



Gastrointestinal stromal tumor: a review of current and emerging therapies

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Abstract

Gastrointestinal stromal tumors (GIST) are rare neoplasms arising from the interstitial cell of Cajal in the gastrointestinal tract. Two thirds of GIST in adult patients have *c-Kit* mutation and smaller fractions have platelet derived growth factor receptor alpha (*PDGFRA*) mutation. Surgery is the only curative treatment for localized disease. Imatinib improves survival when used adjuvantly and in advanced disease. Several targeted therapies have also improved survival in GIST patients after progression on imatinib including sunitinib and regorafenib. Recently, United States Federal and Drug Administration (FDA) approved two new tyrosine kinase inhibitors for the treatment of heavily pretreated advanced/unresectable GIST including avapritinib (a selective inhibitor for *PDGFRA* exon 18 mutation including D842V mutations) and ripretinib (a broad-spectrum kinase inhibitor of *c-Kit* and *PDGFRA*). In this article, we will provide a comprehensive review of GIST including the current standard of care treatment and exploring future paradigm shifts in therapy.

Keywords *c-Kit* mutation · GIST · Imatinib · Regorafenib · Sunitinib · Ripretinib · *PDGFR*

1 Introduction

Gastrointestinal stromal tumors (GIST) are the most common of the rare non-epithelial neoplasms of gastrointestinal tract, accounting for 0.1–3% of gastrointestinal malignancies [1–4]. They were considered smooth muscle sarcomas until being recognized as a distinct disease in 1990s [5]. Interstitial cell of Cajal (ICC), also called gastrointestinal pacemaker cell, regulates the gastrointestinal tract peristalsis and is proposed to be the cell of origin for GIST [6].

GIST occurs mainly in adults with a median age at diagnosis of 60–65 years [7, 8]. The true incidence of GIST varies because of relative lack of unified diagnostic criteria. It ranges from 7 to 15 case per million population per year [3, 8–12], although studies from autopsies suggested a much higher incidence [13, 14]. Majority of the new cases are sporadic and

only 5% of the patients have an associated familial autosomal dominant syndrome [15]. The most common genetic syndromes are type-1 neurofibromatosis (NF-1), Carney's triad, familial GIST syndromes with germline *c-Kit*/platelet derived growth factor receptor alpha (*PDGFRA*) mutations, and Carney–Stratakis syndrome [7, 16]. Pediatric GISTs are rare tumors that have distinct features; they tend to be part of syndromes with female predilection, more indolent in nature, and majority have no *c-KIT* or *PDGFRA* mutations [17, 18].

2 Pathology

GISTs are sub-epithelial growing tumors [6] with three categories of cellular morphology: spindle cell type (70%), epithelioid type (20%), and mixed type (10%) [19, 20]. Spindle cell type is characterized by uniform cells with eosinophilic cytoplasm, ovoid nuclei, and juxta nuclear vacuoles [21]. Epithelioid cell type has round cells and round nuclei with vesicular chromatin [22, 23]. It is called epithelioid due to nested appearance that may be confused with epithelial or melanocytic neoplasms. The mixed type presents either as a transition between spindle and epithelioid type or mixture of both types. There are distinctive immunohistochemical

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markers for GISTs. Kit (CD117) overexpression is found in 90% of GISTs and does not necessarily correlate with *c-Kit* mutation. DOG-1 (Discovered on GIST-1) and PKC theta (Protein Kinase C theta) are two immunohistochemical markers of GIST that are expressed irrespective of Kit/PDGFR mutations [24–27]. Other markers commonly expressed are CD34 that is positive in 70% of GISTs, and desmin in 25%, and less commonly smooth muscle actin (SMA), which is seen in less than 5% of GIST [28].

3 Molecular pathogenesis OF GIST

Most GIST tumors are characterized by oncogenic mutations in *Kit* or *PDGFRA* genes. Different mutations in exon loci of tyrosine kinase genes are associated with clinical features and may predict disease behavior [29].

3.1 *Kit* mutation

The gain-of-function mutations in *Kit* gene, first described by Hirota et al. in 1998, are found in 70–80% of GISTs [30–32]. *Kit* is part of tyrosine kinase III family that includes PDGFRA, PDGFRB, FLT3 and macrophage colony stimulating factor receptor (CSF1R). *Kit* mutation leads to autonomous activity of the enzyme without binding to its ligand stem cell factor (SCF). This induces activation of downstream signals including MAPK, AKT, S6k, STAT1, STAT3, PI3K/mTOR pathway and ETV1 [33, 34]. ETV1 is part of ETS family of transcription factors, acts with Kit to regulate genes that promote GIST growth [35]. Mutations affect different exons of *Kit* gene as missense mutations, insertions, or deletions, most frequently in exon 11 (67%) followed by exon 9 (10%), exon 13 (1%), and exon 17 (1%) [36].

3.2 *PDGFRA* mutation

PDGFRA tyrosine Kinase mutations are mutually exclusive of *Kit* mutations [37]. They most commonly occur in exon 18 (6% of all GISTs) that codes for the activation loop. The most frequent mutation is in exon 18.D842V, which accounts for 60–70% of *PDGFRA* mutated GISTs [31, 38]. Other exons affected are 12 (0.7% of GISTs) which codes the juxta-membrane domain, and 14 (0.1% of GISTs) which codes for the ATP binding domain [30, 37, 39, 40]. These gain-of function mutations lead to activation of downstream signals in a pattern similar to that of *Kit* mutated GIST. Activated signal transduction molecules include MAPK, AKT, STAT1 and STAT3 [39]. Clinically, *PDGFRA* mutated GISTs almost exclusively develop in the stomach, specifically with exon 18 mutation [49]. They often have epithelioid morphology, particularly with exons 18 and 12 mutations. They also show low mitotic activity, and are expected to follow an indolent course [41, 42].

3.3 Wild type *KIT*/wild type *PDGFRA*

Ten to fifteen percent of GISTs lack tyrosine kinase mutations, and are described as *Kit*/*PDGFRA* wild type (WT) [43]. In this subset, 10–20% have succinate dehydrogenase deficiency (SDH) which is characterized by loss of beta subunit of SDH enzyme [44], and 15% have RAS pathway mutations, which can involve RAS/BRAF [45]. The other 50% of *Kit*/*PDGFRA* wild type GISTs have neither SDH deficiency, nor RAS pathway mutations, and hence called quadruple-WT GISTs or true-WT GISTs (account for 5% of all cases of GISTs) [46]. GISTs diagnosed in younger patients are more commonly associated with WT-variant. Eighty-five percent of GIST diagnosed in patients under 23 years are WT [37] [47]. WT-GIST can be sporadic or associated with syndromes, such as NF-1. Twenty-five percent of NF-1 patients develop GIST, which tends to be WT variant [15, 48]. Carney-Stratakis syndrome and Carney's triad are associated with SDH-deficient WT-GIST [49]. Of the WT GISTs, tumors with *SDH* mutations tend to occur in gastric location and to be more predominant in females. *SDHB* loss on IHC with no *SDH* mutation is more common in pediatrics and young adults, occurs more in gastric location, and is exclusively found in female patients [50].

4 Diagnosis of GIST

The site of tumor in gastrointestinal tract has an association impacts clinical presentation; 60% of GISTs arise in stomach, 30% in small intestine, and they less commonly arise in duodenum (5%), rectum and colon (<5%), esophagus and appendix (<1%) [7, 19, 51]. The most common clinical presentation of GIST is gastrointestinal (GI) bleeding. Other symptoms include abdominal pain/discomfort sometimes presenting as an acute abdomen. GIST can also be an incidental diagnosis [52] [53]. Paraneoplastic syndrome has also been reported as an initial presentation [54].

Computed tomography (CT) scan is the preferred radiographic modality for diagnosis. It usually describes GIST as a solid mass with smooth contour and bright enhancement following intravenous iodine-based contrast. Magnetic resonance imaging (MRI) is an alternative for patients unable to receive intravenous iodine contrast [55]. Esophagogastroduodenoscopy (EGD) is typically performed in patients who present with GI bleeding. It is an important diagnostic tool in gastric GIST especially when combined with endoscopic ultrasound (EUS). EUS appearance is typically described as smooth homogenous, and hypoechoic lesion that mostly originates from the muscularis propria [56]. EUS guided fine needle aspiration (FNA) may not be sufficient to confirm the diagnosis [57]. One study reported a high yield of EUS FNA biopsies and high accuracy in diagnosis of

GISTs, with sensitivity of 82%, specificity of 100% and overall accuracy of 86%. Factors thought to increase the diagnostic yield of the FNA were larger lesion size, gastric location, and on-site cytopathology expertise [57]. In potentially resectable GISTs, definitive diagnosis should be obtained by EUS guided FNA biopsy over percutaneous biopsy, a recommendation supported by National Comprehensive Cancer Network (NCCN) guidelines [58], to limit the theoretical risk of peritoneal seeding. Snare biopsies are not preferred due to risk of perforation which carries a worse prognosis in GIST [59]. It is noteworthy that a tissue diagnosis is not always required pre-operatively, unless neoadjuvant treatment is considered to downsize the tumor or in the setting of suspected metastatic disease [58]. Positron emission tomography (PET) scan using fluorodeoxyglucose (FDG) can be helpful for localizing a GIST primary or to clarify uncertain findings on CT scan [60, 61]. PET scan is superior to cross-sectional imaging in detection of early response to therapy [62].

Molecular subtyping is essential after diagnosis of GIST. Tumors that lack *c-kit* and *PDGFRA* mutations should be tested for SDH status [63]. Loss of SDHB expression on immunohistochemistry (IHC) is an accurate diagnostic marker for SDH deficiency [64–66]. Patients with deficient SDH should have tumor and germline sequencing done, to evaluate for *SDHX* germline mutations that are associated with increased risk of other tumors, such as paragangliomas and pheochromocytomas [67]. Patients with SDH-competent GISTs should also be tested for *BRAF*- and *NFI* mutations [68].

5 Prognostic factors

GISTs carry a variable risk of recurrence and metastasis and recent risk stratification models classify GISTs accordingly [69–71]. Complete resection of tumor in surgically treated GISTs was a significant variable that affects overall survival in multiple studies [72–75]. The main factors that determine prognosis of localized GIST are tumor location, size and mitotic rate. Three retrospective studies from the Armed Forces Institute of Pathology (AFIP) contributed to a large portion of prognostic information in literature [52, 53, 76]. Small tumors less than 5 cm with low mitotic index (<5/50 HPF) have low metastatic potential, and tumors larger than 10 cm with high mitotic index (>5/50 HPF) had high metastatic potential [52]. This is regardless of the primary tumor site. However, risk assessment in small tumors with high mitotic index and large tumors with low mitotic index is largely dependent on tumor location. Gastric GISTs that are either >10 cm with low mitotic index or <5 cm with high mitotic index carry a relatively low risk of metastasis [52], while small intestine GISTs with similar features have a relatively higher risk of metastasis [53]. Colorectal GISTs have comparable risk with small intestine

GISTs, while tumors diagnosed outside GI tract have more frequent relapses [77, 78]. Tumor rupture, whether spontaneous or induced surgically, negatively affects disease free survival [79, 80].

Molecular characteristics of the tumor also impact on survival. Despite prior reports in literature of worse survival in *Kit*-Mutated GISTs [81], other reports revealed potential improved survival in tumors that harbor *Kit* mutation [82]. More recent reports reveal a prognostic value of specific *Kit* mutations or deletions: exon 9 mutation [83] and exon 11 deletions of codons 557 to 558 [31, 84, 85] have been associated with poor prognosis and more aggressive disease course. The US-Finnish B2222 phase II study using imatinib proved better objective response rates, event-free survival, and overall survival rates in patients with exon 11 mutations compared to patients with exon 9 mutations or with no KIT mutation identified [86].

6 Treatment of GIST

6.1 Localized GIST and the role of surgery

The most common initial treatment for non-metastatic GIST tumors is surgical resection. The goal of surgery is potential cure and/or palliation if the primary tumor is causing symptoms, most commonly pain, bleeding, and/or obstruction. Non-operative, endoscopic surveillance may play a role in the management of small (< 2 cm in size), asymptomatic, histologically non-aggressive tumors [87], especially in elderly patients with severe comorbidities. The frequency of EUS surveillance is controversial, but the most common approach is to repeat EUS yearly [88]. Beyond these small benign lesions, the great majority of localized tumors should be considered for resection.

The goal of curative surgery is a margin-negative resection. As opposed to adenocarcinomas, this can often be achieved with a relatively, organ-sparing approach (especially in the stomach). Tumors in the small bowel or colorectum, and especially those arising in the esophagus or duodenum, may require more radical resection. Since lymphatic metastases are rare [89], regional lymphadenectomy is not indicated unless the lymph nodes are grossly involved. Of note, lymph node involvement is more common in SDH-mutant GISTs [90]. En bloc resection of adjacent organs may sometimes be necessary for large tumors with direct invasion into these structures. Tumor rupture should be avoided during surgery as this event is linked to local recurrence [60, 87].

Although controversial, positive microscopic margins appear not negatively impact survival [91]. The issue of laparoscopic vs open approach would largely be dependent on tumor size, extent of involvement of surrounding structures, and surgeon's personal experience [60].

6.2 Locally advanced and metastatic GIST

6.2.1 Role of systemic therapy

GIST is typically chemotherapy-resistant compared to other soft tissue tumors [89, 92, 93]. The mainstay of initial systemic therapy is imatinib, which is also the only drug indicated in neoadjuvant and adjuvant settings. However, around 20–30% of patients with GIST who do not express *Kit* mutation will experience treatment failure on imatinib [31, 32].

6.3 Use of imatinib in neoadjuvant setting

Neoadjuvant treatment with imatinib is used to reduce tumor size and potentially decrease the extent of the surgery. However, major radiological responses per RECIST criteria are uncommon despite the more frequent pathological responses. In the RTOG 0132/ACRIN 6665 phase II clinical trial, partial responses were observed in 7% and stable disease in 83% of patients with primary GIST treated with imatinib 600 mg daily [94]. It did appear that preoperative imatinib therapy was feasible and safe as it did not result in increased postoperative complications.

Neoadjuvant therapy does appear to be associated with improvement in resectability and need for less extensive resection. Fiore et al. reported a median tumor size reduction of 34% with use of preoperative imatinib in 15 patients. Three patients initially considered unresectable underwent complete surgery and 7 patients with initial indication for extensive surgery were more conservatively operated on [95]. The phase II APOLLON study administered neoadjuvant imatinib to 41 patients with “locally advanced but potentially resectable” GISTs. Patients received 400 mg daily for 6 months prior to resection. Treatment response was evaluated by 18F-FDG PET/CT scan 2 months from starting treatment. Thirty-four out of 41 patients (83%) underwent resection after a median of 200 days, with 30/34 achieving R0 resection. No patient received postop imatinib, and the m3-year PFS was 85.2% [96]. An Asian multinational phase II study specifically recruited patients with gastric GISTs ≥ 10 cm who were treated with 6–9 months of neoadjuvant imatinib. The primary end point, R0 resection rate was 91%. Patients in this cohort had 98% 2-year PFS and 89% 2-year OS at a median follow-up time of 32 months [97].

MD Anderson Cancer Center reported a phase II clinical trial of preoperative and postoperative imatinib that showed evidence of rapid radiographic response and tumor cell apoptosis in response to imatinib [98]. A subgroup analysis of the prospective trial BFR14 in patients with non-metastatic GIST treated with neoadjuvant imatinib was undertaken. Patients who had resection also received adjuvant imatinib and there was significant improvement in OS and DFS in this subgroup. Overall survival of patients who did not undergo resection was close to those with metastatic GIST [99].

In conclusion, imatinib in the neoadjuvant setting is mainly reserved for patients who may initially have been thought unresectable and in whom reduction in tumor size might result in conversion to resectability. It may also be indicated if downsizing the primary tumor may decrease the extent of the surgery, and hence, the perioperative morbidity. Figure 1 shows an example of response to imatinib neoadjuvant therapy at time of surgical resection.

6.4 Imatinib in adjuvant setting

In the pre-imatinib era, 50% of patients who underwent surgical resection of GISTs, experienced recurrence within 5 years with a 5-year survival rate of 50% [89, 100, 101]. The use of adjuvant imatinib significantly improved the outcomes for GIST patients with intermediate or high risk of recurrence.

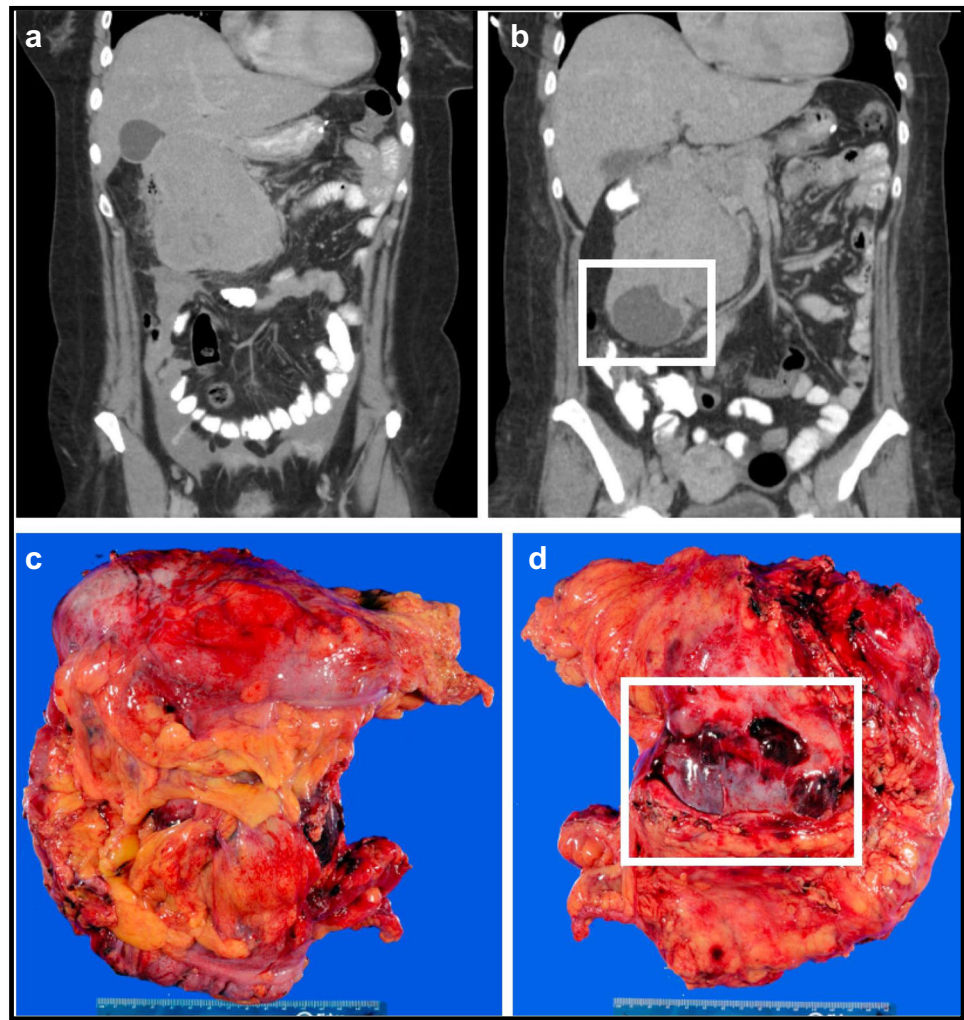
ACOSOG Z9000 trial was the phase II trial of adjuvant imatinib for GIST. Patients with high risk of recurrence after surgical resection received imatinib 400 mg daily for 1 year. They reported 1-, 3-, and 5-year OS rates of 99, 97, and 83%, respectively. Relapse-free survival (RFS) rates at 1-, 3-, and 5 years were 96, 60, and 40% respectively, with a median follow-up time of 7.7 months [102]. Multivariate analysis of this study revealed a lower RFS with larger tumor size, small bowel tumors, high mitotic index, *Kit* exon 9 mutation, and older age.

ACOSOG subsequently conducted a phase III trial that compared one year of adjuvant imatinib to placebo. RFS remained superior in imatinib arm (hazard ratio, 0.6; 95% CI, 0.43 to 0.75; Cox model-adjusted $P < 0.001$). It confirmed the lower RFS with large tumor size, small bowel location, and high mitotic rate, but not tumor genomics. Imatinib did not seem to affect OS [103]. Patients with *Kit* Exon 11 deletion of any type had better RFS with imatinib. This was not demonstrated in patients with *Kit* exon 11 insertions or point mutation, *Kit* exon 9 mutation, *PDGFRA* mutation, or wild-type tumor.

The optimal duration of therapy was further studied by the European Organization for Research and Treatment of Cancer (EORTC) 62024 trial that compared 2 years of 400 mg daily imatinib post resection with observation in 835 patients with intermediate- or high-risk GIST. After 4.7 years median follow-up, the primary end point, imatinib failure-free survival, did not show statistically significant difference between the two arms (87% in the imatinib arm versus 84% in the control arm, hazard ratio, 0.79; 98.5% CI, 0.50 to 1.25; $P = .21$); however, RFS favored imatinib arm at 3 years (84% compared to 66%, log-rank $P < .001$) and 5 years (69% compared to 63%, log-rank $P < .001$) [104].

A phase III trial was conducted by the Scandinavian Sarcoma Group XVIII/AIO comparing 3-year to 1-year adjuvant imatinib for patients with *Kit*-positive GIST who had R0/R1 resection with high risk features of recurrence. Dose of imatinib was 400 mg daily. Patients who received imatinib for 3 years had a statistically significant improvement in

Fig. 1 Fifty-five year old woman initially diagnosed with colonic GIST 9 years ago (Fig. 1a). She underwent 3 months of neoadjuvant imatinib therapy. Note necrosis within the tumor after treatment (white box Fig. 1b). Figure 1c and 1d show the anterior and posterior aspects of the specimen, and the necrotic area is clearly also seen within the white box in Fig. 1d. She is currently without evidence of recurrence



RFS (hazard ratio [HR], 0.46; 95% CI, 0.32–0.65; $P < .001$; 5-year RFS, 65.6% vs 47.9%, respectively) and OS (HR, 0.45; 95% CI, 0.22–0.89; $P = .02$; 5-year survival, 92.0% vs 81.7%) compared to 1 year imatinib arm [105].

Joensuu et al. conducted a second planned analysis of their Scandinavian Sarcoma Group XVIII/AIO trial to investigate whether the survival benefits of 3 years of imatinib have persisted. At a median follow-up of 90 months, the patients who received 3 year of adjuvant imatinib had better RFS (5-year RFS rate was 71.1% versus 52.3%, hazard ratio [HR], 0.60; 95% CI 0.44 to 0.81; $P < .001$) and OS (91.9% versus 85.3% (HR, 0.60; 95% CI, 0.37 to 0.97; $P = .036$) compared to those patients that received only 1 year of adjuvant imatinib [106]. This analysis also showed that most of the benefit was seen in a subgroup of GISTs patients with Kit exon 11 mutation.

Subsequently, the same group published an exploratory analysis focused on predictive role of Kit and *PDGFRA* mutations in patients with GIST treated with adjuvant imatinib. It concluded that patients with *Kit* exon 11 deletion or insertion-

deletion on codons 557 and/or 558 had improved RFS when treated with imatinib for 3 years compared to 1 year. This improved RFS was not found in exon 11 substitution mutations, exon 9 mutations, *PDGFRA* mutation (including D842V mutation), or Wild-type GISTs [107].

NCCN Guidelines recommend 3-year adjuvant imatinib treatment for high-risk GIST after the surgical resection. However, the question that developed subsequently was if extending the adjuvant imatinib treatment to 5 years would have a better impact on RFS and/or OS. PERSIST-5 clinical trial tried to answer this question on a smaller scale using a single arm phase II trial that enrolled 91 patients with high risk Kit-positive primary GIST. The 5- and 8-year estimated RFS rates were 90% (95% CI, 80–95) and 81% (95% CI, 62–91), respectively. The 5-year OS rate was 95% (95% CI, 86–99) [108]. These findings lead to a phase III clinical trial (NCT02413736), aiming to confirm the results on a larger scale with randomization between 3 vs 5 years of adjuvant imatinib.

6.5 Imatinib as first line treatment of metastatic GIST

The anti-tumor effect, safety, and tolerability of imatinib in patients with metastatic or unresectable GIST were determined in patients randomized to receive either 400 mg or 600 mg imatinib daily. Treatment induced a sustained objective response in more than half of the patients treated with either 400 mg or 600 mg [109]. The EORTC phase I and phase II trials, revealed that the highest feasible dose of imatinib was 800 mg daily [110, 111]. Another EORTC study randomized 946 patients to 400 mg imatinib either once- or twice daily. It showed that patients who received imatinib 400 mg twice daily had superior PFS than those who received imatinib once daily. There was no difference in the response rate between the two doses [112]. The phase III trial, S0033, also randomized patients to 400 mg once daily versus 400 mg twice daily. The median progression-free survival was 18 months in patients receiving once daily dose versus 20 months for those received twice daily dose. Median overall survival was 55 months in patients received the lower dose compared to 51 months in patients received the higher dose. There were also high-grade toxicities in the high-dose arm [113].

The randomized EORTIC 62005 trial described *Kit* exon 9 mutation as the strongest adverse risk factor for progression and death in patients, and reported a significant improvement in PFS and reduction of relative risk in patients who have *Kit* exon 9 mutation treated with higher dose (800 mg/day) [32]. The North American phase III SWOG S0033/CALGB 150105 study also showed improvement in response rate in patients with *exon 9 mutation* treated with 800 mg daily of imatinib compared to those who received 400 mg daily [114]. A meta-analysis of 1,640 patients from the two large randomized studies (EORTIC 62005 and III SWOG S0033/CALGB 150105) confirmed a small PFS advantage in patients with *exon 9 mutation* who received high dose Imatinib but without meaningful OS benefit [115].

6.6 Imatinib resistance

Two types of resistance described: primary resistance, in which the tumor progresses during the first six months of treatment, and secondary resistance, which is characterized by tumor progression after six months of being controlled with imatinib treatment. Primary imatinib resistance is mostly seen in GISTs with exon 9 mutation treated with 400 mg imatinib daily, tumors that are *Kit*- and *PDGFRA* wild type—mainly *SDH* deficient GISTs, and those with *PDGFRA* exon 18 D842V mutation [86] [114, 116]. Secondary imatinib resistance likely develops from clonal evolution and/or polyclonal secondary mutations in *Kit* [117–119].

6.7 Treatment options for patients with GIST

Table 1 and Table 3 outline the targeted agents, both FDA approved and non-FDA approved, that are available to patients with GIST. Clinical trials leading to approval of agents for GIST have been summarized in Table 2. FDA approved agents have variable degree of inhibiting tyrosine kinases with some similarity in their mechanism of action. Figure 2 shows the mechanisms of action of targeted drugs in GIST.

1.1. Treatment beyond imatinib

6.7.1 Sunitinib

Sunitinib is an oral tyrosine kinase inhibitor of platelet-derived growth factor receptors (*PDGFRA* and *PDGFRB*) and stem cell factor receptor (*KIT*) that is approved for the treatment of patients with gastrointestinal stromal tumor after disease progression on or intolerance to imatinib. Sunitinib is usually used in the second-line setting. Approval was granted after a phase III clinical trial (NCT00075218) showed an improved median time to progression in comparison to placebo. The side effects profile was noticed to be broader than that of imatinib, most likely secondary to wide inhibition of other tyrosine kinases including vascular endothelial growth factor receptors (*VEGFR1*, *VEGFR2* and *VEGFR3*), Fms-like tyrosine kinase-3 (*FLT3*), colony stimulating factor receptor Type 1 (*CSF-1R*), and the glial cell-line derived neurotrophic factor receptor encoded by *RET* oncogene [120, 121].

6.7.2 Regorafenib

Regorafenib, multi-kinase inhibitor targeting *KIT* and *PDGFR* and other receptors showed significant activity in patients with advanced GIST who progressed after failure of both imatinib and sunitinib in early phase clinical trials [122]. Regorafenib was examined in a phase III clinical trial against placebo and showed a median PFS of 4.8 months in comparison to 0.9 months in the placebo arm with no major changes in OS because of cross over. This led to FDA approval of regorafenib in the third-line setting [123]. Long-term follow-up of one of the initial phase II trials showed a benefit in patients with primary *KIT* exon 11 mutations and those with *SDH*-deficient GIST [124]. Also, in a phase II trial, regorafenib showed prolonged PFS in patients previously treated with imatinib and sunitinib who developed secondary mutations of exon 17 [125]. Regorafenib is being tested against avapritinib (*BLU-285*) in a phase III clinical trial (NCT03465722) as a second or third line and in a phase II clinical trial (NCT02638766) in patients with wild-type GIST.

Table 1 FDA approved agents for patients with GIST

Drug	Mechanism of action	Line of treatment	Major side effects	Clinical trials leading to approval	Dose
Imatinib	Tyrosine kinase inhibitor with activity against kit, PDGFRA and PDGFRB	First line for unresectable and/or metastatic disease Adjuvant treatment following resection with high recurrence risk features	Edema, skin rash, nausea and diarrhea	Phase III	400 mg orally once daily Or 400 mg orally twice daily
Sunitinib	Multitargeted tyrosine kinase inhibitor with activity against KIT, PDGFR, VEGFR1, VEGFR2, VEGFR3, FLT3, CSF-1R, and glial cell-line derived neurotrophic factor receptor	Second line after progression on or intolerance to imatinib	Fatigue, diarrhea, skin changes and nausea	Phase III	50 mg orally once daily, 4 weeks on followed by 2 weeks off; alternative dosage is to use 37.5 mg daily without break
Regorafenib	Inhibitor of membrane-bound and intracellular kinases with activity against KIT and PDGFRA	Third line for patients previously treated with imatinib mesylate and Sunitinib malate	Hypertension, hand–foot skin reaction and diarrhea	Phase III	160 mg orally once daily for the first 21 days of each 28-day cycle
Avapritinib	Kinase inhibitor with activity against PDGFRA exon 18 mutation including PDGFRA D842V mutations	Fourth line for patients with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations	Manageable side effects including nausea, vomiting, peri-orbital edema and anemia	Phase III	300 mg orally once daily
Ripretinib	KIT/PDGFR inhibitor of activation loop mutations	Ripretinib was tested in third line setting. Results were comparable to sunitinib.	alopecia, myalgia, nausea, fatigue and palmar-plantar erythrodysesthesia	Phase III	150 mg or once daily with or without food.

PDGFRA platelet-derived growth factor receptor alpha, *VEGFR* vascular endothelial growth factor receptors, *FLT3* Fms-like tyrosine kinase-3, *CSF-1R* colony stimulating factor receptor type 1

6.7.3 Avapritinib (BLU-285)

Avapritinib, a selective inhibitor of mutated KIT and PDGFRA, was approved by the FDA after the results of the NAVIGATOR phase I trial (NCT02508532). In the dose-expansion part, 20 patients with a PDGFRA D842V-mutant GIST, and 36 patients with a PDGFRA D842V-mutant GIST were enrolled. At data cutoff, 49 (88%; 95% CI 76–95) of 56 patients had an overall response, with 5 (9%) complete responses and 44 (79%) partial responses. No dose-limiting toxicities were observed. Both duration of response (DOR) and median progression-free survival (PFS) were not reached at the time of data cutoff [126]. The role of avapritinib will be determined in the phase III VOYAGER trial (NCT03465722) which is testing regorafenib vs. avapritinib in GIST patients with KIT or PDGFRA in third-line setting.

6.7.4 Ripretinib

Ripretinib, with a dual mechanism of action, is a switch-control tyrosine kinase inhibitor with broad

activity against primary and drug-resistant *KIT*/*PDGFRA* mutants and an inhibitor of all known activation loop mutations [127]. The phase III trial (NCT03353753) and (NCT03673501) led to the approval of ripretinib for patients with advanced GIST after third-line of treatment [128–130]. Median progression-free survival was 6.3 months (95% CI 4.6–6.9) for ripretinib vs. 1.0 months (0.9–1.7) for placebo (HR 0.15 (95% CI 0.09–0.25) with $P < 0.0001$). Ripretinib is being evaluated in an ongoing phase III study (INTRIGUE) in second-line treatment compared with sunitinib (NCT03673501).

7 Experimental agents

Resistance to approved agents is a common clinical dilemma that leads to clinicians to encourage patients to be enrolled in clinical trials once the patient progresses. A list of non-FDA approved agents and some selected clinical trials is provided in Table 3.

Table 2 Clinical trials that led to FDA approved agents

Agent	Phase	ClinicalTrial.gov identifier	Number of patients	Median PFS	Median OS	Comments
Imatinib	III	NCT00009906	746	18 months	55 months	No improved OS for higher imatinib doses (800 mg daily)
Sunitinib	II	NCT00793871	59	46.4 weeks	111.3 weeks	All patients were Asian
	III	NCT00075218	312 (ITP population)	24.1 weeks	Not mature	The median time to tumor progression (TTP) was 27.3 weeks
Regorafenib	III	NCT01271712	199	4.8 months	NR	No significant difference in OS because of the cross over
Avapritinib	I	NCT02508532	43	NR	NR	The overall response rate was 86% with median treatment benefit lasting at least 11 months
Ripretinib	III	NCT03353753	129	6 months	15 months	Ripretinib is being evaluated in an ongoing phase III study (INTRIGUE) in second-line treatment compared to Sunitinib (NCT03673501).

PFS progression-free survival, OS overall survival, NR not reached

7.1 Cabozantinib (XL184)

Cabozantinib, a potent inhibitor of tyrosine kinases targeting MET, VEGFR2 and RET showed antitumor activity in preclinical models through inhibition of tumor growth, proliferation, and angiogenesis, in both imatinib-sensitive and imatinib-resistant models [131]. Phase II trial, EORTC 1317, met its primary endpoint, with median progression-free survival of 6.0

months; this supports further exploration of the role of cabozantinib in GIST in more advanced trials [132].

7.2 Nilotinib

Nilotinib, a selective potent tyrosine kinase inhibitor targeting KIT and PDGFRA, was reported in few case reports to have some response that may reach up to 12 months in patients with

Fig. 2 Mechanism of action of FDA approved agents for patients with GIST

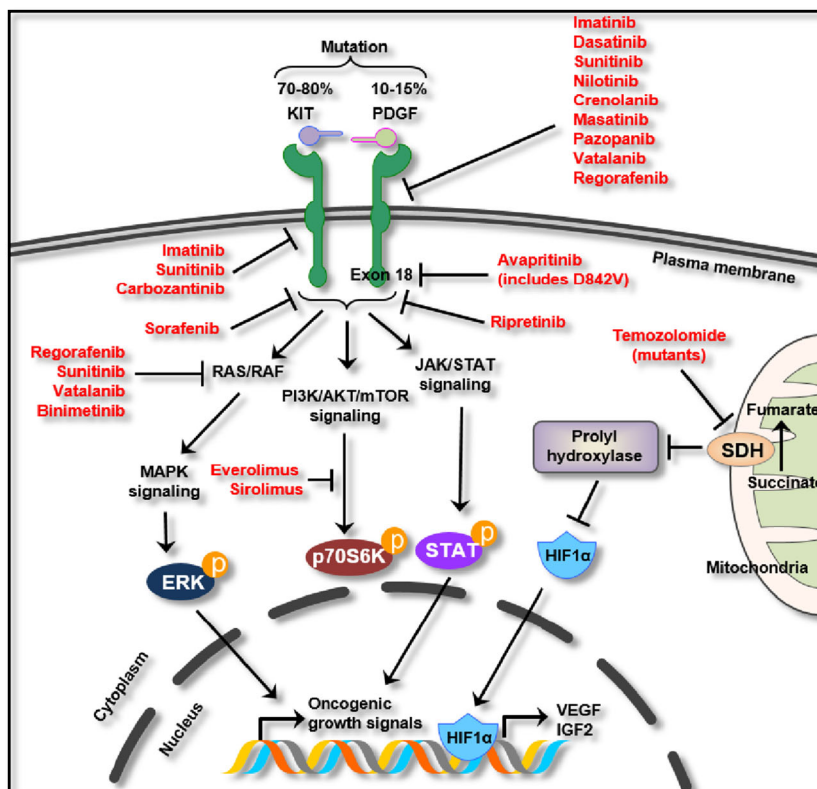


Table 3 Selected clinical trials for non-FDA approved agents

Agent	Mechanism of action	Clinical Trial	ClinicalTrial.gov identifier	Number of patients	PFS	OS	Comments
Cabozantinib	Tyrosine kinase inhibitor targeting kit, MET, AXL and VEGFR	Phase II	NCT02216578	50	6.0 months	-	FDA approved cabozantinib for medullary thyroid cancer and renal cell carcinoma
Nilotinib	Tyrosine kinase inhibitor targeting kit, PDGFR and BCR-ABL kinase	Phase III	NCT00785785	647	-	-	The trial accrual was terminated early because the interim futility analysis showed more progression in the nilotinib arm than in the imatinib arm.
Crenolanib	Tyrosine kinase inhibitor targeting PDGFR	Phase II	NCT01243346	20	-	-	Clinical benefit rate was 31% in patients with D842V PDGFR mutations Crenolanib is being tested in Phase III trial for patients with D842V mutation in <i>PDGFR</i> (NCT02847429)
Masitinib	Tyrosine kinase inhibitor targeting kit and PDGFR	Phase II	NCT00998751	30	41.3 months	NR	Masitinib is being compared to imatinib in phase 3 clinical trial in a first line setting (NCT01694277)
Ponatinib	Tyrosine kinase inhibitor targeting kit, VEGFR, FGFR, and PDGFR	Phase II	NCT01874665	35	-	-	Clinical benefit rate at ≥ 16 weeks was 55% FDA approved for chronic myeloid leukemia (CML)
Pazopanib	Tyrosine kinase inhibitor targeting kit, PDGFR, and FGFR	Phase II Phase II	NCT01323400 NCT01391611	81 25	3.4 months 1.9 months	17.8 months 10.7 months	The inconsistency in the results in trials didn't support approval of pazopanib for GIST patients
Sorafenib	Tyrosine kinase inhibitor targeting kit, PDGFR, FLT3, and VEGFR-1, 2, and 3	Phase II	NCT01091207	38	5.2 months	11.6 months	FDA approved for unresectable hepatocellular carcinoma, advanced renal cell carcinoma and thyroid carcinoma.

PDGFR platelet-derived growth factor receptor alpha, *VEGFR* vascular endothelial growth factor receptors, *FLT3* Fms-like tyrosine kinase-3, *FGFR* fibroblast growth factor receptor, *MET* mesenchymal epithelial transition factor

advanced GIST [133, 134]. Some benefits were noticed in phase I clinical trials [135]. Nilotinib was also tested more in phase II and III clinical trials but the results were not suggestive of major benefits [136–139]. However, it was suggested that the role of nilotinib be re-tested before it is discarded for use as a treatment for GIST [140]. A phase IV clinical trial (NCT01735955), whose purpose is to allow continued use of nilotinib in patients who benefited from it, may give more insight about its role in GIST. The estimated date of reporting the results is April 2023.

7.3 Ponatinib

Ponatinib, which inhibits multiple kinases including KIT, is FDA approved for Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) as well as chronic myeloid leukemia (CML). Ponatinib showed activity against KIT mutated refractory GIST in an *in vivo* setting [141]. It showed some benefits in patients with advanced GIST in a clinical phase II trial (NCT01874665) [142]. And it is currently evaluated currently in a phase II clinical trial to evaluate its role in patients with metastatic and/or unresectable GIST after prior failure or intolerance of Imatinib (NCT03171389). The results of the later study may guide further directions in this regard.

7.4 Pazopanib

Pazopanib, an inhibitor of the VEGFR, PDGFR and stem cell receptor c-KIT, was tested in phase II clinical trial in France. Eighty-one patients were enrolled, and the trial achieved a 40% disease control rate at 4 months using Pazopanib in patients with refractory GIST [143]. This finding was questioned, especially in light of a previous phase II trial in the USA that enrolled 25 patients with a median number of 3 previous agents, showing a median PFS of 1.9 months (95% CI 1.6–5.2), and the a median OS of 10.7 months (95% CI 3.9–NR) [144, 145].

7.5 Masitinib

Masitinib is a highly selective tyrosine kinase inhibitor with activity against wild-type and mutant KIT (exons 9 and 11) [146]. Masitinib was tested to establish safety and efficacy in phase I/II studies in the first-line setting and after the failure of imatinib. Median PFS was 27.2 months in a study population of 30 patients; the response rate was 20% according to RECIST criteria and 84.6% according to FDG-PET response criteria [147, 148]. A phase III clinical trial was initiated to compare the efficacy of masitinib to sunitinib after progression on imatinib (NCT01694277). Masitinib seems to have the potential to obtain approval if the results of this phase III trial are consistent with the findings from the phase I/II studies.

7.6 Crenolanib

Crenolanib, a potent inhibitor of imatinib resistant PDGFRA (including the PDGFRA D842V mutation), is being actively studied in a placebo-controlled phase III trial that completed accrual in August 2020 (NCT02847429) [149]. The previous phase III trial was launched after preclinical studies, while phase I/II clinical trials showed that Crenolanib is a potent inhibitor of Imatinib resistant PDGFRA, including the PDGFRA D842V mutation and plays a potential role in GIST patients. Crenolanib demonstrated a 31% clinical benefit rate with two patients achieving partial response and three patients maintaining stable disease in 16 evaluable and heavily previously treated patients with the PDGFRA D842V mutation [150].

7.7 Sorafenib

Sorafenib, another tyrosine kinase inhibitor of KIT and PDGFRA-mutant kinase in drug-sensitive and drug-resistant GIST, engages in dose-dependent inhibition of GIST tumors [151]. Clinically, two phase II clinical trials and three retrospective analyses showed that sorafenib played some role in the third- or fourth-line settings, mostly after progression after imatinib and Sunitinib [152–156]. One of these phase II clinical trials enrolled 38 patients. It showed a partial response of 13%, while stable disease was 55%, median PFS was 5.2 months (95% CI: 3.4, 7.4), and median OS was 11.6 months [157].

7.8 mTOR inhibitors

The oral mTOR inhibitor everolimus (RAD001) has shown efficacy in GIST refractory to imatinib and sunitinib in a phase I/II clinical trial in which 37% of the patients were progression-free for at least 4 months and 36% achieved stable disease (SD). The most common adverse events were diarrhea, nausea and fatigue [158]. In another phase II study, 9 patients out of 27 showed SD at 16 weeks with controllable adverse events such as anemia, diarrhea, nausea etc. [159]. Another mTOR inhibitor, sirolimus has also demonstrated a benefit in combination with tyrosine kinase inhibitors including Imatinib in a limited number of GIST patients with PDGFRA-D842V mutations. The combination was relatively well tolerated except for skin toxicity in one patient [160, 161].

8 Other options for patients with GIST

Several other systemic therapies are actively being investigated in patients with GIST including immunotherapy, cytotoxic chemotherapy, novel tyrosine kinase inhibitors, binimetinib, selinexor, and few others.

8.1 Immunotherapy

Because inflammation has been implicated in patients with GIST, immunotherapy is being investigated in patients with GIST [162]. Examples include the testing of anti-PD-1 antibody, pembrolizumab, nivolumab with or without ipilimumab, avelumab with axitinib, and vaccine therapy. A durable response was observed in a highly refractory metastatic KIT/PDGFR wild-type GIST following treatment with nivolumab in one reported case [163]. Future directions in immunotherapy for patients with GIST are summarized in Table 4.

8.2 Cytotoxic chemotherapy

A phase II clinical trial is investigating the role of paclitaxel in patients with advanced and/or metastatic GIST after the failure of at least imatinib and sunitinib in patients with low P-glycoprotein expression (NCT03944304).

8.3 Novel tyrosine kinase inhibitors

8.3.1 Anlotinib

Anlotinib, a multi-targeted tyrosine kinase inhibitor with activity against c-KIT, VEGFR, PDGFR, and FGFR inhibitor, which showed broad activity against soft tissue sarcoma and GIST with D842V, D816H, V560G, and V654A mutations is being studied in a phase II trial in patients with advanced GIST after the failure of Imatinib (NCT04106024)

8.3.2 PLX9486 in combination with PLX3397 or sunitinib

The novel tyrosine kinases inhibitor, PLX9486, is being studied in combination with another novel tyrosine kinase inhibitor, PLX3397 or with Sunitinib in a phase I/II trials in patients with locally advanced, unresectable, or metastatic GIST (NCT02401815).

8.4 Temozolomide (TMZ)

Temozolomide (TMZ), an oral alkylating agent approved by the FDA for glioblastoma multiforme (GBM) and refractory anaplastic astrocytoma cancers, is being investigated in phase II clinical trial in patients with SDH-mutant/deficient gastrointestinal stromal tumor (NCT03556384).

8.5 Binimetinib in combination with pexidartinib or imatinib

Binimetinib, a reversible inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activity [164], which is approved for unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, is being studied in a phase I study in combination with pexidartinib (a tyrosine kinase inhibitor that targets colony stimulating factor 1 receptor (CSF1R), KIT proto-oncogene receptor tyrosine kinase (KIT), and FMS-like tyrosine kinase 3 (FLT3) harboring an internal tandem duplication (ITD) mutation and approved for patients with symptomatic tenosynovial giant cell tumor (TGCT)), in patients with advanced gastrointestinal stromal tumor (GIST) (NCT03158103).

Table 4 Future directions in immunotherapy for patients with GIST

Agent	Clinical trial	ClinicalTrial.gov identifier	Comment
PDR001	Phase I/II	NCT03609424	Anti-PD-1 antibody in combination with imatinib is being tested in a 4 th line setting
Pembrolizumab + epacadostat	Phase II	NCT03291054	Epacadostat is a novel inhibitor of indoleamine-2, 3-dioxygenase-1 (IDO1) that is being tested with pembrolizumab in a 2 nd line setting.
Nivolumab ± ipilimumab	Phase II	NCT02880020	Avelumab, monoclonal antibody targeting PD-L1, in combination with axitinib, tyrosine kinase inhibitor are being tested in a 4 th line setting
Avelumab with axitinib	Phase II	NCT04258956	
Vaccine therapy	Phase I	NCT01376505	A vaccine in combination of with two chimeric (Trastuzumab-like and Pertuzumab-like) Human Epidermal Growth Factor Receptor 2 (HER-2) B Cell Peptide is being tested in patients with advanced solid tumors including GIST
Ipilimumab	Phase I	NCT01738139	Ipilimumab, monoclonal antibody targeting CTLA-4, in combination with imatinib is being tested in patients with advanced malignancies including GIST

Binimetinib is also being investigated with imatinib [165]. A phase Ib/II study of MEK162 (binimetinib) in combination with imatinib is actively recruiting patients with untreated advanced GIST to test its effect of combining binimetinib and imatinib in the first line setting (NCT01991379).

8.6 Selinexor

Selinexor, which is FDA approved for patients with relapsed or refractory multiple myeloma, inhibits nuclear export of tumor suppressor proteins (TSPs), growth regulators, and mRNAs of oncogenic proteins by blocking exportin 1 (XPO1). Selinexor is being examined in phase I/II clinical trials in combination with imatinib in patients with metastatic or unresectable GIST (NCT04138381)

8.7 Bispecific antibody

A bispecific antibody, XmAb18087, against somatostatin receptor 2 (SSTR2) and CD3 that showed *in vitro* and *in vivo* activity in GIST via the stimulation of target-dependent T-cell activation is being studied in a phase I study in patients with advanced GIST (NCT03411915).

8.8 Antibody-drug conjugate (ADC)

Monotherapy with DS-6157a, an antibody-drug conjugate, is being studied in a phase I first-in-human study in patients with gastrointestinal stromal tumor (GIST) (NCT04276415).

9 Conclusion

GIST represents the first success story in targeted therapy in patients with non-hematological malignancies. Despite its rarity it is treatable with a high degree of success even in the metastatic setting. Major driver mutation is that of *Kit* followed by *PDGFR*. Imatinib revolutionized the outcome of such patients who respond very poorly to conventional cytotoxic therapy. At this time, patients with advanced disease expect prolonged times of disease control when treated with imatinib as first line therapy. Imatinib also markedly improved the outcome of patients with localized disease who had resection of primary tumor but with high risk of disease recurrence and death. Patients who become either resistant or intolerant to imatinib may benefit from an increasing number of oral agents that include sunitinib, regorafenib, avapritinib, and ripretinib. All these drugs are administered orally and are generally well tolerated. Better understanding of the molecular biology of GIST is currently translated to clinical practice to better manage patients. The identification of the molecular profile of a given patient's tumor can provide prognostic information and also guide treatment choices. All this leads to better

personalized therapies. There are a number of ongoing clinical trials testing newer agents including immunotherapy that may further improve the outcome of patients with drug resistant disease.

Declarations

Informed consent Specific informed consent is not required. Images and radiography are de-identified. Patient in the case included in the article has signed an informed consent preoperatively for possible use of images and pictures for research.

Conflict of interest Asfar Azmi—funding from Janssen and Karyopharm Therapeutics Inc. Consultant for Guidepoint and GLG. Speaker bureau at Karyopharm Therapeutics Inc. All other authors declare that they have no conflict of interest.

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