National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Gastrointestinal Stromal Tumors (GISTs)

Version 1.2022 — January 21, 2022

NCCN.org

NCCN Guidelines for Patients® available at www.nccn.org/patients

Continue

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Gastrointestinal Stromal Tumors (GISTs)

NCCN Guidelines Index
Table of Contents
Discussion

***Margaret von Mehren, MD/Chair †**
Fox Chase Cancer Center

***John M. Kane, III, MD/Vice-Chair ¶**
Roswell Park Comprehensive Cancer Center

Mark Agulnik, MD †
City of Hope National Medical Center

Marilyn M. Bui, MD, PhD ≠
Moffitt Cancer Center

Janai Carr-Ascher, MD, PhD ≠
UC Davis Comprehensive Cancer Center

Edwin Choy, MD, PhD †
Massachusetts General Hospital Cancer Center

Mary Connelly, LSW ¥
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

Sarah Dry, MD ≠
UCLA Jonsson Comprehensive Cancer Center

Kristen N. Ganjoo, MD †
Stanford Cancer Institute

Ricardo J. Gonzalez, MD ¶
Moffitt Cancer Center

Ashley Holder, MD ¶
O'Neal Comprehensive Cancer Center at UAB

Jade Homsi, MD †
UT Southwestern Simmons Comprehensive Cancer Center

Vicki Keedy, MD, MSCI †
Vanderbilt-Ingram Cancer Center

Ciara M. Kelly, MD †
Memorial Sloan Kettering Cancer Center

Edward Kim, MD §
Fred Hutchinson Cancer Research Center/ Seattle Cancer Care Alliance

David Liebner, MD Þ †
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

Martin McCarter, MD ¶
University of Colorado Cancer Center

Sean V. McGarry, MD ¶ т
Fred & Pamela Buffett Cancer Center

Nathan W. Mesko, MD т
Case Comprehensive Cancer Center/ University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Christian Meyer, MD, PhD †
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Alberto S. Pappo, MD €
St. Jude Children's Research Hospital/ University of Tennessee Health Science Center

Amanda M. Parkes, MD ‡ †
University of Wisconsin Carbone Cancer Center

Ivy A. Petersen, MD §
Mayo Clinic Cancer Center

Seth M. Pollack, MD †
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Matthew Poppe, MD §
Huntsman Cancer Institute at the University of Utah

Richard F. Riedel, MD †
Duke Cancer Institute

Scott Schuetze, MD, PhD †
University of Michigan Rogel Cancer Center

Jacob Shabason, MD §
Abramson Cancer Center at the University of Pennsylvania

Jason K. Sicklick, MD ¶
UC San Diego Moores Cancer Center

Matthew B. Spraker, MD, PhD §
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Melissa Zimel, MD т ¶
UCSF Helen Diller Family Comprehensive Cancer Center

NCCN
Lisa E. Hang, PhD
Hema Sundar, PhD
Mary Anne Bergman

[NCCN Guidelines Panel Disclosures]

Continue

‡ Hematology/ Hematologic oncology
Þ Internal medicine
† Medical oncology
т Orthopedics/Orthopedic oncology
≠ Pathology
¥ Patient advocacy
€ Pediatric oncology
§ Radiotherapy/Radiation oncology
¶ Surgery/Surgical oncology
* Discussion writing committee member

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Gastrointestinal Stromal Tumors (GISTs)

Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

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.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Gastrointestinal Stromal Tumors (GISTs)

NCCN Guidelines Index
Table of Contents
Discussion

Updates in Version 1.2022 of the NCCN Guidelines for Gastrointestinal Stromal Tumors (GISTs) from Version 1.2021 include:

GIST-1

Workup at Primary Presentation

- Bullet 2 modified: *Consider* endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB) or *Endoscopic ultrasound-guided core needle biopsy (EUS-CNB)*
  - Management based on the results of initial diagnostic evaluation- Resectable with significant morbidity
    - ◊ Recommendation modified: *If* ~~considering~~ neoadjuvant *therapy is planned, consider biopsy. Based on molecular testing, imatinib or avapritinib...*

GIST-2

- Primary Treatment header changed to *Neoadjuvant Therapy*
- Column 2: "Baseline imaging" changed to *"Mutational testing"*
- Column 3: Category 1 designation was removed for Imatinib

Footnotes:

- Footnote s removed.

GIST-3

Postoperative Outcomes

- Completely resected after preoperative imatinib: Adjuvant imatinib recommendation clarified as follows *for patients with significant risk of recurrence (intermediate or high risk)* (See GIST-A).
- Modified: ~~Persistent microscopic residual disease (R1 resection) or~~ Gross residual disease (R2 resection)

Follow-Up

- Modified: H&P and imaging every 3–6 mo ~~for high risk, every 3–6 mo~~ for 5 y (every 3 mo if high risk), then annually

Footnotes:

- Footnote s modified: The *optimal duration of adjuvant imatinib is unknown. Available data support the use of adjuvant imatinib for at least 3 years*. The PERSIST study...
- Footnote t: *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* is new corresponding to "adjuvant imatinib"

GIST-4

- Primary Treatment header changed to *First-Line Therapy.*

GIST-5

Treatment for Progressive Disease

- Bullet 1, modified for limited progression: imatinib *or avapritinib*
- Bullet 2, modified, *If previously treated with standard dose imatinib*: *Switch* to sunitinib (category 1) or escalate dose of imatinib as tolerated
- Lower pathway, generalized progression, modified: For performance status (PS) 0-2 and progression on imatinib *or avapritinib*
- Bullet 3: List of treatment options were replaced with a link to GIST-D which outlines systemic therapy options for progressive or metastatic disease.

GIST-5 (continued):

- Bullet 4, modified: Dose escalation of imatinib as tolerated (*if previously treated with standard dose imatinib*)

GIST-A (1 of 3)

- Bullet 1, first sentence modified: An endoscopic transmural biopsy would be favored over a percutaneous transperitoneal biopsy, ~~if~~ *as* the risk for peritoneal seeding ~~by the tumor is low~~ *is lower for this technique.*
- 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.*

GIST-A (2 of 3)

Table 1: Gastric GISTs: Proposed Guidelines for Assessing the Malignant Potential

- New statement: *This prognostic assessment applies best to KIT or PDGFRA-positive GISTs whereas succinate dehydrogenase (SDH)-deficient GISTs are more unpredictable.*
- New bullet: *Risk stratification is determined without any prior exposure to tyrosine kinase inhibitor (TKI) therapy*. Also for Table 2.
- Risk Per CAP is a new column:
  - ≤2 cm / ≤5 is *None* and >5 is *None*
  - >2 cm to ≤5 cm / ≤5 is *Very low (1.9%)* and >5 is *Moderate (16%)*
  - >5 cm to ≤10 cm / ≤5 is *Low (3.6%)* and >5 is *High (55%)*
  - >10 cm / ≤5 is *Moderate (10%) and* >5 is *High (86%)*
- Reference 2 modified: *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.

GIST-A (3 of 3)

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

- New statement: *This prognostic assessment applies best to KIT- or PDGFRA-positive GISTs whereas SDH-deficient GISTs 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 Per CAP is a new column:
  - ≤2 cm / ≤5 is *None* and >5 is *Insufficient data - High (54%)*
  - >2 cm to ≤5 cm / ≤5 is *Low (4.3%–8.5%)* and >5 is *High (50%–73%)*
  - >5 cm to ≤10 cm / ≤5 is *Insufficient data - Moderate (24%)* and >5 is *Insufficient data - High (85%)*
  - >10 cm / ≤5 is *High (34%–57%) and* >5 is *High (71%–90%)*

Continued

UPDATES

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Gastrointestinal Stromal Tumors (GISTs)

NCCN Guidelines Index
Table of Contents
Discussion

Updates in Version 1.2022 of the NCCN Guidelines for Gastrointestinal Stromal Tumors (GISTs) from Version 1.2021 include:

GIST-B

Principles of Mutation Testing

- Bullet 4, first sentence modified: GISTs 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.*
- Bullet 5 modified:
  - Third sentence deleted: ~~Ripretinib is indicated for patients with disease progression on imatinib, sunitinib, and regorafenib~~. *Ripretinib is indicated for patients who have received prior treatment with 3 or more kinase inhibitors, including imatinib. An additional clinical benefit may be obtained with the use of ripretinib 150 mg BID upon progression on ripretinib 150 mg daily.*
- Bullet 6, last sentence modified: A small minority of GISTs ~~that retain~~ *with loss of* SDH expression have alternative driver mutations.
- Bullet 7 deleted: Testing for alternative driver mutations is indicated for tumors that are negative for *KIT* or *PDGFRA* mutations.
  - First sentence is new: *All GISTs lacking a KIT or PDGFRA mutation should be tested for SDH deficiency and alternative driver mutations using next-generation sequencing (NGS)*.
  - First sub-bullet deleted: Testing includes assessment for SDHB deficiency by IHC for gastric tumors and SDH mutation testing for SDHB-deficient tumors by IHC.
  - Second sub-bullet modified: In addition, alternative driver mutations using NGS ~~next-generation sequencing (NGS) testing~~ (eg, *BRAF*, *NF1*, *NTRK*, and *FGFR* fusions) should be performed for potential identification of a targeted therapy.
- Bullet 8 modified: GISTs 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. ~~In the absence of KIT and PDGFRA mutations, only a subset of patients with advanced GISTs benefit from imatinib, although tumors known to be SDH deficient or having alternative drivers (eg, *NF1, BRAF*) are unlikely to benefit from 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 GISTs and those with GISTs that have *NF1 or SDH* mutations. Patients with *SDH* mutations are at risk of paraganglioma; 24-hour urine testing is recommended prior to surgery (See GIST-C).

GIST-C

Considerations Prior to Surgery

- Bullet 2 modified: Patients with SDH deficiency or known *SDH* mutations are at risk of paraganglioma and therefore serum/urine catecholamine/metanephrine testing should be considered ~~before an operation~~ *prior to surgery.*

GIST-D (1 of 2)

- This page was reorganized for clarity and to include treatment options for progression of disease on avapritinib.
- Title modified: Systemic Therapy Agents and Regimens for ~~Resectable~~ GISTs ~~with Significant Morbidity~~
  - Neoadjuvant Therapy title modified to include, *for Resectable Disease with Significant Morbidity*
  - Adjuvant Therapy title modified to include, *for Resectable Disease*
    - ◊ Adjuvant imatinib 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"
- Title of the second table was modified to include, "unresectable, progressive, or metastatic disease"
- Additional options after progression on approved therapies
  - Useful in Certain Circumstances
    - ◊ *Ripretinib dose escalation to 150 mg BID (if previously treated with ripretinib 150 mg daily)*
      - – *Zalcberg JR, Heinrich MC, George S, et al. Clinical benefit of ripretinib dose escalation after disease progression in advanced gastrointestinal stromal tumor: an analysis of the INVICTUS study. Oncologist 2021;25:1-8.*

Footnotes:

- Footnote a is new: *Although mutational analysis is required (other than rare circumstances, family history, etc.), it is appropriate to start neoadjuvant imatinib pending confirmation of the mutational analysis.*
- Footnote b modified: Data do not support routine use in ~~wild-type~~ GISTs *without mutation in KIT or with an imatinib-resistant mutation in PDGFRA*.
- Footnote c is new: *For unresectable disease, sunitinib, regorafenib, and pazopanib are special considerations for SDH-deficient GIST.*
- Footnote h is new: *Ripretinib 150 mg daily is indicated for fourth-line therapy. An additional clinical benefit may be obtained with the use of ripretinib 150 mg BID upon progression on ripretinib 150 mg daily.*

NCCN Guidelines Version 1.2022
Gastrointestinal Stromal Tumors (GISTs)

NCCN Guidelines Index
Table of Contents
Discussion

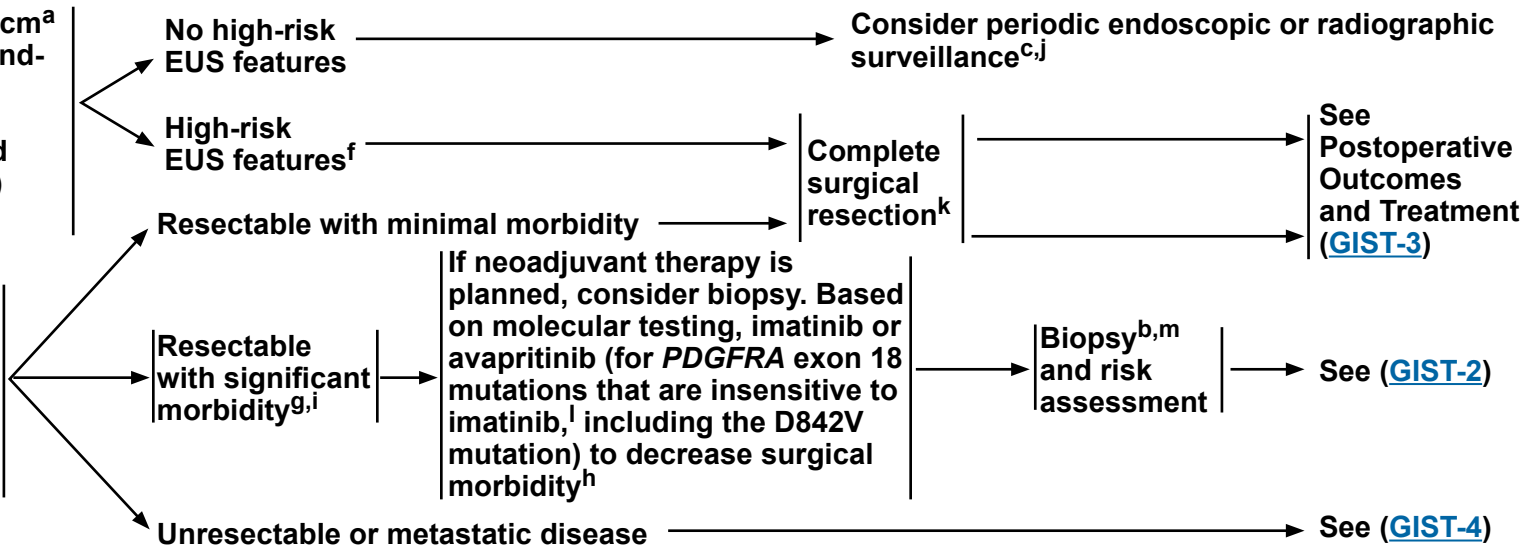
WORKUP AT PRIMARY PRESENTATION

- All patients should be evaluated and managed by a multidisciplinary team with expertise and experience in GIST/sarcoma

- For very small gastric GISTs <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]

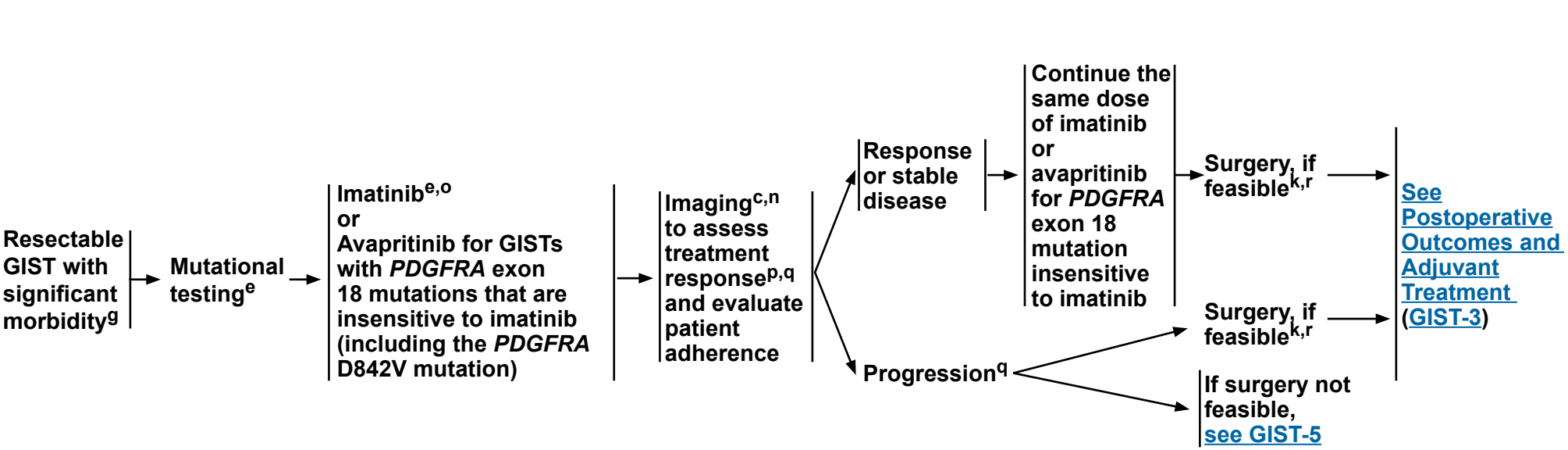
- Mass known to be or clinically suspicious for GIST[d]
  - Imaging[c]
  - Consider chest imaging[c]
  - Genotyping should be performed when medical therapy is being considered[e]

MANAGEMENT BASED ON THE RESULTS OF INITIAL DIAGNOSTIC EVALUATION



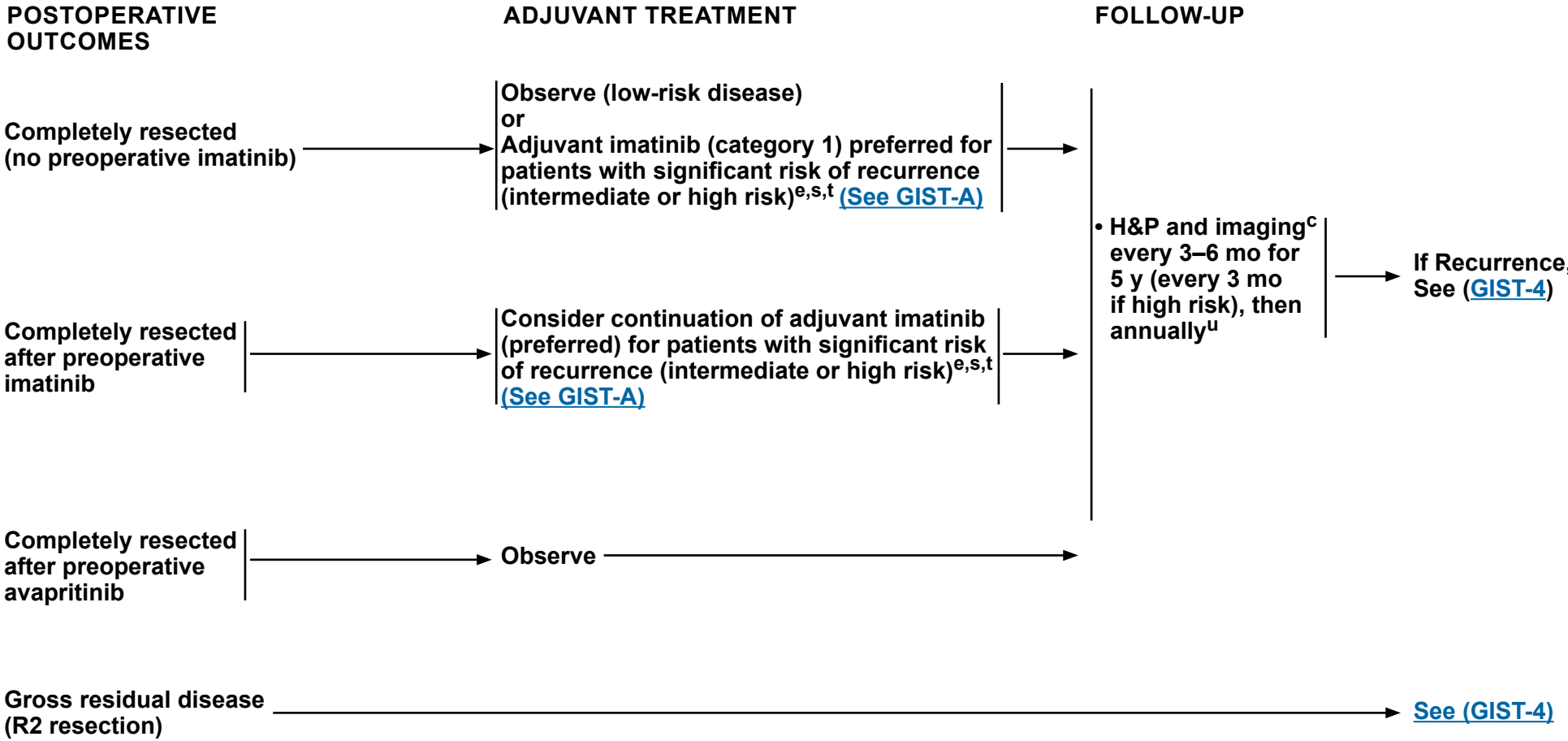
[a] Sepe PS, et al. Nat Rev Gastroenterol Hepatol 2009;6:363-371.
[b] See Principles of Biopsy and Risk Stratification for GISTs (GIST-A).
[c] See Principles of Imaging (GIST-E).
[d] See American Joint Committee on Cancer (AJCC) Staging, 8th Edition (ST-1).
[e] Mutational analysis may predict response to therapy with tyrosine kinase inhibitors (TKIs) (See GIST-B).
[f] Possible high-risk EUS features include irregular border, cystic spaces, ulceration, echogenic foci, and heterogeneity.
[g] Some patients may rapidly become unresectable; close monitoring is essential.
[h] 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.
[i] Neoadjuvant therapy for genotype-sensitive disease should be considered for locally advanced GISTs in certain anatomical locations (eg, rectum, esophageal and esophagogastric junction, duodenum) or if a multivisceral resection would be required to resect all gross tumor.
[j] 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.
[k] See General Principles of Surgery for GIST (GIST-C).
[l] Neoadjuvant imatinib for genotype-sensitive disease may prohibit accurate assessment of recurrence risk following resection (See GIST-A). Testing tumor for mutation is recommended prior to starting preoperative imatinib to ensure tumor has a genotype that is likely to respond to treatment (See GIST-2). Consider neoadjuvant imatinib only if surgical morbidity could be reduced by downsizing the tumor preoperatively. Maximal response may require treatment for 6 months or more to achieve.
[m] See NCCN Guidelines for Soft Tissue Sarcoma if the pathology results indicate sarcomas of GI origin other than GIST.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



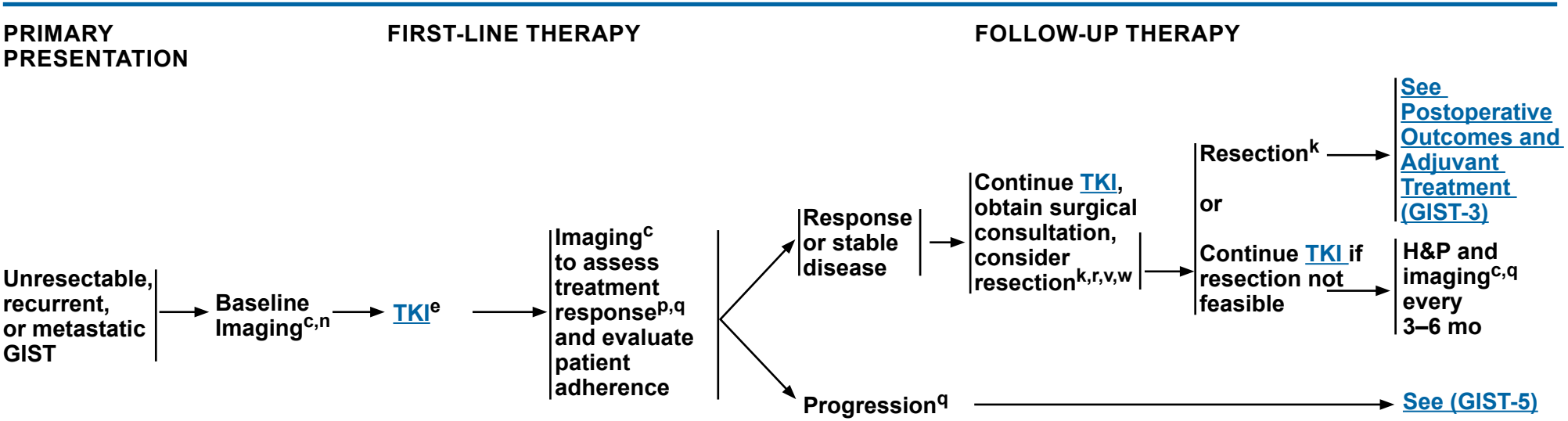
[c] See Principles of Imaging (GIST-E).
[e] Mutational analysis may predict response to therapy with TKIs (See GIST-B).
[g] Some patients may rapidly become unresectable; close monitoring is essential.
[k] See General Principles of Surgery for GIST (GIST-C).
[l] Neoadjuvant imatinib for genotype-sensitive disease may prohibit accurate assessment of recurrence risk following resection (GIST-A). Testing tumor for mutation is recommended prior to starting preoperative imatinib to ensure tumor has a genotype that is likely to respond to treatment (See GIST-2). Consider neoadjuvant imatinib only if surgical morbidity could be reduced by downsizing the tumor preoperatively. Maximal response may require treatment for 6 months or more to achieve.
[n] Consider baseline PET/CT, if using PET/CT during follow-up. PET/CT is not a substitute for CT.
[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] 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 is responding to treatment.
[q] Progression may be determined by abdominal/pelvic CT or MRI with contrast with clinical interpretation; increase in tumor size in the presence of decrease in tumor density is consistent with drug efficacy or benefit. PET/CT scan may be used to clarify if CT or MRI are ambiguous.
[r] 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.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[c] See Principles of Imaging (GIST-E).
[e] Mutational analysis may predict response to therapy with TKIs (See GIST-B).
[s] The optimal duration of adjuvant imatinib is unknown. Available data support the use of adjuvant imatinib 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).
[t] 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.
[u] 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.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[c] See Principles of Imaging (GIST-E).
[e] Mutational analysis may predict response to therapy with TKIs (See GIST-B).
[k] See General Principles of Surgery for GIST (GIST-C).
[n] Consider baseline PET/CT, if using PET/CT during follow-up. PET/CT is not a substitute for CT.
[p] 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 is responding to treatment.
[q] Progression may be determined by abdominal/pelvic CT or MRI with contrast with clinical interpretation; increase in tumor size in the presence of decrease in tumor density is consistent with drug efficacy or benefit. PET/CT scan may be used to clarify if CT or MRI are ambiguous.
[r] 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.
[v] Consider resection or ablation/liver-directed therapy for hepatic metastatic disease.
[w] Resection of metastatic disease, especially if complete resection can be achieved, and may be beneficial in patients on imatinib or sunitinib who have evidence of radiographic response, or limited disease progression.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

TREATMENT FOR PROGRESSIVE DISEASE[x]

Progression

Limited

- Continue with the same dose of TKI and consider the following options for lesions progressing on imatinib or avapritinib:
  - Resection,[k] if feasible
  - Ablation procedures or embolization or chemoembolization
  - Palliative RT (category 2B) for symptomatic lesions or
- If previously treated with standard dose imatinib:
  - Switch to sunitinib (category 1) or escalate dose of imatinib as tolerated

Generalized (widespread, systemic)

For performance status (PS) 0–2 and progression on imatinib or avapritinib:
- Switch to alternate TKI (See GIST-D)
  or
- Dose escalation of imatinib as tolerated (if previously treated with standard dose imatinib)

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

Clinical trial
or
Consider other options listed in GIST-D (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[y]

[k] See General Principles of Surgery for GIST (GIST-C).
[x] Clinical experience suggests that discontinuing TKI therapy, even in the setting of progressive disease, may accelerate the pace of disease progression and worsen symptoms.
[y] Reintroduction of a previously tolerated and effective TKI can be considered for palliation of symptoms. Consider continuation of TKI therapy life-long for palliation of symptoms as part of best supportive care.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF BIOPSY AND RISK STRATIFICATION FOR GISTs

- **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 immunohistochemistry (IHC) for CD117, DOG1, and CD34 and molecular genetic testing for *KIT* and *PDGFRA* mutations.**
- **Diagnosis is based on the Principles of Pathologic Assessment (See NCCN Guidelines for Soft Tissue Sarcoma); referral to centers with expertise and experience in the diagnosis and management of GIST/sarcoma is recommended for cases 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 GISTs behave in an indolent manner, especially when less than 2 cm. See Table 1 (GIST-A 2 of 3) for Proposed Guidelines for Assessing the Malignant Potential.**
  - **For non-gastric GISTs, see Table 2 (GIST-A 3 of 3) for Proposed 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.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PREDICTORS OF GIST BIOLOGIC BEHAVIOR

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

- **This prognostic assessment applies best to *KIT*- or *PDGFRA*-positive GISTs, whereas succinate dehydrogenase (SDH)-deficient GISTs are more unpredictable.**
- **Risk stratification is determined without any prior exposure to tyrosine kinase inhibitor (TKI) therapy.**

Tumor Size	Mitotic Rate[2]	Predicted Biologic Behavior	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 (10%)
	>5 mitoses/50 HPFs	Metastasis rate: 86%	High (86%)

GISTs: Gastrointestinal stromal tumors; 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.
[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.

Continued

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PREDICTORS OF GIST BIOLOGIC BEHAVIOR

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

- **This prognostic assessment applies best to *KIT*- or *PDGFRA*-positive GISTs whereas SDH-deficient GISTs 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]	Predicted Biologic Behavior	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%–52%	High (34%–57%)
	>5 mitoses/50 HPFs	Metastasis rate: 71%–90%	High (71%–90%)

GISTs: Gastrointestinal stromal tumors; 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.
[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.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF MUTATION TESTING

- **Approximately 80% of GISTs have a mutation in the gene encoding the KIT receptor tyrosine kinase; another 5%–10% of GISTs 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 GISTs 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.**
- **GISTs 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. 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 GISTs lack mutations in *KIT* or *PDGFRA*. The vast majority of these GISTs 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 GISTs with loss of SDH expression have alternative driver mutations.**
- **All GISTs lacking a *KIT* or *PDGFRA* mutation should be tested for SDH deficiency and alternative driver mutations using next-generation sequencing (NGS).**
  - **In addition, alternative driver mutations using NGS (eg, *BRAF*, *NF1*, *NTRK*, and *FGFR* fusions) should be performed for potential identification of a targeted therapy.**
- **GISTs 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 GISTs and those with GISTs that have *NF1 or SDH* mutations. Patients with *SDH* mutations are at risk of paraganglioma; 24-hour urine testing is recommended prior to surgery (See GIST-C).**

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

GENERAL PRINCIPLES OF SURGERY FOR GIST

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 GISTs or known translocation-associated GISTs.**
- **As GIST tends to be very friable, 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, piecemeal resection, and incisional biopsy occurring either before or at the time of the operation).**
- **Re-resection is generally not indicated for microscopically positive margins 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 imatinib. 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 laparoscopic approach may be considered for select GISTs in favorable anatomic locations by surgeons with appropriate laparoscopic 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 or Metastatic GIST

Imatinib is the primary therapy for imatinib-sensitive metastatic GIST. Surgery may be indicated for:

- **Limited disease progression refractory to imatinib.**
- **Locally advanced or previously unresectable tumors or low-volume stage IV disease after a favorable response to systemic imatinib therapy.**
- **Management of symptomatic bleeding or obstruction.**

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 deficiency or known *SDH* mutations are at risk of paraganglioma and therefore serum/urine catecholamine/metanephrine testing should be considered prior to surgery.**

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SYSTEMIC THERAPY AGENTS AND REGIMENS FOR GISTs

Neoadjuvant Therapy for Resectable Disease with Significant Morbidity	Adjuvant Therapy for Resectable Disease
Preferred Regimens • Imatinib for GISTs with imatinib-sensitive mutations[a] • Avapritinib for GISTs with *PDGFRA* exon 18 mutations that are insensitive to imatinib (including the D842V mutation)	**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

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

First-line therapy	Second-line therapy	Third-line therapy	Fourth-line therapy	Additional options after progression on approved therapies[d,e]
Preferred Regimen • Imatinib[f,1,2] (category 1) for sensitive mutations or for *PDGFRA* exon 18 mutations (excluding the D842V mutation)	**Preferred Regimen** • Sunitinib[f,6] (category 1) • Dasatinib[7] for patients with *PDGFRA* exon 18 mutations that are insensitive to imatinib (including the PDGFRA D842V mutation)	**Preferred Regimen** • Regorafenib[f,8] (category 1)	**Preferred Regimen** • Ripretinib 150 mg daily[f,9](category 1)	**Useful in Certain Circumstances** • Avapritinib[f,3] • Cabozantinib[10] • Everolimus + TKI[g,11] • Nilotinib[12,13] • Pazopanib[14] • Ripretinib dose escalation to 150 mg BID (if previously treated with ripretinib 150 mg daily)[f,h,15] • Sorafenib[16-18]
Preferred Regimen • Avapritinib[f,3] for GIST with *PDGFRA* exon 18 mutations that are insensitive to imatinib (including the PDGFRA D842V mutation)	• Dasatinib			**Useful in Certain Circumstances** • Ripretinib 150 mg daily • Ripretinib dose escalation to 150 mg BID (if previously treated with ripretinib 150 mg daily)[f,h,15]
Useful in Certain Circumstances • *NTRK* gene-fusion positive GISTs only ▸ Larotrectinib[4] ▸ Entrectinib[5]				

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

See footnotes and references, on GIST-D (2 of 2)

SYSTEMIC THERAPY AGENTS AND REGIMENS FOR GISTs

FOOTNOTES

[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.
[b] Data do not support routine use in GIST without mutation in KIT or with an imatinib-resistant mutation in PDGFRA.
[c] For unresectable disease, sunitinib, regorafenib, and pazopanib are special considerations for SDH-deficient GIST.
[d] Therapies based on identification of driver mutations.
[e] Regimens are ordered alphabetically and not according to order of preference.
[f] FDA-approved TKIs for the treatment of GIST.
[g] TKIs to be considered for use in combination with everolimus include imatinib, sunitinib, or regorafenib.
[h] Ripretinib 150 mg daily is indicated for fourth-line therapy. An additional clinical benefit may be obtained with the use of ripretinib 150 mg BID upon progression on ripretinib 150 mg daily.

REFERENCES

[1] Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002;347:472-480.
[2] Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomized trial. Lancet 2004;364:1127-1134.
[3] Heinrich M, Jones RL, von Mehren M, et al. Clinical response to avapritinib by RECIST and Choi Criteria in ≥4th line and PDGFRA exon 18 gastrointestinal stromal tumors (GIST). Connective Tissue Oncology Society Annual Meeting, Tokyo, Japan, November 15, 2019.
[4] Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adult and children. N Engl J Med 2018 378:731-739.
[5] Demetri GD, Paz-Ares L, Farago AF, et al. Efficacy and safety of entrectinib in patients with NTRK fusion-positive tumours: pooled analysis of STARTRK-2, STARTRK-1 and ALKA-372-001. Presented at the European Society for Medical Oncology Meeting in Munich, Germany; October 12-23, 2018. Oral Presentation.
[6] Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006;368:1329-1338.
[7] Trent JC, Wathen K, von Mehren M, et al. A phase II study of dasatinib for patients with imatinib-resistant gastrointestinal stromal tumor (GIST). J Clin Oncol 2011;29:Abstract 10006.
[8] Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:295-302.
[9] von Mehren M, Serrano C, Bauer S, et al: INVICTUS: A phase III, interventional, double-blind, placebo-controlled study to assess the safety and efficacy of ripretinib as fourth-line therapy in advanced GIST. 2019 ESMO Congress. Abstract LBA87.
[10] Schöffski P, Mir O, Kasper B, et al. Activity and safety of the multi-target tyrosine kinase inhibitor cabozantinib in patients with metastatic gastrointestinal stromal tumour after treatment with imatinib and sunitinib: European Organisation for Research and Treatment of Cancer phase II trial 1317 'CaboGIST' Eur J Cancer 2020;134:62-74.
[11] Choffski P, Reichardt P, Blay JY, et al. A phase I-II study of everolimus (RAD001) in combination with imatinib in patients with imatinib-resistant gastrointestinal stromal tumors. Ann Oncol 2010;21:1990-1998.
[12] Montemurro M, Schoffski P, Reichardt P, et al. Nilotinib in the treatment of advanced gastrointestinal stromal tumours resistant to both imatinib and sunitinib. Eur J Cancer 2009;45:2293-2297.
[13] Sawaki A, Nishida T, Doi T, et al. Phase 2 study of nilotinib as third-line therapy for patients with gastrointestinal stromal tumor. Cancer 2011;117:4633-4641.
[14] Ganjoo KN, Villalobos VM, Kamaya A., et al. A multicenter phase II study of pazopanib in patients with advanced gastrointestinal stromal tumors (GIST) following failure of at least imatinib and sunitinib. Ann Oncol 2014;25:236-40.
[15] Zalcberg JR, Heinrich MC, George S, et al. Clinical benefit of ripretinib dose escalation after disease progression in advanced gastrointestinal stromal tumor: an analysis of the INVICTUS study. Oncologist 2021;26:e2053-e2060.
[16] Montemurro M, Gelderblom H, Bitz U, et al. Sorafenib as third- or fourth-line treatment of advanced gastrointestinal stromal tumour and pretreatment including both imatinib and sunitinib, and nilotinib: A retrospective analysis. Eur J Cancer 2013;49:1027-1031.
[17] Kindler HL, Campbell NP, Wroblewski K, et al. Sorafenib (SOR) in patients (pts) with imatinib (IM) and sunitinib (SU)-resistant (RES) gastrointestinal stromal tumors (GIST): Final results of a University of Chicago Phase II Consortium trial. J Clin Oncol 2011;29:Abstract 10009.
[18] Park SH, Ryu MH, Ryoo BY, et al. Sorafenib in patients with metastatic gastrointestinal stromal tumors who failed two or more prior tyrosine kinase inhibitors: a phase II study of Korean gastrointestinal stromal tumors study group. Invest New Drugs 2012;30:2377-2383.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF IMAGING

Workup

- For very small GIST <2 cm: Perform abdominal/pelvic CT with contrast and/or abdominal/pelvic MRI with contrast.
- For all other GIST:
  - Abdominal/pelvic CT with contrast and/or abdominal/pelvic MRI with contrast
  - Chest imaging using x-ray or CT

Response Assessment

Resectable disease with significant morbidity

- Obtain baseline abdominal/pelvic CT and/or MRI.
- Consider PET/CT
  - Obtain baseline PET/CT if using PET/CT during follow-up; PET is not a substitute for CT.
- Imaging to assess response to preoperative TKI
  - Abdominal/pelvic CT or MRI is indicated every 8–12 weeks.
  - PET may give indication of TKI activity after 2–4 weeks of therapy when rapid readout of activity is necessary.
- Progression may be determined by abdominal/pelvic CT or MRI with clinical interpretation; 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 using abdominal/pelvic CT or MRI every 8–12 weeks.

Definitively unresectable, recurrent, or metastatic disease

- Obtain baseline abdominal/pelvic CT and/or MRI.
- Consider imaging of chest intermittently.
- Consider PET/CT.
  - Obtain baseline PET/CT if using PET/CT during follow-up; PET is not a substitute for CT.
- Imaging to assess response to TKI
- Abdominal/pelvic CT or MRI every 8–12 weeks of initiating therapy; in some patients, it may be appropriate to image before 3 months.
- Progression may be determined by abdominal/pelvic CT or MRI with clinical interpretation; PET/CT may be used to clarify if CT or MRI is ambiguous.

Follow-up

- For completely resected primary disease, perform abdominal/pelvic CT 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 abdominal/pelvic CT every 3–6 months.
- Progression may be determined by CT or MRI with clinical interpretation; PET/CT may be used to clarify if CT or MRI is ambiguous.
- After treatment for progressive disease, reassess therapeutic response with abdominal/pelvic CT or MRI.
  - Consider PET/CT only if CT results are ambiguous.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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

Table 6. **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

Table 7. **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.

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus 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.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Gastrointestinal Stromal Tumors (GISTs)

Discussion

This discussion corresponds to the NCCN Guidelines for Gastrointestinal Stromal Tumors (GISTs). Last updated on March 27, 2018.

Table of Contents

Overview

Gastrointestinal Stromal Tumors

GISTs are the most common STS of the gastrointestinal (GI) tract, resulting most commonly from *KIT* or *PDGFRA* activating mutations.[1] A recent SEER database study calculated the annual incidence of GIST in the United States to be 0.78/100,000 in 2011.[2] GISTs can arise anywhere along the GI tract, but stomach (60%) and small intestine (30%) are the most common primary sites.[2] Duodenum (4%–5%) and rectum (4%) are the less common primary sites, and only a small number of cases have been reported in the esophagus (<1%) and colon and appendix (1%–2%).[2] 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 appendicitis-like pain), which requires immediate medical attention.[3] Liver metastases and/or dissemination within the abdominal cavity are the most common clinical manifestations of malignancy. Lymph node metastases are extremely rare. Metastases in the lungs and other extra-abdominal locations are observed only in advanced cases.

General Principles

Biopsy and Pathologic Assessment

GISTs 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.[3] Recent reports have suggested that definitive diagnosis of GIST requires tissue acquisition via endoscopic ultrasound (EUS)-guided FNA.[4] 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 GISTs (95%) express *KIT* (CD117). Approximately 80% of GISTs have a mutation in the gene encoding the *KIT* receptor tyrosine kinase; another 5% to 10% of GISTs have a mutation in the gene encoding the related *PDGFRA* receptor tyrosine kinase.[5-7] About 10% to 15% of GISTs 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%).[8]

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.[9] KIT mutations have also been identified in the tyrosine kinase domain (exon 13 and exon 17), although they are very rare.[10] The majority of the *PDGFRA* mutations affect exon 18 in the tyrosine kinase domain 2.[9] Few mutations also occur in exon 12 (juxtamembrane domain) and exon 14 (tyrosine kinase domain 1), although they are rare.[11] *KIT* exon 11 mutations are most common in GISTs of all sites, whereas *KIT* exon 9 mutations are specific for intestinal GISTs and *PDGFRA* exon 18 mutations are common in gastric GISTs.[9]

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 GISTs 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 GISTs 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.[12-16] 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 GISTs lacking *KIT/PDGFRA* mutations.[17,18] DOG1 is a calcium-dependent, receptor-activated chloride channel protein and it is expressed in GISTs 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. GISTs with *PDGFRA* mutations had a low *KIT* expression and high DOG1 expression, which can be used in the diagnosis of *KIT*-negative tumors.[19] 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.[3]

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 GISTs, 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%.[20] 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.[21] 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.[2] According to these guidelines, gastric GISTs have an overall indolent behavior and those that are ≤2 cm (irrespective of the mitotic index) are essentially benign, whereas small intestinal GISTs tend to be more aggressive. Rectal GISTs 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 GISTs 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.[22] 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.[23]

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. GISTs 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.[3] 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.[24] Various CT response criteria have been investigated and compared in patients with GIST, including iterations of RECIST, Choi, and WHO criteria. [25-31]

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.[25] 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.[28-30]

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.[32] 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.

GISTs 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 GISTs, respectively. Several case reports have demonstrated that the use of preoperative imatinib enables organ-sparing surgery and improves surgical outcomes in patients with rectal GISTs.[3]

The role for laparoscopy in the resection of GISTs 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.[3] 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.[33]

Laparoscopic approach may be considered for selected GISTs 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 GISTs. However, data on laparoscopic resection of GISTs at other sites are limited.

Targeted Therapy

GISTs 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.[34-38] 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.[39] 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.[35,36,38] 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,[35] at a median follow-up of 10.9 years, no significant differences in survival were observed based on imatinib dose level.[40] 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).[38] 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.[40]

Available data confirm the safety and efficacy of imatinib at 400 mg/d as the initial standard dose to achieve response induction.[35,38] Dose escalation to 800 mg/d is a reasonable option for patients progressing on 400 mg/d.[36]

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).[41] 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).[42] 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%.[43] 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.[44] 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.[41,42,44] 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%.[45-47] 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.[48] 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.[49] 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.[50] 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. [51] 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.[52,53] 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.[54]

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.[55] 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.[56] 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.[57] 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.[58] 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).[59] 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).[60]

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).[61] 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.[62] Recent reports have shown that sunitinib is also associated with cardiotoxicity and hypothyroidism.[63,64] 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.[63] 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.[64]

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.[3]

Impact of Mutational Status on Response to Imatinib or Sunitinib in Patients with Advanced or Metastatic GIST

The presence and type of *KIT* or *PDGFRA* mutation has been identified as the predictor of response to imatinib. In randomized clinical trials, the presence of a *KIT* exon 11 mutation was associated with better response rates, PFS, and OS compared to *KIT* exon 9 mutations or wild-type GIST.[23,65-68]

Long-term follow-up (median 73 months) from the prospective, multicenter, randomized, phase III BFR14 trial by the French Sarcoma Group identified *KIT* exon 11 mutations as an independent prognostic factor for higher PFS and OS in patients treated with standard-dose imatinib when compared with patients who had wild-type GIST or *KIT* exon 9 mutations.[23]

In the US-Finnish B2222 phase II study, PR rates, event-free survival (EFS), and OS rates were better for patients with *KIT* exon 11 mutations than those with *KIT* exon 9 mutations or who had no detectable kinase mutations.[65] The PR rates for patients with *KIT* exon 11 mutations, *KIT* exon 9 mutations, or no detectable kinase mutations were 83.5%, 48%, and no responses, respectively. The presence of *KIT* exon 11 mutations was the strongest prognostic factor reducing the risk of death by more than 95%.

In a randomized EORTC 62005 study, the presence of *KIT* exon 9 mutations was the strongest adverse prognostic factor for risk of progression and death.[66] In this trial, treatment with high-dose imatinib (800 mg/d) resulted in a significantly superior PFS with a reduction of the relative risk of 61% (*P* = .0013) in patients whose tumors expressed a *KIT* exon 9 mutation.[67] In addition, the response rate after crossover from 400

mg daily to 400 mg twice-daily imatinib was much higher among patients with *KIT* exon 9 mutations (57%) than among patients with *KIT* exon 11 mutations (7%).

The North American Intergroup phase III trial (SWOG S0033/CALGB 150105) also confirmed the findings from B2222 and EORTC 62005 studies. Patients with a *KIT* exon 9 mutation treated with 800 mg imatinib had improved response rates compared to those treated with 400 mg imatinib (67% vs. 17%, respectively).[68] However, the PFS advantage observed in the EORTC 62005 study in patients with *KIT* exon 9 mutations treated with high-dose imatinib was not confirmed in the S0033/CALGB 150105 study. The results of the North American Intergroup phase III trial also showed that patients with CD117-negative GIST have similar time to tumor progression but inferior OS compared to those with CD117-positive GIST, suggesting that patients with CD117-negative GIST may benefit from imatinib therapy.[68] Therefore, it is rational to offer *KIT*-negative GIST patients a therapeutic trial of imatinib with close evaluation and follow-up.

A meta-analysis of EORTC 62005 and SWOG S0033/CALGB 150105 phase III trials that randomized 1640 patients with advanced GIST to standard-dose imatinib (400 mg daily) or high-dose imatinib (800 mg daily) showed a benefit in PFS for patients with *KIT* exon 9 mutations treated with 800 mg of imatinib.[69] In a recent international survey that reported the outcome of GIST patients with *PDGFRA* mutations, none of 31 evaluable patients with a *D842V* mutation had a response, whereas 21 of 31 (68%) had disease progression.[70] Median PFS was 2.8 months for patients with a D842V substitution and 28.5 months for patients with other *PDGFRA* mutations. With 46 months of follow-up, median OS was 14.7 months for patients with D842V substitutions and was not reached for patients with other *PDGFRA* mutations.

Follow-up analysis of the 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 RFS when allocated to the 3-year versus 1-year imatinib group.[71] A similar pattern related to duration of treatment was not observed for GISTs harboring other mutations.

Heinrich and colleagues reported that sunitinib induced higher response rates in patients with primary *KIT* exon 9 mutations than those with *KIT* exon 11 mutations (58% vs. 34%, respectively).[72] PFS and OS were significantly longer for patients with *KIT* exon 9 mutations or with wild-type GIST compared to those with *KIT* exon 11 mutations. There were only 4 patients with *PDGFRA* mutations; of these 2 had a primary and one had a secondary *D842V* mutation and did not respond to treatment. In patients with *KIT* exon 11 mutations, PFS and OS were longer for those with secondary exon 13 or 14 mutations compared to those with exon 17 or 18 mutations. Additional studies are needed to confirm these findings. SDH-deficient GIST may have a higher probability of response to sunitinib compared with imatinib in patients with unresectable, recurrent, or metastatic GIST.

Resistance to Imatinib and Sunitinib

While imatinib benefits most patients with advanced GIST, some patients 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 and it is most commonly seen in patients with *KIT* exon 9 mutations treated with imatinib at 400 mg daily, *PDGFRA* exon 18 *D842V* mutations, or those with tumors that lack identifiable activating mutations in *KIT* or *PDGFRA,* the majority of which are *SDH*-deficient GIST.[65,66,68,72] 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*.[73-76] Dose escalation to 800

mg/d or switching to sunitinib is a reasonable option for patients progressing on imatinib 400 mg/d.[36,57,58]

Comprehensive molecular studies investigating the mechanisms of resistance to sunitinib are limited by the small number of patients who are surgical candidates after their disease failed to respond to two different TKI therapies. Nevertheless, available evidence (both clinical and preclinical) indicates that while sunitinib is very sensitive to adenosine triphosphate (ATP)-binding pocket mutations that confer resistance to imatinib, it has little activity against other imatinib-resistant mutations in the *KIT* activation loop.[77-79]

Management of Resistance to Imatinib and Sunitinib

Regorafenib, a multikinase inhibitor with activity against *KIT*, PDGFR, and VEGFR, was approved by the FDA for the treatment of patients with locally advanced, unresectable, or metastatic GIST previously treated with imatinib and sunitinib. In the phase III randomized GRID trial, 199 patients with metastatic and/or unresectable GIST progressing on prior therapy with imatinib and sunitinib were randomized to regorafenib (n = 133) or placebo (n = 66).[80] 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 compared to 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. The most common treatment-related adverse events (grade 3 or higher) were hypertension (23%), HFSR (20%), and diarrhea (5%). Long-term follow-up (median 41 months) from a separate phase II study of regorafenib 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 than patients with *KIT/PDGFRA* wild-type, non-*SDH*-deficient tumors.[81]

Sorafenib,[82-85] nilotinib,[86-90] dasatinib,[91,92] and pazopanib[93,94] have also shown activity in patients with GIST resistant to imatinib and sunitinib. Much of the data on these TKIs comes from phase II studies and retrospective analyses involving a small number of patients.

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% of patients who had stable disease and 13% who had PR).[82] Median PFS and OS were 5.2 months and 11.6 months, respectively; 1-year and 2-year survival rates were 50% and 29%, respectively. In a retrospective analysis of 124 patients with metastatic GIST resistant to imatinib and sunitinib, sorafenib also demonstrated activity resulting in median PFS and OS of 6.4 months and 13.5 months, respectively.[84] It should be noted that patients included in this study had not been treated with regorafenib, and the efficacy of sorafenib following regorafenib therapy in patients with metastatic GIST resistant to imatinib and sunitinib has not been studied.

Nilotinib resulted in a 10% response rate and 37% DCR in a retrospective analysis of 52 patients with advanced GIST resistant to imatinib and sunitinib.[87] Median PFS and OS were 12 weeks and 34 weeks, respectively. In a randomized phase III study of nilotinib as third-line therapy and best supportive care (with or without a TKI) in patients with GIST resistant or intolerant to imatinib and sunitinib (248 patients), the PFS on nilotinib was not found to be superior to best supportive care (109 days vs. 111 days; $P = .56$).[89] In a post hoc subset analysis, patients progressing on both imatinib and sunitinib who had not received any other therapy had an improved OS (>4 months) with nilotinib compared to best supportive care (405 vs. 280 days; $P = .02$). The clinical benefit associated with nilotinib may be specific to subsets of patients with *KIT* exon 17 mutations who were previously treated with imatinib and sunitinib.[90] Additionally, a recent phase III study

investigating nilotinib as an alternative front-line agent to imatinib for unresectable or metastatic GIST was terminated early due to futility.[95]

Dasatinib has demonstrated activity against *PDGFRA* D842V mutation, which confers the highest resistance to imatinib, and it could be an effective treatment option for this group of patients with imatinib-resistant GIST.[91] In the phase II study of 50 patients with advanced GIST resistant to imatinib, dasatinib was associated with a median PFS and OS of 2 and 19 months, respectively, with response assessment by Choi criteria.[92] Median PFS for patients with wild-type GIST was 8.4 months.

Pazopanib has also shown modest activity in unselected, heavily pretreated patients with advanced GIST.[93,94] In a recent randomized, phase II trial comparing pazopanib to best supportive care in patients with 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). [94]

Everolimus in combination with a TKI (ie, imatinib, sunitinib, regorafenib) may also be active in imatinib-resistant GIST.[94,96]

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 GISTs (<2 cm), abdominal/pelvic CT and/or MRI is sufficient. For all other GISTs, 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.[41,43] 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[43,44] or 600 mg.[41,42] 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 GISTs less than 2 cm remains controversial.[3] At present, there are insufficient data to guide the management of very small GISTs (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 GISTs (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.[4,97]

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).[49,52] The panel recommends that postoperative imatinib for at least 36 months should be considered for patients with high-risk GIST.[52,53]

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 GISTs 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.[49,50] 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).[52] Risk stratification after surgical resection should be based on tumor mitotic rate, size, and location.[98] 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.[99] 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.[41-44] 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.[100]

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.[43,44] Several retrospective studies have demonstrated survival benefit of cytoreductive surgery following preoperative imatinib in patients with advanced or metastatic GIST responding to preoperative imatinib.[101-108] 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.[109]

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.[36,57,58] 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.[101,106,110]

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.[3]

Regorafenib (category 1) is recommended for patients with disease progression on imatinib and sunitinib.[80] Based on limited data,[82-94,96] 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.[111,112] 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.[112] 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.[113,114] A recent report from this study confirmed that patients with rapid disease progression after interruption of imatinib had a poorer prognosis.[115] 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.

References

1. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998;279:577-580. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9438854.

2. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006;23:70-83. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17193820.

3. Demetri GD, von Mehren M, Antonescu CR, et al. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Canc Netw 2010;8 Suppl 2:S1-41. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20457867.

4. Sepe PS, Moparty B, Pitman MB, et al. EUS-guided FNA for the diagnosis of GI stromal cell tumors: sensitivity and cytologic yield. Gastrointest Endosc 2009;70:254-261. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19482280.

5. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol 2002;33:459-465. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12094370.

6. Heinrich MC, Corless CL, Duensing A, et al. PDGFRA activating mutations in gastrointestinal stromal tumors. Science 2003;299:708-710. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12522257.

7. Hirota S, Ohashi A, Nishida T, et al. Gain-of-function mutations of platelet-derived growth factor receptor alpha gene in gastrointestinal stromal tumors. Gastroenterology 2003;125:660-667. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12949711.

8. Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med 2006;130:1466-1478. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17090188.

9. Lasota J, Miettinen M. Clinical significance of oncogenic KIT and PDGFRA mutations in gastrointestinal stromal tumours. Histopathology 2008;53:245-266. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18312355.

10. Lasota J, Corless CL, Heinrich MC, et al. Clinicopathologic profile of gastrointestinal stromal tumors (GISTs) with primary KIT exon 13 or exon 17 mutations: a multicenter study on 54 cases. Mod Pathol 2008;21:476-484. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18246046.

11. Corless CL, Schroeder A, Griffith D, et al. PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. J Clin Oncol 2005;23:5357-5364. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15928335.

12. Janeway KA, Kim SY, Lodish M, et al. Defects in succinate dehydrogenase in gastrointestinal stromal tumors lacking KIT and PDGFRA mutations. Proc Natl Acad Sci U S A 2011;108:314-318. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21173220.

13. Italiano A, Chen CL, Sung YS, et al. SDHA loss of function mutations in a subset of young adult wild-type gastrointestinal stromal tumors. BMC Cancer 2012;12:408. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22974104.

14. Oudijk L, Gaal J, Korpershoek E, et al. SDHA mutations in adult and pediatric wild-type gastrointestinal stromal tumors. Mod Pathol 2013;26:456-463. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23174939.

15. Pantaleo MA, Astolfi A, Urbini M, et al. Analysis of all subunits, SDHA, SDHB, SDHC, SDHD, of the succinate dehydrogenase complex in KIT/PDGFRA wild-type GIST. Eur J Hum Genet 2014;22:32-39. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23612575.

16. Doyle LA, Nelson D, Heinrich MC, et al. Loss of succinate dehydrogenase subunit B (SDHB) expression is limited to a distinctive subset of gastric wild-type gastrointestinal stromal tumours: a comprehensive genotype-phenotype correlation study. Histopathology 2012;61:801-809. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22804613.

17. Agaram NP, Wong GC, Guo T, et al. Novel V600E BRAF mutations in imatinib-naive and imatinib-resistant gastrointestinal stromal tumors. Genes Chromosomes Cancer 2008;47:853-859. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18615679.

18. Agaimy A, Terracciano LM, Dirnhofer S, et al. V600E BRAF mutations are alternative early molecular events in a subset of KIT/PDGFRA wild-type gastrointestinal stromal tumours. J Clin Pathol 2009;62:613-616. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19561230.

19. Miettinen M, Wang ZF, Lasota J. DOG1 antibody in the differential diagnosis of gastrointestinal stromal tumors: a study of 1840 cases. Am J Surg Pathol 2009;33:1401-1408. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19606013.

20. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. Am J Surg Pathol 2005;29:52-68. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15613856.

21. Miettinen M, Makhlouf H, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the jejunum and ileum: a clinicopathologic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up. Am J Surg Pathol 2006;30:477-489. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16625094.

22. Wozniak A, Rutkowski P, Schoffski P, et al. Tumor genotype is an independent prognostic factor in primary gastrointestinal stromal tumors of gastric origin: a european multicenter analysis based on ConticaGIST. Clin Cancer Res 2014;20:6105-6116. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25294914.

23. Patrikidou A, Domont J, Chabaud S, et al. Long-term outcome of molecular subgroups of GIST patients treated with standard-dose imatinib in the BFR14 trial of the French Sarcoma Group. Eur J Cancer 2016;52:173-180. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26687836.

24. Prior JO, Montemurro M, Orcurto MV, et al. Early prediction of response to sunitinib after imatinib failure by 18F-fluorodeoxyglucose positron emission tomography in patients with gastrointestinal stromal tumor. J Clin Oncol 2009;27:439-445. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19064982.

25. Choi H, Charnsangavej C, Faria SC, et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. J Clin Oncol 2007;25:1753-1759. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17470865.

26. Dudeck O, Zeile M, Reichardt P, Pink D. Comparison of RECIST and Choi criteria for computed tomographic response evaluation in patients with advanced gastrointestinal stromal tumor treated with sunitinib. Ann Oncol 2011;22:1828-1833. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21289369.

27. Patel SA, Royce TJ, Barysauskas CM, et al. Surveillance Imaging Patterns and Outcomes Following Radiation Therapy and Radical Resection for Localized Extremity and Trunk Soft Tissue Sarcoma. Ann Surg Oncol 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28058559.

28. Schramm N, Englhart E, Schlemmer M, et al. Tumor response and clinical outcome in metastatic gastrointestinal stromal tumors under sunitinib therapy: comparison of RECIST, Choi and volumetric criteria. Eur J Radiol 2013;82:951-958. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23518148.

29. Shinagare AB, Barysauskas CM, Braschi-Amirfarzan M, et al. Comparison of performance of various tumor response criteria in assessment of sunitinib activity in advanced gastrointestinal stromal tumors. Clin Imaging 2016;40:880-884. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27179958.

30. Shinagare AB, Jagannathan JP, Kurra V, et al. Comparison of performance of various tumour response criteria in assessment of

regorafenib activity in advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib. Eur J Cancer 2014;50:981-986. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24388774.

31. Benjamin RS, Choi H, Macapinlac HA, et al. We should desist using RECIST, at least in GIST. J Clin Oncol 2007;25:1760-1764. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17470866.

32. Young H, Baum R, Cremerius U, et al. Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group Eur J Cancer 1999;35:1773-1782. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10673991.

33. Chen K, Zhou YC, Mou YP, et al. Systematic review and meta-analysis of safety and efficacy of laparoscopic resection for gastrointestinal stromal tumors of the stomach. Surg Endosc 2015;29:355-367. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25005014.

34. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002;347:472-480. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12181401.

35. Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet 2004;364:1127-1134. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15451219.

36. Zalcberg JR, Verweij J, Casali PG, et al. Outcome of patients with advanced gastro-intestinal stromal tumours crossing over to a daily imatinib dose of 800 mg after progression on 400 mg. Eur J Cancer 2005;41:1751-1757. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16098458.

37. Blanke CD, Demetri GD, von Mehren M, et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. J Clin Oncol 2008;26:620-625. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18235121.

38. Blanke CD, Rankin C, Demetri GD, et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. J Clin Oncol 2008;26:626-632. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18235122.

39. von Mehren M, Heinrich MC, Joensuu H, et al. Follow-up results after 9 years (yrs) of the ongoing, phase II B2222 trial of imatinib mesylate (IM) in patients (pts) with metastatic or unresectable KIT+ gastrointestinal stromal tumors (GIST) [abstract]. J Clin Oncol 2011;29(15_Suppl):Abstract 10016. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/10016.

40. Casali PG, Zalcberg J, Le Cesne A, et al. Ten-Year Progression-Free and Overall Survival in Patients With Unresectable or Metastatic GI Stromal Tumors: Long-Term Analysis of the European Organisation for Research and Treatment of Cancer, Italian Sarcoma Group, and Australasian Gastrointestinal Trials Group Intergroup Phase III Randomized Trial on Imatinib at Two Dose Levels. J Clin Oncol 2017;35:1713-1720. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28362562.

41. Eisenberg BL, Harris J, Blanke CD, et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate (IM) for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumor (GIST): early results of RTOG 0132/ACRIN 6665. J Surg Oncol 2009;99:42-47. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18942073.

42. McAuliffe JC, Hunt KK, Lazar AJF, et al. A randomized, phase II study of preoperative plus postoperative imatinib in GIST: evidence of rapid radiographic response and temporal induction of tumor cell apoptosis. Ann Surg Oncol 2009;16:910-919. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18953611.

43. Fiore M, Palassini E, Fumagalli E, et al. Preoperative imatinib mesylate for unresectable or locally advanced primary gastrointestinal

stromal tumors (GIST). Eur J Surg Oncol 2009;35:739-745. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19110398.

44. Blesius A, Cassier PA, Bertucci F, et al. Neoadjuvant imatinib in patients with locally advanced non metastatic GIST in the prospective BFR14 trial. BMC Cancer 2011;11:72. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21324142.

45. Eisenberg BL, Judson I. Surgery and imatinib in the management of GIST: emerging approaches to adjuvant and neoadjuvant therapy. Ann Surg Oncol 2004;11:465-475. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15123459.

46. Gold JS, Dematteo RP. Combined surgical and molecular therapy: the gastrointestinal stromal tumor model. Ann Surg 2006;244:176-184. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16858179.

47. DeMatteo RP, Lewis JJ, Leung D, et al. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg 2000;231:51-58. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10636102.

48. Guerin A, Sasane M, Keir CH, et al. Physician Underestimation of the Risk of Gastrointestinal Stromal Tumor Recurrence After Resection. JAMA Oncol 2015;1:797-805. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26204106.

49. Corless CL, Ballman KV, Antonescu CR, et al. Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial. J Clin Oncol 2014;32:1563-1570. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24638003.

50. Dematteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet 2009;373:1097-1104. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19303137.

51. Casali PG, Le Cesne A, Poveda Velasco A, et al. Time to Definitive Failure to the First Tyrosine Kinase Inhibitor in Localized GI Stromal Tumors Treated With Imatinib As an Adjuvant: A European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Intergroup Randomized Trial in Collaboration With the Australasian Gastro-Intestinal Trials Group, UNICANCER, French Sarcoma Group, Italian Sarcoma Group, and Spanish Group for Research on Sarcomas. J Clin Oncol 2015;33:4276-4283. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26573069.

52. Joensuu H, Eriksson M, Sundby Hall K, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. JAMA 2012;307:1265-1272. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22453568.

53. Joensuu H, Eriksson M, Sundby Hall K, et al. Adjuvant Imatinib for High-Risk GI Stromal Tumor: Analysis of a Randomized Trial. J Clin Oncol 2016;34:244-250. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26527782.

54. Joensuu H, Eriksson M, Hall KS, et al. Risk factors for gastrointestinal stromal tumor recurrence in patients treated with adjuvant imatinib. Cancer 2014;120:2325-2333. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24737415.

55. Guilhot F. Indications for imatinib mesylate therapy and clinical management. Oncologist 2004;9:271-281. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15169982.

56. Trent JC, Patel SS, Zhang J, et al. Rare incidence of congestive heart failure in gastrointestinal stromal tumor and other sarcoma patients receiving imatinib mesylate. Cancer 2010;116:184-192. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19885836.

57. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006;368:1329-1338. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17046465.

58. George S, Blay JY, Casali PG, et al. Clinical evaluation of continuous daily dosing of sunitinib malate in patients with advanced gastrointestinal stromal tumour after imatinib failure. Eur J Cancer 2009;45:1959-1968. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19282169.

59. Reichardt P, Kang YK, Rutkowski P, et al. Clinical outcomes of patients with advanced gastrointestinal stromal tumors: safety and efficacy in a worldwide treatment-use trial of sunitinib. Cancer 2015;121:1405-1413. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25641662.

60. Reichardt P, Demetri GD, Gelderblom H, et al. Correlation of KIT and PDGFRA mutational status with clinical benefit in patients with gastrointestinal stromal tumor treated with sunitinib in a worldwide treatment-use trial. BMC Cancer 2016;16:22. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26772734.

61. Chu D, Lacouture ME, Weiner E, Wu S. Risk of hand-foot skin reaction with the multitargeted kinase inhibitor sunitinib in patients with renal cell and non-renal cell carcinoma: a meta-analysis. Clin Genitourin Cancer 2009;7:11-19. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19213662.

62. Zhu X, Stergiopoulos K, Wu S. Risk of hypertension and renal dysfunction with an angiogenesis inhibitor sunitinib: systematic review and meta-analysis. Acta Oncol 2009;48:9-17. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18752081.

63. Chu TF, Rupnick MA, Kerkela R, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. Lancet 2007;370:2011-2019. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18083403.

64. Torino F, Corsello SM, Longo R, et al. Hypothyroidism related to tyrosine kinase inhibitors: an emerging toxic effect of targeted therapy. Nat Rev Clin Oncol 2009;6:219-228. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19333228.

65. Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 2003;21:4342-4349. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14645423.

66. Debiec-Rychter M, Dumez H, Judson I, et al. Use of c-KIT/PDGFRA mutational analysis to predict the clinical response to imatinib in patients with advanced gastrointestinal stromal tumours entered on phase I and II studies of the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer 2004;40:689-695. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15010069.

67. Debiec-Rychter M, Sciot R, Le Cesne A, et al. KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. Eur J Cancer 2006;42:1093-1103. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16624552.

68. Heinrich MC, Owzar K, Corless CL, et al. Correlation of kinase genotype and clinical outcome in the North American Intergroup Phase III Trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 Study by Cancer and Leukemia Group B and Southwest Oncology Group. J Clin Oncol 2008;26:5360-5367. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18955451.

69. Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: a meta-analysis of 1,640 patients. J Clin Oncol 2010;28:1247-1253. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20124181.

70. Cassier PA, Fumagalli E, Rutkowski P, et al. Outcome of patients with platelet-derived growth factor receptor alpha-mutated gastrointestinal stromal tumors in the tyrosine kinase inhibitor era. Clin Cancer Res 2012;18:4458-4464. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22718859.

71. Joensuu H, Wardelmann E, Sihto H, et al. Effect of KIT and PDGFRA Mutations on Survival in Patients With Gastrointestinal Stromal Tumors Treated With Adjuvant Imatinib: An Exploratory Analysis of a Randomized Clinical Trial. JAMA Oncol 2017;3:602-609. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28334365.

72. Heinrich MC, Maki RG, Corless CL, et al. Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. J Clin Oncol 2008;26:5352-5359. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18955458.

73. Antonescu CR, Besmer P, Guo T, et al. Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. Clin Cancer Res 2005;11:4182-4190. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15930355.

74. Heinrich MC, Corless CL, Blanke CD, et al. Molecular correlates of imatinib resistance in gastrointestinal stromal tumors. J Clin Oncol 2006;24:4764-4774. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16954519.

75. Wardelmann E, Merkelbach-Bruse S, Pauls K, et al. Polyclonal evolution of multiple secondary KIT mutations in gastrointestinal stromal tumors under treatment with imatinib mesylate. Clin Cancer Res 2006;12:1743-1749. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16551858.

76. Desai J, Shankar S, Heinrich MC, et al. Clonal evolution of resistance to imatinib in patients with metastatic gastrointestinal stromal tumors. Clin Cancer Res 2007;13:5398-5405. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17875769.

77. Gajiwala KS, Wu JC, Christensen J, et al. KIT kinase mutants show unique mechanisms of drug resistance to imatinib and sunitinib in gastrointestinal stromal tumor patients. Proc Natl Acad Sci U S A 2009;106:1542-1547. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19164557.

78. Guo T, Hajdu M, Agaram NP, et al. Mechanisms of sunitinib resistance in gastrointestinal stromal tumors harboring KITAY502-3ins mutation: an in vitro mutagenesis screen for drug resistance. Clin Cancer Res 2009;15:6862-6870. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19861442.

79. Nishida T, Takahashi T, Nishitani A, et al. Sunitinib-resistant gastrointestinal stromal tumors harbor cis-mutations in the activation loop of the KIT gene. Int J Clin Oncol 2009;14:143-149. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19390946.

80. Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:295-302. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23177515.

81. Ben-Ami E, Barysauskas CM, von Mehren M, et al. Long-term follow-up results of the multicenter phase II trial of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of standard tyrosine kinase inhibitor therapy. Ann Oncol 2016;27:1794-1799. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27371698.

82. Kindler HL, Campbell NP, Wroblewski K, et al. Sorafenib (SOR) in patients (pts) with imatinib (IM) and sunitinib (SU)-resistant (RES) gastrointestinal stromal tumors (GIST): Final results of a University of Chicago Phase II Consortium trial [abstract]. J Clin Oncol 2011;29(15_Suppl):Abstract 10009. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/10009.

83. Park SH, Ryu MH, Ryoo BY, et al. Sorafenib in patients with metastatic gastrointestinal stromal tumors who failed two or more prior tyrosine kinase inhibitors: a phase II study of Korean gastrointestinal stromal tumors study group. Invest New Drugs 2012;30:2377-2383. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22270258.

84. Montemurro M, Gelderblom H, Bitz U, et al. Sorafenib as third- or fourth-line treatment of advanced gastrointestinal stromal tumour and pretreatment including both imatinib and sunitinib, and nilotinib: A retrospective analysis. Eur J Cancer 2013;49:1027-1031. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23140824.

85. Kefeli U, Benekli M, Sevinc A, et al. Efficacy of sorafenib in patients with gastrointestinal stromal tumors in the third- or fourth-line treatment: A

retrospective multicenter experience. Oncol Lett 2013;6:605-611. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24137379.

86. Demetri GD, Casali PG, Blay JY, et al. A phase I study of single-agent nilotinib or in combination with imatinib in patients with imatinib-resistant gastrointestinal stromal tumors. Clin Cancer Res 2009;15:5910-5916. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19723647.

87. Montemurro M, Schoffski P, Reichardt P, et al. Nilotinib in the treatment of advanced gastrointestinal stromal tumours resistant to both imatinib and sunitinib. Eur J Cancer 2009;45:2293-2297. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19467857.

88. Sawaki A, Nishida T, Doi T, et al. Phase 2 study of nilotinib as third-line therapy for patients with gastrointestinal stromal tumor. Cancer 2011;117:4633-4641. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21456006.

89. Reichardt P, Blay JY, Gelderblom H, et al. Phase III study of nilotinib versus best supportive care with or without a TKI in patients with gastrointestinal stromal tumors resistant to or intolerant of imatinib and sunitinib. Ann Oncol 2012;23:1680-1687. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22357255.

90. Cauchi C, Somaiah N, Engstrom PF, et al. Evaluation of nilotinib in advanced GIST previously treated with imatinib and sunitinib. Cancer Chemother Pharmacol 2012;69:977-982. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22119758.

91. Dewaele B, Wasag B, Cools J, et al. Activity of dasatinib, a dual SRC/ABL kinase inhibitor, and IPI-504, a heat shock protein 90 inhibitor, against gastrointestinal stromal tumor-associated PDGFRAD842V mutation. Clin Cancer Res 2008;14:5749-5758. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18794084.

92. Trent JC, Wathen K, von Mehren M, et al. A phase II study of dasatinib for patients with imatinib-resistant gastrointestinal stromal tumor (GIST) [abstract]. J Clin Oncol 2011;29(15_Suppl):Abstract 10006. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/10006.

93. Ganjoo KN, Villalobos VM, Kamaya A, et al. A multicenter phase II study of pazopanib in patients with advanced gastrointestinal stromal tumors (GIST) following failure of at least imatinib and sunitinib. Ann Oncol 2014;25:236-240. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24356634.

94. Mir O, Cropet C, Toulmonde M, et al. Pazopanib plus best supportive care versus best supportive care alone in advanced gastrointestinal stromal tumours resistant to imatinib and sunitinib (PAZOGIST): a randomised, multicentre, open-label phase 2 trial. Lancet Oncol 2016;17:632-641. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27068858.

95. Blay JY, Shen L, Kang YK, et al. Nilotinib versus imatinib as first-line therapy for patients with unresectable or metastatic gastrointestinal stromal tumours (ENESTg1): a randomised phase 3 trial. Lancet Oncol 2015;16:550-560. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25882987.

96. Schoffski P, Reichardt P, Blay JY, et al. A phase I-II study of everolimus (RAD001) in combination with imatinib in patients with imatinib-resistant gastrointestinal stromal tumors. Ann Oncol 2010;21:1990-1998. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20507881.

97. Committee ASoP, Evans JA, Chandrasekhara V, et al. The role of endoscopy in the management of premalignant and malignant conditions of the stomach. Gastrointest Endosc 2015;82:1-8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25935705.

98. Dematteo RP, Gold JS, Saran L, et al. Tumor mitotic rate, size, and location independently predict recurrence after resection of primary gastrointestinal stromal tumor (GIST). Cancer 2008;112:608-615. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18076015.

99. Gold JS, Gonen M, Gutierrez A, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. Lancet Oncol 2009;10:1045-1052. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19793678.

100. Wang D, Zhang Q, Blanke CD, et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumors: long-term follow-up results of Radiation Therapy Oncology Group 0132. Ann Surg Oncol 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22203182.

101. Raut CP, Posner M, Desai J, et al. Surgical management of advanced gastrointestinal stromal tumors after treatment with targeted systemic therapy using kinase inhibitors. J Clin Oncol 2006;24:2325-2331. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16710031.

102. Rutkowski P, Nowecki Z, Nyckowski P, et al. Surgical treatment of patients with initially inoperable and/or metastatic gastrointestinal stromal tumors (GIST) during therapy with imatinib mesylate. J Surg Oncol 2006;93:304-311. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16496358.

103. Andtbacka RH, Ng CS, Scaife CL, et al. Surgical resection of gastrointestinal stromal tumors after treatment with imatinib. Ann Surg Oncol 2007;14:14-24. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17072676.

104. DeMatteo RP, Maki RG, Singer S, et al. Results of tyrosine kinase inhibitor therapy followed by surgical resection for metastatic gastrointestinal stromal tumor. Ann Surg 2007;245:347-352. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17435539.

105. Gronchi A, Fiore M, Miselli F, et al. Surgery of residual disease following molecular-targeted therapy with imatinib mesylate in advanced/metastatic GIST. Ann Surg 2007;245:341-346. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17435538.

106. Sym SJ, Ryu M-H, Lee J-L, et al. Surgical intervention following imatinib treatment in patients with advanced gastrointestinal stromal tumors (GISTs). J Surg Oncol 2008;98:27-33. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18452195.

107. Mussi C, Ronellenfitsch U, Jakob J, et al. Post-imatinib surgery in advanced/metastatic GIST: is it worthwhile in all patients? Ann Oncol 2010;21:403-408. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19628568.

108. Yeh C-N, Chen T-W, Tseng J-H, et al. Surgical management in metastatic gastrointestinal stromal tumor (GIST) patients after imatinib mesylate treatment. J Surg Oncol 2010;102:599-603. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20976730.

109. Van Den Abbeele AD, Badawi RD, Manola J, et al. Effects of cessation of imatinib mesylate (IM) therapy in patients (pts) with IM-refractory gastrointestinal stromal tumors (GIST) as visualized by FDG-PET scanning [abstract]. J Clin Oncol 2004;22(14_Suppl):Abstract 3012. Available at: http://meeting.jco.org/cgi/content/abstract/22/14_suppl/3012.

110. Raut CP, Wang Q, Manola J, et al. Cytoreductive surgery in patients with metastatic gastrointestinal stromal tumor treated with sunitinib malate. Ann Surg Oncol 2010;17:407-415. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19898902.

111. Fumagalli E, Coco P, Morosi C, et al. Rechallenge with Imatinib in GIST patients resistant to second or third line therapy [abstract]. Connective Tissue Oncology Society (CTOS) 15th Annual Meeting; 2009:Abstract 39404. Available at: http://www.ctos.org/meeting/2009/program.asp.

112. Kang YK, Ryu MH, Yoo C, et al. Resumption of imatinib to control metastatic or unresectable gastrointestinal stromal tumours after failure of imatinib and sunitinib (RIGHT): a randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2013;14:1175-1182. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24140183.

113. Blay JY, Le Cesne A, Ray-Coquard I, et al. Prospective multicentric randomized phase III study of imatinib in patients with advanced gastrointestinal stromal tumors comparing interruption versus continuation of treatment beyond 1 year: the French Sarcoma Group. J Clin Oncol 2007;25:1107-1113. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17369574.

114. Le Cesne A, Ray-Coquard I, Bui BN, et al. Discontinuation of imatinib in patients with advanced gastrointestinal stromal tumours after 3 years of treatment: an open-label multicentre randomised phase 3 trial. Lancet Oncol 2010;11:942-949. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20864406.

115. Patrikidou A, Chabaud S, Ray-Coquard I, et al. Influence of imatinib interruption and rechallenge on the residual disease in patients with advanced GIST: results of the BFR14 prospective French Sarcoma Group randomised, phase III trial. Annals of Oncology 2013;24:1087-1093. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23175622.