PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti-Cancer Therapy Protocol

RUXOLITINIB

MYELOFIBROSIS

PROTOCOL REF: MHOARUXO
(Version No. 1.0)

Approved for use in:

- Disease-related splenomegaly or symptoms in adults with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis, **only in patients with intermediate-2 or high-risk disease** (NICE TA386).

Blueteq registration must be completed prior to treatment initiation

Dosage:

Drug	Platelet count (x10^9/L)	Starting Dose
Ruxolitinib	**>200**	20mg orally twice daily
	100 - 200	15mg orally twice daily
	75 - 99	10mg orally twice daily
	50 - 74	5mg orally twice daily

Continuous treatment until disease progression or intolerances occurs.

Dose Escalation:

If insufficient efficacy is considered and blood counts are adequate, then doses may be increased by a maximum of 5 mg twice daily, up to the maximum dose of 25 mg twice daily.

Administration:

The starting dose should not be increased within the first four weeks of treatment and thereafter no more frequently than at 2-week intervals.

Ruxolitinib tablets should be taken orally twice-daily 12 hours apart at the same times each day. The doses can be taken either with or without food. If a dose is missed, the patient should not take an additional dose, but should take the next usual prescribed dose.

Emetogenic risk:

Low.

Supportive treatments:

- Allopurinol 300mg once daily if required for first cycle
- Aciclovir 400mg twice daily

Dosing in renal and hepatic impairment:

<table>
<tr><td rowspan="5">Renal</td><td>CrCl <30mL/min</td><td colspan="2">Starting dose should be reduced by 50% administered twice a day.</td></tr>
<tr><td rowspan="4">End-Stage renal disease on haemodialysis</td><td>Platelet Count (x10^9/L)</td><td>Starting Dose</td></tr>
<tr><td>>200</td><td>20mg PO single dose or 10mg PO 12 hours apart</td></tr>
<tr><td>100 – 200</td><td>15mg PO single dose</td></tr>
<tr><td colspan="2">Administer only on haemodialysis days following dialysis.</td></tr>
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Hepatic	Starting dose should be reduced by 50% to be administered twice a day. Subsequent doses should be adjusted based on monitoring of safety and efficacy. Monitored FBC at least every 1 - 2 weeks for 6 weeks then as clinically indicated thereafter once liver function and blood counts have stabilised. Titrate dose to reduce the risk of cytopenia.

Interactions:

- When ruxolitinib is administered with strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole, itraconazole, erythromycin, clarithromycin) the unit dose of ruxolitinib should be reduced by approximately 50%, to

be administered twice daily. The concomitant use of ruxolitinib with fluconazole doses greater than 200 mg daily should be avoided.

- More frequent monitoring (e.g. twice a week) of haematology parameters and of clinical signs and symptoms of ruxolitinib-related adverse drug reactions is recommended while on strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes.
- Concomitant use of CYP3A4 inducers should be avoided (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or St John's Wort) as they may significantly reduce exposure to ruxolitinib, potentially increasing the risk of therapeutic failure.

For more detailed interactions please refer to the SPC.

Main Toxicities:

RUXOLITINIB
Main Toxicities include Myelosuppression, infection, bruising, dizziness, headache, constipation, diarrhoea, hypertension, weight gain, hypercholesterolaemia, progressive multifocal leukoencephalopathy, elevated lipase, pneumonia, herpes zoster, urinary tract infection. Please refer to product SPC for a full list of toxicities.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2 onwards	Ongoing
Informed Consent	X			
Clinical Assessment	X	X	X	Prior to every cycle
SACT Assessment (to include PS and toxicities)	X	X	X	Prior to every cycle
FBC	X	X	X	Prior to every cycle. A cycle may extend to three months in length once patients are stable on treatment. FBC should be taken within 7 days of prescribing but may be taken up to 14 days prior to prescription at clinician's discretion. Prescribers must check FBC prior to prescribing and document that this check has taken place in the medical notes.
U&E & LFTs	X	X	X	Must have had within 6 months of prescription. Prescribers must check U+E & LFT prior to prescribing and document that these checks have taken place in the medical notes.
Viral Screening (Hep B+ Hep C / HIV / VZZ)	X			
Pregnancy test	X			If clinically indicated
Height and Weight recorded	X			More frequently if appropriate
Consider skin surveillance	X			As clinically indicated if high risk for skin cancer

Dose Modifications and Toxicity Management:

Haematological toxicity:

Dose reductions should be considered based on neutrophil count or if the platelet count decreases during treatment as outlined below, with the goal of avoiding dose interruptions for thrombocytopenia.

Dose Modifications for MF Patients with a Starting Minimum Platelet Count of 100 × 10^9/L

	Dose at time of platelet decline				
	25mg BD	20mg BD	15mgBD	10mg BD	5mg BD
Platelet count (x10^9/L)	**New Dose**				
100 - 125	20mg BD	15mg BD	No change	No change	No change
75 - 99	10mg BD	10mg BD	10mg BD	No change	No change
50 - 74	5mg BD	5mg BD	5mg BD	5mg BD	No change
<50	Stop ruxolitinib. Once recovered above these levels, resume ruxolitinib 5mg PO twice a day and gradually increased based on careful monitoring of FBC including white blood cell count differential.				

Dose Modifications for MF Patients with a Starting Platelet Count of Between 50×10^9/L and 100×10^9/L.

Please note the following dose modifications are off-label and should only be used after careful consideration if the benefits of continuing treatment outweighs the risks.

Current platelet count (x10^9/L)	Dosing recommendation
<25	Interrupt treatment
25 - 35 with <20% decrease during prior 4 weeks	Decrease dose by 5mg OD or maintain the current dose if it is 5mg OD
25 - 35 with ≥20% decrease during prior 4 weeks	Decrease dose by 5mg BD or use 5mg OD if current dose is 5mg BD or OD
≥40 with ≤20% decrease during prior 4 weeks, ANC >1 x 10^9/L and no dose	Increase by dose increments of 5mg OD to a maximum of 10mg BD if response is insufficient.

reduction or treatment interruptions for AE or haematological toxicity during prior 4 weeks	

Neutrophils ($x10^9$/L)	Dose Modification
<0.5	Stop ruxolitinib. Once recovered above these levels, resume ruxolitinib 5mg PO BD and gradually increase based on careful monitoring of FBC including white blood cell count differential.

Avoid abrupt discontinuation as this can cause cytokine storm. If urgent treatment interruption required, consider concurrent corticosteroids, and if possible, taper dose.

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.

References:

1. https://www.medicines.org.uk/emc - Ruxolitinib
2. BNF available via: https://bnf.nice.org.uk/
3. NICE (2016) TA386. https://www.nice.org.uk/guidance/ta386
4. Mesa and Cortes: Optimizing management of ruxolitinib in patients with myelofibrosis: the need for individualized dosing. Journal of Hematology & Oncology 2013 6:79

Circulation/Dissemination

Date added into Q-Pulse	For completion by DCM
Date document posted on the Intranet	For completion by DCM

Version History

Date	Version	Author name and designation	Summary of main changes
July 2023	1.0	**Jade Marsh** **Advanced Pharmacist – Haemato-oncology**	New protocol created