HTA13

How Health Technology Assessment Agencies View Clinical Evidence for Tumor Agnostic Therapies

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Introduction

- Traditionally, tumors have been treated based on their site of origin rather than their specific characteristics.
- Recent advances in powerful technologies that allow for a more rapid and accurate understanding of tumor biology have led to the development of tumor agnostic therapies, which target unique genetic molecular features of the tumor.
- Since health technology assessment (HTA) agencies play a key role in patient access to therapies, it is important to consider the way in which they evaluate tumor agnostic therapies and how this differs from traditional cancer treatments.
- We set out to understand how HTA agencies critique and assess clinical and economic evidence submitted in support of tumor agnostic therapies (typically based on non-comparative basket trials), and how this influences their final decisions.

Methods

- HTA reports were reviewed on May 24, 2022, to understand how evidence from basket trials is viewed and assessed by different HTA agencies.
- A targeted research analysis was conducted, focusing on two tumor agnostic therapies (larotrectinib and entrectinib) and HTA reports from five key markets (Australia, Canada, England, France and Germany).

Results

- Larotrectinib was assessed as a treatment for patients with solid tumors that display a neurotrophic tyrosine receptor kinase (NTRK) gene fusion by all five HTA agencies, while entrectinib was appraised in the same indication by only the English, German and French agencies.
- An overview of the outcomes for the five HTA agencies is presented in **Figure 1**.
- The clinical evidence submitted for each drug was consistent across markets (single-arm Phase 1 dose escalation and Phase 2 basket trials), with several overlapping themes cited by the agencies in their assessments of the evidence **(Figure 2)**.
- Key limitations mentioned included a lack of trial data directly comparing the drug with established management, premature survival data and limited data for each of the tumor types, all of which meant that the size of true benefit of each drug was difficult to measure.
- Lack of data on the potential prognostic importance of NTRK gene fusions and the heterogeneity on anti-tumor response by tumor type was cited as an issue by most agencies.
- In terms of economic evidence, only Australia, Canada and England submitted economic analyses for larotrectinib. The cost-effectiveness estimates were generally deemed very uncertain for the following reasons: lack of direct comparative data, small patient numbers across studies, patient population not representative of real-world population, immaturity of data, and heterogeneity within and between tumor types.
- For entrectinib, an economic analysis was submitted to the English agency only; all modelling approaches were reported as having limitations, such as not accounting for tumor types included in the entrectinib trials and were therefore considered uncertain.
- Despite alignment in critique across markets, the assessments led to divergent outcomes, with some countries granting reimbursement according to the label, or with restricted usage, while others providing an outright rejection/unfavorable opinion **(Figure 1)**.

Conclusions

- Despite an era of personalized healthcare, problems still remain in HTA assessments of tumor agnostic therapies. There is a lack of recognition for tumor agnostic therapy trial designs, with no uniformity in assessment criteria.
- Investment in comprehensive, high-quality gene testing techniques is required to help determine the prognostic value of NTRK gene fusions and inform treatment. In turn, health systems need to be prepared to implement routine diagnostic testing with an NTRK gene fusion detection strategy as part of clinical management.
- There is a need for alignment between HTA bodies and development of adaptive HTA processes to increase positive reimbursement of HTA submissions based on proven surrogate endpoints, alternative clinical trial designs and immature clinical data. Such initiatives will help accelerate patient access to potentially life-saving therapies. This is particularly true in areas such as oncology where the unmet need remains very high.

	Larotrectinib			Entrectinib		
	Label	Appraised (Y/N)	HTA outcome	Label	Appraised (Y/N)	HTA outcome
Australia (PBAC)	Adult and pediatric patients with locally advanced or metastatic solid tumors that: • Have a NTRK gene fusion without a known acquired resistance mutation • Are metastatic or where surgical resection is likely to result in severe morbidity • Have either progressed following treatment or who have no satisfactory alternative therapy	Y	⊖	Adult and pediatric patients 12 years of age and older with solid tumors that: • Have a NTRK gene fusion without a known acquired resistance mutation • Are metastatic or where surgical resection is likely to result in severe morbidity • Have either progressed following treatment or have no satisfactory alternative therapy	N	N/A
Canada (CADTH)	Adult and pediatric patients with solid tumors that: • Have a NTRK gene fusion without a known acquired resistance mutation • Are metastatic or where surgical resection is likely to result in severe morbidity • Have no satisfactory treatment options	Y	✓	Adult patients with unresectable locally advanced or metastatic extracranial solid tumors, including brain metastases, that have: • A NTRK gene fusion without a known acquired resistance mutation • No satisfactory treatment options	N	N/A
England (NICE)	Adult and pediatric patients with solid tumors that display a NTRK gene fusion who have: • A disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity • No satisfactory treatment options	Y	✓	Adult and pediatric patients 12 years of age and older with solid tumors expressing a NTRK gene fusion who have: • A disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity • Not received a prior NTRK inhibitor • No satisfactory treatment options	Y	✓
France (HAS)	Adult and pediatric patients with solid tumors that display a NTRK gene fusion who have: • A disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity • No satisfactory treatment options	Y	⊕	Adult and pediatric patients 12 years of age and older with solid tumors expressing a NTRK gene fusion who have: • A disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity • Not received a prior NTRK inhibitor • No satisfactory treatment options	Y	⊖
Germany (GBA)	Adult and pediatric patients with solid tumors that display a NTRK gene fusion, who have: • A disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity • No satisfactory treatment options	Y	⊖	Adult and pediatric patients 12 years of age and older with solid tumors expressing a NTRK gene fusion who have: • A disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity • Not received a prior NTRK inhibitor • No satisfactory treatment options	Y	⊖

✓ *Reimbursed* ⊕ *Reimbursed in restricted population* ⊖ *Reimbursement application rejected (HTA agency did not recommend that the product be reimbursed for the indication assessed)*

Figure 1. HTA outcomes for larotrectinib and entrectinib in patients with solid tumors harboring a NTRK gene fusion in five key markets.

Information on the labels, appraisals and HTA outcomes were sourced on the date of initial review (May 24, 2022)
CADTH: Canadian Agency for Drugs and Technologies in Health; GBA: Gemeinsamer Bundesausschuss; HAS: Haute Autorité de Santé; HTA: Health technology assessment; N: No; N/A: Not applicable as no appraisal was conducted; NICE: National Institute for Health and Care Excellence; PBAC: Pharmaceutical Benefits Advisory Committee; NTRK: Neurotrophic tyrosine receptor kinase; Y: Yes

	Limitations of clinical and economic evidence presented													
	Larotrectinib									Entrectinib				
	Clinical					Economic				Clinical				Economic
HTA (Agency)	Lack of appropriate comparator	Patient population not generalizable to clinical practice	Heterogeneity in tumor response not assessed	Uncertain benefit on long-term survival	Immature data/lack of evidence	Uncertainty in incremental benefit	Patient population not representative of clinical practice	No representation of heterogeneity in tumor response	Lack of evidence/ comparator data	Lack of evidence/ comparator data	Heterogeneity in tumor response not assessed	Immature survival data	Uncertainty in prevalence of NTRK fusions/ patient population estimates	Uncertainty in incremental benefit
Australia (PBAC)	—	!	—	!	!	!	!	!	!	N/A				
Canada (CADTH)	!	—	!	!	!	!	—	!	!	N/A				
England (NICE)	!	!	!	!	!	!	!	—	—	!	!	!	!	!
France (HAS)	!	—	—	!	!	—	—	—	—	!	!	—	!	—
Germany (GBA)	!	!	!	!	!	—	—	—	—	!	!	—	!	—

! *Highlighted by HTA agency as a limitation of evidence presented*

Figure 2. Key critique details across the five HTA agencies for larotrectinib and enterectinib.

CADTH: Canadian Agency for Drugs and Technologies in Health; CEM: cost-effectiveness model; GBA: Gemeinsamer Bundesausschuss; HAS: Haute Autorité de Santé; HTA: Health technology assessment; N/A: Not applicable as no appraisal was conducted; NICE: National Institute for Health and Care Excellence; NTRK: Neurotrophic tyrosine receptor kinase; PBAC: Pharmaceutical Benefits Advisory Committee

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