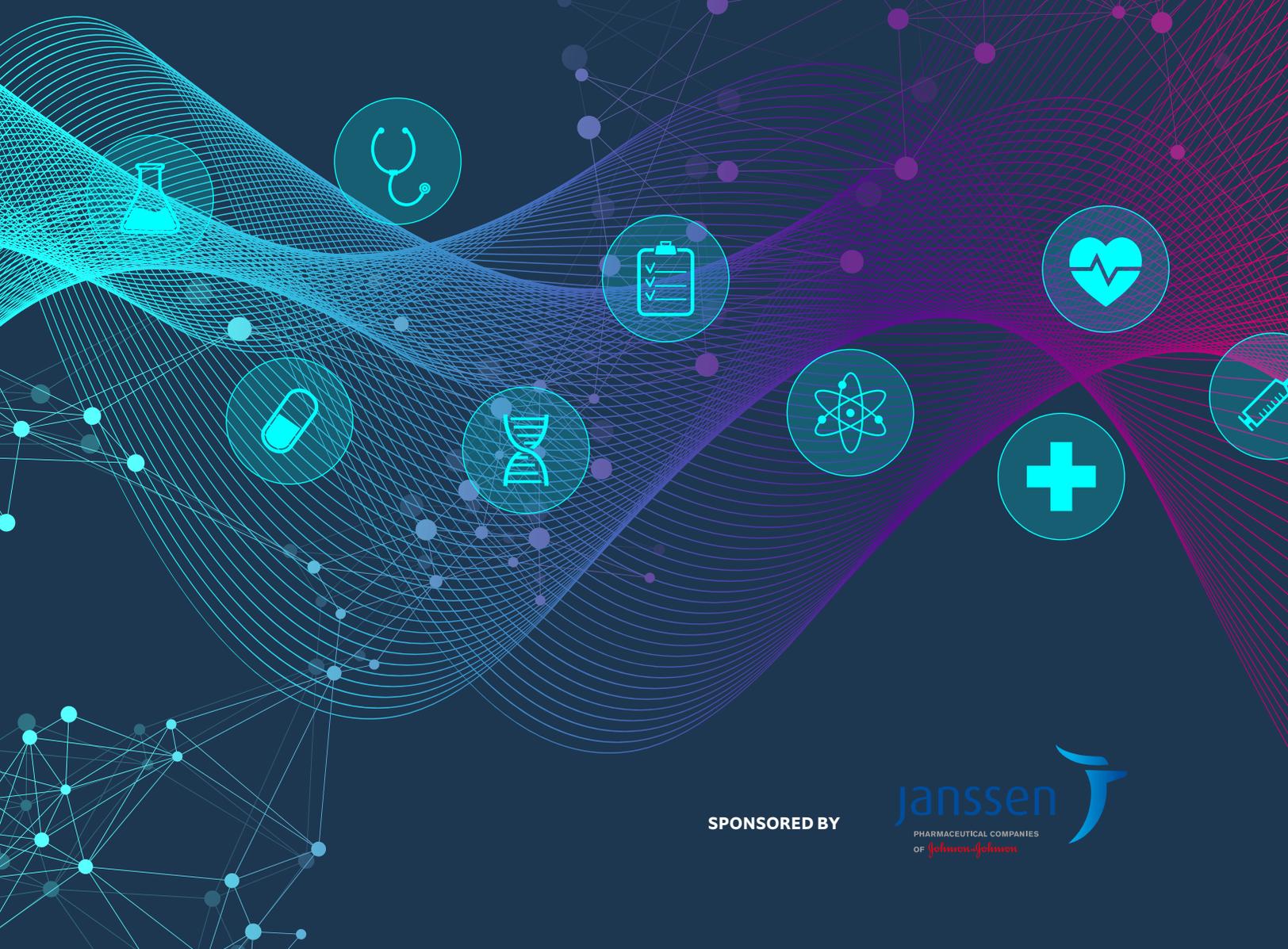


Assessing innovation

How Health Technology Assessment
can adapt to improve the evaluation
of novel cancer therapies in Europe



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About this report

Assessing innovation: How Health Technology Assessment can adapt to improve the evaluation of novel cancer therapies in Europe is an Economist Intelligence Unit report, sponsored by Janssen, which examines the difficulties facing health insurers, other bodies that pay for healthcare (payers) and health technology assessment (HTA) agencies in Europe as they grapple with how to assess a new generation of oncology therapies.

The report focuses on eight European countries and looks at the approval process for twelve new cancer treatments. It includes insights from desk research, a literature review and 13 in-depth interviews with a range of academics, HTA experts and other stakeholders.

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- **Antonella Cardone**, Director, European Cancer Patient Coalition, Brussels
- **Jaime Espin**, Professor, Andalusian School of Public Health, Granada, Spain
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The views of interviewees were their own, and not necessarily those of their affiliated institutions.

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The findings and views expressed in the report do not necessarily reflect the views of the sponsor. The Economist Intelligence Unit research team consisted of Anelia Boshnakova, Andrea Chipman, Jordan Lee, Alan Lovell and Rachna Malik. While every effort has been taken to verify the accuracy of this information, the EIU cannot accept any responsibility or liability for reliance by any person on this report or any of the information, opinions or conclusions set out in this report.

Executive summary

The process of Health Technology Assessment (HTA) has been a key tool used by many European governments over the last two decades to evaluate healthcare innovations and ensure that those paying for healthcare get as much value—and benefit for patients—from their investment as possible.

HTA systems assess the level of innovation and value promised by new medical therapies before making reimbursement decisions. The process has long been a complex one, with the use of HTA varying across the continent, driven by the variation in local context and priorities. European countries have different systems for evaluating new treatments that make use of varied skill sets and use a range of criteria for determining value and deciding whether to pay for them. In many cases, more than one agency is involved in HTA, and in countries with more devolved systems of managing healthcare, regional organisations also have a role in the assessment process.

All the countries discussed in this report have well-developed HTA systems but face growing challenges in assessing the value of the newest innovative treatments, especially in the area of oncology. Many of these innovative products are personalised or targeted at smaller populations, and often have less evidence behind them because of the difficulties in finding enough patients to make up a large Phase 3 clinical trial. Some are part of combination regimes or require companion diagnostics to identify the most appropriate patient groups. These innovations are sometimes categorised under a new class of treatments— advanced therapy medicinal products— which are treatments based on genes, tissues or cells.

For this reason, we refer in this paper to “innovative therapies” rather than “innovative drugs.”

All of these factors mean that existing HTA systems, and associated payer organisations, are finding it increasingly challenging to evaluate and introduce these therapies in an equitable and sustainable fashion. Our empirical analysis of 12 innovative therapies across eight countries shows a large variation in “time to HTA decision” and “time to patient access”, both between countries and between therapies within countries. We describe how reforming the HTA process is likely to involve expansion of more flexible systems for providing access to promising, early-stage therapies, new approaches to building an evidence base for innovative care, and a revisiting of the definition of value. Much of this activity is already happening in the world of HTA, but progress is sometimes slow. Through our analysis, we identify the following key takeaways.

HTA structures and methodology are coming under increasing pressure to adapt

HTA systems designed to assess drugs with existing comparators are being used to evaluate entirely new classes of therapies that are increasingly personalised to small groups and even individual patients. More broadly, manufacturers continue to contend with a lack of consistency in how value is defined within different HTA systems. The newest generation of oncology treatment presents a range of emerging challenges, including increasing costs, a smaller evidence base, more complicated trial designs and the increased use of personalised medicines. This wave of innovation is a good

news story: many of these therapies can hugely improve outcomes for individual patients. However, the potential for delays in access is forcing HTA agencies to change and adapt as they reveal limitations in current assessment, reimbursement, and pricing methodologies.

A greater range of conditional agreements are needed to improve patient access

Many HTA agencies and reimbursement bodies have used a variety of managed entry agreements and conditional approvals for more than a decade, ensuring patient access while analysts are still collecting evidence about a therapy's performance. Given the complexity of the current crop of oncology treatments, a wider range of these agreements is likely to be inevitable. This is likely to include new forms of managed entry agreements and conditional inclusion of some innovative products on lists of reimbursable medicines. While these arrangements have been operating—in one form or another—for some years, they are sometimes challenging to implement. It is important that this period of conditional access is fair for all parties, for payers, industry, and patients, perhaps with the adoption of outcomes-based pricing or risk-sharing approaches before further evaluation using data collected post appraisal. The big challenge is data: its collection and usage.

Improved data collection infrastructure is required

Although better data is key to allowing HTA authorities to accurately assess the efficacy or cost-effectiveness of innovative therapies, the infrastructure for enhanced data collection is lacking in most countries. In addition, HTA agencies need to determine what sort of

evidence they will need to collect (or have manufacturers provide), what criteria will be used to evaluate this evidence, and how to address situations in which multiple therapies are used in combination, or treatments are increasingly personalised. Those evaluating new therapies will also need to consider patient-relevant endpoints, as well as other assessment metrics. These are especially thorny issues, given the impact of these factors on reimbursement decisions and price negotiations.

Greater transparency in the decision-making process should become the norm

Because of the opportunity costs involved—money spent on one population of patients means it is not available elsewhere—many of our interviewees argued for greater transparency. HTAs need to make more explicit the trade-offs involved in appraisals and funding, so that the public will understand better how decisions are made. This may mean renewed focus on value-based pricing and the way in which the notion of value is defined. Transparency was considered particularly important regarding factors likely to be material in pricing negotiations, thus helping to make reimbursement decisions less opaque.

Patient views need to play a greater role in decision-making, as well as deliberation

Tying the above points together is the importance of having patient's values and preferences at the centre of these discussion. While some HTA agencies include patient voices in the discussion process for new therapies, it is often unclear how patient views are considered during deliberations over reimbursement. Greater patient involvement could help

crystallise notions of value. Patient experience is crucial to discussions of clinical benefit, as these are the people who stand to benefit or lose the most from how well the HTA ecosystem adapts to new challenges. Most of our interviewees agreed on the importance of placing the patient at the heart of the process, although several were unsure how to integrate it into the existing HTA process, and whether there was the will to do so. Incorporation of patient priority studies and improvement of patient registries would help produce better data, and be a good start.

Greater harmonisation can be helpful but remains challenging

In recent years, there have been efforts to create collaborative approaches to HTA between different countries and on an EU level—including the proposal in Europe's Beating Cancer Plan

2021 to strengthen cooperation amongst EU Member States for assessing health technology. While these have provided blueprints for avoiding the duplication of labour, different health cultures and spending objectives are unlikely to facilitate harmonisation of the entire HTA process. Harmonisation can help countries pool resources and expertise and standardise methodologies for assessing innovative therapies, although reimbursement and pricing decisions are likely to continue to vary by country. Current harmonisation examples include the BeNeLuxA initiative and the Nordic countries' FINOSE project, as well as the European Network for Health Technology Assessment (EUnetHTA) joint programmes. Expansion of these collaborations could help prevent duplication of efforts on the part of companies and national agencies.

Introduction

The idea of formally assessing health technologies has been with us for around five decades, but its use has accelerated over the past ten to fifteen years. Countries with already strained healthcare budgets have had to make calculations that balance the rise in the cost of state-of-the-art medicines, devices and other therapies against the increasing effectiveness of treatments.

Health Technology Assessment (HTA) is a multidisciplinary process that uses explicit methods to determine the value of a given health technology. According to the International Network of Agencies for Health Technology Assessment (INAHTA), the purpose of the systematic assessment of health technologies is to inform policy decision-making and promote an “equitable, efficient and high-quality health system.”¹ HTAs can be performed at different points of the life-cycle of health technologies, e.g., pre-, during, or post-marketing authorisation, and there is considerable variation in HTA methodologies and processes across Europe.

The European Network for Health Technology Assessment (EUNETHTA)—a network established to create an effective and sustainable structure for HTA across Europe—has created a “core model”; a methodological framework for the production and sharing of HTA information. It covers nine domains, which are split into two categories. First, the domains for a relative effectiveness assessment include the health problem and current use of technology, description and technical characteristics, safety and clinical effectiveness. Second, the national assessment and appraisal domains for member states include cost and economic effectiveness, ethical analysis, organisational aspects, patient

and social aspects and legal aspects.² Although a full HTA considers all nine domains, HTA bodies often take a narrower approach to shorten assessment timelines, focusing mainly on clinical or cost-effectiveness measures, rather than on social, legal, ethical and patient aspects.

The arrival of increasing numbers of innovative therapies

In recent years, there has been a dramatic increase in “innovative therapies”. These are therapies that offer a step-change in the treatment paradigm, introduce a new mechanism of action that is beneficial to patients compared with existing treatments, or treat diseases where there have historically been limited therapies available.³ The pace of innovation has remained high—about ten new cancer medicines have been approved by the European Medicines Agency (EMA) every year between 2012 and 2018 compared to just four every year for the previous decade. A large proportion of cancer medicines approved in the last decade have orphan designations as they are indicated for rare cancers (i.e. cancers with a prevalence of less than 5 per 10,000).⁴

Alongside enhanced prevention and early detection measures, the introduction of innovative oncology treatments has not only improved patients’ quality of life and survival rates but has also changed the natural history of cancer.⁵ To reflect this, we use the term “therapies” rather than “drugs” as sometimes these innovations belong in a new class of treatments—advanced therapy medicinal products—which are treatments based on genes, tissues or cells. They offer ground-breaking new opportunities for the treatment of disease and injury.⁶



The introduction of innovative oncology treatments has not only improved patients' quality of life and survival rates but has also changed the natural history of cancer.

Many innovative oncology medicines target patients with specific biomarkers, or genetic characteristics, which can help predict disease progression and response to treatment. As a result, HTA agencies—and the public and private payers that take advice from them—face increasing difficulties in determining how to assess the value of treatments that involve more tailored patient populations and potentially higher costs. These challenges, and their impact on the pricing of innovative therapies, can in consequence affect patients' access to treatment.

It is not uncommon for these innovative therapies to present to regulatory agencies with a limited, but promising, early evidence base—often from Phase 2 studies—resulting in a greater number of reimbursement recommendations with conditions attached. In most countries in Europe, market access for oncology products can occur outside the traditional process, with access often allowed before HTA decisions are reached.⁷ One example of this is early access schemes, such as the UK's early access to medicines scheme (EAMS), which aims “to give patients with life-threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation.”⁸

While valuable, compassionate access schemes are not a replacement for formal assessment processes. Consequently, it is HTA agencies that

must decide on the level of additional or significant benefit these newer therapies provide compared with existing treatments, as well as whether to recommend that they be reimbursed by payers. This can create inconsistencies in the timeline and reimbursement decisions for innovative treatments both between countries and even within them. “We see differences between countries in terms of the nature and time taken to make decisions,” European Commission Director of Public Health John F. Ryan told the World Cancer Series: Europe Virtual Week conference in November 2020.

HTA organisations are having to adapt to new challenges

Many HTA agencies were set up more than two decades ago (one of the oldest, the Swedish Council on Health Technology Assessment, was founded in 1987) and continue to use methods that haven't changed substantially since their inception. Yet the evolving nature of science and cancer treatment suggests that now may be an appropriate time to review how effectively HTAs can evaluate their associated value.

A 2020 report by the Organisation of Economic Cooperation and Development (OECD) identified four main challenges for both policymakers and payers:⁹

1. The significant uncertainty about the degree of clinical benefit at the time that new medicines receive market entry
2. Pricing of products with multiple indications, many of which may have varying degrees of clinical benefits
3. Pricing of new products that are used in combination treatment regimens as “add-on” therapies
4. The growth of products with high launch prices that threaten the sustainability of health systems.

We would add to this, that there is also growing pressure to incorporate the patient voice into decision-making to a greater extent. Many of our interviewees agreed that in order to address these challenges, some changes to the existing HTA environment will be required. Although they didn't always agree on the nature of the changes needed.

Aims of the study

This research study aims to explore and describe HTA ecosystems in Europe and investigate how different HTA models across countries impact on the accessibility of novel and innovative oncology medicines. The study countries are Belgium, France, Germany, Italy, The Netherlands, Spain,

Sweden, and UK (England). We focussed on these countries as they represent some of Europe's largest economies, they have influential and well established HTA organisations, and serve as examples of the variety of approaches seen across Europe in HTA processes and methods.

We conducted a literature review focused on the HTA landscape in Europe, followed by a series of expert interviews.

To compare the journey of oncology medicines—through HTA assessment to patient access in the eight countries included in our study—we conducted case studies of 12 medicines that received marketing authorisation from the EMA between 2016 and 2020 (**Table 1**). All of the examples selected were in some way “innovative”, on the basis of either being ‘first-in-class’ or otherwise deemed as being novel therapies. The selection therefore is not typical of HTA work, but instead gives an opportunity to examine how HTA agencies have assessed a range of novel cancer therapies.

Full methods are in the appendices (**Appendix 1**).

Supplementary material for this report can be found [here](#).



We see differences between countries in terms of the nature and time taken to make decisions.

John F. Ryan, European Commission
Director of Public Health

Table 1: Therapy/indication and rationale for inclusion

Medicine (Brand name)	Date of EMA approval	Indication	Rationale for inclusion
Polatuzumab vedotin (Polivy)	16/01/2020	Patients with relapsed or refractory diffuse large B–cell lymphoma	First-in-class anti-CD79b antibody
Larotrectinib (Vitrakvi)	19/09/2019	Adults and children with a neurotrophic tyrosine receptor kinase fusion-positive solid tumour	First-in-class NTRK gene fusion inhibitor
Cemiplimab (Libtayo)	28/06/2019	Patients with metastatic or locally advanced cutaneous squamous cell carcinoma	Innovative "step change" according to NICE
Brigatinib (Alunbrig)	22/11/2018	Adults with anaplastic lymphoma kinase positive advanced non-small-cell lung cancer who have been treated with crizotinib	A recent targeted treatment in NSCLC ALK+ (where an unmet need was acknowledged)
Tisagenlecleucel (Kymriah)	22/08/2018	Adults with relapsed or refractory diffuse large B-cell lymphoma after two or more lines of systemic therapy	Gene therapy
Niraparib (Zejula)	16/11/2017	Patients with relapsed, platinum-sensitive high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer	First PARP inhibitor approved for maintenance treatment of recurrent ovarian cancer
Padeliporfin (Tookad)	10/11/2017	Patients with untreated localised prostate cancer	A novel, light-activated drug
Atezolizumab (Tecentriq)	20/09/2017	Patients with locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy	Example medication for an end-of-life indication
Midostaurin (Rydapt)	18/09/2017	Patients with untreated FLT3 mutation positive acute myeloid leukaemia	First-in-class FLT3 inhibitor
Ixazomib (Ninlaro)	21/11/2016	Patients with relapsed or refractory multiple myeloma (combination with lenalidomide and dexamethasone)	First orally-available proteasome inhibitor
Palbociclib (Ibrance)	09/11/2016	Patients with hormone receptor positive, HER2 negative, advanced breast cancer (combination with an aromatase inhibitor)	First-in-class CDK4/6 Inhibitor
Daratumumab (Darzalex)	20/05/2016	Patients with relapsed and refractory multiple myeloma (monotherapy)	First-in-class anti-CD38 monoclonal antibody

Table abbreviations: ALK: Anaplastic lymphoma kinase. NTRK: Neurotrophic Tyrosine Receptor Kinase. NSCLC: Non small-cell lung cancer. PARP: poly ADP ribose polymerase

Note: Medicines are organised by date of EMA approval (most recent first)

HTA models in Europe

The eight countries covered in this paper have had established methods for conducting HTA for at least two decades, yet there are significant differences in the way in which decisions are taken and the criteria that is used. Some have a single HTA agency. For example, the National Health Authority or Haute Autorité de Santé (HAS) in France, the National Health Care Institute or Zorginstituut Nederland (ZIN) in the Netherlands, and the National Institute for Health and Care

Excellence (NICE) in England (and Wales). Other countries, including Belgium, Germany, Italy, Spain and Sweden, have multiple bodies assessing innovative products. In Italy, the Italian Medicines Agency or L'Agenzia Italiana del Farmaco (AIFA) is both the medicines regulatory agency and has responsibility for HTA. **Table 2** shows the HTA, reimbursement and pricing bodies for each country. A fuller comparison can be seen in the **supplementary material (Table S1)**.

Table 2: HTA, reimbursement and pricing bodies for eight European countries

Country	HTA body	Reimbursement body	Pricing body
Belgium	INAMI-RIZIV - National Health Insurance and Disability Institute	Commission for the Reimbursement of Medicines (CRM/CTG) & Minister of Social Affairs	Federal Public Service for Economic Affairs, encompassing two specialised commissions: Commission for Price Regulation, Commission for Pricing of Medicinal Products
England	The National Institute for Health and Care Excellence (NICE)	NICE	NHS England HTA recommendations are not used for pricing decision-making
France	National Health Authority (Haute Autorité de Santé, HAS) CEESP, Commission d'évaluation économique et de santé publique/ Commission for Economic Evaluation and Public Health	HAS CT, (Commission de la transparence/ Transparency committee)	Comité économique des produits de santé (CEPS)/ Economic Committee for Health Products
Germany	The Federal Joint Committee (G-BA). HTAs are also performed by the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG)	All medicines entering the market are reimbursed by sickness funds. However, the G-BA has the legal authority to decide on subsequent prescription restrictions.	National Association of Statutory Health Insurance Funds (GKV-SV) Free pricing in year 1
Italy	Italian Medicines Agency (L'Agenzia Italiana del Farmaco, AIFA)	AIFA Pricing and Reimbursement Committee/Comitato Prezzi e Rimborso (CPR)	AIFA Pricing and Reimbursement Committee/Comitato Prezzi e Rimborso (CPR)

Table 2 (continued): HTA, reimbursement and pricing bodies for eight European countries

Country	HTA body	Reimbursement body	Pricing body
Netherlands	The National Health Care Institute (Zorginstituut Nederland, ZIN)	ZIN: Scientific Advisory Board (WAB) and Appraisal Committee (ACP)	Ministry of Health, Welfare and Sports (VWS)
Spain	Spanish Agency of Medicines and Medical Devices (Agencia Española de Medicamentos y Productos Sanitarios, AEMPS)	Interministerial Commission on Prices of Medicines (CIPM), an advisory body of the Ministry of Health (Ministerio de Sanidad, Consumo y Bienestar Social) MoH, Industry & Economy are represented on the commission.	Interministerial Commission on Prices of Medicines (CIPM), an advisory body of the Ministry of Health (Ministerio de Sanidad, Consumo y Bienestar Social) MoH, Industry & Economy are represented on the commission. MoH negotiates prices.
Sweden	Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket, TLV)	New Therapies Council	The Board of Pharmaceutical Benefits decides pricing and reimbursement for products included in the benefits scheme.

HTA agencies operate in a wider regulatory and reimbursement ecosystem

HTA agencies in each country do not act in a vacuum. Consequently, we sometimes talk of the HTA ecosystem—the network of agencies and institutions who work together to help ensure new drugs are made available to patients in a sustainable and equitable fashion.

When two or more agencies are involved, timelines can be impacted and, in some cases, different levels of expertise are employed. In Belgium, for example, there are two agencies: the Belgian Health Care Knowledge Centre (KCE), which undertakes some HTA cost-effectiveness assessments, and the Committee on Reimbursement of Medicines (CRM) within the Belgian National Institute for Health and Disability Insurance (INAMI/RIZIV). The CRM is a body made up of physicians, hospitals, pharmacies, payers and other stakeholders that advised the country's minister of social affairs about reimbursement. This division, it is suggested, sometimes leads to cases in which expertise isn't

used to its full potential, according to Philippe van Wilder, a professor of pharmacoeconomics and HTA at the Université Libre de Bruxelles.

To illustrate this, Professor van Wilder used the example of a drug for breast cancer which had been recommended for late-stage disease initially and early-stage later on, but approved for reimbursement for late-stage disease only. There had been confusion between the advice of the two organisations because of their distinct and non-interacting function. "They were lucky because the expert reviewing the dossier was an oncologist who was keen on pharmacoeconomics," he says, noting that often dossiers are assigned based on the overall workload, meaning an expert with limited economic knowledge might be evaluating an oncology drug even when an oncologist and economic expertise is available. "This isn't optimising the process by having the split," he adds. Countries such as Italy and Spain also have regional HTA agencies, leading to a possible duplication of effort and conflicting decision-making within countries.

By contrast, agencies such as NICE in the UK has responsibility for both assessment and decision-making on reimbursement of new treatments, thus putting them in a powerful position with regard to negotiations with manufacturers, as it acts as the gate keeper to England's population of 55 million potential patients.

The role of HTA recommendations in reimbursement and price setting varies from country to country. In Sweden, Spain, and Italy, with their regional assessment bodies, they can also vary within the country. In some countries, notably France and the UK, HTA organisations provide specific recommendations about reimbursement, or categorise treatments according to how innovative they are compared with existing therapies. In other countries, such as Spain and Sweden (only for hospital drugs), they limit themselves to synthesising evidence and performing analyses, leaving reimbursement and pricing decisions to separate bodies.

To complicate matters further, Sweden also has separate systems for assessing outpatient or prescription drugs and those given within hospitals, according to Thomas Hofmarcher, research manager at the Swedish Institute for Health Economics. Although the Swedish HTA agency TLV only makes pricing and reimbursement decisions for outpatient drugs, since 2010 it has started to provide analysis for hospital drugs as well, in conjunction with the county council group that recommends new drugs. "Basically, they perform the same assessment as they would have done for an outpatient drug, but they cannot take an actual price and reimbursement decision," he says.

Decision-making criteria also differ from country to country. In France, according to a 2017 study, clinical and economic experts consider disease severity to be the most influential criterion, while in the UK,

cost-effectiveness, using the incremental cost-effectiveness ratio (ICER) was the key factor. Elsewhere experts didn't always agree on which criteria were most significant in their HTA systems.⁷ The eight countries use different classification systems for determining the added therapeutic value of new medicines.

In the case of Belgium and Italy, this means using just one category of added therapeutic value, while both Germany and France have graded classification systems to establish the degree of added benefit over existing treatments, from substantial to non-existent. In France, HAS CT assesses products according to an improvement of actual benefit scale, or Amélioration du Service Médical Rendu (ASMR). The scale contains five rating levels, with rating I representing major improvement, and rating V representing no improvement. Only those treatments with a rating of I to IV are reimbursed.^{10,11}

A range of managed entry agreements for innovative therapies

HTA agencies have used several initiatives to accelerate access to innovative cancer medicines. Many of these incorporate a range of performance-based and managed entry agreements, which give patients access to new treatments while setting out rules for gathering further clinical evidence (including real world evidence) during a set time period.



HTA agencies have used several initiatives to accelerate access to innovative cancer medicines. Many of these incorporate a range of performance-based and managed entry agreements.

In England, the Cancer Drugs Fund (CDF) is designed to allow patients to gain access to new cancer drugs using managed access agreements. These are agreements with manufacturers that determine the cost of the medicine during a defined access period, during which time further evidence is collected to address clinical uncertainty.¹² Italy also has a fund for new oncology treatments that are considered to serve a therapeutic need or add new value; the fund, established in 2017, is capped at EUR500 million.¹³

In the Netherlands, The Ministry of Health, Welfare and Sport has a policy for conditional inclusion in the basic health package of certain medicines that treat rare diseases; funding limits were set at EUR25.5 million in 2020 and EUR26.8 million in 2021, with the expectation that these budgets would cover two to three medicines a year.¹⁴ The Dutch HTA agency, ZIN, and its medicines evaluation agency, have also launched a pilot project to shorten the time from authorisation to reimbursement of treatments.¹⁵

Patient engagement varies from agency to agency, but remains unsatisfactory

Although patient involvement is widely viewed as vital to understanding and assessing the value of health technologies, only a small number of European HTA agencies integrate patients in the assessment process to a meaningful degree. In Belgium, patients are not involved in the HTA process, while in Germany patient organisations are part of the G-BA and can be heard, but have no voting powers. The other six countries involve either patient experts or patient groups at various stages of the process. However, only one HTA, England's NICE, involves patients in recommendations. Although even the NICE

system has drawbacks, says Zack Pemberton-Whiteley, chief executive officer at Leukaemia Care and chair of the global Acute Leukaemia Advocates Network (ALAN). He notes that the agency doesn't offer the opportunity for patients to have a specific meeting focusing on issues that matter the most to them, nor do they have the opportunity to be involved in selecting topics for assessment. "That can have quite a large impact on the process, because in many ways NICE's current processes are not fit for purpose when it comes to appraising treatments for rare conditions," he adds.

Only a small number of European HTA agencies integrate patients in the assessment process to a meaningful degree.



In Sweden, the New Therapies (NT) Council includes a patient representative, but this is a generic patient representative, according to Nils Wilking, an oncologist and professor at the Karolinska Institute in Stockholm, rather than one who necessarily has expertise in the disease being discussed. In the Netherlands, the Ministry of Health severely cut subsidies for patient groups from the ministry's budgets nearly a decade ago, according to Patrick Jeurissen, Professor of Fiscal Sustainability at Radboud University and science officer at the Ministry of Health, Welfare and Sports. Since that time, he says, they have become more dependent on outside funding, including from the pharmaceutical industry, fostering

a perception that they lack independence. A similar perception exists in Germany, according to Antonella Cardone, director of the European Cancer Patient Coalition (ECPC) in Belgium.

Yet, the personalised nature of innovative cancer treatments highlights the importance of patient input, both as a way of contributing real-world evidence and in order to indicate the value that patients ascribe to the treatment. Therefore, many countries are trying to rectify this gap in patient involvement. Over the past few years, some HTA systems—including those in Germany and Sweden—have been using patient-reported outcomes (PROs) in their evaluations. While welcome, a lack of consistency in the ways this information is collected across agencies and across different assessments within the same agency presents challenges for manufacturers.¹⁶

HTA timelines are uneven

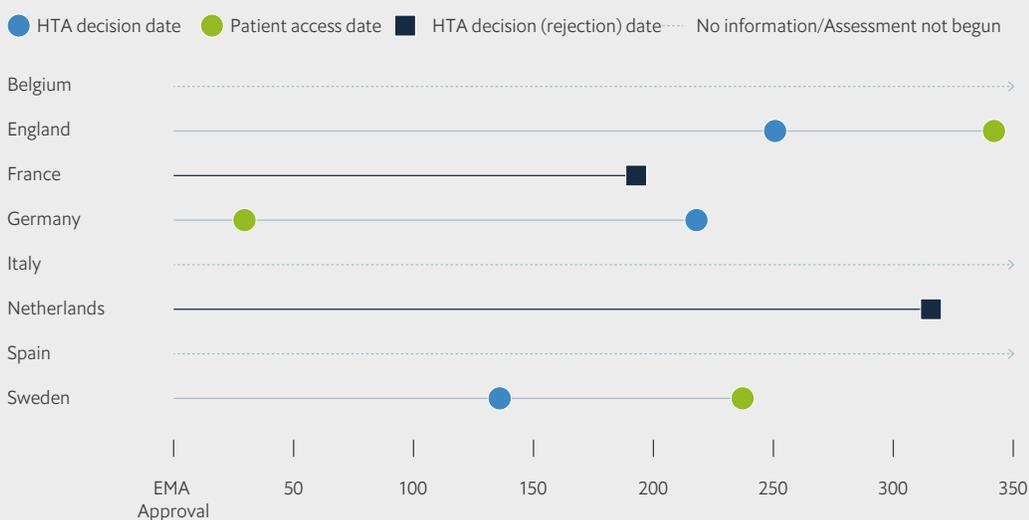
Many factors contribute to the difference in patients' access to innovation across Europe. One of the key factors is the variation in time to assessment between agencies. Germany is the only country in this study in which new medicines are allowed market entry immediately after they are authorised by the

regulator. Once approved, they are reimbursed by the country's sickness funds, unless they belong to an excluded category or the Federal Joint Committee, known as the G-BA, decides not to cover them. HTA assessments are conducted to inform pricing decisions after they have been on the market for a year.¹⁷

In the seven other countries in our study, HTA are required for reimbursement decisions before market entry, and the time this process takes can vary significantly. In Belgium and France, HTA processes take around 90 days to complete, while the other five countries reported a timeframe of 90 to 220 days for a single technology assessment.¹⁸ In some cases, the timeframes for assessment of orphan drugs or innovative cancer medicines provided via special programmes are shorter: 100 days for the assessment of orphan drugs in Italy, and up to 90 days for the assessment of medicines considered for the Cancer Drugs Fund in the UK.^{19,20} All this despite the EU Transparency Directive requiring all countries to reach a decision on pricing and reimbursement within 180 days of marketing authorisation, although this timeframe can be impacted by so-called clock-stops—where the process is interrupted when further evidence is required by the HTA agency.

Box 1**Polatuzumab vedotin (Polivy): variations in due process and reimbursement decisions****Timeline from EMA approval date: Polatuzumab vedotin**

(Measured in days)



Polatuzumab vedotin (Polivy) is one of the most recently conditionally approved technologies by the EMA (16/01/2020). Conditional approvals are “granted in the interest of public health because the medicine addresses an unmet medical need and the benefit of immediate availability outweighs the risk from less comprehensive data than normally required”.²¹ The medication has an orphan designation as it is indicated for people with diffuse large B-cell lymphoma (DLBCL) whose cancer has returned and who are not responding to other treatments or cannot have bone marrow transplantation.²²

The medicine obtained regulatory approval shortly before the arrival of covid-19 in

Europe, and therefore timelines may have been delayed by the pandemic. The medication is reimbursed in England and Germany, but has been rejected in France on the basis of unquantifiable additional benefit. It is also not available in Sweden, while HTAs are still in progress in Italy and Spain. A final reimbursement decision is pending the Netherlands where it was announced in December 2020 that “due to the expected high costs, the Minister of Health, Welfare and Sports will only allow polatuzumab to be included in the basic package after negotiating the price.”²³

For details of data collection see the methods section in **appendix 1**, including the list of HTA publication source URLs in **Table 6**.

Differences in time to HTA decision date and time to patient access date for innovative therapies across Europe can clearly be seen in **Figures 1 and 2**, which look at the 12 therapies reviewed in this study. Both of these time periods are partly due to the length of time agencies take to assess the medicine, and partly dependent on factors outside the control of the wider HTA ecosystem. In particular, they depend on when a reimbursement dossier is submitted by the manufacturer for assessment by the national HTA agency. Unfortunately, such submission dates are often unavailable, so it often isn't clear how much of the time was taken up by delays in submission versus time taken for the assessment itself.

Nevertheless, whatever the reasons for delay, time to HTA decision and time to patient access for individual, innovative therapies, ranges from less than 50 days to nearly a thousand days. There is wide variation both between countries and between the assessments of therapies within countries. There is no clear pattern. For example, our research shows that Midstaurin took the longest period of time of any therapies in the Netherlands, while in

Sweden it was one of the quickest to receive a decision, while in the case of Brigatinib, it was decided upon speedily in England, but was the second slowest in Italy (see **appendix 3, Figures 9 to 20**). **Box 1** gives an example of a recent innovative medicine, polatuzumab vedotin, that reveals how HTA agencies in different countries in Europe are interpreting their role and levels of evidence differently.

Looking across countries reveals that the Netherlands, France, Germany and England are relatively swift in making decisions. Then Italy and Spain, followed by Sweden and Belgium. Some countries are quite consistent in time to decision. This is particularly true of Germany, where the 2011 Pharmaceutical Market Reorganisation Act, known by its German acronym (AMNOG), set specific timelines to maintain consistency. Other countries, such as Sweden, vary dramatically. A similar pattern is seen in time to patient access, although it is notable that it takes long for some countries, in particular France, to go from HTA decision to patient access. The figures also clearly show how Germany provides patient access before HTA decisions are made. An individual example of variation in time to access is given in **Box 2**.

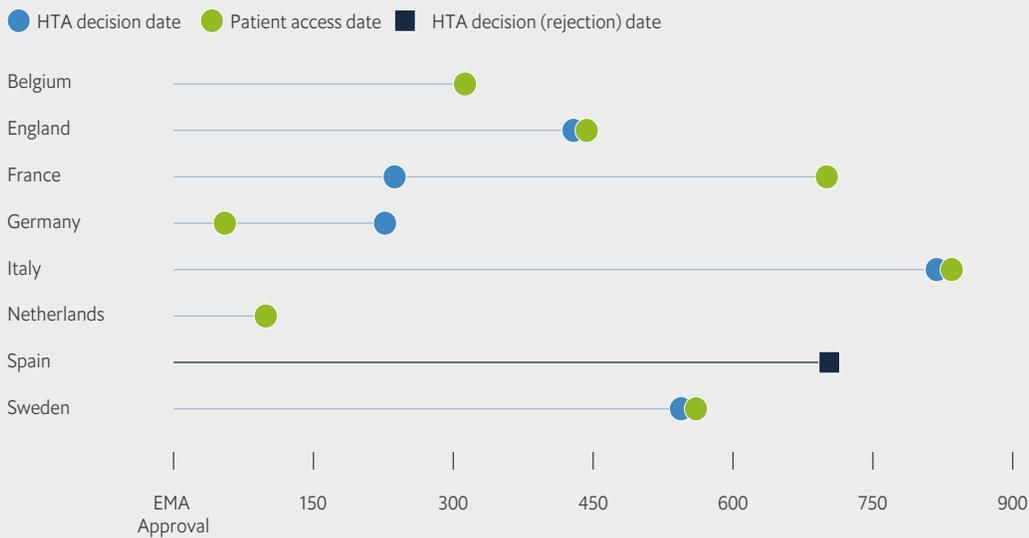
Countries do not only vary in time to access, but also in how many therapies have been assessed by their HTA body. England, France and Germany have assessed all 12 medicines, Sweden 11, Italy 10 with one assessment currently in progress, the Netherlands 9, with two decisions pending. Spain has four HTAs in progress, and data for Belgium is limited. Average times from regulatory approval to HTA decision and patient access, by country and by therapy, can be found in **appendix 2 (Figures 7 and 8)**. Individual drug timelines are shown in **appendix 3 (Figures 9 to 20)**.

Time to HTA decision and time to patient access for individual, innovative therapies, ranges from less than 50 days to nearly a thousand days. There is wide variation both between countries and between the assessments of therapies within countries.



Box 2**Ixazomib (Ninlaro): variations in time to access****Timeline from EMA approval date: Ixazomib**

(Measured in days)



Ixazomib (Ninlaro) received conditional marketing authorisation on 21/11/2016 with an orphan drug designation. It is reimbursed in 7 out of the 8 countries (excluding Spain). The first HTA assessment was conducted by the G-BA in Germany in April 2017, following the procedure for orphan drugs, and the final decision was published in July the same year. France's HTA was also published in 2017, while the other countries HTAs were published in 2018.

Patients in Germany and Belgium had access in 2017, in January and October respectively, while six countries provided access in 2018 and Italy in March 2019.

For details of data collection see the methods section in **appendix 1**, including the list of HTA publication source URLs in **Table 6**.

Figure 1: Time to HTA decision date from EMA approval date for all therapies, by country.

(Measured in days)

Number of days from regulatory approval is shown on the horizontal axis, with dots representing an HTA decision made for one of the 12 therapies. Not all countries have 12 dots as not all countries have published an HTA decision for each therapy. The shaded area represents the EU Transparency Directive requiring all countries to reach a decision on pricing and reimbursement within 180 days of marketing authorisation. As can be seen, few therapies in few countries meet this requirement. For details of data collection see the methods section in appendix 1, including the list of HTA publication source URLs in table 7.

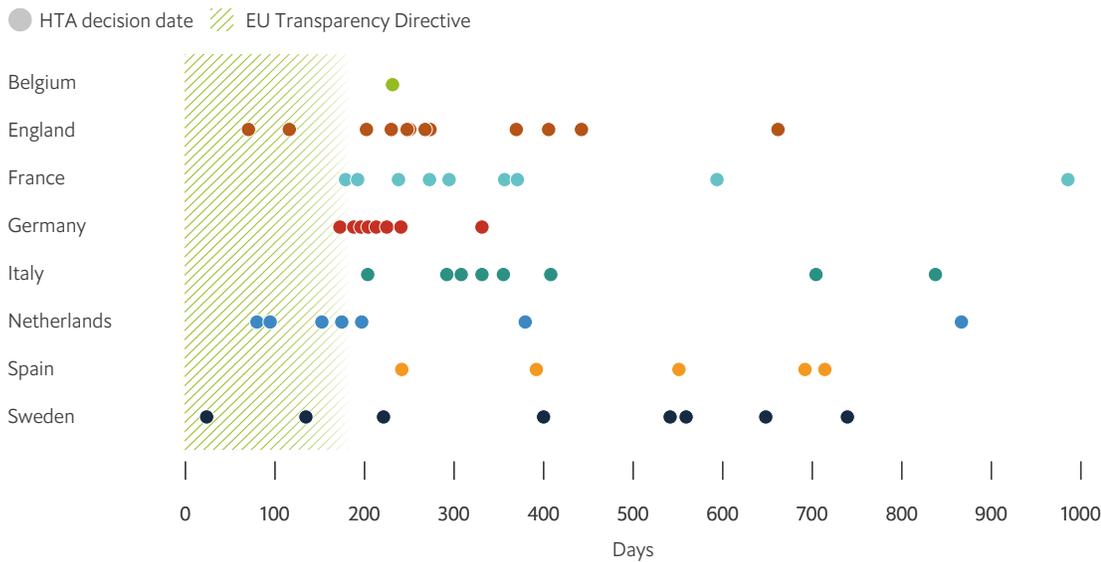
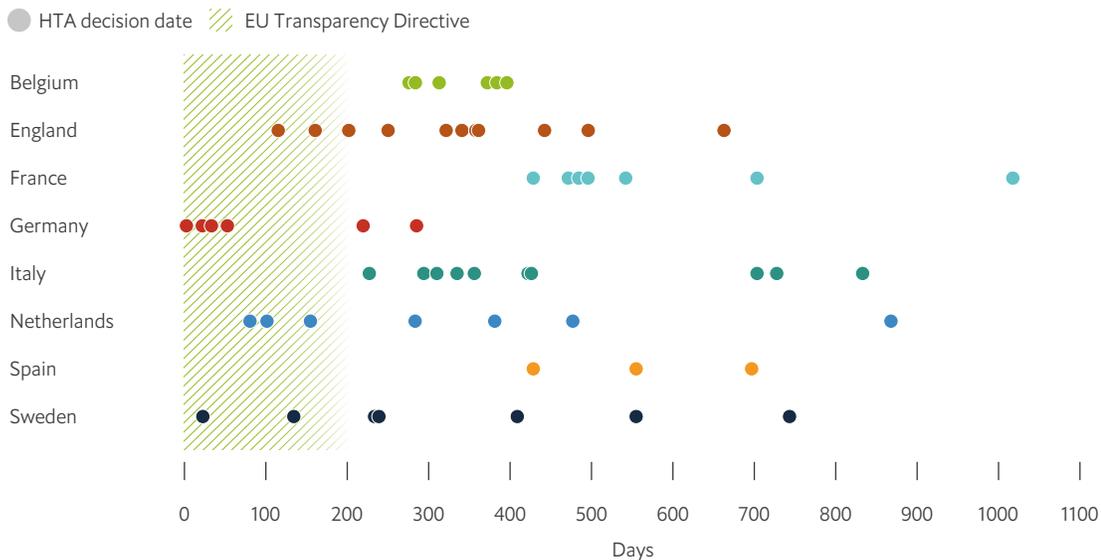


Figure 2: Time to patient access date from EMA approval date for all therapies, by country.

(Measured in days)

Number of days from regulatory approval is shown on the horizontal axis, with each dot representing the granting of patient access for one of the 12 therapies. Not all countries have 12 dots as not all countries have granted patient access for each therapy. The shaded area represents the EU Transparency Directive requiring all countries to reach a decision on pricing and reimbursement within 180 days of marketing authorisation. As can be seen, few therapies in few countries meet this requirement. For details of data collection see the methods section in appendix 1, including the list of HTA publication source URLs in table 7.



Changing times: new challenges for HTA

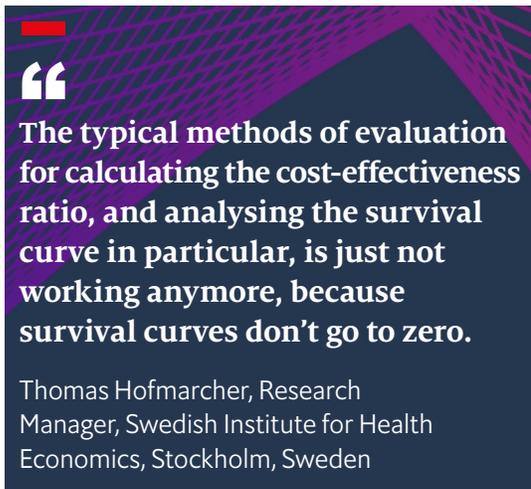
Given the existing complexity and diversity of HTA processes and the structures of agencies in Europe, the arrival of a new generation of oncology therapies is stretching the current systems to the limit. HTAs face a number of challenges. These include having access to only a small or limited evidence base, often with trial endpoints that may not be representative of patient need. Many of those interviewed for this paper observed that the commercial sensitivity of agreements between national governments and manufacturers can conflict with the goal of greater transparency, and that pricing mechanisms are not flexible enough. We describe these challenges in some detail here, clustering them into four main types:

1. A sparse evidence base
2. The wide range of outcome measures used
3. An increasing number of combination therapies, multiple indications and tumour agnostic drugs
4. A lack of transparency.

Therapies with a sparse evidence base but with the potential to transform models of care

Arguably the most significant challenge is the comparatively high degree of evidential uncertainty that accompanies many innovative cancer therapies arriving for assessment. Many have only undergone smaller, single-arm Phase 2 studies, rather than larger Phase 3 studies. One of the reasons for this trend is down to the innovative nature of the drugs themselves, and in particular the number of therapies that offer promising preliminary evidence in areas of unmet need. The aim of Phase 3 randomised controlled trials (RCT) is to enable the comparison of the

new investigational compound to the closest existing standard of care. However, some of the new treatments are so novel, and treat cancers for which there is no suitable existing treatment, that performing a Phase 3 trial is more complicated, and sometimes not feasible. Such trials can be ethically challenging, for they may compare an effective therapy with one that is known to be inferior. Consequently, it can be difficult to interpret results regarding therapeutic benefit when there is only single-arm data available (i.e. with no control arm).



“
The typical methods of evaluation for calculating the cost-effectiveness ratio, and analysing the survival curve in particular, is just not working anymore, because survival curves don't go to zero.
 Thomas Hofmarcher, Research Manager, Swedish Institute for Health Economics, Stockholm, Sweden

Another reason for the increasing arrival of only Phase 2 evidence is the rising number of targeted treatments that are aimed at a small patient base. An extreme example of this is chimeric antigen receptor T-cells, or CAR-T, technology. This is a form of therapy where T-cells have been genetically engineered to give them the ability to target a specific protein in cancer cells. CAR-T therapy can have especially strong results in small groups of patients: this has been especially evident in the case of tisagenlecleucel (Kymriah), a treatment for acute lymphoblastic leukaemia

(ALL), according to Mr. Hofmarcher of the Swedish Institute for Health Economics. “Many of these patients—50% or so—actually achieve a deep response. And for those patients, it can mean that they survive for 15 or more years. So there is actually a cure,” he says. “The typical methods for evaluation for calculating the cost-effectiveness ratio, and analysing the survival curve in particular, is just not working anymore, because survival curves don’t go to zero anymore—they first trend down but then they reach a plateau and level out.”

This pattern, of new medicines arriving at HTAs with an increasingly sparse evidence base, can be seen clearly in our basket of 12 medicines. Figure 3 shows how therapies assessed up to 2018 mostly had Phase 3 trial evidence—i.e., comparative RCTs. However, the five most recently addressed innovative medicines, from 2018 to 2020, were approved with Phase 2 evidence. Some of these trials were single-arm, non-comparative trials; others had a control arm but were either relatively small or non-randomised.*

Figure 3: Main trial type used in HTA decision with the date (where available) of the publication of the HTA report.

In some cases, only a summary of the HTA was available with no information on the included studies—these are shown as grey cells with a date. A blank cell—with no date or colour—means that the HTA may be in progress, or that there is no information on whether it has started. For details of data collection see the methods section in **appendix 1**, including the list of HTA publication source URLs in **Table 6**.

Therapy	Main trial type used in HTA decision with the date (where available) of the publication of the HTA report							
	Belgium	England	France	Germany	Italy	Netherlands	Spain	Sweden
Polatuzumab vedotin (Polivy)		23/09/2020	10/06/2020	11/05/2020		27/11/2020		01/06/2020
Larotrectinib (Vitrakvi)		27/05/2020	09/07/2020	13/01/2020				22/10/2020
Cemiplimab (Libtayo)		07/09/2019	18/03/2020	30/10/2019	23/04/2020	17/09/2019		13/01/2020
Brigatinib (Alunbrig)		20/03/2019	23/10/2019	11/04/2019	14/10/2020	08/12/2019		14/12/2018
Tisagenlecleucel (Kymriah)	11/04/2019	13/03/2019	12/12/2018	13/12/2018	07/08/2019	07/03/2019	25/02/2019	15/04/2020
Niraparib (Zejula)		04/07/2018	13/06/2018	12/03/2018	24/08/2018	20/04/2018	09/10/2019	22/11/2019
Padeliporfin (Tookad)		21/11/2018	10/09/2019	04/10/2018	19/01/2018		21/10/2020	
Atezolizumab (Tecentriq)		13/06/2018	20/02/2019	12/22/2017	27/06/2018	16/03/2018	25/07/2018	20/02/2018
Midostaurin (Rydapt)	01/10/2018	13/06/2018	13/06/2018	09/01/2018	31/07/2018	01/02/2020	21/03/2019	31/01/2018
Ixazomib (Ninlaro)	01/10/2017	07/02/2018	05/07/2017	18/04/2017	19/02/2019	01/03/2017	05/11/2018	17/05/2018
Palbociclib (Ibrance)		01/12/2017	20/12/2017	03/05/2017	23/02/2017	06/12/2017	10/02/2017	09/01/2018
Daratumumab (Darzalex)	01/03/2017	14/03/2018	22/11/2017	01/12/2016	27/06/2017	01/03/2017	17/01/2017	19/4/2018

* Where HTA publication dates were not available, e.g., in some cases for Belgium and the Netherlands, reimbursement decision dates or patient access dates have been used. In some countries only the HTA summary is available in the public domain with no details about the particular studies used in the evaluation. Padeliporfin (Tookad) – Only Italy has assessed and approved this technology. In the UK it was assessed and rejected as there was no difference in cancer-specific or overall survival compared with active surveillance in. Most other countries did not assess this technology, for example in Germany it was considered out of scope.

Measures of clinical effectiveness vary as “overall survival” becomes less relevant

Medicines used in cancer settings with a curative intent, or which otherwise have the potential for long-term benefit, can have significant impacts on the wider health system.

Consequently, says Matteo Ruggeri, research scientist at the Istituto Superiore di Sanità and Professor of Policy and Economics at St. Camillus University of Health Sciences in Italy, evaluating the organisational model within which health systems administer treatment—hospital, clinic or outpatient—is another area where HTA agencies are expected to have an important contribution to make. “You have to begin to account for the fact that if you want to reduce the costs and decide to administer a medicine on an outpatient basis, you have to take into account the possible impact on quality of care,” he says, noting that

there have been some estimates that intensive care, hospital admission and diagnostic care for some treatments can account for between EUR2 billion to EUR3 billion in healthcare costs.

The impact of increasingly diverse and targeted oncology treatments also makes it more difficult to assess products by just using a standard set of outcomes. One of the key measures most HTA agencies were set up to measure is overall survival. However, here medicine is the victim of its own success. In the case of many novel cancer treatments, it may take more than a decade to ascertain progress in overall survival. Nevertheless, overall survival—as opposed to surrogate endpoints focussing on tumour response—is often still used as the endpoint. A shift towards other endpoints, such as intermediate or response-based endpoints, may therefore be necessary. **Table 3** shows how some of these measurements differ.

Table 3: Alternative outcome measures

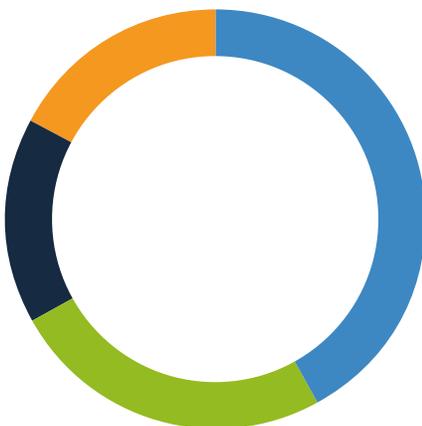
Overall survival (OS)	The time from treatment initiation to death
Overall response rate (ORR)	The proportion of patients who have a partial or complete response to treatment
Disease-free survival (DFS)	The time from treatment initiation to the presence of signs or symptoms of disease
Progression-free survival (PFS)	The time from treatment initiative until disease worsening or progression
Event-free survival (EFS)	The time from treatment initiation to observing a specific ‘event’ such as a symptom, type of pain or a fracture

In our basket of innovative therapies, the most used outcome in the trials assessed by HTA agencies was overall response rate, followed by progression-free survival and overall survival (Figure 4).^{*} Other outcomes were more rarely used. Depending on the stage and type of cancer, some outcomes may be more appropriate than others. But there is a wider issue here of whether surrogate or intermediate outcomes—such as progression free survival—are accepted by HTA agencies. Surrogate or intermediate outcomes may not necessarily be as beneficial to patients, although that depends on the treatment objective, but they are easier and faster to measure than other outcomes that may be clinically more meaningful—therefore they offer a faster route to approval and, ultimately, patient use. Certainly, there is a need for

Figure 4: Type of primary outcome measures in pivotal trial for HTA

For details of data collection see the methods section in **appendix 1**, including the list of HTA publication source URLs in **Table 6**.

Overall response rate **42%** Progression-free survival **25%**
Overall survival **16%** Other **17%**



^{*}The full HTA reports, are only available in some of the countries in our study, for example, England, France and Spain. Other countries provide only a summary of the HTA report, the HTA recommendations or the basis for the reimbursement decision. Where some information about the clinical trials included in the assessment reports was available, we consulted journal publications or clinical trial registries to verify the main outcomes used in the relevant studies.

validated predictors of long-term outcomes that allow timely decisions to be made when overall survival is unlikely to ever be measurable.

Innovative medicines often come in combinations or need associated diagnostic technologies

As “precision” or “targeted”, medicines become a key component of cancer treatment, it is essential to be able to identify patients who are most likely to benefit. France, among other countries, is moving toward reimbursing the cost of biomarker testing, including funding some platforms carrying such tests through support from National Cancer Institute and the Ministry of Health, says Xavier Armoiry, a professor of pharmacy at the University of Lyon.

As the newer oncology medicines are increasingly likely to be combined with other therapies, the process of reimbursement and price setting becomes increasingly stretched.²⁴ “We need to discuss some kind of new payments system, because I believe we have run into limbo when it comes to, for instance, combination therapies with combinations of cancer drugs, because there is no way that you can accommodate the price levels if you have two or more drugs in combinations on patent,” Professor Wilking says. “We’re running into a dead end when it comes to evaluating combination therapies, so we need some kind of new framework, because different companies are not allowed to discuss with one another price agreements and discount agreements.”

Mr. Pemberton-Whiteley agrees that NICE does not have adequate systems for assessing or pricing combination therapies. “There are issues going on in the background there, particularly in regards to combination pricing, where the backbone [core therapy] is often priced at the willingness to pay threshold, and that means that the add-on part of the combination has no route to create value,” he says.

Similar problems are evident with multi-indication therapy pricing, he says, adding that in most cases, NICE approves the primary and most profitable indication for a therapy first, meaning that, without the opportunity for multi-indication pricing, secondary and even third indications “struggle with a lack of flexibility, because they’re being used in an entirely different setting.”



We need to discuss some kind of new payments system, because I believe we have run into limbo when it comes to [...] combinations of cancer drugs, because there is no way that you can accommodate the price levels if you have two drugs on patent.

Nils Wilking, Professor, Karolinska Institute, Stockholm, Sweden

Larotrectinib (Vitravki), a targeted cancer medicine that has been approved for reimbursement in England, France, Germany and Sweden, is an example of a “tumour agnostic” medicine. These are drugs that target molecular abnormalities that can cause cancers across multiple tumour types.²⁵ HTA agencies have always assessed new medicines for additional indications, but with tumour



Paying different amounts for the same drug depending on what type of cancer is being treated is a reality, but one that is challenging to navigate.

agnostic treatments, the process of collecting evidence, evaluating efficacy, and determining reimbursement within each tumour type has become even more complex. Paying different amounts for the same drug depending on what type of cancer is being treated is a reality, but one that is challenging to navigate. Germany is currently the only European country that doesn’t apply any conditions of use for specific sub-populations, reimbursing medicines across all indications listed on the marketing authorisation (although approved indications can be excluded from reimbursement by the G-BA).²⁶

Reimbursement decisions seem increasingly opaque, potentially undermining the credibility of HTAs

The cost of cancer medication as a proportion of cancer spend is rising, partly because of costs of research but also due to the greater extent of available medications for more cancers.⁴ Because this medication spend is becoming a larger proportion of health system spend, it is increasingly under the microscope from a variety of stakeholders. Transparency in how decisions are made was therefore seen as key by several interviewees, and many cited a lack of transparency in reimbursement and pricing decisions as a factor that has the potential to undermine HTA systems.

“There are some basic ideas that need to be put in place in order to look for a better HTA system; the first should be related to transparency in the process”, says Jaime Espin, a professor at Spain’s Andalusian School of Public Health.

“The process of assessment by (France’s) HAS is very transparent and straightforward, but it is becoming difficult to understand how price is determined based on a simple assessment by HAS,” says Professor Armoiry.

England’s NICE is known for having one of the more transparent assessment systems in Europe, and the agency says its reputation for rigour can act as a commercial advantage in price negotiations.

“We look at cost-effectiveness, as well as clinical effectiveness—that’s not the case in all [countries],” says Brad Groves, associate director for managed access at NICE. “And while it is a higher benchmark in England, NICE recommends approximately 80% of licensed drugs. NICE’s cost-effectiveness assessments enable the National Health Service (NHS) to negotiate robust deals with pharmaceutical companies. In our minds, we are balancing the need not only to get value for the NHS but also make the UK an attractive place for pharmaceutical companies to bring their products to market.”



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Jaime Espin, Professor, Andalusian School of Public Health, Granada, Spain



In our minds, we are holding the conflicting need not only to get the best value for the NHS but also make the UK an attractive place for pharmaceutical companies to bring their products to market.

Brad Groves, Associate Director for Managed Access, National Institute for Health and Care Excellence (NICE), UK

Many of the experts interviewed for this paper agree that the current lack of transparency in their country’s HTA systems leads to inequalities and makes it more difficult to explain discrepancies in how agencies decide which new treatments to reimburse. Where there are disagreements, it can also be difficult to detect how final prices are determined. In Sweden and France, HTA agencies’ interpretation of the evidence in a dossier can differ markedly from that of the manufacturer, a process that often results in confidential negotiations and sometimes an undisclosed discount from the company.

Adding to the perception of an opaque and murky process is the fact that regulatory agencies and HTA bodies sometimes appear to be working at cross-purposes. In Sweden, for instance, TLV has been known to overrule decisions made by the EMA, adding additional limitations to drugs that have already been approved, says Professor Wilking of the Karolinska Institute. HTA and regulatory agencies should be independent of one another, as they serve different functions, he says, adding that HTA agencies should respect the EMA approval decision, “The main difference between the regulatory systems and HTA agencies is that HTA looks also at cost.” says Ms. Cardone.

How HTAs are responding to these challenges

HTA agencies have used a variety of approaches that acknowledge the complexity of innovative cancer therapies. Their goal has been to provide effective, equitable and sustainable access for patients. Agencies have made more efforts to consult with manufacturers ahead of the submission of product dossiers, and to consider a wider variety of value-based criteria. Given the unique nature of many new oncology medicines, some agencies are also looking at expanding the involvement of patient groups

and increasing cross-border collaborations as part of the assessment process. Finally, there are a number of agreements already in use to provide market entry with follow-up evaluation of products; here in effect HTAs are hedging longer term reimbursement and pricing decisions until more data can be collected. We describe in this section how HTAs are having to adapt, from early contact long before the HTA process begins, through to HTA harmonisation (**Table 4**).

Table 4: Adaptive process among HTAs

Adaptive process	Potential benefits
Horizon scanning and early contact	HTAs are aware of drug pipelines and manufacturers know what they need to provide, speeding up the entire process
Value assessment	The impact of a treatment is evaluated in the context of patients' and carers' lives and wider society—not only on the healthcare system
Outcomes important to patient	Treatments are assessed based on how they change outcomes that are of importance to patients, rather than just those which are easiest to measure
Patient involvement	Patients, patient representatives and carers are "at the table" when decisions are being made and are empowered to make an impact
Conditional approvals	Therapies are approved for reimbursement with an intention for re-assessment at a later date (e.g. the UK Cancer Drugs Fund)
Reimbursement with conditions	Therapies are approved but with conditions, such as the need for further data collection, commercial agreements or both (e.g. managed entry agreements, also known as risk-sharing or outcomes-based payment). Unlike conditional approvals, no re-assessment is planned
HTA harmonisation	Rather than multiple agencies duplicating effort, harmonisation promises a more efficient approach

Horizon scanning and early contact with manufacturers can streamline processes

Many HTA agencies are taking steps to streamline the assessment process to make it easier for manufacturers to understand the information they will need to provide. Italy's AIFA has a specific format and template that can be used by drug companies when they submit documents for reimbursement, Professor Ruggeri says. He added that the template includes questions about cost-effectiveness that need to be included in a specific format, as well as a section on budget impact.

In Germany, the system appears to be successful on many levels, according to Axel Mühlbacher, a professor of health economics and healthcare management at Hochschule Neubrandenburg. "There is a transparent pathway and innovators can actually introduce their compound or drug," he says. "Companies know how to write a dossier. They are not overwhelmed by the bureaucracy anymore. Before a decision is reached, IQWiG assesses the clinical data submitted, G-BA organizes the appraisal and tries to get everyone aligned and there are some political processes in place that smooth things out."



Many HTA agencies are taking steps to streamline the assessment process to make it easier for manufacturers to understand the information they will need to provide.

On the EU level, meanwhile, the Adaptive Pathways program, in place since 2014, grants conditional approval for new medicines to a restricted patient group based on early data, after which point the real-world evidence generated can be reviewed and a discussion had on expanding, or not, the approved patient population.

One other way in which HTA agencies can prepare for the more complex assessments required by newer oncology therapies is by getting a preview of products that might be coming down the pipeline. Horizon scanning is a tool for identifying "new, emerging or obsolete health technologies that are potentially capable of producing effects on health, healthcare and society which, once marketed, could have a significant clinical and economic impact on the national health service."²⁸ Horizon scanning can complement early contact with manufacturers.

Being aware of the drug pipeline across a range of manufacturers can help ensure that technologies are evaluated at the right time, allowing the full HTA process to go ahead for those that appear to be most innovative and affordable. In England, NICE offers its own scientific advice service to companies that are still many years away from applying for product appraisal; it allows manufacturers to consult with NICE to find out what the key considerations for its committees are, when they are appraising certain topics, how companies should structure their trials and any other research that they are doing. At the beginning of January 2021, NICE launched a new collaboration with other UK agencies, including the Medicines and Healthcare Products Regulatory Agency (MHRA), the Scottish Medicines Consortium, and NHS England and NHS Improvement (NHSE&I) to streamline the licensing and patient access process for new medicines. The project is designed to support and advise companies launching new products in the UK.²⁹

Using value assessments that push beyond classical cost-effectiveness

HTA agencies currently consider a range of economic criteria, including budget impact, and thresholds such as the cost per quality-adjusted life year (QALYs) or the incremental cost-effectiveness ratio (ICER), which is the economic value of an intervention compared with an alternative. In England, new treatments with cost-effectiveness exceeding a willingness-to-pay threshold of more than £30,000 per QALY gained are rarely recommended for reimbursement (via routine NHS funding)³⁰; in the case of oncology medicines, those that exceed this threshold, or instances where there is uncertainty in the cost-effectiveness, are often covered by the Cancer Drugs Fund (CDF).³¹ While few other countries in Europe have an explicit threshold of this sort, many of our interviewees say that products judged to have an ICER of EUR60,000 to EUR80,000 are relatively unlikely to be reimbursed.

Other, non-economic factors are also used. These include burden of disease, severity of disease and unmet medical need. In the Netherlands, assessors take into account “feasibility,” which looks at the sustainability of including the new therapy or care provision in the existing benefits package.²⁶ Sweden also uses broader kinds of “social value judgments” alongside economic factors. There, the three primary factors used to allocate health resources are human dignity, need and solidarity, and cost-effectiveness. Specific legislation for the pharmaceutical reimbursement system priorities human value as the most important of these.²⁶

In the Netherlands, ZIN looks at a variety of criteria, according to Mr. Pomp, an independent health economics consultant

based in Breda. “It looks at all the relevant effects within healthcare, but also outside healthcare,” he says. “For example, if, thanks to a new pharmaceutical, people are able to be more productive or participate in the labour market, then this will also be included.”

France and Germany also make some efforts to assess socioeconomic impact. These include “public health interest” in the case of France, and both direct and indirect costs—including productivity losses due to incapacity and mortality—in the case of Germany. German budget impact analysis is also meant to include any investments or start-up costs required to implement new technologies.



HTAs should examine not just the immediate cost of the treatment, but also the longer-term impact of the treatment.

Antonella Cardone, Director, European Cancer Patient Coalition, Brussels

This approach of considering wider interpretations of value is one way to open up the discussion, argues Ms. Cardone. She agrees that HTAs should examine “not just the immediate cost of the treatment, but also the longer-term impact of the treatment”. Using the example of gene therapies, which can be administered in a single treatment, she adds “this means less cost for the hospital, for society and carers. Patients can go forward to a productive life.”

A focus on outcomes of importance to the patient

Most interviewees agreed that the nature of the newest medicines is making it increasingly important to find a way of integrating patient-relevant endpoints, while at the same time making it more difficult to work out how these can be standardised as part of the assessment process. The use of patient reported outcome measures (PROMs) or patient preference studies are ways of trying to ensure that outcomes that are being used are those that are most relevant to patients. Being transparent about the relevance of endpoints to patients would also help to overcome one of the barriers to greater standardisation of the assessment process. “Every time decision makers are facing a benefit-risk trade-off, they have to rely on their own value judgements,” says Professor Mühlbacher. “If we talk about value, why don’t we talk to the patient about what they value most? Why do we expect decision makers to have clear oversight over patient needs and wants?”



If we talk about value, why don’t we talk to the patient about what they value most?

Axel Mühlbacher, Professor of Health Economics, Hochschule Neubrandenburg, Germany

Complicating matters is the fact that patient preferences can vary, depending on age and circumstances, says Professor Mühlbacher. He recalled the assessment in Germany of a cancer drug; the clinical evidence suggested that the medicine extended survival by only an average of 1.4 months but had substantial side effects. While such a medicine might

The use of patient reported outcome measures (PROMs) or patient preference studies are ways of trying to ensure that outcomes that are being used are those that are most relevant to patients.



have been seen as offering added benefit, freeing it from the need to be priced in line with comparators, IQWiG refused to grant it additional benefit status, in part due to the side effects, with the result that the manufacturer withdrew the drug from the market.

In this particular case, Professor Mühlbacher notes, the side effects involved would probably be intolerable for older patients but less so for a 40-year-old parent of young children. “I actually think that there should be a transparent value judgement and a logic leading to the point where you ask, is there heterogeneity within that group of patients?” he says, adding that as newer cancer therapies increasingly target smaller patient populations with less evidence, it is increasingly important to determine a transparent standard for including patient preferences. “Once you are using QALYS, one takes a societal preference into account, not the patients’ preference,” Professor Mühlbacher adds.

In the Netherlands, the upper price limit of EUR80,000 to EUR120,000 per QALY on new therapies has not been indexed in 12 years, according to Professor Jeurissen. The ZIN uses an algorithm that multiplies this cost-effectiveness by the burden of disease.

Yet, with many of the most innovative therapies remaining on the expensive end of the range, a large number end up being recommended for reimbursement under special arrangements.

How QALYs are calculated is also important. There are many ways to calculate QALYs, based on a variety of questionnaire and survey methods. Some are condition specific, while others are designed to measure generic health status across a wide population. The EQ-5D system—a descriptive system that allows patients to evaluate their health state according to five dimensions: mobility, self-care, usual activities, pain and discomfort and anxiety and depression—is a commonly used measure for comparing patient reported outcomes from treatments.³² However, because it is a generic tool it is not always sufficiently specific for different types of cancer, Mr. Pemberton-Whiteley observes. “The EQ-5D, whilst well-intentioned, often results in a number of situations where it doesn’t accurately reflect what actually matters to patients,” he says.

The characteristics of the newest generation of cancer therapies makes this process even more complicated to navigate, and, arguably, underscores the importance of redefining the measures by which HTA agencies should define value. Indeed, speakers at the World Cancer Series meeting in November 2020 observed a lack of transparency regarding how patient input is used. They remarked that while examples of effective integration of the patient voice exist, they aren’t published and disseminated, so it is hard for them to be replicated by other HTA agencies. Ultimately, says Mr. Pemberton-Whiteley, patient involvement is another area where more data would be useful; developing an evidence base on the benefits of the patient voice to the assessment of innovative therapies could lead to an increase in patient input.

Patient engagement depends on national culture

Alongside research into patient preferences, patients should also be able to participate in the HTA process. Patients have a unique knowledge of diseases, based on their experience. Patient engagement is undoubtedly beneficial, says Mr. Hofmarcher. At the same time, however, he warned that there is a danger that those groups representing more common cancers may have an outsized public voice. “Decisions should not be made based on who is screaming the loudest,” he says. “There are other patient groups with rarer cancers, such as multiple myeloma, and they maybe would not be given the same priority even though their need is maybe higher than those of prostate cancer patients who already have a survival rate of 90%.”

NICE is sometimes seen as a leader on patient engagement, but, says Mr. Pemberton-Whiteley, “if you actually start to delve more deeply, there’s a number of flaws with the current process.” For example, at NICE there isn’t the opportunity to have a specific meeting to focus about the issues that matter the most to patients in the same way there is at the Scottish Medicines Consortium (SMC) with its ‘Patient and Clinician Engagement (PACE) meeting, which involves only SMC representatives, clinicians and patient group representatives.³³ The meeting allows for a discussion on the benefits of a medicine that may not be fully captured in the conventional assessment undertaken by SMC. Meetings result in a PACE statement, agreed by all participants in the meeting.

The involvement of patients in the HTA process doesn’t depend on how wealthy a country is, but on its culture, says Ms. Cardone. Patient involvement is most established in the UK,

and most limited in Germany, she says, largely because of the dependence of German patient organisations on pharmaceutical companies for funding. In Belgium, Professor Van Wilder says, there is “political will” to increase the impact of patient organisations, but also a belief that payers themselves represent patients. This is an opportunity, Professor Van Wilder suggests, to find a greater consensus on who should speak on behalf of patients and their carers.

Managed entry agreements and risk-sharing schemes require better data collection after market entry

In many cases reimbursement recommendations with different conditions attached have been used by HTA agencies to secure access to highly priced oncology medicines, particularly those whose effectiveness is perceived to be uncertain. All of the countries in this study, with the exception of Spain, have used them. Many of these take the form of managed entry agreements (MEAs), also known as risk-sharing agreements. These are most often either financial-based or performance-based, with the former generally more common in our study countries, although other approaches exist (**Figure 5**).³⁴

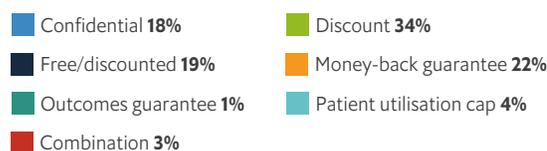
Financial MEAs often take the form of price or volume agreements. They address the budget impact concerns of payers, with manufacturers agreeing to net price reductions of products that are likely to be

high in cost and low in number of patients (or, less commonly, low in cost but high in numbers). Manufacturers are more likely to agree to this approach when in negotiations with large or influential payers who might otherwise deny market access. **Box 3** looks at the example of tisagenlecleucel (Kymriah), where alternative approaches to conditional approval and payment systems have been used.



Figure 5: Types of managed entry agreements applied for oncology drugs across European countries.

Numbers are rounded up, and so add up to 101%. Figure adapted from “Managed Entry Agreements for Oncology Drugs: Lessons from the European Experience to Inform the Future.”³⁴



Performance-based, or outcome-based pricing, addresses the concerns of payers in a different fashion. They are used when there is insufficient information on the efficacy, or even safety, of a treatment. These agreements give patients

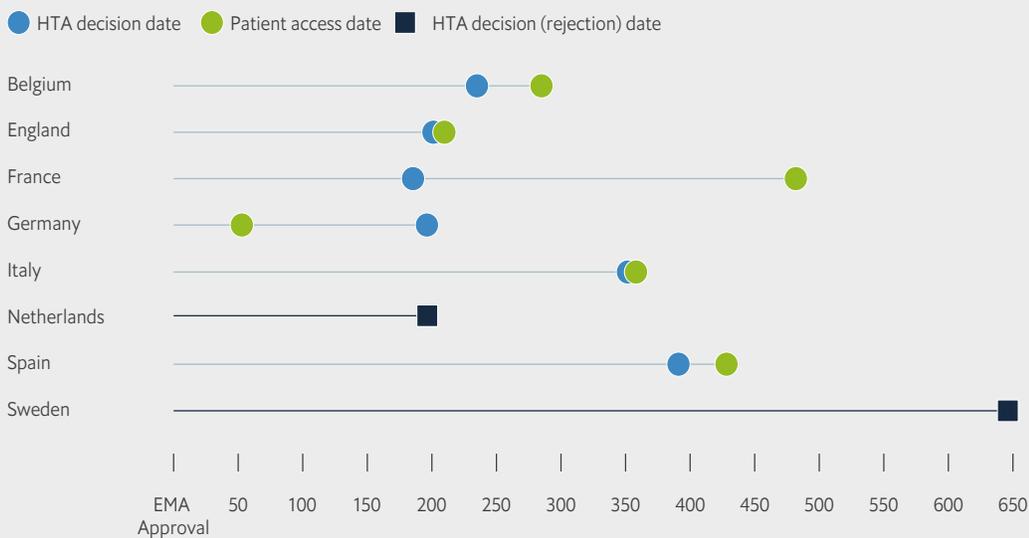
access while allowing manufacturers to collect real-world data for a set number of years.

In Italy, where performance-based MEAs are common, the agreements establish a refund for non-responders at the individual patient level.³⁴

Figure 6: Current reimbursement status for the 12 basket therapies across each country.

In some cases, a positive reimbursement decision is predicated on specific conditions such as requirements for further evidence collection or is subject to various commercial agreements. For more details, see **Table 5**. For details of data collection see the methods section in **appendix 1**, including the list of HTA publication source URLs in **Table 6**.

Therapy	Belgium	England	France	Germany*	Italy	Netherlands	Spain	Sweden
Polatuzumab vedotin (Polivy)		Reimbursed (with conditions)	Not recommended/rejected	Reimbursed	In progress/pending	In progress/pending	In progress/pending	Reimbursed (with conditions)
Larotrectinib (Vitrakvi)		Reimbursed (with conditions)	Reimbursed (with conditions)	Reimbursed	Not assessed/unknown	In progress/pending	In progress/pending	Reimbursed (with conditions)
Cemiplimab (Libtayo)		Reimbursed (with conditions)	Not recommended/rejected	Reimbursed	Reimbursed (with conditions)	Reimbursed	In progress/pending	Not recommended/rejected
Brigatinib (Alunbrig)		Reimbursed (with conditions)	Reimbursed	Reimbursed	Reimbursed (with conditions)	Reimbursed	In progress/pending	Reimbursed (with conditions)
Tisagenlecleucel (Kymriah)	Reimbursed (with conditions)	Reimbursed (with conditions)	Reimbursed (with conditions)	Reimbursed	Reimbursed (with conditions)	Not recommended/rejected	Reimbursed (with conditions)	Not recommended/rejected
Niraparib (Zejula)		Reimbursed (with conditions)	Reimbursed	Reimbursed	Reimbursed (with conditions)	Reimbursed	Reimbursed	Reimbursed (with conditions)
Padeliporfin (Tookad)		Not recommended/rejected	Not recommended/rejected	Not assessed/unknown	Reimbursed (with conditions)	Not assessed/unknown	Not recommended/rejected	Not assessed/unknown
Atezolizumab (Tecentriq)		Reimbursed (with conditions)	Not recommended/rejected	Reimbursed	Reimbursed (with conditions)	Reimbursed	Reimbursed	Not assessed/unknown
Midostaurin (Rydapt)	Reimbursed	Reimbursed (with conditions)	Not recommended/rejected	Reimbursed	Reimbursed (with conditions)	Reimbursed	Reimbursed	Reimbursed
Ixazomib (Ninlaro)	Reimbursed	Reimbursed (with conditions)	Reimbursed (with conditions)	Reimbursed	Reimbursed (with conditions)	Reimbursed (with conditions)	Not recommended/rejected	Reimbursed (with conditions)
Palbociclib (Ibrance)	Reimbursed	Reimbursed (with conditions)	Reimbursed	Reimbursed	Reimbursed (with conditions)	Reimbursed (with conditions)	Reimbursed (with conditions)	Reimbursed (with conditions)
Daratumumab (Darzalex)	Reimbursed	Reimbursed (with conditions)	Reimbursed	Reimbursed	Reimbursed (with conditions)	Reimbursed	Reimbursed	Reimbursed

Box 3**Tisagenlecleucel (Kymriah) - across country variations in reimbursement – focus on mitigation strategies for evidence uncertainty****Timeline from EMA approval date: Tisagenlecleucel**
(Measured in days)

Tisagenlecleucel (Kymriah) is a cell therapy approved under additional monitoring by the EMA with an orphan drug designation. It is reimbursed in the majority of the countries in our study (6 out of 8) with the condition for further evidence collection, and a variety of commercial agreements. For example, Germany uses outcome-based rebates for coverage, while Italy and Spain have introduced a new model of payment—an outcomes-based staged payment in three and two instalments respectively based on individual patients' outcomes.³⁵

Tisagenlecleucel is not reimbursed in Sweden and the Netherlands, due to the deemed significant uncertainty in clinical benefit. The Netherlands HTA states that this therapy can be re-evaluated if further evidence becomes available.

For details of data collection see the methods section in **appendix 1**, including the list of HTA publication source URLs in **Table 6**.

In Germany, such negotiations are built into the fabric of the system. Since 2011, new medicines that receive regulatory approval are automatically reimbursed at the list price for a period of 12 months; after that point, the manufacturer and the country's national association of statutory health insurance funds negotiate a new price based on the prices of appropriate comparators.¹⁷ While this process has its advantages, it does entail administrative burdens, says Mr. Hofmarcher, noting that if each therapy has a separate agreement, the government needs to follow up on the refunds they are supposed to receive from the manufacturer.

Greater dependence on outcomes-based evidence is likely to require an improvement in data collection and registry infrastructure, agrees Mr. Groves of NICE. "There's a huge data requirement in order to do outcome-based pricing and the risks for missing data all sit with the NHS," he adds. "So there is a real question if the NHS is going to negotiate an outcomes-based deal, do they actually have the clinical and financial data to support it?" Doing so will require clinical data collection and finance systems in place to collect the requisite data," he adds.

Mr. Pomp, a Dutch healthcare economics consultant, concurs that it can be difficult for countries to collect the necessary data for re-appraisal of therapies after a conditional approval. In addition, he notes, a country like Germany, which gives automatic short-term reimbursement for products that receive regulatory approval, may offer pharmaceutical companies a stronger negotiating position.

It can be difficult for countries to collect the necessary data for re-appraisal of therapies after a conditional approval.



One way of solving this dilemma is to ensure that payers negotiate a discounted price with the opportunity to top up based on performance, rather than paying a full price and trying to claw back, Mr. Groves says, noting that NICE pays an interim price for drugs included in the Cancer Drugs Fund. While six oncology therapies with Managed Access Agreements have received positive recommendations following further data collection, there will no doubt be other therapies that are less successful.

"The fact that some [medicines] receive negative recommendations at the end of the managed access period is an indicator that actually it's ok to sometimes allow patient access while further data is collected about the clinical effectiveness of a new therapy," he says. "Maybe we don't always get it right. But on balance, giving patients access to these drugs in the meantime, while we establish the true clinical effectiveness of these drugs is perhaps more important than waiting for more complete data to come forward."

Looking at our basket of 12 innovative therapies, **Figure 6** shows the current state of access and reimbursement across our eight countries. As can be seen, reimbursement with conditions (such as MEA's) is commonplace. All but one of the drugs are approved by NICE in England, and all of these have some form of conditional approval or commercial agreement attached. Similarly, over half of the drugs are approved in Italy with conditions attached. Germany, as described above, is an outlier as drugs are available before they are assessed. Fuller details about the basket of drugs can be seen in **Table 5** and **appendix 1**.

The implications of reimbursement with conditions and smaller, targeted populations that are likely to benefit from some of the

newest treatments is that collection of data will be increasingly important, says Laurenz Govaerts, a Ph.D. candidate at Catholic University of Leuven in Belgium. "Now, most drugs obtain reimbursement with specific pay-for-performance indicators in their contract," he says. "There are a lot of contracts and that puts the burden on the reimbursement agency—that means they have to follow up on each drug." In the last few years, the Belgian government set up "healthdata.be", a database which aims to link all Belgian databases so that comprehensive effectiveness data is collected, he adds.

Because of their increasingly common use of performance-based pricing, the National Centre for HTA at the Istituto Superiore di Sanità is working with regional agencies in Trentino, Veneto and Lombardy to produce a joint framework to analyse clinical pathways, especially for lung cancer and melanoma, from the cost-effectiveness point of view, says Professor Ruggeri. "This would allow the linking together of different course of data, and different levels of implementation of data systems. This could be the gold standard," he says. Understanding clinical pathways is important because of their potential impact on quality of care. "The cost-effectiveness approach is very much needed in order to understand how to optimise the entire pathway."



There are a lot of [pay-for-performance] contracts and that puts the burden on the reimbursement agency—that means they have to follow up on each drug.

Laurenz Govaerts, Assistant Professor, Catholic University of Leuven, Leuven, Belgium

Table 5: Types of managed entry agreements, outcomes-based payment schemes and other reimbursement conditions used in basket of therapies

■ Reimbursed
 ■ Not reimbursed

Therapy	Belgium	England	France	Germany	Italy	Netherlands	Spain	Sweden
Polatuzumab vedotin (Polivy)	-	Commercial agreement	-	-	-	-	-	Commercial agreement
Larotrectinib (Vitrakvi)	-	Cancer Drugs Fund, Managed access agreement	Data request	-	-	-	-	Commercial agreement; High-cost protection scheme
Cemiplimab (Libtayo)	-	Cancer Drugs Fund, Managed access agreement	-	-	Commercial agreement; Registry	No information	-	-
Brigatinib (Alunbrig)	-	Commercial agreement	No information	-	Commercial agreement; Registry	No information	-	Commercial agreement; High-cost protection scheme; Data request
Tisagenlecleucel (Kymriah)	No information	Cancer Drugs Fund, Managed access agreement	Data request	-	Outcome-based payment scheme; Registry	-	Outcome-based payment scheme; Registry	-
Niraparib (Zejula)	-	Cancer Drugs Fund, Managed access agreement	Commercial agreement	-	Commercial agreement; Registry	No information	No information	No information
Padeliporfin (Tookad)	-	-	-	-	Commercial agreement; Post-authorization efficacy study	-	-	-
Atezolizumab (Tecentriq)	No information	Commercial agreement	-	-	No information	No information	No information	No information
Midostaurin (Rydapt)	No information	Commercial agreement	-	-	Commercial agreement; Registry	No information	No information	High-cost protection scheme
Ixazomib (Ninlaro)	No information	Cancer Drugs Fund, Managed access agreement	No information	-	Commercial agreement; Registry	No information	-	Commercial agreement; High-cost protection scheme
Palbociclib (Ibrance)	No information	Commercial agreement	No information	-	Commercial agreement; Registry	Commercial agreement	No information	High-cost protection scheme
Daratumumab (Darzalex)	No information	Cancer Drugs Fund, Managed access agreement	No information	-	Commercial agreement; Registry	No information	No information	No information

HTA harmonisation

The large number of European HTA agencies, over 50 of them working in their own silos, is one primary reason why innovative products are taking longer to get to patients, says Ms. Cardone of the ECPC. "There is duplication of work, which means more resources and most of all, from the patient perspective, delay in accessibility of drugs," she adds.

"Cost-effectiveness threshold levels will vary, and you have different healthcare systems within Europe, but I do believe you can evaluate risks and benefits in a common way" says Professor Wilking. "Or you can at least generate data on the quality of new therapy and at what medical risk profile. And then, of course, how much you are willing or able to pay for that product is up to the individual country and their economic situation."

At least a couple of collaborative projects are already underway. In September 2017, Sweden entered the FINOSE pilot with fellow Nordic countries Norway and Finland. "[FINOSE] is a collaboration where these three state agencies jointly assess the drug, both regarding relative effectiveness and also health economics," says Mr. Hofmarcher. "That's a big, big change. One benefit is, of course for companies, because they just have to submit one application. But you still have to make some country-specific adjustments. For the health economic parts, the cost of course has to be national, but you are pooling the resources and making sure you get a faster decision."

Another relatively new project is the BeNeLuxA collaboration between Belgium the Netherlands, Luxembourg, Austria and Ireland, which launched in 2018.³⁶



One benefit of [HTA harmonisation] is, of course for companies, because they just have to submit one application.

Thomas Hofmarcher, Research Manager, Swedish Institute for Health Economics, Stockholm, Sweden

The project allows for joint horizon scanning and reviews, as well as a pooling of resources, according to Mr. van Wilder. Bigger European countries like the UK, Germany and France already had [comprehensive] HTA agencies in place, and they were less keen to develop something on the European level, he says. "Because we are faced with innovation in highly specialised oncology drugs, this is definitely something in which you need a team of experts in clinical practice, in statistics, in research and in pharmacoeconomics."

Yet, steps towards greater harmonisation are likely to remain isolated, due in part to different spending priorities. "I understand the drive towards a common approach to assessing clinical effectiveness," says Mr. Groves of NICE. "But, to be fair, that's the easier part of a health technology appraisal. The difficult

Steps towards greater harmonisation are likely to remain isolated, due in part to different spending priorities.



bit is then applying the economic model and trying to establish what a reasonable price range would be. Unless there is alignment across nation states in terms of the way they want to assess value, it will be a limited benefit.” While Professor Espin and others praised the work of UK agency NICE, he notes that there is no “gold standard” of assessment that will work equally well across European countries.

Indeed, this lack of alignment in assessment of value reflects a difference between HTA systems that define it from a healthcare perspective (i.e., budget impact), versus those that reflect a societal perspective (for example, looking at how an innovative therapy might improve productivity of patients). Even the way in which budget impact is calculated varies from country to country. With spending on medicines and medical therapies in a separate silo from overall hospital budgets, it is difficult to talk about making adjustments across the entire

budgetary infrastructure to take account of new treatments or therapies coming onto the market.

“Different HTA (approaches) may work in one country, but not in another,” says Professor Espin. Indeed, Mr. Pomp suggests that in most countries, HTA agencies face political constraints in carrying out their tasks, making it less likely that harmonisation projects will result in significant economies of scale. “The main challenge is building a good business case for harmonisation,” he adds. “If you can’t really argue that it’s an issue of cost saving or helps to foster market access, then you will not succeed.”

Pricing continues to be the most opaque process of market entry for new therapies, with negotiations taking place in confidential discussions, making it difficult to assess the extent to which value-based pricing or external reference pricing or other considerations ultimately have the upper hand. While BeNeLuxA is looking to explore the idea of collective purchasing, experts interviewed for this paper are sceptical about the ability for HTA collaborations to quickly lead to a common understanding of the priorities to consider in price negotiations.

“The price in the UK is different from the price in the Netherlands because the structure of healthcare system is different,” Professor Jeurissen says. “There are many real ethical problems, and as long as we see such a huge diversity in HTA outcomes across different countries, it also says something about how difficult it is to harmonise them.”



As long as we see such a huge diversity in HTA outcomes across different countries, it also says something about how difficult it is to harmonise them.

Patrick Jeurissen, Professor of Fiscal Sustainability, Radboud University Medical School and Science Officer, Ministry of Health, Welfare and Sport, the Netherlands

Fit for the future: balancing sustainability with access

The novel nature of innovative cancer therapies and their accompanying high-cost tags means that the HTA process will need to adapt to remain fit for purpose. Existing HTA methods were established in a different world, both in terms of the evidence base, range of outcomes used and a whole host of other changes. Our comparison of 12 innovative therapies across eight European countries shows significant differences between countries in terms of time to HTA decision and time to patient access. Within countries there are further large differences between therapies, and the order in which therapies are decided upon differs from country to country. A therapy that is assessed quickly in one country may take the longest time in another country, and vice versa. Such variation is to be expected to some extent, as different countries will have different priorities, but the degree to which differences are apparent, and the almost random nature of differences between and among countries, suggests that the system is under some stress.

Something that we have not described in any detail in this report is the likely effect of Covid-19. Certainly, the pandemic has complicated the HTA process, because of its impact on clinical trials. In April 2020, the EMA published an updated guidance on conducting clinical trials during the pandemic. The guidance emphasises that the pandemic may require that

extraordinary measures are implemented and trials adjusted due to “trial participants being in self-isolation/quarantine, limited access to public places (including hospitals) due to the risk of spreading infection, and health care professionals being committed to critical tasks.”³⁷

While some agencies, such as NICE, have developed rapid guidelines during the pandemic using a different approach to normal,³⁸ it remains unclear what the long-term effects of the pandemic might be on assessments in progress, on agencies as a whole, or indeed its implications for ongoing and future clinical trials. There is a concern among some that HTA’s might be required to focus more on cost-containment rather than facilitating innovation. Put another way, it may be that agencies will be asked to focus their efforts on ‘technology management’ rather than ‘technology adoption’, and evaluate divesting in inefficient services or low-value healthcare.”³⁹

Regardless, however, of the impact of Covid-19, HTA’s will continue to face the same challenges that they faced before the pandemic. One of these is how they will evaluate highly innovative anticancer drugs and therapies and ensure that their introduction is both sustainable and equitable. We suggest below six key takeaways from our research.

Key takeaways

HTA structures and methodology are coming under increasing pressure to adapt:

HTA systems designed to assess drugs with existing comparators are being used to evaluate entirely new classes of therapies that are increasingly personalised to small groups and even individual patients. More broadly, manufacturers continue to contend with a lack of consistency in how value is defined within different HTA systems. The newest generation of oncology treatment presents a range of emerging challenges, including increasing costs, a smaller evidence base, more complicated trial designs and the increased use of personalised medicines. This wave of innovation is a good news story: many of these therapies can hugely improve outcomes for individual patients. However, the potential for delays in access is forcing HTA agencies to change and adapt as they reveal limitations in current assessment, reimbursement, and pricing methodologies.

A greater range of conditional agreements are needed to improve patient access:

Many HTA agencies and reimbursement bodies have used a variety of managed entry agreements and conditional approvals for more than a decade, ensuring patient access while analysts are still collecting evidence about a therapy's performance. Given the complexity of the current crop of oncology treatments, a wider range of these agreements is likely to be inevitable. This is

likely to include new forms of managed entry agreements and conditional inclusion of some innovative products on lists of reimbursable medicines. While these arrangements have been operating—in one form or another—for some years, they are sometimes challenging to implement. It is important that this period of conditional access is fair for all parties, for payers, industry, and patients, perhaps with the adoption of outcomes-based pricing or risk-sharing approach before further evaluation using data collected post appraisal. The big challenge is data: its collection and usage.

Improved data collection infrastructure is required:

Although better data is key to allowing HTA authorities to accurately assess the efficacy or cost-effectiveness of innovative therapies, the infrastructure for enhanced data collection is lacking in most countries. In addition, HTA agencies need to determine what evidence they will need to collect (or have manufacturers provide), what sort of criteria will be used to evaluate this evidence, and how to address situations in which multiple therapies are used in combination, or treatments are increasingly personalised. Those evaluating new therapies will also need to consider patient-relevant endpoints, as well as other assessment metrics. These are especially thorny issues, given the impact of these factors on reimbursement decisions and price negotiations.

Greater transparency in the decision-making process should become the norm: Because of the opportunity costs involved—money spent on one population of patients means it is not available elsewhere—many of our interviewees argued for greater transparency. HTAs need to make more explicit the trade-offs involved in appraisals and funding, so that the public will understand better how decisions are made. This may mean renewed focus on value-based pricing and the way in which the notion of value is defined. Transparency was considered particularly important regarding factors likely to be material in pricing negotiations, thus helping to make reimbursement decisions less opaque.

Patient views need to play a greater role in decision-making, as well as deliberation: Tying the above points together is the importance of having patient's values and preferences at the centre of these discussion. While some HTA agencies include patient voices in the discussion process for new therapies, it is often unclear how patient views are considered during deliberations over reimbursement. Greater patient involvement could help crystallise notions of value. Patient experience is crucial to discussions of clinical benefit, as these are the people who stand to benefit or lose the most from how well the HTA ecosystem adapt to new challenges. Most of our interviewees agreed on the importance of placing the patient

at the heart of the process, although several were unsure how to integrate it into the existing HTA process, and whether there was the will to do so. Incorporation of patient priority studies and improvement of patient registries would help produce better data, and be a good start.

Greater harmonisation can be helpful but remains challenging: In recent years, there have been efforts to create collaborative approaches to HTA between different countries and on an EU level—including a 2018 European Commission proposal to strengthen cooperation amongst EU Member States for assessing health technology. While these have provided blueprints for avoiding the duplication of labour, different health cultures and spending objectives are unlikely to facilitate harmonisation of the entire HTA process. Harmonisation can help countries pool resources and expertise and standardise methodologies for assessing innovative therapies, although reimbursement and pricing decisions are likely to continue to vary by country. Current harmonisation examples include the BeNeLuxA initiative and the Nordic countries' FINOSE project, as well as the European Network for Health Technology Assessment (EUnetHTA) joint programmes. Expansion of these collaborations could help prevent duplication of efforts on the part of companies and national agencies.

Appendix 1. Methods

The research aimed to explore how different HTA models in different countries impact the adoption of innovative oncology medicines. The study countries are Belgium, France, Germany, Italy, The Netherlands, Spain, Sweden, and UK (England). We conducted a literature review focused on the HTA landscape in Europe, followed by a series of expert interviews. The review was not designed to be fully comprehensive—rather, it followed a structured methodology using the following search approaches:

- Bibliographic database searches via Embase.com (MEDLINE and Embase)
- Grey literature searches to identify relevant reports that are not published in the scientific journals and therefore not included in bibliographic databases
- Supplementary search techniques such as internet search using advanced Google search techniques, citation tracking and checking the references in relevant publications.

The bibliographic database searches were limited to English language reports published in the last five years, while the grey literature searches covered a slightly longer period reflecting the realities of the HTA processes in different countries and included publications in languages

other than English. The searches retrieved 1343 articles and after a first sift we identified 308 potentially relevant studies published between 2015 and 2020. After clustering these by themes, we used the most relevant and the most recent publications in the report.

For the review of HTA organisations we extracted data from HTA organisations' websites in the selected eight countries, journal papers and grey literature reports. Relevant documents were used to compare the scope and procedures for new medicines assessment, as well as the processes for decision-making on reimbursement and pricing. The comparison also covered stakeholder engagement and levels of cross-country collaboration for HTA.

To compare the actual availability of innovative oncology medicines in the eight countries, we conducted case studies of 12 products that received marketing authorisation from the European Medicines Agency (EMA) between 2016 and 2020 (**Table 1**). All of the examples selected were in some way "innovative", on the basis of either being 'first-in-class' or otherwise deemed as being novel therapies. The selection therefore is not typical of HTA work, but instead gives an opportunity to examine how HTA agencies have assessed a range of novel cancer therapies.

We collected data to assess the time from EMA regulatory approval to patients' access including the date of HTA publication, the date of reimbursement decision, and the date of market entry. In addition, we gathered data about the reimbursement status of the 12 products for specific indications; the level of evidence and patient outcomes used; and whether the reimbursement decision stipulated any particular conditions or commercial agreements. We used a range of sources to find this information including websites of relevant:

- National bodies responsible for HTA of pharmaceutical products
- Reimbursement decision bodies, payer organisations, Ministries of Health
- National medicines regulatory agencies.

The main sources for HTA publications and reimbursement decision reports by country are listed in **Table 6**. We also commissioned data from the MAESTrO database, developed by Wonder Drug Consulting Pty Ltd.

The searches and data extraction for the medicines case studies were conducted in October and November 2020.

The nature of the data gathering process and the gaps in publicly available material made this a challenging research process. While 100% accuracy can never be guaranteed, we nevertheless made every effort to ensure that the data collected is correct and up to date through triangulation and extensive data checking.

Full evidence tables for each therapy can be found in **supplemental material, Table S2**.

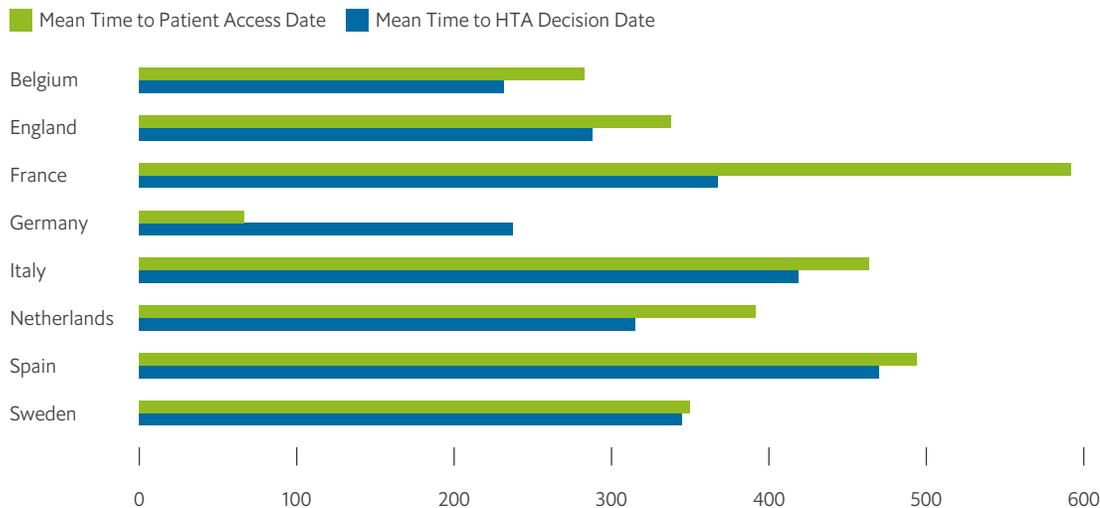
Table 6: Information sources for HTA and reimbursement decisions by country

Country	HTA body	Publications webpage (search or browse)
Belgium	INAMI-RIZIV - National Health Insurance and Disability Institute	https://www.inami.fgov.be/fr/themes/cout-remboursement/par-mutualite/medicament-produits-sante/remboursement/specialites/procedure/Pages/commission-remboursement-medicaments-rapports-evaluation.aspx
England	The National Institute for Health and Care Excellence (NICE)	https://www.nice.org.uk/guidance/published?type=ta
France	National Health Authority (HAS)	https://www.has-sante.fr/jcms/c_412115/fr/comprendre-l-evaluation-des-medicaments
Germany	The Federal Joint Committee (G-BA)	https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/
Italy	Italian Medicines Agency (AIFA)	https://www.aifa.gov.it/web/guest/home
Netherlands	The National Health Care Institute (ZIN)	https://www.zorginstituutnederland.nl/
Spain	Spanish Agency of Medicines and Medical Devices (AEMPS)	https://www.aemps.gob.es/medicamentos-de-uso-humano/informes-de-posicionamiento-terapeutico/
Sweden	Dental and Pharmaceutical Benefits Agency (TLV) & New Therapies Council	https://www.tlv.se/beslut/sok-i-databasen.html https://www.janusinfo.se/nationelltinforandeavlakemedel/managedintroductionthisishowitworks/inenglish/thenewtherapiescouncil.5.4771ab7716298ed82ba9989c.html

Appendix 2. Mean times from EMA approval to HTA decision and patient access

Figure 7 below presents the mean time from EMA approval to HTA decision and patient access by country. The time lag between HTA decision and patient access date varies across countries. The exception is Germany, where all medicines are available to patients almost immediately after marketing authorisation unless they are put on a negative list; HTA takes place after market entry and is used to inform pricing decisions.

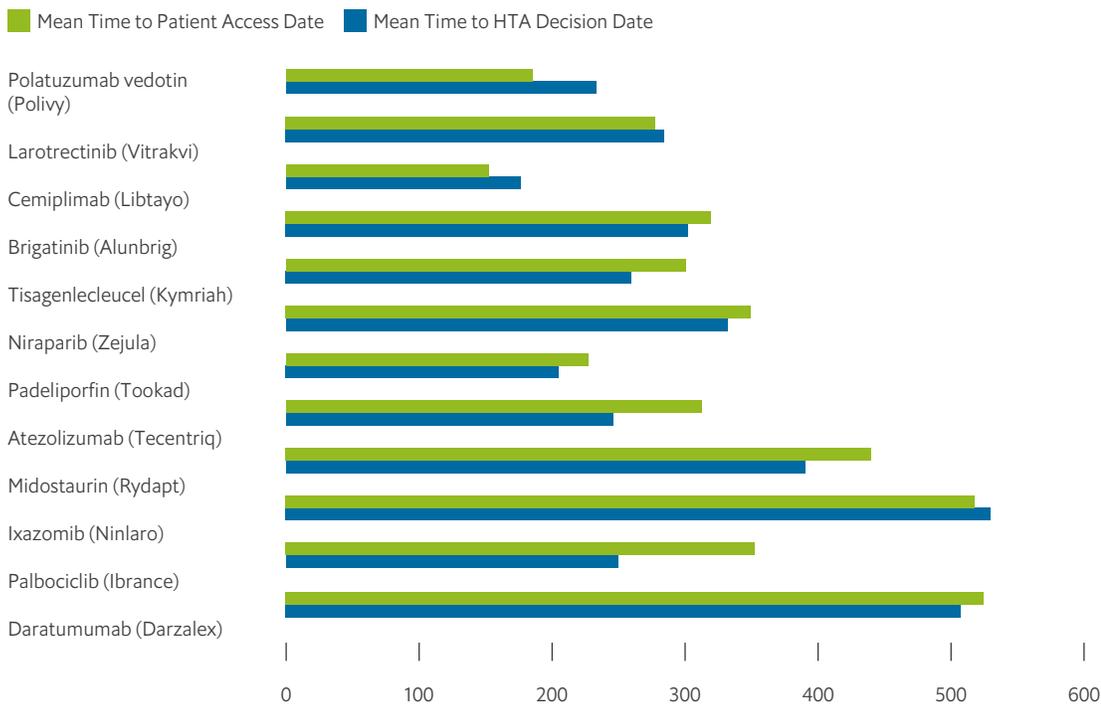
Figure 7: Mean time to HTA decision date and patient access date by country
(Measured in days)



In **Figure 8**, the mean time is presented by therapy. The calculations for each drug are done where data was available for both dates. The data points where these data were unknown were discarded.

Figure 8: Mean time to HTA decision date and patient access date, by therapy (ordered by EMA approval date)

(Measured in days)



Appendix 3. Individual therapy timelines from EMA approval to HTA decision and patient access

Figures 9 to 20, below, show timelines from EMA approval date to the publication of the HTA recommendation and the date when patients get access to the each of the 12 therapies included in our study. Figures are organised by date of EMA approval (most recent first).

Figure 9: Time from EMA approval to HTA decision and reimbursement decision, by country, for polatuzumab vedotin

(Measured in days)

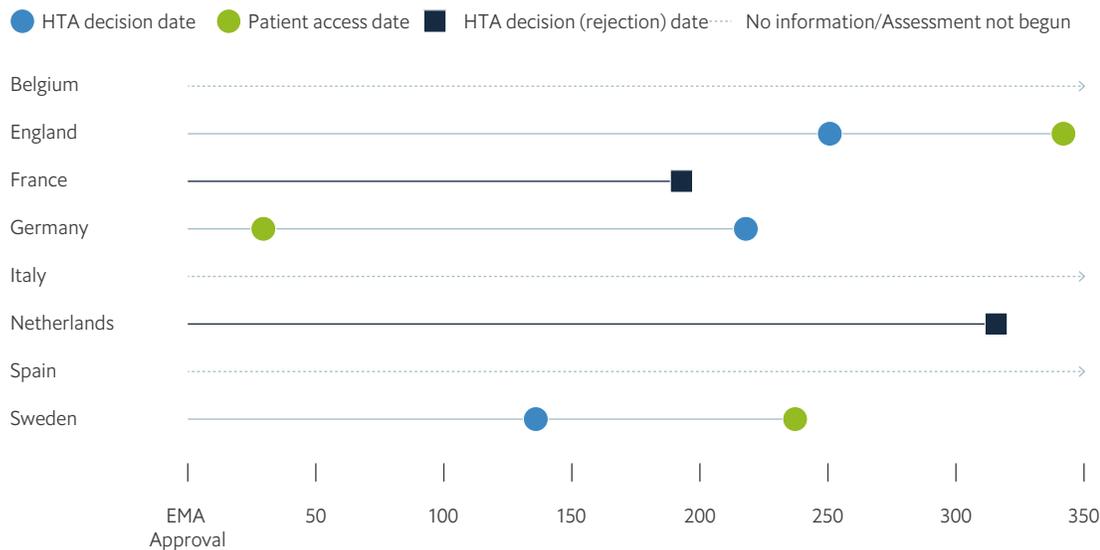


Figure 10: Time from EMA approval to HTA decision and reimbursement decision, by country, for larotrectinib

(Measured in days)

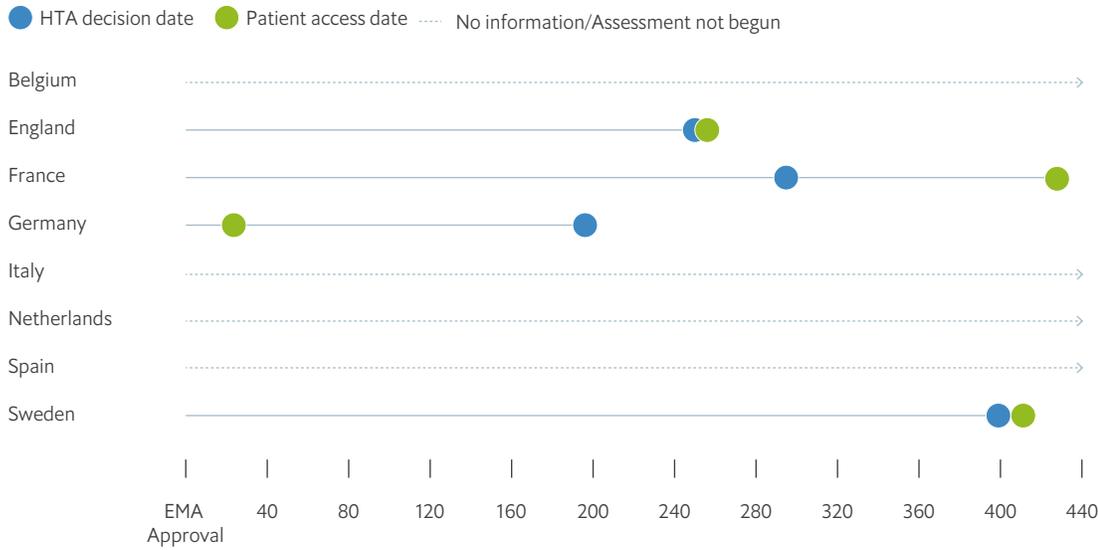


Figure 11: Time from EMA approval to HTA decision and reimbursement decision, by country, for cemiplimab

(Measured in days)

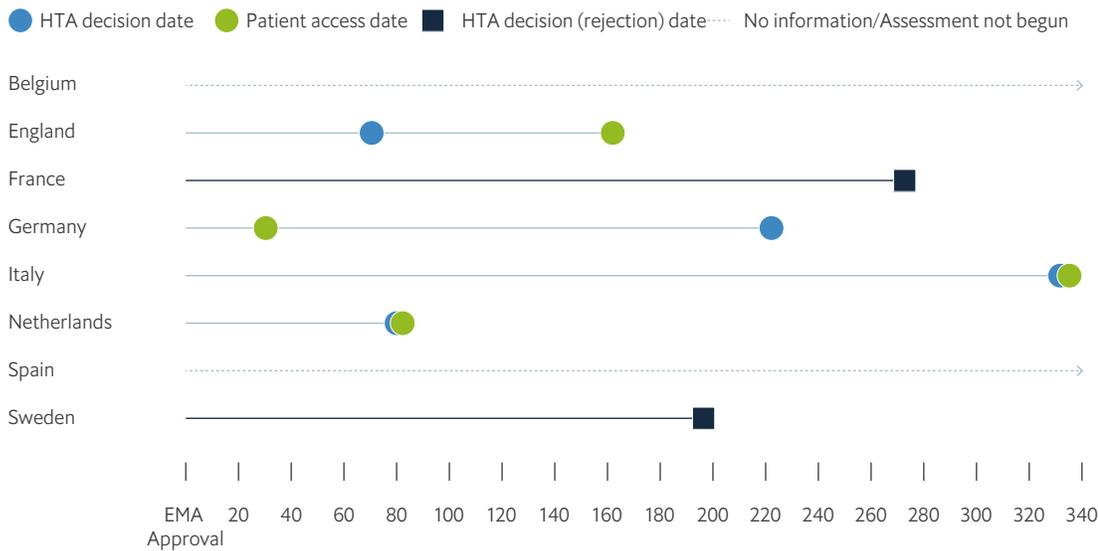


Figure 12: Time from EMA approval to HTA decision and reimbursement decision, by country, for brigatinib

(Measured in days)

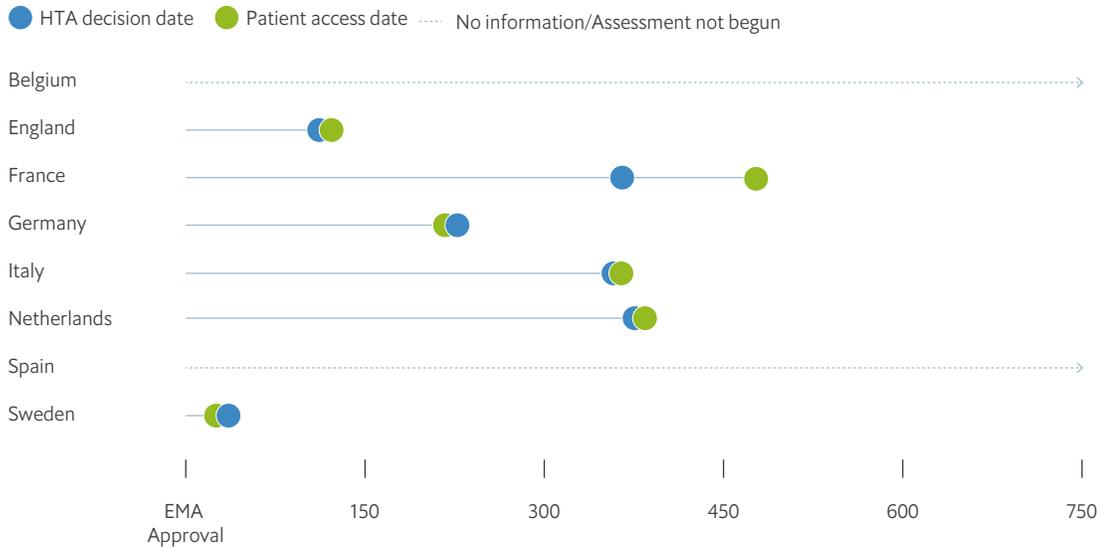


Figure 13: Time from EMA approval to HTA decision and reimbursement decision, by country, for tisagenlecleucel

(Measured in days)

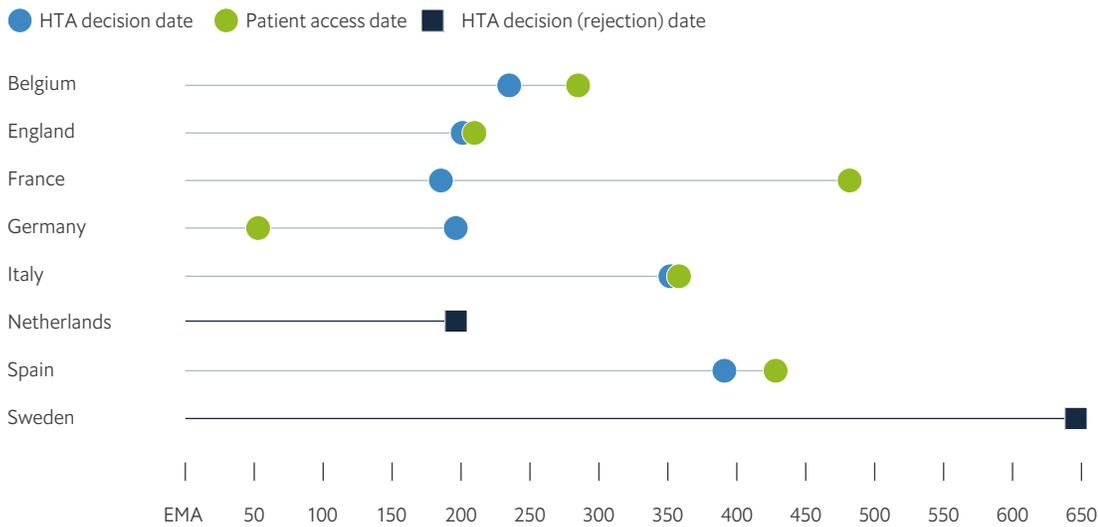


Figure 14: Time from EMA approval to HTA decision and reimbursement decision, by country, for niraparib

(Measured in days)

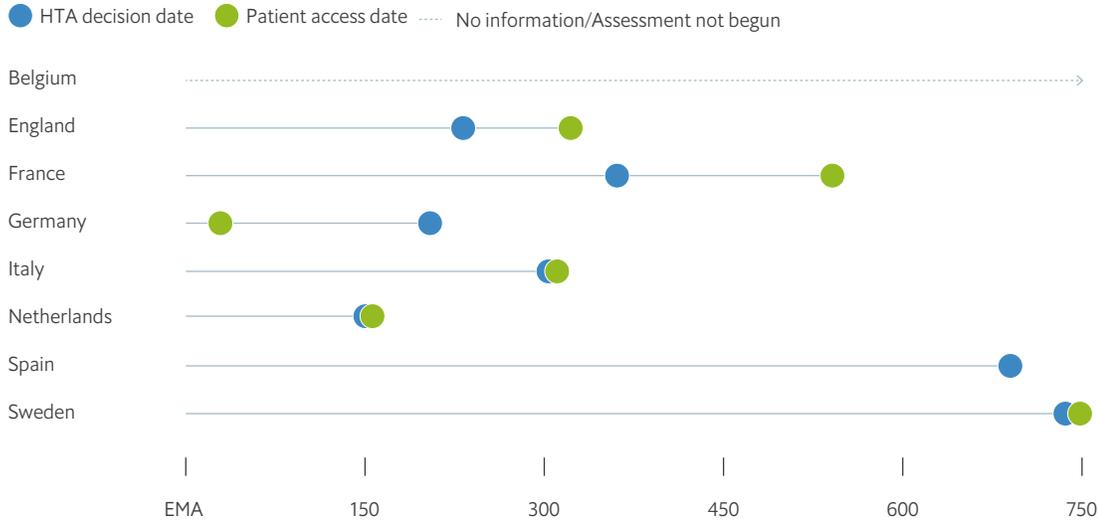


Figure 15: Time from EMA approval to HTA decision and reimbursement decision, by country, for padeliporfin

(Measured in days)

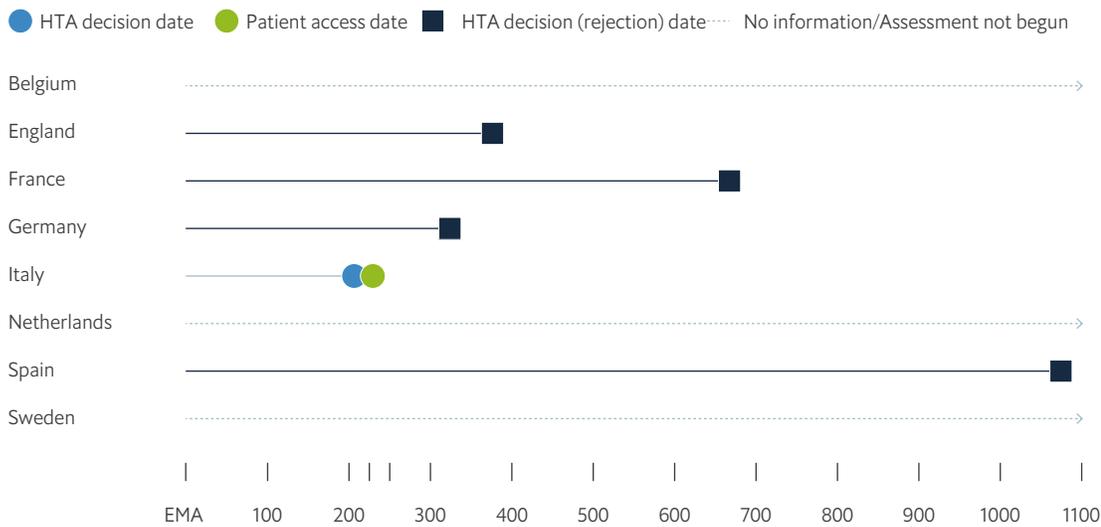


Figure 16: Time from EMA approval to HTA decision and reimbursement decision, by country, for atezolizumab

(Measured in days)

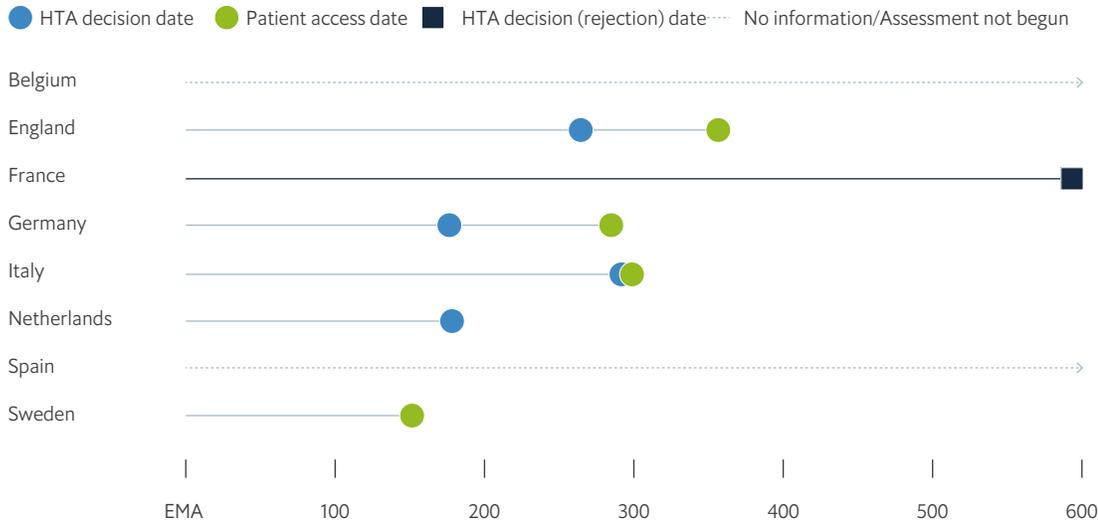


Figure 17: Time from EMA approval to HTA decision and reimbursement decision, by country, for midostaurin

(Measured in days)

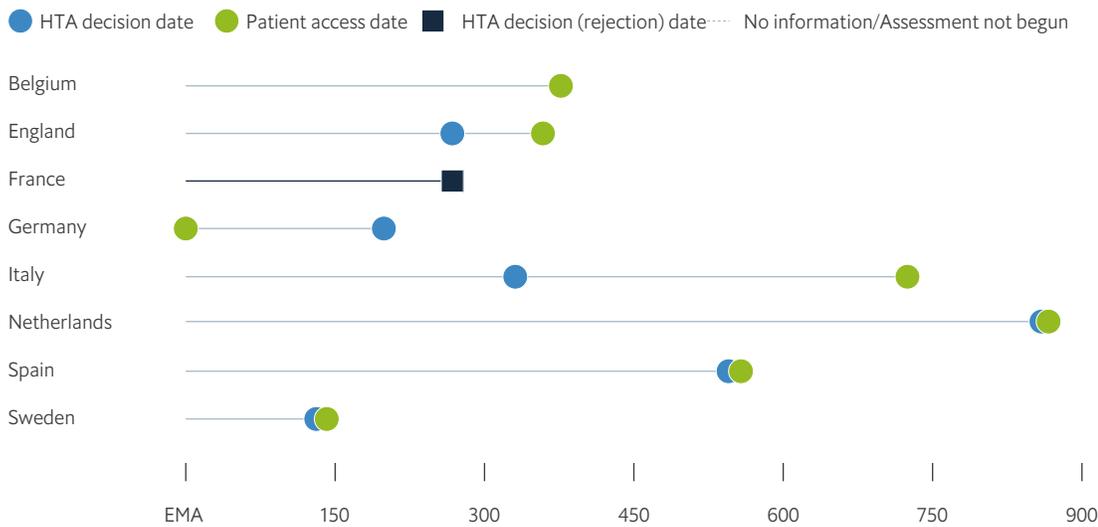


Figure 18: Time from EMA approval to HTA decision and reimbursement decision, by country, for ixazomib

(Measured in days)

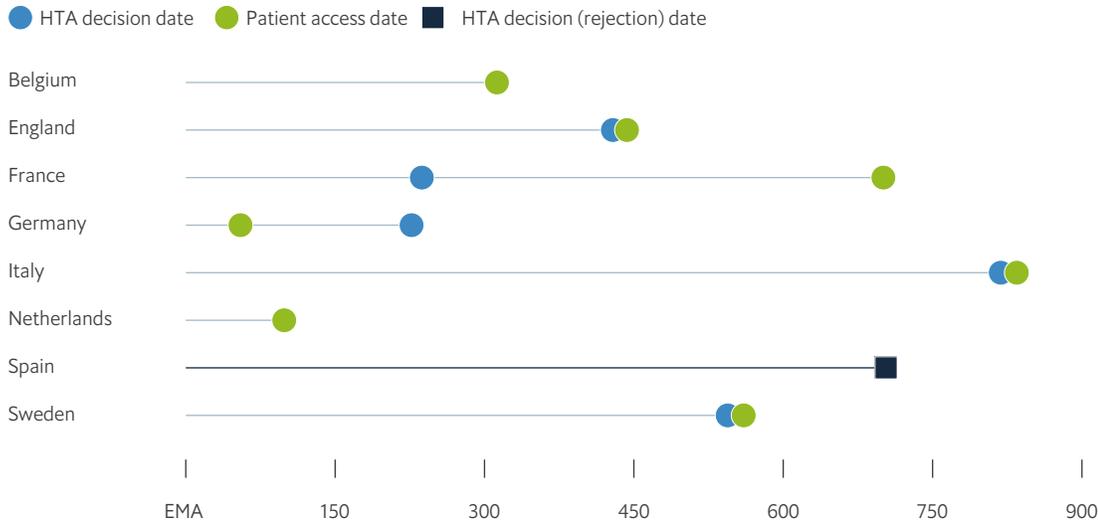


Figure 19: Time from EMA approval to HTA decision and reimbursement decision, by country, for palbociclib

(Measured in days)

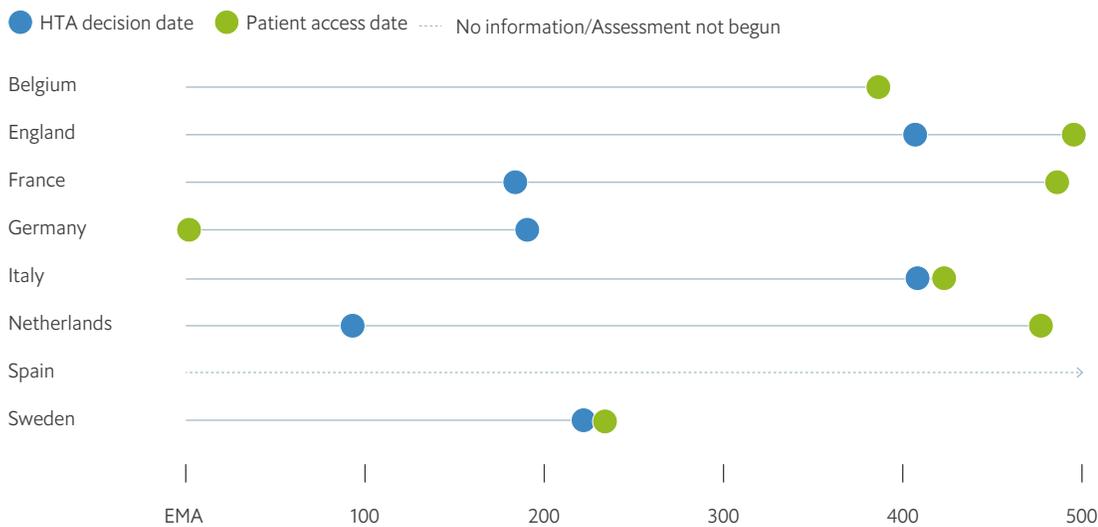
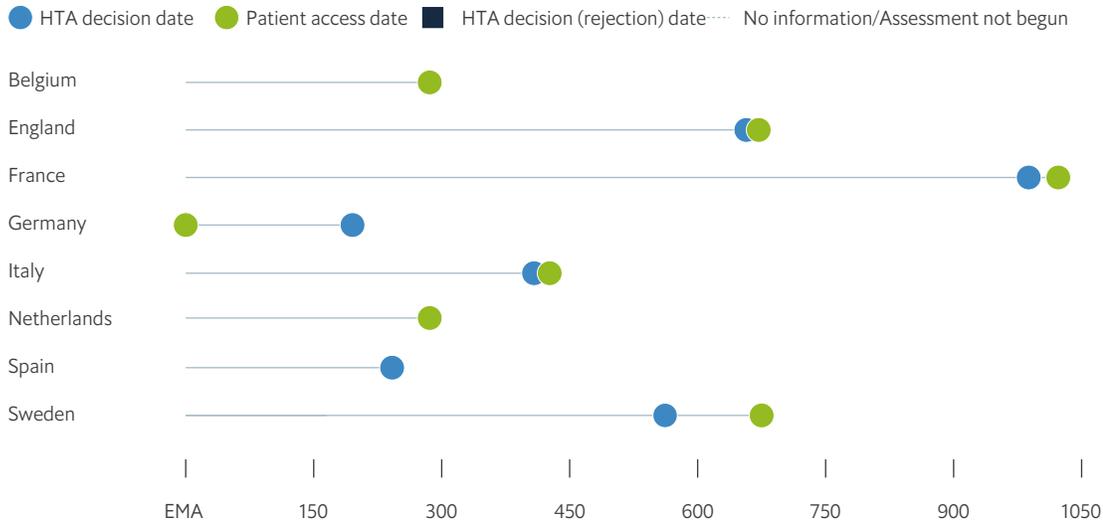


Figure 20: Time from EMA approval to HTA decision and reimbursement decision, by country, for daratumumab

(Measured in days)



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Table S1: Comparison of national HTA ecosystems

Country	HTA body responsible for medicines assessment	Therapeutic value assessment	Economic evaluation	Early access schemes	HTA legal status*	Reimbursement body	Pricing body	Timing of HTA (prior to market entry Y/N)	Special	Patient	Regional influence on adoption of medicines
Belgium	INAMI-RIZIV - National Health Insurance and Disability Institute	Yes Added therapeutic value compared to therapeutic alternatives in the proposed indications	Yes	Yes	Obligatory	Commission for the Reimbursement of Medicines (CRM/CTG) & Minister of Social Affairs	Federal Public Service for Economic Affairs, encompassing two specialised commissions: Commission for Price Regulation, Commission for Pricing of Medicinal Products	Yes <= 90 days Assessment can start before marketing authorisation	"Linked" reimbursement procedure in place for personalised medicines and companion diagnostics	No Patient experts' involvement for the KCE process only (i.e. not for	Low
England	The National Institute for Health and Care Excellence (NICE)	Yes Based on QALYs gained	Yes	Yes	Obligatory (England)	NICE	NHS England HTA recommendations are not used for pricing decision-making	Yes 90-220 days CDF - within 90 days of MA	Yes Cancer Drug Fund (CDF)	Yes	Low
France	National Health Authority (Haute Autorité de Santé, HAS) CEESP, Commission d'évaluation économique et de santé publique)/ Commission for Economic Evaluation and Public Health	Added clinical benefit (amelioration du service médical rendu—ASMR) major (ASMR level I), important (ASMR level II), moderate (ASMR level III), minor (ASMR level IV) or non-existent (ASMR level V)	Yes	Yes	Obligatory	HAS CT, (Commission de la transparence/ Transparency committee)	Comite économique des produits de sante (CEPS)/ Economic Committee for Health Products	Yes <= 90 days (initial assessment)	Yes Reimbursement with conditions attached for all innovative medicines with uncertainty of benefit	Yes Members of patient and consumer association participate on the Transparency Committee and CEESP	Low

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Country	HTA body responsible for medicines assessment	Therapeutic value assessment	Economic evaluation	Early access schemes	HTA legal status*	Reimbursement body	Pricing body	Timing of HTA (prior to market entry Y/N)	Special	Patient	Regional influence on adoption of medicines
Germany	Federal joint Committee (G-BA)	Added therapeutic benefit 6 classifications of benefit (efficacy): - major - considerable - minor 3 categories with no added benefit (non-quantifiable; no added benefit; and lesser benefit)	Yes	Yes	Obligatory: Federal Joint Committee (G-BA) resolution of added benefit for pricing decisions Advisory: IQWiG HTAs produced for G-BA	All medicines entering the market are reimbursed by sickness funds. However, the G-BA has the legal authority to decide on subsequent prescription restrictions.	National Association of Statutory Health Insurance Funds (GKV-SV) Free pricing in year 1	n/a	No	No Other stakeholders may be involved; clinical experts are not involved on a regular basis	Low
Italy	Italian Medicines Agency (L'Agenzia Italiana del Farmaco, AIFA)	Yes Added therapeutic value (GRADE methodology)	Yes	Yes	Obligatory	AIFA Pricing and Reimbursement Committee/Comitato Prezzi e Rimborso (CPR)	AIFA Pricing and Reimbursement Committee/ Comitato Prezzi e Rimborso (CPR)	Yes 180 days 100 days - orphan drugs	Fund for Innovative Medicines in Oncology New reimbursement model, payment at results, used for the first time in 2019 for CAR-T	Yes	High
Netherlands	The National Health Care Institute (Zorginstituut Nederland, ZIN)	Yes Therapeutic value	Yes	Yes	Advisory	ZIN: Scientific Advisory Board (WAB) and Appraisal Committee (ACP)	Ministry of Health, Welfare and Sports (VWS)	Yes between 60 - 365 days	Potentially Promising Care program for expedited patient access	Yes Patient groups	Low

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<https://eiperspectives.economist.com/healthcare/assessing-innovation-health-technology-assessment-europe>

Country	HTA body responsible for medicines assessment	Therapeutic value assessment	Economic evaluation	Early access schemes	HTA legal status*	Reimbursement body	Pricing body	Timing of HTA (prior to market entry Y/N)	Special	Patient	Regional influence on adoption of medicines
Spain	Spanish Agency of Medicines and Medical Devices (Agencia Española de Medicamentos y Productos Sanitarios, AEMPS)	Yes Therapeutic positioning reports (TPRs) AEMPS, General Directorate of Basic Portfolio of the National Health and Pharmacy Service (DGCBSF) & Autonomous Communities (CCAA)	Yes	Yes	Advisory	Interministerial Commission on Prices of Medicines (CIPM), an advisory body of the Ministry of Health (Ministerio de Sanidad, Consumo y Bienestar Social) MoH, Industry & Economy are represented on the commission.	Interministerial Commission on Prices of Medicines (CIPM), an advisory body of the Ministry of Health (Ministerio de Sanidad, Consumo y Bienestar Social) MoH, Industry & Economy are represented on the commission. MoH negotiates prices.	Yes 90-220 days	No	Yes Patient associations	High
Sweden	Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket, TLV)	Yes	Yes	Yes	Obligatory - for pricing decisions	New Therapies Council	The Board of Pharmaceutical Benefits decides on pricing and reimbursement for products included in the benefits scheme.	Yes 90-220 days	No	Yes Patient experts	High

Source: EIU research using organisations' websites; Chamova 2017⁴⁰; EUnetHTA 2018¹⁹

*Definitions: Obligatory: formally established and legally mandated; Advisory: formally established but not legally mandated

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Table S2: Therapy extraction tables

Country	Medicine	EMA approval date	HTA	HTA decision	Patient access date		Time to HTA decision date from EMA approval	Time to patient access date from EMA approval	Top level evidence available for HTA	Primary outcomes in pivotal trial for HTA	Type of reimbursement recommendations
Belgium	Polatuzumab vedotin (Polivy)	16/01/2020	Not assessed	Not applicable	Not applicable	No	--	--	Not applicable	Not applicable	Not applicable
	Larotrectinib (Vitrakvi)	19/09/2019	Not assessed	Not applicable	Not applicable	No	--	--	Not applicable	Not applicable	Not applicable
	Cemiplimab (Libtayo)	28/06/2019	Not assessed	Not applicable	Not applicable	No	--	--	Not applicable	Not applicable	Not applicable
	Brigatinib (Alunbrig)	22/11/2018	No information	No information	No information	No	--	--	Not applicable	Not applicable	Not applicable
	Tisagenlecleucel (Kymriah)	22/08/2018	11/04/2019	11/04/2019	01/06/2019	Yes	232	283	No information	No information	No information
	Niraparib (Zejula)	16/11/2017	Not assessed	Not applicable	Not applicable	No	--	--	Not applicable	Not applicable	Not applicable
	Padeliporfin (Tookad)	10/11/2017	Not assessed	Not applicable	Not applicable	No	--	--	Not applicable	Not applicable	Not applicable
	Atezolizumab (Tecentriq)	20/09/2017	No information	No information	No information	No	--	--	No information	No information	No information
	Midostaurin (Rydapt)	18/09/2017	No information	No information	01/10/2018	Yes	--	378	No information	No information	No information
	Ixazomib (Ninlaro)	21/11/2016	No information	No information	01/10/2017	Yes	--	314	No information	No information	No information
	Palbociclib (Ibrance)	09/11/2016	No information	No information	01/12/2017	Yes	--	387	Phase 3 comparative, randomised	Progression-free survival	No information
	Daratumumab (Darzalex)	20/05/2016	No information	No information	01/03/2017	Yes	--	285	No information	No information	No information

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Country	Medicine	EMA approval date	HTA	HTA decision	Patient access date		Time to HTA decision date from EMA approval	Time to patient access date from EMA approval	Top level evidence available for HTA	Primary outcomes in pivotal trial for HTA	Type of reimbursement recommendations
England	Polatuzumab vedotin (Polivy)	16/01/2020	23/09/2020	23/09/2020	23/12/2020	Yes	251	342	Phase 2 comparative, randomised	Complete response	Commercial arrangement
	Larotrectinib (Vitrakvi)	19/09/2019	27/05/2020	27/05/2020	27/05/2020	Yes	251	251	Phase 2 non-comparative	Overall response rate	CDF, MAA
	Cemiplimab (Libtayo)	28/06/2019	07/09/2019	07/09/2019	07/12/2019	Yes	71	162	Phase 2 non-comparative	Overall response rate	CDF, MAA
	Brigatinib (Alunbrig)	22/11/2018	20/03/2019	20/03/2019	20/03/2019	Yes	118	118	Phase 2 non-comparative	Overall response rate	Commercial arrangement
	Tisagenlecleucel (Kymriah)	22/08/2018	13/03/2019	13/03/2019	13/03/2019	Yes	203	203	Phase 2 non-comparative	Overall response rate	CDF, MAA
	Niraparib (Zejula)	16/11/2017	04/07/2018	04/07/2018	04/10/2018	Yes	230	322	Phase 3 comparative, randomised	Progression-free survival	CDF, MAA
	Padeliporfin (Tookad)	10/11/2017	21/11/2018	21/11/2018	Not reimbursed	No	376	--	Phase 3 comparative, randomised	Absence of definitive cancer and treatment failure	Not applicable
	Atezolizumab (Tecentriq)	20/09/2017	13/06/2018	13/06/2018	13/09/2018	Yes	266	358	Phase 3 comparative, randomised	Overall survival	Commercial arrangement
	Midostaurin (Rydapt)	18/09/2017	13/06/2018	13/06/2018	13/09/2018	Yes	268	360	Phase 3 comparative, randomised	Overall survival	Commercial arrangement
	Ixazomib (Ninlaro)	21/11/2016	07/02/2018	07/02/2018	07/02/2018	Yes	443	443	Phase 3 comparative, randomised	Progression-free survival	CDF, MAA
	Palbociclib (Ibrance)	09/11/2016	20/12/2017	20/12/2017	20/03/2018	Yes	406	496	Phase 3 comparative, randomised	Progression-free survival	Commercial arrangement
	Daratumumab (Darzalex)	20/05/2016	14/03/2018	14/03/2018	14/03/2018	Yes	663	663	Phase 2 non-comparative	Overall response rate	CDF, MAA

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Country	Medicine	EMA approval date	HTA	HTA decision	Patient access date		Time to HTA decision date from EMA approval	Time to patient access date from EMA approval	Top level evidence available for HTA	Primary outcomes in pivotal trial for HTA	Type of reimbursement recommendations
France	Polatuzumab vedotin (Polivy)	16/01/2020	10/06/2020	27/07/2020	Not reimbursed	No	193	--	Phase 2 comparative, randomised	No information	Not applicable
	Larotrectinib (Vitrakvi)	19/09/2019	09/07/2020	10/07/2020	20/11/2020	Yes	295	428	Phase 2 non-comparative	No information	Data request
	Cemiplimab (Libtayo)	28/06/2019	18/03/2020	27/03/2020	Not yet published	No	273	--	Phase 2 non-comparative	Overall response rate	Not applicable
	Brigatinib (Alunbrig)	22/11/2018	23/10/2019	25/11/2019	13/03/2020	Yes	368	477	Phase 2 non-comparative	Overall response rate	No information
	Tisagenlecleucel (Kymriah)	22/08/2018	12/12/2018	22/02/2019	20/12/2019	Yes	184	485	Phase 2 non-comparative	Overall response rate	Data request
	Niraparib (Zejula)	16/11/2017	13/06/2018	14/11/2018	13/05/2019	Yes	363	543	Phase 3 comparative, randomised	Progression-free survival	Commercial agreement
	Padeliporfin (Tookad)	10/11/2017	10/09/2019	10/09/2019	Not reimbursed	No	669	--	Phase 3 comparative, randomised	No information	Not applicable
	Atezolizumab (Tecentriq)	20/09/2017	20/02/2019	07/05/2019	Not reimbursed	No	594	--	Phase 3 comparative, randomised	Overall survival	Not applicable
	Midostaurin (Rydapt)	18/09/2017	13/06/2018	13/06/2018	Not reimbursed	No	268	--	Phase 3 comparative, randomised	Overall survival	Not applicable
	Ixazomib (Ninlaro)	21/11/2016	05/07/2017	18/07/2017	26/10/2018	Yes	239	704	Phase 3 comparative, randomised	Progression-free survival	No information
	Palbociclib (Ibrance)	09/11/2016	03/05/2017	11/05/2017	16/03/2018	Yes	183	492	Phase 3 comparative, randomised	Progression-free survival	No information
	Daratumumab (Darzalex)	20/05/2016	22/11/2017	31/01/2019	04/03/2019	Yes	986	1018	Phase 2 non-comparative	Overall response rate	No information

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Country	Medicine	EMA approval date	HTA	HTA decision	Patient access date		Time to HTA decision date from EMA approval	Time to patient access date from EMA approval	Top level evidence available for HTA	Primary outcomes in pivotal trial for HTA	Type of reimbursement recommendations
Germany	Polatuzumab vedotin (Polivy)	16/01/2020	11/05/2020	20/08/2020	15/02/2020	Yes	217	30	Phase 2 comparative, randomised	Complete response	Not applicable
	Larotrectinib (Vitrakvi)	19/09/2019	13/01/2020	02/04/2020	15/10/2019	Yes	196	26	Phase 2 non-comparative	No information	Not applicable
	Cemiplimab (Libtayo)	28/06/2019	30/10/2019	06/02/2020	01/08/2019	Yes	223	34	Phase 2 non-comparative	Overall response rate	Not applicable
	Brigatinib (Alunbrig)	22/11/2018	11/04/2019	04/07/2019	01/07/2019	Yes	224	221	Phase 2 non-comparative	Overall response rate	Not applicable
	Tisagenlecleucel (Kymriah)	22/08/2018	13/12/2018	07/03/2019	15/10/2018	Yes	197	54	Phase 2 non-comparative	Overall response rate	Not applicable
	Niraparib (Zejula)	16/11/2017	12/03/2018	07/06/2018	15/12/2017	Yes	203	29	Phase 3 comparative, randomised	Progression-free survival	Not applicable
	Padeliporfin (Tookad)	10/11/2017	04/10/2018	04/10/2018	Not applicable	No	328	--	Not applicable	Not applicable	Not applicable
	Atezolizumab (Tecentriq)	20/09/2017	22/12/2017	16/03/2018	02/07/2018	Yes	177	285	Phase 3 comparative, randomised	Overall survival	Not applicable
	Midostaurin (Rydapt)	18/09/2017	09/01/2018	05/04/2018	18/09/2017	Yes	199	0	Phase 3 comparative, randomised	Overall survival	Not applicable
	Ixazomib (Ninlaro)	21/11/2016	18/04/2017	06/07/2017	15/01/2017	Yes	227	55	Phase 3 comparative, randomised	Progression-free survival	Not applicable
	Palbociclib (Ibrance)	09/11/2016	23/02/2017	18/05/2017	09/11/2016	Yes	190	0	Phase 3 comparative, randomised	Progression-free survival	Not applicable
	Daratumumab (Darzalex)	20/05/2016	01/12/2016	01/12/2016	20/05/2016	Yes	195	0	Phase 2 non-comparative	Overall response rate	Not applicable

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Country	Medicine	EMA approval date	HTA	HTA decision	Patient access date		Time to HTA decision date from EMA approval	Time to patient access date from EMA approval	Top level evidence available for HTA	Primary outcomes in pivotal trial for HTA	Type of reimbursement recommendations
Italy	Polatuzumab vedotin (Polivy)	16/01/2020	Not assessed	Not applicable	Not applicable	No	--	--	Not applicable	Not applicable	Not applicable
	Larotrectinib (Vitrakvi)	19/09/2019	Not assessed	Not applicable	Not applicable	No	--	--	Not applicable	Not applicable	Not applicable
	Cemiplimab (Libtayo)	28/06/2019	23/04/2020	26/05/2020	27/05/2020	Yes	333	334	No information	No information	Commercial agreement; Registry
	Brigatinib (Alunbrig)	22/11/2018	14/10/2020	26/10/2020	27/10/2020	Yes	704	705	No information	No information	Commercial agreement; Registry
	Tisagenlecleucel (Kymriah)	22/08/2018	07/08/2019	12/08/2019	13/08/2019	Yes	355	356	No information	No information	Outcome-based payment scheme; Registry
	Niraparib (Zejula)	16/11/2017	24/08/2018	20/09/2018	21/09/2018	Yes	308	309	No information	No information	Commercial agreement; Registry
	Padeliporfin (Tookad)	10/11/2017	19/01/2018	04/06/2018	26/06/2018	Yes	206	228	Phase 3 comparative, randomised	Rate of absence of definite cancer; treatment failure	Commercial agreement; Post-authorization efficacy study
	Atezolizumab (Tecentriq)	20/09/2017	27/06/2018	14/07/2018	15/07/2018	Yes	297	298	No information	No information	No information
	Midostaurin (Rydapt)	18/09/2017	31/07/2018	16/08/2018	16/09/2019	Yes	332	728	No information	No information	Commercial agreement; Registry
	Ixazomib (Ninlaro)	21/11/2016	19/02/2019	08/03/2019	09/03/2019	Yes	837	838	No information	No information	Commercial agreement; Registry
	Palbociclib (Ibrance)	09/11/2016	06/12/2017	22/12/2017	06/01/2018	Yes	408	423	Phase 3 comparative, randomised	Progression-free survival	Commercial agreement; Registry
	Daratumumab (Darzalex)	20/05/2016	27/06/2017	03/07/2017	18/07/2017	Yes	409	424	No information	No information	Commercial agreement; Registry

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Country	Medicine	EMA approval date	HTA	HTA decision	Patient access date		Time to HTA decision date from EMA approval	Time to patient access date from EMA approval	Top level evidence available for HTA	Primary outcomes in pivotal trial for HTA	Type of reimbursement recommendations
Netherlands	Polatuzumab vedotin (Polivy)	16/01/2020	27/11/2020	27/11/2020	No information	No	316	--	Phase 2 comparative, randomised	No information	Not applicable
	Larotrectinib (Vitrakvi)	19/09/2019	No information	No information	No information	No	--	--	Not applicable	Not applicable	Not applicable
	Cemiplimab (Libtayo)	28/06/2019	No information	17/09/2019	17/09/2019	Yes	81	81	No information	No information	No information
	Brigatinib (Alunbrig)	22/11/2018	No information	08/12/2019	08/12/2019	Yes	381	381	No information	No information	No information
	Tisagenlecleucel (Kymriah)	22/08/2018	07/03/2019	07/03/2019	Not reimbursed	No	197	--	Phase 2 non-comparative	Overall Response Rate	Not applicable
	Niraparib (Zejula)	16/11/2017	20/04/2018	20/04/2018	20/04/2018	Yes	155	155	No information	No information	No information
	Padeliporfin (Tosynovis)	10/11/2017	Not assessed	Not applicable	Not applicable	No	--	--	Not applicable	Not applicable	Not applicable
	Atezolizumab (Tecentriq)	20/09/2017	16/03/2018	16/03/2018	No information	Yes	177	--	No information	No information	No information
	Midostaurin (Rydapt)	18/09/2017	No information	01/02/2020	01/02/2020	Yes	866	866	No information	No information	No information
	Ixazomib (Ninlaro)	21/11/2016	No information	No information	01/03/2017	Yes	--	100	No information	No information	No information
	Palbociclib (Ibrance)	09/11/2016	10/02/2017	10/02/2017	01/03/2018	Yes	93	477	Phase 3 comparative, randomised	Progression-free survival	Commercial agreement
	Daratumumab (Darzalex)	20/05/2016	No information	No information	01/03/2017	Yes	--	285	No information	No information	No information

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Spain	Polatuzumab vedotin (Polivy)	16/01/2020	Not assessed	Not applicable	Not applicable	No	--	--	Not applicable	Not applicable	Not applicable
	Larotrectinib (Vitrakvi)	19/09/2019	Not assessed	Not applicable	Not applicable	No	--	--	Not applicable	Not applicable	Not applicable
	Cemiplimab (Libtayo)	28/06/2019	Not assessed	Not applicable	Not applicable	No	--	--	Not applicable	Not applicable	Not applicable
	Brigatinib (Alunbrig)	22/11/2018	Not assessed	Not applicable	Not applicable	No	--	--	Not applicable	Not applicable	Not applicable
	Tisagenlecleucel (Kymriah)	22/08/2018	25/02/2019	17/09/2019	24/10/2019	Yes	391	428	Phase 2 non-comparative	Overall response rate	Outcome-based payment scheme; Registry
	Niraparib (Zejula)	16/11/2017	No information	09/10/2019	No information	Yes	692	--	Phase 3 comparative, randomised	Progression-free survival	No information
	Padeliporfin (Tookad)	10/11/2017	21/10/2020	21/10/2020	Not reimbursed	No	1076	--	Not applicable	Not applicable	Not applicable
	Atezolizumab (Tecentriq)	20/09/2017	25/07/2018	No information	No information	Yes	--	--	Phase 3 comparative, randomised	Overall survival	No information
	Midostaurin (Rydapt)	18/09/2017	No information	21/03/2019	01/04/2019	Yes	549	560	Phase 3 comparative, randomised	Overall survival	No information
	Ixazomib (Ninlaro)	21/11/2016	No information	05/11/2018	Not reimbursed	No	714	--	Phase 3 comparative, randomised	Progression-free survival	Not applicable
	Palbociclib (Ibrance)	09/11/2016	09/01/2018	No information	No information	Yes	--	--	Phase 3 comparative, randomised	Progression-free survival	No information
	Daratumumab (Darzalex)	20/05/2016	17/01/2017	17/01/2017	No information	Yes	242	--	Phase 2 non-comparative	Overall response rate	No information

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Sweden	Polatuzumab vedotin (Polivy)	16/01/2020	01/06/2020	01/06/2020	11/09/2020	Yes	137	239	Phase 2 comparative, randomised	Complete response	Commercial agreement
	Larotrectinib (Vitrakvi)	19/09/2019	22/10/2020	23/10/2020	01/11/2020	Yes	400	409	Phase 2 non-comparative	Overall response rate	Commercial agreement; High-cost protection scheme
	Cemiplimab (Libtayo)	28/06/2019	13/01/2020	13/01/2020	Not reimbursed	No	199	--	Phase 2 non-comparative	Overall response rate	Not applicable
	Brigatinib (Alunbrig)	22/11/2018	14/12/2018	17/12/2018	14/12/2018	Yes	25	22	Phase 3 comparative, randomised	Progression-free survival	Commercial agreement; High-cost protection scheme; Data request
	Tisagenlecleucel (Kymriah)	22/08/2018	15/04/2020	01/06/2020	Not reimbursed	No	649	--	Phase 2 non-comparative	Overall Response Rate	Not applicable
	Niraparib (Zejula)	16/11/2017	22/11/2019	25/11/2019	01/12/2019	Yes	739	745	Phase 3 comparative, randomised	Progression-free survival	No information
	Padeliporfin (Tookad)	10/11/2017	Not assessed	Not applicable	Not applicable	No	--	--	Not applicable	Not applicable	Not applicable
	Atezolizumab (Tecentriq)	20/09/2017	No information	No information	20/02/2018	Yes	--	153	Phase 3 comparative, randomised	Overall survival	No information
	Midostaurin (Rydapt)	18/09/2017	31/01/2018	31/01/2018	31/01/2018	Yes	135	135	Phase 3 comparative, randomised	Overall survival	High-cost protection scheme
	Ixazomib (Ninlaro)	21/11/2016	17/05/2018	22/05/2018	01/06/2018	Yes	547	557	Phase 3 comparative, randomised	Progression-free survival	Commercial agreement; High-cost protection scheme
	Palbociclib (Ibrance)	09/11/2016	15/06/2017	19/06/2017	01/07/2017	Yes	222	234	Phase 3 comparative, randomised	Progression-free survival	High-cost protection scheme
	Daratumumab (Darzalex)	20/05/2016	24/11/2017	29/11/2017	19/04/2018	Yes	558	699	Phase 2 non-comparative	Overall response rate	No information

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