Entrectinib for ROS1-Positive Advanced Non-Small Cell Lung Cancer (NSCLC)

Indication
ROS1-positive advanced non-small cell lung cancer (NSCLC)

Regimen details
Entrectinib (Rozlytrek) capsules 600mg orally daily

Cycle frequency
Continuous treatment dispense monthly

Number of cycles
Until disease progression or unacceptable toxicity

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

Pre-medication
N/A

Emetogenicity
Minimal

Additional supportive medication
Metoclopramide and loperamide with first cycle

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days
Uric acid	14 days
LVEF (if clinically indicated)	14 days
ECG	14 days

Investigations –pre subsequent cycles
FBC, U+E (including creatinine), LFT (including AST), ECG after 1st cycle

Standard limits for administration to go ahead
See under “Dose modifications” below

Dose modifications

Hepatic impairment

No dose adjustment is recommended for patients with mild hepatic impairment. Entrectinib has not been studied in patients with moderate and severe hepatic impairment.

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

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 Rozlytrek 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 Rozlytrek 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 Rozlytrek 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 Rozlytrek 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 Rozlytrek as clinically appropriate
Hyperuricemia	Symptomatic or Grade 4	• Initiate urate-lowering medication • Withhold Rozlytrek until improvement of signs or symptoms • Resume Rozlytrek at same or reduced dose
QT interval prolongation	QTc 481 to 500 ms	• Withhold Rozlytrek until recovered to baseline • Resume treatment at same dose
	QTc greater than 500 ms	• Withhold Rozlytrek 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 Rozlytrek
Transaminase elevations	Grade 3	• Withhold Rozlytrek 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	• Withhold Rozlytrek 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 Rozlytrek
Anaemia or neutropenia	Grade 3 or 4	• Withhold Rozlytrek 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 Rozlytrek 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		

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

- **Serious side effects**

Cognitive disorders

Cognitive disorders, including confusion, mental status changes, memory impairment, and hallucinations, were reported in clinical trials with Rozlytrek. Patients over the age of 65 years experienced a higher incidence of these events than younger patients. Patients should be monitored for signs of cognitive changes.
Based on the severity of cognitive disorders, Rozlytrek treatment should be modified as described in above
Patients should be counselled on the potential for cognitive changes with Rozlytrek treatment. Patients should be instructed not to drive or use machines until symptoms resolve if they experience cognitive disorders

Fractures

Fractures have been reported in 21.9% (7/32) paediatric patients treated with Rozlytrek in clinical trials. Bone fractures were reported in patients less than 12 years of age and were localised in the lower extremity (with a predilection for hip, femur and tibia). Bone fractures in paediatric patients generally occurred with minimal or no trauma. Three patients had more than one occurrence of a fracture and 3 patients had Rozlytrek treatment interrupted due to a fracture. All patients continued Rozlytrek treatment and all but one event of fracture recovered.
Patients with signs or symptoms of fractures (e.g., pain, abnormal gait, changes in mobility, deformity) should be evaluated promptly.

Hyperuricemia

Hyperuricemia has been observed in patients treated with entrectinib. Serum uric acid levels should be assessed prior to initiating Rozlytrek and periodically during treatment. Patients should be monitored for signs and symptoms of hyperuricemia. Treatment with urate-lowering medicinal products should be initiated as clinically indicated and Rozlytrek withheld for signs and symptoms of hyperuricemia. Rozlytrek dose should be modified based on severity as described above

Congestive heart failure

Congestive heart failure (CHF) has been reported across clinical trials with Rozlytrek. These reactions were observed in

patients with or without a history of cardiac disease and resolved upon treatment with diuretics and/or Rozlytrek dose reduction/interruption.
For patients with symptoms or known risk factors of CHF, left ventricular ejection fraction (LVEF) should be assessed prior to initiation of Rozlytrek treatment. Patients receiving Rozlytrek should be carefully monitored and those with clinical signs and symptoms of CHF, including shortness of breath or oedema, should be evaluated and treated as clinically appropriate.
Based on the severity of CHF, Rozlytrek treatment should be modified as described above

QTc interval prolongation
QTc interval prolongation has been observed in patients treated with Rozlytrek in clinical trials.
Use of Rozlytrek should be avoided in patients with a baseline QTc interval longer than 450 ms, in patients with congenital long QTc syndrome, and in patients taking medicinal products that are known to prolong the QTc interval.
Rozlytrek 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 Rozlytrek 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 Rozlytrek are recommended.
Periodic monitoring of ECGs and electrolytes as clinically indicated throughout Rozlytrek treatment, are also recommended.
Based on the severity of QTc prolongation, Rozlytrek treatment should be modified as described above

- **Frequently occurring side effects**

Fatigue, constipation, dysgeusia, oedema, dizziness, diarrhoea, nausea, dysaesthesia, dyspnoea, anaemia, increased weight, increased blood creatinine, pain, cognitive disorders, vomiting, cough, and pyrexia

- **Other side effects**

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

Entrectinib is a weak inhibitor of CYP3A4 and possibly an inhibitor of P-gp, BCRP and OATP1B1

Entrectinib is possibly an inducer of CYP2C8, CYP2C9 or CYP2C19 and hence may decrease warfarin exposure

Co-adminstration of CYP3A4 inducers or inhibitors should be avoided as these may affect the metabolism of Entrectinib

Additional comments

Rozlytrek has moderate influence on the ability to drive and use machines. Patients should be instructed not to drive or use machines until the symptoms resolve, if they experience cognitive adverse reactions, syncope, blurred vision, or dizziness, during treatment with Rozlytrek

References

Roslytrek SPC accessed 4/9/2020

THIS PROTOCOL HAS BEEN DIRECTED BY DR LAU, DESIGNATED LEAD CLINICIAN FOR LUNG CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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