VIA MEDICA

Dodatek konferencyjny / Conference addendum

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2020, tom 5, nr 6, 385–392

ISSN 2543–5248
www.nowotwory.edu.pl

Warsaw Sacroma Meeting
5 grudnia 2020 / 5th December 2020

Advances in the management of gastrointestinal stromal tumors (GISTs)

Monika Dudzisz-Śledź, Piotr Rutkowski

Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw

Gastrointestinal stromal tumors are rare neoplasms developing from cells of Cajal in the gastrointestinal tract. The mainstay of such tumors treatment is surgery, whenever possible. The therapeutic management of inoperable and metastatic disease is based on tyrosine kinase inhibitors and imatinib is the main drug recommended for first line treatment. The introduction of imatinib and other inhibitors improved survival outcomes for this disease, but due to primary and secondary resistance there is still the urgent need for new medications. This paper presents the progress in the systemic therapy of GISTs based on the latest scientific data. The newly developed agents (ripretinib, avapritinib) meet the need to treat patients after the failure of previously available therapies and those with *PDGFRA* mutation D842V associated with resistance to imatinib.

Key words: gastrointestinal stromal tumor, GIST, tyrosine kinase inhibitor, imatinib, regorafenib, sunitinib, sorafenib, avapritinib, repritinib, BLU-285, DCC-2618

Introduction

Gastrointestinal stromal tumors (GIST) develop from interstitial cells of Cajal in the gastrointestinal tract or their precursors. GISTs are rare neoplasms but are also the most common mesenchymal tumors of the gastrointestinal tract. The incidence of GIST in most published studies is reported at 10–15 new cases/100,000 per year and it is reported as having increased during the last decades [1]. GISTs are most often located in the stomach (50–70%) and in the small bowel (30% in the jejunum or ileum, 5% in the duodenum) but less frequently they can be found in other parts of the gastrointestinal tract and also in the omentum, mesentery, peritoneum and pancreas [2, 3]. The median age at diagnosis is about 60–65 years [1, 3, 4]. Small GISTs usually remain asymptomatic but patients with larger tumors may have different symptoms depending on the location of the tumor. Suspicion of possible GIST is usually based on imaging or endoscopic tests and should be confirmed with a pathology test including immunohistchemistry staining and molecular testing. GIST management should be implemented, especially in unresectable and metastatic cases, based on the decision of the multidisciplinary team who are experienced in soft tissue sarcomas.

Diagnostics and molecular abnormalities

Suspicion of GIST is usually done based on imaging and endoscopic studies but this requires confirmation with pathology results. A biopsy is an important step in this diagnosis. There are 2 typical histological patterns of GIST: a spindle cell (60–70% of cases) or epithelioid (30–40% of cases) character, or a combination of both in variable proportions [5]. GISTs stain positive for KIT (CD117) and DOG1. Almost all except about 5% of GISTs are immunohistochemically positive for CD117. These minority of cases refer mostly to GISTs with the *PDGFRA* mutation. DOG1 expression is almost exclusively characteristic for GIST and is independent of the KIT status. Immunohistochemistry is important to differentiate GISTs from other mesenchymal

Jak cytować / How to cite:
Dudzisz-Śledź M, Rutkowski P. ***Advances in the management of gastrointestinal stromal tumors (GISTs).*** *NOWOTWORY J Oncol* 2020; 70: 280–287.

tumors. The differential diagnosis most often includes IHC staining with the following antibodies: CD34, SMA, h-caldesmon, desmin, general cytokeratin or CK18, S100, HMB-45, and melan A. Three of the most important prognostic factors in GIST are: location (gastric GISTs have a better prognosis than the small bowel or rectal GISTs), size and mitotic activity. It is important to note that tumor rupture is an additional adverse prognostic factor. Risk assessment based on the mitotic count, tumor size and tumor location is important for therapeutic decisions as well choosing the follow-up procedures after radical treatment. High-risk patients generally reccure within 1–3 years after the end of adjuvant therapy and low-risk patients may reccure later, but this is much less likely. This should be taken into consideration during follow-up procedures [6]. Mutational status is not included in any risk classification but has an important prognostic value and predictive significance for targeted therapies. GISTs with the *PDGFR D842V* mutation are associated with imatinib resistance and *KIT/PDGFRA* wild type GISTs may have a special clinical presentation and course [6]. Mutations of the *KIT* gene are present in 80–85% of GIST cases. The most common mutation in sporadic GIST (approximately 60%) and the best response to imatinib is the mutation in exon 11 of the *KIT* gene. This mutation is also observed in the familial GIST. Mutation in exon 9 *KIT* is more common in GISTs originating from the small intestine and the colon; this mutation is related to a worse response to imatinib. Patients with a mutation in exon 9 of the *KIT* gene may benefit from a higher dose of imatinib i.e. 800 mg daily and from a sunitinib. Mutations in exon 13 and 17 *KIT* are very rarely present, those aberrations are described in the familial GIST and in such cases a response to imatinib was observed. *PDGFRA* gene mutations are present in 5–8% of GISTs. In the case of mutations in exon 12 and exon 14 of the *PDGFRA* gene, a clinical response to imatinib was observed. Most mutations in exon 18 of the *PDGFRA* gene are present in cases of tumors located in the stomach or the omentum; the *D842V* mutation is resistant to imatinib and sunitinib, while other types of *PDGFRA* mutations are sensitive to them. Wild-type GISTs, i.e. GISTs with no *KIT* or *PDGRA* mutations, constitute 12-15% of cases and are characterized by a poor response to imatinib and a better response to sunitinib. Such cases often include pediatric GISTs (as SDH-deficient), typically GISTs related to NF1 or Carney's triad [3].

The system most often used for GIST staging is the American Joint Committee on Cancer (AJCC) TNM (TNM tumor/node/metastasis) classification system with the latest update from 2018.

Treatment

The treatment of GIST should be implemented, especially in unresectable cases, based on the experience of the GIST management multidisciplinary team and their decision. The therapeutic approach may include endoscopic resection (in the case of small asymptomatic lesions), surgery and medical therapy, and in some cases radiotherapy, chemotherapy, hepatic artery embolization, chemoembolisation of the hepatic artery branches, radiofrequency ablation and supportive care.

Surgical treatment, if possible, remains the mainstay of GIST management. The main goal of surgery is an R0 resection (negative margins). The surgical approach depends on the tumor's location and size, its adherence or invasion into adjacent structures and the patient's general condition and comorbidities. In the case of smaller lesions, the laparoscopic approach can be considered but this needs to follow all rules for oncological surgery. It can be considered especially for GISTs located in the stomach. This procedure is clearly discouraged in patients with large tumors, because of the risk of tumor rupture, which is associated with a very high risk of relapse. Usually GISTs do not metastasize to the lymph nodes and consequently routine local lymph node dissection is not required unless suspected on imaging. Due to the high recurrence potential in each case of GIST, the possible use of adjuvant imatinib should be assessed based on the recurrence risk assessment. In case of R1 resection, it is recommended to assess the possibility to do secondary surgery (re-excision). It should be considered if there is a possibility to determine the location of the primary tumor and if the procedure is not related with serious consequences for the functioning of the gastrointestinal tract. In some cases resection R1 can be acceptable, for example, in cases when the resection R0 is associated with major functional sequalae and there is no response for preoperative systemic therapy, especially for low-risk lesions [4, 6].

Imatinib can be recommended in a preoperative setting until the maximum response is obtained, which usually takes 6–12 months from the beginning of treatment. During preoperative therapy the response has to be strictly assessed with imaging tests so as not to miss disease resistance and progression. The main indications for preoperative imatinib therapy are: a locally advanced tumor not eligible for a non-mutilating surgery like abdominoperineal excision, pelvic exenteration, negative margins (R0 resection) achievement can be problematic or the risk of perforation is high; preoperative treatment can allow for saving surgery like gastric wedge resection instead of gastrectomy, local excision instead of pancreatoduodenectomy [7]. Imatinib should be continued in an adjuvant setting for a total treatment duration of three years. The decision about implementation of adjuvant imatinib should be done based on a risk assessment. Based on the scale of Miettinen and Lasota (2006), which defines the risk assessment of GIST aggressiveness (frequency of metastases or cancer-related death) depending on the location, size, and mitotic activity, there are 6 prognostic groups defined. Adjuvant imatinib for 3 years should be used for patients with a high risk of relapse. 3-years therapy prolonged relapse-free survival (RFS) and overall survival (OS) in comparison to the

one-year treatment. The RFS was 65.6% *vs.* 47.9% for 36-month and 12-month imatinib therapy, respectively, and the five-year OS was 92% *vs.* 81.7%, respectively (NCT00116935) [8]. In 2020 the updated data after a 10-year follow-up of this trial were presented and in the intent-to-treat cohorts for the 36-month group; the 5-year and 10-year OS rates were 92.0% and 79.0%, and in the 12-month group, 85.5% and 65.3%, respectively (HR 0.55, 95% CI 0.37–0.83; p = 0.004). It was concluded that about 50% of deaths can be avoided during the first decade of follow-up after surgery with the 3-year imatinib treatment as compared to the 1-year treatment [9]. Polish real-life data confirmed the efficacy of 3-year adjuvant therapy with imatinib in patients with high-risk molecular profiled GIST. The authors found overrepresentation of exon 9 *KIT* mutants and ruptured tumors in a group of patients with disease relapses [10]. In addition to risk assessment, it is required to perform molecular tests to determine the status of the GIST mutation to avoid treatment of patients with low sensitivity or resistance to imatinib [11, 12].

Imatinib is the standard of care in the first line of unresectable/metastatic disease. The introduction of imatinib to the treatment of GIST was a crucial point in the management of this disease. Median overall survival in patients with advanced/metastatic disease before imatinib was about 12–15 months. In cases of inoperable or metastatic disease, the treatment of choice is the use of imatinib, the tyrosine kinase inhibitor (TKI), in the standard dose of 400 mg per day, orally. The efficacy of imatinib in first line treatment of unresectable or metastatic GISTs was demonstrated in prospective clinical trials [13, 14]. Based on the long-term follow-up of patients treated in prospective clinical trials, the median PFS was about 2–3 years and the median OS was about 5 years. The clinical benefit in prospective clinical trials was mostly due to partial responses (40%) and disease stabilization (36%); complete responses were rarely observed (5–7%). This efficacy has been confirmed in retrospective real-world studies [15, 16].

Primary and early resistance to imatinib during the first 6 months of therapy is observed in about 10–15% of patients with GIST. In responders the acquired resistance may appear along with the duration of treatment. Approximately 40–50% of patients show signs of disease progression in 2–3 years of treatment with imatinib. Most often the acquired resistance results from a new mutation or additional mutations in the *KIT* or *PDGFRA* genes, leading to a conformation change of the receptor and the inability to bind to imatinib.

In case of progression, it is recommended to increase the dose of imatinib to 800 mg daily, and in the case of lack of efficacy, to use sunitinib which is approved for second line treatment at an initial dose of 50 mg daily based on phase III study results (NCT00075218). The use of other TKIs, with different targets in the pathway can help overcome resistance to imatinib. They can also be used in the case of imatinib intolerance. Sunitinib is a multikinase inhibitor that targets PDGFR, KIT, VEGFR (vascular endothelial growth factor) and CSF-1R (colony stimulating factor 1 receptor). In a randomized phase III trial sunitinib was administered 50 mg orally once daily for 4 weeks, followed by a 2-week period off. In this study the median PFS was 27 weeks in sunitinib group in comparison to 6 weeks in the placebo group [17–19]. In case of further progression or sunitinib intolerance, regorafenib and sorafenib are subsequent therapeutic options, although sorafenib is not approved for GIST treatment [20, 21]. Regorafenib, another multikinase inhibitor targeting KIT, PDGFR, VEGFR, FGFR (fibroblast growth factor receptor) and RET, was registered in third-line treatment based on a phase III study named GRID (NCT01271712). In this study, regorafenib was dosed 160 mg daily every 3 out of 4 weeks. The patients treated with regorafenib achieved median PFS of 4.8 months compared to 0.9 months in the placebo group [22].

Taking into consideration the limited options of systemic therapy, re-challenge with previously tolerated and effective TKI for palliation of symptoms in case of PD, can be considered. The results of the randomized study published in 2013 indicate that rechallenge with imatinib can significantly improve PFS and DCR (the disease control rate) in patients with GIST after failure with at least imatinib and sunitinib, although the survival benefit was minimal [23].

Patients who progressed despite prior therapy or recurred should be considered for participation in clinical trials, if available [24]. There are currently ongoing clinical trials with tyrosine kinase inhibitors of KIT and/or *PDGFRA* (sunitinib, regorafenib, crenolanib, ripretinib, avapritinib, cabozantinib, axitinib), immunotherapy (nivolumab and iplimumab, avelumab, pembrolizumab), tyrosine kinase inhibitors of MEK (binimetinib), mTOR inhibitor (temsirolimus) and other molecules [25]. Researchers from the Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland, lead the clinical trial on the combination of axitinib with avelumab (AXAGIST) in imatinib and sunitinib refractory GIST (NCT04258956).

In patients with a preliminary inoperable disease, the resectability should be regularly assessed during treatment with imatinib and surgery should be done if at all possible. Similarly, in patients with oligometastatic disease, who experience response and subsequent stabilization of the lesions in two subsequent imaging tests done within 4–6 months, resection may be considered with the assumption of continuation of systemic therapy after surgery. This approach can improve progression-free survival and overall survival [26–28]. Surgical treatment is not appropriate for patients with multifocal progression during systemic therapy with imatinib or sunitinib.

Recently approved systemic therapies

Recently, two new medications – avapritinib (BLU-285) and ripretinib (DCC-2618) – have been assessed in clinical trials in patients with GIST and included in GIST treatment in clinical

practice. The new medications meet the need to treat patients after the failure of previously available therapies and those with a *PDGFRA* mutation D842V associated with resistance to imatinib.

Avapritinib is approved in Europe in monotherapy for the treatment of adult patients with unresectable or metastatic GIST harboring the platelet-derived growth factor receptor alpha (*PDGFRA*) *D842V* mutation [29]. In the US, the drug is approved for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumors (GIST) harboring a platelet-derived growth factor receptor alpha (*PDGFRA*) exon 18 mutation, including the *PDGFRA D842V* mutations [30].

Avapritinib is a Type 1 kinase inhibitor which demonstrated in vitro activity on the *PDGFRA D842V* and *KIT D816V* mutants associated with resistance to imatinib, sunitinib and regorafenib. The drug demonstrated greater potency against clinically relevant *KIT* exon 11 and *KIT* exon 17 mutants than against the *KIT* wild-type [29, 31]. Avapritinib's safety, tolerability and anti-tumor activity were assessed in patients with advanced GIST in the NAVIGATOR study (NCT02508532) [32]. This was an open-label, phase I study, which consisted of dose-escalation and dose-expansion parts. The study was done over 17 sites in 9 countries. Patients with unresectable GISTs were enrolled into the dose-escalation part of the study (n = 46, among them 20 patients with a *PDGFRA D842V*-mutant GIST). The dose-expansion part of the study included patients with an unresectable *PDGFRA D842V*-mutant GISTs (n = 36) regardless of previous treatment and patients with GISTs with other mutations whose disease either progressed on imatinib alone or on imatinib along with at least one other TKI. Adult patients (at least 18 years old), with an ECOG (Eastern Cooperative Oncology Group) PS 0–2 (performance status), and with adequate organ function were eligible. Avapritinib was administered orally, once daily in the dose-escalation part, starting with a dose of 30 mg, in 28-day cycles. Treatment was continued until unacceptable toxicity, noncompliance, withdrawal of consent, physician decision, disease progression, death, or the closure of the study. Primary endpoints were MTD (maximum tolerated dose), the dose recommended for part 2, safety, and overall response in the dose-expansion part. Safety was assessed in all patients from the dose-escalation part and all patients with the *PDGFRA D842V*-mutant GIST from the dose-expansion part. The secondary endpoints were pharmacokinetics, the clinical benefit rate, the duration of the response, and PFS per mRECIST 1.1. The pre-specified exploratory endpoint was OS (overall survival). The activity was assessed in all patients with *PDGFRA D842V*-mutant GIST who received avapritinib and who had at least one target lesion and at least one post-baseline disease assessment by central radiology. The efficacy was assessed based on mRECIST 1.1. (modified Response Evaluation Criteria in Solid Tumors, version 1.1). Response assessment was done using CT or MRI at screening, on day 1 of cycle 3, every 2 cycles up to cycle 13, and then every 3 months until disease progression or discontinuation. Safety was assessed from the first dose of the study drug until 30 days after the last dose. The AEs were reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 4.03).

The safety population included 82 patients, and the D842V population 56 patients. The median age was 62 years, 60% were men and 76% were white, in the safety population. 98% of patients had metastatic disease and 87% of patients were previously treated with at least one TKI. The median follow-up of patients in the safety population was 19.1 months. In the dose-expansion part of the study, the MTD 400 mg from the dose-escalation part was used. The higher incidence of grade 3 cognitive adverse events (AEs) was observed during the early expansion part of the study and further dose reductions with the 400 mg starting dose after multiple cycles of treatment. The dose was subsequently reduced to 300 mg and eventually recommended for the second part of the study. Most treatment-related adverse events (TRAEs) were grade G1–G2. At the 400 mg dose, the most commonly reported TRAEs G1–G2 were nausea (in 71% of patients), periorbital edema (47%), fatigue (47%) and vomiting (47%). At the 300 mg dose, the most common TRAEs G1-G2 were nausea (in 69% of patients), diarrhea (41%), fatigue (38%) and decreased appetite (38%). TRAEs G3–G4 regardless of the dose, occurred in 57% of patients and the most commonly reported was anemia (in 17% of patients). Drug-related serious AEs of any grade were reported in 26% of patients. The most commonly observed were anemia (4% of patients), pleural effusion (4%), vertigo (2%) and diarrhea (2%). No treatment-related deaths were reported. There were 2 categories of AEs of special interest (AESI) determined: cognitive effects and intracranial bleeding. The first category, cognitive effects (any cause), occurred in 40% of patients and included memory impairment (30%), cognitive disorder (10%), confusional state (9%), and encephalopathy (2%). Cognitive effects were mostly G1 (23%) and resulted in treatment discontinuation in 2% of patients. Intracranial bleeding occurred in 2 patients (2%) and both AEs were G3, reported as possibly related to the study drug. 84% of patients required at least one dose reduction or treatment interruption. In the safety population, 54% of patients discontinued treatment, mostly due to disease progression (32%) and AEs (18%). 11 deaths were reported but there were no treatment-related deaths. In the D842V population 34% of patients discontinued treatment, mostly due to disease progression (7%) and AEs (21%).

The efficacy results for patients with *PDGFRA D842V*-mutation GISTs treated with the approved dose of avapritinib are summarized in table I.

In the patients with *PDGFRA D842V*-mutation GISTs treated at any dose level, confirmed overall responses (according to mRECIST v. 1.1, central review) were reported in 88% of patients (complete response, CR, in 9%; partial response, PR, in 79%; and disease stabilization, SD, in 13%). PFS at 3 months

Table I. The best confirmed response by central assessment per mRECIST v. 1.1 in patients with *PDGFRA* D842V-mutant GISTs in the group treated with avapritinib with a registered dose of 300 mg per day (n = 28) [32]

complete response	1 (4%)
partial response	25 (89%)
stable disease	2 (7%)
disease progression	0 (0%)
overall response	26 (93%; 95% CI 77–99)
clinical benefit	28 (100%; 95% CI 88–100)

was 100% (95% CI 100–100), at 6 months 94% (88–100), and at 12 months 81% (69–93). The estimated OS at 6 months was 100% (95% CI 100–100), at 12 months 91% (83–100), and at 24 months 81% (67–94).

The updated long-term data with the median follow-up of 26 months from the phase I study NAVIGATOR were presented in 2020 during the annual ESMO (European Society for Medical Oncology Conference) [33]. The ORR among 38 patients with *PDGFRA D842V*-mutant GIST treated with avapritinib at a dose 300/400 mg was 95% (CR in 13%, PR in 82%). The median duration of response was 22 months, median PFS was 24 months and median OS was not reached. The PFS and OS rates at 36 months were 34% and 71%, respectively. 21% of patients discontinued treatment due to treatment related AEs. No treatment-related deaths were reported. The most common AEs in 10% of patients with *PDGFRA D842V*-mutant GIST treated at a dose of 300/400 mg were nausea, anemia, diarrhea, fatigue, memory impairment, periorbital edema, decreased appetite, increased lacrimation, abdominal pain, vomiting, peripheral edema, hypokalemia and increased bilirubin.

The results of another study, with the acronym VOYAGER, phase III, open-label, randomized study in patients with locally advanced unresectable or metastatic GIST of avapritinib versus regorafenib in patients previously treated with imatinib and 1 or 2 other TKIs (NCT03465722) were announced by the study sponsor in April, 2020 [34, 35]. In this study the patients were randomized in 1:1 ratio to treatment with avapritinib at a dose of 300 mg daily (n = 240) or regorafenib at a dose of 160 mg per day for 3 weeks out of every 4 weeks (n = 236). The primary endpoint was PFS determined by central radiological assessment per mRECIST v. 1.1. The reported median PFS for the avapritinib group was 4.2 months in comparison to 5.6 months in the regorafenib group. The difference between the arms was not statistically significant. The overall response rate (ORR) was 17% with avapritinib versus 7% for the regorafenib group. The secondary end point of the study included ORR (overall response rate), OS and quality of life.

Ripretinib is approved in the US by the FDA for the treatment of adult patients with advanced gastrointestinal stromal tumors (GIST) who have received prior treatment with 3 or more kinase inhibitors, including imatinib [36]. The drug has not yet been authorized in Europe.

Ripretinib is a switch-control multikinase inhibitor that broadly inhibits *KIT* and *PDGFRA* kinases, including activity for wild-type *KIT* and *PDGFRA* mutations and multiple primary and secondary mutations associated with drug-resistant GISTs. Ripretinib demonstrates a dual mechanism of action and specifically and durably binds to both the switch pocket and the activation loop to lock the kinase in an inactive state. In this way the molecule prevents downstream signalling and cell proliferation. In vitro ripretinib inhibited PDGFRB (platelet derived growth factor receptor β), TIE-2 (angiopoietin-1 receptor), VEGFR2 (vascular endothelial growth factor receptor 2), and BRAF (serine and threonine-protein kinase B-raf), among others [36–38]. A first-in-human phase I study (NCT02571036) in patients with GISTs and other advanced solid tumors determined the recommended phase II dose of ripretinib as 150 mg, once daily. This phase I study included expansion cohorts to assess the clinical benefit in 2 and 3 line treatment in patients with GIST. 150 patients with GIST were enrolled into the study and received the ripretinib dose of at least 100 mg daily. Among them 141 had *KIT* mutations, 8 had *PDGFRA* mutations and 1 patient had SDH-deficient GIST. 114 GIST patients were treated at the dose of 150 mg daily. The patients were previously treated with other TKIs, 19 patients with previous 1 line, 27 with 2 lines and 68 patients with at least 3 lines. The ORR among patients treated with the dose of 150 mg was 14%, the median PF was 24 weeks and for the patients treated in 2. or 3. line, the ORR was 22% and median PFS was 36 weeks. G3–G4 AEs reported by patients treated at the dose of 150 mg daily were asymptomatic lipase increases, anemia, blood bilirubin increased, hypertension, diarrhea, abdominal pain, back pain, hyperkalemia, hyponatremia, hypophosphatemia [39].

Ripretinib was then assessed in the INVICTUS study (NCT03353753) (tab. II). It was a double-blind, randomized, placebo-controlled phase III study in patients with previously treated, advanced GISTs. This study was done in 29 sites in 12 countries. Adult patients (at least 18 years old) with advanced GISTs with progression on at least imatinib, sunitinib and regorafenib or documented intolerance to any of these medications despite dose modifications with an ECOG PS 0–2 as well as adequate organ and bone marrow function were eligible for the study. The patients were randomly assigned in a ratio 2:1 to receive either oral ripretinib 150 mg or placebo, once daily for 28-day cycles. The patients were treated until disease progression, unacceptable toxicity, or consent withdrawal. The patients assigned to the placebo arm were allowed to cross over to ripretinib 150 mg at the time of progression. Randomization stratification was done according to the number of previous therapies and ECOG PS. The efficacy was assessed using mRECIST v. 1.1. Tumor assessments were done using CT scans at screening, then every cycle (for 4 weeks) up to cycle 4. After cycle 4 assessments were continued every other cycle. In patients who crossed over from placebo to the ripretinib arm, tumor assessments were done every other cycle and at

Table II. The summary of efficacy results based on the INVICTUS study [36]

	Ripretinib (n = 85)	Placebo (n = 44)	p value	HR (95% CI)
PFS[a] (median, 95% CI)	6.3 (4.6, 6.9)	1.0 (0.9, 1.7)	< 0.0001	0.15 (0.09, 0.25)
ORR[a] (%) (95% CI)	9 (4.2, 18)	0 (0, 8)		0.0504
OS (median, 95% CI)	15.1 (12.3, 15.1)	6.6 (4.1, 11.6)		0.36 (0.21, 0.62)

PFS – progression free survival; OS – overall survival; ORR – objective response rate; HR – hazard ratio; CI – confidence interval; [a] – assessed by BICR (blinded independent central review)

the end of treatment. During the double-blind period, tumor assessments were done on the basis of BICR (blinded independent central review). Safety was assessed continuously from the signing of the informed consent until 30 days after the last dose of the study treatment. AEs were graded according to NCI-CTCAE v. 4.03. The primary endpoint was PFS, assessed by BICR. The key secondary efficacy endpoint was ORR and other secondary endpoints included OS, time to progression, time to best response, PFS by investigator assessment, QOL (quality of life), safety, disease control rate at 12 weeks and pharmacokinetic/pharmacodynamic analyses. The primary analysis was done in the intention-to-treat population (ITT). ITT was defined as all patients who signed informed consent and were randomized. Safety was assessed in patients who received at least one dose of the study drug. 154 patients were assessed for eligibility. 129 patients were randomly assigned to either the ripretinib group (n = 85) or the placebo group (n = 44). The median follow-up in the ripretinib group was 6.3 months and in the placebo arm it was 1.6 months. The relative dose intensity in the double-blind period was 100% in the ripretinib arm and 97% in the placebo arm. 15 patients did not cross over from the placebo group to the ripretinib group. Median PFS by BICR was 6.3 months (95% CI 4.6–6.9) in ripretinib group versus 1.0 month (0.9–1.7) in the placebo group (HR 0.15, 95% CI 0.09–0.25; p < 0.0001). Median PFS based on investigator assessment was 4.7 months (95% CI 4.2–8.2) in the ripretinib group and 1.0 months (0.9–1.4) in the placebo group (HR 0.19, 95% CI 0.12–0.32). PFS at 6 months was estimated to be 51% for the ripretinib arm and 3.2% for the placebo arm. The median time to progression was 6.4 months (95% CI 4.6–8.4) in the ripretinib group and 1.0 month (0.9–1.7) in the placebo group. Median OS was 15.1 months (95% CI 12.3–15.1) in the ripretinib group and 6.6 months (4.1–11.6) in the placebo group (HR 0.36, 95% CI 0.21–0.62). At 6 months, estimated OS at 6 months was 84.3% for the ripretinib arm and 55.9% for the placebo arm; 12 months estimated OS was 65.4% for the ripretinib arm and 25.9% for the placebo arm.

The most common TRAEs (reported in ≥20% of patients in the ripretinib group) in patients receiving ripretinib were alopecia, fatigue, nausea, myalgia, palmar–plantar erythrodysesthesia and diarrhea. Palmar–plantar erythrodysesthesia was reported in patients treated with ripretinib only and all events were G1 (in 13% of patients) and G2 (8%). The most commonly reported G3–G4 TRAEs in the ripretinib group were lipase increase (in 5% of patients), hypertension (4%), fatigue (2%), and hypophosphataemia (2%). The most commonly reported G3–G4 TRAEs in the placebo group were anaemia (7%), diarrhea (2%), fatigue (2%), dehydration (2%), hyperkalaemia (2%), decreased appetite (2%), acute kidney injury (2%), and pulmonary edema (2%). Treatment-related serious AEs were reported in 8 (9%) of the 85 patients treated with ripretinib and 3 (7%) of the 43 patients receiving placebo. Treatment-related treatment-emergent AEs leading to a dose reduction were reported in 6% of patients in the group who received ripretinib and in 2% of the patients receiving placebo. Treatment-related treatment-emergent adverse events leading to study treatment discontinuation were reported respectively in 5% and 2% of patients. 1 treatment-related death was reported in the placebo and 1 in the ripretinib group.

Role and physical functioning assessed by EORTC-QLQ--C30 as well overall health assessed by EQ-VAS were stable from the beginning to cycle 2 day 1 in the ripretinib group in comparison to decreases observed in the placebo group indicating a clinically relevant difference between ripretinib and the placebo [38].

Conclusions

GISTs are rare diseases and treatment should be based on multidisciplinary team decisions. This approach is especially important for unresectable tumors. The diagnosis must be based on imaging and endoscopic tests, and should be confirmed with pathology tests including IHC and molecular tests from the tissue from the biopsy. The main goal of GIST management is surgery with R0 resection. In some cases there is the need to administer preoperative therapy with imatinib with a careful follow-up during treatment with regards to the possibility of undergoing surgery. In high risk GISTs, perioperative imatinib therapy should be continued up to 3 years in total. In the case of a primarily operative GIST, risk assessment should be done and for high risk patients 3 years imatinib therapy should be implemented. For unresectable locally advanced or metastatic disease, systemic treatment with TKI should be started. The therapeutic options are limited and include imatinib, an increased dose of imatinib, sunitinib, regorafenib and sorafenib. For patients with mutations associated with resistance to imatinib, therapeutic options remain limited.

Recently 2 new medicines – avapritinib and ripretinib – have been assessed in clinical trials in patients with GIST and

implemented in clinical practice in GIST management. The new medications represent significant progress in patients after the failure of previously available therapies and those with a *PDGFRA* mutation D842V associated with resistance to imatinib.

Conflict of interest: consultant and speaker honoraria and travel payment: BMS, MSD, Novartis, Roche, Pierre Fabre, Merc, Sanofi

Monika Dudzisz-Śledź
Maria Sklodowska-Curie National Research Institute of Oncology
Department of Soft Tissue/Bone Sarcoma and Melanoma
ul. Roentgena 5
02–781 Warszawa, Poland
e-mail: Monika.Dudzisz-Sledz@pib-nio.pl

Received and accepted: 17 Nov 2020

References

1. 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.
2. Miettinen M, Lasota J. Gastrointestinal stromal tumors--definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. Virchows Arch. 2001; 438(1): 1–12, doi: 10.1007/s004280000338, indexed in Pubmed: 11213830.
3. Ahmed M. Recent advances in the management of gastrointestinal stromal tumor. World J Clin Cases. 2020; 8(15): 3142–3155, doi: 10.12998/wjcc.v8.i15.3142, indexed in Pubmed: 32874969.
4. Rutkowski P, Szumera-Ciećkiewicz A. Gastrointestinal stromal tumours (GIST) – 2018. Oncol Clin Pract. 2019; 14(6): 399–407, doi: 10.5603/ocp.2018.0053.
5. Graadt van Roggen JF, van Velthuysen ML, Hogendoorn PC. The histopathological differential diagnosis of gastrointestinal stromal tumours. J Clin Pathol. 2001; 54(2): 96–102, doi: 10.1136/jcp.54.2.96, indexed in Pubmed: 11215292.
6. Casali PG, Abecassis N, Aro HT, et al. ESMO Guidelines Committee and EURACAN, ESMO Guidelines Committee and EURACAN. Gastrointestinal stromal tumours: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018; 29(Suppl 4): iv68–iv78, doi: 10.1093/annonc/mdy095, indexed in Pubmed: 29846513.
7. Rutkowski P, Hompes D. Combined Therapy of Gastrointestinal Stromal Tumors. Surg Oncol Clin N Am. 2016; 25(4): 735–759, doi: 10.1016/j.soc.2016.05.006, indexed in Pubmed: 27591496.
8. 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.
9. Joensuu H, Eriksson M, Hall KS, et al. Three versus one year of adjuvant imatinib for high-risk gastrointestinal stromal tumor (GIST): Survival analysis of a randomized trial after 10 years of follow-up. Journal of Clinical Oncology. 2020; 38(15_suppl): 11503–11503, doi: 10.1200/jco.2020.38.15_suppl.11503.
10. Rutkowski P, Ziętek M, Cybulska-Stopa B, et al. The analysis of 3-year adjuvant therapy with imatinib in patients with high-risk molecular profiled gastrointestinal stromal tumors (GIST) treated in routine practice. Eur J Surg Oncol. 2020 [Epub ahead of print], doi: 10.1016/j.ejso.2020.08.004, indexed in Pubmed: 32826113.
11. Wang D, Zhang Q, Blanke CD, et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumors: long-term follow-up results of Radiation Therapy Oncology Group 0132. Ann Surg Oncol. 2012; 19(4): 1074–1080, doi: 10.1245/s10434-011-2190-5, indexed in Pubmed: 22203182.
12. 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.
13. 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.
14. 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.
15. Rutkowski P, Andrzejuk J, Bylina E, et al. What are the current outcomes of advanced gastrointestinal stromal tumors: who are the long-term survivors treated initially with imatinib? Med Oncol. 2013; 30(4): 765, doi: 10.1007/s12032-013-0765-7, indexed in Pubmed: 24217870.
16. Brzozowska M, Wierzba W, Szafraniec-Buryło S, et al. Real-World Evidence of Patient Outcome Following Treatment of Advanced Gastrointestinal Stromal Tumor (GIST) with Imatinib, Sunitinib, and Sorafenib in Publicly Funded Health Care in Poland. Med Sci Monit. 2019; 25: 3846–3853, doi: 10.12659/MSM.914517, indexed in Pubmed: 31121600.
17. 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.
18. Reichardt P, Kang YK, Rutkowski P, et al. Clinical outcomes of patients with advanced gastrointestinal stromal tumors: safety and efficacy in a worldwide treatment-use trial of sunitinib. Cancer. 2015; 121(9): 1405–1413, doi: 10.1002/cncr.29220, indexed in Pubmed: 25641662.
19. Sutent (sunitinib) SmPC. https://www.ema.europa.eu/en/documents/product-information/sutent-epar-product-information_en.pdf.
20. Montemurro M, Gelderblom H, Bitz U, et al. Sorafenib as third- or fourth-line treatment of advanced gastrointestinal stromal tumour and pretreatment including both imatinib and sunitinib, and nilotinib: A retrospective analysis. Eur J Cancer. 2013; 49(5): 1027–1031, doi: 10.1016/j.ejca.2012.10.009, indexed in Pubmed: 23140824.
21. Rutkowski P, Jagielska B, Andrzejuk J, et al. The analysis of the long-term outcomes of sorafenib therapy in routine practice in imatinib and sunitinib resistant gastrointestinal stromal tumors (GIST). Contemp Oncol (Pozn). 2017; 21(4): 285–289, doi: 10.5114/wo.2017.72393, indexed in Pubmed: 29416434.
22. Demetri G, Reichardt P, Kang YK, et al. 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.
23. Kang YK, Ryu MH, Yoo C, et al. Resumption of imatinib to control metastatic or unresectable gastrointestinal stromal tumours after failure of imatinib and sunitinib (RIGHT): a randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2013; 14(12): 1175–1182, doi: 10.1016/S1470-2045(13)70453-4, indexed in Pubmed: 24140183.
24. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), Gastrointestinal Stromal Tumors (GISTs), version 1.2021. 10.2020. 2021.
25. https://www.clinicaltrials.gov/ct2/results?cond=GIST&term=&cntry=&state=&city=&dist=.
26. Bauer S, Rutkowski P, Hohenberger P, et al. Long-term follow-up of patients with GIST undergoing metastasectomy in the era of imatinib -- analysis of prognostic factors (EORTC-STBSG collaborative study). Eur J Surg Oncol. 2014; 40(4): 412–419, doi: 10.1016/j.ejso.2013.12.020, indexed in Pubmed: 24491288.
27. Du CY, Zhou Ye, Song C, et al. Is there a role of surgery in patients with recurrent or metastatic gastrointestinal stromal tumours responding to imatinib: a prospective randomised trial in China. Eur J Cancer. 2014; 50(10): 1772–1778, doi: 10.1016/j.ejca.2014.03.280, indexed in Pubmed: 24768330.
28. Tielen R, Verhoef C, van Coevorden F, et al. Surgery after treatment with imatinib and/or sunitinib in patients with metastasized gastrointestinal stromal tumors: is it worthwhile? World J Surg Oncol. 2012; 10(2): 111–155, doi: 10.1186/1477-7819-10-111, indexed in Pubmed: 22703877.
29. AYVAKYT (avapritinib) SMPC. https://www.ema.europa.eu/en/documents/product-information/ayvakyt-epar-product-information_en.pdf.
30. AYVAKYT (avapritinib) prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212608s000lbl.pdf.
31. Evans EK, Gardino AK, Kim JL, et al. A precision therapy against cancers driven by mutations. Sci Transl Med. 2017; 9(414), doi: 10.1126/scitranslmed.aao1690, indexed in Pubmed: 29093181.
32. 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.
33. Jones RL, Serrano C, von Me, et al. Long-term efficacy, tolerability and overall survival in patients with unresectable or metastatic PDGFRA D842V-mutant gastrointestinal stromal tumor treated with avapritinib: NAVIGATOR phase 1 trial update. Ann Oncol. 2020; 31(Suppl 4): abstract 1621MO.
34. https://clinicaltrials.gov/ct2/show/NCT03465722.
35. https://www.prnewswire.com/news-releases/blueprint-medicines-announces-top-line-results-from-phase-3-voyager-trial-of-avapritinib-versus-regorafenib-in-patients-with-advanced-gastrointestinal-stromal-tumor-301048058.html.
36. QINLOCK (ripretinib) prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213973s000lbl.pdf.
37. 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.
38. Blay JY, Serrano C, Heinrich M, 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.
39. George S, Heinrich M, Chi P, et al. Initial results of phase I study of DCC-2618, a broad-spectrum KIT and PDGFRa inhibitor, in patients (pts) with gastrointestinal stromal tumor (GIST) by number of prior regimens. Annals of Oncology. 2018; 29: viii576–viii577, doi: 10.1093/annonc/mdy299.002.