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

Sorafenib for maintenance treatment following allogeneic haematopoietic cell transplantation for acute myeloid leukaemia associated with a FLT3-ITD mutation (OW18)

June 2023 Review

ONE WALES INTERIM DECISION

Sorafenib for maintenance treatment following allogeneic haematopoietic cell transplantation for acute myeloid leukaemia associated with a FLT3-ITD mutation

Date of original advice: February 2022
Date of current review: June 2023

The following One Wales Medicines Assessment Group (OWMAG) recommendation has been noted by the All Wales Medicines Strategy Group (AWMSG) and ratified by Welsh Government

Using the agreed starting and stopping criteria, sorafenib can be made available within NHS Wales for maintenance treatment following allogeneic stem cell transplantation for acute myeloid leukaemia associated with a FLT3 ITD mutation.

The risks and benefits of the off-label use of sorafenib for this indication should be clearly stated and discussed with the patient to allow informed consent.

Providers should consult the relevant guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

This advice will be reviewed after 3 years or earlier if new evidence becomes available.

Clinician responsibility
Clinicians will be obliged to collect and monitor patient outcomes. Evidence of clinical outcomes will be taken into consideration when reviewing the One Wales Medicines Assessment Group decision.

Health board responsibility
Health boards will take responsibility for implementing One Wales Medicines Assessment Group decisions and ensuring that a process is in place for monitoring clinical outcomes.

One Wales advice promotes consistency of access across NHS Wales.

Starting and stopping criteria for sorafenib for the maintenance treatment following allogeneic haematopoietic cell transplantation for acute myeloid leukaemia associated with a FLT3-ITD mutation

Developed in collaboration with the haematological cancer services, Cardiff and Vale University Health Board.

This treatment is not to be used as a bridge to transplant or as an alternative option to haematopoietic cell transplantation.

Starting criteria:
Patients who have received an allogenic haematopoietic cell transplantation for acute myeloid leukaemia and where:

- There was presence of the FMS-like tyrosine kinase-3 internal tandem duplication (FLT3-ITD) mutation at the time of diagnosis or AML relapse.
- There is no evidence of graft versus host disease (GvHD)
- There are no contraindications to the use of sorafenib
- The patient is not eligible for entry into a clinical trial

Patients who satisfy the eligibility criteria will be prescribed sorafenib following consultation with the patient and/or carer after consideration of potential adverse effects, cautions and contraindications. This consultation should be recorded in the patient's notes.

The recommended dose is 800 mg/day in two divided doses to be adapted according to tolerance. Treatment should start 30-60 days post-transplant and may continue up to a maximum of two years.

Monitoring:

- Full blood count
- Urea and electrolytes
- Liver function tests
- Phosphate and calcium
- Blood glucose

The above tests should be done weekly for month 1 then monthly for 2 months, extended to every two months if the patient is well.

- Blood pressure every 1-2 months
- Thyroid function test (if clinical signs of hypo/hyperthyroidism)
- Electrocardiogram every 1-2 months
- Bone marrow monitoring (morphology, MRD, chimerism) at month 1, 2, 3, 6, 12,18 and 24 post-transplant, but monitoring can be increased as required.
- Clinical symptoms of GvHD
- Clinical evaluation of side effects, refer to Summary of Product Characteristics.

Any other monitoring should be in accordance with the Summary of Product Characteristics for sorafenib. Sorafenib should be transiently discontinued in the case of GvHD requiring systemic treatment with corticosteroids, but may be cautiously resumed once remission of GvHD is documented.

Stopping criteria:

- evidence of morphological relapse on bone marrow examination
- toxicity; a dose reduction may be considered, follow the guidance in the Summary of Product Characteristics.
- patient request
- after two years of sorafenib.

Only one course of treatment may be issued in accordance with this advice. Requests for repeat courses or continuing treatment beyond two years should be explored through funding mechanisms such as the individual patient funding request process.

This ia a summary of new evidence available and patient outcome data collected to inform the review

Background: Acute myeloid leukaemia (AML) is a cancer of the blood and bone marrow 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. Anaemia, bleeding problems and serious infections are common symptoms of AML. FMS-like tyrosine kinase-3 (FLT3) is a transmembrane ligand-activated receptor tyrosine kinase that plays a role in the proliferation, differentiation and apoptosis of hematopoietic cells through various signalling pathways. An FLT3-internal tandem duplication (ITD) mutation occurs in approximately 25% of all AML cases and is associated with relatively poor prognosis so patients are usually referred for allogenic haematopoietic cell transplantation (HCT) in first complete remission. AML relapse is the most frequent type of treatment failure after HCT, especially in patients with FLT3-ITD AML. Based on its mechanism of action tyrosine-kinase inhibitors (TKIs) such as sorafenib have been used in FLT3-ITD mutated AML to reduce the risk of relapse and improve survival.

This use of sorafenib for maintenance treatment following allogenic HCT is currently off-label. Clinicians in Wales consider there is an unmet need and have identified a cohort of people who could benefit from this treatment. This medicine was therefore considered suitable for assessment via the One Wales process.

Current One Wales Decision: Supported for maintenance treatment.

Licence status: Off-label use for this licensed medicine.

Guidelines: There have been no relevant updates to existing guidelines identified.

Licensed alternative medicines or Health Technology Assessment advice for alternative medicines: No new medicines or Health Technology Assessment advice reported.

Effectiveness: A repeat literature search conducted by AWTTC identified two papers which analysed the clinical effectiveness of sorafenib pertinent to the recommendation (See Appendix 1). These included a retrospective study published in August 2022 and a follow up study of the randomised control trial (RCT) NCT02474290 summarised in the original evidence status report. The primary objective of the follow up study was to report on viral infections (see safety section); clinical effectiveness data were reported as secondary endpoints. Overall results are comparable to those seen in the original evidence report with an indication that benefits with sorafenib are sustained.

The retrospective study by Aydin et al (2022) compared a cohort of 21 FLT3-ITD positive AML patients receiving sorafenib maintenance therapy with a control group of 22 patients without maintenance. The cumulative incidence of relapse for the sorafenib group compared to the control group at one (14.6% versus 42.4%), two (14.6% versus 42.4%) or three (14.6% versus 47.3%) years was significantly lower ($p = 0.028$). At 1 year, the pivotal study NCT02474290 reported a cumulative incidence of relapse (primary endpoint) of 7.0% (95% Confidence Interval [CI] 3.1 to

13.1) for patients assigned to sorafenib and 24.5% (95% CI:16.6 to 33.2) for those allocated to placebo (hazard ratio [HR] 0.25, 95% CI 0.11 to 0.57; p = 0.0010). Rates of relapse reported by Aydin et al were slightly higher when compared to the cohort in RCT NCT02474290 for both the sorafenib and control groups, this may in part be due to differences in study design and patient characteristics. The mean age of patients was markedly higher in this study (55 years) compared with the NCT02474290 cohort (35 years). The 3-year culminative incidence of relapse reported as a secondary endpoint in the follow up study of NCT02474290 (Xin et al, 2022) was 13.0% (95% CI: 7.3 to 20.4%) and 34.8% (95% CI: 25.5 to 44.2%), in the sorafenib and control groups respectively (hazard ratio= 0.306, 95% CI:0.162 to 0.579, p < 0.001). This indicates a sustained reduction in relapse rates with sorafenib compared with no maintenance treatment.

Similar to the RCTs included in the original evidence report the median overall survival (OS) had not been reached for the sorafenib group in the retrospective study after a median follow up of 34.7 months. This was compared with 31.4 months in the control group suggesting survival benefits when sorafenib is added as maintenance therapy, however median follow up was longer in the control group (67.9 months). Median OS was not reported in the NCT02474290 follow up study but OS rates for the sorafenib group at 3 years was 79% down slightly from 82.1% reported at two years in the original paper. The corresponding placebo group OS rates were lower than sorafenib at two years (68%) and three (61.4%) years. Overall there is an indication of prolonged survival advantage in the sorafenib group compared with no maintenance treatment.

Safety: A repeat literature search conducted by AWTTC identified one paper which analysed the safety of sorafenib pertinent to the recommendation. This was the follow-up of NCT02474290 (See Appendix 1).

The open-label, randomised phase III trial (n = 202) was followed up by investigating the effect of sorafenib maintenance post-transplantation on Epstein–Barr virus (EBV) and cytomegalovirus (CMV) infections. The primary endpoint was EBV and CMV infections within 3 years post-transplantation. The study had a median extended follow-up post-transplantation of 36.8 months (range: 2.5–67.1) and concluded that sorafenib maintenance post-transplantation did not increase the incidence and mortality of EBV and CMV-associated diseases compared with no maintenance post-transplantation.

Cost-effectiveness: No relevant cost-effectiveness analyses were identified in the repeat literature search.

Budget impact: In the original evidence summary it was estimated that four patients per year would be eligible for two years of treatment with sorafenib maintenance therapy. [CONFIDENTIAL DATA REMOVED] in Wales have been treated with sorafenib for FLT3-ITD mutated AML following the One Wales decision.

Impact on health and social care services: Minimal.

Patient outcome data: Outcome data were provided for six patients, [CONFIDENTIAL DATA REMOVED]

Next review date: June 2026

This document includes evidence published since the last review or full assessment of this medicine for the indication under consideration. It does not replace the original full evidence status report. Any previous reviews and the original full evidence status report are available on request by email to AWTTC@wales.nhs.uk.

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 Review. Sorafenib for acute myeloid leukaemia maintenance. Reference number: OW18. 2023.

References: a full reference list is available on request.

Appendix 1

Reference	Study details	Main results
Aydin et al 2022	Retrospective multi-centre study (n = 43, FLT3-ITD mutated AML) compared 21 patients receiving single-agent sorafenib maintenance therapy in CR after HCT with a control group of 22 patients without maintenance. Sorafenib was initiated after a median of 3 months (IQR: 2.3–3.5) after allogeneic HCT with a median daily dosage of 400 mg (range: 200–800).	The primary endpoint was OS, defined as the time from HCT to death from any cause. The secondary endpoint was the cumulative incidence of relapse (main event), using death without relapse as its competing event. The median follow-up of the entire cohort was 47.7 months (IQR: 28.1–67.3). Median OS was 31.4 months in the control group, while it was not reached in the sorafenib group, (p = 0.016). Median follow-up of the control group was longer with 67.9 months (range: 30.5–78.8) compared to the more recent sorafenib group with 34.7 months (range: 16.9–49.5). At the time of last follow-up, 40.9% (n = 9) of patients of the control group and 81% (n = 17) patients of the sorafenib group were alive and still in CR. The main cause for death in the control group was disease relapse. Cumulative incidence of relapse in the control group at one (42.4% versus 14.6%), two (42.4% versus 14.6%) or three (47.3% versus 14.6%) years were significantly higher than in the sorafenib group(p=0.028). No event for non-relapse mortality occurred in the sorafenib group at 1 (0% versus 9.1%), 2 (0% versus 9.1%), and 3 years (0% versus 13.9%) compared to the control group (p=0.38).

		At time of sorafenib maintenance initiation, five (23.8%) patients displayed grade I acute GVHD of their skin; one patient responded to steroid therapy, while another developed chronic GVHD. During sorafenib maintenance, seven (33.3%) patients experienced new onset of grade I/II acute GVHD, manageable with observation or low-dose steroid therapy. In the control group, eleven (50%) patients developed acute GVHD, of whom eight (36.4%) were classified as grade I/II and 3 (13.6%) as III/IV acute GVHD. A total of 14 patients experienced adverse events mostly involving the skin and the gastro-intestinal tract. Adverse events led to dose reductions in four patients, temporary interruption in five patients lasting a median of 22 days (range: 13–30) and complete withdrawal of sorafenib in four patients.
Xin et al 2022	This was a follow-up of the open-label, randomised phase 3 trial by Xuan et al. It investigated the effect of sorafenib maintenance post-transplantation on the incidence and mortality of on EBV and CMV infections in patients with FLT3-ITD acute myeloid leukaemia (n = 202).	The primary endpoint was EBV and CMV infections within 3 years post-transplantation. Secondary endpoints included the cumulative incidences of relapse, NRM, OS, LFS, and GVHD-free/GRFS at 3 years. The median follow-up was 36.8 (range: 2.5-67.1) months post-transplantation. EBV-DNAemia occurred in 22 (22.0%) patients in the sorafenib group and 23 (22.5%) patients in the control group ($p = 0.925$). CMV-DNAemia occurred in 54 (54.0%) patients in the sorafenib group and 53 (52.0%) patients in the control group ($p = 0.772$). There was no significant difference in the cumulative incidence of EBV-DNAemia for 1- and 3-years ($p = 0.931$ and $p = 0.937$ respectively).

		At the date of statistical analysis, 142 patients survived and 60 died, of whom 21 were in the sorafenib group and 39 were in the control group. Causes of death were leukaemia relapse (n = 31; 7 in the sorafenib group and 24 in the control group), infections (n = 18; 10 in the sorafenib group and 8 in the control group) and GVHD (n = 8; 3 in the sorafenib group and 5 in the control group). The 3-year cumulative incidences of relapse, NRM, OS, LFS, and GRFS were 13.0%, 11.1%, 79.0%, 75.9%, and 65.8% in the sorafenib group and 34.8%, 12.7%, 61.4%, 52.5%, and 46.6% in the control group, respectively ($p < 0.001$, $p = 0.656$, $p = 0.005$, $p < 0.001$, $p = 0.003$). With a median of 18 days after sorafenib initiation, 59 of 100 patients required dose modifications due to adverse events, including 42 dose reductions, 12 dose interruptions, and 5 discontinuations.
CMV: cytomegalovirus; CI: Confidence intervals; CR: complete response; EBV: Epstein Barr virus; GRFS: GVHD-free/relapse-free survival; GVHD: graft versus host disease; HCT: haemopoietic cell transplant; IQR: interquartile range; LFS: leukaemia-free survival; NRM: non-relapse mortality; OS: overall survival		