South African National Essential Medicine List
Tertiary Medication Review Process
Component: Dasatinib Second Line Therapy in Chronic Myeloid Leukaemia

MEDICINE REVIEW

1. Executive Summary

Date: November 2024
Medicine (INN): Dasatinib
Medicine (ATC): L01EA02
Indication (ICD10 code): C92.1
Patient population: Individuals with Chronic Myeloid Leukaemia (CML) who have failed or are intolerant to frontline imatinib therapy.
Prevalence of condition: The South African National Cancer Registry, lists 268 new leukaemia cases in 2022. The registry does not make provision for the reporting of the different types of leukaemia – it also does not differentiate between acute and chronic leukaemia.[1] Approximately 15 to 20% of new adult leukaemia diagnoses are CML and although the incidence of cases refractory/intolerant to imatinib will be low, due to long term survival of patients on therapy prevalence will be higher and may increase over time. Current utilization of nilotinib/dasatinib suggest approximately 280 patients nationwide on second line therapy.[2]
Level of Care: Tertiary
Prescriber Level: Specialist Oncology/Haematology

Key findings

- Nilotinib is currently listed on the Tertiary/Quaternary EML for the management of imatinib-refractory CML. Dasatinib is another alternative which was previously not considered due to price however several dasatinib generics have become available in the South African market, which has substantially decreased the costs of this item. Pricing of dasatinib is now comparable to nilotinib, and both agents are specifically indicated for the management of chronic myeloid leukaemia (CML) refractory or intolerant to imatinib (both by the South African Health Products Regulatory Authority, and in clinical guidelines.
- We conducted a review of the literature to explore the efficacy and safety of dasatinib for CML refractory or intolerant to imatinib, for consideration as an alternative to nilotinib.
- The aim of the review was to establish whether dasatinib and nilotinib could be considered non-inferior to each other in the setting of CML refractory or intolerant to imatinib. The search was limited to systematic reviews and meta-analyses.
- The search identified one systematic review (health-technology assessment) evaluating nilotinib and dasatinib in people with imatinib-resistant and imatinib-intolerant CML for inclusion, Rogers et.al.[6] There was however no head-to-head comparison data of dasatinib to nilotinib.
- Findings:

  Overall Survival (OS)

  - **Dasatinib:** In patients with CML-chronic phase (CP) on dasatinib, only 10% are expected to die within 2 years of commencing therapy. One study with sufficient follow-up (Shah et.al. 2008) found more than 80% of the population should survive for at least 3 years.
  - **Nilotinib:** Only one study was included reporting on OS in patients in CML-CP on nilotinib. It reported that 5-10% of patients are expected to die within 2 years of commencing therapy. No long-term follow-up reported.

  Progression free survival (PFS)

  - **Dasatinib:** Estimated PFS probabilities suggest that at least three quarters of individuals treated with dasatinib in CML-CP can expect survival without disease progression for 2 years or more.

- **Nilotinib**: No published source of estimates for PFS with nilotinib in CMK-CP were identified. Unpublished data from a Phase II multicenter study of nilotinib included in the Pharmaceutical Company (Novartis) submission showed that those receiving nilotinib for CMP-CP can expect > 3 years' PFS.

Response

Cytogenetic response (CyR)

- **Dasatanib:** Complete CyR was shown in 47.8% of all study participants (95% CI 40.6% to 55.0%), significant heterogeneity (I^2 = 85.2%). Complete CyR was reported as 68.1% (95% CI 62.7% to 73.5%) in imatinib intolerant participants, and 37.4% (95% CI 34.2% to 40.5%) in imatinib resistant participants.
- **Nilotinib:** Complete CyR was shown in 35.1% of all study participants (95%CI 23.6% to 46.6%), I^2 = 70.6%, with little differences between imatinib intolerant (34.9%) and imatinib resistant participants (30.3%).

Haematological response

- **Dasatanib:** A complete haematological response was achieved or maintained in 90.7% of all cases (88.1% to 93.4%, I^2 = 62.2%).
- **Nilotinib:** A complete haematological response was achieved in 74.6% of all cases (95% CI 59.1% to 90.1%, I^2 = 85.8%). Complete haematological response was 90% with imatinib intolerant individuals and 78.9% for imatinib resistant participants.

Adverse events

- **Dasatinib**
  - » Haematological adverse events were common in all studies. Grade 3-4 neutropenia and thrombopenia each affected around 50% (+/- 10%) of people taking dasatinib (rates were lower with lower dosing – 100mg daily).
  - » Diarrhoea, dyspnoea, fatigue, headache, nausea, pleural effusion and rash were the other most commonly reported adverse events.
  - » Grade 3-4 non-haematological adverse events were rare, with only dyspnoea and pleural effusion occurring in > 5% of cohorts.
- **Nilotinib**
  - » Haematological adverse events were common. Grade 3-4 neutropenia and thrombocytopenia affected about 30% of participants in the published study.
  - » Most common non-haematological adverse events were constipation, diarrhoea, fatigue, headache, nausea/vomiting, pruritus, rash (1/10 - ¼ of participants experiencing these).
  - » Grade 3 – 4 adverse events were rare, with only rash exceeding 3% incidence.

➡ The presence of BCR/ABL kinase domain mutations may determine the choice of second line therapy as some mutations that occur are sensitive to either nilotinib or dasatinb.

➡ The current buy-out prices of dasatinib and nilotinib are similar.

TERTIARY HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:					
	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
Type of recommendation			X		

Recommendation: It is recommended that dasatinib be included on the Tertiary Essential Medicines List as an alternative to nilotinib for the management of chronic myeloid leukaemia (CML) in patients who are refractory or intolerant to imatinib. Preference of agent should take into account BCR/ABL kinase domain mutations, the most affordable agent at the time, and patient individual characteristics.

Rationale: Dasatinib and nilotinib have similar effects in terms of cytogenetic and haematological responses in both imatinib resistant and imatinib intolerant populations. The price of dasatinib has decreased significantly over the past years due to the availability of generics and is now comparable, and possibly more affordable than nilotinib.

Level of Evidence: Systematic Review of randomised controlled trials and observational studies. (LoE II)

Review indicator: Price changes (dasatinib/nilotinib), new evidence of efficacy and safety.

NEMLC RECOMMENDATION:

NEMLC recommended the inclusion of dasatanib on the Tertiary Essential Medicines List as an alternative to nilotinib for the management of CML in patients who are refractory or intolerant to imatinib.

Monitoring and evaluation considerations:

Uptake of utilisation of dasatinib in comparison to nilotinib.

Research priorities:

2. Name of author(s)/motivator(s)

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Acknowledgements for support to: Solange Durao, Roger Wiseman, Marc Blockman.

3. Author affiliation and conflict of interest details

- J Malherbe: Division of Clinical Haematology, Department Internal Medicine, University of the Free State. No conflicts of interest to declare.
  J Riddin: National Department of Health, Essential Drugs Programme. No conflicts of interest to declare.

4. Introduction/ Background

Chronic Myeloid Leukemia (CML) is caused by a balanced translocation between chromosomes 9 and 22, leading to the formation of the BCR/ABL oncogenic tyrosine kinase. The treatment of CML was revolutionised with the development of the tyrosine kinase inhibitor (TKI) imatinib in the early 2000s, leading to long-term control in the majority of patients. In treatment-responsive patients, survival approaches that of age-matched controls. Unfortunately, a significant proportion of patients either fail or are intolerant to frontline imatinib, which led to the development of the second-line TKIs nilotinib and dasatinib. Reported rates of changing from imatinib varies widely, ranging from a low of 26.5% in 10 years to as high as 37 to 50% in 5 years.[3]

Both nilotinib and dasatinib have been demonstrated to be effective in the second line setting and are included in all CML International treatment guidelines. Nilotinib and dasatinib were both included in 2017 in the WHO essential medicines list for second line therapy in CML.[4]

The presence of BCR/ABL kinase domain mutations may also determine the choice of second line therapy, as some mutations are sensitive to either nilotinib or dasatinib. Certain mutations, most notably T315I, are resistant to both agents and require either ponatinib or asciminib. Mutational analysis is done routinely in patients failing their current treatment regime. The following table shows some examples of mutations and required TKI.[3]

BCR/ABL Mutation	Required TKI
F317L/V/I/C, T315A	Nilotinib
V299L	Nilotinib
Y253H, E255V/K, F359V/I/C	Dasatinib
T315I	Asciminib or Ponatinib

The treatment goal of second line therapy is to regain control of disease and to reach specific clinical and molecular targets for disease control that is associated with improved survival and outcomes. Patients reaching these targets can expect a normal, or near normal age matched life expectancy. Disease control is determined by quantification of the BCR/ABL oncogene by peripheral blood polymerase chain reaction (PCR) testing. The table below shows BCR/ABL transcript levels and goals of therapy at different time points.

Timepoint (from start of therapy)	Optimal response	Warning (assess compliance, monitor closely)	Failure (ensure compliance, change therapy if compliant)
3 months	≤10%	>10%	>10% if confirmed in 1 to 3 months
6 months	≤1%	1 to 10%	>10%
12 months	≤0.1%	>0.1 to 1%	>1%
Any time			Resistance mutations or acquisition of additional chromosomal abnormalities

In the South African public health sector context, imatinib was included on the TQ EML for frontline therapy in March 2014, and nilotinib for second-line therapy in January 2015. Dasatinib has not been included previously due to cost,

but numerous generics have been registered recently, and quotations obtained show relative cost equivalence to nilotinib. This has prompted the review of dasatinib for second line therapy in CML in addition to nilotinib.

Based on international data, CML constitutes approximately 15 to 20% of adult leukaemias and has an annual incidence of 1 to 2 per 100 000 with a slight male predominance.[3] The South African National Cancer Registry, lists 268 new leukaemia cases in 2022. Because the registry does not report the different types of leukaemia, and doesn't distinguish between acute or chronic leukaemias, the exact incidence of CML in South Africa is not known. It can only be estimated that approximately 40 to 50 new CML patients are diagnosed per year. Although the incidence of cases refractory/intolerant to imatinib will be relatively low, due to the long-term survival of patients on therapy prevalence will be higher and may increase over time. Current utilization of nilotinib/dasatinib suggest approximately 280 patients nationwide on second line therapy.

5. Purpose/Objective i.e. PICO

-P *(patient/population):* Chronic Myeloid Leukemia with failure or intolerance to frontline imatinib
-I *(intervention):* Dasatinib 50mg, 70mg, 100mg
-C *(comparator):* Nilotinib 400mg bd
-O *(outcome):* Overall survival, Progression free survival, response rate, adverse events (e.g. toxicity)

Study designs:

As the aim was to determine non-inferiority between nilotinib and dasatinib, the search was limited to systematic reviews and meta-analyses as an initial step, and then consideration of randomized controlled trials (RCTs) comparing nilotinib and dasatinib directly for the outlined indication.

6. Methods:

Search strategy

A literature search was conducted on 26 July 2024 in PubMed and the Cochrane Library using the above PICO (see Appendix 2).

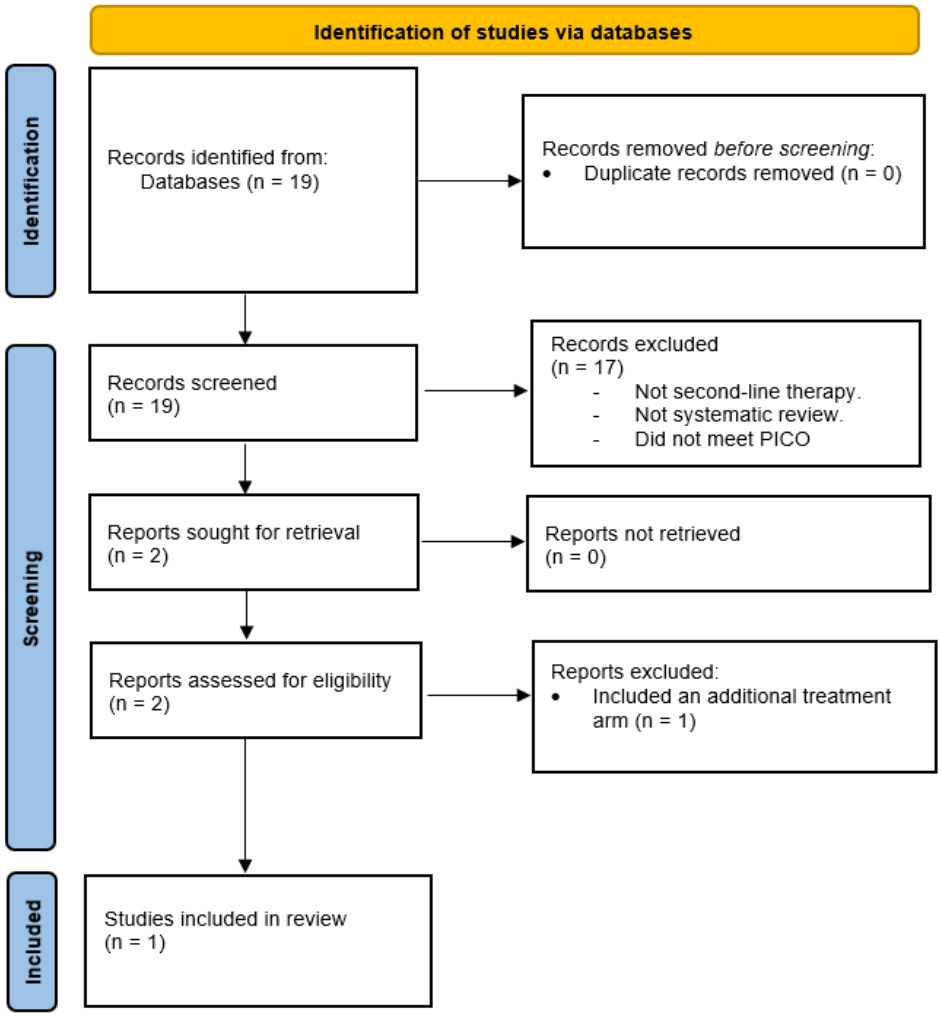
Study Selection

Abstract and title screening was undertaken in duplicate and independently by JM and JR with conflicts resolved through discussion. Final selection was undertaken by JM and JR with review by the Tertiary Expert Review Committee.

Results

Search results

Nineteen systematic reviews were identified in the search *(see appendix 2)*, however following title and abstract screening, 17 were excluded. Two systematic reviews were considered for full text review. One systematic review (Rogers et.al.) more closely met the PICO (however it did not contain head-to-head comparisons of nilotinib and dasatinib). The other study (Lovemore et.al.) also did not include head-to-head comparisons of nilotinib and dasatinib, and included an extra treatment arm not under evaluation and thus was excluded. Rogers et. al. was thus selected as more closely representing the PICO. *See PRISMA diagram below.* A follow up search was conducted for RCTs comparing nilotinib and dasatinib in this setting, however none were identified. *(see appendix 2)*



Excluded studies:

Author, date	***Type of study***	***Reason for exclusion***
Lovemore et.al. May 2012[5]	*Systematic Review and Economic Analysis*	• *Included an additional treatment arm (imatinib high dose) not currently under investigation.* • *All studies evaluating dasatinib and nilotinib included were also included in Rogers et.al.* • *Did not include imatinib intolerant patients.*

Description of included studies

One systematic review was included (Rogers 2012)– see table below for details. *The review is up to date as of June 2009.*

Author, date	***Type of study***	**n**	**Population**	**Comparators**	**Outcomes**	**Effects**
Rogers et.al. April 2012[6]	Systematic Review and Economic evaluation	15 studies (3 RCTs; 12 observational) (see appendix 3)	People with imatinib-resistant and imatinib-intolerant CML	Dasatinib compared to standard of care* Versus Nilotinib compared to standard of care* **High-dose imatinib, interferon-alpha, hydroxycarbamide, acute leukaemia chemotherapy and best supportive care*	The primary outcomes were molecular, CyR and HR rates. Secondary outcomes were time to response, duration of response, PFS, OS, adverse effects of treatment and HRQoL.	Chronic phase: effectiveness data were limited but dasatinib and nilotinib appeared efficacious in terms of obtaining cytogenetic response and haematological response in both ImR and ImI populations.

CyR: cytogenic response; HR: haematological response; PFS: progression free survival; OS: overall survival; HRQoL: health-related quality of life.

Assessment of methodological quality

AMSTAR 2 assessment on Rogers et.al. found it to be of critically low quality with limitations related to no assessment for publication bias, and not listing excluded studies. The included review assessed the quality of clinical effectiveness studies included according to criteria suggested by the NHS Centre for Reviews and Dissemination (CRD), report 4 (*See appendix 4*: Indicators of quality of included studies).

All three of the included randomised controlled trials were found to be considerably flawed largely due to their open-label designs and unclear allocation methods. Additionally, there were no power calculations for any of the RCTs.

Phase I and Phase II observational studies seemed to feature consecutive, prospective recruitment of participants, which can help enhance accuracy and generalisability of research. The Phase II studies were generally good at reporting completely on recruited cohort (intention-to-treat principles).

No case-series included in the systematic review reported any steps to blind outcome assessors.

Effects of interventions

Outcome 1. Overall Survival

Dasatinib

In patients with CML-CP on dasatinib, only 10% are expected to die within 2 years of commencing therapy. One study with sufficient follow-up (Shah et.al. 2008) found more than 80% of the population should survive for at least 3 years.

TABLE 36 Overall survival with dasatinib in CML-CP

Study	Length of follow-up	Dose	Imatinib	*n*	6 months (years)	12 months (years)	18 months (years)	24 months (years)	36 months (years)
Hochhaus *et al.* (2007)[11]	15 months	70 mg b.i.d.	Iml	99	1.000	1.000	1.000		
			ImR	288	0.975	0.955	0.945		
			ImR/Iml	387	0.980	0.965	0.960		
Shah *et al.* (2008)[22]		100 mg q.d.	ImR/Iml	167	0.975	0.970		0.91[b]	0.87[c]
			Iml	43				0.95[d]	
			ImR	124				0.89[d]	
		50 mg b.i.d.	ImR/Iml	168	0.970	0.930		0.90[b]	0.84[c]
		140 mg q.d.	ImR/Iml	167	0.990	0.960		0.94[b]	0.84[c]
		70 mg b.i.d.	ImR/Iml	168	0.960	0.890		0.88[b]	0.80[c]

a Data extracted from update publication.[105]
b Data extracted from abstract presenting updated results.[97]
c Only source for this at the time of writing is a news report: (www.docguide.com/news/content.nsf/news/852571020057CCF6852575CA0063F72E) of what was reported at ASCO on 1 June 2009 (www.abstract.asco.org/AbstView_65_33899.html).
d Data extracted from BMS's submission (appendix 6, table 9).[184]

Nilotinib

Only one study was included reporting on OS in patients in CML-CP on nilotinib. This reported that 5-10% of patients are expected to die within 2 years of commencing therapy. No long-term follow-up reported.

TABLE 64 Overall survival with nilotinib in CML-CP

Study	Dose	Length of follow-up	Imatinib	*n*	6 months (years)	12 months (years)	18 months (years)	24 months (years)	30 months (years)
Kantarjian *et al.* (2007)[106]	400 mg b.i.d.	6 months[a]	ImR/Iml	280	0.995	0.95	0.95		
		Update[b]	ImR/Iml	321		0.95	0.91		
		Further update[c]	ImR/Iml	321	0.995	0.95	0.91	0.88	0.88
		NR[d]	Iml	NR	1.000	0.989	0.955	0.908	0.908
			ImR	NR	0.987	0.937	0.894		

NR, not reported.
a Minimum follow-up.
b Data extracted from abstract presenting '2-year follow-up results' (note also expanded enrolment); not clear to what '2-year' refers – may well be maximum follow-up, as time-to-event outcomes are only given to 18 months;[172] in the Novartis submission, these data are referred to as 'a minimum of 19 months [sic] follow up' (p. 19).[205]
c Data extracted from the text of the Novartis submission.[205]
d Data extracted from its cost-effectiveness model provided by Novartis as part of the submission to NICE.

<u>Outcome 2: Progression free survival (PFS)</u>

Dasatinib

Estimated PFS probabilities suggest that at least three quarters of individuals treated with dasatinib in CML-CP can expect survival without disease progression for 2 years or more.

TABLE 33 Progression-free survival with dasatinib in CML-CP

Study	Dose	Length of follow-up	Imatinib	*n*	6 months (years)	12 months (years)	18 months (years)	24 months (years)	36 months (years)
Talpaz *et al.* (2006)[104]	Mixed/NR		ImR/Iml	40	1	1	1		
Hochhaus *et al.* (2007)[11]	70 mg b.i.d.	8 months	Iml	59	1				
			ImR	127	0.91				
			ImR/Iml	186	0.94				
		15 months	Iml	99	0.995	0.985	0.955		
			ImR	288	0.92	0.88	0.805		
			ImR/Iml	387	0.94	0.905	0.845		
Kantarjian *et al.* (2007)[23]	70 mg b.i.d.		ImR	101	0.975	0.925	0.925	0.86[b]	
Shah *et al.* (2008)[22]	100 mg q.d.		ImR/Iml	167	0.95	0.89		0.80[c]	0.73[d]
			Iml	43				0.87[e]	
			ImR	124				0.77[e]	
	50 mg b.i.d.		ImR/Iml	168	0.94	0.815		0.75[c]	0.72[d]
	140 mg q.d.		ImR/Iml	167	0.93	0.89		0.76[c]	0.60[d]
	70 mg b.i.d.		ImR/Iml	168	0.93	0.78		0.76[c]	0.67[d]

NR, not reported.
a Data extracted from update publication.[105]
b Data extracted from abstract presenting updated results.[89]
c Data extracted from abstract presenting updated results.[97]
d Only source for this at the moment is a news report (www.docguide.com/news/content.nsf/news/852571020057CCF6852575CA0063F72E) of what was reported at ASCO on 1 June 2009 (www.abstract.asco.org/AbstView_65_33899.html).
e Data extracted from BMS's submission (appendix 6, table 9).[184]

Nilotinib

No published source of estimates for PFS with nilotinib in CMK-CP were identified. Unpublished data from a Phase II multicentre study of nilotinib included in the Pharmaceutical Company (Novartis) submission showed that those receiving nilotinib for CMP-CP can expect > 3 years' PFS.

TABLE 62 Progression-free survival with nilotinib in CML-CP

Study	Dose	Length of follow-up	Imatinib	*n*	6 months (years)	12 months (years)	18 months (years)	24 months (years)	36 months (years)
Kantarjian *et al.* (2007)[106]	400 mg b.i.d.	? update[a]	ImR/Iml	321	0.925	0.84	0.73	0.64	0.575
		NR[b]	Iml	NR	0.95	0.91	0.84		
			ImR	NR	0.86	0.77	0.63		
Kantarjian *et al.* (2007)[106]	400 mg b.i.d.	? update[c]	ImR/Iml	321	0.925	0.84	0.73	0.64	0.575

?, unclear; NR, not reported.
a Length of follow-up.
b Data extracted from the cost-effectiveness model provided by Novartis as part of its submission to NICE.
c Data appear to relate to conference abstract presenting '2-year follow-up results' (note also expanded enrolment); not clear to what '2-year' refers – may well be maximum follow-up, as time-to-event outcomes are only given to 18 months;[172] in Novartis submission, these data were referred to as 'a minimum of 19 months [sic] follow up' (p. 19).[205]

Outcome 3: Response Rates

Outcome 3.1 Cytogenetic response (CyR)

Dasatinib

Complete CyR was shown in 47.8% of all study participants (95% CI 40.6% to 55.0%), significant heterogeneity I^2 = 85.2%. Complete CyR was reported as 68.1% (95% CI 62.7% to 73.5%) in imatinib intolerant participants, and 37.4% (95% CI 34.2% to 40.5%) in imatinib resistant participants.

TABLE 15 Complete cytogenetic response to dasatinib in CML-CP

Study	Dose	*n*	κ	%	95% CI
Iml					
[a]Hochhaus *et al.* (2007)[11,105]	70 mg b.i.d.	99	74	74.7	65.0% to 82.9%
Shah *et al.* (2008)[22]	100 mg q.d.	43	27	62.8	46.7% to 77.0%
	50 mg b.i.d.	44	27	61.4	45.5% to 75.6%
	70 mg b.i.d.	41	25	61.0	44.5% to 75.8%
	140 mg q.d.	44	30	68.2	52.4% to 81.4%
Sakamaki *et al.* (2009)[109]	70 mg b.i.d.	12	8	66.7	34.9% to 90.1%
Subtotal [heterogeneity: $Q = 4.56$ (p on 5 df = 0.471); $I^2 = 0.0\%$; $\tau^2 = 0.000$]				**68.1**	**62.7% to 73.5%**
ImR					
[a]Hochhaus *et al.* (2007)[11,105]	70 mg b.i.d.	288	115	39.9	34.2% to 45.8%
Kantarjian *et al.* (2007)[23]	70 mg b.i.d.	101	40	39.6	30.0% to 49.8%
Shah *et al.* (2008)[22]	100 mg q.d.	124	42	33.9	25.6% to 42.9%
	50 mg b.i.d.	124	43	34.7	26.4% to 43.7%
	140 mg q.d.	123	44	35.8	27.3% to 44.9%
	70 mg b.i.d.	127	50	39.4	30.8% to 48.4%
Sakamaki *et al.* (2009)[109]	70 mg b.i.d.	18	5	27.8	9.7% to 53.5%
Subtotal [heterogeneity: $Q = 3.25$ (p on 6 df = 0.777); $I^2 = 0.0\%$; $\tau^2 = 0.000$]				**37.4**	**34.2% to 40.5%**
ImR and/or Iml					
Talpaz *et al.* (2006)[104]	Mixed/NR	40	14	35.0	20.6% to 51.7%
Cortes *et al.* (2007)[38]	Mixed/NR	24	8	33.3	15.6% to 55.3%
Fabarius *et al.* (2007)[79]	Mixed/NR	50	22	44.0	30.0% to 58.7%
Kim *et al.* (2009)[80]	70 mg b.i.d.	13	9	69.2	38.6% to 90.9%
Subtotal [heterogeneity: $Q = 6.28$ (p on 3 df = 0.099); $I^2 = 52.2\%$; $\tau^2 = 0.008$]				43.1	30.5% to 55.7%
Overall pooled estimate				***47.8***	***40.6% to 55.0%***
Heterogeneity: $Q = 107.77$ (p on 16 df = 0.000); $I^2 = 85.2\%$; $\tau^2 = 0.018$					
Heterogeneity between intolerant and resistant strata: $z = 9.65$ ($p = 0.000$)					

a 15-month follow-up.[105]

Major cytogenetic response [number of participants experiencing either complete cytogenetic response or partial cytogenetic response (35% Ph+ cells evident)] was reported as 59% (53.4% to 65.7%).

Nilotinib

Complete CyR was shown in 35.1% of all study participants (95%CI 23.6% to 46.6%), I^2 = 70.6%, with little differences between imatinib intolerant (34.9%) and imatinib resistant participants (30.3%).

TABLE 51 Complete cytogenetic response to nilotinib in CML-CP

Study	Dose	*n*	κ	%	95% CI
Iml					
Kantarjian *et al.* (2007)[106]	400 mg b.i.d.	86	30	34.9	24.9% to 45.9%
ImR					
Kantarjian *et al.* (2006)[103]	Mixed/NR	17	6	35.3	14.2% to 61.7%
Kantarjian *et al.* (2007)[106]	400 mg b.i.d.	194	58	29.9	23.5% to 36.9%
Subtotal [heterogeneity: $Q = 0.2$ (p on 1 df = 0.654); $I^2 = 0.0\%$; $\tau^2 = 0.000$]				**30.3**	**24.1% to 36.5%**
ImR and/or Iml					
Cortes *et al.* (2007)[38]	Mixed/NR	13	2	15.4	1.9% to 45.4%
Tojo *et al.* (2009)[108]	400 mg b.i.d.	16	11	68.8	41.3% to 89.0%
Subtotal [heterogeneity: $Q = 12.15$ (p on 1 df = 0.000); $I^2 = 91.8\%$; $\tau^2 = 0.131$]				**41.7**	**0.0% to 94.0%**
Overall pooled estimate				***35.1***	***23.6% to 46.6%***
Heterogeneity: $Q = 13.61$ (p on 4 df = 0.009); $I^2 = 70.6\%$; $\tau^2 = 0.011$					
Heterogeneity between intolerant and resistant strata: $z = 0.76$ ($p = 0.224$)					

NR, not reported.

Major cytogenetic response [number of participants experiencing either complete cytogenetic response or partial cytogenetic response (35% Ph+ cells evident)] was reported as 52.3% (31.5% to 73.0%).

Outcome 3.2: Haematological response

Dasatinib

A complete haematological response was achieved or maintained in 90.7% of all cases (88.1% to 93.4%), I^2 = 62.2%.

TABLE 25 Complete HR to dasatinib in CML-CP

Study	Dose	*n*	κ	%	95% CI
Iml					
[a]Hochhaus *et al.* (2007)[11,105]	70 mg b.i.d.	99	93	93.9	87.3% to 97.7%
Shah *et al.* (2008)[22]	100 mg q.d.	43	43	100.0	91.8% to 100.0%
	50 mg b.i.d.	44	41	93.2	81.3% to 98.6%
	140 mg q.d.	44	38	86.4	72.6% to 94.8%
	70 mg b.i.d.	41	35	85.4	70.8% to 94.4%
Sakamaki *et al.* (2009)[110]	70 mg b.i.d.	12	12	100.0	73.5% to 100.0%
Subtotal [heterogeneity: $Q = 11.66$ (p on 5 df = 0.040); $I^2 = 57.1\%$; $\tau^2 = 0.001$]				**93.7**	**89.5% to 97.9%**
ImR					
[a]Hochhaus *et al.* (2007)[11,105]	70 mg b.i.d.	288	258	89.6	85.5% to 92.9%
Kantarjian *et al.* (2007)[23]	70 mg b.i.d.	101	94	93.1	86.2% to 97.2%
Shah *et al.* (2008)[22]	100 mg q.d.	124	107	86.3	79.0% to 91.8%
	50 mg b.i.d.	124	113	91.1	84.7% to 95.5%
	140 mg q.d.	123	105	85.4	77.9% to 91.1%
	70 mg b.i.d.	127	111	87.4	80.3% to 92.6%
Sakamaki *et al.* (2009)[109]	70 mg b.i.d.	18	15	83.3	58.6% to 96.4%
Subtotal [heterogeneity: $Q = 6.11$ (p on 6 df = 0.411); $I^2 = 1.8\%$; $\tau^2 = 0.000$]				**89.2**	**87.2% to 91.3%**
ImR and/or Iml					
Talpaz *et al.* (2006)[104]	Mixed/NR	40	37	92.5	79.6% to 98.4%
Cortes *et al.* (2007)[38]	Mixed/NR	24	20	83.3	62.6% to 95.3%
Subtotal [heterogeneity: $Q = 1.12$ (p on 1 df = 0.291); $I^2 = 10.5\%$; $\tau^2 = 0.000$]				**90.1**	**82.3% to 98.0%**
Overall pooled estimate				***90.7***	***88.1% to 93.4%***
Heterogeneity: $Q = 37.01$ (p on 14 df = 0.001); $I^2 = 62.2\%$; $\tau^2 = 0.001$					
Heterogeneity between intolerant and resistant strata: $z = 1.87$ ($p = 0.031$)					

NR, not reported.
a 15 months follow-up.[105]

Nilotinib

A complete haematological response was achieved in 74.6% of all cases (95% CI 59.1% to 90.1%), I^2 = 85.8%. Complete haematological response was 90% with imatinib intolerant individuals and 78.9% for imatinib resistant participants.

TABLE 58 Complete haematological response to nilotinib in CML-CP

Study	Dose	*n*	κ	%	95% CI
Iml					
Kantarjian *et al.* (2007)[106]	400 mg b.i.d.	50	45	90.0	78.2% to 96.7%
ImR					
Kantarjian *et al.* (2006)[103]	Mixed/NR	12	11	91.7	61.5% to 99.8%
Kantarjian *et al.* (2007)[106]	400 mg b.i.d.	135	92	68.1	59.6% to 75.9%
Subtotal [heterogeneity: $Q = 6.94$ (p on 1 df = 0.008); $I^2 = 85.6\%$; $\tau^2 = 0.024$]				**78.9**	**55.9% to 100.0%**
ImR and/or Iml					
Cortes *et al.* (2007)[38]	Mixed/NR	13	10	76.9	46.2% to 95.0%
Tojo *et al.* (2009)[108]	400 mg b.i.d.	16	6	37.5	15.2% to 64.6%
Subtotal [heterogeneity: $Q = 5.49$ (p on 1 df = 0.019); $I^2 = 81.8\%$; $\tau^2 = 0.064$]				**57.3**	**18.7% to 96.0%**
Overall pooled estimate				***74.6***	***59.1% to 90.1%***
Heterogeneity: $Q = 28.17$ (p on 4 df = 0.000); $I^2 = 85.8\%$; $\tau^2 = 0.025$					
Heterogeneity between intolerant and resistant strata: $z = 0.89$ ($p = 0.186$)					

NR, not reported.

Outcome 4: Adverse events

Dasatinib

- Haematological adverse events were common in all studies. Grade 3-4 neutropenia and thrombocytopaenia each affected around 50% (+/- 10%) of people taking dasatinib (rates were lower with lower dosing – 100mg daily).
- Diarrhoea, dyspnoea, fatigue, headache, nausea, pleural effusion and rash were the other most commonly reported adverse events.
- Grade 3-4 non-haematological adverse events were rare, with only dyspnoea and pleural effusion occurring in > 5% of cohorts.

TABLE 38 Haematological AEs (grade 3–4)

Adverse event	Talpaz *et al.*,[104] ImR/Iml, Mixed/ NR	Hochhaus *et al.*,[11] ImR/Iml, 70 mg b.i.d.	Hochhaus *et al.*,[11] 18 months follow-up[a] ImR/Iml, 70 mg b.i.d.	Kantarjian *et al.*,[23] ImR, 70 mg b.i.d.	Shah *et al.*,[22] ImR/Iml, 100 mg q.d.	Shah *et al.*,[22] ImR/Iml, 50 mg b.i.d.	Shah *et al.*,[22] ImR/Iml, 140 mg q.d.	Shah *et al.*,[22] ImR/Iml, 70 mg b.i.d.	Sakamaki *et al.*,[109] ImR/Iml, 70 mg b.i.d.
n	**40**	**186**	**387**	**101**	**167**	**168**	**167**	**168**	**30**
Anaemia (%)		21.5	21.4		9.6	16.1	16.8	16.1	16.7
Leucopenia (%)		24.7	26.9		16.2	25.0	19.8	22.6	26.7
Neutropenia (%)	45.0	49.5	48.6	61.4	32.9	42.9	40.7	40.5	46.7
Thrombopenia (%)	35.0	47.3	48.3	56.4	22.2	31.0	38.3	36.3	50.0

NR, not reported.
a Data extracted from update publication.[105]

Nilotinib

- Haematological adverse events were common. Grade 3-4 neutroenia and thrombocytopaenia affected about 30% of participants in the published study.
- Most common non-haematological adverse events were constipation, diarrhoea, fatigue, headache, nausea/vomiting, pruritus, rash. (1/10 - ¼ experiencing such events).
- Grade 3 – 4 adverse events were rare, with only rash exceeding 3% incidence.

TABLE 66 Adverse events with nilotinib

	CP				
	All grades		Grade 3–4		
	400 mg b.i.d.	Kantarjian *et al.*,[186] ImR/Iml, 400 mg b.i.d.	Expanded access programme[a]	Kantarjian *et al.*,[186] ImR/Iml, 400 mg b.i.d.	Expanded access programme[a]	Tojo *et al.*,[188] ImR/Iml, 400 mg b.i.d.
n	280	1217	280	1217	16
Haematological AEs					
Anaemia (%)				3.0	18.8[c]
Leucopenia (%)					31.3[d]
Neutropenia (%)			28.9	11.0	37.5[e]
Thrombopenia (%)			28.9	18.0	18.8[f]
Non-haematological AEs					
Abdominal pain (%)					
Alopecia (%)					
Anorexia (%)					
Arthralgia (%)					
Back pain (%)					
Chest pain (%)					
Constipation (%)	12.1	6.0	0.0	<1.0	
Diarrhoea (%)	11.4		2.1		
Dry skin (%)					
Eczema (%)					
Erythema (%)					
Fatigue (%)	18.6	8.0	1.1	<1.0	
Headache (%)	18.6	16.0	1.8	2.0	
Hepatic dysfunction (%)					
Malaise (%)					

Adverse effects discussion

The second generation TKIs differ with regards to their toxicity profile, and the choice between either is influenced by comorbidities and age. [3]

Nilotinib is associated with an increased risk of cardiovascular events, and up to 20% of patients may have events over a 10-year period compared to 5% with imatinib. While the risk of cardiovascular events with dasatinib is higher than Imatinib it's significantly lower than nilotinib. Nilotinib should be avoided in patients with a history of coronary heart disease, cerebrovascular events and peripheral arterial disease. Patients with hypertension, hypercholesterolemia and diabetes mellitus may also be at increased risk and may warrant avoidance of nilotinib. A history of pancreatitis is an absolute contraindication for the use of nilotinib.

Dasatinib is associated with pleuro-pulmonary toxicity and cumulative incidence of pleural effusion range from 28 to 35% after 7 years depending on the dose, and sometimes necessitates stopping or changing therapy. A rare, but serious toxicity associated with dasatinib is pulmonary hypertension which are usually reversible with cessation. This occurs in less than 1% of patients. Dasatinib should be avoided in patients with previous or concomitant pleuro-pulmonary disease. Older patients are at higher risk of dasatinib induced toxicity and lower doses may need to be considered.

Alternative agents: None

Costs

Comparative dosing:

- Imatinib 400mg daily
- Nilotinib 400mg 12 hourly
- Dasatinib 100mg daily (range 50 to 140mg daily)

		Dose	Price/pack SEP*	Cost/patient/month	Cost/patient/ year
SEP*	Imatinib	400mg daily	R 6,856.80	R 6,856.80	R 82,281.60
	Nilotinib	400mg 12 hourly	R 36,275.37	R 38,866.47	R 466,397.68
	Dasatinib	100mg daily##	R 15,390.47	R 15,390.47	R 184,685.64

		Dose	Price /pack contract	Cost/patient/month	Cost/patient/ year
CONTRACT PRICE	Imatinib	400mg daily	R224.40**	R 224.40	R 2,692.80
	Nilotinib	400mg 12 hourly	R2,368.67***	R 2,537.86	R 30,454.33
	Dasatinib	100mg daily##	n/a		

		Dose	Price /pack buy out #	Cost/patient/month	Cos/patient/ year
Buy out price	Imatinib	400mg daily			
	Nilotinib	400mg 12 hourly	R2,529.49	R 2,710.17	R 32,522.01
	Dasatinib	100mg daily##	R2,368.00	R 2,368.00	R 28,416.00

**SEP: August 2024 **Current contract: HP04-2024ONC ***Previous contract: HP04 # Buy out prices – National quotation (nilotinib), Provincial quotation (dasatinib) ## Chronic maintenance dose for refractory CM - Doses can range from 50mg to 140mg daily depending on patient response.*

According to current provincial consumption of nilotinib and dasatinib (2024 monthly average), there are approximately 286 (approximately 280 on nilotinib and 6 on dasatinib) on second-line CML treatment.

Assuming these numbers, the budget impact for the second-line CML treatment would be as outlined in table below:

	Dose	Strength	Cost per patient/year	Annual budget impact
Nilotinib	400mg 12 hourly	200mg	R32,522.01	R9,301,296.09
Dasatinib	100mg daily	100mg	R28,416.00	R8,126,976.00

**based on buy-out pricing July 2024*

Potential savings of over R1 million on annual budget impact if majority of volume is put on dasatinib.

Conclusion

Although data is limited, dasatinib and nilotinib both appear to be efficacious in terms of cytogenetic and haematological responses in both imatinib-resistant and imatinib-intolerant populations. Studies had limited follow-up, however both dasatinib and nilotinib showed favourable overall survival, with 90% - 95% of patients expected to survive beyond 2 years after commencing therapy.

With the introduction of dasatinib generics, the price has decreased significantly, and is now comparable to nilotinib; with perhaps opportunities for better pricing with award on national contract.

It is recommended that dasatinib be included in the EML as a second line treatment option for CML as an alternative to nilotinib. Due to differing adverse event profiles and BCR/ABL kinase domain mutations, it is further recommended that both agents be available to provide for specific population needs.

Appendix 1: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☒ Very low ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	There are no direct head-to-head trials comparing nilotinib and dasatinib in the second line setting.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☒ Small ☐ None ☐	**Overall survival** *Dasatinib* 90% of patients with CML-CP are expected to survive beyond 2 years after commencing therapy. *Nilotinib* 90-95% of patients with CML-CP are expected to survive beyond 2 years after commencing therapy. **Complete CyR** *Dasatinib* 68.1% (95% CI 62.7% to 73.5%) in imatinib intolerant participants, and 37.4% (95% CI 34.2% to 40.5%) in imatinib resistant participants. *Nilotinib* 35.1% of all study participants (95%CI 23.6% to 46.6%), I^2 = 70.6%, with little differences between imatinib intolerant (34.9%) and imatinib resistant participants (30.3%). **Haematological response** *Dasatanib:* A complete haematological response was achieved or maintained in 90.7% of all cases (88.1% to 93.4%, I^2 = 62.2%). *Nilotinib:* A complete haematological response was achieved in 74.6% of all cases (95% CI 59.1% to 90.1%, I^2 = 85.8%). Complete haemtological response was 90% with imatinib intolerant individuals and 78.9% for imatinib resistant participants.
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☒ Very low ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	There are no head-to-head studies comparing dasatinib to nilotinib in this patient population.

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large ☐ Moderate ☒ Small ☐ None ☐	The toxicity of dasatinib is well known, and clear guidelines exist on the management of these toxicities. **Dasatinib** Grade 3-4 neutropaenia and thrombocytopenia each affected around 50% (+/- 10%) of people taking dasatinib (rates were lower with lower dosing – 100mg daily). Diarrhoea, dyspnoea, fatigue, headache, nausea, pleural effusion and rash were the other most commonly reported adverse events. Only pleural effusion and dyspnoea occurs in > 5% of patients. **Nilotinib** Grade 3-4 neutropaenia and thrombocytopaenia affected about 30% of participants in the published study. Most common non-haematological adverse events were constipation, diarrhoea, fatigue, headache, nausea/vomiting, pruritus, rash (1/10 - ¼ of participants experiencing these). Only rash exceeded an incidence of 3%.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☐ Favours control ☐ Intervention = Control *or* Uncertain ☒	From available evidence the efficacy of dasatinib and nilotinib in the second line setting is comparable.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes ☒ No ☐ List the members of the group. Nilotinib, Dasatinib List specific exclusion from the group: Ponatinib, asciminib	Comparable efficacy between nilotinib and dasatinib, however both should be available to cater for specific patient characteristics. Rationale for exclusion from the group: Ponatinib not registered, asciminib registered but more costly References:
FEASIBILITY	**Is implementation of this recommendation feasible?** Yes ☒ No ☐ Uncertain ☐	Many dasatinib generics available, simpler dosing of dasatinib.
RESOURCE USE	**How large are the resource requirements?** More intensive ☐ Less intensive ☒ Uncertain/ comparable ☐	Comparable and likely less intensive – see costing section

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [X] Major [ ] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [X] Uncertain [ ]	

Appendix 2: Search Strategy

PubMed (conducted 26 July 2024)

Search	Query	Search details	Results
#3	Dasatinib or nilotinib AND CML: RCTs	(("nilotinib"[Supplementary Concept] OR "nilotinib"[All Fields] OR ("dasatinib"[MeSH Terms] OR "dasatinib"[All Fields])) AND ("chronic myeloid leukaemia"[All Fields] OR "leukemia, myelogenous, chronic, bcr abl positive"[MeSH Terms] OR ("leukemia"[All Fields] AND "myelogenous"[All Fields] AND "chronic"[All Fields] AND "bcr abl"[All Fields] AND "positive"[All Fields]) OR "bcr-abl positive chronic myelogenous leukemia"[All Fields] OR ("chronic"[All Fields] AND "myeloid"[All Fields] AND "leukemia"[All Fields]) OR "chronic myeloid leukemia"[All Fields])) AND (randomizedcontrolledtrial[Filter])	68
#2	Dasatinib AND CML: Meta-analyses and systematic reviews	((dasatinib[MeSH Terms]) OR (nilotinib[MeSH Terms])) AND (chronic myeloid leukemia[MeSH Terms]) AND (meta-analysis[Filter] OR systematicreview[Filter])	19
#1	Dasatinib AND CML	((dasatinib[MeSH Terms]) OR (nilotinib[MeSH Terms])) AND (chronic myeloid leukemia[MeSH Terms])	1253

Cochrane Library (conducted 26 July 2024)

Query	Search details	Results
#1	MeSH descriptor: [Dasatinib] explode all trees	172
#2	MeSH descriptor: [Leukemia, Myelogenous, Chronic, BCR-ABL Positive] explode all trees	704
#3	#1 AND #2	78
#4	#3 PLUS Cochrane review limit	3

Appendix 3: Studies included in Rogers et.al.

TABLE 5 Details of interventions: RCTs

Study	Arm no.	Drug	Dosage notes	Notes
Kantarjian *et al.* (2007)[23]	1	Dasatinib	70 mg b.i.d. Escalated to 180 mg b.i.d for participants with inadequate response at 12 weeks or progression Reduced to 100 mg or 80 mg b.i.d for participants experiencing toxicity	Crossover to the alternative treatment was permitted after confirmed progression, lack of MCyR at the week 12 cytogenetic evaluation or intolerance
	2	Imatinib	400 mg b.i.d. Reduction to 600 mg b.i.d was permitted for toxicity in participants who had not previously received 600 mg b.i.d imatinib	This is study 017 in the BMS submission[184] to NICE
Shah *et al.* (2008)[22]	1	Dasatinib	100 mg q.d. Escalation to 140 mg q.d. allowed for suboptimal response Reduction to 80 mg q.d. allowed for toxicity	This is study 034 in the BMS submission[184] to NICE
	2	Dasatinib	50 mg b.i.d. Escalation to 70 mg b.i.d. allowed for suboptimal response Reduction to 40 mg b.i.d. allowed for toxicity	
	3	Dasatinib	140 mg q.d. Escalation to 180 mg q.d. allowed for suboptimal response Reduction to 80 mg q.d. allowed for toxicity	
	4	Dasatinib	70 mg b.i.d. Escalation to 90 mg b.i.d. allowed for suboptimal response Reduction to 40 mg b.i.d. allowed for toxicity	
Kantarjian *et al.* (2009)[81]	1	Dasatinib	140 mg q.d. Escalation to 180 mg q.d. was allowed for inadequate response (rising percentage of blasts or loss of HR in two consecutive assessments at least 1 week apart; absence of CHR, NEL, or minor HR within 4 weeks; no MCyR after 3 months or no CCyR after 6 months) Interruption or reduction to 80 mg q.d. was allowed in cases of drug toxicity (grade 2 or greater, non-haematological toxicity considered related to dasatinib; ANC 0.5×10^9/l and/or platelets $<100\times10^9$/l for >6 weeks with BM cellularity <10% with blasts <5% or BM cellularity >10% with blasts >5%; or febrile neutropenia with signs of septicaemia)	This is study 035 in the BMS submission[184] to NICE
	2	Dasatinib	70 mg b.i.d. Escalation to 90 mg b.i.d. or reduction to 40 mg b.i.d. permitted; criteria as per arm 1	

NEL, no evidence of leukaemia.

TABLE 6 Study design: RCTs

Study	Additional publications	CP	AP	BC	Country	No. of centres	Inclusion criteria	Exclusion criteria	Method of allocation	Blinding	Therapy common to all participants	Notes
Kantarjian *et al.* (2007)[23]	Shah *et al.* (2006)[82] Shah *et al.* (2006)[83] Cannell (2007)[84] Kantarjian *et al.* (2007)[85] Martinelli *et al.* (2007)[86] Schiffer (2007)[87] Rousselot *et al.* (2008)[88] Rousselot *et al.* (2008)[89]	✓			Not stated (n= 23); authors are from the USA, Brazil, France, Poland, Thailand, Poland, Russian Federation, Hungary and Australia	58	Patients with CML-CP and primary or acquired resistance to conventional doses of imatinib (400–600 mg q.d.), dasatinib-naive, at least 18 years of age and have adequate hepatic and renal function. CP was defined by the presence of <15% blasts, <20% basophils and <30% blasts plus promyelocytes in PB or BM and a platelet count of at least 100,000 per cubic millimetre, with no extramedullary involvement. Primary resistance to imatinib was defined as a lack of CHR after 3 months of imatinib treatment, a lack of any CyR after 6 months of treatment or a lack of a MCyR (Ph+ cells >35%) after 12 months of treatment. Relapse after a HR or MCyR was considered as secondary or acquired resistance	Patients who had received imatinib in the 7 days before the study were ineligible, as were patients who had received imatinib at doses in excess of 600 mg q.d. Patients with known specific BCR–ABL mutations (with high resistance to imatinib) before study entry were excluded	2:1 randomisation (no details of methods used)	Open-label	Not reported	

continued

TABLE 6 Study design: RCTs *(continued)*

Study	Additional publications	CP	AP	BC	Country	No. of centres	Inclusion criteria	Exclusion criteria	Method of allocation	Blinding	Therapy common to all participants	Notes
Shah *et al.* (2008)[22]	Hochhaus *et al.* (2006)[90] Hochhaus *et al.* (2007)[91] Shah *et al.* (2007)[92] Hochhaus *et al.* (2008)[93] Hochhaus *et al.* (2008)[94] Nicaise *et al.* (2008)[95] Porkka *et al.* (2008)[96] Shah *et al.* (2008)[97] Wang *et al.* (2008)[98]	✓			Not stated; authors are from the USA, Republic of South Korea, France, Brazil, Argentina, Mexico, Russian Federation, Australia and Germany	139	Patients at least 18 years of age with Ph+ CML-CP and primary or acquired haematological resistance or intolerance to imatinib were enrolled. Patients were required to have < 15% blasts in PB or BM, < 30% blasts and promyelocytes in PB or BM, < 20% basophils in PB, equal to 100,000/μl platelets (or less if related to prior drug therapy), and no extramedullary involvement (except liver or spleen). Primary resistance to imatinib (400–800 mg q.d.) was defined as no decrease in WBC count after 4 weeks of treatment, no complete HR after 3 months, no MCyR after 6 months and no CCyR after 12 months. Acquired resistance was defined as loss of MCyR (equal to 30% absolute increase in the percentage of Ph+ metaphases), loss of molecular response (concomitant with a 10% Ph+ metaphases at cytogenetic analysis), evidence of a new mutation in the BCR–ABL-kinase domain, or loss of a confirmed CHR (WBC count > 10,000/μl on all assessments over at least a consecutive 2-week period). Intolerance to imatinib was defined as grade 3 or worse toxicity which led to discontinuation of therapy. Patients who tolerated 400 mg q.d. imatinib, but who did not achieve a CCyR and subsequently did not tolerate doses of 600 mg q.d. were considered to be resistant to imatinib	Included but not limited to: treatment with imatinib, IFN, cytarabine therapy or any targeted small-molecule anticancer agent within 7 days of initiation; uncontrolled or significant cardiovascular disease; history of a significant bleeding disorder unrelated to CML; eligibility for immediate autologous or allogeneic SCT; or concurrent incurable malignancy other than CML	A permuted block design was used to assign participants randomly with a 1 : 1 : 1 : 1 ratio	Open-label	Therapies other than dasatinib were prohibited, except hydroxycarbamide (limited to a period of 2 weeks) for treatment of elevated WBC counts ($> 50 \times 10^9$/l). Administration of myeloid growth factors or recombinant erythropoietin was permitted at the discretion of the investigator. Patients were supported with platelet transfusions as required	NCT00123474 CA 180–034

Study	Additional publications	CP	AP	BC	Country	No. of centres	Inclusion criteria	Exclusion criteria	Method of allocation	Blinding	Therapy common to all participants	Notes
Kantarjian *et al.* (2009)[81]	Kantarjian *et al.* (2006)[99] Pasquini *et al.* (2007)[100] Kantarjian *et al.* (2008)[101] Saglio *et al.* (2008)[102]		✓		(*n* = 30) Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Israel, Italy, the Netherlands, Norway, Peru, Philippines, Poland, Republic of Korea, Russian Federation, Singapore, South Africa, Spain, Switzerland, Taiwan, Thailand, the UK and the USA	97	Participants with CML-AP (PB or BM counts of 15–30%); blasts, ≥30% blasts plus promyelocytes, but with < 30% blasts alone; ≥20% basophils, and platelet counts < 100×10^9/l unrelated to drug therapy; patients with clonal evolution or with prior CML-AP (except those defined by elevated basophil count only) who achieved a HR and subsequently progressed were included even if they did not reach the threshold values of percentage of blasts in PB or BM for AP, who had stopped treatment with imatinib following resistance or intolerance. Resistance to imatinib was defined as no HR to imatinib after at least 4 weeks of treatment or a 50% increase in PB blasts after 2 weeks' treatment at 600 mg q.d.; achieved a HR and subsequently no longer met the criteria consistently on all assessments over a consecutive 2-week period while receiving imatinib 600 mg q.d.; or patients initially diagnosed with CML-CP who progressed to CML-AP while receiving imatinib at any dose. Intolerance to imatinib was defined as having grade 3 or greater non-haematological toxicity or grade 4 or greater haematological toxicity lasting for > 2 weeks while on imatinib ≥600 mg q.d. that led to discontinuation of therapy or to dose decrease to ≤400 mg q.d. with loss of HR	Eastern Cooperative Oncology Group (ECOG) performance status > 2; inadequate hepatic or renal function; treatment with imatinib, INF, cytarabine or any targeted small molecule anticancer agent within 7 days of initiation; uncontrolled or significant cardiovascular disease; history of a significant bleeding disorder unrelated to CML; or any concurrent incurable malignancy other that CML	Randomisation (no detail of methods) was stratified by phase and type of disease and imatinib status (resistant or intolerant)	Open-label	CML therapies other than dasatinib were prohibited during the study, with the exception of hydroxycarbamide for elevated WBC counts. Colony-stimulating factors and recombinant erythropoietin were permitted at the discretion of the investigator, according to institutional guidelines. Patients were supported with platelet transfusions as required	CA180–035

TABLE 7 Details of interventions: observational studies

Study	Arm no.	Drug	Dosage	Concurrent treatment	Notes
Kantarjian *et al.* (2006)[103]	1	Nilotinib	Nine dose cohorts, ranging from 50 mg to 1200 mg q.d. and from 400 mg to 600 mg b.i.d.	During the first cycle of therapy or at times of worsening disease before intrapatient dose escalation, patients were allowed to receive cytoreductive therapy (leucapheresis and hydroxycarbamide) to control elevated counts of blasts, platelets or both	Multiple arms with different dosage levels; however, outcomes of interest for effectiveness only reported for all enrolled participants
Talpaz *et al.* (2006)[104]	1	Dasatinib	Dose escalation study (15–240 mg q.d.) The study protocol permitted progression to the administration of continuous daily doses of dasatinib and dose escalation	Unclear	
Cortes *et al.* (2007)[38]	1	Dasatinib	Not reported	Unclear	
	2	Nilotinib	Not reported	Unclear	
Cortes *et al.* (2007)[13]	1	Dasatinib	70 mg b.i.d.; after 4 weeks of treatment, dose escalation to 100 mg b.i.d. was permitted for participants with suboptimal response	No treatment for CML other than dasatinib was permitted during the study – except anagrelide and hydroxycarbamide for treatment of elevated platelet counts (higher than 700×10^9/l) and WBC counts (higher than 50×10^9/l), respectively. Use of hydroxycarbamide was limited to a period of 2 weeks. Administration of colony-stimulating factors and recombinant erythropoietin was permitted at the discretion of the investigator	
Fabarius *et al.* (2007)[79]	1	Dasatinib	Started at a dose of 100–140 mg q.d. (2×50 mg q.d. or 2×70 mg q.d.)	Not clear. Only stated that five patients received allogeneic SCT	
Guilhot *et al.* (2007)[12]	1	Dasatinib	Starting dose 70 mg b.i.d. After 4 weeks of treatment, dose escalation to 100 mg b.i.d. was permitted for participants with suboptimal response	No treatment for CML other than dasatinib was permitted during the study – except anagrelide and hydroxycarbamide for treatment of elevated platelet counts (higher than 700×10^9/l) and WBC counts (higher than 50×10^9/l), respectively. Use of hydroxycarbamide was limited to a period of 2 weeks	
Hochhaus *et al.* (2007)[11,105]	1	Dasatinib	70 mg b.i.d.; escalation to 90 mg b.i.d. permitted for patients with suboptimal response Interruptions or reduction to 50 mg or 40 mg b.i.d. in response to toxicity	No treatment for CML other than dasatinib was permitted during the study – except anagrelide and hydroxycarbamide for treatment of elevated platelet counts (higher than 700×10^9/l) and WBC counts (higher than 50×10^9/l), respectively. Use of hydroxycarbamide was limited to a period of 2 weeks. Administration of colony-stimulating factors and recombinant erythropoietin was permitted at the discretion of the investigator	
Kantarjian *et al.* (2007)[106]	1	Nilotinib	400 mg b.i.d.; escalation to 600 mg b.i.d. allowed if suboptimal response and no safety concerns	Unclear	
le Coutre *et al.* (2008)[107]	1	Nilotinib	800 mg (400 mg b.i.d.) Escalation to 1200 mg (600 mg b.i.d.) was permitted for suboptimal response in the absence of toxicity Reductions to 400 mg daily and subsequently 200 mg daily were permitted for the management of toxicity	Treatment with chemotherapy other than hydroxycarbamide was not permitted within 1 week of starting therapy with nilotinib	
Kim *et al.* (2009)[80]	1	Dasatinib	Starting dose 70 mg b.i.d.	Not reported	

TABLE 7 Details of interventions: observational studies *(continued)*

Study	Arm no.	Drug	Dosage	Concurrent treatment	Notes
Tojo *et al.* (2009)[108]	1	Nilotinib	800 mg (400 mg b.i.d.) Reductions to 400 mg daily and subsequently 200 mg daily were permitted for the management of toxicity	Not reported	
Sakamaki *et al.* (2009)[109]	1	Dasatinib	Phase I: dose escalation at 50 mg b.i.d., 70 mg b.i.d., 90 mg b.i.d. Unclear which participants took which doses Phase two: starting dose 140 mg q.d. (70 mg b.i.d.) Reduction (amount not reported) was permitted for participants with toxicity Escalation (amount not reported) was permitted for participants with suboptimal response	No other anticancer therapy other than ≤ 14 days of hydroxycarbamide for WBC > 50 × 10^9/l	Presented results conflate Phase I (dose escalation) and Phase II (dose steady) results into a single cohort

Study	Additional publications	Design	CP	AP	BC	Country	No. of centres	Inclusion criteria	Exclusion criteria	Notes
Cortes *et al.* (2007)[13]	Ottmann *et al.* (2005)[116] Talpaz *et al.* (2005)[117] Chromik *et al.* (2006)[118] Cortes *et al.* (2006)[119] Martinelli *et al.* (2006)[120] Soverini *et al.* (2006)[77] Ganibacoiti *et al.* (2007)[121] Ottmann *et al.* (2007)[122] Soverini *et al.* (2007)[78] Cortes *et al.* (2008)[123] Porkka *et al.* (2008)[124] Saglio *et al.* (2008)[125]	Case series (prospective)			✓	The USA, Switzerland, Germany, Argentina, Australia, Austria, Belgium, Israel, France, Italy, the Netherlands, Brazil, Canada, Finland, Republic of Korea, the Philippines, Sweden, Taiwan, Thailand and the UK	Multicentre, but number not reported	Patients 18 years of age and older were eligible for inclusion if they had CML in MBC or LBC and were resistant to or intolerant of imatinib therapy. CML-BC was defined as > 30% blasts (myeloid or lymphoid) in PB or BM or extramedullary leukaemic infiltrates (other than in spleen or liver) with PB blast (myeloid or lymphoid) cell morphology Imatinib resistance was defined as progression from CP to BC while receiving 400 mg q.d. or more imatinib or from AP to BC while receiving 600 mg q.d. or more imatinib (or 400–600 mg q.d. if the patient was intolerant of 600 mg q.d. or more). Patients initially diagnosed in BC were classified as having ImR CML if they met the criteria for BC after 4 or more weeks (2 weeks for patients whose disease progressed rapidly) on imatinib 600 mg q.d. or more). Imatinib intolerance was defined as discontinuation of therapy because of toxicity considered at least possibly related to an imatinib dose of 400 mg q.d. or less or to an inability to tolerate imatinib doses higher than 400 mg q.d. For inclusion in the study, patients were required to have adequate hepatic and renal function and an Eastern cooperative Oncology Group (ECOG) performance score of 2 or lower	Exclusion criteria included previous dasatinib therapy, imatinib therapy within 7 days of initiation, uncontrolled or significant cardiovascular disease, or history of a significant bleeding disorder unrelated to CML	START-B START-L #CA180006 #CA180015
Fabarius *et al.* (2007)[79]		Case series (prospective)	✓	✓	✓	Germany		Not clearly defined, other than 'patients with Ph+ and BCR–ABL-positive CML after imatinib failure'	Not reported	

continued

TABLE 8 Study design: observational studies *(continued)*

Study	Additional publications	Design	CP	AP	BC	Country	No. of centres	Inclusion criteria	Exclusion criteria	Notes
Guilhot *et al.* (2007)[12]	Guilhot *et al.* (2005)[126] Cortes *et al.* (2006)[127] Talpaz *et al.* (2006)[128] Guilhot *et al.* (2007)[129] O'Brien (2007)[130] Rea *et al.* (2008)[131] Rea *et al.* (2008)[132]	Case series (prospective)		✓		The USA, Switzerland, Germany, Argentina, Australia, Austria, Belgium, Israel, France, Italy, the Netherlands, Singapore, Sweden, Taiwan, the UK, Brazil and Norway	40	Male and female patients, aged 18 years or older, were eligible for inclusion if they had Ph+ or BCR–ABL-positive CML-AP with primary or acquired haematological resistance or intolerance to imatinib therapy, and had adequate hepatic function. CML-AP was defined as the occurrence of one or more of the following (1) at least 15–30% blasts in PB or BM; (2) at least 30% blasts plus promyelocytes (summed) in blood or BM (but with < 30% blasts alone); (3) at least 20% basophils in blood or BM; or (4) platelet counts $< 100 \times 10^9$/l unrelated to drug therapy The definition of resistance to imatinib differed depending on the initial CML diagnosis Patients with an initial diagnosis of CML-CP were defined as having resistant disease if (1) progression to CML-AP occurred while receiving imatinib 400 mg q.d. or more; or (2) no HR was achieved after at least 4 weeks (or 2 weeks for patients who progressed rapidly) of imatinib 600 mg q.d.) Patients with an initial diagnosis of CML-AP or -BC who had experienced a HR were defined as having resistant disease if progression to CML-AP occurred while receiving imatinib 600 mg q.d. or more (or 400–600 mg q.d. if the patient was intolerant of ≥ 600 mg q.d.) Patients were defined as having Iml CML-AP if they had toxicity which led to a discontinuation of therapy and was considered to be possibly related to imatinib at a dose of ≯ 400 mg q.d. or if they could only tolerate imatinib doses < 400 mg q.d.	Patients who had an ECOG performance status of grade 3 or greater, uncontrolled or significant cardiovascular disease, or a history of a significant bleeding disorder unrelated to CML	#CA180005 START-A

Study	Additional publications	Design	CP	AP	BC	Country	No. of centres	Inclusion criteria	Exclusion criteria	Notes
Hochhaus *et al.* (2007)[11,105]	Hochhaus *et al.* (2005)[133] Baccarani *et al.* (2006)[134] Hochhaus *et al.* (2006)[135] Hochhaus *et al.* (2006)[136] Guilhot *et al.* (2007)[137] Mueller *et al.* (2007)[138] Stone *et al.* (2007)[139] Baccarani *et al.* (2008)[140] Cervantes *et al.* (2008)[141] Goldman and Druker (2001)[142] Cortes *et al.* (2008)[143] Deininger *et al.* (2008)[144] Hochhaus *et al.* (2008)[145] Hochhaus *et al.* (2008)[105] Hochhaus *et al.* (2008)[146] Mauro *et al.* (2008)[147]	Case series (prospective)	✓			(*n* = 20) Australia, Belgium, Canada, Denmark, Finland, France, Germany, Ireland, Israel, Italy, Republic of Korea, the Netherlands, Peru, Singapore, Spain, Sweden, Switzerland, the UK and the USA	75	Patients aged at least 18 years who had ImR or Iml CML in CP. CML-CP was defined as < 15% blasts in PB and BM, < 20% basophils in PB, < 30% blasts plus promyelocytes in PB and BM, platelets at least 100×10^9/l unless thrombopenia was because of recent therapy and no extramedullary involvement other than in liver or spleen The Iml population included patients with progressive CML-CP on imatinib > 600 mg q.d. or those who had resistance to imatinib ≯ 600 mg q.d. and BCR–ABL mutations associated with high-level imatinib resistance ImR was defined as a lack of complete HR after 3 months of imatinib treatment, a lack of any CyR after 6 months of treatment, a lack of an MCyR (Ph+ cells > 35%) after 12 months of treatment, an increasing WBC count on at least two consecutive occasions, or a relapse after a CHR or MCyR. Iml was defined as at least grade 3 non-haematological toxicity or grade 4 haematological toxicity persisting for > 7 days, related to imatinib at any dose	Patients with prior AP or CML-BC; prior dasatinib therapy; imatinib therapy within 7 days of initiation; an ECOG performance status > 1; uncontrolled or significant cardiovascular disease; or a history of a significant bleeding disorder unrelated to CML	CA180013 START-C

continued

TABLE 8 Study design: observational studies *(continued)*

Study	Additional publications	Design	CP	AP	BC	Country	No. of centres	Inclusion criteria	Exclusion criteria	Notes
Kantarjian *et al.* (2007)[106]	Kantarjian *et al.* (2006)[148] le Coutre *et al.* (2006)[149] Cortes *et al.* (2007)[150] Hochhaus *et al.* (2007)[151] Hughes *et al.* (2007)[152] Cortes *et al.* (2007)[153] Martinelli *et al.* (2007)[154] Mueller *et al.* (2007)[155] Rosti *et al.* (2007)[156] Rosti *et al.* (2007)[157] Hochhaus *et al.* (2008)[158] Jabbour *et al.* (2008)[159] Kantarjian *et al.* (2008)[160] Kantarjian *et al.* (2008)[161] Lipton *et al.* (2008)[162] Radich *et al.* (2008)[163] Saglio *et al.* (2008)[164] Clark *et al.* (2009)[165]	Case series (prospective)	✓			Not stated ($n=15$); authors from the USA, Germany, Italy, the Netherlands, France, the UK and Spain	63	Patients with Ph+CML-CP aged at least 18 years who had ImR or Iml, adequate performance status (a WHO performance score of 2), and normal hepatic, renal and cardiac functions. Patients with had ImR had to have been treated with a dose of at least 600 mg q.d. for 3 months	Patients in BC and patients who had received treatment with imatinib for 7 days and with hydroxycarbamide for 2 days prior to nilotinib, were excluded. Potassium and magnesium levels had to be greater than or equal to the lower limit or normal or corrected to within normal range. Patients receiving concomitant medications known to prolong the QT interval or inhibit Cytochrome P_{450}3A4 were excluded if alternative treatments were not possible. ImR was defined as failure to achieve CHR after 3 months or loss of a HR or CyR at any time during treatment with imatinib. Entry criteria for Iml included patients with intolerant symptoms (but who also had never achieved a MCyR with imatinib) and haematological toxicity of grade 4 severity persisting for >7 days. Iml patients who had previously demonstrated sensitivity to imatinib, as evidenced by a prior MCyR, were excluded from participation in the study	NCT00109707 (same as 425, but hard to see connection)

Study	Additional publications	Design	CP	AP	BC	Country	No. of centres	Inclusion criteria	Exclusion criteria	Notes
le Coutre *et al.* (2008)[107]	le Coutre *et al.* (2007)[166] le Coutre *et al.* (2007)[167] le Coutre *et al.* (2007)[168] Saglio *et al.* (2007)[169] Alexander and le Coutre (2008)[170] Apperley *et al.* (2008)[171] Kantarjian *et al.* (2008)[172] le Coutre *et al.* (2008)[173] le Coutre *et al.* (2008)[174] le Coutre *et al.* (2008)[175]	Case series (prospective)		✓		Not stated ($n=10$); authors are from Germany, the USA, South Korea, the UK, Italy, Poland, France, China and Australia		Patients at least 18 years of age and with ImR or Iml CML in AP. Patients were also required to have a WHO performance status score of 2 or lower and normal serum electrolytes as well as normal hepatic, renal and pancreatic function ImR was defined by one of the following criteria during treatment with imatinib at least 600 mg q.d. (1) disease progression from CP to AP occurring during imatinib therapy; (2) disease progression defined as at least a 50% increase in peripheral WBC count, blast count, basophils or platelets during imatinib therapy for AP; or (3) lack of HR in the BM following a minimum of 4 weeks of imatinib therapy for AP Iml was defined as the discontinuation of imatinib therapy because of any of the following: grades 3 or 4 AEs that persisted in spite of optimal supportive care measures, or grade 2 AEs related to imatinib therapy in spite of optimal supportive care measures that persisted for at least 1 month or that recurred more than three times whether or not the dose was reduced or discontinued. The protocol definition of Iml required the lack of an MCyR with imatinib	Patients who had evidence of abnormal cardiac function or cardiac conduction, including individuals who had a myocardial infarction within the previous 12 months, individuals with left ventricular ejection fractions of 45% or less by echocardiogram or multiple-gated acquisition scan and individuals with a history of congenital long QT syndrome or a corrected QT interval of > 450 milliseconds on screening electrocardiogram using QT correction formula (QTcF)	NCT00384228
Kim *et al.* (2009)[80]		Case series (retrospective)	✓	✓	✓	Canada	One	CML patients treated with dasatinib at a single unit, March 2005 to October 2007 [seven with PB large granular lymphocyte (LGL) lymphocytosis]; not explicitly stated whether or not all such patients are included	No	The experience of one participant with Ph+ ALL is also reported in this publication, but has been excluded from consideration here

continued

TABLE 8 Study design: observational studies *(continued)*

Study	Additional publications	Design	CP	AP	BC	Country	No. of centres	Inclusion criteria	Exclusion criteria	Notes
Tojo *et al.* (2009)[108]		Case series (prospective)	✓	✓	✓	Japan	Multicentre, but number of centres not reported (authors are from 16 different centres, including one in Australia)	Japanese patients with ImR or Iml ImR defined according to phase: CP, failure to achieve CHR after 3 months/CyR after 6 months/MCyR after 12 months or loss of HR or CyR following ≥ 3 months of imatinib at ≥ 600 mg q.d. AP/BC, progression to AP/BC during imatinib (≥ 600 mg q.d.) in CP; ≥ 50% increase in WBC, blasts, basophils, or platelets during imatinib in AP/BC; lack of HR after ≥ 4 weeks imatinib in AP/BC In addition, participants receiving < 600 mg q.d. imatinib were eligible if named BCR–ABL mutations detected Iml defined as discontinuation of imatinib because of grade 3–4 AEs or grade 2 AEs lasting ≥ 1 month or recurring more than three times	Performance status score > 2; hepatic, renal or cardiac dysfunction Participants meeting criteria for Iml were excluded if they had achieved an MCyR to imatinib	The experience of seven participants with Ph+ ALL is also reported in this publication, but has been excluded from consideration here
Sakamaki *et al.* (2009)[109]		Case series (prospective)	✓	✓	✓	Japan	Appears to be multicentre (authors come from 22 separate centres), though not explicitly stated	Adult CML aged 20–75 years ImR defined according to phase. CP, in individuals treated with imatinib at ≥ 400 mg q.d.: WBC greater or equal to a twofold increase from nadir to > 20×10^9/l or increase from nadir to ≥ 50×10^9/l; failure to achieve CHR after 3 months/CyR after 6 months/MCyR after 12 months or loss of CHR or MCyR; named BCR–ABL mutations suggestive of ImR detected. AP: progression to BC; progression to AP after HR to imatinib (≥ 400 mg q.d.) in CP; lack of HR after ≥ 4 weeks imatinib (≥ 600 mg q.d.) in AP BC: progression to BC after HR to imatinib (≥ 600 mg q.d.); BC persisted after ≥ 4 weeks imatinib Iml defined according to phase. CP, discontinuation of imatinib because of grade 3–4 non-haematological AEs or grade 4 haematological AEs persisting ≥ 7 days. AP/BC, any toxicity leading to discontinuation of imatinib or dose kept < 400 mg q.d.	None reported	The experience of 13 participants with Ph+ ALL is also reported in this publication, but has been excluded from consideration here

ALL, acute lymphoblastic leukaemia; START-A, SRC/ABL Tyrosine kinase inhibition Activity: Research Trials of dasatinib – accelerated; START-B, SRC/ABL Tyrosine kinase inhibition Activity: Research Trials of dasatinib – MBC; START-C, SRC/ABL Tyrosine kinase inhibition Activity: Research Trials of dasatinib – CP; START-L, SRC/ABL Tyrosine kinase inhibition Activity: Research Trials of dasatinib – LBC.

Appendix 4: Indicators of quality of included studies

TABLE 12 Indicators of quality of included evidence: RCTs

	Kantarjian *et al.* (2007)[23]	Shah *et al.* (2008)[22]	Kantarjian *et al.* (2009)[61]
Is a power calculation provided?	No	No	No
Is the sample size adequate?	NR	NR	NR
Was ethical approval obtained?	Yes	Yes	Yes
Were the study eligibility criteria specified?	Yes	Yes	Yes
Were the eligibility criteria appropriate?	Yes	Yes	Yes
Were patients recruited prospectively?	Yes	Yes	Yes
Was assignment to the treatment groups really random?	Unknown	Unknown	Unknown
Were groups stratified?	No	Yes[a]	Yes[b]
Was the treatment allocation concealed?	No[c]	No[c]	No[c]
Are adequate baseline details presented?	Yes	Yes	Yes[d]
Are the participants representative of the population in question?	Yes	Yes	Yes
Are groups similar at baseline?	Partial[e]	Yes	Partial[f]
Are any differences in baseline adequately adjusted for in the analysis?	Yes[g]	NA	No
Are outcome assessors blind?	No	No	No
Was the care provider blinded?	No[c]	No[c]	No[c]
Are outcome measures relevant to research question?	Yes	Yes	Yes
Are data collection tools shown or known to be valid for the outcome of interest?	Yes	Yes	Yes
Is compliance with treatment adequate?	Unclear	Unclear	Unclear[h]
Are withdrawals/dropouts adequately described?	Yes	Yes	Yes
Are all patients accounted for?	Yes	Yes	Yes
Is the number randomised reported?	Yes	Yes	Yes
Are protocol violations specified?	No	No	Partial[i]
Are data analyses appropriate?	Yes	Partial[j]	Partial[j]
Is analysis conducted on an ITT basis?	Yes	Yes	Yes
Are missing data appropriately accounted for?	NR	NR	Yes
Were any subgroup analyses justified?	Yes	Yes	No
Are the conclusions supported by the results?	No[k]	Partial[l]	Partial[m]
Generalisability	Low[n]	Partial	High
Inter-centre variability	NR	NR	NR
Conflict of interest declared?	Yes[o]	Yes[p]	Yes[q]

NA, not applicable; NR not reported.

a Stratified by lmR or lml.
b By phase, type of disease and imatinib status (resistant or intolerant).
c Open-label.
d More information about previous imatinib regimen would have been useful.
e Well balanced with one exception: approximately twice as many patients in the dasatinib treatment arm (45%) had a BCR–ABL mutation as in the HDI group (22%).
f Reported that groups 'were comparable between the two treatment schedules'; however, significantly more participants in the 70 mg b.i.d. arm were in CHR at study entry.
g Separate analysis provided for participants with BCR–ABL mutation at baseline.
h One participant (140 mg q.d. arm) discontinued therapy owing to protocol violation.
I One reported; exact reasons not given.
j Little formal statistical testing of efficacy outcomes, just repeated narrative comment that they appear 'comparable'.
k Flaws in the study methodology impaired the internal validity of the study results.
l Open-label; lack of power calculation; dose escalation was allowed.
m Little formal testing of differences in efficacy outcomes, just a statement that 'the treatment groups were comparable' and a conclusion that results demonstrate that 'dasatinib 140 mg q.d. has similar efficacy to dasatinib 70 mg b.i.d.'.
n Open-label; relatively small sample size; lack of power calculation; very substantial treatment crossover; results from subgroup analyses were based on small sample size.
o Study supported by BMS; all authors received funding from BMS and, in one case, Novartis.
p Study supported by BMS; authorship includes individuals who are employed by, consult for, receive research funding from and/or own stock in BMS. Consultancy for and research funding from Novartis also declared.
q All lead authors have received funding from manufacturers including BMS and Novartis.

TABLE 13 Indicators of quality of included evidence: observational studies

	Kantarjian *et al.* (2006)[103]	Talpaz *et al.* (2006)[104]	Cortes *et al.* (2007)[38]	Cortes *et al.* (2007)[13]	Fabarius *et al.* (2007)[79]	Guilhot *et al.* (2007)[12]	Hochhaus *et al.* (2007)[11]	Kantarjian *et al.* (2007)[106]	le Coutre *et al.* (2008)[107]	Kim *et al.* (2009)[80]	Sakamaki *et al.* (2009)[109]	Tojo *et al.* (2009)[108]
Is the hypothesis/aim/objective of the study clearly described?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Were the case series collected at more than one centre?	Single centre	Multicentre	Single centre	Multicentre[a]	Single centre	Multicentre	Multicentre	Multicentre	Multicentre	Single centre	Multicentre[b]	Multicentre
Was the main outcome independently assessed?	No	No	Unclear	No	No	No	No	No	No	No	Unclear	Unclear
Are patient characteristics adequately described?	No[c]	No[d]	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No[e]	No[f]
How easy is it to assess generalisability of the results?	Low	Low	Low	Medium	Low	High	High	Medium	High	Low	Low[g]	Low[h]
Are inclusion and exclusion criteria clearly reported?	Yes[i]	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Were data collected prospectively?	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	No	Yes	Yes
Were patients recruited consecutively?	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	No	Unclear	No[j]
Did all the participants receive the same intervention?	Yes[k]	No[l]	Unclear[m]	Yes[k]	Yes[k]	Yes[k]	Yes[k]	Yes[k]	Yes[k]	Unclear	Unclear	Yes[k]
Is the use of any concurrent therapies adequately described?	Unclear	Unclear	Unclear	Yes[n]	Unclear	Unclear	Yes[n]	Unclear	Unclear	Unclear	Yes[o]	Unclear
Was an ITT analysis performed?	No	Yes	NA[p]	No[q]	Yes	Yes	No[q]	Yes[r]	Yes	NA[p]	No[q]	Yes
Are dropouts from the study adequately described?	Yes	Yes	NA[p]	Yes	Unclear	Yes	Yes	Yes	Yes	NA[p]	Unclear	Yes

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