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Gastrointestinal stromal tumours: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up☆

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## **Gastrointestinal stromal tumours: ESMO–EURACAN–GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up†**

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**Highlights:**

- This Clinical Practice Guideline provides key recommendations on the management of gastrointestinal stromal tumours.
- Recommendations have been agreed following a consensus meeting of representatives from ESMO, EURACAN and GENTURIS.
- Authorship includes a multidisciplinary group of experts from several European institutions, India and Japan.
- ESCAT scores are given for genomic alterations with actionable drug matches.

## INTRODUCTION

Gastrointestinal stromal tumours (GISTs) are malignant mesenchymal tumours with a variable clinical behaviour, marked by differentiation towards the interstitial cells of Cajal.<sup>1</sup> GISTs belong to the family of soft tissue sarcomas (STSs) but are treated separately due to their peculiar histogenesis, clinical behaviour and specific therapy. This European Society for Medical Oncology (ESMO)–European Reference Network for Rare Adult Solid Cancers (EURACAN)–European Reference Network for Genetic Tumour Risk Syndromes (GENTURIS) Clinical Practice Guideline (CPG) will cover GISTs while other STSs are covered in the ESMO–EURACAN–European Reference Network for Paediatric Oncology (PaedCan)–GENTURIS STS CPG.<sup>2</sup>

## INCIDENCE AND EPIDEMIOLOGY

GISTs are the most common sarcomas in the gastrointestinal (GI) tract. They are rare tumours with significant variations in reported incidence (from 0.4 to 2 cases per 100,000 per year)<sup>3-5</sup> which are likely due to a number of factors; Firstly, there are methodological issues, as the diagnostic criteria improve over time, leading to variations in diagnosis and recording. Secondly, most established cancer registries record overt ‘malignant’ GIST cases. Most recent data suggest an incidence of about eight cases per million per year.<sup>3,4</sup> Importantly, the latest 2020 WHO Classification of STS and bone sarcoma codes all GISTs, regardless of size, site of origin and mitotic index, as malignant.<sup>1</sup> Thus, GIST epidemiological data may prove more reliable in the near future.

There is a slightly higher incidence of GIST in males. The median age is around 60-65 years, with a wide range. Occurrence in children is very rare. Paediatric GIST represents a clinically and molecularly distinct subset, marked by female predominance, absence of *KIT/PDGFRA* mutations, frequent mutations or silencing of the four genes that encode the subunits of the succinate dehydrogenase (SDH) enzyme complex, gastric multicentric location and possible lymph node metastases.<sup>6</sup>

In a minority of cases the following syndromes are linked to GISTs:

- Carney triad syndrome, marked by hypermethylation of *SDHC* gene of the SDH enzyme complex and clinically characterised by multifocal gastric GISTs,

paraganglioma and pulmonary chondromas (these may occur at different ages) with onset in the teenage and a female predominance.<sup>7</sup>

- Carney-Stratakis syndrome, marked by a germline mutation of one of the subunit (*A, B, C, D*) genes of the SDH enzyme complex and clinically characterised by a dyad of multifocal gastric GIST and paraganglioma, occurring from late teenage years to the 30s, with no gender predominance and lymph node metastatic potential.<sup>8,9</sup>
- Type 1 neurofibromatosis (NF1), marked by a germline mutation of the *NF1* gene, possibly leading to often multicentric GIST, predominantly located in the small bowel.<sup>10</sup>

Families with germ-line autosomal dominant mutations of *KIT* or *PDGFRA* are extremely rare, presenting with multiple GISTs at an early age, possibly along with other associated features. Pigmented skin macules, urticaria pigmentosa and diffuse hyperplasia of the interstitial cells of Cajal in the gut wall can be seen in *KIT* mutant cases,<sup>11</sup> while patients with germline *PDGFRA* mutations may have inflammatory fibroid polyps in addition to multiple gastric GISTs and hand deformities.<sup>12</sup>

## **DIAGNOSIS AND PATHOLOGY/MOLECULAR BIOLOGY**

When small submucosal gastric or duodenal nodules <2 cm in size are detected, endoscopic biopsy may be difficult and laparoscopic/open excision may be the only way to make a histological diagnosis. Many of these small nodules, if diagnosed as GISTs, will be either low-risk or very low-risk, and their clinical significance remains unclear. The standard approach for patients with oesophago-gastric or duodenal submucosal nodules <2 cm is endoscopic ultrasound (EUS) assessment. If biopsy is feasible and a diagnosis of GIST is made, resection should be performed, unless major morbidity is expected (i.e. oesophago-gastric junction, second portion of the duodenum on the medial aspect). Endoscopic resection, when a complete excision without tumour rupture is technically possible, could be an acceptable alternative to conventional full-thickness laparoscopic/open resections to minimise morbidity. As an option, however, patients can choose to undergo active surveillance, depending on site of origin of the tumour, age, life expectancy and comorbidities. Surgical excision could be reserved for patients whose tumour increases in size or becomes symptomatic [IV, C]. If a biopsy is not feasible or results in inadequate material for



diagnosis, active surveillance is generally recommended. As an option, patients can choose to undergo surgical/endoscopic resection also depending on age, life expectancy and comorbidities. When active surveillance is the choice, an evidence-based, optimal follow-up policy is lacking. A logical approach may be to have a short-term first assessment (e.g. at 3 months) and then, in the case of no evidence of growth, the follow-up interval can be increased.

Conversely, the standard approach to rectal nodules is represented by biopsy or excision after endorectal ultrasound assessment and pelvic magnetic resonance imaging (MRI), regardless of the tumour size and mitotic rate. In fact, the risk of progression to a clinically significant GIST at this site is higher than most gastric GISTs, its prognosis is significantly worse and the local implications for surgery are more critical.

The standard approach to tumours  $\geq 2$  cm in size is biopsy/excision because they are associated with a higher risk of progression if confirmed as GIST [IV, C]. If there is an abdominal nodule or a mobile mass in the abdominal cavity not amenable to endoscopic assessment, laparoscopic/open excision is the standard approach. If there is a large mass and surgery is likely to be a multivisceral resection, multiple core needle biopsies are the standard approach. They should be obtained through EUS guidance, or through an ultrasound/computed tomography (CT)-guided percutaneous approach. This may allow the surgeon to plan the best strategy according to the histological diagnosis, enable consideration of neoadjuvant treatment and avoid surgery for diseases for which it is not recommended (e.g. lymphomas, mesenteric fibromatosis and germ cell tumours). The risk of peritoneal contamination or bleeding is negligible if the procedure is properly carried out. Moreover, lesions at risk (e.g. cystic masses and/or mobile masses in the abdomen) should be assessed and biopsied only at specialised centres. Immediate laparoscopic/open excision is an option on an individualised basis, especially if surgery is associated with limited morbidity. If a patient presents with obvious metastatic disease, a biopsy of the metastatic focus (if easier to make in comparison to the primary tumour) is sufficient to establish the diagnosis and decide the treatment. The tumour sample should be fixed in 4% buffered formalin solution (Bouin fixative should not be used, since it prevents molecular analysis).

Pathologically, the diagnosis of GIST relies on morphology and immunohistochemistry, the latter typically being positive for CD117 (*KIT*) and/or DOG1 (Table 1).<sup>13,14</sup> A proportion of GISTs (in the range of 5%) are CD117-negative. The mitotic count has a prognostic value and should be expressed as the number of mitoses on a total area of 5 mm<sup>2</sup> [which should replace, and is equivalent to, the 50 high-power field (HPF) area, in order to avoid variability]. In terms of prognosis, mitotic count is a continuous variable and should therefore be expressed as such. This should also be taken into account when using risk classifications employing thresholds, which are highly artificial. Ki-67 analysis does not replace the mitotic count and is not part of established prognostic systems in this disease. Mutational analysis for known mutations involving *KIT* and *PDGFRA* can confirm the diagnosis of GIST, if doubtful (particularly in rare CD117/DOG1 immunohistochemically-negative GISTs). Mutational analysis has a predictive value for sensitivity to molecular-targeted therapy as well as a prognostic relevance. Its inclusion in the diagnostic work-up of all GISTs should be considered standard practice [II, A] (with the possible exclusion of <2 cm non-rectal GISTs, which are very unlikely ever to be candidates for medical treatment). Centralisation of mutational analysis in a laboratory enrolled in an external quality assurance programme and with expertise in the disease may be useful. Centralised pathological diagnosis is more strongly recommended for GISTs without typical molecular alterations. In rare cases, a *BRAF* mutation or an *NTRK* gene rearrangement may be found, which may have therapeutic implications<sup>15</sup>. In GISTs without detectable mutations in *KIT/PDGFRs*, immunohistochemistry for succinate dehydrogenase complex subunit B (SDHB) is done to identify SDH-deficient GIST. In quadruple-negative GIST (for *KIT/PDGFRs/BRAF/SDH*), an unrecognised underlying NF1 syndrome should be excluded. Even if formalin-fixed paraffin-embedded (FFPE) material allows routine molecular diagnostics, the collection of fresh snap-frozen tissue is encouraged, to allow subsequent molecular assessments, particularly in the context of research. Informed consent for tumour storage (adhering to local and international guidelines) should be sought, enabling later analyses and research.

Multidisciplinary treatment planning is needed, involving pathologists, radiologists, surgeons, medical oncologists, as well as gastroenterologists, nuclear medicine specialists, etc., as applicable. Management should be carried out at reference centres

for sarcomas and GISTs and/or within reference networks sharing multidisciplinary expertise and treating a high number of patients annually. These centres are involved in ongoing clinical trials, in which the enrolment of GIST patients is common practice.

### **Recommendations**

- EUS assessment is the standard approach for patients with oesophago-gastric or duodenal nodules <2 cm [IV, C].
- If a diagnosis of GIST is made on biopsy, resection is performed unless one expects major morbidity. If a biopsy is not feasible, active surveillance is a valid alternative [IV, C].
- Biopsy/excision is the standard approach to tumours  $\geq 2$  cm in size [IV, C].
- Mutational analysis inclusion in the diagnostic work-up of all GISTs should be considered standard practice [II, A] (with the possible exclusion of <2 cm non-rectal GISTs).

### **STAGING AND RISK ASSESSMENT**

The mitotic rate, tumour size and tumour site are important prognostic factors (gastric GISTs have a better prognosis than small bowel or rectal GISTs). Tumour rupture is an additional adverse prognostic factor and should be recorded, regardless of whether it took place before or during surgery. Mutational status has not been incorporated in any risk classification at present, although some genotypes have a distinct natural history<sup>16</sup> and, above all, GISTs without the most typical mutations have peculiar clinical presentations and course. Among mutated GISTs, those with a *PDGFRA* mutation corresponding to D842V are generally associated with a good prognosis. On the contrary, *KIT* exon 11 deletions involving codons 557-558 have been repeatedly reported to be associated with a high risk for relapse.<sup>17</sup>

The American Joint Committee on Cancer (AJCC)–Union for International Cancer Control (UICC) stage classification is rarely used, given the natural history of GISTs. On the contrary, several risk classifications have been proposed to assess the risk of relapse of a localised disease. A widely used risk classification was proposed by the Armed Forces Institute of Pathology, which incorporates the primary mitotic count, tumour size and tumour site, i.e. the three main prognostic factors in localised

GISTs.<sup>18,19</sup> A nomogram utilising all three criteria has been developed on another series.<sup>20</sup> When using these tools, it is important to appreciate that the mitotic index and tumour size are continuous variables, so that thresholds need to be interpreted wisely. Prognostic contour maps were generated through a pool of series of GIST patients not treated with adjuvant therapy, which incorporate the mitotic index and tumour size as continuous variables. In addition, tumour rupture is considered.<sup>21</sup> They have been validated against a reference series.<sup>22</sup> One should be aware that available risk classifications essentially refer to *KIT*-mutated GISTs.

Staging procedures are selected taking into account that most relapses affect the peritoneum and the liver. Triple phase contrast-enhanced abdominal and pelvic CT scan is the investigational method of choice for staging and follow-up. MRI may be an alternative procedure, especially for rectal GISTs, where MRI provides better preoperative staging information.<sup>23</sup> Chest CT scan and routine laboratory testing complement the staging work-up of new patients. The evaluation of fluorodeoxyglucose (FDG) uptake using an FDG-positron emission tomography (PET) scan, or FDG-PET–CT/MRI, may be useful mainly when early detection of the tumour response to molecular-targeted therapy is of special interest or when surgical resection of metastatic disease is considered.<sup>24</sup>

## **MANAGEMENT OF LOCAL/LOCOREGIONAL DISEASE**

The standard treatment of localised GISTs is a complete surgical excision of the lesion, with no dissection of clinically negative lymph nodes [III, A] (Figure 1). If a laparoscopic (including robotic) excision is planned, all principles of oncological surgery should be followed [III, A].<sup>25</sup> A laparoscopic/robotic approach is clearly discouraged in patients who have large tumours, because of the risk of tumour rupture, which is associated with a very high-risk of relapse.<sup>21,22</sup> For selected presentations (small tumours in the upper or lower GI tract), endoscopic excisions may be considered at sarcoma reference centres with experience in endoscopic surgery. In any case, R0 excision is the goal (i.e. an excision whose margins are clear of tumour cells at least at the site of origin in the GI tract). In low-risk GISTs located in unfavourable locations the decision can be made with the patient to accept possibly R1 (microscopically positive) margins [IV, B], given the lack of any formal demonstration that R1 surgery is associated with a worse overall survival (OS).<sup>26</sup> If R1

excision was already carried out, a re-excision is not recommended on a routine basis. Of note, the microscopic margin status should not be used to dictate adjuvant medical therapy decisions.<sup>26</sup>

Adjuvant treatment with imatinib for 3 years was associated with a relapse-free survival (RFS) and OS advantage in comparison with 1 year of therapy in high-risk patients in a randomised trial.<sup>27</sup> Previously, a placebo-controlled trial demonstrated that imatinib given for a planned duration of 1 year could prolong RFS in localised GISTs having a diameter  $\geq 3$  cm with a macroscopically complete resection.<sup>28</sup> Another study comparing adjuvant imatinib for 2 years against surgery alone also demonstrated an improvement in RFS in intermediate- and high-risk GISTs.<sup>29</sup> Therefore, adjuvant therapy with imatinib for 3 years is the standard treatment for patients with a significant risk of relapse [I, A; ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: A]. An individualised shared decision-making process is needed when the risk is intermediate (i.e. in the 30%-50% range)<sup>18,19,30,31</sup> and the risk assessment might be refined also through genotyping the specific *KIT* mutation. One should note that available efficacy data refers to high-risk patients.<sup>18,19,31</sup> Randomised clinical studies are ongoing to test durations of adjuvant therapy longer than 3 years.

The benefit associated with adjuvant imatinib may vary according to the type of *KIT/PDGFR*A mutation, being greater in patients with *KIT* exon 11 deletion mutations.<sup>31,32</sup> Mutational analysis predicts the sensitivity to molecular-targeted therapy as well as the prognosis. There is a consensus that *PDGFR*A D842V-mutated GISTs should not be treated with any adjuvant therapy, given the lack of sensitivity to imatinib of this genotype both *in vitro* and *in vivo* [IV, D], and the current lack of any evidence of efficacy in the adjuvant setting for agents now available active against *PDGFR*A-mutated GIST. Given the data supporting the use of a higher dose of imatinib (800 mg daily) in the case of a *KIT* exon 9 mutation in advanced GIST, some expert clinicians prefer to use this dose even in the adjuvant setting for this genotype [II, B; ESMO Scale for Clinical Accountability of molecular Targets (ESCAT) score: I-A].<sup>33-35</sup> Regulatory constraints may limit this practice of an adjuvant dose of 800 mg daily, which is currently not supported by any prospective evidence. A summary of genomic alterations and actionable drug matches in GISTs is provided in Table 2.

There is a consensus to avoid imatinib or any adjuvant treatment in NF1-related and SDH expression-negative GISTs [IV, D] as well as in *BRAF*-mutated or *NTRK*-rearranged cases. This reflects their lack of sensitivity to imatinib, sunitinib and regorafenib in the advanced setting. European and international cooperation would be vital to determine best practices in the exceedingly rare paediatric GIST.

Tumour rupture is an important adverse prognostic factor. It is defined as tumour spillage or fracture in the abdominal cavity, piecemeal resection, laparoscopic/open incisional biopsy, GI perforation to the abdominal cavity, blood-tinged ascites, or microscopic transperitoneal infiltration into an adjacent structure. In contrast, minor defects of tumour integrity (such as those caused by core needle biopsy), peritoneal tumour penetration, iatrogenic superficial tumour capsule laceration, or microscopically positive margins (R1) are not considered tumour rupture, as the outcome of these patients was shown to be similar to when the removed lesion is intact.<sup>36-38</sup>

In case of tumour rupture, micrometastatic disease can be assumed to exist. This puts the patient at a very high-risk of relapse.<sup>39</sup> Therefore, these patients should be considered for imatinib therapy [IV, A], even though the optimal duration of post-operative imatinib in this patient population is not defined given the uncertainty whether these cases should be considered as already metastatic.

If R0 surgery is not feasible, or it could be achieved through less mutilating, function-sparing surgery in the case of volumetric reduction (this includes total gastrectomy and all other major procedures), pre-treatment with imatinib is standard, as long as the mutation profile of the tumour is sensitive [III, A] (Figure 1).<sup>40, 41</sup> This may also be the case if the surgeon believes that the surgical resection is safer after cytoreduction (e.g. the risk of bleeding and tumour rupture is decreased). A shortcoming may be the lack of a reliable evaluation of mitotic count for accurate risk stratification on biopsy, thus making decisions regarding post-operative therapy challenging. Of note, the presence of bleeding or fistulas does not necessarily prevent neoadjuvant therapy. A biopsy including mutational analysis is recommended to confirm the histological diagnosis and to exclude less sensitive or resistant genotypes to imatinib and the possible choice

of an 800 mg imatinib dose for *KIT* exon 9 mutations.<sup>42</sup> In case of *PDGFRA*-D842V mutations, the use of preoperative avapritinib may be considered [III, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-B]. Surgeons should be actively involved to optimally monitor the patient during cytoreductive treatment and to choose when to carry out surgery, depending on when the treatment goal is achieved. In general, surgery is carried out after 6-12 months of treatment, as after the 12-month time point further shrinkages are rare, while secondary resistance may develop subsequently. Early tumour response assessment is required to avoid delaying surgery in the case of non-responding disease. Functional imaging makes it possible to assess the tumour response very rapidly, within a few weeks, particularly in the absence of mutational analysis. There are limited data to guide the physician on when to stop imatinib before surgery; however, it can be safely stopped a few days or even one day before surgery, to be resumed promptly when the patient recovers from surgery, in order to reach a total of 3 years of treatment.

### **Recommendations**

- The standard treatment of localised GISTs is complete surgical excision of the lesion, with no dissection of clinically negative lymph nodes [III, A]. R0 excision is the goal (i.e. an excision whose margins are clear of tumour cells at least at the site of origin in the GI tract).
- If laparoscopic excision is planned, the technique needs to follow the principles of oncological surgery [III, A].
- In low-risk GISTs located in unfavourable locations the decision can be made with the patient to accept possibly R1 (microscopically positive) margins [IV, B].
- Adjuvant therapy with imatinib 400 mg/day for 3 years is the standard treatment for patients with a significant risk of relapse [I, A; ESMO-MCBS v1.1 score: A].
- In the case of *KIT* exon 9 mutation, adjuvant imatinib at a higher dose of 800 mg daily for 3 years may be considered [II, B; ESCAT score: I-A].
- *PDGFRA* exon 18 *D842V*-mutated GISTs should not be treated with adjuvant therapy [IV, D].
- Adjuvant treatment should be avoided in NF1-related and SDH expression-negative GISTs [IV, D].

- Patients at a very high-risk of relapse due to tumour rupture at the time of surgery should be considered for adjuvant imatinib therapy [IV, A].
- If R0 surgery is not feasible or implies major sequelae and the tumour harbours a sensitive mutation, preoperative treatment with imatinib is standard [III, A]. In case of *PDGFRA*-D842V mutation, neoadjuvant avapritinib may be considered [III, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-B].

## MANAGEMENT OF ADVANCED/METASTATIC DISEASE

Imatinib is the standard treatment for locally-advanced, inoperable and metastatic patients [I, A] (Figure 2),<sup>43-46</sup> including patients previously treated with adjuvant imatinib who did not relapse while receiving it. Imatinib is also the standard treatment for metastatic patients who have had all lesions removed surgically, although surgery is not recommended as a primary approach in the metastatic setting. The standard dose of imatinib is 400 mg daily [I, A]. However, some data suggest that patients with tumours harbouring a *KIT* exon 9 mutation have a significantly higher response rate and better progression-free survival (PFS) on a higher dose level, i.e. 800 mg daily, which is therefore held as standard treatment in this subgroup [III, B; ESCAT score: I-A].<sup>42</sup> Patients with a *PDGFRA* exon 18 D842V mutation are generally insensitive to imatinib<sup>47</sup>. They have now shown sensitivity to avapritinib, which targets this mutation [III, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-B].<sup>48</sup> Avapritinib is able to provide a >90% response rate, with a duration of response in excess of 70% at 1 year. *PDGFRA* mutations other than exon 18 D842V are sensitive to imatinib and are thus best treated with this agent. Important adverse events of avapritinib are neurocognitive toxicity, brain bleeds, and seizures, which need to be recognised early in order to minimise risks that they may undermine treatment continuation.

With regard to SDH-deficient GIST, there may be some benefit from available TKIs, with reports of activity of sunitinib and regorafenib.<sup>49</sup> Other agents are under study, including temozolomide, with interesting preliminary results.<sup>50</sup>

Patients with GIST with *NTRK* re-arrangement are known to have been sensitive to treatment with neurotrophic tyrosine receptor kinase (NTRK) inhibitors such as larotrectinib and entrectinib [III, A; ESMO-MCBS v1.1. score: 3; ESCAT score: I-C].<sup>51</sup>



GIST with *BRAF* mutations may benefit from BRAF inhibitors (including BRAF and MEK inhibitor combinations).<sup>53</sup> This is an off-label indication justified by biological plausibility [V, B; ESCAT score: III-A].<sup>52</sup>

In the metastatic setting, treatment with imatinib should be continued indefinitely, until clinically relevant disease progression or intolerance, since treatment interruption is generally followed by relatively rapid tumour progression, even when lesions have been previously excised surgically [I, A].<sup>54</sup> The patient should be informed about the importance of complying with imatinib therapy, as well as interactions with concomitant medications and food, and the best ways to handle side-effects. Dose intensity should be maintained by proper management of side-effects, and a correct policy of dose reductions and interruptions should be applied in the case of excessive, persistent toxicity. Aside from its potential use to tailor the imatinib dose, assessment of plasma levels may be useful in the case of: (i) patients receiving concomitant medications that put them at a risk of major interactions or patients with previous surgical resections potentially leading to decrease plasma levels; (ii) unexpected toxicities; and (iii) unexpected inadequate response in sensitive genotypes. Currently, evaluation of imatinib plasma levels are not part of the routine care of GIST patients.

Close monitoring of tumour response should be carried out in the early phases of treatment. Follow-up should be continued throughout treatment, since the risk of secondary progression persists over time. Complete excision of residual metastatic disease has been shown to be associated with a good prognosis, provided the patient is responding to imatinib, but it has never been demonstrated prospectively whether this is due to surgery or to patient selection.<sup>55-58</sup> Randomised trials did not prove feasible (being stopped early because of slow accrual), except for a low-power positive trial in which all patients had peritoneal disease.<sup>59</sup> Thus, the surgical decision should be individualised and shared with the patient [III, C]. Surgical excision of progressing disease has not been beneficial in published retrospective series, but surgery of focal progression, such as the 'nodule within a mass', up to one or few nodules/masses when the rest of the disease is still responding, has been associated with a PFS in the same range as for any further-line treatment. Therefore, this may be an option for the individual patient with limited progression, while continuing imatinib at the same dose

[IV, C]. Non-surgical procedures (e.g. local treatment, such as ablations or radiotherapy) may be selected. In the case of tumour progression on 400 mg, an option may be to increase the imatinib dose to 800 mg daily (if treated with the lower dose) [III, B], with the exception of insensitive mutations.<sup>43-46</sup> Dose escalation is particularly useful in the case of a *KIT* exon 9 mutated GIST (if a higher dose was not selected from the beginning) and possibly in the case of fluctuations in drug pharmacokinetics over time. False progression on imaging should be ruled out due to the response patterns (see Response evaluation). Also, patient non-compliance should be ruled out as a possible cause of tumour progression, as well as drug interactions with concomitant medications.

In the case of confirmed progression or rare intolerance on imatinib (after attempts to manage side-effects through expert advice, exploiting dose reductions and possibly plasma level assessment), standard second-line treatment is sunitinib [I, A; ESMO-MCBS v1.1 score: 3].<sup>60</sup> The drug was proven effective in terms of PFS when administered at the dose of 50 mg daily following a '4 weeks on/2 weeks off' regimen. Data have shown that a continuously-dosed daily oral regimen with a lower daily dose (37.5 mg) is effective and well tolerated, although no formal comparison has been carried out within a randomised clinical trial <sup>61</sup>. This schedule can therefore be considered an option [III, C].

After confirmed progression on sunitinib, a prospective placebo-controlled, randomised trial proved that regorafenib, at the dose of 160 mg daily for three out of every four weeks, can prolong PFS. This therapy is therefore standard third-line therapy for patients progressing on or failing to benefit from imatinib and sunitinib [I, A; ESMO-MCBS v1.1 score: 3].<sup>62</sup>

In a prospective, randomised trial patients with metastatic disease progressing on standard therapy (imatinib, sunitinib and regorafenib) were shown to benefit from ripretinib [I, A; ESMO-MCBS v1.1 score: 3].<sup>63</sup>

Patients with metastatic GIST should be considered for participation in clinical trials of new therapies or combinations. There is controlled evidence that patients who have already progressed on imatinib may benefit when re-challenged with the same drug.<sup>64</sup>

Likewise, there is evidence that continuing a treatment with a TKI, even in the case of progressive disease, may slow down progression as opposed to stopping it (if no other option is available at the time), at least in a proportion of patients with a slow progression. Therefore, a re-challenge with imatinib (to which the patient has already been exposed) or continuation of the ongoing therapy beyond progression are options [II, B]. On the other hand, the use of combinations of TKIs outside of clinical studies should be discouraged, because of the potential for considerable toxicity.

Several TKIs have been tested in uncontrolled phase II trials in imatinib-resistant patients, with activity observed in some of them.<sup>65,66</sup>

Radiation therapy may be considered as a palliative resource for selected patients.

### **Response evaluation**

Response evaluation is complex, and early progression should be confirmed by an experienced team. Anti-tumour activity translates into tumour shrinkage in most patients, but some patients may show changes only in tumour density on CT scan, or these changes may precede delayed tumour shrinkage. These changes in tumour radiological appearance should be considered as pointing to a tumour response. Even an initial increase in the tumour size may be indicative of a tumour response if the tumour density on CT scan is decreased.<sup>67</sup> The 'appearance' of new lesions could also be due to the ease in detecting less dense tumours. Therefore, both tumour size and tumour density on CT scan, or consistent changes in MRI or contrast-enhanced ultrasound, should be considered as criteria for tumour response. An FDG-PET scan has proven to be highly sensitive in early assessment of tumour response and may be useful in cases where there is doubt, or when early prediction of the response is particularly useful (e.g. preoperative cytoreductive treatments).<sup>47</sup> However, a small proportion of GISTs have no FDG uptake. The absence of tumour progression after 6 months of treatment is also considered as tumour response.<sup>68</sup> On the other hand, tumour progression may not be accompanied by changes in the tumour size. In fact, some increase in the tumour density within tumour lesions may be indicative of tumour progression. A typical progression pattern is the 'nodule within the mass', by which a portion of a responding lesion becomes hyperdense.<sup>69</sup>

## **Recommendations**

- Imatinib is the standard first-line treatment for locally-advanced, inoperable and metastatic patients, except for GIST without KIT/PDGFR<sub>A</sub> mutations or with a *PDGFR<sub>A</sub>* exon 18 D842V mutation [I, A]. The standard dose of imatinib is 400 mg daily [I, A].
- Imatinib is also the standard treatment for metastatic patients who have had all lesions removed surgically and the tumour harbours a sensitive genotype, although surgery is not recommended as a primary approach in the metastatic setting [I, A].
- Standard first-line treatment for patients with *KIT* exon 9 mutation is imatinib 800 mg daily [III, B; ESCAT score: I-A].
- Standard first-line treatment for patients with *PDGFR<sub>A</sub>* exon 18 D842V mutations is avapritinib 300 mg daily [III, A; ESMO-MCBS v1.1. score: 3; ESCAT score: I-B].
- In the metastatic setting, treatment should be continued indefinitely, unless intolerance or specific patient request to interrupt [I, A]. Surgery of residual metastatic disease should be individualised [III, C].
- Surgical excision of progressing disease should be considered for an individual patient with limited progression, while continuing imatinib [IV, C].
- In the case of tumour progression on 400 mg of imatinib, the dose can be increased to 800 mg daily (with the exception of insensitive mutations) [III, B].
- In the case of confirmed progression or rare intolerance on imatinib, standard second-line treatment is sunitinib 50 mg daily 4 weeks on/ 2 weeks off or, as alternative schedule, 37.5 mg once daily [I, A; ESMO-MCBS v1.1 score: 3].
- Regorafenib, at the dose of 160 mg daily for three out of every four weeks, is the standard third-line therapy for patients progressing on or failing to respond to imatinib and sunitinib [I, A; ESMO-MCBS v1.1 score: 3].
- Ripretinib at the dose of 150 mg daily is the standard fourth-line treatment in patients progressing or intolerant to imatinib, sunitinib, regorafenib [I, A; ESMO-MCBS score v1.1 score: 3].
- SDH-deficient GISTs are insensitive to imatinib and can have some sensitivity to sunitinib and regorafenib [III, B].

- *NTRK*-re-arranged GISTs are sensitive to treatment with NTRK inhibitors [III, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-C].
- *BRAF*-mutated GISTs benefit from BRAF inhibitors (including BRAF MEK inhibitor combinations) [V, B; ESCAT score: III-A].
- Rechallenge with imatinib (to which the patient has already been exposed with evidence of response) or continuation of treatment beyond progression is an option [II, B].
- Radiation therapy may be considered as a palliative resource for selected patients [V, B].

### **FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP**

There are no published data to indicate the optimal routine follow-up policy for surgically treated patients with localised disease. Relapses occur more often to the liver and/or peritoneum. Bone lesions and other sites of metastases may be less rare along the course of metastatic disease treated with several lines of therapy. The mitotic rate likely affects the speed at which relapses take place. Risk assessment based on the mitotic count, tumour size and tumour site may be useful in choosing the routine follow-up policy. High-risk patients often have a relapse within 1-3 years from the end of adjuvant therapy. Low-risk patients may have a relapse later.

Routine follow-up schedules differ across institutions. The optimal follow-up schedules are not known. As an example, at some institutions, high-risk patients undergo a routine follow-up with an abdominal CT scan or MRI every 3-6 months for 3 years during adjuvant therapy (with a tighter clinical follow-up due to the need to manage the side-effects of adjuvant therapy), unless contraindicated, then on cessation of adjuvant therapy every 3 months for 2 years, then every 6 months until 5 years from stopping adjuvant therapy, and annually for an additional 5 years.<sup>70</sup>

For low-risk tumours, the usefulness of a routine follow-up is not known; if selected, this may be carried out with abdominal CT scan or MRI, e.g. every 6-12 months for 5 years.

Very low-risk GISTs probably do not require routine follow-up, although the risk is not zero. X-ray exposure is a factor to consider, especially in low-risk GIST, with abdominal MRI being an alternative.<sup>71</sup>

## **METHODOLOGY**

This CPG has been developed by ESMO in partnership with EURACAN and GENTURIS during a virtual consensus meeting which was held on 5th December 2020. The CPG was developed in accordance with the ESMO standard operating procedures for CPG development <http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology>. Recommended interventions are intended to correspond to the 'standard' approaches for diagnosis, treatment and survivorship on GISTs, according to current consensus among the European and worldwide multidisciplinary sarcoma community of experts. This community was represented by the members of the ESMO Sarcoma Faculty and experts appointed by all institutions belonging to the sarcoma domain of EURACAN–GENTURIS. Experimental interventions considered to be beneficial are labelled as 'investigational'. Other non-standard approaches which may be proposed to the single patient are labelled as 'options' for a shared patient–physician decision in conditions of uncertainty, as long as some supporting evidence (though not conclusive) is available. Algorithms accompanying these guidelines, covering the main typical presentations of disease, are meant to guide the user throughout the text. The relevant literature has been selected by the expert authors. An ESMO-MCBS table with ESMO-MCBS scores is included in Supplementary Table S1. ESMO-MCBS v1.1<sup>72</sup> was used to calculate scores for new therapies/indications approved by the European Medicines Agency (EMA) since 1 January 2016 or the Food and Drug Administration (FDA) since 1 January 2020 (<https://www.esmo.org/guidelines/esmo-mcbs>). The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S2.<sup>73</sup> ESCAT scores have been defined by the authors and validated by the ESMO Translational Research and Precision Medicine Working Group. Statements without grading were considered justified standard clinical practice by the experts.

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Advenchen Laboratories, Novartis, Karyopharm, Blueprint medicines, GEIS and other activity for EORTC; JMB has received honoraria for expert testimony for Lilly, PharmaMar, Eisai, Bayer, invited speaker fee from PharmaMar, Institutional research for PharmaMar, Eisai, Novartis, Immix Biopharma, Lixte, Karyopharm, Bayer, Celgene, Pfizer, BMS, Blueprint Medicines, Deciphera, Nektar Therapeutics, Forma, Amgen, Daiichi-Sankyo, Lilly, AROG Pharmaceuticals, Adaptimmune and GSK; OM has received honoraria for participation in advisory boards for MSD, Megapharm, AstraZeneca, Takeda and Progenetics, invited speaker fees from MSD and Roche; CM has performed non-remunerated activities for International Cancer Imaging Society and EORTC STBSG; OMi has received honoraria for participation in advisory boards for Bayer, Blueprint Medicines, MSD, Pfizer, invited speaker fees from BMS, Eli-Lilly, Ipsen, Roche and Servier, institutional research for Blueprint Medicines, Bayer, Epizyme and Eli-Lilly; EP has received honoraria for participation in advisory boards for SynOx, Daiichi-Sankyo and Deciphera Pharmaceuticals and invited speaker fees from Peer View Educational; MAP has received honoraria for participation in advisory boards for Roche, invited speaker fees from Eli-Lilly, Pfizer, and Novartis, expert testimony from Blueprints Medicine and institutional research grant from Novartis; SPN has received honoraria for participation in advisory board for Immunocore; PR has received honoraria for participation in advisory boards for Bayer, Clinigen, Roche, MSD, Deciphera, Mundibiopharma, PharmaMar, Blueprint Medicines, invited speaker fees from Lilly, PharmaMar, institutional research for PharmaMar, Karyopharm, SpringWorks, AROG Pharmaceuticals, Blueprint, Deciphera, Amgen, Astellas, Epizyme, Lilly, MSD, Pfizer, Novartis and Philogen, membership of German Sarcoma Foundation; PRu has received honoraria for participation in advisory boards for MSD, BMS, Pierre Fabre, Merck, Sanofi, Blueprint Medicines, invited speaker fees from MSD, BMS, Pierre Fabre, Merck, Sanofi, Novartis, institutional research funding from Pfizer, BMS and non-remunerated activities for the Polish Society of Surgical Oncology and ASCO; MS has received honoraria for travel grant from PharmaMar and writing engagement for Lilly; SS has reported a research grant from Johnson & Johnson and research funding from Roche Austria; PS has received honoraria for participation in advisory boards for Deciphera, Blueprint Medicines, Boehringer Ingelheim, Ellipses Pharma, Transgene, Exelixis, Medscape, Guided Clarity, Ysios, Modus Outcomes, Studiecentrum voor Kernenergie, Curio Science, institutional honoraria for advisory

boards for Blueprint Medicines, Ellipses Pharma, Intellisphere, expert testimony for Advanced Medical/Teladoc Health, institutional research funding from CoBioRes NV, Eisai, G1 Therapeutics, Novartis and PharmaMar; SSI Chair of Centre for Personalised Cancer Treatment and Route Personalised Medicine, Dutch Science Agenda, Member of supervisory board for SkylineDX and Scientific advisory committee Pan-Cancer T BV; SJS has received honoraria for participation in advisory board for GSK; KSH reports non-remunerated activity for CTOS as President 2020 and membership of the Scandinavian Sarcoma Group; MAJvdS has performed work in clinical trials or contracted research for which the institution received financial support from Daiichi Sankyo, Implantcast and Carbofix; WTAvdG has received institutional honoraria for participation in advisory boards of Bayer and GSK, institutional research grants from Novartis and Lilly. Consultancy work for SpringWorks; WJvH has received institutional honoraria for participation in advisory board for Belpharma, invited speaker fees from Amgen, expert testimony for Sanofi and MSD, personal travel grant from Novartis and institutional research grant from BMS; TF Reported institutional research funding from the Foundation ARC and Ligue Régionale contre le Cancer, leadership role for ERN GENTURIS (1<sup>st</sup> December DOI details from DOI form); AG has received honoraria for participation in advisory boards for Novartis, Pfizer, Bayer, Lilly, PharmaMar, SpringWorks and Nanobiotix, invited speaker for Lilly, PharmaMar and research grant from PharmaMar; SSta has received honoraria for participation in advisory boards for Bayer, Deciphera, Eli Lilly, Daiichi, Maxivax, Novartis, invited speaker fees from GSK and PharmaMar, expert testimony fee from Bavarian Nordic and Epizyme, institutional research funding from Amgen Dompé, Advenchen, Bayer, Blueprint Medicines, Deciphera, Eli Lilly, Epizyme, Daiichi, GSK, Karyopharm, Novartis, Pfizer, PharmaMar, SpringWorks and Hutchinson MediPharma International Inc., non-remunerated activities for CTOS, Chordoma Foundation, Epithelioid Haemangioendothelioma Foundation, Desmoid Foundation, EORTC STBSG and Italian Sarcoma Group Onlus; AB, AD, AFer, AMF, PJ, DAK, FLG, ABM, MM, CMo, RP, AAS, CS, DS, AT and MU have declared no conflicts of interests.

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**Table 1. Personalised medicine synopsis**

<b>Biomarker</b>	<b>Method</b>	<b>Use</b>	<b>LoE</b>	<b>GoR</b>
Mitotic index	Pathology	Disease classification Prognostic relevance Used for medical treatment decisions	IV	A
<i>KIT</i> mutations	Sanger sequencing or NGS	Disease classification Prognostic relevance Predictive relevance Used for medical treatment decisions Currently actionable/targetable	I	A
<i>PDGFRA</i> mutations	Sanger sequencing or NGS	Disease classification Prognostic relevance Predictive relevance Used for medical treatment decisions Currently actionable/targetable	I/III	A
<i>NTRK</i> mutations	Sanger sequencing or NGS	Disease classification Predictive relevance Used for medical treatment decisions Currently actionable/targetable	III	A
<i>BRAF</i> mutations	Sanger sequencing or NGS	Disease classification Predictive relevance Used for medical treatment decisions Currently actionable/targetable	V	B
<i>SDH</i> mutations/epimutations	IHC	Disease classification Prognostic relevance Predictive relevance Used for medical treatment decisions	I	A

GoR, grade of recommendation; IHC, immunohistochemistry; LoE, level of evidence; NGS, next generation sequencing; PDGFRA, platelet-derived growth factor receptor alpha; SDH, succinate dehydrogenase.

**Table 2. Genomic alterations and actionable drug matches**

<b>Genomic alteration</b>	<b>Drug match</b>	<b>ESCAT score<sup>a,b</sup></b>
<i>KIT</i> mutations	Adjuvant imatinib	I-A <sup>33-35</sup>
<i>PDGFRA</i> D842V mutations	Preoperative avapritinib	I-B <sup>48</sup>
<i>NTRK</i> re-arrangements	NTRK inhibitors (e.g. larotrectinib, entrectinib)	I-C <sup>51</sup>
<i>BRAF</i> mutations	BRAF inhibitors (including BRAF–MEK inhibitor combinations) <sup>c</sup>	III-A <sup>c53</sup>

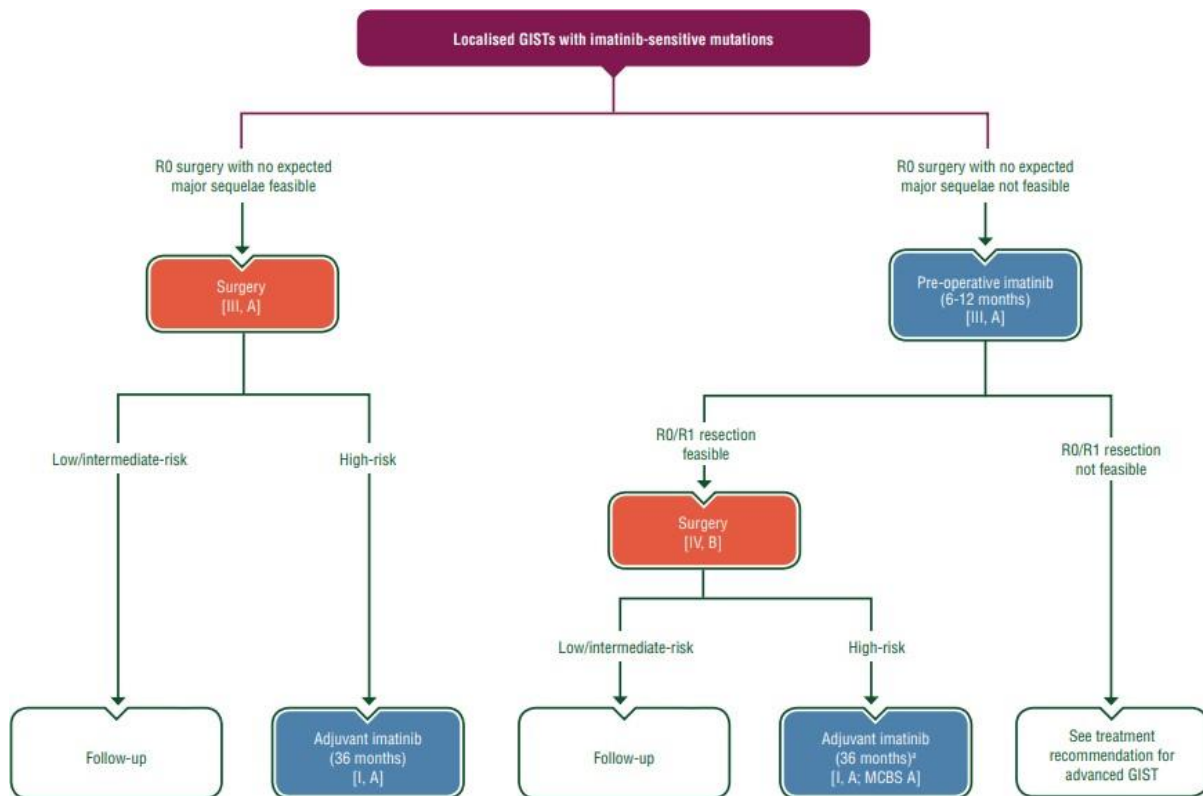
BRAF, v-raf murine sarcoma viral oncogene homolog B1; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; MCBS, ESMO-Magnitude of Clinical Benefit Scale; NTRK, neurotrophic tyrosine receptor kinase; PDGFRA, platelet-derived growth factor receptor alpha.

<sup>a</sup> ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.

<sup>b</sup> I-A, alteration–drug match is associated with improved outcome with evidence from randomised clinical trials showing the alteration–drug match in a specific tumour type results in a clinically meaningful improvement of a survival end point; I-B, alteration–drug match is associated with improved outcome with evidence from prospective, non-randomised clinical trials showing that the alteration–drug match in a specific tumour type, results in clinically meaningful benefit as defined by ESMO MCBS 1.1; I-C, alteration–drug match is associated with improved outcome with evidence from clinical trials across tumour types or basket clinical trials showing clinical benefit associated with the alteration-drug match, with similar benefit observed across tumour types; III-A, alteration–drug match is suspected to improve outcome based on patients with the specific alteration but in a different tumour type, with limited/absence of clinical evidence available for the patient-specific cancer type or broadly across cancer types.<sup>52</sup>

<sup>c</sup> This is an off-label indication justified by biologic plausibility.

**Figure 1: Treatment algorithm for localised GISTs with imatinib-sensitive mutations.**

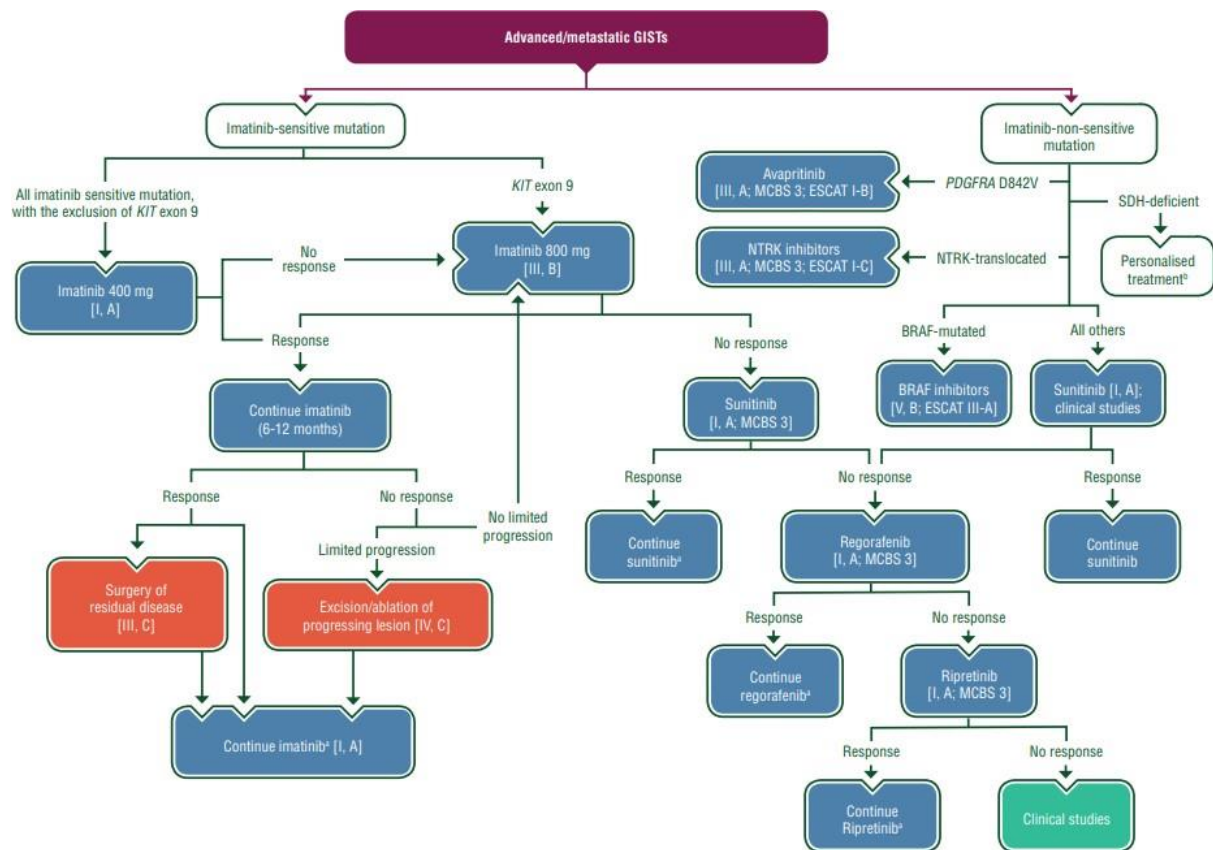


Purple: general categories or stratification; red: surgery; white: other aspects of management; blue: systemic anticancer therapy.

GIST, gastrointestinal stromal tumours; MCBS, ESMO-Magnitude of Clinical Benefit Scale.

<sup>a</sup> 36 months overall, considering adjuvant and neoadjuvant imatinib when preoperative imatinib is given.

**Figure 2: Treatment algorithm for advanced/metastatic GISTs.**



Purple: general categories or stratification; red: surgery; turquoise: combination of treatments or other systemic treatments; white: other aspects of management; blue: systemic anticancer therapy.

BRAF, v-raf murine sarcoma viral oncogene homolog B1; ESCAT, ESMO Scale for Clinical Accountability of molecular Targets; GIST, gastrointestinal stromal tumour; MCBS, ESMO-Magnitude of Clinical Benefit Scale; NTRK, neurotrophic tyrosine receptor kinase; SDH succinate dehydrogenase.

<sup>a</sup> Until progression.

<sup>b</sup> Refer to text

**Gastrointestinal stromal tumours: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up**

**SUPPLEMENTARY MATERIAL**

**Supplementary Table S1. ESMO-MCBS Table for Gastrointestinal stromal tumours**

<b>Therapy</b>	<b>Disease setting</b>	<b>Trial</b>	<b>Control (median)</b>	<b>Absolute survival gain</b>	<b>HR (95% CI)</b>	<b>QoL/ Toxicity</b>	<b>MCBS score<sup>a</sup></b>
Avapritinib	Treatment of adult patients with unresectable or metastatic GIST harbouring the platelet-derived growth factor receptor alpha D842V mutation	A phase I study of BLU-285 in patients with GIST and other relapsed and refractory solid tumours (NAVIGATOR) <sup>1</sup>  Phase I  NCT02508532	Single arm	ORR: 88%  DoR: 70% 12 months+			3 (Form 3)



Entrectinib	Treatment of patients with locally advanced or metastatic cancer whose solid tumours have a neurotrophic tyrosine kinase gene fusion	An open-label, multicenter, global phase 2 basket study of entrectinib for the treatment of patients with locally advanced or metastatic solid tumors that harbor NTRK1/2/3, ROS1, or ALK gene rearrangements (STARTRK-2) <sup>2</sup>  Phase II  NCT02568267	Single arm  PFS control: 11.2 months	ORR gain: 57% DoR gain: 10.4 months			3 (Form 3)
Imatinib	Treatment of adult patients with unresectable or metastatic <i>KIT</i> - positive GIST	Open, randomized, phase II study in patients with unresectable or metastatic gastrointestinal stromal tumors expressing c-kit plus 10-year extension Study (B2222) <sup>3,4</sup>  Phase II  NCT00237185	Single arm  TTP control: 24 months  OS control: 57 months	ORR gain: 68% DoR gain: 29.0 months			4 (Form 3)

Imatinib 3- years	Adjuvant for high-risk GIST patients with <i>KIT</i> -positive GIST removed at surgery	Short (12 Months) versus long (36 months) duration of adjuvant treatment with the tyrosine kinase inhibitor imatinib mesylate of operable GIST with a high risk of recurrence (SSG XVIII) <sup>5,6</sup>  Phase III  NCT00116935	Imatinib 1- year  5-years RFS control: 52.0%	5-years RFS gain: 18.8%	RFS HR: 0.60 (0.44-0.81)		A (Form 1)
Larotrectinib	Refractory NTRK fusion-positive cancers	A phase 2 basket study of the oral TRK inhibitor larotrectinib in subjects with NTRK fusion-positive tumours <sup>7</sup>  Phase II  NCT02576431	Single arm	RR gain: 75% (independent review)  DoR gain: 9+ months			3 (Form 3)

Regorafenib	Third-line after imatinib and sunitinib –patients with histologically confirmed, metastatic or unresectable GIST, with failure of at least previous imatinib and sunitinib	A study of regorafenib plus best supportive care versus placebo plus best supportive care for subjects with metastatic and/or unresectable GIST whose disease has progressed despite prior treatment with at least imatinib and sunitinib (GRID) <sup>8</sup>  Phase III  NCT01271712	Placebo plus best supportive care (crossover allowed)  PFS control: 0.9 months	PFS gain: 3.9 months	PFS HR: 0.27 (0.19-0.39)		3 (Form 2b)
Ripretinib	Treatment for adult patients with advanced GIST who have received prior treatment with three or more kinase inhibitors, including imatinib	A study to assess the safety and efficacy of DCC-2618 in patients with advanced GIST who have received prior anticancer therapies (INVICTUS) <sup>9</sup>  Phase III  NCT03353753	Placebo (crossover allowed)  PFS control: 1.0 months  Median OS: 6.6 months	PFS gain: 5.3 months  OS gain: 8.5 months	PFS HR: 0.15 (0.09-0.25)  OS HR: 0.36 (0.21-0.62) <sup>b</sup>		3 (Form 2b)

Sunitinib	Advanced GIST second-line after imatinib	A study of SU011248 in the treatment of patients with imatinib mesylate (resistant or intolerant, malignant GIST) <sup>10</sup>  Phase III  NCT00075218	Placebo (crossover allowed)  TTP control: 6.4 weeks	TTP gain: 20.9 weeks	TTP HR: 0.33 (0.23-0.47)		3 (Form 2b <sup>c</sup> )
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CI, confidence interval; DoR, duration of response; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; GIST; Gastrointestinal Stromal Tumours ;HR, hazard ratio; NCT, National Clinical Trial; NTRK, neurotrophic tyrosine receptor kinase; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; RFS, relapse free survival; TTP, time to progression.

<sup>a</sup> ESMO-MCBS version 1.1.<sup>11</sup> The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee. <https://www.esmo.org/guidelines/esmo-mcbs/scale-evaluation-forms-v1.0-v1.1>.

<sup>b</sup> Owing to the hierarchal testing procedure of the endpoints, overall survival could not be formally tested for statistical significance because the objective response was not significant.

<sup>c</sup> Scoring of TTP on the same basis as PFS.

**Supplementary Table S2. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System<sup>a</sup>)**

**Levels of evidence**

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions

**Grades of recommendation**

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

<sup>a</sup> Reprinted by permission of Oxford University Press on behalf of the Infectious Diseases Society of America.<sup>12</sup>

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