A British Society for Haematology Guideline on the Diagnosis and Management of Chronic Myeloid Leukaemia

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The management of chronic myeloid leukaemia (CML) has seen considerable change in the last several years, the objective of this guideline is to provide healthcare professionals with clear guidance on the investigation and management of CML in adults and children.

Methodology

This guideline was compiled according to the BSH process described at http://www.b-s-h.org.uk/guidelines. The Grading of Recommendations Assessment (GRADE) nomenclature was used to evaluate levels of evidence and to assess the

strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org.

Literature Review Details

Searches were performed using the online search engine MEDLINE (OVID) and EMBASE (OVID) up to January 2018. Search terms were either: (i) chronic myeloid leukaemia, (ii) leukaemia, myelogenous, chronic, BCR-ABL positive, (iii) chronic leukaemia or (iv) CML or CGL. The following terms were then searched in conjunction with these four baseline terms: protein kinase inhibitor, dasatinib, imatinib, nilotinib, tyrosine kinase inhibitor, TKI, bosutinib, ponatinib, interferon-alpha, bone marrow transplantation, bone marrow transplant or graft, stem cell transplantation, stem cell transplant. Filters were applied to include only publications written in English and studies carried out in humans.

Review of the Manuscript

Review of the manuscript was performed by the British Society for Haematology (BSH) Guidelines Committee Haemato-oncology Task Force, the BSH Guidelines Committee and the haemato-oncology sounding board of the BSH. It was also posted on the members section of the BSH website for comment. This guideline has also been reviewed by patient representatives from CML Support (http://www.cmlsupport.org). These organisations do not necessarily endorse the contents.

Diagnostic criteria and essential investigations

Although CML can be diagnosed from peripheral blood findings in conjunction with positivity for *BCR-ABL1*, we recommend that a bone marrow (BM) aspirate is taken for full karyotype analysis and morphological investigation to confirm the phase of the disease (Arber *et al*, 2016). Detection of additional cytogenetic abnormalities (ACA), particularly 'major route' abnormalities, such as an extra Philadelphia (Ph) chromosome, trisomy 8, isochromosome 17q or trisomy 19, suggests an increased risk of progression to accelerated phase (AP) or blast crisis (BC) (Fabarius *et al*, 2015). However, the negative impact of these abnormalities at diagnosis on survival in adults is not seen in children (Millot *et al*, 2017a). A bone marrow trephine biopsy is not routinely required.

About 95% of CML cases exhibit a Ph chromosome, or a variant, visible on conventional cytogenetic analysis. The remaining cases with a cryptic *BCR-ABL1* fusion may be detected by fluorescence *in situ* hybridisation (FISH) or reverse transcriptase polymerase chain reaction (RT-PCR) (Cross *et al*, 1994).

Most (97-98%) CML cases express a chimaeric mRNA in which *BCR* exon 13 or exon 14 joins *ABL1* exon 2 (e13a2 and e14a2 fusions, respectively). The remaining 2-3% expresses diverse, atypical mRNA fusions involving other exons of *BCR* (usually e1, e6, e8, e19) or *ABL1* (a3). It is important to determine the transcript type prior to treatment to enable effective molecular monitoring of response (Baccarani *et al,* 2019). Currently, there is no clinical utility in performing *BCR-ABL1* kinase domain (KD) mutation analyses at diagnosis in patients in chronic phase (CP). The examination of the patient and the blood and marrow morphology are essential to enable the calculation of a prognostic score, either Sokal or the EUTOS Long Term

Survival (ELTS) score, which may be more discriminatory than Sokal (Pfirrmann *et al*, 2016)(Table 1). ELTS is the only prognostic score of value in children (Salas *et al*, 2015; Millot *et al*, 2017b). Compared to adults, children in CP often present with higher white cell counts, larger spleens relative to body proportion and a greater proportion present in AP or BC (Millot*, et al* 2005).

Table 1: ELTS score

Risk Group	ELTS score*
low-risk group	≤1.5680
intermediate-risk group	>1.5680≤2.2185
high-risk group	>2.2185

* EUTOS Long Term Survival (ELTS) ELTS score = 0.0025 × (age/10)^3 + (0.0615 × spleen size below costal margin)+(0.1052 × blasts in peripheral blood) + (0.4104 × (platelet count ×10^9/l /1000) -0.5). (www.leukemia-net.org/content/leukemias/cml/elts_score/index_eng.html)

Recommendations

- **At diagnosis, a BM aspirate should be performed for full karyotype analysis and to confirm the phase of the disease. Grade 2B**
- **Establishing the fusion type is required for molecular monitoring to guide future management. Grade 1B**
- **It is useful to calculate the EUTOS Long Term Survival (ELTS) score to inform prognosis. Grade 2B**

Primary therapy for patients in chronic phase

Four tyrosine kinase inhibitors (TKIs) - imatinib, and the second generation (2G) TKIs bosutinib, dasatinib and nilotinib, are now licensed for use in newly diagnosed patients, of which all but bosutinib are NICE approved. The 2GTKIs have been trialled directly against imatinib in large phase III randomised studies with remarkably similar results to each other (appendix 1).

The majority of patients diagnosed in 2019 have a realistic prospect of a life expectancy similar to that of the normal population (Bower *et al*, 2016). For many patients there is no reason to choose a 2GTKI over imatinib which has a well-established safety profile with no life-threatening long-term side-effects identified to date (Hochhaus *et al*, 2017a). More patients are likely to die of causes other than their leukaemia, and co-morbidities are more predictive of death (Saussele *et al*, 2015). Furthermore the German CML IV study showed that 88% of imatinib-treated patients (some receiving higher doses of 800mg) achieved a major molecular response (MMR) by 10 years suggesting efficacy similar to that seen with 2GTKIs (Hehlmann *et al,* 2017). In children, first line imatinib therapy achieves 60-70% complete cytogenetic response (CCyR) rates and 45% MMR rates at 12 months (Suttorp *et al*, 2012). However, there are some groups in CP that might benefit from 2GTKIs upfront:

1. Patients with high or intermediate ELTS or Sokal scores in whom a reduction in disease progression has been demonstrated with a first line 2GTKI (Jabbour *et al*, 2014; Larson *et al*, 2012; Cortes *et al*, 2018; Yeung *et al*, 2015).

2. Women who wish to have children, where the more rapid molecular response achieved with a 2GTKI is desirable (see *CML and parenting* section).

3. ‘Younger’ patients, nominally the under 30s, and children, who are excellent candidates for stem cell transplantation if the need arises, and in whom concerns have been raised regarding more aggressive disease at presentation (Castagnetti *et al*, 2015). In a Phase II study as first line therapy in children, dasatinib achieved a 92% CCyR and 52% MMR at 12 months in CP CML leading to a licence for its use (Gore, *et al*, 2018).

The early use of a more potent TKI should be balanced against the risk of inducing and/or exacerbating concomitant illnesses (Table 2). This is particularly pertinent in older patients as the number of co-morbidities increases with advancing age (Saussele et al, 2015). Although there is no evidence that older patients respond less well to TKI (Cortes *et al*, 2003; Brunner *et al*, 2013; Björkholm *et al*, 2011) older subjects may handle drugs differently and/or be receiving other medications affecting the CYP450 pathway (which decrease TKI metabolism and enhance their complications) and hence often require more frequent dose reductions or treatment interruptions than younger patients (Latagliata *et al*, 2013).

Table 2: Guidelines for first-line TKI choice by pre-existing medical condition (adapted from Michael Deininger, personal communication)

Co-morbidity	Bosutinib	Dasatinib	Imatinib	Nilotinib
Hypertension				
Ischaemic heart disease				
Cerebrovascular thrombosis				
Peripheral arterial occlusive disease				
Prolonged QT interval*				
Congestive cardiac failure				
Diabetes mellitus				
Gastrointestinal bleeding**				
Pulmonary hypertension				
Chronic pulmonary disease				
Pancreatitis				
Abnormal liver function				

	No contra-indication
	Low risk of exacerbation of pre-existing condition
	Intermediate risk of exacerbation of pre-existing condition
	Avoid if possible

* Some evidence that all 2GTKI prolong QT.

** Imatinib has been associated with the development of gastric antral vascular ectasia (GAVE)

All patients should have assessment of cardiac risk using the QRisk2 (or equivalent), ECG, baseline estimates of lipid profiles, and fasting glucose and/or HbA1c levels (Valent *et al*, 2017). Given recent data suggesting the use of TKIs may be associated with reactivation of hepatitis viruses, all patients should have pre-treatment hepatitis B and C serology assessments (Ikeda *et al*, 2006).

Recommendations

- **Imatinib is the recommended first line treatment for the majority of adults and children with CML presenting in CP. Grade IA**

- **All patients should have baseline assessment with an ECG, lipid profile, fasting glucose or HbA1c, cardiac risk assessment, and hepatitis B and C screening. Grade 2B**

- **Consider a 2GTKI for:**

    - **patients with a high or intermediate ELTS or Sokal score. Grade 2B**

    - **patients who wish to explore treatment discontinuation at an early stage eg. female patients who wish to become pregnant. Grade 2B**

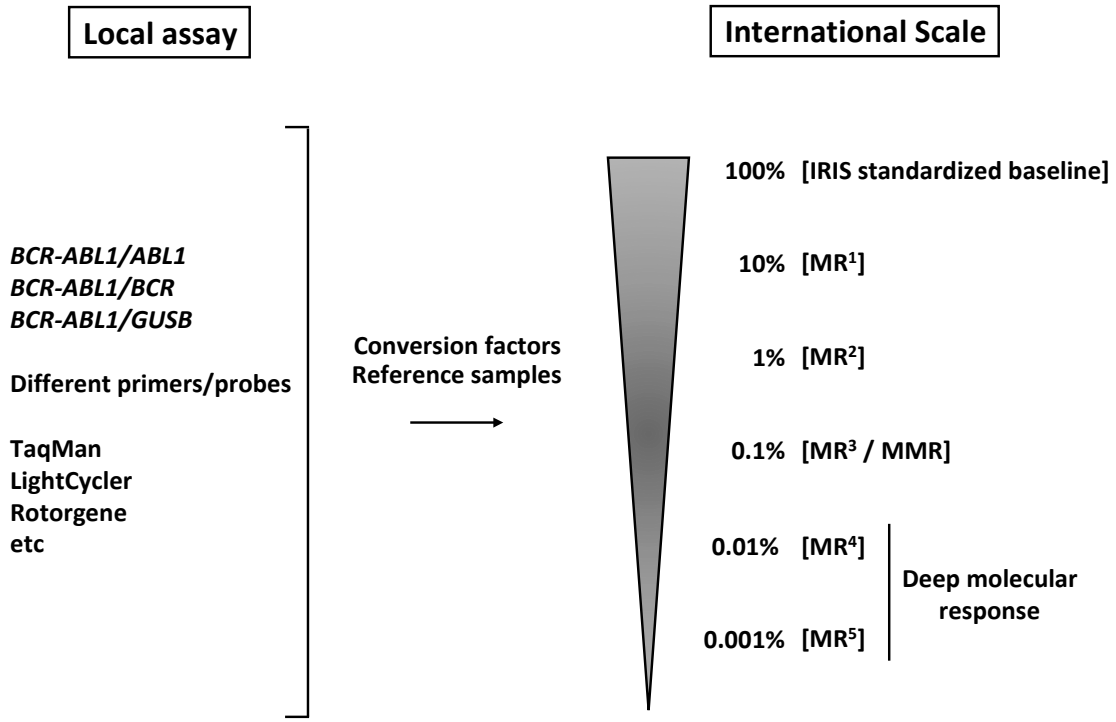
- **Co-morbidities should be assessed to help in the choice of 2GTKI. Grade 2B**

Response criteria and monitoring response to therapy

Assessment of treatment response by molecular monitoring is by far the strongest predictor of outcome, and sequential monitoring can detect inadequate responses and rising levels of disease indicative of developing resistance to the current TKI.

Molecular monitoring should be performed by reverse transcriptase quantitative PCR (RT-qPCR) from total peripheral blood leucocytes using standardised methodologies that adhere to national and international guidelines (Foroni *et al*, 2011; Cross *et al*, 2012, 2015b, 2018). See Figure 1 (Cross *et al*, 2015a). Assessment by digital PCR as an alternative to RT-qPCR may increase in the future, but irrespective of the method used, results should be expressed on the International Scale (IS) (Hughes *et al*, 2006) and indicate the molecular response (MR) level.

Figure 1. The International Scale (IS) for *BCR-ABL1* RT-qPCR measurement. Centres continue to use their established systems for *BCR-ABL1* and convert results to IS using conversion factors (CFs) derived by sample exchange or by the use of calibrated reference reagents. *MMR* major molecular response; *MR4* and *MR5* are four- and five-log reductions, respectively, from the International Randomized Study of Interferon and STI571 (IRIS) standardised baseline.



Laboratories should be accredited, participate in appropriate external quality assurance schemes (currently managed by UKNEQAS LI in the UK) and establish internal quality assurance to measure accuracy and stability of results over time (Branford & Hughes, 2006). Laboratories should also ensure that the limit of detection of their assay is optimised to ensure the ability to detect disease levels down to MR4.5 (4.5 log reduction below baseline) in most patient samples. Patients

with atypical *BCR-ABL1* variants should be monitored using specifically designed assays, by a laboratory with expertise in the methodology.

Bone marrow aspirate, cytogenetic analysis and FISH are not required to monitor response to therapy on a routine basis, but are recommended in selected patients e.g. those with cytopenia to exclude Ph negative (-ve) ACA in Ph -ve cells (Issa et al, 2017), and prior to TKI switch for resistance or in advanced phase.

Response criteria

Haematological and cytogenetic responses still have a role in selected patients (Baccarani *et al*, 2013; Marin *et al*, 2008) - but these recommendations focus on MR criteria. Assessment of response to TKIs early in the treatment course allows patients at risk of poorer survival to be identified. Marin and colleagues demonstrated the importance of early molecular response (EMR - defined as 3-month *BCR-ABL1* transcript <10% IS, MR1) for outcome in over 230 CML patients (Marin et al, 2012a)(appendix 2). Similar results have been reported in children (Millot*, et al* 2014).

Analysis of CML Study IV data showed that *BCR-ABL1* (IS) transcript levels of >1%, MR2, at 6 months were associated with a significantly inferior 5-year overall survival (OS) of 89% versus 96.9% for patients achieving ≤1% (equivalent to CCyR) at 6 months (Hanfstein *et al*, 2012). With longer term TKI treatment, achievement of MMR (*BCR-ABL*1 (IS) <0.1%; MR3) is associated with durable CCyR and excellent event-free survival (EFS) (Druker *et al*, 2006; Hehlmann *et al*, 2011; Hughes *et al,* 2010) (Table 3), although the time by which MMR should be achieved remains controversial (Saussele *et* al, 2018). There is no convincing evidence that achievement of deep molecular remission (DMR), as defined by the EUTOS guidelines, i.e. MR4 or better (Cross *et al*, 2015b), is associated with improved OS in

comparison with patients in MR3 (MMR)(Hehlmann *et al,* 2014). However, achievement of DMR is a requirement for treatment-free remission (TFR) eligibility.

Table 3: Overall Survival according to molecular response during first 12 months after initiation of first-line imatinib

	BCR-ABL1 (IS)	3 months	6 months	12 months	18 months
Hanfstein *et al*, 2012 (5 year OS)	≤1% 1%-10% >10%	97.2% 93.9% 87.0%	96.9% 89.6% 87.9%		
Marin *et al*, 2012b (8 year OS)	≤9.84% >9.84% ≤1.67 >1.67 ≤0.53% >0.53%	93.3% 56.9%	 93.7% 74.7%	 95.4% 74.7%	
Hughes *et al*, 2010 (7 year OS)	≤0.1% 0.1-1% 1-10% >10%		90.3% 93.0% 100% 68.2%	92.5% 96.7% 85.7% 89.2%	94.9% 95.7% 84.0% 89.8%
Hehlmann *et al*, 2011 (3 year OS)	<0.1% ≥0.1%			99% 93%	

Patients on TKI therapy should be monitored every three months until the achievement of a stable MMR (<MR3 - sustained for one year) and thereafter at 3-6 monthly intervals: the precise frequency of monitoring will depend on the individual depth of response, but also on any concerns regarding compliance with therapy and/or previous demonstration of TKI resistance (Claudiani *et al,* 2017).

If the decision is made to stop treatment on the basis of prolonged DMR, then more frequent monitoring is essential during the first 24 months as per the schedule described in the later section *'the potential for discontinuing treatment in some patients'* (Saussele *et al.* 2016). Monitoring of patients post-allogeneic stem cell transplanation (alloSCT) should follow the same schedule as patients on TKI treatment, but often needs individualising.

BCR-ABL1 KD mutational analysis should be performed in the event of treatment failure or 'warning', according to European LeukaemiaNet (ELN) recommendations (Soverini *et al*, 2011; Baccarani *et al*, 2013) and may guide subsequent treatment options (Table 4). Analysis by Sanger sequencing is the current standard approach but greater sensitivity and additional clinical value are afforded by next generation sequencing (NGS) and we should work towards adopting this methodology as routine practice (Kizliors *et al*, 2019; Soverini *et al,* 2020).

Table 4: Clinical significance of *BCR-ABL1* resistance-associated mutations

MUTATION	INTERVENTION
T315I	Allogeneic stem cell transplant (alloSCT), ponatinib, investigational drugs including asciminib (Hughes *et al,* 2019a)
T315A, F317L/V/I/C	Consider nilotinib, bosutinib or ponatinib rather than dasatinib
Y253H, F359V/C/I, E255K/V	Consider dasatinib, bosutinib or ponatinib rather than nilotinib
V299L	Consider nilotinib or ponatinib rather than dasatinib or bosutinib
Any other mutation	Clinical significance unclear: consider high-dose TKI, alternative TKI, alloSCT, investigational drugs

Recommendations

- **Molecular monitoring should be performed by RT-qPCR and, for typical transcripts, expressed according to the IS and by MR level. Grade IA**

- **Laboratories should be accredited, participate in appropriate internal and external quality assurance schemes and ensure that their assay is optimised to detect disease levels down to MR4.5. Grade IB**

- **Monitoring should be every three months until the achievement of a stable MMR (<MR3 - sustained for one year) and thereafter at 3-6 monthly intervals but the individual depth of response, concerns regarding compliance and/or previous TKI resistance will determine the precise frequency. Grade 1B**

- ***BCR-ABL1* KD mutational analysis should be performed in the event of ELN treatment failure or 'warning'. Grade 1B**

Management of patients who are resistant to or intolerant of first line therapy

Patients may discontinue imatinib as first line therapy either due to primary resistance/failure as defined by the ELN guidelines or because of intolerance (Baccarani *et al*, 2013). Studies of second line treatment have tended to include both groups of patients and there are no studies directly comparing the various 2GTKIs in this setting. Comparison is difficult due to the differing patient populations, follow up times and definitions of outcomes used (Hochaus *et al*, 2008; Kantarjian *et al*, 2011a; Gambacorti-Passerini & Brummendorf, 2014; Shah *et al*, 2014; Saglio *et al*, 2010a; Milojkovic *et al*, 2012a). In the absence of specific mutations (Table 4) all three 2GTKIs show evidence of efficacy, with as many as 40% of patients achieving durable CCyR.

Although failure to achieve *BCR-ABL1* (IS) < 10% (MR1) at 3 months identifies a group of patients with poorer survival (Hanfstein *et al*, 2012; Marin *et al*, 2012b), there is no evidence that a change of therapy at this point improves OS. At present, in the absence of a clinical trial, it is reasonable to assess patients on an individual basis, taking into account the level of *BCR-ABL1* (IS), the rate of fall, the initial risk score and any pre-existing co-morbidities before making a decision to continue or switch to second line treatment. However, if by 6 months of therapy patients are clearly failing treatment according to ELN guidelines, a change to a 2GTKI should be made (Table 5).

Dose escalation of imatinib to 600-800mg per day should no longer be considered for those failing standard dose imatinib (Jabbour *et al*, 2009; Cortes *et al*, 2016a), though 600mg could be considered for selected patients with a sub-optimal response (meeting the ELN 'warning' criteria) with no evidence of a mutation and with good tolerance of the standard dose.

Patients receiving 2GTKI therapy due to intolerance of imatinib have better responses than those with initial resistance. Other factors predicting response to second line therapy include a low prognostic (Sokal) score at diagnosis, previous cytogenetic response and absence of cytopenias on imatinib (Milojkovic *et al*, 2010; Jabbour *et al*, 2013).

Patients with non-haematological intolerance to imatinib have a low incidence of cross-intolerance with second line TKIs with 1-4% of patients experiencing the same grade 3/4 adverse event (Cortes *et al*, 2011; Khoury *et al*, 2016). Conversely, recurrence of grade 3/4 haematological adverse events is high (55-86%). These may be managed with dose interruption, dose reduction and cytokine support with

approximately 20% of patients eventually discontinuing treatment. Asciminib (ABL-001) is an allosteric inhibitor of BCR-ABL which has recently shown promise in clinical trials for CML patients, either as a single agent (for TKI resistance/intolerance) or in combination with TKIs (for TKI resistance, including due to T315I) (Hughes *et al,* 2019a).

Table 5. First-line TKI response milestones

***BCR-ABL*1 (IS)**	**3 months**	**6 months**	**12 months**	**>12 months**
>10%	**Consider TKI switch[a]**	**Failure – switch TKI**	**Failure – switch TKI**	**Failure – switch TKI**
1-10%	**Continue same TKI**	**Consider TKI switch[a]**	**Failure – switch TKI**	**Failure – switch TKI**
0.1-1%	**Continue same TKI**	**Continue same TKI**	**Consider TKI switch[a]**	**Consider TKI switch[a]**
<0.1% (MR3;MMR)	**Continue same TKI**	**Continue same TKI**	**Continue same TKI**	**Continue same TKI**
<0.01% (MR4;DMR)	**Continue same TKI**	**Continue same TKI**	**Continue same TKI**	**Consider TFR[b]**

[a]Patients in this category require careful assessment of factors such as age/comorbidities, baseline prognostic factors, cytogenetic response, trajectory of molecular response, compliance, presence of KD mutation, side effects. This intervention is not currently NICE approved in the UK.

[b]see treatment free remission (TFR) section for details of TFR eligibility. Patients should have been on a TKI for at least 3 years, and duration of DMR is important.

Recommendations

- **Change to an alternative TKI should be considered if treatment failure on first line therapy is documented. Grade 1A**

- **The choice of second line therapy in resistant patients is initially guided by *BCR-ABL1* KD mutational analysis. Grade 1B**

- **Dose escalation to 600mg of imatinib per day is reasonable for patients with a sub-optimal response meeting the ELN 'warning' criteria and with good tolerance of the standard dose. Grade 2B**

- **In the absence of specific mutations the patients pre-existing co-morbidities and the known side effect profiles of the 2GTKIs should inform the treatment choice. Grade 2B**

Management of patients with advanced phase disease – accelerated phase (AP) and blast crisis (BC)

5-10% of patients will present in *de novo* AP or BC CML (DeFilipp & Khoury, 2015). Around two-thirds of BC CML is myeloid, and one-third lymphoid or bi-phenotypic. TKI therapy of CML CP has reduced progression to AP/BC from 5-20% per annum to 1-5% (Hehlmann, 2012), although the risk of progression is not uniform over time. Contention exists around the definitions of AP and BC CML (appendix 3), but the ELN criteria are recommended as they have been used in the majority of randomised clinical trials of TKI (Baccarani *et al*, 2013).

Historically, the aim of therapy in advanced phase was to return patients to a second CP (CP2) to maximise the likelihood of success of alloSCT (DeFilipp & Khoury, 2015). The recommended dose of imatinib for newly diagnosed AP or BC CML is 400mg twice daily and dasatinib 140mg once daily. Nilotinib is not licensed for advanced phase CML.

Treatment of patients in accelerated phase

There are no randomised controlled trials of TKI therapy in AP CML, merely multiple single arm studies (appendix 3). Patients presenting with, or progressing to AP on TKI therapy, have a poor prognosis with inferior responses to TKI therapy (Oyekunle

et al, 2013) and a median OS ranging from 9 months (Saussele & Silver, 2015) to 1.4 years (Söderlund *et al*, 2017). Response rates and survival are shown in Table 6. AlloSCT is recommended for the majority of transplant-eligible patients in AP, since several studies have confirmed superior outcomes following transplantation as compared to ongoing TKI therapy (Jiang *et al*, 2011; Xu *et al*, 2015; Nair *et al*, 2015). One exception is patients who present in AP and achieve optimal cytogenetic and molecular responses, where the risk/benefit does not favour transplantation (DeFilipp & Khoury, 2015; Ohanian *et al*, 2014). Approximately 50% of AP patients develop imatinib resistance within 2 years (Hochhaus & La Rosee, 2004). However, durable responses have been obtained in a minority of patients on imatinib with a 7 year PFS of 35% in one study (Palandri *et al*, 2009). The recommendation in this group is to aim for an optimal TKI response ideally with a 2GTKI at milestone timepoints (Table 5) and if these are not reached, proceed to alloSCT if the patient is eligible and a suitable donor is available (Baccarani *et al*, 2013). AP with an excess of lymphoblasts should be treated as per lymphoid BC CML.

Treatment of patients in blast crisis

As in AP CML, there are multiple single arm studies but no randomised controlled trials of TKI therapy in BC CML (appendix 3), with limited data for front-line use of 2GTKIs in *de novo* BC CML. Response rates are shown in Table 6. Responses are not durable, with median response duration of less than 12 months for all TKIs. Although there are no data from comparative studies to indicate that using TKI in combination with chemotherapy is superior to TKI alone, treatment with FLAG-Ida - fludarabine, idarubicin, granulocyte-colony stimulating factor (GCSF) and high dose cytarabine - with or without a TKI, has become the most common approach in the UK, especially if there is significant delay in arranging alloSCT (Milojkovic *et al*,

2012b)(Figure 2). All patients should proceed to alloSCT if they are eligible and have a suitable donor, regardless of response to initial therapy. There is some evidence that dasatinib crosses the blood brain barrier; thus dasatinib may be preferred in combination with conventional chemotherapy and intrathecal chemotherapy for patients with lymphoid BC CML or CNS relapse (Porkka *et al*, 2008). Some patients may have biphenotypic acute leukaemic transformation, and these patients too should receive CNS prophylaxis. Figure 2 summarises the approach to treating advanced phase disease.

Table 6: Response rates and survival in TKI trials in advanced phase CML

Disease phase	TKI	HR (%)	MCyR (%)	OS
AP (de novo)	Imatinib[1]	65-85	28-54	~74% at 12-18 months
AP (resistant / intolerant)	Dasatinib[2]	64-81	33-43	82% at 12 months
	Nilotinib[3]	47-66	29-48	~80% at 18 months
	Bosutinib[4]	57%	40%	NA
Heavily pre-treated AP patients, including T315I	Ponatinib[5]	55%	39%	~84% at 12 months
BC (de novo)	Imatinib[6]	34-60%	11-25%	22-36% at 12 months
BC (resistant / intolerant)	Dasatinib[7]	33-36%	25-56%	22-49% at 12 months
	Nilotinib[8]	21-39%	18-40%	42% at 12 months
	Bosutinib[4]	32%	29%	NA
Heavily pre-treated BC patients, including T315I	Ponatinib[5]	31%	23%	NA

[1]Furtado *et al,* 2015; Hoffman *et al,* 2013; Jiang *et al,* 2011; Kantarjian *et al,* 2002a, 2005; Silver *et al,* 2009; Talpaz *et al,* 2002.

[2]Apperley *et al,* 2009; Guilhot *et al,* 2007; Kantarjian *et al,* 2009.

[3]Kantarjian *et al,* 2006; le Coutre *et al,* 2012; Nicolini *et al,* 2012.

[4]Gambacorti-Passerini *et al,* 2015

[5]Cortes *et al,* 2013

[6]Silver *et al,* 2009; Druker *et al,* 2001; Kanatrjian *et al,* 2002b; Palandri *et al,* 2008; Sawyers *et al,* 2002; Sureda *et al,* 2003.

[7]Cortes *et al,* 2008; Saglio *et al,* 2010a; Talpaz *et al,* 2006.

[8]Kantarjian *et al,* 2006; Giles *et al,* 2012.

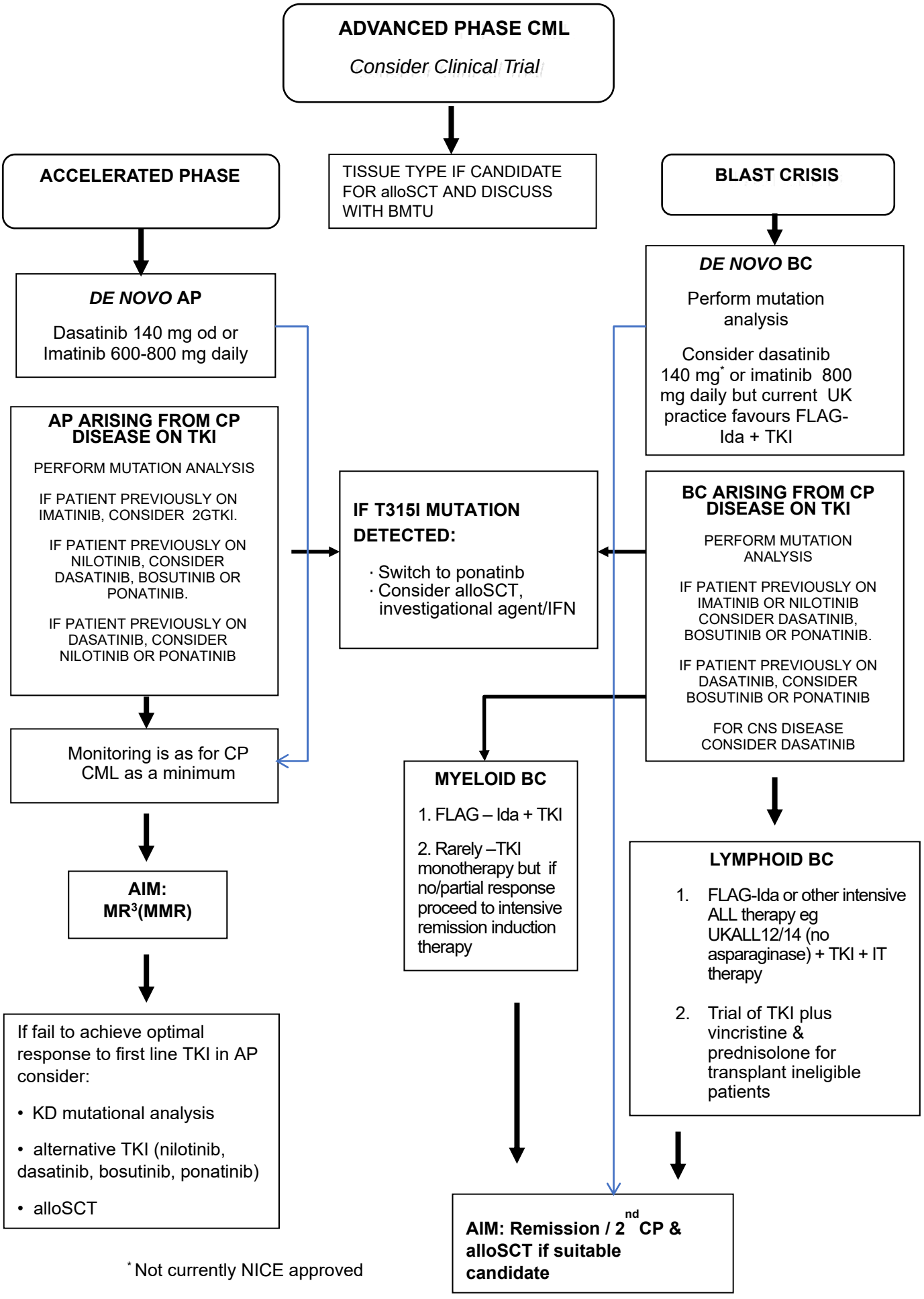


Figure 2. Approach to the patient in advanced phase CML

Recommendations

- **Patients in *de novo* AP CML should ideally be treated with a 2GTKI or, with consideration of alloSCT if sub-optimal response. Grade 1B**

- **All responding, transplant-eligible patients in BC CML should proceed to alloSCT. Grade 1B**

Side effects of tyrosine kinase inhibitors and their management

Side effects are common during TKI treatment but many patients can tolerate these with management as listed in Table 7. Dose reduction or treatment suspension and slow titration back to a dose which achieves an adequate MR is sometimes required. If this does not improve side effects then switching to an alternative TKI may be required as there is little cross intolerance between different TKIs (Steegman *et al,* 2016).

Table 7. Side effects of TKIs and their management

General	Fatigue, insomnia, oedema, sub-conjunctival haemorrhage	Consider: • dose reduction of TKI for side-effects • antihistamines • switching TKI as little cross-reactivity of side effects is seen in clinical practice • topical steroids for symptomatic treatment of skin rash • corticosteroids for elevated liver transaminases • oral steroids for pleural effusion • diuretics may be helpful in the management of peripheral oedema • Loperamide for diarrhoea
Skin and subcutaneous tissue	Severe cutaneous adverse reactions (SCARs), rash, dry skin, itch, alopecia, sweats	
Musculoskeletal	Myalgia, cramp arthralgia	
Gastrointestinal	Nausea, vomiting, anorexia, diarrhoea, constipation	
Hepatobiliary	Abnormal LFTs,* pancreatitis,	
Haematological	Bone marrow suppression	
Renal	Renal impairment	
Infection	Increased risk of infection (due to cytopenia) and possible hepatitis B reactivation	
Metabolism/endocrine	thyroid function abnormalities, glucose intolerance/diabetes, gynaecomastia, erectile dysfunction, effects on fertility and gametogenesis	
Neurological	Headache, migraine, rarely - dizziness, paraesthesia, PRES**	
Cardiorespiratory	Hypertension, pleural or pericardial effusion, heart failure, pulmonary arterial hypertension, arterial or venous thromboembolism, QT prolongation	

*Liver function tests - a rise in bilirubin is commonly noted with nilotinib and may uncover patients with undiagnosed Gilbert's disease. This is not clinically significant and uridine-diphosphoglucuronate glucuronosyltransferase (UDPGT-1A1) genotyping is not indicated.

**Posterior reversible encephalopathy syndrome

Cardiovascular and respiratory side effects

Many CML patients are at high cardiovascular risk because of co-morbidities, and

TKIs may increase these risks.

Cardiovascular risk assessment

Risk should be assessed and treated in collaboration with the patient's GP (https://www.nice.org.uk/guidance/cg181). Patients with previous cardiovascular events should be offered secondary prevention. All others, particularly those on TKIs associated with an increased incidence of arterial thrombotic events (ATEs), should have an assessment of cardiovascular risk (https://www.qrisk.org/) and those with a 10-year risk of >10% should be offered atorvastatin 20mg daily. Aspirin should not be prescribed for primary prevention in asymptomatic patients except those with known carotid artery stenosis >50% (Baigent *et al*, 2009; Piepoli *et al.* 2016). Hypertension is common (>10% with some TKIs; Table 8) but the risk of life-threatening events is low (Chai-Adisaksopha *et al*, 2016). Blood pressure (BP) should be measured before and during TKI treatment, and hypertension treated in collaboration with the GP according to current UK guidelines (https://www.nice.org.uk/guidance/cg127). TKIs should be suspended if the BP is above 180/110mmHg. QT prolongation is rare (Table 8): ECGs should be performed at baseline for patients commencing bosutinib and nilotinib, or when clinically indicated. Patients with a QT interval corrected by Fridericia (QTcF) >450ms (males) or >460ms (females) should have electrolytes measured and be referred for specialist advice. Venous thromboembolic disease is uncommon but ATEs have been reported frequently in patients on nilotinib and ponatinib (Table 8).

Breathlessness

Appropriate investigations include ECG (atrial fibrillation, myocardial infarction) and chest X-ray (pleural or pericardial effusion, heart failure, infection) and echocardiography. Pleural effusions are common with dasatinib. The incidence increases with advancing age (Hughes, *et al,* 2019b) and require suspension of the

TKI until resolution which can take several weeks. TKIs should then be restarted at 50% of the previous dose and then increased until an adequate MR is obtained. An alternative TKI should be started if the effusion recurs - steroids can be used to speed the resolution of the effusion but usually are not needed, and chest drains should be avoided unless required to relieve symptoms. Echocardiography can be helpful when the cause of breathlessness remains unclear to exclude pulmonary arterial hypertension (PAH). Heart failure, PAH and pericardial effusions are rare and can cause non-specific symptoms (Table 8). Treatment is to interrupt the TKI and refer to a specialist. Rarely, a computerised tomography pulmonary angiogram (CTPA) may be required to exclude pulmonary emboli. A trial off TKI treatment, a dose reduction or change in TKI can improve unexplained dyspnoea. Interestingly pulmonary and pericardial adverse events are not reported in children.

Cardiovascular risk and events should be identified and treated appropriately, but it is important to ensure that patients are not denied the opportunity to benefit from TKI treatment unnecessarily when cardiovascular risk can be managed and events treated often without long-term sequelae.

In children, monitoring for long term effects of TKI use include linear growth velocity, pubertal Tanner staging and hormonal profile, thyroid and parathyroid function tests, an annual echocardiogram, HbA1C, and 5 yearly DEXA scanning.

Table 8. Cardiovascular and respiratory side effects of TKIs

	imatinib	bosutinib	dasatinib	nilotinib	ponatinib	treatment options
hypertension	**uncommon*** (<1%)	**common*** 3.9% G1-2 1.6% G3 0% G4	**common** (<10%)	**common** (<10%)	**very* common** (≥10%)	NICE guidance[3], start or increase treatment at >160/100mmHg, suspend TKI at >180/110mmHg
pleural effusions	**uncommon** (<1%)	**common** 4.3% G1-2 1.6% G3 0.1% G4	**very common** 23% G1-2 5% G3-4	**uncommon** (<1%)	**common** (<10%)	suspend TKI, restart TKI at lower dose when resolved. Drainage should not usually be required.
pericardial effusion	**rare*** (<0.1%)	**common** 1.5% G1-2 0.2% G3 0.1% G4	**common** 3% G1-2 1% G3-4	**uncommon (<1%)**	**common** (1.3%)	suspend TKI, symptomatic treatment as required, restart TKI at lower dose when resolved
pulmonary oedema	**uncommon** (<1%)	**uncommon** 0.1% G1-2 0.1% G3 0.1% G4	**common** 1% G1-2 1% G3-4	**uncommon** (<1%)	**not reported**	suspend TKI, symptomatic treatment as required, restart TKI at lower dose when resolved
pulmonary hypertension	**rare** (<0.1%)	**uncommon** 0.4% G1-2 0.1% G3 0 G4	**common** 1% G1-2 1% G3-4	**not known**	**common** (<10%)	suspend TKI, consider alternative TKI at standard dose when resolved
heart failure	**uncommon** (<1%)	**not reported**	**common** 1% G1-2 0% G3-4	**uncommon** (<1%)	**common** (2%)	suspend TKI, heart failure symptoms due to left ventricular systolic dysfunction require cardiological investigation and treatment according to NICE guidance

arterial thrombosis	**not known**	**not reported**	**uncommon** (<1%)	angina, myocardial infarction **common** 6.1%	angina, myocardial infarction **common** 9.6%	suspend TKI , specialist investigation and treatment according to NICE guidance
				cerebro-vascular events **common** 2.2%	cerebro-vascular events **common** 7.3%	
				peripheral arterial occlusive disease **uncommon** 1.4% G3-4	peripheral arterial occlusive disease **common** 6.9%	
venous thrombosis	**not known**	**not reported**	**rare** (<0.1%)	**not known**	DVT/PE **common** 5%	suspend TKI , specialist investigation and treatment according to NICE guidance
QT prolongation	**not reported**	**common** 1.0% G1-2 0.1% G3 0 G4 Baseline ECG is recommended	**uncommon** 1% G3-4	**common** <10% Baseline ECG is recommended	**not known**	suspend TKI , cardiology investigation and treatment

* Frequency of side effects: very common > 10%; common > 1%; uncommon < 1%; rare < 0.1%

(Data from published Summary of Patient Characteristics (SPCs) current at 17/08/17)

As regards how often patients on TKI therapy should be screened for potential toxicity, Table 9 summarises a recommendation for best practice.

	Bosutinib	Dasatinib	Imatinib	Nilotinib	Ponatinib
Laboratory investigations					
FBC	At least 3 monthly	At least 3 monthly	At least 3 monthly	At least 3 monthly	At least 3 monthly
Biochemisty (renal, liver, bone profile)	At least 3 monthly	At least 3 monthly	At least 3 monthly	At least 3 monthly	At least 3 monthly
Lipid profile	Clinical indication	Clinical indication	Clinical indication	12 monthly	12monthly
B-type natriuretic peptide (BNP)*	Clinical indication	12 monthly	Clinical indication	12 monthly	12 monthly
HbA1c	Clinical indication	Clinical indication	Clinical indication	12 monthly	12 monthly
Thyroid function tests (TFT)	Clinical indication	Clinical indication	Clinical indication	Clinical indication	12 monthly
Platelet function	Clinical indication	Clinical indication	Clinical indication	Clinical indication	Clinical indication
Amylase	Clinical indication	Clinical indication	Clinical indication	Clinical indication	Clinical indication
***ABL1* kinase domain mutation**	At warning or failure of response	At warning or failure of response	At warning or failure of response	At warning or failure of response	At warning or failure of response
Other investigations					
Blood pressure	At least 3 monthly	At least 3 monthly	Clinical indication	At least 3 monthly	At least 3 monthly
ECG	Clinical indication	Clinical indication	Clinical indication	Clinical indication	Clinical indication
Echocardiogram	Clinical indication	Clinical indication	Clinical indication	Clinical indication	Clinical indication
Chest X-ray	Clinical indication	Clinical indication	Clinical indication	Clinical indication	Clinical indication

*If raised, proceed to other investigations at bottom of table and consider referral for cardiology opinion

Table 9. Recommended frequency of monitoring for TKI-related toxicity

Recommendations

- **Most side effects of TKIs can be managed by dose interruption or reduction and slow titration back to a dose that maintains MMR (<MR3). Grade 1A**

- **There is little cross intolerance between imatinib and 2GTKI so changing therapy is advised if intolerable side effects occur. Grade 1A**

- **Patients with previous cardiovascular events should be offered secondary prevention via their GP. All patients on TKIs should have a cardiovascular risk assessment and those with a 10-year risk of >10% should be offered atorvastatin 20mg daily. Grade 1B**

- **BP should be measured before and during TKI treatment, and hypertension treated in collaboration with the GP. Grade 2A**

- **Breathlessness should be investigated thoroughly as patients are at risk of alternative causes than pleural effusion. Grade 1A**

Allogeneic stem cell transplantation in CML

Role of allografting in chronic phase

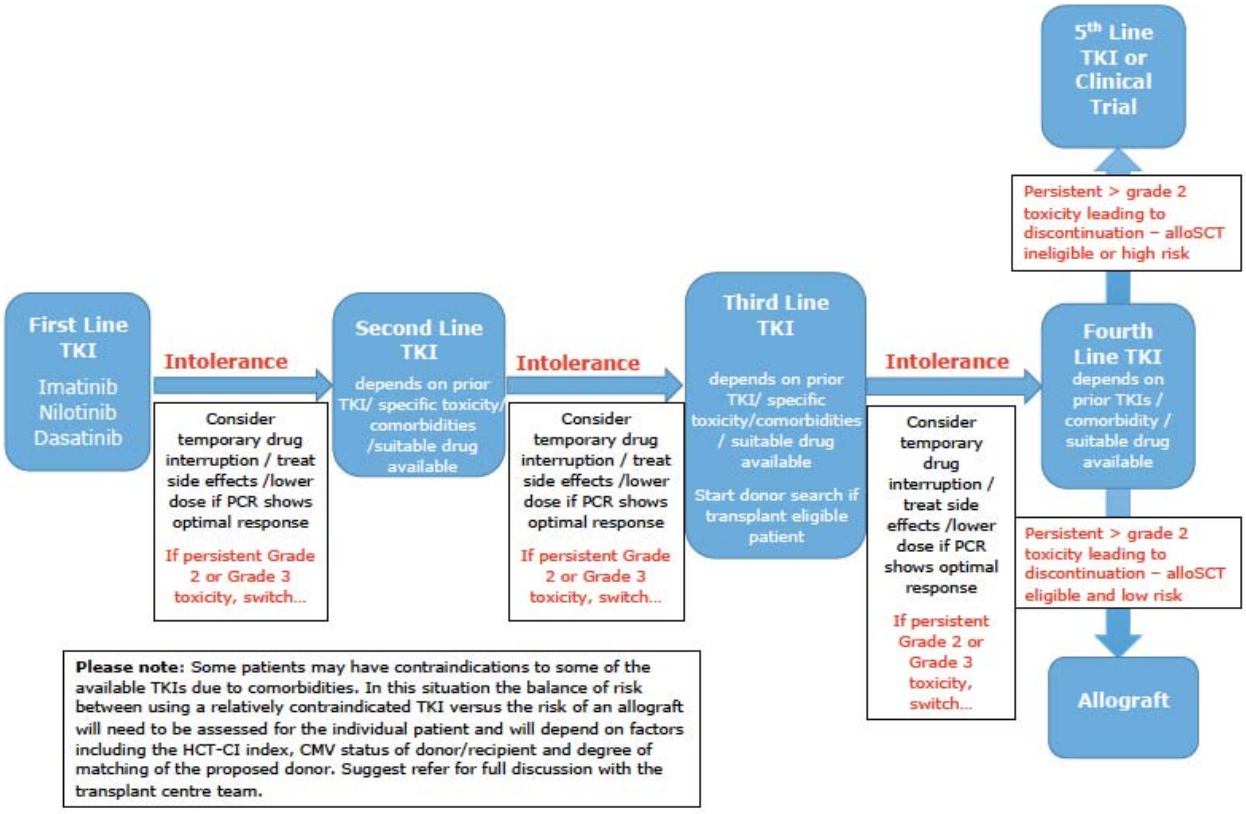
Outcomes for alloSCT in CP CML patients have continued to improve since the 1990s with OS rates of over 85% for CP CML patients receiving a matched-donor transplant (Saussele *et al*, 2010; Gratwohl, 2016).

Current ELN recommendations advise that alloSCT should be reserved for patients who are resistant to or intolerant of at least one 2GTKI and also possibly to a third generation (3G) TKI, i.e. ponatinib, if available (Nicolini *et al*, 2017). As regards the intolerant patient, multiple attempts to find a compatible TKI before alloSCT is considered may be justifiable (Figure 3), though the risk of disease progression must be considered.

The dose intensity of transplant conditioning remains debatable, although a lower CML burden at the time of the transplant may be associated with better outcome (Lee *et al*, 2008), however there is no need to deepen CyR or MR pre alloSCT. Patients who experience post-transplant molecular relapse after a reduced intensity (RIC) conditioning alloSCT can regain molecular remission with donor lymphocyte infusions (DLI) (Heaney *et al*, 2008) or TKI therapy. Since most CP CML patients who need an alloSCT are either resistant to or intolerant of TKI therapy the use of post-transplant TKIs is restricted to patients experiencing late relapse and who have not been exposed to latest generation TKIs.

Existing literature on transplant outcomes in children with CML show inferior OS (60-70% versus 95%) in comparison to TKI therapy alone (Suttorp *et al*, 2011). Hence alloSCT should only be considered in those with TKI resistant mutations, serious side effects, possibly those with persistent lack of compliance and in those in BC (see below).

Figure 3. Management and Role of AlloSCT in Intolerant Patients with CML in Chronic Phase



Role of alloSCT in advanced phase CML

(For patients in AP, see earlier section - *Management of patients with advanced phase disease)*

For patients in BC, achievement of a second chronic phase (CP2) using chemotherapy/alternative TKIs prior to alloSCT is recommended since controlling the more aggressive clone improves OS from 8-11% at 3 years in BC to 35-40% in CP2 (Khoury *et al*, 2012) due to reduced relapse (Xu *et al*, 2015; Oyekunle *et al*, 2013). Survival rates are, however, lower than for patients transplanted in CP1 (Xu *et al*, 2015; Nair *et al*, 2015; Khoury *et al*, 2012) due to higher relapse rates and transplant

related mortality (TRM). In addition the use of post-transplant TKI therapy, where there is a drug available to which the patient is not resistant, is recommended, especially in patients receiving RIC transplants (Oyekunle *et al*, 2013; Palandri *et al*, 2008). The achievement of MR4.5 is important (Saussele *et al*, 2010; Lee *et al*, 2017) and 3-monthly molecular monitoring post-transplant and intervention with donor lymphocyte infusion (DLI) and/or TKI is advised to treat minimal residual disease and/or molecular recurrence (Asnafi *et al*, 2006, Chalandon *et al,* 2014)).

Recommendations

- **AlloSCT should be considered for CP CML patients who are resistant to at least one 2GTKI, though a trial of a 3GTKI is reasonable prior to committing to transplantation. Some patients with intolerance to multiple TKIs may justifiably proceed to 4th line therapy. Grade 2B**
- **Use of TKIs post-transplant may be needed in selected patients previously in AP or BC CML, especially following a RIC transplant. Grade 2B**
- **AlloSCT is recommended for the majority of eligible patients progressing to AP CML, but not those presenting in AP and achieving an optimal cytogenetic and molecular response to TKI therapy. Grade 2A**
- **Achievement of CP2 using chemotherapy/alternative TKIs prior to allograft is recommended. Grade 2A**
- **3-monthly molecular monitoring post-transplant and intervention with DLI and/or TKI (if there is a drug available to which the patient is not resistant) is advised to treat MRD and/or molecular relapse. Grade 2A**

The potential for discontinuing treatment in some patients

Several studies have examined whether molecular remission can be maintained after stopping therapy in patients achieving DMR on TKIs. To date more than 3000 trial patients have discontinued TKI treatment (Hughes & Ross, 2016; Saussele *et al*, 2016; Hochhaus *et al,* 2020)) and these data show that discontinuation of TKI therapy is feasible and safe (appendix 4). Predictive factors for successful treatment discontinuation have identified consistently in several studies to be: time on TKI treatment and duration of MR4 (Etienne *et al*, 2016; Hochhaus *et al*, 2017b; Saussele *et al,* 2018). Reassuringly all patients who lose MR3 (MMR), successfully re-establish this on re-starting TKI therapy. Approximately one third of patients develop a 'withdrawal syndrome' comprising musculoskeletal symptoms - predominantly arthralgia. Although transient, some patients have required corticosteroid therapy (Richter *et al*, 2014).

Most recently, in the UK DESTINY study, patients were stratified between MR3 and MR4 and underwent de-escalating therapy for 12 months with half-dose TKI before withdrawing completely (Clark *et al*, 2017, 2019). These patients have shown a particularly high recurrence-free survival rate (RFS) of 76% at 24 months for those patients in stable MR4, and the same phenomenon has been reported in a large retrospective single centre study (Claudiani, *et al* 2018). These findings suggest that initial dose reduction may be important and, in the absence of any reason not to, it is reasonable that initial dose reduction, as per the DESTINY protocol, is undertaken. The majority of recurrences occur within 6 months of discontinuation (Rousselot *et al,* 2014) but later molecular recurrence (>24 months) have also been noted emphasising the need for ongoing frequent molecular monitoring.

With regards to children, an international collaborative study (STOPImaped) has recommended stopping imatinib in those who achieve a sustained DMR for over 2

years. However, cessation should only be attempted if compliance with monitoring of *BCR-ABL*1 levels upon treatment discontinuation is assured (de la Fuente *et al*, 2014).

Recommendations

- **Any patient considering discontinuation should be discussed at an appropriate haematology multi-disciplinary team meeting (MDT). Grade 1C**

- **Patients should be on an approved TKI therapy for at least 3 years (but preferably 5 years) and should not have:**

    - **a prior history of AP or BC CML. Grade 2A**
    - **previous resistance to any TKI. Grade 2B**
    - **previous detection of a *BCR-ABL*1 KD mutation. Grade 2C**

- **Patients should have a confirmed expression of a typical (e13a2 and/or e14a2) *BCR-ABL*1 transcript and a sustained molecular response of at least MR4 (<0.01% by IS) for the last 2 years verified by a minimum of 4 consecutive (at least 3 months apart) RT-qPCR results. Grade 1A**

- **There should be access to a laboratory that provides *BCR-ABL1* measurement expressed according to IS, with a sensitivity of at least MR4.5 and able to provide results within a turnaround time of 14 days. Grade 1B**

- **Consideration should be given to reducing the dose of TKI by 50% for 12 months prior to discontinuation, with monthly monitoring. Grade 1B**

- **Following discontinuation, monitoring should be:**

    - Monthly for 6 months
    - 6 weekly from 7 to 12 months
    - 2 monthly from 13 to 36 months
    - 3 monthly for year ≥3

    - Grade 2B

- **Re-initiation of TKI treatment should occur within one month of loss of confirmed MR3 (MMR) at full dose of TKI therapy. Grade 1B**

- **Once re-initiated RT-qPCR should be performed 4 weekly until re-establishment of MR3 (MMR). Grade 1B**

- **If MR3 (MMR) is not achieved by 6 months, *BCR-ABL1* KD mutation analysis should be performed. Grade 1B**

CML and parenting

Male patients

Data derived from the pharmacovigilance databases of Novartis (Apperley, 2009; Abruzzese *et al*, 2016) and Bristol-Myers Squibb (Cortes *et al*, 2015) suggest that the risks of adverse consequences of pregnancy for partners of men taking imatinib or dasatinib are similar to the risks in the unaffected population. Less information is available for the remaining TKIs, where it is reasonable to advise male patients considering parenting that there is a degree of uncertainty.

Female patients

1. Presenting in pregnancy

In CP termination should not be advised unless this is at the patient's request. Management depends on the presenting laboratory and clinical parameters and gestational stage. Often the pregnancy can continue to term without intervention, although low dose aspirin and/or low molecular weight heparin are advisable if thrombocytosis is present. An increased risk of congenital abnormalities in children born to women who conceived whilst on imatinib (Pye *et al*, 2008) and dasatinib (Cortes *et al*, 2015) has been reported. The major risk appears to be during organogenesis and it has been suggested that imatinib can be safely introduced in the second and third trimesters. This approach has been challenged by the observation of hydrops fetalis in a woman who started dasatinib in the second trimester (Cortes *et al*, 2015), and supported by reports of detection of TKIs and their

metabolites in cord blood, placental tissue, amniotic fluid, fetal plasma and neonatal urine (Berveiller *et al*, 2012; Burwick *et al*, 2017). It is therefore reasonable to avoid TKIs throughout pregnancy. If treatment is required then the options include leucapheresis, interferon and TKIs. Leucapheresis is the approach offering the least risk to the foetus (Milojkovic & Apperley, 2014). Interferon is generally considered safe in the later stages of pregnancy (Vantroyen & Vanstraelen, 2002). TKIs are also secreted in breast milk and breastfeeding should be avoided while on treatment (Chelysheva *et al,* 2018).

2. Unplanned pregnancies

Pregnancy occurring whilst on a TKI is usually recognised in the first trimester. Treatment should be discontinued immediately and fetal scans performed. Subsequent management of the pregnancy and the CML will be similar to that of women presenting with CML in pregnancy.

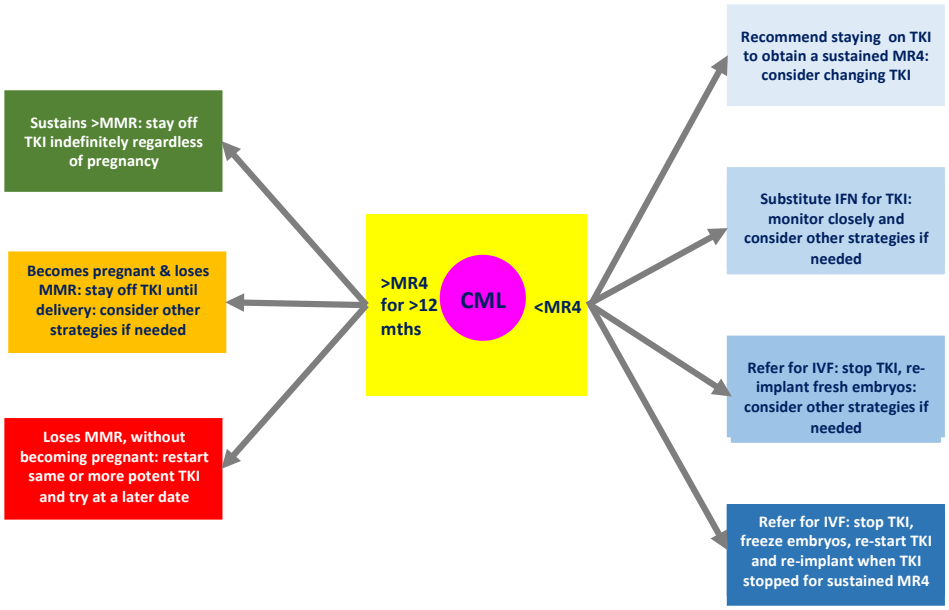
3. Considering pregnancy (Figure 4)

Information available from studies of TFR would suggest that MR4 sustained for at least a year in the absence of prior TKI resistance will enable approximately 50% of women to discontinue TKI indefinitely, and have opportunities to conceive (Mahon *et al*, 2016). The majority of the remainder will have molecular recurrence within the first 6 months but if they become pregnant within this period, they may reach term without developing symptomatic disease.

The more challenging scenario is the woman who wishes to conceive in the absence of a sustained DMR, and this is often associated with older age and/or societal pressures. Patients in stable MMR for 1-2 years who conceive soon after treatment cessation, may be able to complete their pregnancy without the need for any

therapy. Other solutions include substitution of TKI with interferon during the period before and after conception, referral for *in vitro* fertilisation (IVF) procedures and re-implantation of fresh or frozen embryos after a further period of TKI therapy to achieve and consolidate a DMR.

Figure 4. Approach to planned parenting for women with CML



Recommendations

- **The risks of adverse consequences of pregnancy for partners of men taking TKI are similar to the risks in the unaffected population.**
- **For female patients presenting in pregnancy, an individualised approach incorporating the options of no treatment, leucapheresis, alpha interferon and TKI in later pregnancy is required. Grade 1B**
- **Breast feeding should be avoided while on TKI. Grade 1B**

- **Women with CML wishing to conceive should not have had previous TKI resistance and ideally have maintained MR4 for at least 12 months before considering discontinuation. Grade 1B**

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Declaration of Interests

The BSH paid expenses incurred during the writing of this guidance. All authors have made a declaration of interests to the BSH and Task Force Chairs which may be reviewed upon request. AG has received honoraria from Bristol-Myers Squibb (BMS) and Novartis. CP has received honoraria from Ariad/Incyte, Novartis and Pfizer. GS, JB, MC and DM have received honoraria from Ariad/Incyte, BMS, Novartis and Pfizer. JA has received honoraria and research funding from the same companies.

MC has in addition received research funding from Ariad/Incyte, BMS and Novartis. AJM has received honoraria from BMS, Novartis and Pfizer and received research funding, travel, accommodation and expenses from Novartis. HdL has received honoraria from Novartis and Pfizer, and honoraria and research funding from Ariad/Incyte and BMS. NC has received honoraria from Ariad/Incyte and honoraria and research funding and from Novartis. WO has received honoraria from Novartis and Pfizer and research funding from Ariad/Incyte. Other members of the writing group had no conflicts of interest to declare.

Review Process

Members of the writing group will inform the writing group Chair if any new evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be reviewed regularly by the relevant Task Force and the literature search will be re-run every three years to search systematically for any new evidence that may have been missed. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made, an addendum will be published on the BSH guidelines website (www.b-s-h.org.uk).

Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for these guidelines.

Appendix 1

First line TKI therapy

Studies of imatinib versus 2GTKIs show that, with a maximum of 5 years follow-up, there are no differences in OS (Kantarjian *et al*, 2010, 2012; Jabbour *et al*, 2014; Cortes *et al*, 2016b; Saglio *et al*, 2010b; Kantarjian *et al*, 2011b; Larson *et al*, 2012; Hochhaus *et al*, 2016; Cortes *et al*, 2018), although differences are beginning to emerge with respect to a lower incidence of CML-related deaths in the 2GTKI arms, particularly with nilotinib (Hochhaus *et al*, 2016). This is supported by a reduction in the numbers of patients experiencing disease progression on 2GTKI. It is also clear that the 2GTKI not only induce deeper molecular responses in a higher proportion of patients, but also achieve these responses more rapidly (Table 10).

Table 10: Outcome of first line therapy with TKIs, derived from Phase II randomised commercial studies* and TIDEL-II reflecting early switch of imatinib to nilotinib.

	Imatinib vs bosutinib[1]	Imatinib vs dasatinib	Imatinib vs nilotinib[2]	TIDEL-II Single arm
5-yr overall survival (%)	NA	90 vs 91	91.7 vs 93.7	96
PFS (%)	NA	86 vs 85	91 vs 92.2	95
5-yr freedom from CML-related death(%)	NA	NG	93.8 vs 97.7	NG
No. of progressions 12 months 36 months 60 months	 6 vs 4 NA NA	 9 vs 5 13 vs 8 19 vs 12	 11 vs 2 12 vs 2 21 vs 10	 NG 7 NA
No. of patients dying of CML by 5 years		17 vs 9	16 vs 6	5
CCyR (%) 12 months 24 months 36 months	 66.4 vs 77.2 NA NA	 72 vs 83 82 vs 86 83 vs 87	 65 vs 80 77 vs 87 NG	 87 83 NG
MR3 (MMR) (%) 12 months 24 months 60 months	 36.9 vs 47.2 NA NA	 28 vs 46 46 vs 64 64 vs 76	 27 vs 55 44 vs 67 60.4 vs 77	 62 70 NG
MR4 (%) 24 months 60 months	 NA NA	 22 vs 44 NG	 18 vs 33 41.7 vs 65.6	 33 NG
MR4.5 (%) 24 months 60 months	 NA NA	 8 vs 19 33 vs 42	 9 vs 25 31.4 vs 53.5	 32 NG
MR3 (MMR) at 3 years (%) Hasford[d]/Sokal[n] Low Intermediate High	 46.3 vs 58.1** 39.1 vs 44.9** 16.7 vs 34**	 65 vs 83 57 vs 65 42 vs 61	 62.5 vs 76.7 54.5 vs 75.2 38.5 vs 66.7	 }79[3] 72

1 = 12 months follow-up data only available at the FDA approved starting dose of 400mg daily

2 = Nilotinib results given for 300mg bd as this is the dose licensed for use in newly diagnosed patients

3 = results at 24 months

[d] = dasatinib, [n] = nilotinib, NA = not applicable, NG = not given. ** = results at 12 months

* The following studies are included: Kantarjian *et al*, 2010, 2012; Jabbour *et al*, 2014; Cortes *et al*, 2016b; Saglio *et al*, 2010b; Kantarjian *et al*, 2011b; Larson *et al*, 2012; Hochhaus *et al*, 2016; Cortes *et al*, 2018. Direct comparison of the individual trials is not

possible because of differences between studies including eligibility/ineligibility criteria, definitions of response evaluations and methodology of analysis.

Appendix 2

Establishment of response criteria

Several studies later have confirmed the prognostic significance of this EMR milestone (defined as 3-month *BCR-ABL1* transcript <10% IS) including Hanfstein in the CML IV study (Hanfstein *et al*, 2012) where patients with a transcript level >10% IS separated a high-risk group (28% of patients; 5-year OS: 87%) from a group with >1-10% BCR-ABL(IS) (41% of patients; 5-year OS: 94%; P=0.012) and from a group with ≤1% BCR-ABL(IS) (31% of patients; 5-year OS: 97%; P=0.004).

Other studies have confirmed the prognostic significance of this EMR milestone (defined as 3-month *BCR-ABL1* transcript <10% IS) in patients treated with 2GTKIs first line (Jain *et al*, 2013; Hughes *et al*, 2014; Jabbour *et al*, 2014; Brümmendorf *et al*, 2015) or second line (Giles *et al*, 2013; Shah *et al*, 2014), with rates of EMR failure ranging between 8.6% and 24% with first line treatment (Hughes *et al*, 2014; Brümmendorf *et al*, 2015; Giles *et al*, 2013; Shah *et al*, 2014). Several investigators have examined the prognostic value of early dynamics of molecular response, known as halving time or velocity of ratio reduction. (Hanfstein *et al*, 2014; Branford *et al*, 2014). However, such approaches have not yet been adopted into routine clinical practice.

Appendix 3

Definitions of advanced phase

Four organisations – the World Health Organisation (WHO), European LeukaemiaNet (ELN), MD Anderson Cancer Centre (MDACC) and the centre for International Blood and Marrow Transplant Research (IBMTR) - have produced definitions for AP CML and there are 3 definitions (WHO, ELN, IBMTR) (Gratwohl *et al*, 1998; Baccarani *et al*, 2013; Vardiman, 2008) for BC CML (Table 11). The main difference between the different definitions of AP is the percentage of blasts - 20% versus 30%. There is a significant difference in 3-year OS between 20-30% and >30% blasts; 42% versus 10%, respectively (Cortes *et al*, 2006).

Table 11: Comparison of different definitions for AP and BC CML

	AP	BC
WHO (Gratwohl *et al,* 1998)	Defined by presence of one of the following: (1) Blood or marrow blasts 10-19% (2) Blood basophils >20% (3) Persistent thrombocytopenia (<100x10^9/l) (4) Evidence of karyotypic clonal evolution on treatment (5) Treatment refractory leucocytosis, splenomegaly or thrombocytosis (>1000x10^9/l)	Defined by presence of one of the following: (1) Blasts in blood or marrow ≥20% (2) Extramedullary blast proliferation, apart from spleen (3) Large foci or clusters of blasts in the bone marrow biopsy
ELN (Baccarani *et al,* 2013)	Defined by presence of one of the following: (1) Blasts in blood or marrow 15-29%, or blasts plus promyelocytes in blood or marrow >30%, with blasts <30% (2) Basophils in blood ≥20% (3) Persistent thrombocytopenia (<100x10^9/L) unrelated to therapy (4) Clonal chromosome abnormalities in Ph+ cells (CCA/Ph+), major route, on treatment	Defined by presence of one of the following: (1) Blasts in blood or marrow ≥30% (2) Extramedullary blast proliferation, apart from in spleen
IBMTR (Vardiman, 2008)	Defined by presence of one of the following: (1) WBC difficult to control with conventional regimens of busulphan or hydroxycarbamide (2) Rapid doubling of WBC (≤5 days) (3) ≥10% blasts in blood or marrow (4) ≥20% blasts plus promyelocytes in blood or marrow (5) ≥20% basophils plus eosinophils in blood (6) Anaemia or thrombocytopenia unresponsive to busulphan/hydroxycarbamide (7) Persistent thrombocytosis (8) New cytogenetic abnormalities (9) Increasing splenomegaly (10) Development of chloromas or myelofibrosis (11) Patient in CP2 after BC	Defined by presence of one of the following: (1) Presence of ≥30% blasts plus promyelocytes in the blood or bone marrow

Studies of TKIs in advanced phase

Imatinib in *de novo* AP CML : (Furtado *et al*, 2015; Hoffmann *et al*, 2013; Kantarjian *et al*, 2005, 2002b; Silver *et al*, 2009; Talpaz *et al*, 2002) and in BC : (Silver *et al*, 2009; Druker *et al*, 2001; Kantarjian *et al*, 2002a; Palandri *et al*, 2008; Sawyers *et al*, 2002; Sureda *et al*, 2003).

Dasatinib and nilotinib in imatinib failure, in AP: (Apperley *et al*, 2009; Guilhot *et al*, 2007; Kantarjian *et al*, 2009, 2006; Le Coutre *et al*, 2012; Nicolini *et al*, 2012) and in BC : (Kantarjian *et al*, 2006; Cortes *et al*, 2008; Giles *et al*, 2012; Saglio *et al*, 2010a; Talpaz *et al*, 2006).

Bosutinib and ponatinib following resistance or intolerance to two or more TKIs, in AP : (Cortes *et al*, 2013; Gambacorti-Passerini *et al*, 2015), and in BC : (Cortes *et al*, 2013; Gambacorti-Passerini *et al*, 2015).

There are limited data for first-line use of 2GTKIs in *de novo* AP CML and no clear survival advantage for 2GTKIs versus imatinib (Ohanian *et al*, 2014).

Appendix 4

Studies of TKI discontinuation

Treatment discontinuation was first described in the ‘stop imatinib’ or STIM1 study in 2007 (Rousselot *et al*, 2007; Mahon *et al*, 2010) and showed that only 61% of patients had a molecular recurrence with a median follow up of 77 months (range 19-95 months). Subsequently, the EURO-SKI study (Mahon *et al*, 2016; Saussele *et al,* 2018)) demonstrated that the longer a deep response is maintained prior to treatment discontinuation, the higher the chance of successfully stopping therapy without loss of MR3 (MMR) (Table 12).

Table 12. Discontinuation studies following imatinib therapy

	STIM pilot (Rousselot *et al, 2007)* **(N = 12)**	**STIM1** (Mahon, 2010) **(N = 100)**	**TWISTER** (Ross *et al,* 2013) **(N = 40)**	**STIM2** (Nicolini *et al, 2013)* **(N = 200)**	**KeioSTIM** (Matsuki *et al,* 2012) **(N = 41)**	**KIDS** (Lee *et al, 2013)* **(N = 78)**	**EURO-SKI** (Saussele *et al*, 2018)
Treatment prior to suspension of TKI therapy	Imatinib, prior IFN allowed	Imatinib (≥ 3 y); prior IFN allowed	Imatinib (≥ 3 y); prior IFN allowed	Imatinib (≥ 3 y)	Imatinib	Imatinib (> 3 y); includes post-transplant patients	≥ 3 y total TKI therapy (frontline or second-line TKI at study entry)
Response required for attempting TFR	UMRD by RT-qPCR ≥ 2y; non-standardized	UMRD by RT-qPCR (≥ 2 y) confirmed at central laboratory (>MR4.5 sensitivity ≥50,000 ABL1)	UMRD by RT-qPCR (≥ 2 y) and on screening at a central laboratory ≥MR4.5 sensitivity	UMRD by RT-qPCR (≥ 2 y) by central lab (≥ MR4.5 sensitivity ≥50,000 ABL1)	UMRD using qualitative PCR (> 2y)	UMRD[b] by RT-qPCR (≥ 2 y) by central lab (> MR4.5 sensitivity ≥50,000 ABL1)	MR4 by RT-qPCR (≥ 1 y) and on screening at a central laboratory
Definition of molecular relapse/ recurrence	RT-qPCR positive in 2 consecutive results	*BCR-ABL*1 positive in 2 consecutive results (≥ 1 log increase), or loss of MR3 (MMR) at any point	loss of MR3 or two consecutive positive samples at any value	*BCR-ABL*1 positive in 2 consecutive results (≥ 1 log increase), or loss of MR3 (MMR) at any point	≥ 100 copies of *BCR-ABL*1 using TMA	Loss of MR3 (MMR) in 2 consecutive results	Loss of MR3
Rate of TFR, % (median follow-up)	50 % at 6 months (18 months)	Molecular relapse free survival (molRFS) 43%, 40%, 38% at 6,18,60 months	45 % (42 months)	61%, Analysis of 1st 124 patients (12 months)	55%, estimated at 1y (15.5 months)	78.5[a]% estimated at 12 months (14 months)	62 % at 6 months & 56% at 12 months

In addition, there have been a number of studies evaluating stopping treatment after therapy with 2GTKIs [Table 13). Specifically regarding 2GTKIs, the STOP 2GTKI study showed that a higher percentage of patients than in the STIM1 study of

stopping imatinib, around 59% at 12 months, had a TFR. Importantly, a prior history of suboptimal response or resistance to imatinib was found to have a significant impact with a TFR rate at 48 months of 23.08% compared to 62.36% in those with an optimal response (Rea *et al*, 2017).

Table 13. Discontinuation studies following 2GTKI therapy

	STOP 2GTKI	DADI (Imagawa	DESTINY (Clark et	DASFREE	D-STOP

	(Rea *et al,* 2017)	*et al, 2015)*	al, 2019)	**(**Shah *et al,* 2017)	(Kumagai *et al,* 2016)
Enrollment (actual or target)	100 (target) 52 (actual)	75 (actual)	168 (target) 174 (actual)	79 (target) 71 (actual**)**	50 (target) 65 (actual)
Treatment prior to suspension of TKI therapy	≥ 3 y total TKI (on nilotinib or dasatinib at study entry)	Second- or third-line dasatinib	≥ 3 y imatinib, nilotinib, or dasatinib prior to enrollment and 1 y at half-standard dose after enrollment	≥ 2 y dasatinib prior to enrollment	2 y dasatinib
Response required for attempting TFR	UMRD by RT-qPCR at local laboratory (≥ 2 y; ≥ 20^3 control gene copies)	UMRD[c] by RT-qPCR (1 y)	MR3 or MR4 by RT-qPCR 1 y prior to enrollment	≥ MR4.5 by RT-qPCR (≥ 1 y) and on screening at a central laboratory	CMR (MR4.5)
Definition of molecular relapse/ recurrence	Loss of MR3	*BCR-ABL*1 positive at any point	Loss of MR3	Loss of MR3	Loss of CMR (MR4.5)
Rate of TFR or estimated primary completion	59.6% at 12 months	48% (in MR3) at 12 months)	December 2017	63% at 12 months	62.9% (TFS at 12 months)

References

Abruzzese, E., Trawinska, M.M., de Fabritiis, P. & Baccarani, M. (2016) Management of pregnant chronic myeloid leukemia patients. *Expert Review of Hematology*, **9,** 781–791.

Apperley, J. (2009) Issues of imatinib and pregnancy outcome. *Journal of the*

National Comprehensive Cancer Network, **7,** 1050–1058.

Apperley, J.F., Cortes, J.E., Kim, D.-W., Roy, L., Roboz, G.J., Rosti, G., Bullorsky, E.O., Abruzzese, E., Hochhaus, A. & Heim, D. (2009) Dasatinib in the treatment of chronic myeloid leukemia in accelerated phase after imatinib failure: the START A trial. *Journal of Clinical Oncology*, **27,** 3472–3479.

Arber, D.A., Orazi, A., Hasserjian, R., Thiele, J., Borowitz, M.J. & Beau, M.M. (2016) The revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*, **127,** 2391–2405.

Asnafi, V., Rubio, M.T., Delabesse, E., Villar, E., Davi, F., Damaj, G., Hirsch, I., Dhédin, N., Vernant, J.P. & Varet, B. (2006) Prediction of relapse by day 100 BCR-ABL quantification after allogeneic stem cell transplantation for chronic myeloid leukemia. *Leukemia*, **20,** 793-799.

Baccarani, M., Deininger, M.W., Rosti, G., Hochhaus, A., Soverini, S. & Apperley, J.F. (2013) European LeukemiaNet recommendations for the management of chronic myeloid leukemia. *Blood*, **122,** 872–884.

Baccarani M, Castagnetti F, Gugliotta G, Rosti G, Soverini S, Albeer A, Pfirrmann M; International BCR-ABL Study Group. (2019) The proportion of different BCR-ABL1 transcript types in chronic myeloid leukemia. An international overview. *Leukemia*, **33**, 1173-1183.

Baigent, C., Blackwell, L., Collins, R., Emberson, J., Godwin, J., Peto, R., Buring, J., Hennekens, C., Kearney, P.,Meade, T., Patrona, C., Roncaglioni, M.C. & Zanchetti, A. (2009) Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet,* **373,** 1849-1860.

Berveiller, P., Andreoli, A., Mir, O., Anselem, O., Delezoide, A.-L., Sauvageon, H., Chapuis, N. & Tsatsaris, V. (2012) A dramatic fetal outcome following transplacental transfer of dasatinib. *Anti-cancer Drugs*, **23,** 754–757.

Björkholm, M., Ohm, L., Eloranta, S., Derolf, Å., Hultcrantz, M., Sjöberg, J., Andersson, T., Höglund, M., Richter, J. & Landgren, O. (2011) Success story of targeted therapy in chronic myeloid leukemia: a population-based study of patients diagnosed in Sweden from 1973 to 2008. *Journal of Clinical Oncology*, **29,** 2514–2520.

Bower, H., Björkholm, M., Dickman, P.W., Höglund, M., Lambert, P.C. & Andersson, T.M. (2016) Life expectancy of patients with chronic myeloid leukemia approaches the life expectancy of the general population. *Journal of Clinical Oncology*, **34,** 2851–2857.

Branford, S. & Hughes, T. (2006) Diagnosis and monitoring of chronic myeloid leukemia by qualitative and quantitative RT-PCR. *Methods in Molecular Medicine*, **125,** 69–92.

Branford, S., Yeung, D.T., Parker, W.T., Roberts, N.D., Purins, L. & Braley, J.A. (2014) Prognosis for patients with CML and >10% BCR-ABL1 after 3 months of imatinib depends on the rate of BCR-ABL1 decline. *Blood*, **124,** 511–518.

Brümmendorf, T.H., Cortes, J.E., Souza, C.A., Guilhot, F., Duvillié, L., Pavlov, D., Gogat, K., Countouriotis, A.M. & Gambacorti-Passerini, C. (2015) Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukaemia: results from the 24-month follow-up of the BELA trial. *British Journal of Haematology*, **168,** 69–81.

Brunner, A.M., Campigotto, F., Sadrzadeh, H., Drapkin, B.J., Chen, Y., Neuberg, D.S. & Fathi, A.T. (2013) Trends in all-cause mortality among patients with chronic myeloid leukemia. *Cancer*, **119,** 2620–2629.

Burwick, R.M., Kuo, K., Brewer, D. & Druker, B.J. (2017) Maternal, fetal, and neonatal imatinib levels with treatment of chronic myeloid leukemia in pregnancy. *Obstetrics & Gynecology*, **129,** 831–834.

Castagnetti, F., Gugliotta, G., Baccarani, M., Breccia, M., Specchia, G., Levato, L., Abruzzese, E., Rossi, G., Iurlo, A., Martino, B., Pregno, P., Stagno, F., Cuneo, A., Bonifacio, M., Gobbi, M., Russo, D., Gozzini, A., Tiribelli, M., de Vivo, A., Alimena, G. (2015) Differences among young adults, adults and elderly chronic myeloid leukemia patients. *Annals of Oncology*, **26,** 185–192.

Chai-Adisaksopha, C., Lam, W. & Hillis, C. (2016) Major arterial events in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors: a meta-analysis. *Leukemia & Lymphoma*, **57,** 1300–1310.

Chalandon, Y., Passweg, J.R., Guglielmi, C., Iacobelli, S., Apperley, J., Schaap, N.P.M., Finke, J., Robin, M., Fedele, R. & Bron, D. (2014) Early administration of donor lymphocyte infusions upon molecular relapse after allogeneic hematopoietic stem cell transplantation for chronic myeloid leukemia: a study by the Chronic Malignancies Working Party of the EBMT. *Haematologica*, **99,** 1492–1498.

Chelysheva, E., Aleshin, S., Polushkina, E., Shmakov, R., Shokhin, I., Chilov, G. & Turkina, A. (2018) Breastfeeding in patients with chronic myeloid leukaemia: case series with measurements of drug concentrations in maternal milk and literature review. *Mediterranean Journal of Hematology and Infectious Diseases*, **10,** e2018027.

Clark, R.E., Polydoros, F., Apperley, J.F., Milojkovic, D., Pocock, C., Smith, G., Byrne, J.L., de Lavallade, H., O'Brien, S.G. & Coffey, T. (2017) De-escalation of tyrosine kinase inhibitor dose in patients with chronic myeloid leukaemia with stable major molecular response (DESTINY): an interim analysis of a non-randomised, phase 2 trial. *The Lancet Haematology*, **4,** e310–e316.

Clark, R.E., Polydoros, F., Apperley, J.F., Milojkovic, D., Rothwell, K., Pocock, C., Byrne, J., de Lavallade, H., Osborne, W. & Robinson, L. (2019) De-escalation of tyrosine kinase inhibitor therapy before complete treatment discontinuation in patients with chronic myeloid leukaemia (DESTINY): a non-randomised, phase 2 trial. *The Lancet Haematology,* **6,** e375 - e383.

Claudiani, S., Apperley, J.F., Gale, R.P., Clark, R., Szydlo, R., Deplano, S., Palanicawandar, R., Khorashad, J., Foroni, L. & Milojkovic, D. (2017) E14a2 BCR-ABL1 transcript is associated with a higher rate of treatment-free remission

in individuals with chronic myeloid leukemia after stopping tyrosine kinase inhibitor therapy. *Haematologica*, **102,** e297–e299.

Claudiani, S., Apperley, J., Khan, A., Szydlo, R., Nesr, G., Adams, G., Foroni, L., Khorashad, J.S. & Milojkovic, D. (2018) Dose Reduction of First and Second Generation TKIs Is Effective in the Maintenance of Major Molecular Response and May Predict Successful Tfr in CML Patients. *Blood*, **132**:3007.

Cortes, J., Hochhaus, A. & Coutre, P. (2011) D. le Minimal cross-intolerance with nilotinib in patients with chronic myeloid leukemia in chronic or accelerated phase who are intolerant to imatinib. *Blood*, **117,** 5600–5606.

Cortes, J., Kim, D.W., Raffoux, E., Martinelli, G., Ritchie, E., Roy, L., Coutre, S., Corm, S., Hamerschlak, N. & Tang, J.L. (2008) Efficacy and safety of dasatinib in imatinib-resistant or-intolerant patients with chronic myeloid leukemia in blast phase. *Leukemia*, **22,** 2176.

Cortes, J., Souza, C. & Ayala, M. (2016a) Antonio De Switching to nilotinib verses imatinib dose escalation in patients with chronic myeloid leukaemia in chronic phase with suboptimal response to imatinib (LASOR): a randomised, open-label trial. *The Lancet Haematology*, **3,** e581–e591.

Cortes, J., Talpaz, M., O'Brien, S., Giles, F., Beth Rios, M., Shan, J., Faderl, S., Garcia-Manero, G., Ferrajoli, A. & Wierda, W. (2003) Effects of age on prognosis with imatinib mesylate therapy for patients with Philadelphia chromosome-positive chronic myelogenous leukemia. *Cancer*, **98,** 1105–1113.

Cortes, J.E., Abruzzese, E., Chelysheva, E., Guha, M., Wallis, N. & Apperley, J.F. (2015) The impact of dasatinib on pregnancy outcomes. *American Journal of Hematology*, **90,** 1111–1115.

Cortes, J.E., Gambacorti-Passerini, C., Deininger, M.W., Mauro, M.J., Chuah, C., Kim, D.W., Dyagil, I., Glushko, N., Milojkovic, D., Coutre, P., Garcia-Gutierrez, V., Reilly, L., Jeynes-Ellis, A., Leip, E., Bardy-Bouxin, N., Hochhaus, A. & Brümmendorf TH. (2018) *Bosutinib Versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia Results From the Randomized BFORE trial. Journal of Clinical Oncology*, **36,** 231–237.

Cortes, J.E., Kim, D.-W., Pinilla-Ibarz, J. I, Le Coutre, P., Paquette, R., Chuah, C., Nicolini, F.E., Apperley, J.F., Khoury, H.J. & Talpaz, M. (2013) A phase 2 trial of ponatinib in Philadelphia chromosome–positive leukemias. *New England Journal of Medicine*, **369,** 1783–1796.

Cortes, J.E., Saglio, G., Kantarjian, H.M., Baccarani, M., Mayer, J., Shah, N.P., Chuah, C., Casanova, L., Bradley-Garelik, B., Manos, G. & Hochhaus, A. (2016b) Final 5-Year Study Results of DASISION: The Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients Trial. *Journal of Clinical Oncology*, **34,** 2333–2340.

Cortes, J.E., Talpaz, M., O'brien, S., Faderl, S., Garcia-Manero, G., Ferrajoli, A., Verstovsek, S., Rios, M.B., Shan, J. & Kantarjian, H.M. (2006) Staging of chronic myeloid leukemia in the imatinib era. *Cancer*, **106,** 1306–1315.

Le Coutre, P.D., Giles, F.J., Hochhaus, A., Apperley, J.F., Ossenkoppele, G.J.,

Blakesley, R., Shou, Y., Gallagher, N.J., Baccarani, M. & Cortes, J. (2012) Nilotinib in patients with Ph+ chronic myeloid leukemia in accelerated phase following imatinib resistance or intolerance: 24-month follow-up results. *Leukemia*, **26,** 1189.

Cross, N.C., Hochhaus, A. & Muller, M.C. (2015a) Molecular monitoring of chronic myeloid leukemia: principles and interlaboratory standardization. *Annals of Hematology, **94**,* 219-225.

Cross, N.C., Melo, J. V, Feng, L. & Goldman, J.M. (1994) An optimized multiplex polymerase chain reaction (PCR) for detection of BCR-ABL fusion mRNAs in haematological disorders. *Leukemia*, **8,** 186–189.

Cross, N.C., White, H.E., Colomer, D., Ehrencrona, H., Foroni, L. & Gottardi, E. (2015b) Laboratory recommendations for scoring deep molecular responses following treatment for chronic myeloid leukemia. *Leukemia*, **29,** 999–1003.

Cross, N.C., White, H.E., Muller, M.C., Saglio, G. & Hochhaus, A. (2012) Standardized definitions of molecular response in chronic myeloid leukemia. *Leukemia*, **26,** 2172–2175.

Cross, N.C.P., White, H.E., Evans, P.A.S., Hancock, J., Copland, M., Milojkovic, D., Mason, J., Craine, S. & Mead, A.J. (2018) Consensus on BCR-ABL 1 reporting in chronic myeloid leukaemia in the UK. *British Journal of Haematology*, **182,** 777-788.

DeFilipp, Z. & Khoury, H.J. (2015) Management of advanced-phase chronic myeloid leukemia. *Current Hematologic Malignancy Reports*, **10,** 173–181.

de la Fuente, J., Baruchel, A., Biondi, A., de Bont, E., Dresse, M., Suttorp, M. & Millot, F. (2014) Managing children with chronic myeloid leukaemia (CML). Recommendations for the management of CML in children and young people up to the age of 18 years. *British Journal of Haematology*, **167,** 33–47.

Druker, B.J., Guilhot, F., O'brien, S.G., Gathmann, I., Kantarjian, H., Gattermann, N., Deininger, M.W.N., Silver, R.T., Goldman, J.M. & Stone, R.M. (2006) Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *New England Journal of Medicine*, **355,** 2408–2417.

Druker, B.J., Sawyers, C.L., Kantarjian, H., Resta, D.J., Reese, S.F., Ford, J.M., Capdeville, R. & Talpaz, M. (2001) Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *New England Journal of Medicine*, **344,** 1038–1042.

Etienne, G., Guilhot, J., Rea, D., Rigal-Huguet, F., Nicolini, F., Charbonnier, A., Guerci-Bresler, A., Legros, L., Varet, B. & Gardembas, M. (2016) Long-term follow-up of the French Stop Imatinib (STIM1) study in patients with chronic myeloid leukemia. *Journal of Clinical Oncology*, **35,** 298–305.

Fabarius, A., Kalmanti, L., Dietz, C.T., Lauseker, M., Rinaldetti, S. & Haferlach, C. (2015) Impact of unbalanced minor route versus major route karyotypes at diagnosis on prognosis of CML. *Annals of hematology*, **94,** 2015–2024.

Foroni, L., Wilson, G., Gerrard, G., Mason, J., Grimwade, D. & White, H.E. (2011) Guidelines for the measurement of BCR-ABL1 transcripts in chronic myeloid leukaemia. *British Journal of Haematology*, **153,** 179–190.

Furtado, V.F., Santos, G.R., de Carvalho, D.S., Staziaki, P.V., Pasquini, R. & Funke, V.A.M. (2015) Accelerated phase chronic myeloid leukemia: evaluation of clinical criteria as predictors of survival, major cytogenetic response and progression to blast phase. *Revista Brasileira de Hematologia e Hemoterapia*, **37,** 341–347.

Gambacorti-Passerini, C. & Brummendorf, T. (2014) Bosutinib efficacy and safety in chronic phase chronic myeloid leukaemia after imatinib resistance or intolerance: Minimum 24-month follow up. *American Journal of Hematology*, **89,** 732–742.

Gambacorti-Passerini, C., Kantarjian, H.M., Kim, D., Khoury, H.J., Turkina, A.G., Brümmendorf, T.H., Matczak, E., Bardy-Bouxin, N., Shapiro, M. & Turnbull, K. (2015) Long-term efficacy and safety of bosutinib in patients with advanced leukemia following resistance/intolerance to imatinib and other tyrosine kinase inhibitors. *American Journal of Hematology*, **90,** 755–768.

Giles, F.J., Le Coutre, P.D., Pinilla-Ibarz, J., Larson, R.A., Gattermann, N., Ottmann, O.G., Hochhaus, A., Radich, J.P., Saglio, G. & Hughes, T.P. (2013) Nilotinib in imatinib-resistant or imatinib-intolerant patients with chronic myeloid leukemia in chronic phase: 48-month follow-up results of a phase II study. *Leukemia*, **27,** 107.

Giles, F.J., Kantarjian, H.M., Le Coutre, P.D., Baccarani, M., Mahon, F.X., Blakesley, R.E., Gallagher, N.J., Gillis, K., Goldberg, S.L. & Larson, R.A. (2012) Nilotinib is effective in imatinib-resistant or-intolerant patients with chronic myeloid leukemia in blastic phase. *Leukemia*, **26,** 959.

Gore, L., Kearns, P.R., De, C.A.S., Bertrand, Y., Hijiya, N., Stork, L.C., Chung, N.G., Cardos, R.C., Saikia, T. & Fagioli, F. (2018) Dasatinib in Pediatric Patients With Chronic Myeloid Leukemia in Chronic Phase: Results From a Phase II Trial. *Journal of Clinical Oncology,* **36,** 1330–1338.

Gratwohl, A. (2016)The role of hematopoietic stem cell transplantation in chronic myeloid leukemia. In *Chronic Myeloid Leukemia* pp 177–196. Springer.

Guilhot, F., Apperley, J., Kim, D.-W., Bullorsky, E.O., Baccarani, M., Roboz, G.J., Amadori, S., de Souza, C.A., Lipton, J.H. & Hochhaus, A. (2007) Dasatinib induces significant hematologic and cytogenetic responses in patients with imatinib-resistant or-intolerant chronic myeloid leukemia in accelerated phase. *Blood*, **109,** 4143–4150.

Hanfstein, B., Müller, M.C., , R., Erben, P., Lauseker, M., Fabarius, A., Schnittger, S., Haferlach, C., Göhring, G. & Proetel, U. (2012) Early molecular and

cytogenetic response is predictive for long-term progression-free and overall survival in chronic myeloid leukemia (CML). *Leukemia*, **26,** 2096–2102.

Hanfstein, B., Shlyakhto, V., Lauseker, M., , R., Saussele, S. & Dietz, C. (2014) Velocity of early BCR-ABL transcript elimination as an optimized predictor of outcome in chronic myeloid leukemia (CML) patients in chronic phase on treatment with imatinib. *Leukemia*, **28,** 1988–1992.

Heaney, N.B., Copland, M., Stewart, K., Godden, J., Parker, A.N., McQuaker, I.G., Smith, G.M., Crawley, C., Shepherd, P. & Holyoake, T.L. (2008) Complete molecular responses are achieved after reduced intensity stem cell transplantation and donor lymphocyte infusion in chronic myeloid leukemia. *Blood*, **111,** 5252–5255.

Hehlmann, R., Lauseker, M., Jung-Munkwitz, S., Leitner, A., Müller, M.C., Pletsch, N., Proetel, U., Haferlach, C., Schlegelberger, B. & Balleisen, L. (2011) Tolerability-adapted imatinib 800 mg/d versus 400 mg/d versus 400 mg/d plus interferon-α in newly diagnosed chronic myeloid leukemia. *Journal of Clinical Oncology*, **29,** 1634–1642.

Hehlmann, R., Lauseker, M., Saußele, S., Pfirrmann, M., Krause, S., Kolb, H.J., Neubauer, A., Hossfeld, D.K., Nerl, C. & Gratwohl, A. (2017) Assessment of imatinib as first-line treatment of chronic myeloid leukemia: 10-year survival results of the randomized CML study IV and impact of non-CML determinants. *Leukemia*, **31,** 2398.

Hehlmann, R., Müller, M.C., Lauseker, M., Hanfstein, B., Fabarius, A., Schreiber, A., Proetel, U., Pletsch, N., Pfirrmann, M. & Haferlach, C. (2014) Deep molecular response is reached by the majority of patients treated with imatinib, predicts survival, and is achieved more quickly by optimized high-dose imatinib: results from the randomized CML-study IV. *Journal of Clinical Oncology*, **32,** 415–423.

Hehlmann, R. (2012) How I treat CML blast crisis. *Blood*, **120,** 737–747.

Hochhaus, A., Baccarani, M. & Deininger, M. (2008) Dasatinib induces durable cytogenetic responses in patients with chronic myelogenous leukaemia in chronic phase with resistance or intolerance to imatinib. *Leukemia*, **22,** 1200–1206.

Hochhaus, A., Baccarani, M., Silver, R.T., Schiffer, C., Apperley, J.F., Cervantes, F., Clark, R.E., Cortes, J.E., Deininger, M.W. & Guilhot, F. (2020) European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. *Leukemia***, 34,** 966-984.

Hochhaus, A., Larson, R.A., Guilhot, F., Radich, J.P., Branford, S., Hughes, T.P., Baccarani, M., Deininger, M.W., Cervantes, F., Fujihara, S., Ortmann, C.E., Menssen, H.D., Kantarjian, H., Brien, S.G. & Druker, B.J. (2017a). Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia. *New England Journal of Medicine,* **376,** 917-927.

Hochhaus, A., Masszi, T., Giles, F.J., Radich, J.P., Ross, D.M., Casares, M.T.G.,

Hellmann, A., Stentoft, J., Conneally, E. & García-Gutiérrez, V. (2017b) Treatment-free remission following frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: results from the ENESTfreedom study. *Leukemia*, **31,** 1525-1531.

Hochhaus, A. & La Rosee, P. (2004) Imatinib therapy in chronic myelogenous leukemia: strategies to avoid and overcome resistance. *Leukemia*, **18,** 1321.

Hochhaus, A., Saglio, G., Hughes, T.P., Larson, R.A., Kim, D.W., Issaragrisil, S., Coutre, P.D., Etienne, G., Dorlhiac-Llacer, P.E., Clark, R.E., Flinn, I.W., Nakamae, H., Donohue, B., Deng, W., Dalal, D., Menssen, H.D. & Kantarjian, H.M. (2016) Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. *Leukemia*, **30,** 1044–1054.

Hoffmann, V.S., Baccarani, M., Lindörfer, D., Castagnetti, F., Turkina, A., Zaritsky, A., Hellmann, A., Prejzner, W., Steegmann, J.L. & Mayer, J. (2013) The EUTOS prognostic score: review and validation in 1288 patients with CML treated frontline with imatinib. *Leukemia*, **27,** 2016.

Hughes, T., Deininger, M., Hochhaus, A., Branford, S., Radich, J., Kaeda, J. & Monitoring, C.M.L. (2006) patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. *Blood*, **108,** 28–37.

Hughes, T.P., Hochhaus, A., Branford, S., Müller, M.C., Kaeda, J.S., Foroni, L., Druker, B.J., Guilhot, F., Larson, R.A. & O'Brien, S.G. (2010) Long-term prognostic significance of early molecular response to imatinib in newly diagnosed chronic myeloid leukemia: an analysis from the International Randomized Study of Interferon and STI571 (IRIS). *Blood*, **116,** 3758–3765.

Hughes, T.P., Laneuville, P., Rousselot, P., Snyder, D.S., Rea, D., Shah, N.P., Paar, D., Abruzzese, E., Hochhaus, A. & Lipton, J.H. (2019b) Incidence, outcomes, and risk factors of pleural effusion in patients receiving dasatinib therapy for Philadelphia chromosome-positive leukemia. *Haematologica*, **104,** 93–101.

Hughes, T.P., Mauro, M.J., Cortes, J.E., Minami, H., Rea, D., DeAngelo, D.J., Breccia, M., Goh, Y.-T., Talpaz, M. & Hochhaus, A. (2019a) Asciminib in Chronic Myeloid Leukemia after ABL Kinase Inhibitor Failure. *New England Journal of Medicine*, **381,** 2315–2326.

Hughes, T.P. & Ross, D.M. (2016) Moving treatment-free remission into mainstream clinical practice in CML. *Blood*, **128,** 17–23.

Hughes, T.P., Saglio, G., Kantarjian, H.M., Guilhot, F., Niederwieser, D., Rosti, G., Nakaseko, C., De Souza, C.A., Kalaycio, M.E. & Meier, S. (2014) Early molecular response predicts outcomes in patients with chronic myeloid leukemia in chronic phase treated with frontline nilotinib or imatinib. *Blood***, 123,** 1353-1360.

Ikeda, K., Shiga, Y., Takahashi, A., Kai, T., Kimura, H., Takeyama, K., Noji, H., Ogawa, K., Nakamura, A., Ohira, H., Sato, Y. & Maruyama, Y. (2006) Fatal

hepatitis B virus reactivation in a chronic myeloid leukemia patient during imatinib mesylate treatment. *Leukaemia and Lymphoma,* **155**, 47.

Imagawa, J., Tanaka, H., Okada, M., Nakamae, H., Hino, M., Murai, K., Ishida, Y., Kumagai, T., Sato, S. & Ohashi, K. (2015) Discontinuation of dasatinib in patients with chronic myeloid leukaemia who have maintained deep molecular response for longer than 1 year (DADI trial): a multicentre phase 2 trial. *The Lancet Haematology*, **2,** 528–535.

Issa, G.C., Kantarjian, H.M., Wang, F., González, G.N., Borthakur, G., Tang, G., Bueso-Ramos, C.E., Kanagal-Shamanna, R., Lopez, J.E.H. & Zhao, C. (2017) Clinical and Molecular Characterization of Clonal Chromosomal Abnormalities Appearing in Philadelphia-Negative Metaphases of Chronic Phase CML. *Blood,* **130:**47

Jabbour, E., Courte, P. & Cortes, J. (2013) le Prediction of outcomes in patients with Ph+ chronic myeloid leukemia in chronic phase treated with nilotinib after imatinib resistance/intolerance. Leukemia, **27,** 907–913.

Jabbour, E., Kantarjian, H. & Jones, D. (2009) Imatinib mesylate dose escalation is associated with durable responses in patients with chronic myeloid leukemia after cytogenetic failure on standard-dose imatinib therapy. *Blood*, **113,** 2154–2160.

Jabbour, E., Kantarjian, H.M., Saglio, G., Steegmann, J.L., Shah, N.P., Chuah, C., Pavlovsky, C., Mayer, J., Cortes, J., Baccarani, M., Kim, D.W., Bradley-Garelik, M.B., Mohamed, H., Wildgust, M. & Hochhaus, A., Boqué C. (2014) Early response with dasatinib or imatinib in chronic myeloid leukemia: 3-year follow-up from a randomized phase 3 trial (DASISION). *Blood,* **123,** 494–500.

Jain, P., Kantarjian, H., Nazha, A., O'Brien, S., Jabbour, E., Romo, C.G., Pierce, S., Cardenas-Turanzas, M., Verstovsek, S. & Borthakur, G. (2013) Early responses predict better outcomes in patients with newly diagnosed chronic myeloid leukemia: results with four tyrosine kinase inhibitor modalities. *Blood*, **121,** 4867–4874.

Jiang, Q., Xu, L.-P., Liu, D.-H., Liu, K.-Y., Chen, S.-S., Jiang, B., Jiang, H., Chen, H., Chen, Y.-H. & Han, W. (2011) Imatinib mesylate versus allogeneic hematopoietic stem cell transplantation for patients with chronic myelogenous leukemia in the accelerated phase. *Blood*, **117,** 3032–3040.

Kantarjian, H., Cortes, J., Kim, D.-W., Dorlhiac-Llacer, P., Pasquini, R., DiPersio, J., Müller, M.C., Radich, J.P., Khoury, H.J. & Khoroshko, N. (2009) Phase 3 study of dasatinib 140 mg once daily versus 70 mg twice daily in patients with chronic myeloid leukemia in accelerated phase resistant or intolerant to imatinib: 15-month median follow-up. *Blood*, **113,** 6322–6329.

Kantarjian, H., Giles, F. & Bhalla, K. (2011a) Nilotinib is effective in patients with chronic myeloid leukaemia in chronic phase after imatinib resistance or intolerance: 24 month follow up results. *Blood*, **117,** 1141–1145.

Kantarjian, H., Giles, F., Wunderle, L., Bhalla, K., O'Brien, S., Wassmann, B.,

Tanaka, C., Manley, P., Rae, P. & Mietlowski, W. (2006) Nilotinib in imatinib-resistant CML and Philadelphia chromosome–positive ALL. *New England Journal of Medicine*, **354,** 2542–2551.

Kantarjian, H., Shah, N.P., Hochhaus, A., Cortes, J., Shah, S., Ayala, M., Moiraghi, B., Shen, Z., Mayer, J., Pasquini, R., Nakamae, H., Huguet, F., Chuah, C., Bleickardt, E., Bradley-Garelik, M.B., Zhu, C., Szatrowski, T., Shapiro, D. & Baccarani, M. (2010) Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. New England Journal of Medicine, **362,** 2260–2270.

Kantarjian, H., Talpaz, M., O'brien, S., Giles, F., Faderl, S., Verstovsek, S., Garcia-Manero, G., Shan, J., Rios, M.B. & Champlin, R. (2005) Survival benefit with imatinib mesylate therapy in patients with accelerated-phase chronic myelogenous leukemia—Comparison with historic experience. *Cancer*, **103,** 2099–2108.

Kantarjian, H.M., Cortes, J., O'Brien, S., Giles, F.J., Albitar, M., Rios, M.B., Shan, J., Faderl, S., Garcia-Manero, G. & Thomas, D.A. (2002a) Imatinib mesylate (STI571) therapy for Philadelphia chromosome–positive chronic myelogenous leukemia in blast phase. *Blood*, **99,** 3547–3553.

Kantarjian, H.M., Hochhaus, A., Saglio, G., Souza, C., Flinn, I.W., Stenke, L., Goh, Y.T., Rosti, G., Nakamae, H., Gallagher, N.J., Hoenekopp, A., Blakesley, R.E., Larson, R.A. & Hughes, T.P. (2011b) Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial. *Lancet Oncology*, **12,** 841–851.

Kantarjian, H.M., O'Brien, S., Cortes, J.E., Smith, T.L., Rios, M.B., Shan, J., Yang, Y., Giles, F.J., Thomas, D.A. & Faderl, S. (2002b) Treatment of Philadelphia chromosome-positive, accelerated-phase chronic myelogenous leukemia with imatinib mesylate. *Clinical Cancer Research*, **8,** 2167–2176.

Kantarjian, H.M., Shah, N.P., Cortes, J.E., Baccarani, M., Agarwal, M.B., Undurraga, M.S., Wang, J., Kim, D.W., Ogura, M., Pavlovsky, C., Junghanss, C., Milone, J.H., Nicolini, F.E., Robak, T., Droogenbroeck, J., Vellenga, E., Bradley-Garelik, M.B., Zhu, C. & Hochhaus, A. (2012) Dasatinib or imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: 2-year follow-up from a randomized phase 3 trial (DASISION). *Blood,* **119,** 1123–1129.

Kantarjian, H.M., Smith, T.L., McCredie, K.B., Keating, M.J., Walters, R.S., Talpaz, M., Hester, J.P., Bligham, G., Gehan, E. & Freireich, E.J. (1985) Chronic myelogenous leukemia: a multivariate analysis of the associations of patient characteristics and therapy with survival. *Blood*, **66,** 1326–1335.

Khoury, H., Goldberg, S. & Mauro, M. (2016) Cross-intolerance with dasatinib among imatinib-intolerant patients with chronic phase chronic myeloid leukemia. *Clinical Lymphoma Myeloma and Leukaemia*, **16,** 341–349.

Khoury, H.J., Kukreja, M., Goldman, J.M., Wang, T., Halter, J., Arora, M., Gupta, V., Rizzieri, D.A., George, B. & Keating, A. (2012) Prognostic factors for outcomes

in allogeneic transplantation for CML in the imatinib era: a CIBMTR analysis. *Bone Marrow Transplantation*, **47,** 810-816.

Kizilors, A., Crisà, E., Lea, N., Passera, R., Mian, S., Anwar, J., Best, S., Nicolini, F.E., Ireland, R. & Aldouri, M. (2019) Effect of low-level BCR-ABL1 kinase domain mutations identified by next-generation sequencing in patients with chronic myeloid leukaemia: a population-based study. *The Lancet Haematology*, **6,** e276–e284.

de la Fuente, J., Baruchel, A., Biondi, A., de Bont, E., Dresse, M., Suttorp, M. & Millot, F. (2014) Managing children with chronic myeloid leukaemia (CML) Recommendations for the management of CML in children and young people up to the age of 18 years. *British Journal of Haematology*, **167,** 33–47.

Kumagai, T., Nakaseko, C., Nishiwaki, K., Yoshida, C., Ohashi, K., Takezako, N., Takano, H., Kouzai, Y., Murase, T. & Matsue, K. (2016) Discontinuation of dasatinib after deep molecular response for over 2 years in patients with chronic myelogenous leukemia and the unique profiles of lymphocyte subsets for successful discontinuation: a prospective, multicenter Japanese trial (D-STOP Trial). *Blood*, **128:**791.

Larson, R.A., Hochhaus, A., Hughes, T.P., Clark, R.E., Etienne, G., Kim, D.W., Flinn, I.W., Kurokawa, M., Moiraghi, B., Yu, R., Blakesley, R.E., Gallagher, N.J., Saglio, G. & Kantarjian, H.M. (2012) Nilotinib vs imatinib in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: ENESTnd 3-year follow-up. *Leukemia*, **26,** 2197–2203.

Latagliata, R., Ferrero, D., Iurlo, A., Cavazzini, F., Castagnetti, F., Abruzzese, E., Fava, C., Breccia, M., Annunziata, M. & Stagno, F. (2013) Imatinib in very elderly patients with chronic myeloid leukemia in chronic phase: a retrospective study. *Drugs & Ageing*, **30,** 629–637.

Lee, S.-E., Choi, S.Y., Kim, S.-H., Song, H.-Y., Yoo, H.-L., Lee, M.-Y., Kang, K.-H., Hwang, H.-J., Jang, E.-J. & Kim, D.-W. (2017) BCR-ABL1 transcripts (MR4.5) at post-transplant 3 months as an early predictor for long-term outcomes in chronic myeloid leukemia. *The Korean Journal of Internal Medicine*, **32,** 125.

Lee, S.J., Kukreja, M., Wang, T., Giralt, S.A., Szer, J., Arora, M., Woolfrey, A.E., Cervantes, F., Champlin, R.E. & Gale, R.P. (2008) Impact of prior imatinib mesylate on the outcome of hematopoietic cell transplantation for chronic myeloid leukemia. *Blood,* **112,** 3500-3507.

Lee, S., Choi, S.Y., Bang, J., Kim, S., Jang, E., Byeun, J., Park, J., Jeon, H., Oh, Y.J. & Kim, H. (2013) Predictive factors for successful imatinib cessation in chronic myeloid leukemia patients treated with imatinib. *American Journal of Hematology*, **88,** 449–454.

Mahon, F.-X., Réa, D., Guilhot, J., Guilhot, F., Huguet, F., Nicolini, F., Legros, L., Charbonnier, A., Guerci, A. & Varet, B. (2010) Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop

Imatinib (STIM) trial. *The Lancet Oncology*, **11,** 1029–1035.

Mahon, F., Richter, J., Guilhot, J., Hjorth-Hansen, H., Almeida, A., Janssen, J.J.W.M.J.W.M., Mayer, J., Porkka, K., Panayiotidis, P. & Stromberg, U. (2016) Cessation of tyrosine kinase inhibitors treatment in chronic myeloid leukemia patients with deep molecular response: results of the Euro-Ski trial. *Blood,* **128:**787.

Marin, D., Hedgley, C., Clark, R.E., Apperley, J., Foroni, L., Milojkovic, D., Pocock, C., Goldman, J.M. & O'Brien, S. (2012a) Predictive value of early molecular response in patients with chronic myeloid leukemia treated with first-line dasatinib. *Blood*, **120,** 291–294.

Marin, D., Ibrhim, A. & Lucas, C. (2012b) Assessment of BCR-ABL1 transcript levels at 3 months is the only requirement for predicting outcome for patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. *Oncology*, **30,** 232–238.

Marin, D., Milojkovic, D., Olavarria, E., Khorashad, J.S., de Lavallade, H., Reid, A.G., Foroni, L., Rezvani, K., Bua, M. & Dazzi, F. (2008) European LeukemiaNet criteria for failure or suboptimal response reliably identify patients with CML in early chronic phase treated with imatinib whose eventual outcome is poor. *Blood*, **112,** 4437–4444.

Matsuki, E., Ono, Y., Tonegawa, K., Sakurai, M., Kunimoto, H., Ishizawa, J., Hashimoto, N., Shimizu, T., Yamane, A. & Matsushita, M. (2012) Detailed Investigation On Characteristics of Japanese Patients with Chronic Phase CML Who Achieved a Durable CMR After Discontinuation of Imatinib–an Updated Result of the Keio STIM Study. *Blood*, **120**:2788.

Millot, F., Baruchel, A., Guilhot, J., Petit, A., Leblanc, T., Bertrand, Y., Mazingue, F., Lutz, P., Vérité, C. & Berthou, C. (2011) Imatinib is effective in children with previously untreated chronic myelogenous leukemia in early chronic phase: results of the French national phase IV trial. *Journal of clinical oncology*, **29,** 2827–2832.

Millot, F., Dupraz, C., Guilhot, J., Suttorp, M., Brizard, F., Leblanc, T., Güneş, A.M., Sedlacek, P., De Bont, E. & Li, C.K. (2017a) Additional cytogenetic abnormalities and variant t (9; 22) at the diagnosis of childhood chronic myeloid leukemia: The experience of the International Registry for Chronic Myeloid Leukemia in Children and Adolescents. *Cancer*, **123,** 3609–3616.

Millot, F., Guilhot, J., Baruchel, A., Petit, A., Bertrand, Y., Mazingue, F., Lutz, P., Vérité, C., Berthou, C. & Galambrun, C. (2014) Impact of early molecular response in children with chronic myeloid leukemia treated in the French Glivec phase 4 study. *Blood*, **124,** 2408–2410.

Millot, F., Guilhot, J., Suttorp, M., Güneş, A.M., Sedlacek, P., De Bont, E., Li, C.K., Kalwak, K., Lausen, B. & Culic, S. (2017b) Prognostic discrimination based on the EUTOS long-term survival score within the International Registry for Chronic Myeloid Leukemia in children and adolescents. *Haematologica*, **102,** 1704–

1708.

Millot, F., Traore, P., Guilhot, J., Nelken, B., Leblanc, T., Leverger, G., Plantaz, D., Bertrand, Y., Bordigoni, P. & Guilhot, F. (2005) Clinical and biological features at diagnosis in 40 children with chronic myeloid leukemia. *Pediatrics*, **116,** 140–143.

Milojkovic, D., Apperley, J. & Gerrard, G. (2012a) Responses to second-line tyrosine kinase inhibitors are durable: an intention-to-treat analysis in chronic myeloid leukaemia patients. *Blood*, **119,** 1838–1843.

Milojkovic, D. & Apperley, J.F. (2014) How I treat leukemia during pregnancy. *Blood*, **123,** 974–984.

Milojkovic, D., Ibrahim, A., Reid, A., Foroni, L., Apperley, J. & Marin, D. (2012b) Efficacy of combining dasatinib and FLAG-IDA for patients with chronic myeloid leukemia in blastic transformation. *Haematologica*, **97,** 473–474.

Milojkovic, D., Nicholson, E. & Apperley, J. (2010) Early prediction of success or failure of treatment with second-generation tyrosine kinase inhibitors in patients with chronic myeloid leukemia. *Haematologica*, **95,** 224–231.

Nair, A.P., Barnett, M.J., Broady, R.C., Hogge, D.E., Song, K.W., Toze, C.L., Nantel, S.H., Power, M.M., Sutherland, H.J. & Nevill, T.J. (2015) Allogeneic hematopoietic stem cell transplantation is an effective salvage therapy for patients with chronic myeloid leukemia presenting with advanced disease or failing treatment with tyrosine kinase inhibitors. *Biology of Blood and Marrow Transplantation*, **21,** 1437–1444.

Nicolini, F.E., Basak, G.W., Kim, D., Olavarria, E., Pinilla-Ibarz, J., Apperley, J.F., Hughes, T., Niederwieser, D., Mauro, M.J. & Chuah, C. (2017) Overall survival with ponatinib versus allogeneic stem cell transplantation in Philadelphia chromosome-positive leukemias with the T315I mutation. *Cancer*, **123,** 2875–2880.

Nicolini, F.E., Turkina, A., Shen, Z., Gallagher, N., Jootar, S., Powell, B.L., De Souza, C., Zheng, M., Szczudlo, T. & le Coutre, P. (2012) Expanding nilotinib access in clinical trials (ENACT). *Cancer*, **118,** 118–126.

Nicolini, F.E., Noël, M.-P., Escoffre, M., Charbonnier, A., Rea, D., Dubruille, V., Varet, B.R., Legros, L., Guerci, A. & Etienne, G. (2013) Preliminary report of the STIM2 study: a multicenter stop imatinib trial for chronic phase chronic myeloid leukemia de novo patients on imatinib. *Blood*, **122**:654.

Ohanian, M., Kantarjian, H.M., Quintas-Cardama, A., Jabbour, E., Abruzzo, L., Verstovsek, S., Borthakur, G., Ravandi, F., Garcia-Manero, G. & Champlin, R. (2014) Tyrosine kinase inhibitors as initial therapy for patients with chronic myeloid leukemia in accelerated phase. *Clinical Lymphoma, Myeloma and Leukemia*, **14,** 155–162.

Oyekunle, A., Zander, A.R., Binder, M., Ayuk, F., Zabelina, T., Christopeit, M., Stübig, T., Alchalby, H., Schafhausen, P. & Lellek, H. (2013) Outcome of allogeneic SCT in patients with chronic myeloid leukemia in the era of tyrosine kinase inhibitor therapy. *Annals of Hematology*, **92,** 487–496.

Palandri, F., Castagnetti, F., Alimena, G., Testoni, N., Breccia, M., Luatti, S., Rege-Cambrin, G., Stagno, F., Specchia, G. & Martino, B. (2009) The long-term durability of cytogenetic responses in patients with accelerated phase chronic myeloid leukemia treated with imatinib 600 mg: the GIMEMA CML Working Party experience after a 7-year follow-up. *Haematologica*, **94,** 205–212.

Palandri, F., Castagnetti, F., Testoni, N., Luatti, S., Marzocchi, G., Bassi, S., Breccia, M., Alimena, G., Pungolino, E. & Rege-Cambrin, G. (2008) Chronic myeloid leukemia in blast crisis treated with imatinib 600 mg: outcome of the patients alive after a 6-year follow-up. *Haematologica*, **93,** 1792–1796.

Pfirrmann, M., Baccarani, M., Saussele, S., Guilhot, J., Cervantes, F. & Ossenkoppele, G. (2016) Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia. *Leukemia*, **30,** 48–56.

Piepoli, M.F., Hoes, A.W., Agewall, S., Albus, C., Brotons, C., Catapano, A.L., Cooney, M.-T., Corra, U., Cosyns, B. & Deaton, C. (2016) 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *European Heart Journal*, **37,** 2315–2381.

Porkka, K., Koskenvesa, P., Lundán, T., Rimpiläinen, J., Mustjoki, S., Smykla, R., Wild, R., Luo, R., Arnan, M. & Brethon, B. (2008) Dasatinib crosses the blood-brain barrier and is an efficient therapy for central nervous system Philadelphia chromosome–positive leukemia. *Blood*, **112,** 1005–1012.

Pye, S.M., Cortes, J., Ault, P., Hatfield, A., Kantarjian, H., Pilot, R., Rosti, G. & Apperley, J.F. (2008) The effects of imatinib on pregnancy outcome. *Blood*, **111,** 5505–5508.

Rea, D., Nicolini, F.E., Tulliez, M., Guilhot, F., Guilhot, J., Guerci-Bresler, A., Gardembas, M., Coiteux, V., Guillerm, G. & Legros, L. (2017) Discontinuation of dasatinib or nilotinib in chronic myeloid leukemia: interim analysis of the STOP 2G-TKI study. *Blood*, **129,** 846–854.

Richter, J., Söderlund, S., Lübking, A., Dreimane, A., Lotfi, K., Markevärn, B., Själander, A., Saussele, S., Olsson-Strömberg, U. & Stenke, L. (2014) Musculoskeletal pain in patients with chronic myeloid leukemia after discontinuation of imatinib: a tyrosine kinase inhibitor withdrawal syndrome. *Journal of Clinical Oncology*, **32,** 2821–2823.

Rousselot, P., Huguet, F., Rea, D., Legros, L., Cayuela, J.M., Maarek, O., Blanchet, O., Marit, G., Gluckman, E. & Reiffers, J. (2007) Imatinib mesylate discontinuation in patients with chronic myelogenous leukemia in complete molecular remission for more than 2 years. *Blood*, **109,** 58–60.

Rousselot, P., Charbonnier, A., Cony-Makhoul, P., Agape, P., Nicolini, F.E., Varet, B., Gardembas, M., Etienne, G., Réa, D. & Roy, L. (2014) Loss of major molecular response as a trigger for restarting tyrosine kinase inhibitor therapy in patients with chronic-phase chronic myelogenous leukemia who have stopped imatinib after durable undetectable disease. *Journal of Clinical Oncology*, **32,** 424–430.

Ross, D.M., Branford, S., Seymour, J.F., Schwarer, A.P., Arthur, C., Yeung, D.T., Dang, P., Goyne, J.M., Slader, C. & Filshie, R.J. (2013) Safety and efficacy of imatinib cessation for CML patients with stable undetectable minimal residual disease: results from the TWISTER study. *Blood*, **122,** 515–522.

Saglio, G., Hochhaus, A., Goh, Y.T., Masszi, T., Pasquini, R., Maloisel, F., Erben, P., Cortes, J., Paquette, R. & Bradley-Garelik, M.B. (2010a) Dasatinib in imatinib-resistant or imatinib-intolerant chronic myeloid leukemia in blast phase after 2 years of follow-up in a phase 3 study. *Cancer*, **116,** 3852–3861.

Saglio, G., Kim, D.W., Issaragrisil, S., Coutre, P., Etienne, G., Lobo, C., Pasquini, R., Clark, R.E., Hochhaus, A., Hughes, T.P., Gallagher, N., Hoenekopp, A., Dong, M., Haque, A., Larson, R.A. & Kantarjian, H.M. for the ENESTnd Investigators. (2010b) Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *New England Journal of Medicine,* **362,** 2251–2259.

Salas, D.G., Glauche, I., Tauer, J.T., Thiede, C. & Suttorp, M. (2015) Can prognostic scoring systems for chronic myeloid leukemia as established in adults be applied to pediatric patients? *Annals of Hematology*, **94,** 1363–1371.

Saussele, S., Hehlmann, R., Fabarius, A., Jeromin, S., Proetel, U., Rinaldetti, S., Kohlbrenner, K., Einsele, H., Falge, C. & Kanz, L. (2018) Defining therapy goals for major molecular remission in chronic myeloid leukemia: results of the randomized CML Study IV. *Leukemia***, 32**, 1222-1228.

Saussele, S., Krauss, M.P., Hehlmann, R., Lauseker, M., Proetel, U., Kalmanti, L., Hanfstein, B., Fabarius, A., Kraemer, D., Berdel, W.E., Bentz, M., Staib, P., de Wit, M., Wernli, M., Zettl, F., Hebart, H.F., Hahn, M., Heymanns, J., Schmidt-Wolf, I., Schmitz, N., Bartholomäus A., Müller MC; Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung and the German Group. (2015) *Impact of comorbidities on overall survival in patients with chronic myeloid leukemia results of the randomized CML study IV. Blood*, **126,** 42–49.

Saussele, S., Lauseker, M., Gratwohl, A., Beelen, D.W., Bunjes, D., Schwerdtfeger, R., Kolb, H.-J., Ho, A.D., Falge, C. & Holler, E. (2010) Allogeneic hematopoietic stem cell transplantation (allo SCT) for chronic myeloid leukemia in the imatinib era: evaluation of its impact within a subgroup of the randomized German CML Study IV. *Blood*, **115,** 1880–1885.

Saussele, S., Richter, J., Guilhot, J., Gruber, F.X., Hjorth-Hansen, H., Almeida, A., Janssen, J.J.W.M., Mayer, J., Koskenvesa, P. & Panayiotidis, P. (2018) Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. *The Lancet Oncology*, **19,** 747–757.

Saussele, S., Richter, J., Hochhaus, A. & Mahon, F.X. (2016) The concept of treatment-free remission in chronic myeloid leukemia. *Leukemia*, **30,** 1638.

Saussele, S. & Silver, R.T. (2015) Management of chronic myeloid leukemia in blast crisis. *Annals of Hematology*, **94,** 159–165.

Sawyers, C.L., Hochhaus, A., Feldman, E., Goldman, J.M., Miller, C.B., Ottmann, O.G., Schiffer, C.A., Talpaz, M., Guilhot, F. & Deininger, M.W.N. (2002) Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study: Presented in part at the 4hird Annual Meeting of The American Society of Hematology, Orlando, FL, Dec. *Blood*, **99,** 3530–3539.

Shah, N., Guihot, F. & Cortes, J. (2014) Long-term outcome with dasatinib after imatinib failure in chronic-phase chronic myeloid leukaemia: follow up of a phase 3 study. *Blood*, **123,** 2317–2324.

Shah, N.P., Gutiérrez, J.V.G., Jiménez-Velasco, A., Larson, S.M., Saussele, S., Rea, D., Mahon, F.-X., Levy, M., Gómez-Casares, M.T. & Pane, F. (2017) Dasatinib discontinuation in patients (pts) with chronic-phase chronic myeloid leukemia (CML-CP) and stable deep molecular response (DASFREE). *Blood,* **130:**314.

Silver, R.T., Cortes, J., Waltzman, R., Mone, M. & Kantarjian, H. (2009) Sustained durability of responses and improved progression-free and overall survival with imatinib treatment for accelerated phase and blast crisis chronic myeloid leukemia: long-term follow-up of the STI571 0102 and 0109 trials. *Haematologica*, **94,** 743–744.

Söderlund, S., Dahlén, T., Sandin, F., Olsson-Strömberg, U., Creignou, M., Dreimane, A., Lübking, A., Markevärn, B., Själander, A. & Wadenvik, H. (2017) Advanced phase chronic myeloid leukaemia (CML) in the tyrosine kinase inhibitor era–a report from the Swedish CML register. *European Journal of Haematology*, **98,** 57–66.

Soverini, S., Bavaro, L., De Benedittis, C., Martelli, M., Iurlo, A., Orofino, N., Sica, S., Sorà, F., Lunghi, F. & Ciceri, F. (2020) Prospective assessment of NGS-detectable mutations in CML patients with nonoptimal response: the NEXT-in-CML study. *Blood,* **135,** 534–541.

Soverini, S., Hochhaus, A., Nicolini, F.E., Gruber, F., Lange, T. & Saglio, G.(2011) BCR-ABL kinase domain mutation analysis in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: recommendations from an expert panel on behalf of European LeukemiaNet. *Blood*, **118,** 1208–1215.

Steegmann, J.L., Baccarani, M., Breccia, M., Casado, L>F., Garcia-Gutiérrez, V., Hochhaus, A., Kim, D.W., Kim, T.D., Khoury, H.J. & Le Coutre, P. (2016) European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. *Leukemia*, **30,** 1648–1671

Sureda, A., Carrasco, M., de Miguel, M., Martínez, J.A., Conde, E., Sanz, M.A., Díaz-Mediavilla, J. & Sierra, J. (2003) Imatinib mesylate as treatment for blastic

transformation of Philadelphia chromosome positive chronic myelogenous leukemia. *Haematologica*, **88,** 1213–1220.

Suttorp, M., Eckardt, L., Tauer, J.T. & Millot, F. (2012) Management of chronic myeloid leukemia in childhood. *Current Hematologic Malignancy Reports*, **7,** 116–124.

Suttorp, M., Yaniv, I. & Schultz, K.R. (2011) Controversies in the treatment of CML in children and adolescents: TKIs versus BMT? *Biology of Blood and Marrow Transplantation*, **17,** S115–S122.

Talpaz, M., Shah, N.P., Kantarjian, H., Donato, N., Nicoll, J., Paquette, R., Cortes, J., O'brien, S., Nicaise, C. & Bleickardt, E. (2006) Dasatinib in imatinib-resistant Philadelphia chromosome–positive leukemias. *New England Journal of Medicine*, **354,** 2531–2541.

Talpaz, M., Silver, R.T., Druker, B.J., Goldman, J.M., Gambacorti-Passerini, C., Guilhot, F., Schiffer, C.A., Fischer, T., Deininger, M.W.N. & Lennard, A.L. (2002) Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. *Blood*, **99,** 1928–1937.

Valent, P., Hadzijusufovic, E., Hoermann, G., Schernthaner, G.H., Sperr, W.R., Kirchmair, R., Wolf, D. & Füreder W. (2017) Risk factors and mechanisms contributing to TKI-induced vascular events in patients with CML. *Leukaemia Research*, **59,** 47–54.

Vantroyen, B. & Vanstraelen, D. (2002) Management of essential thrombocythemia during pregnancy with aspirin, interferon alpha-2a and no treatment. *Acta Haematologica*, **107,** 158–169.

Vardiman, J.W. (2008) Chronic myelogenous leukaemia, BCR-ABL1 positive. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues***,** 32–37.

Xu, L., Zhu, H., Hu, J., Wu, D., Jiang, H., Jiang, Q. & Huang, X. (2015) Superiority of allogeneic hematopoietic stem cell transplantation to nilotinib and dasatinib for adult patients with chronic myelogenous leukemia in the accelerated phase. *Frontiers of Medicine*, **9,** 304–311.

Yeung, D.T., Osborn, M.P., White, D.L., Branford, S., Braley, J., Herschtal, A., Kornhauser, M., Issa, S., Hiwase, D.K., Hertzberg, M., Schwarer, A.P., Filshie R., Arthur, C.K., Kwan, Y.L., Trotman, J., Forsyth, C.J., Taper, J., Ross, D.M., Beresford, J., Tam, C; Australasian Leukaemia and Lymphoma Group. (2015) TIDELII First line use of imatinib in CML with early switch to nilotinib for failure to achieve time dependent molecular targets. *Blood*, **125,** 915–923.