

# Chronic Myeloid Leukaemia

## A mini review for clinicians

For postgraduate residents (medical and haematology oncology, haematology, internal medicine, cardiology, obstetrics, paediatrics, pathology and molecular laboratory medicine), practising clinicians and medical students

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CONTENTS

|    |                                                   |    |                                        |
|----|---------------------------------------------------|----|----------------------------------------|
| 01 | At a glance                                       | 07 | Management algorithms                  |
| 02 | Clinical presentation, common traps & causes      | 08 | Survivorship, follow-up & late effects |
| 03 | Diagnosis, workup & staging essentials            | 09 | Landmark trials                        |
| 04 | Biology and biomarkers that change treatment      | 10 | Practice pearls & pitfalls             |
| 05 | Local therapy: radiotherapy, surgery & procedures | 11 | Case vignettes: lines of management    |
| 06 | Systemic therapy: indications & options           | 12 | References & guidelines                |

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Updated 17 October 2026. Educational summary written in our own words from current guidelines and primary trials; no drug doses; not advice for an individual patient. Verify current guidelines and Indian regulatory approvals before treatment decisions. Patients and families: please see the patient guides at drharitha.co.in.

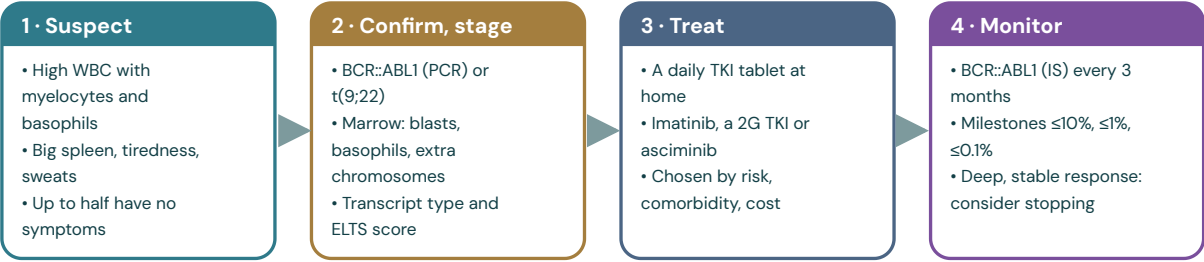
# Chronic Myeloid Leukaemia

Haematological cancers, part 9 · Chronic, accelerated and blast phases · TKI choice and molecular milestones · Resistance, ponatinib and asciminib · Treatment-free remission · Pregnancy · Transplant · Key points for clinicians · Last updated 17 October 2026

## 01 At a glance

- **CML is a myeloproliferative neoplasm driven by one fusion gene:** t(9;22) (the Philadelphia chromosome) joins BCR to ABL1 and makes an always-active tyrosine kinase. It is 15–20% of adult leukaemias, 1–2 per 100,000 a year, with a median age in the 60s in Western registries; Indian hospital series see patients about a decade younger ([Bansal 2013<sup>\[1\]</sup>](#)).
- **Suspect it** from an unexplained high white count with myelocytes and basophils, often with a big spleen; up to half have no symptoms at diagnosis.
- **Confirm in blood, stage in marrow:** BCR::ABL1 by PCR (record the transcript type and a baseline on the International Scale) or FISH; marrow morphology and karyotype decide the phase and find extra chromosomes; the ELTS score sets the risk.
- **Treat every phase with a TKI.** In chronic phase, imatinib (generic, by far the cheapest), a second-generation (2G) TKI or asciminib give the same long-term survival; high ELTS favours a 2G TKI or asciminib. Comorbidity decides among them.
- **Follow the BCR::ABL1 test:** every 3 months until major molecular response (MMR,  $\leq 0.1\%$ ), then every 3–6 months. Milestones  $\leq 10\%$  at 3 months,  $\leq 1\%$  at 6 and  $\leq 0.1\%$  at 12 are "favourable" ([ELN 2025<sup>\[2\]</sup>](#)).
- **Off track?** Adherence and interactions first, then karyotype and a kinase-domain mutation test. T315I → ponatinib or asciminib; after a 2G TKI fails, another 2G TKI rarely works. Start a donor search early.
- **Stopping is possible:** after more than 5 years of TKI (4 for a 2G TKI) and more than 2 years of deep response, 40–50% stay in treatment-free remission.
- **Pregnancy:** women stop TKIs (plan from diagnosis; interferon if counts need control; imatinib or nilotinib only after week 16); men can continue.
- **Advanced phases:** myeloid blast phase is treated like AML ([AML module](#)) and lymphoid blast phase like Ph+ ALL ([ALL module](#)), always with a TKI, then allogeneic transplant if possible.
- **India:** generic imatinib made CML treatable for most; the gaps are adherence (up to one-third miss doses), standardised PCR and access to later-line TKIs and transplant.

CML in one picture: confirm, stage, choose a tablet, then follow the BCR::ABL1 test



With a TKI, life expectancy now approaches that of the general population (Bower 2016), and 40–50% of carefully selected patients who stop the TKI stay in remission. Adherence decides much of this: patients who took 80% or less of their doses never reached a major molecular response (Marin 2010).

**Advanced phases: myeloid blast phase is treated like AML and lymphoid blast phase like Ph+ ALL, always with a TKI, then transplant if possible.**

Figure 1. The four steps (UpToDate CML diagnosis, overview and chronic phase reviews; Bower 2016; Marin 2010; ELN 2025).

## 02 Clinical presentation, common traps & causes

### How chronic myeloid leukaemia presents

#### Symptoms and signs

- Up to half: none (a routine blood count)
- Fatigue 34%, weight loss 20%
- Sweats 15%, abdominal fullness 15%
- Bleeding from platelet dysfunction 21%
- Spleen palpable in 48–76%: early satiety, left-sided pain
- Sternal tenderness, gout

#### Blood film

- Median WBC about 100,000/ $\mu$ L (12,000 to 1,000,000)
- Every stage from myeloblast to neutrophil
- More myelocytes than metamyelocytes
- Basophilia always; eosinophilia in ~90%
- Blasts usually under 2%
- Platelets >600,000/ $\mu$ L in 15–30%

#### Clues to a later phase

- Blasts 10% or more
- Basophils 20% or more
- Platelets falling, not from treatment
- Nodes, skin or soft-tissue masses
- Lymphoblasts on the film
- Low platelets at diagnosis: think of MDS

India: hospital series report a median age of 32–42 years, about a decade younger than in Europe (55) or the United States (66), with more symptoms, bigger spleens and more high-risk scores; the Mumbai population registry, however, shows the usual peak at 55–74 years, so referral patterns explain part of the difference (Bansal 2013; Ganesan 2016).

Figure 2. Presentation (UpToDate CML diagnosis review, citing Savage 1997; Indian data from Bansal 2013 and Ganesan 2016).

### Who gets it, and why

- **Incidence:** 1–2 per 100,000 a year with a slight male excess; median age 66 at diagnosis in the United States. More than one-third of patients in a European population registry were of reproductive age, which makes fertility and pregnancy everyday questions.
- **India:** CML is the commonest adult leukaemia in Indian hospital series. Estimated incidence 0.8–2.2 per 100,000; the Mumbai registry reported age-adjusted rates of 0.71 (men) and 0.53 (women) per 100,000 with the usual peak at 55–74 years, while hospital series report median ages of 32–42 and more symptomatic, high-risk presentations ([Ganesan 2016](#)<sup>[3]</sup>; [Bansal 2013](#)<sup>[1]</sup>).
- **Causes:** ionising radiation is the only known risk factor. There is no familial tendency, and it is not inherited by children.
- **Why advanced presentations still occur:** where access to care is limited, diagnosis is late and more patients present in accelerated or blast phase.

### Common traps

- **Weeks of antibiotics for a "leukemoid reaction".** A persistent high count with myelocytes and basophils needs BCR::ABL1 testing; toxic granules and Döhle bodies favour infection.
- **Hydroxyurea before the spleen is measured.** Record spleen size in centimetres and send samples first: ELTS is not valid after treatment.
- **Blood PCR alone, no marrow.** PCR confirms CML but the marrow finds accelerated or blast phase and extra chromosomes.
- **"PCR negative, so not CML."** Routine kits detect p210 and p190 only; p230 and rare transcripts need FISH, and some Ph-negative cases have cryptic fusions.
- **Changing laboratories.** Results are comparable only on the International Scale in a standardised laboratory; use one laboratory throughout.
- **Low platelets at diagnosis.** Uncommon in chronic phase: think of MDS or an advanced phase.

- **Lymphoblasts on the film.** In a patient with CML this is lymphoid blast phase until proved otherwise.
- **Herbal and over-the-counter medicines.** Some reduce TKI levels (CYP3A4 inducers such as St John's wort) or add to QTc prolongation; acid-suppressing drugs reduce dasatinib and nilotinib absorption.

#### High white count with a left shift: CML or something else? BCR::ABL1 decides

##### Leukemoid reaction

- Infection or inflammation
- Toxic granules, Döhle bodies
- Rarely as high as CML
- BCR::ABL1 negative

##### Atypical CML

- An MDS/MPN, not true CML
- Dysplastic neutrophils
- Anaemia or low platelets
- Older; poor outlook
- BCR::ABL1 negative

##### CMML, CNL, CEL

- CMML: monocytes, dysplasia
- CNL: mature neutrophils, CSF3R
- CEL: abnormal eosinophils
- All BCR::ABL1 negative

##### Other MPNs

- Polycythaemia vera, ET, myelofibrosis
- High platelets or a big spleen
- Separated by BCR::ABL1 testing

Ph-positive acute leukaemia or CML in blast phase? BCR::ABL1 in mature granulocytes (blood FISH), a p210 rather than p190 transcript and typical extra chromosomes favour CML; Ph persisting in myeloid cells after remission points to CML presenting in blast phase. See the ALL module (Ph+ ALL).

Children: juvenile myelomonocytic leukaemia can look similar; CML is rare in children but BCR::ABL1 separates them.

Figure 3. Differential diagnosis (UpToDate CML diagnosis and blast phase reviews). MPNs are covered here only as differentials.

#### SHARE WITH PATIENTS: SYMPTOMS AND SUSPICION

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

[Leukaemia occurs only in children?](#)

[A normal haemoglobin level rules out leukaemia?](#)

[A routine blood test alone can identify every type of leukaemia?](#)

[If there are no swollen lymph nodes, leukaemia is impossible?](#)

## 03 Diagnosis, workup & staging essentials

First visits: confirm in blood, stage in marrow, prepare for a long treatment

Leukocytosis with a left shift → BCR::ABL1 in blood confirms CML; the marrow decides the phase

### Confirm

- Qualitative PCR: transcript type (e13a2/e14a2 in 98%)
- Baseline quantitative PCR on the International Scale
- No Ph on karyotype: FISH (variant or cryptic fusion)
- PCR negative, suspicion high: FISH (rare transcripts)

### Stage (marrow)

- Blast %, basophils, fibrosis
- Karyotype, ≥20 metaphases: extra chromosomes (ACA)
- Blasts raised: flow cytometry (myeloid or lymphoid?)
- No mutation test in new chronic phase

### Before the first tablet

- ELTS score: age, spleen (cm), blasts, platelets
- ECG (QTc), BP, lipids, HbA1c
- Hepatitis B serology; liver, kidney tests
- Every medicine and herb (interactions)
- Plans for pregnancy or fathering a child

Measure the spleen in centimetres below the costal margin before any treatment, hydroxyurea included: the risk scores were built on untreated values. Hydroxyurea is for very high counts or a painful spleen while confirmation is awaited; leukapheresis only for leukostasis (rare in chronic phase; see the AML module).

Figure 4. Work-up (UpToDate CML diagnosis, overview and chronic phase reviews; ELN 2025, Table 1).

### Making the diagnosis

- **CML is a pathological diagnosis:** t(9;22)(q34;q11.2) by banding or FISH and/or BCR::ABL1 by RT-PCR, in blood or marrow. More than 90% show the Ph chromosome on banding; in one large study 15% lacked it (complex or cryptic rearrangements). With high suspicion and a negative karyotype, FISH is mandatory.
- **Marrow at diagnosis** ([ELN 2025](#)<sup>[2]</sup> recommends banding analysis on marrow): hypercellular, granulocytic hyperplasia, myeloid:erythroid ratio up to 20:1, small megakaryocytes, sometimes reticulin fibrosis; about 2% blasts in chronic phase. A marrow can be omitted only when the result would not change treatment (frailty).
- **Atypical transcripts** (about 2%) must be identified at diagnosis: they need FISH, a personalised assay or digital PCR for monitoring.
- **Phase:** ICC keeps three phases (accelerated 10–19% blasts, basophils ≥20%, high-risk extra chromosomes); WHO 2022 recognises only chronic and blast phase, listing high-risk features instead; older ELN criteria (blast phase ≥30%) were used in most trials ([ICC 2022](#)<sup>[4]</sup>, [WHO 2022](#)<sup>[5]</sup>).
- **Leukostasis** is uncommon in chronic phase but can occur with extreme counts (priapism, breathlessness, transient ischaemic attack): hydroxyurea lowers the count within 1–2 days; leukapheresis for symptomatic cases. Emergency care is shared with the acute leukaemias ([AML module, emergencies](#)).

### Which phase? Three classifications use different blast cut-offs

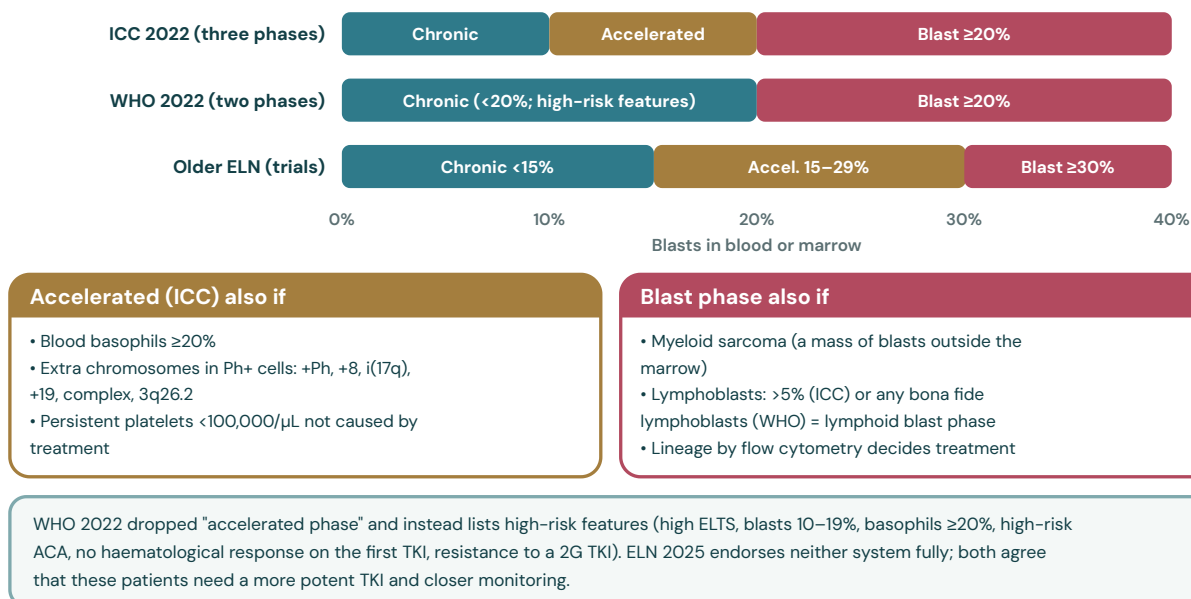
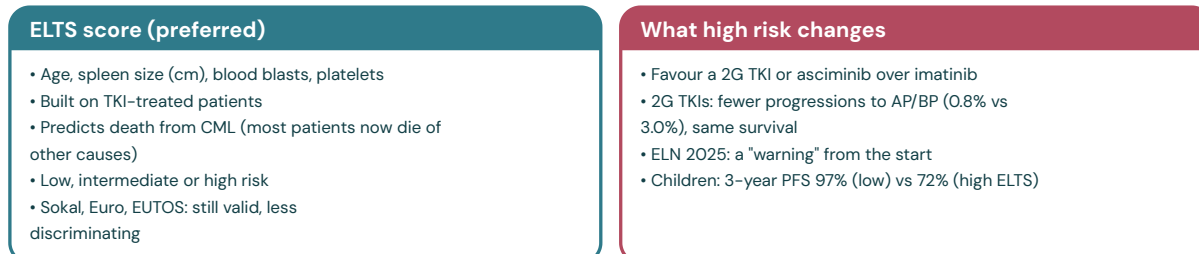


Figure 5. Phases (UpToDate CML diagnosis and accelerated phase reviews; ICC 2022; WHO 2022; ELN 2025, Table 2).

### Risk at diagnosis

- ELTS** (age, spleen size, blood blasts, platelets) was built on TKI-treated patients and best predicts death from CML ([Pfirschmann 2016](#)<sup>[6]</sup>; [Pfirschmann 2020](#)<sup>[7]</sup>). ELN 2025 replaces Sokal, Euro and EUTOS with ELTS; UpToDate accepts any validated score.
- Comorbidity** now predicts survival more than CML itself for many patients: 8-year survival fell from 94% to 46% across Charlson index groups in CML Study IV ([Saussele 2015](#)<sup>[8]</sup>).
- Extra chromosomes at diagnosis** (about 7%): major-route changes (+8, +Ph, i(17q), +19) and 3q26.2, -7/7q-, complex karyotype carry a worse outlook ([Fabarius 2011](#)<sup>[9]</sup>; [Wang 2016](#)<sup>[10]</sup>).

### Risk at diagnosis: the ELTS score, and why comorbidity now matters more



### Eight-year overall survival by comorbidity (Charlson index), CML Study IV

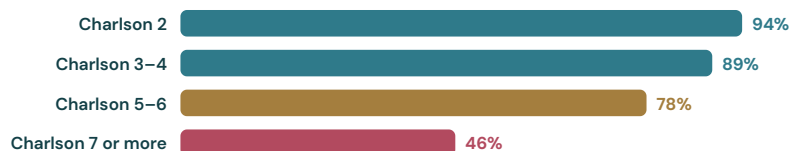


Figure 6. Risk (UpToDate CML diagnosis and chronic phase reviews; Pfirschmann 2016 and 2020; Yun 2016; Saussele 2015; Millot 2026 for children).

### SHARE WITH PATIENTS: TESTS AND DIAGNOSIS

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

[A bone marrow test makes leukaemia spread?](#)

[All leukaemias are the same disease?](#)

[Blood cancer is always hereditary?](#)

## 04 Biology and biomarkers that change treatment

### One fusion gene drives the disease; other changes drive progression

#### The fusion

- t(9;22) joins BCR to ABL1
- Philadelphia (Ph) = the short chromosome 22
- An always-on tyrosine kinase
- More growth, less apoptosis, weaker adhesion to marrow
- Every TKI targets this kinase

#### Transcript types

- p210 (e13a2 or e14a2): about 98%
- e14a2: more successful stopping (ELN 2025)
- p190 (e1a2): rare in CML, typical of Ph+ ALL
- p230 (e19a2): routine PCR may miss it
- Atypical types: FISH or a personalised assay

#### Progression

- Extra chromosomes in >80% of AP/BP: +8, +Ph, i(17q), +19
- TP53 loss in 20–30% of blast phase
- IKZF1 loss: lymphoid; CEBPA block: myeloid
- ASXL1, TET2, DNMT3A: slower response
- Kinase-domain mutations: TKI resistance

Extra chromosomes (ACA) are present at diagnosis in about 7% of chronic phase patients; ELN 2025 treats high-risk ACA as a warning sign. Mutations outside BCR::ABL1 (20–30%) are not tested routinely in chronic phase, but targeted NGS is recommended at blast phase. Large deletions of the derivative chromosome 9 (15–20%) carry a worse outlook.

Figure 7. Biology (UpToDate CML diagnosis review; ELN 2025; Fabarius 2011; Wang 2016).

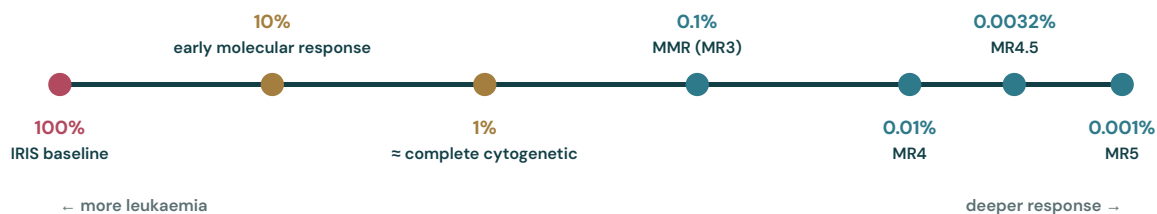
### Biomarkers that change treatment

- **BCR::ABL1 itself:** the target of every TKI and the marker followed for life.
- **Transcript type:** decides how to monitor (rare transcripts need FISH or personalised assays); e14a2 is associated with more successful treatment-free remission; transcripts without ABL1 exon 2 (e13a3, e14a3) are expected to resist asciminib ([ELN 2025<sup>\[2\]</sup>](#)).
- **Extra chromosomes in Ph+ cells:** a warning at diagnosis and a sign of progression if they appear on treatment. Changes in Ph-negative cells (for example trisomy 8) can wax and wane without affecting outcome, but -7/7q- needs marrow follow-up.
- **Kinase-domain mutations:** the only actionable resistance mechanism; tested at warning or unfavourable responses and at progression, not at diagnosis in chronic phase. NGS finds emerging clones earlier than Sanger sequencing and identifies compound mutations.
- **Other somatic mutations** (20–30%; ASXL1 in about 10%): research tools in chronic phase; targeted NGS is recommended at blast phase.

### How response is measured

- **Haematological:** complete haematological response = WBC <10,000/μL, platelets <450,000/μL, no immature cells, basophils <5%, spleen not palpable.
- **Cytogenetic** (≥20 marrow metaphases): complete = no Ph+ cells; major = 1–35%; minor 36–65%; minimal 66–95%; none >95%. Interphase FISH with <1% positive nuclei (≥200 counted) can document complete response. Rarely needed now that PCR is standardised.
- **Molecular** (International Scale, relative to the IRIS baseline): MMR (MR3) ≤0.1%, MR4 ≤0.01%, MR4.5 ≤0.0032%, MR5 ≤0.001%; deep molecular response = MR4 or deeper ([Cross 2012<sup>\[1\]</sup>](#)).

### The BCR::ABL1 ladder: each step down is a ten-fold fall (International Scale, IS)



Deep molecular response (DMR) = MR4 or deeper. Labs should reliably reach MR4.5: that needs at least 32,000 ABL1 control transcripts (10,000 for MR4). A 2-log fall is roughly a complete cytogenetic response. Atypical transcripts (2%) need FISH or a personalised assay.

**India: few laboratories reported on the International Scale (first Indian report, Vellore 2012), and PCR costs more than generic imatinib in many places; use the same accredited laboratory each time.**

Figure 8. Molecular response (UpToDate overview and chronic phase reviews; Cross 2012; ELN 2025, Table 3; Balasubramanian 2012; Ganesan 2016). Log scale.

## 05 Local therapy: radiotherapy, surgery & procedures

### Radiotherapy

- **No routine role in chronic phase CML** in the supplied sources. In blast phase, myeloid sarcoma and CNS disease are managed as in the acute leukaemias ([AML module, radiotherapy](#); [ALL module, radiotherapy](#)).

### Procedures and their pitfalls

- **Bone marrow aspirate and biopsy:** at diagnosis (phase, karyotype) and at resistance or progression; not for routine follow-up of a patient responding on PCR, unless there are unexplained cytopenias or dysplasia.
- **Leukapheresis:** for symptomatic leukostasis when hydroxyurea is not enough, and in pregnancy (alone or with interferon), depending on venous access and availability.
- **Pleural effusions on dasatinib:** chest X-ray, exclude infection, heart failure, kidney disease and progression; some need thoracentesis, a chest drain or pleurodesis, with interruption or dose reduction.
- **Lumbar puncture:** in lymphoid blast phase or with neurological signs; not in neurologically well patients with myeloid blast phase. CNS disease is treated as in ALL or AML (intrathecal therapy, high-dose methotrexate); dasatinib, bosutinib, nilotinib and ponatinib cross the blood-brain barrier.
- **Allogeneic HCT:** reduced-intensity or non-myeloablative conditioning for older (over about 55) or less fit patients; [ELN 2025](#)<sup>[2]</sup> prefers myeloablative conditioning where possible because relapse rises with reduced intensity. Matched sibling or unrelated donors preferred; haploidentical or cord blood acceptable. The TKI may be held during transplant and restarted at count recovery (around day 30–60).

## o6 Systemic therapy: indications & options

### Chronic phase: the first TKI

#### First-line TKI in chronic phase: risk, goals, comorbidity and cost

##### Lower risk (ELTS low/int.)

- Imatinib, a 2G TKI or asciminib: all acceptable
- Same long-term survival
- 2G TKIs and asciminib: faster, deeper responses
- Generic imatinib: by far the cheapest

##### Higher risk (ELTS high)

- A 2G TKI (dasatinib, nilotinib, bosutinib) or asciminib
- Less early progression than imatinib
- ENESTnd: 33 progressions on imatinib vs 12 and 9 on nilotinib
- Same overall survival

##### Goals

- Young, wants to stop or plan a pregnancy: a faster TKI may help
- Older with comorbidity: survival and quality of life first
- Cost and access decide in many Indian clinics

#### Comorbidity: which TKI to avoid

Heart disease, arrhythmia, diabetes, past vascular event

avoid: Nilotinib

Lung disease or risk of pleural effusion

avoid: Dasatinib

Pancreatitis

avoid: Nilotinib, bosutinib, asciminib

Bowel, liver or kidney disease

avoid: Bosutinib

Long-term acid-suppressing drug (PPI)

avoid: Dasatinib, nilotinib (special formulations exist)

Bleeding disorder or anticoagulant

caution: Dasatinib (platelet defect)

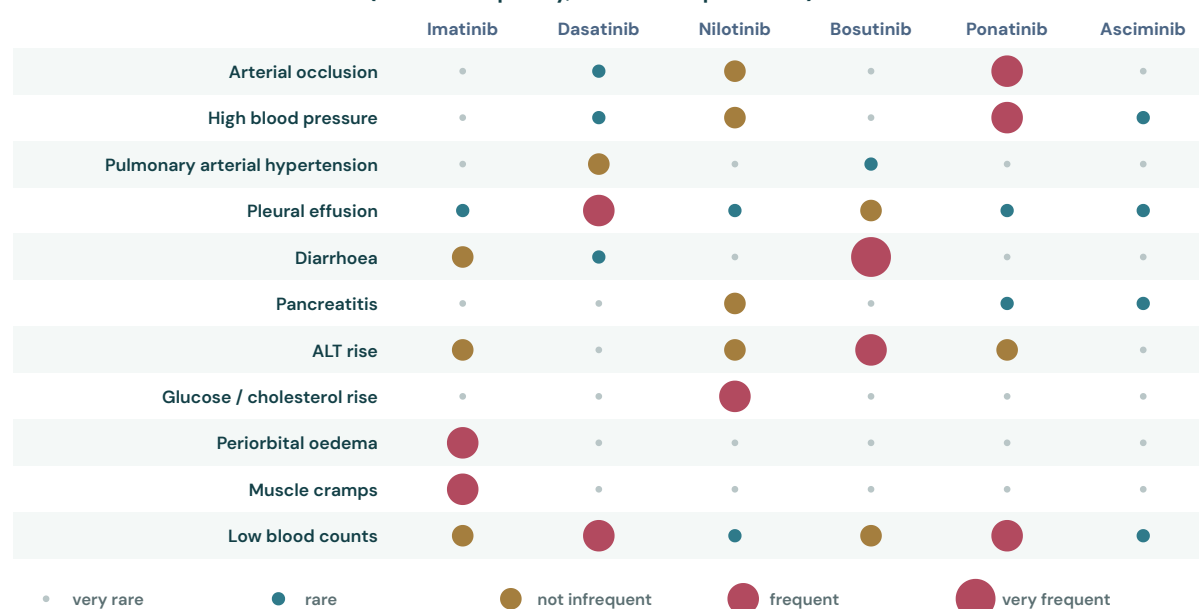
Figure 9. First-line choice (UpToDate chronic phase and overview reviews; Hochhaus 2016 ENESTnd; Yun 2016; ELN 2025). No doses.

- **Why TKIs:** in IRIS, imatinib beat interferon plus cytarabine (18-month PFS 97% vs 92%) with better quality of life; 10-year OS was 84% (most of the control arm crossed over) ([IRIS<sup>\[12\]</sup>](#), [Hochhaus 2017<sup>\[13\]</sup>](#)). Life expectancy now approaches that of the general population ([Bower 2016<sup>\[14\]</sup>](#)), although ELN 2025 notes small residual losses in Swedish data.
- **Imatinib:** the longest safety record; generic; slower to deep response. Fluid retention, periorbital oedema, cramps, nausea, diarrhoea; hypophosphataemia and bone changes. Taken with food.
- **Dasatinib:** once daily with or without food; pleural/pericardial effusions, pulmonary arterial hypertension, bleeding from a platelet defect, QTc. Avoid in lung disease, effusions, bleeding disorders; acid-suppressing drugs reduce absorption (a formulation that tolerates them exists in some markets).
- **Nilotinib:** twice daily with strict food rules (formulations are not interchangeable); arterial occlusive disease, QTc and rare sudden death, raised glucose and cholesterol, pancreatitis. Avoid with diabetes, high cardiovascular risk or a past vascular event ([ENESTnd<sup>\[15\]</sup>](#)).
- **Bosutinib:** diarrhoea (mostly early) and raised liver enzymes; some start low and escalate to improve tolerance. Avoid with bowel, liver or kidney disease.
- **Asciminib:** binds the myristoyl pocket rather than the ATP site; taken without food. Lipase rise, hypertension, musculoskeletal pain. ASC4FIRST: MMR at 96 weeks 74.1% vs 52.0% with investigator-chosen TKIs, event-free survival 85.6% vs 70.6%, fewer discontinuations; overall survival not yet reported ([ASC4FIRST<sup>\[16\]</sup>](#)). FDA-approved first line; EMA only after ≥2 TKIs.
- **2G vs imatinib:** 16 or more trials, faster and deeper responses and fewer transformations with 2G TKIs, no overall survival gain; in a meta-analysis of 8 trials (2974 patients) progression was 0.8% vs 3.0% ([Yun 2016<sup>\[17\]</sup>](#)). Nilotinib and dasatinib were equivalent in the Japanese JALSG CML212 trial ([Matsumura 2024<sup>\[18\]</sup>](#)).

- **Cytoreduction before confirmation:** hydroxyurea for symptomatic splenomegaly or very high counts; it does not affect later milestones ([Kockerols 2022<sup>\[19\]</sup>](#)). Interferon added to a TKI is not recommended (more toxicity, little gain).
- **Lower starting doses** (dasatinib, bosutinib) are being studied to reduce side effects; ELN 2025 cannot yet recommend them routinely.

## Living with a TKI: side effects

Which side effect with which TKI? (relative frequency, ELN 2025 expert table)



Early, mostly mild effects are common to all TKIs (nausea, rash, cramps, oedema, diarrhoea, fatigue, cytopenias) and usually settle. Later effects differ by drug and can appear after years: ask about chest pain, claudication, breathlessness and new symptoms at every visit.

Figure 10. Side-effect map (ELN 2025, Table 8, expert opinion from mainly first-line studies; UpToDate chronic phase review). Dot size = relative frequency, not a percentage.

- **Early effects are mild and usually settle:** nausea (less with food for imatinib and bosutinib), cramps (about half on imatinib; correct electrolytes), rash, oedema, diarrhoea (check for lactose intolerance), fatigue (check thyroid, sleep, mood). Report even grade 1–2 effects early: persistent low-grade effects drive non-adherence.
- **Cytopenias in the first weeks** are mostly the leukaemia clearing: continue if mild; hold or reduce for severe ones; avoid erythropoietin-stimulating agents (thrombosis, no benefit); growth factors occasionally, with the TKI continued.
- **Drug holidays and dose reduction:** a 5–7-day break often resolves a low-grade effect. In patients with at least MMR, dose reduction keeps the response in most: in DESTINY 20–30% lost MMR on half dose, and all regained it on full dose ([Clark 2017<sup>\[20\]</sup>](#)). Avoid long interruptions.
- **Other effects:** hypophosphataemia (nilotinib, imatinib), gynaecomastia with low free testosterone (imatinib), skin hypopigmentation (reported in Indian patients), gastric antral vascular ectasia (rare). No excess of second cancers (1445 patients followed a median of 107 months).

**Heart, vessels and lungs: the late side effects that change the choice of TKI**

| Nilotinib                                                                                                                                                                                                             | Ponatinib                                                                                                                                                                                                              | Dasatinib                                                                                                                                                                                                     | Lower arterial risk                                                                                                                                                                                    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Coronary, cerebral, leg artery disease</li> <li>• QTc; rare sudden death</li> <li>• Higher glucose and cholesterol</li> <li>• Avoid with diabetes or high CV risk</li> </ul> | <ul style="list-style-type: none"> <li>• Arterial occlusion, dose-related</li> <li>• Hypertension, heart failure, liver</li> <li>• Lower dose once BCR::ABL1 &lt;1%</li> <li>• Not for most with CV disease</li> </ul> | <ul style="list-style-type: none"> <li>• Pleural/pericardial effusion: up to 1 in 3</li> <li>• Pulmonary arterial hypertension: stop for good</li> <li>• Bleeding (platelet defect)</li> <li>• QTc</li> </ul> | <ul style="list-style-type: none"> <li>• Imatinib and bosutinib</li> <li>• Asciminib: hypertension, lipase rise</li> <li>• Imatinib: fluid retention</li> <li>• Bosutinib: diarrhoea, liver</li> </ul> |

Before and during treatment (ELN 2025): ECG and blood pressure for everyone; lipids and HbA1c before and every 6–12 months on nilotinib or ponatinib; thyroid tests on ponatinib. Risk is highest in older people and with hypertension, diabetes, high lipids or smoking, whatever the TKI, and in the first years. Treat the risk factors; many clinicians add low-dose aspirin with nilotinib, dasatinib or ponatinib, although benefit is unproven.

**Stop for good, do not just reduce: symptomatic or progressive arterial disease on nilotinib or dasatinib; pulmonary arterial hypertension on dasatinib; recurrent effusions despite dose reduction.**

Figure 11. Cardiovascular and lung toxicity (UpToDate chronic phase and after-failure reviews; ELN 2025, Table 9; Jain 2019; Cortes 2018 PACE; Cortes 2021 OPTIC).

- **Cardiovascular risk** is highest with ponatinib and nilotinib, slightly raised with dasatinib, lower with imatinib and bosutinib; older age, hypertension, diabetes, high lipids and smoking add risk whatever the TKI, especially in the early years ([Jain 2019<sup>\[21\]</sup>](#)).
- **QTc**: ECG at baseline and 1–2 weeks after starting nilotinib or dasatinib, after dose changes and with new QT-prolonging drugs; correct potassium and magnesium.
- **Pancreas and liver**: lipase (and amylase) monthly in the first months on nilotinib, bosutinib or asciminib, or as clinically indicated (ELN 2025); reduce, hold or switch for clinically significant rises. Liver enzymes rise most with bosutinib, imatinib and nilotinib; avoid alcohol and hepatotoxic drugs.

**Monitoring and molecular milestones****Molecular milestones (BCR::ABL1 IS) for 1st, 2nd and 3rd line: ELN 2025 wording**

|                  | Favourable: no switch | Warning: switch may be needed | Unfavourable: switch preferred                       |
|------------------|-----------------------|-------------------------------|------------------------------------------------------|
| <b>Baseline</b>  | —                     | High-risk ACA or high ELTS    | —                                                    |
| <b>3 months</b>  | ≤10%                  | >10%                          | >10% confirmed within 1–3 months                     |
| <b>6 months</b>  | ≤1%                   | >1–10%                        | >10%                                                 |
| <b>12 months</b> | ≤0.1%                 | >0.1–1%                       | >1%                                                  |
| <b>Any time</b>  | ≤0.1%                 | >0.1–1%; loss of ≤0.1% (MMR)  | Loss of response; resistance mutation; high-risk ACA |

Decide on the trend, never on one result: repeat near a threshold within 1–2 months, ask about missed doses and interacting drugs first. "Late responders" whose values keep falling may not need a switch, especially older people with comorbidity: in CML Study IV, 10-year survival was about 80% even when the 3-, 6- or 12-month milestones were missed, but 55% if BCR::ABL1 was still >10% at 12 months.

**A rising PCR without an obvious cause → karyotype, kinase-domain mutation test and a switch.**

Figure 12. Milestones (ELN 2025, Table 4; UpToDate overview and chronic phase reviews; Lauseker 2023).

- **Schedule:** CBC every 2 weeks until complete haematological response (weekly in month 1 in UpToDate's algorithm); BCR::ABL1 (IS) at least every 3 months until MMR is achieved and confirmed, then every 4–6 months (ELN 2025) or 3–6 months (UpToDate); more often if values fluctuate or rise, and around treatment-free remission. Cytogenetic monitoring is no longer routine.
- **Achieving MMR within a year** predicts CML-specific survival close to 100%; a deep response (MR4 or deeper) is what treatment-free remission needs.
- **New ELN 2025 wording:** favourable, warning and unfavourable replace optimal, warning and failure, to stress that a switch depends on the trend, adherence, comorbidity and goals. In CML Study IV, patients who missed the 3-, 6- or 12-month milestones still had about 80% 10-year survival, but only 55% if BCR::ABL1 was still >10% at 12 months ([Lauseker 2023](#)<sup>[22]</sup>). Without early molecular response, switching to dasatinib (DASCERN) deepened responses (MMR 77% vs 44%) without a survival difference.
- **Fit or younger patients seeking treatment-free remission** may switch to a more potent TKI; older or comorbid patients may continue with close monitoring. A confirmed rise without explanation needs karyotype, mutation testing and a switch.

## Resistance and intolerance: second line and beyond

### Response off track or side effects: check, test, then switch

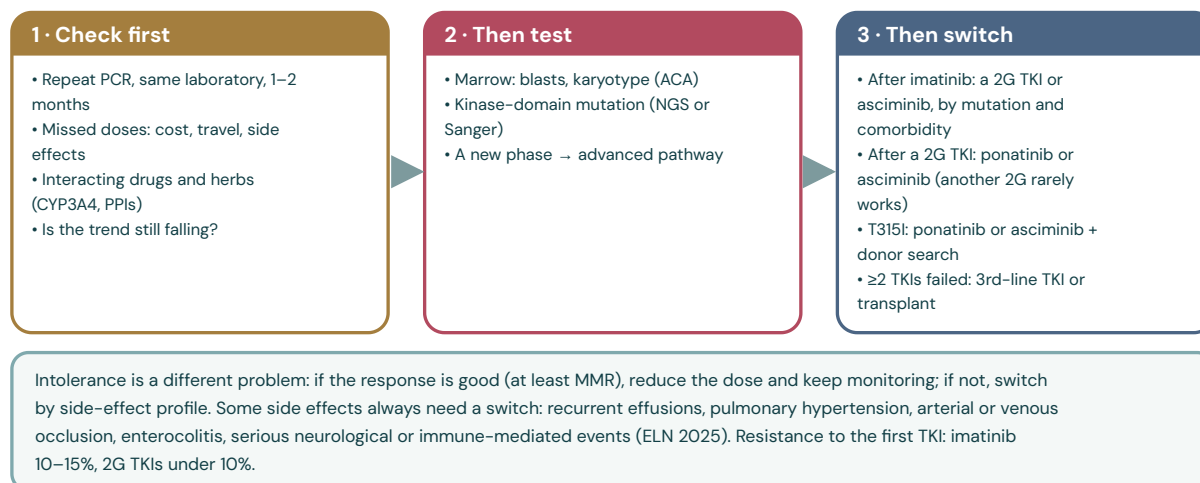


Figure 13. Second line (UpToDate after-failure and overview reviews; ELN 2025).

- **Intolerance** has no consensus definition: persistent or recurrent grade ≥3 non-haematological effects despite management, or lower-grade effects the patient cannot live with. Choose the next TKI by toxicity profile and comorbidity.
- **Resistance:** confirm with repeat PCR, ask about adherence and interacting drugs, then marrow (blasts, karyotype) and kinase-domain mutation testing. ELN 2025 reports unfavourable responses in 15–20% on first line and up to 50% in later lines.
- **After imatinib:** dasatinib, nilotinib, bosutinib or asciminib by mutation and comorbidity; no TKI has proved superior. Dasatinib (7-year data), nilotinib (4-year OS 78%) and bosutinib (2-year OS 91%) all work ([Shah 2016](#)<sup>[23]</sup>; [Giles 2013](#)<sup>[24]</sup>; [Gambacorti-Passerini 2014](#)<sup>[25]</sup>). Dasatinib beat high-dose imatinib ([START-R](#)<sup>[26]</sup>); imatinib dose escalation is a fallback where nothing else is affordable.
- **After a 2G TKI:** another 2G TKI rarely works; ponatinib or asciminib. ASCEMBL (after ≥2 TKIs): MMR at 96 weeks 37.6% with asciminib vs 15.8% with bosutinib, with fewer discontinuations for side effects ([Réa](#)

[2021<sup>\[27\]</sup>](#); [Hochhaus 2023<sup>\[28\]</sup>](#)).

- **T315I** resists imatinib, dasatinib, nilotinib and bosutinib; ponatinib or asciminib (asciminib at a higher dose than for other mutations), with a parallel donor search. In a registry comparison, ponatinib gave better 48-month survival than transplant (73% vs 56%) ([Nicolini 2017<sup>\[29\]</sup>](#)). Omacetaxine is no longer manufactured; olverembatinib is approved only in China.
- **Ponatinib**: PACE (chronic phase, resistant or intolerant to dasatinib/nilotinib): major cytogenetic response 60%, MMR 40%, 5-year OS 73%, but vascular events in 31% ([PACE<sup>\[30\]</sup>](#); [Cortes 2018<sup>\[31\]</sup>](#)). OPTIC: starting higher and reducing once BCR::ABL1 <1% balanced response (44%, 29%, 23% under 1% at 12 months by starting dose) against arterial events (10%, 5%, 3%) ([OPTIC<sup>\[32\]</sup>](#)).
- **Asciminib** in heavily pretreated patients: MMR at 12 months in 48% of evaluable patients and 28% of those with T315I, including some after ponatinib ([Hughes 2019<sup>\[33\]</sup>](#)).
- **After ≥2 TKIs**: a third-line TKI or allogeneic HCT, decided with the patient; donor search should begin at resistance to the first 2G TKI, and transplant referral at resistance to ponatinib and/or asciminib ([ELN 2025<sup>\[2\]</sup>](#)).

#### Kinase-domain mutation → which TKI may still work (ELN 2025, Table 5)

|                                             | Dasatinib | Nilotinib | Bosutinib | Ponatinib | Asciminib |
|---------------------------------------------|-----------|-----------|-----------|-----------|-----------|
| <b>T315I</b>                                | —         | —         | —         | ✓         | ✓         |
| <b>Y253H</b>                                | ✓         | —         | ✓         | ✓         | ✓         |
| <b>E255K/V</b>                              | ✓         | —         | —         | ✓         | ✓         |
| <b>V299L</b>                                | —         | ✓         | —         | ✓         | ✓         |
| <b>F317L/V/I/C, T315A</b>                   | —         | ✓         | ✓         | ✓         | ✓         |
| <b>F359V/I/C</b>                            | ✓         | —         | —         | ✓         | —         |
| <b>M244V</b>                                | ✓         | ✓         | ✓         | ✓         | —         |
| <b>Myristoyl-pocket (A337V/T, P465S...)</b> | ✓         | ✓         | ✓         | ✓         | —         |

Imatinib is not listed: most kinase-domain mutations resist it. Compound mutations (two in the same molecule) resist most TKIs, and some T315I-inclusive ones resist both ponatinib and asciminib. Rare transcripts without ABL1 exon 2 (e13a3, e14a3) are expected to resist asciminib.

The UpToDate in-vitro table agrees on T315I, Y253H, V299L and F317, but also lists bosutinib as an option for E255K/V and F359V, and adds A244V and A465S as asciminib-resistant: read the laboratory report with both tables.

Figure 14. Mutation-guided choice (ELN 2025, Table 5; UpToDate after-failure, accelerated and blast phase reviews). ✓ = recommended option; — = not recommended. In vitro data, not trials.

## Treatment-free remission

**Treatment-free remission (TFR): who can stop, how to watch, what to expect****Who can try (ELN 2025)**

- First chronic phase only
- TKI >5 years (>4 years for a 2G TKI)
- MR4 or deeper for >2 years (optimal: MR4 >3 years or MR4.5 >2 years)
- Typical e13a2/e14a2 transcript
- No resistance (switch for intolerance is fine)
- Reliable IS PCR with fast results; agrees to frequent tests

**What to expect**

- 40–50% stay off treatment
- EURO-SKI: MMR kept by 61% at 6 and 46% at 12 months
- >80% of relapses in the first 6–8 months; late loss up to 14%
- 90–95% regain their response on restarting
- Aches on stopping (polymyalgia, arthralgia) in 20–30%
- Sudden blast phase: ≤0.1%

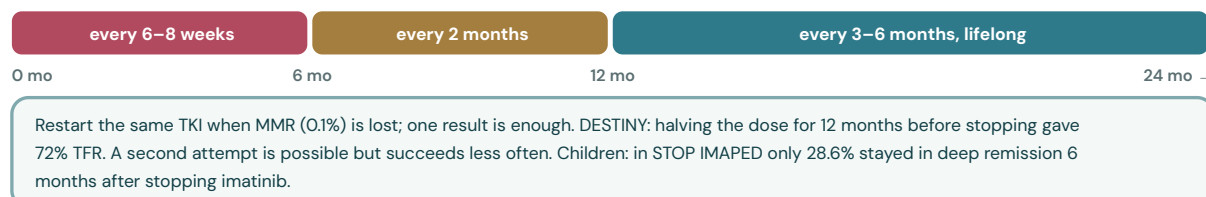
**PCR schedule after stopping**

Figure 15. TFR (ELN 2025, Table 6; UpToDate chronic phase and overview reviews; Saussele 2018; Clark 2019; de Bruijn, STOP IMAPED).

- **A reasonable goal** for most young and middle-aged patients, especially women planning pregnancy and those with troublesome side effects; some, especially older patients, prefer to stay on treatment. Discuss the data and the withdrawal syndrome first.
- **Results:** 40–50% of eligible patients remain off treatment. EURO-SKI (755 patients): MMR kept by 61% at 6 and 46% at 12 months ([EURO-SKI](#)<sup>[34]</sup>). LAST: 77% at 6 and 71% at 12 months, with less fatigue, depression, diarrhoea and sleep disturbance ([LAST](#)<sup>[35]</sup>). Similar after nilotinib and dasatinib ([ENESTfreedom](#)<sup>[36]</sup>, [DASFREE](#)<sup>[37]</sup>). No asciminib data yet.
- **DESTINY:** halving the dose for 12 months before stopping gave 72% TFR in those with MR4 or deeper, and allows restarting at the reduced dose ([DESTINY](#)<sup>[38]</sup>).
- **Monitoring is the safety net:** more than 80% of molecular relapses occur in the first 6–8 months; late loss of MMR in up to 14% after 2 years ([Rousselot 2020](#)<sup>[39]</sup>). Loss of MMR triggers restarting (one result is enough per ELN 2025); mutation testing is not needed; 90–95% regain their response. Sudden blast phase after stopping is very rare (≤0.1%).
- **Not for:** accelerated or blast phase (no data), patients without reliable fast IS-standardised PCR, and children outside expert centres (see section 08).

## Pregnancy and fertility

**Pregnancy and fertility: plan early, avoid TKIs in pregnancy, men can continue****Planning (women)**

- Raise it at diagnosis
- MR4 or deeper: stop as for TFR
- MMR, not MR4: stop and watch, or stop at the first positive test
- Not in MMR: deepen the response first; IVF route in older women
- Japan: planned pregnancies came a median 10.6 years after diagnosis

**Pregnant**

- Stop the TKI at a positive test
- Weeks 0–16: no TKI; interferon if counts need control
- From week 16: imatinib or nilotinib if needed (little placental transfer)
- Avoid dasatinib throughout
- PCR and CBC every 6–8 weeks; early fetal scans
- No TKI while breastfeeding

**Diagnosed in pregnancy**

- WBC <100,000, low/intermediate ELTS: watchful waiting
- Symptoms or high counts: leukapheresis and/or interferon
- High platelets: aspirin and/or LMW heparin
- 76% of 87 women had a normal childbirth (ELN registry)
- Advanced phase: treatment cannot wait; discuss termination

Men: continue the TKI while trying to conceive. In 428 pregnancies of partners of men on TKIs, 93.5% were live births and congenital abnormalities (2.5%) were as in the general population.

Why women stop: about 10% of pregnancies with known outcome after imatinib exposure had fetal abnormalities; dasatinib reaches about 75% of maternal levels in fetal blood. Hydroxyurea: teratogenic in animals, used only briefly.

Figure 16. Parenting (ELN 2025, Table 7; UpToDate chronic phase review; Pye 2008; Cortes 2015; Chelysheva 2024; Kondo 2025). No doses.

- **Women:** all TKIs are potentially teratogenic; risk is assumed from implantation (about 15 days after fertilisation) until organogenesis is complete (around week 16). Imatinib and nilotinib cross the placenta poorly; dasatinib reached 75% of maternal levels in the one case measured. Of 180 imatinib-exposed pregnancies, half with known outcome were normal and about 10% had fetal abnormalities ([Pye 2008](#)<sup>[40]</sup>); dasatinib-exposed pregnancies also had high loss and abnormality rates ([Cortes 2015](#)<sup>[41]</sup>).
- **ELN 2025 parenting guidance:** plan from diagnosis; with MR4 or deeper, stop as for TFR; with MMR, stop and watch, or (for women with regular cycles and access to tests) continue until the first positive pregnancy test; without MMR, deepen the response first (IVF with a planned TKI interruption is an option in older women). During pregnancy: no TKI to week 16; interferon (including pegylated forms) at any time for count control; imatinib or nilotinib after week 16 if CHR is lost or PCR rises fast; avoid dasatinib throughout; PCR and CBC every 6–8 weeks; early and regular fetal scans; no TKI while breastfeeding.
- **Diagnosed in pregnancy:** of 87 women in the ELN registry, 66 (76%) had a normal childbirth with no excess of malformations; treatment was mostly interferon and, after week 16, imatinib ([Chelysheva 2024](#)<sup>[42]</sup>). With WBC <100,000/μL, low or intermediate ELTS and no extra chromosomes, watchful waiting is reasonable; leukapheresis and/or interferon for symptomatic or high counts; aspirin and/or LMW heparin for thrombocytosis. In advanced phase, treatment cannot wait and termination should be discussed with the woman and her family.
- **Planned pregnancies take time:** in a Japanese series of 70 pregnancies, planned pregnancies (during TFR or on interferon) came a median 10.6 years after diagnosis vs 4.1 years for unplanned ones ([Kondo 2025](#)<sup>[43]</sup>).
- **Men:** no convincing effect of TKIs on fertility or on their children; in 428 pregnancies of partners of men on TKIs, live births were 93.5% and congenital abnormalities 2.5%. Men should continue the TKI when trying to conceive ([ELN 2025](#)<sup>[2]</sup>).

## Accelerated and blast phase

**Accelerated and blast phase: de novo or transformed, myeloid or lymphoid****De novo accelerated**

- No prior TKI
- A 2G TKI (dasatinib, nilotinib, bosutinib)
- Responses often like chronic phase
- 21 patients: 90% CCyR on dasatinib or nilotinib
- No attempt to stop the TKI

**Transformed accelerated**

- Arose on a TKI: resistance until proved otherwise
- Adherence; mutation test
- Switch TKI by mutation and comorbidity
- Transplant-eligible: TKI, then allogeneic HCT

**Blast phase**

- ≥20% blasts, myeloid sarcoma or lymphoblasts
- Myeloid (two-thirds): TKI + AML-type induction
- Lymphoid (one-third): TKI + Ph+ ALL regimen
- Lumbar puncture in lymphoid BP
- Allogeneic HCT in remission

TKI choice in blast phase follows prior TKIs and the mutation, not the lineage; avoid imatinib; T315I → ponatinib (asciminib has little blast-phase data). Myeloid BP (104 patients): 5-year OS 30% with TKI + intensive chemotherapy, 28% with TKI + hypomethylating agent, 13% TKI alone, 0% chemotherapy alone. Lymphoid BP: median OS 93 vs 9 months with vs without transplant.

**India (Hyderabad, imatinib era): median survival 61 months in accelerated and 14 months in blast phase.**

Figure 17. Advanced phases (UpToDate accelerated and blast phase reviews; Ohanian 2014; Saxena 2021; Strati 2014; Thota 2014 via Ganesan 2016).

- **De novo accelerated phase:** a 2G TKI rather than imatinib, ponatinib or upfront transplant; 90% complete cytogenetic response in 21 patients on dasatinib or nilotinib ([Ohanian 2014](#)<sup>[44]</sup>). Continue indefinitely; no TFR attempts. BCR::ABL1 <10% at 3 months predicted better survival.
- **Transformed accelerated phase:** adherence, mutation test, switch TKI; transplant-eligible patients proceed to allogeneic HCT once disease is controlled. Dasatinib in imatinib-resistant AP: complete haematological response 50%, complete cytogenetic response 32% ([Kantarjian 2009](#)<sup>[45]</sup>).
- **Myeloid blast phase:** TKI plus AML-type induction (intensive, or a hypomethylating agent ± venetoclax in older patients), then HCT. In 104 patients, 5-year OS was 30% with TKI + intensive chemotherapy, 28% with TKI + HMA, 13% with TKI alone and 0% with chemotherapy alone ([Saxena 2021](#)<sup>[46]</sup>). Ponatinib + FLAG-IDA bridged two-thirds back to chronic phase ([MATCHPOINT](#)<sup>[47]</sup>). Dasatinib alone: short remissions ([Saglio 2010](#)<sup>[48]</sup>).
- **Lymphoid blast phase (one-third):** TKI plus a Ph+ ALL regimen (hyper-CVAD best studied; TKI + steroid or lower intensity if frail; TKI + blinatumomab or inotuzumab emerging); lumbar puncture. With hyper-CVAD + TKI, median OS was 93 months with transplant vs 9 months without ([Strati 2014](#)<sup>[49]</sup>). See the [ALL module \(Ph+ ALL\)](#).
- **TKI in blast phase:** chosen by prior TKIs and mutation, not lineage; avoid imatinib; T315I → ponatinib. Continue the TKI during induction and keep the dose despite cytopenias in responding patients (support with transfusion). After remission monitor PCR every 3 months for 2 years.
- **Relapsed or refractory blast phase:** very poor outlook; repeat mutation testing, clinical trial, donor lymphocytes or second HCT after transplant, otherwise palliation.

## Allogeneic transplant

**Allogeneic transplant in the TKI era: fewer patients, better results****Who to consider**

- Blast phase, once back in chronic phase or remission
- Transformed accelerated phase
- Resistance to ponatinib and/or asciminib
- Intolerance of every TKI
- Start the donor search at resistance to the first 2G TKI

**What to expect**

- The only proven cure
- After TKI failure in chronic phase: up to 80% 5-year survival, early deaths 10–20%
- Advanced phase: 37–59% survival in small series
- Reduced-intensity in advanced CML: 5-year OS 33%
- A prior TKI does not worsen transplant results

After transplant: BCR::ABL1 PCR at least every 3 months early on, then 6-monthly for life; a TKI or donor lymphocytes for molecular relapse. ELN 2025: haploidentical donors mean almost everyone has a donor; outcome depends on phase (first chronic phase vs later) and performance status, not on the number of TKIs given before.

Figure 18. Transplant (UpToDate overview, after-failure, accelerated and blast phase reviews; Kebriaei 2007; Lübking 2019; ELN 2025).

- **Indications:** blast phase once back in chronic phase or remission; transformed accelerated phase; chronic phase failing ponatinib and/or asciminib or intolerant of all TKIs. Transplant of resistant blast phase outside a study is not recommended ([ELN 2025](#)<sup>[2]</sup>).
- **Outcomes:** up to 80% 5-year survival after TKI failure in chronic phase, with 10–20% early mortality; advanced phase 37–59% in small series; reduced-intensity in advanced CML 33% 5-year OS with 39% transplant-related mortality at 2 years ([Kebriaei 2007](#)<sup>[50]</sup>). In a Swedish population series, outcomes in the TKI era were reported by phase ([Lübking 2019](#)<sup>[51]</sup>).
- **After transplant:** PCR at least every 3 months early, then 6-monthly for life; TKI and/or escalating donor lymphocyte infusions for molecular relapse; TKI given before transplant in advanced phase is restarted once engraftment is secure.

**India: check availability and cost before planning**

- **Generic imatinib** is widely available and inexpensive; patient-assistance programmes (GIPAP, Max Foundation) and generics made it reachable for most patients, and at Tata Memorial generic imatinib gave the same responses as the innovator ([Parikh 2013](#)<sup>[52]</sup>). ELN 2025 puts generic imatinib at as little as US\$200–500 a year.
- **Dasatinib and nilotinib** have been available in India, including generics ([Ganesan 2016](#)<sup>[3]</sup>); check current price and supply.
- **Bosutinib, asciminib and ponatinib:** current Indian availability and cost were not verified for this page; check with the pharmacy before planning second- or third-line treatment.
- **Testing:** IS-standardised BCR::ABL1 PCR, NGS mutation testing and a laboratory that confirms MR4.5 with a two-week turnaround (needed for TFR) are not available everywhere; few Indian laboratories reported on the International Scale ([Balasubramanian 2012](#)<sup>[53]</sup>).
- **Pregnancy and transplant:** confirm access to interferon (including pegylated forms) and to allogeneic HCT, including haploidentical donors.

**SHARE WITH PATIENTS: TREATMENT AND HOPE**

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

[CML patients always need lifelong hospital-based chemotherapy?](#)

[Chronic leukaemia always turns into acute leukaemia?](#)

Every leukaemia patient needs chemotherapy immediately?

Chemotherapy is the only treatment for leukaemia?

Every leukaemia patient needs a bone marrow transplant?

Leukaemia can never be cured?

## Quick reference: tests, settings, options, problems

**Table A. Diagnosis, staging and baseline tests, and what they change**

| Test                                                           | When                                                                               | What it changes                                                  | Pitfalls                                                                                       |
|----------------------------------------------------------------|------------------------------------------------------------------------------------|------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| CBC + blood film                                               | Every suspected case; every 2 weeks until CHR                                      | Left-shifted granulocytes, basophils, blasts; phase clues        | Leukemoid reaction looks similar: BCR::ABL1 decides                                            |
| Qualitative PCR (transcript type) + quantitative PCR (IS)      | At diagnosis, blood                                                                | Confirms CML; sets the baseline for all later monitoring         | Routine kits detect p210 and p190 only; p230 and rarer types need FISH or a personalised assay |
| Marrow: morphology + karyotype (≥20 metaphases)                | At diagnosis; at resistance or progression                                         | Phase (blasts, basophils, fibrosis); extra chromosomes (ACA)     | FISH alone misses ACA; not needed for routine follow-up                                        |
| FISH for BCR::ABL1                                             | No Ph on karyotype; atypical transcripts                                           | Finds variant or cryptic fusions                                 | Interphase FISH ≥200 nuclei can document CCyR                                                  |
| Flow cytometry                                                 | Blasts raised                                                                      | Myeloid vs lymphoid blast phase → AML-type vs ALL-type induction | Any lymphoblasts should raise suspicion of lymphoid BP                                         |
| ELTS score                                                     | Before any treatment                                                               | High risk → 2G TKI or asciminib; ELN "warning"                   | Spleen in cm below the costal margin; values after hydroxyurea are not valid                   |
| ECG (QTc), BP, lipids, HbA1c                                   | Baseline; lipids/HbA1c every 6–12 months on nilotinib or ponatinib                 | Avoid nilotinib with high CV risk; QT drugs                      | Repeat ECG 1–2 weeks after starting nilotinib or dasatinib                                     |
| Hepatitis B serology; liver, kidney tests; lipase as indicated | Baseline                                                                           | Reactivation risk; bosutinib dose; pancreatitis                  | Lipase may rise without pancreatitis                                                           |
| Kinase-domain mutation (NGS or Sanger)                         | Warning or unfavourable response, progression, blast phase; not at diagnosis in CP | Which TKI can still work (mutation figure, section O6)           | Not needed after loss of MMR during TFR                                                        |
| HLA typing (patient and siblings)                              | Blast phase, transformed AP, resistance to a 2G TKI                                | Early donor search                                               | Haploidentical donors widen access                                                             |

**Table B. Treatment by setting**

| Setting                                 | Usual approach                            | Alternatives                           | Key points                                                        |
|-----------------------------------------|-------------------------------------------|----------------------------------------|-------------------------------------------------------------------|
| Chronic phase, ELTS low or intermediate | Imatinib (generic), a 2G TKI or asciminib | —                                      | Same long-term survival; 2G/asciminib reach deep responses faster |
| Chronic phase, ELTS high                | A 2G TKI or asciminib                     | Imatinib if nothing else is affordable | Fewer early progressions than imatinib                            |

| Setting                                               | Usual approach                                                     | Alternatives                                      | Key points                                                |
|-------------------------------------------------------|--------------------------------------------------------------------|---------------------------------------------------|-----------------------------------------------------------|
| Very high count or painful spleen before confirmation | Hydroxyurea for days                                               | Leukapheresis only for leukostasis                | Start the TKI as soon as BCR::ABL1 is confirmed           |
| Warning at a milestone                                | Check adherence and interactions; repeat PCR in 1–2 months         | Switch TKI if the trend does not fall             | Late responders may stay on the same TKI                  |
| Unfavourable / resistant after imatinib               | Mutation test; a 2G TKI or asciminib                               | Higher-dose imatinib if no other option           | Choice by mutation, comorbidity and cost                  |
| Resistant after a 2G TKI                              | Ponatinib or asciminib                                             | Another 2G TKI rarely works                       | Start donor search now                                    |
| T315I                                                 | Ponatinib or asciminib                                             | Allogeneic HCT if inadequate response             | Asciminib for T315I needs a higher dose than usual        |
| Intolerance with a good response                      | Dose reduction with close monitoring                               | Switch by side-effect profile                     | Some toxicities always need a switch                      |
| Stable deep response                                  | TFR attempt if ELN criteria met                                    | Dose halving for a year first (DESTINY)           | Monitor every 6–8 weeks for 6 months                      |
| Planning pregnancy (woman)                            | Deep response, then stop as for TFR                                | Stop at first positive test (MMR, regular cycles) | Interferon if counts need control; TKI only after week 16 |
| De novo accelerated phase                             | A 2G TKI                                                           | —                                                 | No TFR attempts                                           |
| Transformed accelerated phase                         | TKI by mutation, then allogeneic HCT                               | TKI alone if not eligible                         | Adherence and mutation test first                         |
| Myeloid blast phase                                   | TKI + AML-type induction (intensive or HMA ± venetoclax), then HCT | TKI alone (palliative)                            | See the AML module                                        |
| Lymphoid blast phase                                  | TKI + Ph+ ALL regimen (or TKI + blinatumomab/inotuzumab), then HCT | TKI + steroid if frail                            | Lumbar puncture; see the ALL module                       |

**Table C. Treatment options: evidence and best fit**

| Option             | Best fit                                        | Evidence                                                                                                         | Watch for                                                                       |
|--------------------|-------------------------------------------------|------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| Imatinib (generic) | Lower-risk CP; cost-limited care; CV disease    | <a href="#">IRIS<sup>[12]</sup></a> , <a href="#">IRIS 10-year<sup>[13]</sup></a> ; generic = innovator in India | Cramps, periorbital oedema, fluid retention, nausea, diarrhoea                  |
| Dasatinib          | High-risk CP; second line; pancreatitis history | <a href="#">CA180-Q34<sup>[23]</sup></a>                                                                         | Effusions, pulmonary hypertension, bleeding, QTc; avoid in lung disease         |
| Nilotinib          | High-risk CP without CV risk; second line       | <a href="#">ENESTnd<sup>[15]</sup></a>                                                                           | Arterial events, glucose and lipids, QTc, pancreatitis; twice daily, food rules |
| Bosutinib          | CV disease; second line                         | <a href="#">Gambacorti-Passerini 2014<sup>[25]</sup></a>                                                         | Early diarrhoea, liver enzymes; avoid in GI, liver or kidney disease            |
| Asciminib          | First line (FDA); after ≥2 TKIs; T315I          | <a href="#">ASC4FIRST<sup>[16]</sup></a> , <a href="#">ASCEMBL<sup>[27]</sup></a>                                | Lipase, hypertension; take without food; myristoyl-pocket mutations resist      |
| Ponatinib          | T315I; failure of a 2G TKI; blast phase         | <a href="#">PACE<sup>[31]</sup></a> , <a href="#">OPTIC<sup>[32]</sup></a>                                       | Arterial occlusion, hypertension, liver; reduce the dose once BCR::ABL1 <1%     |
|                    |                                                 |                                                                                                                  |                                                                                 |

| Option          | Best fit                                                    | Evidence                                                                                     | Watch for                                          |
|-----------------|-------------------------------------------------------------|----------------------------------------------------------------------------------------------|----------------------------------------------------|
| Interferon alfa | Pregnancy (any trimester)                                   | <a href="#">Chelysheva 2024</a> <sup>[42]</sup>                                              | Slow count control; molecular response not assured |
| Hydroxyurea     | Short cytoreduction before confirmation                     | <a href="#">Kockerols 2022</a> <sup>[19]</sup>                                               | Does not change milestones; teratogenic in animals |
| Allogeneic HCT  | Blast phase, transformed AP, failure of ponatinib/asciminib | <a href="#">Lübking 2019</a> <sup>[51]</sup> , <a href="#">Nicolini 2017</a> <sup>[29]</sup> | Early mortality 10–20%; GVHD; lifelong PCR after   |

**Table D. Managing problems during treatment**

| Problem                                                  | First steps                                                                   | Then                                                           | Points                                                                      |
|----------------------------------------------------------|-------------------------------------------------------------------------------|----------------------------------------------------------------|-----------------------------------------------------------------------------|
| Nausea, cramps, rash, oedema, diarrhoea, fatigue (early) | Symptomatic care; take imatinib and bosutinib with food; correct electrolytes | Brief interruption (5–7 days) or dose adjustment               | Usually settle; ask about lactose intolerance with diarrhoea                |
| Low counts in the first weeks                            | Continue if mild: it is the leukaemia clearing                                | Hold or reduce for severe cytopenias; growth factors rarely    | Avoid ESAs; transfusion for symptomatic anaemia                             |
| Breathless or coughing on dasatinib                      | Chest X-ray; look for effusion, pneumonitis, infection, heart failure         | Interrupt or reduce; drain if large                            | Recurrent effusions or pulmonary hypertension: switch for good              |
| Chest pain, claudication, TIA on nilotinib or ponatinib  | Urgent CV assessment                                                          | Stop that TKI; switch (imatinib, bosutinib or TFR if eligible) | Control BP, glucose, lipids, smoking from the start                         |
| QTc prolongation                                         | Correct potassium and magnesium; stop QT-prolonging drugs                     | Dose adjustment or switch                                      | ECG 1–2 weeks after starting nilotinib or dasatinib                         |
| Raised lipase or abdominal pain                          | Check lipase; image if symptomatic                                            | Reduce or hold; switch if it persists                          | Nilotinib, bosutinib, asciminib, ponatinib                                  |
| Bleeding or bruising on dasatinib                        | Platelet count; review antiplatelets and anticoagulants                       | Drug holiday usually enough                                    | Qualitative platelet defect with normal counts                              |
| Aches after stopping the TKI                             | Simple analgesia or an NSAID                                                  | Short steroid course occasionally                              | Withdrawal syndrome in 20–30%; usually self-limiting                        |
| Missed doses, cost or travel problems                    | Ask at every visit; involve family; patient-assistance programmes             | Simplify the schedule; generic options                         | Adherence ≤80%: no MMR (Marin 2010)                                         |
| New medicine or herb                                     | Check CYP3A4 interactions and QT effect                                       | Choose an alternative                                          | PPIs reduce dasatinib and nilotinib absorption (special formulations exist) |

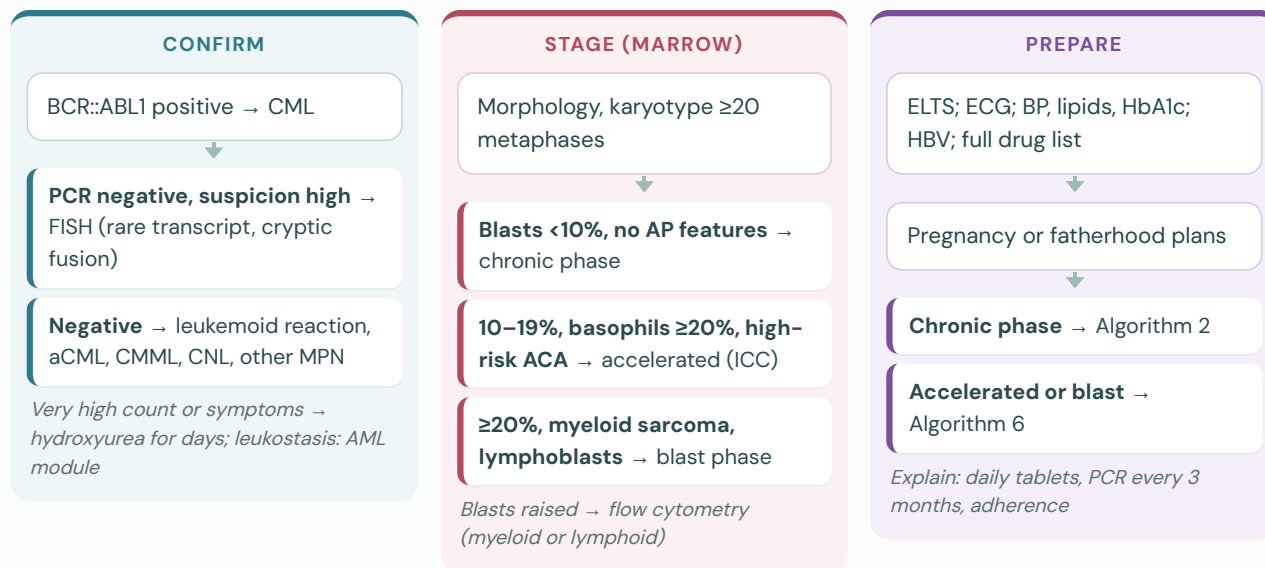
## 07 Management algorithms

Six decision paths pull together sections 02–06.

### ALGORITHM 1

### Suspected CML: from a high white count to a phase and a plan

**Leukocytosis with myelocytes and basophils, often a big spleen** → blood film; blood BCR::ABL1 (qualitative + quantitative PCR) or FISH; spleen size in cm before any hydroxyurea

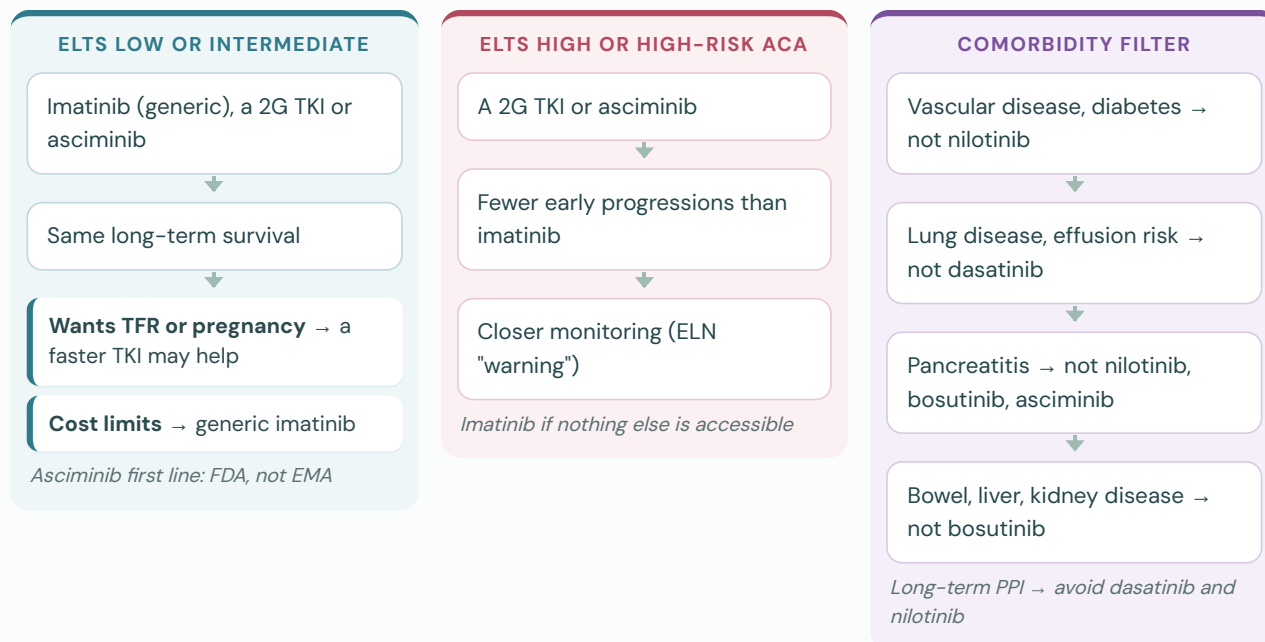


Before treatment: transcript type recorded · one IS-standardised laboratory for every PCR · drug access arranged (generic or assistance programme).

## ALGORITHM 2

## Chronic phase: choosing the first TKI

**Chronic phase confirmed** → ELTS risk, comorbidities, interacting drugs, goals (stopping, pregnancy), cost

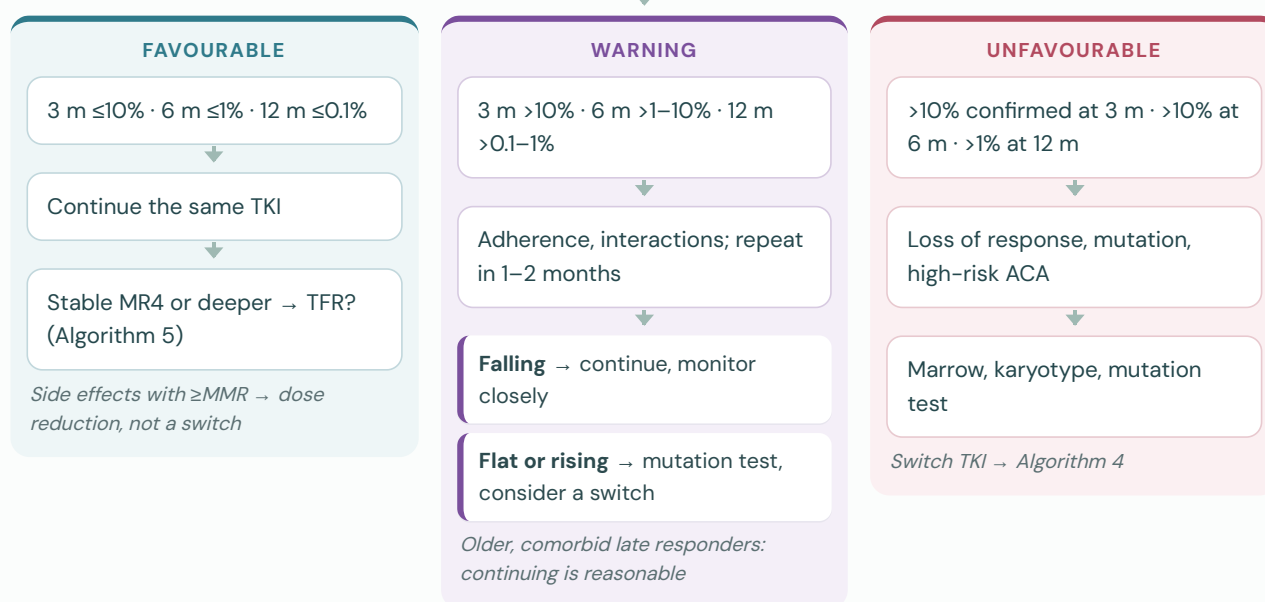


All: CBC every 2 weeks until CHR · BCR::ABL1 (IS) at 3, 6 and 12 months (Algorithm 3) · ECG 1–2 weeks after starting nilotinib or dasatinib · treat cardiovascular risk factors.

## ALGORITHM 3

## Monitoring: what to do with each BCR::ABL1 result

**BCR::ABL1 (IS) at 3, 6 and 12 months, then every 3–6 months in MMR** → compare with ELN 2025 milestones; look at the trend

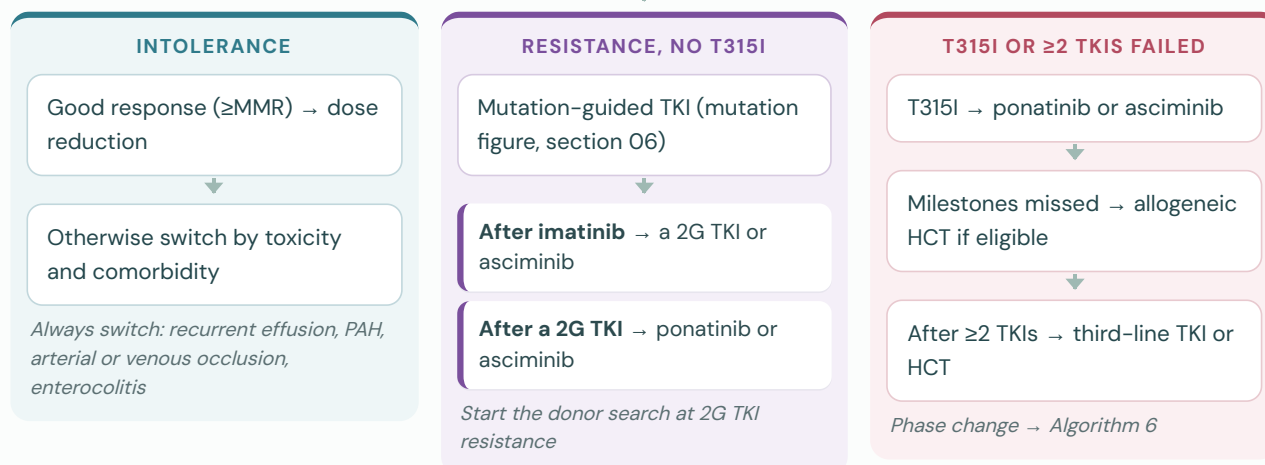


Same milestones for 2nd and 3rd line · a rising PCR without explanation is resistance until proved otherwise · confirm results near a threshold before acting.

## ALGORITHM 4

## Resistance or intolerance in chronic phase

**Off track or intolerant** → confirm with repeat PCR; adherence, interactions; marrow and kinase-domain mutation if resistant

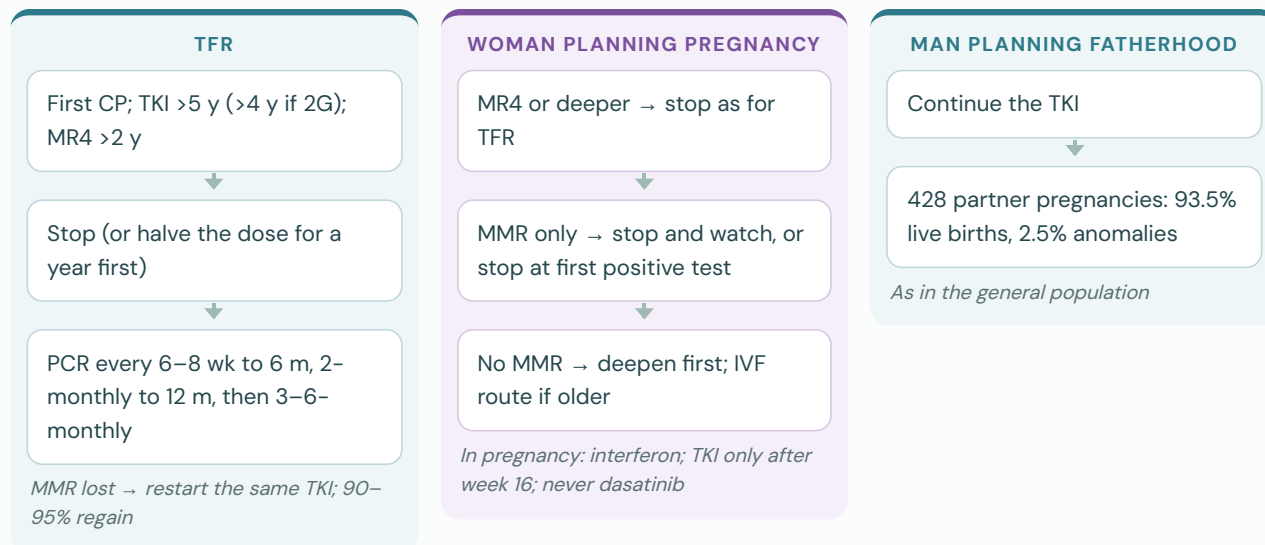


Response targets on 2nd and 3rd line are the same as first line · ASCSEMBL: asciminib beat bosutinib after ≥2 TKIs · India: check access to ponatinib and asciminib early.

## ALGORITHM 5

## Stopping treatment (TFR) and planning a pregnancy

**Stable deep response, or a wish for pregnancy** → ELN 2025 criteria; reliable IS PCR with fast results; an informed patient

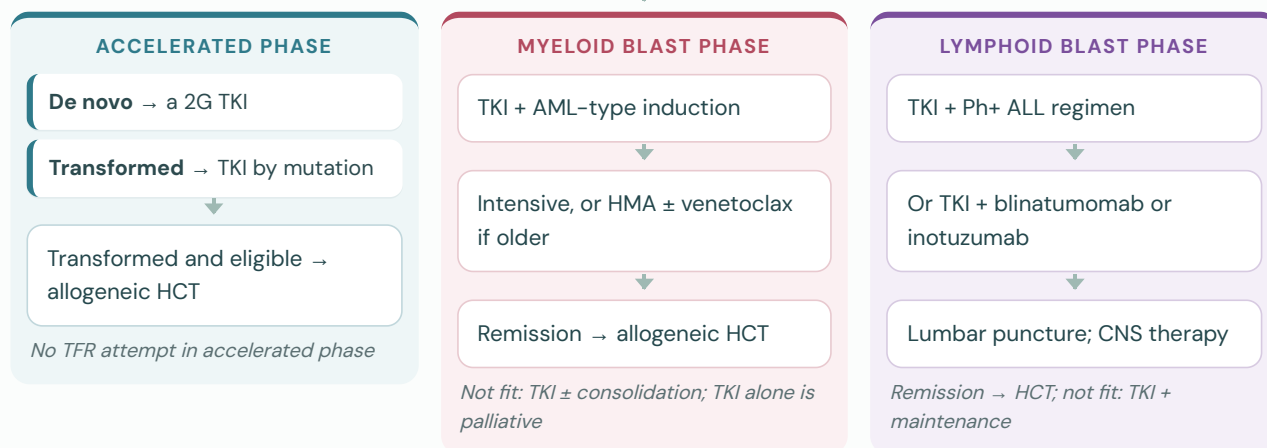


No TKI while breastfeeding · aches after stopping in 20–30% · children: stopping succeeds less often (STOP IMAPED: 28.6% at 6 months).

## ALGORITHM 6

## Accelerated and blast phase

**Accelerated or blast phase** (new or on a TKI) → marrow with flow cytometry and karyotype; kinase-domain mutation (NGS); fitness; HLA typing now



TKI by prior TKI and mutation, not lineage · avoid imatinib · T315I → ponatinib · leukostasis, tumour lysis, infection: AML module · Ph+ ALL regimens: ALL module.

## o8 Survivorship, follow-up & late effects

- **Lifelong follow-up:** PCR as in Algorithm 3 for as long as the TKI is taken, and lifelong after stopping or after transplant; blood pressure, glucose, lipids and symptoms of vascular disease at visits.
- **Quality of life:** patients over 60 on imatinib reported quality of life similar to their peers, but younger patients reported worse; one-third to one-half have symptoms that affect mood or daily life. Ask about fatigue, cramps, diarrhoea and mood; dose reduction in deep responders and treatment-free remission can help.
- **Adherence is treatment:** with  $\geq 90\%$  adherence 95% reached MMR at 6 years vs 28% below that, and none with  $\leq 80\%$  ([Marin 2010](#)<sup>[54]</sup>). In India non-adherence affects up to one-third and shortens event-free survival ([Ganesan 2011](#)<sup>[55]</sup>). Ask kindly and specifically; involve family; link to assistance programmes.
- **Long-term issues:** cardiovascular disease (nilotinib, ponatinib); hypophosphataemia and bone changes; gynaecomastia; thyroid (ponatinib); fertility and pregnancy planning; no excess of second cancers.
- **Children and adolescents** need growth, puberty, thyroid and bone surveillance and endocrinology input when growth falls (figure below; [Milot 2025](#)<sup>[56]</sup>).

### Children are different: CML in childhood is shown here only as a contrast

#### Children and adolescents

- Under 3% of childhood leukaemias
- Median age about 12; bulky disease (big spleen, very high WBC)
- Blast crises more often lymphoid
- TKI by ELTS group; transplant not first line
- Growth slows on imatinib: height, puberty, thyroid, bone
- Stopping succeeds less often

#### Adults

- Median age 66 in the US; 32–42 in Indian hospital series
- Comorbidity and cardiovascular risk shape TKI choice
- Blast crises mostly myeloid
- Pregnancy and stopping are planned from the start
- 40–50% stay off treatment after stopping

Registry of 535 children: 3-year OS 97.4%; 3-year PFS 97.1%, 91.7% and 72.0% for low, intermediate and high ELTS. Growth (German CML-PAED II): median height fell by 0.35 SD at 12 months and 0.76 SD at 24 months on imatinib, and only 18% grew normally between months 12 and 18; in Japan about a quarter ended below their target adult height. Growth failure on imatinib has also been reported from India (Bansal 2012).

Figure 19. Children vs adults (UpToDate chronic phase review; Milot 2025 and 2026; Stiehler 2024; Shima 2024 (JPLSG); COG CML Working Group 2019; Bansal 2012; Indian adult ages from Bansal 2013). Childhood CML belongs to the future Pediatric Oncology card.

### SHARE WITH PATIENTS: LIFE DURING AND AFTER TREATMENT

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

A normal blood count means leukaemia has completely disappeared?

If leukaemia returns after treatment, nothing can be done?

Leukaemia patients must avoid all physical activity and social contact?

Children cured of leukaemia can't lead normal adult lives?

## 09 Landmark trials

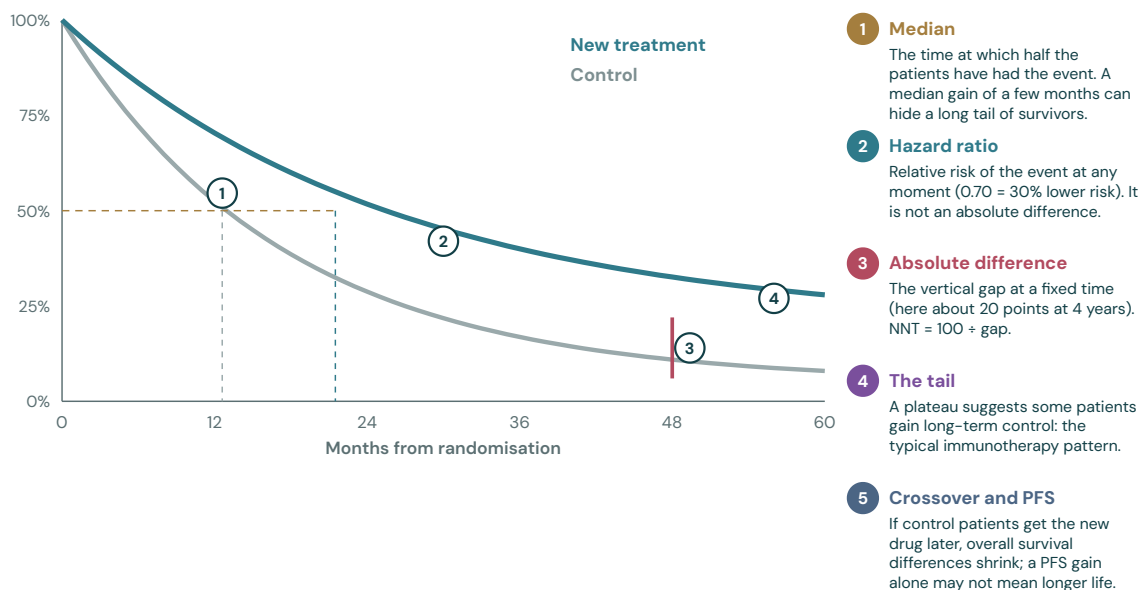
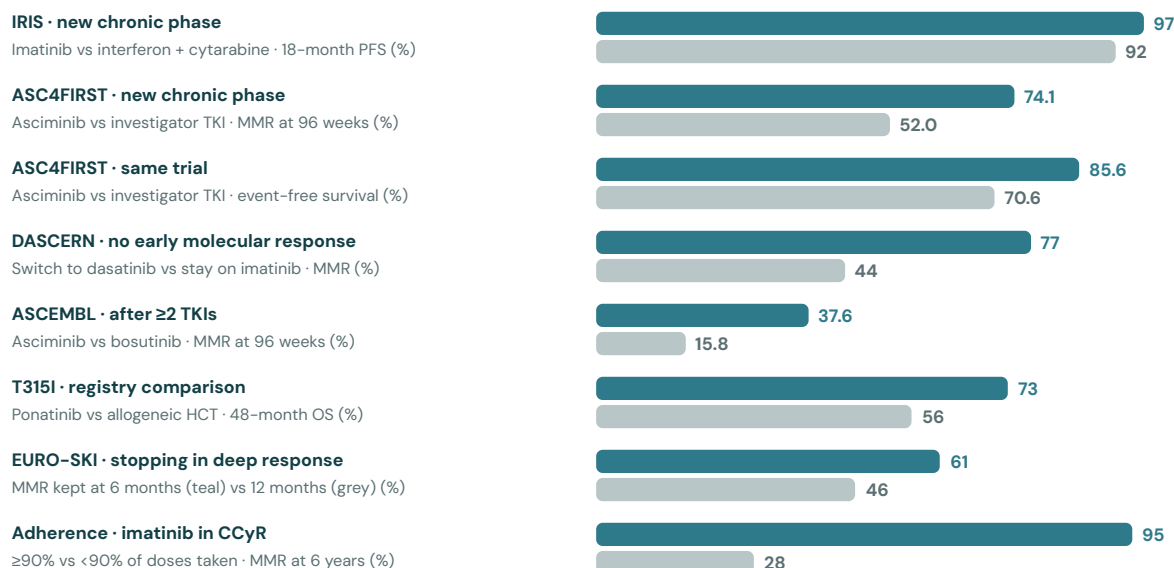


Figure 20. How to read a survival curve (illustrative). Use the absolute gap at a fixed time and overall survival, not the median or PFS alone, when weighing benefit against toxicity and cost.

### The trials behind today's choices



Grey = comparator unless stated. No first-line trial has shown an overall survival gain over imatinib.

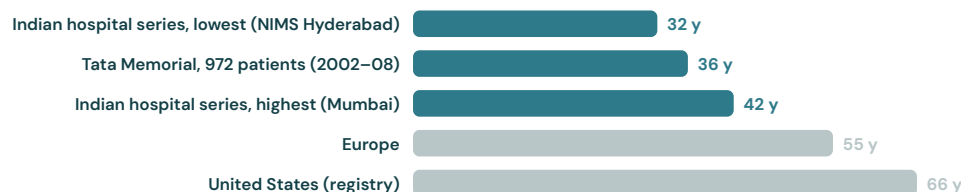
Figure 21. Landmark results (UpToDate chronic phase and after-failure reviews: O'Brien 2003, Cortes 2026, Hochhaus 2023, Nicolini 2017, Saussele 2018, Marin 2010; DASCERN as reported in ELN 2025).

- IRIS** (1106 patients): imatinib vs interferon + cytarabine; 18-month PFS 97% vs 92%; 10-year OS 84% ([O'Brien 2003](#)<sup>[12]</sup>).
- ENESTnd** (846): nilotinib vs imatinib; 33 progressions on imatinib vs 12 and 9 on the two nilotinib arms; more cardiovascular events on nilotinib ([Hochhaus 2016](#)<sup>[15]</sup>).

- **ASC4FIRST** (405): asciminib vs investigator-chosen TKI; MMR at 96 weeks 74.1% vs 52.0%; fewer grade  $\geq 3$  events and discontinuations ([Cortes 2026](#)<sup>[16]</sup>).
- **ASCEMBL**: after  $\geq 2$  TKIs, asciminib vs bosutinib; MMR 37.6% vs 15.8% at 96 weeks ([Hochhaus 2023](#)<sup>[28]</sup>).
- **PACE and OPTIC**: ponatinib works after 2G TKI failure and for T315I; response-based dose reduction lowers arterial risk ([PACE](#)<sup>[31]</sup>, [OPTIC](#)<sup>[32]</sup>).
- **EURO-SKI, LAST, DESTINY**: stopping is safe with monitoring; about half stay off treatment ([EURO-SKI](#)<sup>[34]</sup>, [LAST](#)<sup>[35]</sup>, [DESTINY](#)<sup>[38]</sup>).
- **India**: Tata Memorial (972 patients, median age 36): OS 86% at a median follow-up of 51 months, equal responses on generic and innovator imatinib ([Parikh 2013](#)<sup>[52]</sup>).

### CML in India: younger at referral, generics widely used, adherence and testing are the gaps

#### Median age at presentation (years)



#### Outcomes and care



Imatinib reached most Indian patients through a patient-assistance programme (GIPAP, Max Foundation) and generics; at Tata Memorial generic imatinib gave the same responses as the innovator. ELN 2025 puts generic imatinib at as little as US\$200–500 a year, often less than the yearly cost of monitoring. Second-line TKIs, standardised PCR and transplant remain hard to reach for many (Ganesan 2016).

Figure 22. Indian data (Bansal 2013 and the 2016 South Asian J Cancer summary of the IJMPO 2013 centre reports; Parikh 2013; Ganesan 2011 and 2016; ELN 2025). Hospital series, different eras: not comparable with population registries.

## 10 Practice pearls & pitfalls

- **"Resistance" is often missed tablets.** Ask at every visit, kindly and specifically, before ordering a mutation test.
- **Measure the spleen before hydroxyurea.** ELTS needs untreated values.
- **One laboratory, one scale.** Trends mean nothing if the laboratory or method changes.
- **Know the transcript.** p230 and rare transcripts are invisible to routine PCR: monitor with FISH or a personalised assay.
- **Never switch on one result.** Trend, adherence, interactions and the patient's goals come first.
- **After a 2G TKI fails, go to ponatinib or asciminib (or transplant),** not to another 2G TKI.
- **Lymphoblasts in a "chronic phase" patient** mean lymphoid blast phase until proved otherwise: flow cytometry and a lumbar puncture.
- **Unexplained falling platelets on treatment** can mean progression: marrow and karyotype.
- **Check every new prescription:** azoles, macrolides, PPIs and QT-prolonging drugs interact with dasatinib and nilotinib.
- **Talk about pregnancy at diagnosis** with every woman of child-bearing age; men can continue their TKI.
- **Loss of MMR after stopping: restart.** No mutation test is needed.
- **Generic imatinib is a legitimate first choice:** same long-term survival as newer TKIs at a fraction of the cost.

## 11 Case vignettes: lines of management

Nine cases from the clinic.

### CASE 1 Chronic phase · low ELTS · generic imatinib

#### A routine count before a hernia operation

34 years, man

WBC 86,000/ $\mu$ L

Spleen 4 cm

A 34-year-old shop owner from Nellore has a blood count before a hernia repair: WBC 86,000/ $\mu$ L with myelocytes, metamyelocytes and 6% basophils, 1% blasts; haemoglobin 12.1 g/dL; platelets 410,000/ $\mu$ L. He feels well; the spleen is 4 cm below the costal margin.

*Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?*

1

#### CONFIRM AND STAGE

Blood qualitative PCR: e14a2 (p210); baseline quantitative PCR on the International Scale. Marrow: chronic phase, 2% blasts; karyotype 46,XY,t(9;22) in 20 of 20 metaphases, no extra chromosomes.

2

#### RISK AND BASELINE

ELTS low. ECG, BP, lipids and HbA1c normal; hepatitis B negative; no interacting medicines. Surgery can wait until counts are controlled.

3

#### CHOOSE

Lower risk: imatinib, a 2G TKI or asciminib are all acceptable. He pays himself: generic imatinib with food, and a written plan for missed doses.

4

#### FOLLOW

CBC every 2 weeks to complete haematological response; BCR::ABL1 4% at 3 months, 0.6% at 6 and 0.07% at 12: favourable each time. PCR every 3–6 months; discuss stopping once criteria are met.

#### TEACHING POINTS

- Measure the spleen before any hydroxyurea: ELTS needs untreated values.
- Any first-line TKI gives the same long-term survival; generic imatinib costs least.
- Record the transcript type: monitoring depends on it.

**See:** Sections 03 and 06, Algorithms 1–3.

### CASE 2 High ELTS · diabetes · TKI choice

#### A big spleen and high sugars

56 years, woman

Spleen 14 cm

HbA1c 8.4%

A 56-year-old teacher from Ongole has had abdominal fullness and weight loss for 3 months. WBC 214,000/ $\mu$ L, 3% blasts, 8% basophils, platelets 780,000/ $\mu$ L; spleen 14 cm. She has diabetes (HbA1c 8.4%) and hypertension.

*Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?*

1

#### STAGE

Marrow: chronic phase (blasts <10%, basophils <20%, no extra chromosomes); transcript e13a2. ELTS high.

2

#### FIRST TKI

High risk favours a 2G TKI or asciminib. Diabetes and hypertension argue against nilotinib; with no lung disease, dasatinib is reasonable, bosutinib an alternative.

**3 BEFORE STARTING**

Hydroxyurea for a few days after samples and spleen measurement; ECG; correct potassium and magnesium; ECG again 1–2 weeks after starting dasatinib.

**4 LOOK AFTER THE VESSELS**

Glucose and blood pressure to target with her physician; lipids every 6–12 months; ask about chest pain and claudication at every visit.

**TEACHING POINTS**

- High ELTS: fewer early progressions with a 2G TKI or asciminib, same overall survival.
- Comorbidity chooses among the 2G TKIs.
- Cardiovascular risk factors matter whatever the TKI.

**See:** Section O6 (first TKI, side effects), Algorithm 2.

**CASE 3 Warning at 3 months · adherence****The tablets ran out**

29 years, man

BCR::ABL1 18% at 3 months

Generic imatinib

A 29-year-old construction worker from Gudur started generic imatinib for chronic phase CML (ELTS low). At 3 months BCR::ABL1 is 18% (IS). He admits stopping for 3 weeks while working in another town, where he could not refill his prescription.

*Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?*

**1 CLASSIFY**

BCR::ABL1 >10% at 3 months = warning (ELN 2025); unfavourable only if confirmed within 1–3 months.

**2 FIND THE CAUSE**

Missed doses explain it. Ask about side effects, cost, travel, alcohol, other medicines and herbs; involve his family; enrol him in an assistance programme with a pharmacy near his work.

**3 REPEAT**

PCR in the same laboratory after 4–6 weeks of regular tablets: 6%. At 6 months 0.8%: favourable.

**4 IF IT HAD NOT FALLEN**

Marrow karyotype, kinase-domain mutation test and a switch to a 2G TKI or asciminib by the result.

**TEACHING POINTS**

- Check adherence before declaring resistance.
- One result never decides a switch: follow the trend.
- Up to one-third of Indian patients miss doses, and it worsens outcome.

**See:** Section O6 (monitoring), section O8, Algorithm 3.

**CASE 4 Resistance · T315I****A rising PCR after two good years**

44 years, man

BCR::ABL1 0.9% → 2.4%

Imatinib, then dasatinib

A 44-year-old auto-rickshaw driver from Kavali reached MMR on imatinib and lost it after 3 years; no mutation was found and he switched to dasatinib. Over 6 months his BCR::ABL1 has risen from 0.9% to 2.4% despite regular tablets.

*Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?*

### 1 CONFIRM AND TEST

Repeat PCR confirms the rise. Marrow: chronic phase, no new extra chromosomes. NGS: T315I.

### 2 CHOOSE

T315I resists imatinib, dasatinib, nilotinib and bosutinib: ponatinib or asciminib (asciminib at a higher dose than usual). No vascular disease, so either is reasonable.

### 3 ACCESS

Availability and cost may be the barrier in India: involve the pharmacy and assistance programmes early, and record a fallback plan.

### 4 PREPARE TRANSPLANT

HLA-type him and his siblings now; if milestones are missed on ponatinib or asciminib, proceed to allogeneic HCT.

#### TEACHING POINTS

- After a 2G TKI fails, another 2G TKI rarely works.
- Begin the donor search at resistance to the first 2G TKI.
- For T315I, ponatinib gave better 48-month survival than transplant in a registry comparison (73% vs 56%).

**See:** Section O6 (resistance and mutation figure), Algorithm 4.

#### CASE 5 Dasatinib · pleural effusion

### Breathless on dasatinib

61 years, woman

MMR on dasatinib

Right effusion

A 61-year-old woman from Nellore, in MMR after 2 years of dasatinib, has had breathlessness and a dry cough for 3 weeks. Chest X-ray: a moderate right pleural effusion. No fever; echocardiography is normal.

*Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?*

### 1 EXCLUDE OTHER CAUSES

Infection, heart failure, kidney disease, progression: counts normal, still in MMR.

### 2 TREAT

Interrupt dasatinib; drain because she is breathless. Restart at a reduced dose once it settles; she stays in MMR.

### 3 IF IT RECURS

Recurrent effusion despite dose reduction → switch (imatinib, nilotinib, bosutinib or asciminib, chosen by comorbidity).

### 4 WATCH FOR PAH

Breathlessness without effusion on dasatinib → echocardiography for pulmonary arterial hypertension; if confirmed, stop dasatinib permanently.

#### TEACHING POINTS

- Up to one-third develop effusions on dasatinib; lower doses reduce the risk.
- In responders, reduce the dose before switching.
- Pulmonary arterial hypertension means stopping dasatinib for good.

**See:** Section O6 (side effects), Table D.

**CASE 6** Treatment-free remission

## Can I stop the tablets?

48 years, man

MR4.5 for 4 years

Imatinib for 7 years

A 48-year-old bank officer from Nellore has taken imatinib for 7 years; BCR::ABL1 has been undetectable at MR4.5 sensitivity in the same IS laboratory for 4 years. He asks to stop.

*Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?*

**1 ELIGIBLE?**

First chronic phase, e14a2, no resistance, more than 5 years of TKI, MR4.5 for more than 2 years: meets the ELN 2025 optimal criteria; results come back within 2 weeks.

**2 COUNSEL**

About half stay off treatment; most relapses come in the first 6–8 months; restarting works in 90–95%; aches in 20–30%.

**3 MONITOR**

PCR every 6–8 weeks for 6 months, every 2 months to 12 months, then every 3–6 months for life.

**4 OUTCOME**

At 5 months BCR::ABL1 0.15% (MMR lost): imatinib restarted; MR4 again by 4 months. A second attempt later is possible but less likely to succeed.

**TEACHING POINTS**

- Loss of MMR, not of MR4, triggers restarting.
- No mutation test is needed after loss of MMR in TFR.
- Aches after stopping are a withdrawal syndrome, not relapse.

**See:** Section O6 (treatment-free remission), Algorithm 5.

**CASE 7** Pregnancy

## Diagnosed at 10 weeks of pregnancy

25 years, woman

10 weeks pregnant

WBC 64,000/μL

A 25-year-old woman from Kavali, 10 weeks into her first pregnancy, has WBC 64,000/μL with myelocytes and basophils, platelets 520,000/μL and a spleen 3 cm below the costal margin. BCR::ABL1 is positive (e13a2). She feels well.

*Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?*

**1 STAGE AND RISK**

Marrow: chronic phase, no extra chromosomes; ELTS low.

**2 PLAN**

WBC <100,000/μL, low ELTS, no extra chromosomes: watchful waiting with counts and obstetric scans; no TKI in the first trimester.

**3 IF COUNTS RISE**

Interferon (usable throughout pregnancy) and/or leukapheresis; aspirin and/or LMW heparin if platelets climb. After week 16 imatinib (or nilotinib) can be started if needed; never dasatinib.

**4 AFTER DELIVERY**

Start a TKI after delivery; discuss breastfeeding versus starting treatment, since TKIs pass into breast milk.

**TEACHING POINTS**

- 76% of women diagnosed in pregnancy had a normal childbirth in the ELN registry.
- Organogenesis runs to about week 16: no TKI before then.
- No TKI while breastfeeding.

**See:** Section O6 (pregnancy and fertility), Algorithm 5.

**CASE 8** Lymphoid blast phase**Bone pain and lymphoblasts on imatinib**

22 years, man

Blasts 46%

TdT+, CD19+

A 22-year-old student from Gudur, on imatinib for 2 years with irregular follow-up, presents with bone pain and fever. WBC 58,000/ $\mu$ L with 46% blasts; platelets 31,000/ $\mu$ L.

*Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?*

1

**DIAGNOSE**

Flow cytometry: TdT+, CD19+, CD10+ blasts = lymphoid blast phase; BCR::ABL1 also in mature granulocytes (CML, not de novo Ph+ ALL). Karyotype: extra Ph, i(17q). NGS: no T315I.

2

**STABILISE**

Tumour lysis precautions, transfusion and infection care as for acute leukaemia (AML module, emergencies).

3

**INDUCE**

A TKI chosen by prior TKI and mutation (not imatinib) plus a Ph+ ALL-type induction; lumbar puncture with CNS-directed therapy.

4

**CONSOLIDATE**

HLA typing at diagnosis; allogeneic HCT in remission (median OS 93 vs 9 months with vs without transplant in one series); TKI restarted after engraftment.

**TEACHING POINTS**

- One-third of blast crises are lymphoid; they have more treatment options than myeloid ones.
- Choose the TKI by prior TKIs and mutation, not by lineage.
- Treat as Ph+ ALL: see the ALL module.

**See:** Section O6 (accelerated and blast phase), Algorithm 6, ALL module (Ph+ ALL).

**CASE 9** Child · contrast**A 12-year-old who stopped growing**

12 years, boy

Imatinib 2 years

Height falling

A 12-year-old boy from Ongole with chronic phase CML (WBC 310,000/ $\mu$ L and a 15 cm spleen at diagnosis) is in MMR after 2 years of imatinib, but his height has fallen from the 50th to the 15th centile.

*Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?*

1

**RECOGNISE**

Growth slowing on imatinib is common before and during puberty (German cohort: median height fell 0.76 SD by 24 months).

2

**ASSESS**

Paediatric endocrinology: growth velocity, puberty staging, thyroid function, bone health.

3

**DECIDE WITH A PAEDIATRIC CML CENTRE**

TKI choice per the 2025 international paediatric recommendations; transplant is not first line.

4

**LONG VIEW**

Stopping can be considered after a sustained deep response but succeeds less often than in adults; growth improved in some children during TKI breaks.

**TEACHING POINTS**

- Children present with bulkier disease than adults.
- Height, puberty, thyroid and bone must be followed in every child on a TKI.
- Childhood CML is shown here only as a contrast.

**See:** Section O8 (contrast figure).

## 12 References & guidelines

- European LeukemiaNet 2025 recommendations for CML; NCCN Guidelines: Chronic Myeloid Leukemia (current version); International Consensus Classification and WHO 5th edition (2022); international pediatric CML expert panel recommendations (chronic phase 2025, blast phase 2023).
- Cross-checked in October 2026 against 6 UpToDate topic reviews: chronic myeloid leukemia: pathogenesis, clinical manifestations, and diagnosis; overview of the treatment of chronic myeloid leukemia; chronic myeloid leukemia in chronic phase: initial treatment; treatment of chronic phase chronic myeloid leukemia after failure of the initial tyrosine kinase inhibitor; accelerated phase chronic myeloid leukemia: diagnosis and treatment; and chronic myeloid leukemia–blast phase: diagnosis and treatment. Trial citations come from the reference lists of these reviews, except the ELN 2025 recommendations (full text read), the pregnancy and paediatric papers and the Indian papers found and verified by web search on 17 October 2026, and the Indian series cited from the reference list of Ganesan and Kumar (2016).
- Reviewed and approved by Dr. Haritha Chiramana, 18 October 2026.

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Journal, year, volume and first page (or DOI); each links to PubMed.

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7. **ELTS vs Sokal (Pfirrmann 2020)**: 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 CML. *Leukemia* 2020;34:2138. [PubMed](#) [Diagnosis, risk and prognosis](#)
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Educational summary for health professionals, written in our own words from current guidelines and primary trials. No drug doses are given. Hodgkin, aggressive B-cell, indolent B-cell, T-cell and cutaneous lymphomas are parts 1–5, multiple myeloma is part 6, acute myeloid leukaemia part 7 and acute lymphoblastic leukaemia part 8; CLL is covered in the indolent B-cell module; other myeloproliferative neoplasms appear here only as differentials, and childhood CML only as a contrast. Verify current guidelines, Indian regulatory approvals and individual patient factors before treatment decisions.