SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

BOSUTINIB
CHRONIC MYELOID LEUKAEMIA (CML)

PROTOCOL REF: MPHABOSHA
(Version No. 1.1)

Approved for use in:

Chronic, accelerated and blast phase Philadelphia chromosome (BCR-ACL) positive (Ph+) chronic myeloid leukaemia (CML) previously treated with one or more tyrosine kinase inhibitors and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options **(TA401)**.

Blueteq registration must be completed prior to initiation.

Note: Bosutinib is licensed but is **not funded** by NHS England in newly diagnosed (BCR-ACL) positive (Ph+) chronic myeloid leukaemia (CML).

Dosage:

Chronic, accelerated and blast phases

Drug	Dose	Route	Frequency
Bosutinib	500mg*	PO	Once daily continuous

*In practice, patients are usually started on a dose of 400mg daily to minimise GI toxicity, with the dose titrated up depending on response to treatment and tolerability.

Consider increase up to 600mg once daily if suboptimal response.

Dose escalation may be considered in those who do not experience severe or persistent moderate adverse reactions, under any of the following circumstances:

- Failure to achieve Complete Haematological Response (CHR) by week 8.
- Failure to achieve BCR-ABL transcript level <10% by week 12.

Administration:

- Diarrhoea is common during initial weeks of therapy but often settles with conservative management.
- Each dose should be taken with food. If a dose is missed by more than 12 hours, the patient should not be given an additional dose. Tablets should not be broken or cut.
- Patients should be encouraged to report severe oedema early to their haematology team.
- Bosutinib may result in a clinically significant decline in renal function. Closely monitor patient with existing risk factors for renal dysfunction, including concomitant use of medicinal products with potential for nephrotoxicity, such as diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and nonsteroidal anti-inflammatory drugs (NSAIDs).

Emetogenic risk:

Low risk

Supportive treatments:

- Consider allopurinol 300mg once daily during first cycle
- Loperamide 2mg when required (max 16mg/day)

Dosing in renal and hepatic impairment:

Renal	
Creatinine clearance (mL/min)	**Dose Adjustment**
30 - 50	400mg once daily (dose escalation to 500mg once daily)
<30	300mg once daily (dose escalation to 400mg once daily)

Hepatic	
Child Pugh A - C	200mg once daily

Interactions:

- Concomitant use of CYP3A4 inducers including dexamethasone, phenytoin, carbamazepine, rifampicin, and phenobarbital should be avoided as this may significantly reduce exposure to bosutinib.
- Concomitant use of CYP3A4 inhibitors including ketoconazole, itraconazole, voriconazole, erythromycin, clarithromycin and grapefruit juice should be avoided as this may significantly increase exposure to bosutinib.
- Concomitant use of antacids or proton pump inhibitors may reduce exposure to bosutinib. Short-acting antacids should be considered with differing administration times (i.e. bosutinib mane, antacid evening).
- Bosutinib should be used with caution in patients who have or may develop prolongation of QT, including those patients taking anti-arrhythmic or other medicinal products that may lead to QT prolongation.

Please refer to the relevant SPC for more information on interactions.

Main toxicities:

Bosutinib
Infection, anaemia, neutropenia, thrombocytopenia, leucopenia, hypersensitivity, reduced appetite, dehydration, hyperkalaemia, hypophosphataemia, dizziness, headache, tinnitus, hypertension, pleural effusion, cough, diarrhoea, vomiting, abdominal pain, nausea, GI haemorrhage, pancreatitis, gastritis, deranged LFTs, hepatotoxicity, rash, photosensitivity, arthralgia, AKI, oedema, prolonged QTc. Hepatitis B reactivation.

Investigations and treatment plan:

	Pre	C1 week 1	C1 Week 2	C1 Week 3	C1 Week 4	Cycle 2+	Ongoing
Informed Consent	X						
Clinical Assessment	X	X				X	Prior to every cycle
SACT Assessment (including toxicity assessment and PS)	X	X				X	Prior to every cycle
ECHO	X						If history of cardiac disease
ECG	X		X				Repeat if clinically indicated
SOKAL Index	X						
BCR-ABL PCR	X					X	Monthly for the first three months, three monthly thereafter.
Lipid profile, glucose, CK, Urate	X						
FBC, U&E & LFTs	X		X	X	X	X	Weekly FBC for 4 weeks then monthly. Minimum of monthly LFTs for 3 months. **Prescribers must check FBC prior to prescribing and document that this check has taken place in the medical notes. SACT assessment will not include checking of this parameter in this instance.**
Amylase & Lipase	X						Then as clinically indicated
Blood Pressure	X				X		Repeat as clinically indicated
Height	X						
Weight	X					X	Prior to every cycle
Pregnancy test	X						If clinically indicated
Hepatitis B/ C and HIV testing	X						

Dose Modifications and Toxicity Management:

Haematological toxicity:

Proceed with cycle if:

ANC ≥ 1.0 $x10^9$/L	Platelets ≥ 50 $x10^9$/L

Dose Adjustment for haematological toxicity	
ANC <1 $x10^9$/L And / or Platelets < 50 $x10^9$/L	1. Stop bosutinib treatment 2. Resume treatment within 2 weeks at the same dose if ANC > 1.0 $x10^9$/L and/or platelets > 50 $x10^9$/L 3. If counts remain low for > 2 weeks, reduce dose by 100mg and resume treatment. 4. If cytopenia recurs, reduce dose by 100mg upon recovery and resume treatment Doses less than 300mg/day have not been evaluated

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:

Clinically significant moderate or severe non-haematological toxicity	Interrupt bosutinib. Resume at 300mg once daily when toxicity has resolved. If clinically appropriate consider re-escalating to 400mg once daily.
Liver transaminases > 5 x ULN	Interrupt bosutinib. Resume at 400mg once daily when ≤ 2.5 x ULN. If recovery takes > 4 weeks, consider discontinuing bosutinib.
Liver transaminases ≥ 3 x ULN *and* bilirubin > 2 x ULN *and* ALP < 2 x ULN	Discontinue bosutinib.
Diarrhoea grade 3 / 4	Interrupt bosutinib. Resume at 400mg OD once daily upon recovery to grade ≤ 1.

References:

1. NICE (2016) TA401. https://www.nice.org.uk/guidance/ta401 Accessed 22/8/23.
2. Pfizer. Bosulif 400mg film-coated tablets (Bosutinib). Summary of Product Characteristics. Updated 17/5/2022. Accessed on 22/8/2023
3. MHRA (2016) Drug Safety Update: BCR-ABL tyrosine kinase inhibitors: risk of hepatitis B reactivation
4. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.

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
Dec 2020	1.0	**Mark Nelson Senior Pharmacist HO**	**New Protocol**
Oct 2023	1.1	**Jennifer Gibson Principal Pharmacist HO**	**3 yearly review. Transferred to new template. Toxicity information updated.**