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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.

**REFERENCES**

1 **Miettinen M**, Lasota J. Gastrointestinal stromal tumors--definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. *Virchows Arch* 2001; **438**: 1-12 [PMID: 11213830]

2 **Mazur MT**, Clark HB. Gastric stromal tumors. Reappraisal of histogenesis. *Am J Surg Pathol* 1983; **7**: 507-519 [PMID: 6625048]

3 **Corless CL**, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. *J Clin Oncol* 2004; **22**: 3813-3825 [PMID: 15365079 DOI: 10.1200/JCO.2004.05.140]

4 **Søreide K**, Sandvik OM, Søreide JA, Giljaca V, Jureckova A, Bulusu VR. Global epidemiology of gastrointestinal stromal tumours (GIST): A systematic review of population-based cohort studies. *Cancer Epidemiol* 2016; **40**: 39-46 [PMID: 26618334 DOI: 10.1016/j.canep.2015.10.031]

5 **DeMatteo RP**, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg* 2000; **231**: 51-58 [PMID: 10636102]

6 **Kobayashi K**, Gupta S, Trent JC, Vauthey JN, Krishnamurthy S, Ensor J, Ahrar K, Wallace MJ, Madoff DC, Murthy R, McRae SE, Hicks ME. Hepatic artery chemoembolization for 110 gastrointestinal stromal tumors: response, survival, and prognostic factors. *Cancer* 2006; **107**: 2833-2841 [PMID: 17096432 DOI: 10.1002/cncr.22336]

7 **Pawlik TM**, Vauthey JN, Abdalla EK, Pollock RE, Ellis LM, Curley SA. Results of a single-center experience with resection and ablation for sarcoma metastatic to the liver. *Arch Surg* 2006; **141**: 537-43; discussion 543-4 [PMID: 16785353 DOI: 10.1001/archsurg.141.6.537]

8 **DeMatteo RP**, Shah A, Fong Y, Jarnagin WR, Blumgart LH, Brennan MF. Results of hepatic resection for sarcoma metastatic to liver. *Ann Surg* 2001; **234**: 540-57; discussion 540-57; [PMID: 11573047]

9 **Franquemont DW**. Differentiation and risk assessment of gastrointestinal stromal tumors. *Am J Clin Pathol* 1995; **103**: 41-47 [PMID: 7817943]

10 **Fletcher CD**, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, Miettinen M, O'Leary TJ, Remotti H, Rubin BP, Shmookler B, Sobin LH, Weiss SW. Diagnosis of gastrointestinal stromal tumors: A consensus approach. *Hum Pathol* 2002; **33**: 459-465 [PMID: 12094370]

11 **Miettinen M**, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. *Am J Surg Pathol* 2005; **29**: 52-68 [PMID: 15613856]

12 **Brierley JD**, Gospodarowicz, Wittekind C. TNM classification of malignant tumours. International union against cancer (UICC). 8th ed. New York: Wiley-Blackwell, 2016; 127-130

13 **Hirota S**, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, Kawano K, Hanada M, Kurata A, Takeda M, Muhammad Tunio G, Matsuzawa Y, Kanakura Y, Shinomura Y, Kitamura Y. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science* 1998; **279**: 577-580 [PMID: 9438854]

14 **Heinrich MC**, Corless CL, Duensing A, McGreevey L, Chen CJ, Joseph N, Singer S, Griffith DJ, Haley A, Town A, Demetri GD, Fletcher CD, Fletcher JA. PDGFRA activating mutations in gastrointestinal stromal tumors. *Science* 2003; **299**: 708-710 [PMID: 12522257 DOI: 10.1126/science.1079666]

15 **Agaram NP**, Wong GC, Guo T, Maki RG, Singer S, DeMatteo RP, Besmer P, Antonescu CR. Novel V600E BRAF Mutations in Imatinib-Naive and Imatinib-Resistant Gastrointestinal Stromal Tumors. *Genes Chromosomes Cancer* 2008; **47**: 853-859 [DOI: 10.1002/gcc.20589]

16 **Agaimy A**, Terracciano LM, Dirnhofer S, Tornillo L, Foerster A, Hartmann A, Bihl MP. V600E BRAF mutations are alternative early molecular events in a subset of KIT/PDGFRA wild-type gastrointestinal stromal tumours. *J Clin Pathol* 2009; **62**: 613-616 [PMID: 19561230 DOI: 10.1136/jcp.2009.064550]

17 **Gaal J**, Stratakis CA, Carney JA, Ball ER, Korpershoek E, Lodish MB, Levy I, Xekouki P, van Nederveen FH, den Bakker MA, O'Sullivan M, Dinjens WN, de Krijger RR. SDHB immunohistochemistry: a useful tool in the diagnosis of Carney-Stratakis and Carney triad gastrointestinal stromal tumors. *Mod Pathol* 2011; **24**: 147-151 [PMID: 20890271 DOI: 10.1038/modpathol.2010.185]

18 **Joensuu H**, Roberts PJ, Sarlomo-Rikala M, Andersson LC, Tervahartiala P, Tuveson D, Silberman S, Capdeville R, Dimitrijevic S, Druker B, Demetri GD. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med* 2001; **344**: 1052-1056 [PMID: 11287975 DOI: 10.1056/NEJM200104053441404]

19 **Heinrich MC**, Corless CL, Demetri GD, Blanke CD, von Mehren M, Joensuu H, McGreevey LS, Chen CJ, Van den Abbeele AD, Druker BJ, Kiese B, Eisenberg B, Roberts PJ, Singer S, Fletcher CD, Silberman S, Dimitrijevic S, Fletcher JA. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. *J Clin Oncol* 2003; **21**: 4342-4349 [PMID: 14645423 DOI: 10.1200/JCO.2003.04.190]

20 FDA approves Gleevec for expanded use in patients with rare gastrointestinal cancer. FDA News Release online 2012-01-31. Available from URL: https: //www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm289760.htm

21 **Joensuu H**, Eriksson M, Sundby Hall K, Hartmann JT, Pink D, Schütte J, Ramadori G, Hohenberger P, Duyster J, Al-Batran SE, Schlemmer M, Bauer S, Wardelmann E, Sarlomo-Rikala M, Nilsson B, Sihto H, Monge OR, Bono P, Kallio R, Vehtari A, Leinonen M, Alvegård T, Reichardt P. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. *JAMA* 2012; **307**: 1265-1272 [PMID: 22453568 DOI: 10.1001/jama.2012.347]

22 **Andtbacka RH**, Ng CS, Scaife CL, Cormier JN, Hunt KK, Pisters PW, Pollock RE, Benjamin RS, Burgess MA, Chen LL, Trent J, Patel SR, Raymond K, Feig BW. Surgical resection of gastrointestinal stromal tumors after treatment with imatinib. *Ann Surg Oncol* 2007; **14**: 14-24 [PMID: 17072676 DOI: 10.1245/s10434-006-9034-8]

23 **Heinrich MC**, Owzar K, Corless CL, Hollis D, Borden EC, Fletcher CD, Ryan CW, von Mehren M, Blanke CD, Rankin C, Benjamin RS, Bramwell VH, Demetri GD, Bertagnolli MM, Fletcher JA. Correlation of kinase genotype and clinical outcome in the North American Intergroup Phase III Trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 Study by Cancer and Leukemia Group B and Southwest Oncology Group. *J Clin Oncol* 2008; **26**: 5360-5367 [PMID: 18955451 DOI: 10.1200/JCO.2008.17.4284]

24 **DeMatteo RP,** Ballman KV, Antonescu CR, Corless C, Kolesnikova V, von Mehren M, McCarter MD, Norton J, Maki RG, Pisters PWT, Demetri GD, Brennan MF, Owzar K, the American College of Surgeons Oncology Group (ACOSOG) Intergroup Adjuvant GIST Study Team for the Alliance for Clinical Trials in Oncology. Long-term results of adjuvant imatinib mesylate in localized, high-risk, primary gastrointestinal stromal tumor (GIST): ACOSOG Z9000 (Alliance) intergroup phase 2 trial. *Ann Surg* 2013; **258**: 422–429 [PMID: 23860199 DOI: 10.1097/SLA.0b013e3182a15eb7]

25 FDA Approves New Treatment for Gastrointestinal and Kidney Cancer. FDA News Release online 2006-01-26. Available from URL: https: //www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108583.htm

26 **Heinrich MC**, Maki RG, Corless CL, Antonescu CR, Harlow A, Griffith D, Town A, McKinley A, Ou WB, Fletcher JA, Fletcher CD, Huang X, Cohen DP, Baum CM, Demetri GD. Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. *J Clin Oncol* 2008; **26**: 5352-5359 [PMID: 18955458 DOI: 10.1200/JCO.2007.15.7461]

27 FDA approves Stivarga for advanced gastrointestinal stromal tumors. FDA News Release online 2013-02-15. Available from URL: https: //www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm340958.htm

28 **Ben-Ami E**, Barysauskas CM, von Mehren M, Heinrich MC, Corless CL, Butrynski JE, Morgan JA, Wagner AJ, Choy E, Yap JT, Van den Abbeele AD, Solomon SM, Fletcher JA, Demetri GD, George S. Long-term follow-up results of the multicenter phase II trial of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of standard tyrosine kinase inhibitor therapy. *Ann Oncol* 2016; **27**: 1794-1799 [PMID: 27371698 DOI: 10.1093/annonc/mdw228]

29 **Park SH**, Ryu MH, Ryoo BY, Im SA, Kwon HC, Lee SS, Park SR, Kang BY, Kang YK. Sorafenib in patients with metastatic gastrointestinal stromal tumors who failed two or more prior tyrosine kinase inhibitors: a phase II study of Korean gastrointestinal stromal tumors study group. *Invest New Drugs* 2012; **30**: 2377-2383 [PMID: 22270258 DOI: 10.1007/s10637-012-9795-9]

30 **Demetri GD**, Casali PG, Blay JV, von Mehren M, Morgan JA, Bertulli R, Ray-Coquard I, Cassier P, Davey M, Borghaei H, Pink D, Debiec-Rychter M, Cheung W, Bailey SM, Veronese ML, Reichardt A, Fumagalli E, Reichardt P. A Phase I Study of Single-Agent Nilotinib (AMN107) or in Combination with Imatinib in Patients with Imatinib-Resistant Gastrointestinal Stromal Tumors. *Clin Cancer Res* 2009; **15**: 5910–5916 [PMID: 19723647 DOI: 10.1158/1078-0432.CCR-09-0542]

31 **Trent JC,** Wathen K, von Mehren M, Samuels BL, Staddon AP, Choy E, Butrynski JE, Chugh R, Chow WA, Rushing DA, Forscher CA, Baker LH, Schuetze S. A phase II study of dasatinib for patients with imatinib-resistant gastrointestinal stromal tumor (GIST). *J Clin Oncol* 2011; **29** Suppl: Abstr 10006

32 Trial of Dasatinib in Advanced Sarcomas. First received 2007-04-20. Last updated 2016-10-12. Available from URL: https: //clinicaltrials.gov/ct2/show/NCT00464620

33 Dasatinib as First-Line Therapy in Treating Patients With Gastrointestinal Stromal Tumors. First received 2007-12-05. Last updated 2017-02-17. Available from URL: https: //www.clinicaltrials.gov/ct2/show/NCT00568750?term=NCT00568750&rank=1

34 **Mir O**, Cropet C, Toulmonde M, Cesne AL, Molimard M, Bompas E, Cassier P, Ray-Coquard I, Rios M, Adenis A, Italiano A, Bouché O, Chauzit E, Duffaud F, Bertucci F, Isambert N, Gautier J, Blay JY, Pérol D. Pazopanib plus best supportive care versus best supportive care alone in advanced gastrointestinal stromal tumours resistant to imatinib and sunitinib (PAZOGIST): a randomised, multicentre, open-label phase 2 trial. *Lancet Oncol* 2016; **17**: 632-641 [PMID: 27068858 DOI: 10.1016/S1470-2045(16)00075-9]

35 **Falchook GS**, Trent JC, Heinrich MC, Beadling C, Patterson J, Bastida CC, Blackman SC, Kurzrock R. BRAF mutant gastrointestinal stromal tumor: first report of regression with BRAF inhibitor dabrafenib (GSK2118436) and whole exomic sequencing for analysis of acquired resistance. *Oncotarget* 2013; **4**: 310-315 [PMID: 23470635 DOI: 10.18632/oncotarget.864]

36 **Dickson MA**, Okuno SH, Keohan ML, Maki RG, D'Adamo DR, Akhurst TJ, Antonescu CR, Schwartz GK. Phase II study of the HSP90-inhibitor BIIB021 in gastrointestinal stromal tumors. *Ann Oncol* 2013; **24**: 252-257 [PMID: 22898035 DOI: 10.1093/annonc/mds275]

37 **Janeway KA**, Kim SY, Lodish M, Nosé V, Rustin P, Gaal J, Dahia PL, Liegl B, Ball ER, Raygada M, Lai AH, Kelly L, Hornick JL, O'Sullivan M, de Krijger RR, Dinjens WN, Demetri GD, Antonescu CR, Fletcher JA, Helman L, Stratakis CA. Defects in succinate dehydrogenase in gastrointestinal stromal tumors lacking KIT and PDGFRA mutations. *Proc Natl Acad Sci U S A* 2011; **108**: 314-318 [PMID: 21173220 DOI: 10.1073/pnas.1009199108]

38 Phase II Trial of Vandetanib in Children and Adults with Wild-Type Gastrointestinal Stromal Tumors. First received 2013-12-14. Last updated 2017-02-7. Available from URL: https: //clinicaltrials.gov/ct2/show/NCT02015065?term=SDH and GIST&rank=1

39 Study of the Glutaminase Inhibitor CB-839 in Solid Tumors. First received 2014-02-14. Last updated 2016-08-18. Available from URL: https: //clinicaltrials.gov/ct2/show/NCT02071862?term=SDH and GIST&rank=2

40 **Ran L,** Sirota I, Cao Z, Murphy D, Chen Y, Shukla S, Xie Y, Kaufmann MC, Gao D, Zhu S, Rosi F, Wongvipat J, Taguchi T, Tap WD, Mellinghoff IK, Besmer P, Antonescu CR, Chen Y, Chi P. Combined inhibition of MAP kinase and KIT signaling synergistically destabilizes ETV1 and suppresses GIST tumour growth. *Canc Discov* 2015; **5**: 304-315 [DOI: 10.1158/2159-8290.CD-14-0985]

41 MEK162 in Combination With Imatinib Mesylate in Patients With Untreated Advanced Gastrointestinal Stromal Tumor (GIST). First received 2013-11-18. Last updated 2016-08-31. Available from URL: https: //clinicaltrials.gov/ct2/show/NCT01991379?term=MEK and GIST&rank=1

42 **Falkenhorst J,** Grunewald S, Mühlenberg T, Marino-Enriquez A, Reis A, Corless C, Heinrich M, Treckmann J, Podleska LE, Schuler M, Jonathan Fletcher JA, Bauer S. Inhibitor of Apoptosis Proteins (IAPs) are commonly dysregulated in GIST and can be pharmacologically targeted to enhance the pro-apoptotic activity of imatinib. *Oncotarget* 2016; **7:** 41390–41403 [PMID: 27167336 DOI: 10.18632/oncotarget.9159]

43 **Chen LL**, Chen X, Choi H, Sang H, Chen LC, Zhang H, Gouw L, Andtbacka RH, Chan BK, Rodesch CK, Jimenez A, Cano P, Jones KA, Oyedeji CO, Martins T, Hill HR, Schumacher J, Willmore C, Scaife CL, Ward JH, Morton K, Randall RL, Lazar AJ, Patel S, Trent JC, Frazier ML, Lin P, Jensen P, Benjamin RS. Exploiting antitumor immunity to overcome relapse and improve remission duration. *Cancer Immunol Immunother* 2012; **61**: 1113-1124 [PMID: 22198309 DOI: 10.1007/s00262-011-1185-1]

44 **Demetri GD**, von Mehren M, Antonescu CR, DeMatteo RP, Ganjoo KN, Maki RG, Pisters PW, Raut CP, Riedel RF, Schuetze S, Sundar HM, Trent JC, Wayne JD. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. *J Natl Compr Canc Netw* 2010; **8** Suppl 2: S1-41; quiz S42-4 [PMID: 20457867]

45 The ESMO/European Sarcoma Network Working Group. Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014; **25** (Suppl 3): 21–26 [PMID: 25210085 DOI: 10.1093/annonc/mdu255]

46 **Blay JY**, Landi B, Bonvalot S, Monges G, Ray-Coquard I, Duffaud F, Bui NB, Bugat R, Chayvialle JA, Rougier P, Bouché O, Bonichon F, Lassau N, Vanel D, Nordlinger B, Stoeckle E, Meeus P, Coindre JM, Scoazec JY, Emile JF, Ranchère D, Le Cesne A. [Recommendations for the management of GIST patients]. *Bull Cancer* 2005; **92**: 907-918 [PMID: 16266874]

47 **Nishida T**, Hirota S, Yanagisawa A, Sugino Y, Minami M, Yamamura Y, Otani Y, Shimada Y, Takahashi F, Kubota T. Clinical practice guidelines for gastrointestinal stromal tumor (GIST) in Japan: English version. *Int J Clin Oncol* 2008; **13**: 416-430 [PMID: 18946752 DOI: 10.1007/s10147-008-0798-7]

48 **Kang YK**, Kang HJ, Kim KM, Sohn T, Choi D, Ryu MH, Kim WH, Yang HK. Clinical practice guideline for accurate diagnosis and effective treatment of gastrointestinal stromal tumor in Korea. *Cancer Res Treat* 2012; **44**: 85-96 [PMID: 22802746 DOI: 10.4143/crt.2012.44.2.85]

49 **Blackstein ME**, Blay JY, Corless C, Driman DK, Riddell R, Soulières D, Swallow CJ, Verma S. Gastrointestinal stromal tumours: consensus statement on diagnosis and treatment. *Can J Gastroenterol* 2006; **20**: 157-163 [PMID: 16550259]

50 **Reid R,** Bulusu R, Carroll N, Eatock M, Geh I, Judson I, O’Dwyer P, Warren B, Seddon B, Hill G. Guidelines for the management of gastrointestinal stromal tumours (GIST). 2009: 1-55. Available from URL: http: //www.augis.org/wp-content/uploads/2014/05/GIST\_Management\_Guidelines\_180809.pdf

51 **Koo DH**, Ryu MH, Kim KM, Yang HK, Sawaki A, Hirota S, Zheng J, Zhang B, Tzen CY, Yeh CN, Nishida T, Shen L, Chen LT, Kang YK. Asian Consensus Guidelines for the Diagnosis and Management of Gastrointestinal Stromal. Tumor Cancer Res Treat 2016; **48**: 1155–1166 [PMID: 27384163 DOI: 10.4143/crt.2016.187]

52 **Joensuu H**, Vehtari A, Riihimäki J, Nishida T, Steigen SE, Brabec P, Plank L, Nilsson B, Cirilli C, Braconi C, Bordoni A, Magnusson MK, Linke Z, Sufliarsky J, Federico M, Jonasson JG, Dei Tos AP, Rutkowski P. Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. *Lancet Oncol* 2012; **13**: 265-274 [PMID: 22153892 DOI: 10.1016/S1470-2045(11)70299-6]

53 **Heinrich M**, Rankin C, Blanke CD, Demetri GD, Borden EC, Ryan CW, von Mehren M, Blackstein ME, Priebat DA, Tap WD, Maki RG, Corless CL, Fletcher JA, Owzar K, Crowley JJ, Benjamin RS, Baker LH. Correlation of Long-term Results of Imatinib in Advanced Gastrointestinal Stromal Tumors With Next-Generation Sequencing Results: Analysis of Phase 3 SWOG Intergroup Trial S0033. *JAMA Oncol* 2017; Epub ahead of print [PMID: 28196207 DOI: 10.1001/jamaoncol.2016.6728]

54 **Poort H**, van der Graaf WT, Tielen R, Vlenterie M, Custers JA, Prins JB, Verhagen CA, Gielissen MF, Knoop H. Prevalence, Impact, and Correlates of Severe Fatigue in Patients With Gastrointestinal Stromal Tumors. *J Pain Symptom Manage* 2016; **52**: 265-271 [PMID: 27233141 DOI: 10.1016/j.jpainsymman.2016.02.019]

55 **Dressler JA**, Palazzo F, Berger AC, Stake S, Chaudhary A, Chojnacki KA, Rosato EL, Pucci MJ. Long-term functional outcomes of laparoscopic resection for gastric gastrointestinal stromal tumors. *Surg Endosc* 2016; **30**: 1592-1598 [PMID: 26169640 DOI: 10.1007/s00464-015-4384-6]

56 **Dematteo RP**. Personalized therapy: prognostic factors in gastrointestinal stromal tumor (GIST). *J Gastrointest Surg* 2012; **16**: 1645-1647 [PMID: 22752549 DOI: 10.1007/s11605-012-1944-0]

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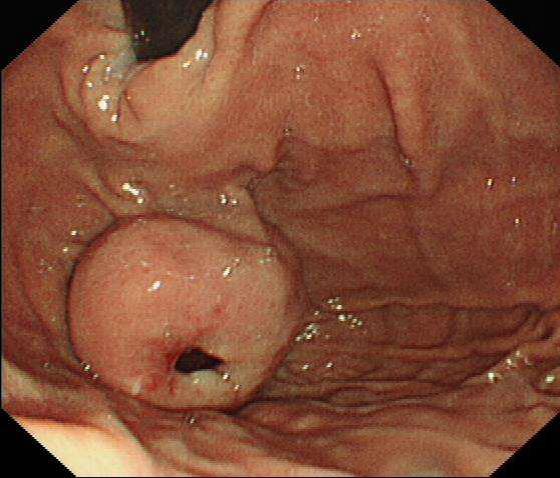
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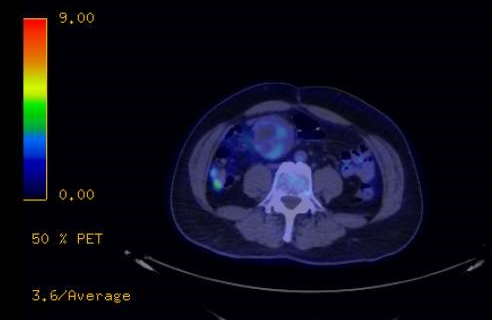
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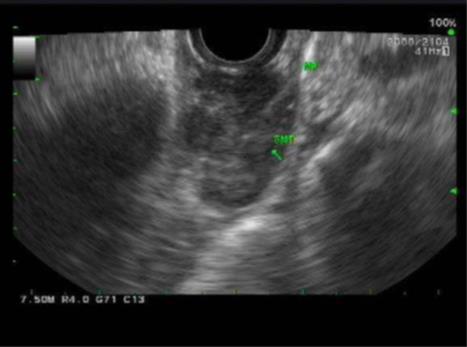
**Figure 1 Gastroscopy view of a gastric gastrointestinal stromal tumors.** A 4 cm × 4 cm in diameter gastric fundal submucosal tumor with a central ulceration associated with a recent bleed.



**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)  AZD2171  Vatalanib (PTK787)  OSI-930  TKI258  DCC-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)  AUY922  AT13387 | 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:  MEK162  AKT inhibitors:  perifosine  mTOR inhibitors:  everolimus (RAD001)    temsirolimus (Torisel) | NCT01991379  NCT00455559 [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.