PROFESSIONAL GUIDELINES FOR
CLINICAL CYTOGENETICS

CHRONIC MYELOID LEUKAEMIA &
OTHER MYELOPROLIFERATIVE
NEOPLASMS (2011) v1.00

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1 INTRODUCTION

Professional guidelines for cytogenetics laboratories aim to incorporate the standards imposed by regulatory bodies (Clinical Pathology Accreditation (CPA) [1] and by statute (Clinical Governance) while taking into account current practice in the UK. Elements of the service not subject to statute may be varied according to local constraints and agreements. It must be noted that these guidelines are minimum requirements and that professional judgment is of paramount importance for many circumstances.

It is important that laboratories are aware of, and comply with, any additional requirements relating to cytogenetic analyses which may be set by national clinical trials.

Cytogenetic laboratories should provide onward referral to specialist laboratories when necessary, or advice on where appropriate further testing may be performed.

The use of ‘must’ in this document indicates a requirement and the use of ‘should’ indicates a recommendation. Where there appears to be contradiction between available guidelines, the most recently published should be taken to apply to all.

All cytogenetic laboratories must be accredited to nationally or internationally accepted standards. Laboratories must participate in an External Quality Assessment Scheme for all aspects of their service for which a scheme is available [2].

These guidelines relate to Chronic Myeloid Leukaemia and other myeloproliferative neoplasms and make up part of the Haemato-Oncology Best Practice Guidelines. They should be used in conjunction with the following documents; Professional Guidelines for Clinical Cytogenetics: General Best Practice Guidelines (2007) [3], Professional Guidelines for Clinical Cytogenetics: Haemato-oncology (2007) [4].
2 CHRONIC MYELOID LEUKAEMIA

2.1 Introduction

Chronic myeloid leukaemia (CML) is a myeloproliferative neoplasm which originates in a pluripotent stem cell in the bone marrow [5]. CML accounts for 15% of leukaemia and may occur at any age.

The cytogenetic hallmark of CML is the t(9;22)(q34;q11) translocation, resulting in a Philadelphia chromosome which can be detected by chromosome analysis in 90 – 95% of cases at diagnosis. This translocation gives rise to a BCR-ABL1 fusion gene on the derivative chromosome 22, the Philadelphia (Ph) chromosome. The remaining 5-10% of cases have either variant translocations involving other chromosomes in addition to 9 and 22, or have a cryptic translocation between chromosomes 9 and 22 which cannot be detected by G-band metaphase analysis. In such cases, a BCR-ABL1 gene fusion can be demonstrated by FISH or RT-PCR.

In the appropriate bone marrow morphological context, BCR-ABL1 fusion is pathognomonic of CML, and BCR-ABL1 negative myeloproliferative neoplasms are classified as different diseases (see MPN below).

The BCR-ABL1 gene product is a cytoplasmic protein with enhanced tyrosine kinase activity which leads to constitutive activation of several signal transduction pathways causing CML. BCR-ABL1 tyrosine kinase inhibitors (TKIs) have been developed as therapeutic agents for CML. Imatinib is the current first-line treatment for patients with chronic phase CML; however, other TKIs are being evaluated. Demonstration of t(9;22) or a BCR-ABL1 gene rearrangement is required to identify those patients where BCR-ABL1 TKI therapy is likely to be beneficial.

Response to treatment can be determined cytogenetically by reduction in the proportion of abnormal cells, preferably by metaphase G-band analysis of marrow, or interphase FISH (iFISH) of marrow or blood for BCR-ABL1 (see 2.3.1 and 2.3.2 note 7). Once a complete cytogenetic response (CCgR) has been achieved (see Appendix Table 1: Definitions of Cytogenetic Response), response to treatment should be monitored using real-time quantitative polymerase chain reaction (RT-qPCR) for BCR-ABL1 [6,7].
2.2 Diagnostic testing

2.2.1 Flow Chart 1: CML analysis guidelines (diagnostic)

Notes.

1. For chromosome analysis, bone marrow cultures may be more likely than blood cultures to produce adequate numbers of metaphase cells. Samples should be sent in heparinised containers or in heparinised medium. It is recommended that a method of cell counting be used, so that culture densities may be optimised to approximately 1x10⁶/ml.

For a particularly rapid result, a 'direct' harvest (ie same day as sample receipt) or uncultured cells (including bone marrow or blood smear slides) can be used for interphase BCR/ABL1 FISH analysis.

If RT-PCR and/or molecular testing for mutations associated with MPN is required, RNA and DNA extraction should be coordinated with the molecular genetics provider for efficient processing and use of samples.
Score for the Ph chromosome and other obvious abnormalities, particularly those which may be associated with disease progression: +Ph, +8, +19, +21, -Y, i(17q). It is important to establish if additional changes are present at diagnosis since these are considered a potential ‘warning’ according to ELN guidelines, where a ‘warning’ is defined as a characteristic of the disease which may adversely affect the patient’s response to imatinib therapy and thus the patient may require more stringent and careful monitoring [6]. Characterisation of secondary changes is also necessary to assist the interpretation of results from subsequent samples.

If the result shows a variant translocation, it is recommended that the presence of a BCR-ABL1 rearrangement is confirmed by FISH (this also establishes the signal pattern to inform any future FISH monitoring).

i.e. cytogenetically cryptic, BCR-ABL1 fusion positive CML.

If BCR-ABL1 fusion negative, further scoring of G-banded metaphases may be warranted to look for chromosome abnormalities associated with MPN: in particular +8, +9, del(13q), del(20q). Other, rarer recurrent abnormalities should be borne in mind if these are suggested by the referral information.

2.2.2 Interpretation and reporting

In the majority of cases, a standard t(9;22) / BCR-ABL1 positive result will be obtained, consistent with CML. Other scenarios include:

**Variant translocations**: these are considered to have a similar outcome to classical t(9;22) cases when treated with imatinib or 2nd generation TKI [8].

**Additional chromosome abnormalities in Ph positive cells**: at diagnosis, these do not necessarily have any impact on patient outcome; however their presence is regarded as a ‘warning’ according to ELN guidelines.

**Deletions of ABL1, BCR or ABL1-BCR from the der(9)**: these may be detected in some cases in the course of FISH analysis. Before the advent of imatinib, such deleted cases were linked with adverse clinical outlook, but imatinib is reported to nullify this prognostic difference [9, 10]. In view of these studies, it is not mandatory to report der(9) deletions.
The atypical signal patterns resulting from der(9) deletions may reduce the specificity of FISH for disease monitoring – see 2.3.2, note 8.

2.3 Follow-up testing

2.3.1 Frequency of testing and sample requirements

Frequency of testing
ELN guidelines [6] recommend G-band metaphase analysis of marrow at 3 and 6 months post-treatment, then at least every 6 months until a complete cytogenetic response (CCgR) has been achieved and then confirmed in a subsequent sample.

After a confirmed CCgR has been achieved, cytogenetics should not be routinely required in the majority of patients, and monitoring of blood by RT-qPCR is the preferred approach. However, cytogenetic monitoring of patients who have developed Ph negative abnormal clones should be continued.

Frequency of cytogenetic testing may also be determined by participation in a clinical trial eg SPIRIT2.

Sample requirements
If available, bone marrow is the sample of choice whilst a patient has cytogenetically detectable disease. In clinical trials, the definitions of cytogenetic response are based on metaphase G-band analysis, so this is the recommended monitoring approach in the initial post-treatment phase.

Marrow G-band analysis is preferred to interphase FISH (iFISH) since G-band analysis can detect Ph negative abnormal clones and also karyotypic evolution within the Ph positive clone. However, if only blood is available, interphase FISH for BCR-ABL1 may be used to measure response (with caution - see 2.3.2 note 8).

CCgR can be confirmed by iFISH of blood using BCR/ABL1 extra signal, dual colour or dual fusion probes and scoring at least 100 nuclei. Once CCgR is established, RT-qPCR on peripheral blood is recommended for follow up studies.
2.3.2 Flow chart 2: CML follow-up testing and analysis

Notes

1. G-band metaphase analysis of blood cannot be used to define cytogenetic response per se, but may be used to identify karyotypic evolution.

2. If the level of Ph+ve cells is close to the boundary of a defined response category, then it may be necessary to score more than 20 metaphases to establish the level of the Ph positive clone. During scoring for Ph status, analysts should be vigilant regarding possible new secondary abnormalities.

3. Defines complete cytogenetic response (CCgR).

4. Score for BCR-ABL1 +ve cells using metaphase FISH. Score minimum of 20 if positive and minimum of 30 if negative. G-band metaphase analysis should also be considered to look for evidence of disease progression or for Ph negative abnormal clones, depending on disease status.
G-band analysis should always be carried out in instances of no response / suboptimal response or loss of response, or in cases with appearance of myelodysplastic features, unexplained anaemia, leucopenia or thrombocytopenia.

If a bone marrow sample is not available, the level of cytogenetically detectable disease may be determined on blood using iFISH. NB: accurate interpretation of FISH studies requires knowledge of the baseline signal pattern at presentation.

Some studies (e.g. [11, 12]) have shown discrepancies between BCR/ABL1 iFISH scores obtained from unselected screening of whole blood and scores obtained from selective screening of neutrophil/granulocyte nuclei. This is thought to be due to the presence of varying proportions of normal lymphocytes in blood, which are dependant on the level of myelosuppression during the initial treatment phase. It has been proposed that selective scoring of neutrophils/granulocytes more accurately corresponds to the values obtained by marrow metaphase chromosome analysis. Reports should specify clearly whether BCR/ABL1 FISH results are based on screening of selected or unselected cells.

Cases with variant Ph translocations or der(9) deletions may give rise to atypical FISH signal patterns including signal patterns with only a single fusion signal. If the signal pattern can be confused with co-localisation in a normal cell, deleted cases should be monitored by iFISH only if a tri-colour probe system produces an informative signal pattern, which can be used to distinguish genuine fusion signals from signal co-localisation in normal cells.

Post-transplant
Cytogenetic analysis may be indicated post-transplant if a patient has mixed chimaerism or if rapidly increasing disease levels are indicated by RT-qPCR.

2.3.3 Interpretation and reporting of results

Definitions of cytogenetic and molecular reponse
ELN have published definitions for cytogenetic and molecular responses to imatinib treatment in CML [6]. These are listed in Table 1 in the Appendix. These definitions should be used in the interpretation and in the reporting of results to define cytogenetic and molecular responses to treatment.
For example:

The decrease in the level of the Ph positive clone to NN% in the current sample represents a partial cytogenetic response to imatinib (1-35% Ph positive metaphase cells).

ELN have also published definitions of overall response to imatinib, as first-line therapy in chronic phase, at designated time points. These are given in Table 2 in the Appendix. It is not mandatory to use these response definitions; however, if results are to be classified, ELN definitions should be used, and the report should also include a caveat that standard imatinib therapy has been assumed.

For example:

A CCgR after 12 months is considered a good response to treatment according to ELN guidelines (Baccarani et al., J Clin Oncol. 2009 Dec 10;27(35):6041-51).

This patient has not yet achieved a cytogenetic response (CgR). Assuming standard imatinib therapy, according to the ELN guidelines, no CgR at 6 months post commencement of treatment is classed as treatment failure (Baccarani et al., J Clin Oncol. 2009 Dec 10;27(35):6041-51).

NB: response criteria for second generation TKIs as first-line treatment have not yet been defined.

Loss of CCgR

For patients who have lost a CCgR, ELN guidelines recommend BCR-ABL1 kinase domain (AKD) mutation analysis before changing to other TKIs or alternative therapies. It may therefore be useful to include in the report a recommendation as to where AKD mutation testing may be obtained.

**Additional chromosome abnormalities in the Ph positive clone post-treatment**

Clonal evolution may reflect the selection of treatment-resistant clones within continuing chronic phase disease, or, in the context of appropriate haematological changes, may indicate disease acceleration or transformation to acute leukaemia (blast phase). The interpretation is straightforward if the abnormality detected is specific to acute leukaemia, or is an i(17q) and is consistent with bone marrow morphology, but unexpected additional abnormalities, even when recognised secondary findings in CML, may be transient and of no clinical significance. If the abnormality is present in two
consecutive samples, however, this is a definition of treatment failure [6] since it implies emergence of a resistant clone: it is not necessarily an indication of transformation in the absence of appropriate haematological evidence.

**Ph negative abnormal clones**

In patients treated with TKIs including imatinib, dasatinib and nilotinib, new clonal karyotype abnormalities are occasionally detected in Ph negative cells (Ph negative abnormal clones). In particular, trisomy 8, abnormalities of chromosome 7, and sex chromosome anomalies have been observed. These clones are usually of unknown significance, but have occasionally been associated with myelodysplasia [13, 14]. For follow-up samples, it is therefore recommended that – in addition to screening for Ph status – metaphases should be screened for such Ph negative abnormal clones, with particular attention being directed to chromosomes 5, 7, 8, 13, 20, X and Y.

Unless there are clinical or haematological grounds to suspect a second haematological disorder, additional chromosome abnormalities in Ph negative cells should be reported cautiously, since these clones are not necessarily malignant. Further regular cytogenetic monitoring of bone marrow should be recommended.

### 2.4 Reporting time guidelines

The urgency with which analyses need to be undertaken and reported is variable and, in general, this may be best assessed through liaison between the laboratory and the referring clinician over individual cases.

**Request for rapid diagnostic result:**

95% should have a preliminary report issued within 3 working days (FISH, RT-PCR, +/- karyotype)

**Request for rapid chromosome analysis (eg ? progression):**

95% should have a preliminary report issued within 7 calendar days

**Full chromosome analysis following rapid result:**

95% should be reported within 14 calendar days

**Routine / follow up referral:**

95% should be reported within 21 calendar days
3 OTHER MYELOPROLIFERATIVE NEOPLASMS

3.1 Introduction

The BCR-ABL1-negative Myeloproliferative Neoplasms (MPN) are a heterogeneous group of clonal stem cell disorders. They are represented in the WHO classification by a number of different disease categories, including classic MPNs (Polycythaemia vera (PV), Essential thrombocythaemia (ET) and Primary myelofibrosis (PMF), other MPN, MPN overlapping with Myelodysplastic syndrome (MDS) and a new group of rare myeloid and lymphoid neoplasms with eosinophilia, defined by recognised chromosomal translocations [5].

Cytogenetic abnormalities are not usually specific, and general markers of myeloid malignancy are found. The incidence of chromosome abnormalities varies considerably between different MPNs. While normal karyotype results must be regarded as uninformative, detection of a chromosome abnormality can be diagnostically useful to confirm a clonal neoplastic disorder, and cytogenetic analysis is incorporated into a number of diagnostic algorithms [15-18].

By definition, the distinction of MPN from CML requires exclusion of t(9;22)/BCR-ABL1, and this may be the only test required in a diagnostic work-up. Absence of t(9;22) or BCR-ABL1 is necessary in the differential diagnosis of CML from non-classic MPN:
- Chronic neutrophilic leukaemia (CNL),
- Chronic eosinophilic leukaemia, not otherwise specified (CEL-NOS),
- Chronic myelomonocytic leukaemia (CMML),
- Myeloproliferative neoplasm, unclassifiable (MPN, U).

It is also important to identify CML mimicking ET or PMF, particularly where morphology is suggestive [18, 19].

Role and limitations of cytogenetic analysis in MPN

Cytogenetic studies are not essential for the diagnosis of most MPN cases but Haematologists may refer cases by local agreement.

There are no specific cytogenetic abnormalities that will confirm transformation to myelofibrosis or acute leukaemia, although karyotype evolution to complex karyotypes, particularly with abnormalities of 5q, 7 and 17p, is strongly suggestive.
Cytogenetics, supplemented by FISH or molecular genetics, is required to define the WHO disease groups characterised by specific gene rearrangements (PDGFR or FGFR1-rearranged neoplasms) and to distinguish these from the majority of eosinophilic neoplasms, CEL-NOS and hypereosinophilic syndrome (HES). It is particularly important to identify the PDGFR rearranged cases because of the therapeutic option of tyrosine kinase inhibitors (TKI).

**Role of molecular analysis**

_JAK2_ mutations (V617F or exon 12) are found in nearly all cases of PV, and this analysis has assumed central importance in the diagnosis of PV and in distinguishing PV from secondary polycythaemia. _JAK2_ V617F mutation is also present in approximately 50% of ET and PMF and therefore mutation screening can help to exclude reactive thrombocytosis and fibrosis.

Cytogenetics will help to demonstrate clonality in the remainder of PMF but, apart from exclusion of CML, is rarely helpful in ET because of the low abnormality rate.

Ideally, MPN patient pathways should include molecular exclusion of _JAK2_ V627F for PV, ET, and PMF (and _BCR-ABL1_ for ET), before referral for cytogenetic analysis.

Full cytogenetic analysis can aid the characterisation of MPN with polycythaemia, and is indicated as a second line test in _JAK2_-negative cases where absolute erythrocytosis, without obvious secondary cause is still apparent [20].

There are few reports of cytogenetic studies in systemic mastocytosis (SM). No specific chromosome abnormalities are recognised, but the presence of a _KIT_ D816V mutation can be diagnostically helpful.

The molecular markers associated with MPN, such as mutations of _JAK2_, _MPL_, _TET2_ and _KIT_ are the focus of much interest because of their potential as targets for therapy and it is anticipated that the requirement for molecular genetic testing will progress significantly in coming years [21].
3.2 Sample Requirements at Diagnosis

Although JAK2 V617F can be detected in peripheral blood, fresh bone marrow aspirate is the tissue of choice for full cytogenetic analysis. Marrow can be cultured and harvested fixed cells stored for testing at a later date, depending on examination of bone marrow morphology and the results of initial tests.

**FISH for BCR-ABL1 only**

Heparinised bone marrow or blood samples are suitable for detection of a Philadelphia translocation or BCR-ABL1 gene rearrangement at diagnosis. If full cytogenetic analysis is not indicated, it is acceptable to test samples for BCR-ABL1 by FISH or RT-PCR only, to exclude CML, which should be by local agreement with referring haematologists. Uncultured cells, including bone marrow or blood smears, or ‘direct’ or short-term cultures are suitable material to test for BCR-ABL1 by interphase FISH. If such material is BCR-ABL1 positive, then G-band analysis should be carried out on the current sample or on a subsequent marrow/blood (2.2.1 note 2).

3.3 Analysis

**Cytogenetic analysis**

Different levels of investigation are possible depending on the specific requirements of the case. If G-band analysis is indicated, then this should be carried out as per guidelines for other myeloid disorders such as AML and MDS. If an abnormal karyotype is found, 5 abnormal metaphases should be fully analysed, with a further 5 metaphases scored for the same and additional obvious changes. In the event of a normal karyotype, 20 metaphases must be examined with at least 10 fully analysed and the remainder scored for obvious abnormalities.

**Supplementary FISH or Molecular Analysis**

Laboratories offering services for HES and SM should be able to provide comprehensive testing for these diseases, including FISH and/or molecular testing for specific abnormalities. Alternatively, samples may be forwarded to a suitable centre if confirmatory testing is required to identify patients with specific genetic abnormalities. In particular:
• CEL and HES: Cases with persistent unexplained eosinophilia (whether formally diagnosed as HES or not) should be screened for the cytogenetically cryptic FIP1L1-PDGFRA fusion by FISH or by RT-PCR using peripheral blood or bone marrow. Metaphase analysis should be considered for cases that test negative for FIP1L1-PDGFRA. Follow-up molecular analysis may be performed for cases that show visible rearrangements of relevant regions: e.g. 4q11-12, PDGFRA; 5q31-32, PDGFRB; 8p11-12, FGFR1; 9p24, JAK2; 9q34, ABL1. If chromosome analysis is successful, then further testing by FISH for PDGFRB or FGFR1 may not be cost effective: these abnormalities are usually microscopically visible by G-banding and cryptic cases have not yet been reported [22, 23]. Furthermore, these abnormalities are very rare [probably fewer than two new cases per year in the UK - Prof N Cross, pers. comm].

• For any rearrangements of ABL1, PDGFRA or PDGFRB detected by FISH, it is important to characterise the fusion gene by molecular analysis, in order to allow monitoring of residual disease following TKI therapy. If this testing is not available locally, samples may be referred onward to a suitable laboratory.

• SM: the majority of patients harbour a clonal KIT D816V mutation, the detection of which may prove clonality; however it is not an essential criterion for diagnosis and does not currently indicate treatment with a specific TKI. If testing is requested, bone marrow is the optimum sample, and a sensitive molecular assay or selection of CD117+ cells should be employed. If this testing is not available locally, samples may be referred onward to a suitable laboratory for testing. FIP1L1-PDGFRA has also been described in some cases of SM, but only in patients with peripheral blood and/or bone marrow eosinophilia.

3.4 Reporting
The detection of a cytogenetically abnormal clone supports a diagnosis of neoplasia. Comments regarding prognosis in MPN are rarely helpful and should not be made in cytogenetic reports.
3.5 Reporting time guidelines

All cases should be treated as routine referrals: 95% should be reported within 21 calendar days.

4 APPENDIX

Table 1 – Definitions of cytogenetic and molecular responses (Baccarani et al. 2009)

<table>
<thead>
<tr>
<th>Cytogenetic Response (CgR)</th>
<th>Ph+ve levels</th>
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</thead>
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<tr>
<td>No Response</td>
<td>96-100%</td>
</tr>
<tr>
<td>Minimal</td>
<td>66-95%</td>
</tr>
<tr>
<td>Minor Response</td>
<td>36-65%</td>
</tr>
<tr>
<td>Partial Response</td>
<td>1-35%</td>
</tr>
<tr>
<td>Complete Response / Cytogenetic Remission (CCgR)</td>
<td>0%</td>
</tr>
</tbody>
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Based on Ph positive metaphase cells in marrow.

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<th>Molecular Response (MR)</th>
<th>Log Reduction (LR)</th>
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<tr>
<td>Less than Major Molecular Response</td>
<td>&lt; 3 LR</td>
</tr>
<tr>
<td>Major Molecular Response (MMR)</td>
<td>&gt;= 3 LR - in two consecutive samples</td>
</tr>
<tr>
<td>Complete Molecular Response / Molecular Remission</td>
<td>BCR-ABL1 negative - in 2 consecutive</td>
</tr>
<tr>
<td></td>
<td>samples of adequate sensitivity (&gt;= 4</td>
</tr>
<tr>
<td></td>
<td>LR)</td>
</tr>
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### Table 2 – ELN definitions of response to first-line imatinib treatment in chronic phase (Baccarani et al. 2009)

<table>
<thead>
<tr>
<th>Response</th>
<th>Optimal</th>
<th>Suboptimal</th>
<th>Failure</th>
<th>Warnings</th>
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<tbody>
<tr>
<td>Diagnosis</td>
<td>CHR</td>
<td>No CgR</td>
<td>&lt;CHR</td>
<td>High risk CML. ACA.</td>
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<td>3 months</td>
<td>At least Minor CgR (&lt;65% Ph+ve)</td>
<td>(&gt;95% Ph+ve)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>Partial CgR (1-35% Ph+ve)</td>
<td>&lt; Partial CgR (&gt;35% Ph+ve)</td>
<td>No CgR</td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>CCgR (0% Ph+ve)</td>
<td>Partial CgR (1-35% Ph+ve)</td>
<td>&lt; Partial CgR (&gt;35% Ph+ve)</td>
<td>&lt; MMR (&lt; 3 log reduction)</td>
</tr>
<tr>
<td>18 months</td>
<td>MMR ( &gt; 3 log reduction)</td>
<td>&lt; MMR (&lt; 3 log reduction)</td>
<td>&lt; CCgR (&gt;1% Ph+ve)</td>
<td></td>
</tr>
<tr>
<td>Anytime</td>
<td>Stable or improving MMR</td>
<td>Loss of MMR ACA in Ph+ve cells AKD mutations (imatinib partial insensitivity)</td>
<td>Loss of CHR. Loss of CCgR. AKD mutations (imatinib resistant).</td>
<td>Any significant increase in BCR/ABL1 transcripts. Ph –ve abnormal clones</td>
</tr>
</tbody>
</table>

CHR = Complete Haematological Response; ACA = Additional chromosome abnormalities

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5 **REFERENCES**


8. Batty N, Kantarjian H, Borthakur G et al. (2008). Patients with chronic myeloid leukaemia with variant Philadelphia chromosome (Ph) translocations have a similar outcome as those with classic Ph when treated with imatinib or 2nd generation TKI. Blood 112: 1108 (abstr 3228).


6 Version Control

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