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Greater Manchester Cancer

Diagnosis and Management of Chronic Myeloid Leukaemia

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1.0 Introduction

CML occurs with an incidence of approximately 1-1.5 in 100 000/year. More recent studies estimate survival rates for CML at approximately 90% at 5 years. Mortality rates have decreased by ~70% in the UK since the early 1970s. This is largely due to the introduction of tyrosine kinase inhibitors (TKIs) which have revolutionised therapy for CML. However TKIs present challenges in terms of monitoring, toxicity and discussions regarding withdrawing treatment.

2.0 Investigation and Diagnosis

All new patients presenting with CML should have the following examinations and investigations:-

Examination

- Full clinical examination including documentation of spleen and liver size below the costal margin
- Check for retinal haemorrhages
- Check for priapism (males) & any other signs of vascular stasis

Blood Tests

- Full blood count with manual differential
- Routine biochemistry including U&E, LFTs, alb, calcium, LDH and urate
- Peripheral blood for RT-PCR for identification of BCR-ABL transcript. This must be performed even if diagnosis has been confirmed by FISH/G banding as it is used as a baseline for monitoring treatment.
- Virology including Hepatitis B & C, HIV

Bone Marrow Aspirate (+/- trephine)

- Differential analysis, including blast percentage
- Chromosome banding analysis/cytogenetics for G banding and FISH for BCR-ABL
- Consider immunophenotyping where morphology suggests elevated blast percentage

Cytogenetic analysis and FISH are performed by the Cytogenetics Laboratory at The Christie NHS Foundation Trust. RT-PCR for BCR-ABL can be performed on 10 ml EDTA-anticoagulated blood sent by first class post to Molecular Genetics Lab, Department of Haematology, CMFT (0161 276 8034).

If allogeneic HSCT is being considered:

- HLA typing of patient and siblings.
- Consider volunteer unrelated donor (VUD) search.

Where possible, register the patient with local/regional CML patient registry- see http://nww.rlbuht.nhs.uk/cmlregister/default.aspx.

3.0 Assessment of disease status

	WHO criteria (2008)	ELN criteria (2013)
Chronic phase	• Blasts <10% in bone marrow and peripheral blood; • Peripheral blood basophils <20%; • Absence of other criteria of accelerated phase or blast crisis	
Accelerated Phase	• Blasts in blood or marrow 10–19% • Basophils in blood ≥20% • Persistent thrombocytopenia (<100 × 10^9/L) unrelated to therapy • CCA (clonal chromosomal abnormalities)/Ph+ (i.e. cytogenetic evolution) on treatment • Thrombocytosis (>1000 × 10^9/L) unresponsive to therapy. • Increasing spleen size and increasing WBC count unresponsive to therapy	• Blasts in blood or marrow 15–29%, or blasts plus promyelocytes in blood or marrow >30%, with blasts <30% • Basophils in blood ≥20% • Persistent thrombocytopenia (<100 × 109/L) unrelated to therapy • Clonal chromosome abnormalities in Ph+ cells (CCA/Ph+) on treatment
Blast crisis	• Blasts in blood or marrow ≥20% • Extramedullary blast proliferation, spleen excluded • Large foci or clusters of blasts in the bone marrow biopsy	• Blasts in blood or marrow ≥30% • Extramedullary blast proliferation, spleen excluded (e.g. chloroma)

Should blast transformation of CML be considered, it is important to determine by morphology and immunophenotyping of the blood and marrow whether the transformation is myeloid (approx. 70%) or lymphoid (approx. 30%).

4.0 Prognostic Scoring Systems

It may be helpful for patients in the **chronic phase** to have a prognostic score (e.g. HASFORD, SOKAL and EUTOS) calculated at baseline. These are listed in Appendix 1.

5.0 Management of chronic phase CML

(a) Leukapheresis

Leukapheresis should be considered as an urgent approach to reduce the white cell count rapidly if there are signs of leukostasis (e.g. deteriorating level of consciousness, papilloedema, retinal venous engorgement/haemorrhages or priapism). If a patient is likely to require leukapheresis, early discussion with a centre offering this facility is advisable (i.e. The Christie or Manchester Royal Infirmary).

(b) Hydroxycarbamide

If active treatment to bring down the white cell count prior to starting tyrosine kinase inhibition is required while confirmation of diagnosis is awaited, hydroxycarbamide (hydroxyurea) is recommended at a dose of 1g to 6g a day in divided doses depending on clinical need. It is

usually well tolerated, although gastrointestinal symptoms may occur, particularly with higher doses. Renal and hepatic function should be monitored before and during treatment and the initial dose should be reduced by 50% if eGFR is <60 ml/min. In patients with elevated white cell counts, allopurinol 300 mg/day (reduced in renal and hepatic impairment) should be given and an adequate intake of fluids maintained.

(c) Definitive treatments

All patients should be discussed in the relevant Haematology MDT.

If available and deemed suitable, patients should be considered for a clinical trial.

Patients not wishing to enrol/ineligible for clinical trials should be offered a tyrosine kinase inhibitor (TKI) as first line therapy.

NICE Guidelines (TA426, December 2016) recommend the use of **imatinib, dasatinib** or **nilotinib** for untreated, chronic-phase Philadelphia-chromosome-positive chronic myeloid leukaemia in adults. NICE does not currently provide guidance over which should be used as first line, providing the company provides the drug within the discount agreed in the relevant patient access scheme.

Generic imatinib is recommended as the first choice TKI due to the significant current cost differential and lack of proven mortality benefit versus any of the second generation TKIs. Guideline prices (access date 29.6.17, BNF) are ~£2500 p.a. for generic imatinib versus ~£18,000 p.a. for either nilotinib or dasatinib (with agreed NHS discount).

Recommended doses with TKI therapy are:

Imatinib: 400mg OD in the chronic phase (may be increased to 600mg/day)
Dasatanib: 100mg OD
Nilotinib: 300mg BD

While the second generation TKIs nilotinib and dasatinib induce deeper and more rapid molecular responses than imatinib, this has not to date been demonstrated to translate into improved clinical outcomes including survival. Furthermore, second generation TKIs are frequently associated with more deleterious ADRs which may represent an important consideration for some patients. For example, dasatinib is associated with pleural effusion in 19% of patients over 5 years compared to 1% of patients treated with imatinib (data from SPIRIT2). Likewise, nilotinib is associated with elevations in blood cholesterol and glucose and an increased frequency of cardiovascular events, including ischaemic heart disease, ischaemic cerebrovascular disease and peripheral vascular disease (by comparison with patients treated with imatinib).

In view of the elevated cardiovascular risk associated with nilotinib it is recommended that all patients starting the drug have a Q-risk score calculated and glucose, blood pressure and lipid profile monitored. An ECG as well as tests for amylase and thyroid function tests should be performed at baseline.

First line use of second generation TKIs should be limited to clinical situations where a faster and deeper molecular response is deemed essential, for example in high risk patients (e.g. from prognostic scoring) or in those presenting in accelerated phase. Patient co-morbidities and side effect profiles are further important considerations. For example, elderly patients are more likely to develop pleural effusions on dasatinib, and use of nilotinib in patients with established cardiovascular disease should be carefully considered.

Further details supporting these recommendations may be found in Appendix 2.

Specific side effect profiles of the TKIs

This is not an exhaustive list. Please see the BNF or www.medicines.org.uk for further specific details.

Imatinib	Dasatinib	Nilotinib
• GI side effects: nausea, diarrhoea. • Fluid retention • Cramps	• Pleural effusion • Dyspnoea • Thrombocytopenia • Pulmonary hypertension	• Adverse cardiac events including ischaemic heart disease, cerebrovascular events and peripheral vascular disease. • Hypertension • QT interval prolongation • Hypercholesterolaemia • Hyperglycaemia • Thyrotoxicosis

6.0 Management of advanced phase disease

Advanced disease comprises **accelerated phase (AP) and blast crisis (BC).**

Some patients may present in AP or BC, however the majority progress to BC following TKI failure.

Patients presenting in AP are typically responsive and should be treated with TKIs, preferably with the more potent second generation TKIs according to Baccarani et al. (2015). They should be considered for allogeneic stem cell transplantation (SCT) if they fail to achieve an optimal response.

Patients presenting in BC are also responsive to TKIs, although the risk of relapse is high and thus all should be considered for allogeneic SCT (Baccarani et al., 2015).

Mutational analysis is recommended in AP and BC either prior to treatment or at any point during treatment when the trajectory of the molecular response appears sub-optimal. In CP it is likewise appropriate when the trajectory of the molecular response is sub-optimal.

NICE guidelines (2016)

- Endorse the use of **higher doses of imatinib** (600mg OD which may be increased up to 800mg daily, given as 400mg BD) for:-
    - Patients who **present** in **accelerated phase or blast-crisis**
    - Patients who present in chronic phase and **progress** to the accelerated phase or blast crisis phase **if they have not received imatinib before.**
- High dose imatinib is **not recommended** for treating Philadelphia-chromosome-positive chronic myeloid leukaemia in adults whose disease is **imatinib-resistant.**
- **Dasatinib** and **nilotinib** may be used to treat **accelerated phase CML** in adults if they cannot have imatinib, are imatinib resistant and if companies provide the drugs with the agreed discounts.

Doses recommended in accelerated phase or blast crisis (BNF):-

- **Imatinib:** 600mg OD increased if necessary to max 800mg daily in two divided doses
- **Dasatinib:** 140mg OD increased if necessary to 180mg OD
- **Nilotinib:** 400mg BD

Chemotherapy maybe required before allogeneic SCT to control disease. This would usually be an AML induction regime for patients in myeloid blast crisis and an ALL induction regimen for patients in lymphoid blast crisis.

7.0 Monitoring of patients on TKIs

Monitoring of treatment is generally divided into haematological, cytogenetic and molecular response. Definitions are as follows:-

Complete Haematological Response:

Platelet count <450; WBC <10; no immature myeloid lineage cells in PB; basophils <5%; no palpable spleen

The first goal of treatment is to achieve a normal blood count and resolution of splenomegaly. This is the definition of a complete haematological response (CHR) and is achieved in at least 95% of patients with any of the three licensed TKIs (imatinib, dasatinib and nilotinib) within 6 weeks.

Complete Cytogenetic Response (CCyR)

No Ph+ve metaphases or <1% Bcr:Abl +ve nuclei when 200 nuclei analysed

The second goal of treatment is to achieve clearance of the Ph chromosome from the marrow. This should be assessed by G banding through analysis of at least 20 metaphases. FISH should only be used for assessment of CCyR when <1% of nuclei are positive and at least 200 nuclei have been assessed.

Cytogenetic response can be classified as:-

Ph positive marrow metaphases (%)	Designation
0	Complete cytogenetic response (CCyR)
1-35	Partial cytogenetic response (PCyR)
36-95	Minor cytogenetic response
>95	None

Complete Molecular Response

This is assessed by RQ-PCR of a peripheral blood sample and is expressed according to the International Scale (IS) as the ratio of BCR:ABL1 (leukaemic) transcripts to ABL1 (normal) transcripts. It is reported as BCR-ABL1:ABL1 ratio (%) on a log scale as a reduction below the standard baseline.

A BCR-ABL1:ABL1 ratio of <0.1% corresponds to a major molecular response (MMR). The depth of molecular response can then be further classified as below:-

BCR:ABL1%	Log reduction	Depth of response
0.1	3	MMR (MR 3.0)
0.01	4	MR4.0
0.0032	4.5	MR4.5
0.001	5	MR5.0

Patients with no detectable transcripts should be referred to as having 'molecularly undetectable leukaemia'.

ELN (European Leukaemia Network) recommendations (2013)

- Monitoring can be performed using a molecular or cytogenetic test or both depending on laboratory facilities. Wherever possible both are recommended until a MMR and CCyR has been achieved. Then RQ-PCR may be sufficient.

- **Molecular testing:-**
  - RQ-PCR should be performed every 3 months until an MMR is attained, then every 3-6 months.
  - Levels may vary over time, partly due to laboratory techniques. However, if transcript levels have increased >5-fold in a single follow up then the test should be repeated at a shorter time interval and patients should be questioned about compliance.

- **Cytogenetics:-**
  - Must be performed by CBA (chromosome banding analysis) of marrow cell metaphases, counting at least 20 metaphases at 3, 6 and 12 months until a CCyR is achieved and then every 12 months. CBA can be substituted by FISH of peripheral blood cells only when a CCyR has been achieved.

- **Warning**
  - In case of warning, it is recommended to repeat all tests, cytogenetic and molecular more frequently, even monthly.

- **Treatment failure/progression to AP or BC**
  - Cytogenetics of marrow cell metaphases, PCR and mutational analyses should be performed.

- **Dysplastic morphology/myelodysplasia**
  - If dysplastic morphology or other features of myelodysplasia develop, histopathologic and cytogenetic studies of bone marrow are recommended.

- In practice, it may be unrealistic and undesirable to the patient to perform bone marrow cytogenetic assessment as frequently as is recommended above and thus flexibility may be exercised. Many physicians may choose to delay BM cytogenetic assessment to 6 months to improve the likelihood of documenting a CCyR. However, all patients must have at least one BM cytogenetics documenting a CCyR.

- Several groups have shown that the threshold of complete cytogenetic response correlates very well with a BCR-ABL1/ABL1 ratio of 1%; molecular monitoring alone may therefore be adequate for patients who decline a marrow examination for CCR assessment at 12+ months of treatment.

- Many patients may elect to be monitored with RQ-PCR only, although the gold standard remains annual BM cytogenetics.

Summary of suggested monitoring

Test	Frequency
FBC	2 weekly until CHR then 3 monthly
Bone marrow for cytogenetics/FISH	**3, 6 and 12 months**. Once patients have achieved a **CCyR** a repeat should be considered **every 12 months**. Consideration could be given to peripheral blood FISH for patients in known CCyR
RQ-PCR on peripheral blood	**3 monthly.** ELN recommend that this should be done indefinitely, providing this is an informative test at presentation.

8.0 Treatment failure or intolerance on 1st line TKIs

The following table is adapted from the European Leukemia Net (Baccarani et al, 2013) guidelines which updated the previous 2009 guidelines.

'Failure' necessitates a change in treatment because the impaired response means that the patient is at a significant risk of progression and death.

'Warning' is an intermediate category. It is acknowledged by the authors that there is no solid data to make specific recommendations on how the treatment should be changed to improve the response.

Definition of the response to TKIs (any TKI) as first line treatment.

N.B. Definitions are the same for patients in CP, AP and BC and apply also to second line treatment, when first line treatment was changed due to **intolerance.**

	Optimal	**Warning**	**Failure**
Baseline	N/A	High risk or CCA/Ph+, major route	N/A
3 months	BCR-ABL1:ABL1 ratio ≤10% and/or Ph+≤35%	BCR:ABL1:ABL1 ratio >10% and/or Ph+ 36-95%	Non CHR and/or Ph+>95%
6 months	BCR:ABL1:ABL1 ratio <1% and/or Ph+ 0 (CCyR)	BCR:ABL1:ABL1 ratio 1-10% and/or Ph+ 1-35%	BCR-ABL1:ABL1 ratio >10% and/or Ph+ >35%
12 months	BCR-ABL1:ABL1 ratio ≤0.1% (MMR)	BCR-ABL1:ABL1 ratio 0.1-1%	BCR-ABL1:ABL1 ratio >1% and/or Ph+>0
Then, and at any time	BCR:ABL1:ABL1 ratio ≤0.1%	CCA/Ph-(-7, or 7q-)	Loss of CHR Loss of CCyR Confirmed loss of MMR Mutations CCA/Ph+

CCA: Clonal chromosome abnormalities
Major route: High risk score + CCA/Ph+

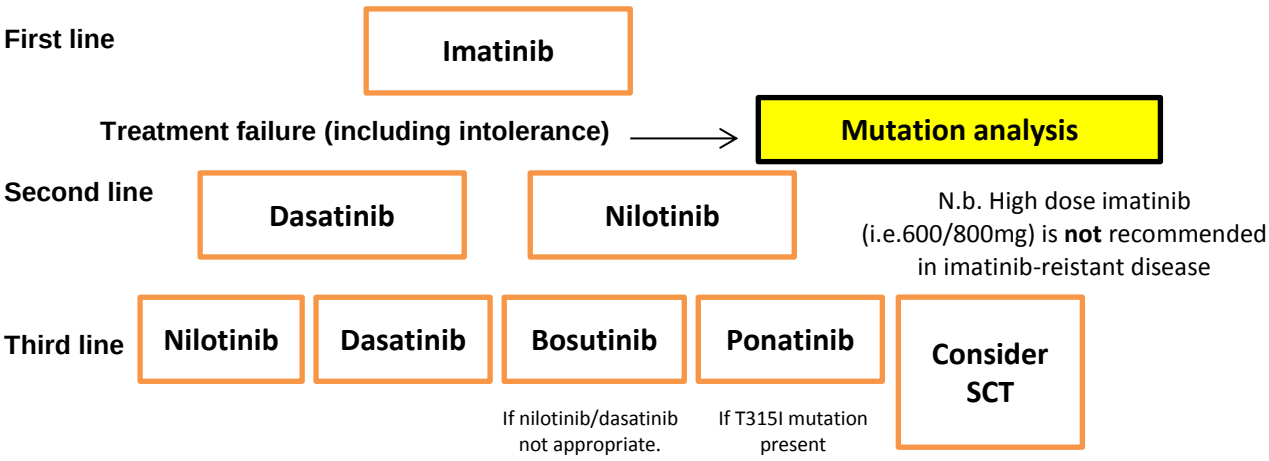
Definition of response to second line therapy in the case of failure of imatinib

N.b. Definitions based primarily on data for nilotinib and dasatinib but can also be used provisionally for bosutinib and ponatinib until more data are available.

	Optimal	Warning	Failure
Baseline	N/A	No CHR or loss of CHR on imatinib Or lack of CyR to first line TKI Or high risk	N/A
3 months	BCR:ABL1:ABL1 ratio ≤10% and/or Ph+<65%	BCR:ABL1:ABL1 ratio >10% and/or Ph+ 65-95%	No CHR and/or Ph+>95% Or New mutations
6 months	BCR:ABL1:ABL1 ratio ≤10% and/or Ph <35%	Ph+ 35-65%	BCR-ABL1:ABL1 ratio >10% and/or Ph+ >65% and/or new mutations
12 months	BCR-ABL1:ABL1 ratio <1% and/or Ph+ 0 (CCyR)	BCR-ABL1:ABL1 ratio 1-10% And/or Ph+ 1-35%	BCR-ABL1:ABL1 ratio >10% and/or Ph+>35% and/or new mutations
Then,and at any time	BCR-ABL1:ABL1 ratio ≤0.1%	CCA/Ph-(-7, or 7q-) Or BCR:ABL1 >0.1%	Loss of CHR Loss of CCyR or PCyR Confirmed loss of MMR New mutations CCA/Ph+

Treatment Recommendations in the Case of Treatment Failure

Based on NICE guidelines 2016 and Review of ELN Recommendations (Baccarani et al., 2015).



There are no direct comparisons of second line therapies in the literature. Choice should be guided by patient characteristics, including comorbidities and sensitivity to the side effect profile of the various TKIs, combined with the results of mutation analysis.

BCR-ABL1 kinase point mutations are present in approximately 50% of patients with treatment failure and progression. Over 80 amino acid substitutions have been associated with resistance to imatinib. Dasatinib and nilotinib resistance are associated with a smaller spectrum of mutations. The T315I mutation is associated with resistance to all TKIs with the exception of ponatinib. NICE is due to publish guidelines in June 2017 which provisionally authorises use of ponatinib in chronic, accelerated or blast phase CML when the T315I mutation is present.

Mutation analysis is performed at West Midlands Regional Genetics Laboratory in Birmingham. Please send sample with the completed form (appendix 4) either directly to Birmingham or via the Molecular Diagnostics Center at CMFT.

A list of mutations and information regarding sensitivity to TKIs is presented here:

Hochhaus A, Ernst T, Eigendorff E, La Rosee P. Causes of resistance and treatment choices of second and third line treatment in chronic myelogenous leukaemia patients. *Ann Haematol:* 94: 133-140.

9.0 Discontinuing TKIs

Most international guidelines recommend that patients who are responding optimally to TKI therapy should continue on treatment indefinitely. Discontinuation of TKI following a prolonged period of molecularly undetectable disease (e.g. 2 yrs) is currently under investigation in clinical trials.

Where there are strong reasons to consider discontinuation of TKI the following points arising from studies to date should be considered:

1. Should only be considered in patients with molecularly undetectable leukaemia for > 2 years
2. Most relapses occur within 6 months of stopping TKIs and most patients failing a treatment free period do so with an exponential increase in BCR-ABL, rising approximately 1 log per month. Thus close monitoring, with high quality and timely RQ-PCR, particularly during the first 6 months is essential.
3. For patients remaining in treatment-free response beyond the first 6 months, the risk of relapse is lower, and less frequent testing, e.g., every 2 to 3 months, may be sufficient.
4. The question of how long to continue monitoring is more difficult to answer. The latest reported loss of TFR was at 42 months, and thus long term monitoring is necessary.

Further information may be found in Appendix 3.

10.0 Pregnancy

Patients taking TKIs should be advised to use barrier methods of contraception and to avoid pregnancy (males and females).

Patients who wish to become pregnant (or father a child) should have careful pre-pregnancy planning and counselling about feasibility and relative risk.

Given the specialist management required, patients should be discussed on a case by case basis with regional or national experts with experience in this area.

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Appendix 1 - Prognostic Scoring Systems

It may be helpful for patients in the **chronic phase** to have a prognostic score (e.g. **HASFORD, SOKAL and EUTOS)** calculated at baseline. These are listed in Appendix 1.

N.B. Spleen is measured by manual palpation and expressed as maximum distance below costal margin.

Sokal score = Exp[0.0116 (age−43.4 years)
+0.0345 (spleen size−7.51)
+0.188 ([platelets/700]2−0.563)+0.0887 (blasts−2.1)]

Low risk <0.8 **Intermediate risk 0.8–1・2** **High risk >1.2**

Hasford score = (0.6666×age [0 when age <50 years; otherwise 1] + (0.042 ×spleen size (cm below costal margin)) + (0.0584×blasts [%]) +(0.0413 ×eosinophils [%]) + (0.2039 × basophils [0 when basophils <3%;otherwise 1]) + (1.0956 × platelet count [0 when platelets<1500 per µL; otherwise 1]) × 1000

Low risk <780
Intermediate risk 780–1480
High risk >1480

Eutos score= (Spleen (cm beneath costal margin) x4) + (basophils (% of PB leukocytes) x 7)

Low risk ≤ 87; **High risk >87**

For online calculators see:-

Hasford and Sokal:
http://www.leukemianet.org/content/leukemias/cml/cml_score/index_eng.html

Eutos:
http://www.leukemianet.org/content/leukemias/cml/eutos_score/index_eng.html

Appendix 2 – Data on comparative trials of imatinib versus second generation TKIs

The **SPIRIT 2 trial** (unpublished, provisional results from abstracts and notes on CML presentations, ASH 2014) randomised 814 participants with newly diagnosed CML to treatment with either imatinib or dasatinib. Provisional results suggest MR3 (major molecular response) rate at one year was 58.4% with dasatinib compared to 43.1% with imatinib ($p<0.001$) however there was no difference in disease progression or overall survival. Furthermore dasatinib was associated with pleural effusion in 19.0% of patients over 5 years (16.9% of which required a chest drain) compared to only 0.7% of patients treated with imatinib. Dasatinib was also associated with higher rates of thrombocytopenia and significantly higher rates of dyspnoea in the absence of pleural effusion, compared to imatinib.

Similarly Kantarjian et al (2010) (**DASISION study**) demonstrated superiority of dasatinib versus imatinib for complete cytogenetic response (cCCyR) (77% vs. 66%, P = 0.007) and major molecular response(MMR) (46% vs. 28%, P<0.0001)in 519 randomised patients at 12 months. Differences between cCCyR and MMR remained at 5 year follow up, however overall five-year progression-free survival (PFS) and overall survival (OS) rates were similar across treatment arms (PFS: 85% -dasatinib, 86%-imatinib); OS: 91%- dasatinib, 90%-imatinib). As above, thrombocytopenia and pleural effusion occurred more commonly with dasatinib, however imatinib was more commonly associated with other adverse side effects including fluid retention, nausea, vomiting and muscle inflammation.

The **ENESTnd study** (Saglio et al., 2010) randomly assigned 846 participants with newly diagnosed CML to nilotinib 300 mg or 400mg BD versus imatinib 400 mg OD. They established a significantly higher rate of CCyR with nilotinib after 1 and 2 years (80% vs 65%, and 87% vs 77%), and a significantly higher rate of MMR with nilotinib after 1 year (50% vs 27%) and 3 years. Molecular response rates continued to be superior at 5 year follow up (Hochhaus et al.,2016) with 54% of patients in the nilitonib 300mg BD arm achieving a MR4.5 versus 31% of patients in the imatinib arm. However, rates of progression free survival and overall survival at 5 years for standard dose nilotinib (300mg BD) versus imatinib were not significantly different (PFS: nilotinib- 92.2% versus imatinib- 91.0%, p = 0.68; OS: nilotinib 93.7% versus imatinib 91.7%, p = 0.48). Nilotinib was associated with elevations in blood cholesterol and glucose and an increased frequency of cardiovascular events, including ischaemic heart disease, ischaemic cerebrovascular disease and peripheral vascular disease.

Appendix 3 – Further data on TKI discontinuation trials

The EURO-SKI study (European Stop Tyrosine Kinase Inhibitor Trial in Chronic Myeloid Leukemia) is the largest study of its kind to date, recruiting 821 patients with CML from 11 European Countries. Final results are awaited, however an interim analysis of 200 patients was conducted in 2014 (Mahon et al., 2014). Eligibility criteria included: confirmed deep molecular response (MR4, BCR-ABL <0.01%) for at least one year; and on TKI treatment for at least 3 years. The majority of patients (97%) were taking imatinib. The median duration of TKI therapy was 8 years. Recurrence of CML, defined as loss of MMR, was observed in 47% of patients treated <8 years, compared to 26% of patients treated for >8 years (p= 0.005). Furthermore, initial data suggested that longer durations of MR4 were associated with a significantly reduced risk of remission. 46% of patients in MR4 <5 years lost MMR within 6 months compared to 32% of patients in MR4 >5 years. TKI cessation was well tolerated, although a significant number of participants were noted to experience myalgia in the weeks following cessation.

Hughes and Ross (2016) review the evidence for cessation of TKIs in CML and attempt to establish criteria for the safe cessation of TKIs. They summarise the results of key studies to date. The STIM study (Mahon et al., 2010) evaluated 100 patients on imatinib with MR5.0 for at least 2 years. At 12 months 61% of patients had relapsed. However, all patients who relapsed responded well to the re-introduction of imatinib. The trigger to resume TKI was a loss of UMRD (undetectable minimal residual disease, roughly equivalent to MR4.5). Similar results were reported in the TWISTER study (Australasian Leukaemia & Lymphoma group Trial of Withdrawing Imatinib in Stable Remission), where 47.1% of patients achieved treatment free remission (TFR) after 24 months after achieving UMRD on imatinib for at least 2 years. Both studies reported higher treatment free remission rates in Sokal low risk patients. Both studies also reported that most patients regained UMRD within 3 to 6 months of restarting imatinib treatment in response to a rather conservative RQ-PCR–defined trigger. Studies with less conservative triggers for resuming TKI have reported even higher treatment free remission rates, for example the KIDS study (Korean Imatinib Discontinuation Study)(Lee et al, 2016) used loss of MMR as a trigger for resuming TKIs and found that 59% of the 90 patients remained in TFR at 2 years.

The authors conclude that the safety data from the TFR studies reported to date is sufficiently reassuring to offer all eligible patients a supervised test of TKI withdrawal and have devised criteria to guide when discontinuation of TKI might be appropriate, see table below:-

Criteria	Green	Yellow	Red
Institutional criteria met (per table 1)	Yes	-	No
Sokal score at diagnosis	Non-high	High	-
BCR-ABL transcript at diagnosis	Typical - B2A2 or B3A2 (e13a2 or e14a2)	Atypical, but can be accurately quantified	Not quantifiable
CML past history	CP only	Resistance or KD mutation	Prior AP or BC
Response to first line TKI therapy	Optimal	Warning	Failure
Duration of all TKI therapy	> 8 years	3–8 years	< 3 years
Depth of deep molecular response	MR4.5	MR4.0	Not in MR4.0
Duration of deep molecular response monitored in a standardized laboratory	> 2 years	1–2 years	< 1 year

All green lights: strong recommendation to consider TKI withdrawal

Any yellow lights: only consider TKI withdrawal in high priority circumstances (e.g. significant toxicity or planned pregnancy)

Any red lights: TKI withdrawal not recommended except in clinical trial

Figure 1. Criteria to guide selection of patients suitable for a TFR attempt. KD, kinase domain; AP, accelerated phase; BC, blast crisis.

Appendix 4 – Request form for BCR-ABL Mutation Analysis (Birmingham)

CPA ACCREDITED LABORATORY

West Midlands Regional Genetics Laboratory
MOLECULAR GENETICS REFERRAL

Birmingham Women's Health Care NHS Trust
Edgbaston, Birmingham B15 2TG
Tel: (0121) 627 2710 Fax: (0121) 627 2711

Please complete all boxes (in ball point pen), or use patient information label.
* = please circle or delete as appropriate. Referrals for Cytogenetics require a separate BLUE form.

Surname	First name(s)	Reg. No.	CG Number

DOB	Sex	Type * NHS/Private	NHS Number	Ethnic Origin (if relevant, e.g. for CF)	Date Sample Taken

Address	Referring Clinician Consultant or GP Name in full	Medical Specialty
	Referral Centre Hospital, practice etc. Name in full	Ward
Postcode	Type of Sample: * Venous Blood / Cord Blood / Bone Marrow Skin / Other (please specify):	Extraction Required * DNA/RNA

Disease:

Name of affected relative (s)

Relationship of this person to affected relative (Please give details)

SIGNATURE

Status
Please circle:
1) Affected
2) ? Affected
3) At risk
4) Obligate carrier by family history
5) Possible carrier by family history
6) Population risk
7) Not at risk
8) Prenatal diagnosis

Test(s) Required
Please circle:
1) Mutation screen
2) Family studies
3) Confirmation of familial mutation
4) Predictive testing - please give next appointment date:
5) Send to other Lab (please supply details)
6) DNA/RNA banking only
7) For research only
8) Other - please specify:

Patient Consent

Has consent been given for:

Testing for this referral reason? **YES/NO**

Residual samples* being stored for use in future ethically approved research? **YES/NO**

For deceased patients, has consent been given to store this sample? **YES/NO**

FOR CLARIFICATION SEE OVERLEAF

E-mail: genetics.lab@bwhct.nhs.uk Website: http://www.bwhct.nhs.uk/wmrgl
For replacement forms please contact laboratory or see website

Blood and bone marrow samples for molecular analysis
Should be placed in **EDTA** tubes