GASTROINTESTINAL STROMAL TUMOR (GIST) TREATMENT REGIMENS (Part 1 of 2)

Clinical Trials: The NCCN recommends cancer patient participation in clinical trials as the gold standard for treatment.

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced healthcare team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are provided only to supplement the latest treatment strategies.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available. The NCCN Guidelines® are a consensus statement of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

REGIMEN	DOSING
Preoperative Therapy in Resectable GIST with Negative Margins and Risk of Significant Morbidity[1]	
Note: All recommendations are Category 2A unless otherwise indicated.	
Imatinib[2-6]	Imatinib 400mg orally once daily; increase to 400mg twice daily in patients with documented KIT exon 9 mutation as clinically tolerated.
Preoperative Therapy in Definitively Unresectable, Recurrent, or Metastatic GIST[1]	
Imatinib (Category 1)[2-6]	Imatinib 400mg orally daily; increase to 400 mg twice daily, as clinically indicated, in patients showing clear signs or symptoms of disease progression at a lower dose and in the absence of severe adverse drug reactions.
Adjuvant Therapy Following Complete Gross Resection of GIST[1]	
Imatinib[2,7]	Imatinib 400mg orally once daily; has been given for up to 1 year in a clinical trial.
Kit (CD117) Positive Unresectable and/or Metastatic Malignant GIST[1]	
Imatinib[2,8-11]	Imatinib 400mg orally once daily; increase to 400mg twice daily if disease progression occurs or in patients with documented KIT exon 9 (or exon 11) mutation as clinically tolerated.
Intolerance to Imatinib or Disease Progression[1]	
Sunitinib (Category 1)[12-14]	Sunitinib 50mg orally once daily given in 6-week cycles with 4 weeks on and 2 weeks off.[a] **OR** Sunitinib 37.5mg orally once daily without interruption.[b]
Disease Progression Despite Prior Imatinib or Sunitinib Therapy[1]	
Regorafenib (Category 1)[15,16c]	Regorafenib 160mg orally once daily. Given in 4-week cycles with 3 weeks on and 1 week off.
Disease Progression Despite Prior Imatinib, Sunitinib, or Regorafenib Therapy[d]	
None of the drugs listed below are FDA-approved for the treatment of GIST. Recommendations are based on limited data.	
Sorafenib[17-19]	Sorafenib 400mg orally twice daily until disease progression or development of intolerance.
Nilotinib[20,21]	Nilotinib 400mg orally twice daily. Reduce to once daily in case of intolerance.
Dasatinib[22]	Dasatinib 70mg orally twice daily (for patients with D842V mutation).
Pazopanib[23]	Pazopanib 800mg orally once daily until disease progression or unacceptable toxicity.

[a] Consider dose reduction to a minimum of 37.5mg daily if given with a strong CYP3A4 inhibitor or dose increase to a maximum 87.5mg daily if given with a CYP3A4 inducer.

[b] Consider dose reduction to a minimum of 25mg daily if given with a strong CYP3A4 inhibitor or a dose increase to a maximum 62.5mg daily if given with concomitant CYP3A4 inducer.

[c] For additional treatment caveats, please see the NCCN Soft Tissue Sarcoma Guidelines for Dosing and Administration of Regorafenib for GIST (v 1.2015, page 33)[1]

[d] Imatinib, sunitinib, and regorafenib are the only three FDA agents approved for the treatment of GIST.

continued

GASTROINTESTINAL STROMAL TUMOR (GIST) TREATMENT REGIMENS (Part 2 of 2)

References

1. NCCN Clinical Practice Guidelines in Oncology™. Soft Tissue Sarcoma. v 2.2016. Available at: http://www.nccn.org/professionals/ physician_gls/pdf/sarcoma.pdf. Accessed September 27, 2016.
2. Gleevec [prescribing information]. East Hanover, NJ: Novartis Corp.; 2015.
3. 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.
4. Eisenberg BL, Harris J, Blanke CD, et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate (IM) for advanced primary and metastatic/recurrent operable 3 gastrointestinal stromal tumor (GIST): early results of RTOG 0132/ACRIN 6665. *J Surg Oncol.* 2009;99:42–47.
5. 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.
6. 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.
7. Demattео RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localized, primary gastrointestinal stromal tumor: a randomised, double-blind, placebo-controlled trial. *Lancet.* 2009;373:1097–1104.
8. 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.
9. Heinrich MS, 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.
10. Debiec-Rychter M, Sciot R, Le Cesne A, et al. KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stomal tumors. *Eur J Cancer.* 2006;42:1093–1103.
11. Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST). 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.
12. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumor after failure of imatinib: a randomised controlled trial. *Lancet*. 2006;368:1329–1338.
13. Sutent [prescribing information]. New York, NY: Pfizer Corp.; 2015.
14. George S, Blay JY, Casali PG, et al. Clinical evaluation of continuous daily dosing of sunitinib malate in patients with advanced gastrointestinal stromal tumor after imatinib failure. *Eur J Cancer*. 2009;45:1959–1968.
15. Stivarga [prescribing information]. Wayne, NJ: Bayer HealthCare Pharmaceuticals Inc; 2015.
16. Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumors after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet.* 2013;381(9863):295–302.
17. Montemurro M, Gelderblom H, Bitz U, et al. Sorafenib as third- or fourth-line treatment of advanced gastrointestinal stromal tumor and pretreatment including both imatinib and sunitinib, and nilotinib: A retrospective analysis. *Eur J Cancer.* 2013;49(5):1027–1031.
18. 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.
19. 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(6):2377–2383.
20. Montemurro M, Schoffski P, Reichardt P, et al. Nilotinib in the treatment of advanced gastrointestinal stromal tumors resistant to both imatinib and sunitinib. *Eur J Cancer.* 2009;45:2293–2297.
21. 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.
22. 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.
23. 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(1):236–40.

(Revised 10/2016)