Chronic Myeloid Leukaemia Guidelines

Approved by Pathway Board for Haematological Malignancies

Coordinating author: Heather Oakervee, Bart’s Health NHST

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These guidelines should be read in conjunction with the latest National Cancer Drug Fund information, and all applicable national/international guidance.

The prescribing information in these guidelines is for health professionals only. It is not intended to replace consultation with the Haematology Consultant at the patient’s specialist centre. For information on cautions, contraindications and side effects refer to the up-to-date prescribing information. While great care has been taken to see that the information in this section is accurate, the user is advised to check the doses and regimens carefully and if there is any uncertainty about the guidance provided, you should discuss your queries with a Haematology Consultant or Senior Pharmacist. No set of guidelines can cover all variations required for specific patient circumstances. It is the responsibility of the health care practitioners using them to adapt them for safe use within their institutions and for the individual needs of patients.
All patients presenting for investigation of possible haematological malignancies should undergo a full new patient bleed. This should include:

- FBC and film, Clotting, Group and Save, DAT, Ferritin and iron studies, Vitamin B12 and Folate
- U+E, LFT, bone, CRP, LDH, urate, autoimmune profile
- CMV IgG, VZV IgG, HBsAg, HbcAb, AntiHCV IgG, Anti HAV IgG, HIV 1&2
- Research bloods to local tissue bank and/or the SIHMDS tissue bank where appropriate consent has been obtained.

1.1 Investigation and Diagnosis

All patients presenting with CML should undergo the following investigations:

- Full clinical examination including
  - documentation of spleen and liver size in cm below the costal margin
  - presence of lymphadenopathy
  - Where possible documentation of spleen size by USS
- Full blood count and full manual differential
- Routine biochemistry – including U&E, LFTs, alb, Ca, LDH and urate
- Bone marrow aspirate (+/- trephine)
  - Aspirate to report: full differential including blasts and promyelocytes
  - Cytogenetics: for G banding and FISH for Bcr:Abl
  - Immunophenotyping
- Peripheral blood for RT-PCR for identification of transcript
  - This must be sent even if the diagnosis has already been confirmed on FISH/ G banding as required as a baseline for monitoring therapy.
- Tissue typing of patient and siblings for patients under 65 years only. This should be done for all patients with ‘warning signs at baseline or who do not achieve optimal responses but some centres may choose to type all patients and siblings especially if there may later be delays with obtaining samples for logistical reasons (e.g. live abroad)

1.2 Assessment of disease Status (WHO Criteria – ELN in Appendix 1)

Chronic Phase:
- Blasts <10% in bone marrow and peripheral blood;
- Peripheral blood basophils <20%;
- no other criteria of accelerated phase or blast crisis

Accelerated Phase:
- Blasts of 10-19% in blood or bone marrow
- Peripheral blood basophilia > 20%
- Persistant thrombocytopenia (<100) or thrombocytosis (>1000) unrelated to or unresponsive to therapy
- increasing WBC count unresponsive to therapy
- Cytogenetic evidence of clonal evolution

Blast Crisis
- Blasts >20% in bone marrow or peripheral blood
- Presence of extramedullary blastic disease
- Large foci or clusters of blasts in the bone marrow biopsy (if performed)
Prognostic Scoring Systems
All patients should have a HASFORD, SOKAL, and EUTOS score calculated at presentation.

HASFORD Score: 0.666 when age $\geq$ 50 + (0.042 x spleen) + 1.0956 when platelet count > 1500 x 10^9/l + (0.058 x blast cells) + 0.20399 when basophils > 3% + (0.0413 x eosinophils) x 100

Low Risk ≤ 780; Intermediate Risk 781-1480; High Risk >1480

SOKAL Score: 0.0116 x (age in years – 43.4) + 0.0345 x (spleen – 7.52) + 0.188 x [(platelet count/700)^2-0.563] + 0.0887 x (blast cells – 2.10)

Low risk < 0.8; Intermediate Risk 0.8-1.2; High risk >1.2

EUTOS Score: Spleen x 4 + basophils x 7
Low risk ≤ 87; High risk >87

An online calculator can be found at
Hasford and Sokal: [http://www.leukemia-net.org/content/leukemias/cml/cml_score/index_eng.html](http://www.leukemia-net.org/content/leukemias/cml/cml_score/index_eng.html)

Eutos: [http://www.leukemia-net.org/content/leukemias/cml/eutos_score/index_eng.html](http://www.leukemia-net.org/content/leukemias/cml/eutos_score/index_eng.html)

Hasford and Sokal scores predate the introduction of TKI therapy but have been validated in the post TKI era.
Management of Patients

General Management and Supportive Care

In the main patients with CML present as outpatients and most do not require admission for investigation unless they have a specific complication requiring such, irrespective of WBC. They do however, requiring very frequent outpatient or day unit review (up to daily) during the initial induction.

- All patients must be discussed in a compliant MDT.
- Patients under 25 years old must also be discussed in the TYA MDT.
- Local, network and BCSH guidelines should be followed for blood product support, use of growth factors and management of neutropenia.
- All patients should receive allopurinol to reduce the risk of tumour lysis syndrome. This can be discontinued following cytoreduction. In patients with very high WBCs then consideration to iv hydration maybe necessary.
- Patients should have a named keyworker and should have appropriate psychological support.
- Adherence to therapy is critical in achieving and maintaining response. Adherence often falls after initial diagnosis and attention should be paid to ensuring patients maintain adherence to their treatment schedule.
- Women should be advised to use adequate contraception whilst on TKIs and discuss planning of pregnancy with their physician or keyworker.
- Consideration should be given to offering men sperm banking at presentation. If not done at presentation then this must subsequently be offered to those few who require chemotherapy and/or allogeneic transplantation.

Management of leucostasis

- Therapeutic leucopheresis should be considered in patients with life threatening or organ threatening symptoms of leucostasis – such as deteriorating conscious level, priapism, retinal vein engorgement/haemorrhage.
- Leucopheresis provides only a temporary reduction in white count and should not delay cytoreductive therapy; the risks of leucopheresis should be assessed against any potential benefit.
- Cytoreduction with hydroxyurea can provide rapid count control (although high doses such as 4g bd maybe required).
- Physicians may choose to initiate cytoreduction in patients with CML whilst awaiting confirmation of the diagnosis but it is not necessary to cytoreduce patients prior to the introduction of a TKI.

Aims of therapy

- Attainment of Complete Cytogenetic Remission remains the Gold Standard; attainment of major molecular response is sought after at least 18 months of therapy.

Monitoring therapy (See Table 1)

ELN recommend that:

- All patients should receive RT-PCR for Bcr:Abl at 3 months and thereafter at 3 monthly intervals indefinitely, provided this is an informative test at presentation.
- All patients should have a bone marrow performed at 3, 6 and 12 months. Once patients have achieved a Complete Cytogenetic Remission (CCyR) this should be repeated every 12 months. Consideration could be given to use of peripheral blood FISH for patients in known CCyR.

In practice

- All patients must have RT-PCR at 3 months. Bcr:abl monitoring should not be undertaken prior to 3 months as it is uninformative.
- If this meets optimal response criteria (Bcr:abl <10%) and the patient is known to have a reliable marker for molecular monitoring then some physicians and patients may reasonably choose to delay the BM Cytogenetic assessment to 6 months to improve the likelihood of documenting a CCyR as criteria for failure at 3 months are Ph+ve >95%.
- All patients must have at least one bone marrow cytogenetic assessment documenting CCyR. However, if patients have an informative RT-PCR then many patients elect to be followed on RT-PCR only, although the gold standard remains annual bone marrow cytogenetic assessment. If patients opt out of bone
marrow assessment then a bone marrow should be triggered by a rise in Bcr:abl of 0.5 log on 2 occasions or failure to achieve response milestones.

**Mutation analysis**
- Should be performed in any patient failing to achieve any defined milestone, loss of CCyR or a rising Bcr:Abl ratio (on 2 occasions)

**Measurement of Response**
- Complete Haematological Response
  - Platelet count <450; WBC <10; No immune granulocytes in PB, basophils <5%; no palpable spleen
- Cytogenetic Responses – these should be assessed by G-bandng and at least 20 metaphases analysed; FISH should only be used for assessment of CCyR when at <1% of nuclei are positive and at least 200 nuclei have been assessed.
  - Complete (CCyR): No Ph+ve metaphases or <1% Bcr:Abl +ve nuclei when 200 nuclei analysed
  - Partial (PcyR): 1-35% Ph+ve metaphases
  - Minor: 36-65% Ph+ve metaphases
  - Minimal: 66-94% Ph+ve metaphases
  - No Cytogenetic response : >95% Ph+ve metaphases
- Molecular Response
  - This is best assessed according to the International Scale (IS) as the ratio of BCR-ABL1 transcripts to ABL1 transcripts and is expressed and reported as BCR-ABL1 % on a log scale as a reduction below the standard baseline.

<table>
<thead>
<tr>
<th>Bcr:Abl1%</th>
<th>Log Reduction</th>
<th>Corresponding Response</th>
<th>Minimal no of ABL transcripts required for assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.1</td>
<td>3</td>
<td>MMR (MR&lt;sup&gt;3.0&lt;/sup&gt;)</td>
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</tr>
<tr>
<td>0.01</td>
<td>4</td>
<td>MR&lt;sup&gt;4.0&lt;/sup&gt;</td>
<td>10000</td>
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<tr>
<td>0.0032</td>
<td>4.5</td>
<td>MR&lt;sup&gt;4.5&lt;/sup&gt;</td>
<td>32000</td>
</tr>
<tr>
<td>0.001</td>
<td>5</td>
<td>MR&lt;sup&gt;5.0&lt;/sup&gt;</td>
<td>100000</td>
</tr>
</tbody>
</table>

**Definitions of deep responses**
- BCR-ABL1 Ratio of ≤0.1% corresponds to a major molecular response
- MR<sup>4.0</sup> is defined as either:
  - detectable disease with <0.01% BCR-ABL1 (IS) or
  - undetectable disease in cDNA with > 10,000 ABL transcripts
- MR<sup>4.5</sup> is defined as either:
  - detectable disease with <0.032% BCR-ABL1 (IS) or
  - undetectable disease in cDNA with > 32,000 ABL transcripts
- The term Complete Molecular Remission should not be used
- Patients with undetectable transcripts should be referred to as having 'molecularly undetectable leukaemia' with the specification of the number of the control gene transcript copies.

**First line therapy**

**Chronic Phase**
All patients should be enrolled where possible into a clinical trial. Centres, where a trial is not available should consider referral to a open centre.

For patients ineligible for a clinical trial or where a trial is not available:
- Imatinib 400mg and Nilotinib 300mg bd are both approved by NICE for first line therapy.
- At present no survival difference between the two has been demonstrated.
Most patients (>70%) will achieve a Major molecular response with imatinib and as such is generally recommended as first line for initial therapy
- Subgroups of patients who may derive more benefit from initial use of a second generation TKI may include those with a high SOKAL score at presentation or those patients who may require a treatment free interval in the foreseeable future (e.g. for pregnancy) as second generation TKIs achieve deeper responses more rapidly.

Patients require at least fortnightly (initially weekly) counts for the first 2 months of therapy. Treatment should be interrupted if Neutrophils <1x10^9/l or platelets <50x10^9/l. Generally the same dose can be reinstated but if cytopenias recur or take more than 2 weeks to recover then a dose reduction maybe required. Isolated neutropenia maybe treated with G-CSF.

For directions regarding safety monitoring, dose modifications, interactions and dietary requirements please see Tables 4,5, and 6.

Table 2 summarises the ELN response criteria. Patients in the warning area should be followed more closely to ensure they do not meet failure criteria.

To have confirmed loss of MMR; this must be seen in two consecutive tests, of which one must have a BCR:ABL1 transcript ≥ 1%.

Second line and subsequent line therapy for Chronic Phase CML

Indications
- Patients may be switched for either treatment failure or intolerance.
- All patients should have a mutation analysis sent prior to switching to allow informed decision prior to switching.
- In cases of treatment failure, physicians should ensure that adherence to treatment is not the cause of failure. Poor adherence maybe due to intolerance or maybe due to frequent drug interruptions for toxicities

Treatment failure
- Patients meeting the ELN criteria for failure (Table 2) should be switched to an alternative TKI.

Intolerance to therapy
- A patient is deemed to be intolerant to a TKI if one or more of the following criteria are met:
  - Any life threatening Grade 4 non-haematological toxicity
  - Any Grade 3 or 4 non-haematological toxicity that persists despite dose reduction and optimal symptomatic measures.
  - Grade 3 or 4 haematological toxicity that is unresponsive to supportive measures and would require dose reduction below the accepted minimal effective dose.
  - Any combination of non-haematological toxicities of any grade that persist despite supportive measures and in the patients and physician’s opinion compromise quality of life to such an extent that a change of therapy is justified.

Choice of Second line therapy
- Treatment choice is dependant on mutation analysis and availability of funded treatments.
- For patients treated with imatinib first line, nilotinib is approved by NICE for use as second line for treatment failure or intolerance.
- There is currently no NICE approved 2nd line therapy for patients treated with nilotinib as first line or those treated with Dasatinib in first line (e.g. part of SPIRIT-2).
- Dasatinib, Ponatinib and Bosutinib are funded in certain circumstances via the Cancer Drugs Fund.
- All applications to the CDF must have been agreed by the MDT and the patients treatment must be managed under the supervision of a haemat-oncologist, competent in the use of systemic anti-cancer therapy.

CDF Criteria for Dasatinib in patients with Chronic Phase CML
- Patient has documented resistance or intolerance to Imatinib
- Patients meets ELN criteria for imatinib failure or has Grade 3 or 4 adverse events when treated with imatinib
• Patients has previously not been treated with nilotinib but has resistance to imatinib associated with a tyrosine kinase domain mutation known to be resistant to nilotinib i.e. F359C/V or Y253H or the patient has experienced Grade 3 or 4 adverse events when treated with nilotinib.

• **CDF Criteria for Bosutinib in patients with Chronic Phase CML**
  • Patient has documented resistance or intolerance to Imatinib
  • Patients meets ELN criteria for imatinib failure or has Grade 3 or 4 adverse events when treated with imatinib
  • Patients has previously not been treated with nilotinib but has resistance to imatinib associated with a tyrosine kinase domain mutation known to be resistant to nilotinib i.e. F359C/V or Y253H or the patient has experienced Grade 3 or 4 adverse events when treated with nilotinib.
  • Patient has intolerance to Dasatinib (Grade 3 or 4 event)
  • Patients are refractory to Nilotinib or Dasatinib

• **CDF Criteria for Ponatinib in patients with Chronic Phase CML**
  • Any patient with a documented T315I mutation.

**Common Side effects and monitoring of patients**
A schedule for monitoring of these patients is set out in Table 4. For simplicity a single monitoring schedule is recommended. Table 6 lists links to the SPC for up to date side effect profiles and guides to dose moditification.

• **Imatinib**
  o Standard dose 400mg od
  o Most widely used and greatest information on safety profile
  o Most common side effects – nausea, fatigue (usually after long duration of therapy), periorbital oedema, and more rarely bone pain.
  o Can be taken with or without food but nausea generally improved by taking after meals

• **Nilotinib**
  o Standard dose for newly diagnosed patients is 300mg bd and for 2nd line patients 400mg bd
  o Medication needs to be taken at strictly at 12 hour intervals following a 2 hour fast and 1 hour prior to any food. There are food interactions e.g. grapefruit, starfruit, Seville oranges.
  o Prolongation of QTc is reported and ECG monitoring at the commencement of therapy is required.
  o There is an increase in cardiac events in patients on nilotinib and careful attention needs to be paid to ensuring Blood pressure is well controlled and other cardiac risk factors are monitored and managed (e.g. cholesterol, blood glucose)
  o Rash is common at commencement and often subsides.

• **Dasatinib**
  o Standard dose is 100mg od
  o Main side effects are pleural effusions and rarely pericardial effusions, which should be looked for if the patient has relevant symptoms.
  o If these occur then patients can usually continue on the medication but may require interruption and a dose reduction.

• **Bosutinib**
  o Standard dose is 500mg od (max is 600mg od)
  o If switching for intolerance of 2 other TKIs then consideration maybe given to starting at a lower dose (e.g. 200mg) and slowly incrementing.
  o Main side effects are GI toxicity

• **Ponatinib**
  o Usual dose 45mg od
  o Rash is a common side effect
  o There are considerable concerns regarding arterial and venous thrombotic events and other risk factors should be minimised where possible.

**Switching between TKIs**
A wash out of up to 2 weeks (generally >1 week) is recommended when switching between imatinib and dasatinib. When switching between other TKIs this is not mandated but in practice a short wash out (generally a week) is given to most patients.
Referral to Specialist Centre

- All patients failing a second generation TKI should be referred to the local Level 3 centre – ie. Following nilotinib if used first line, or following imatinib and nilotinib if imatinib used first line.
- Patients with significant toxicity should be discussed and/or referred to the local Level 3 centre as intolerance may be manageable with dose reductions.

Allogeneic Haematopoetic Stem Cell Transplantation in Chronic Phase CML

- Allogeneic HSCT remains the only curative therapy in CML but is associated with the risk of significant procedure related morbidity and mortality and is dependent on the identification of a suitable donor. It should generally only be considered in patients <65 years old as the morbidity rises significantly following this.
- Tissue typing of siblings and patient should occur at presentation in patients who may be suitable candidates for allogeneic transplantation with Warning features; and at failure of 1st line TKI.
- Patients failing second generation TKIs at 1st or 2nd line, who are intolerant of two TKIs or who have a T315I mutation should have an unrelated donor search if no family donor is identified and consideration given to allogeneic transplantation.

Treatment discontinuation

- There are numerous trials ongoing at present aiming to ascertain if patients in deep molecular responses can safely discontinue therapy.
- At present, patients who are responding optimally to therapy, outside of a clinical trial should continue therapy indefinitely.
- There will be exception patients, who for a variety of reasons, have to stop therapy. Such patients should be monitored monthly.

Accelerated Phase and Blast Crisis CML

- Patients presenting with accelerated phase CML are considered to be biologically similar to high risk chronic phase and treatment with TKIs are a priority.
- In patients progressing to AP or BC during any TKI therapy the response to any treatment is poorer and less durable so allogeneic stem cell transplantation is recommended for all eligible patients.

- **AP and BC in newly diagnosed TKI naïve patients**
  - Imatinib 400mg bd or Dasatinib 70mg bd or 140mg od
  - Allogeneic donor search
  - Allogeneic stem cell transplant for all patients in BC and in patients in AP who do not achieve an optimal response.
  - Chemotherapy maybe required before alloSCT to control disease. This would usually be an AML induction regimen for patients in myeloid blast crisis and an ALL induction regimen for patients in Lymphoid blast crisis.

- **AP and BC as progression from CP in patients on TKIs**
  - Any of the TKIs not previously used
  - Check for mutations - ponatinib should be given to patients with T315I mutations
  - Proceed to allogeneic SCT in all eligible patients
  - AML or ALL chemotherapy is frequently required to make patients eligible for SCT.

Pregnancy and other special circumstances

- **Male patients wishing to father a child**
  - There does not appear to be any increase in risk to the child but many centres still recommend stopping for 2-3 months prior to attempted conception. There is increasing consensus that this may not be necessary and many centres no longer recommend any period off therapy. In part this decision will be informed by the degree of risk acceptable to the patient in terms of stopping therapy and risk to the child.

- **Women wishing to concieve**
  - Imatinib carries a significant risk of foetal abnormalities and miscarriage (approximately 25%)
  - Patients should stop imatinib prior to trying to conceive. There is variation in the period that patients are recommended to be off therapy prior to attempting conception. Many centres recommend 3 months,
although some centres suggest that 7-10 days is sufficient.

- Ideally this should occur when patients have been in at least an MR3 (MR4 is preferable) for at least 2 years.
- Patients should undergo close monitoring with monthly RT-PCR analysis
- Consideration should be given to commencement of interferon if the RT-PCR transcript levels start to rise.

- Women who become pregnant whilst on TKIs
  - Should be advised to discontinue TKIs immediately
  - Should be advised of the risk of miscarriage, stillbirth and congenital abnormalities.
  - The risk is less well known with 2nd generation TKIs but is thought to be higher.
  - Women should be given the option of termination of pregnancy or continuation.
  - Women electing to consider continuing their pregnancy should be referred to a high risk obstetric clinic as soon as possible for assessment of foetal viability and a subsequent anomaly scan so they can make an informed decision at the end of the 1st Trimester.

- Patients presenting in pregnancy
  - Should be managed jointly between a haemato-oncologist and an obstetrician with the full involvement of the mother.
  - Appropriate consideration should be given to the early delivery of the baby.
  - It is desirable that there is some attempt to control the WBC and platelet count in pregnancy. Hydroxycarbamide is teratogenic in animals and occasional stillbirths and congenital abnormalities have been reported. It should therefore be avoided. Alternative treatments include α-interferon, which is known to be safe in pregnancy, and leucopheresis. This is the most widely used technique.
  - Based on published evidence, a reasonable recommendation for the management of CML in first chronic phase presenting in pregnancy would be:
    - Initial leucopheresis to control the white count, together with allopurinol and aspirin therapy, especially if there is associated thrombocytosis.
    - Instigation of α-interferon to maximum tolerated dose to control WBC <60x10^9/l and platelets <400 x10^9/l until delivery.
    - No precautions need to be taken at delivery assuming stable blood counts. Normal vaginal delivery should be possible.
  - Management of patients presenting in pregnancy in accelerated phase or blast crisis will require management and options discussed on an individual basis. Fortunately, this is a rare event.

- Breastfeeding
  - Breastfeeding is contraindicated in patients on TKIs.

London Cancer CML Guidelines 2015-16 v1.0
Table 1: ELN Guidelines for monitoring therapy

<table>
<thead>
<tr>
<th>Timepoint</th>
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</table>
| At Diagnosis       | • Metaphase Cytogenetics by G banding  
                    • FISH – especially if Ph_ve, to identify variant cryptic translocations  
                    • Qualitative PCR – for identification of transcript type |
| During treatment   | • Quantitive, realtime PCR (RQ-PCR) for the determination of BCR/ABL1 transcript level on the iterations acale, to be performed every 3 months until MMR (BCR-ABL <0.15, or MR3.0, then every 3 to 6 months,  
                    • CBA of marrow cells metaphases (at least 20 banded metaphases), to be performed at 3,6,12 months until a CcyR has been achieved, then every 12 months. Once a CcyR is achieved FISH on blood cells can be used. IF an adequate molecular monitoring can be assured then cytogenetics can be spared. |
| Failure            | • RQ-PCR, mutational analysis, and CBA of marrow cell metaphases  
                    • Immunophenotyping in blast crisis |
| Warning            | • Molecular and cytogenetics to be performed more frequently.  
                    • CBA of bone marrow metaphases recommended in case of myelodysplasia or Clonal chromosome abnormalities in Ph negative cells with chromosome 7 |
Table 2: ELN Guidelines for Definition of Response to TKIs in first line

<table>
<thead>
<tr>
<th></th>
<th>Optimal</th>
<th>Warning</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>N/A</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>3 months</td>
<td>BCR:ABL1 ≤10%; +/- Ph+ve ≤35%</td>
<td>BCR:ABL1 &gt;10% Ph+ve 36-95%</td>
<td>No CHR achieved +/- Ph+ve &gt;95%</td>
</tr>
<tr>
<td>6 months</td>
<td>BCR:ABL1≤1% and CCyR</td>
<td>BCR:ABL1 1-10% +/- PH+ve 1-35%</td>
<td>BCR:ABL &gt;10% Ph+ve &gt;35%</td>
</tr>
<tr>
<td>12 months</td>
<td>BCR:ABL1≤ 0.1%</td>
<td>BCR:ABL 0.1-1%</td>
<td>BCR:ABL &gt;1% No CCyR</td>
</tr>
<tr>
<td>Then at any time</td>
<td>BCR:ABL1≤ 0.1%</td>
<td>CCA in Ph-ve cells (-7 or -7q)</td>
<td>Loss of CHR Loss of CCyR Confirmed loss of MMR Mutations CCA in Ph+ve cells</td>
</tr>
</tbody>
</table>

Confirmed loss of MMR must be seen in two consecutive tests, of which one must have a BCR:ABL1 transcript ≥ 1%
Table 3: ELN Guidelines for Definition of response to 2\textsuperscript{nd} line therapy, following failure of imatinib

<table>
<thead>
<tr>
<th></th>
<th>Optimal</th>
<th>Warning</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>N/A</td>
<td>• No CHR or loss of CHR on imatinib</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lack of CyR to 1\textsuperscript{st} line TKI</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• High Risk</td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>BCR:ABL ≤ 10%;</td>
<td>BCR:ABL &gt;10%</td>
<td>No CHR achieved</td>
</tr>
<tr>
<td></td>
<td>+/- Ph+ve &lt;65%</td>
<td>Ph+ve 65-95%</td>
<td>+/- Ph+ve &gt;95% or New mutations</td>
</tr>
<tr>
<td>6 months</td>
<td>BCR:ABL ≤ 10% and/or Ph+ve ≤ 35%</td>
<td>Ph+ve 35-65%</td>
<td>BCR:ABL &gt;10% and/or New mutations</td>
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<tr>
<td>12 months</td>
<td>BCR:ABL ≤ 0.1% and/or Ph+ve 0</td>
<td>BCR:ABL 1-10% and/or Ph+ve 1-35%</td>
<td>BCR:ABL &gt;10% and/or New mutations</td>
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<tr>
<td>Then at any time</td>
<td>BCR:ABL ≤ 0.1%</td>
<td>CCA in Ph-ve cells (-7 or -7q) or BCR:ABL &gt;0.1%</td>
<td>Loss of CHR</td>
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<td>Loss of CcyR or PCyR</td>
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<td>Confirmed loss of MMR</td>
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<td>New Mutations</td>
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<td></td>
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<td>CCA in Ph+ve cells</td>
</tr>
</tbody>
</table>

Confirmed loss of MMR + in two consecutive tests, of which one must have a BCR:ABL1 transcript ≥ 1%
**Table 4: Safety monitoring of patients on TKIs.**

Prior to treatment: ECG, Echo, lipid profile, glucose, amylase, CK, FBC, U&E, LFT, Bone

Weekly in first month on treatment: ECG, FBC, U&E, LFT, Bone

Monthly for next 2 months: ECG, FBC, U&E, LFT and Bone, glucose amylase, CK

3-4 monthly: Lipids, glucose, amylase, CK, FBC, U&E, LFT, Bone

All patients should have blood pressure checked at all visits
CXR should be performed in all patients who are SOB for assessment of pleural effusion
Consideration should also be given to repeat Echo – for exclusion of pericardial effusion and reassessment of left ventricular function as this can be affected by all TKIs.
Table 5: Links to Summary of Medicinal Products and Adverse event listing

<table>
<thead>
<tr>
<th>Medication</th>
<th>Link</th>
</tr>
</thead>
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Appendix 1

List of Criteria for the definition of Accelerated Phase and Blast Crisis

Accelerated Phase

ELN Criteria:  - Blasts in blood or bone marrow 15-29% or blasts plus promyelocytes in blood or marrow >30% with blasts <30%
  - Basophils in blood ≥ 20%
  - Persistant thrombocytopenia (<100x10^9/l) unrelated to therapy
  - Clonal Chromosome abnormalities in Ph+ve cells (CCA/Ph+ve), major route, on treatment

WHO Criteria:  - Blasts in blood or marrow 10-19%
  - Basophils in blood ≥ 20%
  - Persistant thrombocytopenia (<100x10^9/l) unrelated to therapy
  - CCA/Ph+ve on treatment
  - Thromobocytosis (>1000x10^9/l) unresponsive to therapy
  - Increasing spleen size and increasing WBC unresponsive to therapy

Blast Phase

ELN Criteria:  - Blasts in blood or marrow ≥ 30%
  - Extramedullary blast proliferation, apart from spleen

WHO Criteria:  - Blasts in blood or marrow ≥ 20%
  - Extramedullary blast proliferation, apart from spleen
  - Large foci or clusters of blasts in the bone marrow biopsy