Cost-Effectiveness of Dasatinib and Nilotinib for Imatinib-Resistant or -Intolerant Chronic Phase Chronic Myeloid Leukemia

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ABSTRACT

Objectives: To estimate the cost-effectiveness of dasatinib and nilotinib compared with high-dose imatinib for people with chronic phase chronic myeloid leukemia, which are resistant to normal-dose imatinib and compared with interferon-α for people intolerant to imatinib, from the perspective of the UK National Health Service. Methods: An area under the curve partitioned survival model was developed to estimate the cost-effectiveness of dasatinib and nilotinib. Clinical effectiveness evidence was taken mostly from single-arm trials. Results: Both progression-free survival and overall survival are highly uncertain. In the base case, patients take nilotinib for much less time than dasatinib. Nilotinib is expected to dominate high-dose imatinib, yielding slightly more (0.32) quality-adjusted life years (QALY) at slightly less cost (£21,100 [pounds sterling]) per person. Dasatinib is predicted to provide slightly more (0.53) QALY at substantially greater cost (£48,900), yielding a very high incremental cost-effectiveness ratio of £91,500 QALY against high-dose imatinib. Cost-effectiveness, however, changes radically under the plausible assumption that the drugs are taken for the same time. For people intolerant to imatinib, nilotinib is expected to yield an incremental cost-effectiveness ratio of £104,700/QALY, and dasatinib £82,600/QALY compared with interferon-α. Further, both drugs represent poor value for money for a range of plausible structural assumptions. Conclusions: The model should be viewed as an exploratory analysis of the cost-effectiveness of dasatinib and nilotinib because it relies on many assumptions. Whilst clinical data remains immature, the cost-effectiveness of dasatinib and nilotinib for imatinib-resistant people is highly uncertain. Both nilotinib and dasatinib are highly unlikely to be cost-effective versus interferon-α for people intolerant to imatinib.

Keywords: chronic myeloid leukemia, cost-effectiveness, cost-utility, dasatinib, decision analytic modeling, Glivec, imatinib, nilotinib, Sprycel, Tasigna.

Introduction

Chronic myeloid leukemia (CML) is a form of cancer affecting the blood, which is characterized by excessive proliferation of white blood cells in bone marrow and circulating blood. The molecular hallmark is the presence of an acquired BCR-ABL fusion gene in myeloid progenitors. In the United Kingdom, an estimated 530 new cases of CML are diagnosed each year [1].

Traditionally, CML has been regarded as a progressive disease that evolves through three phases. The initial chronic phase, during which the disease is stable and slow to progress, is followed after a variable interval by progression through an accelerated phase to a rapidly fatal blast crisis. Most people (approximately 90%) are diagnosed during the chronic phase [2].

Imatinib was the first tyrosine kinase inhibitor in CML, and has been widely used. Trials of imatinib are ongoing, but current evidence suggests that people whose disease responds to treatment with imatinib may remain symptom-free for at least 10 years [3]. Current National Health Service (NHS) treatment options for CML include imatinib and allogeneic hematopoietic stem cell transplantation [4]. Stem cell transplantation is not a treatment option for many people. Resistance to imatinib is a well documented clinical problem and may be primary (initial refractoriness to imatinib) or acquired (develops during treatment) [5,6]. Imatinib resistance has been variously defined. For instance, in a recent clinical trial of dasatinib, imatinib resistance was defined as a lack of complete hematological response after 3 months of imatinib treatment, a lack of any cytogenetic response after 6 months of treatment, a lack of a major cytogenetic response (Ph-positive cells >35%) after 12 months of treatment, an increasing white blood cell count on at least two consecutive occasions or a relapse after a complete hematological response or major cytogenetic response [7]. Imatinib intolerance is frequently defined as at least grade 3 non-hematological toxicity or grade 4 hematological toxicity persisting for more than 7 days, related to imatinib at any dose [7]. Available treatment options for imatinib-resistant or -intolerant disease include dasatinib, nilotinib, high-dose imatinib (800 mg per day), interferon-α, and hydroxyurea. Dasatinib (Sprycel, Bristol-Myers Squibb Company, Princeton, NJ) and nilotinib (Tasigna®, Novartis Pharmaceuticals Corporation, East Hanover, NJ) are oral second generation tyrosine kinase inhibitors with activity against a range of tyrosine kinases. Dasatinib and nilotinib are licensed for the treatment of adults with chronic and acceler-
ated phase CML with resistance or intolerance to prior therapy, including imatinib, and who received accelerated approval for this indication by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) [8,9]. Dasatinib is also licensed for the treatment of blast phase CML.

The cost-effectiveness of dasatinib or nilotinib for treatment of CML has not previously been published in full by a financially independent research team. Bristol-Myers Squibb (BMS), the manufacturer of dasatinib, and Novartis, the manufacturer of nilotinib, recently made submissions to the National Institute of Health and Clinical Excellence (NICE), which included cost-effectiveness analyses for dasatinib and nilotinib [3]. In addition, dasatinib has recently been assessed as a good value for money compared with high-dose imatinib for patients resistant to standard dose imatinib in Sweden, according to a study with financial support from BMS [10]. The decision analytic model, and subsequent cost-effectiveness analysis, presented here formed part of the independent assessment report submitted to NICE (by the authors) and were used to inform the NICE Health Technology Appraisal process [3].

The analysis is confined to people starting treatment in chronic phase CML. We have not modeled people starting treatment in accelerated phase or blast phase CML because we found no appropriate clinical effectiveness data for a comparative treatment [3]. Based on advice from our expert advisory group, we chose high-dose imatinib as the most appropriate comparator for people resistant to normal-dose imatinib and imatinib-resistant for people intolerant to imatinib [3].

**Methods**

**Model structure**

An area under the curve partitioned survival Markov-type model (see for example [11]) was developed to model disease progression in CML and treatment effectiveness of all drugs. In this type of model, the number of patients in each health state at any time is determined directly from the underlying survival curves. This was preferred to a conventional Markov approach for two reasons. First, it bypassed the need to estimate transition probabilities and second, it avoided the need for additional assumptions, such as whether death was permitted from all health states. The model was written in Microsoft Excel (Microsoft Corporation, Redmond, WA). The structure of the model was informed by a review of the available literature, clinical guidelines for treatment of CML, and expert opinion on the clinical progression of the disease [3].

Five health states were used to represent progression of CML: chronic phase on second line treatment, chronic phase on third line treatment, accelerated phase, blast crisis, and death. At the end of each cycle people either remain in their current health state or move to a more severe state. The time between second-line treatment discontinuation and death is treated as a single meta-state, comprising chronic phase on third-line treatment, accelerated phase, and blast crisis. This means that, in terms of its internal logic, the model has only three states: chronic phase on second-line treatment, death, and all time in between. Once occupancy of these states has been calculated, the post–second-line discontinuation (pre-death period) is split into three parts: first, a period estimating time in blast crisis is deducted, then time in accelerated phase is deducted, and time on third-line treatment in chronic phase is estimated as the remainder. For simplicity, for the purposes of discounting, it is assumed that all people enter accelerated phase and blast crisis just before the mean overall survival time for each treatment. It is necessary to model time on third-line treatment in chronic phase because the definitions of progression included criteria other than development of accelerated phase CML [3], and clinical experience indicates that people may spend several years in the chronic phase after developing signs of “progression,” which results in treatment cessation (see Figure 2 in Jabbour et al. [12]).

Two separate models were implemented: one simulating a cohort of people resistant to normal-dose imatinib, and one simulating people who are intolerant to imatinib. All people enter the model in chronic phase CML on second line treatment, having failed on treatment with normal-dose imatinib. In common with the clinical trials of dasatinib and nilotinib, the male to female ratio was assumed 1:1 and people were assumed to start second-line treatment aged 56. People were modeled until age 100, giving a 44-year horizon (effectively lifetime), and a 2-month model cycle (short enough to capture all clinical events), with half-cycle corrections. Future costs and benefits were discounted at 3.5% per year [13].

Follow-up of trials of dasatinib and nilotinib are short, and patients typically survive for many years with chronic phase CML. Therefore overall survival was very immature at data cut-off (e.g., 89% alive after 2 years on dasatinib for imatinib-resistant patients and 88% alive after 1.6 years on nilotinib imatinib-resistant patients). Consequently, we did not extrapolate the empirical overall survival. Instead, overall survival was estimated according to the proportion of people for each treatment that achieved a major cytogenetic response (MCyR), a known surrogate for overall survival [3,14,15]. In summary, Weibull curves were specified for CML-crisis mortality for responders (achieving a MCyR) and non-responders (not achieving a MCyR). In common with Anstrom et al. [15], we assumed a constant hazard ratio between these curves. A review of trials of normal-dose imatinib yielded a pooled estimate of the hazard ratio as 0.370 (95% confidence interval [CI], 0.156–0.876) [3]. We applied this hazard ratio to all treatments. Next, these curves were adjusted for non-CML mortality [3,16]. Finally, the Weibull parameters were estimated by calibrating the modeled overall survival for high-dose imatinib against the empirical overall survival for high-dose imatinib from Jabbour et al. [12]. This trial was selected because it provides the longest available estimate of overall survival in a population taking a tyrosine kinase inhibitor in a population who have failed on normal-dose imatinib. The overall survival curve for any treatment was then calculated as the sum of the overall survival curve for responders and the curve for non-responders, weighted by the proportion of people achieving a MCyR for that treatment.

Duration of treatment is a key input in the estimation of the costs of the drugs. In the trials, all drugs were taken until disease progression, occurrence of serious adverse events or death. Therefore, the estimated treatment duration survival curves were based on the extrapolated progression-free survival (PFS) from the relevant trials. The projected PFS curve for those people who stopped treatment due to adverse events or other causes was deducted, weighted by the proportion of people who stopped treatment for each drug. Ideally, the PFS curve for those people who stopped treatment due to serious adverse events or other causes would be assumed to follow the PFS survival curve for no active treatment. Given that such data is unavailable, however, the curve was assumed to follow the modeled overall PFS for interferon-α, where we assumed that interferon-α delays progression only slightly compared with no drug treatment. Following consultation with our expert advisors, we assumed that patients would stop drug treatment mostly due to serious adverse events, at 3 months.

PFS was estimated allowing for general mortality and separately for progression excluding general mortality. PFS for high-dose imatinib was estimated as follows. First, PFS excluding general mortality was assumed to follow a Weibull curve. Similar to the estimation of overall survival above, overall PFS (including general mortality) was calculated from progression excluding general mortality plus the rate of general mortality. Next, this overall PFS was compared with the empirical PFS from Jabbour et al. [12]. Then, the parameters of the Weibull curve for PFS, which excludes general mortality, were estimated by regressing the expected
populations should be obtained; where possible data should rep-
separate parameter inputs for imatinib-resistant and -intolerant
on each drug and patient population.

We found no data on the time people spend in accelerated phase
and blast crisis following chronic phase treatment with dasatinib,
nilotinib, and high-dose imatinib. This is not surprising because
these drugs are relatively new, and people typically take many years
from diagnosis to reach these health states. In common with other
models of the cost effectiveness of treatment for CML [17–20], time
spent in accelerated phase and blast crisis was assumed independ-
ent of treatment arm. This assumption seems reasonable, given
that second line treatment typically stops several years before people
enter these health states. In particular, mean times in accelerated
and blast phases of 9.6 and 13.1 months respectively were assumed,
taken from a previous cost-effectiveness analysis in CML in which
these values were estimated from published survival curves [20].

In the base case, the costs of treating adverse events, and the
disutility associated with their incidence are not explicitly in-
cluded, except via a lower utility while on treatment with interfer-
on-α compared with the other drugs. This simplifying assumption
was adopted for the following three reasons: (1) the incidence of
serious adverse events on high-dose imatinib, dasatinib, and nilo-
tinib is relatively low [3]; (2) clinical opinion suggests that the cost
of treating people with these adverse events is likely to be low; (3)
given the substantial model structural and parameter uncertainty,
modeling the costs and disutilities associated with adverse events
would introduce spurious accuracy.

Ideally, the parameter inputs would have been drawn from
randomized trials directly comparing the various treatments sim-
ulated in the model. In the absence of such evidence, we were
regrettably forced to rely on estimates taken from a heterogeneous
collection of observational studies with single arms (or single rel-
vant arms). Some of the guiding principles for the derivation of
model inputs were as follows: derive as many parameters as pos-
sible from the same trial for a given treatment; wherever possible,
separate parameter inputs for imatinib-resistant and -intolerant
populations should be obtained; where possible data should rep-
resent a large sample size and long follow-up. Patient baseline
characteristics for the relevant trials are given in the online Ap-

Clinical effectiveness

Major cytogenetic response rates. Our systematic review of clinical
effectiveness identified several trials in which MCyR is reported
for each treatment [3]. It is important to recognize that MCyR rates
reflect best-ever status on treatment (as opposed to current status
at the time of analysis). This means that, as follow-up extends,
response rates can only increase. Hence, it was imperative to use
model parameters with MCyR rates that represent the likelihood
of response at a single, uniform juncture for each comparator. On
scrutiny of the evidence, we selected 12 months as the follow-up
time that could most accurately be derived or approximated for
each of the comparators for imatinib-resistant CML; and 6-month
follow-up for imatinib-intolerant CML (as MCyRs were available
only at this follow-up time in the trials; Table 1).

Treatment duration. Here, we explain our choice of PFS and our
choice of rates of premature discontinuation from treatment, both of
which are used to estimate treatment duration, as explained above.
For dasatinib and nilotinib, PFS split according to imatinib-resistant
and -intolerant people from the relevant clinical trials are not pub-
lished [21,22]. Instead, for dasatinib, the following PFS data was used,
which was provided in the submission of Bristol-Myers Squibb to
NICE [23]: 0.77 for imatinib-resistant people and 0.87 for imatinib-
intolerant people at 2-year follow-up. For nilotinib, the following PFS
data was used, which was provided in the submission of Novartis to
NICE [24]: 0.864, 0.769, and 0.632 for imatinib-resistant people and
0.951, 0.906, and 0.845 for imatinib-intolerant people at 6, 12, and 18
months, respectively. For high-dose imatinib, the full Kaplan-Meier
PFS curve over 7-year follow-up from Jabbour et al. [12] was used, the
same trial from which the MCyR was sourced. For interferon-α, the
full Kaplan-Meier PFS curve over 2-year follow-up from the Interna-
tional Randomized Study of Interferon and STI571 (IRIS) trial [6] was
used, our source for other parameters for this treatment.

The treatment withdrawal rates at 3 months were taken from
the same trials as those for PFS, except for high-dose imatinib
which was calculated as a pooled estimate over several trials of
high-dose imatinib [3], given that the withdrawal rate is not re-
ported in Jabbour et al. [12]. The rates were 10.2% dasatinib, 23.2%
nilotinib, 14.8% high-dose imatinib, 55.3% interferon-α.
Health state utilities
A review of the literature identified six sources of utility values for CML [3]. From these, the following utilities were chosen for people in chronic phase: for dasatinib, nilotinib, and high-dose imatinib, 0.85 (standard error of the mean [SE], 0.004), for the interferon-α arm; on second-line interferon-α treatment, 0.71 (SE, 0.008), for the interferon-α arm; on third-line treatment, 0.85 (SE, 0.004). The utility for all people, regardless of treatment arm in accelerated phase, was 0.73 (SE, 0.06) and in blast crisis 0.52 (SE, 0.08). These data were collected during the IRIS trial, as reported elsewhere [19,20] and used in a previous assessment of imatinib for CML [25]. The utilities are drawn from a large sample of people, using the EuroQol five-dimensional questionnaire (EQ-5D), which is preferred in the NICE reference case [13]. Given that utility values for people taking dasatinib and nilotinib in chronic phase are not cited in the literature, we set these values equal to the value for high-dose imatinib in chronic phase based on clinical opinion and the similarity of the incidence of adverse events by treatment.

Resource use and costs
Assumptions for resource use were based on expert opinion and are given in Tables 2 and 3. The perspective for costs is that of the UK NHS and personal social services.

Based on a sample of UK clinicians, Bristol-Myers Squibb assumed that third-line treatment would cost £2079 (pound sterling) per 2 months, and would consist of tyrosine kinase inhibitors, hydroxychemamide, and stem cell transplantation. We have also made this assumption (Table 3).

For consistency between the costs of second line drugs and clinical outcomes, it is necessary to model the amounts of the second line drugs actually taken while on treatment in the relevant clinical trials. The dose intensity of a drug is defined as the amount of drug administered in a clinical trial as a proportion of the amount that would have been administered if there had been no dose reductions or dose interruptions. The dose intensity estimates are taken from the same trials from which we sourced the MCyR (Table 1). Ideally, mean dose intensities would be used in our model,

Fig. 2 – Base case cost-effectiveness acceptability curves for (A) imatinib-resistant and (B) imatinib-intolerant people. Costs are given in pounds sterling (£). QALY, quality-adjusted life years; WTP, willingness-to-pay threshold.
ties are used for all drugs except high-dose imatinib. The et al.[12]. In summary, the following dose intensities were chosen: was used for high-dose imatinib, calculated from Figure 5 in Jabbour tinib 92% (SE, 1.3%), and interferon- Interferon- dasatinib 100% (SE, 2.0%), nilotinib 100% (SE, 1.3%), high-dose ima- inantly described[11]. The cost of a single district nurse visit during cases, administration is carried out by district nurses, as previ- munity nurse)[26]. Inflating this value to 2009 to 2010 prices[26], 2006 to 2007 is quoted as £24 in pound sterling (Schema 9.1, Com- 2-month model cycle of £409. We do not adjust the cost of admin- estimates £27 (SE, £3) per visit. This implies an average cost per and therefore incur no administration costs. Interferon- is taken at home. We assume that 75% of people administer inter- ranges of dose intensities across all people in the trials. Dasatinib, nilotinib, and high-dose imatinib are all taken orally, and therefore incur no administration costs. Interferon-α dose and administration schedules are taken from the IRIS trial, with the assumption (based on clinical opinion) that interferon-α will be taken at home. We assume that 75% of people administer interferon-α themselves, or with the help of a care giver, and in 25% of cases, administration is carried out by district nurses, as previ- ously described[11]. The cost of a single district nurse visit during 2006 to 2007 is quoted as £24 in pound sterling (Schema 9.1, Community nurse)[26]. Inflating this value to 2009 to 2010 prices[26], estimates £27 (SE, £3) per visit. This implies an average cost per 2-month model cycle of £409. We do not adjust the cost of admin- istration according to the dose intensity of interferon-α because doses tend to be reduced, rather than omitted completely[11].

### Sensitivity analyses

One-way sensitivity analyses and probabilistic sensitivity analyses were performed by varying effectiveness, utility, and cost parameters. One thousand simulations of the model were run in the probabilistic sensitivity analysis. For the probabilistic sensitivity analysis, utilities followed beta distributions with SE given above, non-drug costs followed gamma distributions with SE given in Table 3, dose intensities by normal distributions with standard errors given above.

Uncertainty in PFS for all treatments was modeled by consid- ering the uncertainty in PFS at a certain single time point. This was estimated from Peto’s formula[27]. For all treatments except high- dose imatinib, uncertainty in PFS was modeled by allowing the parameter of the exponential distribution to vary in such a way that the PFS probability at the single time point varied as a beta distribution. For high-dose imatinib, the same method was ad-

### Table 1 – Major cytogenetic rates used in the model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean MCyR (s.e.)</th>
<th>Source</th>
<th>Follow-up (months)</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dasatinib (imatinib-resistant)</td>
<td>58.1% (4.4%)</td>
<td>Unpublished data from Shah et al. [21] provided by BMS as part of the NICE consultation process.</td>
<td>12</td>
<td>Only available estimate at currently recommended dose of dasatinib</td>
</tr>
<tr>
<td>Nilotinib (imatinib-resistant)</td>
<td>52.4% (3.6%)</td>
<td>Approximated by linear interpolation between published 6-month rate (94/194 = 48.5%); Kantarjian et al. [22] and 18-month rate (128/228 = 56.1%; data provided by Novartis as part of the NICE consultation process).</td>
<td>12</td>
<td>Only available estimate</td>
</tr>
<tr>
<td>High-dose imatinib</td>
<td>44.0% (5.4%)</td>
<td>35 reported MCyRs + 2 additional cases known to be in MCyR at study baseline/84 = 44.0%; Jabbour et al. [16]</td>
<td>61</td>
<td>Estimates of overall survival, PFS, and MCyR rate all originate from the same study.</td>
</tr>
<tr>
<td>Dasatinib (imatinib-intolerant)</td>
<td>74.4% (6.7%)</td>
<td>Shah et al. [21]</td>
<td>6</td>
<td>Only available estimate at currently recommended dose of dasatinib</td>
</tr>
<tr>
<td>Nilotinib (imatinib-intolerant)</td>
<td>46.5% (5.4%)</td>
<td>Kantarjian et al. [22]</td>
<td>6</td>
<td>Only available estimate</td>
</tr>
<tr>
<td>Interferon-α</td>
<td>22.1% (1.8%)</td>
<td>O’Brien et al. [6]</td>
<td>18</td>
<td>Recent, large trial. Estimates of overall survival, PFS and MCyR rate all originate from the same study</td>
</tr>
</tbody>
</table>

BMS, Bristol-Myers Squibb; MCyR, major cytogenetic response; NICE, National Institute of Health and Clinical Excellence; PFS, progression-free survival.

but these are not reported for all drugs. Instead, median dose intensities are used for all drugs except high-dose imatinib. The mean dose was used for high-dose imatinib, calculated from Figure 5 in Jabbour et al.[12]. In summary, the following dose intensities were chosen: dasatinib 100% (SE, 2.0%), nilotinib 100% (SE, 1.3%), high-dose imatinib 92% (SE, 1.3%), and interferon-α 56% (SE, 0.9%), where the standard errors were calculated from the sample sizes and reported ranges of dose intensities across all people in the trials.

Dasatinib, nilotinib, and high-dose imatinib are all taken orally, and therefore incur no administration costs. Interferon-α dose and administration schedules are taken from the IRIS trial, with the assumption (based on clinical opinion) that interferon-α will be taken at home. We assume that 75% of people administer interferon-α themselves, or with the help of a care giver, and in 25% of cases, administration is carried out by district nurses, as previously described[11]. The cost of a single district nurse visit during 2006 to 2007 is quoted as £24 in pound sterling (Schema 9.1, Community nurse)[26]. Inflating this value to 2009 to 2010 prices[26], estimates £27 (SE, £3) per visit. This implies an average cost per 2-month model cycle of £409. We do not adjust the cost of administration according to the dose intensity of interferon-α because doses tend to be reduced, rather than omitted completely[11].

### Table 2 – Second line drug costs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand name</th>
<th>Dose and frequency</th>
<th>Price*</th>
<th>Cost per 2-month cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dasatinib</td>
<td>Sprycel</td>
<td>100 mg once per day</td>
<td>50 mg, 56-tab pack = £2337.97</td>
<td>£5,080</td>
</tr>
<tr>
<td></td>
<td>Tasigna</td>
<td>400 mg twice per day</td>
<td>200 mg, 112-cap pack = £2432.85</td>
<td>£5,286</td>
</tr>
<tr>
<td></td>
<td>Glivec</td>
<td>400 mg twice per day</td>
<td>400 mg, 30-tab pack = £1604.08</td>
<td>£6,505</td>
</tr>
<tr>
<td></td>
<td>Referon-A</td>
<td>Target dose: 5 million units per square meter body surface area per day = 8.65 MU per person per day (1.73 m² body area)†</td>
<td>0.5-mL (4.5 million-unit) prefilled syringe = £22.60</td>
<td>£2,643</td>
</tr>
<tr>
<td>Cytarabine (used with interferon-α)</td>
<td></td>
<td>20mg per m² body per day for 10 days per month†</td>
<td>20 mg/mL, 5-mL vial = £4.00</td>
<td>£28</td>
</tr>
</tbody>
</table>

Costs are given in pounds sterling (£).

* All price data taken from British National Formulary No. 58[29].
† Dosing regimen taken from International Randomized Study of Interferon and STI571 (IRIS) trial [6].
opted, but fixing the parameter gamma of the Weibull distribution and varying the parameter lambda.

Uncertainty in overall survival for all treatments was modeled in the following ways. First, the cytogenetic response rates for all treatments were varied according to a normal distribution, with standard errors given in Table 1. Second, the hazard ratio between responders and non-responders was varied as a log-normal distribution. Third, uncertainty in the empirical overall survival data for high-dose imatinib was modeled by considering the uncertainty in overall survival at a certain single time point, again estimated from Peto’s formula [27]. In this case, the parameter gamma of the Weibull distribution was fixed, and the parameter lambda was allowed to vary in such a way that the overall survival probability at the single time point varied as a beta distribution.

Results

**Imatinib-resistant people**

All treatments are expected to yield similar survival gains, with median overall survival ranging from 9.4 years for high-dose imatinib to 10.8 years for dasatinib (Table 4, Fig. 1). This order of overall survival reflects the relative proportion of people with a MCyR for each treatment. Conversely, in the base-case analysis, the time spent on treatment varies greatly. People are predicted to take dasatinib for an average of 6.5 years, whereas people are predicted to take nilotinib or high-dose imatinib for less than half this time. Consequently, the expected per patient second-line drug cost is far higher on dasatinib compared with either nilotinib or high-

<table>
<thead>
<tr>
<th>Item</th>
<th>Population</th>
<th>Frequency</th>
<th>Mean cost (SE)</th>
<th>Cost per 2-month model cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultant outpatient visits</td>
<td>CP treated</td>
<td>4 visits/year</td>
<td>£121 (£12) per visit*</td>
<td>£81</td>
</tr>
<tr>
<td></td>
<td>CP not treated</td>
<td>4 visits/year</td>
<td>£81</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AP</td>
<td>1 visit/month</td>
<td>£243</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BC</td>
<td>2 visits/month</td>
<td>£486</td>
<td></td>
</tr>
<tr>
<td>Bone marrow tests</td>
<td>CP treated</td>
<td>2 tests/year</td>
<td>£615 (£62) per test\†</td>
<td>£205</td>
</tr>
<tr>
<td></td>
<td>CP not treated</td>
<td>none</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AP</td>
<td>none</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BC</td>
<td>none</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>X-rays</td>
<td>CP treated</td>
<td>none</td>
<td>£29 (£2) per visit\‡</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>CP not treated</td>
<td>none</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AP</td>
<td>none</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BC</td>
<td>3/month</td>
<td>£175</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>CT scans</td>
<td>CP treated</td>
<td>none</td>
<td>£103 (£3) per scan\§</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>CP not treated</td>
<td>none</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AP</td>
<td>none</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BC</td>
<td>0.5/month</td>
<td>£103</td>
<td></td>
</tr>
<tr>
<td>Blood transfusions</td>
<td>CP treated</td>
<td>none</td>
<td>£490 (£49)/transfusion\¶</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>CP not treated</td>
<td>none</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AP</td>
<td>none</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BC</td>
<td>1/month</td>
<td>£981</td>
<td></td>
</tr>
<tr>
<td>Third line treatment</td>
<td>CP treated</td>
<td>continuous</td>
<td>£2,079 (£208) per 2 months\‖</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>CP not treated</td>
<td>continuously</td>
<td>£2,079</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AP</td>
<td>continuously</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BC</td>
<td>continuously</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Inpatient terminal care</td>
<td>CP treated</td>
<td>None</td>
<td>£119 (£7) per day#</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>CP not treated</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AP</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BC</td>
<td>1 stay/month, each stay 3 days</td>
<td>£715</td>
<td></td>
</tr>
</tbody>
</table>

CT, computed tomography; SE, standard error of the mean; CP, chronic phase; AP, accelerated phase; BC, blast crisis.

Costs are given in pounds sterling (£).

\* £108 per visit (n = 1) [30], consultant led follow-up attendance, outpatient face to face, specialty code 370, medical oncology (attendance without treatment) total attendances. £121 inflated to 2009 to 2010 [26]. Standard error set at 10% of mean.

\† £547 per test (no range given) [31] admitted patient care mandatory tariff. HRG code S36. £615 inflated to 2009 to 2010 [26]. Standard error set at 10% of mean.

\‡ £26 (interquartile range £22–£27, n = 4) [30], radiology services – outpatient, HRG code RA28Z. £29 inflated to 2009 to 2010 [26]. Standard error calculated from interquartile range and sample size n.

\§ £92 (interquartile range £66–£114, n = 143) [30], NHS trusts and PCTs combined. Radiology services – outpatient. HRG code RA08Z. £103 inflated to 2009 to 2010 [26]. Standard error calculated from interquartile range and sample size n.

\¶ From a survey of UK clinicians by Bristol-Myers Squibb [3]. Includes alternative tyrosine kinase inhibitors hydroxycarbamide and stem cell transplantation. Standard error set at 10% of mean.

\‖ £106 (interquartile range £71–£107, n = 18) [30]. NHS trusts and PCTs combined ward attenders. Service code 800. Clinical oncology (attendance without treatment). Total attendances. £119 inflated to 2009 to 2010 [26]. Standard error calculated from interquartile range and sample size n.
Table 4 – Base case results for imatinib-resistant people.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dasatinib</th>
<th>Nilotinib</th>
<th>High-dose imatinib</th>
<th>Dasatinib vs. high-dose imatinib</th>
<th>Nilotinib vs. high-dose imatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life years, mean, undiscounted (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic phase 2nd-line drugs</td>
<td>6.5 (4.95–8.89)</td>
<td>2.44 (1.66–3.10)</td>
<td>2.68 [2.02–3.90]</td>
<td>3.82 [1.29–6.55]</td>
<td>–0.24 [–1.80 to 0.56]</td>
</tr>
<tr>
<td>Chronic phase 3rd-line treatment</td>
<td>5 (1.24–8.89)</td>
<td>8.65 (3.74–12.75)</td>
<td>7.79 (3.40–11.55)</td>
<td>–2.79 [–5.23 to -0.02]</td>
<td>0.86 [–0.39 to 3.06]</td>
</tr>
<tr>
<td>Accelerated phase*</td>
<td>0.8 (0.8)</td>
<td>0.8 (0.8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Blast crisis*</td>
<td>1.09 (1.09)</td>
<td>1.09 (1.09)</td>
<td>1.09 (1.09)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total, mean</td>
<td>13.4 (7.81–16.95)</td>
<td>12.98 (7.90–16.90)</td>
<td>12.37 (7.83–15.99)</td>
<td>1.04 (0.08–2.55)</td>
<td>0.62 (–0.04 to 1.71)</td>
</tr>
<tr>
<td>Accelerated phase*</td>
<td>7.846 (5.25–15.92)</td>
<td>7.63 (5.33–15.86)</td>
<td>7.311 (5.14–14.44)</td>
<td>0.535 (0.08–3.69)</td>
<td>0.318 (–0.04 to 2.37)</td>
</tr>
<tr>
<td>Costs, mean, discounted</td>
<td>Nilotinib dominates</td>
<td>Nilotinib dominates</td>
<td>Nilotinib dominates</td>
<td>Nilotinib dominates</td>
<td>Nilotinib dominates</td>
</tr>
<tr>
<td>2nd-line drug</td>
<td>£161,432 (£110,143)</td>
<td>£70,143 (£59,136)</td>
<td>£88,883 (£83,532)</td>
<td>£73,548 (£73,639)</td>
<td>£18,740 (£7,655)</td>
</tr>
<tr>
<td>Other</td>
<td>£59,893 (£51,186)</td>
<td>£91,136 (£83,532)</td>
<td>£83,532 (£72,639)</td>
<td>£73,548 (£62,639)</td>
<td>£7,655 (£7,655)</td>
</tr>
<tr>
<td>Total</td>
<td>£221,325 (£161,130)</td>
<td>£161,330 (£151,136)</td>
<td>£172,415 (£156,062)</td>
<td>£146,091 (£146,091)</td>
<td>£11,086 (£11,086)</td>
</tr>
<tr>
<td>Cost/life year</td>
<td>£47,153</td>
<td>Nilotinib dominates</td>
<td>£91,499</td>
<td>Nilotinib dominates</td>
<td>Nilotinib dominates</td>
</tr>
</tbody>
</table>

Costs are given in pounds sterling (£). 95% CI, 95% confidence interval; QALY, quality-adjusted life years. * Uncertainty not simulated.

dose imatinib. The difference in time in chronic phase on second-line treatment is counterbalanced by time in chronic phase on third line treatment, which is predicted to last 5 years in the dasatinib arm, compared with about 8 years for those taking nilotinib or high-dose imatinib. As stipulated in the model structure, the times in accelerated and blast phases are equal for all treatments.

In the base-case analysis, nilotinib dominates high-dose imatinib; nilotinib is expected to yield 0.32 more quality-adjusted life years (QALYs) at £11,100 (pound sterling) less per patient (Table 4). Dasatinib is predicted to provide 0.53 more QALYs than high-dose imatinib at substantially greater cost (£48,900), yielding a very high incremental cost-effectiveness ratio (ICER) of £91,500 QALY. Dasatinib is predicted to provide 0.22 more QALYs than nilotinib at substantially greater cost (£60,000), yielding a very high ICER of £277,700 QALY.

The modeled overall survival for high-dose imatinib was fitted to empirical trial data, so a very close fit between actual and predicted overall survival for high-dose imatinib was obtained. The predicted overall survival for dasatinib and nilotinib were modeled completely independently of the empirical overall survival for these treatments (because the empirical data is very immature). Despite this, the overall survival curves from our model predict the empirical data reasonably well for the short period of the trial follow-up. At 2 years, the modeled overall survival for dasatinib was 0.86 compared with the empirical value of 0.89, and at 1.58 years, the modeled overall survival for nilotinib was 0.88 compared with the empirical value of 0.88.

Full one-way deterministic sensitivity analyses are reported in Rogers et al. [3] and in the online Appendix in Supplemental Materials at: 10.1016/j.jval.2011.07.006. Some key results for nilotinib versus high-dose imatinib are as follows. Nilotinib dominates high-dose imatinib in most sensitivity analyses. Furthermore, nilotinib provides very good value for money compared with high-dose imatinib in all analyses except when PFS for nilotinib is set equal to that for dasatinib (and hence the mean treatment durations are approximately equal), in which case the ICER is £128,000 QALY. This is an important sensitivity analysis because the evidence provided from the drug manufacturers indicates that the mean treatment duration for dasatinib is much longer than for nilotinib (see the Methods section), and it appears counterintuitive that PFS for the two drugs is very different, whereas overall survival is very similar (as we assume in our base case). Furthermore, it appears that clinical opinion in the NICE assessment for these drugs was that dasatinib and nilotinib would be taken for approximately the same time (NICE Appraisal Consultation, http://guidance.nice.org.uk/TA/Wave99/Consultation/DraftGuidance).

In our base-case analysis, dasatinib is taken for far longer than nilotinib. Given that there is considerable structural uncertainty in the assumed relationship between response rate and overall survival, overall survival was modeled in a completely different way in one sensitivity analysis. Setting the time in post-progression survival in the nilotinib arm equal to the value for high-dose imatinib yields and ICER of £114,000 QALY, where nilotinib costs less and provides less benefit that high-dose imatinib. Setting the MCyR for high-dose imatinib at the upper 95% CI of 54.6% yields and ICER of £202,000 QALY, where nilotinib again costs less and provides less benefit than high-dose imatinib. Setting the PFS for high-dose imatinib equal to the lower 95% CI limit yields an ICER of £11,000 QALY.

The cost-effectiveness of nilotinib is far less sensitive to reasonable changes in many other parameters (e.g., the dose intensities of the drugs), the proportion of people who discontinue treatment prematurely, the overall survival hazard ratio between responders and non-responders, uncertainty in the empirical overall survival for high-dose imatinib, medical management costs, costs of treating adverse events (based on assumptions from the Novartis model [24]), and utilities (see [3] and online Appendix in Supplemental Materials at: 10.1016/j.jval.2011.07.006).

The ICER for dasatinib versus high-dose imatinib remains above £30,000 QALY in all but one sensitivity analysis. In particular, when PFS for dasatinib is set equal to that for nilotinib or high-dose imatinib, dasatinib then dominates high-dose imatinib. We repeat that the sensitivity analysis whereby PFS for dasatinib is set equal to that for nilotinib (and therefore mean treatment durations are very similar) is very important, given the clinical opinion in the NICE assessment for these drugs.

Clinical data for dasatinib was taken from Shah et al. [21] because people in this trial took dasatinib at the recommended dose of 100 mg/d. However, when all the dasatinib clinical effectiveness data is taken from either of the two other trials of dasatinib [7,28], in which people took dasatinib at 140 mg/d, then dasatinib appears even less cost effective. Next, although the ICER varies con-
siderably when the MCyR rates are varied within their 95% CI, it remains high. Indeed, even assuming every patient achieves a response on dasatinib, the ICER is £34,500 QALY. Furthermore, the ICER remains high, at £43,200 QALY when we recalculate overall survival by setting the time in post-progression survival in the dasatinib arm equal to the value for high-dose imatinib.

As mentioned above, the ICER is particularly high because people are predicted to take dasatinib for a long time. Even assuming the lower 95% CI for dasatinib PFS, the ICER remains high at £46,700 QALY. Cost-effectiveness is far less sensitive to changes in many other parameters, including dose intensities of the drugs, overall survival hazard ratio between responders and non-responders, uncertainty in the empirical overall survival for high-dose imatinib, medical management costs, costs of treating adverse events (based on assumptions from the Bristol-Myers Squibb model [23]), and utilities (see [3] and the online Appendix in Supplemental Materials at: 10.1016/j.jval.2011.07.006).

We now turn to the probabilistic sensitivity analysis. In the base-case analysis, dasatinib generated more QALYs than high-dose imatinib in 95% of the simulations, whereas nilotinib generated more QALYs in 90%. Dasatinib costs more than high-dose imatinib per patient in virtually all simulations and nilotinib costs more than high-dose imatinib in 9% of simulations. At a willingness-to-pay threshold of £30,000 QALY, nilotinib provides the best value for money in virtually all simulations (Fig. 2A).

Next, in the sensitivity analysis whereby we set PFS for nilotinib equal to that for dasatinib, high-dose imatinib is expected to provide best value for money for willingness-to-pay thresholds up to £100,000 QALY (Fig. 3A). In the sensitivity analysis whereby we set PFS for dasatinib equal to that for nilotinib, nilotinib is expected to provide best value for money for willingness-to-pay thresholds up to £57,000 QALY, thereafter, dasatinib provides best value for money (Fig. 3B).

**Imatinib-intolerant people**

Large differences in overall survival are predicted, with interferon-α yielding the shortest survival and dasatinib the longest...
Table 5 – Base case results for imatinib-intolerant people.

<table>
<thead>
<tr>
<th></th>
<th>Dasatinib</th>
<th>Nilotinib</th>
<th>Interferon-α</th>
<th>Dasatinib- interferon-α</th>
<th>Nilotinib- interferon-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life years mean, undiscounted (95% CI)</td>
<td>10.77</td>
<td>6.79</td>
<td>2.04</td>
<td>8.73</td>
<td>4.75</td>
</tr>
<tr>
<td>Chronic phase 2nd-line drugs</td>
<td>(5.51–15.52)</td>
<td>(4.12–9.63)</td>
<td>(1.72–2.72)</td>
<td>(3.34–13.40)</td>
<td>(1.61–7.38)</td>
</tr>
<tr>
<td>Chronic phase 3rd-line treatment</td>
<td>1.94</td>
<td>3.87</td>
<td>6.82</td>
<td>–4.88</td>
<td>–2.95</td>
</tr>
<tr>
<td>Accelerated phase*</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Blast crisis*</td>
<td>1.09</td>
<td>1.09</td>
<td>1.09</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total, mean</td>
<td>14.6</td>
<td>12.55</td>
<td>10.75</td>
<td>3.85</td>
<td>1.8</td>
</tr>
<tr>
<td>Total, median</td>
<td>(7.98–18.76)</td>
<td>(7.65–15.93)</td>
<td>(7.12–13.99)</td>
<td>(0.84–6.60)</td>
<td>(0.26–3.19)</td>
</tr>
<tr>
<td>Total QALYs, mean, discounted</td>
<td>8.463</td>
<td>7.406</td>
<td>6.229</td>
<td>2.235</td>
<td>1.177</td>
</tr>
<tr>
<td>Costs, mean, discounted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd-line drug</td>
<td>£244,926</td>
<td>£169,771</td>
<td>£15,936</td>
<td>£228,990</td>
<td>£153,835</td>
</tr>
<tr>
<td>Other</td>
<td>£38,515</td>
<td>£52,320</td>
<td>£98,818</td>
<td>–£50,303</td>
<td>–£46,498</td>
</tr>
<tr>
<td>Total</td>
<td>£283,441</td>
<td>£222,092</td>
<td>£98,818</td>
<td>£184,623</td>
<td>£123,273</td>
</tr>
<tr>
<td>Cost/life year</td>
<td>£47,951</td>
<td>£68,570</td>
<td>£46,498</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost/QALY</td>
<td>£82,619</td>
<td>£104,698</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Costs are given in pounds sterling (£). 95% CI, 95% confidence interval; QALY, quality-adjusted life years.

* Uncertainty not simulated.

(5). People taking dasatinib and nilotinib spend the majority of their lives in chronic phase on second-line treatment, whereas those on interferon-α spend most time in chronic phase on third-line treatment. For this reason, and because dasatinib and nilotinib are far more expensive per person per day than interferon-α, the expected per patient drug costs are far higher on dasatinib and nilotinib compared with interferon-α.

Compared with interferon-α, nilotinib is expected to yield 1.2 more QALYs at £123,000 more per patient, yielding a very high ICER of £104,700 QALY; dasatinib is expected to yield 2.2 more QALYs at £185,000 more per patient, also yielding a very high ICER of £82,600 QALY (Table 5); and dasatinib is expected to yield 1.1 more QALYs than nilotinib at £61,300 more per patient, also yielding a high ICER of £58,000 QALY.

The predicted overall survival is lower for all treatments than the empirical overall survival [3]. Therefore, in a sensitivity analysis, overall survival was calibrated to the most mature data available in an imatinib-intolerant population, and which was used for the nilotinib data [22]. There is then no substantive change in the cost-effectiveness estimates: the ICER for dasatinib versus interferon-α increases to £107,600 QALY, and for nilotinib versus interferon-α ICER is £132,900 QALY.

In virtually all simulations of the probabilistic sensitivity analysis, both dasatinib and nilotinib incur greater lifetime costs and benefits than interferon-α. Interferon-α is predicted to provide the best value for money at all but the highest levels of willingness-to-pay threshold (Fig. 2B).

Discussion

Given the structural assumptions in our base case, dasatinib is highly unlikely to be cost-effective versus high-dose imatinib for people resistant to normal-dose imatinib (ICER £91,500 QALY), even when most key parameters are individually or simultaneously varied within plausible ranges. Given that dasatinib is cheaper per patient per day (at the intended doses) and is predicted to give slightly greater life expectancy, one might expect dasatinib to dominate high-dose imatinib. This is not the case for two main reasons. First, we predict that dasatinib is typically taken for far longer than high-dose imatinib (a mean of 6.5 vs. 2.7 years in the deterministic base case), thus incurring far greater drug costs. Second, we estimate that the dose intensity for high-dose imatinib is lower than for dasatinib (92% vs. 100%). As a result, estimated second-line drug costs for dasatinib are typically about twice as high as for high-dose imatinib.

Although we predict that dasatinib is typically taken for far longer than nilotinib (6.5 vs. 2.4 years) in our base case, life expectancy is similar on both drugs [32]. This may appear counterintuitive. Furthermore, it appears that clinical opinion in the recent NICE assessment for these drugs was that dasatinib and nilotinib would be taken for approximately the same time. Therefore, the sensitivity analysis whereby we set PFS for dasatinib equal to that for nilotinib, the ICER for dasatinib versus interferon-α remains high at £64,000 QALY.

Nilotinib dominates high-dose imatinib in the base case: nilotinib is predicted to yield 0.32 more QALYs at £11,100 less per pa-
tient. Furthermore, nilotinib provides very good value for money in all analyses except when PFS for nilotinib is set equal to that for dasatinib, in which case the ICER is £128,000 QALY. Again, we emphasize the importance of the sensitivity analysis.

The impact of an assumed relationship between overall survival and MCyR was tested in a sensitivity analysis in which the surrogate approach was discarded and, instead, post-progression survival was set equal for all treatments. This made very little difference to the cost-effectiveness of nilotinib, but substantially improved the cost-effectiveness of dasatinib (ICER fell to £43,200 QALY) because the far longer PFS seen with dasatinib was directly reflected in longer overall survival for dasatinib.

For imatinib-intolerant people, the ICERS for nilotinib and dasatinib versus interferon-α are high in all analyses. This is because the predicted QALY gains, although considerable, are insufficient to outweigh the very high estimated costs of the new drugs. Both nilotinib and dasatinib are far more expensive than interferon-α per person per day, and are predicted to be taken for far longer.

Kantarjian et al. [28] is the one relevant randomized study comparison of dasatinib and high-dose imatinib. Nevertheless, this study was not considered due to substantial patient crossover at an early follow-up time. Instead, estimates of clinical effectiveness are limited to a heterogeneous collection of observational evidence.

Effectiveness data are limited, but dasatinib and nilotinib appear efficacious in terms of obtaining cytogenetic and hematological responses in both imatinib-resistant and -intolerant populations. Given the limited evidence base, it is more difficult to assess the extent to which dasatinib and nilotinib induce greater frequencies and/or degrees of response, which may impact on long-term outcomes.

The strengths of this assessment include the comprehensive, explicit, and systematic literature searches used to locate evidence for the review of clinical effectiveness and to inform the economic modeling study, which is the information that is most certain (cytogenetic response rates) to predict long-term outcomes and the extensive exploration of uncertainty. The model predicts the empirical data well: the fits to PFS distributions are good and the imatinib-resistant model closely agrees with the empirical immature overall survival. The fit to the empirical imatinib-intolerant overall survival is less convincing. However, the fit was very good using an alternative method of calibrating modeled overall survival.

The model should be viewed as an exploratory analysis of the cost-effectiveness of dasatinib and nilotinib because it relies on many assumptions. Some of the most substantive assumptions are as follows. First, all clinical effectiveness data (e.g., MCyR and PFS) have necessarily been taken from single-arm trials, not from randomized controlled trials, and progression is defined slightly differently across trials. Second, a relationship is assumed between overall survival and MCyR, and

- This relationship is the same for all treatments. Although this appears reasonable for treatment with dasatinib and nilotinib, there is no evidence to support this assumption;
- The timing, duration, and depth of MCyR do not modify the relationship;
- The overall survival hazard ratio between responders and non-responder in trials of first-line therapy with normal dose imatinib remains constant over time and is transferable to the second-line treatments;
- The overall survival of imatinib-resistant patients taking high-dose imatinib is used to calibrate the surrogate relationship between MCyR and overall survival for all comparators in imatinib-resistant and imatinib-intolerant CML.

Third, duration of treatment is estimated from PFS with a deduction for premature discontinuations. Given that the PFS data is very immature, it is extrapolated many years into the future. Fourth, third-line treatments are implicitly, not explicitly, modeled due to lack of data. Fifth, treatment-related adverse events incur no utility decrement and no costs. Finally, the utilities for people taking dasatinib and nilotinib are assumed equal to that for high-dose imatinib.

Given that the effectiveness data were taken from multinational clinical trials and the cost data were based on practice relevant to the UK NHS, the cost-effectiveness results are applicable to other countries only if the costs are similar to those in other countries. Nonetheless, the modeling framework can easily be adapted, with relevant cost data, to inform on health policy decisions in other countries.

In their submission to NICE [23], BMS predicted that dasatinib would dominate high-dose imatinib, which is in stark contrast to our prediction that dasatinib is not cost-effective. This is mainly attributable to differences in the modeled experience of people taking high-dose imatinib. In particular, BMS predicted far higher treatment costs on high-dose imatinib than we did and per patient discounted costs of imatinib acquisition were £243,000 (BMS) versus £89,000 (present study) for the following two reasons. First, and most importantly, BMS predicted average imatinib treatment duration of 8.8 years whereas we predict 2.7 years. This difference arises because we use different clinical effectiveness data for imatinib. We use Jabbour et al. [12] whereas BMS used Kantarjian et al. [28]. We prefer Jabbour et al. [12] because of the extensive treatment crossover in Kantarjian et al. [3].

Second, BMS assumed a dose intensity of 100% for high-dose imatinib, whereas we assume 92%, taken from Jabbour et al. [12]. If the BMS figure for treatment cost of high-dose imatinib is assumed, then our model also predicts that dasatinib dominates high-dose imatinib.

Dasatinib has been assessed as good value for money versus high-dose imatinib for people resistant to standard dose imatinib in the Swedish healthcare system, according to a study with financial support from BMS [10]. Based on a societal perspective, the incremental cost is €6880 (in Euros) per QALY, and allowing for direct costs only, €7207 per QALY (approximately £6500 [pound sterling] per QALY). Given that this is a Swedish study, there are many factors that differ from our analysis, including discount rates, background mortality rates, unit prices, and resource use. Nonetheless, the most important reason for the clear discrepancy between the assessments of the cost-effectiveness of dasatinib appears to be the fact that they predict that patients will take high-dose imatinib for much longer than we do. This explains the fact that they predict very similar per patient discounted drug acquisition costs for dasatinib (£277,800) and imatinib (£278,200), whereas we predict far higher drug acquisition costs for dasatinib (£161,400) compared with imatinib (£88,900). This appears to be the same reason that explains most of the discrepancy in cost-effectiveness results between our model and that of BMS for the NICE submission, namely that we use different clinical effectiveness data for imatinib: we used Jabbour et al. [12] whereas BMS used Kantarjian et al. [28]. We repeat that we favor Jabbour et al. because of the extensive treatment crossover in Kantarjian et al. [3].

In their submission to NICE [24], Novartis, the manufacturer of nilotinib, agree with our prediction that nilotinib dominates high-dose imatinib. Nevertheless, there is a major structural difference between our models: Novartis estimates overall survival as PFS plus time in accelerated phase plus time in blast crisis, whereas we estimate overall survival according to the MCyR for each treatment. We disagree with the Novartis estimation of overall survival because there may be a substantial period during which people are in chronic phase, off second-line treatment [3].

Several randomized clinical trials of the interventions are underway [3]. It is perhaps surprising that these are all open studies, given that the drugs are taken orally, and thus relatively easily blinded. A three-way, double blind, randomized clinical trial of dasatinib, nilotinib, and high-dose imatinib would be most useful for informing a cost-effective model.

This study describes the cost-effectiveness analysis of nilotinib for treatment of CML, and the cost-effectiveness analysis of dasatinib for treatment of CML conducted by a research team indepen-
dent of financial support from the pharmaceutical industry. In conclusion, we suggest that until longer follow up data for PFS and overall survival are available, the cost-effectiveness of dasatinib and nilotinib for imatinib-resistant people is highly uncertain. Our findings that both nilotinib and dasatinib may not be cost-effective versus interferon-α for people intolerant to imatinib are based on plausible structural assumptions. We reiterate that our model is reliant on many substantial assumptions. The most critical shortcoming is that our model is necessarily parameterized on the basis of a heterogeneous collection of observational data, in which the key outcome measures, MCyr and PFS, have been defined and measured in different ways, at different times, in different populations. We recommend that the structure of our model be re-used when higher quality data becomes available.

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Supplemental materials

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