Review Article

Perspectives on the evolving state of the art management of gastrointestinal stromal tumours

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Abstract: Gastrointestinal stromal tumours (GISTs) represent a very exciting tumour entity for the medical oncologist. There has been extensive clinical and preclinical research dissecting the natural behaviour, molecular landscape and therapeutic responsiveness of this rare mesenchymal tumour. Various molecular subtypes of GIST have a differing prognostic and predictive relevance in the state of the art management of the disease. Emerging mature clinical trial data gathered over the last one and half decade provided substantial molecular profiling information in understanding the success and eventual failure of treatment. In our review of the most relevant literature we aim to guide the clinician in tailoring neoadjuvant, adjuvant and palliative treatment of GIST alongside the different, now well established molecular subgroups of GISTs.

Keywords: Gastrointestinal stromal tumours (GISTs); *KIT*; *PFGFRA*; molecular subgroups; "wild type" GIST (WT-GIST); succinate dehydrogenase (SDH) deficiency; *NF-1*; *BRAF*

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Introduction

Gastrointestinal stromal tumours (GISTs) account to almost one fifth of all sarcomas, making them the most common mesenchymal tumour (1). GISTs can originate from any part of the gastrointestinal tract, from the oesophagus to the rectum, while extra-intestinal sites of origins are extremely rare. GISTs are thought to arise from the phenotypically similar interstitial cells of Cajal residing in the muscular layer of the digestive tract; stomach and small intestine are the most frequent locations of origin (2,3). The aggressiveness/malignant potential of GISTs vary pending on tumour size, mitotic activity, and the anatomical origin itself. Surgical resection is the only curative treatment modality for localized GIST and constitutes definitive therapy in up to two thirds of these cases (4,5). Although a significant proportion of patients will be cured with surgery alone, approximately 40% will eventually relapse, the great majority within the first 5 years (6). The Armed Forces Institute of Pathology Risk Group Classification is still one of the most widely used system for the assertion of the risk of recurrence after curative surgery (3). This classification system does not incorporate the accumulated vast knowledge in terms of mutational landscape of GISTs (7).

The discovery of the KIT tyrosine kinase receptor and subsequently that of the mutually exclusive *KIT* and platelet-derived growth factor receptor (*PDGFRA*) gain of function mutations have provided a paradigm shift in the way we classify, diagnose and treat GISTs (7,8). The different segments of the KIT transmembrane receptor (extracellular domain, transmembrane hinge, juxtamembrane domain, intracellular tyrosine kinase domain) all have a specific designated role in the process of tyrosine kinase activation.

In up to 82–87% of GISTs activating mutations in either the KIT (69–83%) or the homologous PDGFRA receptor (12–14%) lead to constitutive, ligand-independent activation ultimately leading to increased cell proliferation, apoptosis inhibition. The most frequent *KIT* 'hot spot' mutations are in exon 11 (encoding the juxtamembrane domain), less frequently in exon 9 (extracellular domain) and rarely in exon 13 (ATP-binding region) and exon 17 (activation loop of the kinase) (7,9). Deletions affecting codons 557–558 of exon 11 of the *c-KIT* gene account to around a quarter of all GIST cases (10). *KIT* mutations in exon 9 (7–15% of all GIST cases) are characterized by A502-Y503 codon duplications, with up to 80% of the cases originating outside the stomach, mainly from the small intestine (11,12). The frequency of primary exon 13 and 17 mutations is around 1–2%, these tumours mostly arising from the small bowel rather than the stomach (13). The 60–65% of *PDGFRA* mutations are p.D842V substitutions involving the second kinase domain (corresponding to exon 17 of KIT) (14).

The 10–15% of all adult GISTs have no detectable mutations in *KIT* or *PDGFRA* receptors and historically are referred to as 'wild-type' (WT) GISTs. About half of all *KIT/PDGFRA* WT-GISTs have inactivating mutations in the genes coding one of the four (SDHA, SDHB, SDHC and SDHD) subunits of the succinate dehydrogenase (SDH) complex (15,16). The lack of KIT mutations does not affect the KIT protein expression of these tumours; they have a predilection for the stomach, display a multi-lobulated/multi-nodular growth pattern and are prone to metastasize to the lymph nodes (16). In the absence *KIT/PDGFRA* mutations, most infrequently further mutations in the *BRAF* (V600E), *HRAS*, *NRAS* or *PIK3CA* genes of the downstream signalling pathway have been detected (7,17). NF1-associated GISTs characterized by the somatic inactivation of the WT *NF1* allele constitute a small subgroup of KIT/PDGFRA WT-GISTs. These frequently multicentric, mostly small intestinal tumours present as small, low mitotic index lesions and display a favourable long-term outcome with low recurrence and metastases rates (7). Most recently a small subgroup of "Quadruple WT-GIST" has been identified, characterized by lack of mutations in any of the known *KIT*, *PDGFRA*, *BRAF*, *RAS* or *NF1* genes while retaining an intact SDH complex (SDHB IHC positive, and no mutations in *SDH*). The detailed characterization of this sub-group is still ongoing (18).

With its ubiquitous role in the pathogenesis of GISTs, KIT emerged as a universal therapeutic target. The pronounced clinical efficacy of imatinib (a competitive inhibitor of the ATP-binding domain) in GIST was confirmed one and a half decades ago (8). In the advanced/metastatic setting imatinib offers an overall 80% disease control rate (objective response or stable disease), a median progression-free survival (PFS) of approximately 20 months and a median overall survival (OS) of around 50 months (19).

Neoadjuvant treatment

While assessing the upfront resectability of GISTs is strictly speaking a surgical decision, multidisciplinary teams specialized in the management of GISTs need to establish the potential beneficial effects of down-staging prior to curative surgery. There are several clinical scenarios where neoadjuvant treatment can be indicated, including prospect of multi-visceral resection, risk of a mutilative surgery and low chances of a complete R0 resection. Current guidelines recommend neoadjuvant treatment for unresectable GISTs or those resectable tumors where there is a risk of significant morbidity (5). Up so far the role of neoadjuvant imatinib treatment has not been assessed within the frame of randomized phase III trials, nevertheless retrospective series and some prospective phase II trials have demonstrated the efficacy and safety of neoadjuvant imatinib in locally advanced GISTs (20-22).

We consider mutational status analysis essential in tailoring a neoadjuvant treatment plan. The standard treatment dose is 400 mg of imatinib once a day (5). A higher dosage of imatinib 800 mg/day) for *KIT* exon 9-mutated GISTs is suggested by international guidelines as a significant PFS advantage has been demonstrated in the metastatic setting (5,23). There is no randomized clinical trial evidence in regard of the optimal length of neoadjuvant imatinib therapy; nevertheless, a 6–9 months' treatment interval can be recommended to minimize the risk of tumour progression on treatment (5,21,22).

The EORTC sarcoma centers study analyzed disease-free survival (DFS) and disease-specific survival (DSS) in 161 patients with locally advanced, non-metastatic GISTs who received neoadjuvant imatinib. The tumor resection after preoperative imatinib, with a median time on therapy of 40 weeks was R0 in 83% of the patients. Only two patients out of the 161 have demonstrated disease progression during neoadjuvant therapy. Five-year DSS/DFS rates were 95/65%, respectively with a median OS of 104 months. The most common mutations affected exon

11 KIT (65%) (23). In terms of postoperative treatment, locally advanced GISTs are all to be considered high risk for relapse, regardless the postoperative pathology readings. In the EORTC sarcoma centers study poorer DFS was related not only to primary tumor location in small bowel but also to lack of postoperative treatment (23). In another more recently published, smaller series of 76 patients whom received neoadjuvant imatinib, lack of adjuvant imatinib was the only factor related to inferior PFS and OS (24). The authors of this review would suggest strongly considering adjuvant imatinib therapy for all patients whom received neoadjuvant treatment prior to primary tumour resection.

Within the frame of a desperate need of pronounced response for tumour down-staging, one needs to maximize the chances of efficacious treatment. A Cmin threshold of 760 ng/mL was associated with prolonged PFS in the treatment of advanced GIST patients. There is an established relationship between imatinib trough concentration and outcomes in the treatment of advanced GISTs (25). Therapeutic dose monitoring shall be considered for all patients undergoing neoadjuvant treatment, wherever such a service is at hand. It must be noted that there is a low, around 3% risk of intratumoural bleeding with upfront neoadjuvant imatinib treatment, thus patients need close clinical monitoring in the first few weeks of therapy (26).

The neoadjuvant treatment for GISTs with genotypes refractory/resistant to licensed tyrosine kinase inhibitors (TKIs) is very difficult. More recently, BLU-285, a mutation-specific inhibitor of kinases with mutations in *KIT* D816V and *PDGFRA* D842V showed promising clinical activity in the advanced setting. The results of the dose escalation part of a phase I study confirmed strong clinical activity of BLU-285 in *PDGFRA* D842-mutant advanced GISTs with an overall response rate (ORR) of 60%(27).

Another oral small-molecule inhibitor crenolanib also demonstrated some, as compared to BLU-285 less impressive, clinical activity in metastatic *PDGFRA*-mutant (including D842V-mutated kinase) with a single objective response out of seven patients treated (28).

Adjuvant treatment

Microscopic complete resection with histologically negative margins (R0) without rupturing the tumor is the optimal standard treatment for localized GISTs. Although a significant proportion of patients will be cured with surgery alone, approximately 40% will eventually relapse, the great majority within the first 5 years after the operation (5,6). With the proven impressive efficacy of imatinib in controlling advanced disease, its' use was swiftly extended into to the adjuvant treatment of GIST (29).

The Z9001 trial data suggests that high-risk patients (tumor size >10 cm and high mitotic rate) derive a greater efficacy from adjuvant therapy (30). The use of adjuvant imatinib is not recommended for low and very low risk GISTs, however there is no consensus for those with intermediate risk tumours (5). Based on the results of the three pivotal Phase III adjuvant trials regardless of the classification scheme used, patients identified as intermediate risk had a clinical course similar to that of the low-risk group (5). For patients with intermediate risk tumours the risks and benefits of treatment and the lack of clinical data unequivocally supporting a survival benefit in this subgroup should be thoroughly explained and debated. The currently recruiting French GIST randomized phase II trial comparing imatinib over 3 years versus surveillance in intermediate-risk patients with a high-risk genomic grade index might help us defining a sub-group meriting adjuvant treatment (31).

Molecular profiling as prognostic and predictive tool in adjuvant decision making

There are several risk-stratification schemes in use for operable GISTs which help determine the need of adjuvant treatment for high-risk tumours. The most widely used are the National Institutes of Health consensus classification and its modified version, alongside the Armed Forces Institute of Pathology (AFIP) criteria. The AFIP classification is currently still the most frequently used one in the everyday practice in Europe. Large tumour size, high mitosis count, non-gastric location, presence of rupture, and male sex have all been proven independent adverse prognostic factors (6).

Over the last decade a vast amount of knowledge has built up in terms of understanding the prognostic and predictive relevance of different genetic subtypes of GIST (7). Deletions affecting codons 557-558 of exon 11 of the *c-KIT* gene have been associated with an aggressive, metastasizing phenotype and indicate an overall poor prognosis (10). In the Polish registry study 80% of 557/558 codon deleted GISTs stratified as high-risk tumours, with a lower 5-year relapse free survival (RFS) rate as compared with any other *KIT* exon 11 mutations but also with other exon 11 deletions that have not involved codons

557/558 (12). In the Multinational European Contica GIST Database analysis the poor prognostic impact of *KIT*del-inc557/558 on patients' survival was only significant in GIST localized to the stomach. Twice as many patients with gastric GIST harbouring *KIT*del-inc557/558 relapsed 5 years after surgery than with other *KIT* exon 11 mutations (61% *vs.* 29%). It is important to remember that in stomach GISTs classified as AFIP non–high risk the presence of *KIT* del-inc557/558 remained an important prognosticator for poor outcome in comparison with other *KIT* exon 11 mutations, *KIT* exon 9 and *PDGFRA* exon 18 mutations (14). In the ACOSOG Z 9001 trial the 1 year of imatinib arm was only superior to placebo in terms of RFS in the *KIT* exon 11 deleted subgroup; none of the GISTs with *KIT* exon 11 point mutations or insertions, exon 9 mutations, *PDGFRA*-mutant tumors or WT-GISTs had a statistically significant delay in recurrence as compared to placebo (32). The underrepresentation of KIT exon 11 substituted GISTs in advanced/metastatic trials (1.6–1.86%) as compared to population-based studies (15.5–28.6%) are most probably in keeping with a more indolent clinical behaviour of this genotype. These tumours are characterised by low mitotic activity and small size at presentation with 5-year RFS rate of 50.7% as opposed to *KIT* deleted (28.1%) or duplicated GISTs (40.0%) (7,12,14). Duplications in *KIT* exon 11 have been associated with gastric tumour location and a more favourable clinical course (12,33).

In contrast to some historical observations (34) KIT exon 9 mutations *per se* do not have a relative (as compared with *KIT* exon 11 mutations of non-gastric origin) negative prognostic relevance. The worse prognosis of *KIT* exon 9 mutants is related to the non-gastric tumour location itself rather than to an intrinsic aggressive biologic nature of this mutation (11,14). In the meta GIST pooled analysis of two pivotal Phase III trials comparing 400 *vs.* 800 mg daily imatinib dose in the advanced setting, the sole predictive factor of response was the presence of *KIT* exon 9 mutation. The estimated risk of progression or death was reduced by 42% in the high-dose arm (compared with the standard-dose arm) in the *KIT* exon 9 mutated subgroup, without an OS advantage (19). Given the data supporting the use of a higher dose of imatinib in the case of an exon 9 KIT mutation in advanced GIST, many clinicians prefer to use the 800 mg/day imatinib dose even in the adjuvant treatment of high-risk patients. Beyond the obvious regulatory/licensing restrictions limiting this practice, it must be emphasized that no controlled trial supports higher dosing in the adjuvant setting.

Gastric *KIT* exon 13 mutant GISTs are slightly larger and of a higher risk group than gastric GISTs on average, while the clinical behaviour of small intestinal GISTs with *KIT* exon 13 or *KIT* exon 17 mutations are similar to other small intestinal GISTs (7).

The markedly lower representation of *PDGFRA*-mutated GISTs in advanced clinical trials (around 2% *vs.* 12–14% in population studies) is in keeping with a comparatively benign clinical behaviour of these tumours. Moreover, *PDGFRA* mutant GISTs are almost exclusively of gastric origin (90–93%), thus belonging to a better prognostic group (7,12). *PDGFRA* exon 18 mutation status correlates with excellent 5-year DFS of 75%, in contrast to *KIT* exon 9 and *KIT*del-inc557/558 mutated tumours. Interestingly, no significant difference in DFS figures was observed between *PDGFRA* p.D842V versus other *PDGFRA* exon 18 mutations (12). There is consensus that PDGFRA D842V mutated GIST should not be treated with any adjuvant therapy, given the lack of sensitivity of this genotype both *in vitro* and *in vivo* (7). The excellent survival of patients with tumours harbouring *PDGFRA* mutations in the placebo group of the ACOSOG Z 9001 trial provide a good additional argument that these patients may not require adjuvant treatment (32).

It must be emphasized that the prognosis of SDH deficient GISTs cannot be predicted by size and mitotic rate as even small, mitotically inactive SDH deficient GISTs may metastasize. Interestingly when metastases do occur they may be strikingly indolent, sometimes remaining stable for years or decades (15). In a recently published study *SDHA* mutations were associated with statistically significant better clinical outcome as compared with *KIT/PDGFRA* mutations and *KIT/PDGFRA* WT without SDH deficiency. All survival analyses (from diagnosis of primary tumours and from diagnosis of metastatic disease) confirmed a far more indolent course of disease for patients with *SDHA* mutated WT-GISTs (35).

The majority of NF1-associated GISTs present as small, low mitotic index lesions and they are associated with quite favourable long-term clinical outcomes reflected in low recurrence and metastases rates (36). Interestingly NF-1 associated GISTs arising from the duodenum display an aggressive behaviour, being large mitotically active tumours with pronounced metastatic potential (37).

More recently, the combined prognostic value of the most relevant genetic GIST subtypes has been analyzed in a series of 451 untreated primary localized GISTs for *KIT*, *PDGFRA* and *BRAF* mutations and offered further proof

that mutational status is a significant prognostic indicator of OS in treatment naive, localized GISTs. Based on multivariable Cox regression models the authors identified three distinct molecular risk groups. Group I, consisting of *PDGFRA* exon 12, *BRAF* and *KIT* exon 13-mutated cases, exhibited the best clinical outcome. The intermediate risk (HR =3.06) Group II, included 'Triple-Negative', *KIT* exon 17, *PDGFRA* exon 18 D842V, and *PDGFRA* exon 14-mutated GISTs. Group III, comprised of *KIT* exon 9 and exon 11 and *PDGFRA* non-D842V exon 18 mutant GISTs, displayed the worst clinical outcome (HR =4.52) (38). This study clearly highlighted the combined prognostic impact of mutational status on the natural history of GIST.

Inclusion of molecular prognostic grouping into currently used clinico-pathologic risk stratification criteria could clearly fine tune the decision-making process for adjuvant therapy. The authors of this review strongly believe that these important findings will have to be swiftly incorporated into international guidelines directing treatment (*Table 1*).

Optimal length of adjuvant treatment

According to the OS findings in the SSGXVIII/AIO trial, 3 years of adjuvant imatinib therapy are the recommended standard of care for patients with GIST with high-risk features. At a median follow-up of 90 months, patients randomized to 3-year imatinib dosing had a significantly improved OS (92% *vs.* 85% for the 1-year arm) (39). The results of 2 years *vs.* surveillance EORTC phase III trial examined the so called imatinib failure-free survival (IFFS) the time to initiation of a different TKI following recurrence was no different in between treatment and control arms (87% *vs.* 84% respectively). There was a slight trend toward IFFS benefit in the high-risk subgroup (40).

With the never-ending debates around the ability of imatinib to actually eradicate disease altogether (as opposed to a 'cytostatic effect' of the drug), there is a drive to extend the length of treatment well beyond 3 years. In a phase II trial of 91 high-risk GIST patients with sensitive mutations 5 years of adjuvant imatinib treatment led to 5-year 90% RFS and 95% OS rates. 7 "true" recurrences were recorded, with 6 occurring 7.4 to 23.1 months after imatinib discontinuation. Only one patient with a high-risk *PDGFRA* D842V mutant gastric GIST recurred while on treatment (41). It is worth noting that half of the patients discontinued treatment early, though only a minority of all patients (16%) discontinued due to adverse events. Two currently recruiting randomized trials for high-risk GIST patients compare the current 3-year long standard of care with 5 and 6 years of treatment respectively (42,43).

The SSGXVIII/AIO study proved that tumor rupture is a highly unfavourable prognostic factor, with the overwhelming majority of these patients relapsing at 5 years after surgery (39). Independently from conventional risk-stratification schemes, these patients all should be offered adjuvant treatment. The optimal length of "adjuvant" treatment in these virtually metastatic patients, is as uncertain as for other high-risk groups; nevertheless, one would offer indefinite imatinib treatment pending on other high risk features of the tumours.

Management of advanced GIST

Almost half of advanced GIST patients treated with imatinib have a survival longer than 5 years, with approximately one fifth of patients showing a long-lasting disease control for more than 10 years. It must be noted that patients with advanced GISTs who have a *KIT* exon 11 mutation have a superior prognosis as compared with all other mutation subtypes (44,45). The SWOG Intergroup Trial S0033 univariate analysis of OS by *KIT* exon 11mutant, *KIT* exon 9 mutant, and *KIT/PDGFRA* WT genotypes revealed median survival times of 66, 38, and 40 months, respectively. In long-term survivors more responses [complete response (CR) + partial response (PR)], were seen in the *KIT* exon 11 mutant genotype group than in the *KIT/PDGFRA* WT or *KIT* exon 9 groups: 70%, 48% and 50% respectively. The median PFS for patients with *KIT* exon 11 mutations was 25 months compared to 17 months for patients with *KIT* exon 9 mutations and 13 months for those with WT genotype. Interestingly no difference in PFS/OS were found amongst patients whose GIST had different classes of *KIT* exon 11 mutations (45).

In the pooled analysis of the two pivotal Phase III trials comparing 400 *vs.* 800 mg daily imatinib dose the sole predictive factor of response was the presence of *KIT* exon 9 mutation. The estimated risk of progression or death was reduced by 42% in the high-dose arm (compared with the standard-dose arm) in patients with *KIT* exon 9 mutated tumours. However, no significant difference in OS was seen between patients treated with 400 and 800 mg imatinib, irrespective of mutational status. The study concluded that for most patients, the recommended daily dose is 400 mg daily, with the exception of *KIT* exon 9 mutated tumours where the 800 mg dose can be considered (19).

Table 1 Clinical relevance of different molecular subtypes of GIST in the adjuvant setting

Genotype	Biological behaviour (untreated)	Current standard (high risk)	Special considerations (authors' opinion)
KIT exon 11 deleted (inc557/558)	Aggressive, metastasizing phenotype	Imatinib 400 mg 3 years	Single subgroup with RFS benefit in the Z9001 trial
	80% high-risk tumours		Adjuvant treatment shall be discussed for AFIP intermediate-risk patients
	Poor OS even with gastric location		Enrolment to >3 years of imatinib trials encouraged
	Non-high risk (AFIP) tumours showing poor long term outcomes		
KIT exon 11 SNS	Low mitotic activity and small size at presentation Excellent 5-year RFS rates	Imatinib 400 mg 3 years	
KIT exon 11 duplicate	Gastric tumour location	Imatinib 400 mg 3 years	
	Relatively favourable clinical course		
KIT exon 9 mutant	Aggressive behaviour associated with non-gastric location of these tumours; not of relative prognostic relevance on its own	Imatinib 400 mg 3 years	800 mg dose can be extremely carefully considered
KIT exon 13 mutant	Slightly larger and of a higher risk group when gastric location	Imatinib 400 mg 3 years	
PDGFRA D842V mutant	Indolent clinical behaviour	No treatment	
	Excellent 5 years OS rate		
	Almost exquisite gastric location		
PDGFRA/KIT WT SDH deficient	Even small, mitotically inactive GISTs may metastasize	Imatinib 400 mg 3 years	
	Strikingly indolent natural course when metastatic		
NF1-asssociated	Small, Low Mitotic Index Lesions At Presentation Low Recurrence And Metastases Rates (Except Duodenal Primary)	Imatinib 400 mg 3 years	

GIST, gastrointestinal stromal tumour; RFS, relapse free survival; SNS, single nucleotide substituted; OS, overall survival.

PDGFRA exon 18 D842 V mutant GISTs have been long considered as insensitive to imatinib treatment (46). In contrast to the common perception, in a recent large multicenter observational study reported objective response to imatinib in a small proportion of patients with PDGFRA D842V-mutated GISTs. The 12.5% of 16 patients with the mutation had partial response, 18.8% had stable disease and 56.3% had progressive disease (PD) as best response according to Choi criteria, with a median TTP of 8.0 months (47). We can conclude that as patients with *PDGFRA* D842V-mutated GISTs should not be universally denied imatinib, especially in clinical scenarios where no other TKI is available.

In a small series of seven metastatic NF1-associated GIST patients, three out of the four imatinib treated patients showed primary resistance to the treatment (all 3 tumours were KIT/PDGFRA WT-GISTs). The fourth metastatic patient with an exon 18 mutated tumour had temporary stable disease (SD). Median OS for this 4-patient cohort was 21 months (48).

The pivotal BFR14 trial addressed the very important clinical question whether imatinib dosing interruption in the metastatic setting would have a detrimental effect on outcomes, or not. According to their results the

interruption of imatinib leads to a very rapid progression in most patients, thus such an approach is inappropriate, unless excessive toxicity occurs (49). There is some clinical benefit of increasing the dose of imatinib to 800 mg/day upon PD as some further disease control can be achieved in a third of the patients (50,51).

It must be noted that disease progression in the real-life setting might be due to the suboptimal pharmacological serum concentration of imatinib. A Cmin imatinib concentration of above 760 ng/mL was associated with a prolonged PFS (24).

It is highly debatable whether replacing imatinib (which has got an incredibly mild side effect profile) in the first line setting with a more toxic combination of several agents will ever be of clinical relevance. Nevertheless, there are attempts to explore whether alternating different, potent TKIs in the first line setting would be of any effect on delaying emergence of secondary resistance. The ongoing phase II, randomised, open-label ALT-GIST study evaluates the use of an alternating regimen of imatinib and regorafenib for the first-line treatment of advanced GIST (52).

Secondary imatinib resistance

Acquisition of *KIT* or *PDGFRA* secondary mutations represent the most frequent mechanism of imatinib resistance in GIST. Radiological evidence of clonal resistance can be detected as the appearance of one or more areas of increased vascularity within a previously responding or stable lesion. These lesions can precede by several months' PD according to RECIST (53). Secondary mutations are more likely to be found in patients who initially harboured *KIT* exon 11 mutations (73%) as compared to *KIT* exon 9 mutations (19%) (54).

Sunitinib and regorafenib have been approved for imatinib resistant GIST based on placebo controlled randomized Phase III trials (55,56).

Sunitinib is a potent multi-target (including *KIT and PDGFRA)* TKI licensed for second-line therapy after imatinib failure, given at 50 mg/day dose in 4 weeks on/2 weeks off treatment schedule (55). Unfortunately, the side effect profile of sunitinib is far less advantageous as compared to imatinib, leading to frequent dose reductions and treatment discontinuations. A continuously administered dosed daily oral regimen of 37.5 mg lower daily dose has proved itself as an effective and well tolerated alternative of administration, and can be supported as an on an individualized basis (57).

Primary mutational status has proved to be of a predictive value in the second line setting as well. Sunitinib treatment of KIT exon 9 mutants and KIT/PDGFRA WT-GISTs led to extended PFS and median OS as compared to other genotypes, including KIT exon 11 mutants. Secondary mutations had also a predictive value, whereas gatekeeper mutations in the *KIT* ATP-binding pocket were associated with increased sunitinib sensitivity. Activation loop mutations involving exon 17 *KIT* are mostly insensitive to sunitinib (54).

Regorafenib is another oral broad spectrum multi-target TKI that inhibits KIT and PDGFRA as well. In the licensing phase III trial a median PFS of 4.8 months was achieved for patients initially randomized to regorafenib compared with the placebo arm (HR 0.27, 95% CI: 0.19–0.39, P<0.0001). (56). Regorafenib proved to be efficacious in all genetic subtypes of GISTs including exon 9 and *PDGFRA* D842V mutants (58). Nevertheless, according to long-term follow-up results of a phase II trial *KIT* exon 11 mutant GISTs had an impressive median PFS of 13.4 months, while *KIT/PDGFRA* WT and SDH complex proficient tumors had a mere median PFS of 1.6 months (59).

In patients where the bulk of their metastatic disease is well controlled with a specific TKI and where there is solely unifocal PD detected, cytoreductive surgery can be considered as an alternative to changing course of systemic treatment. In a large two-institutional series of 400 operations the outcomes of cytoreductive surgery in unifocal progressors was similar to the expected efficacy of an eventual sunitinib switch (60).

BLU-285 is a mutation-specific inhibitor of kinases with mutations in *KIT* D816V and *PDGFRA* D842V, in which most TKIs are ineffective. The results of the dose escalation part of a phase I study were recently presented at the 2017 ASCO meeting and showed that BLU-285 is well tolerated on a QD schedule at doses up to the MTD of 400 mg and that its exposure at 300–400 mg QD provides broad coverage of primary and secondary *KIT/PDGFRA* mutants. BLU-285 has strong clinical activity in *PDGFRA* D842-mutant GISTs with an ORR of 60% per central review, whereas median PFS was not reached at the time of the report. It also demonstrates important anti-tumor activity including radiographic response and prolonged PFS in heavily pre-treated, *KIT*-mutant GISTs at doses of 300–400 mg QD (27). Based on these encouraging data, planning is underway for a phase III randomized study of

BLU-285 in third-line metastatic GISTs.

The oral small-molecule inhibitor crenolanib exhibits activity against FLT3 and the PDGFRs (including D842V-mutated kinase). In a phase II trial of metastatic *PDGFRA*-mutant GIST seven patients demonstrated objective response in one–and SD in three (28). A randomized, double-blind, placebo-controlled, multicenter, phase III trial of crenolanib in subjects with advanced or metastatic GIST with D842V mutation in the *PDGFRA* gene is ongoing (61).

DCC-2618, a potent pan-KIT and PDGFRα kinase switch control inhibitor has shown activity across a broad range of TKI treatment-emergent mutations. In a Phase I dose-escalation study of oral 150 mg daily DCC-2618 FDG-PET scans were performed at baseline and after 3 weeks of treatment during the escalation phase and computed tomography (CT) scans were done every 2 treatment cycles. DCC-2618 was well tolerated by patients. FDG PET scans showed that 22 of the 32 (69%) patients with *KIT* or *PDGFR* -mutant GIST had a partial metabolic response according to EORTC criteria. Of the 37 evaluable patients, 5 patients achieved partial response per RECIST. Fourteen of the 24 evaluable patients receiving DCC-2618 at doses of 100 mg/day demonstrated PFS lasting more than 6 months, including 9 patients on DCC-2618 at >cycle 10 (62). As DCC-2618 showed encouraging disease control in heavily pre-treated GIST patients demonstrating objective responses and achieving prolonged stable disease, a Phase III clinical study was opened to evaluate the safety and efficacy of DCC-2618 for treating patients with advanced GISTs. The INVICTUS randomised, double-blind, placebo-controlled, international, multicentre trial seeks to assess the tolerability of DCC-2618 compared to placebo in patients with advanced GIST whose previous therapies have included imatinib, sunitinib, and regorafenib (63). A second Phase III study is planned later this year evaluating DCC-2618 in second-line GIST patients who have progressed or are intolerant to front-line therapy with imatinib.

Conclusions

GISTs are the most common type of mesenchymal tumours of the digestive tract, mainly defined by the presence or lack of mutually exclusive gain-of-function mutations in the *KIT* and *PDGFRA* receptors. WT-GISTs are a rather heterogeneous group with no detectable mutation in either the *KIT* or the *PDGFRA* receptor genes. WT-GISTs can classified into two large groups, based on SDH complex proficiency. Detailed mutational analysis in alternative pathways helps further sub-classify WT-GISTs.

KIT exon 11 mutant patients are twice as likely to respond to imatinib than those with exon 9 mutant or WT-GISTs with a progression free and OS advantage as compared to all non-*KIT* exon 11 mutant GISTs. *KIT* exon 9 mutant GISTs are more likely to respond to the higher 800 mg dose of imatinib, and in the advanced setting patients can be started *ab ovo* on the higher dose. The *PDGFRA D842V* isoform with a substitution involving codon D842 in exon 18 is generally believed to lead to primary imatinib resistance. Caution should be exercised when it comes to therapeutic decisions as recent data suggests some response to imatinib in this subset of tumours.

While SDH-deficient 'pediatric-type' GISTs have been previously attributed absolute primary imatinib-resistance, most recent reports suggest imatinib responsiveness in SDHA-mutated tumours. Acquisition of secondary mutations in either *KIT* or *PDGFRA* represents the most frequent mechanism of imatinib resistance in GIST. Adjuvant therapy in "high risk" WT-GIST and the optimal systemic treatment for metastatic WT-GIST remain debatable 'hot topic' questions, with no clear-cut clinical guidelines.

Mutational analysis of GISTs holds an equally important predictive and prognostic value in the neoadjuvant, adjuvant and palliative treatment of the disease. Genetic profiling helps tailoring the best treatment and its' sequence, while also setting expectations of treatment response. Early enrolment into clinical trials needs to take priority in situations where efficacy of available treatment is highly questionable, saving the patient from unnecessary toxicity.

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Footnote

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