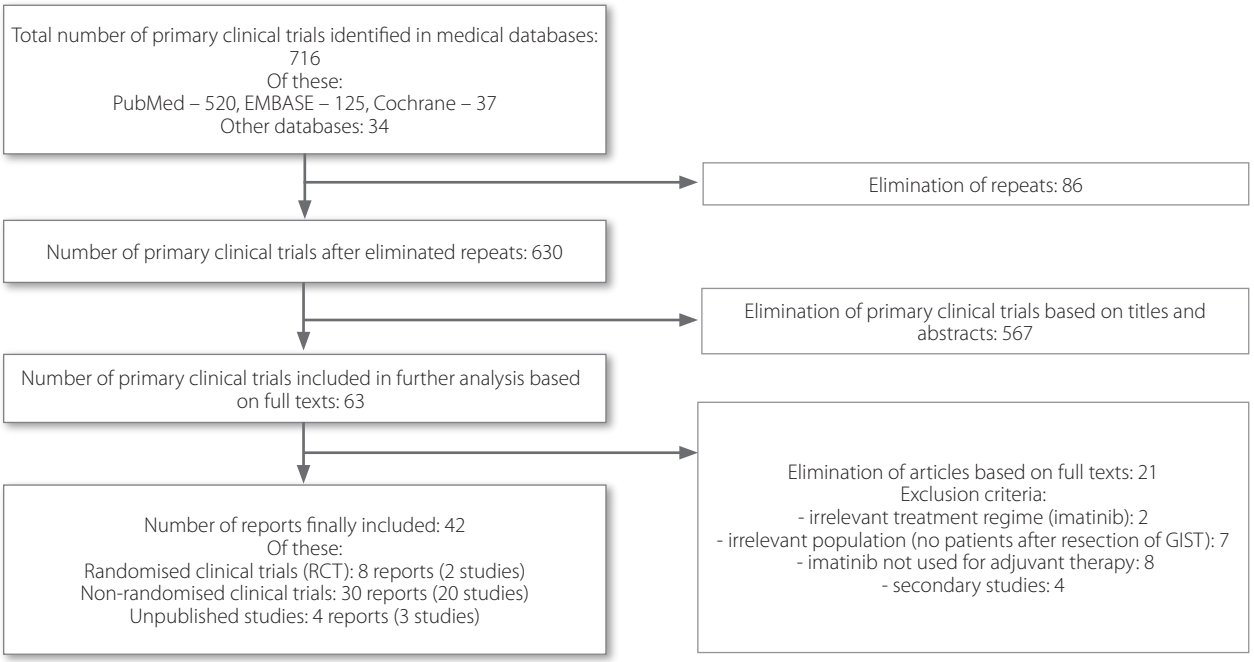



TABLE 1.
Characteristics of clinical trials included in the analysis and evaluating the use of adjuvant imatinib in adult patients after the complete resection of GIST [18–21, 23–31].

| Study | Study design (methodology) | Population and number of patients | Treatment | Treatment duration and follow-up |
|---|---|---|---|---|
| **Randomised clinical trials** | | | | |
| DeMatteo et al. ACOSOG Z9001 [18–21] | Phase III randomised, double-blind, placebo-controlled, superiority, multicentre clinical trial carried out in the USA and Canada in 2002–2007 | Patients with undefined risk of disease recurrence. Study group – imatinib: N = 359, control group – placebo: N = 354 | 400 mg oral imatinib once a daily | Treatment duration: 12 months. Follow-up: median 19.7 months, range: 0–56.4 |
| Joensuu et al. SSG XVIII AIO [23–26] | Phase III randomised, open-label, placebo-controlled, superiority, multicentre clinical trial carried out in Scandinavia and Germany in 2004–2008 | Patients at a high risk of disease recurrence. Study group – 36 months imatinib therapy: N = 198, control group – 12 months imatinib therapy: N = 199 | | Treatment duration: 12 or 36 months. Follow-up: median 54 months, quartile range: 41–66 |
| **Non-randomized clinical trials** | | | | |
| Li et al. 2011 [27] Li et al. 2009 [28] Shen et al. 2008 [29] | Prospective, non-randomised, open-label, single-centre phase II controlled clinical trial | Patients at moderate or high risk of disease recurrence. Study group – imatinib: N = 56, control group – no intervention: N = 49 | 400 mg oral imatinib once a daily | Treatment duration: 36 months. Follow-up: median 45 months, range: 43.1–46.9 |
| Jiang et al. 2011 [30] | Prospective, non-randomised, single--centre clinical trial with a control group | Patients at high risk of disease recurrence. Study group – imatinib: N = 35, control group – no intervention: N = 55 | | Treatment duration: median 33.8 months. Follow-up: median 44 months, range: 12–101 |
| Nilsson et al. 2007 [31] | Pilot, non-randomised, single-centre clinical trial with historical controls | Patients at high risk of disease recurrence. Study group – imatinib: N = 23, control group – no intervention: N = 48 | | Treatment duration: 12 months Follow-up: median 40 months |

as the follow-up period for patients included in clinical trials. A detailed description of the study design for both randomised clinical trials is presented in table 1.

The ACOSOG Z9001 study demonstrated a statistically significant improvement in relapse-free survival after a 12 month treatment with adjuvant imatinib compared with placebo (tab. 2). The estimated 1-year relapse-free survival of patients was 98% in the imatinib arm compared with 83% in the placebo arm. Statistically significant benefit of imatinib compared with placebo in improving relapse-free survival was found in all patient groups, irrespectively of the size of the resected tumour [18–21]. The retrospective analysis of results demonstrated the highest benefits of adjuvant imatinib in patients with GIST after the resection of a tumour who were at high or moderate risk (NCCN–AFIP–AJCC classification) or high risk (NIH classification) of disease relapse. No benefit from adjuvant imatinib was observed in the low and very low risk groups of patients. Table 3 presents estimated relapse-free survival rates for patients who were followed for 12 and 24 months after receiving adjuvant imatinib, including the risk of disease relapse according to NIH and NCCN–AFIP–AJCC classifications [17].

The follow-up period in the ACOSOG Z9001 trial was relatively short (median 19.7 months) and no statistically significant improvement in the overall survival was observed during that period in the analysed population after adjuvant imatinib. In the ACOSOG Z9001 trial the follow-up of patients who received 12-month adjuvant treatment demonstrated an increased rate of patients with disease recurrence within 6 months from the end of treatment [18–21]. The results of other clinical trials also indicated that most cases of disease relapse in the high risk population occurred during the first 2 years following tumour resection [31, 60]. This means that the duration of adjuvant treatment should be longer than the standard 12 month period.

These results were considered in another randomised clinical trial (SSG XVIII AIO) that included patients after the resection of GIST with a high risk of disease recurrence [23–26] and compared 12 months with 36 months of adjuvant imatinib. The study demonstrated that prolonged 36-month treatment with adjuvant imatinib resulted in statistically significant improvement in recurrence-free survival, but also overall survival of GIST patients with a high risk of GIST recurrence when compared with a standard 12-month therapy (tab. 2). The 5-year overall survival was 92.0% in patients assigned for 36 months of imatinib vs. 81.7% in patients assigned for a standard 12-month adjuvant imatinib therapy. The 5-year recurrence-free survival was 47.9% in the group assigned for 12 months of imatinib vs. 65.6%

TABLE 2.
Clinical efficacy of adjuvant imatinib in patients after the complete resection of primary KIT-positive GIST – results from randomised trials [18–21, 23–26].

| Study | Analysed end point | Study group vs. control group | HR-95% CI) | p-value |
|---|---|---|---|---|
| DeMatteo et al. ACOSOG Z9001 [18–21] | recurrence-free survival | 12 months imatinib therapy vs. placebo | 0.35 (0.22–0.53) | < 0.0001 |
| | overall survival | | 0.66 (0.22–2.03) | 0.47 |
| Joensuu et al. SSG XVIII AIO [23–26] | recurrence-free survival | 36 months vs. 12 months imatinib therapy | 0.46 (0.32–0.65) | < 0.0001 |
| | overall survival | | 0.45 (0.22–0.89) | 0.019 |

TABLE 3.
Clinical efficacy of adjuvant imatinib in patients after the complete resection of primary KIT-positive GIST – results from ACOSOG Z9001 clinical trial, including the risk of disease recurrence [17].

| Evaluation criteria for risk of disease recurrence | Risk of recurrence | Rate of recurrence-free patients imatinib vs. placebo | |
|---|---|---|---|
| | | 12 months | 24 months |
| NIH | low | 100 vs. 98.7 | 100 vs. 95.5 |
| | moderate | 100 vs. 94.8 | 97.8 vs. 89.5 |
| | high | 94.8 vs. 64.0 | 80.7 vs. 46.6 |
| NCCN–AFIP–AJCC | very low | 100 vs. 98.1 | 100 vs. 93.0 |
| | low | 100 vs. 100 | 97.8 vs. 100 |
| | moderate | 97.9 vs. 90.8 | 97.9 vs. 73.3 |
| | high | 98.7 vs. 56.1 | 79.9 vs. 41.5 |

in the group assigned for 36 months of imatinib. The analysis stratified by time in the study and focused on the risk of disease recurrence or death revealed a substantial benefit of 36-month adjuvant therapy compared with 12-month therapy during 12 to 24 months and 24 to 36 months after randomisation (HR = 0.26 [95% CI: 0.13–0.53] and HR = 0.17 [95% CI: 0.07–0.39], respectively). No significant differences were found in the recurrence-free survival during the first 12 months after randomisation or after 36 months of randomisation [23–26].

The analysis of the safety profile carried out based on the results of the clinical trial [18–21] demonstrated that imatinib therapy compared with placebo caused a statistically significant increase ($p < 0.05$) in the risk of gastrointestinal adverse events (diarrhoea: RR = 20.47 [95% CI: 11.05–37.95], nausea: RR = 1.91 [95% CI: 1.57–2.33], vomiting: RR = 1.83 [95% CI: 1.33–2.52]), fatigue: RR = 1.39 (95% CI: 1.19–1.63), neutropenia: RR = 2.63 (95% CI: 1.63–4.26), anaemia: RR = 1.74 (95% CI: 1.41–2.14), oedema, overall: RR = 1.81 (95% CI: 1.33–2.46) and periorbital oedema: RR = 3.26 (95% CI: 2.46–4.31). Most of these adverse events were graded from mild to moderate. Serious adverse events recorded with statistically significant higher frequency in the group assigned for imatinib compared with the placebo group included: dermatitis: Peto OR = 7.80 (95% CI: 2.37–25.65), hepatic enzyme elevations (alanine aminotransferase: Peto OR = 7.75 [95% CI: 2.08–28.85] and aspartate aminotransferase: Peto OR = 7.70 [95% CI: 1.74–34.12]), fainting: Peto OR = 7.63 [95% CI: 1.07–54.44], neutropenia: RR = 3.75 (95% CI: 1.06–13.34), diarrhoea: RR = 20.27 (95% CI: 8.36–49.15), periorbital oedema: Peto OR = 7.63 (95% CI: 1.07–54.44) and exfoliative rash: Peto OR = 7.75 (95% CI: 2.08–28.85) [21]. Prolonged therapy with adjuvant imatinib from 12 months to 36 months was associated with statistically significant ($p < 0.05$) increase in the occurrence of the following adverse events: periorbital oedema: RR = 1.25 (95% CI: 1.09–1.45), elevated blood creatinine: RR = 1.46 (95% CI: 1.13–1.91), elevated lactate dehydrogenase: RR = 1.34 (95% CI: 1.14–1.70), diarrhoea: RR = 1.23 (95% CI: 1.01–1.52), leucopoenia: RR = 1.36 (95% CI: 1.07–1.74) and muscle cramps: RR = 1.58 (95% CI: 1.23–2.05). However, the extension of therapy from 12 to 36 months did not increase the risk of any serious or life-threatening adverse events [23–26].

## STUDIES WITH LOWER LEVELS OF EVIDENCE – NON-RANDOMISED CLINICAL TRIALS AND CASE REPORTS

Non-randomised clinical trials with a control group retrieved during the systematic review included populations of patients at high or moderate risk of disease recurrence after the complete resection of GIST [27–31]. Patients that received adjuvant imatinib therapy were compared with patients who received no medical intervention after tumour resection. A detailed characterisation of trials included in the meta-analysis is presented in table 1. Because of the high similarity in methodology between studies carried out by Li et al. [27–29] and Jiang et al. [30], regarding: comparison of the study group with the control group not receiving any intervention, identical methods in both trials, similar criteria for patient inclusion, identical dosage of imatinib, comparable duration of treatment and follow-up periods, similar size of the analysed groups, and the evaluation of the same end point (recurrence-free survival), we decided to carry out a meta-analysis for these trials focused on the primary end point, i.e. recurrence-free survival.

In the study by Li et al. [27–29] the efficacy of the used adjuvant imatinib was evaluated for the population at moderate and high risk of disease recurrence according to the NIH classification. Results from this study regarding control patients who had the complete tumour resection but received no adjuvant therapy, and in whom a 3-year recurrence-free survival was recorded clearly demonstrated the crucial role of risk evaluation for disease recurrence in prognosis. In the control group of patients at moderate and high risk of disease recurrence the recurrence-free survival 3 years after tumour resection was 73% and 31%, respectively. The use of imatinib in a 36-month adjuvant therapy increased the 3-year recurrence-free survival of patients at moderate and high risk of disease recurrence to 95% and 85%, respectively (increase by 22% and 54%). These results confirm that the patients who are at high risk of recurrence benefit most from adjuvant imatinib therapy. This is also supported by the results from two other analysed non-randomised trials with a control group carried out on patients at high risk of disease recurrence. In this population of patients the recurrence-free survival rate increased from 27.5% in the group who only had the resection of GIST, to 88% in the group that received adjuvant imatinib therapy (median follow-up was 33.8 months) [30]. In the study by Nilsson et al. the median follow-up period was 36 months. Only 4% of patients in the adjuvant treatment group developed recurrent disease compared with as many as 67% of patients in the control group that received no medical intervention after tumour resection [31]. Summarizing, the use of treatment with adjuvant imatinib increased, depending on the study, the 1-year (by 18–29%), 2-year (by about 50%) and 3-year recurrence-free survival (by 54–60%) in patients who had the resection of GIST with high risk of recurrence. The results of the analysed non-randomised trials with a control group confirmed the efficacy of treatment with adjuvant imatinib in patients who are at high

risk of disease recurrence: HR = 0.16 (95% CI: 0.07–0.38); p = 0.000, in patients at a moderate risk of recurrence: HR = 0.14 (95% CI: 0.02–1.15); p = 0.031, and in the population including both these groups: HR = 0.19; p < 0.001. Meta-analysis of results from the studies by Li et al. [27–29] and Jiang et al. [30] focused on data obtained solely in groups of patients at high risk of disease recurrence confirmed that the used treatment with adjuvant imatinib prolonged recurrence-free survival: HR = 0.14 (95% CI: 0.07–0.28); p < 0.0001 [27–30] (fig. 2).

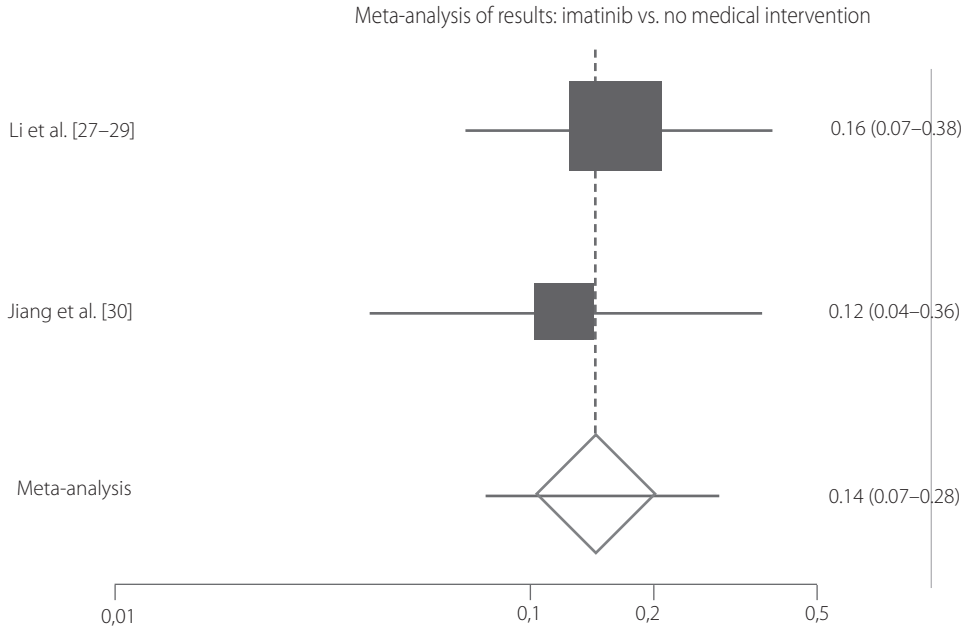
Among the above-mentioned studies, the parameter of overall survival was evaluated only in one analysed clinical trial by Li et al. [27–29]. The prolonged therapy (36 months) with adjuvant imatinib resulted in statistically significant improvement of overall survival: HR = 0.25 (95% CI: 0.07–0.93); p = 0.025, despite the fact that the evaluation of this parameter included both populations of patients at moderate and high risk of disease recurrence.

The identified studies without a control group and regarding the use of adjuvant imatinib were carried out only in the population at high risk of disease recurrence after the complete resection of GIST [32–42]. Results from four studies [33, 35, 36, 40] demonstrated that in the analysed clinical trials the 1-year recurrence-free survival was 94–97.9%, 2-year recurrence-free survival was 73–93.3%, and 3-year recurrence-free survival was 59–61% in patients who received adjuvant imatinib. The results of the above-mentioned studies show a correlation between the duration of therapy and recurrence-free survival rate. In the population of patients treated with imatinib for 12 months the 2--year recurrence-free survival was 73% [33], and in the group of patients treated with imatinib for 24 months it was about 93% [35, 36]. This indicates clinical benefits resulting from imatinib therapy longer than 12 months. None of the identified case reports recorded disease recurrence during the therapy with adjuvant imatinib [47–52, 54, 55]. During imatinib therapy patients suffered from nausea, periorbital oedema, facial oedema and eyelid oedema, and drug dose had to be reduced because of these complaints [52, 54]. In one case treatment had to be discontinued because of exfoliative dermatitis [53].

## DISCUSSION

The use of effective adjuvant therapy appears to be very important in the population of patients at high risk of disease recurrence [61]. Imatinib is currently the only drug recommended for adjuvant therapy in adult patients with significant (high and moderate [62]) risk of disease recurrence after the resection of KIT (CD 117)-positive gastrointestinal stromal tumour (GIST)

FIGURE 2.
Meta-analysis of results for recurrence-free survival in the population of patients who are at high risk of disease recurrence following the resection of KIT-positive GIST.



[11, 17]. Results from the randomised clinical trial ACOSOG Z9001 indicated statistically significant benefit of adjuvant imatinib compared with placebo in improving recurrence-free survival [18–21]. Clinical benefits of adjuvant therapy are positively correlated with increasing risk of disease recurrence. There was no statistically significant difference in overall survival between the studied groups. However, the clinical trial [18–21] is still in progress and only interim results have been published. Findings from a longer follow-up period (the completion of the trial is planned for 2018) will provide more accurate information on overall survival.

In patients with metastatic GIST imatinib should be used until disease progression or the drug's toxic effects are observed, while in patients after the resection of primary GIST the treatment period should be defined. The optimum duration of adjuvant treatment is now the key problem regarding imatinib therapy, and is the subject of studies in progress [56–59]. The results of the analysed studies including a control group demonstrated, however, that prolonged adjuvant treatment improves recurrence-free survival. The use of imatinib in a 36-month adjuvant therapy increased 3-year and 5-year recurrence-free survival in about 85% and 66% of patients, respectively [23–27]. Compared with about 60% and 48% recurrence-free survival in patients assigned for 12-month imatinib therapy [23–26, 33, 40] this shows the significant benefit of prolonged adjuvant therapy. It is also worth emphasizing that the correlation between the duration of therapy and delay in disease recurrence was observed in all analysed studies, regardless of significant differences in their methodology. Moreover, prolonged use of adjuvant imatinib (36 months) resulted in statistically significant improvement in overall survival, both in patients assigned for 12-month therapy and those who only had resection for GIST [23–27]. The above results provided the background for the recommendations released on 20 January 2012 by the Committee for Medicinal Products for Human Use (CHMP) at the European Medicines Agency (EMA) on the European Union approval to update the imatinib label to include 3-year adjuvant treatment for GIST patients after surgery [63]. In August 2011, the US National Comprehensive Cancer Network (NCCN) also updated its clinical practice guidelines to recommend the consideration of at least 36 months of adjuvant therapy with imatinib for patients with high risk of GIST recurrence [64]. Valuable information on the optimum duration of adjuvant treatment will certainly be provided by currently pending clinical trials evaluating the use of adjuvant imatinib in the analysed recommendation. One of these trials (NCT00867113) is evaluating the clinical efficacy of 5-year imatinib therapy [56]. The potential risk of developing resistance to the used drug is a problem to be considered in relation to the prolonged duration of adjuvant therapy. The clinical studies reviewed in our meta-analysis demonstrated the efficacy of reintroduced therapy with imatinib in patients who had disease recurrence after discontinued adjuvant treatment [27–29].

Currently, the therapy with adjuvant imatinib is recommended for patients with a significant risk of recurrence defined based on the classification system considering the size and location of the tumour within the gastrointestinal tract, and mitotic count. However, there may be other prognostic factors influencing the risk of disease recurrence and the efficacy of the used therapy. One of these includes mutations in *KIT* and *PDGFRA* genes, which are characteristic for 85–90% and 3–5% of GIST cases, respectively, and allow for the prognosis of imatinib efficacy in the population of patients with metastatic GIST [65, 66]. One of the analysed trials [23–26] demonstrated the statistically significant benefit of 36 months of adjuvant imatinib compared with 12 months therapy with respect to recurrence-free survival in the subpopulation of patients with *KIT* exon 11 mutations. Other studies [27–29] also demonstrated that *KIT* exon 11 mutations are associated with longer recurrence-free survival in the group of patients treated with adjuvant imatinib in comparison with causal treatment, although the observed effect was not statistically significant. The results of the study currently being carried out by the European Organization for Research and Treatment of Cancer (EORTC), identifier NCT00103168, will certainly answer many questions regarding adjuvant therapy with imatinib. This randomised clinical trial includes about 750 patients after complete resection of primary KIT-positive GIST. Outcomes in the population included in the NCT00103168 trial are expected to provide more detailed identification of the patients that benefit most from the adjuvant imatinib, as the trial covers patients who are at high and moderate risk of disease recurrence according to NIH criteria [58, 59].

## CONCLUSIONS

Imatinib is currently the only option for adjuvant therapy in patients after the resection of GIST. The use of adjuvant imatinib for at least 12 months significantly increases recurrence-free survival. The highest efficacy of adjuvant imatinib is observed in the subpopulation of patients at high risk of recurrence. Recent studies demonstrated that therapy with adjuvant imatinib extended from 12 to 36 months increased the overall survival of patients after the resection of GIST.

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