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ANALYSIS

How should we assess the clinical and cost effectiveness of histology independent cancer drugs?

Sophie Cooper, Jacoline Bouvy and colleagues discuss the challenges that histology independent cancer drugs will pose for NICE and the NHS

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A histology independent cancer drug targets all solid tumours with a certain genomic mutation, regardless of the primary tumour's histology.[1] The US Food and Drug Administration (FDA) has approved three histology independent drugs (pembrolizumab, larotrectinib, and entrectinib) since 2017, and the European Medicines Agency (EMA) approved the first histology independent drug for the European market in 2019 (larotrectinib) (fig 1). Health technology assessment (HTA) bodies, including the National Institute for Health and Care Excellence (NICE), will therefore soon have to assess the value of these drugs to healthcare systems. Histology independent drugs are indicated for a multitude of tumour types, as long as they express the mutation. The prevalence of these mutations is often low, so the clinical evidence to inform reimbursement decisions for histology independent drugs will be immature and based on studies with extremely small sample sizes. This will make it challenging to assess whether the drug will provide value for money to health systems such as the NHS.

Clinical evidence for histology independent cancer drugs

NICE in England requires evidence of a drug's clinical and cost effectiveness to decide whether the drug should be recommended for use in the NHS. Methods to inform these recommendations are commonly referred to as HTA, and the organisations responsible for making these recommendations as HTA bodies. Methods and processes vary between countries, but HTA usually starts around the time a new drug receives a marketing authorisation from the EMA. National HTA bodies will assess the added value of the drug to their healthcare systems, and the clinical studies available to inform HTA are usually those that supported the marketing authorisation. However, although a marketing authorisation can be granted when there is enough evidence that the drug is efficacious and safe to use, HTA bodies also need to be satisfied the drug is clinically effective and offers good value for money.

Because the prevalence of the biomarkers that are targeted by histology independent drugs can be low, conducting randomised controlled trials is not always feasible. Histology independent drugs are developed in basket trials instead, which can test a drug in multiple rare indications simultaneously. A basket trial's population consists of patients with many different tumour histologies but the same genomic mutation, who will all receive the same drug. Basket trials do not usually include a comparator arm, which makes randomisation impossible. They generally have the primary endpoint of objective response rate, which captures the number of patients who have had a minimum pre-defined reduction in tumour size. Response rate allows the pooling of responses across different tumour histologies but is a surrogate outcome for progression-free survival and overall survival, which are typically preferred for HTA.[2] When only response data are available, assumptions need to be made about the drug's clinical benefit, which increases the uncertainty in the HTA. NICE assesses a drug's clinical effectiveness based on health outcomes that are important to patients and their carers.[3] To be recommended by NICE, a drug must show an effect on survival or health related quality of life.[3]

Regulatory agencies such as the EMA can grant marketing authorisation if enough evidence shows the drug's positive benefit-risk ratio, which does not necessarily require evidence of how well the drug compares with other treatments. The EMA and the FDA have considered that a high response rate with a long duration of response in a basket trial is enough to support a histology independent cancer drug's efficacy (fig 1). The

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response rate of 55 patients treated with larotrectinib in a basket trial including 17 different tumour histologies, for example, was 75%, with 71% of those responses lasting >1 year (fig 1).[4]

When a drug is approved by regulators based on a single arm trial, its clinical effectiveness can only be estimated by indirect comparisons with external controls (data from an unrelated, previously conducted study). This can result in biased effectiveness estimates, so HTA bodies are usually cautious about drawing conclusions from such evidence.[5] External controls for histology independent drugs that target a novel biomarker will include people with and without the biomarker. In such cases, there is no way of knowing whether people with the biomarker who take the histology independent drug would have had a better, similar, or worse prognosis than a patient who received the comparator treatment. So, when we know only the average treatment effect in the external control population and have no reliable evidence on the biomarker's prognostic properties, estimating the clinical effectiveness of a histology independent drug will be extremely difficult.

Histology independent drugs that have received marketing authorisations from the FDA or the EMA thus far did not have a standardised diagnostic test available at the time. This will make it difficult to assess how well basket trial populations reflect eligible patients in clinical practice, as the testing strategy in the NHS will probably differ from the patient selection strategy used in the basket.

Although NHS England has announced the introduction of a new NHS Genomic Medicine Service that will provide routine genomic testing in England, the service is still in the process of being rolled out in the NHS.[6] Unless all patients with cancer receive routine genomic testing, it will be difficult to predict which patients will be treated with a histology independent cancer drug in the NHS. Treating NHS patients earlier or later in the treatment pathway than patients in the basket trial will change the relevant comparator treatment, which differs by treatment line and tumour type. This will complicate estimating the drug's clinical and cost effectiveness before the drug is introduced in clinical practice.

A histology independent indication is likely to cover many clinically distinct subpopulations of tumour that have different standard treatments. So, patients' baseline disease stage, prognosis, health related quality of life, and healthcare costs will vary across tumour types covered by the marketing authorisation. This will lead to substantial variation in relevant outcomes that influence the clinical and cost effectiveness of the drug. Normally, HTA includes subgroup analysis for clinically distinct subgroups. But basket trials recruit only a few patients with each histology, leading to insufficient statistical power for subgroup analysis. In such cases, NICE will need to make a recommendation based on the average cost effectiveness of the drug across the patient population covered by a histology independent marketing authorisation. This might not convey enough information to decision makers about whether the drug provides value for money for all the different tumour histologies.

These problems, together with the lack of mature data on progression-free and overall survival, will make reimbursement decisions difficult. Without sufficient evidence to support a recommendation, healthcare systems might have to restrict patient access to the drug. Decision makers might be willing to grant conditional patient access until a final recommendation is made when more evidence is available; for example, after postauthorisation studies are finalised or through the Cancer Drugs Fund. But not every healthcare system has processes and infrastructure in place that would allow for conditional reimbursement. Most HTA bodies, including NICE, plan periodic reassessment of recommendations; others reassess randomly or never revisit recommendations.[7] HTA evaluations should be appropriately timed so that enough evidence is available to inform a recommendation.

The lack of clinical evidence for a wide range of possible tumour types will make it difficult for clinicians to make evidence based recommendations on the best treatment option for a patient who is identified in clinical practice with a biomarker positive tumour that is covered by the marketing authorisation but was not included in the basket trial. Data collection in clinical practice will be essential to reduce the uncertainty about how the drug should be used in the NHS and to enable patients and clinicians to make informed decisions.

Collecting data on the clinical effectiveness of histology independent drugs, through postmarketing studies or data collection in clinical practice, might help reduce clinical uncertainty and will enable more informed recommendations to be made. However, European payers and HTA bodies remain hesitant to use data collection arrangements on a wide scale.[8] Many payers prefer to manage decision uncertainty by negotiating price discounts rather than using more complex arrangements that require data collection.

Introduction into healthcare systems

Managed access funds, such as the Cancer Drugs Fund in England (box 1), could support the introduction of histology independent cancer drugs into healthcare systems.[9] In other countries, initiatives such as the European network for HTA might help to explore data collection possibilities. In countries that do not have a managed access fund, HTA bodies might rely on postauthorisation evidence generated as part of the drug's conditions for marketing authorisation or other planned or ongoing studies sponsored by the company that makes the drug.

Box 1: The Cancer Drugs Fund

The Cancer Drugs Fund provides a mechanism for data collection to reduce clinical uncertainty about a cancer drug outside of the clinical development programme. This can be particularly helpful for rare cancers, for which clinical trial recruitment is low. When a NICE appraisal committee recommends a cancer drug for use through the Cancer Drugs Fund, data can be collected through the Public Health England systemic anti-cancer therapy dataset. Other data sources can also be used, including ongoing clinical trials, patient registries, or named patient programmes. Drugs must meet several criteria to enter the fund: they must have the potential to be cost effective at the current price, and there must be uncertainty about their clinical effectiveness that could be reduced through additional data collection.[9] Cancer drugs spend a limited time in the fund (usually not longer than two years) to facilitate the data collection, after which NICE needs to make a final recommendation on whether the drug should be used in the NHS.

Drug companies, regulatory agencies, and HTA bodies should work together to discuss the evidence generation strategy for histology independent drugs before they enter the market. The use of basket trials for these types of drugs can make the job of HTA bodies much more difficult. Early interactions with companies can help HTA bodies make relatively informed recommendations, especially around facilitating timely discussion about what additional data collection might be required. This will enable reimbursement decisions to be made without causing unnecessary delays to patient access. Some of the challenges that HTA bodies face now that the first histology independent cancer drugs are coming to market could have been prevented or mitigated through earlier and better consideration of HTA evidence requirements, using mechanisms such as the European Medicines Agencies adaptive pathways initiative.[10] Even with these mechanisms available, companies can decide whether they seek early interactions or not.

Postauthorisation evidence generation

Regulatory agencies frequently require the collection of additional safety or efficacy data as part of the conditions for marketing authorisation. But one study found that patient registries requested by the EMA were hindered by delayed start times, low patient accrual rates, and delayed completion of studies.[11] Another study found that evidence of survival benefit was still not available for 44 of 68 cancer drug indications a median of 5.4 years after they were approved without evidence of a survival benefit at marketing authorisation.[12] Even when postauthorisation studies are being planned or under way, they might not be able to rapidly decrease the substantial uncertainty about a histology independent cancer drug's clinical and cost effectiveness.

Conclusions

Histology independent cancer drugs might offer substantial health benefits to patients and could provide treatment options for patients with rare tumour types, for whom none currently exists. The evidence available to inform HTAs, however, will be so limited that assessing whether the drug should be recommended for use in the NHS will be difficult. Basket trials provide evidence on only the few histologies that were included in the trial, and without a standard diagnostic test we can't predict which patients would receive the drug in practice and, therefore, estimate the clinical and cost effectiveness of the drug. Even if a drug has a similar absolute effect across different histologies, the variation in clinical context and costs in each setting will affect the estimates that inform reimbursement decisions.

Healthcare systems wanting to facilitate patient access to histology independent cancer drugs will need to rely on postauthorisation evidence generation, as the marketing authorisation is likely to be granted without mature evidence on the drug's efficacy on progression-free survival and overall survival. For future histology independent drugs, companies should seek early scientific advice from HTA bodies to avoid a lack of evidence delaying patient access. For the histology independent cancer drugs that are already being appraised by HTA bodies, we don't know whether decision makers will deem the substantial uncertainty about the drugs' clinical and cost effectiveness acceptable against the drugs' potential health benefits. The Canadian Agency for Drugs and Technologies in Health (an HTA body) published a "do not reimburse" recommendation for larotrectinib in November 2019.[13] Whether patients will gain access to these new drugs will vary in different countries, depending on the opportunities for conditional reimbursement arrangements, infrastructure for postauthorisation evidence generation, and the willingness and appetite for risk sharing between healthcare systems and companies.

Key messages

- A histology independent cancer drug targets any solid tumour with a certain genomic mutation, regardless of the histology of the primary tumour. Its therapeutic indication therefore will include a multitude of tumour sites, as long as they express the mutation
- These drugs are developed in basket trials that do not include a comparator arm or randomisation procedure, that include only a handful of patients per tumour type, with the primary endpoint of objective response rate. This will make it very challenging to assess whether the drug provides value for money to the NHS
- Companies developing histology independent cancer drugs should seek scientific advice from HTA bodies to ensure they consider evidence requirements to assure timely patient access
- Healthcare systems that want to facilitate patient access to these drugs will need to rely on postauthorisation data collection to reduce the substantial uncertainty about the drugs' long term benefits in absence of mature progression-free and overall survival data available to inform health technology assessment

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Figure

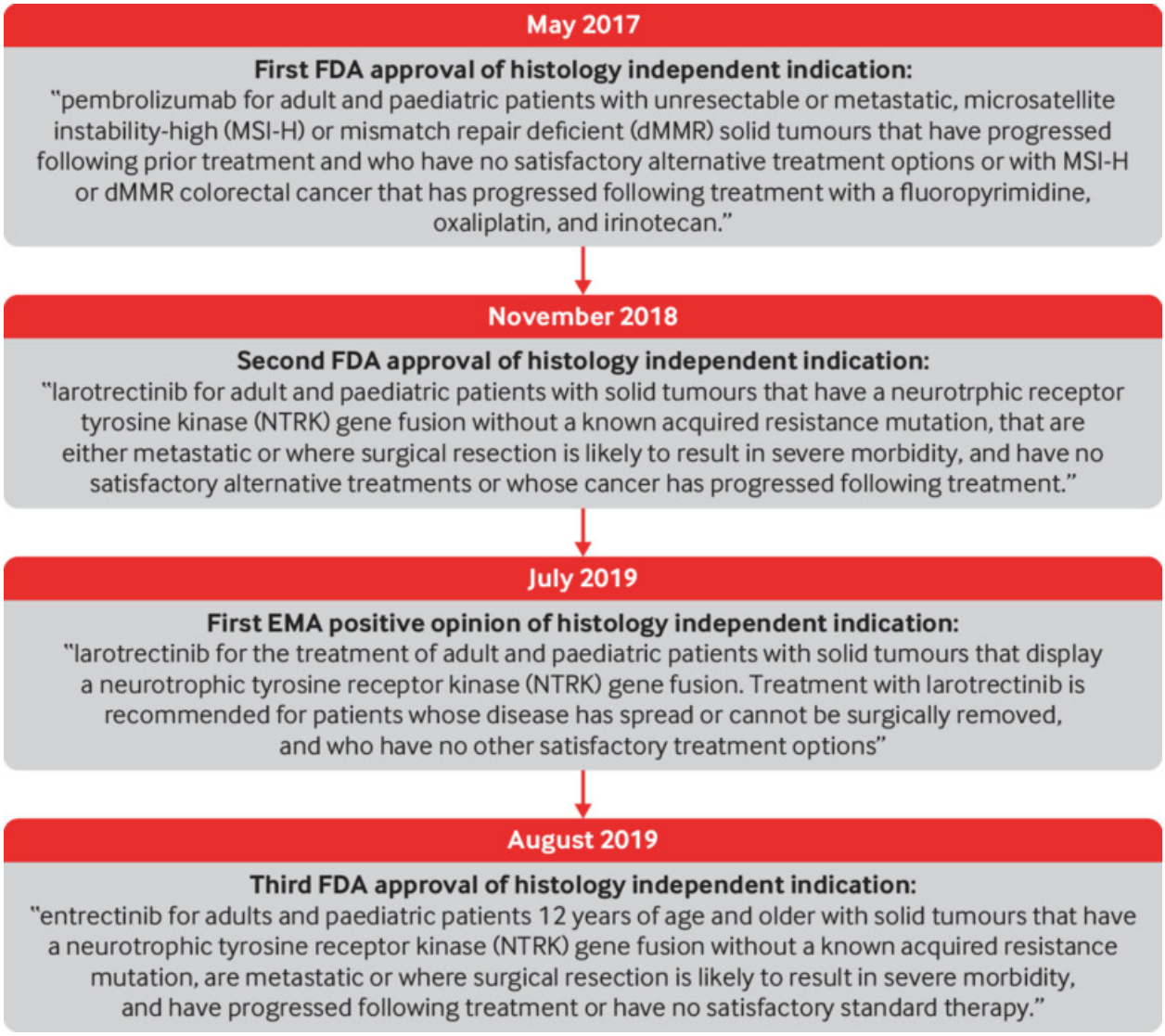

Fig 1 Timeline of regulatory approvals of histology independent cancer drugs in the United States and Europe. Pembrolizumab was never submitted for a histology independent indication to the European Medicines Agency (EMA). FDA=Food and Drug Administration