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Multiple Technology Appraisal

Dasatinib, nilotinib and standard-dose imatinib for the first line treatment of chronic myeloid leukaemia (incl part-review of TA 70)

Evaluation Report

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

Dasatinib, nilotinib and standard-dose imatinib for the first line treatment of chronic myeloid leukaemia (incl part-review of TA 70)

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- Novartis Pharmaceuticals
- The Chronic Myeloid Leukaemia Support Group
- Royal College of Pathologists and the British Committee for Standards in Haematology

No comments were received from the Royal College of Nursing or the Department of Health

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- Professor Jane Apperley, clinical expert, nominated by Bristol Myers Squibb and Royal College of Physicians

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- Professor Jane Apperley, clinical expert, nominated by Bristol Myers Squibb and the Royal College of Physicians
- Professor Richard Clark, clinical expert, nominated by the Royal College of Pathologists
- Sandy Craine, patient expert, nominated by The Chronic Myeloid Leukaemia Support Group

- Richard Willoughby, patient expert, nominated by The Chronic Myeloid Leukaemia Support Group
- Diane Tomlinson, NHS Commissioning expert, nominated by NHS North Yorkshire and York

Any information supplied to NICE which has been marked as confidential has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia

This document is a summary of the evidence and views submitted by consultees and the Assessment Group. It highlights key issues for discussion at the first Appraisal Committee meeting. NICE prepares the overview before it receives consultees' comments on the assessment report. The sources of evidence used in the preparation of this document are given in appendix A.

1 Background

1.1 The condition

Chronic myeloid leukaemia (CML) is a cancer of myeloid blood cells characterised by overproduction of granulocytes in blood and bone marrow. More than 90% of people diagnosed with CML have an acquired chromosomal abnormality, the Philadelphia chromosome, which is caused by reciprocal translocations between chromosomes 9 and 22. These translocations result in a *BCR-ABL* fusion gene that encodes an active tyrosine kinase protein. This protein leads to uncontrolled cell proliferation. People with Philadelphia-chromosome-negative CML have different translocations that result in the same *BCR-ABL* fusion gene and its tyrosine kinase protein.

CML has three phases. The initial chronic phase lasts for several years. In this phase the symptoms are usually mild and non-specific and can include fatigue, weight loss, night sweats, anaemia, a feeling of 'fullness' and a tender lump on the left side of the abdomen caused by enlargement of the spleen. Approximately 90% of people with CML are diagnosed during the chronic phase. In approximately half of these cases CML is asymptomatic and is diagnosed as a result of a routine blood test. The disease then progresses to an accelerated phase that lasts for 6–24 months. During this phase disease progression is more rapid, and immature

blast cells in blood and bone marrow proliferate. Symptoms include bruising, bleeding and infections. The final phase is called the blast phase because a blast cell crisis occurs. There is a rapid increase in immature forms of cells, which replace normal cells in bone marrow and affect other organs. Symptoms include fever, sweating, pain and enlargement of organs. When this phase is reached, CML is often fatal within 3–6 months.

CML is diagnosed by finding characteristic cells in blood and bone marrow. The Philadelphia chromosome is identified using cytogenetic techniques involving the examination of chromosomes under a microscope, fluorescence in situ hybridisation and reverse transcriptase–polymerase chain reaction to detect products of the *BCR-ABL* gene. Various criteria, including the percentage of blast cells in blood or bone marrow, have been proposed to define the accelerated and blast crisis phases.

CML is a rare disease with an annual incidence of approximately 1 per 100,000 people. It accounts for about one in six cases of leukaemia in adults. It is estimated that about 560 people are diagnosed with CML in the UK each year. Slightly more men than women are diagnosed (annual age-standardised rate 1.2 per 100,000 for men and 0.7 per 100,000 for women). The median age at diagnosis is 60 years.

1.2 Current management

A potential cure for CML is an allogeneic stem cell transplant, also known as bone marrow transplantation, but patient characteristics and the lack of availability of a matched donor mean this is not possible for many people. However, the progression of CML can be slowed by imatinib, a first-generation tyrosine kinase inhibitor (TKI). Imatinib produces high rates of remission in the chronic phase but is less effective when the disease has progressed. Imatinib is associated with improved survival, with the latest results of the follow-up of the IRIS (International Randomised Study of Interferon versus STI571) trial (8-year follow-up) showing overall survival of 85%. After the introduction of imatinib into routine clinical practice, 5-year relative survival increased from 27.1% in 1990–92 to 48.7% in 2002–04, for all age groups combined ($p < 0.0001$ for the trend). ‘Guidance on the

use of imatinib for chronic myeloid leukaemia' (NICE technology appraisal guidance 70) recommends standard-dose imatinib (that is 400 mg per day) as first-line treatment for people with Philadelphia-chromosome-positive CML in the chronic phase. It also recommends imatinib (600 mg per day) as an option for people who initially present in the accelerated phase or with blast crisis, and for people who present in the chronic phase and then progress to the accelerated phase or blast crisis if they have not received imatinib previously. NICE has recently issued draft guidance in a Final Appraisal Determination (August 2011) for 'Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant CML (part review of NICE technology appraisal guidance 70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance'. This draft guidance recommends nilotinib for the treatment of chronic or accelerated phase Philadelphia-chromosome-positive CML in adults whose CML is resistant to treatment with standard-dose imatinib or who have imatinib intolerance, and if the manufacturer makes nilotinib available with the discount agreed as part of the patient access scheme. The Final Appraisal Determination does not recommend dasatinib or high-dose imatinib for these indications. It does not constitute final guidance to the NHS.

Response to treatment is assessed haematologically by examining the peripheral blood and cytogenetically by searching for the Philadelphia chromosome in bone marrow aspirates. A molecular response can be assessed using polymerase chain reaction techniques.

A complete haematological response has been defined as all of the following being maintained for at least 4 weeks: white blood cell count no higher than the upper limit of normal, absolute neutrophil count at least 1 x 10^9/litre, platelet count below 450 x 10^9/litre and no higher than the upper limit of normal, no blast cells or promyelocytes in peripheral blood, less than 2% basophils in peripheral blood, and no extramedullary involvement.

A complete cytogenetic response is defined as absence of the Philadelphia-positive chromosome in at least 20 cells in metaphase in a bone marrow aspirate. A partial cytogenetic response is defined as 35% or fewer Philadelphia-positive

chromosomes in metaphase in a bone marrow aspirate. If a person has experienced either of these responses, they are defined as having had a major cytogenetic response.

2 The technologies

Table 1 Summary description of technologies

Non-proprietary name	Dasatinib	Nilotinib	Imatinib
Proprietary name	Sprycel	Tasigna	Glivec
Manufacturer	Bristol-Myers Squibb	Novartis Pharmaceuticals	Novartis Pharmaceuticals
Dose	Chronic phase: 100 mg once daily Accelerated phase and blast crisis: 140 mg once daily	Chronic phase: 300 mg twice daily Patients with chronic or accelerated phase CML with resistance or intolerance to prior therapy: 400 mg twice daily	Chronic phase: standard dose of 400 mg once daily escalated to a maximum of 800 mg per day (400 mg twice daily) Accelerated phase and blast crisis: standard dose of 600 mg once daily escalated to a high dose of 800 mg per day (400 mg twice daily)
Acquisition cost (BNF edition 62)	Packs of 60 tablets: 20 mg – £1252.48 50 mg – £2504.96 70 mg – £2504.96 80 mg – £2504.96 Pack of 30 tablets: 100 mg – £2504.96 140 mg – £2504.96	Pack of 112 capsules: 150 mg – £2432.85 200 mg – £2432.85	Pack of 60 tablets: 100 mg – £862.19 Pack of 30 tablets: 400 mg – £1724.39

Dasatinib

Dasatinib is a second-generation TKI. It is an orally active inhibitor of *SRC* and the Src-family kinases. The Src family of tyrosine kinases is involved in cell growth, differentiation, migration and survival, and many are involved in oncogenesis,

tumour metastasis and angiogenesis. Dasatinib has been shown to directly inhibit 21 out of 22 mutant forms of *BCR-ABL* resistant to imatinib.

Dasatinib has a UK marketing authorisation for the treatment of adults with newly diagnosed Philadelphia chromosome-positive CML in the chronic phase. The most common reported side effects with dasatinib are headache, pleural effusion, shortness of breath, cough, diarrhoea, nausea, vomiting, abdominal pain, skin rash, musculoskeletal pain, infections, haemorrhage, superficial oedema, fatigue, fever, neutropenia, thrombocytopenia and anaemia.

The acquisition cost of dasatinib at a daily dose of 100 mg is £83.50 per day (excluding VAT; 'British national formulary' [BNF] edition 62). The average cost of dasatinib treatment in the chronic phase is £30,477 per year, based on a daily dose of 100 mg. Costs may vary in different settings because of negotiated procurement discounts.

Nilotinib

Nilotinib is a second-generation TKI. It is an orally active phenylaminopyrimidine derivative of imatinib. Nilotinib does not inhibit the Src-family of tyrosine kinases. Studies performed in vitro suggest that nilotinib inhibits 32 of 33 mutant *BCR-ABL* forms resistant to imatinib at physiologically relevant concentrations.

Nilotinib has a UK marketing authorisation for the treatment of adults with newly diagnosed Philadelphia chromosome positive CML in the chronic phase. The most common side effects with nilotinib are thrombocytopenia, neutropenia, anaemia, headache, nausea, constipation, diarrhoea, rash, pruritus, fatigue and increased blood levels of lipase and bilirubin. The US Food and Drug Administration (FDA) has stipulated that nilotinib must carry a 'black box' warning for possible heart problems due to QTc prolongation, which may lead to an irregular heart beat and possible sudden death. Nilotinib is also contraindicated in people with hypokalaemia, hypomagnesaemia or long QT syndrome.

The acquisition cost of nilotinib at a twice daily dose of 300 mg (150 mg tablets) is £86.89 per day (excluding VAT; BNF edition 62). The average cost of nilotinib

treatment in the chronic phase is £31,715 per year, based on a twice daily dose of 300 mg. Costs may vary in different settings because of negotiated procurement discounts.

Imatinib

Imatinib is a first-generation TKI. It is an orally active inhibitor designed to competitively inhibit *BCR-ABL* tyrosine kinase activity. By blocking specific signals in cells expressing the *BCR-ABL* protein, imatinib reduces the uncontrolled proliferation of white blood cells that is a characteristic feature of the disease.

Imatinib has a UK marketing authorisation for the treatment of adults and paediatric patients with newly diagnosed Philadelphia chromosome (*BCR-ABL*) positive CML for whom bone marrow transplantation is not considered as the first-line of treatment. The most common side effects with imatinib are nausea, vomiting, oedema (fluid retention), muscle cramps, skin rash, diarrhoea, abdominal pain, headache and fatigue.

The acquisition cost of imatinib at a daily dose of 400 mg is £57.48 per day (excluding VAT; BNF edition 62). The average cost of imatinib treatment in the chronic phase is £20,980 per year, based on a daily dose of 400 mg. Costs may vary in different settings because of negotiated procurement discounts.

3 The evidence

3.1 Clinical effectiveness

The Peninsula Technology Assessment Group (PenTAG) conducted a systematic review of evidence on the clinical efficacy of dasatinib, nilotinib and standard-dose imatinib compared with each other and with other treatment options in treatment-naive people with newly diagnosed, Philadelphia chromosome positive CML in the chronic phase.

Two randomised controlled trials were identified that met the inclusion criteria of the PenTAG systematic review: one comparing dasatinib and imatinib (DASISION ['Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid

leukemia'] trial; Kantarjian et al. 2010) and one comparing nilotinib and imatinib (ENESTnd ['Evaluating nilotinib efficacy and safety in clinical trials of newly diagnosed'] trial; Saglio et al. 2010). The DASISION study provided an additional seven conference abstracts and the ENESTnd study provided an additional six conference abstracts. One conference abstract of a systematic review assessing first-line treatments for CML and one journal article were identified and provided indirect comparisons of dasatinib and nilotinib (Mealing et al. [2010] and Signorovitch et al. [2011]). Additional data were also retrieved from the manufacturer submissions for dasatinib and nilotinib.

3.1.1 Study characteristics

The DASISION trial

The DASISION trial was a multi-national open-label randomised controlled trial to assess the efficacy and safety of dasatinib (100 mg once daily, n = 259) compared with imatinib (400 mg once daily, n = 260) in newly diagnosed (3 months or less) people with chronic phase CML. The primary outcome was complete cytogenetic response within 12 months. Secondary outcomes included major molecular response at any time, time to confirmed complete cytogenetic response (defined as a complete cytogenetic response on two consecutive assessments at least 28 days apart) and major molecular response, rates of complete cytogenetic response and major molecular response by 12 months, progression-free survival and overall survival. Adverse events were assessed continuously for all study participants. All study participants had a minimum follow-up of 12 months, with a median duration of 14 months treatment for dasatinib and 14.3 months for imatinib.

The ENESTnd trial

The ENESTnd trial was a multi-centre open-label randomised controlled trial to assess the efficacy and safety of nilotinib (300 mg twice daily, n = 282 or 400 mg twice daily, n = 281) compared with imatinib (400 mg once daily, n = 283) in newly diagnosed (6 months or less) people with chronic phase CML. Only nilotinib 300 mg twice daily is licensed for the first-line treatment of CML in the chronic phase. The primary outcome was major molecular response at 12 months. Secondary outcomes included complete cytogenetic response by 12 months, time

to and duration of major molecular response, progression to advanced phase or blast crisis phase CML, and event-free and progression-free survival. Adverse events of all study participants who received at least one dose of a study drug were monitored. All study participants had a minimum follow-up of 12 months, with a median duration of 14 months treatment.

3.1.2 Baseline population characteristics

Participants in the DASISION and ENESTnd trials were of a similar age (46–49 years) and gender distribution (56–63% male).However the median age was younger than that of the general population, in which the median age at diagnosis is 58 years (including people diagnosed in the accelerated phase or blast crisis phase). Study participants were stratified to prognostic risk groups (low, intermediate or high risk) by the Hasford risk score for the DASISION trial and the Sokal risk score for the ENESTnd trial. Risk distribution was fairly similar between both trials with ENESTnd reporting a slightly lower percentage of people with intermediate risk and a slightly higher percentage with high risk, compared with DASISION. Both trials included people who had an Eastern Cooperative Oncology Group (ECOG) performance status score of between 0 and 2. The exclusion criteria were slightly different for the two trials and were based on the known adverse events of the drugs (for example, pleural effusion for dasatinib and QT interval prolongation for nilotinib). The two trials used different measures of response as primary outcomes (complete cytogenetic response for DASISION and major molecular response for ENESTnd), although both trials reported the other measure of response as a secondary outcome.

3.1.3 Assessment of study quality

The Assessment Group, PenTAG, considered that both the DASISION and ENESTnd trials were good quality international, multicentre, open-label phase III randomised controlled trials. However, there was no discussion of how people were randomised in either trial. The trials were reported as open-label so treatment allocation concealment, and outcome assessors or carer blinding was not possible. The Assessment Group commented that these factors have been demonstrated to potentially bias results of randomised controlled trials, although these are unlikely

to have an impact as the outcomes of the trials were objective. Baseline patient characteristics were similar across treatment groups and were well reported in both trials. According to PenTAG's quality assessment of both trials, the statistical analysis and handling of data were well reported. However, it was also noted that the large contribution from both manufacturers to the study and manuscript development would represent a strong conflict of interest. Finally, the study populations were not completely representative of a UK CML population, as a result of the lower median age in both trials, the high proportion of Asian people in the ENESTnd trial and the unknown ethnicity of participants in the DASISION trial.

3.1.4 Treatment status

The DASISION trial reported that, at 12 months follow-up, 85% and 81% of people continued to receive treatment with dasatinib and imatinib respectively. At 24 months follow-up, 77% and 75% of people continued to receive treatment with dasatinib and imatinib respectively. The ENESTnd trial reported that at 12 months follow-up 84% and 79% of people continued to receive treatment with nilotinib and imatinib respectively. At 24 months follow-up, 75% and 68% of people continued to receive treatment with nilotinib and imatinib respectively. The primary causes of discontinuation, which were similar across treatment groups in both trials, were drug-related adverse events, disease progression and suboptimal response or treatment failure.

3.1.5 Assessment of clinical effectiveness

Complete cytogenetic response

Both the DASISION and ENESTnd trials reported complete cytogenetic response at 12, 18 and 24 months follow-up. DASISION also reported confirmed complete cytogenetic response (based on two consecutive assessments 28 days apart) at 12, 18 and 24 months follow-up. PenTAG calculated the relative risk of complete cytogenetic response for dasatinib and nilotinib compared with imatinib. The results are presented in Table 2. Both trials also reported complete cytogenetic response by risk group categorisation at 12 months, and the DASISION trial also reported complete cytogenetic response by risk group at 18 months follow-up.

The DASISION trial reported that statistically significantly more people receiving dasatinib had a complete cytogenetic response compared with people taking imatinib at 12 months, but not at 18 or 24 months follow-up. A statistically significantly higher proportion of people receiving dasatinib had a confirmed complete cytogenetic response compared with people receiving imatinib at 12 months and 18 months, but not at 24 months follow-up. At 12 and 18 months follow-up, complete cytogenetic response rates were higher for people taking dasatinib across all risk categories compared with people taking imatinib.

The ENESTnd trial reported that statistically significantly more people receiving nilotinib had a complete cytogenetic response compared with people taking imatinib at 12, 18 and 24 months follow-up. For people taking nilotinib, complete cytogenetic response rates were higher across all risk categories compared with people taking imatinib at 12 months.

Table 2 Complete cytogenetic response

Study	DASISION			ENESTnd		
Intervention	Dasatinib 100 mg once daily	Imatinib 400 mg once daily	RR (95% CI)	Nilotinib 300 mg twice daily	Imatinib 400 mg once daily	RR (95% CI)
CCyR rates 12 months (%)	216/259 (83)	186/260 (72)	1.17 (1.06 to 1.28)	226/282 (80)	184/283 (65)	1.20 (1.08 to 1.34)
CCyR rates 18 months (%)	218/259 (84)	203/260 (78)	1.08 (0.98 to 1.17)	240/282 (85)	209/283 (74)	1.11 (1.01 to 1.21)
CCyR rates 24 months (%)	223/259 (86)	213/260 (82)	1.05 (0.97 to 1.13)	245/282 (87)	218/283 (77)	1.10 (1.01 to 1.19)
CCyR rates 12 months confirmed (%)	199/259 (77)	182/260 (66)	1.16 (1.04 to 1.30)			
CCyR rates 18 months confirmed (%)	202/259 (78)	182/260 (70)	1.11 (1.00 to 1.24)			
CCyR rates 24 months confirmed (%)	207/259 (80)	192/260 (74)	1.08 (0.98 to 1.19)			
CCyR, complete cytogenetic response; CI, confidence interval; RR, relative risk.						

Major molecular response

The DASISION and ENESTnd trials reported major molecular response rates at 12 and 18 months follow-up and 12 and 24 months follow-up, respectively. Both trials also reported major molecular response at any time (cumulative major molecular response rates, which included patients who may have relapsed or been lost to follow-up) up to 12, 18 and 24 months. PenTAG calculated the relative risk of major molecular response for dasatinib and nilotinib compared with imatinib. The results are presented in

Table 3. Both trials also reported major molecular response by risk group categorisation at 12, 18 and 24 months follow-up.

The DASISION trial reported that statistically significantly more people receiving dasatinib had a major molecular response compared with people taking imatinib at 12 and 18 months follow-up. A statistically significantly higher proportion of people taking dasatinib also had a major molecular response at any time compared with people taking imatinib at 12, 18 and 24 months follow-up. At 12, 18 and 24 months follow-up, major molecular response rates were higher for people taking dasatinib across all Hasford risk categories compared with people taking imatinib.

The ENESTnd trial reported that statistically significantly more people receiving nilotinib had a major molecular response compared with people taking imatinib at 12 and 24 months follow-up. A statistically significantly higher proportion of people taking nilotinib also had a major molecular response at any time compared with people taking imatinib at 12, 18 and 24 months follow-up. At 12, 18 and 24 months follow-up, major molecular response rates were higher for people taking nilotinib across all Sokal risk categories compared with people taking imatinib.

Table 3 Major molecular response

Study	DASISION			ENESTnd		
Intervention	Dasatinib 100 mg once daily	Imatinib 400 mg once daily	RR (95% CI)	Nilotinib 300 mg twice daily	Imatinib 400 mg once daily	RR (95% CI)
MMR rates 12 months (%)	119/259 (46)	73/260 (28)	1.63 (1.29 to 2.09)	125/282 (44)	62/283 (22)	2.02 (1.56 to 2.65)
MMR rates 18 months (%)	145/259 (56)	96/260 (37)	1.52 (1.25 to 1.85)			
MMR rates 24 months (%)				175/282 (62)	105/283 (37)	1.67 (1.40 to 2.00)
MMR at any time (12 months) (%)	135/259 (52)	88/260 (34)	1.54 (1.25 to 1.91)	154/282 (57)	76/283 (30)	2.03 (1.63 to 2.55)
MMR at any time (18 months) (%)	148/259 (57)	107/260 (41)	1.39 (1.15 to 1.67)	186/282 (66)	113/283 (40)	1.65 (1.40 to 1.95)
MMR at any time (24 months) (%)	166/259 (64)	120/260 (46)	1.39 (1.18 to 1.64)	201/282 (71)	124/283 (44)	1.67 (1.40 to 1.89)
CI, confidence interval; MMR, major molecular response; RR, relative risk.						

Complete molecular response

The DASISION trial reported that at 18 months follow-up, complete molecular response rates were statistically significantly higher for people receiving dasatinib compared with people taking imatinib (13% versus 7%, p = 0.04) and this difference was maintained at 24 months follow-up (17% versus 8%, p = 0.002). The ENESTnd trial reported that at 12 months follow-up, complete molecular response rates were statistically significantly higher for people receiving nilotinib compared with people taking imatinib (13% versus 4%, p < 0.001) and this difference was maintained at 24 months follow-up (26% versus 10%, p < 0.001).

Time to complete cytogenetic response and major molecular response

The DASISION trial reported that at 12, 18 and 24 months follow-up, time to a complete cytogenetic response and a confirmed complete cytogenetic response was statistically significantly shorter for people receiving dasatinib compared with people taking imatinib (both hazard ratios [HRs] 1.5, p < 0.0001). The median time

to a confirmed complete cytogenetic response was 3.1 and 5.6 months for dasatinib and imatinib respectively. The time to a major molecular response was also statistically significantly shorter for people receiving dasatinib (HR 2.0, $p < 0.0001$) compared with people taking imatinib at 12 months follow-up. The median time to major molecular response was 6.3 and 9.2 months for dasatinib and imatinib respectively. These statistically significant differences were maintained at 18 and 24 months follow-up.

The ENESTnd trial reported that the median time to major molecular response was statistically significantly shorter for people receiving nilotinib (8.3 versus 11.1 months, $p < 0.0001$) compared with people receiving imatinib. It was also reported that, of those people who had a major molecular response at 12 months follow-up, 93% of people taking nilotinib and 92% of people taking imatinib maintained this response at 24 months.

Progression to accelerated phase or blast crisis

The DASISION trial reported that at 12 months follow-up, five people taking dasatinib and nine people taking imatinib had progressed to advanced phase or blast crisis. At 24 months follow-up, 9 people taking dasatinib and 15 people taking imatinib had progressed to advanced phase or blast crisis. The ENESTnd trial reported that the rate of progression to advanced phase or blast crisis was statistically significantly lower for people taking nilotinib compared with people taking imatinib at 12 months (2 versus 11 people, $p = 0.01$) and 24 months follow-up (2 versus 17 people, $p = 0.0003$).

Survival

The DASISION trial reported that rates of progression-free survival and overall survival were similar for dasatinib and imatinib at 12 months (progression-free survival 96% versus 97%; overall survival 97% versus 99%), 18 months (progression-free survival 95% versus 94%; overall survival 96% versus 98%) and 24 months follow-up (progression-free survival 94% versus 92%; overall survival 95% versus 95%). The ENESTnd trial reported no significant differences in progression-free survival between nilotinib and imatinib at 24 months follow-up (98% versus 95%, $p = 0.07$). No significant differences in overall survival were

reported between nilotinib and imatinib at 18 months (99% versus 97%, p = 0.28) or 24 months follow-up (97% versus 96%, p = 0.64) respectively.

Adverse events

The DASISION trial reported that discontinuation rates owing to adverse events at 12 months follow-up were 5% and 4% for people taking dasatinib and imatinib respectively. Haematological event rates were similar between the two treatment arms at 12, 18 and 24 months follow-up except for grade 3 or 4 thrombocytopenia events, for which nearly twice as many events were experienced by people taking dasatinib (19–20%) compared with people taking imatinib (10–11%). People taking imatinib experienced an increased frequency of fluid retention and superficial oedema across all grades at 12, 18 and 24 months follow-up. People taking dasatinib experienced higher rates of pleural effusion (10–14%) compared with people taking imatinib (0%) at 12, 18 and 24 months follow-up. Other non-haematological events, including rash, vomiting, nausea and myalgia, were lower at each follow-up time-point for people taking dasatinib compared with imatinib.

The ENESTnd trial reported that discontinuation rates owing to adverse events were 5% and 7% at 12 months follow-up and 6% and 9% at 24 months follow-up for nilotinib and imatinib respectively. Haematological event rates across all grades were lower for people taking nilotinib compared with people taking imatinib at 12 months follow-up. Grade 3 or 4 neutropenia events were approximately double for people taking imatinib (20%) compared with nilotinib (12%). Non-haematological events, including nausea, diarrhoea, vomiting and muscle spasm events, were approximately three times higher for people taking imatinib compared with people taking nilotinib across all grades. Oedema events across all grades, including eyelid and periorbital oedema, were also higher for imatinib compared with nilotinib. Conversely, rash, headache, pruritus and alopecia events were up to three times higher for nilotinib compared with imatinib across all grades. Adverse events across all grades at 24 months follow-up were similar to those reported at 12 months follow-up.

Nilotinib carries a FDA ‘block box’ warning for possible heart problems caused by QT interval prolongation, where prolonged cardiac ventricular repolarisation can

result in ventricular tachycardia and death. No people in the ENESTnd trial experienced an increased QT interval of more than 500 milliseconds (at which complexities may arise) at 12, 18 or 24 months follow-up. Finally, the number of hospitalisations, hospital days and length of stay were lower for nilotinib compared with imatinib at 12 months follow-up.

Health-related quality of life

Health-related quality of life was not reported in the DASISION or ENESTnd trials.

Indirect comparison of dasatinib and nilotinib

No trials were identified by PenTAG that directly compared dasatinib and nilotinib. Therefore, an indirect comparison of nilotinib with dasatinib was carried out using results from the DASISION and ENESTnd trials. The primary outcomes reported by PenTAG were major molecular response and complete cytogenetic response at 12 months follow-up. As part of its submission, Bristol-Myers Squibb commissioned a mixed treatment comparison (conducted by Oxford Outcomes, 2010) to indirectly compare nilotinib with dasatinib for major molecular response and complete cytogenetic response at 12 months follow-up. An update to this review, incorporating additional 18-month follow-up complete cytogenetic response data for dasatinib compared with imatinib, was also conducted (Oxford Outcomes, 2011). These mixed treatment comparisons also included randomised controlled trials of historical interventions such as hydroxyurea and interferon-based treatments. As the results presented in

Table 4 show, no statistically significant differences were identified in any of the analyses between dasatinib and nilotinib for major molecular response, complete cytogenetic response or complete molecular response at 12 and 24 months follow-up.

Table 4 Indirect comparison of nilotinib (300 mg twice daily) with dasatinib (100 mg daily)

Outcome	PenTAG review		Bristol-Myers Squibb review (2010)		Bristol-Myers Squibb review (2011)	
	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
MMR at 12 months	1.28	0.77 to 2.16	1.33	0.77 to 2.15	1.35	0.84 to 2.20
Best MMR at 12 months	1.53	0.93 to 2.51				
CCyR at 12 months	1.09	0.61 to 1.92	1.13	0.61 to 1.93	1.05	0.45 to 2.43
Confirmed CCyR at 12 months	1.28	0.74 to 2.20				
CCyR at 18 months					1.30	0.73 to 2.29
CCyR at 24 months	1.44	0.76 to 2.76				
Confirmed CCyR at 24 months	1.40	0.77 to 2.56				
Complete molecular response at 24 months	1.37	0.66 to 2.82				
CCyR, complete cytogenetic response; CI, confidence interval; MMR, major molecular response.						

Another study identified by PenTAG conducted a matching-adjusted indirect comparison of nilotinib and dasatinib from the DASISION and ENESTnd trials (Signorovitch et al. 2011). In this study, individual patient data for people receiving nilotinib 300 mg were weighted to match the baseline characteristics for people taking dasatinib including, age, gender, ECOG performance status score and haematology lab values. After matching, people taking nilotinib had statistically significantly higher major molecular response rates (56.8% versus 45.9%, p = 0.001) and overall survival (99.5% versus 97.3%, p = 0.046) compared with people taking dasatinib.

Assessment of evidence to support using complete cytogenetic response and major molecular response as surrogate outcomes

Because of short-term follow-up, the DASISION and ENESTnd trials both provided surrogate outcomes (complete cytogenetic response and major molecular response) as indicators of potential longer-term patient benefit. Therefore, PenTAG conducted a systematic review to assess the evidence base for using cytogenetic response and molecular response as surrogate measures for survival and health-related quality of life in people receiving TKI treatment.

The systematic review identified 11 publications, all related to imatinib, which reported both potential surrogate outcomes (complete cytogenetic response and major molecular response) and final patient-relevant outcomes (progression-free survival and overall survival). Of these, five were reports of two cohort studies, one was a report of a single randomised controlled trial and five were reports of the IRIS randomised controlled trial.

For each study, levels of overall survival and progression-free survival were extracted by response stratum at each year after randomisation up to the latest follow-up point reported. In most of the studies, overall survival and progression-free survival were reported in Kaplan-Meier survival curves using landmark analysis to evaluate differences in the final patient-relevant outcomes between people whose disease did and didn't respond. PenTAG selected 12 months after the start of imatinib treatment as the landmark for its analysis, because the DASISION and ENESTnd trials considered the rate of major molecular response

and confirmed complete cytogenetic response at 12 months as primary endpoints, respectively. A weighted average of both the overall survival and progression-free survival at different yearly intervals were estimated for people whose disease did and didn't respond according to the initial number of people in the two groups.

Survival by level of cytogenetic response

The pooled weighted average of overall survival and progression-free survival (and their 95% CIs) at 12 month intervals following initiation of imatinib treatment for chronic phase CML by level of cytogenetic response are presented in

Table 5.

Table 5. Pooled weighted average of overall survival and progression-free survival (95% confidence interval) by level of cytogenetic response

Time	OS % (95% CI)		PFS % (95% CI)	
	CCyR	No CCyR	CCyR	No CCyR
12 months	100 (99.3 to 100)	100 (98.1 to 100)	100 (99.3 to 100)	98.9 (94 to 98.9)
24 months	98.1 (96.5 to 98.9)	94.0 (89.7 to 96.5)	98.8 (97.4 to99.4)	94.3 (87.7 to 97.6)
36 months	97.5 (95.9 to 98.5)	89.0 (83.8 to 92.6)	97.6 (95.9 to 98.5)	85.5 (77.1 to 91.4)
48 months	98.0 (95.3 to 99.3)		97.6 (95.9 to 98.5)	85.5 (77.1 to 91.4)
60 months	97.4 (94.9 to 98.6)	74.1 (62.4 to 82.4)	96.8 (95 to 97.9)	75.2 (64.9 to 82.5)
72 months			95.5 (93.1 to 97.0)	80 (56.7 to 91.5)
CCyR, complete cytogenetic response; CI, confidence interval; OS, overall survival; PFS, progression-free survival.				

Survival by level of molecular response

The pooled weighted average overall survival and progression-free survival (and their 95% CIs) at 12 month intervals after the start of imatinib treatment for chronic phase CML by level of molecular response are presented in

Table 6.

Table 6 Pooled weighted average of overall survival and progression-free survival (95% confidence interval) by level of molecular response

Time	OS % (95% CI)		PFS % (95% CI)	
	MMR	No MMR	MMR	No MMR
12 months	100 (99.1 to100)	100 (99.4 to 100)	100 (98.5 to 100)	99.6 (97.8 to 99.9)
24 months	100 (99.1 to100)	96.7 (95.0 to 97.9)	99.2 (97.1 to 99.8)	94.0 (87.9 to 97.3)
36 months	99.2 (97.9 to 99.8)	95.7 (93.8 to 97.1)	98.6 (97.3 to 99.3)	94.3 (92.1 to 95.8)
48 months	96.7 (94.4 to 97.9)	93.3 (91.0 to 95.0)	96.6 (93.7 to 98.3)	91.0 (84.4 to 95.4)
60 months	96.6 (94.9 to 97.9)	91.2 (88.6 to 93.2)	95.8 (92.7 to 97.8)	89.0 (82.0 to 93.9)
72 months	92.5 (87.6 to 95.9)	90.0 (87.0 to 92.3)	99.0 (95.3 to 99.6)	
84 months	96.0 (93.2 to 97.5)	89.2 (83.5 to 93.4)	99.0 (95.3 to 99.6)	89.9 (84.2 to 93.9)
CI, confidence interval; MMR, major molecular response; OS, overall survival; PFS, progression-free survival.				

Overall surrogate outcome conclusions

PenTAG highlighted that the systematic review identified evidence of an association between complete cytogenetic response and major molecular response at 12 months and survival but that this was based on the imatinib treatment arms of three observational cohort studies and two randomised controlled trials. The three observational cohort studies were considered to be level two evidence, rather than the best quality evidence of a comparison of surrogate response according to randomised treatment allocation (level one evidence). Evidence of any association between surrogate outcomes (complete cytogenetic response and major molecular response) and longer-term patient-relevant outcomes was not available for dasatinib and nilotinib.

However, the Assessment Group reported that this evidence did consistently show that people who experienced either a complete cytogenetic response or major molecular response after 12 months of imatinib treatment experienced better long-term (up to 7 years) overall survival and progression-free survival than people

whose disease did not respond at 12 months follow-up. The Assessment Group highlighted a number of limitations with its review, which were a consequence of the paucity and quality of data available (that is, aggregate data instead of individual patient data). Overall, the Assessment Group concluded that, in the absence of evidence of the adequacy of these surrogates for dasatinib and nilotinib as first-line treatments for chronic phase CML, and assuming a TKI's class-specific relationship between the surrogate outcomes and the patient-relevant outcomes, these results can be potentially applied to other drugs in the same class.

3.2 Cost effectiveness

The Assessment Group conducted a systematic review of the cost-effectiveness evidence of dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of people with CML. The review did not identify any published full cost-effectiveness analyses meeting the inclusion criteria. Five conference abstracts were identified, of which three evaluated resource use and costs associated with using TKIs for the management of CML; one examined long-term survival outcomes after treatment with dasatinib, imatinib and nilotinib; and one modelled the lifetime costs and quality-adjusted life years (QALYs) of people with chronic phase CML starting treatment with nilotinib or imatinib. The Assessment Group noted that there was insufficient detail in the abstracts or reports to undertake a detailed critical appraisal of the methods used and to establish whether they related to first or second-line treatments.

3.2.1 Manufacturer submissions

Bristol-Myers Squibb – dasatinib

Bristol-Myers Squibb developed a 'time in state' (area under the curve) model to assess the cost effectiveness of dasatinib (100 mg daily), nilotinib (600 mg daily) and standard-dose imatinib (400 mg daily) as first-line treatments for people with CML. The analysis was conducted from a UK NHS perspective using a 40-year time horizon. It was based on a starting age of 46 years (the average age of people in the DASISION trial) until 86 years. Costs and benefits were discounted at an annual rate of 3.5%. The health states modelled as monthly cycles represented the

chronic phase, advanced phases (accelerated or blast phase) and death. In the chronic phase, people may also have been receiving first or second-line TKI treatment, or third-line treatment, which consisted of stem cell transplantation, chemotherapy, or a combination of chemotherapy and TKI treatment (dasatinib or imatinib). In the advanced phase people may also have been receiving third-line treatment or in-hospital palliative care. For people receiving first-line dasatinib, second-line treatment was nilotinib (800 mg daily). For people receiving first-line nilotinib (600 mg daily), second-line treatment was dasatinib. For people receiving first-line standard-dose imatinib, second-line treatment was split on a 50:50 basis between dasatinib and nilotinib (800 mg daily).

The impact of TKI treatments on CML progression and survival was estimated using a combination of data on the effect of TKIs on cytogenetic response and data on the impact of cytogenetic response on progression-free survival and overall survival. Treatment effect was defined as the probability that each TKI achieves a complete cytogenetic response, partial cytogenetic response and less than partial response (calculated as the residual of complete and partial cytogenetic response) at 12 months. Clinical effectiveness data for cytogenetic response to first-line TKI treatment were taken directly from the DASISION and ENESTnd randomised controlled trials and an unpublished systematic review and mixed treatment comparison commissioned by Bristol-Myers Squibb (see

Table 4, section 3.1.5). It was assumed that the effectiveness of second-line TKI treatment was the same as second-line treatment after imatinib because data for second-line treatment after dasatinib and nilotinib were not available. Data for second-line treatment were based on the PenTAG health technology assessment published in 2011 on dasatinib and nilotinib for imatinib-resistant or intolerant CML.

Progression-free survival and overall survival were estimated from cytogenetic response after first-line TKI treatment and not second-line treatment. Data for overall survival and progression-free survival according to different levels of cytogenetic response were taken from two published sources: the imatinib treatment arm from the IRIS study was used to estimate overall survival for complete and partial cytogenetic response for all three TKI treatments; data for overall survival for a less than partial response for dasatinib and nilotinib were taken from a UK Medical Research Council-funded randomised controlled trial comparing interferon with cytotoxic chemotherapy for the treatment of CML in the chronic phase; and progression-free survival for all levels of cytogenetic response were also taken from the IRIS study. The IRIS study covered a period of 6 years during which the majority of people receiving first-line imatinib remained alive and were on first-line treatment at the end of the trial. Therefore, to extrapolate beyond the trial data, a Weibull parametric survival function was used to predict overall survival and progression-free survival.

Discontinuation and switch rates for first-line dasatinib and nilotinib were based on 12-month treatment failure rates (defined as 'less than partial cytogenetic response') from the DASISION and ENESTnd trials respectively. For first-line imatinib, 12-month discontinuation and switch rates were estimated for people with partial and less than partial cytogenetic response from an observational study of 224 people taking imatinib with chronic phase CML recruited from a single UK centre. (For further details, see pages 49–52 of the manufacturer's submission).

Health state utility values were obtained from a cross-sectional study based in the UK, US, Australia and Canada using the time trade-off method. The utility values were based on survey responses from a sample of the general population (n = 353, of which 97 were from the UK). The Bristol-Myers Squibb model

assumed that only people with complete cytogenetic response had disease that responded and that those with either partial or less than partial response had disease that didn't respond. For people who received a stem cell transplant, Bristol-Myers Squibb used a baseline utility value of 0.71, taken from the Southampton Health Technology Assessments Centre (SHTAC) assessment report published in 2011 on dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant CML. Utility values were calculated for each phase based on response and for post stem cell transplant and are presented in Table 7.

Table 7. Health state utility values for each phase based on response

Health state	Utility value
Chronic phase (response)	0.85
Chronic phase (no response)	0.68
Accelerated phase (response)	0.79
Accelerated phase (no response)	0.50
Blast phase (response)	0.50
Blast phase (no response)	0.31
Post stem cell transplant	0.71

Bristol-Myers Squibb also included utility decrement weights to account for any treatment-related haematological adverse events. These were derived from the chemotherapy literature and a Liverpool Reviews and Implementation Group assessment report published in 2006 on erlotinib for the treatment of relapsed non-small cell lung cancer. If utility estimates for adverse events were not available, a 5% (-0.05) decrement was assumed. Annual haematological event rates for first and second-line TKI treatments were taken from the DASISION, ENESTnd and IRIS trials and an earlier Bristol-Myers Squibb submission for second-line CML.

Drug acquisition costs were taken from the BNF 61. Bristol-Myers Squibb assumed the same BNF-derived cost for first and second-line nilotinib, which does

not reflect the price discount available under the approved patient access scheme. Dose intensities for the three first-line TKIs were 100% in the first 2 years of treatment. From the third year of treatment onwards, the dose intensities for each TKI were estimated by Bristol-Myers Squibb as dasatinib 90.1%, nilotinib 88.8% and standard-dose imatinib 94.0%.

Costs associated with outpatient visits, tests and hospitalisations were also included in the model. The expected level of resource use according to disease phase and level of response were estimated from a survey of six UK haematologists. Adverse event costs were also included for serious haematological events. For people receiving third-line treatment, Bristol-Myers Squibb assumed that 30.6% received stem cell transplantation, 50.0% received a combination of chemotherapy and TKI treatment and 18.2% received palliative care. Bristol-Myers Squibb assumed that the cost of stem cell transplantation consisted of a one-off cost of £80,000 plus an additional monthly cost of 2,400, which was taken from the SHTAC assessment report published in 2011 on dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant CML. Other third-line treatment costs included those associated with chemotherapy, TKI treatment and palliative care.

A summary of the key outputs from the Bristol-Myers Squibb economic model, including the base-case incremental cost-effectiveness ratios (ICERs) for dasatinib compared with nilotinib and standard-dose imatinib are presented in Table 8.

Table 8 Summary of outputs from Bristol-Myers Squibb economic model

	Dasatinib	Imatinib	Nilotinib
PFS (years)*	19.16	17.14	19.28
OS (years)*	20.46	18.83	20.59
QALYs	10.64	9.89	10.70
Drug costs (£)	343,545	249,526	360,237
Other costs (£)	154,672	228,767	146,376
Total costs (£)	498,217	478,293	506,613
Incremental costs per QALY gained			
Dasatinib vs imatinib		£26,305	
Dasatinib vs nilotinib		£144,778 (nilotinib provided more benefit at greater cost than dasatinib)	
* Undiscounted OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year.			

In one-way sensitivity analyses, the input parameters that had the greatest effect on the ICERs were the monthly first-line drug acquisition costs, dose intensities for dasatinib and nilotinib and 12-month response rates. The results of the probabilistic sensitivity analyses showed that, at a threshold of £30,000, the probabilities of dasatinib being cost effective compared with standard-dose imatinib and nilotinib were 63% and 100% respectively.

PenTAG critique of Bristol-Myers Squibb submission of cost-effectiveness evidence

In its critique of the cost-effectiveness evidence submitted by Bristol-Myers Squibb, PenTAG commented that the overall approach and the sources and justification of estimates were reasonable. However, PenTAG identified a number of specific concerns with the economic model. First, a number of formulae errors were identified in the model, which when corrected for, changed the ICERs to £36,000 per QALY gained for dasatinib compared with imatinib and to £103,000 per QALY gained for dasatinib compared with nilotinib (dasatinib now providing more benefit at greater cost than nilotinib). At the time of submission to NICE, Bristol-Myers Squibb was unable to incorporate in its model the reduced price of first- and second-line nilotinib under the approved patient access scheme discount. This was because Bristol-Myers Squibb did not have knowledge of the patient access

scheme discount. When this discounted price was applied in the model by the Assessment Group (along with correction of formulae errors), the ICER for dasatinib compared with imatinib increased to £45,600 per QALY gained and nilotinib dominated dasatinib (that is, nilotinib was more effective and less costly). PenTAG also noted that the Bristol-Myers Squibb model assumed that dasatinib was taken in combination with other chemotherapy drugs as a third-line treatment during the advanced phase in all treatment arms, and that half of all patients in the imatinib and nilotinib treatment arms eligible for second-line treatment received dasatinib, which is not recommended in draft guidance produced by NICE (see section 1.2). When the model was adjusted by PenTAG so that dasatinib was not taken as third-line treatment, the ICER for dasatinib compared with imatinib increased further, from £45,600 to £64,000 per QALY gained. Nilotinib also continued to dominate dasatinib. When the model was further adjusted by PenTAG so that dasatinib was not taken as a second-line treatment, and instead it was assumed that all people eligible for second-line treatment in the imatinib arm received nilotinib, the ICER for dasatinib compared with imatinib increased further, from £64,000 to £96,000 per QALY gained.

Other concerns highlighted by PenTAG were that the starting age of the cohort, which was 46 years, was considerably lower than the mean age of people with newly diagnosed CML in the UK (56 years). Also, the model did not adopt a lifetime time horizon and may have overestimated the period that people with CML will survive as it was run for a cohort between 46 and 86 years of age, at which point approximately 20% of the cohort were still alive. Finally, PenTAG noted that, although the cost and proportions of people who received stem cell transplantation had a significant impact on the ICERs, the source of the estimates of these parameters was unclear. For PenTAG's full critique of the model presented by Bristol-Myers Squibb, see pages 125–128 of the assessment report.

Novartis – nilotinib

Novartis developed a Markov model to assess the cost effectiveness of nilotinib 600 mg daily compared with standard-dose imatinib as first-line treatments in people with chronic phase CML. The analysis was conducted from a UK NHS and

Personal Social Services perspective using a lifetime horizon with costs and benefits discounted at 3.5%. Patients entered the model in the chronic phase. The model estimated when one TKI treatment would fail and hence when the person was switched to an alternative treatment. At each cycle, people had a probability of remaining on current treatment, progressing to an alternative treatment or dying. People were able to remain in chronic phase, accelerated phase or blast phase for more than one cycle and could die from non-CML causes at any time. People that received a transplant could die from transplant-related mortality or remain well. People that were treated with hydroxyurea had a probability of progressing to advanced phase. On progression to advanced or blast phase, all people were assumed to receive hydroxyurea treatment. Patients in advanced disease phase had a probability of progressing to blast phase, and finally from blast phase to CML-related death. In the blast phase, people could only die as a result of CML. The model used monthly cycles for the first 6 months followed by quarterly cycles thereafter.

Novartis modelled two different scenarios to reflect the availability of second-generation TKIs as second-line treatment. In the first scenario, which was the base-case analysis used by the manufacturer, second-line treatment consisted of dasatinib (100 mg daily) followed by stem cell transplant or hydroxyurea as third-line treatment. In the second scenario, second-line treatment consisted only of stem cell transplant or hydroxyurea with no third-line treatment available.

The impact of first-line TKI treatment on CML progression and survival was estimated using a combination of data on the effect of TKIs on time to discontinuation and the relationship between time to discontinuation and progression-free and overall survival. In order to model lifetime costs and QALYs, the available evidence was extrapolated within the economic model.

Time to discontinuation rates for first-line nilotinib or imatinib were estimated by fitting a Weibull survival curve to Kaplan-Meier data of first-line treatment failure from the ENESTnd trial. Time to discontinuation rates for second-line dasatinib were estimated from a randomised controlled trial of dasatinib after first-line imatinib treatment failure. No published data on dasatinib after first-line nilotinib

were available. Novartis assumed that dasatinib following first-line nilotinib would be less effective in comparison to following imatinib. Therefore, time to discontinuation rates were weighted downwards using data from a published long-term follow-up study of dasatinib and nilotinib as third-line treatments following two prior TKIs. The effectiveness of stem cell transplantation as second- or third-line treatment was estimated using data from an observational study that modelled survival based on pre-stem cell transplant risk scores in people diagnosed with CML. Novartis then used this data to estimate survival functions for two separate groups: a high-risk group consisting of people who experienced poor survival and a low-risk group who experienced good long-term survival after stem cell transplant. For second- or third-line hydroxyurea treatment, time spent in chronic phase was estimated as the difference between time to discontinuation and progression-free survival curves, based on people in the IRIS study who were resistant to first-line imatinib treatment. Survival estimates for hydroxyurea treatment in the accelerated phase or blast crisis phase were estimated by extrapolating survival curves from a separate study of people for whom imatinib treatment failed in the accelerated phase or blast crisis phase. Overall survival for each TKI treatment was then estimated as the cumulative result of the model's estimated time to discontinuation of first-, second- and third-line treatment (see pages 85–93 of the manufacturer's submission for further details).

Utility values were based on EQ-5D responses from people receiving standard-dose imatinib in the IRIS study. Based on this study, the modelled baseline utilities were 0.854 for the chronic phase and 0.595 for the accelerated or blast crisis phase health states. Disutilities corresponding to grade 3 and 4 adverse events relating to TKI treatments were estimated from utility values taken from the published literature. These were then weighted by the duration and probability of experiencing the adverse event, to calculate the overall disutility. These disutilities were applied only within the first 18 months for first- and second-line TKIs. Disutilities associated with adverse events for each TKI were nilotinib 0.010, standard-dose imatinib 0.016 and dasatinib 0.019. Novartis did not identify any published evidence of utility values after stem cell transplant for CML. Therefore, an assumed baseline utility value of 0.813 was used, with a further decrement of

0.079, which was taken from a study of chronic graft-versus-host disease following bone marrow transplant. This utility decrement was applied to the long-term utility for 52% of people after transplant to reflect common adverse events associated with stem cell transplant.

Drug acquisition costs were taken from the BNF 61. For nilotinib, Novartis applied an approved patient access scheme discount, such that the daily cost of nilotinib as first- or second-line treatment was equivalent to the cost of imatinib 400 mg. Costs associated with grade 3 or 4 adverse events, routine hospital appointments for administration and monitoring and inpatient stay for end-of-life care were also included in the model. When published data were not available, resource use was estimated from clinical specialist opinion. The total one-off cost of stem cell transplant was assumed to be £99,224 and was derived from a weighted average of the costs reported by the London Specialised Commissioning Group Workshop.

A summary of the key outputs from the Novartis economic model, including the base-case ICERs for nilotinib compared with standard-dose imatinib for scenarios with or without dasatinib as second-line treatment, are presented in Table 9.

Table 9 Summary of outputs from Novartis economic model

	Scenario A: dasatinib as 2nd-line treatment (base case)		Scenario B: SCT or HU as 2nd-line treatment	
	Nilotinib	Imatinib	Nilotinib	Imatinib
PFS (years)*	12.66	11.94	10.64	9.30
OS (years)*	13.54	12.83	11.38	9.97
QALYs	10.40	9.85	8.71	7.62
Drug costs (£)	172,303	181,322	114,771	104,038
Other costs (£)	45,070	46,422	55,872	61,977
Total costs (£)	217,373	227,744	170,643	166,015
ICERs per QALY gained				
Nilotinib vs imatinib (scenario A)	-£34,889 (nilotinib dominates imatinib)			
Nilotinib vs imatinib (scenario B)	£5908			
* Undiscounted HU, hydroxyurea; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; SCT, stem cell transplant.				

In one-way sensitivity analyses, the input parameters that had the greatest impact on the ICERs were the first-line drug acquisition costs for nilotinib without the patient access scheme discount (in scenario A) and the time to discontinuation of first-line TKI treatments (in scenario B). The results of the probabilistic sensitivity analysis indicated that nilotinib had a 100% probability of being cost effective compared with imatinib at a threshold of £30,000 per QALY (scenario A).

PenTAG critique of Novartis submission of cost-effectiveness evidence

PenTAG commented that the overall approach, and the sources and justification of estimates, were reasonable. However, PenTAG identified several areas of uncertainty. First, the model did not incorporate major molecular response and complete cytogenetic response rates from the ENESTnd trial, both of which are important measures of clinical effectiveness. There was also high uncertainty around the cost and utility of people who had a stem cell transplant, which had a significant impact on the estimated ICERs. For PenTAG's full critique of the Novartis economic model, see pages 132–133 of the assessment report.

3.2.2 PenTAG cost-effectiveness analyses

For the cost-effectiveness analysis of first-line TKI treatments for CML PenTAG identified two major sources of uncertainty. First, the clinical-effectiveness evidence from the DASISION and ENESTnd trials was immature, with current follow-up of only 2 years. Given that CML is a chronic disease, with survival from diagnosis of approximately 15–20 years, it was necessary to extrapolate clinical-effectiveness data over many years, thus introducing substantial uncertainty. Second, the relative cost effectiveness of first-line TKI treatments was heavily influenced by PenTAG's assumptions about subsequent lines of treatment and there was much uncertainty around the nature and cost of these treatments. As a result of this extensive structural uncertainty, PenTAG presented a range of deterministic scenario analyses, which varied according to key structural assumptions. Furthermore, because it was not possible for PenTAG to designate any one scenario as the most plausible, a single base-case analysis was not presented. A summary of the scenario analyses modelled by PenTAG are presented in Table 10.

The structure of the PenTAG model is shown below in

Figure 1. The model was a state-transition model with states for the main disease phases and for the different possible treatments within each phase. People entered the model in the chronic phase. At the end of each cycle, people had a probability of remaining in their current health state, progressing to an alternative state or dying.

Table 10 Summary of scenario analyses produced using the PenTAG economic model

<table>
<tr><th>1st-line treatments</th><th>2nd-line treatments</th><th>3rd-line treatments</th><th>Simplified method?</th><th>Cumulative survival method</th><th>MMR surrogate survival method</th><th>CCyR surrogate survival method</th></tr>
<tr><td>Imatinib
Dasatinib
Nilotinib</td><td>HU or SCT</td><td>None</td><td>No</td><td>1</td><td>1a</td><td>1b</td></tr>
<tr><td>Imatinib
Dasatinib
Nilotinib</td><td>HU or SCT</td><td>None</td><td>Yes</td><td>2</td><td>2a</td><td>2b</td></tr>
<tr><td>Imatinib
Dasatinib</td><td>Nilotinib</td><td>HU or SCT</td><td rowspan="2">No</td><td rowspan="3">3</td><td rowspan="3">3a</td><td rowspan="3">3b</td></tr>
<tr><td>Nilotinib</td><td>HU or SCT</td><td>None</td></tr>
<tr><td>Imatinib
Dasatinib</td><td>Nilotinib</td><td>HU or SCT</td><td rowspan="2">Yes</td></tr>
<tr><td>Nilotinib</td><td>HU or SCT</td><td>None</td><td>4</td><td>4a</td><td>4b</td></tr>
<tr><td colspan="7">Cells shaded black indicate the scenario analyses conducted.
CCyR, complete cytogenetic response; HU, hydroxyurea; MMR, major molecular response; SCT, stem cell transplant.</td></tr>
</table>

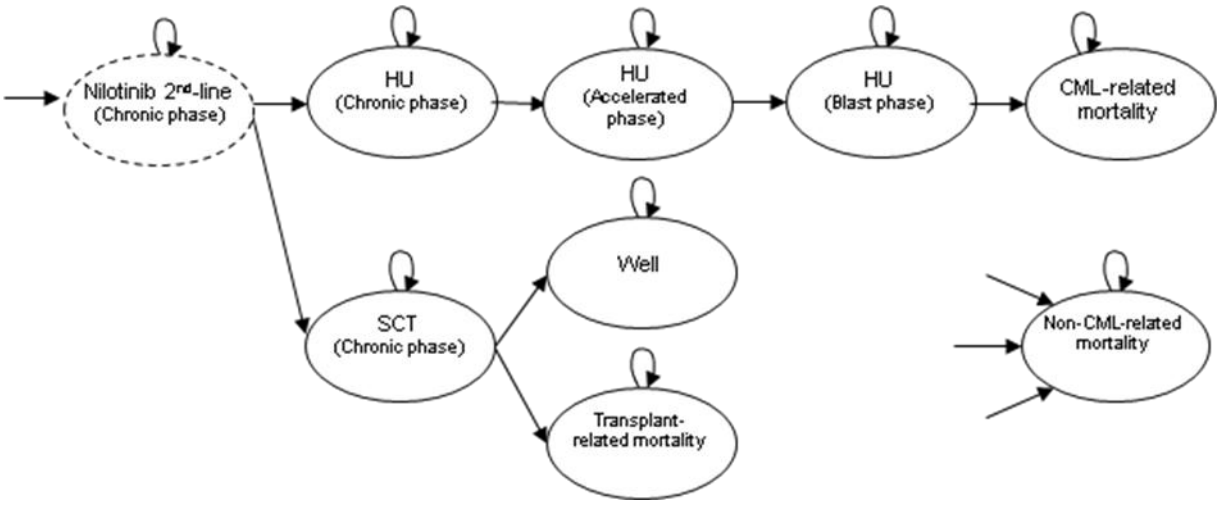
In scenarios 1 and 2 (including the ‘a’ and ‘b’ scenarios), the PenTAG model assumed that, after first-line TKI treatment failure, all people in the chronic phase progressed directly to a mixture of hydroxyurea or stem cell transplant as second-line treatment, with no further lines of treatment before reaching the accelerated or blast crisis phase. In scenarios 3 and 4, PenTAG assumed that people receiving first-line imatinib or dasatinib progressed to second-line nilotinib, as represented by the dotted ellipse in

Figure 1. These people then progressed to a mixture of stem cell transplant and hydroxyurea as third-line treatment, before reaching the accelerated or blast crisis phase. For people whose disease failed to respond to first-line nilotinib, it was assumed that they would progress directly to hydroxyurea or stem cell transplant as second-line treatment, with no further lines of treatment before reaching the accelerated or blast crisis phase.

For simplicity, PenTAG assumed that people in all three treatment arms who progressed to the accelerated or blast crisis phase would only receive hydroxyurea treatment. This was justified mainly because of a lack of evidence on the effectiveness of TKI treatments in the advanced stages of CML.

For each scenario the model cycle length was 3 months with a half-cycle correction. A lifetime (50 years) horizon was used, based on a mean age at diagnosis of chronic phase CML of 57 years. The analyses were conducted from a UK NHS and Personal Social Services perspective, with costs and benefits discounted at a rate of 3.5%.

Figure 1 Structure of PenTAG model



Estimation of survival

PenTAG used two alternative approaches to estimating survival in its model: the cumulative survival approach, which was used for the base-case cost-effectiveness analysis, and the surrogate-predicted survival approach using either major molecular response or complete cytogenetic response at 12 months, which was used in sensitivity analyses.

In the cumulative survival approach (scenarios 1, 2, 3 and 4), overall survival was estimated as the cumulative result of the duration of successive treatments. In scenarios 1 and 2, overall survival for each treatment arm was estimated as the

sum of time on first-line treatment and overall survival following either hydroxyurea or stem cell transplant. In scenarios 3 and 4, overall survival for the dasatinib and imatinib treatment arms was equal to the sum of time on first-line treatment, time on second-line nilotinib and overall survival following either hydroxyurea or stem cell transplant. This method ignored the complete cytogenetic response and major molecular response rates from the DASISION and ENESTnd trials. An important assumption behind this approach was that overall survival after second-line nilotinib and after second or third-line hydroxyurea or stem cell transplant was independent of previous treatment.

In order to estimate the mean duration of first-line TKI treatments in its economic model, PenTAG extrapolated treatment duration data using Weibull survival curves from the DASISION, ENESTnd and IRIS trials respectively. The estimated mean first-line treatment durations used in the economic model were imatinib 7.1 years, dasatinib 7.8 years and nilotinib 9.0 years. To estimate survival on hydroxyurea after first-line TKI failure, PenTAG used survival data from a subgroup of 61 people who received a range of treatments following resistance or intolerance to imatinib from a single cohort study. This resulted in an estimated mean overall survival on hydroxyurea following TKI failure of 7.0 years and a 5-year survival of 50%. Because of a lack of relevant data, it was also assumed that overall survival on hydroxyurea was independent of previous treatment. The estimated mean time on hydroxyurea in accelerated phase and blast crisis phase was 9.6 month and 6 months respectively. These estimates were then used to calculate transition probabilities from accelerated phase to blast crisis phase, and from chronic phase to accelerated phase, while on hydroxyurea treatment.

The proportion of people having a stem cell transplant after first-line TKI failure was based on clinician opinion, which indicated a sharp decline in the estimated proportion of people who would receive a stem cell transplant in the chronic phase after the age of 65 and that no people aged older than 75 would be likely to receive a stem cell transplant. To estimate overall survival following a stem cell transplant, PenTAG used data from a study of people with chronic phase CML receiving stem cell transplants in a London hospital between 2000 and 2010. Of

these, 74% survived to 3 years and 72% to 6 years. Finally, the model needed the estimated duration of second-line nilotinib treatment in people for whom first-line dasatinib or imatinib failed (scenarios 3 and 4). PenTAG extrapolated data from a phase II study of imatinib-resistant people who received second-line nilotinib treatment. This resulted in an estimated mean time on second-line nilotinib treatment of 2.4 years. For detailed methods of how overall survival based on the cumulative survival approach was estimated, see pages 155–170 of the PenTAG assessment report.

In the surrogate survival approach (all 'a' and 'b' scenarios), overall survival for the three first-line TKI treatments was estimated using a surrogate relationship based on major molecular response at 12 months (scenarios 1a, 2a, 3a and 4a) or complete cytogenetic response at 12 months (scenarios 1b, 2b, 3b and 4b). PenTAG did not model scenarios 3a, 3b, 4a and 4b because the historical overall survival data used to estimate the major molecular response and complete cytogenetic response surrogate relationships did not reflect the use of second-line nilotinib. The methods of estimating overall survival based on the surrogate relationships with major molecular response and complete cytogenetic response are described on pages147–155 of the assessment report and are based on the results of PenTAG's clinical-effectiveness systematic review and network meta-analysis of surrogate outcomes at 12 months. PenTAG found that the modelled data appeared to closely predict the overall survival observed in the DASISION and ENESTnd trials and the longer-term survival data from the imatinib treatment arm in the IRIS randomised controlled trial.

PenTAG also generated some scenario analyses using a simplified method. In this approach (applied in scenarios 2, 2a, 2b and 4), mean costs and QALYs after TKI treatment (first- or second-line) were set to be equal across the treatment arms. PenTAG included this approach to allow for the 'pure' cost effectiveness of first-line TKI treatments and second-line nilotinib, given the high uncertainty around the nature and costs of subsequent lines of treatment and the likelihood that people would be treated with first-line TKIs for many years (see pages 141–143 of the assessment report for further details).

A summary of the advantages and disadvantages of each of the scenarios modelled by PenTAG is provided in table 34, page 145 of the assessment report.

Utility and cost input parameters

PenTAG undertook a systematic review to identify relevant CML health state utility values for its economic model. Two studies based on a large sample of people receiving imatinib treatment in the IRIS trial were identified that estimated EQ-5D utility values for CML health states. After adjusting for the mean age at diagnosis (57 years), a utility value of 0.83 was estimated for the chronic phase health state for all three first-line TKI treatments and for people receiving hydroxyurea as second- or third-line treatment. For people in the accelerated phase and blast phase, utility values of 0.73 and 0.52 were used respectively. For people receiving a stem cell transplant as second- or third-line treatment in the chronic phase, it was assumed that people at low risk (75%) would incur a disutility of 0.041 and people at high risk (25%) would incur a disutility of 0.079. Both disutilities were subtracted from general England and Wales population age-related utility values (for further details see pages 171–174 of the assessment report).

Cost estimates in the PenTAG economic model included drug acquisition costs, adverse event costs and a range of medical management costs such as consultant outpatient visits and hospitalisation. All costs were inflated to 2011–12 values where appropriate.

Drug acquisition costs for the three TKI treatments and hydroxyurea were taken from BNF 61 and MIMS (see Table 1). The cost of first- and second-line nilotinib used in the PenTAG model also reflected the approved patient access scheme discount, which was provided by Novartis. Dose intensities for the three TKI treatments were applied to the costs, in order to accurately reflect the amount of the drugs administered in the relevant clinical trials. The average dose densities used for first-line dasatinib, nilotinib and imatinib were 99%, 92% and 100% respectively. These were based on the dose intensities used in both manufacturer submissions. For second-line nilotinib, an average dose intensity of 99% was taken from a phase II trial of nilotinib for people resistant to or intolerant of

imatinib. For second- and third-line hydroxyurea, an assumed average dose intensity of 100% was used.

The PenTAG economic model included treatment of grade 3 or 4 adverse events related to first or second-line TKIs. Rates of grade 3 or 4 adverse events were taken from the DASISION and ENESTnd trials for the first 12 months of treatment. Only the cost of treating neutropenia, thrombocytopenia and anaemia were included because other grade 3 or 4 events were experienced by no more than 1% of people in both trials. As the number of additional adverse events from 13 to 24 months was so small, only events in the first year of TKI treatment were included in the model.

The costs of medical management and monitoring were largely based on those used in the Bristol-Myers Squibb economic model, which were based on clinical specialist opinion. These costs, which differed for the chronic and advanced (accelerated and blast crisis) phase, included nurse and consultant outpatient visits, tests and hospital inpatient stay. For people receiving a stem cell transplant as second- or third-line treatment, a one-off mean per-patient cost (£81,600) was applied, which was based on similar assumptions used in the Novartis economic model, and were followed by monthly drug and monitoring costs of longer-term post-stem cell transplant care. It was also assumed that people in the blast crisis phase would incur the extra costs of palliative care (for further details see pages 179–183 of the assessment report).

PenTAG cost-effectiveness results

A summary of the base-case cost-effectiveness results for scenarios 1–4 is presented in Table 11. A more detailed breakdown of the results for each of the modelled scenarios, including modelled survival and costs, is presented in pages 186–206 of the assessment report.

PenTAG noted the wide variation in the cost-effectiveness results across the four scenarios in the base-case analysis. The ICERs for nilotinib compared with imatinib ranged from £26,000 per QALY gained (scenario 2) to £36,000 per QALY gained (scenario 1). In scenarios 3 and 4, nilotinib generated fewer lifetime QALYs

but generated significant cost savings compared with imatinib followed by second-line nilotinib. In all scenarios, dasatinib was either dominated by nilotinib or generated ICERs of over £300,000 per QALY gained compared with imatinib. PenTAG again highlighted that this wide variation in the cost-effectiveness results reflected the significant structural uncertainty in the modelling of first-line TKIs for CML, including the substantial impact of assumptions about second- and third-line treatment sequences following first-line TKI failure.

Table 11. Summary of cost-effectiveness results for scenario analyses 1–4 from the PenTAG model

	Discounted cost (£)	Undiscounted life-years	Discounted QALYs	Incremental cost (£)*	Incremental QALYs*	ICER (£ per QALY*
Scenario 1: cumulative survival without 2nd-line nilotinib						
Imatinib – then HU/SCT	186,827	16.5	9.0			
Nilotinib – then HU/SCT	201,808	17.4	9.4	14,981	0.4	36,000
Dasatinib – then HU/SCT	253,172	16.8	9.2	51,363	-0.3	Dominated by nilotinib
Scenario 2: cumulative survival, simplified method, without 2nd-line nilotinib						
Imatinib – then HU/SCT	186,627		9.0			
Nilotinib – then HU/SCT	204,222		9.7	17,395	0.7	26,000
Dasatinib – then HU/SCT	254,166		9.3	67,338	-0.4	Dominated by nilotinib
Scenario 3: cumulative survival, with 2nd-line nilotinib						
Nilotinib – then HU/SCT	201,808	17.4	9.4			
Imatinib – then nilotinib	222,398	17.3	9.5	20,590	0.1	213,000
Dasatinib – then nilotinib	287,487	17.6	9.7	65,089	0.1	460,000
Scenario 4: cumulative survival, simplified method, with 2nd-line nilotinib						
Nilotinib – then HU/SCT	198,517		9.1			
Imatinib – then nilotinib	222,398		9.5	23,881	0.5	50,000
Dasatinib – then nilotinib	288,241		9.7	65,834	0.2	307,000

* Each technology is compared with the next most effective non-dominated alternative

HU, hydroxyurea; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SCT, stem cell transplant.

PenTAG presented one-way deterministic sensitivity analyses for scenarios 1–4 separately for dasatinib compared with imatinib, and nilotinib compared with imatinib (please see Table 12 and Table 13 in Appendix B: PenTAG deterministic sensitivity analyses). For scenarios 1 and 2 (no second-line nilotinib), the cost-

effectiveness results for nilotinib compared with imatinib ranged from nilotinib dominating imatinib (when time on first-line TKI was assumed to be 7.0 years for both treatments instead of 8.9 years for nilotinib and 7.0 years for imatinib in the base case analyses) to £70,000 per QALY gained in scenario 1 and £48,000 per QALY gained in scenario 2 (when a 25% drug price reduction was assumed for imatinib). The lowest ICERs for dasatinib compared with imatinib were £110,000 and £82,000 per QALY gained in scenarios 1 and 2 respectively.

For scenarios 3 and 4, which assumed the use of second-line nilotinib, nilotinib was predicted to generate fewer costs and QALYs than imatinib followed by second-line nilotinib in the majority of sensitivity analyses. For scenario 3, the cost-effectiveness results for imatinib followed by second-line nilotinib compared with nilotinib ranged from £59,000 per QALY gained (when mean survival after stem cell transplantation was decreased from 17 to 5.7 years) to nilotinib dominating imatinib (when discount rates were set to zero and when time on first-line nilotinib and imatinib was increased to 13.8 years and 11.7 years). For scenario 4, the ICERs for imatinib followed by second-line nilotinib compared with nilotinib ranged from £20,000 per QALY gained (when a 25% drug price reduction was assumed for imatinib) to £80,886 per QALY gained (when time on first-line nilotinib or imatinib was increased). The lowest ICERs for dasatinib compared with imatinib were £298,000 and £259,000 per QALY gained in scenarios 3 and 4 respectively.

The input parameters that had the greatest impact on the ICERs for nilotinib compared with imatinib were the assumption of a 25% reduction in the price of imatinib upon patent expiry in 2016 and changes to the dose intensities of first-line nilotinib or imatinib. Assuming a 25% reduction in the price of imatinib only upon patent expiry, the ICERs for nilotinib compared with imatinib increased from £36,000 to £70,000 per QALY gained in scenario 1 and from £26,000 to £48,000 per QALY gained in scenario 2. In scenarios 3 and 4, the ICERs for imatinib followed by second-line nilotinib compared with nilotinib decreased from £213,000 to £63,000 per QALY gained and from £50,000 to £20,000 per QALY gained respectively. When the dose intensity of first-line nilotinib was increased from 92% to100%, the ICER in scenario 1 for nilotinib compared with imatinib increased to

£63,000 per QALY gained, and the ICER in scenario 2 increased to £44,000 per QALY gained. In scenarios 3 and 4, the ICERs for imatinib followed by second-line nilotinib compared with nilotinib decreased to £93,000 and £26,000 per QALY gained respectively. When the dose intensity of imatinib was increased from 100% to 106% (the value used in the Novartis model), the ICER for nilotinib compared with imatinib decreased to £19,000 per QALY gained in scenario 1, and decreased to £15,000 per QALY gained in scenario 2. In scenarios 3 and 4, the ICERs for imatinib followed by second-line nilotinib compared with nilotinib increased to £286,000 and £65,000 per QALY gained respectively. Other influential parameters on the ICERs for nilotinib compared with imatinib included assumptions around stem cell transplantation (cost, proportion of people receiving stem cell transplant and post transplant survival), treatment duration of first-line TKI, time on hydroxyurea in the chronic phase, and medical management costs in the chronic phase.

PenTAG also presented one-way deterministic sensitivity analyses based on the surrogate survival method in which overall survival was estimated from response according to major molecular response or complete cytogenetic response at 12 months (scenarios 1a, 1b, 2a and 2b). When overall survival was estimated from major molecular response rates, the ICERs for nilotinib compared with imatinib increased to £53,000 per QALY gained in scenario 1a and to £36,000 per QALY gained in scenario 2a. This was because the gain in overall survival for nilotinib was 0.6 years using this method, compared with 0.9 years when based on the cumulative survival method. Conversely, when overall survival was estimated from complete cytogenetic response rates, the ICERs for nilotinib compared with imatinib decreased to £29,000 per QALY gained in scenario 1b and to £22,000 per QALY gained in scenario 2b. This was because the estimated gain in overall survival for nilotinib compared with imatinib increased from 0.9 to 1.3 years when using this method. PenTAG also noted that in both scenarios, the ICERs for dasatinib compared with imatinib remained very high when the surrogate survival method was used. For further details of the results of all of the deterministic sensitivity analyses conducted by PenTAG, see pages 208-220 of the assessment report.

PenTAG chose not to conduct and present probabilistic sensitivity analyses because of the large amount of structural uncertainty, related to the estimation of long-term survival and subsequent treatment sequences following first-line TKI failure in their model.

3.2.3 Comparison of PenTAG, Bristol-Myers Squibb and Novartis economic models

PenTAG explored the differences in the results produced by the three economic models. It was noted that scenario 1 in the PenTAG model used the closest structural assumptions to the Novartis model scenario (scenario 2) in which no second-line TKI treatments were assumed. However, the models predicted substantially different ICERs for the comparison of nilotinib and imatinib: PenTAG produced an ICER of £36,000 per QALY gained and Novartis an ICER of £6000 per QALY gained. The main causes of these differences were the higher incremental QALYs gained for people taking imatinib after stem cell transplant and hydroxyurea (in chronic phase) treatments, the higher incremental costs of first-line TKI treatment (including medical management costs), and the lower cost savings of stem cell transplant predicted for people taking first-line nilotinib in the PenTAG model.

The higher incremental QALYs gained for people taking imatinib in the PenTAG model were explained by the fact that fewer (5% versus 8%) people taking first-line nilotinib had a stem cell transplant compared with imatinib and predicted life expectancy after stem cell transplantation was higher (17.3 years versus 5.7 years) compared with the Novartis model. The higher incremental QALYs were also explained by the fact that hydroxyurea was taken in the chronic phase for longer overall (5.0 years versus 1.6 years) and typically later in the nilotinib treatment arm in the PenTAG model, which resulted in QALYs being discounted more for people taking nilotinib. The higher incremental costs of first-line nilotinib treatment (including medical management) in the PenTAG model were because of the lower dose intensity used for first-line imatinib (100% versus 106%) and the higher per-patient medical management costs (£1111 versus £276) compared with the Novartis model. The lower cost savings of stem cell transplant for people

taking first-line nilotinib in the PenTAG model compared with the Novartis model were explained by the fact that the PenTAG model predicted a smaller difference in the proportion of people (-5% versus -8%) who had a stem cell transplant in the nilotinib arm compared with the imatinib arm. In the PenTAG model, it was assumed that the proportion of people who had a stem cell transplant decreased linearly with age, whereas Novartis assumed a flat rate of 75% up to 65 years and 0% thereafter (for further details see pages 220–232 of the assessment report).

PenTAG noted that it was only possible to compare scenario 3 in its model (in which people taking dasatinib and imatinib could receive second-line nilotinib) and the Bristol-Myers Squibb model after it was corrected for errors and adjusted so that all people received second-line nilotinib. As PenTAG stated that it was not possible to adjust the Bristol-Myers Squibb model so that no people in the nilotinib treatment arm could receive a second-line TKI after treatment failure, a comparison was made between dasatinib and imatinib only. Both models predicted very high ICERs for dasatinib compared with imatinib: PenTAG generated an ICER of £460,000 per QALY gained and Bristol-Myers Squibb an ICER of £95,000 per QALY gained. Although both models generated similar cost differences between dasatinib and imatinib, the PenTAG model predicted smaller QALY gains for the dasatinib treatment arm.

4 Equalities issues

No potential equalities issues were raised by either Bristol-Myers Squibb or Novartis in their submissions or by PenTAG in its assessment report.

In an equality impact assessment during the scoping phase of this appraisal, it was noted that consultees at an earlier scoping workshop for a proposed single technology appraisal of nilotinib commented that pregnant women and children may be excluded from the drug by the marketing authorisation. Consultees at an earlier scoping workshop for a proposed single technology appraisal of dasatinib were concerned that a minority of people with CML who were not Philadelphia chromosome positive would be excluded from the guidance and may therefore be excluded from treatment. Consultees at this workshop also commented that the

majority of people with CML are older and that there tends to be an age bias in prescribing treatments for CML (older people may have less access to effective treatments). It was also stated that when standard treatments (imatinib) fail, stem cell transplant may be considered, but that people from ethnic minorities usually have less access to transplants technologies (that is, donors are less frequently available).

In the appraisal of dasatinib, high-dose imatinib and nilotinib for imatinib-resistant and intolerant CML, the Bristol-Myers Squibb submissions stated that, if high-dose imatinib, dasatinib, or nilotinib are not recommended for people with imatinib-resistant CML, then allogeneic stem cell transplantation is the only treatment that may be clinically effective. However, only a small number of people who have imatinib-resistant CML are eligible for allogeneic stem cell transplantation. Bristol-Myers Squibb stated that this raises equity issues in relation to race, age, and comorbidity. In relation to race, Bristol-Myers Squibb stated that there is a lack of suitable transplant donors in the UK except for people who are white. In relation to age, they stated that a typical suitable allogeneic stem cell transplantation patient is young (< 45 years) with no significant comorbidities, and that older people are likely to have a greater number of associated comorbidities, whilst also experiencing more significant morbidity and mortality. In relation to comorbidities, Bristol-Myers Squibb stated that if young people with comorbidities could not have second generation TKIs, they would be restricted to what is, at best, supportive treatment. It stated that this would be unacceptable clinical management.

5 Issues for consideration

Clinical effectiveness

There is evidence that dasatinib and nilotinib are more effective than imatinib as measured by complete cytogenetic response and major molecular response. However, there is limited data to assess longer term patient relevant outcomes such as survival and health-related quality of life.

There is observational evidence from imatinib treatment studies supporting the use of complete cytogenetic response and major molecular response at 12 months as surrogates for progression-free survival and overall survival in people in chronic phase CML. Can these results be applied to the second generation TKIs, dasatinib and nilotinib?

No trials have directly compared the clinical effectiveness of dasatinib and nilotinib. However, an indirect comparison analysis showed no difference between dasatinib and nilotinib for the primary outcomes of complete cytogenetic response and major molecular response at 12 months and 24 months follow up.

Cost effectiveness

PenTAG do not provide a single base case upon which to compare the cost-effectiveness of first-line dasatinib, nilotinib and standard-dose imatinib because of uncertainty around (a) extrapolating the available short-term clinical effectiveness data over many years and; (b) subsequent lines of treatment after first-line TKI failure.

Instead they present cost-effectiveness results for 4 main scenarios: 1) Cumulative survival method without second-line nilotinib; 2) Cumulative survival, simplified method, without second-line nilotinib; 3) Cumulative survival method with second-line nilotinib; 4) Cumulative survival, simplified method, with second-line nilotinib.

Which of these scenarios are the most plausible from which to estimate the relative cost-effectiveness of first-line TKI treatments for people in chronic phase CML?

Is the simplified approach used in scenarios 2 and 4 by PenTAG, where per patient costs and outcomes occurring after first-line TKI treatment are assumed equal between treatment arms, appropriate?

Which of the subsequent treatment pathways modelled by PenTAG following first-line TKI failure are the most appropriate – the assumption of second-line hydroxyurea or stem cell transplant for all three comparators (scenarios 1 and 2) or the assumption of second-line nilotinib for dasatinib and imatinib (scenarios 3 and

4)? Are there other possible treatment pathways, following first-line TKI failure, that could have been considered in the model?

Which of PenTAG's alternative approaches to estimating overall survival in their economic model is the most plausible: the cumulative survival approach (as used in the base case analysis for scenarios 1 to 4) or the surrogate survival approach, (used in scenarios 1a, 1b, 2a and 2b)?

PenTAG highlighted that scenario 1 of its model used the closest structural assumptions to the Novartis model scenario (scenario 2) in which no second-line TKI treatments were assumed. However, the models predicted substantially different ICERs for the comparison of nilotinib and imatinib (£36,000 and £6000 per QALY gained respectively). This was explained mostly by differences in:

- the proportion of people taking first line nilotinib compared with imatinib who received a stem cell transplant (5% fewer patients in the PenTAG model versus 8% fewer patients in the Novartis model)
- predicted life expectancy after stem cell transplantation (17.3 years in the PenTAG model versus 5.7 years in the Novartis model)
- the length of time on hydroxyurea in chronic phase (5.0 years in the PenTAG model versus 1.6 years in the Novartis model),
- the dose intensity used for first-line imatinib (100% in the PenTAG model versus 106% in the Novartis model)
- the medical management costs per-patient whilst on TKIs (£1111 in the PenTAG model versus £276 in the Novartis model)

Which of the assumptions listed above are the most plausible?

PenTAG noted that it was possible to compare scenario 3 of its model (in which people taking dasatinib and imatinib could receive second-line nilotinib) and the Bristol-Myers Squibb model but only after it was corrected for errors and adjusted so that dasatinib was not taken as a second- or third-line treatment and all people eligible for second-line treatment in the imatinib arm received nilotinib. Were the adjustments made by PenTAG appropriate?

6 Authors

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October 2011

Appendix A: Sources of evidence considered in the preparation of the overview

A The assessment report for this appraisal was prepared by Peninsula Technology Assessment Group (PenTAG):

- Hoyle M, Pavey T, Ciani O et al. Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia: systematic reviews and economic analyses. September 2011

B Submissions or statements were received from the following organisations:

I Manufacturers/sponsors

- Bristol-Myers Squibb
- Novartis Pharmaceuticals

II Professional/specialist, patient/carer and other groups:

- Joint submission from: National Cancer Research Institute/Royal College of Physicians/Royal College of Radiologists/Association of Clinical Pathologists/Joint Collegiate Council for Oncology
- NHS North Yorkshire & York

C Additional references used:

Loveman E, Cooper K, Bryant J et al. Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia: a systematic review and economic evaluation. February 2011

Appendix B: PenTAG deterministic sensitivity analyses

Table 12. PenTAG sensitivity analyses for nilotinib compared with imatinib

Parameter	Base case	Sensitivity analysis	Scenario 1 (No 2nd-line nilotinib)	Scenario 2 (No 2nd-line nilotinib, Simplified Method)	Scenario 3 (2nd-line nilotinib)	Scenario 4 (2nd-line nilotinib, Simplified Method)
Base case	N/A	N/A	**£36,000**	**£26,000**	**£213,000§**	**£50,000§**
General						
Discounting costs & benefits	3.5% p.a.	0% p.a.	£40,000	£30,000	Nilotinib dominates	£55,000§
Treatment pathways						
Proportion receiving SCT	Mean 28% nilotinib, 33% imatinib, decreases with age	31% at all ages (BMS assumption)	£32,000	£26,000	£92,000§	£52,000§
		75% if age < 65 (Novartis)	£43,000	£27,000	£290,000§	£49,000§
		Halve % at all ages	£31,000	£26,000	£107,000§	£52,000§
Effectiveness						
Time on 1st-line TKI	8.9 years nilotinib, 7.0 years imatinib	7.0 years nilotinib, 7.0 years imatinib	nilotinib dominates	nilotinib dominates	£87,000§	£43,000§
		13.8 years nilotinib, 11.7 years imatinib (IRIS)	£23,000	£20,000	nilotinib dominates	£80,886§
Time on 2nd-line nilotinib	Mean 2.5 years	Same as mean time on 1st-line nilotinib = 8.9 years	n/a	n/a	£71,000§	£43,000§
Survival after SCT	Mean approximately 17 years	Mean 5.7 years (Novartis)	£22,000	£23,000	£59,000§	£54,000§
Time in CP on HU	Mean 5 years	Mean 1.6 years (Novartis)	£31,000	£24,000	£375,000§	£52,000§
OS estimated by Cumulative Survival or Surrogate Survival	Cumulative Survival	Cumulative survival means, MMR survival difference	£48,000	£32,000	n/a	n/a
		Cumulative survival means, CCyR survival difference	£26,000	£20,000	n/a	n/a
		Surrogate survival means, MMR survival difference	£53,000	£36,000	n/a	n/a
		Surrogate survival means, CCyR survival difference	£29,000	£22,000	n/a	n/a
Costs						
Drug price reduction on patent expiry	0% nilotinib, 0% imatinib	0% nilotinib, 25% imatinib	£70,000	£48,000	£63,000§	£20,000§
		25% nilotinib, 25% imatinib	£54,000	£38,000	£116,000§	£30,000§

Dose intensities	92% 1st-line nilotinib, 100% imatinib, 99% 2nd-line nilotinib	100% 1st-line nilotinib, 100% imatinib, 99% 2nd-line nilotinib	£63,000	£44,000	£93,000§	£26,000§
		92% 1st-line nilotinib, 106% imatinib (Novartis), 99% 2nd-line nilotinib	£19,000	£15,000	£286,000§	£65,000§
		92% 1st-line nilotinib, 100% imatinib, 92% 2nd-line nilotinib	n/a	n/a	£187,000§	£45,000§
Cost SCT	£81,603	£40,801	£40,000	£27,000	£228,000§	£50,000§
		£163,205	£27,000	£24,000	£183,000§	£51,000§
Medical management costs after SCT	£113 per month	£57 per month	£36,000	£26,000	£215,000§	£50,000§
Medical management costs in CP	£370 per month	£185 per month	£30,000	£23,000	£200,000§	£48,000§
		£741 per month	£48,000	£33,000	£239,000§	£55,000§
Medical management costs in AP and BC	£1,113 per month	£2,227 per month	£35,000	£26,000	£217,000§	£51,000§
AEs costs	£166 per patient imatinib, £119 per patient nilotinib	£1,660 per patient imatinib, £,1190 per patient nilotinib	£35,000	£26,000	£217,000§	£51,000§
Utilities						
Utilities		Equal to Novartis	£35,000	£26,000	£209,000§	£50,000§
		Reduce all utilities by 0.10	£41,000	£30,000	£236,000§	£57,000§
§ Nilotinib provides fewer QALYs at less cost than imatinib						

Table 13. PenTAG sensitivity analyses for dasatinib compared with imatinib

Parameter	Base case	Sensitivity analysis	Scenario 1 (No 2nd-line nilotinib)	Scenario 2 (No 2nd-line nilotinib, Simplified Method)	Scenario 3 (2nd-line nilotinib)	Scenario 4 (2nd-line nilotinib, Simplified Method)
Base case	N/A	N/A	**£425,000**	**£262,000**	**£460,000**	**£307,000**
General						
Discounting costs & benefits	3.5% p.a.	0% p.a.	£345,000	£236,000	£347,000	£259,000
Treatment pathways						
Proportion receiving SCT	Mean 32% dasatinib, 33% imatinib, decreases with age	31% at all ages (BMS assumption)	£345,000	£253,000	£404,000	£300,000
		75% if age < 65 (Novartis)	£552,000	£272,000	£601,000	£319,000
		Halve % at all ages	£339,000	£251,000	£385,000	£296,000
Effectiveness						
Time on 1st-line TKI	7.7 years dasatinib, 7.0 years imatinib	7.0 years dasatinib, 7.0 years imatinib	imatinib dominates	imatinib dominates	imatinib dominates	imatinib dominates
		12.5 years dasatinib, 11.7 years imatinib (IRIS)	£574,000	£434,000	£650,000	£515,000
Time on 2nd-line nilotinib	Mean 2.5 years	Same as mean time on 1st-line nilotinib = 8.9 years	n/a	n/a	£682,000	£508,000
Survival after SCT	Mean approximately 17 years	Mean 5.7 years (Novartis)	£252,000	£229,000	£298,000	£271,000
Time in CP on HU	Mean 5 years	Mean 1.6 years (Novartis)	£366,000	£235,000	£382,000	£269,000
OS estimated by Cumulative Survival or Surrogate Survival	Cumulative Survival	Cumulative survival means, MMR survival difference	£258,000	£176,000	n/a	n/a
		Cumulative survival means, CCyR survival difference	£110,000	£82,000	n/a	n/a
		Surrogate survival means, MMR survival difference	£313,000	£202,000	n/a	n/a
		Surrogate survival means, CCyR survival difference	£131,000	£91,000	n/a	n/a
Costs						
Drug price reduction on patent expiry	0% dasatinib, 0% imatinib	25% dasatinib, 25% imatinib	£436,000	£269,000	£472,000	£315,000
Dose intensities	100% imatinib, 99% dasatinib, 99% 2nd-line	106% imatinib (Novartis), 99% dasatinib,	£379,000	£234,000	£410,000	£274,000

	nilotinib	99% 2nd-line nilotinib				
		100% imatinib, 99% dasatinib, 92% 2nd-line nilotinib	n/a	n/a	£460,000	£307,000
Cost SCT	£81,603	£40,801	£430,000	£263,000	£464,000	£308,000
		£163,205	£415,000	£260,000	£452,000	£305,000
Medical management costs after SCT	£113 per month	£57 per month	£425,000	£262,000	£460,000	£307,000
Medical management costs in CP	£370 per month	£185 per month	£419,000	£258,000	£454,000	£303,000
		£741 per month	£437,000	£269,000	£471,000	£314,000
Medical management costs in AP and BC	£1,113 per month	£2,227 per month	£424,000	£261,000	£459,000	£306,000
AEs costs	£166 per patient imatinib, £282 per patient dasatinib	£1,660 per patient imatinib, £2,820 per patient dasatinib	£432,000	£266,000	£467,000	£312,000
Utilities						
Utilities		Equal to Novartis	£416,000	£260,000	£451,000	£304,000
Utilities		Reduce all utilities by 0.10	£483,000	£299,000	£524,000	£351,000

Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence

Dasatinib, Nilotinib, and standard dose Imatinib for the first-line treatment of chronic myeloid leukaemia: systematic reviews and economic analyses

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Source of funding: This report was commissioned by the NIHR HTA Programme as project number 08/226/01.

About the Peninsula Technology Assessment Group (PenTAG)

PenTAG is part of the Institute of Health Service Research at the Peninsula College of Medicine and Dentistry. PenTAG was established in 2000 and currently has two major work streams: independent health technology assessments (HTAs) for NICE and the NIHR HTA programme, and evidence synthesis work in relation to the needs of the SW Peninsula Collaboration for Applied Health Research and Care (PenCLAHRC), as well as for other local and national decision-makers.

The group is multi-disciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics. The Peninsula College of Medicine and Dentistry is a school within the Universities of Plymouth and Exeter. The Institute of Health Research is made up of discrete by methodologically related research groups, among which HTA is a strong and recurring theme.

Recent HTA projects include:

- Bendamustine for the 1st-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate: a critique of the submission from Napp.
- The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of TA111): a systematic review and economic model.
- Ofatumumab (Arzerra®) for the treatment of chronic lymphocytic leukaemia in patients who are refractory to fludarabine and alemtuzumab: a critique of the submission from GSK.
- Everolimus for the 2nd-line treatment of advanced and/or metastatic renal cell carcinoma.
- The clinical and cost-effectiveness of sunitinib for the treatment of gastrointestinal stromal tumours: a critique of the submission from Pfizer.
- The clinical- and cost-effectiveness of lenalidomide for multiple myeloma in people who have received at least one prior therapy: an evidence review of the submission from Celgene.
- Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma: a systematic review and economic model.
- Machine perfusion systems and cold static storage of kidneys from deceased donors.

For more information about PenTAG and our other or previous work, please visit:

www.sites.pcmd.ac.uk/pentag

Declared competing interests of the authors: None

Acknowledgements

We would particularly like to thank the Expert Advisory Group for their help throughout the project. We would like to thanks Kevin Marsh (Chief Economist, Matrix Evidence) for providing overall direction for the critique of manufacturers' submissions. Alex Smith (Research Fellow, Epidemiology and Genetics Unit, Department of Health Sciences, University of York) for data related to the Haematological Malignancy Research Network. Jessica Whitton (Senior Commissioning Manager, South West Specialised Commissioning Group, Bristol) for information related to stem cell transplantation. Mike Millen (Senior Commissioning Manager, London Specialised Commissioning Group) for information related to the costing of stem cell transplantation. Professor Rod Taylor (PenTAG, University of Exeter) for his guidance related to surrogate outcomes. Daniel Chalk (Associate Research Fellow, PenCHORD, University of Exeter) and Michael Allen (Senior Modeller, PenCHORD, University of Exeter) for checking the PenTAG economic model. Jamie Peters for the WinBUGS analysis and methods. We would like to acknowledge the help Sue Whiffin and Jenny Lowe for their administrative support throughout the project.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Hoyle M, Pavey T, Ciani O, Crathorne L, Jones-Hughes T, Cooper C, Osipenko L, Venkatachalam M, Rudin C, Ukoumunne O, Garside R, Anderson R. Dasatinib, nilotinib and standard dose imatinib for the first-line treatment of chronic myeloid leukaemia: systematic reviews and economic analyses. (2011) University of Exeter (Report for NICE).

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DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

Terms and Definitions

Term	Definition
Allogeneic transplant	A bone marrow or stem cell transplant using marrow from another person.
Basophilia	An excess number of basophils, a rare type of white cell, found in the peripheral blood.
Blast cells	Immature cells found in and produced by the bone marrow. Not normally found in the peripheral blood.
Bone Marrow	The soft substance that fills bone cavities. It is composed of mature and immature blood cells and fat. Red and white blood cells and platelets are formed in the bone marrow.
Bone Marrow Transplant	A procedure where a patient's bone marrow is replaced by healthy bone marrow. The bone marrow to be replaced may be deliberately destroyed by high doses of chemotherapy and/or radiation therapy. The replacement marrow may come from another person, or it may be previously harvested from the patient's own marrow
Chemotherapy	The treatment of a disease by chemicals to destroy cancer cells. Chemotherapy can affect the whole body.
Cytogenetic response	A response to treatment at the level of chromosomal abnormalities. In the case of CML, assessed by counting the number of Ph+ cells in metaphase (usually 20 metaphases are analysed). A complete response generally means no Ph+ cells, a partial response leaves up to 35% Ph+ cells evident and with a minor response from 35% to 95% Ph+ cells are still evident
Cytopenia	A reduction in the number of cells circulating in the blood.
EQ-5D	A European quality of life questionnaire containing five physical and psychological dimensions
Extramedullary disease	Disease occurring outside the bone marrow.
Haematological response	A haematological response refers to the normalisation of blood cell counts. CML causes over proliferation of WBCs which treatments aims to lower and categories of response indicate the extent to which this occurs. Typically, the haematological response is classified as complete if WBC <10 x 109/l, platelets <450 109/l, no immature cells in the peripheral blood with normal differential count, and disappearance of symptoms and signs
Hydroxyurea	A drug used in the treatment of CML which inhibits DNA synthesis
Incremental cost-effectiveness ratio	Demonstrates the total additional cost per QALY gained of one alternative over another. There is no particular point at which an alternative is said to be "cost-effective" as this will be a policy decision. The larger the incremental cost-effectiveness ratio the less likely it is to be cost-effective.
Interferon-α	Interferon is a protein derived from human cells. It has a role in fighting viral infections by preventing virus multiplication in cells. IFN-α (alpha) is made by leucocytes. It is often used as first line therapy in CML.
Kaplan-Meier estimator	Also known as the product limit estimator, is an estimator for estimating the survival function from life-time data. In medical research, it is often used to measure the fraction of patients living for a certain amount of time after treatment
Landmark analysis	A form of survival analysis where only patients who have survived a specified period of time are included.
Leukocytes	White blood cells which are responsible for fighting infections.
Leukopheresis	A process of removing excess white blood cells from the peripheral blood.
Leukopenia	A reduced number of white cells in the blood – it may affect a single cell type or all white cells.

Metaphase	The second phase of mitosis (cell division). Cells in this phase of division are used for cytogenetic analysis in CML to identify the proportion of Ph+ chromosomes
Mitosis	A division of cells which consists of four phases - prophase, metaphase, anaphase and telophase.
Myelocytes	Committed progenitor cells produced by, and found in, the bone marrow which develop into mature leukocytes.
Neutropenia	A decrease in neutrophils (white blood cells) circulating on the blood.
Neutrophil	The most common type of white blood cell in humans and mammals (also known as neutrophil granulocytes)
Oncogene	A gene that has the potential to cause cancer
Peripheral blood	In this report, peripheral blood refers to blood in the circulatory system
Platelet	Small fragments of cells found in the blood which help to form clots and control bleeding (also called Thrombocytes)
Promyelocytes	Committed progenitor cells produced by and found in the bone marrow which develop into myelocytes.
Stem cells	Very early progenitor cells which divide and mature to become all the types of cells which make up the blood and immune system.
Thrombocytes	Platelets (fragments of bone marrow cells) found in the blood which help to form clots and control bleeding.
Thrombopenia	A reduced number of thrombocytes (platelets) in the blood.
Toxicity	The quality of being poisonous. The National Cancer Institute (NCI) grade toxicity levels of treatments as 1 – mild, 2 – moderate, 3 – severe and 4 – life-threatening.
Tyrosine kinase	An enzymatic protein which adds phosphate residues to other proteins in the cell. In CML the abnormal tyrosine kinase, BCR-ABL, phosphorylates proteins which cause cellular proliferation.
Weibull distribution	A continuous probability distribution usually used in survival analysis

List of Abbreviations

Abbreviation	In full
ABL	Abelson oncogene
AE	Adverse event
AlloHSCT	Allogenic haematopoietic stem cell transplant
AP	Accelerated phase
BCR	Breakpoint cluster region
BCR-ABL	Oncogene fusion protein consisting of BCR and ABL
BMS	Bristol Myers Squibb
BNF	British National Formulary
BC	Blast crisis
CCyR	Complete cytogenetic response
CHR	Complete haematological response
CI	Confidence interval
CML	Chronic myeloid leukaemia
CP-CML	Chronic myeloid leukaemia in chronic phase
CMR	Complete molecular response
CP	Chronic phase
CRD	Centre for Reviews and Dissemination
CCyR	Complete cytogenetic response
CyR	Cytogenetic response
ECOG	European Cooperative Oncology Group
EFS	Event free survival
EMEA	European Medicines Agency
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridisation (FISH)
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRQoL	Heath related quality of life
ICER	Incremental cost-effectiveness ratio
IFN	Interferon
IFN-α	Interferon-alpha
IRIS	International Randomised Study of Interferon versus STI571
ITT	Intention to treat
MCyR	Major cytogenetic response
mg	Milligrams
MIMS	Monthly Index of Medical Specialities
MHR	Major haematological response
MMR	Major molecular response
NHS	National Health Service
NICE	National Institute of Clinical Excellence
OS	Overall survival
PAS	Patient Access Scheme
PCR	Polymerase chain reaction
PE	Pleural effusion
PFS	Progression-free survival
Ph-	Philadelphia negative cell
Ph+	Philadelphia positive cell
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS	Personal social services
QALY	Quality adjusted life year
QoL	Quality of life

qPCR	Real time quantitative polymerase chain reaction
QT	In cardiology, the time between the start of the Q wave and the end of the T wave of a heart's electrical cycle
QTc	Same as the QT interval (above) but corrected for the person's heart rate
RCT	Randomised clinical trial
RR	Relative risk
RT-PCR	Reverse transcriptase polymerase chain reaction
SCT	Stem cell transplantation
SD	Standard deviation
SE	Standard error
TKI	Tyrosine kinase inhibitor
WBC	White blood cell
WHO	World Health Organisation

1. SUMMARY

1.1. Background

Chronic myeloid leukaemia is one of the blood cancers in which there is an overproduction of one type of white blood cell, the granulocytes, by the bone marrow. The typical chronic myeloid leukaemia progression course has three phases: the chronic phase, the accelerated phase and the blast crisis phase. The molecular characteristic of chronic myeloid leukaemia is the presence of an acquired BCR-ABL fusion gene in multi-potent stem cells. More than 90% of people diagnosed with chronic myeloid leukaemia have an acquired (non-inherited) chromosomal abnormality, and are said to be Philadelphia chromosome positive.

Chronic myeloid leukaemia is diagnosed by the presence of a characteristic pattern of cells in the blood and bone marrow in conjunction with specific cytogenetic and molecular abnormalities. At presentation, patients typically have an enlarged spleen and a raised white blood cell count, with higher than normal numbers of immature white blood cells. Bone marrow biopsy typically shows very little fat present and the bone marrow space occupied entirely with large numbers of leukaemia cells.

An estimated 530 cases of chronic myeloid leukaemia are newly diagnosed in the UK each year. Approximately 60% of those diagnosed with chronic myeloid leukaemia are male. Chronic myeloid leukaemia occurs in all age groups, although it is uncommon in those below the age of 30; the mean age at diagnosis is 57 years.

Disease monitoring plays a key role in assessing response to therapy and detecting early relapse. Several measures of disease status are used for monitoring; blood counts (haematological response), the proportion of Philadelphia chromosomes in bone marrow aspirate (cytogenetic response) and the presence (or absence) and number of BCR-ABL transcripts in peripheral blood and bone marrow (molecular response).

Currently, the only known curative treatment for chronic myeloid leukaemia is allogeneic haematopoietic stem cell transplantation, either from a matched related or unrelated donor. With the advent of a new class of drugs for the treatment of chronic myeloid leukaemia, known as tyrosine kinase inhibitors, with imatinib being the first, the natural history of the disease has been markedly changed. Current evidence suggests that patients whose disease responds favourably to treatment with imatinib may remain essentially symptom-free for at

least 10 years. UK guidelines recommend imatinib as a 1st-line treatment for chronic myeloid leukaemia in the chronic phase.

Nilotinib and dasatinib were initially developed for the treatment of patients resistant or intolerant to imatinib, and were selected due to their potency and activity against mutated forms of BCR-ABL1. Nilotinib and dasatinib are now being considered as alternative treatments to imatinib as a 1st-line treatment.

1.1.1. Recent draft guidance FAD for 2nd-line CML treatment

The whole of this technology assessment report has been prepared in the context of changing draft guidance about the use of the same drugs for 2nd-line treatment of CML after imatinib as 1st-line treatment. In the draft guidance on 18th August 2011, NICE has recommended nilotinib, for the treatment of the chronic and accelerated phases of CML (chronic myeloid leukaemia) that is resistant or intolerant to standard-dose imatinib. Dasatinib and high-dose imatinib, are not recommended in the draft guidance. Consultees have the opportunity to appeal against the draft guidance. Until NICE issues final guidance, NHS bodies should make decisions locally on the funding of specific treatments. This draft guidance does not mean that people currently taking dasatinib or high-dose imatinib will stop receiving them. They have the option to continue treatment until they and their clinicians consider it appropriate to stop.

1.2. Objectives

This technology assessment reviews the available evidence for the clinical and cost-effectiveness of dasatinib, nilotinib and standard dose imatinib for the 1st-line treatment of Philadelphia chromosome positive chronic myeloid leukaemia according to their marketing authorisation. The assessment draws on relevant evidence to determine what, if any, is the clinical and cost-effectiveness of the interventions compared to each other as 1st-line treatment in the chronic phase.

The questions addressed are:

In chronic phase

- What is the clinical effectiveness of 1st-line treatment for newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia with dasatinib or with nilotinib or with imatinib (standard dose), using each of the three treatments as comparators?
- What is the cost-effectiveness of 1st-line treatment for newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia with dasatinib or with nilotinib or with imatinib (standard dose), using each of the three treatments as comparators?

1.3. Methods

The assessment comprises a systematic review of clinical and cost-effectiveness studies, a review and critique of manufacturer submissions and a *de novo* economic analysis.

1.4. Clinical effectiveness methods

1.4.1. Clinical effectiveness systematic review

For the assessment of effectiveness, a literature search was conducted in a range of electronic databases including MEDLINE, EMBASE and the Cochrane Library (2002- May 2011)

Studies were included if they were of:

- Randomised controlled trials or systematic reviews of randomised controlled trials
- Adults with chronic phase chronic myeloid leukaemia, naïve to any treatment specifically directed against CML
- Interventions: dasatinib, nilotinib or imatinib (standard dose)
- Comparators: imatinib or nilotinib where the intervention is dasatinib; imatinib or dasatinib where the intervention is nilotinib; dasatinib or nilotinib, where the intervention is standard dose imatinib

All steps in the review (screening, data extraction, quality appraisal) were performed by one main reviewer and checked independently by a second. Quality was assessed using criteria specified by the Centre for Reviews and Dissemination. Synthesis was narrative apart from an indirect treatment comparison to estimate the relative effectiveness of nilotinib and dasatinib.

1.4.2. Surrogate outcomes systematic review

Due to the lack of long-term follow-up in the identified trials, the potential impact of surrogate outcomes on survival or progression-free survival is particularly important. We therefore conducted a review of the evidence for complete cytogenetic response and major molecular response as markers for long term outcomes such as survival. For the surrogate outcomes review, the literature search procedures were the same as the clinical effectiveness review except, study design was extended to any observational or experimental study that reported the association between complete cytogenetic response and/or major molecular response and any one of the final patient-relevant outcomes (progression free survival; overall survival; health related quality of life).

For each study, levels of overall survival and progression free survival were extracted by level of cytogenetic or molecular response at each year following trial recruitment (or randomisation) up to the latest follow up point reported. At each point in time, a pooled weighted (for study size) and unweighted mean (and standard error) of overall survival and progression free survival for responder and non-responder strata was calculated. The difference between the mean estimate overall survival and progression free survival in the responder and not responder group was tested using parametric (paired t-test) and non-parametric (Wilcoxon) approaches at $p \leq 0.05$ level of statistical significance.

1.5. Clinical Effectiveness: Results

1.5.1. Number and quality of clinical effectiveness studies

The searches identified 3,228 titles and abstracts. Two clinical trials (dasatinib vs imatinib and nilotinib vs imatinib), with each providing supplementary data via conference abstracts and conference presentations, were included. No direct comparisons of dasatinib vs nilotinib were identified. Overall, the quality of both studies was considered good.

1.5.2. Summary of benefits and risks

Survival (event-free, progression-free and overall) was not significantly different for dasatinib or nilotinib compared to imatinib with the 24-month follow-up data available.

For the 1st-line treatment of adults with newly diagnosed chronic myeloid leukaemia, both dasatinib and nilotinib appear to have a statistically significant advantage over imatinib for response outcomes.

The rates of **complete cytogenetic response** (CCyR) and **major molecular response** (MMR) were higher for patients receiving **dasatinib** compared with **imatinib** at 12-months follow-up (CCyR: 83% vs 72%, $p < 0.001$; MMR: 46% vs 28%, $p < 0.0001$). The significant difference remained for MMR at 18-months follow-up (56% vs 37%, $p < 0.001$). At 12-months follow-up the time to a CCyR and MMR was significantly shorter for dasatinib compared to imatinib (CCyR, 3.1 months vs 5.6 months; MMR, 6.3 months vs 9.2 months). At 18-months and 24-months follow-up, patients receiving dasatinib were still significantly more likely to achieve a CCyR and MMR.

The rates of **complete cytogenetic response** and **major molecular response** were higher for patients receiving **nilotinib** compared with **imatinib** at 12-months follow-up (CCyR; 80% vs 65%, $p < 0.001$; MMR: 44% vs 22%, $p < 0.0001$). At 24-months follow-up nilotinib continued to be significantly superior compared to imatinib (CCyR: 87% vs 77%, $p < 0.001$; MMR: 62% vs 37%, $p < 0.001$). The median time to MMR was significantly shorter ($p < 0.0001$) for patients receiving nilotinib (8.6 months, 95% CI 8.3-11.1) compared to patients receiving imatinib (11.1 months, 95% CI 8.5-13.6).

All three drugs were well tolerated with discontinuation due to adverse events < 10% (after 24-months). Adverse event data (24-months) showed a higher rate of pleural effusion for patients receiving **dasatinib** (14%) compared with imatinib (0%), with twice as many grade 3/4 thrombocytopenia events for dasatinib (20%) compared to imatinib (11%). Non-haematalogical events generally appeared lower for dasatinib compared with imatinib, including fluid retention, superficial oedema, rash, vomiting, nausea and myalgia.

Haematological events across all grades were lower for patients receiving **nilotinib** compared to imatinib. For non-haematological events, nausea, diarrhoea, vomiting and muscle spasms events were up to three times higher for patients receiving imatinib compared to nilotinib

across all grades. Conversely rash, headache, pruritius and alopecia events were up to three times higher with nilotinib 300mg compared with imatinib across all grades. The FDA has stipulated that nilotinib should carry a 'black box' warning for possible heart problems due to QTc prolongation, that may lead to an irregular heart beat and possibly sudden death.

With no head to head trials comparing dasatinib and nilotinib, an indirect comparison was carried out, which showed no difference between dasatinib and nilotinib for complete cytogenetic response or major molecular response rates at 12-months follow-up (CCyR: odds ratio 1.09, 95% CI 0.61 – 1.92; MMR: odds ratio 1.28 95% CI 0.77 – 2.16).

1.5.3. Summary of surrogate outcomes review

This assessment identified evidence of the association between cytogenetic response and molecular response, and survival in patients treated with a tyrosine kinase inhibitor for chronic phase chronic myeloid leukaemia from the imatinib arms of three cohort studies and two randomised controlled trials. No evidence from dasatinib or nilotinib studies were identified.

These studies consistently show that patients who experience either a complete cytogenetic response or major molecular response following 12 months imatinib treatment have better long-term (5-year) overall survival (CCyR: 97.4% vs 74.1%; MMR: 96.6% vs 91.2%) and progression free survival (CCyR: 96.8% vs 75.2%; MMR: 95.8% vs 89%) than patients who are non-responders at 12-months. However, these differences were not shown to be statistically significant. This may be because we only had study level data, rather than individual patient level data.

There is observational association (level 2) evidence supporting the use of complete cytogenetic response and major molecular response at 12 months as surrogates for overall all-cause survival and progression-free survival in chronic myeloid leukaemia patients in chronic phase. This evidence is based entirely on imatinib treatment studies and thus the generalisation of these results to the other tyrosine kinase inhibitors, dasatinib and nilotinib, must be carefully considered.

1.6. Cost-effectiveness: Methods

1.6.1. Cost-effectiveness systematic review

For the cost-effectiveness review, the inclusion and exclusion criteria were the same as for the clinical effectiveness review, excepting study design where full cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses and cost-consequence analyses were included.

1.6.2. Appraisal of manufacturers' submissions

The cost-effectiveness analyses reported in the manufacturers' submissions to NICE were critically appraised using established frameworks, including the NICE reference case.

Two manufacturers' submissions were available for this appraisal. Bristol-Myers Squibb (the manufacturer of dasatinib) and Novartis (manufacturer of nilotinib and imatinib) both provided a full economic model, although using quite different approaches for extrapolating survival and estimating costs and QALYs beyond the short time horizon of the main trials. In addition, some of the assumed treatment sequences following failure of 1st line TKIs – in particular those involving dasatinib as 2nd line treatment - may now be less relevant (following NICE's recent draft guidance FAD that nilotinib but neither dasatinib nor high-dose imatinib should be used for such patients; the draft guidance FAD for 2nd line CML for high-dose imatinib, dasatinib and nilotinib, is available on the NICE website at http://guidance.nice.org.uk/TA/WaveR/99).

1.6.3. PenTAG cost-effectiveness analysis: methods

Our cost-effectiveness modelling attempted to provide a range of scenario analyses to reflect the significant structural uncertainty and related different approaches to estimating overall survival. We used:

1. A Cumulative Survival approach, in which overall survival is the cumulative result of the time on 1st- 2nd- and (where relevant) 3rd line treatments, plus time in accelerated (AP) and blast crisis (BC) phases. This is similar to the modelling approach used in the Novartis submission for nilotinib.

2. A Surrogate Survival approach, in which overall survival is estimated from 12-month CCyR and MMR response rates from the two key trials (ENESTnd and DASISION)

combined with the relationship of these surrogate outcomes to longer term survival. This was based on our systematic review of such relationships in trials and observational studies of imatinib. This is similar to the broad modelling approach adopted in the BMS submission for dasatinib, but with different assumptions to determine times in the intervening disease states.

The model structure was a state-transition model which accounted for costs and QALYs during the following possible disease or treatment states in the chronic phase: 1st line TKI, 2nd-line TKI, 2nd or 3rd line stem cell transplant, and 2nd or 3rd line hydroxyurea (HU). Advanced phase CML, always after some time on HU in chronic phase, comprised the accelerated phase (AP) followed by blast crisis (BC).

The model cycle length is three months, and the model time horizon is 50 years, or age 107, at which, time all people have died. Future costs and benefits are discounted at 3.5% per annum, and the perspective is that of the NHS and Personal Social Services.

Because of the considerable variability, importance and uncertainty surrounding treatment pathways and disease progression post-TKIs, we also generated some scenario analyses using a Simplified Method, in which the per person costs and QALYs after treatment with TKIs were set to be equal across the treatment arms.

Under the Cumulative Survival approach, time to treatment discontinuation was extrapolated using trial data for time on TKI treatment (1st or 2nd line) and the fitting of Weibull curves. Time on treatment with hydroxyurea was estimated first by estimating overall survival following hydroxyurea in chronic CML, and then calculating the constant transition probabilities between chronic phase and AP, AP and BC, and BC and death that would achieve the same overall survival (and given mean duration in AP and BC of 9.6 and 6 months).

Under the Surrogate Survival approach (which was used only in scenarios where TKIs were not used as 2nd-line treatment), overall survival was predicted from the meta-analysis of either CCyR or MMR at 12 months, and the proportions in the relevant two trials who achieved these responses. These extrapolations adjusted for non-CML related mortality and made use of historical data from imatinib trials.

Costs while being treated with TKIs include: drug acquisition costs (adjusted for dose intensity), the cost of treating the main serious adverse events during the first year of treatment (neutropenia, thrombocytopenia, and anaemia), and the estimated costs of medical management (monitoring visits and tests). These were based on a mixture of trial data (adverse event rates) and a recent unpublished survey of six CML clinicians (conducted by Oxford Outcomes consultancy for BMS).

The cost of stem cell transplant (SCT) was based on a 2009 estimation of these costs by the London Specialised Commissioning Group supplemented by data and expert advice from other sources, and included both an initial (i.e. one-off) transplant procedure cost, plus ongoing costs for monitoring and treatment of chronic complications. The cost for chronic phase patients who have failed TKIs but not received a SCT assumed drug treatment costs of hydroxyurea plus the same medical management costs of being on TKIs.

The cost of treatment while in the accelerated or blast phases of CML assumed substantially higher medical management costs (again based on the Oxford Outcomes survey of six CML clinicians) plus hydroxyurea drug treatment (as a proxy for the more varied range of possible treatments in these phases). Also, at death, at the end of the blast crisis, some one-off palliative care costs were included.

Social preference (utility) weights for chronic phase on TKI, chronic phase on hydroxyurea, accelerated phase and blast crisis phase were based on EQ-5D values from patients in the imatinib arm of the IRIS trial. For chronic CML these were age-adjusted to reflect typically decreasing quality of life over time. Patients receiving SCT either reverted to a value slightly below the health related quality of life of the general population (if long-term survivors) or experienced a utility decrement due to the main chronic adverse effects.

1.7. Cost-effectiveness: findings and results

1.7.1. Summary of economic evaluations

Our literature search did not identify any published full economic evaluations meeting the inclusion criteria. Although we identified five potentially relevant conference abstracts of economic studies, there is insufficient detail in the abstracts to undertake a critical appraisal of the methods used, and full papers or reports were not provided by the contact authors.

1.7.2. Industry submissions

Dasatinib

Bristol-Myers Squibb use a 'time in state' (area under the curve) model extrapolating chronic myeloid leukaemia related survival and progression free survival data for dasatinib compared to imatinib and nilotinib.

The base case analysis produces ICERs of:

- £26,000 per QALY for dasatinib in comparison to imatinib as 1st-line tyrosine kinase inhibitor, and
- £145,000 per QALY for nilotinib in comparison to dasatinib (nilotinib more QALYs at greater cost than dasatinib) as a 1st-line tyrosine kinase inhibitor.
- The sensitivity analysis shows the key parameters to which the model is sensitive: drug costs, overall survival, and the cost of stem cell transplant.

The Bristol Myers-Squibb model contained a number of formula errors. After correcting for these errors it predicts ICERs of:

- £36,000 per QALY for 1st-line dasatinib compared to 1st-line imatinib, and
- £103,000 per QALY for dasatinib compared to nilotinib (dasatinib more QALYs at greater cost than nilotinib).

In the original model the cost of nilotinib used by Bristol Myers-Squibb does not account for the Patient Access Scheme discount applied to nilotinib.

[redacted]

Including this change, the Bristol Myers-Squibb model predicts an ICER of £46,000 per QALY for dasatinib compared to imatinib. When comparing dasatinib to nilotinib, the model predicts that nilotinib is more effective and less costly. However, it is acknowledged that BMS were unable to account for the discount as did not have knowledge of the PAS discount at the time of their submission.

Further, BMS assume that dasatinib is taken in combination with other drugs as a 3rd-line treatment during the advanced phase in all treatment arms. However, in the NICE draft guidance FAD for 2nd-line CML treatment it was commented that this is not evidence-based (the draft guidance FAD for 2nd line CML for high-dose imatinib, dasatinib and nilotinib, is available on the NICE website at http://guidance.nice.org.uk/TA/WaveR/99). When the BMS model is adjusted so that dasatinib is not taken 3rd-line, the ICER of dasatinib vs. imatinib increases further, from £46,000 to £64,000 per QALY, and nilotinib is still more effective and less costly than dasatinib.

Finally, BMS assume that half of all patients in the imatinib and nilotinib treatment arms take dasatinib as 2nd-line treatment. In the NICE draft guidance FAD, dasatinib was not recommended for 2nd-line CML treatment (the draft guidance FAD for 2nd line CML for high-dose imatinib, dasatinib and nilotinib, is available on the NICE website at http://guidance.nice.org.uk/TA/WaveR/99). When the BMS model is adjusted so that dasatinib is not taken 2nd-line, and instead when we assume that all 2nd-line patients in the imatinib arm take nilotinib 2nd-line, the ICER of dasatinib vs. imatinib increases further, from £64,000 to £96,000 per QALY. There appears to be no simple way to adjust BMS' model to disallow patients taking dasatinib 2nd-line.

In summary, BMS' adjusted model yields an ICER for dasatinib vs. imatinib of £96,000 per QALY. Further, nilotinib is more effective and less costly than dasatinib.

Nilotinib

Novartis use a Markov approach to model the cost-effectiveness of nilotinib compared to the current standard of care (imatinib 400mg daily). This model has nine states. Patients enter the model in the chronic phase. The model estimates when one treatment fails, the patient is switched to an alternative treatment. At the end of each cycle, patients have a probability of remaining on current treatment, progressing to an alternative treatment or dying.

The Novartis model predicts that nilotinib is both more effective and less costly compared to imatinib, when followed by dasatinib as 2nd-line treatment. However, in the NICE draft guidance FAD, dasatinib was not recommended for 2nd-line CML treatment (the draft guidance FAD for 2nd line CML for high-dose imatinib, dasatinib and nilotinib, is available on the NICE website at http://guidance.nice.org.uk/TA/WaveR/99). In a scenario analysis

without dasatinib as 2nd-line treatment, the model predicts an ICER of £6,000 per QALY for nilotinib in comparison to imatinib.

The sensitivity analysis shows the key parameters which the cost-effectiveness results are sensitive to are:

- drug costs (i.e. without Patient Access Scheme), and
- time to discontinuation of 1st-line tyrosine kinase inhibitor.

No major formula errors have been identified in the Novartis model.

1.7.3. PenTAG cost-effectiveness modelling

We present cost-effectiveness results for each of four main "Scenarios". In Scenario 1, we do not model 2nd-line nilotinib. In Scenario 2, again, we do not model 2nd-line nilotinib, but we use the Simplified Method, whereby the post-TKI per-patient costs and QALYs are set to be equal across treatment arms. We believe that this approach is appropriate due to the substantial uncertainty in the type, and associated costs and quality of life of post-TKI treatments. Scenario 3 is the same as Scenario 1, but allowing for 2nd-line nilotinib, which has recently been recommended in the draft guidance FAD by NICE (the draft guidance FAD for 2nd line CML for high-dose imatinib, dasatinib and nilotinib, is available on the NICE website at http://guidance.nice.org.uk/TA/WaveR/99). Similarly, Scenario 4 is the same as Scenario 2, but allowing for 2nd-line nilotinib.

1st-line dasatinib is predicted to provide very poor value for money vs. 1st-line imatinib regardless of the model structure (whether we allow for 2nd-line treatment with nilotinib and regardless of when parameters are varied within plausible ranges); with ICERs of between £262,000 and £460,000 per QALY.

Conversely, the findings for the cost-effectiveness of 1st-line nilotinib vs. 1st-line imatinib are more complex. Assuming 1st-line imatinib is followed by 2nd-line nilotinib (i.e. Scenarios 3 and 4), on nearly all occasions, nilotinib is predicted to yield slightly fewer QALYs (-0.1 or -0.5) at lower cost than imatinib (between £20,600 and £23,900 lower). This is because 1st-line imatinib, but not 1st-line nilotinib, is followed by 2nd-line nilotinib, and the 2nd-line nilotinib extends overall survival. Furthermore, still assuming patients can take 2nd-line nilotinib after imatinib, 1st-line nilotinib almost always provides good value for money versus

imatinib (using the standard threshold of willingness to pay for additional QALYs, but implicitly for a disinvestment relative to current practice). Under these scenarios, the small estimated QALY losses implied by using 1st line nilotinib would yield NHS cost savings of either £213,000 per QALY or £50,000 per QALY. The only occasions when 1st-line nilotinib may represent worse value for money than 1st-line imatinib are when we allow for drug price decreases on patent expiry, and when the dose intensity of 1st-line nilotinib is [redacted] to 100%.

When we assume 1st-line imatinib is not followed by 2nd-line nilotinib (Scenarios 1 and 2), 1st-line nilotinib often lies close to the £30,000 per QALY willingness to pay threshold (with base case ICERs for these two scenarios of £26,000 or £36,000 per QALY). However, 1st-line nilotinib always represents poor value for money relative to the £20,000 per QALY threshold, except when the dose intensity of imatinib is increased from [redacted] to 106% where 106% is Novartis' estimate.

Still assuming 1st-line imatinib is not followed by 2nd-line nilotinib, the following parameters strongly influence the cost-effectiveness of 1st-line nilotinib and whether 1st-line nilotinib is cost-effective at a willingness to pay of £30,000 per QALY;

- Proportion of patients receiving SCT on failure of 1st-line TKI imatinib and nilotinib,
- Treatment duration of 1st-line imatinib and nilotinib,
- Survival after SCT,
- Time on HU in CP after imatinib and nilotinib failure,
- Whether we model CCyR and MMR response rates via surrogate relationships,
- Reduction in the prices of imatinib and nilotinib on patent expiry,
- Dose intensities of imatinib and nilotinib,
- Cost of SCT operation,
- Monthly medical management cost whilst in CP.

We do not conduct and present probabilistic sensitivity analyses because of the unusually large amount of structural uncertainty that is inherent in the present decision problem(s). This

structural uncertainty relates to both the variety of ways in which long-term survival might be estimated, and uncertainty surrounding the possible sequences and mixes of treatments post 1st line TKI failure. As a result, we believe that structural uncertainty would dominate total (structural and parameter) uncertainty, and therefore that if we presented PSAs based just on parameter uncertainty, this would be of little use to the committee and be potentially misleading.

1.8. Discussion

1.8.1. Clinical effectiveness main findings

Only two randomised trials were identified: one of dasatinib vs. imatinib, and one of nilotinib vs imatinib. Both trials had only two years' follow-up. There were no head to head trials of dasatinib vs nilotinib Both dasatinib 100mg (once daily; DASISION trial) and nilotinib 300mg (twice daily; ENESTnd trial) have a statistically significant advantage compared to the first generation tyrosine kinase inhibitor imatinib 400mg (once daily) as measured by cytogenetic or molecular response, however there is insufficient data to assess longer term patient relevant outcomes (progression free survival, overall survival, health related quality of life). Rates of complete cytogenetic response and major molecular response for dasatinib and nilotinib were higher, more rapidly attained, and deeper (molecular response) compared to imatinib. All three drugs were well tolerated with discontinuation due to adverse events < 10%. Indirect comparison analysis showed no difference between dasatinib and nilotinib for the primary outcomes of complete cytogenetic response or major molecular response at 12-months or 24-months follow-up.

There is observational association evidence supporting the use of complete cytogenetic response and major molecular response at 12 months as surrogates for progression free survival and overall survival in chronic phase CML patients. This is based entirely on imatinib treatment studies. There is no evidence about the adequacy of these surrogates for dasatinib and nilotinib as 1st-line therapies. Assuming there is a tyrosine kinase inhibitor class-specific relationship between the surrogate outcomes and the patient-relevant outcomes, these results can be potentially applied to other drugs in the same class, although this has yet to be proven.

1.8.2. Cost-effectiveness main findings

We do not provide a single base case upon which to compare the cost-effectiveness of 1st-line nilotinib, dasatinib and imatinib because our model relies on numerous important assumptions. While there is no clear preference for one scenario over another, only Scenarios 3 and 4 involve nilotinib as a 2nd line treatment. Through these scenario analyses and the deterministic sensitivity analyses we have concentrated on exploring and explaining key structural assumptions in the model.

Of special note are the analyses whereby OS is adjusted to match that experienced in historical trials of imatinib according to whether a CCyR or MMR is achieved. The findings differ according to whether the surrogate relationship is based on CCyR or MMR. Using CCyR substantially improves the cost-effectiveness of 1st-line nilotinib vs. imatinib, whereas the reverse is true when using the MMR surrogate relationship.

We have also presented sensitivity analyses which explore the impact of reduced prices of the TKIs on patent expiry. We believe this is highly relevant to this appraisal, especially given that imatinib will lose patent protection very soon, in the year 2016 (N.B. this is after the currently tabled review date fot this NICE guidance). We do not estimate the likely price cut on patent expiry, but even assuming a modest 25% reduction, the cost-effectiveness of 1st-line nilotinib worsens dramatically. Further still, if we model patients who start 1st-line TKIs in the future, so-called "future incident cohorts", the cost-effectiveness of nilotinib worsens still further.

1.8.3. Comparison of PenTAG with Novartis model results

Scenario 1 in the PenTAG model uses the closest structural assumptions to the Novartis model in which no 2nd-line TKIs are assumed. However the models predict substantially different ICERs for nilotinib vs. imatinib, which span the usually accepted cost-effectiveness thresholds.

- PenTAG ICER £36,000 per QALY
- Novartis ICER £6,000 per QALY

Note that Scenario 1 is only one of our four Scenarios, all with their advantages and disadvantages, and that it does not involve the 2nd line use of TKIs for any of the 1st line treatments.

The difference in cost-effectiveness is explained mostly by the following differences in assumptions in the models. All these differences act to make the cost-effectiveness of nilotinib vs. imatinib worse in the PenTAG model vs. the Novartis model;

- Proportions of patients receiving a SCT as a function of age,
- We assume much longer survival after SCT than Novartis,
- We assume much longer on HU in CP than Novartis,
- We assume a slightly lower dose intensity of imatinib than Novartis,
- We assume much greater medical management costs per patient per unit time whilst on TKIs than Novartis.

We believe that we have a better estimate for the medical management cost per patient per unit time whilst on TKIs. However, whilst we prefer our estimates of the other quantities to the estimates chosen by Novartis, we acknowledge that they are rather uncertain.

1.8.4. Comparison of PenTAG with BMS model results

The only comparison possible between our model and BMS' model relates to our Scenario 3, where we model 2nd-line nilotinib, and using BMS' model corrected for errors and adjusted so that all patients receive nilotinib 2nd-line. We do not attempt a detailed comparison of our results because;

- we presents the results of BMS' model after we have made several corrections and adjustments,

- both models predict that dasatinib is very poor value vs. imatinib, with ICERs of £460,000 per QALY with our model and £95,000 per QALY with BMS' corrected and adjusted model,

- we disagree with BMS' method of estimating OS via a historical surrogate relationship because this relationship does not reflect the use of 2nd-line nilotinib, whereas BMS model 2nd-line nilotinib.

1.8.5. Strengths and limitations of clinical effectiveness systematic review

The strengths of this systematic review are that it was conducted by an independent research team using the latest evidence to a pre-specified protocol. The main limitations were a lack of long term evidence on dasatinib and nilotinib used 1st-line in the populations of interest; the lack of evidence for the use of surrogate outcomes with dasatinib and nilotinib; no head to head trials of dasatinib vs nilotinib.

1.8.6. Strength and limitations of cost-effectiveness systematic review

The strengths of this systematic review are that it was conducted by an independent research team using the latest evidence to a pre-specified protocol. The main limitation was a lack of any studies reporting the cost-effectiveness of dasatinib and nilotinib.

1.8.7. Strengths and limitations of the appraisal of industry submissions

This was conducted by an independent research team using a number of established frameworks to identify strengths and weaknesses.

1.8.8. Strengths and limitations of the PenTAG economic model

1.8.8.1. Strengths

- We have developed a model which is capable of using either a surrogates based estimation of OS, a cumulative treatment duration approach, or a combination of both. It is therefore also more capable of exploring the key differences between the Novartis and BMS models and our modelling assumptions.

- It is based on the best available research evidence, from UK and more recently treated patients wherever available.

- Where research evidence lacking, we have checked key assumptions and parameter inputs with relevant clinical and other experts, or surveys of clinicians where available.

- Good calibration of model survival outputs against IRIS data (imatinib arm only).

1.8.8.2. Limitations

Given that CML is a chronic condition, and that the main two RCTs provide very immature data on progression-free survival, treatment duration and overall survival, the cost-effectiveness estimates of dasatinib and nilotinib are inevitably highly uncertain. The main limitations are therefore:

- Immaturity of empirical trial data relative to life expectancy - forcing either reliance on surrogate relationships or cumulative survival/treatment duration assumptions.

- Overall great uncertainty about the very heterogeneous treatment and care pathways that CML patients may follow - there are very many potential care and disease state paths which might be followed, depending on how different people respond to treatment, their age, disease severity, availability of matched donors (for SCT), mutations which predict responsiveness to 2nd generation TKIs. This includes not modelling complex treatment sequences in advanced disease (e.g. 2nd and 3rd chronic phases, and SCT following disease progression), and not modelling possible cessation of TKIs in those who experience a deep and durable initial response.

- Uncertainty over both which treatment sequences of alternative TKIs are seen as clinically feasible, and what clinical effectiveness (and treatment duration, and dose intensity) would be for some combinations (especially for dasatinib after nilotinib or nilotinib after dasatinib).

- Uncertainty in evidence regarding treatments post-TKI failure in chronic phase: proportion getting SCT; HU as proxy for what in reality would be a range of treatments that might be offered (e.g. IFN and other chemotherapies).

- Also, uncertainty in survival and treatment costs following either SCT or HU.

- Very limited sources of evidence for utility weights, and none available for post TKI failure in chronic phase. Also, no valid and reliable studies were available to reflect possible health related quality of life decrement of being on TKIs but not responding to them. Single source for AP and BC based on very small numbers (n=8 and 15).

- The types and cost of care in AP and BC phases was uncertain. We may have underestimated, but discounting, the fact that we predict similar durations in these states across treatment arms, and other reasons mean that this probably has only a minor impact on the ICERs). Also, with the widespread use of TKIs, the AP phase may in effect not exist for many patients now. Further, more effective treatment regimes in AP or BC may allow 2nd or 3rd chronic phases, or create sufficient recovery for SCT to be reconsidered. Our model does not capture these possibilities.

- For the Surrogate Survival method, we consider only the proportion of patients with a response at 12 months. We do not consider the depth, speed of achieving, and duration of the MMR or CCyR. Given that dasatinib and nilotinib are superior to imatinib in all these respects, and given that the historical surrogate data is based on OS for patients taking imatinib, it is likely that we underestimate OS for dasatinib and nilotinib. We also assume that, for a given response rate, OS is independent of treatment arm.

There is considerable current interest in being able to stop treatment, or reduce dose, in patients who respond very well to treatment and this might be where the benefit of the newer TKIs might be eventually demonstrated. However, it is currently impossible to incorporate these possibilities into the model without more data from relevant ongoing trials.

1.9. Conclusions

From the two trials available, both the second generation TKIs dasatinib and nilotinib have a statistically significant advantage compared to the first generation TKI imatinib 400mg as measured by surrogate outcomes. However, there is insufficient data to assess longer term patient relevant outcomes (e.g. PFS, OS, HRQoL). All three drugs were well tolerated with discontinuation due to adverse events < 10%.

With no head to head data available, an indirect comparison analysis showed no difference between dasatinib and nilotinib for the primary outcomes of CCyR or MMR at 12-months or 24-months follow-up.

Based entirely on imatinib treatment, there is observational association evidence supporting the use of complete cytogenetic response and major molecular response at 12 months as surrogates for OS and PFS in chronic phase CML patients. In the absence of evidence of adequacy of these surrogates for dasatinib and nilotinib, and assuming a TKI class-specific relationship between the surrogate outcomes and the patient-relevant outcomes, these results can be potentially applied to other drugs in the same class.

Taking into account the treatment pathways for chronic myeloid leukaemia patients, i.e. assuming the use of 2nd-line nilotinib, 1st-line nilotinib appears to be more cost-effective compared to 1st-line imatinib for most scenarios. Dasatinib was not cost-effective if decision thresholds of £20,000 per QALY or £30,000 per QALY are used, compared to imatinib and nilotinib.

1.10. Suggested research priorities

- Given the immature stage of trials assessing dasatinib or nilotinib compared to imatinib, longer term follow-up data is required and will be available from the ongoing and currently recruiting trials. As well as the pre-specified clinical outcomes (such as CCyR, MMR, and survival) these should report both treatment duration and dose intensity information for those treated if they are to be useful in estimating the long-term cost-effectiveness of the treatments.

- With no current head to head data for dasatinib and nilotinib, an RCT assessing the two therapies directly or with an additional imatinib arm would be valuable.

- More research-based data for the assessing the predictive usefulness of surrogate outcomes (such as MMR and CCyR) within the chronic myeloid leukaemia population, especially for dasatinib and nilotinib.

- Uncertainty in the cost-effectiveness analysis would be substantially reduced with better and more UK-specific data on: the incidence and cost of stem cell transplant in patients with chronic CML.

- Data on health-related quality of life for people in all stages of CML, and when on different treatments is lacking. Studies should ideally use the EQ-5D or SF-36 generic health related quality of life measures in order to allow social preference weights for the different states to be estimated.

- Research to reflect the whole sequence of CML treatment, as opposed to 'cross-sectionally' at each line of treatment.

2. BACKGROUND

2.1. Description of health problem

Chronic myeloid leukaemia (CML) is one of the blood cancers in which there is an overproduction of one type of white blood cell, the granulocytes, by the bone marrow. The typical CML progression course is triphasic: the chronic phase, the accelerated phase and the blast crisis phase, with the latter two being grouped together as advanced phase.[1]

2.1.1. Molecular mechanism

The molecular characteristic of CML is the presence of an acquired BCR-ABL fusion gene in multi-potent stem cells. More than 90% of people diagnosed with CML have an acquired (non-inherited) chromosomal abnormality caused by a reciprocal translocation between chromosomes 9 and 22 in an individual stem cell. The result is a shortened 22q which is called the Philadelphia chromosome.[2, 3] More specifically, the Abelson oncogene (ABL1) which is located on chromosome 9, translocates to the BCR (breakpoint cluster region) gene on chromosome 22. The result is a fusion gene, BCR-ABL, and its corresponding protein, a constitutively active BCR-ABL tyrosine kinase. BCR-ABL tyrosine kinase is not controlled by normal cellular mechanisms and its presence leads to enhanced cell proliferation, resistance to apoptosis (programmed cell death) and genomic instability. These are key features in the pathophysiology of CML.[4, 5] Within the CML population approximately 10% of people do not have a demonstrable Philadelphia chromosome but have a complex of different translocations that still results in the formation of the BCR-ABL gene and its product.[6]

2.1.2. Diagnosis

CML is diagnosed by the presence of a characteristic pattern of cells in the blood and bone marrow in conjunction with specific cytogenetic and molecular abnormalities.

At presentation, patients typically have an enlarged spleen and a raised white cell count, with higher than normal numbers of immature white blood cells. Bone marrow biopsy typically shows very little fat present and the bone marrow space occupied entirely with large numbers of leukaemia cells.[7]

The presence of the Philadelphia chromosome is important both in terms of diagnosis and for monitoring responses to treatment. It is usually demonstrated by cytogenetic techniques which involve examining bone marrow cells in mitosis under a microscope to allow visualisation of metaphase chromosomes.[8] This test can also identify additional clonal chromosomal abnormalities in Philadelphia positive cells (clonal cytogenetic evolution), which may be important indicators of prognosis. The technique requires at least 20 to 30 bone marrow cells in mitosis which can be difficult to achieve.[9] There are considerable sampling errors because of the relatively small numbers of cells examined and the infrequency of measurement because bone marrow examination is a relatively invasive, though minor, procedure. The sensitivity is approximately 5% if 20 metaphase chromosomes are examined.[6]

Fluorescence *in situ* hybridisation (FISH) is a sensitive and quantitative method used to detect specific chromosomal aberrations, not only in cells undergoing metaphase but in interphase nuclei as well.[6, 10] It uses specific fluorescent probes to map the chromosomal location of genes and identify other genetic abnormalities. In the case of CML, the probe looks for the BCR-ABL fusion gene in bone marrow or peripheral blood cells.[10] This test is usually performed in addition to the conventional cytogenetic test and uses approximately 200 bone marrow or blood cells for interphase FISH.[6] The limit of detection is between 1% and 5% abnormal cells.[6]

Reverse transcriptase polymerase chain reaction (RT-PCR) to detect BCR-ABL transcripts is also sometimes used to provide confirmation of diagnosis in CML. In this technique, the level of BCR-ABL transcripts is measured in peripheral blood or bone marrow and can detect one CML cell in 100,000 normal cells.[6] This qualitative technique is a simplified version of **real time quantitative PCR (qPCR)** which is used to detect and quantify the level of BCR-ABL transcripts in a sample, and can be used to monitor disease progression and molecular response to treatment more closely. All the above diagnostic techniques are currently recommended in the UK for the confirmation of CML diagnosis.[8]

2.1.3. Natural history and clinical presentation

With the advent of a new class of drugs called tyrosine kinase inhibitors (TKI) for the treatment of CML, imatinib being the first (see Section 2.5.1), the natural history of the disease has been markedly changed. Current evidence suggests that patients whose disease

responds favourably to treatment with imatinib may remain essentially symptom-free for at least 10 years.[7] The following paragraphs describe the natural history of the disease in the absence of imatinib treatment.

Traditionally, CML has been regarded as a progressive disease that evolves through three phases. The initial **chronic phase (CP)** during which the disease is stable and slow to progress is followed after a variable interval by progression through an **accelerated phase (AP)** to a rapidly fatal **blast crisis (BC)**. In approximately one third of patients there is no demonstrable accelerated phase with the disease progressing directly from the chronic phase to the blast crisis. Transition between the phases may be gradual or rapid.

Chronic phase

Most people (approximately 90%) with CML are diagnosed during the chronic phase.[1] Symptoms tend to be mild and non-specific and may include tiredness, anaemia, a feeling of 'fullness' or a tender lump on the left side of the abdomen caused by enlargement of the spleen, night sweats and weight loss. Approximately half of patients in the chronic phase are asymptomatic and are diagnosed as a result of a routine blood test.[7]

Hydroxycarbamide can be used to control the white blood count but does not alter the natural history of the disease.[11] In patients treated with hydroxycarbamide, the chronic phase, although variable in length, typically lasts between three and five years, during which time the patient may be well, with stable white blood cell counts.

Accelerated phase

The accelerated phase lasts for six to 24 months during which progression is more rapid. The accelerated phase is associated with increases in the percentage of immature blast cells seen in blood and bone marrow rather than fully differentiated cells.[7] Evidence of cytogenetic abnormalities in addition to the Philadelphia chromosome (clonal evolution; see Table 1 for definition) is also an indication of disease progression.[12] New symptoms such as bruising or bleeding and infections may become apparent together with a worsening of additional symptoms.[13]

Blast crisis

Also known as blastic phase, the blast crisis is usually fatal within three to six months of onset.[7] This phase is characterised by the rapid expansion of a population of differentiation-

arrested blast cells (immature and non-functioning cells). So much of the bone marrow becomes replaced with immature cells that the other blood cells are prevented from functioning. An increased proportion of blast cells are found in blood and bone marrow, and blast cells may also spread to tissues and organs beyond the bone marrow (extramedullary blast involvement). The blast crisis may be associated with significant symptoms including fever, sweats, pain, weight loss, hepato-splenomegaly, enlarged lymph nodes and extramedullary disease.[13-15]

Although the three phases of CML are well-recognised clinically, there are several descriptions of defining criteria available in the literature. Varying definitions have been used in clinical trials. In 2001, the World Health Organisation proposed a new classification system with the intention to refine the criteria for accelerated and blast crisis.[16] The 4th edition of this document was released in October 2008.[17] Table 1 describes the criteria used to define the accelerated and blast crisis recommended by the WHO and those used in a recent single arm clinical study of nilotinib, however the trials in this report and other current single arm studies do not report their criteria.[18-21] The implication is that more stringent criteria may be used in current trials.

Table 1 List of the criteria used to define the accelerated and blast crisis as recommended by the WHO and as used in recent clinical trials

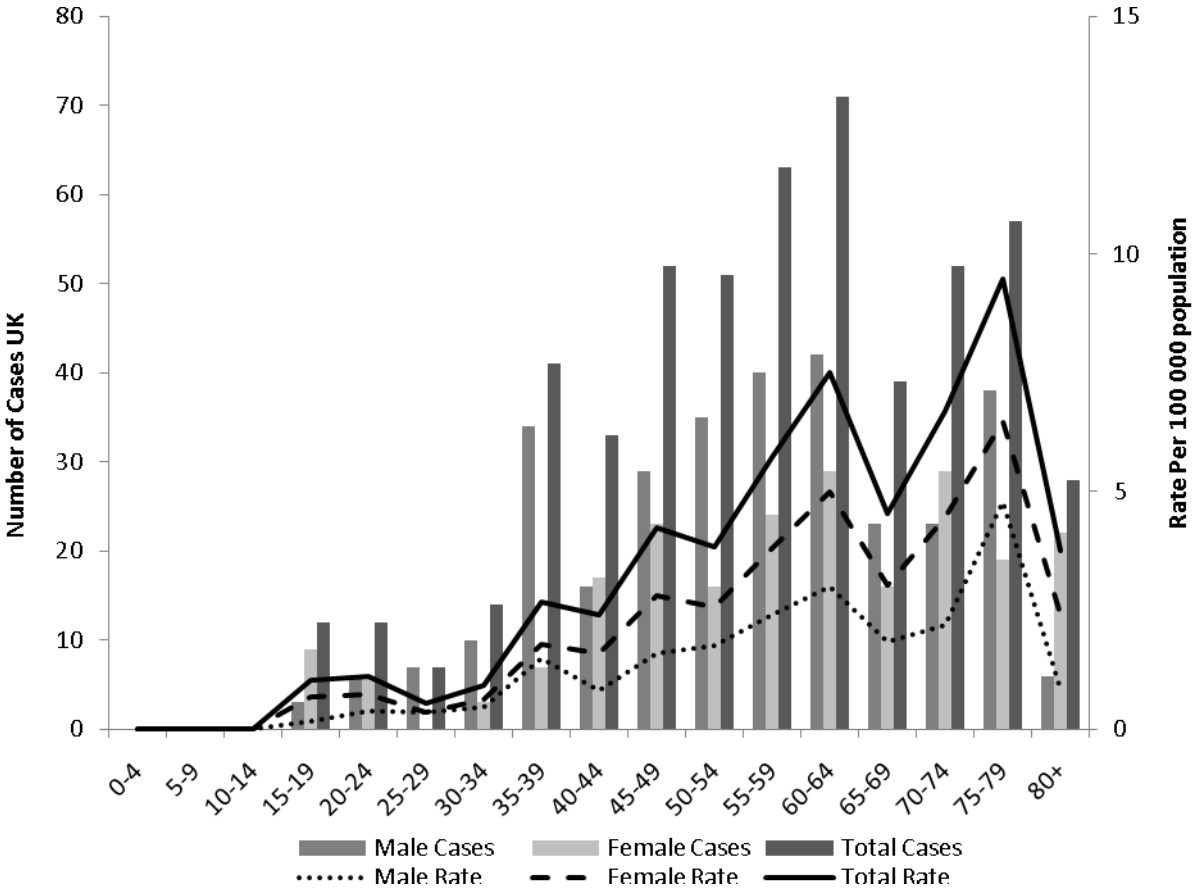
WHO criteria[17]	Criteria used in a recent trials[21]
Accelerated phase	
Blast cells in blood or bone marrow 10% to 19%	Blast cells in blood or bone marrow 15% to 29%; blast cells plus promyelocytes in blood or bone marrow more than 30% with blast cells less than 30%
Basophils in blood 20% or more	Basophils in blood 20% or more
Persistent thrombocytopenia (platelet count less than 100 x 10^9/L) uncontrolled by therapy	Persistent thrombocytopenia (platelet count less than 100 x 10^9/L) unrelated to therapy
Thrombocytosis (platelet count greater than 1000 x 10^9/L) unrelated to therapy	Not included
Increasing spleen size and increasing WBC count unresponsive to therapy	Not included
Cytogenetic evidence of clonal evolution (the appearance of additional genetic abnormalities that were not present at the time of diagnosis	
Blast crisis	
Percentage of blast cells in blood or bone marrow (≥ 20%)	Percentage of blast cells in blood or bone marrow (≥ 30%)
Extramedullary blast proliferation or large foci OR clusters of blasts in the bone marrow biopsy	Extramedullary blast involvement excluding the liver and spleen

2.2. Epidemiology of chronic myeloid leukaemia

2.2.1. Incidence

The Haematological Malignancy Research Network (HMRN) based in Yorkshire estimate that 530 cases of CML are newly diagnosed in the UK each year; an annual age-standardised rate of 1.1 per 100,000 for men and 0.7 per 100,000 for women.[22]

Figure 1 shows the annual estimated incidence of CML in the UK with age and sex distributions. The data are extrapolated from those collected within the HMRN region whose population of 3.7 million is broadly representative of the UK as a whole. Approximately 60% of those diagnosed with CML are male. CML occurs in all age groups, although it is uncommon in those below the age of 30; the median age at diagnosis is 58 years (this includes all phases).[22]



Source: Haematological Malignancy Research Network (www.hmrn.org)

Figure 1 Annual estimated incidence in the UK, by age and sex

2.2.2. Prognosis

There are two prognostic staging scores for CML in common use – the Sokal score[23] and the Euro or Hasford score,[24] details of how the scores are calculated are shown in Table 2. Both scores are used to determine if a patient is at low, intermediate or high risk of death and may also predict response to treatment. Both must be applied at diagnosis, prior to any treatment. The Sokal score is based on age, spleen size and platelet and peripheral blood blast count. The Hasford score also includes data on eosinophil and basophil counts. The level and timing of haematologic, cytogenetic and molecular responses provides important prognostic information and it is widely accepted goal for patients to achieve a complete cytogenetic response (CCyR) within 18 months of CML therapy.[1, 6] Both scores were developed prior to the introduction of tyrosine kinase inhibitors (TKI) (the Hasford score in response to improvements in survival seen with IFN treatment) but they appear to have some value in predicting response to treatment with TKI's.

Table 2 Calculation of prognostic risk scores using the Sokal and Hasford scores

	Calculation using the Sokal score[23]	Calculation using the Hasford score[24]
Age	0.116 x (age – 43.4)	0.666 when age ≥ 50 years
Spleen[a]	0.0345 x (spleen – 7.51)	0.042 x spleen
Platelet count, x 10^9/L	0.188 x [platelet count ÷ 700)^2 – 0.563]	1.0956 when platelet count ≥1500 x 10^9/L
Blood myeloblasts, %	0.0887 x (myeloblasts – 2.10)	0.0584 x myeloblasts
Blood basophils, %	NA	0.20399 when basophils > 3%
Blood eosinophils, %	NA	0.0413 x eosinophils
Relative risk[b]		
Low	< 0.8	≤ 780
Intermediate	0.8 to 1.2	781 to 1480
High	> 1.2	> 1480

Source: Baccarani and colleagues[25]
NA = not applicable
a= centimetres below costal margin, maximum distance
b = Relative risk for the Sokal calculation is expressed as the exponential of the total, the Hasford risk score is expressed as the total x 1000

At the 18 month follow-up of the IRIS trial of imatinib and IFN, 49%, 67% and 76% of people with high, intermediate and low risk Sokal scores respectively had achieved a CCyR.[26] This relationship was maintained at the 48 month update with patients with a high Sokal score having a 69% probability of achieving a complete cytological response compared with 84% and 91% for patients with intermediate and low risk scores respectively.[27] A similar relationship was seen with molecular response at 12 months; 38% of those in the high risk group had a reduction from baseline of at least 3 log in BCR-ABL transcripts as compared with 45% in the intermediate risk group and 66% of those in the low risk group (p=0.007).[28]

The trials in this assessment, ENESTnd and DASISION, use the Sokal and Hasford staging score respectively.[20, 29] The ENESTnd study reported at 12-months, that rates of CCyR for study arms nilotinib (300mg), nilotinib (400mg) and imatinib (400mg) were 74%, 63% and 49% respectively for patients at high risk (Sokal). Rates of major molecular response (MMR) for study arms nilotinib (300mg), nilotinib (400mg) and imatinib (400mg) were 41%, 32% and 17% respectively for patients at high risk (Sokal).

The DASISION study reported at 12-months, that rates of CCyR for study arms dasatinib (100mg) and imatinib (400mg) were 78% and 64% respectively for patients at high risk (Hasford). Rates of MMR for study arms dasatinib (100mg) and imatinib (400mg) were 31% and 16% respectively for patients at high risk (Hasford) (see sections 4.2.3.1 and 4.2.3.2 for full results). Comparability between ENESTnd and DASISION risk score responses should be treated with caution, with between trial differences potentially resulting from the different risk group scoring systems adopted.

2.2.3. Survival

The most recently available survival statistics for all leukaemia in the UK are based on data collected from 2001 to 2007.[30] The five-year relative survival (survival of patients taking into account other causes of death) rate was 39.7% for men and 41.0% for women up to 2006, with a predicted rate of 42.7% for 2007. [30] The predicted ten-year survival rate for 2007 was 33.8% for men and 35.3% for women.[30] With less survival statistics available for CML, the IRIS trial of imatinib (section 2.5.1) reports overall survival at eight-years of 85% for patients receiving imatinib.

Recent analysis of survival amongst CML patients in the United States, derived from the 1973-2006 limited-use database of the Surveillance, Epidemiology and End Results Program of the United States National Cancer Institute suggests a dramatic recent increase in long term survival for people with CML since the introduction of imatinib into routine clinical practice.[31] For all age groups combined, 5-year relative survival increased from 32.5 % in 1990-1992 to 54.6% in 1999-2006 ($p<0.05$). For the period 1999-2006, 5-year relative survival was approximately 78.0% for age groups 15-44 and 45-54, 63% for 55-64, 39.5% for 65-74 and 24.7% for the 75+ age group.[31] There were indications from the data of improvements in long term survival in the older age groups, but long term prognosis remained poor and essentially unchanged for the oldest patients (75+ age group).[31]

2.3. Disease monitoring and treatment response

Disease monitoring plays a key role in assessing response to therapy and detecting early relapse. Several measures of disease status are used for monitoring; blood counts (haematological response), the proportion of Philadelphia chromosomes in bone marrow aspirate (cytogenetic response) and the presence or absence (qualitative molecular response) and number (quantitative molecular response) of BCR-ABL transcripts in peripheral blood and bone marrow using PCR technology. In clinical trials, cytogenetic responses are variously defined as complete, partial, overall, major and minor and the definitions vary according to the phase of the disease in which a patient is diagnosed (Table 3).

The following definitions are commonly used to describe response in chronic disease.

Haematological response

Classification of haematological response varies widely among trials. Hochhaus and colleagues provide a definition of a Complete Haematological Response (CHR) as[32]

(1) White blood cell count no more than the upper limit of normal

(2) Absolute neutrophil count at least 1 x 10^9/L

(3) Platelet count less than 450 x 10^9/L and no more than the institutional upper limit of normal

(4) No blasts or promyelocytes in peripheral blood

(5) Less than 2% basophils in peripheral blood

(6) No extramedullary involvement, with all of these being maintained for four weeks.

Other trials have used variations of this definition including some or all of the elements. The trials in this assessment do not report haematological response.

Cytogenetic response (CyR)

The definition of cytogenetic response appears to be fairly standard across most trials and is split into complete, partial, minor, minimal and none (Table 3). A CCyR is defined as absence of the Philadelphia chromosome among at least 20 cells in metaphase in a bone

marrow aspirate.[32] A commonly used additional term is major cytogenetic response, which encompasses complete and partial.

Table 3 Definition of cytogenetic response

	Percentage of Ph+ chromosomes in metaphase in bone marrow (%)
Complete (major)	None
Partial (major)	1 – 35
Minor	36 – 65
Minimal	66 – 95
None	> 95

Source: Hochhaus and colleagues[32]

Molecular response

In people with a CCyR, quantitative PCR techniques can be used to monitor the level of BCR-ABL transcripts in peripheral blood (and sometimes bone marrow). A complete molecular response (CMR) has been defined as undetectable levels of BCR-ABL in an assay that can detect a reduction from baseline of at least 4.5 logs. An MMR is a standardised BCR-ABL/ABL ratio of less than 0.1% which is equivalent to a 3 log reduction from the 100% baseline for untreated patients.[28, 33]

2.3.1. Surrogate outcomes

In the absence of long-term follow-up, the above measures of treatment response may be regarded as 'surrogate outcomes' for patient-relevant outcomes (overall survival, disease progression, quality of life), with cytogenetic response and molecular response used as the primary outcomes in current trials.[18-21] The use of surrogate outcomes rather than more patient-relevant outcomes may be easier, more economical and provide earlier results.[34] This can lead to faster licensing time and dissemination of new treatments.[35] The use of surrogate outcomes is essential in phase 2 and phase 3 trials aiming to establish a drug's potential benefit.[36] However, the use of surrogate outcomes can also be harmful where there is a lack of an independent causal association between a change in the surrogate outcomes and a change in the patient-relevant outcomes, thus the evaluation and validation of employing a surrogate outcome is warranted.[34-36] The value of surrogate outcomes can be judged against a hierarchy of evidence, which ranges from biologically plausible relationships (weak evidence), to changes in the surrogate corresponding to equal changes in the patient-relevant outcome, assessed by clinical trials (strong evidence).[34, 35]

Schrover and colleagues reported on the development of a predictive survival model for chronic phase CML patients, according to cytogenetic response rates in seven interferon based RCT's. [37] They estimated a weighted odds ratio for the survival of patients who achieved a major cytogenetic response (MCyR) when compared with those who did not of seven (95% CI 5 – 11) at two years and five (95% CI 3 – 8) at four years. Median survival was increased by 1.8 years for every 25 percentage point increase in MCyR rate. The predictive model reported by Schrover and colleagues provides support for cytogenetic response predicting long-term survival within interferon class treatments for chronic phase CML. The evidence for the use of surrogate outcomes within the TKI (imatinib, dasatinib and nilotinib) class of chronic phase CML treatment is unclear, and may not be available particularly for the newer second generation TKIs. Therefore, only imatinib may provide evidence for the use of surrogate outcomes within the TKI drug class (see Chapter 5, p. 101).

2.3.2. Disease progression

Typically, disease progression describes the process in which the disease develops into the accelerated phase or to blast crisis. Differences in the definition of accelerated phase have resulted in the use of more specific definitions of disease progression. The definition of progression used in a trial of this assessment relies on participants meeting any one of the four criteria:[20]

1. Development of accelerated phase or blast crisis CML
2. Loss of complete haematological response
3. Increase in Ph-positive bone marrow metaphases to more than 35%
4. Increasing WBC count (a doubling of white-cell count to more than $20x10^9$ per litre in the absence of complete haematologic response

2.4. Treatment

2.4.1. Allogeneic stem cell transplant

Currently, the only known curative treatment for CML is allogeneic haematopoietic stem cell transplantation (alloHSCT), either from a matched related or unrelated donor.[38, 39] Patient

age, disease phase and duration, the degree of mismatch between patient and donor and therapy before transplantation all influence outcome. Younger patients in chronic phase receiving a transplant from a matched sibling donor soon after diagnosis have the best prognosis.[40] Two studies have shown similar outcomes for transplantation in patients with chronic phase CML using either a fully matched related or unrelated donor, with 5-year survival rates greater than 70% for people aged 50 years and younger who undergo transplantation within a year of diagnosis.[41, 42] Results are less promising for those in accelerated and blast crisis phases.[39]

The morbidity and mortality of alloHSCT is considerable; transplant related mortality ranges from 15-40%.[43]

AlloHSCT is not a treatment option for many people, either for reasons related to age at diagnosis (the median age for diagnosis of CML is 59 years, and many patients are considered to be unsuitable for a transplant at diagnosis) or lack of a suitable donor.[6] UK recommendations propose the use of AlloHSCT with failure of imatinib and or second generation TKIs, or where younger patients have progressed to the advanced phase.[8]

2.5. Medical treatment

UK guidelines (see Section 2.8) recommend imatinib as a 1st-line treatment for CML in the chronic phase.

2.5.1. Imatinib

Imatinib (STI571; trade name Gleevec or Glivec, Novartis) is an orally administered TKI.

2.5.1.1. Pharmacology

Imatinib is a first generation TKI, specifically designed to inhibit the BCR-ABL fusion protein by occupying the ATP-binding pocket of the ABL-kinase domain. This prevents a change in conformation of the protein to the active form of the molecule. By blocking the ATP-binding site, imatinib reduces cell proliferation and stops disease progression. [5]

2.5.1.2. Licensing

In the UK, imatinib is licensed (since 07/11/2001) for the treatment of adults with chronic, accelerated or blast crisis CML. Imatinib has also received approval for this indication by the FDA and EMEA. Imatinib has orphan drug status.

2.5.1.3. Adverse events

The adverse events of imatinib treatment are reported in detail in (Section 4.2.4). The most common serious side effects (seen in more than 1 in 10 patients) are weight increase, headache, nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, oedema, rash, muscle cramps and spasms, fatigue, neutropenia (low white blood cell counts), thrombocytopenia (low blood platelet counts) and anaemia (low red blood cell counts).[44]

2.5.1.4. Dose

For chronic phase patients, the recommended dose for adults is 400mg taken once a day, increased if required to 800mg daily in divided doses. For accelerated or blast crisis the recommended dose is 600mg once daily, increased if required to 800mg daily in divided doses. The dose can be altered based on patient response.[44]

2.5.1.5. Cost

According to the current edition of Monthly Index of Medical Specialities (MIMS) (July 2011), the cost of treatment with imatinib at a dose of 400mg, 600mg and 800mg per day is £57.48, £86.22 and 114.96 respectively.[45] These prices reflect the 7% increase as of April 2011.

2.5.1.6. Efficacy

The efficacy data for imatinib is based on a large open-label, randomised clinical trial (IRIS) in which a total of 1106 people with newly diagnosed, chronic phase CML received either imatinib or interferon-alpha plus low-dose cytarabine.[26] After a median follow-up of 19 months, the estimated rate of a major cytogenetic response at 18 months was 87.1% in the imatinib group and 34.7% in the control group ($p<0.001$). Corresponding figures for a CCyR were 76.2% and 14.5% ($p<0.001$).[26]

Patients who received imatinib continue to be followed up; after a median follow-up of 60 months, Kaplan–Meier estimates of cumulative CCyR rates were 87.0%. An estimated 7% of patients had progressed to accelerated phase CML or blast crisis and the estimated overall survival of patients who received imatinib as initial therapy was 89.0%.[27]

The most recent data from key imatinib trials, at eight years follow-up, reports 55.0% of patients randomised to imatinib remained on treatment. Event free survival (pre-specified event while on therapy, e.g. loss of CHR or CCyR, discontinuation due toxicity, progression to accelerated/blast phase, death) was 81%, no disease progression to accelerated or blast crisis was 92% and overall survival was 85% (93% for CML related deaths only and patients prior to stem-cell transplant).[46] The annual rates of progression to accelerated phase or blast crisis in yr 4 to 8 after initiation of therapy were 0.9%, 0.5%, 0%, 0%, & 0.4%, respectively. However, with the high cross-over rate of the interferon arm, comparison results were not reported.

There are serious limitations in the interpretation of these results as 45% of the patients had abandoned the study by 8 years and patients were censored at the moment of discontinuing the imatinib. This particularly affects those patients who discontinued imatinib due to intolerance and patients who failed to achieve a cytogenetic response and abandoned the study to receive other therapies before having an "event." Consequently, the OS and EFS reported in IRIS are likely to be substantial overestimates. Marin and colleagues report an intention-to-treat analysis in 204 patients treated with imatinib 400 mg/d as 1st-line therapy. [47] In the study, the 5-year probabilities of CCyR, MMR, OS, progression-free survival (PFS), and EFS were similar to the ones reported in the IRIS study. For example, the EFS (defined as in the IRIS study) was 81.3% (confidence interval, 73.0%–87.5%), which is similar to the 83% rate in the IRIS study. However, with EFS redefined to include as "event" those patients who had discontinued imatinib due to toxicity or lack of a cytogenetic response, the recalculated EFS was 62.7%. In other words, the probability of having abandoned the imatinib therapy at 5 years due to toxicity, progression, or unsatisfactory response was 37.3%.

Notwithstanding this, it has been recently shown that patients taking imatinib who achieve a durable CMR can potentially stop treatment without molecular relapse. Mahon and colleagues showed patients with a median of 50 months imatinib therapy had molecular free relapse rates of 41% at 12-months and 38% at 24-months, after discontinuation of imatinib.[48]

The definition of longer term treatment end-points employed by TKI studies will have an impact on perceived differences between trials. Based on 435 early chronic phase CML patients, Kantarjian and colleagues recently showed PFS/EFS rates of 96%, 90%, 89% and 81%, when applying different definitions in the research literature.[49] The definitions are drawn from the researcher own centre, IRIS and the two studies included in this review, DASISION and ENESTnd.[20, 26, 29] It was concluded that uniform definitions of PFS and EFS are needed.

2.6. Description of new interventions

Nilotinib and dasatinib were initially developed for the treatment of patients resistant or intolerant to imatinib, and were selected due to their potency and activity against mutated forms of BCR-ABL1.[50] Nilotinib and dasatinib are now being considered as alternative treatments to imatinib as a 1st-line treatment.

Two phase II trials report efficacy data for nilotinib. Rosti and colleagues reported on 73 chronic phase untreated Ph+ CML patients (nilotinib, 400mg twice daily): 97% showed complete haematologic response, 96% achieved CCyR and 85% achieved a MMR, at 12-months. [21] At three months, 78% achieved CCyR and 52% MMR. Cortes and colleagues reported, of 51 early chronic phase CML patients observed for at least three months (nilotinib, 400mg twice daily), 98% achieved a CCyR, and 76% achieved a MMR.[18] Responses occurred rapidly, with 96% of patients achieving CCyR by 3 months and 98% achieving CCyR by 6 months.

A similar study of dasatinib by Cortes and colleagues reported, on 50 early chronic phase CML patients observed for at least three months (dasatinib, 100mg once daily or 50mg twice daily): 98% achieved a CCyR and 82% achieved a MMR, with 94% of patients achieving CCyR by 6 months.[19]

2.6.1. Dasatinib

Dasatinib (BMS-354825; trade name Sprycel®, Bristol Myers Squibb) is a second generation TKI.

2.6.1.1. Pharmacology

Dasatinib is a highly potent, orally active TKI, which can bind to both the active and inactive conformation of the ABL kinase domain.[6, 51] In vitro, dasatinib is shown to be active against almost all imatinib-resistant BCR-ABL mutations and is 350 times more potent than imatinib.[52, 53]

2.6.1.2. Licensing

Since 2006 the EMEA has approved dasatinib for the treatment of adults with chronic, accelerated or blast crisis CML with resistance or intolerance to prior therapy including imatinib. In December 2010, the EMEA extended the licence for its use as a 1st-line treatment for adults newly diagnosed with chronic phase CML. Dasatinib has also received approval for this indication by the FDA (October 2010). Dasatinib has orphan drug status.

2.6.1.3. Adverse events

The adverse events of dasatinib treatment are reported in detail in (Section 4.2.4). The most common (seen in more than 1 in 10 patients) reported side effects in the trials are headache, pleural effusion, shortness of breath, cough, diarrhoea, nausea, vomiting, abdominal pain, skin rash, musculoskeletal pain, infections, haemorrhage, superficial oedema (swelling), fatigue, fever, neutropenia (low white blood cell counts) and thrombocytopenia (low blood platelet counts), and anaemia (low red blood cell counts).[54] Grade 3 and 4 haematological adverse events in recent trials were approximately 21%, 10-19% and 6-10% for neutropenia, thrombocytopenia and anaemia respectively.[19, 20]

2.6.1.4. Dose

For chronic phase patients, the recommended dose for adults over 18 is 100mg taken once a day, increased if required to 140mg once a day. For accelerated or blast crisis the recommended dose is 140mg once daily, increased if required to 180mg once a day. The dose can be altered based on patient response.[54]

2.6.1.5. Cost

According to the current edition of the BNF (61; 2011), the cost of treatment with dasatinib at a dose of 100mg once a day is £83.50 per day (140mg - £116.90; 180mg – £150.30), and is available as 20, 50, 70 and 100mg tablets[55]

2.6.2. Nilotinib

Nilotinib (AMN107; trade name Tasigna®, Novartis) is a second generation TKI.

2.6.2.1. Pharmacology

Nilotinib is an orally active phenylaminopyrimidine derivative of imatinib and is approximately 10 to 50 times more potent than imatinib at inhibiting BCR-ABL.[56] Studies performed *in vitro* suggest that nilotinib inhibits 32 of 33 mutant BCR-ABL forms resistant to imatinib at physiologically relevant concentrations.[57, 58] Nilotinib, like imatinib, binds to the inactive conformation of ABL, but with a slightly better topographical fit.[15]

2.6.2.2. Licensing

Since 2007, the EMEA has approved nilotinib for the treatment of adults with chronic and accelerated phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib. Nilotinib has not been approved for use in the blast crisis. In September 2010, the EMEA extended the licence for its use as a 1st-line treatment for adults newly diagnosed with chronic phase CML. Nilotinib has also received approval for this indication by the FDA (June 2010). Nilotinib has orphan drug status.

2.6.2.3. Adverse events

The adverse events of nilotinib treatment are reported in detail in (Section 4.2.4). The most common side effects with nilotinib (reported by more than 1 patient in 10) are headache, nausea (feeling sick), constipation, diarrhoea, rash, pruritus (itching), fatigue (tiredness) and increased blood levels of lipase (an enzyme produced by the pancreas) and bilirubin, thrombocytopenia (low blood platelet counts), neutropenia (low white blood cell counts), anaemia (low red blood cell counts).[59] Grade 3 and 4 haematological adverse events in recent trials were approximately 12, 12 and 5% for neutropenia, thrombocytopenia and anaemia respectively.[18, 20] The FDA has stipulated that nilotinib carry a 'black box' warning for

possible heart problems due to QTc prolongation, that may lead to an irregular heart beat and possibly sudden death. Nilotinib has been shown to prolong cardiac ventricular repolarisation, which can result in ventricular tachycardia and death. Nilotinib should not be used in patients who have hypokalemia, hypomagnesemia or long QT syndrome.[60]

2.6.2.4. Dose

In newly diagnosed patients with chronic phase CML, the recommended dose is 300mg twice a day. The recommended starting dose for chronic or accelerated phase CML who do not respond to, or tolerate other treatments, is 400mg twice daily.[59]

2.6.2.5. Cost

According to the current edition of MIMS (July 2011) and BNF (61; 2011), the cost of nilotinib £86.89 per day at a twice daily dose of 300mg (150 mg tablets) and 400mg (200 mg tablets.[61, 62]

[redacted]

2.7. Quality of life (QoL)

Assessment of health related quality of life (HRQoL) has become an important feature of cancer trials, enabling evaluation of treatment effectiveness from the perspective of the person with the condition and facilitating improved clinical decision making.

There are several general HRQoL instruments for people with cancer that can be used to assess quality of life both in research studies and in clinical practice e.g. the Functional Assessment of Cancer Therapy scale and the European Organisation for Research and Treatment of Cancer QLQC-30. Disease specific instruments for CML appear not to have been widely used in clinical trials.

A recent systematic review of HRQoL in CML highlighted the relative paucity of research and methodological shortcomings in this area.[63] Only one study identified, addressed the effect of a TKI on QoL, with imatinib shown to be superior compared to interferon in terms of HRQoL, but was only measured in the first year of treatment.[64] The review concluded that monitoring of HRQoL and side effects of CML treatment from the patient's perspective will

be of importance to determine the net clinical benefit of new therapies.[63] Assessment of QoL in CML is further discussed in Section 4.2.5.

2.8. Current service provision

In 2009, the European LeukaemiaNet recommend in the chronic phase, imatinib 400mg daily as a 1st-line treatment for all patients, with dasatinib, nilotinib or higher dose imatinib as 2nd-line treatment. 3rd-line treatment is continued dasatinib or nilotinib with an option for alloHSCT, and alloHSCT after dasatinib or nilotinib failure.[50] In 2007, the British Committee for Standards in Haematology also recommend imatinib daily as a 1st-line treatment for all patients, with higher dose imatinib or dasatinib and potentially nilotinib as 2nd-line treatments.[8] These guidelines are due to be updated July 2012. NICE guidance on chronic myeloid leukaemia (TA70-2003) recommends imatinib for the 1st-line treatment of adults with the Philadelphia-chromosome type of CML in the chronic phase.

2.9. Current use of new interventions in the NHS

Anecdotal evidence suggests that dasatinib and nilotinib are currently widely used in the NHS in England and Wales following failure of treatment with imatinib. NICE has recently provided guidance on the use of nilotinib or dasatinib as 2nd-line treatment of chronic myeloid leukaemia. In the draft guidance on 18th August 2011, NICE has recommended nilotinib, for the treatment of the chronic and accelerated phases of CML (chronic myeloid leukaemia) that is resistant or intolerant to standard-dose imatinib. Dasatinib and high-dose imatinib, are not recommended in the draft guidance. Consultees have the opportunity to appeal against the draft guidance. Until NICE issues final guidance, NHS bodies should make decisions locally on the funding of specific treatments. This draft guidance does not mean that people currently taking dasatinib or high-dose imatinib will stop receiving them. They have the option to continue treatment until they and their clinicians consider it appropriate to stop.

3. DEFINITION OF THE DECISION PROBLEM

The purpose of this technology assessment report is to assess the clinical and cost-effectiveness of dasatinib, nilotinib and imatinib (standard dose) for the first-line treatment of chronic myeloid leukaemia. Decision modelling to estimate the cost-effectiveness of alternative ways of using health technologies should start with a clearly defined decision problem.

3.1. Decision problem

A decision problem comprises a clear definition of (i) the targeted patient population and health problem, (ii) the alternative treatment pathways to which they might be exposed, (iii) and the main outcomes against which those pathways will be compared.

3.1.1. Interventions and comparators

Table 4 below shows the three treatment pathways that will be evaluated using the decision model, assuming that 2nd line use of TKIs is or is not available within the NHS. For a description of how these admittedly simplified treatment sequences were arrived at, please see the cost-effectiveness analysis methods (Section 8.1, p. 135).

Table 4 Treatment pathways to be compared by the decision model

Treatment pathways to be compared by the decision model, without 2nd line use of TKIs (Scenarios 1 & 2)

	Initial ('1st line') treatment	2nd line treatment in chronic phase (if 1st line fails/intolerant)	Treatment in accelerated phase or blast crisis
1	Dasatinib, 100mg (or 140mg if required) once daily	EITHER stem cell transplant OR Hydroxyurea	Hydroxyurea + medical management
2	Nilotinib, 300mg twice daily	EITHER stem cell transplant OR Hydroxyurea	Hydroxyurea + medical management
3	Imatinib, 400mg once daily	EITHER stem cell transplant OR Hydroxyurea	Hydroxyurea + medical management

Treatment pathways to be compared by the decision model, with nilotinib available as 2nd line treatment (Scenarios 3 & 4)

	Initial ('1st line') treatment	2nd line treatment in chronic phase (if 1st line fails/intolerant)	3rd line treatment in chronic phase (if 2nd line fails)	Treatment in accelerated phase or blast crisis
1	Dasatinib, 100mg (or 140mg if required) once daily	Nilotinib 400mg twice daily	EITHER stem cell transplant OR Hydroxyurea	*Hydroxyurea + medical management*
2	Nilotinib, 300mg twice daily	EITHER stem cell transplant OR Hydroxyurea	*Not applicable*	*Hydroxyurea + medical management*
3	Imatinib, 400mg once daily	Nilotinib 400mg twice daily	EITHER stem cell transplant OR Hydroxyurea	*Hydroxyurea + medical management*

Apart from those relating to cytogenetic or molecular response at 12 months, no important and statistically significant sub-group differences emerged in the clinical effectiveness evidence.

3.1.2. Population

Adults with newly diagnosed, chronic phase, Philadelphia chromosome positive CML. If possible newly diagnosed, chronic phase CML without genetic mutation (non-Philadelphia chromosome) will also be considered. In reality, for consistency, the patient population modelled will have to closely mirror the populations in the main trials from which the effectiveness estimates are derived.

3.1.3. Outcomes

The main outcomes that will determine the development of the decision model are:

- Life-time quality-adjusted life-years
- Life-time care costs (NHS & PSS)

However, the modelling may also usefully estimate the following outcomes in the short- or long-term:

- Progression-free survival
- Time to progression
- Overall survival
- Response rates – cytogenetic, molecular and haematological
- Time to treatment failure
- Adverse effects of treatment

3.2. Overall aims and objectives of assessment

This technology assessment reviews the available evidence for the clinical and cost-effectiveness of Dasatinib, Nilotinib and Imatinib (standard dose) for the 1st-line treatment of Philadelphia chromosome positive CML according to their marketing authorisation. The assessment draws on relevant evidence to determine what, if any, is the clinical and cost-effectiveness of the interventions compared to each other in the chronic phase.

The policy questions addressed are:

In chronic phase

- What is the clinical effectiveness of 1st-line treatment for newly diagnosed Philadelphia chromosome positive CML with dasatinib or with nilotinib or with imatinib (standard dose), using each of the three treatments as comparators?

- What is the cost-effectiveness of 1st-line treatment for newly diagnosed Philadelphia chromosome positive CML with dasatinib or with nilotinib or with imatinib (standard dose), using each of the three treatments as comparators?

4. ASSESSMENT OF CLINICAL EFFECTIVENESS

The clinical effectiveness of dasatinib, nilotinib and imatinib was assessed by a systematic review of published evidence. The review was undertaken following the general principles published by the NHS Centre for Reviews and Dissemination and the PRISMA guidlines.[65, 66]

4.1. Methods for reviewing effectiveness

4.1.1. Identification of studies

The search strategy comprised of the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers and manufacturer submissions
- Follow-up on mentions of potentially relevant on-going trials noted in previous NICE guidance on imatinib for CML.

The main electronic databases of interest were:

MEDLINE (Ovid); EMBASE; The Cochrane Library including the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, DARE, NHS EED and HTA databases; NRR (National Research Register); Web of Science (including Conference Proceedings Citation Index); Current Controlled Trials; Clinical Trials.gov; FDA website; EMEA website. These were searched from search end-date of the last technology appraisal report on this topic October 2002.[67]

The searches were developed and implemented by a trained information specialist (CC) using the search strategy detailed in the technology appraisal by Thompson Coon and colleagues as the starting point (see Appendix 1 for full search strategy).[68] This strategy was reviewed by PenTAG including a clinical expert (CR).

Relevant studies were identified in two stages using predefined inclusion and exclusion criteria (See Appendix 2 for full research protocol). One reviewer (TP) examined all titles and abstracts, with two reviewers (TJ-H and LC) each examining approximately 50% each of all titles and abstracts (therefore all titles and abstracts were examined by at least two

reviewers). Full texts of any potentially relevant studies were obtained. The relevance of each paper was assessed independently by two reviewers (TP and TJ-H) and any discrepancies resolved by discussion.

4.1.2. Inclusion and exclusion criteria

4.1.2.1. Inclusion criteria

For the review of clinical effectiveness, in the first instance, only systematic reviews of randomised controlled trials (RCTs) and RCTs were considered. However, if key outcomes of interest were not measured at all in the included RCTs we discussed whether extending the range of included studies to other study designs. Other study designs were not required after scrutiny of the included RCTs. The systematic reviews were used as a source for finding further studies and to compare with our systematic review. Systematic reviews provided as part of manufacturers' submissions were treated in a similar manner.

Population: Adults with chronic phase CML, naïve to any treatment specifically directed against CML

Interventions:

- Dasatinib
- Nilotinib
- Imatinib (400mg standard dose)

Each should be employed in accordance with the marketing authorisation and in the populations indicated in Section 2.6, noting that CML without genetic mutation is outside the existing marketing authorisations.

Comparators:

- Imatinib or nilotinib where the intervention is dasatinib; imatinib or dasatinib where the intervention is nilotinib; dasatinib or nilotinib, where the intervention is standard dose imatinib.

Outcomes: All potentially relevant outcomes in the included studies were considered, particularly those capturing:

- Response rates – cytogenetic, molecular and haematological
- Event-free survival
- Progression-free survival
- Time to progression
- Overall survival
- Time to treatment failure
- Adverse effects of treatment
- Health-related quality of life.

4.1.2.2. Exclusion criteria

Studies were excluded if they did not match the inclusion criteria, particularly:

- Non-randomised studies (except if agreed by PenTAG, in the absence of RCTs)
- Animal models
- Preclinical and biological studies
- Narrative reviews, editorials, opinions
- Non-English language papers
- Reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality.

4.1.3. Data abstraction strategy

Data were extracted by one reviewer (TP) using a standardised data extraction form and checked independently by a second (T J-H). Disagreements were resolved by discussion, with involvement of a third reviewer if necessary. Data extraction forms for each included study are included in Appendix 3.

4.1.4. Quality assessment strategy

The methodological quality of randomised controlled studies was assessed according to criteria specified by the Centre of Reviews and Dissemination (CRD).[66] Quality was assessed

by one reviewer (TP) and judgements were checked by a second (TJH or LC). Any disagreement was resolved by discussion, with involvement of a third reviewer if necessary.

4.1.4.1. Internal Validity

The instrument sought to assess the following considerations:

- Was the assignment to the treatment groups really random?
- Was the treatment allocation concealed?
- Were the groups similar at baseline in terms of prognostic factors?
- Were the eligibility criteria specified?
- Were outcome assessors blinded to the treatment allocation?
- Was the care provider blinded?
- Was the patient blinded?
- Were point estimates and a measure of variability presented for the primary outcome measure?
- Did the analyses include an intention-to-treat (ITT) analysis?
- Were withdrawals and dropouts completely described?

In addition, methodological notes were made for each included study, with the reviewer's observation on: sample size and power calculations; participant attrition; methods of data analysis; and conflicts of interest.

4.1.4.2. External validity

External validity was judged according to the ability of a reader to consider the applicability of findings to a patient group and service setting. Study findings can only be generalisable if they provide enough information to consider whether a cohort is representative of the affected population at large. Therefore studies that appeared to be typical of the UK CML population with regard to these considerations were judged to be externally valid.

4.1.5. Methods of data synthesis

Data were tabulated and discussed in a narrative review. Given the paucity of data, a meta-analysis was not conducted.

Mixed treatment indirect comparisons were used as far as data allowed to facilitate comparison between the drugs for which there are no head to head data for dasatinib and nilotinib. From the data provided from the included trials, indirect comparisons are based on raw unadjusted results in the form of unadjusted odds ratios. The indirect log odds ratio and corresponding variance were calculated using standard formulae presented in the appendix of Bucher and colleagues.[69] Assuming the sampling distribution of the log odds ratio to be normally distributed, the Wald method was used to construct 95% confidence intervals for the odds ratio and calculate the p-value. A fixed effect approach was used which assumes that the relative effect of the interventions is the same across the two study populations.[69] To check this assumption we compared the baseline characteristics between trials. The participants were similar with respect to median age, the percentage of males, median time between diagnosis and randomisation, median white cell count and median platelet count. It was not possible to use more sophisticated methods (e.g. sensitivity analyses and sub-group analyses) to validate the assumption of similar relative effects since we did not have access to the original data.

4.1.6. Handling company submissions to NICE

All clinical effectiveness data included in the pharmaceutical company submissions to NICE were assessed to see if they met the inclusion criteria and had not already been identified from published sources.

4.2. Results of clinical effectiveness

4.2.1. Identification of evidence

The electronic searches retrieved a total of 3,227 titles and abstracts. Two additional papers were found by hand searching of reference lists, with two papers retrieved from updated searches. No additional papers were found by searching the bibliographies of included studies. Two thousand five hundred and ten papers were excluded on title and abstract. Full text of the remaining 35 papers was requested for more in-depth screening. The process is illustrated in detail in Figure 2.

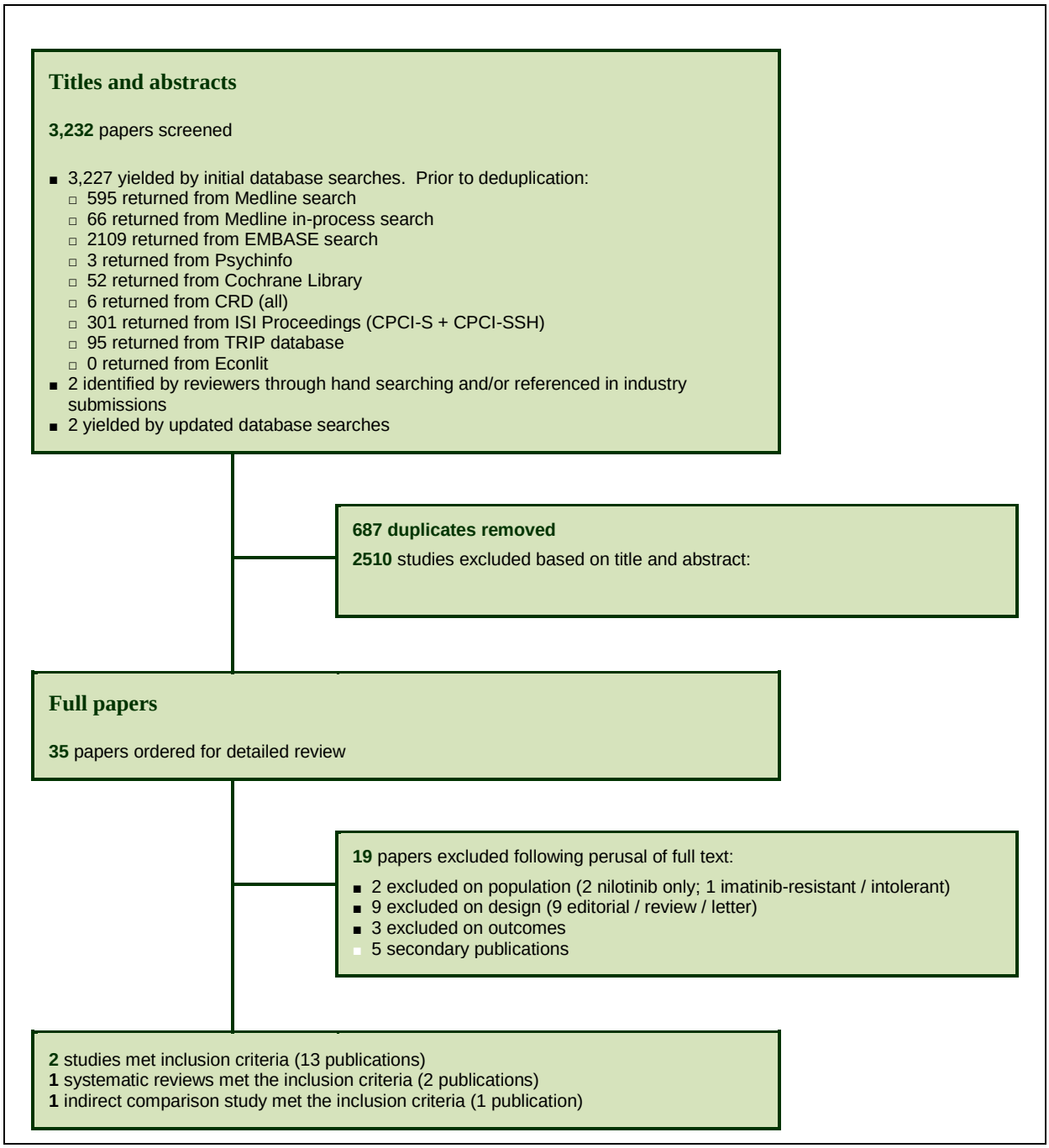


Figure 2 Flow diagram study inclusion process clinical effectiveness

Two clinical randomised controlled trials were included, one each studying dasatinib and nilotinib versus imatinib (Table 5), with any additional abstracts or presentations related to the trials also included.[20, 29] A further trial was identified, but was published only as a conference abstract. As sufficient detail was not available to make assessments of methodological quality, this was not formally included in the systematic review, with a summary of results available in Appendix 6.[70] Kantarjian and colleagues (dasatinib) provided an additional six conference

abstracts/presentations.[29, 71-77] Saglio and colleagues (nilotinib) provided an additional 24-month follow-up paper and five conference abstracts/presentations.[20, 78-83] One conference abstract of a systematic review assessing CML as a 1st-line treatment was identified and provided indirect comparison analysis of dasatinib and nilotinib.[84] Another paper also provided indirect comparison analysis of dasatinib and nilotinib.[85] Additional data was also retrieved from the industry submissions of Bristol-Myers Squibb (2011, unpublished; dasatinib) and Novartis (2011, unpublished; nilotinib).[86,87]

The details of studies retrieved as full papers and subsequently excluded, along with the reasons for their exclusion are detailed in Appendix 5.

Table 5 Summary of included studies (RCT's)

Study	Year published	Study type	N	Intervention	Comparator	Supplementary publications
Kantarjian et al[29] **DASISION**	2010	RCT, 2-arm	519	Dasatinib	Imatinib	Saglio et al.[71] (cardiovascular comorbidities) Guilthot et al.[72] (baseline medications) Schiffer et al.[73] (lymphocytosis) Khoury et al.[74] (baseline comorbidities) Shah et al.[75] (18-month follow-up data) Kantarjian et al.[76] (18-month follow-up data) Kantarjian et al.[77] (24-month follow-up data) Bristol-Myers Squibb[86] (Industry submission)
Saglio et al[20] **ENESTnd**	2010	RCT, 3-arm	561	Nilotinib (300mg) Nilotinib (400mg)	Imatinib	Beaumont et al.[78] (hospitalisation) Hochhaus et al.[79] (MMR by Sokal group, EFS) Larson et al.[80] (18-month cardiac safety profile) Hughes et al.[81] (18-month follow-up data) Hughes et al.[82] (24-month follow-up data) Kantarjian et al.[83] (24-month follow-up data) Novartis[87] (Industry submission)

4.2.2. Assessment of effectiveness

4.2.2.1. Study characteristics

Dasatinib versus Imatinib

Kantarjian and colleagues report on the DASISION trial, a multi-national open label phase 3 randomised controlled trial.[29] Newly diagnosed chronic phase patients were randomised to either dasatinib (100mg, n = 259) or imatinib (400mg, n = 260). The trial has been reported in one full publication, with seven conference abstract/presentations providing additional data. Inclusion and exclusion criteria are detailed in Table 6. The aim of the study was to assess the efficacy and safety of dasatinib (100mg) compared to imatinib (400mg). The primary outcome was CCyR within 12-months, with a secondary outcome of MMR (at any time). Other secondary outcomes are detailed in Table 6.

Participants were randomly assigned, in a 1:1 ratio stratified by Hasford score (see section 2.2.2 for definition), to receive either dasatinib (100mg daily) or imatinib (400mg daily). All participants had a minimum follow-up of 12-months, with a median duration of 14-months treatment for dasatinib and 14.3-months for imatinib. The median dose of dasatinib was 99mg per day and 400mg for imatinib.

Conference abstracts/presentations with additional data assessed:

- Whether baseline CV conditions, baseline comorbidities and medications impacted the efficacy and safety of the drugs (see section 4.2.3.10).[71, 72, 74]
- Whether the safety profile, responses and outcomes in patients with sustained lymphocytosis was determined (see section 4.2.3.10).[73]
- 18-month and 24-month follow-up data[75-77]

Nilotinib versus Imatinib

Saglio and colleagues report on the ENESTnd trial, a multi-centre open label phase 3 randomised controlled trial.[20] Newly diagnosed chronic phase patients were randomised to either nilotinib (300mg, n = 282) or nilotinib (400mg, n = 281) or imatinib (400mg, n = 283). The trial has been reported in one full publication and six conference abstracts/presentations providing additional data. Inclusion and exclusion criteria are detailed in Table 7. The aim of

the study was to assess the efficacy and safety of nilotinib (300mg or 400mg) compared to imatinib (400mg). Nilotinib 300mg is licensed for 1st-line treatment of CML, with nilotinib 400mg licensed for 2nd-line treatment of CML. The current BNF (61) only provides indication for the use of nilotinib for 2nd-line treatment of CML (i.e. 400mg). The primary outcome was MMR at 12-months, with a secondary outcome of CCyR by 12-months, other secondary outcomes are detailed in Table 7.

Participants were randomly assigned, in a 1:1:1 ratio stratified by Sokal score (see Section 2.2.2 for definition), to receive either nilotinib (300mg twice daily) or nilotinib (400mg twice daily) or imatinib (400mg daily). All participants had a minimum follow-up of 12-months, with a median duration of 14-months treatment for all study groups. The median dose of nilotinib was 592mg per day (nilotinib 300mg twice daily), was 779mg per day (nilotinib 400mg twice daily) and 400mg for imatinib.

Papers and conference abstracts/presentations with additional data assessed:

- Hospitalisation of patients (see section 4.2.4).[78]
- Cardiac safety profile of the study drugs (see section 4.2.4).[80]
- MMR stratified by Sokal score at 12-months.[79]
- 18-month and 24-month follow-up data.[81-83]

Table 6 Study characteristics dasatinib versus imatinib

Study	Inclusion criteria	Exclusion criteria	Primary outcomes	Secondary outcomes
DASISION[29]	• Newly diagnosed (≤ 3-months • ECOG score at least 0 to 2 • No prior TKI treatment • Adquate hepatic and renal function	• Serious or uncontrolled medical disorders or cardiovascular disease • History of serious bleeding disorder, concurrent cancer, previous chemotherapy, pleural effusion at baseline	• Complete cytogenetic response (CCyR) (within 12-months)	• Major molecular response (MMR) (at any time) • Time to confirmed CCyR and MMR response • Rates of CCyR and MMR response by 12-months • Progression-free survival • Overall survival
Outcome definition and collection:				
A CCyR was defined as the absence of Ph-positive metaphases, determined on the basis of G-banding in at least 20 cells in metaphase per bone marrow sample. A confirmed CCyR was defined as a CCyR documented on two consecutive assessments at least 28 days apart. An MMR was defined as a BCR-ABL transcript level of 0.1% or lower on the international scale, corresponding to a reduction by at least 3-log from standardised baseline level. Adverse events were assessed continuously for all participants and were graded according to the Common Terminology Criteria for Adverse Events. A chest radiograph was obtained for all participants to check for pleural effusion due to previous reported levels in dasatinib patients.[88]				

Table 7 Study characteristics nilotinib versus imatinib

Study	Inclusion criteria	Exclusion criteria	Primary outcomes	Secondary outcomes
ENESTnd[20]	• Newly diagnosed (≤ 6-months) ECOG score 0-2 • No prior TKI treatment (except imatinib ≤ 2-weeks) • Adquate organ function	• Impaired cardiac function • Medication affecting liver enzymes or QT interval prohibited	• Major molecular response (MMR) (at 12-months)	• Complete cytogenetic repsonse (CCyR) (by 12-months) • Rate of MMR and CCyR over time • Time to and duration of MMR and CCyR. • Rate of BCR-ABL/ABL ratio of ≤0.01% and ≤0.0032% at 12 months. • Event-free survival • Progression free survival • Progression to AP/BC Overall survival. • Safety • Dose intensity • Pharmacokinetics
Outcome definition and collection:				
An MMR was defined as a BCR-ABL transcript level of 0.1% or lower on the international scale, corresponding to a reduction by at least 3-log from standardised baseline level, assessed by means of RQ-PCR. Samples were collected monthly for three months, and every three months thereafter. Adverse events of all participants who received at least one dose of a study drug were monitored				

4.2.2.2. Population characteristics – baseline

Dasatinib versus Imatinib

For the DASISION[29] trial, the population demographic, disease status and use of previous therapies were well matched (see Table 8 for details).

Nilotinib versus Imatinib

For the ENESTnd[20] trial, the population demographic, disease status and use of previous therapies were well matched (see Table 8 for details).

Table 8 Population baseline characteristics

Study	DASISION[29]		ENESTnd[20]		
Intervention	Dasatinib (100mg)	Imatinib (400mg)	Nilotinib (300mg)	Nilotinib (400mg)	Imatinib (400mg)
N	259	260	282	281	283
Age, median yrs (range)	46 (18-24)	49 (18-78)	47 (18-85)	47 (18-81)	46 (18-80)
Male (%)	144 (56)	163 (63)	158 (56)	175 (62)	158 (56)
Race or ethnic group (%) Asian Black White Other	–	–	 76 (27) 12 (4) 170 (60) 24 (9)	 66 (23) 11 (4) 185 (66) 19 (7)	 71 (25) 7 (2) 187 (66) 18 (6)
ECOG performance score (%) 0 1 2	 213 (82) 46 (18) 0	 205 (79) 53 (20) 2 (1)	–	–	–
Risk Group[a] Low Intermediate High	 86 (33) 124 (48) 49 (19)	 87 (33) 123 (47) 50 (19)	 103 (37) 101 (36) 78 (28)	 103 (37) 100 (36) 78 (28)	 104 (37) 101 (36) 78 (28)
Time since diagnosis, median days (range)	31 (0-296)	31 (0-244)	31 (0-182)	31 (3-189)	28 (1-183)
White-cell count-×10−9/litre, median (range)	25.1 (2.5-493)	23.5 (1.4-475)	23 (2-247)	23 (2-435)	26 (3-482)
Platelet count-×10−9/litre, median (range)	448 (58-1880)	390 (29-2930)	424 (90-3880)	374 (103-1819)	375 (66-2232)
Peripheral-blood blasts %, median (range)	1 (0-10)	1 (0-11)	–	–	–
Peripheral-blood basophils %, median (range)	4 (0-27.8)	4 (0-19.5)	–	–	–
Bone marrow blasts %, median (range)	2 (0-14)	2 (0-12)	–	–	–
Haemoglobin-g/dl, median (range)	–	–	12 (5.5-17.6)	12 (6.2-17.6)	12.2 (6.4 – 17.1)
Spleen size ≥10 cm below costal margin (%)	–	–	31 (11)	34 (12)	40 (14)

Study	DASISION[29]		ENESTnd[20]		
Atypical BCR-ABL transcripts (%)	3 (1)	1 (<1)	5 (2)	1 (<1)	2 (1)
Previous therapy for CML (%)			[redacted]	[redacted]	[redacted]
Hydroxyurea	189 (73)	190 (73)			
Anagrelide	8 (3)	3 (1)			
Imatinib (≤ 2 weeks)	3 (1)	4 (2)			

a = Hasford risk-DASISION, Sokal risk-ENESTnd

Comparability of baseline population characteristics between trials

With no head to head trial of dasatinib and nilotinib and an indirect comparison analysis conducted (see section 4.2.6), comparability between the trials are discussed. Participants in the DASISION and ENESTnd trials were of a similar age and gender distribution.[20, 29] However, the median age (46-49 years) was younger than that of the general population where the median age at diagnosis is 58 years (this includes AP/BC patients). Risk group scores were measured by the Hasford risk score for the DASISION trial and the Sokal risk score for the ENESTnd trial.[20, 29] However, risk distribution was fairly similar between trials with ENESTnd reporting a slightly lower percentage of patients with intermediate risk and a slightly higher percentage with a high risk, compared with DASISION.[20, 29] The ECOG performance status for both trials included patients between a score 0-2. As shown in Table 6 and Table 7, the exclusion criteria were slightly different for the two trials and based on the known adverse events of the drugs (e.g. pleural effusion for dasatinib and QT prolongation for nilotinib). Further, the two trials had different responses as primary outcomes for the trials, namely CCyR and MMR for DASISION and ENESTnd respectively. However, both trials reported the other response as a secondary outcome.

4.2.2.3. Assessment of study quality

Dasatinib versus Imatinib

The DASISION trial is a good quality international, multicentre, open-label, phase 3, randomised controlled trial.[29] There is no discussion regarding how patients were randomised. The trial was reported as open-label, therefore allocation concealment of the patients, outcome or carer blinding was not possible. These criteria have been demonstrated to potentially bias results of RCTs; however this is unlikely to have an impact as the outcomes of the trial are objective. Baseline groups are similar and well reported. The statistical

analysis and handling of data is also well reported. Although a sample size calculation is not reported, the groups are of a similar size to the ENESTnd trial, which does report a sample size calculation (Table 9).[20] The large contribution from Bristol-Myers Squibb to the study and manuscript construction would provide a strong conflict of interest. The study population is not wholly representative of a UK CML population, as a result of the lower median age and the large contribution of Asian patients to the study population.

Nilotinib versus Imatinib

The ENESTnd trial is a good quality international, multicentre, open-label, phase 3, randomised controlled trial.[20] There is no discussion regarding how patients were randomised. The trial was reported as open-label, therefore allocation concealment of the patients, outcome or carer blinding was not possible. These criteria have been demonstrated to potentially bias results of RCTs; however this is unlikely to have an impact as the outcomes of the trial are objective. Baseline groups are similar and well reported. The statistical analysis and handling of data is also well reported (Table 9). The large contribution from Novartis to the study and manuscript construction would provide a strong conflict of interest. The study population is not wholly representative of a UK CML population, as a result of the lower median age and the unknown ethnicity of the patients.

Table 9 Summary of quality assessment – all included trials

	DASISION[29]	ENESTnd[20]
Study design	RCT	RCT
Is a power calculation provided?	No	Yes
Is the sample size adequate?	Not reported	Yes
Was ethical approval obtained?	Yes	Yes
Were the study eligibility criteria specified?	Yes	Yes
Were the eligibility criteria appropriate?	Yes	Yes
Were patients recruited prospectively?	Yes	Yes
Was assignment to the treatment groups really random?	Not reported	Not reported
Were groups stratified?	Yes	Yes
Was the treatment allocation concealed?	No	No
Were adequate baseline details presented?	Yes	Yes
Were the participants representative of the population in question?	Yes	Yes
Were the groups similar at baseline?	Yes	Yes
Were baseline differences adequately adjusted for in the analysis?	Yes	Yes
Were the outcome assessors blind?	No	No
Was the care provider blind?	No	No
Are the outcome measures relevant to the research question?	Yes	Yes
Is compliance with treatment adequate?	Yes	Yes
Are withdrawals/dropouts adequately described?	Yes	Yes
Are all patients accounted for?	Yes	Yes
Is the number randomised reported?	Yes	Yes
Are protocol violations specified?	Yes	Yes
Are data analyses appropriate?	Yes	Yes
Is analysis conducted on an ITT basis?	Yes	Yes
Are missing data appropriately accounted for?	Yes	Yes
Were any sub-group analyses justified?	Not reported	N/A
Are the conclusions supported by the results?	Yes	Yes
Conflict of interest declared?	Yes	Yes

NA: not applicable.

4.2.2.4. Treatment status

Dasatinib versus Imatinib

The DASISION trial reports (Table 10), at 12-months follow-up 85% and 81% of patients still continued to receive treatment with dasatinib and imatinib respectively.[29] Reported discontinuation rates for dasatinib and imatinib were, drug related adverse events (5% vs 4%), disease progression (4% vs 5%) and treatment failure (2% vs 4%). At 18-months follow-up, 81% and 80% of patients still continued to receive treatment with dasatinib and imatinib respectively.[75] At 24-months follow-up, 77% and 75% still continued to receive treatment with dasatinib and imatinib respectively. [77] Reported discontinuation rates for dasatinib and imatinib were, drug related adverse events (7% vs 5%), disease progression (5% vs 7%) and treatment failure (3% vs 4%). Significant differences were not reported.

Nilotinib versus imatinib

The ENESTnd trial reports (Table 11), at 12-months follow-up 84% and 79% of patients still continued to receive treatment with nilotinib 300mg (licensed for 1st-line treatment of CML) and imatinib respectively.[20] Discontinuation rates for nilotinib 300mg and imatinib were, drug related adverse events (5% vs 7%), disease progression (<1% vs 4%) and suboptimal response/treatment failure (2% vs 4%). At 24-months follow-up 75% and 68% of patients still continued to receive treatment with nilotinib 300mg and imatinib respectively.[83] Discontinuation rates for nilotinib 300mg and imatinib were, drug related adverse events (6% vs 9%), disease progression (<1% vs 4%) and suboptimal response/treatment failure (9% vs 13%) (Novartis, 2011).[87] Significant differences were not reported.

At 12-months, only a small percentage, approximately double the number of imatinib patients in ENESTnd (21) had to discontinue due to adverse events compared with imatinib patients in DASISION (11). However, it is unknown whether this is due to different measurement techniques of adverse events, difference in the population characteristics between trials, or chance.

Table 10 Treatment status dasatinib versus imatinib (DASISION)

	12-months follow-up[29]		18-months follow-up[75]		24-months follow-up[77]	
Adverse Events	Dasatinib (N = 258)	Imatinib (N = 258)	Dasatinib (N = 258)	Imatinib (N = 258)	Dasatinib (N = 258)	Imatinib (N = 258)
	Number of patients (%)					
Received treatment	258 (100.0)	258 (100.0)	258 (100.0)	258 (100.0)	258 (100.0)	258 (100.0)
Continue to receive treatment	218 (85.0)	210 (81.0)	209 (81.0)	206 (80.0)	199 (77.0)	194 (75.0)
Discontinued treatment	40 (15.0)	48 (19.0)	49 (19.0)	52 (20.0)	59 (23.0)	64 (25.0)
Had drug-related adverse events	13 (5.0)	11 (4.3)	15 (6.0)	10 (4.0)	18 (7.0)	12 (5.0)
Haematologic, including cytopenia	4 (1.6)	3 (1.2)	6 (2.3)	3 (1.2)	6 (2.3)	4 (1.6)
Nonhematologic	9 (3.5)	8 (3.1)	–	–	12 (5)	8 (3.0)
Diseased progressed	11 (4.3)	14 (5.4)	–	–	14 (5)	17 (7.0)
Increased white-cell count	1 (0.4)	0	–	–	–	–
Loss of complete haematological response	0	0	–	–	–	–
Loss of major cytogenetic response	1 (0.4)	4 (1.6)	–	–	–	–
Progression to accelerated or blastic phase	5 (1.9)	9 (3.5)	6 (2.3)	9 (3.5)	9 (3.5)	15 (5.8)
Death	4 (1.6)	1 (0.4)	–	–	16 (6.0)	14 (5.0)
Treatment failed	6 (2.3)	10 (3.9)	–	–	8 (3.0)	11 (4.0)
Did not have complete haematologic or cytogenetic response at 6-months	2 (0.8)	4 (1.6)	–	–	–	–
Had less than partial cytogenetic response at 12-months	3 (1.2)	6 (2.3)	–	–	–	–
Did not have a complete cytogenetic response at 18-months	1 (0.4)	0	–	–	–	–
Had adverse event unrelated to drug	3 (1.2)	1 (0.4)	–	–	–	–
Withdrew consent	2 (0.8)	3 (1.2)	–	–	–	–
Became pregnant	2 (0.8)	0	–	–	–	–
Did not adhere to therapy	0	2 (0.8)	–	–	–	–
Was lost to follow-up	0	3 (1.2)	–	–	–	–
Requested to discontinue	2 (0.8)	1 (0.4)	–	–	–	–
Had other reason	1 (.04)	3 (1.2)	–	–	–	–

Grey cells = not reported

Table 11 Treatment status nilotinib versus imatinib (ENESTnd)

	12-months follow-up[20]			24-months follow-up[83, 87]		
Adverse event	Nilotinib 300mg (N = 282)	Nilotinib 400mg (N = 281)	Imatinib 400mg (N = 283)	Nilotinib 300mg (N = 282)	Nilotinib 400mg (N = 281)	Imatinib 400mg (N = 283)
	Number of patients (%)					
Received treatment	279 (99)	278(99)	279 (99)	279 (99)	278(99)	279 (99)
Still on Study	268 (95)	271 (96)	274 (97)	262 (93)	267 (95)	260 (92)
Continue to receive treatment	236 (84)	230(82)	224 (79)	210 (75)	220 (78)	191 (68)
Discontinued treatment	46 (16)	51 (18)	59 (21)	72 (25)	61 (22)	92 (32)
Adverse event(s)	13 (5)	26 (9)	21 (7)	[redacted]	[redacted]	[redacted]
Abnormal laboratory value(s)	6 (2)	5 (2)	3 (1)	[redacted]	[redacted]	[redacted]
Abnormal test procedure result(s)	0 (0)	1 (<1)	1 (<1)	[redacted]	[redacted]	[redacted]
Subject's condition no longer requires drug	1 (<1)	0 (0)	0 (0)	[redacted]	[redacted]	[redacted]
Withdrew consent	6 (2)	5 (2)	3 (1)	[redacted]	[redacted]	[redacted]
Was lost to follow-up	2 (<1)	2 (<1)	1 (<1)	[redacted]	[redacted]	[redacted]
Death	2 (<1)	0 (0)	0 (0)	3 (1)	1 (<1)	0 (0)
Diseased progressed	2 (<1)	2 (<1)	10 (4)	2 (<1)	4 (1)	12 (4)
Protocol deviation	4 (1)	5 (2)	4 (1)	[redacted]	[redacted]	[redacted]
Suboptimal response/ treatment failure	10 (4)	5 (2)	16 (6)	[redacted]	[redacted]	[redacted]

4.2.3. Assessment of clinical effectiveness

4.2.3.1. Complete cytogenetic response

Cytogenetic responses are shown in Table 12. DASISION and ENESTnd reports CCyR at 12, 18 and 24 months follow-up. DASISION reports confirmed CCyR (i.e. two assessments 28 days apart) for 12, 18 and 24-months follow-up, which ENESTnd do not. Both trials report CCyR by risk group categorisation at 12-months. Complete cytogenetic response is the primary outcome in the DASISION trial.

Figure 3 and Figure 4 summarise the CCyR data. We present these on 2 axes – available follow-up data (Figure 3) and potential long-term survival (Figure 4).

Dasatinib versus Imatinib

The DASISION trial reports significantly more patients taking dasatinib (83%) achieved a CCyR compared to patients taking imatinib (72%) at 12-months follow-up (p = 0.001; RR 1.17, 95% CI 1.06-1.28).[29] This difference was not significant at 18-months (84% vs 78%, p = 0.093; RR 1.08, 95% CI 0.98-1.17) or 24-months (86% vs 82%, p = 0.23; RR 1.05, 95% CI 0.97-1.13).[76, 77] There was a significant difference for patients with a confirmed CCyR (i.e. two assessments 28 day apart) at 12-months (77% vs 66 %, p = 0.007; RR 1.16, 95% CI 1.04-1.30) and 18-months (78% vs 70%, p = 0.037; RR 1.11, 95% CI 1.00-1.24) follow-up.[29, 75]

At 24-months follow-up there was no significant difference for patients with a confirmed CCyR (80% vs 74%, p = 0.12; RR 1.08, 95% CI 0.98-1.19).[77] Differences between confirmed and non-confirmed CCyR suggest more transitory responses may be seen with imatinib.

At 12-months follow-up, CCyR rates were higher for patients receiving dasatinib across all Hasford risk categories compared with imatinib, with rates among those categorised as high risk of 78% and 64% for dasatinib and imatinib respectively.[29] At 18-months follow-up, confirmed CCyR rates remained higher for patients receiving dasatinib across all Hasford risk categories compared with imatinib.[75]

Nilotinib[I] versus Imatinib

The ENESTnd trial reports significantly more patients taking nilotinib 300mg (80%) achieved a CCyR compared to patients taking imatinib (65%) at 12-months follow-up (p=0.001; RR 1.23, 95% CI 1.11-1.36).[20] At 18-months follow-up rates of CCyR for nilotinib 300mg and imatinib were 85% and 74% respectively (p < 0.001; RR 1.15, 95% CI 1.09-1.25).[81] At 24-months, nilotinib 300mg (87%) continued to be significantly superior compared to imatinib (77%) (p = 0.0018; RR 1.13, 95% CI 1.04-1.22).[83] For patients receiving nilotinib 300mg, CCyR rates were higher across all Sokal risk categories compared with imatinib at 12-months and 24-months follow-up with high risk CCyR rates of 74% vs 49% (12-months) and 81% vs 59% (24-months) for nilotinib 300mg and imatinib respectively.[20, 83, 87]

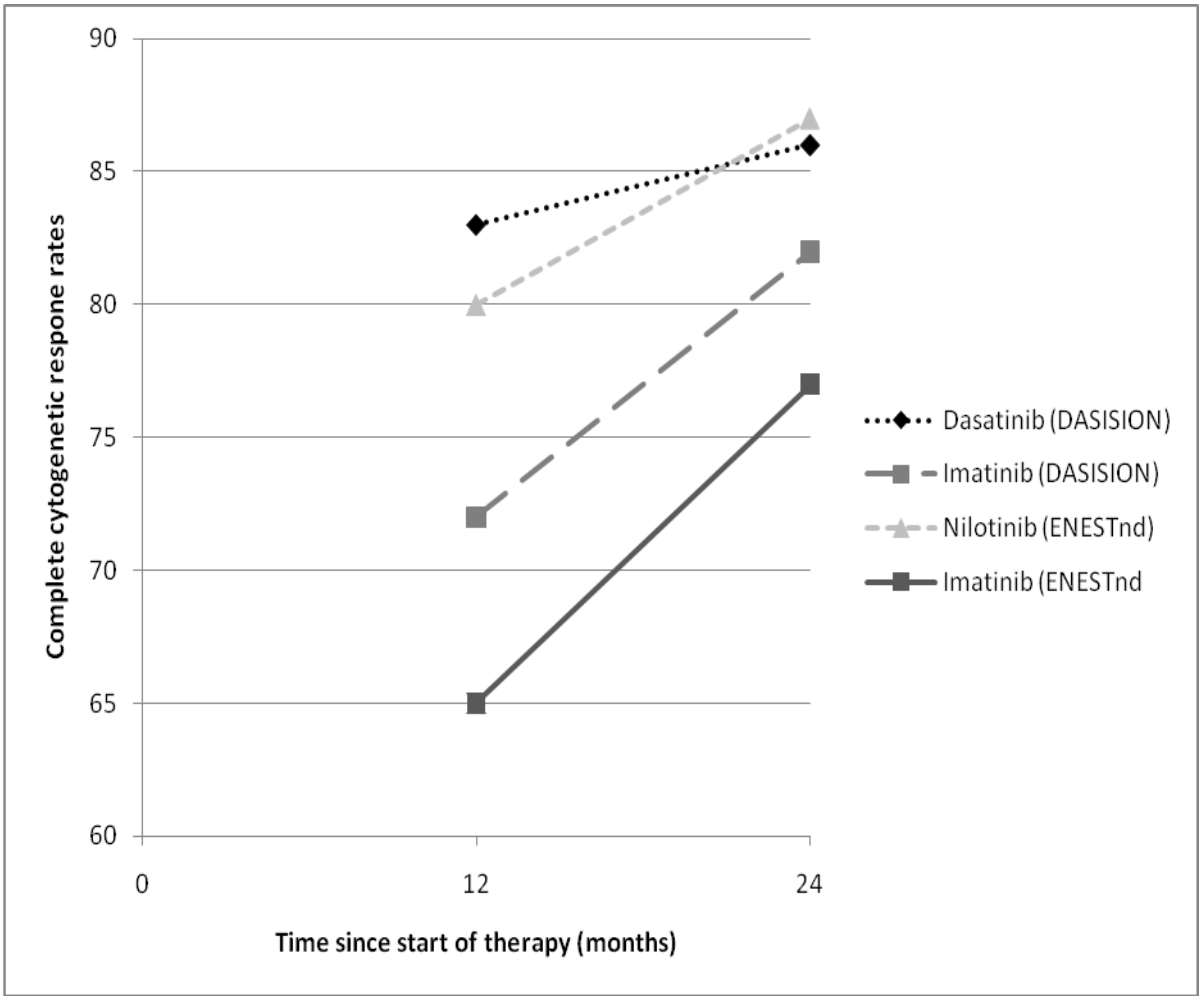


Figure 3 Complete cytogenetic response (24-months) all patients

[I] Nilotinib 300mg licensed for 1st-line treatment of CML

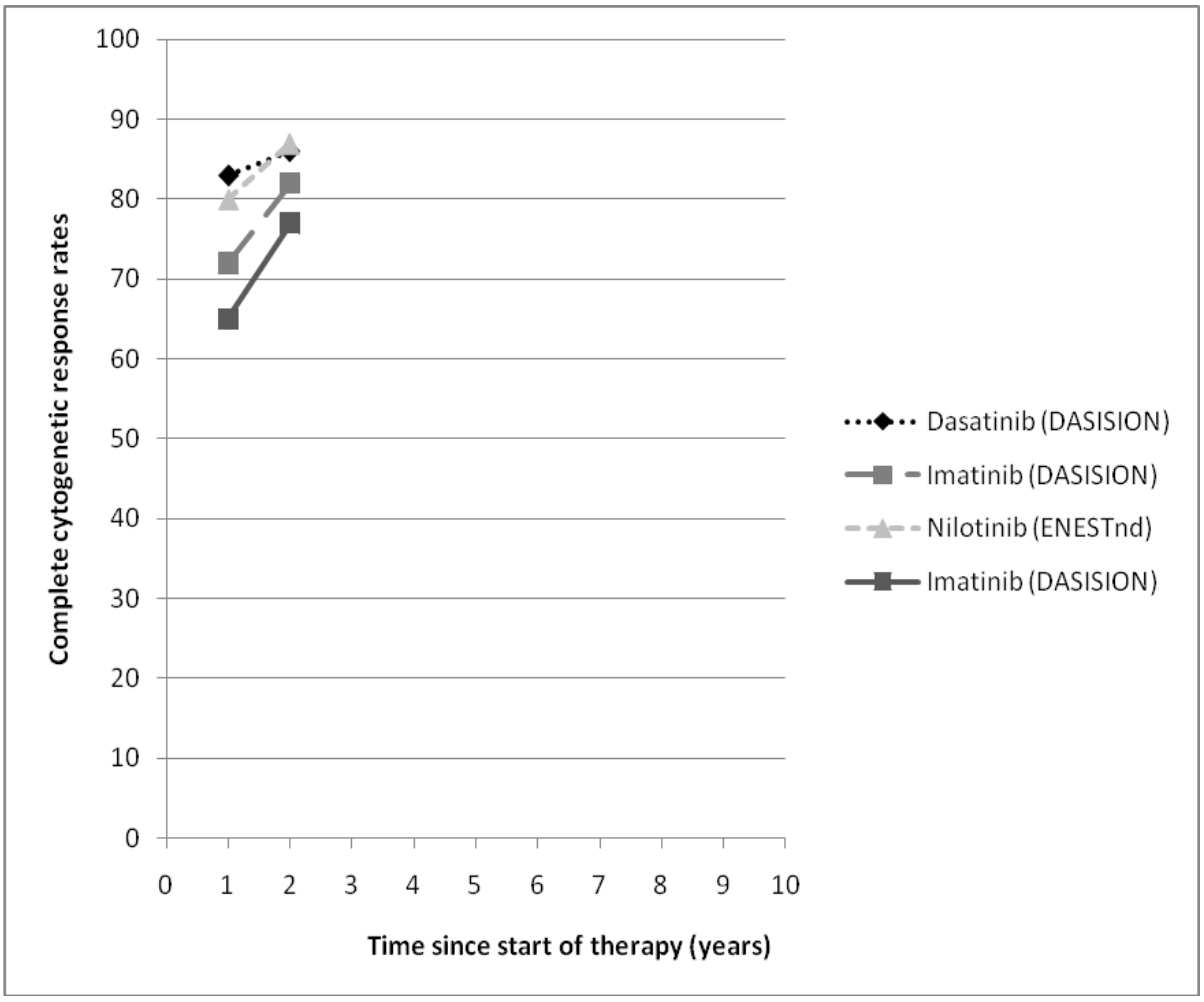


Figure 4 Complete cytogenetic response (10 years) all patients

Table 12 Complete cytogenetic response

Study	DASISION[29, 75-77]				ENESTnd[20, 81, 83, 87]						
Intervention	Dasatinib (100mg)	Imatinib (400mg)	p-value	RR (95% CI)[d]	Nilotinib (300mg)	p-value	RR (95% CI) [d,#]	Nilotinib (400mg)	p-value	RR (95% CI) [d,#]	Imatinib (400mg)
CCyR rates 12-months[a] (%)	216/259 (83)	186/260 (72)	0.001	1.17 (1.06-1.28)	226/282 (80)	0.001	1.23 (1.11-1.36)	220/281 (78)	0.001	1.20 (1.08-1.34)	184/283 (65)
CCyR rates 18-months[a] (%)	218/259(84)	203/260(78)	0.093	1.08 (0.98-1.17)	240/282 (85)	< 0.001	1.15 (1.09-1.25)	230/281 (82)	0.017	1.11 (1.01-1.21)	209/283 (74)
CCyR rates 24-months[a] (%)	223/259(86)	213/260(82)	0.23	1.05 (0.97-1.13)	245/282 (87)	0.0018	1.13 1.04-1.22)	238/281 (85)	0.016	1.10 (1.01-1.19)	218/283 (77)
CCyR rates 12-months confirmed[b]	199/259 (77)	172/260 (66)	0.007	1.16 (1.04-1.30)	–	–	–	–	–	–	–
CCyR rates 18-months confirmed[b] (%)	202/259 (78)	182/260 (70)	0.037	1.11 (1.00-1.24)	–	–	–	–	–	–	–
CCyR rates 24-months confirmed[b] (%)	207/259 (80)	192/260 (74)	0.12	1.08 (0.98-1.19)							
Risk group CCyR rates 12-months[c] (%)			–	–		–	–		–	–	
Low	81/86 (94)	66/87 (76)			[redacted]			[redacted]			[redacted]
Intermediate	97/124 (78)	88/123 (72)									
High	38/49 (78)	32/50 (64)			58/78 (74)			49/78 (63)			38/78 (49)
Risk group CCyR rates 18-months confirmed[b,c] (%)			–	–	–	–	–	–	–	–	–
Low	79/86 (92)	63/87 (72)									
Intermediate	88/124 (71)	87/123 (71)									
High	36/49 (73)	32/50 (64)									
Risk group CCyR rates 24-months confirmed[c] (%)						–	–		–	–	
Low					94/103 (91)			97/103 (94)			94/104 (90)
Intermediate					88/101 (87)			85/100 (85)			78/101 (77)
High					63/78 (81)			56/78 (72)			46/78 (59)

a = ITT analysis; b = confirmed CCyR (i.e. two assessments 28 days apart); c = Hasford risk-DASISION,-Sokal risk, ENESTnd; d = PenTAG calculated # = relative risk compared with imatinib
Grey cells = not reported

4.2.3.2. Major molecular response

Table 13 shows MMR in the two key trials. DASISION and ENESTnd reports MMR at 12, 18 and 24-months follow-up. ENESTnd reports MMR at any time (12 and 24-month cumulative, MMR may be lost at specific time-point). DASISION reports MMR at any time (12 and 18-month cumulative). Both trials report MMR by risk group categorisation at 12-months, 18-months and 24-months. Major molecular response is the primary outcome in the ENESTnd trial.

Figure 5 and Figure 6 summarise the MMR data. We present these on 2 axes – available follow-up data (Figure 5) and potential long-term survival (Figure 6).

Dasatinib versus Imatinib

The DASISION trial reports significantly more patients taking dasatinib (46%) achieved a MMR compared to patients taking imatinib (28%) at 12-months follow-up ($p < 0.0001$; RR 1.63, 95% CI 1.29-2.09) and 18-months follow-up (56% vs 37%, $p = 0.001$; RR 1.52, 95% CI 1.25-1.85), and at 24-months follow-up.[29, 76] A significant difference also seen for a MMR at any time at 12-months (52% vs 34%, $p < 0.001$; RR 1.54, 95% CI 1.25-1.91), 18-months (57% vs 41%, $p = 0.001$; RR 1.39, 95% CI 1.15-1.67) and 24-months follow-up (64% vs 46%, $p = 0.001$; RR 1.39, 95% CI 1.18-1.64)[29, 75, 77]

At 12-months follow-up, MMR rates were higher for patients receiving dasatinib across all Hasford risk categories, than patients receiving imatinib.[29] At 18-months follow-up, MMR rates remained higher for patients receiving dasatinib across all Hasford risk categories, than patients receiving imatinib, with MMR rates of 51% and imatinib 30% for dasatinib and imatinib respectively among those categorised as high risk.[75] At 24-months follow-up, MMR rates remained higher for patients receiving dasatinib across all Hasford risk categories, than patients receiving imatinib, with MMR rates of 57% and imatinib 38% for dasatinib and imatinib respectively among those categorised as high risk.[77]

Nilotinib[II] versus Imatinib

The ENESTnd trial reports significantly more patients receiving nilotinib 300mg (44%) achieved a MMR compared to patients taking imatinib (22%) at 12-months follow-up (p = 0.001; RR 2.02, 95% CI 1.56-2.65).[20] At 24-months follow-up, MMR rates continued to be significantly higher for patients receiving nilotinib 300mg (62%) compared to patients receiving imatinib (37%) (p = 0.001; RR 2.02, 95% CI 1.56-2.65).[82] A significant difference was also seen for a MMR at any time between nilotinib 300mg and imatinib at 12-months (57% vs 30%), [redacted] 18-months (66% vs 40%, p < 0.001; RR 1.65, 95% CI 1.40-1.95) and 24-months follow-up (71% vs 44%, p = 0.001; RR 1.67, 95% CI 1.40-1.89).[81, 83, 87]

[redacted] At 18-months follow-up, MMR rates were higher for patients receiving nilotinib 300mg across all Sokal risk categories compared with imatinib, with MMR rates of 59% and 28% for nilotinib 300mg and imatinib respectively among those categorised as high risk.[81] At 24-months follow-up, MMR rates remained higher for patients receiving nilotinib 300mg across all Sokal risk categories, than patients receiving imatinib, with MMR rates of 65% and 32% for nilotinib and imatinib respectively among those categorised as high risk.[83]

[II] Nilotinib 300mg licensed for 1st-line treatment of CML

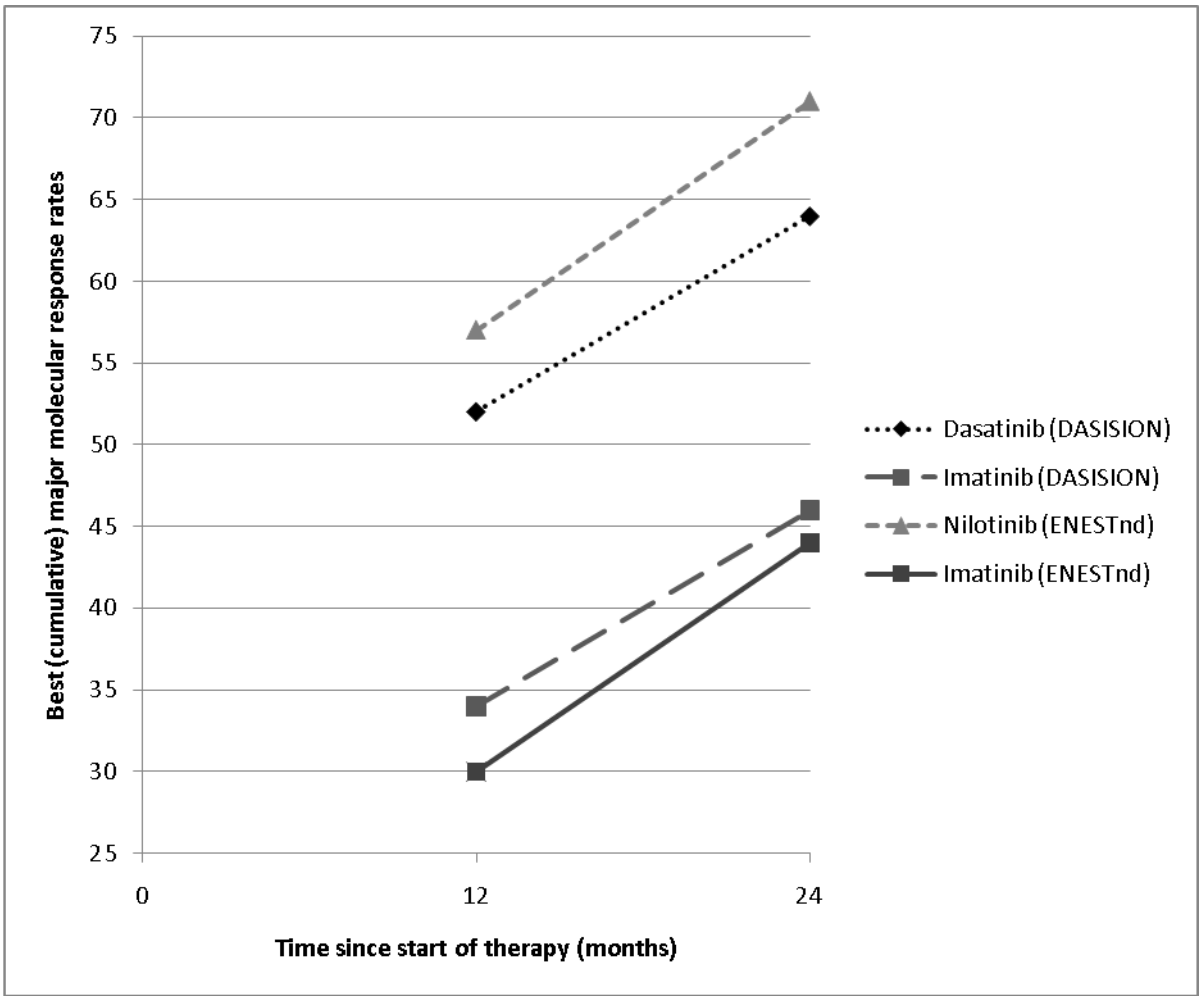


Figure 5 Major molecular response (24-months) all patients

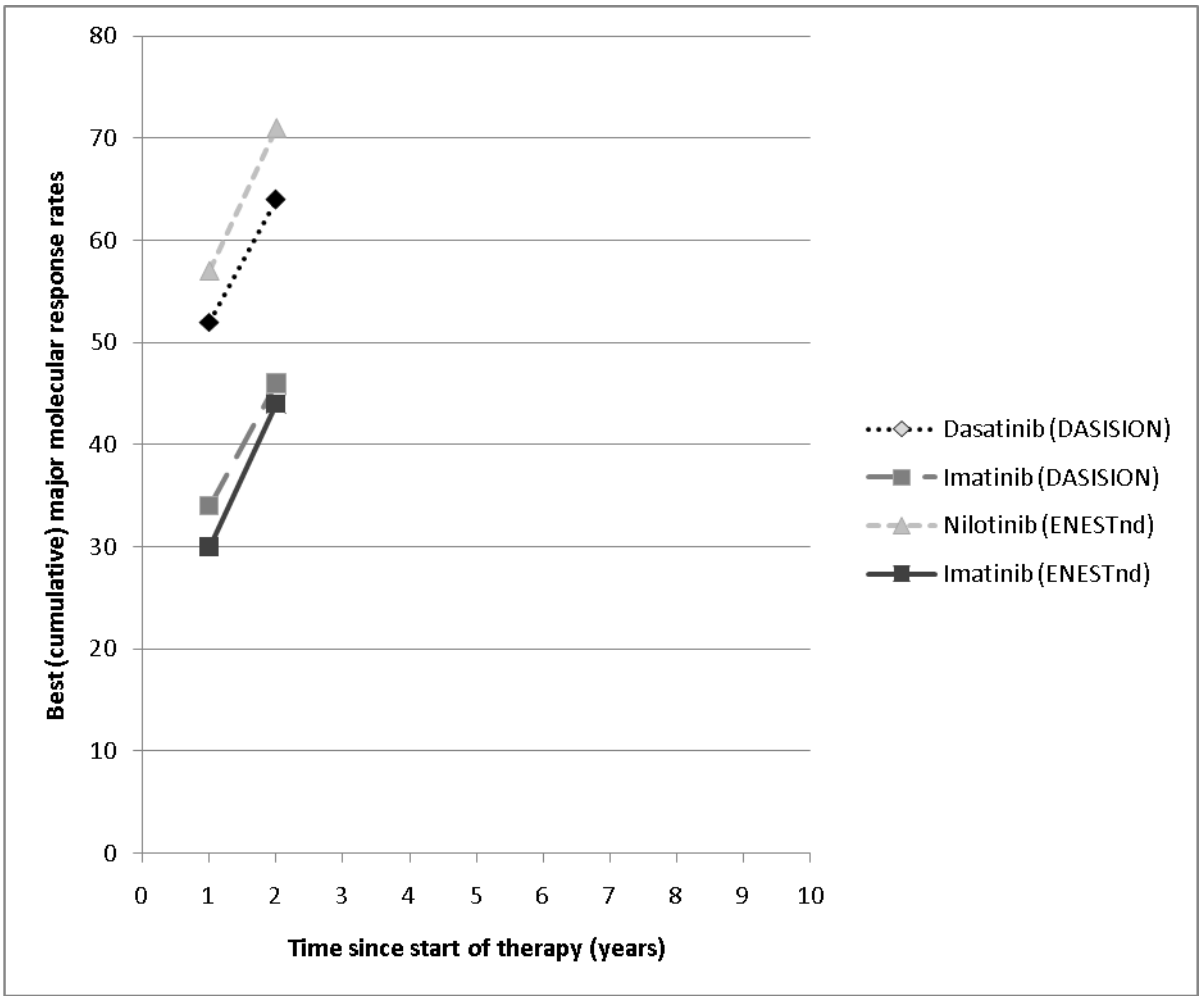


Figure 6 Major molecular response (10 years) all patients

Table 13 Major molecular response

Study	DASISION[29, 75-77]				ENESTnd[20, 81-83]						
Intervention	Dasatinib (100mg)	Imatinib (400mg)	p-value	RR (95% CI) [d]	Nilotinib (300mg)	p-value	RR (95% CI) [d, #]	Nilotinib (400mg)	p-value	RR (95% CI) [d, #]	Imatinib (400mg)
MMR 12-months[a] (%)	119/259 (46)	73/260 (28)	<0.001	1.63 (1.29-2.09)	125/282 (44)	0.001	2.02 (1.56-2.65)	121/281 (43)	0.001	1.97 (1.51-2.58)	62/283 (22)
MMR 18-months[a] (%)	145/259(56)	96/260(37)	<0.001	1.52 (1.25-1.85)	–	–	–	–	–	–	–
MMR 24-months[a] (%)	–	–	–	–	175/282 (62)	<0.001	1.67 (1.40-2.00)	165/281 (59)	<0.001	1.58 (1.32-1.90)	105/283 (37)
MMR at any time (12-months)[a,b] (%)	135/259 (52)	88/260 (34)	<0.001	1.54 (1.25-1.91)	[redacted](57)	[redacted]	[redacted]	[redacted](54)	[redacted]	[redacted]	[redacted](30)
MMR at any time (18-month)[a,b](%)	148/259 (57)	107/260 (41)	<0.001	1.39 (1.15-1.67)	186/282 (66)	<0.001	1.65 (1.40-1.95)	174/281 (62)	<0.001	1.55 (1.31-1.84)	113/283 (40)
MMR at any time (24-month)[a,b] (%)	166/259(64)	120/260(46)	<0.001	1.39 (1.18-1.64)	201/282 (71)	<0.001	1.67 (1.40-1.89)	187/281 (67)	<0.001	1.52 (1.30-1.78)	124/283 (44)
Risk group MMR rates 12-months[c] (%)			–	–		–	–		–	–	
Low	48/86 (56)	31/87 (36)			[redacted]			[redacted]			[redacted]
Intermediate	56/124 (45)	34/123 (28)									
High	15/49 (31)	8/50 (16)			(41)			(32)			(17)
Risk group MMR rates 18-months[c] (%)			–	–		–	–		–	–	
Low	54/86 (63)	42/87 (48)			71/103 (70)			71/103 (69)			53/104 (51)
Intermediate	69/124 (56)	49/123 (40)			69/101 (67)			63/100 (63)			39/101 (39)
High	25/49 (51)	15/50 (30)			46/78 (59)			40/78 (51)			22/78 (28)
Risk group MMR rates 24-months[c] (%)			–	–		–	–		–	–	
Low	63/86 (73)	49/87 (56)			75/103 (73)			76/103 (74)			68/104 (65)
Intermediate	76/124 (61)	62/123 (50)			75/101 (74)			67/100 (67)			44/101 (44)
High	28/49 (57)	19/50 (38)			51/78 (65)			44/78 (56)			25/78 (32)

a = ITT analysis; b = cumulative (MMR may be lost by time-point); c = Hasford risk Kantarjian, Sokal risk, Saglio; d = PenTAG calculated; # = relative risk compared with imatinib
Grey cells = not reported

4.2.3.3. Complete molecular response

Results for CMR from the two key trials are shown in Table 14. ENESTnd reports CMR at 12, 18 and 24-months. DASISION reports CMR at 18 and 24-months.

Dasatinib versus Imatinib

The DASISION trial reports, at 18-months CMR (BCR-ABL 0.0032%) rates were significantly higher for patients receiving dasatinib (13%, p = 0.04; RR 1.79, 95% CI 1.00-3.24) compared to patients receiving imatinib (7%).[75] This difference was maintained at 24-months follow-up for dasatinib (17%, p = 0.002; RR 2.10, 95% CI 1.26-3.57) compared to imatinib (8%).[77]

Nilotinib[III] versus Imatinib

The ENESTnd trial reports, at 12-months, CMR (BCR-ABL ≤0.0032%) rates were significantly higher for patients receiving nilotinib 300mg (13%, p < 0.001; RR 3.38, 95% CI 1.70-6.93) compared to patients receiving imatinib (4%).[20] At 18-months, CMR (BCR-ABL ≤0.0032%) rates were significantly higher for patients receiving nilotinib 300mg (21%, p < 0.001; RR 3.48, 95% CI 2.04-6.09) compared to patients receiving imatinib (6%).[81] At 24-months, CMR (BCR-ABL ≤0.0032%) rates continued to be significantly higher for patients receiving nilotinib 300mg (26%, p < 0.001; RR 2.62, 95% CI 1.72-4.03) compared to patients receiving imatinib (10%).[83]

At 24-months follow-up, CMR rates were higher for patients receiving nilotinib 300mg across all Sokal risk categories, than patients receiving imatinib, with CMR rates of 21% and 5% for nilotinib and imatinib respectively among those categorised as high risk.[83]

[III] Nilotinib 300mg licensed for 1st-line treatment of CML

Table 14 Complete molecular response

Study	DASISION[75, 77]				ENESTnd[20, 81, 83]						
Intervention	Dasatinib (100mg)	Imatinib (400mg)	p-value	RR (95% CI) [b]	Nilotinib (300mg)	p-value	RR (95% CI) [b, #]	Nilotinib (400mg)	p-value	RR (95% CI) [b, #]	Imatinib (400mg)
CMR 12-months[a] (BCR-ABL ≤0.0032%) (%)	–	–	–	–	37/282 (13)	<0.001	3.38 (1.70-6.93)	34/281 (12)	<0.001	3.11 (1.56-6.43)	11/283 (4)
CMR 18-months[a] (BCR-ABL ≤0.0032%) (%)	34/259 (13)	18/260 (7)	0.04	1.79 (1.00-3.24)	59/282 (21)	<0.001	3.48 (2.04-6.09)	48/233 (17)	<0.001	2.84 (1.64-5.04)	17/283 (6)
CMR 24-months[a] (BCR-ABL ≤0.0032%) (%)	44/259 (17)	21/260 (8)	0.002	2.10 (1.26-3.57)	73/282 (26)	<0.001	2.62 (1.72-4.03)	59/281 (21)	<0.001	2.12 (1.37-3.32)	28/283 (10)
Risk group CMR rates 24-months[c] (%)	–	–	–	–		–	–		–	–	
Low					25/103 (24)			30/103 (29)			10/104 (10)
Intermediate					33/101 (33)			13/100 (13)			15/101 (15)
High					16/78 (21)			16/78 (21)			4/78 (5)

a = ITT analysis; b = PenTAG calculated, c = sokal risk, # = relative risk compared with imatinib

4.2.3.4. Time to CCyR and MMR

Dasatinib versus Imatinib

The DASISION trial reports, at 12-months, 18-months and 24-months follow-up the time to a CCyR and a confirmed CCyR was significantly shorter for patients receiving dasatinib compared to imatinib (both HR 1.5, $p < 0.0001$).[29, 77, 89] The median time to a confirmed CCyR was 3.1 and 5.6 months for dasatinib and imatinib respectively (BMS, 2011).[86]

The time to a MMR was also significantly shorter for patients receiving dasatinib (HR 2.0, $p < 0.0001$) compared to patients receiving imatinib at 12-months follow-up (HR 2.0, $p < 0001$).[29] The median time to MMR was 6.3 and 9.2 months for dasatinib and imatinib respectively (BMS, 2011).[86] At 18-months and 24-months follow-up, patients receiving dasatinib were significantly still more likely to achieve a MMR (HR 1.84, $p < 0001$; HR 1.69, $p < 0001$).[75, 77]

Nilotinib versus Imatinib

The ENESTnd trial reports, the median time to MMR was significantly shorter ($p < 0.0001$) for patients receiving nilotinib 300mg (8.3 months, 95% CI 5.8-8.3) compared to patients receiving imatinib (11.1 months, 95% CI 8.5-13.6).[83]

4.2.3.5. Durability of MMR

Dasatinib versus Imatinib

No information about durability of MMR was available for dasatinib.

Nilotinib versus Imatinib

The ENESTnd study reports, of patients who achieved an MMR at 12-months, 93% of patients receiving nilotinib 300mg and 92% of patients receiving imatinib were still in MMR at 24-months.[83]

4.2.3.6. Progression to accelerated phase or blast crisis

Dasatinib versus Imatinib

The DASISION trial reports, at 12-months progression to AP or BC was not significantly different for patients receiving imatinib (n = 9) compared to patients receiving dasatinib (n = 5).[29] At 18-months there was only one extra progression, in a patient treated with imatinib.[76] At 24-months rates were imatinib (n = 15) compared to dasatinib (n = 9)

Nilotinib versus Imatinib

The ENESTnd trial reports, rates of progression to AP or BC was significantly higher at 12-months for imatinib (n = 11), compared to nilotinib 300mg (n = 2, p = 0.01), and at 24-months (2 vs 12, p = 0.005)[20, 83] Of note, the rate of progression to AP/BC in the ENESTnd study for imatinib is considerably higher than that previously reported for imatinib in the IRIS study.

4.2.3.7. Time to progression

Dasatinib versus Imatinib

Time to progression was not reported for dasatinib.

Nilotinib versus Imatinib

The ENESTnd trial reports, time to progression to AP or BC was significantly better for nilotinib 300mg (p = 0.01) and 400mg (p = 0.004) compared with imatinib at 12-months follow-up.[20]

4.2.3.8. Time to treatment failure

Time to treatment failure was not reported in the DASISION or ENESTnd trials.[20, 29]

4.2.3.9. Survival

This section reports on overall survival, progression free survival and event free survival. Progression free survival is usually defined as all cause death or progression to AP/BC, but

definition may be subjective to the trial. Event free survival is defined by the researchers of the trials and usually includes all cause death, progression to AP/BC and loss of response. Results and details of the trial survival definitions are shown in Table 15. Figure 7 and Figure 8 summarise the overall survival data.

We present these on 2 axes – available follow-up data (Figure 5) and potential long-term survival (Figure 6), as an indication of the immaturity of this data in relation to expected long-term survival.

Dasatinib versus Imatinib

The DASISION trial reports (Table 15) that PFS and OS were not statistically different between dasatinib and imatinib at 12-months (PFS 96% vs 97%; OS 97% vs 99%) 18-months (PFS 94.9% vs 93.7; OS 96 vs 97.9 %) and 24-months follow-up (PFS 96=3.7% vs 92.1%; OS 95.3% vs 95.2%), as calculated by PenTAG. [29, 75, 77]

Nilotinib[IV] versus Imatinib

At 12-months follow-up, the ENESTnd trial reports (Table 15) no significant difference in EFS compared to imatinib (95.7%) for nilotinib 300mg (97.6%, p = 0.09) and significantly higher EFS for nilotinib 400mg (99.6%, p = 0.001), with differences maintained at 24-months follow-up.[79, 83] Progression free survival at 24-months was also not significantly different for nilotinib 300mg (98%, p = 0.07) and significantly higher for nilotinib 400mg (97.7%, p = 0.04) compared to imatinib (95.2%).[83]

At 18-months, OS was not significantly different for nilotinib 300mg (98.5%, p = 0.28) and significantly higher for nilotinib 400mg (99.3%, p = 0.03) compared to imatinib (96.9%).[81] At 24-months OS was not significantly different for either dose of nilotinib compared to imatinib, 97.4%, p = 0.64; 97.8%, p = 0.21; 96.3% respectively.[83]

[IV] Nilotinib 300mg licensed for 1st-line treatment of CML, Nilotinib 400mg licensed for 2nd-line treatment of CML

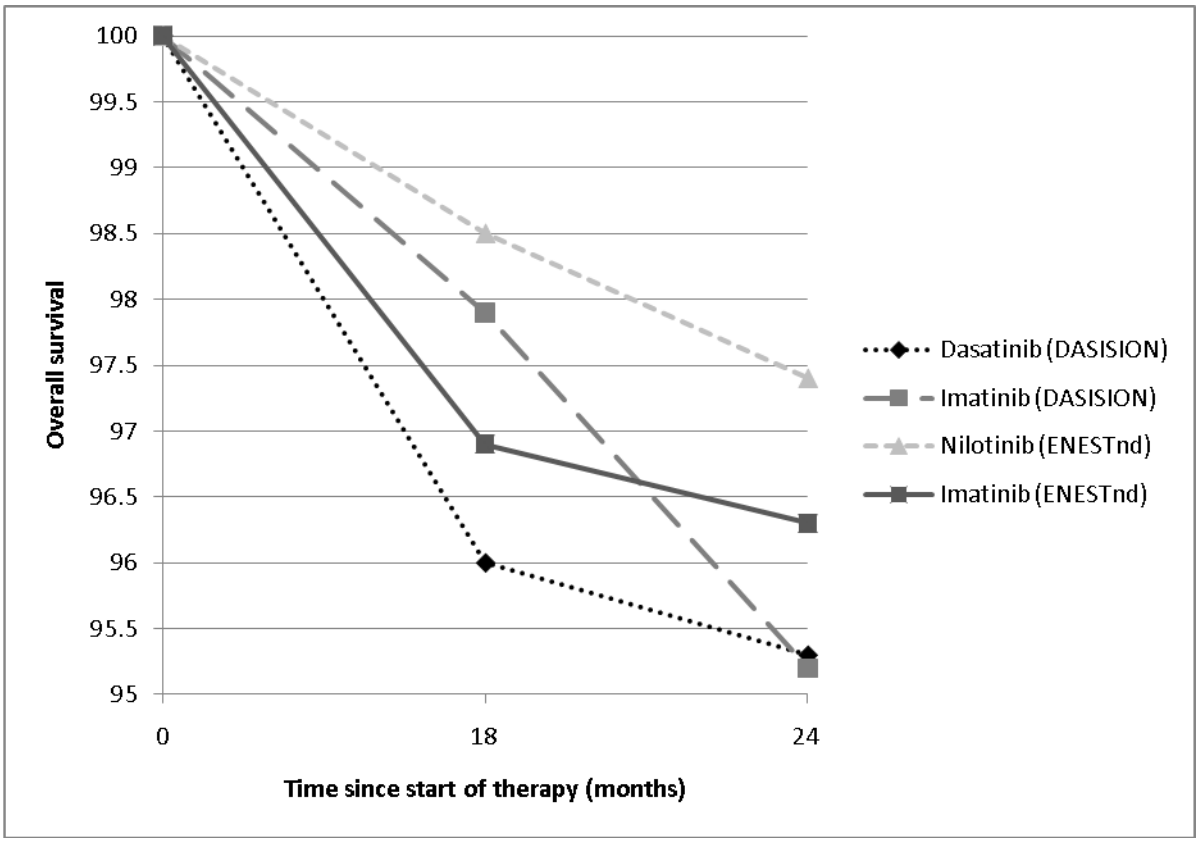


Figure 7 Overall survival (24-months axis)

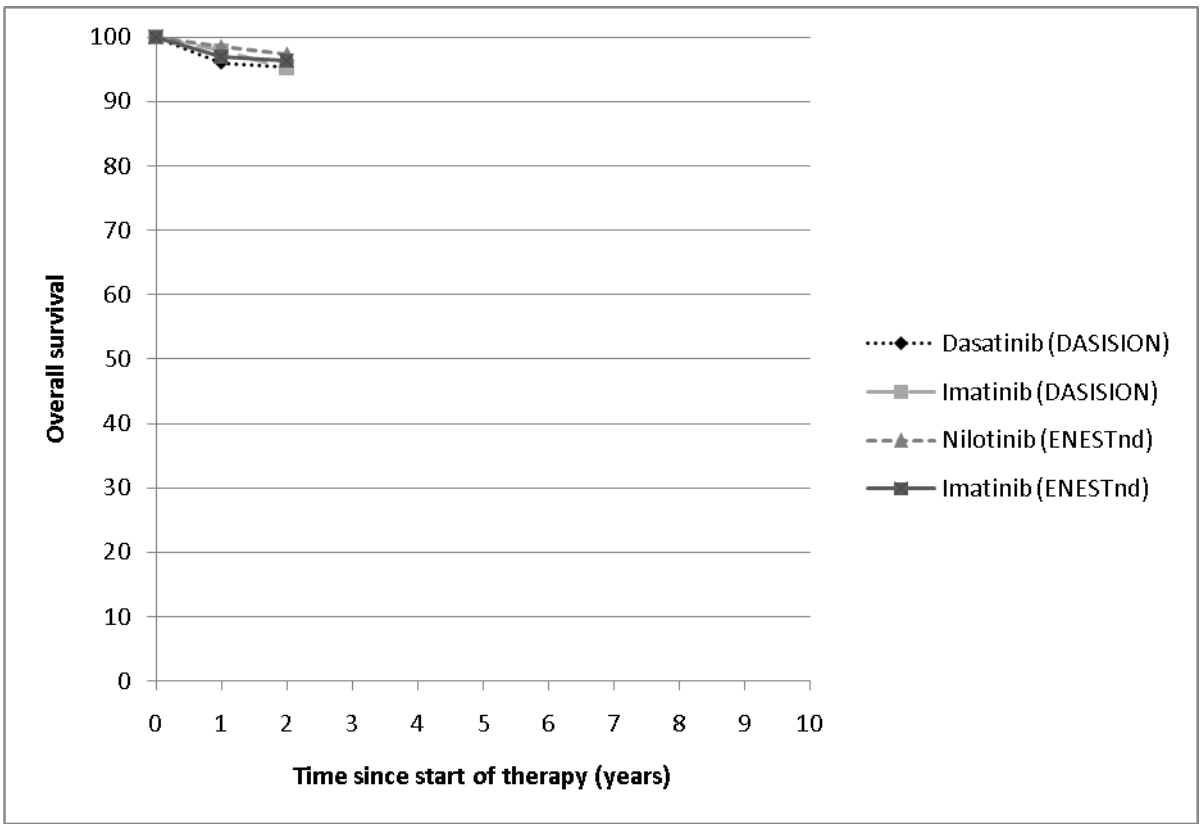


Figure 8 Overall survival (10 years axis)

Table 15 Survival (progression free, event free, overall)

Study	**DASISION**[29, 75, 77]			**ENESTnd**[79, 81, 83]				
Intervention	Dasatinib (100mg)	Imatinib (400mg)	p-value	Nilotinib (300mg)	p-value	Nilotinib (400mg)	p-value	Imatinib (400mg)
Event-free survival[a] 12-months	–	–	–	97.6%	0.09	99.6	0.001	95.7
Event-free survival[a] 24-months	–	–	–	96.4%	0.12	97.8	0.01	93.6
Event-free survival[b] 24-months	84.8%	83.8%	–	–	–	–	–	–
Progression free survival[c] 12-months	96%	97%	–	–	–	–	–	–
Progression free survival[c] 18-months	94.9%	93.7%	–	–	–	–	–	–
Progression free survival[c,d] 24-months	93.7%	92.1%	–	98%	0.07	97.7%	0.04	95.2%
Overall survival 12-months	97%	99%	–	–	–	–	–	–
Overall survival 18-months	96%	97.9%	–	98.5%	0.28	99.3%	0.03	96.9%
Overall survival 24-months	95.3%	95.2%	–	97.4%	0.64	97.8%	0.21	96.3%

a = defined as death from any cause, progression to AP/BC, loss of CCyR, loss of partial CyR or loss of complete haematologic response[79]
b = defined as no progression, failure or intolerance
c = progression defined as a doubling of white cell count to more than $20x10^9$, absence of complete haemotalogic response, increase in Ph-positive metaphases to more than 35%, progression to AP/BC, death from any cause[29]
d = PFS defined as progression to AP/BC or death by any cause[20]

4.2.3.10. Supplementary Publications

As well as the main trial reports, supplementary publications present a number of additional analyses, which are reported in this section.

Dasatinib versus Imatinib (DASISION)

Four supplementary publications were identified:

- Saglio and colleagues report on the efficacy and safety of dasatinib and imatinib by baseline cardiovascular comorbidities.[71]
- Guilhot and colleagues report on the efficacy and safety of dasatinib and imatinib by use of baseline medications.[72]
- Khoury and colleagues report on the efficacy and safety of dasatinib and imatinib by baseline comorbidities.[74]
- Schiffer and colleagues report on the responses of patients experiencing lymphocytosis.[73]

Baseline cardiovascular condition, medication or comorbidities generally had no impact on efficacy and safety of dasatinib or imatinib as a 1st-line treatment for CML.[71, 72, 74] Schiffer and colleagues reported on the responses of patients with lymphocytosis (an increase in thymus and natural killer white blood cells) compared to those without at 14-months follow-up.[73] For patients taking dasatinib, CCyR rates were slightly higher for patients with lymphocytosis (84% of N = 61) compared to those without (75% of N = 197). For patients taking imatinib, CCyR rates were lower for patients with lymphocytosis (50% of N = 14) compared to those without (70 % of 244).

Nilotinib versus Imatinib (ENESTnd)

One supplementary publication was identified and presented below, number of hospitalisations (p. 94).[78]

4.2.4. Adverse events

Results for adverse events are shown in Table 16 and Table 17 for the DASISION and ENESTnd trials respectively. Both trials report the measurement of similar haematological and nonhaematological events, with ENESTnd also reporting biochemical abnormalities.

Dasatinib versus Imatinib

The DASISION trial reports, both the drugs were well tolerated with discontinuation due to adverse events at 5% and 4% for dasatinib and imatinib respectively (12-months).[29] At 12 months, 18 months and 24-months follow-up, rates of haematological events were similar between dasatinib and imatinib (all grades and grades 3-4), except grade 3 or 4 thrombocytopenia where there were nearly twice as many events in the dasatinib arm (19-20%) compared to the imatinib arm (10-11%).[29, 75, 77] An increased frequency of fluid retention and superficial oedema was displayed for patients receiving imatinib across all grades at 12 months, 18 months and 24-months follow-up.[29, 77, 89] Rates of pleural effusion were higher for patients receiving dasatinib (10-14%) compared to patients receiving imatinib (0%).[29, 77, 89] Other nonhaematalogical events, including rash, vomiting, nausea and myalgia, generally appeared lower across time points for dasatinib compared with imatinib.

Table 16 Adverse events dasatinib vs imatinib (DASISION)

	12-months follow-up[29]				18-months follow-up[75]				24-months follow-up[77]			
Adverse Events	Dasatinib (N = 258)		Imatinib (N = 258)		Dasatinib (N = 258)		Imatinib (N = 258)		Dasatinib (N = 258)		Imatinib (N = 258)	
	Number of patients (%)[a]											
Haematologic	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Neutropenia	168 (65)	54 (21)	150 (58)	52 (20)	–	57 (22)	–	52 (20)	–	62 (24)	–	54(21)
Thrombocytopenia	181 (70)	49 (19)	160 (62)	26 (10)	–	49 (19)	–	26 (10)	–	52 (20)	–	28 (11)
Anaemia	232 (90)	26 (10)	217 (84)	18 (7)	–	28 (11)	–	18 (7)	–	28 (11)	–	21 (8)
Bleeding	–	–	–	–	–	< 1	–	1	–	< 1	–	1
Nonhaematologic adverse event	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Fluid retention	49 (19)	1	108 (42)	1	59 (23)	–	111 (43)	–	65 (25)	–	111 (43)	–
Superficial oedema	23 (9)	0	93 (36)	<1	26 (10)	–	93 (36)	–	28 (11)	–	93 (36)	–
Pleural effusion	26 (10)	0	0	0	31 (12)	–	0	–	36 (14)	–	0	–
Other	13 (5)	1	21 (8)	<1	–	–	–	–	–	–	–	–
Diarrhoea	44 (17)	<1	44 (17)	1	46 (18)	–	49 (19)	–	49 (19)	–	54 (21)	–
Nausea	21 (8)	0	52 (20)	0	23 (9)	–	54 (21)	–	26 (10)	–	59 (23)	–
Vomiting	13 (5)	0	26 (10)	0	13 (5)	–	26 (10)	–	13 (5)	–	26 (10)	–
Myalgia	15 (6)	0	31 (12)	0	15 (6)	–	31 (12)	–	–	–	–	–
Muscle inflammation	10 (4)	0	44 (17)	<1	10 (4)	–	49 (19)	–	10 (4)	–	49 (19)	–
Musculoskeletal pain	28 (11)	0	36 (14)	<1	31 (12)	–	41 (16)	–	31 (12)	–	41 (16)	–
Rash	28 (11)	0	44 (17)	1	28 (11)	–	49 (19)	–	28 (11)	–	49 (19)	–
Headache	31 (12)	0	26 (10)	0	–	–	–	–	–	–	–	–
Fatigue	21 (8)	<1	26 (10)	0	21 (8)	–	28 (11)	–	23 (9)	–	28 (11)	–

a = where events ≤ 1 only % reported

Nilotinib[V] versus Imatinib

The ENESTnd trial reports, both drugs were well tolerated with discontinuation due to adverse events at 5%, 9% and 7 % for nilotinib 300mg, 400mg and imatinib respectively at 12-months and 6%, 10% and 9% at 24-months (Novartis, 2011).[20, 87] At 12-months follow-up haematological events across all grades were lower for patients receiving either dose of nilotinib compared to imatinib. Most grade 3/4 haematological events were also lower, with neutropenia events approximately double for patients receiving imatinib (20%) compared with nilotinib 300mg (12%) and 400mg (10%).[20] For non-haematological events, nausea, diarrhoea, vomiting and muscle spasm events were approximately three times higher for patients receiving imatinib compared to both doses of nilotinib across all grades. Across all grades, oedema events were also higher for patients taking imatinib compared with both doses of nilotinib, particularly eyelid and periorbital oedema.[20] Conversely, rash, headache, pruritius and alopecia events were up to three times higher for both doses of nilotinib compared with imatinib across all grades.[20]

[redacted]

Biochemical abnormalities of grade 3/4 were uncommon in any study arm. Across all grades, increased bilirubin, glucose, ALT and AST were more common for patients receiving nilotinib 300mg and 400mg. Biochemical abnormalities are normally manageable and not clinically important.[20] As previously stated, nilotinib carries a 'black box' warning for possible heart problems due to QTc prolongation, where prolonged cardiac ventricular repolarisation can result in ventricular tachycardia and death. No patient in the ENESTnd study had an increased QTc of more than 500 msec (where complexities may arise) at 12, 18 or 24-months follow-up.[20, 80, 83]

The number of hospitalisations, hospital days and length of stay were lower for nilotinib 300mg compared to imatinib. There were more hospitalisations for patients receiving nilotinib 400mg compared to imatinib, the length of stay and hospital days were lower.[78]

[V] Nilotinib 300mg licensed for 1st-line treatment of CML, Nilotinib 400mg licensed for 2nd-line treatment of CML

Table 17 Adverse events nilotinib vs imatinib (ENESTnd)

	12-months follow-up[20]						24-months follow-up[82, 83, 87]					
Adverse event	Nilotinib 300mg (N = 279)		Nilotinib 400mg (N = 277)		Imatinib 400mg (N = 280)		Nilotinib 300mg (N = 279)		Nilotinib 400mg (N = 277)		Imatinib 400mg (N = 280)	
	Number of patients (%)[a]											
Haematologic	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Neutropenia	120 (43)	33 (12)	106 (38)	27 (10)	189 (68)	56 (20)	41 (15)	33 (12)	30 (11)	31 (11)	57 (20)	59 (21)
Thrombocytopenia	133 (48)	28 (10)	136 (49)	33 (12)	156 (56)	24 (9)	48 (17)	28 (10)	54 (20)	33 (12)	48 (17)	25 (9)
Anaemia	105 (38)	9 (3)	105 (38)	9 (3)	132 (47)	14 (5)	18 (6)	11 (4)	24 (9)	11 (4)	46 (16)	14 (5)
Nonhaematologic	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Rash	86 (31)	<1	100 (36)	7 (3)	32 (11)	1	89 (32)	<1	103 (37)	8 (3)	36 (13)	6 (2)
Headache	39 (14)	1	58 (21)	1	23 (8)	0	39 (14)	1	61 (22)	1	25 (9)	<1
Nausea	32 (11)	<1	54 (19)	1	86 (31)	0	39 (14)	<1	59 (21)	1	95 (34)	0
Alopecia	22 (8)	0	36 (13)	0	11(4)	0	25 (9)	0	36 (13)	0	14 (5)	0
Pruritus	41 (15)	<1	36 (13)	<1	15 (5)	0	45 (16)	<1	36 (13)	<1	17 (6)	0
Myalgia	27 (10)	<1	28 (10)	0	28 (10)	0	28 (10)	<1	28 (10)	0	31 (11)	0
Fatigue	30 (11)	0	25 (9)	1	22 (8)	<1	31 (11)	0	25 (9)	<1	28 (10)	<1
Vomiting	13 (5)	0	24 (9)	1	40 (14)	0	14 (5)	0	25 (9)	1	50 (18)	0
Diarrhoea	22 (8)	1	18 (6)	0	60 (21)	1	22 (8)	<1	20 (7)	0	73 (26)	1
Muscle spasm	20 (7)	0	17 (6)	1	67 (24)	1	22 (8)	0	20 (7)	<1	75 (27)	<1
Peripheral oedema	14 (5)	0	15 (5)	0	38 (14)	0	14 (5)	0	17 (6)	0	42 (15)	0
Eyelid oedema	2 (1)	0	5 (2)	<1	37 (13)	<1	<1	0	6 (2)	<1	45 (16)	<1
Periorbital oedema	1 (<1)	0	2 (1)	0	34 (12)	0	<1	0	1	0	39 (14)	0
Biochemical abnormality	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased total bilrubin	149 (53)	10 (4)	171 (62)	21 (8)	27 (10)	<1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased alkaline	59 (21)	0	76 (27)	0	92 (33)	<1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

phosphate												
Decreased phosphate	88 (32)	13 (5)	94 (34)	13 (5)	126 (45)	21 (8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased glucose	100 (36)	17 (6)	113 (41)	10 (4)	57 (20)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased lipase	67 (24)	16 (6)	80 (29)	16 (6)	30 (11)	9 (3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increase amylase	42 (15)	1 (<1)	51 (18)	1	35 (12)	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biochemical abnormality	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased creatinine	13 (5)	0	15 (5)	0	36 (13)	<1	–	–	–	–	–	–
Increased ALT	184 (66)	11 (4)	203 (73)	25 (9)	57 (20)	7 (2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased AST	112 (40)	4 (1)	134 (48)	8 (3)	65 (23)	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Hospitalisation[78]								
	Nilotinib 300mg (N = 279)	p-value#	Nilotinib 400mg (N = 277)	p-value#	Imatinib 400mg (N = 280)	–	–	–
Number of hospitalisations	48	–	74	–	57	–	–	–
Total hospital days	434	–	591	–	642	–	–	–
Length of stay, days-median (range)	4 (1-64)	–	4 (1-101)	–	5 (1-86)	–	–	–
Hospital days per 1000 patient days	2.72	0.057	3.69	0.681	3.99	–	–	–

a = where events ≤ 1 only % reported

4.2.5. Health-related quality of life

Health related quality of life was not reported in the DASISION[29] or ENESTnd[20] trials.

4.2.6. Indirect comparison of dasatinib and nilotinib

No trials comparing dasatinib and nilotinib head to head. However, an indirect comparison of nilotinib to dasatinib was carried out using results from the DASISION and ENESTnd trials.[20, 29]

The primary outcomes reported are MMR by 12 months and CCyR by 12 months. Because the DASISION trial reported *complete cytogenetic response* as well as *confirmed complete cytogenetic response*, two sets of results are reported for the CCyR outcome.[29] As shown in Table 18 there was no difference between dasatinib and nilotinib for CCyR, MMR or CMR rates at 12-months follow-up or 24-months follow-up.

Oxford Outcomes conducted an indirect comparison of dasatinib and nilotinib based on the data from the DASISION and ENESTnd trials.[20, 29, 84] The indirect results for 12-months follow-up showed no statistical difference between dasatinib and nilotinib for CCyR or MMR data.

[redacted]

Signorovitch and colleagues report on the indirect comparison of the DASISION and ENESTnd trials, with individual patient data for patients receiving nilotinib (ENESTnd).[20, 29, 85] Individual patient data for patients receiving 300mg nilotinib were weighted to match the baseline characteristics reported for patients receiving dasatinib including age, gender, ECOG performance and haematology lab values. After matching patients receiving 300mg nilotinib compared to dasatinib had significantly higher rates of MMR (56.8% vs 45.9%, p = 0.001) and OS (99.5 vs 97.3, P = 0.046). CCyR was not assessed due to different measurement procedures of the trials. We have analysed CCyR as we believe they are sufficiently similar to warrant comparison.

Table 18 Mixed treatment analysis comparing nilotinib to dasatinib

Outcome	Comparison[b20, 29, 77, 90]	PenTAG (current review)		Oxford outcomes (2010)		[redacted]	
		odds ratio	95% CI	odds ratio	95% CI	[redacted]	[redacted]
Major molecular response at 12-months	Nilotinib (300mg) versus Dasatinib	1.28	0.77-2.16	1.33	0.77-2.15	[redacted]	[redacted]
	Nilotinib (400mg) versus Dasatinib	1.24	0.74-2.08	1.28	0.74-2.06	[redacted]	[redacted]
Best major molecular response by 24-months	Nilotinib (300mg) versus Dasatinib	1.53	0.93-2.51	–	–	[redacted]	[redacted]
	Nilotinib (400mg) versus Dasatinib	1.22	0.75-2.00	–	–	[redacted]	[redacted]
Complete cytogenetic response at 12-months	Nilotinib (300mg) versus Dasatinib	1.09	0.61-1.92	1.13	0.61-1.93	[redacted]	[redacted]
	Nilotinib (400mg) versus Dasatinib	0.95	0.54-1.67	0.99	0.54-1.67	[redacted]	[redacted]
Complete confirmed cytogenetic response at 12-months[a]	Nilotinib (300mg) versus Dasatinib	1.28	0.74-2.20	–	–	[redacted]	[redacted]
	Nilotinib (400mg) versus Dasatinib	1.12	0.65-1.92	–	–	[redacted]	[redacted]
Complete cytogenetic response by 18-months	Nilotinib (300mg) versus Dasatinib	–	–	–	–	[redacted]	[redacted]
	Nilotinib (400mg) versus Dasatinib	–	–	–	–	[redacted]	[redacted]
Complete cytogenetic response at 24-months	Nilotinib (300mg) versus Dasatinib	1.44	0.76-2.76	–	–	–	–
	Nilotinib (400mg) versus Dasatinib	1.21	0.64-2.28	–	–	–	–
Complete confirmed cytogenetic response at 24-months[a]	Nilotinib (300mg) versus Dasatinib	1.40	0.77-2.56	–	–	–	–
	Nilotinib (400mg) versus Dasatinib	1.17	0.65-2.12	–	–	–	–
Complete molecular response at 24-months	Nilotinib (300mg) versus Dasatinib	1.37	0.66-2.82	–	–	–	–
	Nilotinib (400mg) versus Dasatinib	1.04	0.50-2.17	–	–	–	–

a = Using an outcome referred in the DASISION[29] trial as "Confirmed complete cytogenetic response" (i.e. two assessment at least 28 days apart) for dasatinib arm
b = Comparisons are taken from ENESTnd and DASISION trials follow-up data (12-24 months);
[redacted]

4.3. Overall clinical effectiveness conclusions

From the two trials available, both the second generation TKIs dasatinib 100mg (once daily; DASISION trial) and nilotinib 300mg (twice daily; ENESTnd trial) have a statistically significant advantage compared to the first generation TKI imatinib 400mg (once daily) as measured by surrogate outcomes, however there is insufficient data to assess longer term patient relevant outcomes (e.g. PFS, OS, HRQoL). Rates of CCyR and MMR for the second generation TKI were higher, more rapidly attained, and deeper (MMR) compared to imatinib.

All three drugs were well tolerated with discontinuation due to adverse events < 10%.

With no head to head data available, an indirect comparison analysis was conducted between dasatinib and nilotinib. There was no difference between dasatinib and nilotinib for the primary outcomes of CCyR or MMR at 12-months or 24-months follow-up. The results of the DASISION and ENESTnd trials are summarised in Table 19 and Table 20 respectively

Table 19 Summary of DASISION results (dasatinib)

DASISION[29] (dasatinib 100mg versus imatinib 400mg)	
CCyR	• Rates of CCyR and confirmed CCyR were significantly higher (11%) for patients receiving dasatinib compared to imatinib at 12-months ($p < 0.008$), but not at 24-months (4%, $p > 0.1$). • CCyR rates were higher across all Hasford risk groups. • The difference in confirmed CCyR rates were maintained at 18-months. • Time to a CCyR was shorter for patients receiving dasatinib at 12, 18 and 24-months (HR 1.5, $p < 0.0001$) .
MMR	• Rates of MMR were significantly higher (18%) for patients receiving dasatinib compared to imatinib at 12-month ($p < 0.001$), which was maintained at 18-months (19%, $p < 0.001$). • MMR rates were higher across all Hasford risk groups. • Time to a MMR was also shorter for patients receiving dasatinib at 12-months (HR 2.0, $p < 0.0001$), 18-months (HR 1.84, $p < 0.0001$) and 24-months (HR 1.69, $p < 0.0001$).
Survival	• Progression free survival and overall survival were similar between dasatinib and imatinib at 12-months (PFS 96% vs 97%; OS 97% vs 99%), 18-months follow-up (PFS 94.9% vs 93.7; OS 96 vs 97.9 %) and 24-months (PFS 93.7% vs 92.1; OS 95.3 vs 95.2 %).
Adverse events	• Rates of haematological events were similar between dasatinib and imatinib. • Except grade 3 or 4 thrombocytopenia where there were nearly twice as many events in the dasatinib arm (19%) compared to the imatinib arm (10%). • Pleural effusion rates were higher for patients receiving dasatinib (12%) compared to patients receiving imatinib (0%). • Rates of nonhaematalogical events demonstrated higher rates of fluid retention and superficial oedema for patients receiving imatinib across all grades. • Other nonhaematalogical events generally appeared lower for dasatinib compared with imatinib, including rash, vomiting, nausea and myalgia.

Table 20 Summary of ENESTnd results (nilotinib)

ENESTnd[20] (nilotinib 300mg versus imatinib 400mg)	
CCyR	• Rates of CCyR were significantly higher (15%) for patients receiving nilotinib 300mg compared to imatinib at 12-months ($p < 0.001$). • CCyR rates were higher across all Sokal risk groups. • The difference in CCyR rates were maintained at 18 and 24-months ($p < 0.002$).
MMR	• Rates of MMR were significantly higher (22%) for patients receiving dasatinib compared to imatinib at 12-month ($p <0.001$). • MMR rates were higher across all Sokal risk groups. • The difference in MMR rates were maintained at 18 and 24-months [redacted] • Median time to MMR was significantly shorter ($p < 0.0001$) for patients receiving nilotinib 300mg (8.6 months, 95% CI 8.3-11.1) compared to patients receiving imatinib (22.1 months, 95% CI 19.5-27.6). • For patients with an MMR at 12-months, 93% receiving nilotinib 300mg and 92% receiving imatinib were still in MMR at 24-months.
Survival	• Progression free survival at 24-months was not statistically different for nilotinib 300mg (98%) compared to imatinib (95.2%). • At 18 and 24-months, overall survival was not statistically different for nilotinib 300mg (98.5%; 97.4%) compared to imatinib (96.9%; 96.3%).
Adverse events	• Haematological events across all grades were lower for patients receiving nilotinib 300mg compared to imatinib. • For non-haematological events, nausea, diarrhoea, vomiting and muscle spasms events were up to three times higher for patients receiving imatinib compared to nilotinib 300mg across all grades. • Conversely rash, headache, pruritius and alopecia events were up to three times higher nilotinib 300mg compared with imatinib across all grades.

5. ASSESSMENT OF EVIDENCE TO SUPPORT THE USE OF CCyR AND MMR AS SURROGATE OUTCOMES

Due to short-term follow-up, DASISION and ENESTnd trials both provide surrogate outcomes as indicators of potential patient benefit. For a biomarker to be accepted as an appropriate surrogate measure of the final outcome, the following criteria should be met:

1. evidence of biological plausibility of relationship between the surrogate outcome and the final patient-relevant outcome (from pathophysiological studies and/or understanding of the disease process);

2. evidence demonstrating consistent association between surrogate outcome and final patient-relevant outcome (from observational studies);

3. evidence demonstrating treatment effects on the surrogate correspond to treatment effects on the patient-relevant outcome (from randomised clinical trials (RCTs)).[35]

As discussed in Section 2.3.1 two published trials have both presented evidence supporting (major or complete) cytogenetic response as a surrogate outcome in the prediction of all cause survival for CML patients in chronic phase receiving first line interferon treatment.[37, 92] Our initial literature searches (Section 4.2.1) failed to identify an assessment of the evidence for the use of cytogenetic response or molecular response as acceptable surrogate outcome for long-term (≥ 1 year) overall survival within the TKI class of therapies (i.e. imatinib, dasatinib and nilotinib) for the first line treatment of chronic phase CML.

We therefore undertook this systematic review to assess the evidence base for the use of cytogenetic response and molecular response as surrogate measures for survival or health related quality of life with dasatinib, nilotinib and imatinib.

5.1. Methods for reviewing effectiveness of surrogate outcome measures

This systematic review was undertaken following the general principles published by the NHS Centre for Reviews and Dissemination and the PRISMA guidelines.[65, 66]

5.1.1. Identification of studies

The search strategy comprised of the following main elements:

- Searching of electronic databases
- Scrutiny of bibliographies of retrieved papers and manufacturer submissions.

The following databases were searched: MEDLINE (Ovid); EMBASE; The Cochrane Library (including the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, DARE, NHS EED and HTA databases); NRR (National Research Register); Web of Science (including Conference Proceedings); Current Controlled Trials; Clinical Trials.gov; FDA website; EMEA website. These were searched from search end-date of the last technology appraisal report on this topic October 2002.[67]

The searches were written by CC with advice from TP, RA, RT, OC and RG. The surrogate terms circulated were crossed-checked with against a previous review of surrogate outcomes and CR for sensitivity and inclusion.[93]

5.1.2. Inclusion and exclusion criteria

5.1.2.1. Inclusion criteria

Studies were included if they met the following criteria:

Population: Adults with chronic phase CML, naïve to any IFN or TKI treatment.

Interventions: Dasatinib or nilotinib or imatinib in accordance with the marketing authorisation.

Comparators: Any or none

Outcomes:

Final patient-relevant outcomes

- Progression-free survival
- Overall all cause survival
- Health-related quality of life.

Potential surrogate outcomes

- Complete cytogenetic response
- Major molecular response

Study design: Any observational or experimental study that reported the association between complete cytogenetic response and/or major molecular response AND any one of the above final patient-relevant outcomes.

We excluded conference abstracts, narrative reviews, editorials, opinion pieces, non English language papers, individual case studies.

Studies were selected in two stages. First, two reviewers (TP and OC) examined all titles and abstracts. Second, full texts of any potentially relevant studies were obtained and relevance of each paper assessed independently by the same two reviewers according to the inclusion and exclusion criteria and any discrepancies resolved by discussion.

5.1.3. Data extraction strategy

Study characteristics and surrogate/final outcome data were extracted by one reviewer (OC) using a standardised data extraction form and independently checked by a second (TP or RT). Data digitalization software (WinDIG Version 2.5) was used to extract data from Kaplan Meier survival curves. Disagreements were resolved by discussion, with involvement of a third reviewer if necessary. Data extraction forms for each included study are included in Appendix 4.

5.1.4. Quality assessment strategy

The methodological quality of included studies was assessed according to a modified list of criteria specified by the Centre of Reviews and Dissemination (CRD). Quality was assessed by one reviewer (OC) and judgements were checked by a second (TP or RT).

5.1.4.1. Internal Validity

The instrument sought to assess the following considerations:

- Is the hypothesis/aim/objective of the study clearly described?

- Were the case series collected at more than one centre?
- Are patient characteristics adequately described?
- Are inclusion and exclusion criteria clearly reported?
- Were data collected prospectively?
- Were patients recruited consecutively?
- Did all the participants receive the same intervention?
- Is the use of any concurrent therapies adequately described?
- Was an ITT analysis performed?
- Were dropouts from the trial adequately described?

In addition, data about population, treatment discontinuation and subsequent therapies, surrogate endpoints response and patient relevant outcomes were recorded (see Appendix 4).

5.1.4.2. External validity

External validity was judged according to the ability of a reader to consider the applicability of findings to the UK CML population.

5.1.5. Methods of data synthesis

An initial review of included studies revealed two key limitations. Firstly, there was a lack of data reported to assess the trial level association between TKI treatment effects on complete cytogenetic response and TKI treatment effect on patient-relevant outcome. This would be needed for high level evidence of surrogacy. Secondly, there was no presentation of data of the association of complete cytogenetic response or major molecular response and health-related quality of life. It was therefore decided to focus on studies that reported overall survival and/or progression free survival stratified by either complete cytogenetic response or major molecular response.[37, 92]

For each study, levels of OS and PFS were extracted by response stratum at each year following trial recruitment (or randomisation) up to the latest follow up point reported. In most studies OS and PFS data were reported in Kaplan-Meier curves using landmark analysis to evaluate differences in the final patient-relevant outcomes between responder and non-responders. The landmark method determines each patient's response at a fixed time point, with survival estimates calculated from that time point and associated statistical tests being

conditional on patients' landmark responses.[VI] Note that in this method, patients who die before the landmark time point are excluded from the analysis.[94]

We selected 12 months after the start of 1st-line TKI therapy as the landmark for our analysis, as the DASISION and ENESTnd trials consider respectively the rate of major molecular response and confirmed complete cytogenetic response at 12 months after randomisation as primary endpoints.[20, 29] A weighted average of the OS and PFS at different yearly intervals was estimated for both the responders and non-responders by taking into account the initial number of patients in the two groups. Wilson 95% confidence intervals were derived for each point estimate assuming binomial distributed variables and no censoring of data.[95] Analyses were carried out using STATA© v.11.2 (StataCorp, Texas, US).

5.2. Results

5.2.1. Identification of evidence

The electronic searches retrieved a total of 5,033 titles and abstracts. Two papers were found by updated databases searches; 3 were identified by reviewers through hand searching and/or referenced in industry submissions. These papers were then excluded based on title and abstract because of the population was treated with interferon or they were conference abstracts. [96-98]

After de-duplication, 3,555 papers were screened and the majority of them were excluded on title and abstract. Full text of the remaining 63 papers was requested for more in-depth screening. The process is illustrated in detail in Figure 9. The last step of the process was the inclusion of selected papers in the quantitative analysis for the assessment of both complete cytogenetic response and major molecular response as surrogate measure for OS and PFS. Where a study had been reported in several publications, it was considered only once according to the type of relationship reported (CCR and/or MMR vs OS and/or PFS) and the paper reporting maximum follow-up was used. One study from India was deemed not externally valid in portraying UK CML patients population and treatment response.[99] Although reporting on OS and PFS stratified by level of cytogenetic response it was therefore

[VI] In the included papers, the survival probabilities were referred to the starting of the treatment rather than to the time of response.

excluded from the quantitative analysis. The details of studies excluded on full review, along with the reasons for their exclusion are detailed in Appendix 5.

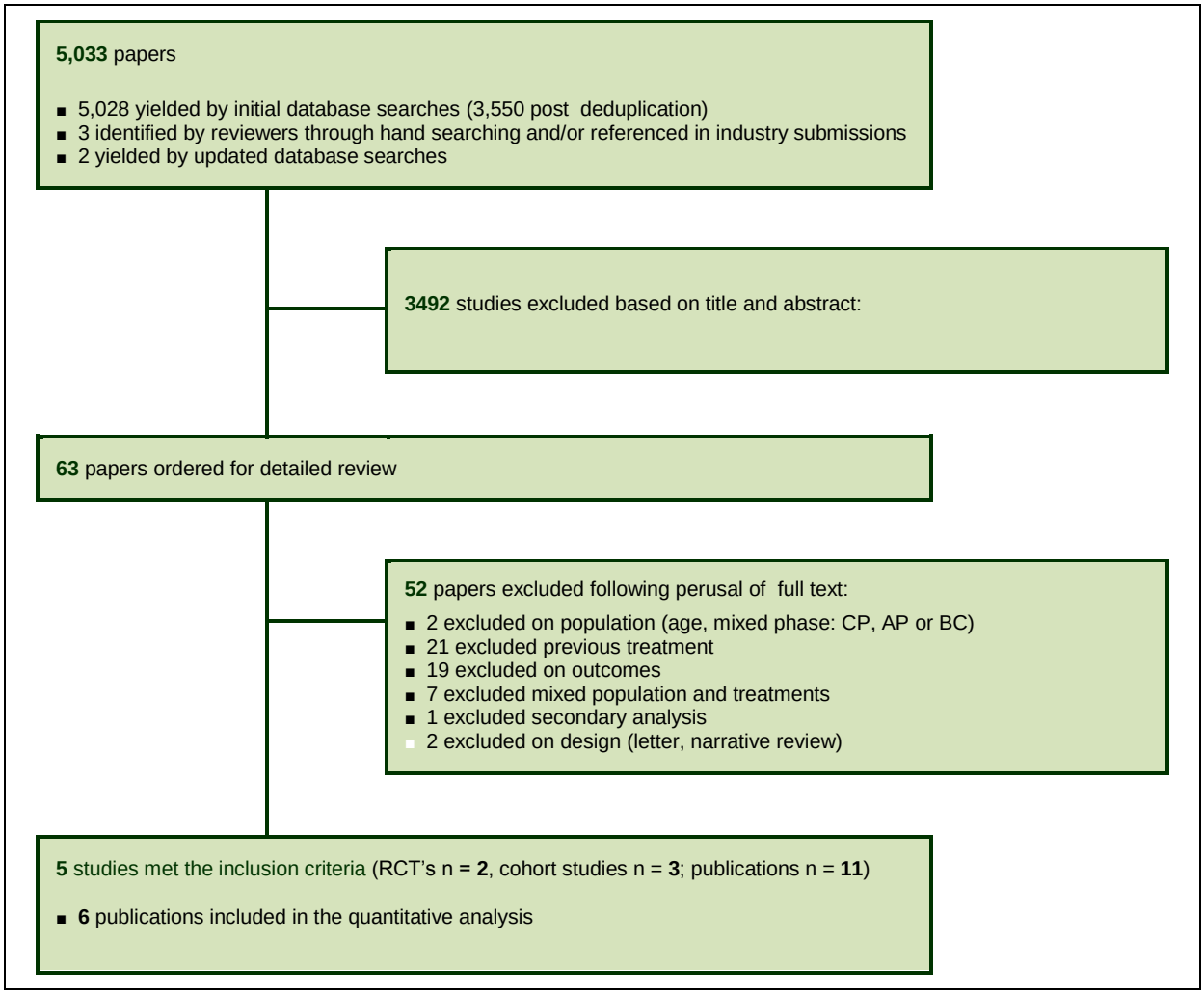


Figure 9 Flow diagram study inclusion process surrogate outcomes

5.2.2. Assessment of surrogate evidence

5.2.2.1. Study and population characteristics

Eleven publications were included, all related to imatinib, reporting on five separate studies (Table 21). They are five reports of two cohort/single-arm studies, a single report of an RCT and five reports of the IRIS RCT. Differences in details about the same study extracted from different papers are due to different follow-up and different analyses carried on.[27, 28, 99-107] No studies were identified considering patients with CML who were treated by dasatinib or nilotinib.

Table 21 General characteristics of included studies

Study (Country)	Authors	Year published	Study type	N (imatinib arm)	Median age (range)	Intervention	Comparator	Follow-up (months)
(UK)	De Lavallade et al.[100]	2008	Cohort/single arm	204	46 (18-79)	Imatinib	None	38
	Marin et al.[106]	2008	Cohort/single arm	224	46 (18-79)	Imatinib	None	46
(India)	Rajappa et al.[99]	2008	Cohort/single arm	201	32 (18-72)	Imatinib	None	29
(US)	Kantarjian et al.[104]	2006	Cohort/single arm	279	48 (15-84)	Imatinib	None	42
	Kantarjian et al.[105]	2008	Cohort/single arm	276	48 (15-84)	Imatinib	None	48
(Germany)	Hehlmann at al.[101]	2011	RCT	324	54 (16-88)	Imatinib	Imatinib400 mg/d combined with IFN imatinib800 mg/d	43
IRIS (International)	Druker er al.[27]	2006	RCT	553	50 (18-70)	Imatinib	IFN-α plus cytarabine	60
	Hochhaus et al. [102]	2009	RCT	551	50 (18-70)	Imatinib	IFN-α plus cytarabine	70
	Hughes et al.[28]	2003	RCT	333	51 (18-70)	Imatinib	IFN-α plus cytarabine	25
	Hughes et al.[103]	2010	RCT	476	50 (20-69)	Imatinib	IFN-α plus cytarabine	77
	Roy et al.[107]	2006	RCT (Retrospective comparison)	551	50 (18-70)	Imatinib	IFN-α plus cytarabine	42

Only the arm receiving imatinib standard dose 1st-line therapy was considered from each RCT study, because the IRIS trial was inadequate to demonstrate a survival benefit for imatinib versus interferon-alpha therapy in newly diagnosed Philadelphia chromosome (Ph)-positive chronic-phase chronic myelogenous leukemia (CML) due to the high rate of crossover (65% at 72 month follow-up) from interferon-alpha to imatinib.[102] Hehlmann and colleagues on the other hand, compare the 400mg/d imatinib with the high dose therapy (i.e. 800mg/d) or combined therapy with interferon.[108]

The number of patients in the imatinib arm varied from 201 up to 553, with a median age between 32 and 54 years (overall range, 15-88). The median follow-up ranged from 25 to 77 months, thus some evidence on the treatment effect on survival at 6 or 7 years after the initiation of imatinib is available. Two publications are UK studies, as many as US studies; one publication sets in Germany, one in India, while the IRIS trial is a multicentre international study.

The inclusion criteria for the studies were similar, patients with newly diagnosed (within 6 months of study entry)[VII] Ph+ chronic myeloid leukemia in chronic phase, previously untreated with the exception of hydroxyurea and anagrelide.

5.2.2.2. Assessment of study quality

Table 22 illustrates the results of the quality assessment performed on the 11 included publications.

As a number of publications reported different analyses based on the same study population we individually assessed a number of quality features associated with each of these studies separately, such as whether the ITT principle was applied.

[VII] Kantarijan et al.[105] include 5 (2%) patients with a CML duration lower than 12 months.

Table 22 Summary of quality assessment of included studies

	DeLavallade et al.[100]	Marin et al.[106]	Rajappa et al.[99]	Kantarjian et al.[104]	Kantarjian et al.[105]	Hehlmann at al.[108]	Druker er al.[27]	Hochhaus et al.[102]	Hughes et al.[28]	Hughes et al.[103]	Roy et al.[107]
Is the hypothesis/ aim/objective of the study clearly described?	Yes		Yes	Yes		Yes	Yes				
Were the case series collected at more than one centre?	No		No	No		No	Yes				
Are patient characteristics adequately described?	Yes		Yes	Yes		Yes	Yes				
Are inclusion and exclusion criteria clearly reported?	Yes		Yes	Yes		Yes	Yes				
Is the use of any concurrent therapies adequately described?	Yes		No	Unclear		Yes	Yes				
Were patients recruited consecutively?	Yes		Unclear	Unclear		Unclear	Unclear				
Were data collected prospectively?	Yes	No	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes[a]	No
Did all the participants receive the same intervention?	Yes	Yes	Yes	Unclear	No	Yes	Yes[b]	Yes[a]	Yes[c]	Yes[d]	Yes[a]
Was an ITT analysis performed?	No	No	No	No	No	No	No	No	No	No	No
Were dropouts from the trial adequately described?	Yes	Yes	No	No	No	Yes	Yes	Yes	No	No	Yes

a = Analysis on IRIS imatinib arm subpopulation
b = The study focuses on patients randomized to receive imatinib regardless of whether crossover occurred.
c = The study focuses on patients randomized to receive imatinib who did not crossover to the other treatment
d = The study focuses on patients in the imatinib arm of the IRIS trial with at least 1 BCR-ABL transcript measurement

5.2.2.3. Analysis of overall survival and progression free survival by cytogenetic and molecular response

For the purpose of this analysis, we focused on four main outcomes:

Final patient-relevant outcomes

- Overall survival, calculated since the start of imatinib therapy (or diagnosis) until death from any cause or date of last visit;

- Progression-free survival, described as survival without evidence of progression to accelerated or blastic phase disease.[27, 100, 102, 103, 106] Or survival without evidence of accelerated-phase or blast-crisis disease, white-cell count increasing, loss of complete hematologic or cytogenetic response or death from any cause during therapy.[28, 99, 101, 104, 105, 107]

Potential surrogate outcomes

- Complete cytogenetic response, defined as absence of the Philadelphia chromosome among at least 20 cells in metaphase in a bone marrow aspirate (see 2.3 Disease Monitoring and treatment response), as opposed to no complete cytogenetic response;

- Major molecular response, a standardised BCR-ABL/ABL ratio of less than 0.1% which is equivalent to a 3 log reduction from the 100% baseline for untreated patients (see Section 2.3 Disease Monitoring and treatment response), as opposed to no major molecular response.

To prevent double counting, patient cohorts presented in more than one paper were included only once in the analysis. Selection was based on the study reporting the longest follow-up and an appropriate comparison between responder (complete cytogenetic vs not complete cytogenetic responders or major-molecular vs not major-molecular responders (Table 23). This choice is based on the primary endpoints assessed in the key trials assessing the clinical effectiveness of dasatinib and nilotinib, which consider respectively the rate of major molecular response and confirmed complete cytogenetic response at/by 12 months after randomization.[20, 29] Kantarjian and colleagues compare patients showing a major cytogenetic response (≤35% Ph-positive chromosomes in bone marrow aspirates) with patients without a

major-cytogenetic response at 12 months;[VIII] whereas other studies compare patients with a complete cytogenetic response with patients with minor cytogenetic response, no major molecular response or no cytogenetic response at all.[102, 104-106] Molecular response is often assessed after a certain degree of cytogenetic response has been reached, so four out of seven papers present the final outcomes by a conjoint assessment of complete cytogenetic and major molecular response.

Table 23 Comparisons between responders and non-responders to treatment

Authors	Final outcome by level of CR		Final outcome by level of MMR	
	OS	PFS	OS	PFS
De Lavallade et al.[100]	CCyR vs No CCyR	CCyR vs No CCyR	CCyR+MMR vs CCyR+No MMR	CCyR+MMR vs CCyR+No MMR
Marin et al.[106]	CCyR vs Failure[a]	CCyR vs No CCyR	-	-
Kantarjian et al.[104]	MCyR vs No MCyR	-	CCyR+MMR vs CCyR + No MMR	-
Kantarjian et al.[105]	CCyR vs Minor CyR	CCyR vs Minor CyR	MMR vs No MMR	MMR vs No MMR
Hehlmann at al.[101]	-	-	MMR vs No MMR	MMR vs No MMR
Druker er al.[27]	-	CCyR vs No MCyR	-	CCyR + MMR vs No CCyR + No MMR
Hochhaus et al.[102]	-	CCyR vs No CyR	-	-
Hughes et al.[28]	-	CCyR + MMR vs No CCyR	-	CCyR + MMR vs CCR + No MMR
Hughes et al.[103]	-	-	MMR vs No MMR	MMR vs No MMR
Roy et al.[107]	CCR vs No CCR	-	-	-

a = Marin et al. (2008) provide results according to the European LeukemiaNet for failure or suboptimal response. We considered the survival at 5 years for patients with failure at 12 months (less than partial cytogenetic response) and PFS for patients with failure at 18 months (less than complete cytogenetic response).

The shaded cells indicate papers providing data for the different quantitative analyses, by surrogate outcome and patient-relevant outcome

[VIII] The group of people achieving a minor cytogenetic response at 12 months after the 1st-line treatment initiation (n = 5) in Kantarjian and colleagues[105] study report was excluded from the pooled overall survival average estimate.

As previously described (Section 5.1.5), 12-month landmark analysis after the starting of the imatinib therapy was selected for this analysis. Although this method should consider the survival of patients starting from the date when the event (CCyR or MMR) presents itself, survival data in the studies refer to the beginning of the first line therapy, hence the realignment of the year points survival probabilities towards a common time reference was not required.

5.2.2.4. Survival by level of cytogenetic response

Figure 10 shows the weighted pooled overall survival (95% CI) at yearly intervals after the initiation of imatinib treatment by cytogenetic response. Three publications provided data for the estimates.[100, 105, 107] The impact of failing to achieve a CCyR at 12 months becomes increasingly apparent over time with increasing differences in OS between those who respond and those who do not. No non-responder group data at 48 months is reported. It was decided not to include the non-responder group data from Kantarjian and colleagues, because they included five patients who developed a minor cytogenetic response at 12 months.[105]

The weighted average of the PFS by complete cytogenetic response at 12 months at yearly intervals after the initiation of imatinib therapy is shown in Figure 11. The estimates were obtained by the three papers which reported PFS across groups with different level of cytogenetic response.[100, 102, 105] The plotted values and the uncertainty around the estimates of OS and PFS by cytogenetic response are given in Table 24.

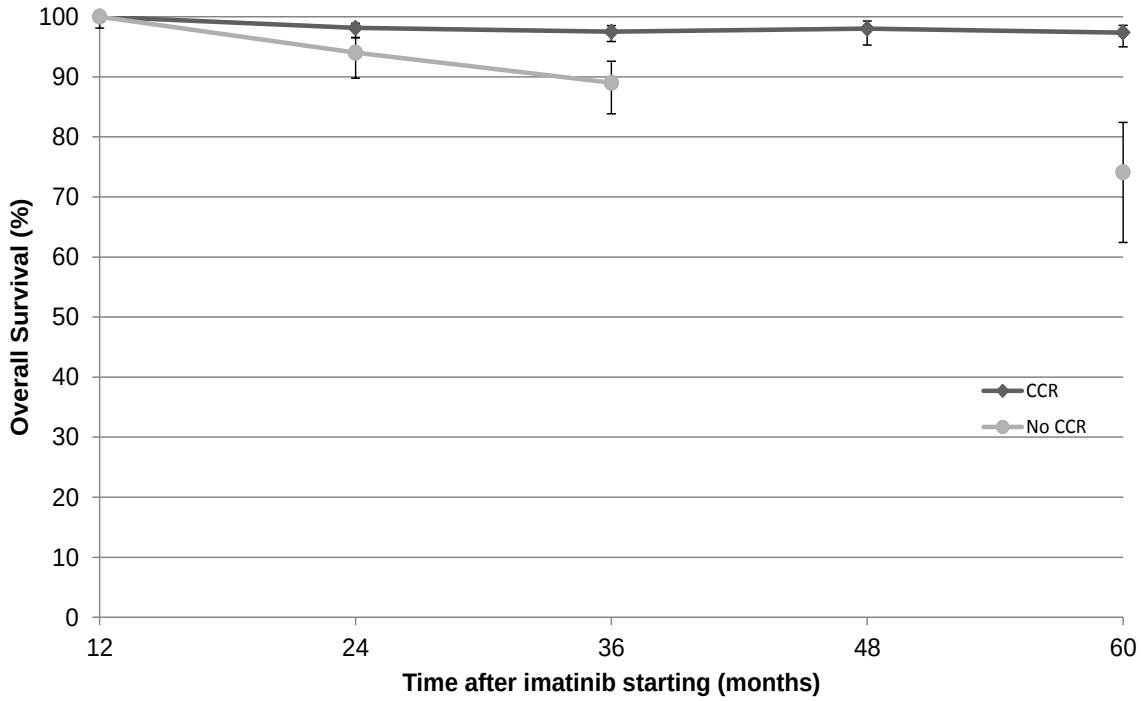


Figure 10 Pooled weighted average (95% CI) of overall survival by level of cytogenetic response at yearly intervals after 1st-line imatinib initiation

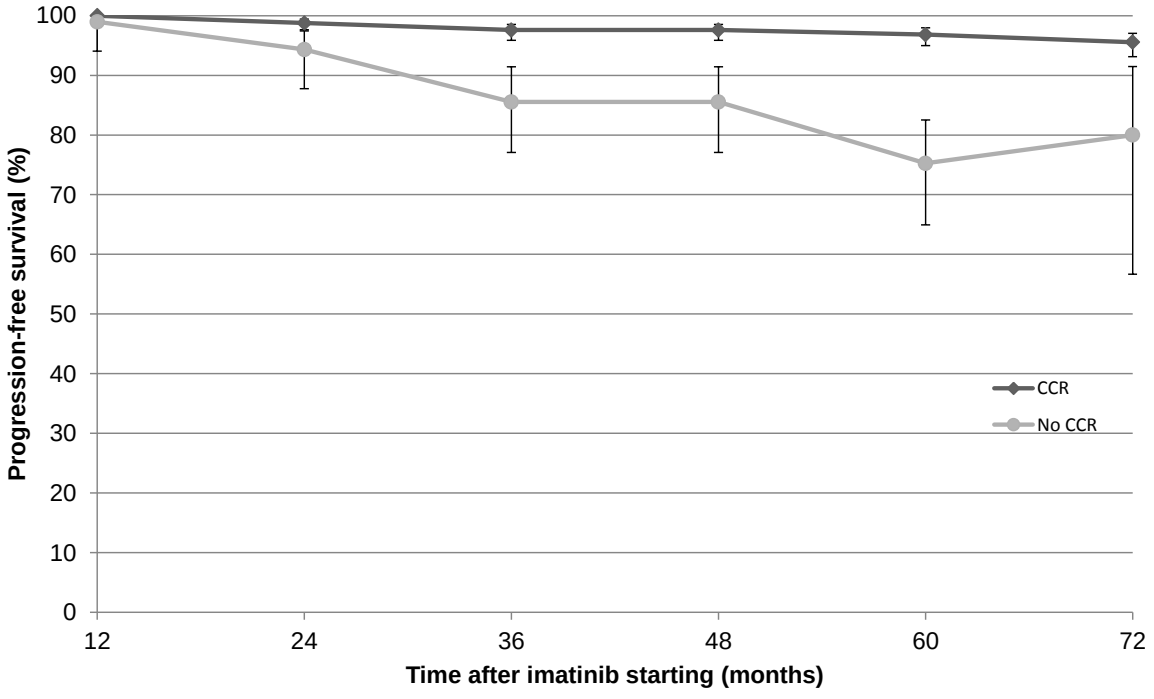


Figure 11 Pooled weighted average (95% CI) of progression free survival by level of cytogenetic response at yearly intervals after 1st-line imatinib initiation

Table 24 Pooled weighted average of overall and progression free survival (95%CI) by level of cytogenetic response at 12 months after the starting of imatinib therapy

Time	OS % (95% CI)		PFS (95% CI)	
	CCyR	No CCyR	CCyR	No CCyR
12 mo	100 (100 - 99.3)	100 (100 - 98.1)	100 (100 - 99.3)	98.9 (99.8 - 94)
24 mo	98.1 (98.9 - 96.5)	94 (96.5 - 89.7)	98.8 (99.4 - 97.4)	94.3 (97.6 - 87.7)
36 mo	97.5 (98.5 - 95.9)	89 (92.6 - 83.8)	97.6 (98.5 - 95.9)	85.5 (91.4 - 77.1)
48 mo	98 (99.3 - 95.3)	-	97.6 (98.5 - 95.9)	85.5 (91.4 - 77.1)
60 mo	97.4 (98.6 - 94.9)	74.1 (82.4 - 62.4)	96.8 (97.9 - 95)	75.2 (82.5 - 64.9)
72 mo	-	-	95.5 (97.0 - 93.1)	80 (91.5 - 56.7)

Grey cell = not reported

5.2.2.5. Survival by level of molecular response

Figure 12 shows the weighted average OS at yearly intervals after the start of the 1st-line therapy for chronic phase CML by level of molecular response. Three publications provided data for the estimates.[101, 103, 105] It is worth specifying Hehlmenn and colleagues[108] considered in the OS curves by landmark analysis of MMR at 12 months for the whole study population (N = 848) because, independent of the treatment approach (imatinib 400mg/d, imatinib 800mg/d, imatinib 400mg/d + IFN-α), they found MMR vs no MMR at 12 months was associated with better PFS (99% vs 95%; p =.0143 at 3 years) and OS (99% vs 95%; p =.0156 at 3 years). Consistent with the weighting approach used in this report, the number of units involved in the construction of Kaplan-Meier curves, the overall sample size population in this case, was considered.

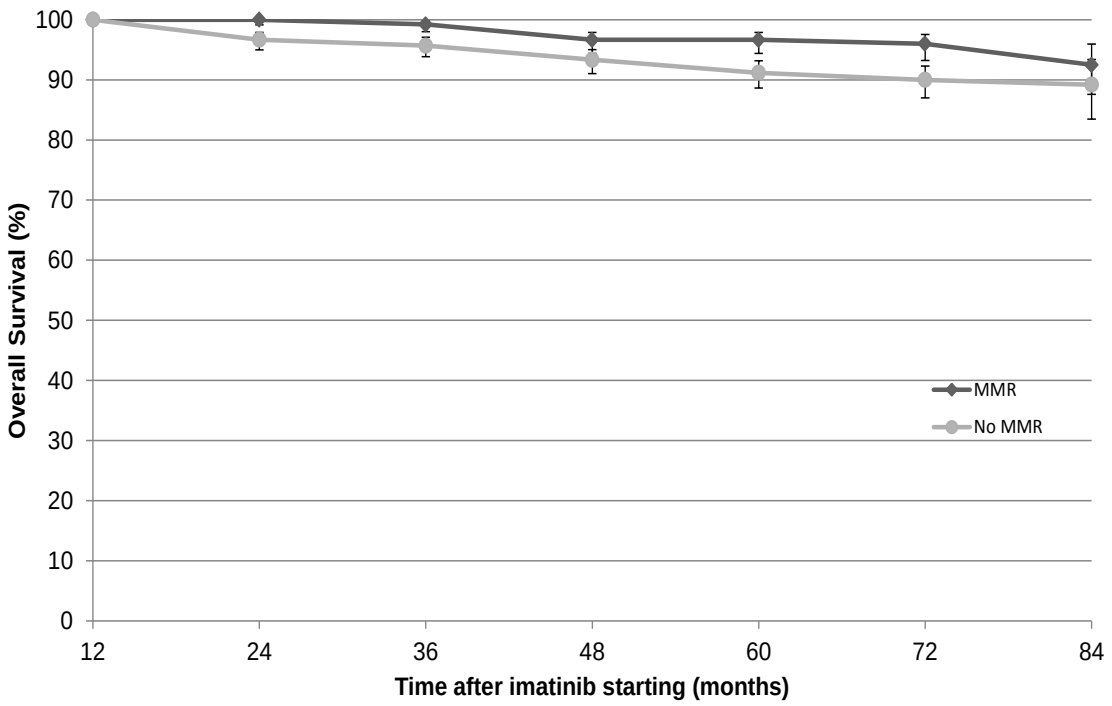


Figure 12 Pooled weighted average (95% CI) of overall survival by level of molecular response at yearly intervals after 1st-line imatinib initiation

The pooled progression free survival by major molecular response at 12 months after the starting of imatinib therapy for CP CML is shown in Figure 13. The estimates are derived from three publications which reported on progression free survival for groups of patients presenting different levels of molecular response. [101, 103, 105]

No non-responder PFS estimate at 72 months after therapy initiation was reported. The IRIS report by Hughes and colleagues shows progression-free survival curves by BCR-ABL transcript levels at 12 months converted to the International Scale (IS) (i.e. ≤0.1%, >0.1% - ≤1%, >1% - ≤10%, >10%) up to 84 months follow up. [103] These curves provide data for the PFS for patients achieving MMR at 12 months, defined as ≤ 0.1% IS, but not for the cumulative group of patients who do not achieve MMR at 12 months. The same authors give a tabulated value for the 7 year PFS in patients with no MMR at 12 months landmark time. The plotted values and the uncertainty around the estimates of OS and PFS by level of molecular response are given in Table 25.

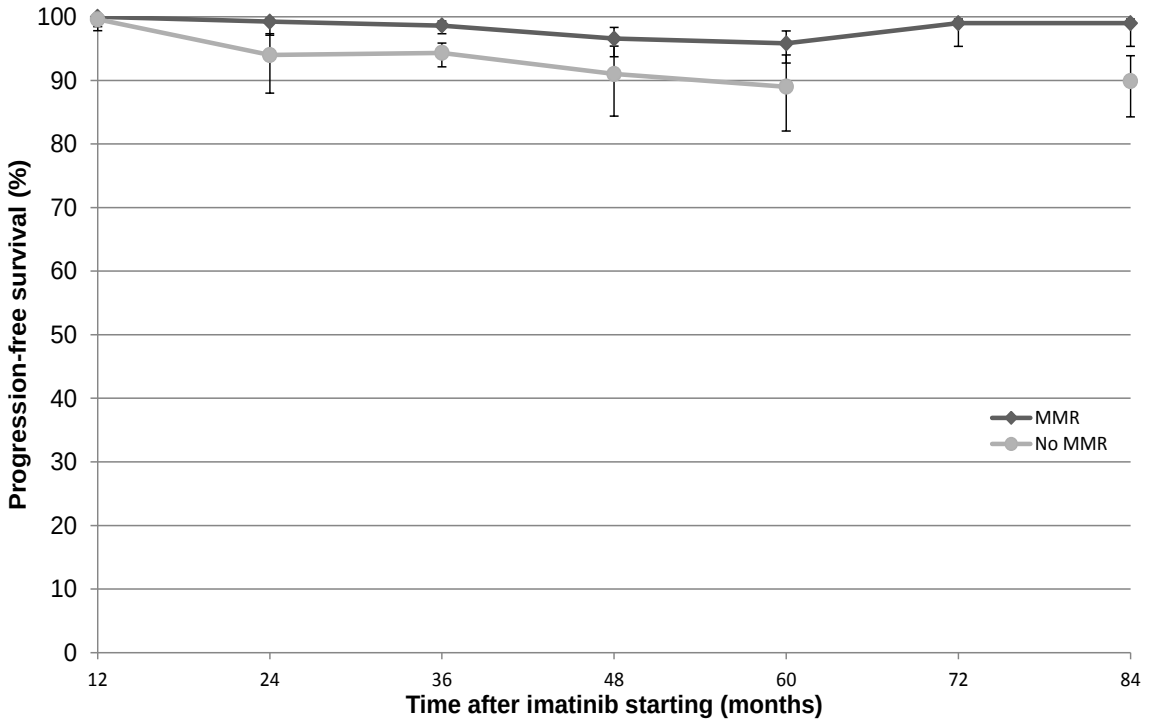


Figure 13 Pooled weighted average (95% CI) of progression free survival by level of molecular response at yearly intervals after 1st-line imatinib initiation

Table 25 Pooled weighted average of overall and progression free survival (95%CI) by level of molecular response at 12 months after the starting of imatinib therapy

Time	OS % (95% CI)		PFS % (95% CI)	
	MMR	No MMR	MMR	No MMR
12 mo	100 (100 - 99.1)	100 (100 - 99.4)	100 (100 - 98.5)	99.6 (99.9 - 97.8)
24 mo	100 (100 - 99.1)	96.7 (97.9 - 95)	99.2 (99.8 - 97.1)	94 (97.3 - 87.9)
36 mo	99.2 (99.8 - 97.9)	95.7 (97.1 - 93.8)	98.6 (99.3 - 97.3)	94.3 (95.8 - 92.1)
48 mo	96.7 (97.9 - 94.4)	93.3 (95.0 - 91.0)	96.6 (98.3 - 93.7)	91 (95.4 - 84.4)
60 mo	96.6 (97.9 - 94.9)	91.2 (93.2 - 88.6)	95.8 (97.8 - 92.7)	89 (93.9 - 82.0)
72 mo	92.5 (95.9 - 87.6)	90 (92.3 - 87.0)	99 (99.6 - 95.3)	-
84 mo	96 (97.5 - 93.2)	89.2 (93.4 - 83.5)	99 (99.6 - 95.3)	89.9 (93.9 - 84.2)

Grey cells = not reported

5.3. Overall surrogate outcome conclusions

The endpoints assessed as surrogates for the target clinical outcomes are complete cytogenetic response and major molecular response, in the 12 months after the 1st-line treatment (imatinib) initiation for chronic phase chronic myelogenous leukemia. A plausible biological rationale for the adoption of the two endpoints is clear after the disease mechanism and the definition of CCyR and MMR have been explained (see section 2.1 and 2.3). Although biological plausibility is a basic step towards the identification of a surrogate endpoint, it is alone not sufficient for an endpoint to be accepted as a surrogate outcome. Evidence of an association between the endpoint and final patient-related outcome is also needed. Ideally evidence should be in the form of multiple randomised controlled trials which have assessed the effects of the treatment on both the endpoint marker and final patient-relevant outcome.[35, 93] However, this systematic review only identified evidence of the association between cytogenetic response and molecular response in patients and survival treated with TKI for chronic phase CML from the imatinib arms of three cohort studies and two randomised controlled trials. This observational comparison is considered level 2 evidence, rather than the best quality evidence a comparison of surrogate response according to randomised treatment allocation (level 1 evidence).[109] In addition, evidence is not available for dasatinib and nilotinib.

Nevertheless these studies do consistently show that patients who experience either a complete cytogenetic response or major molecular response following 12 months imatinib treatment have better long-term (up to 7-years) overall survival and progression free survival

than patients who do not respond at 12-months. Our inability to further explore the validation of the surrogate outcomes is limited by the amount and quality of data available (i.e. aggregate data instead of individual patient data). Other limitations include:

- The reliance on the landmark analysis (patients who die before the landmark time point are excluded from analysis and response may, confoundingly, act as a surrogate marker for patients with favourable prognosis)[94]
- The pooling of sub-populations from different trials (although the exclusion criteria applied yielded very similar groups)
- The assumption of no censoring for the estimation of 95% confidence interval for the weighted average OS and PFS.[94]

A strength is that we chose to approach the problem of deriving survival curves for patients in CP CML conditioning to their achievement of either a CCR or MMR at 12 months after the 1st-line treatment initiation, in a systematic way, using all the available evidence to obtain weighted average estimates for the OS and PFS to inform the cost-effectiveness model discussed in this report (see Section 8.2.1).

Table 26 Summary of surrogate outcomes

Summary
In summary, there is observational association evidence supporting the use of complete cytogenetic response and major molecular response at 12 months as surrogates for OS and PFS in CML patients in chronic phase. This is based entirely on imatinib treatment studies. In the absence of evidence of adequacy of these surrogates for dasatinib and nilotinib as 1st-line therapies for CP CML, assuming a TKI's class-specific relationship between the surrogate outcomes and the patient-relevant outcomes, these results can be potentially applied to other drugs in the same class.

6. Cost-effectiveness: systematic review

6.1. Methods

We undertook a systematic literature search to identify economic evaluations of the therapies under investigation, which were carried out in line with the scope of the current assessment. Appendix 1 outlines in detail the search strategy used and databases searched. Manufacturer submissions to NICE were reviewed to identify additional studies.

All titles and abstracts were examined. The relevance of each paper was assessed according to the inclusion and exclusion criteria. The review was carried out by two researchers (RA and LC).

6.2. Results

Our literature search did not identify any published full economic evaluations meeting the inclusion criteria. However, we identified five conference abstracts which met the specified inclusion criteria. Three evaluated resource utilisation and costs associated with the use of TKIs for the management of CML,[110-112] one examined long-term survival outcomes following treatment with dasatinib, imatinib and nilotinib;[113] and, one estimated lifetime QALYs and costs of Ph+ CML chronic phase patients initiating therapy with nilotinib or imatinib using a literature-based Markov model.[114]

There is insufficient detail in the abstracts or reports to undertake a detailed critical appraisal of the methods used, nor to rule out that some of them may relate to 2nd line treatment with nilotinib or dasatinib. The corresponding authors were contacted but no additional information was received; however, a summary of study characteristics and results is given below (Table 27).

Table 27 Summary of abstracts identified in the literature review

Study characteristics	Ovanfors et al (2011)[114]	Simons et al (2009)[110]	Szabo et al (2010)[112]	Taylor et al (2010)[113]	Wu et al (2010)[111]
Intervention	NIL 300 mg BID	DAS and NIL	TKIs (DAS, IMAT)	DAS, NIL, IMAT	TKIs with PE
Comparator	IMAT 400 mg QD	No comparator	No comparator (not head-to-head)	No comparator (not head-to-head)	TKIs no PE
Patient population	Newly-diagnosed Ph+ CML patients	CML patients	CML patients	Newly diagnosed CML	CML patients
Analysis by CML stage	Chronic	Unknown	Chronic; accelerated; blast	Chronic	Unknown
Model type	Literature-based Markov model	Not relevant[b]	Not relevant[c]	Disease model	Not relevant[a]
Time horizon	Lifetime	Unknown	Unknown	Unknown	Unknown
Perspective	Sweden	Unknown	UK	Unknown	Unknown
Discounting	Unknown	Unknown	Unknown	Unknown	Unknown
Effectiveness data	ENESTnd and IRIS	Unknown	Unknown	DASISION (DAS and IMAT) and ENESTnd (NIL)	MarketScan and Ingenix Impact databases (2001-2009)
Base-case results	Discounted incrememental cost per LY and cost per QALY are estimated at US$21,028 and US$22,914, respectively.	Total costs are US$2,721.29 and US$426.44 for monitoring parameters for NIL and DAS respectively	Higher costs were associated with patients not responding to treatment in each CML phase	QALYs and LYs were 12.238 and 14.727 for DAS; 11.506 and 13.822 for IMAT; and, 12.016 and 14.426 for NIL.	Compared to PE-free patients. PE patients have a substantial economic burden with higher PE-related costs. CML-related costs, and total medical cost
Source of funding	Unknown; although author list suggests industry-linked (Novartis)	Unknown; although author list suggests industry-linked (B-MS)	Unknown; although author list suggests industry-linked (B-MS)	Unknown; although author list suggests industry-linked (B-MS)	Unknown

Bid, twice daily; B-MS, Bristol-Myers Squibb; CML, chronic myeloid leukaemia; DAS, dasitinib; IMAT, imatinib; LYs, life years; NIL, nilotinib; PE, pleural effusion; Ph+, Philadelphia chromosome; QALYs, quality-adjusted life years; TKIs, tyrosine kinase inhibitors;

[a] Comparison of health utilisation and costs between CML patients treated with a TKI who developed a PE and their matched PE-free controls

[b] Translation of monitoring as per FDA approved product labelling for AEs and laboratory abnormalities into annual ancillary costs for dasatinib and nilotinib in the treatment of CML

[c] Calculated UK-specific resource use and cost associated with the treatment of CML

7. Assessment of industry submissions

7.1. Introduction

Two manufacturer submissions were received for this MTA. Bristol Myers-Squibb (BMS) provided a full economic model for dasatinib. Novartis provided a full economic model for nilotinib. In this section a summary of the critique of these two economic models are presented. The full critique of the two models is available in Appendix 7. There are two major sources of uncertainty in estimating the cost-effectiveness of dasatinib and nilotinib for 1st-line treatment of CML. First, the clinical effectiveness evidence from the DASISION RCT of dasatinib vs. imatinib and the ENESTnd RCT of nilotinib vs. imatinib is extremely immature, with current follow-up of only 2 years. Therefore, given that CML is a chronic disease, with current survival from diagnosis of around 15 to 20 years, it is necessary to extrapolate clinical effectiveness over many years, thus introducing substantial uncertainty.

7.2. Bristol Myers-Squibb Submission

7.2.1. Scope of the submission

The submission from BMS considers the use of dasatinib for the 1st-line treatment of people with chronic myeloid leukaemia (CML) as an alternative to the standard dose of imatinib (400mg daily) or nilotinib (600mg daily).

The clinical effectiveness outcomes considered are:

- Overall survival,
- Progression free survival,
- Response rates,
- Adverse effects of treatment
- Health-related quality of life

The outcomes for the economic analysis are:

- incremental cost per quality-adjusted life-year
- incremental cost per life year gained

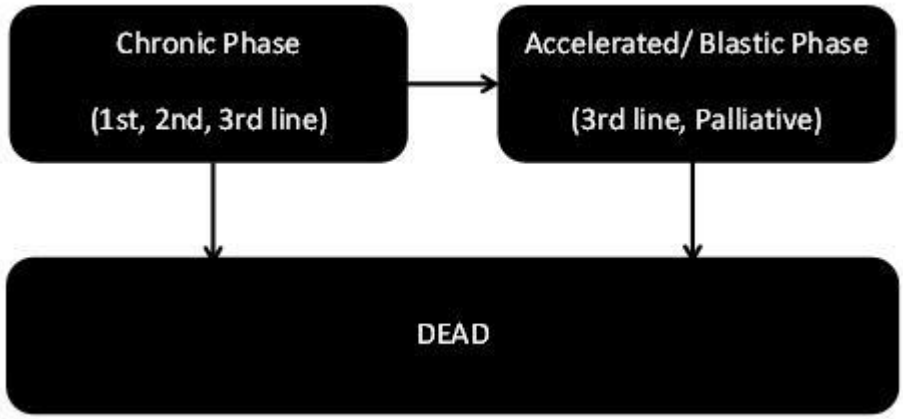
In order to derive these outcomes the following costs have been considered:

- cost of 1st, 2nd- line TKI's
- cost of post-TKI failure 2nd or 3rd-line treatment
- the cost of treating serious adverse events.

The time horizon for the economic analysis is between 46 and 86 years old, and costs are considered from an NHS perspective. No subgroup analysis is conducted for the economic evaluation.

7.2.2. Summary of submitted cost-effectiveness evidence

The manufacturer uses a 'time in state' (area under the curve) model extrapolating CML related survival and progression-free survival data. The health states represent the chronic phase, and accelerated/blast phases as well as death. Within the chronic phase patients may also be in first, second or third line treatment, while in the accelerated/blast phases they may be receiving either 3rd line treatments or palliative care. Time is modelled in blocks of 1 month (Figure 14).



Source: Figure 5, p.40 of BMS submission

Figure 14 Bristol Myers-Squibb model structure

BMS have modelled one scenario with three different comparators. The interventions and sequence of treatments are summarised in Table 28.

Table 28 Interventions and comparator sequences in BMS model (daily doses)

Line of treatment	Intervention	Comparator 1	Comparator 2
1st-line	Dasatinib (100mg)	Imatinib (400mg)	Nilotinib (600mg)
2nd-line	Nilotinib (800mg)	Dasatinib (100mg) or Nilotinib (800mg) (50:50 spilt)	Dasatinib (100mg)
3rd-line	SCT or chemo/combination therapy or in-hospital palliative care	SCT or chemo/combination therapy or in-hospital palliative care	SCT or chemo/combination therapy or in-hospital palliative care

The BMS base case analysis produces ICERs of (Table 29):

- £26,000 per QALY for dasatinib in comparison to imatinib as 1st-line TKI, and
- £145,000 per QALY for nilotinib compared to dasatinib (nilotinib provides more benefit at greater cost than dasatinib) as a 1st-line TKI.

The sensitivity analysis shows the key parameters to which the model is sensitive:

- drug costs,
- overall survival
- the cost of stem cell transplant

The BMS model contained a number of formula errors. After correcting for these errors the BMS model predicts ICERs of:

- £36,000 per QALY for 1st-line dasatinib compared to 1st-line imatinib, and
- £103,000 per QALY for dasatinib compared to nilotinib (dasatinib provides more benefit at greater cost than nilotinib).

Table 29 Breakdown of costs and benefits in the BMS model (original submission)

		Dasatinib	Imatinib	Nilotinib
PFS (years, undisc.)	Mean	19.16	17.14	19.28
PY (years, undisc.)	Mean	1.30	1.69	1.31
Life years (undisc.)	Mean	20.46	18.83	20.59
QALYs (disc.)	PFS	9.50	7.97	9.66
	PY	1.14	1.92	1.04
	Total	**10.64**	**9.89**	**10.70**
1st-line drug cost (disc.)		£283,209	£84,836	£282,887
2nd-line FC drug acquisition cost (disc.)		£60,336	£164,690	£77,350
3rd-line treatment cost (disc)		£82,324	£145,215	£75,619
Adverse events 1st-line (disc.)		£2,321	£818	£1,291
Adverse events 2nd-line (disc.)		£412	£1,159	£562
Adverse events 3rd-line (disc)		£310	£616	£265
SCT*(disc.)		£5,350	£10,093	£4,954
Other		£63,955	£70,864	£63,685
Total costs (disc.)		£498,217	£478,293	£506,613
ICERs				
Cost / life-year gained (Dasatinib vs. Imatinib)				£32,785
Cost / life-year gained (Dasatinib vs. Nilotinib)				£116,447
Cost / QALY (Dasatinib vs. Imatinib)				£26,305
Cost / QALY (Dasatinib vs. Nilotinib)				£144,778

Abbreviations: PFS = progression free survival, PY = progressed years (i.e. years in accelerated and blast phase), QALYs = quality adjusted life years, SCT disc = stem cell transplant discounted.
**In the BMS model in the 3rd line treatment 30.6% receive SCT pre-progression and 50% post-progression*

In the original model, the cost of nilotinib used by BMS does not account for the PAS discount applied to nilotinib.

[redacted] Including this change, the BMS model predicts an ICER of £45,600 per QALY for dasatinib compared to imatinib. When comparing dasatinib to nilotinib, the model predicts that nilotinib is more effective and less costly.

Further, BMS assume that dasatinib is taken as a 3rd-line treatment in all treatment arms. However, in the NICE draft guidance FAD[IX], dasatinib was not recommended (the draft guidance FAD for 2nd line CML for high-dose imatinib, dasatinib and nilotinib, is available on the NICE website at http://guidance.nice.org.uk/TA/WaveR/99). When the BMS model is adjusted so that dasatinib is not taken 3rd-line, the ICER of dasatinib vs. imatinib increases further, from £45,600 to £64,000 per QALY, and nilotinib is still more effective and less costly than dasatinib.

Finally, BMS assume that half of all patients in the imatinib and nilotinib treatment arms eligible for 2nd-line treatment, take dasatinib. Again, in the NICE draft guidance FAD, dasatinib was not recommended (the draft guidance FAD for 2nd line CML for high-dose imatinib, dasatinib and nilotinib, is available on the NICE website at http://guidance.nice.org.uk/TA/WaveR/99). When the BMS model is adjusted so that dasatinib is not taken 2nd-line, and instead when we assume that all 2nd-line patients in the imatinib arm take nilotinib 2nd-line, the ICER of dasatinib vs. imatinib increases further, from £64,000 to £96,000 per QALY. There appears to be no simple way to adjust BMS' model to disallow patients taking dasatinib 2nd-line.

In summary, BMS' adjusted model yields an ICER for dasatinib vs. imatinib of £96,000 per QALY. Further, nilotinib is more effective and less costly than dasatinib.

7.2.3. Commentary on the robustness of the submitted evidence

Strengths

- The approach taken to modelling is reasonable although quite complex
- The sources and justification of estimates are also generally reasonable
- Resource use is largely based on a survey of six UK clinicians who manage patients with CML.

[IX] In the draft guidance on 18th August 2011, NICE has recommended nilotinib, for the treatment of the chronic and accelerated phases of CML (chronic myeloid leukaemia) that is resistant or intolerant to standard-dose imatinib. Dasatinib and high-dose imatinib, are not recommended in the draft guidance. Consultees have the opportunity to appeal against the draft guidance. Until NICE issues final guidance, NHS bodies should make decisions locally on the funding of specific treatments. This draft guidance does not mean that people currently taking dasatinib or high-dose imatinib will stop receiving them. They have the option to continue treatment until they and their clinicians consider it appropriate to stop.

Weaknesses

- There are a number of formulae errors in the BMS model. When corrected, the base case ICER changes from £26,000 to £36,000 per QALY for dasatinib in comparison to imatinib; and from £145,000 to £103,000 per QALY for dasatinib in comparison to nilotinib.

- BMS does not account for the reduced price of nilotinib due to the PAS discount. In addition to the formulae errors, if the [redacted] discount in the price of nilotinib in 1st-line and 2nd-line is accounted for, the best case ICER for the BMS model is £45,600 per QALY for dasatinib compared to imatinib. When comparing dasatinib to nilotinib, the model predicts that nilotinib is more effective and less costly. However, it is acknowledged that BMS were unable to account for the discount as did not have knowledge of the PAS discount at the time of their submission.

- The starting age of the simulated cohort, 46 years, is considerably lower than the mean age of newly diagnosed CML patients in the UK (56 years).

- The model does not adopt a lifetime time horizon. Instead the model is run until the cohort is 86 years old, at which point 20% of the cohort is still alive. If the model is extended to the age of 100, 10 per cent of the population is still alive. Assuming an equal distribution of males and females, data from the ONS predict that 2 per cent of those alive at 46 will be alive at the age of 100. This suggests that BMS overestimate the period that those with CML will survive.

- BMS uses 42 month follow up data from a RCT to predict overall survival for those with a complete, partial and 'less than partial' cytogenetic response to treatment at 12 months[107] Survival data is digitally extracted from published Kaplan-Meier curves and fitted to a Weibull distribution. There is no use of MMR response rates, the model only uses cytogenetic response rates.

- BMS outline the effectiveness of 2nd-line TKI's in their submission. However, this data is not used to model the effectiveness of 2nd-line therapy.

- There are a number of assumptions with the BMS model which are not defined in detail. In addition, several parameters within the manufacturer submission do not reflect the data which is used in the model. For example, the data used to estimate the progression free survival (PFS) curves (explained in Table 19 p. 47 of the manufacturer submission) does not match the data in the model. Also, the source quoted for PFS data in the submission is Hochhaus and colleagues.[102] However, the model appears to be using data from Druker and colleagues which is a study with a shorter follow up period.[27] If the model is updated to use data from Hochhaus and colleagues the ICER change as follows:
    - Dasatinib compared to imatinib: from £36,052 to £42,556 per QALY
    - Dasatinib compared with nilotinib: from £103,483 to £103,593 per QALY.
- BMS assume that dasatinib is taken 2nd- and 3rd-line. Given that BMS prepared their submission before NICE's recent draft guidance FAD on 2nd-line TKIs, BMS's assumption on the use of dasatinib 2nd- and 3rd-line was reasonable. However, in the NICE draft guidance FAD, dasatinib 2nd- and 3rd-line was not recommended (the draft guidance FAD for 2nd line CML for high-dose imatinib, dasatinib and nilotinib, is available on the NICE website at http://guidance.nice.org.uk/TA/WaveR/99). When BMS' model is adjusted to remove dasatinib 2nd- and 3rd-line, the cost-effectiveness of dasatinib worsens substantially, as quantified above.
- BMS developed a highly complex model in an area where data is not of high quality. We believe the cost-effectiveness model could have been developed in a simpler way.
- It is not clear how BMS calculated the cost of Stem Cell Transplant (SCT). [redacted]
- On several occasions, the BMS report of the modelling differs from the actual model.

7.2.4. Areas of uncertainty

The BMS model does not provide the raw data which was used to fit the overall survival and time to treatment discontinuation curves. However, the choice of distribution and coefficients of the distribution appear to be correct on the basis of graphs showing the observed data and the fitted curves.

A considerable area of uncertainty is the chosen sequence of 2nd-line TKI treatments that might follow failure of different 1st-line TKIs. This is partly because the submission was prepared before NICE's draft guidance FAD on the use of dasatinib, nilotinib or high-dose imatinib as 2nd-line treatments (the draft guidance FAD for 2nd line CML for high-dose imatinib, dasatinib and nilotinib, is available on the NICE website at http://guidance.nice.org.uk/TA/WaveR/99). However, uncertainty also results from the fact that data on the effectiveness of 2nd-line TKI treatments is only available following the use of imatinib as 1st-line treatment.

7.2.5. Key Issues

- The BMS model does not use the cost of nilotinib agreed under the PAS in their submission. However, it is acknowledged that BMS were unable to account for the discount as did not have knowledge of the PAS discount at the time of their submission.

- The BMS model is structured in such a way that it would require significant changes to run it without 2nd-line treatment, should this be required by NICE.

- The time horizon chosen by the BMS model does not reflect the lifetime of a CML patient. In the model, nearly 20 per cent of the population is still alive in the last cycle (86 years old), suggesting that the model overestimates the period that those with CML will survive.

- The BMS model has a number of formulae errors, correcting for which impacts on the ICER.

- The cost and proportions of patients who receive SCT have a significant impact on ICERs, but the source of BMS's estimates of these parameters is unclear. Clinical

opinion is required to assess whether the BMS assumption on the provision and costing of SCT is appropriate.

7.3. Novartis Submission

7.3.1. Scope of the submissions

The submission from Novartis considers the use of nilotinib for the 1st-line treatment of people with chronic myeloid leukaemia (CML) as an alternative to the standard dose of imatinib (400mg daily). In one analysis, dasatinib is used in the cost-effectiveness model as 2nd-line treatment when 1st-line treatment with imatinib or nilotinib fails. In the other analysis, no 2nd-line TKIs are assumed.

The clinical effectiveness outcomes considered are:

- progression free survival
- time to discontinuation,
- adverse effects of treatment
- health-related quality of life

The outcomes for the economic analysis were:

- incremental cost per quality-adjusted life-year
- incremental cost per life year gained

In order to derive these outcomes the following costs were estimated in the model:

- cost of 1st and 2nd-line TKI's,
- cost of post-TKI failure 2nd or 3rd-line treatment
- the cost of treating adverse events

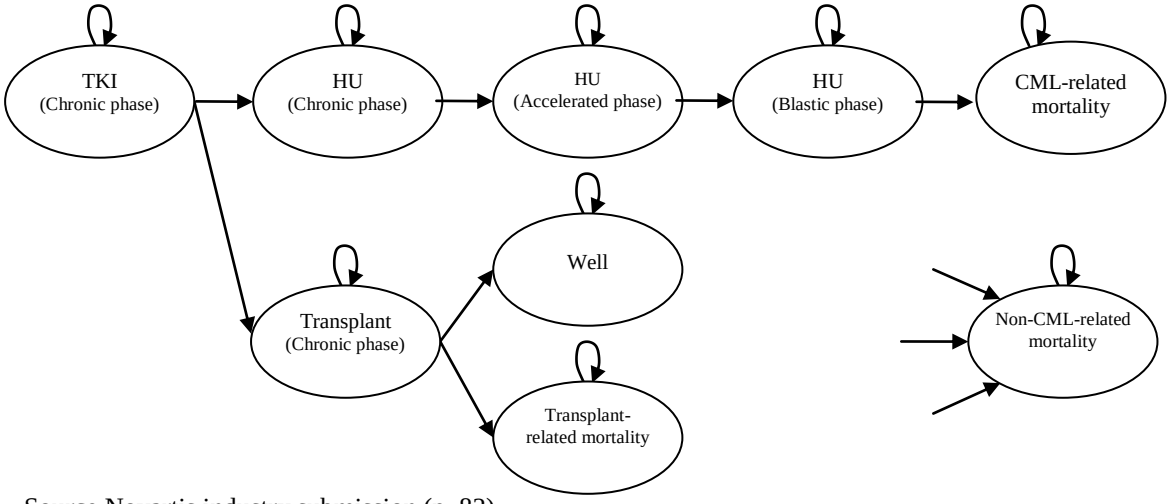
The time horizon for the economic analysis is lifetime and costs are considered from the NHS perspective.

The Novartis cost-effectiveness modelling reflects a cost discount (Patient Access Scheme (PAS) for the cost of 1st-line nilotinib [redacted]

[redacted]. This equates to a [redacted] from the NHS List Price for a 28-day pack of nilotinib. Their cost of 2nd-line nilotinib also reflects this cost discount (also a PAS). No subgroup analyses are conducted for the economic evaluation, although a policy scenario without the use of second-generation TKIs is simulated.

7.3.2. Summary of submitted cost-effectiveness evidence

The manufacturer uses a Markov approach to model the cost-effectiveness of nilotinib compared to the current standard of care (imatinib 400mg daily). This model has nine states. Patients enter the model in the chronic phase. The model estimates when one treatment fails and hence the patient is switched to an alternative treatment. At the end of each cycle, patients have a probability of remaining on current treatment, progressing to an alternative treatment or dying (Figure 15).



Source Novartis industry submission (p. 82)

Figure 15 Novartis model structure

Novartis modelled two different scenarios to reflect the availability or not of 2nd generation TKIs as 2nd-line treatment. The interventions and sequence of treatment is summarised in Table 30.

Table 30 Interventions and comparator sequences in Novartis model

Line of treatment	Scenario 1		Scenario 2	
	Nilotinib	Imatinib	Nilotinib	Imatinib
1st-line	Nilotinib (600)mg	Imatinib (400mg)	Nilotinib (600)mg	Imatinib (400mg)
2nd-line	Dasatinib (100mg)	Dasatinib (100mg)	SCT or HU	SCT or HU
3rd-line	SCT or HU	SCT or HU	n/a	n/a

The Novartis model predicts that nilotinib is both more effective and less costly compared to imatinib (dominates), when followed by dasatinib as 2nd-line treatment. In a scenario analysis without dasatinib as 2nd-line treatment, the model predicts an ICER of £5,908 per QALY for nilotinib in comparison to imatinib (Table 31).

The sensitivity analysis shows the key parameters to which the cost-effectiveness results are sensitive to are:

- drug costs (i.e. without PAS)
- time to discontinuation of 1st-line TKI

No major formula errors have been identified in the Novartis model.

Table 31 Breakdown of costs and benefits in the Novartis model

		Nilotinib/Das	Imatinib/Das	Nilotinib	Imatinib
PFS (years, undisc.)	Mean	12.66	11.94	10.64	9.30
PY (years, undisc.)	Mean	0.88	0.90	0.74	0.68
Life years (undisc.)	Mean	13.54	12.83	11.38	9.97
QALYs (disc.)	PFS	9.93	9.38	8.31	7.25
	PY	0.47	0.48	0.40	0.37
	Total	**10.40**	**9.85**	**8.71**	**7.62**
1st-line drug cost (disc.)		£114,771	£104,038	£114,771	£104,038
2nd-line FC drug acquisition cost (disc.)		£57,532	£77,284	refer to SCT	refer to SCT
3rd-line treatment cost (disc)		£170	£175	£411	£147
Adverse events 1st-line (disc.)		£111	£178	£111	£178
Adverse events 2nd-line (disc.)		£37	£51	n/a	n/a
Adverse events third –line (disc)		n/a	n/a	n/a	n/a
SCT (disc.)		£28,772	£31,183	£42,383	£49,986
Other		£15,979	£14,835	£12,966	£11,667
Total costs (disc.)		**£217,373**	**£227,744**	**£170,643**	**£166,015**

ICERs	
Cost / life-year gained (Nilotinib vs. Imatinib, with 2nd line)	-(£27,739)
Cost / life-year gained (Nilotinib vs. Imatinib, without 2nd line)	£4,701
Cost / QALY (Nilotinib vs. Imatinib, with 2nd line)	**-(£34,889)**
Cost / QALY (Nilotinib vs. Imatinib, without 2nd line)	**£5,908**

Abbreviations: PFS = progression free survival, PY = progressed years (i.e. years in accelerated and blast phase), QALYs = quality adjusted life years, SCT disc = stem cell transplant discounted.

7.3.3. Commentary on the robustness of submitted evidence

Strengths

- The approach taken to modelling is reasonable
- The sources and justification of estimates are also generally reasonable

Weaknesses

- Novartis make no use of the major molecular and complete cytogenetic response rates from the RCT of nilotinib vs. imatinib, both of which are important indicators of clinical effectiveness.
- We believe that Novartis' method of estimating the time on HU in CP is flawed.

7.3.4. Areas of uncertainty

The Novartis model does not provide the raw data which was used to fit the overall survival and time to treatment discontinuation curves. However, the choice of distribution and coefficients of the distribution appear to be correct on the basis of graphs showing the observed data and the fitted curves.

Another area of uncertainty is the chosen sequence of 2nd-line TKI treatments that might follow the failure of different 1st-line TKIs. This is partly because this submission was prepared before NICE's draft guidance FAD on the use of dasatinib, nilotinib or high-dose imatinib as 2nd-line treatments (the draft guidance FAD for 2nd line CML for high-dose imatinib, dasatinib and nilotinib, is available on the NICE website at http://guidance.nice.org.uk/TA/WaveR/99). However, uncertainty also results from the fact that data on the effectiveness of 2nd-line TKI treatments is only available following the use of imatinib as 1st-line treatment.

Another area of uncertainty is regarding the cost and utility of stem cell patients. Assumptions around SCT significantly impact the model. Novartis uses a one-off cost of £99,224 for each transplant with a post transplant utility for survivors of 0.813.

7.3.5. Key Issues

- Novartis uses a patient access scheme (PAS) for pricing nilotinib as 1st-line treatment. This has significant impact on the results.
- Novartis make no use of the major molecular and complete cytogenetic response rates from the RCT of nilotinib compared to imatinib, both of which are important indicators of clinical effectiveness.
- The cost and the proportions of patients who receive Stem Cell Transplant differ between the Novartis and BMS models and has a significant impact on ICERs. Clinical opinion is required to assess whether the BMS assumption on the provision and costing of SCT is appropriate.

7.4. Summary of manufacturers cost-effectiveness submissions

A summary of the two cost-effectiveness submissions is displayed in Table 32

Table 32 Summary of cost-effectiveness submissions

- Novartis use patient access scheme (PAS) for pricing nilotinib as 1st-line treatment. This has significant impact on cost-effectiveness, and BMS were unable to reflect this in their model.
- BMS and Novartis assume different 2nd- and 3rd-line treatments. BMS assume both dasatinib and nilotinib are available 2nd-line. In one analysis, Novartis assume only dasatinib is available 2nd-line, and in their other analysis, they assume neither dasatinib nor nilotinib is available 2nd-line. However, in the NICE draft guidance FAD, nilotinib, but not dasatinib was recommended to be used 2nd-line. We have adjusted BMS' model to reflect NICE's guidance (the draft guidance FAD for 2nd line CML for high-dose imatinib, dasatinib and nilotinib, is available on the NICE website at http://guidance.nice.org.uk/TA/WaveR/99).
- The time horizon chosen by the BMS model does not reflect the lifetime of a CML patient. In the model, nearly 20 per cent of the population is still alive in the last cycle (86 years old).
- The BMS model has a number of formulae errors, correcting for which impacts ICER.
- The cost and the proportions of patients who receive stem cell transplant differ between the models and has a significant impact on ICERs.

8. PenTAG cost effectiveness analyses

There are various approaches to modelling the costs and effectiveness of treatments for CML, as exemplified by the quite different approaches taken by the two manufacturers of nilotinib and dasatinib for this MTA. In the following sections we describe:

- An overview of the main alternative modelling approaches, given key sources of uncertainty
- The choice of approaches (scenarios) for which we produce cost-effectiveness results
- The methods for estimating or extrapolating survival and occupancy of key health/treatment states

We then describe the value, source and justification for all utility, cost and other input parameters used in the model

8.1. Approaches to modelling treatments for chronic myeloid leukaemia

There are two major sources of uncertainty in estimating the cost-effectiveness of dasatinib and nilotinib for 1st-line treatment of CML. First, the clinical effectiveness evidence from the DASISION RCT of dasatinib vs. imatinib and the ENESTnd RCT of nilotinib vs. imatinib is extremely immature, with current follow-up of only 2 years. Therefore, given that CML is a chronic disease, with current survival from diagnosis of around 15 to 20 years, it is necessary to extrapolate clinical effectiveness over many years, thus introducing substantial uncertainty. Second, cost-effectiveness is heavily influenced by our assumptions for subsequent lines of treatment, and there is much uncertainty about the nature and the cost of such treatment.

Given this extensive structural uncertainty, we believe that it is useful to present a range of deterministic scenario analyses, depending on key structural assumptions, which we believe cover the main plausible structural assumptions. Furthermore, given that it is not possible to designate any one scenario as the most plausible, we do not present a single base case analysis.

Our scenario analyses are presented in Table 33 below. It shows two alternative assumptions relating to possible treatment sequences following the failure of 1st line TKIs (table rows), three alternative approaches to estimating survival (right-hand columns), and also some scenarios in which only costs and benefits during 1st-line treatment are compared (the Simplified Method). The three alternative methods for estimating cost-effectiveness are:

- Cumulative Survival method - in which overall survival is estimated as the cumulative result of the duration of successive treatments.
- Surrogate Survival method – in which overall survival is estimated from the 12-month treatment response, either using CCyR or MMR
- Simplified Method – in which the per patient costs and benefits occurring after treatment with TKIs are assumed equal between treatment arms.

Each of these methods is described in the following sections, together with their advantages and disadvantages for evaluation different 1st and 2nd line TKI treatment sequences.

Table 33 Summary of scenario analyses produced using the PenTAG model

1st-line treatments	2nd-line treatments	3rd-line treatments	Simplified method?	Cumulative Survival method	MMR Surrogate Survival method	CCyR Surrogate Survival method
Imatinib	HU or SCT	None	No	**1**	**1a**	**1b**
Dasatinib						
Nilotinib						
Imatinib	HU or SCT	None	Yes	**2**	**2a**	**2b**
Dasatinib						
Nilotinib						
Imatinib	Nilotinib	HU or SCT	No	**3**	**3a**	**3b**
Dasatinib						
Nilotinib	HU or SCT	None				
Imatinib	Nilotinib	HU or SCT	Yes	**4**	**4a**	**4b**
Dasatinib						
Nilotinib	HU or SCT	None				

NB. Cells shaded black indicate the scenario analyses conducted

We did not model Scenarios 3a, 3b, 4a and 4b (Table 33). This is because the historical overall survival data used to estimate the surrogate relationships did not reflect the use of 2nd-line nilotinib. Therefore while these analyses include the use of a TKI as 2nd line treatment, the relative effectiveness of this treatment compared with those having HU or SCT 2nd line would not be captured in any survival modelling based solely on the surrogate relationship.

8.1.1. PenTAG model structure

The PenTAG cost-effectiveness model is a state-transition model with states for the main disease phases, and for the different possible treatments within the chronic phase. It is very similar to the Novartis model in terms of states and allowable transitions.

Patients enter the model in the chronic phase. During each model cycle, a patient is assumed to be in one of the health states. In Figure 16, arrows represent possible transitions between health states. At the end of each cycle, patients have a probability of remaining on their health state (shown by circular arrows), progressing to an alternative state or dying (Figure 16). In Scenarios 3 and 4, after 1st-line treatment failure, patients in the imatinib and dasatinib treatment arms progress to 2nd-line nilotinib, shown in Figure 16 by the dotted ellipse. Patients in the nilotinib arm progress directly to HU or SCT. In Scenarios 1 and 2, all patients progress directly to HU or SCT after 1st-line TKI.

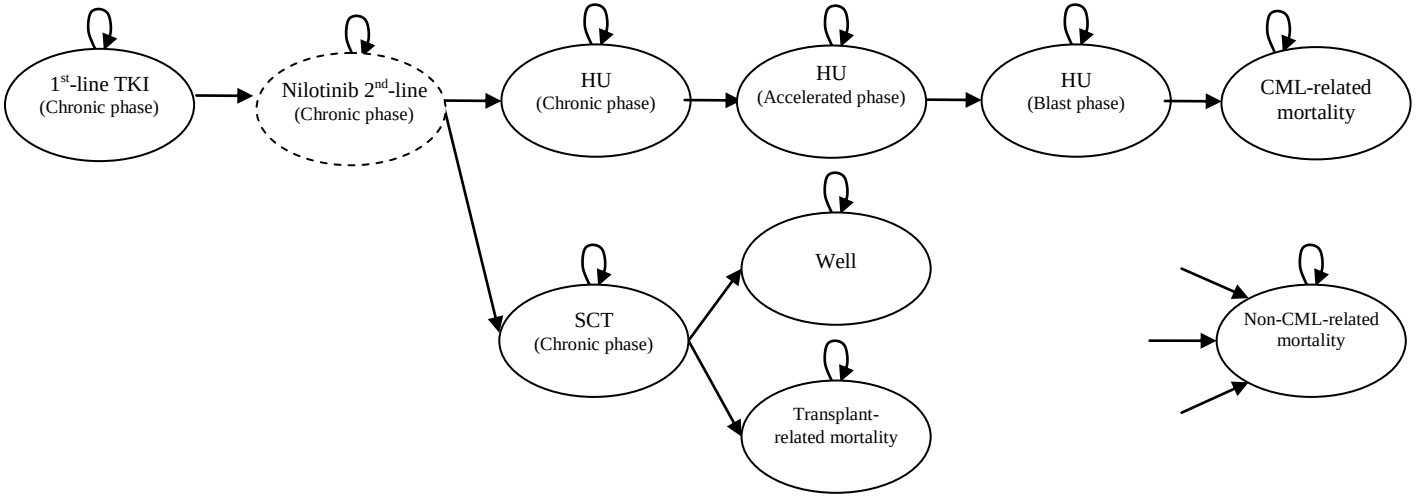


Figure 16 Structure of PenTAG cost-effectiveness model

8.1.2. Cumulative Survival approach

In this approach, overall survival (OS) for each treatment arm is estimated in Scenarios 1 and 2 (Table 33) as the sum of time on 1st-line treatment and overall survival following either HU or SCT. For Scenarios 3 and 4, OS for the nilotinib comparator is as for Scenarios 1 and 2, whereas OS for the imatinib and dasatinib arms equal the sum of time on 1st-line treatment, time on 2nd-line nilotinib and overall survival following either HU or SCT. This general approach is the same as that used by Novartis (see Section 8.7.1 for comparison). The method ignores the CCyR and MMR response rates from the two main RCTs of 1st-line dasatinib vs. imatinib and 1st-line nilotinib vs. imatinib.

An important assumption in this approach is that OS after 2nd-line nilotinib and OS after HU or SCT is independent of previous treatment. In the Cumulative Survival method, the time-independent annual transition probability from CP to AP whilst people take HU was assumed to be the same for all three treatment arms.

8.1.3. Surrogate-predicted survival approach

In this approach, OS for all three treatment comparators is estimated using a surrogate relationship based on MMR at 12 months on 1st line TKI (Scenarios 1a and 2a), and in a separate analysis, on CCyR at 12 months (Scenarios 1b and 2b). The methods of estimating OS based on the surrogate relationships with MMR and CCyR are described in Section 8.2.1, p147, and are based on the results of our clinical effectiveness systematic review and meta-analysis of surrogate outcomes (Section 5.2.2.3).

Modelling for these scenarios only uses the proportion of patients with or without a response at 12 months. We also assume that, for a given response rate, OS is independent of 1st line treatment comparator.

The model does not reflect possible differences in the depth, speed of achieving, or duration of a response. Given that dasatinib and nilotinib are believed to be superior to imatinib in all these respects (see Novartis and RCP submissions and our clinical effectiveness systematic review, section 4.3), and given that the historical surrogate data is all based on OS for patients taking imatinib, it is possible that this method underestimates OS for dasatinib and nilotinib, but the extent of this is unquantifiable.

The BMS modelling also predicts OS by a surrogate relationship based on CCyR, but not on MMR. Novartis do not model OS by a surrogate method, instead using only the Cumulative Survival method (see Sections 8.7.1 and 8.8, comparing the PenTAG with the manufacturers' economic analyses). Our scenario analyses which make use of the surrogate-based survival relationships, do so by adjusting the analyses based on the Cumulative Survival approach. In the following paragraphs, we describe adjustments to the Cumulative Survival model needed to reflect the surrogate OS for the three treatment arms estimated in Section 8.2.1, p147.

It is not surprising that OS for each treatment arm under the Cumulative Survival method is different to OS as predicted by the MMR and CCyR surrogate relationships, given that the Cumulative Survival method relies on numerous assumptions which have a cumulative impact. Specifically, in the Results section (Section 8.6, p. 183), we show that OS under the Cumulative Survival method is far shorter, at approximately 16-18 years, than under the Surrogate Survival methods, at approximately 21-23 years. We are then faced with the decision of how to adjust the model, which is based on the Cumulative Survival method, so that it predicts OS specific to each treatment as estimated by the Surrogate Survival method. BMS achieved this by leaving unaltered the transition probabilities under the Cumulative Survival method, but setting the transition probabilities which determine the times in AP and BC as the "balancing items" so as to achieve the surrogate OS experienced in historical trials of imatinib.

We ruled out this approach because this would result in unrealistically long mean times in AP plus BC of approximately 5-8 years, the difference between typical OS predicted under the surrogate relationship and typical OS under the Cumulative Survival method. In practice, typical times in these advanced disease states are believed to be 6 months to a year (see Section 8.2.3.2).

For the transition probabilities in the PenTAG model, the mean times corresponding to 1st-line TKIs and 2nd-line nilotinib were not altered (from their Cumulative Survival model values) because they are informed by good evidence from high quality trials. This left three choices: either;

(1) adjust the annual transition probability from CP to AP whilst people take HU

(2) adjust mortality after the SCT operation

(3) some combination of the above.

These choices seemed plausible given that the corresponding transition probabilities are informed by poorer quality evidence. The third option was ruled out as too complex. The second option was ruled out because even if we assumed that all patients are completely cured after SCT, then the modelled OS is still shorter than OS predicted from the surrogate relationships. The first option was selected as it was possible to model OS from the surrogate relationship. Under the Surrogate Survival method, this probability was unique for each treatment arm.

A pair of analyses was performed for each of Scenarios 1a, 1b, 2a and 2b (Table 33, p. 136). First, the transition probability from CP to AP whilst people take HU, unique to each treatment arm, was set to precisely match the mean OS from the appropriate surrogate relationship. Second, the transition probability from CP to AP for the imatinib treatment arm was left unadjusted (as in the Cumulative Survival method), but the transition probabilities from CP to AP for the nilotinib and dasatinib treatment arms were adjusted so as to model the *differences* in OS between treatment arms from the surrogate OS. These adjustments are shown graphically in the Results section in Figure 41, p216. The purpose of the second analysis was to capture the essence of OS estimated by the historical surrogate data, which is the magnitude of the difference in OS according to response (See Chapter 5, p. 101).

8.1.4. Simplified Method

In this simplified approach (used in Scenarios 2, 2a, 2b and 4 in Table 33), the post-TKI (1st-line TKIs and 2nd-line nilotinib) *per patient* costs and QALYs are set to be equal across treatment arms. The costs and QALYs whilst patients are on TKIs are modelled specific to each treatment arm, exactly as normal. However, because slightly different proportions of patients will have died during the time when they are taking 1st- or 2nd-line TKIs, there will still be small differences in the total costs and QALYs accrued after this time point between the treatments compared.

Specifically, suppose the total discounted per patient post-TKI treatment cost in the imatinib treatment arm is given as C_{im}, and suppose the proportion of patients who are still alive and start 2nd- or 3rd-line treatment on HU or SCT in the imatinib and nilotinib treatment arms are P_{im} and P_{nil} respectively (which are calculated from Scenarios 1 or 3, Table 33). Then we estimate the total discounted per patient post-TKI treatment cost in the nilotinib treatment arm as;

$$\frac{P_{nil}}{P_{im}} C_{im}$$

and similarly for the dasatinib treatment arm. The total discounted per patient post-TKI treatment QALYs in the nilotinib and dasatinib treatment arms are calculated similarly. In the Results section, we show that the proportions still alive and starting 2nd- or 3rd-line treatment on HU or SCT are similar across the three treatment arms, since the durations of TKI treatments are similar across treatments. Therefore, this method largely equalises all post-TKI costs and QALYs between treatment arms.

One further adjustment is performed when using the Simplified analysis method in combination with the Surrogate Survival method (Scenarios 1a, 1b, 2a, 2b; Table 33, p. 136). In these Scenarios, relative survival between treatment arms is modelled by setting the time on HU in CP as a function of treatment arm in order to recreate the modelled OS based on surrogate data (Section 8.1.3, p. 139). In this case, if denoting T_{im} and T_{nil} as the mean times on HU in CP for those patients who receive this treatment in the imatinib and nilotinib treatment arms respectively, then we estimate the total discounted per patient post-TKI treatment cost in the nilotinib treatment arm as;

$$\frac{T_{nil}}{T_{im}} \frac{P_{nil}}{P_{im}} C_{im}$$

and similarly for the dasatinib arm, and for the QALYs in the dasatinib and nilotinib treatment arms.

This Simplified Method clearly does not represent our best estimate of the courses of treatments after resistance or intolerance to TKIs. However, we include this Scenario to represent largely the cost-effectiveness of the treatment arms allowing for the "pure" cost-effectiveness of 1st-line TKIs and 2nd-line nilotinib. Also, we believe this analysis may be

useful given the substantial uncertainty in the nature and costs of subsequent lines of treatment. This is especially true given that we predict that patients will take 1st-line TKIs for many years (between 7 and 9 years, see Results). Therefore, in the Simplified Method analysis the results should not reflect the treatments post TKIs, which remain uncertain, and also start about 8 years from diagnosis) and their associated costs and QALYs.

8.1.5. Perspective, discounting and time horizon

The model cycle length is three months, and the model time horizon is 50 years, or age 107, at which, time all people have died. A model half-cycle correction is applied.

Future costs and benefits (QALYs) are discounted at 3.5% per year, and the perspective is that of the NHS and Personal Social Services, in accordance with the NICE Reference Case.

8.1.6. Modelled treatment sequences post 1st line treatment

8.1.6.1. Treatment sequences in chronic phase chronic myeloid leukaemia

As presented in Table 33, p136, in Scenarios 1 (a & b), 2 (a & b), 3 and 4, we assumed patients with chronic phase CML received either stem cell transplant (SCT) or HU for 2nd- or 3rd -line treatment, and no further lines of treatment before reaching AP or BC. The proportion of people with CML who receive SCT are deemed to receive it immediately following TKI failure.

Scenarios 3 and 4 represent our best estimate of the probable future lines of treatment, and reflects NICE's draft guidance FAD[X] to recommend nilotinib - but neither dasatinib nor high-dose imatinib - as 2nd-line treatment after imatinib in CML (the draft guidance FAD for 2nd line CML for high-dose imatinib, dasatinib and nilotinib, is available on the NICE website at http://guidance.nice.org.uk/TA/WaveR/99). Here, for the nilotinib as 1st line treatment comparator, we again assume a mixture of SCT and HU for 2nd-line treatment, but no further

[X] In the draft guidance on 18th August 2011, NICE has recommended nilotinib, for the treatment of the chronic and accelerated phases of CML (chronic myeloid leukaemia) that is resistant or intolerant to standard-dose imatinib. Dasatinib and high-dose imatinib, are not recommended in the draft guidance. Consultees have the opportunity to appeal against the draft guidance. Until NICE issues final guidance, NHS bodies should make decisions locally on the funding of specific treatments. This draft guidance does not mean that people currently taking dasatinib or high-dose imatinib will stop receiving them. They have the option to continue treatment until they and their clinicians consider it appropriate to stop.

lines of treatment. In contrast, in the imatinib and dasatinib comparators, we assume that all patients will receive nilotinib 2nd-line, and a mixture of SCT and HU for 3rd-line treatment.

8.1.6.2. Treatments in accelerated and blast phase

The range of treatments that CML patients may receive in the advanced stages of disease is wide, and quite variable between patients. We are aware from our clinical experts that these might include the use of TKIs, various chemotherapies, reconsideration for SCT, and However, for simplicity we assume that patients take only hydroxyurea in AP and BC. We believe this is justified mainly because of a lack of evidence relating to the effectiveness of the these treatments in the advanced stages of CML, and believe it would be inconsistent to include their costs but not their effects. Further, in common with the manufacturers' analyses, we felt it would be too difficult to create a well-evidenced sub-model for the advanced phases of disease which included SCT or the possibility of 2nd or 3rd chronic phases.

8.1.6.3. Treatment pathways not modelled

When we assume treatment with HU in chronic phase CML, it is likely that in reality a wider mixture of treatments would be offered, including other chemotherapies and interferon-alpha. Although we have costed for the use of HU only, our survival data following HU relies on data where a mixture of post-TKI treatments have been used (see Section 8.2.3.1).

As discussed in the previous section, we also chose not to model SCT, other forms of chemotherapy, or the possibility of 2nd or subsequent chronic phases after entering either of the advanced phases of disease.

There is some limited evidence that some patients on TKIs with a deep and durable response may be taken off treatment, as they are effectively cured.[48] We have not modelled this possibility.

8.1.7. Summary of scenario analyses

The relative merits of our scenario analyses are presented in Table 34 below.

Table 34 Relative merits of PenTAG scenario analyses

	Scenario 1	Scenario 1a	Scenario 1b	Scenario 2	Scenario 2a	Scenario 2b	Scenario 3	Scenario 4
Advantages								
Equity across treatment arms because same number of lines of therapy	✔	✔	✔	✔	✔	✔		
Cost-effectiveness of 1st line drugs not affected by cost-effectiveness of 2nd line nilotinib	✔			✔				
MMR from two RCTs used, which is a known predictor of survival		✔			✔			
CCyR from two RCTs used, which is a known predictor of survival			✔			✔		
Nature of subsequent lines of treatment uncertain, this issue is bypassed				✔	✔	✔		✔
Cost-effectiveness of 1st line drugs only marginally affected by cost-effectiveness of subsequent treatment				✔	✔	✔		✔
Subsequent lines of treatment are our best estimate of future treatments on NHS given NICE's draft guidance FAD* recommendations on 2nd line drugs, such related medical costs should be modelled							✔	
Allows treatment with 2nd line nilotinib, which NICE's draft guidance FAD* has recently recommended							✔	✔
Disadvantages								
Does not use any response rates from RCTs	✔			✔			✔	✔
2nd line nilotinib not modelled, although recently recommended in the NICE draft guidance FAD*	✔	✔	✔	✔	✔	✔		
Survival does not reflect exact nature of 2nd line treatment		✔	✔					
Only marginally affected by subsequent lines of treatment, and their related medical costs				✔	✔	✔		✔
Cost-effectiveness of 1st line drugs affected by cost-effectiveness of 2nd line nilotinib							✔	✔

* = In the draft guidance on 18th August 2011, NICE has recommended nilotinib, for the treatment of the chronic and accelerated phases of CML (chronic myeloid leukaemia) that is resistant or intolerant to standard-dose imatinib. Dasatinib and high-dose imatinib, are not recommended in the draft guidance. Consultees have the opportunity to appeal against the draft guidance. Until NICE issues final guidance, NHS bodies should make decisions locally on the funding of specific treatments. This draft guidance does not mean that people currently taking dasatinib or high-dose imatinib will stop receiving them. They have the option to continue treatment until they and their clinicians consider it appropriate to stop.

In the context of an MTA, a secondary purpose of the economic model produced by the independent technology assessment/review group is to enable consideration and comparison of the similarities and implications of the modelling approaches used by the manufacturers.

Table 35 on the following page therefore shows the scenarios analysed with the PenTAG model and how they relate to the model-based cost-effectiveness analyses provided by Novartis and BMS

Table 35 Summary of scenario analyses in Novartis and BMS models

1st-line	2nd-line	3rd-line	Model all costs?	Cumulative survival method	MMR surrogate survival method	CCyR surrogate survival method
Imatinib / nilotinib	HU or SCT	None	Yes	**Novartis 1**	**1a**	**1b**
Imatinib / nilotinib	HU or SCT	None	No, only costs whilst on 1st-line drugs	**2**	**2a**	**2b**
Imatinib	Nilotinib	HU or SCT	Yes	**3**	**3a**	**3b**
Dasatinib	Nilotinib	HU or SCT				
Nilotinib	HU or SCT	None				
Imatinib	Nilotinib	HU or SCT	No, only costs whilst on 1st-line or 2nd-line TKIs	**4**	**4a**	**4b**
Dasatinib	Nilotinib	HU or SCT				
Nilotinib	HU or SCT	None				
Imatinib	50% Nilotinib: 50% dasatinib	SCT or dasatinib-based therapy				**BMS**
Dasatinib	Nilotinib					
Nilotinib	Dasatinib					
Imatinib / nilotinib	Dasatinib	HU or SCT		**Novartis 2**	**n/a**	**n/a**

Note that Novartis' analysis in the last row of this table (their 'base case scenario') is probably no longer valid, given that in the NICE draft guidance FAD, dasatinib as 2nd-line treatment for CML was not recommended (the draft guidance FAD for 2nd line CML for high-dose imatinib, dasatinib and nilotinib, is available on the NICE website at http://guidance.nice.org.uk/TA/WaveR/99). It is acknowledged that this was unknown to Novartis at the time of their submission. However, Novartis' 'Scenario A' analysis in the first row of this table, where no TKI is assumed 2nd-line, is still valid and therefore of interest (see the comparison of Novartis' results with PenTAG Scenario 1 analysis at the end of the cost-effectiveness Section 8.7.1). BMS only model a single scenario.

8.2. Effectiveness parameters and assumptions

8.2.1. Surrogate-predicted overall survival (for SS only)

Overall survival for all three treatment arms was estimated using a surrogate relationship based on CCyR at 12 months, and in a separate analysis, on MMR at 12 months. In each case, overall survival was estimated in four stages;

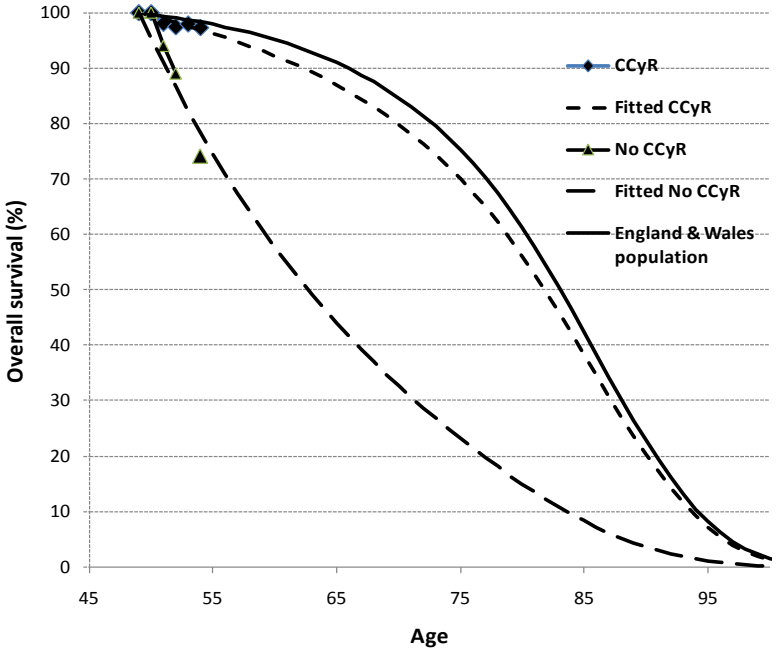
Stage 1: Overall survival for responders, and separately for non-responders, was estimated as a function of time using imatinib arm data from a meta-analysis of trials of imatinib 1st-line (including the IRIS RCT). The estimates of OS for responders and non-responders, separately for cytogenetic response and molecular response, using a meta-analysis are given in Section 5.2.2.3, p. 110 (Chapter 5).

Stage 2: Mortality due to CML was estimated from this historical imatinib trial data. Mortality was assumed to occur due to CML-related causes and non-CML causes. Given limited historical data, the probability of CML-related death was assumed to be constant over time. Non-CML mortality was taken from UK life tables,[115] and the age at diagnosis was estimated as the average age at diagnosis across all historical trials, weighted by the number of responders or non-responders in each trial, as appropriate. The probability of CML-related death was estimated using the Excel "Solver" function in such as way that the sum of squares of differences between the actual historical OS and modelled OS at each year was minimised. The actual historical OS and fitted OS are shown in Figure 17.

Stage 3: Overall survival was estimated separately for responders and non-responders given a cohort of patients starting 1st-line treatment at age 57 (the mean age at diagnosis for our modeling, and at present in the UK). Overall survival was estimated by applying mortality from the general population with starting age 57 and the appropriate estimate of CML-related mortality from Stage 2.

Stage 4: Overall survival was estimated for each treatment arm (imatinib, dasatinib, nilotinib) by averaging the responder and non-responder OS, estimated in Stage 3, weighted by the proportion of patients who did and did not achieve a response to 1st-line treatment at 12 months, see Figure 18 below. Our estimates of mean OS based on these estimation methods are given in Figure 19.

Finally, we compare our estimates of expected OS with the actual 24 month OS from the RCT ENESTnd, the RCT DASISION, and with the longer term imatinib survival data from the IRIS trial of imatinib vs. interferon-alpha.



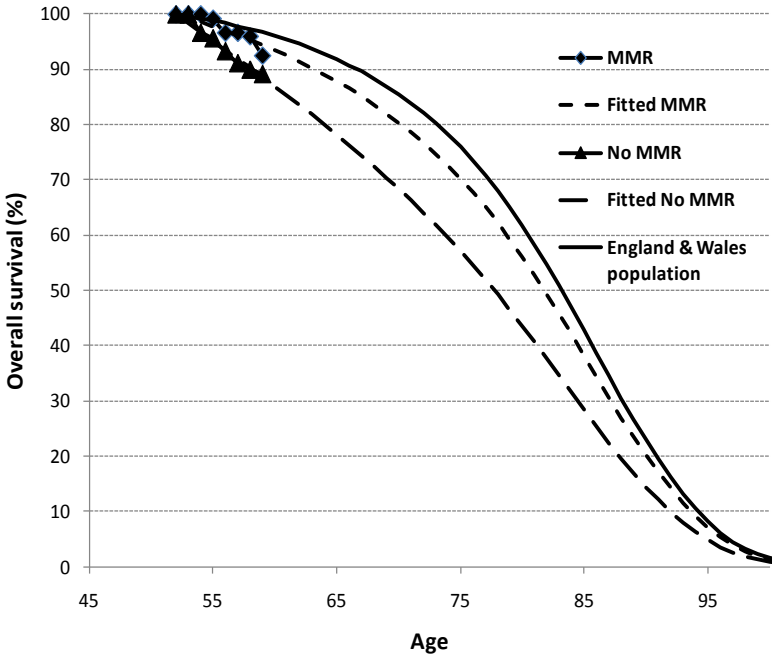


Figure 17 Historical vs. fitted OS for patients (a) with and without a CCyR and (b) with and without a MMR

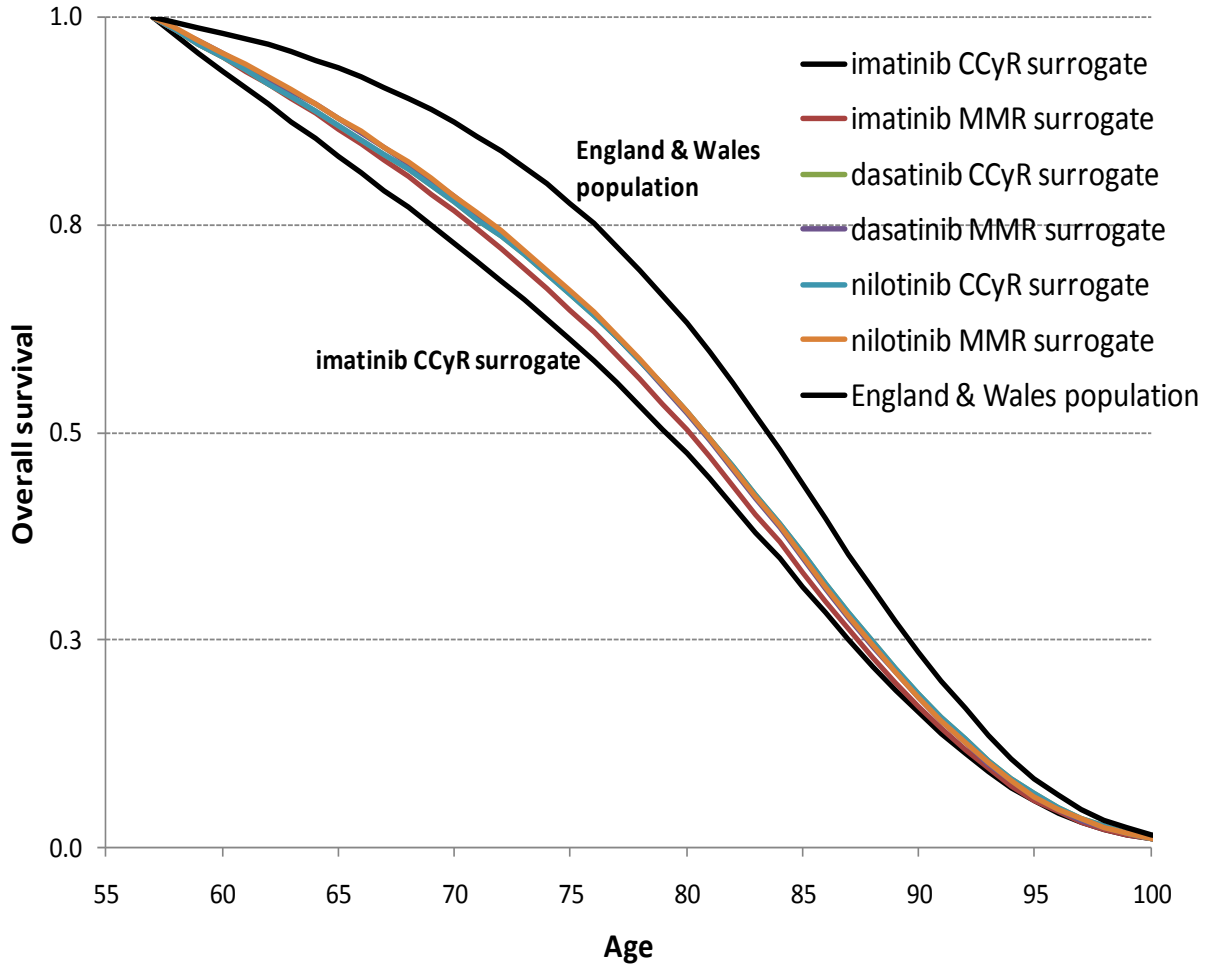


Figure 18 Overall survival for each treatment arm estimated by surrogate relationship based on CCyR and separately MMR

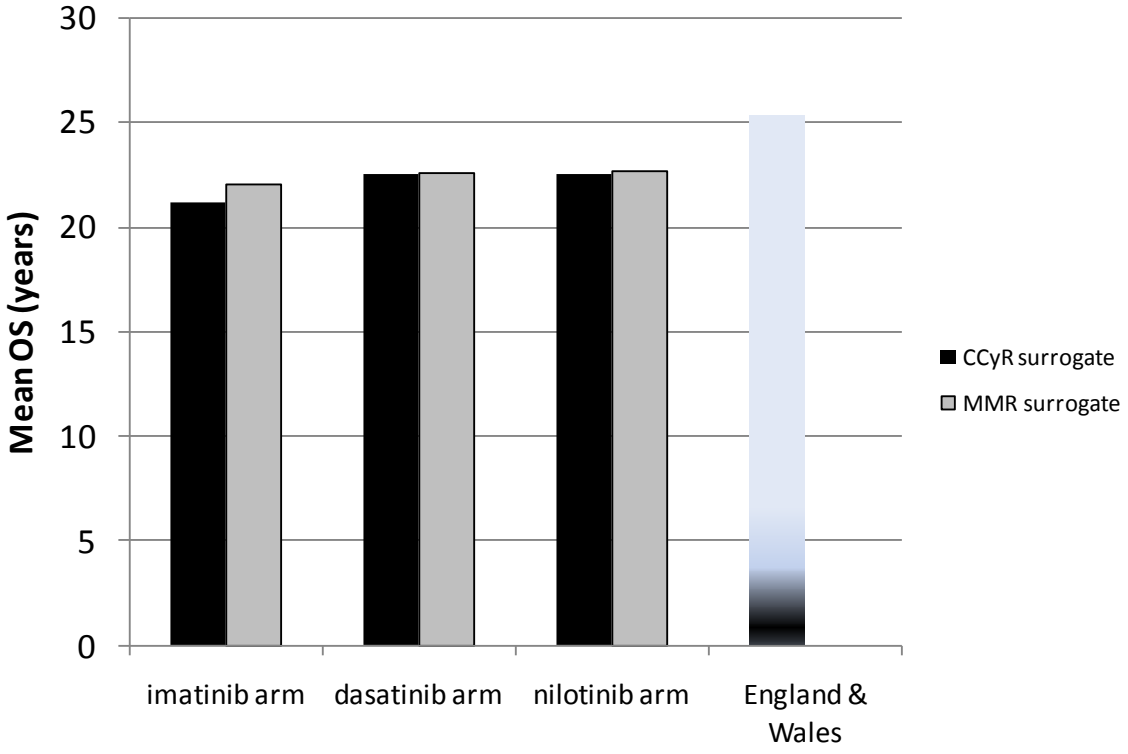


Figure 19 Estimated mean overall survival as a function of surrogate measure used and treatment arm, treatment started at age 57

Comparison of actual and expected overall survival

Given that the OS from the RCTs of 1st-line dasatinib and nilotinib is very immature, it is difficult to gauge the accuracy of the modelled OS shown in Figure 18. Nonetheless, it appears that the modelled OS is consistent with this data. At 2 years follow-up;

- dasatinib empirical OS was 95% based on DASISION trial data, compared to 97% in the model based on either the CCyR and MMR surrogate relationships,[77]
- nilotinib empirical OS was 97% based on ENESTnd trial data, compared to 97% in the model based on either the CCyR and MMR surrogate relationships,[87]

- imatinib empirical OS was 95% and 96% in the dasatinib and nilotinib RCTs respectively, compared to 96% in the model based on the CCyR surrogate relationship and 97% based on the MMR surrogate relationship.[77, 87]

In addition, the estimated OS for the imatinib arm closely predicts the actual OS in the imatinib arm of the IRIS RCT (Figure 20). This is not a completely independent verification of OS by this method, because some of the data on OS for imatinib responders and non-responders from the IRIS RCT was also used to estimate the OS surrogate relationships. However, other historical data also heavily influenced the surrogate OS estimates so it is a useful calibration of the model's survival outputs using this method (See Chapter 5, Section 5.2.2.1, p. 106).

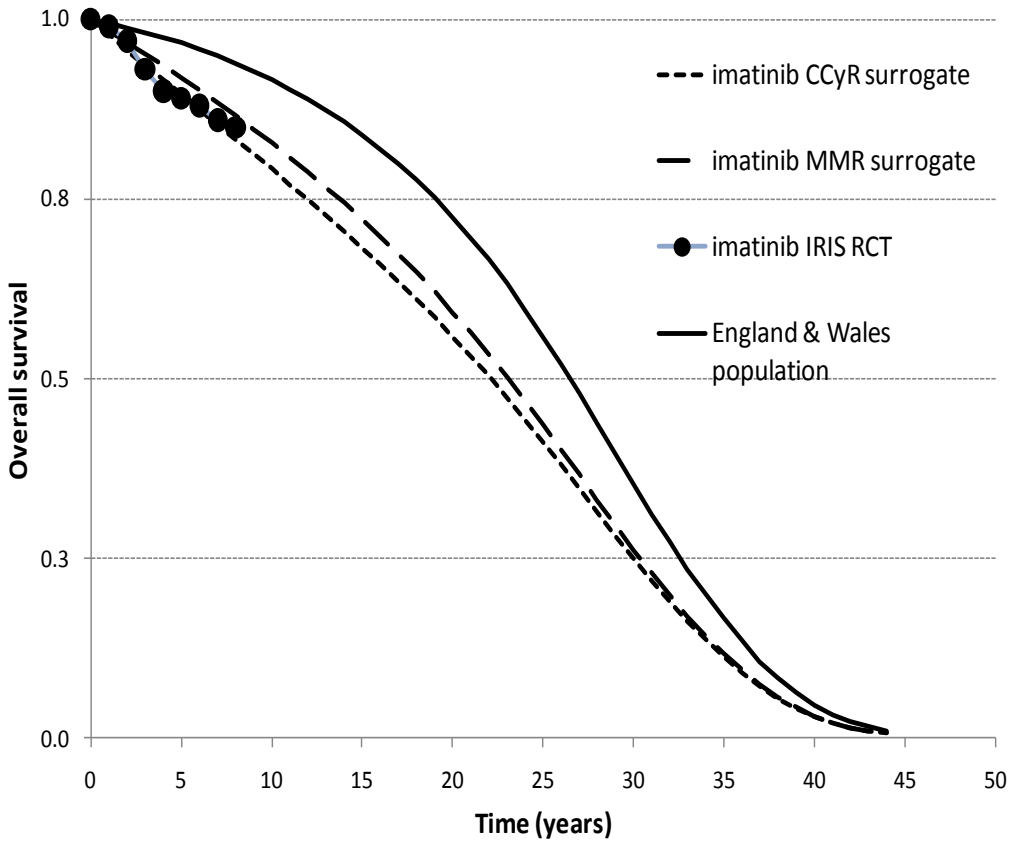


Figure 20 Overall survival for the imatinib treatment arm estimated by surrogate relationship compared to actual OS from IRIS RCT

8.2.1.1. Estimated complete cytogenetic response and major molecular response at 12 months by 1st-line treatment

Estimates of response rates for CCyR and MMR are available for imatinib and dasatinib from DASISSION and for imatinib and nilotinib (300mg) from ENESTnd (see Table 36 and Table 37).[20, 29]

Table 36 Data for estimation of response rates for complete cytogenetic response

	Imatinib				Dasatinib				Nilotinib (300mg)			
	Number responders	Total participants	Response rate	s.e.	Number responders	Total participants	Response rate	s.e.	Number responders	Total participants	Response rate	s.e.
Kantarjian et al[29]	73	260	0.281	0.028	119	259	0.459	0.031	-	-	-	-
Saglio et al[20]	63	283	0.219	0.025	-	-	-	-	125	282	0.443	0.03

Table 37 Data for estimation of response rates for major molecular response

	Imatinib				Dasatinib				Nilotinib (300mg)			
	Number responders	Total participants	Response rate	s.e.	Number responders	Total participants	Response rate	s.e.	Number responders	Total participants	Response rate	s.e.
Kantarjian et al[29]	186	260	0.715	0.028	216	259	0.834	0.023	-	-	-	-
Saglio et al[20]	184	283	0.650	0.028	-	-	-	-	226	282	0.801	0.024

Since estimates of response rates are required for all three treatments in the cost-effectiveness model, a mixed treatment comparison (MTC) approach was taken using the data above. The method is described in Appendix 7. The imputed and overall estimated response rates for CCyR and MMR are shown in Table 38 and Table 39 respectively. Note that, as required, the overall response rate estimates for CCyR and MMR are weighted in favour of the trial report estimates rather than the imputed estimates.

Table 38 Trial-specific and overall estimates of complete cytogenetic response

	Imatinib		Dasatinib		Nilotinib (300mg)	
	Response rate	s.e.	Response rate	s.e.	Response rate	s.e.
Kantarjian et al	0.281	0.028	0.459	0.031	0.525	0.057
Saglio et al	0.219	0.025	0.380	0.055	0.443	0.030
Meta-analysed for model	**0.246**	0.018	**0.440**	0.027	**0.460**	0.026

Table 39 Trial-specific and overall estimates of major molecular response

	Imatinib		Dasatinib		Nilotinib (300mg)	
	Response rate	s.e.	Response rate	s.e.	Response rate	s.e.
Kantarjian et al	0.715	0.028	0.834	0.023	0.844	0.031
Saglio et al	0.650	0.028	0.786	0.042	0.801	0.024
Meta-analysed for model	**0.683**	0.020	**0.823**	0.020	**0.817**	0.019

8.2.2. Overall survival by subsequent treatment and disease phase

8.2.3. Duration of 1st-line TKI treatment

The mean time on 1st-line treatment for imatinib, dasatinib and nilotinib are very important quantities in the estimation of the cost-effectiveness of 1st-line nilotinib and dasatinib vs. imatinib. We used the following sources of data;

- for nilotinib, we used treatment duration data up to 2.5 years follow-up from the RCT ENESTnd.[20]

- for dasatinib, we used treatment duration data up to 2 years follow-up from the RCT DASISION.[29]

- for imatinib, we used 3 sources of data: from ENESTnd, DASISION, and the IRIS RCT, which has up to 8 years follow-up.

Follow-up was limited to just 2 or 2.5 years in the RCTs of 1st-line nilotinib and dasatinib. Given that a large proportion of patients were still on treatment at this time (0.65 to 0.80), it was necessary to extrapolate these proportions. This was achieved by using data from the IRIS RCT of 1st-line imatinib vs. interferon-alpha, with follow-up extending to 8 years. We deemed this trial as appropriate because this is the longest follow-up TKI treatment duration data which currently exists.

Treatment duration for all three drugs was estimated in the following three stages, described below, and which assumes that temporal pattern of treatment discontinuation in the new drugs would be broadly similar.

- In Stage 1, we modelled the treatment duration of imatinib in the IRIS RCT.

- In Stage 2, we modelled the treatment duration of dasatinib from DASISION, the treatment duration of nilotinib from ENESTnd, the treatment duration of imatinib DASISION and ENESTnd

- In Stage 3, we synthesised these quantities to estimate the modelled treatment durations for imatinib, dasatinib and nilotinib.

Stage 1

First, we fit a curve to the proportion of patients on imatinib treatment in the IRIS RCT. The empirical data was taken from the following publications: Druker and colleagues, O'Brien and colleagues, Hochhaus and colleagues, Deininger and colleagues.[27, 46, 102, 116] Treatment cessation due to non-CML mortality was modelled independently of treatment cessation due to any other causes. Non-CML mortality was modelled by using mortality of a the general population in England & Wales with starting age 50 years, the median starting age in the IRIS RCT. We modelled treatment cessation due to any other causes as a Weibull distribution, which is most commonly used in survival analysis, Figure 21. Fitting was achieved by minimising the sums of squares of differences between actual and modelled

treatment duration. The resulting parameters of the Weibull distribution, which modelled treatment cessation due any causes except non-CML mortality were: lambda = 0.093, gamma = 0.861. Including all causes of treatment cessation ("fitted with general mortality" in Figure 21), the mean treatment duration was 13.0 years.

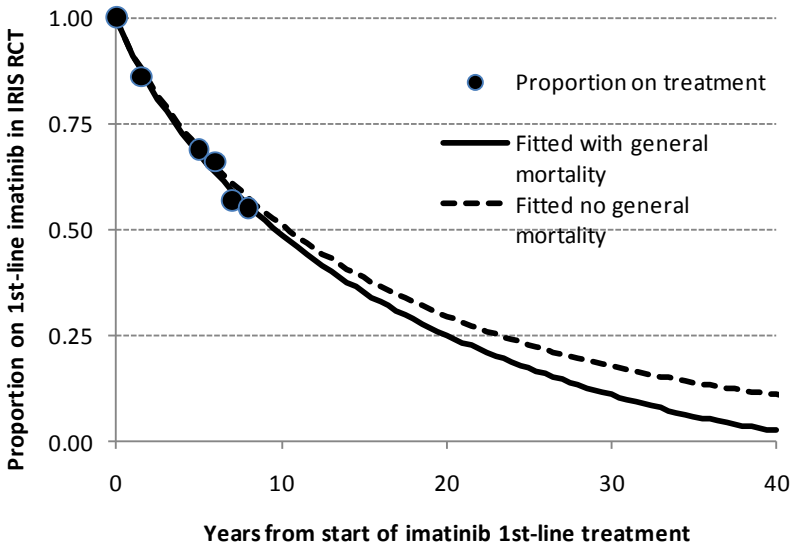


Figure 21 Actual vs. modelled imatinib treatment duration in IRIS RCT

Stage 2

Next, the proportion of patients on nilotinib treatment in the nilotinib vs. imatinib (ENESTnd) RCT was modelled, again splitting out non-CML mortality, and modelling the remaining causes of treatment cessation as a Weibull distribution. Given such short follow-up in the nilotinib vs. imatinib RCT, it was not reasonable to estimate a shape parameter from the data from this trial. Instead, *we assumed the same shape parameter of the Weibull distribution (of gamma = 0.861) as estimated in the longer-duration IRIS RCT for imatinib* (Stage 1). This strongly impacts the extrapolated nilotinib treatment duration. When modelling non-CML mortality, a starting age of 57 years for 1st-line treatment of CML was assumed, our estimate for general age at diagnosis of the patient population in the UK (see Section 8.3, p. 170).

In the ENESTnd RCT of nilotinib vs. imatinib, 12-month data on nilotinib and imatinib treatment discontinuation is given in the online Appendix of the paper describing this RCT.[20] However, the most up to date data on treatment discontinuation is the 24-month data, which

is provided by Novartis in their report to NICE, and used in their model. Therefore, in common with Novartis, we based our estimate of nilotinib and imatinib treatment duration in this RCT on the Kaplan-Meier data provided by Novartis (p38) (Figure 22 below). This yielded parameter lambda = 0.144, and a mean treatment duration of 8.5 years (Figure 23). If instead we had modelled treatment cessation due to causes other than non-CML mortality as an exponential distribution, i.e. not using the shape parameter from the IRIS RCT, then the mean nilotinib treatment duration would have been 6.9 years. However, we repeat that we believe this method is less sound, because it does not use the valuable information on treatment duration at longer follow-up from the IRIS RCT.

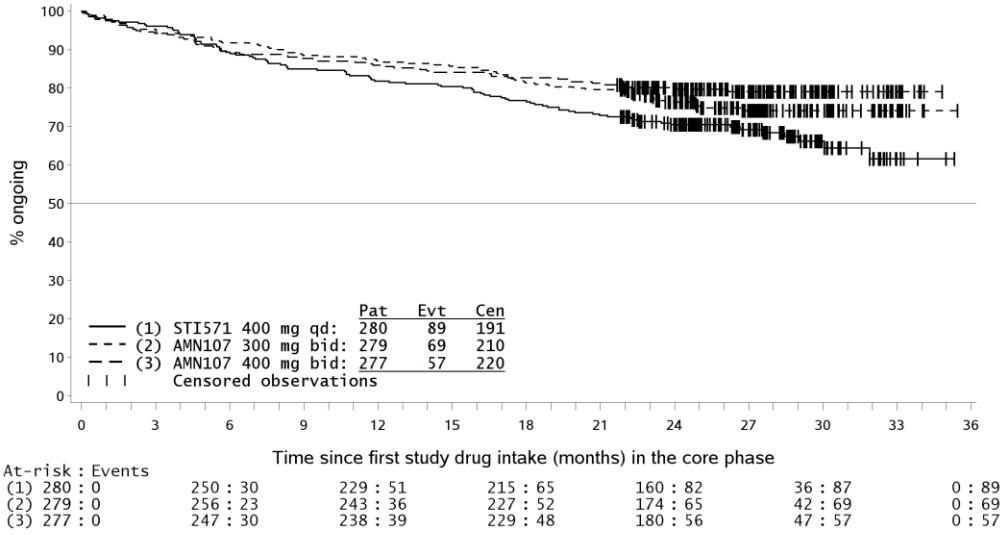


Figure 22 Kaplan-Meier estimates of time on treatment in 1st-line nilotinib vs. imatinib RCT

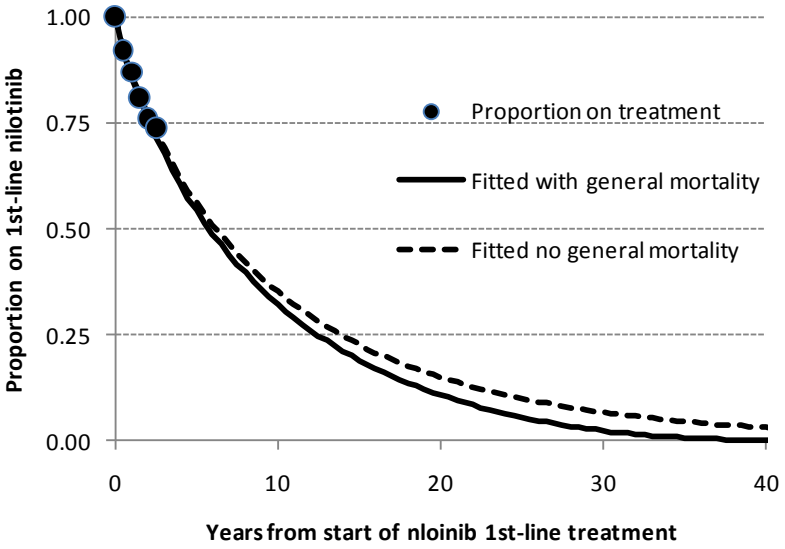


Figure 23 Actual vs. modelled nilotinib treatment duration in nilotinib vs. imatinib RCT

Data for treatment duration in the RCT of dasatinib vs. imatinib was taken from Kantarjian and colleagues for 12 months data, Shah and colleagues for 18 months data from conference slides by Kantarjian and colleagues and 24 months data.[29, 77, 89]

Exactly the same procedure was then followed for dasatinib, imatinib in the dasatinib RCT and imatinib in the nilotinib RCT (See Figure 24, Figure 25 and Figure 26), with the corresponding lambda parameters equal to 0.150, 0.166 and 0.190, and corresponding mean treatment duration values of 8.2, 7.5 and 6.6 years. If instead we had modelled treatment cessation due to causes other than non-CML mortality as an exponential distribution - i.e. not using the shape parameter from the IRIS RCT - then the mean treatment durations would have been much shorter: 6.6, 6.0 and 5.4 years.

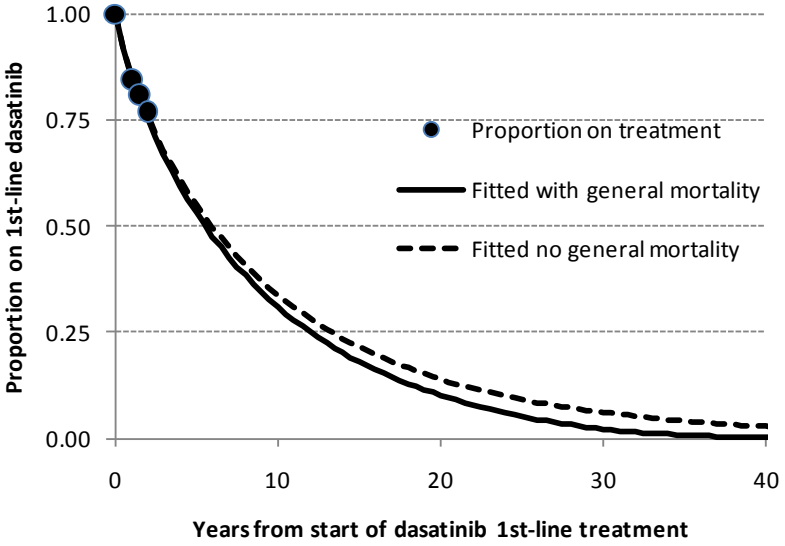


Figure 24 Actual vs. modelled dasatinib treatment duration in dasatinib vs. imatinib RCT

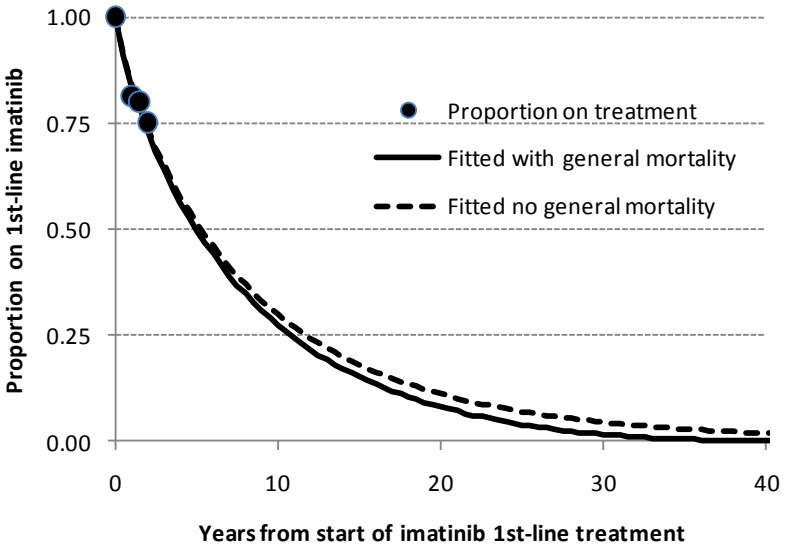


Figure 25 Actual vs. modelled imatinib treatment duration in dasatinib vs. imatinib RCT

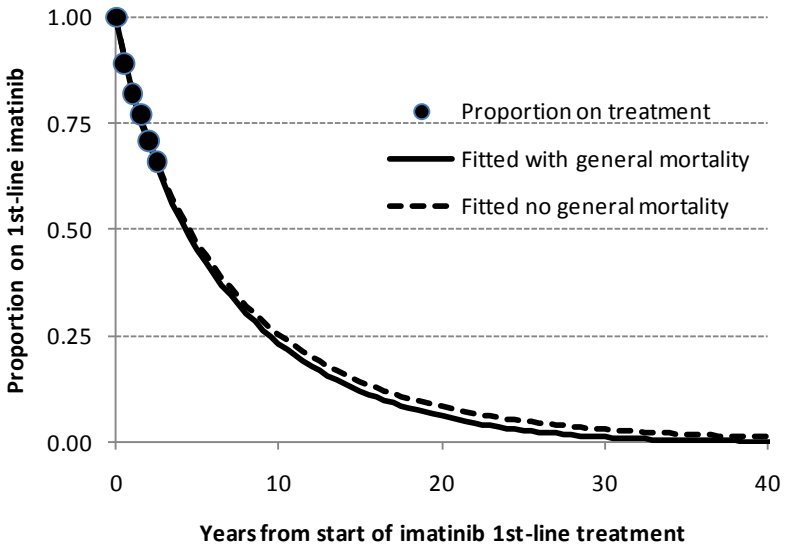


Figure 26 Actual vs. modelled imatinib treatment duration in nilotinib vs. imatinib RCT

All the fitted curves are shown together in Figure 27 below. This clearly shows the model's prediction that the treatment duration of dasatinib and nilotinib will be considerably shorter than treatment duration extrapolated from the IRIS RCT. One possible reason may be the lack of any 2nd line TKI treatment following imatinib during the IRIS trial, so participants stayed on imatinib longer.

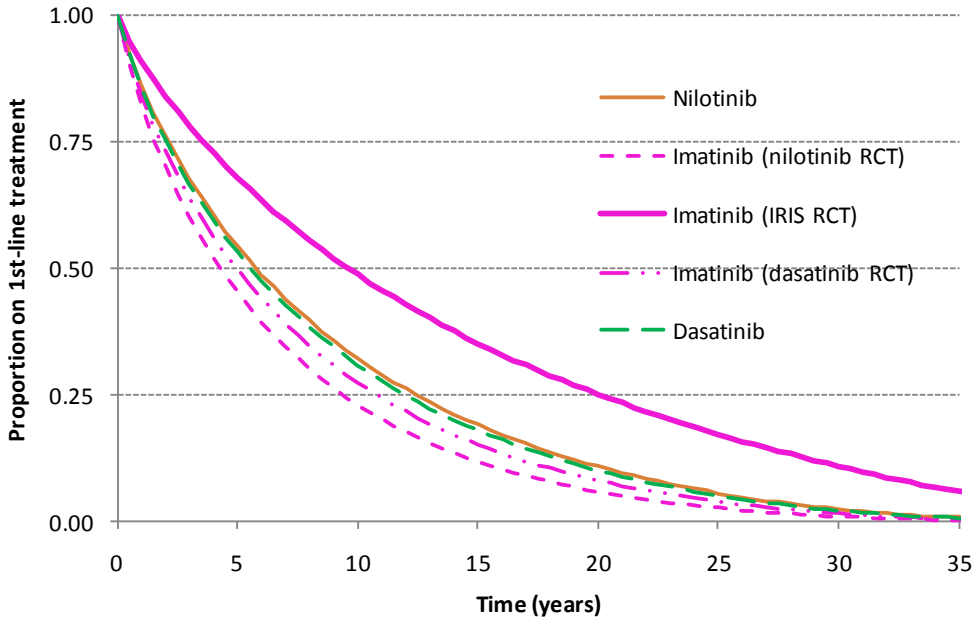


Figure 27 1st-line treatment durations before adjustment for indirect comparison

Stage 3

In this final stage, the treatment duration curves were adjusted for the purposes of the indirect comparison between the three 1st-line treatments (Figure 28, and Table 40 below). The treatment duration for imatinib was estimated in such a way that the mean treatment duration (excluding non-CML mortality) was set to the average of the mean imatinib treatment duration (excluding non-CML mortality) in the RCT DASISION and the mean imatinib treatment duration (excluding non-CML mortality) in the RCT ENESTnd. It was appropriate to take the average duration from the two RCTs as this is consistent with our estimate of average response rates for patients taking all 1st-line drugs in our mixed treatment comparison (Section 8.2.1.1, p153). In addition, the shape parameter gamma was unchanged at 0.861, the value estimated from the IRIS RCT. Given that treatment cessation due to non-CML mortality is a relatively minor cause of cessation, the modelled mean duration for imatinib is approximately equal to the modelled mean duration for imatinib in the ENESTnd and DASISION RCTs (Figure 28, and Table 40 below).

Next, parameter lambda for the treatment duration of nilotinib was adjusted by the ratio of lambda for imatinib for the indirect comparison and lambda for imatinib from the nilotinib vs. imatinib RCT. The shape parameter gamma was unchanged at 0.861. This adjustment follows that suggested by Bucher and colleagues. Treatment duration for dasatinib was similarly adjusted for the indirect comparison.

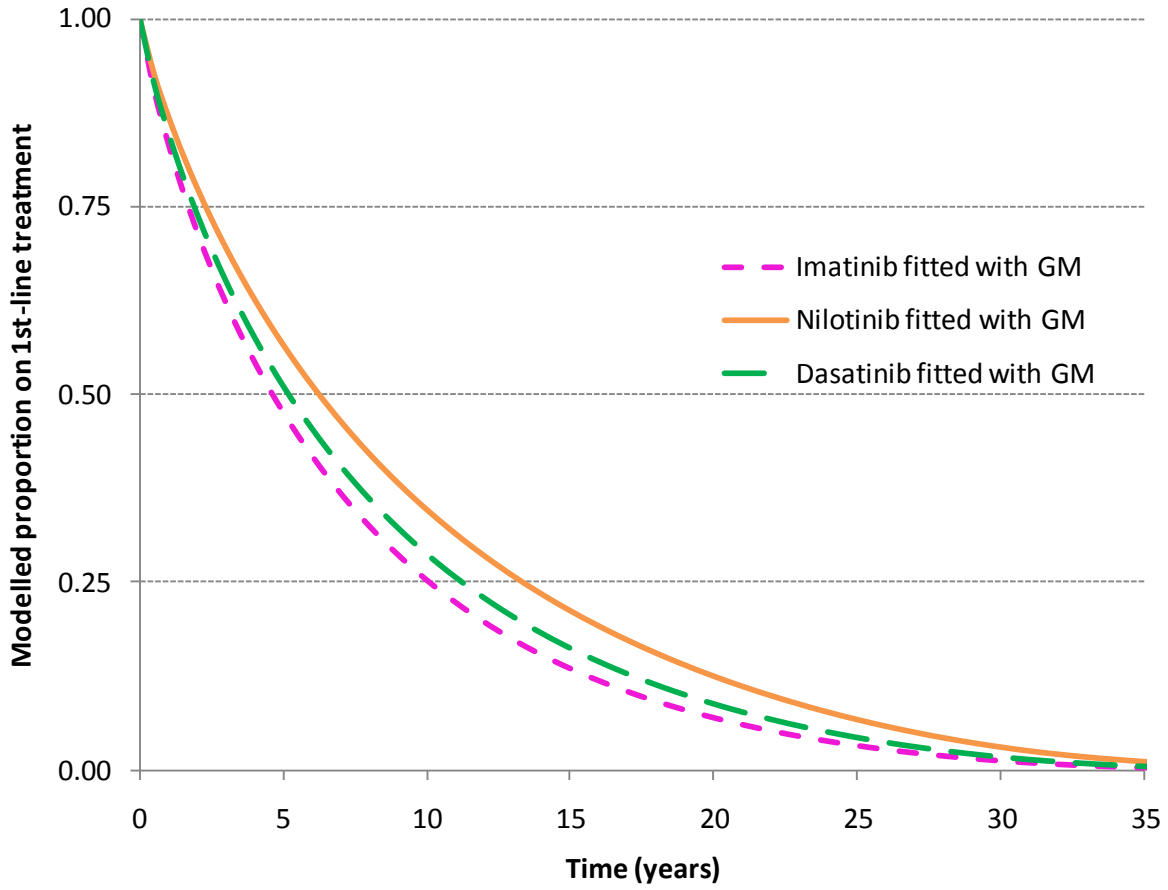


Figure 28 1st-line treatment durations after adjustment for indirect comparison

Table 40 Estimated mean 1st-line treatment duration (years) for model

Trial data used for estimation	imatinib	nilotinib	dasatinib
DASISION	7.5	-	8.2
ENESTnd	6.6	8.5	-
IRIS RCT	13.0	-	-
Modelled for indirect comparison	7.1	9.0	7.8

8.2.3.1. Overall survival on hydroxyurea following TKI failure

Given a lack of evidence for survival on hydroxyurea following TKI therapy, we have adopted the same strategy as the Novartis (2009) submission to NICE for 2nd-line nilotinib for chronic phase patients resistant or intolerant to imatinib (p36 Novartis 2009 submission) to

estimate survival on hydroxyurea following TKI failure.[117] This is based on a cohort study by Kantarjian and colleagues who present combined results for a sub-group of 'other' patients who are resistant or intolerant to imatinib.[118] The 61 patients of this sub-group received a range of treatments treatments including tipifarnib, ionafarnib, decitabine, cytarabine, homoharringtonine and IFN, with 12 receiving hydroxyurea. Survival when taking hydroxyurea is assumed to be the same as that of the 'other' treatment arm for imatinib intolerant patients, even though, as acknowledged by Novartis in their 2009 report, some of the non-hydroxyurea treatments in this treatment group may prolong survival as compared to hydroxyurea. However, Novartis' consultation with clinical experts for their 2nd-line submission also suggested that this was a reasonable assumption given the lack of available relevant data on hydroxyurea in this setting.[117] Given the lack of relevant data, and in common with Novartis in their current submission, we assume that OS on hydroxyurea is independent of previous treatment. Given these limitations, our estimate of OS hydroxyurea following TKI failure is uncertain.

The Kaplan-Meier estimates of OS on hydroxyurea were read off at yearly intervals from Figure 2a of Kantarjian and colleagues.[118] As previously, two sources of mortality were modelled: CML-specific and non-CML. Non-CML mortality was modelled assuming the median initial age in the Kantarjian and colleagues study of 54 years.[118] The probability of CML-specific mortality was assumed to be constant over time. This probability was adjusted in such a way as to minimise the sums of squares of differences between the actual and modelled survival (Figure 29). This yielded a mean OS of 7.0 years for this trial, and a 5-year survival of 50%. Note that OS on hydroxyurea is lower in our model, because we assume that patients start 1st-line treatment at age 57, and these 1st-line treatments are taken for 7 to 9 years, so patients start 2nd-line line hydroxyurea aged approximately 65 years.

The derivation of our estimated time on HU in chronic phase, shown in Figure 29, is explained in the next section.

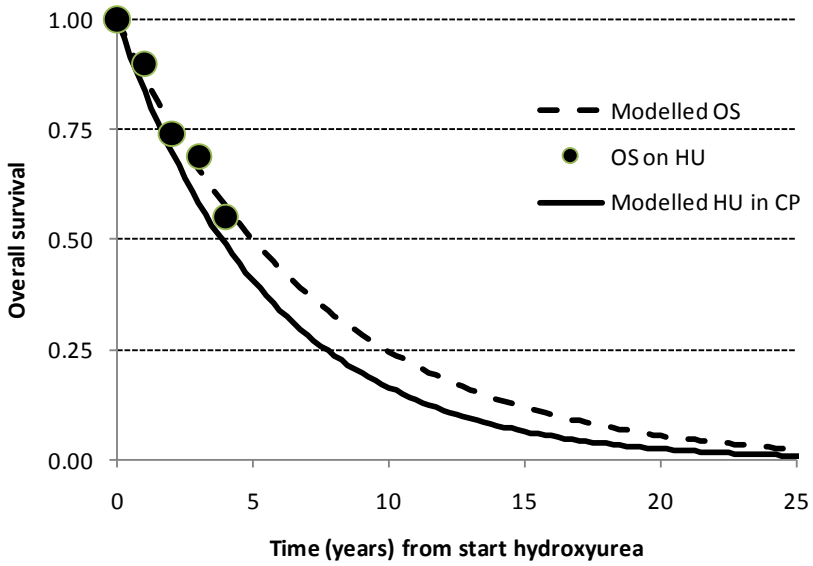


Figure 29 Actual vs. modelled overall survival for hydroxyurea following TKI failure. Kaplan-Meier data is from Kantarjian and colleagues[118]

8.2.3.2. Time on hydroxyurea in chronic phase, and time in accelerated phase and blast crisis

In common with the current Novartis analysis, the previous CML disease and treatment model developed by PenTAG in 2009 (of 2nd-line treatment for chronic phase patients resistant or intolerant to imatinib) assumed that time spent in AP and BC is independent of treatment arm. The mean time in AP was 9.6 months and in BC 13.1 months using this source. These values were in turn taken from a previous cost-effectiveness analysis in CML in which the time in AP and BC was calculated from published survival curves.[119-121]

Given the similarity in the estimates, but also the uncertainty around the time spent in the advanced phases, we have adopted the same estimate as the PenTAG (2009) model for the duration of AP (9.6 months). However, for the BC phase, current clinical opinion suggests a considerably shorter duration than the previous estimates used, with life expectancy about 3-6 months (see stated Considerations in NICE's draft guidance FAD for 2nd line CML for high-dose imatinib, dasatinib and nilotinib, this is available on the NICE website at http://guidance.nice.org.uk/TA/WaveR/99, the committee recommendations are draft – consultees have the opportunity to appeal against them and final guidance has not been issued on this appraisal topic). Also in common with Novartis, we applied constant probabilities of transition from AP to BC and from BC to death.

We now explain our derivation of the time on HU in CP, as shown in Figure 29. First, as explained in the previous Section (8.2.3.1), we model general population mortality whilst people are on HU in CP. We also specify a constant annual probability of 0.71 of transition from AP to BC, corresponding to our estimate of mean time in AP of 0.8 years (=9.6 months). Similarly, we specify a constant annual probability of 0.87 of transition from BC to death, corresponding to our revised estimate of mean time in BC of 0.5 years (=6 months). In addition, we specified a constant probability of transition from CP to AP. Given that we have modelled OS on HU as explained in the previous section, this then specifies the constant probability of transition from CP to AP on HU. In the model, this was achieved by using the Solver function in Excel. This yields the constant quarterly probability of 0.043 of transition from CP to AP while on HU.

8.2.4. Proportion of patients receiving stem cell transplant post TKI failure

In all scenarios, some patients are assumed to receive SCT and some HU, as 2nd or 3rd-line treatment after TKI failure (Table 33, p136). We did not identify any published evidence on the proportion of patients receiving SCT after 1st-line TKI failure. We therefore asked three of our clinical experts the proportion of patients that they believed would receive SCT, specifically after failure of TKIs, and at different ages. The similarity of their responses was notable, particularly the steep drop in the estimated percentage of patients who would receive an SCT in the chronic phase after the age of 65. Over the age of 75, all three clinicians said that no chronic phase CML patients would be likely to receive a SCT. To approximate the responses that we received from our clinical experts, we first estimated the percentage of patients who receive an SCT for each of a range of ages (see Table 41). Because of both the high cost of SCT, and its important impact on life-expectancy for those that survive to five years or more, these key assumptions will be varied in sensitivity analysis. For ease of modelling, we then estimated the proportion of patients receiving a SCT as a simple linear function of time by least squares (Figure 30).

Table 41 Age-related proportions of patients receiving a stem cell transplant

Age at which TKIs fail	% of patients who get an SCT
55-59 years	60%
60-64 years	40%
65-69 years	15%
70-74 years	5%
75+ years	0%

Source: Expert Advisory Group

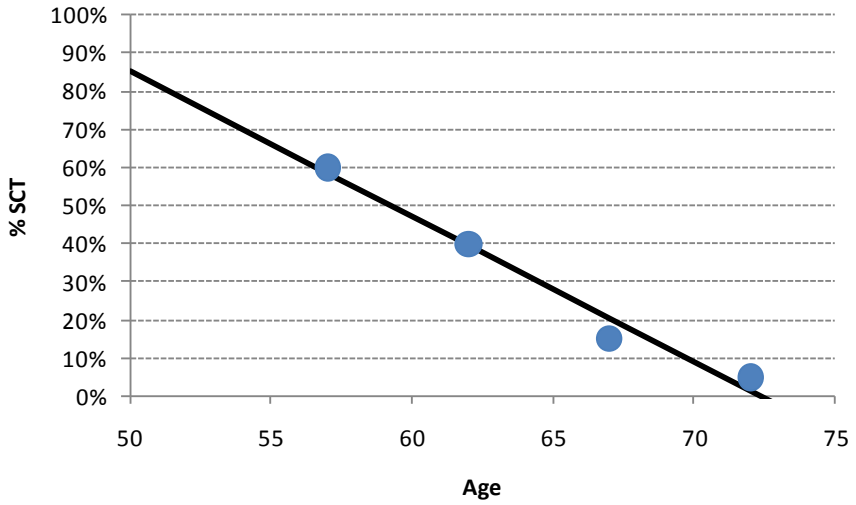


Figure 30 Proportion of patients receiving a SCT as a function of age in the PenTAG model

The corresponding equation is:

Proportion receiving SCT = 2.75 – 0.038 x age (years) [for ages 55 – 72]

and proportion receiving SCT = 0 [for ages greater than 72].

8.2.4.1. Overall survival following stem cell transplant

We reviewed a number of potential published sources for estimating OS following stem cell transplant, including those used in the manufacturer's models. Novartis' source relates to a

cohort of European patients in which only 30% were CML patients, and the data manipulation to estimate the likely survival of the CML sub-group involves the assumption that the mean pre-transplant eligibility/European Group for Blood and Marrow Transplantation (EBMT) risk score for CML patients is 4.[122] The whole data set, as used by Novartis, is also from patients transplanted between 1980 and 2005. Graphs in the Gratwohl paper (their Figure 2A and 2B) further indicate that CML patients, and patients transplanted in the most recent period (2001-05), have the greatest survival compared with other diseases and the whole cohort as used by Novartis.[122]

This produces an estimate of survival at 5 years (34% for those with a risk score of 4) which seems far lower than other published estimates in CML patients we identified and reviewed.[123-125] EBMT registry data as cited in Pavlu et al: 61% survival at 2 years, and higher (66% to 70%) in those CML patients transplanted in the first chronic phase.[125, 126]

We therefore used an alternative UK-based source. This is a review and analysis of 173 CML patients who received SCTs in chronic phase at Hammersmith Hospital, London between 2000 to 2010.[125] Of these patients, 74% survived to 3 years and 72% to 6 years. This is also very similar to the survival estimate from the US Center for Bone Marrow & Transplant Research, who analysed data from 1,309 patients transplanted between 1999 and 2004; their 3-year survival estimate for chronic phase CML patients undergoing transplant post-imatinib was 72%.[123]

Similar to Novartis, we modelled OS following SCT by assuming that patients fall in to one of two distinct groups – those who have high mortality soon after transplant, and those who have low mortality. Investigation of possible fits to the Hammersmith Hospital data revealed a plausible solution that:

(1) The high risk group has constant probability of death of 0.55 (lower dotted line in Figure 31 below).

(2) the low risk group has mortality equal to that of the general England & Wales population (upper dotted line in Figure 31).

(3) 25% of patients are in the high risk group.

The survival of the resulting total population then closely matched the empirical survival data (continuous line in Figure 31). Note that it is not important whether these two groups are clinically plausible. Instead, it is the survival function for all patients combined (continuous line in Figure 31) that should appear plausible compared with available empirical estimates. (A further substantial advantage of modelling survival according to the weighted average of two cohorts is that it greatly simplifies modelling, and bypasses the need for transition probabilities related to the time spent in the SCT health state.)

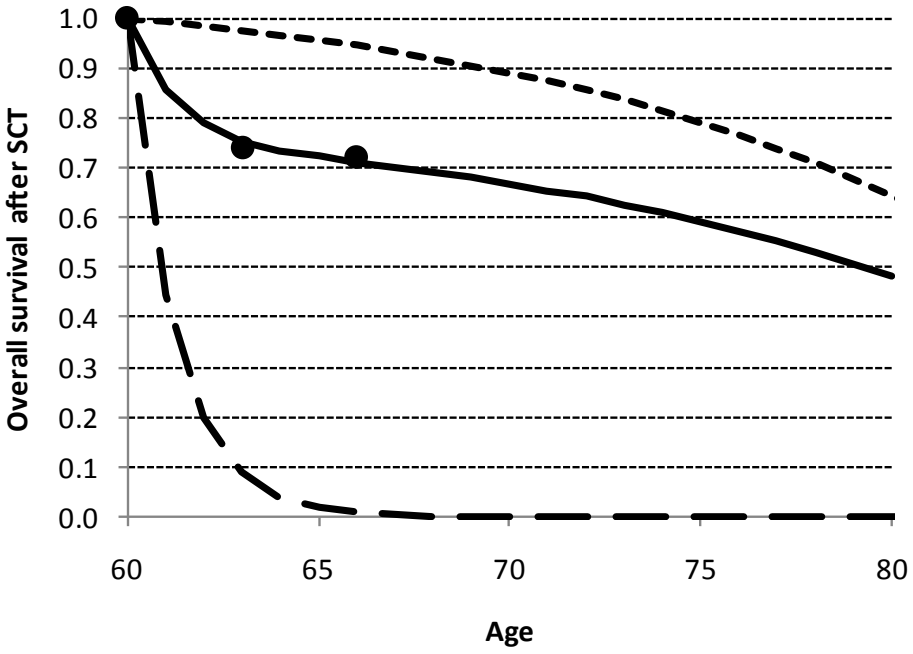


Figure 31 Modelled OS following SCT vs. actual OS from Hammersmith Hospital, 2000-2010

The life expectancy for patients having a SCT aged 60 is then 17.4 years, compared to 22.8 years in the general England & Wales population.

8.2.5. Duration of 2nd-line nilotinib treatment

Second-line nilotinib is modelled in Scenarios 3 and 4 only (Table 33, p136). In these scenarios, we assume that all patients initially randomised to imatinib or dasatinib take nilotinib after 1st-line treatment failure. Patients randomised to nilotinib take either HU or a SCT after nilotinib failure. We are aware of no clinical evidence of nilotinib after dasatinib

failure. However, there has been a Phase II single-arm trial of nilotinib after imatinib failure.[127] In the absence of further data, we assume the duration of 2nd-line nilotinib is independent of whether dasatinib or imatinib was taken 1st-line.

The proportion of all patients (70% imatinib-resistant and 30% imatinib–intolerant) still on 2nd-line nilotinib treatment from the single-arm trial is reported as 0.47 at 2 years.[128] But the proportion is most recently reported as 0.39 at 2 years in an update publication, Kantarjian and colleagues.[129] Also, in their model, Novartis present the Kaplan-Meier data for the proportion of imatinib-resistant (not imatinib-intolerant) patients still on 2nd-line nilotinib treatment from 0 to 2 years. We assume that it is merely coincidental that their proportion at 2 years is the same as the published value of 0.47 from the 2008 abstract for both imatinib-resistant and –intolerant patients combined. Therefore, we used the Kaplan-Meier data presented by Novartis for imatinib-resistant patients only. We fitted an exponential curve to this data, and this yielded a mean time on treatment of 2.4 years. Given that the duration of treatment was short, it was not necessary to model treatment cessation due to non-CML mortality.

8.3. Cohort starting age (age at diagnosis with chronic phase CML)

As stated in our background section (Section 2.2.1, p. 41) the estimated mean age at diagnosis of CML patients in the UK is 58 years, according to data reported by the Haematological Malignancy Research Network (HMRN). We corresponded with the epidemiologist at the HMRN to obtain their current estimate of the age at diagnosis of those CML patients who are diagnosed in the chronic phase (the relevant population to this MTA).

Using data for 192 patients, diagnosed with CML in chronic phase between September 2004 and August 2010, the mean age at diagnosis was 57 years (Std Dev = 17; data kindly analysed and supplied by Dr Alex Smith, HMRN, Dept of Health Sciences, University of York). These data are not from UK-wide sources, but actually from 14 hospitals mainly in the Yorkshire and Humber region of England.

Our cost-effectiveness modelling uses a starting age at diagnosis of 57 years.

8.4. Utility parameters and assumptions

8.4.1. Health related quality of life literature

We undertook a systematic literature search to identify studies which had either directly or indirectly elicited social preference weights or 'utilities' for different CML health states. Appendix 1 shows the full search strategy used and databases searched. Manufacturer submissions to NICE were also reviewed to identify any additional studies.

Because this was to update the search previously conducted in 2009 for our technology assessment of the same drugs for 2nd line treatment of CML, titles and abstracts from the bibliographic searches were only examined for the years 2009-2011. The review was carried out by one researcher (RA).

Our searches identified only one new study of relevance, the 2010 study by Szabo and colleagues which used the Time-Trade-Off (TTO) technique to elicit valuations of seven CML health state descriptions from 339 members of the public in the USA, Canada, UK (UK n=97), and Australia.[130] This study, and the EQ-5D derived utility values from the IRIS trial reported by Reed and colleagues and previously supplied in a Novartis submission, appear to be the only two research-based sources of utility values for health-related quality of life in people with CML (excluding those based on clinicians' estimates).[117, 119]

8.4.2. Utilities in PenTAG model

Our choice of utilities is given in Table 42 below.

Table 42 Utilities used in PenTAG model

	Mean (se)	Source
1st-line (chronic phase)		
dasatinib, nilotinib, imatinib	0.83 (0.004) at diagnosis, age 57, decreasing with age	Based on Reed et al[119] from IRIS RCT
2nd/ 3rd line (chronic phase)		
SCT	75% patients (low risk group) utility equal to general population minus 0.041. 25% (high risk) utility general population minus 0.079[a]	Decrement value from Lee et al.[131]
hydroxycarbamide	As dasatinib, nilotinib, imatinib 1st-line	Based on Reed et al[119] from IRIS RCT
Accelerated phase		
hydroxycarbamide	0.73 (0.06)	Dalziel[a] et al.[67]
Blast phase		
hydroxycarbamide	0.52 (0.08)	Dalziel[a] et al.[67]

[a] Dalziel et al in turn cite unpublished IRIS study data contained in the 2003 Novartis submission to NICE.

In our cost-effectiveness model we chose to use the EQ-5D based valuations of CML health states previously reported by Reed and colleagues, and supplemented by the unpublished data from the same trial (IRIS) for the AP and BC phases of the disease (Personal communication from Dr Shelby Reed, 5th July 2011, and Novartis data cited in Dalziel et al 2004).[67] This data was collected for patients taking imatinib during the IRIS trial, as reported by Reed and colleagues and used by Dalziel and colleagues in a previous HTA of imatinib for CML.[67, 119] These data are drawn from a large sample of patients, using the EQ-5D, which is preferred in the NICE reference case.[132]

It was necessary to estimate utility values for people taking dasatinib and nilotinib in chronic phase, because no values are cited in the literature. In common with BMS and Novartis, we set these values equal to the value for imatinib in chronic phase based on clinical opinion and the similarity of the incidence of adverse events by treatment.

The utilities for accelerated and blast phase reported by Reed and colleagues are slightly different from those quoted by Dalziel and colleagues, although both are taken from the IRIS trial originally.[26, 119, 133] In Reed and colleagues' analysis, no difference was assumed between accelerated and blast phase since the observed difference in values was not

statistically significant. We have therefore used the utility values cited by Dalziel and colleagues in our model.

Utilities decrease with increasing age.[134] In common with Novartis (but not BMS), we adjusted the utilities in the model for age using the following equation (Ara & Brazier 2010);[134]

Utility = 0.951 + 0.021*male – 0.000259*age – 0.000033*age^2.

The estimated utility of people taking imatinib in chronic phase CML of 0.854 from Reed and colleagues is for patients of mean age 50 in the IRIS trial.[119] Given the formula from Ara & Brazier (2010), the mean utility of a member of the general population aged 50, assuming 58% male (our assumption for CML population) is 0.867. This implies a disutility of 0.867 – 0.854 = 0.013 for patients taking imatinib in chronic phase CML compared to the general population. Therefore, for patients taking either imatinib, dasatinib or nilotinib in CP, we assumed general population utilities as a decreasing function of age with a disutility of 0.013 at all ages.

We assume that the utility for patients taking hydroxycarbamide in chronic phase equals that for the TKIs, and we further assume the same decrease in utility over time.

We do not model additional utility decrements associated with adverse events in the base-case.

8.4.3. Utility: after stem cell transplant

Although patients who survive SCT can, in most cases, be regarded as 'cured', in the early years following the transplant many patients will experience complications such as graft-versus-host disease and serious infections (due to the after-effects of myeloablation and the use of immunosuppressive agents).[135] As well as increasing mortality risk, these complications have inevitable quality of life impacts.[136, 137]

Novartis assume that 52% of those receiving SCT experience a 0.079 utility decrement compared to patients in CP taking dasatinib, nilotinib or imatinib for the rest of their lives, while the other 48% experience the same utilities as patients in CP taking TKIs. This disutility is based on the quality of life impact of chronic graft-versus-host disease in a 1997

health state preference elicitation study by Lee and colleagues (conducted with 12 US clinicians familiar with bone marrow transplant patients).[131]

In the absence of other research evidence, our assumption for the utility of survivors after SCT is similar to that of Novartis. We modelled OS following SCT by assuming that patients are in one of two groups – a high risk group with a constant high probability of death, and a low risk group with mortality equal to that of the general England & Wales population (Section 8.2.4.1, p167). In the low risk group, we assume that 52% of patients, those with chronic graft-versus-host disease, have a disutility of 0.079 compared with the general population of England & Wales (not versus people in CP on TKIs as Novartis assume). The remaining 48% of patients are effectively cured of CML, and therefore experience the age-related utility of the general population of England & Wales. Hence, on average, patients in the low risk group have a disutility of 52% x 0.079 = 0.041 compared with the general population of England & Wales. We further assume that patients in the high risk group have a disutility of 0.079 versus patients taking TKIs in CP. This reflects the earlier impact of many of the post-transplant complications, and that chronic graft-versus-host disease is one of a number of possible serious complications.

8.5. Cost parameters and assumptions

We model the following costs, which are inflated to 2011–12 values where appropriate:

- Drug acquisition
- Treatment for adverse events
- A range of medical management costs, including nurse treatment, consultant outpatient visits, bone marrow tests, and hospitalisation.

In addition to the cost of drug acquisition, mean drug costs per person allow for treatment duration (see Section 8.2.3, page 155, Section 8.2.5, p169) and dose intensity (see Section 8.5.1.1, page 176).

8.5.1. Drug acquisition costs

Table 43 and **Error! Reference source not found.** present the drug prices. The prices of dasatinib and hydroxycarbamide were taken from BNF 61 2010,

[redacted]

[redacted] and the price of imatinib was taken from MIMS, which is more up to date than the lower price in BNF 61 2010.[62, 138] NICE have agreed these sources of price information.

Table 43 Drug prices used in the PenTAG model

Dose and frequency	Price	Cost per 3-month model cycle
Dasatinib (Sprycel®)		
100mg per day	£2,504.96 per 50mg 60-tab pack, £2,504.96 per 100mg 30-tab pack	£7,624
Nilotinib (Tasigna®)		
1st-line: 300mg per day (150mg twice a day) 2nd-line: 400mg per day (200mg twice a day)	[redacted]	[redacted]
Imatinib (Glivec®)		
400mg once daily	£862.19 per 100mg 60-tab pack, £1,724.39 per 400mg 30-tab pack	£5,249
Hydroxycarbamide		
20–30 mg/kg daily or 80 mg/kg every third day	£10.47 per 500mg, 100-cap pack	£36#

assumed 25mg/kg daily, 75kg patient

[redacted]

In common with Novartis, we assume that the main alternative treatment to SCT after TKI failure is hydroxyurea (HU or hydroxycarbamide). This drug costs only £36 per 3 months (Table 43 above). However, hydroxycarbamide may not be the only, or even the main treatment for patients post-TKI failure who do not receive a SCT (and we have taken our survival estimates for patients on HU for 2nd or 3rd line treatment from a study population in which patients were taking several other treatments such as interferon-α, homoharringtonine, and cytarabine). Therefore, to reflect the broader mix of drugs that such patients might receive, the cost of treatment with HU is varied widely in the sensitivity analyses.

8.5.1.1. Dose intensities

For consistency between the costs of the drugs and the clinical outcomes, it is necessary to model the amounts of the drugs actually taken in the relevant clinical trials. The dose intensity of a drug is defined as the amount of drug administered in a trial as a proportion of the amount that would have been administered if there had been no dose reductions or dose interruptions. This does not include people who withdraw from treatment due to adverse events. Mean dose intensities per person used in our model are given in Table 44.

Table 44 Dose intensities used in the PenTAG model

Drug	Treatment line	Mean dose intensity	Source
Dasatinib	1st-line	99%	BMS submission, page 27
Nilotinib	1st-line	[redacted]	Novartis submission, page 75
Nilotinib	2nd-line	99%	Kantarjian et al[129] Blood paper
Imatinib	1st-line	[redacted]	Novartis submission, page 75
Hydroxycarbamide	2nd-& 3rd-line	100%	PenTAG assumption

In the absence of a published estimate of the mean dose intensity for 1st-line dasatinib, this was estimated as 99% which is the *median* dose intensity cited by BMS (p27 BMS report). The mean dose intensity for 1st-line nilotinib of [redacted] was provided by Novartis, who state that this came from their analysis at 12-months (p75 Novartis report). The mean dose intensity for imatinib of 106% was provided by Novartis, who state that this came from their analysis at 12-months (p75 Novartis report) of the nilotinib vs. imatinib RCT, with mean dose of [redacted] vs. 400mg planned dose. However, Novartis actually used a dose intensity of imatinib of [redacted], which they cite on p105 of their report, which they state came from their analysis at 24-months.[87] However, they do not state that this is a mean dose intensity. Given that this mean actually represents a median dose intensity, we have chosen the mean dose intensity of [redacted] from their 12-month analysis.[20] Our estimate of [redacted] is consistent with the median dose intensity of imatinib of 100% from the dasatinib vs. imatinib RCT (p27 BMS report). Our estimate is also consistent the mean dose intensity at 6 years for imatinib in the IRIS RCT of 100% for the 364 patients who remained on imatinib at 6 years.[102]

Our estimate of the mean dose intensity of 2nd-line nilotinib of 99% is taken from the single-arm trial of nilotinib for people resistant to or intolerant of imatinib.[127] The mean dose

intensity is not reported, however, we used the *median* dose intensity of 789mg/day, out of a planned dose of 800mg/day. Given that hydroxycarbamide is extremely cheap compared to the other drugs, we have not searched the literature for a mean dose intensity, rather we have simply assumed 100%.

We understand that imatinib will come off European patent in 2016.[139] It is likely that its price will then come down considerably. In a sensitivity analysis, we model setting the price reduction on patent expiry to 25% for all drugs, and setting the price reduction to 25% for imatinib and dasatinib and 0% for nilotinib (See Section 8.6.6.8., p. 218)

8.5.2. Cost of serious adverse events

We included an estimate of the cost of treating selected serious (grade 3 or 4) adverse events while on 1st line or 2nd line TKIs. Based on the reported rates of different adverse events during the first 12 months of treatment, we decided to include only the cost of treating neutropenia, thrombocytopenia and anaemia. No other types of grade 3 or 4 adverse event were experienced by more than 1% of patients in either of the main RCTs (i.e. DASISION and ENESTnd). Although there were very few patients experiencing grade 3 or 4 pleural effusions with dasatinib, because this complication is quite common at lower grades and specific to this TKI, we also estimated the cost of these. The number of additional adverse events from months 13 to 24 was so small that we chose to model only adverse events during the first year of treatment with TKIs. Rates of adverse events costed in the model are shown in Table 45.

Table 45 Rates of the main serious adverse events in the DASISION and ENESTnd trials

	Dasatinib	Nilotinib (300mg)	Imatinib (Dasision)	Imatinib (ENESTnd)
Neutropenia (Grade 3 & 4)	20.9%	11.8%	20.2%	20.0%
Thrombocytopenia (Grade 3 & 4)	19.0%	10.0%	10.1%	8.6%
Anaemia (Grade 3 & 4)	10.1%	3.2%	7.0%	5.0%
Pleural effusion (All grades)	10.1%	0.0%	0.0%	0.0%

Source: see Table 16 and Table 17 in clinical effectiveness review

The cost of treating each of these four types of adverse event was taken from the Oxford Outcomes study, and using a weighted average of the cost of treating a patient experiencing these complications when hospitalised or not hospitalised. They were also inflated from the 2008 to the 2011 values.

Table 46 Unit cost of treating the main serious adverse events

	Cost of treating if hospitalised	Cost of treating if not hospitalised	% that would be hospitalised	£ 2008 cost per AE	£ 2011 cost per AE
Neutropenia (Grade 3 & 4)	£1,668	£279	14.0%	£473	£497
Thrombocytopenia (Grade 3 & 4)	£1,234	£467	0.5%	£471	£494
Anaemia (Grade 3 & 4)	£324	£324	0.7%	£324	£340
Pleural effusion (All grades)		£30	0%	£30	£31

Source: Oxford Outcomes

Table 47 below shows the resulting annual cost of treating the main grade 3/4 adverse events, and the cost of treating pleural effusions in those taking imatinib. The incidence rates of patients experiencing neutropenia, thrombocytopenia and anaemia in those taking Nilotinib as 2nd line treatment are 29%, 29% and 3.2% (sourced from Kantarjian et al[127], except for anaemia which is assumed to be the same as for 1st line treatment with nilotinib).

Table 47 Costs of the main serious adverse events (during first year after starting treatment)

	1st line treatment			2nd line treatment
	Dasatinib	Nilotinib (300mg)	Imatinib[a]	Nilotinib (400mg)
Neutropenia	£104	£59	£99	£144
Thrombocytopenia	£94	£50	£46	£144
Anaemia	£34	£11	£21	£11
Pleural effusion	£47	-	-	-
Total annual cost:	£280	£119	£166	£299

[a] based on weighted annual incidence from imatinib arm of DASISION and ENESTnd trials.

8.5.3. Cost of other medical management and monitoring

We based our medical management and monitoring costs on the mean frequency of hospital outpatient appointments and tests reported by the Oxford Outcomes 2009 survey of six UK-based CML clinicians. Like the estimates used in the BMS cost-effectiveness model, this was based on the frequency of routine appointments and tests after the first three months of treatment, and separately for patients in the chronic and advanced phase. They were also inflated to 2011 prices and adjusted for some tests where our clinical expert believed the frequency from the Oxford Outcomes survey was unrealistic or illogical (e.g. having a frequency of mutation analysis, when only one such test per patient would be conducted; personnel communication C. Rudin, 31st July 2011). Note that, unlike the BMS modelling analyses, we did not include different costs for patients responding and not responding to treatment. This is for simplicity, and because the time that most patients are not responding to treatment, and before they are switched to a new treatment, should be relatively small relative to overall time in 1st or 2nd line treatment. Also, in the questions that distinguished patients as either responding or not responding to treatment in the Oxford Outcomes cost survey (used by BMS) response was not defined; so it is wholly unclear whether this related to cytogenetic, molecular or some other type or level of treatment response for those who answered this survey.

Table 48 below shows the resulting estimates of the medical management costs per quarter for patients in the chronic and advanced phases (accelerated phase and blast crisis).

Table 48 PenTAG medical management costs

	Frequency (per month)[a]	Unit cost (£ 2009)[c]	Monthly cost (£ 2010)
Chronic phase:			
Nurse-led outpatient appointments	0.4	£100	40.00
Haematologist/Oncologist-led outpatient appointments	0.9	£127	114.30
Tests (various)[b]	See note[b]	various	216.07
Hospital in patient – ward days	0	£246	0
Hospital in patient – ICU days	0	£1,219	0
Chronic phase total:			**370**
Advanced phase:			
Nurse-led outpatient appointments	0.5	£100	50.00
Haematologist/Oncologist-led outpatient appointments	1.3	£127	165.10
Tests (various)[b]	See note[b]	various	352.45
Hospital in patient – ward days	1.72	£246	423.83

Hospital in patient – ICU days	0.1	£1,219	121.90
Advanced phase total:			**1,113**

[a] frequencies as reported in Table 30 (p.56) of BMS's submission to NICE
[b] The frequencies and cost of the following tests were included (based on the Oxford Outcomes 2009 clinician survey): complete blood count (CBC); cytogenetic analysis; bone marrow aspiration with biopsy; FISH; PCR; flow cytometry; cytochemistry analysis; blood film exam; chest X-ray; CT scan of chest; blood chemistry; C-reactive protein (CRP); EKG; upper endoscopy (EGD).
[C] See unit costs used by BMS (Table 39, p.65 of their submission) mostly sourced from the National Schedule of Reference Costs or the Unit Costs of Health and Social Care (Curtis 2009), except: correction to the unit cost of a nurse-led and consultant-led haematology or oncology outpatient appointment – used NSRC 2009-10 estimates for face to face non-admitted outpatient appointments.

8.5.4. Cost of care post TKI-failure

8.5.4.1. Cost of stem cell transplant (2nd or 3rd line)

Estimating the NHS cost of adult stem cell transplantation is complicated by a number of factors:

- It is a complex multi-stage process (typically presented as 8 phases, from decision to transplant to after 100 days follow-up).[140]
- The resource use and cost of many phases differs for related and unrelated donors, and also for example, depending on whether related donor SCT recipients may have reduced intensity chemotherapy (reduces transplant cost), or whether unrelated donor SCT recipients require more or less myelo-ablative therapy.
- The cost categories and HRGs within the National Schedule of Reference Costs are relatively new and their use is still evolving. They do not appear to cover all phases of the SCT process. (There is anecdotal evidence from specialist commissioners that the HRGs may not yet be consistently used in cost submissions from NHS Trusts and PCTs).
- The costs vary considerably in different parts of England and Wales, and from trust to trust, for example depending on overhead allocation rates, critical care costs, and the prices paid for obtaining out-of-area unrelated donor cells.

Like the Novartis analysis, we therefore based our base case per patient cost estimate for an SCT on an unpublished September 2009 report by the London Specialised Commissioning Group, which is the most comprehensive and UK-based cost and pricing analysis of adult bone marrow and stem cell transplantation currently available (personnel communication, Mr

Mike Millen, LSCG, 29th July 2011). They report a mean cost of transplant for phases 1 to 6 – that is from "decision to transplant and donor selection" (= phase 1), through "transplant inpatient admission" (= phase 4), to day 100 post-transplant (= phase 6) – of £47,500 (£ 2009) for related donor allografts and £79,600 for unrelated donor.

For the cost of transplant phases 1 to 6, we took a weighted average of these two costs, based on assumed 25%:75% split of related (usually sibling) vs. unrelated (volunteer) donor transplants (Sources: Ashfaq et al. 2010, and personal communication from the SW Specialist Commissioning Manager, 14th July 2011; NB. same split as assumed by Novartis submission), and inflated to 2011 costs.[141]

For the short-term cost of phases 7 and 8 (i.e. from 100+ days post-transplant to approximately 2 years) we also estimated the cost of antifungal drugs used and the cost of repeat donor lymphocyte infusions. The mean costs for both of these are also taken from the 2009 London SCG analysis, but the mean per patient cost of donor lymphocyte infusions has been based on three years of data relating to adult allogeneic stem cell transplants from University of Bristol Hospital (personnel communication Jessica Whitton, Senior Commissioning Manager, SW Specialised Commissioning Group, 27th July 2011).

Table 49 below shows the estimation of our base case cost of SCT.

Table 49 Per patient cost of a stem cell transplant

	Related donor	Unrelated donor	Source and notes
Cost for phases 1- 6 (£ 2009)	£47,500	£79,600	London SCG[140]
Inflated to 2011 (i.e. 2 years)	£49,115	£82,306	PSSRU - Curtis[142]
% split of related vs unrelated:	25%	75%	Ashfaq et al.[141]
Weighted average:	£74,008		
PLUS cost of antifungal drugs	£5,369		London SCG[140] (weighted average)
PLUS donor lymphocyte infusions	£2,225		London SCG[140] (weighted average, also using University Hospital Bristol data[a] on % of related and unrelated donor patients receiving different numbers of DLIs)
Mean per patient cost of	**£81,600[b]**		

SCT			

[a] Of UHB's related donor SCT recipients, 42% received at least 1 DLI (and of these 53% had 1, 32% had 2, 10% had 3, and 5% had 4. Of UHB's unrelated (volunteer) donor SCT recipients, 14% received at least 1 DLI (and of these 87% had 1 and 17% had 3.
[b] Rounded to the nearest £100.

We also estimated the cost of SCT by an alternative method, starting with the National Schedule of Reference Costs HRG cost estimate for an inpatient stay for "peripheral blood STC in adults" (code SA28A = National average cost of £34,783, just for phase 4 of transplant process) and then used a table in the LSCG report which shows the percentage split of total costs across transplant phases (1 to 6) to estimate the total cost of phases 1, 2, 3, 5 and 6 (from decision to transplant to 100 days post-transplant). The estimate from this method comes out as £81,300 – very close to our first method. The method above was used in the model.

8.5.4.2. Longer term following stem cell transplant

Unlike the Novartis submission, we chose to include an estimate of the cost of long term care following SCT, especially to reflect the monitoring and treatment of longer term complications like cGvHD. Our estimate of £113 per month for those suffering cGvHD includes (a) the NHS cost of a quarterly specialist appointment with a clinical haematologist (£125 per appointment) plus (b) the estimated cost of immunosuppressive drug therapies (either cyclosporine with prednisolone, or mycophenolate with prednisolone for the base case assumptions). The calculation of these cost estimates is shown in Table 50 below. An estimate of the monthly cost of a more intensive immunosuppressive drug therapy regime, typically for treating more severe cGvHD is also shown (cyclosporine, mycophenolate, methotrexate and prednisolone), and this higher estimate is used in sensitivity analysis.

Table 50 Estimation of ongoing drug and monitoring costs after SCT

Immunosuppressive regime	Drug costs[a]	Quarterly appointments		% split	
Cyclosporin (50mg bd) plus Prednisolone (20mg od)	£65.96	£42	£107.62	60%	£64.57
Mycophenolate (1g bd) plus Prednisolone (20mg od)	£80.32	£42	£121.97	40%	£48.79
Weighted mean cost per month:					**£113**

[a] Based on unit costs of drugs from the NHS Drug Tariff (Mycophenolate Mofetil 500mg - £28.40 for 50 tablets; Prednisolone 5mg tablets £2.58 for 28 tablets) and the BNF 61 (Cyclosporin 50mg, £27.00 for 30 tablets).

8.5.5. Cost of care in advanced phases

8.5.5.1. Accelerated phase

In addition to the substantially higher costs of medical management (outpatient appointments and tests; see section 8.5.3) we assumed that patients in the accelerated phase would be treated with hydroxyurea. We acknowledge that this is a considerable simplification of the range of possible treatments that people in this heterogeneous group are likely to receive; CML patients within the accelerated or blast crisis phase may receive stem cell transplant following chemotherapy or TKIs as an adjunct to chemotherapy. However, while the use of some TKIs in the accelerated phase is licenced, the evidence for their effectiveness in the advanced phases of the disease is very limited (and the recent NICE draft guidance FAD on nilotinib, dasatinib and high-dose imatinib in 2nd line treatment of CML emphasised this, the draft guidance FAD for 2nd line CML for high-dose imatinib, dasatinib and nilotinib, is available on the NICE website at http://guidance.nice.org.uk/TA/WaveR/99).

8.5.5.2. Blast crisis

The quarterly care costs for patients in the blast crisis phase were assumed to be the same as in the accelerated phase, but with the addition at death of an inpatient palliative care stay (£425) plus two non-medical specialist palliative care home visits (£72 each).

8.6. PenTAG cost-effectiveness results

We first present and discuss the base case results for the different scenarios, and then the results of the sensitivity analyses. For the base case analyses we first present the results based on Scenario 1, the full results of the Cumulative Survival method without 2nd-line nilotinib. Next we present the results of Scenario 2, which is the same as Scenario 1, but using the Simplified Method (which equalises post-TKI costs and outcomes). Next, we present the results of Scenario 3, which is the same as Scenario 1, but allowing 2nd-line nilotinib, and finally, Scenario 4, the same as Scenario 2, but allowing for 2nd-line nilotinib (as presented in Table 33, p. 136).

The results for the scenarios which based Surrogate Survival methods (1a and 1b for MMR-based, and 2a and 2b for CCyR-based) are presented in Section 8.6.6.7, p. 215.

Note that we have chosen not to conduct and present probabilistic sensitivity analyses because of the unusually large amount of structural uncertainty that is inherent in the present decision problem(s). This structural uncertainty relates to both the variety of ways in which long-term survival might be estimated, and uncertainty surrounding the possible sequences and mixes of treatments post 1st line TKI failure. As a result, we believe that structural uncertainty would dominate total (structural and parameter) uncertainty, and therefore that if we presented PSAs based just on parameter uncertainty, this would be of little use to the committee. Furthermore, it might actually mislead users of our report who do not appreciate the substantial structural uncertainty.

Theoretically, it would have been possible to incorporate some of the structural uncertainty in to a PSA by some kind of model averaging. For example, we present scenario analyses with and without 2nd-line nilotinib. To incorporate the uncertainty in whether we assume use of 2nd-line nilotinib, we could have assigned a probability to the use of 2nd-line nilotinib, and present just one analysis. However, we believe that it would be more helpful to the committee to present the two analyses separately, thus allowing the committee to decide for themselves which scenario they prefer, i.e. allowing them to use their expert judgement to estimate the probability of 2nd-line nilotinib use for themselves.

8.6.1. Summary of cost-effectiveness results

Table 51 below shows the cost-effectiveness results for scenarios 1 to 4, conventionally with comparators in order of increasing effectiveness, and the ICERs representing the incremental costs and QALYs gained by moving to the next most effective non-dominated. In the more detailed results tables in the rest of the chapter the incremental cost-effectiveness ratios are calculated relative to the current best clinical practice in the NHS (imatinib as 1st line), and then between nilotinib and dasatinib.

The variation in cost-effectiveness results across the four scenarios is considerable, with the ICERs for nilotinib compared with imatinib being either above (Scenario 1) or below (Scenario 2) the £30,000 cost-effectiveness threshold, or - in Scenarios 3 and 4 - generating slightly fewer lifetime QALYs than imatinib followed by nilotinib, but yielding significant cost-savings. However, in all Scenarios dasatinib is shown to be either dominated (by nilotinib) or have an ICER relative to imatinib of over £300,000 per QALY gained. These widely different cost-effectiveness results again reinforce the significance of structural

uncertainty in the modelling of CML including the substantial impact of assumptions regarding 2nd and 3rd line treatment sequences following 1st line TKI failure.

The interpretation of the ICERs for Scenarios 3 and 4 is unusual, because having nilotinib as 2nd line treatment after imatinib or dasatinib – but of course not after nilotinib failure – results in the nilotinib comparator being both less effective and more costly, over patients' lifetimes, than the current best practice treatment, imatinib. Depending on which modelling assumptions are used, this means that adopting nilotinib as first line treatment yields considerable cost savings for relatively modest QALY losses per patient (either £213,000 or £50,000 of savings yielded per QALY lost, in Scenario analyses 3 and 4). This is discussed further in the following sections and in the Discussion.

Table 51 Summary of cost-effectiveness results for Scenario analyses 1 to 4

	Discounted cost (£)	Undiscounted Life-years	Discounted QALYs	Incremental cost (£)	Incremental QALYs	ICER (£ per QALY)
Scenario 1: Cumulative Survival without 2nd line Nilotinib						
Imatinib - then HU/SCT	186,827	16.5	9.0			
Nilotinib - then HU/SCT	201,808	17.4	9.4	14,981	0.4	36,000
Dasatinib - then HU/SCT dominated	253,172	16.8	9.2	51,363	-0.3	Dasatinib dominated by nilotinib
Scenario 2: Cumulative Survival without 2nd line Nilotinib						
Imatinib - then HU/SCT	186,627		9.0			
Nilotinib - then HU/SCT	204,222		9.7	17,395	0.7	26,000
Dasatinib - then HU/SCT dominated	254,166		9.3	67,338	-0.4	N/A
Scenario 3: Cumulative Survival with 2nd line Nilotinib						
Nilotinib - then HU/SCT	201,808	17.4	9.4			
Imatinib - then Nilotinib	222,398	17.3	9.5	20,590	0.1	213,000[a]
Dasatinib - then Nilotinib	287,487	17.6	9.7	65,089	0.1	460,000
Scenario 4: Cumulative Survival with 2nd line Nilotinib						
Nilotinib - then HU/SCT	198,517		9.1			
Imatinib - then Nilotinib	222,398		9.5	23,881	0.5	50,000[a]

Dasatinib - then Nilotinib	288,241		9.7	65,834	0.2	307,000

[a] Given that Imatinib as 1st line treatment is current best clinical practice, these ICER estimates can be seen as representing the amount of *cost savings yielded* per QALY *lost* by having nilotinib first line rather than imatinib.

8.6.2. Results Scenario 1: Cumulative Survival method without 2nd-line nilotinib

Table 52 presents the cost-effectiveness results for Scenario 1.

Table 52 Cost-effectiveness results for Scenario 1

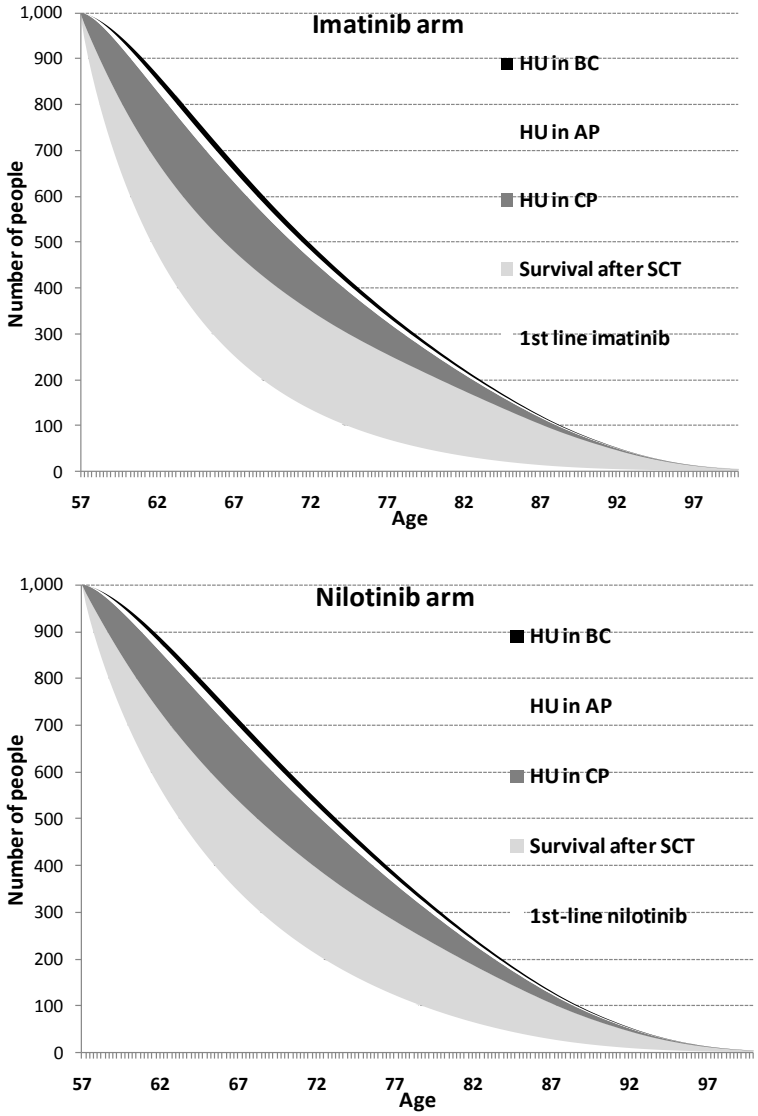
	Imatinib	Nilotinib	Dasatinib	Nilotinib-Imatinib	Dasatinib-Imatinib	Nilotinib-Dasatinib
Life years (undiscounted)						
1st-line TKI	7.0	8.9	7.7	1.9	0.7	1.2
2nd-line nilotinib	-	-	-	-	-	-
SCT	5.8	4.9	5.5	-0.9	-0.4	-0.6
HU CP	2.9	2.8	2.9	-0.1	-0.0	-0.1
HU AP	0.5	0.4	0.5	-0.0	-0.0	-0.0
HU BC	0.3	0.3	0.3	-0.0	-0.0	-0.0
Overall survival (mean)	**16.5**	**17.4**	**16.8**	**0.9**	**0.3**	**0.6**
Overall survival (median)	15.0	16.3	15.4	1.3	0.4	0.9
Mean age start						
1st-line TKI	57	57	57	0.0	0.0	0.0
2nd-line nilotinib	-	-	-	-	-	-
SCT	64	66	65	1.9	0.7	1.2
HU CP	64	66	65	1.9	0.7	1.2
HU AP	69	71	70	1.8	0.7	1.1
HU BC	70	72	71	1.8	0.7	1.1
Cohort split ¶						
% starting 2nd-line nilotinib	0%	n/a	0%	n/a	0%	n/a
% starting SCT/HU	90%	84%	88%	-6%	-2%	-4%
% SCT (whole cohort)	33%	28%	32%	-5%	-2%	-3%
% SCT (eligible cohort)	37%	34%	36%	-3%	-1%	-2%
% HU (whole cohort)	56%	56%	56%	-1%	0%	-1%
% HU (eligible cohort)	63%	66%	64%	3%	1%	2%

	Imatinib	Nilotinib	Dasatinib	Nilotinib-Imatinib	Dasatinib-Imatinib	Nilotinib-Dasatinib
% AP (whole cohort)	49%	48%	49%	-2%	0%	-1%
% BC (whole cohort)	49%	48%	49%	-2%	0%	-1%
Life years (undisc. eligible cohort¶)						
1st-line TKI	7.0	8.9	7.7	1.9	0.7	1.2
2nd-line nilotinib	-	-	-	-	-	-
SCT	17.4	17.2	17.3	-0.2	-0.1	-0.1
HU CP	5.1	5.0	5.1	-0.1	-0.0	-0.1
HU AP	0.9	0.9	0.9	-0.0	-0.0	-0.0
HU BC	0.6	0.6	0.6	-0.0	-0.0	-0.0
QALYs (discounted)						
1st-line TKI	4.5	5.5	4.9	1.0	0.4	0.6
2nd-line nilotinib	-	-	-	-	-	-
SCT	2.6	2.2	2.4	-0.4	-0.2	-0.3
HU CP	1.5	1.4	1.5	-0.1	-0.0	-0.1
HU AP	0.2	0.2	0.2	-0.0	-0.0	-0.0
HU BC	0.1	0.1	0.1	-0.0	-0.0	-0.0
Total	**9.0**	**9.4**	**9.2**	**0.4**	**0.2**	**0.3**
Costs (discounted)						
1st-line TKI	£118,635	£133,386	£184,774	£14,751	£66,139	-£51,388
1st-line AEs	£166	£119	£282	-£47	£116	-£163
1st-line medical management	£25,115	£30,693	£27,199	£5,578	£2,084	£3,494
2nd-line nilotinib	-	-	-	-	-	-
2nd-line nilotinib AEs	-	-	-	-	-	-
2nd-line nilotinib med man	-	-	-	-	-	-
SCT transplant	£24,486	£20,646	£23,005	-£3,840	-£1,482	-£2,359
SCT medical management	£2,562	£2,148	£2,401	-£415	-£161	-£254
HU acquisition in CP	£282	£264	£276	-£19	-£6	-£12
HU CP medical management	£8,747	£8,171	£8,553	-£577	-£194	-£383
HU AP acq + med management	£4,098	£3,828	£4,007	-£270	-£91	-£179
HU BC acq + med management	£2,735	£2,555	£2,675	-£180	-£61	-£120
Total	**£186,827**	**£201,808**	**£253,172**	**£14,981**	**£66,345**	**-£51,363**
Cost / LYG				£17,000	£210,000	-£92,000
Cost / QALY				**£36,000**	**£425,000**	**-£195,000**

¶ The "eligible" cohort consists of those people who are alive and eligible to receive the relevant treatment, as opposed to the "whole cohort", being all patients starting 1st-line treatment.

8.6.2.1. Scenario 1: survival results

The relative proportions of patients in each health state for each treatment over time are displayed in Figure 33 below. The mean duration in each health state for each treatment (as reported in Table 52 above) is represented in these graphs by the area under each curve. For example, mean survival after SCT is represented by the light shaded area. Virtually all patients are predicted to have died by age 97, 20 years from start of 1st-line treatment.



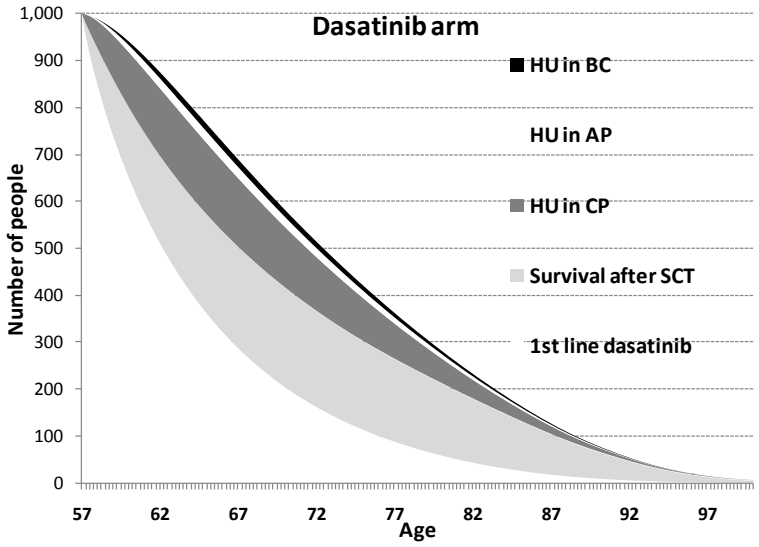


Figure 32 Scenario 1 cohort composition over time by treatment arm

As previously explained (Figure 28, p. 163) we predict that the mean duration of 1st-line treatment is least for people on imatinib (7.0 years), greater for dasatinib (7.7 years), and greatest for nilotinib (8.9 years) (Table 52 Figure 33).

We predict similar mean survival times after SCT for all treatment arms, but with shortest duration in the nilotinib arm (4.9 years), longer in the dasatinib arm (5.5 years) and longest in the imatinib arm (5.8 years) (Table 52). This order is explained by three factors. First, fewest people reach 2nd-line treatment in the nilotinib arm (84%), and most reach 2nd-line treatment in the imatinib arm (90%) (Table 52), because this reflects the relative duration of 1st-line treatment, and the longer people spend on 1st-line treatment, the greater the mortality. Also, the lower the proportion reaching 2nd-line treatment, the lower the mean survival time after SCT averaged over all patients starting 1st-line treatment. Second, we assume that the proportion of patients receiving SCT declines with increasing age (Section 8.2.4, p. 166). Given that people are generally slightly older when they have a SCT in the nilotinib arm (66 years old), compared to the imatinib arm (64 years old), this also reduces the proportion of patients having SCT in the nilotinib arm, relative to the other treatment arms. Combined we predict that only 28% of patients in the nilotinib arm receive a SCT, with similar proportions in the imatinib and dasatinib arms (32% and 33%). Third, the mean survival after a SCT, for those patients who receive a SCT (the "eligible" cohort in Table 52), is marginally lower in the nilotinib arm (17.2 years), than the imatinib arm (17.4 years). This is due to the fact that

people typically receive a SCT slightly older in the nilotinib arm, as explained above, and therefore general mortality is greatest in the nilotinib arm.

The mean time on HU in CP, averaged over all patients initially starting 1st-line treatment is almost the same across treatment arms: 2.8 years for nilotinib and 2.9 years for imatinib and dasatinib. There are two treatment-dependent factors that operate in different directions here. First, of those patients who reach 2nd-line treatment, the highest proportion received HU in the nilotinib arm (66%, the "eligible patients" in Table 52), and the lowest proportion received HU in the imatinib arm (63%). The explanation is similar to that given in the previous paragraph for the proportion of eligible patients who receive SCT. In this case, a large proportion receive HU in the nilotinib arm because patients are typically slightly older when they start 2nd-line treatment, and the proportion of eligible patients who receive HU increases with age (as the proportion who receive SCT decreases with age). Second, as stated in the previous paragraph, the proportion of patients who receive 2nd-line treatment is least in the nilotinib arm. Together, these factors cancel out, resulting in the same proportion of all patients who start 1st-line treatment taking HU in CP, 56% in all treatment arms (Table 52).

The mean time on HU in AP, averaged over all patients initially starting 1st-line treatment is almost the same across treatment arms: 0.4 years for nilotinib and 0.5 years for imatinib and dasatinib. Similarly, the proportion of all patients randomised to 1st-line treatment who receive HU in AP is almost the same across treatment arms, at 48-49%. Again, this is explained by two competing treatment-dependent influences that cancel out. First, we might expect that the proportion of all patients who receive HU in AP to be least for the nilotinib arm because the proportion of patients who reach 2nd-line treatment is least in this arm (84% nilotinib arm vs. 90% imatinib arm). Conversely, the greatest proportion of those patients who receive 2nd-line treatment who receive HU do so in the nilotinib arm (66% nilotinib arm vs. 63% imatinib arm), and it is necessary to pass through the HU in CP state in order to reach the HU in AP state.

Finally, mean time on HU in BC, averaged over all patients initially starting 1st-line treatment is the same across treatment arms, at 0.3 years. This is explained as in the previous paragraph for the mean time on HU in AP, and the fact that we assume no mortality on HU in AP, given such a short time in AP.

Notice that the mean undiscounted life years for those patients who receive the relevant treatment, the eligible cohorts in Table 52, are very nearly independent of treatment arm. Any slight differences between arms is due to the slight differences in general mortality due to the slight differences in mean ages at the start of each treatment. Also notice that the life expectancy of those patients who take SCT, at about 17 years, is far higher than for those patients who take HU in AP, at approximately 6.5 years (the sum of the mean times on HU in CP, AP and BC). We predict a long life expectancy after SCT because we assume that 75% of patients who have a SCT subsequently experience the same mortality as the general population of England & Wales.

Overall survival from time of starting 1st-line treatment, which reflects the sum of the times on the component lines of treatments, is similar across treatment arms, but greatest in the nilotinib arm (17.4 years) and least in the imatinib arm (16.5 years). The difference in overall survival between the nilotinib and imatinib arms, at 0.9 years, is less than the difference in the time on 1st-line nilotinib and 1st-line imatinib, at 1.9 years. This is because a lower proportion of patients received SCT in the nilotinib arm (28%) compared to the imatinib arm (33%), and life expectancy after SCT is high, at about 17 years.

We now turn to the estimated QALYs in Table 52. First notice that the relative differences in discounted QALYs between treatment arms is consistent with the relative differences in undiscounted life years. For example, both life years and QALYs are 5% higher in the nilotinib arm than in the imatinib arm. Next, the ratio of discounted QALYs to undiscounted life years is approximately 55% in all arms. This is accounted for by the rather substantial discounting, given high life expectancies of approximately 17 years, and by the application of utility values which are typically approximately 0.80, averaged over the entire cohort, over all time.

8.6.2.2. Scenario 1: cost results

We now turn to the expected costs per person. The expected costs of 1st-line drug acquisition are by far the largest single cost item (Table 52) and account for the largest incremental costs vs. the imatinib arm (Figure 33). Notice further, that the mean acquisition costs of imatinib and nilotinib are fairly similar (£119,000 and £133,000 respectively), whereas the cost of dasatinib is far higher, at about £185,000. The expected drug acquisition costs are calculated as the product of the mean drug acquisition cost per person per unit time and the discounted

mean duration of drug treatment.

[redacted]

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The expected costs of medical management during 1st-line treatment and the expected cost of the SCT operation are the next largest single cost items (Table 52). The expected medical management costs during 1st-line treatment are greatest in the nilotinib arm and least in the imatinib arm reflecting the order of duration of 1st-line treatments.

The expected cost of a SCT, averaged over all patients, at about £21,000 is least for nilotinib and greatest for imatinib because the proportion of all patients who have a SCT is least for the nilotinib arm (28%) and greatest for the imatinib arm (33%).

All other costs contribute only marginally to the incremental costs. The per patient medical management costs after SCT are least in the nilotinib arm, also because the proportion of all patients who have a SCT is least for the nilotinib arm (28%). Although the absolute per patient costs of medical management whilst taking HU in CP are rather large, the incremental costs vs. imatinib are small because we predict similar mean per patient duration of HU in CP, at about 2.9 years. The incremental costs of HU acquisition and medical management in AP and BC are very small for the same reason. The costs of AEs whilst on 1st-line treatment and the cost of HU acquisition in CP are both extremely small.

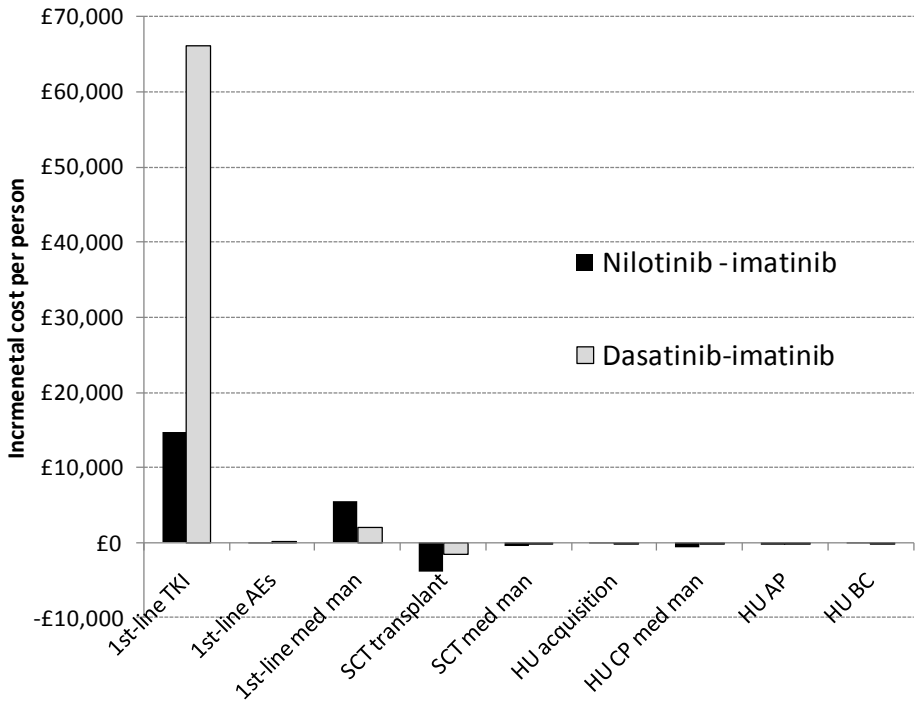


Figure 33 Scenario 1 incremental costs vs. imatinib treatment arm

8.6.2.3. Scenario 1: cost-effectiveness results

Combining all the information on expected costs and QALYs per person, we estimate the following cost-effectiveness results (Table 52, Figure 34);

- nilotinib vs. imatinib ICER of £36,000 per QALY
- dasatinib vs. imatinib ICER of £425,000 per QALY
- nilotinib dominates dasatinib.

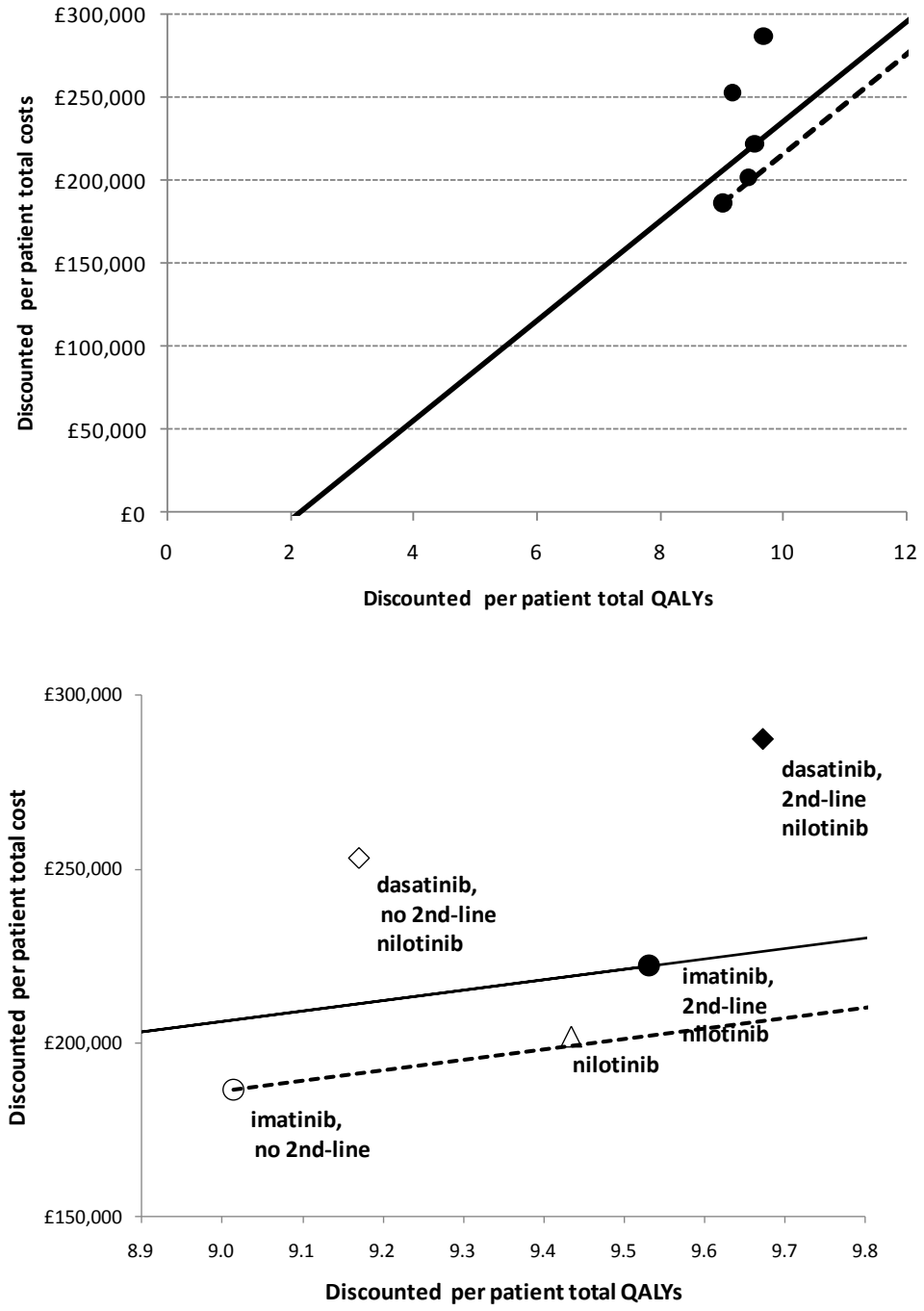


Figure 34 Cost-effectiveness results for Scenarios 1 and 3, (wide axes top and narrow x-axes bottom)

Figure 34 displays the results from both Scenarios 1 and 3 on the same cost-effectiveness plane. Filled symbols represent treatment arms which include 2nd-line treatment with nilotinib, and empty symbols represent treatment arms without 2nd-line nilotinib. The top graph shows that the difference in QALYs between the arms is rather small, but the difference in total costs per person is large. In both graphs, the continuous line represents a

willingness to pay of £30,000 per QALY compared to treatment with imatinib followed by nilotinib, and the dotted line represents a willingness to pay of £30,000 per QALY compared to treatment with imatinib without 2nd-line nilotinib. Scenario 1 concerns the empty symbols only, and Scenario 3 concerns the filled symbols plus the treatment arm with nilotinib first line.

For Scenario 1, the symbol for nilotinib lies just above the £30,000 willingness to pay line based on imatinib 1st-line with no nilotinib 2nd-line, which reflects the fact that the ICER of nilotinib vs. imatinib is £36,000 per QALY, only slightly above £30,000 per QALY.

For Scenario 1, the symbol for dasatinib without 2nd-line nilotinib lies well above the willingness to pay line, which reflects the very high ICER of dasatinib vs. imatinib of £425,000 per QALY.

We discuss the results from Scenario 3 in Section 8.6.4, p. 199 below.

8.6.3. Results Scenario 2: Cumulative Survival, Simplified method, without 2nd-line nilotinib

In the Simplified Method, the post-TKI (1st-line TKIs) per-patient costs and QALYs are set equal across treatment arms. The costs and QALYs whilst patients are on TKIs are modelled specific to each treatment arm, i.e. exactly as normal (Section 8.1.4, p. 141). The method substantially reduces the impact of the nature, costs and utilities associated with treatments post 1st-TKIs. We believe this is useful given that these treatments will typically be taken many years in the future and given the substantial uncertainty in the nature and costs of such treatments. Table 53 presents the cost-effectiveness results for Scenario 2.

Table 53 Cost-effectiveness results for Scenario 2

	Imatinib	Nilotinib	Dasatinib	Nilotinib-Imatinib	Dasatinib-Imatinib	Nilotinib-Dasatinib
QALYs (discounted)						
1st-line TKI	4.5	5.5	4.9	1.0	0.4	0.6
2nd-line nilotinib	-	-	-	-	-	-
SCT	2.6	2.4	2.5	-0.2	-0.1	-0.1
HU CP	1.5	1.4	1.5	-0.1	-0.0	-0.1
HU AP	0.2	0.2	0.2	-0.0	-0.0	-0.0
HU BC	0.1	0.1	0.1	-0.0	-0.0	-0.0
Total	**9.0**	**9.7**	**9.3**	**0.7**	**0.3**	**0.4**
Costs (discounted)						
1st-line TKI	£118,635	£133,386	£184,774	£14,751	£66,139	-£51,388
1st-line AEs	£166	£119	£282	-£47	£116	-£163
1st-line medical management	£25,115	£30,693	£27,199	£5,578	£2,084	£3,494
2nd-line nilotinib	-	-	-	-	-	-
2nd-line nilotinib AEs	-	-	-	-	-	-
2nd-line nilotinib med man	-	-	-	-	-	-
SCT transplant	£24,486	£22,935	£23,954	-£1,551	-£532	-£1,019
SCT medical management	£2,562	£2,400	£2,507	-£162	-£56	-£107
HU acquisition in CP	£282	£259	£274	-£23	-£8	-£15
HU CP medical management	£8,747	£8,030	£8,492	-£717	-£256	-£462
HU AP acq + med management	£4,098	£3,838	£4,009	-£260	-£89	-£171
HU BC acq + med management	£2,735	£2,562	£2,676	-£173	-£59	-£114
Total	**£186,827**	**£204,222**	**£254,166**	**£17,395**	**£67,338**	**-£49,943**
Cost / QALY				**£26,000**	**£262,000**	**-£123,000**

The proportions still alive and starting 2nd- or 3rd-line treatment on HU or SCT are similar across the three treatment arms (from 84% for nilotinib to 90% for imatinib), since the durations of TKI treatments are similar across treatments. Therefore, this method largely nets off all post-TKI costs and QALYs between treatment arms. For example, the incremental QALYs associated with time after SCT is -0.2 for nilotinib – imatinib, which is smaller than the corresponding figure of -0.4 from Scenario 1, and the incremental per person cost of SCT operations is -£1,551 for nilotinib – imatinib (Figure 35 below), compared to -£3,840 in Scenario 1 (Table 52, p186).

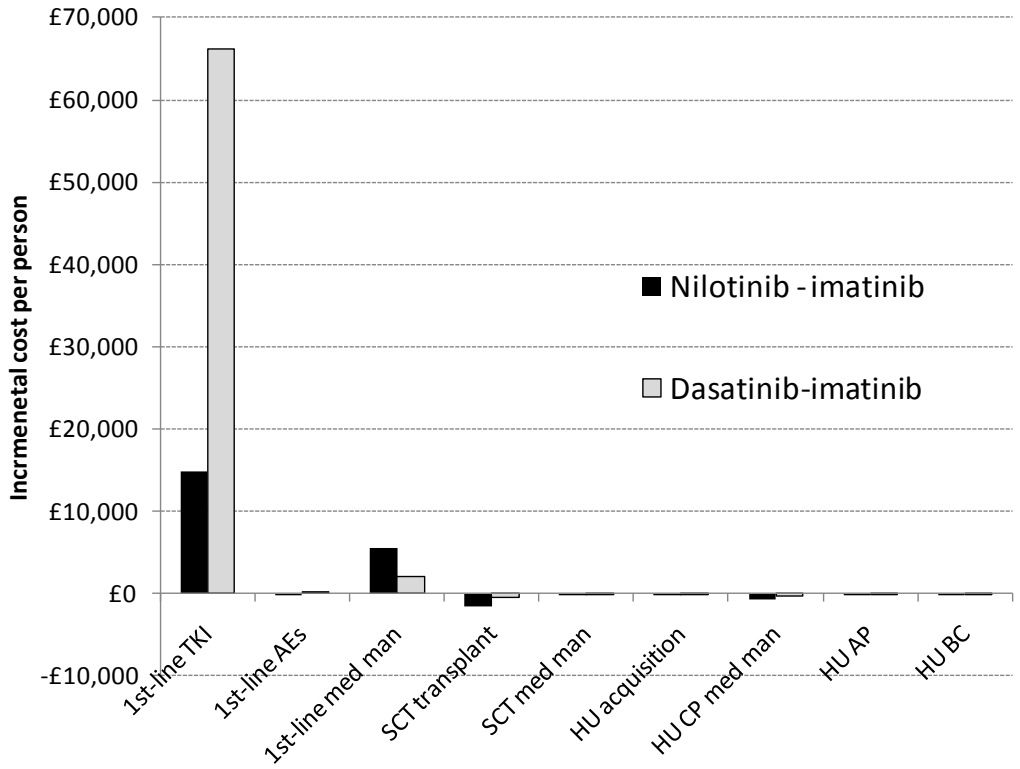


Figure 35 Scenario 2 incremental costs vs. imatinib treatment arm

Combining all the information on expected costs and QALYs per person, we estimate the following cost-effectiveness results (Table 53, Figure 36);

- nilotinib vs. imatinib ICER of £26,000 per QALY
- dasatinib vs. imatinib ICER of £262,000 per QALY
- nilotinib dominates dasatinib (dasatinib costs more and confers less benefits).

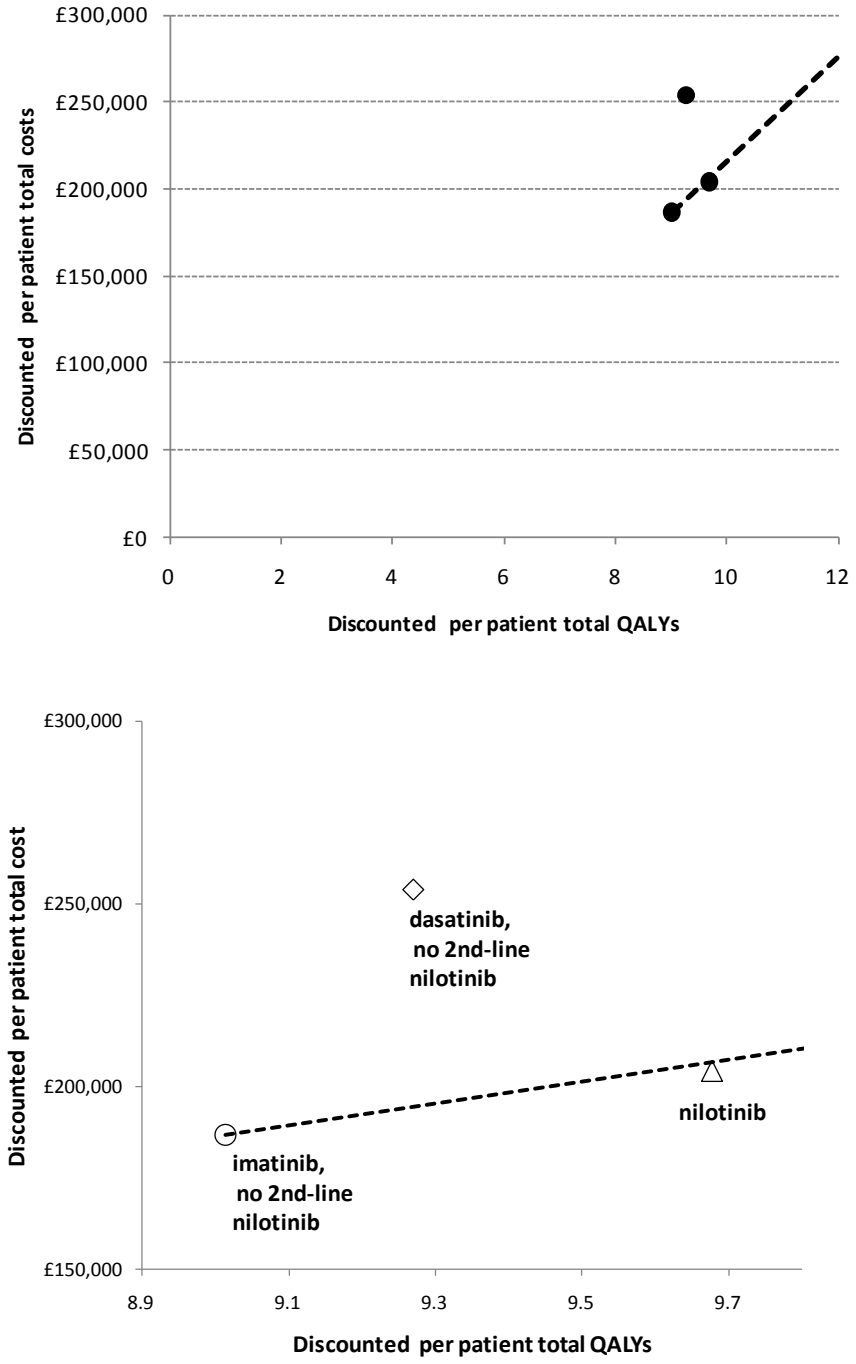


Figure 36 Cost-effectiveness results for Scenario 2 (wide axes top and narrow axes bottom)

As in Figure 34, the dotted line in Figure 36 represents a willingness to pay of £30,000 per QALY compared to treatment with imatinib.

The ICER for nilotinib vs. imatinib falls from £36,000 per QALY under Scenario 1 to £26,000 per QALY under the Simplified Method. This is a result of increasing the

importance of the costs and QALYs associated with TKI treatment relative to the costs and QALYs of treatments after TKI failure.

8.6.4. Results Scenario 3: Cumulative Survival method with 2nd-line nilotinib

Table 54 presents the cost-effectiveness results for Scenario 3.

Table 54 Cost-effectiveness results for Scenario 3

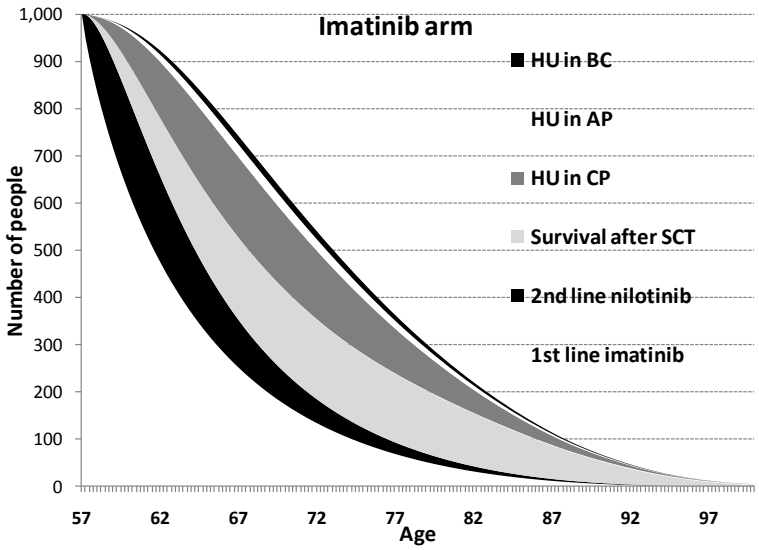
	Imatinib	Nilotinib	Dasatinib	Nilotinib-Imatinib	Dasatinib-Imatinib	Nilotinib-Dasatinib
Life years (undiscounted)						
1st-line TKI	7.0	8.9	7.7	1.9	0.7	1.2
2nd-line nilotinib	2.2	-	2.2	-2.2	-0.1	-2.2
SCT	4.2	4.9	3.9	0.7	-0.3	1.0
HU CP	3.0	2.8	3.0	-0.3	-0.0	-0.2
HU AP	0.5	0.4	0.5	-0.0	-0.0	-0.0
HU BC	0.3	0.3	0.3	-0.0	-0.0	-0.0
Overall survival (mean)	**17.3**	**17.4**	**17.6**	**0.1**	**0.3**	**-0.2**
Overall survival (median)	16.0	16.2	16.5	0.2	0.5	-0.3
Mean age start						
1st-line TKI	57	57	57	0.0	0.0	0.0
2nd-line nilotinib	64	66	65	1.9	0.7	1.2
SCT	66	66	67	-0.3	0.6	-0.9
HU CP	66	66	67	-0.3	0.6	-0.9
HU AP	71	71	72	-0.3	0.6	-0.9
HU BC	72	72	73	-0.3	0.6	-0.9
Cohort split ¶						
% starting 2nd-line nilotinib	90%	-	88%	-	-2%	-
% starting SCT/HU	86%	84%	84%	-2%	-2%	0%
% SCT (whole cohort)	26%	28%	24%	3%	-2%	4%
% SCT (eligible cohort)	30%	34%	29%	4%	-1%	5%
% HU (whole cohort)	61%	56%	60%	-5%	-1%	-5%
% HU (eligible cohort)	70%	66%	71%	-4%	1%	-5%
% AP (whole cohort)	52%	48%	51%	-4%	-1%	-3%
% BC (whole cohort)	52%	48%	51%	-4%	-1%	-3%
Life years (undisc eligible cohort) ¶						
1st-line TKI	7.0	8.9	7.7	1.9	0.7	1.2
2nd-line nilotinib	2.5	-	2.5	-2.5	-0.0	-2.5
SCT	16.4	17.2	16.3	0.8	-0.1	0.9
HU CP	5.0	5.0	5.0	0.0	-0.0	0.0
HU AP	0.9	0.9	0.9	-0.0	-0.0	-0.0
HU BC	0.6	0.6	0.6	-0.0	-0.0	-0.0

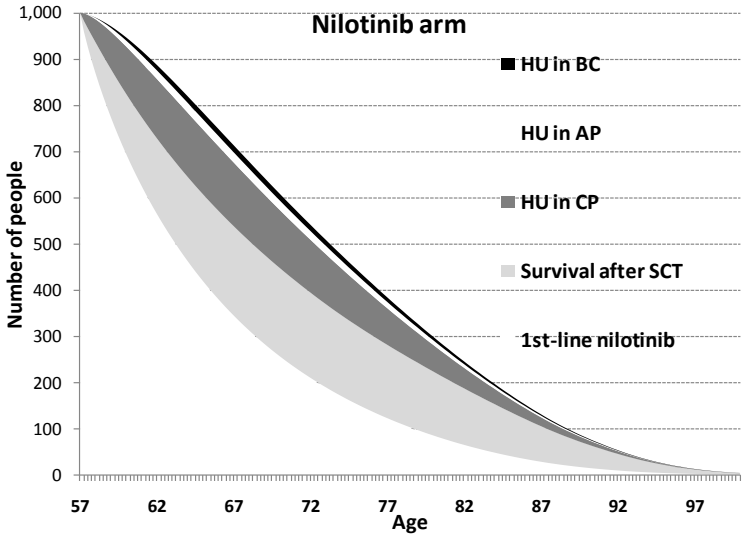
	Imatinib	Nilotinib	Dasatinib	Nilotinib-Imatinib	Dasatinib-Imatinib	Nilotinib-Dasatinib
QALYs (discounted)						
1st-line TKI	4.5	5.5	4.9	1.0	0.4	0.6
2nd-line nilotinib	1.4	-	1.3	-1.4	-0.1	-1.3
SCT	1.8	2.2	1.7	0.4	-0.1	0.5
HU CP	1.5	1.4	1.5	-0.1	-0.0	-0.0
HU AP	0.2	0.2	0.2	-0.0	-0.0	-0.0
HU BC	0.1	0.1	0.1	-0.0	-0.0	-0.0
Total	**9.5**	**9.4**	**9.7**	**-0.1**	**0.1**	**-0.2**
Costs (discounted)						
1st-line TKI	£118,635	£133,386	£184,774	£14,751	£66,139	-£51,388
1st-line AEs	£166	£119	£282	-£47	£116	-£163
1st-line medical management	£25,115	£30,693	£27,199	£5,578	£2,084	£3,494
2nd-line nilotinib	£35,393	£0	£34,096	-£35,393	-£1,297	-£34,096
2nd-line nilotinib AEs	£299	£0	£299	-£299	£0	-£299
2nd-line nilotinib med man	£7,568	£0	£7,291	-£7,568	-£277	-£7,291
SCT transplant	£17,724	£20,646	£16,601	£2,921	-£1,123	£4,044
SCT medical management	£1,784	£2,148	£1,667	£364	-£116	£480
HU acquisition in CP	£280	£264	£272	-£16	-£8	-£8
HU CP medical management	£8,665	£8,171	£8,425	-£495	-£241	-£254
HU AP acq + med man	£4,060	£3,828	£3,947	-£232	-£113	-£119
HU BC acq + med man	£2,710	£2,555	£2,634	-£155	-£75	-£79
Total	**£222,398**	**£201,808**	**£287,487**	**-£20,590**	**£65,089**	**-£85,678**
Cost / LYG				-£240,000	£205,000	£371,000
Cost / QALY				**£213,000§**	**£460,000**	**£360,000§**

¶ The "eligible" cohort consists of those people who are alive and eligible to receive the relevant treatment, as opposed to the "whole cohort", being all patients starting 1st-line treatment.
§ Nilotinib represents better value for money than comparator at willingness to pay thresholds of £20,000 and £30,000 per QALY

8.6.4.1. Scenario 3: survival results

The relative proportions of patients in each health state for each treatment over time are displayed in Figure 37 below. Virtually all patients are predicted to have died by age 97, 20 years from start of 1st-line treatment.





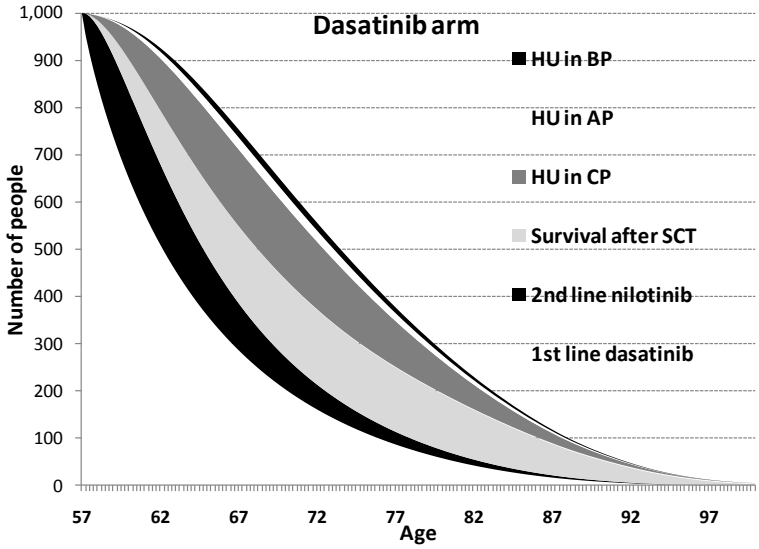


Figure 37 Scenario 3 cohort composition over time by treatment arm

By design, the mean durations of 1st-line TKI treatment are the same in this Scenario as in Scenarios 1 and 2.

In the imatinib and dasatinib treatment arms, for those patients who take 2nd-line nilotinib, we predict a mean time on 2nd-line nilotinib of 2.5 years, which reflects the findings from the single arm trial of 2nd-line nilotinib.[118] Clearly there is no 2nd-line nilotinib in the nilotinib arm.

The proportion of patients who have a SCT in both the imatinib and dasatinib arms is lower than in Scenario 1 because people are typically older when they reach this treatment option, because of the extra line of treatment with nilotinib, and because the proportion receiving a SCT declines with age. For example, in the imatinib arm, 26% of patients are predicted to receive a SCT after 2nd-line nilotinib, compared to 33% in Scenario 1 (no 2nd-line nilotinib). This explains why the expected survival time after SCT, averaged over the whole cohort, is lower in this Scenario compared to Scenario 1. For example, for the imatinib arm, the mean survival is 4.2 years in Scenario 3 vs. 5.8 years in Scenario 1.

The proportion of patients who receive HU in CP in the imatinib arm, at 61%, is higher than in Scenario 1, at 56%. This is also because the 2nd-line nilotinib delays the time when patients are eligible for SCT or HU, and because the proportion receiving a SCT declines with age, and therefore the proportion receiving HU increases with age. Similarly, in the dasatinib arm, the corresponding proportions receiving HU are 60% and 56%.

8.6.4.2. Scenario 3: cost results

The incremental per patient drug costs are given in Figure 38. First, by design, the incremental costs of acquisition of 1st-line TKIs, of treatment for 1st-line AEs and of medical management whilst on 1st-line TKI are exactly as in Scenario 1 (Figure 33, p193). Next, there are substantial cost savings, approximately £35,000 per patient, in the nilotinib arm by having no cost for 2nd-line nilotinib acquisition, and having no cost of medical management whilst on 2nd-line nilotinib (approximately £7,500 per patient). Notice that the mean acquisition cost of 2nd-line nilotinib, at approximately £35,000 per patient is substantially lower than the mean acquisition cost of 1st-line nilotinib, at approximately £133,000 per patient. This is because we assume that nilotinib is taken for far less time as a 2nd-line treatment (typically 2.5 years), than as a 1st-line treatment (typically 8.9 years).

The incremental per patient cost of a SCT for nilotinib vs. imatinib, is higher in Scenario 3 than in Scenario 1. This is because, as explained in the previous section, the proportion of patients who receive a SCT falls when we allow for 2nd-line nilotinib, because people are typically older when they receive a SCT, and because nilotinib is taken 2nd-line only in the imatinib and dasatinib arms. All other incremental costs are similar to those in Scenario 1.

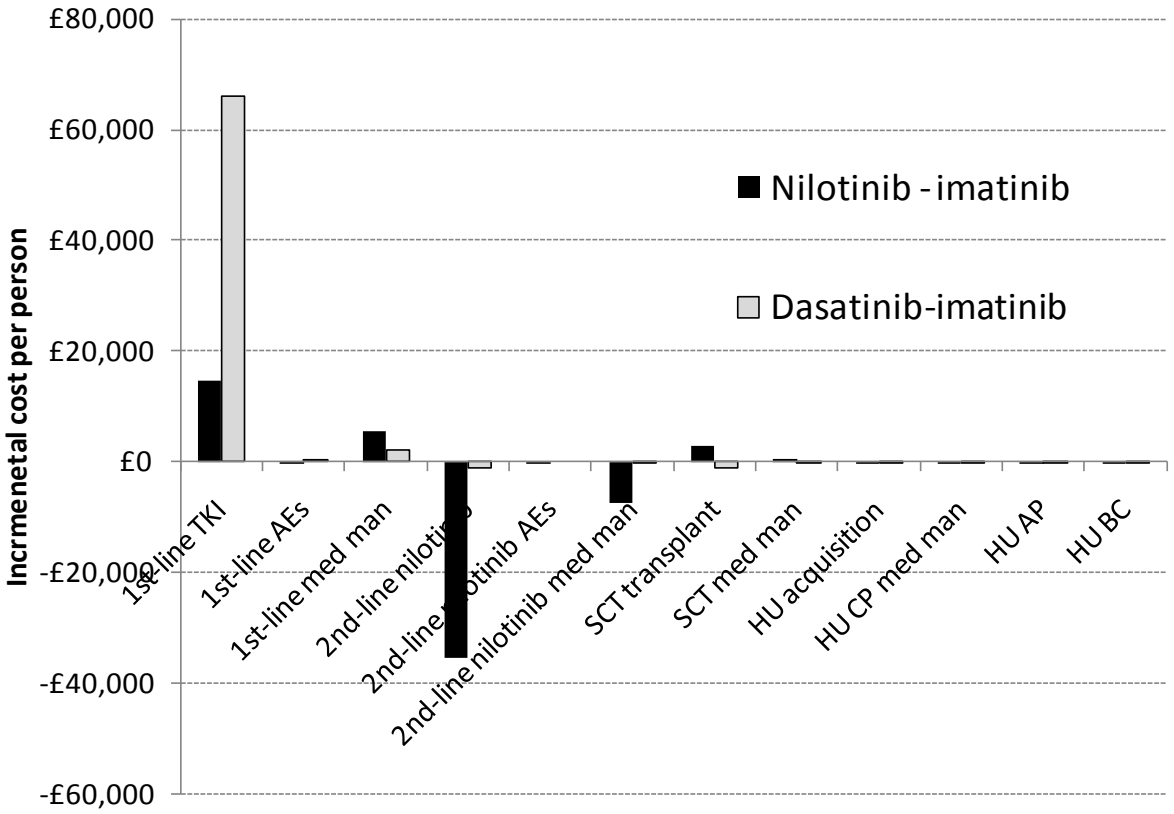


Figure 38 Incremental costs vs. imatinib treatment arm

8.6.4.3. Scenario 3: cost-effectiveness results

Combining all the information on expected costs and QALYs per person, we estimate the following cost-effectiveness results (Table 54, Figure 34, p194);

- nilotinib vs. imatinib ICER of £213,000 per QALY, whereby the nilotinib arm provides slightly fewer QALYs (-0.1) at far less cost (-£21,000) than the imatinib arm. This implies that the nilotinib arm provides far better value for money than the imatinib arm at willingness to pay thresholds of £20,000 and £30,000 per QALY.

- dasatinib vs. imatinib ICER of £425,000 per QALY, whereby the dasatinib arm provides slightly more QALYs (0.1) at far more cost (£65,000) than the imatinib arm. This implies that the dasatinib arm provides far worse value for money than the imatinib arm at willingness to pay thresholds of £20,000 and £30,000 per QALY.

- nilotinib vs. dasatinib ICER of £360,000 per QALY, whereby the nilotinib arm provides slightly fewer QALYs (-0.2) at far less cost (-£86,000) than the dasatinib arm. This implies that the nilotinib arm provides far better value for money than the imatinib arm at willingness to pay thresholds of £20,000 and £30,000 per QALY.

These results are displayed graphically in Figure 34, along with the results from Scenario 1.

8.6.5. Results Scenario 4: Cumulative Survival, Simplified method, with 2nd-line nilotinib

To reiterate, in the Simplified Method, the post-TKI (1st-line TKIs and 2nd-line nilotinib) per-patient costs and QALYs are set equal across treatment arms. The costs and QALYs whilst patients are on TKIs are modelled specific to each treatment arm, i.e. exactly as in the previous Scenario 3. Table 55 presents the cost-effectiveness results for Scenario 4.

Table 55 Cost-effectiveness results for Scenario 4

	Imatinib	Nilotinib	Dasatinib	Nilotinib-Imatinib	Dasatinib-Imatinib	Nilotinib-Dasatinib
QALYs (discounted)						
1st-line TKI	4.5	5.5	4.9	1.0	0.4	0.6
2nd-line nilotinib	1.4	-	1.3	-1.4	-0.1	-1.3
SCT	1.8	1.8	1.8	-0.0	-0.0	-0.0
HU CP	1.5	1.5	1.5	-0.0	-0.0	0.0
HU AP	0.2	0.2	0.2	-0.0	-0.0	-0.0
HU BC	0.1	0.1	0.1	-0.0	-0.0	-0.0
Total	**9.5**	**9.1**	**9.7**	**-0.5**	**0.2**	**-0.7**
Costs (discounted)						
1st-line TKI	£118,635	£133,386	£184,774	£14,751	£66,139	-£51,388
1st-line AEs	£166	£119	£282	-£47	£116	-£163
1st-line medical management	£25,115	£30,693	£27,199	£5,578	£2,084	£3,494
2nd-line nilotinib	£35,393	£0	£34,096	-£35,393	-£1,297	-£34,096
2nd-line nilotinib AEs	£299	£0	£299	-£299	£0	-£299
2nd-line nilotinib med man	£7,568	£0	£7,291	-£7,568	-£277	-£7,291
SCT transplant	£17,724	£17,267	£17,293	-£458	-£432	-£26
SCT medical management	£1,784	£1,738	£1,740	-£46	-£43	-£3
HU acquisition in CP	£280	£273	£271	-£7	-£9	£2
HU CP medical management	£8,665	£8,448	£8,393	-£218	-£273	£55
HU AP acq + med man	£4,060	£3,955	£3,961	-£105	-£99	-£6
HU BC acq + med man	£2,710	£2,640	£2,643	-£70	-£66	-£4
Total	**£222,398**	**£198,517**	**£288,241**	**-£23,881**	**£65,843**	**-£89,724**
Cost / QALY				**£50,000§**	**£307,000**	**£130,000§**

§ Nilotinib represents better value for money than comparator at willingness to pay thresholds of £20,000 and £30,000 per QALY

As in Scenario 2, the proportions still alive and starting 2nd- or 3rd-line treatment on HU or SCT are similar across the three treatment arms (84% for nilotinib and dasatinib and 86% for imatinib), since the durations of 1st- and 2nd-line TKI treatments are similar across treatment arms. Therefore, as in Scenario 2, this method largely nets off all post-TKI costs and QALYs between treatment arms. For example, the incremental QALYs associated with time after SCT is 0.0 for nilotinib – imatinib, compared to the corresponding figure of 0.4 from Scenario 3, and the incremental per person cost of SCT operations is -£460 for nilotinib – imatinib (Figure 39 below), compared to £2,900 in Scenario 3 (Table 54, p199).

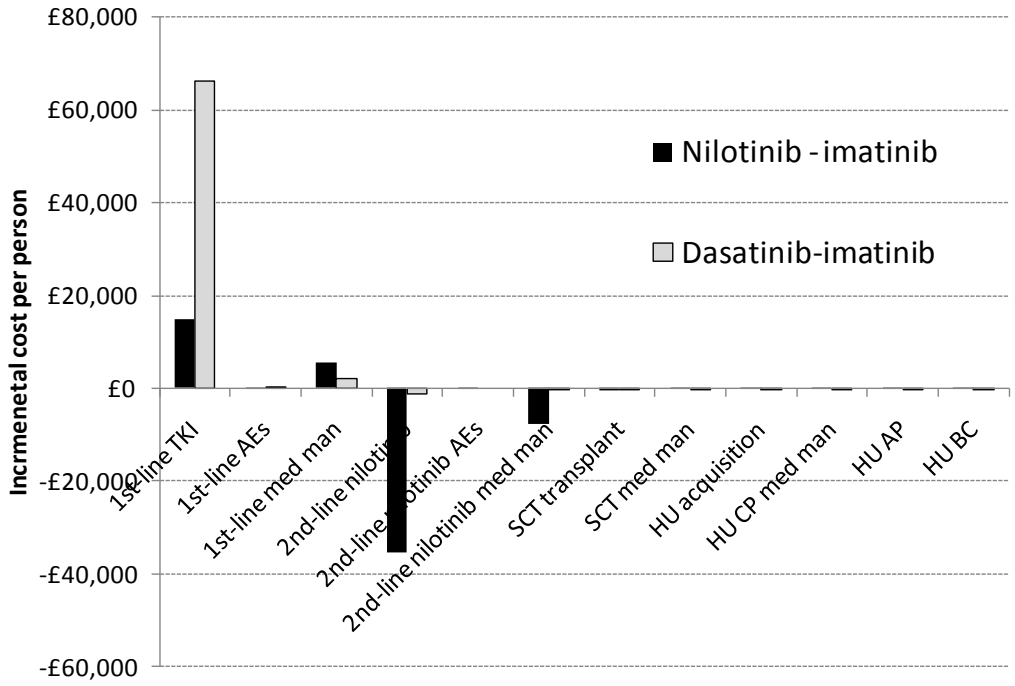


Figure 39 Scenario 4 incremental costs vs. imatinib treatment arm

Combining all the information on expected costs and QALYs per person, we estimate the following cost-effectiveness results (Table 53, Figure 40);

- nilotinib vs. imatinib ICER of £50,000 per QALY, whereby the nilotinib arm provides fewer QALYs (-0.5) at less cost (-£24,000) than the imatinib arm. As in Scenario 3, this implies that the nilotinib arm provides better value for money than the imatinib arm at willingness to pay thresholds of £20,000 and £30,000 per QALY.

- dasatinib vs. imatinib ICER of £307,000 per QALY, whereby the dasatinib arm provides slightly more QALYs (0.2) at far more cost (£66,000) than the imatinib arm. As in Scenario 3, this implies that the dasatinib arm provides far worse value for money than the imatinib arm at willingness to pay thresholds of £20,000 and £30,000 per QALY.

- nilotinib vs. dasatinib ICER of £130,000 per QALY, whereby the nilotinib arm provides fewer QALYs (-0.7) at far less cost (-£90,000) than the dasatinib arm. As in Scenario 3, this implies that the nilotinib arm provides far better value for money than the imatinib arm at willingness to pay thresholds of £20,000 and £30,000 per QALY.

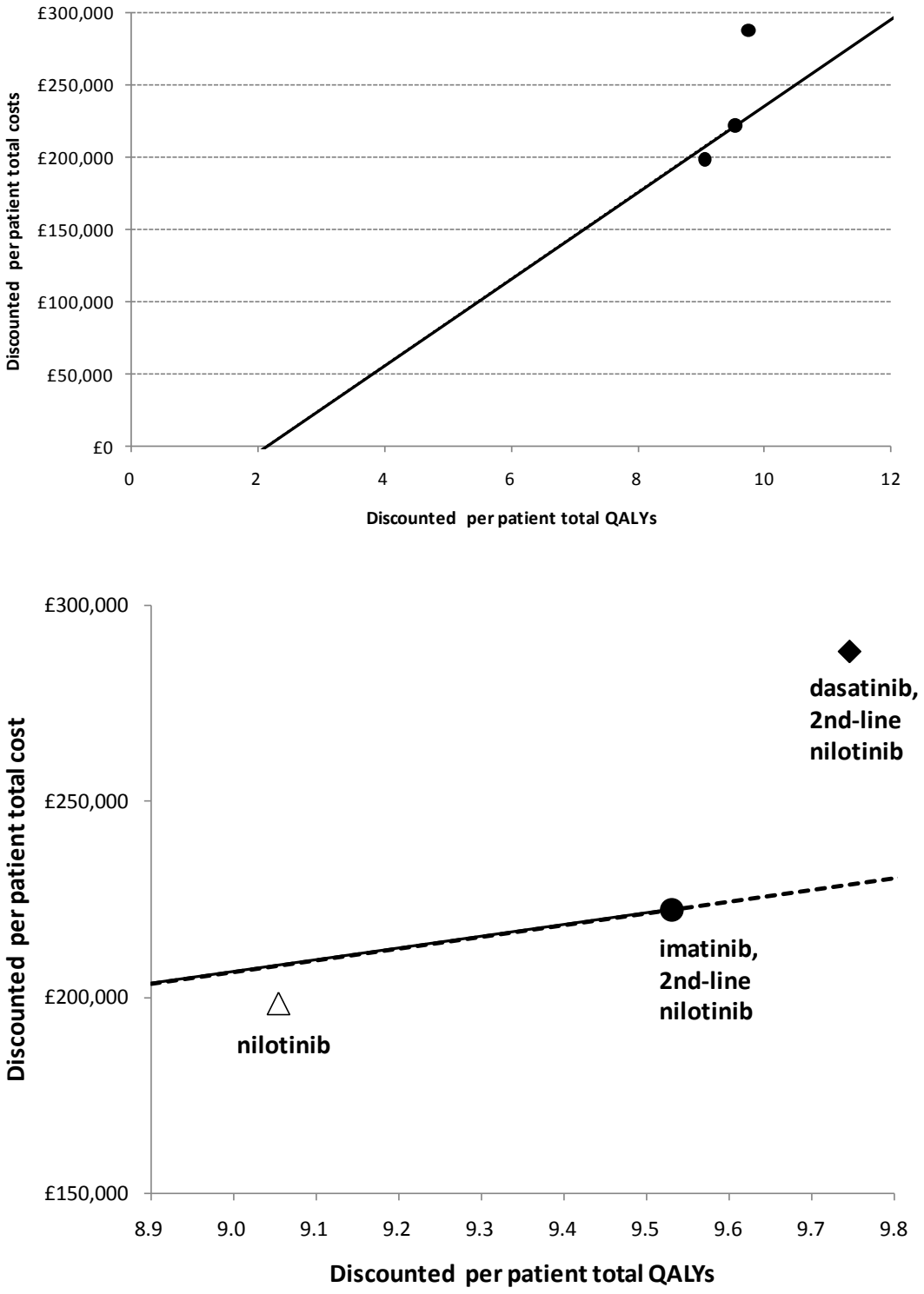


Figure 40 Cost-effectiveness results for Scenario 4 (wide axes top) and narrow axes bottom)

The dotted line in Figure 40 represents a willingness to pay of £30,000 per QALY compared to treatment with imatinib followed by 2nd-line nilotinib.

8.6.6. Deterministic sensitivity analyses

We now present the deterministic sensitivity analyses. Where relevant, the analyses are performed for each of the four modelling Scenarios.

Sensitivity analyses for nilotinib vs. imatinib are reported in Table 56 and for dasatinib vs. imatinib in Table 57 below.

The sensitivity analyses were chosen on the basis of either general interest (for example, assuming no discounting), plausibility (for example, modelling drug price falls on patent expiry), or using Novartis' assumptions.

ICERs are shaded black if the drug is less cost-effective than imatinib at a willingness to pay threshold of £30,000 per QALY. The shading is grey if the drug is more cost-effective than imatinib at a threshold of £30,000 per QALY, but less cost-effective than imatinib at £20,000 per QALY. There is no shading if the drug is more cost-effective than imatinib at a threshold of £20,000 per QALY.

For Scenarios 3 and 4 (imatinib is followed by 2nd-line nilotinib) in Table 56, in nearly all occasions, nilotinib is predicted to yield fewer QALYs and less cost than imatinib. Nilotinib then lies in the south-west quadrant of the cost-effectiveness plane relative to imatinib. In this case, the ICERs are denoted by the § symbol. ICERs above £30,000 per QALY imply that nilotinib is better value for money than imatinib at that threshold, contrary to the usual interpretation. When we assume that patients take 2nd-line nilotinib after imatinib, nilotinib almost always provides good value for money versus imatinib.

For Scenarios 1 and 2 (no 2nd-line nilotinib), nilotinib often lies close to the £30,000 per QALY willingness to pay threshold. However, nilotinib is always poor value for money at the £20,000 per QALY threshold, except when the dose intensity of imatinib is increased from [redacted] to 106%.

We focus our discussion of the results on the comparison of nilotinib vs. imatinib rather than on dasatinib vs. imatinib. This is because the cost-effectiveness of nilotinib is often close to the threshold, and because dasatinib is always very poor value for money vs. imatinib.

Table 56 Sensitivity analyses for nilotinib vs. imatinib

Parameter	Base case	Sensitivity analysis	Scenario 1 (No 2nd-line nilotinib)	Scenario 2 (No 2nd-line nilotinib, Simplified Method)	Scenario 3 (2nd-line nilotinib)	Scenario 4 (2nd-line nilotinib, Simplified Method)
Base case	N/A	N/A	**£36,000**	**£26,000**	**£213,000§**	**£50,000§**
General						
Discounting costs & benefits	3.5% p.a.	0% p.a.	£40,000	£30,000	Nilotinib dominates	£55,000§
Treatment pathways						
Proportion receiving SCT	Mean 28% nilotinib, 33% imatinib, decreases with age	31% at all ages (BMS assumption)	£32,000	£26,000	£92,000§	£52,000§
		75% if age < 65 (Novartis)	£43,000	£27,000	£290,000§	£49,000§
		Halve % at all ages	£31,000	£26,000	£107,000§	£52,000§
Effectiveness						
Time on 1st-line TKI	8.9 years nilotinib, 7.0 years imatinib	7.0 years nilotinib, 7.0 years imatinib	nilotinib dominates	nilotinib dominates	£87,000§	£43,000§
		13.8 years nilotinib, 11.7 years imatinib (IRIS)	£23,000	£20,000	nilotinib dominates	£80,886§
Time on 2nd-line nilotinib	Mean 2.5 years	Same as mean time on 1st-line nilotinib = 8.9 years	n/a	n/a	£71,000§	£43,000§
Survival after SCT	Mean approximately 17 years	Mean 5.7 years (Novartis)	£22,000	£23,000	£59,000§	£54,000§
Time in CP on HU	Mean 5 years	Mean 1.6 years (Novartis)	£31,000	£24,000	£375,000§	£52,000§
OS estimated by Cumulative Survival or Surrogate Survival	Cumulative Survival	Cumulative survival means, MMR survival difference	£48,000	£32,000	n/a	n/a
		Cumulative survival means, CCyR survival difference	£26,000	£20,000	n/a	n/a
		Surrogate survival means, MMR survival difference	£53,000	£36,000	n/a	n/a
		Surrogate survival means, CCyR survival difference	£29,000	£22,000	n/a	n/a
Costs						
Drug price reduction	0% nilotinib,	0% nilotinib, 25% imatinib	£70,000	£48,000	£63,000§	£20,000§

Parameter	Base case	Sensitivity analysis	Scenario 1 (No 2nd-line nilotinib)	Scenario 2 (No 2nd-line nilotinib, Simplified Method)	Scenario 3 (2nd-line nilotinib)	Scenario 4 (2nd-line nilotinib, Simplified Method)
Base case	N/A	N/A	**£36,000**	**£26,000**	**£213,000§**	**£50,000§**
on patent expiry	0% imatinib	25% nilotinib, 25% imatinib	£54,000	£38,000	£116,000§	£30,000§
Dose intensities	[redacted] 1st-line nilotinib, [redacted] imatinib, 99% 2nd-line nilotinib	100% 1st-line nilotinib, [redacted] imatinib, 99% 2nd-line nilotinib	£63,000	£44,000	£93,000§	£26,000§
		[redacted] 1st-line nilotinib, 106% imatinib (Novartis), 99% 2nd-line nilotinib	£19,000	£15,000	£286,000§	£65,000§
		[redacted] 1st-line nilotinib, [redacted] imatinib, [redacted] 2nd-line nilotinib	n/a	n/a	£187,000§	£45,000§
Cost SCT	£81,603	£40,801	£40,000	£27,000	£228,000§	£50,000§
		£163,205	£27,000	£24,000	£183,000§	£51,000§
Medical management costs after SCT	£113 per month	£57 per month	£36,000	£26,000	£215,000§	£50,000§
Medical management costs in CP	£370 per month	£185 per month	£30,000	£23,000	£200,000§	£48,000§
		£741 per month	£48,000	£33,000	£239,000§	£55,000§
Medical management costs in AP and BC	£1,113 per month	£2,227 per month	£35,000	£26,000	£217,000§	£51,000§
AEs costs	£166 per patient imatinib, £119 per patient nilotinib	£1,660 per patient imatinib, £,1190 per patient nilotinib	£35,000	£26,000	£217,000§	£51,000§
Utilities						
Utilities		Equal to Novartis	£35,000	£26,000	£209,000§	£50,000§
		Reduce all utilities by 0.10	£41,000	£30,000	£236,000§	£57,000§

§ Nilotinib provides fewer QALYs at less cost than imatinib

Table 57 Sensitivity analyses for dasatinib vs. imatinib

Parameter	Base case	Sensitivity analysis	Scenario 1 (No 2nd-line nilotinib)	Scenario 2 (No 2nd-line nilotinib, Simplified Method)	Scenario 3 (2nd-line nilotinib)	Scenario 4 (2nd-line nilotinib, Simplified Method)
Base case	N/A	N/A	**£425,000**	**£262,000**	**£460,000**	**£307,000**
General						
Discounting costs & benefits	3.5% p.a.	0% p.a.	£345,000	£236,000	£347,000	£259,000
Treatment pathways						
Proportion receiving SCT	Mean 32% dasatinib, 33% imatinib, decreases with age	31% at all ages (BMS assumption)	£345,000	£253,000	£404,000	£300,000
		75% if age < 65 (Novartis)	£552,000	£272,000	£601,000	£319,000
		Halve % at all ages	£339,000	£251,000	£385,000	£296,000
Effectiveness						
Time on 1st-line TKI	7.7 years dasatinib, 7.0 years imatinib	7.0 years dasatinib, 7.0 years imatinib	imatinib dominates	imatinib dominates	imatinib dominates	imatinib dominates
		12.5 years dasatinib, 11.7 years imatinib (IRIS)	£574,000	£434,000	£650,000	£515,000
Time on 2nd-line nilotinib	Mean 2.5 years	Same as mean time on 1st-line nilotinib = 8.9 years	n/a	n/a	£682,000	£508,000
Survival after SCT	Mean approximately 17 years	Mean 5.7 years (Novartis)	£252,000	£229,000	£298,000	£271,000
Time in CP on HU	Mean 5 years	Mean 1.6 years (Novartis)	£366,000	£235,000	£382,000	£269,000
OS estimated by Cumulative Survival or Surrogate Survival	Cumulative Survival	Cumulative survival means, MMR survival difference	£258,000	£176,000	n/a	n/a
		Cumulative survival means, CCyR survival difference	£110,000	£82,000	n/a	n/a
		Surrogate survival means, MMR survival difference	£313,000	£202,000	n/a	n/a
		Surrogate survival means, CCyR survival difference	£131,000	£91,000	n/a	n/a

Parameter	Base case	Sensitivity analysis	Scenario 1 (No 2nd-line nilotinib)	Scenario 2 (No 2nd-line nilotinib, Simplified Method)	Scenario 3 (2nd-line nilotinib)	Scenario 4 (2nd-line nilotinib, Simplified Method)
Base case	N/A	N/A	**£425,000**	**£262,000**	**£460,000**	**£307,000**
Costs						
Drug price reduction on patent expiry	0% dasatinib, 0% imatinib	25% dasatinib, 25% imatinib	£436,000	£269,000	£472,000	£315,000
Dose intensities	[redacted] imatinib, 99% dasatinib, 99% 2nd-line nilotinib	106% imatinib (Novartis), 99% dasatinib, 99% 2nd-line nilotinib	£379,000	£234,000	£410,000	£274,000
		[redacted] imatinib, 99% dasatinib, [redacted] 2nd-line nilotinib	n/a	n/a	£460,000	£307,000
Cost SCT	£81,603	£40,801	£430,000	£263,000	£464,000	£308,000
		£163,205	£415,000	£260,000	£452,000	£305,000
Medical management costs after SCT	£113 per month	£57 per month	£425,000	£262,000	£460,000	£307,000
Medical management costs in CP	£370 per month	£185 per month	£419,000	£258,000	£454,000	£303,000
		£741 per month	£437,000	£269,000	£471,000	£314,000
Medical management costs in AP and BC	£1,113 per month	£2,227 per month	£424,000	£261,000	£459,000	£306,000
AEs costs	£166 per patient imatinib, £282 per patient dasatinib	£1,660 per patient imatinib, £2,820 per patient dasatinib	£432,000	£266,000	£467,000	£312,000
Utilities						
Utilities		Equal to Novartis	£416,000	£260,000	£451,000	£304,000
Utilities		Reduce all utilities by 0.10	£483,000	£299,000	£524,000	£351,000

8.6.6.1. Sensitivity analyses: Discounting

Although CML is a chronic disease, discounting has little impact on the ICERs.

8.6.6.2. Sensitivity analyses: Proportion receiving SCT

First note that the ICERs for the Simplified Method (Scenarios 2 and 4) are largely independent of our assumption for the proportion of patients receiving a SCT. This is as intended, because the Simplified Method is designed to ensure that cost-effectiveness is insensitive to the nature, costs and QALYs of treatments post-TKIs.

In Scenario 1, the ICER of nilotinib vs. imatinib falls from £36,000 to £31,000 per QALY when we halve the proportion receiving SCT at all ages. This is because now, a relatively smaller number of people receive SCT in the imatinib arm compared to the nilotinib arm, and it is more cost-effective to be in the health state following a SCT compared to the health state of receiving HU treatment in CP, AP and then BC.

This assertion that it is more cost-effective for patients to receive a SCT than to receive HU is demonstrated as follows. The ICER between the treatment arm of 1st-line imatinib, following by 100% patients taking SCT vs. 1st-line imatinib, following by 100% patients taking HU is £14,000 per QALY. Also the corresponding ICER starting with 1st-line nilotinib is £15,000 per QALY.

In Scenario 1, the ICER of nilotinib vs. imatinib increases from £36,000 to £43,000 per QALY with Novartis' assumption that 75% of patients have a SCT if they are < 65 years old, and no patients receive a SCT if they are older. This is because the difference in the proportion of people who receive a SCT between imatinib and nilotinib increases from 5% to 8%, and as we have just demonstrated, SCT is more cost-effective that treatment with HU.

Dasatinib remains very poor value for money against imatinib regardless of our assumption for proportion receiving SCT.

8.6.6.3. Sensitivity analyses: Time on 1st-line TKI

We consider two sensitivity analyses concerning duration of 1st-line TKI treatment. These parameters are worthy of sensitivity analysis because they strongly affect cost-effectiveness

and because duration of all 1st-line treatments are uncertain, given that the two 1st-line RCTs are very immature.

First, we assume all treatments have the same mean duration as for imatinib, at 7.0 years.

[redacted]

Imatinib dominates dasatinib because it is far less expensive per person per day.

Next, the absolute mean times on 1st-line TKIs were based on that for imatinib in the IRIS RCT. At the same time, the hazard ratios were still taken from the RCT of 1st-line nilotinib vs. imatinib and dasatinib vs. imatinib. This yields mean times on treatment of 11.7 years for imatinib, 13.8 years for nilotinib and 12.5 years for dasatinib.

8.6.6.4. Sensitivity analyses: Time on 2nd-line nilotinib

The time on 2nd-line nilotinib is relevant only in Scenarios 3 and 4. Our estimate of the mean time on 2nd-line nilotinib, at 2.5 years, is probably robust because it is taken from a single arm, high-quality study. Nonetheless, when we increase the mean duration substantially to 8.9 years, which is our assumption for the duration on 1st-line nilotinib, the cost-effectiveness of nilotinib vs. imatinib deteriorates, but nilotinib still remains cost-effective at a willingness to pay of £30,000 per QALY.

8.6.6.5. Sensitivity analyses: Survival after SCT

Our estimated mean survival after SCT of approximately 17 year is uncertain, given that our evidence is observational and we have no relevant evidence after failure of nilotinib or dasatinib. Novartis estimate a far shorter mean survival after SCT of 5.7 years. Assuming this shorter survival time, the ICER for nilotinib vs. imatinib under Scenario 1 falls from £36,000 to £22,000 per QALY and under Scenario 2, from £26,000 to £23,000 per QALY. In both cases, cost-effectiveness improves because being in the post-SCT health state is now less cost-effective, because patients still incur the initial cost of the operation, but live less long. In addition, more patients have a SCT on imatinib (33%) than on nilotinib (28%).

8.6.6.6. Sensitivity analyses: Time on HU in CP

Our estimated mean time on HU in CP of 5 years is uncertain, given that our evidence is based on a study which included a mixture of treatments in addition to HU, and because we have no relevant evidence after failure of nilotinib or dasatinib. Novartis estimate a far shorter time on HU in CP of 1.6 years. Assuming this shorter survival time, the ICER for nilotinib vs. imatinib under Scenario 1 falls from £36,000 to £31,000 per QALY and under Scenario 2, from £26,000 to £24,000 per QALY.

8.6.6.7. Sensitivity analyses: Surrogate overall survival

We now consider the sensitivity analyses whereby we retain the model structure under the Cumulative Survival method, but adjust the time on HU in CP to reflect the OS experienced in historical trials. We believe that these sensitivity analyses are very important, because they are the only analyses which use the CCyR and MMR rates reported for 1st-line treatment with the three TKIs. The methods are explained in Section 8.1.3, p139. However, to summarise briefly, we present four sensitivity analyses (1a, 1b, 2a, 2b, as presented in Table 33, p. 136) for each of Scenarios 1 and 2. In the first analysis, the mean OS on imatinib is left unchanged, but the mean OS for nilotinib and dasatinib are adjusted to reflect the differences in OS between nilotinib, dasatinib and imatinib which are estimated from the surrogate analysis based on MMR . The second analysis repeats the first analysis, but using the surrogate relationship based on CCyR (scenario 1b and 2b). In the third analysis, OS for all treatments are forced to equal OS estimated for each treatment based on the historical MMR surrogate. The final analysis is the same, but based on the historical CCyR surrogate. The resulting mean survival times are given in Figure 41 below. Figure 42 below shows how OS as estimated by the Cumulative Survival method is far shorter than by the Surrogate Survival method (upper graph). In the third and fourth sensitivity analyses, the modelled OS is then adjusted to match the OS based on the surrogate experience (lower graph).

The sensitivity analyses reveal that the cost-effectiveness of nilotinib vs. imatinib worsens when we base OS on the MMR surrogate relationship, regardless of whether the OS of imatinib is adjusted to reflect that from the surrogate relationship. This is because we estimate only a slight advantage in OS, 0.6 years, for people taking nilotinib vs. imatinib based on the MMR surrogate relationship, and this is less than the difference of 0.9 years based on the Cumulative Survival Method. Conversely, the cost-effectiveness of nilotinib vs. imatinib improves when

we base OS on the CCyR surrogate relationship, regardless of whether the OS of imatinib is adjusted to reflect that from the surrogate relationship. This is because we estimate a slightly greater advantage in OS, 1.3 years, for people taking nilotinib vs. imatinib based on the CCyR surrogate relationship than the 0.9 years based on the Cumulative Survival Method.

Dasatinib remains very poor value for money when using OS based on the Surrogate Method.

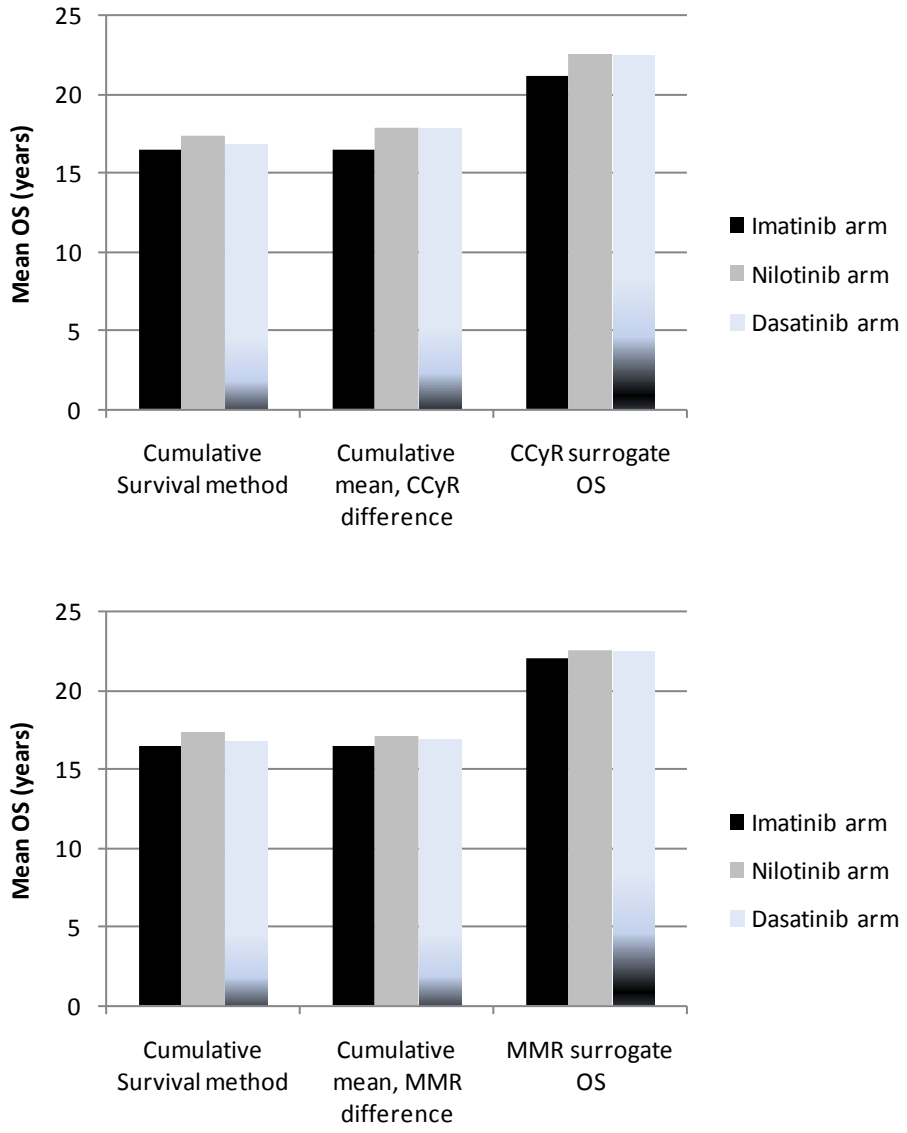


Figure 41 Modelled OS by treatment arm as a function of method of estimating OS for methods related to MMR surrogate OS (upper graph) and CCyR surrogate OS (lower graph)

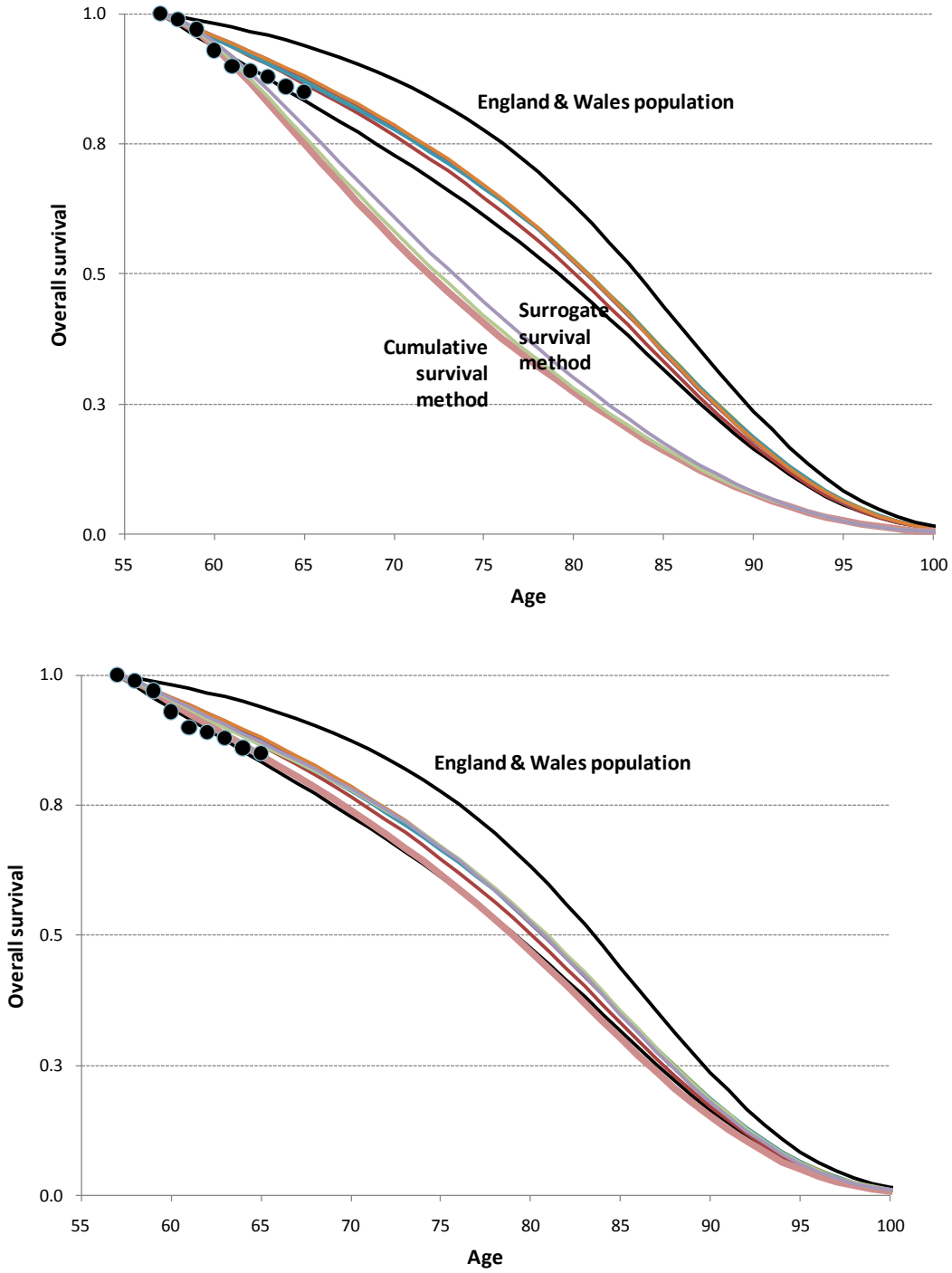


Figure 42 OS based on Cumulative Survival vs. Surrogate Survival.

Note: The top figure compares OS modelled by the Surrogate Survival method and the Cumulative Survival method by treatment and response type. The bottom graph shows OS when adjusted to reflect that from the surrogate data. The filled circles represent OS from the IRIS RCT

8.6.6.8. Sensitivity analyses: Patent expiry

Imatinib will lose patent protection in England & Wales in just a few years, in the year 2016 (N.B. this is after the currently tabled review date fot this NICE guidance).[139] Also, dasatinib comes off patent in 2020 and nilotinib in 2023.[143, 144] Given that NICE's recommendations from this HTA will come in to force in the year 2012, it will be only 4 years before imatinib loses patent protection. Two sensitivity analyses were considered: first setting the price reduction on patent expiry to 25% for all drugs, and second setting the price reduction to 25% for imatinib and dasatinib and 0% for nilotinib. The reduction of 25% is not evidence-based, however, we believe that this gives a guide to the possible changes in cost-effectiveness. In one sensitivity analysis, we model no price change for nilotinib, because this assumes that the price reduction on patent expiry will be relative to the list price of nilotinib, not to the price of nilotinib under the Patient Access Scheme.

[redacted]

In Scenario 1, assuming a 25% reduction in the prices of nilotinib and imatinib, the ICER for nilotinib vs. imatinib increases from £36,000 to £54,000 per QALY. This is for two reasons. Most importantly, imatinib is far closer to patent expiry than nilotinib. Second, we predict that patients take nilotinib for longer than imatinib. Also in Scenario 1, assuming a 25% reduction in the price of imatinib only, with no change in the price of nilotinib, the ICER increases from £36,000 to £70,000 per QALY.

In Scenario 4 (Simplified Method, with 2nd-line nilotinib), nilotinib changes from being cost-effective versus imatinib (although providing fewer QALYs) to being on the border of cost-effectiveness.

Dasatinib becomes even worse value for money versus imatinib when we allow for price reduction on patent expiry.

These sensitivity analyses all assume patients starting TKI treatment in the year 2012. If instead, we model patients starting treatment in the future, so-called "future incident cohorts", all ICERs increase further. For example, modelling patients starting treatment in the year 2016, and assuming a 25% reduction in the prices of both nilotinib and imatinib, under Scenario 1, the ICER for nilotinib vs. imatinib increases from £36,000 to £74,000 per QALY. Under Scenario 2, the ICER for nilotinib vs. imatinib increases from £26,000 to £51,000 per QALY.

In addition, under Scenario 4 (with 2nd-line nilotinib, Simplified Method), nilotinib changes from being good value for money (although less beneficial), to be on the borderline of value.

8.6.6.9. Sensitivity analyses: Dose intensities

The ICERs of nilotinib vs. imatinib are very sensitive even to small changes in the dose intensities. Our estimate of the dose intensity of 1st-line nilotinib, at [redacted], is taken from Novartis, and is evidence based. However, when we [redacted] this to 100%, a value which is not evidence-based, the ICER under Scenario 1 increases from £36,000 to £63,000 per QALY, and the ICER under Scenario 2 increases from £26,000 to £44,000 per QALY.

Conversely, when leave the dose intensity of 1st-line nilotinib unchanged at [redacted], and increase the dose intensity of imatinib from [redacted] to 106% which is the value used by Novartis, then nilotinib becomes substantially better value. The ICER under Scenario 1 decreases from £36,000 to £19,000 per QALY, and under Scenario 2 from £26,000 to £15,000 per QALY.

These analyses highlight the crucial importance of the dose intensities in estimating the cost-effectiveness of nilotinib.

When the dose intensity of 2nd-line nilotinib is changed from the evidence-based value of 99% to [redacted], being the same as for 1st-line nilotinib, the cost-effectiveness of nilotinib in Scenarios 3 and 4 worsens slightly.

8.6.6.10. Sensitivity analyses: Cost of SCT

The ICERs of nilotinib vs. imatinib are fairly sensitive to changes in the cost of a SCT from our evidence-based estimate of £81,603. When the cost is increased, nilotinib becomes better value for money because a smaller proportion of the total cohort is predicted to have a SCT in the nilotinib arm than in the imatinib arm.

8.6.6.11. Sensitivity analyses: Medical management in CP

The ICERs are fairly sensitive to the monthly cost of medical management in CP, whether on TKIs or HU. For example, in Scenarios 1 and 2 (no 2nd-line nilotinib), the ICER of nilotinib vs. imatinib increases when the cost is increased. This is because we predict that patients will spend longer in CP taking TKIs or HU in the nilotinib arm than in the imatinib arm.

8.6.6.12. Sensitivity analyses: Other costs

All ICERs are insensitive to all other costs: of medical management after SCT, medical management in AP and BC, and treatment of AEs.

8.6.6.13. Sensitivity analyses: Utilities

All ICERs are virtually unchanged when we use Novartis' utilities. This is because we use the same age-dependent utilities whilst patients are taking TKIs or HU in CP, and because the remaining utilities differ only slightly.

When all utilities are reduced by 0.10, the ICERs for nilotinib vs. imatinib in Scenarios 1 and 2 increase slightly. This is because we predict more QALYs in the nilotinib arm compared to the imatinib arm. However, we caution that the reduction of 0.10 is not evidence-based, but is arbitrary.

8.7. Comparison of PenTAG model with industry submissions

8.7.1. Comparison of PenTAG model vs. Novartis model

Scenario 1 in the PenTAG model uses the closest structural assumptions to the Novartis model in which no 2nd-line TKIs are assumed. However the models predict substantially different ICERs for nilotinib vs. imatinib, which span the usually accepted cost-effectiveness thresholds.

- PenTAG ICER £36,000 per QALY
- Novartis ICER £6,000 per QALY

Note that Scenario 1 is only one of our four Scenarios, all with their advantages and disadvantages.

First, we explain the causes of this difference in cost-effectiveness, and justify our choice of assumptions. Second, we describe some further key differences in model predictions. Third, in order to assess the impact of assumptions on cost-effectiveness, we adjust Novartis' model sequentially so that it becomes more like our model.

8.7.1.1. Causes of difference in cost-effectiveness Novartis vs. PenTAG

Table 58 below compares the results from the PenTAG Scenario 1 and the Novartis analysis with no 2nd-line TKI. The difference in cost-effectiveness is explained mostly by the following differences in the models. All these differences act to make the cost-effectiveness of nilotinib vs. imatinib worse in the PenTAG model vs. the Novartis model;

- Incremental QALYs in SCT: PenTAG -0.42 vs. -0.26 Novartis.
- Incremental QALYs on HU in CP: PenTAG -0.11 vs. 0.01 Novartis.
- Incremental costs on 1st-line TKIs: PenTAG £14,751 vs. £10,733 Novartis.
- Incremental medical management costs on 1st-line TKIs: PenTAG £5,578 vs. £1,365 Novartis.
- Incremental cost of SCT operation: PenTAG -£3,840 vs.-£7,603 Novartis.

These key differences are highlighted in Table 58. If just these incremental results from our model are used, then Novartis' ICER increases from £6,000 to £36,000 per QALY, which matches the result from our model. This demonstrates that it is these incremental differences that drive the difference in cost-effectiveness estimates.

Table 58 Comparison of key outputs: PenTAG vs. Novartis

	PenTAG	Novartis§	PenTAG	Novartis§	PenTAG	Novartis§
	Imatinib		Nilotinib		Nilotinib-Imatinib	
Life years (undiscounted)						
1st-line TKI	7.0	5.5	8.9	7.3	1.9	1.7
SCT	5.8	3.1	4.9	2.7	-0.9	-0.5
HU CP	2.9	0.6	2.8	0.7	-0.1	0.1
HU AP	0.5	0.3	0.4	0.4	0.0	0.0
HU BC	0.3	0.3	0.3	0.4	0.0	0.0
Overall survival	**16.5**	**10.0**	**17.4**	**11.4**	**0.9**	**1.4**
Cohort split ¶						
% starting SCT/HU	90%	94%	84%	90%	-6%	-4%
% SCT (whole cohort)	33%	55%	28%	47%	-5%	-8%

	PenTAG	Novartis§	PenTAG	Novartis§	PenTAG	Novartis§
% SCT (eligible cohort)	37%	58%	34%	52%	-3%	-6%
% HU (whole cohort)	56%	39%	56%	43%	-1%	4%
% HU (eligible cohort)	63%	42%	66%	48%	3%	6%
% AP (whole cohort)	49%	38%	48%	42%	-2%	4%
% BC (whole cohort)	49%	38%	48%	42%	-2%	4%
Life years (undisc. eligible cohort) ¶						
1st-line TKI	7.0	5.5	8.9	7.3	1.9	1.7
SCT	17.4	5.7	17.2	5.7	-0.2	0.0
HU CP	5.1	1.6	5.0	1.6	-0.1	0.0
HU AP	0.9	0.8	0.9	0.8	0.0	0.0
HU BC	0.6	0.8	0.6	0.8	0.0	0.0
QALYs (discounted)						
1st-line TKI	4.54	3.77	5.52	4.75	0.98	0.98
SCT	2.61	1.66	2.18	1.40	-0.42	-0.26
HU CP	1.54	0.38	1.43	0.39	-0.11	0.01
HU AP	0.22	0.13	0.21	0.14	-0.01	0.00
HU BC	0.11	0.13	0.10	0.13	-0.01	0.00
Total	**9.01**	**6.07**	**9.43**	**6.81**	**0.42**	**0.74**
Costs (discounted)						
1st-line TKI	£118,635	£104,038	£133,386	£114,771	£14,751	£10,733
1st-line AEs	£166	£178	£119	£111	-£47	-£67
1st-line medical management	£25,115	£5,460	£30,693	£6,825	£5,578	£1,365
SCT transplant	£24,486	£49,986	£20,646	£42,383	-£3,840	-£7,603
SCT medical management	£2,562	£0	£2,148	£0	-£415	£0
HU acquisition in CP	£282	£73	£264	£76	-£19	£3
HU CP medical management	£8,747	£271	£8,171	£279	-£577	£8
HU AP acquisition + med man	£4,098	£844	£3,828	£874	-£270	£30
HU BC acquisition + med man	£2,735	£1,613	£2,555	£1,665	-£180	£52
End of life cost		£3,541		£3,389		-£152
Total costs	**£186,827**	**£166,003**	**£201,808**	**£170,373**	**£14,981**	**£4,370**
Cost / LYG					**£17,000**	**£5,000**
Cost / QALY					**£36,000**	**£6,000**

§ Novartis report only total life years, total costs, total QALYs, cost per LYG and cost / QALY for each treatment (p116 Novartis report). We have calculated all other values in this table from Novartis' model.

¶ The "eligible" cohort consists of those people who are alive and eligible to receive the relevant treatment, as opposed to the "whole cohort", being all patients starting 1st-line treatment.

8.7.1.2. Difference in QALYs after SCT

There are two important components to the QALYs after SCT which apply to both models. First, the proportion of patients who receive a SCT from all patients who start 1st-line treatment, and second, the mean time after SCT for those who have a SCT.

The first component, the proportion of patients who receive a SCT from all patients who start 1st-line treatment actually works against the observation that incremental QALYs are lower in our model compared to the Novartis model. In our model, 5% fewer patients have a SCT on nilotinib compared to imatinib, compared to 8% in the Novartis model.

However, the second component dominates. In our model, life expectancy after SCT is about 17.3 years, compared to 5.7 years in the Novartis model.

It is difficult to be certain whether we or Novartis have a better estimate for the life expectancy after SCT, for people having a SCT after 1st-line imatinib or nilotinib, given that we both rely on observational evidence.

8.7.1.3. Difference in QALYs on HU in CP

We predict slightly lower QALYs on HU in CP in the nilotinib arm compared to the imatinib arm, whereas Novartis predict virtually the same QALYs. Initially, it appears surprising that we predict lower QALYs for the nilotinib arm compared to the imatinib arm, 1.54 vs. 1.43, given that we predict very similar mean times on HU in CP, averaged over all patients starting 1st-line treatment (2.88 vs. 2.79 years). The difference is due to discounting, given that HU is taken in CP typically later in the nilotinib arm than in the imatinib arm.

Furthermore, the slight difference in discounted time on HU is magnified more in our model, because we assume that patients take HU in CP for much longer than do Novartis, 5.0 years vs. 1.6 years. However, as stated (See Appendix 7, p. 395), we believe that Novartis' method of calculating time on HU in CP following TKI failure is flawed.

The difference between the models is not explained by utilities, because we and Novartis use the same utilities whilst on HU in CP.

8.7.1.4. Difference in costs of 1st-line TKIs

We predict that the mean acquisition cost of 1st-line nilotinib is £14,800 greater than the acquisition cost of 1st-line imatinib. Novartis assume a smaller difference, at £10,700.

There are two factors that influence this difference between models. Most importantly, we assume a lower dose intensity for imatinib, at [redacted], than Novartis, at 106%. Using Novartis' estimate in our model, we predict an incremental cost of £7,600. Thus, changing the dose intensity overcompensates for the difference in costs.

As mentioned above, although both estimates of dose intensity are provided by Novartis, we favour 100% for the reasons given above (see Section 8.5.1.1 p. 176). The mean acquisition cost of 1st-line TKIs is also a function of the mean time on 1st-line TKIs.

8.7.1.5. Difference in costs of medical management whilst on 1st-line TKIs

We predict substantially higher, £5,600 mean medical management costs whilst patients are taking 1st-line nilotinib than imatinib. Conversely, Novartis assume similar costs, at £1,400.

This is explained almost exclusively by the fact that we assume far higher medical management costs per patient, per 3 months at £1,111, than Novartis, at £276. Indeed, when we use Novartis' estimate of £276 in our model, the incremental per patient cost falls from £5,600 to £1,400, the same value as predicted by Novartis.

We believe our estimate of medical management costs whilst patients are taking TKIs, at £1,111 per patient per 3 months, is preferable to Novartis' estimate. Our estimate is based on an extensive survey of clinicians performed by Oxford Outcomes for their submission on behalf of BMS for this appraisal. A range of resource uses are included, e.g. cost of nurse time, haematologist visits, bone marrow aspiration, blood count, cytogenetic analysis. On the other hand, Novartis' estimate is not based on a comprehensive survey, but is minimalistic, reflecting only the cost of out-patient appointments.

8.7.1.6. Difference in cost of SCT operation

We predict that the mean cost of SCT operations, averaged over all patients starting 1st-line treatment, is lower, by approx £3,800, in the nilotinib arm than in the imatinib arm. Novartis estimate a greater difference, at approx. £7,600.

The difference between models is mostly explained by the fact that we predict a smaller difference in the proportion of all patients who have a SCT in the nilotinib arm compared to the imatinib arm: -5% for us vs. -8% for Novartis. In both models, fewer patients are predicted to have a SCT in the nilotinib arm than in the imatinib arm. This in turn is a function of the differences in the assumed proportions of patients who have a SCT as a function of age. We assume a linear decrease as a function of age, whereas Novartis assume a flat rate of 75% up to age 65, and 0% thereafter.

The difference in the mean cost of SCT per patient is explained only to a small extent by the assumed cost of a SCT. We assume £81,600, compared to Novartis £99,200. Specifically, changing our assumed cost to equal that of Novartis changes our incremental costs from £3,800 to £4,700.

It is difficult to be certain whether we or Novartis have more accurate estimates of the proportions of patients having a SCT as a function of age and the cost of a SCT because both assumptions are rather subjective.

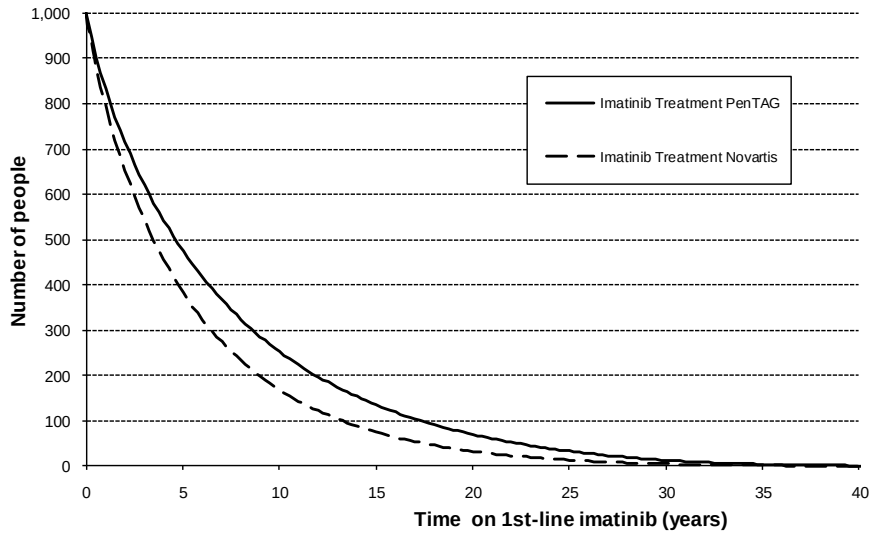
8.7.2. Further key differences in model predictions

8.7.2.1. Time on 1st-line treatment

We predict longer expected times on 1st-line nilotinib and imatinib than Novartis. Specifically, the mean time on imatinib in the PenTAG model is 7.0 years compared to 5.5 years in the Novartis model, and the mean time on nilotinib in the PenTAG model is 8.9 years compared to 7.3 years in the Novartis model. Figure 43 below shows these differences.

Novartis and us both fit Weibull distributions to the time on 1st-line treatment, and we both use the same empirical data from the trial of 1st-line imatinib vs. nilotinib. However there are two reasons that explain the differences in time on treatment. First, we adjust our estimates of the time on treatment of both imatinib and nilotinib from the RCT of 1st-line imatinib vs. nilotinib to perform the indirect comparison of all three TKIs, imatinib, nilotinib and dasatinib, as

explained in the Methods section. Novartis do not make this adjustment. Second, whereas we fit a curve to the Kaplan-Meier probabilities from the RCT of 1st-line imatinib vs. nilotinib, Novartis did not. Instead, they first adjust the Kaplan-Meier probabilities. For example, at 12 months follow-up, the Kaplan-Meier estimate of the proportion of patients still on 1st-line nilotinib is 0.870, whereas Novartis adjust this to 0.861 and then fit a Weibull curve to this figure. Novartis do not justify this adjustment, and the reason for the adjustment is not clear to us.



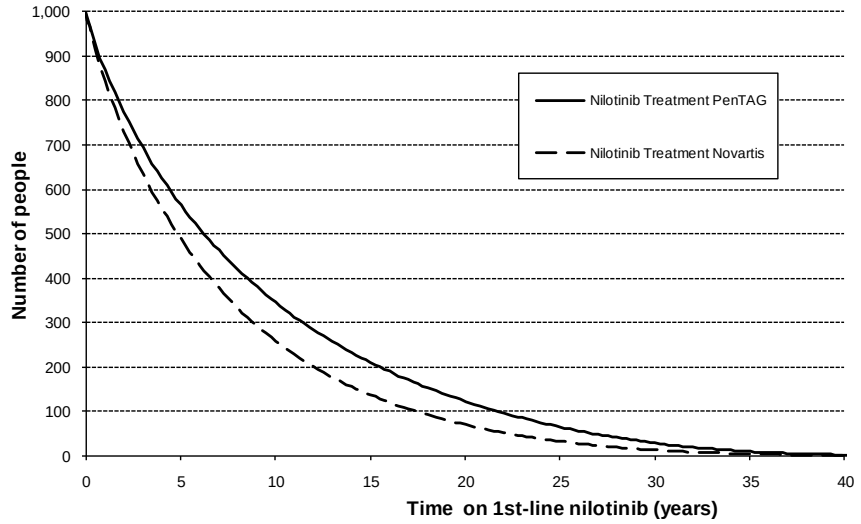


Figure 43 Time on 1st-line treatment with imatinib (upper figure) and nilotinib (lower figure) – PenTAG vs. Novartis

8.7.2.2. Overall survival

Novartis predict much shorter OS than us for both treatment arms, see Figure 44 and Figure 45 below. This is because they predict much shorter times on HU in CP (5.0 years us vs. 1.6 years Novartis) and survival after SCT (17.3 years us vs. 5.7 years Novartis), and slightly shorter times on 1st-line nilotinib and imatinib than us as mentioned in Section 8.7.1.1, p221, and in the previous section.

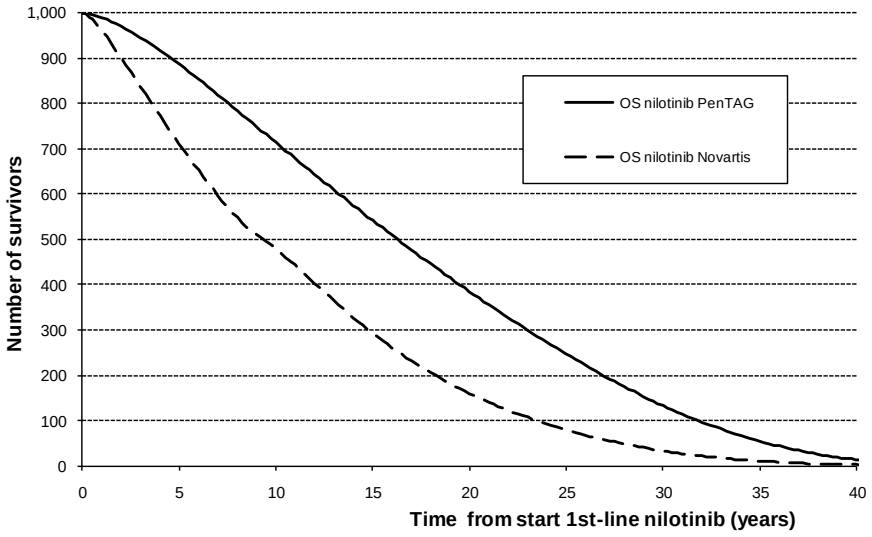


Figure 44 Overall survival (nilotinib) PenTAG vs. Novartis

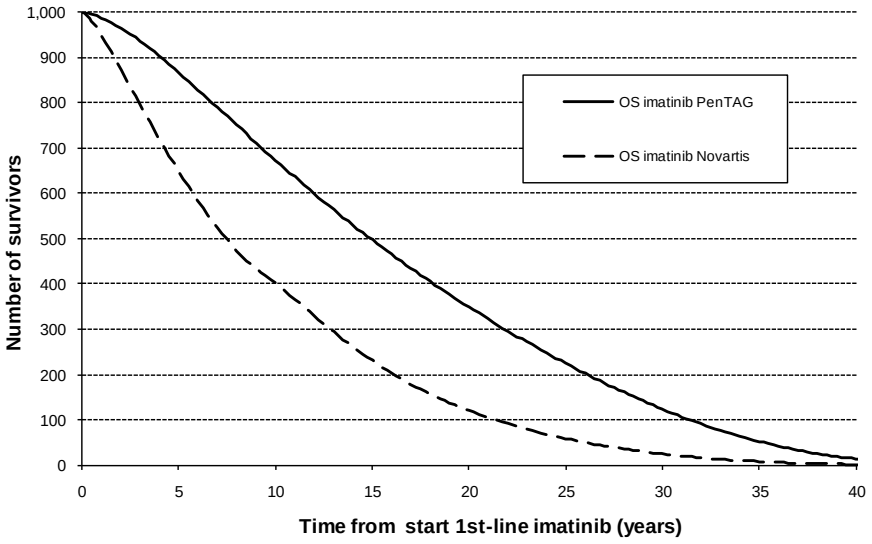


Figure 45 Overall survival (imatinib) PenTAG vs. Novartis

8.7.3. Adjustments to Novartis model

In order to further explore what is driving the difference in cost-effectiveness between the models, the following key parameters were identified;

- Time on 1st-line TKI treatment
- Mean cost of 1st-line treatment and medical management costs per patient
- SCT parameters
- Utility values

Where differences between the key parameters were identified, the PenTAG values were input in to the Novartis model and the resulting impact on the ICER was analysed.

8.7.3.1. Time on 1st-line treatment

As explained above, we predict longer expected times on 1st-line nilotinib and imatinib than Novartis. When the PenTAG treatment discontinuation rates for 1st-line treatment are input in to the Novartis model, the ICER for nilotinib vs. imatinib decreases only slightly, from £6,000 to £4,000 per QALY.

8.7.3.2. Costs

Taking the Novartis ICER of £4,000 per QALY updated for the PenTAG times on 1st-line treatment as the starting point, Table 59 below summarises the difference in input costs between the two models, and the change in the Novartis ICER when PenTAG costs are used.

Table 59 Variation in costs – PenTAG vs. Novartis model

Cost (per person per 3 months)	PenTAG	Novartis	Updated ICER from Novartis model using PenTAG Values*
1st line nilotinib	[redacted]	[redacted]	£12,000
1st line imatinib	£5,249	£5,547	
Medical mgmt 1st line TKI	£1,111	£276	£18,000
Medical mgmt HU_CP	£1,111	£138	£18,000
Medical mgmt HU_AP	£3,340	£826	£18,000
Medical mgmt HU_BP	£3,340	£1,657	£18,000

**The changes in ICERs are building on top of the previous changes. Therefore, the change in cost of 1st line nilotinib is based on an increase from £4,000 per QALY.*

As shown in Table 59, imatinib is slightly more expensive in the Novartis model than in the PenTAG model. As stated above, this is because Novartis assume a higher dose intensity for imatinib, 106%, than us [redacted]. Although this difference is dose intensities is small, it impacts strongly on cost-effectiveness given also that incremental QALYs are small. Using the PenTAG drug costs in the Novartis model causes the ICER increases from £6,000 to £12,000 per QALY.

As mentioned above, we assume far higher medical management costs whilst patients are taking TKIs or HU in CP compared to Novartis. Given that we both predict a longer time on

treatment of 1st-line nilotinib vs. imatinib, by approx 1.8 years, our higher medical management costs make the ICER increase further, from £12,000 to £18,000 per QALY.

8.7.3.3. Assumptions related to SCT

There are considerable differences around the use of SCT between the PenTAG and Novartis models. First, Novartis assume 75% of patients who reach 2nd-line treatment aged less than 65 have a SCT, and no patients older than 65 receive a SCT. Conversely, we assume a linear decrease in the proportion having a SCT with increasing age. Further, we predict far longer survival after SCT (17.3 years) than Novartis (5.7 years) (Table 58 above).

Out of all patients starting 1st-line treatment, fewer patients receive a SCT in the PenTAG analysis compared to the Novartis analysis. In Novartis' model, 47% of patients in the nilotinib arm receive a SCT, and 55% of patients in the imatinib arm (Table 58 above). When we alter Novartis' model for our assumptions on the proportions having a SCT and survival after SCT, the updated Novartis model matches the prediction from the PenTAG model that 28% of those in the nilotinib arm receive a SCT, compared to 33% of those in the imatinib arm. The ICER then increases further, from £18,000 to £25,000 per QALY, for the reason stated in Section 8.7.1.2, p. 223, that we then predict substantially fewer QALYs after SCT in the nilotinib arm than in the imatinib arm. When we further changes Novartis' assumption that a SCT costs £99,225 to our value of £81,603, the ICER increases slightly, from £25,000 to £27,000 per QALY.

8.7.3.4. Utility values

There are only slight differences in the utility values used in the PenTAG and Novartis models. Both models vary utility by age in exactly the same way. Furthermore, the utilities whilst patients are taking TKIs and HU in CP are equal in both models. Utility assumptions are slightly different between models for post-SCT and whilst in AP and BP. Indeed, the ICER remains at £27,000 per QALY when we update Novartis' model for our assumed utilities.

8.7.3.5. Time on HU

We assume a much longer mean time on HU in CP than Novartis 5.0 vs. 1.6 years, where these values are averaged over people who receive HU, rather than people starting 1st-line treatment. The mean time in AP is very similar between the models. When Novartis' model is further

updated for our times on HU in CP, AP and BC, the ICER increases only slightly, from £27,000 to £29,000 per QALY.

8.8. Comparison of PenTAG model vs. BMS model

The only comparison possible between our model and BMS' model relates to our Scenario 3, where we model 2nd-line nilotinib, and using BMS' model corrected for errors and adjusted so that all patients receive nilotinib 2nd-line. Given that we cannot adjust BMS' model so that no patients in the nilotinib arm take a TKI on nilotinib failure, here, we consider the dasatinib and imatinib treatment arms only.

This section is brief for the following reasons;

- we presents the results of BMS' model after we have made several corrections and adjustments,

- both models predict that dasatinib is very poor value vs. imatinib, with ICERs of £460,000 per QALY with our model and £95,000 per QALY with BMS' corrected and adjusted model,

- we disagree with BMS' method of estimating OS via a historical surrogate relationship because this relationship does not reflect the use of 2nd-line nilotinib, whereas BMS model 2nd-line nilotinib. Indeed, it is for this reason that we did not attempt to model surrogate OS when we modelled 2nd-line nilotinib (Scenarios 3 and 4).

We estimate far longer OS than BMS of approximately 17.5 years vs. 12.5 years (Table 60). It is therefore surprising that we estimate similar discounted QALYs. This is largely because we assume that utilities decline with age, whereas BMS do not.

Although we estimate far lower total costs per patient than BMS, incremental total costs are similar, although this is probably purely coincidental.

Table 60 Comparison of key outputs: PenTAG vs. BMS

	PenTAG	BMS§	PenTAG	BMS§	PenTAG	BMS§
	Imatinib		Dasatinib		Dasatinib-Imatinib	
Life years (undiscounted)	17.3	12.3	17.6	12.9	0.3	0.6
QALYs (discounted)	9.5	9.8	9.7	10.6	0.1	0.8
Costs (discounted)	£222,000	£378,000	£287,000	£457,000	£65,000	£79,000
Cost / QALY					**£460,000**	**£95,000**

9. DISCUSSION

9.1. Main findings

9.1.1. Clinical effectiveness

Both dasatinib 100mg (once daily; DASISION trial) and nilotinib 300mg (twice daily; ENESTnd trial) have a statistically significant advantage compared to the first generation TKI imatinib 400mg (once daily) in regards to surrogate outcomes (e.g. CCYR and MMR), however there is insufficient data to assess longer term patient relevant outcomes (e.g. progression free survival, overall survival, health related quality of life). Rates of complete cytogenetic response and major molecular response for dasatinib and nilotinib were higher, more rapidly attained, and deeper (molecular response) compared to imatinib. All three drugs were well tolerated with discontinuation due to adverse events < 10%. Indirect comparison analysis showed no difference between dasatinib and nilotinib for the primary outcomes of complete cytogenetic response or major molecular response at 12-months or 24-months follow-up.

There is observational association evidence supporting the use of complete cytogenetic response and major molecular response at 12 months as surrogates for progression free survival and overall in chronic phase – chronic myeloid leukaemia patients. This is based entirely on imatinib treatment studies. In the absence of evidence of adequacy of these surrogates for dasatinib and nilotinib as 1st-line therapies, and assuming a tyrosine kinase inhibitor class-specific relationship between the surrogate outcomes and the patient-relevant outcomes, these results can be potentially applied to other drugs in the same class.

9.1.2. Cost-effectiveness

The whole of this technology assessment report has been prepared in the context of changing draft guidance about the use of the same drugs for 2nd-line treatment of CML after imatinib as 1st-line treatment. In the draft guidance on 18th August 2011, NICE has recommended nilotinib, for the treatment of the chronic and accelerated phases of CML (chronic myeloid leukaemia) that is resistant or intolerant to standard-dose imatinib. Dasatinib and high-dose imatinib, are not recommended in the draft guidance. Consultees have the opportunity to appeal against the draft guidance. Until NICE issues final guidance, NHS bodies should make decisions locally on the funding of specific treatments. This draft guidance does not mean that

people currently taking dasatinib or high-dose imatinib will stop receiving them. They have the option to continue treatment until they and their clinicians consider it appropriate to stop.

We do not provide a single base case upon which to compare the cost-effectiveness of 1st-line nilotinib, dasatinib and imatinib because our model relies on numerous important assumptions. Furthermore, in many cases, there is no clear preference for one assumption over another. Instead, we present cost-effectiveness results for each of four main "Scenarios". In Scenario 1, we do not model 2nd-line nilotinib. In Scenario 2, again, we do not model 2nd-line nilotinib, but we use the Simplified Method, whereby the post-TKI per-patient costs and QALYs are set equal across treatment arms. We believe that this approach is appropriate due to the substantial uncertainty in the nature, and associated costs and quality of life of post-TKI treatments several years in the future, which is when patients will typically become eligible for such post-TKI treatments. Scenario 3 is the same as Scenario 1, but allowing for 2nd-line nilotinib, which has recently been recommended in the NICE draft guidance FAD (the draft guidance FAD for 2nd line CML for high-dose imatinib, dasatinib and nilotinib, is available on the NICE website at http://guidance.nice.org.uk/TA/WaveR/99). Similarly, Scenario 4 is the same as Scenario 2, but allowing for 2nd-line nilotinib.

1st-line dasatinib is predicted to provide very poor value for money vs. 1st-line imatinib regardless of the model structure e.g. whether we allow for 2nd-line treatment with nilotinib and regardless of when parameters are varied within plausible ranges.

Conversely, the findings for the cost-effectiveness of 1st-line nilotinib vs. 1st-line imatinib are rather complex.

Assuming 1st-line imatinib is followed by 2nd-line nilotinib, in nearly all occasions, nilotinib is predicted to yield fewer QALYs at less cost than imatinib. This is because 1st-line imatinib, but not 1st-line nilotinib, is followed by 2nd-line nilotinib, and the 2nd-line nilotinib extends overall survival. Furthermore, assuming patients take 2nd-line nilotinib after imatinib, 1st-line nilotinib almost always provides good value for money versus imatinib. The only occasions when 1st-line nilotinib may represent worse value for money than 1st-line imatinib are when we allow for drug price decreases on patent expiry, and when the dose intensity of 1st-line nilotinib is increased [redacted] to 100%.

Next, when we assume 1st-line imatinib is not followed by 2nd-line nilotinib, 1st-line nilotinib often lies close to the £30,000 per QALY willingness to pay threshold. However, 1st-line

nilotinib always represents poor value for money at the £20,000 per QALY threshold, except when the dose intensity of imatinib is increased from [redacted] to 106% where 106% is Novartis' estimate.

Still assuming 1st-line imatinib is not followed by 2nd-line nilotinib, the following parameters strongly influence the cost-effectiveness of 1st-line nilotinib and whether 1st-line nilotinib is cost-effective at a willingness to pay of £30,000 per QALY;

- Proportion of patients receiving SCT on failure of 1st-line TKI imatinib and nilotinib,
- Treatment duration of 1st-line imatinib and nilotinib,
- Survival after SCT,
- Time on HU in CP after imatinib and nilotinib failure,
- Whether we model CCyR and MMR response rates via surrogate relationships,
- Reduction in the prices of imatinib and nilotinib on patent expiry,
- Dose intensities of imatinib and nilotinib,
- Cost of SCT operation,
- Monthly medical management cost whilst in CP.

Of special note are the analyses whereby OS is adjusted to match that experienced in historical trials of imatinib according to whether a CCyR or MMR is achieved. The findings differ according to whether the surrogate relationship is based on CCyR or MMR. Using CCyR substantially improves the cost-effectiveness of 1st-line nilotinib vs. imatinib, whereas the reverse is true with the MMR surrogate relationship.

Also of special note are the analyses whereby the prices of the TKIs are reduced on patent expiry. We believe this is highly relevant to this appraisal, especially given that imatinib will lose patent protection very soon, in the year 2016. We do not estimate the likely price cut on patent expiry, but even assuming a modest 25% reduction, the cost-effectiveness of 1st-line nilotinib worsens dramatically. Further still, if we model patients who start 1st-line TKIs in the future, so-called "future incident cohorts", the cost-effectiveness of nilotinib worsens still further.

9.2. Strengths and limitations of systematic review of clinical effectiveness

The strengths of this systematic review are that it was conducted by an independent research team using the latest evidence to a pre-specified protocol.

The main limitation was lack of long term evidence on dasatinib and nilotinib used 1st-line in the populations of interest, providing only immature data. Further, there was only one trial for the each of the 2nd generation TKI's, namely dasatinib vs. imatinib and nilotinib vs. imatinib. This results in no head to head trials of dasatinib and nilotinib. With the immaturity of the data, primary endpoints of the trials are currently assessed using surrogate outcomes (i.e. CCyR and MMR). However, there is a lack of evidence for the use of surrogate outcomes for 2nd generation TKI's, with evidence only available for imatinib. It is assumed that the surrogate relationship exists for drugs of the same class.

9.3. Strength and limitations of systematic review of cost-effectiveness

The strengths of this systematic review are that it was conducted by an independent research team using the latest evidence to a pre-specified protocol. However, we identified no studies reporting the cost-effectiveness of dasatinib and nilotinib.

9.4. Strengths and limitations of the appraisal of industry submissions

This was conducted by an independent research team using a number of established frameworks to identify strengths and weaknesses.

9.5. Strengths and limitations of the PenTAG economic model

9.5.1. Strengths

- Our assessment of the cost-effectiveness of drugs for CML is independent. We have carefully compared our model and the results of our analysis with those of Novartis, and in so doing, we have highlighted areas in common and those where there is disagreement.

- Our model adheres to the NICE reference case methods and has been extensively checked. In addition to our four basic Scenario analyses, we also present numerous one-way deterministic sensitivity analyses. We have chosen carefully for plausibility and to reflect the key areas of uncertainty and disagreements between ourselves and Novartis' modelling. This has involved developing a model which is capable of using either a surrogates based estimation of OS, or a cumulative treatment duration approach, or combinations of the two approaches. It is therefore also more capable of exploring the differences between Novartis and BMS model.

- It is based on best available research evidence, from UK and recent patients wherever available and of reliable quality.

- Where research evidence lacking, we have checked key assumptions and parameter inputs with relevant clinical and other experts – for example, to inform our estimate cost of SCT, and the percentage who would get SCT at different ages.

- Good calibration of model survival outputs against IRIS data (Imatinib arm).

9.5.2. Limitations

Given that CML is a chronic condition, and that the main two RCTs provide very immature data on progression free survival, treatment duration and overall survival, our estimates of the cost-effectiveness of dasatinib and nilotinib are necessarily highly uncertain. They are also based on very small differences in clinical effectiveness outcomes between dasatinib and nilotinib. The following main sources of uncertainty exist in our modelling.

- Immaturity of empirical trial data relative to life expectancy - forcing either reliance on surrogate relationships or cumulative survival/treatment duration approach. There is therefore considerable extrapolation from 12 to 30 month follow-up data using a variety of curve fitting methods.

- Overall great uncertainty over the very heterogeneous treatment and care pathways that CML patients may follow - there are very many potential care and disease state paths which might be followed depending on how different people respond to treatment, their age, disease severity, availability of matched donors (for SCT), mutations which predict responsiveness to 2nd gen TKIs etc etc. This includes not modelling complex treatment

sequences in advanced disease (e.g. 2nd and 3rd chronic phases, and SCT following disease progression), and not modelling possible cessation of TKIs in those who experience a deep and durable initial response.

- Some of the uncertainty regarding treatment sequences after 1st line TKIs was because the NICE draft guidance FAD recommendation for 2nd line use of nilotinib, dasatinib or high-dose imatinib after standard-dose imatinib, was not released until very recently (18th August, 2011, the draft guidance FAD for 2nd line CML for high-dose imatinib, dasatinib and nilotinib, is available on the NICE website at http://guidance.nice.org.uk/TA/WaveR/99). This meant that we could not choose the most plausible scenarios to model, or finalise exactly how to model them, until later than would normally be the case.

- Uncertainty over both which treatment sequences of alternative TKIs are seen as clinically feasible, and what clinical effectiveness (and treatment duration, and dose intensity) would be for some combinations (especially for dasatinib after nilotinib or nilotinib after dasatinib).

- Uncertainty in evidence regarding treatments that would be received post-TKI failure in chronic phase: proportion getting SCT; also, using HU as proxy for what in reality would be a range of treatments that might be offered (e.g. IFN and other chemotherapies).

- Considerable uncertainty in survival and treatment costs either following SCT or with HU.

- Very limited sources of evidence for utility weights, and none available for post TKI failure in chronic phase. Also, no valid and reliable studies were available to reflect possible health related quality of life decrement of being on TKIs but not responding to them. Single source for AP and BC based on very small numbers (n=8 and 15).

- The types and cost of care in AP and BC phases was uncertain. We may have underestimated these, but discounting, and the fact that we predict similar durations in these states across treatment arms, mean that this probably has only a minor impact on the ICERs. Also, with the widespread use of TKIs, the AP phase may in effect not exist for many patients now. Further, more effective treatment regimes in AP or BC may

allow 2nd or 3rd chronic phases, or create sufficient recovery for SCT to be reconsidered. Our model does not capture these various treatment possibilities within advanced phase CML.

- An important assumption of the Cumulative Survival method is that OS after 2nd-line nilotinib and OS after HU or SCT is independent of previous treatment. There is very little research evidence to assess whether this assumption is plausible or not.

- For the Surrogate Survival method, we consider only the proportion of patients with a response at 12 months. We do not consider the depth, speed of achieving, and duration of a MMR or CCyR. Given that dasatinib and nilotinib are superior to imatinib in all these respects (see Novartis report), and given that the historical surrogate data is based on OS for patients taking imatinib, it is likely that we underestimate OS for dasatinib and nilotinib. We also assume that, for a given response rate, OS is independent of treatment arm.

There is considerable current interest in being able to stop treatment, or reduce dose, in patients who respond very well to treatment and this might be where the benefit of the newer TKIs might be eventually demonstrated.[48] However, it is impossible to incorporate these ideas into the model without much more follow-up from the RCTs of dasatinib and nilotinib.

We have chosen not to conduct and present probabilistic sensitivity analyses because of the unusually large amount of structural uncertainty that is inherent in the present decision problem(s). This structural uncertainty relates to both the variety of ways in which long-term survival might be estimated, and uncertainty surrounding the possible sequences and mixes of treatments post 1st line TKI failure. As a result, we believe that structural uncertainty would dominate total (structural and parameter) uncertainty, and therefore that if we presented PSAs based just on parameter uncertainty, this would be of little use to the committee. Furthermore, it might actually mislead users of our report who do not appreciate the substantial structural uncertainty.

Theoretically, it would have been possible to incorporate some of the structural uncertainty in to a PSA by some kind of model averaging. For example, we present scenario analyses with and without 2nd-line nilotinib. To incorporate the uncertainty in whether we assume use of 2nd-line nilotinib, we could have assigned a probability to the use of 2nd-line nilotinib, and present just one analysis. However, we believe that it would be more helpful to the committee

to present the two analyses separately, thus allowing the committee to decide for themselves which scenario they prefer, i.e. allowing them to use their expert judgement to estimate the probability of 2nd-line nilotinib use for themselves.

10. Conclusions

10.1. Implications

From the two trials available, both the second generation TKIs dasatinib and nilotinib have a statistically significant advantage compared to the first generation TKI imatinib 400mg as measured by surrogate outcomes. However, there is insufficient data to assess longer term patient relevant outcomes (e.g. PFS, OS, HRQoL). All three drugs were well tolerated with discontinuation due to adverse events < 10%.

With no head to head data available, an indirect comparison analysis showed no difference between dasatinib and nilotinib for the primary outcomes of CCyR or MMR at 12-months or 24-months follow-up.

Based entirely on imatinib treatment, there is observational association evidence supporting the use of complete cytogenetic response and major molecular response at 12 months as surrogates for OS and PFS in chronic phase CML patients. In the absence of evidence of adequacy of these surrogates for dasatinib and nilotinib, and assuming a TKI class-specific relationship between the surrogate outcomes and the patient-relevant outcomes, these results can be potentially applied to other drugs in the same class.

Taking into account the treatment pathways for chronic myeloid leukaemia patients, i.e. assuming the use of 2nd-line nilotinib, 1st-line nilotinib appears to be more cost-effective compared to 1st-line imatinib for most scenarios. Dasatinib was not cost-effective if decision thresholds of £20,000 per QALY or £30,000 per QALY are used, compared to imatinib and nilotinib.

10.2. Suggested research priorities

- Given the immature stage of trials assessing dasatinib or nilotinib compared to imatinib, longer term follow-up data is required and will be available from the ongoing and currently recruiting trials. As well as the pre-specified clinical outcomes (such as CCyR, MMR, and survival) these should report both treatment duration and dose intensity information for those treated if they are to be useful in estimating the long-term cost-effectiveness of the treatments.

- With no current head to head data for dasatinib and nilotinib, an RCT assessing the two therapies directly or with an additional imatinib arm would be valuable.

- More research-based data for the assessing the predictive usefulness of surrogate outcomes (such as MMR and CCyR) within the chronic myeloid leukaemia population, especially for dasatinib and nilotinib.

- Uncertainty in the cost-effectiveness analysis would be substantially reduced with better and more UK-specific data on: the incidence and cost of stem cell transplant in patients with chronic CML.

- Data on health-related quality of life for people in all stages of CML, and when on different treatments is lacking. Studies should ideally use the EQ-5D or SF-36 generic health related quality of life measures in order to allow social preference weights for the different states to be estimated.

- Research to reflect the whole sequence of CML treatment, as opposed to 'cross-sectionally' at each line of treatment.

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144. US Food and Drug Administration. Orange Book: approved drug products with therapeutic equivalence evaluations - dasatinib. 2011; Available from: http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=021986&Product_No=001&table1=OB_Rx.

Dasatinib, Nilotinib, and standard dose Imatinib for the first-line treatment of chronic myeloid leukaemia

Produced by Peninsula Technology Assessment Group (PenTAG), Peninsula College of Medicine and Dentistry, University of Exeter

APPENDICES

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[1] Appendices references contains duplicates from the main report

Appendix 1: Literature search strategy

The Strategy: Notes

The strategy was based upon the previous PenTAG review on this population and for this set of interventions.[1]

All controlled syntax and population/intervention terminology have been double-checked for currency, or for any form of update, as well as the possibility of entirely new terms or themes existing for this population and set of interventions.

Four additional lines have been incorporated for this review. With reference to the Medline strategy (by way of example) lines 3 and 15 were incorporated in testing and have been retained for the sake of completeness. For line 3, it is noted as unlikely that references would appear using only the acronym CML as an expression of the population without referring to, or defining first, Chronic Myeloid Leukaemia, but it is a common point of reference within title and abstract of texts, so a viable inclusion to the strategy in view of sensitivity. Similarly, with line 15, this is another way of referring to the Philadelphia Chromosome (as reflected in Emtree's controlled syntax) and has been incorporated for the sake of sensitivity.[2]

Lines 10 and 11 were incorporated at the advice of our local clinical expert, Dr Claudius Rudin, who critically appraised this strategy. The lines reflect concepts usually defined in reference to our population and interventions and so have been incorporated into the search both at his advice and for the sake of overall completeness. We are grateful to him for his time and advice on this stage of the assessment.

Syntax and Limits: Notes

Population

We have searched explicitly for Chronic stage Myeloid Leukaemia (via controlled syntax (line 4 of the Medline strategy) and free-text (line 3 of the Medline strategy)) as well as more broadly, and therefore more sensitivity, using the controlled syntax (where available) and free text for the broader, over-arching, population group, Myeloid Leukaemia. This is to ensure any unlikely deficiencies in indexing or referencing to the Chronic stage of the broader Myeloid population. Accordingly, any 'rogue' references which are implicitly Chronic stage but are not explicitly defined as such, can be picked up in the literature via screening.

Intervention

The interventions have been operationalised using both their formal and informal naming as well as their numerical drug forms. Over the OVID platform this has been done using multiple placing (.mp.)[II] for the syntax lines expressing the intervention (drug) names, to ensure all theoretical bases have been covered, as well as expressing the numerical form via free-text. In Embase, the relevant controlled syntax (Emtree) for the drugs has also been incorporated.

Limits

The relative youth of the interventions in question means there is comparatively little data in the field when compared with other interventions for this population (i.e. Imantnib). Accordingly, we ran our searching without recourse to methodological filters (RCTs etc) which opens a broader field of results for this review (for example, observational studies) as mentioned in the protocol.

Limits have been applied (where the databases have allowed) to exclude studies carried out on Animals as well as to limit returns to the date parameters of this assessment (2002-current) and to English Language studies.

Results

All results were exported from the databases into a bibliographic tool (Refworks)[III] to manage the results before the aggregate volume was de-duplicated using the internal tool in Endnote X4. The result was passed to the review team in RIS format. Copies of the result, a file of duplicates which have been removed, a file containing the library before duplication, as well as individual files of each database search have been retained and held in RIS format.

Surrogate Outcomes

As the screening developed, the possibility of requiring deeper literature on surrogate outcomes was raised. One outcome, major molecular response, had been introduced to the search by our Expert but an alternate measure, Complete Cytogenic Response, was not explicitly defined within the search syntax.

[II] title, original title, abstract, name of substance word, subject heading word

[III] Except ISI proceedings and Embase which were imported directly into Endnote X4

A search of this term (and the acronym CCyR) was conducted in Medline using the same project interventions which retrieved 15 results. These results were cross-checked and de-duplicated against the main review library which confirmed that all 15 results had been captured in the original search.

Whilst confidant that this result suggested we had captured all relevant literature on these outcomes project-wide, we nevertheless repeated the search across the portfolio of resources used for the initial search. Of the 308 references retrieved in this search, every single reference was found to have already been retrieved and was, therefore, a duplicate record. Whilst this search retrieved no unique references it does seek to confirm that saturation of these terms had already been achieved in the first search. The terms themselves appear well-embedded within the relevant literature for this review.

As the surrogate terms for dasatinib and nilotinib had already been captured in the clinical effectiveness review, an additional search used the intervention imatinib. The alternate comparator, interferon, whilst not explicit as a comparator in this review, will have been captured in this search as it the key comparator to imatinib, but data from the Schrover et al (2006) has also been used to support this point. The same database sources were searched for this review as for the clinical effectiveness review.

As the search was operationalised without recourse to limits (other than the project timelines and limits to Human only references) these unfiltered results have a broad applicability for the project.

The results annex and detailed search syntax for this search is at the bottom of this annex.

Notes on an additional search: The Cochrane Library

The Cochrane Library was in the process of updating from *Issue 2 of 12, Feb 2011* to *Issue 3 of 12, Feb 2011*, when the initial searching was run. Rather than hold up the overall search delivery, we searched issue 2 in the first instance.

A second search of the Cochrane Library was run on Thursday, March 17th 2011 when the update to issue 3 was complete and the results from this search were de-duplicated against the results found when the search of issue 2 was conducted. Both searches yielded 51 hits and

accordingly the de-duplication found no unique data in the new update. A record of the search is included below the first Cochrane search.

Citation Alerts

We put citation alerts on the two papers identified as includable in the review process. The alerts were screened as they arose by way of updating searches.

Main search

Database: Medline

Host: Ovid

Date Parameters: 1948 to February week 4 2011

Date Searched: Monday, March 7th 2011

Hits: 595

1. myeloid$ leuk?emia$.mp.
2. Leukemia, Myeloid/
3. (CML).tw.
4. leukemia, myeloid, chronic-phase/
5. leukemia, myeloid, chronic, atypical, bcr-abl negative/
6. exp leukemia, myelogenous, chronic, bcr-abl positive/
7. myelogenous$ leuk?emia$.mp.
8. myelocytic$ leuk?emia$.mp.
9. leukemia, myelomonocytic, chronic/
10. major cytogenetic response.ti,ab.
11. major molecular response.ti,ab.
12. Or/1- 11
13. Philadelphia Chromosome/
14. (Philadelphia adj1 Chromosome).mp.
15. (PH1 or PH 1 adj3 Chromosome).mp.
16. Or/13-15
17. 12 or 16
18. nilotinib.mp.
19. "4-methyl-N-(3-(4-methylimidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-((4-pyridin-3-ylpyrimidin-2-yl)amino)benzamide".mp.
20. tasigna.mp.
21. ((amn107 or amn-107 or amn) adj "107").mp.
22. Or/18-21
23. dasatinib.mp.
24. sprycel.mp.

25. (BMS354825 or BMS 354825 or BMS-354825).mp.
26. Or/23-25
27. 22 or 26
28. 17 and 27
29. Animals/ not Humans/
30. 28 NOT 29
31. limit 30 to English language
32. limit 31 to yr="2002 -Current"

Database: Medline in Process

Host: Ovid

Date Parameters: March 04, 2011

Date Searched:

Hits: 66

1. myeloid$ leuk?emia$.mp.
2. (CML).tw.
3. myelogenous$ leuk?emia$.mp.
4. myelocytic$ leuk?emia$.mp.
5. major cytogenetic response.ti,ab.
6. major molecular response.ti,ab.
7. Or/1- 6
8. (Philadelphia adj1 Chromosome).mp.
9. (PH1 or PH 1 adj3 Chromosome).mp.
10. Or/8-9
11. 7 or 10
12. nilotinib.mp.
13. "4-methyl-N-(3-(4-methylimidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-((4-pyridin-3-ylpyrimidin-2-yl)amino)benzamide".mp.
14. tasigna.mp.
15. ((amn107 or amn-107 or amn) adj "107").mp.
16. Or/12-15
17. dasatinib.mp.
18. sprycel.mp.
19. (BMS354825 or BMS 354825 or BMS-354825).mp.
20. Or/17-19
21. 16 or 20
22. 11 and 21
23. limit 22 to English language
24. limit 23 to yr="2002 -Current"

Database: Psycinfo

Host: Ovid

Date Parameters: 1806 to March Week 1 2011

Date Searched: Monday, March 7th 2011

Hits: 3

1. myeloid$ leuk?emia$.mp.
2. (CML).tw.
3. myelogenous$ leuk?emia$.mp.
4. myelocytic$ leuk?emia$.mp.
5. major cytogenetic response.ti,ab.
6. major molecular response.ti,ab.
7. Or/1- 6
8. (Philadelphia adj1 Chromosome).mp.
9. (PH1 or PH 1 adj3 Chromosome).mp.
10. Or/8-9
11. 7 or 10
12. nilotinib.mp.
13. "4-methyl-N-(3-(4-methylimidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-((4-pyridin-3-ylpyrimidin-2-yl)amino)benzamide".mp.
14. tasigna.mp.
15. ((amn107 or amn-107 or amn) adj "107").mp.
16. Or/12-15
17. dasatinib.mp.
18. sprycel.mp.
19. (BMS354825 or BMS 354825 or BMS-354825).mp.
20. Or/17-19
21. 16 or 20
22. 11 and 21
23. Animals/ not Humans/
24. 22 NOT 23
25. limit 24 to English language
26. limit 25 to yr="2002 -Current"

Database: Embase

Database Host: Ovid

Date Parameters: 1980 to 2011 Week 09

Date Searched: Monday, March 7th 2011

Hits: 2109

1. myeloid$ leuk?emia$.mp.
2. myelogenous$ leuk?emia$.mp.
3. myelocytic$ leuk?emia$.mp.
4. chronic myeloid leukemia/
5. (CML).tw.
6. myeloid leukemia/
7. major cytogenetic response.ti,ab.
8. major molecular response.ti,ab.
9. Or/1-8
10. Philadelphia 1 Chromosome/
11. (Philadelphia adj1 Chromosome).mp.
12. (PH1 or PH 1 adj3 Chromosome).mp.
13. Or/10-12
14. 9 OR 13
15. Nilotinib/
16. nilotinib.mp.
17. tasigna.mp.
18. (amn107 or amn-107 or (amn adj "107")).mp.
19. Or/15-18
20. dasatinib/
21. dasatinib.mp.
22. sprycel.mp.
23. (BMS354825 or BMS 354825 or BMS-354825).mp.
24. Or/20-23
25. 19 OR 24
26. 14 AND 25
27. limit 26 to English language
28. limit 27 to yr="2002 -Current"
29. ((animal$ or nonhumans) not human$).sh,hw.
30. 28 NOT 29

Database: Cochrane Library (Reviews, DARE, CENTRAL, HTA, NHS EEDS)

Database Host: Cochrane (http://www.thecochranelibrary.com/view/0/index.html)

Date Parameters: Issue 2 of 12, Feb 2011 (Updating)

Date Searched: Monday, March 7th 2011

Hits: 52 (CENTAL =45 + HTA =6 + NHS EED =1)

1. CML
2. myeloid* leukaemia*
3. myeloid* leukemia*
4. myelogenous* leukemia*

5. myelogenous* leukaemia*
6. myelocytic* leukemia*
7. myelocytic* leukaemia*
8. major cytogenetic response
9. major molecular response
10. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11. Philadelphia Chromosome
12. #10 OR #11
13. nilotinib
14. tasigna
15. amn107
16. amn-107
17. #13 OR #14 OR #15 OR #16
18. dasatinib
19. sprycel
20. BMS354825
21. BMS 354825
22. BMS-354825
23. #18 OR #19 OR #20 OR #21 OR #22
24. #17 OR #23
25. #12 AND #24 Restrict YR 2002 -2011

Database: Cochrane Library (Reviews, DARE, CENTRAL, HTA, NHS EEDS)

Database Host: Cochrane (http://www.thecochranelibrary.com/view/0/index.html)

Date Parameters: Issue 3 of 12, Feb 2011

Date Searched: Thursday, March 17th 2011

Hits: 52 (CENTAL =45 + HTA =6 + NHS EED =1)

NB: This is the update search to the above search, undertaken when the data update from issue 2 to 3 had been completed. It incorporates the surrogate terms.

1. CML
2. myeloid* leukaemia*
3. myeloid* leukemia*
4. myelogenous* leukemia*
5. myelogenous* leukaemia*
6. myelocytic* leukemia*
7. myelocytic* leukaemia*
8. major cytogenetic response
9. major molecular response
10. Complete Cytogenic Response

11. CCyR
12. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
13. Philadelphia Chromosome
14. #12 OR #13
15. nilotinib
16. tasigna
17. amn107
18. amn-107
19. #15 OR #16 OR #17 OR #18
20. dasatinib
21. sprycel
22. BMS354825
23. BMS 354825
24. BMS-354825
25. #20 OR #21 OR #22 OR #23 OR #24
26. #19 OR #25
27. #14 AND #26 Restrict YR 2002 -2011

Database: CRD all (DARE, HTA and NHS EEDS)

Database Host: Centre for Reviews and Dissemination (http://www.crd.york.ac.uk/crdweb/)

Date Parameters:

Date Searched: Monday, March 7th 2011

Hits: 6 (HTA =5 + NHS EEDS =1)

1. CML
2. myeloid* leukaemia*
3. myeloid* leukemia*
4. myelogenous* leukemia*
5. myelogenous* leukaemia*
6. myelocytic* leukemia*
7. myelocytic* leukaemia*
8. major cytogenetic response
9. major molecular response
10. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11. Philadelphia Chromosome
12. #10 OR #11
13. nilotinib
14. tasigna
15. amn107
16. amn-107
17. #13 OR #14 OR #15 OR #16

18. dasatinib
19. sprycel
20. BMS354825
21. BMS 354825
22. BMS-354825
23. #18 OR #19 OR #20 OR #21 OR #22
24. #17 OR #23
25. #12 AND #24 Restrict YR 2002 -2011

Database: Science Citation Index Expanded SCI-EXPANDED + Conference Proceedings Citation Index- Science (CPCI-S) + Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH)

Host: ISI

Date parameters: 1900 - Present

Date Searched: Monday, March 7th 2011

Hits: 1021

1. TS=(myeloid* leukaemia*) OR TS=(myeloid* leukemia*)
2. TS=(myelogenous* leukemia*) or TS=(myelogenous* leukaemia*)
3. TS=(myelocytic* leukaemia*) OR TS=(myelocytic* leukemia*)
4. #1 OR #2 OR #3
5. (“Philadelphia Chromosome”)
6. #4 OR #5
7. TS=(nilotinib) OR TS=(tasigna) OR TS=(amn107) OR TS=(amn-107) OR TS=(amn adj "107")
8. TS=(dasatinib) OR TS=(sprycel) OR TS=(BMS354825) OR TS=(BMS 354825) OR TS=(BMS-354825)
9. #7 OR #8
10. #6 and #9

Database: TRIP

Database Host: http://www.tripdatabase.com/

Date Parameters:

Date Searched: Monday, March 7th 2011

Hits: 95

(CML or myeloid* leukaemia* or myeloid* leukemia* or myelogenous* leukemia* or myelogenous* leukaemia* or myelocytic* leukemia* or myelocytic* leukaemia* or Philadelphia Chromosome) AND (nilotinib or dasatinib)

Database: Econlit

Host: Ebscohost

Date Parameters:

Date Searched: Tuesday, March 8th 2011

Hits: 0

1. (Myeloid Leukaemia or Myeloid Leukemia)
2. (Myelogenous Leukaemia or Myelogenous Leukemia)
3. (Myelocytic Leukaemia or Myelocytic Leukemia)
4. (Philadelphia Chromosome)
5. S1 or S2 or S3 or S4
6. (dasatinib or nilotinib or tasigna or sprycel)
7. S5 AND S6

Clinical Trial	
Current Controlled Trials	Hand Searched
Clinical Trials.gov	(207) – Data not included in main review
NRR (National Research Register)	Hand Searched
EMEA website	Hand Searched
FDA website	Hand Searched

Surrogate outcomes search

Database: Medline

Host: Ovid

Date Parameters: 1948 to March Week 2 2011

Date Searched: Thursday, March 17th 2011

Hits: 44

1. Complete Cytogenetic Response.ti,ab.
2. Complete Cytogenic Response.ti,ab.
3. CCyR.tw.
4. Or/1-3
5. nilotinib.mp.
6. "4-methyl-N-(3-(4-methylimidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-((4-pyridin-3-ylpyrimidin-2-yl)amino)benzamide".mp.
7. tasigna.mp.
8. ((amn107 or amn-107 or amn) adj "107").mp.

9. Or/5-8
10. dasatinib.mp.
11. sprycel.mp.
12. (BMS354825 or BMS 354825 or BMS-354825).mp.
13. Or/10-12
14. 9 or 13
15. 4 and 14
16. limit 15 to english language

Database: Medline in Process

Host: Ovid

Date Parameters: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations March 16, 2011

Date Searched: Thursday, March 17th 2011

Hits: 3

1. Complete Cytogenetic Response.ti,ab.
2. Complete Cytogenic Response.ti,ab.
3. CCyR.tw.
4. Or/1-3
5. nilotinib.mp.
6. "4-methyl-N-(3-(4-methylimidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-((4-pyridin-3-ylpyrimidin-2-yl)amino)benzamide".mp.
7. tasigna.mp.
8. ((amn107 or amn-107 or amn) adj "107").mp.
9. Or/5-8
10. dasatinib.mp.
11. sprycel.mp.
12. (BMS354825 or BMS 354825 or BMS-354825).mp.
13. Or/10-12
14. 9 or 13
15. 4 and 14
16. limit 15 to english language

Database: PsycINFO

Host: Ovid

Date Parameters: 1806 to March Week 2 2011

Date Searched: Thursday, March 17th 2011

Hits: 0

1. Complete Cytogenetic Response.ti,ab.
2. Complete Cytogenic Response.ti,ab.
3. CCyR.tw.
4. Or/1-3
5. nilotinib.mp.
6. "4-methyl-N-(3-(4-methylimidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-((4-pyridin-3-ylpyrimidin-2-yl)amino)benzamide".mp.
7. tasigna.mp.
8. ((amn107 or amn-107 or amn) adj "107").mp.
9. Or/5-8
10. dasatinib.mp.
11. sprycel.mp.
12. (BMS354825 or BMS 354825 or BMS-354825).mp.
13. Or/10-12
14. 9 or 13
15. 4 and 14
16. limit 15 to english language

Database: Embase

Host: Ovid

Date Parameters: 1980 to 2011 Week 10

Date Searched: Thursday, March 17th 2011

Hits: 199

1. Complete Cytogenetic Response.ti,ab.
2. Complete Cytogenic Response.ti,ab.
3. CCyR.tw.
4. Or/1-3
5. nilotinib.mp.
6. "4-methyl-N-(3-(4-methylimidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-((4-pyridin-3-ylpyrimidin-2-yl)amino)benzamide".mp.
7. tasigna.mp.
8. ((amn107 or amn-107 or amn) adj "107").mp.
9. Or/5-8
10. dasatinib.mp.
11. sprycel.mp.
12. (BMS354825 or BMS 354825 or BMS-354825).mp.
13. Or/10-12
14. 9 or 13
15. 4 and 14

16. limit 15 to english language

Database: Cochrane Library (Reviews, DARE, CENTRAL, HTA, NHS EEDS)

Database Host: Cochrane (http://www.thecochranelibrary.com/view/0/index.html)

Date Parameters: Issue 3 of 12, Feb 2011

Date Searched: Thursday, March 17th 2011

Hits: 7 (CENTAL =7)

1. Complete Cytogenetic Response
2. Complete Cytogenic Response
3. CCyR
4. #1 or #2 or #3
5. nilotinib
6. tasigna
7. amn107
8. amn-107
9. #5 OR #6 OR #7 OR #8
10. dasatinib
11. sprycel
12. BMS354825
13. BMS 354825
14. BMS-354825
15. #10 OR #11 OR #12 OR #13 OR #14
16. #9 OR #15
17. #4 AND #16

Database: CRD all (DARE, HTA and NHS EEDS)

Database Host: Centre for Reviews and Dissemination (http://www.crd.york.ac.uk/crdweb/)

Date Parameters:

Date Searched: Thursday, March 17th 2011

Hits: 0

1. Complete Cytogenetic Response
2. Complete Cytogenic Response
3. CCyR
4. #1 or #2 or #3
5. nilotinib
6. tasigna
7. amn107

8. amn-107
9. #5 OR #6 OR #7 OR #8
10. dasatinib
11. sprycel
12. BMS354825
13. BMS 354825
14. BMS-354825
15. #10 OR #11 OR #12 OR #13 OR #14
16. #9 OR #15
17. #4 AND #16

Database: Science Citation Index Expanded SCI-EXPANDED + Conference Proceedings Citation Index- Science (CPCI-S) + Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH)

Host: ISI

Date parameters: 1900 - Present

Date Searched: Thursday, March 17th 2011

Hits: 62

1. TS=("Complete Cytogenetic Response")
2. TS=("Complete Cytogenic Response")
3. TS=("CCyR")
4. #1 OR #2 OR #3
5. TS=(nilotinib) OR TS=(tasigna) OR TS=(amn107) OR TS=(amn-107) OR TS=(amn adj "107")
6. TS=(dasatinib) OR TS=(sprycel) OR TS=(BMS354825) OR TS=(BMS 354825) OR TS=(BMS-354825)
7. #4 OR #5
8. #3 and #6

Surrogate outcomes additional search

1. Complete Cytogenetic Response.ti,ab.
2. Complete Cytogenic Response.ti,ab.
3. CCyR.tw.
4. major cytogenetic response.ti,ab.
5. major molecular response.ti,ab.
6. Surrogate adj3 outcome$1
7. Or/1-6
8. (Imatinib).mp.
9. (Gleevec or Glivec).mp.

10. (STI571 or STI-571 or (STI adj1 571)).mp.
11. Or/8-10
12. exp Interferon-alpha/
13. interferon.mp.
14. Or/12-13
15. 11 OR 14
16. 7 AND 15
17. limit 16 to english language

Results additional surrogates search	
Database	Hits
Medline	390
Medline in Process	20
Embase	828
CRD	13
Cochrane Library	40
SSCI and SCI	510
Total	**1801**
- Endnote De-Duplication	592
- Manual De-duplication	199
N=	1010

Quality of life search

1. myeloid$ leuk?emia$.mp.
2. Leukemia, Myeloid/
3. (CML).tw.
4. leukemia, myeloid, chronic-phase/
5. leukemia, myeloid, chronic, atypical, bcr-abl negative/
6. exp leukemia, myelogenous, chronic, bcr-abl positive/
7. myelogenous$ leuk?emia$.mp.
8. myelocytic$ leuk?emia$.mp.
9. leukemia, myelomonocytic, chronic/
10. major cytogenetic response.ti,ab.
11. major molecular response.ti,ab.
12. Or/1- 11
13. Philadelphia Chromosome/
14. (Philadelphia adj1 Chromosome).mp.
15. (PH1 or PH 1 adj3 Chromosome).mp.
16. Or/13-15
17. 12 or 16
18. Quality of Life/
19. ((quality adj3 life) or life quality or QOL).ti,ab.
20. (HRQL or HRQOL or HRQol).ti,ab.
21. (value adj2 life).ti,ab. or Value of Life/

22. (life adj2 qualit$3).tw.
23. (quality-adjusted life year$1 or QALY or QALYs).ti,ab. or Quality-Adjusted Life Years/
24. daly.ti,ab.
25. (disabilit$3 adj2 life).ti,ab.
26. Health Status Indicators/
27. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).tw.
28. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
29. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).tw.
30. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
31. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).tw.
32. (euroqol or euro qol or eq5d or eq 5d).tw.
33. (hye or hyes or health$ year$ equivalent$).tw.
34. hui$1.tw.
35. rosser.tw.
36. (willing$ adj2 pay).tw.
37. willing$ adj2 accept.tw.
38. standard gamble$.tw.
39. (health adj3 (utilit$3 or value$2 or preference$2)).tw.
40. (visual analog$3 scale or VAS).tw.
41. patient preference$2.tw.
42. (person$ trade-off or person$ trade off or (PTO)).ti,ab.
43. (Contingent value or contingent valuation).ti,ab.
44. (discrete choice).ti,ab.
45. (health status).ti,ab. or Health Status/
46. ((quality adj3 (wellbeing index)) or QWB).ti,ab.
47. (health utilities index or (HUI)).ti,ab.
48. (time trade off or time tradeoff or (TTO)).ti,ab.
49. (utility or utilities).ti,ab.
50. (disutil$).ti,ab.
51. (disability).tw.
52. (wellbeing or well-being or well being or qwb).ti,ab.
53. quality of well being.tw.
54. quality of wellbeing.tw.
55. Or/18-54
56. 17 and 55
57. Limit 56 to English Language
58. Limit 57 to “1990-Current”

Results quality of life search	
Database	**Hits**
Medline	540
Medline in Process	22
Embase	1000
NHS EED via CRD	32
NHS EED via the Cochrane Library	16
Psycinfo	15
Econlit	21
Total	**1646**
Endnote De-duplication	- 436
Manual De-duplication	-107
Total Hits for Screening	1103

Appendix 2: Protocol

Technology Assessment Report commissioned by the NETSCC HTA Programme on behalf of the National Institute for Health and Clinical Excellence

HTA 08/226/01

FINAL PROTOCOL

February 2011

Title of the project:

Dasatinib, nilotinib and standard dose imatinib for the first-line treatment of chronic myeloid leukaemia (including part-review of TA 70)

Name of TAR team and project 'lead'

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Plain English Summary

Chronic myeloid leukaemia is one of the blood cancers. Although it has serious consequences for the patient, the outlook with treatment is more favourable than might be expected. The typical age when chronic myeloid leukaemia becomes apparent is between 50 and 60 years and the average life expectancy is at least 15 years.

This project will examine the evidence on how good a number of drugs (dasatinib, nilotinib and standard dose imatinib) are for treating chronic myeloid leukaemia immediately after the disease has been diagnosed, as the first treatment that the patient receives. Concerning this use, the project will update the evidence previously presented to the National Institute of Health and Clinical Excellence in the case of imatinib and review for the first time evidence on dasatinib and nilotinib. The assessment will also assess whether the reviewed drugs are likely to be considered good value for money for the NHS.

Decision problem

Purpose

Chronic myeloid leukaemia (CML) is one of the blood cancers in which there is an overproduction of one type of white blood cell, the granulocytes, by the bone marrow. CML progresses slowly through three identifiable phases: the chronic phase, the accelerated phase and the blast crisis (transformation) phase, with the latter two being grouped together as advanced phase. In some cases categorisation can be difficult and there are various criteria for defining the three phases of CML.

The majority of people are diagnosed in the chronic phase. The course of the chronic phase is initially stable with most people remaining responsive to treatment; around 60% of people will remain in chronic phase and in complete cytogenic remission for at least 5 years. From the chronic phase, people with CML either go through the accelerated phase or move straight into blast crisis. The accelerated phase is a poorly defined period. Blast crisis generally lasts for between 3-6 months and is a terminal stage in which the disease transforms into a fatal acute leukaemia.

Ninety-five percent of people with CML have a specific chromosomal abnormality commonly known as the 'Philadelphia chromosome'. This is caused by an exchange of genetic material between two chromosomes (known as reciprocal translocation); between parts of the long arms of chromosome 22 and chromosome 9. It is associated with fusion of the breakpoint cluster region (BCR) and Abelson (ABL) genes and the production of an abnormal tyrosine kinase oncoprotein. BCR-ABL is the only known cause of CML.

CML is a rare disease with an incidence of approximately 1 per 100,000 people every year. It accounts for about one in six cases of leukaemia in adults. Approximately 600 to 800 people are diagnosed with CML in England and Wales each year. It has been estimated that median life expectancy is at least 15 years. The median age at diagnosis is between 50 and 60 years. NICE technology appraisal guidance 70 in 2003 recommends imatinib, a tyrosine-kinase inhibitor, as first-line treatment for people with Philadelphia chromosome positive CML in the chronic phase.[3, 4] However since then other tyrosine-kinase inhibitors have been developed and are being used in the initial treatment of CML. NICE is thus up-dating TAG 70 concerning the evidence on imatinib, and considering for the first time evidence on

dasatinib and nilotinib as first-line treatment for people with Philadelphia chromosome positive CML in the chronic phase. The question referred to NICE is, "To appraise the clinical and cost effectiveness of dasatinib, nilotinib and standard-dose imatinib within their licensed indications for the first-line treatment of chronic myeloid leukaemia (including part-review of TA70)."

In addition, outside this appraisal, NICE is currently appraising dasatinib and nilotinib for imatinib-intolerant CML. An appraisal of dasatinib, nilotinib and high-dose imatinib for imatinib-resistant CML (part-review of TA70) is also underway.

Interventions

The technology assessment report (TAR) will consider three pharmaceutical interventions:

- Dasatinib (Sprycel, Bristol Myers Squibb)
- Nilotinib (Tasigna, Novartis Pharmaceuticals)
- Imatinib (standard dose) (Glivec, Novartis Pharmaceuticals)

All of these are oral tyrosine kinase inhibitors (TKIs). These particular TKIs work by blocking specific signals in cells expressing the BCR-ABL protein, which reduces the uncontrolled proliferation of white blood cells. Imatinib and nilotinib have a high specificity for the BCR-ABL protein, whilst dasatinib acts on multiple targets.

Dasatinib (100mg daily) has a marketing authorisation for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive CML in the chronic phase. Nilotinib (400/300mg twice daily) has a marketing authorisation for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive CML in the chronic phase. Imatinib has a marketing authorisation for use in adult and paediatric patients with newly diagnosed Philadelphia chromosome positive CML for whom bone marrow transplantation is not considered as the first-line of treatment. The recommended starting dosage of imatinib is 400mg/day for patients in chronic phase CML. This is the "standard dose" for the purposes of this appraisal.

Relevant comparators

The main comparators of interest are the alternative interventions particularly:

- Dasatinib vs imatinib (standard dose)
- Nilotinib vs imatinib (standard dose
- Dasatinib vs nilotinib

Population and relevant sub-groups

Adults with newly diagnosed, chronic phase, Philadelphia chromosome positive CML. If possible newly diagnosed, chronic phase CML without genetic mutation will also be considered, clearly noting that this population is outside the marketing authorisation of the drugs of interest. No other sub-groups of interest have been identified.

- Outcomes to be addressed
- The following outcomes will be measured:
- Event-free survival
- Progression-free survival
- Time to progression
- Overall survival
- Response rates – cytogenetic, molecular and haematological
- Time to treatment failure
- Adverse effects of treatment
- Health-related quality of life

Methods for synthesis of evidence of clinical effectiveness

The assessment report will include a systematic review of the evidence for clinical effectiveness of dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia. The review will be undertaken following the general principles published by the NHS Centre for Reviews and Dissemination.[5] The components of the review question will be:

Population: Adults with chronic phase CML, naïve to any treatment specifically directed against CML

Interventions: Dasatinib or nilotinib or imatinib (standard dose). Each should be employed in accordance with the marketing authorisation and in the populations indicated in the previous paragraph, noting that CML without genetic mutation is outside the existing marketing authorisations.

Comparators: The alternative interventions, particularly imatinib (standard dose) or nilotinib where the intervention is dasatinib, or imatinib (standard dose) or dasatinib where the intervention is nilotinib.

Outcomes: All potentially relevant outcomes in the included studies will be considered, particularly those capturing:

- Event-free survival
- Progression-free survival
- Time to progression
- Overall survival
- Response rates – cytogenetic, molecular and haematological
- Time to treatment failure
- Adverse effects of treatment
- Health-related quality of life.

Search strategy

- The search strategy will comprise the following main elements:
- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers and manufacturer submissions
- Follow-up on mentions of potentially relevant on-going trials noted in previous NICE guidance on imatinib for CML.

The main electronic databases of interest will be:
MEDLINE (Ovid); PubMed; EMBASE; The Cochrane Library including the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, DARE, NHS EED and HTA databases; NRR (National Research Register); Web of Science Proceedings; Current

Controlled Trials; Clinical Trials.gov; FDA website; EMEA website. These will be searched from search end-date of the last technology appraisal report[4] on this topic October 2002.
The searches will be developed and implemented by a trained information specialist using the search strategy detailed in the technology appraisal by Thomson Coon *et al* as the starting point (see Appendix A for more information).[1]

Inclusion criteria

For the review of clinical effectiveness, in the first instance, only systematic reviews of randomised controlled trials (RCTs) and RCTs will be considered. However, if key outcomes of interest are not measured at all in the included RCTs we will discuss whether extending the range of included study designs i.e. to controlled clinical trials could be of value and feasible in the time available with NICE. The systematic reviews will be used as a source for finding further included studies and to compare with our systematic review. Systematic reviews provided as part of manufacturer's submissions will be treated in a similar manner. These criteria may be relaxed for consideration of adverse events, for which observational studies may be included.
Titles and abstracts will be examined for inclusion by two reviewers independently. Disagreement will be resolved by consensus.

Exclusion criteria

Studies will be excluded if they do not match the inclusion criteria, particularly:

- Non-randomised studies (except if agreed, in the absence of RCTs)
- Animal models
- Preclinical and biological studies
- Narrative reviews, editorials, opinions
- Non-English language papers
- Reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality.

Data extraction strategy

Data will be extracted independently by one reviewer using a standardised data extraction form and checked by another. Discrepancies will be resolved by discussion, with involvement of a third reviewer if necessary.

Quality assessment strategy

Consideration of study quality will be based on the guidelines set out by the NHS Centre for Reviews and Dissemination and include the following factors for RCTs:[5]

- Timing, duration and location of the study
- Method of randomisation
- Allocation concealment
- Blinding
- Numbers of participants randomized, excluded and lost to follow up.
- Whether intent to treat analysis is performed
- Methods for handling missing data
- Appropriateness of statistical analysis.

This framework will be adapted should other study designs subsequently be included. Quality will be assessed independently by one reviewer and checked by another, discrepancies again being resolved by discussion, with involvement of a third reviewer if necessary.

Methods of analysis/synthesis

Data will be tabulated and discussed in a narrative review. Where appropriate, meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes based on intention to treat analyses.

Meta-analysis will be carried out using fixed and random effects models, using RevMAN supplemented with STATA or equivalent software as required. Heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the χ^2 test for homogeneity and the I^2 statistic. Mixed treatment comparisons will be used as far as data allows to facilitate comparison between the drugs for which there is no direct comparison.

Methods for synthesising evidence of cost-effectiveness

Review question

For the interventions and populations indicated above, the existing evidence on cost-effectiveness will be systematically reviewed.

Search strategy

The searches will again be developed and implemented by a trained information specialist using the search strategy detailed in the technology appraisal by Thomson Coon *et al*[1] as the starting point. The range of sources searched will include those for clinical effectiveness and extend to include NHS EED and Econlit. October 2002 will again be the starting point.

Study selection criteria and procedures

The inclusion and exclusion criteria for the systematic review of economic evaluations will be identical to those for the systematic review of clinical effectiveness, except:
Non-randomised studies will be included (e.g. decision model based analyses, or analyses of patient-level cost and effectiveness data alongside observational studies).

Full cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses and cost consequence analyses will be included. (Economic evaluations which only report average cost-effectiveness ratios will only be included if the incremental ratios can be easily calculated from the published data.)

Stand alone cost analyses based in the UK NHS will also be sought and appraised.
Based on the above inclusion/exclusion criteria, study selection will be made by one reviewer. In addition, a random sample of the inclusion decisions will be checked by a second reviewer.

Study quality assessment

The methodological quality of the economic evaluations will be assessed by one reviewer according to internationally accepted criteria such as the Consensus on Health Economic Checklist (CHEC) questions developed by Evers *et al*.[6] Any studies based on decision models will also be assessed against the International Society for Pharmacoecnomics and Outcomes Research (ISPOR) guidelines for good practice in decision analytic modelling.[7]

Data extraction strategy

Data will be extracted by one researcher into two summary tables: one to describe the study design and characteristics of each economic evaluation and the other to describe the main results. The tables may need to be split into a number of sub-tables if the number of included studies is large. The entries will be checked by a second reviewer.

In the study design table the main headings will include: author and year; model type or trial based; study design (e.g. cost-effectiveness analysis [CEA], cost utility analysis [CUA] or cost-analysis); service setting/country; study population; comparators; research question; perspective, time horizon, and discounting; main costs included; main outcomes included; sensitivity analyses conducted; and other notable design features.

For modelling-based economic evaluations a supplementary Study Design table will record further descriptions of: model structure (and note its consistency with the study perspective, and knowledge of disease/treatment processes; sources of transition and chance node probabilities; sources of utility values; sources of resource use and unit costs; handling of heterogeneity in populations; evidence of validation (e.g. debugging, calibration against external data, comparison with other models).

In the results table for each comparator we will show; incremental cost; incremental effectiveness/utility and incremental cost-effectiveness ratio(s). Excluded comparators on the basis of dominance or extended dominance will also be noted. The original authors' conclusions will be noted, and also any issues they raise concerning the generalisability of results. Finally the reviewers' comments on study quality and generalisability (in relation to the TAR scope) of their results will be recorded.

Synthesis of extracted evidence

Narrative synthesis, supported by the data extraction tables, will be used to summarise the evidence base.

Economic Modelling

The general approach will be consistent with the NICE reference standard.[8] A new cost-effectiveness analysis will be carried out from the perspective of the UK NHS and Personal Social Services (PSS) using a decision analytic model. This will build on the modelling

approach used in a recent technology appraisal by PenTAG on a closely related topic and be informed by modelling approaches used in other related NICE appraisals and published cost-effectiveness literature reviewed (see Section 6).[1]

Model structure will be determined on the basis of available research evidence and clinical expert opinion.

The sources of parameter values that determine the effectiveness of the interventions being compared will be obtained from our own systematic review of clinical effectiveness or other relevant research literature. Where required parameters are not available from good quality published studies in the relevant patient group we may use data from manufacturer submissions to NICE.

Cost data will be identified from NHS and PSS reference costs or, where these are not relevant, will be extracted from published work and/or sponsor submissions to NICE. If insufficient data are retrieved from published sources, costs may be derived from individual NHS Trusts or groups of Trusts.

To reflect health related quality of life, utility values will be sought either directly from relevant research literature or indirectly from quality of life studies.

Analysis of uncertainty will focus on costs and utilities, assuming cost per QALY can be estimated. Uncertainty will be explored through one way sensitivity analysis and, if the data and modelling approach permit, probabilistic sensitivity analysis (PSA). The outputs of PSA will be presented using plots on the cost-effectiveness plane and cost-effectiveness acceptability curves.

A life-time time horizon will be taken for our analysis and both cost and outcomes (QALYs) will be discounted at 3.5%.[8]

We will collate the available relevant material necessary to inform an assessment of the applicability of the End of Life Criteria.

The TAR team cannot guarantee to consider any data or information relating to the technologies if received after 03/06/11.

Handling the company submissions

All data submitted by the manufacturers will be considered if received by the TAR team no later than 03/06/11. Data arriving after this date will not be considered.

If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission will be assessed against NICE's guidance on the Methods of Technology Appraisal and will also be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used.[8] Where the TAR team have undertaken further analyses, using models submitted by manufacturers or via de novo modelling and cost effectiveness analysis, a comparison will be made of the alternative models used for the analysis.

Expertise in this TAR team

Name	Institution	Expertise
Toby Pavey	PenTAG, Peninsula Medical School, University of Exeter	Systematic reviewing, project management and overall lead for clinical effectiveness)
Louise Crathorne	PenTAG, Peninsula Medical School, University of Exeter	Systematic reviewing
Tracey Jones-Hughes	PenTAG, Peninsula Medical School, University of Exeter	Systematic reviewing
Martin Hoyle	PenTAG, Peninsula Medical School, University of Exeter	Economic modelling and overall lead for cost-effectiveness
Kevin Marsh	Matrix Knowledge	Health economics (provisional, to be confirmed)
Chris Cooper	PenTAG, Peninsula Medical School, University of Exeter	Information science

Claudius Rudin	Royal Devon and Exeter Foundation Trust	Clinical expert
Ruth Garside	PenTAG, Peninsula Medical School, University of Exeter	Support for systematic reviews
Rob Anderson	PenTAG, Peninsula Medical School, University of Exeter	Overall project lead and project guarantor
Chris Hyde	PenTAG, Peninsula Medical School, University of Exeter	Protocol development

TAR Centre

About PenTAG:

The Peninsula Technology Assessment Group (PenTAG) is part of the Institute of Health Service Research (IHSR) at the Peninsula Medical School. PenTAG was established in 2000 and carries out independent Health Technology Assessments HTAs) for the UK HTA Programme, systematic reviews and economic analyses for the NICE (Technology Appraisal and Centre for Public Health Excellence) and systematic reviews as part of the Cochrane Collaboration Heart Group, as well as for other local and national decision-makers. The group is multi-disciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics. The Peninsula Medical School is a school within the Universities of Plymouth and Exeter. The IHSR is made up of discrete but methodologically related research groups, among which HTA is a strong and recurring theme.

Recent projects include:

- The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of TA111): a systematic review and economic model
- Dasatinib and nilotinib for imatinib-resistant or -intolerant chronic myeloid leukaemia: a systematic review and economic evaluation.
- Systematic review of the effectiveness and cost-effectiveness of weight management schemes for the under fives.

- Barriers to and facilitators for the effectiveness of multiple risk factor programmes aimed at reducing cardiovascular disease within a given population: a systematic review of qualitative research.
- Population and community programmes addressing multiple risk factors to prevent cardiovascular disease: a qualitative study into how and why some programmes are more successful than others.
- Barriers to and facilitators of conveying information to prevent first occurrence of skin cancer: a systematic review of qualitative research.
- The harmful health effects of recreational ecstasy: a systematic review of observational evidence.
- The use of surrogate outcomes in model-based cost-effectiveness analyses: a survey of UK health technology assessment reports.
- The effectiveness and cost-effectiveness of cochlear implants for severe to profound deafness in children and adults: a systematic review and economic model.
- The effectiveness and cost-effectiveness of methods of storing donated kidneys from deceased donors: a systematic review and economic model.
- Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma: a systematic review and economic model.
- The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end stage renal disease patients on dialysis. systematic review and economic evaluation.
- The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly-diagnosed high grade glioma. Systematic review and economic evaluation.
- The effectiveness and cost-effectiveness of cardiac resynchronisation therapy for heart failure. Systematic review and economic evaluation.
- Inhaled corticosteroids and long-acting beta2-agonists for the treatment of chronic asthma in adults and children aged 12 years and over: a systematic review and economic analysis.
- Inhaled corticosteroids and long-acting beta2-agonists for the treatment of chronic asthma in children under the age of 12 years: a systematic review and economic analysis.

Competing interests of authors

None

Timetable/milestones

Event	Expected due date
Final scope	04/02/11
Final protocol due	11/02/11
Consultee information meeting (CIM) (if applicable)	To be confirmed
Manufacturers' submissions	03/06/11
ERG Appraisal Report due	06/09/11
1st Appraisal Committee meeting	08/11/11
2nd Appraisal Committee meeting	08/02/12

Appendix 3: Clinical effectiveness data extraction forms

Data Extraction - DASISION

Study details[9]	Population	Arms	Outcomes
Study: Kantarjian et al. (2010) **Design:** RCT **CML phase:** Newly diagnosed chronic **Country:** Multinational **Number of centres:** Multilocation (109) **Length of follow-up:** 5-years (minimum)	**Inclusion criteria (Total randomised n = 519):** • Newly diagnosed (≤ 3-months • ECOG score at least 0 to 2 • No prior TKI treatment • Adquate hepatic and renal function **Exclusion criteria:** • Serious or uncontrolled medical disorders or cardiovascular disease • History of serious bleeding disorder, concurrent cancer, previous chemotherapy, pleural effusion at baseline	**Arms *n* = 2** **Arm 1** **Dasatinib** **N:** 259 **Drug:** Dasatinib **Starting daily dose (mg):** 100mg **Median dose:** 99mg **Dosage details:** Interuptions, reductions or esculations based on criteria (supplementary appendix) **Concurrent treatment:** Prior treatment with anagrelide or hydroxyurea allowed **Duration of treatment:** 14 months **Arm 2** **Imatinib** **N:** 260 **Drug:** Imatinib **Starting daily dose (mg):** 400mg **Median dose:** 400mg **Dosage details:** Interuptions, reductions or esculations based on criteria (supplementary appendix) **Concurrent treatment:** Prior treatment with anagrelide or hydroxyurea allowed **Duration of treatment:** 14.3 months	▪ **Primary outcome:** ▪ Complete cytogenetic response (CCyR) (within 12-months) • Defined as the absense of Ph-positive metaphases, determined on the basis of G-banding in at least 20 cells in metaphase per bone marrow sample. • Samples collected within 6 weeks of randomisation and every 3 months thereafter. • Samples with fewer than 20 cells in metaphase , assessment repeated within 4-weeks • A confirmed CCyR was defined as a CCyRdocumented on two consecutive assessments at least 28 days apart. ▪ **Secondary outcomes:** ▪ Major molecular response (MMR) (at any time) • Assessed by quantitative RT-PCR assay. Total RNA was extracted form peripheral-blood samples (5 to 10 ml) • Collected baseline and every 3-months • An MMR was defined as a BCR-ABL transcript level of 0.1%or lower on the international scale, corresponding to a reduction by at least 3-log from the standardised baseline level • Time to confirmed CCyR and MMR
Notes The disease was considered to have progressed if any of the following occurred: a doubling of the white-cell count to more than 20×10^9 per litre in the absence of complete hematologic response; a loss of complete hematologic response; an increase in Ph-positive bone marrow metaphases to more than 35%; progression to accelerated phase or blastic-phase CML; or death from any cause.			

			response • Rates of CCyR and MMR response by 12-months • Progression-free survival • Overall survival

Baseline characteristics[9]

	Dasatinib (N = 259)	Imatinib (N = 260)
Age:		
Median-yr	46	49
Range-yr	18-84	18-78
>65-yr (%)	20 (8)	24 (9)
Sex – no. (%)		
Male	144 (56)	163 (63)
Female	115 (44)	97 (37)
ECOG status – no. (%)		
0	213 (82)	205 (79)
1	46 (18)	53 (20)
2	0	2 (1)
Hasford risk – no. (%)		
Low	86 (33)	87 (33)
Intermediate	124 (48)	123 (47)
High	49 (19)	50 (19)
Time from diagnosis to randomisation – mo		
Median	1	1
Range	0.03-9.7	0.1-8.0
White-cell count — $\times 10^{-9}$/litre		
Median	25.1	23.5
Range	2.5-493.0	1.4-475.0
Platelet count — $\times 10^{-9}$/litre		
Median	448	390
Range	58-1880	29-2930
Peripheral-blood blasts — %		
Median	1.0	1.0

Range	0.0-10.0	0.0-11.0
Peripheral-blood basophils — %		
Median	4.0	4.0
Range	0.0-27.8	0.0-19.5
Bone marrow blasts — %		
Median	2.0	2.0
Range	0.0-14.0	0.0-12.0
***BCR-ABL* transcript type — no. (%)**		
b2a2 andb3a2	253 (98)	255 (98)
b2a3	1 (<1)	1 (<1)
b3a3	1 (<1)	1 (<1)
Rare variant	3 (1)	1 (<1)
Previous therapy for CML — no. (%)		
Hydroxyurea	189 (73)	190 (73)
Anagrelide	8 (3)	3 (1)
Imatinib	3 (1)	4 (2)

Results 12-months[9]

	Dasatinib (N = 259)			Imatinib (N = 260)			
Response 12-months	no.	%	(95% CI)	no.	%	(95% CI)	p
Confirmed CCyR by 12-months (i.e. two assessments)	199	77	(71-82)	172	66	(60-72)	0.007
Complete CyR 12-months (one assessment)	216	83	(78-88)	186	72	(66-72)	0.001
MMR at any time (12-month paper)	135	52	(46-58)	88	34	(28-40)	<0.0001
MMR response 12-months	119	46	(40-52)	73	28	(23-34)	<0.0001
Rates of CCyR at 12-months (Hasford risk)							
Low	81	94	–	66	76	–	–
Intermediate	97	78	–	88	72	–	–
High	38	78	–	32	64	–	–
Rates of MMR at 12-months (Hasford risk)							
Low	48	56	–	31	36	–	–
Intermediate	56	45	–	34	28	–	–
High	15	31	–	8	16	–	–

Treatment Status 12-months	Dasatinib (N = 259)	Imatinib (N = 260
	No. (%)	
Received treatment	258 (100.0)	258 (100.0)
Continue to receive treatment	218 (84.5)	210 (81.4)
Discontinued to receive treatment	40 (15.5)	48 (18.6)
Had drug-related adverse events (12-month)	13 (5.0)	11 (4.3)
Haematologic, including cytopenia (12-month)	4 (1.6)	3 (1.2)
Nonhematologic	9 (3.5)	8 (3.1)
Diseased progressed	11 (4.3)	14 (5.4)
Increased white-cell count	1 (0.4)	0
Loss of complete haematological response	0	0
Loss of major cytogenetic response	1 (0.4)	4 (1.6)
Progression to accelerated or blastic phase (12- months)	5 (1.9)	9 (3.5)
Death	4 (1.6)	1 (0.4)
Treatment failed	6 (2.3)	10 (3.9)
Did not have complete haematologic or cytogenetic response at 6-months	2 (0.8)	4 (1.6)
Had less than partial cytogenetic response at 12-months	3 (1.2)	6 (2.3)
Did not have a complete cytogenetic response at 18-months	1 (0.4)	0
Had adverse event unrelated to drug	3 (1.2)	1 (0.4)
Withdrew consent	2 (0.8)	3 (1.2)
Became pregnant	2 (0.8)	0
Did not adhere to therapy	0	2 (0.8)
Was lost to follow-up	0	3 (1.2)
Requested to discontinue	2 (0.8)	1 (0.4)
Had other reason	1 (.04)	3 (1.2)

Adverse Events 12-months	Dasatinib (N = 258)		Imatinib (N = 258)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4

	% of patients			
Cytopenia				
Neutropenia (12-month)	65	21	58	20
Thrombocytopenia (12-month)	70	19	62	10
Anemia (12-month)	90	10	84	7
Nonhaematologic adverse event				
Fluid retention (12-month)	19	1	42	1
Superficial edema (12-month)	9	0	36	<1
Pleural effusion (12-month)	10	0	0	0
Other	5	1	8	<1
Diarrhea (12-month)	17	<1	17	1
Nausea (12-month)	8	0	20	0
Vomiting (12-month)	5	0	10	0
Myalgia (12-month)	6	0	12	0
Muscle inflammation (12-month)	4	0	17	<1
Musculoskeletal pain (12-month)	11	0	14	<1
Rash (12-month)	11	0	17	1
Headache	12	0	10	0
Fatigue (12-month)	8	<1	10	0

Results cardio-vascular conditions 12-months[10]

	Dasatinib (N = 258)		**Imatinib (N = 258)**	
Response 12-months	Any CV condition	No CV condition	Any CV condition	No CV condition
	% of patients			
CCyR	86	83	76	71
MMR	63	43	26	28

Adverse Events CV 12-months	**Dasatinib (N = 259)**		Imatinib (N = 258)	
	Any CV condition	No CV condition	Any CV condition	No CV condition
	% of patients			
Cytopenia				

Neutropenia (12-month)	5	24	17	21
Thrombocytopenia (12-month)	9	21	10	11
Nonhaematologic adverse event				
Fluid retention (12-month)	35	16	57	39
Superficial edema (12-month)	16	7	48	33
Pleural effusion (12-month)	23	7	0	0
Vomiting (12-month)	12	11	21	16
Myalgia (12-month)	9	11	14	18
Rash (12-month)	12	11	21	16
Cardiac	7	5	10	2

Results additional baseline medications 12-months[11]

	Dasatinib (N = 259)			**Imatinib (N = 260)**		
Response 12-months	No. of medications			No. of medications		
	0	1-3	≥4	0	1-3	≥4
	% of patients					
CCyR	79	85	87	76	70	71
MMR	43	49	42	35	26	23

	Dasatinib (N = 259)			**Imatinib (N = 258)**		
Adverse Events 12-months	No. of medications			No. of medications		
	0	1-3	**≥4**	0	1-3	≥4
	% of patients					
Cytopenia (grade 3/4)						
Neutropenia	29	13	31	31	18	11
Thrombocytopenia	28	17	13	9	9	17
Nonhaematologic adverse event (all grades)						
Diarrhea	17	19	13	13	19	17
Fluid retention	9	23	24	41	44	37
Superficial edema	7	8	16	25	41	31
Pleural effusion	1	13	13	0	0	0

Nausea/vomiting	12	9	18	25	23	23
Myalgia	12	10	11	28	13	14
Rash	6	12	18	19	16	20

Results lymphocytosis 14-months[12]

	Lymphocytosis			
	Dasatinib (N = 259)		**Imatinib (N = 260)**	
Response 12-months	Yes	No	Yes	No
	% of patients			
CCyR	83.6	75.1	50	69.7
MCyR	91.8	83.3	50	82.8

	Lymphocytosis			
	Dasatinib (N = 259)		**Imatinib (N = 258)**	
Adverse Events 12-months	Yes	No	Yes	No
	% of patients			
Nonhaematologic adverse event (all grades)				
Fatigue	16.4	9.1	7.1	11.9
Pleural effusion	18	7.6	0	1
Myalgia	11.5	18.8	7.1	24.2

Results baseline comorbidities 12-months[13]

	Comorbidities					
	Dasatinib (N = 259)			**Imatinib (N = 260)**		
Response condition 12-months	diabetes	Hepatobiliary conditions	hyperlipidemia	diabetes	Hepatobiliary conditions	hyperlipidemia
	% of patients					

CCyR	67	78	96	69	75	79
MMR	44	56	59	15	29	32

Response age 12-months	< 46	46-65	>65	< 46	46-65	>65
	% of patients					
CCyR	88	78	85	70	70	83
MMR	45	47	50	26	30	29

	Dasatinib (N = 259)		**Imatinib (N = 258)**	
Adverse Events 12-months	No. of medications		No. of medications	
	Any CB (n = 193)	No CB (n = 66)	Any CB (n = 192)	No CB (n = 68)
	% of patients			
Cytopenia (grade 3/4)				
Neutropenia	22	17	20	21
Thrombocytopenia	18	23	9	13
Nonhaematologic adverse event (all grades)				
Diarrhea	18	17	20	10
Fluid retention	19	20	47	28
Pleural effusion	11	8	0	0
Nausea/vomiting	14	5	24	22
Myalgia	12	8	16	19
Rash	14	5	15	21

Results 18-months[14, 15]

	Dasatinib (N = 259)			**Imatinib (N = 260)**			
Response 18-months	no.	%	(95% CI)	no.	%	(95% CI)	p
Confirmed CCyR by 18-months (i.e. two assessments)	202	78	–	182	70	–	0.037
CCyR 18-months (one assessment)	218	84	–	203	78	–	0.093

MMR at any time 18-month abstract	148	57	–	107	41	–	<0.001
MMR response 18-months	145	56	–	96	37	–	<0.001
CMR 18-months(BCR-ABL ≤0.0032%)	34	13	–	18	7	–	–
Rates of CCyR at 18-months (Hasford risk)							
Low	76	92	–	63	72	–	–
Intermediate	88	71	–	87	71	–	–
High	36	73	–	32	64	–	–
Rates of MMR at 18-months (Hasford risk)							
Low	54	63	–	42	48	–	–
Intermediate	69	56	–	49	40	–	–
High	25	51	–	15	30	–	–
Progression-free survival at 18-months	–	94.9	–	–	93.7	–	–
Overall survival at 18-months	–	96	–	–	97.9	–	–

Treatment Status 18-months	**Dasatinib (N = 259)**	**Imatinib (N = 260**
	No. (%)	
Received treatment	258 (100.0)	258 (100.0)
Continue to receive treatment	209 (81)	206 (80)
Discontinued to receive treatment	49 (19)	52 (20)
Had drug-related adverse events (18-month)	15 (6)	10 (4)
Haematologic, including cytopenia (12-month)	6 (2.3)	3 (1.2)
Progression to accelerated or blastic phase (18- months)	6 (2.3)	9 (3.5)

	Dasatinib (N = 258)		**Imatinib (N = 258)**	
Adverse Events 18-months	All grades	Grade 3 or 4	All grades	Grade 3 or 4
	% of patients			
Cytopenia				
Neutropenia (18-month)	–	22	–	20
Thrombocytopenia (18-month)	–	19	–	10
Anemia (18-month)	–	11	–	7
Bleeding	–	0.8	–	1.2

Nonhaematologic adverse event					
Fluid retention (18-month)	23	–	43	–	
Superficial edema (18-month)	10	–	36	–	
Pleural effusion (18-month)	12	–	0	–	
Diarrhea (18-month)	18	–	19	–	
Nausea (18-month)	9	–	21	–	
Vomiting (18-month)	5	–	10	–	
Myalgia (18-month)	6	–	12	–	
Muscle inflammation (18-month)	4	–	19	–	
Musculoskeletal pain (18-month)	12	–	16	–	
Rash (18-month)	11	–	17	–	
Fatigue (18-month)	8	–	11	–	

Results 24-months[16]

	Dasatinib (N = 259)			**Imatinib (N = 260)**			
Response 24-months	no.	%	(95% CI)	no.	%	(95% CI)	p
Confirmed CCyR by 24-months (i.e. two assessments)	207	80	–	192	74	–	0.037
CCyR 24-months (one assessment)	223	86	–	213	82	–	0.23
MMR at any time 24-month	166	64	–	120	46	–	<0.001
CMR 24-months(BCR-ABL ≤0.0032%)	44	17	–	21	8	–	–
Rates of MMR at 24-months (Hasford risk)							
Low	63	73	–	49	56	–	–
Intermediate	76	61	–	62	50	–	–
High	28	57	–	19	38	–	–
Progression-free survival at 24-months	–	93.7	–	–	92.1	–	–
Overall survival at 24-months	–	95.3	–	–	95.2	–	–

Treatment Status 24-months	**Dasatinib (N = 259)**	**Imatinib (N = 260**
	No. (%)	
Received treatment	258 (100.0)	258 (100.0)

Continue to receive treatment	199 (77)	194 (75)
Discontinued to receive treatment	59 (23)	64 (25)
Had drug-related adverse events (18-month)	18 (7)	12 (5)
Haematologic, including cytopenia (12-month)	6 (2.3)	4(1.6)
Nonhematologic	12 (5)	8 (3)
Diseased progressed	14 (5)	17 (7)
Progression to accelerated or blastic phase (18- months)	9 (3.5)	15 (5.8)
Death	16 (6)	14 (5)
Treatment failed	8 (3)	11 (4)

	Dasatinib (N = 258)		**Imatinib (N = 258)**	
Adverse Events 24-months	All grades	Grade 3 or 4	All grades	Grade 3 or 4
	% of patients			
Cytopenia				
Neutropenia (18-month)	–	24	–	21
Thrombocytopenia (18-month)	–	20	–	11
Anemia (18-month)	–	11	–	8
Bleeding	–	< 1	–	1
Nonhaematologic adverse event				
Fluid retention (18-month)	25	–	43	–
Superficial edema (18-month)	11	–	36	–
Pleural effusion (18-month)	14	–	0	–
Diarrhea (18-month)	49 (19)	–	21	–
Nausea (18-month)	26 (10)	–	23	–
Vomiting (18-month)	13 (5)	–	10	–
Myalgia (18-month)	–	–	12	–
Muscle inflammation (18-month)	10 (4)	–	19	–
Musculoskeletal pain (18-month)	31 (12)	–	16	–
Rash (18-month)	28 (11)	–	19	–
Fatigue (18-month)	23 (9)	–	11	–

Quality appraisal - DASISION	
Is a power calculation provided?	NO
Is the sample size adequate?	NOT REPORTED
Was ethical approval obtained?	YES
Were the study eligibility criteria specified?	YES
Were the eligibility criteria appropriate?	YES
Were patients recruited prospectively?	YES
Was assignment to the treatment groups really random?	NOT REPORTED
Were groups stratified?	YES
Was the treatment allocation concealed?	NO
Are adequate baseline details presented?	YES
Are the participants representative of the population in question?	YES
Are groups similar at baseline?	YES
Are any differences in baseline adequately adjusted for in the analysis?	YES
Are outcome assessors blind?	NO
Was the care provider blinded?	NO
Are outcome measures relevant to research question?	YES
Are data collection tools shown or known to be valid for the outcome of interest?	YES
Is compliance with treatment adequate?	YES
Are withdrawals/dropouts adequately described?	YES
Are all patients accounted for?	YES
Is the number randomised reported?	YES
Are protocol violations specified?	YES
Are data analyses appropriate?	YES
Is analysis conducted on an ITT basis?	YES
Are missing data appropriately accounted for?	YES
Were any subgroup analyses justified?	N/A
Are the conclusions supported by the results?	YES
Conflict of interest declared?	YES

Data extraction - ENESTnd

Study details[17]	**Population**	**Arms**	**Outcomes**
Study: Saglio (2010) **Design:** RCT **CML phase:** Newly diagnosed chronic **Country:** USA, UK **Number of centres:** Multilocation (63) **Length of follow-up:** 5-years (minimum) **Notes**	**Inclusion criteria (Total randomised n = 846):** • Newly diagnosed (≤ 6-months) • ECOG score of at least 2 • No prior TKI treatment (except imatinib ≤ 2-weeks) • Adquate organ function ▫ **Exclusion criteria:** • Impaired cardiac function • Medication affecting liver enzymes or QT interval prohibited	**Arms *n* = 3** **Arm 1** **Nilotinib** **N:** 282 **Drug:** Dasatinib **Starting daily dose (mg):** 300mg twice daily **Median dose:** 592mg **Dosage details:** Patients could discontinue therapy because of treatment failure (including progression), intolerable side effects, or other reasons. Dose escalation of nilotinib was not permitted. **Concurrent treatment:** Prior treatment with anagrelide or hydroxyurea allowed **Duration of treatment:** 14 months **Arm 2** **Nilotinib** **N:** 281 **Drug:** Nilotinib **Starting daily dose (mg):** 400mg twice daily **Median dose:** 779mg **Dosage details:** Patients could discontinue therapy because of treatment failure (including progression), intolerable side effects, or other reasons. Dose escalation of nilotinib was not permitted.	▪ **Primary oucome:** ▪ Major molecular response (MMR) (at 12-months) • An MMR was defined as a BCR-ABL transcript level of 0.1%or lower on the international scale, corresponding to a reduction by at least 3-log from the standardised baseline level • Assessed by means of RQ-PCR • Samples collected at baseline, monthly for 3 months, and every 3 months thereafter. ▪ **Secondary outcomes:** ▪ Complete cytogenetic repsonse (CCyR) (by 12-months) • Bone marrow cytogenetic analysis performed at baseline and at months 6, 12, 18, 24 • Complete blood counts measured at baseline, weeks 1, 2 and 4, monthly until month 6, then every 3 months. ▪ ▪ Rate of MMR and CCyR over time ▪ Time to and duration of MMR and CCyR. Rate of BCR-ABL/ABL ratio of ≤0.01% and ≤0.0032% by international scale at 12 months. Event-free survival (EFS; event defined as loss of CHR, loss of PCyR, loss of CCyR, progression to AP/blast

		Concurrent treatment: Prior treatment with anagrelide or hydroxyurea allowed **Duration of treatment:** 14 months **Arm 3** **Imatinib** **N:** 283 **Drug:** Nilotinib **Starting daily dose (mg):** 400mg **Median dose:** 400mg **Dosage details:** Patients could discontinue therapy because of treatment failure (including progression), intolerable side effects, or other reasons. An escalation in the imatinib dose to 400 mg twice daily was permitted in patients who had a suboptimal response or treatment failure, as defined by the European LeukemiaNet. **Concurrent treatment:** Prior treatment with anagrelide or hydroxyurea allowed **Duration of treatment:** 14 months	crisis [BC], or death from any cause during treatment). Progression free survival (defined as progression to AP/BC or death from any cause during treatment). Progression to AP/BC (defined as progression to AP/BC or CML-related death). Overall survival. Safety. ▪ Dose intensity. ▪ Pharmacokinetics. ▪ ▪

Baseline characteristics[17]			
	Nilotinib (300mg; N = 282)	Nilotinib (400mg; N = 281)	Imatinib (400mg; N = 283)
Age:			
Median (range) -yr	47 (18-85)	47 (18-81)	46 (18-80)
Sex – no. (%)			
Male	158 (56)	175 (62)	158 (56)
Race or ethnic group – no. (%)			
Asian[17]	76 (27)	66 (23)	71 (25)
Black	12 (4)	11 (4)	7 (2)
White	170 (60)	185 (66)	187 (66)
Other	24 (9)	19 (7)	18 (6)
Sokal risk group– no. (%)			
Low	103 (37)	103 (37)	104 (37)
Intermediate	101 (36)	100 (36)	101 (36)
High	78 (28)	78 (28)	78 (28)
Time since diagnosis (range) – days			
Median	31 (0-182)	31 (3-189)	28 (1-183)
White-cell count — $\times 10^{-3}/mm^3$			
Median	23 (2-247)	23 (2-435)	26 (3-482)
Platelet count — $\times 10^{-3}/mm^3$			
Median	424 (90-3880)	347 (103-1819)	375 (66-2232)
Haemoglobin (range) — g/dl			
Median	12.0 (5.5-17.6)	12.0 (6.2-17.6)	12.2 (6.4-17.1)
Spleen size ≥ 10 cm below costal margin — no. (%)	31 (11)	34 (12)	40 (14)
Chromosomal abnormalities in addition to the Philadelphia Chromosome	34 (12)	44 (16)	31 (11)
Previous therapy for CML — no. (%)	2 (1)	1 (<1)	4 (1)

Results 12-months[17, 18]											
	Nilotinib (300mg)				Nilotinib (400mg)				Imatinib (400mg)		
Response 12-months[17, 18]	no.	%	(95% CI)	p	no.	%	(95% CI)	p	no.	%	(95% CI)
Rates of MMR at 12-months (ITT)	125/282	44	–	0.001	121/281	43	–	0..001	62/283	22	–
Rates of MMR at 12-months (assessed)	124/242	51	–	–	120/240	50	–	–	63/235	27	–
Rates of MMR at 15-months (assessed)	87/154	57	–	–	88/155	57	–	–	48145	33	–
Rates of MMR at 18-months (assessed)	50/83	60	–	–	44/78	56	–	–	23/89	26	–
Rates of CCyR at 12-months (ITT)	226/282	80	–	0.001	220/281	78	–	0.001	184/283	65	–
Rates of CCyR at 12-months (assessed)	226/244	93	–	–	219/236	93	–	–	184243	76	–
Rates of CCyR at 12-months (high Sokal risk)	58/78	74	–	–	49/78	63	–	–	38/78	49	–
BCR-ABL ≤ 0.1%[a]	–	57	–	–	–	54	–	–	–	30	–
BCR-ABL ≤ 0.01%[a]	–	24	–	–	–	21	–	–	–	10	–
BCR-ABL ≤ 0.0032%[a]	–	13	–	–	–	12	–	–	–	4	–
MMR by Sokal group											
Low	–	41	–	0.0238	–	53	–	<.0001	–	26	–
Intermediate	–	51	–	<.0001	–	40	–	0.0085	–	23	–
High	–	41	–	0.0008	–	32	–	0.0252	–	17	–
Event-free survival	–	97.6	–	0.0898	–	99.6	–	0.0012	–	95.7	–

Treatment Status 12-months[17]	Nilotinib (300mg)	Nilotinib (400mg)	Imatinib (400mg)
	No. (%)		
Received treatment	279 (99)	288(99)	279 (99)
Continue to receive treatment	236 (84)	230(82)	224 (79)
Discontinued to receive treatment	46 (16)	51 (18)	59 (21)
adverse event(s)	13 (5.0)	26 (9)	21 (7)
Abnormal laboratory value(s)	6 (2)	5 (2)	3 (1)
Abnormal test procedure result(s)	0 (0)	1 (<1)	1 (<1)
Subject's condition no longer requires drug	1 (<1)	0 (0)	0 (0)
Withdrew consent	6 (2)	5 (2)	3 (1)
Was lost to follow-up	2 (<1)	2 (<1)	1 (<1)

Death	2 (<1)	0 (0)	0 (0)
Diseased progressed	2 (<1)	2 (<1)	10 (4)
Protocol deviation	4 (1)	5 (2)	4 (1)
Suboptimal response/ treatment failure	10 (4)	5 (2)	16 (6)

Adverse Events 12-months[17]	Nilotinib (300mg; N = 279)		Nilotinib (400mg; N = 277)		Imatinib (400mg; N = 280)	
	All grades	**Grade 3 or 4**	**All grades**	**Grade 3 or 4**	**All grades**	**Grade 3 or 4**
	No. of patients (%)					
Haematologic						
Neutropenia	120 (43)	33 (12)	106 (38)	27 (10)	189 (68)	56 (20)
Thrombocytopenia	133 (48)	28 (10)	136 (49)	33 (12)	156 (56)	24 (9)
Anemia	105 (38)	9 (3)	105 (38)	9 (3)	132 (47)	14 (5)
Nonhaematologic adverse event						
Rash	86 (31)	1 (<1)	100 (36)	7 (3)	32 (11)	4 (1)
Headache	39 (14)	3 (1)	58 (21)	3 (1)	23 (8)	0
Nausea	32 (11)	1 (<1)	54 (19)	3 (1)	86 (31)	0
Alopecia	22 (8)	0	36 (13)	0	11(4)	0
Pruritus	41 (15)	1 (<1)	36 (13)	1 (<1)	15 (5)	0
Myalgia	27 (10)	1 (<1)	28 (10)	0	28 (10)	0
Fatigue	30 (11)	0	25 (9)	2 (1)	22 (8)	1 (<1)
Vomiting	13 (5)	0	24 (9)	3 (1)	40 (14)	0
Diarrhea	22 (8)	2 (1)	18 (6)	0	60 (21)	3 (1)
Muscle spasm	20 (7)	0	17 (6)	2 (1)	67 (24)	2 (1)
Peripheral edema	14 (5)	0	15 (5)	0	38 (14)	0
Eyelid edema	2 (1)	0	5 (2)	1(<1)	37 (13)	1 (<1)
Periorbital edema	1 (<1)	0	2 (1)	0	34 (12)	0
Biochemical abnormality						
Increased total bilrubin	149 (53)	10 (4)	171 (62)	21 (8)	27 (10)	1 (<1)
Increased alkaline phosphate	59 (21)	0	76 (27)	0	92 (33)	1 (<1)
Decreased phosphate	88 (32)	13 (5)	94 (34)	13 (5)	126 (45)	21 (8)
Increased glucose	100 (36)	17 (6)	113 (41)	10 (4)	57 (20)	0
Increased lipase	67 (24)	16 (6)	80 (29)	16 (6)	30 (11)	9 (3)
Increase amylase	42 (15)	1 (<1)	51 (18)	3 (1)	35 (12)	4 (1)

Increased creatinine	13 (5)	0	15 (5)	0	36 (13)	1 (<1)
Increased ALT	184 (66)	11 (4)	203 (73)	25 (9)	57 (20)	7 (2)
Increased AST	112 (40)	4 (1)	134 (48)	8 (3)	65 (23)	3 (1)

Results hospitalisation 12-months[19]

	Nilotinib (300; N = 282)	p	Nilotinib (400; N = 281)	p	Imatinib (N = 283)
Number of hospitalisations	48		74		57
Total hospital days	434		591		642
Length of stay, days					
Mean (SD)	9.04 (23.95)		7.99 (15.20)		11.26 (15.98)
Hospital days per 1,000 patient days	2.72	0.057	3.69	0.61	3.99

Time off from usual activities, average hours per week

	Nilotinib (300; N = 282)		p	Nilotinib (400; N = 281)		p	Imatinib (N = 283)	
	N	Mean (SD)		N	Mean (SD)		N	Mean (SD)
Baseline	247	9.33 (18.40)	0.882	240	9.20 (19.79)	0.870	234	10.02 (22.08)
3-month change for baseline	225	-5.03 (19.98)	0.218	210	-2.85 (19.78)	0.544	206	-5.83 (20.58
12-month change from baseline	195	-6.66 (20.57)	0.799	190	-6.17 (15.76)	0.570	171	-7.06 (26.63)

Results cardiac safety[20]

	Nilotinib (300; N = 279)	Nilotinib (400; N = 277)	Imatinib (N = 280)
QT prolongation, % of patients			
Absolute QTcF >500 msec	0	0	0
QTcF increase >30 msec	26	26	18
QTcF increase >60 msec	0.4	0.7	0
Mean (%)LVEF change (SD)			
6-month	+1.2 (1.71)	+1.2 (1.77)	+1.2 (2.02)
12-month	+1.3 (2.33)	+1.3 (1.99)	+1.3 (2.29)
Discontinued therapy			

QT prolongation	0		0	0
LVEF	0		0	0
Ischemic heart disease event	1		2	<1
Left ventricular dysfunction	1		4	<1

Response results 18-month[21]

	Nilotinib (300; N = 282)	p	Nilotinib (400; N = 281)	p	Imatinib (N = 283)
	% of patients				
MMR at any time, % of patients	66	<.0001	62	<.0001	40
Sokal group, % of patients					
Low	70		69		51
Intermediate	67		63		39
High	59		51		28
Complete molecular response (BCR-ABL ≤ 0.0032%), % of patients	21	<.0001	17	<.0001	6
CCyR, % of patients	85	<.001	82	<.017	74
Suboptimal response (12-months)	2		2		11
Treatment failure (12-months)	3		2		8
Estimated OS (at 18-months), %	98.5	0.28	99.3	0.03	96.9
	No. of patients (%)				
Progression to AP/BC					
Excluding clonal evolution, n (%)	2 (0.7)	<.006	1 (0.4)	<.003	12 (4.2)
including clonal evolution, n (%)	2 (0.7)	<.001	3 (1.2)	<.002	17 (6.9)
Total deaths, patient (n)	5		2		9
CML-related deaths	2		1		8

Results 24-months[22, 23]

	Nilotinib (300mg)				Nilotinib (400mg)				Imatinib (400mg)		
Response 24-months[22, 23]	no.	%	(95% CI)	p	no.	%	(95% CI)	p	no.	%	(95% CI)
Rates of MMR at 24-months (ITT)	175/282	62	–	<0.001	165/281	59	–	<0.001	105/283	37	–

MMR at any time 24-months (ITT)	201/282	71	–	<0.001	187/281	67	–	<0.001	124/283	44	–
Rates of CCyR at 24-months (ITT)	245/282	87	–	0.001	238/281	85	–	0.017	218/283	74	–
BCR-ABL ≤ 0.0032% [a]	–	26	–	<0.001	–	21	–	–	–	10	0.004
MMR by Sokal group											
Low	–	73	–	0.0238	–	74	–	<.0001	–	65	–
Intermediate	–	74	–	<.0001	–	67	–	0.0085	–	44	–
High	–	65	–	0.0008	–	56	–	0.0252	–	32	–
Progression free survival	–	98	–	0.07	–	97.7	–	0.04	–	95.2	–
Overall Survival	–	97.4	–	0.64	–	97.8	–	0.21	–	96.3	–

Treatment Status 24-months[23]	Nilotinib (300mg)	Nilotinib (400mg)	Imatinib (400mg)
	No. (%)		
Received treatment	279 (99)	288(99)	279 (99)
Continue to receive treatment	210 (75)	220(78)	191 (68)
Discontinued to receive treatment	72 (25)	61 (22)	92 (32)
Death	3 (1)	1 (<1)	0 (0)
Diseased progressed	2 (<1)	4 (1)	12 (4)
Protocol deviation	4 (1)	5 (2)	4 (1)
Suboptimal response/ treatment failure	24 (9)	5 (2)	36 13)

Adverse Events 24-months[22]	Nilotinib (300mg; N = 279)		Nilotinib (400mg; N = 277)		Imatinib (400mg; N = 280)	
	All grades	**Grade 3 or 4**	**All grades**	**Grade 3 or 4**	**All grades**	**Grade 3 or 4**
	No. of patients (%)					
Haematologic						
Neutropenia	–	33 (12)	–	31 (11)	–	59 (21)
Thrombocytopenia	–	28 (10)	–	33 (12)	–	25 (9)
Anemia	–	11 (4)	–	11 (4)	–	14 (5)
Nonhaematologic adverse event						

Rash	86 (31)	1 (<1)	89 (32)	<1	103 (37)	8 (3)
Headache	39 (14)	3 (1)	39 (14)	1	61 (22)	1
Nausea	32 (11)	1 (<1)	39 (14)	<1	59 (21)	1
Alopecia	22 (8)	0	25 (9)	0	36 (13)	0
Pruritus	41 (15)	1 (<1)	45 (16)	<1	36 (13)	<1
Myalgia	27 (10)	1 (<1)	28 (10)	<1	28 (10)	0
Fatigue	30 (11)	0	31 (11)	0	25 (9)	<1
Vomiting	13 (5)	0	14 (5)	0	25 (9)	1
Diarrhea	22 (8)	2 (1)	22 (8)	<1	20 (7)	0
Muscle spasm	20 (7)	0	22 (8)	0	20 (7)	<1
Peripheral edema	14 (5)	0	14 (5)	0	17 (6)	0
Eyelid edema	2 (1)	0	<1	0	6 (2)	<1
Periorbital edema	1 (<1)	0	<1	0	1	0

Quality appraisal - ENESTnd	
Is a power calculation provided?	YES
Is the sample size adequate?	NOT REPORTED
Was ethical approval obtained?	YES
Were the study eligibility criteria specified?	YES
Were the eligibility criteria appropriate?	YES
Were patients recruited prospectively?	YES
Was assignment to the treatment groups really random?	NOT REPORTED
Were groups stratified?	YES
Was the treatment allocation concealed?	NO
Are adequate baseline details presented?	YES
Are the participants representative of the population in question?	YES
Are groups similar at baseline?	YES
Are any differences in baseline adequately adjusted for in the analysis?	YES
Are outcome assessors blind?	NO
Was the care provider blinded?	NO
Are outcome measures relevant to research question?	YES
Are data collection tools shown or known to be valid for the outcome of interest?	YES
Is compliance with treatment adequate?	YES
Are withdrawals/dropouts adequately described?	YES
Are all patients accounted for?	YES
Is the number randomised reported?	YES
Are protocol violations specified?	YES
Are data analyses appropriate?	YES
Is analysis conducted on an ITT basis?	YES
Are missing data appropriately accounted for?	YES
Were any subgroup analyses justified?	N/A
Are the conclusions supported by the results?	YES
Conflict of interest declared?	YES

Appendix 4: Surrogate data extraction forms

General characteristics								
Authors Year	**Country**	**Year**	**Design**	**No. of centers**	**Treatment**	**No. of arms**	**Follow-up**	**Note**
De Lavallade et al.[24] 2008	UK	2000-2006	Cohort single arm	1	Imatinib 400mg/d	1	Median: 38months Range: 12 to 85	

Population				
Authors Year	**Inclusion Criteria**	**Exclusion Criteria**	**Sample size**	**Note**
De Lavallade et al. 2008	Consecutive adult patients with BCR-ABL-positive CML in CP. Treatment started within 6 months of diagnosis.	No prior treatment for leukemia other than hydroxyurea.	204	17 of these patients included in IRIS trial.

Subsequent treatment and treatment duration		
Authors Year	**Criteria for interruption**	**Patients on treatment and subsequent therapy**
De Lavallade et al. 2008	"Dose was reduced in the presence of grades 3 to 4 toxicity with the aim of maintaining imatinib at or greater than 300 mg/d. Initially, the criteria for dose escalation were applied as in the IRIS study,1,3 but as more evidence emerged, dose increases reflected those recommended by the European LeukemiaNet.7 Similarly, the criteria for discontinuing Imatinib varied as new tyrosine kinase inhibitors became available."	"At the time of data analysis 54 patients (26%) had permanently discontinued imatinib after a median time of 15.5 months (range, 0.5 to 64 months). Reasons for discontinuation included adverse events (n=7), loss of CHR or progression to accelerated or blastic phase (n=26), loss of MCyR (n=3), and failure to achieve MCyR while still in CHR (n=18). After discontinuing imatinib, 18 patients underwent allogeneic stem-cell transplantation (four while still in CP) and the remaining 36 received one or more of hydroxyurea, interferon-α, dasatinib, nilotinib, or other agents. The dose of imatinib was increased in 75 patients (37%)."

Surrogate Outcomes					
Authors Year	**Surrogate outcomes**	**Surrogate outcomes (definition)**	**Results**	**Time points**	**Note**
De Lavallade et al. 2008	**CCyR**	The failure to detect any Ph+ metaphases in two consecutive bone marrow examinations with a minimum of 30 metaphases examined	1year cumulative incidence: 57.4% 5year cumulative incidence: 82.7% (95%CI: 76.1%-87.8%) 159(77%) (median time, 7 months; range, 3 to 55.4) but lost in 14(8.8%)	Bone marrow morphology and cytogenetics were assessed at diagnosis and every 3 months until patients achieved CCyR.	Cumulative incidence of best CCyR according to cytogenetic response at 3 and 6 months reported.
	MCyR	Combination of complete and partial cytogenetic response (≤35% Ph+ metaphases)	1year cumulative incidence: 71.1% 5year cumulative incidence: 85.1% (95%CI:82.8%-93.0%)		
	Loss of CCyR	Detection of one or more Ph+ marrow metaphases, confirmed by a subsequent study	14(8.8%)		
	MMR	A 3-log reduction in BCR-ABL transcript levels on the basis of two consecutive molecular studies	1year cumulative incidence: 12.3% 5year cumulative incidence: 50.1% (95%CI: 41.5%-58.6%) 80(39%) (median time, 15.7 months; range, 2 to 73) but lost in 8(10%)	BCR-ABL transcripts in the blood were measured at 6- to 12-week intervals.	Samples obtained for quantitative real-time PCR were also analyzed for kinase domain mutations.
	CMR	Two consecutive samples with no detectable transcripts	1year cumulative incidence: 0.5% 5year cumulative incidence: 8.3% 10 (5%) (median time, 30.7 months; range, 12 to 67.4) but lost in 4(40%)		

Patient relevant outcomes					
Authors Year	**Patient-relevant outcomes**	**Patient-relevant outcomes (definition)**	**Results**	**Results stratified by level of response**	**Note**
De Lavallade et al. 2008	**PFS**	Survival without evidence of accelerated or blastic phase disease	5year probability: 2.7%	At 1 year: 121patients with CCyR PFS: 96% 72patients failed to achieve CCyR PFS: 74% At 5 year: 121patients with CCyR PFS: 96% 72patients failed to achieve CCyR PFS: 74%	No significant difference in PFS or OS if patients achieving CCyR are subclassified by MMR
	EFS	Death from any cause, progression resulting from CP, loss of CHR, loss of MCyR or increasing white cell count	5year probability: 81.3% (95%CI: 73.0%-87.5%) 5year probability[IV]: 62.7% (95%CI: 55.0%-70.2%)		
	OS		5year probability: 83.2%	At 1 year: 121patients with CCyR OS: 98% 72patients failed to achieve CCyR OS: 74.1%	

[IV] Include in the definition 18 patients discontinuing Imatinib because they failed to achieve a MCyR but did not lose CHR and 7 patients intolerant to Imatinib.

General characteristics								
Authors Year	**Country**	**Year**	**Design**	**No. of centers**	**Treatment**	**No. of arms**	**Follow-up**	**Note**
Druker et al.[25] 2006 (IRIS)	International	2000-2001	Randomized clinical trial	Multicenter	Imatinib 400mg/d orally or subcutaneous IFN-α	2	Median: 60 months Mean 50±19 5-year follow up	

Population				
Authors Year	**Inclusion Criteria**	**Exclusion Criteria**	**Sample size**	**Note**
Druker et al. 2006	Eligible patients had to be between 18 and 70 years of age, must have been diagnosed with Ph-positive CML in CP within 6 months before study entry.	No previous treatment except for HU or anagrelide.	1106 (553 in each arm)	359 (65%) patients had crossed over to Imatinib, 14 (3%) had switched to the IFN therapy. 382 patients continued Imatinib first line, 18% of them with different dosage. Focus on Imatinib 1st-line treated patients.

Subsequent treatment and treatment duration		
Authors Year	**Criteria for interruption**	**Patients on treatment and subsequent therapy**
Druker et al. 2006	"Patients receiving imatinib who did not have a complete hematologic response within 3 months or whose bone marrow contained more than 65% Ph-positive cells at 12 months could have a stepwise increase in the dose of imatinib to 400 mg orally twice daily as long as there were no dose-limiting adverse events."	382/553 (69%) in the imatinib group continued with their initial assigned treatment. 14/553 (3%) switched to Interferon. Other 157/553 (28%) discontinued 1st-line treatment: 23 (4%) patients discontinued therapy for AE, 25 (5%) withdraw consent, 10 (2%) died, 15 (3%) violated the protocol, 5 (<1%) loss to follow-up, 16(3%) had stem cell transplantation. In patients remaining in first line therapy 6% received 600mg/d, 4% received 800mg/d, 8% received less than 400mg/d. "

Surrogate outcomes					
Authors Year	**Surrogate outcomes**	**Surrogate outcomes (definition)**	**Results**	**Time points**	**Note**
Druker et al. 2006	**CCyR**	No Ph-positive metaphases on the basis of G-banding in at least 20 cells in metaphase per sample	At 12months: 382/553 (69%) At 60 months: 368/382 (96%) 481/553 (87%)		
	MCyR	Complete plus partial responses on the basis of G-banding in at least 20 cells in metaphase per sample	At 12months: 470/553 (85%) At 60 months: 509/553 (92%)		
	PCyR	1% to 35% Ph-positive metaphases on the basis of G-banding in at least 20 cells in metaphase per sample			
	MR	Results were expressed as "log reductions" below a standardized baseline derived from a median ratio of BCR-ABL to BCR obtained from 30 untreated patients with chronic-phase CML.	At 1 year: 66/124 (53%) with ≥-3log 27/124 (22%) with ≥-4log At 4 years: 99/124 (80%) with ≥-3log 51/124 (41%) with ≥-4log	Signs of a molecular response were sought every 3 months after a CCyR was obtained	

Patient relevant outcomes					
Authors Year	**Patient-relevant outcomes**	**Patient-relevant outcomes (definition)**	**Results**	**Results stratified by level of response**	**Note**
Druker et al. 2006	**PFS**	Survival without evidence of accelerated or blastic phase disease	At 60 months: 93% (95% CI, 90 to 96) 35/553 (6%) progressed to AP or BP Annual rate of progression: 1.5% 2.8% 1.6% 0.9% 0.6%	At 60 months: 97% (95%CI 94 to 99) Among 350 patients with CCyR at 12 months 93% (95%CI 87 to 99) among 86 patients with PCyR 81% (95%CI 70 to 92) among 73 patients without MCyR 100% among 139 patients with CCyR and -3log BCR-ABL transcripts at 12 or 18 months 98% among 54 patients with CCyR and less than -3log BCR-ABL transcripts at 18 months 87% among 88 patients without CCyR Annual rate of progression for patients in CCyR: 2.1% 0.8% 0.3% 0%	Analyses of survival and event-free survival, using the Kaplan–Meier method according to the ITT principle and using all data available, regardless of whether crossover occurred. Survival graphs (Fig. 2, Fig. 3, Fig. 4) * After censoring for patients who had died for causes unrelated to CML or transplantation
	EFS	Events were defined by the first occurrence of any of the following: death from any cause during treatment, progression to the AP or BP of CML, or loss of a complete hematologic or	At 60 months: 83% (95%CI, 79 to 87)		

		major cytogenetic response			
	OS		At 60 months: 89% (95%CI 86 to 92) 95% (95%CI 93 to 98)*		

General characteristics								
Authors Year	**Country**	**Year**	**Design**	**No. of centers**	**Treatment**	**No. of arms**	**Follow-up**	**Note**
Hehlmann et al.[26] 2011	Germany	July 2002 to April 2009	RCT (randomized treatment optimization trial)	Multicenter	Monotherapy imatinib 400mg/d versus imatinib 400 mg/d combined with IFN-_ versus imatinib 800 mg/d	3	Median follow-up was 28 months in the imatinib 800 mg/d arm, 43 months in the 400 mg/d arm, and 48 months in the imatinib plus IFN- arm.	The 800 mg/day Imatinib arm started later

Population				
Authors Year	**Inclusion Criteria**	**Exclusion Criteria**	**Sample size**	**Note**
Helmann 2011	Newly diagnosed patients with CP-CML		1012	Median age 54 Range (16-88) for 325 people in Imatinib 400mg/d arm

Subsequent treatment and treatment duration		
Authors Year	**Criteria for interruption**	**Patients on treatment and subsequent therapy**
Helmann 2011	Treatment interruptions were discouraged and permitted only for grades 3 and 4 adverse events. Simultaneous CYP3A4 inhibitors were avoided. If imatinib treatment failed, either stem-cell transplantation or risk-adapted drug treatment was recommended. After approval of second-generation tyrosine kinase inhibitors (TKIs) for 2nd-line treatment, either nilotinib or dasatinib was recommended. In older patients who were not eligible for transplantation, hydroxyurea was recommended if second-generation TKIs were not effective.	The data here refers to the 400mg/d Imatinib arm. 325 randomized patients, 43 months median follow-up. At 1 year, patients still receiving standard dose Imatinib were 271. 24 patients discontinued treatment at 12 mo, 4 died, 4 underwent SCT, 8 received 2nd generation TKI, 5 received HU/IFN. 236 (73%) were under 400mg/d Imatinib at latest follow up.

Surrogate outcomes					
Authors Year	**Surrogate outcomes**	**Surrogate outcomes (definition)**	**Results**	**Time points**	**Note**
Helmann 2011	**CCyR**	Definitions followed the recommendations published by the European LeukemiaNet.	Tab. 2 CCyR at 6, 12, 18, 24 months for the 3 arms (400mg/d N= 306, 800mg/d N=328, Imatinib+IFN, N=336)		
	MMR	Definitions followed the recommendations published by the European LeukemiaNet.	Tab. 2 MMR at 6, 12, 18, 24 months for the 3 arms (400mg/d N= 306, 800mg/d N=328, Imatinib+IFN, N=336)	Patients had to have an analysis within an interval of 9 to 15 months.	
	CMR	Definitions followed the recommendations published by the European LeukemiaNet.	Tab. 2 CMR at 6, 12, 18, 24 months for the 3 arms (400mg/d N= 306, 800mg/d N=328, Imatinib+IFN, N=336)		

Patient relevant outcomes					
Authors Year	**Patient-relevant outcomes**	**Patient-relevant outcomes (definition)**	**Results**	**Results stratified by level of response**	**Note**
Helmann et al. 2011	**PFS**	PFS was defined by survival free of AP and BC. Starting date for all time-to-event analyses was the date of diagnosis.	At 3 years: PFS was 94% (95% CI, 92% to 95%) At 2 year: Total 49 (4.8%) 800mg/d 21 (6.2%) 400mg/d 16 (4.9%) Imatinib+IFN 12 (3.4%)	At 3 years Independent of treatment approach, MMR vs no MMR at 12 months was associated with better PFS (99% [95% CI, 97% to 100%] v 95%[95% CI,93%to 97%]; P.0143) MMR vs >1% on the international scale at 12 months showed better PFS (99%[95%CI,97% to 100%] v 94%[95%CI,90% to 97%]; P .0023) No difference was observed in the group with 0.1% to < 1% on the international scale, which is closely correlated with CCR(PFS,97%[95%CI,94%to 99%];	PFS curves not reported. No stratification by Cytogenetic response, but OS is given by 0.1%-_ 1% IS transcripts level (which has been shown to closely correlate with complete cytogenic remission)
	OS		At 3 years: OS 95% (95% CI, 93% to 97%) with no differences between treatment arms At 2 years: OS Total 96.6 800mg/d 96.0 400mg/d 96.9 Imatinib+IFN 96.8	At 5 years CCR versus no CCR at 12 months was associated with better survival (96% *v* 91%; *P*_.0154). At 3 years OS (99% [95% CI,97% to 100%] v95%[95% CI,93%to 97%]; P.0156)	"A possible advantage of high-dose therapy is supported by the higher rate of CCR during the first 2 years, which is an

			Deaths: Total 30 (3.0%) 800mg/d 11 (3.3%) 400mg/d 9 (2.8%) Imatinib+IFN 10 (2.9%)	MMR vs >1% on the international scale at 12 months showed better OS (99% [95% CI, 97% to 100%] v 93% [95% CI, 90% to 96%]; P .0011) No difference was observed in the group with 0.1% to < 1% on the international scale, which is closely correlated with CCR OS, 98% [95% CI, 95% to 100%]	accepted surrogate marker for OS, and by the high CMR rates, which demonstrate the depth of molecular remissions."

General characteristics								
Authors Year	**Country**	**Year**	**Design**	**No. of centers**	**Treatment**	**No. of arms**	**Follow-up**	**Note**
Hochhaus et al.[27] 2009 (IRIS)	International	2000-2001	Randomized clinical trial	Multicenter	Imatinib 400mg orally once daily or IFN administered subcutaneously plus cytarabine.	2	Median: 70 months Range 0.2–78 months* 6-year follow-up for the last patient recruited	*Duration of treatment with Imatinib

Population				
Authors Year	**Inclusion Criteria**	**Exclusion Criteria**	**Sample size**	**Note**
Hochhaus et al. 2009	Adult patients (aged 18–70 years) with previously untreated Ph+ CML-CP diagnosed within 6 months of study entry.	Only prior therapy permitted with hydroxyurea or anagrelide.	1106 (553 in each arm)	65% patients crossed over to Imatinib, 3% patients crossed over to the alternative therapy. 364 (66%) patients initially assigned to Imatinib were still receiving study treatment after 6 year follow-up. 239 of 359 patients who crossed over to Imatinib were still receiving the treatment at 6 year follow-up. This study focuses on patients initially randomized to imatinib.

Subsequent treatment and treatment duration		
Authors Year	**Criteria for interruption**	**Patients on treatment and subsequent therapy**
Hochhaus et al. 2009	Stepwise dose escalation of imatinib to 400mg twice daily was permitted if there were no dose-limiting adverse events (AEs) on imatinib 400 mg once daily and if any of the following criteria were met: failure to achieve a complete hematologic response (CHR) within 3 months; bone marrow contained more than 65% Phþ metaphase cells at 12 months or loss of major cytogenetic response (MCyR).	In total, 364 of 553 (66%) patients randomized to imatinib were still receiving study treatment after 6 years of follow-up. 18 (3%) patients randomized to imatinib discontinued study treatment (six patients discontinued due to lack of efficacy, one patient due to unconfirmed loss of CCyR and 11 patients for other reasons including withdrawal of consent or lost to follow-up). The median (mean±s.d., range) last dose given at the time of discontinuation of imatinib study treatment was 400 mg (467±179, 100–800 mg). Other reasons for study discontinuation included: stem cell transplantation (3%), protocol violation (3%), death (2%) and loss to follow-up (1%). The last reported daily dose of imatinib in this group was 400mg in 83% of patients, and 300 mg in 7% of patients; a dose greater than 400 mg was reported for 10% of patients (600mg (6%) and 800 mg (4%)).

Surrogate outcomes					
Authors Year	**Surrogate outcomes**	**Surrogate outcomes (definition)**	**Results**	**Time points**	**Note**
Hochhaus et al. 2009	**CCyR**	At least 20 metaphase cells were analyzed to determine CyR. 0% Ph+	Last follow-up: 349/553 (63%) At 6 months: 228/529 (41%)	Cytogenetic bone marrow assessments annually	
	MCyR	At least 20 metaphase cells were analyzed to determine CyR. Definition of MCyR previously reported.	Any time: 490/553 (89%) (49/490 (10%) have documented loss MCyR)		
	PCyR	>0-35% Ph+	At 6 months: 92/529 (17%)		

	Minor/Minimal CyR	>35-95% Ph+	At 6 months: 39/529 (7%)		
	No CyR	>95% Ph+	At 6 months: 19/529 (3%)		

Patient relevant outcomes					
Authors Year	**Patient-relevant outcomes**	**Patient-relevant outcomes (definition)**	**Results**	**Results stratified by level of response**	**Note**
Hochhaus et al. 2009	**PFS**	Progression to AP or BP	At 6 years: 93% (95%CI 91 to 95) Annual rate of progression: 1.5% 2.8% 1.6% 0.9% 0.5% 0%	Annual rate of progression in patients with CCyR (N=456): 2.1% 0.7% 0.3% 0% 6 year rate without progression*: 97% (CCyR) 94% (PCyR) 85% (minor/minimal CyR) 80% (no CyR)	Survival graphs (Fig. 3) * Landmark analysis on 529 patients divided according to their CyR status at 6 months
	EFS	An event was defined as loss of CHR or MCyR, progression to AP or BC, an increase in WBC count to >20x10^9/l or death from any cause during treatment.	At 6 years: 83% (95%CI 80 to 86) 86/553 (16%) experiencing an event at any time Annual event rate: 3.3% 7.5% 4.8% 1.5% 0.8% 0.4%	Annual event rate in patients with CCyR (N=456): 5.4% 2.3% 1.1% 0.3% At 72 months*: 91% (CCyR) 85% (PCyR) 58% (minor/minimal CyR) 59% (no CyR)	Survival graphs (Fig. 3) * Landmark analysis on 529 patients divided according to their CyR status at 6 months

	OS		At 6 years: 88% (95%CI 85 to 92) 95% (95%CI 92 to 97)*		*After censoring for patients who had died for causes unrelated to CML or transplantation

General characteristics								
Authors Year	**Country**	**Year**	**Design**	**No. of centers**	**Treatment**	**No. of arms**	**Follow-up**	**Note**
Hughes et al.[28] 2003 (IRIS)	International	2000-2001	Randomized clinical trial	Multicenter	Imatinib 400mg/d or IFN-α plus cytarabine	2	Median: 25 months Max: 31	

Population				
Authors Year	**Inclusion Criteria**	**Exclusion Criteria**	**Sample size**	**Note**
Hughes et al. 2003	Patients 18 to 70 years of age were enrolled within six months after receiving a diagnosis of CML in the CP. Patients could have received no previous treatment for the disease except HU and anagrelide.		1106 (553 in each arm) Median 51 Range (18-70) in N=408 patients with CCR and N=333 patients with CCR and PCR	

Subsequent treatment and treatment duration		
Authors Year	**Criteria for interruption**	**Patients on treatment and subsequent therapy**
Hughes et al. 2003	"Patients could cross over to the other group if strict definitions of treatment failure or intolerance were met. Details of the study design, conduct, and treatment plan have been reported previously. 26"	"…The remaining patients were not included in the analysis: 50 either had disease progression or had discontinued imatinib for other reasons before 12 months of treatment, and 135 had no quantitative PCR sample available."

Surrogate outcomes					
Authors Year	**Surrogate outcomes**	**Surrogate outcomes (definition)**	**Results**	**Time points**	**Note**
Hughes et al. 2003	**CCyR**		At 6 months: 50% Imatinib 3% IFN At 12 months: 240/553 (43%) 25/553 (4%) At 19 months: 408/553 (74%) Imatinib 47/553 (8%) IFN 12-months rate of remission: 68% Imatinib, 7% IFN	Samples collected at the baseline, within 2 weeks after CCyR and every 3 months thereafter.	
	MR	The primary *BCR-ABL* Values calculated as a percentage of *BCR* were converted to reflect the reduction in the value with use of a standardized logarithmic (base 10) scale.	At the time of CCyR*: Median -2.5log (IQR 2.0 – 3.2) Imatinib Median -2.2log(IQR 1.5-2.6) IFN At 15 months after CCyR: Median -3.7log Imatinib Median -2.5log IFN Proportion of patients with > -3log (MMR)**: 39/120 (32%) Imatinib 0/12 (0%) IFN After 6 months: 50/120 (42%) Imatinib 2/120 (13%) IFN After 12 months***: 137/240 (57%) Imatinib 6/25 (24%)IFN		*Median reduction in transcripts level by time after CCyR (Fig. 1) **Patients with CCyR at the first assessment ***39% of all patients in the imatinib group and 2% in the IFN group

Patient relevant outcomes					
Authors Year	**Patient-relevant outcomes**	**Patient-relevant outcomes (definition)**	**Results**	**Results stratified by level of response**	**Note**
Hughes et al. 2003	**PFS**	Progression was defined as death, the development of accelerated-phase or blast-crisis CML, an increasing white-cell count, or the loss of complete hematologic or major cytogenetic response.	Progression rate 26/365 (7%) (Death 1/26, Progression to AP or BP 8/26)	At 24 months 100% (CCyR + MMR) 95% (CCyR + reduction less than 3log) 85% (no CCyR)	* Survival graph (Fig. 3)

General characteristics								
Authors Year	**Country**	**Year**	**Design**	**No. of centers**	**Treatment**	**No. of arms**	**Follow-up**	**Note**
Hughes et al. 2010 (IRIS)	International	2000-2001	Randomized clinical trial	Multicenter	Imatinib 400mg/d or IFN-α plus cytarabine	2	Median: 77 months	

Population				
Authors Year	**Inclusion Criteria**	**Exclusion Criteria**	**Sample size**	**Note**
Hughes et al. 2010	Patients enrolled on the imatinib arm of the IRIS trial with at least 1 *BCR-ABL* transcript measurement		476	Median 50yr, range (20-69) IQR (39, 59) SD (13.2) Mean(48.2) For the substudy population ITT population (553 pts) Median 50, Range (39-58), IQR (39,58) SD (12.6), Mean (48.2)

Surrogate outcomes					
Authors Year	**Surrogate outcomes**	**Surrogate outcomes (definition)**	**Results**	**Time points**	**Note**
Hughes et al. 2010	**MMR**	MMR represents a 3-log reduction in *BCR-ABL* transcripts, and is defined as ≤ 0.1% IS	At 84 months: 87% Proportion of patients in MMR with CCyR: At 3 months 33.3% (N=51) At 6 months: 48% (N=127) At 9 months: 47.1% (N=138) At 12 months: 62.1% (N=177) At 18 months: 77.9% (N=163)	Samples for RQ-PCR were collected after achievement of CCyR, at regular intervals or at physicians' discretion	
	MR	*BCR-ABL* transcript levels from individual laboratories converted to the international scale (IS)	Proportion of patients with transcripts level > 0.1% and ≤ 1.0% with CCyR: At 3 months 41.2% (N=51) At 6 months: 41.7% (N=127) At 9 months: 39.9% (N=138) At 12 months: 32.8% (N=177) At 18 months: 16.6% (N=163)		

Patient relevant outcomes					
Authors Year	**Patient-relevant outcomes**	**Patient-relevant outcomes (definition)**	**Results**	**Results stratified by level of response**	**Note**
Hughes et al. 2010	**PFS**	Survival without AP or BC progression		7year PFS rate: MMR 6months 96.2% (95%CI 92-100) MMR 12 months 100% MMR 18 months 100% No MMR 6 months 93% (95%CI 89-97) No MMR 12 months 89.9% (95%CI 85-95) No MMR 18 months 90.1% (95%CI 84-97)	Landmark analyses were run to determine whether BCR-ABL (IS) values at 6, 12, and 18 months were predictive of long-term outcomes. Survival graphs (Fig. 4)
	EFS	The time from treatment start until any of the following events that occur during study treatment: (i) loss of CHR, (ii) loss of major cytogenetic response (MCyR), (iii) progression to AP/BC, or (iv) death due to any cause		7year EFS: MMR 6months 85.1% (95%CI 76-94) 84.4% (95%CI 75-94)* MMR 12 months 91% (95%CI 85-97) 86.6% (95%CI 80-94)* MMR 18 months 94.9% (95%CI 91-99) 92.3% (95%CI 87-98)* No MMR 6 months 83.5% (95%CI 78-89) 71.6% (95%CI 64-79)* No MMR 12 months 79.4% (95%CI 73-86) 73.1% (95%CI 65-81)*	*Including loss of CCyR as an event Survival graphs (Fig. 2)

				No MMR 18 months 75.3% (95%CI 66-85) 65.4% (95%CI 54-77)*	
	OS			7year OS rate: MMR 6months 90.31% (95%CI 83-97) MMR 12 months 92.5% (95%CI 88-97) MMR 18 months 94.9% (95%CI 91-99) No MMR 6 months 89% (95%CI 85-94) No MMR 12 months 89.2% (95%CI 84-94) No MMR 18 months 89.8% (95%CI 84-96)	

General characteristics								
Authors Year	**Country**	**Year**	**Design**	**No. of centers**	**Treatment**	**No. of arms**	**Follow-up**	**Note**
Kantarjian et al.[29] 2006	US	2000-2004	Cohort study	1	Frontline therapies with 400 mg daily imatinib mesylate orally, 600 mg daily or 800 mg orally daily	1 (+ an historic group of IFN treated patients for comparison)	Median 42months range (12-66) in Imatinib group	"The survival by imatinib mesylate dose was identical, justifying their inclusion as 1 treatment group for comparative survival analysis"

Population				
Authors Year	**Inclusion Criteria**	**Exclusion Criteria**	**Sample size**	**Note**
Kantarjian et al. 2006	Adults with newly diagnosed Ph-positive early chronic-phase CML (ie, within 6 months from diagnosis)		279 (73 at 400mg/d dose, 12 at 600mg/d, 194 at 800mg/d) "Their survival by imatinib dose was identical justifying their inclusion as 1 treatment group"	Median 48 range (15-84) N=279

Subsequent treatment and treatment duration		
Authors Year	**Criteria for interruption**	**Patients on treatment and subsequent therapy**
Kantarjian et al. 2006	-	Seven patients on imatinib mesylate (5 from related donors, 2 from unrelated donors) and 97 patients on interferon (63 from related donors, 30 from unrelated donors, 4 from donors unspecified) underwent allogeneic stem cell transplantation (SCT) in chronic phase. Five of the 7 patients who received transplants after imatinib mesylate remain alive without evidence of disease (NED) after a median follow-up of 17 months (range, 2-34 months).

Surrogate outcomes					
Authors Year	**Surrogate outcomes**	**Surrogate outcomes (definition)**	**Results**	**Time points**	**Note**
Kantarjian et al. 2006	**CCyR**	Disappearance of Ph-positive cells (0% Ph-positive) by routine cytogenetic analysis	Latest follow-up: 243/279 (87%) Median time 3 months		
	PCyR	Reduction of Ph-positive cells to 1% to 34%	Latest follow-up: 17/279 (6%) Median time 3 months		
	MCyR	A major cytogenetic response referred to reduction of Ph-positive cells to less than 35%			
	MMR	BCR-ABL/ABL transcript levels less than 0.05%.	163/267 (61%)		267 patients had a follow-up molecular test performed

Patient relevant outcomes					
Authors Year	**Patient-relevant outcomes**	**Patient-relevant outcomes (definition)**	**Results**	**Results stratified by level of response**	**Note**
Kantarjian et al. 2006	**TFS**	Transformation-free survival was calculated from the date of start of therapy until progression to accelerated-blastic phase.		(Estimated) 3 year TFS 98% (MMR at 1year) 95% (no MMR at 1year)	Therapy (imatinib mesylate vs IFN), entered into the model after accounting for the effect of the independent pretreatment factors, remained a significant independent factor favoring imatinib mesylate therapy (hazard ratio, 0.44; *P* < .01). Survival of patients in CCyR was not different by whether they achieved a MMR or not
	PFS	Progression-free survival was calculated from the date of start of therapy, until cytogenetic or hematologic resistance or relapse, or progression to accelerated-blastic phase		(Estimated) 3 year PFS 98% (MMR at 1year) 94% (no MMR at 1year)	
	OS	Survival was calculated from the date of start of therapy.	(Estimated) 3year survival: 96% (Estimated) 5year survival: 88% (Survival graph Fig. 1)	(Estimated) 3 year survival 98% (CCyR at 1year, N=210) 100% (PCyR at 1 year, N=21) 75% (MinorCyR at 1year, N= 6) 84% (no MCyR at 1year) 88% (no CR at 1year, N=11) (Survival graph Fig. 3) (Estimated) 5 year survival 94% (CCyR at 1 year) 94% (PCyR at 1 year)	

General characteristics								
Authors Year	**Country**	**Year**	**Design**	**No. of centers**	**Treatment**	**No. of arms**	**Follow-up**	**Note**
Kantarjian et al. 2008	US	1998 -	Cohort single arm	1	Imatinib mesylate	1	Median: 48 months Range: 4-78	Limitations of the study: heterogeneous group and imatinib doses; methodology of molecular studies

Population				
Authors Year	**Inclusion Criteria**	**Exclusion Criteria**	**Sample size**	**Note**
Kantarjian et al. 2008	Adults with a diagnosis of Ph-positive CML in early chronic phase (diagnosis of CML for less than 12 months) referred to our institution		276	Median Age 48 (15-84)

Surrogate outcomes					
Authors Year	**Surrogate outcomes**	**Surrogate outcomes (definition)**	**Results**	**Time points**	**Note**
Kantarjian et al. 2008	**CCyR**	Disappearance of Ph-positive cells (0% Ph-positive) by routine cytogenetic analysis	The incidence of complete cytogenetic response at 3, 6, 12, 18, 24, 36, 48 months, at last follow-up, and overall are shown in Figure 1.	Response status was evaluated every 3 months in the first year and every 6 months in the	
	Durable CCyR	CCyR lasting continuously for at	Any		

		least 3 months (documented twice), 6 months (documented 3 times), or 12 months (documented 3–4 times)	247/276 (89%) <6 months 32/276 (12%) 6–11 months 18/276 (7%) 12–23 months 48/276 (17%) 24 months or more 149/276 (54%) CCyR durable for 12 months: 76% in high-dose Imatinib 59% with standard –dose Imatinib	subsequent 4 years.	
	MMR	BCR-ABL/ABL transcript levels <0.1% by real-time Taq human-based QPCR done on peripheral blood or marrow samples. This represents a 3-log reduction from the average baseline for untreated patients in our laboratory	The incidences of major (QPCR 0.1% or less) molecular and complete molecular responses at 3, 6, 12, 18, 24, 36, 48 months, at last follow-up, and overall are shown in Figure 1.		
	Durable MMR	MMR lasting continuously for at least 3 months (documented twice), 6 months (documented 3 times), or 12 months (documented 3–4 times)	Any 201/269 (75%) <6 months 55/269 (20%) 6–11 months 30/269 (11%) 12–23 months 30/269 (11%) 24 months or more 86/269 (32%) MMR durable for 12 months: 45% in high-dose Imatinib 39% with standard –dose Imatinib		
	Durable CMR	Undectable BCR-ABL level	Any		

		lasting continuously for at least 3 months (documented twice), 6 months (documented 3 times), or 12 months (documented 3–4 times)	100/269 (37%) <6 months 59/269 (22%) 6–11 months 16/269 (6%) 12–23 months 10/269 (4%) 24 months or more 15/269 (6%)		

Patient relevant outcomes					
Authors Year	**Patient-relevant outcomes**	**Patient-relevant outcomes (definition)**	**Results**	**Results stratified by level of response**	**Note**
Kantarjian et al. 2008	**PFS**	PFS was defined as being on therapy without any of the following: loss of a cytogenetic response (Ph positivity increase by at least 30% or to above 65%), loss of hematologic response, progression to accelerated or blastic phase, or death from any cause during therapy. Loss of major molecular response in a patient who is still in at least a major cytogenetic response is not considered to define progression.		PFS is shown in Figure 5A–D. PFS at 6, 12, 18, and 24 months by molecular response only in patients who were in complete cytogenetic response are shown in Figure 7A–D. PFS by whether patients achieved a durable complete cytogenetic response (for at least 12 months), or major (for at least 12 months) and complete molecular response (for at least 6 months), are shown in Figure 8A–C.	Durable CCyR and durable MMRfor at least 12 months predicted better PFS rates.
	OS			Survival from 6, 12, 18, and	OS was not

				24 months by cytogenetic response at these time points is shown in Figure 2A–D. Survival from 6, 12, 18, and 24 months by molecular response in all patients is shown in Figure 4A–D. Survival at 6, 12, 18, and 24 months by molecular response only in patients who were in complete cytogenetic response are shown in Figure 6A–D.	different at by whether patients had achieved these durable responses or not.

General characteristics								
Authors Year	**Country**	**Year**	**Design**	**No. of centers**	**Treatment**	**No. of arms**	**Follow-up**	**Note**
Marin et al.[30] 2008	UK	2000-2007	Cohort single arm	1	Imatinib 400mg/d	1	Median: 46 months Range: 13-43	

Population				
Authors Year	**Inclusion Criteria**	**Exclusion Criteria**	**Sample size**	**Note**
Marin et al. 2008	Consecutive adult patients with *BCR-ABL*–positive CML in CP who received imatinib as 1st-line therapy. Imatinib was started within 6 months of diagnosis and no patient had received any previous antileukemia treatment other than hydroxyurea.		224	17 patients were included in the International Randomized Study of Interferon and STI571 (IRIS) study. Same cohort as DeLavallade 2008 Median age 46.1 (18-79)

Subsequent treatment and treatment duration		
Authors Year	**Criteria for interruption**	**Patients on treatment and subsequent therapy**
Marin et al. 2008	-	A total of 29 patients discontinued the imatinib therapy, although still in CP, 8 resulting from toxicity and 21 resulting from unsatisfactory response. The dose of imatinib was increased more than 400 mg per day in 94 (42%) patients; 21 patients (9.4%) had the imatinib increased during the first year of therapy.

Surrogate outcomes					
Authors Year	**Surrogate outcomes**	**Surrogate outcomes (definition)**	**Results**	**Time points**	**Note**
Marin et al. 2008	**CCyR**	Failure to detect any Ph chromosome-positive metaphases in 2 consecutive bone marrow examinations with a minimum of 30 metaphases examined	173/224 (77%)	BM morphology and cytogenetics were assessed at diagnosis and then every 3 months until patients achieved complete cytogenetic response (CCyR). Thereafter, patients were monitored by real-time quantitative polymerase chain reaction (RQ-PCR) and annual bone marrow examinations	Probability of CCyR and loss of CCyR according to failure and suboptimal response at different time points available (Table 2) Probability of CCyR according to the criteria for failure also in survival graph (Fig. 2) Loss of CCyR according to level of MR in Fig. 4
	MCyR	Combination of complete and partial cytogenetic responses (≤35% Ph+ metaphases).	190/224 (85%)		
	Loss of CCyR	Detection of one or more Ph+ marrow metaphases, also confirmed by a subsequent study, in a patient who had previously achieved CCyR.			
	Failure	No cytogenetic response (Ph_ _ 95%) at 6 months or less than PCyR (Ph<35%) at 12 months or less than CCyR at 18 months or loss of CCyR at any time	At 3 months: 8/224 At 6 months: 37/224 At 12 months: 50/224 At 18 months:		

			66/224		
	Suboptimal response	Less than PCyR at 6 months or Less than complete CCyR at 12 months or less than MMR at 18 months or loss of MMR at any time.	At 6 months: 28/224 At 12 months: 45/224 At 18 months: 91/224		
	MMR	MMR was defined as a 3 log reduction in transcript levels11 based on 2 consecutive molecular studies	97/224 (43%)		Patients in CCyR who had failed to achieve MMR at 12 or 18 months were more likely to lose their CCyR than patients who did achieve MMR, 23.6% versus 2.6% ($P < .04$) and 24.6% versus 0% ($P < .006$), respectively
	CMR	CMR was defined as 2 consecutive samples with no detectable transcripts provided that control gene copy numbers were adequate.			

Patient relevant outcomes

Authors Year	**Patient-relevant outcomes**	**Patient-relevant outcomes (definition)**	**Results**	**Results stratified by level of response**	**Note**
Marin et al. 2008	**PFS**	PFS was defined as survival without evidence of accelerated or blastic phase disease	25/224(11 %) progressed to AP or BP	5year survival At 3 months: 56.2 (95%CI 37.1-73.6) in Failure 84.6 (95%CI 77.8-89.6) in No Failure At 6 months: 73.4 (95%CI 64.9-80.4) in Failure 87.1 (95%CI 81.4-91.2) in No Failure 87.1 (95%CI 85.0-88.9) in CyR (N=185) 72.8 (95%CI 64.4-79.9) in No CyR (N=34) 91.5 (95%CI 88.1-94.0) in MCyR (N=157)	PFS according to suboptimal response at different time points available (Table 2) PFS according to the criteria for failure in survival graph (Fig. 2) At 6 months being in MCyR (RR= 3.3, $P < .017$) is independent predictor for PFS. At 12 months, the only independent predictors for PFS

				70.4 (95%CI 62.1-77.6) in No MCyR (N=62) At 12 months: 76.0 (95%CI 65.1-84.3) in Failure 90.0 (95%CI 85.4-93.3) in No Failure 90.0 (95%CI 86.9-92.4) in MCyR (N=169) 76.3 (95%CI 67.7-83.2) in No MCyR (N=46) 96.2 (95%CI 94.3-97.5) in CCyR (N=127) 74.4 (95%CI 70.3-78.1) in No CCyR (N=88) 94.4 (95%CI 86.5-97.8) in MMR (N=32) 85.3 (95%CI 81.7-88.3) in No MMR (N=183) At 18 months: 76.4 (95%CI 67.8-83.3) in Failure 97.1 (95%CI 92.5-98.9) in No Failure 97.1 (95%CI 94.1-98.6) in CCyR (N=132) 76.5 (95%CI 70.8-81.4) in No CCyR (N=65) 94.5 (95%CI 89.2-97.3) in MMR (N=41) 87.5 (95%CI 80.2-94.2) in No MMR (N=156) At any time 6.95 (95%CI 2.2-21.7) in Loss of CCyR (N=17) 0.04 (95%CI 0.0005-15654) in loss of MMR (N=10) 5 year PFS 72.8% more than 95% Ph+ (N=34) 74.9% 36% to 95% Ph+ (N=28) 91.5% MCyR (N=-157) 5 year PFS 76.3% No CyR (N=46) 81.5% MCyR but No CCyR (N=42) 96.2% CCyR (N=-127)	were: (1) being in CCyR (RR = 4.5, *P* < .02) and (2) prior loss of CCyR (RR =24, *P*<.036). At 18 months, the only independent predictor for PFS was being in CCyR (RR = 6.9, *P* < .005).

	OS		13/224 (6%) died	5year survival At 3 months: 60.2 (95%CI 40.2-79.8) in Failure 93.2 (95%CI 86.7-96.7) in No Failure At 6 months: 81.8 (95%CI 70.2-89.6) in Failure 95.5 (95%CI 89.8-98.1) in No Failure 94.9 (95%CI 92.3-96.7) in CyR (N=185) 84.6 (95%CI 72.5-92.0) in No CyR (N=34) 93.2 (95%CI 83.7-97.3) in MCyR (N=157) 74.2 (95%CI 58.8-85.3) in No MCyR (N=62) At 12 months: 87.1 (95%CI 81.7-91.1) in Failure 95.1 (95%CI 91.3-97.3) in No Failure 95.1 (95%CI 90.6-97.5) in MCyR (N=169) 86.7 (95%CI 75.5-93.2) in No MCyR (N=46) 98.4 (95%CI 95.9-99.4) in CCyR (N=127) 86.0(95%CI 79.1-90.9) in No CCyR (N=88) 96.4 (95%CI 85.2-99.2) in MMR (N=32) 93.4 (95%CI 88.3-96.4) in No MMR (N=183) At 18 months: 87.8 (95%CI 74.2-94.7) in Failure 98.5 (95%CI 95.0-99.6) in No Failure 98.5 (95%CI 93.9-99.6) in CCyR (N=132) 87.6 (95%CI 80.5-92.3) in No CCyR (N=65) 95.6 (95%CI 89.8-98.2) in MMR (N=41) 94.5 (95%CI 85.4-98.1) in No MMR (N=156) At any time 3.2(95%CI 1.1-15.4) in Loss of CCyR (N=17) 0.04(95%CI .0003-21675) in loss of MMR (N=10)	OS according to suboptimal response at different time points available (Table 2)

General characteristics								
Authors Year	**Country**	**Year**	**Design**	**No. of centers**	**Treatment**	**No. of arms**	**Follow-up**	**Note**
Rajappa et al.[31] 2008	India	2003-2006	Cohort single arm	1	Imatinib standard oral dose 4000mg/d	1	Median: 29.5 months Range: 3-58	

Population				
Authors Year	**Inclusion Criteria**	**Exclusion Criteria**	**Sample size**	**Note**
Rajappa et al. 2008	All adult patients with newly diagnosed untreated chronic phase CML who were treated with IM.	No other non-prescription drugs or indigenous medicines were allowed.	201	Median age 32 (18-72)

Subsequent treatment and treatment duration		
Authors Year	**Criteria for interruption**	**Patients on treatment and subsequent therapy**
Rajappa et al. 2008	Doses were escalated when patients showed clinical or laboratory evidence of progression.	Among all patients, 43 (21%) needed temporary discontinuations in IM therapy due to adverse events. Reasons for treatment discontinuations included myelosuppression in 26 (13%), 11 (5%) for skin reactions and unknown in 6 (3%). The mean daily dose was 346 mg or 86% of scheduled. No patient needed permanent discontinuation of IM therapy. The dose of IM was escalated to 600 – 800 mg for patients who had clinical or laboratory evidence of progression. None took dasatinib or underwent allogenic stem cell transplantation. At a median of 29 months, 94% patients are alive and on follow-up. Nine (4%) have died and 4 (2%) are lost for follow-up.

Surrogate outcomes					
Authors Year	**Surrogate outcomes**	**Surrogate outcomes (definition)**	**Results**	**Time points**	**Note**
Rajappa et al. 2008	**CCyR**	Standard criteria for complete hematological response (CHR), CCR, partial cytogenetic response (PCR), minor response (Minor CR) and no response (NR) were applied (IRIS definition)	113/201 (56%)	The bone marrow cytogenetics was repeated at least once every year.	
	PCyR		45/201 (23%)		
	Minor CR		35 (17%)		
	No CR		8/201 (4%)		

Patient relevant outcomes					
Authors Year	**Patient-relevant outcomes**	**Patient-relevant outcomes (definition)**	**Results**	**Results stratified by level of response**	**Note**
Rajappa et al. 2008	**PFS**	PFS was defined by any of the following events whichever occurred first: death from any cause, the development of AP CML or BP CML (defined by the presence of at least 20 percent blasts in the blood or bone marrow), loss of CHR, loss of CR (defined as an increase in Ph+ cells in metaphase by at least 30 percentage points).	At 29 months: 77%	At 29 months: 88% in CCyR 64% in other CR conditions	Survival graph (Fig. 1, Fig. 2)
	OS	Survival was calculated from initiation of treatment with IM to death from any cause or lost to follow-up	At 29 months: 94% 9/201 (4%) dead 4/201 (2%) lost to follow-up	At 29 months: 100% in CCyR 94% in other CR conditions	Survival graph (Fig. 3, Fig. 4)

General characteristics								
Authors Year	**Country**	**Year**	**Design**	**No. of centers**	**Treatment**	**No. of arms**	**Follow-up**	**Note**
Roy et al.[32] 2006	France (CML91) International (IRIS)	1991-1996 CML91 2000-2001 IRIS	Retrospective comparison of two RCTs	Multicenter	Imatinib 400mg/d vs IFN-α plus Ara-C	(2)	IRIS Median 42months range (0.59-42) CML91 Median42 range (5.32-42)	

Population				
Authors Year	**Inclusion Criteria**	**Exclusion Criteria**	**Sample size**	**Note**
Roy et al. 2006	Adults older than 18 years of age with Philadelphia chromosome–positive CML in chronic phase, diagnosed within the preceding 6 months, based on the date of the first cytogenetic analysis. Patients from the French CML91 trial were randomly assigned to the IFN- plus Ara-C; the current comparison analyzed only the 551 patients initially assigned to the imatinib arm, who actually received imatinib at the initial dose of 400 mg daily.		551 IRIS Median age 50, range (18-70) 325 CML91	

Subsequent treatment and treatment duration		
Authors Year	**Criteria for interruption**	**Patients on treatment and subsequent therapy**
Roy et al. 2006		A total of 130 patients (24%) in the imatinib group discontinued the treatment ($P < .001$). Time to discontinuation was 41.8 months (range, 0.16-42 months) The most common reason was lack of efficacy or intolerance, which occurred more frequently with the IFN-α plus Ara-C treatment. A few patients (14 of 551) in the IRIS trial assigned to the imatinib arm crossed over to IFN- α plus Ara-C combination. At the time of analysis, 38 patients (7%) had proceeded to bone marrow transplantation in the IRIS study. Nine patients died during treatment (8 receiving imatinib; 1, the IFN plus Ara-C combination).

Surrogate outcomes					
Authors Year	**Surrogate outcomes**	**Surrogate outcomes (definition)**	**Results**	**Time points**	**Note**
Roy et al. 2006	**CCyR**	Absence of Ph-positive cells on karyotype analysis		IRIS the cytogenetic analyses were performed every 3 months for the first 12 months and every 6 months thereafter. CML91 study, cytogenetics at 3 months was optional; however, they were performed at 6, 9, and 12 months for the first 12 months, and every 4 months thereafter.	
	MCyR	The sum of complete and partial cytogenetic responses.			
	Partial CR	Decrease of Ph-positive marrow metaphase cells to 1% to 34% in CML91 or 1% to 35% in IRIS;			

Patient relevant outcomes					
Authors Year	**Patient-relevant outcomes**	**Patient-relevant outcomes (definition)**	**Results**	**Results stratified by level of response**	**Note**
Roy et al. 2006	**PFS**	The term "survival free of transformation" (ie, accelerated phase, blast crisis patients, and death) will be used in this analysis. The definitions of AP and BC differed slightly between the 2 trials. The percentage of peripheral blasts was slightly lower in the CML91 study for the diagnosis of accelerated and blastic phases (15% and 30% for IRIS vs 10% and 20% for CML91, respectively).		At 3 years: For patients who achieved CCyR at 12 months, survival rates 96% (95% CI: 94-98) and 92% (95% CI: 85-99) for imatinib and IFN- plus Ara-C groups, respectively.	

Appendix 5: Excluded studies

Excluded studies – clinical effectiveness	
Paper	**Exclude (reason)**
Abraham (2010)	Review article
Baccarani et al. (2010)	Duplication, full paper included
Botteman et al. (2010)	No relevant outcomes
Cortes (2009)	Review article
Giles et al. (2010)	Review article
Hughes et al. (2010b)	Not relevant populations
Jabbour, et al. (2007)	Review article
Kantarjian et al. (2010b)	Duplication, full paper included
Larson et al. (2010b)	Duplication, full paper included
Le Coutre et al. (2010)	Not relevant populations
MacNeil (2010)	Review article
Minami et al. (2010)	Not relevant populations
Ogura et al. (2010)	Duplication, full paper included
Quintas-Cardama et al. (2008)	No relevant outcomes
Research Report (2009)	Review article
Saglio et al. (2010b)	Duplication, full paper included
Shah, N. (2007)	Review article
Wei et al. (2010)	Review article
Wendling (2010)	Review article

Excluded studies – cost-effectiveness	
Paper	**Exclude (reason)**
Bouwmans et al. (2009)	Previously treated population
Guerin et al. (2010)	Study design
Juarez-Garcia (2009)	Previously treated population
Ovanfors et al. (2011)	Insufficient information
Simons et al. (2009)	Insufficient information
Szabo et al. (2010)	Insufficient information
Taylor et al. (2010)	Insufficient information
Taylor et al. (2007)	Previously treated population
Wu et al. (2010)	Insufficient information

Excluded studies – surrogate outcomes	
Paper	**Exclude (reason)**
Al-Kali et al. (2010)	Final outcome not stratified by level of response.
Alvarado et al. (2009)	Data derived from different trials
Anstrom et al. (2004)	Not relevant populations.
Aziz et al. (2007)	Previously treated population
Aziz et al. (2010)	Previously treated population
Bee et al. (2006)	Previously treated population
Braziel et 2002	Previously treated population
Cervantes et al (2010)	Final outcome not stratified by level of response.
Cortes et al. (2005)	Previously treated population
Cortes et al. (2006)	Previously treated population
Cortes et al. (2010 Das)	Final outcome not stratified by level of response.
Cortes et al. (2010 Nil)	Final outcome not stratified by level of response.
El-Zimaity et al. (2004)	Final outcome not stratified by level of response.
Furukawa et al. (2011)	Previously treated population, not relevant populations.
Guilhot et al. (2009)	Final outcome not stratified by level of response.
Huntly et al. (2003)	Previously treated population
Jabbour et al. (2009)	Not relevant populations.
Jiang et al. (2010)	Previously treated population
Kanda et al. (2008)	Previously treated population
Kantarjian et al 2002	Previously treated population
Kantarjian et al. (2003)	Final outcome not stratified by level of response.
Khorashad et al. (2008)	Final outcome not stratified by level of response.
Kim et al. (2010)	Previously treated population
Koffi et al. (2010)	Final outcome not stratified by level of response.
Mahmoud et al. (2009)	No relevant outcomes
Marin et al. (2005)	No relevant final outcomes
Marin et al. (2009)	No relevant outcomes
Matsuo et al. (2007)	Previously treated population
Medhi et al. (2010)	Not relevant populations.
Moran, Valia et al. (2011)	Not relevant populations.
Muller et al. 2008	Final outcome not stratified by level of response.
Nagai et al. (2010)	Final outcome not stratified by level of response.
Nannya et al. (2008)	Not relevant populations.
O'Brien et Deininger (2003)	Final outcome not stratified by level of response.
O'Brien et al. (2003)	Final outcome not stratified by level of response.

O'Brien et al. (2008)	Final outcome not stratified by level of response.
Palandri et al. (2007)	Letter to the Editors.
Palandri et al. (2009)	Previously treated population
Palandri et al. (2010)	Final outcome not stratified by level of response.
Piazza et al. (2006)	Not relevant populations.
Press et al. (2006)	Not relevant populations, previously treated population
Press et al. (2007)	Not relevant populations, previously treated population
Qin et al. (2009)	Previously treated population
Quintas-Cardama et al. (2009)	Previously treated population
Quintas-Cardama et al. (2009)	Review article
Rosti et al. (2009)	No relevant final outcomes
Santos et al. (2010)	Previously treated population
Schrover et al. (2006)	Results (survival by cytogenetic response) are estimated from IFN-α population.
Sheehy et al. (2008)	Previously treated population
Shepherd et al. (2008)	Previously treated population
Sugita et al. (2008)	Previously treated population
Wang et al. (2003)	Previously treated population

Appendix 6: Ongoing trials

Study Characteristics S0325				
Study	**Drug therapy**	**Inclusion criteria**	**Exclusion criteria**	**Outcomes**
S0325[33]	• Dasatinib • Imatinib	• Newly diagnosed	• Unknown	• Haematological response • Complete cytogenetic response • Major molecular response • Overall survival • Progression free survival

Summary of results 12-months S0325[33]					
	Dasatinib (N = 123)		Imatinib (N = 123)		
Response 12-months	no.	%	no.	%	p
Haematological response	104	86	111	90	0.25
Complete CyR 12-months	55/67	82	40/58	69	0.097
MMR	39/90	59	39/90	59	0.042
CMR	21/99	21	13/90	14	0.26
Overall survival	123	100	66	99	0.60
Progression free survival	123	99	88	96	0.19

Treatment Status 12-months	Dasatinib (N = 123)	Imatinib (N = 123)
	No. (%)	
Discontinued to receive treatment	38	47
Had drug-related adverse events (12-month)	18 (15)	13 (11)
Death	5	2
Withdrew consent	3 (2)	8 (7)
Had other reason	12 (10)	24 (20)

Adverse Events 12-months	Dasatinib (N = 258)		Imatinib (N = 258)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4
	% of patients			
Cytopenia				
Thrombocytopenia (12-month)		18		8
Nonhaematologic adverse event				
Pleural effusion (12-month)	11		2	

Study characteristics SPIRIT 2[34]

Study	Drug therapy	Inclusion criteria	Exclusion criteria	Outcomes
SPIRIT 2[34]	• Dasatinib • Imatinib	• Male or female patients ≥ 18 years of age. Patients must have all of the following: • be enrolled within **3 months** of initial diagnosis of CML-CP (date of initialdiagnosis is the date of first cytogenetic analysis), • cytogenetic confirmation of the Philadelphia chromosome or variants of (9;22) translocations; patients may have secondary chromosomal abnormalities in addition to the Philadelphia chromosome. • < 15% blasts in peripheral blood and bone marrow; Confidential Version 1.4 Page 14 of 69 20th March 2008 • (b) < 30% blasts plus promyelocytes in peripheral blood and bone marrow; < 20% basophils in peripheral blood, ≥ 100 x 109/L platelets no evidence of extramedullary leukaemic involvement,	• Patients with Ph-negative, BCR-ABL-positive, disease are **NOT** eligible for the study. • Any prior treatment for CML with: any tyrosine kinase inhibitor (eg imatinib, dasatinib, nilotinib); busulphan; interferon-alpha; homoharringtonine; cytosine arabinoside; any other investigational agents (hydroxycarbamide and anagrelide are the only drugs permitted). **NB patients will be ineligible for the study if they have received ANY prior therapy with interferon-alpha or imatinib. NO exceptions.** • Patients who received prior chemotherapy • Patient who have had any form of prior haemopoietic stem cell transplant. • Patients with an ECOG Performance Status Score ≥ 3. • Patients with serum bilirubin, SGOT/AST, SGPT/ALT, or creatinine concentrations > 2.0 x the institutional upper limit of the normal range. • Patients with International normalised ratio (INR) or partialthromboplastin time (PTT) > 1.5 x IULN**,** with the exception of patients on treatment with oral anticoagulants. • Patients with *uncontrolled* medical disease such as diabetes	Primary outcome: • Event free survival at 5-years Secondary outcomes: • Complete cytogenetic response 2-years • Treatment failure rates 5-years • Complete haematological response • Levels of molecular response • Quality of life • Overall survival 2years and 5-years • Broad comparison of costs

		with the exception of hepatosplenomegaly. • Written voluntary informed consent.	mellitus, thyroid dysfunction, neuropsychiatric disorders, infection, angina, or Grade 3/4 cardiac problems as defined by the New York Heart Association Criteria. • Patients with known positivity for human immunodeficiency virus (HIV). • Patients who have undergone major surgery within 4 weeks of Study Day1, or who have not recovered from prior major surgery. • Patients who are: (a) pregnant, (b) breast feeding, (c) of childbearing potential without a negative pregnancy test prior to Study Day 1, and (d) male or female of childbearing potential unwilling to use barrier contraceptive precautions throughout the trial. • Patients with a history of another malignancy either currently or within the past five years, with the exception of basal cell skin carcinoma or cervical carcinoma *in situ*. • Patients with a history of non-compliance to medical regimens or who are considered potentially unreliable.	
SPIRIT 2 is a Phase III, multicentre, open-label, prospective randomised trial comparing imatinib 400 mg daily versus dasatinib 100 mg daily in patients with newly-diagnosed chronic phase Chronic Myeloid Leukaemia. The Study began in 2008 and aims to recruit 810 patients, with currently over 400 recruited.				

Appendix 7: Full critique of manufacturers cost-effectiveness submission

Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia (CML)

Originally produced by: Matrix Evidence

Abridged version produced by: PenTAG

Original Authors:
Kevin Marsh, Chief Economist, Matrix Evidence
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Please note: In the draft guidance on 18th August 2011, NICE has recommended nilotinib, for the treatment of the chronic and accelerated phases of CML (chronic myeloid leukaemia) that is resistant or intolerant to standard-dose imatinib. Dasatinib and high-dose imatinib, are not recommended in the draft guidance. Consultees have the opportunity to appeal against the draft guidance. Until NICE issues final guidance, NHS bodies should make decisions locally on the funding of specific treatments. This draft guidance does not mean that people currently taking dasatinib or high-dose imatinib will stop receiving them. They have the option to continue treatment until they and their clinicians consider it appropriate to stop.

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Abbreviations and Acronyms

AE	adverse event
AP	accelerated phase
BD	bis die (twice daily)
BM	bone marrow
BMS	Bristol Myers Squibb
BNF	British National Formulary
BC	blast crisis
CCyR	complete cytogenetic response
cDNA	complementary DNA
CHR	complete haematological response
CI	confidence interval
CML	chronic myeloid leukaemia
CMR	complete molecular response
CP	chronic phase
CyR	cytogenetic response
HD	high dose
HU	hydroxyurea
HRQoL	heath related quality of life
ICD-O	International Classification of Diseases of Oncology
ICER	incremental cost-effectiveness ratio
IFN	interferon-a
MCyR	major cytogenetic response
MHR	major haematological response
MIMS	monthly index of medical specialities
MMR	major molecular response
NICE	National Institute of Clinical Excellence
OS	overall survival
OD	once daily
PAS	patient access scheme
PCyR	partial cytogenetic response
PFS	progression-free survival
Ph-	Philadelphia negative cell
Ph+	Philadelphia positive cell
PY	progressed years
QALY	quality adjusted life year
QoL	quality of life
qPCR	real time quantitative PCR
RCT	randomised controlled trial
SCT	stem cell transplantation
SD	standard deviation
SE	standard error

SHTAC	Southampton Health Technology Assessments Centre
TKI	tyrosine kinase inhibitor
TTP	time to progression

Terms and Definitions

Allogeneic transplant	A bone marrow or stem cell transplant using marrow from another person.
Blast cells	Immature cells found in and produced by the bone marrow. Not normally found in the peripheral blood.
Bone Marrow	The soft substance that fills bone cavities. It is composed of mature and immature blood cells and fat. Red and white blood cells and platelets are formed in the bone marrow.
Bone Marrow Transplant	A procedure where a patient's bone marrow is replaced by healthy bone marrow. The bone marrow to be replaced may be deliberately destroyed by high doses of chemotherapy and/or radiation therapy. The replacement marrow may come from another person, or it may be previously harvested from the patient's own marrow.
Chemotherapy	The treatment of a disease by chemicals to destroy cancer cells. Chemotherapy can affect the whole body.
Cytogenetic response	A response to treatment at the level of chromosomal abnormalities. In the case of CML, assessed by counting the number of Ph+ cells in metaphase (usually 20 metaphases are analysed). A complete response generally means no Ph+ cells, a partial response leaves up to 35% Ph+ cells evident and with a minor response from 35% to 95% Ph+ cells are still evident.
EQ-5D	A European quality of life questionnaire containing five physical and psychological dimensions.
Haematological response	A haematological response refers to the normalisation of blood cell counts. CML causes over proliferation of WBCs which treatments aims to lower and categories of response indicate the extent to which this occurs. Typically, the haematological response is classified as complete if WBC <10 x 109/l, platelets <450 109/l, no immature cells in the peripheral blood with normal differential count, and disappearance of symptoms and signs
Hydroxyurea	A drug used in the treatment of CML which inhibits DNA synthesis.
ICER	Demonstrates the total additional cost per QALY gained of one alternative over another. There is no particular point at which an alternative is said to be "cost-effective" as this will be a policy decision. The larger the incremental cost-effectiveness ratio the less likely it is to be cost-effective.
Interferon-α	Interferon is a protein derived from human cells. It has a role in fighting

	viral infections by preventing virus multiplication in cells. IFN-α (alpha) is made by leucocytes. It is often used as 1st line therapy in CML.
Kaplan-Meier estimator	Also known as the product limit estimator, is an estimator for estimating the survival function from life-time data. In medical research, it is often used to measure the fraction of patients living for a certain amount of time after treatment
Leukocytes	White blood cells which are responsible for fighting infections.
Metaphase	The second phase of mitosis (cell division). Cells in this phase of division are used for cytogenetic analysis in CML to identify the proportion of Ph+ chromosomes.
Myelocytes	Committed progenitor cells produced by, and found in, the bone marrow which develop into mature leukocytes.
Weibull distribution	A continuous probability distribution usually used in survival analysis

1. BMS submission

1.1. Summary

1.1.1. Scope of the submissions

The submission from BMS considers the use of dasatinib (SPRYCEL®) for the 1st line treatment of people with chronic myeloid leukaemia (CML) as an alternative to the standard dose of imatinib (400mg daily) or nilotinib (600mg daily).

The clinical effectiveness outcomes considered are overall survival, progression free survival, response rates, adverse effects of treatment and health-related quality of life.

The outcomes for the economic analysis are incremental cost per quality-adjusted life-year, and incremental cost per life year gained. In order to derive these outcomes the following costs have been considered: cost of 1st, 2nd line TKI's, cost of post-TKI failure 2nd or 3rd line treatment, and the cost of treating serious adverse events. The time horizon for the economic analysis is between 46 and 86 years old, and costs are considered from an NHS perspective. No subgroup analysis is conducted for the economic evaluation.

1.1.2. Summary of submitted cost-effectiveness evidence

The manufacturer uses a 'time in state' (area under the curve) model extrapolating CML related survival and progression-free survival data. The health states represent the chronic phase, and accelerated/blast phases as well as death. Within the chronic phase patients may also be in 1st, 2nd or 3rd line treatment, while in the accelerated/blast phases they may be receiving either 3rd line treatments or palliative care. Time is modelled in blocks of 1 month.

The BMS base case analysis produces ICERs of:

- £26,305 per QALY for dasatinib in comparison to imatinib as 1st line TKI, and
- £144,778 per QALY in comparison to nilotinib as a 1st line TKI.

The sensitivity analysis shows the key parameters to which the model is sensitive: drug costs, overall survival, and the cost of stem cell transplant.

The BMS model contained a number of formula errors. After correcting for these errors the BMS model predicts ICERs of:

- £36,052 per QALY for 1st line dasatinib compared to 1st line imatinib, and
- £103,483 per QALY for dasatinib compared to nilotinib.

In the original model the cost of nilotinib used by BMS does not account for the PAS discount applied to nilotinib. If the cost of nilotinib is adjusted to reflect the [redacted] decrease in the cost of nilotinib due to PAS, the cost of nilotinib in 1st line and 2nd line is reduced from £2,664 per month to [redacted] per month. Including this change, the BMS model predicts an ICER of £45,600 per QALY for dasatinib compared to imatinib. When comparing dasatinib to nilotinib, the model predicts that nilotinib is more effective and less costly.

Further, BMS assume that dasatinib is taken as a 3rd-line treatment in all treatment arms. However, in the NICE draft guidance FAD, dasatinib was not recommended (the draft guidance FAD for 2nd line CML for high-dose imatinib, dasatinib and nilotinib, is available on the NICE website at http://guidance.nice.org.uk/TA/WaveR/99). When the BMS model is further adjusted so that dasatinib is not taken 3rd-line, the ICER of dasatinib vs. imatinib increases further, from £45,600 to £64,000 per QALY, and nilotinib is still more effective and less costly than dasatinib.

Finally, BMS assume that half of all patients in the imatinib and nilotinib treatment arms eligible for 2nd-line treatment, take dasatinib. Again, in the NICE draft guidance FAD, dasatinib was not recommended (the draft guidance FAD for 2nd line CML for high-dose imatinib, dasatinib and nilotinib, is available on the NICE website at http://guidance.nice.org.uk/TA/WaveR/99). When the BMS model is further adjusted so that dasatinib is not taken 2nd-line, and instead when we assume that all 2nd-line patients in the imatinib arm take nilotinib 2nd-line, the ICER of dasatinib vs. imatinib increases further, from £64,000 to £96,000 per QALY. There appears to be no simple way to adjust BMS' model to disallow patients taking dasatinib 2nd-line.

In summary, BMS' adjusted model yields an ICER for dasatinib vs. imatinib of £96,000 per QALY. Further, nilotinib is more effective and less costly than dasatinib.

1.1.3. Commentary on the robustness of the submitted evidence

Strengths

- The approach taken to modelling is reasonable although quite complex
- The sources and justification of estimates are also generally reasonable
- Resource use is largely based on a survey of six UK clinicians who manage patients with CML.

Weaknesses

- There are a number of formulae errors in the BMS model. When corrected, the base case ICER changes from £26,305 to £36,052 per QALY for dasatinib in comparison to imatinib; and from £144,778 to £103,483 per QALY for dasatinib in comparison to nilotinib.
- Unfortunately, due to BMS not having knowledge of the PAS, BMS does not account for the reduced price of nilotinib due to the PAS discount. In addition to the formulae errors, if the [redacted] discount in the price of nilotinib in 1st line and 2nd line is accounted for, the best case ICER for the BMS model is £45,600 per QALY for dasatinib compared to imatinib. When comparing dasatinib to nilotinib, the model predicts that nilotinib is more effective and less costly.
- The starting age of the simulated cohort, 46 years, is considerably lower than the mean age of newly diagnosed CML patients in the UK (56 years).
- The model does not adopt a lifetime time horizon. Instead the model is run until the cohort is 86 years old, at which point 20% of the cohort is still alive. If the model is extended to the age of 100, 10 per cent of the population is still alive. Assuming an equal distribution of males and females, data from the ONS predict that 2 per cent of those alive at 46 will be alive at the age of 100. This suggests that BMS overestimate the period that those with CML will survive.
- BMS uses 42 month follow up data from a RCT to predict overall survival for those with a complete, partial and 'less than partial' cytogenetic response to treatment at 12

months. Survival data is digitally extracted from published Kaplan-Meier curves and fitted to a Weibull distribution. There is no use of MMR response rates, the model only utilises cytogenetic response rates.

- BMS outline the effectiveness of 2nd line TKI's in their submission. However, this data is not used to model the effectiveness of 2nd line therapy.

- There are a number of assumptions with the BMS model which are not defined in detail. In addition, several parameters within the manufacturer submission do not reflect the data which is used in the model. For example, the data used to estimate the progression free survival (PFS) curves explained in Table 19 within the manufacturer submission does not match the data in the model. Also, the source quoted for PFS data in the submission is *Hochhaus et al*. However, the model appears to be using data from *Drunker et al* which is a study with a shorter follow up period. If the model is updated to use data from *Hochhaus et al* the ICER change as follows:

    - Dasatinib compared to imatinib: from £36,052 to £42,556 per QALY

    - Dasatinib compared with nilotinib: from £103,483 to £103,593 per QALY.

- BMS assume that dasatinib is taken 2nd- and 3rd-line. Given that BMS prepared their submission before NICE's recent draft guidance FAD on 2nd-line TKIs, BMS's assumption on the use of dasatinib 2nd- and 3rd-line was reasonable. However, in the NICE draft guidance FAD dasatinib 2nd- and 3rd-line was not recommended (the draft guidance FAD for 2nd line CML for high-dose imatinib, dasatinib and nilotinib, is available on the NICE website at http://guidance.nice.org.uk/TA/WaveR/99). When BMS' model is adjusted to remove dasatinib 2nd- and 3rd-line, the cost-effectiveness of dasatinib worsens substantially, as quantified above.

- BMS developed a highly complex model in an area where data is not of high quality. We believe the cost-effectiveness model could have been developed in a simpler way.

- It is not clear how BMS calculated the cost of Stem Cell Transplant (SCT). [redacted]

[redacted]

- On several occasions, the BMS report of the modelling differs from the actual model.

Areas of uncertainty

The BMS model does not provide the raw data which was used to fit the overall survival and time to treatment discontinuation curves. However, the choice of distribution and coefficients of the distribution appear to be correct on the basis of graphs showing the observed data and the fitted curves.

A considerable area of uncertainty is the chosen sequence of 2nd line TKI treatments that might follow failure of different 1st line TKIs. This is partly because the submission was prepared before NICE's draft guidance FAD on the use of dasatinib, nilotinib or high-dose imatinib as 2nd line treatments (the draft guidance FAD for 2nd line CML for high-dose imatinib, dasatinib and nilotinib, is available on the NICE website at http://guidance.nice.org.uk/TA/WaveR/99). However, uncertainty also results from the fact that data on the effectiveness of 2nd line TKI treatments is only available following the use of imatinib as 1st line treatment.

1.1.4. Key Issues

- Unfortunately, The BMS model does not use the cost of nilotinib agreed under the PAS in their submission.

- The BMS model is structured in such a way that it would require significant changes to run it without 2nd line treatment, should this be required by NICE.

- The time horizon chosen by the BMS model does not reflect the lifetime of a CML patient. In the model, nearly 20 per cent of the population is still alive in the last cycle (86 years old), suggesting that the model overestimates the period that those with CML will survive.

- The BMS model has a number of formulae errors, correcting for which impacts ICER.

- The cost and proportions of patients who receive SCT have a significant impact on ICERs, but the source of BMS's estimates of these parameters is unclear. Clinical opinion is required to assess whether the BMS assumption on the provision and costing of SCT is appropriate.

1.2. Background

1.2.1. Critique of manufacturer's description of underlying health problem

In section 2 of their submission BMS adequately describe the underlying health problem. BMS state the median age for disease onset to be 65, and the disease prevalence in England and Wales is ~2,660 patients (2003 data from NICE TA 70).[35] BMS use the following timeline to report phase duration of the disease:

- Chronic phase: 3-5 years
- Accelerated Phase 2-15 months
- Blast Crisis: 3-6 months

1.2.2. Critique of manufacturer's overview of current service provision

BMS use current treatment as counterfactual - imatinib 400mg for 1st line treatment of CML. However, the BMS cost-effectiveness analysis also compares their drug dasatinib with nilotinib. In their submission BMS correctly use the recently updated cost of £1,724.39 per 30-tab pack for imatinib, which has not yet been published by BNF but is listed in MIMS.

1.3. Critique of manufacturer's definition of decision problem

1.3.1. Population

The population in the BMS submission are the adults with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia in the chronic phase. This is an adequate description of the population under consideration, and concurs with that defined in the NICE Scope.

The BMS model uses an average age of 46 years old. This choice is based on the average age of patients in the DASISON Trial.[9]

1.3.2. Intervention sequences

BMS have modelled one scenario with three different comparators. The interventions and sequence of treatments are summarised in Table 1.

Table 1 Interventions and comparator sequences in BMS model (daily doses)

Line of treatment	Intervention	Comparator 1	Comparator 2
1st line	Dasatinib (100mg)	Imatinib (400mg)	Nilotinib (600mg)
2nd line	Nilotinib (800mg)	Dasatinib (100mg) or Nilotinib (800mg) (50:50 spilt)	Dasatinib (100mg)
3rd line	SCT or chemo/combination therapy or in-hospital palliative care	SCT or chemo/combination therapy or in-hospital palliative care	SCT or chemo/combination therapy or in-hospital palliative care

1.3.3. Outcomes

In the BMS model the outcomes for the economic analysis are: incremental cost per quality-adjusted life year and incremental cost per life-year gained. There is no discussion of appropriate ways for measuring these outcomes in the decision problem section. However, these are the appropriate outcomes for this assessment.

1.3.4. Time Frame

The BMS manufacturer submission state that a life time horizon is used; which is an appropriate timeline for modelling CML. However, in the BMS model nearly 20 per cent of the population is alive at the end of the last cycle (86 years old).

1.4. Economic evaluation

1.4.1. Overview of manufacturer's economic evaluation

The BMS base case analysis produces an ICER of £26,305 per QALY for dasatinib compared to imatinib as 1st line TKI, and £144,778 per QALY for dasatinib compared to nilotinib as a 1st line TKI. Overall, we found BMS' economic model and evaluation to be based on plausible structural assumptions and input parameters, with the following exceptions:

- The time horizon of the model does not follow a significant proportion of the population till death. Within the last cycle (86 years old) of the mode nearly 20 per cent of the population remain alive.
- In the context of the availability of 2nd generation TKIs for 2nd line treatment the model ignores any additional effectiveness of 2nd and 3rd line treatments.
- The patient access scheme discount for 1st and 2nd line nilotinib was not incorporated into the model.
- A number of assumptions and parameters used within the model are not reflected in the manufacturer's submission. In addition, there are discrepancies between the values stated in the manufacturer's submission and the model.
- A number of formulae errors have been identified in the model.

A full list of outputs from the original BMS model is presented below in Table 2.

Table 2 Breakdown of costs and benefits in the BMS model (original submission)

		Dasatinib	Imatinib	Nilotinib
PFS (years, undisc.)	Mean	19.16	17.14	19.28
PY (years, undisc.)	Mean	1.30	1.69	1.31
Life years (undisc.)	Mean	20.46	18.83	20.59
QALYs (disc.)	PFS	9.50	7.97	9.66
	PY	1.14	1.92	1.04
	Total	10.64	9.89	10.70

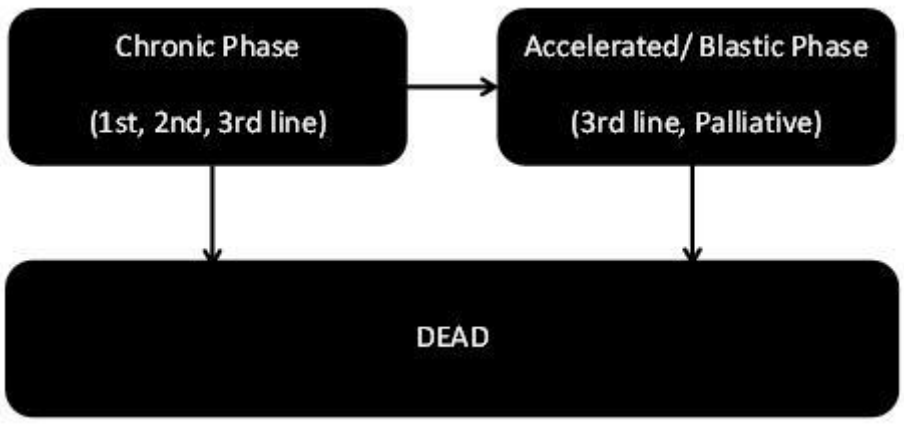
1st-line drug cost (disc.)	£283,209	£84,836	£282,887
2nd-line FC drug acquisition cost (disc.)	£60,336	£164,690	£77,350
3rd line treatment cost (disc)	£82,324	£145,215	£75,619
Adverse events 1st-line (disc.)	£2,321	£818	£1,291
Adverse events 2nd-line (disc.)	£412	£1,159	£562
Adverse events 3rd –line (disc)	£310	£616	£265
SCT*(disc.)	£5,350	£10,093	£4,954
Other	£63,955	£70,864	£63,685
Total costs (disc.)	£498,217	£478,293	£506,613
ICERs			
Cost / life-year gained (Dasatinib vs. Imatinib)			£32,785
Cost / life-year gained (Dasatinib vs. Nilotinib)			£116,447
Cost / QALY (Dasatinib vs. Imatinib)			£26,305
Cost / QALY (Dasatinib vs. Nilotinib)			£144,778

Abbreviations: PFS = progression free survival, PY = progressed years (i.e. years in accelerated and blast phase), QALYs = quality adjusted life years, SCT disc = stem cell transplant discounted.
**In the BMS model in the 3rd line treatment 30.6% receive SCT pre-progression and 50% post-progression*

1.4.2. Model Structure

BMS developed a 'time in state' (area under the curve) model, with the health states representing the early (CP) and advanced (AP/BP) stages as well as death.[36] This is based on extrapolating CML related survival data and progression-free survival data (Botteman et al 2010).[37] Time is presented in blocks of 1 month, and patients were simulated from age 46 years until age 86.

In the chronic phase, patients can be on 1st, 2nd or 3rd line treatment. Palliative care is only for patients in advanced phases (i.e. AP/BP). The model distinguishes between disease stages (CP, AP/BP) and lines of treatment (1st, 2nd or 3rd).



Source: Figure 5, p.40 of BMS submission

Figure 1 BMS model structure

The model is developed from the NHS perspective.

1.4.3. Natural history

The impact of TKIs on CML progression and survival is estimated using a combination of data on the effect of TKIs on cytogenetic response (CyR), and data on the impact of CyR on progression free and overall survival.

1.4.3.1. Effect Data

Effect is defined as the probability that each TKI achieves a complete, partial and less than partial response. Full response is defined as complete cytogenetic response – i.e. 0 per cent Ph+ metastases at 12 months. Partial response is defined as partial cytogenetic response – i,e. <= 35 per cent Ph+ metastases at 12 months. And less than partial response is defined as failed cytogenetic response – i.e. > 35 per cent Ph+ metastases. The less than partial response is calculated as the residual of full and partial.

The clinical effectiveness data for those achieving a complete response in 1st line therapy is taken from an unpublished systematic review commissioned by BMS.[38] This comprises a systematic review and network meta-analysis by Mealing and colleagues which pooled the effect estimates from the DASISION trial and another smaller trial by South West Oncology Group, updated to incorporate data presented at ASH 2010 and other peer-reviewed journals.[39]

The clinical effectiveness data for those achieving a partial response in 1st line therapy is taken directly from the respective RCTs - DASISON trial, for those receiving dasatinib and imatinib, and ENESTnd trial for those receiving nilotinib. Table 3 outlines the effectiveness of 1st line therapy based on CyR category.

Table 3 Effectiveness of 1st line therapy at 12 months by CyR type (complete, partial , less than partial)

	Full	Partial	< Partial
Dasatinib 100mg	77.1%	4.3%	18.6%

Imatinib 400mg	62.4%	14.6%	23.0%
Nilotinib 600mg	77.7%	4.3%	18.0%

Source: Table 20 and 21 of BMS submission

The effectiveness of 2nd line TKI is assumed to be the same as 2nd line treatment post imatinib as data for 2nd line treatment post dasatinib and nilotinib is not available. The data for 2nd line treatment is based on a report by Peninsula Technology Assessment Group.[1] Table 4 outlines the effectiveness of 2nd line therapy based on response category.

Table 4 Effectiveness of 2nd line therapy at 12 months by CyR type (complete, partial, less than partial)

	Full	Partial	Less than partial
Dasatinib 100mg	47.8%	14.2%	38.0%
Imatinib 800mg	16.3%	16.3%	67.4%
Nilotinib 800mg	35.1%	15.3%	49.6%

1.4.3.2. Survival estimates

Both PFS and OS are modelled from CyR post 1st line treatment. Data on the effectiveness of 2nd line therapy is not used to estimate either PFS or OS.

Surrogate outcome measures (e.g. level of CyR or molecular response) have been used in modelling CML as there is evidence that short-term response on these measures is predictive of longer term survival or progression-free survival. Also, the relationship between short-term cytogenetic response and long-term prognosis is believed (by BMS) to be similar for imatinib, dasatinib, and nilotinib, although no references or research is cited to support this claim.

In the BMS model, CyR (and in particular a complete, 'partial' or 'less than partial' response at 12 months) is used as a predictor of both PFS and OS. This relationship has been demonstrated in the clinical literature and used in a recently published model of interventions for imatinib resistant CML patients.[32, 40-42]

The data for the overall survival curve and progression free survival curves are taken from a number of different sources. Table 5 summarises the sources used.

Table 5 Data sources for modelling overall survival and progression free survival curves in BMS model

Curve	Dasatinib	Imatinib	Nilotinib
Overall survival			
Complete cytogenetic response	Roy et al 2006 (IRIS Study)[32]	Roy et al 2006 (IRIS Study)[32]	Roy et al 2006 (IRIS Study)[32]
Partial cytogenetic response	Roy et al 2006 (IRIS Study)[32]	Roy et al 2006 (IRIS Study)[32]	Roy et al 2006 (IRIS Study)[32]
< Partial cytogenetic response	Allen et al 1995[43]	Roy et al 2006 (IRIS Study)[32]	Allen et al 1995[43]
Progression free survival (all responses)	Hochhaus et al 2009 (IRIS Study)[27]	Hochhaus et al 2009 (IRIS Study)[27]	Hochhaus et al 2009 (IRIS Study)[27]

For patients receiving imatinib, long-term survival data is available from trial data. For patients receiving dasatinib and nilotinib, long term survival information is unavailable since dasatinib and nilotinib have only recently been licensed for use in newly diagnosed CML patients (December 2010).

The Roy and colleagues (IRIS Study) paper is a clinical trial focussing on the effectiveness of imatinib in comparison to interferon.[32] Only data from patients in the imatinib arm of the IRIS study was used. It is assumed that the estimated overall survival for those on dasatnib and nilotinib with a complete and partial cytogenetic response is the same as for those on imatinib, therefore data from Roy and colleagues is used for all three comparators for complete and partial CyR.[32] This assumption seems reasonable. It should be noted that the age group of the IRIS study is marginally older than the population which is modelled; 50 years old in comparison to 46 years old.

Data for the overall survival curve for a less than partial response for dasatinib and nilotinib is obtained from Allen et al 1995, which is a clinical trial focusing on the effectiveness of interferon in comparison to cytotoxic drugs for the treatment of CML.[43] It is assumed that the effectiveness of interferon for those with a less than partial CyR is similar to those with a less than partial cytogenetic response on dasatinib and nilotinib. In addition, the age group of

the trial is significantly older than the population which is modelled – 57 years old vs. 46 years old.

The IRIS clinical trial data covers a period of 6 years. However, the majority of patients receiving imatinib in this trial were still both alive and on 1st line therapy at the end of the trial (i.e. not progressed).[25, 27] Therefore, the long term trends of overall survival and progression free survival are not known. To extrapolate beyond the trial data, both the overall survival curves and progression free survival curves are based on Weibull distributions.

1.4.4. Health related quality of life

Health state utilities were taken from Szabo and colleagues and are reproduced in Table 6.[44] Szabo and colleagues is a UK, US, Australia, and Canada based study which derives utility values based on the Time Trade-Off method. The utility values are based on interviewer-administered survey responses from a sample of the general population (n = 353, of which 97 were from the UK). Respondents were provided with descriptions of CML related health states which were derived in consultation with medical professionals, and which characterized the chronic phase, accelerated phase, and blast phase for both responding and non-responding states and adverse events.

Table 6 Health state utilities used in BMS model

State	Value	Source
CP (responder)	0.8500	Szabo et al (2010) [44]
CP (non-responder)	0.6800	Szabo et al (2010) [44]
AP (responder)	0.7900	Szabo et al (2010) [44]
AP (non-responder)	0.5000	Szabo et al (2010) [44]
BP (responder)	0.5000	Szabo et al (2010) [44]
BP (non-responder)	0.3100	Szabo et al (2010) [44]
Progressed phase[V] (dasatinib)	0.6346	Calculated
Progressed phase (imatinib)	0.5967	Calculated

[V] BMS uses different utility for those in progressed phase as based on their model structure in a given state a patient can respond to treatment or progress while in the Novartis model, when the person becomes a non-responder, he/she moves to another state which has different utility.

Progressed phase (nilotinib)	0.6361	Calculated
Post SCT	0.7100	[redacted]

The BMS model assumes that only patients with a full cytogenetic response receive the higher utility value and that those with either a partial or less than partial response receive the lower value.

Utility associated with the AP/BP health state was derived from the above values. The challenge in deriving these estimates is the lack of knowledge surrounding the proportion of time an individual can expect to spend in each health state. To derive the AP/BP health state utility it is assumed that patients spend 2/3 of time in the AP, and 1/3 of in the BP. These time proportions are then applied to the probability of responding and the associated utility values outlined in Table 6 above.

For individuals who receive stem cell transplants, BMS use a baseline utility value of 0.71. [redacted]

The adverse event (AE) decrements (Table 7) are derived primarily from the chemotherapy literature, and in particular previous NICE submissions. Where utility estimates for AEs were not available from the non-CML literature a 5% (-0.05) decrement was assumed as no reference has been identified.

Table 7 Utility weights for adverse events used in the BMS model

Event	Value	Source
Anaemia	-0.0730	NICE 2006; LRIG 2006[46]
Diarrhoea	-0.0480	NICE 2006; LRIG 2006[46]
Dyspnoea	-0.0500	Doyle et al 2008[47]
GI haemorrhage	-0.0500	Assumption
Infection	-0.0500	Assumption
Neutropenia	-0.1600	Tabberer et al 2006[48]
Pneumonia	-0.0500	Assumption
Pyrexia	-0.0500	Assumption
Rash	-0.0500	Assumption
Thrombocytopenia	-0.0500	Assumption

We did not use the more recent TTO valuations of health states reported by Szabo and colleagues in our model because their methods do not meet the NICE reference case requirements, and because the study has a number of other notable weaknesses (see Box below).[44] (Being a TTO study in members of the public, the valuations produced by Szabo and colleagues does not reflect "changes in HRQL as reported directly from patients" and does not use the EQ-5D which is NICE's preferred measure of HRQL in adults.[8]

Box 1. Weaknesses of the TTO study by Szabo and colleagues[44]

- Although it is claimed that each health state description described the "typical patient experience" of a person in that phase of CML (and either responding or not responding to treatment), at no point in the process of developing and testing these descriptions were patients with CML involved – only clinical experts and descriptions of symptoms in the literature were consulted
- The difference in the health state descriptions for those responding and not responding to treatment is phrased entirely in terms being anxious and upset about the treatment not working and in terms of fear about the future: viz. (for chronic phase CML) "My doctor has told me that my treatment is not working. This has made me anxious and upset" and "I worry about my condition getting worse and I worry about my family. I understand that my health condition may get worse. I avoid making plans for the future". Note that these distinctions are again based on how doctors perceive that CML patients are impacted when they are told they are not responding to treatment, and may bear little relation to the person's wider health status and how it actually impacts on their quality of life.
- It might be questioned whether a standard 10-year lifetime horizon for the TTO exercise may have biased responses, or at least whether they were compatible with assessing some of the states where life expectancy might nowadays be considerably longer than this.

Szabo and colleagues also go on to make a number of misinformed criticisms of the EQ-5D based utilities from the IRIS study: firstly, they claim that IRIS did not collect EQ-5D data from patients in the accelerated or blast phase (they did; albeit in much smaller numbers); secondly, they claim that the pooling of data from different countries in the IRIS trial undermines the validity and applicability of the IRIS based EQ-5D valuations (this seems

flawed, because the English language EQ-5D was used in all four English-speaking countries, and UK-based valuations of the EQ-5D health states were used).[44]

1.4.5. Resources and costs

Only direct medical costs incurred by the NHS (including staffing and primary care) are included in the model. All values have been inflated to 2010 using the HCPS pay and prices inflation index.[49]

1.4.5.1. Drug costs

Drug costs in the BMS model are identified from the BNF (2011). Where multiple options for achieving the same daily dose were available BMS used a weighted average in the final calculation. BMS assumes the same BNF-derived cost for 1st line and 2nd line nilotinib, (and therefore neither of these reflects the reduced price now available via the recently approved Patient Access Schemes). Table 8 presents the costs used in the model.

Table 8 Drug Costs used in the BMS model

Medication	Unit Dose	Pack description	Pack price
Dasatinib	50mg	60-tab pack	£2,504.96
	100mg	30-tab pack	£2,504.96
Imatinib	100mg	60-tab pack	£862.19*
	400mg	30-tab pack	£1,724.39*
Nilotinib	150mg	112-cap pack	£2,432.85**
	200mg	112-cap pack	£2,432.85

***** Values taken from Novartis PPRS modulation announcement; MIMS
******Assumption (see text)

1.4.5.2. Adverse events costs

To cost adverse events, BMS uses a number of sources:

- Oxford Outcomes costing study (a survey of 6 UK-based clinicians who care for CML patients)[38]
- national UK databases

- previous NICE oncology appraisals
- expert opinion/ assumption.

Where data from the national schedule of reference costs is used, all information on elective and non-elective admissions has been identified and a weighted average was used in the model.

In deriving the cost estimate for each type of adverse event BMS have taken into account the proportion of people hospitalised for each AE and unit costs for an AE for those who were hospitalised and those who were not hospitalised. Separate values were specified for disease stage (CP or AP/BP). In deriving the final estimates used in the model BMS have assumed that two thirds of time in the AP/BP state is spent in the AP stage and one third in the BP stage. Table 9 below presents adverse event costs used in the BMS model.

Table 9 Treatment costs of adverse event used in the BMS model

Event	Unit Costs		Sources/Comments*
	CP	AP/BP	
Anaemia	£344.52	£385.30	
Diarrhoea	£82.17	£82.17	
Dyspnoea	£169.17	£504.35	
Fatigue	£21.90	£21.90	Derived from previous NICE appraisal*
GI bleeding	£1,082.61	£1,516.00	
Headache	£809.16	£809.16	NHS SRC (Currency code AA31Z)*
Infection	£574.88	£1,334.54	
Leukopenia	£503.75	£954.23	Assumed same as neutropenia
Nausea	£270.90	£270.90	Derived from previous NICE appraisal*
Neutropenia	£503.75	£954.23	
Pleural effusion	£184.43	£286.01	
Pneumonia	£949.09	£1,928.47	
Pyrexia	£295.59	£733.59	
Skin rash	£152.62	£188.02	
Thrombocytopenia	£501.21	£583.13	
Vomiting	£0.00	£0.00	Assumed no additional cost of treatment

*The gaps in the sources is a result of the BMS submission not providing clarity on the sources of all cost data.

1.4.5.3. Stem-cell transplant cost

The BMS model uses an estimated monthly cost of [redacted] for the remainder of SCT survivor's lives, [redacted] This was regarded as an implausibly high level of ongoing costs by the NICE Appraisal Committee which considered second generation TKIs after resistance or intolerance to imatinib (the draft guidance FAD for 2nd line CML for high-dose imatinib, dasatinib and nilotinib, is available on the NICE website at http://guidance.nice.org.uk/TA/WaveR/99, the committee recommendations are draft – consultees have the opportunity to appeal against them and final guidance has not been issued on this appraisal topic).

The overall cost of 3rd line treatment was adjusted so that only the proportion of patients who undergo stem cell transplantation actually incur this one-off and an additional ongoing cost.

1.4.5.4. Other costs

Other costs include outpatient visits, hospitalisation costs, various tests and scans. A full list of other costs used in the BMS model is presented in Table 43 in the Appendices.

1.4.6. Discounting

Costs and benefits were both discounted at annual rates of 3.5%, in line with the NICE reference case (NICE 2009).

1.4.7. Sensitivity analysis

Deterministic and probabilistic sensitivity analyses have been conducted and presented. One way SA was used to test the impact of disutility values (adverse events). Additional parameters that BMS tested in the SA are presented in Table 10.

Table 10 Parameters varied in SA

Parameter	Set to:	Dasatinib 100mg vs nilotinib 600mg	Dasatinib 100mg vs imatinib 400mg
Monthly cost of 1st line dasatinib	2000/3000	✓	✓
Dose intensity (dasatinib, Yr3+)	1/0.75	✓	✓
12 mo full response (1st line imatinib)	0.5/0.8		✓
Monthly cost of 1st line imatinib	1500/2500		✓
12 mo no response (1st line imatinib)	0.65/0.65		✓
Benefit disc rate (pa)	0/0.06		✓
ICU ward days (CP non-resp)	0.5/1		✓
ICU ward days (CP resp)	0.5/1		✓
Monthly cost of 2nd line dasatinib	2000/3000	✓	✓
Monthly post SCT cost	1200/3600		✓
Dose intensity (imatinib, yr 3+)	1/0.75		✓
12 mo full response (1st line dasatinib)	0.7/0.9	✓	✓
Monthly cost of 2nd line nilotinib	1500/4000	✓	✓
Monthly cost of 1st line nilotinib	2000/3000	✓	
Dose intensity (nilotinib 3yr+)	1/0.75	✓	
12 mo full response (1st line nilotinib)	0.7/0.9	✓	
12 mo no response (1st line dasatinib)	0.786/0.786	✓	
12 mo switch rate (<partial, dasatinib)	0.25/0.75	✓	
12 mo no response (1st line nilotinib)	0.8/0.8	✓	
Dose intensity (nilotinib, Yr1)	0.9/0.8	✓	
Dose intensity (dasatinib, Yr 1)	0.9/0.8	✓	

It was concluded that the model is sensitive to changes in the majority of parameters, and that the key drivers of cost-effectiveness are costs and QoL.

1.4.8. Model validation

In order to assess the clinical validity of the model results, a selection of key model outputs have been estimated (Table 44 in BMS submission) and presented. Given that all currently available long term data as well as clinical opinion were used to construct the model, validation of these results is complex and largely indirect. However, BMS compared the results from this model with those from other models (Reed at al 2008, [redacted], PenTAG 2009, Ghatnekar et al 2010), and with additional short term clinical data not used in model construction.[1, 42, 50, 51]

Uncertainty has been characterised through the use of statistical distributions. BMS presents the choice of distributions and the justification for each parameter category.

1.4.9. Major concerns with the BMS model

- Unfortunately, the BMS model does not use the cost of nilotinib agreed under the PAS in their submission.
- The time horizon chosen by the BMS model does not reflect the lifetime of a CML patient. In the model, nearly 20 per cent of the population is still alive in the last cycle (86 years old), suggesting that the model overestimates the period that those with CML will survive.
- A number of assumptions and parameters used within the model are not reflected in the manufacturer's submission. In addition, there are discrepancies between the values stated in the manufacturer's submission and the model.
- A number of formulae errors have been identified in the model.
- Unfortunately, BMS assume that dasatinib is taken 2nd- and 3rd-line. However, this has recently not been recommended in the NICE draft guidance FAD (the draft guidance FAD for 2nd line CML for high-dose imatinib, dasatinib and nilotinib, is available on the NICE website at http://guidance.nice.org.uk/TA/WaveR/99).
- The sources used to estimate the cost and proportions of patients who receive SCT are unclear.

1.5. Critical appraisal frameworks

This section summarises a critique of the BMS model. It is divided into the following two sub-sections:

- Appraisal of the BMS approach against general checklists.
- A critique of the BMS in light of the specific research problem.

1.5.1. Quality checklists

The BMS model has been appraised against the following commonly used quality checklists:

- NICE Reference Case Nice 2008 – Table 11.[8]

- Drummond and colleagues (Tables 12).[52]
- Philips and colleagues for decision model-based economic evaluations (Tables 13).[53]

Table 11 Critical appraisal of BMS dasatinib model based on NICE Reference Case (National Institute for Health and Clinical Excellence 2008)[8]

NICE reference case requirement		Critical Appraisal	Reviewer comment
Defining the decision problem	The scope developed by the Institute	✓	
Comparator	Therapies routinely used in the NHS, including technologies regarded as current best practice	✓	Comparator is either imatinib 400mg daily and nilotinib 600 mg daily.
Perspective on costs	NHS and PSS	✓	
Perspective on outcomes	All health effects on individuals	✓	Disutility of adverse events are included. Where disutility values could not be identified a value of -0.05 was assumed.
Type of economic evaluation	Cost effectiveness analysis	✓	
Synthesis of evidence on outcomes	Based on a systematic review	✓	Oxford Outcomes 2010 – interventions used as 1st line treatment for CML.
Measure of health benefits	QALYs	✓	
Source of data for measurement of HRQL	Reported directly by patients and/or carers	✓	Health state values based on *Szabo et al 2010* which is an interviewer based survey from non-CML patients.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	✓	
Discount rate	3.5% pa for costs and health effects	✓	
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	✓	

Table 12 Critical appraisal of BMS dasatinib model based on checklist from Drummond and colleagues (Drummond et al. 1997)[52]

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question?	✓	-
Is there a clear description of alternatives (i.e. who did what to whom, where, and how often)?	✓	-
Has the correct patient group / population of interest been clearly stated?	✓	No patient subgroups.
Is the correct comparator used?	✓	Imatinib 400mg daily and Nilotinib 600mg daily.
Is the study type reasonable?	✓	Standard area under the curve model.
Is the perspective of the analysis clearly stated?	✓	UK NHS & PSS
Is the perspective employed appropriate?	✓	-
Is effectiveness of the intervention established?	✓	
Has a lifetime horizon been used for analysis, if not has a shorter time horizon been justified?	x	At the last cycle of the model nearly 20 per cent of the population is alive. The model needs to be extended to reflect a lifetime horizon.
Are the costs and consequences consistent with the perspective employed?	✓	All costs from UK NHS & PSS perspective.
Is differential timing considered?	✓	
Is incremental analysis performed?	✓	
Is sensitivity analysis undertaken and presented clearly?	✓	Univariate and probabilistic sensitivity analyses clearly presented.

Table 13 Critical appraisal of BMS dasatinib model based on Philips et al. (2006) for model-based analyses.[53]

Dimension of quality			Comments
Structure			
S1	Statement of decision problem/objective	✓	
S2	Statement of scope/perspective	✓	NHS and PSS perspective. Cost and benefit inputs are consistent with the perspective. Scope of model stated.
S3	Rationale for structure	✓	Cohort model is appropriate.
S4	Structural assumptions	?	Model assumptions are not explained clearly in the report. Model is highly complex.
S5	Strategies / comparators	✓	See S1.
S6	Model type	✓	Cohort model is appropriate.
S7	Time horizon	?	A life-time horizon should have been adopted, however nearly 20 per cent of the population is alive at the last cycle.
S8	Disease states / pathways	✓	The disease states: chronic phase, accelerated phase, blast phase , and death are commonly used for CML.
S9	Cycle length	✓	1 month is appropriate.
Data			
D1	Data identification	✓	Data identification methods are well described.
D2	Pre-model data analysis	✓	.
D2a	Baseline data	✓	Baseline data from Oxford Outcomes Systematic Review.
D2b	Treatment effects	✓	
D2c	Quality of life weights (utilities)	✓	
D3	Data incorporation	?	Several explanations in the manufacturer's submissions do not reflect the model.
D4	Assessment of uncertainty	✓	
D4a	Methodological	✓	
D4b	Structural	✓	
D4c	Heterogeneity	✓	No patient subgroups, as appropriate.
D4d	Parameter	✓	Probabilistic and univariate sensitivity analyses performed.
Consistency			
C1	Internal consistency	?	Several logical errors identified within the cost-effectiveness model.
C2	External consistency	✓	

✓indicates 'clear', X indicates 'concerns',? indicates 'some concerns'

1.5.2. Critique of the modelling approach and structure

The description of the BMS model (section 1.4) identified a number of specific concerns with the BMS model. This section considers the implications of these concerns for the accuracy of the ICERs generated by the BMS model. Each concern is discussed in turn. The next section

then concludes with a summary of the ICERs once relevant updates have been made to the model.

Formulae errors in the model

There were several formulae errors which were identified in the model calculations. Table 14 summarises these errors and Table 15 summarises the impact on the ICER.

Table 14 Formulae errors identified in the BMS model

Description of error	Location (cell's in Trace tab)
Major errors	
The QALY value of all those in a health state is based on the following formula: (((those in CP – those with SCT)*QALY)+ ((those in AP/BP – those with SCT)*QALY)+ ((those with SCT)*QALY). In the original formula there are two mistakes: 1. The SCT patients which are being subtracted are from the next cycle instead of the current cycle, and 2. The number of SCT patients which are being subtracted is the cumulative value instead of the incremental value. For example, in cell IF75, based on the original calculation there are negative values of people in health states since the cumulative number of patients are being subtracted.	Column IF, IM, and IT
The probability of switching treatment from imatinib at 12m when under < partial response: "*PCT12MonthNCyRSwitchIMAT*" is input as 100% this contradicts table 25 in the manuf. submission where it clearly states this should be 58%.	CX20
The formula is using the wrong probability of switching i.e. formula uses *Pct18MonthPCyRSwitch* but should be using *Pct18MonthPCyRSwitchIMAT*.	CS26
Minor errors	
The probability of switching at 18m is applied to both cells where it should only be cell CU37.	CU37 and CU38
The calculation of cost for 3rd line resource use for those who are new AP/BP patients (i.e. cell KP8) is using the population of new arrivals from next cycle instead of current cycle.	Column GE and HL and HC
Formula is not using mortality adjusted population	Column GG and GH
Resource use cost was using dasatinib mortality unadjusted population for both CP and AP/BP	Column GS and HE
Formula is not using mortality adjusted population	Column GS GT

Terms in italics are defined variable names within the Excel spreadsheet

Table 15 Impact of formula errors on ICERs

ICER	Original values			After formula corrections		
	ICER	Incremental cost	Incremental QALY	ICER	Incremental cost	Incremental QALY
Dasatinib vs. Imatinib	£26,305	£19,924	0.76	£36,052	£29,834	0.83
Dasatinib vs. Nilotinib	£144,728	(-£8,396)	-0.06	£103,482	(-£8,782)	-0.08

Application of PAS costs for nilotinib

The BMS model does not incorporate the new reduced price of nilotinib for 1st and 2nd line under PAS. With [redacted] discount in nilotinib, the best estimate ICER for dasatinib compared to imatinib is £45,600 per QALY. In the case of dasatinib compared to nilotinib, nilotinib is less costly and more effective.

Predicted survival

The structure of the BMS cohort-based cost-effectiveness model is appropriate. The use of the chronic phase, accelerated phase, and blast phase is appropriate and consistent with the clinical disease progression in trials.

However, a key concern with the model is that it does not adopt a lifetime time horizon, despite the submission stating that such a time horizon is adopted. The model runs for a cohort between 46 and 86 years old, at which point nearly 20 per cent of the population remain alive. This suggests that the model overestimates the period that those with CML will survive.

This raises a number of questions of the BMS model. First, the model adopted a young onset age. Having stated that the average age of onset as 65 years old, BMS start the model at 46 years old. Furthermore, this onset age group is substantially younger than the population on which the trial data is established – 57 years old.

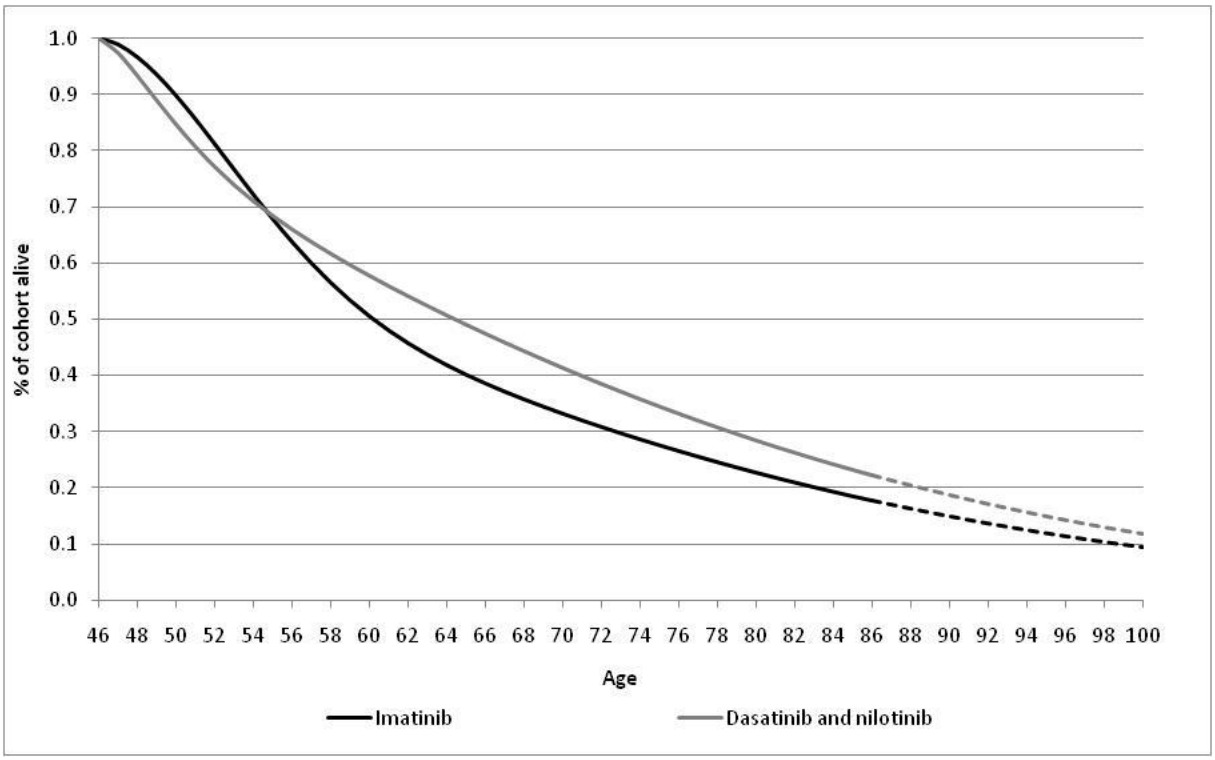


Figure 2 Overall survival predicted by BMS model

Graph produced by technology assessment group (i.e. not from BMS submission)

Second, the model seems to be overestimating the period of overall survival. Figure 2 above shows cohort survival as predicted by the model until age 86 years, and as extrapolated beyond the model period by the review team (dashed line). At the end of the period modelled by BMS, nearly 20 per cent of the cohort is still alive. Extending this survival trend beyond the model period demonstrates this implies that 10 per cent of the cohort would be alive at age 100 years. This compares with 2 per cent of the non CML population alive at 46 who would be alive at 100 years (ONS).

The impact on the ICERs of the extension to the period of the model to 100 years old is:

- The ICER for dasatinib compared to imatinib reduces from £36,052 to £31,456 per QALY.
- The ICER for dasatinib compared to nilotinib is reduced from £103,482 to £98,319 per QALY.

As summarised in section 1.4, estimates of survival are derived from the relationship between CyR and survival taken from the literature. Specifically, BMS state the source for the progression free survival curves as data from Hochhaus and colleagues, which is a 6 year follow-up study of patients receiving imatinib in the 1st line.[27] However, in the cost-effectiveness model, it appears that data from Druker and colleagues is used instead, which is a 5 year follow up study of patients receiving imatinib.[25] The data extrapolated from Druker and colleagues estimate nearly identical progressions free survival curves for those with a partial response and those with a less than partial response.[25] In comparison, data from Hochhaus and colleagues estimate a higher progression free survival curve for those with a partial response in comparison to those with a less than partial response.[27] When the progression free survival coefficients estimated by Hochhaus and colleagues are input into the model the ICER for dasatnib compared to nilotinib increases from £45,600 to £52,574 per QALY.[27] When comparing dasatnib to nilotinib, nilotinib continues to be dominant.

1.5.3. Updated BMS results

Table 16 below presents updated results after the formula error correction and in adjustment of nilotinib cost for 1st and 2nd line therapy to equal PAS [redacted]. These results do not reflect the adjustments to the model to disallow dasatinib as 2nd- and 3rd-line.

Table 16 Breakdown of costs and benefits in the BMS model (corrected for formula errors and nilotinib PAS cost)

		Dasatinib	Imatinib	Nilotinib
PFS (years, undisc.)	Mean	19.16	17.14	19.28
PY (years, undisc.)	Mean	1.30	1.69	1.31
Life years (undisc.)	Mean	20.46	18.83	20.59
QALYs (disc.)	PFS	10.16	9.17	10.24
	PY	0.48	0.64	0.48
	Total	**10.64**	**9.81**	**10.72**
1st-line drug cost (disc.)		£283,308	£88,483	[redacted]
2nd-line FC drug acquisition cost (disc.)		£39,949	£135,876	£77,319
3rd line treatment cost (disc)		£82,062	£135,775	£75,416
Adverse events 1st-line (disc.)		£2,322	£854	£1,292
Adverse events 2nd-line (disc.)		£412	£1,156	£562
Adverse events 3rd –line (disc)		£309	£565	£264
SCT (disc.)		£5,325	£9,281	£4,935
Other		£63,899	£67,861	£63,971
Total costs (disc.)		**£477,585**	**£439,851**	**£411,108**
ICERs				
Cost / life-year gained (Dasatinib vs. Imatinib)				£62,093
Cost / life-year gained (Dasatinib vs. Nilotinib)				(-£922,003)
Cost / QALY (Dasatinib vs. Imatinib)				£45,600
Cost / QALY (Dasatinib vs. Nilotinib)				(-£783,367)

1.5.4. Updated BMS model to disallow dasatinib as 2nd- and 3rd-line.

As explained above, BMS assume dasatinib is taken as 2nd- and 3rd-line. Technically, we adjusted BMS' model to disallow these options as follows.

First, to disallow dasatinib 3rd-line, in worksheet "3rdLineResUse", cell D13 is changed from 0% to 100%, and cell D16 is changed from 80% to 0%. The ICER of dasatinib vs. imatinib then increases from £45,600 to £64,000 per QALY.

Next, to disallow dasatinib 2nd-line, in worksheet "Rx Sequence", cell D12 changed from 50% to 0%, and cell D13 changed from 50% to 100%. The ICER of dasatinib vs. imatinib then increases from £64,000 to £96,000 per QALY.

2. Novartis submission

2.1. Summary

2.1.1. Scope of the submissions

The submission from Novartis considers the use of nilotinib (Tasigna®) for the 1st line treatment of people with chronic myeloid leukaemia (CML) as an alternative to the standard dose of imatinib (400mg daily). Dasatinib is used in the cost-effectiveness model as 2nd line treatment when 1st line treatment with imatinib or nilotinib fails.

The clinical effectiveness outcomes considered are progression free survival, time to discontinuation, adverse effects of treatment and health-related quality of life.

The outcomes for the economic analysis were incremental cost per quality-adjusted life-year, and incremental cost per life year gained. In order to derive these outcomes the following costs were estimated in the model: cost of 1st and 2nd line TKI's, cost of post-TKI failure 2nd or 3rd line treatment, and the cost of treating adverse events. The time horizon for the economic analysis is lifetime and costs are considered from the NHS perspective.

The Novartis cost-effectiveness modelling reflects a cost discount (Patient Access Scheme (PAS) for the cost of 1st line nilotinib [redacted]. This equates to a discount of [redacted] from the NHS List Price for a 28-day pack of nilotinib. Their cost of 2nd line nilotinib also reflects this cost discount (also a PAS). No subgroup analyses are conducted for the economic evaluation, although a policy scenario without the use of 2nd generation TKIs is simulated.

2.1.2. Summary of submitted cost-effectiveness evidence

The manufacturer uses a Markov approach to model the cost-effectiveness of nilotinib compared to the current standard of care (imatinib 400mg daily). This model has nine states. Patients enter the model in the chronic phase. The model estimates when one treatment fails and hence the patient is switched to an alternative treatment. At the end of each cycle, patients have a probability of remaining on current treatment, progressing to an alternative treatment or dying.

The Novartis model predicts that nilotinib is both more effective and less costly compared to imatinib, when followed by dasatinib as 2nd line treatment. In a scenario analysis without dasatinib as 2nd line treatment, the model predicts an ICER of £5,908 per QALY for nilotinib in comparison to imatinib. The sensitivity analysis shows the key parameters which the cost-effectiveness results are sensitive to are drug costs (i.e. without PAS), and time to discontinuation of 1st line TKI.

No major formula errors have been identified in the Novartis model.

2.1.3. Commentary on the robustness of submitted evidence

Strengths

- The approach taken to modelling is reasonable
- The sources and justification of estimates are also generally reasonable

Weaknesses

- Novartis make no use of the major molecular and complete cytogenetic response rates from the RCT of nilotinib vs. imatinib, both of which are important indicators of clinical effectiveness.
- We believe that Novartis' method of estimating the time on HU in CP is flawed.

2.1.4. Areas of uncertainty

Novartis model does not provide the raw data which was used to fit the overall survival and time to treatment discontinuation curves. However, the choice of distribution and coefficients of the distribution appear to be correct on the basis of graphs showing the observed data and the fitted curves.

Another area of uncertainty is the chosen sequence of 2nd line TKI treatments that might follow the failure of different 1st line TKIs. This is partly because this submission was prepared before NICE's forthcoming draft guidance FAD on the use of dasatinib, nilotinib or high-dose imatinib as 2nd line treatments (the draft guidance FAD for 2nd line CML for high-dose imatinib, dasatinib and nilotinib, is available on the NICE website at http://guidance.nice.org.uk/TA/WaveR/99). However, uncertainty also results from the fact

that data on the effectiveness of 2nd line TKI treatments is only available following the use of imatinib as 1st line treatment.

Another area of uncertainty is regarding the cost and utility of stem cell patients. Assumptions around SCT significantly impact the model. Novartis uses a one-off cost of £99,224 for each transplant with a post transplant utility for survivors of 0.813m, which decreases with age.

2.1.5. Key Issues

- Novartis uses patient access scheme (PAS) for pricing nilotinib as 1st line treatment. This has significant impact on the results.
- Novartis make no use of the major molecular and complete cytogenetic response rates from the RCT of nilotinib compared to imatinib, both of which are important indicators of clinical effectiveness.
- The cost and the proportions of patients who receive Stem Cell Transplant differ between the Novartis and BMS models and has a significant impact on ICERs. Clinical opinion is required is BMS assumption on the provision and costing of SCT is appropriate.

2.2. Background

2.2.1. Critique of manufacturer's description of underlying health problem

In section 1 of their submission Novartis adequately describe the underlying health problem. Novartis state the median age for disease onset to be 55 and disease prevalence in England and Wales as ~2,660 patients (2003 data from NICE TA 70). Novartis use the following timeline to report phase duration of the disease:

- Chronic phase: 3-5 years
- Accelerated Phase: 1-2 years
- Blast Crisis: 3-12 months

2.2.2. Critique of manufacturer's overview of current service provision

Novartis use current treatment as the counterfactual (imatinib 400mg for 1st line treatment of CML) and the recently updated cost of £1,724.39 per 30-tab pack for imatinib, which has not yet been published by BNF but is listed in MIMS.

2.3. Critique of manufacturer's definition of decision problem

2.3.1. Population

The Novartis submission considers adult patients with Ph+ CML diagnosed in chronic phase and who do not initially receive a stem cell transplant (SCT). This is an adequate description of the population under consideration, and concurs with that defined in the NICE Scope.

Novartis' model uses an average age of 57. This choice is based on the average age of patients in the ENESTnd Trial.

2.3.2. Intervention sequences compared

Novartis modelled two different scenarios to reflect the availability or not of 2nd generation TKIs as 2nd line treatment. The interventions and sequence of treatment is summarised in Table 17.

Table 17 Interventions and comparator sequences in Novartis model

Line of treatment	Scenario 1		Scenario 2	
	Nilotinib	Imatinib	Nilotinib	Imatinib
1st line	Nilotinib (600)mg	Imatinib (400mg)	Nilotinib (600)mg	Imatinib (400mg)
2nd line	Dasatinib (100mg)	Dasatinib (100mg)	SCT or HU	SCT or HU
3rd line	SCT or HU	SCT or HU	n/a	n/a

2.3.3. Outcomes

In the Novartis model, outcomes of the economic analysis were: incremental cost per quality-adjusted life year, and incremental cost per life-year gained. There was no discussion of

appropriate ways for measuring these outcomes in the decision problem section. However, these are the appropriate outcomes for this assessment.

2.3.4. Time Frame

Novartis used a life time horizon; which is an appropriate timeline for modelling CML.

2.4. Overview of manufacturer's economic evaluation

The Novartis model estimates that nilotinib 1st line followed by dasatinib as 2nd line treatment would be both more effective (generating 0.55 extra discounted QALYs per patient) and less costly (£10,371 cheaper per patient) than imatinib followed by dasatinib. Without dasatinib as 2nd line treatment, the model predicts an ICER of £5,908 per QALY for 1st line nilotinib in comparison to imatinib.

Overall, we found the Novartis model to be robust. A full list of outputs from the original Novartis model is presented below in Table 18.

The base case results in the Novartis report (p111) are different to those in the model. However, deterministic results in Appendix (p132) agree with the model.

Table 18 Breakdown of costs and benefits in the Novartis model

		Nilotinib/Das	Imatinib/Das	Nilotinib	Imatinib
PFS (years, undisc.)	Mean	12.66	11.94	10.64	9.30
PY (years, undisc.)	Mean	0.88	0.90	0.74	0.68
Life years (undisc.)	Mean	13.54	12.83	11.38	9.97
QALYs (disc.)	PFS	9.93	9.38	8.31	7.25
	PY	0.47	0.48	0.40	0.37
	Total	10.40	9.85	8.71	7.62
1st-line drug cost (disc.)		[redacted]	£104,038	[redacted]	£104,038
2nd-line FC drug acquisition cost (disc.)		£57,532	£77,284	refer to SCT	refer to SCT
3rd line treatment cost (disc)		£170	£175	£411	£147
Adverse events 1st-line (disc.)		£111	£178	£111	£178
Adverse events 2nd-line (disc.)		£37	£51	n/a	n/a
Adverse events 3rd –line (disc)		n/a	n/a	n/a	n/a
SCT (disc.)		£28,772	£31,183	£42,383	£49,986
Other		£15,979	£14,835	£12,966	£11,667
Total costs (disc.)		£217,373	£227,744	£170,643	£166,015

ICERs	
Cost / life-year gained (Nilotinib vs. Imatinib, with 2nd line)	-(£27,739)
Cost / life-year gained (Nilotinib vs. Imatinib, without 2nd line)	£4,701
Cost / QALY (Nilotinib vs. Imatinib, with 2nd line)	**-(£34,889)**
Cost / QALY (Nilotinib vs. Imatinib, without 2nd line)	**£5,908**

Abbreviations: PFS = progression free survival, PY = progressed years (i.e. years in accelerated and blast phase), QALYs = quality adjusted life years, SCT disc = stem cell transplant discounted

2.4.1. Model Structure

A Markov model was developed in MS Excel 2007 for a hypothetical cohort of 1000 patients. The cycle length in the model is 1 month for the first 6 months, and then 3 months. A lifetime horizon is assumes in the model, with a final age of 100.

Equal numbers of male and female patients enter the model at the age of 57. Patients enter the model in chronic phase (CP). The model estimates when one treatment will fail and hence the patient is switched to an alternative treatment. At each cycle, patients have a probability of remaining on current treatment, progressing to an alternative treatment or dying (see Figure 3 below). Patients are able to remain in CP, accelerated phase (AP) or blast phase (BP) for more than one cycle, and they may die from other causes at any time. Patients that receive

a transplant may die from transplant-related mortality or remain well. Patients that are treated with HU have a probability of progressing to AP. On progression to AP or BP, all patients are assumed to receive HU therapy. Patients in AP have a probability of progressing to BP, and finally from BP to CML-related mortality. In BP, patients may only die as a result of CML. The Novartis model is developed from the NHS perspective.

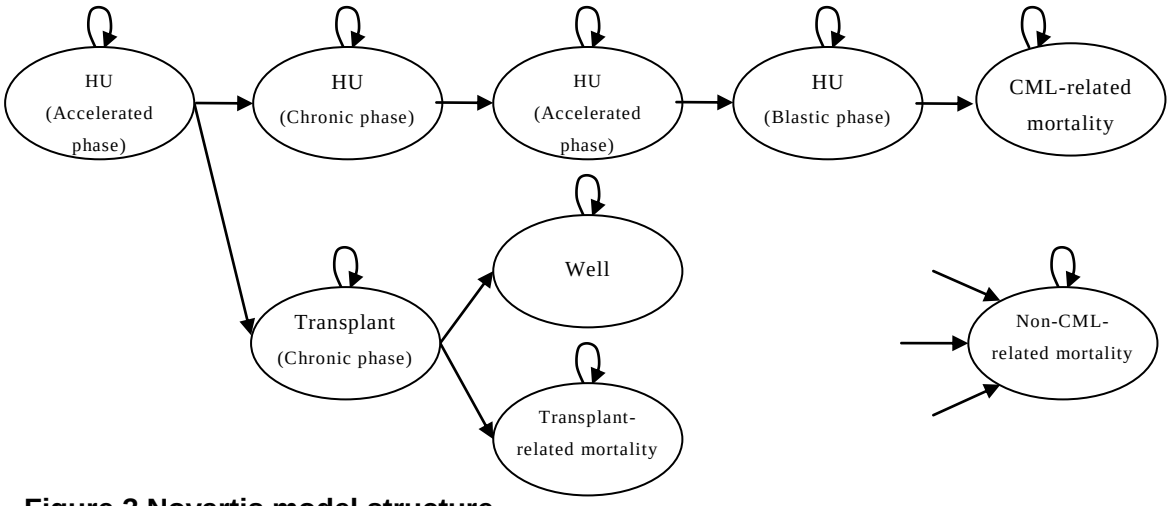


Figure 3 Novartis model structure

2.4.2. Natural history

The impact of TKIs on CML progression and survival is estimated using a combination of data on the effect of TKIs on discontinuity of treatment, and data on the relationship between discontinuity and progression free and overall survival.

2.4.2.1. Effect data

The Novartis model uses time to treatment discontinuation as the primary measure of the clinical effectiveness of the different treatments. The data for time to treatment discontinuation data used in the Novartis model are provided in Table 19. Table 20 summarises the multiple sources from which these data are taken.

Table 19 Discontinuation rates used in Novartis model

	1st line		2nd line (dasatnib)		3rd line CP (HU)	HU AP	HU BP
1st line treatment	Imatinib	Nilotinib	Imatinib	Nilotinib	Imatinib & Nilotinib	Imatinib & Nilotinib	Imatinib & Nilotinib
Per month – for first 6 months in model	0.05*	0.13*	0.28	0.22	0.052	0.104	0.101
Per 3 months for > 6 months in model	0.034*	0.026*	0.80	0.63	0.149	0.280	0.274

** Probability of discontinuing treatment in continuous, therefore the average value of the period is reported*

Table 20 Data source for time to treatment discontinuation in Novartis model

Curve	1st line	2nd line	HU
Nilotinib	ENESTnd trial (24 Month Clinical Study Report)	Shah et al. (2010)[54] & Garg et al. (2009)[55]	CAMN107A 2101 trial
Imatinib	ENESTnd trial (24 Month Clinical Study Report)	Shah et al. (2010)[54]	CAMN107A 2101 trial

The data for 1st line treatment is provided by the ENESTnd Trial (referred to as CAMN107A2303 in some parts of the industry submission). The trial assesses the clinical effectiveness of nilotinib in comparison to imatinib for newly diagnosed chronic phase CML patients, with a mean age of 47 years. The trial had a significantly younger starting population than the one included in the Novartis model (i.e. 56 years old).

The data for 2nd line treatment is taken from two sources – Shah and colleagues & Garg and colleagues.[54, 55] The Shah and colleagues trial measured the effectiveness of dasatinib as 2nd line treatment after imatinib failure. Shah and colleagues report the proportion remaining on treatment at 24 months. Based on this the monthly probability of discontinuing dasatinib post-imatinib is estimated as 0.22 and the quarterly probability is estimated as 0.63.

There is no study measuring the effectiveness of 2nd line dasatinib following nilotinib. It was assumed that 2nd line dasatinib following nilotinib would be less effective in comparison to

when following 1st line imatinib. In order to derive a lower effectiveness the effectiveness reported by Shah and colleagues was averaged with the effectiveness reported by Garg and colleagues who measure the effectiveness of dasatinib as 3rd line therapy. Similar to Shah and colleagues, Garg and colleagues report the proportion remaining on treatment at the end of the study. Based on this data the monthly probability of discontinuing dasatinib post nilotinib is estimated as 0.28 and the quarterly probability is estimate as 0.80. However, the median age for patients receiving dasatinib as 3rd line treatment in the study was 53 years old which is slightly younger than the modelled population (56 years old).

Novartis state that the time spent in CP[VI] on HU therapy is based on data reflecting the time in CP following 2nd line TKI treatment failure. The difference between the time to discontinuation and progression free survival curves is used to derive the number of years in CP on HU. In order for this logic to be consistent, the PFS data should reflect progression only to the AP/BP. However, the data used to populate the progression free survival curve accounts for progression due other reasons than progression to AP and BP, such as poor haematological response. Therefore the estimated time spent in CP on HU is not completely accurate. In addition, the source used to derive the PFS is not identified in the model. In the model it appears that the PFS data was fit to an exponential curve. Based on the data there is a 0.052 monthly probability of discontinuing HU in CP, and the quarterly probability is 0.149.

The time spent in the AP and BP on HU is from the Kantarjian et al 2007 study.[56] Novartis fit the data from the study to a number of different distributions to find the best way to extrapolate the data. Based on this an exponential curve was used. The exponential curve predicted a monthly probability of discontinuing HU in the AP of 0.104, and a quarterly probability of 0.228. The monthly probability of discontinuing HU in the BP and ultimately leading to CML related death is 0.101 and the quarterly probability is 0.274.

Novartis assume that time on HU and survival associated with SCT is independent of previous TKI treatments. For example, as can be seen in Table 19, it is assumed that the effectiveness of HU is the same for both imatinib and nilotinib. In addition, these discontinuation rates are applied in both the scenario where 2nd line TKIs are available and

[VI] Data on time in state is presented in Table 29 (Section 4.2)

the scenario where they are not available. Therefore it is assumed that HU is equally effective following nilotinib and dasatinib failure, as it is with only nilotinib failure.

2.4.2.2. Survival data

Overall survival of patients is predicted based on the time to treatment discontinuation summarised in the previous section, which were used to determine transition probabilities within the Markov model. That is, survival is the cumulative result of the model's assumptions about treatment discontinuation of 1st, 2nd and 3rd line treatments (previous section). Figure 4 shows the overall survival predicted by the Novartis model. It demonstrates that at 100 years the entire population has died.

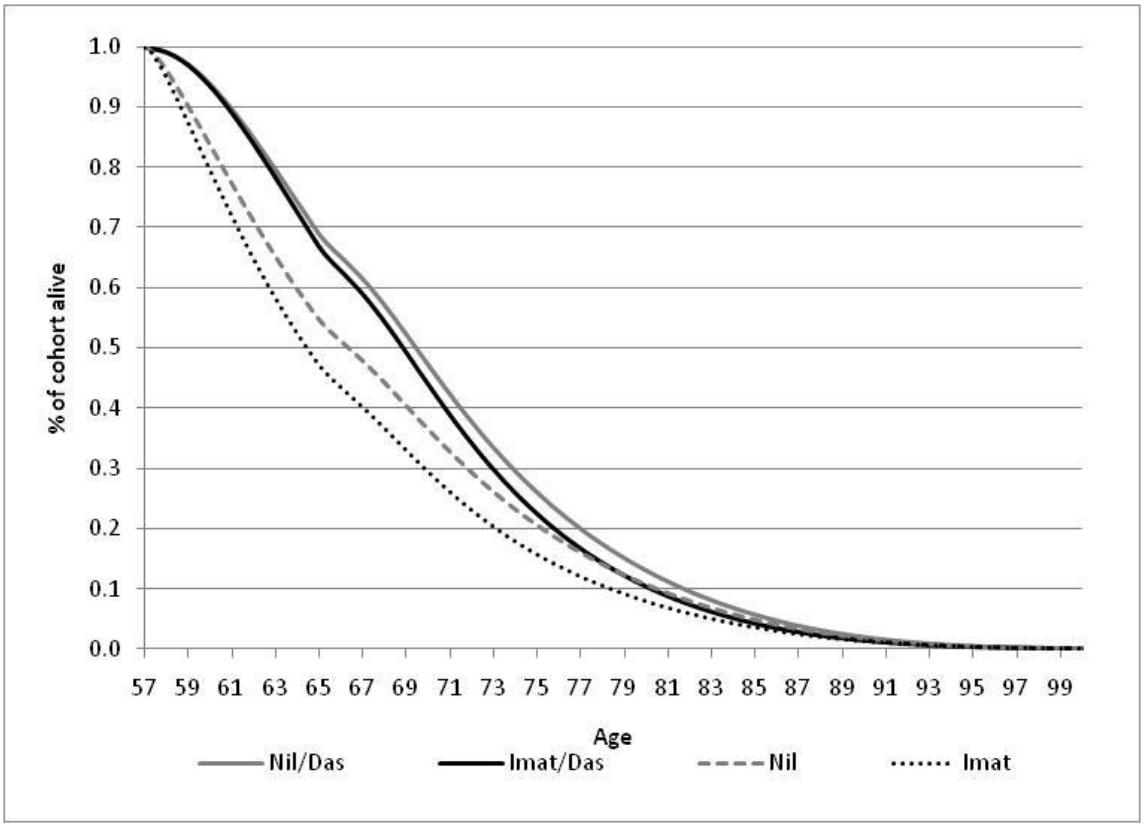


Figure 4 Predicted overall survival –Novartis

Time spent in AP and BP is based on data from Kantarjian et al 2007, and is assumed to be the same independent of prior treatment.[56] In order to model cost and QALY gains over a lifetime, the available evidence was extrapolated within the economic model.

2.4.3. Health related quality of life

Novartis used evidence from a model-based cost-effectiveness analysis in which the utility estimates were based on responses to the EQ-5D preference-based measure of health-related quality of life of patients in the IRIS study who were receiving standard-dose imatinib.[50] Based on this paper, the modelled baseline utility of being in CP is assumed to be 0.854, while the baseline utility of being in AP or BC is 0.595. These utilities were assumed to be independent of drug therapy[VII].

Sensitivity analyses around the baseline utility values were conducted using utility values reported by Szabo and colleagues.[44] Szabo and colleagues is a UK, US, Australia, and Canada based study which derives utility values based on the Time Trade-Off method. The utility values are based on interviewer-administered survey responses from a sample of the general population (n = 353, of which 97 were from the UK). Respondents were provided with descriptions of CML related health states which were derived in consultation with medical professionals, and which characterized the chronic phase, accelerated phase, and blast phase for both responding and non-responding states and adverse events.

The utilities are adjusted for age to take account of the fact that:

- Patients in the modelled cohort (starting age, 57 years) are older than patients in the IRIS study (mean age: 50 years) from which the EQ-5D utility values were obtained.
- The average utility of a given population decreases as age increases, e.g. the utility of patients remaining in good health in the chronic phase will not remain constant but will decline gradually over time due to aging. Assuming a constant utility by health state over time ignores the natural decline in quality of life associated with co-morbidities etc, potentially over-estimating the benefits of treatment.

[VII] In the Novartis model utility is associate only with a given state as a person changes the state as he/she becomes a non-responder, thus it is reasonable for Novartis not to provide utility weight for non-responder as BMS has done.

However, neither the Novartis report nor the model provide explanation about or further details on how the age adjustment calculation was undertaken.

The utility weights associated with stem cell transplant used in the Novartis model is 0.813. Further, in the base case analysis, a decrement of 0.079 was applied to the long-term utility for 52% of patients following transplant to reflect common adverse events associated with SCT.[57] Given that this relates to only one specific AE associated with allo-SCT, it is likely to be an underestimate of the utility decrement experienced by patients following allo-SCT. Table 21 below presents utility weights that Novartis used in their model.

Table 21 Utility weights used by Novartis

State	Utility	Source
Health states		
CP (1st and 2nd line)	0.854	Reed et al. 2004 (assumption for 2nd line)[50]
AP (1st and 2nd line)	0.595	Reed et al. 2004 (assumption for 2nd line)[50]
BC (1st and 2nd line)	0.595	Reed et al. 2004 (assumption for 2nd line)[50]
Adverse events		
Disutility associated with AEs on Nilotinib	0.010	Calculated
Disutility associated with AEs on Imatinib	0.016	Calculated
Disutility associated with AEs on HU	0.000	Assumption
Disutility associated with AEs on Dasatinib	0.019	Calculated
Stem Cell Transplant (high/low risk groups)	0.813	Assumption
Utility decrement associated with Stem Cell Transplant	0.079	Lee et al. (1997)[57]
Applied to 52% of SCT recipients		

Only grade 3 and 4 AEs for TKI therapies were incorporated into the model because they are the most likely to impact upon quality of life and incur additional resource use beyond the routine appointments of these patients (a list of AEs is included in Table 23). It was assumed that grade 3 and 4 AEs would occur only within the first 18 months of treatment because the trial data suggest that very few grade 3 and 4 AEs occur beyond this time period. It was assumed that HU therapy would not typically be associated with grade 3 and 4 AEs; hence

disutility effects were only applied within the first 18 months for 1st line treatment with nilotinib and imatinib, and 2nd line treatment with dasatinib.

Novartis searched the literature to identify utility values for common grade 3 and 4 AEs related to CML treatment with TKIs. AEs that were associated with substantial utility or cost impacts were included within the analysis. Where utilities were not available for these AEs related to CML, utilities associated with AEs for similar diseases were included. In general these utilities were not based on EQ-5D data owing to the limited availability of this evidence. These utilities were used along with the duration of the AE and the probability of experiencing the AE to calculate the disutility of experiencing AEs resulting from 1st line nilotinib or imatinib treatment and from 2nd line dasatinib treatment.

2.4.4. Resources and costs

Only direct medical costs are incorporated into the model. These include the costs associated with the different drug therapies, routine hospital appointments for administration and monitoring, and treatment for grade 3 and 4 AEs.

2.4.4.1. Drug costs

Drug costs used by Novartis are mainly taken from the BNF and are presented in Table 22

Table 22 Quarterly drug costs used by Novartis

TKI treatment	Quarterly drug cost, including dose-intensity adjustments
1st line imatinib	£5,547
1st line nilotinib (with PAS)	[redacted]
1st line nilotinib (without PAS)	£7,319
2nd line dasatinib	£7,034

NB. Dose intensity adjustments are [redacted] of the standard licensed doses of nilotinib and imatinib respectively, based the ENESTnd trial data at 24 months.

Novartis applies a cost discount (PAS) to nilotinib.

[redacted]

For imatinib 400 mg, the cost of the 30-day pack is £1,724, equivalent to a daily cost of £57.50. This equates to a [redacted] from the NHS List Price of a 28-day pack of nilotinib. The current NHS List Price of 28-day pack of nilotinib is £2,433 (600mg); under the PAS, the cost per pack is [redacted].

2.4.4.2. Adverse events costs

The costs of grade 3 and 4 AEs were considered because these were more likely to incur additional resource use beyond the regular intensive follow-up of these patients. The costs of grade 1 and 2 AEs were excluded as clinical expert opinion suggested that these would typically require minimal treatment and hence would have limited resource implications. Treatment for each AE was based on clinical expert opinion. The monthly costs of AEs associated with each therapy were weighted by their respective costs. Adverse events costs used by Novartis are presented in Table 23.

Table 23 Adverse events costs used in Novartis model

Adverse event	Cost (£)*	Assumption/source
Anaemia	£911	One red blood cell transfusion (Varney and Guest (2003) inflated from 2000/01 to 2010/11). [58]
Neutropenia	-	Minimal treatment
Thrombocytopenia	£537	Weighted cost: grade 3 (64%) and grade 4 (36%)
Grade 3	-	*No treatment assumed for grade 3*
Grade 4	*£1,493*	*Three platelet transfusion (Varney and Guest (2003) inflated from 2000/01 to 2010/11).*[58]
GI bleed	£5,233	Five in-patient days (NHS Reference Costs 2008/09 inflated to 2010/11)[59] plus Cost of therapeutic endoscopic procedure (NHS Reference Costs 2008/09 inflated to 2010/11)[59] plus Three transfusions of platelet plus two transfusions of red blood cells (Varney and Guest (2003) inflated from 2000/01 to 2010/11).[58]
CNS bleed	£4,306	Five in-patient days (NHS Reference Costs 2008/09 inflated to 2010/11)[59] plus Five transfusions of platelet (Varney and Guest (2003) inflated from 2000/01 to 2010/11).[58] plus One CT scan (NHS Reference Costs 2008/09 inflated to 2010/11).[59]
Pleural effusion	£2,775	Weighted cost: grade 3 (64%) and grade 4 (36%)

Grade 3	£680	*Two in-patient days (NHS Reference Costs 2008/09 inflated to 2010/11)*[59]
Grade 4	£6,500	*One week intensive care "Adult Critical Care - 1 Organs Supported" (NHS Reference Costs 2008/09 inflated to 2010/11)*[59]
Pericardial effusion	£1,963	Five in-patient days plus cost of 2 echocardiograms (NHS Reference Costs 2008/09 inflated to 2010/11).[59]
CHF/cardiac dysfunction	£874	Weighted cost: Grade 3 (64%) and Grade 4 (36%)
Grade 3	£262	2 echocardiograms (NHS Reference Costs 2008/09 inflated to 2010/11).[59]
Grade 4	£1,963	Five in-patient days plus cost of 2 echocardiograms (NHS Reference Costs 2008/09 inflated to 2010/11).[59]

2.4.4.3. Other costs

Based on clinical opinion, Novartis include the following appointments:

- Patients in CP have a routine appointment at the start of treatment, with successive visits at intervals of 1 week, 2 weeks, 4 weeks and every 6 weeks thereafter.
- Patients in AP are assumed to have six routine appointments per quarter.
- Patients in BC are assumed to have twelve routine appointments per quarter.

Based on clinical advice, the routine appointments are assumed to be an out-patient visit, during which patients would receive a full blood chemistry test and physical examination at every second appointment.

Patients are also likely to receive around three bone marrow tests during treatment. Since these are low-cost tests, the model assumes that their cost is absorbed within the estimated cost of an out-patient visit.

The cost of each routine visit was therefore taken to be £138 (NHS reference costs 2008/09 – 'Clinical Haematology: NHS Trusts Consultant Led Follow up Attendance Non-Admitted Face to Face' inflated to 2010/11).[59]

Novartis has also assumed based on clinical advice that patients will require, on average, a two-week in-patient stay as end of life care.

The cost of allo-SCT, in the first 100 days, is assumed to be £99,224 derived from a weighted average of the costs reported by the London Specialised Commissioning Group Workshop for

related and unrelated donors, taking into account the cost of antifungal and donor lymphocyte infusion (DLI).[60]

Table 24 summarises the other costs used in the model.

Table 24 Other costs used in the Novartis model

Parameter	Value	Source
Cost of routine appointment (outpatient visit)	£138	NHS reference costs 2008/09 (inflated to 2010/11)[59]
Cost of in-patient visits	£340	NHS reference costs 2008/09 (inflated to 2010/11)[59]
Cost of intensive care	£929	NHS reference costs 2008/09 (inflated to 2010/11)[59]
Cost of red blood cell transfusion	£911	Varney and Guest, 2003 (inflated from 2000/01 to 2010/11)[58]
Cost of platelet transfusion	£498	Varney and Guest, 2003 (inflated from 2000/01 to 2010/11)[58]
Therapeutic endoscopic procedure	£218	NHS reference costs 2008/09 (inflated to 2010/11)[59]
CT scan	£118	NHS reference costs 2008/09 (inflated to 2010/11)[59]
Echocardiogram	£131	NHS reference costs 2008/09 (inflated to 2010/11)[59]

2.4.5. Discounting

All costs and QALYs are discounted by 3.5% as recommended by NICE

2.4.6. Sensitivity analysis

A one-way sensitivity analysis is run to determine the impact of uncertainty in the following variables:

- Cost of allo-SCT
- Cost of treating adverse events
- Cost of 1st line nilotinib treatment without the PAS.
- Costs without dose adjustment.
- The impact of the disutility of allo-SCT

- Baseline health state values (in CP and AP, BC)
- Disutility associated with AE

Other parameters such as time horizon, age of patients and probability of receiving allo-SCT have also been tested.

Probabilistic sensitivity analysis (PSA) has been undertaken to explore the impact of joint uncertainty in all model parameters upon the cost-effectiveness results.

2.4.7. Model validation

No information on internal or external validation is presented by the manufacturer.

2.4.8. Major concerns with Novartis model

- The Novartis model makes no use of cytogenetic or molecular response rates from the ENESTnd trial.

2.5. Critical appraisal frameworks

This section summarises a critique of the Novartis model. It is divided into the following two sub-sections:

- Appraisal of the Novartis approach against general checklists.
- A critique of the Novartis in light of the specific research problem.

2.5.1. Quality checklists

The model was appraised against the following commonly used quality checklists:

- NICE Reference Case NICE 2008 (Table 25)[8]
- Drummond and colleagues (Table 26)[52]
- Philips and colleagues for decision model-based economic evaluations (Table 27)[53]

Table 25 Critical appraisal of Novartis nilotinib model based on NICE Reference Case 2008[8]

NICE reference case requirement		Critical Appraisal	Reviewer comment
Defining the decision problem	The scope developed by the Institute	✓	
Comparator	Therapies routinely used in the NHS, including technologies regarded as current best practice	✓	Comparator is imatinib 400mg daily. The model does not directly compare against 1st line dasatinib which is the other current option available to patients.
Perspective on costs	NHS and PSS	✓	
Perspective on outcomes	All health effects on individuals	✓	Disutility of adverse events are included. Where disutility values could not be identified a value of -0.05 was assumed.
Type of economic evaluation	Cost-effectiveness analysis	✓	
Synthesis of evidence on outcomes	Based on a systematic review	✓	Oxford Outcomes 2010 – interventions used as 1st line treatment for CML.
Measure of health benefits	QALYs	✓	
Source of data for measurement of HRQL	Reported directly by patients and/or carers	✓	Health state values based on Reed et al 2004 based on the EQ-5D responses from patients within the IRIS study, The disutility values for adverse events are mostly not based on EQ-5D data.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	✓	
Discount rate	3.5% pa for costs and health effects	✓	
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	✓	

Table 26 Critical appraisal of Novartis nilotinib model based on checklist from Drummond et al[52]

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question?	✓	-
Is there a clear description of alternatives (i.e. who did what to whom, where, and how often)?	✓	-
Has the correct patient group / population of interest been clearly stated?	✓	No patient subgroups.
Is the correct comparator used?	✓	Imatinib 400mg daily. Dasatinib is not included in the analysis, only as a 2nd line treatment.
Is the study type reasonable?	✓	Standard Markov model.
Is the perspective of the analysis clearly stated?	✓	UK NHS & PSS
Is the perspective employed appropriate?	✓	-
Is effectiveness of the intervention established?	✓	
Has a lifetime horizon been used for analysis, if not has a shorter time horizon been justified?	✓	
Are the costs and consequences consistent with the perspective employed?	✓	All costs from UK NHS & PSS perspective.
Is differential timing considered?	✓	
Is incremental analysis performed?	✓	-
Is sensitivity analysis undertaken and presented clearly?	✓	Univariate and probabilistic sensitivity analyses clearly presented,

Table 27 Critical appraisal of Novartis nilotinib model based on Philips et al[53]

Dimension of quality			Comments
Structure			
S1	Statement of decision problem/objective	✓	
S2	Statement of scope/perspective	✓	NHS and PSS perspective. Cost and benefit inputs are consistent with the perspective. Scope of model stated.
S3	Rationale for structure	✓	Cohort model is appropriate.
S4	Structural assumptions	✓	Model assumptions are mostly explained clearly in the report. Overall, we are satisfied with the structural assumptions.
S5	Strategies / comparators	✓	See S1.
S6	Model type	✓	Cohort model is appropriate.
S7	Time horizon	✓	
S8	Disease states / pathways	✓	The disease states: chronic phase, accelerated phase, blast phase , and death are commonly used for CML.
S9	Cycle length	✓	3 month cycle is appropriate. The model accounts for a shorter cycle length in the beginning of the model to capture effect of adverse events.
Data			
D1	Data identification	✓	Data identification methods are well described.
D2	Pre-model data analysis	✓	.
D2a	Baseline data	✓	Baseline data from RCT ENESTnd Trial.
D2b	Treatment effects	✓	
D2c	Quality of life weights (utilities)	✓	
D3	Data incorporation	✓	Data incorporated in the model is referenced. See point D2.
D4	Assessment of uncertainty	✓	
D4a	Methodological	✓	
D4b	Structural	✓	
D4c	Heterogeneity	✓	No patient subgroups, as appropriate.
D4d	Parameter	✓	Probabilistic and univariate sensitivity analyses performed.
Consistency			
C1	Internal consistency	✓	
C2	External consistency	✓	

✓ indicates 'clear', X indicates 'concerns',? indicates 'some concerns'

2.5.2. Critique of the modelling approach and structure

The approach adopted by Novartis was considered to be robust. Two issues were identified in the review of the model.

- The Novartis model makes no use of cytogenetic or molecular response rates from the ENESTnd trial.
- There are uncertainties around the cost and the proportions of patients who receive Stem Cell.

At this stage no further analysis has been undertaken to investigate these issues.

3. Comparison of manufacturers' models

3.1. Background

Both BMS (in section 2 of their report) and Novartis (in section 1 of their report) adequately describe underlying health problem in their reports. BMS state the median age for disease onset to be 65 while Novartis quotes median age as 55.

Table 28 shows that the duration of disease phases for those who are not treated differs slightly between the manufacturers' descriptions of CML.

Table 28 CML phase duration if untreated

	Chronic Phase	Accelerated Phase	Blast Crisis
BMS	3-5 years	2-15 months	3-6 months
Novartis	3-5 years	1-2 years	3-12 months

3.2. Model outputs compared: state occupancy

This section describes and compares the main state occupancy and survival data predicted by each model. Table 29 presents time spent in each phase as predicted by the model. Tables 30 present the time spent in each line of treatment in two models.

Table 29 Time spent in each phase (undiscounted, in years)

Phase	BMS*			Novartis			
	Dasatinib	Imatinib	Nilotinib	Nilotinib/Das	Imatinib/Das	Imatinib	Nilotinib
Chronic	19.16	17.14	19.28	12.66	11.94	9.30	10.64
Accelerated	1.30	1.69	1.31	0.44	0.45	0.34	0.37
Blast				0.44	0.45	0.34	0.37
Start age	46			57			
Mean age at death	66.46	64.83	66.59	70.54	69.83	66.97	68.38

*****_data presented from the corrected BMS model_

Table 29 demonstrates that the mean age of death in the two models is similar. This is partly explained by the different starting ages in the models. Given the earlier starting age in the BMS model, a similar age of death is produced by predicting much longer periods in each phase. This is the result of the different methods for predicting survival. In the BMS model

the OS and PFS curves determine the proportion of the population in the AP/BP over time. In comparison in the Novartis model the proportion in AP/BP is determined by the discontinuation rate of HU in the CP.

Table 30 Time spent in each line of treatment (undiscounted, in years) in the BMS and Novartis models

Model	Treatment arm	1st line		2nd line		3rd line	
		Description	Time	Description	Time	Description	Time
BMS*	Dasatinib	Dasatinib (100mg)	14.29	Nilotinib (800mg)	3.16	SCT or chemo/combination therapy or in-hospital palliative care	3.01
	Imatinib	Imatinib (400mg)	5.09	Dasatinib (100mg) or Nilotinib (800mg)	9.02	SCT or chemo/combination therapy or in-hospital palliative care	4.72
	Nilotinib	Nilotinib (600mg)	13.64	Dasatinib (100mg)	4.29	SCT or chemo/combination therapy or in-hospital palliative care	2.67
Novartis	Nilotinib/Dasatinib	Nilotinib (600)mg	7.28	Dasatinib (100mg)	2.68	SCT or HU	3.58
	Imatinib/Dasatinib	Imatinib (400mg)	5.53	Dasatinib (100mg)	3.55	SCT or HU	3.75
	Nilotinib	Nilotinib (600)mg	7.28	SCT or HU	4.10	n/a	n/a
	Imatinib	Imatinib (400mg)	5.53	SCT or HU	4.44	n/a	n/a

* *data presented from the corrected BMS model*

3.3. Drug costs

There is slight variation in the cost of treatment across the BMS and Novartis models. This is due to different dose intensity assumptions between BMS and Novartis, rather than listed costs used by the manufacturers. Table 31 outlines the drug costs which are used.

Table 31 TKI drug costs used in models

	BMS		Novartis	
TKI treatment	Cost per pack (see Table 4.1.5.1) for details	per day	Quarterly drug cost, including dose-intensity adjustments	per day
1st line imatinib	£1,724.39	£57.48	£5,547.00	£60.62
1st line nilotinib (with PAS)	n/a	n/a	[redacted]	[redacted]
1st line nilotinib (without PAS)	£2,432.85	£86.89	£7,319.00	£79.99
Dasatinib	£2,504.96	£83.50	£7,034.00	£76.87

Unfortunately, because of the timing when the industry submissions had to be supplied to NICE, the price of nilotinib used by BMS did not reflect the price discount recently approved under a Patient Access Scheme (two PASs: one for 2nd line and one for 1st line). If the cost of nilotinib is adjusted to reflect the [redacted] in the cost of nilotinib due to PAS, the cost of nilotinib in 1st line and 2nd line is reduced from £2,664 per month to [redacted] per month. Based on this change the BMS predicts an ICER of £45,600 for dasatinib vs. imatinib. When comparing dasatinib vs. nilotinib, the model predicts that nilotinib is more effective and less costly, therefore nilotinib is the dominant comparator.

3.4. Other costs

In the BMS model there are three significant disease management costs: (i) costs associated with the management of chronic phase patients taking TKIs, and post-progression phase patients, (ii) costs associated with 3rd line CP and AP/BP patients who do not receive SCT and (iii) costs of SCT patients.

The resource use costs associated with each response category and costs associated with 3rd line therapy for non SCT patients are based on data from the Oxford Outcomes UK Costing Study.[38] This study identified the resource use and costs for treating patients with CML in the UK, as well as the frequency and length of hospital stay of patients with CML for managing serious (grade 3/ 4) treatment-related adverse events and disease sequelae observed to occur in over five percent of CML patients enrolled in the large clinical trials. The Oxford

Outcomes costing study incorporated a literature review, responses from six clinicians to the resource use questionnaire developed by Oxford Outcomes, and analysis of UK hospitalisation data from Hospital Episodes Statistics and the Cardiff Research Consortium. The results of the study are presented by type of CML patient.

[redacted]:

[redacted]

Thus, [redacted] references previous BMS submission, while current BMS submission references [redacted] and unfortunately, this approach provides no explanation for SCT cost derivation.

The Oxford Outcomes costing study quotes the cost of bone marrow transplant at £52,638 (£2008).[38] It is unclear why BMS used other cost estimates from the Oxford Outcomes costing study and have not used this one. The original source used by BMS to cost SCT could not be traced.

In the Novartis model there are also three similar disease management costs: (i) costs associated with management of CP, AP, and BP patients, (ii) costs associated with treatment of patients who do not receive SCT (post-TKI failure), and (iii) costs of STC patients. The management costs refer to the cost of routine appointments; each routine appointment costs £138.[59] The number of routine appointments varies by time, and is based on personal communication with medical experts. The cost of routine appointments over time can be found in table 32. Patients who do not receive SCT are assumed to move to HU therapy which is £38 per 3 months *(BNF, 2010).* The cost of STC is £99,224 based on data from the London Specialised Commissioning Group's report on the cost of Bone Marrow Transplant.[60]

Table 32 Cost of routine appointments in Novartis model

Month	Number of routine appointments	Cost of routine appointments 1st and 2nd line therapy – nilotinib/imatinib
1	3	£414
2	1	£138
3	0	£0
4	1	£138
5	0	£0
6	1	£138
> 7	2	£276*

* *after 7 months the cost is a 3 month cost*

Table 33 provides a comparison of general resources costs across the two models – i.e. outpatients visits, tests, hospitals stays, etc.

Table 33 Resource use (e.g. patient visits, tests, hospital stays) per month for patients in chronic, accelerated, and blast phase (excluding drug costs)

Phase	BMS			Novartis		
	Dasatinib	Imatinib	Nilotinib	Nilotinib	Imatinib	Dasatinib
Chronic phase	£407	£405	£451	[£0,£414]*	[£0,£414]*	[£0,£414*}
Accelerated phase	£490	£488	£539	£92	£92	£92
Blast phase				£182	£182	£182

* refer to Table 32

It is evident from Table 33 that resource costs are different across the two models. Overall BMS appears to have larger resource costs. This may imply that the Novartis model has underestimated disease management costs. In addition, the BMS model accounts for resource costs associated with patients who receive a SCT. However, in the Novartis model there are no additional resource costs associated with SCT patients, only the cost of the transplant is considered. Table 34 shows the additional resource use associated with 3rd line therapy for non SCT patients.

Table 34 Treatment costs per month for non-SCT patients post TKI failure

	BMS		Novartis	
Phase	Probability of not receiving SCT	Cost of care per month	Probability of not receiving SCT	Cost of care per month
Chronic phase	69.2%	£2,467	25%*	£38
Accelerated phase/Blast phase	50.0%	£4,836	n/a	n/a

* *In the Novartis model, there is a 25 per cent chance of not receiving a SCT up to the age of 65, after 65 the probability increases to a 100 per cent chance of not receiving a SCT.*

It is clear from Table 34 BMS has substantially higher monthly costs associated with the treatment of patients without SCT. In the Novartis model patients who do not receive a SCT move to HU therapy which has a minimal cost of £38 per month. In the BMS model patients who do not receive a SCT are assumed to receive either chemotherapy care (in chronic phase) or hospital care (in AP/BP); both of which are at a considerable cost. In addition, the BMS model assumes it is possible to receive a SCT in the chronic phase and the AP/BP in comparison to the Novartis model where SCT is only available to CP patients. Table 35 summarises the differences in costs associated with receiving SCT between both models.

Table 35 Percentage of cohort receiving SCT and cost of SCT

	BMS			Novartis			
	Dasatinib	Imatinib	Nilotinib	Nilotinib/Das	Imatinib/Das	Imatinib	Nilotinib
Percentage receiving SCT	7.6	13.8	7.0	33.2	36.0	54.7	47.8
Cost of SCT	[redacted]			£99,224			

In the Novartis model a more substantial percentage of the population receive a SCT, even when including 2nd line TKIs. This is driven by Novartis' assumption that if TKI failure occurs, 75 per cent of patients under 65 years old will receive a SCT. This assumption is tested within the Novartis model and is shown not to impact the ICER greatly. In comparison, in the BMS model if TKI failure occurs there, is a 30.8 per cent change of receiving a SCT in the chronic phase for any age, and a 50 per cent chance of receiving a SCT in the AP and BP at any age which is based on data from the Oxford Outcomes study.[38] The probability of receiving a SCT used by BMS is tested in the additional sensitivity analysis performed by PenTAG.

[redacted] This cost is significantly higher than the cost of STC predicted by Novartis (£99,224 per transplant). When accounted for the formulae errors and discounted price of nilotinib in the 1st and 2nd line due to PAS, if the one-off cost of SCT per QALY from the Novartis model is input in the BMS model, while removing the [redacted], there is a substantial increase in the ICER value, from £27,639 to £78,791 per QALY for dasatinib compared to imatinib. The inclusion of an [redacted] is inflating the cost for all patients receiving SCT. The assumption made by BMS increases the total cost of imatinib as more patients in the imatinib arm receive SCT. The approach used by BMS is based on viewing SCT solely as a cost, since any treatment benefit is implicitly included in the ITT survival data used to inform the parametric survival analysis discussed previously (Section 1.4.3.2).

3.5. Adverse event costs

Both the BMS and Novartis models account for adverse events, but differ in the types of adverse events which are included. The BMS model incorporates a wider range of adverse events in comparison to Novartis. Table 36 summarises the types of adverse events which are included in each model.

Table 36 Adverse events comparison

Type of adverse event	BMS	Novartis
Anemia	✓	✓
Diarrhoea	✓	-
Dyspnea	✓	-
Fatigue	✓	-
Headache	✓	-
Infection and Infestations	✓	-
Leukopenia	✓	-
Nausea	✓	-
Neutropenia	✓	✓
Pleural effusion	✓	✓
Pyrexia	✓	-
Skin Rash	✓	-
Thrombocytopenia	✓	✓
Vomiting	✓	-
GI bleed	-	✓
CNS bleed	-	✓

The estimated cost of adverse events also differs between the models. Table 37 outlines the cost of adverse events per month by phase of disease. As the incidence rates of adverse events are very small, the difference in costs only has a small impact on the ICER and therefore costs were not tested with additional sensitivity analysis by PenTAG.

Table 37 Cost of adverse events per month by phase of disease

		Dasatinib	Imatinib	Nilotinib
BMS	CP	£20.83	£16.88	£12.07
	AP/BP	£0.00	£28.29	£26.19
Novartis	CP	£23.34	£11.61	£6.95
	AP/BP*	n/a	n/a	n/a

* *In Novartis model, AP/BP implies you are on HU treatment, and the models does not account for adverse events under HU*

Another difference between the two models is the assumption about the duration of adverse events. In the BMS model adverse events occur through the lifetime of the model and are based on the proportion of the cohort in CP and AP/BP. In the Novartis model, the incidence of adverse events is assumed to only last up to 18 months. Therefore after 18 months, there is no cost of adverse events.

3.6. Health-related quality of life

The BMS and Novartis model use different sources for the utility associated within each disease state. Table 38 outlines the differences between the utility values.

Szabo and colleagues is a UK, US, Australia, and Canada based study which derives utility values based on the Time Trade-Off method.[44] The utility values are based on interviewer-administered survey responses from a sample of the general population (n = 353, of which 97 were from the UK). Respondents were provided with descriptions of CML related health states which were derived in consultation with medical professionals.

Reed and colleagues estimate utility values based on responses to EQ-5D questionnaires from patients in the IRIS study receiving standard dose imatinib.[50] The average age of patients in the study was 50 years old. Due to the younger age of the participants in the study compared with the cohort in the Novartis model, adjustments were made to the utility values to reflect age. The adjustment to utility values is not clearly described in either the manufacturer's submission or the cost-effectiveness model.

Table 38 Utility value and sources for each health state

	BMS		Novartis	
State	Value	Source/Notes	Value	Source/Notes
CP	0.8500	Responder (Szabo et al 2010)[44]	0.854*	(Reed et al 2004)[50] Same value assumed for 2nd line
	0.6800	Non-responder (Szabo et al2010)[44]		
AP	0.7900	Responder (Szabo et al 2010)[44]	0.595*	(Reed et al 2004)[50] Same value assumed for 2nd line
	0.5000	Non-responder (Szabo et al 2010)[44]		
BP	0.5000	Responder (Szabo et al 2010)[44]	0.595*	(Reed et al 2004)[50] Same value assumed for 2nd line
	0.3100	Non-responder (Szabo et al2 010)[44]		
SCT	0.7100	[redacted]	0.813	Assumption Disutility associated with SCT (0.079) is applied Lee et al. (1997)[57]

* The values in the Novartis model should be compared to the "responder" value in the BMS models. **The utility weights for non-responders on BMS model were applied to both partial and less than partial responders. ** The utility weights in the Novartis model decrease with age, as explained in section 2.4.4.

The two biggest differences in utility values between the models appear to be within the AP and for SCT patients. To test the differences in utility values, the value for the AP estimated by Reed et al is input into the BMS model for AP responders.[50] In addition, post SCT value used by BMS is input into the Novartis model. Table 39 outlines the subsequent changes in ICER's due to changes in the utility values. The table shows the changes in the utility values have a minor impact on the ICER.

Table 39 Impact on ICER with changes in utility values

Value	Novartis		BMS	
	Nilotinib vs. Imatinib with 2nd line Dasatinib	Nilotinib vs. Imatinib without 2nd line Dasatinib	Dasatinib vs. Imatinib	Dasatinib vs. Nilotinib
Original unadjusted	(-£34,889)	£5,908	£36,052	£103,483
AP (0.595)	-	-	£35,538	£104,451
SCT (0.71)	-(£33,893)	£5,658	-	-

The disutility of adverse events also differs between the models. Table 40 outlines the disutility of adverse events by phase of disease. As the disutility of adverse events is minimal, the difference in values is likely to have only a small impact on the ICER and therefore values were not tested with additional sensitivity analysis.

Table 40 Disutility of adverse events by phase of disease

		Dasatinib	**Imatinib**	**Nilotinib**
BMS	CP	0.005	0.004	0.002
	AP/BP	0.004	0.004	0.004
Novartis	CP	0.19	0.16	0.10
	AP/BC*	n/a	n/a	n/a

** In Novartis model, AP/BC implies you are on HU treatment, and the model does not account for adverse events under HU.*

A major difference between the two models is the assumption about the duration of adverse events. In the BMS model adverse events occur through the lifetime of the model and are based on the proportion of the cohort in CP and AP/BC. In the Novartis model, the incidence of adverse events is assumed to only last up to 18 months. Therefore after 18 months, there is no disutility of adverse events.

4. Discussion

4.1. Summary of cost-effectiveness issues

- Novartis use patient access scheme (PAS) for pricing nilotinib as 1st line treatment. This has significant impact on the results, and is unfortunately not reflected in the BMS model.

- BMS and Novartis use different 2nd and 3rd line treatments. BMS assume dasatinib and nilotinib are both available as 2nd line treatments. In one scenario, Novartis assume that only dasatinib is available 2nd-line, whereas in another scenario, they assume no TKI 2nd-line. However, NICE's draft guidance FAD has recently recommended nilotinib, but not dasatinib 2nd-line (the draft guidance FAD for 2nd line CML for high-dose imatinib, dasatinib and nilotinib, is available on the NICE website at http://guidance.nice.org.uk/TA/WaveR/99).

- The time horizon chosen by the BMS model does not reflect the lifetime of a CML patient. In the model, nearly 20 per cent of the population is still alive in the last cycle (86 years old).

- The BMS model has a number of formulae errors, correcting for which impacts ICER.

- The cost and the proportions of patients who receive Stem Cell Transplant differ between the models and has a significant impact on ICERs.

Appendix

Table 41 Unit costs used in the BMS model

Event	Cost	Source
Outpatient visits		
Nurse	£25	Curtis (2008) section 8.6. Value represent the hourly rate for a GP practice nurse[49]
Haematologist/oncologist	£108	Curtis (2008) section 13.5. Value represent the hourly rate for a general medical consultant[49]
Tests		
Complete blood count (CBC)	£2.97	NHS SRC*. Currency code DAP823
Cytogenetic analysis	£17.03	NHS SRC. Currency code DAP838
Bone marrow aspiration with biopsy	£637.10	NHS SRC. (original value £565.26)**
FISH	£17.03	NHS SRC. Currency code DAP838
PCR	£1.34	NHS SRC. Currency code DAP841
Flow cytometry	£87.01	NHS SRC. Currency code DA08
Cytochemistry analysis	£17.03	NHS SRC. Currency code DAP838
Blood film exam	£2.97	NHS SRC. Currency code DAP823
Chest X-ray		
CT scan chest	£116.72	NHS SRC. Currency codes RA08Z – RA14Z
Blood chemistry	£1.34	NHS SRC. Currency code DAP841
Kinase domain mutation	£87.01	NHS SRC. Currency code DA08
C-reactive protein (CRP)	£7.42	NHS SRC. Currency code DAP831
EKG	£131	NHS SRC. (currency codes EA46Z, EA47SZ)
Upper endoscopy (EGD)	£221.14	NHS SRC. (currency codes FZ26A, FZ27C)
Hospitalisation		
Day on a general ward	£246.41	NHS SRC. Weighted average of all non-elective excess bed day costs
Day in ICU	£1,219	NHS SRC. Currency codes XC01Z-XC07Z (Burns, Spinal Injuries and general critical care)
Day in hospice	£233	Curtis (2008) section 1.5 Nursing-Led Inpatient Unit (NLIU) for intermediate care[49]
Other		
Blood transfusion	£57.07	NHS SRC. service code 821
Donor lymphocyte infusion	£57.07	Assumed same as blood transfusion
Platelet transfusion	£57.07	Assumed same as blood transfusion
Lumbar puncture	£87	NHS SRC. Currency code DA08

Appendix 8: WinBUGs MTC analysis of CCyR and MMR response rates

The method of conducting the Mixed Treatment Comparison (MTC) for the CCyR and MMR in the two RCTs of 1st-line dasatinib and nilotinib involves two steps.

First, a fixed effects MTC model (Lu and Ades, 2006) was used in WinBUGS (Spiegelhalter et al, 2003) to impute estimates of the response rates for CCyR and MMR for dasatinib from Saglio and colleagues and for nilotinib (300mg) from Kantarjian and colleagues (the shaded cells in Table 38 and Table 39, Main Report, p. 153). The MTC model allows estimation of the shaded cells using the precision of the available data. The WinBUGS code for this analysis is given below;

```
model{

for(i in 1:N)  {   logit(p[i])<-mu[s[i]]+ d[t[i]] - d[b[i]]
                   r[i]~dbin(p[i],n[i])  }
for(j in 1:NS)  {   mu[j]~dnorm(0,.0001)}

d[1]<-0
for (k in 2:NT) {d[k] ~ dnorm(0,.0001) }

}
```

To fit this model, it was assumed that the total number of participants for the dasatinib arm of Saglio and colleagues would have been 282 (as in the nilotinib arm) had dasatinib also been included in the trial. Similarly, it was assumed that the total number of participants for the nilotinib arm of Kantarjian and colleagues would have been 259 (as in the dasatinib arm) had nilotinib also been included in the trial. Prior distributions, intended to be vague, were placed on the estimates of the trial baseline and treatment effects (e.g. $\mu_j \sim N(0,10000)$ and $d_k \sim N(0,10000)$ in the WinBUGS code). The impact of using different vague priors and different assumptions on the assumed total number of participants in the dasatinib arm of Saglio and colleagues and the nilotinib arm of Kantarjian and colleagues was assessed.

Second, all estimated response rates (those reported and those imputed from above) are assumed to follow a normal distribution. A fixed effects meta-analysis (Sutton et al, 2000)

was then undertaken in WinBUGS to obtain an overall estimate of response rate for each treatment. Prior distributions, intended to be vague, were placed on the unknown parameters. A burn-in of 20,000 iterations was used for both of the above steps, with estimates based on a sample of 200,000 iterations. Convergence of the analysis was checked using the trace, auto-correlation and density plots within WinBUGS.

The analyses were deemed to have been based on convergent samples and there was no impact on the results by assuming different prior distributions for the unknown parameters. There was no impact of assuming alternative total numbers of participants in the dasatinib arm of Saglio and colleagues and the nilotinib arm of Kantarjian and colleagues.

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PENINSULA MEDICAL SCHOOL
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PenTAG

ADDENDUM to Final Report for NICE

Dasatinib, Nilotinib, and standard dose Imatinib for the first-line treatment of chronic myeloid leukaemia

For NICE Appraisal Committee Meeting, 8th November 2011

Prepared and sent by PenTAG, 3rd November 2011

In response to the comments made by Novartis on our Final Report to NICE, we have now changed our base case results for the cost-effectiveness of nilotinib vs. imatinib and dasatinib vs. imatinib. These amended base case results reflect our acceptance of Novartis' comments in relation to the lower cost of ongoing medical management in chronic phase CML than we originally assumed.

In addition, also in response to Novartis's comments, we explore the impact on the estimated ICERs of altered assumptions about survival post SCT, and dose intensity while on imatinib.

The following text and tables present:

(a) an account justifying the changes in the base case assumptions relating to medical management costs during the chronic phase.
(b) tables of revised base case estimates and selected sensitivity analyses.
(c) an account of the uncertainty and alternative plausible assumptions relating to dose intensity while on imatinib and survival following stem cell transplant.
(d) text and tables exploring the impact of these alternative assumptions on the cost-effectiveness of nilotinib *vs* imatinib.

Of the following tables of revised cost-effectiveness results, Tables 1 and 3 are entirely new (to provide new sensitivity analyses), the sensitivity analyses in Table 2 and Table 4 should replace Table 56 and Table 57 (pp.209-212), and the summary of cost-effectiveness results in Table 5 should replace Table 51 (p.186)

Revised medical management costs

Novartis correctly state that during chronic phase CML, alongside other monitoring test costs, we originally assumed a monthly frequency of:

0.4 visits with a nurse

0.9 visits with a haematologist/oncologist, and

0.3 bone marrow aspirations.

These figures were taken from the 2009 Oxford Outcomes survey of 6 UK-based CML clinicians (see p179 our report).

Novartis claim that this is an overestimate the frequency of **outpatient visits**. They claim that it is more reasonable to assume one visit per 3 to 6 months, based on current ELN guidelines. They also claim that we over-estimate the frequency of bone marrow aspirations.

We have presented Novartis' criticisms to our clinical advisor, and he agrees that we have over-estimated these quantities. He believes that it is more likely that NHS patients on a TKI would be seen at week 2, week 4, month 2, month 4 and then 3-monthly. Patients on hydroxyurea would be seen about every 6 weeks. Furthermore, patients would rarely be seen by a nurse (without a consultant). Our advisor claims that clinical practice for **bone marrow aspiration** varies from only a single test, to tests at month 0, 3, 6, 12, 18 and 24 or until CCyR, but not after 24 months.

Given this new information and current European treatment guidelines, we have calculated revised base case cost-effectiveness estimates assuming lower medical management costs during the chronic phase. The modelling for our revised estimates now assumes:

- one visit to a haematologist/oncologist every 3 months for patients on a TKI, i.e. 0.33 visits per month.
- one visit to a haematologist/oncologist every 6 weeks for patients hydroxyurea, i.e. 0.72 visits per month.
- no outpatient nurse visits.
- no bone marrow aspirations (given that some clinicians give no repeat tests and given that for those cases when repeat aspirations are given, costs would cancel to a large extent between treatment arms).

We can safely ignore the initial higher frequency of visits when patients start taking TKIs, as these costs effectively cancel out between treatment arms (because virtually all patients on 1st-line TKIs are still on treatment at 4 months). We leave all other assumptions for the costs of medical management unchanged (see p180 our report), although these contribute only marginally.

These new cost assumptions give a mean medical management cost of £169 per month per patient on TKIs in chronic phase and £317 per patient on HU in chronic phase.

Revised results for nilotinib vs imatinib are given in Table 1 below. This table also shows ICERs that reflect both our original and possible revised assumptions for imatinib dose-intensity and survival post-SCT. Revised results for dasatinib vs imatinib are given in Table 3 later.

Table 1 ICERs (£/QALY) for nilotinib vs. imatinib according to assumption for dose intensity of imatinib, mean survival after SCT and modelling structure. In all cases, the cost of medical management in CP per month is changed from PenTAG original submission, see text.

Mean survival post SCT	PenTAG original base case	17 years (original PenTAG analysis)		7.5 years (Novartis' estimate from Pavlu et al.)	
Dose intensity imatinib		[redacted] (original PenTAG analysis)	106% (Novartis' estimate)	[redacted] (original PenTAG analysis)	106% (Novartis' estimate)
Scenario 1 (no 2nd-line nilotinib)	£36,000	£25,000	£8,000	£17,000	£6,000
Scenario 2 (no 2nd-line nilotinib, simplified method)	£26,000	£20,000	£9,000	£18,000	£8,000
Scenario 3 (2nd-line nilotinib)	£213,000§	£192,000§	£265,000§	£61,000§	£84,000§
Scenario 4 (2nd-line nilotinib, simplified method)	£50,000§	£46,000§	£61,000§	£49,000§	£65,000§

§ Nilotinib provides fewer QALYs at less cost than imatinib

Notice that using the updated medical management costs, and assuming a revised dose intensity for imatinib of 106%, our assumed mean survival after SCT affects the cost-effectiveness of nilotinib only marginally in Scenarios 1 and 2.

Table 2 gives the sensitivity analyses for nilotinib vs. imatinib using our revised base case assumption for the cost of medical management. Here, we show the same sensitivity analyses as in Table 56, p209 in our report. In this case, the dose intensity of imatinib remains at [redacted] and the mean time after SCT remains at 17 years.

Table 2 Sensitivity analyses for ICERs for nilotinib vs. imatinib using revised base case assumption for cost of medical management

Parameter	Base case	Sensitivity analysis	Scenario 1 (No 2nd-line nilotinib)	Scenario 2 (No 2nd-line nilotinib, Simplified Method)	Scenario 3 (2nd-line nilotinib)	Scenario 4 (2nd-line nilotinib, Simplified Method)
Base case	N/A	N/A	**£25,000**	**£20,000**	**£192,000§**	**£46,000§**
General						
Discounting costs and benefits	3.5% p.a.	0% p.a.	£30,000	£24,000	nilotinib dominates	£51,000§
Treatment pathways						
Proportion receiving SCT	Mean 28% nilotinib, 33% imatinib, decreases with age	31% at all ages (BMS assumption)	£24,000	£20,000	£86,000§	£48,000§
		75% if age < 65 (Novartis)	£28,000	£20,000	£286,000§	£45,000§
		Halve % at all ages	£23,000	£20,000	£98,000§	£48,000§
Effectiveness						
Time on 1st-line TKI	8.9 years nilotinib, 7.0 years imatinib	7.0 years nilotinib, 7.0 years imatinib	nilotinib dominates	nilotinib dominates	£75,000§	£38,000§
		13.8 years nilotinib, 11.7 years imatinib (IRIS)	£14,000	£13,000	nilotinib dominates	£79,000§
Time on 2nd-line nilotinib	Mean 2.5 years	Same as mean time on 1st-line nilotinib = 8.9 years	n/a	n/a	£61,000§	£37,000§
Survival after SCT	Mean approximately 17 years	Mean 5.7 years (Novartis)	£16,000	£17,000	£54,000§	£49,000§
Time in CP on HU	Mean 5 years	Mean 1.6 years (Novartis)	£22,000	£18,000	£341,000§	£49,000§
OS estimated by Cumulative Survival or Surrogate Survival	Cumulative Survival	Cumulative survival means, MMR survival difference	£35,000	£25,000	n/a	n/a
		Cumulative survival means, CCyR survival difference	£17,000	£15,000	n/a	n/a
		Surrogate survival means, MMR survival difference	£40,000	£29,000	n/a	n/a
		Surrogate survival means, CCyR survival difference	£19,000	£17,000	n/a	n/a

Parameter	Base case	Sensitivity analysis	Scenario 1 (No 2nd-line nilotinib)	Scenario 2 (No 2nd-line nilotinib, Simplified Method)	Scenario 3 (2nd-line nilotinib)	Scenario 4 (2nd-line nilotinib, Simplified Method)
Base case	N/A	N/A	**£25,000**	**£20,000**	**£192,000§**	**£46,000§**
Costs						
Drug price reduction on patent expiry	0% nilotinib, 0% imatinib	0% nilotinib, 25% imatinib	£60,000	£42,000	£42,000§	£16,000§
		25% nilotinib, 25% imatinib	£44,000	£31,000	£95,000§	£27,000§
Dose intensities	[redacted] 1st-line nilotinib, [redacted] imatinib, 99% 2nd-line nilotinib	100% 1st-line nilotinib, [redacted] imatinib, 99% 2nd-line nilotinib	£53,000	£37,000	£72,000§	£22,000§
		[redacted] 1st-line nilotinib, 106% imatinib (Novartis), 99% 2nd-line nilotinib	£8,000	£9,000	£265,000§	£61,000§
		[redacted] 1st-line nilotinib, [redacted] imatinib, [redacted] 2nd-line nilotinib	n/a	n/a	£166,000§	£41,000§
Cost SCT	£81,603	£40,801	£30,000	£21,000	£207,000§	£46,000§
		£163,205	£16,000	£17,000	£162,000§	£47,000§
Medical management costs after SCT	£113 per month	£57 per month	£26,000	£20,000	£194,000§	£46,000§
Medical management costs in CP	£56 per month TKIs, £106 per month HU	£28 per month TKIs, £53 per month HU	£25,000	£19,000	£189,000§	£46,000§
		£112 per month TKIs, £211 per month HU	£27,000	£21,000	£196,000§	£47,000§
Medical management costs in AP and BC	£1,113 per month	£2,227 per month	£24,000	£19,000	£196,000§	£47,000§
AEs costs	£166 per patient imatinib, £119 per patient nilotinib	£1,660 per patient imatinib, £1,190 per patient nilotinib	£24,000	£19,000	£196,000§	£47,000§
Utilities						
Utilities		Equal to Novartis	£25,000	£20,000	£201,000§	£46,000§
		Reduce all utilities by 0.10	£22,000	£19,000	£130,000§	£47,000§

§ Nilotinib provides fewer QALYs at less cost than imatinib

Effect of changes to cost-effectiveness of dasatinib

Table 3 below gives the updated PenTAG ICERs for dasatinib vs. imatinib given the changes in medical management costs prompted by the comments from Novartis. It also shows the ICERs with the alternative assumptions for imatinib dose intensity and survival after SCT (see following sections). Dasatinib clearly remains very poor value for money in all scenarios.

Table 3 ICERs (£/QALY) for dasatinib vs. imatinib according to assumption for dose intensity of imatinib, mean survival after SCT and modelling structure. In all cases, the cost of medical management in CP per month is changed from PenTAG original submission, see text.

		Mean survival post SCT			
	PenTAG original base case	17 years (original PenTAG analysis)		7.5 years (Novartis' estimate from Pavlu et al.)	
Dose intensity imatinib		[redacted] (original PenTAG analysis)	106% (Novartis' estimate)	[redacted] (original PenTAG analysis)	106% (Novartis' estimate)
Scenario 1 (no 2nd-line nilotinib)	£425,000	£414,000	£369,000	£263,000	£234,000
Scenario 2 (simplified method, no 2nd-line nilotinib)	£262,000	£256,000	£228,000	£228,000	£204,000
Scenario 3 (with 2nd-line nilotinib)	£460,000	£450,000	£400,000	£310,000	£275,000
Scenario 4 (simplified method, with 2nd-line nilotinib)	£307,000	£301,000	£268,000	£271,000	£241,000

Table 4 gives the sensitivity analyses for dasatinib vs. imatinib using our revised base case assumption for the cost of medical management. Here, we show the same sensitivity analyses as in Table 57, p211 in our report. In this case, the dose intensity of imatinib remains at [redacted] and the mean time after SCT remains at 17 years.

Table 4 Sensitivity analyses for dasatinib vs. imatinib

Parameter	Base case	Sensitivity analysis	Scenario 1 (No 2nd-line nilotinib)	Scenario 2 (No 2nd-line nilotinib, Simplified Method)	Scenario 3 (2nd-line nilotinib)	Scenario 4 (2nd-line nilotinib, Simplified Method)
Base case	N/A	N/A	**£414,000**	**£256,000**	**£450,000**	**£301,000**
General						
Discounting costs & benefits	3.5% p.a.	0% p.a.	£335,000	£229,000	£338,000	£253,000
Treatment pathways						
Proportion receiving SCT	Mean 32% dasatinib, 33% imatinib, decreases with age	31% at all ages (BMS assumption)	£338,000	£247,000	£397,000	£294,000
		75% if age < 65 (Novartis)	£537,000	£265,000	£584,000	£312,000
		Halve % at all ages	£331,000	£246,000	£378,000	£290,000
Effectiveness						
Time on 1st-line TKI	7.7 years dasatinib, 7.0 years imatinib	7.0 years dasatinib, 7.0 years imatinib	Imatinib dominates	Imatinib dominates	Imatinib dominates	Imatinib dominates
		12.5 years dasatinib, 11.7 years imatinib (IRIS)	£565,000	£427,000	£641,000	£508,000
Time on 2nd-line nilotinib	Mean 2.5 years	Same as mean time on 1st-line nilotinib = 8.9 years	n/a	n/a	£673,000	£501,000
Survival after SCT	Mean approximately 17 years	Mean 5.7 years (Novartis)	£246,000	£224,000	£292,000	£266,000
Time in CP on HU	Mean 5 years	Mean 1.6 years (Novartis)	£356,000	£229,000	£373,000	£263,000
OS estimated by Cumulative Survival or Surrogate Survival	Cumulative Survival	Cumulative survival means, MMR survival difference	£250,000	£171,000	n/a	n/a
		Cumulative survival means, CCyR survival difference	£104,000	£77,000	n/a	n/a
		Surrogate survival means, MMR survival difference	£303,000	£196,000	n/a	n/a
		Surrogate survival means, CCyR survival difference	£124,000	£86,000	n/a	n/a
Costs						

Parameter	Base case	Sensitivity analysis	Scenario 1 (No 2nd-line nilotinib)	Scenario 2 (No 2nd-line nilotinib, Simplified Method)	Scenario 3 (2nd-line nilotinib)	Scenario 4 (2nd-line nilotinib, Simplified Method)
Base case	N/A	N/A	**£414,000**	**£256,000**	**£450,000**	**£301,000**
Drug price reduction on patent expiry	0% dasatinib, 0% imatinib	25% dasatinib, 25% imatinib	£425,000	£262,000	£462,000	£308,000
Dose intensities	[redacted] imatinib, 99% dasatinib, 99% 2nd-line nilotinib	106% imatinib (Novartis), 99% dasatinib, 99% 2nd-line nilotinib	£369,000	£228,000	£400,000	£268,000
		[redacted] imatinib, 99% dasatinib, [redacted] 2nd-line nilotinib	n/a	n/a	£451,000	£301,000
Cost SCT	£81,603	£40,801	£419,000	£257,000	£454,000	£302,000
		£163,205	£405,000	£254,000	£442,000	£299,000
Medical management costs after SCT	£113 per month	£57 per month	£415,000	£256,000	£451,000	£301,000
Medical management costs in CP	£56 per month TKIs, £106 per month HU	£28 per month TKIs, £53 per month HU	£414,000	£255,000	£449,000	£300,000
		£112 per month TKIs, £211 per month HU	£416,000	£257,000	£452,000	£302,000
Medical management costs in AP and BC	£1,113 per month	£2,227 per month	£414,000	£255,000	£449,000	£300,000
AEs costs	£166 per patient imatinib, £282 per patient dasatinib	£1,660 per patient imatinib, £2,820 per patient dasatinib	£421,000	£260,000	£458,000	£306,000
Utilities						
Utilities		Equal to Novartis	£413,000	£255,000	£448,000	£299,000
Utilities		Reduce all utilities by 0.10	£362,000	£248,000	£402,000	£291,000

Table 5 Summary of revised cost-effectiveness results for Scenarios 1 to 4

	Discounted cost (£)	Undiscounted Life-years	Discounted QALYs	Incremental cost (£)	Incremental QALYs	ICER (£ per QALY)
Scenario 1: Cumulative Survival without 2nd line Nilotinib						
Imatinib - then HU/SCT	£159,000	16.5	9.0			
Nilotinib - then HU/SCT	£170,000	17.4	9.4	£11,000	0.4	£25,000
Dasatinib - then HU/SCT	£224,000	16.8	9.2	£54,000	-0.3	Dasatinib dominated by nilotinib
Scenario 2: Cumulative Survival without 2nd line Nilotinib – simplified method						
Imatinib - then HU/SCT	£159,000		9.0			
Nilotinib - then HU/SCT	£172,000		9.7	£13,000	0.7	£20,000
Dasatinib - then HU/SCT	£225,000		9.3	£53,000	-0.4	Dasatinib dominated by nilotinib
Scenario 3: Cumulative Survival with 2nd line Nilotinib						
Nilotinib - then HU/SCT	£170,000	17.4	9.4			
Imatinib - then Nilotinib	£188,000	17.3	9.5	£19,000	0.1	£192,000[a]
Dasatinib - then Nilotinib	£252,000	17.6	9.7	£63,000	0.1	£450,000
Scenario 4: Cumulative Survival with 2nd line Nilotinib – simplified method						
Nilotinib - then HU/SCT	£166,000		9.1			
Imatinib - then Nilotinib	£188,000		9.5	£22,000	0.5	£46,000[a]
Dasatinib - then Nilotinib	£253,000		9.7	£65,000	0.2	£301,000

[a] Given that imatinib as 1st line treatment is current best clinical practice, these ICER estimates can be seen as representing the amount of *cost savings yielded* per QALY *lost* by having nilotinib first line rather than imatinib.

Dose intensity

Novartis disagree with our assumed mean dose intensity of imatinib of [redacted]. Instead, they prefer 106% which they used in their model.

Novartis disagree with our claim that the *mean* dose intensity over 6 years of people in the IRIS RCT is 100%, for the 364 patients who remained on imatinib at 6 year, which we sourced from Hochhaus et al (2009). Instead, Novartis believe that the 100% refers to the *median* dose intensity, and they claim that the *mean* dose intensity over 6 years was 467/400. However, we disagree with Novartis' criticism of our claim. The mean dose intensity of 467/400 refers to the single last dose given at the time of discontinuation of imatinib study treatment. The subsequent paragraph in Hochhaus et al (2009) states that "among patients who received imatinib as initial therapy for CML, … the average daily dose over the 6-year period was 402mg … for the 364 patients who remained on imatinib." Therefore, we still maintain that the mean dose intensity from the IRIS RCT, which has extensive 6-year follow up, was 402/400 = 100%.

Concerning the ERNEST RCT of nilotinib vs. imatinib, we agree with Novartis that it is preferable to use the estimated dose intensity at 24 months, rather than 12 months, because this would be consistent with the data for treatment duration.

Novartis claim that we referred to the dose intensities of 423.0mg (106%) for imatinib and [redacted] as medians, but this is not true.

Furthermore, we believe that our decision to use the 12-month estimate of dose intensity for imatinib of [redacted] quoted by Novartis on p75 of their submission was reasonable given that the 24-month dose intensity of 106% quoted by Novartis on p105 of their submission was not clearly identified as being a mean or a median value, whereas the [redacted] 12-month value was clearly marked as a mean value.

However, Novartis now state clearly that the dose intensity of imatinib in the RCT of nilotinib vs. imatinib of 106% is a mean, not a median. Therefore, we agree with Novartis that it is instructive to estimate the cost-effectiveness of nilotinib using this value, rather than the value of [redacted] which we used.

In summary, we have two possible estimates for the dose intensity of nilotinib;

- 100% from the IRIS RCT,
- 106% from the RCT of nilotinib vs. imatinib

The first value has the advantage that it is using much more mature data (6 years vs. 2 years). The second value has the advantage that it is consistent with the treatment duration Kaplan-Meier data for imatinib from the RCT of nilotinib vs. imatinib. We think it is not clear which value is preferable.

In Table 1 and 3 above we explore the impact of these alternative assumptions on the ICERs.

Survival following SCT

Novartis make a well-reasoned case that our model assumptions relating to survival following SCT may be over-optimistic, leading to the mean survival of those having an SCT after TKI failure of around 17 years. They consider using a lower estimate of mean survival of 10 years to be more plausible for patients who receive SCT after TKIs, because (Novartis argue) they have higher SCT risk scores by virtue of being both older and more years post-diagnosis.

The problem with current published evidence, including the Pavlu et al 2011 paper on which we have relied (data from 2000 to 2010), is that the cohorts of CML patients in whom post SCT survival estimates are based spans the introduction and widespread use of imatinib as the recommended 1st line treatment in chronic phase CML. Therefore, they inevitably include a subgroup of younger, lower-risk SCT patients who received SCT as 1st line treatment soon after diagnosis, and these patients would have higher mean survival than current recipients of SCT in chronic phase CML, who are on average older and less well by the time they need or are offered an SCT (i.e. after imatinib failure).

On the basis of Novartis's comment, while we can understand the logic for suggesting a shorter mean survival post SCT than 17 years, we can find no published evidence to say *how much* shorter than 17 years it would be. Also, 17 years life expectancy at age 65 (the mean age when people receive an SCT in our model) is still about 5 years lower life-expectancy than the 22.5 years that is the normal life-expectancy of 65 year-olds. Perhaps Prof. Jane Apperley or the other clinical expert advisers to the committee can shed light on this particular gap in quantitative evidence and what a reasonable mean survival is now likely to be in these patients?

On p214 of our report we already acknowledged that our estimate of mean survival following SCT of 17 years is uncertain, and we therefore provide a sensitivity analysis whereby we assume a much shorter mean survival of 5.7 years (p214 our report), equal to Novartis' assumption. The ICER for nilotinib vs. imatinib under Scenario 1 then falls from £36,000 to £22,000 per QALY and under Scenario 2, from £26,000 to £23,000 per QALY. If we also assume the revised dose intensity of imatinib of 106%, not [redacted] then the ICER under Scenario 1 falls from £19,000 to £12,000 per QALY, and under Scenario 2, from £15,000 to £13,000 per QALY. Note that we do not endorse Novartis' estimated survival of 5.7 years post-SCT. Instead, we use this to gauge the sensitivity of the cost-effectiveness of nilotinib to this assumption.

Novartis then claim that the most relevant estimate of the 6-year survival probability after SCT from graphs in Pavlu et al. probably lies between 30% and 60%. Suppose we estimate this probability as the mid-point of this range, i.e. 45%. If, for simplicity, we assume that survival after SCT follows an exponential distribution (constant hazard of death over time), this then specifies the parameter of the exponential distribution as 0.133, with mean survival of 7.5 years.

In Table 1 and 3 above we explore the impact of this altered assumption on the ICERs.

Minor correction to reporting of response rates from trials

For complete cytogenetic response (CCyR) and complete molecular response (CMR), there is a discrepancy between the tables and the text in our report.

The response rates for CCyR and CMR of both the DASISION and ENESTnd trials are 'by' response rates and correct in the tables in our report (Table 12, p. 78 and Table 14, p. 85), but the associated text contains 'at' when it should be 'by' (Section 4.2.3.1, p. 75-76 and Section 4.2.3.3, p. 84).

Comments from Bristol-Myers Squibb on the Assessment Report

Dasatinib, Nilotinib, and standard dose Imatinib for the first-line treatment of chronic myeloid leukaemia: systematic reviews and economic analyses

28 November 2011

Thank you for your invitation to comment on the Assessment Report (AR) **Dasatinib, Nilotinib, and standard dose Imatinib for the first-line treatment of chronic myeloid leukaemia: systematic reviews and economic analyses** prepared by the Peninsula Technology Assessment Group (PenTAG).

In this reply, we highlight the following:

1. Key points arising from our review of the AR
2. Procedural issues which have compromised our review of the AR and the economic model
3. Comments on the AG's criticisms of the BMS model
4. Comments made by the AG on their own model
5. Comments on the AG model
6. Other points and factual inaccuracies

1. Key points arising from our review of the Report

Fair consideration of the evidence for dasatinib

At 1.1.1, the Assessment Group (AG) note the *"whole of this technology assessment report has been prepared in the context of changing draft guidance about the use of the same drugs for 2nd line treatment of CML, after imatinib as 1st line treatment"*. This same section notes the content of the draft recommendation issued by NICE on 18 August 2011 and correctly states that consultees have the opportunity to appeal against the draft guidance. To confirm, Bristol-Myers Squibb (BMS) has appealed the Final Appraisal Determination (FAD).

Much of the AR is heavily reliant on the FAD being translated into final guidance. This is perhaps inappropriate as it has resulted in the evidence for dasatinib (as well as imatinib) in the 2nd line setting not being considered, and as a consequence, BMS feel impacts upon the correct consideration of the evidence in the 1st line setting.

BMS feel that possibly a better process would have been to include the evidence for all relevant comparators for consideration, rather than pre-empting the outcome of the appraisal in 2nd line. Alternatively, the Institute could have delayed the appraisal process, allowing the AG to include only those treatment scenarios recommended following the completion of the appraisal for 2nd line treatment.

Hydroxyurea as a 2nd line treatment option

BMS feel that HU has been inappropriately elevated (i.e. considered as a 2nd line treatment option) within this assessment for the following reasons:

- During the 2nd line treatment appraisal, feedback to the AG from clinical experts (including members of AG's own Expert Advisory Group) confirm that HU is not an active agent in this setting, but is rather part of overall medical management.
- The AG themselves state, *"Hydroxycarbamide can be used to control the white blood count but does not alter the natural history of the disease."* **(page 39)**.
- Inclusion of HU prior to 1st line TKI use **(Table 8, p68)** in both the DASISION and ENESTnd studies confirms the inappropriateness of considering HU as an appropriate treatment post 1st line TKI therapy.

Treatment scenarios

It would be expected that if dasatinib is excluded as a 2nd line treatment, nilotinib would be predicted to yield less QALYs for a lower cost. This treatment paradigm essentially removes 2nd line TKI therapy completely – reducing cost, but at the significant expense of patient outcomes. BMS consider setting up such a treatment paradigm based on the current 2nd line FAD is somewhat premature and may bias the appraisal.

2. Procedural issues which have compromised our review of the Report and the economic model

BMS has been disadvantaged in its review of the AR, the appendices and the economic model because the Institute has failed to provide adequate time for review:

- The Report and Appendices were supplied to BMS on 20 September, 2011
- The economic model was supplied to BMS on 30 September, 2011
- The Report was withdrawn on 30 September, 2011 and the Institute requested all copies of the original report be destroyed
- The time allowed for review was therefore 12 working days, instead of the normal time of 20 working days
- Effective review has also been hindered by supplying the economic model with dummy data in place of CiC data, thus preventing proper assessment of the model against the values discussed in the report.

BMS twice requested additional time for review:

- BMS requested an extension to the period for review on September 30, 2011, noting late delivery of the model and receipt of the updated reports. This request was declined on October 03, 2011. The Institute noted that only three pages of the report were affected by an error although the specifics of the errors were not provided.

- BMS made a further request for additional review time on October 06, 2011. This request followed feedback from several internal BMS reviewers who noted that as the Institute had requested all copies of the original report be destroyed, this had been done...but it meant that their annotations

to the original report had also been destroyed. Thus, each reviewer had, in effect, to restart their review of the documents once the amended report was received. This request was declined by the Institute on October 07.

As a result, BMS have been unable to review the documents provided to the level of detail we believe appropriate. While we appreciate the Institute carefully schedules each appraisal it is unfortunate that we have not been provided with adequate time for review at such an early stage in the appraisal process.

3. Comments on the AG's review of the BMS model

3.1. Noted strengths of the BMS model

The AG reviewed the BMS model against a number of check lists and (while this is not reported in the main body of the ERG report) the findings are summarised below:

- The model was deemed fully compliant with the NICE reference case **(Table 11, P.379)**
- With the exception of the choice of time horizon, the model was deemed fully compliant with the Drummond et al. check list **(Table 12 P. 380)**
- The model scored very well on the Philips et al. checklist with 18 of the 22 questions achieving the highest score and the remaining four middle scores. No poor scores were noted **(Table 13 P. 381)**

Therefore, when compared against numerous benchmarks, the BMS model is of high quality and reflects the natural history of CML. Given that a PSA is generated it arguably outscores the AG model on these checklists.

3.2. Formulae errors *(in responding to these comments we are using the version of the model titled "FirstLineCMLModel_NICE_FINAL_23May2011.xlsm" and the revised PenTAG report).*

Close inspection of the wiring errors listed by the AG shows that of the 8 found, only 3 are major and the other 5 minor.

For the committee's benefit we have replicated the table from the original report along with additional columns stating whether or not we agree/disagree to the presence of the error, and the cumulative impact on the ICER (including it in addition alongside the previous errors).

However, BMS require clarification regarding the AG comment in relation to error #1.

> The summary of the formula used is correct, but in the model stated above cell IF75 contains a formula resulting in the number 53.56 and tracing back all input cells these are also positive (see column entries in DU to ED and LC to LF). Hence, there is no reference to a negative numbers of patients in health states.

In relation to error #2.

> The 58% switching rates refers to patients on dasatinib and nilotinib whereas the 100% used (correctly in the model) refers to patients on imatinib. The rationale for the difference was that clinicians were more likely to keep patients on 2nd line treatment than 1st line, and also that patients who did not respond would be aware of 2nd line treatments and so more willing to switch.

BMS therefore consider the model to be technically correct.

After correcting the model for the relevant wiring errors the revised ICER for dasatinib vs. imatinib was approximately £27,800 per QALY gained and £150,700 for dasatinib vs. nilotinib. BMS is happy to provide a revised version of our model to the AG, as we believe it would be of value for them to review this to ensure the approach we have used to correct our model is in line with their process.

When corrected for the errors identified, the ICER is still below £30,000 per QALY gained.

	Description of error	Agree/ disagree	Impact on ICER (DAS vs. IMAT)
	Major errors		
1	The QALY value of all those in a health state is based on the following formula: (((those in CP – those with SCT)*QALY)+ ((those in AP/BP – those with SCT)*QALY)+ ((those with SCT)*QALY). In the original formula there are two mistakes: 1. The SCT patients which are being subtracted are from the next cycle instead of the current cycle, and 2. The number of SCT patients which are being subtracted is the cumulative value instead of the incremental value. For example, in cell IF75, based on the original calculation there are negative values of people in health states since the cumulative number of patients are being subtracted.	Disagree, see text above	Not tested
2	The probability of switching treatment from imatinib at 12m when under < partial response: "*PCT12MonthNCyRSwitchIMAT*" is input as 100% this contradicts table 25 in the manuf. submission where it clearly states this should be 58%.	Disagree, see text above	Not tested
3	The formula is using the wrong probability of switching i.e. formula uses *Pct18MonthPCyRSwitch* but should be using *Pct18MonthPCyRSwitchIMAT*.	Agree	Revised ICER £22,000 / QALY gained
	Minor errors		
4	The probability of switching at 18m is applied to both cells where it should only be cell CU37.	Agree	Revised ICER £23,900 / QALY gained
5	The calculation of cost for 3rd line resource use for those who are new AP/BP patients (i.e. cell KP8) is using the population of new arrivals from next cycle instead of current cycle.	Agree	Revised ICER £23,900 / QALY gained
6	Formula is not using mortality adjusted population	Agree	Revised ICER £23,800 / QALY gained
7	Resource use cost was using dasatinib mortality unadjusted population for both CP and AP/BP	Agree	Revised ICER £27,800 / QALY gained
8	Formula is not using mortality adjusted population	Agree	Revised ICER £27,800 / QALY gained

3.3. Lower starting age than would appear in a UK CML population

Given that the key data sources used in the model were the DASISION and ENESTnd trials, the starting age was set to that observed in these trials to ensure consistency, and could be viewed as a strength in the model. To list this as a model weakness is arguable.

In contrast, BMS feel that to take data from one source and assume it holds for patients who are approximately 10 years older could possibly be viewed as more of a weakness.

3.4. Lack of knowledge of the Nilotinib PAS

BMS do not consider that our lack of awareness of something which was being considered in confidence outwith BMS can realistically be considered as a weakness of the model.

3.5. Non-use of a lifetime horizon

The AG are correct in this assumption. We apologise for this oversight. The error is caused by extrapolation of the CCyR survival curve.

3.6. No use of MMR, solely CCyR

CCyR has been shown to be a strong predictor of both overall and progression free survival and long term data was available from the same patient group for both. In contrast, we identified no long term data on MMR as a surrogate, and it is not clear from where the AG data arise due the absence of referencing. For these reasons, BMS feel the listing of this as a weakness of the model is unduly critical.

3.7. Discrepancies between model values and report

The example given in the report arose due to the fact that the 6 year data became available very shortly before submission and the dossier was not updated. For the record, the model contains both data sources and a switch to toggle between the two.

3.8. Lack of inclusion of 2nd line benefit associated with treatment

BMS consider this assumption to introduce a strong bias against dasatinib, in that the benefit of all 2nd line therapies are assumed to be as effective as high dose imatinib. The committee should be aware of this when viewing the ICERs generated using the BMS model. Assuming that the £36,000 per QALY gained estimate is correct, were the benefit of treatment to be included, the true ICER would be lower.

3.9. Use of dasatinib in 3rd line

This seems to represent the opinion of the AG and not reflect routine clinical practice whereby dasatinib will indeed be used in this context. As such, it is difficult to understand why the modelling of routine clinical practice represents a 'weakness' in the model.

3.10. Development of a complex model

CML is a complex disease with a large number of interventions and treatment sequences available to the practicing haematologist. While the AG are correct in that a simpler model could be constructed, as noted above, such a model would not reflect the underlying disease and would rely on the concept of constant probabilities rather than the inherent time dependencies in the underlying disease model. Hence, as we have shown above, the 'simpler' model envisioned by the AG is not a model of CML, rather a model of the AG's perception of CML.

3.11. Lack of explanation as to the derivation of the cost of SCT

We would be grateful if the AG could explain which part of the cost they feel has been incorrectly estimated since the value used in the BMS model (£80,000) is very close to the value used in their model (£81,000). In addition, the cost of ongoing, post-SCT care was taken from the model developed by the AG on behalf of NICE for the appraisal of second line CML. Again, the 'weakness' in the BMS model is questionable.

3.12. There are a number of places where the AG have misunderstood the model and have reported this in such a manner as to make it appear less robust than is the case:

i) *"There appears to be no simple way to adjust BMS' model to disallow patients taking second line dasatinib"* **(P.360).** This is not the case as the model has inbuilt parameters for the proportion of patients on 2nd line dasatinib, nilotinib and imatinib for each intervention. It is a minor step to set one cell to 0%. We do not understand how the AG, in their review, did not identify the relevant cells.

ii) *"The BMS model is structured in such a way that it would require significant changes to run it without 2nd line treatment."* **(P.363).** Again, this is not the case as the cells mentioned above can all be set to 0%, effectively removing 2nd line treatment from the model.

iii) The final ICER of £96,000 per QALY gained is generated on the basis of the draft FAD being implemented in full, including the Novartis PAS. Neither of these conditions currently hold.

It is important to note when the appropriate wiring errors are corrected, the ICER generated by the BMS model is still below £30,000 per QALY gained. As mentioned previously, BMS believe it would be of value for the AG to review the revised model to ensure the approach we have used to correct our model is line with their approach.

4. Comments made by the AG on their own model

It may be helpful to the committee for us to collate comments made by the AG on their own model since the report is substantial, a large number of results are generated, and a succinct summary may be helpful.

The cumulative survival approach:

- Ignores CCyR and MMR response rates from the DASISION and ENESTnd clinical trials **(P.139)**
- Relies on numerous assumptions which have a cumulative impact **(P.140)**
- Does not include second line nilotinib **(Scenarios one and two,P.145)**
- Results are only marginally affected by subsequent lines of treatment and their related medical costs **(Scenarios two and four P.145)**

The surrogate predicated survival approach:

- Does not reflect possible depth, speed of achieving or duration of response and hence may underestimate OS for dasatinib and nilotinib **(P.139)**
- Survival does not reflect exact nature of 2nd line treatment **(Scenario 1a, 1b P.145)**

- Results are only marginally affected by subsequent lines of treatment and their related medical costs **(Scenarios 2a, 2b P.145)**

The simplified method:

- *"Clearly does not represent out best estimate of the courses of treatment after resistance or intolerance to TKI's"* **(P.142)**

All of these issues are major weaknesses in themselves, and when viewed collectively BMS feel demonstrate that the AG model is not fit for purpose.

5. Comments on the AG model

5.1. Approach used to model cumulative survival is inconsistent with the underlying disease. General description of the problem

Clinically, there is a proven causal link between complete cytogenic response and survival (Druker et al 2006). It has been postulated that individuals who achieve this endpoint can look forward to a life expectancy approaching that of an age and gender matched person in the general population. In contrast, the prognosis in patients who fail to respond to treatment (i.e. who achieve no cytogenic response after treatment for 1 year) is very poor, and of the order of 5 to 6 years. Those who experience a partial response will have a prognosis somewhere between the two values.

A recent indirect comparison meta-analysis concluded that the probability of achieving this key endpoint was approximately 65% for newly diagnosed patients receiving imatinib and 85% for those receiving dasatinib (Mealing et al 2010). The results from the AG indirect comparison meta-analysis are in line with these results. Authors have predicted differences in life expectancy for the two products of between 2 and 8 years (Botteman F et al 2010, Mealing et al 2011, Botteman et al M 2011). A 'Back of the envelope' calculation (whereby complete responders would be assumed to live 30 years and non-responders 10 years), when combined with the above mentioned response probabilities would give a difference in undiscounted survival of approximately 3 years.

However, in all scenarios, the values generated by the AG are markedly lower than the values discussed above. Scenarios 1 and 3 result in a difference of 0.3 undiscounted life years **(Tables 52 and 54)**. While appropriate results are not reported for Scenarios 2 and 4 **(Tables 53 and 55)**, given that the discounted QALY difference in both cases is very low (0.3 and 0.2) it is highly likely that similar differences in undiscounted life years would be generated.

BMS therefore consider the model is failing to represent the underlying disease as a consequence of it severely underestimating the benefit of second generation therapy generating enormous ICERs. By not accurately representing the underlying disease – the starting point for all health economic models – the results from the AG model are not appropriate for the purposes of decision making.

In the remainder of this section we explore the likely reasons for the discrepancy between the results generated by the AG model and those seen in patients with CML.

Reason one

The method used to model time on first line treatment is inconsistent with the underlying data which results in incorrect treatment durations being modelled

Survival in the AG model is the cumulative total of the number of patients alive on all lines of therapy. Hence, to explore the modelling of survival it is necessary to explore the modelling of treatment duration.

The method used to model time on treatment can be summarised as follows:

- Fit parametric survival curves to the best long term imatinib data
- Use the scale factor from this study to model survival in all arms of ENESTnd and DASISION
- 'Adjust' the derived values using average proportions based on the imatinib arms of all studies.

The predicted undiscounted time on 1st line treatment for each of the three interventions, by scenario, is presented for the committee's benefit in **Table 1**. The choice of approach has no effect on time on treatment.

Table 1: Mean time spent on first line treatment in the AG model

Model setting	Imatinib	Dasatinib	Nilotinib
Cumulative OS, no 2nd line nilotinib	7.0 yrs	7.7 yrs	8.9 yrs
Cumulative OS, 2nd line nilotinib	7.0 yrs	7.7 yrs	8.9 yrs
Cumulative mean, MMR difference	7.0 yrs	7.7 yrs	8.9 yrs
Cumulative mean, CCyR difference	7.0 yrs	7.7 yrs	8.9 yrs
Surrogate mean, MMR difference	7.0 yrs	7.7 yrs	8.9 yrs
Surrogate mean, CCyR difference	7.0 yrs	7.7 yrs	8.9 yrs

Approach used to model long term data for time on imatnib

When it was launched, imatinib 400mg daily represented a step change in the treatment of CML. While response rates were noteworthy, a significant minority of patients experienced intolerance or resistance to the drug. ELN guidelines state that patients who fail to have a complete cytogenic response to treatment by 18 months should switch to another treatment option (stem cell transplantation or another TKI). The indirect comparison meta-analysis by Mealing et al. (2010) derived a 12 month CCyR rate for imatinib of 65%.

Nonetheless, the method used by the AG to model mortality has resulted in expected time on imatinib (based on 8 year data from the IRIS clinical trial) of 13.0 years. The corresponding values for time on nilotinib and dasatinib were 8.5 and 8.2 years respectively. Hence, when the best data for each intervention is used the time on treatment is highest for the intervention with the poorest resistance/intolerance profile (imatinib). The AG attempt to correct for this counter-intuitive outcome by using data from other trials; the central flaw, however, still remains.

Approach used to adjust fitted values

It is interesting to note that the rationale put forward by the AG for the use of a common scaling factor is the unreliability of direct evidence to inform the relevant parameter. In effect, the AG assume a proportional hazard Weibull model holds. The graph of 24 month time on treatment for nilotinib and imatinib (**ERG report, Figure 22**) can be used to test this hypothesis since approximately 20% of individuals had ceased nilotinib and 30% had ceased imatinib.

The following can be shown:

1. the assumption of a common slope parameter does not hold
2. a gamma value of 0.861 is outside the derived 95% confidence intervals surrounding slope parameters for both interventions in the ENESTnd clinical trial

The consequence, the AG's method to derive time on 1st line treatment for all interventions is flawed and downplays the benefit of dasatinib (fitted 8.2 years, used in model 7.8 years – **Table 40 P.163**) and inflates the time spent on nilotinib (fitted 8.5 years, used 9 years).

BMS are happy to provide supportive documentation so that the AG and the AC can ensure our approach is acceptable to them.

<u>Reason two</u>

The method used to model time on second line treatment is inconsistent with the biology of CML and results in unreliable estimates of treatment duration

Hydroxyurea (HU) is an antineoplastic drug used primarily to control white blood cell count; it has no plausible biological mode of action on either the Philadelphia chromosome or the bcr-abl oncoprotien. Therefore, HU has no clinical impact on the natural history of CML and this is the primary reason that the clinical community use this intervention only when they have exhausted all TKI treatment options

and when patients are ineligible for a SCT. Thus, the main aim of treatment with HU in this context is palliative.

In their model the AG assume that HU is used as a 2nd line treatment option with the following additional assumptions:

- The probability of CML related death is constant over time **(see cell O9, worksheet 'HU OS')**
- The probability of disease progression is constant over time **(see cell O20, worksheet 'HU OS')**

In effect, given that HU has no impact on the underlying disease, the AG implies that in their model of the natural history of the disease, the probabilities of either CML related death or disease progression occurring are constant over time, and will be the same on the first day of diagnosis as in the 20th year of the illness. Common sense, and the nature of cancer biology in general, suggest these assumptions are unrealistic.

As a result, the model predicts that patients who receive 2nd line HU will spend large amounts of time on treatment in the chronic phase (CP) state before progressing. The derived totals for the amount of time spent in the in the 'Undiscounted mean' under each of the 6 pre-programmed scenarios is presented in **Table 2 (cell V3 on all Markov traces)**. Depending on the choice of scenario, and remembering that patients will have had CML for on average over 7 years before treatment commencement, the model predicts that treatment will last for between approximately 3 and 9 years.

Table 2: Mean time spent on second line HU in the AG model

Model setting	Imatinib	Dasatinib	Nilotinib
Cumulative OS, no 2nd line nilotinib	2.9 yrs	2.8 yrs	2.8 yrs
Cumulative OS, 2nd line nilotinib	3.0 yrs	3.0 yrs	2.8 yrs
Cumulative mean, MMR difference	2.9 yrs	3.1 yrs	2.5 yrs
Cumulative mean, CCyR difference	2.9 yrs	4.0 yrs	3.3 yrs
Surrogate mean, MMR difference	9.0 yrs	9.2 yrs	8.6 yrs
Surrogate mean, CCyR difference	8.0 yrs	9.2 yrs	8.5 yrs

Further confusion arises when the mean time on second line SCT is tabulated in the same manner **(Table 3, values taken from cell U3 on all Markov traces)**. In this respect it is worth making the committee aware that SCT remains the only curative intervention for CML and so long term survival estimates would be expected.

Table 3: Mean time spent on second line SCT in the AG model

Model setting	Imatinib	Dasatinib	Nilotinib
Cumulative OS, no 2nd line nilotinib	5.8 yrs	5.5 yrs	4.9 yrs
Cumulative OS, 2nd line nilotinib	4.2 yrs	3.9 yrs	3.9 yrs
Cumulative mean, MMR difference	5.8 yrs	5.5 yrs	4.9 yrs
Cumulative mean, CCyR difference	5.8 yrs	5.5yrs	4.9 yrs
Surrogate mean, MMR difference	5.8 yrs	5.5 yrs	4.9 yrs
Surrogate mean, CCyR difference	5.8 yrs	5.5 yrs	4.9 yrs

We expect the AG will confirm that the correct values for SCT patients should be those presented in the row headed 'undiscounted mean (for those in a state)' rather than those in the row headed 'undiscounted mean'. While this would make the SCT numbers more reflective of the real world (survival circa 17 years), the effect on the HU numbers is bizarre, with treatment durations of between approximately 5 and 16 years depending on the choice of scenario **(Table 4 below)**. Further, under the surrogate mean approach the model appears to predict that treatment with HU is nearly as efficacious as SCT.

Table 4: Mean time (yrs) spent on second line SCT/ HU contingent on being in state in the AG model

Model setting	Imatinib		Dasatinib		Nilotinib	
	HU	SCT	HU	SCT	HU	SCT
Cumulative OS, no 2nd line nilotinib	5.1	17.4	5.1	17.3	5.0	17.2
Cumulative OS, 2nd line nilotinib	5.0	16.4	5.0	16.3	5.0	17.2
Cumulative mean, MMR difference	5.1	17.4	5.5	17.3	4.5	17.2
Cumulative mean, CCyR difference	5.1	17.4	7.2	17.3	5.9	17.2
Surrogate mean, MMR difference	15.9	17.4	16.4	17.3	15.5	17.2
Surrogate mean, CCyR difference	14.2	17.4	16.4	17.3	15.3	17.2

The conclusion is that the approach used to model time on 2nd line treatment is deeply flawed, contributing to the poor predictive accuracy of OS and undermining the results.

5.2. Modelling overall survival: conclusions

The approach used by the AG to estimate the benefit of treatment (additional life) has the following flaws:

- It is predicated on a proportional hazard approach which is not in line with the underlying disease
- It does not include differences in response probabilities
- It assumes that any benefit of treatment is expressed in time on second line HU rather than first line TKI use
- It allows for more time on second line treatment with no clinical benefit than on first line treatment with a second generation TKI
- It appears to assume that second line HU may be as efficacious as second line SCT

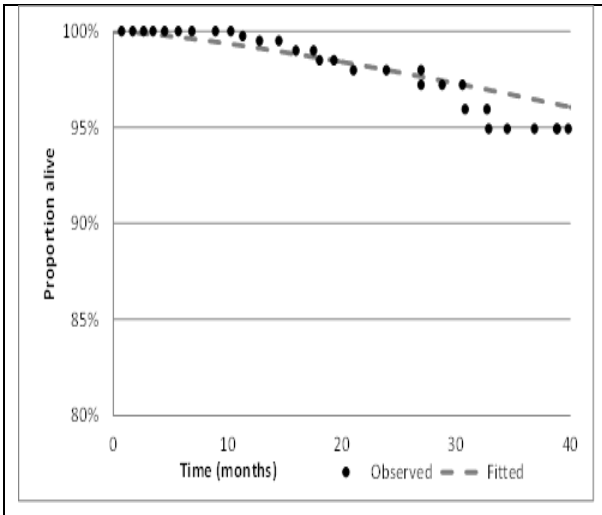
5.3. The approach used to model survival via a surrogate endpoint is deeply flawed

In addition to the above concerns regarding the clinical plausibility of the results derived for the surrogate mean scenarios, BMS would like to make the committee aware of our concerns with the method used to model the surrogate clinical endpoints.

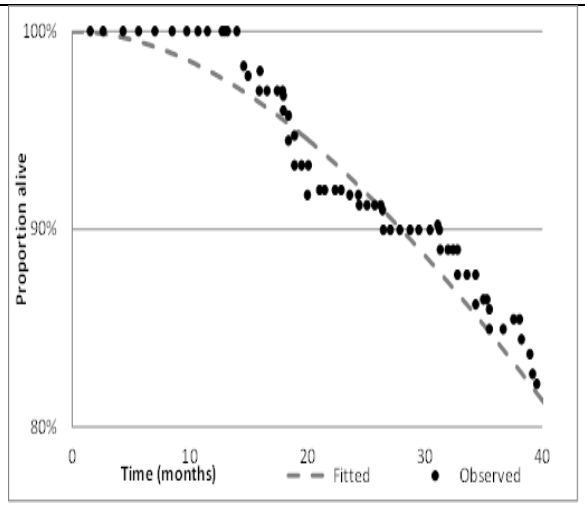
While the CCyR and MMR response rates appear to be derived from a valid indirect comparison, BMS consider the approach used to model CML related death could be improved upon. The primary data source is the IRIS randomised trial, although the precise source is not stated. We presume, however, that the source is the 5 year follow up study published by Druker et al. (2006); 42 month data is presented for each of the cytogenic response categories (CCyR, no CCyR) in Kaplan-Meier plot format.

Extraction of the survival curves into Excel and the fitting of parametric survival functions results in the plots presented in **Figure 1**. It is not clear as to the source of the MMR data as the Druker study does not contain any relevant information.

Figure 1: Fitting of parametric survival curves to reported long term IRIS survival data



CCyR, R^2=0.94, Lambda: 0.0003, Gamma: 1.328



No CCyR, R^2= 0.97, Lambda: 0.0001, Gamma: 1.885

The parameters used to create the functions are also listed in **Figure 1.** Broadly speaking, the gamma value defines the rate of change, with a value below one corresponding to a decreasing rate over time, a value greater than one an increasing rate, and a value of one a constant rate. The gamma values used above are both significantly greater than one meaning that the rate in the data presented in the key paper is increasing over time.

In contrast, the AG has chosen to use a constant rate of progression in the model **(see cells AQ5 and AX5 worksheet Surr OS)**. In effect, the model is saying that the probability of CML related death is the same whether a patient has had the disease for 1 day or 20 years. A similar argument arises for the modelling of MMR.

Consequently, even when adjusting for background non-CML mortality, the predicted mean survival (especially for those who do not respond) is far too high (CCR; 24.4 years, Non-CCyR: 14.3 years, MMR: 24.2 years, No MMR: 21.3 years). The figures for MMR are striking, suggesting that achieving the highest possible level of response to treatment only offers an additional 3 years of life – and that if this level is not achieved, a patient will still live for over 20 years!

These small differences in a patient's prognosis, with and without response, clearly diminish the importance of the proportion of patients who respond overall. A recent indirect comparison meta-analysis of first line treatments concluded that treatment with dasatinib was significantly associated with achieving MMR (Odds ratio 2.23 dasatinib compared to imatinib: Table 12 BMS submission document).

Despite the superior performance on this key clinical endpoint the predicted difference for dasatinib compared to imatinib is a mere 0.6 years. The approach used in the AG model, therefore, is not in line with the clinical evidence and strongly biases all results against dasatinib.

5.4. <u>The presumption that the Nilotinib second line PAS should be included in the analysis is flawed and biases all results against dasatinib.</u>

5.5. <u>The choice of second line treatments used in the model is flawed and unreflective of routine clinical practice</u>

We have noted repeatedly during the 2nd line appraisal of dasatinib in patients who are either resistant to, or intolerant of, imatinib, the consideration of HU as a valid treatment option is fundamentally flawed. A basic understanding of the role of HU in the treatment of CML confirms this, and this position is supported by written responses from numerous clinical experts.

The AG first line CML model offers two treatment permutations:

- Switching to either HU or SCT following failure on first line therapy
- Switching to nilotinib upon failing imatinib or dasatinib and to HU/ SCT upon failing nilotinib

The treatment options are predicated on the absence of dasatinib from 2nd line therapy, even though dasatinib is licensed in this setting and recommended by international guidelines (Baccarani et al 2009, O'Brien et al 2009).

The first of these positions implies that once an individual has had one TKI they will never have another. The second position suggests that a patient who fails nilotinib is somehow "different" to one who fails dasatinib, implying that they are eligible for a SCT (whereas the dasatinib patient is not and has to be given a second TKI before being considered for SCT). We would appreciate the opinion of the clinical community to these treatment scenarios. It is worth noting that both BMS and Novartis included 2nd line dasatinib in their models.

In addition, we would appreciate the clinical community's thoughts on the use of "no treatment" as 3rd line following failure of 2nd line HU. In particular, this assumption is likely to bias against dasatinib when comparing to nilotinib in Scenarios 3and 4.

It is unclear how 3rd line treatment costs are included in the model? However, the 3 monthly cost of HU is erroneously assumed to be £36 and despite the one-off cost associated with SCT being high (circa £80,000) the follow on costs are very low (£340 per three months). In contrast, the three month cost of nilotinib is (in the version of the model provided to BMS) approximately £7,900. Hence, the total cost of 2nd line nilotinib incurred in the dasatinib arm is £53,500 whereas the cost of 2nd line SCT/HU in the nilotinib arm is approximately £30,000. Of note is the fact that patients in the dasatinib arm still appear to be incurring costs associated with SCT/HU. A crude analysis whereby the nilotinib costs in the dasatinib arm are included in the nilotinib arm as a proxy for the cost of 2nd line TKI usage results in dasatinib dominating.

5.6. <u>The AG failed to generate a key output used in reimbursement, namely a probabilistic sensitivity analysis</u>

One of the key components of any economic evaluation is a full assessment of the impact of uncertainty on the cost-effectiveness results, and in particular the impact of the combined uncertainty in all parameters. This is the reason why NICE explicitly ask for a probabilistic sensitivity analysis (PSA) in their reference case. As noted in the guide to technology appraisal *"In non-linear decision models, probabilistic methods provide the best estimates of mean costs and outcomes"*.

As noted in section 5.8.7 of the methods guideline

"The computational methods used to implement an appropriate model structure may occasionally present challenges in conducting probabilistic sensitivity analysis. The use of model structures that limit the feasibility of probabilistic sensitivity analysis should be clearly specified and justified. Models should always be fit for purpose, and should enable a thorough consideration of the decision uncertainty associated with the model structure and input parameters. The choice of a 'preferred' model structure or programming platform should not result in the failure to express uncertainty."

The structure of the AG model is not overly complex and it would be a straightforward matter, if the model were parameterised correctly to develop a probabilistic analysis. We believe that this was not possible due to the heavy reliance on the Solver® add-in for Microsoft Excel to generate model

parameters. This approach uses techniques drawn from numerical analysis to generate values that best fit the data. However, it does not generate intervals around this mean estimate.

While a full review of the structure of the model was not possible given the restricted time available, The AG have used the Solver routine to estimate the following key parameters:

- Fixed death probabilities for CCyR/ No CCyr
- Probability of transition from CP to AP/BP (all treatment options)
- Probability of transition from AP to BP (all treatment options)
- Probability of CML death on HU
- Time on first line treatment (all drugs)
- Time on second line nilotinib
- Fixed probability of death post SCT

Hence, it would appear that the reason for not generating a probabilistic analysis is not the high level of decision uncertainty or the complexity of the underlying disease but the method used by the AG to derive constant (i.e. time independent) values for all key parameters. This is a major failing as it deprives the committee of key information required to make a rational decision on the use of first line treatment for CML.

It is not clear from the AG report whether or not Novartis generated probabilistic results. Despite the AG criticising the BMS model for complexity we captured the underlying disease in a manner that did not assume constant transition rates between disease states and provided the committee with probabilistic results.

6. Other points and factual inaccuracies

- Section 1.5.2

  "24 month CCyR and MMR rates are not reported for dasatinib" – these are reported:

  - CCyR 86% vs 82% (no p value) for Dasatinib and imatinib respectively
  - MMR 64% vs 46% (P<0.0001) for Dasatinib and imatinib respectively

- Summary of surrogate outcomes review **(page 21)** – the conclusion is made that the evidence compiled on CCyR (and MMR) as a surrogate marker is based entirely on imatinib studies and these may not be generalisable to dasatinib and nilotinib.

  This shows perhaps a misunderstanding with regards to the underlying disease as CCyR has been shown to be a robust surrogate outcome marker and is independent of the treatment used to achieve this. Over time, it has become accepted (through clinical evidence) that CCyR as a surrogate can be translated from IFN to imatinib, and there is no logical clinical basis for not expecting this to be true for both dasatinib or nilotinib.

- Section 1.8.8.2

  It is stated that limitations of the cost effectiveness include using HU as a surrogate for what in reality would be a range of other treatments including IFN and chemotherapy.

  HU CANNOT be used as a surrogate for these other treatments as it is effectively a palliative therapy which does not alter the underlying biology of the disease, whereas both IFN and chemotherapy have the potential to do so.

- Section 2.2.3

  Not all leukaemias are CML, and so the survival statistics presented for "all leukaemia" displayed in the first paragraph of this section are irrelevant as they include patients with (for example) acute leukaemias – which are a totally different clinical entity to CML, and for which survival rates are much lower. The IRIS clinical trial is the best source for CML survival stats in the TKI era.

- Section 4.2.2.1
  Primary endpoint was *confirmed* CCyR **(paragraph 1 and Table 6)**

- Section 4.2.2.2

  The comments on **page 69** regarding risk distributions between the two trials suggests a lack of understanding of the two scoring systems. It is not surprising that there was a slightly higher proportion of patients with a High Risk score in ENESTnd, as it has been established that for a given patient population, the Hasford categorisation places fewer patients in the high risk group than does the Sokal categorisation (Hasford et al 2001).

- Section 4.2.2.3 **Page 70**: comments on population in DASISION not being representative of UK population due to (1) low median age and (2) a large contribution of Asian patients into the dasatinib study

  However:

  - The low age is not representative of the average CML patient across EU and the US, but is more or less representative of the age of CML patient in trials (see IRIS study – median age 50)
  - no data are presented for ethnicity for DASISION (**Table 8)**, so it is unclear as to how the AG drew any conclusion about the ethnicity of the patients in the dasatinib study.

- Section 4.2.3.1:

  The AG only discuss 12 and 18 month response rates with regard to Hasford risk categories. However, CCyR rates also remained higher for dasatinib at 24 month follow up across all Hasford risk categories compared to imatinib.

- Section 4.2.3.6:

  It may be helpful for the committee to be aware that the transformation rates presented by the AG for ENESTnd and DASISION are defined differently. ENESTnd reports transformation to AP/BC for patients during treatment, wheras DASISION includes transformations that have occurred after discontinuation of dasatinib. For completeness, the corresponding figures for ENESTnd when post discontinuation transformation are included are 9 for nilotinib 300mg and 18 for the imatinib group (Hochhaus et al 2011) as opposed to 9 for dasatinib and 15 for imatinib in DASISION.

- Section 4.2.3.9:

  BMS believe paragraph 2 should refer to figures 7 and 8. In addition, Figure 7 is on a much expanded scale which attempts to exaggerate a difference in OS that is not clinically relevant.

- Page 242:

  "More research-based data for the assessing the predictive usefulness of surrogate outcomes (such as MMR and CCyR) within the chronic myeloid leukaemia population, especially for dasatinib and nilotinib." BMS consider that such research is not needed, as the value of CCyR as a surrogate endpoint is now very well established and recognised amongst the clinical community. In addition, research is ongoing to better validate MMR as a surrogate endpoint.

Yours sincerely

[redacted]

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Comments from Novartis on the Assessment Report for the Health Technology Appraisal of Nilotinib, Dasatinib and standard dose imatinib for the first-line treatment of Chronic Myeloid Leukaemia

Thank you for your invitation to comment on the above Assessment Report prepared by PenTAG and released in September 2011. We are pleased that the Report concludes that nilotinib is both clinically and cost-effective compared with both dasatinib and imatinib. We consider the Report to be of good quality, representing a thorough review of the evidence. In the economic analysis, we are largely in agreement with the AG's approach and conclusions. We note that the AG has modelled various scenarios which is necessary given the current uncertainty over the treatment pathway following imatinib failure as we await the outcome of the second-line appraisal. We strongly believe that the scenarios which include second-generation TKIs represent the most likely clinical practice. Nonetheless, both we and the AG have investigated a scenario in which no second-line TKI is available. It is in this scenario that the differences between our assumptions and those of the AG have the most effect. Consequently, we have focussed our comments on these elements.

We have also noted inconsistencies in the reporting and interpretation of the clinical data. These are presented in summary format, with individual instances tabulated in the appendix.

Our comments on the AR are structured as follows:

1. CLINICAL EFFECTIVENESS

    1.1. Introduction

    1.2 Discussion of key points

2. ECONOMIC ANALYSIS

    2.1. Outline of key points arising from the Report

    2.2. Detailed discussion of key points

3. SUMMARY

4. Appendix – additional comments

5. References

1. CLINICAL EFFECTIVENESS

1.1 Introduction

We support the conclusion made by PenTAG that nilotinib is clinically effective in this setting and that nilotinib is significantly more effective than the current standard of care, imatinib. However, with regards to dasatinib, and the ENESTnd and DASISION trials, there are some inaccurate representations of the data and differences which we have clarified in our response as below:

> Method of analysis and presentation of data in both the ENESTnd and DASISION trials.
> 'By' and 'At' analysis – a different method of analysis and reporting is used in ENESTnd compared to DASISION which needs to be taken into consideration when indirectly comparing results of both trials

1.2 Discussion of key points

- **Method of analysis and presentation of data in both the ENESTnd and DASISION trials**

We are pleased to note that PenTAG considered the quality of the ENESTnd study design to be good.

Novartis has, however, noted misleading representation of the data and differences between the method of reporting ENESTnd and DASISION trial data in the Assessment Report which we would like to take the opportunity to correct and clarify.

First noted in the Summary of benefits and risks (section 1.5.2), although repeatedly misrepresented throughout the majority of the Assessment Report, is the implication that both trials present all responses in the same way, i.e. using the 'at' analysis. The difference in this analytical approach is key as it affects the conclusion of effectiveness of the two agents.

The DASISION trial uses a 'by' analysis to report its primary and secondary endpoints (i.e CCyR, MMR, CMR). ENESTnd reports its primary endpoint of MMR and some additional reports of MMR and CMR at varying timepoints, uses the 'at' analysis. The 'at' analysis is more stringent and conservative. The difference between the two types of analyses is explained below:

To clarify:
'At' – refers to responses achieved 'at' a specific timepoint. It only includes responses where patients are actually in, for example MMR, 'at' that timepoint (e.g. 12 months). If MMR was achieved prior to that timepoint, but then lost, or the patient discontinued treatment, the response was not included in the reported 'at' analysis.

'By' - refers to the achievement of response 'by' the timepoint and includes any responses achieved up to and including that timepoint even though the response may have been lost prior the assessment timepoint or the patient may have discontinued treatment

Kantarjian et al. (2011) conducted a review of 2nd generation TKIs s frontline therapy. His review explains the differences further:

"*...the simple difference between reporting responses in patients 'at' a specific time point versus 'by' a specific timepoint can influence results and the ability to compare efficacy rates across studies*."[1]

Indirectly comparing data based on the two different analyses does not therefore compare 'like for like'. Additionally, it is incorrect to state DASISION endpoints are reported 'at' any timepoint as analysis in that study is done as a 'by' analysis.

The table below highlights which responses are reported using which analysis method in the ENESTnd trial.

Summary of ENESTnd key responses differentiated by 'at' and 'by' analysis methods

Response	**'at' analysis Nilotinib 300mg bd vs imatinib 400mg od**		**'by' analysis Nilotinib 300mg bd vs imatinib 400mg od**	
	12 months	**24 months**	**12 months**	**24 months**
MMR	44% vs 22% [2, 3] (p=<0.0001)	62% vs 37%[4] (p=<0.0001)	55% vs 27% [3] (p=<0.0001)	71% vs 44% [4,5] (p=<0.0001)
CCyR	NR	NR	80% vs. 65% [2] (p<0.0001)	87% vs. 77% [4,5] (p=0.0018)
CMR[4]	11.7% vs. 3.9%[2]	NR	24% vs. 10% [3]	44% vs. 20%[4,5] (p = 0.0018)
CMR[4.5]	4.3% vs. 0.1%[2]	NR	13% vs. 4% [2]	26% vs. 10%[4,5] (p= 0.016)

We believe PenTAG may have used the ENESTnd 'at' figures of 44% vs 22%, p=<0.001, at 12 months (nilotinib 300mg bd vs imatinib 400mg bd arms, respectively, p=0.001%) when comparing with the DASISION 12 month data which is reported as 'by' (46% vs. 28% p=,0.0001). Similarly PenTAG appears to have done the same for the 18 and 24 month data. By definition, the 'at' figures are clearly numerically lower than the 'by' figures and would therefore lead to a bias in a comparison of the results.

The discrepancy in differentiating between and using the 'by' and 'at' analyses is also noted in several sections of the assessment report which have been highlighted in a table in the appendix, along with other additional comments.

1. ECONOMIC ANALYSIS

2.1 Summary of key points arising from the Report

We are broadly in agreement with the Assessment Group (AG) on many areas of the modelling approach. We also agree that data are lacking in certain areas, and that it is somewhat unclear as to what a reasonable assumption might be in such cases. There appear to be four key areas of discrepancy which exert a significant effect on the model results for one of the possible scenarios in particular: nilotinib v imatinib, with no second-line TKIs (AG Scenario 1). In practice, we expect that clinicians will use TKIs in the second-line setting. However, in the absence of final guidance from NICE, it is unclear what will be available and, hence, this scenario must at least be considered.

The four key areas for further discussion are:

- choice of dose intensity;
- the proportions of patients receiving Stem Cell Transplant (SCT) and the associated survival (we also comment on cost of SCT, although we concur with the AG on this point);
- the assumptions used in the modelling of hydroxyurea;
- the medical management costs.

Each of these is considered in turn below. There are also a number of minor comments (including typos and errors) which we have tabulated for ease of cross-reference with the Assessment Report.

2.2 Detailed discussion of the key points

2.2.1 Dose intensity

We consider that the ENESTnd 24-month data should be used for mean dose since this corresponds directly with the efficacy data. In line with the AG's comments in a previous appraisal (see PenTAG's AR for 2nd line), mean dose is to be preferred in these analyses and median is an inferior measure. It is certainly not appropriate to use imatinib's efficacy results from 24m in conjunction with the dosing levels from 12 months, as is currently the case in the AG's analysis.

As per the reference (Table 12-2 of the 24m-CSR, provided with our submission), the Novartis model uses mean dose intensities from the 24m analysis of 423.0 mg for imatinib and [redacted] mg for nilotinib. These are incorrectly referred to as *median* dose intensities in the Assessment Report. The AG has used the mean dose of imatinib from the 12-month analysis (which we presume to be 401.5 mg; this is redacted in the Report for confidentiality reasons). We do not believe the 12-month dose is relevant because it does not accord with the efficacy data which is taken from the 24-month analysis.

Patients in the imatinib arm of ENESTnd were allowed to dose-escalate to either 600mg or 800mg per day. This occurred when the response to the standard 400mg dose was inadequate. Thus, it is

entirely plausible that the mean dose would have been somewhat higher than 400 mg/day, particularly at the later time-point of 24 months when more patients on imatinib had effectively 'failed' on the 400 mg dose. Indeed, at 12m, only 15.7% of patients were taking an increased dose of imatinib (hence the mean dose of 401.5 mg); by 24m, almost twice as many (29%) patients in the imatinib arm had actual dose intensity greater than 400mg, giving a mean dose for the overall group of 423.0 mg.

In addition, the Report quotes an analysis of IRIS at six years as reinforcing their assumption of a lower dose intensity for imatinib. The Report quotes a mean dose of 400 mg from this analysis but, in fact, this is the *median* dose. The *mean* dose is 467 mg (SD +/- 179, range 100-800). (Hocchaus et al,2009). This would seem to support our assumption of a higher dose intensity rather than undermine it.

2.2.2 Time on HU in CP

There are two issues concerning the assumptions relating to the modelling of HU. The first is *how* we modelled time on HU in chronic phase (CP); the second is the plausibility of the projected number of years patients remain on HU in CP. We do not expect our modelling approach to have exerted a strong influence on the validity of the estimate generated; and we do not believe that it is likely that patients will spend five years on HU whilst in Chronic Phase having already failed a first-line TKI.

In terms of modelling approach, the Novartis model uses the difference between the time to discontinuation and progression free survival curves to derive the number of years in CP on HU. As the Assessment Group have highlighted, the estimated time spent in CP on HU is an *approximation only*, because the definition for PFS from the study (CAMN107A2101) includes loss of CHR & loss of MCyR, as well as progression to AP & BC and death. However, it seems likely that those patients who discontinue a TKI due to loss of CHR or loss of MCyR will not stay in CP for a long period and this will, therefore, have a limited impact on the estimate given.

As regards time on HU, our model projected time on HU in CP to be 1.6 years, with overall time on HU (CP + AC + BC) to be 3.41 years. There is no evidence on the effectiveness of HU in the second-line or third-line setting. The FAD for the second-line appraisal states: "For people receiving interferon alfa or hydroxycarbamide in the chronic phase, the prognosis is poor, with a median life expectancy of around 5 years". Given that these patients would spend one to two years in AP and/or BC, this suggests that they could not stay in CP for longer than three to four years. In response to the ACD for the second-line appraisal, both Prof Apperley and the Royal College of Physicians noted that the five-year survival relates to patients who receive HU from the point of initial diagnosis; such patients will be younger and healthier than patients who have failed one or more TKIs. Accordingly, three to four years in CP is perhaps an upper bound, with time spent in CP after TKI failure being less.

We note that SHTAC (in the second-line appraisal) suggested that time of HU in CP should be 3.5 years. This was accepted by the appraisal committee and so we have used this value in our model, with results presented below:

Table 1 Probabilistic Sensitivity Analysis results for alternative time in HU

Discounted	Costs	LYs	QALYs	Cost per LY gained	Cost per QALY gained
Imatinib-Dasatinib	£233,225	10.78	8.38	-	-
Nilotinib-Dasatinib	£220,785	11.12	8.65	-£37,195	-£46,744
Imatinib	£172,077	8.66	6.70	-	-
Nilotinib	£175,177	9.55	7.41	£3,501	£4,414

2.2.3 Stem Cell Transplant

2.2.3.1. Proportion of patients who receive SCT

In our model, we assumed that 75% of patients under 65 that discontinued first-line treatment would receive a SCT. Overall, this meant that 47% of nilotinib and 55% of imatinib patients received a SCT. It does not mean that SCT was an option for 75% of all patients. Since this is an area where the data provide little clear direction, we have investigated two further possibilities below. An alternative assumption would be that based on the RCP comments in response to the ACD for the appraisal of nilotinib, dasatinib and imatinib for the treatment of CML in the second-line setting, that state that fewer than 30% of patients would receive SCT. In Table 2 the proportion of patients receiving SCT in the nilotinib arm is 29%, in Table 3 the proportion of patients receiving SCT in the imatinib arm is 29%.

Table 2 Probabilistic Sensitivity Analysis results - .Proportion of patients below age threshold with a donor (2nd line) = 47%. Overall % getting SCT: nilotinib = 29%, imatinib = 34%.

Discounted	Costs	LYs	QALYs	Cost per LY gained	Cost per QALY gained
Imatinib-Dasatinib	£222,040	10.05	7.79	-	-
Nilotinib-Dasatinib	£210,221	10.40	8.07	-£33,086	-£41,401
Imatinib	£154,235	7.90	6.07	-	-
Nilotinib	£159,663	8.81	6.80	£5,967	£7,460

Table 3 Probabilistic Sensitivity Analysis results - Proportion of patients below age threshold with a donor (2nd line) = 40%. Overall % getting SCT: nilotinib = 25%, imatinib = 29%.

Discounted	Costs	LYs	QALYs	Cost per LY gained	Cost per QALY gained
Imatinib-Dasatinib	£220,369	10.06	7.79	-	-
Nilotinib-Dasatinib	£208,690	10.43	8.09	-£31,970	-£39,981
Imatinib	£151,329	7.90	6.07	-	-
Nilotinib	£157,280	8.82	6.80	£6,451	£8,057

2.2.3.2 Cost of SCT

The cost of SCT is a strong driver of the model. There are large differences between the assumptions made by BMS and those made by both the AG and Novartis. Although it appears that the AG and Novartis assumption differs by approximately £19,000, in fact we assume very similar costs for the procedure itself, plus first one-hundred days (AG costs £80,000; Novartis costs £79,000). The additional costs assumed in our model come from our assumption that long-term costs will add 25%, to give a total of £99,000. We consider that our assumptions are plausible, and possibly conservative, because long term costs are uncertain. The RCP comment in their response to the appraisal of nilotinib, dasatinib and imatinib (second line) that SCT is associated with significant morbidity. We consider that managing these morbidities is likely to incur higher costs than those assumed in our model or the AG model.

2.2.3.3 Survival following SCT

We note that the AG has used the recent paper by Pavlu *et al*. We do not agree that it is appropriate to use the six-year survival of 72% from this paper because it relates to the whole cohort of patients in first CP, not the subgroup of patients who reflect those being considered in this appraisal. The relevant six-year survival produced by the Pavlu analysis lies somewhere between 30 and 60%.

The EBMT transplantation risk score system that is widely used is as follows:

Prognostic factors	Risk score
Age	
Less than 20 y	0
20-40 y	1
More than 40 y	2
Interval from diagnosis to HSCT	
1 y or less	0
More than 1 y	1
Disease phase	
Chronic	0
Accelerated	1
Blastic	2
Donor-recipient sex match	
Female donor and male recipient	1
Any other match	0
Donor type	
HLA-identical sibling	0
Any other	1

(Baccarani 2006)

From the Pavlu *et al* paper, it is our understanding that the group undergoing transplant in first CP will include patients who are under 40, whereas the starting age in our model was 57 years. It will also

include patients who receive a transplant within the first year of diagnosis, whereas the vast majority of patients that are considered in the model will, on the basis that they must first fail a first-line TKI, be beyond the first year after diagnosis. At best, we expect that they will meet the criteria to score 3 on the EBMT risk scale. Using figure 5 of the Pavlu *et al* paper, this suggests a six-year survival of 60%. In fact, at least some of the patients are likely to be at risk score 4 or worse, where six-year survival is no more than 45% and may be as low as 30%.

Basing outcome on the full cohort from the Pavlu *et al* data generates a median survival following SCT of 17 years. This does not seem plausible since it suggests that, on average, those treated with SCT having already failed a TKI will have a near normal life-expectancy.

It addition, it should be noted that two of the references cited by the AG to support higher overall survival from SCT were based on cohorts of patients with a mean age well below the average start age of the cohort. In Lee *et al* , for patients who had received prior imatinib the average age was 38 years, with only 17% over 50 years; for patients who had not received prior imatinib the average age was 37 years , with only15% of patients over 50 years. In Saussele *et al* the median age of the cohort was 37 years (range 16-56 years).

An alternative assumption has been investigated: applying the 10-year survival that was considered robust during the second-line appraisal to the current Novartis model produces the following results:

Table 4 Probabilistic Sensitivity analysis results for mean survival after SCT of 10 years

Undiscounted	Costs	LYs	QALYs	Cost per LY gained	Cost per QALY gained
Imatinib-Dasatinib	£289,569	14.78	11.26	-	-
Nilotinib-Dasatinib	£278,890	15.33	11.68	-£19,645	-£25,246
Imatinib	£202,624	12.76	9.64	-	-
Nilotinib	£213,398	13.79	10.46	£10,393	£13,120

Discounted	Costs	LYs	QALYs	Cost per LY gained	Cost per QALY gained
Imatinib-Dasatinib	£232,764	11.03	8.53	-	-
Nilotinib-Dasatinib	£220,227	11.32	8.76	-£42,570	-£52,595
Imatinib	£170,793	9.52	7.29	-	-
Nilotinib	£173,941	10.19	7.84	£4,650	£5,716

Deterministic results for comparison:

Discounted	Costs	LYs	QALYs	Cost per LY gained	Cost per QALY gained
Imatinib-Dasatinib	£227,603	10.80	8.35	-	-
Nilotinib-Dasatinib	£216,537	11.13	8.62	-£33,276	-£41,132
Imatinib	£165,769	9.30	7.12	-	-
Nilotinib	£170,176	10.00	7.70	£6,257	£7,676

2.2.4 Medical Management Costs

The costs assumed by the AG exceed ours by some margin. In CP this appears to be because we assume far fewer visits and less regular tests for ongoing monitoring of patients. The AG assumed an average of 1.3 outpatient visits (0.4 nurse-led + 0.9 haematology lead) per month throughout the chronic phase and regular monthly testing amounting to £216.07 per month. The ELN guidelines recommend that patients in molecular response should be reviewed every three months for loss of response and those in cytogenetic response be reviewed every 6 months. It is, therefore, implausible that clinicians would monitor patients as frequently as 1.5 times a month just for routine visits as indicated in the AR. It is also unlikely that the tests specified in the AR would be carried out as frequently as stated. Based on clinical opinion, Novartis assumes that patients in CP have a routine appointment at the start of treatment, with successive visits at intervals of 1 week, 2 weeks, 4 weeks and every 6 weeks thereafter. Patients in AP are assumed to have six routine appointments per quarter, whilst patients in BC are assumed to have twelve routine appointments per quarter. Based on clinical advice, the routine appointment would be an out-patient visit, during which patients would receive a full blood chemistry test and physical examination at every second appointment.

In contrast, the AG assumes 0.3 bone marrow aspirations with biopsy per month, at a cost of £674 per test. This accounts for £202 of the total costs of £370 per month. It is unlikely that every patient will require a biopsy every three months for the duration of their post CML diagnosis lifetime.

However, if we acknowledge that medical management costs are unclear and our model is re-run using higher cost estimates following the first 6 months, the following results are obtained:

Table 5 Costs doubled to £184 per month (£552 per quarter)

Discounted	Costs	LYs	QALYs	Cost per LY gained	Cost per QALY gained
Imatinib-Dasatinib	£240,971	10.18	7.91	-	-
Nilotinib-Dasatinib	£229,026	10.53	8.19	-£33,607	-£42,223
Imatinib	£176,506	8.11	6.27	-	-
Nilotinib	£180,920	9.00	6.97	£4,980	£6,260

Table 6 Costs increased to £370 per month (£4,440 per quarter) consistent with the AG's Report, table 48 p 179.

Discounted	Costs	LYs	QALYs	Cost per LY gained	Cost per QALY gained
Imatinib-Dasatinib	£257,107	10.18	7.91	-	-
Nilotinib-Dasatinib	£246,221	10.54	8.19	-£30,809	-£38,698
Imatinib	£186,496	8.11	6.27	-	-
Nilotinib	£193,527	9.00	6.97	£7,949	£9,993

3. SUMMARY

We are pleased that the Report concludes that nilotinib is both clinically and cost-effective compared with both dasatinib and imatinib. Overall, we consider that the Assessment Report is balanced and of good quality. However, in the areas of dose intensity, SCT, time on HU in CP, and medical management costs, we consider that the assumptions made by the AG may not represent what is seen in clinical practice.

Although the clinical section is well presented, it is important to ensure that data for response rates are reported using the correct terminology to avoid confusion and ensure that any comparisons are 'like for like'. Further, we strongly request fair representation of the safety profile of nilotinib when compared with dasatinib in particular relating to QTc interval.

4. APPENDIX – additional comments

Additional Comments on the Assessment Report

Page	Issue	comment
Section 1.8.2	Speculating on future prices of imatinib following patent expiry	The patent expiry is four years away and, as acknowledged by the Assessment Group, the Committee is likely to set a review date for this appraisal which precedes the patent expiry. Updated effectiveness data are likely to be available by this time and the costs of other drugs under consideration may also have changed so such early speculation about the price of imatinib alone is not helpful to the current decision.
133	The AG states that Novartis make no use of the major molecular and complete cytogenetic response rates from the RCT of nilotinib compared to imatinib	1. Previous experience shows that using surrogate markers is often criticised and we have made an attempt to move away from this approach by using what we know about how long patients stay on drug. As is clear from the AR, confusion abounds between the 'at' and 'by' analyses which also underlines why, in this case, it is less than ideal to be relying upon them for extrapolation purposes. 2. Our current approach, using time to discontinuation also offered the advantage of maintaining consistency between the Novartis first- and second-line submissions, which were originally scheduled to be submitted within two weeks of each other.
139/147	The AG state that their surrogate model does not reflect possible differences in the depth, speed of achieving, or duration of a response.	The depth of, speed of achieving, and duration of response is known to affect the long-term outcomes of treatment[9]. By not incorporating these elements, it is likely that the efficacy of nilotinib has been underestimated.
154/155	The labels on the MMR and CCyR tables are the wrong way round	Typo

Additional Comments on the Appendices of the Assessment Report for nilotinib, dasatinib and imatinib first-line

Appendix no.	Page no.	Issue	Comment/Actions
1	257	Cut off date for lit review = 070311	A recently published indirect comparison of nilotinib and dasatinib by Signorovitch et al (2011) provides additional information, demonstrating that nilotinib achieves significantly higher rates of molecular response and overall survival than dasatinib by Month 12[7].

			A review paper by Giles et al. (2010) focuses on nilotinib vs. imatinib but also looks at DASISION 12 month data as a comparison and the independent trials by the GIMEMA and MDACC groups[8]. A review paper indirectly comparing 2nd generation TKIs in frontline use by Kantarjian et al. (2011) specifically looks at ENESTnd and DASISION data by month 12 and highlights the differences in reporting 'by' and 'at' and also looks at the independent trials from GIMEMA and MDACC[5]. The Assessment Group and Appraisal Committee may also wish to be aware that 36m data for the ENESTnd trial will be presented at the ASH meeting in December 2011. In addition, the QOL data from ENESTnd will be presented as an oral presentation.
6	350	S0325 study of das v im quotes significant difference for MMR but the values are identical	Error. The dasatinib % should be 43, the imatinib numbers should be 58/99
7	371	"The IRIS trial data covers a period of 6 years. However, the majority of pts receiving imatinib in this trial were still both alive and on 1st-line therapy at the end of the trial (i.e. not progressed)."	1. The available data for IRIS now extend to eight years (Deininger, ASH 2009 – Blood 114:1126). At that time point, 55% of patients were still on imatinib, although it is unclear from the abstract how many of these were on 400 mg and how many had been dose-escalated. 2. Alive and on first-line therapy does not mean same as "not progressed".
7	385	Typo which suggests dasatinib v nilotinib ICER is 45,600 down to 52,574	This is the dasatinib v imatinib ICER.
7	391	Our base case results are not as per model, but deterministic ones in the appendix are.	We presented our probabilistic results as base case so not verifiable without running the model
7	398 + 416	Unclear info on age adjustment	As stated in the Novartis report, the average utility of a given population decreases as age increases (Ara &

			Brazier 2010) For instance, the utility of patients remaining in good health in the chronic phase will not remain constant but will decline gradually over time due to aging. The mean utility of a patient in any given health state was therefore adjusted to reflect the fact that the average utility of a given population decreases as age increases. Full details of this calculation are given in the model (in the utility_adjust sheet). In common with the Novartis model, the AG also undertake the same age-adjustment of utilities with the exception of one minor difference: an equal 50%-50% male to female population split was assumed in the Novartis model, whereas the AG assume a 58%-42% male to female population split. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010;13:509-18.)
7	403	Under heading "major concerns" "The Novartis model makes no use of cytogenetic or molecular response rates from the ENESTnd trial."	See above for page 133 of the AR.
7	415	Only list six AEs as having been included in the Novartis model	Should be eight. We also considered pericardial effusion and CHF/cardiac disease.

Table highlighting sections of the Assessment Report which misleadingly represent the 'by' and 'at' analysis

Section number	AR statement and Novartis comments
AR 1.8.1	*"Indirect comparison analysis showed no difference between dasatinib and nilotinib for the primary outcomes of complete cytogenetic response and major molecular response at 12 or 24 months follow-up"* The statement above is incorrect firstly because it implies that the data from both trials is reported in the same manner, i.e. using the 'at' analysis as above. ENESTnd reports its' primary MMR 'at' 12 months and DASISION conversely reports MMR 'by' 12 months. *In addition, the statement is fundamentally incorrect by stating that "there is no*

	difference between dasatinib and nilotinib for the primary outcomes...". The primary endpoint of CCyR in the DASISION trial was met and was statistically significant by 12 months; however, the statistical significance was not maintained by 24 months with only a 4% difference between CCyR in the dasatinib arm compared to the imatinib arm at that time (86% vs. 82% respectively). In contrast, in ENESTnd CCyR rates were significantly superior at both 12 and 24 months, showing continued superiority of nilotinib compared to imatinib up to the latest data cut. The same comment applies to section 4.3 and the statement: "There was no difference between dasatinib and nilotinib for the primary outcomes of CCyR or MMR at 12-months or 24 months follow up.
AR 1.9	*"an indirect comparison analysis showed no difference between dasatinib and nilotinib for the primary outcomes of CCyR or MMR at 12 months or 24 months of follow-up"* Please refer to our comments above.
AR 4.2.3.1	**Sub-section titled: Complete cytogenetic response:** *"DASISION and ENESTnd reports CCyR at 12, 18 and 24 months follow up"* CCyR for both trials was reported 'by' 12 and 24 months.
AR 4.2.3.1	**Sub-section titled: Dasatinib vs. imatinib:** *"at 24 months follow-up there was no significant difference for patients with a confirmed CCyR"* This should be 'by' 24 months.
AR 4.2.3.1	**Sub-section titled: Nilotinib vs. imatinib** Section refers throughout to CCyR responses in ENESTnd as 'at' each timepoint, however this should be CCyR *'by'* 12, 18 and 24 months.
AR 4.2.3.2	*"DASISION and ENESTnd reports MMR at 12, 18 and 24-months follow-up. ENESTnd reports MMR at any time (12 and 24-month cumulative, MMR may be lost at specific time-point). DASISION reports MMR at any time (12 and 18-month cumulative)."*

	As above, the DASISION trial reports MMR 'by' 12, 18 and 24 months and not 'at' 12, 18 or 24 months. ENESTnd reports MMR 'at' 12 and 24 months and additionally MMR 'by' 12, 18 and 24. The 'by' figures of ENESTnd allow for a more comparable indirect comparison with the DASISION trial.
AR 4.3	Table 19 – please note that the references to 'by' and 'at' data are not correctly interpreted in the CCyR or MMR line and should be corrected accordingly: CCyR in DASISION was 'by' all timepoints not 'at' Rates of MMR in DASISION were 'by' all timepoints not 'at'

Additional Clinical Points	
AR 1.5.2	*"At 18 months and 24 months follow-up, patients receiving dasatinib were still significantly more likely to achieve a CCyR and MMR"* In addition to the point already made, that the analysis is incorrectly stated to be 'at' 18 and 24 months when it was reported 'by' these timepoints in the DASISION trial, the statement that they are both statistically significant is inaccurate. Whilst the 'by' 12 month analysis showed significance at the Primary Endpoint CCyR rate dasatinib vs. imatinib), this significance was not maintained by 18 or 24 months, indeed by 24 months there was only a 4% difference in rates of CCyR between dasatinib and imatinib (86% vs. 82% for dasatinib vs. imatinib arms respectively) indicating that imatinib response rates 'by' this time point are catching up. Further to this, at the end of the summary section the Report again refers to there being no difference between dasatinb and nilotinib for CCyR or MMR at 12 months follow-up, when there is a difference as clarified in earlier sections.
AR 4.2.3.1	Both 'confirmed' and 'unconfirmed' CCyR rates are referred to in this section. It is correct to highlight that there is a difference. ENESTnd, reported only 'unconfirmed' CCyR rates. However the DASISION trial reports both unconfirmed and confirmed responses in the 12 month publication..It is therefore important in any indirect comparison between the trials to ensure 'like for like' figures are used and compare 'unconfirmed' with 'unconfirmed'. It is unclear whether the correct figures have been used in the indirect comparison to ensure the trials were fairly compared.
AR 2.2.2	– *"...it is widely accepted goal for patients to achieve a complete cytogenetic response (CCyR) within 18 months of CML therapy."* The European LeukemiaNet (ELN) recommendations last published by Baccarani in 2009, state that 12 months is the optimal response timeline for achievement of CCyR and at least a partial CCyR (pCCyR) should be achieved by 6 months.
AR .5.2	*"The FDA has stipulated that nilotinib should carry a 'black box' warning for possible*

	heart problems due to QTc prolongation, that may lead to an irregular heart beat and sudden death" We believe it is misleading to present the US label for nilotinib, whilst making no reference to the UK label. This warning in the US does not reflect the current dataset for nilotinib. The reference to QTc prolongation in the nilotinib SPC is contained in the '4.4: Special warnings and precautions' section and carries very similar wording to that in the UK dasatinib SPC due to the fact that QTc prolongation is a TKI class effect and as such is not limited to nilotinib. This point does not seem to be clear in the Assessment Report. Where the Report has referred to QTc prolongation with nilotinib, this is not mentioned for dasatinib. Novartis strongly request fair representation of the safety profile of nilotinib when compared with dasatinib in particular relating to QTc interval The UK SPCs for both nilotinib and dasatinib carry very similar mentions of QTc prolongation and hypokalaemia and hypomagnesaemia, both being listed in the 'Special Warnings and Precautions' sections of the SPCs for both nilotinib and dasatinib.
AR 2.6.2.3	*"The FDA has stipulated that nilotinib carry a 'black box' warning for possible heart problems due to QTc prolongation, that may lead to an irregular heart beat and possible sudden death. Nilotinib has been shown to prolong cardiac ventricular repolarisation which can result in ventricular tachycardia and possibly sudden death. Nilotinib should not be used in patients who have hypokalemia, hypomagnesemia or long QT syndrome".* Please see comments on QTc prolongation above under the responses to section 1.5.2.
AR 4.1.2.1	Although the GIMEMA and MDACC trials use an unlicensed dose of nilotinib in newly diagnosed patients, they should be included in terms of providing further evidence of nilotinib's safety profile or the responses and benefits of nilotinib in this setting, supporting that seen in the ENESTnd trial. Additionally there is longer follow-up for these trials which further support the registration data. The GIMEMA trial which has the longest follow-up of 3 years suggests that responses seen with nilotinib continue to improve, with high OS and PFS rates (97% and 97% respectively) and only 1 patient progressed by the 3 year data cut[6]
AR 4.2.4	*"....nilotinib carries a 'black box' warning for possible heart problems due to QTc prolongation, where prolonged cardiac ventricular repolarisation can result in ventricular tachycardia and death."* Relating to this statement, please see comments on QTc prolongation above under the responses to section 1.5.2.

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CML Support Group: Comments on the PenTAG ; Technology Assessment Report (TAR) for:

"Dasatinib, Nilotinib, dasatinib and standard dose imatinib for first line treatment of chronic myeloid leukaemia: systematic reviews and economic analyses."

Preamble

We support the principle of evidence based medicine as we do the use of health technology appraisals to asses the clinical and cost effectiveness of therapeutic interventions for defined indications.

We recognize the difficulties Appraisal Committees face when confronted by Reports from Assessment Groups charged with a commitment to a definitive and rigorous analysis yet faced with a very diverse clinical reality together with data that is often fragmented and short term.

Given this situation we also have regard of the difficulties faced by PenTAG, the Assessment Group, in their attempt at cost effectiveness modelling and critiques of industry models.

Background

In this assessment PenTag have no dasatinib versus nilotinib Randomized Clinical Trial (RCT) data to access and had only two years data from the DASISION (dasatinib vs imatinib) and ENESTnd (nilotinib vs imatinib) "good" quality RCTs (as assessed by PenTAG: 1.5.1.) to resource.

As a result only an "indirect comparison of nilotinib to dasatinib was able to be carried out using results from the DASISION and ENESTnd trials" (4.2.6.) to establish clinical effectiveness.

The standard systematic review and meta analysis that attempts to synthesize relevant studies of the same intervention(s) was in the latter case not undertaken (4.1.5.) and in the former limited to the two RCT's mentioned above (4.1.2.1) although supplemented by additional data in conference abstracts, presentations and papers based on the two trials.

The two RCTs were described as providing "insufficient data to assess longer term patient relevant outcomes" (1.9)

Patient relevant outcomes are defined as progression-free survival, overall survival and healthy related quality of life.

As a result, and because "treatment duration" is also uncertain, "cost effectiveness estimates of dasatinib and nilotinib are inevitably highly uncertain" (both references: 1.8.8.2).

For the cost effectiveness analysis PenTAG, after a systematic literature review, was not able to discover any "published full economic evaluations meeting the inclusion criteria" (6.2. & 1.7.1.).

Instead of presenting a single base case analysis; PenTAG's own cost effective analysis was accomplished by constructing various modelling "scenarios" for analysis although they concluded "it is not possible to designate any one scenario as the most plausible" (8.1.).

Three different methods were then deployed to work through the scenarios with additional sensitivity analyses for relevant parts of each scenario.

In addition to the lack of long term data already mentioned; PenTAG also noted the "very heterogenous treatment and care pathways that CML patients may follow" (1.8.8.2.) contributed to "extensive structural uncertainty" (8.1.) in their cost effectiveness modeling

Uncertainty also appears all pervasive because there was an "unusually large amount of structural uncertainty that is inherent in the present decision problem(s) " (1.7.3. and 8.6.)

Report limitations

In summary PenTAG were confronted by what they considered to be a significant lack of clinical and cost effectiveness evidence, a level of multi variated care and treatment pathways that presented major analytic challenges, together with problems resident in the formulation of the decision problem they were tasked to produce an assessment for.

Unsurprisingly the TAR is heavily qualified throughout, often reliant on PenTAG assumptions, populated with evidence that is admitted to be of uncertain status and includes the proffering of various scenarios for consideration without a stated Assessment Group preference.

The level of uncertainty referred in the Report is such that it prompted PenTAG to describe no less than six "suggested research priorities" (1.10) be addressed in the future.

Our comments on the TAR consist of observations of particulars and a more general objection to the approach taken although we recognize that this is in part influenced by PenTAG's remit to provide an analysis of the two relevant industry manufacturers cost effectiveness modelling.

Observations on some of the Report's particulars (in no particular order):

1. Cost effectiveness scenarios:

PenTAG have no developed a cost effectiveness scenario developed where patients simply remain on any (single one) of the three comparators indefinitely as 1st line therapy when durable defined surrogate outcomes are achieved.

The presumption seems to be that either this will not occur or, given that there remains a possibility of it not occurring, modelling should proceed on the assumption that it does not.

The logic seems to be that given approximately 40% of patients on first line imatinib fail and move to 2nd or 3rd line treatments any assessment of the cost effectiveness of a TKI (or at least the TKIs used as comparators in this assessment) must necessarily incorporate costs of 2nd and 3rd line treatments, including nilotinib, even though some 60% of patients, in the case of imatinib, will not progress to 2nd or 3rd line treatment.

Evidence from the two trials (DASISION & ENESTnd) confirms dasatinib and nilotinib dominate imatinib with very high durability of response with 77% and 75% still continuing to receive treatment with dasatinib and nilotinib respectively in their RCTs (4.2.2.4.) at 24 months.

Yet there is no attempt to model cost effectiveness for any imatinib,dasatinib or nilotinib patient populations that do not loose durability of response, do not fail and do not therefore progress to access 2nd or 3rd line treatments.

This seems perverse; the more so given that the appraisal is for first line treatment only.

2. Surrogate markers and data sufficiency:

PenTAG posit that there is only an associative relationship, or to be more precise an "observational association (level 2) evidence" (1.5.3), between the surrogates of a defined complete cytogenetic response (CCyR) and defined major molecular response (MMR) (at 12 months) and overall or progression free survival in chronic phase.

We accept that relapse after attaining either of these states (as defined in the Report) remains a possibility after 12 months (or thereafter) use of any of the comparator TKIs. Notwithstanding such an event; steady progression towards

complete molecular remission (CMR), passing through CCyR and MMR as intermediate stages, is the key indicator of a likely future outcome of progression free survival or overall survival.

We also accept that many patients do not attain CMR but remain at MMR but often at a greater log reduction than defined as MMR in the Report.

Leading CML clinicians are agreed that speed and depth of molecular response plays a crucial role in achieving durable progress towards CMR.

PenTAG find both dasatinib and nilotinib to have "a statistically significant advantage" over imatinib as measured by cytogenetic or molecular response (ie surrogate outcomes) but conclude "there is insufficient data to assess longer term patient outcomes" (ie progression free survival, overall survival & health related quality of life)" (both 1.8.1.)

NICE received concerns expressed about the advisability of the timing of the MTA based on the limited data available (see "Response to consultee and commentator comments on the draft scope" p.10 Response of NCRI/RCP/RCR/ACP/JCCO and the Royal College of Pathologists, BSH and RCP consultees).

NICE have responded by stating they have a commitment to:

"..issue guidance as close as possible to the time of marketing authorisation"

It appears that PenTAG make no allowance for the commitment by NICE in their addressing the decision problem since they repeatedly stress that the data they are confronted with is too immature, insufficient and short term for them to model from a single base case.

Our response is that the data cannot be anything but short term given the time constraint imposed by NICE.

This applies not only to the two Randomized Control Trials PenTAG limit themselves to in their analysis but of course also affects the possibility of any balancing function being provided by other studies in a systematic review and meta analysis.

The decision by PenTAG to omit both other studies in a systematic review and conduct no meta analysis due to prevailing paucity is in turn time dependent but also limited by rigidly applied inclusion criteria which exclude observational studies that could better inform the Report.

PenTAG also seem not to have grasped that the operative environment for patients and clinicians is the molecular rather than what is sometimes described as the "morphological".

In the molecular environment descriptors such as "symptom free", "cure", "overall survival" lack precision since (as PenTAG acknowledge) we are forever limited to that which is detectable (by the limits of PCR methodology).

Indeed it is disease state at molecular level (and its detectability at that level) that defines the 'morphological' level although at this level its description would carry secondary status because of its transformation into grosser terminology.

In addition we know it is possible to be asymptomatic or symptom free at a diagnosis which is serendipitous (PenTAG cite 50% of patients diagnosed in chronic phase), are aware of quiescent presence (of progenitor CML stem cell(s)), recognize the possibility of BCR-ABL activity in the general population that does not transform into CML (patients), accept the concept of a "functional cure" and possible relapse in the longer term following apparently successful stem cell transplantation.

In short clinicians and patients are well aware of limitations imposed upon them in their understanding of CML but nevertheless grasp the transformative possibility offered by TKIs in their being able to ensure the "patient relevant outcome" of maintaining routine everyday life into the foreseeable future at a progression free or undetectable level of residual disease.

For them there is a TKI "class specific relationship between surrogate outcomes and patient -relevant outcomes" (1.8.1) because absence of BCR-ABL levels to the point defined as deeper log reduction MMR or CMR constitutes progression free survival.

3. Imatinib patent expiry in 2016 (date quoted id PenTAG's 8.5.1.1):

PenTAG have undertaken a sensitivity analysis on the price impact of expiry.

They state (1.8.2.) "this is highly relevant to this appraisal" given a (suggested) price cut would result in the cost effectiveness of 1st line nilotinib to worsen "dramatically" with an initial price reduction of 25% modelled (8.5.1.1.) deteriorating even further once future CML patient cohorts are considered.

However, they note that this would occur "after the currently tabled review date " (8.6.6.8.) for the TA 70 guidance but do not mention that patent expiry would also be after the introduction of value based pricing and the abolition of the PPRS.

Given the lack of detail provided to date of future pricing for products that have already been subject to appraisal coupled with the uncertain passage of the Health & Social Care Bill in its entirety through the legislative process; our view is that any discussion of likely pricing scenarios following patent expiry after the introduction of value based pricing/PPRS abolition should be excluded from the Report and appraisal process.

4. Hyroxycarbamide (HU):

(i) The Report notes (2.8.) the European LeukaemiaNet and British Committee for Standards in Haematology recommendations for the treatment of CML. There is no mention of HU as a treatment, no matter in what line, in either document yet there is continual discussion throughout the Report of its use as such.

HU is used for symptom control with one such use being palliative but has no other place in current CML therapeutic practice.

(ii) The Report notes elsewhere (2.1.3.) that HU "can be used to control the white blood count but does not alter the natural history of the disease" and is, in principle, not capable of achieving either CCyR or MMR.

All TKI's together with SCT exhibit that capability and thus, in principle, offer a final patient relevant outcome. We cannot understand HU's introduction in any cost effectiveness analysis (as it is in for example Table 4) other than as a occasional cost of medical management of the disease in much the same manner as costs of interventions used to control adverse events following a treatment line that offers a final patient relevant outcome.

(iii) HU as "proxy for what in reality would be a range of treatments that might be offered (eg IFN and other chemotherapies)" (1.8.8.2) (8.1.6.3.).

Although the Report concedes "some of the non-hydroxyurea treatments in this treatment group may prolong survival compared to hydroxyurea" (8.2.3.1.).

The issue here is that inteferon is a biological rather than chemotherapeutic agent and dragooning it with chemotherapy agents as if it were a class member is not acceptable.

(iv) It is profoundly disappointing that there is no mention in the PenTAG analysis of recruitment to a clinical trial for a TKI other than the TKI comparators of this assessment.

In current clinical practice eventual failure on all of the comparator TKIs would routinely lead specialist clinicians to consider recruitment onto clinical trials of other TKIs as a therapeutic option rather than pursue a 2nd or 3rd line treatment option of HU that would be ethically suspect in circumstances of such RCT availability.

Current relevant clinical trials are for bosutinib NCT 00574873/ NCT 00261846 or the ponatinib PACE Clinical Trials.

(v) 8.6.6.6. Sensitivity analyses: Time on HU in CP

"Our estimated mean time on HU in CP of 5 years is uncertain, given that our evidence is based on a study which included a mixture of treatments in

addition to HU, and because we have no relevant evidence after failure of nilotinib or dasatinib."

We assume this does not refer to HU in CP from diagnosis which simply would not occur in clinical practice and would in any case presumably imply comparator status for HU which is not included in the appraisal.

Time on HU must therefore be following failure of 1st line TKI treatment and therefore, at 5 years, be a highly suspect mean time.

For this reason why attempt to model it?

5. Availability of dasatinib to CML patients in England:

The Report notes that "Anecdotal evidence suggests that dasatinib and nilotinib are currently widely used in the NHS in England and Wales following failure of treatment with imatinib" (2.9.)

Assuming the failure of appeals and implementation of "NICE's recent draft guidance FAD that nilotinib but neither dasatinib nor high-dose imatinib should be used" (1.6.2.) for patients failing 1st line standard dose imatinib it would, we believe, be implausible for this Appraisal Committee to recommend first line use of dasatinib.

The outcome of that appeal process will be established before the FAD of this appraisal is published and we would argue, given the assumption in the previous paragraph, this places a strong bias on this Committee to arrive at a determination that would be negative.

Otherwise there is a possibility of there being a (small) 1st line standard dose imatinib, and subsequent 2nd line nilotinib failure, patient population denied 2nd line dasatinib existing alongside a currently existing 2nd line dasatinib patient population (for whom availability of the drug will remain post FAD) and a future patient population for whom dasatinib will be available as 1st line use.

In summary a positive recommendation for dasatinib for 1st line use would therefore be difficult to provide a rationale for if there were a negative recommendation for its 2nd line use.

6. Imatinib cessation:

Although the Report acknowledges the "considerable current interest in being able to stop treatment, or reduce dose, in patients who respond very well to treatment and this might be where the benefit of the newer TKIs might eventually be demonstrated" (9.5.2.) there was no attempt to incorporate this "interest" into the model even though the trial data is of a duration considerably longer than that of the DASISON and ENESTnd RCTs (2.5.1.6.)

The multi centre STIM (stop imatinib) clinical trial commenced in 2007 and is ongoing.

We cannot understand the logic involved in arguing that a sensitivity analysis be conducted for the expiry of the imatinib patent yet no such analysis be conducted for cessation despite an admission that "some limited evidence" (8.1.6.3.) is available.

This seems inconsistent especially given its obvious significant impact in any cost effectiveness modelling.

7. The potency and activity of nilotinib & dasatinib

Whilst the Report is unequivocal in its recognition of the clinical potency of nilotinib and dasatinib versus imatinib (9.1.1.) in terms of higher rates of CCyR & MMR which were "more rapidly attained" and obtained a "deeper (molecular response)" reservations were expressed as to "longer term patient outcomes" due to "insufficient data" (all 9.1.1.).

There was, however, very little discussion and no substantial recognition accorded to the clinical novelty of both drugs with respect to their activity against mutated forms of the BCR-ABL fusion gene.

Both drugs are active (differently) against mutated genes that imatinib lacks activity against although both are also active, and more so than imatinib, against those imatinib is active against.

8. The role of TKIs in "combination" therapies

Established practice in much of oncology/haemo-oncology is the use of combined interventions to obtain the most efficacious of outcomes.

We were therefore surprised that there was no mention of the use of imatinib in reduced intensity allografts (although such allografts are mentioned 8.5.4.1.) post transplant.

The use of imatinib (and currently nilotinib amongst the other TKIs) in reduced intensity stem cell transplantation (RISCT) offers considerable cost economies whilst also extending the possibility of transplantation to older patients for whom it had previously been contraindicated.

The Report offers SCT only as a uniform stand alone 2nd or 3rd line therapy albeit one subject, as the Report notes, to uncertainties as to procedure and costs.

We recommend a sensitivity analysis be conducted that includes this type of RISCT.

<u>Minor additional points (ordered alphabetically)</u>

A. Interfeon-a:

Terms and Definitions: (p. 12) Interferon-a: is "often used as firstline therapy in CML" . This is not true in England.

B. Incidence of CML:

"Approximately 600 to 800 people are diagnosed with CML in England and Wales each year." Decision Problem: (p.275)

1.1. Background: (p. 17) "An estimated 530 cases of chronic myeloid leukaemia are newly diagnosed in the UK each year." (repeated 2.2.1.)

Since the UK includes Scotland and N. Ireland in addition to England and Wales one of these figures for diagnosis must be very substantially incorrect.

C. Age related issues:

(i) Decision problem: (p. 275) For CML "It is expected that median life expectancy is at least 15 years."

8.1. Approaches to modelling treatments for chronic myeloid leukaemia: (p.137) "... given that CML is a chronic disease, with current survival from diagnosis of around 15 to 20 years" (repeated 7.1.& 8.1.)

(a) If it is postulated that median life expectancy over the history of the disease if left untreated is either "at least 15 years" or "around 15 to 20 years" this is not the case.

(b) If it is (more likely) postulated, "when treated", it is difficult to understand the derivation of this "current survival" figure other than the mean age of newly diagnosed CML patients cited as either 56 years (7.2.3.), 58 years (2.2.1. & 4.2.2.2.), 57 years (1.1. & 8.2.1. but also 8.3.) and "between 50 and 60 years" (Decision Problem. p.275) to which an addition is presumably made to reach UK life expectancy figures (8.2.1.) although this is unclear given the addition made would not exactly match current figures.

(ii) There is no data of that duration for imatinib survival (ie 15 to 20 years) since the earliest imatinib data is from 1999 (2.2.3.) and the Report cites those responding favourably to imatinib as being "symptom free for at least 10 years" (2.1.3.).

(iii) There is modelled overall survival (OS) data presented for SCT aged 60 of 17.4 years compared to 22.8 years in the general England and Wales populations (8.2.4.1.). It is unclear what relationship this has to the figures in (b).

(iv) Scenario 1 of the PenTAG model notes "Virtually all patients are predicted to have died by age 97, 20 years from the start of 1st line treatment" (8.6.2.1. & 8.6.4.1.) which would assume an age of 77 as the start of treatment age. No

explanation is offered of this very late start date which would (approximately) be the end date of survival in (b) above.

Summary of CML Support Group's position and recommendations

We would argue that the very considerable limitations to their Report that PenTAG list (1.8.8.2.) taken together with suggested priorities for future research (1.10.) and our own comments limit this Committee, or indeed any Committee, in the production of an appraisal to such an extent that it would lack even the low power status of a "least implausible" appraisal of the assessment.
The best descriptor available to characterize any appraisal in these circumstances would be "educated guesswork" rather than the end product of a deliberative exercise resulting from a careful consideration of evidence, contained in the assessment, that was necessary and sufficient to meet that demanded by the decision problem.

We would suggest that PenTAG, or another Technology Assessment Group, be instructed to (i) relax the inclusion criteria to admit evidence other than from RCT, (ii) seek an incorporation of evidence recognized to place limitations on the Report into the assessment and (iii) an acceptance that there is a TKI class specific relationship between the surrogates examined and patient relevant outcomes.

In particular for (i) non-randomized studies (ii) stop in treatment (STIM trial) and also treatment sequences of alternative TKIs that are not the comparator TKIs of this TAR.

Acceptance of these three suggestions together with a strategic recognition of the limitations of the classical RCT in clinical settings where stratified medicine is increasingly prevalent, especially for diseases already recognized as rare, would permit an assessment that would be much more fit for purpose for appraisal by the Committee.

We are aware that NICE is already reviewing the "Guide to the methods of technology appraisal" and that the advent of value based pricing will include consideration, on a thoroughgoing basis, of "therapeutic innovation" (plus "societal benefit" and "burden of illness").

Outcomes of the review and future broader policy development concerning healthcare evaluation will presumably result in a reformed health technology assessment environment that will be suitable for advances achieved in current and future biotechnology and biomedical research.

Finally, reliance on short term RCT data alone yet constrained by a requirement to produce an assessment (and ultimately guidance) where that data will be

found wanting (exhibit “paucity”) and therefore inevitably result in a negative recommendation due to “weak” evidence does not, we feel, constitute a health technology appraisal process operating at optimal levels of efficiency.

Note. We are of course aware that the TAR is not the only resource on which the Committee relies and in this particular case the evidence of leading clinicians will be of critical importance.

The Royal College of Pathologists
Pathology: the science behind the cure

Comments from the Royal College of Pathologists and British Committee for Standards in Haematology on the Assessment Report of Dasatinib, nilotinib and standard-dose imatinib for the first line treatment of chronic myeloid leukaemia (incl part-review of TA 70)

This report from PenTAG assesses the available data on first line use of the second generation tyrosine kinase inhibitors (2G TKI) dasatinib and nilotinib. The clinical issues for first line use are simpler that the recent appraisal of these drugs for second line use in patients failing imatinib.

In general, the clinical information and statements appear to be sound. The precision of the assessment's conclusions therefore rests on the accuracy and design of the various models which have been applied to deduce cost–effectiveness. There are some points to consider:

1) The authors discuss the need to use surrogate endpoints for survival, and devote a section of this assessment to reviewing their use. This concludes that there is evidence that the achievement of either complete cytogenetic response (CCR) or major molecular response (MMR) at 12 months correlates with survival over the next 7 years, which is correct. However, it is also stated that this evidence is only available for imatinib, and that there are no data for dasatinib or nilotinib. This is also true, but there are also data with interferon (IFN), correlating the degree of cytogenetic response with long term survival. References 37 and 92 are mentioned but there are other IFN data that agree with this. It may therefore be that the correlation of CCR or MMR with overall survival is not therapy-specific, and is related to the degree of control of the underlying CML.

2) Little is made of the impact of 2G TKI on the rate of disease progression. A surprising finding already apparent at 12 months is the 3-fold higher progression rate with imatinib compared to nilotinib in ENESTnd (and a similar though non-significant trend in DASISION in favour of dasatinib). This is rather dismissed since in ENESTnd the progression rate on imatinib is higher than that in the earlier IRIS study. However, the interpretation of long-term outcome data from IRIS is complicated by the fact that only 55% of patients remain on imatinib at 7 years, thus 'editing out' patients with poorer responses from later follow-up. It is more likely that IRIS gave a falsely low incidence of disease progression, and that the imatinib progression rate in ENESTnd is more representative. Of note, the progression rate on imatinib at 12 months is similar in ENESTnd, DASISION and also the bosutinib first line study BELA. As aired in section 5, it is clear that progression free survival (PFS) is closely related to overall survival, reflecting the inadequacy of available treatment for advanced phase disease.

Overall, the conclusions on p241 and in the lengthier initial summary section are reasonable. Some interesting suggestions for further clinical research are made on p241-2, which it would be useful to air at the appraisal meeting in November.

[redacted]

Comments on Technology Assessment Report

Dasatinib, Nilotinib, and standard dose Imatinib for the first-line treatment of chronic myeloid leukaemia: systematic reviews and economic analyses

Jane Apperley

18th October 2011

This is a comprehensive review of the efficacy and cost effectiveness of the tyrosine kinase inhibitors (TKI), dasatinib and nilotinib as first line treatments for chronic myeloid leukaemia (CML) compared to imatinib. The authors have built sophisticated models of the various phases of the disease, incorporating periods of time and efficacy of various therapeutic interventions. In addition they have conducted a critical analysis of models submitted by each of the manufactuers. Their overall conclusion is that 1st line nilotinib is cost effective compared to imatinib if they assume that nilotinib can be used as second line in patients treated first with imatinib, and that dasatinib is not cost-effective compared to imatinib, The differences in the costs of QALYs between nilotinib and dasatinib is considerable.

The authors acknowledge a number of limitations in their study not least of which is the paucity of information on the use of front-line nilotinib and dasatinib so that models of efficacy and duration of treatment have to be extrapolated from immature data. They state that with the information available that both dasatinib and nilotinib appear to be more effective as front-line therapy than imatinib and that with current knowledge there does not seem to be any differences in efficacy between the two. For the reviewer not fully familiar with this level of disease modelling the conclusion that one of these drugs is cost-effective and the other is not could be explained by a difference in cost or a difference in efficacy or some combination of the two. Since the conclusion is that there are no differences in efficacy the result must be due to the cost of one being less than the other but the enormity of the difference in cost per QALY needs further validation.

There are a number of reasons why the analyses as performed could lead to such a conclusion:

1. The authors have had to work on the assumption that in the UK only nilotinib can be used as second line therapy for patients resistant and/or intolerant to imatinib, because of the outcome of the FAD for nilotinib and dasatinib as salvage therapies, in which nilotinib is recommended but dasatinib is not. However, at present this is only draft guidance as appeals have been lodged against this finding. In addition in some patients failing imatinib there will always be individual patients in whom there

are good medical reasons for the use of dasatinib over nilotiinib, including co-morbidities such as diabetes, high alcohol intake etc and the presence of kinase domain mutations that render the disease resistant to nilotinib. Requests for the use of dasatinib as the first second-line therapy will continue to be made to local funding bodies and the Cancer Drugs Fund, unless the draft guidance is over-turned on appeal. I hope that PenTAG have already conducted the alternative analyses should dasatinib be approved after the appeal.

2. The use of TKI for CML has been the subject of a number of NICE evaluations over the past decade, each requiring a technology appraisal and each of these containing a number of disease models and a number of different statistical analyses. It is remarkable that none of these disease models are the same and this in itself casts doubt on the ability to draw conclusions from the current design. In particular are the recurrent problems of trying to model the time spent on each of the interventions, when there are literally no data to guide the model. Since the introduction of the TKI, hydroxycarbamide is rarely used in the long-term treatment of CML. It continues to be used soon after diagnosis, usually to debulk the tumour and relieve symptoms while waiting to gather information regarding the presence of the Bcr-Abl oncogene and/or confirm eligibility for clinical trials. It is sometimes used when patients are found to be resistant to at least two but usually three or four TKI and is used in the short-term for patients who have progressed to blast crisis and are not suitable for AML-like therapies prior to a stem cell transplant. This reviewer cannot see a time in which any UK physician will routinely use hydroxycarbamide for second line therapy in place of a TKI, and this reflects the difficulties in defining failure to any individual TKI. We are all very familiar with the definitions of imatinib failure as published by the ELN, and these are very useful when a potentially effective alternative agent is available. For instance for the patient who fails to achieve a complete cytogenetic response (CCyR) at 18 months on imatinib but remains in chronic phase with well controlled blood counts there is a good indication to try one or more of bosutinib, dasatinib, nilotinib or ponatinib, depending on availability through normal sources or clinical trials, and the milestone of response at a particular timepoint is a good trigger. However for the patient who fails to get a CCyR on a second or third agent but who continues to have well controlled blood counts and to remain in chronic phase, the treatment of choice will be either to continue the same agent or return to imatinib. Since in many instances the second line agent is better tolerated than imatinib it is often difficult to persuade a patient to return to imatinib. What does not happen in clinical practice, except in very rare circumstances, is that TKI are stopped and hydroxycarbamide started. In the current model, if a patient were to ‘fail’ upfront nilotinib or dasatinib according to ELN criteria the chances are that they will either continue the same drug, change to the other second line agent (perhaps because of a kinase domain mutation), enter a

clinical trial of a new agent or combination of agents, proceed to stem cell transplant, or be given imatinib to control their counts. They will not, in the first instance, be prescribed hydroxycarbamide. Therefore the prolonged times on this agent (whether this is 1.6 or > 5 years) are unrealistic.

3. As with previous models little consideration seems to have been given to the fact that if the need to change the front-line drug is that of failure of response, this patient has defined themselves as a patient with poor risk biological disease and is unlikely to have a long-term prognosis. In the models that were built for both front-line and second-line treatment, the assumption has been made that these patients will live longer than the average patient in the pre-TKI era. This is not and cannot (biologically) be true. The only intervention that might achieve this is stem cell transplant which has limited applicability.

4. In building the model the authors do not seem to have given sufficient consideration to the reason for discontinuing the first drug and the assumption appears to be drug resistance (with the flaw noted in point 3 above). In fact at least half of the patients discontinuing their front-line agent do so because of intolerance. Many of these cases respond very well in terms of tolerability and efficacy to an alternative TKI and remain on the second drug for long periods of time. For this reviewer the disease models would have been more convincing if they had acknowledged the two reasons for discontinuation and built different pathways for each scenario. In utilising the discontinuation rate for imatinib from the IRIS study there does not appear to have been sufficient consideration for the change in clinical practice over that period of time and how these might have influenced the change to another therapy. For instance early on, when the durability of responses to imatinib were unknown, patients who were otherwise responding well, received stem cell transplants. When imatinib was licensed and became freely available in the USA patients withdrew from the study but continued the drug. Novartis had limited ability to obtain on-going information on patients who had withdrawn consent to participation in the trial. The sum total of these reasons for discontinuation underestimate the long-term efficacy of imatinib. As the second generation drugs became available patients who were responding well to imatinib but who were experiencing chronic low to medium grade toxicities were willing to try and alternative agent. The availability of new drugs is a reason to change in itself but when the patient gets the latest drug as front-line and the alternative is hydroxycarbamide, they are unlikely to discontinue unless they have high-grade toxicities.

5. There are data emerging form a number of groups that might permit the development of a rather simpler model. At least 4 groups have reported recently, either in manuscript, meeting abstracts or in meeting presentations, that response

to any TKI can be predicted after three months of therapy using quantitative RT-PCR. These presentations will likely result in full manuscripts within the next few months. The figure emerging from these is that about 25% of patients will be identified as having a low chance of responding in the long-term to imatinib. This figure is likely to be less, maybe 15%, when the same analyses are applied to the second generation drugs.. The more relevant piece of information emerging from at least three of these studies is that this poor prognosis stays with the patient irrespective of the next interventions. It would seem that the likelihood of a patient who has a low RT-PCR at 3 months obtaining CCyR is virtually 100% whereas patients without low RT-PCRs at 3 months have only a 50% chance of achieving CCyR and a prolonged survival. This information might enable a more realistic model to be built, where the change in therapy comes much earlier than previously thought and efficacy of subsequent interventions can be modelled with some reliability.

6. The model has been built on information from the Yorkshire Haematological Malignancy Research Network (HMRN) that the median age of onset of CML in the UK is 57 years. This is somewhat less than that taught in medical school and emerging from large North European population based registries. Indeed the recent report from the National Cancer Intelligence Network (NCIN) is that HMRN data underestimate the incidence of CML in older patients. A more realistic figure is in the early 60s.

7. The data from the randomised studies are limited in number and what is available is immature. The national study for newly diagnosed patients in the UK is one of imatinib versus dasatinib. The study will have completed accrual in mid-2012 and 12 month data will be available on all patients in mid-2013. Similar studies are on-going throughout the world and more data will emerge shortly as to the efficacy and tolerability of the second generation drugs. To build such sophisticated models on the basis of such limited data introduces too much uncertainty to be convinced by the findings.

This reviewer accepts the difficulties and complexities in building the models but the end result is repeatedly that they do not reflect clinical practice. For this reason it has been, and continues to be, difficult to accept the findings and a prelude to further confusion.

PenTAG reply to responses from Novartis and BMS on PenTAG report to NICE on dasatinib, nilotinib and imatinib for 1st-line CML

For NICE Appraisal Committee Meeting, 8th November 2011

Prepared and sent by PenTAG, 2nd November 2011

We find the responses from Novartis to be helpful and generally reasonable. In response to their comments, we have now changed our base case results for the cost-effectiveness of nilotinib vs. imatinib and dasatinib vs. imatinib. These amended base case results reflect our acceptance of Novartis's comments in relation to the lower cost of ongoing medical management in chronic phase CML than we originally assumed. In response to Novartis's comments we also explore the impact on the estimated ICERs of altered assumptions about survival post SCT, and dose intensity while on imatinib.

By contrast, after detailed consideration of all points raised in the 17-page response from BMS, we find almost all of them to be either poorly founded or implicit acceptance of our modelling approaches – because no specific criticism is made, nor a more defensible approach suggested. On closer scrutiny of their comments, our explanations below will hopefully dispel any impression from BMS that our model is deficient in the ways that they claim.

Therefore, we have not changed our opinion of the BMS model and nor have we changed our base case or any sensitivity analyses having carefully considered their comments.

Novartis

- p1 second sentence. To say that we found nilotinib to be cost-effective is an over-simplification. We provided numerous sensitivity analyses, and the ICER for nilotinib vs. imatinib varies either side of the £20,000 and £30,000 per QALY willingness to pay threshold

- Section 1.2: We did try to apply 'at' and 'by' in the correct manner, noting the difference in definition and how this affects the response rates, i.e. 'by' would produce a higher response rate. However, the response rates were not always reported simply as 'at' and 'by' and

interpretation of whether the values were ‘at’ or ‘by’ was based on all sources of information for a specified time-point. This is particularly applicable to major molecular response (MMR). As shown in Table 1 below (Table 13, page 83, PenTAG report), for the DASISON trial, the 12-months MMR rates are 46 % and 28% for dasatinib and imatinib respectively. The source for these figures reports ‘response rate’.[1] The 12-month MMR at any time (i.e. ‘by’) rates are 52% and 34% for dasatinib and imatinib respectively. The source of these figures reports ‘at any time’, i.e. by.[2] The same principle applies for the DASISION trial at 18-months, where the sources use ‘response rate’ , and ‘at any time’.[3, 4] Given that the ‘at any time’ (i.e. ‘by’) rates are higher than the ‘response rates’. We believe, based on the information available to us from the trials, this table and information contained is correctly labelled.

For complete cytogenetic response (CCyR) and complete molecular response (CMR), we acknowledge that there is a discrepancy between the tables and the text in our report.

The response rates for CCyR and CMR of both the DASISION and ENESTnd trials are ‘by’ response rates and correct in the tables, but the text contains ‘at’. However, given that the response rates provided in the tables are comparable between both trials for CCyR and CMR (using ‘by’), then the indirect comparison analysis is not affected, as it used the values as presented in the tables.

Table 1 Major molecular response

Study	**DASISION**				**ENESTnd**						
Intervention	Dasatinib (100mg)	Imatinib (400mg)	p-value	RR (95% CI) [d]	Nilotinib (300mg)	p-value	RR (95% CI) [d, #]	Nilotinib (400mg)	p-value	RR (95% CI) [d, #]	Imatinib (400mg)
MMR 12-months[a] (%)	119/259 (46)	73/260 (28)	<0.001	1.63 (1.29-2.09)	125/282 (44)	0.001	2.02 (1.56-2.65)	121/281 (43)	0.001	1.97 (1.51-2.58)	62/283 (22)
MMR 18-months[a] (%)	145/259(56)	96/260(37)	<0.001	1.52 (1.25-1.85)	–	–	–	–	–	–	–
MMR 24-months[a] (%)	–	–	–	–	175/282 (62)	<0.001	1.67 (1.40-2.00)	165/281 (59)	<0.001	1.58 (1.32-1.90)	105/283 (37)
MMR at any time (12-months)[a,b] (%)	135/259 (52)	88/260 (34)	<0.001	1.54 (1.25-1.91)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMR at any time (18-month)[a,b](%)	148/259 (57)	107/260 (41)	<0.001	1.39 (1.15-1.67)	186/282 (66)	<0.001	1.65 (1.40-1.95)	174/281 (62)	<0.001	1.55 (1.31-1.84)	113/283 (40)
MMR at any time (24-month)[a,b] (%)	166/259(64)	120/260(46)	<0.001	1.39 (1.18-1.64)	201/282 (71)	<0.001	1.67 (1.40-1.89)	187/281 (67)	<0.001	1.52 (1.30-1.78)	124/283 (44)

Dose intensity (Novartis Section 2.2.1)

Novartis disagree with our assumed mean dose intensity of imatinib of [redacted] . Instead, they prefer 106% which they used in their model.

First, we agree with Novartis that dose intensities should be estimated by mean values, not medians.

Second, Novartis disagree with our claim that the *mean* dose intensity over 6 years of people in the IRIS RCT is 100%, for the 364 patients who remained on imatinib at 6 year, which we sourced from Hochhaus et al (2009). Instead, Novartis believe that the 100% refers to the *median* dose intensity, and they claim that the *mean* dose intensity over 6 years was 467/400. However, we disagree with Novartis' criticism of our claim. The mean dose intensity of 467/400 refers to the single last dose given at the time of discontinuation of imatinib study treatment. The subsequent paragraph in Hochhaus et al (2009) states that "among patients who received imatinib as initial therapy for CML, … the average daily dose over the 6-year period was 402mg … for the 364 patients who remained on imatinib." Therefore, we still maintain that the mean dose intensity from the IRIS RCT, which has extensive 6-year follow up, was 402/400 = 100%.

Concerning the ERNEST RCT of nilotinib vs. imatinib, we agree with Novartis that it is preferable to use the estimated dose intensity at 24 months, rather than 12 months, because this would be consistent with the data for treatment duration.

Novartis claim that we referred to the dose intensities of 423.0mg (106%) for imatinib and [redacted] as medians, but this is not true.

Furthermore, we believe that our decision to use the 12-month estimate of dose intensity for imatinib of [redacted] quoted by Novartis on p75 of their submission was reasonable given that the 24-month dose intensity of 106% quoted by Novartis on p105 of their submission was not identified as being a mean or a median value, whereas the [redacted] 12-month value was clearly marked as a mean value.

However, Novartis now state clearly that the dose intensity of imatinib in the RCT of nilotinib vs. imatinib of 106% is a mean, not a median. Therefore, we agree with Novartis that it is instructive to estimate the cost-effectiveness of nilotinib using this value, rather than the value of [redacted] which we used. In this case, the ICERs for nilotinib vs. imatinib change as shown in Table 2 below.

In summary, we have two possible estimates for the dose intensity of nilotinib;

- 100% from the IRIS RCT,
- 106% from the RCT of nilotinib vs. imatinib

The first value has the advantage that it is using much more mature data (6 years vs. 2 years). The second value has the advantage that it is consistent with the treatment duration Kaplan-Meier data for imatinib from the RCT of nilotinib vs. imatinib. We think it is not clear which value is preferable.

Table 2 ICERs (£/QALY) for nilotinib vs. imatinib according to assumption for dose intensity of imatinib and modelling structure

	Dose intensity imatinib	
	[redacted] (original PenTAG analysis)	106% (Novartis' estimate)
Scenario 1 (no 2nd-line nilotinib)	£36,000	£19,000
Scenario 2 (no 2nd-line nilotinib, simplified method)	£26,000	£15,000
Scenario 3 (2nd-line nilotinib)	£213,000§	£286,000§
Scenario 4 (2nd-line nilotinib, simplified method)	£50,000§	£65,000§

§ Nilotinib provides fewer QALYs at less cost than imatinib

Time on HU in CP (Novartis Section 2.2.2)

In summary, Novartis claim that it is not possible to estimate the mean time on HU in CP with any certainty. In their submission, they estimated this quantity as 1.6 years. They believe that our estimate of 5 years is too high, citing a figure of 3.5 years which they say was accepted by the appraisal committee for 2nd-line CML.

First, we agree that the mean time on HU in CP after TKI is uncertain.

In the second paragraph of their response, Novartis defend their methodology of estimating the mean time on HU in CP of 1.6 years as the difference between the time to discontinuation and PFS. They concede that this difference does not strictly equal the time in CP because patients can progress for reasons other than progression to AP / BC.

Novartis claim that there is no evidence on the effectiveness of HU in the 2nd- or 3rd-line setting. However, the data we used, from Kantarjian et al (Section 8.2.3.1) was for patients who were intolerant of, or resistant to imatinib, although admittedly, these patients took a range of treatments, with only a minority of patients taking HU.

In our report, we performed a sensitivity analysis whereby we reduced the estimated mean time on HU in CP from 5 to 1.6 years, to equal Novartis' assumption (p215 our report). The ICER for Scenario 1 then falls from £36,000 to £31,000 per QALY and for Scenario 2 from £26,000 to £24,000 per QALY.

Now suppose we reduce the estimated mean time on HU in CP from 5 to 3.5 years, as Novartis now recommend as plausible (and anecdotally supported by the appraisal committee for 2nd-line CML),

then the ICER of nilotinib vs. imatinib for Scenario 1 falls only incrementally, from £36,000 to £34,000 per QALY and for Scenario 2 from £26,000 to £25,000 per QALY.

If we then further assume a dose intensity for imatinib of 106%, as discussed above, the ICER for Scenario 1 falls incrementally from £19,000 to £18,000 per QALY and for Scenario 2 remaining at £15,000 per QALY.

In summary, whilst we agree that the mean time on HU in CP is uncertain, varying it within a wide plausible range has little impact on the cost-effectiveness of nilotinib. We still maintain that we have used the best published evidence to estimate this parameter.

Stem cell transplantation (Novartis Section 2.2.3)

Proportion of patients who receive SCT (Novartis Section 2.2.3.1)

We agree with Novartis' claim that in their model, 47% of nilotinib patients and 55% of imatinib patients received a SCT.

Novartis then cite the RCP's assumption that fewer than 30% of patients would receive a SCT. We note that our estimated proportions of patients receiving a SCT, 28% for nilotinib and 33% for imatinib, are reasonably consistent with the opinion of the RCP.

We believe this requires no further comment.

Cost of SCT (Novartis Section 2.2.3.2)

Novartis claim that the cost of a SCT is a strong driver of cost-effectiveness. However, our estimated costs are similar (£81,000 us, vs. £99,000 Novartis), and as we explain in Section 8.7.1.6 (p225), this difference accounts for very little of the difference in estimated cost-effectiveness of nilotinib between our model and Novartis' model.

Survival following SCT (Novartis Section 2.2.3.3)

Novartis make a well-reasoned case that our model assumptions relating to survival following SCT may be over-optimistic, leading to the mean survival of those having an SCT after TKI failure of around 17 years. They consider using a lower estimate of mean survival of 10 years to be more plausible for patients who receive SCT after TKIs, because (Novartis argue) they have higher SCT risk scores by virtue of being both older and more years post-diagnosis.

The problem with current published evidence, including the Pavlu et al 2011 paper on which we have relied (data from 2000 to 2010), is that the cohorts of CML patients in whom post SCT survival estimates are based spans the introduction and widespread use of imatinib as the recommended 1st

line treatment in chronic phase CML. Therefore, they inevitably include a subgroup of younger, lower-risk SCT patients who received SCT as 1st line treatment soon after diagnosis, and these patients would have higher mean survival than current recipients of SCT in chronic phase CML, who are on average older and less well by the time they need or are offered an SCT (i.e. after imatinib failure).

On the basis of Novartis's comment, while we can understand the logic for suggesting a shorter mean survival post SCT than 17 years, we can find no published evidence to say *how much* shorter than 17 years it would be. Also, 17 years life expectancy at age 65 (the mean age when people receive an SCT in our model) is still about 5 years lower life-expectancy than the 22.5 years that is the normal life-expectancy of 65 year-olds. Perhaps Prof. Jane Apperley or the other clinical expert advisers to the committee can shed light on this particular gap in quantitative evidence and what a reasonable mean survival is now likely to be in these patients?

On p214 of our report we already acknowledged that our estimate of mean survival following SCT of 17 years is uncertain, and we therefore provide a sensitivity analysis whereby we assume a much shorter mean survival of 5.7 years (p214 our report), equal to Novartis' assumption. The ICER for nilotinib vs. imatinib under Scenario 1 then falls from £36,000 to £22,000 per QALY and under Scenario 2, from £26,000 to £23,000 per QALY. If we also assume the revised dose intensity of imatinib of 106%, not [redacted], then the ICER under Scenario 1 falls from £19,000 to £12,000 per QALY, and under Scenario 2, from £15,000 to £13,000 per QALY. Note that we do not endorse Novartis' estimated survival of 5.7 years post-SCT. Instead, we use this to gauge the sensitivity of the cost-effectiveness of nilotinib to this assumption.

Novartis then claim that the most relevant estimate of the 6-year survival probability after SCT from graphs in Pavlu et al. probably lies between 30% and 60%. Suppose we estimate this probability as the mid-point of this range, i.e. 45%. If, for simplicity, we assume that survival after SCT follows an exponential distribution (constant hazard of death over time), this then specifies the parameter of the exponential distribution as 0.133, with mean survival of 7.5 years. When we adjust our model to recreate this mean survival following SCT, and assuming a dose intensity of imatinib of [redacted], the ICER for nilotinib vs. imatinib under Scenario 1 falls from £36,000 to £23,000 per QALY and under Scenario 2, from £26,000 to £23,000 per QALY (see Table 3 below). If instead, we assume a dose intensity of imatinib of 106%, the ICER under Scenario 1 falls further from £19,000 to £12,000 per QALY and under Scenario 2, from £15,000 to £14,000 per QALY.

Table 3 ICERs (£/QALY) for nilotinib vs. imatinib according to assumption for dose intensity of imatinib, mean survival after SCT and modelling structure

Mean survival post SCT	17 years (original PenTAG analysis)		7.5 years (Novartis' estimate from Pavlu et al.)	
Dose intensity imatinib	[redacted] (original PenTAG analysis)	106% (Novartis' estimate)	[redacted] (original PenTAG analysis)	106% (Novartis' estimate)
Scenario 1 (no 2nd-line nilotinib)	£36,000	£19,000	£23,000	£12,000
Scenario 2 (no 2nd-line nilotinib, simplified method)	£26,000	£15,000	£23,000	£14,000
Scenario 3 (2nd-line nilotinib)	£213,000§	£286,000§	£67,000§	£90,000§
Scenario 4 (2nd-line nilotinib, simplified method)	£50,000§	£65,000§	£53,000§	£69,000§

§ Nilotinib provides fewer QALYs at less cost than imatinib

Medical management costs (Novartis Section 2.2.4)

First, Novartis correctly state that during chronic phase CML, we assume 0.4 visits with a nurse and 0.9 visits with a haematologist/oncologist per month, and 0.3 bone marrow aspirations per month. These figures were taken from the 2009 Oxford Outcomes survey of 6 UK-based CML clinicians (p179 our report). The cost-effectiveness of nilotinib is far more sensitive to medical management costs during chronic phase CML than accelerated phase or blast crisis, therefore we focus on CP.

Novartis claim that we over-estimate the frequency of out-patient visits. They claim that it is more reasonable to assume one visit per 3 to 6 months. They also claim that we over-estimate the frequency of bone marrow aspirations.

We have presented Novartis' criticisms to our clinical advisor, and he agrees that we have over-estimated these quantities. He believes that it is more likely that patients on a TKI would be seen at week 2 , week 4, month 2, month 4 and then 3-monthly. Patients on hydroxyurea would be seen about every 6 weeks. Furthermore, patients would rarely be seen by a nurse (without a consultant). Our advisor claims that clinical practice for bone marrow aspiration varies from only a single test, to tests at month 0, 3, 6, 12, 18 and 24 or until CCyR, but not after 24 months.

Given this new information, for the purposes of modelling, for patients on a TKI, we assume one visit to a haematologist/oncologist every 3 months, i.e. 0.33 visits per month and for patients on HU, one visit every 6 weeks, i.e. 0.72 visits per month. We can safely ignore the higher frequency of visits when patients start taking TKIs, these costs effectively cancel between treatment arms (given that virtually all patients on 1st-line TKIs are still on treatment at 4 months). Again for modelling, we

assume no bone marrow aspirations given that some clinicians give no repeat tests and given that for those cases when repeat aspirations are given, costs cancel to a large extent between treatment arms. We leave all other assumptions for the costs of medical management unchanged (see p180 our report), although these contribute only marginally. This gives a mean of £169 per month per patient on TKIs in CP and £317 per patient on HU in CP. Revised results for nilotinib vs imatinib are given in Table 4 below. Revised results for dasatinib vs imatinib are given in Table 6 later.

We apologise for the error in our original assumptions for the cost of medical management in CP.

Table 4 ICERs (£/QALY) for nilotinib vs. imatinib according to assumption for dose intensity of imatinib, mean survival after SCT and modelling structure. In all cases, the cost of medical management in CP per month is changed from PenTAG original submission, see text.

Mean survival post SCT	**17 years (original PenTAG analysis)**		**7.5 years (Novartis' estimate from Pavlu et al.)**	
Dose intensity imatinib	**[redacted] (original PenTAG analysis)**	**106% (Novartis' estimate)**	**[redacted] (original PenTAG analysis)**	**106% (Novartis' estimate)**
Scenario 1 (no 2nd-line nilotinib)	£25,000	£8,000	£17,000	£6,000
Scenario 2 (no 2nd-line nilotinib, simplified method)	£20,000	£9,000	£18,000	£8,000
Scenario 3 (2nd-line nilotinib)	£192,000§	£265,000§	£61,000§	£84,000§
Scenario 4 (2nd-line nilotinib, simplified method)	£46,000§	£61,000§	£49,000§	£65,000§

§ Nilotinib provides fewer QALYs at less cost than imatinib

Notice that using the updated medical management costs, and assuming a revised dose intensity for imatinib of 106%, our assumed mean survival after SCT affects the cost-effectiveness of nilotinib only marginally in Scenarios 1 and 2.

Table 5 gives the sensitivity analyses for nilotinib vs. imatinib using our revised base case assumption for the cost of medical management. Here, we show the same sensitivity analyses as in Table 56,

p209 in our report. In this case, the dose intensity of imatinib remains at [redacted] and the mean time after SCT remains at 17 years.

Table 5 Sensitivity analyses for ICERs for nilotinib vs. imatinib using revised base case assumption for cost of medical management

Parameter	Base case	Sensitivity analysis	Scenario 1 (No 2nd-line nilotinib)	Scenario 2 (No 2nd-line nilotinib, Simplified Method)	Scenario 3 (2nd-line nilotinib)	Scenario 4 (2nd-line nilotinib, Simplified Method)
Base case	N/A	N/A	**£25,000**	**£20,000**	**£192,000§**	**£46,000§**
Treatment pathways						
Proportion receiving SCT	Mean 28% nilotinib, 33% imatinib, decreases with age	31% at all ages (BMS assumption)	£24,000	£20,000	£86,000§	£48,000§
		75% if age < 65 (Novartis)	£28,000	£20,000	£260,000§	£45,000§
		Halve % at all ages	£23,000	£20,000	£98,000§	£48,000§
Effectiveness						
Time on 1st-line TKI	8.9 years nilotinib, 7.0 years imatinib	7.0 years nilotinib, 7.0 years imatinib	nilotinib dominates	nilotinib dominates	£75,000§	£38,000§
		13.8 years nilotinib, 11.7 years imatinib (IRIS)	£14,000	£13,000	nilotinib dominates	£79,000§
Time on 2nd-line nilotinib	Mean 2.5 years	Same as mean time on 1st-line nilotinib = 8.9 years	n/a	n/a	£61,000§	£37,000§
Survival after SCT	Mean approximately 17 years	Mean 5.7 years (Novartis)	£16,000	£17,000	£54,000§	£49,000§
Time in CP on HU	Mean 5 years	Mean 1.6 years (Novartis)	£22,000	£18,000	£341,000§	£49,000§
OS estimated by Cumulative Survival or Surrogate Survival	Cumulative Survival	Cumulative survival means, MMR survival difference	£35,000	£25,000	n/a	n/a
		Cumulative survival means, CCyR survival difference	£17,000	£15,000	n/a	n/a
		Surrogate survival means, MMR survival difference	£40,000	£29,000	n/a	n/a
		Surrogate survival means, CCyR survival difference	£19,000	£17,000	n/a	n/a
Costs						
Drug price reduction on patent expiry	0% nilotinib, 0% imatinib	0% nilotinib, 25% imatinib	£60,000	£42,000	£42,000§	£16,000§
		25% nilotinib, 25% imatinib	£44,000	£31,000	£95,000§	£27,000§

Parameter	Base case	Sensitivity analysis	Scenario 1 (No 2nd-line nilotinib)	Scenario 2 (No 2nd-line nilotinib, Simplified Method)	Scenario 3 (2nd-line nilotinib)	Scenario 4 (2nd-line nilotinib, Simplified Method)
Base case	N/A	N/A	**£25,000**	**£20,000**	**£192,000§**	**£46,000§**
Dose intensities	[redacted] 1st-line nilotinib, [redacted] imatinib, 99% 2nd-line nilotinib	100% 1st-line nilotinib, [redacted] imatinib, 99% 2nd-line nilotinib	£53,000	£37,000	£72,000§	£22,000§
		[redacted] 1st-line nilotinib, 106% imatinib (Novartis), 99% 2nd-line nilotinib	£8,000	£9,000	£265,000§	£61,000§
		[redacted] 1st-line nilotinib, [redacted] imatinib, [redacted] 2nd-line nilotinib	n/a	n/a	£166,000§	£41,000§
Cost SCT	£81,603	£40,801	£30,000	£21,000	£207,000§	£46,000§
		£163,205	£16,000	£17,000	£162,000§	£47,000§
Medical management costs after SCT	£113 per month	£57 per month	£26,000	£20,000	£194,000§	£46,000§
Medical management costs in AP and BC	£1,113 per month	£2,227 per month	£24,000	£19,000	£196,000§	£47,000§
AEs costs	£166 per patient imatinib, £119 per patient nilotinib	£1,660 per patient imatinib, £,1190 per patient nilotinib	£24,000	£19,000	£196,000§	£47,000§
Utilities						
Utilities		Equal to Novartis	£25,000	£20,000	£201,000§	£46,000§
		Reduce all utilities by 0.10	£21,000	£18,000	£157,000§	£48,000§

§ Nilotinib provides fewer QALYs at less cost than imatinib

Effect of changes to PenTAG on cost-effectiveness of dasatinib

Table 6 below gives the updated PenTAG ICERs for dasatinib vs. imatinib given the changes prompted by the comments from Novartis. Dasatinib clearly remains very poor value for money in all scenarios.

Table 6 ICERs (£/QALY) for dasatinib vs. imatinib according to assumption for dose intensity of imatinib, mean survival after SCT and modelling structure. In all cases, the cost of medical management in CP per month is changed from PenTAG original submission, see text.

		Mean survival post SCT			
	PenTAG original base case	17 years (original PenTAG analysis)		7.5 years (Novartis' estimate from Pavlu et al.)	
Dose intensity imatinib		[redacted] (original PenTAG analysis)	106% (Novartis' estimate)	[redacted] (original PenTAG analysis)	106% (Novartis' estimate)
Scenario 1 (no 2nd-line nilotinib)	£425,000	£414,000	£369,000	£263,000	£234,000
Scenario 2 (simplified method, no 2nd-line nilotinib)	£262,000	£256,000	£228,000	£228,000	£204,000
Scenario 3 (with 2nd-line nilotinib)	£460,000	£450,000	£400,000	£310,000	£275,000
Scenario 4 (simplified method, with 2nd-line nilotinib)	£307,000	£301,000	£268,000	£271,000	£241,000

Additional comments (Novartis Section 4: Appendix)

Patent expiry

Novartis claim that our analyses of the cost-effectiveness of nilotinib vs. imatinib when we allow for possible price falls of the drugs on patent expiry are not helpful. We believe this is an issue for the NICE committee to debate. However, we caution that the cost-effectiveness of nilotinib will worsen substantially under possible plausible estimates of price cuts on patent expiry. For example, if we change just the medical management costs in CP as described above, then the ICER under Scenario 1 (Table 5) increases substantially, from £25,000 to £60,000 per QALY, and under Scenario 2, from

£20,000 to £42,000 per QALY when we model patients diagnosed with CML in the year 2012, and assume a modest 25% fall in the price of imatinib on patent expiry in 2016 (and no change in price of nilotinib on patent expiry in 2023 because it is already offered at a discounted PAS price).

For patients diagnosed with CML in 2015, that is, one year before the patent for imatinib expires, the ICER under Scenario 1 increases substantially, from £25,000 to £82,000 per QALY, and under Scenario 2, from £20,000 to £56,000 per QALY.

Whilst NICE may review the cost-effectiveness of 1st-line TKIs a few years hence, we believe that it is still important to model possible price cuts on patent expiry for the current appraisal. This is because patients who are diagnosed with CML in 2012 are expected to continue to take imatinib for a mean of 7 years, i.e. until the year 2019. Therefore, the generic price of imatinib is relevant for the 3 years from 2016 to 2019. Further still, for patients diagnosed in 2015, the generic price of imatinib is relevant for the 6 years from 2016 to 2022.

Use of response rates in economic modelling

We agree with Novartis that there are problems with the use of response rates for the purposes of economic modelling. In particular, several substantial assumptions must be made to allow us to use the response rates as surrogates for clinical outcomes such as overall survival. However, we believe that is worthwhile presenting sensitivity analyses based on the surrogate response rates relationships. Furthermore, there are substantive assumptions associated with the Cumulative Survival method which Novartis have used exclusively, and which we also consider.

Novartis mention the potential confusion associated with having two definitions of response: "by" and "at" a certain time. Whilst this is indeed a potential source of confusion, this alone should certainly not derail an economic evaluation based on this surrogate outcome.

Novartis also justify their decision not to use a surrogate relationship because they want their 1st-line CML model to be consistent with their 2nd-line model. However, we believe that the most appropriate modelling structure for the 1st-line CML appraisal should be that which best estimates the cost-effectiveness of the 1st-line TKIs.

Typo's for Tables on pages 154 and 155 acknowledged, labels are the wrong way round.

BMS

Comments on the AG's review of the BMS model (BMS Section 3)

Formulae errors (BMS Section 3.2).

Formula error #1 We maintain that this is indeed an error in BMS' model.

For example, consider cell IF7, worksheet "Trace". The formula in this cell has 4 terms corresponding to the QALYs associated with each health state group – responders, non responders, progressed and SCT. Total QALYs are calculated by taking the number of people in each health state and subtracting the number of people with SCT. However, the QALYs associated with progressed individuals are negative (-1.951). This is because there are no individuals in the progressed phase (cell ED7) yet 3 people have received SCT in this phase (cell LF8). This highlights our observation that the SCT patients that are subtracted are from the next cycle not the current cycle. In addition, our second point, that the cumulative SCT patients each cycle are subtracted, is seen in columns LC to LP where the formula is previous cells SCT + current cells SCT.

Formula error #2 reflects the fact that, in BMS' report (p50, Table 25), the probability that patients, who have achieved less than a partial response on 1st-line imatinib, discontinue 1st-line imatinib is 58%. This is the same probability as for patients on 1st-line dasatinib or imatinib (p49 BMS report). However, as we say in our report (p382, Table 14), in the model, the probability for 1st-line imatinib is 100%, not 58%. BMS reply by stating that they do not believe they have made an error;

"The 58% switching rates refers to patients on dasatinib and nilotinib whereas the 100% used (correctly in the model) refers to patients on imatinib. The rationale for the difference was that clinicians were more likely to keep patients on 2nd line treatment than 1st line, and also that patients who did not respond would be aware of 2nd line treatments and so more willing to switch."

BMS still do not admit that there is an inconsistency between their model and the description of it in their report. Instead, they now defend the use of a discontinuation rate of 100% for 1st-line imatinib, even though they did not make this argument in their submission.

Therefore, we maintain that error #2 is indeed an error in BMS' model because it remains a clear discrepancy between the parameters they have described and justified as being in the model, and those actually in their model.

Formula errors #3 - #8 BMS agree with all the remaining logical errors in their model.

Age at diagnosis (BMS Section 3.3)

In our report, we criticise BMS for assuming an age at diagnosis of CML of 46 years. Whilst we agree with BMS that this age is consistent with the ages at the start of 1st-line treatment in the RCTs of

dasatinib vs. imatinib and nilotinib vs. imatinib, we still maintain that it would have been more appropriate to assume an age of approx. 57 years, as we did in our model (p170 our report), because this is the mean age at diagnosis in chronic phase CML patients in the UK.

In general, we have some sympathy with BMS' assertion that it is arguably more appropriate to choose an age consistent with the clinical trials. However, we believe that an exception should be made in this case because BMS (and indeed we) take only very limited data directly from the 1st-line RCTs, given that the data is very immature. Instead, we rely heavily on clinical data from other sources, such as from historical trials for the purposes of the surrogate relationships.

However, we do not believe this as an important issue, witness by the fact that the revised ICERs we produced using BMS' model all assume BMS' starting age of 46 years and do not greatly alter the main result.

Nilotinib PAS (BMS Section 3.4)

In our report, we stated that BMS could clearly not be blamed for not modelling the nilotinib PAS, e.g. p126 our report. However, it is a substantive discrepancy between their cost assumptions and those that this Appraisal has to consider in the light of the PAS, so needed to be noted.

Time horizon (BMS Section 3.5)

To repeat, our criticism of BMS' model is (p126 our report);

"The model does not adopt a lifetime time horizon. Instead the model is run until the cohort is 86 years old, at which point 20% of the cohort is still alive. If the model is extended to the age of 100, 10 per cent of the population is still alive. Assuming an equal distribution of males and females, data from the ONS predict that 2 per cent of those alive at 46 will be alive at the age of 100. This suggests that BMS overestimate the period that those with CML will survive."

BMS concede the error.

No use of MMR, solely CCyR (BMS Section 3.6)

BMS defend their use of CCyR, but not MMR, as the appropriate surrogate outcome, saying that they could find no suitable historical data for MMR. Furthermore, they claim that we did not reference the sources of historical data for the purposes of our MMR surrogate relationship. This is simply false. On p115, the relevant reference numbers are 101, 103, 105, which correspond to Hehlmann et al, Hughes et al, and Kantarjian et al.

Discrepancies between model values and report (BMS Section 3.7)

BMS concede and explain the difference between their report, and the actual values in their model which fed into to their base case ICERs. No reply is necessary.

Lack of inclusion of 2nd line benefit associated with treatment (BMS Section 3.8)

BMS are responding to our criticism that, although response rates to 2nd-line TKIs are hard-coded in their model, these values are not used in the calculation of ICERs from their model. BMS argue that, by not modelling these response rates, they are being conservative. However, we believe that it is impossible to make such a claim without proper modelling.

Use of dasatinib in 3rd line in the chronic phase (BMS Section 3.9)

BMS argue that it is not a weakness that they model 3rd-line dasatinib in chronic phase CML patients, stating that dasatinib could be used in routine 3rd-line practice. However, as we state on a number of occasions in our report, we believe that it is not appropriate to model treatments which NICE have assessed and is not currently recommending. The 2nd- and 3rd-line use of dasatinib is an example of such a treatment, on the basis of the current draft guidance FAD.

Development of a complex model (BMS Section 3.10)

Whilst there is impressive demonstration of technical skill in BMS' model, we still maintain our overall judgement that BMS' model is too complex given the quality and amount of research data currently available. Of course, all modellers and modelling teams develop their own preferences for striking the appropriate balance between simplicity and complexity given available evidence, so as to balance the goals of accuracy, transparency and the risk of errors.

Cost of SCT (BMS Section 3.11)

There are two issues here.

First, BMS' one-off cost of a SCT of [redacted] In contrast to what BMS claim, we do not say it has been "incorrectly estimated", but only that they have not described how their figure was estimated. BMS also assume an ongoing cost post SCT of [redacted] Using BMS' model with our estimate of the ongoing cost, dasatinib appears substantially worse value for money.

Second, as we state on p127 of our report, we could not trace the original source of BMS' estimated costs. BMS cite the SHTAC report on dasatinib and nilotinib for 2nd-line CML; however, the SHTAC report in turn cites a previous BMS submission to NICE. BMS now claim that their figures were taken from "the model developed by the AG on behalf of NICE for the appraisal of 2nd-line CML", where we assume the AG they refer to is SHTAC.

We believe that if BMS are to successfully claim [redacted], they must clearly cite an authoritative and traceable source.

AG misunderstanding of BMS model (BMS Section 3.12)

We agree with BMS that their model can easily be adjusted so that patients starting on 1st-line imatinib are no longer allowed to take 2nd-line dasatinib. This is achieved by setting cell D12 to 0% and D13 to 100% in worksheet "Rx Sequence".

We originally believed that the BMS model cannot easily be adjusted so that patients starting on 1st-line nilotinib are no longer allowed to take 2nd-line dasatinib. We believed that we cannot simply set cell D18 to 0%, because when this is done, the following error message appears;

"ERROR. VALUES ENTERED DO NOT ADD UP TO 100%"

However, on closer inspection, we believe that despite this error message, BMS' model works as required, i.e. no 2nd-line TKIs are modelled. We apologise for our mistake.

Comments made by the AG on their own model (BMS Section 4)

BMS make a number of criticisms of the three different modelling approaches (Cumulative Survival, Surrogate Survival, and 'Simplified Approach') but we are not sure why they do this given that (a) we already clearly acknowledge these different weaknesses of these modelling approaches in our report, and (b) many of these weaknesses are inevitably shared by either the Novartis (cumulative survival) or the BMS (surrogate survival) model. In short, we are none the clearer about which ones they believe are avoidable weaknesses of these alternative approaches.

Cumulative Survival approach

In Table 34, p145 of our report, we clearly acknowledge a range of advantages and disadvantages of the Cumulative Survival method and the Surrogate Survival method. In response to BMS' specific criticisms;

- the Cumulative Survival method does indeed ignore the CCyR and MMR response rates. This is why we also used the Surrogate Survival method.

- the Cumulative Survival method does indeed rely on numerous assumptions, as do the economic models submitted by BMS and Novartis. However, we believe that BMS' model is too complex given the quality of the data, whereas the complexity of our model and Novartis' model is more commensurate with the amount and reliability of available data.

- we present scenarios whereby we allow for 2nd-line nilotinib and scenarios where we do not allow for 2nd-line nilotinib.

- we present scenarios based on a Simplified Approach whereby subsequent treatments have only a marginal impact on cost-effectiveness. We also present scenarios, whereby we model subsequent treatments in full. We believe this flexibility is to our credit, and importantly allows comparison and exploration of both manufacturers' divergent approaches to modelling the cost-effectiveness of these drugs.

Surrogate Survival approach

- This is the method chosen by BMS. Neither we nor BMS explicitly model the depth, speed of achieving or duration of response. We are not aware of any relevant data to allow for such analysis.

- When BMS say "Survival does not reflect exact nature of 2nd line treatment" it is not clear why they repeat this acknowledged weakness of the Surrogate survival approach.

- see comment above concerning our simplified approach. We justify this approach carefully on p141 of our report.

BMS conclude that "all these issues are major weakness in themselves, and when viewed collectively BMS feel demonstrate that the AG model is not fit for purpose". Conversely, we believe that we have provided the Appraisal Committee with a good range of plausible modelling scenarios, based as much as possible on the best available evidence, upon which to base their deliberations.

To claim, on the basis of these already acknowledged weaknesses, that our model is "not fit for purpose" is totally unjustified.

Other comments on the AG model (BMS Section 5)

Cumulative survival method (BMS Section 5.1)

As clearly acknowledged in Table 34, p145 of our report, we believe that there are various advantages and disadvantages of the Cumulative Survival method and for the Surrogate Survival method. For this reason, we present estimated costs effectiveness and ICERs using both methods.

Time on 1st-line TKI

Our method of modelling the time on 1st-line TKI is clearly described on p155-163 of our report. BMS correctly state that the mean time on 1st-line TKI is independent of our choice of Scenario, but they do not then state why they perceive this to be a weakness of our analysis. Note that we provide alternative estimates of time on 1st-line TKI in our sensitivity analyses (p209 – 212).

Next, as partially explained by BMS, we estimate the following unadjusted mean times on 1st-line TKI taken directly from the appropriate RCT;

- 13.0 years for imatinib from IRIS RCT,
- 7.5 years for imatinib from dasatinib vs. imatinib RCT,
- 6.6 years for imatinib from nilotinib vs. imatinib RCT,

- 8.5 years for nilotinib from nilotinib vs. imatinib RCT,
- 8.2 years for nilotinib from dasatinib vs. imatinib RCT.

Note that BMS do not mention the 7.5 years for imatinib from dasatinib vs. imatinib RCT and the 6.6 years for imatinib from nilotinib vs. imatinib RCT. Given that the RCTs of dasatinib and nilotinib are very immature, we then use information on the long-term treatment duration of imatinib from the relatively mature IRIS RCT to adjust our estimates of mean treatment duration on nilotinib and dasatinib. Finally, we then appropriately perform an indirect comparison between the dasatinib and nilotinib RCTs.

BMS identify no flaw in this methodology. Hence, we do not believe that our model is subject to a "central flaw".

Next, as BMS correctly state, we do indeed assume proportional hazards between the treatment durations for the three 1st-line TKIs. Given the immaturity of treatment duration for dasatinib and nilotinib, we believe that this is a reasonable assumption. Indeed, we have "gone the extra mile" in using relevant information from the relatively mature IRIS RCT.

BMS then claim that the proportional hazards assumption does not hold for treatment duration in the nilotinib vs. imatinib RCT (Figure 22, p158), but they provide no justification for this statement.

Under the heading "Approach used to adjust fitted values", BMS then claim that the gamma value (shape) of 0.861 which we used for all treatments, taken from our analysis of the IRIS RCT, lies outside the 95% confidence interval for both nilotinib and imatinib in the nilotinib vs. imatinib RCT. But, again, they provide no justification for this statement. Furthermore, we believe that given that the nilotinib and dasatinib RCTs are very immature, to estimate the shape parameter based on data from these trials alone would constitute spurious accuracy. Nonetheless, when we fit both the shape and scale parameters of the Weibull based on minimising the sums of squares of differences, we estimate a shape parameter for nilotinib of 0.82 and for imatinib of 0.80, which are both consistent with our assumed value of 0.86.

Finally, as BMS correctly state, we do slightly increase the estimated duration of nilotinib treatment from the trial-estimated value and slightly decrease the duration of dasatinib treatment from the trial-estimated value. This is the result of applying currently accepted best practice methods for conducting indirect comparisons in this context.

Time on HU or SCT

BMS claim that HU is used when all TKIs have been exhausted and when patients are not eligible for SCT. They then claim that we assume HU is used as a 2nd-line treatment. In fact, in one Scenario, we assume that HU is taken 2nd-line, and in another Scenario, we assume that HU is taken 3rd-line. In both cases, HU is taken when all TKIs have been exhausted and when patients are not eligible for SCT.

Next, BMS correctly state that we assume the probability of CML-related death for patients taking HU is constant over time and the probability of disease progression (from CP to AP) for patients taking HU is constant over time. However, we disagree with BMS' suggestion that we assume that these probabilities "will be the same on the first day of diagnosis as in the 20th year of the illness". This is because, on diagnosis, we assume that patients take a TKI, not HU. Next BMS claim that

"common sense and the nature of cancer biology in general" suggest that our assumption of constant probabilities of death and progression whilst on HU are unrealistic. However, BMS provide no evidence to support this allegation, and we are baffled by the suggestion that common sense can extend to a topic as technically challenging as survival on drugs for cancer ! On the contrary, given the dearth of evidence on rates of progression and death for patients on 2nd- and 3rd-line HU, we maintain that our assumption of time-independent rates of transition is appropriate and parsimonious.

Next, BMS present a table (Table 2) of the estimated mean times on HU from our model for a variety of modelling Scenarios. For clarity, these values are the mean times on HU from the time of diagnosis, not the mean times on HU for patients who reach treatment with HU. BMS claim that there is "confusion" associated with these figures, but they do not state why they find the figures confusing.

Next, BMS present a table (Table 3) of the equivalent values for SCT. Again, they find the figures "confusing", without saying why. As an aside, we agree with all figures in Tables 2 and 3 except that all mean times after SCT in the nilotinib treatment arm should be 4.9 years.

BMS next correctly indicate that there are two types of mean time as we state above: mean times on HU from diagnosis ("undiscounted mean"), and mean times on HU for patients who reach treatment with HU ("undiscounted mean (for those in a state)"). BMS then correctly quote the mean times on HU for patients who reach treatment with HU from our model in their Table 4. For the Cumulative Survival Scenarios, the mean time on HU for patients who reach treatment with HU is typically about 5-6 years, and the mean survival after SCT for patients who receive a SCT is typically approx. 17 years. This is consistent with BMS' indirect assertion that the mean time on HU should be less than the mean survival after SCT.

Next, under the Surrogate Survival methods, the mean time on HU for patients who reach treatment with HU is typically about 15 years. We discuss this in detail in Section 8.1.3, p139 of our report. In summary, in order to model OS as predicted from the surrogate relationships, it was necessary to alter the estimated mean time on one or more intervening treatments. The mean times on TKIs were not altered because these were taken from high quality RCTs. The mean survival after SCT was also not altered because it was not possible to replicate the OS from the surrogate relationships. This left only one possibility, to alter the mean time on HU. This gives the unrealistically high estimated mean time on HU of about 15 years.

To be clear, ee do not suggest that it is realistic to expect patients to spend 15 years on 2nd-line HU after failure of 1st-line TKI. Instead, we believe that this method still captures the essential features of the surrogate relationship, which is the overall survival advantage of dasatinib and nilotinib versus imatinib predicted by the response rates at 12 months. Furthermore, this highlights the extreme difficulty of modelling complex sequences of treatments given very limited, immature clinical evidence.

Modelling overall survival: conclusions (BMS Section 5.2)

See our comments to BMS Section 5.1.

Surrogate Survival method (BMS Section 5.3)

BMS claim that the primary historical data we used to parameterise our surrogate overall survival relationships was the IRIS RCT. They also claim that the "precise source is not stated". First, it is an oversimplification to claim that our primary data source was the IRIS RCT. Second, details of the historical data we used are clearly given on p112 - 116 of our report.

In summary, for the CCyR surrogate relationship, we used refs 100, 105 and 107 in our report, DeLavallade et al (2008), Kantarjian et al (2008), and Roy et al (2006). The last source reported on the IRIS RCT. The trials reported by Kantarjian et al (2008) and Roy et al (2006) were the primary data sources. For the MMR surrogate relationship, we used refs 101, 103 and 105 in our report, which correspond to Hehlmann et al, Hughes et al (2010), and Kantarjian et al. Hughes et al reported on the IRIS RCT. This trial gave us the longest follow up, but provided only one data point. The other trials, reported in to Hehlmann et al and Kantarjian et al. provided a substantial amount of data.

Our identification and choice of historical data was informed by a carefully conducted systematic review of the literature, to which we devote an entire chapter (Chapter 5, p101). Similar thoroughness is not shown by BMS in their choice of historical data, nor a suggestion made for a more scientifically defensible approach

Next, BMS display overall survival data as a function of cytogenetic response from the IRIS RCT. They then fit a Weibull function to OS for patients with a CCyR and separately for patients without a CCyR. They find that the shape parameter, gamma, of the Weibull is greater than 1 in both cases, which they correctly state implies an increasing probability of death over time. They then correctly state that, under the Surrogate Survival method, we assume the probability of CML-related death is constant over time. Of course, the overall probability of death increases over time in line with the general population. BMS then correctly quote the estimated mean survival according to response from our model. BMS then claim that we over-estimate OS, and state that we should have modelling an increasing rate of CML-related mortality over time.

We have three criticisms of BMS' analysis. First, as explained above, whilst BMS predict an increasing rate of CML-related mortality over time based on the 3 ½ follow-up data from IRIS, we base our surrogate relationships on a broader base of trials. Second, the follow-up of our synthesised data is longer than used by BMS: we used 5 years follow-up for CCyR vs. 3 ½ years from BMS. In addition, we used 7 years follow-up for MMR whilst BMS did not model MMR. Therefore, arguably we have a more reliable source of data upon which to estimate surrogate survival. Third, even at 7 years follow up, about 90% of patients are still alive. Therefore, we believe that there is insufficient evidence to estimate the shape parameter of the Weibull. To claim that we can, we think introduces spurious accuracy. Instead, it is more appropriate to assume a constant probability of mortality over time. Nonetheless, we have estimated the shape parameters of the Weibull using our more comprehensive historical data as 0.78 for CCyR, 1.86 no CCyR, 2.2 for MMR, 1.2 no MMR. Clearly, the shape parameters vary widely, which is to be expected with such immature data. Furthermore, these estimates are mean values obtained from summary data. Only analysis of the underlying IPD would reveal the true uncertainty in the shape parameters, and we suspect this would be substantial.

BMS then correctly state that the difference in predicted OS between patients with a MMR and those without using our surrogate relationship is small, at 3 years. First, whilst these results may appear surprising, as stated above, they are calculated based on a thorough systematic review of historical trial data, and therefore should be respected. For example, in the IRIS trial, OS at 7 years for patients with MMR at 12 months was 92% which is very similar to the corresponding value for patients without a MMR, of 89% (Hughes et al 2010). Second, we can only speculate on the causes of such a small difference in OS, but we should remember that it is difficult to achieve a MMR, indeed more difficult than a CCyR. Therefore, there will doubtless be many patients who do not achieve a MMR, but who have good prognosis. Note that the difference in predicted OS using our cytogenetic surrogate relationship is much greater, at 10 years. Had we not presented MMR-based surrogate survival we would no doubt have also been criticised by BMS.

Nilotinib PAS (BMS Section 5.4)

BMS claim that it is not appropriate to model the PAS for 2nd-line nilotinib. Contrary to this, NICE have asked us to assume the PAS applies to both 1st- and 2nd-line nilotinib.

Modelling HU and SCT (BMS Section 5.5)

BMS imply that we should have modelled 2nd-line dasatinib, stating that dasatinib is licensed for 2nd-line and recommended by international guidelines. Whilst we agree that dasatinib is licensed for 2nd-line CML, we believe that it would be wrong to model a treatment which has been assessed by, and not recommended by NICE.

BMS then correctly state that in our Scenarios 1 and 2, once a patient has had one TKI, they will never have another. They then claim that our Scenarios 3 and 4 suggest that "a patient who fails nilotinib is somehow "different" to one who fails dasatinib". They then correctly state that both BMS and Novartis modelled 2nd-line dasatinib (although Novartis present a scenario where this is not the case). However, NICE's judgement on 2nd-line TKIs was released after BMS and Novartis submitted their economic evaluations.

Next, BMS appear to suggest that we model "no treatment" as 3rd-line, following failure of 2nd-line HU. This is incorrect – we assume that patients take HU until progression to AP.

BMS then claim that our estimate of the 3-monthly cost of HU of £36 is incorrect. However, they do not give what they consider to be the correct cost.

BMS then correctly quote our assumed cost of a SCT of approx. £80,000 and follow-on costs of £340 per 3 months. The remainder of the final paragraph in Section 5.5 is quite difficult to understand.

PSA (BMS Section 5.6)

As stated on p28 of our report;

"*We do not conduct and present probabilistic sensitivity analyses because of the unusually large amount of structural uncertainty that is inherent in the present decision problem(s). This structural uncertainty relates to both the variety of ways in which long-term survival might be estimated, and uncertainty surrounding the possible sequences and mixes of treatments post 1st line TKI failure. As a result, we believe that structural uncertainty would dominate total (structural and parameter) uncertainty, and therefore that if we presented PSAs based just on parameter uncertainty, this would be of little use to the committee and be potentially misleading*."

BMS accuse us of lying. They believe that the true reason why we did not provide a PSA was because we used the Excel Solver function to calculate deterministic values. This is incorrect. BMS further claim that the lack of a PSA is "*a major failing as it deprives the committee of key information required to make a rational decision on the use of first line treatment for CML*." We disagree, as explained in the quote from our report above.

Other issues (BMS Section 6)

Section 1.5.2:

Nowhere in this section does it say "24 month CCyR and MMR are not reported" in fact we chose not to report the combined CCyR and MMR 24-month (as with the other time-point) in this summary section, as CCyR at 24-months was not statistically significantly different.

Relevance of imatinib OS surrogate relationships to nilotinib and dasatinib surrogate relationships

BMS correctly state that we believe that it is not certain whether it is possible to generalise the historical surrogate relationships between response rates on imatinib and OS on imatinib to the corresponding relationships for nilotinib and dasatinib. BMS then disagree with this view. Instead, they believe that the imatinib surrogate relationships with OS clearly extend directly to surrogate relationships with nilotinib and dasatinib. Conversely, we believe that we are correct to question this assumption. Instead, we believe that this question can only be resolved once we have long-term survival for patients on nilotinib and dasatinib.

Section 1.8.8.2 HU as proxy for other treatments

The section relates to the proportion of people who would get a different therapy after TKI failure, with HU used as a proportional proxy not a biological one.

Section 2.2.3 Survival statistics

While 'all leukaemia's' may not be directly relevant to this CML report, this was the only available data sourced, without relying on the IRIS trial, which had a large cross-over rate.

Section 4.2.2.1 Primary endpoint of DASISION trial

Agreed, this should say 'confirmed complete cytogenetic response'

Section 4.2.2.2 Risk scoring

This section is merely reporting the risk distribution of the two trials and does not aim to question the ramifications of any slight differences.

Section 4.2.2.3 Patient population in DASISION trial

You seemed to have answered your own question, yes 50 is the median age representative of a trial population but, not the UK population where it is 58. Although ethnicity is not reported, the online registered details (at clinicalrials.gov) provide study locations.

Section 4.2.3.1 Response rates in DASISION trial

Data for CCyR rates at 24-months for risk groups was not available to us.

Section 4.2.3.6 Transformation rates in ENESTnd DASISION trials

Agreed, the definitions between the trials are different.

Figure citations

Agreed typo, should be Figures 7 and 8.

Indeed Figure 7 is not clinically relevant, the exaggeration is to show has the data can be misleading after two years, but when we look at Figure 8 over 10-years in reality we only have immature data on overall survival. Figure 7 is not used to favour or bias the therapies under investigation.

Surrogate outcomes in CML

CCyR is a very well known biomarker among the clinical community but it has not been statistically validated according to a meta-analytic framework considering individual patient data. Moreover, even if the surrogacy status of the biomarker had been confirmed on the basis of the copious evidence from the interferon-alpha studies, the quantification of the relationship between the surrogate and the final outcomes when using dasatinib and nilotinib would still be valuable, since the adoption of a treatment belonging to a drug class different from the interferon it's likely to have an impact on that.

References:

1. Kantarjian H, Shah NP, Hochhaus A, Cortes J, Shah S, Ayala M, et al. Dasatinib versus Imatinib in Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia. *New England Journal of Medicine* 2010;**362**:2260-70.
2. Bristol-Myers Squibb. Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia (CML). Industry Submission2011.
3. Shah N, Kantarjian H, Hochhaus A, Cortes JE, Bradley-Garelik MB, Zhu C, et al. Dasatinib Versus Imatinib In Patients with Newly Diagnosed Chronic Myeloid Leukemia In Chronic Phase (CML-CP) In the DASISION Trial: 18-Month Follow-up. *Blood (ASH Annual Meeting Abstracts)* 2010;**116**:206-.
4. Kantarjian H, Shah NP, Cortes JE, Baccarani M, Bradley-Garelik MB, Zhu C, et al. Dasatinib or imatinib (IM) in newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP): Two-year follow-up from DASISION. *ASCO Meeting Abstracts* 2011;**29**:6510.

Executive summary

Overview

In this appraisal, we have demonstrated that dasatinib is clinically more effective, as well as more cost effective, than imatinib, the current standard of care.

In the pivotal clinical trial, 12-month data have shown that dasatinib is superior to imatinib in terms of complete cytogenetic response (CCyR) rates. CCyR rate is a reliable prognostic predictor for long-term clinical benefits in CML. Progression free survival (PFS) and overall survival (OS) are related to time to and length of such response. Patients who achieve CCyR early in treatment have improved PFS and OS, while those who do not respond to treatment early generally face disease progression.

Dasatinib gives higher and faster CCyR and molecular response compared to imatinib, the current standard of care, and has the potential for improved OS. The narrower spectrum of mutations associated with resistance to dasatinib (compared with imatinib) suggests additional potential for less resistance to dasatinib.

Because of better CCyR rate, dasatinib reduces the risk of progression to second-line treatment. Due to the expense of second-line treatment, this may result in a reduction in overall costs associated with treatment of CML.

Further benefits of dasatinib include the fact that as a once daily oral therapy independent of meal-times, dasatinib is easy to self-administer and has minimal impact on service delivery. This could have consequences for improved patient compliance, which is known to be related to a better clinical outcome.

Side effects of dasatinib are well characterised and easily managed. In particular there were no major grade 3/4 toxicities. There are no new safety signals associated with first-line compared with second-line treatment.

Dasatinib is a designated orphan medicine, so comparative data to support this appraisal are inevitably scarce. However, there is robust clinical evidence that dasatinib is more effective than imatinib, and economic studies demonstrate that dasatinib is cost effective compared with standard-dose imatinib (400mg).

Without a recommendation to allow first-line use of dasatinib, future CML patients in England and Wales may have to accept less effective therapy, a reduced quality of life and a diminished life expectancy, possibly at an increased cost to the NHS. BMS therefore request that dasatinib is recommended as a first-line treatment option for CML in England and Wales.

The UK approved name, brand name, marketing status and principal mechanism of action of the proposed technology.

Dasatinib, SPRYCEL®.

Dasatinib was first approved in the EU on 20 November 2006 for all indications except first-line treatment which was approved in the EU on 6 December 2010.

Dasatinib is a highly-potent inhibitor *in vitro* of the BCR-ABL tyrosine kinase, an enzyme that plays a critical role in the pathogenesis of chronic myeloid leukaemia (CML). Dasatinib blocks these enzymes at nanomolar concentrations, binding to and inhibiting not only BCR-ABL and SRC family but also a number of other selected oncogenic kinases including c-KIT, ephrin (EPH) receptor kinases, and PDGFβ

receptor (Sprycel SmPC 2010). This binding blocks phosphorylation of substrate proteins, which prevents the activation or over-expression of various pathways responsible for transforming normal cells into malignant cells.

The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost.

Film-coated tablet

20mg, available in packs of 60 tablets (£1252.48 per pack)

50mg, 70mg available in packs of 60 tablets (£2504.96 per pack)

80mg, 100mg, 140mg available in packs of 30 tablets (£2504.96 per pack)

The indication(s) and any restriction(s).

Dasatinib is indicated for the treatment of adult patients with:

- newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase
- chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib mesilate.
- Ph+ acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy

Dasatinib is contraindicated in cases of hypersensitivity to the active substance or excipients. Caution is recommended in the following instances: concomitant use with drugs that potently inhibit cytochrome P450 (CYP) 3A4, patients with hepatic impairment, patients taking drugs that inhibit platelet function or anticoagulants, patients who have or may develop prolongation of QTc (including those with hypokalaemia or hypomagnesaemia, congenital long QT syndrome, patients taking anti-arrhythmic drugs or other drugs which lead to QT prolongation, and cumulative high dose anthracycline therapy), and patients who have, or with risk factors for, cardiac disease. Dasatinib should not be used in pregnant or lactating women.

The recommended course of treatment.

The recommended starting dose for chronic phase CML is 100 mg dasatinib once daily, administered orally. Treatment is continued until disease progression or until no longer tolerated by the patient, but is not continued until death.

Dose escalation to 140 mg once daily is recommended in patients with chronic phase CML who do not achieve a haematological or cytogenetic response at the recommended starting dose. 140 mg once daily is the approved dose for accelerated and blast phase CML.

The main comparator(s).

Nilotinib, Imatinib (standard dose, 400mg daily).

Whether the key clinical evidence in the submission comes from head-to-head randomised controlled trials (RCTs), from an indirect and/or mixed treatment comparison, or from non-randomised studies.

Key clinical evidence: a multinational open label randomised Phase III clinical study in patients newly diagnosed with chronic phase CML, comparing dasatinib at 100 mg once daily (OD) and imatinib at 400 mg OD (DASISION; Kantarjian et al 2010). This publication reports data from the 12-month analysis; data from the 18-month timepoint have since been presented in abstract form only (Shah et al 2010) and are not discussed further pending presentation of the full 18-month and 24-month analyses later in 2011.

This study is supported by the results of a Phase IIb study with dasatinib (Radich et al 2010).

The Phase III ENESTnd study compares nilotinib with imatinib in newly-diagnosed chronic phase CML (Saglio et al 2010).

There are no studies that directly compare dasatinib and nilotinib head-to-head. Consequently, a mixed treatment comparison (MTC) was conducted.

The main results of the RCTs and any relevant non-RCT evidence.

In the DASISION trial, dasatinib treatment produced a significantly higher CCyR rate by 12 months compared with imatinib (83% vs 72%, p <0.001) in newly diagnosed chronic phase CML. Dasatinib's superior efficacy over imatinib was also confirmed through subpopulation analyses and by secondary endpoints. MMR rate, a key secondary endpoint, was significantly higher by 12 months in dasatinib-treated patients compared with imatinib-treated patients (46% vs. 28%, p <0.0001). Dasatinib-treated patients also achieved cytogenetic and molecular responses significantly earlier compared with imatinib-treated patients. Time to events data with 12 months of follow-up showed a non-detrimental effect of dasatinib.

Dasatinib demonstrated higher response rates, faster time to response and a safety profile that was similar to imatinib in newly diagnosed CML patients with a minimum of 12 months of follow-up.

In the MTC, results for dasatinib and nilotinib showed no statistically significant differences between the two products on all endpoints.

In relation to the economic evaluation, details of: the type of economic evaluation and justification for the approach used; the pivotal assumptions underlying the model/analysis; the mean costs, outcomes and incremental cost-effectiveness ratios (ICERs) from the evaluation.

The approach used is similar to that presented by Botteman et al. in a review of methods for extrapolating CML related survival data (Botteman et al 2010) (Table 1). A 'time in state' (area under the curve) model (Briggs et al 2006) was developed, with the health states representing the early (CP) and advanced (AP/BP) stages as well as death, and time being in blocks of one month. A schematic of the patient pathway is presented in **Error! Reference source not found.**. In addition, patients can be on either first, second or third line treatment in all phases; however, according to clinicians' opinion, palliative care is only for patients in advanced phases (i.e. AP/BP). Note that the model distinguished between disease staging (CP, AP/BP) and line of treatment (first-line, second-line, third-line).

Table 1 Key assumptions in the economic model

Assumption	Rationale / justification
Disease prognosis is predicated on early cytogenetic response	Trial literature supports this hypothesis
Long term benefit of treatment (progression free and overall survival) is based on response to first line treatment at one year	Long term response category specific ITT data used in model construction. Hence, the benefits incurred by patients switching treatment early are implicitly included in the reported Kaplan-Meier plots
Non-CML mortality included in addition to information from clinical trials	CML-related death is not a common event in early stages of CML in CP (e.g. 12 months). Clinical trial program recruited mainly young patients and so long term non-CML related death effectively not accounted for.
Different data sources used to model treatment specific prognosis in patients who has a less than partial cytogenetic response to treatment at one year	Based on information provided by clinical advisory panel. Individuals who fail 2nd generation TKI treatments (i.e. dasatinib and nilotinib) were assumed to have a poor prognosis
Individuals can switch treatment for response related reasons at 3, 12 and 18 months	In line with current ELN guidelines
Individuals can switch treatment for other reasons during every month	In line with what has been observed long term in clinical trials
For 2nd generation TKIs (dasatinib and nilotinib), the discontinuation rates due to adverse events are assumed to decrease over time; For 1st generation TKI (imatinib), constant rates are assumed	In line with comments from clinical advisory panel. Unlike the 1st generation TKI, clinicians tend to keep patients on 2nd generation TKIs as long as possible since the only option left post-2nd line treatment would be BMSCT, which is not suitable for all patients, and is associated with high risk. Therefore, it is assumed that patients on 2nd generation TKIs would have lower discontinuation rates than those on 1st generation TKIs, other things being equal.
Permanent treatment cessation has not been included in the base-case of the model. No patients get the benefit of treatment without incurring the costs	Although there is evidence in high quality journals that 'permanent treatment cessation' happens for patients on TKI treatment, it is still early stage and not yet the clinical practice. We therefore include such scenarios in the sensitivity analysis
In deriving post progression costs, 2/3 of time is spent in the AP state and 1/3 in the BP state	Broadly in line with the clinical literature
SCT occurs only in third line therapy	In line with current ELN clinical guidelines
3rd line treatment in the CP state is different to post progression treatment	In line with comments made by clinical advisory group. Post progression treatment (treatments for advanced phases of CML) can include acute myeloid leukaemia (AML) related treatment (a combination of chemotherapies) in addition to the 3rd line treatment options
Vial sharing does not occur when deriving the cost of IFN based therapy	In line with common modelling practice
Where an adverse event was not reported in the literature it was assumed not to occur	In line with common modelling practice
Where no data on utility decrement were	In line with current modelling practice

Assumption	Rationale / justification
identified, a nominal value (-0.05) was used	

Tabulation of the base-case results as follows:

Table 2 Base-case cost-effectiveness results

	Dasatinib 100mg	Imatinib 400mg	Nilotinib 600mg
Technology acquisition cost	£283,209	£84,836	£282,887
Other costs	£215,008	£393,457	£223,726
Total costs	£498,217	£478,293	£506,613
Difference in total costs		+£19,924	-£8,396
LYG	12.94	12.33	13.01
LYG difference		0.61	-0.07
QALYs	10.64	9.89	10.70
QALY difference		0.76	-0.06
ICER		**£26,305**	**£144,778**

LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio

Executive summary

Nilotinib overview

Nilotinib is a second-generation tyrosine kinase inhibitor (TKI), specifically designed to target BCR-ABL, the single known cause of chronic myeloid leukaemia (CML). Nilotinib has demonstrated superior efficacy as a first-line treatment for Philadelphia chromosome positive (Ph+) CML over imatinib, the current standard of care, in all levels of response. Nilotinib achieved significantly higher rates of major molecular response (MMR) and complete cytogenetic response (CCyR) than imatinib at 12 months (MMR, 44% vs 22%; CCyR, 80% vs 65%; $p < 0.0001$ for both comparisons), and differences remained statistically significant at 24 months.[1,2] As expected, the higher rates of MMR and CCyR achieved with nilotinib translated into significantly lower rates of progression to accelerated phase (AP)/blast crisis (BC) at 12 and 24 months, and improved progression-free survival at 24 months. In addition, the number of CML-related deaths in patients receiving nilotinib was half that in patients receiving imatinib (n = 5 (1.8%) vs n = 10 (3.5%)).[1,2] These improvements in response, disease progression and overall survival seen with nilotinib were achieved without any increase in adverse events (AEs), and indeed were accompanied by lower rates of haematological, gastrointestinal, and fluid-retention AEs, than seen with imatinib. With the proposed Patient Access Scheme (PAS) these benefits can be achieved [redacted] for first-line treatment of newly diagnosed Ph+ CML-CP.

CML overview and treatment goals

CML is a progressive, life-threatening, haematopoietic neoplasm, and comprises three phases: chronic phase (CP), accelerated phase (AP) and blastic phase (also known as blast crisis (BC)).[3] Most patients are diagnosed in CP, and a key therapeutic goal is to maintain patients in this early phase of the disease by reducing disease to undetectable levels.

Current clinical recommendations support achievement of an MMR, defined as a ≥ 3 log reduction in BCR-ABL transcripts [BCR-ABL/control gene of ≤ 0.1%] as a clinical endpoint for assessing treatment response in CML, and suggest achieving MMR by 18 months should be considered as optimal response.[4-6] This reflects the fact that disease progression is negligible in patients achieving an MMR.[7] In contrast, some patients achieving a CCyR only (defined as having no detectable Ph+) may progress to AP/BC.[7,8] Furthermore, achievement of earlier and deeper molecular responses, (i.e. greater reductions in BCR-ABL levels) [9-11] and durable molecular responses (i.e. MMR that are maintained at all assessments)[12] translate into improved event-free survival and freedom from progression.[10]

Clinical effectiveness and safety for nilotinib as first-line treatment for newly-diagnosed patients

Four clinical studies have assessed nilotinib as a first-line treatment for newly diagnosed patients with Ph+ CML-CP. The phase III, randomised, controlled trial Evaluating Nilotinib Efficacy and Safety in Clinical Trials – Newly Diagnosed Patients (ENESTnd), which formed the basis for first-line registration of nilotinib, compared the licensed dose of nilotinib 300 mg BD with imatinib 400 mg OD.[2] The other three studies were non-randomised, and assessed the efficacy and safety of nilotinib 300 mg BD (All Ireland Cooperative Oncology Research Group study)[13,14] or nilotinib 400 mg BD (MD Anderson Cancer Center and Gruppo Italiano Malattie EMatologiche dell'Adulto studies).[15-17]

The ENESTnd study was an open-label, randomised, multicentre, comparative study conducted at 217 centres in 35 countries, with five centres in the UK. In total, 846 patients were randomised to nilotinib 300 mg BD, nilotinib 400 mg BD and imatinib 400 mg OD, representing a large patient cohort in this rare disease. The primary endpoint of the study was MMR rate at 12 months, and secondary endpoints included rate of CCyR, progression to AP/BC, progression-free survival and overall survival (at 12 and 24 months).

The 12-month results have been published in The New England Journal of Medicine in June 2010,[2] and results for 24 months follow-up were presented at the annual meeting of the American Society of Hematology (ASH) in December 2010.[1] Results reported for the ENESTnd study clearly demonstrate superior efficacy for nilotinib 300 mg BD over imatinib 400 mg OD for all endpoints assessed at both 12 and 24 months. MMR rate at 12 months for nilotinib 300 mg was double that achieved with imatinib (44% vs 22%, $p < 0.0001$)[2] and remained significantly higher at 24 months (62% vs 37%, $p < 0.0001$).[18] MMRs were achieved more rapidly with nilotinib 300 mg BD than imatinib (median time to MMR according to Kaplan–Meier analyses: 8.6 months vs 22.1 months, $p < 0.0001$), and significantly more patients receiving nilotinib 300 mg BD achieved undetectable disease (BCR–ABL ≤ 0.0032%) by 24 months [redacted].[18, 51] Given the prognostic implications of achievement of MMR and undetectable disease, these results suggest that nilotinib will confer significant overall survival advantages over imatinib with further follow-up.

Nilotinib 300 mg BD was also associated with a significantly higher rate of CCyR compared to imatinib both by 12 months (80% vs 65%, $p < 0.0001$)[2] and by 24 months (87% vs 77%, $p = 0.0018$).[18] A higher response rate was evident in the nilotinib-treated group at the first assessment of cytogenetic response at 6 months (67% vs 45%). Differences in CCyR rates between treatments were evident across all three Sokal risk groups. The well accepted correlation of CCyR with overall survival and progression-free survival further substantiates the expectation that nilotinib will confer significant overall survival advantages over imatinib with additional follow up.

As expected, the higher rates of MMR achieved with nilotinib, translated into significantly lower rates of progression to accelerated phase (AP)/blast crisis (BC) and improved progression-free survival. At 24 months rates of progression were 0.7% in the nilotinib 300 mg arm, vs 4.2% with imatinib ($p = 0.0059$), and progression-free survival was 98.0% vs 95.2%. In addition, there were fewer CML-related deaths in patients receiving nilotinib compared to

those receiving imatinib (n = 5 (1.8%) vs n = 10 (3.5%)). Kaplan–Meier estimates of overall survival at 24 months favour nilotinib 300 mg BD over imatinib; with the relatively short duration of follow-up and the inclusion of CML-unrelated deaths in the analysis, the difference is not statistically significant (97.4% vs 96.3%, p = 0.6485). Additional results from ENESTnd after 36 months of follow-up will be presented at ASH in December 2011 and will allow more robust analyses of differences in overall survival and progression-free survival between nilotinib and imatinib.

These improvements in therapeutic outcome were achieved without any increase in adverse events (AEs). Indeed nilotinib 300 mg BD was associated with lower rates of haematological, gastrointestinal and fluid-retention AEs than imatinib. Over 24 months, only 6% of patients discontinued nilotinib 300 mg BD because of AEs compared with 9% for imatinib.[18] The safety profile of nilotinib in this setting was also consistent with that observed for nilotinib in the second-line setting, both in the registration trial and in the ENACT study (Expanding Nilotinib Access in Clinical Trials - the largest study in CML-CP to date, involving approximately 1400 patients),[19-23] and is further supported by results from the three non-randomised studies of nilotinib in the first-line setting.

Health economics evidence

A cost-utility analysis is presented that assumes a lifetime horizon. The analysis evaluates treatment with nilotinib 300 mg BD compared with imatinib 400 mg OD, which is the standard care for the treatment of people with newly diagnosed CML in CP. In the base case, the treatment pathway is modelled to reflect current clinical practice. Upon diagnosis, patients receive first-line treatment with a TKI, which in this case is either nilotinib or imatinib. Those who discontinue treatment as a result of treatment failure, suboptimal response or adverse events receive treatment with a second-line TKI. In the model dasatinib is used as the second-line treatment in both arms for consistency. Patients who discontinue second-line treatment receive a stem

cell transplant (SCT) or, if they are not eligible, hydroxyurea (HU) therapy. Patients who progress to AP and BP are assumed to receive HU.

Time to discontinuation (TTD) has been used to model the effectiveness of nilotinib and imatinib in the first-line setting. TTD broadly takes into account people in whom treatment fails and those who experience adverse events that lead to termination of therapy. It also takes into account the costs accrued while on treatment without applying additional assumptions. All direct medical costs are incorporated into the model. These include drug costs, costs of routine hospital appointments, and costs associated with treatment for grade 3 and 4 AEs.

Novartis has proposed a Patient Access Scheme (PAS) that will [redacted], and this is incorporated into all analyses. In the base case (probabilistic results), a treatment pathway with imatinib provides 10.17 life years (LYs) and 7.90 quality adjusted life years (QALYs) at a cost of £232,941. A treatment pathway with nilotinib provides 10.52 LYs and 8.18 QALYs at a cost of £220,416. Treatment with nilotinib dominates treatment with imatinib in this analysis, with an incremental cost effectiveness ratio (ICER) of -£44,909 per QALY gained. A scenario analysis is presented in which patients do not receive second-line TKI treatment. Patients who discontinue first-line treatment with nilotinib or imatinib receive SCT or HU. This scenario may provide a clearer assessment of these treatments when considered in isolation, although it is not reflective of current practice. Nilotinib remains cost effective compared with imatinib in this scenario, with an ICER of £4,483 per QALY gained.

The probabilistic sensitivity analysis (PSA) further demonstrates the superior cost-effectiveness of nilotinib over imatinib. The PSA shows that nilotinib is the cost-effective treatment at all willingness-to-pay thresholds, and that there is no probability of imatinib being cost-effective within the thresholds that are considered acceptable to the NHS. Several sensitivity analyses have been

performed that vary the TTD, costs, utilities, time horizon and age limit for SCT. In all cases, nilotinib is either dominant or cost-effective.

A budget impact analysis is presented that covers a five-year period following the launch of nilotinib in the first-line setting. Assuming an annual incidence of 475 people in England and Wales with CML-CP and the treatment discontinuations used in the model, 1461 people will be eligible for first-line treatment by 2015. Based on market research, Novartis assumes that [redacted] of these patients will be taking nilotinib. Under this assumption, the NHS will [redacted] in five years by using nilotinib in place of imatinib. Nilotinib is therefore demonstrated to be good value for money for the NHS based on both clinical efficacy and cost-effectiveness.

Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia (including part-review of NICE technology appraisal guidance 70**)**

Statement

Submitted by [redacted] on behalf of the following organisations:

NCRI/RCP/RC/ACP/JCCO

Comments coordinated by [redacted]

What is the place of the technology in current practice?

We would like to know how the condition is currently treated in the NHS. Is there significant geographical variation in current practice? Are there differences in opinion between professionals as to what current practice should be? What are the current alternatives to the technology and what are their respective advantages and disadvantages? Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations. If you are familiar with the evidence base for the technology, please comment on whether the use of the technology in clinical practice reflects that observed under clinical trial conditions. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes? What is the relative significance of any side effects or adverse reactions? In what ways do these have an impact on the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in the clinical trials but have come to light subsequently during routine clinical practice?

Chronic myeloid leukaemia (CML) is a triphasic disease characterised by the presence of the Philadelphia chromosome which itself contains the fusion oncogene BCR-ABL. This gene encodes a dysregulated tyrosine kinase with enhanced autophosphorylation. Without treatment the disease is uniformly fatal with a life expectancy of less than 5 years. The true incidence of CML in the UK is unknown. It is probably underestimated by statistics emanating from the Cancer Registries because the disease is usually diagnosed in haematology rather than histopathology laboratories, and the former are not required to submit the diagnoses of new malignancies to the Cancer registry.

The treatment of CML has changed dramatically over the last decade because of the introduction of drugs targeting the causative oncoprotein, Bcr-Abl. The first of these was the tyrosine kinase inhibitor, imatinib. Imatinib rapidly normalises the blood count (haematological remission) in more than 95% of patients presenting in chronic phase. It also induces a considerable reduction in tumour load as evidenced by the loss of cells containing the Philadelphia chromosome when the bone marrow was examined by conventional chromosome analysis. This state is known as complete cytogenetic remission (CCyR) and is achieved in approximately 75% of patients after 18 months of treatment. About 40% of patients achieve a greater reduction in tumour load as indicated by the detection of the RNA encoding BCR-ABL only by highly sensitive molecular methodology (RT-PCR). This state is known as major molecular remission (MMR). For the majority of patients who achieve CCyR (see later) and for those who obtain MMR, the long-term prognosis is excellent with current projections of overall survival being near-normal life expectancy. This is an important finding because it confirms both CCyR and MMR as excellent surrogate markers of long-term outcome. In approximately 5% of patients the RT-PCR for BCR-ABL becomes negative indicating complete molecular remission. Trials in France and Australia are currently investigating whether the imatinib can be stopped in this latter group of patients without recurrence of leukaemia. In all other patients treatment is life-long. The results of studies of imatinib for newly diagnosed patients were sufficiently convincing to change clinical practice worldwide such that imatinib became the

treatment of choice for newly diagnosed patients by 2001. This is standard practice in the UK and our experts are not aware of any geographical differences or inequality of access in any patient groups.

However some 25% of patients presenting in chronic phase fail to achieve CCyR and an additional 15% will lose this previously established excellent response. At least 60% of patients fail to achieve MMR and can never be considered for cessation of therapy, let alone cure. For patients with durable CCyR but no MMR, the disease becomes a chronic lifelong burden, with the requirement to take daily oral medication until death from other causes. The tyrosine kinase inhibitors are generally well tolerated compared to conventional chemotherapeutic agents but have low grade chronic toxicities that impact considerably on quality of life. For the 40% of patients who do not achieve or who lose CCyR, the disease could potentially return to the prognosis of the pre-imatinib era. A number of more potent second generation tyrosine kinase inhibitors (2G-TKI) have been developed. Some are licensed (dasatinib and nilotinib) and others are in clinical development (bosutinib and ponatinib). They are capable of inducing durable CCyR in about 50% of patients who demonstrate resistance to imatinib and in about 60% of those who were intolerant of imatinib. Although the spectrum of adverse events is similar for all these drugs it is remarkable that individual patients do not seem to develop cross intolerance and it is commonplace that one of these drugs will be well tolerated even after a previous agent has been discontinued for intolerance, It is important to note that the NICE technology appraisals of dasatinib and nilotinib for imatinib resistance and/or intolerance have not yet reported (some 5 years after the drugs were licensed in Europe) and there are undoubtedly geographical variations and inequity of access to these drugs across the UK.

Approximately 20% of patients will not respond to a strategy of initial therapy with imatinib followed by a 2G-TKI if resistant or intolerant. For these patients their disease has a poor prognosis and is certainly not better than the outcome of patients treated with earlier approaches. In fact their prognosis is probably worse than these patients as they have demonstrated resistance to targeted therapy suggesting a biological progression of their disease such that the leukaemic process is now dependent on pathways other than Bcr-Abl. One piece of supporting evidence for this last statement is that a considerable proportion of the patients who fail imatinib show early disease progression (within the first three years) to accelerated phase and blast crisis when their disease is almost uniformly fatal. From the seminal study of imatinib versus the previous gold standard of interferon and cytosine arabinoside (the IRIS study), the incidence of disease progression became negligible after the 4^{th} year of treatment.

For patients who fail all TKI and remain in chronic phase the treatment options are the drugs that were used prior to the introduction of imatinib or in selected cases, allogeneic stem cell transplantation. The previous standard of care for the majority of patients with chronic phase CML was a life-long combination of hydroxycarbamide and interferon plus or minus cytosine arabinoside. Busulphan, an alkylating agent, was commonly used until the late 1980s and although this remains a useful cytotoxic agent in some situations, it became a less popular choice for early phase disease because of toxicity. With optimal use of interferon, approximately 10-15% of patients achieved CCyR. Patients who obtained a CCyR or even a partial cytogenetic response (> 65% Ph-negative) experienced a statistically significant improvement in survival compared to those with lesser or no cytogenetic responses. Unfortunately interferon is a poorly tolerated drug with both short and long-term side effects and in retrospect was probably used less frequently in elderly patients. The overall survival of patients treated with interferon is 6-7 years but the median survival of those who achieved CCyR on interferon is greater than 10 years. Exact data for patients in CCyR on interferon is no longer available as many converted to imatinib when it became available. It is highly likely that a patient destined to achieve CCyR on interferon will be contained within the cohort that achieve CCyR

on imatinib and highly unlikely that any patient who fails to achieve CCyR on imatinib or a 2G-TKI will obtain this disease state on interferon

Approximately 30% patients with CML are suitable for allogeneic stem cell (bone marrow) transplantation. In contrast to best responses on interferon (and indeed imatinib), patients surviving a transplant are considered to be cured. Suitability is based on age and the availability of an HLA-matched donor (related or unrelated). The success of transplant is clearly associated with a number of factors including age, disease phase, source of donor, time to transplant and gender match of donor and recipient (collectively known as the EBMT score). Patients defined as good risk by these factors could expect a survival in excess of 80% at 5 years. Patients with poor risk factors had inferior survivals (largely due to transplant related mortality) but certain of these factors also conferred a poor survival on interferon (disease phase and disease duration), and without transplantation the disease was inevitably fatal. Because of this, transplant remains an important consideration in the management of patients but there is no doubt that procedural related mortality continues to be an obstacle to its widespread use.

In 2006 a group of international experts achieved a consensus regarding the management of newly diagnosed patients and advised that imatinib should become the first line therapy for all. This consensus statement is colloquially known as the ELN guidelines (Baccarani et al, Blood 2006 108:1809-20). With validation of the guidelines in an independent cohort of patients (Marin et al, Blood 2008)and additional experience, these recommendations were re-issued in 2009 with very minor changes (Baccarani et al, J Clin Onc 2009).

The substantial efficacy of 2G-TKI in the setting of imatinib intolerance or resistance, together with a lack of evidence of additional toxicity, led to phase II and III trials of dasatinib, nilotinib and bosutinib in the first line setting. Because overall CCyR rates are approximately 80% if imatinib is used as frontline treatment and 2G-TKI given only for failure, the prediction was that all three agents would induce durable CCyR rates in at least 80% of newly diagnosed patients by 18 months. There was also a considerable expectation that they would also increase the rates of MMR. Improved early response rates might benefit patients in at least two ways. First the early progression to advanced phase disease and subsequently death might be avoided in a larger proportion of patients. Second very deep responses might be seen in a larger number of patients such that more can eventually cease all therapy.

Two phase II studies of upfront nilotinib have been reported, one performed at the MD Anderson Cancer Center (MDACC) in Houston, USA and the other by the Italian leukaemia trial group (GIMEMA) (Rosti G, et al. Blood 2009, Cortes J, et al. J Clin Oncol 2010). One phase II study of upfront dasatinib was also performed at MDACC (Cortes J, et al. J Clin Oncol). The numbers of patients contained within these studies were relatively modest (50 in each of the MDACC studies and 73 in the GIMEMA trial) but the CCyR rates were remarkable, being in excess of 95% at 12 months. These trials were followed by three phase III studies each using a 2G-TKI at one or more doses with imatinib 400mg daily as the comparator. Although the 12 month CCyR rates were not as impressive and much closer to the 80% originally predicted, they were higher than in the patients randomised to imatinib, reaching statistical significance for nilotinib in the ENESTnd study (Saglio et al, NEJM, 2010) and dasatinib in the DASISION study (Kantarjian et al, NEJM, 2010). CCyR rates were not significantly different at 12 months in the BELA study of bosutinib versus imatinib although there was a trend in this direction, but the 12 month MMR rates were statistically significantly higher for all of bosutinib, dasatinib and nilotinib versus imatinib. There are at least three other important results from the early reports of these studies. First 80% of patients achieved CCyR at 12 months, whereas the previous timepoint for this milestone with imatinib was 18 months, suggesting that the proportion of patients obtaining CCyR might increase further with additional follow-up. Second the

rate of progression to advanced phase disease in the first 12 months from diagnosis was lower in patients who received a 2G-TKI upfront than in patients in imatinib, reaching significant levels for nilotinib and bosutinib. Finally the 2G-TKI were at least as well tolerated as imatinib with similar rates of discontinuation for adverse events.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Patients who present in, or who progress to, accelerated phase or blast crisis, have a much worse prognosis than those in chronic phase. Accelerated phase clearly contains a heterogeneous group of patients with considerable variation in their survival. Some patients presenting in, or progressing to acceleration without prior exposure to imatinib, can respond very well to the drug and have prolonged survivals not dissimilar to those of chronic phase patients. However the majority of patients in acceleration will eventually experience disease progression to blast crisis Patients who progress to accelerated phase on imatinib do not respond to increased doses and require alternative approaches. Patients presenting in or progressing to blast crisis have an extremely poor prognosis. The only chance of long-term survival is some form of therapy to restore a second chronic phase followed by an allogeneic transplant form a related or unrelated donor, but the procedural related mortality and risk of leukaemia recurrence are high.

Patients in either acceleration or blast crisis do respond to 2G TKI. Some patients in acceleration respond remarkably well, achieving durable CCyR but we have no way of distinguishing these patients from those who respond less well before treatment is initiated. Both dasatinib and nilotinib are licensed for the treatment of accelerated phase disease but have not been tested in a phase II study to compare outcome with standard dose imatinib, It is unlikely that the drugs will perform less well than imatinib, Some patients in blast crisis do return to chronic phase on 2G TKI but the responses are generally short-lasting and their worth is to create a window of opportunity in which to perform a transplant.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)? If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

The technology should be used only in specialist clinics. Patients on TKI require regular blood counts and a proportion will become pancytopenic requiring temporary discontinuation of treatment and/or supplementation with growth factors and blood products. More importantly patients require regular monitoring by chromosomal analysis of bone marrow, RT-PCR of peripheral blood and kinase domain mutation analysis at the time of resistance. The results of this testing are used to confirm response and to indicate the need for a change in treatment. Such a change in treatment might include consideration of transplantation or trials of experimental agents which can only be delivered in highly specialised centres. These drugs are extremely expensive and must be used appropriately. Specialist nursing may play an important role in the future. Patients who are responding extremely well may be managed by senior nurses with access to services that provide the methodology and interpretation of RT-PCR and mutation analysis. Such nurses are likely to be linked to specialist haematology hospital departments.

2G-TKI for first line treatment are currently only available in the UK in the context of clinical trials. The NCRI SPIRIT2 study is an academic initiated phase III study of imatinib 400mg daily versus

dasatinib 100mg daily. It has currently accrued approximately 50% of the target number and is well supported by haematologists throughout the UK. Nilotinib is available in the Novartis sponsored single arm ENEST1st study of 300mg bd which is of some value because of the inclusion of a well designed study to monitor adherence to therapy.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, if available, compares with current alternatives used in the UK. Is the technology easier or more difficult to use and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its use? ***If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include the requirement for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.***

As described above the use of dasatinib and nilotinib as first line therapy induces higher CCyR and MMR rates and lower rates of progression to advanced phase disease than standard dose imatinib. The two drugs have a similar spectrum of side effects to imatinib, are equally well tolerated and require identical monitoring practices. The fact that MMR rates are higher than with imatinib suggests the attractive possibility that more patients will eventually achieve RQ-PCR negativity and be candidates for stopping therapy. Approximately 10% of patients achieve molecular negativity on imatinib and of these early results suggest that about 40% can stop treatment in the long-term. MMR rates on dasatinib and nilotinib are twice as high as imatinib at 12months so a realistic expectation might be that the drugs will be able to be stopped in approximately 10% of patients

Any additional sources of evidence?

Are you aware of any relevant evidence which may not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence or information from registries and other nationally coordinated clinical audits. Any such additional information must be accompanied by sufficient detail to enable a judgement to be made as to the quality of the evidence and to enable potential sources of bias to be determined.

Updates of the ENESTnd, DASISION and BELA studies are expected at one or other of the ASCO (May 2011), EHA (June 2011) and ASH (Dec 2011) meetings, These will provide longer follow up which will give important information on response rates, durability of response, rates of disease progression and drug tolerability.

Implementation issues

How would possible guidance have an impact on the delivery of care for patients with this condition? Would there be any need for NHS staff to be educated and trained? Would any additional resources be required (for example, facilities or equipment)? Under the Department of Health and Welsh Assembly Government, the NHS is required to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisals. This provision has to be made within 3 months from the date of publication of the guidance. If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and Welsh Assembly Government to vary this direction. Please note that NICE cannot suggest variation in the direction on the basis of budgetary constraints alone.

If NICE approves the technology for first line therapy of CML, there will be an effective therapy for more than 80% of such patients, so one would expect improvements in overall, progression-free and event-free survivals.

The specialist knowledge and laboratory assays that will be required for the new technology are similar to those used for imatinib. Achievements of CCyR and MMR should be documented, if only to identify as early as possible those patients who are failing these treatments and who should be offered alternative therapy, In fact one of the factors that directly impacts the outcome of allogeneic stem cell transplantation is a time period from diagnosis to transplant in excess of one year. For patients who were first given imatinib and then a trial of a 2G-TKI, if deemed to have failed imatinib, this period of time was inevitably exceeded. The use of 2G-TKI as first line therapy will identify poor responders within 12 months, allow early referral for transplant and improve the outcome of this alternative therapy

Given that these drugs are not only relatively expensive but are given for life, then there may be an argument to develop a national registry of patients with CML that not only documents all new diagnoses but records simple data relating to response to various therapies. This would require some investment in data management and analysis but could be linked with the Cancer Registries.

Novartis have taken the initiative to develop a registry of female patients who become pregnant whilst taking imatinib and nilotinib, in spite of medical recommendations to use effective contraception. The aim is to collect information relating to any effects on the disease, the pregnancy and the fetus. There should be a similar collection of data for dasatinib and also for male patients who father children whilst taking 2G TKI as there are no data relating to the effects on fertility and teratogenicity.

North Yorkshire and York NHS
Primary Care Trust

Multiple Technology Appraisal

Dasatinib, nilotinib and standard-dose imatinib for the first line treatment of chronic myeloid leukaemia (incl part-review of TA 70)

From NHS North Yorkshire & York – commissioner perspective

The current commissioning arrangements are informed from the existing NICE guidance and incorporate commissioning arrangements from our respective cancer networks of which there is a trinetwork arrangement which includes Yorkshire, Humber & East Coast and Trent Cancer networks.

At present the recommended 1st line primary agent for treatment of CML in the chronic phase is imatinib 400mg assuming that entry in to a clinical trial is not an option. For patients diagnosed in the accelerated phase or blast phase, imatinib remains the 1st line agent of choice but at a higher dose than 400mg which I understand will be out with the scope of this appraisal but it is relevant for us to highlight current practice as this will have a bearing on cost.

Imatinib, dasatinib and nilotinib are all oral agents, and therefore there is no immediate obvious resource advantage/disadvantage of any one therapy above the other when considering the provision of the drug for the patient or any subsequent impact on service delivery. All three agents would be expected to be prescribed and monitored by the specialist, there may be arrangements for a homecare provider (thus VAT free) to dispense and deliver the treatment depending upon hospital contracts and therefore they remain on an equal footing from that perspective. We do not consider that this is an innovative technology; furthermore, since all of these agents are currently in use within the NHS, there are no new immediate safety concerns to address as far as we are aware.

At present we are uncertain until the technology appraisal is completed whether there is a significant clinical advantage for the 2nd generation tyrosine kinase inhibitors dasatinib or nilotinib above imatinib for all or a subgroup(s) of patients which is clinically and cost effective. We are aware of local cancer network guidance which proposes factors which would influence choice of agent when considering dasatinib or nilotinib (co-morbidities including cardiovascular disease, autoimmune disease) but these are not considering these agents in the 1st line setting.

The NHS cost for one year of treatment with imatinib 400mg is significantly lower (£19,000) than dasatinib (£30,000) and nilotinib (£29,000) with dasatinib and nilotinib being priced competitively at present (unless local procurement agreements result in substantive differences), however, as a commissioner we need to consider the procurement costs now and in the longer term. Should there be a recommendation to offer imatinib, dasatinib or nilotinib as a 1st line agent, then based on standard dose imatinib, this would generate an additional cost pressure to this programme budget. In light of the current financial challenged presented within the NHS at present, it is likely that, despite the overall number of patients with CML being relatively few, that

decommissioning in either this or another programme budget would be necessary. We do however, recognise that the dose of imatinib may be titrated upwards and that indeed the current cost comparisons therefore may not be entirely correct. It is noted that within this appraisal the standard dose of imatinib will only be considered, but it would be useful to get a clincians view to whether in clinical practice the higher dose of imatinib (800mg daily) is used in this setting or not. One further consideration to acknowledge is that the patent expiry for imatinib (Glivec) is expected in 2016 and therefore it is expected that potential savings would be possible on this programme budget in the longer term if imatinib remains 1st choice without clinical compromise.

Should there be any recommendation for all patients or a subgroup regarding choice of agent based on genetic mutations due to the presence of kinase domain mutations, we would ask for consideration of the evidence and costs including any associated costs and resources associated with conducting mutation testing.

At present, we are not aware of any likely patient access scheme (PAS) that is linked to this technology, our experiences to date would advocate that historically such schemes are convoluted thus are not delivering the anticipated savings and indeed serve to cost the NHS in terms of staff resources to unpick the nuances and ensure payments are made to the commissioner for these PbR excluded drugs. With that in mind we would ask that should any schemes be proposed, that a straightforward direct discount is the most practical option to administer ensuring transparency to provider and commissioner and ensures delivery of any savings.

NICE Technology Appraisal Clinical Expert Invitation - Leukaemia (Chronic myeloid) - dasatinib, nilotinib and standard-dose imatinib (1st line)

Jane Apperley

Personal Statement

Background: chronic myeloid leukaemia (CML) is a triphasic disease characterised by the presence of the Philadelphia chromosome which itself contains the fusion oncogene BCR-ABL. This gene encodes a dysregulated tyrosine kinase with enhanced autophosphorylation. Without treatment the disease is uniformly fatal with a life expectancy of less than 5 years. The true incidence of CML in the UK is unknown but is probably just less than 1 per 100,000 population per annum. The prevalence of the disease has changed dramatically in recent years because of the highly significant improvements in treatment.

The treatment of CML has changed dramatically over the last decade because of the introduction of drugs targeting the causative oncoprotein, Bcr-Abl. The first of these was the tyrosine kinase inhibitor, imatinib. Imatinib rapidly normalises the blood count (haematological remission) in more than 95% of patients presenting in chronic phase. It also induces a considerable reduction in tumour load as evidenced by the loss of cells containing the Philadelphia chromosome when the bone marrow was examined by conventional chromosome analysis. This state is known as complete cytogenetic remission (CCyR) and is achieved in approximately 75% of patients after 18 months of treatment. About 40% of patients achieve a greater reduction in tumour load as indicated by the detection of the RNA encoding BCR-ABL only by highly sensitive molecular methodology (RT-PCR). This state is known as major molecular remission (MMR). In approximately 5% of patients the RT-PCR for BCR-ABL becomes negative indicating complete molecular remission. One French study has shown that about 40% of patients who have well-established RT-PCR negativity (minimum 2 years) can stop the drug without disease recurrence (median follow-up about 2 years). Further European and Australian studies are underway to substantiate this result. In the UK we plan a study of de-escalation and/or stopping treatment in patients with deep molecular responses. The rationale behind de-escalation is twofold. First to see if these patients with excellent sensitivity to TKI can maintain these responses on lowed (and therefore less expensive) doses , and second to see if the ability to maintain these deep responses on smaller drug dosages can predict more accurately those who might be able to cease treatment in the longer-term. Although we predict that a sizeable minority (maybe 20%) might be managed long-term on lower doses, it is important to remember that actually stopping treatment long-tem is currently applicable only to a very small proportion of individuals. In all other patients treatment will be life-long.

Alternative therapies: prior to the introduction of imatinib the standard of care for the majority of patients with chronic phase CML was a life-long combination of hydroxycarbamide and interferon. Busulphan, an alkylating agent, was commonly used until the late 1980s and although this remains a useful cytotoxic agent in some situations, it became a less popular choice for early phase disease because of toxicity. With optimal use of interferon, approximately 10-15% of patients achieved CCyR. Patients who obtained a CCyR or even a partial cytogenetic response (> 65% Ph-negative) experienced a statistically significant improvement in survival compared to those with lesser or no

cytogenetic responses. Unfortunately interferon is a poorly tolerated drug with both short and long-term side effects and in retrospect was probably used less frequently in elderly patients. The overall survival of patients treated with interferon is 6-7 years but the median survival of those who achieved CCyR on interferon is greater than 10 years. Exact data for patients in CCyR on interferon is no longer available as many converted to imatinib when it became available. These data remain critically important because they reflect the ability to use CCyR as an accurate prediction of long-term survival. The value of CCyR as a surrogate marker of survival has now been confirmed for imatinib (see below).

Approximately 30% patients with CML are suitable for allogeneic stem cell (bone marrow) transplantation. In contrast to best responses on interferon (and indeed imatinib), patients surviving a transplant are considered to be cured. Suitability is based on age and the availability of an HLA-matched donor (related or unrelated). The success of transplant is clearly associated with a number of factors including age, disease phase, source of donor, time to transplant and gender match of donor and recipient (collectively known as the EBMT score). Patients defined as good risk by these factors could expect a survival in excess of 80% at 5 years. Patients with poor risk factors had inferior survivals (largely due to transplant related mortality) but certain of these factors also conferred a poor survival on interferon (disease phase and disease duration), and without transplantation the disease was inevitably fatal. Because of this, transplant remains an important consideration in the management of patients but there is no doubt that procedural related mortality continues to be an obstacle to its widespread use.

Use of surrogate makers of survival: because the survival of patients who achieved CCyR on interferon was better than in patients without such cytogenetic responses, the prediction was that patients who achieved CCyR on imatinib would have a similarly prolonged survival. With prolonged follow-up this prediction was confirmed. Overall duration of chronic phase can now only be estimated statistically but would appear to be in excess of 12 years. In 2006 a group of international experts achieved a consensus regarding the management of newly diagnosed patients and advised that imatinib should become the first line therapy for all. This consensus statement is colloquially known as the ELN guidelines (Blood 2006 108:1809-20).

Intolerance to and failure of imatinib: although the results of imatinib are remarkable, some 20-25% of patients fail to achieve CCyR (perhaps 10% because they cannot tolerate the drug and 15% because the drug is ineffective) and 10-15% will lose this excellent response. As a result perhaps 35-40% of patents will require alternative therapy. The most recent information available from the IRIS study (the seminal phase III randomized study of imatinib versus the previous best treatment, interferon and cytosine arabinoside) showed that at 8 years only 55% of patients remained on imatinib within the study. Although some of these patients came out of the study but remained on imatinib (because of the drug becoming commercially available during the time course of the trial) it is fair to say that with time, tolerability of imatinib has become a real problem for many patients. Compared to conventional cytotoxic drugs and to interferon, imatinib is well tolerated with approximately 90% of patients able to take the drug long-term without Grade 3 or 4 side effects. However there are some rather common side-effects that may not reach grade 3 or 4 severity but are intensely debilitating over a prolonged period. These include profound fatigue and lethargy, and gastrointestinal disturbances such as nausea, abdominal cramps, frequency of bowel motion and diarrhoea. Such side-effects interfere with quality of life and the ability to lead a normal life but

when there was no alternative effective therapy patients were prepared to tolerate these toxicities (although there are now increasing concerns regarding compliance). The Phase I and II studies of the 2G-TKI indicated that side-effects experienced on any one of the drugs are not necessarily experienced on any of the others. Now that dasatinib and nilotinib have become available as second line treatments patients have changed treatments and in many cases find the second generation TKI (2GTKI) much better tolerated.

With specific reference to patients in whom imatinib is ineffective, i.e. imatinib failures, the mechanism of resistance is not clear in the majority of patients. A significant minority of patients in chronic phase and a higher proportion of those in advanced phases, demonstrate mutations in the Abl kinase domain rendering the enzyme partially or completely resistant to imatinib. More than 50 different mutations rendering complete or partial insensitivity to imatinib have now been described. The 2G-TKI were designed to achieve kinase inhibition in the presence of these mutations and were initially available through Phase I and II clinical trials. They achieved useful responses including CCyR in approximately 50% of patients in chronic phase with imatinib resistance and in higher proportions of those with imatinib intolerance, and these responses were achieved irrespective of the presence or not of mutations. Although it is important to emphasise that the development of a mutation that renders the individual resistant to a 2GTKI is a relatively rare event, patients who received a 2GTKI because of a mutation-related resistance to imatinib are more likely to develop a further mutation rendering resistance to the 2GTKI than those who never had a mutation. The spectrum of mutations is rather different and predictably there are many fewer individual mutations (because dasatinib and nilotinib were known to be effective in the presence of most of them). Also certain mutations arise on treatment with nilotinib (E255K/V, Y253H, and F359C/V) which are sensitive to dasatinib, and others arise on dasatinib (V299L, F317I/L) that are sensitive to nilotinib. This is one reason why availability of both of the currently licensed 2GTKI is important. A few patients develop the T315I mutation which is resistant to imatinib, bosutinib, dasatinib and nilotinib. Phase II studies are currently underway with the latest TKI, ponatinib, that does inhibit this particular mutation.

Disease progression: patients destined to progress who present in, or who progress to, accelerated phase or blast crisis, have a much worse prognosis than those in chronic phase. Accelerated phase clearly contains a heterogeneous group of patients with considerable variation in their survival. Some patients presenting in, or progressing to acceleration without prior exposure to imatinib, can respond very well to the drug and have prolonged survivals not dissimilar to those of chronic phase patients. However the majority of patients in acceleration will eventually experience disease progression to blast crisis Patients who progress to accelerated phase on imatinib do not respond to increased doses and require alternative approaches. These include allogeneic stem cell transplantation, 2G TKI, AML-like chemotherapy, hydroxycarbamide, busulphan, homoharringtonine or experimental therapy. Patients presenting in or progressing to blast crisis have an extremely poor prognosis. They are treated with high dose imatinib (if no prior exposure), 2G TKI AML-like chemotherapy, high dose hydroxycarbamide etc but none of these approaches achieve long-term remission. The only chance of long-term survival is some form of therapy to restore a second chronic phase followed by an allogeneic transplant form a related or unrelated donor, but the procedural related mortality and risk of leukaemia recurrence are high.

An important finding from the IRIS study was that the chance of progression to advanced phase is highest in the first 2-3 years after diagnosis. As no patient will die of their disease whilst in chronic

phase, the only way to reduce disease related deaths is to intensify treatment early after diagnosis in all patients or have some way of pre-selecting these patients with inherently poor prognosis (by clinical parameters or biomarkers) so that treatment can be intensified on an individual basis. This is not currently possible for all patients. However two clinical risk scores (Sokal and Euro/Hasford) have been widely used for many years and their prognostic value has been confirmed in the TKI era. Although patients with high risk Sokal/Euro scores can respond well and durably to imatinib, as a group they are more likely to fail imatinib or to lose previously established responses. A cogent argument can be made for treating these patients as aggressively as possible at diagnosis.

2GTKI as first line therapy: the ability of the first of the 2GTKI, dasatinib and nilotinib, to durably rescue 50% of patients who were resistant to and/or intolerant of imatinib, led logically to phase III studies of their use in newly diagnosed patients. DASISION randomised patients to imatinib 400mg daily or dasatinib 100mg daily and ENESTnd randomised patients to imatinib 400mg daily or one of two doses of nilotinib, 300mg bd or 400mg bd. Both studies reported 12 month data in the New England Journal of Medicine confirming that each of the 2GTKI had superiority over imatinib in terms of rates of complete cytogeneic and major molecular remissions. The two year data have been presented at major international haematology meetings and the three year data for nilotinib will be presented at the American Society of Haematology in December and for dasatinib at ASCO in June 2012.

Because the 2GTKI are more potent than imatinib, both were expected to achieve cytogenetic and molecular remissions faster than imatinib. The outstanding questions related to whether with time, they would achieve these remissions in more patients (i.e, would the rates of remission on imatinib catch up over time with those on the 2GTKI), would the remissions be durable and would the 2GTKI be tolerated as well as imatinib over a longer period of time.

The two year data for dasatinib continue to show superior major molecular remission (MMR) (3 log reduction in tumour load) rates at 64% for dasatinib compared to 46% for imatinib. Importantly the rates of a 4.5 log reduction in tumour load are higher for dasatinib at 17% than for imatinib at 8%. This particular milestone is important because this is the level of tumour load reduction that renders a patient eligible for consideration of stopping therapy in the longer term. Very few patients have lost MMR and none have lost a 4.5 log reduction in tumour load. Dasatinib was equally well tolerated as imatinib so concerns about excess toxicities appear unfounded, at least in the short term. The two year data for nilotinib are equally as impressive. MMR rates are 44% for imatinib and, 67% and 71% for the 400mg bd and 300mg bd doses of nilotinib respectively. A 4.5 log reduction in tumour load was seen in 10%, 21% and 26% of patients randomised to imatinib, nilotinib 400mg bd and 300mg bd respectively. Responses were durable and both imatinib and nilotinib 300mg bd were equally well tolerated. Nilotinib at 400mg bd had more toxicity but no better efficacy than at 300mg bd, hence the decision of Novartis to recommend 300mg bd as the standard starting dose.

The data clearly remain relatively immature but confirm the expected superiority of 2GTKI over imatinib in the first line setting. Early concerns about tolerability appear unfounded and indeed both trials have very good data to suggest that the incidence of grade ¾ toxicity falls with time, such that very few patients developed toxicity in the second year. Both studies show a decrease in the rate of disease progression in the first two years of the 2GTKI compared to imatinib and we would expect this eventually to be reflected in survival. This difference reaches statistical significance in ENESTnd

(and indeed in the BELA study of imatinib versus bosutinib) but is a trend in DASISION. A major problem in designing trials in CML is that the survival is so good with first line imatinib (as patients failing this will receive a 2GTKI or a transplant and be salvaged) that many years will have to elapse before a survival advantage can be demonstrated. Thus it is important to consider surrogate marker such as CCyR rates. In addition, although progression to advanced phase is now a rare event in CML, the ability of the 2GTKI to reduce this rate in the first two years is very important, as these patients cannot be rescued through salvage therapy.

In summary I am in favour of both drugs being available for upfront treatment of newly diagnosed patients.

Appendix D – Clinical specialist statement template

Dasatinib, nilotinib and standard-dose imatinib for the first line treatment of chronic myeloid leukaemia (incl part-review of TA 70)

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Richard E CLARK

Name of your organisation Royal Liverpool University Hospital

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **Yes**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **Yes**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? **No**
- other? (please specify)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Current first line standard treatment is imatinib 400mg daily (NICE approved; TA 70). There is no geographical variation, nor any disagreement amongst professional about this, except on whether the current appraisal technologies might be superior. The alternatives to imatinib first line are all inferior; hydroxycarbamide and interferon both offer an inferior progression-free and overall survival, and allogeneic transplantation has a mortality of about 20% upward.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Patients who are already have advanced disease at diagnosis have a high chance of losing a response to imatinib, and transplantation is preferred wherever feasible. Other than that, there aren't really any different subgroups except that patients fare worse if they present with skin or other extra-haemopoietic sites of disease, or with additional chromosomal abnormalities beyond a single Philadelphia translocation.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Only in haematology clinics, under supervision of a consultant haematologist. No special additional professional groups are required.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

The two technologies are already available, and there is considerable experience in their use in CML. However, this is almost entirely in the setting of imatinib resistance / intolerance (i.e. second line); nilotinib though not dasatinib is NICE approved in this setting (FAD; under appeal currently).
However, there is an ongoing national trial (SPIRIT2; 510 patients recruited as of Sept 2011) in which 50% of patients receive dasatinib as first line therapy. Prior to this there was a smaller trial in which 50% of patients received nilotinib first line.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

To my knowledge, there are currently no UK guidelines that comment on the current technologies as first line agents. These may be awaiting this current NICE appraisal!

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Both the current appraisal technologies will not pose any particular problems; they (like standard imatinib) are oral therapies. Very few drug interactions are problematic; problems have been confined to strong modifiers of CYP isoenzymes, e.g. for epilepsy control, but this appears no different from standard imatinib.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

There is no need for any new stopping/ starting rules, as these aspects are similar to those for existing imatinib. No additional tests are needed; patients likely to develop side effects cannot be identified in advance.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

I don't think anyone will have experience of either of the technologies for first line treatment, outside of the context of a clinical trial; certainly not in the UK. SPIRIT2, the current randomised phase III trial of dasatinib vs. imatinib, has recruited 510 UK patients. The 2 other randomised phase III trials of these technologies (DASISION and ENESTnd) both recruited in 25+ countries, some of which may have had somewhat differing health care systems to that in the UK. These trials have used sensible though surrogate endpoints (complete cytogenetic remission and major molecular response rates). The use of these surrogate endpoints was aired during the recent appraisal of these technologies as second line agents; good though indirect data support their use to predict long term progression-free survival.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

In general, both drugs are well tolerated. Earlier concerns about cardiac safety have not been confirmed in subsequent datasets; nevertheless the nilotinib 'black box' warning, though unjustified, persists.
Of greater practical importance are significant pleural effusions in about 12% of dasatinib treated patients (so best avoided in heart failure and significant lung disease) and the ~1% risk of pancreatitis with nilotinib.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

I am unaware of any such additional material.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

If approved, either technology could be readily implemented as a straight substitute for existing standard imatinib. No special training or additional resources would be needed.

Dasatinib, nilotinib and standard-dose imatinib for the first line treatment of chronic myeloid leukaemia (incl part-review of TA 70)

A Personal Statement – Sandy Craine

Background

My treatment pathway could be described as an object lesson in the heterogeneity of CML as a disease and its varied treatment pathways, as well as a pertinent example of the shift in therapy brought about by the success of the the phase 1 clinical trials (Druker et al 1998) which proved the concept that inhibition of tyrosine kinase inhibits the production of bcr/Abl (the oncogene identified as the marker of Ph+CML) which translates into progression free survival over the long term for the majority of patients diagnosed in chronic phase.

I was diagnosed with Ph+CML in late chronic phase in December 1998. I have been treated at the Hammersmith Hospital London since that time.

I considered myself to be asymptomatic, although I did feel unusually tired and had recently experienced some abdominal discomfort. Although these symptoms were rather nebulous the abdominal discomfort prompted me to consult my GP. She identified an enlargement of my spleen and referred me to my local hospital for blood tests. Although I was not aware at this stage that this might be indicative of a possible life threatening disease, the urgent call from the hospital asking me to attend the haematology clinic did raise feelings of alarm.

Within 24 hours I was diagnosed with Ph+ CML in accelerated, or at least late chronic stage. Fortunately, I was referred for treatment to Professor John Goldman at Hammersmith Hospital, a world renowned centre of excellence in CML.

In January 1999, I was told that my prognosis was that, without a stem cell transplant, the only available intervention that might halt progression to blast phase, I would be unlikely to survive beyond 12 months.
Neither Interferon Alpha, nor HU were considered appropriate therapies.

I was extremely fortunate to be within the very small percentage of people who have a sibling with a closely HLA matched profile and who was willing to donate his own stem cells in order to save my life.
Preparations were made to collect his stem cells, which were successfully harvested and safely stored within the specialist facility.

A rational treatment pathway- my experience.
I was disturbed by the overall mortality and morbidity figures for stem cell transplantation in CML and, although I was reassured by the excellence of the transplant unit and by the haematology team's expertise, I was still unsure whether this was the only treatment option available to me. My consultant was sympathetic and respected my need to take time to come to terms with my diagnosis. Plans for the SCT were put on hold, although I was carefully monitored to make sure my disease did not progress
further.

I was aware that phase 1 clinical trials of a 'revolutionary' oral therapy (STI571-i matinib) had opened in the USA and that the initial patient cohort were responding very well. I discussed the trial with my doctors, who were cautiously supportive of my enrolling in the phase ll trial. In August 1999 I traveled with my family to Portland Oregon, USA and was enrolled as the first patient on a phase ll trial of imatinib for accelerated Ph+CML.

Imatinib (400mg) produced a complete haematolgical response within 4 weeks and within 8 weeks all evidence of blast cells had retreated from my marrow and I returned to the UK for ongoing care, still within the clinical trial.

Over the next 12months and with an increase in dose to 600mg, I had a major cytogenetic response and within 16 months reached CcyR. By early 2001, I had achieved MMR and remained on 600mg imatinib.

In early 2003 my molecular results were becoming less stable. An imatinib resistant break-point mutation was identified and I was advised that over time I would relapse into PH positivity and my disease would progress.

At that point, neither dastatinib nor nilotinib were in clinical trial and I was advised to go ahead with my previously planned stem cell transplant.

The Leukaemia Unit at Hammersmith had an ongoing combination study open using non myeloblative (low intensity) stem cell transplantation + initiation of 400mg imatinib at day 35 post transplant for 11months + on reactivation of the disease (likely) incremental infusions of the donor's previously banked mature lymphocytes- a process called DLI would be given to to eradicate the residual disease.

The question was whether, given that I had developed an IM resistant mutation, I would, after the transplant, regain sensitivity to imatinib.

No one could be sure of the answer to this question but the consensus was, thanks to 3 years treatment with imatinib which had reduced my disease to a very low molecular level, the preconditioning treatment with chemotherapy drugs prior to SCT, would destroy most, if not all, the marrow

cells. Therefore IM resistant cells would be dealt with, at least for a long enough period post transplant to ensure that DLI (donor lymphocyte infusions) would have time to produce a Graft vs Leukaemia effect and eradicate all residual disease.

Prolog

I was enrolled in the study and responded well. I have been negative for bcr/abl since 2005 and considered to be CML free, although I still hesitate to use the word 'cure'.

I do not need to take any drugs to maintain my current bcr/abl negative status, but I am always mindful that there remains a potential for relapse, even from a successful stem cell transplant. However, I am confident that should I ever relapse and find my life is once again threatened by CML , it would be successfully controlled by TKI therapy.

NOTE. According to data from ongoing clinical study and clinical practice, my particular IM resistant mutation (Y253H) is controlled better by dasatinib rather than nilotinib.

Technology Appraisal Report.

I understand this report has assessed three tyrosine kinase inhibitors (TKIs) that are currently authorised as first line (imatinib) and second line (nilotinib and dasatinib) use in Ph+ CML in the UK.

I hope that my treatment experience as described above illustrates the dramatic changes ushered in by this innovative therapy over the last 12 years. Treatment with TKIs represents a paradigm shift in the management of CML which has undeniably been responsible for improved patient outcomes on an international basis.

CML was, just over a decade ago, a rare but fatal disease for those 1-2 per 100,000 per population who are unfortunate enough to develop it.

For those eligible for stem cell transplantation, the risks of transplant related mortality and morbidity remained high, even for those transplants judged as a success, chronic GVHD had an unacceptable impact on quality of life.

Nilotinib and dasatinib, as 2nd generation TKIs, represent examples of ongoing technological innovation, showing an undeniable improvement in the depth and speed of molecular responses year on year, in particular in newly diagnosed CML in CP.

I continue to follow developments in therapy and am acutely aware of the responses of patients who are on these newer drugs. The majority of patients currently treated with imatinib do not need to change therapy and get access to 2nd or 3rd line treatments.
Some 60% of patients currently prescribed imatinib as 1st line therapy continue to maintain their MMR/CMR responses.

Patients are very well aware of the constraints under which their clinicians operate, but nevertheless recognise the transformative possibilities offered by TKI therapy in ensuring the most desired 'patient relevant outcome' i.e of maintaining the routine of everyday (normal) life over the long term and into the foreseeable future, in other words, a functional cure.

Second generation TKIs can further increase the percentage which forms this majority, not simply because of their clinically measurable increases in efficacy over imatinib, but because the molecular targets of both inhibitors extend far beyond those for which imatinib targets.

It is the minority (40%) of this patient population, who will derive particular clinical benefit from dasatinib and/or nilotinib. Patients for whom imatinib has either an intolerable side effect profile, and/or will never produce the desired optimal molecular response. For this group of patients, both drugs represent an innovative

transformation of the previous therapeutic landscape that existed before their development and availability.

Access to TKI therapy means, for the majority of patients diagnosed in chronic phase, that CML is rendered, at worst, an inconvenience rather than a terminal disease.

As Director of CML Support Group, I endorse the CML Support Group comment on the TAR.

Sandy Craine

18th October 2011

Dasatinib, nilotinib and standard-dose imatinib for the first line treatment of chronic myeloid leukaemia (incl part-review of TA 70)

Personal Statement – Richard Willoughby (CML Patient)

Introduction

I am a CML patient. I was diagnosed aged 42 in May 2009, in chronic phase, and have been on 400mg imatinib since. I am treated at the Hammersmith Hospital, with joint care at the West Middlesex. My response has been excellent: my leukaemia has been undetectable by PCR (PCRU, also complete molecular response or CMR) since early November 2009.

I understand this appraisal to be assessing the various tyrosine kinase inhibitors (TKIs) currently authorised for first line treatment of CML in the UK and that I may be able to assist the Committee with a patient's perspective on these technologies. As a patient on standard dose imatinib, my story is perhaps illustrative of the dramatic change TKIs have brought to CML treatment and patient outcomes. I am also well aware of second generation TKIs since, like many patients, I follow developments in therapy with great interest, and hear the stories of patients who are on these newer drugs.

Treatment on imatinib - my story

I was diagnosed at my local hospital, the West Middlesex. However, as it was quickly recognised that I have an atypical translocation, I was referred to the Hammersmith. It was felt that the experts at the Hammersmith would be in the best position to advise on treatment for my particular CML. They see the widest variety of CML patients, are experts in the disease, and were best placed to say which of the various drugs might work best for me, and/or whether an alternative approach might be necessary.

The experts at the Hammersmith immediately reassured me that there was no reason why I should not do well on the standard of care, 400mg imatinib. They took me through the various expectations and stages in response to imatinib, and explained that should it not work, there were various options, including increasing the dose, or changing to a second generation TKI such as dasatinib or nilotinib. I felt particularly reassured that these experts were fully

on top of the latest developments in CML therapy and that they really knew how to manage the condition, which drugs to choose and how to use them.

Older treatments such as hydroxyurea and interferon were not presented as an option at all (hydroxyurea wasn't even mentioned) whether first, second or third line, as they have no prospect of changing the course of my disease. A bone marrow transplant was very much presented as a last resort. The chances of finding a donor and the risks associated with the procedure in terms of morbidity and mortality, as well as long term complications, made it very unattractive indeed. I was told transplants are almost never suggested as first line therapy, and increasingly rarely second line without trying second or third line TKI therapy first. What was presented was a treatment plan that meant starting on one TKI, to be followed, if necessary (and hopefully not), by a second or third TKI. Only after that would other options be considered. Based on what I have heard about patient care outside the UK, this is in accordance with what goes on elsewhere in developed countries at least.

The Hammersmith also offered me a clinical trial comparing dasatinib and imatinib for first line use, although I declined. I felt it important, with my condition, to keep my options open. I was told about the second generation TKIs, which were intended initially for resistance or intolerance, but which also were more potent. Knowing these were around as a second or third option definitely comforted me but I decided to try the standard of care first.

Like all CML patients, initially I was very anxious. I had lots of worries. Would my CML respond? Would I be able to tolerate the drug? What if I didn't respond? What about my family? There is a stark realisation that your life depends on taking a pill every day.

As the months went by, and my doctors saw my response, I became less worried. Indeed, my response to imatinib has been remarkable. I achieved complete haematological response in about 3 weeks and CMR in less than 6 months. I know this puts me in the top group of imatinib responders, and from everything I have been told and read, while there are no guarantees of course, my prospects seem very good. This is particularly remarkable when coupled with the fact that in the 2 ½ years since my diagnosis I have had less than two weeks off work because of CML, and those were in the initial stages pre and immediately post diagnosis, in particular taking a little time to recover from bone marrow biopsies. Now I simply have routine follow up appointments every three months or so.

I have had a few minor side effects on imatinib. My neutrophil count dropped a little below normal but recovered quickly. Now, while I get the peculiar imatinib muscle cramps, nausea from time to time, occasional stomach upset, and acid reflux (treated with omeprazole), I experience little inconvenience other than having to take my pill each day. These are a small price to pay indeed for what I have received in exchange – successful management of what was a fatal condition, and without having either to endure the debilitating effects of chemotherapy (or interferon) or run the very considerable risks, and face the complications, associated with a bone marrow transplant. My daily life is barely affected. There is now even the possibility that I may be able to stop therapy altogether in due course.

It never ceases to amaze me how incredible and amazing this is and that patients diagnosed in 2011 and beyond have such dramatically different prospects compared to those diagnosed 20 or even 15 years ago, because of the developments in TKI drug therapy. Not only are their prospects for survival dramatically better, this can be achieved with relatively little impact on their daily lives. The drugs exist that will allow all this to happen for the vast majority of patients, and new ones are being developed to help yet more patients. I feel very lucky to have been diagnosed in this era and not before the advent of TKIs.

Second generation TKIs - dasatinib and nilotinib

Right at the outset I was made aware that imatinib doesn't work for all CML patients, and that some cannot tolerate the drug. I was also told that the depth of response can vary, and everything I have read since has reinforced that view. While I believe this is being actively worked on, I don't think it is possible to tell at the outset which patients may do better on which drugs, who may have an intolerance problem and who may develop resistance.

As a patient, it seems crucial to me, if we are to improve outcomes for more patients, that clinicians have the widest choice of therapy. While it may not be possible to tell which TKI may work best for which patient, patients know that failure on one doesn't necessarily mean failure on another. It is also becoming generally understood by patients that the second generation TKIs are better than imatinib in terms of overall response, in addition to their role in second line usage, where they are saving the lives of patients who fail or cannot tolerate imatinib. So what does all of this mean for patients?

First, and most importantly, the trials seem to show that the risk of progression to advanced disease, already low with imatinib, is even lower on the new drugs. I understand from reading about the ongoing trials that not only do dasatinib and nilotinib achieve deep responses (MMR or CMR) in more patients, and do so faster, they also reduce the progression rate in the crucial early years. Every patient wants to avoid progression – we know that advanced disease is so much harder to treat. I think of CML as a little bit like a nuclear reactor – if you can suppress the reaction involved it shouldn't ever get out of hand, but you must actively control it. If however you lose control and it gets out of hand, regaining control may be impossible. So, all patients want to get the best response and to keep it under control with the lowest risk of progression.

Secondly, of great interest for patients is the prospect of being able to reduce their dosage or come off therapy altogether, if they have a deep response. Patients are aware of the trial in France (STIM - or Stop Imatinib) which seems to suggest that those with the deepest responses to imatinib had a 50/50 chance of being able to stop therapy altogether. This is very exciting because it suggests a proportion of patients could be cured by drug therapy alone. I believe the UK is looking at a similar trial. If the number of patients who could "stop" therapy can be increased with second generation drugs (and trials indicate a greater number reach CMR and more quickly than on imatinib), the benefits for all are obvious.

For all these reasons, I believe the choice of appropriate therapy for a given patient should be placed firmly in the hands of the clinicians, and a decision taken in consultation with their patients. CML, and CML patients, are not uniform and it is the expert clinicians who know the best treatment strategies for a given patient. They should have all the options available. This means the widest choice of all available therapies so that optimal results, and accordingly better outcomes, with the best quality of life, can be achieved in greater numbers. More patients will survive, and more may be likely to be able to stop therapy. It is incredible that all this has become possible through the advent of TKIs, which have so dramatically changed outcomes for CML patients, and rendered the old therapies redundant.

Richard Willoughby
14 October 2011

Appendix K – Expert statement declaration form

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Multiple Technology Appraisal (MTA)

Dasatinib, nilotinib and standard-dose imatinib for the first line treatment of chronic myeloid leukaemia (incl part-review of TA 70)

Expert statement declaration form

Please sign and return by email to:
Laura.Donegani@nice.org.uk

If email is not possible, please return by fax to Laura Donegani, Administrator **on** 020 7061 9755
or by post to: NICE, Level 1A, City Tower, Piccadilly Plaza, Manchester, M1 4BD

I confirm that:

- I agree with the content of the statement submitted by **NHS North Yorkshire & York** and consequently I will not be submitting a personal statement.

Name: Diane Tomlinson

Signed:

Date: 22/September/2011