Clinical Commissioning Policy:

Sorafenib maintenance for adults with FLT3-internal tandem duplication (FLT3-ITD) acute myeloid leukaemia (AML) undergoing allogeneic haematopoietic stem cell transplantation (allo-HSCT) [URN:2262]

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Summary

Sorafenib maintenance is recommended to be available as a routine commissioning treatment option for adults with FLT3-internal tandem duplication (FLT3-ITD) acute myeloid leukaemia (AML) undergoing allogeneic haematopoietic stem cell transplantation (allo-HSCT) within the criteria set out in this document.

The policy is restricted to certain age groups as there is insufficient evidence to confirm safety and/or it is not recommended through the licence authorisation process to be used in those age groups not included in the policy.

Committee discussion

Clinical Panel considered the evidence base and the recommendation was made to progress the policy as for routine commissioning. Please see Clinical Panel reports for full details of Clinical Panel's discussion.

Clinical Priorities Advisory Group committee papers can be accessed on the NHS England website.

What we have decided

NHS England has carefully reviewed the evidence to treat adults with FLT3-internal tandem duplication (FLT3-ITD) acute myeloid leukaemia (AML) undergoing allogeneic haematopoietic stem cell transplantation (allo-HSCT) with sorafenib maintenance therapy. We have concluded that there is enough evidence to make the treatment available at this time.

The evidence review which informs this commissioning position can be accessed on the NHS England website.

Links and updates to other policies

NHS England has no other policies relating to the use of sorafenib maintenance in adults with FLT3-ITD AML undergoing allo-HSCT.

Plain language summary

About FLT3-internal tandem duplication (FLT3-ITD) acute myeloid leukaemia (AML)

Acute myeloid leukaemia (AML) is a type of cancer affecting young blood cells in the bone marrow, which is the soft inner part of the bone. In healthy individuals these young blood cells, known as stem cells, develop into red blood cells, platelets, and some types of white blood cell.

In AML, some of these stem cells do not develop fully and instead become abnormal leukaemia cells. These can stop the bone marrow from working properly and can also spread to other parts of the body. The word acute means that the leukaemia can develop fairly quickly.

Multiple factors influence how the disease progresses, including the presence of specific genetic mutations. One of most common mutations in AML is a change to the genetic instructions for producing a protein called fms-like tyrosine kinase 3 (FLT3). The FLT3 protein is part of a family of proteins called receptor tyrosine kinases (RTKs). Under normal circumstances, FLT3 stimulates growth, division (proliferation) and survival of young cells in the bone marrow. Changes in this gene encourages these cells to multiply uncontrollably and is highly unfavourable.

There are two recognised types of change that can occur to the genetic instructions for this protein:

- FLT3-Internal Tandem Duplication (FLT3-ITD): involving multiple copies of the gene in a row. This mutation occurs in 20-25% of individuals with AML.
- FLT3-Tyrosine Kinase Domain (TKD): involving a single change or gene deletions.

Individuals with the FLT3 mutation tend to have lower survival rates than those without the mutation. Their disease is more likely to return, or relapse, after treatment (the treatments are described in the next section ‘About current treatment'). This policy outlines recommendations for individuals with the FLT3-ITD mutation who have received a certain type of stem cell transplant called allogeneic haematopoietic stem cell transplant (allo-HSCT) which is described below.

About current treatment

AML progresses rapidly and individuals require immediate treatment. Current standard treatment for FLT3-ITD AML is with chemotherapy, delivered in two phases:

- Induction is the first phase of treatment. The goal is to clear the blood of leukaemia cells, and to reduce the number of leukaemia cells in the bone marrow to normal.
- Consolidation is the second phase of treatment. Chemotherapy is administered in cycles to destroy residual disease (the small number of leukaemia cells that are still present yet unable be detected).

FLT3-ITD AML is an aggressive haematological malignancy, and these individuals are rarely cured by chemotherapy alone. Further treatment may be required with stem cell transplantation in suitable patients. Allogeneic haematopoietic stem-cell transplantation (allo-HSCT) uses healthy blood stem cells from a donor to replace bone marrow that's not producing enough healthy blood cells. Allo-HSCT improves the survival of these

individuals, however, leukaemia relapse remains high, occurring in 30-59% of patients (Bazarbachi et al, 2020). These individuals have a very poor prognosis with predicted 1-year overall survival rates after relapse of less than 20%. There is currently no alternative treatment to prevent disease relapse in individuals with FLT3-ITD AML who have undergone allo-HSCT.

About sorafenib maintenance

Sorafenib is a multikinase inhibitor which blocks the action of the abnormal FLT3 protein which causes cells to multiply uncontrollably. It has been proposed as a potential maintenance therapy in patients with FLT3-ITD AML who have undergone allo-HSCT. It is administered as daily tablets. It is currently licenced for use in the treatment of adults with hepatocellular carcinoma, advanced renal cell carcinoma and thyroid carcinoma (SmPC). Maintenance therapy with sorafenib following allo-HSCT may target residual disease through selective inhibition of FLT3-ITD positive AML blasts (Bazarbachi et al, 2020).

Sorafenib is not licenced for the use in FLT3-ITD AML, and therefore, use will be off-label. Safety and efficacy of sorafenib has not been established in children (<18 years old).

Epidemiology and needs assessment

The treatment is indicated for adults diagnosed with FLT3-ITD AML who have undergone allo-HSCT. There are approximately 3,100 new cases of AML in the UK per annum, with an incidence greater in males than females (Cancer Research UK, 2021).

Approximately 600 adult allo-HSCT transplants are performed for individuals with AML in the UK per annum. An estimated 25% of these recipients would have been diagnosed with FLT3-ITD positive disease. At least one third of them (~50 patients) would relapse within two years from transplant. Maintenance with sorafenib post allo-HSCT may reduce the number of individuals who relapse.

Implementation

Inclusion criteria

Adult patients (aged 18 years and above[1]) with a confirmed diagnosis of FLT3-ITD AML who meet **ALL** of the following criteria:

- Received allo-HSCT
- Exhibit adequate engraftment (absolute neutrophil count of ≥1·0×10⁹ cells/l and non-transfused platelets of ≥30×10⁹/l) at the time of sorafenib initiation
- Commence sorafenib at no later than 4 months post allo-HSCT.

Exclusion criteria

Patients who meet **ANY** of the following criteria are not eligible for treatment with sorafenib under this policy:

[1] This policy is applicable to adults (≥18 years) due to lack of safety data in children. Post-pubescent access is permitted as outlined in NHS England Policy 170001/P Commissioning Medicines for Children in Specialised Services

- Individuals with contraindications to sorafenib, as outlined in the summary of product characteristics (SmPC)
- Uncontrolled graft-versus-host-disease[2] (GvHD)
- Persistent liver dysfunction (total bilirubin ≥2 times the upper limit of normal [ULN] or alanine aminotransferase or aspartate aminotransferase ≥2×ULN)[3]
- Persistent renal dysfunction (creatinine ≥2×ULN or creatinine clearance <30mL/min)[4]
- Individuals with severe concomitant conditions for whom the MDT determines that sorafenib maintenance cannot be delivered safely

Starting criteria

Treatment and initiation of sorafenib should be agreed with a suitable multi-disciplinary team (MDT) which includes at least two consultants with significant experience in the treatment of FLT3-ITD AML.

Individuals who are receiving anticoagulation therapy or other medications that increase the risk of bleeding, for example, but not limited to, warfarin, aspirin, heparin and direct oral anticoagulants should be avoided. Strong inducers of Cytochrome P450 3A4 (CYP3A4) enzyme, e.g., St. John's Wort, rifampicin, phenytoin, and carbamazepine must be avoided whilst patients are on sorafenib maintenance[5].

Sorafenib maintenance should commence following adequate engraftment post allo-HSCT and no later than 4 months post allo-HSCT. Individuals may receive this treatment for a maximum duration of 24 months post allo-HSCT, irrespective of the start date or any treatment breaks.

Stopping criteria

A decision to stop using sorafenib should be made by the treating clinician if **ANY** one of the following occur:

- Serious adverse events e.g., anaphylaxis or severe allergic reaction
- Grade 3 or grade 4 GvHD[6]
- Elapse 24-months following allo-HSCT
- Relapse whilst on treatment
- Patient decision to stop treatment.

Dosing

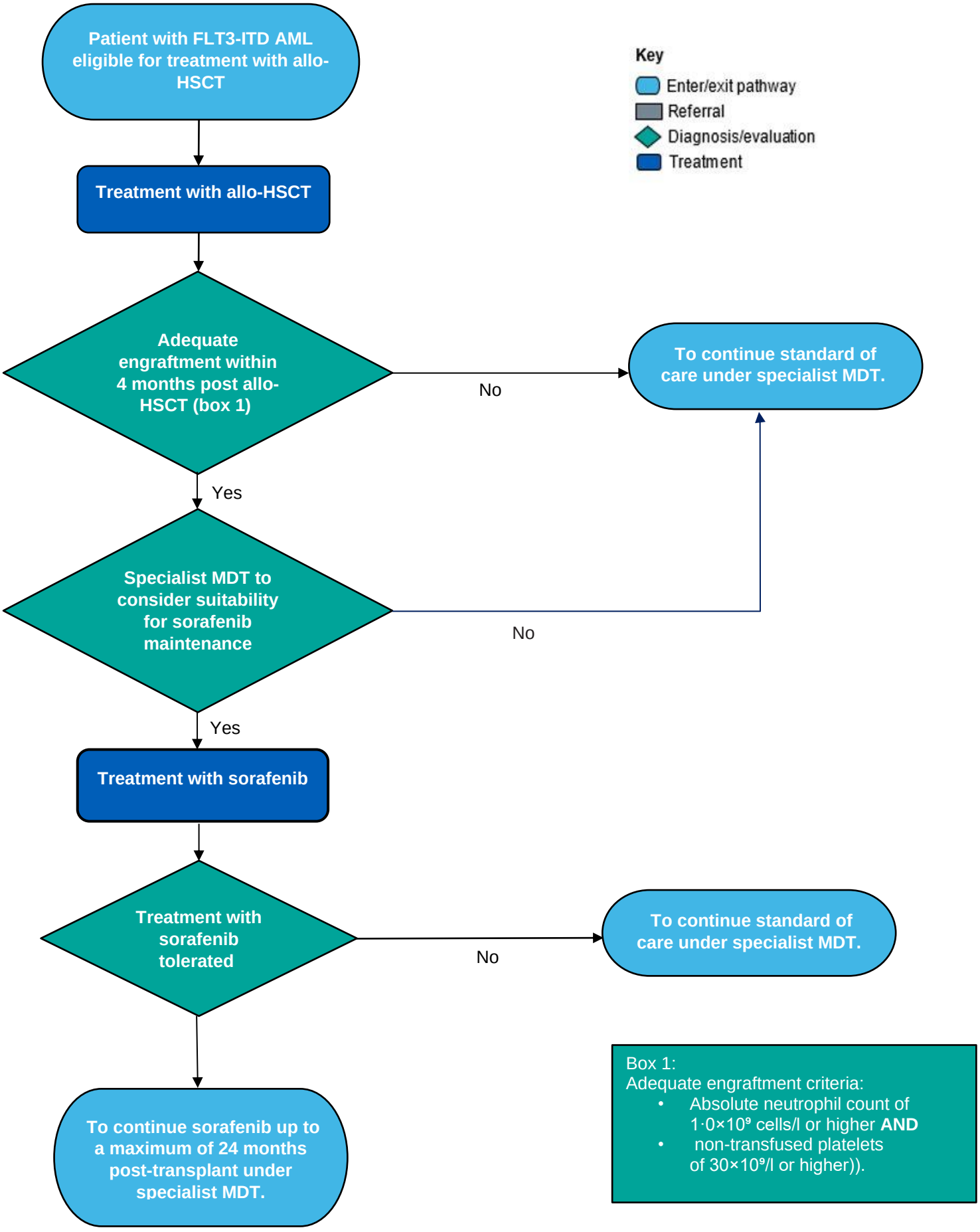
Sorafenib is given orally. Initial starting dose is 200mg twice a day and escalated to 400mg twice a day. Treatment must not exceed 24 months post allo-HSCT, irrespective of the start date or any treatment breaks.

[2] Graft versus Host Disease (GvHD) is a complication of allo-HSCT. Uncontrolled GVHD is classified by the requirement of >0.5 mg/kg prednisolone or equivalent (Brunner et al, 2016).
[3] Clinical consensus advises the following limits for renal dysfunction due to the vulnerability of this patient cohort. These criteria are in line with clinical trials (NCT02474290).
[4] Clinical consensus advises the following limits for liver dysfunction due to the vulnerability of this patient cohort. These criteria are in line with clinical trials (NCT02474290).
[5] Sorafenib is a non-selective kinase inhibitor and its interactions with medications above can cause issues in transplant patients (aspirin and sorafenib together increase myelotoxicity/bleeding, warfarin/LMWH increases bleeding risks, St John's wort decreases sorafenib action). These criteria are in line with clinical trials (EudraCT: 2010-018539-16).
[6] Sorafenib may be temporarily suspended or stopped on a case-by-case basis.

Monitoring

A formal medical review to assess the tolerability of treatment, and to determine whether the treatment should continue, should take place within the first 8 weeks of treatment initiation. If treatment is tolerated, sorafenib can be continued up until the maximum of 24 months post allo-HSCT.

Patient pathway



Governance arrangements

Service Specification:

- Cancer: Chemotherapy (Adult) B15/S/a

Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined. Any provider organisation treating patients with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

Please note that this is an off-label use of sorafenib, therefore Trust policy regarding unlicensed medicines should apply.

Mechanism for funding

Sorafenib maintenance within the criteria set out in this document will be commissioned and funded by NHS England under existing arrangements for the provision of specialised services.

Audit requirements

Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined. This information is collected to inform future policy revisions.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base, then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment, and victimisation, to advance equality of opportunity, and to foster good relations

between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and

- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Definitions

Acute myeloid leukaemia (AML)	Acute myeloid leukaemia (AML) is a cancer of myeloid stem cells in the bone marrow.
FLT3-Internal Tandem Duplication (FLT3-ITD)	FLT3-Internal Tandem Duplication (FLT3-ITD) is a mutation involving multiple copies of the gene in a row. This mutation occurs in 20-25% of individuals with AML.
Allogeneic haematopoietic stem cell transplantation (Allo-HSCT)	Allogeneic haematopoietic stem cell transplantation (allo-HSCT) is a procedure in which a portion of a healthy donor's stem cell or bone marrow is obtained and prepared for intravenous infusion.
Graft-Versus-Host-Disease (GvHD)	Graft-Versus-Host-Disease is a life-threatening complication that can occur following allo-HSCT. In GvHD, the donated bone marrow or peripheral blood stem cells view the recipient's body as foreign, and the donated cells/bone marrow attack the body.
Cytochrome P450 3A4 (CYP3A4)	CYP3A4 belongs to the cytochrome P450 family of enzymes. These are found in the liver and are involved in the metabolism of drugs. An inducer of CYP3A4, e.g. rifampicin, can increase the rate of metabolism of sorafenib, and therefore decrease sorafenib concentration and potentially making sorafenib less effective.

References

1. Bazarbachi, A., Bug, G., Baron, F., Brissot, E., Ciceri, F., Dalle, I., Döhner, H., Esteve, J., Floisand, Y., Giebel, S., Gilleece, M., Gorin, N., Jabbour, E., Aljurf, M., Kantarjian, H., Kharfan-Dabaja, M., Labopin, M., Lanza, F., Malard, F., Peric, Z., Prebet, T., Ravandi, F., Ruggeri, A., Sanz, J., Schmid, C., Shouval, R., Spyridonidis, A., Versluis, J., Vey, N., Savani, B., Nagler, A., Mohty, M. (2020). Clinical practice recommendation on hematopoietic stem cell transplantation for acute myeloid leukemia patients with FLT3-internal tandem duplication: a position statement from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Haematologica*,*105(6),* 1507-1516. https://doi.org/10.3324/haematol.2019.243410.
2. Cancer Research UK. Acute Myeloid Leukaemia Statistics (2021). Available at: Acute myeloid leukaemia (AML) statistics | Cancer Research UK.
3. Brunner, M., Li, S., Fathi, T., Wadleigh, M., Ho, T., Collier, K., Connolly, C., Ballen, K., Cutler, S., Dey, R., El-Jawahri, A., Nikiforow, S., McAfee, L., Koreth, J., Deangelo, J., Alyea, P., Antin, H., Spitzer, R., Stone, M., Soiffer, J., Chen, B. (2016). Haematopoietic cell transplantation with and without sorafenib maintenance for patients with FLT3-ITD acute myeloid leukaemia in first complete remission. *British journal of haematology*, *175*(3), 496–504. https://doi.org/10.1111/bjh.14260.