Healthcare decision-making for tumour-agnostic therapies in Europe: lessons learned

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The tumour-agnostic authorisations of larotrectinib and entrectinib shifted the paradigm for indication setting. European healthcare decision-makers agreed on their therapeutic potential but diverged primarily in identified uncertainties concerning basket trial designs and endpoints, prognostic value of neurotrophic tropomyosin receptor kinase (*NTRK*) gene fusions, and resistance mechanisms. In addition, assessments of relevant comparators, unmet medical needs (UMNs), and implementation of NTRK-testing strategies diverged. In particular, the tumour-specific reimbursement recommendations and guidelines do not reflect tumour-agnostic thinking. These differences indicate difficulties experienced in these assessments and provide valuable lessons for future disruptive therapies. As we discuss here, early multistakeholder dialogues concerning minimum evidence requirements and involving clinicians are essential.

Keywords: tumour-agnostic therapy; NTRK gene fusions; basket trial; indication setting; prognostic biomarker; uncertainty; stakeholder alignment; healthcare decision-making; medicine lifecycle

Introduction

Tumour-agnostic therapies target tumours independent of their location, tissue, or histology.[(p1)] These therapies hold potential as efficacious treatments because of their targeted nature and flexible application (e.g., without the need for off-label prescribing), which allows the treatment of patients who would otherwise not be covered under a marketing authorisation (MA).[(p2),(p3)] However, such a major alteration in thinking on indication setting induces challenges to evidence generation. Therefore, these therapies can be disruptive to the assessments by healthcare decision-makers.[(p2)] Agnostic MAs awarded by the European Medicines Agency (EMA) were first granted to larotrectinib and entrectinib to target *NTRK* gene fusions in solid tumours.[(p4),(p5)] This MA marked a new step in the paradigm shift toward personalised medicine based on pathophysiological pathways and biomarker expression rather than on globally used international classifications of diseases based on location (e.g., lung cancer).[(p6),(p7)]

The differences in how uncertainty is assessed have become particularly visible in the fragmentation of the European system, comprising both centralised and decentralised elements. Evidence for the tumour-agnostic therapies larotrectinib and entrectinib was generated in single-arm basket trials instead of in randomised controlled trials (RCTs).[(p8),(p9)] The basket design was used to include a small number of patients for each solid tumour location that all exhibited the oncogenic *NTRK* gene

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fusion. Given the multitude of different comparators available, the single-arm nature further increased the level of uncertainty resulting from the lack of a randomised comparison.[p10]

Based on this evidence, the EMA approved both therapies as last-line options. This approval spans the full range of patients with *NTRK* gene fusion, in particular those with nonsmall-cell lung carcinomas (NSCLC), colorectal cancer (CRC), papillary thyroid carcinomas, brain tumours, and sarcomas.[p4],[p5] The agnostic last-line nature of the therapies subsequently posed a major challenge to European health technology assessment (HTA) organisations.[p11] Assessing the relative effectiveness for reimbursement proved difficult without a clear standard of care. Moreover, the position of the therapies in the clinical treatment pathway is based on numerous tumour type-specific guidelines.

Larotrectinib and entrectinib show that the European sequential decision-making process described above (pivotal trial design, regulatory and HTA decision-making, and guideline development) might not have been ready to assess and implement agnostic therapies. In particular, they point out the diversity in uncertainty considerations within the assessments resulting from the decision-makers' different remits and national contexts. To prevent fragmentation in this sequence of recommendations and to minimise double or conflicting efforts, it is crucial to study these differences and how they affect each other.[p12],[p13] The experience with tumour-agnostic therapies provides a worthwhile opportunity to assess this alignment and evaluate whether the current approaches were optimal for generating access to these therapies. This experience will provide lessons for the assessment and implementation of similar alterations in thinking in the near future. These lessons should inform the method guidelines for the EU HTA regulation (EU-HTAR) that underpin the joint clinical assessments for oncology products, which are foreseen to take off in 2025.

Document review and content analysis

In this review, we focus on the European healthcare decision-making context. We start with a description of the development and assessment in pivotal trials, regulatory and HTA reports, and clinical guidelines. Subsequently, we identify the differentiating and overarching uncertainties among decision-makers. Therefore, this analysis considers all scientific publications of the Phase I, II, and III clinical trials for larotrectinib and entrectinib. Furthermore, the initial European Public Assessment Reports (EPARs) of the EMA, summaries of product characteristics (SmPCs), reports on orphan designations and withdrawal, and the European Commission (EC) decision documents on MA were collected. Given that HTAs are performed nationally, France, Germany, England, and The Netherlands were included, in line with previous research.[p14],[p15],[p16] Assessment and appraisal reports focussing on clinical assessment were extracted from the websites of Haute Autorité de Santé (HAS, France), the Gemeinsamer Bundesausschuss and Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (G-BA/IQWiG, Germany), the National Institute for Health and Care Excellence (NICE, UK), and the National Health Care Institute (ZIN, The Netherlands). Finally, all European Society for Medical Oncology (ESMO) guidelines on solid tumours were consulted to gather statements on therapies for gene fusions. The aforementioned documents are publicly available and were collected for the study until October 1, 2022.

From the scientific publications, decision-makers' documents, and guidelines, we extracted information that was thematically synthesised along the PICO framework (patient population, intervention, comparator(s), and outcomes; Table 1). Furthermore, information (if available) on trial design, dates of submissions and publications, applied regulatory or HTA pathways and procedures, decision-makers' conclusions, recommendations or

TABLE 1

Overview of data collected during data extraction

Documents	Topics	Items collected
Published Phase I, II and III trials	General + study design	Data quality
↓		Scientific advice
EPARs		Regulatory and HTA pathways and procedures
↓		Recommendations, conclusions or decisions
HTA reports from France, Germany, the Netherlands, England	Population	Tumour-agnostic indication
		Tumour types
↓		Subpopulations
ESMO Guidelines		Orphan designation
	Intervention	Dosing and administration
		Prognostic value of biomarker
		Concomitant diagnostic testing
		Treatment pathways
		Mechanisms of resistance
	Comparator	Comparator choice
		Consequences of lacking comparator
		Larotrectinib versus entrectinib
		Current treatment landscape and corresponding unmet medical need
	Outcomes	Considered endpoints
		Relevance of endpoints
		Missing endpoints and post-authorisation or follow-up data

decisions, and the explicitly described uncertainties were extracted from the sources. Something was considered an uncertainty if it was described in the reports as being unavailable, inaccurate, conflicting, or non-understandable, and as posing risks or affecting decisions.[p17] An overview of the development approach and the most relevant recommendations and considerations is presented in the results, which are outlined separately for the clinical trials, the regulatory review, the HTAs and clinical guideline recommendations, following the PICO framework. A general section on study design considerations is also included. The results are subsequently compared across the decision-makers in the discussion to identify the overarching and cross-cutting uncertainties, and lessons for future disruptive therapies are presented based on these uncertainties.

Clinical trials

General/study design

The designs of Phase I and II trials for larotrectinib and entrectinib were similar, comprising multicentre, open-label, single-arm basket trial designs (see Table S1 in the supplemental information online for a detailed overview of these trials).[p9],[p18],[p19],[p20] The Phase II and paediatric trials were still ongoing for both at the time of analysis.[p21] The duration of the trials for entrectinib was typically 1 year shorter than for larotrectinib at 64–70 months versus 83 months for Phase I and 85–109 months versus 94–120 months planned for Phase II.[p9],[p18],[p19],[p20]

Population

The trials for entrectinib included patients with c-ros oncogene 1 (ROS1) or anaplastic lymphoma kinase (ALK) molecular alterations, eventually resulting in fewer evaluable patients with NRTK fusions (54 for entrectinib versus 159 for larotrectinib).[p9],[p20],[p22] For larotrectinib, the included population was younger than for entrectinib, enrolling patients as young as 1-month old (versus 2-years old) in the paediatric group and from 12-years old versus 18-years old in the adult trial, respectively.[p8],[p22],[p23],[p24],[p25] The pooled analysis for larotrectinib included children, whereas the paediatric entrectinib trials were analysed separately.[p22],[p24],[p25],[p26] The pooled analysis for larotrectinib explicitly excluded patients with a primary central nervous system (CNS) tumour and enrolled fewer patients with CNS metastases (8% for larotrectinib versus 22% for entrectinib).[p26] For both therapies, the largest share of patients was diagnosed with sarcomas, although the size of the share differed significantly (44% for larotrectinib versus 24% for entrectinib). Other major tumour types included lung cancer (8% versus 19%), salivary gland cancer (both 13%), thyroid tumours (16% versus 9%), and breast cancer (13% versus 1%). Generally, the included tumour types were comparable for both therapies.[p26],[p27]

Intervention

Both therapies are administered orally. Larotrectinib is taken twice daily, and entrectinib once daily.[p26],[p27] The entrectinib dose was built up to the maximum tolerated dose (MTD) of 600 mg/m^2,[p24] whereas the dose for larotrectinib was kept constant at 100–150 mg/m^2 in Phase II, not reaching an MTD.[p26]

Comparator

Neither of the products was directly compared with any form of standard of care (SoC), because all the trials were single-armed.[p28]

Outcomes

For both therapies, the primary endpoint in Phase II was the objective response rate (ORR). The entrectinib trials also included duration of response (DoR) as a primary endpoint. Secondary endpoints involved time to response (TTR), progression-free survival (PFS), and overall survival (OS). Entrectinib trials also included quality of life (QoL) as a secondary endpoint, whereas larotrectinib trials only included QoL in the paediatric trial.[p21] Using the same median follow-up (12.9 months), the ORR for larotrectinib appeared higher compared with that for entrectinib, at 79% [95% confidence interval (CI) 72–85] versus 57% (95% CI 43–71), respectively.[p26],[p27] The duration of treatment, PFS, and OS were not reached at cutoff in any of the trials. For larotrectinib, the number of grade 3 adverse events assessed as related to treatment was slightly higher (14% versus 10% for entrectinib).

Marketing authorisations

General/study design

Larotrectinib applied for MA before the launch of the priority medicines (PRIME) scheme of the EMA and did not receive scientific advice. Entrectinib received scientific advice as part of PRIME on four occasions for the *NTRK* indication.[p4],[p5] The EMA recommended the use of a basket trial design supporting registration in multiple tumour types and gene arrangements, and the two-step assay for identifying eligible patients. They also discussed the use of ORR as a primary endpoint, the clinical meaningfulness of a 20% response rate, primary and secondary efficacy analyses, sample size requirements for the three *NTRK* genotypes, and the statistical approach for the pooled analysis. The position of the EMA on each of these topics is not publicly available.[p4] For larotrectinib, an accelerated assessment procedure was pursued. The EMA considered this not appropriate, because 'the uncertainties [...] required a thorough review of the quality, clinical pharmacology and clinical efficacy aspects'.[p5] Entrectinib was never considered for accelerated assessment because it was not recognised to be of major public health interest owing to the 'uncertainty in quantifying UMN for entrectinib over crizotinib in the context of the ROS1-positive NSCLC indication', even though the data in patients with *NTRK* gene fusions were considered 'promising'.[p4] Conditional MA (i.e., with postauthorisation requirements) was granted to larotrectinib on September 19, 2019 after a unanimous vote by 29 member state representatives, 10 months before the conditional MA of entrectinib (May 28, 2020), which was not unanimous by three divergent opinions.[p4],[p5] Those three representatives considered the data set too small, 'allowing small changes in the size of cohorts to have large effects on the observed ORR'. Therefore, they did not conclude on a positive benefit–risk ratio or whether entrectinib would address the UMN to a similar extent as larotrectinib.[p4]

Population

The authorised tumour-agnostic indication for larotrectinib includes patients with primary CNS tumours, in contrast to the developer's submitted application (Table 2). The EMA argued that there was 'no scientific rationale for exclusion', despite its exclusion from the pooled analysis.[p5] The requested indication as initial therapy in case of 'no adequate/acceptable standard treatment option' was replaced by the EMA with 'no satisfactory treatment option'.[p4],[p5] This would allow for 'bypassing therapies of limited efficacy that are currently nevertheless recommended in therapy guidelines'. The EPAR for larotrectinib stated that this was appropriate given the 'high likelihood of early and durable response in most of the studied tumour types', despite the uncertainty about effects on OS.[p5] Both larotrectinib and entrectinib were initially granted orphan designations for specific tumour sites, all of which were withdrawn by the EMA despite meeting the criteria.[p5],[p29],[p30] The EMA argued that 'a tissue independent therapeutic indication cannot be considered to be within the scope of a limited number of orphan designations covering separate tumour types'.[p31]

Intervention

For both therapies, a major concern of the EMA was the role of *NTRK* gene fusions as oncogenic drivers. This was emphasised by the lack of studies on *NTRK* gene fusions as a target to reduce tumour progression. For all nonrare tumour types, it was uncertain whether the impact of larotrectinib on the prognosis depended on a gene fusion partner.[p5] Similarly, for entrectinib, the types of mutation and extent to which they related to treatment efficacy were unclear. This lack of clarity was resolved by the implementation of postauthorisation requirements to obtain this information.[p4] In addition, the EMA demanded confirmation of *NTRK* gene fusion by a validated test before initiation of treatment for both therapies. Major concerns were expressed about acquired resistance with long-term or subsequent use of multiple *NTRK* inhibitors.[p4],[p5]

Comparator

Conditional MA requires a therapy to fulfil UMN criteria. To meet these criteria, either there should be no current satisfactory diagnosis, prevention, or treatment authorised or the therapy should provide a major therapeutic advantage over authorised alternatives.[p32] In this context, estimates of ORR and PFS for conventional chemo- and targeted therapies were provided for treatment with larotrectinib. The low efficacy of these treatments was generally expected in this last-line indication. Accordingly, the EMA concluded that the ORR and PFS ranges of larotrectinib were favourable, or at least comparable, to those of nontargeted alternatives.[p5] However, no OS advantage of larotrectinib over SoC options could be confirmed.[p5] The EPAR for entrectinib notes that, for the fulfilment of UMNs, the clinical data and uncertainties of larotrectinib should be taken into account.[p4] Given that the postauthorisation requirements for larotrectinib were not completed, it was not yet possible to confirm its full benefit. Therefore, entrectinib potentially addresses the same UMNs to a similar extent as was expected for larotrectinib, despite the limitations of the comparison. The EMA noted that, for both therapies, the evaluation of safety data and interpretation of time-to-event endpoints in single-arm trials are inherently unreliable.[p4],[p5] Therefore, for entrectinib, the therapeutic effect on PFS and OS could not be disentangled from the effects resulting from differences in prognosis across tumour types. Hence, a comparison between entrectinib and the SoC for each tumour type was made to 'contextualise' the results. However, the low number of patients per stratum limits the interpretation of the results.[p4]

Outcomes

Despite the overall ORR being considered outstanding for both products (ORR: 72% for larotrectinib, 64% for entrectinib according to the EPARs; i.e., shorter follow-up and smaller number of patients evaluated than in the aforementioned clinical trial publications[p26],[p27]), the magnitude of effect per tumour type remained unclear. This lack of clarity was attributable to small sample sizes (for some, just one patient), widely varying ORRs

TABLE 2

Requested and approved initial indications for larotrectinib and entrectinib[a]

Drug	Requested indication	Authorised indication
Larotrectinib	Treatment of adult and paediatric patients with locally advanced or metastatic solid tumours (**excluding primary CNS tumours**) with *NTRK* gene fusion after prior standard therapy or **as initial therapy** when there is no adequate treatment option	**Monotherapy** for treatment of adult and paediatric patients with solid tumours that display an NTRK gene fusion, who have (i) disease that is locally advanced, metastatic or where **surgical resection** is likely to result in severe morbidity, and (ii) **no satisfactory treatment options**
Entrectinib	Adult and paediatric patients with *NTRK* fusion-positive locally advanced or metastatic solid tumours, who have progressed following prior therapies or **as initial therapy** when there are no acceptable standard therapies and patients with **ROS1-positive, advanced NSCLC**	As **monotherapy**, indicated for treatment of adult and paediatric patients **12 years** of age and older, with solid tumours that have an *NTRK* gene fusion, who have a disease that is locally advanced, metastatic, or where **surgical resection** is likely to result in severe morbidity, and who have **not received a prior NTRK inhibitor**, who have **no satisfactory treatment options** As **monotherapy**, indicated for treatment of **adult patients** with ROS1-positive, advanced NSCLC **not previously treated with ROS1 inhibitors**

[a] Differences between requested and authorised indications are shown in bold.

TABLE 3

Overview of indications as recommended by the various HTA organisations[a]

HTA recommendation	Larotrectinib	Entrectinib
HAS	**Favourable opinion** for reimbursement only for treatment of paediatric patients with refractory or relapsed, locally advanced or metastatic infantile fibrosarcoma or another soft tissue sarcoma with *NTRK* gene fusion Maintenance of this opinion is subject to submission of comparative data for VITRAKVI (larotrectinib) versus SoC in these patients within a maximum period of 12 months, as well as implementation of exhaustive registry identifying all children treated with VITRAKVI in France **Unfavourable opinion** for reimbursement in other paediatric indications included in MA and in adults with solid tumours that display an *NTRK* gene fusion; who have a disease that is locally advanced, metastatic, or where surgical resection is likely to result in severe morbidity, AND who have no satisfactory treatment options	**Unfavourable opinion** for reimbursement in adult and paediatric patients 12 years of age and older with solid tumours expressing a neurotrophic *NTRK* gene fusion, who have a disease that is locally advanced, metastatic, or where surgical resection is likely to result in severe morbidity, who have not received a prior *NTRK* inhibitor, and who have no satisfactory treatment options
IQWiG and G-BA	IQWiG concluded that **added benefit** of larotrectinib compared with best supportive care is **not proven** for adult and paediatric patients with solid tumours that display an *NTRK* gene fusion, who have a disease that is locally advanced, metastatic, or where surgical resection is likely to result in severe morbidity and who have no satisfactory treatment options G-BA decided on the added benefit, resulting in inclusion in Annex XII	IQWiG concluded that **added benefit** of entrectinib compared with best supportive care or surgical resection (likely to result in severe morbidity) is **not proven** for adult and paediatric patients from 12 years of age with solid tumours that display an *NTRK* gene fusion, who have a disease that is locally advanced, metastatic, or where surgical resection is likely to result in severe morbidity and who have not yet received an *NTRK* inhibitor and who have no satisfactory treatment options G-BA decided on the added benefit, resulting in inclusion in Annex XII
NICE	Not recommended for routine use in NHS, but considered for use in **Cancer Drug Fund** as option for treating adults and children who have solid tumours (including primary cerebral tumours) that have an *NTRK* gene fusion AND disease that is locally advanced or metastatic, or for which surgical resection is likely to result in severe morbidity AND who have no satisfactory treatment options, only if the conditions in managed entry agreement are followed	Not recommended for routine use in NHS, but considered for use in **Cancer Drug Fund** as option for treatment of patients aged 12 and over who have solid tumours (including primary cerebral tumours) that have an *NTRK* gene fusion AND disease that is locally advanced or metastatic, or for which surgical resection is likely to result in severe morbidity AND who have no satisfactory treatment options, only if conditions in managed entry agreement are followed
ZIN	**Conditional inclusion** recommendation in the national health insurance package for adult and paediatric patients with solid tumours harbouring an *NTRK* gene fusion Suitable assessment framework will be developed, and additional data will be generated before compliance with established medical science and medical practice will be assessed	**Conditional inclusion** recommendation in national health insurance package for adult and paediatric patients with solid tumours harbouring an *NTRK* gene fusion Suitable assessment framework will be developed, and additional data will be generated before compliance with established medical science and medical practice will be assessed

[a] Main recommendations on larotrectinib and entrectinib by each HTA organisation are shown in bold.

(0–100%), and uncertainty regarding tissue origin as an effect modifier.[(p4),(p5)] To support the tumour-agnostic indication, the ORR for larotrectinib was stratified according to *NTRK* gene fusion status, showing an ORR of 88% for *NTRK*-positive patients versus a complete response (CR) of 0% and partial response (PR) of 2% in *NTRK*-negative patients. The EMA indicated that the *NTRK* gene fusion is rare in common tumour types; thus, information on *NTRK* status and efficacy data was limited for those tumour types. For this reason, common tumour types might have shown a lower ORR and DoR compared with tumour types with higher NTRK prevalence.[(p4),(p5)] For larotrectinib, the TTR, DOR, and tumour shrinkage were emphasised as being crucial in advanced tumour types and, therefore, results were considered clinically meaningful.[(p5)] By contrast, for entrectinib, it was reported that clinically relevant effects 'may be anticipated' because the DOR appeared durable, although uncertain, owing to limited patient numbers.[(p4)] The postauthorisation requirements for both therapies should confirm the tissue-independent efficacy and potential resistance mechanisms. For larotrectinib, two postauthorisation requirements focussed on paediatric (neuro)developmental toxicity and dosing. For entrectinib, one postauthorisation requirement assessed the impact of genetic and molecular alterations on efficacy.

Health technology assessments

General/study design

All HTA organisations considered the same trials and highlighted the challenges imposed by the basket trial design and corresponding statistical analyses regarding patient heterogeneity, as well as the lack of comparison with other therapies. As an example, HAS considered the 'proof of concept studies incapable of supporting the clinical benefit'.[(p33)] As such, the tumour-

TABLE 4

Overview of findings for each PICO element

Similarities and general considerations	Contradicting considerations
General/study design	
• None of the decision-makers considered evidence sufficient for accelerated assessment or unconditional approval for tumour-agnostic indication	• Although criticised for its limited size, basket design was accepted by EMA, whereas HTA organisations described strong methodological uncertainties for establishing efficacy and effectiveness and lack of generalisability to clinical practice population
• Single-arm nature of basket trial was criticised by all decision-makers because of hampering assessment of time-to-event endpoints, safety data, and UMN	• Based on various policy tools available to countries and institutions, uncertainties were managed differently (through additional data collection, pricing strategies, later treatment lines, etc.)
• Scientific advice provided for entrectinib, as second tumour-agnostic therapy, did not result in reduced uncertainty compared with larotrectinib	
Population	
• Most assessment methods and frameworks appeared to not be ready for tumour-agnostic indications	• Scientific rationale used as an argument by EMA to fully adopt the agnostic indication (e.g., include CNS tumours) appeared to be too large an uncertainty for HTA organisations. Clinical guidelines did not appear to adopt agnostic thinking, because the therapies were only recommended in guidelines on tumour types included in trials
	• Broad wording in EMA indication could allow for flexibility in clinical practice, but complicates positioning in clinical treatment pathway and quantification of eligible patients and estimate utilisation at HTA level. None of the guidelines specified the broad language
Intervention	
• All three decision-making groups raised uncertainties regarding prognostic value of *NTRK* gene fusions and their generalisability across tumour types	• Different *NTRK* gene fusion-testing policies proposed by EMA, HTA organisations, and in clinical guidelines, reflecting different views on implementation of these therapies
	• Acquired resistance to TRK inhibitors was a major concern in EMA and HTA assessments, but sarcoma consensus guideline recommends sequential use based on theoretical scientific rationale
Comparator	
• None of the organisations aimed to distinguish between efficacy/effectiveness or safety of larotrectinib versus entrectinib	• HTA organisations perceived uncertainties concerning comparators, for some because of choice of specific comparators and, for others, complete lack of comparators. This resulted in different comparative assessments at each organisation
	• Determining UMN requires assessment of available therapies. The numerous treatment options resulting from differences in national guidelines and in specific tumour types and treatment lines led to variation in considered UMN across decision-makers
Outcomes	
• All decision-makers preferred PFS or OS data, also specifically reported for each tumour type	• EMA appeared more accepting of ORR as primary endpoint compared with HTA organisations and clinical guideline developers
	• Difference in uncertainties perceived across decision-makers rendered EMA postauthorisation requirements insufficient for other decision-makers

agnostic therapies are only partially or conditionally reimbursed in each country, and all organisations requested additional evidence through national registries. HAS concluded that both therapies demonstrated an 'insufficient' clinical benefit (SMR) and 'absent' clinical added value (ASMR), except larotrectinib in the case of children with infantile soft tissue sarcomas. Here, it could have a 'limited role' after the failure of previous treatments.[(p33),(p34)] IQWiG argued that the added benefit for both therapies in the German context could not be proven.[(p35),(p36)] However, the subsequent reimbursement decision by the G-BA was positive (Table 3).[(p37),(p38)] ZIN indicated that the 'innovative nature' of the therapies made it unattainable to assess the 'established medical science and medical practice' under the current assessment framework.[(p39),(p40)] Hence, both therapies were candidates for conditional inclusion in the basic care package. However, to meet the criteria for conditional inclusion, the procedural policy framework had to be broadened. This would allow ZIN to develop a novel assessment framework, while additional data, in line with the postauthorisation requirements of the EMA and supplemented by Dutch registry data, would be generated by the developer. Both products have since been conditionally reimbursed for 3.5 years. NICE did not recommend either of the therapies for routine use in the NHS, but included both in their Cancer Drug Fund, which is a funding mechanism for products with high uncertainty under the condition of additional data collection.[(p41),(p42),(p43)] Simple discount patient access schemes and commercial managed access agreements were applied to manage uncertainties in England.[(p41),(p43)]

Population

More than the EMA, HTA organisations struggled with the heterogenic nature of the trial population, resulting in poor characterisation across tumour types and between patients exhibiting the *NTRK* gene fusion and those that did not. IQWiG stated that the only reliable approach was to stratify and perform analyses for each tumour type individually.[p36] The ambiguous 'satisfactory' in the indication induced more heterogeneity in terms of treatment lines and disease stages among patients in clinical practice (Table 3).[p41] For this reason, HTA organisations expressed difficulty in estimating the number of eligible patients to assess the UMN and predict the budget for treatment. Nonetheless, in line with the EMA, they recognised that there was UMN for the overall population.[p33],[p34],[p39],[p40] The trial population was not considered generalisable to clinical practice, because progression under previous treatment had not been an inclusion criterion and rare tumour types were overrepresented, and common tumour types were underrepresented compared with clinical practice.[p41],[p43] Additionally, the lack of patient characteristics further complicated the generalisability of effects.[p33],[p36],[p41] Furthermore, the discrepancy between the trial and the EMA indication regarding primary CNS tumours amplified this concern. HTA organisations stated that, with only a theoretical rationale for the effect, it was difficult to establish the relative effectiveness of the treatments.[p41] In line with the EMA assessment, the lack of data on use in paediatric patients was stressed.[p33],[p36]

Intervention

Testing patients with solid tumours for *NTRK* gene fusion was not yet routine in any of the countries assessed.[p33],[p36],[p39],[p41] Identification of eligible patients in practice was difficult, mainly because the prevalence in common tumours is very low (0.5–1% in NSCLC and CRC), whereas the prevalence is higher in rare tumours (up to 95% in fibrosarcoma).[p4],[p5] The organisational impact of introducing routine testing on the health care system was one of the major reasons that HAS did not recommend the use of entrectinib.[p33],[p34] The EMA discussion on the prognostic effect of *NTRK* gene fusions compared with other prognostic factors was continued in the HTA setting. Also in line with the EMA, HTA organisations reported that it was unclear whether tissue-specific mechanisms would lead to bypassing the response or whether the tropomyosin receptor kinase (TRK) would become resistant over time.[p41],[p43] The positioning of larotrectinib and entrectinib in the clinical treatment pathway was difficult because of the diversity in tumour types and the unclear population definition.[p41],[p43]

Comparator

The preferred comparator for the indirect comparison varied across HTA organisations, including best supportive (palliative) care in common tumour types, chemotherapy in rare tumour types, any SoC for the included tumour types and treatment lines, and surgical resection that would likely result in severe morbidity.[p33],[p34],[p35],[p36],[p41],[p43] The institutions generally reported that it was not possible to name one comparator, making the comparison difficult or even impossible unless these could be compared per tumour type.[p35],[p36] HAS also justified the negative recommendation for entrectinib by stating that larotrectinib was already available as an alternative.[p34] In England, the developer included a naive indirect comparison with a pooled comparator arm using the last-line treatments for all tumour types, as reported in NICE guidelines, assuming equal natural histories for all patients. The weighted averages of the PFS and OS were considered to introduce bias in multiple ways and, therefore, were unable to account for heterogeneity and to adjust for prognostic factors. Nevertheless, two separate comparisons were considered for decision-making.[p41] Similarly, in Germany for entrectinib, the developer submitted an indirect comparison against a pooled comparator arm. However, the comparison was disregarded because G-BA required a tumour-specific analysis.[p37]

Outcomes

In contrast to the regulatory assessment of ORR, which was described as outstanding, HTA organisations indicated that it was unrealistic to assume a sufficiently large effect on any endpoint that could not result from systematic bias for any of the tumour entities.[p36] Additionally, HTA organisations reported that important endpoints were missing, such as OS and QoL data, as well as patient-relevant endpoints. HAS noted that the benefit–risk ratio was 'not adequately established'.[p33],[p34] Generally, the data were described as immature concerning PFS and OS estimates, which is why the endpoints of the modelled survival curves were uncertain. NICE concluded that, with great uncertainty, both products have 'the potential' to meet their end-of-life criterion (i.e., extending patient lives by at least 3 months compared with SoC). All HTA organisations referred to the EMA postauthorisation requirements as relevant additional evidence to resolve some of the uncertainties. However, where the EMA requirements focused on histology-independent efficacy and establishing a more precise magnitude of effect, the HTA perspective focused on long-term OS and PFS endpoints, QoL health utility measures, identification of the number of patients being tested (positively) for *NTRK*, patients starting treatment, and characterising these groups by tumour site.

Clinical guideline recommendations

General/study design

At the time of data collection, the ESMO had 46 guidelines on solid tumours. Thirty-two (70%) had been updated since the MA of larotrectinib in 2019 (Table S2 in the supplemental information online). Ten guidelines (31%) mentioned tumour-agnostic therapies. Of these, one only mentioned larotrectinib because entrectinib was not yet approved at that point. These were solely guidelines for tumour types that were well represented in the trials (e.g., sarcomas, CRC, breast, gastrointestinal, lung, and thyroid cancer). Four sarcoma and CRC guidelines explicitly noted that the therapies were 'recommended' or 'SoC'.[p44],[p45],[p46],[p47] The other guidelines described the therapies as 'a possible consideration' or noted that 'there are' tumour-agnostic options and that *NTRK* gene fusions are 'targetable by' or 'sensitive to' these therapies.[p48],[p49],[p50],[p51],[p52],[p53] The guideline for NSCLC (2018) mentioned both therapies despite them not having been authorised at that point (Figure 1).[p51]

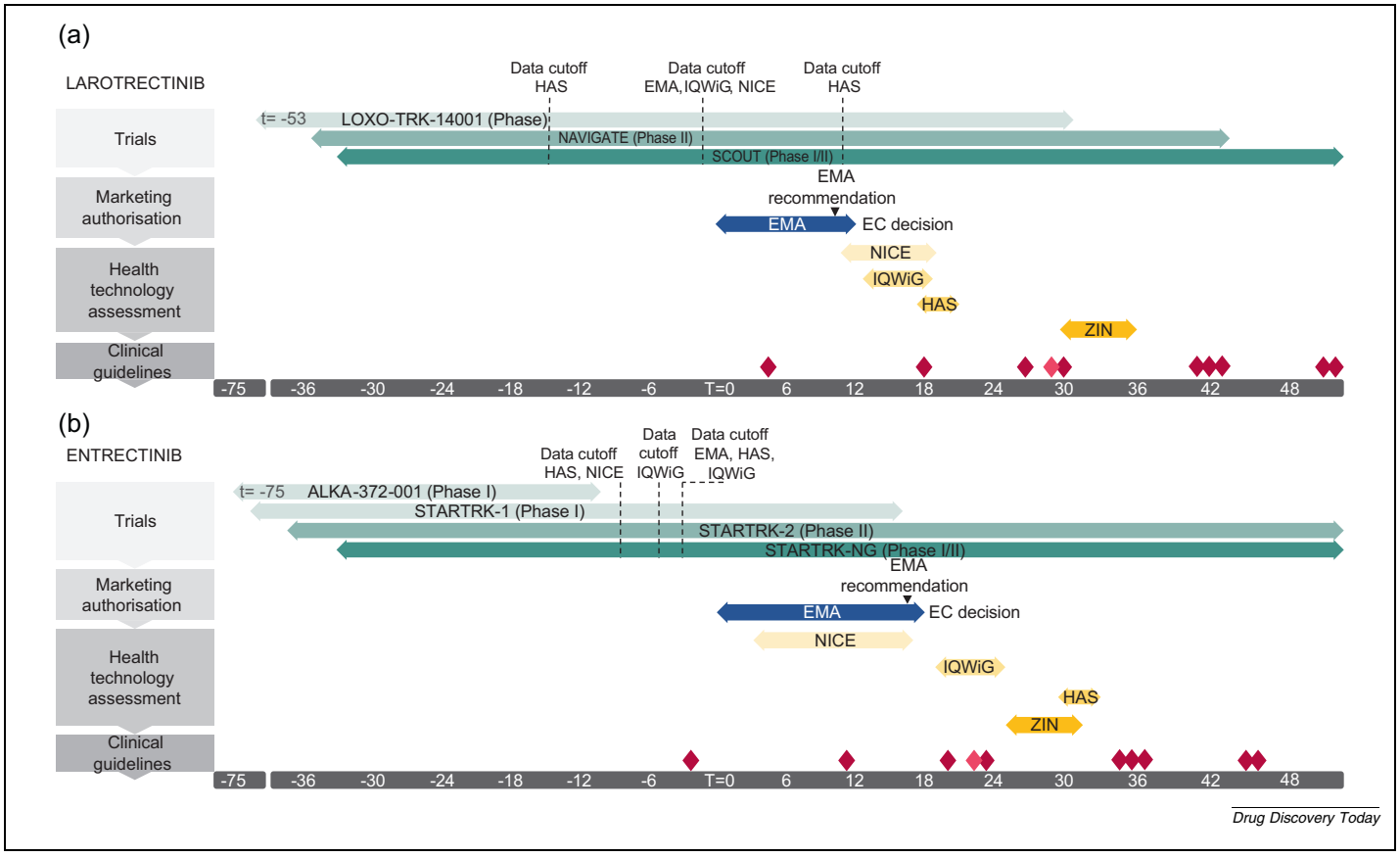

FIGURE 1

Timeline of major trial and patient access recommendations for **(a)** larotrectinib and **(b)** entrectinib in the early assessment lifecycle. Time is indicated in months, with T = 0 being the submission of the dossier to the European Medicines Agency (EMA). Green indicates the duration of the trials, blue indicates the duration of the EMA assessment, yellow indicates the duration of the health technology assessments (HTAs), and red indicates the publication of clinical guidelines (the consensus statement is lighter red/pink). Gemeinsamer Bundesausschuss (G-BA) procedures are included in the IQWiG timelines. Abbreviations: EC, European Commission; EMA, European Medicines Agency; HAS, Haute Autorité de Santé; IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; NICE, National Institute for Health and Care Excellence; ZIN, National Health Care Institute.

It was recommended that patients participate in open trials until the routine use of the products. In line with the different postauthorisation data requirements of the HTA organisations, the advanced breast cancer guideline indicated that prospective registries should be created to collect data on all patients treated with these innovative approaches.[p49]

Population

In contrast to most clinical practice guidelines, which were developed for individual tumour types, the ESMO-Magnitude of Clinical Benefit Scale (EMSO-MCBS) score followed the agnostic thinking, spanning the full tumour-agnostic indication.[p54] Only in the case of sarcomas, the largest group enrolled in the trials, with high *NTRK* prevalence, was a consensus guideline on patients with *NTRK* fusions developed.[p44] The sarcoma guideline concluded that TRK inhibitors provide effective treatment options. However, in contrast to the EMA indication, it stated that the efficacy in primary CNS tumours was only confirmed for larotrectinib. Following the agnostic approach and in line with EMA and HTA comments, the guideline explicitly stated that patients with infantile fibrosarcoma had not been enrolled in the trials for entrectinib, but provided a positive recommendation because of the high *NTRK* prevalence in these patients. Across all guidelines, variations from first to third or fourth-line treatment recommendations were observed. This was enabled by the broad wording in the EMA indication, but confirmed the positioning uncertainties of HTA organisations.

Intervention

Although regulatory and HTA organisations appeared cautious toward the oncogenic driver capacity of *NTRK* gene fusions, the sarcoma consensus guideline stated that 'NTRK gene fusions have been shown to persist in tumours over time, suggesting that these remain the dominant oncogenic driver over the course of different treatments'.[p44] This provided the rationale for the acceptance of a sequential TRK inhibitor treatment approach, despite elaborately discussed concerns on acquired resistance by the EMA and HTA organisations.[p44] ESMO rated the prognostic value of *NTRK* gene fusions as *I-C* on their scale for clinical actionability of molecular targets (ESCAT). This rating is indicative of readiness for routine use, although with caution because of the evidentiary limitations of the basket trial design.[p55] Addi-

tionally, the soft tissue and visceral sarcoma guideline argued for routine *NTRK* testing because of the 'prognostic and predictive relevance of NTRK rearrangements', whereas the EMA and HTA organisations had doubted the prognostic and predictive value.[p46] Multiple other guidelines indicated that the *NTRK* gene fusions should be confirmed before treatment start, although they recommended different tests, such as RNA confirmation, whole-genome sequencing, molecular confirmation with sequence tagged sites, or a combination of immunohistochemistry and next-generation sequencing (whether RNA or DNA), with the latter also being recommended by the EMA.[p45],[p46],[p47],[p49],[p50],[p52],[p53] The metastatic CRC (low in NTRK gene fusions) guideline pragmatically proposed testing only after previous treatment failure, which would considerably reduce the impact of testing on healthcare systems, which was a major concern of HAS.[p47] This recommendation stands in contrast to the guidelines on salivary gland as well as those for soft tissue and visceral sarcomas (both high in *NTRK* gene fusions), which stressed that testing for *NTRK* gene fusions is recommended, because it has 'great implications for treatment choice'.[p45],[p46]

Comparator

None of the guidelines explicitly stated a preference for either larotrectinib or entrectinib. However, the difference in tone in the sarcoma consensus guideline suggests a preference for larotrectinib,[p44] which is described as having shown 'robust clinical efficacy' in a 'combined analysis of three Phase I/II trials including 159 patients', with 'objective responses and durable disease control in primary CNS and brain metastases'. By contrast, entrectinib is described as having 'demonstrated efficacy in 54 patients with TRK fusion cancers in one of three Phase I/II trials', with 'clinically meaningful and durable intracranial responses in brain metastases'. No (in)direct comparisons with other treatments were made in any of the guidelines, and neither did they attempt to indicate when other therapies may be 'unsatisfactory'. However, some guidelines indicate that the targeted nature of the two therapies provides a more favourable toxicity profile compared with some other options, such as chemotherapy.[p53]

Outcomes

Both therapies were rated with an ESMO-MCBS score of 3 (out of 5).[p54] This is not considered a substantial magnitude of clinical benefit (which is only indicated by scores 4 or 5). However, it is the highest score possible for treatments studied in single-arm trials for orphan diseases or high UMN indications without QoL data. Most guidelines assessed the effects of larotrectinib and entrectinib solely for specific tumour types, looking at ORR and PFS reported specifically for that group of patients. This has led to much variation in the interpretation of the results. In contradiction to the agnostic HTA assessments, the sarcoma consensus paper described the results as having a 'favourable safety profile, together with robust clinical efficacy, translated into rapid, sustained, and clinically meaningful improvements in quality of life in the majority of patients'.[p44] Not all guidelines were this positive, as shown in the advanced breast cancer guideline, which listed the voting outcomes on the treatment recommendation.[p49] Only 29% of the panel members voted in favour of the recommendation, while 47% indicated that there was insufficient data to make the recommendation and 24% abstained from voting. As opposed to the EMA and HTA reports, none of the guidelines discussed desired endpoints for decision-making that are not (yet) available.

Lessons for future treatments shifting indication-paradigms

The decision to authorise larotrectinib and entrectinib for their tumour-agnostic indication was the first of its kind in Europe. However, many more personalised treatments are in development and approval trends are changing.[p1] It is likely that the uncertainties observed for the therapies discussed here will also apply to paradigm-shifting therapies, such as other tumour-agnostic therapies or individually designed private neoantigens, in the near future.[p56] To ensure an efficient access process, it is vital to discuss the origin of these uncertainties as well as how they could be managed. An overview of the major overarching and cross-cutting uncertainty considerations for larotrectinib and entrectinib is provided in Table 4. Tools such as horizon scanning allow institutions to anticipate emerging therapies and improve the readiness of generated evidence and decision-making frameworks by prompting early multistakeholder dialogue.[p57] Such dialogue could also result in better-aligned advice on evidence generation toward developers.

Discuss differences in acceptance of uncertainty

Differences in accepting uncertainty regarding treatment with larotrectinib and entrectinib are evident among decision-makers. While decision-makers had the same evidence at hand, differences in acceptance emerged because of varying remits and differing operating contexts (e.g., the EMA assesses the benefit–risk balance, and HTA organisations assess relative effectiveness and differ among themselves in whether and how they consider other aspects, such as cost-effectiveness and budget impact).[p58],[p59] Most notable was the interpretation of endpoints. Even though all decision-makers preferred (progression-free) survival data, the EMA was more accepting of the 'outstanding' ORR in the context of the benefit–risk balance than were the HTA organisations and clinical guideline developers in the context of reimbursement and treatment pathway recommendations. Importantly, the accepted argumentation underlying the recommendations critically differed. Trust in the scientific rationale behind the agnostic indication was sufficient for the EMA to include primary CNS tumours in its indications, whereas HTA organisations and clinical guideline developers were reluctant to accept this argument. Similarly, one of the guidelines indicated that the scientific rationale behind a durable response to TRK inhibitors sufficed to recommend sequential treatment with multiple TRK inhibitors, whereas both the EMA and HTA organisations elaborately expressed their concerns about acquiring resistance to the therapies.

In the assessment of UMN, the EMA stated that ORR and PFS estimates were favourable over, or at least comparable to, conventional chemo- and targeted therapies. The EMA concluded on a high UMN for larotrectinib, although, in the case of

entrectinib, some regulators considered this need to already be filled by larotrectinib. HTA organisations presented diverse and uncertain assessments of the UMN, because they considered the numerous SoC options in the different treatment lines for each tumour type. This might have had profound implications on the direction of the recommendations because a higher UMN could increase the acceptance of uncertainty.[p14],[p17],[p60] For some HTA organisations, UMN is even used as a formal criterion for decision-making.[p61],[p62]

Given the different remits and diverse acceptance of uncertainty, it is key to discuss a priori the evidence and methods that should prevent or reduce uncertainty. Therefore, it is pivotal to develop a framework for assessing and evaluating the uncertainties of these types of treatment.[p17] For example, the current method guidelines for joint clinical assessments established by EUnetHTA21 and consolidated in the methodology subgroup under the EU-HTAR do not explicitly address such uncertainties.[p63] Based on further experience with these treatments and in close relation to the other stakeholders, guidelines supporting joint clinical assessments on populations, comparisons, endpoints, and the applicability and validity of evidence could be adapted if felt necessary by the EU HTA community.

Use early multistakeholder dialogue to establish evidentiary criteria

Currently, seven product–indication combinations have been approved for tumour-agnostic indications in the USA versus three in Europe.[p64],[p65] Moreover, in April 2024, the Committee for Medicinal Products for Human Use (CHMP) recommended to extend the *NTRK* indication of entrectinib to paediatric patients older than 1 month.[p66] This could suggest that European decision-makers in general have a more critical attitude toward these indications or that the complex decentralised decision-making processes in Europe are insufficiently aligned to facilitate access to therapies that introduce such new thinking on indication. Given the differences in remits of decision-makers, different perspectives exist on the data required for these recommendations.[p14],[p16],[p67],[p68],[p69],[p70] This differentiation was evident in comments on the basket trials for both therapies. All decision-makers commented on the limited number of included patients per individual tumour type, but only the EMA seemed to consider it acceptable (although ZIN eventually agreed to this in the early approval of larotrectinib and entrectinib based on the newly developed assessment framework).[p71] HTA organisations perceived the design as not matching scientific standards, complicating generalisability and being incapable of proving clinical benefit for this indication or tumour types individually. Similarly, clinical guidelines considered the endpoints relevant to a specific tumour type rather than following the tumour-agnostic rationale.[p10] Additionally, because of the lack of a comparator, all decision-makers noted that time-to-event endpoints and safety data were difficult to interpret. Moreover, HTA organisations would have preferred some form of comparison in the basket design for the establishment of relative effectiveness.[p72],[p73],[p74] Both the limited patient numbers in each basket, as well as the single-arm nature of the study, contributed to the difficulty in assessing the prognostic value of *NTRK* gene fusion, the most important assumption underlying the agnostic indication.[p75] Decision-makers' divergent viewpoints, such as opinions on which data were needed to demonstrate whether *NTRK* gene fusions are oncogenic drivers, yield important insights for future therapies. Clearly, the prognostic value must be further established before MA to be acceptable to the subsequent decision-makers.[p75],[p76]

An early multistakeholder dialogue focussing on development strategies for tumour-agnostic therapies for European patients is crucial to avoid potential limitations in the evidence going forward. Early multistakeholder dialogue, in which the minimum evidentiary requirements to assess the efficacy and effectiveness of tumour-agnostic therapies would be established upfront, is a concept that has been proposed previously.[p67] For example, these dialogues could discuss what would be considered a homogeneous effect across tumour locations and what should be the minimum ORR overall and in each location. Such an approach is taken by the Dutch Society for Medical Oncology (NVMO) when assessing new oncology products, which have a specific module with criteria for nonrandomised studies.[p77] Additionally, potential development strategies for tumour-agnostic therapies could include a stepwise introduction through the conduct of multiple RCTs, a basket trial with a limited number of tumour locations and more patients per location, or multiarm trials. These strategies will introduce different types of uncertainty (e.g., missing tumour locations or later access for some tumour locations), but they might enable more evaluable patients per tumour location, as was desired by HTA organisations and guideline developers. As such, it could provide more precise effectiveness estimates in subgroups. These alternative strategies could also facilitate a comparative strategy that is currently lacking because other study protocols showed that comparative basket trials have been performed.[p78],[p79],[p80],[p81],[p82] The feasibility of these alternative approaches to obtain a tumour-agnostic indication was demonstrated by pembrolizumab for microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) solid tumours, which was the first tumour-agnostic indication in the USA.[p83] This indication was pursued after some tumour-specific MSI-H/dMMR indications had been authorised based on separate RCTs. Additionally, the dabrafenib and trametinib combination was authorised for BRAF V600-mutated cancers in the USA based on a multiarm clinical trial.[p56]

The preferences of stakeholders for each of these strategies and their corresponding uncertainties should be weighed case-by-case and discussed before trial design and assessment.[p73],[p84] Early multistakeholder dialogues could be used to discuss which questions might or might not be answered (in a timely manner) and which require postauthorisation data or other risk management strategies. This approach should determine whether these evidence-generation strategies, accompanied by their uncertainties, outweigh the benefits of (directly) granting a full tumour-agnostic indication. If the discussed strategy is broadly supported by stakeholders (developers, regulators, HTA representatives, clinicians, trialists, and patients), such dialogues could prevent or reduce some of the uncertainties and improve mitigation or anticipation of the remainder.[p17],[p67] However, reaching agreement across institutions could prove difficult.[p85],[p86],[p87] Early multistakeholder dialogue was perceived by European healthcare experts as a concept preceding or in parallel to scientific consul-

tations. In this way, it acts as an extension to the current parallel joint scientific consultations by the EMA and EUnetHTA21, allowing for a translation of the discussed evidence generation and uncertainty considerations into scientific advice for the health technology developer.[p67],[p88]

Optimise parallel joint scientific consultations

For entrectinib, the EMA provided scientific advice on the tumour-agnostic indication as part of the PRIME scheme. However, the EMA still listed a considerable number of uncertainties regarding the pivotal trials, the MA vote lacked consensus (in contrast to larotrectinib), and HTA organisations described many challenges and adopted recommendations that were slightly more restrictive than for larotrectinib.[p4],[p34],[p35],[p43] Without exact knowledge of the underlying discussions, this leaves the impression that the scientific advice procedures could have been used more optimally. Developer guidance provided by NICE, which was in place before the introduction of the tumour-agnostic therapies, stated the recommendation to seek scientific advice from HTA organisations as well as from the EMA.[p43],[p89] However, it is unclear from the documents whether this happened, what might have been discussed, or whether recommendations were followed by the health technology developers.

The postauthorisation requirements imposed by the EMA focused on resolving its major remaining uncertainties, confirming the tissue-independent efficacy, exploring mechanisms for resistance, and assessing the long-term safety and effects of genetic molecular alterations.[p76] HTA organisations likewise expressed concerns about confirming the tissue-independent efficacy of the therapies, while also expressing concerns regarding the lack of (long-term) OS and QoL data, low generalisability of the trial population to clinical practice, lack of comparative evidence, and undefined treatment pathways in different tumour locations.[p73] Notably, if better aligned on content and timing, the EMA's postauthorisation requirements could have also addressed some HTA concerns.[p16],[p73],[p90],[p91] Other concerns can only be studied through additional (real-world) studies, such as the implementation of *NTRK* testing strategies and other eligibility criteria to allow more continuous monitoring and management of access to these therapies in clinical practice. The use of real-world studies should be discussed in early dialogues.[p90],[p91] Such discussions could be considered in the EU-HTAR and revision of the general pharmaceutical legislation that seek to strengthen joint parallel scientific consultations by the EMA and HTA organisations.[p92],[p93]

Involve clinicians in all healthcare decision-making processes along the medicine lifecycle

The broadness of the language used in the EMA indication aimed to allow for flexibility in clinical decision-making, enabling access to treatment for patients who might otherwise be excluded (i.e., patients for which therapies of limited efficacy are recommended in guidelines).[p4],[p5] The use of larotrectinib and entrectinib by such patients was also recommended in various guidelines. However, the broadness of the indication was difficult for HTA organisations to translate into specific treatment lines in which the products would be used. In addition, HTA organisations expressed concerns about the financial and organisational impact of *NTRK* gene fusion testing on their healthcare systems.[p72],[p89] Consequently, the number of eligible patients was difficult to determine. If *NTRK* gene fusion-testing strategies or other eligibility criteria are not properly implemented, there is a risk of inappropriate or cost-ineffective treatment, which could also lead to a substantial budgetary impact.

Besides the challenges for regulators, HTA organisations, and guideline developers, the variation in guideline recommendations emphasises the difficulties that prescribing clinicians might experience when discussing the available evidence with their patients. Informing patients about the effectiveness and side effects that can be expected in their unique situation is particularly complicated by the small number of trial patients per tumour location. It is important to involve clinicians in decision-making processes along the medicine lifecycle. For example, clinical evidence preferences (e.g., on endpoints or side effects) and practical implementation considerations (e.g., testing strategies) could be discussed with clinicians during the early multistakeholder dialogues. In addition, the effects that accepting uncertainty in the recommendations for tumour-agnostic therapies has on clinical treatment practice should be carefully considered in decision-making. Some of the uncertainties accepted in MA or reimbursement decisions trickle down as uncertainties for patients when making treatment decisions.[p17]

However, the guidelines also provided opportunities. First, they provided a rather pragmatic, sometimes stepwise, approach to testing procedures and treatment line strategies. For example, some guidelines recommended testing only after the failure of previous tumour-specific treatments. Second, the guidelines considered the endpoints for individual tumour locations rather than following the agnostic rationale. This resulted in the uptake of larotrectinib and entrectinib in guidelines only for tumour locations that were most represented in the trials, which were the tumour locations with the highest prevalence of *NTRK* gene fusions. The guideline uptake resolved the concerns of the EMA and HTA regarding the over-representation of rare diseases and under-representation of common diseases, which likewise contrasted the tumour-agnostic thinking because representation was mostly in line with the prevalence of *NTRK* gene fusions.[p4],[p5]

These examples reflect the time-related nature of some uncertainties considered by regulators and in HTAs because guideline recommendations naturally resolved some of them. Therefore, the examples stress the relevance of the early and continuous involvement of the clinical perspective in the decision-making processes along the medicine lifecycle. Although clinicians are often involved at some point(s) in the regulatory and HTA processes, more timely and continuous involvement could be valuable, combining all stakeholder perspectives ideally before the design of the trial.[p94] In addition, reassessments by the EMA and HTA organisations in a lifecycle approach and living guidelines could address uncertainties in a more timely manner as new evidence becomes available.[p16],[p95],[p96] Lastly, the distinction based on prevalence and representation visible in clinical guidelines (i.e., the clinical perspective) could also provide opportunities for economic risk management strategies in the form of pricing and reimbursement based on *NTRK* prevalence.

Concluding remarks

Tumour-agnostic therapies, which target tumours independent of location or histology, introduced a new approach to indication-setting for personalised medicine. Studying the disruption to healthcare decision-making caused by this shift in indication setting and the limitations to the underlying evidence provides valuable lessons for future therapies sharing similar alterations in evidence generation and assessment.

All decision-makers agreed to the potential of both therapies but addressed the limited population size for each tumour location. Differences in the acceptance of uncertainty were observed in the basket trials designed to establish the efficacy/effectiveness of the treatment and the prognostic value of *NTRK* gene fusions as a biomarker and ORR as the primary endpoint. This discrepancy in acceptance led to differences in accepting the rationales behind tumour agnosticism and the effectiveness of sequential treatment with multiple TRK inhibitors. Uncertainty because of the lack of comparator has resulted in diverse comparative strategies and varying conclusions regarding the UMN. Similar differences were observed for *NTRK* gene fusion-testing approaches. These varying uncertainty considerations affected the sequential decision-making process, as illustrated by the broad indications for therapies, which resulted in difficulties in defining and quantifying patient populations at the HTA level. Generally, tumour-agnostic therapies required high acceptance of uncertainty by decision-makers, which resulted in differences in the way this uncertainty was perceived.

For future disruptive therapies, early multistakeholder dialogue among regulators, HTA organisations, clinicians, and patients is recommended to discuss the development strategies and minimum evidence requirements for establishing a tumour-agnostic indication and practical issues, such as testing strategies to identify suitable patients. This discussion should be followed by (or in parallel to) scientific consultations for health technology developers. This approach could improve the suitability of scientific consultations and postauthorisation requirements for all decision-makers. In doing so, it could prevent or reduce uncertainty, or at least allow for the anticipation and mitigation of uncertainty. These dialogues and the joint parallel scientific consultations should involve clinicians early and continuously as a means for preventing uncertainties and aligning decisions to the needs of clinical treatment practice.

Authors' contributions

M.H. and L.B. conceptually shaped the review. C.H. collected documents and extracted the data under the supervision of M. H. and L.B. C.H. and M.H. performed the content analysis and prepared the manuscript, while G.S., A.M., W.G., and L.B. provided input on the analysis, and reviewed and edited the manuscript. All authors approved the final version.

Declaration of interests

This study was conducted and finalised while M.H. was a PhD candidate at Utrecht University. After her PhD, she started working for Roche Nederland B.V. W.G. worked part-time for the Dutch National Health Care Institute (Zorginstituut Nederland) during the conduct of this study. G.S. received institutional research support from Agendia, AstraZeneca, Merck, Novartis, Roche, and Seagen, and consulting fees from Biovica and Seagen, all outside the scope of this study. The other authors have no competing interests to declare.

CRediT authorship contribution statement

Milou A. Hogervorst: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Christine C. van Hattem:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis. **Gabe S. Sonke:** Writing – review & editing, Investigation. **Aukje K. Mantel-Teeuwisse:** Writing – review & editing, Investigation. **Wim G. Goettsch:** Writing – review & editing, Investigation. **Lourens T. Bloem:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Investigation, Conceptualization.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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