Indication	For the treatment of NTRK fusion-positive solid tumours if: • the disease is locally advanced or metastatic or surgery could cause severe health problems and • they have not had an NTRK-inhibitor before and • they have no satisfactory treatment options. For the treatment of ROS1-positive recurrent, locally advanced or metastatic non-small cell lung cancer (NSCLC) previously untreated with a ROS1 inhibitor.
Treatment Intent	Palliative
Frequency and number of cycles	Repeat every 28 days Continuous until disease progression or unacceptable toxicity or patient choice or (where applicable) potentially curative surgery takes place. NB: A formal medical review should be scheduled to occur by the start of the second cycle (month) of treatment.
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • FBC, U&Es (including Mg^{2+} and Ca^{2+}) and LFTs at each cycle. • Uric acid should be monitored prior to treatment then as clinically indicated • ECG at baseline and prior to cycle 2 and then monitor periodically throughout treatment as clinically indicated. Avoid entrectinib in patients with a baseline QTc interval longer than 450 ms, in patients with congenital long QTc syndrome, and avoid (or use caution and undertake regular ECGs) in patients taking medicinal products that are known to prolong the QTc interval. • In patients with known cardiac risk factors undertake ECHO / MUGA prior to treatment and as clinically indicated throughout treatment. Avoid in patients with electrolyte imbalances or significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina, and bradyarrhythmias. • For NTRK fusion-positive indication: A PET/CT/MR scan of index assessable/measurable disease must be done prior to commencing entrectinib and repeated 10 weeks after the start of treatment (if not indicated before 10 weeks on account of assessing risk of disease progression). • **Hepatic Impairment:** No dose adjustment is recommended in hepatic impairment. Patients with severe hepatic impairment (Child-Pugh C) should be closely monitored. • **Renal Impairment:** No dose adjustment required in mild or moderate (CrCl >/= 30ml/min) renal impairment. Not recommended in patients with severe renal impairment (CrCl <30ml/min) as data is too limited. • **Dose modification:** Dosing interruption or dose reduction may be required based on individual safety and tolerability. First dose reduction: 400mg taken orally once daily. Second dose reduction: 200 mg taken orally once daily Entrectinib should be permanently discontinued if the patient is unable to tolerate 200mg po od. • See table 1 for dose modifications for adverse effects. • **<u>Common drug interactions</u>: (for comprehensive list refer to BNF/SPC)** ○ Avoid concurrent use with moderate or strong CYP3A inhibitors (ketoconazole, itraconazole, clarithromycin, and voriconazole) . If co-administration cannot be avoided, reduce entrectinib to 200mg once daily with moderate CYP3A inhibitors and 100mg once daily with strong CYP3A inhibitors and limit the use of the CYP3A inhibitor to 14 days. After discontinuation of a strong or moderate CYP3A inhibitor,

	resume the dose that was taken prior to initiating the CYP3A inhibitor. A wash-out period of 3 to 5 elimination half -lives may be required for CYP3A inhibitors with a long half-life. Concomitant use with strong or moderate CYP3A inducers (e.g. phenytoin, rifampicin, carbamazepine, phenobarbital, St John's Wort) should be avoided. Patients should not drink grapefruit juice or eat grapefruit or Seville oranges whilst taking entrectinib. Entrectinib is a weak inhibitor of CYP3A4 ; caution when entrectinib is administered together with CYP3A4 substrates with a narrow therapeutic range (e.g., cisapride, cyclosporin, ergotamine, fentanyl, pimozide, quinidine, tacrolimus, alfentanil and sirolimus). • **Adverse reactions:** o Cognitive disorders including confusion, mental status changes, memory impairment and hallucinations can occur. Withhold and then resume at same or reduced dose upon improvement or permanently discontinue depending on severity. o Bone fractures: There is an increased risk of fracture whilst taking entrectinib, not always related to trauma. Patients should be advised to report pain, changes in movement, or bone abnormalities. o Patients should be monitored for signs of hyperuricaemia and congestive heart failure. • **Missed dose:** If a dose is missed, then it should be taken as soon as the patient remembers unless it is less than 12 hours before the next dose, in which case the patient should not take the missed dose. If a patient vomits immediately after taking a dose, instruct patients to repeat that dose. • Patients should be advised that entrectinib can have an effect on their ability to drive and use machines. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Macmillan information sheet.
References	KMCC protocol MULTI-019 V1 SPC accessed online 04.09.2023

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1 Recommended Dosage Modifications for adverse reactions

Adverse reaction	Severity*	Dosage modification
Congestive heart failure	Symptomatic with middle to moderate activity or exertion, including where intervention is indicated (Grade 2 or 3)	• Withhold Entrectinib until recovered to less than or equal to Grade 1 • Resume at reduced dose
	Severe with symptoms at rest, minimal activity, or exertion or where intervention is indicated (Grade 4)	• Withhold Entrectinib until recovered to less than or equal to Grade 1 • Resume at reduced dose or discontinue as clinically appropriate
Cognitive disorders	Intolerable, but moderate changes interfering with activities of daily living (Intolerable Grade 2)	• Withhold Entrectinib until recovery to less than or equal to Grade 1 or to baseline • Resume at same dose or reduced dose, as clinically needed
	Severe changes limiting activities of daily living (Grade 3)	• Withhold Entrectinib until recovery to less than or equal to Grade 1 or to baseline • Resume at reduced dose
	Urgent intervention indicated for event (Grade 4)	• For prolonged, severe, or intolerable events, discontinue Entrectinib as clinically appropriate
Hyperuricemia	Symptomatic or Grade 4	• Initiate urate-lowering medication • Withhold Entrectinib until improvement of signs or symptoms • Resume Entrectinib at same or reduced dose
QT interval prolongation	QTc 481 to 500 ms	• Withhold Entrectinib until recovered to baseline • Resume treatment at same dose
	QTc greater than 500 ms	• Withhold Entrectinib until QTc interval recovers to baseline • Resume at same dose if factors that cause QT prolongation are identified and corrected • Resume at reduced dose if other factors that cause QT prolongation are <u>not</u> identified
	Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia	• Permanently discontinue Entrectinib
Transaminase elevations	Grade 3 (> 5 – 20 x ULN)	• Withhold Entrectinib until recovery to less than or equal to Grade 1 or to baseline • Resume at same dose if resolution occurs within 4 weeks • Permanently discontinue if adverse reaction does not resolve within 4 weeks • Resume at a reduced dose for recurrent Grade 3 events that resolve within 4 weeks
	Grade 4 (> 20 x ULN)	• Withhold Entrectinib until recovery to less than or equal to Grade 1 or to baseline • Resume at reduced dose if resolution occurs within 4 weeks

		• Permanently discontinue if adverse reaction does not resolve within 4 weeks • Permanently discontinue for recurrent Grade 4 events
	ALT or AST > 3 times ULN with concurrent total bilirubin > 2 times ULN (in the absence of cholestasis or haemolysis)	• Permanently discontinue Entrectinib
Anaemia or neutropenia	Grade 3 or 4 (Neuts < 1 x 10^9/l or Hb < 80g/l)	• Withhold Entrectinib until recovery to less than or equal to Grade 2 or to baseline • Resume at the same dose or reduced dose, as clinically needed
Other clinically relevant adverse reactions	Grade 3 or 4	• Withhold Entrectinib until adverse reaction resolves or improves to recovery or improvement to Grade 1 or baseline • Resume at the same or reduced dose, if resolution occurs within 4 weeks • Consider permanent discontinuation if adverse reaction does not resolve within 4 weeks • Permanently discontinue for recurrent Grade 4 events
* Severity as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0		

Repeat every 28 days

Day	Drug	Dose	Route	Administration
Day 1	**ENTRECTINIB**	**600mg**	PO	OD Swallow capsules whole. Do not open, crush, chew, or dissolve the contents of the capsule. Available as 100mg and 200mg capsules
	Metoclopramide	10mg		10mg up to three times a day PRN. Do not take for more than 5 days continuously. Dispense on Cycle 1 only, then only if required.
	Loperamide	2mg	PO	Take two capsules (4mg) after first loose stool, then one capsule (2mg) after each loose stool when required. (Maximum 16mg per day). Dispense on Cycle 1 only, then only if required.