SORAFENIB maintenance for FLT3-ITD positive AML

Clinical Commissioning Policy [URN:2262]

Sorafenib is a multi-kinase inhibitor which has been NHS approved for use as post-transplant maintenance in FLT-3 internal tandem duplication (FLT3-ITD) acute myeloid leukaemia (AML).

Blueteq completion required.
Prescribe on Aria (cancer treatment)

INDICATION

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

1. Received allogenic haematopoietic stem cell transplant (allo-HSCT)
2. Exhibit adequate engraftment consisting of:
   - Absolute neutrophil count (ANC) more than or equal to 1.0 × 10^9 cells/L
     AND
   - Non-transfused platelets of more than or equal to 30 × 10^9/L at the time of sorafenib initiation
3. Commence sorafenib at **no later than 4 months** post allo-HSCT.

CONTRA-INDICATIONS

- Uncontrolled graft vs host disease (GvHD).
- Persistent liver dysfunction consisting of:
  - Total bilirubin more than or equal to 2 times the upper limit of normal [ULN] **and/or**
  - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) more than or equal to 2 × ULN
- Persistent renal dysfunction defined as:
  - Serum creatinine more than or equal to 2 × ULN **or** creatinine clearance (CrCl) less than 30mL/min
- Use in individuals who are receiving anticoagulation therapy or other medications that increase the risk of bleeding should be avoided.

PRE-ASSESSMENT

1. Blood test – FBC, U&Es, coagulation screen, LDH, calcium, creatinine, LFTs, thyroid function, glucose
2. ECG, urine protein dip and blood pressure at baseline
3. Ensure FLT3-ITD status of diagnostic bone marrow.
4. Check pre-transplant HBsAg and HBcAb result and recent HBV DNA.
5. Discussion with women of child-bearing potential (WOCBP) with regards to teratogenicity and requirement for barrier methods of contraception. Male subjects whose sexual partners are

WOCBP must use a double barrier method of contraception, one of which includes a condom, during treatment and for 3 months after the end of treatment.

6. Urine pregnancy test – In WOCBP before initiation (or where treatment restarted after more than 1 month break for settlement of toxicity) unless they are confirmed post-menopausal, have been sterilised or undergone a hysterectomy.
7. Consent documented to ensure patient is informed of risks and benefits of treatment with sorafenib.

DRUG REGIMEN/CYCLE FREQUENCY

Starting dose	**200mg** (1 tablet) PO **twice a day**
Target dose	**400mg** (2 tablets) PO **twice a day**

Tablets should be taken on an empty stomach, at least one hour before or two hours after food. Swallow whole with a glass of water, do not break, crush or chew.

Dose titration: Increase dose by 200mg (1 tablet) at least every 4 weeks to the maximum tolerated dose, not exceeding the stated target dose.

Cycle frequency: 28 day - continuous administration.

Duration: Maximum total treatment 24 months (2 years) from date of HSCT cell infusion (day 0).

The 24 months duration is fixed and starts from the date of the allo-HSCT regardless of the start date of sorafenib or the need for any treatment breaks. **Sorafenib must be initiated within 4 months of day 0.**

STOPPING CRITERIA

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

- Serious adverse events e.g., anaphylaxis or severe allergic reaction
- GvHD grade 3 or 4.
- Relapse whilst on treatment.
- Patient decision to stop treatment.

ROUTINE MONITORING

- FBC, U&Es, LFTs, calcium, magnesium and phosphate – baseline and repeated at weeks 2 and 4, then every 4 weeks.
- ECG – Baseline, repeat at week 2 post-initiation or 2 weeks following dose increase.
- Blood pressure – Baseline then periodic routine monitoring particularly in first 6 weeks.
- Thyroid function – Baseline then 3 monthly.
- Urine protein – Baseline then 2 - 3 monthly unless clinically indicated.
- Amylase / lipase – routine monitoring is not recommended in the absence of clinical symptoms; acute pancreatitis is rare. Amylase and lipase serum levels are known to be elevated during sorafenib treatment.

- Latent hepatitis B reactivation – Monitor HBV DNA 3-monthly in susceptible patients as per local guidance, many patients indicated for prophylaxis may already be established on therapy during HSCT.

EMETOGENECITY

Minimal – prophylaxis not required.

DOSE MODIFICATIONS

Dose levels / recommendations

A dose level is defined as one 200mg (1 tablet) step. The maximum permitted dose is 400mg BD. The minimum permitted and NHS commissioned dosing is 200mg BD.

Some data is available to support dosing reductions to 200mg **once daily** and 200mg **every other day** whilst maintaining sufficient FTL3-ITD inhibition (Pratz et al, 2020), however these dose reductions are outside of the scope of the commissioned criteria and may require Trusts to agree local treatment funding to continue unless an exception is permitted by the commissioner.

Haematologic Toxicity

Criteria	Action
Absolute neutrophil count (ANC)	
Less than, or equal to, **1.0** x 10^9/L	Reduce to next dose level.
Less than, or equal to, **0.5** x 10^9/L	Withhold treatment until neutrophils recover to more than **1.0** x 10^9/L, and restart at next lower dose level
Platelets (Plt)	
Less than, or equal to, **50** x 10^9/L	Withhold treatment until acceptable platelet recovery, and restart at next lower dose level
Haemoglobin (Hb)	
Less than 80 g/L and attributed to sorafenib	Withhold treatment until acceptable Hb recovery, and restart at next lower dose level

Non-hematologic toxicity

Renal impairment

Not recommended in patients with CrCl less than 30 ml/min or where serum creatinine is more than 2 x ULN. Sorafenib is metabolised primarily in the liver, however patients with significant renal dysfunction have been known to be less tolerant of dose increases and may require longer treatment interruption for toxicity management.

Renal toxicity (such as nephrotic syndrome, interstitial nephritis) secondary to sorafenib is rare however has been reported. As such urine protein should be periodically checked throughout treatment.

Hepatic impairment / Gastrointestinal toxicity

Criteria	Action
Hepatic derangements Total bilirubin more than or equal to 2 x ULN **and/or** ALT or AST more than or equal to 2 × ULN	Withhold treatment until toxicity resolution. Ensure GvHD as a differential has been investigated.
Diarrhoea (non-GvHD related) Grade 1 - 2 Grade 3	Manage symptomatically with loperamide. Consider 1 dose level reduction if distressing to patient. Delay treatment until toxicity has resolved to Grade 2 or less. Ensure appropriate investigation and management of graft vs host disease. Dose can recommence at 200mg BD, or last tolerated dose, once resolved to grade 1 and if GvHD is controlled.

Cardiac toxicity

Cardiotoxicity	**Pre-existing cardiac disease (e.g. reduced LVEF) -** initiate and escalate treatment cautiously. Additional echo monitoring during dose escalation may be considered. The incidence of cardiac events in an AML population in the SORMAIN trial was low. In metastatic solid tumour indications, a higher number of patients have been known to experience cardiotoxicity, including LVEF decline. **Cardiac ischaemia and/or infarction –** Consider temporary or permanent discontinuation
QT prolongation	**QTc interval > 450msec at initiation:** Monitor QTc interval closely, discontinue other known QTc prolonging medication where possible and optimise any electrolyte abnormalities. **QTc interval > 500msec:** Check magnesium and potassium and correct any abnormalities. Where possible discontinue other QT prolonging medications. Consider cardiology referral. Withhold sorafenib until QTC < 500msec. Resume at 200mg PO BD and re-escalate with ECG monitoring if tolerated.
Hypertension	**Grade 2 – Systolic BP 140 - 159 mmHg or diastolic BP 90 - 99 mmHg OR persistent increase by >20 mm Hg (diastolic)** • Initiate antihypertensives and continue monitoring.

	Grade 3 - Systolic BP over 160 mmHg, or diastolic BP over 100 mmHg • Withhold treatment, optimise antihypertensives. Once BP in acceptable range reduce sorafenib by 1 dose level and restart therapy. Monitor closely. **Grade 4 – Uncontrollable hypertension** • Consider temporary or permanent discontinuation

Dermatologic Toxicity*

Hand-Foot Syndrome	Frequency	Action
Grade 2 Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities.	1st occurrence	Continue treatment with sorafenib and consider topical therapy for symptomatic relief. *If no improvement within 7 days, see below*
	No improvement within 7 days at reduced dose **or** 2nd / 3rd occurrence	Interrupt treatment until toxicity resolves to Grade 1 or less. When resuming treatment, decrease sorafenib dose by one level.
	4th occurrence	Discontinue sorafenib treatment
Grade 3 Moist desquamation, ulceration, blistering, or severe pain of the hands or feet, resulting in inability to work or perform activities of daily living.	1st occurrence	Interrupt treatment until toxicity resolves to Grade 1 or less. When resuming treatment, decrease sorafenib dose by one dose level
	2nd occurrence	Interrupt sorafenib until resolved or improved to Grade 1 When resuming treatment, decrease sorafenib dose by one dose level When sorafenib is resumed, decrease dose by 2 dose levels (see Table 3)
	3rd occurrence	Discontinue sorafenib treatment
Skin graft vs host disease		Delay dose until controlled.

*There is limited information on management of toxicity in AML and this information has been derived from guidelines for patients being treated for hepatocellular carcinoma

Other non-specific toxicities

CTCAE v5.0 Grading	Action
0 - 2	None
3	Interrupt until Grade < 2, resume one dose level below last dose.
4	Clinical decision - consider treatment discontinuation

INTERACTIONS

The following list of interactions is not exhaustive and serves as a guide only for clinical management. Individual patient factors and circumstances should also be taken into consideration during decision-making.

- **P-glycoprotein Substrates -** Sorafenib has been shown to inhibit p-glycoprotein therefore systemic exposure to p-gp substrates is expected to increase.
- **Sorafenib with CYP Inhibitors and Substrates** - Sorafenib inhibits CYP2B6 and CYP2C8 *in vitro*. Systemic exposure to substrates of CYP2B6 and CYP2C8 is therefore expected to increase when co-administered with sorafenib, however in most cases this should not be to a clinically significant degree. Caution should be exercised with narrow therapeutic range medicines such as warfarin.
- **CYP3A4 Inducers –** Co-administration may decrease sorafenib metabolism and result in decreased plasma concentrations. Other inducers of CYP3A4 activity may also increase metabolism of sorafenib and thus decrease sorafenib concentrations.
- **CYP3A4 Inhibitors and CYP Isoform Substrates -** *In vitro* and *in vivo* data suggest that: 1) sorafenib is unlikely to be altered by CYP3A inhibitors, and 2) sorafenib is unlikely to alter the metabolism of substrates of CYP2C19, CYP2D6, and CYP3A4.
- **UGT 1A1 and 1A9 substrates –** Sorafenib inhibits glucuronidation (metabolism) via UGT1A1 and UGT1A9.

Medication / Interaction types	Clinical management
CYP3A4 inducers e.g., carbamazepine, phenytoin, phenobarbitone, rifampicin, St John's Wort, macrolide antibiotics	Avoid combination particularly if use expected to be long term / monitor for decreased clinical response to sorafenib.
Drugs that may prolong the QTc interval e.g., azole antifungals, tricyclic antidepressants, antiarrhythmics	Avoid combination / minimise additional risk factors (e.g. correct electrolyte imbalances, rationalise medicines) and monitor ECG for signs of cardiac arrhythmia
P-glycoprotein substrates e.g., digoxin, ciclosporin, tacrolimus, dabigatran, edoxaban, letermovir	Avoid combination / monitor cautiously with therapeutic drug monitoring where available and adjust therapy as indicated. Letermovir – Changes in metabolism and interaction with P-gp may increase serum concentrations though not to clinically relevant degrees, use with caution.
UGT 1A1 and 1A9 substrates e.g., estradiol, propofol, paracetamol, mycophenolate, letermovir	Avoid combination where possible, otherwise monitor closely for adverse effects or toxicity. Letermovir – Changes in metabolism and interaction with P-gp may increase serum concentrations though not to clinically relevant degrees, use with caution.
Neomycin	Avoid combination or monitor for decreased clinical response to sorafenib

Direct oral anticoagulants (DOACs) e.g. apixaban, rivaroxaban, edoxaban, dabigatran	Avoid and consider alternate anticoagulation with low molecular weight heparin (LMWH).
Vitamin K antagonists e.g. warfarin, acenocoumarol, phenindione	Use with caution - monitor regularly for changes in prothrombin time, International Normalised Ratio (INR) or clinical bleeding episodes.

Unlikely to interact (not an exhaustive list):

- Aciclovir, valganciclovir
- Pentamidine
- Fluconazole – little effect on QTc at prophylactic doses
- Ambisome, caspofungin, micafungin
- Beta-blockers, amlodipine, furosemide, ACE-inhibitors / ARBs
- Penicillins, cephalosporins (e.g., cefalexin), meropenem, ciprofloxacin, levofloxacin, doxycycline, clarithromycin, azithromycin

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SURGICAL INTERVENTIONS

Sorafenib should be discontinued 14 days prior to any surgery and restarted about 4 weeks after.

KEY ADVERSE EFFECTS

This is an abbreviated list, for full information please consult product summary at electronic medicines compendium.

- Fatigue
- Diarrhoea
- Nausea (mild)
- Hand-foot syndrome (palmar plantar erythema (PPE))
- Alopecia (late effect – partial hair loss / thinning)
- Rash
- Anorexia
- Arthralgia and muscle spasm
- Haemorrhage
- Pruritus
- Erythema
- Dry skin
- QT prolongation
- Laboratory test abnormalities (Increased lipase and amylase, transaminitis)
- Proteinuria
- Hypophosphatemia, hypocalcaemia
- Hypothyroidism (rare – hyperthyroidism)
- Hypertension, headache

- Rarely - arrhythmias, cardiac ischemia/infarction/failure, drug induced hepatitis.

Drug-induced Hepatitis

Reactivation risk – Moderate

- HBsAg positive patients, **or** HBsAg negative with HBcAb positive- Prophylaxis with tenofovir/entecavir dependent on HBV DNA level as per local guidance (B-17 Management of Hep B and C Allo/Auto BMT Recipients) with HBV and ALT monitoring minimum 3-monthly.

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DOCUMENT CONTROL

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Review

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Dr Kirsty Sharplin, Consultant Haematologist Donna Constantine, Advanced Cancer Pharmacist	New Document	Jan 2024	1.0	Jan 2026
Dr Kirsty Sharplin, Consultant Haematologist Donna Constantine, Advanced Cancer Pharmacist	Addition of information on amylase and lipase monitoring. Addition of information on pre-existing cardiotoxicity.	March 2025	1.1	Jan 2026