Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2294

entrectinib 100mg and 200mg hard capsules (Rozlytrek®)

Roche Products Ltd

4 December 2020

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission considered under the orphan equivalent process

entrectinib (Rozlytrek®) is accepted for use within NHSScotland.

Indication under review: as monotherapy for the treatment of adult patients with ROS1-positive, advanced non-small cell lung cancer (NSCLC) not previously treated with ROS1 inhibitors.

In a phase II study in patients with ROS1-positive advanced NSCLC, the objective response rate was 72%.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium

Indication

Entrectinib as monotherapy is indicated for the treatment of adult patients with ROS1-positive, advanced non-small cell lung cancer (NSCLC) not previously treated with ROS1 inhibitors.[1]

Dosing Information

The recommended dose is 600mg once daily.

It is recommended that patients are treated with entrectinib until disease progression or unacceptable toxicity. Management of adverse reactions may require temporary interruption, dose reduction, or discontinuation of treatment, in case of specified adverse reactions or based on the prescriber's assessment of the patient's safety or tolerability.

A validated assay is required for the selection of patients with ROS1-positive NSCLC. ROS1-positive status must be established prior to initiation of entrectinib therapy. Treatment with entrectinib should be initiated by a physician experienced in the use of anticancer medicinal products.

Further details are included in the Summary of product characteristics (SPC).[1]

Product availability date

August 2020

Entrectinib has conditional marketing authorisation from the European Medicines Agency (EMA).

Entrectinib meets SMC orphan equivalent criteria for this indication.

Summary of evidence on comparative efficacy

Entrectinib is an orally-active tyrosine kinase inhibitor (TKI) that inhibits the tropomyosin receptor tyrosine kinases TRKA, TRKB and TRKC (encoded by the neurotrophic tyrosine receptor kinase [NTRK] genes NTRK1, NTRK2 and NTRK3, respectively), proto-oncogene tyrosine-protein kinase ROS (ROS1), and anaplastic lymphoma kinase (ALK). This leads to inhibition of cancer cell lines from multiple tumour types with NTRK, ROS1, and ALK fusion genes.[1]

Key evidence for this indication is from STARTRK-2, an ongoing, single-arm, international, phase II basket study. STARTRK-2 recruited adults with histologically- or cytologically-confirmed locally advanced or metastatic solid tumours with specified gene rearrangements. Disease was required to be measurable as assessed locally according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. The pre-specified subgroup of patients relevant to this indication were those who had ROS1 positive non-small cell lung cancer (NSCLC) (n=78) and only these patients will be discussed further. Patients with CNS involvement were eligible for recruitment. Prior anticancer therapy was permitted excluding ROS1 inhibitors. Recruited patients had Eastern Cooperative Oncology Group (ECOG) performance status score ≤2 and adequate hepatic function.[2]

Patients received entrectinib 600mg orally once daily. Treatment continued until documented radiographic progression as assessed by blinded independent central review (BICR), unacceptable toxicity, or withdrawal of consent. Patients were allowed to continue treatment after BICR-confirmed disease progression, at the discretion of the investigator and with the sponsor's approval, if they were perceived to be gaining clinical benefit. Patients discontinuing study treatment were followed-up for survival and remained on study until death, loss of follow-up, or withdrawal of consent, whichever occurred first.[2]

The primary outcome was objective response rate (ORR), defined as the proportion of patients with a confirmed complete or partial response according to RECIST v1.1 as assessed by BICR. A confirmed response was a response that persisted on repeat-imaging ≥4 weeks after initial documentation of response.[2] The primary outcome was assessed in all patients who received at least one dose of entrectinib and had measurable disease (as per investigator's assessment) at baseline.[2]

The company also presented an 'integrated analysis' including data from a subgroup of patients from three studies, ALKA, STARTRK-1 and STARTRK-2. ALKA and STARTRK-1 were single-arm, multicentre, open-label, phase I studies. All studies recruited adults with advanced or metastatic solid tumours with specified genetic alterations. The subgroup of patients included in the integrated analysis were those with ROS1-positive NSCLC with measurable disease at baseline. This analysis included 9 patients from the ALKA study, 7 patients from STARTRK-1 and 78 from STARTRK-2 who received at least one dose of entrectinib at or above 600mg daily and had at least 12 months of follow-up.[3, 4]

In STARTRK-2, at the clinical cut-off date 01 May 2019 (all patients had ≥12 months follow-up) the ORR was 72%.[3] This was considered by the investigator to be clinically relevant as the lower bound of the 95% CI was >50%. In the integrated analysis at the clinical cut-off date 01 May 2019, after median survival follow up of 20.9 months the ORR was 73%.[1, 3] The primary and selected secondary outcome results are presented in Table 1 below.

Table 1: Primary and selected secondary outcome results for STARTRK-2 and the integrated analysis (ALKA, STARTRK-1 and STARTRK-2), data cut-off 01 May 2019.[1, 3]

	STARTRK-2 (n=78)	Integrated analysis (n=94)
Primary outcome		
Objective response rate*	72%	73%
Complete response	12%	12%
Partial response	60%	62%
Stable disease	6.4%	6.4%
Progressive disease	9.0%	8.5%
Non-complete response/progressive disease**	3.8%	3.2%
Missing or unevaluable	9.0%	8.5%

Secondary outcomes		
Median duration of response, months (co-primary outcome in the integrated analysis)	14.9	16.5
Number of patients with PFS event	46	54
Median progression-free survival (PFS), months	15.7	16.8
Number of patients with overall survival event	24	25
Median overall survival, months	30.8	NE
KM estimate of survival at 18 months	72%	76%
Time to CNS progression, months	24.8	24.8
Number of patients with CNS progression event	35	40

*Including complete and partial responses. **Patients were categorised as having non-complete response/progressive disease if they had non-target lesions (as assessed by BICR), but had measurable disease at baseline as assessed by investigator. CNS: central nervous system, NE: not estimable, KM: Kaplan-Meier.

Efficacy results are presented in the SPC for 161 patients with ROS1-positive metastatic NSCLC who were enrolled in one of ALKA, STARTRK-1, or STARTRK-2, received entrectinib 600mg orally once daily, and who had at least 6 months of follow-up. The ORR was 67% (108/161). A complete response was reported in 8.7% of patients and partial response in 58%.[1]

In the subgroup of patients with CNS metastases at baseline, assessed by BICR (n=34/94) in the integrated analysis the ORR was 68%, median duration of response was 14.9 months, PFS 9.9 months, and overall survival 28.3 months. Intracranial ORR was 50% and the median duration of intracranial response 12.9 months.[3, 5]

Health Related Quality of Life (HRQoL) was assessed in STARTRK-2 using the European Organisation for Research and Treatment of Cancer (EORTC) core Quality of Life Questionnaires, QLQ-C30 and QLQ-LC13. At baseline, patients reported moderate-to-high scores for QLQ-C30. In general, patients maintained or improved on baseline HRQoL with the exception of cognitive functioning, where clinically meaningful worsening was observed at specific time points. According to the QLQ-LC13, patients reported moderate lung symptom burden and severe cough at baseline with immediate improvement on study treatment.

A randomised controlled trial versus crizotinib in treatment naïve ROS1-positive NSCLC patients is to be conducted. The primary outcome will be PFS in the subgroup of patients with CNS metastases at baseline. The clinical study report should be submitted to EMA by 31 December 2027.

An unanchored matching-adjusted indirect comparison (MAIC) was performed to compare entrectinib (integrated analysis of data from the ALKA, STARTRK-1, and STARTRK-2 studies) with crizotinib (PROFILE 1001 study) in adult patients with ROS1-positive locally advanced or metastatic

NSCLC. Individual entrectinib-treated patients were assigned statistical weights that adjusted for their over- or under-representation relative to that observed in the crizotinib study. Hazard ratios for overall survival and progression-free survival (PFS) were estimated using weighted Cox proportional hazards model. ORR and treatment discontinuation due to adverse events were also included as outcomes. Confidence intervals for all outcomes were generally wide and the majority spanned 1 indicating that no evidence of a difference was identified.

Summary of evidence on comparative safety

No comparative safety data are available. The SPC notes that the most common adverse reactions (≥20%) observed for all patients who received entrectinib in clinical studies regardless of genomic subtype (n=504) were fatigue (45%), constipation (43%), dysgeusia (42%), dizziness (40%), oedema (37%), diarrhoea (34%), nausea (32%), dysaesthesia (29%), anaemia (28%), dyspnoea (27%), increased weight (26%), increased blood creatinine (25%), pain (24%), cognitive disorders (24%), vomiting (23%), cough (21%), and pyrexia (20%). The most frequent serious adverse reactions (≥2%) were lung infection (5.2%), dyspnoea (4.6%), cognitive impairment (3.8%), and pleural effusion (2.4%).[1]

The company presented safety data for the ROS1 safety population including patients from ALKA, STARTRK-1 and STARTRK-2 who had received at least one dose of entrectinib (n=210, data cut-off 31 October 2018). The median duration of treatment was 7.4 months.

Any treatment-emergent adverse event (AE) was reported by 99% (208/210) of patients and these were considered treatment-related in 93%. The proportion of patients reporting a grade 3 or higher treatment-related AE was 36%, patients with a reported serious AE was 37%, patients with a dose reduction due to treatment emergent AEs was 30%, the proportion of AEs that led to dose interruptions was 45% and patients discontinuing therapy due to an AE was 7.6%.

The most frequently reported treatment-emergent AEs of any grade with an incidence >10% were: constipation (49%), dysgeusia (47%), dizziness (43%), fatigue (40%), diarrhoea (36%), weight increase (33%), peripheral oedema (33%), nausea (28%), cough (23%), myalgia (23%), vomiting (22%), and anaemia (21%).

The EMA concluded that the overall safety profile was manageable.[5]

Summary of clinical effectiveness issues

NSCLC accounts for 80% to 90% of lung cancers and the majority of lung cancers are diagnosed at an advanced stage and therefore often associated with a poor prognosis. CNS metastases are common in advanced NSCLC and are associated with reduced life expectancy and a considerable reduction in quality of life. A number of molecular alterations have been identified in NSCLC and some are key oncogenic drivers.[6-9] ROS1 rearrangements are rare and occur in approximately 1%

to 2% of patients with NSCLC. [6, 7, 9] Crizotinib, another TKI, has been accepted for use within NHSScotland for the treatment of adults with ROS1-positive advanced NSCLC (SMC 1329/18). Some patients may receive carboplatin and pemetrexed chemotherapy first-line or second-line after crizotinib. Entrectinib meets SMC orphan equivalent criteria.

Entrectinib would provide another targeted treatment option with CNS activity for patients with ROS1-positive, advanced NSCLC not previously treated with ROS1 inhibitors. Approximately a third of patients in the integrated analysis had not received previous treatment for metastatic disease. Entrectinib is expected to be used as a first-line treatment option however may also be used second-line and exploratory analyses have identified similar efficacy in patients who had or had not received prior systemic therapy.[10]

Clinical experts consulted by SMC considered that entrectinib is a therapeutic advancement as it has CNS activity.

Key strengths

- The phase II STARTRK-2 study reported an ORR of 72% in patients with ROS1-positive advanced NSCLC who had not previously received a ROS1 inhibitor. The median duration of response was 14.9 months and median overall survival was 30.8 months.
- Results from the integrated analysis (including data from the ALKA, STARTRK-1 and STARTRK-2 studies) were similar.
- In the subgroup of patients in the integrated analysis with CNS metastases at baseline, the ORR was 68% and median duration of response was 14.9 months.

Key uncertainties

- The available evidence is from small single-arm phase I and II studies which are prone to bias. The lack of blinding or randomisation in particular weaken the internal validity of the findings.
- No direct comparative efficacy are available. The MAIC presented by the company was associated with limitations including heterogeneity between studies, small sample size (reduced further after matching), and wide confidence intervals that spanned 1. Due to the limitations, the results of the MAIC are uncertain.
- The STARTRK-2 study is ongoing, further results are awaited. Overall survival data are immature and in the integrated analysis median overall survival had not been reached.

Where a medicine has conditional marketing authorisation, SMC has the opportunity to issue interim accepted advice subject to re-evaluation where the committee considers that there is uncertainty around the clinical analysis and the requirements for additional evidence that have been specified by the EMA (known as specific obligations) are expected to address key uncertainties in the evidence presented by the submitting company. Entrectinib was granted a conditional marketing authorisation from the EMA but there are no specific obligations relating to this indication and interim acceptance was not considered relevant in this instance.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of entrectenib, as an orphan equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- ROS1-positive NSCLC is a very rare lung cancer. It often occurs in non-smokers and affects a younger population than the more common lung cancers. Affected patients are often still working and caring for dependents. Advanced NSCLC is incurable and diagnosis is devastating for patients. Progressive, debilitating symptoms including breathlessness, fatigue, weight loss, and pain can be very difficult to manage and significantly affect patients' quality of life. In addition, brain metastases are particularly common in ROS1-positive NSCLC and result in reduced ability to carry out daily activities (for example driving), reducing independence and increasing care needs.

- There are limited treatment options for patients with advanced ROS1-positive NSCLC and clear unmet need. Treatment usually includes crizotinib followed by chemotherapy. Entrectinib has good CNS penetration and intracranial response and brain metastases, a frequent debilitating problem, may be controlled or prevented.

- Disease control in patients who respond to entrectinib may result in reduced symptoms and improved duration and quality of life. This could enable patients to remain independent for longer, they may be able to work and participate in family life including caring for children/older relatives. Prolonging the time to progression and the need for chemotherapy is also beneficial.

- Entrectinib is a well-tolerated oral treatment that can be taken at home. Dosing is once daily, compared with twice daily for crizotinib, which may benefit patients. Although visits to oncology clinics for monitoring would be required, no significant service implications are expected.

Additional Patient and Carer Involvement

We received a patient group submission from the Roy Castle Lung Cancer Foundation, which is a registered charity. The Roy Castle Lung Cancer Foundation has received 7.5% pharmaceutical company funding in the past two years, with none from the submitting company. A representative from the Roy Castle Lung Cancer Foundation participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis to evaluate entrectinib versus crizotinib for the treatment of advanced NSCLC in adult ROS1-positive patients, not previously treated with ROS1 inhibitors. The time horizon for the analysis was 30 years. A partitioned survival model was used, with three health states including progression-free, post-progression and dead. Cycle length was 30 days. The perspective for the model was NHS Scotland and all costs and effects were discounted at 3.5%.

In the analysis, patients received entrectinib at the licensed dose until discontinuation due to progression or toxicity as observed for ROS1-positive patients in a 3-study "integrated analysis" (ALKA, STARTRK-1 and STARTRK-2). Crizotinib at the licensed dose was assumed to be discontinued only due to progression as observed in the PROFILE 1001 study. No dose adjustments were accounted for in the analysis.

Comparative efficacy data (PFS and overall survival [OS]) used in the economic model came from the MAIC described above. Data on OS, PFS and time on treatment (ToT) were modelled beyond the median trial follow-up period in each case informed by best statistical fit. The exponential (best fit) was used for the extrapolation of both PFS and OS for entrectinib. The same distribution was used in the comparator arm where the HR derived from the MAIC were applied. The ToT curve for entrectinib was extrapolated using the exponential parametric distribution (second best fit). As data on time on treatment for crizotinib were not available from the main clinical study (PROFILE 1001), an assumption was made that patients in the crizotinib arm were treated until progression.

Utility weight in the progression-free health state came from EQ-5D-3L data collected in the STARTRK-2 study for ROS1-positive patients. This was derived using a linear model with time from treatment initiation as a fixed effect and slope and intercept as random effects. Utility weight in the progressed health state of 0.66 was obtained from PROFILE 1007 study (crizotinib) for progressed patients with ALK-positive NSCLC who were treated with docetaxel monotherapy. Utility values were adjusted for age using the Brazier multiplier.[11] One-off utility decrements associated with adverse events were also applied in the model.

Aside from costs of medicines, other costs included were GP visits, outpatient hospital and cancer nurse visits as well as biochemistry, complete blood count and CT scans. The post-progression health state also included the cost of subsequent therapy and palliative care for approximately two-thirds of the patients and the rest were assumed to only receive palliative care. The distribution of subsequent treatments was as observed for entrectinib-treated patients in the integrated analysis and adapted to reflect current UK practice. A one-off cost of managing treatment-related grade ≥3 adverse events at rates observed for patients included in the indirect comparison, was also included in the analysis.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price for entrectinib.

Base case results at list prices for crizotinib and entrectinib are presented in the table below:

Table 2: Base case results (list price for both medicines)

Technologies	Inc. LYG	ICER (£/QALY)
Crizotinib	-	
Entrectinib	0.93	Entrectinib dominant

The results presented do not take account of the PAS for crizotinib but that was considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for crizotinib due to commercial confidentiality and competition law issues.

The most substantial ICER increases from the presented scenario analyses were associated with assumptions of relative effectiveness (PFS and OS) as well as duration of treatment effect for entrectinib as shown in table 3 below.

Table 3: Selected scenario analyses (list price for both medicines)

	Scenario	Base case	ICER
	Base case	-	Dominant
1	Equal PFS (HR=1)	PFS HR = 1.11	Dominant
2	Equal OS (HR=1)	OS HR = 0.77	SW quadrant*
3	Equal PFS and OS (HR=1)	PFS HR=1.11; OS HR = 0.77	SW quadrant*
4	PFS as defined by IA (HR=1.51)	PFS as defined by BICR	Dominant
5	Crizotinib efficacy from PROFILE 1001 (exponential curve) (naïve comparison)	Relative efficacy based on MAIC	SW quadrant*
6	No PFS and OS treatment effect post 24 months for entrectinib	Continuous treatment effect (OS and PFS)	£80,058
7	Entrectinib ToT for crizotinib	ToT = PFS for crizotinib	£25,736
8	Entrectinib ToT with PFS (BICR) HR applied for crizotinib	ToT = PFS for crizotinib	£8,233
9	Entrectinib ToT with PFS (IA) HR applied for crizotinib	ToT = PFS for crizotinib	Dominant
10	Entrectinib ToT=PFS	As observed	£8,283
11	Dose adjustment for entrectinib and crizotinib	100% RDI for entrectinib and crizotinib	Dominant
12	Lower utility value for progressed patients (0.593)	Base case utility value for progressed patients (0.66)	Dominant

Abbreviations: *SW, south-west quadrant – entrectinib less costly but less effective; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; IA, investigator assessment; BICR, blinded independent clinical review; MAIC, matching adjusted indirect comparison; ToT, time on treatment; RDI, relative dose intensity;

The main limitations with the analysis were:

- Lack of direct comparative effectiveness data for entrectinib and crizotinib in the population of interest. The main efficacy data in the model were derived from an unanchored matching adjusted indirect comparison (MAIC) of integrated data set from three single arm studies (two Phase I and one Phase II) for entrectinib and one Phase I study for crizotinib in a mixture of previously treated and treatment naïve patients.
- Uncertainties associated with the extent and duration of relative treatment effect (PFS and OS hazard ratios) for entrectinib vs crizotinib. Cost-effectiveness results are sensitive to varying the size and duration of treatment effect as shown in scenario analyses (scenarios 1-6). Furthermore, time on treatment data for crizotinib were unavailable (scenarios 7-10).
- Uncertainties around the utility weight used in the progressed health state as it was obtained for a population in different indication (ALK- positive). Furthermore, the model assumed patients who received subsequent treatments to have the same progressed utility value as those who only receive palliative care. Although, this oversimplification potentially leads to an overestimation of utility for entrectinib due to its slightly lower progression-free survival, results remained stable in a scenario analysis (scenario 12).
- Uncertainties around the cost of subsequent therapies due to duration of treatments as observed for entrectinib-treated patients in an integrated analysis of three studies with a shorter follow-up and a smaller sample size (n=53) than the main clinical effectiveness dataset used in the model, which may lead to an underestimation of subsequent therapy costs.

The Committee considered the benefits of entrectinib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as entrectinib is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, the Committee accepted entrectinib for use in NHSScotland.

*Other data were also assessed but remain confidential.**

Additional information: guidelines and protocols

The European Society for Medical Oncology (ESMO) published 'Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up' in February 2002, last update September 2018. This guidance notes that testing for ROS1 rearrangement should be systematically carried out in advanced nonsquamous NSCLC. Crizotinib is recommended as a first-line treatment option in patients with stage IV NSCLC with ROS1 rearrangement. In patients with ROS1-positive NSCLC, who have not received crizotinib in the first-line setting, single-agent crizotinib may be offered as second-line therapy. In those who have received crizotinib first-line, platinum-based chemotherapy is a treatment option in the second-line setting.[8]

Additional information: comparators

Crizotinib

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per month (£)
entrectinib	600mg orally once daily	£5,160

Costs from company submission. Costs do not take patient access schemes into consideration.

Additional information: budget impact

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

References

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This assessment is based on data submitted by the applicant company up to and including 16 October 2020.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.