AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Evidence Status Report: sorafenib for maintenance treatment following allogeneic haematopoietic cell transplantation for acute myeloid leukaemia associated with a FLT3-ITD mutation

February 2022

KEY FINDINGS

Licence status

Sorafenib is not licensed for maintenance treatment following allogeneic stem cell transplantation for acute myeloid leukaemia associated with a FLT3-internal tandem duplication (ITD) mutation; its use in this indication is off-label.

Clinical evidence

The evidence of clinical efficacy of sorafenib in this setting comes mainly from two clinical trials. Both trials concluded sorafenib maintenance therapy reduces the risk of relapse and death after haematopoietic cell transplantation for FLT3-ITD positive acute myeloid leukaemia.

Safety

No new safety signals have been observed for sorafenib in this indication. Results from both clinical efficacy trials show sorafenib was generally well tolerated and adverse effects are often managed with dose reductions.

Patient factors

Sorafenib is administered orally twice a day for two years. Bone marrow and blood monitoring is standard of care for acute myeloid leukaemia patients. Clinical experts state increased blood test frequency is required in year two for sorafenib treated patients to monitor for toxicity.

Cost effectiveness

There are no studies on the cost effectiveness of sorafenib for this indication.

Budget impact

The addition of sorafenib to the treatment pathway for two years would be associated with a cost of between [commercial in confidence text removed] and [commercial in confidence text removed] depending on dose and treatment response rates. Resulting in a net additional cost of [commercial in confidence text removed] in year one and [commercial in confidence text removed] in year two, assuming no treatment (watch and wait) as the alternative. This is based on four patients per year estimated by specialist clinicians consulted by All Wales Therapeutics and Toxicology Centre (AWTTC).

Impact on health and social care services

Minimal increased use of existing services.

Innovation and/or advantages

Welsh clinical experts indicate an unmet need in this population and an absence of any alternative licenced maintenance treatments that prevent relapse of acute myeloid leukaemia.

BACKGROUND

Clinicians in Wales consider there is an unmet need and have identified a cohort of patients who could benefit from this treatment. All Wales Therapeutics and Toxicology Centre (AWTTC)-sought clinical expert opinion reiterates the prognosis for relapsed FLT3-internal tandem duplication (ITD) positive acute myeloid leukaemia (AML) is extremely poor with survival < 10% if relapse occurs in the first six months post-transplant. The probability of disease recurrence is over 50% and AML relapse is the most frequent type of treatment failure after haematopoietic cell transplantation (HCT), especially in high-risk patients with FLT3-ITD AML[1]. Survival rates are also poor if relapse occurs between months 6 - 24 post-transplant. Within this cohort, options are extremely limited and so the international community has recognised that upfront treatment to prevent relapse carries the best chance of improved outcomes[2].

Target group

The indication under consideration is maintenance treatment following allogeneic HCT for AML associated with a FLT3-ITD mutation.

Marketing authorisation date: *Not applicable, off-label*

Sorafenib is not licensed for maintenance treatment following allogeneic HCT for AML associated with a FLT3-ITD mutation; its use in this indication is off-label.

Sorafenib is licensed for the treatment of hepatocellular, renal and thyroid cancer[3].

Dosing information

The European Society for Blood and Marrow Transplantation (EBMT) recommends post-transplant maintenance sorafenib at a dose of 400 mg/day in two divided doses[2]. Patients with minimal residual disease (MRD)-positive AML may receive 800 mg/day in two divided doses, to be adapted according to tolerance. Sorafenib should be transiently discontinued in the case of graft versus host disease (GvHD) requiring systemic treatment with corticosteroids, but may be cautiously resumed once remission of GvHD is documented[2].

Clinical background

AML is a cancer of the blood and bone marrow[4]. It is characterised by clonal proliferation derived from primitive haematopoietic stem cells or progenitor cells. Abnormal differentiation of myeloid cells results in a high level of immature malignant cells and fewer differentiated red blood cells, platelets and white blood cells[5].

FMS-like tyrosine kinase-3 (FLT3) is a transmembrane ligand-activated receptor tyrosine kinase that is normally expressed by hematopoietic stem cells and early myeloid and lymphoid progenitor cells. FLT3 plays a role in the proliferation, differentiation and apoptosis of hematopoietic cells through various signalling pathways[6]. FLT3 gene mutations are found in about 30% of newly diagnosed cases of AML. The FLT3-ITD mutation is most common, occurring in approximately 25% of all AML cases[7].

The exact underlying cause of AML is unknown but includes environmental exposure, previous chemotherapy treatment and can occur secondary to pre-existing haematological disorders and certain genetic conditions[4]. However, in the majority of cases, it appears as a *de novo* malignancy in previously healthy individuals[8].

AML typically presents with a rapid onset of symptoms that are attributable to bone marrow failure including pallor, fatigue, fever, weight loss and shortness of breath and may be fatal within weeks or months when left untreated[4,5]. Prognosis with AML varies substantially depending on cytogenetics, mutation status, age, and comorbidities[9]. An FLT3-ITD mutation is associated with relatively poor prognosis so patients are usually referred for allogenic HCT in first complete remission[2]. Post allogenic HCT prognosis remains poor due to higher rates of early relapse and lack of response to chemotherapy salvage[10].

Based on their mechanism of action tyrosine-kinase inhibitors (TKIs) such as sorafenib and midostaurin have been used in FLT3 mutated AML. Studies are presented below on the use of sorafenib in the maintenance setting.

Incidence/prevalence

AML accounted for less than 1% of all new cancer cases in the UK in 2016-2018[11]. AML has an annual incidence rate of 4.1 per 100,000 and the median age at diagnosis is 72 Years[12]. In the UK in 2016-2018, on average each year more than 4 in 10 new cases (42%) were in people aged 75 and over[11]. Five-year survival percentage is highest in patients under 40 Years old (52%), with survival generally decreasing with increasing age (< 4% for patients ≥ 70 Years old)[12].

In Wales, there is an average of 164 new cases of AML diagnosed each year[11], and 141 deaths[11].

Current treatment options and relevant guidance

Chemotherapy is the treatment of choice for patients who are considered fit enough to tolerate intensive regimens[13]. The early goals of treatment are to achieve complete remission (< 5% blasts on bone marrow morphology) and reduce the risk of relapse. The long-term goal is to improve disease-free survival and overall survival, with minimum possible treatment-related toxicities. For younger patients (< 60 years of age) treated with intensive chemotherapy, the overall goal is disease cure. In older patients, the main aim is to achieve a complete remission that extends the patient's life to a good-quality standard[13].

The first phase of treatment is induction therapy which aims to reduce tumour burden and restore normal haematopoiesis and includes a combination of two or more chemotherapy medicines[13]. Consolidation therapy follows to prevent any risk of relapse by eliminating any residual disease[14]. For eligible patient's, high dose chemotherapy followed by an HCT may be given at this stage. Patients receiving an HCT should be monitored for signs or symptoms of acute or chronic GVHD[13]. After consolidation therapy/HCT is completed, maintenance treatment is recommended to help keep the leukaemia in remission. For post HCT patients there is currently no standard approved maintenance treatment. For those patients not receiving HCT, the NICE pathway treatment options include azacitidine and midostaurin[15-17]. The maintenance phase lasts for about 2 years in an outpatient setting[14]. The FLT3 mutation is associated with poorer outcomes, such as a higher risk of relapse (up to

60% within the first 2 years of induction therapy)[18]. Currently gilteritinib monotherapy is recommended as an option for treating relapsed or refractory FLT3 mutation positive AML in adults[18]. Donor lymphocyte infusion (DLI) is predominately used to treat and prevent relapse after HCT by exploiting the graft-versus-leukaemia (GvL) effect of donor derived T cells[19]. However, DLI might increase the risk of severe life-threatening complications such as GvHD as well as severe infections[19].

Clinical practice recommendations for diagnosis, treatment and follow-up have been published by the EBMT[2]. and suggest post-transplant AML maintenance therapy with a FLT3 inhibitor (except for patients with active acute GvHD). Sorafenib has been identified as a potential maintenance therapy following HCT, demonstrating benefit with regards to survival and improved outcomes[2]. The European Society for Medical Oncology (ESMO) state that guidance for targeted agents are either not available, or are still under investigation[20]. EBMT state that sorafenib could be considered as the preferred option at this time, pending investigation of other agents[2].

SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

Efficacy

Evidence for the efficacy of sorafenib in this setting comes principally from two clinical trials; SORMAIN and NCT02474290[9,21].

SORMAIN was a randomised, placebo-controlled study that investigated whether maintenance therapy with sorafenib can improve outcome after allogeneic HCT in high risk FLT3-ITD positive AML[9]. A total of 83 patients (median age 54 years) were randomly assigned to sorafenib maintenance (n = 43) or placebo (n = 40) at 60 to 100 days post HCT. The dose of study medication was incremented from 400 mg to 800 mg per day and continued for 24 months or until occurrence of relapse or intolerable toxicity[9].

The primary endpoint of relapse-free survival (RFS) was calculated as time from randomisation to either AML relapse or death from any cause. At the time of the RFS data entry lock, median follow-up was 41.8 months. The median RFS was not reached in the sorafenib group and was 30.9 months in the placebo group[9]. Primary and secondary outcome results are detailed in Table 1.

Table 1. Results from SORMAIN trial[9]

	Sorafenib n = 43	Placebo n = 40
Median RFS*	not reached	30.9 months
HR for relapse or death (95% CI;)	0.39 (0.18 to 0.85) p = 0.013	
24-month probability RFS (95% CI) Corresponding HR for relapse or death (95% CI)	85.0% (70% to 93%) 0.256 (0.10 to 0.65) p = 0.002	53.3% (36% to 68%)
24-month probability OS (95% CI) Corresponding HR for relapse or death (95% CI)	90.5% (77% to 96%) 0.241 (0.08 to 0.74) p = 0.007	66.2% (49% to 79%)
Median OS†	not reached	not reached
HR for death (95% CI)†	0.52 (0.24 to 1.11) p = 0.086	

*median follow-up was 41.8 months †median follow-up duration of 55.1 months CI: confidence interval; HR: hazard ratio; OS: overall survival; RFS: relapse-free survival

Relapse mortality was significantly higher in the placebo group compared with sorafenib (14 versus 4 deaths respectively, p = 0.01). In contrast, non-relapse mortality did not differ between the two treatment arms. Of the 25 relapsing patients, 18 (72%) were treated with sorafenib, 17 patients were treated with chemotherapy (68%), and 6 patients (24%) underwent second HCT with no statistically significant differences between the two arms[9].

NCT02474290 included a total of 202 patients (median age 35 years) randomly assigned to sorafenib maintenance (400 mg orally twice daily; n = 100) or no maintenance (n = 102) at 30 to 60 days post-transplantation[21]. The primary endpoint of cumulative incidence of relapse assessed at 1-year post-transplantation, was 7.0% (95% Confidence Interval [CI] 3.1 to 13.1) for patients assigned to sorafenib and 24.5% (16.6 to 33.2) for those allocated to no maintenance (hazard ratio [HR] 0.25, 95% CI 0.11 to 0.57; p = 0.0010). Primary and secondary outcomes are detailed in Table 2. Median follow-up was 21.3 months post-transplantation. A total of 49 patients died, 17 were in the sorafenib group and 32 were in the no maintenance group. Causes of death were leukaemia relapse (n = 24; five in the sorafenib group and 19 in the no maintenance group), infections (n = 16; eight in each group), GVHD (n = 7; three in the sorafenib group and four in the no maintenance group), thrombotic microangiopathy (n = 1; placebo group), and acute left heart failure (n = 1; sorafenib group). Median overall survival (OS) and leukaemia-free survival (LFS) was not reached in either group[21].

Table 2. Results from NCT02474290 trial[21]

	Sorafenib n = 100	**No maintenance n = 102**
1-year cumulative incidence of relapse (95% CI)	7.0% (3.1 to 13.1)	24.5% (16.6 to 33.2)
HR (95% CI)	0.25 (0.11 to 0.57) p = 0.0010	
2-years cumulative incidence of relapse (95% CI)	11.9% (6.2 to 19.6)	31.6% (22.6 to 41.1)
HR (95 % CI)	0.29 (0.15 to 0.58) p < 0.0001	
Relapsed patients (n)	11	32
Median time to relapse (95% CI)	11.6 months (4.8 to 16.8)	5.7 months (4.6 to 10.6)
2-year OS (95% CI)	82.1% (72.6 to 88.5)	68.0% (57.8 to 76.2)
HR (95% CI)	0.48 (0.27 to 0.86) p = 0.012	
2-year leukaemia-free survival (95% CI)	78.9% (69.0 to 85.9)	56.6% (46.1 to 65.8)
HR (95% CI)	0.37 (0.22 to 0.63); p < 0.0001	
CI: confidence interval; HR: hazard ratio; OS: overall survival		

Further supportive evidence is available from a retrospective study using data from the EBMT registry[22]. Four hundred and sixty-two patients (mean age 50 years) were included, 28 of whom received sorafenib post-transplant as maintenance therapy.

Sorafenib was initiated at a median of 55 days post-transplant (range 1 to 173) at a median dose of 800 mg (range 200 to 800 mg) daily[22]. Post-transplant sorafenib maintenance as a time-dependent variable significantly reduced the relapse incidence (RI) (HR = 0.39; p = 0.05), and improved LFS (HR = 0.35; p = 0.01), OS (HR = 0.36; p = 0.03) and GvHD-free, relapse-free survival (GRFS) (HR = 0.44; p = 0.02). Using pair-matched analysis (26 sorafenib and 26 control patients), two-year LFS and OS were, respectively, 79% and 83% for patients in the sorafenib group versus 54% and 62% for controls. Comparison using the Cox model confirmed that prophylactic or pre-emptive sorafenib significantly reduced RI (HR = 0.38; p = 0.046) and improved LFS (HR = 0.37; p = 0.02), and OS (HR = 0.32; p = 0.007) without affecting non-relapse mortality (NRM)[22].

Chen et al. conducted a phase I trial to determine the safety and to define the maximum tolerated dose (MTD) of sorafenib when given as maintenance following HCT[23]. Secondary endpoints included progression-free survival (PFS) and OS with median follow up of 16.7 in surviving patients (see Table 3). Twenty-two patients (median age 54 years) were enrolled, at HCT 19 patients were in clinical remission and three had primary refractory disease although two had < 5% bone marrow blasts prior to HCT through the use of salvage agent sorafenib. In total, 3 of the 22 patients received sorafenib prior to HCT[23].

Table 3. Results from Chen et al. study[23]

	Year 1	Year 2
Entire cohort (n = 22)		
PFS (90% CI)	85% (66% to 94%)	72% (49% to 86%)
OS (90% CI)	95% (79% to 99%)	78% (51% to 91%)
Conventional complete remission patients (n = 19)		
PFS (90% CI)	95% (76% to 99%)	86% (61% to 96%)
OS (90% CI)	100%	78% (51% to 91%)
CI: confidence interval; PFS: progression-free survival; OS: overall survival		

The maximum tolerated dose was found to be 400 mg twice daily, although drug interruptions and dose reductions were common, 200 mg twice daily dose appeared to be as effective and was better tolerated[23].

A retrospective pilot study by Shi et al. compared sorafenib (n = 24, group A) with prophylactic DLI (n = 12, group B) or no treatment (n = 32, group C) to prevent relapse in 68 FLT3-ITD positive AML patients who received allogenic HCT. Sorafenib was initiated a median of 83 days post transplantation and was continued for a median of 238 days. The median patient age of this group was 24 years[24]. Sorafenib patients had statistically significantly higher OS and LFS rates at 2-years when compared to DLI and placebo. The 2-year cumulative incidence of relapse (CIR) was significantly different between sorafenib versus placebo but not versus DLI (see Table 4). There were no significant differences across the three groups in the 2-year post-transplant NRM[24].

Table 4. Results from Shi et al study[24].

	Group A (sorafenib) n = 24	Group B (DLI) n = 12	Group C (no treatment) n = 32
2-Year OS	95.8%	75%	67.0%
	A vs B OS: p = 0.043	B vs C OS: p = 0.718	A vs C OS: p = 0.018
2-Year LFS	95.8%	66.7%	60.9%
	A vs B LFS: p = 0.031	B vs C LFS: p = 0.628	A vs C LFS: p = 0.007.
2-Year CIR	4.2%,	25.0%,	33.4%,
	A vs B CIR p = 0.197	B vs C CIR p = 0.611	A vs C CIR p = 0.017
2-Year NRM	0.0%	8.3%	6.8%
CIR: cumulative incidence of relapse; DLI: donor lymphocyte infusion; LFS: leukaemia-free survival; NRM: non-relapse mortality; OS: overall survival			

A systematic review and meta-analysis of randomised controlled trials compared the efficacy and safety of maintenance therapy with observation or placebo in patients with AML after allogenic HCT[25]. The search yielded five trials including 736 patients. Maintenance therapy consisted of TKIs in three studies (sorafenib two studies; midostaurin one study) and hypomethylating agents (HMAs) in two studies (decitabine and azacitidine 1 study each)[25]. Maintenance therapy was associated with an improved OS, HR = 0.61 (95% CI 0.47 to 0.80). Subgroup analysis revealed advantage in OS with either TKI or HMA maintenance. RFS was also improved in the maintenance arm compared with the placebo arm HR = 0.51 (95% CI 0.40 to 0.66)[25].

Safety

The clinical safety of sorafenib have been studied in patients with hepatocellular carcinoma, advanced renal cell carcinoma and differentiated thyroid carcinoma[3]. Adverse events associated with sorafenib, reported in ≥ 1 in 10 patients, include infection, lymphopenia, anorexia, hypophosphataemia, haemorrhage, hypertension, diarrhoea, nausea, vomiting, constipation, dry skin rash, hand foot skin reaction, alopecia, pruritus, arthralgia, fatigue and fever[3].

The meta-analysis by Pasvolsky et al. shows that post-transplant maintenance therapy in AML patients is effective in improving RFS and OS, with a satisfactory safety profile[25]. The most common adverse events observed in the Chen et al study were skin rashes (n = 8) and GI symptoms (diarrhoea, n = 7; nausea, n = 5; weight loss, n = 5 and abdominal pain, n = 4) which improved with drug interruptions or dose reductions[23]. The majority of the skin rashes appeared clinically consistent with acute GVHD; however, they all resolved with temporary holding of sorafenib. There was one case of acute GVHD (grade 2 skin disease) after starting sorafenib, the 12-month cumulative incidence of chronic GVHD was 38% (90% CI, 21% to 56%)[23].

Results from both efficacy trails show sorafenib was generally well tolerated[9,21].

Across both efficacy trials, dose reductions were performed in 63 of 143 (44.1%) of sorafenib patients due to adverse events. There were 14 study drug discontinuations, the most frequent adverse events associated with sorafenib dose modifications were

acute GVHD, haematological adverse events and skin-related adverse events. There were no treatment related deaths in either trial[9,21].

The most frequently reported grade ≥ 3 adverse events in both efficacy trials for sorafenib included: acute/chronic GVHD (51.4%; two were reported as treatment related in NCT02474290); infections (25.4%; one was reported as treatment related in SORMAIN), haematological changes (neutropenia and thrombocytopenia) (17.6%; six were reported as treatment related across both trials) and gastrointestinal toxicity (12.0%; two were reported as treatment related in SORMAIN trial)[9,21].

Discussion

The results of both efficacy trials are supportive of sorafenib maintenance therapy to reduce the risk of relapse and death after HCT for FLT3-ITD positive AML. In SORMAIN the relapse rate was only 15% after 2 years in those receiving maintenance sorafenib which appears to be a clinically meaningful improvement[8]. A limitation of SORMAIN was its premature termination because of inadequate enrolment. Also, nine SORMAIN patients were treated upfront with midostaurin. Limitation of the NCT02474290 trial was it was a non-blinded and non-placebo controlled study, which might carry a higher risk of bias. Sorafenib was also only administered six-months post-transplantation. The patient demographics also slightly differed between trials as the median age in SORMAIN was 54 years but the median age in NCT02474290 was 35 years. Around half of the patients in this latter study also received sorafenib pre-transplant (sorafenib and no maintenance group). This differs to how sorafenib will be used in NHS Wales, which would be as maintenance post-transplant only. These factors may favour treatment and may in part be why the relapse rates were lower than for previously reported outcomes in FLT3 mutated AML[18]. The results of the phase I study by Chen et al. are limited by the small sample size and heterogeneity of patient characteristics. The study included six patients older than the age of 60 and stated the inclusion of older patients may lead to increased relapse rate[23].

There is no official published treatment protocol for maintenance sorafenib to treat AML associated with a FLT3-ITD mutation. The evidence from a review generated by international leukaemia or transplant experts, mostly from the EBMT, attempts to develop a position statement on best approaches. This review states ‘maintenance therapy duration is not firmly established, but a minimum of 2 years is recommended, depending on tolerance’[2].

Sorafenib is administered orally which allows administration at home by patients or carers. Sorafenib is already licensed for use in other cancer treatments so the safety profile is well documented. The use of sorafenib as maintenance therapy to reduce the risk of relapse and death after HCT for FLT3-ITD positive AML was not associated with significantly more adverse effects than placebo. Toxicity has been managed with dose reductions, which was seen in 63 of 143 (44%) patients across both efficacy trials[9,21].

All studies identified by AWTTC concluded that sorafenib maintenance therapy reduces the risk of relapse and death after HCT for FLT3-ITD positive AML however, the benefits of altered duration of the maintenance period needs further investigation. In the absence of an appropriate clinical trial, sorafenib could be considered as the preferred option, but the role of other FLT3 inhibitors warrants investigation.

Cost-effectiveness evidence

There are currently no cost effectiveness data available.

BUDGET IMPACT

The recommended post-transplant maintenance dose of sorafenib is 400 mg/day in two divided doses. Patients with MRD-positive disease may receive 800 mg/day in two divided doses, adapted according to tolerance[2]. The list price of sorafenib is £2567 (200 mg tablets;112 pack)[26]. [Commercial in confidence text removed]. Clinical experts confirm that current practice in Wales would include bone marrow and blood monitoring during the maintenance period as standard of care. There would be increased blood monitoring associated with Year 2 in sorafenib patients to monitor for toxicity. Table 5 details the medicine and administration costs for sorafenib at both recommended doses. This includes VAT added to the medicine price.

Table 5. Estimated annual cost of sorafenib in Wales (per patient)

	Year 1	Year 2
Sorafenib (Nexavar®) (200 mg tablets;112 pack)	¶¶	¶¶
Annual drug administration costs*	£208	£208
Annual additional monitoring costs†	£0	£48
Annual total cost 400 mg/day	¶¶	¶¶
Annual total cost 800 mg/day	¶¶	¶¶

¶¶commercial in confidence figure removed
*****Assumes 'Deliver Exclusively Oral Chemotherapy (outpatient)'- National Schedule of Reference Costs (HRG codes SB11Z)[27]
†Assumes 'monthly blood test monitoring Clinical biochemistry and Haematology' - National Schedule of Reference Costs (HRG codes DAPS04 and DAPS05)[27]

If the patient relapses during the maintenance period, then gilteritinib is licensed for treating relapsed or refractory AML. It is assumed that all patients will receive gilteritinib on relapse in this scenario[18]. Initiation of gilteritinib is subject to electrocardiogram (ECG) and blood chemistry monitoring at specified intervals during treatment (National Schedule of Reference Costs HRG codes SB11Z, EY51Z and DAPS04 respectively)[27,28], these costs have been included in the budget impact assumptions.

According to clinical experts in Wales, approximately four patients each year would be treated with sorafenib. They indicate that the alternative to using sorafenib would be a watch and wait approach in most cases, although some patients may go on to receive DLI. For simplicity, it is assumed that the comparator is no treatment. Table 6 shows the net budget impact assuming that all four eligible patients receive 400 mg daily of sorafenib for 12 months compared with the same four patients receiving no treatment (watch and wait approach).

Using the data from the NCT02474290 trial, the median time to relapse was 11.6 months for sorafenib and 5.7 months for placebo with relapse rates at 1 year of 7% and 25% respectively[21]. Cumulative relapse rate in year 2 was 12% for sorafenib and 31% for no treatment (15% and 46% in SORMAIN respectively). Therefore, it is assumed that no patients treated with sorafenib relapse, and one patient on no treatment relapses after 6 months (subsequently receiving six-months of gilteritinib) in year 1. In year 2, one patient in the sorafenib group relapses and goes on to gilteritinib treatment for 9 months. In the no treatment group, the patient who relapsed in year 1 receives a further 3 months in year 2, and two new relapsed patients receive 6 and 9 months of gilteritinib treatment. Using the two-year OS data from the NCT02474290 trial, with rounding, it is assumed that in year 2 there are two deaths in the no treatment group and 1 death in the sorafenib group. For further visualisation of the individual patient pathways please see appendix 1.

Table 6. Estimated annual acquisition costs in Wales

	Year 1	Year 2
Number of people eligible for treatment	**4**	**8**
Scenario without sorafenib*		
Number of patients	4	8
Number of new relapses	1	2
Total number of relapsed patients receiving gilteritinib	1	3
Number of deaths	0	2
Scenario with sorafenib*		
Number of patients	4	8
Number of new relapses	0	1
Total number of relapsed patients receiving gilteritinib	0	1
Number of deaths	0	1
Estimated costs of above scenarios		
Total annual costs without sorafenib	¶¶	¶¶
Total annual costs with sorafenib†	¶¶	¶¶
Annual net cost§	¶¶	¶¶

¶¶commercial in confidence figure removed
*See appendix 1 for estimated patient pathways
†Based on 400 mg daily dosing
§may not compute due to rounding

The annual net cost in table 6 is based on patients receiving 400 mg a day. If all patients received 800 mg a day the annual net cost would be [commercial in confidence text removed] in year 1 and [commercial in confidence text removed] in year 2. As a high dose modification rate was seen in both efficacy trials, the 400 mg dose is likely to be a more realistic assumption than 800 mg.

Budget impact issues

- Additional monitoring costs have been included based on what the clinical expert advises will be required in extension to current standard of care.
- The budget impact analysis is for 2 years based on the maintenance therapy duration recommendation by EBMT[2]. The budget impact was capped at 2 years as there is limited data in the literature beyond this meaning extrapolation of costs is unlikely to be accurate. As One Wales reviews decisions at 12 months, further data may be available for more accurate forecast in the future.
- Mortality and relapse rates and OS are based on the two efficacy trials. NCT02474290 was the larger study and provided relapse rates for year 1 which was used to base the budget impact figures. However, SORMAIN was conducted in Europe so may be more representative of Welsh patients and therefore rates for both were used for patient outcome and cost projection.
- The budget impact has only considered drug costs for maintenance therapy.
- Patients that go on to receive gilteritinib after relapse may then receive DLI, but this has not been included in the budget impact for simplicity.
- The budget impact assumes that patients remain on 400 mg daily of sorafenib and there are no disruptions to treatment. No patient discontinues treatment due to toxicity.
- The analysis does not include costs of adverse events.

ADDITIONAL FACTORS

Prescribing unlicensed medicines

Sorafenib is not licensed to treat this indication and is therefore ‘off-label’. Providers should consult the relevant guidance on prescribing unlicensed medicines before any off-label medicines are prescribed.

Care has been taken to ensure the information is accurate and complete at the time of publication. However, the All Wales Therapeutics and Toxicology Centre (AWTTC) do not make any guarantees to that effect. The information in this document is subject to review and may be updated or withdrawn at any time. AWTTC accept no liability in association with the use of its content. An Equality and Health Impact Assessment (EHIA) has been completed in relation to the One Wales policy and this found there to be a positive impact. Key actions have been identified and these can be found in the One Wales Policy EHIA document.

Information presented in this document can be reproduced using the following citation: All Wales Therapeutics & Toxicology Centre. Evidence Status Report. Sorafenib Reference number: OW18. 2022.

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Appendix 1 Estimated pathway of individual patients for budget impact

Patient	Year 1				Year 2			
Scenario without sorafenib								
1								
2								
3								
4								
5								
6								
7								
8								
Scenario with sorafenib								
1								
2								
3								
4								
5								
6								
7								
8								

Key (each cell represents a 3-month time period)
Sorafenib or no treatment
Relapse - gilteritinib
Death