PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Gilteritinib
Relapsed or Refractory
Acute Myeloid Leukaemia (AML)

PROTOCOL REF: MPHAGRRAML
(Version No. 1.0)

Approved for use in:

- Gilteritinib monotherapy is recommended as an option for treating relapsed or refractory FLT3-mutation-positive acute myeloid leukaemia (AML) in adults (NICE TA642)
- Gilteritinib must not be given as maintenance therapy after a haematopoietic stem cell transplant.

*********Blueteq registration is required*********

Dosage:

Drug	Dose	Route	Frequency
Gilteritinib	**120mg**	Oral	Once daily

- Cycle length is 28 days.
- Response may be delayed; therefore, continuation of treatment at the initial prescribed dose for up to 6 months should be considered to allow time for a clinical response.
- In the absence of a response after 4 weeks of treatment, the dose can be increased to 200mg once daily, if tolerated or clinically warranted.
- Treatment should continue until the patient is no longer clinically benefiting from gilteritinib or until unacceptable toxicity occurs

Administration:

Gilteritinib tablets can be taken with or without food. They should be swallowed whole with water and should not be broken or crushed. Gilteritinib tablets should be administered at the same time each day. If a dose is missed or not taken at the usual time, the dose should be administered as soon as possible on the same day, and patients should return to the normal schedule the following day. If vomiting occurs after dosing, patients should not take another dose but should return to the normal schedule the following day.

Emetogenic risk:

Low emetogenic risk

Supportive treatments:

- Allopurinol 300mg daily (or reduced dose in renal impairment), for 7 days – cycle 1 only
- Aciclovir 400mg twice daily
- Ciprofloxacin 500mg twice daily (if ongoing cytopenias)
- Posaconazole 300mg twice daily (loading) for 1 day, then 300mg once daily thereafter (if ongoing cytopenias)

Dosing in renal and hepatic impairment:

Renal	Mild to moderate renal impairment (CrCl ≥ 30 ml/min): no dose adjustment is required. Severe renal impairment (15 ≤ CrCL < 30 ml/min): no clinical experience in this patient group.

Hepatic	No dose adjustment is required for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Gilteritinib is not recommended for use in patients with severe (Child-Pugh Class C) hepatic impairment, as safety and efficacy have not been evaluated in this population.

Parameters	1 point	2 points	3 points
Total bilirubin (µmol/L)	< 34	34–50	> 50
Serum albumin (g/L)	> 35	28–35	< 28

	Prothrombin time, prolongation (s) *Or* INR	< 4 < 1.7	4–6 1.7-2.3	> 6 >2.3
	Ascites	None	Mild to Moderate (diuretic responsive)	Severe (diuretic refractory)
	Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory to medication)

INR: International Normalised Ratio.
Child-Pugh Class A = 5-6 points
Child-Pugh Class B = 7-9 points
Child-Pugh Class C = 10 or more points
Please note: assessment of Child-Pugh Class is to help guide clinical teams when prescribing and pharmacists when screening.

Interactions:

- Co-administration of CYP3A/P-gp inducers (e.g. phenytoin, rifampicin and St. John's Wort) may lead to decreased gilteritinib exposure and consequently a risk for lack of efficacy. Therefore, concomitant use of gilteritinib with strong CYP3A4 / P-gp inducers should be avoided.
- Caution is required when concomitantly prescribing gilteritinib with medicinal products that are strong inhibitors of CYP3A and/or P-gp (e.g. voriconazole, itraconazole, posaconazole, clarithromycin, erythromycin, captopril, carvedilol, ritonavir, azithromycin) because they can increase gilteritinib exposure. Alternative medicinal products that do not strongly inhibit CYP3A and/or P-gp activity should be considered instead.
- **Voriconazole and posaconazole** can be used as fungal prophylaxis at the same time as gilteritinib (at full dose) with careful monitoring of gilteritinib toxicity, in particular ECG changes. Dose-reduce if any toxicity occurs.
- **Effects of gilteritinib on other medicinal products**
- Gilteritinib may reduce the effects of medicinal products that target the 5-HT_{2B} receptor or sigma nonspecific receptors (e.g. escitalopram, fluoxetine, sertraline). Therefore,

concomitant use of gilteritinib with these products should be avoided unless use is considered essential for the care of the patient.

Main toxicities:

The most frequent **adverse reactions** noted have been blood creatine kinase increases, ALT increases, AST increases, blood alkaline phosphatase increases, diarrhoea, fatigue, nausea, constipation, cough, peripheral oedema, dyspnea, dizziness, hypotension, pain in extremity, asthenia, arthralgia and myalgia.

The most frequent **serious adverse reactions** noted have been diarrhoea, ALT increases, dyspnea, AST increases and hypotension. Other clinical significant serious adverse reactions included differentiation syndrome, electrocardiogram QT prolongation and posterior reversible encephalopathy syndrome.

Investigations and treatment plan:

	Pre-Cycle 1	Cycle 1 Day 8	Cycle 1 Day 15	Pre-Cycle 2+	Cycle 2 D8
Informed Consent	X				
Clinical Assessment	X			X	Prior to every cycle
SACT Assessment (including toxicity assessment and PS)	X			X	Prior to every cycle
Mutational Status	X				Ensure FLT3 (ITD or TKD) mutational status is confirmed and documented in notes prior to administration of therapy.
ECG	X	X	X	X	Before initiation of treatment, on day 8 & 15 of cycle 1 and before the start of the next three subsequent cycles of treatment
Creatine Kinase level	X		X	X	Prior to initiation of treatment, on C1D15 and monthly afterwards for the duration of treatment.
FBC	X			X	
U&E & LFTs (including magnesium)	X			X	Electrolyte abnormalities must be corrected
Height	X				Prior to initiating treatment
Weight	X			X	Prior to every cycle
Virology screening (Hep B cAg SA, Hepatitis C, HIV). COVID 19 screening	X				
Serum pregnancy test (if applicable)	X				If clinically indicated

Dose Modifications and Toxicity Management:

Haematological toxicity:

No dose reduction for disease related abnormality. These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

Symptom	Dose Modification
Differentiation syndrome	• Symptoms of differentiation syndrome include fever, dyspnoea, pulmonary oedema, hypotension, weigh gain, rash, renal dysfunction • If differentiation syndrome is suspected, administer corticosteroids and initiate haemodynamic monitoring. • Stop gilteritinib if severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids. • Resume gilteritinib at the same dose when signs and symptoms improve to Grade 2 or lower.
Posterior reversible encephalopathy syndrome	• Symptoms include headache, visual disturbance, confusion, seizures. • Discontinue gilteritinib
QTc interval >500 msec	• Interrupt gilteritinib. • Resume gilteritinib at a reduced dose (120mg to 80mg or 200mg to 120mg) when QTc interval returns to within 30 msec of baseline or ≤ 480 msec.
QTc interval increased by >30 msec on ECG on day 8 of cycle 1	• Confirm with ECG on day 9. • If confirmed, consider dose reduction to from 120mg to 80mg or 200mg to 120mg
Symptoms of pancreatitis	• Interrupt gilteritinib until pancreatitis is resolved. • Resume treatment with gilteritinib at a reduced dose (120mg to 80mg or 200mg to 120mg).
Other Grade 3a or higher toxicity considered related to treatment	• Interrupt gilteritinib until toxicity resolves or improves to Grade 1 • Resume treatment with gilteritinib at a reduced dose (120mg to 80mg or 200mg to 120mg).

Planned HSCT	• Stop treatment with gilteritinib one week prior to administration of the conditioning regimen for HSCT. Continuation of gilteritinib after successful HSCT is not commissioned

References:

1. NICE Technology Appraisal. ''Gilteritinib for treating relapsed or refractory acute myeloma leukaemia'', Technology appraisal guidance [TA642]. Published Date: 12 August 2020
2. Summary of Product Characteristics, Xospata 40mg Film Coated Tablets, Astellas Pharma Ltd, Available at www.emc.org.uk, last updated 13th Nov 2019. Accessed 05/10/20
3. Lancet Oncology (2019). Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Accessed on 28/09/2020

Circulation/Dissemination

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Version History

Date	Version	Author name and designation	Summary of main changes
August 2022	1.0	**Daniel Dutton – Advanced Pharmacist**	V1 New Regimen Protocol