haematologica
Journal of the Ferrata Storti Foundation

Management of chronic myeloid leukemia with tyrosine kinase inhibitors: adverse events, toxicities and therapy dosing

by Vivian G. Oehler, Ellin Berman and Ivan J. Huang

Received: August 13, 2025.
Accepted: March 2, 2026.

Citation: Vivian G. Oehler, Ellin Berman and Ivan J. Huang. Management of chronic myeloid leukemia with tyrosine kinase inhibitors: adverse events, toxicities and therapy dosing. Haematologica. 2026 Mar 12. doi: 10.3324/haematol.2025.288334 [Epub ahead of print]

Management of chronic myeloid leukemia with tyrosine kinase inhibitors: adverse events, toxicities and therapy dosing

Vivian G. Oehler[1,2], Ellin Berman[3], and Ivan J. Huang[4,5]

[1]Translational Science and Therapeutics Division, Fred Hutchinson Cancer Center, Seattle, WA, USA
[2]Department of Medicine, Division of Hematology and Oncology, University of Washington, Seattle, WA, USA
[3]Leukemia Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[4]Hematologic Malignancies, Fred Hutchinson Cancer Center, Seattle, WA, USA
[5]Department of Pharmacy, University of Washington Medical Center, Seattle, WA, USA

Corresponding Author:

Vivian G. Oehler

Mailing address: 1100 Fairview Ave N, D3-193, Seattle, WA 98109

Telephone number: 206-667-1340

Email address: voehler@fredhutch.org

Author Contributions

VGO wrote the manuscript and created tables and figures

EB edited the manuscript

IJH edited the manuscript and created tables and figures

Disclosures

VGO: PI clinical trials: Novartis, Ascentage Pharma, Terns, Shenzhen TargetRx ; Consulting: Novartis, Terns, Takeda

EB: none

IJH: none

Running title: TKIs in CML: toxicity and management

Abstract

Targeted therapies have made near normal life span an attainable goal for many patients with chronic phase (CP) chronic myeloid leukemia (CML). Most patients require years of therapy and not everyone may be able to discontinue treatment permanently without CML recurrence. *BCR::ABL1* targeted tyrosine kinase inhibitors (TKIs) including ATP binding site and allosteric inhibitors that bind to the myristoyl pocket are associated with treatment-emergent adverse events (TEAEs) that may compromise quality of life and well-being. Although alternative treatment options exist, side effects may persist, or new ones occur after a therapy switch. Using a case-based approach, this review examines the incidence of non-hematologic and hematologic TEAEs with specific therapies, provides guidance on AE management, and describes the impact of therapy dose reduction on efficacy and tolerability.

Introduction

For the majority of chronic phase (CP) chronic myeloid leukemia (CML) patients, successful treatment with tyrosine kinase inhibitors (TKIs) abrogates the risk for CML-related death and leads to a near normal life span[1]. Therapies include TKIs targeting the ATP binding site such as the 1st generation TKI imatinib; the 2nd generation (2G)-TKIs dasatinib, nilotinib, bosutinib, flumatinib (China) and radotinib (South Korea); the 3rd generation (3G)-TKIs ponatinib and olverembatinib (China); and asciminib, the allosteric inhibitor engaging the myristoyl pocket[2-13]. The treatment landscape continues to evolve with asciminib approval extended to first and second-line CP CML in the US, Canada, Japan, and a recommendation for approval by the European Medicines Agency. In addition, there are ongoing trials of new inhibitors. Tolerability as measured by frequency, severity, and duration of adverse events (AEs) and time to discontinuation are important secondary endpoints of ongoing clinical trials. Asciminib has demonstrated an excellent tolerability profile for specific AEs. However, imatinib with its excellent long-term safety profile and 2G TKIs with potency in resistant CML remain essential treatments. From a cost-perspective, imatinib, dasatinib, and more recently, nilotinib and bosutinib are now available as generic therapies.

Given excellent overall survival (OS) and the long duration of treatment, optimizing health-related quality of life (HRQOL), which includes perception of both physical and mental health over time, is a crucial component of care. Minimizing treatment-emergent adverse events (TEAEs) and avoiding organ damaging toxicities are paramount. Successful therapy discontinuation, also known as treatment-free remission (TFR), is one long-term strategy to eliminate TEAEs. In addition to a definitive and detailed review by Lipton and colleagues, organizations such as European Leukemia Net (ELN) and National Comprehensive Cancer Network (NCCN) provide detailed guidance on management of TEAEs[14-16]. The importance of communication between health care providers and patients to optimize tolerability and HRQOL is highlighted by the CML Survey on Unmet Needs (CML SUN) study, a large mixed methods

approach study, which included qualitative interviews and quantitative surveys of 361 CP CML patients and 198 physicians from 11 countries[17]. In this study only 67% and 55% of patients were satisfied that their current treatment maintained or improved QOL and had no or manageable side effects, respectively. Impacts on physical well-being, social life, work life, and mental health were frequent. Using a case-based approach, this review will discuss the incidence of and management strategies for specific non-hematologic and hematologic TEAEs. These are summarized in Tables 1-3 for all approved therapies[2-11, 14, 16, 18-33]. Because therapy dose reduction, when possible, is also an important strategy to reduce TEAEs, outcomes on lower than standard dosing will also be reviewed.

Case 1: The patient is a 64-year-old male with low-risk CP CML by the EUTOS long-term survival (ELTS) score [34]. Past medical history is notable for hypertension, hyperlipidemia, type 2 diabetes mellitus and cardiovascular disease. A drug-eluting stent to the left anterior descending artery was placed 5 years prior to the diagnosis of CML. Imatinib 400 mg daily was started first-line 24 months ago. After 12 months of therapy *BCR::ABL1* transcripts are 0.05% International Scale (IS) consistent with major molecular response (MMR, *BCR::ABL1* transcripts ≤ 0.1% IS) and after 18 months *BCR::ABL1* transcripts have declined to 0.008% IS (MR4, *BCR::ABL1* ≤ 0.01% IS). The patient shares with you that he struggles with fluid retention, including both periorbital and peripheral edema, muscle cramps at least once weekly, and intermittent nausea despite anti-emetic therapy. The patient has perceived some improvements in peripheral lower extremity edema with the use of knee-high compression stockings. Electrolytes are within normal limits including calcium, potassium, and phosphate. The patient is interested in future imatinib discontinuation but given the persistence of TEAEs and the need for several more years of therapy, he asks about imatinib dose reduction or alternative therapies. The patient shares that he would prefer to continue imatinib, if possible. He is

planning on retiring in 9 months and the low cost of generic imatinib in the US has relieved some of his anxiety about medication costs.

Imatinib dose reduction in CP CML: impact on non-hematologic TEAEs and outcomes.

In the IRIS study that led to approval of imatinib as front-line therapy, superficial edema, nausea, and muscle cramps were reported in 59%, 49%, and 49% of patients, respectively (Table 1)[24, 25]. Imatinib dose reduction can improve both the frequency and severity of TEAEs as was reported in a recent Chinese single center retrospective study of 716 patients receiving imatinib as initial therapy[35]. Among 198 patients who reduced dose to 200 or 300 mg daily due to TEAEs, the frequency of all grade TEAEs, of which edema, GI discomfort, fatigue, and muscle spasm were the most common, decreased from 86% to 46%[35].These findings are similar to earlier retrospective studies that observed that TEAEs improved in 62.2% of patients with MR4 or MR4.5 (*BCR::ABL1* ≤ 0.003% IS) who reduced imatinib dose to 300 mg daily[36, 37]. Among patients with MR4 or MR4.5, almost all maintained or deepened response after imatinib dose reduction to 300 mg daily. The prospective UK Phase 2 cohort study DESTINY examined the impact of a 50% dose reduction for 12 months (with planned interim analysis) prior to TKI discontinuation[38, 39]. Entry criteria included TKI therapy for at least 3 years and MMR or MR4 for at least one year prior to enrollment. Among 174 CP CML patients, 148 reduced imatinib dose to 200 mg daily, 10 reduced dasatinib to 50 mg daily and 16 reduced nilotinib to 200 mg twice daily. The median duration of TKI use was 7.7 years and 6.5 years in the MMR and MR4 cohorts, respectively. In the interim analysis after dose reduction 9 patients (18.75%) in the MMR cohort and 3 patients (2.48%) in the MR4 cohort lost MMR. Within the first 3 months after dose reduction, improvements of periorbital edema, rash, nausea, diarrhea, lethargy, and hair thinning were reported. MMR or deeper molecular responses were achieved again by all patients restarting therapy for molecular recurrence. Among patients with MR4 who maintained MR4 for 12 months after dose reduction, recurrence-free survival was 72% (95% CI 64-80) after

TKI discontinuation, supporting that TFR for patients in MR4 was not compromised by dose reduction prior to stopping therapy[38]. Both the single center study from China and another retrospective real world practice review of 298 cases, including 90 patients receiving imatinib, reported no difference in the probability of remaining in MMR on reduced imatinib dosing for patients in either MMR or MR4 at the time of dose reduction[35, 40]. The achievement of MR4, MR4.5 or TFR was also not compromised[35]. However, conclusions from these studies on the efficacy of 200 mg imatinib dosing in patients in MMR, but without deeper responses, are limited by small patient numbers. The impact on subsequent TFR remains unclear in this group and could be compromised; thus, caution is warranted.

The timing of dose reduction is also important. For some patients dose reductions early in treatment, particularly within the first 12 months, may compromise outcomes especially for lower potency therapies such as imatinib. In the phase 2 Japan Adult Leukemia Study Group CML202 study overall survival (OS) and event-free survival (EFS) in patients receiving 400 mg vs 300 mg daily were not statistically significantly different[41]. However, patients receiving imatinib dosing < 300 mg daily had inferior response rates and survival outcomes. In the retrospective single center study from China, a shorter duration of MMR (< 23 months) prior to dose reduction was also associated with a higher incidence of loss of MMR[35].

For patients with loss of molecular response (e.g., loss of MMR or loss of complete cytogenetic response (CCyR), *BCR::ABL1* ≤ 1% IS) on reduced dose, a change in therapy should be considered if therapy dose cannot be re-escalated, especially if TFR is a goal[42]. Alternative therapy should also be considered if TEAEs persist on reduced dose as long-term HRQOL is critical. Lastly, the impact of dose reduction in patients with high-risk features such as high clinical risk scores and/or specific molecular features (e.g., additional cytogenetic abnormalities, *ASXL1* mutations), and/or slow *BCR::ABL1* transcript decline is unknown. As these features are associated with poorer molecular response failure-free survival, these patients may be at risk with early dose reduction[43-48].

Case 1 outcome:

The patient had only recently achieved MR4 six months before the visit. After discussion, imatinib dose was reduced to 300 mg daily. Edema and nausea improved with dose reduction to 300 mg daily. MR4 was maintained and MR 4.5 achieved 12 months later with imatinib 300 mg daily. A plan to discuss further imatinib dose reduction to 200 mg daily followed by discontinuation if response is maintained and the patient completes at least 4-5 years of therapy was made[15, 38, 39].

Case 2: The patient is a 61-year-old female with a past medical history notable for hypertension managed with losartan and a new diagnosis of low ELTS risk CP CML. She works long hours as a litigator and strongly prioritizes becoming eligible for TKI discontinuation. She is interested in front-line 2G TKI because the cumulative incidence of deep molecular response is higher[4]. You discuss the increased risk for pleural effusion with standard dosing of dasatinib and that the risk is higher in older patients[4, 49]. The patient is worried about side effects such as diarrhea, headache, and pleural effusion and asks whether a lower dose of dasatinib may be started preemptively without compromising outcomes.

2G TKI dosing in CP CML: impact on non-hematologic TEAEs and outcomes:

Dasatinib

Retrospective analyses and comparative analyses have supported improved tolerance and sustained efficacy for lower dasatinib dosing[40, 50]. A significant toxicity of dasatinib is pleural effusion. On the front-line phase 3 DASISION study by 5 years, pleural effusion was seen in 28% of dasatinib-treated patients vs 0.8% of imatinib treated patients[4]. As second line therapy, the cumulative incidence of pleural effusion by 7 years was 28% for patients receiving 100 mg

daily on the CA180-034/dose-optimization study of dasatinib[3]. Retrospective studies of lower dasatinib dosing (50 mg and 70 mg) have supported efficacy and improved tolerance[51-53].

Prospective data supporting the initiation of 50 mg daily in newly diagnosed predominantly low and intermediate-risk (Sokal score) CP patients is provided by a US single arm study of 81 patients[54-56]. Median age was 47 years (range, 19–84 years). At 12 months the cumulative incidence of CCyR was 94%, MMR was 79%, MR4 was 52% and MR4.5 was 43% and at 60 months was 98%, 95%, 83%, and 82%, respectively[56]. Given the absence of randomized data for 100 mg vs 50 mg daily, propensity score analysis was used to compare low dose dasatinib-treated patients (N=77) to a historical cohort receiving 100 mg daily (N=77)[57]. No statistically significant differences in molecular responses, event-free survival or overall survival were observed and fewer TEAEs were observed in the 50 mg group. More patients receiving standard dose vs lower dose dasatinib interrupted treatment within the first 12 months (40 (52%) vs 5 (7%), respectively) and more patients discontinued therapy (10% vs 3%, respectively). Pleural effusions of any grade were seen in 21% vs 5% of patients treated with 100 mg vs 50 mg, respectively ($p = .02$).

Data supporting an even lower starting dose in older Japanese patients were reported in a prospective single-arm, multicenter study, DAVLEC[58]. Fifty-two newly diagnosed CP CML patients enrolled with a median age of 77.5 years. Dasatinib was started at 20 mg daily and dose escalation was permitted at 3, 6, and 9 months. MMR was achieved at 12 months in 60% (31/52) of evaluable patients and 44% (23) of patients continuing 20 mg daily. MR4 and MR4.5 were achieved in 27% and 14%, respectively. Whether this very low dose approach is as effective in patients of other ethnic/racial backgrounds remains unknown and further studies are needed. Alternative dosing strategies such as intermittent TKI dosing are also feasible and do not appear to compromise efficacy[59, 60]. Lastly, dose optimization using a therapeutic drug monitoring (TDM) approach is an appealing patient-centered approach to maximize efficacy and

minimize TEAEs, however such approaches are not currently clinically available at most centers[61].

Nilotinib and bosutinib

For other 2G TKIs, the risk for specific TEAEs can be mitigated by using lower doses. Nilotinib use is associated with an increased risk for cardiovascular, cerebrovascular, and peripheral arterial events, termed arterial occlusive events (AOEs) and risk is associated with the dose used. At 5- and 10-years follow-up of the first-line randomized phase 3 ENESTnd study AOEs were reported in 7.5% and 16.5% vs 13.4% and 23.5% vs 2.1% and 3.6% of patients receiving nilotinib 300 mg twice daily, nilotinib 400 mg twice daily, or imatinib 400 mg daily, respectively[5, 30]. The ENESTswift trial provides support for a lower dosing approach for nilotinib 2nd line at 300 mg twice daily, vs approved dosing of 400 mg twice daily, for intolerant, but not resistant CP CML patients[62]. The NILO-RED observational study demonstrated the feasibility and safety of nilotinib dose reduction to daily dosing[63]. Among 81 patients in MMR, MR4, or MR 4.5 nilotinib was reduced to 450 mg once daily (86.6%), 400 mg daily (10.4%) or 300 mg daily (3%) and only 2 patients lost MMR on reduced dose. Although unknown, it is possible that additional nilotinib dose reduction could further limit AOEs.

Bosutinib dosing at 400 mg daily or higher is associated with high rates of nausea, diarrhea, and increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT)[22]. A comprehensive retrospective review of a phase 1/2 study of bosutinib in later lines, reported the impact of bosutinib dose reduction in 2nd line (CP2L) or 3rd line (CP3L)[64]. Dose reductions were associated with improvements in diarrhea (33% 400 mg, 54% 300 mg), nausea (26% 400 mg, 29% 300 mg), and vomiting (9% 400 mg, 23% 300 mg). Among patients with CCyR or MMR prior to bosutinib dose reduction, only 2% of CP2L and no CP3L patients lost this response. In the first-line randomized phase 3 BFORE study comparing bosutinib to imatinib, after bosutinib dose reduction to 300 mg daily, 45.1% achieved MMR and 17.1% maintained

MMR for more than 6 months[7, 32, 65]. TEAEs including diarrhea, thrombocytopenia, nausea, vomiting, and anemia were reported to decrease by > 10%. Based on these observations, an incremental dose increase approach is recommended by expert panels[66]. Typically, bosutinib is initiated at 200-300 mg daily and the dose is escalated based on molecular response. The safety of this approach was supported by several studies. In the phase 2 GIMEMA BEST study, 63 CP CML patients initiated bosutinib at 200 mg daily as 2nd line therapy and escalated at 2-week intervals to 300 or 400 mg daily[67, 68]. Diarrhea and nausea were reported to be lower with this approach. Notably, most patients remained on low dose therapy with 73% and 6% remaining on 300 mg and 200 mg daily, respectively. At 12 months the MMR rate was 59%. The probability of achieving or maintaining MMR was 78%, MR4 was 54%, and MR4.5 was 46% by 36 months. The BODO study, which also examined an incremental bosutinib dose increase strategy, also reported good efficacy with 79% of patients achieving MMR[69].

Although dose reduction is an effective strategy to reduce TEAEs, there are several toxicities for which a change in therapy is the preferred approach (Table 2). These TEAEs include AOEs, recurrent pleural effusions (dasatinib), pulmonary hypertension (dasatinib), severe hypertension (ponatinib, asciminib) not responsive to antihypertensive therapies, enterocolitis, neurotoxicity, or other immune-mediated adverse events (e.g., pericarditis, myocarditis, nephritis)[70, 71].

Case 2 outcome:

The patient started dasatinib 50 mg daily and *BCR::ABL1* transcripts declined to 1.5% IS after 3 months of therapy. MMR (0.04% IS) and MR4 (0.009% IS) were achieved at 9 and 12 months, respectively. The first treatment months were characterized by fatigue and grade 1 thrombocytopenia with platelets ranging from 111-135 x10^{9}/L. The patient also complained of headaches once per month, but no diarrhea or nausea. Fatigue improved substantially after 4

months of therapy. Platelet counts remained in a similar range and dasatinib 50 mg daily was continued.

Case 3. The patient is a 52-year-old female diagnosed with CP CML with high-risk ELTS score. Complete blood count at presentation showed a white blood cell count of 345 $x10^9$/L, hemoglobin of 8.3 g/dL, platelet count of 125 $x10^9$/L, and 2% circulating blasts; the spleen was palpable at 10 cm below the costal margin. Bone marrow aspirate was consistent with CP; 3% blasts were detected by flow cytometry; and grade 2 reticulin fibrosis was reported. Conventional cytogenetics demonstrated t(9;22)(q34;q11.2) in all 20 cells examined; no additional cytogenetic abnormalities were detected. Dasatinib 100 mg daily was started but the patient developed severe thrombocytopenia (platelets 21 $x10^9$/L) with persistent moderate anemia (hemoglobin 8.1 g/dl) and mild neutropenia (ANC 1.3 $x10^9$/L). Dasatinib was held for 4 weeks and restarted at a reduced dose of 50 mg daily once platelets recovered to 75 $x10^9$/L; 4 weeks later platelets had decreased to 18 $x10^9$/L and dasatinib was held again. A bone marrow exam 6 months after diagnosis showed CP CML with no evidence of cytogenetic or molecular response, but no clonal cytogenetic evolution. Sequencing by NGS revealed a T315I mutation. Ponatinib was started at 15 mg daily due to severe thrombocytopenia and the patient was referred to the local academic center for assistance with management.

Strategies for the management of severe hematologic toxicity

Hematologic toxicities are common after therapy initiation for all approved TKIs, and rates are substantially higher in patients with accelerated or blast phase[72]. The incidence of all grade cytopenias has ranged from 30-90% across studies of CP CML; grade 3/4 toxicity is more uncommon and has been reported in 10-30% of newly diagnosed CP CML patients on therapy(Table 1)[18-23]. It is difficult to compare risk for anemia, neutropenia, or thrombocytopenia

between individual drugs although 2 larger meta-analyses focused mainly on CP CML patients have attempted to do so[73, 74]. Both studies identified more frequent cytopenias with dasatinib vs other TKIs, either all grade[74] or grade 3/4[73]. Increased rates of cytopenias were also observed with higher drug doses.

The mechanisms of severe hematologic toxicity while on TKI therapy have not been fully elucidated. Although targeting of PDGFRA and cKIT by imatinib, for example, may directly suppress normal hematopoiesis, interactions between CML cells, the bone marrow microenvironment, and normal hematopoietic cells are also salient[75-77]. Clinically, severe cytopenias are more frequently observed in the setting of a higher burden of CML. Earlier pre-clinical studies demonstrated that *BCR::ABL1* positive stem/progenitor cells not only outcompete normal hematopoietic cells but also create a suppressive environment for normal hematopoiesis through the secretion of specific cytokines that favor expansion of myeloid cells over other lineages and may even create an environment favoring apoptosis of normal hematopoietic stem/progenitor cells vs *BCR::ABL1* positive cells[78, 79]. Anemia and thrombocytopenia, as seen in this patient, at presentation may also be a risk factor for more severe cytopenias on treatment[80]. Factors associated with myelosuppression include bone marrow fibrosis and the appearance of Ph negative clonal evolution on therapy, as has been described for trisomy 8[81]. Age-related clonal hematopoiesis with somatic mutations in *TET2* or *DNMT3A* may also play a role. For isolated grade 1 or 2 hematologic toxicity, therapy may be continued with close monitoring. Management for patients with grade 3/4 hematologic toxicity is problematic (Table 3). Prescribing information recommends that therapy be held when ANC is $<1.0 \times 10^9$/L or platelets are $<50 \times 10^9$/L[18-23]. Therapy is resumed once ANC or platelets are above these thresholds again.

Early studies supported poorer cytogenetic response rates for patients receiving imatinib and requiring dose reductions for myelosuppression and/or grade 3/4 anemia[82, 83]. However, a

retrospective review of dose reductions and interruptions of 2G TKI therapies reported no impact on response rate, perhaps because of the increased potency of 2G TKI and, as discussed earlier, the efficacy of TKIs at lower than standard recommended doses[84]. However, failure-free survival was worse for patients unable to continue therapy. For the rare group of patients with *BCR::ABL1* transcripts persistently > 10%, repeated therapy holds for recurrent cytopenias may contribute to limited molecular response and poorer outcomes. The pattern may recur after switching to another therapy[74]. Recurrent cytopenias may also be a sign of disease progression and a bone marrow exam is indicated in this setting. For the rare patients with recurrent severe cytopenias who cannot receive consistent TKI therapy, NCCN and ELN suggest consideration of hematopoietic cell transplantation (HCT)[15, 16, 85]. For patients who are not eligible for HCT, a recent study highlighted that continuation of low dose therapy vs no therapy may limit the risk for disease progression[86].

Growth factors including GCSF for neutropenia, erythropoiesis stimulating agents (ESAs) for anemia and thrombopoietin receptor agonists (TPO-RA) for severe thrombocytopenia have been examined[83, 87-91]. A retrospective single center review of 608 CP patients treated with various imatinib doses (after interferon alpha in 50% of cases) reported a > 2 g/dL increase in hemoglobin in 80% of patients[83]. Thrombosis was seen in 8.5% of patients who received ESA vs 2.6% of those who did not (P = .0025)[83]. Early studies also supported the use of GCSF in patients with imatinib induced neutropenia[89]. Preclinical studies even suggested that GCSF may enhance imatinib efficacy in quiescent CML stem cells[92]. However, a subsequent small clinical study of 30 patients showed no benefit for the combination, but no significant risks with GCSF use were identified[93]. A recent phase 2 study reported on the use of the TPO-RA eltrombopag in CML patients with grade 3 or higher thrombocytopenia[90]. Eltrombopag was initiated at 50 mg/day, with dose escalation up to 300 mg daily allowed every 2 weeks. Fifteen patients with CML were enrolled. After a median of 18 months (range, 5-77 months), 12/15 patients with CML achieved complete platelet response. The median peak

platelet count among responders was 154 x10^9/L (range, 74-893 x10^9/L). Among CML patients 5 could re-escalate the TKI dose and 9 improved their response. One patient discontinued therapy due to toxicity (elevated transaminases). Non-occlusive deep venous thrombosis was reported in one patient receiving ponatinib with eltrombopag. Another study of 21 patients documented increases in platelet counts in 16 of 21 patients receiving eltrombopag with 4 patients having adverse events[91]. The improvements in thrombocytopenia observed in CML patients enrolled in these studies was likely also due, in part, to the ability to continue CML therapy, achieve molecular response, and thus potentially remove the myelosuppressive effects of CML on normal hematopoiesis. The impact of longer-term use of eltrombopag in CML is unknown, but some concern may be warranted given reports of clonal evolution in aplastic anemia[94].

Ponatinib dosing in CP CML

Ponatinib is approved for the treatment of T315I mutated CML and for resistant or intolerant CML in later lines (generally ≥ 3rd line)[23]. Ponatinib dose reduction is a crucial component of management due to the risk of AOEs with this drug. In the pivotal phase 2 PACE trial of heavily pre-treated and resistant CP CML patients OS at 5 years was 73% and progression-free survival was 53%[8]. AOEs were reported in 26%, but a retrospective re-examination of the data estimated AOEs at 17% based on independent cardiovascular adjudication[95]. Hypertension may occur soon after ponatinib initiation and contributes to AOE risk and aggressive management in this setting is important[23]. In response to these observations, the phase 2 OPTIC study examined the impact of response-based dosing on outcomes[9]. This study randomized 283 patients 1:1:1 to three dosing cohorts: 45 mg (A), 30 mg (B), and 15 mg (C) daily. There was a mandatory dose reduction to 15 mg daily upon achievement of *BCR::ABL1* ≤1% IS for cohorts A and B. By 12 months *BCR::ABL1* ≤1% IS was achieved in 51.6%, 35.5%, and 25.3% of patients in cohorts A, B, and C, respectively, and

responses were maintained after dose reduction to 15 mg for cohorts A and B in 73% and 79% of patients, respectively[9]. A dose dependent impact on AOEs was observed, with 9.6% of patients experiencing an AOE in cohort A vs 3.2% in cohort C. A recent analysis estimated that response-adjusted dosing reduced the risk for AOEs by ~60%[96]. For patients with T315I mutations by 12 months *BCR::ABL1* ≤1% IS was achieved by 60% of patients in cohort A vs 25% and 11% in cohorts B and C, respectively. Consequently, close monitoring and dose escalation based on molecular response should be considered if lower doses of ponatinib are initiated.

Case 3 outcome:

Ponatinib and high dose asciminib (200 mg twice daily) are the only approved targeted therapies for CML with a T315I mutation[19, 23]. *BCR::ABL1* transcripts prior to ponatinib initiation were 65% IS. Ponatinib dose was escalated to 30 mg daily after 3 weeks. Grade 3 thrombocytopenia recurred and ponatinib was held for 3 weeks. The role of HCT was discussed but was not possible due to a lack of social and caregiver support. Eltrombopag was started at 50 mg and escalated to 100 mg daily after two weeks. Ponatinib was restarted at 15 mg and dosed continuously. Over a period of 4 months platelets slowly increased from 22 $x10^9$/L to 82 $x10^9$/L and concurrently *BCR::ABL1* transcripts declined from 21% to 1.34%. Over the next 2 months eltrombopag was tapered off, *BCR::ABL1* declined to 0.27% IS and platelets remained between 100-120 $x10^9$/L. MMR was achieved 3 months later and maintained with 2 years follow-up on continued ponatinib 15 mg daily.

Allosteric inhibitors and hematologic and non-hematologic TEAEs:

Asciminib was approved by the FDA in 2021 for patients ≥3rd line use based on the results of the phase 3 randomized ASCEMBL study which compared asciminib vs bosutinib[10, 19]. Asciminib

was approved at a higher dose of 200 mg twice daily for patients with T315I mutations based on the results of the phase 1 study[97]. Long-term follow-up, including emerging HRQOL data, from these studies demonstrate excellent tolerability, although rates of hematologic AEs are similar to other TKIs[10, 98, 99]. Front-line approval of asciminib is based on the phase 3 ASC4FIRST study which randomized patients to asciminib vs imatinib or 2G TKI. Superior MMR rates at 48 weeks and 96 weeks were seen in patients receiving asciminib vs imatinib and vs all investigator selected TKIs (includes patients receiving imatinib or 2G TKIs)[11, 100]. The tolerability asciminib is highlighted by the lower rates of grade ≥3 TEAEs reported in 38% vs 44.4% vs 54.9% of asciminib, imatinib or 2G TKI treated patients, respectively. At week 48 fewer patients discontinued therapy with asciminib due to TEAEs (4.5% vs 11.1% vs 9.8%, respectively) and fewer patients required dose adjustments or treatment interruptions (30% vs 39.4% vs 52.9%, respectively). Relative to imatinib treated patients, asciminib treated patients had lower rates of diarrhea, nausea, muscle spasms, periorbital/face edema and relative to 2G TKI treated patients, asciminib treated patients had lower rates of diarrhea, nausea, headaches, rash, and elevations of AST, ALT, and lipase. Pleural effusion is rare with asciminib, and the risk for AOEs appears low based on currently available data[10, 98]. Other allosteric inhibitors are under evaluation in clinical trials including TERN-701 and TGRX-678. These drugs represent an important advancement in limiting intolerances for CML patients on therapy.

For patients receiving imatinib or 2G TKIs, doses lower than recommended by prescribing information are a reasonable first-step strategy for management of TEAEs. Recent reports have highlighted that for some patients serial intolerances on subsequent TKIs may occur[101]. Whether this observation is true for asciminib is unclear. For patients struggling with TEAEs and with slow molecular responses, asciminib is a good alternative choice. These observations are particularly relevant early in the treatment course when responses associated

with OS are still being achieved. For patients with significant side effects on asciminib, there are limited data regarding outcomes on doses lower than the recommended starting dose.

Conclusion

Although therapy discontinuation is the goal of many patients and can lead to resolution of many TEAEs and improvements in HRQOL, not all patients are able to stop and ~50% need to restart therapy due to molecular recurrence[102-104]. Consequently, strategies to limit TEAEs without compromising response are crucial. Asciminib, given its efficacy and tolerability, is an important addition to the treatment arsenal. With the availability of generics, the cost of some TKIs continues to decline steeply, which can reduce health care costs and help limit patient anxieties associated with high-cost drugs. New allosteric inhibitors are under evaluation in clinical trials and the future of CML may include these drugs as well. Moreover, appropriate dose adjustment of imatinib, 2G TKI and other 3G TKI therapies to improve tolerance while maintaining efficacy remains a crucial part of CP CML management (Figure 1). The importance of dose selection is highlighted by ongoing clinical trials of novel CML therapies, which are examining more than one dose in expansion cohorts to identify more comprehensively the best dose that balances efficacy with tolerability. Nonetheless, caution starting lower doses is warranted in patients with higher risk CP CML with high clinical risk scores (e.g., ELTS score) or higher risk genetic features such as *ASXL1* mutations, which are associated with inferior molecular response and the acquisition of mutations in *BCR::ABL1*[45-48]. Continued awareness of therapy intolerances and toxicities experienced by patients coupled with shared decision making between health care teams and patients can ensure optimal outcomes, improved HRQOL, and long-term safety.

REFERENCES

1. Bower H, Bjorkholm M, Dickman PW, Hoglund M, Lambert PC, Andersson TM. Life Expectancy of Patients With Chronic Myeloid Leukemia Approaches the Life Expectancy of the General Population. J Clin Oncol. 2016;34(24):2851-2857.
2. Hochhaus A, Larson RA, Guilhot F, et al. Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia. N Engl J Med. 2017;376(10):917-927.
3. Shah NP, Rousselot P, Schiffer C, et al. Dasatinib in imatinib-resistant or -intolerant chronic-phase, chronic myeloid leukemia patients: 7-year follow-up of study CA180-034. Am J Hematol. 2016;91(9):869-874.
4. Cortes JE, Saglio G, Kantarjian HM, et al. Final 5-Year Study Results of DASISION: The Dasatinib Versus Imatinib Study in Treatment-Naive Chronic Myeloid Leukemia Patients Trial. J Clin Oncol. 2016;34(20):2333-2340.
5. Kantarjian HM, Hughes TP, Larson RA, et al. Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis. Leukemia. 2021;35(2):440-453.
6. Cortes JE, Kantarjian HM, Brummendorf TH, et al. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. Blood. 2011;118(17):4567-4576.
7. Brummendorf TH, Cortes JE, Milojkovic D, et al. Bosutinib versus imatinib for newly diagnosed chronic phase chronic myeloid leukemia: final results from the BFORE trial. Leukemia. 2022;36(7):1825-1833.
8. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. Blood. 2018;132(4):393-404.
9. Cortes J, Apperley J, Lomaia E, et al. Ponatinib dose-ranging study in chronic-phase chronic myeloid leukemia: a randomized, open-label phase 2 clinical trial. Blood. 2021;138(21):2042-2050.
10. Hochhaus A, Rea D, Boquimpani C, et al. Asciminib vs bosutinib in chronic-phase chronic myeloid leukemia previously treated with at least two tyrosine kinase inhibitors: longer-term follow-up of ASCEMBL. Leukemia. 2023;37(3):617-626.
11. Hochhaus A, Wang J, Kim DW, et al. Asciminib in Newly Diagnosed Chronic Myeloid Leukemia. N Engl J Med. 2024;391(10):885-898.
12. Kwak JY, Kim SH, Oh SJ, et al. Phase III Clinical Trial (RERISE study) Results of Efficacy and Safety of Radotinib Compared with Imatinib in Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia. Clin Cancer Res. 2017;23(23):7180-7188.
13. Jabbour E, Oehler VG, Koller PB, et al. Olverembatinib After Failure of Tyrosine Kinase Inhibitors, Including Ponatinib or Asciminib: A Phase 1b Randomized Clinical Trial. JAMA Oncol. 2025;11(1):28-35.
14. Lipton JH, Brummendorf TH, Gambacorti-Passerini C, Garcia-Gutierrez V, Deininger MW, Cortes JE. Long-term safety review of tyrosine kinase inhibitors in chronic myeloid leukemia - What to look for when treatment-free remission is not an option. Blood Rev. 2022;56:100968.
15. Apperley JF, Milojkovic D, Cross NCP, et al. 2025 European LeukemiaNet recommendations for the management of chronic myeloid leukemia. Leukemia. 2025;39(8):1797-1813.
16. National Comprehensive Cancer Network. Chronic Myeloid Leukemia (Version 1.2026). https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf. Accessed January 20, 2026.
17. Lang F, Pemberton-Whiteley Z, Clements J, et al. Improving chronic myeloid leukemia management and quality of life: patient and physician survey on unmet needs from the CML SUN survey. Haematologica. 2026;111(2):597-608.

18. Novartis. TASIGNA (nilotinib) [package insert]. U.S. Food and Drug Administration website.https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/022068s041lbl.pdf. Revised 2/8/2024. Accessed 7/15/2025.
19. Novartis Pharmaceuticals Corporations. Scemblix (asciminib) [package insert]. U.S. Food and Drug Administration website. accessdata.fda.gov/drugsatfda_docs/label/2021/215358s000Orig2lbl.pdf. Revised October 2024. Accessed 7/15/2025.
20. Novartis Pharmaceutical Corporation. Gleevec (imatinib mesylate) [package insert]. U.S. Food and Drug Administration website. www.accessdata.fda.gov/drugsatfda_docs/label/[Year]/[File name].pdf. Revised [Date of revision]. Accessed 7/15/2025.
21. Bristol Myers Squibb. SPRYCEL (dasatinib) [package insert]. U.S. Food and Drug Administration website.https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/021986s027lbl.pdf. Revised 2/8/2023. Accessed 7/15/2025.
22. PF PRISM CV. BOSULIF (bosutinib) [package insert]. U.S. Food and Drug Administration website.https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/203341s024lbl.pdf. Revised 4/20/2023. Accessed 7/15/2025.
23. Takeda Pharmaceuticals USA. ICLUSIG (ponatinib) [package insert]. U.S. Food and Drug Administration website.https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/203469s035lbl.pdf. Revised 2/15/2022. Accessed 7/15/2025. [cited; Available from:
24. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2003;348(11):994-1004.
25. Hochhaus A, O'Brien SG, Guilhot F, et al. Six-year follow-up of patients receiving imatinib for the first-line treatment of chronic myeloid leukemia. Leukemia. 2009;23(6):1054-1061.
26. Shah NP, Kim DW, Kantarjian H, et al. Potent, transient inhibition of BCR-ABL with dasatinib 100 mg daily achieves rapid and durable cytogenetic responses and high transformation-free survival rates in chronic phase chronic myeloid leukemia patients with resistance, suboptimal response or intolerance to imatinib. Haematologica. 2010;95(2):232-240.
27. Kantarjian HM, Shah NP, Cortes JE, et al. Dasatinib or imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: 2-year follow-up from a randomized phase 3 trial (DASISION). Blood. 2012;119(5):1123-1129.
28. Giles FJ, Abruzzese E, Rosti G, et al. Nilotinib is active in chronic and accelerated phase chronic myeloid leukemia following failure of imatinib and dasatinib therapy. Leukemia. 2010;24(7):1299-1301.
29. Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med. 2010;362(24):2251-2259.
30. Hochhaus A, Saglio G, Hughes TP, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. Leukemia. 2016;30(5):1044-1054.
31. Brummendorf TH, Cortes JE, de Souza CA, et al. Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukaemia: results from the 24-month follow-up of the BELA trial. Br J Haematol. 2015;168(1):69-81.
32. Cortes JE, Gambacorti-Passerini C, Deininger MW, et al. Bosutinib Versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia: Results From the Randomized BFORE Trial. J Clin Oncol. 2018;36(3):231-237.

33. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med. 2013;369(19):1783-1796.
34. Pfirrmann M, Clark RE, Prejzner W, et al. The EUTOS long-term survival (ELTS) score is superior to the Sokal score for predicting survival in chronic myeloid leukemia. Leukemia. 2020;34(8):2138-2149.
35. Li Z, Zhang X, Zhao Y, et al. Imatinib dose reduction after major molecular response in chronic-phase chronic myeloid leukemia. Cancer. 2025;131(1):e35565.
36. Carella AM, Lerma E. Durable responses in chronic myeloid leukemia patients maintained with lower doses of imatinib mesylate after achieving molecular remission. Ann Hematol. 2007;86(10):749-752.
37. Park SJ, Choi IK, Seo HY, et al. Reduced dose of imatinib for patients with chronic myeloid leukemia and low body surface area. Acta Haematol. 2007;118(4):219-221.
38. Clark RE, Polydoros F, Apperley JF, et al. De-escalation of tyrosine kinase inhibitor therapy before complete treatment discontinuation in patients with chronic myeloid leukaemia (DESTINY): a non-randomised, phase 2 trial. Lancet Haematol. 2019;6(7):e375-e383.
39. Clark RE, Polydoros F, Apperley JF, et al. De-escalation of tyrosine kinase inhibitor dose in patients with chronic myeloid leukaemia with stable major molecular response (DESTINY): an interim analysis of a non-randomised, phase 2 trial. Lancet Haematol. 2017;4(7):e310-e316.
40. Claudiani S, Apperley JF, Szydlo R, et al. TKI dose reduction can effectively maintain major molecular remission in patients with chronic myeloid leukaemia. Br J Haematol. 2021;193(2):346-355.
41. Ohnishi K, Nakaseko C, Takeuchi J, et al. Long-term outcome following imatinib therapy for chronic myelogenous leukemia, with assessment of dosage and blood levels: the JALSG CML202 study. Cancer Sci. 2012;103(6):1071-1078.
42. Bidikian A, Jabbour E, Issa GC, Short NJ, Sasaki K, Kantarjian H. Chronic myeloid leukemia without major molecular response after 2 years of treatment with tyrosine kinase inhibitor. Am J Hematol. 2023;98(4):639-644.
43. Cross NCP, Ernst T, Branford S, et al. European LeukemiaNet laboratory recommendations for the diagnosis and management of chronic myeloid leukemia. Leukemia. 2023;37(11):2150-2167.
44. Fernandes A, Shanmuganathan N, Branford S. Genomic Mechanisms Influencing Outcome in Chronic Myeloid Leukemia. Cancers (Basel). 2022;14(3):620.
45. Shanmuganathan N, Wadham C, Shahrin N, et al. Impact of additional genetic abnormalities at diagnosis of chronic myeloid leukemia for first-line imatinib-treated patients receiving proactive treatment intervention. Haematologica. 2023;108(9):2380-2395.
46. Bidikian A, Kantarjian H, Jabbour E, et al. Prognostic impact of ASXL1 mutations in chronic phase chronic myeloid leukemia. Blood Cancer J. 2022;12(10):144.
47. Schonfeld L, Rinke J, Hinze A, et al. ASXL1 mutations predict inferior molecular response to nilotinib treatment in chronic myeloid leukemia. Leukemia. 2022;36(9):2242-2249.
48. Shanmuganathan N, Yeung DT, Wadham C, et al. Impact of ASXL1 at diagnosis in patients with CML receiving frontline potent TKIs: high risk of kinase domain mutations. Blood. 2025;146(23):2821-2832.
49. Hughes TP, Laneuville P, Rousselot P, et al. Incidence, outcomes, and risk factors of pleural effusion in patients receiving dasatinib therapy for Philadelphia chromosome-positive leukemia. Haematologica. 2019;104(1):93-101.
50. Shin DY, Park S, Jang E, et al. Early dose reduction of dasatinib does not compromise clinical outcomes in patients with chronic myeloid leukemia: A comparative analysis of two prospective trials. Leuk Res. 2024;143:107542.
51. Latagliata R, Stagno F, Annunziata M, et al. Frontline Dasatinib Treatment in a "Real-Life" Cohort of Patients Older than 65 Years with Chronic Myeloid Leukemia. Neoplasia. 2016;18(9):536-540.

52. Chuah CT, Nakamae H, Shen ZX, Bradley-Garelik MB, Kim DW. Efficacy and safety of dasatinib versus imatinib in the East Asian subpopulation of the DASISION trial of newly diagnosed chronic myeloid leukemia in chronic phase. Leuk Lymphoma. 2014;55(9):2093-2100.
53. Shin H, Ha JE, Zang DY, et al. Appropriate Starting Dose of Dasatinib Based on Analyses of Dose-Limiting Toxicities and Molecular Responses in Asian Patients With Chronic Myeloid Leukemia. Clin Lymphoma Myeloma Leuk. 2021;21(6):e521-e529.
54. Naqvi K, Jabbour E, Skinner J, et al. Long-term follow-up of lower dose dasatinib (50 mg daily) as frontline therapy in newly diagnosed chronic-phase chronic myeloid leukemia. Cancer. 2020;126(1):67-75.
55. Naqvi K, Jabbour E, Skinner J, et al. Early results of lower dose dasatinib (50 mg daily) as frontline therapy for newly diagnosed chronic-phase chronic myeloid leukemia. Cancer. 2018;124(13):2740-2747.
56. Gener-Ricos G, Haddad FG, Sasaki K, et al. Low-Dose Dasatinib (50 mg Daily) Frontline Therapy in Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia: 5-Year Follow-Up Results. Clin Lymphoma Myeloma Leuk. 2023;23(10):742-748.
57. Jabbour E, Sasaki K, Haddad FG, et al. Low-dose dasatinib 50 mg/day versus standard-dose dasatinib 100 mg/day as frontline therapy in chronic myeloid leukemia in chronic phase: A propensity score analysis. Am J Hematol. 2022;97(11):1413-1418.
58. Murai K, Ureshino H, Kumagai T, et al. Low-dose dasatinib in older patients with chronic myeloid leukaemia in chronic phase (DAVLEC): a single-arm, multicentre, phase 2 trial. Lancet Haematol. 2021;8(12):e902-e911.
59. Malagola M, Iurlo A, Abruzzese E, et al. Molecular response and quality of life in chronic myeloid leukemia patients treated with intermittent TKIs: First interim analysis of OPTkIMA study. Cancer Med. 2021;10(5):1726-1737.
60. Malagola M, Iurlo A, Bucelli C, et al. The Italian Multicentric Randomized OPTkIMA Trial on Fixed vs Progressive Intermittent TKI Therapy in CML Elderly Patients: 3-Years of Molecular Response and Quality of Life Monitoring After Completing the Treatment Plan. Clin Lymphoma Myeloma Leuk. 2024;24(5):323-331.
61. Rousselot P, Mollica L, Guilhot J, et al. Dasatinib dose optimisation based on therapeutic drug monitoring reduces pleural effusion rates in chronic myeloid leukaemia patients. Br J Haematol. 2021;194(2):393-402.
62. Hiwase D, Tan P, D'Rozario J, et al. Efficacy and safety of nilotinib 300 mg twice daily in patients with chronic myeloid leukemia in chronic phase who are intolerant to prior tyrosine kinase inhibitors: Results from the Phase IIIb ENESTswift study. Leuk Res. 2018;67:109-115.
63. Rea D, Cayuela JM, Duluoq S, Etienne G. Molecular Responses after Switching from a Standard-Dose Twice-Daily Nilotinib Regimen to a Reduced-Dose Once-Daily Schedule in Patients with Chronic Myeloid Leukemia: A Real Life Observational Study (NILO-RED). Blood. 2017;130(Supplement 1):318.
64. Kota V, Brummendorf TH, Gambacorti-Passerini C, et al. Efficacy and safety following bosutinib dose reduction in patients with Philadelphia chromosome-positive leukemias. Leuk Res. 2021;111:106690.
65. Deininger MW, Brümmendorf TH, Milojkovic D, et al. Outcomes before and after dose reduction in patients with newly diagnosed chronic myeloid leukemia receiving bosutinib or imatinib. J Clin Oncol. 2021;39(15_suppl):7039.
66. Cortes JE, Apperley JF, DeAngelo DJ, et al. Management of adverse events associated with bosutinib treatment of chronic-phase chronic myeloid leukemia: expert panel review. J Hematol Oncol. 2018;11(1):143.
67. Castagnetti F, Bocchia M, Abruzzese E, et al. P698: bosutinib dose optimization in the second-line treatment of elderly cml patients: extended 3-year follow-up and final results of the best study. Hemasphere. 2022;6:593-594.

68. Castagnetti F, Gugliotta G, Bocchia M, et al. Dose Optimization in Elderly CML Patients Treated with Bosutinib after Intolerance or Failure of First-Line Tyrosine Kinase Inhibitors. Blood. 2019;134(Supplement_1):496.
69. Isfort S, Manz K, Teichmann LL, et al. Step-in dosing of bosutinib in pts with chronic phase chronic myeloid leukemia (CML) after second-generation tyrosine kinase inhibitor (TKI) therapy: results of the Bosutinib Dose Optimization (BODO) Study. Ann Hematol. 2023;102(10):2741-2752.
70. Haddad FG, Kantarjian H. Navigating the Management of Chronic Phase CML in the Era of Generic BCR::ABL1 Tyrosine Kinase Inhibitors. J Natl Compr Canc Netw. 2024;22(1):e237116.
71. Oehler VG, Huang IJ, Siu C, et al. Dose Modifications in the Management of Chronic Phase Chronic Myeloid Leukemia: Who, What, and When. J Natl Compr Canc Netw. 2024;22(9):e247044.
72. Talpaz M, Shah NP, Kantarjian H, et al. Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. N Engl J Med. 2006;354(24):2531-2541.
73. Fachi MM, Tonin FS, Leonart LP, Rotta I, Fernandez-Llimos F, Pontarolo R. Haematological adverse events associated with tyrosine kinase inhibitors in chronic myeloid leukaemia: A network meta-analysis. Br J Clin Pharmacol. 2019;85(10):2280-2291.
74. Kronick O, Chen X, Mehra N, et al. Hematological Adverse Events with Tyrosine Kinase Inhibitors for Chronic Myeloid Leukemia: A Systematic Review with Meta-Analysis. Cancers (Basel). 2023;15(17):4354.
75. Deininger M, Buchdunger E, Druker BJ. The development of imatinib as a therapeutic agent for chronic myeloid leukemia. Blood. 2005;105(7):2640-2653.
76. Holyoake TL, Jiang X, Drummond MW, Eaves AC, Eaves CJ. Elucidating critical mechanisms of deregulated stem cell turnover in the chronic phase of chronic myeloid leukemia. Leukemia. 2002;16(4):549-558.
77. Patterson SD, Copland M. The Bone Marrow Immune Microenvironment in CML: Treatment Responses, Treatment-Free Remission, and Therapeutic Vulnerabilities. Curr Hematol Malig Rep. 2023;18(2):19-32.
78. Lin H, Monaco G, Sun T, et al. Bcr-Abl-mediated suppression of normal hematopoiesis in leukemia. Oncogene. 2005;24(20):3246-3256.
79. Zhang B, Ho YW, Huang Q, et al. Altered microenvironmental regulation of leukemic and normal stem cells in chronic myelogenous leukemia. Cancer Cell. 2012;21(4):577-592.
80. McLigeyo A, Rajab J, Oyiro P, et al. Baseline blood count levels increase odds of cytopenia among CML patients in Kenya: a case control study. BMC Cancer. 2022;22(1):128.
81. Feldman E, Najfeld V, Schuster M, Roboz G, Chadburn A, Silver RT. The emergence of Ph-, trisomy -8+ cells in patients with chronic myeloid leukemia treated with imatinib mesylate. Exp Hematol. 2003;31(8):702-707.
82. Sneed TB, Kantarjian HM, Talpaz M, et al. The significance of myelosuppression during therapy with imatinib mesylate in patients with chronic myelogenous leukemia in chronic phase. Cancer. 2004;100(1):116-121.
83. Santos FP, Alvarado Y, Kantarjian H, et al. Long-term prognostic impact of the use of erythropoietic-stimulating agents in patients with chronic myeloid leukemia in chronic phase treated with imatinib. Cancer. 2011;117(5):982-991.
84. Santos FP, Kantarjian H, Fava C, et al. Clinical impact of dose reductions and interruptions of second-generation tyrosine kinase inhibitors in patients with chronic myeloid leukaemia. Br J Haematol. 2010;150(3):303-312.
85. Shah NP, Bhatia R, Altman JK, et al. Chronic Myeloid Leukemia, Version 2.2024, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2024;22(1):43-69.
86. Vrablova L, Klamova H, Skoumalova I, et al. Treatment with low-dose tyrosine kinase inhibitors due to significant haematologic toxicity in patients with CML with prolonged treatment

failure prevents haematologic progression. Hematol Transfus Cell Ther. 2024;46 Suppl 6(Suppl 6):S171-S181.
87. Cesini L, Frieri C, Barate C, et al. Erythropoietin treatment in chronic phase chronic myeloid leukemia patients treated with frontline imatinib who developed late anemia. Eur J Haematol. 2020;105(3):286-291.
88. Cortes J, O'Brien S, Quintas A, et al. Erythropoietin is effective in improving the anemia induced by imatinib mesylate therapy in patients with chronic myeloid leukemia in chronic phase. Cancer. 2004;100(11):2396-2402.
89. Quintas-Cardama A, Kantarjian H, O'Brien S, et al. Granulocyte-colony-stimulating factor (filgrastim) may overcome imatinib-induced neutropenia in patients with chronic-phase chronic myelogenous leukemia. Cancer. 2004;100(12):2592-2597.
90. Shoukier M, Borthakur G, Jabbour E, et al. The effect of eltrombopag in managing thrombocytopenia associated with tyrosine kinase therapy in patients with chronic myeloid leukemia and myelofibrosis. Haematologica. 2021;106(11):2853-2858.
91. Liu L, Chen Y, Liang Y, et al. The efficacy and safety of eltrombopag in treating TKI-induced thrombocytopenia in patients with chronic myeloid leukemia. Hematology. 2023;28(1):2248434.
92. Jorgensen HG, Copland M, Allan EK, et al. Intermittent exposure of primitive quiescent chronic myeloid leukemia cells to granulocyte-colony stimulating factor in vitro promotes their elimination by imatinib mesylate. Clin Cancer Res. 2006;12(2):626-633.
93. Gallipoli P, Stobo J, Heaney N, et al. Safety and efficacy of pulsed imatinib with or without G-CSF versus continuous imatinib in chronic phase chronic myeloid leukaemia patients at 5 years follow-up. Br J Haematol. 2013;163(5):674-676.
94. Patel BA, Groarke EM, Lotter J, et al. Long-term outcomes in patients with severe aplastic anemia treated with immunosuppression and eltrombopag: a phase 2 study. Blood. 2022;139(1):34-43.
95. Januzzi JL, Garasic JM, Kasner SE, et al. Retrospective analysis of arterial occlusive events in the PACE trial by an independent adjudication committee. J Hematol Oncol. 2022;15(1):1.
96. Jabbour E, Apperley J, Cortes J, et al. Dose modification dynamics of ponatinib in patients with chronic-phase chronic myeloid leukemia (CP-CML) from the PACE and OPTIC trials. Leukemia. 2024;38(3):475-481.
97. Cortes JE, Sasaki K, Kim DW, et al. Asciminib monotherapy in patients with chronic-phase chronic myeloid leukemia with the T315I mutation after >/=1 prior tyrosine kinase inhibitor: 2-year follow-up results. Leukemia. 2024;38(7):1522-1533.
98. Hochhaus A, Kim DW, Cortes JE, et al. Asciminib monotherapy in patients with chronic myeloid leukemia in chronic phase without BCR::ABL1(T315I) treated with at least 2 prior TKIs: Phase 1 final results. Leukemia. 2025;39(5):1114-1123.
99. Rea D, Boquimpani C, Mauro MJ, et al. Health-related quality of life of patients with resistant/intolerant chronic phase chronic myeloid leukemia treated with asciminib or bosutinib in the phase 3 ASCEMBL trial. Leukemia. 2023;37(5):1060-1067.
100. Cortes JE, Hughes TP, Wang J, et al. Asciminib Demonstrates Superior Efficacy and Safety in Newly Diagnosed Chronic Myeloid Leukemia in the ASC4FIRST Trial. Blood. 2025 Dec 15. doi: 10.1182/blood.2025029210. [Epub ahead of print]
101. Busque L, Harnois M, Delage R, et al. S159: Quebec CML research group analysis of treatment patterns in chronic myelogenous leukemia: switching is driven by intolerance and similar across tyrosine kinase inhibitors and lines of treatment. Hemasphere. 2022;6:60-61.
102. Atallah E, Schiffer CA, Radich JP, et al. Assessment of Outcomes After Stopping Tyrosine Kinase Inhibitors Among Patients With Chronic Myeloid Leukemia: A Nonrandomized Clinical Trial. JAMA Oncol. 2021;7(1):42-50.

103. Schoenbeck KL, Atallah E, Lin L, et al. Patient-Reported Functional Outcomes in Patients With Chronic Myeloid Leukemia After Stopping Tyrosine Kinase Inhibitors. J Natl Cancer Inst. 2022;114(1):160-164.
104. Flynn KE, Atallah E, Lin L, et al. Patient- and physician-reported pain after tyrosine kinase inhibitor discontinuation among patients with chronic myeloid leukemia. Haematologica. 2022;107(11):2641-2649.

Table 1. Incidence of Therapy-Associated TEAEs of Interest

Nonhematologic	TEAE Incidence (%)											
	Imatinib[a,b,c,d]		Dasatinib[e,f,g,h]		Nilotinib[i,j,k,l]		Bosutinib[m,n,o]		Ponatinib[p,q,r,s]		Asciminib[t,u,v]	
Gastrointestinal	All	G3/4	All	G3/4	All	G3/4	All	G3/4	All	G3/4	All	G3
Nausea	49.5	1.3	10	-	22	2	37	-	29	0.7	12	0.
Vomiting	22.5	2	5	-	15	<1	21	1	19	1.5	<10	-
Diarrhea	45.4	3.3	22	1	19	1	75	9	20	0.7	13	-
Constipation	11.4	0.7	1-10	-	20	<1	13	-	42	2.6	<10	-
Dyspepsia	18.9	0	1-10	-	10	-	13.4	0.7	-	-	-	-
Cardiovascular												
Congestive Cardiac Failure	0.1-1	-	2	<1	-	-	1-10	-	3.1	-	1.9	-
Hypertension	0.1-1	-	1-10	-	10	1	10	5	42	30	14	7
Arterial Occlusive Events[w]	3.6	-	5	-	24.8	-	7.5	-	14-31	6-17	5.1	-
Pulmonary Arterial Hypertension	0.01-0.1	-	5	1	U	-	1-10	-	-	-	-	-
QT Prolongation	-	-	<1	-	0.4-4.1	<1	1-10	U	-	-	0.9	-
Fluid Retention												
Superficial edema	59.9	1.5	14	-	9	<1	15	-	3.8-17	<3.7	<10	-
Pleural or Pericardial Effusion	<6.9	<1.3	28	3	2.2	0.7	6	0.7-4.4	9	-	2.1	-
Musculoskeletal Pain												
Muscle Cramps	49.2	2.2	5	-	12	-	-	-	14	-	-	-
Musculoskeletal Pain	47	5.4	14	-	15	<1	1-10	-	11	1.5	24-25	1.5-
Joint Pain/Arthralgia	31.4	2.5	7	-	22	<1	18	1	61	9	13	0.
Myalgia	24.1	1.5	7	-	19	<1	1-10	-	24	1.1	<25	-
Dermatology												
Rash	40.1	2.9	14	-	38	<1	40	2	75	9	18-19	0.
Dry Skin	6.7	0.5	1-10	-	12	-	-	-	42	3.3	-	-
Other												
Osteopenia/Osteoporosis	-	-	P	-	-	-	-	-	-	-	-	-
Headache	37	0.5	14	-	32	3	22	1	43	3.3	14-21	0.5-
Abdominal Pain	36.5	4.2	11	-	15-18	2	39	2	54	11	14	0.
Nasopharyngitis	30.5	-	-	-	27	-	13.4	0.4	12	-	<15	-
Hemorrhage	28.9	1.8	8	1	2.9	1.1	1-10	-	23	3	<10	-
Venous Thromboembolism	-	-	-	-	-	-	-	-	6	5.8	-	-
Fatigue	38.8	1.8	11	<1	23	1	33	1	44	3.7	18-20	0.6
Hematologic												
Anemia	44.6	3.1	90	10	38	3	22	4.5	35	14	24-37	2-2
Neutropenia	60.8	14.3	65	21	43	12	12.3	7.5	55	22	43-46	12-
Thrombocytopenia	56.6	7.8	70	19	48	10	35.8	14.2	65	31	46-48	12-
Biochemical												
AST or ALT Elevation	43.2	4.7	-	<1	47-72	1-4	25.7-33.6	10.4-20.9	35-41	3.6-6	21-26	0.6-
Total bilirubin elevation	-	0.9	-	1	59	4	6.3	-	13	0.9	12	-
Increased lipase	-	-	-	-	28	9	20.9	13.4	40	14	15-37	4.5-
Hyperglycemia	-	-	-	-	50	7	42	2.7	54	7	-	-
Decreased Phosphate	-	10	-	7	-	8	54	9	34	10	18	6
Increased Potassium	-	1	-	-	-	2	23	-	20	2.2	48	2.
Decreased Potassium	-	2	-	-	-	<1	24	-	-	-	11	-

TEAE information is extracted from prescribing information and clinical trial data that led to FDA approval front-line (including initial and long-term follow-up data, when available). Where reports vary, ranges are reported. TEAEs for nilotinib are based on reports of 300 mg twice daily dosing. We acknowledge that incidence rates vary between studies, including those for the same drugs in later-therapy lines.

Abbreviations: AOE, arterial occlusive event; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor, P, reported in pediatric patients; U, unknown frequency

a. O'Brien SG, et al. N Engl J Med. 2003;348(11):994-1004

b. Druker BJ et al. N Engl J Med. 2006 Dec 7;355(23):2408-17

c. Hochhaus A, et al. N Engl J Med. 2017;376(10):917-27

d. Imatinib. Prescribing information. Novartis Pharmaceuticals Corporation; 2024. Accessed August 1, 2025. Available at: https://www.novartis.com/us-en/sites/novartis_us/files/gleevec_tabs.pdf

e. Shah NP, et al. Haematologica. 2010;95(2):232-40

f. Kantarjian HM, et al. Blood. 2012;119(5):1123-9.

g. Cortes, JE et al. J Clin Oncol. 2016;34(20):2333-40.

h. Dasatinib tablets. Prescribing information. Bristol Myers Squibb; 2024. Accessed August 1, 2025. Available at: https://packageinserts.bms.com/pi/pi_sprycel.pdf

i. Based on nilotinib 300 mg twice daily cohort; Saglio G, et al. N Engl J Med. 2010;362(24):2251-9.

j. Based on nilotinib 300 mg twice daily cohort; Hochhaus A, et al. Leukemia. 2016;30(5):1044-54

k. Based on nilotinib 300 mg twice daily cohort; Kantarjian H, et al. Leukemia. 2021;35(2):440-53.

l. Nilotinib. Prescribing information. Novartis Pharmaceuticals Corporation; 2024. Accessed August 1, 2025. Available https://www.novartis.com/us-en/sites/novartis_us/files/tasigna.pdf

m. Cortes JE, et al. J Clin Oncol. 2018;36(3):231-7.

n. Brümmendorf TH, et al., Leukemia. 2022 Jul;36(7):1825-1833.

o. Bosutinib. Prescribing information. Pfizer; 2024. Accessed August 1, 2025. Available at: https://labeling.pfizer.com/showlabeling.aspx?id=884

p. Cortes JE, et al. N Engl J Med. 2013;369(19):1783-96

q. Cortes JE et al., Blood. 2018;132(4):393-404.

r. Cortes J, et al. Blood. 2021;138(21):2042-50.

s. Ponatinib. Prescribing information. Takeda; 2024. Accessed August 1, 2025. Available at: https://www.iclusig.com/sites/default/files/2023-02/iclusig-prescribing-information.pdf

t. Hochhaus A et al. N Engl J Med. 2024;391(10):885-898.

u. Hochhaus A et al. Leukemia. 2023;37(3):617-626.

v. Asciminib. Prescribing information. Novartis Pharmaceuticals Corporation; 2024. Accessed August 1, 2025. Availab https://www.novartis.com/us-en/sites/novartis_us/files/scemblix.pdf

w. Veltmaat L, Cortes JE, Blood. 2024;143(10):858-865.

Table 2. Recommended Management for Nonhematologic Therapy-Associated TEAEs of Interest

Nonhematologic	Clinical Intervention		TKI Therapy Modification (conditions not resolved despite optimal clinical intervention)[a,b]	Additional Comments[a,b]
	Non-Pharmacologic[a,b]	Pharmacologic[a,b]		
Gastrointestinal				
Nausea	• Diet modification +/- hydration • Refer to gastroenterologist and dietitian	• Antiemetic	• Dose reduction (with close monitoring) or switch TKI if persistent	• Diet modification: smaller, more frequent meals, take medication with food (except nilotinib [capsule formulation] and asciminib avoid spicy/fatty food • Hydration: oral hydration for lower grade toxicities but IV hydration may be indicated more severe cases • Acid reducer: Antacid > Histamine H2 Rece Antagonists (H2RA) > Proton pump inhibito (PPI), select based on drug-drug interaction
Vomiting				
Diarrhea		• Anti-diarrheal		
Constipation		• Laxative		
Dyspepsia		• Acid Reducer		
Cardiovascular				
Congestive Cardiac Failure	• Refer to cardiologist		• Dose reduction or switch TKI if persistent	
Hypertension	• Diet/lifestyle modification • Refer to cardiologist • Refer to vascular surgery for peripheral arterial disease	• Guideline-directed therapy optimization[c,d,e,f,g]	• Switch TKI for severe or persistent hypertension not responding to antihypertensive medications (more common with ponatinib and asciminib)	• Lifestyle modification: consider a low sodiu diet • Guideline-directed therapy optimization[c,d] • Select therapy with consideration of drug-d interactions
Arterial Occlusive Events			• Switch TKI whenever possible for the onset of new arterial and/or vascular adverse events (more common with nilotinib or ponatinib)	• Guideline-directed therapy optimization[c,e,f] • Select therapy with consideration of drug-d interactions
Pulmonary Arterial Hypertension	• Monitor for shortness of breath/fainting • Refer to cardiologist or pulmonary vascular specialist	• Diuretic +/- Corticosteroid +/- sildenafil	• Switch TKI (more common with dasatinib)	
QT Prolongation	• Monitor for hypokalemia/hypomagnesemia	• Minimize/avoid concurrent QT prolonging medications • Correct electrolytes if needed	• Switch TKI if persistent (more common with nilotinib)	
Fluid Retention				
Superficial Edema	• Monitor for weight gain, peripheral and periorbital edema, bloating	• Diuretic	• Dose reduction (with close monitoring) or switch TKI if persistent)	• Lifestyle modification: consider compressio stockings (lower extremity edema)
Pleural or Pericardial Effusion	• Monitor for shortness of breath, chest pain, or cough • Echocardiogram to assess left ventricular ejection fraction, elevation of pulmonary arterial systolic pressure and presence of pericardial effusion • Refer to pulmonologist for consideration of thoracentesis • Refer to cardiology for consideration of pericardiocentesis	• Diuretic +/- Corticosteroid	• Dose reduction or switch TKI for recurrence (more common with dasatinib)	
Musculoskeletal Pain				
Muscle Cramps	• Ensure adequate hydration, consider tonic water (muscle cramps) • Assess creatine kinase	• Electrolyte (potassium/calcium) supplementation	• Dose reduction (with close monitoring) or switch TKI if persistent	• Lifestyle modification: hydration, correct electrolyte abnormalities, and light exercis able
Musculoskeletal Pain				
Joint Pain/Arthralgia				
Myalgia				
Dermatology				
Rash	• Topical moisturizers, particularly after shower or bath • Consider referral to dermatologist	• Antihistamine +/- Corticosteroid (topical)	• Dose reduction (with close monitoring) • For rash that requires interruption of treatment, consider TKI switch if the rash recurs after re-starting treatment	• Lifestyle modifications: avoid prolonged su exposure and avoid prolonged bathing in h water • Antihistamine/Corticosteroid /Antibiotic: topical antihistamine or corticosteroid can considered for low grade toxicity. Short-ter systemic corticosteroid and/or systematic antibiotic can be considered in severe case consultation with a dermatologist • Topical Moisturizer: alcohol-free moisturize In addition, for dry skin, moisturizers with exfoliants such as ammonium-lactate, lacti acid, salicylic acid, or urea may be consider (can cause burn and dermatology consulta is recommended)
Dry Skin				

or Non-pharmacologic, Pharmacologic Clinical Intervention, TKI Therapy Modification, and Additional omments sections, we have adapted some recommendations from Lipton JH et al (Blood Rev. 2022 ov:56:100968) and National Comprehensive Cancer Network Chronic Myeloid Leukemia Guidelines Version .2026 — July 16, 2025.
bbreviations: ALT, alanine transaminase; AOE, arterial occlusive event; AST, aspartate transaminase; TEAE, eatment-emergent adverse event; TKI, tyrosine kinase inhibitor

a. Lipton JH et al. Blood Rev. 2022 Nov:56:100968.
b. National Comprehensive Cancer Network. Chronic Myeloid Leukemia (Version 1.2026). https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf. Accessed August 1, 2025.
c. Whelton PK, et al. J Am Coll Cardiol 2018;71:e127-e248.
d. Mancia G, et al. J Hypertens 2023;41:1874-2071.
e. Gornik HL, et al. Circulation. 2024 Jun 11;149(24):e1313-e1410.
f. Bushnell C, et al. Stroke. 2024 Dec;55(12):e344-e424.
g. Rao SV, et al. Circulation. 2025 Apr;151(13):e771-e862.

Table 3. Recommended Management for Hematologic, Biochemical, and Other Therapy-Associated TEAEs of Interest

	Clinical Intervention		TKI Therapy Modification (conditions not resolved despite optimal clinical intervention)[a,b]	Additional Comments[a,b]
	Non-Pharmacologic[a,b]	Pharmacologic[a,b]		
Hematologic				
Anemia	• Monitor for new shortness of breath or fatigue	• For grade 3 or 4, erythropoiesis-stimulating agents may be considered	• Dose reduction (with close monitoring) or switch TKI if persistent. Cross intolerance is common.	• Monitor complete blood counts regularly
Neutropenia	• Monitor for infection symptoms	• For grade 4, granulocyte-colony stimulating factor may be considered		
Thrombocytopenia	• Monitor for bruising, bleeding	• For grade 4, thrombopoietin receptor agonists may be considered		
Biochemical				
AST or ALT Elevation	• Monitor for jaundice / brown urine • Monitor liver function tests	• Minimize/Avoid concurrent medications with risk of hepatotoxicity	• Dose reduction (with close monitoring) or switch TKI if persistent	
Total bilirubin elevation				
Increased lipase	• Monitor for abdominal pain • Consider imaging by contrast enhanced CT or MRI		• Dose reduction (with close monitoring) or switch TKI if persistent, (most common with nilotinib, ponatinib, and asciminib)	
Hyperglycemia	• Monitor blood glucose at baseline and periodically • Refer to endocrinologist	• If diabetic, optimize anti-diabetic medications	• Dose reduction (with close monitoring) or switch TKI if persistent (most common with nilotinib)	
Decreased Phosphate	• Monitor electrolytes	• Correct electrolytes	• Dose reduction (with close monitoring) or switch TKI if persistent	
Increased Potassium				
Decreased Potassium				
Other				
Osteopenia/Osteoporosis	• Vitamin D level at baseline and periodically	• Data for bone modifying agents are limited		
Headache	• Sleep hygiene, caffeine management • Consider referral to neurologist (e.g., headache clinic)	• Acetaminophen-based therapy or NSAIDs if needed	• Dose reduction (with close monitoring) or switch TKI if persistent	
Abdominal Pain	• Monitor liver function tests, amylase and lipase • Imaging studies	• Determined by etiology	• Dose reduction (with close monitoring) or switch TKI if persistent	
Nasopharyngitis	• Monitor for signs/symptoms of infection • Refer to otolaryngologist	• Over-the-counter pain relievers and/or anti-inflammatory medications	• Dose reduction (with close monitoring) or switch TKI if persistent	
Hemorrhage	• Monitor for signs/symptoms of bleeding			
Venous Thromboembolism	• Monitor signs/symptoms of thrombosis	• Anticoagulation based on patient specific factors (e.g., renal function)		
Fatigue	• Lifestyle modification	• No data to support the use of stimulant medications	• Dose reduction (with close monitoring) or switch TKI if persistent	• Lifestyle modification: maintain active lifestyle (routine exercise) physically able

For Non-pharmacologic, Pharmacologic Clinical Intervention, TKI Therapy Modification, and Additional Comments sections, we have adapted some recommendations from Lipton JH et al (Blood Rev. 2022 Nov:56:100968) and National Comprehensive Cancer Network Chronic Myeloid Leukemia Guidelines Version 1.2026 — July 16, 2025.

Abbreviations: ALT, alanine transaminase; AOE, arterial occlusive event; AST, aspartate transaminase; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor; NSAID, nonsteroidal anti-inflammatory drugs

a. Lipton JH et al. Blood Rev. 2022 Nov:56:100968.

b. National Comprehensive Cancer Network. Chronic Myeloid Leukemia (Version 1.2026). https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf. Accessed August 1, 2025.

c. Whelton PK, et al. J Am Coll Cardiol 2018;71:e127-e248.

d. Mancia G, et al. J Hypertens 2023;41:1874-2071.

e. Gornik HL, et al. Circulation. 2024 Jun 11;149(24):e1313-e1410.

f. Bushnell C, et al. Stroke. 2024 Dec;55(12):e344-e424.

g. Rao SV, et al. Circulation. 2025 Apr;151(13):e771-e862.

Figure Legends
Figure 1. Overview of toxicity management

Figure 1: Overview of toxicity management