National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Entrectinib for treating NTRK fusion-positive solid tumours [ID1512]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Roche	The wording of the remit is accurate.	Thank you for your comment. No action required.
Timing issues	Roche	Entrectinib is likely to deliver clinical benefits to a group of advanced-stage cancer patients who have limited treatment options available. As such, the appraisal should be treated as urgent.	Comment noted. No action required.

Comment 2: the draft scope

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Background information	Roche	Although largely accurate, we have provided a number of suggestions below to add to the completeness of this information.	

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		In reference to the expression of TRK proteins, please note that alongside expression in human neuronal tissue, these proteins are also expressed in extra-neuronal tissue (Coppola et al 2004).	Thank you for your comment. The scope has been amended accordingly to include expression in extra-neuronal tissue.
		In terms of the occurrence of NTRK fusions, it is worth emphasising that the presence of these genomic alterations are believed to be mutually exclusive of other genomic aberrations: this means that the eligible patient population is unlikely to overlap with those with other known molecular targets (e.g. ALK, ROS1, BRCA) (Passiglia et al 2016). It is also worth highlighting that the current treatment options described are representative of all stages of cancer, but for the advanced patient population covered by this appraisal systemic therapies (e.g. chemotherapy, hormone therapy, immunotherapy) are generally much more common than surgery or radiotherapy. As NTRK fusions require confirmation through genomic screening (e.g. Next Generation Sequencing [NGS]) it is important to introduce the role of the NHS Genomic Medicines Service to provide context for this appraisal. The Genomic Medicines Service was launched in October 2018, building upon the success of the 100,000 Genomes Project and acting as a key step in the NHS move towards its vision of “Improving Outcomes Through Personalised Medicine” (NHS England, 2016). The Genomic Medicines Service is seen as a key asset for the NHS in achieving this vision. The NHS investment in the	Comments noted. The background section of the scope provides an overview of the disease area. More detailed information can be presented in the companies’ evidence submissions. No action required.

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		Genomic Medicines strategy has been conducted on the assumption that while being initially cost-incurring, it will become more and more cost-effective as yet-unknown novel targets and approaches are identified in the future and efficiencies in screening and diagnosis are realised (Department of Health and Social Care, 2017).	
The technology/ intervention	Roche	Please note that entrectinib is currently being studied in four single-arm basket trials which are likely to inform the regulatory approval, one of which includes the STARTRK-2 Phase II study described in the draft scope, as well as two adult Phase I studies and a Phase I-II paediatric study. The adult studies have been pooled and presented as an integrated analysis (Demetri et al 2018) and will be submitted to the EMA and NICE in this format, whilst the paediatric data will be presented separately.	Thank you for your comment. The technology section of the scope has been amended accordingly to reflect the additional studies.
Population	Roche	It is important to note that the word 'alternative' is not aligned with the current draft marketing authorisation, and could lead to a misalignment with the evidence base from the clinical trials. The current draft marketing authorisation wording is as follows: [redacted] We do not believe that additional groups should be considered separately.	Thank you for your comment. The scope has been amended accordingly. Thank you for your comment. Subgroups were specified in the draft scope because of the heterogeneity of patients included in the key trials. These have

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			been included in the scope so that potential exploratory analyses of these subgroups can be presented, if evidence allows.
Comparators	Roche	Currently there is no standard of care specifically targeting NTRK-fusion positive solid tumours however treatment may follow current practice for the individual tumour types. Although current treatments will vary significantly between tumour types, in general terms the majority of patients are likely to receive a form of chemotherapy as the mainstay of management at this stage of treatment. A proportion of patients may receive palliative surgery and/or radiotherapy, particularly for the treatment of central nervous system metastases. Evidence suggests that the presence of NTRK-fusions is often mutually exclusive of other oncogenomic drivers (Passiglia et al 2015), therefore it is not expected that patients will be eligible for other targeted therapies. Given the large number of potential combinations of chemotherapy, it is not possible to define one approach as 'best alternative care': this represents one of the key challenges for the assessment of a tumour-agnostic therapy. For the purposes of health technology assessment, it may be necessary to estimate the costs and outcomes for an 'average' chemotherapy comparator, and utilise scenario analyses to test the influence of changes in the costs or outcomes of this comparator on the cost-effectiveness of entrectinib.	Thank you for your comment. The comparator for this appraisal is worded as 'Established management without entrectinib' to capture the range of cancer types and pathways which may be seen in this appraisal. Comment noted. No action required.
Outcomes	Roche	The outcomes stated are expected to represent the key benefits and harms of a cancer medicine such as entrectinib.	Thank you for your comment. No action required.

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Economic analysis	Roche	Roche do not agree that the costs associated with testing for NTRK fusions should be considered within the base case, with only a sensitivity analysis where costs are excluded. Our belief is that the base case decision problem should assume that patients have previously been identified as eligible for treatment, with a number of sensitivity analyses conducted to reflect the different potential screening screening. Our grounds for this position are as follows: 1) Section 5.9.1 of the reference case states that "if a diagnostic test to establish the presence or absence of this biomarker is carried out solely to support the treatment decision for the specific technology, the associated costs of the diagnostic test should be incorporated into the assessments of clinical and cost effectiveness." We acknowledge that this will be the case where the presence of a biomarker will identify eligibility for a single course of action (e.g. IHC/FISH testing for HER2 status). However, the utility of Next Generation Sequencing spans far beyond the identification of a single rare genomic alteration such as an NTRK-fusion. For example, patients may be identified as eligible for a clinical trial or an alternative current (or future) funded medicine, or information may be obtained on heritable risk factors that can realise spillover health benefits for the individual's family and cost efficiencies for the health care system (Buchanan et al 2013; NICE 2018; Phillips et al 2018; Department of Health and Social Care 2017). Given the rarity of NTRK fusions, in reality genomic screening will never be conducted solely for the purpose of identifying an entrectinib eligible patient. 2) The assessment of cost-effectiveness of Next Generation Sequencing for cancer is complex and could be justified as an entirely separate decision problem to the assessment of entrectinib (Phillips et al 2018). In particular, when considering the rarity of NTRK-fusions (0.7% of	Thank you for your comment. As noted, Section 5.9 (companion diagnostics) of the reference guide outlines the methods for assembling and synthesising evidence on the technology being appraised in order to estimate its clinical and cost effectiveness. As testing supports the treatment decision for entrectinib, the associated costs of the diagnostic test should be incorporated into the assessment of clinical and cost effectiveness. A sensitivity analysis should be provided without the cost of the diagnostic test. When appropriate, the diagnostic accuracy of the test for the particular biomarker of treatment efficacy should be examined and, when appropriate, incorporated in the

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		solid tumours), the costs and outcomes associated with genomic screening would skew the drivers of the cost-effectiveness analysis towards those related to the screening process, effectively moving the focus away from the assessment of entrectinib itself. A sensitivity analysis will not provide sufficient information on the sensitivities within the model to allow the committee to consider the evidence base and key decision uncertainties for whether to recommend entrectinib. 3) Screening costs will vary on a tumour-by-tumour basis, and may disadvantage patients with tumours where fewer/no reflex tests are used in clinical practice. Please see "Equality" below for further discussion. For these reasons we feel it is much more appropriate to consider the cost-effectiveness of entrectinib assuming screening and identification has occurred prior to entry in the model, with the use of multiple scenario and/or sensitivity analyses allowing for the separate consideration of different screening scenarios.	economic evaluation. No action required.
Equality and Diversity	Roche	Under the Equality Act 2010, all patients with cancer are considered disabled from the point of diagnosis. Roche believe a potential risk exists that, if subgroups were considered according to tumour site of origin, eligible patients with rarer tumour types (e.g. thyroid cancer) may be disadvantaged in terms of achieving a positive reimbursement decision, when compared to more common cancers (e.g. non-small cell lung cancer). This would be the result of two factors: 1) As discussed in the "Economic Analysis" section, the draft scope currently requires consideration of screening costs in the base case analysis; our concerns with this approach are described in more detail	Thank you for your comment. The potential equality issue identified was considered a function of the clinical condition and not the technology under assessment and therefore is not considered an equalities issue. No action required.

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		above. However, if these costs were to be included, the cost-effectiveness of a next-generation sequencing (NGS) as a diagnostic tool is heavily influenced by the number of separate diagnostic tests currently utilised within current practice, and therefore the cost-offsets that can be achieved by replacing these. For example, the cost-effectiveness of NGS in non-small cell lung cancer has gradually improved as the number of targeted interventions increases over time (Pennel et al 2018). As a result, rare cancers without targeted therapies may be disadvantaged by the lower number of existing targeted therapies available and associated diagnostic tests, compared to more common cancers. 2) Similarly, the majority of research investment has historically focused on the four 'common' cancer types comprising 53% of total cancer incidence (lung, breast, colorectal and pancreatic cancer) (NCRI 2018; Cancer Research UK 2015). This is likely to lead to more precise estimates of current outcomes for common vs rarer tumour types. As the comparative outcomes for current practice are expected to be a key driver of cost-effectiveness in this appraisal, subgroups of people with rare cancers may be disadvantaged due to a higher level of decision-making uncertainty than common cancer types. We do not believe that specific sources of evidence are likely to help consider the impacts described above. However, clinical expert opinion may be required to a greater extent within the appraisal process, particularly when understanding outcomes for the rarer cancer types.	Comment noted. No action required.
Other considerations	Roche	It is worth highlighting that a number of issues and challenges exist with the appraisal of tumour-agnostic medicines, for example the selection of relevant comparators and a paucity of evidence relevant to a genomically-defined patient population.	Comment noted. No action required. The committee is aware that the evidence base will necessarily be weaker for some technologies,

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			such as technologies used to treat patients with very rare diseases. This will be taken into account in their decision making.
		It is commonly accepted that in the era of precision medicine, an umbrella term which includes tumour-agnostic oncology medicines, close collaboration and flexibility will be required between the NHS, academia, industry and the public to enable incorporation into clinical practice (NHS England, 2016). Roche are keen to work flexibly with other stakeholders to achieve a solution that supports the evaluation of entrectinib, but also supports the evaluation of future tumour-agnostic indications. We have provided suggestions to some of the potential challenges in this comment form, and would welcome the input of NICE and other stakeholders on how best to address these.	Comments noted. No action required. There will be opportunities to address these potential challenges during the course of the appraisal. There will be technical engagement between NICE and the company and other stakeholders as part of the technology appraisal process.
		It is also worth highlighting that entrectinib will be one of the first tumour-agnostic cancer medicine to be evaluated by NICE. Although a previous scoping workshop for NTRK-fusion positive solid tumours had been conducted for ID1299, given the challenges expected with this appraisal Roche would like to repeat our request for an 'in-person' workshop to discuss the scope and approach to the appraisal with relevant stakeholders. We	Comments noted. No action required.

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		believe this would enable more meaningful discussion than a teleconference and potentially enable a more efficient appraisal process itself.	
Innovation	Roche	As the first tumour-agnostic indication to be appraised by NICE, entrectinib represents a step-change in the treatment of cancer, changing the focus of targeted treatment to the underlying genetic characteristics of the cancer and providing important benefits to a group of patients with tumour types where treatment options have been historically limited. Next Generation Sequencing has also been hypothesised to result in health-related benefits beyond the QALY, representing a challenge in the consideration of these outcomes within current decision-making frameworks (Buchanan et al, 2013).	Comment noted. The company submission can expand on the potential innovative nature of the technology, in particular its potential to make a significant and substantial impact on health-related benefits that are unlikely to be included in the QALY calculation during assessment. No action required. Comment noted. No action required.
Questions for consultation	Roche	**What is the population size for NTRK fusion-positive advanced solid tumours?** We anticipate the population size to be up to [redacted] in England and Wales. However, this estimate is uncertain and subject to successful screening and identification of these patients. Currently we expect that only a small minority of NTRK-fusion positive patients are identified within the NHS.	Thank you for your comment. No action required.

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		Which solid tumour sites are most commonly associated with NTRK fusion mutation? Frequency across solid tumour sites is generally quite low across the majority of solid tumour types and estimated at 0.7%. This is supported by a recent estimate from Genomics England, which found that at least 30 of 4142 cancer patients within the genomic dataset had NTRK fusions.	Thank you for your comment. No action required.
		How will entrectinib be used in clinical practice? We anticipate that entrectinib will be used in a similar manner to the clinical trial, in that treatment will continue on a daily basis until disease progression or unmanageable toxicity.	Thank you for your comment. No action required.
		Would entrectinib be used differently based on tumour site? We expect that entrectinib will be used in a similar fashion for the majority of tumour types. However, in certain scenarios (for example, soft tissue sarcoma), entrectinib may also support the downsizing of a tumour for potential surgical intervention.	Thank you for your comment. No action required.
		Will testing for NTRK fusion-positive expression in advanced solid tumours be available routinely in the NHS? Our understanding from the Genomic Laboratory Hubs is that they intend to implement the use of a broad panel to support cancer testing, as high throughput will enable this testing to be viable from a cost perspective and therefore NTRK is likely to be routinely screened even if the results are not	Thank you for your comment. No action required.

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		currently reported. This would make it simple to expand to include this as a routine part of the test directory. **Where do you consider entrectinib will fit into an existing NICE pathway?** This is likely to align with the entrectinib marketing authorisation. Typically for cancers with an acceptable standard of care, entrectinib would be viewed as an option at second line or later following progression. However, for some metastatic cancer types (for example, cholangiocarcinoma, pancreatic cancer or cancer of unknown primary) the current first-line standard of care may not be deemed acceptable at which point entrectinib may be appropriate. **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** Yes: although significant progress is being made in this area, we do not believe the practicalities of screening are fully established. For example, currently processes are not in place for addition of new genomic tests to the Testing Directory. However, we believe that entrectinib represents an opportunity to establish a pragmatic route for incorporation of new genomic tests into the testing panel, and are keen to support the NHS in developing systems to achieve this.	Thank you for your comment. No action required. Thank you for your comment. No action required.
Any additional comments on the draft scope	Roche	References are provided below where cited within our response: • Coppola V, Barrick C, Southon E, et al. Ablation of TrkA function in the immune system causes B cell abnormalities. Development. 2004 Oct;131(20):5185-95 • Passiglia F, Caparica R, Giovannetti E, et al. The potential of neurotrophic tyrosine kinase (NTRK) inhibitors for treating lung cancer. Expert	References noted. No action required.

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		Opin Investig Drugs. 2016;25(4):385-92 • NHS England. Improving Outcomes Through Personalised Medicine. Published 2016 • Department of Health and Social Care. Annual report of the Chief Medical Officer 2016: generation genome. Published 2017 • Demetri G, Paz-Ares L, Farago A et al. Efficacy and safety of entrectinib in patients with NTRK fusion-positive tumours: Pooled analysis of STARTRK-2, STARTRK-1, and ALKA-372-001. *Annals of Oncology*, Volume 29, Issue suppl_9, 1 November 2018, mdy483.003 • Buchanan J, Wordsworth S, Schuh A. Issues surrounding the health economic evaluation of genomic technologies. Pharmacogenomics. 2013;14(15):1833-47. • National Institute for Health and Care Excellence. Next-generation sequencing panel for solid tumour cancers in children: Medtech Innovation Briefing [MIB133]. Published 2018 • Phillips KA, Deverka PA, Marshall DA, et al. Methodological Issues in Assessing the Economic Value of Next-Generation Sequencing Tests: Many Challenges and Not Enough Solutions. Value Health. 2018;21(9):1033-1042. • Pennell N, Mutebi A, Zhou Z et al. Economic impact of next generation sequencing vs sequential single-gene testing modalities to detect genomic alterations in metastatic non-small cell lung cancer using a decision analytic model. J*ournal of Clinical Oncology* 36, no. 15_suppl (May 2018) 9031-9031 • National Cancer Research Institute (NCRI). Spend by research category and disease site. 2018; accessed December 2018. Available from: https://www.ncri.org.uk/ncri-cancer-research-database/spend-by-research-category-and-disease-site/ • Cancer Research UK. Cancer incidence for common cancers (2015 statistics). Accessed December 2018. Available from:	

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		https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/common-cancers-compared	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

No consultees/commentators indicated they had no comments.