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LEARNINGS FROM THE ASSESSMENTS OF ENTRECTINIB AND LAROTRECTINIB

Health technology assessment challenges associated with tumour-agnostic therapies

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Table of Contents

Executive Summary

A paradigm shift is occurring in cancer care with the introduction of tumour-agnostic therapies, for which the indication is defined by the molecular signature of the tumour rather than by its location. Several agents have already gained regulatory approval, including pembrolizumab for solid tumours with high microsatellite instability (MSI-H) or high tumour mutational burden (TMB-H), and larotrectinib and entrectinib for neurotrophic tyrosine receptor kinase (NTRK) fusion-positive solid tumours, and many other emerging molecules are set to enter the market over the next decade.

For healthcare systems, one of the biggest challenges lies in the clinical and economic assessment of these therapies, and subsequent decisions regarding reimbursement. As head-to-head data and comparative analyses remain a challenge for tumour-agnostic therapies, clinical evidence provided at the time of regulatory or reimbursement dossier submissions may include indirect comparisons to real-world data (RWD), or intrapatient analyses. In addition, testing costs and value need to be considered, given the need for broad genomic profiling platforms to facilitate patient identification and matching to novel treatments. The evaluation framework of each country's health technology assessment (HTA) agency determines how these challenges are currently addressed.

This report provides an analysis of HTA agency assessments and reimbursement decisions for entrectinib and larotrectinib across England, Germany, France, Canada, Denmark, Sweden and Scotland. Overall, 13 reimbursement decisions (six for entrectinib, seven for larotrectinib) with publicly accessible documents were analysed to understand the assessment outcomes and what evidence may have influenced them.

ASSESSMENT OUTCOMES

Seven of the 13 submissions (four for entrectinib and three for larotrectinib) resulted in reimbursement with no restrictions, while four assessments (two for each drug) resulted in rejections. Two larotrectinib assessments led to partial reimbursement decisions, both of which were restricted to paediatric populations. The main reasons for negative or partial positive recommendations were uncertainty about the clinical data and cost-effectiveness, heterogeneity in patient characteristics, and inability to define the natural history for NTRK fusions. Notably, two countries reached different decisions when assessing the two therapies.

HTA CHARACTERISTICS

The HTA agencies included in this study differed in terms of their structure and methodologies, with four of the seven countries requiring cost-effectiveness analyses and two of the countries allowing for conditional reimbursement. The type of HTA framework and methods used by each HTA agency were found to have an impact on the assessment outcome. For example, the availability of a conditional approval pathway was shown to facilitate access to tumour-agnostic therapies, while taking uncertainties into consideration.

EVIDENCE EVALUATION

The uncertainty about the clinical data was the biggest concern for payers, especially when non-traditional types of data were used, such as pooled analyses from single-arm trials, intrapatient analyses, etc. In one case, however, resubmission with additional data and longer patient follow-up led to the reversal of a negative recommendation to full reimbursement. Results of intrapatient/Growth Modulation Index (GMI) analyses (usually defined as a ratio of progression-free survival [PFS] on the last line of therapy to PFS on the most recent line of therapy) were submitted in

the evidence package of both therapies in addition to clinical trial data. Most HTA agencies viewed these supportive analyses positively. Only three of the submissions included RWD, possibly reflecting the fact that some HTA agencies do not accept RWD, or perhaps indicating the limited availability of these data at the time of the assessments.

All assessments (implicitly or explicitly) considered best supportive care (BSC) as a comparator for the tumour-agnostic therapies, although different approaches were taken by each HTA agency. In nine of the 13 submissions, an economic evaluation was included; seven of these were cost-effectiveness analyses, and two were cost analyses. In two countries, a pricing negotiation was permitted to take place simultaneously with the evaluation, and in two others conditional reimbursement was allowed, potentially influencing the assessment outcome. Testing costs were included in all cost-effectiveness analyses. For ten of the 13 submissions, testing was discussed as part of the assessment.

In conclusion, our analysis showed that different evidence requirements and criteria were utilised by HTA agencies in their assessments of larotrectinib and entrectinib. While some countries did not issue conditional approvals or accept the submission of RWD, the ability to provide additional data cuts, longer-term follow-up and RWD were crucial in reversing the negative reimbursement recommendation for larotrectinib in Canada. This finding highlights the importance of non-traditional supportive data sets and generating longer-term data in the assessment of tumour-agnostic therapies.

Considering the variability in how relative efficacy and costs were assessed by the HTA agencies, and in the type of analyses deemed appropriate to use, HTA guidelines specific to tumour-agnostic therapies that are currently in development, along with new policy initiatives, should help to ensure that future tumour-agnostic therapies are assessed in a more consistent manner.

1 Introduction

As the understanding of cancer biology increases, precision oncology, defined as the molecular profiling of tumours to identify targetable genomic alterations, is rapidly developing and becoming established in clinical practice (Schwartzberg et al., 2017; Malone et al., 2020; Thomas et al., 2020). Tumour-agnostic therapies, for which the indication is solely defined by the molecular signature of the tumour, independently of its location (e.g. NTRK fusion-positive solid tumours), are an increasingly important part of precision oncology. So far, three tumour-agnostic agents have gained regulatory approval in several markets: pembrolizumab for MSI-H or TMB-H solid tumours (FDA, 2017; FDA, 2020), and larotrectinib (FDA, 2018; EMA, 2019) and entrectinib (FDA, 2019; EMA, 2020) for NTRK fusion-positive solid tumours in the USA, Europe, Canada, Israel and Japan, among others. In the next five to ten years, many more tumour-agnostic molecules are expected to enter the market. As of 2019, 78 molecules with definite or potential tumour-agnostic indications were in development (IQVIA, 2020).

The introduction of tumour-agnostic therapies into clinical practice represents a paradigm shift in cancer care and requires significant progress in genomic testing capabilities (broad gene panels; next-generation sequencing [NGS] equipment; data analytics) and increased oncologist knowledge to account for tumour-specific genomic profiles in patients' treatment plans. For healthcare systems, a critical challenge associated with the introduction of tumour-agnostic therapies is their clinical and economic assessment and subsequent reimbursement decisions (Husereau et al., 2014; Jørgensen et al., 2008; Towse et al., 2017; Gaultney et al., 2021; Rodes Sanchez et al., 2020; Faulkner et al., 2020).

Practically, the assessment of tumour-agnostic therapies brings two new challenges. Firstly, the nature of the clinical evidence provided at the time of regulatory submission differs from the 'traditional evidence' such as randomised double-blind study results provided for other types of therapies (Li et al., 2020; Garralda et al., 2019; Dickson et al., 2020). Since the genomic alterations of interest are typically rare, patient numbers are low. Consequently, tumour-agnostic therapies are tested in single-arm basket trials, which recruit patients sharing the same genomic alteration but presenting with different tumour types (usually more than 10 different types), and thus receiving different standards of care. To mitigate the absence of a comparative arm, drug developers may include new types of evidence in their HTA dossiers, such as indirect comparisons to RWD or intrapatient analyses (Eichler et al., 2020; Krebs et al., 2021). Additionally, when the genomic alterations of interest are newly identified targets, patients may not have been tested in the past, meaning natural disease history data are lacking.

Secondly, the requirement for broad genomic profiling platforms, using large gene panels to facilitate patient identification and matching to novel treatments, demands that testing costs and value should be considered in the clinical and economic value assessment of tumour-agnostic treatments.

The way these challenges are addressed also depends on the evaluation framework used by the HTA agency of each country, which encompasses: the authority of the local HTA agency over the access and reimbursement process (decision binding or advisory), its remit (clinical and/or economic assessment), the methodology used in the economic assessment (cost-effectiveness or cost analysis), and the approach (sequential or not) undertaken to carry out the clinical and economic evaluations. The appropriate clinical and economic value assessments for tumour-agnostic therapies are of critical importance considering the number of molecules currently in development (IQVIA, 2020). Moreover, many of the challenges faced in the assessment of tumour-agnostic therapies (e.g. single-arm studies; small cohorts; comparison to RWD) are common to other advanced therapies

and medicinal products (e.g. gene-, cell- and tissue-based therapies) currently being developed for rare and non-rare diseases.

We set out to better understand how entrectinib and larotrectinib have been assessed by seven HTA agencies internationally (Canada, Denmark, England, France, Germany, Scotland and Sweden) and to derive learnings from these assessments. Our analysis is structured around the following research questions: (i) What evidence was considered appropriate for the assessment? (ii) How (criteria; methods) were evidence packages assessed? (iii) What were the assessment outcomes and their (reported) rationale?

2 Methods

A focused review of the websites of HTA agencies and regulatory authorities was conducted between 11 September 2020 and 10 September 2021 to find information pertaining to HTA assessments and reimbursement decisions for entrectinib and larotrectinib. In total, 24 reimbursement decisions were identified. As not all HTA agencies make their assessments publicly available, decisions found were further filtered according to the availability of a detailed assessment report. Based on this, 13 public assessment reports were retained for further analysis. A list of the assessments with no detailed reports can be found in Supplementary Table 1. Subsequently, the public assessment documents for entrectinib and larotrectinib were analysed using a set of pre-defined parameters to determine the methods used by each HTA agency and the final outcomes.

The parameters included: general HTA information (such as date of submission, length of review and indication sought for reimbursement); trial design used and feedback on said trial design; evidence package used and feedback on said evidence package; value assessment method and value recognition; final outcome of the assessment (reimbursement or no reimbursement); and post-assessment requirements. All information pertaining to these parameters was captured to be used for further analysis. The list of parameters as well as the sub-criteria used in the analysis can be found in Supplementary Table 2.

In the below, we first present the reimbursement outcomes identified in our review and then describe and discuss the parameters that may have influenced these outcomes.

3 Results

3.1 Reimbursement Outcomes

In total, 13 reimbursement decisions were identified from seven countries with publicly accessible documents. Six of these assessments were for entrectinib and seven were for larotrectinib. In five of the seven countries, assessments were performed on both therapies; two of these (France and Sweden) reached different decisions in their assessments for the two drugs. Table 1 gives an overview of the assessment outcomes.

TABLE 1: ENTRECTINIB AND LAROTRECTINIB ASSESSMENTS OUTPUTS

Country, outcome date)	Product	Recommendation			Unmet need recognised	Efficacy				Cost-effectiveness included	Testing assessment
		Outcome (Conditional)	Per tumour or per label	Paeds included		Clinical cut-off date	Assessed as pooled data/ per tumour type	Source of comparator	Inclusion of intrapatient analysis/ supporting RWD		
England, 2020 (NICE, 2020b)	Laro	+ (+)	Label	+ (no limit)	+	n=102	Both	Literature (BSC for common cancers and chemo for rare cancers)	+ / –	+ (ERG created a response-based model which used the Bayesian hierarchical model. ERG discredited Bayer's previous line of therapy model)	+ (included in clinical and economic evaluations)
England, 2020 (NICE, 2020c)	Entrec	+ (+)	Label	+ (≥12 years)	+	May 2018 (n=54*)	Both	Literature (BSC)	+ / –	+ (ERG created a response-based model which used data from patients with tumours who did not respond as proxy for control - this model used the Bayesian hierarchical model) - ERG generated results for each tumour type	+ (included in clinical and economic evaluations)
Germany, 2020 (G-BA, 2020a, 2020b)	Laro	+ (no additional benefit) (–)	Label	+ (no limit)	N/A	July 2018 (ePAS2; n=93)	Both	Literature (BSC or surgical resection)	– / –	–	–
Germany, 2021 (G-BA, 2021a,	Entrec	+ (no additional	Label	+ (≥12	N/A	Oct 2018	Both	Literature (BSC, surgical resection),	– / + (Flatiron	–	–

Country, outcome date)	Product	Recommendation			Unmet need recognised	Efficacy				Cost-effectiveness included	Testing assessment
		Outcome (Conditional)	Per tumour or per label	Paeds included		Clinical cut-off date	Assessed as pooled data/ per tumour type	Source of comparator	Inclusion of intrapatient analysis/ supporting RWD		
2021b)		benefit) (–)		years)				Flatiron	comparative data)		
France, 2020 (HAS, 2020b)	Laro	+ (+)	Tumour (IFS; paed STS)	+ (no limit)	+	July 2017 and July 2019	Both	Literature (chemo, targeted therapy, hormonal therapy or end of life when all options are exhausted)	– / –	–	+ (not included in economic evaluation, but discussed in clinical)
France, 2021 (HAS, 2021)	Entrec	– (–)	N/A	– (not included in submission)	+	Oct 2018		Literature (chemo, targeted therapy, hormonal therapy or end of life when all options are exhausted)	– / –	–	+ (not included in economic evaluation, but discussed in clinical)
Canada, 2019 (CADTH, 2019)	Laro	– (–)	N/A	+ (request: age ≥1 month)	+	July 2018 (OS based on Feb 2018 cut-off)	Both	Literature (BSC for NSCLC, CRC, thyroid; trifluridine + tipiracil, BSC for CRC; pembro + platinum, nivo, BSC for lung; lenvatinib, BSC for thyroid)	+ / –	+ (pooled ICER and 6 individual ICERs for CRC, NSCLC, melanoma, thyroid, adult STS, and paed STS)	+ (included in economic evaluation)
Canada, 2021 (CADTH,	Laro	+ (–)	Label	+ (no limit)	+	July 2019	Both	Literature (N/A full report is not out)	+ / + (4 RWE	+ (pooled ICER, and individual	+ (included in

Country, outcome date)	Product	Recommendation			Unmet need recognised	Efficacy				Cost-effectiveness included	Testing assessment
		Outcome (Conditional)	Per tumour or per label	Paeds included		Clinical cut-off date	Assessed as pooled data/ per tumour type	Source of comparator	Inclusion of intrapatient analysis/ supporting RWD		
2021b)						and July 2020			studies to address CADTH concerns)	ICERs in non-GIST STS [adults], paeds with IFS, NSCLC)	economic evaluation)
Scotland, 2021 (SMC, 2021)	Entrec	+ (–)	Label	+ (≥12 years)	+	May 2018 (n=54) Oct 2018 (n=54) Oct 2018 (n=74)	Pan-tumour†	Literature (BSC)	+ / –	+ (pooled ICER for all tumour types, and another pooled ICER excluding neuroendocrine and pancreatic)	+ (included in clinical and economic evaluations)
Denmark, 2021 (DMC, 2021a)	Laro	– (–)	N/A	+ (no limit)	+	July 2018 Feb 2019 July 2019	Pan-tumour (tumour-specific data not submitted)	Literature (BSC or placebo)	+ / –	– (no cost-effectiveness analysis was provided but cost analysis was done)	+ (included in clinical and economic evaluations)
Denmark, 2021 (DMC, 2021b)	Entrec	– (–)	N/A	+ (≥12 years)	+	Oct 2018	Both (OS and PFS presented for each tumour type where available)	Literature (BSC or placebo)	+ / –	– (no cost-effectiveness analysis was provided but cost analysis was done)	+ (included in clinical and economic evaluations)

Country, outcome date)	Product	Recommendation			Unmet need recognised	Efficacy				Cost-effectiveness included	Testing assessment
		Outcome (Conditional)	Per tumour or per label	Paeds included		Clinical cut-off date	Assessed as pooled data/ per tumour type	Source of comparator	Inclusion of intrapatient analysis/ supporting RWD		
Sweden, 2020 (TLV, 2020)	Laro	+ (–)	Label (need to start <18 years)	+ (no limit)	+	July 2019 (n=55)	Pan-tumour	Literature (BSC, palliative chemo, surgery)	+ / –	+ (pooled ICER; scenario analysis for adults and children)	+ (included in scenario analysis in economic evaluation and in adults - testing in children is standard)
Sweden, 2021 (TLV, 2021b)	Entrec	+ (–)	Label	+ (≥12 years)	+	Oct 2018 (n=74)	Pan-tumour	Literature (BSC, chemo, surgery)	– / + (Flatiron analysis)	+ (pooled ICER; scenario analysis for testing costs and hazard rates for death)	+ (included in tumour types where *NTRK* testing is not standard)

*Included five additional adults with primary CNS tumours and seven children with NTRK gene fusions in efficacy population.
†HTA requested a scenario analysis excluding neuroendocrine and pancreatic tumours – outliers.
BSC, best supportive care; CADTH, Canadian Agency for Drugs and Technologies in Health; chemo, chemotherapy; CNS, central nervous system; CRC, colorectal cancer; DMC, Danish Medicines Council; entrec, entrectinib; ePAS2, extended primary analysis set; ERG, evidence review group; G-BA, Gemeinsame Bundesausschuss (German Federal Joint Committee); GIST, gastrointestinal stromal tumour; HAS, Haute Autorité de Santé (French National Authority for Health); HTA, Health Technology Assessment; ICER, incremental cost-effectiveness ratio; IFS, infantile fibrosarcoma; laro, larotrectinib; N/A, not applicable; nivo, nivolumab; NICE, National Institute for Health and Care Excellence, NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; OS, overall survival; paed, paediatric; pembro, pembrolizumab; PFS, progression-free survival; RWD, real-world data; RWE, real-world evidence; SMC, Scottish Medicines Consortium, STS, soft tissue sarcoma, TLV, Tandvårds- och Läkemedelsförmånsverket (Swedish Dental and Pharmaceutical Benefits Agency).

Seven assessments (four of entrectinib and three of larotrectinib) resulted in reimbursement for the label population with no restrictions. Two larotrectinib assessments in France and Sweden resulted in partial reimbursement decisions; both were restricted to paediatric populations. Four assessments resulted in rejections: two in Denmark and one each in Canada and France. The main reasons for negative or partial positive recommendations were uncertainty about the clinical data, heterogeneity, and the inability to define the natural history of NTRK fusions.

HTA agencies in Germany, France and Denmark evaluated the relative effectiveness of therapies compared with standards of care, via Clinical Added Value (CAV; in French 'Amélioration du Service Médical Rendu' [ASMR]). Neither entrectinib nor larotrectinib were awarded an added benefit compared with standard of care in any of the three countries. In Germany, both therapies were categorised as having no added benefit, while in Denmark an added benefit could not be determined. In France, larotrectinib was categorised as CAV/ASMR V (i.e. no improvement) for paediatric patients with infantile fibrosarcoma and soft tissue sarcomas and a moderate Clinical Benefit (CB; in French 'Service Médical Rendu' or SMR). However, for adults and other paediatric populations, the CB/SMR was deemed 'insufficient'.

3.2 HTA characteristics

The characteristics of each HTA agency included in this analysis are outlined in Table 2. In summary, four of the seven agencies included require cost-effectiveness analyses. In England and Scotland, a pricing negotiation was allowed to take place at the same time as the evaluation, and England and France were the only countries in this sample in which conditional reimbursement was allowed.

3.3 Type of health economic analysis performed

Nine of the 13 (69%) submissions included an economic evaluation; France and Germany's submissions did not. Seven of these economic evaluations (78%) were cost-effectiveness analyses and two (22%) were cost analyses. Six of the seven (86%) HTA agencies required pooled and individual incremental cost-effectiveness ratios (ICERs) for some tumour types (i.e. a pooled ICER alone was not sufficient), and all of them expressed concerns around uncertainties with the cost-effectiveness analysis. In England, a response-based model using a Bayesian hierarchical model was favoured by the HTA agency. However, in other countries, the economic model was based on weighting the response according to the distribution of tumour types in the larotrectinib or entrectinib trials.

TABLE 2: HEATH TECHNOLOGY ASSESSMENT CHARACTERISTICS

Country	Published assessment documents	Economic evaluation	Type of economic evaluation	Sequential or simultaneous*	Decision on reimbursement or advisory	Conditional reimbursement pathway	Clinician representation	Patient representation
England (NICE)	Yes	Yes	Cost-effectiveness	Simultaneous	Decision	Yes	Yes	Yes
Germany (G-BA)	Yes	Yes	N/A	N/A	Advisory	No	Yes	Yes
France (HAS)	Yes	Yes	Yes	Sequential	Advisory†	Yes	Yes	Yes
Canada (CADTH)	Yes	Yes	Cost-effectiveness	Simultaneous	Advisory†	No	Yes	Yes
Scotland (SMC)	Yes	Yes	Cost-effectiveness	Simultaneous	Decision	No	Yes	Yes
Denmark (DMC)	Yes	Yes	Cost analysis	Simultaneous	Advisory	No	Yes	Yes
Sweden (TLV)	Yes	Yes	Cost-effectiveness	Simultaneous	Decision	No	No	No

* Refers to whether costs and efficacy are assessed simultaneously or if a clinical assessment must be passed before an economic assessment can be conducted.

†Although the HTA agency does not make the actual decision regarding reimbursement, in most cases the Ministry of Health follows the HTA agency's advice.

CADTH, Canadian Agency for Drugs and Technologies in Health; DMC, Danish Medicines Council; G-BA, Gemeinsame Bundesausschuss (German Federal Joint Committee); HAS, Haute Autorité de Santé (French National Authority for Health); N/A, not applicable; NICE, National Institute for Health and Care Excellence; SMC, Scottish Medicines Consortium; TLV, Tandvårds- och Läkemedelsförmånsverket (Swedish Dental and Pharmaceutical Benefits Agency).

3.4 Comparators

All assessments included BSC as a comparator for the tumour-agnostic therapies. BSC was defined as palliative care after exhaustion of available treatment options. Other comparators, such as hormonal therapy, targeted therapy, and chemotherapy, were also included in seven of the 13 (54%) assessments (England, Canada, France, Sweden, and Scotland). Differences in the choice of comparators (excluding BSC) could be explained by different timelines for the regulatory approvals or variations in local standards of care and clinical practice, or could signify different interpretations of the label wording (e.g. around exhaustion of acceptable treatment options: the definition of an "acceptable" treatment option could have varied widely).

Direct comparative efficacy analyses versus BSC included the use of a blended comparator arm drawing from multiple sources in the literature as well as a landmark analysis, where the non-responders of the respective trials were used as a proxy for the prognosis of BSC. Some countries (Germany and France), however, did not find it feasible to conduct any form of comparative analysis against BSC. The variance in the approaches should be noted; it may reflect the differing evidence that HTA systems typically assess, while still fitting into existing frameworks.

3.5 Acceptance of RWD and additional analyses to support clinical trial data

Although BSC was employed as a comparator in all countries, there were significant differences in the approaches taken by HTA agencies, such as discrepancies in the inclusion and use of comparative evidence (e.g. the use of RWD) and whether the assessment was exclusively tumour-agnostic or also included tumour-specific data. These variances between the countries could be explained by several factors, including differences in the data packages available at the time of submission as well as in the data actually submitted to the HTA agencies.

Eight of the 13 submissions (62%) included intrapatient/GMI analyses as part of the submission package. The GMI is defined as a ratio of the PFS on the last line of therapy (in this case, either entrectinib or larotrectinib) to PFS on the most recent line of therapy. While this analysis does not inform on the relative efficacy of the tumour-agnostic therapy versus BSC, it could be seen as a supplementary measure to provide context on the magnitude of benefit provided by the therapy.

Additionally, RWD were used as supportive evidence in three of the 13 submissions (23%) (Germany, Sweden [entrectinib]; Canada [larotrectinib]). RWD from the Flatiron Health Database were included in the entrectinib submissions as 'synthetic' comparator arms in Germany and Sweden. In Germany, the analyses were disregarded due to methodological limitations, while the Swedish HTA agency considered this analysis helpful to support the evaluation. In the Canadian assessment of larotrectinib, RWD were incorporated as supporting evidence on the oncogenicity and natural history of NTRK gene fusions (Bazhenova et al. 2021; Bridgewater et al. 2021) rather than as a source of comparative evidence, and this provided additional evidence on the unmet need.

The National Institute for Health and Care Excellence (NICE; England) and Haute Autorité de Santé (HAS; French National Authority for Health) are the only HTA agencies that provide conditional reimbursement in the event of RWD supplementing clinical data (Table 2). In general, France does not accept RWD as part of the evidence package for evaluation and requires data from a randomised clinical trial. However, in France, a positive recommendation was issued for larotrectinib in areas of very high unmet need, and subsequently, the generation of RWD was requested for the reimbursed

populations. In England, entrectinib and larotrectinib were both reimbursed through the Cancer Drug Fund, following their recommendation as treatment options by NICE. Using this pathway, the National Health Service (NHS) can make therapies available according to conditions in the managed access agreement, which typically requires additional data generated from trials and other potential sources. A recent NICE consultation indicated that the agency intends to develop further guidance on the use of RWD and their value (NICE, 2020a).

3.6 Inclusion of testing costs

Testing was discussed as part of the assessment for 11 of the 13 submissions (85%; all countries except Germany, both submissions). Testing costs were included as part of all cost-effectiveness analyses.

Testing costs were typically subjected to sensitivity analyses, and the choice of testing strategy was found to be an important parameter. In England and Scotland, scenario analyses were performed with testing costs assigned to both arms to varying degrees. In the reports, it was recognised that entrectinib and larotrectinib are not the only drivers of wider testing such as NGS, but that such testing may occur regardless of the availability of these and future tumour-agnostic therapies.

The reports also showed that testing costs heavily impacted the cost-effectiveness of tumour-agnostic treatments. In some HTA reports, it was acknowledged that further testing, independent of entrectinib and larotrectinib, could ultimately lower future costs.

4 Discussion

Our analysis of 13 entrectinib and larotrectinib submissions from seven HTA agencies internationally showed that different evidence requirements and criteria were used to assess tumour-agnostic therapies. Overall, the assessment outcomes were mixed, with seven of the 13 submissions resulting in reimbursement. Reimbursement outcomes for entrectinib and larotrectinib assessments were relatively evenly distributed, with four versus three approvals and two versus two rejections, respectively. Interestingly, this review found that partial reimbursements (in France and Sweden) were restricted to paediatric populations. This may indicate a higher flexibility and willingness to pay for new therapies to treat childhood cancers.

Different HTA characteristics could influence the assessment and reimbursement decision for tumour-agnostic therapies. As an example, the option of conditional reimbursement in some countries may allow acceptance of currently available evidence with the caveat that additional data should be provided at an agreed later date. England and France were the only countries to have an established conditional reimbursement pathway in place, allowing therapies with data uncertainty to receive funding recommendations. These pathways were put to use as in England both entrectinib and larotrectinib were reimbursed through the Cancer Drug Fund, while in France larotrectinib was given conditional approval. In addition, the possibility to have simultaneous negotiation of the confidential net price could possibly improve patient access in the presence of uncertain data.

Uncertainty about the clinical data was highlighted as the biggest concern by payers, especially when non-traditional data sets were used, and this contributed to negative or partial funding recommendations in some countries. Ensuring that the available evidence fits into the established

methods for assessing relative efficacy may be a challenge in some cases. However, carrying out a randomised controlled trial with a relevant comparator, the gold standard for the evaluation of pharmaceuticals, is generally not feasible for tumour-agnostic therapies targeting rare genomic alterations (Lozano-Ortega et al., 2019). Often a single relevant comparator cannot be chosen, and the rarity of the specific mutations or tumour types can prohibit head-to-head comparisons. In this context, it is interesting that in the three countries that evaluate the relative effectiveness of therapies based on the clinical data alone (Germany, Denmark and France (for the official analysis)), there was no award of 'added clinical value'. This suggests that those countries may need to reconsider how their approach could be modified to deal with these therapies and some types of advanced medicinal therapy products more generally. Likewise, it is noteworthy that the three countries trying to re-think how they assess tumour-agnostic therapies (Canada, Sweden and England) are all so-called 'cost-per QALY' countries.

The Canadian Agency for Drugs and Technologies in Health (CADTH) gave larotrectinib a negative recommendation during the first assessment in 2019 (CADTH, 2019). The CADTH reviews clinical and economic data simultaneously and uses a deliberative framework to make final reimbursement recommendations (CADTH, 2016). The framework focuses on the overall clinical benefit of the drug under review, alignment with patient values, cost-effectiveness and feasibility of adoption into the health system. The overall clinical benefit is determined based on effectiveness, safety, burden of illness and need. The cost-effectiveness analysis is based on costs per quality-adjusted life years gained and per life year gained using the list price of the drug. In contrast with NICE in England, prices are not simultaneously negotiated during the CADTH review: CADTH assessment is based on the list price. However, the larotrectinib dossier was resubmitted to CADTH in 2020 with additional data cuts, longer follow-up, and RWD, which then garnered a positive funding recommendation (CADTH, 2021b). This demonstrates that additional data cuts and follow-up can play a significant role in acquiring a positive recommendation when the uncertainty in the data is evident.

Differences were also seen in the economic evaluations across different HTA agencies. Because population heterogeneity also introduces uncertainty to the calculation of a single tumour-agnostic ICER, some HTA agencies requested ICERs for individual tumour types. This approach, however, has added limitations due to the small sample size of each tumour subgroup. Hence, the generated ICERs may not be very meaningful. Consolidating these findings with the fact that testing costs appear to have a significant impact on the overall ICER suggests that the economic evaluation of future tumour-agnostic treatments may yield vastly different results.

BSC was either the only comparator or one of several comparators used in the assessments reviewed here. The choice of comparator could affect the outcome of the comparative efficacy assessment, as well as the results of an economic analysis, as costs would depend on the specific comparator treatment. Differences within individual countries regarding the choice of comparator may be due to variable timelines for regulatory approval and may also reflect different views on the status of the two therapies versus current standards of care; BSC is mostly perceived as palliative, while options such as targeted therapy, chemotherapy and surgery have an antineoplastic scope.

Overall, there was significant variability in the assessment of relative efficacy and in the type of analyses deemed appropriate to use. In the absence of comparative clinical trial data, various supportive analyses were incorporated into the assessments. Eight assessments included intrapatient/GMI analyses in their assessment reports as supportive analyses for PFS data and most HTA agencies viewed such analyses as a useful tool for providing context for clinical trial results. On the other hand, RWD were only incorporated into three assessments (for two of these, they were used to provide a 'synthetic' control arm; for one other, they were used as supporting evidence on the oncogenicity and natural history of NTRK gene fusions). This number seems relatively low but, of the three assessments that did incorporate RWD, two found them to be supportive in decision-making. The low number of assessments with RWD could be due to some of the HTA agencies not accepting

RWD, or potentially due to the limited availability of RWD at the time of the assessment. Given the nature of RWD, large-scale data collection is typically not possible before a therapy has received regulatory approval. A follow-up on future assessments and potential re-assessments would provide a better measure of the acceptance of RWD as a data source for tumour-agnostic therapies, and further guidance is required to clarify what is acceptable in terms of indirect comparisons moving forwards.

Lastly, testing was typically found to be an additional cost in the use of entrectinib and larotrectinib, and these costs had a significant impact on the calculated ICERs. There were some exceptions where broader testing such as NGS is already established (e.g. in Sweden for paediatric patients). Increasing the availability of testing platforms such as NGS, which can serve a variety of different patient population and inform (multiple) treatment decisions for a broad range of medicines, could lower the incremental costs assigned to individual therapies. Currently, there is a risk for attributing the costs of upgrading the national testing programmes to a single or limited number of treatments. More comprehensive testing has more potential benefits than discovering only NTRK fusions; NTRK inhibitors are just the first of several upcoming tumour-agnostic therapies in development.

Considering the different approaches to the clinical and health economic assessments, there is an need for more guidance on how HTA assessments and economic models should be structured for future tumour-agnostic molecules. Currently, countries that reject therapies solely because of uncertainty in the clinical data, but neither allow RWD in submissions or do not provide clear directions on how to generate acceptable RWD, nor have post-launch arrangements where RWD could be generated, do not seem to help themselves or patients very much. Some HTA systems however have developed, or are in the process of developing, internal guidelines for the assessment of tumour-agnostic therapies. This is a necessary and useful approach to ensure that future tumour-agnostic therapies are assessed consistently.

4.1 Limitations

This analysis is primarily based on the information gathered from publicly available reports. The level of detail in these reports varies and they may not provide a complete overview of the assessments undertaken and the methods used. Other factors such as political pressure, healthcare financing, and confidential pricing may also play a role in the final outcomes. In particular, the specific price agreement could be very influential. In addition, it is assumed that pharmaceutical companies submit relatively similar sets of data to different countries. There might, however, be some variability in what data are submitted and applications may to some degree already be tailored to meet the specific requirements and methodologies of the particular HTA system. The applications themselves are not always available and it is therefore not possible to assess the consistency of the submitted data.

Due to the timing of our analysis, we focused on early-launch countries, which may introduce a bias. Pharmaceutical companies may determine their launch sequence based on factors such as price levels and HTA characteristics and this analysis could be influenced by the countries being pre-selected as suitable for early launch. Later HTA assessments are also able to evaluate data with longer follow-up and new evidence, which may have come to light after the initial submissions. The overall picture (percentage of positive versus negative decisions, etc.) may look different as more countries finalise their assessments.

The sample size of countries with available detailed assessment reports was relatively small. This could lead to a bias as the included countries may not be representative of all HTA assessments that have been carried out to date. Furthermore, in some countries, we had to base our analysis on the assessment of only one of the two therapies, as the other may not have been assessed yet. It is, therefore, difficult to ascertain whether the outcome of the assessment reflects the local HTA's

approach and appetite for tumour-agnostic therapies in general or if it could be related to the specific drug.

Of the 11 reimbursement decisions that did not have a detailed assessment report publicly available and were therefore not included in this analysis, nine (82%) resulted in reimbursement, and two (18%) resulted in a rejection. The lack of detailed reports for these decisions makes it difficult to determine the reasoning behind these decisions. It is, however, interesting to note that most of these assessments resulted in approvals.

Although both larotrectinib and entrectinib are TRK inhibitors, there are differences between them that could influence reimbursement decisions, including variations in the available evidence (e.g. population size and duration of follow-up). The approach taken by the pharmaceutical companies might also differ and this could also influence the decisions. Some of the identified challenges may be unique to agents targeting NTRK fusion-positive tumours and are not necessarily pertinent to future tumour-agnostic agents.

4.2 Recommendations for further research, practice and policy

Several policy initiatives exist or are being developed that could potentially influence future HTA assessments of tumour-agnostic therapies. To date, specific guidance for the HTA assessment of tumour-agnostic therapies has been developed in Canada (CADTH, 2021a), England (Palmer et al., 2021), and France (HAS, 2020a).

The Canadian HTA agency was the first to release formal economic model guidance for tumour-agnostic molecules (CADTH, 2021a). The guidance requires an ICER to be reported by tumour site and line of therapy and the use of Bayesian hierarchical methods if the cohort has fewer than 30 patients. The guidance also suggests the model should be designed as a Markov model rather than a partitioned survival model. While the guidance is not yet a requirement, it may have major implications for the future evaluation of tumour-agnostic molecules in Canada.

The Swedish HTA agency, Tandvårds- och Läkemedelsförmånsverket (TLV), also recently released a report on the economic assessment and payment model of the broader "precision medicine and ATMP therapies", in which tumour-agnostic therapies are included (TLV, 2021a). These guidelines will likely be very influential in addressing some of the points raised as part of this analysis and may help bring consistency to the approaches for comparative assessments and economic evaluation. They may also lead to the evolution of trial designs to meet the specific evidence challenges of tumour-agnostic therapies.

Examples of other important initiatives include:

England: The NHS is actively building partnerships with academia and industry to realise the potential of personalised medicines. This is done via the Accelerated Access Collaborative (AAC) programme, which aims to help streamline the adoption of new innovations in healthcare (NICE, 2021). The AAC has created a specific working group dedicated to tumour-agnostic therapies. Genomic testing initiatives are in place (e.g. 100,000 Genomes Project [Genomic England website]; NHS Genomic Medicine Service [NHS website]), and there is also the potential to supplement trial data with RWD in the context of the Cancer Drug Fund to address uncertainties identified by the NICE HTA process.

Sweden: The Swedish government has long had the ambition "to lead the international transition to precision medicine" (Government Offices of Sweden, 2020). Genomic Medicine Sweden (GMS), founded in 2018 with the aim of "translating innovation in genomics into clinical practice and

implementing a sustainable infrastructure for precision medicine in Sweden" (GMS website), is an important part of this strategy. Another is Vision Zero Cancer, a broad collaboration founded in 2019 and financed by Vinnova, the Swedish innovation agency, to better integrate cancer research and innovation into the healthcare system (Vision Zero Cancer website). In this context, the introduction of NGS diagnostic techniques such as FoundationOne CDx® and precision oncology therapies such as entrectinib enables them to test the precision medicine concept within the Swedish healthcare system.

In addition to these initiatives, close dialogue between HTA organisations and pharmaceutical developers should be pursued to further expand access to tumour-agnostic therapies in other countries. As both parties break new ground, it is crucial that there is alignment on the challenges associated with evidence generation for tumour-agnostic molecules. It is, however, also important to have alignment on future endeavours: dialogue can help ensure that evidence generated for future molecules will meet HTA requirements more effectively and that the treatment landscape is prepared to accommodate novel options.

5 Conclusion

Our analysis of 13 submissions from seven countries showed that different evidence requirements and criteria were utilised by HTA agencies in their assessments of larotrectinib and entrectinib. While some countries did not issue conditional approvals or accept the submission of RWD, the ability to provide additional data cuts, longer-term follow-up and RWD were crucial in reversing the negative reimbursement recommendation for larotrectinib in Canada. These findings highlight the importance of non-traditional supportive data sets and generating longer-term data in the assessment of tumour-agnostic therapies.

We also observed that the characteristics of different HTA agencies influenced the assessment and reimbursement decisions made for larotrectinib and entrectinib and may potentially limit the opportunity for other tumour-agnostic therapies to be reimbursed. We found evidence of significant variability in how relative efficacy and costs were assessed by the HTA agencies and in the type of analyses deemed appropriate to use. HTA guidelines specific to tumour-agnostic therapies that are currently in development, along with new policy initiatives, are needed to ensure that future tumour-agnostic therapies are assessed in a consistent and fair manner.

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Appendix

SUPPLEMENTARY TABLE 1: HTA ASSESSMENTS WITH NO DETAILED ASSESSMENT REPORT

Country and product	Reimbursement decision
Finland – Entrectinib (Kela, Rozlytrek)	Positive
Finland – Larotrectinib (Kela, Vitrakvi)	Positive
Israel – Entrectinib (The Israeli Drug Registry, 2020a)	Positive
Israel – Larotrectinib (The Israeli Drug Registry, 2020b)	Positive
Japan – Entrectinib*	Positive
Slovenia – Entrectinib (ZZZS, 2021)	Positive
Slovenia – Larotrectinib (ZZZS, 2020)	Positive
Netherlands – Larotrectinib (Zorginstituut Nederland, 2021a)	Positive – conditional approval
Netherlands – Entrectinib (Zorginstituut Nederland, 2021b)	Positive – conditional approval
Czech Republic – Larotrectinib (SÚKL, 2021)	Negative
Latvia – Larotrectinib (Zāļu valsts aģentūras, 2020)	Negative

*There is no source or public document available for Japan, as an HTA assessment is not necessary

SUPPLEMENTARY TABLE 2: PARAMETERS AND SUB0CRITERIA USED IN ANALYSIS

Category	Criteria to characterise HTA review of tumour-agnostic therapies for each country
General HTA information	Date of HTA submission
	Length of HTA review
	Indication sought for reimbursement
	Clinical studies used in the submission
	ECOD, CCOD, and number of patients used in the submission
Feedback on trial design	Feedback on PICO
	Feedback on trial design (single arm; basket; size)
	Feedback on use of ORR as surrogate endpoint for PFS/OS
Feedback on evidence package	Feedback on the efficacy results
	Feedback on economic data/cost-effectiveness
	Feedback on intrapatient comparison approach to address historical outcomes on previous therapies
	Feedback on natural history data quality to address *NTRK* gene fusion as an oncogenic driver in all tumour types
	Feedback on epidemiology data quality
	Feedback on commitment of comparison vs RWD comparator to address lack of comparative data
	Feedback on estimated utility for comparator (for CUA countries)
Value assessment method	Adaptation of value assessment framework to account for TA medicine specificity
	Willingness to perceive rare/orphan aspect of *NTRK*+ population
	Sequential/simultaneous assessment of clinical and economic efficiency?
	Chosen comparator for the assessment
	Assessment of pooled data (TA) or per tumour type?
	Inclusion of testing accuracy in clinical value assessment

	Inclusion of testing cost in economic assessment
	Inclusion of clinicians' perspectives in HTA review
	Inclusion of patients' perspectives in HTA review
Value recognition (yes/partially/no)	Recognition of unmet medical need
	Recognition of low budget impact due to low disease prevalence
	Recognition of value to test a broad gene panel vs single-gene test
	Recognition of prognostic value of *NTRK* fusion
Assessment outcome	Breadth of indications where positive benefit assessment was granted (none; selected; pan-tumour)
	Rationale for final outcome
	Flexible Pricing Solution found?
Post-assessment requirements	Unconditional/conditional reimbursement
	Data requirement before reassessment (if conditional reimbursement)
	Managed Entry Agreements (MEA) approach

CCOD, clinical cut-off date; CUA, cost utility analysis; ECOD, enrolment cut-off data; HTA, Health Technology Assessment; NTRK, neurotrophic tyrosine receptor kinase; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PICO, patient/population, intervention, comparison and outcomes; RWD, real-world data; TA, tumour agnostic.

Author Contributions

All authors were involved in revising the manuscript critically for important intellectual content, approved the final version, and agree to be accountable for the work. Niels J. Brogaard and Reema Abdul-Ghani carried out the data analysis. Niels J. Brogaard, Reema Abdul-Ghani and Alexandre Bréant drafted the manuscript.

Disclosure of Potential Conflicts of Interest

Niels J. Brogaard, Reema Abdul-Ghani and Alexandre Bréant are employees of F. Hoffmann-La Roche Ltd.

Arnaud Bayle, as part of the Drug Development Department (DITEP), declares the following: Principal/sub-investigator of clinical trials for Abbvie, Adaptimmune, Adlai Nortye USA Inc, Aduro Biotech, Agios Pharmaceuticals, Amgen, Argen-X Bvba, Arno Therapeutics, Astex Pharmaceuticals, AstraZeneca Ab, Aveo, Basilea Pharmaceutica International Ltd, Bayer Healthcare Ag, Bbb Technologies Bv, Beigene, BicycleTx Ltd, Bioalliance Pharma, Blueprint Medicines, Boehringer Ingelheim, Boston Pharmaceuticals, Bristol Myers Squibb, Ca, Celgene Corporation, Chugai Pharmaceutical Co, Cullinan-Apollo, Curevarc, Daiichi Sankyo, Debiopharm, Eisai, Eisai Limited, Eli Lilly, Exelixis, Faron Pharmaceuticals Ltd, Forma Tharapeutics, Gamamabs, Genentech, Glaxosmithkline, H3 Biomedicine, F. Hoffmann-La Roche Ag, Imcheck Therapeutics, Innate Pharma, Institut De Recherche Pierre Fabre, Iris Servier, Iteos Belgium SA, Janssen Cilag, Janssen Research Foundation, Kura Oncology, Kyowa Kirin Pharm. Dev, Lilly France, Loxo Oncology, Lytix Biopharma As, Medimmune, Menarini Ricerche, Merck Sharp & Dohme Chibret, Merus, Molecular Partners Ag, Nanobiotix, Nektar Therapeutics, Novartis Pharma, Octimet Oncology Nv, Oncoethix, Oncopeptides, Onyx Therapeutics, Orion Pharma, Oryzon Genomics, Ose Pharma, Pfizer, Pharma Mar, Pierre Fabre Medicament, Plexxikon, Roche, Sanofi Aventis, Seattle Genetics, Sotio A.S, Syros Pharmaceuticals, Taiho Pharma, Tesaro, Turning Point Therapeutics, Xencor; Research grants from Astrazeneca, BMS, Boehringer Ingelheim, GSK, INCA, Janssen Cilag, Merck, Novartis, Pfizer, Roche, Sanofi; Non-financial support (drug supplied) from Astrazeneca, Bayer, BMS, Boringher Ingelheim, GSK, Medimmune, Merck, NH TherAGuiX, Pfizer, Roche.

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- Drivers of, and incentives for, the uptake of pharmaceuticals and prescription medicines
- Competition and incentives for improving the quality and efficiency of health care
- Incentives, disincentives, regulation and the costs of R&D for pharmaceuticals and innovation in medicine
- Capturing preferences using patient-reported outcomes measures (PROMs) and time trade-off (TTO) methodology
- Roles of the private and charity sectors in health care and research
- Health and health care statistics

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