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**Current research and treatment for gastrointestinal stromal tumors**

Lim KT *et al.* Advances in GISTs

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**Abstract**

Gastrointestinal Stromal Tumors (GISTs) are the commonest mesenchymal tumors of the gastrointestinal tract and have since gained considerable research and treatment interest especially in the last two decades. GISTs are driven by the mutations commonly in KIT gene and less commonly in platelet-derived growth factor receptor alpha (PDGFRA) gene, *BRAF* gene and succinate dehydrogenase (SDH) gene. GISTs behave in a spectrum of malignant potential and both the tumor size and mitotic index are the commonest used prognostic criteria. Whilst surgical resection can offer the best cure, targeted therapy in the form of tyrosine kinase inhibitors (TKIs) have revolutionized the management options. As the first line TKI, imatinib offers treatment for advanced and metastatic GISTs, adjuvant therapy in high risks GISTs and as a neoadjuvant agent to downsize the large tumors prior to resection. The emergence of drug resistance has altered some treatment options including prolonging the first line TKI from one to three years, increasing the dose of TKI or switching to second line TKI. Other newer TKIs such as sunitinib and regorafenib may offer some treatment options for imatinib-resistant GISTs. Research to find a new molecular targeted therapy is being evaluated such as the inhibitors of BRAF, heat shock protein 90 (HSP90), glutamine, mitogen-activated protein kinase (MAPK) signaling, Inhibitors of Apoptosis Proteins (IAPs) antagonist and even immunotherapy. This editorial review summarizes the recent research trials and potential treatment targets that may influence our future patient-specific management of GISTs. The current guidelines in GISTs management from Europe, North America and Asia are highlighted.

**Key words:** Gastrointestinal Stromal Tumors; *KIT* gene; Platelet-derived growth factor receptor alpha gene; BRAF gene; Succinate dehydrogenase gene; CD117; Tyrosine kinase inhibitor; Molecular targeted therapy

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**Core tip:** Research in the histogenesis of gastrointestinal Stromal Tumors (GISTs) identified gene mutations in KIT, PDGFRA and BRAF. The discovery of tyrosine kinase inhibitors (TKIs) allows targeted therapy in metastatic and high risk resected GISTs. However, the emergence of TKI-resistant GISTs has raised some important treatment issues. Newer TKIs and alternative targeted therapy within the domain of BRAF and mitogen-activated protein kinase signaling pathway, HSP90 and SDH inhibition are being investigated and appear to be promising. Many clinical trials are undertaken and still ongoing to define the best molecular targeted therapy for GISTs. The European, American and Asian guidelines on GISTs provide useful resources for the specialists dealing with these interesting tumors.

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**INTRODUCTION**

Gastrointestinal Stromal Tumors (GISTs) account for less than 1% of all gastrointestinal tumors and the prevalence of histological type comes after adenocarcinoma and lymphoma. GISTs are however the commonest mesenchymal tumors of the gastrointestinal tract[1]. Historically, GISTs were classified as leiomyomas or leiomyosarcomas due to smooth muscle features under light microscopy.

GISTs were first termed in 1983 by Mazur and Clark who discovered the majority of gastric wall tumors were not derived from smooth muscle and nerve sheath origin using immunohistochemistry[2]. GISTs are believed to arise from the interstitial cells of Cajal or their precursors and heterogeneous histologically showing spindle cells (70%), epitheloid cells (20%) and mixed cells (10%)[3]. The histogenesis of GISTs has since gained considerable research and treatment interest.

In a systematic review of population-based cohort studies on GISTs by Soreide K et al showed the incidence ranges from low 0.43 per 100000 per year in Shanxi Province, China to high 1.6-2.2 per 100000 per year in Korea[4].The cohort of 13550 patients from 19 countries gave the reported age ranging from 10-100 years with median age in the 60s, whilst both male and female has about equal distribution. The anatomical locations of GISTs are commonly found in the stomach (55.6%), small bowel (31.8%) and less common in colon and rectum (6%), other various locations (5.5%) and oesophagus (0.7%)[4].

Primary GISTs are commonly symptomatic in about 80% cases presenting with gastrointestinal bleeding or obstructive symptoms and abdominal pain. Incidental asymptomatic GISTs are discovered in less than 20% cases during other gastrointestinal endoscopy or imaging investigations.

The diagnostic tests for GISTs may include gastrointestinal endoscopy (Figure1), computed tomography (CT) scan (Figure 2), magnetic resonance imaging (MRI) scan and 18fluoro-deoxyglucose-positron emission tomography (18FDG-PET) scan (Figure 3). Endoscopic ultrasound scan (EUS) (Figure 4) with fine needle aspiration (FNA) biopsy (Figure 5) may be useful in confirming GISTs histologically.

Open or laparoscopic complete surgical R0 resection of GISTs (Figure 6) are the only potentially curative treatment but certain high risk features of the resected GISTs give rise to recurrence of the disease. DeMatteo *et al*[5] reviewed 200 patients with GISTs treated and followed up at a single institution showed 46% had primary disease, 47% had metastasis and 7% had isolated local recurrence. Eighty patients with primary disease and underwent complete resection had 5-year survival rate of 54%. The survival was predicted by tumor size but not microscopic resection margin. However, the tumor recurrence was noted to occur at the original primary tumor site, peritoneum and liver. These data predated the use of TKI. In later years, the treatment options for residual or progressive liver metastases of GISTs included hepatic artery embolization, radiofrequency ablation or liver resection[6-8].

Historical assessment of the malignant potential in GISTs were based on the criteria of tumor size, mitotic count, proliferating cell nuclear antigen and proliferation index which then classified into low and high risk subgroups[9]. Subsequently, different risk stratification systems for GISTs were proposed such as the National Institutes of Health (NIH) consensus criteria (Fletcher’s criteria based on size and mitotic count) and the Armed Forces Institute of Pathology (AFIP) criteria (Mittinen’s criteria based on size, mitotic count and tumor site) and the 8th edition of the International Union Against Cancer (UICC) utilizing TNM classification in addition to a grade category based on mitotic count[10-12].

According to the NIH criteria for primary GISTs, the distribution of risk are categorised as very low risk (15%), low risk (30%), intermediate risk (22%) and high risk (33%)[10]. Table 1 shows the commonly used criteria for assessing malignant risk of GISTs. Other factors associated with a higher malignant risk of GISTs are the presence of necrosis, high cellularity, invasion to serosa or adjacent structure and rich vascularity. In addition, factors associated with a higher risk of recurrence of GISTs are now recognised to be incomplete R1 or R2 resection margin, tumour rupture and spillage during surgery.

**GENETIC MUTATIONS IN GISTs**

The landmark article by Hirota *et al*[13] discovered that GISTs express the proto-oncogene KIT and this KIT gene mutation provides growth stimulation of GISTs. *c-KIT* also known as CD 117, is a protein and a type of a receptor tyrosine kinase found on the surface of a variety of cell types and it is also a type of tumor marker. The binding of stem cell factor to the extracellular domain of *c-KIT* induces receptor dimerization and activation of downstream signalling pathways responsible for pro-growth signals within the cells.

Another landmark article by Heinrich *et al*[14] later discovered those GISTs lacking KIT expression have mutations related to platelet-derived growth factor receptor alpha (PDGFRA). Overall, KIT or PDGFRA mutations are found in 85% and 5% of GISTs respectively.

Agaram *et al*[15] later discovered BRAF mutation in imatinib-naïve and imatinib-resistant GISTs. This BRAF mutation in GISTs is quite rare accounting < 1%[16]. It is noted that these KIT, PDGFRA and BRAF gene mutations are mutually exclusive.

“Wild-type” GISTs are previously referred to GISTs lacking in any mutation in KIT and PDGFRA. This “wild type“ terminology should be avoided now that new mutations are discovered in BRAF genes and genes encoding the protein succinate dehydrogenase (SDH). About 12-15% of adult GISTs and 90% of paediatric GISTs lacking KIT or PDGFRA or BRAF mutations are classified into SDH-deficient and non-SDH-deficient groups. SDH-deficient group includes Carney triad (GISTs, pulmonary chondroma and extra-adrenal paraganglioma) and Carney-Stratakis syndrome (GISTs and paraganglioma)[17].

The vast majority of KIT mutations are localised in exon 11 (juxtamembrane domain; about 70%), exon 9 (extracellular dimerization motif; 10%–15%), exon 13 (tyrosine kinase 1 domain; 1%–3%), and exon 17 (tyrosine kinase 2 domain and activation loop; 1%–3%)[18]. Secondary KIT mutations in exons 13, 14, 17, and 18 are commonly identified in post-imatinib biopsy specimens, after the patients have developed the acquired resistance. ​The mutations of PDGFRA are noted to be localised in exon 12, 14, 18 and more specifically 18 D842V. The mutation of BRAF is identified and localised to exon 15 V600E[15]. The mutations of SDH gene are found to be localised to subunit B, C and D[17]. Table 2 summarizes the frequency of different genetic mutations in GISTs.

**TYROSINE KINASE INHIBITORS AND BIOLOGICAL THERAPY IN GISTs**

Whilst complete surgical resection of GISTs can offer the best cure, targeted therapy in the form of TKIs has altered our management options. A landmark case report by Joensuu *et al*[18] described the effect of a TKI called STI571 in a patient with a metastatic GIST and the evaluation of MRI and 18FDG-PET scans showed a very dramatic reduction of GIST.

STI571 was the first TKI also called imatinib, approved by US Food and Drug Administration (FDA) in 2002 for the treatment of unresected or metastatic GISTs. In 2008, imatinib was approved for adjuvant use in high risk resected GISTs patients to prevent recurrence[19]. In 2012, FDA granted the extension of standard one year imatinib therapy to three years due to increase in overall patient survival[20,21]. An important study demonstrated that imatinib when used as a neoadjuvant therapy was found to decrease the tumor volume and was associated with improved complete surgical resection in the locally advanced primary GISTs[22].

In a trial examining the relationship between kinase genotype and treatment outcome for 428 patients treated with either 400 mg or 800 mg daily doses of imatinib confirmed the favorable impact of KIT exon 11 genotype when compared with KIT exon 9 and wild-type genotype for patients with advanced GISTs[23].

The American College of Surgeons Oncology Group led a trial studying the long term outcome of patients categorized as high risk of recurrence that had complete gross GISTs resection followed by adjuvant Imatinib 400mg/day for one year. After a median follow-up of 7.7 years, the 1-, 3-, and 5-year overall survival rate was 99%, 97%, and 83% respectively, which compared favorably with a historical 5 year overall survival rate of 35%. The 1-, 3-, and 5-year recurrence-free survival rate was 96%, 60%, and 40% respectively. On univariate analysis, age and mitotic rate were associated with overall survival. On multivariate analysis, the recurrence-free survival rate was lower with increasing tumor size, small bowel site, KIT exon 9 mutation, high mitotic rate, and older age[24**]**.

TKIs other than imatinib are considered as second generation TKIs such as sunitinib, regorafenib, sorafenib, nilotinib, dasatinib and pazopanib. Table 3 summarizes the implication of different mutations in GISTs and their response to TKI therapy.

Sunitinib was approved by the FDA for the treatment of imatinib-resistant GISTs in 2006 and is considered as second line TKI[25]. Heinrich *et al*[26] discovered the clinical activity of sunitinib after imatinib failure is significantly influenced by both primary and secondary mutations in the predominant pathogenic kinases that implicate the optimum treatment of patients with GISTs.

Regorafenib was approved by FDA in 2013 to treat advanced GISTs that cannot be surgically removed and resistant to other TKI, is considered as third line TKI[27]. The long term follow up results of the multicenter phase II trial of regorafenib in patients with metastatic or unresectable GISTs after failure of imatinib and sunitinib showed benefit in patients with primary KIT exon 11 mutations and SDH-deficient GISTs[28].

The use of other TKIs apart from imatinib, sunitinib and regorafenib is still being evaluated and debatable. In a Korean clinical trial in 2012, sorafenib was shown to maintain disease control in one third of the patients with metastatic GISTs who have otherwise failed two or more TKIs[29].

In a phase I study of single agent nilotinib or in combination with imatinib in patients with imatinib-resistant GIST showed some partial clinical response but required phase II doses for further evaluation[30].

In a phase II study of imatinib-resistant GISTs treated with dasatinib, there was a significant activity by objective response rate but did not meet the predefined 6 month progression-free survival rate of 30%[31].There is an American phase II clinical trial of dasatinib in advanced sarcoma including GISTs patients and a European phase II trial of dasatinib as first line therapy in GISTs patients[32,33]. Both trials has stopped recruiting participants and the conclusion of the study will be expected in future.

In a phase II French trial, Mir O et al showed that pazopanib plus best supportive care improves progression-free survival compared with best supportive care alone in patients with advanced GISTs resistant to imatinib and sunitinib. This trial provides reference outcome data for future studies of targeted inhibitors in the third-line setting for this group of patients[34].

Other TKIs identified in clinical trials include masitinib (AB1010), crenolanib (CP-868,596), AZD2171, vatalanib (PTK787), OSI-930, TKI258 and DCC-2618 (Table 4). A biologics inhibitor of KIT and PDGFRA called olaratumab (IMC-3G3) was trialed (NCT01316263) but the development was put on hold and the stage 2 of this study was not completed.

**CURRENT RESEARCH IN GISTs**

The emergence of TKI-resistant GISTs has led to further research in understanding of this treatment failure and the alternative signaling mechanism conferring GISTs survival. The research to find new drugs, particularly targeted therapy is being evaluated.

Agaram *et al*[15] found that BRAF mutations appear to be associated with a higher malignant risks and resistance to TKI compared to those with KIT and PDGFRA mutations. Kinase inhibitors targeting BRAF may be considered as an effective therapeutic option in this GISTs subset. Falchook *et al*[35] published the first report on BRAF inhibitor, dabrafenib (GSK2118436) which showed prolonged anti-tumor activity in V600E BRAF mutated GIST patient. There is presently no trial in GISTs looking at BRAF inhibitors.

In a phase II trial study of heat shocked protein 90 inhibitor, BIIB021 given to the patients with GISTs refractory to imatinib and sunitinib, showed some promising response[36]. This result encourages future development of HSP90 inhibitors in TKI-resistant GISTs. A next phase study evaluating BIIB021 in GISTs is therefore warranted.

Testing for germ line mutations in SDH is presently recommended for patients with GISTs lacking mutations in KIT, PDGFRA and BRAF[37]. There is an ongoing phase II trial of vandetanib in children and adult with “wild type” GISTs but currently not recruiting participants and the estimated study conclusion will be available in 2023[38]. Another study currently recruiting participants is the glutamine inhibitor CB-839 trial in solid tumors including SDH-deficient GISTs[39].

Ran *et al*[40] recently reported the combined inhibition of mitogen activated kinase (MAPK) and KIT signaling synergistically destabilizes the transcription factor called ETV1 and suppresses GISTs growth. The combination of MAPK and TKI inhibitors to target ETV1 may provide an effective therapeutic strategy in GISTs clinical management. There is currently a trial recruiting participants to study MEK162 in combination with imatinib in patients with untreated advanced GISTs[41].

In another emerging target category, Falkenhorst *et al*[42] discovered the Inhibitor of Apoptosis Proteins (IAPs) such as XIAP and survivin are commonly dysregulated in GIST. Future study to assess the combination of imatinib with an IAP antagonist such as YM155 to enhance the pro-apoptotic activity in GISTs is therefore needed.

There was a clinical trial study looking at the role of immunotherapy by combining peginterferon α-2b with imatinib for treatment of stage III/IV GISTs and gave a highly promising clinical outcomes. The trial was terminated early in 2012 in preparation for a larger future trial[43]. Table 4 summarizes the potential treatment targets in GISTs under clinical trials. The trials information was obtained from <https://clinicaltrials.gov/ct2/home> online.

**CURRENT TREATMENT GUIDELINES IN GISTs**

Most countries have their own clinical practice guidelines for GISTs such as the American National Comprehensive Cancer Network (NCCN) (2010 Update), the European Society of Medical Oncology (ESMO) (2012), the French National Federation of Cancer Centers consensus guidelines (in French) (2005), the Japan Society of Clinical Oncology (JSCO) (2008), the Korean GISTs Guidelines (2012 Update), the Canadian Advisory Committee on GISTs statement (2006) and Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS) (2009)[44-50]. Most recently, the Asian Consensus Guidelines (2016) for the diagnosis and management of GISTs was published to promote optimal care for Asian population[51].

The NCCN task force report update on GISTs management is quite comprehensive and detailed over 41 pages. It described the epidemiology from the Surveillance, Epidemiology, and End Results data from the National Cancer Institute, the clinical presentation, the pathology and differential diagnosis using immunohistochemistry and gene expression profiling, the recommendations for diagnosing GISTs, the significance of KIT and PDGFRA mutation status, the recommendations for mutational analysis, the management of adult versus pediatric patients with GISTs, the principles of surgery for GISTs, the need for multidisciplinary management for primary, recurrent or metastatic GISTs and the imaging of GISTs[44].

In the ESMO clinical practice guidelines on GISTs, it described the incidence of GISTs in Europe, the strategy to diagnose GISTs, the stage classification and risk assessment (does not recommend TNM classification), the staging procedure using CT, MRI and FDG-PET scan, the treatment planning involving multidisciplinary team for localized and metastatic disease, the response evaluation and optimal follow up for different risk categories[45].

In the Asian consensus guidelines for diagnosis and management of GISTs, some points were highlighted. Firstly, it recommends the minimal three years treatment with imatinib before and after surgery for high risk GISTs. Secondly, it recommends early evaluation of tumor response after one month of neoadjuvant imatinib treatment, when genotyping is not feasible for primary gastric GISTs. Thirdly, it suggested a prospective study on the feasibility and efficacy of high dose imatinib therapy in Asian patients. Lastly, it recommends imatinib rechallenge instead of discontinuing TKI treatment if third-line regorafenib is not available or failed[51].

In summary of these published treatment guidelines, the general consensus is complete surgical resection of GISTs as the first step when possible. Surgery is potentially curative for primary GISTs that have not metastasized and the probability of recurrence will depend on the malignant potential risk stratification criteria.

GISTs that are initially inoperable may be given neoadjuvant therapy with first line TKI, imatinib to improve resectability. Following complete removal of primary GISTs, patients with a higher risk of tumor recurrence may consider adjuvant therapy with first line TKI. Patients with metastatic GISTs disease, even if removed, will benefit from TKI to maintain disease control.

For patients with imatinib-resistant GISTs, sunitinib is a second-line drug treatment whilst regorafenib is the third-line drug for imatinib or sunitinib-resistant GISTs. Some drugs approved for other conditions may be prescribed off-label for GISTs at a physician's discretion but with a caveat and clinicians are advised to follow the local guidelines. New molecular targeted drugs are being tested in many clinical trials and some are still under development. An algorithm for the management of GISTs based on the summary of current guidelines is included (Figure 7).

**PROGNOSIS**

Data from pooled analysis of 2560 patients diagnosed with operable GISTs who were not given adjuvant therapy gave the estimated 15-year recurrence-free survival after surgery at 59.9%[52]. Whilst in a trial previously alluded to with those resected GISTs which deemed high risk were subsequently treated with imatinib showed the 5-year overall survival rate of 83%[24]. In a different follow-up study to assess the long term survival of 695 patients with metastatic GISTs who were treated with imatinib, the estimated 10-year overall survival is 23%[53].

There was an interesting Dutch study which highlighted severe fatigue occurred in 30% of patients with GISTs and in 33% of patients with GISTs who took TKIs. The disabling fatigue was associated with psychological distress and physical function[54].

In another survey study looked at the long term functional outcomes of laparoscopic resection of gastric GISTs utilizing the Gastrointestinal Quality of Life Index (GIQLI). Most patients reported no change in symptoms and the GIQLI scores were within the normal range, with minimal effect on long term quality of life[55].

**FUTURE GISTS TREATMENT TRENDS**

About 5 years ago, DeMatteo RP proposed a concept of personalized therapy for GISTs[56]. With accumulating research data in biology, such as genetic mutations and adjuvant or neoadjuvant therapy with systemic drugs, it is considered true that personalized assessment and therapy may appear to be future trend for GISTs management.

Complete surgical resection of GISTs is the gold standard of primary treatment when possible with or without the adjunct of molecular targeted drug therapy. Through the understanding of the mutations of GISTs and the treatment resistance with TKI, new treatment ideas such as combination trials of TKI plus other drugs, TKI plus surgery in specified sequences, newer lines TKI, inhibitors of BRAF, heat shock protein inhibitors, inhibitors of downstream pathways such as MAPK, IAP inhibitors and immunotherapy may play an important molecular targeted therapy in future.

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**Figure 1 Gastroscopy view of a gastric gastrointestinal stromal tumors.** A 4 cm × 4 cm in diameter gastric fundal submucosal tumor with a central ulceration associated with a recent bleed.



**Figure 2 Computed tomography scan image of a gastric gastrointestinal stromal tumors.** A submucosal tumor measuring 7.7 cm × 7.6 cm × 7.2 cm in dimension was located on the posterior wall of gastric antrum. An ill-defined hypodensity within the mass could represent area of necrosis.



**Figure 3 18FDG-PET scan views of a small bowel gastrointestinal stromal tumors.** There is a mildly FDG avid mass adjacent to the jejunal anastomosis with SUVmax 3.4 suggestive of a local recurrence.



**Figure 4 Endoscopic ultrasonography images of esophageal gastrointestinal stromal tumors.** A distal esophageal submucosal lesion measuring 2.6 cm × 1.3 cm in diameter noted to be well circumscribed, heterogeneous with hypoechoic echotexture without disruption of wall architecture and no perilesional lymph node.



**Figure 5 Endoscopic ultrasound scan and fine needle aspiration image of an esophageal gastrointestinal stromal tumors.** A EUS FNA was performed using a 22F procore needle with onsite cytotech.



**Figure 6 Macroscopic image of a recurrent small bowel gastrointestinal stromal tumors.** A picture of a large enbloc resection specimen of a small bowel mesentery and jejunum was taken along a separate smaller metastatic mesenteric nodule.

Other appropriate MDT referral

Risk stratification and genetic mutation analysis

Imatinib as palliative or neoadjuvant treatment

**Recurrence**: MDT discussion, consider imatinib or other TKI or further resection

If imatinib and sunitinib resistant, consider regorafenib

If TKIs resistant, consider inclusion in appropriate clinical trials

Escalate dose if required

Surgery if GIST becomes resectable

Metastatic/unresectable

**High risk**: consider adjuvant imatinib for at least 3 years

CT at 3 months for 2 years, then 6 monthly for 2 years and then annually

**Intermediate risk**: consider adjuvant imatinib for 3 years

CT at 3 months, then 6 monthly for 2 years and then annually for 5 years

**Low risk**: CT at 3 months and clinical follow up

**Very low risk**: clinical follow up

GIST

Localized/resectable

Baseline CT and histological confirmation

CT at 1-3 months

Not GIST

Surgical resection

Histological confirmation

Diagnostic work up and MDT discussion for the management of GISTs

If imatinib resistant, consider sunitinib

**Figure 7 Algorithm for the management of gastrointestinal stromal tumors.**

**Table 1 National Institutes of Health *vs* Armed Forces Institute of Pathology criteria for assessing malignant risk of gastrointestinal stromal tumors**

|  |  |  |
| --- | --- | --- |
| Degree of risk | NIH criteria | AFIP criteria |
| Unknown | - | < 2 cm and ≤ 5 mitotic index |
| Very low | < 2 cm and < 5 mitotic index | ≤ 5 cm and ≤ 5 mitotic index |
| Low | 2-5 cm and < 5 mitotic index | Gastric: > 5 cm and ≤ 5 mitotic index |
|  |  | Others: 2-5 cm and ≤ 5 mitotic index |
| Intermediate or Moderate | 5-10 cm and < 5 mitotic index | Gastric: > 10 cm and ≤ 5 mitotic index or > 2-5 cm and > 5 mitotic index |
|  | > 5 cm and 6-10 mitotic index | Others: 5-10 cm and ≤ 5 mitotic index |
| High | > 5 cm and > 5 mitotic index | Gastric: > 5 cm and > 5 mitotic index |
|  | > 10 cm and any mitotic index | Others: > 10 cm and > 5 mitotic index |
|  | Any size and > 10 mitotic index |  |

Mitotic index = Number of mitoses per 50 high-power field. NIH: National Institutes of Health; AFIP: Armed Forces Institute of Pathology.

**Table 2 Frequency of genetic mutations in gastrointestinal stromal tumors**

|  |  |  |  |
| --- | --- | --- | --- |
| KIT mutation (about 85%) | PDGFRA mutation (about 5%) | BRAF mutation (< 1%) | SDH mutation (12%-15% adult, 90% paediatric GIST)  |
| Exon 11 (about 70%) | Exon 18 (about 5%)  | Exon 15 V600E | Subunit B,C and D |
| Exon 9 (10%-15%) | Exon 12 (1%) |  |  |
| Exon 13 (1%-3%) | Exon 14 (< 0.5%) |  |  |
| Exon 17 (1%) | Exon 18 D842V (about 0%) |  |  |

**Table 3 Implication gastrointestinal stromal tumors mutations and response to targeted therapy**

|  |  |  |  |
| --- | --- | --- | --- |
| KIT mutation | Imatinib[23] | Sunitinib[25] | Regorafenib[28] |
| Exon 11 | Objective response (OR) 63%  | Clinical benefit (CB) 34% | Increased sensitivity |
| Exon 9 | OR 37%. Intermediate sensitivity. Higher dose 800mg more effective in metastatic disease than 400mg daily | CB 34% | Unknown |
| Exon 13 | OR 40%. Sensitivity as primary mutation. Resistance as secondary mutation | CB 100% | Unknown |
| Exon 14 | Resistance as secondary mutation | Unknown | Unknown |
| Exon 17 | OR 25%. Primary mutation sensitive in vitro. Resistance as secondary mutation | CB 0% | Unknown |
| PDGFRA mutation |  |  |  |
| Exon 18 | OR 50% | CB 0% | Unknown |
| Exon 12 | Increased sensitivity | CB 0% | Unknown |
| Exon 14 | Increased sensitivity in vitro | Unknown | Unknown |
| Exon 18 D842V | Decreased sensitivity | Decreased sensitivity | Unknown |
| BRAF mutation | Resistance | Resistance | Unknown |
| SDH mutation | Decreased sensitivity | Unknown | Increased sensitivity |
| No KIT, PDGFRA and BRAF mutation | OR 28%.  | CB 56% | Some activity |

Objective response (OR) is defined as a complete or partial response by Response Evaluation Criteria for Solid Tumors (RECIST) criteria; excludes non-evaluable patients. Clinical benefit (CB) is defined as response or stable disease for 6 months or more according to RECIST.

**Table 4 Potential treatment targets for gastrointestinal stromal tumors**

|  |  |  |
| --- | --- | --- |
| Categories | Name | ClinicalTrials.gov Identifier |
| TKI of KIT and PDGFRA | Masitinib (AB1010)Crenolanib (CP-868,596)AZD2171Vatalanib (PTK787)OSI-930TKI258DCC-2618 | NCT00998751 [U] Eur J Cancer. 2010; 46(8):1344-51.NCT02847429 [R], NCT01243346 [C] Clin Cancer Res. 2012; 18(16):4375-84.NCT00385203 [C] Clin Cancer Res. 2014; 20(13):3603-12.NCT00117299 [C], NCT00655655 [A]NCT00513851 [C]NCT01478373 [C] , NCT01440959 [C] NCT02571036 [R] |
| Biologic inhibitors of KIT and PDGFRA | Olaratumab (IMC-3G3) | NCT01316263 [C]  |
| HSP90 inhibitors | Retaspimycin (IPI-5040) BIIB021 (CNF2024)Ganetespib (STA-9090)AUY922AT13387 | NCT00276302 [C], NCT00688766 [T]NCT00618319 [C]NCT01039519 [C]NCT01389583 [R], NCT01404650 [C]NCT01294202 [C] |
| Inhibitors of pathways downstream of KIT and PDGFRA | RAS/RAF/MEK/ERK/MAPK inhibitors:MEK162AKT inhibitors: perifosinemTOR inhibitors: everolimus (RAD001)  temsirolimus (Torisel)  | NCT01991379NCT00455559 [C] J Clinc Oncol 2009. 27, No 15S: 10563)NCT01275222 [C], NCT00510354 [C], NCT02071862 [R]NCT00700258 [R] |
| Cell cycle inhibitors | Alvocidib (Flavopiridol) | NCT00098579 [C] |
| Insulin-like growth factor pathway inhibitors | OSI-906 | NCT01560260 [C] Curr Treat Options Oncol. 2014; 15(3):493-506. |

[R] = Recruiting, [T] = Terminated, [C] = Completed, [A] = Active, not recruiting, [U] = Unknown. PDGFRA: Platelet-derived growth factor receptor alpha.