Entrectinib (Lung/NTRK gene fusion solid tumours)

Indication

ROS1-positive advanced non-small-cell lung cancer (NSCLC) in adults who have not previously had ROS1 inhibitors.

A validated assay is required for the selection of patients with ROS1-positive NSCLC. ROS1-positive status must be established prior to initiation of therapy.

(NICE TA643)

Solid tumours that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion when disease is locally advanced or metastatic or for which surgical resection is likely to result in severe morbidity and who have no satisfactory systemic treatment options and have not previously had NTRK inhibitor therapy.

(NICE TA644)

ICD-10 codes

Codes with a prefix C34

Regimen details

Drug	Dose	Route
Entrectinib	600mg OD	PO

Cycle frequency

Continuous

Number of cycles

Continued until disease progression or unacceptable toxicity.

Administration

Entrectinib is available in 100mg and 200mg hard capsules.

The hard capsules should be swallowed whole and must not be opened or dissolved since the contents of the capsule are very bitter. It can be taken with or without food but should not be taken with grapefruit or grapefruit juice.

If a planned dose is missed, patients can make up that dose unless the next dose is due within 12 hours. If vomiting occurs immediately after taking a dose of entrectinib, patients may repeat that dose.

Pre-medication

Nil

Emetogenicity

This regimen has mild emetic potential.

Additional supportive medication

Not routinely required

Extravasation

N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+Es (including creatinine)	14 days
LFTs	14 days
Uric acid	Baseline
ECG	Baseline

Echocardiogram required if known risk factors for congestive heart failure

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	Monthly
U+Es (including creatinine)	Monthly
LFTs	Monthly
Uric acid	Monthly
ECG	After 1 month of treatment, thereafter as clinically indicated

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥1.0 x 10^9 /L
Platelets	≥ 100 x 10^9 /L
Haemoglobin (Hb)	≥ 80g/L
Creatinine clearance (CrCl)	≥ 30ml/min
ALT	≤5 x ULN
Bilirubin	≤2 x ULN
QTc	<450ms

Dose modifications

Dose level	Dose
Full dose	600mg once daily
First dose reduction	400mg once daily
Second dose reduction	200mg once daily

Treatment should be permanently discontinued if patients are unable to tolerate a dose of 200 mg once daily.

- **Haematological toxicity**

Anaemia or neutropenia	Grade 3 or 4 (Neutrophils <1.0 x 10^9/L or Hb < 80g/L)	• Withhold until recovery (neutrophils > 1.0 x 10^9/L and Hb >80g/L) or to baseline • Resume at the same dose or reduced dose, as clinically needed

If platelet count < 100 x10^9/L discuss with prescriber.

- **Renal impairment**

No dose adjustment is required in patients with mild or moderate renal impairment. Entrectinib has not been studied in patients with severe renal impairment.

- **Hepatic impairment**

No dose adjustment is required to the starting dose for patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. No dose adjustment is required for severe hepatic impairment (Child Pugh C) but patients should be carefully monitored for hepatic function and adverse reactions and dose reduce accordingly.

Deranged LFTs during treatment should be managed as per table below:

ALT/AST	Action
Grade 3 (5-20 x ULN)	• Withhold until recovery to ≤ Grade 1 (<3x ULN) 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 until recovery to ≤ Grade 1 (<3 xULN) 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 >3 x ULN with bilirubin >2 x ULN (in the absence of cholestasis or haemolysis)	• Permanently discontinue

- **Other toxicities**

Cognitive disorders: including confusion, mental status changes, memory impairment, and hallucinations, were reported in clinical trials. Patients over the age of 65 years experienced a higher incidence of these events. Patients should be monitored for signs of cognitive changes. Patients should be instructed not to drive or use machines until symptoms resolve if they experience cognitive disorders.

Grade	Action
Intolerable Grade 2 (Intolerable, but moderate changes interfering with activities of daily living (ADL))	• Withhold until recovery to ≤ Grade 1 or to baseline • Resume at same dose or reduced dose, as clinically needed
Grade 3 (Severe changes limiting ADL)	• Withhold until recovery to ≤ Grade 1 or to baseline • Resume at reduced dose
Grade 4 (Urgent intervention indicated)	• For prolonged, severe, or intolerable events, discontinue

Hyperuricemia: serum uric acid levels should be assessed prior to initiating entrectinib and periodically during treatment. Patients should be monitored for signs and symptoms of hyperuricemia. For symptomatic or grade 4 hyperuricaemia, initiate urate-lowering medication, withhold entrectinib until improvement of signs or symptoms and then resume entrectinib at same or reduced dose.

QTc interval prolongation: use of entrectinib should be avoided in patients with a baseline QTc interval longer than 450 ms, those with congenital long QTc syndrome, and in those taking medicinal products that are known to prolong the QTc interval. Entrectinib should be avoided in patients with electrolyte imbalances or significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina, and bradyarrhythmias. If in the opinion of the treating physician, the potential benefits of entrectinib in a patient with any of these conditions outweigh the potential risks, additional monitoring should be performed and a specialist consultation should be considered.

Assessment of ECG and electrolytes at baseline and after 1 month of treatment with entrectinib are recommended. Periodic monitoring of ECGs and electrolytes as clinically indicated throughout treatment, are also recommended.

If QTc interval prolonged, refer to table below:

QTc 481 - 500 ms	• Withhold until recovered to baseline • Resume treatment at same dose
QTc > 500 ms	• Withhold 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

Congestive heart failure (CHF):

Grade	**Action**
Symptomatic with middle to moderate activity or exertion, including where intervention is indicated (Grade 2 or 3)	• Withhold until recovered to ≤ Grade 1 • Resume at reduced dose
Severe with symptoms at rest, minimal activity, or exertion or where intervention is indicated (Grade 4)	• Withhold until recovered ≤ Grade 1 • Resume at reduced dose or discontinue as clinically appropriate

For any other Grade 3 or 4 toxicity withhold entrectinib until toxicity recovers to ≤Grade 1 or baseline. If toxicity resolves within 4 weeks resolve at same dose or reduced dose. Consider permanent discontinuation of entrectinib if adverse reaction does not resolve within 4 weeks. If recurrent Grade 4 reaction, discontinue Entrectinib.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Lung infection
Pleural effusion
Myelosuppression
Congestive heart failure
QTc prolongation

- **Frequently occurring side effects**

Anaemia
Fatigue
Constipation/Diarrhoea
Dysgeusia
Oedema
Dizziness
Nausea
Dysaesthesia
Dyspnoea
Vomiting
Cough
Pyrexia
Urinary tract infection
Anorexia
Cognitive disorders
Headache
Raised transaminases
Rash
Myalgia/Arthralgia

- **Other side effects**

Increased blood creatinine
Hyperuricaemia

Significant drug interactions – for full details consult product literature/ reference texts

Strong or moderate CYP3A inhibitors (including, but not limited to, ritonavir, saquinavir, ketoconazole, itraconazole, voriconazole, posaconazole, grapefruit or Seville oranges): co-administration increases entrectinib plasma concentration, which could increase the frequency or severity of adverse reactions. Therefore, the concomitant use of strong or moderate CYP3A inhibitors should be avoided. If co-administration is unavailable refer to SPC for information regarding dose reductions for entrectinib.

Strong or moderate CYP3A or P-gp inducers (including, but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's Wort, ritonavir)**:** co-administration decreases entrectinib plasma concentrations, which may reduce efficacy of entrectinib, and should be avoided.

Additional comments

Women of childbearing potential: entrectinib may cause foetal harm when administered to a pregnant woman. Women of childbearing potential 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 with entrectinib and for 3 months after the last dose.

Lactose intolerance: entrectinib contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

References

- Summary of Product Characteristics Entrectinib (Roche) accessed 24 August 2023 via www.medicines.org.uk
- National Institute for Health and Care Excellence. NICE Technology Appraisal Guidance 643 accessed 24 August 2023 via www.nice.org.uk
- National Institute for Health and Care Excellence. NICE TA644 accessed 24 August 2023.
- Dziadziuszko R, Krebs MG, De Braud F et al. Updated integrated analysis of the efficacy and safety of entrectinib in locally advanced or metastatic ROS1 fusion–positive non–small-cell lung cancer. Journal of Clinical Oncology 2021; 39(11): 1253-1263.
- Doebele, R, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet oncology 2020; 21(2): 271-282.

Written/reviewed by: Dr R Squires (Oncology SpR, UHBW NHS Trust), Dr C Comins (Consultant Oncologist, UHBW NHS Trust)

Checked by: Kate Gregory (Lead Pharmacist for SACT Protocols, SWAG Cancer Alliance)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBW NHS Trust, SWAG Cancer Alliance)

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