National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Gastrointestinal Stromal Tumors

Version 2.2024 — July 31, 2024

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NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

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National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Gastrointestinal Stromal Tumors

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NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

Updates in Version 2.2024 of the NCCN Guidelines for Gastrointestinal Stromal Tumors from Version 1.2024 include:

GIST-E 1 of 4
- Neoadjuvant therapy for resectable disease with significant morbidity
  - *NTRK* gene fusion-positive: Repotrectinib added as a category 2B, Useful in Certain Circumstances recommendation

GIST-E 2 of 4
- First-line and second-line (if not previously given) therapy
  - *NTRK* gene fusion-positive: Repotrectinib added as a category 2A, Useful in Certain Circumstances recommendation

GIST-E 3 of 4
- Reference added: Solomon BJ, Drilon A, Lin JJ, et al. Repotrectinib in patients (pts) with NTRK fusion-positive (NTRK +) advanced solid tumors, including NSCLC: Update from the phase I/II TRIDENT-1 trial. Annals of Oncology 2023;34:S787-S788.

Updates in Version 1.2024 of the NCCN Guidelines for Gastrointestinal Stromal Tumors from Version 1.2023 include:

GIST-1

Workup at Primary Presentation

Footnotes:
- e, modified: Mutational analysis may predict response to therapy with tyrosine kinase inhibitors (TKIs) (See GIST-B). *Tumors with succinate dehydrogenase (SDH) deficiency or NF1 mutations that lack mutations in KIT/PDGFRA may be considered for observation as most, but not all, have more indolent behavior* (also for GIST-2, GIST-3, and GIST-4).

GIST-2

Footnotes:
- p, modified: *FDG*-PET/CT may give indication of imatinib efficacy after 2–4 weeks of therapy when rapid readout of activity is necessary. ~~Diagnostic abdominal/pelvic CT or MRI with contrast is indicated every 8–12 weeks; routine long-term PET/CT follow-up is rarely indicated~~. Frequency of response assessment imaging may be decreased if patient's disease is responding to treatment. See Principles of Imaging (GIST-F), (also for GIST-4).
- q, modified: Progression may be determined by *contrast-enhanced* ~~abdominal/pelvic~~ CT or MR imaging ~~with contrast~~ with clinical interpretation; *FDG*-PET/CT scan may be used to clarify if CT or MRI are ambiguous. Increase in tumor size in the presence of decrease in tumor density is consistent with drug efficacy or benefit. See Principles of Imaging (GIST-F).

GIST-3
- To simplify the page: Gross residual disease (R2 resection) and tumor rupture pathways were combined.

Footnotes:
- t, new: *Completely resected (R0/R1)* See GIST-C.
- v, modified: The optimal duration of adjuvant imatinib is unknown. Available data support the use of adjuvant imatinib *for high-risk disease* for at least 3 years. The PERSIST study has shown the feasibility of 5-year adjuvant imatinib with no evidence of recurrence in patients with imatinib-sensitive GIST (Raut CP, et al. JAMA Oncol 2018;4:e184060).

GIST-4

Primary Presentation
- Column 2, bullet 2 new: *Mutational testing (NGS) + SDHB IHC*
- Column 2, bottom pathway modified: Life-long systemic therapy is recommended *for* TKI-*sensitive GIST*

Footnotes:

Footnote removed: Consider baseline PET/CT, if using PET/CT during follow-up. PET/CT is not a substitute for CT.

Continued
UPDATES

Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

Updates in Version 1.2024 of the NCCN Guidelines for Gastrointestinal Stromal Tumors from Version 1.2023 include:

GIST-A (1 of 3)

Principles of Biopsy and Risk Stratification for GIST

- Bullet 2, second sentence modified: Several ancillary techniques are recommended in support of GIST diagnosis, including IHC for SDHB, CD117, *and* DOG1, ~~and CD34~~ and molecular genetic....
- Bullet 4, subbullets 3 and 4 modified: ~~Proposed~~ Guidelines for Assessing the Malignant Potential

GIST-A (2 of 3)

- Modified, Table 1: Gastric GIST: ~~Proposed~~ Guidelines for Assessing the Malignant Potential

GIST-A (3 of 3)

- Modified, Table 2: Non-Gastric (includes small bowel and colorectal GIST): ~~Proposed~~ Guidelines for Assessing the Malignant Potential

GIST-B

Principles of Mutation Testing

- Bullet 7:
  - Sub-bullet 2, new: *Tissue biopsy is preferred; novel approaches (eg, circulating tumor DNA [ctDNA]) may be appropriate in select cases.*
  - Sub-bullet 3, new: *If a molecular profile has been completed that is negative for mutations, consider consulting the laboratory that performed the test or an expert in molecular testing (pathologist, medical geneticist, etc.) to ensure the ordered test is able to detect all molecular aberrations of interest. If not, re-testing to include appropriate tests is required.*
- Bullet 9, new: *NF1-associated GIST typically arise in the small bowel, may be multifocal, and often have an indolent biology. They should be tested for classic mutations in KIT and PDGFRA because they may contain those as well. Patients who have an NF1-associated GIST should be referred for genetic counseling if they have not been evaluated previously. Data supporting the use of TKI for NF1-associated GIST in the absence of a KIT or PDGFRA mutation are limited. Participation in a clinical trial can be considered.*

GIST-C

General Principles of Surgery

- Title, modified: General Principles of Surgery f~~or GIST~~
- Primary (Resectable) GIST: Bullet 5, modified to include... *(R1)* on final pathology
- Metastatic GIST: Bullet 5, removed: Peritoneal cytoreduction or liver metastasectomy should be considered for resection of metastatic disease

GIST-E (2 of 4)

Systemic Therapy Agents and Regimens for Unresectable, Progressive, or Metastatic Disease

- Fourth-line Therapy, modified: Ripretinib 150 mg daily (*if not previously received)* (category 1)

GIST-E (3 of 4)

- References were updated

GIST-F

Principles of Imaging

- New statement: *CT is performed with contrast. CT imaging of the chest can be performed with or without contrast, as clinically indicated. MRI is performed with and without contrast, unless contraindicated.*
- *CT abdomen/pelvis with contrast and/or MRI with and without contrast* is a new bullet/sub-bullet in the following settings:
  - Workup
  - Response Assessment
  - Definitively unresectable, recurrent, or metastatic disease
  - Follow-up

WORKUP AT PRIMARY PRESENTATION

- All patients should be evaluated and treated by a multidisciplinary team with expertise and experience in gastrointestional stromal tumors (GIST)

- For very small gastric GIST <2 cm[a]
  - Consider endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB)[b] or Endoscopic ultrasound-guided core needle biopsy (EUS-CNB)
  - Imaging[c]

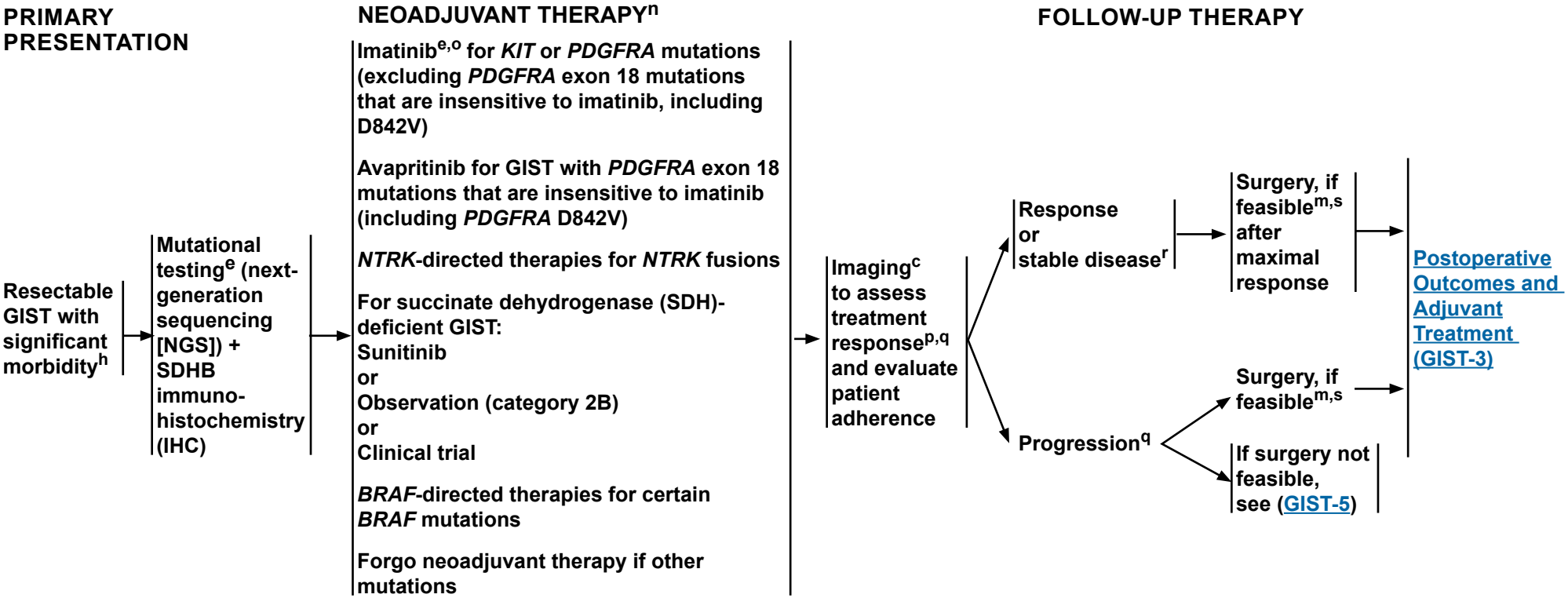
- Mass known to be or clinically suspicious for GIST[d]
  - Imaging[c]
  - Consider chest imaging[c]
  - Genotyping should be performed when medical therapy is being considered[e]

MANAGEMENT BASED ON THE RESULTS OF INITIAL DIAGNOSTIC EVALUATION

- No high-risk EUS features → Consider periodic endoscopic or radiographic surveillance[c,l]
- High-risk EUS[f] or biopsy features[g] → Complete surgical resection[m] → Postoperative Outcomes and Treatment (GIST-3)
- Resectable with minimal morbidity → Complete surgical resection[m] → Postoperative Outcomes and Treatment (GIST-3)
- Resectable with significant morbidity[h,i,j] → If neoadjuvant therapy is planned, biopsy[b,k] for diagnosis, molecular testing, and if feasible risk stratification → See (GIST-2) for neoadjuvant therapy based on molecular testing[n] to decrease surgical morbidity
- Unresectable or metastatic disease → (GIST-4)

[a] Sepe PS, et al. Nat Rev Gastroenterol Hepatol 2009;6:363-371.
[b] Principles of Biopsy and Risk Stratification for GIST (GIST-A).
[c] Principles of Imaging (GIST-F).
[d] See American Joint Committee on Cancer (AJCC) Staging, 8th Edition (ST-1).
[e] Mutational analysis may predict response to therapy with tyrosine kinase inhibitors (TKIs) (GIST-B). Tumors with succinate dehydrogenase (SDH) deficiency or *NF1* mutations that lack mutations in *KIT/PDGFRA* may be considered for observation as most, but not all, have more indolent behavior.
[f] Possible high-risk EUS features include irregular border, cystic spaces, ulceration, echogenic foci, and heterogeneity.
[g] Possible high-risk pathologic biopsy features include the presence of mitoses and/or tumor necrosis.
[h] Some patients may rapidly become unresectable; close monitoring is essential.
[i] Extensive surgery associated with significant morbidity (ie, total gastrectomy to reduce risk of recurrence in stomach) is generally not recommended for SDH-deficient GIST with multifocal disease.
[j] Neoadjuvant therapy for genotype-sensitive disease should be considered for locally advanced GIST in certain anatomical locations, (eg, rectum, esophageal and esophagogastric junction, duodenum), if a multivisceral resection would be required to resect all gross tumor, or in patients who have significant comorbidities and are not fit for surgery.
[k] See NCCN Guidelines for Soft Tissue Sarcoma if the pathology results indicate sarcomas of gastrointestinal origin other than GIST.
[l] Endoscopic ultrasonography surveillance should only be considered after a thorough discussion with the patient regarding the risks and benefits. Evans J, et al. Gastrointest Endosc 2015;82:1-8.
[m] See General Principles of Surgery (GIST-C) and Principles of Interventional Oncology (GIST-D).
[n] Neoadjuvant therapy for genotype-sensitive disease may prohibit accurate assessment of recurrence risk following resection (GIST-A). Testing tumor for mutation is recommended prior to starting preoperative therapy to ensure tumor has a genotype that is likely to respond to treatment (GIST-2). Consider neoadjuvant therapy only if surgical morbidity could be reduced by downsizing the tumor preoperatively (GIST-E). Maximal response may require treatment for 6 months or more to achieve. Once maximal response is achieved, consider surgical resection.

Note: All recommendations are category 2A unless otherwise indicated.



[c] Principles of Imaging (GIST-F).

[e] Mutational analysis may predict response to therapy with TKIs (GIST-B). Tumors with SDH deficiency or NF1 mutations that lack mutations in *KIT/PDGFRA* may be considered for observation as most, but not all, have more indolent behavior.

[h] Some patients may rapidly become unresectable; close monitoring is essential.

[m] See General Principles of Surgery (GIST-C) and Principles of Interventional Oncology (GIST-D).

[n] Neoadjuvant therapy for genotype-sensitive disease may prohibit accurate assessment of recurrence risk following resection (GIST-A). Testing tumor for mutation is recommended prior to starting preoperative therapy to ensure tumor has a genotype that is likely to respond to treatment (see above). Consider neoadjuvant therapy only if surgical morbidity could be reduced by downsizing the tumor preoperatively (GIST-E). Maximal response may require treatment for 6 months or more to achieve. Once maximal response is achieved, consider surgical resection.

[o] Medical therapy is the usual course of treatment. However, patient may proceed to surgery if bleeding or symptomatic tumor or poor treatment tolerance.

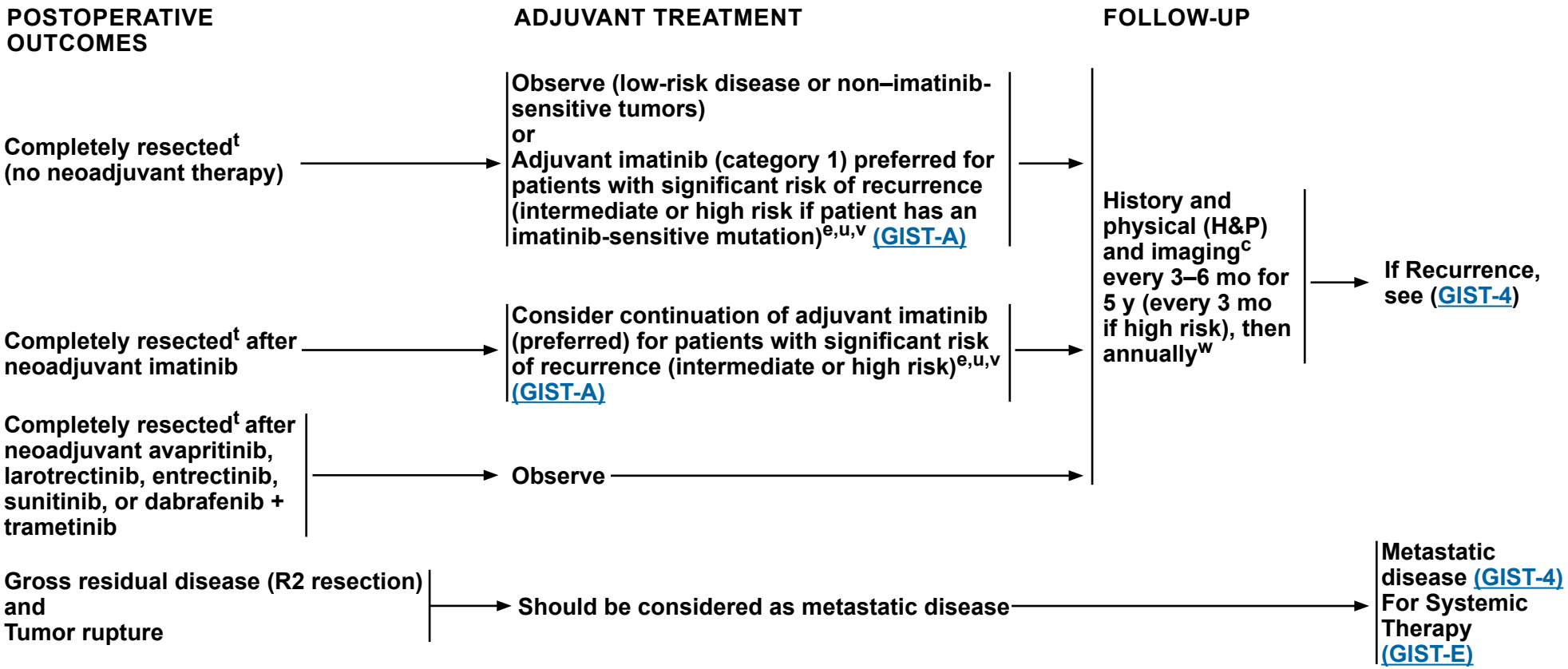
[p] FDG-PET/CT may give indication of imatinib efficacy after 2–4 weeks of therapy when rapid readout of activity is necessary. Frequency of response assessment imaging may be decreased if patient's disease is responding to treatment. See Principles of Imaging (GIST-F).

[q] Progression may be determined by contrast-enhanced CT or MR imaging with clinical interpretation; FDG-PET/CT scan may be used to clarify if CT or MRI are ambiguous. Increase in tumor size in the presence of decrease in tumor density is consistent with drug efficacy or benefit. See Principles of Imaging (GIST-F).

[r] Monitor for maximal response if feasible; if maximal response is achieved proceed to surgery.

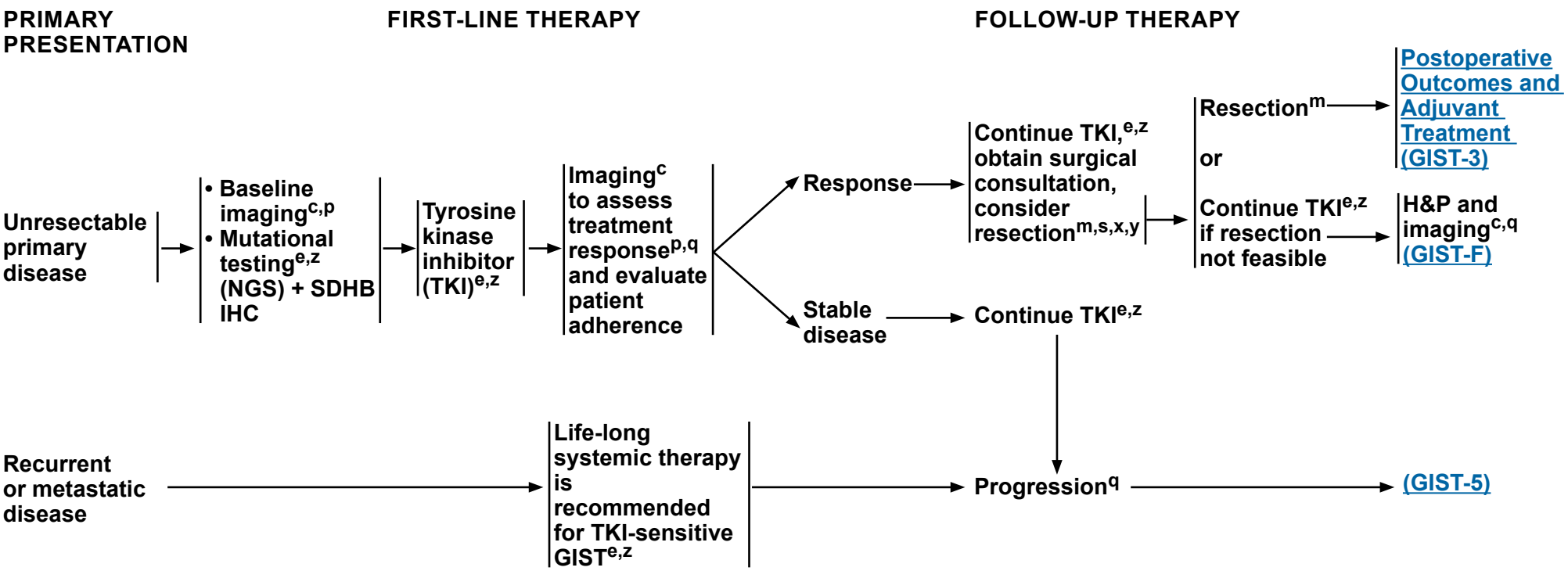
[s] Collaboration between medical oncologist and surgeon is necessary to determine the appropriateness and timing of surgery, following major response or sustained stable disease. Maximal response may require treatment for 6 months or more to achieve.

Note: All recommendations are category 2A unless otherwise indicated.



[c] Principles of Imaging (GIST-F).
[e] Mutational analysis may predict response to therapy with TKIs (GIST-B). Tumors with SDH deficiency or *NF1* mutations that lack mutations in *KIT/PDGFRA* may be considered for observation as as most, but not all, have more indolent behavior.
[t] Completely resected (R0/R1). See GIST-C.
[u] Some stratification schemes have included tumor rupture, which has been associated with a much higher risk of recurrence. Nishida T, et al. Ann Surg Oncol 2018;25:1961-1969 and Rutkowski P, et al. Ann Surg Oncol 2007;14:2018-2027.
[v] The optimal duration of adjuvant imatinib is unknown. Available data support the use of adjuvant imatinib for high-risk disease for at least 3 years. The PERSIST study has shown the feasibility of 5-year adjuvant imatinib with no evidence of recurrence in patients with imatinib-sensitive GIST (Raut CP, et al. JAMA Oncol 2018;4:e184060).
[w] Less frequent surveillance may be acceptable for very small tumors (<2 cm), unless they are associated with high mitotic rate.

Note: All recommendations are category 2A unless otherwise indicated.



[c] Principles of Imaging (GIST-F).
[e] Mutational analysis may predict response to therapy with TKIs (GIST-B). Tumors with SDH deficiency or *NF1* mutations that lack mutations in *KIT/PDGFRA* may be considered for observation as most, but not all, have more indolent behavior.
[m] General Principles of Surgery (GIST-C) and Principles of Interventional Oncology (GIST-D).
[p] FDG-PET/CT may give indication of imatinib efficacy after 2–4 weeks of therapy when rapid readout of activity is necessary. Frequency of response assessment imaging may be decreased if patient's disease is responding to treatment. See Principles of Imaging (GIST-F).
[q] Progression may be determined by contrast-enhanced CT or MR imaging with clinical interpretation; FDG-PET/CT scan may be used to clarify if CT or MRI are ambiguous. Increase in tumor size in the presence of decrease in tumor density is consistent with drug efficacy or benefit. See Principles of Imaging (GIST-F).
[s] Collaboration between medical oncologist and surgeon is necessary to determine the appropriateness and timing of surgery, following major response or sustained stable disease. Maximal response may require treatment for 6 months or more to achieve.
[x] Consider resection or ablation/liver-directed therapy for hepatic metastatic disease.
[y] Resection of metastatic disease, especially if complete resection can be achieved, may be beneficial in patients on imatinib or sunitinib who have evidence of radiographic response, or limited disease progression.
[z] See Systemic Therapy Agents and Regimens for Unresectable, Progressive, or Metastatic Disease (GIST-E).

Note: All recommendations are category 2A unless otherwise indicated.

TREATMENT FOR PROGRESSIVE DISEASE[aa]

Progression

Limited →

- **Continue with the same dose of TKI and consider the following options for lesions progressing on imatinib or avapritinib:**
  - **Resection,[m] if feasible**
  - **Ablation procedures or embolization or chemoembolization (GIST-D)**
  - **Palliative radiation therapy (RT) (category 2B) for symptomatic lesions or**
- **If previously treated with standard-dose imatinib:**
  - **Switch to sunitinib (category 1) (GIST-E)**
  - **Dose escalation of imatinib as tolerated (if previously treated with standard-dose imatinib; may be most effective for patients with *KIT* exon 9 mutation)**

Generalized (widespread, systemic) →

For performance status (PS) 0–2 and progression on imatinib or avapritinib:

- **Switch to alternate TKI (GIST-E)**
  or
- **Dose escalation of imatinib as tolerated (if previously treated with standard-dose imatinib; may be most effective for patients with *KIT* exon 9 mutation)**

→ **If disease is progressing despite prior therapies, consider the following options:**

Clinical trial
or
Consider other options listed in GIST-E (based on limited data)
or
Consider repeat tumor biopsy to potentially identify uncommon mutations that may have a corresponding targeted therapy
or
Best supportive care[bb]

[m] General Principles of Surgery (GIST-C) and Principles of Interventional Oncology (GIST-D).
[aa] Clinical experience suggests that discontinuing TKI therapy, even in the setting of progressive disease, may accelerate the pace of disease progression and worsen symptoms.
[bb] Reintroduction of imatinib can be considered for palliation of symptoms. Consider continuation of imatinib for palliation of symptoms as part of best supportive care.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF BIOPSY AND RISK STRATIFICATION FOR GIST

- **An endoscopic transmural biopsy would be favored over a percutaneous transperitoneal biopsy, as the risk for peritoneal seeding is lower for this technique. However, percutaneous image-guided biopsy may be appropriate for the confirmation of locally advanced or metastatic disease. Consideration of biopsy should be based on the suspected tumor type and extent of disease. Biopsy is necessary to confirm the diagnosis of primary GIST prior to the initiation of preoperative therapy.**

- **Morphologic diagnosis based on microscopic examination of histologic sections is the standard for GIST diagnosis. Several ancillary techniques are recommended in support of GIST diagnosis, including IHC for SDHB, CD117, and DOG1, and molecular genetic testing for *KIT* and *PDGFRA* mutations, as well as other potential drivers (eg, *BRAF*, *NF1*, *NTRK*, *and FGFR* fusions). See GIST-B.**

- **Diagnosis is based on the Principles of Pathologic Assessment (NCCN Guidelines for Soft Tissue Sarcoma); referral to centers with expertise and experience in the diagnosis and management of GIST/sarcoma is recommended for those patients with complex or unusual histopathologic features.**

- **Risk stratification:**
  - **Pathologic grading by mitotic rate may not be accurate in small biopsies. Neoadjuvant therapy that has evidence of pathologic treatment effect will not yield accurate mitotic information. In this situation, risk stratification may need to be based on clinical parameters, size, and anatomic location in the absence of mitotic rate.**
  - **Tumor size and mitotic rate are used to predict the malignant potential of GIST, although it is notoriously difficult to predict the biologic behavior of GIST based on pathologic features alone; thus, guidelines for risk stratification by tumor site have been developed.**
  - **Most gastric GIST behave in an indolent manner, especially when less than 2 cm. See Table 1 (GIST-A 2 of 3) for Guidelines for Assessing the Malignant Potential.**
  - **For non-gastric GIST, see Table 2 (GIST-A 3 of 3) for Guidelines for Assessing the Malignant Potential.**
    - ◊ **GIST of the small intestine tends to be more aggressive than its gastric counterpart.**
    - ◊ **GIST of the colon is most commonly seen in the rectum; colorectal GIST tends to have an aggressive biological behavior, and tumors with mitotic activity can recur and metastasize despite a small size of <2 cm.**
  - **Some stratification schemes have included tumor rupture, which has been associated with a much higher risk of recurrence.**

Continued

Note: All recommendations are category 2A unless otherwise indicated.

PREDICTORS OF GIST BIOLOGIC RISK

Table 1: Gastric GIST: Guidelines for Assessing the Malignant Potential[1]

- **This prognostic assessment applies best to *KIT*- or *PDGFRA*-positive GIST, whereas SDH-deficient GIST are more unpredictable.**
- **Risk stratification is determined without any prior exposure to TKI therapy.**

Tumor Size	Mitotic Rate[2]	Risk	Risk Per CAP[2]
≤2 cm	≤5 mitoses/50 HPFs	Metastasis rate: 0%	None
	>5 mitoses/50 HPFs	Metastasis rate: 0%*	None
>2 cm to ≤5 cm	≤5 mitoses/50 HPFs	Metastasis rate: 1.9%	Very low (1.9%)
	>5 mitoses/50 HPFs	Metastasis rate: 16%	Moderate (16%)
>5 cm to ≤10 cm	≤5 mitoses/50 HPFs	Metastasis rate: 3.6%	Low (3.6%)
	>5 mitoses/50 HPFs	Metastasis rate: 55%	High (55%)
>10 cm	≤5 mitoses/50 HPFs	Metastasis rate: 12%	Moderate (12%)
	>5 mitoses/50 HPFs	Metastasis rate: 86%	High (86%)

CAP: College of American Pathologists; HPFs: High-power fields; *Predicted rate based on tumor category with very small numbers

[1] Data from Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Sem Diag Path 2006;23:70-83. In the original paper, percentages referred to the percentage of patients with progressive disease, whereas low, moderate, and high referred to the risk of metastases.

[2] The mitotic rate should be measured in the most proliferative area of the tumor, and reported as the number of mitoses per 50 HPF of tissue. Per 50 HPF is a total of 5 mm^2. For most modern microscopes, 20 to 25 HPF 40 x lenses/fields encompasses 5 mm^2. Data from Laurini JA. Protocol for the Examination of Resection Specimens from Patients with Gastrointestinal Stromal Tumors (GIST). Version 4.2.0.0, June 2021. Available at: https://documents.cap.org/protocols/Stomach.GIST_4.2.0.0.REL_CAPCP.pdf. Prognostic contour maps are another source that provides information about risk of recurrence of GIST after surgery. Joensuu H, Vehtari A, Riihimaki J, et al. Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. Lancet Oncol 2012;13:265-274.

Continued

Note: All recommendations are category 2A unless otherwise indicated.

PREDICTORS OF GIST BIOLOGIC RISK

Table 2: Non-Gastric GIST (includes small bowel and colorectal GIST): Guidelines for Assessing the Malignant Potential[1]

- **This prognostic assessment applies best to *KIT*- or *PDGFRA*-positive GIST whereas SDH-deficient GIST are more unpredictable. For anatomic sites not listed in this table, such as esophagus, mesentery, and peritoneum, or in the case of "insufficient data," it is best to use risk criteria for jejunum/ileum.**
- **Risk stratification is determined without prior exposure to TKI therapy.**

Tumor Size	Mitotic Rate[2]	Risk	Risk Per CAP[2]
≤2 cm	≤5 mitoses/50 HPFs	Metastasis rate: 0%	None
	>5 mitoses/50 HPFs	Metastasis rate: 50%–54%	Insufficient data - High (54%)
>2 cm to ≤5 cm	≤5 mitoses/50 HPFs	Metastasis rate: 1.9%–8.5%	Low (4.3%–8.5%)
	>5 mitoses/50 HPFs	Metastasis rate: 50%–73%	High (50%–73%)
>5 cm to ≤10 cm	≤5 mitoses/50 HPFs	Metastasis rate: 24%	Insufficient data - Moderate (24%)
	>5 mitoses/50 HPFs	Metastasis rate: 85%	Insufficient data - High (85%)
>10 cm	≤5 mitoses/50 HPFs	Metastasis rate: 34%–57%	High (34%–57%)
	>5 mitoses/50 HPFs	Metastasis rate: 71%–90%	High (71%–90%)

CAP: College of American Pathologists; HPFs: High-power fields

[1] Data from Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Sem Diag Path 2006;23:70-83. In the original paper, percentages referred to the percentage of patients with progressive disease, whereas low, moderate, and high referred to the risk of metastases.

[2] The mitotic rate should be measured in the most proliferative area of the tumor, and reported as the number of mitoses per 50 HPF of tissue. Per 50 HPF is a total of 5 mm^2. For most modern microscopes, 20 to 25 HPF 40 x lenses/fields encompasses 5 mm^2. Data from Laurini JA. Protocol for the Examination of Resection Specimens from Patients with Gastrointestinal Stromal Tumors (GIST). Verson 4.2.0.0, June 2021. Available at: https://documents.cap.org/protocols/Stomach.GIST_4.2.0.0.REL_CAPCP.pdf. Prognostic contour maps are another source that provides information about risk of recurrence of GIST after surgery. Joensuu H, Vehtari A, Riihimaki J, et al. Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. Lancet Oncol 2012;13:265-274.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF MUTATION TESTING

- **Approximately 80% of GIST have a mutation in the gene encoding the KIT receptor tyrosine kinase; another 5%–10% of GIST have a mutation in the gene encoding the related PDGFRA receptor tyrosine kinase. The presence and type of *KIT* and *PDGFRA* mutations are not strongly correlated with prognosis.**

- **The mutations in *KIT* and *PDGFRA* in GIST result in expression of mutant proteins with constitutive tyrosine kinase activity. Testing for *KIT* and *PDGFRA* mutations should be performed if TKIs are considered as part of the treatment plan since the presence of mutations (or absence of mutations) in specific regions of the *KIT* and *PDGFRA* genes are correlated with response (or lack of a response) to specific TKIs.**

- **Specific mutations in *KIT* or *PDGFRA* show some correlation with tumor phenotype, but mutations are not strongly correlated with the biologic potential of individual tumors. The accumulated data show that *KIT* mutations are not preferentially present in high-grade tumors, and can also be found in small incidental tumors as well as tumors that have an indolent course. Similarly, mutational analysis of *PDGFRA* cannot be used to predict the behavior of individual tumors.**

- **GIST have different response rates to imatinib based upon the tumor mutation status: *KIT* exon 9 mutations have a lower response rate and progression-free survival (PFS) than exon 11 tumors at 400 mg, but dosing at 400 mg BID has been associated with better PFS. Most *PDGFRA* mutations are associated with a response to imatinib, with the exception of D842V, which is unlikely to respond to imatinib and most other approved TKIs for GIST except for avapritinib.**

- **Metastatic disease with acquired drug resistance is usually the result of secondary, imatinib-resistant mutations in *KIT* or *PDGFRA*. Sunitinib treatment is indicated for patients with imatinib-resistant tumors or imatinib intolerance. Regorafenib is indicated for patients with disease progression on imatinib and sunitinib. Ripretinib is indicated for patients who have received prior treatment with 3 or more kinase inhibitors, including imatinib. Ripretinib is also an option for GIST with *PDGFRA* exon 18 mutations that are insensitive to imatinib and were previously treated with both avapritinib and dasatinib. An additional clinical benefit may be obtained with the use of ripretinib 150 mg BID upon progression on ripretinib 150 mg daily. Referral to clinical trial is strongly recommended for patients with mutations resistant to imatinib, sunitinib, regorafenib, ripretinib, and avapritinib.**

- **About 10%–15% of GIST lack mutations in *KIT* or *PDGFRA*. The vast majority of these GIST have functional inactivation of the SDH complex, which can be detected by lack of expression of SDHB on IHC. Inactivation of the SDH complex may result from a mutation or from epigenetic silencing. A small minority of GIST with loss of SDH expression have alternative driver mutations.**

- **All GIST lacking a *KIT* or *PDGFRA* mutation should be tested for SDH deficiency and alternative driver mutations using NGS.**
  - **Alternative driver mutations (eg, *BRAF*, *NF1*, *NTRK*, and *FGFR* fusions) may be detected by NGS to identify potential targeted therapies.**
  - **Tissue biopsy is preferred; novel approaches (eg, circulating tumor DNA [ctDNA]) may be appropriate in select cases.**
  - **If a molecular profile has been completed that is negative for mutations, consider consulting the laboratory that performed the test or an expert in molecular testing (pathologist, medical geneticist, etc.) to ensure the ordered test is able to detect all molecular aberrations of interest. If not, re-testing to include appropriate tests is required.**

- **GIST with *SDH* mutations typically arise in the stomach in younger individuals, frequently metastasize, may involve lymph nodes, and usually grow slowly. They are usually resistant to imatinib. SDH-deficient tumors may benefit from therapy with sunitinib or regorafenib. Referral to a genetic counselor for germline testing assessment is recommended for all patients with SDH-deficient GIST and those with GIST that have *SDH* mutations. Patients with *SDH* germline mutations are at risk of paraganglioma; 24-hour urine testing is recommended prior to surgery (GIST-C).**

- ***NF1*-associated GIST typically arise in the small bowel, may be multifocal, and often have an indolent biology. They should be tested for classic mutations in *KIT* and *PDGFRA* because they may contain those as well. Patients who have an *NF1*-associated GIST should be referred for genetic counseling if they have not been evaluated previously. Data supporting the use of TKI for *NF1*-associated GIST in the absence of a *KIT* or *PDGFRA* mutation are limited. Participation in a clinical trial can be considered.**

Note: All recommendations are category 2A unless otherwise indicated.

GENERAL PRINCIPLES OF SURGERY

Primary (Resectable) GIST

The surgical procedure performed should aim to resect the tumor with histologically negative margins.

- **Given the limited intramural extension, extended anatomic resections (such as total gastrectomy) are rarely indicated. Segmental or wedge resection to obtain negative margins is often appropriate.**
- **Lymphadenectomy is usually not required given the low incidence of nodal metastases; however, resection of pathologically enlarged nodes should be considered in patients with known SDH-deficient GIST or known translocation-associated GIST.**
- **As GIST tends to be very fragile, every effort should be made not to violate the pseudocapsule of the tumor (ie, avoid tumor rupture—any tumor spillage or fracture, laceration of the tumor capsule with or without macroscopic spillage, and piecemeal resection).**
- **Incisional biopsy occurring either before or at the time of the operation should be strictly avoided.**
- **Re-resection is generally not indicated for microscopically positive margins (R1) on final pathology.**

Resection should be accomplished with minimal morbidity and, in general, complex multivisceral resection should be avoided. If the surgeon feels that a multivisceral resection may be required, then multidisciplinary consultation is indicated regarding a course of preoperative therapy (ie, imatinib or avapritinib). Similarly, rectal GIST should be approached via a sphincter-sparing approach. If abdominoperineal resection (APR) would be necessary to achieve a negative margin resection, then preoperative imatinib should be considered.

A minimally invasive approach may be considered for select GIST in favorable anatomic locations by surgeons with appropriate minimally invasive experience.

- **All oncologic principles of GIST resection must still be followed, including preservation of the pseudocapsule and avoidance of tumor spillage.**
- **Resection specimens should be removed from the abdomen in a plastic bag to prevent spillage or seeding of port sites.**

Unresectable GIST

Molecularly guided therapy is the primary treatment for unresectable GIST; see Principles of Systemic Therapy (GIST-E). Surgery may be indicated for:

- **Previously unresectable tumors after a favorable response to systemic therapy.**
- **Management of symptomatic bleeding, obstruction, or perforation.**

Metastatic GIST

Molecularly guided therapy is the primary therapy for metastatic GIST. Surgery (peritoneal cytoreduction and/or liver metastasectomy) may be indicated in the following order:

- **Stage IV disease after a favorable response to systemic therapy when complete cytoreduction of peritoneal and/or hepatic disease can be accomplished by an experienced surgeon**
- **Unifocal progression of disease that is refractory to TKI therapy when other sites of disease are having a favorable response to therapy**
- **Low-volume multifocal progressive disease that is safely resectable**
- **Management of symptomatic bleeding, obstruction, or perforation**

Considerations Prior to Surgery

- **Imatinib can be stopped right before surgery and restarted as soon as the patient is able to tolerate oral medications. If other TKIs such as sunitinib, regorafenib, ripretinib, or avapritinib are being used, therapy should be stopped at least one week prior to surgery and can be restarted based on clinical judgment or recovery from surgery.**
- **Patients with SDH-deficient tumors or known *SDH* mutations are at risk of paraganglioma and therefore serum/urine catecholamine/metanephrine testing should be performed prior to surgery.**

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF INTERVENTIONAL ONCOLOGY

Catheter-Directed Therapies

- Catheter-directed therapies allow minimally invasive treatment of liver disease in select patients, including those unable to tolerate surgical resection or lesions not amenable to surgery.
- Intra-arterial therapies produce cell death by inducing ischemia and/or locally delivering cytotoxic agents or radiation to hepatic tumors. Specific intra-arterial therapies include transarterial (bland) embolization (TAE), transarterial chemoembolization (TACE), and transarterial radioembolization (TARE).
  - Transarterial Embolization (TAE)
    - TAE involves delivery of embolic agents within hepatic arteries supplying liver tumors with the goal of vessel stasis.
    - TAE may be considered for treatment of liver metastases refractory to imatinib or imatinib and sunitinib.[1,2]
  - Transarterial Chemoembolization (TACE)
    - TACE consists of conventional TACE and drug-eluting bead TACE (DEB-TACE). Conventional TACE involves targeted infusion of chemotherapeutic medications in addition to embolic agents and lipiodol into tumoral blood supply while DEB-TACE drug delivery is through embolic beads loaded with chemotherapeutic medication.
    - TACE can be an effective and a well-tolerated treatment in patients with GIST with liver metastases not responsive to TKIs.[3,4]
  - Transarterial Radioembolization (TARE)
    - TARE utilizes beta particle emitting microspheres by yttrium-90 decay to induce tumoricidal effects through local brachytherapy. TARE can be performed with either glass or resin microspheres.
    - TARE can be a safe and effective treatment option for patients with hepatic metastatic GIST whose disease does not respond to TKIs.[5]
- Patient selection
  - Multidisciplinary discussion can be performed to identify candidates who may benefit from catheter-directed therapies.
  - Patients whose disease progresses on TKI therapies may be considered for transarterial treatments.
  - Unresectable liver-dominant metastases or patients with medical comorbidities prohibiting surgical resection may be considered for catheter-directed therapies.
  - Absolute contraindications to catheter-directed therapies are few, but include:
    - Uncorrectable coagulopathy
    - Active infection in the planned treatment area
    - Decompensated liver failure (relative based on treatment approach)

Continued

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF INTERVENTIONAL ONCOLOGY

Ablation

- **Tumor ablation involves application of thermal or non-thermal therapies to a tumor to achieve cell death. Thermal ablation achieves tissue destruction by the induction of extreme hypothermia (cryoablation) or hyperthermia (radiofrequency ablation [RFA], microwave ablation, laser ablation, and high-intensity focused ultrasound [HIFU]). Non-thermal ablation such as irreversible electroporation (IRE) results in permanent cellular membrane injury.**
  - **Ablation modality can be based on tumor size, location, and adjacent critical structures to optimize treatment effect while limiting potential adverse events.**
  - **Ablation can include the target lesion in addition to a margin of radiologically normal tissue to ensure complete local treatment.**
  - **Adjunct passive and active thermoprotective techniques, such as hydrodissection, may be used to protect adjacent critical structures during percutaneous ablation.**
- **Specific considerations in ablation of metastatic disease**
  - **Liver metastases**
    - ◊ **Thermal ablation in patients previously treated with TKI is feasible and safe.[6,7,8]**
    - ◊ **Intraoperative ablation may be complementary to surgical resection to obtain complete response in patients with metastatic disease that may have otherwise been inoperable.[9]**
- **Patient selection**
  - **Multidisciplinary discussion can be performed to identify candidates who may benefit from ablative therapies.**
  - **Patients whose disease progresses on conventional therapy with TKIs can be considered for ablation.**
  - **Unresectable metastases or patients with medical comorbidities prohibiting surgical resection should be considered for image-guided ablation.**
  - **Absolute contraindications to image-guided ablation are few, but include:**
    - ◊ **Uncorrectable coagulopathy**
    - ◊ **Active infection in the planned treatment area**
    - ◊ **Inability to displace or protect adjacent critical structures (relative based on risk-benefit discussion)**

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Note: All recommendations are category 2A unless otherwise indicated.

SYSTEMIC THERAPY AGENTS AND REGIMENS FOR GIST

Neoadjuvant Therapy for Resectable Disease with Significant Morbidity

Preferred Regimens

- Imatinib for *KIT* or *PDGFRA* mutations (excluding *PDGFRA* exon 18 mutations that are insensitive to imatinib, including D842V)[a]
- Avapritinib for GIST with *PDGFRA* exon 18 mutations that are insensitive to imatinib (including *PDGFRA* D842V)[1,2]

Useful in Certain Circumstances

***NTRK* gene fusion-positive GIST**

- Larotrectinib
- Entrectinib
- Repotrectinib[3] (category 2B)

SDH-deficient GIST

- Sunitinib

***BRAF* V600E mutated GIST**

- Dabrafenib + trametinib[4]

Adjuvant Therapy for Resectable Disease

Preferred Regimen

- Adjuvant imatinib[b] for patients with significant risk of recurrence, intermediate or high risk (category 1 following complete resection with no preoperative imatinib; category 2A following complete resection after preoperative imatinib); see GIST-3.

[a] Although mutational analysis is recommended (other than rare circumstances, family history, etc.), it is appropriate to start neoadjuvant imatinib pending confirmation of the mutational analysis. Sharma AK, et al. Clin Cancer Res 2021;27:5334-5342.

[b] Data do not support routine use in GIST without mutation in *KIT* or with an imatinib-resistant mutation in *PDGFRA*.

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Note: All recommendations are category 2A unless otherwise indicated.

SYSTEMIC THERAPY AGENTS AND REGIMENS FOR UNRESECTABLE, PROGRESSIVE, OR METASTATIC DISEASE

First-line Therapy	Second-line Therapy	Third-line Therapy	Fourth-line Therapy	Additional Options After Progression on Approved Therapies[c,d]
Preferred Regimen • Imatinib[e,5,6] (category 1) for sensitive mutations (excluding *PDGFRA* exon 18 mutations that are insensitive to imatinib including D842V)	**Preferred Regimen** • Sunitinib[e,11] (category 1) • For patients intolerant of second-line sunitinib, consider changing to ripretinib 150 mg daily[f,12]	**Preferred Regimen** • Regorafenib[e,14] (category 1)	**Preferred Regimen** • Ripretinib 150 mg daily[f,15] (if not previously received) (category 1)	**Useful in Certain Circumstances** • Avapritinib[e,1-2,7] • Cabozantinib[16] • Everolimus + TKI[g,17] • Nilotinib[18,19] • Pazopanib[20] • Ponatinib[h,21] • Ripretinib dose escalation to 150 mg BID (if previously treated with ripretinib 150 mg daily)[e,i,22,23] • Sorafenib[24-26]
Preferred Regimen • Avapritinib[e,1-2,7] for GIST with *PDGFRA* exon 18 mutations that are insensitive to imatinib (including *PDGFRA* D842V)	• Dasatinib[13] (Other recommended regimen)			**Useful in Certain Circumstances** • Ripretinib 150 mg daily • Ripretinib dose escalation to 150 mg BID (if previously treated with ripretinib 150 mg daily)[e,i,21]
Useful in Certain Circumstances • *NTRK* gene fusion-positive GIST only ▸ Larotrectinib[8] ▸ Entrectinib[9] ▸ Repotrectinib[3] • SDH-deficient GIST ▸ Sunitinib ▸ Regorafenib ▸ Pazopanib ▸ Imatinib/binimetinib[10] (category 2B) • *BRAF* V600E mutated GIST ▸ Dabrafenib + trametinib[4]	**Useful in Certain Circumstances** • *NTRK* gene fusion-positive GIST only ▸ Repotrectinib[3] (if not previously given)			

[c] Therapies based on identification of driver mutations. See GIST-B.
[d] Regimens are ordered alphabetically and not according to order of preference.
[e] FDA-approved TKIs for the treatment of GIST.
[f] Ripretinib is FDA-approved for the treatment of adult patients with advanced GIST who have received prior treatment with 3 or more kinase inhibitors, including imatinib.
[g] TKIs to be considered for use in combination with everolimus include imatinib, sunitinib, or regorafenib.
[h] Ponatinib demonstrated activity in advanced GIST, particularly in patients with *KIT* exon 11 mutant disease.
[i] An additional clinical benefit may be obtained with the use of ripretinib 150 mg BID upon progression on ripretinib 150 mg daily.

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References on GIST-E (3 of 4)

SYSTEMIC THERAPY AGENTS AND REGIMENS FOR GIST
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Note: All recommendations are category 2A unless otherwise indicated.

SYSTEMIC THERAPY AGENTS AND REGIMENS FOR GIST
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Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF IMAGING

CT is performed with contrast. CT imaging of the chest can be performed with or without contrast, as clinically indicated. MRI is performed with and without contrast, unless contraindicated.

Workup

- For very small GIST <2 cm: CT abdomen/pelvis with contrast and/or MRI with and without contrast
- For all other GIST:
  - CT abdomen/pelvis with contrast and/or MRI with and without contrast
  - Chest imaging (x-ray or CT)

Response Assessment

Resectable disease with significant morbidity

- Obtain baseline contrast-enhanced abdomen/pelvis CT and/or MRI
- Consider FDG-PET/CT
  - Obtain baseline FDG-PET/CT if using FDG-PET/CT during follow-up
  - FDG-PET/CT, with a non-diagnostic CT, is not a substitute for a diagnostic CT
- Imaging to assess response to preoperative TKI
  - ◊ CT abdomen/pelvis with contrast and/or MRI with and without contrast every 8–12 weeks
  - FDG-PET/CT may give indication of TKI activity after 2–4 weeks of therapy when rapid readout of activity is necessary
- Progression may be determined by CT or MRI with clinical interpretation; FDG-PET/CT may be used to clarify if CT or MRI is ambiguous
- For R2 resection or discovery of metastatic disease
  - Assess response to postoperative TKI via CT abdomen/pelvis with contrast and/or MRI with and without contrast every 8–12 weeks

Definitively unresectable, recurrent, or metastatic disease

- Obtain baseline contrast-enhanced abdomen/pelvis CT and/or MRI
- Consider intermittent chest imaging (x-ray or CT)
- Consider FDG-PET/CT
  - Obtain baseline FDG-PET/CT if using FDG-PET/CT during follow-up
  - FDG-PET/CT, with a non-diagnostic CT, is not a substitute for a diagnostic CT
- Imaging to assess response to TKI
  - CT abdomen/pelvis with contrast and/or MRI with and without contrast every 8–12 weeks after initiating therapy
    - ◊ In some patients, it may be appropriate to image before 3 months
- Progression may be determined by CT or MRI with clinical interpretation; FDG-PET/CT may be used to clarify if CT or MRI is ambiguous

Follow-up

- For completely resected primary disease, perform CT abdomen/pelvis with contrast and/or MRI with and without contrast every 3–6 months for 3–5 years, then annually
  - Less frequent imaging surveillance may be acceptable for low-risk or very small tumors (<2 cm)
  - More frequent imaging surveillance may be required for patients with high-risk disease who discontinue TKI therapy
- For incompletely resected disease or discovery of metastatic disease during surgery, perform CT and/or MRI every 3–6 months
- Progression may be determined by CT or MRI with clinical interpretation; FDG-PET/CT may be used to clarify if CT or MRI is ambiguous
- After treatment for progressive disease, reassess therapeutic response with CT or MRI
  - Consider FDG-PET/CT only if CT/MRI results are ambiguous

Note: All recommendations are category 2A unless otherwise indicated.

American Joint Committee on Cancer (AJCC) Staging System for Gastrointestinal Stromal Tumor (8th ed, 2017)

Definitions for T, N, M

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less
T2	Tumor more than 2 cm but not more than 5 cm
T3	Tumor more than 5 cm but not more than 10 cm
T4	Tumor more than 10 cm in greatest dimension

N	**Regional Lymph Nodes**
N0	No regional lymph node metastasis or unknown lymph node status
N1	Regional lymph node metastasis

M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis

Grading for GIST is dependent on mitotic rate

Low	5 or fewer mitoses per 5 mm^2, or per 50 HPF
High	Over 5 mitoses per 5 mm^2, or per 50 HPF

AJCC Anatomic Stage/Prognostic Groups

*Gastric GIST**

	T	N	M	Mitotic Rate
Stage IA	T1 or T2	N0	M0	Low
Stage IB	T3	N0	M0	Low
Stage II	T1	N0	M0	High
	T2	N0	M0	High
	T4	N0	M0	Low
Stage IIIA	T3	N0	M0	High
Stage IIIB	T4	N0	M0	High
Stage IV	Any T	N1	M0	Any rate
	Any T	Any N	M1	Any rate

*Small Intestinal GIST***

	T	N	M	Mitotic Rate
Stage I	T1 or T2	N0	M0	Low
Stage II	T3	N0	M0	Low
Stage IIIA	T1	N0	M0	High
	T4	N0	M0	Low
Stage IIIB	T2	N0	M0	High
	T3	N0	M0	High
	T4	N0	M0	High
Stage IV	Any T	N1	M0	Any rate
	Any T	Any N	M1	Any rate

*Note: Also to be used for omentum.
**Note: Also to be used for esophagus, colorectal, mesenteric, and peritoneal.

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ABBREVIATIONS

APR	abdominoperineal resection
CAP	College of American Pathologists
ctDNA	circulating tumor DNA
DEB-TACE	drug-eluting bead transarterial chemoembolization
EUS-CNB	endoscopic ultrasound-guided core needle biopsy
EUS-FNAB	endoscopic ultrasound-guided fine-needle aspiration biopsy
GIST	gastrointestinal stromal tumors
HIFU	high-intensity focused ultrasound
H&P	history and physical
HPF	high-power field
IHC	immunohistochemistry
IRE	irreversible electroporation
NGS	next-generation sequencing
PFS	progression-free survival
PS	performance status
RFA	radiofrequency ablation
SDH	succinate dehydrogenase
TACE	transarterial chemoembolization
TAE	transarterial embolization
TARE	transarterial radioembolization
TKI	tyrosine kinase inhibitor

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Discussion

This discussion corresponds to the NCCN Guidelines for Gastrointestinal Stromal Tumors (GIST). The following pages were updated on September 1, 2022: MS-2 & MS-11 to MS-16. The remaining sections were updated on March 27, 2018.

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Overview

Gastrointestinal stromal tumors (GIST) are the most common STS of the GI tract, resulting primarily from *KIT* or *PDGFRA* activating mutations.[1] The annual incidence of GIST in the United States is estimated to be between 0.68 to 0.78 per 100,000.[2-5] GIST can arise anywhere along the GI tract, but stomach (60%) and small intestine (30%) are the most common primary sites.[6] Duodenum (4%–5%) and rectum (4%) are less common primary sites, and only a small number of cases have been reported in the esophagus (<1%) and colon and appendix (1%–2%).[6] In very rare occasions, GIST can occur in extraintestinal sites. Patients with a suspected GIST may present with a variety of symptoms, which may include early satiety, abdominal discomfort due to pain or swelling, intraperitoneal hemorrhage, GI bleeding, or fatigue related to anemia. Some patients may present with an acute abdomen (as a result of tumor rupture, GI obstruction, or peritonitis-like pain), which requires immediate medical attention. Liver and/or the peritoneal surfaces are the most common sites of metastases, whereas lymph node metastases are extremely rare, except in select GIST subtypes. Metastases in the lungs, bone, and other extra-abdominal locations are observed only in advanced cases.

General Principles

Biopsy and Pathologic Assessment

GIST are soft and fragile tumors. The decision to obtain a biopsy should be based on the suspected tumor type and the extent of disease. Biopsy is necessary to confirm the diagnosis of primary GIST prior to the initiation of preoperative therapy.[7] Recent reports have suggested that definitive diagnosis of GIST requires tissue acquisition via endoscopic ultrasound (EUS)-guided FNA.[8] EUS-guided FNA (EUS-FNA) biopsy of primary site is preferred over percutaneous biopsy due to the risk of tumor hemorrhage and intra-abdominal tumor dissemination. Percutaneous image-guided biopsy may be appropriate for confirmation of metastatic disease.

Morphologic diagnosis based on careful microscopic examination of adequate tumor tissue is essential to confirm the diagnosis of GIST. Pathology report should include anatomic location, size, and an accurate assessment of the mitotic rate measured in the most proliferative area of the tumor and reported as the number of mitoses in 50 high-power fields (HPFs) (equivalent to 5 mm^2 of tissue). The differential diagnosis of GIST should be considered for any GI sarcoma, as well as for any other intra-abdominal sarcoma. The panel recommends referral to centers with expertise in sarcomas for cases with complex or unusual histopathologic features.

Most GIST (95%) express *KIT* (CD117). Approximately 80% of GIST have a mutation in the gene encoding the *KIT* receptor tyrosine kinase; another 5% to 10% of GIST have a mutation in the gene encoding the related *PDGFRA* receptor tyrosine kinase.[9-11] About 10% to 15% of GIST have no detectable *KIT* or *PDGFRA* mutations (wild-type GIST). Other commonly expressed markers include CD34 antigen (70%), smooth muscle actin (25%), and desmin (less than 5%).[12]

Most of the *KIT* mutations occur in the juxtamembrane domain encoded by KIT exon 11 and some are detected in the extracellular domain encoded by exon 9.[13] KIT mutations have also been identified in the tyrosine kinase domain (exon 13 and exon 17), although they are very rare.[14] The majority of the *PDGFRA* mutations affect exon 18 in the tyrosine kinase domain 2.[13] Few mutations also occur in exon 12 (juxtamembrane domain) and exon 14 (tyrosine kinase domain 1), although they are rare.[15] *KIT* exon 11 mutations are most common in GIST of all sites, whereas *KIT* exon 9 mutations are specific for intestinal GIST and *PDGFRA* exon 18 mutations are common in gastric GIST.[13]

Immunohistochemical staining for CD117, DOG1, and/or CD34 and molecular genetic testing to identify *KIT* and/or *PDGFRA* mutations are useful in the diagnosis of GIST. However, *KIT* positivity alone may not be sufficient to confirm the diagnosis and, conversely, the absence of *KIT* and/or *PDFGRA* mutations does not exclude the diagnosis of GIST. In GIST with *PDGFRA* mutations, immunostaining with *PDGFRA* has been shown to be helpful in discriminating between *KIT*-negative GIST and other GI mesenchymal lesions.

Loss-of-function mutations in the *SDH* gene subunits or loss of SDHB protein expression by IHC have been identified in a majority of wild-type GIST lacking *KIT* and *PDGFRA* mutations; these findings have led to the use of the term SDH-deficient GIST, which is preferred over the older term, wild-type GIST, for this subset of GIST.[16-20] SDHB IHC can be useful for the diagnosis of *SDH*-deficient GIST. *BRAF* exon 15 mutation (V600E) has also been reported in a small subset of patients with intestinal high-risk GIST lacking *KIT/PDGFRA* mutations.[21,22] DOG1 is a calcium-dependent, receptor-activated chloride channel protein and it is expressed in GIST independent of mutation type. DOG1 expression was not different between the *KIT/PDGFRA* mutant or wild-type GIST, but there was a clear distinction between tumors with *PDGFRA* and *KIT* mutations. GIST with

PDGFRA mutations had a low *KIT* expression and high DOG1 expression, which can be used in the diagnosis of *KIT*-negative tumors.[23] DOG1 immunostaining may be useful for cases that cannot be categorized as GIST based on CD117 immunostaining and mutation testing for *KIT* and *PDGFRA*. DOG1 and *KIT* could be used together in difficult cases exhibiting unexpected *KIT* negativity or positivity.[7]

Tumors lacking *KIT* and *PDGFRA* mutations should be considered for further evaluations such as SDHB immunostaining. If the tumor is *SDH*-deficient, germline testing for *SDH* mutations would be indicated. Inactivating *NF1* mutations or activating *BRAF* mutations are present in a small minority of tumors that lack *KIT* and *PDGFRA* mutations but retain *SDH* expression.

Prognostic Factors

Tumor size and the mitotic rate are the most widely used pathologic features for the risk stratification of GIST. However, it is difficult to predict the malignant potential of GIST based on these features alone. In a long-term follow-up of 1765 patients with gastric GIST, Miettinen and colleagues reported that the metastatic rate was 86% for tumors >10 cm with a mitotic index of >5 mitoses/50 HPFs, whereas tumors of the same size with a mitotic index of <5 mitoses/50 HPFs have a relatively low metastatic rate of 11%.[24] In a subsequent report involving 906 patients with small intestinal GIST, tumors >10 cm with a mitotic index of ≤5 mitoses/50 HPF had a metastatic rate of 50%, which is a contrast to that reported for gastric GIST with similar tumor parameters.[25] Therefore, in addition to the tumor size and mitotic rate, tumor site has also been included in the guidelines developed by Miettinen and colleagues for the risk stratification of primary GIST.[6] According to these guidelines, gastric GIST have an overall indolent behavior and those that are ≤2 cm (irrespective of the mitotic index) are essentially benign, whereas small intestinal GIST tend to be more aggressive. Rectal GIST are also very aggressive, and tumors <2 cm with a mitotic index of >5 mitoses/50 HPFs have a higher risk of recurrence and malignant potential.

Mutations can be found in high-grade tumors as well as in small incidental GIST and tumors that have a benign course. Therefore, *KIT* mutational status is not used to determine the malignant potential of a primary GIST. Tumor genotype has been shown to be an independent prognostic factor based on review of 1056 patients with localized GIST in the ConticaGIST database. Factors associated with poorer DFS were *KIT* exon 9 duplication, *KIT* exon 11 deletions, nongastric site, larger tumor size, and high mitotic index, whereas *PDGFRA* exon 18 mutations were associated with better prognosis.[26] Long-term follow-up (median 73 months) from the BFR14 trial by the French Sarcoma Group identified female sex as an independent prognostic factor for higher PFS and OS in patients treated with standard-dose imatinib.[27]

The presence and the type of *KIT* or *PDGFRA* mutation status are predictive of response to TKI therapy in patients with advanced or metastatic GIST. GIST with *SDH* mutations are also less sensitive to TKIs. They typically arise in the stomach and are observed in younger individuals, frequently metastasize, may feature lymph node involvement, and tend to grow slowly. See *Impact of Mutational Status on Response to Imatinib or Sunitinib in Patients with Advanced or Metastatic GIST* in this Discussion.

Imaging

In patients with GIST, imaging is used for diagnosis, initial staging, restaging, monitoring response to therapy, and performing follow-up surveillance of possible recurrence. Contrast-enhanced CT is the imaging modality of choice to characterize an abdominal mass, as well as to evaluate its extent and the presence or absence of metastasis at the initial staging workup for biopsy-proven GIST. PET helps to differentiate active

tumor from necrotic or inactive scar tissue, malignant from benign tissue, and recurrent tumor from nondescript benign changes. PET provides significant value to the standard CT images, because changes in the metabolic activity of tumors often precede anatomic changes on CT. However, PET is not a substitute for CT. PET/CT may be used to clarify ambiguous findings seen on CT or MRI or to assess complex metastatic disease in patients who are being considered for surgery. Even in this clinical setting there is no clear evidence that PET provides significant information that cannot be obtained using IV contrast-enhanced CT. PET may be of benefit in patients with IV contrast allergy, particularly for peritoneal disease; MRI with or without contrast usually yields excellent anatomical definition of liver metastases.[7] If clinicians consider using PET to monitor therapy, a baseline PET should be obtained prior to the start of therapy.

Response Assessment

To assess response to TKI therapy, abdominal/pelvic CT or MRI is indicated every 8 to 12 weeks. PET may give an indication of imatinib activity after 2 to 4 weeks if rapid read-out is necessary.[28] Various CT response criteria have been investigated and compared in patients with GIST, including iterations of RECIST, Choi, and WHO criteria. [29-35]

Experts have advocated that the CT response criteria proposed by Choi are much better than RECIST criteria to assess the response of GIST to TKI therapy. Choi criteria have been validated in one center in patients with GIST who had not previously received TKI therapy.[29] However, these criteria are not universally accepted, they have not been validated for patients who have received several targeted therapies, and the ease of use outside specialized centers is unknown. Some recent studies have supported the use of RECIST, WHO, or volumetric criteria for sunitinib or regorafenib response assessment following progression on imatinib.[32-34]

The EORTC developed metabolic response criteria for tumors evaluated with PET that provide definitions for complete metabolic response, partial metabolic response, stable metabolic disease, or disease metabolic progression.[36] However, since there is a 95% correlation between the information from regular contrast-enhanced CT and PET/CT, CT with IV contrast is the preferred routine imaging modality for patients with GIST on TKI therapy.

Surgery

Surgery is the primary treatment of choice for patients with localized or potentially resectable GIST lesions. Preoperative imatinib can be considered to decrease surgical morbidity. If persistent metastatic or residual tumor remains after surgery, then imatinib should be continued as soon as the patient is able to tolerate oral intake.

GIST are fragile and should be handled with care to avoid tumor rupture. The goal is to achieve complete gross resection of the tumor with an intact pseudocapsule. After removal of any suspected GIST, postoperative pathology assessment is essential to confirm the diagnosis. Segmented or wedge resection to obtain negative margins is often appropriate. Lymphadenectomy is usually not required given the low incidences of nodal metastases, but resection of pathologically enlarged nodes should be considered in patients with *SDH*-deficient GIST. Resection should be accomplished with minimal morbidity and complex multivisceral resection should be avoided. Re-resection is generally not indicated for microscopically positive margins on final pathology. If abdominoperineal resection would be necessary to achieve a negative margin, then preoperative imatinib should be considered. If the surgeon feels that a complex surgical procedure is required, then a multidisciplinary consultation regarding the use of preoperative imatinib is recommended.

Sphincter-sparing surgery and esophagus-sparing surgery should be considered for rectal and gastroesophageal junction GIST, respectively. Several case reports have demonstrated that the use of preoperative imatinib enables organ-sparing surgery and improves surgical outcomes in patients with rectal GIST.[7]

The role for laparoscopy in the resection of GIST continues to expand. Although prospective studies are lacking, literature reports based on a small series of patients and retrospective analyses have demonstrated that not only are laparoscopic or laparoscopic-assisted resections possible, but they are also associated with low recurrence rates, short hospital stay duration, and low morbidity.[7] A meta-analysis of 19 studies (n = 1060 GIST cases) revealed no difference in long-term outcomes of GIST resections using laparotomy and laparoscopy, but laparoscopic approaches were associated with less blood loss, lower complication rates, and shorter hospital stays.[37]

Laparoscopic approach may be considered for selected GIST in favorable anatomic locations such as anterior wall of the stomach, jejunum, and ileum. The same surgical principles of complete macroscopic resection, including the preservation of the pseudocapsule and avoidance of tumor rupture, should be followed during laparoscopy. Resection specimen should be removed from the abdomen in a plastic bag to avoid spillage or seeding of port sites. Laparoscopic surgery could be feasible in other anatomic sites, such as smaller rectal GIST. However, data on laparoscopic resection of GIST at other sites are limited.

Targeted Therapy

GIST have previously been documented to be resistant to conventional chemotherapies. Since *KIT* activation occurs in the majority of cases of GIST, KIT inhibition has emerged as the primary therapeutic modality along with surgery for the treatment of GIST.

Imatinib

Imatinib, a selective inhibitor of the KIT protein tyrosine kinase, has produced durable clinical benefit and objective responses in most patients with GIST. In phase II and III studies, imatinib has resulted in high overall response rates and exceptionally good PFS in patients with unresectable and/or metastatic GIST, inducing objective responses in more than 50% of the patients.[38-42] In February 2002, the FDA approved use of imatinib for the treatment of patients with *KIT*-positive unresectable and/or metastatic malignant GIST. Long-term follow-up results of the B2222 study (n = 147, randomly assigned to receive 400 or 600 mg of imatinib daily) confirmed that imatinib induces durable disease control in patients with advanced GIST.[43] The estimated 9-year OS rate was 35% for all patients, 38% for those with CR or PR, and 49% for those with stable disease. Low tumor bulk at baseline predicted for longer TTP and improved OS.

Two separate phase III studies (EORTC 62005 study and the S0033/CALGB 150105 study) have assessed the efficacy of imatinib at two initial dose levels (400 mg daily vs. 800 mg daily, given as 400 mg twice a day) in patients with metastatic or unresectable GIST.[39,40,42] Both studies showed equivalent response rates and OS for both dose levels. Higher dose of imatinib was associated with more side effects than the lower dose in both studies. Although initial findings from the EORTC 62005 study (n = 946) suggested an earlier TTP for patients receiving 400 mg daily,[39] at a median follow-up of 10.9 years, no significant differences in survival were observed based on imatinib dose level.[44] In the 400-mg daily vs. 800-mg daily cohort, 10-year PFS rates were 9.5% versus 9.2% (HR, 0.91; 95% CI, 0.79–1.04; *P* = .18) and 10-year OS rates were 19.4% and 21.5%, respectively (HR, 0.93; 95% CI, 0.80–1.07; *P* = .31). Similarly, the S0033/CALGB 150105 study (n = 746) reported identical response rates (40% vs. 42%, respectively) at a median follow-up of 4.5 years and there were no statistical differences in PFS (18 months for low-dose arm vs. 40 months for higher-dose arm) and median OS (55 and 51 months,

respectively).[42] Following progression on 400 mg daily, 33% of patients who crossed over to the higher dose achieved objective response rates and stable disease. Among the patients who crossed over to the 800-mg daily dose after progression in EORTC 62005 study (n= 196, 47%), median PFS was 2.76 months.[44]

Available data confirm the safety and efficacy of imatinib at 400 mg/d as the initial standard dose to achieve response induction.[39,42] Dose escalation to 800 mg/d is a reasonable option for patients progressing on 400 mg/d.[40]

Preoperative Imatinib

The RTOG 0132/ACRIN 6665 is the first prospective study that evaluated the efficacy of preoperative imatinib (600 mg/d) in patients with potentially resectable primary disease (30 patients) or potentially resectable recurrent or metastatic disease (22 patients).[45] Among patients with primary GIST, PR and stable disease were observed in 7% and 83% of patients, respectively. In patients with recurrent or metastatic GIST, PR and stable disease were observed in 4.5% and 91% of patients, respectively. The estimated 2-year OS rate was 93% and 91% for patients with primary GIST and those with recurrent or metastatic GIST, respectively. The estimated 2-year PFS rate was 83% and 77%, respectively.

In a study conducted at MD Anderson Cancer Center, 19 patients undergoing surgical resection for primary GIST (with or without metastases) or recurrent disease (local or metastatic) were randomized to receive 3, 5, or 7 days of preoperative imatinib (600 mg daily).[46] The response rate assessed by FDG-PET and dynamic CT was 69% and 71%, respectively. Median DFS of patients treated with surgery and imatinib was 46 months. Tumor size was a predictor of recurrence after postoperative imatinib. However, in this study, there was no histologic evidence of cytoreduction within 3 to 7 days of preoperative imatinib.

In another prospective study, Fiore and colleagues reported that preoperative imatinib improved resectability and reduced surgical morbidity in patients with primary GIST, unresectable or resectable through a major surgical procedure with significant surgical morbidity. Median size reduction was 34% and the estimated 3-year PFS rate was 77%.[47] Imatinib was continued postoperatively for 2 years in all patients.

In the subgroup analysis of patients with non-metastatic, locally advanced, primary GIST treated with imatinib within the prospective BFR14 phase III study, preoperative imatinib was associated with a PR rate of 60% (15 of 25 patients), and 36% (9 of 25 patients) of patients underwent surgical resection of primary tumor after a median of 7.3 months of imatinib treatment.[48] All patients who underwent resection were treated with postoperative imatinib. The 3-year PFS and OS rates were 67% and 89%, respectively, for patients who underwent resection. All patients who underwent resection were treated with postoperative imatinib.

While the results of these prospective studies have demonstrated the safety and efficacy of preoperative imatinib in patients undergoing surgical resection, survival benefit could not be determined since all patients included in 3 of these studies also received postoperative imatinib postoperatively for 2 years.[45,46,48] Maximal response may require treatment for ≥6 months. Preoperative imatinib may prohibit accurate assessment of recurrence risk and should be considered only if surgical morbidity could be reduced by downstaging the tumor preoperatively. At the present time, the decision to use preoperative imatinib for patients with resectable primary or locally advanced or recurrent GIST should be made on an individual basis.

Postoperative Imatinib

Surgery does not routinely cure GIST. Complete resection is possible in approximately 85% of patients with primary tumors. At least 50% of these patients will develop recurrence or metastasis following complete

resection and the 5-year survival rate is about 50%.[49-51] Median time to recurrence after resection of primary high-risk GIST is about 2 years. A retrospective review of 506 patients with completely resected GIST revealed the potential for underestimating risk of recurrence, particularly in the case of intermediate size, intermediate-level mitotic count, and non-gastric tumors.[52] The data suggested that at least 3 years of adjuvant treatment was associated with higher RFS for patients with higher-risk disease. Multiple randomized studies have investigated the optimal duration of adjuvant therapy for resected GIST.

Imatinib therapy was investigated in a phase III, double-blind study (ACOSOG Z9001) that randomized patients with primary localized GIST (≥3 cm in size) to postoperative imatinib 400 mg (317 patients) or placebo (328 patients) for one year after complete resection.[53] At a median follow-up of 74 months, the RFS rate was significantly higher in the imatinib arm compared to placebo (HR, 0.6; 95% CI, 0.43–0.75; Cox model adjusted $P < .001$). OS was not significantly different between the imatinib and placebo arms.[54] Further analyses revealed that imatinib therapy was associated with higher RFS in patients with *KIT* exon 11 deletions (but not *KIT* exon 11 insertion or point mutation, *KIT* exon 9 mutation, *PDGFRA* mutation, or wild-type tumor). Tumor genotype was not associated with RFS in the placebo arm.

An intergroup randomized trial (EORTC-62024: NCT00103168) compared observation with 2 years of adjuvant imatinib following R0/R1 resection in 908 patients with localized, intermediate, or high-risk GIST. [55] RFS for imatinib versus observation was 84% versus 66% at 3 years and 69% versus 63% at 5 years ($P < .001$). However, the endpoint of 5-year imatinib failure-free survival (IFFS) did not reach significance at 87% versus 84% (HR, 0.79; 98.5% CI, 0.50–1.25; $P = .21$).

The results of another randomized phase III study from the Scandinavian Sarcoma Group (SSG XVIII/AIO) suggest that a longer duration of postoperative imatinib improves RFS and OS for patients with a high estimated risk of recurrence after surgery.[56,57] In this study, patients with a high risk for GIST recurrence after surgery were randomized to 12 months (n = 200) or 36 months (n = 200) of postoperative imatinib. After a median follow-up of 90 months, RFS and OS were significantly longer in the 36-month group compared to the 12-month group (5-year RFS: 71.1% vs. 52.3%, respectively; $P < .001$; 5-year OS: 91.9 % vs. 85.3% respectively; $P = .036$). The highest risk for recurrence was observed among patients with non-gastric GIST and tumors with high mitotic count.[58]

Management of Toxicities

The most common side effects of imatinib include fluid retention, diarrhea, nausea, fatigue, muscle cramps, abdominal pain, and rash. The side effect profile may improve with prolonged therapy.[59] Serious side effects (such as liver function test [LFT] abnormalities, lung toxicity, low blood counts, and GI bleeding) have rarely been reported and often improve after imatinib has been withheld. LFT abnormalities are seen in fewer than 5% of patients. Leukopenia is quite rare and imatinib has only rarely been associated with neutropenic fever. In a retrospective analysis of 219 consecutive patients treated with imatinib, grade 3 or 4 cardiotoxicity occurred in 8.2% of patients who were manageable with medical therapy, and infrequently required dose reduction or discontinuation of imatinib.[60] The side effect profile may improve with prolonged therapy and can be managed with appropriate supportive care measures. If life-threatening side effects occur with imatinib that cannot be managed by maximum supportive treatment, then sunitinib should be considered after discontinuing imatinib.

Sunitinib

Sunitinib is a multitargeted TKI that can induce objective responses and control progressive disease in patients with imatinib-resistant GIST. SDH-deficient GIST may have a higher probability of response to sunitinib.

In a randomized, phase III, placebo-controlled study, sunitinib produced significant, sustained clinical benefit in patients with imatinib-resistant or imatinib-intolerant GIST.[61] In patients with imatinib-resistant GIST, sunitinib resulted in a significant improvement in median time to progression (27.3 vs. 6.4 weeks) and significantly greater estimated OS. Sunitinib treatment induced PR in 14 patients (6.8%) and stable disease (≥22 weeks) in 36 patients (17.4%) versus no PRs and stable disease in 2 patients (1.9%) on placebo. In the imatinib-intolerant group, 4 out of 9 patients randomized to sunitinib achieved PR and one patient had progressive disease. In contrast, 3 of the 4 patients randomized to placebo had progressive disease at the time of analysis and no PR was observed. Sunitinib was generally well tolerated. In January 2006, sunitinib received FDA approval for the treatment of GIST after disease progression on or intolerance to imatinib.

The safety and efficacy of sunitinib on a continuous daily dosing schedule at 37.5 mg was evaluated in an open-label, multicenter, randomized phase II study in patients with advanced GIST after imatinib failure.[62] Patients were randomized (1:1) to receive continuous daily sunitinib (37.5 mg/d) either in the morning or in the evening for 28 days (one cycle). The primary endpoint was the clinical benefit rate (CBR) defined as the percentage of patients with CRs, PRs, or stable disease for 24 weeks or more based on RECIST criteria. The overall CBR was 53% (13% of patients had a PR and 40% had stable disease). Median PFS and OS were 34 weeks and 107 weeks, respectively. The most commonly reported treatment-related adverse events (diarrhea, fatigue, and nausea) were consistent with those known to be associated with sunitinib intermittent dosing. Treatment-related hypertension and hypothyroidism (experienced by 28% and 12% of patients, respectively) were successfully managed with appropriate supportive care measures. Both of these adverse events have also been associated with the long-term use of sunitinib on intermittent dosing. The results of this study suggest that continuous daily dosing appears to be an effective alternative dosing strategy with acceptable safety for patients with imatinib-resistant/-intolerant GIST.

Results were recently reported from an international study of sunitinib safety and efficacy in patients with imatinib-resistant/-intolerant advanced GIST (n = 1124).[63] The median PFS was 8.3 months (95% CI, 8.0–9.4 months) and the median OS was 16.6 months (95% CI, 14.9–18.0 months); safety findings were in line with previous studies. In a follow-up retrospective analysis of a subset of this trial population (n = 230), PFS was significantly better for patients with a primary mutation in *KIT* exon 9 compared to those with a primary mutation in exon 11 (12.3 months vs. 7 months; HR, 0.59; 95% CI, 0.39–0.89; *P* = .011).[64]

Management of Toxicities

Sunitinib-related toxicities can often be managed with dose interruptions or reductions. Fatigue, nausea, and vomiting were dose-limiting toxicities for sunitinib in clinical trials. Other common toxicities include hematologic toxicities (ie, anemia, neutropenia), diarrhea, abdominal pain, mucositis, anorexia, and skin discoloration. Sunitinib is associated with a significant risk of developing hand-foot skin reaction (HFSR).[65] Early detection and proper management of HFSR is vital during treatment with sunitinib. HFSR can be prevented with routine application of emollient lotions. If it is significant, interruption of therapy is indicated; if it is severe, dose reduction should be considered.

Hypertension is a common side effect reported in clinical trials, since sunitinib targets vascular endothelial growth factor receptor (VEGFR). However, the risk is higher in patients with renal cell carcinoma (RCC) compared to those with non-RCC.[66] Recent reports have shown that sunitinib is also associated with cardiotoxicity and hypothyroidism.[67,68] In a retrospective analysis of the data from phase I-II studies, 11% of patients had an adverse cardiovascular event including CHF in 8% of patients and

absolute reduction in the left ventricular ejection fraction (LVEF) in 28% of patients.[67] In a prospective, observational cohort study, abnormal serum thyroid-stimulating hormone (TSH) concentrations were documented in 62% of patients and the risk for hypothyroidism increased with the duration of therapy.[68]

Close monitoring for hypertension and LVEF is essential in patients receiving sunitinib, especially in patients with a history of heart disease or cardiac risk factors. Routine monitoring (every 3–6 months) of TSH is indicated. If hypothyroidism is suggested, patients should receive thyroid hormone replacement therapy. Patients should monitor their blood pressure closely and those who experience an increase in blood pressure should be treated with antihypertensives.[7]

Impact of Mutational Status on Tumor Response to First-Line Tyrosine Kinase Inhibitors in Patients with Advanced or Metastatic GIST

GIST are generally more resistant to traditional systemic chemotherapeutic agents and radiation therapy (RT) than other STS subtypes; therefore, treatment options for patients with advanced or metastatic GIST were historically limited.[69] The discovery that many GIST are driven by constitutively activated KIT or PDGFRA receptor tyrosine kinases was a significant breakthrough, enabling GIST to be managed with targeted therapies. TKIs have now emerged as the standard-of-care treatment for patients with advanced or metastatic GIST (GIST-4 and GIST-D 1 of 2). Imatinib, the first TKI approved for the treatment of patients with GIST, is clinically active against many GIST in the first-line setting.[44,70] However, not all GIST are responsive to imatinib, as tumor response is primarily dependent on tumor mutational status.

GIST with KIT or PDGFRA Mutations

Imatinib-Sensitive Mutations

Up to ~80% of GIST have a *KIT* mutation, while 5%–10% have a *PDGFRA* mutation.[15,71-73] The presence and type of *KIT* or *PDGFRA* mutations are not strongly correlated with prognosis. However, the presence (or absence) of mutations in specific regions of *KIT* and *PDGFRA* genes are associated with a response to specific TKIs.

In randomized trials evaluating imatinib in the advanced disease setting, the presence of a *KIT* exon 11 mutation was associated with better response rates, median progression-free survival (PFS), and median overall survival (OS) than *KIT* exon 9 mutations or non-mutated *KIT* or *PDGFRA*.[27,70,73-75] Long-term follow-up (median 73 months) from the randomized, phase III BFR14 trial by the French Sarcoma Group identified *KIT* exon 11 mutations as an independent prognostic factor for longer PFS and OS in patients treated with standard-dose imatinib when compared with *KIT* exon 9 mutations or non-mutated *KIT*.[27] In the US-Finnish B2222 phase II study, imatinib was associated with better outcomes for patients with *KIT* exon 11 mutations than those with *KIT* exon 9 mutations or who had no detectable kinase mutations.[70] The partial response (PR) rates for patients with *KIT* exon 11 mutations, *KIT* exon 9 mutations, or no detectable kinase mutations were 83.5%, 47.8%, and 0%, respectively. The presence of *KIT* exon 11 mutations was the strongest prognostic factor reducing the risk of death by more than 95%.

GIST with *KIT* exon 9 mutations treated with imatinib generally have a lower response rate and PFS than those with *KIT* exon 11 tumors at a dose of 400 mg daily, but imatinib 400 mg two times a day (BID) may lead to a better response and PFS. In the randomized EORTC 62005 study, the presence of *KIT* exon 9 mutations was the strongest adverse prognostic factor for risk of progression and death.[73] High-dose imatinib (400 mg BID) resulted in a significantly superior PFS with a reduction in the relative risk of 61% (P = .0013) in patients whose tumors expressed a *KIT* exon 9 mutation compared with the standard 400 mg/day imatinib dose.[73] Additionally, the response rate after crossover from 400 mg daily to 400 mg BID imatinib was higher in patients with *KIT* exon 9 mutations (57%) than patients with *KIT* exon 11 mutations (7%). Similarly, results from the phase III SWOG S0033/CALGB 150105 trial showed that imatinib at 400 mg BID resulted in a higher response rate in patients with a *KIT* exon 9 mutation than those with imatinib at 400 mg once daily (67% vs. 17%, respectively).[75] A meta-analysis of EORTC 62005 and SWOG S0033/CALGB 150105 trials that randomized 1640 patients with advanced GIST to standard-dose imatinib (400 mg daily) or high-dose imatinib (400 mg BID) showed a benefit in PFS for patients with *KIT* exon 9 mutations treated with high-dose imatinib.[76]

While most GIST with *PDGFRA* mutations are associated with a response to imatinib, those with certain mutations, such as D842V,

generally do not respond.[11,15] In a survey of patients with confirmed *PDGFRA* mutations, none of 31 evaluable patients with a D842V mutation had a response to imatinib, and 21 of 31 (68%) experienced disease progression.[77] The median PFS was 2.8 months for patients with D842V compared with 28.5 months for patients with other *PDGFRA* mutations (eg, indels in exon 18). With 46 months of follow-up, the median OS was 14.7 months for patients with D842V and not reached for patients with other *PDGFRA* mutations.

Imatinib is included in the guidelines as a category 1 preferred first-line treatment option for patients with advanced or metastatic GIST with imatinib-sensitive mutations; however, it is not recommended for the treatment of GIST with *PDGFRA* exon 18 mutations that are insensitive to imatinib, especially D842V (GIST-4 and GIST-D 1 of 2).

In the adjuvant setting, a longer duration of imatinib treatment may be beneficial for patients with GIST that have certain *KIT* mutations. Follow-up analysis of a randomized phase III study from the Scandinavian Sarcoma Group (SSG XVIII/AIO) revealed that patients with GIST harboring a *KIT* exon 11 deletion appear to benefit most from longer-duration imatinib, showing higher recurrence-free survival (RFS) when allocated to the 3-year versus 1-year imatinib group.[78] A similar pattern related to duration of treatment was not observed for GIST harboring other mutations.

Imatinib-Insensitive Mutations

GIST with imatinib-insensitive mutations such as *PDGFRA* D842V are managed differently than most GIST. Avapritinib is a TKI approved for the treatment of patients with unresectable or metastatic GIST with a *PDGFRA* exon 18 mutation, including D842V mutations.[79,80] The approval of avapritinib for GIST was based on results from the open-label, single-arm phase I NAVIGATOR trial that evaluated the safety and antitumor activity of avapritinib in 56 patients with *PDGFRA* D842V-containing GIST that were unresectable and/or metastatic.[81,82] In the long-term analysis of the trial, at data cut-off (median follow-up of 27.5 months), the overall response rate (ORR) with avapritinib was 91%, with a median duration of response (DOR) of 27.6 months.[82]

Given these data, the panel recommends avapritinib as the preferred first-line treatment option for patients with unresectable, progressive, or metastatic GIST with imatinib-resistant *PDGFRA* D842V mutations or other *PDGFRA* exon 18 mutations that are known to be imatinib-insensitive (GIST-4 and GIST-D 1 of 2).

GIST Without KIT or PDGFRA Mutations

Approximately 10%–15% of GIST lack a mutation in either *KIT* or *PDGFRA*.[16,71] Most of these have functional inactivation of the succinate dehydrogenase (SDH) complex (either from mutations or epigenetic silencing leading to a lack of SDH protein expression),[16] which has been shown to be a cause of tumorigenesis. GIST with SDH deficiency generally lack the gain-of-function tyrosine kinase mutations found in the majority of GIST;[83] therefore, certain TKIs (specifically imatinib) have limited efficacy in this setting.[84]

However, TKIs with activity against vascular endothelial growth factor receptor (VEGFR) can be considered as potential options for SDH-deficient GIST. Data from two small retrospective studies suggested that sunitinib may be active in SDH-deficient GIST.[85,86] Although sunitinib targets KIT and PDGFRA, it is also active against other kinases, including VEGFR.[87] Regorafenib is another TKI with activity against VEGFR, and was reported to be clinically active against SDH-deficient GIST in a small number of patients.[88,89] In a phase II study, prolonged disease control was achieved in one patient with SDH-deficient GIST treated with pazopanib, another TKI that targets VEGFR.[90,91] Based on these limited data, the guidelines recommend consideration of sunitinib, regorafenib, and pazopanib as options for unresectable SDH-deficient

GIST (GIST-D 1 of 2 and GIST-D 2 of 2). There are other potential treatments on the horizon for patients with SDH-deficient GIST; for example, temozolomide has shown promise in this setting based on preclinical data,[92] and is currently undergoing clinical testing (NCT03556384).

GIST with *NTRK* fusions in the absence of *KIT/PDGFRA* mutations may occur.[93-95] *NTRK* fusion is an actionable alteration, as both larotrectinib and entrectinib were granted accelerated approval by the U.S. Food and Drug Administration (FDA) for the treatment of solid tumors with *NTRK* gene fusions.[96,97] In a combined analysis of three studies, larotrectinib resulted in an ORR of 75% (based on independent review) in children and adults with locally advanced or metastatic *NTRK* fusion-positive solid tumors, including GIST.[98] An integrated analysis of three trials found that entrectinib led to an objective response in 57% of adults with locally advanced or metastatic *NTRK* fusion-positive solid tumors.[99] The guidelines recommend larotrectinib and entrectinib as preferred first-line treatment options for patients with unresectable, progressive, or metastatic GIST that are *NTRK*-fusion positive (GIST-D 1 of 2).

Other genomic events, such as alterations in *BRAF, NF1*, and *FGFR,* may also occur in GIST.[21,95,100-104] The guidelines do not recommend specific therapies for GIST with these alterations; however, the presence of these genomic events could be used to identify potential targeted therapy options. For example, combination therapy with dabrafenib and trametinib was recently approved by the FDA for the treatment of patients with advanced solid tumors with *BRAF* V600E mutations.[105]

Management of Resistance to Tyrosine Kinase Inhibitors

Resistance to Imatinib

While imatinib improves outcomes for patients with advanced or metastatic GIST, many will develop resistance to the drug. Primary imatinib resistance is defined as the evidence of clinical progression developing during the first 6 months of imatinib therapy; this is most commonly seen in patients with *KIT* exon 9 mutations treated with imatinib at 400 mg daily, *PDGFRA* D842V mutations, or those with tumors that lack identifiable activating mutations in *KIT* or *PDGFRA,* the majority of which are SDH-deficient GIST, thus underscoring the importance of genotyping GIST.[70,74,75,106] Secondary resistance is seen in patients who have been on imatinib for more than 6 months with an initial response or disease stabilization followed by progression, most commonly because of the outgrowth of tumor clones with secondary mutations in *KIT*.[107-110]

For GIST with limited progression following the standard imatinib dose regimen, several options are available (GIST-5). The same dose of imatinib can be continued, while also considering resection (if feasible), ablation procedures/embolization/chemoembolization, or palliative RT (category 2B) for symptomatic lesions. The TKI can also be switched to sunitinib (category 1); alternatively, dose escalation of imatinib to 800 mg/day (400 mg BID) is another option.[40,61,62] Data have suggested that certain patients with GIST, particularly those with *KIT* exon 9 mutations, may derive benefit from imatinib dose escalation.[76,111] For patients with performance status (PS) 0–2 and generalized disease progression following treatment with imatinib 400 mg/day, the guidelines recommend switching to an alternate TKI or escalating the dose of imatinib, as tolerated (GIST-5 and GIST-D 1 of 2).

The approval of sunitinib for the treatment of patients with imatinib-refractory or intolerant GIST was primarily based on a phase III randomized controlled study in 312 patients with advanced GIST that were resistant or intolerant to prior imatinib treatment.[61,112] The median time to tumor progression was 27.3 weeks in the sunitinib group versus 6.4 weeks in the placebo group (hazard ratio [HR] 0.33; $P < .0001$).

The clinical activity of sunitinib in imatinib-resistant GIST can vary depending on the presence of primary and secondary *KIT* mutations. One study found that second-line sunitinib induced higher clinical benefit (PR or stable disease for ≥6 months) in patients with imatinib-resistant/intolerant GIST with primary *KIT* exon 9 mutations than those with *KIT* exon 11 mutations (58% vs. 34%, respectively).[106] Median PFS and OS were significantly longer for patients with *KIT* exon 9 mutations or non-mutated *KIT* than those with *KIT* exon 11 mutations. In patients with *KIT* exon 11 mutations, median PFS and OS were longer for those with secondary exon 13 or 14 mutations compared to those with exon 17 or 18 mutations. Although sunitinib appears to have activity against tumors with *KIT* adenosine triphosphate (ATP)-binding pocket mutations (exons 13 and 14) that confer resistance to imatinib, it has little activity against tumors with imatinib-resistant mutations in the *KIT* activation loop (exons 17 and 18).[113-115]

Based on these data, sunitinib (category 1) is recommended as a preferred second-line option for patients with unresectable, progressive, or metastatic GIST previously treated with imatinib (GIST-D 1 of 2).

For patients with a *PDGFRA* D842V mutation or other *PDGFRA* exon 18 mutations that are insensitive to imatinib, the guidelines recommend dasatinib as a second-line option. The clinical evidence supporting use of dasatinib as a second-line therapy is described in more detail in the *Resistance to Avapritinib* section.

Resistance to Imatinib and Sunitinib

Regorafenib, a multikinase inhibitor with activity against KIT, PDGFR, VEGFR, and others, can be considered for patients with locally advanced, unresectable, or metastatic GIST previously treated with imatinib and sunitinib.[88] The FDA approval of regorafenib in this setting was based on results from the phase III randomized GRID trial, where regorafenib versus placebo was evaluated in 199 patients with metastatic and/or unresectable GIST that progressed on prior therapy with imatinib and sunitinib.[116] The median PFS (4.8 months vs. 0.9 months; $P < .0001$) and the disease control rate (DCR; 53% vs. 9%) were significantly higher for regorafenib than placebo. The PFS rates at 3 and 6 months were 60% and 38%, respectively, for regorafenib compared to 11% and 0%, respectively, for placebo. The HR for OS was 0.77 with 85% of patients in the placebo arm crossing over to regorafenib due to disease progression. Long-term follow-up (median 41 months) from a phase II study in unresectable or metastatic GIST (n = 33) suggested that patients with *KIT* exon 11 mutations or SDH-deficient GIST may derive a greater PFS benefit from regorafenib than *KIT/PDGFRA* wild-type, non-SDH–deficient tumors.[89] Given these data, regorafenib (category 1) is included in the guidelines on GIST-D 1 of 2 as a preferred third-line option following imatinib and sunitinib.

Resistance to Imatinib, Sunitinib, and Regorafenib

Ripretinib, a TKI that inhibits KIT and PDGFRA kinases, is approved by the FDA for adults with advanced GIST who have received prior treatment with 3 or more kinase inhibitors, including imatinib.[117] In the phase III INVICTUS trial, ripretinib 150 mg daily was evaluated against placebo in patients with advanced GIST who were previously treated with imatinib, sunitinib, and regorafenib.[118] The median PFS of the ripretinib group was 6.3 months, compared with 1.0 months in the placebo group ($P < .0001$). Ripretinib (category 1) is recommended in the guidelines as a preferred fourth-line option for patients with unresectable, progressive, or metastatic GIST after treatment with imatinib, sunitinib, and regorafenib (GIST-D 1 of 2).

In a follow-up analysis of INVICTUS, dose escalation of ripretinib to 150 mg BID was evaluated in 43 patients who experienced disease progression while on ripretinib 150 mg daily.[119] The median OS was 18.4 months for patients who switched to ripretinib 150 mg BID, compared

with 14.2 months for patients from INVICTUS who experienced disease progression but did not undergo dose escalation. The median PFS after receiving the first dose of 150 mg BID was 3.7 months. The guidelines include dose escalation of ripretinib to 150 mg BID as an option for patients who experience disease progression while on ripretinib 150 mg daily (GIST-D 1 of 2).

Resistance to Imatinib, Sunitinib, Regorafenib, and Ripretinib

Other TKIs are recommended in the guidelines as off-label options after disease progression on approved therapies (GIST-D 1 of 2). Much of the data on these TKIs are derived from phase II studies and retrospective analyses involving a small number of patients. Additionally, many of these studies only included patients previously treated with imatinib and sunitinib, but not regorafenib and/or ripretinib.

A few studies have evaluated sorafenib as an option for some patients with advanced or metastatic GIST.[120-123] In a prospective, multicenter, phase II study of 38 patients with unresectable, KIT-positive GIST that had progressed on imatinib and sunitinib, sorafenib resulted in a DCR of 68% (55% had stable disease and 13% had PR).[120] Median PFS and OS were 5.2 months and 11.6 months, respectively. In a retrospective analysis of 124 patients with metastatic GIST resistant to imatinib and sunitinib, the median PFS and OS of patients who received sorafenib was 6.4 months and 13.5 months, respectively.[122]

Another TKI that can be considered is nilotinib.[124-128] In a retrospective analysis of 52 patients with advanced imatinib- and sunitinib-resistant GIST, nilotinib resulted in a 10% response rate and 37% DCR.[125] Median PFS and OS were 12 weeks and 34 weeks, respectively. In a randomized phase III study of nilotinib as third-line therapy in patients with GIST resistant or intolerant to imatinib and sunitinib (248 patients), the PFS on nilotinib was not superior to best supportive care (109 days vs. 111 days; *P* = .56).[127] In a post hoc analysis, nilotinib led to an improved OS (>4 months) compared with best supportive care (405 days vs. 280 days; *P* = .02) in patients whose disease progressed on both imatinib and sunitinib. This clinical benefit may be specific to patients with secondary *KIT* exon 17 mutations.[128] In a phase III trial that evaluated nilotinib versus imatinib in the first-line setting, none of the patients with *KIT* exon 9 mutations treated with nilotinib achieved an objective response. Additionally, nilotinib resulted in a shorter PFS than imatinib in those with *KIT* exon 9 mutations, suggesting that nilotinib is not effective for this mutation type.[129]

Pazopanib also has modest activity in unselected, heavily pretreated patients with advanced GIST.[90,130] In a randomized, phase II trial comparing pazopanib to best supportive care in imatinib- and sunitinib-resistant GIST (n = 81), median PFS was 3.4 months versus 2.3 months, respectively (HR, 0.59; 95% CI, 0.37–0.96; *P* = .03).[130]

Cabozantinib is another TKI that may be considered for patients whose disease has progressed on approved therapies.[131] Everolimus in combination with a TKI (ie, imatinib, sunitinib, regorafenib) may also be active in imatinib-resistant GIST.[132]

For a complete list of additional options for GIST that have progressed on approved therapies, please see GIST-D 1 of 2.

Resistance to Avapritinib

For GIST that become avapritinib-resistant, several options are recommended (GIST-5). For limited disease progression, avapritinib treatment can be continued while also considering additional options, such as resection (if feasible), ablation procedures, embolization, chemoembolization, or palliative RT (category 2B) for symptomatic lesions. For patients with generalized disease progression following first-line avapritinib who also have PS 0–2, the guidelines recommend switching to an alternate TKI. Several studies have suggested that

dasatinib can be considered as another option for GIST with *PDGFRA* D842V.[133-135] Dasatinib has been shown to be a potent inhibitor of cells expressing the *PDGFRA* D842V mutation *in vitro*.[133] Additionally, a single arm, open-label study evaluated the antitumor activity of dasatinib in 50 patients with advanced imatinib-refractory GIST.[135] The primary endpoint (>30% 6-month PFS) was not met, as the 6-month PFS was 29%. However, the study provided evidence that dasatinib may have some clinical activity in this population, as a partial tumor response was observed in 25% of patients, including one with an imatinib-resistant *PDGFRA* exon 18 (D842V) mutation. Therefore, the guidelines recommend dasatinib as a preferred second-line therapy option for patients with *PDGFRA* exon 18 mutations (including D842V) whose disease has become resistant to either avapritinib or imatinib (GIST-D 1 of 2).

Ripretinib is another TKI that exhibits broad activity against both KIT and PDGFRA (including D842V) in the preclinical setting;[136] however, additional clinical trials are needed to confirm the efficacy of ripretinib against GIST with *PDGFRA* D842V mutations. The guidelines recommend ripretinib 150 mg daily as an option that may be useful in certain circumstances for GIST that progress following avapritinib and dasatinib (GIST-D 1 of 2). Dose escalation of ripretinib to 150 mg BID can also be considered.

Other Options for Progressive Disease

In addition to the systemic therapies described above, other options are recommended for progressive disease (GIST-5). Resection (if feasible), ablation procedures, embolization, or chemoembolization are options for patients with limited disease progression; palliative RT is another alternative for those with symptomatic lesions. If the disease continues to progress despite prior therapies, a repeat tumor biopsy can be considered to potentially identify uncommon mutations that may have a corresponding targeted therapy.[137,138] Clinical trials and best supportive care are also recommended. Reintroduction of a previously tolerated and effective TKI can be considered for palliation of symptoms. Continuation of life-long TKI therapy can be considered for palliation of symptoms as part of best supportive care.

Initial Evaluation and Workup

All patients should be managed by a multidisciplinary team with expertise in sarcoma. Essential elements of the workup include the H&P, primary site and chest imaging, EUS in selected patients, endoscopy as indicated (if not previously done), and surgical assessment. Genotyping is recommended for cases in which medical therapy is anticipated. For very small GIST (<2 cm), abdominal/pelvic CT and/or MRI is sufficient. For all other GIST, workup includes baseline abdominal/pelvic CT and/or abdominal/pelvic MRI, along with chest imaging using CT or x-ray. PET/CT can be considered. Baseline PET/CT should be performed if PET/CT will be used during follow-up.

Treatment Guidelines

Resectable Disease

Primary/Preoperative Treatment

Surgery is the primary treatment for all patients with GIST (2 cm or greater) that are resectable without significant risk of morbidity. Preoperative imatinib may be beneficial as primary treatment for patients with GIST that is resectable with negative margins but with a significant risk of morbidity.[45,47] The use of preoperative imatinib may, however, prohibit the accurate assessment of recurrence risk. Preoperative imatinib should be considered only if surgical morbidity could be reduced by downstaging the tumor prior to resection. Close monitoring is essential because some patients may rapidly become unresectable. In prospective studies, preoperative imatinib has been tested at a daily dose of either 400 mg[47,48] or 600 mg.[45,46] The guidelines recommend an initial dose of 400 mg daily. Patients with documented *KIT* exon 9 mutations may benefit from dose escalation up to 800 mg daily (given as 400 mg twice daily), as tolerated.

Baseline imaging is recommended prior to the start of preoperative imatinib. To assess response to TKI therapy, abdominal/pelvic CT or MRI is indicated every 8 to 12 weeks. PET may give an indication of imatinib activity after 2 to 4 weeks if rapid read-out is necessary. Since the optimal duration of preoperative therapy remains unknown, in patients with disease that is responding to therapy, imatinib should be continued until maximal response (defined as no further improvement between 2 successive CT scans, which can take as long as 6–12 months). However, it is not always necessary to wait for a maximal response to perform surgery. Surgery is recommended if bleeding and/or symptoms are present. For patients with disease that is responding to treatment, response assessment imaging can be performed less frequently. Progression may be determined by abdominal/pelvic CT or MRI with clinical interpretation, relying on PET/CT as needed to clarify ambiguous results. Assess medication adherence before determining that therapy was ineffective. If there is no progression, continuation of the same dose of imatinib is recommended and resection should be considered, if possible. If there is progression, surgery is recommended after discontinuing imatinib. In patients taking preoperative imatinib, dosing can be stopped right before surgery and resumed as soon as the patient is able to tolerate oral medications following surgery, regardless of surgical margins. Collaboration between the medical oncologist and the surgeon is necessary to determine the appropriateness of surgery following major response or stable disease.

However, the management of incidentally encountered small GIST less than 2 cm remains controversial.[7] At present, there are insufficient data to guide the management of very small GIST (less than 2 cm) discovered incidentally on endoscopy, and the usefulness of regular EUS surveillance has not been established. Complete surgical resection is the mainstay of treatment in symptomatic patients. For a subset of patients with very small gastric GIST (less than 2 cm) with no high-risk EUS features (ie, irregular

extra-luminal border, heterogeneous echo pattern, presence of cystic spaces, echogenic foci), periodic endoscopic or radiographic surveillance may be considered.[8,139]

Postoperative Treatment

Based on results of the ACOSOG Z9001 study and the randomized phase III study SSGXVIII/AIO (NCT00116935), the guidelines recommend postoperative imatinib following complete resection for primary GIST with no preoperative imatinib for patients at intermediate or high risk of recurrence (category 1).[53,56] The panel recommends that postoperative imatinib for at least 36 months should be considered for patients with high-risk GIST.[56,57]

Estimation of risk of recurrence is important in selecting patients who would benefit from postoperative therapy following complete resection. In the ACOSOG Z9001 study, risk stratification was based only on tumor size and postoperative imatinib improved RFS in patients with GIST 3 cm or larger; however, it was statistically significant in patients with intermediate (6 cm or greater and less than 10 cm) and high risk (greater than 10 cm) of recurrence.[53,54] In the SSGXVIII/AIO study, risk stratification was based on tumor size, site, mitotic count, and rupture; survival benefit was seen in patients with high risk of recurrence (mitotic index of >5 mitoses/50 HPF, size >5 cm, non-gastric location, and tumor rupture).[56] Risk stratification after surgical resection should be based on tumor mitotic rate, size, and location.[140] Gold and colleagues have developed a nomogram, taking into account tumor size, site, and mitotic index, to predict RFS after resection of localized primary GIST.[141] This nomogram accurately predicts RFS after resection of localized primary GIST and might be useful for patient care, interpretation of study results, and selection of patients for postoperative imatinib therapy.

For patients with complete resection following preoperative imatinib, the panel agreed that continuation of imatinib (at the same dose that induced objective response) is warranted. The panel acknowledged that while data from single and multicenter studies support the continuation of postoperative imatinib for 2 years following surgery, the exact duration of postoperative imatinib in this group of patients has not been studied in randomized studies.[45-48] The long-term analysis of the RTOG 0132 study suggested that a high percentage of patients progressed after discontinuation of 2-year postoperative imatinib therapy.[142]

For patients with completely resected disease who did not receive preoperative imatinib, postoperative imatinib is recommended for patients with intermediate or high-risk disease (category 1). Observation can be considered for completely resected, low-risk disease.

In patients with persistent gross disease following resection (R2 resection) who received preoperative imatinib, additional resection may be considered to remove residual disease. Imatinib treatment should be continued following re-resection regardless of surgical margins until progression. Postoperative imatinib should be initiated following resection if the patient did not receive prior imatinib therapy.

Unresectable, Metastatic, or Recurrent Disease

Baseline imaging is recommended prior to initiation of treatment. Imatinib (category 1) is the primary treatment for patients with advanced, unresectable, or metastatic GIST. Imatinib has been shown to improve resectability and reduce surgical morbidity in patients with documented unresectable GIST or in patients for whom resection would carry the risk of severe postoperative functional deficit.[47,48] Several retrospective studies have demonstrated survival benefit of cytoreductive surgery following preoperative imatinib in patients with advanced or metastatic GIST responding to preoperative imatinib.[143-150] No definitive data exist to prove whether surgical resection improves clinical outcome in addition to TKI therapy for patients with resectable metastatic GIST. Prospective phase III

studies are underway to assess whether or not resection changes outcome in patients with unresectable metastatic GIST responding to TKI therapy.

Providers should consider resection if complete resection can be obtained in primary metastatic disease. To assess response to TKI therapy, abdominal/pelvic CT or MRI is indicated every 8 to 12 weeks. PET may give an indication of imatinib activity after 2 to 4 weeks if rapid read-out is necessary. If there is no progression, resection can be considered following surgical consultation. Imatinib should be continued if resection is not feasible. At this time, continuous use of imatinib is recommended for metastatic GIST until progression. The patient should be maintained on the same dose, and the dose of imatinib should not be increased if patients remain stable without objective progression of the disease. Termination of imatinib in patients with GIST that is refractory to imatinib has been shown to result in a flare phenomenon, which in turn indicates that even in patients with progressive disease on imatinib therapy, there are some tumor cells for which imatinib may still be effective.[151]

Recurrence following complete resection should be managed as described for unresectable or metastatic disease, because recurrent disease represents locoregional metastatic or infiltrative spread of the malignancy and carries essentially the same prognosis as distant metastases overall.

Progressive Disease

Progression is defined as the appearance of a new lesion or an increase in tumor size and may be determined by abdominal/pelvic CT or MRI with clinical interpretation, using PET/CT as needed to clarify ambiguous results. Medication adherence should be assessed prior to determining that therapy is ineffective.

Dose escalation of imatinib up to 800 mg daily (given as 400 mg twice daily) as tolerated or switching to sunitinib (category 1) are included as options for patients with progressive disease (limited disease or widespread systemic disease in patients with good performance status) on standard-dose imatinib.[40,61,62] All clinical and radiological data, including lesion density on CT and patient compliance to treatment with standard-dose imatinib, should be assessed prior to dose escalation of imatinib or switching to sunitinib.

For patients with limited progressive disease on standard-dose imatinib, second-line therapy with sunitinib should be initiated only if the majority of disease is no longer controlled by imatinib; consideration of other therapeutic interventions for progressing lesion(s) is warranted. Surgical resection should be considered in carefully selected patients with limited progressive disease that is potentially easily resectable.[143,148,152] However, incomplete resections are frequent with high complication rates. The guidelines have included, only for patients with limited progressive disease, continuation of imatinib at the same initial dose and treatment of progressing lesions with resection, RFA, chemoembolization (category 2B), or palliative RT (category 2B) for rare patients with bone metastases.[7]

Regorafenib (category 1) is recommended for patients with disease progression on imatinib and sunitinib.[116] Based on limited data,[90,120-128,130,132-134] the guidelines have also included sorafenib, dasatinib, nilotinib, pazopanib, and everolimus plus TKI as additional options for patients who are no longer receiving clinical benefit from imatinib, sunitinib, or regorafenib, although much of the data regarding the potential benefit of these agents were collected in the pre-regorafenib era.

In patients with progressive disease no longer receiving benefit from current TKI therapy, re-introduction of previously tolerated and effective TKI therapy for palliation of symptoms can be considered.[153,154] The results of a recent randomized study demonstrated that imatinib rechallenge significantly improved PFS and DCR in patients with

advanced GIST after failure of at least imatinib and sunitinib.[154] However, the duration of survival benefit was brief due to continued progression of TKI-resistant clones.

Any patient who has disease progression despite prior therapy or who has a recurrence, regardless of presentation, should be considered for enrollment in a clinical trial, if an appropriate trial is available.

Continuation of TKI Therapy

The optimal duration of TKI therapy in patients with responding or stable disease is not known. The results of a prospective, multicenter, randomized phase III study (BFR14) show that there was a significant increase in the rate of progressive disease when imatinib therapy was interrupted in patients with advanced disease that was stable or responding to imatinib therapy.[155,156] A recent report from this study confirmed that patients with rapid disease progression after interruption of imatinib had a poorer prognosis.[157] More importantly, the quality of response upon reintroduction of imatinib did not reach the tumor status observed at randomization.

The panel strongly recommends that TKI therapy at the prescribed daily dose should be continued as long as patients are receiving clinical benefit (response or stable disease). The panel also feels that life-long continuation of TKI therapy for palliation of symptoms should be an essential component of best supportive care. However, short interruptions for one to two weeks, when medically necessary, have not been shown to negatively impact disease control or other outcomes.

Surveillance

Patients with completely resected, incompletely resected, or metastatic GIST should have a thorough H&P every 3 to 6 months; abdominal/pelvic CT scan should be performed every 3 to 6 months for 3 to 5 years, then annually. Less frequent surveillance may be acceptable for low-risk or very small tumors (<2 cm). Progression may be determined by CT or MRI with clinical interpretation; PET/CT can be considered to clarify ambiguous CT results.

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