Systemic Anti Cancer Treatment Protocol

Entrectinib
NTRK Gene Fusion-positive Solid Tumours
ROS1-positive NSCLC

PROTOCOL REF: MPHAENTLU
(Version No: 1.1)

Approved for use in:

- In adults and children over 12 years with solid tumours (including primary cerebral tumours) that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion and fulfil the following criteria:
    - Disease is locally advanced or metastatic or for which surgical resection is likely to result in severe morbidity AND no other satisfactory treatment options available.
    - No previous treatment with NTRK inhibitor.
- In ROS1-positive recurrent or locally advanced or metastatic non-small-cell lung cancer previously untreated with a ROS1 inhibitor therapy.
- Performance Status: 0, 1 or 2.

Blueteq registration required for both indications but registration for solid tumours with NTRK gene fusion requires the completion of TWO forms*

***Blueteq registration is required-prior to initiation of treatment** with Entrectinib, this **covers the funding of the first TWELVE weeks ONLY** of treatment. PET/CT/MR scans of index assessable/measureable disease and also of the brain must be done prior to commencing treatment and repeated at 10 weeks from the start of treatment (if not indicated before 10 weeks on account of assessing risk of disease progression). A RECIST response on the repeated assessment must be made and **another blueteq form will need to be completed detailing this information for continuation of funding for Entrectinib BEYOND the initial 12 week period.**

Baseline liver function tests must be reviewed prior to completing consent process (Please refer to 'Dosing in renal and hepatic impairment'). As per trial, adequate hepatic function was characterised by the following:

- AST and ALT ≤ 3.0 × ULN (≤ 5.0 × ULN if liver metastases are present)
- Bil ≤ 2.0 × ULN (patients with a known history of Gilbert's syndrome and/or isolated elevations of indirect bilirubin were included in the trial)

Special Precautions for Use

Entrectinib **should be avoided in patients with a baseline QTc interval longer than 450 ms,** in patients with congenital long QTc syndrome and it should not be taken alongside medicinal products that are known to prolong the QTc interval.

Entrectinib should be avoided in patients with significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina, and bradyarrhythmias. If the clinical team decide that the benefits of treatment outweigh the potential risks, additional monitoring should be performed (regular clinic follow-up to monitor for signs/symptoms and review ECGs) and input from specialist cardiology team should be sought.

Dosage:

Drug	Dosage	Route	Frequency
Entrectinib	600mg**	Oral	Once daily continuously

Until unacceptable toxicity or disease progression

****Please NOTE: dosing applies for patients over 18 years of age or those aged 12-18 years with BSA ≥ 1.51m^2)**

One month supply will be issued at each visit

Administration:

Entrectinib capsules should be swallowed whole (must not be opened or dissolved) with water and can be taken with or without food.

Patient should avoid any food or drink containing **grapefruit and grapefruit juice, Seville oranges, or pomelos** within 7 days prior to start of treatment and until treatment discontinuation, as these have been shown to inhibit CYP3A4 activity.

Entrectinib can cause foetal harm. Women of childbearing age must use highly effective contraception methods during treatment and up to 5 weeks after the last dose of entrectinib. Male patients with female partners of childbearing potential must use highly effective contraceptive methods during treatment and for 3 months after the last dose (refer to 'Drug Interactions' section).

Contains lactose- patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Emetogenic risk:

Minimal to low emetogenic potential

Supportive treatments:

Metoclopramide 10mg three times a day when required.

Dosing in renal and hepatic impairment:

Renal	GFR 30-90 ml/min- no dose adjustment required GFR < 30 ml/min- use with caution as not studied in this patient group.

Hepatic	Mild hepatic impairment (Child-Pugh Class A)- no dose adjustment is recommended Moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment - not studied this patient group use with caution.

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

	(g/L)			
	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.
Refer to 'Dose Modifications and Toxicity Management' section for entrectinib-induced hepatotoxicity.

Drug Interactions Supportive treatments:

CYP3A4 and P-gp substrates/inhibitors/inducers	Co-administration of entrectinib with **midazolam** can result in increased midazolam serum levels. Caution is advised when administered together. **Dabigatran** is a sensitive P-gp substrate. It is not known what effect entrectinib may have on dabigatran. Use with caution. CYP3A4 substrates with a narrow therapeutic range can interact with entrectinib to cause an increased risk of adverse drug reactions. Examples include **cyclosporine, tacrolimus, alfentanil, fentanyl and sirolimus.** Co-administration of entrectinib with CYP3A/P-gp inducers (e.g. **carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin**) or strong and moderate CYP3A/P-gp inhibitors (e.g. **ritonavir, saquinavir, ketoconazole, itraconazole,**

	voriconazole, posaconazole, grapefruit or Seville oranges, verapamil, nifedipine, felodipine, paroxetine) should be avoided. If concurrent use of strong or moderate inhibitors of CYP3A4 is unavoidable, dose adjustment of entrectinib is required.
BRCP/(OATP)1B1/ PXR regulated enzymes substrates	Caution is advised when sensitive oral BCRP substrates (e.g. **methotrexate, mitoxantrone, topotecan**) or sensitive oral OATP1B1 substrates (e.g. **atorvastatin, pravastatin, rosuvastatin repaglinide, bosentan**) are co-administered with entrectinib, due to the risk of increased absorption. Co-administration of entrectinib with CYP2C8, CYP2C9 or CYP2C19 (PXR-regulated enzymes) substrates (e.g. **repaglinide, warfarin, tolbutamide or omeprazole**) may decrease their exposure.
Oral contraceptives (OC)	Unknown whether entrectinib may reduce the effectiveness of OCs. Women advised to add a barrier method.
Medical products with potential to prolong QT interval should be avoided	Antiarrythmic agents: amiodarone, sotalol Antibiotics: azithromycin, ciprofloxacin, clarithromycin, levofloxacin Antimalarials: chloroquine Antipsychotic: haloperidol Calcium channel blockers: bepridil Opioids: methadone 5-HT3 receptor antagonists: ondansetron (IV)
Proton Pump Inhibitors (PPI)	No dose adjustments are required when entrectinib is co-administered with PPIs or other drugs that raise gastric pH.

This list is not exhaustive. Refer to SmPC for full details on interactions. For any interaction queries please contact Cytopharmacy.

Main Toxicities:

The most common adverse reactions (≥20%) were fatigue, constipation, dysgeusia (taste disturbances), **oedema**, dizziness, diarrhoea, nausea, dysaesthesia (abnormal sensation- painful itchy, burning or aching sensation), **dyspnoea**, anaemia, increased weight, increased blood creatinine, urinary retention, pain, **cognitive disorders**

(confusion, mental status changes, memory impairment, and hallucinations. More common in patients over 65 years), vomiting, cough, and pyrexia.
The most frequent serious adverse reactions (≥2%) were lung infection, dyspnoea, cognitive impairment and pleural effusion.

Based on the severity of toxicities, dose should be modified as described in 'Dose Modifications and Toxicity Management' section.

Refer to 'Investigations and Treatment Plan' for monitoring criteria and signs/symptoms to watch out form.

Investigations and Treatment Plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing
Clinical Assessment	X		X	X		Every cycle for first 3 cycles then every 3 cycles or as clinically indicated.
ECG	X		X			ECG to be carried out at baseline and after 1 month of treatment. Periodic monitoring of ECGs should be carried out and reviewed by the clinical team due to risk of QT prolongation[a]
LVEF assessment (ECHO/MUGA)	X					At baseline for patients with symptoms or known risk factors for congestive heart failure (CHF) then as clinically indicated[b].
SACT Assessment (to include PS and toxicities)	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	Every cycle
U&E & LFT (ALT,AST and Bilirubin) Including Magnesium	X	X	X	X	X	Every cycle Serum electrolyte abnormalities (specifically magnesium and potassium) need to be corrected as these are risk factors for QT prolongation
CrCl (Cockroft and Gault) or eGFR		X	X	X	X	Every cycle
Serum uric acid	X					At baseline and repeated periodically as clinically indicated[c]

LDH	X	X	X	X	X	Every cycle--for clinician to review if raised. To be assessed in combination with symptoms and radiological progression
CT scan	X			X*		***CT scan to be carried out at baseline then at 6-7 weeks for ROS1 positive tumours and at 10 weeks for NTRK positive solid tumours,** then every three months or as clinically indicated
Informed Consent	X					
Full set of observations	X					Repeat if clinically indicated
Weight recorded	X	X	X	X	X	Every cycle
Height recorded	X					

a. **Monitor for signs of QT prolongation (palpitations, dyspnoea, chest pain, dizziness, near fainting or fainting)**
b. **Monitor for dyspnoea or oedema**
c. **Monitor for severe painful joints, joint stiffness/redness/swelling, and difficulty moving affected joints. Urate-lowering medicinal products should be initiated as clinically indicated.**

Dose Modifications and Toxicity Management:

Management of adverse reactions may require temporary interruption, dose reduction, or discontinuation of treatment. Entrectinib dose may be reduced up to 2 times, based on tolerability. Treatment should be permanently discontinued if patients are unable to tolerate a dose of 200 mg once daily.

Dose Reduction Schedule	**Dose Level**
Recommended dose	600mg once daily
First dose reduction	400mg once daily
Second dose reduction	200mg once daily

Haematological toxicity:

Proceed on day 1 of each cycle if:

ANC ≥ 1.0 x 10^9/L	Haemoglobin ≥ 80 g/L

Neutropenia	ANC < 1.0 x 10^9 /L	Withhold entrectinib until recovery to Grade 2 (ANC ≥ 1.0 x 10^9 /L) <u>Dose reduce by 1 dose level if:</u> Grade 3 neutropenia (ANC <1.0 – 0.5 x 10^9 /L) + Fever ≥ 38°C and/or infection or Grade 4 neutropenia (ANC <0.5 x 10^9 /L)
Anaemia	Hb < 80g/L	Withhold entrectinib until recovery to Grade 2 (Hb ≥ 80g/L).Review weekly and transfuse if symptomatic or Hb<80 on second measurement <u>Dose reduce by 1 dose level if:</u> More than 1 episode of Grade 3 anaemia (Hb < 80g/L) requiring repeated transfusions. Or Grade 4- life-threatening anaemia requiring urgent intervention

Non-haematological Toxicity:

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 (>10 mg/dL or >0.59 mmol/L)	• 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 not identified
	Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia	• Permanently discontinue entrectinib
Transaminase elevations	Grade 3 AST or ALT > 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 AST or ALT > 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 greater than 3 times ULN with concurrent total bilirubin greater than 2 times ULN (in the absence of cholestasis or haemolysis)	• Permanently discontinue entrectinib
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		

Additional Information

Reporting of all suspected adverse reactions for patients on entrectinib is particularly important as it is a newly licensed medication. Reporting allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions in accordance with the training provided and the pharmacovigilance protocol.

References:

Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastaticNTRK fusion-positive solid tumours: Integrated analysis of three phase 1–2 trials. *The Lancet Oncology*. 2020;21(2):271-282. doi: http://dx.doi.org/10.1016/S1470-2045(19)30691-6.
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Drilon A, Siena S, Dziadziuszko R, et al. Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: Integrated analysis of three phase 1–2 trials. *The Lancet Oncology*. 2020;21(2):261-270. doi: http://dx.doi.org/10.1016/S1470-2045(19)30690-4. Protocol available at:
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NICE TA644 Entrectinib for treating NTRK fusion-positive solid tumours. Published 12th August 2020.

NICE TA643 Entrectinib for treating ROS1-positive advanced non-small-cell lung cancer. Published 12th August 2020.