Sorafenib (AML)

Please note this protocol has been produced in a new format that is currently being piloted. Any feedback on this new format should be sent to SSGMeetings@uhbw.nhs.uk

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Indication

Adult patients (≥ 18 years old) with a confirmed diagnosis of FLT-3-ITD AML who meet the following criteria:

- Have received an allogeneic haematopoietic stem cell transplant (allo-HSCT)
- Exhibit adequate engraftment consisting of:
  - Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L
  - Non-transfused platelet count ≥ 30 x 10^9/L at the time of sorafenib initiation
- Sorafenib is commenced no later than 4 months post allo-HSCT

Exclusions:

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

(NHSE Clinical Commissioning Policy)

Response Rates

Phase II SORMAIN trial

- Sorafenib (n=43) vs placebo (n=40)
- Relapse free survival at 24 months: 85.0% vs 53.3%

Regimen details

Drug	Dose	Route
Sorafenib	200-400mg BD*	PO

* Starting dose is 200mg BD, after 2 weeks escalate to 400mg OM and 200mg ON and after a further 4 weeks escalate to 400mg BD as tolerated.

Cycle frequency
28 days continuous

Number of cycles
Until disease relapse, unacceptable toxicity or grade 3 or 4 GvHD occurs up to a maximum treatment duration of 24 months (2 years) from date of haematopoietic stem cell infusion (day 0) regardless of the start date of Sorafenib treatment or the need for treatment breaks.

Pre-medication
Nil

Supportive medication
Patients should be supplied with loperamide and metoclopramide on commencing treatment.

Patients should be advised to apply regular moisturiser to their hands and feet throughout treatment and to avoid activities that put pressure on hands and feet to minimise the risk of developing palmar plantar erythema.

Emetogenicity
This regimen has low emetogenic potential.

Administration
Sorafenib is available as 200mg tablets.

The dose should be taken without food or with a low or moderate fat meal. If the patient intends to have a high fat meal, sorafenib tablets should be taken at least 1 hour before or 2 hours after the meal. The tablets should be swallowed with a glass of water. If a dose is missed that dose should be omitted and the next dose taken at the usual time.

Mandatory investigations – pre first cycle

Additional investigations advised pre-first cycle

Investigation	Validity period
FBC	7 days
U&E (including creatinine)	7 days
LFTs	7 days
Calcium	7 days
Magnesium	7 days
Thyroid function	7 days
Albumin	7 days
Blood pressure*	7 days
ECG for QTc interval**	7 days
Urine dip for proteinuria	7 days

* Blood pressure should be well controlled prior to commencing treatment.
** Review concomitant medications that may also lead to QTc prolongation. Electrolyte abnormalities, such as hypokalaemia, hypocalcaemia or hypomagnesaemia must be corrected prior to commencing treatment.
** Consider echocardiogram if concerns about cardiac status.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	Every 2 weeks for first month then monthly
U&E (including creatinine)	Every 2 weeks for first month then monthly
LFTs	Every 2 weeks for first month then monthly
Ca	Every 2 weeks for first month then monthly
Mg	Every 2 weeks for first month then monthly
Albumin	Every 2 weeks for first month then monthly
Thyroid function	Every three months
Blood pressure*	Weekly for first month, then monthly
ECG for QTc interval	Every 2 weeks for first month, 2 weeks after dose increase, then periodically as indicated
Urine dip for protein	Baseline then 2-3 monthly

* Hypertension may develop within a week of commencing TKIs. Patients should be encouraged to monitor their blood pressure at home regularly, ideally daily.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer must be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 30 x 10^9/L
Creatinine clearance (CrCl)	≥ 40ml/min
Bilirubin	≤ 2 x ULN
AST/ALT	≤ 2 x ULN
Albumin	>25g/L
QTc	<500ms

Dose modifications

Dose level	Dose
1	200mg twice daily
2	400mg OM, 200mg ON (i.e. 600mg daily)
3	400mg twice daily

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.

Haematological toxicity

Toxicity	Dose
Neutrophils ≤ 1.0 x 10^9/L	Reduce to next dose level
Neutrophils ≤ 0.5 x 10^9/L	Withold treatment until neutrophils recover to >1.0 x 10^9/L then restart at next lower dose level
Platelets ≤ 30 x 10^9/L	Withold treatment until platelet recovery to >30, then restart at next lower dose level
Haemoglobin ≤ 80g/L attributed to Sorafenib	Withold treatment until Hb maintained >80g/L unsupported, then restart at next lower dose level

Renal impairment

No dose adjustment is required in patients with mild, moderate or severe renal impairment.

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

The SPC states that no dose adjustment is required for patients with mild or moderate hepatic impairment and that there are no data for patients with severe hepatic impairment. However, the table below, adapted from the pharmacokinetic study by Miller, is a useful guide for choosing a starting dose for patients with hepatic impairment. If the patient tolerates the starting dose, then a dose increase can be considered at consultant's discretion.

Albumin	Bilirubin		ALT/AST	Sorafenib dose
≥ 25 g/L	<2 x ULN	AND	≤ 2x ULN	400mg BD
≥ 25 g/L	≥2 x ULN	AND/OR	≥ 2xULN	Withold and ensure GvHD as a differential has been investigated
< 25g/L	Any	AND	Any	200mg OD

- **Skin Toxicity**

Grade 2 or higher palmar plantar erythema or rash may require a 1-2 week break in treatment until resolved to Grade ≤ 1. The patient should be advised to moisturise their hands and feet regularly, and to keep them cool. Once symptoms have resolved to ≤ Grade 1, sorafenib may be re-introduced at next dose reduction level.

Grade 1	Numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort, which does not disrupt normal activities.	The patient should be advised to moisturise their hands and feet regularly, and to keep them cool. Low potency topical steroids, or urea-containing creams may be useful.
Grade 2	Painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities.	Withold sorafenib, once resolved/improved to grade 1 reduce one dose level If recurrent on >3 occasions consider permanently discontinuing sorafenib
Grade 3	Moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort, which cause the patient to be unable to work or perform activities of daily living.	Withold sorafenib, once resolved/ improved to grade 1 reduce one dose level If recurrent on >2 occasions consider permanently discontinuing sorafenib Ensure GvHD as a differential excluded

Other toxicities

Toxicity	Definition	Action/Dose adjustment
QT prolongation	QTc interval >500msec	• Withhold Sorafenib until QTc<500msec • Resume at 200mg BD and re-escalate with ECG monitoring as tolerated • Check Mg and K and correct any abnormalities • Discontinue any other QT prolonging medications where possible • Consider cardiology referral
Hypertension	Systolic BP 140-159 or diastolic BP 90-99 OR persistent increase by 20mm Hg (diastolic)	Initiate anti-hypertensives and continue treatment with monitoring
	Systolic BP >160mmHg or diastolic >100mmHg	• Withold treatment, optimise anti-hypertensives. • Restart at next lower dose level once BP controlled. • If diastolic BP not controlled to <100 mmHg on therapy, reduce sorafenib by another dose level and monitor BP closely
Diarrhoea	Increase stool frequency >4-6 stools/day	Manage symptomatically with loperamide, if distressing to patient, consider next dose level reduction
	Increase in stool frequency >7 stools/day or interfering with ADLs	Withold treatment, ensure GvHD as a differential has been investigated, once controlled restart at next dose level

Side Effects

SORMAIN trial:

Toxicity		Any grade (%)
Haematological	Neutropenia	2.4
	Thrombocytopenia	4.8
Non-haematological	Infections	26.2
	GI toxicity (vomiting, nausea, diarrhoea)	14.3
	Electrolyte alterations	14.3
	Skin toxicity	11.9
	Cardiotoxicity and renal insufficiency	9.5
	Liver toxicity (ALT, AST increased)	4.8

Specific drug related side effects:

Common (>10%)	Uncommon (1-10%)	Rare (<1%)
Infections	Myelosuppression	Hyperthyroidism
Anorexia	Hypothyroidism	Reversible posterior leukoencephalopathy
Electrolyte disturbances	Dysgeusia	Hypertensive crisis
Haemorrhage	Tinnitus	Interstitial lung disease
Hypertension	Rhinorrhoea	Pancreatitis
Diarrhoea, constipation	Dysphonia	Drug induced hepatitis
Nausea, vomiting	Stomatitis	Stevens-Johnson syndrome, toxic epidermal necrolysis
Rash, pruritis	Dyspepsia, GORD	QT prolongation
Palmar-plantar erythrodysesthesia	Myalgia	Hypersensitivity reactions, anaphylactic reaction
Arthralgia	Proteinuria	
Fatigue	Raised transaminases	
Raised lipase, raised amylase		

Additional information

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

Significant drug interactions – for full details consult product literature/ reference texts

CYP3A4 inhibitors (e.g. ketoconazole, voriconazole, clarithromycin, ritonavir): avoid co-administration these may increase plasma concentrations of sorafenib.

Grapefruit and grapefruit juice: avoid as an inhibitor of CYP3A4 and may increase plasma concentrations of sorafenib.

Inducers of CYP3A4 (e.g. rifampicin, phenytoin, carbamazepine, St Johns Wort): avoid co-administration as these may reduce exposure 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

Coumarin anticoagulants, e.g. Warfarin: Avoid if possible as may cause elevation and fluctuation in INR. Consider switching to low molecular weight heparin.

Direct oral anticoagulants (DOACs) e.g. apixaban, rivaroxaban, edoxaban, dabigatran. Avoid and consider alternate anticoagulation with low molecular weight heparin (LMWH).

P-gp subtrates e.g digoxin: sorafenib inhibits P-gp which may lead to increased plasma concentrations of P-gp substrates

Neomycin: interferes with enterohepatic recycling of sorafenib, reducing sorafenib exposure.

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 Pgp may increase serum concentrations though not to clinically relevant degrees, use with caution.

References

- NHS England. 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). Version 1 6th November 2023. Accessed 5th December 2024 via NHSE CCP 2262.
- Summary of Product Characteristics – Sorafenib (Bayer) accessed 5th December 2024 via www.medicines.org.uk
- Burchert, A. et al. Sorafenib maintenance after allogeneic haematopoietic stem cell transplantation for acute myeloid leukaemia with FLT3-Internal Tandem Duplication mutation (SORMAIN). J Clin Oncol 2020:38(26):2993-3002
- Miller AA, Murry DJ, Owzar K et al Phase I and pharmacokinetic study of sorafenib in patients with hepatic or renal dysfunction: CALGB 6030. J Clin Oncol 2009; 27:1800-1805

Version	Issue date	Review date	Revision	Written/Checked/Authorised
1	Dec 2024	Dec 2027	New protocol	Written: Dr C Besley (Consultant Haematologist, UHBW NHS Trust) Checked: Kate Gregory (Lead Pharmacist for SACT protocols, SWAG Cancer Alliance) Authorised: Dr J Braybrooke (Consultant Oncologist, UHBW NHS Trust and SWAG Cancer Alliance)

Schedule of investigations and treatment plan

Activity	Pre-tx	Cycle 1 Day 15	Cycle 2	Cycle 3	Cycle 4	Ongoing
Informed consent	x					
Clinical assessment	x	x	x	x	x	Monthly
FBC	x	x	x	x	x	Monthly
U&E, LFTs, Calcium, Magnesium, Albumin	x	x	x	x	x	Monthly
CrCl	x	x	x	x	x	Monthly
TFTs	x				x	Every 3 months
Blood pressure	Should be well-controlled prior to starting tx	x	x	x	x	Monthly (patients should be encouraged to monitor BP at home)
ECG for QTc interval	x	x	x	x		2 weeks post any dose increase or as indicated
Urine dip for proteinuria	x			x		Every 2-3 months
Weight recorded	x					Repeat if necessary