Systemic Anti-Cancer Therapy Protocol

Ripretinib for Gastrointestinal Stromal Tumours (Expanded Access Program)

Protocol Reference: MPHARIPSA
(Version No: 1.0)

Approved for use in:

Treatment of adult patients with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with 3 or more kinase inhibitors, including imatinib.

Via Clinigen Expanded Access Program.

Dosage:

Drug	Dosage	Route	Frequency
Ripretinib	150mg*	Oral	Once a day*

Cycle length every 28 days. Supplied as 50mg tablets every 28 days.

*Dose escalation:

Option to dose escalate to **150mg twice daily** upon radiographic confirmation of disease progression.

Patients who have had disease progression as confirmed by RECIST based on radiologic assessment may increase to ripretinib 150mg twice daily regimen. The patient must undergo assessment within 2 weeks prior to escalation to determine whether higher dose is appropriate.

Emetogenic risk:

Low

Supportive treatment:

None

Renal and Hepatic Dosing:

Dose Modifications	
Renal	No dose adjustment is necessary in mild or moderate impairment. Use with caution in moderate to severe impairment, discuss with consultant.
Hepatic	No dose adjustment for subjects with mild hepatic insufficiency. Use with caution in moderate to severe impairment, discuss with consultant.

Drug Interactions:

- Strong CYP3A Inhibitors: Monitor more frequently for adverse reactions. E.g. Clarithromycin, Grapefruit juice, Itraconazole, Posaconazole, Voriconazole.
- Strong CYP3A Inducers: Avoid concomitant use of strong CYP3A inducers. E.g. dexamethasone, carbamazepine, phenytoin, phenobarbital, rifampin, rifabutin, and rifampacin

Guidance for Dose Modifications and Toxicity Management:

Starting dose	1st dose reduction	2nd dose reduction
150mg OD	100mg OD	50mg OD
150mg BD	100mg BD	150mg OD

Haematological / Non-haematological toxicities:

Dose Modifications	
Haematological	Neutrophils >1.0 x10^9/L and platelets >50 x10^9/L continue at usual dose with no interruptions. Discuss with consultant if below these limits.
Elderly population	No change

Counselling points:

- Advise patients that hypertension may develop during treatment and that blood pressure should be monitored regularly during treatment.
- Embryo-Foetal Toxicity- Advise pregnant women and females of reproductive potential of the potential risk to a foetus. Advise females of reproductive potential to inform the sarcoma team of a known or suspected pregnancy. Advise females of reproductive potential to use effective contraception during treatment and for at least 1 week after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with and for at least 1 week after the final dose.
- Take at approximately the same time each day. If dose is twice daily take at least 6 hours apart.
- Swallow tablets whole, with 250mLs of water with or without food.
- Avoid grapefruit juice.
- Miss dose if not taken within 8 hours (4 hours if twice daily) of usual time
- If vomiting occurs don't re-take dose.

Investigations and treatment plan:

	Before Treatment	Prior to each cycle	Ongoing
Informed Consent	X		
Clinical Assessment	X	X	
SACT Assessment	X	X	
Observations (Blood pressure/ Pulse/ Temperature/ Respiratory rate)	X	X	
FBC, LFT, U+E	X	X	
Height	X		
Weight	X	X	
ECG	If clinically indicated		

Dose interruption due to planned medical procedure:

- For procedures that occur while the patient is ripretinib, the extent of the procedure and rate of healing following the procedure must be taken into consideration. The following guidance applies:
    - Planned minimally invasive surgery: ripretinib must be interrupted for 3 days prior to and 3 days after surgery.
    - Planned major surgeries: ripretinib must be interrupted for a minimum of 5 days prior to surgery and continuation of ripretinib must be determined after consultation with oncologist.
    - Unplanned surgery: ripretinib must be interrupted immediately, and continuation of ripretinib must be determined after consultation with the oncologist.
    - Radiotherapy: ripretinib must be interrupted for 5 days prior to and 5 days after radiotherapy.

Main Toxicities:

- The most common adverse reactions (≥20%) were alopecia, fatigue, nausea, abdominal pain, constipation, myalgia, diarrhoea, decreased appetite, palmar-plantar erythrodysesthesia, and vomiting. The most common Grade 3 or 4 laboratory abnormalities (≥4%) were increased lipase and decreased phosphate.
- Report of cardiac issues related to BNP.

Adverse reactions:

Adverse reaction	Severity*	2nd dose reduction
Arthralgia/Myalgia and Dermatologic toxicities e.g. Palmar-Plantar	Grade 1	Supportive measures and continue at same dose.
	Grade 2	Withhold until Grade ≤1 or baseline. If recovered within 7 days, resume at same dose; otherwise resume at reduced dose.

Erythrodysesthesia Syndrome (PPES)		Consider re-escalating if maintained at Grade ≤1 or baseline for at least 28 days. If event recurs, withhold until Grade ≤1 or baseline and then resume at a reduced dose regardless of time to improvement. If after dose reduction, the event is maintained at Grade 1 or baseline for at least 1 cycle (28 days) of dosing, consider re-escalating ripretinib by 1 dose level.
	Grade 3	Withhold for at least 7 days or until Grade ≤1 or baseline (maximum 28 days). Resume at a reduced dose. Consider re-escalating if maintained at Grade ≤1 or baseline for at least 28 days.
	Grade 4	Discontinue ripretinib, especially if affecting ADLs.
Steven-Johnson Syndrome	If a patient experiences Stevens-Johnson syndrome, ripretinib must be permanently discontinued. The patient to be immediately referred to a hospital for clinical evaluation and supportive care. Caution for recurrence of Stevens-Johnson syndrome with other similar agents (TKIs for GIST)	
Hypertension (If BP remains controlled for at least 1 full cycle (28 days), ripretinib dose can be re-escalated with consultant's approval)	Grade 1 Prehypertension (Systolic BP 120-139mmHg or Diastolic 80-89mmHg)	Continue BP monitoring. Continue ripretinib at current dose.
	Grade 2 Systolic BP 140-159 mmHg or	Treat BP to achieve diastolic BP ≤90mmHg and or systolic ≤140mmHg.

	diastolic BP 90-99 mmHg Or Symptomatic increase by > 20 mmHg (diastolic BP) or to > 140/90 mmHg, if previously within normal limits	If BP was previously within normal limits, start antihypertensive monotherapy. If patient was already on antihypertensive medication, titrate dose up. Continue ripretinib if symptomatic increase by 20mmHg (diastolic BP) until symptoms resolve and diastolic BP ≤90mmHg. On resuming ripretinib, continue at same level.
	Grade 3 Systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg Or More than 1 drug or more intensive therapy than previously indicated	Treat BP to achieve diastolic BP ≤90mmHg and or systolic ≤140mmHg. Start antihypertensive medication and/or Increase current antihypertensive medication and/or Add additional antihypertensive medication If symptomatic, hold ripretinib until diastolic BP ≤90mmHg and/or systolic BP ≤140mmHg, and symptoms resolve. On resuming ripretinib, continue at the same dose level. If BP is not controlled with addition of a new or more intensive therapy, reduce ripretinib by 1 dose level. If Grade 3 hypertension recurs despite ripretinib dose reduction and antihypertensive therapy, reduce ripretinib by 1 additional dose level.

	Grade 4	Treat BP and then permanently discontinue ripretinib.
Left Ventricular Systolic Dysfunction	Grade 3 or Grade 4	Permanently discontinue ripretinib
Other Adverse Reactions	Grade 3 or 4	Withhold until Grade ≤1 or baseline and then resume at a reduced dose; otherwise permanently discontinue. Consider re-escalating if no recurrence of the adverse reaction for at least 28 days. If Grade 3 or 4 recurs, permanently discontinue Ripretinib.

*Severity as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0

References:

1) Deciphera 2618-99-001 Protocol 2019
2) Deciphera INVESTIGATOR'S BROCHURE RIPRETINIB (DCC-2618) 2020
3) Ripretinib for Gastrointestinal Stromal Tumours, Sarcoma Pathway Group, UCLH Cancer Collaborative; The Cancer Alliance for north and east London Protocol 2020