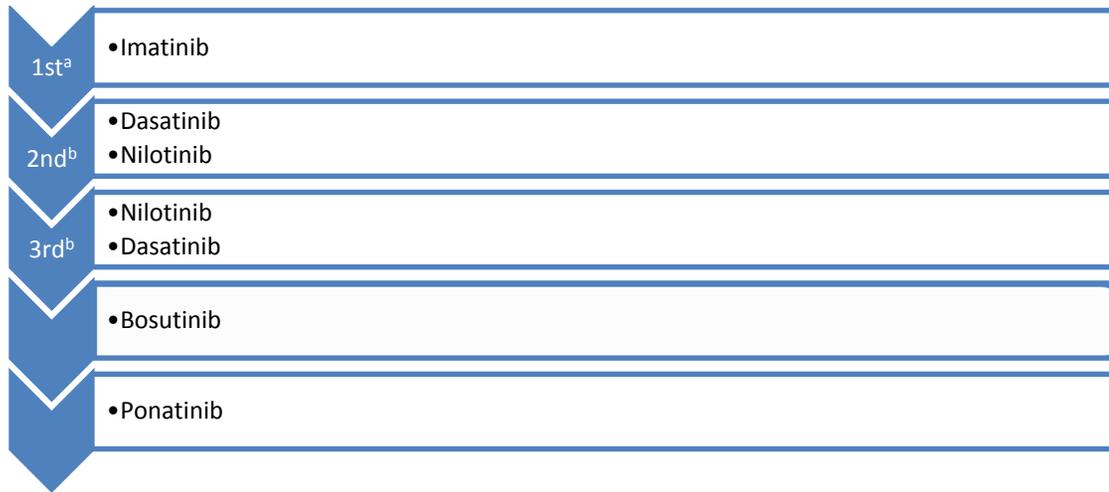


Tyrosine Kinase Inhibitor (TKI) Therapeutic Flow Chart for the Treatment of CML

A. Flow Chart



B. Rationale and Supporting Evidence

^aFirst-line Therapy

- Imatinib, the first approved TKI for CML, has been shown to provide durable responses in an 8-year follow up of the IRIS study with OS 93% [1]
 - Most long-term safety data of all agents (no new safety signals noted)
- Dasatinib, a second-generation TKI, is supported by a 3-year follow up of DASISION with OS 93%; MMR 46% at 12 months [2]
- Nilotinib, a second-generation TKI, is supported by a 3-year follow up of ENESTnd with OS 94%; MMR 44% at 12 months [3]
 - Impact of early response (MMR at 12 months) on survival remains to be determined
 - It is theorized that high-risk patients may benefit from a second-generation TKI as first-line therapy, but there is no supporting data and the optimal treatment for these patients remains to be determined
- Unless a contraindication exists, imatinib should be the preferred first-line therapy

^bSecond-line and Subsequent Therapies

- Guidelines (ELN, NCCN) recommend that choice of TKI take the following into consideration: side effect profile, kinase mutation profile, drug interactions, adherence issues, pre-existing comorbidities [4, 5, 6]
- Second-line TKI recommended for patients on imatinib who do not meet treatment milestones at 12 months (BCR-ABL1 transcripts > 10% (IS), lack of at least partial cytogenetic response (PCyR) of bone marrow cytogenetics).
- Evidence for use of bosutinib as a 4th TKI is supported by a small subset (n=3) of patients within a phase 2 trial (Khoury, 2012) and a retrospective evaluation (n=30) of patients in Spain (Garcia-Gutierrez, 2015)
- Refer to [Tyrosine Kinase Inhibitor Comparison Chart for CML](#) for notable differences among agents

C. Monitoring

- Refer to TKI Comparison Chart for baseline and follow-up toxicity monitoring recommendations for each agent.
- Recommendations for response monitoring are found in Table 1.

Table 1. Recommendations for Monitoring Response to TKI Therapy and Mutational Analysis

Test	Recommendations
Bone Marrow Cytogenetics	<ul style="list-style-type: none"> • At diagnosis to establish disease phase. If collection of bone marrow is not feasible, FISH on peripheral blood specimen using dual probes for BCR and ABL1 genes is an acceptable method of confirming diagnosis of CML • At 3 months and 6 months after initiation of TKI therapy, if QPCR (IS) is not available. • At 12 months and beyond from the initiation of TKI therapy. If there is no CCyR or MMR. Absence of MMR in the presence of a CCyR is not considered a treatment failure. • For patients with less than CCyR at 12 months and beyond, bone marrow cytogenetics should be repeated at 3 months after change of therapy to alternate TKI to document CCyR. • Rising levels of BCR-ABL1 transcript (1-log increase) without a MMR.
QPCR (IS)	<ul style="list-style-type: none"> • At diagnosis. • Every 3 months after initiation of treatment. After CCyR has been achieved, every 3 months for 2 years and every 3-6 months thereafter. • If there is a rising level of BCR-ABL1 transcript (1-log increase) with a MMR, QPCR should be repeated in 1-3 months.
BCR-ABL1 kinase domain mutation analysis	<p>Chronic phase</p> <ul style="list-style-type: none"> • Inadequate initial response to TKI therapy (BCR-ABL1 transcripts > 10% (IS) or lack of PCyR at 3 and 6 months or less than a CCyR or BCR-ABL1 transcripts > 1% (IS) at 12 months). • Any sign of loss of response (defined as hematologic or cytogenetic relapse). • 1-log increase in BCR-ABL1 transcript levels and loss of MMR. <p>Disease progression to accelerated or blast phase.</p>

D. Tyrosine Kinase Inhibitor Comparison Chart for CML

Generic name	Imatinib	Dasatinib	Nilotinib	Bosutinib	Ponatinib
Trade name	Gleevec	Sprycel	Tasigna	Bosulif	Iclusig
FDA approved indications	1. newly diagnosed Ph+ CML in CP 2. Ph+ CML in BC, AP after IFN- α therapy 3. Ph+ ALL 4. MDS/MPD 5. ASM 6. HES and/or CEL 7. DFSP 8. GIST 9. Ph+ CML CP in peds	1. newly diagnosed Ph+ CML in CP 2. Ph+ CML in CP, AP or BP with imatinib R/I 3. Ph+ ALL with R/I to prior therapy	1. CML CP and AP in adults R/I to imatinib-based therapy 2. newly diagnosed Ph+ CML in CP	1. Ph+ CML in CP, AP or BP with R/I to prior therapy	1. Treatment of T315I+ CML in CP, AP or BP or T315I Ph+ ALL 2. CP, AP, BP-CML or Ph+ALL for whom no other TKI is indicated
Dosing (oral) CP AP BP	400 mg once daily 600 mg once daily to 400 mg BID	100 mg once daily 140 mg once daily 140 mg once daily	300 mg BID 400 mg BID	500 mg once daily w/food	45 mg once daily 45 mg once daily 45 mg once daily
Dosing in hepatic impairment	25% dose reduction in severe hepatic impairment	Adjustment not needed; use with caution	Lower dose	200 mg once daily	30 mg once daily
Dosing in renal impairment	If CrCl 40-59 ml/min, do not exceed 600 mg daily; If CrCl 20-39 ml/min, start with 50% \downarrow , then \uparrow as tolerated; max dose 400 mg	Less than 4% excreted renally; no studies done	No renal excretion	If CrCl 30-50 ml/min, starting dose 400 mg once daily; If CrCl < 30 ml/min, starting dose 300 mg once daily	Renal excretion ~5%; no studies done
Formulations	100, 400 mg scored tabs; Coating contains ferric oxide; use 400 mg tab for large doses to \downarrow iron exposure	20, 50, 70, 80, 100, 140 mg film-coated tabs	150, 200mg hard caps	100, 500 mg tablets	15, 45 mg tablets
Boxed warnings	None	None	QT prolongation, sudden death	None	Vascular occlusion, heart failure, hepatotoxicity
Contraindications	None	None	Hypokalemia, hypomagnesemia, long QT syndrome	Hypersensitivity	None

	Imatinib	Dasatinib	Nilotinib	Bosutinib	Ponatinib
Precautions/ warnings	Fluid retention Myelosuppression CHF/LV dysfunction Hepatotoxicity Bleeding-related events ^b Pregnancy category D GI irritation Hypothyroidism	Myelosuppression Bleeding-related events ^a Fluid retention QT prolongation CHF/MI/LV dysfunction Pregnancy category D Lactose-containing Pulmonary Arterial Hypertension (PAH) Hypothyroidism	Myelosuppression QT prolongation ↑ serum lipase ↑ LFT's Electrolyte abnormality Pregnancy category D Lactose-containing Total gastrectomy Hypothyroidism	GI toxicity Myelosuppression Hepatotoxicity Fluid Retention Pregnancy category D	Arterial/Venous occlusion Heart failure Hepatotoxicity HTN Pancreatitis Neuropathy Ocular toxicity Hemorrhage Fluid retention Cardiac arrhythmias Myelosuppression Tumor Lysis Syndrome Impaired wound healing Pregnancy category D
Adverse events	Newly diagnosed (> 10%): Fluid retention (62%); Nausea (49%); Muscle cramps (49%); Diarrhea (45%); Rash (40%) Other CML trials (> 10%): Fluid retention (72%); Nausea (71%); Muscle cramps (28%); Vomiting (54%); Diarrhea (43%)	Newly diagnosed (> 10%): Neutropenia (22%); Thrombocytopenia (19%); Anemia (11%); Fluid retention (23%); Diarrhea (18%); Headache (12%); Musculoskeletal pain (12%); Rash (11%) Imatinib R/I (> 20%): Myelosuppression (36%) Fluid retention (34%); Diarrhea (27%); Headache (33%); Musculoskeletal pain (19%); Rash (17%); Hemorrhage (11%)	Newly diagnosed (> 10%): Rash (36%); Pruritus (19%); Nausea (19%); Constipation (15%); Headache (28%); Fatigue (19%); Neutropenia (12%); Thrombocytopenia (10%); Anemia (4%) Imatinib R/I (>10%): Rash (36%); Pruritus (32%); Nausea (37%); Fatigue (32%); Headache (35%), Thrombocytopenia (30%), Neutropenia (31%), Anemia (11%)	Imatinib R/I (>20%): Diarrhea (82%); Nausea (46%); Thrombocytopenia (41%); Vomiting (39%); Abdominal pain (37%); Rash (35%); Anemia (27%); Pyrexia (26%); Fatigue (24%)	TKI R/I (> 20%): HTN (53-71%); Rash (34-54%); Abdominal pain (34-49%); Fatigue (31-39%); Headache (25-39%); Dry skin (24-39%); Constipation (24-47%); Arthralgia (13-26%); Nausea (22-32%); Pyrexia (23-32%)
Drug-drug interactions	CYP3A4 inhib/inducers; Warfarin, acetaminophen	CYP3A4 inhib/inducer; antacids, H2A, PPIs	QT prolongators; CYP3A4 inhibitors; antacids, H2A, PPIs and P-gp	CYP3A or P-gp inhibitors CYP3A inducers PPIs P-gp substrates	CYP3A4 inhibitors; CYP3A4 inducers

	Imatinib	Dasatinib	Nilotinib	Bosutinib	Ponatinib
Drug-food interactions	Take with food and water; Avoid grapefruit products	Take with or without food; Avoid grapefruit products	Take on empty stomach; Avoid grapefruit products	Take with food; Avoid grapefruit products	Take with or without food
REMS	None	Medication guide	Medication guide	None	Medication guide
Baseline toxicity monitoring	CBC; LFT's; TFT's (thyroidectomy pts); Pregnancy test (if applicable)	<u>Baseline CV monitoring^d</u> Clinical CV assessment, including BP; fasting glucose ACI; fasting lipid panel ACI Echocardiogram ACI with low threshold for patient with cardiopulmonary sx; ECG; Ankle-brachial index ACI <hr/> Electrolytes (esp K, Mg); CBC; Pregnancy test (if applicable)	<u>Baseline CV monitoring^d</u> Clinical CV assessment, including BP; fasting glucose; fasting lipid panel; ECG baseline, 7 days after start & with dose changes; Ankle-brachial index; Echocardiogram ACI; <hr/> Electrolytes (esp K, Mg); CBC; serum lipase; LFTs Pregnancy test (if applicable)	<u>Baseline CV monitoring^d</u> Clinical CV assessment, including BP; Fasting glucose ACI; Fasting lipid panel ACI; Echocardiogram ACI; ECG ACI; Ankle-brachial index ACI; <hr/> GI issues (D/N/V) CBC; LFT's; Pregnancy test (if applicable)	<u>Baseline CV monitoring^d</u> Clinical CV assessment, including BP; Fasting glucose; Fasting lipid panel; Echocardiogram ACI; ECG ACI; Ankle-brachial index; <hr/> CBC; LFT's; serum lipase; uric acid; eye exam; Pregnancy test (if applicable)
Follow-up toxicity monitoring <i>Recs provided should be used as a guide; therapy should continue during the monitoring process; use clinical judgement; do not hold prescriptions while awaiting monitoring</i>	CBC weekly x 1 month; Biweekly x 2nd month then periodically (q 2-3 mos); s/sx of CHF/LV dysfxn; LFT's q month (or ACI); Serum TSH on day 1 of each cycle ^f	<u>CV monitoring at 1 month^d</u> Clinical CV assessment; BP check ACI <hr/> <u>CV monitoring at 3-6 months^d</u> Clinical CV assessment; BP check ACI; Fasting glucose ACI; Fasting lipid panel ACI; Echocardiogram ACI with low threshold for patient with cardiopulmonary sx; ECG ACI; Ankle-brachial index ACI <hr/> Serum TSH on day 1 of each cycle ^f ; CBC; Electrolytes periodically; s/sx bleeding	<u>CV monitoring at 1 month^d</u> Clinical CV assessment; BP check ACI <hr/> <u>CV monitoring at 3-6 months^d</u> Clinical CV assessment; BP check Fasting glucose; Fasting lipid panel; Ankle-brachial index; ECG ACI and with any dose changes; Echocardiogram ACI <hr/> Serum TSH on day 1 of each cycle ^f ; CBC q 2 weeks x 2 mos, then monthly; Electrolytes periodically; Serum lipase periodically; LFTs periodically	<u>CV monitoring at 1 month^d</u> Clinical CV assessment ACI; BP check ACI <hr/> <u>CV monitoring at 3-6 months^d</u> Clinical CV assessment; BP check ACI; Fasting glucose ACI; Fasting lipid panel ACI; Echocardiogram ACI; ECG ACI; Ankle-brachial index ACI <hr/> GI toxicity (D/N/V) CBC weekly x 1 month, then monthly (and ACI); LFT's q month x 3 (and ACI);	<u>CV monitoring at 1 month^d</u> Clinical CV assessment; BP check <hr/> <u>CV monitoring at 3-6 months^d</u> Clinical CV assessment; BP check Fasting lipid panel; Ankle-brachial index; Fasting glucose ACI; Echocardiogram ACI; ECG ACI <hr/> s/sx of neuropathy; s/sx bleeding; CBC q 2 weeks x 3 mos, then monthly (or ACI); LFT's q month (or ACI); Serum lipase q 2 weeks x 2 months, then monthly (or ACI); Eye exam ACI

	Imatinib	Dasatinib	Nilotinib	Bosutinib	Ponatinib
Sensitivity to BCR-ABL1 mutations ^c		Y253H E255K/V F359C/V	V299L F317L	F317L Y253H F359C/I/V	T315I
Handling	Avoid exposure to crushed/broken tablets	Avoid exposure to crushed/broken tablets	??	Avoid exposure to crushed/broken tablets	Avoid exposure to crushed/broken tablets
Clinical situations that may direct TKI preference	Patient with significant peripheral edema	Patient with pancreatitis, elevated bilirubin, uncontrolled DM, CML involving CNS	Patient at significant risk of pleural/pericardial effusions, PAH, or a high bleed risk	Patient at baseline risk of QT-prolongation	Patient harbors T315I mutation; Patient not a candidate for any other TKI
ECOG PS of study participants	0 - 2	0 - 2	0 - 2	0 - 1	0 - 2
Monthly cost estimates ^e	400 mg PO daily \$140/day	100 mg PO daily \$204/day	300 mg PO BID \$209/day	500 mg PO daily \$184/day	45 mg PO daily \$240/day

Key: CML=chronic myelogenous leukemia, Ph+=Philadelphia chromosome positive; CP=chronic phase; BC=blast crisis; AP=accelerated phase; IFN=interferon; ALL=acute lymphoblastic leukemia; MDS=myelodysplastic syndrome; MPD=myeloproliferative diseases; ASM=aggressive systemic mastocytosis; HES=hypereosinophilic syndrome; CEL=chronic eosinophilic leukemia; DFSP=dermatofibrosarcoma protuberans; GIST=gastrointestinal stromal tumor; R/I = resistance/intolerance; PAH = pulmonary arterial hypertension; ACI = as clinically indicated; ^a mostly associated with thrombocytopenia, although some events are independent of platelet count; ^b gr 3, 4 bleeds: 1.8% in CML trials; 12.9% in GIST trials; ^c Hughes T, et al. J Clin Oncol 2009; Muller MC, et al. Blood 2009; Khoury HJ, et al. Blood 2012; Cortes JE, et al. N Engl J Med 2012; ^d Moslehi JJ, Deininger M. TKI-Associated CV Toxicity in CML. J Clin Oncol 2015; 33: DOI: 10.1200/JCO.2015.62.4718 ^e BIG4 pricing as of 10/8/2015; ^f Fallahi P, et al. Thyroid Dysfunctions Induced by TKIs. Expert Opin Drug Saf 2014; 13: 723.

D. References

1. Deininger M, O'Brien SG, Guilhot F, et al. International Randomized Study of Interferon vs. STI571 (IRIS) 8-year follow up: Sustained Survival and Low Risk for Progression of Events in Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Treated with Imatinib. *Blood* 2009; 114: Abstract 1126.
2. Jabbour E, Kantarjian HM, Saglio G, et al. Early Response with Dasatinib or Imatinib in Chronic Myeloid Leukemia: 3-year follow up from a Randomized Phase 3 Trial (DASISION). *Blood* 2014; 123: 494.
3. Larson RA, Hochhaus A, Clark RE, et al. Nilotinib vs. Imatinib in Patients with Newly Diagnosed Philadelphia chromosome-positive Chronic Myeloid Leukemia in Chronic Phase: ENESTnd 3-year follow up. *Leukemia* 2012; 26: 2197.
4. Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet Recommendations for the Management of Chronic Myeloid Leukemia. *Blood* 2013; 122: 872.
5. Baccarani M, Castagnetti F, Gugliotta G, Rosti G. A Review of the European LeukemiaNet Recommendations for the Management of CML. *Ann Hematol* 2015; 94: S141.
6. O'Brien S, Radich JP, Abboud CN, Akhtari M, et al. Chronic Myelogenous Leukemia, version 1.2015. *J Natl Compr Canc Netw*. 2014; 12:1590.
7. Muller MC, Cortes JE, Kim DW, et al. Dasatinib Treatment of Chronic-Phase Chronic Myeloid Leukemia: Analysis of Responses According to Preexisting *BCR-ABL* mutations. *Blood* 2009; 114: 4944.
8. Hughes T, Saglio G, Branford S, et al. Impact of Baseline *BCR-ABL* Mutations on Response to Nilotinib in Patients with Chronic Myeloid Leukemia in Chronic Phase. *J Clin Oncol* 2009; 27: 4204.
9. Jabbour E, Kantarjian H. Chronic Myeloid Leukemia: 2014 Update on Diagnosis, Monitoring and Management. *Am J Hematol* 2014; 89: 548.
10. Khoury RJ, Cortes JE, Kantarjian HM, et al. Bosutinib is Active in Chronic Phase Chronic Myeloid Leukemia after Imatinib and Dasatinib and/or Nilotinib Therapy Failure. *Blood* 2012; 119: 3403.
11. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. A Phase 2 of Ponatinib in Philadelphia Chromosome-Positive Leukemias. *N Engl J Med* 2013; 369: 1783.
12. Hughes T, Deininger M, Hochhaus A, et al. Monitoring CML Patients Responding to Treatment with Tyrosine Kinase Inhibitors: Review and Recommendations for Harmonizing Current Methodology for Detecting *BCR-ABL* Transcripts and Kinase Domain Mutations and for Expressing Results. *Blood* 2006; 108: 28-37.
13. Imatinib (Gleevec) Prescribing Information. Novartis Pharmaceuticals Corporation. East Hanover, New Jersey. January 2015.
14. Dasatinib (Sprycel) Prescribing Information. Bristol-Myers Squibb. Princeton, New Jersey. August 2015.
15. Nilotinib (Tysigna) Prescribing Information. Novartis Pharmaceuticals Corporation. East Hanover, New Jersey. January 2015.
16. Bosutinib (Bosulif) Prescribing Information. Pfizer Labs, New York, New York. November 2014.
17. Ponatinib (Iclusig) Prescribing Information. ARIAD Pharmaceuticals, Inc. Cambridge, Massachusetts. September 2014.
18. Garcia-Gutierrez V, Maestro B, Martinez-Trillo A, et al. Bosutinib appears to be safe with low cross intolerance, in Patients Treated in 4th Line. Results of the Spanish Compassionate Use Program. *Am J Hematol*. 2015 May;90(5):429-33. doi: 10.1002/ajh.23973. Epub 2015 Mar 30.