Emilia Babula[1, 2*], Aleksandra Sikora[1, 2*], Paweł Sobczuk[1], Piotr Rutkowski[1]

[1]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[2]Faculty of Medicine, Medical University of Warsaw, Poland
*Contributed equally

Ripretinib in the treatment of patients with advanced gastrointestinal stromal tumors (GIST)

Address for correspondence:

Paweł Sobczuk, MD PhD

Department of Soft Tissue/Bone Sarcoma
and Melanoma, Maria Skłodowska-Curie
National Research Institute of Oncology
ul. Roentgena 5, 02–781 Warsaw, Poland
phone: +48 225462031
e-mail: pawel.sobczuk@nio.gov.pl

ABSTRACT

Gastrointestinal stromal tumors (GISTs) are relatively rare in the population (0.4 to 2 cases per 100 000 per year) and account for approximately 1–2% of gastrointestinal cancers. According to the latest 2020 World Health Organization (WHO) classification of sarcomas, all GISTs are malignant, regardless of their size or mitotic index. In the systemic treatment of GIST, KIT tyrosine kinase receptor and platelet-derived growth factor receptor (PDGFRA) inhibitors, such as imatinib, sunitinib, or regorafenib, are used. The effectiveness of imatinib is significantly reduced in the case of secondary mutations in the *KIT* gene. The latest drug from the group of KIT inhibitors, ripretinib, was the first to show efficacy against most mutations associated with resistance, as well as in wild-type GIST, in which mutations in KIT and PDGFRA are not found. Analysis of the INVICTUS study showed a beneficial effect of ripretinib at the recommended dose of 150 mg/day on progression-free survival (PFS) in patients with advanced or metastatic GIST previously treated with at least three other inhibitors. However, the preliminary results of the phase III INTRIGUE study did not show an improvement in PFS in patients receiving ripretinib compared to sunitinib in the second-line therapy of GIST patients. Ripretinib has a favorable and acceptable safety profile and is recommended for treating patients with advanced GIST in the fourth line of treatment. In this article, we summarize the most essential data on the efficacy and safety of ripretinib in treating GIST patients and the recommendations for its use.

Keywords: GIST, KIT, PDGFRA, ripretinib, tyrosine kinase inhibitor

Oncol Clin Pract 2024; 20, 1:40–51

Introduction

Gastrointestinal stromal tumors (GISTs) are among the most common mesenchymal tumors developing in the digestive tract [1, 2]. Compared to other tumors in this localization, they are very rare. The incidence is estimated as from 0.4 to 2 cases per 100 000 people per year, 1–2% of all gastrointestinal cancers [3]. They can develop at any age, with the peak incidence at 65 years of age and similar frequency in women and men [4, 5]. The most common primary location of GIST is the stomach (60–65%) and the small intestine (20–25%); to a lesser extent, the large intestine (6%), esophagus (0.7%), and other locations (5.5%) [4, 6, 7]. Symptoms of gastrointestinal stromal tumors are not specific and depend on the tumor's location, stage of advancement, and its size. The most common symptoms are chronic bleeding from the gastrointestinal tract, anemia, bloating, abdominal pain, and an early feeling of satiety [8].

Gastrointestinal stromal tumors is most often caused by an activating somatic mutation in the genes of the tyrosine kinase receptor (*KIT*) (Tab. 1) or the

Table 1. Molecular classification of gastrointestinal stromal tumors (GISTs)

Mutation	Estimated frequency [%]	Most common location	Characteristics
KIT-mutated (approximately 80%)			
Exon 9 (or exon 8)	5–10	Small intestine, stomach, colon, rectum	Lower sensitivity to imatinib at a dose of 400 mg/d. Sensitivity to sunitinib, regorafenib, avapritinib, ripretinib
Exon 11 (deletions, including del. 557-558, missense mutations, insertions, other)	60–70	Stomach, small intestine, colon, rectum	Responds best to imatinib; sensitive to sunitinib, regorafenib, avapritinib, ripretinib. Present in familial GISTs
Exon 13 (K542E)	< 1		Clinical response to imatinib only in some patients. Less sensitive to sunitinib. Sensitive to regorafenib, avapritinib, ripretinib. Present in familial GISTs
Exon 17 (D820Y, N822K, Y823D)	1		Not sensitive to imatinib. Sensitive to avapritinib and ripretinib, some to sunitinib and regorafenib. Present in familial GISTs
PDGFRA-mutated (approximately 15%)			
Exon 12 (e.g. V561D)	< 1	Stomach	Observed response to imatinib except — D842V mutation (insensitive). D842V mutation highly sensitive to avapritinib
Exon 14 (N659K)	< 1		
Exon 18 (e.g. D842V)	10–15		
KIT and *PDGFRA* wild-type, *SDH*-competent			
NF1 mutation	1–2	Small intestine	Indolent course, associated with type I neurofibromatosis. Possibly insensitive to available KIT inhibitors
BRAF mutation	< 1	Small intestine, stomach	Possibly insensitive to available KIT inhibitors. Ripretinib inhibits BRAF *in vitro*
HRAS, *NRAS*, or *KRAS* mutation	Very rare	Unknown	Insensitive to KIT inhibitors
Translocations (fusions of *FGFR1*, *NTRK3 RTK*, or other)	Very rare	Small intestine, colon, rectum	Insensitive to KIT inhibitors. Sensitive to NTRK inhibitors (for *NTRK* rearrangements)
KIT and *PDGFRA* wild-type, *SDH*-deficient			
SDHA, SDHB, SDHC, or *SDHD* mutation (including Carney--Stratakis Syndrome)	Approximately 3	Stomach, small intesitne (less often)	Epithelial cells. Common in pediatric and young adult GISTs. Often metastases to lymph nodes, indolent course. Insensitive to imatinib, better response to sunitinib
Lack of SDHB expression (including Carney's triad)	< 1	Stomach	

platelet-derived growth factor alpha (*PDGFRA*) genes, which leads to disruption of the process of replacing old cells with new ones and causes their excessive proliferation and formation of a neoplastic lesion [9]. *KIT, PDGFRA*, and *PDGFRB* belong to the same family of type III tyrosine kinase receptors, and their mutations are mutually exclusive [7, 10, 11]. Both KIT and PDGFRA are structurally and functionally homologous. Both consist of an extracellular domain, a transmembrane domain, a transmembrane fragment, and a cytoplasmic kinase domain. For KIT, the stem cell factor (SCF) is the activating ligand, while for PDGFRA, it is the platelet-derived growth factor (PDGFA) [2].

Gastrointestinal stromal tumors probably originate from precursors of Cajal cells that express KIT (CD117) and are located in the muscular layer of the gastrointestinal tract and are responsible for intestinal peristaltic movement [9].

In most cases (85%), the mutation associated with GIST is known [2]. The ratio of the frequency of key mutations, along with their typical location and characteristics, is presented in Table 1 [7, 12]. From 70 to 80% of patients have activating mutations in the *KIT* proto-oncogene (CD117), leading to constitutive activation of KIT, with the largest number (60–70%) of mutations affecting the paramembrane domain

encoded by exon 11 [13], followed by the extracellular domain encoded by exon 9 (7–10%) [14]. Exon 11 mutations are most often deletions in the reading frame, insertions, substitutions, missense mutations, or their combinations [7, 15]. The kinase domain of *KIT* with exon 9 mutation is essentially the same as in wild-type KIT, which is essential in sensitivity to inhibition [7]. Mutations in exon 13 within the activation loop and exon 17 are sporadic. These mutations occur in tumors arising in the small and large intestines, rarely observed in gastric GISTs, and their gene expression profile differs from tumors with the *KIT* exon 11 mutation [16]. Mutations associated with *KIT* lead to the arrest of intracellular pathways, i.e., MAPK (RAF, MEK, and MAPK), PI3K-AKT, and STAT3, which regulate gene expression, cell division, differentiation, motility, and apoptosis [7, 17].

Further 10–15% of GIST cases involve mutations in the *PDGFRA* gene [18]. From 10 to 15% of patients with no detectable *KIT* or *PDGFRA* mutations are classified as "wild-type" GIST [18]. Most new cases of GIST are spontaneous, and only 5% are associated with genetic syndromes such as neurofibromatosis type 1 (NF1), succinate dehydrogenase (SDH) enzyme deficiency; Carney's triad, primary familial GIST syndrome; and Carney-Stratakis syndrome [19].

The most effective and, indeed, the only method that can ensure a complete cure of primary and localized GISTs is surgical resection of the tumor [20]. In the case of inoperable tumors, neoadjuvant treatment with imatinib can reduce the tumor mass [11, 21].

Imatinib is also used as an adjuvant treatment in patients after complete resection of the primary GIST with a high risk of recurrence [22–24]. It is not used for wild-type or *PDGFRA-D842V* mutant GISTs or for *NF1*-associated GISTs without SDH expression, as well as for *BRAF* mutations or *NTRK* rearrangements [5].

In the case of unresectable and metastatic GISTs, systemic treatment with kinase inhibitors is the standard. In the first-line treatment, international guidelines recommend the use of imatinib, which, after observation for more than 4 years, showed an approximately 4-fold increase (from 12–15 months to approximately 5 years) in median overall survival (mOS) in the group of patients with advanced GIST. Imatinib therapy for inoperable or metastatic GISTs rarely gives a complete response — it is found only in about 5–7% of patients [11]. About half are partial remissions, and in 36%, the disease is stabilized. From 10 to 15% of cases, correctly qualified for treatment (GIST CD117+), are characterized by primary and early resistance to treatment observed during the first 6 months of treatment [25]. On the other hand, in about 40–50% of patients, secondary resistance and disease progression are observed within 2–3 years of imatinib treatment [11, 26]. Imatinib is most effective in treating GIST with primary mutations, including *KIT* mutations within exon 11 (intracellular paramembrane domain) (Fig. 1). In the case of the presence of *KIT* exon 9 mutations, which are less sensitive to imatinib, according to the meta-analysis of the studies EORTC 62005 and SWOG S0033/CALGB 15105, a higher starting dose of imatinib (800 mg/day) should be used as opposed to the standard dose of 400 mg/day [11, 27]. The second line of treatment is sunitinib [median progression-free survival (PFS) 6–8 months] [11], and the third line is regorafenib (median PFS 4.4–4.8 months) [28], which are also KIT inhibitors [29].

For the *PDGFRA-D842V* mutation, insensitive to imatinib regardless of the dose, treatment with avapritinib is indicated [30], which in the phase I NAVIGATOR clinical trial achieved a response rate of 91%, with median PFS (mPFS) of 34 months and an estimated 3-year overall survival (OS) rate of 71% [31].

Disease progression during treatment with kinase inhibitors is most often due to new secondary mutations in *KIT* or *PDGFRA*, which are located mainly in the *KIT* ATP binding domain (exons 13 and 14) or the activation loop (exons 17 and 18) and, in the case of *PDGFRA,* in the ATP binding domain (exons 13, 14, 15) [32]. Recent studies show that ripretinib is advantageous in treating secondary mutations, as it inhibits other kinases, such as PDGFRB, TIE2, VEGFR2, and BRAF *in vitro* (Fig. 1) [33–35].

Mechanism of action, pharmacokinetics, and pharmacodynamics of ripretinib

Ripretinib is a new inhibitor of tyrosine kinases, particularly KIT kinase, which has found its application in treating unresectable and resistant forms of GISTs [33, 36]. Unlike its predecessors — imatinib, sunitinib, and regorafenib — it has the broadest spectrum of activity [35]. Ripretinib, as the first of the KIT inhibitors, is applicable in inhibiting all tested *KIT* and *PDGFRA* mutations, except for the D842V mutation, but also in wild-type GISTs. It inhibits other kinases such as PDGFRB, TIE2, VEGFR2, and BRAF *in vitro* [33–35].

All three currently used KIT inhibitors — imatinib, sunitinib, and regorafenib — bind to the inactive conformation of KIT or PDGFRA; therefore, they are classified as type II inhibitors [35, 37]. On the other hand, ripretinib, which belongs to the same group, exhibits exceptional activity in active KIT structures, which was
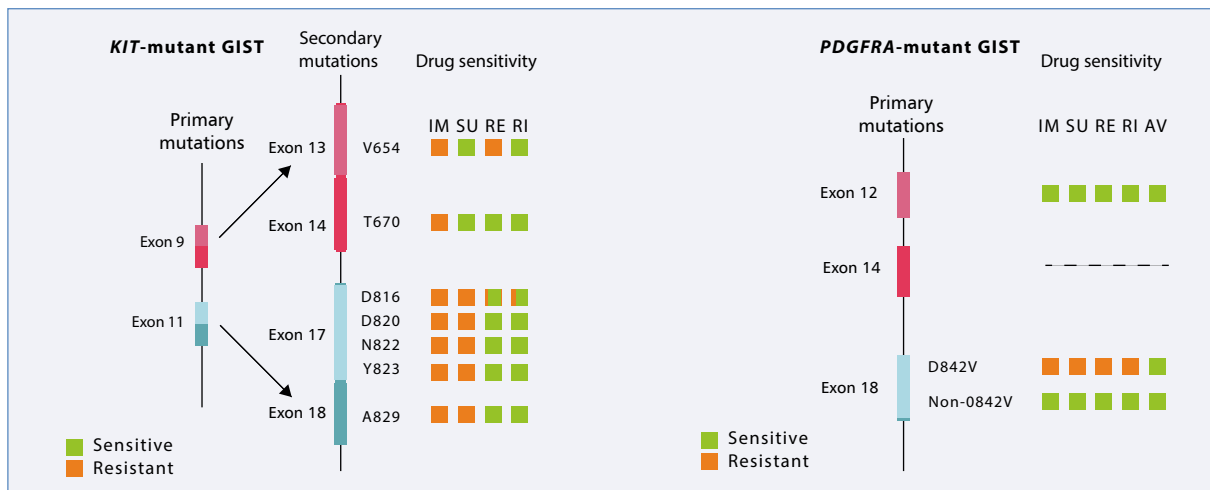
Figure 1. Comparison of the activities of kinase inhibitors used in the treatment of gastrointestinal stromal tumor (GIST) in relation to the most common primary and secondary mutations found in GISTs; AV — avapritinib; IM — imatinib; RE — regorafenib; RI — ripretinib; SU — sunitinib

previously attributed only to type I inhibitors [35]. For this reason, ripretinib can inhibit not only primary but also secondary mutations [35, 38]. Its innovative mechanism of action is based on the inhibition of two domains related to exon 11 and exon 9, regardless of the type of mutation, primary or secondary [39].

Ripretinib has a dual-pronged effect. It is an antagonist because it blocks the phosphorylation of the switch and the activation loop, preventing the transformation of KIT into the active form. At the same time, it plays a stabilizing role [34, 36]. In *in vitro* studies, ripretinib potently inhibited further tumor cell proliferation and KIT phosphorylation and induced apoptosis in all cell lines harboring mutations in *KIT* (exons 9, 11, 13, 14, 17, 18) and *PDGFRA* (exons 12, 14, 18). Therefore, it has a beneficial effect in the treatment of other myeloproliferative diseases, e.g., in mast cell leukemia (MCL) or systemic mastocytosis (SM), where KIT mutations can be detected in over 90% of cases [35, 40].

Preclinical studies aimed at determining ripretinib safety profile were conducted on research groups of mice [35], rats, and dogs. Common side effects observed in all groups included skin changes, hyperpigmentation, and an increase in the activity of liver enzymes [41]. In addition, vomiting and abnormal stools were observed in the group of tested dogs [41]. Studies in pregnant rats and rabbits have shown that ripretinib can be teratogenic and cause fetal harm or complete pregnancy loss. On this basis, women of childbearing age and their partners should use effective contraception during treatment with ripretinib

and one week after its completion [42]. The effect of ripretinib on oral contraceptives has not been studied [35, 41].

Ripetinib is metabolized in hepatocytes by CYP3A, while excretion is renal. Co-administration of ripretinib with CYP3A inhibitors (ketoconazole, erythromycin, clarithromycin, itraconazole, ritonavir, posaconazole, voriconazole, and grapefruit juice) potentiates its effects and increases the risk of adverse reactions. At the same time, using ripretinib with strong CYP3A inducers reduces its anticancer effect [34]. Mild or moderate renal or hepatic impairment is not an indication for dose reduction [41]. In the INVICTUS study, of the 85 patients who received 150 mg daily ripretinib, 24% were aged 65–74, and only 9% were aged ≥ 75. This group was too small to determine significant clinical differences in the effect of the same dose in different age groups [42].

The half-life for ripretinib is four hours, and for its equally active metabolite DP-5439, 15.6 hours [34]. Ripretinib and DP-5439 are highly bound to plasma proteins (both human serum albumin (99.8% and 99.7%, respectively) and α-1-acid glycoprotein (99.4% and > 99.8%) [34], which is a contraindication to its use in patients with extreme renal or hepatic insufficiency. The elimination half-life of ripretinib and DP-5439 is 14.8 and 17.8 hours, respectively [34]. So far, studies on the presence of ripretinib in breast milk have not been conducted [42]. Due to the long half-life of ripretinib and its metabolites, breastfeeding is not recommended during and up to one week after treatment [43].

Efficacy of ripretinib in clinical trials

Phase I/II trials

The first open-label multicenter phase I clinical trial of ripretinib was conducted in 2015–2019 [44]. Two hundred fifty-eight adult patients were enrolled, including 184 patients with advanced GIST who were intolerant or had progressed to more than one line of systemic therapy. The main objective was to evaluate the safety, dose-limiting toxicity (DLT), maximum tolerated dose (MTD), and initial anticancer activity [44].

Patients in the dose escalation phase (n = 68) received ripretinib 20–200 mg twice daily or 100–250 mg once daily in repeated 28-day cycles until disease progression, unacceptable toxicity, or withdrawal of consent. Three dose-limiting adverse events were reported during the study — an asymptomatic grade 3 increase in lipase that occurred with 100 mg twice daily and 200 mg twice daily and an asymptomatic increase in creatine phosphokinase grade 4 with 150 mg once daily. An MTD could not be established, and the final determination of the recommended phase 2 dose (RP2D) of 150 mg/day was based on analysis of the safety profile, pharmacokinetics, and pharmacodynamics [44].

The study showed that ripretinib showed beneficial results already in earlier lines of treatment. For second-line patients, median PFS was 10.7 months [95% confidence interval (CI) 5.5–13.8]; in the third-line — 8.3 months (95% CI 5.5–11.1) and 5.5 months (95% CI 3.6–6.2) in the fourth and subsequent lines. The objective response rate (ORR) was 19.4%, 14.3%, and 7.2%, respectively [44].

The results of this study contributed to initiation of further studies on ripretinib in the treatment of advanced GISTs, including a phase III study (INVICTUS study, NCT03353753) and a study comparing ripretinib with sunitinib in the second-line treatment (INTRIGUE study, NCT03673501).

Phase III INVICTUS trial

The randomized phase III INVICTUS trial (NCT03353753) was a double-blind placebo-controlled trial [33]. The study aimed to test the efficacy and safety of ripretinib as a fourth-line therapy in GIST. The study enrolled 129 adult participants diagnosed with advanced GIST who were intolerant to or had failed prior treatment with at least three lines of anticancer therapy (including imatinib, sunitinib, and regorafenib).

Patients were randomized into two groups in a 2:1 ratio to receive either ripretinib (n = 85) or placebo (n = 44). Patients took 150 mg of ripretinib daily, and in case of adverse reactions, the dose was reduced to 100 mg and 50 mg. In patients with disease progression, the dose was escalated to 300 mg/day [42]. It has been shown that the use of ripretinib at a dose of 150 mg/day may correlate with the occurrence of cardiac dysfunction; therefore, it was recommended to assess ejection fraction before starting treatment and to monitor it during treatment [33].

The primary endpoint was PFS, and the secondary was ORR and OS. Median PFS in the blinded central assessment was 6.3 months (95% CI 4.6–8.1) for ripretinib versus 1.0 months (95% CI 0.9–1.7) for placebo [hazard ratio (HR) = 0.16; 95% CI 0.10–0.2] [33, 45]. For comparison, median PFS in clinical trials for sunitinib in the second line was 5.6 months, and for regorafenib in the third line — 4.8 months [28, 46]. Objective responses were found in 9.4% of patients treated with ripretinib. Long-term data from the INVICTUS study demonstrated that ripretinib showed a clinical improvement in overall survival (OS) from 6.3 months (95% CI 4.1–10.0) to 18.2 months (95% CI 13.1–30.7) (HR = 0.41; 95% CI 0.26–0.65) [45].

Interesting data are provided by the analysis of 29 patients receiving placebo who subsequently received ripretinib after progression. Clinical benefit in this group was already observed after one month of treatment, and two patients had a partial response to treatment. Median PFS in this group was 4.6 months [95% CI 1.8–not reached (NE)]. Median OS, calculated from the start of the study, was 11.6 months in the cross-over group (95% CI 6.3–NE) [47].

When assessing the impact of ripretinib on quality of life (QoL), the INVICTUS study (NCT03353753) showed that patients in the drug group rated their quality of life higher than patients in the placebo group. Self-assessment of health status using the VAS EQ-5D-5L questionnaire in patients receiving ripretinib showed an increasing trend, while it decreased in the placebo group [48]. Patients treated with ripretinib assessed their physical functioning as improving, while patients from the placebo group reported its deterioration [48, 49]. In summary, patients receiving ripretinib showed a statistically significant improvement in general health and QoL compared to patients receiving placebo, which showed that ripretinib, apart from favorable PFS and OS, also showed a favorable safety profile [48].

The risk of bias in the study was assessed as low. The study's limitations include the randomization process, as a result of which the compared groups were heterogeneous regarding age. In the placebo group, the percentage of patients aged ≥ 65 years was 50% while in the study

group, it was 33%. Patients aged ≥ 75 years also prevailed in the group treated with a placebo (22.7%) compared to the group treated with ripretinib (9.4%) [50].

Phase III INTRIGUE trial

The randomized multicenter open-label phase III trial INTRIGUE was completed in March 2022 [51]. The study aimed to compare the efficacy and safety profile of ripretinib with sunitinib in the second line of treatment in patients with advanced GISTs with disease progression on imatinib treatment. The study included 453 patients aged ≥ 18 years, assigned into two groups in a 1:1 ratio — 226 in the ripretinib group and 227 in the sunitinib group [52].

Inclusion criteria included confirmed *KIT/PDGFRA* mutation, disease progression or insensitivity to imatinib, and ECOG performance status ≤ 2. Ripretinib was used at a dose of 150 mg/day for 42 days, and sunitinib at 60 mg/day according to the schedule of 4 weeks of treatment and two weeks off [52].

The primary endpoint was PFS studied in two intention-to-treat (ITT) populations: patients with *KIT* exon 11 mutations and the entire study population. Secondary endpoints included ORR, OS, safety, and QoL.

Median PFS for ripretinib and sunitinib in the *KIT* exon 11 mutation group was 8.3 and 7.0 months, respectively (HR = 0.88; 95% CI 0.66–1.16; p = 0.36) and in the overall population 8.0 and 8.3 months, respectively (HR = 1.05; 95% CI 0.82–1.33; p = 0.72), which showed no benefit of ripretinib over sunitinib [51]. The ORR was higher for ripretinib than sunitinib in the *KIT* exon 11 ITT population (23.9% *vs.* 14.6%, p = 0.03) and the overall group (21.7% *vs.* 17.6%, p = 0.27). When comparing the safety profiles, ripretinib was associated with fewer grade 3-4 adverse events (41.3% *vs.* 65.6%, p < 0.0001) and better patient-reported tolerance [51].

The results showed that ripretinib was not superior to sunitinib in terms of PFS. However, it showed a more favorable safety profile and a higher response rate than sunitinib. The study's authors emphasize that a longer follow-up is indicated to make an adequate comparison of OS because median OS has not yet been reached [51].

An exploratory analysis of the effect of mutations found in circulating DNA (ctDNA) on treatment outcomes was also performed. Patients with exon 11 mutations in addition to exon 17 or 18 *KIT* mutations had longer PFS (14.2 *vs.* 1.5 months), OS (NE *vs.* 17.5 months), and higher ORR (44.4% *vs.* 0%) for ripretinib than sunitinib, while sunitinib was superior in PFS (4.0 *vs.* 15.0 months), OS (24.5 *vs.* NE month), and ORR (9.5% *vs.* 15.0%) for mutations in *KIT* exon 13 or 14 [53].

A QoL assessment using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire QLQ-C30 showed that patients on sunitinib experienced greater impairment than patients on ripretinib (C7 D29: −22.7 *vs.* −8.7). In patients treated with sunitinib, side effects intensified with each subsequent day of the cycle, while in the case of ripretinib, side effects did not show cyclical variability [51]. The impact of skin lesions on patients' quality of life as measured by the Dermatology Life Quality Index was significantly lower for ripretinib than for sunitinib (C7 D29: 14.3% *vs.* 26.0%) [51].

Adverse events

Patients (n = 450) treated with ripretinib had similar drug-related adverse events in phase I–II and phase III studies. Most were grade 1 or 2 [33, 44, 51] (Tab. 2). The most common adverse event was alopecia (Tab. 2), which occurred in 62% of patients in the phase I–II study and 49% and 64.1% in the two phase III studies. Other common (> 20%) adverse events were fatigue, myalgia, constipation, nausea, palmar-plantar erythrodysesthesia syndrome, anorexia, and diarrhea.

In grades 3 and 4, most adverse events were associated with increased blood pressure (5.6% in phase I–II, 4%, and 8.5% in phase III studies) and increased lipase (17.6% in phase I–II and 5% in phase III of the study). Equally common (> 2%) were abdominal pain, fatigue, anemia, and hypophosphatemia [33, 44, 51].

A total of 20 (4.4%) patients discontinued treatment due to drug-related adverse events [33, 44, 51], namely: 5.6% in phase I–II, 5% in phase III INVICTUS, and 3.6% in the phase III INTRIGUE trial. One treatment-related death was reported in the phase III INVICTUS study (cause unknown; death during sleep) [33].

Different groups of patients, pharmacokinetics, and pharmacodynamics of individual KIT inhibitors prevent absolute comparison of their safety profile; however, it allows for visualing the type and frequency of their occurrence (Tab. 3 [28, 33, 52, 54–57]). When using ripretinib, the most common side effect is alopecia, for regorafenib and sunitinib — hand-foot syndrome, and for imatinib — edema [26, 33, 46, 58]. Moreover, it has been shown that sunitinib can cause leukopenia, neutropenia, lymphopenia, and thrombocytopenia [46, 58]. The majority of adverse events for all KIT inhibitors were in Grades 1–2 [28, 58]. In the INTRIGUE study comparing the safety profile of ripretinib to sunitinib in the second line of treatment, ripretinib was associated with fewer grade 3–4 adverse events (41.3% *vs.* 65.6 for sunitinib) and better self-measured tolerability outcomes [51].

Table 2. Comparison of the incidence of adverse events with ripretinib (150 mg) in clinical trials [33, 44, 51]

Adverse events	Phase I–II trials [44] (n = 142) No. (%)		Phase III INVICTUS trial [33] (n = 85), No. (%)		Phase III INTRIGUE trial [51] (n = 223) No. (%)		Overall n = 450 No. (%)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Alopecia	88 (62.0)	–	42 (49.0)	–	143 (64.1)	–	273 (60,7)	–
Fatigue	74 (52.1)	4 (2.8)	20.0 (24)	2 (2.0)	84 (37.3)	7 (3.1)	178 (39.6)	13 (2.9)
Myalgia	69 (48.6)	0	23 (27.0)	1 (1.0)	81 (36.3)	4 (1.8)	173 (38.4)	5 (1.1)
Nausea	63 (44.4)	2 (1.4)	21 (25.1)	1 (1.0)	53 (23.8)	2 (0.9)	137 (30.4)	5 (1.1)
Hand-foot syndrome	61 (43.0)	1 (0.7)	18 (21.0)	–	59 (26.5)	3 (1.3)	138 (30.7)	4 (0.9)
Constipation	56 (39.4)	0	13 (15.0)	0	78 (35.0)	1 (0.4)	147 (32.7)	1 (0.2)
Lack of appetite	46 (32.4)	2 (1.4)	12 (14.0)	1 (1.0)	60 (26.9)	2 (0.9)	118 (26.2)	5 (1.1)
Diarrhea	44 (31.0)	3 (2.1)	17 (20.0)	1 (1.0)	42 (18.8)	2 (0.9)	103 (22.9)	6 (1.3)
Stomach pain	29 (20.4)	13 (9.2)	–	–	58 (26.0)	6 (2.7)	84 (18.7)	19 (4.2)
Muscle cramps	42 (29.6)	0	10 (12.0)	–	–	–	52 (11.6)	–
Lipase elevation	14 (9.9)	25 (17.6)	4 (5.0)	4 (5.0)	–	–	18 (4)	29 (6.4)
Body weight loss	39 (27.5)	0	13 (15.0)	–	–	–	52 (11.6)	–
Vomiting	37 (26.1)	1 (0.7)	–	–	–	–	37 (8.2)	1 (0.2)
Headache	36 (25.4)	1 (0.7)	–	–	–	–	36 (8)	1 (0.2)
Arthritis	32 (22.5)	0	10 (12.0)	–	–	–	42 (9.3)	–
Dry skin	32 (22.5)	0	–	–	–	–	32 (7.1)	–
Hypertension	24 (16.9)	8 (5.6)	4 (5.0)	3 (4.0)	59 (26.5)	19 (8.5)	87 (19.3)	30 (6.7)
Anemia	19 (13.4)	10 (7.0)	2 (2.0)	1 (1.0)	–	–	21 (4.7)	11 (2.4)
Back pain	27 (19.0)	2 (1.4)	–	–	–	–	27 (6)	2 (0.4)
Dyspnea	25 (17.6)	3 (2.1)	–	–	–	–	25 (5.6)	3 (0.7)
Cough	25 (17.6)	0	–	–	–	–	25 (5.6)	–
Vertigo	25 (17.6)	0	–	–	–	–	25 (5.6)	–
Hypophosphatemia	17 (12.0)	7 (4.9)	3 (4.0)	2 (2.0)	–	–	20 (4.4)	9 (2)
Rash	23 (16.2)	0	–	–	–	–	23 (5.1)	–

Real-world evidence

The results of the INVICTUS study are confirmed by data from clinical pratice. Administration of ripretinib to 22 patients from Taiwan and Hong Kong diagnosed with advanced unresectable or metastatic GIST showed efficacy similar to that obtained in the INVICTUS study. The final survival analysis included 20 patients treated with ripretinib at 150 mg daily [59]. The observation period was one year, and the median observation period after treatment with ripretinib was 10.4 months [59]. Median PFS was 6.1 months, and median OS was not reached [59]. The safety profile of ripretinib was comparable to the INVICTUS study, and the most common adverse event reported by patients was alopecia, which was observed in 55% of patients [59]. The study also showed that an albumin level below 3.5 was an independent adverse prognostic factor for PFS [59].

Similar results were also obtained in a single-arm phase II study (NCT04282980) in the Chinese population. The final analysis included 38 patients diagnosed with advanced GIST who underwent therapy with at least three kinase inhibitors [60]. Median PFS was 7.2 months (90% CI 2.9–7.3), and the ORR was 18.4% (95% CI 7.7–34.3) [60]. The majority of adverse events that occurred in 37 (94.9%) patients were Grade 1-2, reflecting the well-tolerated treatment in the INVICTUS study. The most common side effect was alopecia, which occurred in 17 patients (43.6%) [60].

Table 3. Comparison of the incidence of the most common adverse reactions by KIT inhibitor in phase III clinical trials [28, 33, 52, 54–57]

Adverse event	Imatinib 400 mg n = 428 [54, 55] No. (%)		Imatinib 800 mg n = 472 [56] No. (%)		Sunitinib n = 228 [57] No. (%)		Regorafenib n = 132 [28] No. (%)		Ripretinib n = 308 [33, 52] No. (%)	
	Overall	Grade 3–4	Overall	Grade 3–4	Overall	Grade 3–4	Overall	Grade 3–4	Overall	Grade 3–4
Hand–foot syndrome	–	–	–	–	24 (10.5)	8 (3.5)	56 (42.42)	20 (15.2)	77 (25.0)	3 (1.0)
Edema	274 (64.0)	7 (1.6)	412 (87.3)	43 (9.1)	–	–	–	–	–	–
Nausea	156 (36.4)	9 (2.1)	286 (60.6)	15 (3.2)	63 (27.6)	3 (1.3)	16 (12.1)	1 (0.8)	75 (24.4)	3 (1.0)
Diarrhea	151 (35.3)	12 (2.8)	268 (56.8)	25 (5.3)	77 (33.8)	8 (3.5)	40 (30.3)	5 (3.8)	60 (19.5)	3 (1.0)
Myalgia	–	–	–	–	–	–	14 (10.6)	1 (0.8)	105 (34.1)	5 (1.6)
Fatigue	178 (41.6)	8 (1.9)	374 (79.2)	51 (10.8)	85 (37.3)	18 (7.9)	39 (29.6)	2 (1.5)	106 (34.4)	9 (2.9)
Dermatitis, rash	101 (23.6)	11 (2.6)	220 (46.6)	25 (5.3)	36 (15.8)	2 (0.9)	18 (13.6)	2 (1.5)	–	–
Stomach pain	109 (25.5)	14 (3.3)	–	–	–	–	–	–	–	–
Alopecia	–	–	–	–	–	–	24 (18.2)	2 (1.5)	185 (60.1)	–
Hypertension	–	–	–	–	27 (11.8)	9 (3.9)	49 (37.1)	23 (17.4)	66 (21.4)	22 (7.1)
Stomatitis	–	–	–	–	36 (15.8)	1 (0.4)	38 (28.8)	2 (1.5)	–	–
Skin discoloration	–	–	–	–	62 (27.2)	0 (0.0)	–	–	–	–
Constipation	–	–	87 (18.4)	7 (1.5)	–	–	–	–	91 (29.5)	1 (0.3)
Lack of appetite	–	–	–	–	46 (20.2)	0 (0.0)	–	–	73 (23.7)	3 (1.0)
Vomiting	78 (18.22)	8 (1.9)	180 (38.1)	13 (2.8)	39 (17.1)	1 (0.4)	–	–	–	–
Anemia	–	–	461 (97.7)	79 (16.7)	133 (58.3)	9 (3.9)	–	–	–	–
Fever	–	–	81 (17.2)	6 (1.3)	–	–	–	–	–	–

In both studies, in case of disease progression, patients had the option of increasing the dose of ripretinib to 300 mg daily [59, 60].

In a retrospective study conducted in Great Britain on a group of 45 patients, after 21.5 months of observation, ripretinib at a dose of 150 mg/day achieved mPFS of 7.4 months (95% CI 5.6–10.0) [61]. In the case of 23 patients with disease progression after receiving the 300 mg dose, mPFS was further 5.9 months (95% CI 3.5–9.2) [61]. Overall, PFS and OS were 12.2 (95% CI 7.9–17.6) and 14.0 (95% CI 9.9–NA) months, respectively. There was no relationship between the number of previous lines of treatment and survival after ripretinib initiation. Primary mutation in *KIT* exon 11 was associated with a better prognosis [61].

Ripretinib in clinical practice guidelines

According to the latest Polish [Polish Society of Clinical Oncology (PTOK)] and international [European Society for Medical Oncology (ESMO), European Reference Network on Rare Adult Cancers (EURACAN), European Reference Network on GENetic TUmour RIsk Syndromes (GENTURIS), National Comprehensive Cancer Network (NCCN) 2022] guidelines, the standard in the treatment of advanced, inoperable, or metastatic GIST is the inclusion of KIT inhibitors. In the case of imatinib-sensitive GISTs, it is the first line of treatment at a dose of 400 mg/day. If *KIT* exon 9 mutation is present, an increased dose of imatinib of 800 mg/day can be considered, according to the
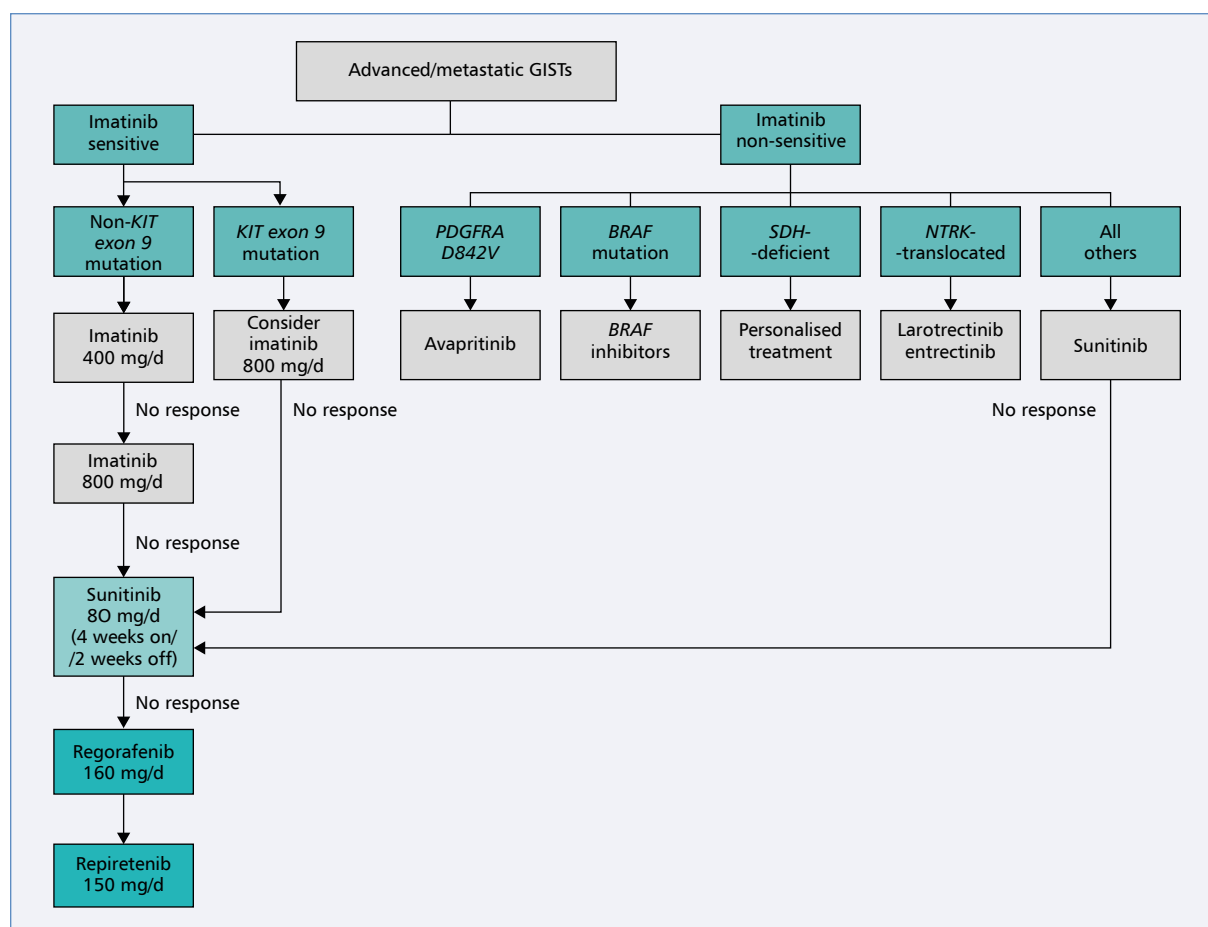
Figure 2. Treatment algorithm in advanced or metastatic gastrointestinal stromal tumors (GISTs) [5, 11]

scheme presented in Figure 2 [5, 11]. In patients with the *PDGFRA* D842V mutation, neoadjuvant treatment with avapritinib achieves a favorable result [5]. In the case of further progression of inoperable lesions, the remaining KIT inhibitors: sunitinib, regorafenib, and ripretinib, are recommended in the appropriate order, according to the scheme presented in Figure 2 [5].

According to the latest Polish and international guidelines (ESMO 2022 and NCCN 2022), ripretinib is the preferred option for fourth-line treatment in patients with inoperable, progressive, or metastatic GIST after treatment with imatinib, sunitinib, and regorafenib at a dose of 150 mg/day [5]. The guidelines also include increasing the dose of ripretinib to 150 mg twice daily as an option for patients whose disease has progressed while taking the drug at a dose of 150 mg/day [62, 63]. Further clinical trials are needed to confirm the efficacy of ripretinib in the treatment of GIST with *PDGFRA D842V* mutations. In the case of progression of GIST with the *PDGFRA D842V* mutation after the use of avapritinib or dasatinib, the guidelines allow

the use of ripretinib at a dose of 150 mg/day as an option that may show a positive treatment effect [35]. It is also possible to consider increasing the dose to 150 mg twice daily [62].

Practical recommendations

Ripretinib is an oral-only drug. It should be taken at the same time every day, with or without food [5]. The tablets should not be divided, crushed, or chewed [41, 42]. The standard dose is 150 mg/day, as three 50 mg tablets taken together [5]. The recommended dose in patients with severe renal impairment has not been established, and clinical data on the use of ripretinib at creatinine clearance (CLcr) < 30 mL/min are limited [41]. Mild hepatic impairment is not an indication for dose modification. In patients with moderate or severe hepatic impairment, the overall effectiveness of treatment should be closely monitored; the recommended dose in this case is not known [41].

Table 4. Summary of clinical trial results with ripretinib in patients with advanced gastrointestinal stromal tumor (GIST) [33, 44, 51]

	Phase I–II trial [44] (n = 142)			Phase III INVICTUS trial [33] (n = 85)	Phase III INTRIGUE trial [51] (n = 223)	
Line of therapy	2	3	4	4	2	
Mutations	All patients			All patients	All patients	*KIT* exon 11
Median PFS [months] (95% CI)	10.7 (5.5–13.8)	8.3 (5.5–11.1)	5.5 (3.6–6.2)	6.3 (4.6–8.1)	8.0 (0.82–1.33)	8.3 (0.66–1.16)
Median OS [months] (95% CI)	Not reached			18.2 (13.1–30.7)	Not reached	
ORR [%] (95% CI)	19.4 (7.5–37.5)	14.3 (4.0–32.7)	7.2 (2.7–15.1)	9.4 (4.2–17.7)	21.7	23.9 (17.6–31.2)

CI — confidence interval; ORR — objective response rate; OS — overall survival; PFS — progression-free survival

Clinical trials have shown no clinically significant differences between elderly patients (> 65 years) and younger patients (age ≥ 18 years to ≤ 65). The drug's safety profile in children has not been studied [42].

Contraindications to the use of ripretinib include hypersensitivity to the active substance or any of the excipients listed in the list of excipients, i.e., crospovidone (E1202), hypromellose acetate succinate, lactose monohydrate, magnesium stearate (E470b), microcrystalline cellulose (E460), silica, colloidal hydrate (E551) [5, 41, 42].

Conclusions

The identification of activating mutations in the KIT gene and the confirmation of the effectiveness of imatinib, which was initially used in the treatment of chronic myeloid leukemias, was a breakthrough in the treatment of GISTs. However, longer-term follow-up showed the presence of primary or secondary resistance to imatinib treatment and, thus, the need for new therapeutic options. In the following years, sunitinib, sorafenib, and regorafenib were added to the standard set of drugs for GIST patients, and the latest molecule that is used in this indication is ripretinib. The studies conducted so far indicate the activity of this drug in a particular group of patients, and it allows them to achieve median PFS of over 6 months in the 4th line of treatment and over 8 months in the second line of treatment (Tab. 4 [33, 44, 51]). The higher efficacy of ripretinib compared to sunitinib in the second line of treatment has not been demonstrated; therefore, according to the national and international guidelines, it can be used only in the fourth line after prior treatment with imatinib, sunitinib, and regorafenib. Treatment tolerance is satisfactory and allows for maintaining a good quality of life. Further studies and analyses are underway to identify the subgroups of patients in whom the drug is most effective.

Article Information and Declarations

Author contributions
E.B.: literature review, preparation of the original version of the manuscript, preparation of figures; A.S.: literature review, preparation of the original version of the manuscript, preparation of figures; P.S.: preparation of the work concept, literature review; preparation of the final version of the manuscript, supervision of the team; P.R.: preparation of the final version of the manuscript, supervision of the team.
All authors approved the final version of the manuscript.

Supplementary material

None.

References

1. Kelly CM, Gutierrez Sainz L, Chi P. The management of metastatic GIST: current standard and investigational therapeutics. J Hematol Oncol. 2021; 14(1): 2, doi: 10.1186/s13045-020-01026-6, indexed in Pubmed: 33402214.

2. Corless CL, Barnett CM, Heinrich MC. Gastrointestinal stromal tumours: origin and molecular oncology. Nat Rev Cancer. 2011; 11(12): 865–878, doi: 10.1038/nrc3143, indexed in Pubmed: 22089421.

3. Cassier PA, Ducimetière F, Lurkin A, et al. A prospective epidemiological study of new incident GISTs during two consecutive years in Rhône Alpes region: incidence and molecular distribution of GIST in a European region. Br J Cancer. 2010; 103(2): 165–170, doi: 10.1038/sj.bjc.6605743, indexed in Pubmed: 20588273.

4. Søreide K, Sandvik OM, Søreide JA, et al. Global epidemiology of gastrointestinal stromal tumours (GIST): A systematic review of population-based cohort studies. Cancer Epidemiol. 2016; 40: 39–46, doi: 10.1016/j.canep.2015.10.031, indexed in Pubmed: 26618334.

5. Casali PG, Blay JY, Abecassis N, et al. Gastrointestinal stromal tumours: ESMO–EURACAN–GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2022; 33(1): 20–33, doi: 10.1016/j.annonc.2021.09.005, indexed in Pubmed: 34560242.

6. Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med. 2006; 130(10): 1466–1478, doi: 10.5858/2006-130-1466-GSTROM, indexed in Pubmed: 17090188.

7. Blay JY, Kang YK, Nishida T, et al. Gastrointestinal stromal tumours. Nat Rev Dis Primers. 2021; 7(1): 22, doi: 10.1038/s41572-021-00254-5, indexed in Pubmed: 33737510.

8. Nishida T, Blay JY, Hirota S, et al. The standard diagnosis, treatment, and follow-up of gastrointestinal stromal tumors based on guidelines. Gastric Cancer. 2016; 19(1): 3–14, doi: 10.1007/s10120-015-0526-8, indexed in Pubmed: 26276366.

9. Fletcher CDM, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Int J Surg Pathol. 2002; 10(2): 81–89, doi: 10.1177/106689690201000201, indexed in Pubmed: 12075401.

10. Hanks SK, Quinn AM, Hunter T. The protein kinase family: conserved features and deduced phylogeny of the catalytic domains. Science. 1988; 241(4861): 42–52, doi: 10.1126/science.3291115, indexed in Pubmed: 3291115.

11. Rutkowski P, Koseła-Paterczyk H, Kozak K, et al. Postępowanie diagnostyczno-terapeutyczne u chorych na mięsaki tkanek miękkich u dorosłych — zalecenia ekspertów. Onkol Prakt Klin Edu. 2023; 9(3): 149–180.

12. Klug LR, Khosroyani HM, Kent JD, et al. New treatment strategies for advanced-stage gastrointestinal stromal tumours. Nat Rev Clin Oncol. 2022; 19(5): 328–341, doi: 10.1038/s41571-022-00606-4, indexed in Pubmed: 35217782.

13. Singer S, Rubin BP, Lux ML, et al. Prognostic value of KIT mutation type, mitotic activity, and histologic subtype in gastrointestinal stromal tumors. J Clin Oncol. 2002; 20(18): 3898–3905, doi: 10.1200/JCO.2002.03.095, indexed in Pubmed: 12228211.

14. Roberts KG, Odell AF, Byrnes EM, et al. Resistance to c-KIT kinase inhibitors conferred by V654A mutation. Mol Cancer Ther. 2007; 6(3): 1159–1166, doi: 10.1158/1535-7163.MCT-06-0641, indexed in Pubmed: 17363509.

15. Mol CD, Dougan DR, Schneider TR, et al. Structural basis for the autoinhibition and STI-571 inhibition of c-Kit tyrosine kinase. J Biol Chem. 2004; 279(30): 31655–31663, doi: 10.1074/jbc.M403319200, indexed in Pubmed: 15123710.

16. Kang DY, Park CK, Choi JS, et al. Multiple gastrointestinal stromal tumors: Clinicopathologic and genetic analysis of 12 patients. Am J Surg Pathol. 2007; 31(2): 224–232, doi: 10.1097/01.pas.0000213318.66800.94, indexed in Pubmed: 17255767.

17. Duensing A, Medeiros F, McConarty B, et al. Mechanisms of oncogenic KIT signal transduction in primary gastrointestinal stromal tumors (GISTs). Oncogene. 2004; 23(22): 3999–4006, doi: 10.1038/sj.onc.1207525, indexed in Pubmed: 15007386.

18. Debiec-Rychter M, Sciot R, Le Cesne A, et al. EORTC Soft Tissue and Bone Sarcoma Group, Italian Sarcoma Group, Australasian Gastrointestinal Trials Group. KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. Eur J Cancer. 2006; 42(8): 1093–1103, doi: 10.1016/j.ejca.2006.01.030, indexed in Pubmed: 16624552.

19. Vanden Bempt I, Vander Borght S, Sciot R, et al. Comprehensive targeted next-generation sequencing approach in the molecular diagnosis of gastrointestinal stromal tumor. Genes Chromosomes Cancer. 2021; 60(4): 239–249, doi: 10.1002/gcc.22923, indexed in Pubmed: 33258138.

20. Burch J, Ahmad I. Gastrointestinal Stromal Cancer. In: StatPearls 2022. StatPearls Publishing LLC, Treasure Island (FL) 2022.

21. Rutkowski P, Gronchi A, Hohenberger P, et al. Neoadjuvant imatinib in locally advanced gastrointestinal stromal tumors (GIST): the EORTC STBSG experience. Ann Surg Oncol. 2013; 20(9): 2937–2943, doi: 10.1245/s10434-013-3013-7, indexed in Pubmed: 23760587.

22. Joensuu H, Eriksson M, Sundby Hall K, et al. Adjuvant Imatinib for High-Risk GI Stromal Tumor: Analysis of a Randomized Trial. J Clin Oncol. 2016; 34(3): 244–250, doi: 10.1200/JCO.2015.62.9170, indexed in Pubmed: 26527782.

23. Joensuu H, Eriksson M, Sundby Hall K, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. JAMA. 2012; 307(12): 1265–1272, doi: 10.1001/jama.2012.347, indexed in Pubmed: 22453568.

24. Joensuu H, Wardelmann E, Sihto H, et al. Effect of KIT and PDGFRA Mutations on Survival in Patients With Gastrointestinal Stromal Tumors Treated With Adjuvant Imatinib: An Exploratory Analysis of a Randomized Clinical Trial. JAMA Oncol. 2017; 3(5): 602–609, doi: 10.1001/jamaoncol.2016.5751, indexed in Pubmed: 28334365.

25. Blanke CD, Demetri GD, von Mehren M, et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. J Clin Oncol. 2008; 26(4): 620–625, doi: 10.1200/JCO.2007.13.4403, indexed in Pubmed: 18235121.

26. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med. 2002; 347(7): 472–480, doi: 10.1056/NEJMoa020461, indexed in Pubmed: 12181401.

27. Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST). Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: a meta-analysis of 1,640 patients. J Clin Oncol. 2010; 28(7): 1247–1253, doi: 10.1200/JCO.2009.24.2099, indexed in Pubmed: 20124181.

28. Demetri GD, Reichardt P, Kang YK, et al. GRID study investigators. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013; 381(9863): 295–302, doi: 10.1016/S0140-6736(12)61857-1, indexed in Pubmed: 23177515.

29. Mazzocca A, Napolitano A, Silletta M, et al. New frontiers in the medical management of gastrointestinal stromal tumours. Ther Adv Med Oncol. 2019; 11: 1758835919841946, doi: 10.1177/1758835919841946, indexed in Pubmed: 31205499.

30. Heinrich MC, Jones RL, von Mehren M, et al. Avapritinib in advanced PDGFRA D842V-mutant gastrointestinal stromal tumour (NAVIGATOR): a multicentre, open-label, phase 1 trial. Lancet Oncol. 2020; 21(7): 935–946, doi: 10.1016/S1470-2045(20)30269-2, indexed in Pubmed: 32615108.

31. Jones R, Serrano C, Mehren Mv, et al. Avapritinib in unresectable or metastatic PDGFRA D842V-mutant gastrointestinal stromal tumours: Long-term efficacy and safety data from the NAVIGATOR phase I trial. Eur J Cancer. 2021; 145: 132–142, doi: 10.1016/j.ejca.2020.12.008.

32. Grunewald S, Klug LR, Mühlenberg T, et al. Resistance to Avapritinib in PDGFRA-Driven GIST Is Caused by Secondary Mutations in the PDGFRA Kinase Domain. Cancer Discov. 2021; 11(1): 108–125, doi: 10.1158/2159-8290.CD-20-0487, indexed in Pubmed: 32972961.

33. Blay JY, Serrano C, Heinrich MC, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2020; 21(7): 923–934, doi: 10.1016/S1470-2045(20)30168-6, indexed in Pubmed: 32511981.

34. Dhillon S. Ripretinib: First Approval. Drugs. 2020; 80(11): 1133–1138, doi: 10.1007/s40265-020-01348-2, indexed in Pubmed: 32578014.

35. Smith BD, Kaufman MD, Lu WP, et al. Ripretinib (DCC-2618) Is a Switch Control Kinase Inhibitor of a Broad Spectrum of Oncogenic and Drug-Resistant KIT and PDGFRA Variants. Cancer Cell. 2019; 35(5): 738–751.e9, doi: 10.1016/j.ccell.2019.04.006, indexed in Pubmed: 31085175.

36. Mohammadi M, Gelderblom H. Systemic therapy of advanced/metastatic gastrointestinal stromal tumors: an update on progress beyond imatinib, sunitinib, and regorafenib. Expert Opin Investig Drugs. 2021;

30(2): 143–152, doi: 10.1080/13543784.2021.1857363, indexed in Pubmed: 33252274.

37. DiNitto JP, Deshmukh GD, Zhang Y, et al. Function of activation loop tyrosine phosphorylation in the mechanism of c-Kit auto-activation and its implication in sunitinib resistance. J Biochem. 2010; 147(4): 601–609, doi: 10.1093/jb/mvq015, indexed in Pubmed: 20147452.

38. Lostes-Bardaji MJ, García-Illescas D, Valverde C, et al. Ripretinib in gastrointestinal stromal tumor: the long-awaited step forward. Ther Adv Med Oncol. 2021; 13: 1758835920986498, doi: 10.1177/1758835920986498, indexed in Pubmed: 33473249.

39. Pilco-Janeta DF, García-Valverde A, Gomez-Peregrina D, et al. Emerging drugs for the treatment of gastrointestinal stromal tumors. Expert Opin Emerg Drugs. 2021; 26(1): 53–62, doi: 10.1080/14728214.2021.1896704, indexed in Pubmed: 33645383.

40. Arock M, Sotlar K, Akin C, et al. KIT mutation analysis in mast cell neoplasms: recommendations of the European Competence Network on Mastocytosis. Leukemia. 2015; 29(6): 1223–1232, doi: 10.1038/leu.2015.24, indexed in Pubmed: 25650093.

41. EMA. Quinlock Charakterystyka Produktu Leczniczego.

42. Pharmaceuticals., D., QINLOCK™ (ripretinib) tablets: US prescribing information 2020.

43. Ripretinib, in Drugs and Lactation Database (LactMed). 2006, National Library of Medicine (US): Bethesda (MD).

44. Janku F, Abdul Razak AR, Chi P, et al. Switch Control Inhibition of KIT and PDGFRA in Patients With Advanced Gastrointestinal Stromal Tumor: A Phase I Study of Ripretinib. J Clin Oncol. 2020; 38(28): 3294––3303, doi: 10.1200/JCO.20.00522, indexed in Pubmed: 32804590.

45. Mehren Mv, Heinrich MC, George S, et al. 1540P Ripretinib as ≥4th-line treatment in patients with advanced gastrointestinal stromal tumor: Long-term update from the phase III INVICTUS study. Annals of Oncology. 2021; 32: S1120–S1121, doi: 10.1016/j.annonc.2021.08.870.

46. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet. 2006; 368(9544): 1329–1338, doi: 10.1016/S0140-6736(06)69446-4, indexed in Pubmed: 17046465.

47. Serrano C, Heinrich M, George S, et al. O-13 Efficacy and safety of ripretinib as ≥4th-line therapy for patients with gastrointestinal stromal tumor following crossover from placebo: Analyses from INVICTUS. Ann Oncol. 2020; 31: 236, doi: 10.1016/j.annonc.2020.04.066.

48. Heinrich M, George S, Zalcberg J, et al. Quality of life (QoL) and self-reported function with ripretinib in ≥4th-line therapy for patients with gastrointestinal stromal tumors (GIST): Analyses from INVICTUS. J Clin Oncol. 2020; 38(15_suppl): 11535–11535, doi: 10.1200/jco.2020.38.15_suppl.11535.

49. Schöffski P, George S, Heinrich MC, et al. Patient-reported outcomes in individuals with advanced gastrointestinal stromal tumor treated with ripretinib in the fourth-line setting: analysis from the phase 3 INVICTUS trial. BMC Cancer. 2022; 22(1): 1302, doi: 10.1186/s12885-022-10379-9, indexed in Pubmed: 36514034.

50. Załącznik do Raportu oceny technologii o wysokiej innowacyjności w ramach Funduszu Medycznego za rok 2022, nr 18: Qinlock (ripretynib) we wskazaniu: w leczeniu dorosłych pacjentów z zaawansowanym nowotworem podścieliskowym przewodu pokarmowego (GIST), którzy byli wcześniej leczeni trzema lub więcej inhibitorami kinazy, w tym imatynibem. Opracowanie analityczne 18.02.2022.

51. Bauer S, Jones RL, Blay JY, et al. Ripretinib Versus Sunitinib in Patients With Advanced Gastrointestinal Stromal Tumor After Treatment With Imatinib (INTRIGUE): A Randomized, Open-Label, Phase III Trial. J Clin Oncol. 2022; 40(34): 3918–3928, doi: 10.1200/JCO.22.00294, indexed in Pubmed: 35947817.

52. Heinrich M, Jones R, Gelderblom H, et al. INTRIGUE: A phase III, randomized, open-label study to evaluate the efficacy and safety of ripretinib versus sunitinib in patients with advanced gastrointestinal stromal tumor previously treated with imatinib. J Clin Oncol. 2022; 40(36_suppl): 359881–359881, doi: 10.1200/jco.2022.40.36_suppl.359881.

53. Bauer S, Jones R, George S, et al. Mutational heterogeneity of imatinib resistance and efficacy of ripretinib vs sunitinib in patients with gastrointestinal stromal tumor: ctDNA analysis from INTRIGUE. J Clin Oncol. 2023; 41(36_suppl): 397784–397784, doi: 10.1200/jco.2023.41.36_suppl.397784.

54. Raut CP, Espat NJ, Maki RG, et al. Efficacy and Tolerability of 5-Year Adjuvant Imatinib Treatment for Patients With Resected Intermediate- or High-Risk Primary Gastrointestinal Stromal Tumor: The PERSIST-5 Clinical Trial. JAMA Oncol. 2018; 4(12): e184060, doi: 10.1001/jamaoncol.2018.4060, indexed in Pubmed: 30383140.

55. Dematteo RP, Ballman KV, Antonescu CR, et al. American College of Surgeons Oncology Group (ACOSOG) Intergroup Adjuvant GIST Study Team. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet. 2009; 373(9669): 1097–1104, doi: 10.1016/S0140-6736(09)60500-6, indexed in Pubmed: 19303137.

56. Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet. 2004; 364(9440): 1127–1134, doi: 10.1016/S0140-6736(04)17098-0, indexed in Pubmed: 15451219.

57. Demetri GD, Garrett CR, Schöffski P, et al. Complete longitudinal analyses of the randomized, placebo-controlled, phase III trial of sunitinib in patients with gastrointestinal stromal tumor following imatinib failure. Clin Cancer Res. 2012; 18(11): 3170–3179, doi: 10.1158/1078-0432.CCR-11-3005, indexed in Pubmed: 22661587.

58. Zalcberg JR. Ripretinib for the treatment of advanced gastrointestinal stromal tumor. Therap Adv Gastroenterol. 2021; 14: 17562848211008177, doi: 10.1177/17562848211008177, indexed in Pubmed: 33948116.

59. Lin LC, Huang WK, Yen CC, et al. Compassionate Use of Ripretinib for Patients With Metastatic Gastrointestinal Stromal Tumors: Taiwan and Hong Kong Experience. Front Oncol. 2022; 12: 883399, doi: 10.3389/fonc.2022.883399, indexed in Pubmed: 35847924.

60. Li J, Cai S, Zhou Y, et al. Efficacy and Safety of Ripretinib in Chinese Patients with Advanced Gastrointestinal Stromal Tumors as a Fourth- or Later-Line Therapy: A Multicenter, Single-Arm, Open-Label Phase II Study. Clin Cancer Res. 2022; 28(16): 3425–3432, doi: 10.1158/1078-0432.CCR-22-0196, indexed in Pubmed: 35686969.

61. Napolitano A, Lim SY, Lopez LFF, et al. 80P Expanded access program use of ripretinib in advanced GIST patients in the United Kingdom. ESMO Open. 2023; 8(1): 101117, doi: 10.1016/j.esmoop.2023.101117.

62. von Mehren M, Kane JM, Riedel RF, et al. NCCN Guidelines® Insights: Gastrointestinal Stromal Tumors, Version 2.2022. J Natl Compr Canc Netw. 2022; 20(11): 1204–1214, doi: 10.6004/jnccn.2022.0058, indexed in Pubmed: 36351335.

63. Zalcberg JR, Heinrich MC, George S, et al. Clinical Benefit of Ripretinib Dose Escalation After Disease Progression in Advanced Gastrointestinal Stromal Tumor: An Analysis of the INVICTUS Study. Oncologist. 2021; 26(11): e2053–e2060, doi: 10.1002/onco.13917, indexed in Pubmed: 34313371.