Healthcare Improvement Scotland

National Cancer Medicines Advisory Group (NCMAG) Programme

NCMAG116 Dasatinib | Advice Document v1.0 | July 2024

Dasatinib for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) integrated with chemotherapy [A]

NCMAG Decision | this off-label, off-patent use is **supported** as an alternative option to on-label treatments.

This advice applies only in the context of the confidential pricing agreements in NHSScotland, upon which the decision was based, or confidential pricing agreements or list prices that are equivalent or lower.

[A] NCMAG considers proposals submitted by clinicians for use of cancer medicines outwith SMC remit. For more detail on NCMAG remit please see our website.

Decision rationale

After consideration of all the available evidence regarding the clinical benefits and harms, the Council were **satisfied** with the clinical effectiveness case for dasatinib in the proposed population. After consideration of all relevant information under the decision-making framework for value judgements the Council made a decision to **support** this use.

Governance Arrangements

Each NHS board must ensure all internal governance arrangements are completed before medicines are prescribed. The benefits and risks of the use of a medicine should be clearly stated and discussed with the patient to allow informed consent.

Proposal Details	
Proposers	NHSScotland Haematologists
Medicine Name	Dasatinib
Cancer type	Acute Lymphoblastic Leukaemia (ALL)
Proposed off-label[B] use	For the treatment of adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL), when integrated with chemotherapy[1, 2].

NHS SCOTLAND

Medicine Details	Form: Film coated tablet Dose: The recommended starting dosage of dasatinib for newly diagnosed Ph+ ALL in adults is 100 mg administered orally once daily or as clinically recommended. Dasatinib should be taken consistently either in the morning or evening.
Advice eligibility criteria	Newly diagnosed Philadelphia Positive Acute Lymphoblastic Leukaemia (Ph+ ALL)

[B] Dasatinib has a marketing authorisation for the following indications:

- 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.
- Ph+ acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy.
- Paediatric patients with: newly diagnosed Ph+ CML in chronic phase (Ph+ CML-CP) or Ph+ CML-CP resistant or intolerant to prior therapy including imatinib. Newly diagnosed Ph+ ALL in combination with chemotherapy

1. Current Management Context

Acute Lymphoblastic Leukaemia incidence, prognosis and symptoms

Acute lymphoblastic leukemia (ALL) is a blood cancer that develops rapidly with the overproduction of immature B-cells or T-cells. The vast majority of Philadelphia-positive (Ph+) ALL cases are of B-cell lineage. Ph+ ALL is caused by a translocation of the BCR-ABL1 driver mutation oncogene.

In 2021, there were 30 cases of ALL registered in Scotland among individuals aged 20 years and older[3]. Ph+ ALL is more common in older patients, representing 25% of adult cases and rising to over 50% in patients over 50 years old[4].

Historically, Ph+ ALL was characterised as having the worst prognosis; however, with the introduction of tyrosine kinase inhibitors (TKIs), survival rates have improved. In the UK, the estimated 5-year overall survival for Ph+ ALL patients range from 27% (40 year or over) to 57% (15 to 39 years)[5].

Common symptoms of ALL include spontaneous bleeding, fatigue, infections, fever, weight loss, and swollen lymph nodes. Due to the aggressive nature of ALL patients require urgent treatment and supportive therapy on diagnosis which usually requires an admission to hospital[6].

Efficacy outcomes used in Ph+ ALL

The primary goal of therapy in newly diagnosed Ph+ ALL is to achieve cure, if possible, which may depend on patient's fitness to tolerate treatment. The aim of treatment is to minimise treatment-related mortality, including infections, bleeding, and thromboembolism, while achieving bone marrow recovery with an absence of leukaemia cells and minimal residual disease (MRD) negativity. In general, older studies measured efficacy using outcomes like complete remission (CR) which is defined as less than 5% of blasts in bone marrow, no evidence of leukaemia cells in peripheral blood and recovery of neutrophil and platelet counts. MRD, a recently developed highly sensitive measure of response, predicts patient outcomes and guides treatment decisions[7].

Ph+ ALL treatment pathway in Scotland

The treatment of newly diagnosed Ph+ ALL currently involves induction therapy with imatinib (a first generation TKI), steroids, multi-agent chemotherapy and monoclonal antibodies. After induction, the treatment response is assessed to inform the decision to proceed with an allogeneic stem cell transplant (SCT). If a transplant is not performed after the first complete remission, patients who can tolerate it will typically receive intensified chemotherapy aimed at preventing central nervous system (CNS) relapse and consolidating remission, followed by maintenance treatment. Older patients have high relapse rates despite maintenance treatment and may not be able to tolerate intense chemotherapy treatment[8].

Due to the effectiveness of TKIs, the benefit of stem cell transplants at first CR is more uncertain. Patients responding well to TKIs may experience long-term durable remission without a transplant. Stem cell transplants offer a potential cure for 50% of recipients, albeit with significant

toxicity and a 10-20% risk of treatment-related mortality. The option of a stem cell transplant is considered based on the patient's age, co-morbidities and donor availability[6].

Pharmacology of dasatinib

Dasatinib is a TKI that inhibits the BCR-ABL protein, along with other signalling pathways in leukaemia cells, thereby leading to leukaemia cell death. It is a second-generation TKI that can overcome leukaemia cell resistance to imatinib (excluding resistance due to T315I mutation) as well as crossing the blood-brain barrier[11].

International context for proposed off-label use

The European Society for Medical Oncology (ESMO), the National Comprehensive Cancer Network (NCCN), and the European Leukaemia Network (ELN) support the use of dasatinib and other TKIs as front-line therapy for Ph+ ALL[6, 9, 10]. The Australian Therapeutics Good Authority has licensed dasatinib, integrated with chemotherapy, for the treatment of newly diagnosed Ph+ ALL in adults[1, 2].

The types of chemotherapy backbones vary internationally, with North America tending to use 8 cycles of HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone, high dose methotrexate and cytarabine) followed by maintenance treatment, while in the UK treatment is usually induction, intensification and consolidation with multi-agent chemotherapy followed by maintenance. Patients usually receive a TKI indefinitely with dose interruptions in case of toxicity e.g. low blood counts[6, 9, 10].

2. Evidence Review Approach

A literature search to identify clinical and economic evidence was conducted on key electronic databases including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, major international health technology agencies, as well as a focused internet search. The search strategy comprised both Medical Subject Headings and keywords. The main search concepts were dasatinib, Philadelphia chromosome positive and acute lymphoblastic leukaemia. Titles and abstracts were screened by one reviewer with a second opinion sought by another reviewer when required. The included key research study was critically appraised using the Risk of bias in non-randomised studies for interventions (ROBINS-I).

3. Clinical Evidence Review Summary

Clinical Efficacy Evidence

Three phase II studies were identified as relevant to the proposal, all single-arm[12-14]. Two out of the three used upfront cyclophosphamide, vincristine, doxorubicin, and dexamethasone administered as hyperfractionated therapy (hyperCVAD) chemotherapy with dasatinib while the Sugiura et al (2016) study began patients on dasatinib with steroids before commencing the chemotherapy regimen[14]. The two Ravandi studies included patients 18 years or older with previously untreated Ph+ ALL, with an Eastern Cooperative Oncology Group (ECOG) performance

status of 2 or less, with adequate renal or liver function[12, 13]. One of the Ravandi et al (2016) studies allowed individuals who had been pre-treated with chemotherapy, prior to the detection of the Philadelphia chromosome abnormality (n=94)[13]. In both Ravandi et al studies, dasatinib was introduced twice daily at a dose of 50mg for the first 14 days of each of the 8 cycles, which was later amended to a once daily dose of 100mg[12, 13]. In the Sugiura et al study patients were included if they were aged between 15 and 64 years with newly diagnosed Ph+ ALL, with an ECOG performance status of less than 3, with adequate renal or liver function[14]. Dasatinib was started as 140mg once daily in the initial induction phase followed by 100mg daily from induction phase 2[14]. Both Ravandi et al studies were conducted in the US, one was conducted at a single site, and one was a multicenter study, while Sugiura et al study was a multicentre study conducted in Japan[12-14]. Details of the included studies can be found in Table 1.

Table 1: Individual study baseline characteristics.

Study	Chemo+TKI	Age	Gender	ECOG	Other
Ravandi et al 2015[12] N=72 US	hyperCVAD dasatinib[a]	Median 55 (range 21-80) 46 (64%) >50y	55% male	NR	Median WBC: 12 x10^9/L Range (0.4-658.1)
Ravandi et al 2016[13] N=94 US	hyperCVAD + dasatinib[a]	Median 44 (range 20-60) 23(24%) >50y	55% female	NR	Median WBC: 10x10^9/L
Sugiura et al[14] N=78 Japan	Two step induction[b]	Median 44.5 (range 16-64) 25(32.1%) >55y	47% male	0-1 73(94%) 2: 4(5%) 3: 1(1%)	Median WBC: 32.5 x10^9/L Range (0.9-443.2

Chemo = chemotherapy; ECOG = Eastern Cooperative Oncology Group; HyperCVAD = cyclophosphamide, vincristine doxorubicin, dexamethasone, high dose methotrexate and cytarabine administered as hyperfractionated therapy; NR = not reported; TKI = tyrosine kinase inhibitor; WBC = white blood cells; y = years

[a]Dasatinib was initially administered as 50mg twice daily but after protocol amendment dosing was changed to 100mg once daily. Dasatinib was administered for the first 14 days of the first cycle then 70mg once daily continuous from cycle 2.

[b]Up front steroid, followed by dasatinib 140mg once daily with steroid (step one induction) then step 2 included dasatinib 100mg once daily.

The key outcome for both Ravandi et al studies was the proportion of patients achieving a complete response (CR), which was defined as the presence of fewer than 5% blasts in the bone marrow, with more than 1x10^9/L neutrophils and more than 100x10^9/L platelets in the peripheral

blood and no extramedullary disease[12, 13]. Other outcomes of interest included disease free survival, defined as the time of CR until relapse or death due to any cause, event free survival (EFS), defined as the beginning of treatment until an event occurred, including relapse, death (during induction or death during CR) and overall survival (OS) defined as the time from diagnosis to death. The Sugiura et al study's primary outcome was 3-year EFS, with secondary outcomes including 3-year OS and response[14]. Definitions were consistent with the Ravandi et al studies.

The median cycles received was 6 (range 1 to 8) which was reported in one study (Ravandi et al 2015) and median follow up across all three studies ranged from 36 months to 67 months. The median age ranged from 44 to 55, proportion of males ranged from 47% to 55%, median white blood count at baseline ranged from $10x10^9$/L to 32.5 $x10^9$/L and ECOG performance status was only reported in one study, with the majority having a performance score of 0-1 (94%). Complete response was similar between the studies, with the majority achieving a complete response. The proportion of patients receiving a stem cell transplant (SCT) varied between the studies ranging from 11% to 74%.

Table 2: Key outcomes for studies of first line use of dasatinib (primary outcomes in bold)

	Ravandi et al 2015[12] N=72	**Ravandi et al 2016[13] N= 94**	**Sugiura et al 2022[14] N=78**
Follow up (months) (range)	67 (33 to 97)	36 (NR)	48 (20 to 66)
Complete remission	69 (94%)	83 (88%)	78 (100%)
No (%) receiving SCT	12 (17%)	41 (49%)[a]	58 (74%)[a]
MRD negativity rate Pre-SCT Post-SCT			 76% 95%
DFS Median (months) (95% CI)	31 (0.3 to 97)	NR	NR
EFS Median (months) (95% CI) Estimated 3y Rate (95% CI)	27 (0.2 to 97)	NR 55% (46% to 66%)	NR **66.2% (54.4-75.5)**
RFS Estimated 3y rate PT	NR	**76% (63% to 91%)**	NR
OS Median (months) (95% CI) Deaths Estimated survival rate	 47 (range 0.2 to 97) 39 5y 46%	 NR 28 3y 69% (52% to 79%)	 NR NR 3y 80.5% (69.7-87.7)

MRD = minimal residual disease; SCT = stem cell transplant; DFS = disease free survival; EFS = event free survival; OS = overall survival; CI = confidence interval; NR = not reached; PT = post-transplant; RFS = relapse free survival; y = years

[a] SCT part of the protocol

Patient reported outcomes

No patient reported outcome data were reported across the included studies.

Safety evidence

The first report of the Ravandi et al 2015 study was after 35 patients and included detailed toxicity data[15]. During the induction phase (dasatinib plus chemotherapy) of the first report of the Ravandi et al 2015 study[15], the most common grade 3/4 adverse events (AEs) included infections: n=24 (69%), renal failure: n=6 (21%) and metabolic abnormalities: n=21 (60%). In the subsequent cycles (dasatinib plus chemotherapy) the most common grade 3/4 AEs were infections: n=26 (84%), haemorrhage: n=11 (35%) and metabolic abnormalities: n=11 (35%)[15]. All but two patients received the prescribed 100mg of dasatinib, with two patients receiving a brief (3 days) dose reduction to 70mg due to infection[15]. In the final report, Ravandi et al 2015, the AEs appear similar to the earlier report. Twelve patients discontinued treatment and an alternative TKI was started. In patients who discontinued due to toxicities reasons included pleural effusions (n=6), pulmonary artery hypertension (n=2) and gastrointestinal bleeding (n=2). In the Ravandi et al 2016 study AEs in both the induction and the consolidation phases were mostly grades 1 and 2, with most cases of grade 3 or higher toxicity due to myelosuppression. Seventy three percent of patients in the consolidation phase had a dose reduction for at least one cycle[13]. Finally, in the Sugiura et al study toxicity was mainly mild in induction phase 1 (dasatinib plus prednisolone, no chemotherapy), although grade 4 thrombocytopenia was reported in 49% of patients. In induction phase 2 (dasatinib plus intensive chemotherapy), 94% of patients experienced grade 4 neutropenia and 5% experienced grade 4 sepsis. In cycle 1 of the consolidation phase 1 (dasatinib plus chemotherapy), 99% and 9% of patients experienced grade 4 neutropenia and sepsis respectively[14].

Quality assessment of clinical evidence

The evidence to support this proposal came from three phase 2 single arm studies which are inherently poor in quality, mainly due to the lack of comparative data. Overall, on applying the ROBINS-I tool to all studies, they were either assessed as having a low risk or a moderate risk of bias. Bias due to confounding was assessed to be high in all studies as no appropriate analysis method was used to control for confounding. Due to the lack of blinded outcome assessment the outcome measure could have been influenced by knowledge of the intervention received.

Clinical effectiveness considerations

Dasatinib in combination with chemotherapy has been shown to induce complete haematological and durable remission.

Across the studies, haematological CR rates (including incomplete blood count recovery) ranged from 88% to 100%. The median EFS was 27 months in Ravandi et al 2015. In the Sugiura et al and Ravandi et al 2016 studies the estimated 3-year EFS rates were 66% and 55%, respectively and MRD negativity ranged from 53% to 71%. Achieving MRD negativity is associated with a favourable outcome[10].

The Ravandi et al 2015 study reported a median overall survival of 47 months and 5-year overall survival rate of 46%; SCT was associated with poorer survival and may have resulted in lower overall survival (7 out of the 12 transplanted patients died due to SCT complications, which was attributed to the older patient cohort)[12].

In the Sugiura et al and Ravandi et al 2016 studies the estimated 3-year overall survival rates were 81% and 69%, respectively[13-15]. The confidence intervals across the studies were either wide due to a low number of events and immaturity of the data, or the confidence intervals were not reported, which increases the uncertainty of the treatment effect estimate. The Sugiura et al and Ravandi et al 2016 reported better survival outcomes, which may be due to the design of the studies focusing on SCT and the inclusion of a younger patient population[13, 14]. Concomitant and subsequent treatments (plus variation in these) may affect interpretation of the effects of dasatinib.

The evidence comes from open-label single arm studies that are at risk of bias, which adds to the uncertainty of interpreting the results. However, the consistency of the observed effects in more than 200 patients across different trials, time points and geographical locations provides some reassurance about the treatment effect.

The efficacy of dasatinib compared to imatinib for newly diagnosed patients (both in combination with chemotherapy) is uncertain.

The available evidence is non-comparative with no placebo-controlled arms or active control arms using alternative TKIs. There are no indirect comparisons available comparing dasatinib to imatinib in the newly diagnosed setting. A randomised controlled trial comparing dasatinib with imatinib in this setting is not anticipated.

Imatinib, a first generation TKI, was licensed for newly diagnosed Ph+ ALL based on haematological response rate of 93% and a major cytogenetic response rate of 90%. DFS and OS consistently exceeded 1 year and were superior to historical controls[16] . The estimated 4-year overall survival for imatinib in combination with chemotherapy for newly diagnosed patients ranges from 38% to 52%, with a 5-year overall survival ranging from 33% to 43%[17-22]. The higher survival rates in the Sugiura et al. and Ravandi 2016 studies may suggest better survival outcomes with dasatinib. However, naïve comparisons of data do not account for significant clinical and methodological differences between studies and need to be interpreted with caution as the comparisons are very uncertain.

Comparative data is available for these medicines in a population with newly diagnosed chronic myelogenous leukaemia (CML), an indolent form of leukaemia with prolonged survival. In a large (n=519) randomised phase III study, single agent dasatinib was compared to single agent imatinib, with a minimum follow-up of five years for all patients. There was an improvement in the secondary outcome of Major Molecular Response, with dasatinib achieving 76% and imatinib 44%[23] . This comparative data in a CML population may provide insights on the comparative efficacy of dasatinib to imatinib, however it is uncertain if these findings are generalisable to an ALL population, where the form of leukaemia is more aggressive.

The results may be generalisable to the NHSScotland population but there are some generalisability concerns of the available evidence

The NHS Scotland Cancer Medicines Outcomes Programme – Public Health Scotland (CMOP-PHS) provided a management report on the use of TKIs in patients with Philadelphia positive ALL in Scotland from 2015-2023. This report was used to assess the generalisability of findings reported in the literature to patients in Scotland. The CMOP-PHS report is available on request from PHS.

There are some generalisability concerns with the evidence:

- Differences in the chemotherapy backbone used in studies may reduce the generalisability of the results.
- Dosing of dasatinib varied in the studies, with the most frequently used dose being 100mg once daily.
- In the Sugiura study, patients who did not receive a SCT were offered maintenance therapy for only one year, and dasatinib was not administered indefinitely, which is the proposed practice, potentially further reducing the generalisability to the Scottish population.
- The Sugiura study was carried out in Japan, and differences between Scottish and Japanese patients, including pharmacogenomics, may affect the generalisability of the results[14].

There were no unexpected safety signals compared to the on-label indication of dasatinib

Dasatinib's safety profile is well described in the CML population, based on study data for nearly 1,000 patients, with comparable safety to imatinib. The comparative safety evidence for CML is not confounded by multi-agent chemotherapy, as the CML studies used either imatinib or dasatinib monotherapy[23, 24]. There is less robust safety data for Ph+ ALL population[25]. Across the studies, there were high rates of Grade 3 or 4 toxicities, mainly due to myelosuppression. This may be attributed to the high disease burden of ALL, the combined use of multi-agent chemotherapy, high dose steroids, or dasatinib. As there were no active control or placebo-controlled arms in the studies, there is uncertainty regarding the safety profile; however, no unexpected toxicities were reported.

The most serious non-haematological adverse effects were pleural effusions, metabolic abnormalities, kidney dysfunction, infection, bleeding, and neurological issues. The chemotherapy regimens used in the studies differed from those used in Scotland. Nonetheless, the side effects observed are consistent with the expected safety profile of dasatinib when used in combination with chemotherapy for the treatment of newly diagnosed Ph+ ALL.

Additional Considerations

Dasatinib is a second-generation TKI that crosses the blood-brain barrier although the clinical impact of this is not clear from published studies. Dasatinib has been shown to lead to deeper

responses compared to imatinib in the CML population. Improved efficacy may result in fewer patients requiring SCT or chimeric antigen receptor (CAR)-T cell therapy, which have significant treatment related morbidity and mortality.

The ESMO Magnitude of Clinical Benefit Scale was applied to the Sugiura study. This is a three-point scale in the curative setting. Dasatinib scored the highest on this scale which is considered as offering substantial clinical benefit. The 3-year Event-Free Survival was 66%, which was above the pre-specified target of 60%. This 60% target was based on the outcomes of a previous trial using imatinib by the same study group and similar eligibility criteria.

4. Patient group summary

A joint Patient group partner statement was received from Blood Cancer UK and Leukaemia care, both organisations are registered charities. Blood Cancer UK has received 1.61% pharmaceutical company funding in the past two years. Leukaemia Care has received 18.82% pharmaceutical company funding in the past two years. A representative from Leukaemia Care participated in the NCMAG Council meeting. The key points from the joint submission are summarised below:

- ALL is a rare and rapidly progressing form of leukaemia. ALL symptoms appear quickly with many patients receiving a diagnosis following an emergency presentation, which the patient group partners noted can have a profound impact on the psychological health of the patient.

- Symptoms include fatigue, bone and joint pain, rapid weight loss and bruising and bleeding, which can impact on patients' ability to participate in normal activities like work, education and exercise.

- Treatment with intensive chemotherapy can be gruelling for patients, causing significant disruption to their lives. The addition of novel TKIs has revolutionised the care of newly diagnosed ph+ ALL with positive outcomes potentially reducing the need for a stem cell transplant, which is associated with significant treatment-related morbidity and mortality. Ph+ ALL can become resistant to imatinib impacting patients' prognosis. Dasatinib can be effective against mutations which cause resistance to imatinib.

5. Benefit-risk balance

This is an off-label use of dasatinib for the treatment of newly diagnosed Ph+ ALL. Dasatinib in combination with chemotherapy has been shown to induce haematological complete remission and achieve MRD negativity. One study reported an estimated 5-year overall survival rate of 46% and other studies reported estimated 3-year survival rates of 69% and 81%. However, there are some generalisability concerns with the available evidence.

Dasatinib's efficacy and safety compared to on-label imatinib is uncertain. The Ravandi et al 2016 and Sugiura et al studies report longer overall survival with dasatinib than the published imatinib

studies. Naïve comparisons do not account for clinical and methodological differences between studies and need to be interpreted with caution as the comparisons are very uncertain. There are no publications comparing the safety profiles of dasatinib and imatinib in Ph+ ALL.

6. Council Review |Clinical benefit-risk balance evaluation

After consideration of all the available evidence regarding the clinical benefits and harms, the Council were satisfied that the case had been made for the clinical effectiveness of dasatinib. Under the decision-making framework for value judgements, Council considered the clinical case to be compelling. Support for the clinical case is based on a recommended dasatinib starting dose of 100 mg administered orally once daily in combination with chemotherapy or as clinically recommended.

7. Economic Evidence Review Summary

Economic Overview

Type of economic evaluation

No relevant published cost-utility analysis was identified in the literature search. Therefore, a de-novo cost-comparison was performed.

Population, intervention, comparator and outcomes

The patient population was adults, 20 years of age and older, newly diagnosed with Ph+ ALL eligible for treatment with dasatinib. The comparator, based on it being the preferred option across the NHSScotland regional cancer networks, was imatinib. The economic analysis, being a cost-comparison, did not take into account any clinical outcomes or health-related quality of life.

Costs

Based on the proposed dosing, dasatinib was costed at 140mg once daily until discontinuation. However, as noted in section 3, there was variation in dosage across different studies and council supported the lower dose of 100mg daily based on the key supporting studies. Costs for both dosing regimens at list price are the same. Imatinib was costed with an initial two weeks of 400mg, followed by 600mg thereafter, taken once daily until discontinuation. The cost of chemotherapy, steroids and monoclonal antibodies were not included in the cost-comparison. These are expected to be administered along both dasatinib and imatinib and may have a minimal impact in incremental costs. The treatment duration was established based on the median DFS, as demonstrated by the clinical data, which showed a DFS of 31 months for dasatinib and 22 months for imatinib (Ravandi et al. 2015 and Naval et al. 2015, respectively)[12, 20].

Given the absence of comparative safety data for dasatinib versus imatinib, the incremental costs associated with adverse events were uncertain. The costs of managing pleural effusion in the hospital (non-elective short stay) for patients on dasatinib are presented separately (National Schedule of NHS Costs 2020-21, accessed May 2024). The proportion of pleural effusions for dasatinib 140mg OD patient group was sourced from the Ravandi et al. (2015)[12].

Results

These exclude value added tax (VAT).

Using the BNF NHS indicative price for the cheapest generic alternative (accessed May 2024), the medicine acquisition cost of 140 mg of dasatinib, taken once daily for a treatment duration of 31 months, was £38K per patient.

Compared with 22 months of imatinib, 31 months of dasatinib increased medicine acquisition costs by £27.72K per patient (BNF NHS indicative list prices accessed May 2024). When including adverse events this figure was £27.98K.

The Council considered results using confidential NHSScotland medicine pricing agreements in decision making. NCMAG is unable to publish the results using confidential pricing due to commercial in confidence issues.

Cost-effectiveness considerations

Generalisability of the cost comparison

NHSScotland national framework prices for both dasatinib and imatinib were considered in confidence to increase the generalisability of the net costs. As of May 2024, branded dasatinib is available as a single 140mg tablet with confidential Patient Access Schemes (PAS). However, lower cost generic versions, in strengths of 100mg and 20mg as film-coated tablets, are also available. The cost of generic versions was used in the base case.

Limitations of the cost comparison

Due to an absence of a published cost-utility analysis, the analysis only compares costs. The results of the cost-comparison show that dasatinib in first line setting is a cost-increasing intervention compared to imatinib. Given the evidence supporting the clinical benefit of this intervention, it may offer clinical benefit compared to its comparator. However, given the absence of a quality-adjusted life year (QALY) estimate, an incremental cost-effectiveness ratio (ICER) is not available, and the cost-effectiveness remains unknown.

The analysis uses median DFS as a proxy for the average duration of treatment. However, as the DFS refers to the time from achieving CR until relapse or death, it may not accurately represent the treatment duration because it may only include those who responded to the treatment. The EFS would be a more accurate measure as it is calculated from the beginning of treatment until an event. However, due to the unavailability of EFS for imatinib, DFS was used for both medicines' treatment durations for consistency. Moreover, it can vary due to multiple patient-specific factors such as relapse, intolerance, resistance, SCT, or death. In addition, there may be dose reductions or treatment interruptions. Due to issues of data paucity, inclusion of these parameters would likely have increased uncertainty and were therefore not considered in the calculation of medicine acquisition costs. It was assumed that treatment would continue uninterrupted for the full duration of treatment.

The medicine acquisition cost of dasatinib was based on the oral administration of dasatinib 140mg. As noted in section 3, the dosage varied across studies, with evidence-base supporting lower dose

of 100mg daily dasatinib. For imatinib, the acquisition cost was determined based on an initial two weeks of 400mg of imatinib, followed by 600mg thereafter, taken once daily until discontinuation. However, in practice, the dosage may vary according to the patient's tolerance.

There is uncertainty around subsequent treatments following dasatinib. The cost comparison analysis does not include the potential costs, or cost avoidance, of these treatments.

As explained in Section 1, patients responding well to TKIs may experience long-term durable remission without a transplant. The introduction of dasatinib may alleviate burden on healthcare services by reducing the need for SCT or CAR-T therapy (which have significant associated costs) in some of this patient population. However, due to lack of evidence on number of transplants avoided, this has not been included in the cost-comparison.

Finally, due to absence of comparative safety data for dasatinib versus imatinib, the incremental costs associated with adverse events other than pleural effusion were not considered in the cost-comparison.

Summary

The cost-comparison indicated that dasatinib is a cost-increasing intervention compared to imatinib in the first line setting. Given the clinical evidence supporting the benefit of this intervention, it may offer clinical benefit compared to imatinib. However, in the absence of an analysis to quantify treatment benefits in relation to costs, an ICER was not available, and the cost-effectiveness remains unknown.

8. Council review | Cost-effectiveness evaluation

After consideration of the available evidence, the Council accepted that the proposed intervention was cost-increasing, and that in the absence of a cost-effectiveness analysis, the cost-effectiveness remained unknown. In this situation Council was able to consider other relevant information including service impact and estimated net medicines budget impact under the decision-making framework for value judgements.

9. Service Impact

Dasatinib is an oral treatment that would be used instead of imatinib in the newly diagnosed setting. Dasatinib may cause pleural effusions which may require outpatient monitoring or inpatient treatment. It is estimated that approximately 10 patients per year may start treatment with dasatinib in the newly diagnosed setting in Scotland. Overall, dasatinib is not expected to have a significant service impact.

10. Budget Impact

In the absence of a cost-effectiveness analysis, a detailed budget impact analysis was conducted.

Patient uptake

The patient uptake was calculated using epidemiological data presented in Section 1. This leads to an approximate number of 8 adult patients, 20 years of age and older, newly diagnosed with Ph+ ALL in Scotland and eligible for treatment with dasatinib each year. No adjustments were made for treatment discontinuations or interruptions. The base case assumed that 100% of eligible patients would receive treatment with TKI.

Per patient medicine cost and treatment duration

As the intervention will be distributed from secondary care, medicine prices in the budget impact analysis include VAT.

Based on proposed dosing, dasatinib was costed at 140mg once daily until discontinuation. However, as noted in section 3, there was a variation in dosage across different studies. The budget impact of the evidence-based, and council supported, lower dose of 100mg daily dasatinib was explored in scenario 1 (Table 4). Imatinib was costed with an initial two weeks of 400mg, followed by 600mg thereafter, taken once daily until discontinuation. Costs were not discounted. NHSScotland national framework prices for both dasatinib and imatinib were considered in confidence to increase the generalisability of the net costs.

The treatment duration was established based on the median DFS, as demonstrated by the clinical data, which showed a DFS of 31 months for dasatinib and 22 months for imatinib (Ravandi et al. 2015 and Naval et al. 2015, respectively)[12, 20]. The medicine acquisition costs in the first year are capped at 12 months of treatment. A higher medicine acquisition cost corresponding to the steady states in the second and third years onwards, for imatinib and dasatinib respectively, has been presented. This approach accounts for patients who begin their treatment in the first year and continue into the subsequent years, assuming they do not discontinue therapy during this time.

Comparator displacement

The introduction of dasatinib was assumed to displace 100% of imatinib in the eligible patient population. A lower displacement of 75% is explored in Scenario 2.

Results

In Year 1 the net medicines budget impact was estimated to be £88K based on an uptake of 8 patients and duration of therapy capped at 12 months. In the steady state the net medicines budget impact was estimated to be £266K based on an uptake of 8 patients and duration of therapy in line with median DFS. All figures are calculated using BNF list price (accessed May 2024) and include VAT.

Table 3 | Budget impact analysis base case results (BNF list prices)

	Year 1	Steady state
Dasatinib in newly diagnosed Ph+ ALL		
Acquisition cost[a]	£17,532	£45,291
Imatinib in newly diagnosed Ph+ ALL		
Acquisition cost[b]	£6,522	£12,028
Number of adult patients		
Newly diagnosed and eligible for TKI	8	8
Displacement		
Percentage of imatinib displaced by dasatinib	100%	100%
Budget Impact		
Net budget impact	£88,079	£266,102

[a] Based on the oral administration of dasatinib 140mg, taken once daily for 12 months in the first year and 31 months in the steady state, which would be achieved in year 3.

[b] Based on the oral administration of imatinib 400mg for two weeks followed by 600mg, taken once daily for 12 months in the first year and 22 months in the steady state, which would be achieved in year 2.

Scenario considerations

The following table presents a budget impact (net medicines cost) scenarios, exploring data based on alternate assumptions.

Table 4 | Scenario analyses (List price; Including VAT)

#	Analysis	Scenario description	Dasatinib acquisition cost per patient		Imatinib acquisition cost per patient		Total number of patients treated	Budget impact – Net medicine costs	Budget impact – Net medicine costs
			Year 1	Steady state	Year 1	Steady state		Year 1	Steady state
	Base case		£17,532[a]	£45,291[a]	£6,522[c]	£12,028[c]	8	£88,079	£266,102
1	Scenario 1	100 mg dasatinib	£17,532[b]	£45,291[b]	£6,522[c]	£12,028[c]	8	£88,079	£266,102
2	Scenario 2	75% displacement of imatinib	£17,532[a]	£45,291[a]	£6,522[c]	£12,028[c]	8	£66,059	£199,576

[a] Based on the oral administration of dasatinib 140mg, taken once daily for 12 months in the first year and 31 months in the steady state, which would be achieved in year 3.

[b] Based on the oral administration of dasatinib 100mg, taken once daily for 12 months in the first year and 31 months in the steady state, which would be achieved in year 3.

[c] Based on the oral administration of imatinib 400mg for two weeks followed by 600mg, taken once daily for 12 months in the first year and 22 months in the steady state, which would be achieved in year 2.

Limitations

In addition to the limitations listed in Section 7, the estimated number of patients who will need dasatinib was subject to uncertainty. Since the duration of treatment exceeds two years, for both imatinib and dasatinib, the number of patients treated within the service can increase in the following years. This has been captured in the steady state budget impact by considering patients who begin their treatment in the first year and continue into the subsequent years, assuming they do not discontinue therapy during this time. However, discontinuation can occur due to various reasons such as relapse, intolerance, SCT, or death, and the time to discontinuation can vary significantly. The annual budget impact is based on assumption that the therapy with dasatinib or imatinib would continue uninterrupted for the full year. Therefore, the actual budget impact may be lower than base case, as it assumes that all patients would continue treatment until steady state and receive uninterrupted treatment. As a result, the base case estimate may be an overestimate. Furthermore, the medicine acquisition cost of dasatinib was based on the oral administration of dasatinib 140 mg. As noted in section 3, dosing of dasatinib varied in the studies, with the most frequently used dose being 100mg once daily. This is explored in Scenario 1 (Table 4).

Finally, the proposal form noted treatment being accessed through individual patient treatment requests. Therefore, the Year 1 budget impact of the proposal may be overestimated as some patients may already be receiving dasatinib and these costs have not been accounted for.

Summary

The use of dasatinib will increase the budget impact compared to imatinib in this patient group. For 31 months of treatment with dasatinib, the medicine acquisition cost was expected to be £18K in year 1 and £45K in the steady state, compared to £7K in year 1 and £12K in the steady state for 22 months of treatment with imatinib. Based on an estimated uptake of 8 patients, the estimated net medicines budget impact was £88K in year 1 and £266K in steady state. All figures are based on BNF list prices, using the NHS indicative price for the cheapest generic alternative (accessed May 2024), and include VAT. The proposal form and real-world data suggests that dasatinib is currently being accessed, which may be through individual patient requests.

The Council considered the net medicines budget impact using more favourable confidential NHSScotland medicine pricing agreements in decision making. NCMAG is unable to publish the budget impact using confidential pricing due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the relevant discount pricing.

Separate information will be supplied by the boards to facilitate budget impact assessment.

11. Council review | Overall proposal evaluation

After consideration of all relevant information under the Decision-making framework for value judgements the Council made a decision to support this use. Support is based on a recommended dasatinib starting dose of 100 mg administered orally once daily in combination with chemotherapy, or as clinically recommended.

12.Acknowledgements

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13.References

1. Australian Public Assessment Report for Dasatinib Proprietary Product Name: Sprycel Sponsor: Bristol-Myers Squibb Australia Pty Ltd: January 2019 https://www.tga.gov.au/sites/default/files/auspar-dasatinib-190123.pdf accessed 10 June 2024.

2. AUSTRALIAN PRODUCT INFORMATION DASATINIB ARX (DASATINIB) TABLETS https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-02657-3&d=20240625172310101Accessed 10 June 2024.

3. Public Health Scotland Leukaemia statistics https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fwww.publichealthscotland.scot%2Fmedia%2F18382%2Fi_cancer_leukaemias.xls&wdOrigin=BROWSELINK Acessed 14 May 2024.

4. Foa R, Chiaretti S. Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia. New England Journal of Medicine. 2022;386(25):2399-411.

5. Haematological malignancy research network: survival statistics, https://hmrn.org/statistics/survival Accessed: 25 May 2024

6. Hoelzer D, Bassan R, Boissel N, Roddie C, Ribera J, Jerkeman M. ESMO Clinical Practice Guideline interim update on the use of targeted therapy in acute lymphoblastic leukaemia. Annals of Oncology. 2024;35(1):15-28.

7. Ravandi F, Jorgensen JL, Thomas DA, O'Brien S, Garris R, Faderl S*, et al.* Detection of MRD may predict the outcome of patients with Philadelphia chromosome-positive ALL treated with tyrosine kinase inhibitors plus chemotherapy. Blood. 2013;122(7):1214-21.

8. Wieduwilt MJ. Ph+ ALL in 2022: is there an optimal approach? Hematology. 2022;2022(1):206-12.

9. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Acute Lymphoblastic Leukemia Version 4.2023 — February 05, 2024.

10. Gökbuget N, Boissel N, Chiaretti S, Dombret H, Doubek M, Fielding A*, et al.* Management of ALL in adults: 2024 ELN recommendations from a European expert panel. Blood. 2024;143(19):1903-30.

11. Mylan. Dasatinib. Summary of product characteristics. Electronic Medicines Compendium. https://www.medicines.org.uk/emc/product/14399/smpc. Last updated 25 July 2023.

12. Ravandi F, O'Brien SM, Cortes JE, Thomas DM, Garris R, Faderl S*, et al.* Long-term follow-up of a phase 2 study of chemotherapy plus dasatinib for the initial treatment of patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Cancer. 2015;121(23):4158-64.

13. Ravandi F, Othus M, O'Brien SM, Forman SJ, Ha CS, Wong JYC*, et al.* US Intergroup Study of Chemotherapy Plus Dasatinib and Allogeneic Stem Cell Transplant in Philadelphia Chromosome Positive ALL. Blood Adv. 2016;1(3):250-9.

14. Sugiura I, Doki N, Hata T, Cho R, Ito T, Suehiro Y*, et al.* Dasatinib-based 2-step induction for adults with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood advances. 2022;6(2):624-36.

15. Ravandi F, O'Brien S, Thomas D, Faderl S, Jones D, Garris R*, et al.* First report of phase 2 study of dasatinib with hyper-CVAD for the frontline treatment of patients with Philadelphia chromosome-positive (Ph +) acute lymphoblastic leukemia. Blood. 2010;116(12):2070-7.

16. Novartis Pharmaceuticals UK Ltd. imatinib mesilate. Summary of product characteristics. Electronic Medicines Compendium. https://www.medicines.org.uk/emc/product/5566/smpc. Last updated 17 Jan 2024.

17. Fielding AK, Rowe JM, Buck G, Foroni L, Gerrard G, Litzow MR*, et al.* UKALLXII/ECOG2993: addition of imatinib to a standard treatment regimen enhances long-term outcomes in Philadelphia positive acute lymphoblastic leukemia. Blood. 2014;123(6):843-50.

18. Tanguy-Schmidt A, Rousselot P, Chalandon Y, Cayuela J-M, Hayette S, Vekemans M-C*, et al.* Long-Term Follow-Up of the Imatinib GRAAPH-2003 Study in Newly Diagnosed Patients with De Novo Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: A GRAALL Study. Biology of Blood and Marrow Transplantation. 2013;19(1):150-5.

19. Lim SN, Joo YD, Lee KH, Kim DY, Lee JH, Lee JH*, et al.* Long-term follow-up of imatinib plus combination chemotherapy in patients with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. Am J Hematol. 2015;90(11):1013-20. Epub 20151012.

20. Naval D, Deborah T, Farhad R, Jorge C, Rebecca G, Elias J*, et al.* Final report of a phase II study of imatinib mesylate with hyper-CVAD for the front-line treatment of adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Haematologica. 2015;100(5):653-61.

21. Hatta Y, Mizuta S, Matsuo K, Ohtake S, Iwanaga M, Sugiura I*, et al.* Final analysis of the JALSG Ph+ALL202 study: tyrosine kinase inhibitor-combined chemotherapy for Ph+ALL. Annals of Hematology. 2018;97(9):1535-45.

22. Daver N, Thomas D, Ravandi F, Cortes J, Garris R, Jabbour E*, et al.* Final report of a phase II study of imatinib mesylate with hyper-CVAD for the front-line treatment of adult patients with Philadelphia chromosome-positive acute lymphoblastic Leukemia. Haematologica. 2015;100(5):653-61.

23. Cortes JE, Saglio G, Kantarjian HM, Baccarani M, Mayer J, Boqué C*, et al.* Final 5-Year Study Results of DASISION: The Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients Trial. J Clin Oncol. 2016;34(20):2333-40. Epub 20160523.

24. Radich JP, Kopecky KJ, Appelbaum FR, Kamel-Reid S, Stock W, Malnassy G*, et al.* A randomized trial of dasatinib 100 mg versus imatinib 400 mg in newly diagnosed chronic-phase chronic myeloid leukemia. Blood. 2012;120(19):3898-905.

25. European Medicines Association, Scientific Discussion (SPRYCEL), https://www.ema.europa.eu/en/documents/scientific-discussion/sprycel-epar-scientific-discussion_en.pdf acessed 30 May 2024.

This advice represents the view of the NCMAG Council and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Minor document amendments

Date	Previous version	Amendment	Updated version	Approved by