A review of health technology assessments conducted for tumour-agnostic therapies across the UK and EU4

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HTA61

01 BACKGROUND

- Tumour-agnostic therapies target common genetic and molecular features across multiple tumour types.[1]
- Unlike traditional treatments, which are often specific to one type of cancer, these therapies offer the potential to treat a wide range of cancers by focusing on shared mechanisms such as gene mutations, cellular pathways, or immune targets.[1,2]
- Two medications have gained regulatory approval in Europe for a tumour-agnostic indication: larotrectinib and entrectinib, both for neurotrophic tyrosine receptor kinase (NTRK) fusion-positive solid tumours.[3,4]
- Several tumour-agnostic therapies are expected to receive approval over the next decade.[5]

02 OBJECTIVES

- This study reviewed health technology assessments (HTAs) conducted for larotrectinib and entrectinib across the EU4 (France, Germany, Italy, Spain) and the UK (England, Scotland).

03 METHODS

- A targeted review of HTA agency websites (National Institute for Health and Care Excellence [NICE], Scottish Medicines Consortium [SMC], Gemeinsamer Bundesausschuss [G-BA], Haute Autorité de Santé [HAS], Agenzia Italiana del Farmaco [AIFA], Agencia Española de Medicamentos y Productos Sanitarios [AEMPS]) was conducted on the 12th of April 2024 to identify HTA documentation for larotrectinib and entrectinib.
- The reimbursement outcome, clinical and economic evidence and the HTA body evaluation of the submitted evidence were analysed.

04 RESULTS

Outcomes

Identified HTAs

- A total of 11 HTAs were identified across 6 countries: 5 for larotrectinib and 6 for entrectinib.

Reimbursement outcomes and key drivers

- Positive reimbursement outcomes were achieved in 91% (10/11) of the assessments (**Table 1**).
  - Non-conditional, non-restrictive outcomes (5 HTAs [Scotland,[6] Germany,[7,8] and Italy[9,10]]) were primarily driven by clinically relevant overall response rates (ORRs).[6–10] In Germany, the absence of a comparison to the appropriate comparator therapy (ACT) resulted in a "no additional benefit" rating in both assessments.[7,8]
  - Conditional outcomes (additional data collection requests; 4 HTAs [England[11,12] and Spain[13,14]]) were driven by the absence of a trial comparator, immature survival data, and concerns about the generalisability of the trial populations to real-world practice.[11–14]
  - A restricted reimbursement for larotrectinib in France to 2 tumour types was due to a perceived lower clinical benefit or insufficient data in the other tumour types.[15]
  - The negative reimbursement outcome for entrectinib in France was due to an unfavourable efficacy/safety profile, a limited trial follow-up period, the absence of a trial comparator, and the availability of larotrectinib.[16]

Clinical evidence

Submitted clinical evidence and HTA body evaluation

- In all assessments (100%; 11/11), data were derived from open-label, single-arm phase 1 or 2 trials.[156–14,16] In 90% of these (10/11) data were pooled across multiple tumour types;[6–14,16] In the assessment for larotrectinib in France, tumour-specific data for 2 tumour types were presented.[15]
  - A major critique across assessments was the absence of a trial comparator.[6–8,12,15]
- Due to the absence of a trial comparator, synthetic comparator analyses were submitted in 55% (6/11) of assessments (**Table 2**).[6–8,11,12,15]
  - Comparative analyses were accepted in England and Scotland (3/6; 50% of assessments).[6,8,11,12] However, NICE and the SMC acknowledged that the analyses were associated with potential biases and that uncertainty in the clinical benefit remained.[6,8,11,12]
  - In France and Germany (3/6; 50% of assessments) the G-BA and HAS stated that they were unable to assess comparative efficacy due to methodological issues with the analyses, such as missing patient covariates or data not reflecting clinical practice.[7,8,15]

Economic

Submitted economic model and HTA body evaluation

- Where required (27% of assessments [3/11; England and Scotland]), a single cost-utility analysis model generating a pooled incremental cost-effectiveness ratio (ICER) across multiple tumour types was submitted (**Table 3**).[6,11,12]
  - In England, NICE stated that the modelled populations, based on the distribution of tumour types in the trial, were not generalisable to NHS practice.[12]
  - In Scotland, the SMC accepted the pooled analysis after scenario analyses demonstrated that the ICER remained reasonably stable to the exclusion of individual tumour types.[6]
- In 66% (2/3) of the economic analyses, testing costs to identify NTRK-fusion-positive patients were incorporated into the sponsor's base-case model.[6,12]
  - In England, NICE requested the inclusion of testing costs for larotrectinib as testing for NTRK mutations across all tumour types is not standard practice in NHS England.[11]
  - Both NICE and the SMC considered testing costs for entrectinib to be uncertain, pending the establishment of a national service for genomic testing.[6,12]

Table 1: Overview of reimbursement outcomes and key drivers for the 11 HTAs

Country	Drug	Recommendation		Key drivers of outcome
		Outcome (condition/restriction) detail)	Per tumour or per label	
Cost-effectiveness markets				
England	Laro[11]	+ (+) for use within the CDF	Label	• Clinically relevant ORR • Uncertain survival (immature data) • Concerns on population generalisability to NHS practice • (*Entr only*) Some CE estimates exceeded WTP threshold
	Entr[12]			
Scotland	Entr[6]	+ (-)	Label	• Clinically relevant ORR • Orphan designation permitted greater economic uncertainty
Clinical-effectiveness markets				
Germany	Laro[7]	+ (-) no additional benefit	Label	No data comparing against ACT (BSC and surgery)
	Entr[8]			
France	Laro[15]	+ (+) minor improvement in ASMR; approved on the basis of further RWD collection	Per tumour*	• High ORRs in IFS and other STSs • Uncertainty of efficacy/safety in other tumour types • Lack of trial comparator; unadjusted ITC unsuitable due to methodological limitations
	Entr[16]	- (-)	NA	• Limited data from single-arm study • Significant toxicity and limited follow-up • Alternative (Laro) already available* • No comparison to Laro* • Several lines of chemo (BSC) also available
Italy	Laro[9]	+ (-)	Label	Clinically relevant ORR
	Entr[10]			
Spain	Laro[13]	+ (+) on the basis of further data from ongoing studies	Label	• Clinically relevant ORR • Low rate of SAEs and treatment discontinuations • (*Laro only*) No OS and PFS in specific tumour types (pooled data)
	Entr[14]			

+(-), approved without any restriction or conditions; +(+) approved with conditions or restrictions; -(-) not approved
*IFS and other paediatric STSs only
ACT, appropriate comparator therapy; ASMR, Amélioration du service médical rendu; BSC, best standard of care; CDF, Cancer Drugs Fund; CE, cost-effectiveness; Entr, entrectinib; HTA, health technology assessment; IFS, infantile fibrosarcoma; ITC, indirect treatment comparison; Laro, larotrectinib; NA, not applicable; NHS, National Health Service; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RWD, real-world data; SAE, serious adverse event; STS, soft tissue sarcoma; WTP, willingness to pay

Table 2: Analyses used to derive a synthetic comparator

	Larotrectinib					Entrectinib					
	England[11]	Germany[7]	France[15]	Italy[9]	Spain[13]	England[12]	Scotland[6]	Germany[8]	France[16]	Italy[10]	Spain[14]
Comparative analyses											
Unadjusted ITC	✓					✓	✓	✓			
Response-based analysis	✓					✓					
Previous line of treatment	✓	✓	✓			✓					
PSM											
PSW			✓					✓			

ITC, indirect treatment comparison; PSM, propensity score matching; PSW, propensity score weighting;
Unadjusted ITC: Individual arms of different trials are compared naively as if they were from one single controlled trial
Response-based analyses: Uses effectiveness data on non-responders as a proxy for patients not receving an active treatment;
Previous line of treatment: Compares the outcomes for people on the drug with their outcomes on the previous line of therapy;
PSM: Compares treatment outcomes across matched sets of treated and untreated subjects who share a similar value of the propensity score;
PSW: Uses the propensity score to balance baseline patient characteristics in treated and untreated groups by weighting each individual by the inverse probability of receiving their actual treatment

Table 3: Summary of submitted economic evidence

Country	Drug	Submitted model	Key feedback from HTA body				
			Model structure	Population	ICER	Testing costs	Additional comments
England	Laro[11]	A 3-state survival model with comparator arm generated using 12 engines per tumour type, with each generating its own outcomes, QoL, and costs. Results were pooled and weighted by tumour type distribution in the Laro trials	The appropriate model structure is uncertain and could be explored more fully when data from CDF are available	The modelled population is not representative of NHS practice, and effectiveness data by tumour type would be required to improve generalisability	Highly uncertain due to immature trial survival data	Diagnostic testing costs should be included	Laro was likely to be cost-effective if it met the EOL criteria
	Entr[12]	A 3-state survival model used NICE HTAs to derive median PFS and OS data for the comparator arm. These values were averaged, applied to IPD data, converted to means, and weighted by tumour type in the Entr trials	Same as above	Same as above	Highly uncertain due to immature trial survival data and modelled population	Not appropriate to include diagnostic testing costs in comparator arm	Entr may be cost-effective with a PAS if it met EOL criteria
Scotland	Entr[6]	A 3-state survival model used median PFS and OS from literature for the comparator arm, converted to mean values via exponential extrapolation	Producing CE results by tumour type is challenging due to small patient numbers with each tumour type in pooled Entr study data	Requested scenario analyses showed the ICER to be reasonably stable to the exclusion of individual tumour types, reducing the uncertainty in the pooled ICER	Highly uncertain due to immature trial survival data	Uncertainty regarding testing cost allocation due to NHS Scotland's future commitment to routine NGS testing for all cancer patients	–

CE, cost-effectiveness; CDF, cancer drugs fund; Entr, entrectinib; EOL, end of life; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; Laro, larotrectinib; NGS, next generation sequencing; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; QoL, quality of life

05 DISCUSSION AND CONCLUSIONS

- **While reimbursement outcomes for larotrectinib and entrectinib were predominantly positive, variations in assessment criteria lead to disparities in evidence acceptance and reimbursement outcomes between HTA agencies.**
- **Uncertainty in the comparative clinical benefit was a key concern; while synthetic comparative analyses were accepted in England and Scotland, perceived methodological limitations in these analyses meant that agencies in Germany and France were unable to assess them.**
- **Conditional outcomes based on further data collection were common, highlighting the value of real-world registries such as the CDF's Systemic Anti-Cancer Therapy (SACT) in managing the uncertainty in the evidence base for tumour-agnostic therapies.**
- **To ensure timely and equitable access to tumour-agnostic therapies, HTA frameworks that clearly outline clinical and economic requirements are required.**

References

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